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SYNTHESIS OF AZAANALOGUES OF BIOLOGICALLY ACTIVE 3-[(1H-PYRROL-2-YL)METHYLENE]-1-METHYLINDOLIN-2-ONES

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By the interaction of isatin and its 1-substituted derivatives with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate, 3-(2-(1H-imidazol-2-yl)hydrazylidene)indolin-2-ones were synthesized.

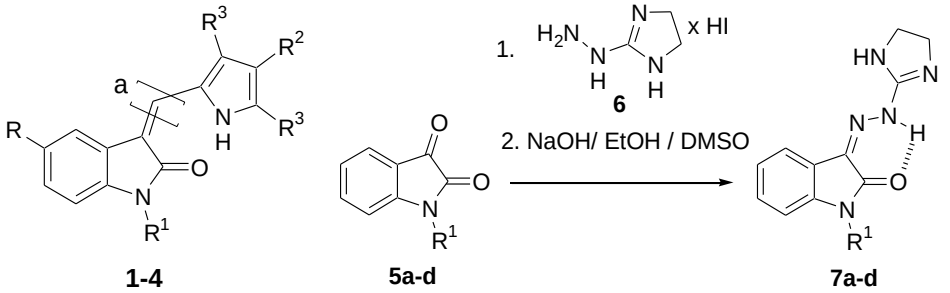
The compounds obtained are the simplest analogues of biologically active 3-substituted indolin-2-ones.

References 2.

It is known that various indolin-2-one derivatives exhibit pronounced antitumor activity due to inhibitory properties against a variety of cellular tyrosine kinase receptors (RTKs) by inhibiting ligand-dependent autophosphorylation of kinases in submicromolar doses [1]. Among well-known drugs are 3-substituted indolin-2-one **1** (Semaxanib, SU5416), which has shown high antikinase activity against the receptor for vascular endothelial growth factor (VEGFR-1) and (VEGFR-2), an antitumor drug Sunitinib **2** (Sunitinib, SU 11248), a multiple kinase inhibitor (VEGFR)-1, VEGFR-2, PDGFRb, fms-like tyrosine kinase-3), as well as piperidin-1-ylmethyl derivative **3** (drug Z24) angiogenesis inhibitor and 3-(dimethylamino)propyl derivative **4** (preparation TMP-20) with pronounced antitumor activity *in vivo*. Since the main structural elements responsible for the biological activity of the class of compounds under discussion are the fragments of indolin-2-one and pyrrole linked by a linker (**a**), in the present study by the interaction of isatin and its 1-substituted derivatives **5a-d** with 2-hydrazino-4,5-dihydro-1H-imidazole **6**, 3-(2-(1H-imidazol-2-yl)hydrazylidene)indolin-2-ones **7a-d** were synthesized, two of which were prepared and characterized as bases. In the synthesized compounds, a fragment

of indolin-2-one and 4,5-dihydroimidazole are linked by a hydrazine residue, which allows to trace the influence of the nature of the five-membered nitrogen heterocycle and the linking chain on the biological activity. The synthesis of target compounds is presented in the Scheme:

Scheme



1-4 **5a-d** **7a-d**

1: R, R^1, R^2, R^3 = H, H, H, Me; **2**: H, H, $Et_2N(CH_2)_2NHCO$), Me; **3**: H, $CH_2N(CH_2)_5$, H, H; **4**: Cl, $Me_2N(CH_2)_3$, H, H; **5a-d, 7a-d**: R^1 = H (**a**), Bn (**b**), *n*-pentyl (**c**), Ac (**d**).

Since on the basis of physicochemical data we have not yet been able to establish the exact geometric structure of derivatives **7a-d**, a preliminary choice of the configuration of synthesized compounds was made in favor of (*Z*)-isomers in which the formation of an energetically favorable intramolecular N-H-O-hydrogen connection with the formation of a six-membered cycle took place.

The toxicity and antitumor activity of compounds **7a** and **7d** were studied. In the study of acute toxicity, it was found that LD_{100} of compounds was 1750 *mg*/*kg*, and MTD was 900 *mg*/*kg*.

