



**DEVELOPMENT OF ANTI-HBV STRATEGIES IN JEMBER:
INTEGRATING PREVALENCE, MOLECULAR
SURVEILLANCE, AND *IN SILICO* SCREENING**

*Submitted to fulfill part of the requirements for obtaining a Master's degree in the
Master of Pharmacy study program*

THESIS

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DEDICATION

This thesis is dedicated to:

1. Allah SWT, for His endless blessings and guidance, empowering those who strive for goodness and seek knowledge;
2. My beloved parents, Rusfandi and Mariyah, who have nurtured, educated, and guided me with unconditional love, prayers, patience, hard work, motivation, advice, and everything that has enabled me to complete this thesis;
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MOTTO

“Whoever sets out in search of knowledge is considered as striving in the path of Allah until he returns”
(H.R. Tirmidzi)

“Affirm with faith, strive with knowledge, and convey through deeds”
(The Muslim Students' Association)

“Dare with dreams, tawakkal with effort, and sincerely supplicate with prayers.”
(Noer Sidqi Muhammadiy)

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Hereby declare that the thesis entitled: *Development of Anti-HBV Strategies In Jember: Integrating Prevalence, Molecular Surveillance, and In Silico Screening* is entirely my own work, except where the sources of cited material are clearly acknowledged. This thesis has not been submitted to any institution previously and is not a plagiarized work. I take full responsibility for the authenticity and accuracy of its content, in adherence to the principles of scientific integrity that must be upheld.

This work was supported by the PAN ASEAN Coalition for Epidemic and Outbreak Preparedness (PACE-UP) through the Master Modul Project. PACE-UP serves as a regional hub for global health and pandemic preparedness in Asia, driven by a multidisciplinary consortium involving North-South and South-South partnerships, with financial support from the German Academic Exchange Service (DAAD).

This statement is made truthfully, without any pressure or coercion from any party, and I am willing to accept academic sanctions should this statement prove to be untrue in the future.

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ABSTRAK

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Hepatitis B merupakan masalah kesehatan global yang signifikan, disebabkan oleh virus Hepatitis B (HBV) yang dapat mengakibatkan infeksi akut dan kronis, sirosis hati, serta kanker hati. HBV dapat ditularkan secara horizontal melalui kontak dengan cairan infeksius dan secara vertikal dari ibu ke anak. Indonesia memiliki prevalensi Hepatitis B yang tinggi, namun penelitian terkait genotipe HBV di wilayah tertentu, seperti Kabupaten Jember, masih terbatas. Penelitian ini bertujuan untuk mengidentifikasi prevalensi infeksi Hepatitis B okult (OBI) dan mengidentifikasi genotipe HBV di Kabupaten Jember, Jawa Timur. Sampel serum dikumpulkan dari 330 donor darah dan 14 pasien positif HBsAg di Kabupaten Jember. Seluruh DNA HBV sampel diisolasi dan diamplifikasi menggunakan nested PCR pada wilayah S/P genom HBV. Genotipe HBV ditentukan melalui proses sequencing. Analisis filogenetik dilakukan menggunakan perangkat lunak Seqman, MAFFT, Mega 11, dan BioEdit. Dari 330 donor darah, 9 sampel (2,8%) positif HBV DNA, menunjukkan adanya OBI. Dari 14 sampel pasien positif HBsAg, 2 sampel (14,29%) menunjukkan hasil negatif setelah di amplifikasi menggunakan nested PCR. Hal ini menyoroti keterbatasan uji HBsAg dan pentingnya teknik molekuler untuk diagnosis yang lebih akurat. Hasil analisis filogenetik diketahui bahwa sampel positif merupakan genotipe B subgenotipe B3 sebanyak 5 sampel dan subgenotipe B4 sebanyak 4 sampel. Terdapat berbagai mutasi pada gen S dan RT yang dapat mempengaruhi deteksi HBsAg serta resistensi terhadap terapi antivirus. Prevalensi OBI di Kabupaten Jember secara signifikan lebih tinggi dibandingkan rata-rata global. Penelitian ini menekankan pentingnya mengombinasikan metode pengujian HBsAg dan PCR untuk mendiagnosis Hepatitis B secara akurat serta mencegah penularannya melalui donor darah. Hasil molecular docking menunjukkan bahwa lamivudine dan tenofovir menunjukkan penurunan aktivitas berdasarkan nilai ΔG dibandingkan dengan wild type. Sedangkan telbivudine merupakan obat dinilai masih sensitive terhadap HBV yang berkembang di jember berdasarkan uji secara molecular docking.

Kata Kunci: *Hepatitis B, Infeksi Hepatitis B Okult (OBI), Genotipe HBV, Molecular Docking, Nested PCR, Uji Serologis, DNA HBV, Jember, Indonesia, Prevalensi.*

RINGKASAN

Pengembangan Strategi Anti-HBV di Jember: Integrasi Prevalensi, Surveilans Molekuler, dan Skrining *In Silico*: Noer Sidqi Muhammadiy: 232220101007: 2024: 62 Halaman: Fakultas Farmasi: Universitas Jember

Hepatitis adalah peradangan hati yang dapat disebabkan oleh virus atau agen non-infeksius, dengan risiko komplikasi serius seperti sirosis dan kanker hati. Terdapat lima jenis utama virus yang menyebabkan terjadinya hepatitis yakni HAV, HBV, HCV, HDV, dan HEV yang memiliki perbedaan pada cara penularan, tingkat keparahan, dan pencegahan. Virus hepatitis menyebabkan sekitar 1,4 juta kematian setiap tahun; Hepatitis B menyumbang 47% dari total tersebut. Kasus baru HBV di Indonesia dilaporkan meningkat dari 0,2% pada tahun 2013 menjadi 0,4 % pada tahun 2018 dengan total kasus mencapai 17,5 juta jiwa pada tahun 2022. Keunikan lain dari HBV yakni setelah pasien sembuh dari infeksi HBV, DNA HBV tidak benar-benar hilang dari sel hepar penyintas. Hal ini terkait kemampuan HBV bertahan karena memiliki sifat okultisme (OBI) dengan cara membiarkan DNA HBV tetap dalam bentuk cccDNA, bentuk inilah yang dapat bertahan lama. Meskipun tidak aktif secara agresif namun bentuk cccDNA HBV masih dapat melakukan translasi dalam jumlah yang sangat sedikit dan dapat menularkan pada individu lainnya. Hal ini sangat berbahaya karena OBI tidak dapat dideteksi menggunakan rapid tes antigen antibodi seperti HBsAg tes. Salah satu yang mempengaruhi tingkat keparahan dari infeksi HBV yakni jenis genotipe HBV yang menginfeksi. Penelitian tentang OBI dan genotipe HBV di Pulau Jawa, termasuk Jember, masih sangat terbatas. Oleh karena peneliti ingin melakukan penelitian terkait hal ini untuk mengetahui prevalensi OBI dan jenis genotipe yang tersebar di Kabupaten Jember, sehingga hasil dari penelitian ini diharapkan menjadi rujukan untuk membuat kebijakan pencegahan dan tatalaksana terapi infeksi HBV di Kabupaten Jember. Untuk mendukung terciptanya tatalaksana terapi yang efektif dan efisien maka peneliti juga melakukan analisis secara komputasi atau *molecular docking* antara obat – obat yang biasa dipakai di Indonesia dengan sekuens DNA yang didapat dari hasil analisis OBI dan genotipe pada penelitian ini. Hal ini bertujuan untuk mengevaluasi sensitivitas terhadap mutasi HBV di Jember. Sehingga penelitian ini juga diharapkan dapat memberikan rekomendasi obat yang efektif dan efisien untuk infeksi HBV yang terjadi di Kabupaten Jember.

Penelitian ini merupakan jenis penelitian deskriptif eksploratif dengan metode *cross – sectional*. Sampling sampel serum donor darah normal dilakukan di Palang Merah Indonesia (PMI) Kabupaten Jember, dan sebagai kontrol positif peneliti juga melakukan sampling serum darah pasien HBsAg positif di ambil dari Rumah Sakit Umum Daerah dr. Soebandi Jember, Rumah Sakit Perkebunan Jember Klinik, dan Rumah Sakit Umum Kaliwates Jember. Semua responden mengisi dan telah menyetujui *informed consent* yang diberikan oleh peneliti. Kemudian isolasi DNA HBV dan *nested PCR* dilakukan di VG – Care, 108 Military Central Hospital, Hanoi, Vietnam. Isolasi DNA menggunakan QIAamp DNA Mini kit. *Nested PCR* menggunakan dua tahap dengan primer khusus (HBV 022, 065, 066 untuk outer; HBV 024, 041, 064 untuk inner PCR) dengan menargetkan region S/P (332 bp)

genom HBV. Hasil positif DNA HBV atau OBI akan dikirim ke *Institute of Tropical Medicine, University of Tübingen*, Jerman untuk dilakukan sekuensing dan analisis filogenetik. Sekuens DNA hasil penelitian ini disusun menggunakan perangkat lunak SeqMan dan kemudian disejajarkan (*alignment*) menggunakan MAFFT versi 7. Analisis filogenetik dilakukan dengan menggunakan perangkat lunak MEGA 11, dengan metode neighbor-joining serta model evolusi K2+G, dan nilai bootstrap sebanyak 1000 untuk memastikan keandalan pohon filogenetik. Pohon filogenetik yang dihasilkan kemudian divisualisasikan menggunakan platform iTOL. Selanjutnya, analisis mutasi pada sekuens DNA dilakukan menggunakan perangkat lunak BioEdit dan geno2pheno. Kemudian sekuens DNA HBV (OBI) yang diperoleh dengan berbagai mutasi selanjutnya digunakan sebagai reseptor dalam uji *molecular docking*. Struktur 3D dari sekuens DNA HBV diprediksi dengan PyMOL, sedangkan ligan diperoleh dari database PubChem. Obat yang di uji sebagai ligan yakni tenofovir, adefovir, entecavir, lamivudine, dan telbivudine. Hasil molecular docking divisualisasikan menggunakan *BIOVIA Discovery Studio*.

Hasil analisis DNA HBV pada sampel serum donor darah kami menemukan prevalensi OBI sebesar 2,8% atau 9 dari 330 sampel donor darah positif DNA HBV dengan metode *nested* PCR. Semua sampel OBI merupakan genotipe B. Dari 9 sampel tersebut 5 diantaranya di kategorikan sebagai HBV subgenotipe B3 yakni A6, A8, A25, D59, dan E20. Sedangkan 4 sampel lainnya yakni A23, C24, C32 dan E28 di kategorikan sebagai HBV subgenotipe B4. Semua sampel OBI memiliki mutasi yang beragam pada domain RT Pol dan S. pada domain S mutasi P127T and N207S terdapat pada 55,6% dari sampel OBI. Sedangkan pada domain RT Pol mutasi N124H dan N134D ditemukan pada semua sampel yang terkonfirmasi OBI. Mutasi pada domain S berpengaruh terhadap kemampuan sensitivitas dari rapid tes, sedangkan pada domain RT Pol berhubungan dengan resistensi anti virus. Kemudian semua sekuens DNA yang didapat di lakukan *molecular docking* terhadap obat anti virus yang di gunakan di Indonesia. Hasilnya menunjukkan bahwa lamivudine dan tenofovir memiliki nilai ΔG yang paling kecil dengan stabilitas paling rendah, hal ini menunjukkan kemungkinan adanya penurunan sensitivitas lamivudine dan tenofovir terhadap HBV yang tersebar di Kabupaten Jember, sedangkan telbivudine memiliki nilai ΔG yang paling besar diantara obat lain yang mengindikasikan kemungkinan besar telbivudine masih sangat sensitif terhadap HBV yang ada di Jember.

Kesimpulan dari penelitian ini yakni prevalensi OBI yang di temukan yakni 2,8% dengan genotipe B dan subgenotipe B3 dan B4. Obat lamivudine memiliki potensi mengalami resistensi berdasarkan nilai ΔG yang lebih kecil dibandingkan *wild type*. Sedangkan telbivudine masih sangat sensitive terhadap HBV yang tersebar di Kabupaten Jember.

SUMMARY

Development of Anti-HBV Strategies In Jember: Integrating Prevalence, Molecular Surveillance, and *In Silico* Screening: Noer Sidqi Muhammadiy: 232220101007: 2024: 62 Page: Faculty of Pharmacy: University of Jember

Hepatitis is an inflammation of the liver that viral or non-infectious agents may cause, and carries the risk of serious complications such as cirrhosis and hepatocellular carcinoma. There are five major types of hepatitis viruses—HAV, HBV, HCV, HDV, and HEV—each differing in transmission route, disease severity, and methods of prevention. Hepatitis viruses are responsible for approximately 1.4 million deaths annually, with Hepatitis B accounting for 47% of the total. In Indonesia, the incidence of new HBV cases increased from 0.2% in 2013 to 0.4% in 2018, with a total of 17.5 million cases reported by 2022. A unique characteristic of HBV is its ability to persist in hepatocytes even after clinical recovery has occurred. This is due to its occult nature (Occult Hepatitis B Infection or OBI), in which HBV DNA remains in the form of covalently closed circular DNA (cccDNA), a stable form capable of persisting long-term. Although cccDNA is not actively active, it may still undergo limited translation and has the potential to be transmitted to others. This condition is particularly concerning as OBI cannot be detected using routine antigen-antibody rapid tests such as HBsAg tests. One factor that influences the severity of HBV infection is the viral genotype. Research on OBI and HBV genotypes, especially in Java Island and specifically Jember, remains limited. Therefore, this study aims to investigate the prevalence of OBI and the circulating HBV genotypes in the Jember Regency. The findings are expected to inform public health policies for the prevention and management of HBV infection in this region. To support the development of effective and efficient antiviral therapies, this study also includes computational analysis through molecular docking between commonly used antiviral agents in Indonesia and the HBV DNA sequences obtained from the OBI and genotype analysis.

This study employs a descriptive exploratory research design using a cross-sectional approach. Serum samples from healthy blood donors were collected at the Indonesian Red Cross (PMI) in Jember Regency. As positive controls, serum samples from HBsAg-positive patients were collected from Dr. Soebandi Regional General Hospital, Jember Klinik Plantation Hospital, and Kaliwates General Hospital. All participants provided informed consent before sample collection. HBV DNA isolation and nested PCR were conducted at VG-Care, 108 Military Central Hospital, Hanoi, Vietnam, using the QIAamp DNA Mini Kit. Nested PCR was performed in two stages using specific primers (HBV 022, 065, 066 for the outer PCR; HBV 024, 041, 064 for the inner PCR), targeting the S/P region (332 bp) of the HBV genome. Positive HBV DNA or OBI samples were sent to the Institute of Tropical Medicine at the University of Tübingen, Germany, for sequencing and phylogenetic analysis. The DNA sequences were assembled using SeqMan software and aligned using MAFFT version 7. Phylogenetic trees were constructed using MEGA 11 software with the neighbor-joining method and the K2+G evolutionary model, and 1000 bootstrap replications were performed to

ensure reliability. The resulting trees were visualized using the iTOL platform. Subsequent mutation analysis was performed using BioEdit and geno2pheno software. The HBV DNA sequences (OBI) with identified mutations were then used as receptors in molecular docking tests. The 3D structures of HBV sequences were predicted using PyMOL, while ligand structures were obtained from the PubChem database. The antiviral agents tested as ligands included tenofovir, adefovir, entecavir, lamivudine, and telbivudine. Docking results were visualized using BIOVIA Discovery Studio.

The analysis of HBV DNA from donor serum samples revealed an OBI prevalence of 2.8%, with 9 out of 330 blood donor samples testing positive for HBV DNA via nested PCR. All OBI samples were identified as genotype B. Among them, 5 samples (A6, A8, A25, D59, and E20) were classified as subgenotype B3, while the remaining 4 samples (A23, C24, C32, and E28) were subgenotype B4. All OBI samples exhibited various mutations in both the RT Pol and S domains. In the S domain, P127T and N207S mutations were found in 55.6% of OBI samples. In the RT Pol domain, N124H and N134D mutations were detected in all confirmed OBI samples. Mutations in the S domain may impair detection by rapid tests, while those in the RT Pol domain are associated with antiviral resistance. All DNA sequences were subjected to molecular docking with antiviral agents used in Indonesia. The results showed that lamivudine and tenofovir had the lowest ΔG values and the least stable interactions, indicating potentially reduced sensitivity to circulating HBV strains in Jember. In contrast, telbivudine exhibited the highest ΔG values, suggesting that it remains highly effective against HBV in this region.

In conclusion, the prevalence of OBI in Jember Regency was found to be 2.8%, with HBV genotype B being the dominant strain, specifically subgenotypes B3 and B4. Lamivudine and tenofovir showed a potential for resistance, based on its lower ΔG values compared to the positive control. Conversely, telbivudine remains highly sensitive and potentially effective for treating HBV infections in Jember.

PREFACE

All praises and gratitude are due to Allah SWT for His blessings and grace, enabling the author to complete this thesis titled: “Development of Anti-HBV Strategies In Jember: Integrating Prevalence, Molecular Surveillance, and In Silico Screening” This thesis is prepared as a requirement to fulfill the completion of a Master’s degree (S2) program at the Faculty of Pharmacy, University of Jember.

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LIST OF NOTATIONS

ΔG	: Binding Affinity
$^{\circ}\text{C}$	: Degrees Celsius
bp	: Base pairs
g	: Grams
IU/mL	: International Units per milliliter
mg	: Milligrams
ml	: Milliliter
ng	: Nanograms
μL	: Microliters
μg	: Micrograms

LIST OF TERMS AND ABBREVIATIONS

Abbreviations/Terms	Meaning and Description
ADMET	Absorption, Distribution, Metabolism, and Excretion
cccDNA	Covalently Closed Circular DNA
CHB	Chronic Hepatitis B
DDB1	DNA damage-binding protein 1
DNA	Deoxyribonucleic Acid
HBeAg	Hepatitis B e Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HIV	Human Immunodeficiency Virus
iTOL	Interactive Tree of Life
K2+G	Kimura 2-Parameter + Gamma Distribution
L175S	Leucine (L) to Serine (S) substitution at position 175
L209V	Leucine (L) to Valine (V) substitution at position 209
L217R	Leucine (L) to Arginine (R) substitution at position 217
M198I	Methionine (M) to Isoleucine (I) substitution at position 198
MAFFT	Multiple Alignment using Fast Fourier Transform
MEGA	Molecular Evolutionary Genetics Analysis
N123H	Asparagine (N) to Histidine (H) substitution at position 123
N124H	Asparagine (N) to Histidine (H) substitution at position 124
N134D	Asparagine (N) to Aspartic Acid (D) substitution at position 134
N207S	Asparagine (N) to Serine (S) substitution at position 207
NF- κ B	Nuclear Factor Kappa B
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NTCP	Sodium Taurocholate Cotransporting Polypeptide
OBI	Occult Hepatitis B Infection
ORFs	Open Reading Frames
PCR	Polymerase Chain Reaction
pgRNA	Pregenomic RNA
QSAR	Quantitative Structure-Activity Relationship
rcDNA	relaxed circular DNA
Risikesdas	Riset Kesehatan Dasar (Basic Health Research)
RT Pol	Reverse Transcriptase Polymerase
S/P	Surface/Pre-region
S135Y	Serine (S) to Tyrosine (Y) substitution at position 135

Abbreviations/Terms	Meaning and Description
S193L	Serine (S) to Leucine (L) substitution at position 193
SMC5/6	Structural Maintenance of Chromosomes 5/6
SVPs	Subviral Particles
T189I	Threonine (T) to Isoleucine (I) substitution at position 189
V184A	Valine (V) to Alanine (A) substitution at position 184
V207M	Valine (V) to Methionine (M) substitution at position 207
VG – Care	Vietnamese-German Center for Medical Research
WHO	World Health Organization
Y161F	Tyrosine (Y) to Phenylalanine (F) substitution at position 161
Y206C	Tyrosine (Y) to Cysteine (C) substitution at position 206

CHAPTER I. INTRODUCTION

1.1. Background

Hepatitis is a condition characterized by liver inflammation caused by infections (viruses) or non-infectious agents, potentially leading to various health issues, including mortality. Generally, the five main types of hepatitis viruses that infect humans are A, B, C, D, and E, each varying in transmission methods, disease severity, and prevention strategies (World Health Organization, 2023a). Hepatitis B can cause both acute and chronic hepatitis infections increasing the risk of cirrhosis and liver cancer. The transmission of hepatitis B can spread through horizontal transmission (unprotected sex, sharing syringes, or contact with infected blood) and vertical transmission (from mother to her baby during childbirth) (Tripathi and Mousa, 2023). Hepatitis B can survive outside the body for up to 7 days and can infect unvaccinated individuals if it enters their body. Incubation for the hepatitis B virus typically requires 30 to 180 days with the detection of genetic material occurring within 30 to 60 days of infection (World Health Organization, 2023b). Many newly infected show don't have symptoms, but some may experience acute symptoms that can last for several weeks, such as jaundice, dark urine, fatigue, nausea, vomiting, abdominal pain, and a lot of people will recover from acute illness, chronic hepatitis B can lead to progressive liver disease and complications such as cirrhosis and HCC (World Health Organization, 2023b).

