Design and Identification of Lead Compounds Targeting Nipah G Attachment Glycoprotein by In Silico Approaches

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Authors’ contributions

This work was carried out in collaboration among all authors. *All authors read and approved the final manuscript.

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ABSTRACT

Nipah virus (NiV) caused several outbreaks in Asian countries, including the latest one from the Kerala state of India. There is no drug available against NiV till now, despite its urgent requirement. There are reports about the anti-influenza viral drug Favipiravir, which has positively affected the Nipah virus in vitro models. In the current work, we have provided a computational screening for NiV inhibitors. Twenty-two designed compounds from favipiravir and Nipah glycoprotein, 3D11, were chosen and performed molecular docking to analyse the various conformations and interactions with the amino acids; further, their physicochemical and ADMET properties were also computed. The compound 5_Favipiravir have an excellent docking score (-6.16 kcal/mol), followed by compound 4_Favipiravir and 19_Favipiravir with docking score of -5.50 and -5.38 kcal/mol respectively. The three compounds had the respective heterocyclic moieties such as pyrazole, imidazole and pyrazinone. All the twenty-two designed compounds obey the Lipinski rule of five, which infer that they will not have problems with oral bioavailability. Thus, it is concluded that the incorporated heterocyclic groups in favipiravir can add to the anti-Nipah activity; hence it can act as future leads for the treatment for the disease caused by Nipah virus.

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1. INTRODUCTION

Nipah virus (NiV) is an evolving virus that can cause severe respiratory disease and deadly encephalitis in humans, including paramyxovirus (Henipavirus, Paramyxovirinae subfamily, family Paramyxoviridae, the order of Mononegavirales). Several significant individual outbreaks occurred in the twenty-first century beginning in Bangladesh and India in 2001 [1]. Similar explosions were also reported in two villages in the Philippines in 2014. In Kerala, a southern Indian state, the latest uprising started in May 2018 [2,3].

Therapy is limited to treatment and support. In preventing hospital-acquired infections, standard infection prevention procedures and barrier nursing strategies are critical as NiV encephalitis can be transmitted from person to person. Ribavirin, a hepatitis C antiviral drug, has also proved helpful in vitro, but to date, human trials have not been completed with doubt regarding the clinical usefulness of ribavirin [4,5]. Ribavirin is a therapy that is approved or tolerated for a variety of viral infections [6]. In vitro experiments showed that ribavirin acts against replication of Hendra and Nipah viruses [7,8].

Furthermore, it was earlier demonstrated that anti-malarial drug chloroquine blocks the essential proteolytic processing required to develop the structure and function of Hendra F glycoprotein virus and chloroquine [9] and, not surprisingly, was later shown to inhibit Nipah and Hendra infection in cell culture [10]. There have been two experiments in hamsters and one in non-human primates (African Green Monkey (A Green monkey)) that only delayed treatment with ribavirin but not prevented death following infection by Nipah Virus [11,12]. The use in the post-exposure therapy in ferret models of a human monoclonal antibody targeting Nipah G glycoprotein has been tested and has proved to be effective [13,14].

The chemical modification of the pyrazine analogue initially screened for in vitro anti-influenza virus activity in cells discovered Favipiravir [15]. Favipiravir inhibits influenza viral RNA polymerase [16] and is a versatile and effective inhibitor that works against all subtypes and strains of the flu virus, including those susceptible or immune to neuraminidase and M2 inhibitors on the market. Antiviral activities against other RNA viruses were also demonstrated by Favipiravir [17]. These data indicate that favipiravir is potent medicine for treating influenza virus infections and various RNA viruses.

Favipiravir disrupted the viral genome in the centre of the replication process in a drug additive test. Antiviral favipiravir action was attenuated by purine nucleosides or purine bases, suggesting that favipiravir interacts with purine nucleosides instead of pyrimidine nucleosides [16].

Nowadays, computer-aided drug design is one of the essential techniques of rational drug design. The in silico study involves different computational methods which help to reduce the time and cost of the drug discovery process [18]. The high-throughput automated screening method is time-consuming, as more compounds must be trialled. Structure-based drug design is helpful to find out the new lead compound, which is active against the target. This process required a lesser number of compounds that may take into the trial [19].

