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Structure-Based Virtual Screening, Design, Synthesis and Biological Evaluation of 3-Sulfonamido Substituted Quinazolinones as Anti-Zika Viral Agents

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Abstract

Quinazolines have engaged a distinctive position in heterocyclic chemistry and its derivatives have fascinated significant engrossment within the latest years for their flexile effects in chemistry and pharmacology. Quinazolines are nitrogen containing heterocyclic ring which own biological and pharmaceutical influence due to its various activities like anti viral, antibacterial, antifungal, anti-malarial, anticonvulsant, anti-inflammatory, anti-HIV, anti tumor, anti viral and analgesic etc. In this research, quinazolines were subjected to Structure-based virtual screening against the Zika Virus NS2B-NS3 protease (PDB ID: 5GXJ). Top lead molecules were studied for molecular docking and simulation studies and HITS were identified by understanding their important pharmacophoric features and novel compounds as 3-Sulfonamido substituted quinazolinones were designed, synthesized and undergo molecular docking and simulation studies. The synthesized compounds are to be characterized by by melting point, TLC, IR, NMR and Mass spectral data. Docking studies were conducted for these derivatives on the PDB ID: 5GXJ by using AutoDock Vina 1.5.6 software. The molecules are to be evaluated for their possible anti-zika viral activity.

Keywords: Quinazolines, nitrogen containing heterocycles, Structure-based Virtual Screening, Molecular Docking, anti-zika viral activity.

INTRODUCTION

Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. In 1869, Griess *et al*., synthesized the first quinazoline derivative 2-cyano 3,4-dihydro-4-oxoquinazoline by condensation process [1,2]. Bischler and Lang synthesized similar quinazoline analogs by decarboxylation of the 2-carboxy compound [3]. In 1903, Gabriel and Colman synthesized several quinazoline derivatives and studied its properties in detail [4]. Quinazolines and its derivatives exemplify one of the most prominent classes of compounds, which possess a wide range of pharmacological activities like analgesic[6], antioxidant [6,7], anti-inflammatory[7,8],anti-hypertensive[9], antitubercular[10], anti-bacterial[10,12], anti-viral[13,14] and anticancer[15,16], anti-obesity[17], anti-psychotic[18], anti-diabetes[19], etc.

Zika virus is an emerging mosquito-borne pathogen capable of severely damaging developing fetuses as well as causing neurological abnormalities in adults. The molecular details of how Zika virus causes pathologies that are unique among the flavivirus family remain poorly understood and have contributed to the lack of Zika antiviral therapies. The ZIKV genome is a positive-sense RNA that is translated by the host cell machinery into a single-chain polyprotein precursor comprising both structural and nonstructural (NS) components. Flavivirus replication requires the activity of the encoded viral protease, which along with host proteases cleaves the polyprotein, releasing mature viral proteins and allowing formation of the replication complex.[22]

Figure 1: Structure of NS2B-NS3 Preotease of Zika Virus.

SIMILARITY OF NS2B/NS3 PROTEASE WITH HCV PROTEASE

NS2B-NS3 protease is responsible for all cytoplasmic cleavages including at junctions between NS2A/NS2B, NS2B/NS3, NS3/NS4A and NS4B/NS5 proteins and within the capsid, NS2A and NS4A proteins. Similar to NS3-NS4A protease from hepatitis C virus, the flavivirus NS2B-NS3 protease is essential for the virus replicative cycle, and thus constitutes an ideal target for antiviral drug development. There are only three existing drugs as anti zika viral agents i.e., Candesartan cilexetil, Arbidol, Hydroxychloroquine.

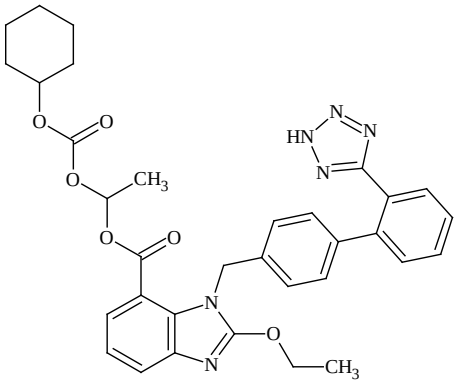


Fig.2: Candesartan cilexetil

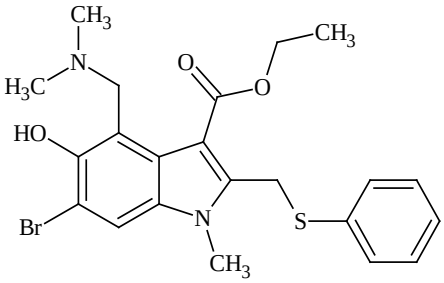


Fig.3: Arbidol

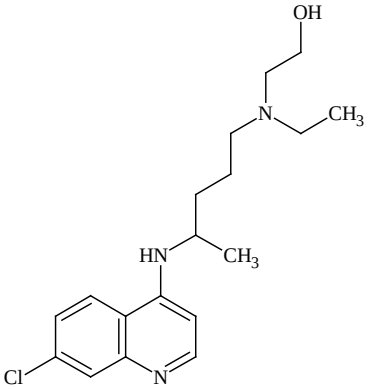


Fig.4: Hydroxychloroquine

MATERIALS AND METHODS

All the chemicals (reagents and solvents) were purchased from commercial suppliers (Merck grade) Sigma Aldrich, Avra, and SD Fine Chem. Ltd and they were used further without purification.

Melting Point Apparatus

The melting points of the synthesized compounds were taken in the open capillary tubes using Chemline company CL726 melting apparatus.

Thin Layer Chromatography

Purity of the compounds was checked by TLC using silica gel G (0.5mm thickness)coated over glass plate (12 x 20 cm). For the determination R_f value the dried silica gel G coated over glass plate were used.

Preparation of TLC plate: By using distilled water silica gel G slurry is prepared andpoured on to a glass plate which is maintained on a level surface. The slurry is spread uniformly on the surface of the glass plate. After setting, the plates are dried in an oven at 50ºC or 15 minutes for activating the TLC plate. Chromatogram was developed by ascending technique when solvent front travelled appropriate distance; plates were taken out and dried. The location of spot was detected using iodine chamber.

R_f = Distance travelled by solute / Distance travelled by solvent

Infrared Spectroscopy

The IR Spectra of the synthesized compounds were recorded at RBVRR women's College of Pharmacy by Shimadzu-FT/IR spectrophotometer in KBr disc. The IR value was measured in cm^{-1}.

Nuclear Magnetic Resonance

The H-NMR Spectra of the synthesized compounds were recorded at Central Facilities for Research and Development, Osmania University, Hyderabad by Bruker 300 MHz FT- NMR using $CDCl_3$(Deuteriated Chloroform) as internal standard. The PMR (Proton Magnetic Resonance) spectroscopic values are measured in δ ppm in DMSO-d6.

Mass Spectroscopy

Mass spectra was recorded in Schimadzu Mass Spectrometer.

RESULTS AND DISCUSSION:

Virtual Screening

100 quinazolinones structures were extracted from the CHEMBL database using various filters and these were subjected to virtual screening against HCV viral Protease (PDB ID: 2OC1) and Zika viral Protease(PDB ID: 5XGJ) by using **PyRx** software.