According to the WHO, hepatitis viruses cause 1.4 million deaths worldwide each year due to acute hepatitis infection, HCC, and liver cirrhosis, with mortality rising. Since 2000 hepatitis C and B have been responsible for 48% and 47% of these deaths, respectively (Kementarian Kesehatan Republik Indonesia, 2020). In 2019, the WHO estimated that 296 million people were living with chronic Hepatitis B infection with 1.5 million new infections each year (World Health Organization, 2023b). Southeast Asia has approximately 61 million Hepatitis B cases, with Indonesia having the highest prevalence (Nguyen *et al.*, 2020). Data from Riset Kesehatan Dasar (Riskesdas) showed diagnosed hepatitis

CHAPTER 2. LITERATURE REVIEW

2.1. Viral Infection and Hepatitis

The globalization trend has led to an increased spread of infectious diseases, with viral infections emerging as major global health threats, exemplified by the COVID-19 pandemic and monkeypox outbreaks. Viruses, which are small particles containing genetic material (DNA or RNA), replicate only within host cells. While some viruses, like hepatitis viruses, are endemic in regions with poor sanitation, most viral infections affect the gastrointestinal (e.g., hepatitis viruses) and respiratory tracts (e.g., COVID-19) (Kotra, 2019). Viral transmission occurs rapidly through contact with infected individuals or contaminated surfaces, particularly endangering immunocompromised individuals, the elderly, newborns, and those with underlying health conditions (Barker, Stevens and Bloomfield, 2001).

Viral pathogenesis requires a sufficient viral load, interaction with susceptible cells, and an inadequate host immune response. Each virus has distinct mechanisms of entry, such as hepatitis viruses targeting digestive tract epithelial cells and COVID-19 infecting respiratory epithelial cells. These entry pathways influence disease progression, determining whether infections remain localized or spread systemically (Burrell, Howard and Murphy, 2017). The infection process is shaped by three main factors: the virus, the host, and the environment. After entry, viruses undergo incubation and latency periods before reaching the immunogenicity threshold needed to trigger an immune response. Incubation periods vary, with localized infections (e.g., respiratory viruses) having shorter durations (2-5 days), while blood-borne viruses (e.g., rabies) exhibit longer latency (Figure 2.1.1). Immunogenicity varies across viruses; some, like measles and rubella, induce lifelong immunity, whereas others, such as HIV-1, evade immune responses through complex mechanisms (Kaslow, 2014).

CHAPTER 3. RESEARCH METHODOLOGY

3.1. Type of Research

The type of this research is exploratory and descriptive with a cross-sectional study method through genomic analysis of hepatitis B and an epidemiological study of Occult Hepatitis B Infection.

3.2. Location and Time of Research

This study was conducted from February 2024 to July 2024 at different locations for sample preparation and testing. Sample preparation was carried out at the Biochemistry Laboratory of the Faculty of Medicine, University of Jember. DNA extraction and Nested PCR were performed at the Vietnamese-German Center for Medical Research (VG-CARE), 108 Military Central Hospital, Vietnam. Positive HBV results from the Nested PCR were then sent to the Institute of Tropical Medicine, Universitätsklinikum Tübingen, Tübingen, Germany, for purification, sequencing, and genotype determination.

3.3. Population and Samples of Research

The samples in this study consisted of serum from HBsAg-reactive patients and serum from blood donors who tested negative for HBsAg, anti-HCV, anti-HIV, and syphilis using rapid tests. Serum from HBsAg-reactive patients was collected from hospitals in Jember Regency, including dr. Soebandi Regional Hospital, Jember Klinik General Hospital, Kaliwates General Hospital, Citra Husada Hospital, and Bina Sehat Hospital. Meanwhile, serum samples from blood donors were collected from the Blood Donor Bank of Palang Merah Indonesia (PMI) in Jember Regency.

3.4. Ethical Clearance

The Ethics Committee of the Faculty of Medicine, University of Jember (Jember, Indonesia) has approved the research protocol with Ethics Approval

CHAPTER 4. RESULT AND DISCUSSION

5.1. Basic Characteristics of Samples

Three hundred thirty serum samples were collected from prospective blood donors at the Indonesian Red Cross (PMI) in Jember Regency. All donors were residents of Jember Regency, with the youngest being 16 years old, the oldest 65 years old, and a median age of 37 years. The ratio of female to male donors was 1:5. Additionally, we collected 14 samples from HbSAg-reactive (+) patients from Dr. Soebandi Regional Hospital (RSDS), Jember Klinik Hospital (RSJK), and Kaliwates General Hospital (RSUK). The patients' ages ranged from 27 to 74 years, with a median age of 45. The ratio of female to male patients was 1:2. The basic characteristics data are presented in Table 4.1.1.

5.2. Optimization of Nested PCR

Optimization was conducted in two stages, namely annealing temperature optimization and DNA template concentration optimization. The main procedure for nested PCR was based on previous studies conducted by Tung *et al.*, 2022; Hoan *et al.*, 2021; Al Baqlani *et al.*, 2014; and Oluyinka *et al.*, 2015, with modifications made to the nested PCR temperature settings due to differences in laboratory conditions and PCR equipment used in this study. The results of the annealing temperature optimization are presented in Figures 4.2.2 (A) and (B), which demonstrate that the nested PCR performed using the Mastercycler Nexus PCR machine in the VG Care laboratory yielded optimal results under the following conditions for the outer PCR: initial denaturation at 94°C for 3 minutes, denaturation at 94°C for 30 seconds, annealing at 55°C for 30 seconds, extension at 72°C for 30 seconds, and final extension at 72°C for 10 minutes, for a total of 35 cycles. For the inner PCR, the conditions were similar to those of the outer PCR, except for the annealing temperature, which was optimized at 63°C for 30 seconds, with a total of 30 cycles.

CHAPTER 5. CONCLUSION AND RECOMENDATIONS

5.1. Conclusion

1. The study concludes that the prevalence of OBI in Jember Regency is 2.8%, which is significantly higher than the global OBI prevalence of 0.3%. This finding indicates a considerable hidden burden of HBV infection in the region. Additionally, two out of fourteen HBsAg-positive samples tested negative by nested PCR, suggesting the possibility of false-positive HBsAg results. However, this remains a hypothesis and requires further investigation for validation.
2. Genotype analysis of all OBI-positive samples indicated that all belonged to genotype B. Further subgenotyping revealed that five samples were classified as subgenotype B3 (A6, A8, A25, D59, and E20), while four samples were classified as subgenotype B4 (A23, C24, C32, and E28). This suggests that genotype B, particularly subgenotypes B3 and B4, predominates in HBV strains circulating in the Jember region.
3. The molecular docking analysis revealed reduced binding affinities between mutated HBV proteins and five antiviral ligands, with Lamivudine and Tenofovir consistently demonstrating the most notable decrease in binding efficacy. Mutations observed in the pre S/S and Reverse Transcriptase Polymerase gene domains, such as P127T, N270S, N124H, and N134D, likely alter the structural conformation of the binding sites. The most common types of molecular interactions involved van der Waals forces, hydrogen bonds, and carbon-hydrogen bonds.

5.2. Recomendations

Researchers recommend that to accurately diagnose HBV patients and prevent the spread of HBV through blood donation, testing should be conducted using both HBsAg and PCR methods. Additionally, Further experimental

validation is required to confirm the biological impact of the mutations on antiviral therapeutic efficacy in cases of occult hepatitis B infection (OBI). The researchers also emphasize the need for further studies on the three-dimensional structural characterization of the HBV DNA, particularly in the conserved S/P region, through crystallographic approaches. In addition, continuous monitoring of the therapeutic effectiveness of antiviral agents, especially nucleos(t)ide analogs, is essential to anticipate and manage potential resistance due to viral mutations.

LIST OF REFERENCES

- Abdelnabi, Z., Saleh, N., Baraghithi, S., Glebe, D., & Azzeh, M. (2014). Subgenotypes and mutations in the s and polymerase genes of hepatitis b virus carriers in the west bank, palestine. *PLoS ONE*, 9(12), 1–16. <https://doi.org/10.1371/journal.pone.0113821>
- Adelusi, T. I., Oyedele, A. Q. K., Boyenle, I. D., Ogunlana, A. T., Adeyemi, R. O., Ukachi, C. D., Idris, M. O., Olaoba, O. T., Adedotun, I. O., Kolawole, O. E., Xiaoxing, Y., & Abdul-Hammed, M. (2022). Molecular modeling in drug discovery. *Informatics in Medicine Unlocked*, 29(February), 100880. <https://doi.org/10.1016/j.imu.2022.100880>
- Agu, P. C., Afiukwa, C. A., Orji, O. U., Ezech, E. M., Ofoke, I. H., Ogbu, C. O., Ugwuja, E. I., & Aja, P. M. (2023). Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. *Scientific Reports*, 13(1), 1–18. <https://doi.org/10.1038/s41598-023-40160-2>
- Ahmed, E. A., Mohammed, A. E., Mohamed Nour, B. Y., Talha, A. A., Hamid, Z., Elshafia, M. A., Elshafia, M. A., & Salih, M. E. (2022). The Possibilities of Chronic Renal Failure Patients Contracting Occult Hepatitis B Virus Infection, Sudan. *Advances in Microbiology*, 12(03), 91–102. <https://doi.org/10.4236/aim.2022.123008>
- Al Baqlani, S. A., Sy, B. T., Ratsch, B. A., Al Naamani, K., Al Awaidy, S., Al Busaidy, S., Pauli, G., & Bock, C. T. (2014). Molecular epidemiology and genotyping of hepatitis B virus of HBsAg-positive patients in Oman. *PLoS ONE*, 9(5), 1–10. <https://doi.org/10.1371/journal.pone.0097759>
- Alavian, S. M., Carman, W. F., & Jazayeri, S. M. (2013). HBsAg variants: Diagnostic-escape and diagnostic dilemma. *Journal of Clinical Virology*, 57(3), 201–208. <https://doi.org/10.1016/j.jcv.2012.04.027>
- Allain, J. P. (2004). Occult hepatitis B virus infection. *Transfusion Clinique et Biologique*, 11(1), 18–25. <https://doi.org/10.1016/j.tracli.2003.11.007>
- Araujo, N. M., Branco-Vieira, M., Silva, A. C. M., Pilotto, J. H., Grinsztejn, B., de Almeida, A. J., Trepo, C., & Gomes, S. A. (2008). Occult hepatitis B virus infection in HIV-infected patients: Evaluation of biochemical, virological and molecular parameters. *Hepatology Research*, 38(12), 1194–1203. <https://doi.org/10.1111/j.1872-034X.2008.00392.x>
- Aydın, M., Tekin, S., Sayan, M., & Akhan, S. (2019). Molecular Characterization of Hepatitis B Virus Strains Isolated from Chronic Hepatitis B Patients in Southeastern Region of Turkey. *Viral Hepatitis Journal*, 25(2), 40–44. <https://doi.org/10.4274/vhd.galenos.2019.2019.0015>
- Barker, J., Stevens, D., & Bloomfield, S. F. (2001). Spread and prevention of some common viral infections in community facilities and domestic homes. *Journal of Applied Microbiology*, 91(1), 7–21. <https://doi.org/10.1046/j.1365-2672.2001.01364.x>
- Baroroh, S.Si., M.Biotek., U., Muscifa, Z. S., Destiarani, W., Rohmatullah, F. G., & Yusuf, M. (2023). Molecular interaction analysis and visualization of

- protein-ligand docking using Biovia Discovery Studio Visualizer. *Indonesian Journal of Computational Biology (IJCB)*, 2(1), 22. <https://doi.org/10.24198/ijcb.v2i1.46322>
- Bartholomeusz, A., & Locarnini, S. A. (2006). Antiviral drug resistance: Clinical consequences and molecular aspects. *Seminars in Liver Disease*, 26(2), 162–170. <https://doi.org/10.1055/s-2006-939758>
- Bello, K. (2023). The Principles and New Approaches in Nested Polymerase Chain Reactions. *Journal Data Mining Genomics Proteomics*, 14(2). <https://doi.org/10.4172/2153-0602.23.14.285>
- Bottecchia, M., Madejón, A., Sheldon, J., García-Samaniego, J., Barreiro, P., & Soriano, V. (2008). Hepatitis B virus genotype A2 harbours an L217R polymorphism which may account for a lower response to adefovir. *Journal of Antimicrobial Chemotherapy*, 62(3), 626–627. <https://doi.org/10.1093/jac/dkn207>
- Broquetas, T., & Carrión, J. A. (2022). Current Perspectives on Nucleos(t)ide Analogue Therapy for the Long-Term Treatment of Hepatitis B Virus. *Hepatic Medicine: Evidence and Research*, Volume 14(July), 87–100. <https://doi.org/10.2147/hmer.s291976>
- Bubonja-Šonje, M., Peruč, D., Abram, M., & Mohar-Vitezić, B. (2024). Prevalence of occult hepatitis B virus infection and characterisation of hepatitis B surface antigen mutants among adults in western Croatia. *Annals of Hepatology*, 29(1). <https://doi.org/10.1016/j.aohp.2023.101156>
- Buhlig, T. S., Bowersox, A. F., Braun, D. L., Owsley, D. N., James, K. D., Aranda, A. J., Kendrick, C. D., Skalka, N. A., & Clark, D. N. (2020). Molecular, evolutionary, and structural analysis of the terminal protein domain of hepatitis B virus polymerase, a potential drug target. *Viruses*, 12(5), 1–19. <https://doi.org/10.3390/v12050570>
- Burrell, C. J., Howard, C. R., & Murphy, F. A. (2017). Pathogenesis of Virus Infections. *Fenner and White's Medical Virology*, January, 77–104. <https://doi.org/10.1016/b978-0-12-375156-0.00007-2>
- Caligiuri, P., Cerruti, R., Icardi, G., & Bruzzone, B. (2016). Overview of hepatitis B virus mutations and their implications in the management of infection. *World Journal of Gastroenterology*, 22(1), 145–154. <https://doi.org/10.3748/wjg.v22.i1.145>
- Candotti, D., & Laperche, S. (2018). Hepatitis B virus blood screening: Need for reappraisal of blood safety measures? *Frontiers in Medicine*, 5(FEB), 1–10. <https://doi.org/10.3389/fmed.2018.00029>
- CDA Foundation. (2022). *Data Infeksi Hepatitis B dan Hepatitis C di Indonesia*. <https://cdfound.org/polaris-countries-dashboard/>
- Centers for Disease Control and Prevention. (2024). *Global Viral Hepatitis*. Centers for Disease Control and Prevention. <https://www.cdc.gov/hepatitis/global/index.html>
- Chaudhuri, V., Tayal, R., Nayak, B., Acharya, S. K., & Panda, S. K. (2004). Occult hepatitis B virus infection in chronic liver disease: Full-length genome and analysis of mutant surface promoter. *Gastroenterology*, 127(5), 1356–1371. <https://doi.org/10.1053/j.gastro.2004.08.003>

- Choi, Y. M., Lee, S. Y., & Kim, B. J. (2019). Naturally occurring hepatitis B virus mutations leading to endoplasmic reticulum stress and their contribution to the progression of hepatocellular Carcinoma. *International Journal of Molecular Sciences*, 20(3). <https://doi.org/10.3390/ijms20030597>
- Chothia, C., & Lesk, A. M. (1986). The relation between the divergence of sequence and structure in proteins. *The EMBO Journal*, 5(4), 823–826. <https://doi.org/10.1002/j.1460-2075.1986.tb04288.x>
- Chu, S. V., Vu, S. T., Nguyen, H. M., Le, N. T., Truong, P. T., Vu, V. T. T., Phung, T. T. B., & Nguyen, A. T. V. (2021). Fast and Sensitive Real-Time PCR Detection of Major Antiviral-Drug Resistance Mutations in Chronic Hepatitis B Patients by Use of a Predesigned Panel of Locked-Nucleic-Acid TaqMan Probes. *Journal of Clinical Microbiology*, 59(10), 1–16. <https://doi.org/10.1128/JCM.00936-21>
- Coppola, N., Onorato, L., Minichini, C., Di Caprio, G., Starace, M., Sagnelli, C., & Sagnelli, E. (2015). Clinical significance of hepatitis B surface antigen mutants. *World Journal of Hepatology*, 7(27), 2729–2739. <https://doi.org/10.4254/wjh.v7.i27.2729>
- Dahiya, M., Tai, T., Hussaini, T., Ritchie, G., Matic, N., Yoshida, E. M., & Lowe, C. F. (2025). Virological Response to Lamivudine and Tenofovir Treatment in a Mono-infected Chronic Hepatitis B Patient with Potential Tenofovir Resistance: A Case Report. *Journal of Clinical and Translational Hepatology*, 13(1), 84–87. <https://doi.org/10.14218/JCTH.2024.00248>
- Datta, S., Banerjee, A., Chandra, P. K., Chakraborty, S., Basu, S. K., & Chakravarty, R. (2007). Detection of a premature stop codon in the surface gene of hepatitis B virus from an HBsAg and antiHBc negative blood donor. *Journal of Clinical Virology*, 40(3), 255–258. <https://doi.org/10.1016/j.jcv.2007.08.003>
- Datta, S., Chatterjee, S., Veer, V., & Chakravarty, R. (2012). Molecular Biology of the Hepatitis B Virus for Clinicians. *Journal of Clinical and Experimental Hepatology*, 2(4), 353–365. <https://doi.org/10.1016/j.jceh.2012.10.003>
- de Almeida, R. W., do Amaral Mello, F. C., Menegoy, I. V., do Espírito Santo, M. P., Ginuino, C. F., de Sousa, P. S. F., Villar, L. M., Lampe, E., & Lewis-Ximenez, L. L. (2017). Detection and molecular characterisation of a diagnosis escape variant associated with occult hepatitis B virus in Brazil. *Memorias Do Instituto Oswaldo Cruz*, 112(7), 485–491. <https://doi.org/10.1590/0074-02760160477>
- Di Stefano, M., Faleo, G., Leitner, T., Zheng, W., Zhang, Y., Hassan, A., Alwazze, M. J., Fiore, J. R., Ismail, M., & Santantonio, T. A. (2023). Molecular and Genetic Characterization of Hepatitis B Virus (HBV) among Saudi Chronically HBV-Infected Individuals. *Viruses*, 15(2), 1–13. <https://doi.org/10.3390/v15020458>
- Dinas Kesehatan Provinsi JawaTimur. (2022). *Profil Kesehatan Provinsi Jawa Timur Tahun 2022*. [https://dinkes.jatimprov.go.id/userfile/dokumen/PROFIL KESEHATAN JATIM 2022](https://dinkes.jatimprov.go.id/userfile/dokumen/PROFIL%20KESEHATAN%20JATIM%202022)
- DiPiro, J. T., Yee, G. C., Haines, S. T., Nolin, T. D., Ellingrod, V. L., & Posey, L. M. (2023). *DiPiro's Pharmacotherapy: A Pathophysiologic Approach*. In

