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2-ARYL-3-(5-PHENYL[1,2,4]TRIAZOLO[4,3-*C*]QUINAZOLIN-3-YL)-1,3-THIAZOLIDIN-4-ONES AS HCV NS5B RNA POLYMERASE INHIBITORS

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ABSTRACT

A novel series of 2-aryl-3-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)-1,3-thiazolidin-4-ones 4a-k with varied electronic environment due to aryl moiety present on 2nd position of thiazolidinone has been designed, synthesized by one-pot three-component synthesis and characterized by their spectral data. *In-silico* molecular docking studies are carried out using low energy conformer of compounds 4a-k in the active domain of Hepatitis C virus NS5B RNA polymerase (protein ID: 3FRZ). Their aptness in regulating the functions were studied, from their interaction energies, calculated using the scoring functions, depicted that the ligands 4h (–7.813) and 4j (–7.885), bearing 2-chlorophenyl and 2-furyl substituents respectively, showed most fitting interactions than the standard filibuvir (–7.764), establishing as good inhibitors of HCV (Hepatitis C virus) and may evolve as potent antiviral agents.

Keywords: Thiazolidin-4-one derivatives, Synthesis, Molecular docking, Hepatitis C virus NS5B RNA polymerase inhibitors.

INTRODUCTION

Hepatitis C is an infectious disease affecting primarily the liver, caused by the Hepatitis C virus (HCV/HVC) [1]. The infection is often asymptomatic, but chronic infection can lead to liver cancer, or life-threatening esophageal and gastric varices [1]. HCV is a polyprotein, which undergoes maturational processing in the cytoplasm or in the endoplasmic reticulum of infected cells to generate structural and Non-Structural (NS) viral proteins *viz*. NS2, NS3, NS4A, NS4B, NS5A and NS5B. Among the NS proteins, NS3 liberates NS5B RNA dependent RNA polymerase (NS5B RdRp), the catalytic core of the HCV replication machinery [2]. NS5B is not expressed in uninfected cells, and due to its unique features it has been an attractive target for the development of safe antiviral drugs. Hence, there is a need to design, synthesize and develop selective NS5B RdRp inhibitors with no adverse effects.

The emergence of new viral pandemics, resurfacing of microbial diseases, increasing prevalence of systemic diseases coupled with the unvanquished scourge viral infections underline the imperative need for the discovery of new drug scaffolds. Heterocyclics have seen unparallel progress owing to their wide natural occurrence, specific chemical reactivity and broad spectrum of pharmacological utility. Quinazoline being core skeleton in many natural and synthetic heterocycles possesses wide range of biological and pharmacological properties particularly, antimicrobial [3], anticancer [4], COX-2 inhibitors [5] and antitumor [6]. Many triazoles display prominent biological activities like antimicrobial [7], anti-inflammatory [8], anticancer [9] and antiviral [10]. Triazole fused to another heterocyclic ring has focused attention, displaying a broad spectrum of biological activities [11-12]. Thiazolidinones are core structures in various pharmaceuticals with wide range of biological activities like anticancer [13], anti-HIV [14] and antibacterial [15].

Encouraged by these reports, in view of the previous rationale [16,17] and in our continued interest on the synthesis of new pharmacodynamic heterocyclics [18-23],

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it was thought of interest to design and synthesize a novel series of 2-aryl-3-(5-phenyl[1,2,4]triazolo[4,3-*c*] quinazolin-3-yl)-1,3-thiazolidin-4-ones **4a-k** that are structurally related to the reported anti-HCV pharmacophores (Figure 1). In the present work, docking studies are carried out by varying substitution pattern on 2nd position of thiazolidinone to confer different electronic environment aiming at finding selective New Chemical Entities (NCEs) and to elucidate the Structure Activity Relationship (SAR).

