Journal of Siberian Federal University. Chemistry 2023 16(2): 168–179
~ ~ ~

EDN: SIKRGW

УДК 615.28:577.113.3

Thymidine Based Potential Antimicrobial Agents Through In Silico DFT Calculations

Mohammed A. Hosen and Sarkar M. A. Kawsar*
Laboratory of Carbohydrate and Nucleoside Chemistry (LCNC),
University of Chittagong
Chittagong, People's Republic of Bangladesh

Received 07.09.2022, received in revised form 05.04.2023, accepted 02.05.2023

Abstract. Modification of the hydroxyl (–OH) group of thymidine by acylation may cause changes in the antimicrobial and anticancer properties of thymidine which is investigated in this study. The current study is concentrated towards the in silico computational study of different in silico and bioactivity investigations. We relate the optimization of thymidine and its acylated analogs by applying density functional theory (DFT) with B 3LYP/3–21G level theory to demonstrate their thermal, frontier molecular orbital, the density of states (DOS) and molecular electrostatic potential (MESP) properties. All the analogs were found with enriched score than their parent atom which indicates the theoretical stability of these compounds. To deeply realize these observations molecular docking studies have been performed against human PARP1 (*E.coli*-BL21, PDB: 4ZZZ) and remarkable binding energies and non-covalent interactions were observed. Bioactivity data exhibited that compounds consisted of standard values in predicted cases. Moreover, toxicity data showed a safer level of the score for all studied thymidine analogs. This work demonstrates that potential thymidine analogs bind to bacterial pathogens for circumventing their activities and opens avenues for the development of newer drug candidates that can target bacterial and fungal pathogens.

Keywords: thymidine analogs, quantum mechanical calculation, molecular docking, toxicity and bioactivity prediction.

Acknowledgements. The authors are indebted to the Ministry of Science and Technology (2021–2022, Phy's-591), University of Chittagong, Bangladesh for financial assistance to carry out this research work.

Citation: Hosen M. A., Kawsar S. M. A. Thymidine based potential antimicrobial agents through In silico DFT calculations. J. Sib. Fed. Univ. Chem., 2023, 16(2), 168–179. EDN: SIKRGW

* Corresponding author E-mail address: akawsarabe@yahoo.com

Потенциальные противомикробные агенты на основе тимидина с помощью расчетов In Silico DFT

М. А. Хосен, С.М.А. Кавсар
Лаборатория химии углеводов и нуклеозидов (LCNC),
Университет Читтагонга
Народная Республика Бангладеш, Читтагонг

Аннотация. Модификация гидроксильной (–OH) группы тимидина путем ацилирования может вызвать изменения в антимикробных и противоопухолевых свойствах тимидина, которые исследуются в данной работе. Текущее исследование сосредоточено на вычислительном изучении in silico различных исследований in silico и биоактивности. Мы связываем оптимизацию тимидина и его ацилированных аналогов с применением теории функционала плотности (DFT) с теорией уровней B 3LYP/3–21G, чтобы продемонстрировать их тепловые свойства, пограничную молекулярную орбиталь, плотность состояний (DOS) и молекулярный электростатический потенциал (MESP). Все аналоги были обнаружены с показателем, превышающим их исходный атом, что указывает на теоретическую стабильность этих соединений. Чтобы глубже осознать эти наблюдения, были проведены исследования молекулярного докинга против PARP1 человека (*E.coli*-BL21, PDB: 4ZZZ) и обнаружены значительные энергии связи и нековалентные взаимодействия. Данные о биологической активности показали, что соединения в прогнозируемых случаях соответствовали стандартным значениям. Более того, данные о токсичности показали более безопасный уровень оценки для всех изученных аналогов тимидина. Эта работа демонстрирует, что потенциальные аналоги тимидина связываются с бактериальными патогенами, чтобы обойти их активность, и открывает возможности для разработки новых лекарственных препаратов-кандидатов, которые могут воздействовать на бактериальные и грибковые патогены.

Ключевые слова: аналоги тимидина, квантово-механический расчет, молекулярная стыковка, прогнозирование токсичности и биологической активности.

Благодарности. Авторы выражают благодарность Министерству науки и технологий (2021–2022, Phy's-591), Университету Читтагонга (Бангладеш) за финансовую помощь в проведении этой исследовательской работы.

Цитирование: Хосен М. А., Кавсар С. М.А. Потенциальные противомикробные агенты на основе тимидина с помощью расчетов In Silico DFT. Журн. Сиб. федер. ун-та. Химия, 2023, 16(2). С. 168–179. EDN: SIKRGW