- McGraw hill LLC (12th ed., Vol. 12). McGraw Hill.
- Dzudzor, B., Nsowah, K. K., Agyemang, S., Vento, S., Amarh, V., Boima, V., & Tachi, K. (2024). Overt and occult hepatitis B virus infection detected among chronic kidney disease patients on haemodialysis at a Tertiary Hospital in Ghana. *PLoS ONE*, 19(3 March), 1–13. <https://doi.org/10.1371/journal.pone.0290917>
- Efficient implementation of hepatitis B surface antigen confirmatory neutralization tests. (2024). In *Journal of Infection and Chemotherapy* (Vol. 30, Issue 1, pp. 29–33).
- Enriquez-Navarro, K., Maldonado-Rodriguez, A., Rojas-Montes, O., Torres-Ibarra, R., Bucio-Ortiz, L., De la Cruz, M. A., Torres-Flores, J., Xoconostle-Cazares, B., & Lira, R. (2020). Identification of mutations in the S gene of hepatitis B virus in HIV positive Mexican patients with occult hepatitis B virus infection. *Annals of Hepatology*, 19(5), 507–515. <https://doi.org/10.1016/j.aohp.2020.06.002>
- Fan, J., Wang, Y., Xiong, H., Guo, X., & Cheng, Y. C. (2014). Impact of the rti187V polymerase substitution of hepatitis B virus on viral replication and antiviral drug susceptibility. *Journal of General Virology*, 95, 2523–2530. <https://doi.org/10.1099/vir.0.066886-0>
- Gerlich, W. H., Glebe, D., Kramvis, A., & Magnus, L. O. (2020). Peculiarities in the designations of hepatitis B virus genes, their products, and their antigenic specificities: a potential source of misunderstandings. *Virus Genes*, 56(2), 109–119. <https://doi.org/10.1007/s11262-020-01733-9>
- Hadi, S. N. (2021). POLYMERASE CHAIN REACTION (PCR). In B. Prakoso & K. Setiawan (Eds.), *BUKU AJAR TEKNIK-TEKNIK DASAR BIOTEKNOLOGI* (pp. 23–32). UNSOED Press.
- Hamidi-Fard, M., Makvandi, M., Samarbaf-Zadeh, A., Hajiani, E., Shayesteh, A., & Masjedizadeh, A. (2013). Mutation analysis of hepatitis B virus reverse transcriptase region among untreated chronically infected patients in Ahvaz city (South-West of Iran). *Indian Journal of Medical Microbiology*, 31(4), 360–365. <https://doi.org/10.4103/0255-0857.118882>
- Han, J. J., Hu, Y. A., Nan, Y., Chen, Y., & Yang, Y. L. (2023). Decreased expression of HBV surface antigen (HBsAg) with sK122R and sV96A co-mutation is associated with an ineffective antibody response in a chronic hepatitis B patient. *Infection, Genetics and Evolution*, 111(February), 1–7. <https://doi.org/10.1016/j.meegid.2023.105431>
- He, X., Wang, F., Huang, B., Chen, P., & Zhong, L. (2015). Detection and analysis of resistance mutations of hepatitis B virus. *International Journal of Clinical and Experimental Medicine*, 8(6), 9630–9639.
- Hirano, A., Iwashita, K., Ura, T., Sakuraba, S., Shiraki, K., Arakawa, T., & Kameda, T. (2019). The binding affinity of uncharged aromatic solutes for negatively charged resins is enhanced by cations via cation– π interactions: The case of sodium ion and arginine. *Journal of Chromatography A*, 1595, 97–107. <https://doi.org/10.1016/j.chroma.2019.02.043>
- Hoan, N. X., Hoechel, M., Tomazatos, A., Anh, C. X., Pallerla, S. R., Linh, L. T. K., Binh, M. T., Sy, B. T., Toan, N. L., Wedemeyer, H., Bock, C. T.,

- Kremsner, P. G., Meyer, C. G., Song, L. H., & Velavan, T. P. (2021). Predominance of hbv genotype b and hdv genotype 1 in vietnamese patients with chronic hepatitis. *Viruses*, 13(2), 1–12. <https://doi.org/10.3390/v13020346>
- Hosseini, S. Y., Sanaei, N., Fattahi, M. R., Malek-Hosseini, S. A., & Sarvari, J. (2019). Association of HBsAg mutation patterns with hepatitis B infection outcome: Asymptomatic carriers versus HCC/cirrhotic patients. *Annals of Hepatology*, 18(4), 640–645. <https://doi.org/10.1016/j.aohp.2018.12.006>
- Hoy, M. A. (2019). DNA Amplification by the Polymerase Chain Reaction: Providing a Revolutionary Method for All Biologists. In *Insect Molecular Genetics*. <https://doi.org/10.1016/b978-0-12-815230-0.00007-8>
- Hu, K. Q. (2002). Occult hepatitis B virus infection and its clinical implications. *Journal of Viral Hepatitis*, 9(4), 243–257. <https://doi.org/10.1046/j.1365-2893.2002.00344.x>
- Hudu, S. A., Harmal, N. S., Saeed, M. I., Alshrari, A. S., Malik, Y. A., Niazlin, M. T., Hassan, R., & Sekawi, Z. (2016). Molecular and serological detection of occult hepatitis B virus among healthy hepatitis B surface antigen-negative blood donors in Malaysia. *African Health Sciences*, 16(3), 677–683. <https://doi.org/10.4314/ahs.v16i3.6>
- Huong, N. T. C., Trung, N. Q., Luong, B. A., Tram, D. B., Vu, H. A., Bui, H. H., & Le, H. P. T. (2022). Mutations in the HBV PreS/S gene related to hepatocellular carcinoma in Vietnamese chronic HBV-infected patients. *PLoS ONE*, 17(4 April), 1–19. <https://doi.org/10.1371/journal.pone.0266134>
- Im, Y. R., Jagdish, R., Leith, D., Kim, J. U., Yoshida, K., Majid, A., Ge, Y., Ndow, G., Shimakawa, Y., & Lemoine, M. (2022). Prevalence of occult hepatitis B virus infection in adults: a systematic review and meta-analysis. *The Lancet Gastroenterology and Hepatology*, 7(10), 932–942. [https://doi.org/10.1016/S2468-1253\(22\)00201-1](https://doi.org/10.1016/S2468-1253(22)00201-1)
- Jiang, X., Chang, L., Yan, Y., Ji, H., Sun, H., Xiao, Y., Song, S., Feng, K., Nuermaimaiti, A., & Wang, L. (2022). Role of S protein transmembrane domain mutations in the development of occult hepatitis B virus infection. *Emerging Microbes and Infections*, 11(1), 2184–2196. <https://doi.org/10.1080/22221751.2022.2114849>
- Kao, J. H. (2011). Molecular epidemiology of hepatitis B virus. *Korean Journal of Internal Medicine*, 26(3), 255–261. <https://doi.org/10.3904/kjim.2011.26.3.255>
- Kao, J. H. (2021). Hepatitis B virus and liver disease. In *Hepatitis B Virus and Liver Disease*. <https://doi.org/10.1007/978-981-16-3615-8>
- Kaslow, R. A. (2014). Viral infections of humans: Epidemiology and control. In *Viral Infections of Humans: Epidemiology and Control*. <https://doi.org/10.1007/978-1-4899-7448-8>
- Kementerian Kesehatan Republik Indonesia. (2018). Laporan Nasional RISKESDAS 2018. In *Badan Penelitian dan Pengembangan Kesehatan* (Vol. 44, Issue 8). [http://www.yankes.kemkes.go.id/assets/downloads/PMK No. 57 Tahun 2013 tentang PTRM.pdf](http://www.yankes.kemkes.go.id/assets/downloads/PMK%20No.%2057%20Tahun%202013%20tentang%20PTRM.pdf)
- Kementerian Kesehatan Republik Indonesia. (2020). *Rencana Aksi Nasional*

- Pencegahan dan Pengendalian Hepatitis.*
https://www.globalhep.org/sites/default/files/content/action_plan_article/files/2022-05/RAN HEP 2020-2024 KDT_0.pdf
- Kementerian Kesehatan Republik Indonesia. (2023). *Manajemen Program Hepatitis B dan C*. Kementerian Kesehatan Republik Indonesia.
https://cdn.who.int/media/docs/default-source/searo/indonesia/non-who-publications/2023-guideline-for-program-management-of-hepatitis-b-and-c.pdf?sfvrsn=f7373309_1&download=true
- Khalil, M. I. (2021). Different types of PCR and their function. *Global Scientific Journal*, 9(2), 758–768. <https://doi.org/10.11216/gsj.2021.02.48315>
- Kho-Herman, S. G. R., & Chan, H. L. Y. (2017). Stopping nucleos(t)ide analog treatment in chronic hepatitis B — Who and when? *Liver Research*, 1(2), 135–139. <https://doi.org/10.1016/j.livres.2017.06.002>
- Kotra, L. P. (2019). Viral disease. *The Laboratory Rat*, 541–568. <https://doi.org/10.1016/B978-0-12-814338-4.00013-1>
- Lazarevic, I. (2014). Clinical implications of hepatitis B virus mutations: Recent advances. *World Journal of Gastroenterology*, 20(24), 7653–7664. <https://doi.org/10.3748/wjg.v20.i24.7653>
- Lazarevic, I., Banko, A., Miljanovic, D., & Cupic, M. (2019). Immune-escape hepatitis B virus mutations associated with viral reactivation upon immunosuppression. *Viruses*, 11(9). <https://doi.org/10.3390/v11090778>
- Lipinski, C. A. (2004). Lead- and drug-like compounds: The rule-of-five revolution. *Drug Discovery Today: Technologies*, 1(4), 337–341. <https://doi.org/10.1016/j.ddtec.2004.11.007>
- Locarnini, S., & Mason, W. S. (2006). Cellular and virological mechanisms of HBV drug resistance. *Journal of Hepatology*, 44(2), 422–431. <https://doi.org/10.1016/j.jhep.2005.11.036>
- Lorenz, T. C. (2012). Polymerase Chain Reaction: Basic Protocol Plus Troubleshooting and Optimization Strategies. *Journal of Visualized Experiments*, 63(e3998), 1–15. <https://doi.org/10.3791/3998>
- Mabunda, N., Zicai, A. F., Ismael, N., Vubil, A., Mello, F., Blackard, J. T., Lago, B., Duarte, V., Moraes, M., Lewis, L., & Jani, I. (2020). Molecular and serological characterization of occult hepatitis b among blood donors in Maputo, Mozambique. *Memorias Do Instituto Oswaldo Cruz*, 115(8), 1–7. <https://doi.org/10.1590/0074-02760200006>
- Maden, S. F., Sezer, S., & Acuner, S. E. (2016). Fundamentals of Molecular Docking and Comparative Analysis of Protein–Small-Molecule Docking Approaches. *Intech*, 11, 13. <https://www.intechopen.com/books/advanced-biometric-technologies/liveness-detection-in-biometrics>
- Mak, L. Y., Wong, D. K. H., Pollicino, T., Raimondo, G., Hollinger, F. B., & Yuen, M. F. (2020). Occult hepatitis B infection and hepatocellular carcinoma: Epidemiology, virology, hepatocarcinogenesis and clinical significance. *Journal of Hepatology*, 73(4), 952–964. <https://doi.org/10.1016/j.jhep.2020.05.042>
- Maulida, R., Setiawan, B., Nirmalasari, N., Aflanie, I., & Suhartono, E. (2024). DOCKING MOLEKULER FITOKIMIA DAUN KATUK (*Sauropus*

- androgynus) SEBAGAI MODULATOR ENZIM CATHEPSIN. *Homeostasis*, 7(3), 597–604. <https://ppjp.ulm.ac.id/journals/index.php/hms/article/download/14583/7772>
- Mazlan, A. H., Aqhmah, M. H., Najib, M., Hassan, M. H., Yusoff, R. M., & Hatta, F. H. M. (2024). Effect of DNA Template Concentration on Standard Polymerase Chain Reaction. *International Journal of Pharmaceuticals, Nutraceuticals and Cosmetic Science (IJPNaCS)*, 7(1), 1–11. <https://doi.org/10.24191/IJPNaCS.v7i1.01>
- Menéndez-Arias, L., Álvarez, M., & Pacheco, B. (2014). Nucleoside/nucleotide analog inhibitors of hepatitis B virus polymerase: Mechanism of action and resistance. *Current Opinion in Virology*, 8, 1–9. <https://doi.org/10.1016/j.coviro.2014.04.005>
- Michitaka, K., Hiraoka, A., Tsuruta, M., Aibiki, T., Okudaira, T., Yamago, H., Iwasaki, R., Tsubouchi, E., Watanabe, T., Yoshida, O., Abe, M., Ninomiya, T., & Hiasa, Y. (2018). A study on false positive results of hepatitis B surface antigen (HBsAg) test: Frequency of samples considered false positives in relation to the HBsAg concentration. *The Japan Society of Hepatology*, 56(1), 641–646. http://scioteca.caf.com/bitstream/handle/123456789/1091/RED2017-Eng-8ene.pdf?sequence=12&isAllowed=y%0Ahttp://dx.doi.org/10.1016/j.regsciurbeo.2008.06.005%0Ahttps://www.researchgate.net/publication/305320484_SISTEM_PEMBETUNGAN_TERPUSAT_STRATEGI_MELESTARI
- Mirabelli, C., Surdo, M., Van Hemert, F., Lian, Z., Salpini, R., Cento, V., Cortese, M. F., Aragri, M., Pollicita, M., Alteri, C., Bertoli, A., Berkhout, B., Micheli, V., Gubertini, G., Santoro, M. M., Romano, S., Visca, M., Bernassola, M., Longo, R., ... Svicher, V. (2015). Specific mutations in the C-terminus domain of HBV surface antigen significantly correlate with low level of serum HBV-DNA in patients with chronic HBV infection. *Journal of Infection*, 70(3), 288–298. <https://doi.org/10.1016/j.jinf.2014.10.015>
- Modise, L., Sithebe, N., & Mufhandu, H. (2024). Investigation of hepatitis B virus mutations associated with immune escape and drug resistance in human immunodeficiency virus-infected patients. *F1000Research*, 12, 1232. <https://doi.org/10.12688/f1000research.132498.2>
- Mu, S.-C., Wang, G.-M., Jow, G.-M., & Chen, B.-F. (2011). Impact of Universal Vaccination on Intrafamilial Transmission of Hepatitis B Virus. *Journal of Medical Virology*, 83, 783–790. <https://doi.org/10.1002/jmv>
- Mu, S. C., Lin, Y. M., Jow, G. M., & Chen, B. F. (2009). Occult hepatitis B virus infection in hepatitis B vaccinated children in Taiwan. *Journal of Hepatology*, 50(2), 264–272. <https://doi.org/10.1016/j.jhep.2008.09.017>
- Munshi, S. U., Tran, T. T. T., Vo, T. N. T., Tabassum, S., Sultana, N., Nguyen, T. H., Jahan, M., Le, C. N., Baker, S., & Rahman, M. (2017). Molecular characterization of hepatitis B virus in Bangladesh reveals a highly recombinant population. *PLoS ONE*, 12(12), 1–16. <https://doi.org/10.1371/journal.pone.0188944>
- Mustika, S., & Daryadijaya, D. (2019). Prevalence of Hepatitis B Infection Among Male Prisoners in Malang. *The Indonesian Journal of Gastroenterology*,

- Hepatology and Digestive Endoscopy*, 20(1), 7–10. https://www.researchgate.net/publication/362404223_Prevalence_of_Hepatitis_B_Infection_Among_Male_Prisoners_in_Malang
- Nguyen, M. H., Wong, G., Gane, E., Kao, J.-H., & Dusheiko, G. (2020). Hepatitis B Virus: Advances in Prevention, Diagnosis, and Therapy. *Clinical Microbiology Reviews*, 33(2), 1-38-. <https://doi.org/https://doi.org/10.1128/CMR.00046-19>. Copyright
- Nishimaki, T., & Sato, K. (2019). An Extension of the Kimura Two-Parameter Model to the Natural Evolutionary Process. *Journal of Molecular Evolution*, 87(1), 60–67. <https://doi.org/10.1007/s00239-018-9885-1>
- Oluyinka, O. O., Van Tong, H., Bui Tien, S., Fagbami, A. H., Adekanle, O., Ojurongbe, O., Bock, C. T., Kremsner, P. G., & Velavan, T. P. (2015). Occult hepatitis B virus infection in Nigerian blood donors and hepatitis B virus transmission risks. *PLoS ONE*, 10(7), 1–13. <https://doi.org/10.1371/journal.pone.0131912>
- Ostankova, Y. V., Serikova, E. N., Semenov, A. V., Zueva, E. B., Valutite, D. E., Schemelev, A. N., Zurochka, V. A., & Totolian, A. A. (2022). Molecular and genetic characterization of the hepatitis B virus full-length genome sequences identified in HBsAg-negative blood donors in Ural Federal District. *Zhurnal Mikrobiologii Epidemiologii i Immunobiologii*, 99(6), 637–650. <https://doi.org/10.36233/0372-9311-325>
- Ozeki, I., Nakajima, T., Suii, H., Tatsumi, R., Yamaguchi, M., Kimura, M., Arakawa, T., Kuwata, Y., Ohmura, T., Hige, S., Karino, Y., & Toyota, J. (2018). Analysis of hepatitis B surface antigen HBsAg using high-sensitivity HBsAg assays in whom HBsAg seroclearance was confirmed by conventional assays. *Hepatology Research*, 48(3), E263–E274. <https://doi.org/https://doi.org/10.1111/hepr.12979>
- Ozvoldik, K., Stockner, T., & Krieger, E. (2023). YASARA Model-Interactive Molecular Modeling from Two Dimensions to Virtual Realities. *Journal of Chemical Information and Modeling*, 63(20), 6177–6182. <https://doi.org/10.1021/acs.jcim.3c01136>
- Pallier, C., Castéra, L., Soulier, A., Hézode, C., Nordmann, P., Dhumeaux, D., & Pawlotsky, J.-M. (2006). Dynamics of Hepatitis B Virus Resistance to Lamivudine. *Journal of Virology*, 80(2), 643–653. <https://doi.org/10.1128/jvi.80.2.643-653.2006>
- Pantsar, T., & Poso, A. (2018). Binding affinity via docking: Fact and fiction. *Molecules*, 23(8), 1DUMMY. <https://doi.org/10.3390/molecules23081899>
- Patient, R., Hourieux, C., & Roingeard, P. (2009). Morphogenesis of hepatitis B virus and its subviral envelope particles. *Cellular Microbiology*, 11(11), 1561–1570. <https://doi.org/10.1111/j.1462-5822.2009.01363.x>
- PEDOMAN NASIONAL PELAYANAN KEDOKTERAN TATA LAKSANA HEPATITIS B, Pub. L. No. HK.01.07/MENKES/322/2019, Keputusan Menteri Kesehatan (2019). <http://scioteca.caf.com/bitstream/handle/123456789/1091/RED2017-Eng-8ene.pdf?sequence=12&isAllowed=y%0Ahttp://dx.doi.org/10.1016/j.regsciurbeco.2008.06.005%0Ahttps://www.researchgate.net/publication/305320484>