MATERIALS AND METHODS

Sigma–Aldrich chemicals are used as such without further purification. Purified reagent grade solvents are used for the synthetic, spectroscopic and physical studies. Progress of the reaction and purity of the compounds were checked by thin-layer chromatography (TLC) on pre-coated silica gel F-254 plates from Merck and compounds visualized by exposure to UV light. Column chromatography was performed on silica gel 60-120 mesh. Melting points were determined with a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Fourier transform-infrared (FT-IR) spectrometer, using KBr pellet. ^{1}H and ^{13}C NMR spectra in DMSO-d_6 were recorded on a Varian Gemini spectrometer, operating at 300 MHz and 75 MHz, respectively. The chemical shifts were reported as parts per million (δ ppm) down field using TMS as an internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were obtained on a VG micromass 7070H spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer.

EXPERIMENTAL

Synthesis of 4-chloro-2-phenylquinazoline (2)

To a stirred thionyl chloride (30 mL), 2-phenylquinazolin-4(3*H*)-one 1 (5 mmol) was added slowly followed by DMF (5 mL) dropwise and the mixture was refluxed for 90 min at 80 ^{0}C. The reaction mixture was cooled and the excess thionylchloride was removed under reduced pressure. The residue thus obtained was dissolved in dichloromethane (60 mL) and washed with a saturated solution of sodium carbonate, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the solid obtained was recrystallized from ethanol to give compound **2** as brown solid; IR (KBr, cm^{-1}): 3053 (Ar-H), 1616 (C=N), 1603 (C=C), 689 (C-Cl); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.61 -7.73 (m, 4H, ArH), 7.89- 7.93 (m, 2H, ArH), 8.17-8.22(m, 3H, ArH); MS *m*/*z*: 240 (M^+), 242 ($M^+ + 2$).

Synthesis of 5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-amine (3)

A mixture of compound **2** (2.82 g, 0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (20 mL) was refluxed for 8 h. The reaction mixture was cooled to room temperature and the solid separated, was filtered off, dried, and purified by coloumn chromatography (silica gel 60-120 mesh) using EtOAc: n-hexane (3:2) as eluent to afford pure compound **3** as brown solid; IR (KBr, cm^{-1}): 3423, 3363 (NH_2), 3038 (Ar-H), 1622 (C=N), 1601 (C=C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 5.38 (bs, 2H, NH_2), 7.48-7.58 (m, 4H, ArH), 7.72-7.80 (m, 2H, ArH), 7.99-8.15(m, 3H, ArH); MS *m*/*z*: 261 (M^+).

General procedure for the synthesis of 2-aryl-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-ones (4a-k)

To a stirred mixture of compound **3** (0.01 mol), aryl/heteroaryl aldehyde (0.01 mol), thioglycolic acid (0.02 mol) in dry toluene (20 mL) was added $ZnCl_2$ (0.01 mol), and refluxed for 5 h at 110 °C. After cooling, the filtrate was concentrated to dryness under reduced pressure and the residue was taken-up in ethyl acetate. The ethyl acetate layer was washed with 5% sodium bicarbonate solution and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness at reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel with hexane-ethylacetate as eluent to get the pure compounds **4a-k** in 64-72 % yield.

2-phenyl-3-(5-phenyl[1,2,4]triazolo[4,3-c]quinazolin-3-yl)-1,3-thiazolidin-4-one (4a)

Orange solid; yield 72%; mp 160–162 °C; IR (KBr, cm^{-1}) : 3061 (Ar-H), 1709 (C=O), 1627 (C=N), 1602 (C=C), 757 (C-S-C); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.72 (s, 2H, CH_2-CO), 5.82 (s, 1H, N-CH-S), 6.42-6.60 (m, 2H, ArH), 6.75-7.10 (m, 3H, ArH), 7.44-7.56 (m, 4H, ArH), 7.76-7.83 (m, 2H, ArH), 8.10-8.25(m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 35.6, 69.6, 116.3, 127.4, 128.3, 129.5, 131.1, 131.9, 132.4, 133.8, 138.4, 140.1, 149.6, 158.8, 163.7, 172.0; MS *m*/*z*: 423 (M^+). *Anal.* Calcd for $C_{24}H_{17}N_5OS$: C, 68.07; H, 4.05; N, 16.54. Found: C, 68.01; H, 3.99; N, 16.53.