Introduction

Thymidine and its nucleotide analogs also have a role in the activity of the central nervous system as signalling agent [1]. It has the anti-depression capability and hepatocyte proliferation [2]. Thymidine also plays role in sleep-promoting and anti-epileptic effects and develops memory function and influences neuronal plasticity [3]. In addition, thymidine and some of its bioactive analogs behave

as antimetabolites, when their extracellular concentrations are greater than those physiological limits [4]. Nucleoside analogs are, in recent times, found as a backbone of many drugs for the treatment of infectious diseases caused by HIV, hepatitis B or C viruses, and herpes viruses [5]. NAs have immense clinical importance as medicinal agents because of their antiviral and anticancer activities [6] have been the drugs of choice for the treatment of various viral diseases such as herpes simplex (HSV-1), human cytomegalovirus, varicella-zoster, human immunodeficiency virus (HIV) type-1, human hepatitis B (HBV) and C (HCV) [7], ebola [8], dengue [9], and Zika [10]. Additionally, 2′-deoxynucleosides such as idoxuridine, trifluridine, doxudine, vidarabine, and brivudine have been used for treating herpes virus infections [11, 12]. Certain 2′,3′-dideoxynucleosides such as zidovudine, didanosine, zalcitabine, stavudine, and abacavir have proved to be the most effective therapeutic agents against HIV [13]. The modifications in the sugar moiety, namely ribofuranose or deoxyribofuranose of nucleosides include changes in the sugar substituents, replacement of the oxygen with another atom, addition of heteroatom in the sugar ring, ring size variations, and replacement with acyclic moiety [14–19]. These alterations may produce remarkable variations in biological activity and degree of selective toxicity according to their respective chemical and physical properties [20–26]. The modified compounds exhibited a broad-spectrum biological activity. Thymidine derivatives such as telbivudine are antiviral drugs used in HBV treatment [27]. Some current research revealed that thymidine analogs as well as nucleobases are a pharmacologically diverse family, which includes cytotoxic compounds, antimicrobial agents and immune suppressive molecules [28–31].

The alterations in the sugar moiety of nucleosides with replacement of the oxygen/atom or groups, and the addition of heteroatoms in the sugar ring, ring size variations, and replacement with acyclic moiety [10, 22, 32]. These modifications can produce remarkable variations in biological activity and the degree of selective toxicity [33, 34]. The modified compounds have exhibited broad-spectrum biological activity [35, 36]. Thymidine derivatives such as telbivudine are antiviral drugs used in HBV treatment [37]. Some recent research revealed that thymidine analogs, as well as nucleobases, are a pharmacologically diverse family, which includes cytotoxic compounds, antimicrobial agents and immune-suppressive molecules [10, 31, 38].

Keeping in view these features mentioned above as well as our successive ambition to find novel drugs [39–43], we report herein the in silico computational evaluation of several thymidine-based esters **2–6** with different aliphatic and aromatic to explore their quantum mechanical calculation, molecular docking against human PARP1 along with the prediction of toxicity and bioactivity prediction.

Experimental

Methods and employed materials

The following software were used in the present study: i) Gaussian 09, ii) AutoDock 4.2.6, iii) Swiss-Pdb 4.1.0, iv) Python 3.8.2, v) Discovery Studio 4.1, vi) PyMOL 2.3, vii) admetSAR server (http://lmmd.ecust.edu.cn/admetsar2/about) and SwissADME free web tools (http://www.swissadme.ch) were employed to calculate the pharmacokinetic properties.

Geometry Calculation

In computational chemistry, quantum mechanical methods are widely used to calculate thermal, molecular orbital and molecular electrostatic properties. Geometry optimisation and further

modification of all synthesised analogs were carried out using the Gaussian 09 program. Density functional theory (DFT) three-parameter hybrid model, Lee, Yang and Parr's (LYP) correlation functional under a 3–21G basis set, was employed to optimise and predict their thermal and molecular orbital properties.

Thermodynamic Analysis

A simple alteration of the chemical structure significantly influences structural properties, including thermal and molecular orbital properties. The spontaneity of a reaction and the stability of a product can be calculated from the free energy and enthalpy values [40]. Highly negative values are more likely to gain thermal stability. In drug design, hydrogen bond formation and non-bonded interactions are also influenced by the dipole moment. Free energy (G) is a significant criterion to represent the interaction of binding partners, whereby negative values are favourable for spontaneous binding and interaction. In the current study, the thymidine analogs possessed greater negative values for *E*, *H* and *G* versus the parent thymidine. Hence, this indicates that the attachment of an acyl group could improve interaction and the binding of these molecules with different microbial enzymes.

Frontier Molecular Orbitals (FMO)

Frontier molecular orbital features, HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) were counted at the same level of theory. For each of the thymidine analogs, the HOMO-LUMO energy gap, hardness (η), and softness (*S*) were calculated from the energies of the frontier HOMO and LUMO as reported, considering Parr and Pearson's interpretation of DFT and Koopman's theorem [41] on the correlation of chemical potential (μ), electronegativity (χ) and electrophilicity (ω) with HOMO and LUMO energy (ε). The following equations were used to calculate global chemical reactivity by analysing molecular orbital features.

$$\eta = \frac{[\varepsilon\mathrm{LUMO} - \varepsilon\mathrm{HOMO}]}{2}$$

$$S = \frac{1}{\eta}$$

Molecular Electrostatic Potential map analysis

In computer-aided drug design, atomic charges are employed to investigate the connectivity between the structure and biological activity of a drug. The molecular electrostatic potential (MEP) is used globally as a reactivity map displaying An MEP counter map is a simple way of predicting how different geometry could interact. The importance of MEP lies in the fact that it simultaneously shows the molecular size and shape, as well as positive, negative and neutral electrostatic potential regions in terms of colour grading, which is very useful in the research of molecular structure, along with the physicochemical properties relationship [42].