S.No:	CHEMBL ID	HCV Viral NS3-4A Protease (PDB ID: 2OC1)	Zika Viral NS2B-NS3 Protease (PDB ID: 5XGJ)
1.	CHEMBL3040806	-8.6	-9.5
2.	CHEMBL350589	-8.9	-9.6
3.	CHEMBL1461153	-8.2	-9.8
4.	CHEMBL300585	-8.6	-10.6
5.	CHEMBL3914795	-8.1	-9.9

Table 1: Virtual screening results of HCV Viral Protease and Zika Viral Protease for with Quinazolines:

Therefore, from the above results by virtual screening of quinazoline moieties with NS2B-NS3 protease of Zika virus which in turn is structurally similar to NS3/4A protease of HCV, it is understood that the following 5 hit molecules are having possible activity against Zika virus. Figure 5 illustrates the structures of the five hit molecules obtained from virtual screening results:

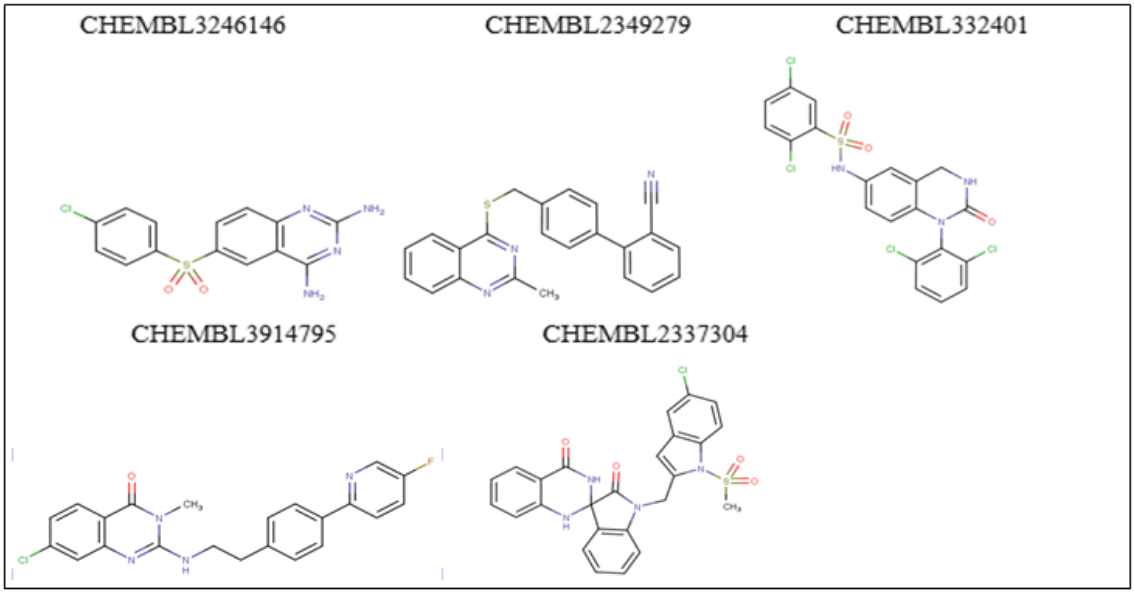
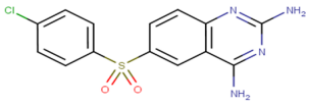
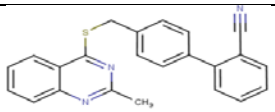
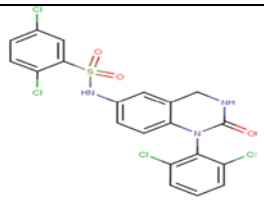
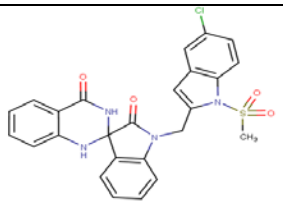
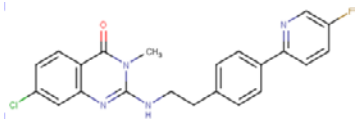


Figure 5: Structures of selected 5 hit molecules with their CHEMBL ID's.

Molecular Docking

As the binding affinity studies between ligands and their receptors form the basis of physiological activity and pharmacological effects of chemical compounds. We carried out docking studies to investigate the correct binding pose of the novel molecules with NS2B-NS3 Protease by using **AutoDock Vina 1.5.6** software. (Table 2, fig.4)

Table 2: Molecular Docking interactions of 5 hit molecules obtained from virtual screening results

S.No.	Structure of the lead molecule	Hydrogen bond interactions	Other interactions	Docking scores
1.	 CHEMBL3246146	Hydrogen bonding with TYR1130, GLY1133, HIS1051.	**Hydrophobic** interactions- ALA1132, VAL1036, VAL1056. **Hydrophilic** interactions- GLY1103, THR1034SER1135.	-8.1
2.	 CHEMBL2349279	Hydrogen bonding with THR1034	**Hydrophobic** interactions with ALA1132. **Hydrophilic** interactions with GLN1035, GLY1103.	-7.2
3.	 CHEMBL332401	Hydrogen bonding with THR1034	**Hydrophobic** interactions with ALA1132. **Hydrophilic** interactions with GLN1035, GLY1103.	-7.2
4.	 CHEMBL2337304	Hydrogen bonding with TRP1063	**Hydrophobic** interactions with LEU1076, VAL1155, LEU1030, TRP1069. **Hydrophilic** interactions with LYS1073, LYS1119.	-8.9
5.	 CHEMBL3914795	-	**Hydrophobic** interactions with VAL1134, LEU1031, ALA1125, ALA1132. **Hydrophilic** interactions with THR1034, GLY1131, ARG1029, HIS1151.	-8.3

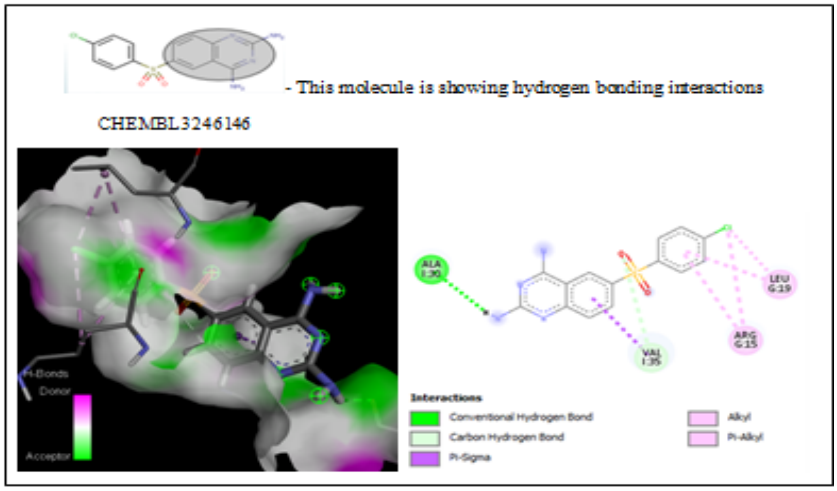


Figure 6: Binding interactions of CHEMBL3246146. Green dotted lines show hydrogen bonding interactions of NH_2 with ALA1132

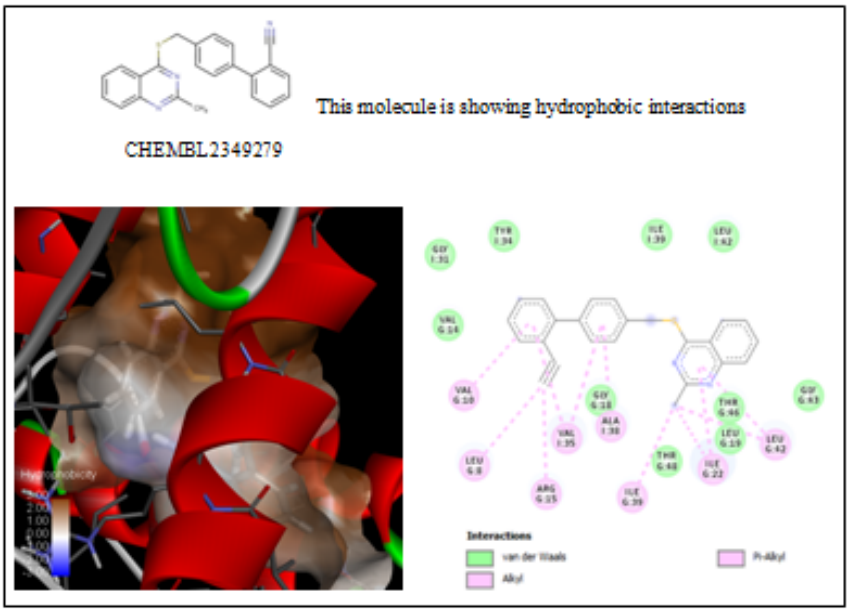


Figure 7: Binding interactions of CHEMBL2349279. Pink coloured dotted lines indicate hydrophobic interactions.