RESULTS AND DISCUSSION

The synthesis of a novel series of 2-aryl-3-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)-1,3-thiazolidin-4-ones **4a-k** (as outlined in scheme 1) commenced from the commercially available anthranilamide, which on oxidative cyclocondensation with benzaldehyde gave the 2-phenylquinazolin-4(3*H*)-one **1** in 98% yield [19]. The compound **1** on reflux for 2 h with thionylchloride in presence of *N*,*N*-dimethyl formamide (DMF) resulted the 4-chloro-2-phenyl quinazoline **2** in 81% yield. The intermediate **2** on treating with thiosemicarbazide in ethanol afforded the 5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-amine **3** in 68% yield. The title compounds 2-aryl-3-(5-phenyl[1,2,4] triazolo[4,3-*c*]quinazolin-3-yl)-1,3-thiazolidin-4-ones **4a–k** have been synthesized in 64–72% yield by one-pot

cyclocondensation of compound **3** with different aryl/heteryl aldehydes in presence of thioglycolic acid and $ZnCl_2$.

All the newly synthesized compounds have been satisfactorily established on the basis of elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and Electron Ionization (EI) mass spectral data. In the IR spectra of compounds **4a–k**, disappearance of the broad bands at 3423, 3363 cm^{-1} (NH_2) and appearance of a band at about 760 cm^{-1} (C-S-C) shows the evidence of ring closure, involving the $–NH_2$ group of compound **3**.

Similarly, the absence of ^{1}H-NMR signal for the $–NH_2$ protons at about δ 5.38 and the presence of signals at about δ 3.75 and δ 5.86 *ppm* corresponding to $-CH_2$-CO and -N-CH-S protons respectively of thiazolidinone ring, is the further proof of ring closure involving NH_2 group of compound **3**. Further support was also obtained from the ^{13}C NMR spectra. For all the compounds **4a–k**, the signals corresponding to the carbons appeared at about 35.8, 70.0 and 171.6 ppm of thiazolidinone; 149.8 and 158.6 ppm of triazole; 116.4, 128.1, 129.6, 131.4, 132.4, 138.6 and 163.8 ppm of quinazoline. In summary, all the newly synthesized compounds exhibited satisfactory spectral data in consistent with their structures.

MOLECULAR DOCKING STUDIES

Anti-HCV docking: Protein ID: 3FRZ of compounds (4a-k)

Docking studies for biological evaluation continues to hold pronounced assurance in the field of computer based drug design, to avoid long-term risky human trials and to reduce animal testing of synthesized compounds. Indeed, these studies open the door to unfold the biological processes within a shorter computational timeframe without compromising the accuracy, providing new insights in further stages of analysis at the atomic level.

The X-ray crystallographic structure of HCV RdRp was obtained from Protein Data Bank (PDB) with ID: 3FRZ is used for docking studies by using maestro [24]. It was further optimized with prepared wizard [25] and the refined protein structure minimized with macro model minimization [26], this is a method to get low energy conformations of the protein to release any unwanted strain in protein crystal structure as well in homology model. The refined protein used for grid generation with glide module from Schrödinger [24, 26, 27].

All molecules were drawn with maestro interface [20], further minimized with conformational search [27] to get global minima of the structure for the individual molecule. The low energy conformer used for docking [28]. The docking method is XP (Extra Precision). The molecular modeling software installed on high end workstations (Dell Precision T5500, with 500GB hard disk and 16GB RAM with 4GB graphic card capacity).

