Synthesis of Substituted Pyrrole Derivatives Based on 8-azaspiro[5.6]dodec-10-ene Scaffold

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Article

Synthesis of Substituted Pyrrole Derivatives Based on 8-Azaspiro[5.6]dodec-10-ene Scaffold

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Abstract: This work describes the synthesis and X-ray diffraction properties of spirocyclic compounds based on 8-azaspiro[5.6]dodec-10-ene. Diasteriomerically pure pyrrole derivatives were prepared from the spirocyclic 1,2,3-triazole using a coupling reaction. The resulting compounds were characterized via ^{1}H and ^{13}C NMR spectroscopy and HRMS, and the crystallographic characteristics of one of them were studied by X-ray diffraction.

Keywords: spirocycle; pyrrole; 1,2,3-triazole, azaspiro

1. Introduction

Cancer is one of the most fatal diseases in the world. Millions of cases of cancer are diagnosed every year, and cancer also causes the death of millions of people. Many factors lead to the cancer generation, including, for example, environmental influences or heredity [1]. There are two main problems of anticancer drugs: non-selectivity for cancer cells and drug resistance. According to the literature, most of FDA approved anticancer drugs between 2010 and 2015 contain a N-heterocycle in chemical structure [2].

Nowadays, heterocyclic chemistry has a fundamental role in the drug discovery. Pyrrole derivatives are of great importance in drug design [3]. Pyrrole-based compounds have a wide range of biological activity. Among them are derivatives with anticancer [4,5], antiviral [6], antidiabetic [7], anti-inflammatory [8] e.t.c.

Figure 1 shows some pyrrole derivatives that exhibit anticancer activity. Sunitinib (**1**) is a multitargeted tyrosine kinase inhibitor and used for treatment of two types of cancer: renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) [9,10]. Compound **2** is a strong inhibitor of tubulin polymerization and cancer cell growth, specifically, of the P-glycoprotein-overexpressing NCI-ADR-RES and Messa/Dx5MDR cell lines [11]. Ulixertinib (**3**) is a pyrrole-based protein kinase inhibitor with high potency and selectivity for ERK1/2 (extracellular signal-regulated protein kinase) and is approved for the treatment of cancer [12]. Therefore, it is not surprising that, from a statistical analysis of the presence of this ring in known drugs and natural products, it resulted among the top ten rings and therefore considered a privileged motif for drug design [13,14].

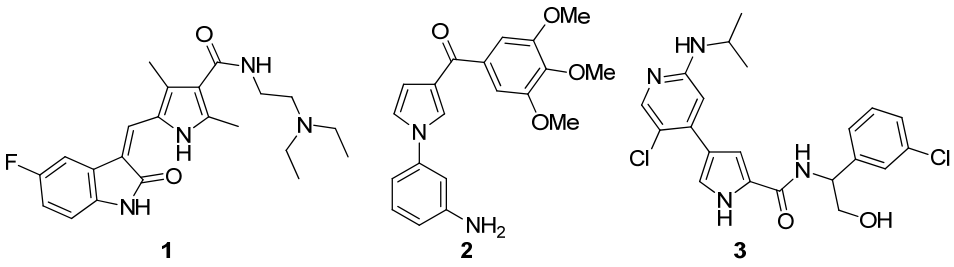

Figure 1. Pyrrole-based derivatives with anticancer activity.

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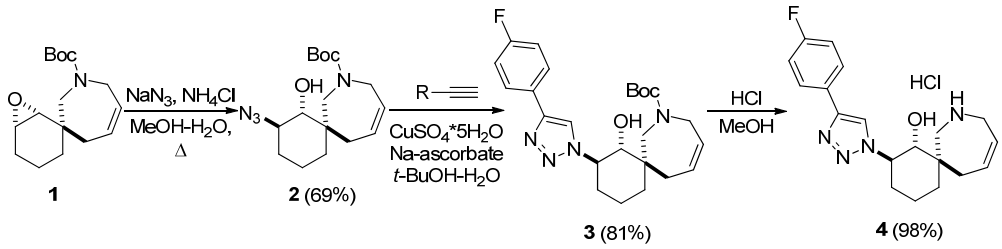
In addition, nowadays, the scaffold rigidification is one of the most sought after strategy by medicinal chemists for the design and realization of new drug generations. [15]. Although saturated rings and planar aromatic rings can influence ligand binding entropy, it has been suggested that compounds with too many planar rings have suboptimal physical properties [16,17].