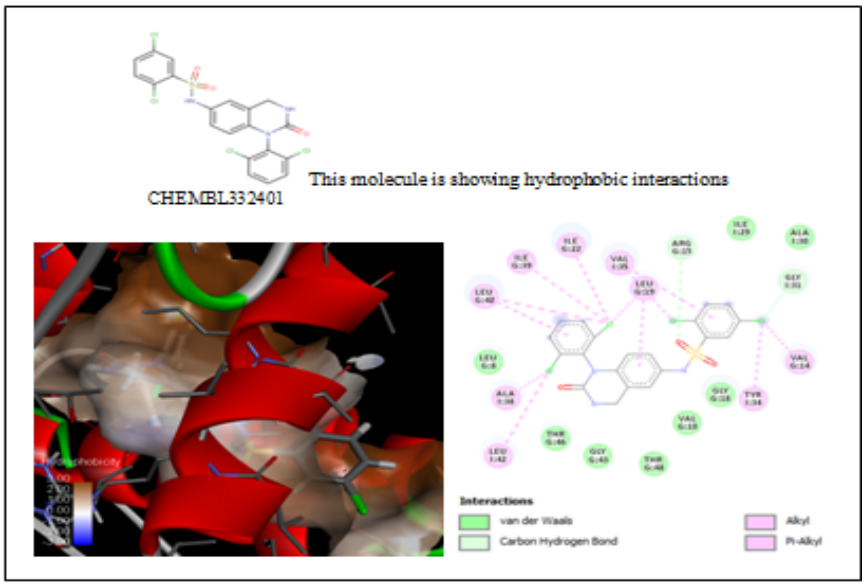


Figure 8: Binding interactions of CHEMBL332401. Pink coloured dotted lines indicates hydrophobic interactions.

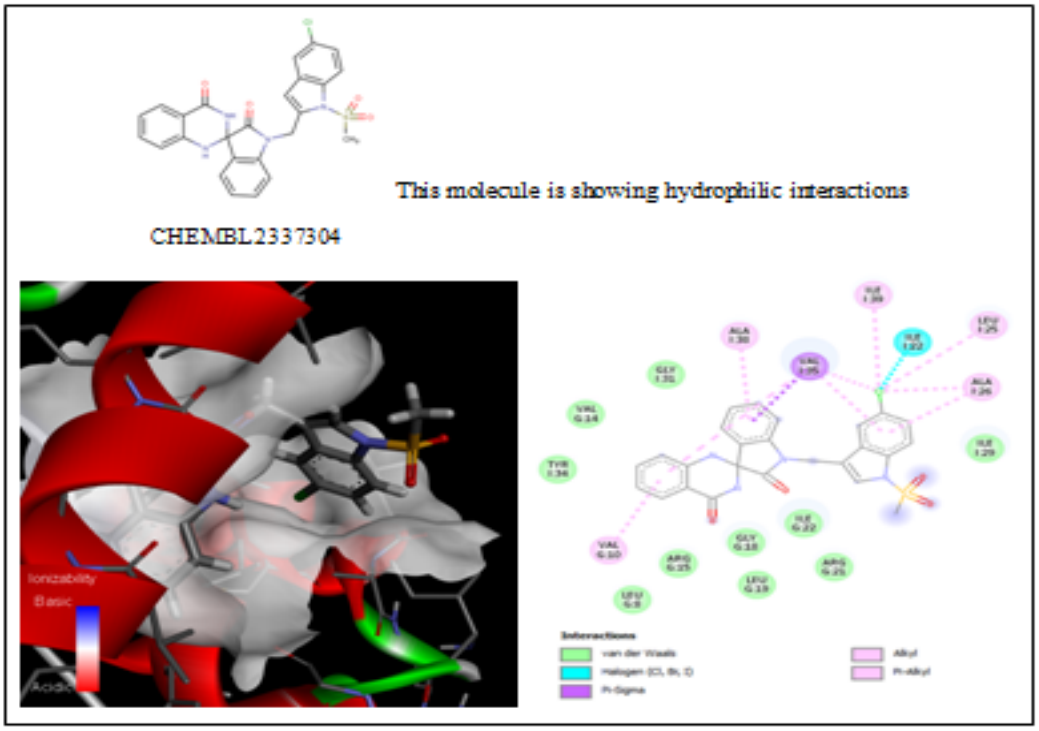


Figure 9: Binding interactions of CHEMBL332401. Pink coloured dotted lines indicates hydrophobic interactions.

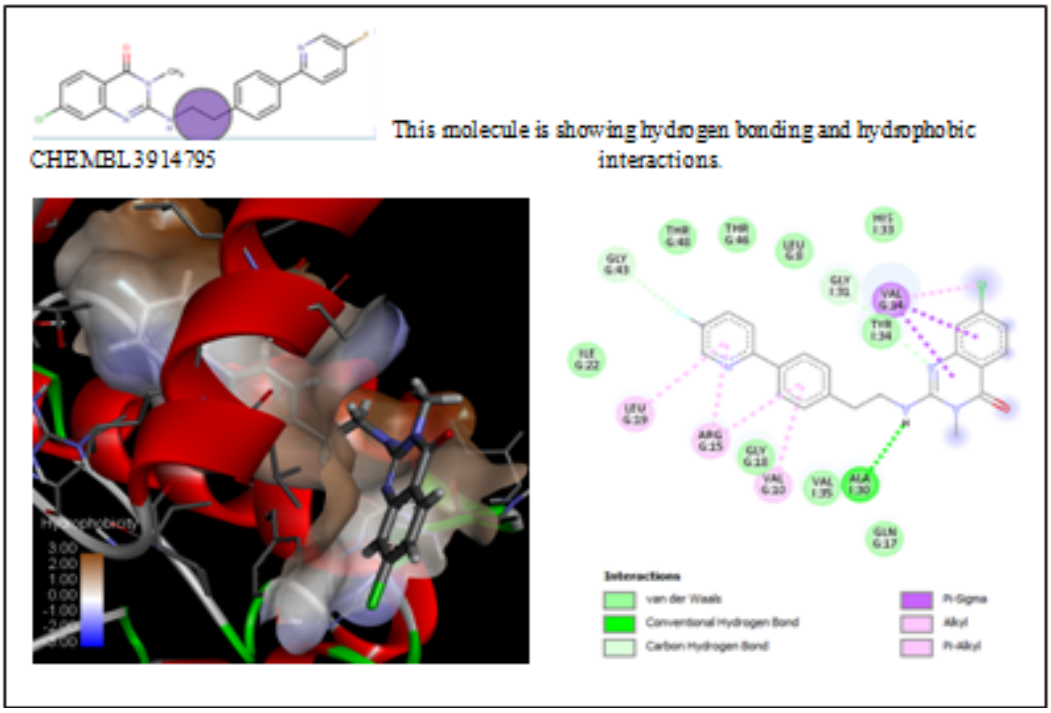


Figure 10: Binding interactions of CHEMBL332401. Green dotted lines indicate hydrogen bonding interactions and pink coloured dotted lines indicates hydrophobic interactions.