Protein selection and molecular docking

The crystal 3D structure of human PARP-1 (*E.coli*-BL21, PDB: 4ZZZ) was recuperated in the pdb format from the protein data bank. PyMol (version 1.3) software packages were employed to remove all heteroatoms and water molecules. Energy minimisation of the protein was performed by using a

Swiss-PdbViewer (version 4.1.0). Furthermore, a molecular docking study against the human PARP-1 was conducted on the optimized drugs.

Bioactivity and toxicity prediction

In the present study, the Molinspiration online server (https://www.molinspiration.com/cgi-bin/properties) was utilised to analyse the drug-like properties of lead compounds. The Molinspiration cheminformatics engine allows the fast prediction of biological activity and virtual screening of large collections of molecules, and the selection of molecules with the highest probability, to show biological activity. For this reason, the best-identified esters were evaluated using pkCSM for their in silico pharmacokinetics parameters to avoid the failure of the esters during clinical trials and to improve their chances of reaching the stage of potential candidate drugs.

Results and discussion

In the present study, thymidine analogs have been modified with different aliphatic and aromatic chains (**2**–**6**) and were attempted to perform geometrical optimization to understand the mode of their antimicrobial behaviour.

Structural information of designed thy derivatives

Atomic identification and structural variation of substituted cytidine derivatives have displayed in Fig. 1. Different acylating (lauroyl, palmitoyl, myristoyl, trityl and 4-*t*-butylbenzoyl) groups were subjected to modification of hydroxyl (–OH) group of thymidine to observe the variety of biological activities.

Thermodynamic Analysis

The highest free energy is (–4616.601 Hartree) observed for thymidine ester (**6**) It also showed the highest enthalpy (–4616.519 Hartree) and highest electronic energy (–4616.520 Hartree). The dipole moment value of a molecule is very significant to describe its electronic properties, wherein a high dipole moment value of a molecule causes more intermolecular interactions. A high dipole moment value reveals a more polar nature. Three thymidine esters (**3**, **4** and **6**) have an improved dipole moment, enhancing a molecule's polar nature and promoting binding affinity, hydrogen bonding, and nonbonding interaction with the receptor protein. The highest dipole moment was (5.911 Debye) observed for thymidine ester (**6**), whereas thymidine ester (**5**) showed the lowest value (4.098 Debye). The scores for all parameters gradually increased with the number of carbon atoms in the substituents (**2–6**). The 4-*t*-butylbenzoyl ester had better scores for all parameters, as evidenced by thymidine ester (**6**), which had the highest free energy of the therapeutics under investigation and showed a markedly improved dipole moment. It is reasonable to propose that the modifying hydroxyl (–OH) groups of thymidine significantly increases its thermodynamic properties.

Frontier Molecular Orbitals (FMO)

The frontier molecular orbitals are the most important orbitals in a molecule, as they are consistently considered when studying chemical reactivity and kinetic stability. The electronic absorption relates to the transition from the ground to the first excited state and is mainly described as one electron