In this context, the present *In-silico* molecular docking investigation merits in understanding the indispensable role of the designed and synthesized NCEs **4a-k** as antiviral drugs. To achieve this mission, compounds are oriented in the active domain of targeted protein retrieved from PDB site with ID: 3FRZ and their aptness in regulating the functions were studied from their interaction energies, calculated using the scoring functions.

Analysis of the binding patterns and their corresponding docking score, between each newly synthesized chemical entities **4a-k** against target protein, NS5B RNA dependent RNA polymerase (RdRp) with protein ID: 3FRZ. A narrow variation in the binding affinities (Table 2), reveals that the core pharmacophoric motif, 2-phenyl-3-(5-phenyl[1,2,4]triazolo [4,3-*c*]quinazolin-3-yl)-1,3-thia-zolidin-4-ones, played a major role in showing best fitness in the active domain of receptor. To establish novel insights of binding interactions of ligands **4a-k** in the vicinity of receptor compared to the standard filibuvir depicted that ligands bearing, 2-chlorophenyl **4h** (–7.813) and furyl **4j** (–7.885) showed high binding affinities than other compounds including the standard filibuvir (–7.764) retaining hydrophobic residues, Met423, Leu419, Tyr477, Ile482, Leu497, Leu474 and Trp528. In addition, quinazoline and C=O of ligand **4h**, showed π-π interaction and H-bonding (2.27 A^0) respectively with the residue Tyr477 (Fig. 2). Furan and quinazoline of ligand **4j**, depicted π-π interaction with residues Arg501 and Arg422 respectively along with two H-bonds in between oxygen atom of furan and side chain of Arg501 (2.07 A^0), and –C=O of thiazolidinone and backbone of Ser476 (2.09 A^0) (Fig. 4). Besides, this binding pattern of both **4h** and **4j** illustrated almost alike as standard filibuvir (Figs. 3, 5 and 6).

This analysis unveil that ligands **4h** and **4j** depicted most fitting interactions than the standard Filibuvir, may evolve as good inhibitors of HCV and develop as potent antiviral agents and hydrophobic interaction with residue Tyr477 and H-bonding with residues Ser476 and Arg501 may regulate RNA dependent RNA polymerase (RdRp).

Table 1. Physical data of the synthesized compounds

Compound	Ar	Yield (%)	M.P (^{o}C)
2	—	81	123–125
3	—	68	181–183
4a	Phenyl	72	160–162
4b	4-chlorophenyl	70	158–160

4c	4-nitrophenyl	65	142–144
4d	4-hydroxy-3-methoxyphenyl	68	164–163
4e	4-(dimethylamino)phenyl	69	159–161
4f	4- hydroxyphenyl	64	171–173
4g	3-nitrophenyl	67	168–171
4h	2-chlorophenyl	65	170–172
4i	2-hydroxyphenyl	68	166–169
4j	2-furyl	67	170–172
4k	5-(1,3-benzodioxole)	66	161–163