Molecular docking of 5 hit molecules with NS2B-NS3 protease exhibit satisfactory results and so the essential pharmacophoric features from these molecules which are responsible for the basic antiviral activity were understood and incorporated on the basic quinazolinone moiety to design a new lead molecule with its derivatives. (Fig.5).

The designed lead and its derivatives were made to undergo molecular properties and toxicity prediction using **OSIRIS Property Explorer** software and bioactivity prediction using **Molinspiration** software. (Table 3,4)

DESIGN OF THE LEAD MOLECULE FROM SIMILAR STRUCTURES AND THEIR PHARMACOPHORIC FEATURES

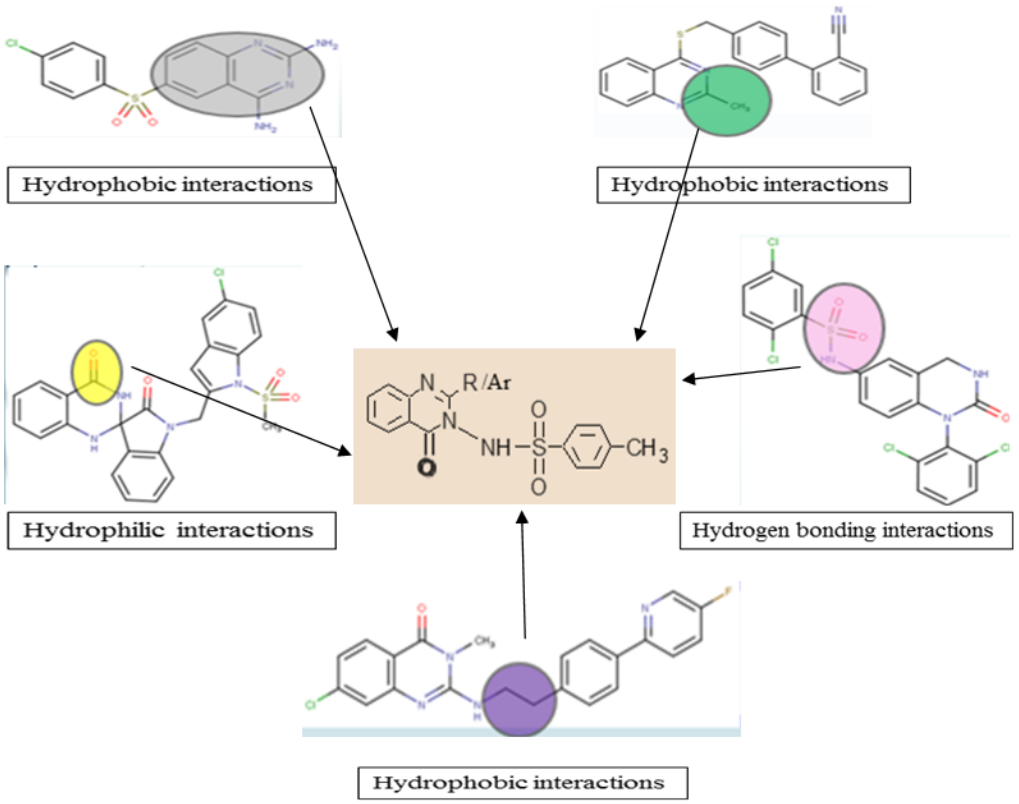
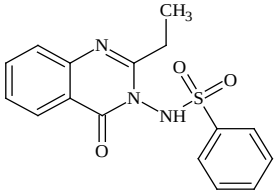
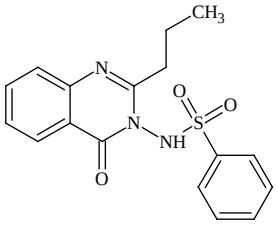


Figure 11: Design of the new lead molecule from the hits.

Molecular Properties and Toxicity Prediction of the Quinazolinone-benzenesulfonamide derivatives using OSIRIS Property Explorer

On the basis of drug likeness, compounds were predicted to be promising druggable candidates. The toxicity of the compounds was also predicted using Osiris, most of the compounds amongst the synthesized ones showed non-tumorigenic and non-reproductive effects, which further supports the drug features in the molecules. This toxicity prediction would be useful for the selection of compounds to test in animal models.

Table 3: Molecular Properties and Toxicity Prediction of the Quinazolinone-benzenesulfonamide derivatives using OSIRIS Property Explorer

S.No.	Molecules	MOL.WT	cLogP	LogS	Druglikeness	Mutagenic	Reproductive effects
1.		329.0	0.65	-1.68	3.65	None	None
2.		343.0	1.1	-1.95	5.88	None	None

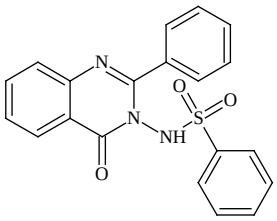
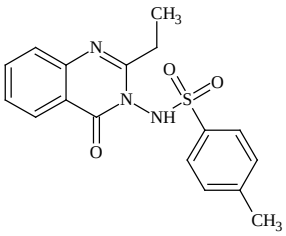
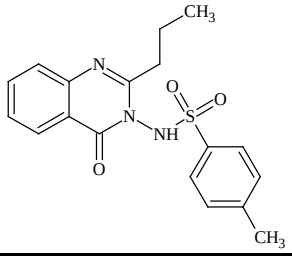
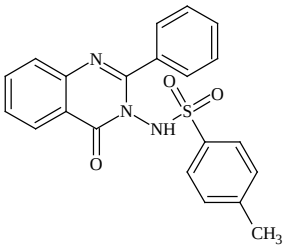
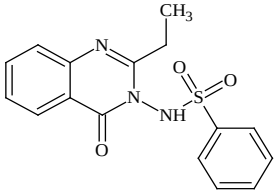
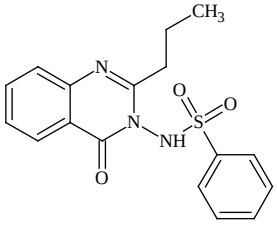
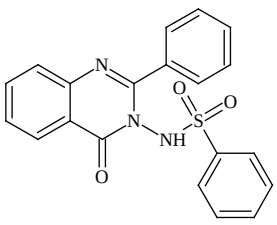
S.No.	Molecules	MOL.WT	cLogP	LogS	Druglikeness	Mutagenic	Reproductive effects
3.		377.0	1.61	-2.58	2.93	None	None
4.		343.0	0.99	-2.03	2.72	None	None
5.		357.0	1.44	-2.3	4.94	None	None
6.		391.0	1.95	-2.3	2.08	None	None

Table 4: Bioactivity Prediction studies of Quinazolinone-benzenesulfonamide derivatives using Molinspiration software

S.No	Molecules	miLogP	TPSA	natoms	MW	nOH	nOHNH	nviolations	nrotb	volume
1.		2.38	81.07	23	329.38	6	1	0	4	276.83
2.		2.88	81.07	24	343.41	6	1	0	5	293.64
3.		3.84	81.07	27	377.43	6	1	0	4	314.88