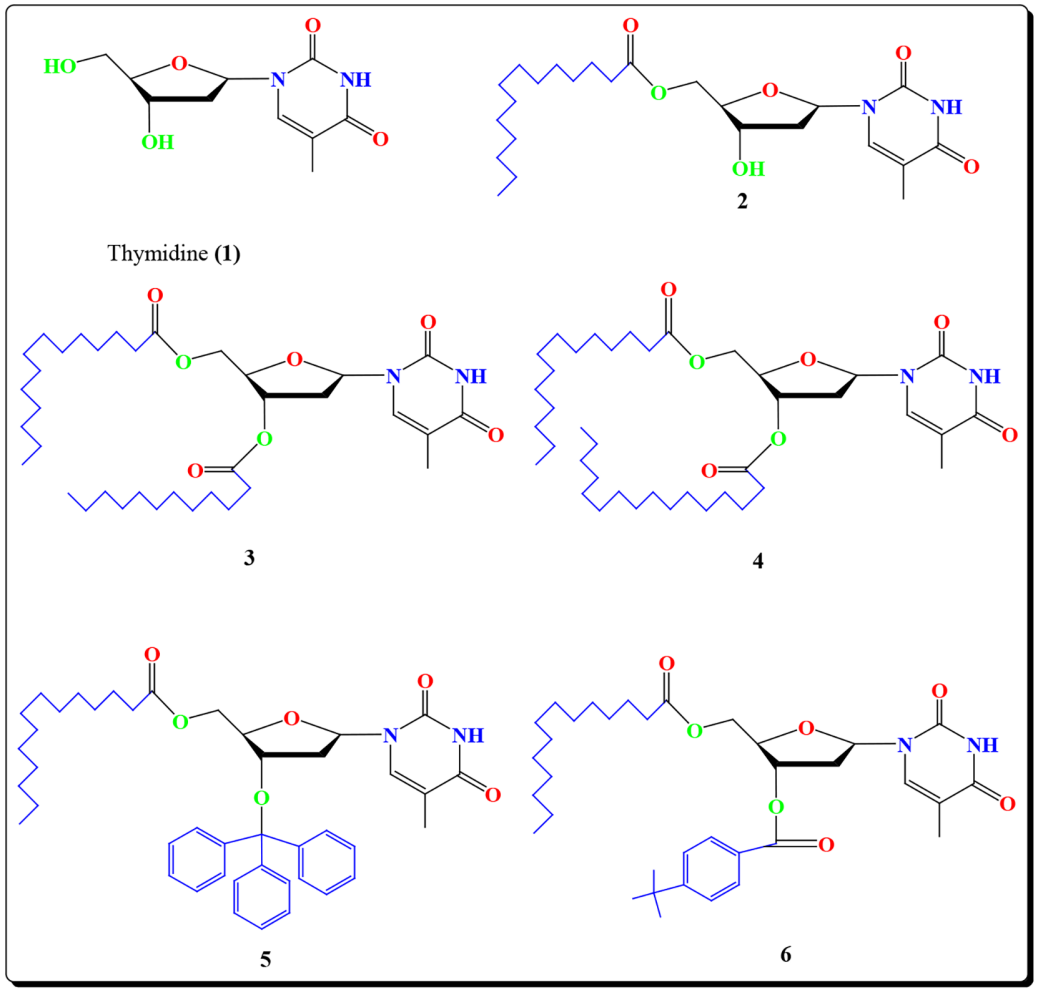

Fig. 1. Chemical structure of designed thymidine analogs (2–6)

excitation from HOMO to LUMO. It was found that thymidine ester (**4**) had a slightly higher energy gap value (5.782 eV), and the thymidine ester (**3**) had a slightly lower energy gap value (5.485 eV) than that of the other esters. The thymidine ester (**2**) had chemical hardness and softness values of 3.044 eV and 0.38 eV respectively, where the hardness value was highest among all the esters. On the other hand, the thymidine ester (**5**) had the lowest chemical hardness (2.689 eV) as well as the highest chemical softness (0.371 eV). Thymidine ester (**6**) had a -$C(CH_3)_3$ functional group in the aromatic ring, which is the reason behind this high chemical reactivity.

Molecular Electrostatic Potential map analysis

The molecular electrostatic potential (MEP) is used globally as a reactivity map displaying the most suitable region for the electrophilic and nucleophilic attack of charged point-like reagents on organic molecules. It helps interpret the biological recognition process and hydrogen bonding interaction. The MEP of the title analog is obtained based on the B 3LYP with the basis set at 3–21G for an optimised result, as shown in Fig. 2. Different colours represent the different values of electrostatic