In continuation of the in silico studies conducted earlier [20,21], in this study, we have designed 22 compounds of favipiravir containing pyrazine as the moiety and other heterocyclic rings to identify novel inhibitors of NiV using different in silico methods. Molecular docking, physicochemical properties and ADMET properties were determined by using Schrodinger software. The comparison of in silico results was made with standard drug favipiravir.

2. METHODOLOGY

2.1 Reaction Enumeration

In this method, numerous compounds can be generated as a derivative of the parent compound. There is a possibility to replace the substituent based on the chemical nature of the compounds. In this study, the hydrogen atom in the amino group of Favipiravir was replaced with aromatic monocyclic groups available in Schrodinger enumeration databases [22] (Table 1).
### Table 1. Chemical structures and SMILES of the designed compounds

| S. NO. | Ligand ID   | Chemical structure | R1       |
|--------|-------------|--------------------|----------|
| 1.     | 1_Favipiravir | ![Image](image1.png) | pyrrole  |
| 2.     | 2_Favipiravir | ![Image](image2.png) | furan    |
| 3.     | 3_Favipiravir | ![Image](image3.png) | thiophene|
| 4.     | 4_Favipiravir | ![Image](image4.png) | imidazole|
| 5.     | 5_Favipiravir | ![Image](image5.png) | pyrazole |
| 6.     | 6_Favipiravir | ![Image](image6.png) | oxazole_2|
| 7.     | 7_Favipiravir | ![Image](image7.png) | isoxazole_2|
| S. NO. | Ligand ID  | Chemical structure            | R1            |
|-------|------------|-------------------------------|---------------|
| 8     | 8_Favipiravir | ![Chemical structure 8](image) | thiazole_2    |
| 9     | 9_Favipiravir | ![Chemical structure 9](image) | isothiazole_2 |
| 10    | 10_Favipiravir | ![Chemical structure 10](image) | 125_triazole  |
| 11    | 11_Favipiravir | ![Chemical structure 11](image) | 125_oxadiazole |
| 12    | 12_Favipiravir | ![Chemical structure 12](image) | 124_thiadiazole |
| 13    | 13_Favipiravir | ![Chemical structure 13](image) | tetrazole     |
| 14    | 14_Favipiravir | ![Chemical structure 14](image) | benzene       |
| S. NO. | Ligand ID | Chemical structure | R1   |
|-------|-----------|--------------------|------|
| 15.   | 15_Favipiravir | ![Chemical structure](image1) | pyridine |
| 16.   | 16_Favipiravir | ![Chemical structure](image2) | pyridone |
| 17.   | 17_Favipiravir | ![Chemical structure](image3) | pyridazinone |
| 18.   | 18_Favipiravir | ![Chemical structure](image4) | pyrimidone-1 |
| 19.   | 19_Favipiravir | ![Chemical structure](image5) | pyrazinone |
| 20.   | 20_Favipiravir | ![Chemical structure](image6) | pyrazine |
| 21.   | 21_Favipiravir | ![Chemical structure](image7) | pyridazine |
2.2 Ligand Preparation

All the ligands were neutralised, desalted, prevented from tautomers generation to retain a specific chirality by the Ligprep application tool in Schrodinger [23]. Only one structure was generated per ligand.

2.3 Protein Preparation

The specific Nipah protein 3D11 was imported from the protein data bank (PDB) [24] and processed by the Protein Preparation Wizard application tool in Schrodinger. Pre-processing of the protein was done by assigning bond orders by adding hydrogen, creating zero-order bonds to metals, creating disulphide bonds, filling the missing side chain and loops by using the prime module. All the water molecules were deleted beyond 5 Å, from the hetero groups. The hetero states of the ligand were maintained in the pH range 7±2.

2.4 Receptor Grid Generation

Grid generation specifies the 3D (X,Y,Z-axis) location where the ligand binds. A grid was generated for the minimised protein by using the tool Receptor Grid Generation in Schrodinger.

2.5 Ligand Docking

Ligand docking was performed by Glide-XP application in Schrodinger [25] in the Glide --XP panel, the receptor grid generated was uploaded, and the prepared ligands were imported as out.maegz file to the working panel. In the precision tab, XP (extra precision) was selected, and the method adopted was flexible docking in ligand sampling [24].

2.6 Physicochemical Properties

The physicochemical properties were calculated by QikProp application of Schrodinger software [26]. The prepared ligands were selected and incorporated into the Qikprop tool and processed. The properties Molecular weight, Log P, QPlogPo/w, donor-HB, accept-HB, which analyse Lipinski Rule of five [27] were assessed.