Table 2. HCV docking: Protein ID: 3FRZ of compounds 4a-k

Ligand	H-bond			Residue ID	Docking Score	Rank
	Atom / group	Nature	Distance (A^0)			
4a	C=O of thiazolidinone	H-acceptor	2.77	$-NH_2$ of Tyr477	-5.759	6
	Nitrogen atom of triazole	H-acceptor	2.68	$-NH_2$ of Ser476		
4b	C=O of thiazolidinone	H-acceptor	2.10	$-NH_2$ of Ser476	-5.259	12
	Nitrogen atom of triazole	H-acceptor	2.10	$-NH_2^+$ of Arg501		
4c	Nitrogen atom of triazole	H-acceptor	2.56	$-NH_2$ of Ser476	-5.737	7
4d	C=O of thiazolidinone	H-acceptor	1.86	$-NH_2$ of Ser476	-6.714	4
	-OH phenyl	H-acceptor	2.21	$-NH_3^+$ Lys533		
4e	C=O of thiazolidinone	H-acceptor	2.04	$-NH_2^+$ of Arg501	-5.992	5
	Nitrogen atom of quinazoline	H-acceptor	2.72	$-NH_2$ of Ser476		
4f	C=O of thiazolidinone	H-acceptor	2.32	$-NH_2^+$ of Arg501	-5.561	11
4g	C=O of thiazolidinone	H-acceptor	2.60	$-NH_2$ of Ser476	-5.602	10
	C=O of thiazolidinone	H-acceptor	2.63	$-NH_2$ of Arg501		
4h	C=O of thiazolidinone	H-acceptor	2.27	$-NH_2$ of Tyr477	-7.813	2
4i	C=O of thiazolidinone	H-acceptor	1.86	$-NH_2$ of Ser476	-5.635	9
	-OH phenyl	H-acceptor	2.00	$-NH_3^+$ Lys533		
4j	C=O of thiazolidinone	H-acceptor	2.09	$-NH_2$ of Ser476	-7.885	1
	Oxygen atom of furan	H-acceptor	2.07	$-NH_2$ of Arg501		
4k	Nitrogen atom of triazole	H-acceptor	2.76	$-NH_2^+$ of Arg501	-5.638	8
	C=O of thiazolidinone	H-acceptor	2.08	$-NH_2$ of Ser476		
Filibuvir	C=O of pyranone	H-acceptor	2.11	$-NH_2$ of Ser476	-7.764	3
	–OH of pyranone	H-acceptor	2.34	$-NH_2^+$ of Arg501		
	–OH of pyranone	H-donor	2.48	C=O of Trp528		

Fig 1. Rational drug design of target molecules 4a-k

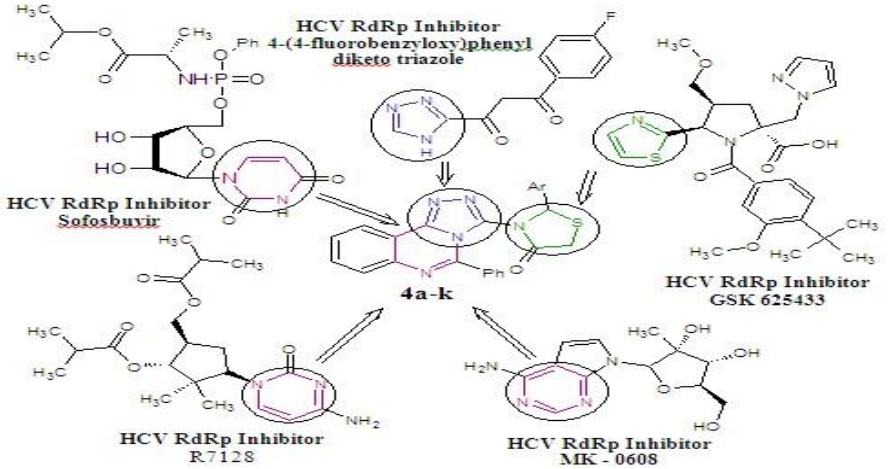


Fig 2. 3D orientations and 2D interactions of ligand 4h in active domain of NS5B RdRp depicting hydrophobic residues, Met423, Leu419, Tyr477, Ile482, Leu497, Leu474 and Trp528; quinazoline and -C=O of ligand 4h, showing □□□ interaction and H-bonding (2.27 A^0) respectively with residue Tyr477.