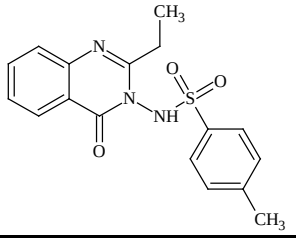
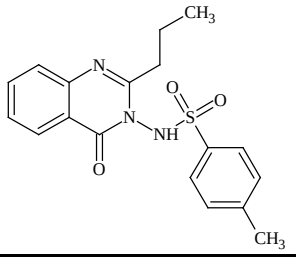
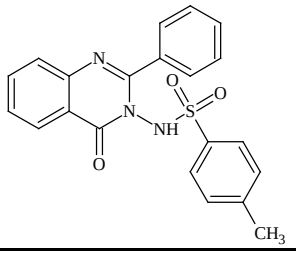
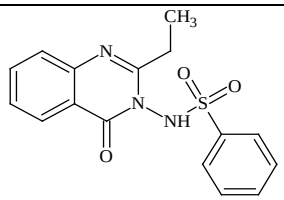
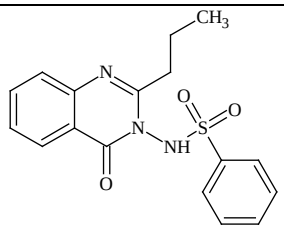
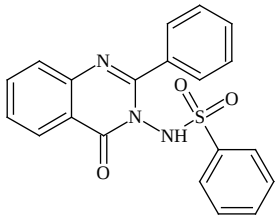
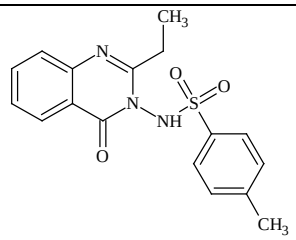
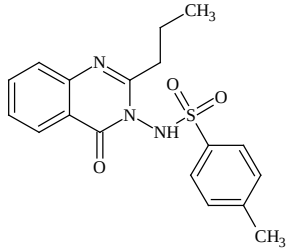
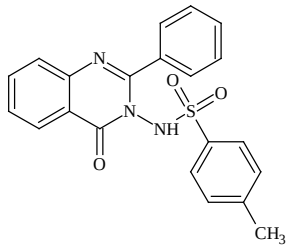
S.No	Molecules	miLogP	TPSA	natoms	MW	nOH	nOHNH	nviolations	nrotb	volume
4.		2.83	81.07	24	343.41	6	1	0	4	293.40
5.		3.33	81.07	25	357.44	6	1	0	5	310.20
6.		4.28	81.07	28	391.45	6	1	0	4	331.44

Table 5: Molecular Docking results of quinazolinone benzenesulfonamide derivatives using AutoDock Vina 1.5.6 software

Molecular docking studies of the title compounds were carried out to understand the correct binding pose of the compounds with PDB ID: 5XGJ with the HITS.

S.No.	Structure of the molecule	Hydrogen bonds	Other Interactions	Docking Scores
1.	 *N-(2-ethyl-4-oxoquinazolin-3(4H)-yl)benzenesulfonamide*	2 Hydrogen bonds with ASN1152.	**Hydrophobic** interactions with LEU1085, LEU1149, TRP1083, ILE1123, VAL1155. **Hydrophilic** interactions with GLY1148, ASN1152.	-7.3
2.	 *N-(4-oxo-2-propylquinazolin-3(4H)-yl)benzenesulfonamide*	Hydrogen bond with GLY1133	**Hydrophobic** interactions with ALA1132. **Hydrophilic** interactions with SER1135, THR1034, ARG1029, HIS1051.	-7.2
3.	 *N-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzenesulfonamide*	Hydrogen bond with ARG1029.	**Hydrophobic** interactions with ALA1132, PRO1131, ALA1132. **Hydrophilic** interactions with SER1135, GLY1133, ASP1129, ARG1029, THR1034	-8.6

S.No.	Structure of the molecule	Hydrogen bonds	Other Interactions	Docking Scores
4.	 *N-(2-ethyl-4-oxoquinazolin-3(4H)-yl)-4-methylbenzene-1-sulfonamide*	Hydrogen bonding with ALA1132	**Hydrophobic** interactions with VAL1036, ALA1132, **Hydrophilic** interactions with SER1135, GLY1133, ARG1029, HIS1051, THR1027.	-8.5
5.	 *4-methyl-N-(4-oxo-2-propylquinazolin-3(4H)-yl)benzene-1-sulfonamide*	Hydrogen bonding with VAL1036	**Hydrophobic** interactions with VAL1036, ALA1132, TYR1150. **Hydrophilic** interactions with GLY1133, ARG1029, THR1034, SER1135, HIS1051	-8.9
6.	 *4-methyl-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzene-1-sulfonamide*	Hydrogen bonding with VAL1126.	**Hydrophobic** interactions with ala1132, val1126. **Hydrophilic** interactions with ARG1029, GLY1151	-7.2

**Pharmacokinetic Property Prediction of the Title compounds **

- Pharmacokinetic properties of the title compounds were predicted using an online freeware SwissADME

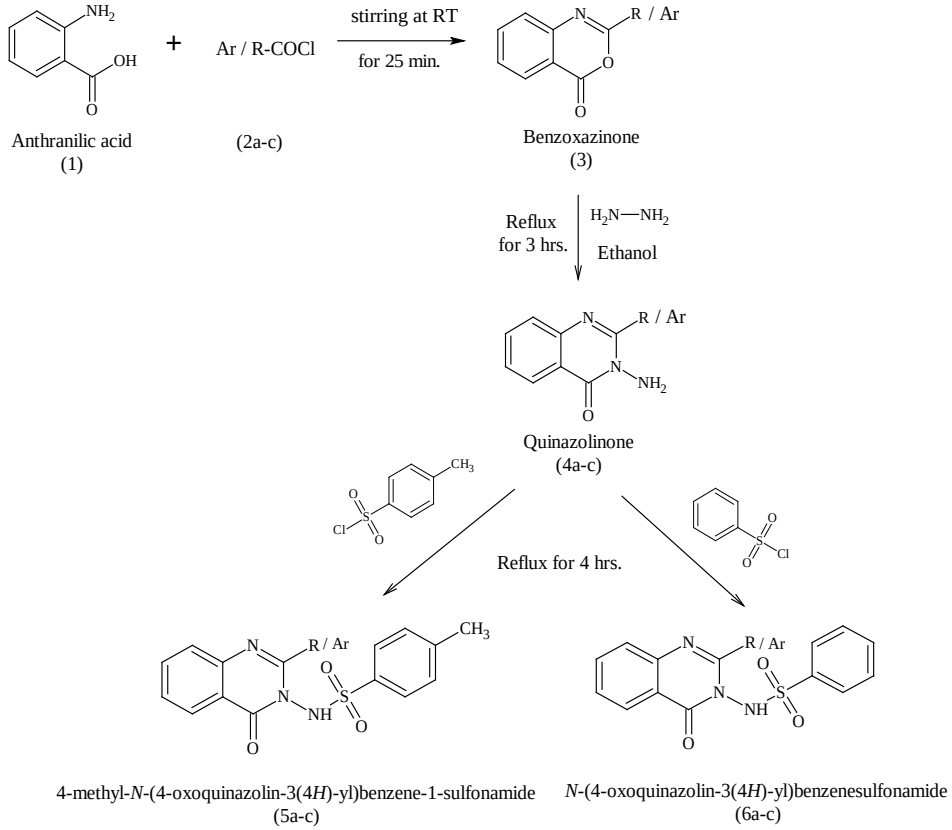
Table 6: Pharmacokinetics Properties Prediction studies of Quinazolinone-benzenesulfonamide derivatives using SwissADME software

