chemistry proceedings

MDPI

Proceeding Paper

1′-Homocarbocyclic Nucleoside Analogs with an Optically Active Substituted Bicyclo[2.2.1]Heptane Scaffold †

Constantin I. Tănase [1,*], Constantin Drăghici [2], Anamaria Hanganu [2], Lucia Pintilie [1], Maria Maganu [2], Vladimir V. Zarubaev [3], Alexandrina Volobueva [3] and Ekaterina Sinegubova [3]

[1] National Institute for Chemical-Pharmaceutical Research and Development, 112 Vitan Av., 031299 Bucharest 3, Romania; luciapintilie@gmail.com
[2] Organic Chemistry Center "C.D.Nenitescu", 202 B Splaiul Independentei, 060023 Bucharest, Romania; cst_drag@yahoo.com (C.D.); anamaria_hanganu@yahoo.com (A.H.); mmaganu@yahoo.com (M.M.)
[3] Department of Virology, Pasteur Institute of Epidemiology and Microbiology, 197101 St. Petersburg, Russia; zarubaev@gmail.com (V.V.Z.); sasha-khrupina@mail.ru (A.V.); sinek489@gmail.com (E.S.)
* Correspondence: cvtanase@gmail.com
† Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: https://ecsoc-24.sciforum.net/.

Abstract: An optically active bicyclo[2.2.0]heptane fragment was introduced in the molecule of new 1′-homonucleosides on a 2- 6-chloro-amino-purine scaffold to obtain 6-substituted carbocyclicnucleozide analogs as antiviral compounds. The synthesis was realized by a Mitsunobu reaction of the base with the corresponding bicyclo[2.2.0]heptane intermediate, and then the nucleoside analogs were obtained by substitution of the 6-chlorime with selected pharmaceutically accepted amines. A molecular docking study of the compounds on influenza, HSV and low active coronavirus was realized. Experimental screening of the compounds on the same viruses is being developed and soon will be finished.

Keywords: bicyclo[2.2.0]heptane; 1′-homonucleoside; guanine; 2-amino-6-substituted purine; antiviral; influenza; herpes simplex virus; molecular docking

Citation: Tănase, C.I.; Drăghici, C.; Hanganu, A.; Pintilie, L.; Maganu, M.; Zarubaev, V.V.; Volobueva, A.; Sinegubova, E. 1′-Homocarbocyclic Nucleoside Analogues with an Optically Active Substituted Bicyclo[2.2.1]Heptane Scaffold. *Chem. Proc.* **2021**, *3*, 16. https://doi.org/10.3390/ecsoc-24-08367

Academic Editors: Julio A. Seijas and M. Pilar Vázquez-Tato

Published: 14 November 2020

1. Introduction

Nucleosides are a recognized class of antiviral and anticancer drugs. The resistance acquired in time and the toxicity are the main factors that motivated the discovery of new more active and selective analogs. The modifications were realized on the nucleobase and/or on the sugar moiety. With guanine and 2-amino-6-substituted purine as nucleobase, recognized carbocyclic nucleoside drugs or active compounds studied in different clinical phases, like carbovir and its prodrug abacavir (with 6-cyclopropylamino substituent), entecavir, lobucavir and cyclohexenyl G, and also recognized acyclic nucleosides like acyclovir, ganciclovir, penciclovir and their valine esters valaciclovir, valganciclovir and famciclovir became recognized as milestone compounds in the treatment of antiviral and anticancer diseases [1,2].

1′-Homonucleosides, due to the methylene group between nucleobase and sugar moiety, are structurally a class of compounds closer to acyclic nucleosides than nucleosides. In this class, there are also compounds with guanine, 6-chloro-2-aminopurine or 6-substituted-2-aminopurine as nucleobase with potential antiviral or anticancer activity (Figure 1): compound **II** has antiherpetic activity, compound **III** has activity against HCMV and Epstein–Barr virus, compound **IV**, with a 2,2,3-trimethylcyclopentanol, is active against HIV-1 and HIV-2, and compound **V**, with a cyclopenta[*c*]pyrazole moiety, is very active against VZV/TK$^-$ strain.