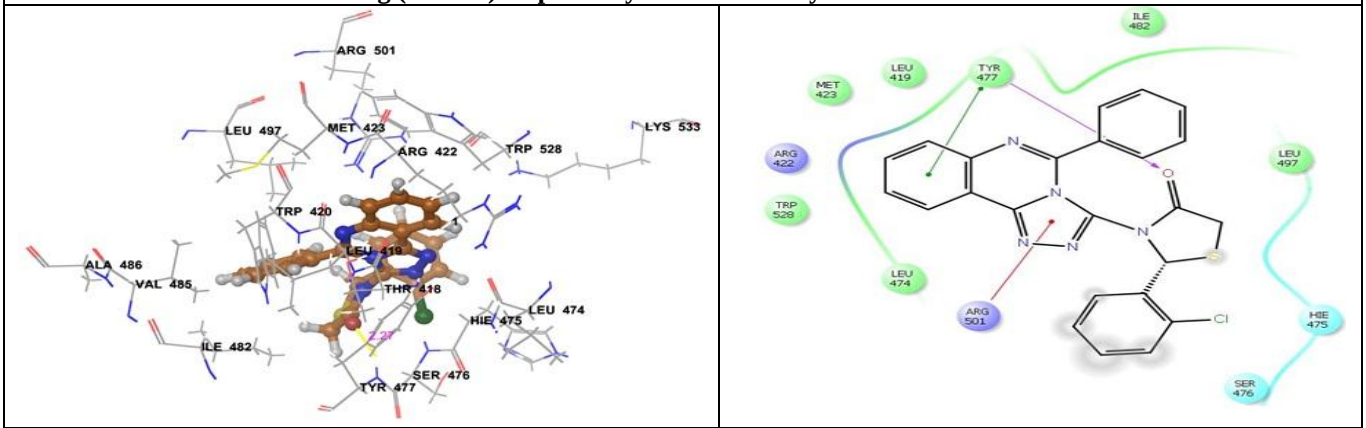


Fig 3. Overlay 3D orientation of ligand 4h (brown) engrossed with standard filibuvir in active domain of NS5B RdRp.

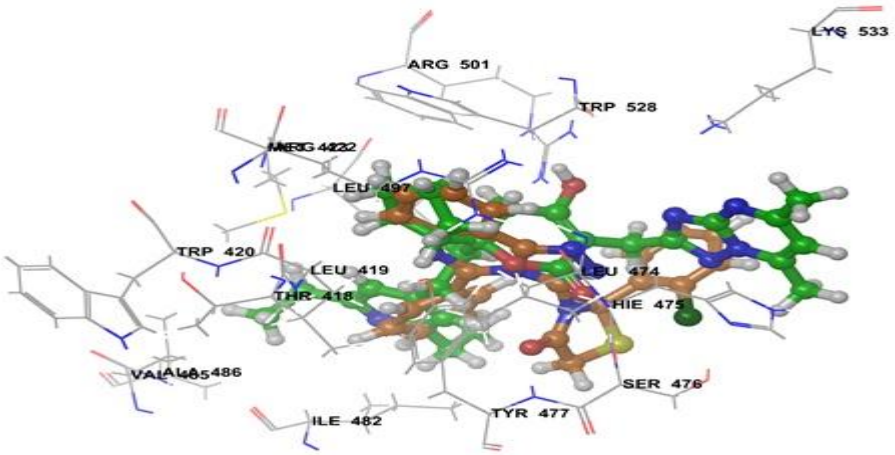


Fig 4. 3D orientations and 2D interactions of ligand 4j in active domain of NS5B RdRp representing Π-Π interactions between furan and quinazoline of ligand 4j and residues Arg501 and Arg422 respectively along with two H-bonds in between oxygen atom of furan and side chain of Arg501 (2.07 A^0) and –C=O of thiazolidinone and backbone of Ser476 (2.09 A^0)