Pharmacokinetic Properties	5a	5b	5c	6a	6b	6c
GI absorption	High	High	High	High	High	High
BBB permeant	No	No	No	No	No	No
P-gp substrate	No	No	No	No	No	No
CYP1A2 inhibitor	no	no	Yes	no	no	Yes
CYP2C19 inhibitor	No	Yes	Yes	No	Yes	Yes
CYP2C9 Inhibitor	No	Yes	Yes	No	Yes	Yes
CYP2D6 Inhibitor	No	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No	No
Log K_p (skin permeation)	-6.57 cm/s	-6.41 cm/s	-6.03 cm/s	-6.75 cm/s	-6.58 cm/s	-6.20 cm/s

SYNTHESIS

New series of 5a-c and 6a-c were synthesized by a known convenient method. 3-Sulphonamido quinazolinone derivatives were synthesized from 3-amino quinazoline-4-one (4a-c). The compounds were characterized by IR, NMR and Mass Spectrometry. 3-Amino Quinazoline 4-ones were synthesized by isosteric replacement of various 2-aryl benzamido-4-benzoxazin-4-one (3a-c) with hydrazine hydrate. 2-Substituted-4*H*-3,1-benzoxazin-4-ones were in turn prepared by the reaction of anthranilic acid with various acid chlorides as shown in the scheme. (fig.6)

Synthetic Scheme



S.No.	-R
5a	$-CH_2CH_3$
5b	$-CH_2CH_2CH_3$
5c	$-C_6H_5$
6a	$-CH_2CH_3$
6b	$-CH_2CH_2CH_3$
6c	$-C_6H_5$

Figure 12: Synthetic scheme

Experimental

Step 1: Synthesis of Anthranilic acid from Phthalic Anhydride:

Step 1(a): Preparation of Pthalimide: Phthalic anhydride (0.06moles) and urea (0.03moles) was taken in 250ml RBF and heated on an oil bath/ sand bath/ heating mantle at 130-135ºC till the contents melts, froth up and become solid. Remove the flame and allow cooling. Add water (abt. 50ml) to disintegrate the solid. Filter the crude product with little water and recrystallize from ethanol to obtain the white product. TLC:

M.p 230ºC, Yield-92%.

Step 1(b): Preparation of Anthranilic Acid: Dissolve 7.5 gram Sodium hydroxide in 40ml water and cool in an ice bath to about 0ºC temp., and add 2.1ml of Bromine solution to it. To this solution, add 6 grams pthalimide and neutralize the solution with conc.HCl. Filter the solution of anthranilic acid, wash with water and recrystallize with hot water. Collect the acid on Buchner funnel and dry at 100ºC.

M.P-145ºC, yield – 85%.

Step 2: Preparation of Benzoxazinone from anthranilic acid: To a solution of anthranilic acid (1.37g, 0.01moles) in pyridine (30ml) was added benzoylchloride (2.8g, 0.02mol) and the mixture was stirred on magnetic stirrer for 1 hr at room temperature and then washed with 5% Sodium Carbonate solution (20ml) to remove the pyridine

and unreacted benzoyl chloride, again washed with water and then filtered, dried to get the crude product and recrystallized with ethyl acetate and hexane mixture. Mp: 118ºC, yield- 2g.

2-propyl-4H-3,1-benzoxazin-4-one (3b): White powder, yield – 63%, mp: 164-171ºC characterized by the appearance of cyclic ester (C=O) stretching at 1712.43 cm^{-1}, C-H Stretching at 3195.60 cm^{-1} and N=C stretching at 1650.10 cm^{-1}.

2-phenyl-4H-3,1-benzoxazin-4-one (3c): White crystalline powder, yield- 73%, mp: 180-185ºC, characterised by the appearance of cyclic ester (C=O) stretching at 1701.22 cm^{-1}, C-H stretching at 3093.82 cm^{-1} and N=C stretching at 1647.21 cm^{-1}.

Step 3: Synthesis of 3-amino Quinazoline-4-one: To a solution of compound benzoxazin-4-one (0.01mole) in 50ml of absolute ethanol and hydrazine hydrate (0.03 mole) was added and the reaction mixture was refluxed for 3 hrs. On cooling, the precipitate formed was filtered off and recrystallized by ethanol.

3-amino-2-propylquinazolin-4(3H)-one (4b): White powder, yield – 192-200 ºC characterized by 1769 (C=O lactone); 1625 (C=N), 1315 (C-N); 1474 and 1605 (C=C aromatics); 3036 (sp^2 CH).

3-amino-2-phenylquinazolin-4(3H)-one (4c): White cyrtalline powder, yield - 80%, mp: 210-215ºC characterized by IR (KBr, V_{max}, cm^{-1}): 1769 (C=O lactone); 1625 (C=N); 1315 (C-N); 1474 and 1605 (C=C aromatics); 3036 (sp2 CH); 762 (C-Cl); 1272 (C-O-C).

Step 4: Synthesis of 3-sulfonamido substituted Quinazolin-4-one: An equimolar quantity of quinazoline derivative (0.03mole) and benzene sulfonylchloride (0.42ml, 0.003mole) and dioxane 10ml and few drops of trietheylamine was refluxed for 4 hours by monitoring the progress with TLC. Then the mixture was poured into ice cold water. A pale yellow colored solid was obtained and recrystallized by ethanol.

4-methyl-N-(4-oxo-2-propylquinazolin-3(4H)-yl) benzene-1-sulfonamide (5b): White powder, yield – 80%, mp: 202-210ºC is characterized by the appearance of C-C (s) at 1543 cm^{-1}; S=O (s) at 1023 cm^{-1}; N-H (S)at 3445 cm^{-1}; C=O (S) at 1602 cm^{-1}; CH_3(S) at 2879 cm^{-1}; Ar C=C (s) at 1460cm^{-1}.

4-methyl-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzene-1-sulfonamide(5c):White crystalline powder, Yield: 79%, mp: 220-225ºC is characterized by the appearance of C-C (s) at 1554 cm^{-1}; S=O (s) at 1054 cm^{-1}; N-H (S)at 3433 cm^{-1}; C=O (S) at 1600 cm^{-1}; CH_3 (S) at 2897 cm^{-1}; Ar C=C (s) at 1458 cm^{-1}. NMR values: ^{1}H NMR: δ 2.32 (3H, s), 7.32 (2H, ddd, *J* = 8.1, 1.8, 0.4 Hz), 7.42-7.69 (8H, 7.57 (dddd, *J* = 8.1, 7.4, 2.6, 0.4 Hz), 7.49 (ddd, *J* = 7.9, 7.5, 1.5 Hz), 7.62 (ddd, *J* = 8.1, 1.5, 0.4 Hz), 7.47 (ddd, *J* = 7.8, 7.5, 1.4 Hz), 7.56 (ddd, *J* = 7.8, 1.5, 0.4 Hz), 7.66 (tt, *J* = 7.4, 1.7 Hz)), 8.15 (1H, ddd, *J* = 7.9, 1.4, 0.4 Hz), 8.22 (2H, dddd, *J* = 8.1, 1.7, 1.5, 0.4 Hz)

N-(4-oxo-2-propylquinazolin-3(4H)-yl)benzenesulfonamide (6b): White powder, Yield: 76%, mp: 241-245ºC is characterized by the appearance of S=O (s) at 1054 cm^{-1}; N-H (S)at 3433 cm^{-1}; C=O (S) at 1600 cm^{-1}; Ar C=C (s) at 1458 cm^{-1}; N=C (s) at 1653 cm^{-1}.