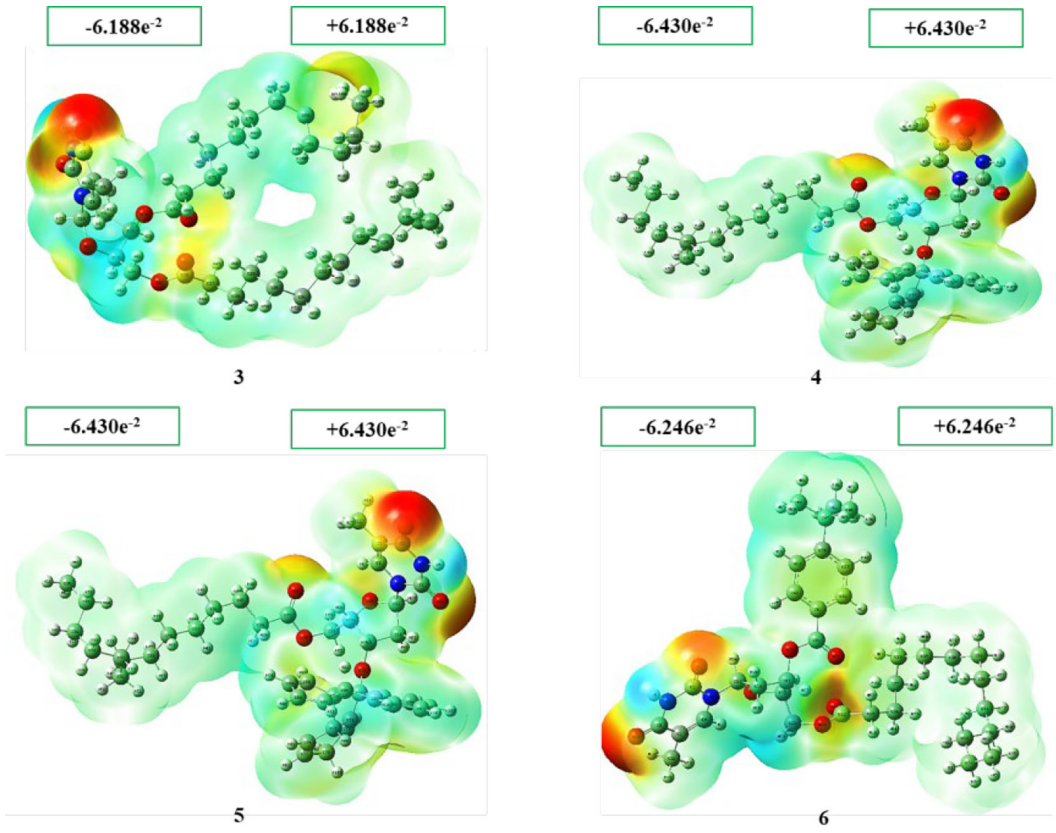

Fig. 2. MEP of the molecular electrostatic potential of thymidine analogs (3–6)

potential, with potential increases in the order red < orange < yellow < green < blue. The red colour displays the maximum negative area, which shows favourable sites for electrophilic attack; the blue indicates the colour the maximum positive area favourable for a nucleophilic attack. The green colour represents zero potential areas.

Molecular docking analysis

According to the results obtained from docking screening, five analogs (**2–6**) with the strongest binding energies were selected to describe the binding mode of the potential thymidine analogs. Fig. 3 depicts the docked conformation of the most active complex (**6**) based on docking studies. The results show that thymidine analogs (**2–6**) (–6.5, –7.5, –7.2, –7.3, –8.5 and –8.2 kcal/mol) are the most potent compound. The binding sites were mainly located in a hydrophobic cleft bordered by the amino acid residues Tyr889, Tyr896, Tyr907, Ile872, Ile895, His862, Pro881, Lys903, Met890, Leu985, Arg878, and Ala880. There are ten prominent hydrogen bond contacts with four different amino acids: Asn767, Asn868, Gly863, Gly888, Met890, Glu759, Glu988, Ser864, Tyr907, Lys903, Asp170, His 862 and Arg878 respectively. The thymidine analogs (**5** and **6**) had additional benzene rings in the thymidine, providing a high density of electrons in the molecule, indicated by the highest binding score. These results show that modification of the –OH group along with an aromatic ring molecule increased the binding affinity, while the addition of hetero groups like $–C(CH_3)_3$, caused

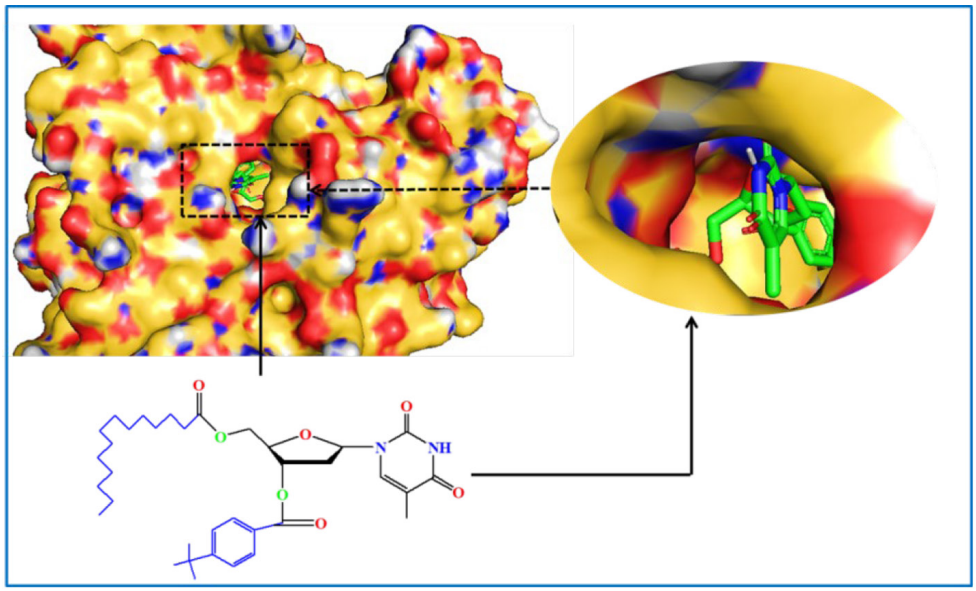

Fig. 3. (**A**); Docking pose (space-filling model) and 2D interaction map of analog **6** with *E. coli* (4ZZZ)

some fluctuations in binding affinities; however, modification with halogenated aromatic rings increased the binding affinity.

Bioactivity and toxicity analysis

The bioactivity score of the lead thymidine analogs has been predicted with a combination of GPCR, ion channel modulator, kinase inhibitor, nuclear receptor ligands, protease inhibitor, and enzyme inhibitor, which was employed to identify the efficacy of molecules to qualify for drug development. The larger the bioactivity score, the higher the probability of the specific molecule being active. If the bioactivity score of molecules is greater than 0.00, they have promising biological activity, and a score ranging from 0.50 to 0.00 is considered to be moderately active, but if the value is less than –0.50, it is presumed to be inactive. The bioactivity score of all designed thymidine analogs is displayed in Table 1. The values obtained for the bioactivity score show that analogs (**2**, **3** and **6**) revealed promising efficacy.