2.7 ADMET Properties

The ADMET properties were computed by the QikProp application of Schrodinger software [28]. The prepared ligand was selected and incorporated into the Qikprop tool and processed. The features such as QPPCaco, % Human oral absorption, QPlogKhsa, SASA, QPlogHERG was analysed.

3. RESULTS AND DISCUSSION

3.1 Molecular Docking

In the present study, twenty-two designed compounds and Nipah glycoprotein, 3D11, were chosen and performed molecular docking to analyse the various conformations and interactions with the amino acids (Fig. 1). On further analysis of the results, thirteen favipiravir derivatives (5_Favipiravir, 4_Favipiravir, 19_Favipiravir, 8_Favipiravir, 15_Favipiravir, 12_Favipiravir, 18_Favipiravir, 20_Favipiravir, 17); article no. JPRI.72296; James et al.; JPRI, 33(40A): 156-169, 2021;
22_Favipiravir, 1_Favipiravir, 3_Favipiravir, 6_Favipiravir, 21_Favipiravir) were found to have docking scores higher than the standard favipiravir, suggesting that they might have an excellent binding with the Nipah virus protein. The docking scores and amino acid interactions are tabulated in Tables 2 & 3; 2D and 3D conformations are reported in Figs. 2-4.

Table 2. Docking results of ligand interacting with the active site of 3D11 protein

| S.No | Ligand ID  | Glide XP docking score (kcal/mol) | Glide energy (kcal/mol) | Heterocyclic group               |
|------|------------|-----------------------------------|-------------------------|----------------------------------|
| 1.   | 5_Favipiravir | -6.16                             | -32.86                  | Pyrazole                         |
| 2.   | 4_Favipiravir | -5.50                             | -36.06                  | Imidazole                        |
| 3.   | 19_Favipiravir | -5.38                             | -37.21                  | Pyrazinone                       |
| 4.   | 8_Favipiravir | -4.37                             | -31.05                  | Thiazole_2                       |
| 5.   | 15_Favipiravir | -4.37                             | -32.19                  | Pyridine                         |
| 6.   | 12_Favipiravir | -4.35                             | -31.74                  | 124_thiadiazole                  |
| 7.   | 18_Favipiravir | -4.31                             | -31.55                  | pyrimidone-1                     |
| 8.   | 20_Favipiravir | -4.31                             | -31.58                  | Pyrazine                         |
| 9.   | 22_Favipiravir | -4.12                             | -31.43                  | 135_triazine                     |
| 10.  | 1_Favipiravir  | -3.92                             | -30.85                  | Pyrrole                          |
| 11.  | 3_Favipiravir  | -3.85                             | -32.14                  | Thiophene                        |
| 12.  | 6_Favipiravir  | -3.75                             | -32.03                  | oxazole_2                        |
| 13.  | 21_Favipiravir | -3.73                             | -31.76                  | Pyridazine                       |
| 14.  | 7_Favipiravir  | -3.44                             | -33.99                  | isoaxazole_2                     |
| 15.  | 2_Favipiravir  | -3.41                             | -32.28                  | Furan                            |
| 16.  | 10_Favipiravir | -3.41                             | -32.49                  | 125_triazole                     |
| 17.  | 13_Favipiravir | -3.29                             | -37.39                  | Tetrazole                        |
| 18.  | 11_Favipiravir | -3.28                             | -32.21                  | 125_oxadiazole                   |
| 19.  | 9_Favipiravir  | -3.24                             | -31.72                  | isothiazole_2                    |
| 20.  | 17_Favipiravir | -3.09                             | -33.25                  | Pyridazine                       |
| 21.  | 16_Favipiravir | -2.98                             | -30.63                  | Pyridone                         |
| 22.  | 14_Favipiravir | -1.81                             | -27.61                  | Benzene                          |
| 23.  | Favipiravir    | -3.70                             | -19.23                  | Standard                         |
Table 3. Ligand interactions with the protein 3D11