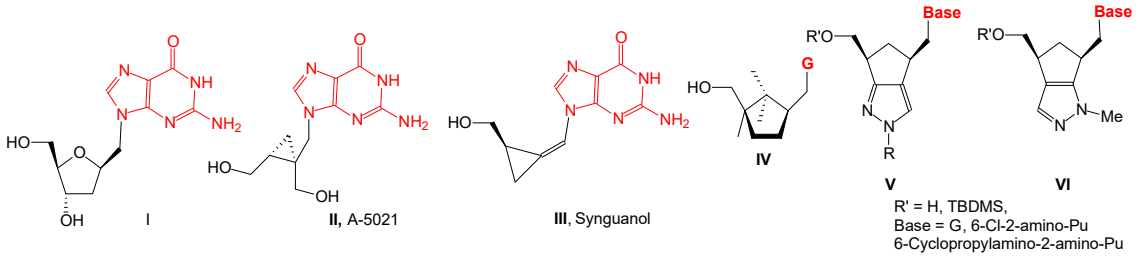


Figure 1. 1′Homonucleosides with guanine and 6-substituted-2-aminopurine as nucleobases.

Previously we used an optically active bicyclo[2.2.1]heptane moiety to obtain new L-type carbocyclic nucleosides, **VII** (Figure 2), and some of them presented antiviral activity against influenza virus or coxsackievirus B4 [3]. Then new HSV-1 1′-homocarbanucleoside analogs, **VIII**, were synthesized with nucleobase: U, 5-FU, T, C, Ad, 6-Cl-purine and 6-substituted purine. Two compounds had lower IC_{50} (15 ± 2 and 21 ± 4 μM) and one equal to that of acyclovir (IC50: 28 ± 4 μM). In the present paper, we present the synthesis, molecular docking study and antiviral activity of a number of compounds **VIII**, in which base is 2-amino-6-chloropurine, guanine, 2,6-diaminopurine and 2-amino-6-substitutedpurine.

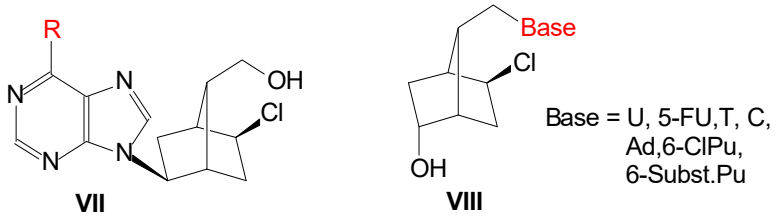
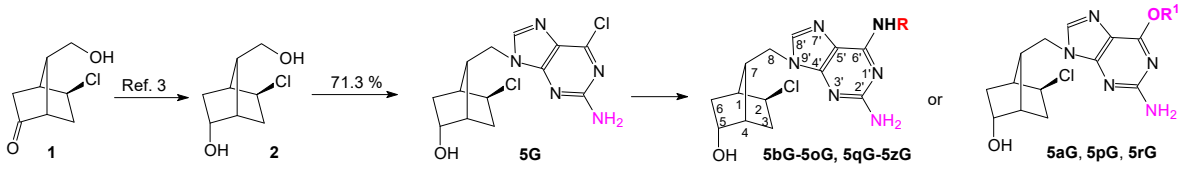


Figure 2. L-Carbanucleosides and 1′-homocarbanucleosides with a bicyclo[2.2.1]heptane skeleton.