Table 1. Determination of the drug-likeness score of thymidine analogs through molinspiration cheminformatics online server

Drugs	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	-0.15	-0.34	-0.19	-1.25	-0.75	0.93
2	0.22	0.22	-0.10	-0.54	-0.19	0.58
3	0.04	-0.54	-0.27	-0.55	-0.21	0.15
4	-0.09	-0.87	-0.47	-0.81	-0.20	-0.07
5	-0.25	-1.13	-0.69	-1.03	-0.29	-0.28
6	-0.01	-0.43	-0.18	-0.58	-0.29	0.24

Conclusion

In the current study, the novel characteristic stability and biochemical behaviour of thymidine and its analogs are investigated. All the designed MGP analogs have a HOMO-LUMO gap lower than thymidine and resulting that modified compounds were may more reactive than the parent drug. Insertion of various aliphatic and aromatic groups in thymidine structure can significantly improve their biological activity mode. These observations were clarified by molecular docking that revealed the promising antmicrobial efficacy of thymidine analogs. Many of these analogs showed notable binding interactions and binding energy with the target protein. The five thymidine analogs (**2–6**) have shown in silico potent ability to fight human PARP1 (*E. coli*-BL21). These analogs were analyzed for their toxicity and bioactivity properties which expressed that all the analogs have improved drug-likeness scores as well as an interesting result in terms of biological activity. This research may be useful to explore the chemical, thermal, physicochemical, biological and bioactivity properties of thymidine analogs.

Author contributions

MAH performed the computational study and wrote the manuscript. S.M.A.K. supervised, designed, edited and improved the manuscript. All authors have read and approved the final version of this paper.

Declaration of interest

The authors declare no conflict of interest.

References

[1] Dobolyi A., Juhasz G., Kovacs Z., Kardos J. Uridine function in the central nervous system. *Current Topics in Medicinal Chemistry* 2011. 11(8), 1058–1067.

[2] Carlezon W.A., Mague S.D., Parow A.M., Stoll A.L., Cohen B.M., Renshaw P.F. Antidepressant-like effects of uridine and omega-3 fatty acids are potentiated by combined treatment in rats. *Biological Psychiatry* 2005. 57(4), 343–350.

[3] Siegel D., Hui H.C., Doerffler E., Clarke M.O., Chun K., Zhang L., Neville S., Carra E., Lew W., Ross B., Wang Q., Wolfe L., Jordan R., Soloveva V., Knox J., Perry J., Perron M., Stray K.M., Barauskas O., Mackman R.L. Discovery and synthesis of a phosphoramidate prodrug of a Pyrrolo[2,1-f] [triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of ebola and emerging viruses. *Journal of Medicinal Chemistry* 2017. 60(5), 1648–1661.

[4] Rahman M., Sanjida J., Devi S.R., Rahman M., Islam M., Hossain M.K., Kanaly A.R., Fuji Y., Hayashi N., Ozeki Y., Kawsar S.M.A. Selective acylation of some carbohydrate derivatives using the direct method. *Journal of the Bangladesh Chemical Society* 2017. 29(2), 21–28.

[5] Yamamoto T., Koyama H., Kurajoh M., Shoji T., Tsutsumi Z., Moriwaki Y. Biochemistry of uridine in plasma. *Clinica Chimica Acta; International Journal of Clinical Chemistry* 2011. 412(19–20), 1712–1724.

[6] Amin M.R., Yasmin F., Hosen M.A., Dey S., Mahmud S., Saleh M.A., Hasan I., Fujii Y., Yamada M., Ozeki Y., Kawsar S.M.A. Synthesis, antimicrobial, anticancer, PASS, molecular docking, molecular dynamic simulations and pharmacokinetic predictions of some methyl β-D-galactopyranoside analogs. *Molecules* 2021. 26, 1–25.

[7] Kawsar S.M.A., Khaleda M., Refat A., Manchur M. A., Koide Y., Ozeki Y. Infrared, ^{1}H-NMR spectral studies of some methyl 6-*O*-myristoyl-α-D-glucopyranoside derivatives: assessment of antimicrobial effects. *International Letters of Chemistry Physics and Astronomy* 2015. 58, 122–136.

[8] Islam S., Hosen M. A., Sajjad A., Muhammad T. U.Q., Dey S., Hasan I., Fujii Y., Ozeki Y., Kawsar S. M.A. Synthesis, antimicrobial, anticancer activities, PASS prediction, molecular docking, molecular dynamics and pharmacokinetic studies of designed methyl α-D-glucopyranoside esters. *Journal of Molecular Structure* 2022. 1260, 132761.

[9] Kawsar S.M.A., Ferdous J., Mostafa G., Manchur M. A. A Synthetic approach of D-glucose derivatives: spectral characterization and antimicrobial studies. *Chemistry and Chemical Technology Journal* 2014. 8(1), 19–27.