| S.No | Ligand ID     | Hydrophobic interaction with ligand                        | Polar interaction with ligand | H-bond with ligand | pication |
|------|---------------|----------------------------------------------------------|-------------------------------|--------------------|----------|
| 1.   | 5_Favipiravir | Tyr 309, Ile 304, Ile 401, Phe 369, Tyr 401, Ile 408, Leu 409 | Thr 308, Ser 307, Ash 306, Ser 405, Hid 406 | Thr 308, Hid 406, Tyr 407 | -        |
| 2.   | 4_Favipiravir | Tyr 308, Leu 305, Ile 304, Leu 409, Phe 369, Ile 408 Tyr 407, Ile 401 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Thr 308, Ile 304, Hid 406, Arg 402 | -        |
| 3.   | 19_Favipiravir | Tyr 309, Leu 305, Ile 304, Phe 369, Ile 401, Tyr 407, Leu 409 | Thr 308, Ser 307, Asn 306, Ser 405, Hid 406 | Ser 307, Hid 406 | Arg 402  |
| 4.   | 8_Favipiravir | Tyr 309, Leu 305, Ile 304, Ile 401, Phe 369, Tyr 407, Leu 409 | Thr 308, Ser 307, Asn 306, Ser 405, Hid 406 | Ile 304, Hid 406 | Arg 402  |
| 5.   | 15_Favipiravir | Tyr 309, Leu 305, Ile 304, Leu 409, Phe 369, Ile 401, Tyr 407, Ile 401 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Thr 308, Tyr 407, Arg 402 | -        |
| 6.   | 12_Favipiravir | Tyr 309, Leu 305, Ile 304, Ile 401, Phe 369, Tyr 407, Leu 409 | Thr 308, Ser 307, Asn 306, Ser 405, Hid 406 | Ile 304, Hid 406 | Arg 402  |
| 7.   | 18_Favipiravir | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Ser 407, Asn 406, Tyr 407, Arg 402 | -        |
| 8.   | 20_Favipiravir | Tyr 309, Leu 305, Ile 304, Phe 369, Ile 401, Tyr 407, Leu 409 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Thr 308, Tyr 407, Arg 402 | -        |
| 9.   | 22_Favipiravir | Tyr 309, Leu 305, Ile 304, Ile 401, Tyr 407, Leu 409 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Hid 406, Ile 304 | Arg 402  |
| 10.  | 1_Favipiravir  | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401, Leu 409, Phe 369 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Hid 406, Ile 304 | Arg 402  |
| 11.  | 3_Favipiravir  | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401, Leu 409, Phe 369 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Thr 308, Ile 304 | Arg 402  |
| 12.  | 6_Favipiravir  | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401, Leu 409, Phe 369 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Hid 406, Ile 304 | Arg 402  |
| 13.  | 21_Favipiravir | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401, Leu 409, Phe 369 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Thr 308, Ile 304 | Arg 402  |
| 14.  | 7_Favipiravir  | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401, Leu 409, Phe 369 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Hid 406, Ile 304 | Arg 402  |
| 15.  | 2_Favipiravir  | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401, Leu 409, Phe 369 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Hid 406, Ile 304 | Arg 402  |
| 16.  | 10_Favipiravir | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401, Leu 409, Phe 369 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Hid 406, Thr 308, Arg 402 | -        |
| 17.  | 13_Favipiravir | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401, Leu 409, Phe 369 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Hid 406, Tyr 407 | Arg 402  |
### Table

| S.No | Ligand ID | Hydrophobic interaction with ligand | Polar interaction with ligand | H-bond | pi-cation |
|------|-----------|-----------------------------------|--------------------------------|---------|-----------|
|      | vir       | Ile 401, Leu 409, Phe 369 | Asn 306, Hid 406, Ser 405 | 407, Ile 401 | 402       |
| 18.  | 11_Favipiravir | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 408, Ile 401, Leu 409, Phe 369 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Tyr 407 | Arg 402 |
| 19.  | 9_Favipiravir | Ile 304, Leu 305, Tyr 309, Ile 401, Tyr 407, Leu 409 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Thr 308, Hid 406 | Arg 402 |
| 20.  | 17_Favipiravir | Tyr 309, Leu 305, Ile 304, Ile 401, Tyr 407, Leu 409 | Thr 308, Ser 307, Asn 306, Ser 405, Hid 406, Thr 308, Hid 406 | Arg 402 |
| 21.  | 16_Favipiravir | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Thr 308 | Arg 402 |
| 22.  | 14_Favipiravir | Tyr 309, Leu 305, Ile 304, Tyr 407, Ile 401 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Ser 307, Tyr 407, Hid 406 | Arg 402 |
| 23.  | Favipiravir | Tyr 309, Ile 304, Leu 409, Tyr 407, Ile 401 | Thr 308, Ser 307, Asn 306, Hid 406, Ser 405 | Ser 307, Tyr 407, Hid 406 | Arg 402 |