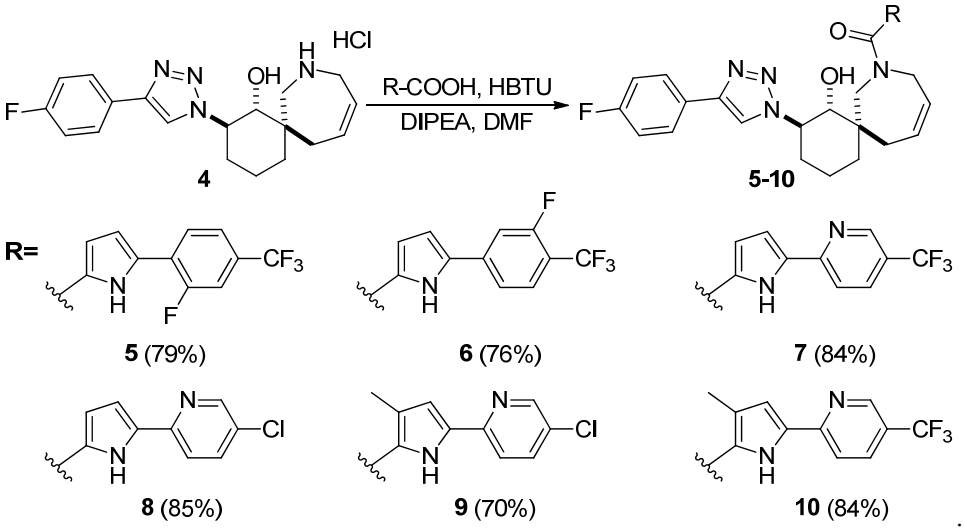
2. Results and Discussion

In a recent work, a set of spirocyclic derivatives based on 8-oxaspiro[5.6]dodecane were synthetized and in-vitro profiled against the hNNMT target to evaluate their anticancer therapeutic potential [18]. Based on their synthetic pathway, the replacement of an the replacement of an oxygen atom with a nitrogen atom, thus to obtain an additional point for the functionalization of spirocycles, was envisioned. Therefore, a new synthetic approach was developed for the production of epoxide **1** from commercially available reagents. Scheme 1 shows the synthesis of 1,2,3-triazole **4**, which contains an unprotected nitrogen atom in 7-membered ring. The Azide **2** was obtained from compound **1** by epoxide ring opening with azide-anion. Then, the 1,2,3-triazole **3** was synthesized by a "click-reaction" with the 1-ethynyl-4-fluorobenzene and using $CuSO_4 \times 5H_2O$ and Na-ascorbate. The amine hydrochloride **4** was obtained by removing the protecting group under acidic condition. The stereochemistry of such compounds were assigned by a comparison with a similar structures from the literature [19].



Scheme 1. Synthesis of amine **4**.

Then compounds **5-10** were synthesized from amine hydrochloride **4** using a coupling reaction. *N,N,N′,N′*-tetramethyl-O-(1H-benzotriazol-1-yl)-uronium hexafluoro-phosphate (HBTU) was used as the activating agent, while the corresponding acids used have been already characterized and described in the literature [6,20]. All target compounds **5-10** were obtained in yields of 70-85%.



Scheme 2. Synthesis of compound **5-10**.

The structure of compound **8** was confirmed by X-ray diffraction analysis (Figure 2).

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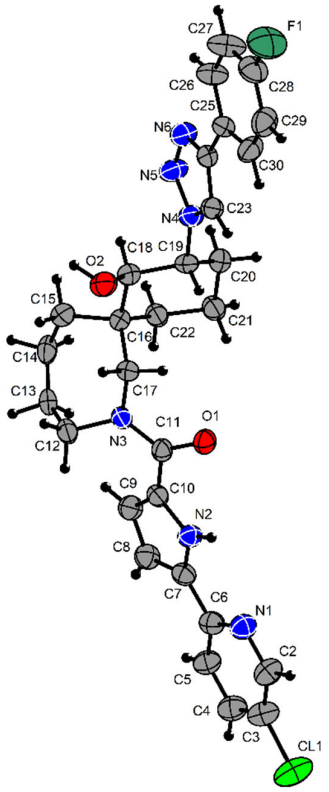

Figure 2. X-ray molecular structure of compound **8** with atom labeling.

Green = Fluorine atom; Red = Oxygen atoms; Grey = Carbon atoms; Blue = Nitrogen atoms; Black = Hydrogen atoms.