2. Results

Synthesis of the new 1′-homocarbanucleosides with an optically active bicyclo[2.2.1]heptane fragment as sugar moiety and guanine, 6-O-alkyl-guanine, 2,6-diaminopurine and 2-amino-6-N-substitutedpurine as nucleobase started from diol **2**, was obtained crystallized by $NaBH_4$ reduction of the keto-compound **1** [3]. The unprotected diol **2** was used in the Mitsunobu reaction with 2-amino-6-chloropurine, taking into account that the primary alcohol will react more quickly than the secondary one. Indeed, the primary alcohol reacted selectively to give the key nucleoside intermediate **5G** isolated by simple crystallization in 71.3% yield (Scheme 1). For comparison, 6-chloropurine reacted with diol **2** in the same Mitsunobu reaction in 67.6% yield [4,5].



Scheme 1. Synthesis of new 1′-homocarbanucleoside analogs with guanine and 2-amino-6-substituted purine as nucleobase.

The following 1′-homocarbocyclic nucleosides were synthesized by substitution of the chlorine atom with ammonia, with primary or secondary pharmacological amines, with methoxide or ethoxide or by substitution with hydroxyl (acid hydrolysis) to the guanine, all in good yield [6]. Twenty-four new compounds were obtained, fully characterized and used for antiviral screening against influenza, herpes simplex virus and low active coronavirus.

A molecular docking study was realized using CLC Drug Discovery Workbench Software, on 24 compounds to obtain accurate predictions about the structure and interactions of the studied compounds in complex with a protein/enzyme receptor to evaluate the biological activity.

In this study, some protein/enzyme receptors that were imported from a protein data bank were used (http://www.rcsb.org/:PDB, accessed on September 2020):

Herpes simplex type-1 thymidine kinase (PDB ID 2KI5).
Wild-type influenza N2 neuraminidase (PDB ID 4H52).
SARS coronavirus main protease (PDB ID:3TNT).

Docking evaluation against herpes simplex type-1 thymidine kinase: docking studies were performed to achieve accurate predictions on the optimized conformations for both ligand and protein target to form a stable complex. All ligands were docked on the crystal structure of the *herpes simplex type-1 thymidine kinase* (PDB ID: 2KI5). The docking pose of the co-crystallized AC2 interacting with amino acid residues of the active site is shown in Figure 3. The oseltamivir and ribavirin were taken as reference ligands to compare the docking results of all the studied compounds. The docking studies revealed that the **5jG** compound has the best docking score −66.42 (RMSD: 0.55) (Table 1, Figure 4).

Table 1. Docking score of ligands.

Ligand	PDB ID: 2KI5		PDB ID: 4H52		PDB ID: 3TNT	
	Score	**RMSD (Å)**	**Score**	**RMSD (Å)**	**Score**	**RMSD (Å)**
Co-crystallized	−49.29	0.71	−49.94	0.21	−82.61	2.41
Oseltamivir	−46.52	0.02	−54.44	0.62	−48.75	1.96
Ribavirin	−47.48	0.009	−49.66	1.02	−44.73	0.47
5G	−56.24	0.02	−51.08	0.27	−48.31	0.02
5aG	−63.14	0.01	−42.49	0.01	−48.31	0.04
5bG	−60.18	0.01	−48.23	0.19	−51.18	0.14
5cG	−50.98	0.05	−47.88	0.87	−59.63	0.28
5dG	−35.83	0.03	−54.81	0.72	−57.15	0.15
5eG	−43.80	0.23	−50.95	1.04	−60.92	0.35
5fG	−27.82	0.02	−46.04	0.28	−60.85	0.08
5gG	−13.47	0.18	−46.27	0.10	−62.98	0.50
5hG	+1.06	0.03	−45.50	1.72	−65.84	0.04
5iG	−65.51	0.19	−64.95	0.28	−64.07	1.46
5jG	**−66.42**	0.55	−51.86	0.79	−75.00	0.77
5jjG	−61.71	0.04	−57.33	1.37	**−81.11**	1.90
5kG	−59.01	0.60	**−67.57**	0.58	−65.73	0.55
5lG	−51.11	1.16	−54.69	1.14	−73.07	0.29
5mG	−65.46	0.45	−59.33	0.78	−62.74	1.21
5nG	−65.07	0.05	−59.18	0.96	−63.65	0.50
5oG	+1.37	0.04	−50.88	0.19	−62.38	0.45
5pG	−56.25	0.007	−41.01	0.25	−48.16	0.02
5rG	−53.58	0.22	−48.02	0.09	−53.66	0.06
5qG	−51.17	0.06	−46.27	0.10	−61.64	0.22
5sG	−58.31	0.02	−50.72	0.99	−62.51	0.54
5tG	−54.19	0.04	−55.52	0.80	−67.67	0.75
5uG	−58.66	0.13	−53.11	0.03	−68.96	0.42
5zG	−56.23	0.07	−42.23	0.26	−56.91	0.16