### 3.2 Binding of 5_Favipiravir with 3D11

The active amino acids in the protein 3D11, which made hydrophobic interaction with the 5_Favipiravir was found to be Tyr 309, Ile 304, Ile 401, Phe 369, Tyr 401, Ile 408, Leu 409; polar interaction was Thr 308, Ser 307, Asp 306, Ser 405, Hid 406 and hydrogen bond was Thr 308, Hid 406, Tyr 407. It showed a docking score of -6.165 kcal/mol compared with the standard drug Favipiravir (-3.706 kcal/mol) (Figs. 2a & 2b).

### 3.3 Binding of 4_Favipiravir with 3D11

The docking score of 4_Favipiravir with 3D11 is -5.501 kcal/mol compared with the standard drug Favipiravir (-3.706 kcal/mol). The amino acids in the protein 3D11 which are responsible for hydrophobic interactions are Tyr 308, Leu 305, Ile 304, Leu 409, Phe 369, Tyr 401, Ile 401; polar interactions are Thr 308, Ser 307, Asp 306, Ser 405, Hid 406 and hydrogen bondings are Thr 308, Ile 304, Hid 406, Arg 402 (Figs. 3a & 3b).

### 3.4 Binding of 19_Favipiravir with 3D11

The compound 19_Favipiravir interacted with the protein 3D11 with the docking score of -5.38 kcal/mol. The respective active amino acids Tyr 309, Leu 305, Ile 304, Phe 369, Ile 401, Tyr 407, Leu 409 made hydrophobic interaction with ligand; Thr 308, Ser 307, Asn 306, Ser 405, Hid 406 are responsible for polar interaction with ligand; Ser 307, Hid 406 for H-bond; and the particular amino acid for Arg 402 pi-cation (Figs. 4a & 4b).

### 3.5 Physicochemical Properties and Rule of Five Properties

All the compounds have their molecular weight below 500 ranging from 150-260. The calculated log P value of the compounds is below 5. The compounds under investigation possess hydrogen bond donors (<5) and hydrogen bond acceptors (<10) within the limit. Based on the experimental values (Table 4), it was found that all the compounds have values within the normal range, and there is no violation of Lipinski’s rule of five. Hence the compounds are expected to possess excellent oral bioavailability.

### 3.6 In silico ADMET Studies

The results show that compounds have better scores for Caco-2 permeability, human oral absorption, Total solvent accessible surface area, human serum albumin binding (Table 5).
James et al.; JPRI, 33(40A): 156-169, 2021; Article no.JPRI.72296

Fig. 2a. 2D Conformation of 5_Favipiravir with 3D11 protein

Fig. 2b. 3D Conformation of 5_Favipiravir with 3D11 protein

Fig. 3a. 2D Conformation of 4_Favipiravir with 3D11 protein
Fig. 3b. 3D Conformation of 4_Favipiravir with 3D11 protein

Fig. 4a. 2D Conformation of 19_Favipiravir with 3D11 protein

Fig. 4b. 3D Conformation of 19_Favipiravir with 3D11 protein
### Table 4. Physicochemical properties of designed compounds