4. Materials and Methods

NMR spectra were recorded on Bruker Avance 400 instrument with operating frequency of 400 and 100 MHz, respectively, and calibrated using residual undeuterated chloroform (δH = 7.27 ppm) and $CDCl_3$ (δC = 77.16 ppm) or undeuterated dimethyl sulfoxide (DMSO) (δH=2.50 ppm) and DMSO-d6 (δC = 39.51 ppm) as internal references. The following abbreviations are used to set multiplicities: s = singlet, d =doublet, t = triplet, q = quartet, m = multiplet, br = broad. The purity of the final compounds was checked by liquid chromatography-mass-spectrometry (LCMS) in a Shimadzu LCMS-2010A using three types of detection systems such as EDAD, ELSD, and UV. High Resolution Mass Spectra (HRMS) were registered on a Sciex TripleTOF 5600+. We used commercial reagents and solvents without further purification. Reactions were monitored by thin-layer chromatography (TLC) performed on Merck TLC Silica gel plates (60 F254), using a UV light for visualization and basic aqueous potassium permanganate or iodine fumes as a developing agent.^{1}H and^{13}C.

General procedure for synthesis of compounds 5-10:

N,N-Diisopropylethylamine (DIPEA) (1 equiv.) was added to an appropriate acid (1 equiv.) followed by DMF (10 mL) and then *N,N,N',N'*-tetramethyl-O-(1H-benzotriazol-1-yl)-uronium hexafluorophosphate (HBTU) (1 equiv.). The resulting solution was stirred for 2 min and added to a solution of appropriate amine (0.1 g, 1 equiv.) and DIPEA (1.1 equiv.) in DMF (10 mL) in a one portions. The reaction mixture was stirred overnight; DMF was evaporated, and the residue was dissolved in DCM (50 mL per 1 g of crude product) and successively washed with 5%aqueous NaOH and 10% tartaric acid solutions (25 mL per 1 g of crude product). The organic layer was dried over Na_2SO_4, filtered, evaporated. Crude product was purified by flash chromatography using hexanes/EtOAc mixture as eluent (from 3:1 to 1:2) to give the target compounds.

(5-(2-fluoro-4-(trifluoromethyl)phenyl)-1H-pyrrol-2-yl)((1RS,2RS,6RS)-2-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)-1-hydroxy-8-azaspiro[5.6]dodec-10-en-8-yl)methanone (5)

M = 125 mg, slightly yellow powder. Yield = 79%. Rf = 0.6 in hexane/EtOAc 1:2.

^{1}H-NMR (400 MHz, $CDCl_3$) δ:1.29 - 1.56 (m, 2 H), 1.61 - 1.79 (m, 2 H), 1.98 - 2.16 (m, 2 H), 2.28 (d, J=11.8 Hz, 1 H), 3.03 (dd, J=14.2, 2.1 Hz, 1 H), 3.24 (d, J=14.2 Hz, 1 H), 3.54 (t, J=10.7 Hz, 1 H), 4.15 (dd, *J*=17.0, 3.1 Hz, 1 H), 4.34 (d, J=14.5 Hz, 1 H), 4.60 - 4.71 (m, 1 H), 4.95 (d, J=17.5 Hz, 1 H), 5.15 (d, J=10.8 Hz, 1 H), 5.60 (d, J=10.5 Hz, 1 H), 5.80 - 5.90 (m, 1 H), 6.63 - 6.68 (m, 1 H), 6.71 - 6.77 (m, 1 H), 7.09 (t, J=8.7 Hz, 2 H), 7.36 - 7.44 (m, 2 H), 7.71 (t, J=7.9 Hz, 1 H), 7.79 (dd, J=8.6, 5.4 Hz, 2 H), 7.89 (s, 1 H), 10.17 (br. s., 1 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.2, 32.4, 34.5, 36.7, 47.9, 50.3, 52.3, 63.4, 78.2, 111.3 (d, J=4.6 Hz), 114.1 (dq, J=3.9, 26.2 Hz), 114.9, 115.7 (d, J=21.6 Hz, 2 C), 120.0, 121.7 (m), 122.5 (d, J=11.6 Hz), 123.6 (dq, J=2.4, 272.2 Hz), 124.8, 125.7, 127.4 (d, J=3.3 Hz), 127.5 (d, J=8.1 Hz, 2 C), 127.7 (d, J=4.1 Hz), 128.5, 128.5 (d, J=7.7 Hz), 130.5 (dq, J=8.3, 33.5 Hz), 146.0, 158.5 (d, J=250.1 Hz), 162.6 (d, J=246.6 Hz), 163.0

HRMS (ESI) m/z: calcd for $C_{31}H_{29}F_5N_5O_2$ $[M+H]^+$ 598.2236, found 598.2233.