_SISTEM PEMBETUNGAN TERPUSAT STRATEGI MELESTARI

- Pollicino, T., Raffa, G., Costantino, L., Lisa, A., Campello, C., Squadrito, G., Levvero, M., & Raimondo, G. (2007). Molecular and functional analysis of occult hepatitis B virus isolates from patients with hepatocellular carcinoma. *Hepatology*, 45(2), 277–285. <https://doi.org/10.1002/hep.21529>
- Poortahmasebi, V., Poorebrahim, M., Sadeghi, A., Abazari, M. F., Sadredinamin, M., Hasanpoor, E., & Jazayeri, S. M. (2020). Conformational analysis of hepatitis B virus surface antigen mutations among HIV-positive patients diagnosed with occult hepatitis B virus. *Future Virology*, 14(12), 813–827. <https://doi.org/10.2217/fvl-2019-0096>
- Pubchem. (2025a). *Adenofir*. National Institute of Health. <https://pubchem.ncbi.nlm.nih.gov/compound/Adefovir>
- Pubchem. (2025b). *Entecavir*. National Institute of Health. <https://pubchem.ncbi.nlm.nih.gov/compound/Entecavir>
- Pubchem. (2025c). *Lamivudine*. National Institute of Health. <https://pubchem.ncbi.nlm.nih.gov/compound/Lamivudine#section=2D-Structure>
- Pubchem. (2025d). *Telbivudine*. National Institute of Health. <https://pubchem.ncbi.nlm.nih.gov/compound/Telbivudine#section=2D-Structure>
- Pubchem. (2025e). *Tenofovir*. National Institute of Health. <https://pubchem.ncbi.nlm.nih.gov/compound/Tenofovir>
- Rollando, R., Maulada, F., Afthoni, M. H., Monica, E., Yuniati, Y., & Nugraha, A. T. (2023). Screening Carica Papaya Compounds as an Antimalarial Agent: In Silico Study. *Tropical Journal of Natural Product Research*, 7(5), 2895–2903. <https://doi.org/10.26538/tjnpr/v7i5.9>
- Sadeghi, A., Shirvani-Dastgerdi, E., Tacke, F., Yagmur, E., Poortahmasebi, V., Poorebrahim, M., Mohraz, M., Hajabdolbaghi, M., Rasoolinejad, M., Abbasian, L., Jafari, R., Fakhari, Z., Norouzi, M., Ebrahimian, A., Geravand, B., Alavian, S. M., & Jazayeri, S. M. (2017). HBsAg Mutations Related to Occult Hepatitis B Virus Infection in HIV-Positive Patients Result in a Reduced Secretion and Conformational Changes of HBsAg. *Journal of Medical Virology*, 89, 246–256. <https://doi.org/10.1002/jmv>
- Saitou, N., & Nei, M. (1987). The neighbor-joining method: a new method for reconstructing phylogenetic trees. *Molecular Biology and Evolution*, 4(4), 406–425. <https://doi.org/10.1093/oxfordjournals.molbev.a040454>
- Saitta, C., Pollicino, T., & Raimondo, G. (2022). Occult Hepatitis B Virus Infection: An Update. *Viruses*, 14(7). <https://doi.org/10.3390/v14071504>
- Salmaso, V., & Moro, S. (2018). Bridging molecular docking to molecular dynamics in exploring ligand-protein recognition process: An overview. *Frontiers in Pharmacology*, 9(AUG), 1–16. <https://doi.org/10.3389/fphar.2018.00923>
- Salpini, R., Battisti, A., Piermatteo, L., Carioti, L., Anastasiou, O. E., Gill, U. S., Di Carlo, D., Colagrossi, L., Duca, L., Bertoli, A., La Rosa, K. Y., Fabeni, L., Iuvra, A., Malagnino, V., Cerva, C., Lichtner, M., Mastroianni, C. M., De Sanctis, G. M., Paoloni, M., ... Svicher, V. (2020). Key mutations in the C-

- terminus of the HBV surface glycoprotein correlate with lower HBsAg levels in vivo, hinder HBsAg secretion in vitro and reduce HBsAg structural stability in the setting of HBeAg-negative chronic HBV genotype-D infection. *Emerging Microbes and Infections*, 9(1), 928–939. <https://doi.org/10.1080/22221751.2020.1757998>
- Samadi, E., Mirshahabi, H., Motamed, N., & Sadeghi, H. (2020). Prevalence of Occult Hepatitis B Virus Infection in Hemodialysis Patients Using Nested PCR. *Reports of Biochemistry and Molecular Biology*, 9(1), 82–88. <https://doi.org/10.29252/rbmb.9.1.82>
- Seed, C. R., Maloney, R., Kiely, P., Bell, B., Keller, A. J., & Pink, J. (2015). Infectivity of blood components from donors with occult hepatitis B infection - results from an Australian lookback programme. *Vox Sanguinis*, 108(2), 113–122. <https://doi.org/10.1111/vox.12198>
- Shirvani-Dastgerdi, E., Winer, B. Y., Celià-Terrassa, T., Kang, Y., Tabernero, D., Yagmur, E., Rodríguez-Frías, F., Gregori, J., Luedde, T., Trautwein, C., Ploss, A., & Tacke, F. (2017). Selection of the highly replicative and partially multidrug resistant rtS78T HBV polymerase mutation during TDF-ETV combination therapy. *Journal of Hepatology*, 67(2), 246–254. <https://doi.org/10.1016/j.jhep.2017.03.027>
- Siburian, M. D., Utama, A., Dhenni, R., Arnelis, Fanany, I., Intan, M. D. B., Kurniasih, T. S., Andriani, F., Afadlal, S., Julianto, E. B., Rasman, W. S., Zubir, N., & Mathew, G. (2013). High prevalence of hepatitis B virus genotype C/C1 in the Minangkabau ethnic group in Indonesia. *Virology Journal*, 10, 1–11. <https://doi.org/10.1186/1743-422X-10-27>
- Strik, H. J., Thornton, J. M., & Howard, C. R. (1992). A topological model for hepatitis B surface antigen. *Intervirology*, 33, 148–158. <https://pubmed.ncbi.nlm.nih.gov/1500275/>
- Sunbul, M. (2014). Hepatitis B virus genotypes: Global distribution and clinical importance. *World Journal of Gastroenterology*, 20(18), 5427–5434. <https://doi.org/10.3748/wjg.v20.i18.5427>
- Svicher, V., Gori, C., Trignetti, M., Visca, M., Micheli, V., Bernassola, M., Salpini, R., Gubertini, G., Longo, R., Niero, F., Ceccherini-Silberstein, F., De Sanctis, G. M., Spanò, A., Cappiello, G., & Perno, C. F. (2009). The profile of mutational clusters associated with lamivudine resistance can be constrained by HBV genotypes. *Journal of Hepatology*, 50(3), 461–470. <https://doi.org/10.1016/j.jhep.2008.07.038>
- Takuissu, G. R., Kenmoe, S., Atsama, M. A., Okobalembe, E. A., Mbagu, D. S., Ebogo-Belobo, J. T., Bowo-Ngandji, A., Oyono, M. G., Magoudjou-Pekam, J. N., Kame-Ngasse, G. I., Menkem, E. Z., Ngaloumo, A. A. S., Banlock, A. T. R., Feudjio, A. F., Zemnou-Tepap, C., Meta-Djoms, D., Mviena, G. L. N., Eloundou, I. N., Yéngué, J. F., ... Ndip, L. (2022). Global epidemiology of occult hepatitis B virus infections in blood donors, a systematic review and meta-analysis. *PLoS ONE*, 17(8 August), 1–14. <https://doi.org/10.1371/journal.pone.0272920>
- Tamura, K., Stecher, G., & Kumar, S. (2021). MEGA11: Molecular Evolutionary Genetics Analysis Version 11. *Molecular Biology and Evolution*, 38(7), 3022–

3027. <https://doi.org/10.1093/molbev/msab120>
- Thermo Fisher Scientific. (2024). *Tm Calculator*. Thermo Fisher Scientific. <https://www.thermofisher.com/id/en/home/brands/thermo-scientific/molecular-biology/molecular-biology-learning-center/molecular-biology-resource-library/thermo-scientific-web-tools/tm-calculator.html>
- Tripathi, N., & Mousa, O. Y. (2023). Hepatitis B. In *StatPearls [Internet]*. StatPearls Publishing, NCBI.
- Tung, T. T., Schmid, J., Nghia, V. X., Cao, L. C., Linh, L. T. K., Rungsung, I., Sy, B. T., My, T. N., The, N. T., Hoan, N. X., Meyer, C. G., Wedemeyer, H., Kremsner, P. G., Toan, N. L., Song, L. H., Bock, C. T., & Velavan, T. P. (2022). Low Risk of Occult Hepatitis B Infection among Vietnamese Blood Donors. *Pathogens*, 11(12). <https://doi.org/10.3390/pathogens11121524>
- Venkatakrishnan, B., & Zlotnick, A. (2016). The Structural Biology of Hepatitis B Virus: Form and Function. *Annual Review of Virology*, 3, 429–451. <https://doi.org/10.1146/annurev-virology-110615-042238>
- Wang, J., Liu, Y., Liao, H., Liu, L., Chen, R., Si, L., Luo, D., Huang, B., Li, L., Jiang, J., & Xu, D. (2020). The sK122R mutation of hepatitis B virus (HBV) is associated with occult HBV infection: Analysis of a large cohort of Chinese patients. *Journal of Clinical Virology*, 130(December 2019). <https://doi.org/10.1016/j.jcv.2020.104564>
- Wang, J., Zhu, B., Lu, M., & Yang, D. (2017). Hepatitis B virus preS/S gene mutations and their clinical implications. *Annals of Blood*, 2(4), 17–17. <https://doi.org/10.21037/aob.2017.10.01>
- Wei, L., & Ploss, A. (2021). Mechanism of hepatitis b virus cccdna formation. *Viruses*, 13(8). <https://doi.org/10.3390/v13081463>
- World Health Organization. (2023a). *Hepatitis*. WHO. https://www.who.int/health-topics/hepatitis#tab=tab_1
- World Health Organization. (2023b). *Hepatitis B*. World Health Organization. <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>
- World Health Organization. (2024a). *Global Hepatitis Report 2024*. <https://www.who.int/publications/i/item/9789240091672>
- World Health Organization. (2024b). Guidelines for the Prevention, Diagnosis, Care and Treatment for People with Chronic Hepatitis B Infection. In *Infectious Diseases and Immunity* (Vol. 4). World Health Organization. <https://doi.org/10.1097/ID9.0000000000000128>
- Wu, C., Shi, H., Lu, M., Xu, Y., & Chen, X. (2013). A case of hepatitis B reactivation in an anti-HBs positive, anti-HBc positive non-Hodgkin's lymphoma patient. *Virologica Sinica*, 28(1), 49–52. <https://doi.org/10.1007/s12250-013-3285-x>
- Yamani, L., Triani, E., Amin, M., Juniastuti, J., Utsumi, T., Soetjipto, S., Nasronudin, N., Yano, Y., Hotta, H., Hayashi, Y., & Lusida, M. (2020). Prevalence and genotype distribution of hepatitis B virus among migrant workers in Lombok Island, Indonesia. *Asian Pacific Journal of Tropical Medicine*, 13(1), 8–16. <https://doi.org/10.4103/1995-7645.273568>
- Yano, Y., Azuma, T., & Hayashi, Y. (2015). Variations and mutations in the hepatitis B virus genome and their associations with clinical characteristics.

- World Journal of Hepatology*, 7(3), 583–592. <https://doi.org/10.4254/wjh.v7.i3.583>
- Yildiz, O., Aygen, B., Demirtürk, N., Demirdal, T., Inan, D., Yildirmak, T., Kantürk, A., & Tütüncü, E. (2011). Lamivudine resistance mutations in patients infected with hepatitis B virus genotype D. *World Journal of Gastroenterology*, 17(45), 4987–4992. <https://doi.org/10.3748/wjg.v17.i45.4987>
- Yuan, S., Chan, H. C. S., & Hu, Z. (2017). Using PyMOL as a platform for computational drug design. *Wiley Interdisciplinary Reviews: Computational Molecular Science*, 7(2), 1–10. <https://doi.org/10.1002/wcms.1298>
- Yuen, M. F., Wong, D. K. H., Lee, C. K., Tanaka, Y., Allain, J. P., Fung, J., Leung, J., Lin, C. K., Sugiyama, M., Sugauchi, F., Mizokami, M., & Lai, C. L. (2011). Transmissibility of hepatitis B virus (HBV) infection through blood transfusion from blood donors with occult HBV infection. *Clinical Infectious Diseases*, 52(5), 624–632. <https://doi.org/10.1093/cid/ciq247>
- Zardecki, C., Dutta, S., Goodsell, D. S., Voigt, M., & Burley, S. K. (2016). RCSB Protein Data Bank: A Resource for Chemical, Biochemical, and Structural Explorations of Large and Small Biomolecules. *Journal of Chemical Education*, 93(3), 569–575. <https://doi.org/10.1021/acs.jchemed.5b00404>
- Zhang, Z. H., Wu, C. C., Chen, X. W., Li, X., Li, J., & Lu, M. J. (2016). Genetic variation of hepatitis B virus and its significance for pathogenesis. *World Journal of Gastroenterology*, 22(1), 126–144. <https://doi.org/10.3748/wjg.v22.i1.126>
- Zhou, H. X., & Pang, X. (2018). Electrostatic Interactions in Protein Structure, Folding, Binding, and Condensation. *Chemical Reviews*, 118(4), 1691–1741. <https://doi.org/10.1021/acs.chemrev.7b00305>
- Zhu, Y., Alqahtani, S., & Hu, X. (2021). Aromatic rings as molecular determinants for the molecular recognition of protein kinase inhibitors. *Molecules*, 26(6), 1–18. <https://doi.org/10.3390/molecules26061776>
- Ziaee, M., Javanmard, D., Sharifzadeh, G., Namaei, M. H., & Azarkar, G. (2016). Genotyping and mutation pattern in the overlapping MHR region of HBV isolates in southern khorasan, eastern Iran. *Hepatitis Monthly*, 16(10). <https://doi.org/10.5812/hepatmon.37806>
- Zoulim, F. (2006). In vitro models for studying hepatitis B virus drug resistance. *Seminars in Liver Disease*, 26(2), 171–180. <https://doi.org/10.1055/s-2006-939759>

LIST OF APPENDIX

Appendix 1. Ethical Clearance



KEMENTERIAN PENDIDIKAN, KEBUDAYAAN,
RISET, DAN TEKNOLOGI
UNIVERSITAS JEMBER
FAKULTAS KEDOKTERAN
KOMITE ETIK PENELITIAN KESEHATAN (KEPK)
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KETERANGAN PERSETUJUAN ETIK
ETHICAL APPROVAL

Nomor: **624** /UN25.1.10.2/KE/2024

Komisi Etik Fakultas Kedokteran Universitas Jember dalam upaya melindungi hak asasi dan kesejahteraan subyek penelitian kedokteran, telah mengkaji dengan teliti protokol berjudul :

The Ethics Committee of the Faculty of Medicine, Jember University, With regards of the protection of humanrights and welfarein medical research, has carefully reviewed the proposal entitled :

Prevalence And Molecular Surveillance Of Hepatitis In Jember And Its Surrounding

Peneliti Utama : Prof. Dr.rer.nat. Kartika Senjarini, M.Si.
Name of the principal investigator

NIM : 197509132000032001

Nama Institusi : Fakultas MIPA Universitas Jember
Name of Institution

Dan telah menyetujui protokol tersebut diatas.
And approved the above mentioned proposal

Masa berlaku persetujuan etik ini 1 tahun

Jember, **05 FEB 2024**
Ketua Komisi Etik Penelitian Kesehatan

dr. Ayu Munawaroh/Aziz, M. Biomed
NIP. 198903132014042002

Appendix 2. Research Recommendation Letter From The Agency For National Unity And Politics Of Jember Regency (Read ; Badan Kesatuan Bangsa Dan Politik Kabupaten Jember (Bakesbangpol))

2/20/24, 5:04 PM



J-KREP - JEMBER KESBANGPOL REKOMENDASI PENELITIAN - BAKESBANGPOL - KABUPATEN JEMBER

PEMERINTAH KABUPATEN JEMBER BADAN KESATUAN BANGSA DAN POLITIK

Jalan Letjen S Parman No. 89 Telp. 337853 Jember

Kepada

Yth. Sdr. Daftar terlampir
di -
Jember**SURAT REKOMENDASI**

Nomor : 074/0667/415/2024

Tentang

PENELITIAN

Dasar : 1. Permendagri RI Nomor 7 Tahun 2014 tentang Perubahan atas Permendagri RI Nomor 64 Tahun 2011 tentang Pedoman Penerbitan Rekomendasi Penelitian
2. Peraturan Bupati Jember No. 46 Tahun 2014 tentang Pedoman Penerbitan Surat Rekomendasi Penelitian Kabupaten Jember

Memperhatikan : Surat FAKULTAS MATEMATIKA DAN ILMU PENGETAHUAN ALAM, UNIVERSITAS JEMBER, 19 Februari 2024, Nomor: 04/8/UN.25.1.9/LT/2023, Perihal: Permohonan Penerbitan Surat Ijin Penelitian

MEREKOMENDASIKAN

Nama : Prof. Dr.rer.nat Kartika Senjarini, M.Si.
NIM : 3509215309750001
Daftar Tim : Daftar terlampir
Instansi : Universitas Jember / Fakultas Matematika dan Ilmu Pengetahuan Alam
Alamat : Jl. Kalimantan No.37, Krajan Timur, Jemberlor, Kec. Sumbersari, Kabupaten Jember, Jawa Timur 68121
Keperluan : Melaksanakan kegiatan penelitian *dengan judul/terkait* Prevalensi dan surveilansi molekuler penyakit hepatitis di Jember dan sekitarnya (PrevalenceMolecular Surveillance Of Hepatitis In JemberIts Surrounding)
Lokasi : 1. Palang Merah Indonesia (PMI) Jember
2. RSD dr. Soebandi Jember
3. RSU Kaliwates
4. RS Perkebunan Jember Klinik
5. RS Bina Sehat
6. RS Citra Husada Jember
Waktu Kegiatan : 20 Februari 2024 s/d 20 Mei 2024

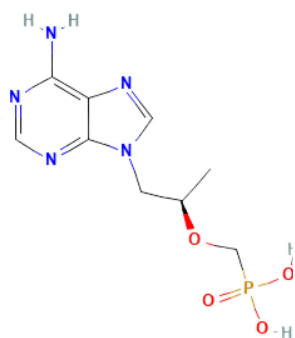
Apabila tidak bertentangan dengan kewenangan dan ketentuan yang berlaku, diharapkan Saudara memberi bantuan tempat dan atau data seperlunya untuk kegiatan dimaksud.

1. Kegiatan dimaksud benar-benar untuk kepentingan Pendidikan.
 2. Tidak dibenarkan melakukan aktivitas politik.
 3. Apabila situasi dan kondisi wilayah tidak memungkinkan akan dilakukan penghentian kegiatan.
- Demikian atas perhatian dan kerjasamanya disampaikan terimakasih.