[10] Alam A., Rana K. M., Hosen M. A., Dey S., Bezbaruah B., Kawsar S. M.A. Modified thymidine derivatives as potential inhibitors of SARS-CoV: PASS, in vitro antimicrobial, physicochemical and molecular docking studies. *Physical Chemistry Research* 2022. 10, 391–409.

[11] Gawande N.G., Shingare M. S. Synthesis of some thiazolylthiosemicarbazides, triazoles, oxazoles, thiadiazoles & their microbial activity. *Indian Journal of Chemistry* 1987. 26, 387–394.

[12] Hamuy R., Berman B. Topical antiviral agents for herpes simplex virus infections. *Drugs Today* 1998. 34(12), 1013–1025.

[13] Kawsar S.M.A., Uddin S., Manchur M. A., Fujii Y., Ozeki Y. Acylation of D-glucose derivatives over C_5H_5N: spectral characterization and *in vitro* antibacterial activities. *International Journal of Biological Chemistry* 2015. 9, 269–282.

[14] Kabir A.K.M.S., Kawsar S. M.A., Bhuiyan M. M.R., Rahman M. S., Chowdhury M. E. Antimicrobial screening studies of some derivatives of methyl a-D-glucopyranoside. *Pakistan Journal of Scientific and Industrial Research* 2009. 52, 138–142.

[15] Kawsar S.M.A., Hamida A. A., Sheikh A. U., Hossain MK., Shagir A. C., Sanaullah A. F.M., Manchur M. A., Imtiaj H., Ogawa Y., Fujii Y. Chemically modified uridine molecules incorporating acyl residues to enhance antibacterial and cytotoxic activities. *International Journal Organic Chemistry* 2015. 5(4), 232–245.

[16] Misbah M.M.H., Ferdous J., Bulbul M. Z.H., Chowdhury T. S., Kawsar S. M.A. An efficient and easy route for the synthesis of methyl β-D-galactopyranoside derivatives. *Journal of the Bangladesh Chemical Society* 2019. 31(2), 49–57.

[17] Kabir A.K.M.S., Kawsar S. M.A., Bhuiyan M. M.R., Rahman M. S., Banu B. Biological evaluation of some octanoyl derivatives of methyl 4,6-*O*-cyclohexylidene-a-D-glucopyranoside. *Chittagong University Journal of Biological Sciences* 2008. 3, 53–64.

[18] Bulbul M.Z.H., Chowdhury T. S., Misbah M. M.H., Ferdous J., Dey S., Hasan I., Fujii Y., Ozeki Y., Kawsar S. M.A. Synthesis of new series of pyrimidine nucleoside derivatives bearing the acyl moieties as potential antimicrobial agent, *Pharmacia* 2021. 68(1), 23–34.

[19] Arifuzzaman M., Islam M. M., Rahman M. M., Mohammad A. R., Kawsar S. M.A. An efficient approach to the synthesis of thymidine derivatives containing various acyl groups: characterization and antibacterial activities. *ACTA Pharmaceutica Sciencia* 2018. 56(4), 7–22.

[20] Islam M.M., Arifuzzaman M., Rahman M. M., Rahman M. A., Kawsar S. M.A. Novel methyl 4,6-*O*-benzylidene-a-D-glucopyranoside derivatives: synthesis, structural characterization

and evaluation of antibacterial activities. *Hacettepe Journal of Biology and Chemistry* 2019. 47(2), 153–164.

[21] Misbah M.M.H., Ferdous J., Bulbul M. Z.H., Chowdhury T. S., Dey S., Hasan I., Kawsar S. M.A. Evaluation of MIC, MBC, MFC and anticancer activities of acylated methyl β-D-galactopyranoside esters. *International Journal of Biosciences* 2020. 16(4), 299–309.

[22] Alam A., Hosen M. A., Islam M., Ferdous J., Fujii Y., Ozeki Y., Kawsar S. M.A. Synthesis, antibacterial and cytotoxicity assessment of modified uridine molecules. *Current Advances in Chemistry and Biochemistry* 2021. 6, 114–129.

[23] Kawsar S.M.A., Kumar A. Computational investigation of methyl α-D-glucopyranoside derivatives as inhibitor against bacteria, fungi and COVID-19 (SARS-2). *Journal of the Chilean Chemical Society* 2021. 66(2), 5206–5214.

[24] Kawsar S.M.A., Faruk M. O., Rahman M. S., Fujii Y., Ozeki Y. Regioselective synthesis, characterization and antimicrobial activities of some new monosaccharide derivatives. *Scientia Pharmaceutica* 2014. 82(1), 01–20.

[25] Farhana Y., Amin M. R., Hosen A., Kawsar S. M.A. Bromobenzoylation of methyl α-D-mannopyranoside: synthesis and spectral characterization. *Journal of Siberian Federal University Chemistry* 2021. 14(2), 171–1838.

[26] Kawsar S.M.A., Hosen M. A., Fujii Y., Ozeki Y. Thermochemical, DFT, molecular docking and pharmacokinetic studies of methyl β-D-galactopyranoside esters. *Journal of Computational Chemistry & Molecular Modeling* 2020. 4(4), 452–462.