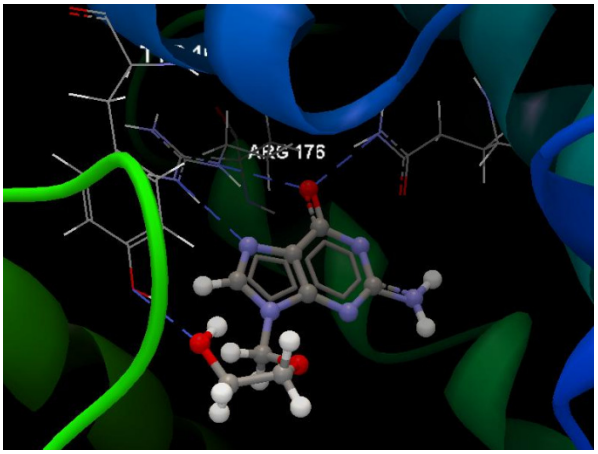


Figure 3. Hydrogen bond (blue dotted lines) between AC2 and amino acid residues from the binding site of 2KI5**.**

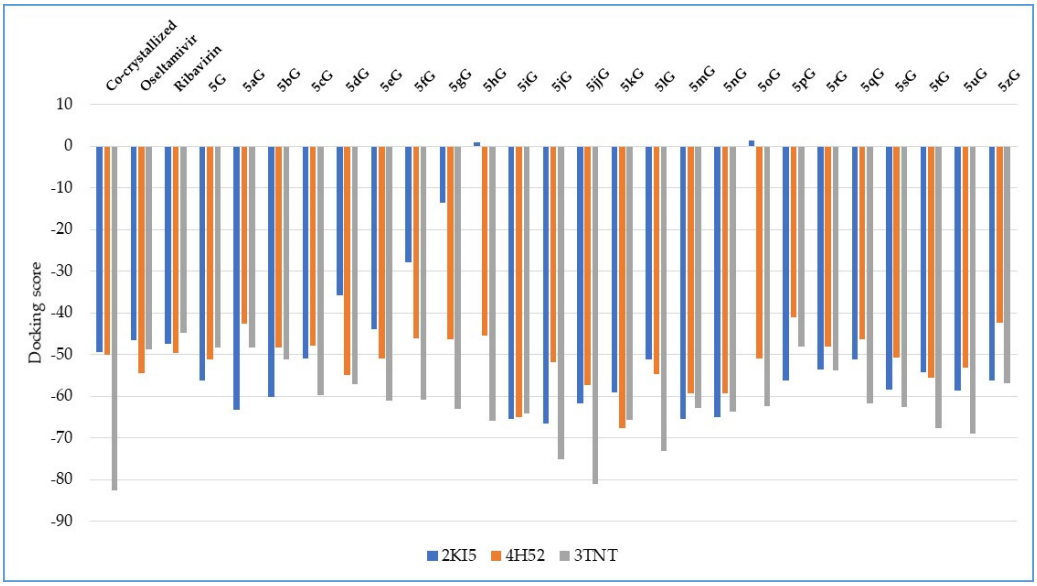


Figure 4. Docking score of the compounds, comparative with the docking score of the co-crystallized and with the docking score of the reference drugs oseltamivir and ribavirin.

The docking pose of the **5jG** compound is shown in Figure 5.