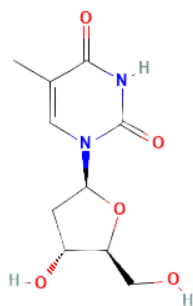
Appendix 3. List of Material

No	Material	Spesification
1	QIAmp DNA Mini Kit	Qiagen GmbH, Hilden, Germany
2	Eppendorf Tube	Eppendorf
3	PCR Tube	Thermo Scientific, USA
5	Etanol	- 1000 µl 200 µl (Vertex)
6	Microtip or Pipet Tip	200 µl (With Filter) 10 µl (Vertex) 10 µl (with Filter)
7	Handsglove or Handscoon	V Glove Size M HBV-022_F HBV-065_R
8	Primer	HBV-066_R HBV-024_F HBV_041_R HBV_064_R
9	Corral Load Buffer 10x	Qiagen GmbH, Hilden, Germany
10	Buffer 10x	Qiagen GmbH, Hilden, Germany
11	Taq DNA Polymerase	Qiagen GmbH, Hilden, Germany
12	dNTPs mix 10mM	Qiagen GmbH, Hilden, Germany
13	ddH ₂ O	Thermo Scientific, USA
14	Agarose Gel	-
15	TAE Liquid	-
16	DNA Ladder 100 Bp	New England Biolabs, USA
17	Buffer AE	Thermo Scientific, USA
18	Loading Dye 6x	Thermo Scientific, USA

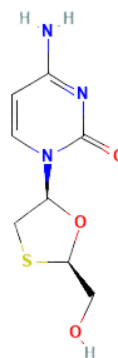
Appendix 4. Structure of Ligands



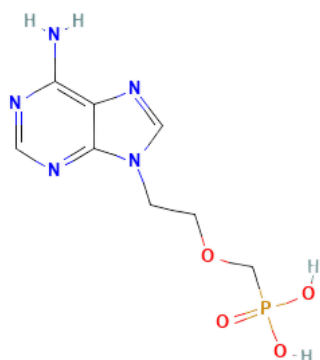
Gambar 1. Struktur
tenofovir (Pubchem,
2025e)



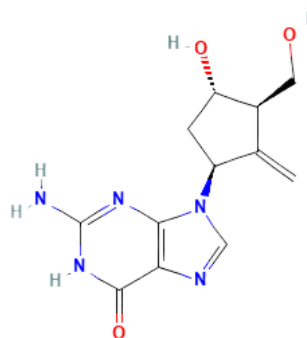
Gambar 2. Struktur
telbivudine (Pubchem,
2025d)



Gambar 3. Struktur
lamivudine (Pubchem,
2025c)

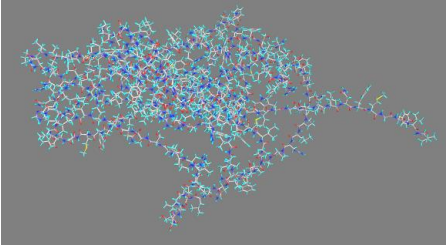
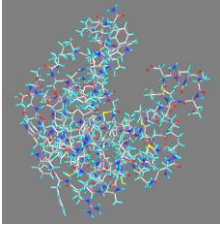
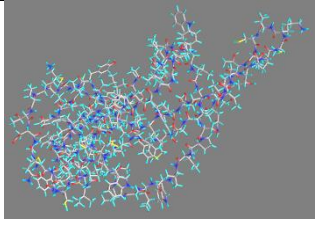
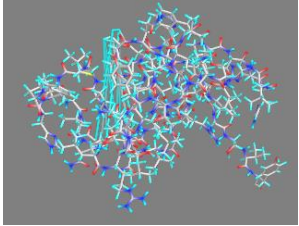
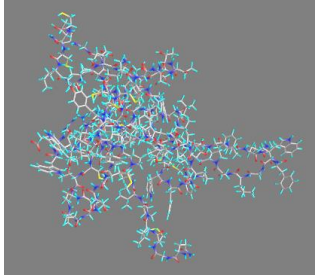


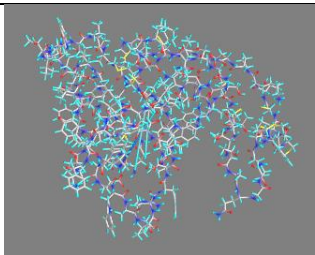
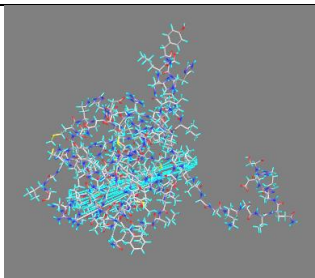
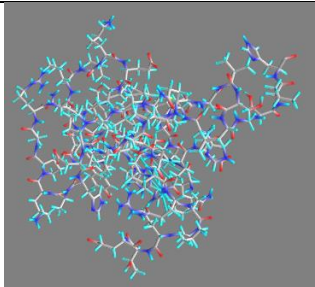
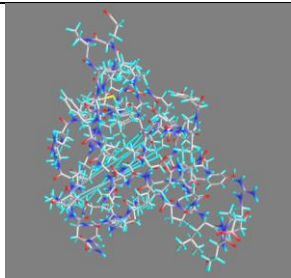
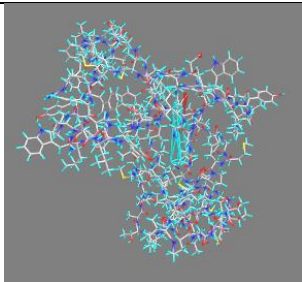
Gambar 4. Struktur adenofir
(Pubchem, 2025a)



Gambar 5. Struktur entecavir (Pubchem,
2025b)

Appendix 5. The translated sequences and 3D structural predictions of HBV DNA from OBI samples

Samples	Translation	Prediction of 3D Structur
Wild type (A0A679D LW0)	EHHIRIPRTPARVTGGVFLVDKN PHNTAESRLVVDQSQFSRGDHRV SWPKFAVPNLQSLTNLLSSNLSW LSLDVSAAFYHLPLHPAAMPHELL VGSSGLSRYVARLSSNSRILNHQ RGTMQNLHDYCSRNLVVSLLLL YQTFGRKLHLYSHPIILGFRKIPM GVGLSPFLLAQFTSAICSVVRRAF PHCLAFSYMDDVVLGAKSVQHL ESLFTAVTNFLLSLGIHLNPNKTK RWGYSLNFMGYV	
A6	QGMLPVCPLIPGSSTTSTGPCKTC TTPAQGTSMFPSCCCTKPTDGNC TCIPSSWAFKFLWEWASVRF SWLSSLVPFVQWFVGLSPTVWL L	
A8	QGMLPVCPLIPGSSTTSTGPCKTC TTTAQGTSMFPSCCCTKPTDGNC TCIPSSWAFKYLWEWASVRF SWLSSLVPFVQWFVGLSPIVWLS VIWMMWFWGPSLCNILSP	
A23	LKVCCPFVL*FQDHQPPAPDHAE PARLLLKEPLCFPHVAVQNL RTE TAPVFPSHHLGLSQNTYGS GPQSVSLGSVY*CHLFSGS*GFPP LSGFQLYGY*YGI GGQVCTAS*V	
A25	QGMLPVCPLIPGSSTTSTGPCKTC TTTAQGTSMFPSCCCTKPTDGNC TCIPSSWAFKYLWEWASVRF SWLLVPFVQWFVGLSPIVWLSVI WMMWFWGPSLYS	

Samples	Translation	Prediction of 3D Structur
C24	QGMLPVCPLIPGSSTTSTGPCRTC TTTAQGTSMFPSCCCTKPDGNCT CI PIPSSWAFAYLWEWASVRFSW LSLLVPFVQWFVGLSPTVWLSVI WMMWYWGP	
C32	SRYVARLSSNSRIHHQHRTMQN LHDSCSRNLYVSLMLLYKTYGR KLHLYSHPIILGFRKIPMGVGLSP FLLAQFTSAVCSVVRRAFPHCLA FSYMDDVVLGAKSVQHRES	
D59	VCCPFVL*FQDHQPPAPDHAKPA RLLLKEPLCFPHVAVQNLRTETA PVFPSHHLGLSQNSYGSGPQSVS LGSVH*CHLFSGS*GFPPLSGFQL YG*CGFGGQV	
E20	LKVCCPFVL*FQDHQPPAPDHAK PARLLLKEPLCFPHVAVQNL RTE TAPVFPSRHLGLSQNTYGS GPQS VSPGSVY*CHLFSGS*GFPPLSGF QLYG*CGFGGQVCTAS*V	
E28	GEYQGMLPVCPLIPGSSTTSTGPC RTCTTTAQGTSMFPSCCCTKPTD GNCTCIPISSWAFAYLWEWAS VRFSWL SLLVPFVQWFVGLSPTV WLSVIWMMWYWGPSLYSI	

Appendix 6. Result of Molecular Docking

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
d59_135398508_uff_e=422.05	-50	0	0
d59_135398508_uff_e=422.05	-50	21625	19575
d59_135398508_uff_e=422.05	-49	2141	19494
d59_135398508_uff_e=422.05	-49	21581	19582
d59_135398508_uff_e=422.05	-48	6603	3147
d59_135398508_uff_e=422.05	-48	2671	1842
d59_135398508_uff_e=422.05	-48	2214	20672
d59_135398508_uff_e=422.05	-47	24343	22465
d59_135398508_uff_e=422.05	-47	22689	20671
d59_159269_uff_e=293.18	-60	0	0
d59_159269_uff_e=293.18	-58	542	1906
d59_159269_uff_e=293.18	-49	21447	18768
d59_159269_uff_e=293.18	-49	3271	2041
d59_159269_uff_e=293.18	-48	1659	14903
d59_159269_uff_e=293.18	-48	12608	10199
d59_159269_uff_e=293.18	-47	21367	1963
d59_159269_uff_e=293.18	-47	22803	20249
d59_159269_uff_e=293.18	-46	19174	17448
d59_464205_uff_e=609.73	-61	0	0
d59_464205_uff_e=609.73	-56	236	1791
d59_464205_uff_e=609.73	-55	5798	4336
d59_464205_uff_e=609.73	-55	21514	19731
d59_464205_uff_e=609.73	-54	6073	4031
d59_464205_uff_e=609.73	-54	18295	16201
d59_464205_uff_e=609.73	-54	5256	4104
d59_464205_uff_e=609.73	-53	5245	3963
d59_464205_uff_e=609.73	-53	6657	5057
d59_60172_uff_e=582.80	-58	0	0
d59_60172_uff_e=582.80	-53	5921	4418
d59_60172_uff_e=582.80	-51	2332	1624
d59_60172_uff_e=582.80	-51	5886	4063
d59_60172_uff_e=582.80	-49	3301	2791
d59_60172_uff_e=582.80	-48	2001	1658
d59_60172_uff_e=582.80	-48	21854	20049
d59_60172_uff_e=582.80	-48	4596	3514
d59_60172_uff_e=582.80	-47	22399	2045
d59_60825_uff_e=527.89	-50	0	0
d59_60825_uff_e=527.89	-49	2314	1942
d59_60825_uff_e=527.89	-49	3991	2483
d59_60825_uff_e=527.89	-49	1888	1662

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
d59_60825_uff_e=527.89	-48	4074	2803
d59_60825_uff_e=527.89	-47	20176	1909
d59_60825_uff_e=527.89	-46	5883	3419
d59_60825_uff_e=527.89	-45	19482	184
d59_60825_uff_e=527.89	-45	19159	17904
control_positif_a0a679dlw0_135398508_uff_e=422.05	-57	0	0
control_positif_a0a679dlw0_135398508_uff_e=422.05	-57	22165	19729
control_positif_a0a679dlw0_135398508_uff_e=422.05	-56	4407	2796
control_positif_a0a679dlw0_135398508_uff_e=422.05	-55	20899	18287
control_positif_a0a679dlw0_135398508_uff_e=422.05	-55	31087	29248
control_positif_a0a679dlw0_135398508_uff_e=422.05	-54	23011	2147
control_positif_a0a679dlw0_135398508_uff_e=422.05	-54	16046	14049
control_positif_a0a679dlw0_135398508_uff_e=422.05	-54	426	3011
control_positif_a0a679dlw0_135398508_uff_e=422.05	-53	17043	15564
control_positif_a0a679dlw0_159269_uff_e=293.18	-58	0	0
control_positif_a0a679dlw0_159269_uff_e=293.18	-57	8106	5927
control_positif_a0a679dlw0_159269_uff_e=293.18	-56	23284	21766
control_positif_a0a679dlw0_159269_uff_e=293.18	-56	982	8614
control_positif_a0a679dlw0_159269_uff_e=293.18	-55	4845	3006
control_positif_a0a679dlw0_159269_uff_e=293.18	-55	538	2008
control_positif_a0a679dlw0_159269_uff_e=293.18	-55	535	2262
control_positif_a0a679dlw0_159269_uff_e=293.18	-54	9064	7013
control_positif_a0a679dlw0_159269_uff_e=293.18	-52	3695	1983
control_positif_a0a679dlw0_464205_uff_e=609.73	-65	0	0
control_positif_a0a679dlw0_464205_uff_e=609.73	-62	3509	2861
control_positif_a0a679dlw0_464205_uff_e=609.73	-62	8152	6536
control_positif_a0a679dlw0_464205_uff_e=609.73	-61	4533	295
control_positif_a0a679dlw0_464205_uff_e=609.73	-60	6822	4439
control_positif_a0a679dlw0_464205_uff_e=609.73	-60	9542	7083
control_positif_a0a679dlw0_464205_uff_e=609.73	-59	9484	6568
control_positif_a0a679dlw0_464205_uff_e=609.73	-59	8069	648
control_positif_a0a679dlw0_464205_uff_e=609.73	-58	7499	5421
control_positif_a0a679dlw0_60172_uff_e=582.80	-64	0	0
control_positif_a0a679dlw0_60172_uff_e=582.80	-63	8106	6368
control_positif_a0a679dlw0_60172_uff_e=582.80	-62	2021	1423
control_positif_a0a679dlw0_60172_uff_e=582.80	-60	7093	5162
control_positif_a0a679dlw0_60172_uff_e=582.80	-57	9268	657

Ligand	Binding Affinity	rmsd/u b	rmsd/l b
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control_positif_a0a679dlw0_60172_uff_e=582.80	-55	9815	734
control_positif_a0a679dlw0_60172_uff_e=582.80	-55	7714	7089
control_positif_a0a679dlw0_60825_uff_e=527.89	-58	0	0
control_positif_a0a679dlw0_60825_uff_e=527.89	-54	5492	43
control_positif_a0a679dlw0_60825_uff_e=527.89	-52	6002	4746
control_positif_a0a679dlw0_60825_uff_e=527.89	-51	2494	2189
control_positif_a0a679dlw0_60825_uff_e=527.89	-51	6729	5099
control_positif_a0a679dlw0_60825_uff_e=527.89	-50	5951	3667
control_positif_a0a679dlw0_60825_uff_e=527.89	-50	5876	3438
control_positif_a0a679dlw0_60825_uff_e=527.89	-49	6881	5577
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a25_135398508_uff_e=422.05	-57	3682	3349
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a25_464205_uff_e=609.73	-56	6706	4596
a25_464205_uff_e=609.73	-56	7387	5189
a25_464205_uff_e=609.73	-56	27	1941
a25_60172_uff_e=582.80	-59	0	0
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Ligand	Binding Affinity	rmsd/u b	rmsd/l b
a25_60172_uff_e=582.80	-58	7047	5677
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a25_60172_uff_e=582.80	-56	5895	4144
a25_60172_uff_e=582.80	-56	7345	5412
a25_60172_uff_e=582.80	-56	4435	2972
a25_60172_uff_e=582.80	-56	18299	16663
a25_60172_uff_e=582.80	-56	799	5088
a25_60825_uff_e=527.89	-54	0	0
a25_60825_uff_e=527.89	-52	2976	2435
a25_60825_uff_e=527.89	-52	10505	9683
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a6_135398508_uff_e=422.05	-56	15475	1391
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a6_159269_uff_e=293.18	-60	4877	3336
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a6_464205_uff_e=609.73	-64	0	0
a6_464205_uff_e=609.73	-61	3228	2101
a6_464205_uff_e=609.73	-60	5114	3304
a6_464205_uff_e=609.73	-60	18095	15777
a6_464205_uff_e=609.73	-60	5228	3995
a6_464205_uff_e=609.73	-60	3316	2809
a6_464205_uff_e=609.73	-59	3848	278
a6_464205_uff_e=609.73	-59	5224	3107

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
a6_464205_uff_e=609.73	-59	16454	13989
a6_60172_uff_e=582.80	-66	0	0
a6_60172_uff_e=582.80	-65	2033	1359
a6_60172_uff_e=582.80	-59	4687	2865
a6_60172_uff_e=582.80	-58	387	2493
a6_60172_uff_e=582.80	-58	5616	4651
a6_60172_uff_e=582.80	-58	3682	2809
a6_60172_uff_e=582.80	-56	4423	284
a6_60172_uff_e=582.80	-56	5035	3247
a6_60172_uff_e=582.80	-56	18185	16014
a6_60825_uff_e=527.89	-54	0	0
a6_60825_uff_e=527.89	-52	612	3293
a6_60825_uff_e=527.89	-51	458	3928
a6_60825_uff_e=527.89	-48	14869	13053
a6_60825_uff_e=527.89	-48	1476	13893
a6_60825_uff_e=527.89	-48	15529	13999
a6_60825_uff_e=527.89	-47	6106	3504
a6_60825_uff_e=527.89	-47	16537	13504
a6_60825_uff_e=527.89	-46	16442	15506
c24_135398508_uff_e=422.05	-66	0	0
c24_135398508_uff_e=422.05	-64	16879	14854
c24_135398508_uff_e=422.05	-64	3601	254
c24_135398508_uff_e=422.05	-64	5166	3292
c24_135398508_uff_e=422.05	-63	16719	14612
c24_135398508_uff_e=422.05	-62	3348	2164
c24_135398508_uff_e=422.05	-61	3576	2479
c24_135398508_uff_e=422.05	-61	5273	3147
c24_135398508_uff_e=422.05	-61	3373	2718
c24_159269_uff_e=293.18	-70	0	0
c24_159269_uff_e=293.18	-63	4715	2443
c24_159269_uff_e=293.18	-62	5055	2949
c24_159269_uff_e=293.18	-61	5574	1774
c24_159269_uff_e=293.18	-60	16348	13582
c24_159269_uff_e=293.18	-60	5156	3718
c24_159269_uff_e=293.18	-59	19949	18215
c24_159269_uff_e=293.18	-57	2766	2017
c24_159269_uff_e=293.18	-56	15785	1343
c24_464205_uff_e=609.73	-59	0	0
c24_464205_uff_e=609.73	-59	4946	2245
c24_464205_uff_e=609.73	-57	1978	1038
c24_464205_uff_e=609.73	-56	2199	169
c24_464205_uff_e=609.73	-56	2247	1672

Ligand	Binding Affinity	rmsd/u b	rmsd/l b
c24_464205_uff_e=609.73	-55	4894	3556
c24_464205_uff_e=609.73	-55	4349	2003
c24_464205_uff_e=609.73	-55	4938	318
c24_464205_uff_e=609.73	-55	4078	1761
c24_60172_uff_e=582.80	-58	0	0
c24_60172_uff_e=582.80	-56	4874	3378
c24_60172_uff_e=582.80	-56	5528	31
c24_60172_uff_e=582.80	-56	4855	3395
c24_60172_uff_e=582.80	-55	28439	26783
c24_60172_uff_e=582.80	-55	5225	3476
c24_60172_uff_e=582.80	-55	2092	1233
c24_60172_uff_e=582.80	-54	14002	12768
c24_60172_uff_e=582.80	-53	15098	14126
c24_60825_uff_e=527.89	-56	0	0
c24_60825_uff_e=527.89	-55	2667	204
c24_60825_uff_e=527.89	-55	17926	1564
c24_60825_uff_e=527.89	-55	2008	1912
c24_60825_uff_e=527.89	-54	18535	16939
c24_60825_uff_e=527.89	-54	6787	4845
c24_60825_uff_e=527.89	-53	13475	12494
c24_60825_uff_e=527.89	-52	18385	15729
c24_60825_uff_e=527.89	-52	13386	1162
e20_135398508_uff_e=422.05	-73	0	0
e20_135398508_uff_e=422.05	-60	2552	2026
e20_135398508_uff_e=422.05	-58	5901	358
e20_135398508_uff_e=422.05	-57	4099	2734
e20_135398508_uff_e=422.05	-56	3342	1853
e20_135398508_uff_e=422.05	-56	6035	3408
e20_135398508_uff_e=422.05	-55	3673	2135
e20_135398508_uff_e=422.05	-54	2937	2004
e20_135398508_uff_e=422.05	-52	4632	3357
e20_159269_uff_e=293.18	-61	0	0
e20_159269_uff_e=293.18	-58	5661	4224
e20_159269_uff_e=293.18	-57	5438	3553
e20_159269_uff_e=293.18	-54	5071	2046
e20_159269_uff_e=293.18	-53	4202	3124
e20_159269_uff_e=293.18	-52	6526	3794
e20_159269_uff_e=293.18	-52	5279	2171
e20_159269_uff_e=293.18	-52	2144	1661
e20_159269_uff_e=293.18	-51	4208	3361
e20_464205_uff_e=609.73	-58	0	0
e20_464205_uff_e=609.73	-58	2592	14