(5-(3-fluoro-4-(trifluoromethyl)phenyl)-1H-pyrrol-2-yl)((1RS,2RS,6RS)-2-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)-1-hydroxy-8-azaspiro[5.6]dodec-10-en-8-yl)methanone (6)

M = 120 mg, white powder. Yield = 76%. Rf = 0.6 in hexane/EtOAc 1:2.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 - 1.52 (m, 2 H), 1.60 - 1.76 (m, 2 H), 1.96 - 2.30 (m, 3 H), 2.95 - 3.18 (m, 2 H), 3.54 (t, J=10.8 Hz, 1 H), 4.00 (d, J=15.2 Hz, 1 H), 4.35 (d, J=14.5 Hz, 1 H), 4.67 (t, J=9.6 Hz, 1 H), 4.83 (d, J=17.0 Hz, 1 H), 5.39 - 5.61 (m, 2 H), 5.78 - 5.90 (m, 1 H), 6.51 (d, J=2.1 Hz, 2 H), 7.06 (t, J=8.6 Hz, 2 H), 7.29 - 7.37 (m, 2 H), 7.51 (t, J=7.9 Hz, 1 H), 7.65 (dd, J=8.5, 5.4 Hz, 2 H), 7.78 (s, 1 H), 10.70 (br. s., 1 H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.2, 32.6, 34.3, 36.8, 48.0, 50.2, 52.3, 63.3, 78.1, 109.5, 112.8 (d, J=22.3 Hz), 115.4, 115.6 (d, J=21.6 Hz, 2 C), 116.4 (dq, J=12.7, 33.2 Hz), 119.9, 120.2 (d, J=3.1 Hz), 122.7 (q, J=271.6 Hz), 124.9, 126.0, 127.4, 127.4 (d, J=8.1 Hz, 2 C), 127.7 (dq, J=1.8, 4.4 Hz), 128.3, 133.1, 137.4 (d, J=8.7 Hz),145.8, 160.1 (dq, J=2.2, 254.9 Hz), 162.5 (d, J=246.6 Hz), 163.1.

HRMS (ESI) m/z: calcd for $C_{31}H_{29}F_5N_5O_2$ $[M+H]^+$ 598.2236, found 598.2238.

((1RS,2RS,6RS)-2-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)-1-hydroxy-8-azaspiro[5.6]dodec-10-en-8-yl)(5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrol-2-yl)methanone (7)

M = 128 mg, slightly brown powder. Yield = 84%. Rf = 0.5 in hexane/EtOAc 1:2.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 - 1.56 (m, 2 H), 1.58 - 1.79 (m, 2 H), 1.97 - 2.20 (m, 2 H), 2.28 (d, J=11.6 Hz, 1 H), 3.03 (dd, J=14.2, 2.1 Hz, 1 H), 3.23 (d, J=14.4 Hz, 1 H), 3.53 (t, J=10.7 Hz, 1 H), 4.15 (dd, J=17.3, 3.3 Hz, 1 H), 4.35 (d, J=14.5 Hz, 1 H), 4.62 - 4.73 (m, 1 H), 4.95 (d, J=16.6 Hz, 1 H), 5.15 (d, J=11.0 Hz, 1 H), 5.58 (d, J=10.4 Hz, 1 H), 5.79 - 5.89 (m, 1 H), 6.60 - 6.68 (m, 1 H), 6.75 - 6.82 (m, 1 H), 7.09 (t, J=8.7 Hz, 2 H), 7.63 (d, J=8.4 Hz, 1 H), 7.76 - 7.88 (m, 3 H), 7.91 (s, 1 H), 8.72 (s, 1 H), 10.57 (br. s., 1 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.2, 32.3, 34.4, 36.7, 47.9, 50.2, 52.3, 63.4, 78.2, 109.9, 115.3, 115.7 (d, J=21.6 Hz, 2 C), 118.4, 120.2, 123.7 (q, J=272.0 Hz), 124.3 (q, J=33.2 Hz), 124.8 (br.), 126.2, 127.4, 127.5 (d, J=8.1 Hz. 2 C), 128.5, 133.2, 133.9 (q, J=3.3 Hz), 146.0, 146.5 (q, J=4.1 Hz), 152.1, 162.5 (d, J=246.6 Hz), 163.0.

HRMS (ESI) m/z: calcd for $C_{30}H_{29}F_4N_6O_2$ $[M+H]^+$ 581.2283, found 581.2284.