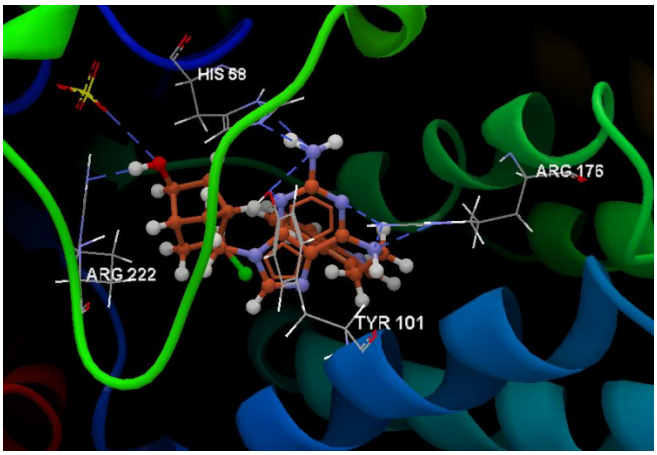


Figure 5. Hydrogen bond (blue dotted lines) between **5jG** compound and amino acid residues from the binding site of 2KI5**.**

After analyzing the data obtained from the docking study, it was observed that all the compounds were placed in the same binding site of 2KI5 as the co-crystallized (Figure 6).

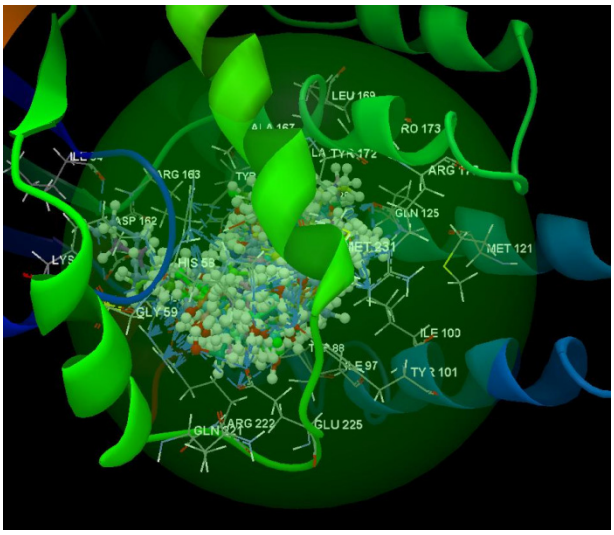


Figure 6. Docking pose of the co-crystallized AC2, of the oseltamivir and ribavirin and of the studied compounds in the binding site of 2KI5.

Docking evaluation against wild-type influenza N2 neuraminidase**:** docking studies were performed to achieve accurate predictions on the optimized conformations for both ligand and protein target to form a stable complex. All ligands were docked on the crystal structure of the *wild-type influenza N2 neuraminidase* (PDB ID: 4H52). The docking pose of the co-crystallized **FSI A 508** interacting with amino acid residues of the active site is shown in Figure 7. Oseltamivir and ribavirin were taken as reference ligands to compare the docking results of all the studied compounds. The docking studies revealed that the **5kG** compound has the best docking score −67.57 (RMSD: 0.58) (Table 1, Figure 4). The docking pose of the **5kG** compound is shown in Figure 8.

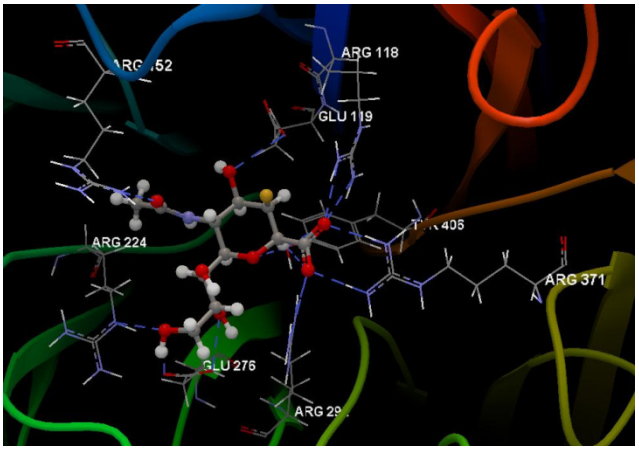


Figure 7. Hydrogen bond (blue dotted lines) between FSI A 508 and amino acid residues from the binding site of 4H52.