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
e20_464205_uff_e=609.73	-56	3174	2554
e20_464205_uff_e=609.73	-56	3229	2285
e20_464205_uff_e=609.73	-55	1959	1406
e20_464205_uff_e=609.73	-54	4952	3578
e20_464205_uff_e=609.73	-54	4667	2825
e20_464205_uff_e=609.73	-53	402	2693
e20_464205_uff_e=609.73	-52	2636	2087
e20_60172_uff_e=582.80	-59	0	0
e20_60172_uff_e=582.80	-59	147	1045
e20_60172_uff_e=582.80	-57	2185	1283
e20_60172_uff_e=582.80	-54	413	2838
e20_60172_uff_e=582.80	-54	3661	251
e20_60172_uff_e=582.80	-53	451	2751
e20_60172_uff_e=582.80	-53	3067	2459
e20_60172_uff_e=582.80	-53	3701	271
e20_60172_uff_e=582.80	-53	3603	2345
e20_60825_uff_e=527.89	-51	0	0
e20_60825_uff_e=527.89	-50	3355	2548
e20_60825_uff_e=527.89	-49	432	3243
e20_60825_uff_e=527.89	-49	5965	3512
e20_60825_uff_e=527.89	-48	574	4525
e20_60825_uff_e=527.89	-48	5362	3714
e20_60825_uff_e=527.89	-48	3495	2898
e20_60825_uff_e=527.89	-47	5204	4019
e20_60825_uff_e=527.89	-46	2319	1792
c32_135398508_uff_e=422.05	-65	0	0
c32_135398508_uff_e=422.05	-62	2588	2036
c32_135398508_uff_e=422.05	-60	4321	2828
c32_135398508_uff_e=422.05	-58	3164	1747
c32_135398508_uff_e=422.05	-57	5905	2979
c32_135398508_uff_e=422.05	-57	2526	1254
c32_135398508_uff_e=422.05	-55	6385	2438
c32_135398508_uff_e=422.05	-55	3432	1704
c32_135398508_uff_e=422.05	-54	15337	11969
c32_159269_uff_e=293.18	-63	0	0
c32_159269_uff_e=293.18	-59	3334	2124
c32_159269_uff_e=293.18	-58	3984	2513
c32_159269_uff_e=293.18	-57	2248	1235
c32_159269_uff_e=293.18	-56	2611	1853
c32_159269_uff_e=293.18	-56	4141	2879
c32_159269_uff_e=293.18	-56	10517	988
c32_159269_uff_e=293.18	-55	14584	12108

Ligand	Binding Affinity	rmsd/u b	rmsd/l b
c32_159269_uff_e=293.18	-53	1312	11181
c32_464205_uff_e=609.73	-61	0	0
c32_464205_uff_e=609.73	-60	5286	3517
c32_464205_uff_e=609.73	-60	3583	2609
c32_464205_uff_e=609.73	-60	507	315
c32_464205_uff_e=609.73	-60	5273	3232
c32_464205_uff_e=609.73	-58	4992	2927
c32_464205_uff_e=609.73	-58	3525	2506
c32_464205_uff_e=609.73	-57	3835	2291
c32_464205_uff_e=609.73	-55	5479	4463
c32_60172_uff_e=582.80	-55	0	0
c32_60172_uff_e=582.80	-55	3786	2891
c32_60172_uff_e=582.80	-54	3919	2754
c32_60172_uff_e=582.80	-54	4217	261
c32_60172_uff_e=582.80	-53	2188	1257
c32_60172_uff_e=582.80	-53	4768	272
c32_60172_uff_e=582.80	-53	3481	2201
c32_60172_uff_e=582.80	-53	4267	2544
c32_60172_uff_e=582.80	-53	5342	3885
c32_60825_uff_e=527.89	-55	0	0
c32_60825_uff_e=527.89	-54	2591	2042
c32_60825_uff_e=527.89	-52	4546	3703
c32_60825_uff_e=527.89	-52	14125	12955
c32_60825_uff_e=527.89	-52	604	3376
c32_60825_uff_e=527.89	-51	11954	11498
c32_60825_uff_e=527.89	-50	5825	3527
c32_60825_uff_e=527.89	-49	6033	3397
c32_60825_uff_e=527.89	-48	5922	3267
e28_135398508_uff_e=422.05	-64	0	0
e28_135398508_uff_e=422.05	-60	30365	28328
e28_135398508_uff_e=422.05	-60	30427	28718
e28_135398508_uff_e=422.05	-59	6336	2708
e28_135398508_uff_e=422.05	-58	3205	1721
e28_135398508_uff_e=422.05	-58	2795	1135
e28_135398508_uff_e=422.05	-58	862	5632
e28_135398508_uff_e=422.05	-58	8802	6596
e28_135398508_uff_e=422.05	-57	5803	3085
e28_159269_uff_e=293.18	-61	0	0
e28_159269_uff_e=293.18	-59	5291	1979
e28_159269_uff_e=293.18	-58	5809	2206
e28_159269_uff_e=293.18	-57	2783	2069
e28_159269_uff_e=293.18	-56	5904	3102

Ligand	Binding Affinity	rmsd/u b	rmsd/l b
e28_159269_uff_e=293.18	-55	547	2063
e28_159269_uff_e=293.18	-55	4612	3266
e28_159269_uff_e=293.18	-54	7739	5778
e28_159269_uff_e=293.18	-53	7378	5964
e28_464205_uff_e=609.73	-63	0	0
e28_464205_uff_e=609.73	-59	6178	4268
e28_464205_uff_e=609.73	-59	217	1764
e28_464205_uff_e=609.73	-57	6438	4352
e28_464205_uff_e=609.73	-57	3828	2815
e28_464205_uff_e=609.73	-57	836	6463
e28_464205_uff_e=609.73	-56	2183	1649
e28_464205_uff_e=609.73	-56	6786	4753
e28_464205_uff_e=609.73	-56	787	6035
e28_60172_uff_e=582.80	-63	0	0
e28_60172_uff_e=582.80	-59	6271	4189
e28_60172_uff_e=582.80	-59	2695	1329
e28_60172_uff_e=582.80	-58	6239	4412
e28_60172_uff_e=582.80	-58	1791	1515
e28_60172_uff_e=582.80	-57	3901	3168
e28_60172_uff_e=582.80	-57	3008	1782
e28_60172_uff_e=582.80	-56	2511	1692
e28_60172_uff_e=582.80	-56	6504	4302
e28_60825_uff_e=527.89	-55	0	0
e28_60825_uff_e=527.89	-55	7485	6508
e28_60825_uff_e=527.89	-54	8146	7149
e28_60825_uff_e=527.89	-53	8431	7412
e28_60825_uff_e=527.89	-50	75	6601
e28_60825_uff_e=527.89	-49	9237	7924
e28_60825_uff_e=527.89	-49	6123	3731
e28_60825_uff_e=527.89	-49	8686	7553
e28_60825_uff_e=527.89	-48	5579	289
a23_135398508_uff_e=422.05	-52	0	0
a23_135398508_uff_e=422.05	-52	1894	17036
a23_135398508_uff_e=422.05	-48	17885	16227
a23_135398508_uff_e=422.05	-47	17035	15855
a23_135398508_uff_e=422.05	-47	22076	18233
a23_135398508_uff_e=422.05	-47	181	16125
a23_135398508_uff_e=422.05	-47	22511	19519
a23_135398508_uff_e=422.05	-47	376	2807
a23_135398508_uff_e=422.05	-47	22616	18807
a23_159269_uff_e=293.18	-50	0	0
a23_159269_uff_e=293.18	-46	4463	2699

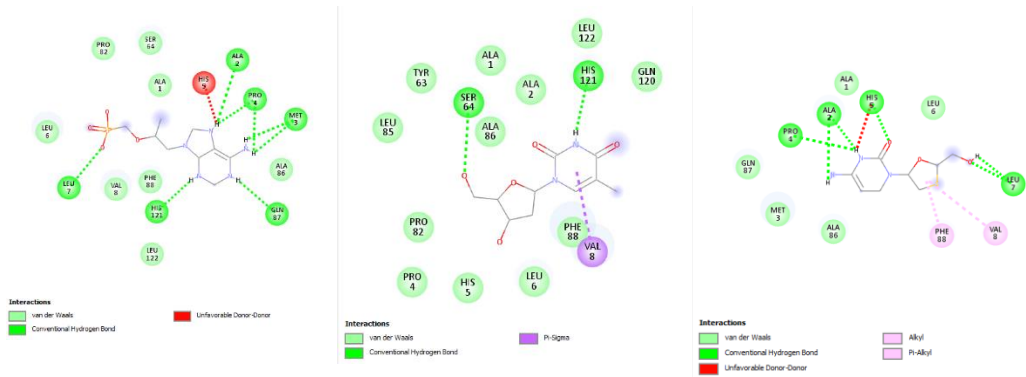
Ligand	Binding Affinity	rmsd/u b	rmsd/l b
a23_159269_uff_e=293.18	-46	18741	1691
a23_159269_uff_e=293.18	-45	5276	2562
a23_159269_uff_e=293.18	-44	5513	3262
a23_159269_uff_e=293.18	-44	4086	3108
a23_159269_uff_e=293.18	-44	15213	13135
a23_159269_uff_e=293.18	-44	17768	16003
a23_159269_uff_e=293.18	-43	16818	14958
a23_464205_uff_e=609.73	-53	0	0
a23_464205_uff_e=609.73	-51	2686	1726
a23_464205_uff_e=609.73	-51	3325	185
a23_464205_uff_e=609.73	-50	4124	2623
a23_464205_uff_e=609.73	-49	207	1016
a23_464205_uff_e=609.73	-49	17807	16448
a23_464205_uff_e=609.73	-46	21483	19697
a23_464205_uff_e=609.73	-46	24017	22299
a23_464205_uff_e=609.73	-46	17144	15787
a23_60172_uff_e=582.80	-56	0	0
a23_60172_uff_e=582.80	-55	2156	19823
a23_60172_uff_e=582.80	-55	197	943
a23_60172_uff_e=582.80	-53	21543	1934
a23_60172_uff_e=582.80	-49	2005	18228
a23_60172_uff_e=582.80	-49	20952	1999
a23_60172_uff_e=582.80	-48	13415	11645
a23_60172_uff_e=582.80	-48	15124	1302
a23_60172_uff_e=582.80	-48	3721	2642
a23_60825_uff_e=527.89	-46	0	0
a23_60825_uff_e=527.89	-45	22498	20419
a23_60825_uff_e=527.89	-44	2804	2225
a23_60825_uff_e=527.89	-44	14045	1293
a23_60825_uff_e=527.89	-43	13406	11294
a23_60825_uff_e=527.89	-43	20934	19317
a23_60825_uff_e=527.89	-42	22096	2044
a23_60825_uff_e=527.89	-41	20669	19949
a23_60825_uff_e=527.89	-41	12818	11929
a8_135398508_uff_e=422.05	-61	0	0
a8_135398508_uff_e=422.05	-61	10272	9367
a8_135398508_uff_e=422.05	-60	10204	9288
a8_135398508_uff_e=422.05	-59	11277	9781
a8_135398508_uff_e=422.05	-59	989	7578
a8_135398508_uff_e=422.05	-58	25907	24409
a8_135398508_uff_e=422.05	-57	3141	1651
a8_135398508_uff_e=422.05	-57	10846	8736

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
a8_135398508_uff_e=422.05	-55	2902	2132
a8_159269_uff_e=293.18	-60	0	0
a8_159269_uff_e=293.18	-59	26765	25352
a8_159269_uff_e=293.18	-58	3068	1759
a8_159269_uff_e=293.18	-57	27755	26542
a8_159269_uff_e=293.18	-56	2901	192
a8_159269_uff_e=293.18	-55	20592	18747
a8_159269_uff_e=293.18	-54	5211	2079
a8_159269_uff_e=293.18	-53	11417	10395
a8_159269_uff_e=293.18	-52	5701	222
a8_464205_uff_e=609.73	-60	0	0
a8_464205_uff_e=609.73	-57	13167	11678
a8_464205_uff_e=609.73	-56	7428	607
a8_464205_uff_e=609.73	-55	33662	31918
a8_464205_uff_e=609.73	-55	6241	3866
a8_464205_uff_e=609.73	-55	33584	31835
a8_464205_uff_e=609.73	-55	14263	12973
a8_464205_uff_e=609.73	-55	5369	3205
a8_464205_uff_e=609.73	-55	219	1824
a8_60172_uff_e=582.80	-56	0	0
a8_60172_uff_e=582.80	-54	4265	3434
a8_60172_uff_e=582.80	-54	168	15647
a8_60172_uff_e=582.80	-54	11702	10227
a8_60172_uff_e=582.80	-53	29502	28059
a8_60172_uff_e=582.80	-53	29749	28376
a8_60172_uff_e=582.80	-52	28116	26597
a8_60172_uff_e=582.80	-52	2048	1445
a8_60172_uff_e=582.80	-52	12918	11355
a8_60825_uff_e=527.89	-56	0	0
a8_60825_uff_e=527.89	-52	27961	26603
a8_60825_uff_e=527.89	-49	28223	27181
a8_60825_uff_e=527.89	-49	5916	2914
a8_60825_uff_e=527.89	-48	5723	2871
a8_60825_uff_e=527.89	-48	1733	1486
a8_60825_uff_e=527.89	-48	34039	33173
a8_60825_uff_e=527.89	-48	11591	10255
a8_60825_uff_e=527.89	-48	28652	27163

Table description: control_positif_a0a679dlw0 (Wild type); 60172 (Adenovir); 135398508 (Entecavir); 60825 (Lamivudine); 159269 (Telbivudine); 464205 (Tenofovir)

Appendix 7. Molecular Interaction Between Ligan and Receptor

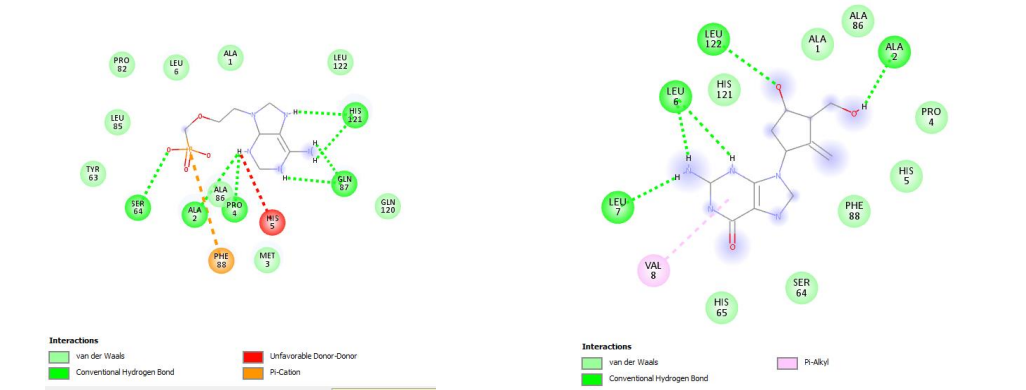
1. Wild Type



Tenofovir

Telbivudine

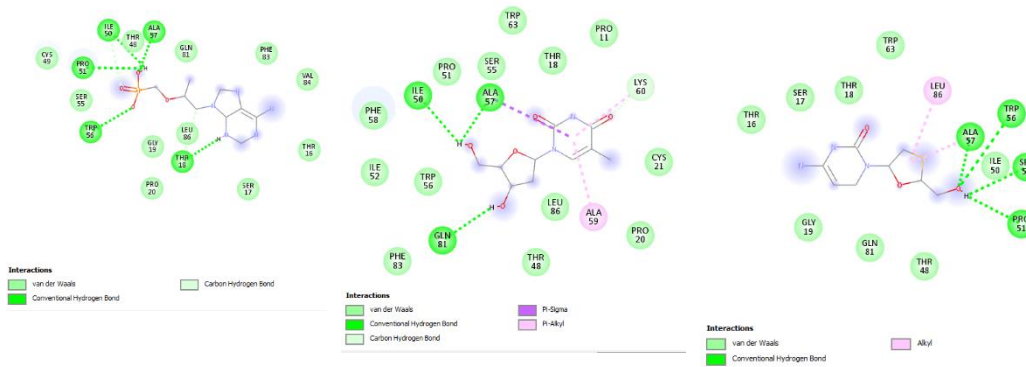
Lamivudine



Adenovir

Entecavir

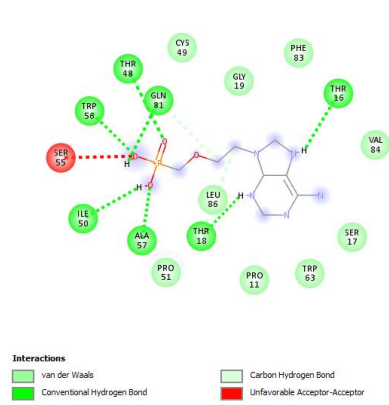
2. A6



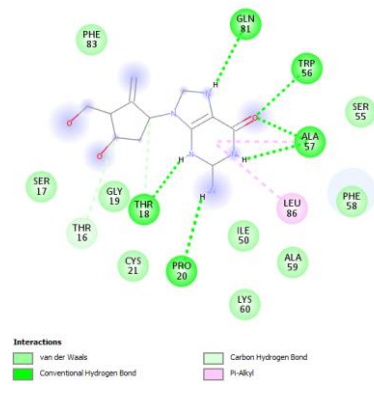
Tenofovir

Telbivudine

Lamivudine

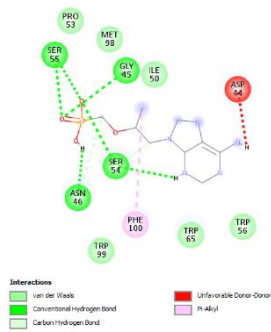


Adenovir

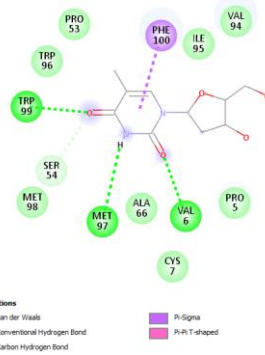


Entecavir

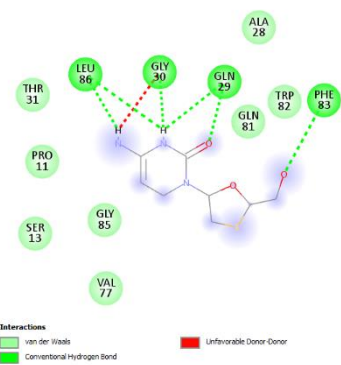
3. A8



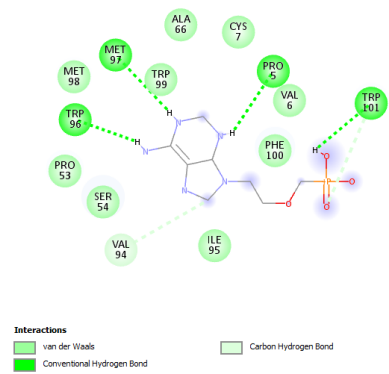
Tenofovir



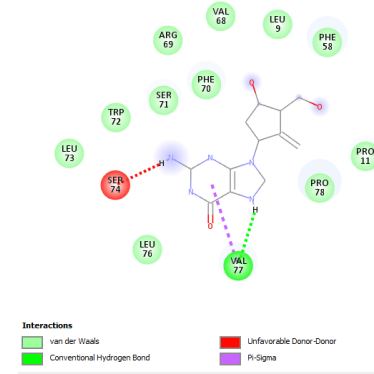
Telbivudine



Lamivudine

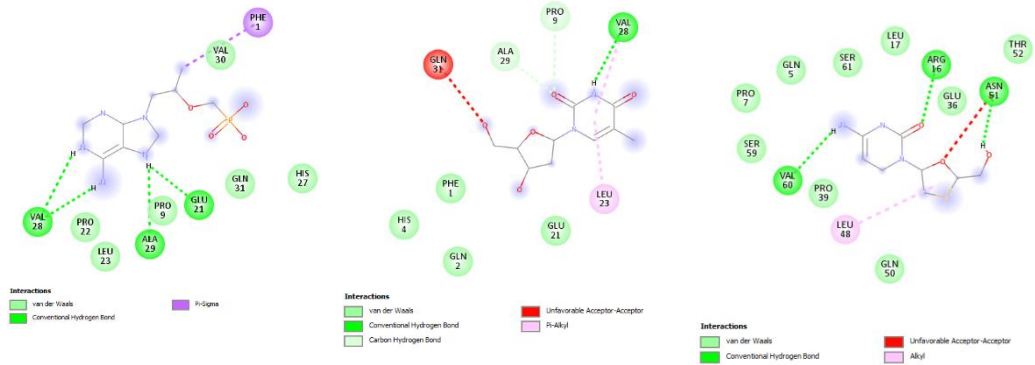


Adenovir



Entecavir

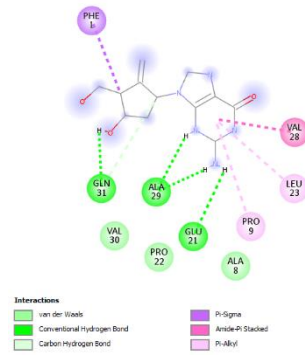
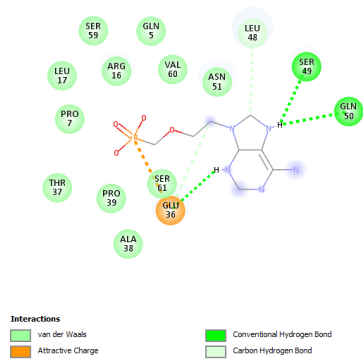
4. A23