| S.No | Ligand ID   | Molecular weight | Log P | QPlogPo/w | Donor HB | acceptHB | PSA | Volume | rotor |
|------|-------------|------------------|-------|-----------|----------|----------|-----|--------|-------|
| 1.   | 1_Favipiravir | 222.17           | 1.09  | 1         | 4.5      | 101.67   | 679.24 | 2      |
| 2.   | 2_Favipiravir | 223.16           | 0.96  | 0         | 4.5      | 96.55    | 652.07 | 2      |
| 3.   | 3_Favipiravir | 239.22           | 1.89  | 0         | 4        | 87.45    | 701.9  | 2      |
| 4.   | 4_Favipiravir | 223.16           | 0.93  | 0         | 4.5      | 115.54   | 668.16 | 2      |
| 5.   | 5_Favipiravir | 223.16           | 0.25  | 1         | 5.5      | 117.88   | 667.93 | 2      |
| 6.   | 6_Favipiravir | 224.15           | -0.17 | 0         | 6        | 110.71   | 643.75 | 2      |
| 7.   | 7_Favipiravir | 224.15           | -0.14 | 0         | 5.5      | 115.39   | 658.81 | 2      |
| 8.   | 8_Favipiravir | 240.21           | 0.64  | 0         | 5.5      | 100.31   | 692.72 | 2      |
| 9.   | 9_Favipiravir | 240.21           | 0.94  | 0         | 5.5      | 102.80   | 690.09 | 2      |
| 10.  | 10_Favipiravir| 224.15           | -1.28 | 0         | 8        | 123.08   | 662.64 | 2      |
| 11.  | 11_Favipiravir| 225.13           | -0.98 | 0         | 6.5      | 134.14   | 645.72 | 2      |
| 12.  | 12_Favipiravir| 241.19           | -0.22 | 0         | 6.5      | 115.89   | 681.29 | 2      |
| 13.  | 13_Favipiravir| 225.14           | -2.24 | 0         | 9        | 141.58   | 650.65 | 2      |
| 14.  | 14_Favipiravir| 233.20           | 2.01  | 0         | 4        | 87.18    | 734.08 | 2      |
| 15.  | 15_Favipiravir| 234.18           | 0.63  | 0         | 5.5      | 100.13   | 719.83 | 2      |
| 16.  | 16_Favipiravir| 250.18           | 0.15  | 0         | 6.5      | 119.78   | 746.36 | 2      |
| 17.  | 17_Favipiravir| 251.17           | -0.10 | 0         | 6.5      | 134.32   | 736.88 | 2      |
| 18.  | 18_Favipiravir| 251.17           | -0.88 | 0         | 8        | 132.63   | 733.63 | 2      |
| 19.  | 19_Favipiravir| 251.17           | -0.40 | 1         | 7.5      | 140.89   | 729.52 | 2      |
| 20.  | 20_Favipiravir| 235.17           | -0.06 | 0         | 6.5      | 112.10   | 710.12 | 2      |
| 21.  | 21_Favipiravir| 235.17           | -0.48 | 0         | 7        | 116.08   | 706.66 | 2      |
| 22.  | 22_Favipiravir| 236.16           | -0.90 | 0         | 7.5      | 125.05   | 697.30 | 2      |
| 23.  | Favipiravir   | 157.10           | -0.40 | 1         | 4        | 104.95   | 479.10 | 1      |

### Table 5. Predicted in silico ADMET properties of designed compounds

| S.No: | Ligand ID | QPPCaco | % Human oral absorption | QPlogKhsa | SASA | Rule of five | Rule of three |
|-------|-----------|---------|-------------------------|-----------|------|-------------|---------------|
| 1.    | 1_Favipiravir | 241.05  | 76.01                   | -0.42     | 427.51 | 0           | 0             |
| 2.    | 2_Favipiravir | 442.62  | 79.96                   | -0.77     | 405.89 | 0           | 0             |
| 3.    | 3_Favipiravir | 488.16  | 86.16                   | -0.49     | 438.51 | 0           | 0             |
| 4.    | 4_Favipiravir | 148.07  | 71.28                   | -0.73     | 422.93 | 0           | 0             |
| 5.    | 5_Favipiravir | 124.55  | 65.93                   | -0.61     | 422.39 | 0           | 0             |
| 6.    | 6_Favipiravir | 263.69  | 69.28                   | -1.20     | 402.63 | 0           | 0             |
| 7.    | 7_Favipiravir | 106.36  | 62.36                   | -1.02     | 418.44 | 0           | 0             |
| 8.    | 8_Favipiravir | 311.78  | 75.34                   | -0.92     | 435.19 | 0           | 0             |
| 9.    | 9_Favipiravir | 208.38  | 73.97                   | -0.80     | 435.75 | 0           | 0             |
| 10.   | 10_Favipiravir| 123.58  | 56.88                   | -1.68     | 420.02 | 0           | 0             |
| 11.   | 11_Favipiravir| 54.08   | 52.22                   | -1.33     | 409.07 | 0           | 0             |
| 12.   | 12_Favipiravir| 133.8   | 63.68                   | -1.22     | 433.66 | 0           | 0             |
| 13.   | 13_Favipiravir| 43.03   | 43.04                   | -1.98     | 414.66 | 0           | 0             |
| 14.   | 14_Favipiravir| 499.11  | 87.03                   | -0.40     | 455.04 | 0           | 0             |
| 15.   | 15_Favipiravir| 270.53  | 74.17                   | -0.84     | 447.20 | 0           | 0             |
| 16.   | 16_Favipiravir| 168.00  | 67.69                   | -1.03     | 460.59 | 0           | 0             |
| 17.   | 17_Favipiravir| 99.13   | 62.05                   | -1.06     | 456.99 | 0           | 0             |
| 18.   | 18_Favipiravir| 91.90   | 56.88                   | -1.47     | 453.78 | 0           | 0             |
| 19.   | 19_Favipiravir| 58.34   | 56.17                   | -0.82     | 453.00 | 0           | 0             |
| 20.   | 20_Favipiravir| 183.49  | 67.06                   | -1.14     | 443.57 | 0           | 0             |
| 21.   | 21_Favipiravir| 122.98  | 61.50                   | -1.28     | 440.37 | 0           | 0             |
| 22.   | 22_Favipiravir| 90.32   | 56.65                   | -1.44     | 439.99 | 0           | 0             |
| 23.   | Favipiravir   | 111.54  | 61.2                    | -0.74     | 318.63 | 0           | 0             |
4. CONCLUSIONS