N-(4-oxo-2-phenylquinazolin-3(4H)-yl)benzenesulfonamide (6c): White crystalline powder, Yield: 81%, mp: 250-255ºC is characterized by the appearance of S=O (s) at 1154 cm^{-1}; N-H (S)at 3430cm^{-1}; C=O (S) at 1605 cm^{-1}; Ar C=C (s) at 1430 cm^{-1}; N=C (s) at 1620 cm^{-1}. NMR values: ^{1}H NMR: δ 7.42-7.69 (9H, 7.57 (dddd, *J* = 8.1, 7.4, 2.6, 0.4 Hz), 7.49 (ddd, *J* = 7.9, 7.5, 1.5 Hz), 7.47 (ddd, *J* = 7.8, 7.5, 1.4 Hz), 7.63 (tt, *J* = 7.6, 1.5 Hz), 7.54 (dddd, *J* = 8.0, 7.6, 1.5, 0.4 Hz), 7.56 (ddd, *J* = 7.8, 1.5, 0.4 Hz), 7.66 (tt, *J* = 7.4, 1.7 Hz)), 7.76 (2H, dtd, *J* = 8.0, 1.5, 0.4 Hz), 8.15 (1H, ddd, *J* = 7.9, 1.4, 0.4 Hz), 8.22 (2H, dddd, *J* = 8.1, 1.7, 1.5, 0.4 Hz).

DISCUSSION

New series of 5a-c and 6a-c were synthesized by a known convenient method. 3-Sulphonamido quinazolinone derivatives were synthesized from 3-amino quinazoline 4-one (4a-c). The compounds were characterized by IR, NMR and Mass Spectrometry. 3-Sulfonamido Substituted Quinazolin-4-ones were synthesized by isosteric replacement of various 2-aryl benzamido-4 -benzoxazin-4 -one (3a-c) with hydrazine hydrate. 2-Substituted-4*H*-3, 1-benzoxazin-4-ones were in turn prepared by the reaction of anthranilic acid with various acid chlorides. The synthesized compounds were then evaluated with physical and spectral data.

CONCLUSION

In the present investigation 100 molecules from CHEMBL database were retrieved and subjected to virtual screening against PDB ID: 5XGJ. Five HITS with highest scores were selected and by understanding the basic pharmacophoric features, a new lead molecule was designed and from that a new series of 3- Sulphonamido substituted quinazolinones (5a-c, 6a-c) were subjected to molecular docking and toxicity prediction studies. All the title compounds were having potent anti-zika viral activity and were found to be safe. These molecules were synthesized and all the synthesized compounds characterized by physical and spectral data.

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REFERENCES

[1] P. Griess,"Ueber die einwirkung des cyans auf anthranilsaure", *Berichte* 2(1869) 415, 418.

[2] P. Griess,"Ueber die einwirkung von cyan auf amidobenzoesaure undanthranilsaure in wasserigerlosung," *Berichte* (1878) 1985, 1988, 11.

[3] Bischler, M. Lang, Zurkenntniss der phenmiazinderivate," *Chem. Ber*. (1895) 28 279.

[4] S. Gabriel, J. Colman, "Zurkenntniss des pyrimidins und methylirter pyrimidine" *Chem. Ber*. (1903)36, 3379, 3385.

[5] D. Wang, F.Gao, "Quinazoline Derivatives: Synthesis and Bioactivities," *Chem. Cent. J*. 7 (2013) 95, 110.

[6] M. Asif: "Chemical Characteristics, Synthetic Methods, and Biological Potential of Quinazoline and Quinazolinone Derivatives," *Int. J. Med. Chem.* 18 (2014) 395, 397.

[7] K.P. Rakesh, H.M. Manukumar, D. C. Gowda, "Schiff's Bases of Quinazolinone Derivatives: Synthesis and SAR Studies of a Novel Series of Potential Anti-Inflammatory and Antioxidants," *Bioorg. Med. Chem. Lett*., 25(2015)1072, 1077.

[8] J. Hu, Y. Zhang, L. Dong, Z. Wang, L. Chen, D. Liang, D. Shi, X. Shan, G. Liang, "Design, Synthesis and Biological Evaluation of Novel Quinazoline Derivatives as Anti-Inflammatory Agents Against Lipo-polysaccharide-Induced Acute Lung Injury in Rats," *Chem. Biol. Drug Des.* 85 (2015) 672, 684.

[9] V.G. Ugale, S.B. Bari, "Quinazolines: New Horizons in Anticonvulsant Therapy," *Eur. J. Med. Chem.* 80 (2014) 447, 501.

[10] T.P. Selvam, A. Sivakumar, P.P. Prabhu, "Design and Synthesis of Quinazoline Carboxylates Against Gram-positive, Gram-negative, Fungal Pathogenic Strains, and Mycobacterium Tuberculosis," *J. Pharm. BioAllied Sci*. 6 (2014)278, 284.

[11] Q. Ji, D. Yang, X. Wang, C. Chen, Q. Deng, Z. Ge, L. Yuan, X. Yang, F. Liao, "Design, Synthesis and Evaluation of Novel Quinazoline-2,4-dione Derivatives as Chitin Synthase Inhibitors and Anti-fungal Agents," *Bioorg. Med. Chem.* 22(2014) 3405, 3413.

[12] E. Jafari, M.R. Khajouei, F. Hassan zadeh, G.H. Hakimelahi, G.A. Khodarahmi: "Quinazolinone and Quinazoline Derivatives: Recent Structures with Potent Anti-Microbial and Cytotoxic Activities," *Res. Pharm. Sci*. 11 (2016) 1, 14.

[13] R. Al-Salahi, H.A. Abuelizz, H.A. Ghabbour, R. El-Dib, M. Marzouk, "Molecular Docking Study and Anti-Viral Evaluation of 2-Thioxo-Benzo[g]Quinazolin-4(3H)-one Derivatives," *Chem. Cent. J*. 19 (2016) 10, 21.

[14] Z. Wan, D. Hu, P. Li, D. Xie, X. Gan, "Synthesis, Anti-Viral Bioactivity of Novel 4-Thioquinazoline Derivatives Containing Chalcone Moiety," *Molecules* 20(2015) 11861, 11874.

[15] S. Ravez, O. Castillo-Aguilera, P. Depreux, L. Goossens, "Quinazoline Derivatives as Anti-Cancer Drugs: A Patent Review" (2011-present), *Expert Opin.Ther. Pat*. 25 (2015) 789, 804.

[16] S. Mehndiratta, S. Sapra, G. Singh, M. Singh, K. Nepali, "Quinazolines as Apoptosis Inducers and Inhibitors: A Review of Patent Literature," *Recent Pat.Anti-Cancer Drug Disco*v. 11 (2016) 2, 66.

[17] Sasmal S, Balaji G, Kanna Reddy HR, Balasubrahmanyam D, Srinivas G, Kyasa S,SasmalPK, Khanna I, Talwar R, Suresh J, Jadhav VP, Muzeeb S, Shashikumar D,Harinder Reddy K, Sebastian VJ, Frimurer TM, Rist Ø, Elster L, Högberg T, "Design and Optimization of Quinazoline Derivatives as Melanin Concentrating Hormone Receptor 1 (MCHR1) Antagonists," *Bioorg Med ChemLett* 2012, 22:3157–3162.

[18] Alvarado M, Barceló M, Carro L, Masaguer CF, Raviña E, "Synthesis and Biological Evaluation of New Quinazoline and Cinnoline Derivatives as Potential Atypical Antipsychotics," *ChemBiodivers* 2006, 3:106–117.

[19] Malamas MS, Millen J, "Quinazoline acetic acids and related analogs as aldose reductase inhibitors," *J Med Chem* 1991, 34:1492–1503.

[20] Prabhakar "Characterization and Biological Evaluation of Quinazoline Derivatives as Novel Anti-Microbial Agents" *Organic Chemistry Current Research Synthesis* (2015) Volume 5, Issue 4, page no.1-2.