Tenofovir

Telbivudine

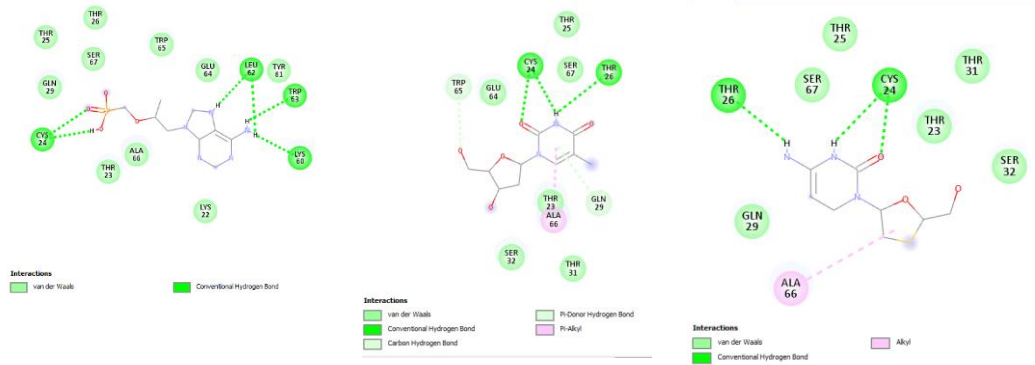
Lamivudine



Adenovir

Entecavir

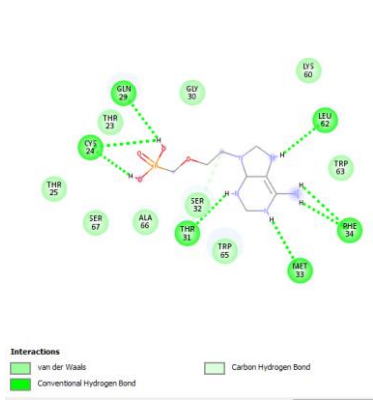
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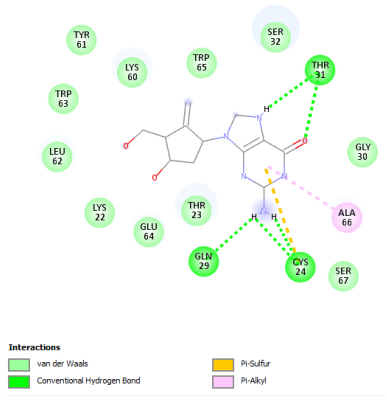
Tenofovir

Telbivudine

Lamivudine

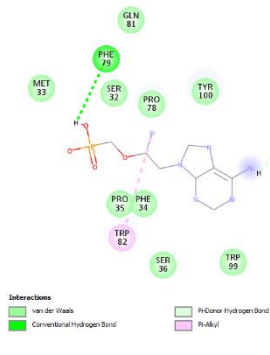


Adenovir

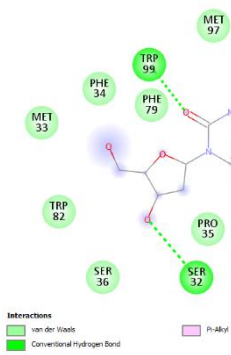


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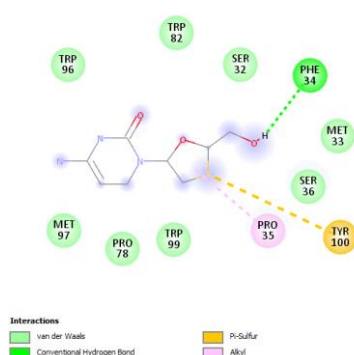
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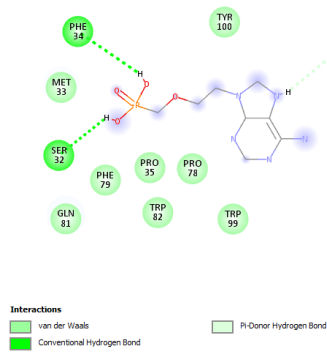
Tenofovir



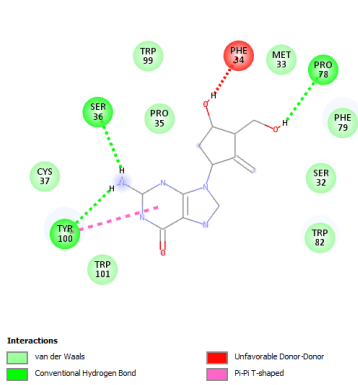
Telbivudine



Lamivudine

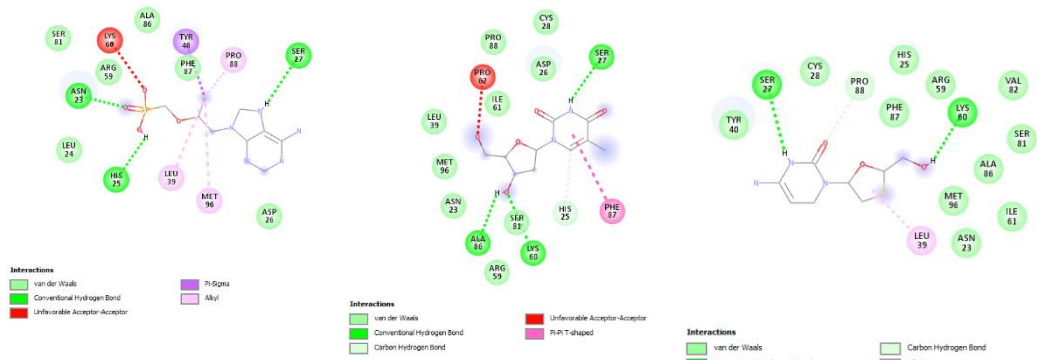


Adenovir



Entecavir

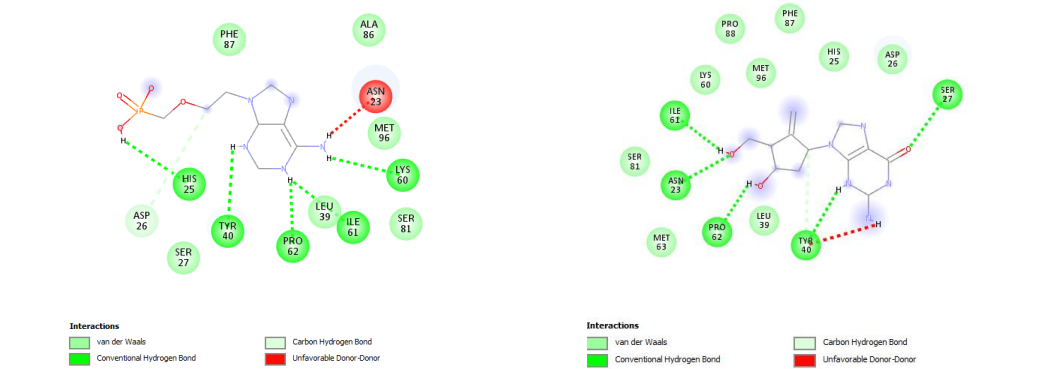
7. C32



Tenofovir

Telbivudine

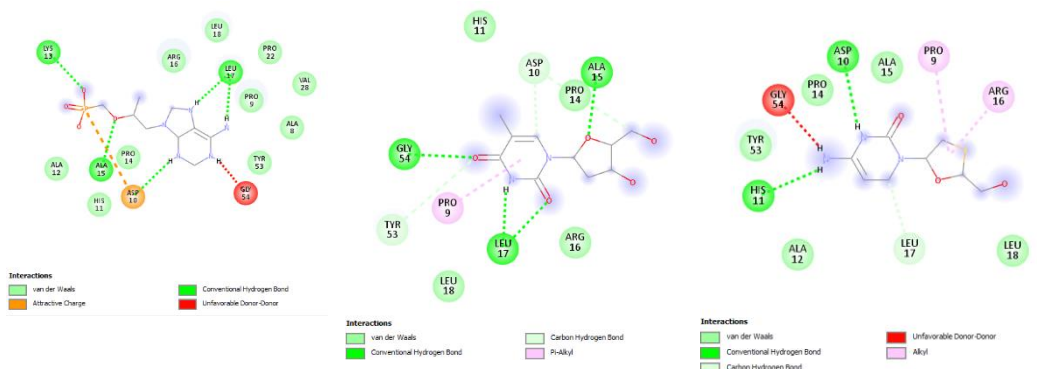
Lamivudine



Adenovir

Entecavir

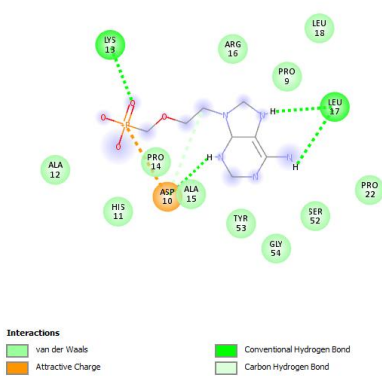
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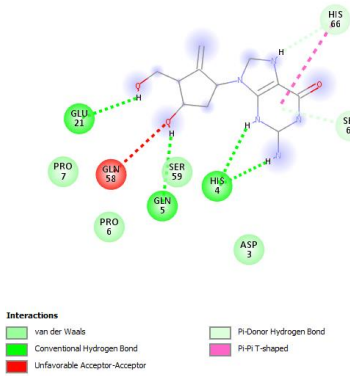
Tenofovir

Telbivudine

Lamivudine

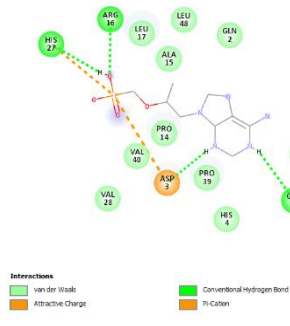


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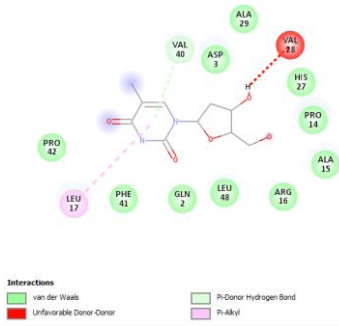


Entecavir

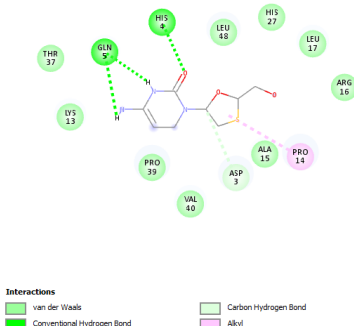
9. E20



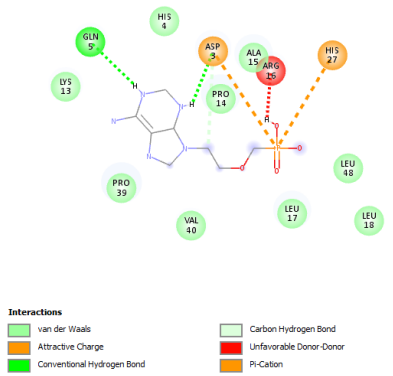
Tenofovir



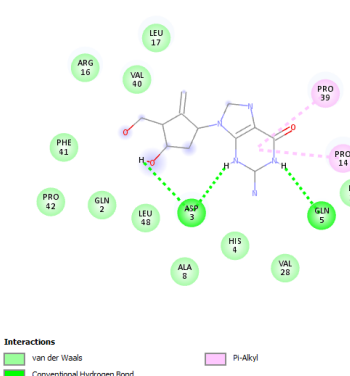
Telbivudine



Lamivudine

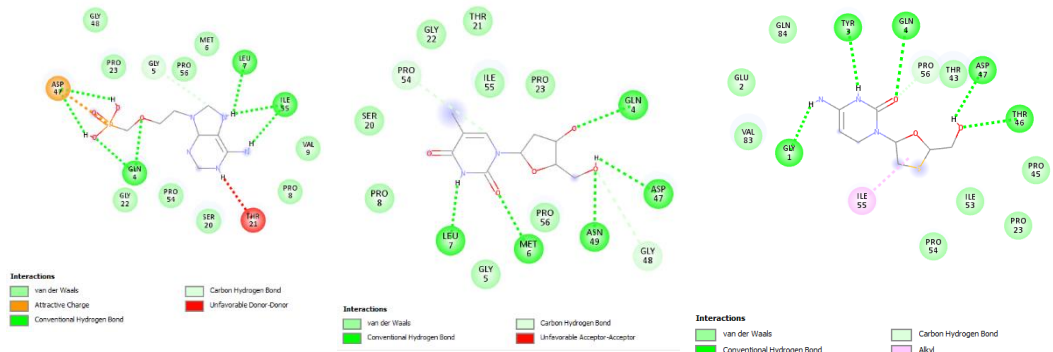


Adenovir



Entecavir

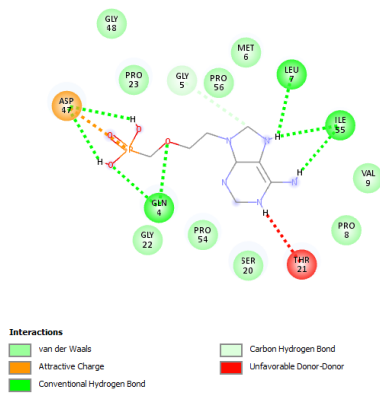
10. E28



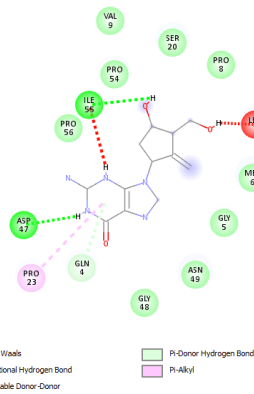
Tenofovir

Telbivudine

Lamivudine



Adenovir



Entecavir

Appendix 8. Molecular Interaction Characteristics between HBV Samples and Antiviral Compounds

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
Control Positive	Adenofir	Conventional Hydrogen Bond: Arg 128, Ser 68; Van der Waals: Leu 67, Tyr 131, Trp 69, Leu 32, Leu 145, Ser 127, Asn 129, Ser 209, Leu 210, Phe 211, Leu 130, Lys 144; Unfavorable Positive-Positive: Arg 128; Unfavorable Positive-Positive: Arg 143	- Hydrogen Bond (Conventional Hydrogen Bond) - Unfavorable (Unfavorable Positive-Positive, Unfavorable Positive-Positive)	X: -20,7647 Y: -101,424 Z: -25,4899
	Lamivudine	Van der Waals: Phe 211, Leu 210, Ser 209, Ser 127; Conventional Hydrogen Bond: Arg 128, Ser 68; Carbon Hydrogen Bond: Arg 143; Alkyl: Leu 145	- Hydrogen Bond (Conventional Hydrogen Bond, Carbon Hydrogen Bond) - Hydrophobic (Alkyl)	X: -20,343 Y: -102,104 Z: -26,3342
	Telbivudine	Van der Waals: Arg 5, Ile 6, Pro 7, Ser 68, Arg 128, Leu 70, Trp 69, Lys 144; Pi-Alkyl: Leu 145; Conventional Hydrogen Bond: Leu 67, Leu 145, Arg 143	- Hydrophobic (Pi-Alkyl) - Hydrogen Bond (Conventional Hydrogen Bond)	X: -14,8864 Y: -104,811 Z: -25,9166
	Tenofovir	Van der Waals: Leu 32, Phe 185, Leu 67, Trp 69, Asn 129, Leu 130, Lys 144, Phe 211, Leu 145, Tyr 131; Conventional Hydrogen	Hydrogen Bond (Conventional Hydrogen Bond, Carbon Hydrogen Bond)	X: -19,7921 Y: -101,222 Z: -25,1269

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
A6	Entecavir	Bond: Ser 68, Arg 128, Ser 209; Carbon Hydrogen Bond: Arg 143; Unfavorable Positive-Positive: Arg128, Arg 143; Unfavorable Donor-Donor: Leu 210	• Unfavorable (Unfavorable Positive-Positive, Unfavorable Donor-Donor)	
		Van der Waals: Ser 127, Cys 126, His 187, Leu 189, Cys 188, Leu 62, Asn 61, Gln 205, Glu 208; Carbon Hydrogen Bond: His 206; Conventional Hydrogen Bond: Asn 129, Leu 207, Thr 60; Hydrophobic: Pi-Alkyl	• Hydrogen Bond (Conventional Hydrogen Bond, Carbon Hydrogen Bond) • Hydrophobic (Pi-Alkyl)	X: -35,2166 Y: -107,336 Z: -23,4055
	Adenofir	Unfavorable Acceptor-Acceptor: Ser 55; Conventional Hydrogen Bond: Thr 48, Gln 81, Trp 56, Ile 50, Ala 57, Thr 18, Thr 16; Van der Waals: Cys 49, Gly 19, Phe 83, Val 84, Ser 17, Trp 63, Pro 11, Pro 51, Leu 86; Carbon Hydrogen Bond: Leu 86, Gln 81	• Hydrogen Bond (Conventional Hydrogen Bond, Carbon Hydrogen Bond) • Unfavorable	X: 12,1583 Y: 36,127 Z: -53,0597
	Lamivudine	Alkyl: Leu 86, Ala 57; Conventional Hydrogen Bond: Ala 57, Trp 56, Ser 55, Pro	• Hydrogen Bond (Conventional Hydrogen Bond) • Hydrophobic (Alkyl)	X: 12,9958 Y: 35,7309 Z: -54,4629

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
		51; Van der Waals: Ile 50, Thr 48, Gln 81, Gly 19, Thr 16, Ser 17, Thr 18, Trp 63		
	Telbivudine	Pi-Alkyl: Ala 59, Lys 60; Pi-Sigma: Ala 57; Conventional Hydrogen Bond: Ala 57, Ile 50, Gln 81; Carbon Hydrogen Bond: Lys 60; Van der Waals: Leu 86, Thr 48, Phe 83, Trp 56, Ile 52, Phe 58, Pro 51, Ser 55, Thr 18, Trp 63, Pro 11, Cys 21, Pro 20	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Pi-Sigma; Pi-Alkyl)	X: 15,2411 Y: 37,7477 Z: -53,1471
	Tenofovir	Conventional Hydrogen Bond: Ala 57, Ile 50, Pro 51, Trp 56, Thr 18; Carbon Hydrogen Bond: Thr 18, Ile 50; Van der Waals: Ser17, Thr 16, Val 84, Phe 83, Gln 81, Thr 48, Cys 49, Ser 55, Leu 86, Gly 19, Pro 20	Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond)	X: 11,9985 Y: 36,2902 Z: -54,7238
	Entecavir	Pi-Alkyl: Leu 86, Ala 57; Conventional Hydrogen Bond: Thr 18, Pro 20, Ala 57, Trp 56, Gln 81; Carbon Hydrogen Bond: Thr 18, Thr 16; Van der Waals: Ile 50, Ala 59,	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Pi-Alkyl)	X: 13,1351 Y: 35,6683 Z: -54,8422