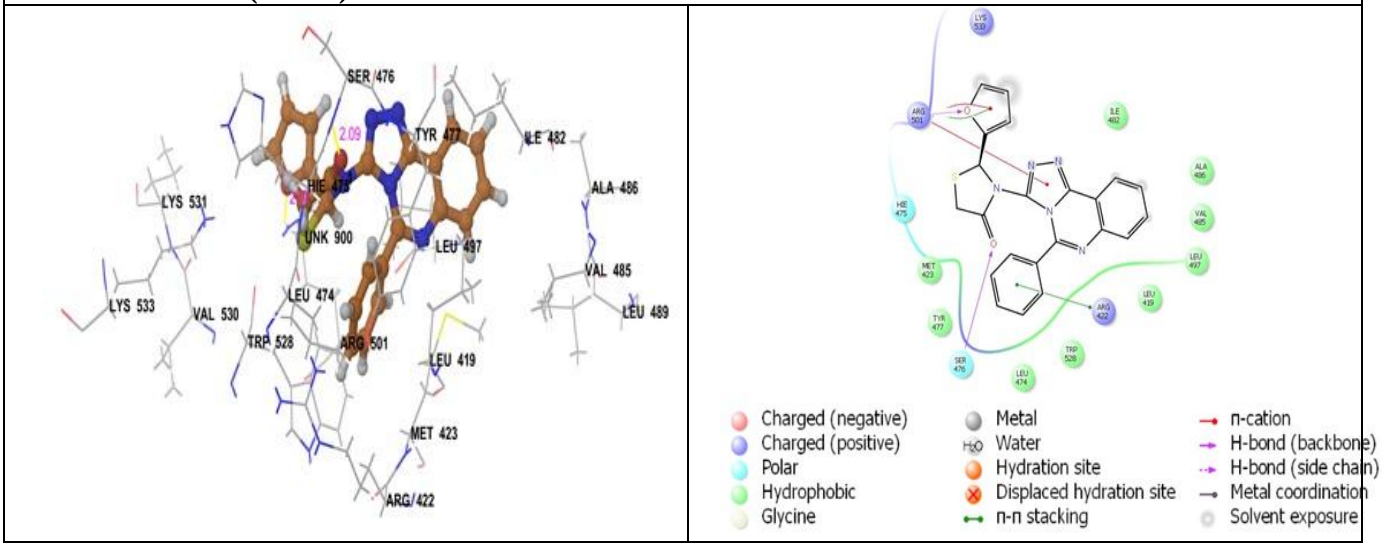


Fig 5. Overlap 3D orientations of ligand 4j (brown) depicting alike binding modes as standard filibuvir (green) in active domain of NS5B RdRp