In chemotherapeutic experiments *in vivo*, these compounds were administered intraperitoneally daily for 6 *days* at a dose of 150 *mg*/*kg*. It was found that imidazolines **7a** and **7d** exhibited weak antitumor activity against sarcoma 180 of mice, inhibiting tumor growth by 28.4% (compound **7a**) and 40.3% (compound **7d**) and both compounds were inactive in the Ehrlich ascites carcinoma model.

Experimental part

IR spectra were recorded on a "Nicolet Avatar 330" in vaseline oil. ^1H and ^{13}C NMR spectra were obtained on a Varian "Mercury-300 VX" instrument with a frequency of 300.8 *MHz* and 75.46 *MHz*, in a DMSO-d_6 – CCl_4, 1:3 mixture, and the internal standard was TMS. TLC was performed on "Silufol UV-254" plates in the system water - methanol - ethyl acetate, 1: 2: 10), visualization – in UV light.

1-Substituted indolin-2-ones 7a-d. An equimolar mixture of 0.0055 *mol* of 1-substituted isatin **5a-d** and 2-hydrazino-4,5-dihydroimidazole iodohydrate **6**

[2] in 15 *ml* of absolute methanol was boiled for 2*hr* and left overnight. The precipitated iodine hydrate of the compound was filtered off and dried. To obtain the bases of the synthesized compounds, the obtained salt was dissolved in DMSO, neutralized with a 20% alcohol solution of NaOH, poured into water; the precipitate formed was filtered off, dried and recrystallized from ethanol.

(*Z*)-3-[2-(4,5-Dihydro-1H-imidazol-2-yl)hydrazylidene]indolin-2-one iodohydrate (7a) was obtained by the interaction of indoline-2,3-dione with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate **(6).** The yield 63.5%, mp > 320 °C (base yield 78.6%, mp 242-244°C, R_f 0.63). IR spectrum, ν, *cm*$^{-1}$: 3460, 3392, 3161 (NH_2^+, NH), 1712 (CO), 1650, 1612 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm, *Hz*: 3.91 br.s (4H, 2·NCH_2); 6.93 br.d (1H, J = 7.8, C_6H_4); 7.05 td (1H, J = 7.6, 0.8 C_6H_4); 7.32 td (1H, J = 7.7, 1.2, C_6H_4); 7.63 br.d (1H, J = 7.4, C_6H_4); 9.10 br.s (2H, 2·NH); 11.18 br.s (1H, NH); 12.78 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 43.1 (2·NCH); 110.9 (CH); 119.0 (CH); 121.4 (CH); 122.1 (CH); 131.7; 138.0; 142.7; 158.2; 161.5. Found, %: C 57.47; H 5.04; N 30.27. $C_{11}H_{11}N_5O$. Calculated, %: C 57.63; H 4.84; N, 30.55.

(*Z*)-1-Benzyl-3-(2-(4,5-dihydro-1H-imidazol-2-yl)hydrazylidene]indolin-2-one (7b) was prepared by reacting 1-benzylindoline-2,3-dione with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate **(6).** Yield 67.7%, mp 294-295 °C, R_f 0.67. IR spectrum, ν, *cm*$^{-1}$: 3448, 3200 (NH), 1704 (CO), 1614 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm, *Hz*: 3.62 br.s (4H, 2·NCH_2); 4.91 br.s (2H, CH_2Ph); 6.65 br.s (1H, J = 7.7, C_6H_4); 6.90 br.s (1H, J = 7.4, C_6H_4); 7.04 br.s (1H, J = 7.5, C_6H_4); 7.60 br.s (1H, J = 7.3, C_6H_4); 7.16-7.32 m (5H, C_6H_4); 7.85 br.s (2H, 2·NH). ^{13}C NMR spectrum, δ, ppm: 41.9 (CH_2), 42.1 (2·NCH_2), 108.2 (CH), 118.3 (CH), 121.1 (CH), 123.3, 127.10 (CH), 127.12 (2·CH), 128.5 (2.CH), 132.3, 137.2, 139.9, 156.5, 169.1. Found, %: C 67.83; H 5.15; N 21.77. $C_{18}H_{17}N_5O$. Calculated, %: C 67.70; H 5.37; N 21.93.