Twenty-two compounds were designed from the compound favipiravir and screened for their anti-Nipah activity by molecular docking and their ADMET properties were computed. The compound 5_Favipiravir have an excellent docking score, i.e., -6.16 kcal/mol, followed by compound 4_Favipiravir and 19_Favipiravir with docking score of -5.50 and -5.38 kcal/mol respectively. The three compounds had the respective heterocyclic moieties such as pyrazole, imidazole and pyrazinone. On further analysis of the results, thirteen favipiravir derivatives were found to have docking scores higher than the standard favipiravir, suggesting that they might have an excellent binding with the Nipah virus protein. All the twenty-two designed compounds obey the Lipinski rule of five, which infer that they will not have problems with oral bioavailability. Thus, it is concluded that the incorporated heterocyclic compounds can add to the anti-Nipah activity; hence it can act as future leads for the treatment for the disease caused by the Nipah virus.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ang BS, Lim TC, Wang L. Nipah virus infection. Journal of clinical microbiology. 2018;56(6).
2. Paul L. Nipah virus in Kerala: a deadly Zoonosis. Clinical Microbiology and Infection. 2018;24(10):1113-4.
3. Daszak P, Zambrana-Torrelio C, Bogich TL, Fernandez M, Epstein JH, Murray KA, Hamilton H. Interdisciplinary approaches to understanding disease emergence: the past, present, and future drivers of Nipah virus emergence. Proceedings of the National Academy of Sciences. 2013;110(Supplement 1):3681-8.
4. Banerjee S, Gupta N, Kodan P, Mittal A, Ray Y, Nischal N, Soneja M, Biswas A, Wig N. Nipah virus disease: A rare and intractable disease. Intractable & rare diseases research. 2019;2018-01130.
5. Sidwell RW, Huffman JH, GP Khare L, Allen B, JT Witkowski R, Robins K. Broad-spectrum antiviral activity of virazole: 1-f8-D-ribofuranosyl-1, 2, 4-triazole-3-carboxamide. Science. 1972; 177(4050): 705-6.
6. Snell NJ. Ribavirin-current status of a broad spectrum antiviral agent. Expert opinion on pharmacotherapy. 2001; 2(8):1317-24.
7. Aljofan M, Saubern S, Meyer AG, Marsh G, Meers J, Mungall BA. Characteristics of Nipah virus and Hendra virus replication in different cell lines and their suitability for antiviral screening. Virus research. 2009; 142(1-2):92-9.
8. Wright PJ, Crameri G, Eaton BT. RNA synthesis during infection by Hendra virus: an examination by quantitative real-time PCR of RNA accumulation, the effect of ribavirin and the attenuation of transcription. Archives of virology. 2005; 150(3):521-32.
9. Pager CT, Wurth MA, Dutch RE. Subcellular localisation and calcium and pH requirements for proteolytic processing of the Hendra virus fusion protein. Journal of virology. 2004;78(17):9154-63.
10. Porotto M, Orefice G, Yokoyama CC, Mungall BA, Realubit R, Sganga ML, Aljofan M, Whitt M, Glickman F, Moscona A. Simulating henipavirus multicycle replication in a screening assay leads to identification of a promising candidate for therapy. Journal of virology. 2009; 83(10):5148-55.
11. Freiberg AN, Worthy MN, Lee B, Holbrook MR. Combined chloroquine and ribavirin treatment does not prevent death in a hamster model of Nipah and Hendra virus infection. The Journal of general virology. 2010;91(Pt 3):765.
12. Georges-Courbot MC, Contamin H, Faure C, Loth P, Baize S, Leyssen P, Neyts J,
Deubel V. Poly (l)-poly (C12U) but not ribavirin prevents death in a hamster model of Nipah virus infection. Antimicrobial agents and chemotherapy. 2006;50(5):1768-72.