(5-(5-chloropyridin-2-yl)-1H-pyrrol-2-yl)((1RS,2RS,6RS)-2-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)-1-hydroxy-8-azaspiro[5.6]dodec-10-en-8-yl)methanone (8)

M = 123 mg, white powder. Yield = 85%. Rf = 0.5 in hexane/EtOAc 1:2.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.37 - 1.58 (m, 2 H), 1.63 - 1.78 (m, 2 H), 2.07 (d, J=10.7 Hz, 1 H), 2.12 - 2.26 (m, 1 H), 2.34 (d, J=11.5 Hz, 1 H), 3.02 - 3.60 (m, 3 H), 4.17 (dd, J=17.1, 3.7 Hz, 1 H), 4.42 (d, J=14.4 Hz, 1 H), 4.69 (td, J=11.1, 4.1 Hz, 1 H), 4.98 - 5.21 (m, 2 H), 5.60 (d, J=11.7 Hz, 1 H), 5.82 - 5.93 (m, 1 H), 6.63 - 6.73 (m, 2 H), 7.12 (t, J=8.7 Hz, 2 H), 7.51 (d, J=8.5 Hz, 1 H), 7.64 (dd, J=8.5, 2.4 Hz, 1 H), 7.84 (dd, J=8.6, 5.4 Hz, 2 H), 7.94 (s, 1 H), 8.48 (d, J=2.1 Hz, 1 H), 10.35 (br. s., 1 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.2, 32.3, 34.2 (br.), 37.0 (br.), 48.0, 50.3, 52.4 (br.), 63.4, 78.1, 108.6, 115.5, 115.8 (d, J=21.7 Hz, 2 C), 119.7, 120.3, 124.8, 125.3, 127.5 (d, J=3.3 Hz), 127.6 (d, J=8.1 Hz, 2 C), 128.4, 130.1, 133.8, 136.5, 146.0, 147.3, 148.4, 162.6 (d, J=246.6 Hz), 163.2.

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HRMS (ESI) m/z: calcd for $C_{29}H_{29}ClFN_6O_2$ $[M+H]^+$ 547.2019, found 547.2024.

(5-(5-chloropyridin-2-yl)-3-methyl-1H-pyrrol-2-yl)((1RS,2RS,6RS)-2-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)-1-hydroxy-8-azaspiro[5.6]dodec-10-en-8-yl)methanone (9)

M = 103 mg, white powder. Yield = 70%. Rf = 0.6 in hexane/EtOAc 1:2.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 - 1.56 (m, 2 H), 1.66 - 1.75 (m, 2 H), 2.02 - 2.23 (m, 5 H), 2.25 - 2.36 (m, 1 H), 3.04 - 3.23 (m, 2 H), 3.58 (t, J=8.4 Hz, 1 H), 4.03 (d, J=18.3 Hz, 1 H), 4.41 (d, J=14.5 Hz, 1 H), 4.50 - 4.60 (m, 1 H), 4.65 (d, J=17.7 Hz, 1 H), 5.10 (br. s., 1 H), 5.44 - 5.55 (m, 1 H), 5.75 - 5.86 (m, 1 H), 6.48 (d, J=2.2 Hz, 1 H), 7.09 (t, J=8.7 Hz, 2 H), 7.44 (d, J=8.6 Hz, 1 H), 7.59 (dd, J=8.5, 2.4 Hz, 1 H), 7.79 (dd, J=8.6, 5.4 Hz, 2 H), 7.89 (s, 1 H), 8.39 (d, J=1.9 Hz, 1 H), 9.82 (br. s., 1 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.8, 20.2, 32.1, 34.5 (br.), 37.0 (br.), 48.5 (br.), 50.1, 53.9 (br.), 63.5, 78.5, 110.0, 115.8 (d, J=21.7 Hz, 2 C), 119.3, 120.4, 123.4, 123.8, 125.7 (br.), 127.4 (d, J=3.3 Hz), 127.5 (d, J=8.1 Hz, 2 C), 127.7, 129.5, 132.2, 136.5, 146.0, 147.7, 148.2, 162.6 (d, J=246.6 Hz), 165.6.

HRMS (ESI) m/z: calcd for $C_{30}H_{31}ClFN_6O_2$ $[M+H]^+$ 561.2176, found 561.2172.