(*Z*)-1-Pentyl-3-(2-(4,5-dihydro-1H-imidazol-2-yl)hydrazylidene]indolin-2-one (7c) was prepared by reacting 1-pentylindoline-2,3-dione with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate **(6).** Yield 75.7%, mp 130-132°C, R_f 0.64. IR spectrum, ν, *cm*$^{-1}$: 3385, 3127 (NH), 1691 (CO), 1650, 1611 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm, *Hz*: 0.91t (3H, J = 6.6, CH_3), 1.29-1.43 m (4H, 2·CH_2), 1.61-1.72 m (2H, CH_2), 3.71 t (2H, J = 7.1, NCH_2), 3.87 s (4H, 2·NCH_2), 6.91 br.s (1H, J = 7.8, C_6H_4), 7.03 br.d (1H, J = 7.5, C_6H_4), 7.27 br.d (1H, J = 7.8, 7.4, C_6H_4), 7.65 br.d (1H, J = 7.4, C_6H_4), 9.34 br.s (2H, 2·NH). Found, %: C 64.41; H 7.25; N 23.44. $C_{16}H_{21}N_5O$. Calculated, %: C 64.19; H 7.07; N 23.39.

(*Z*)-1-Acetyl-3-(2-(4,5-dihydro-1H-imidazol-2-yl)hydrazylidene]indolin-2-one iodo-hydrate (7d) was prepared by reacting 1-acetylindoline-2,3-dione with 2-hydrazino-4,5-dihydro-1H-imidazole iodohydrate **(6).** Yield 59.9%, mp 235-237°C, $R_f$base 0.57. IR spectrum, ν, *cm*$^{-1}$: 3240, 3120 (NH_2^+, NH), 1729, 1710 (CO), 1647, 1610 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm, *Hz*: 2.68 s (3H, CH_3), 3.96 s (4H, 2.N·CH_2), 7.32 td (1H, J = 7.6, 0.8, C_6H_4), 7.48 ddd (1H, J =

8.1, 7.6, 1.4, C_6H_4), 7.88 br.s (1H, J = 7.5, C_6H_4), 8.19 br.s (1H, J = 8.1, C_6H_4), 9.04 br.s (2H, NH·HI), 12.78 br.s (1H, NH). Found, %: C 57.38; H 5.03; N 25.60. $C_{16}H_{21}N_5O$. Calculated, %: C 57.56; H 4.83; N 25.82.

ԿԵՆՍԱԲԱՆՈՐԵՆ ԱԿՏԻՎ 3-[(1-Հ-ՊԻՐՈԼ-2-ԻԼ)ՄԵԹԻԼԵՆ]-1-ՄԵԹԻԼԻՆԴՈԼԻՆ-2-ՈՆԵՐԻ ԱԶԱՆՄԱՆԱԿՆԵՐԻ ՍԻՆԹԵԶԸ

Մ. Ա. ԻՐԱԴՅԱՆ, Ն. Ս. ԻՐԱԴՅԱՆ, Հ. Մ. ՍՏԵՓԱՆՅԱՆ և Ա. Ա. ՀԱՐՈՒԹՅՈՒՆՅԱՆ

Իզատինի և նրա 1-տեղակալված ածանցյալների և 2-հիդրազինո-4,5-դիհիդրո-1Հ-իմիդազոլի յոդհիդրատի փոխազդեցությամբ սինթեզվել են 3-(2-(1Հ-իմիդազոլ-2-իլ)հիդրազիլիդեն)ինդոլին-2-ոններ: Ստացված միացությունները կենսաբանորեն ակտիվ 3-տեղակալված ինդոլին-2-ոնների պարզագույն նմանակներն են:

СИНТЕЗ АЗААНАЛОГОВ БИОЛОГИЧЕСКИ АКТИВНЫХ 3-[(1-*Н*-ПИРРОЛ-2-ИЛ)МЕТИЛЕН]-1-МЕТИЛИНДОЛИН-2-ОНОВ

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Взаимодействием изатина и его1-замещенных производных с йодгидратом 2-гидразино-4,5-дигидро-1*Н*-имидазола синтезированы 3-(2-(1Н-имидазол-2-ил)гидразилиден)индолин-2-оны.

Полученные соединения представляют собой простейшие аналоги биологически активных 3-замещенных индолин-2-онов.

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