13. Bossart KN, Zhu Z, Middleton D, Klipper J, Cramer G, Bingham J, McEachern JA, Green D, Hancock TJ, Chan YP, Hickey AC. A neutralising human monoclonal antibody protects against lethal disease in a new ferret model of acute nipah virus infection. PLoS Pathog. 2009;5(10):e1000642.

14. Zhu Z, Bossart KN, Bishop KA, Cramer G, Dimitrov AS, McEachern JA, Feng Y, Middleton D, Wang LF, Broder CC, Dimitrov DS. Exceptionally potent cross-reactive neutralisation of Nipah and Hendra viruses by a human monoclonal antibody. The Journal of infectious diseases. 2008;197(6):846-53.

15. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proceedings of the Japan Academy, Series B. 2017;93(7):449-63.

16. Furuta Y, Takahashi K, Kuno-Maekawa M, Sangawa H, Uehara S, Kozaki K, Nomura N, Egawa H, Shiraki K. Mechanism of action of T-705 against influenza virus. Antimicrobial agents and chemotherapy. 2005;49(3):981-6.

17. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral research. 2013;100(2):446-54.

18. Shoichet BK. Virtual screening of chemical libraries. Nature. 2004;432(7019):862-5.

19. Ripphausen P, Nisius B, Bajorath J. State-of-the-art in ligand-based virtual screening. Drug discovery today. 2011;16(9-10):372-6.

20. James JP, Kumar P, Kumar A, Bhat KI, Shastry CS. In Silico Anticancer Evaluation, Molecular Docking and Pharmacophore Modeling of Flavonoids against Various Cancer Targets. Letters in Drug Design & Discovery. 2020;17(12):1485-501.

21. Kodical DD, James JP, Deepthi K, Kumar P, Cyriac C, Gopika KV. ADMET, Molecular docking studies and binding energy calculations of Pyrimidine-2-Thiol Derivatives as Cox Inhibitors. Research Journal of Pharmacy and Technology. 2020;13(9):4200-6.

22. Konze KD, Bos PH, Dahlgren MK, Leswing K, Tubert-Brohman I, Bortolato A, Robbason B, Abel R, Bhat S. Reaction-based enumeration, active learning, and free energy calculations to rapidly explore synthetically tractable chemical space and optimise potency of cyclin-dependent kinase 2 inhibitors. Journal of chemical information and modeling. 2019;59(9):3782-93.

23. Schrödinger release 2020-1; LigPrep, Schrödinger, LLC, New York, NY, 2020.

24. Xu K, Rajashankar KR, Chan YP, Himanen JP, Broder CC, Nikolov DB. Host cell recognition by the henipaviruses: crystal structures of the Nipah G attachment glycoprotein and its complex with ephrin-B3. Proceedings of the National Academy of Sciences. 2008;105(29):9953-8.

25. Schrödinger release 2020-1; Glide-XP, Schrödinger, LLC, New York, NY, 2020.

26. Friesner RA, Murphy RB, Repasky MP, Frye LL, Greenwood JR, Halgren TA, Sanschagrin PC, Mainz DT. Extra precision glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein–ligand complexes. Journal of medicinal chemistry. 2006;49(21):6177-96.

27. Schrödinger release 2020-1; QikProp, Schrödinger, LLC, New York, NY, 2020.

28. Lipinski CA. Lead-and drug-like compounds: the rule-of-five revolution. Drug Discovery Today: Technologies. 2004;1(4):337-41.

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