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
		Lys 60, Cys 21, Gly 19, Ser 17, Phe 83, Ser 55, Phe 58		
A8	Adenofir	Carbon Hydrogen Bond: Val 94, Trp 101; Conventional Hydrogen Bond: Trp 96, Met 97, Pro 5, Trp 101; Van der Waals: Ser 54, Pro 53, Met 98, Trp 99, Ala 66, Cys 7, Val 6, Phe 100, Ile 95	Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond)	X: 109,186 Y: -10,5638 Z: -59,978
	Lamivudine	Conventional Hydrogen Bond: Leu 86, Gly 30, Gln 29, Phe 83; Unfavorable Donor-Donor: Gly 30; Van der Waals: Val 77, Gly 85, Ser 13, Pro 11, Thr 31, Ala 28, Gln 81, Trp 82	- Hydrogen Bond (Conventional Hydrogen Bond) - Unfavorable (Unfavorable Donot-Donor)	X: 97,8209 Y: 13,4285 Z: -68,2426
	Telbivudine	Pi-Sigma: Phe 100; Carbon Hydrogen Bond: Ser 54; Conventional Hydrogen Bond: Val 6, Met 97, Trp 99; Van der Waals: Ile 95, Val 94, Pro 5, Cys 7, Ala 66, Met 98, Trp 96, Pro 53	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (pi-sigma; pi-pi T-Shaped)	X: 109,499 Y: -9,64255 Z: -60,1108

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
	Tenofovir	Unfavorable Donor-Donor: Asp 44; Pi-Alkyl: Phe 100; Carbon Hydrogen Bond: Ser 54, Asn 46; Conventional Hydrogen Bond: Ser 54, Asn 46, Ser 55, Gly 45; Van der Waals: Pro 53, Met 98, Ile 50, Thr 43, Trp 56, Trp 65, Trp 99	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Pi-Alkyl) - Unfavorable (Unfavorable donor – donor)	X: 100,319 Y: -15,6087 Z: -53,9625
	Entecavir	Unfavorable Donor-Donor: Ser 74; Pi-Sigma: Val 77; Van der wall: Leu 76, Leu 73, Trp 72, Ser 71, Phe 70, Arg 69, Val 68, Leu 9, Phe 58, Pro 11, Pro 78; Conventional Hydrogen Bond: Val 77	- Hydrogen Bond (Conventional Hydrogen Bond) - Hydrophobic (Pi-Sigma) - Unfavorable (Unfavorable donor – donor)	X: 94,2395 Y: 4,38622 Z: -65,1464
A23	Adenofir	Attractive Charge: Glu 36; Carbon Hydrogen Bond: Leu 48, Glu 36; Conventional Hydrogen Bond: Glu 36, Ser 49, Gln 50; Van der Waals: Ser 61, Ala 38, Pro 39, Thr 37, Pro7, Leu 17, Arg 16, Val 60, Asn 51, Gln 5, Ser 59	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Electrostatic (Attractive Charge)	X: 8,1142 Y: -27,153 Z: 41,269

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
	Lamivudine	Alkyl: Leu 48; Conventional Hydrogen Bond: Val 60, Arg 16, Asn 51; Van der Waals: Gln 50, Pro 39, Ser 59, Pro 7, Gln 5, Ser 61, Leu 17, Glu 36, Thr 52; Unfavorable Acceptor-Acceptor: Asn 51	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Alkyl) - Unfavorable (Unfavorable Acceptor-Acceptor)	X: 8,577 Y: -27,7327 Z: 40,4981
	Telbivudine	Unfavorable Acceptor-Acceptor: Gln 31; Pi-Alkyl: Leu 23, Val 28; Conventional Hydrogen Bond: Val 28; Van der Waals: Phe 1, His 4, Gln 2, Glu 21; Carbon Hydrogen Bond: Ala 29, Pro 9	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Pi-Alkyl) - Unfavorable (Unfavorable Acceptor-Acceptor)	X: 5,69695 Y: -41,1617 Z: 26,4825
	Tenofovir	Pi-Sigma: Phe 1; Conventional Hydrogen Bond: Val 28, Ala 29, Glu 21; Van der Waals: Pro 22, Leu 23, Pro 9, Gln 31, His 27, Val 30	- Hydrogen Bond (Conventional Hydrogen Bond) - Hydrophobic (Pi-Sigma)	X: 6,51581 Y: -43,069 Z: 26,9165

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
A25	Entecavir	Pi-Sigma: Phe 1; Amide-Pi Stacked: Val 28; Pi-Alkyl: Leu 23, Pro 9; Van der Waals: Ala 8, Pro 22, Val 30; Conventional Hydrogen Bond: Glu 21, Ala 29, Gln 31; Carbon Hydrogen Bond: Gln 31	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Pi-Sigma; Amide-Pi Stacked; Pi-Alkyl)	X: 6,30281 Y: -42,5021 Z: 26,5874
		Conventional Hydrogen Bond: Gln 29, Cys 24, leu 62, Phe 34, Met 33, Thr 31; Van der Waals: Gly 30, Lys 60, Trp 63, Trp 65, Ser 32, Ala 66, Ser 67, Thr 25, Thr 23; Carbon Hydrogen Bond: Ser 32	Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond)	X: 94,353 Y: 3,8998 Z: -60,7311
	Lamivudine	Alkyl: Ala 66; Conventional Hydrogen Bond: Cys 24, Thr 26; Van der Waals: Gln 29, Ser 67, Thr 25, Thr 23, Thr 31, Ser 32	- Hydrogen Bond (Conventional Hydrogen Bond) - Hydrophobic (Alkyl)	X: 96,251 Y: 2,22816 Z: -64,7747
	Telbivudine	Pi-Alkyl: Ala 66; Conventional Hydrogen Bond: Cys 24, Thr 26; Carbon Hydrogen Bond: Gln 29; Pi-Donor Hydrogen Bond: Trp 65; Van der Waals: Ser 32, Thr 23, Thr 31 ; Glu 64, Thr 25, Ser 67	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond; Pi-Donor Hydrogen Bond) - Hydrophobic (Pi-Alkyl)	X: 95,6258 Y: 3,1922 Z: -64,464

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
C24	Tenofovir	Conventional Hydrogen Bond: Cys 24, Leu 62, Trp 63, Lys 60; Van der Waals: Lys 22, Ala 66, Thr 23, Gln 29, Ser 27, Thr 25, Thr 26, Trp 65, Glu 64, Tyr 61	Hydrogen Bond (Conventional Hydrogen Bond)	X: 96,2422 Y: 6,18904 Z: -62,6507
		Pi-Alkyl: Ala 66; Conventional Hydrogen Bond: Thr 31, Cys 24, Gln 29; Van der Waals: Ser 67, Thr 23, Glu 64, Lys 22, Leu 62, Trp 63, Tyr 61, Lys 60, Trp 65, Ser 32, Gly 30; Pi-Sulfur: Cys 24	- Hydrogen Bond (Conventional Hydrogen Bond) - Hydrophobic (Pi-Alkyl) - Other (Pi-Sulfur)	X: 96,0781 Y: 4,40844 Z: -63,1749
	Adenofir	Pi-Donor Hydrogen Bond: Trp 96; Conventional Hydrogen Bond: Phe 34, Ser 32; Van der Waals: Met 97, Trp 99, Pro 78, Trp 82, Pro 35, Phe 79, Gln 81, Met 33, Tyr 100	Hydrogen Bond (Conventional Hydrogen Bond; Pi-Donor Hydrogen Bond)	X: 104,593 Y: 17,1668 Z: -54,4018
		Pi-Sulfur: Tyr 100; Alkyl: Pro 35; Conventional Hydrogen Bond: Phe 34; Van der Waals: Ser 32, Trp 82, Trp 96, Met 97, Pro 78, Trp 99, Ser 36, Met 33	- Hydrogen Bond (Conventional Hydrogen Bond) - Hydrophobic (Alkyl) - Other (Pi-Sulfur)	X: 105,585 Y: 16,9009 Z: -53,3015
	Lamivudine (60825)			

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
	Telbivudine (159269)	Pi-Alkyl: Pro 78; Conventional Hydrogen Bond: Ser 32, Trp 99, Trp 96; Van der Waals: Pro 35, Ser 36, Trp 82, Met 33, Phe 34, Phe 79, Met 97	- Hydrogen Bond (Conventional Hydrogen Bond) - Hydrophobic (Pi-Alkyl)	X: 104,221 Y: 16,8379 Z: -55,1604
	Tenofovir (464205)	Pi-Donor Hydrogen Bond: Trp 96; Conventional Hydrogen Bond: Phe 79; Pi-Alkyl: Trp 82; Van der Waals: Pro 35, Phe 34, Ser 36, Trp 99, Met 97, Tyr 100, Pro 78, Ser 32, Gln 81, Met 33	- Hydrogen Bond (Conventional Hydrogen Bond; Pi-Donor Hydrogen Bond) - Hydrophobic (Pi-Alkyl)	X: 104,432 Y: 17,4995 Z: -55,5082
	Entecavir	Unfavorable Donor-Donor: Phe 34; Conventional Hydrogen Bond: Pro 78, Tyr 100, Ser 36; Pi-Pi T-Shaped: Tyr 100; Van der Waals: Met 33, Phe 79, Ser 32, Trp 82, Trp 101, Cys 37, Pro 35, Trp 99	- Hydrogen Bond (Conventional Hydrogen Bond) - Hydrophobic (Pi-Pi T-shaped) - Unfavorable (Unfavorable Donor-Donor)	X: 105,908 Y: 17,9007 Z: -57,7563
C32	Adenofir	Unfavorable Donor-Donor: Asn 23; Carbon Hydrogen Bond: Asp 26; Conventional Hydrogen Bond: His 25, Tyr 40, Pro 62, Ile 61, Lys 60; Van der Waals:	Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond)	X: 74,196 Y: 57,9929 Z: -17,5882

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
		Phe 87, Ala 86, Met 96, Ser 81, Leu 39, Ser 27	Unfavorable (Unfavorable Donor-Donor)	
	Lamivudine	Alkyl: Leu 39; Conventional Hydrogen Bond: Ser 27, Lys 60; Carbon Hydrogen Bond: Pro 88; Van der Waals: Tyr 40, Cys 28, Phe 87, His 25, Arg 59, Val 82, Ser 81, Ala 86, Met 96, Ile 61, Asn 23	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Alkyl)	X: 72,1504 Y: 57,2583 Z: -18,8778
	Telbivudine	Pi-Pi-Shaped: Phe 87; Carbon Hydrogen Bond: His 25; Unfavorable Acceptor-Acceptor: Pro 62; Conventional Hydrogen Bond: Ser 27, Lys 60, Ala 86; Van der Waals: Ser 81, Arg 59, Asn 23, Met 96, Leu 39, Ile 61, Asp 26, Pro 88, Cys 28	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Pi-Pi T-shaped) - Unfavorable (Unfavorable Acceptor-Acceptor)	X: 73,1503 Y: 57,09 Z: -17,6537
	Tenofovir	Unfavorable Acceptor-Acceptor: Lys 60; Pi-Sigma: Tyr 40; Alkyl: Pro 88, Leu 39, Met 96; Conventional Hydrogen Bond:	- Hydrogen Bond (Conventional Hydrogen Bond) - Hydrophobic (Pi-Sigma; Alkyl)	X: 72,0458 Y: 57,9108 Z: -16,8493

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
D59		Asn 23, His 25, Ser 27; Van der Waals: Asp 26, Leu 24, Arg 59, Phe 87, Ala 86, Ser 81	• Unfavorable (Unfavorable Acceptor-Acceptor)	
		Conventional Hydrogen Bond: Ile 61, Asn 23, Pro 62, Tyr 40, Ser 27; Van der Waals: Leu 39, Met 63, Ser 81, Lys 60, Met 96, Pro 88, Phe 87, His 25, Asp 26; Carbon Hydrogen Bond: Tyr 40; Unfavorable Donor-Donor: Tyr 40	• Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) • Unfavorable (Unfavorable Donor-Donor)	X: 72,2926 Y: 58,6778 Z: -18,7832
	Adenofir	Attractive Charge: Asp 10; Carbon Hydrogen Bond: Asp 10; Conventional Hydrogen Bond: Leu 17, Lys 13, Asp 10; Van der Waals: Ala 12, His 11, Pro 14, Ala 15, Tyr 15, Tyr 53, Gly 54, Ser 52, Pro 22, Pro 9, Leu 18, Arg 16	• Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) • Electrostatic (Attractive Charge)	X: 4,21256 Y: 4,85216 Z: -7,66948
		Unfavorable Donor-Donor: Gly 54; Alkyl: Pro 9, Arg 16; Carbon Hydrogen Bond: Leu 17; Conventional Hydrogen Bond: His 11,	• Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond)	X: 1,74205 Y: 4,59332 Z: -7,8049

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
		Asp 10; Van der Waals: Leu 18, Ala 12, Tyr 53, Pro 14, Ala 15	- Hydrophobic (Alkyl) - Unfavorable (Unfavorable Donor-Donor)	
	Telbivudine	Pi-Alkyl: Pro 9; Carbon Hydrogen Bond: Tyr 53, Asp 10; Conventional Hydrogen Bond: Leu 17, Gly 54, Ala 15; Van der Waals: Leu 18, Arg 16, Pro 14, His 11	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Pi-Alkyl)	X: 2,74785 Y: 5,5562 Z: -8,25305
	Tenofovir	Unfavorable Donor-Donor: Gly 54; Attractive Charge: Asp 10; Conventional Hydrogen Bond: Asp 10, Ala 15, Lys 13, Leu 17; Van der Waals: His 11, Pro 14, Ala 12, Arg 16, Leu 18, Pro 9, Pro 22, Val 28, Ala 8, Tyr 53	- Hydrogen Bond (Conventional Hydrogen Bond) - Electrostatic (Attractive Charge) - Unfavorable (Unfavorable Donor-Donor)	X: 4,17846 Y: 4,97446 Z: -7,90531
	Entecavir	Unfavorable Acceptor-Acceptor: Gln 58; Pi-Donor Hydrogen Bond: His 66, Ser 64; Pi-Pi-Shaped: His 66; Conventional Hydrogen Bond: Gln 5, His 4, Glu 21; Van der Waals: Ser 59, Asp 3, Pro 6, Pro 7	- Hydrogen Bond (Conventional Hydrogen Bond; Pi-Donor Hydrogen Bond) - Hydrophobic (Pi-Pi T-shaped)	X: -1,24944 Y: -15,7009 Z: -4,74059

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
E20	Adenofir	Unfavorable Donor-Donor: Arg 16; Attractive Charge: Asp 3; Carbon Hydrogen Bond: Asp 3 Pi-Cation: His 27; Conventional Hydrogen Bond: Asp 3, Gln 5; Van der Waals: Leu 48, Leu 18, Leu 17, Val 40, Pro 39, Lys 13, Pro 14, His 4, Ala 15	Unfavorable (Unfavorable Acceptor-Acceptor)	
			- Electrostatic (Attractive Charge; Pi-Cation) - Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Unfavorable (Unfavorable Donor-Donor)	X: 12,1396 Y: -6,56856 Z: -5,51068
	Lamivudine	Alkyl: Pro 14; Carbon Hydrogen Bond: Asp 3; Conventional Hydrogen Bond: Gln 5, His 4; Van der Waals: Thr 37, Lys 13, Pro 39, Val 40, Ala 15, Arg 16, Leu 17, His 27, Leu 48	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Alkyl)	X: 12,669 Y: -5,88347 Z: -5,526
	Telbivudine	Unfavorable Donor-Donor: Val 28; Pi-Alkyl: Leu 17; Pi-Donor Hydrogen Bond: Val 40; Van der Waals: Pro 42, Phe 41, Gln	- Hydrogen Bond (Pi-Donor Hydrogen Bond) - Hydrophobic (Pi-Alkyl)	X: 9,5549 Y: -8,34595 Z: -4,75765

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
		2, Leu 48, Arg 16, Ala 15, Pro 14, His 27, Asp 3, Ala 29	• Unfavorable (Unfavorable Donor-Donor)	
	Tenofovir	Attractive Charge: Asp 3; Pi-Cation: His 27; Hydrogen Bond: His 27, Arg 16, Gln 5; Van der Waals: Leu 17, Ala 15, Leu 48, Gln 2, Lys 13, His 4, Pro 39, Pro 14, Val 40, Val 28	• Hydrogen Bond (Hydrogen Bond) • Electrostatic (Attractive Charge; Pi-Cation)	X: 12,0387 Y: -6,6335 Z: -5,64961
	Entecavir	Pi-Alkyl: Pro 39, Pro 14; Conventional Hydrogen Bond: Gln 5, Asp 3; Van der Waals: Lys 13, Val 28, His 4, Ala 8, Leu 48, Gln 2, Pro 42, Phe 41, Arg 16, Val 40, Leu 17	• Hydrogen Bond (Conventional Hydrogen Bond) • Hydrophobic (Pi-Alkyl)	X: 11,0816 Y: -5,73585 Z: -5,49482
E28	Adenofir	Attractive Charge: Asp 47; Unfavorable Donor-Donor: Thr 21; Carbon Hydrogen Bond: Gly 5; Conventional Hydrogen Bond: Asp 47, Leu 7, Ile 55, Gln 4; Van der Waals: Gly 22, Pro 54, Ser 20, Pro 8, Val 9, Met 6, Pro 56, Pro 23, Gly 48	• Electrostatic (Attractive Charge) • Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) • Unfavorable (Unfavorable Donor-Donor)	X: -2,58108 Y: 15,2893 Z: -38,3316

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
	Lamivudine	Alkyl: Ile 55; Carbon Hydrogen Bond: Pro 56; Conventional Hydrogen Bond: Gly 1, Tyr 3, Gln 4, Asp 47, Thr 46; Van der Waals Thr 43, Pro 45, Pro 23, Ile 53, Pro 54, Val 83, Glu 2, Gln 84	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Hydrophobic (Alkyl)	X: 1,20711 Y: 19,8278 Z: -42,4648
	Telbivudine	Carbon Hydrogen Bond: Pro 54, Gly 48; Conventional Hydrogen Bond: Leu 7, Met 6, Asn 49, Asp 47, Gln 4; Unfavorable Acceptor-Acceptor: Gln 4; Van der Waals: Pro 56, Gly 5, Pro 8, Ser 20, Gly 22, Thr 21, Ile 55, Pro 23	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Unfavorable (Unfavorable Acceptor-Acceptor)	X: -1,51255 Y: 15,6553 Z: -38,1296
	Tenofovir	Attractive Charge: Asp 47; Unfavorable Donor-Donor: Thr 21; Unfavorable Acceptor-Acceptor: Gln 4; Conventional Hydrogen Bond: Ile 55, Leu 7, Gln 4; Carbon Hydrogen Bond: Pro 54, Gly 5; Van der Waals: Pro 56, Met 6, Pro 8, Val 9, Ser 20, Gly 22, Pro 23	- Hydrogen Bond (Conventional Hydrogen Bond; Carbon Hydrogen Bond) - Electrostatic (Attractive Charge) - Unfavorable (Unfavorable Donor-Donor; Unfavorable Acceptor-Acceptor)	X: -2,39188 Y: 15,3412 Z: -38,3684

Samples	Antivirals	Residu	Type of Bond	Binding Coordinates
	Entecavir	Unfavorable Donor-Donor: Leu 7; Unfavorable Donor-Donor: Ile 55; Pi-Alkyl: Pro 23; Pi-Donor Hydrogen Bond: Gln 4; Conventional Hydrogen Bond: Asp 47, Ile 56; Van der Waals: Pro 56, Pro 54, Val 9, Ser 20, Pro 8, Met 6, Gly 5, Asn 49, Gly 48	- Hydrogen Bond (Conventional Hydrogen Bond; Pi-Donor Hydrogen Bond) - Hydrophobic (Pi-Alkyl) - Unfavorable (Unfavorable Donor-Donor; Unfavorable Donor-Donor)	X: -1,357 Y: 15,8063 Z: -38,3795