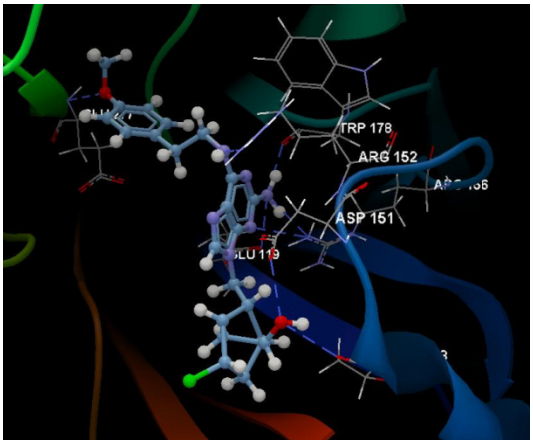


Figure 8. Hydrogen bond (blue dotted lines) between the **5kG** compound and amino acid residues from the binding site of 4H52.

After analyzing the data obtained from the docking study, it was observed that all the compounds were placed in the same binding site of 4H52 as the co-crystallized (Figure 9).

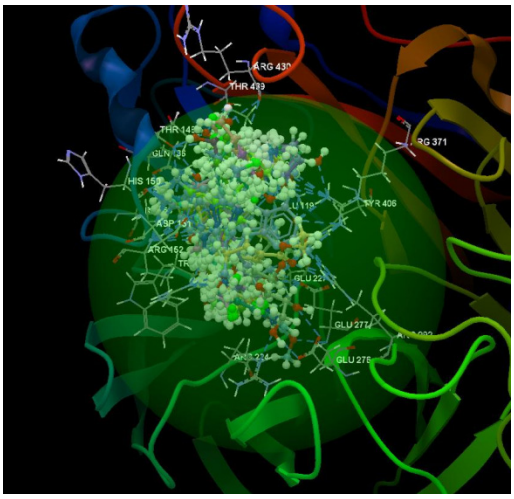


Figure 9. Docking pose of the co-crystallized **FSI A 508**, of the oseltamivir and ribavirin and of the studied compounds in the binding site of 4H52.

Docking evaluation against SARS coronavirus main protease: docking studies were performed to achieve accurate predictions on the optimized conformations for both ligand and protein target to form a stable complex. All ligands were docked on the crystal structure of the *SARS coronavirus main protease* (PDB ID: 3TNT). The docking pose of the co-crystallized **G85A 501** interacting with amino acid residues of the active site is shown in Figure 10. Oseltamivir and ribavirin were taken as reference ligands to compare the docking results of all the studied compounds. The docking studies revealed that the **5jjG** compound has the best docking score −81.11 (RMSD: 1.90) (Table 1, Figure 4). The docking pose of the **5jjG** compound is shown in Figure 11.

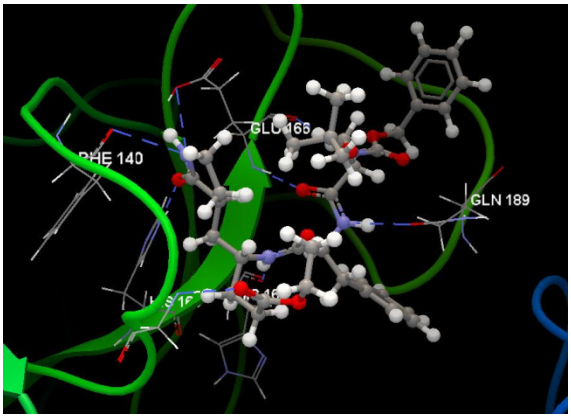


Figure 10. Hydrogen bond (blue dotted lines) between G85A 501 and amino acid residues from the binding site of 3TNT.