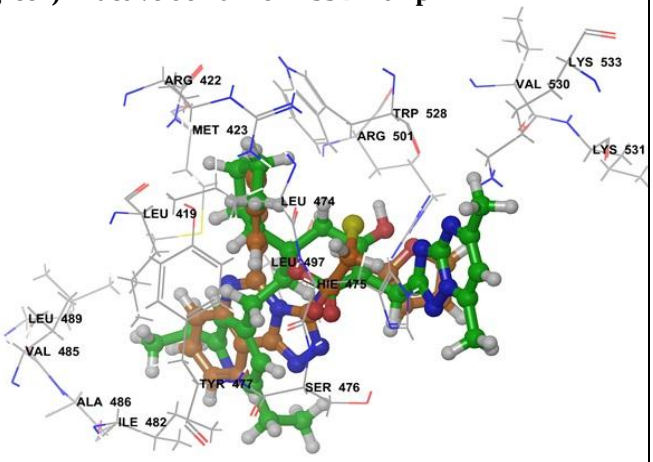
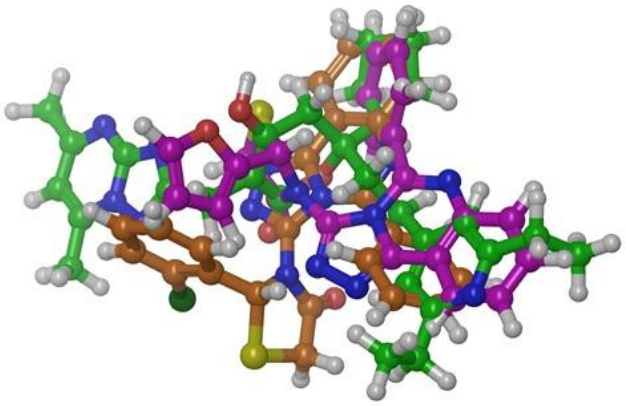
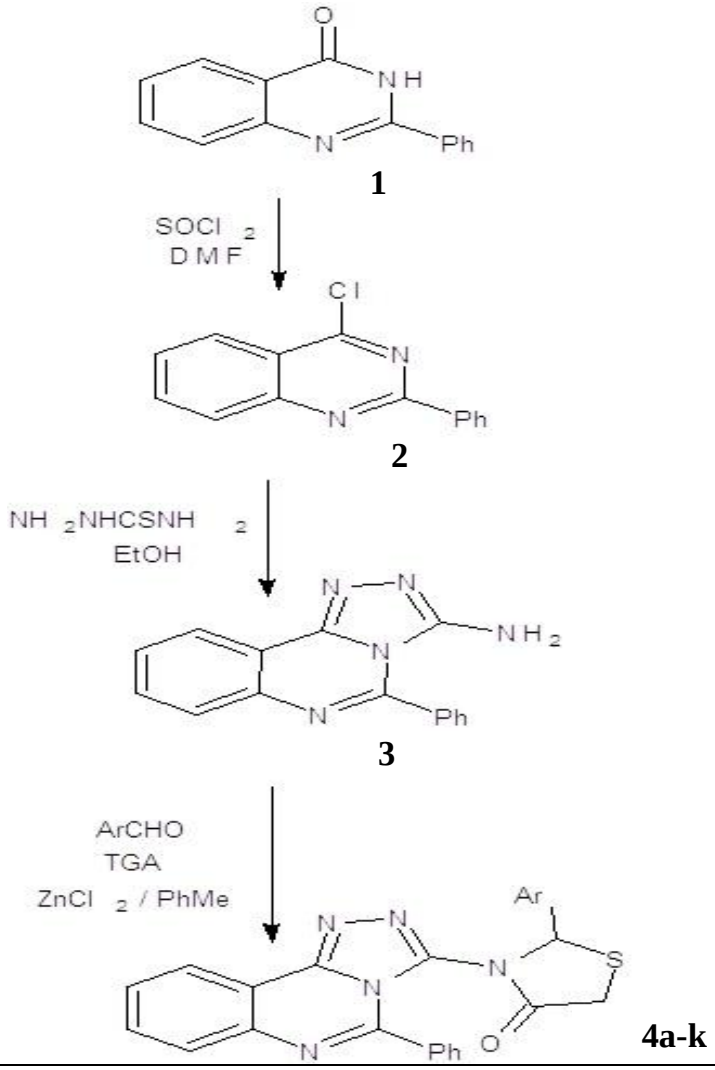


Fig 6. 3D orientations of ligand 4h (brown) and 4j (purple) almost engrossing with standard filibuvir (green) in the active domain of RdRp



Scheme 1. Schematic route for the synthesis of 2-aryl-3-(5-phenyl[1,2,4]triazolo[4,3-*c*]quina-zolin-3-yl)-1,3-thiazolidin-4-ones 4a-k.



CONCLUSION

A novel series of 2-aryl-3-(5-phenyl[1,2,4]triazolo[4,3-*c*]quinazolin-3-yl)-1,3-thiazolidin-4-ones **4a–k** with varied electronic environment due to aryl moiety present on 2nd position of thiazolidinone has been designed, synthesized. *In-silico* molecular docking studies revealed that ligands **4h** (–7.813) and **4j** (–7.885) depicted most fitting interactions than the standard filibuvir (–7.764), may evolve as good inhibitors of HCV and develop as potent antiviral agents; and hydrophobic interaction with residue Tyr477 and H-bonding with residues Ser476 and Arg501 may regulate RdRp. These promising results are reliable however, can be subjected for preclinical studies to arrive at the conclusion on these molecules for their clinical use.

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