((1RS,2RS,6RS)-2-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)-1-hydroxy-8-azaspiro[5.6]dodec-10-en-8-yl)(3-methyl-5-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrrol-2-yl)methanone (10)

M = 129 mg, white powder. Yield = 84%. Rf = 0.6 in hexane/EtOAc 1:2.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36 - 1.58 (m, 2 H), 1.71 - 1.84 (m, 2 H), 2.06 - 2.24 (m, 5 H), 2.33 (d, J=11.6 Hz, 1 H), 3.07 - 3.28 (m, 2 H), 3.60 (t, J=10.5 Hz, 1 H), 4.06 (d, J=18.6 Hz, 1 H), 4.43 (d, J=14.4 Hz, 1 H), 4.51 - 4.71 (m, 2 H), 4.95 (br. s., 1 H), 5.48 - 5.57 (m, 1 H), 5.79 - 5.90 (m, 1 H), 6.61 (d, J=2.3 Hz, 1 H), 7.10 (t, J=8.7 Hz, 2 H), 7.58 (d, J=8.4 Hz, 1 H), 7.76 - 7.91 (m, 4 H), 8.70 (s, 1 H), 9.87 (br. s., 1 H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.7, 20.2, 32.1, 34.6 (br.), 37.0 (br.), 48.5 (br), 50.1, 53.9 (br.), 63.6, 78.5, 111.3, 115.8 (d, J=21.6 Hz, 2 C), 118.0, 120.3, 123.8 (q, J=272.0 Hz), 123.9 (q, J=33.0 Hz), 123.9, 124.4, 125.7 (br.), 127.4 (d, J=3.1 Hz), 127.5 (d, J=8.1 Hz, 2 C), 127.9 (br.), 131.8, 133.9 (q, J=3.3 Hz), 146.1, 146.4 (q, J=4.2 Hz), 152.4 (d, J=1.3 Hz), 162.6 (d, J=246.6 Hz), 165.5.

HRMS (ESI) m/z: calcd for $C_{31}H_{31}F_4N_6O_2$ $[M+H]^+$ 595.2439, found 595.2427.

Crystallography Details

The data of **8** were collected by using STOE diffractometer Pilatus100K detector, focusing mirror collimation Cu Kα (1.54086Å) radiation, rotation method mode. STOE X-AREA software was used for cells refinement and data reduction. Data collection and image processing was performed with X-Area 1.67 (STOE & Cie GmbH, Darmstadt, Germany, 2013). Intensity data were scaled with LANA (part of X-Area) in order to minimize differences of intensities of symmetry-equivalent reflections (multi-scan method)."

Crystallization of molecules 8 has a tendency to form twins, and despite numerous attempts we were unable to find a single crystal. A sample of two crystals (basf 0.49) was studied.

Under refinement the positional and thermal parameters of the atoms, reflections from twin crystal were used but the positions of some reflections coincided, which affected the value of the R-factor and the refinement process.

Cell_parameters: a = 9.750(1) Å, b = 10.3730(1) Å, c = 26.349(2) Å, α 103.156(3), β 96.11(1)°.

γ 102.875; V= 2649.7(4), Z=4, d_{calc}=1.376 Mg/m3. Crystal class is monoclinic, space group $P2_1/n$. Absorption coefficient 1.662 mm^{-1}

The structures were solved and refined with SHELX program [21]. The non-hydrogen atoms were refined by using the anisotropic full matrix least-square procedure.

Hydrogen atoms were placed in the calculated positions and allowed to ride on their parent atoms [C-H 0.93-0.98; Uiso 1.2 Ueq(parent atom)]. The position of the hydrogen atom at the (O2-H21) hydroxy group was determined from Fourier synthesis and was freely refined in the isotropic approximation. The oxygen group O2-H21 (Fig.2) forms a hydrogen bond with the oxygen atom $O1^i$ (angle O2-H21…$O1^i$ 162(10)^o , distance H21-$O1^i$ - 1.83(12)Å thereby forming endless chains of molecules along the **b** axis.

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Refinement was made against 25016 reflections. 363 parameters were refined using 0 restraints. The final R 0.107 against 8272 $F^2>2\sigma(F^2)$. Molecular geometry calculations were performed with the SHELX program, and the molecular graphics were prepared by using DIAMOND software [22].

CCDC-2305668 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic

Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

5. Conclusions

As a result, we obtained the target pyrrole derivatives **5**-**10**, which synthesis was validated and the compounds were fully characterized by spectral analysis methods. The structure of **8** was also studied by X-ray diffraction analysis, which confirmed that diastereomerically pure products were obtained. The biological activity of the obtained compounds are to be explored as soon as any appropriated panel assay will be available for this project

Supplementary Materials: The following data are available online. ^{1}H-NMR, ^{13}C-NMR, 2D correlation spectra ^{1}H-^{1}H (COSY, NOESY), ^{1}H-^{13}C (HSQC) and HR-MS of **8**.