[27] Tahmida S., Hosen M. A., Alam M. S., Emran T. B., Kawsar S. M.A. Uridine derivatives: antifungal, PASS outcomes, ADME/T, drug-likeliness, molecular docking and binding energy calculations. *Medicine Science International Medical Journal* 2021. 10(4), 1373–1386.

[28] Rana K.M., Ferdous J., Hosen A., Kawsar S. M.A. Ribose moieties acylation and characterization of some cytidine analogs. *Journal of Siberian Federal University Chemistry* 2020. 13(4), 465–478.

[29] Alam A., Hosen M. A., Hosen A., Fujii Y., Ozeki Y., Kawsar S. M.A. Synthesis, characterization, and molecular docking against a receptor protein FimH of *Escherichia coli* (4XO8) of thymidine derivatives. *Journal of the Mexican Chemical Society* 2021. 65(2), 256–276.

[30] Devi S.R., Jesmin S., Rahman M., Manchur M. A., Fujii Y., Kanaly R. A., Ozeki Y., Kawsar S. M.A. Microbial efficacy and two step synthesis of uridine derivatives with spectral characterization. *ACTA Pharmaceutica Sciencia 2019.* 57(1), 47–68.

[31] Hosen M.A., Alam A., Islam M., Fujii Y., Ozeki Y., Kawsar S. M.A. Geometrical optimization, PASS prediction, molecular docking, and in silico ADMET studies of thymidine derivatives against FimH adhesin of *Escherichia coli. Bulgarian Chemical Communications* 2021. 53(3), 327–342.

[32] Shagir A.C., Bhuiyan M. M.R., Ozeki Y., Kawsar S. M.A. Simple and rapid synthesis of some nucleoside derivatives: structural and spectral characterization. *Current Chemistry Letters* 2016. 5, 83–92.

[33] Farhana Y., Amin M. R., Hosen M. A., Bulbul M. Z.H., Dey S., Kawsar S. M.A. Monosaccharide derivatives: Synthesis, antimicrobial, PASS, antiviral, and molecular docking studies against sars-cov-2 m^{pro} inhibitors. *Cellulose Chemistry and Technology* 2021. 55, 477–499.

[34] Kawsar S.M.A., Islam M., Jesmin S., Manchur M. A., Hasan I., Rajia S. Evaluation of the antimicrobial activity and cytotoxic effect of some uridine derivatives. *International Journal of Biosciences* 2018. 12(6), 211–219.

[35] Maowa J., Alam A., Rana K. M., Dey S., Hosen A., Fujii Y., Hasan I., Ozeki Y., Kawsar S. M.A. Synthesis, characterization, synergistic antimicrobial properties and molecular docking of sugar modified uridine derivatives. *Ovidius University Annals of Chemistry* 2021. 32(1), 6–21.

[36] Rana K.M., Maowa J., Alam A., Hosen A., Dey S., Hasan I., Fujii Y., Ozeki Y., Kawsar S. M.A. In silico DFT study, molecular docking, and ADMET predictions of cytidine analogs with antimicrobial and anticancer properties. *In Silico Pharmacology* 2021. 9, 1–24.

[37] Ching L.L., Edward G., Yun F.L., Hsu C. W., Thongsawat M. D.S. Telbivudine versus lamivudine in patients with chronic hepatitis B. *New England Journal of Medicine* 2007. 357, 2576–2588.

[38] Kawsar S.M.A., Hosen M. A. An optimization and pharmacokinetic studies of some thymidine derivatives. *Turkish Computational and Theoretical Chemistry (TC&TC)* 2020. 4(2), 59–66.

[39] Hosen M.A., Munia N. S., Al-Ghorbani M., Baashen M., Almalki F. A., Hadda T. B., Ali F., Mahmud S., Saleh M. A., Laaroussi H., Kawsar S. M.A. Synthesis, antimicrobial, molecular docking and molecular dynamics studies of lauroyl thymidine analogs against SARS-CoV-2: POM study and identification of the pharmacophore sites. *Bioorganic Chemistry* 2022. 125, 105850.

[40] Kawsar S.M.A., Hosen M. A., Alam A., Islam M., Ferdous J., Fujii Y., Ozeki Y. Thymidine derivatives as inhibitors against novel coronavirus (SARS-CoV-2) main protease: theoretical and computational investigations. *Advances in Chemistry Research* 2021. 69, 89–*12*9.

[41] Cohen N., Benson S. W. Estimation of heats of formation of organic compounds by additivity methods. *Chemical Reviews* 1993. 93(7), 2419–2438.

[42] Lee C., Yang W., Parr R. G. Development of the colle-Salvetti correlation-energy formula into a functional of the electron density. *Physical Review B* 1988. 37, 785–789.

[43] Kawsar S.M.A., Hosen M. A., Chowdhury T. S., Rana K. M., Fujii Y., Ozeki Y. Thermochemical, PASS, molecular docking, drug-likeness and in silico ADMET prediction of cytidine derivatives against HIV-1 reverse transcriptase. *Revista de Chimie* 2021. 72, 159–178.