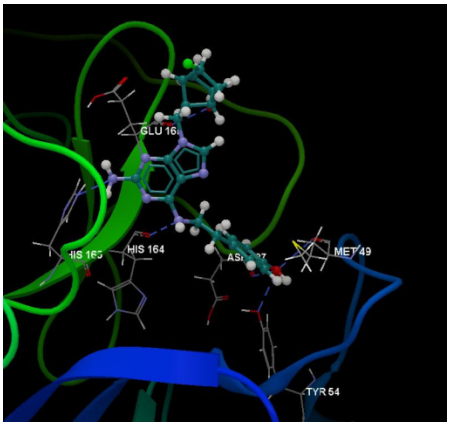


Figure 11. Hydrogen bond (blue dotted lines) between the **5jjG** compound and amino acid residues from the binding site of 3TNT.

After analyzing the data obtained from the docking study, it was observed that all the compounds were placed in the same binding site of 3TNT as the co-crystallized (Figure 12).

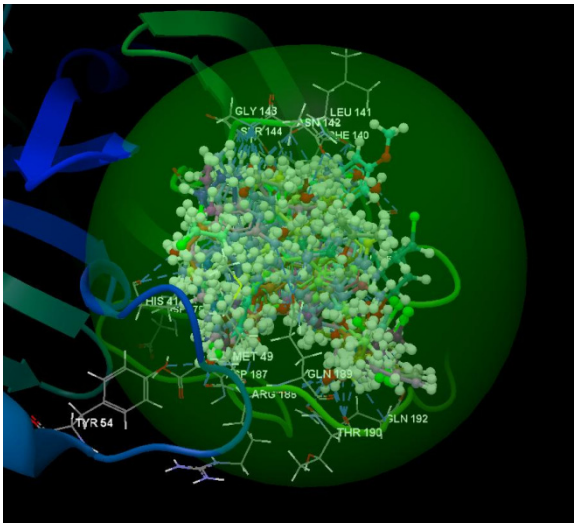


Figure 12. Docking pose of the co-crystallized **G85A 501**, of the oseltamivir and ribavirin and of the studied compounds in the binding site of 3TNT.

Important molecular properties—molecular weight, flexible bonds, the number of hydrogen bond donors, the number of hydrogen bond acceptors and log P—were calculated (Table 2). These parameters can predict if a molecule possesses properties that might turn it into an orally active drug, according to Lipinski's rule of five. The number of violations of the Lipinski rules allows one to evaluate drug likeness for a molecule. According to the data presented in Table 2, only the **5lG** compound failed with respect to the Lipinski rules (Lipinski violation is 1, hydrogen bond donors >5).

Table 2. Calculated properties of ligands.

Compound	Atoms	Weight (Daltons)	Flexible Bonds	Lipinski Violations	Hydrogen Donors	Hydrogen Acceptors	Log P
AC2 A *	26	224.20	4	0	3	8	0.50
FSI A 508 **	38	310.25	5	0	5	9	−1.72
G85A 501 ***	95	652.78	20	2	4	12	3.69
Oseltamivir	50	312.40	8	0	3	6	1.70
Ribavirin	29	244.20	3	0	5	9	−3.05
5G	36	328.20	2	0	3	6	1.67
5aG	37	309.75	2	0	4	7	0.69
5bG	38	308.77	2	0	5	7	0.36
5cG	45	348.83	4	0	4	7	1.58
5dG	51	376.88	4	0	4	7	2.30
5eG	54	390.91	4	0	4	7	2.84
5fG	49	378.86	3	0	3	8	0.79
5gG	53	391.90	3	0	3	8	0.98
5hG	56	405.92	4	0	3	8	1.34
5iG	54	412.92	6	0	4	7	2.98
5jG	58	451.95	6	0	5	8	3.11
5jJG	55	428.92	6	0	5	8	2.63
5kG	58	442.94	7	0	4	8	2.95
5lG	56	444.91	6	1	6	9	2.27
5mG	54	416.91	7	0	4	9	1.10
5nG	56	405.92	6	0	4	8	1.55
5oG	58	420.94	5	0	5	9	0.04
5pG	40	323.78	3	0	3	7	1.01
5rG	43	337.80	4	0	3	7	1.38
5qG	58	442.94	7	0	5	8	2.36
5sG	50	399.88	5	0	4	8	1.49
5tG	50	399.88	5	0	4	8	1.45
5uG	50	399.88	5	0	4	8	1.45
5zG	44	336.82	3	0	3	7	1.17