Author Contributions: Conceptualization, A.A. and A.V.K., methodology, A.V.K; I.R.I. performed the chemical synthesis. The registration and interpretation of the NMR data and structure characterization of both compounds were conducted by I.R.I. and A.V.K. X-ray crystallography study of the crystals was carried out by V.A.T. writing—original draft preparation, I.R.I. and A.V.K.; writing—review and editing, V.A.T. and A.A. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Not applicable.

Acknowledgments: The study was performed using equipment purchased at the expense of the Development Program of Moscow State University. We thank Dr Ivan A. Godovikov for assistance with the NMR experiments. This study was conducted within the state program of the TIPS RAS.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Chhikara, B.S.; Parang, K. Global Cancer Statistics 2022: The Trends Projection Analysis. *Chem Biol Lett* **2023**, *10*, 451.
2. Barghi Lish, A.; Foroumadi, A.; Kolvari, E.; Safari, F. Synthesis and Biological Evaluation of 12-Aryl-11-Hydroxy-5,6-Dihydropyrrolo[2″,1″:3′,4′]Pyrazino[1′,2′:1,5]Pyrrolo[2,3- *d*]Pyridazine-8(9 *H*)-One Derivatives as Potential Cytotoxic Agents. *ACS Omega* **2023**, acsomega.3c04167, doi:10.1021/acsomega.3c04167.
3. Moghadam, E.S.; Mireskandari, K.; Abdel-Jalil, R.; Amini, M. An Approach to Pharmacological Targets of Pyrrole Family From Medicinal Chemistry Viewpoint. *MRMC* **2022**, *22*, 2486–2561, doi:10.2174/1389557522666220325150531.
4. Li Petri, G.; Spanò, V.; Spatola, R.; Holl, R.; Raimondi, M.V.; Barraja, P.; Montalbano, A. Bioactive Pyrrole-Based Compounds with Target Selectivity. *European Journal of Medicinal Chemistry* **2020**, *208*, 112783, doi:10.1016/j.ejmech.2020.112783.
5. Kilic-Kurt, Z.; Bakar-Ates, F.; Aka, Y.; Kutuk, O. Design, Synthesis and in Vitro Apoptotic Mechanism of Novel Pyrrolopyrimidine Derivatives. *Bioorganic Chemistry* **2019**, *83*, 511–519, doi:10.1016/j.bioorg.2018.10.060.
6. Curreli, F.; Ahmed, S.; Benedict Victor, S.M.; Iusupov, I.R.; Belov, D.S.; Markov, P.O.; Kurkin, A.V.; Altieri, A.; Debnath, A.K. Preclinical Optimization of Gp120 Entry Antagonists as Anti-HIV-1 Agents with Improved Cytotoxicity and ADME Properties through Rational Design, Synthesis, and Antiviral Evaluation. *J. Med. Chem.* **2020**, *63*, 1724–1749, doi:10.1021/acs.jmedchem.9b02149.
7. Li, Z.; Pan, M.; Su, X.; Dai, Y.; Fu, M.; Cai, X.; Shi, W.; Huang, W.; Qian, H. Discovery of Novel Pyrrole-Based Scaffold as Potent and Orally Bioavailable Free Fatty Acid Receptor 1 Agonists for the Treatment of Type 2 Diabetes. *Bioorganic & Medicinal Chemistry* **2016**, *24*, 1981–1987, doi:10.1016/j.bmc.2016.03.014.
8. Szczukowski, Ł.; Redzicka, A.; Wiatrak, B.; Krzyżak, E.; Marciniak, A.; Gębczak, K.; Gębarowski, T.; Świątek, P. Design, Synthesis, Biological Evaluation and in Silico Studies of Novel Pyrrolo[3,4-

d]Pyridazinone Derivatives with Promising Anti-Inflammatory and Antioxidant Activity. *Bioorganic Chemistry* **2020**, *102*, 104035, doi:10.1016/j.bioorg.2020.104035.

9. Motzer, R.J.; Hutson, T.E.; Tomczak, P.; Michaelson, M.D.; Bukowski, R.M.; Oudard, S.; Negrier, S.; Szczylik, C.; Pili, R.; Bjarnason, G.A.; et al. Overall Survival and Updated Results for Sunitinib Compared With Interferon Alfa in Patients With Metastatic Renal Cell Carcinoma. *JCO* **2009**, *27*, 3584–3590, doi:10.1200/JCO.2008.20.1293.
10. Demetri, G.D.; Van Oosterom, A.T.; Garrett, C.R.; Blackstein, M.E.; Shah, M.H.; Verweij, J.; McArthur, G.; Judson, I.R.; Heinrich, M.C.; Morgan, J.A.; et al. Efficacy and Safety of Sunitinib in Patients with Advanced Gastrointestinal Stromal Tumour after Failure of Imatinib: A Randomised Controlled Trial. *The Lancet* **2006**, *368*, 1329–1338, doi:10.1016/S0140-6736(06)69446-4.
11. La Regina, G.; Bai, R.; Coluccia, A.; Famiglini, V.; Pelliccia, S.; Passacantilli, S.; Mazzoccoli, C.; Ruggieri, V.; Sisinni, L.; Bolognesi, A.; et al. New Pyrrole Derivatives with Potent Tubulin Polymerization Inhibiting Activity As Anticancer Agents Including Hedgehog-Dependent Cancer. *J. Med. Chem.* **2014**, *57*, 6531–6552, doi:10.1021/jm500561a.
12. Sullivan, R.J.; Infante, J.R.; Janku, F.; Wong, D.J.L.; Sosman, J.A.; Keedy, V.; Patel, M.R.; Shapiro, G.I.; Mier, J.W.; Tolcher, A.W.; et al. First-in-Class ERK1/2 Inhibitor Ulixertinib (BVD-523) in Patients with MAPK Mutant Advanced Solid Tumors: Results of a Phase I Dose-Escalation and Expansion Study. *Cancer Discovery* **2018**, *8*, 184–195, doi:10.1158/2159-8290.CD-17-1119.
13. Bianco, M.D.C.A.D.; Marinho, D.I.L.F.; Hoelz, L.V.B.; Bastos, M.M.; Boechat, N. Pyrroles as Privileged Scaffolds in the Search for New Potential HIV Inhibitors. *Pharmaceuticals* **2021**, *14*, 893, doi:10.3390/ph14090893.
14. Kombarov, R.; Altieri, A.; Genis, D.; Kirpichenok, M.; Kochubey, V.; Rakitina, N.; Titarenko, Z. BioCores: Identification of a Drug/Natural Product-Based Privileged Structural Motif for Small-Molecule Lead Discovery. *Mol Divers* **2010**, *14*, 193–200, doi:10.1007/s11030-009-9157-5.
15. Zheng, Y.-J.; Tice, C.M. The Utilization of Spirocyclic Scaffolds in Novel Drug Discovery. *Expert Opinion on Drug Discovery* **2016**, *11*, 831–834, doi:10.1080/17460441.2016.1195367.
16. Ritchie, T.J.; Macdonald, S.J.F. The Impact of Aromatic Ring Count on Compound Developability – Are Too Many Aromatic Rings a Liability in Drug Design? *Drug Discovery Today* **2009**, *14*, 1011–1020, doi:10.1016/j.drudis.2009.07.014.
17. Lovering, F. Escape from Flatland 2: Complexity and Promiscuity. *Med. Chem. Commun.* **2013**, *4*, 515, doi:10.1039/c2md20347b.
18. Iusupov, I.R.; Lukyanenko, E.R.; Altieri, A.; Kurkin, A.V. Design and Synthesis of Fsp3-Enriched Spirocyclic-Based Biological Screening Compound Arrays via DOS Strategies and Their NNMT Inhibition Profiling. *ChemMedChem* **2022**, *17*, e202200394, doi:10.1002/cmdc.202200394.
19. Iusupov, I.R.; Lyssenko, K.A.; Altieri, A.; Kurkin, A.V. (1RS,2RS,6RS)-2-(6-Amino-9H-Purin-9-Yl)-8-Azaspiro[5.6]Dodec-10-En-1-Ol Dihydrochloride. *Molbank* **2022**, *2022*, M1495, doi:10.3390/M1495.
20. Curreli, F.; Ahmed, S.; Benedict Victor, S.M.; Iusupov, I.R.; Spiridonov, E.A.; Belov, D.S.; Altieri, A.; Kurkin, A.V.; Debnath, A.K. Design, Synthesis, and Antiviral Activity of a Series of CD4-Mimetic Small-Molecule HIV-1 Entry Inhibitors. *Bioorganic & Medicinal Chemistry* **2021**, *32*, 116000, doi:10.1016/j.bmc.2021.116000.
21. Sheldrick, G.M. A Short History of *SHELX*. *Acta Crystallogr A Found Crystallogr* **2008**, *64*, 112–122, doi:10.1107/S0108767307043930.
22. Brandenburg, K.; Berndt, M. DIAMOND, Version 2.1 e. *Crystal Impact GbR, Bonn, Germany* **1999**.