* PDB ID: 2KI5; ** PDB IB: 4H52; *** PDB ID: 3TNT.

The compounds were screened against influenza virus and two compounds, **5fG** and **5gG**, had SI of 25 and 23 (IC_{50} = 8 μM and 12.8 μM) and two SI of 10 (**5kG**, IC_{50} = 24 μM and **5sG**, IC_{50} = 29 μM). The screening of the compounds against HSV and low active coronavirus is being developed and soon will be finished.

In conclusion, a number of 24 new 1′-homonucleoside with a 2-amino-6-substituted purine as nucleobase and an optically active bicyclo[2.2.0]heptane scaffold were synthesized, and a molecular docking study on three viruses and an experimental screening of the compounds against influenza virus were realized.

3. Patents

Tanase, C.; Pintilie, L. New 1′-homocarbanucleoside analogs with a constrained bicyclo[2.2.0]heptane fragment and 2-amino-6-substituted purine as nucleobase. Patent request A/00290/27.05.2020.

Author Contributions: Conceptualization, C.I.T.; methodology, C.I.T.; molecular docking L.P.; IR analysis, M.M.; NMR spectroscopy, C.D. and A.H.; antiviral screening, V.V.Z., A.V. and E.S.; writing—original draft preparation, C.I.T. and L.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Ministry of Education and Research, UEFISCDI, grant number NUCLEU: PN 19-41 01 01.

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

References

1. Balzarini, J.; Naesens, L.; De Clercq, E. New antivirals—Mechanism of action and resistance development. *Curr. Opin. Microbiol*. **1998**, *1*, 535–546.
2. De Clerck, E.; Neyts, J. Antiviral Agents Acting as DNA or RNA Chain Terminator. In *Handbook of Experimental Pharmacology 189*; Kräusslich, H.-G., Bartenschlager, R., Eds.; Springer Science & Business Media: Berlin/Heidelberg, Germany, 2008; pp. 54–60.
3. Tănase, C.; Drăghici, C.; Cojocaru, A.; Galochkina, A.V.; Orshanskaya, J.R.; Zarubaev, V.V.; Shova, S.; Enache, C.; Maganu, M. New carbocyclic N^6-substituted adenine and pyrimidine nucleoside analogues with a bicyclo[2.2.1]heptane fragment as sugar moiety; synthesis, antiviral, anticancer activity and X-ray crystallography. *Bioorg. Med. Chem.* **2015**, *23*, 6346–6354.
4. Tănase, C.; Drăghici, C.; Hanganu, A.; Pintilie, L.; Maganu, M.; Volobueva, A.; Sinegubova, E.; Zarubaev, V.; Neyts, J.; Jochman, D.; et al. New HSV-1 Anti-Viral 1′-Homocarbocyclic Nucleoside Analogs with an Optically Active Substituted Bicyclo[2.2.1]Heptane Fragment as A Glycoside Moiety. *Molecules* **2019**, *24*, 2446.
5. Tănase, C.; Pintilie, L.; Mihai, E. New 1′-homocarbonucleoside Analogs with a Constrained Bicyclo[2.2.1]heptane Fragment. Patent Request A/00316/30.05. 2019.
6. Tanase, C.; Pintilie, L. New 1′-homocarbanucleoside Analogs with a Constrained bicyclo[2.2.0]heptane Fragment and 2-amino-6-substituted Purine as Nucleobase. Patent request A/00290/27.05. 2020.