[21] Akranth Marella "Quinoline Review Article" A Versatile Heterocyclic," *Saudi Pharmaceutical Journal*, 2013Volume 21, Issue 1, 2013, Pages 1-12.

[22] Niementowski, S. V., "Synthesen der Chinolinderivate". *Chemische Berichte, (1894). 27(2): 1394–1403.*

[23] Niementowski, S.V. Orzechowski, B. "Synthesen der Chinolinderivate aus Anthranilsaure und Aldehyden," *Chemische Berichte*, (1895), 28 (3), 2809-2822.

[24] *Niementowski, S. V.* "Ueber die Einwirkung des Benzoylessigesters auf Anthranilsäure (III. Mittheilung über Synthesen der Chinolinderivate)"**.** *Chemische Berichte, (1905). 38 (2): 2044–2051.*

[25] Niementowski S. V. "Uber die Einwirkug des Benzoylessigesters auf Anthranilsaure," Chemische Berichte, (1907), 40 (4), 4285-4294.

[26] *Manske, R. H. "The Chemistry of Quinolines". Chem. Rev, (1942)..30: 127.*

[27] *Hisano, T., "Recent Studies on the Modified Niementowski 4-Quinazolone Synthesis: A Review," Org. Prep. Proced. Int., (1973), 5 (4): 145–193.*

[28] Rester U, "From Virtuality to Reality - Virtual Screening in Lead Discovery and Lead Optimization: A Medicinal Chemistry Perspective," *Current Opinion in Drug Discovery & Development*, (July 2008), 11 (4): 559–68.

[29] Rollinger JM, Stuppner H, Langer T "Virtual Screening For The Discovery of Bioactive Natural Products" *Progress in Drug Research*, (2008) 65. pg. 211, 213–49.

[30] Walters WP, Stahl MT, Murcko MA "Virtual Screening – An Overview". *Drug Discov. Today*. (1998). 3 (4): 160–178.

[31] Bohacek RS, Mc Martin C, Guida WC "The Art and Practice of Structure-based Drug Design: A Molecular Modeling Perspective". *Med. Res. Rev.*, (1996). 16 (1): 3–50.

[32] McGregor MJ, Luo Z, Jiang X "Chapter 3: Virtual Screening in Drug Discovery," *Drug Discovery Research. New Frontiers in the Post-Genomic Era.*, (June 11, 2007). Wiley-VCH: Weinheim, Germany. pp. 63–88.

[33] Gillet V, "Ligand-Based and Structure-Based Virtual Screening," *The University of Sheffiel*, (2013).

[34] Mc Innes C "Virtual Screening Strategies in Drug Discovery". *Current Opinion in Chemical Biology*, (October 2007), 11 (5): 494–502.

[35] Sun H, "Pharmacophore-based Virtual Screening". *Current Medicinal Chemistry*, (2008) 15 (10): 1018–24.

[36] Willet P, Barnard JM, Downs GM "Chemical Similarity Searching," *Journal of Chemical Information and Computer Sciences*, (1998), 38 (6): 983–996.

[37] Rush TS, Grant JA, Mosyak L, Nicholls A, "A Shape-based 3-D Scaffold Hopping Method and its Application to a Bacterial Protein-Protein Interaction," *Journal of Medicinal Chemistry*, (March 2005) 48 (5): 1489–95.

[38] Ballester PJ, Westwood I, Laurieri N, Sim E, Richards WG "Prospective Virtual Screening with Ultrafast Shape Recognition: The Identification of Novel Inhibitors of Arylamine N-Acetyl Transferases". *Journal of the Royal Society, Interface*, (February 2010), 7 (43): 335–42.

[39] Kumar A, Zhang KY "Advances in the Development of Shape Similarity Methods and Their Application in Drug Discovery". *Frontiers in Chemistry*, (2018), 6: 315.

[40] Li H, Leung KS, Wong MH, Ballester PJ, "USR-VS: A Web Server for Large-Scale Prospective Virtual Screening Using Ultrafast Shape Recognition Techniques". *Nucleic Acids Research*, (July 2016), 44 (W1): W436–41.

[41] Sperandio O, Petitjean M, Tuffery P "wwLigCSRre: A 3D Ligand-based s\Server for Hit Identification and Optimization," *Nucleic Acids Research*, (July 2009), 37 (Web Server issue): W504–9.

[42] Evanthia Lionta, George Spyrou, Demetrios K. Vassilatis and Zoe Cournia*, "Structure-Based Virtual Screening for Drug Discovery: Principles, Applications and Recent Advances," *Current Topics in Medicinal Chemistry*, 2014, *14*, 1923-1938.

[43] Lavecchia, A.; Di Giovanni, C., "Virtual Screening Strategies in Drug Discovery: A Critical Review," *Curr. Med. Chem.*, 2013, 20, (23), 2839-2860.

[44] Reddy, A.S.; Pati, S.P.; Kumar, P.P.; Pradeep, H.N.; Sastry, G.N., "Virtual Screening in Drug Discovery – A Computational Perspective," *Curr. Pro. Pept. Sci.*, 2007, 8, (4), 329-351.

[45] Cheng, T.; Li, Q.; Zhou, Z.; Wang, Y.; Bryant, S.H., "Structure based Virtual Screening for Drug Discovery: A Problem-Centric Review," *AAPS J.*, 2012, 14, (1), 133-141.

[46] Köppen, H., "Virtual Screening - What Does It Give Us?" *Curr. Opin. Drug Discov. Devel.*,2009, 12, (3), 397-407.
[47] Morris, G.M.; Huey, R.; Lindstrom, W.; Sanner, M.F.; Belew, R.K.; Goodsell, D.S.; Olson, A.J. "Autodock4 and AutoDock-Tools4: Automated Docking with Selective Receptor Flexibility," *J. Comput. Chem.*, 2009, 16, 2785-2791.
[48] Ewing, T.J.; Makino, S.; Skillman, A.G.; Kuntz, I.D. "DOCK 4.0 Search Strategies for Automated Molecular Docking of Flexible Molecule Databases," *J. Comput. Aided. Mol. Des.*, 2001, 15, 411–428.
[49] Rarey, M.; Kramer, B.; Lengauer, T.; Klebe, G., "A Fast Flexible Docking Method Using an Incremental Construction Algorithm," *J. Mol. Biol.*, 1996, 261, (3), 470–489.
[50] Friesner, R.A.; Banks, J.L.; Murphy, R.B.; Halgren, T.A.; Klicic, J.J.; Mainz, D.T.; al. e. "Glide: A New Approach for Rapid, Accurate Docking and Scoring, Method and Assessment of Docking Accuracy," *J. Med. Chem.*, 2004, 47, 1739–1749.
[51] Jones, G.; Willett, P.; Glen, R.C.; Leach, A.R.; Taylor, R, "Development and Validation of A Genetic Algorithm for Flexible Docking," *J. Mol. Bio.*, 1997, 267, (3), 727–748.
[52] Jain, A.N. "Surflex: Fully Automatic Flexible Molecular Docking Using a Molecular Similarity-based Search Engine," *J. Med. Chem.*, 2003, 46, (4), 499–511.
[53] Venkata chalam, C.M.; Jiang, X.; Oldfield, T.; Waldman, M. "Ligand Fit: A Novel Method for the Shape-directed Rapid Docking of Ligands to Protein Active Sites," *J. Mol. Graph. Model.*, 2003, 21, 289–307.
[54] Vlachakis, D.; Tsagrasoulis, D.; Megalooikonomou, V.; Kossida, S., "Introducing Drugster: A Comprehensive and Fully Integrated Drug Design; Lead and Structure Optimization Toolkit," *Bioinformatics*, 2013, 29, (1),126-128.
[55] Zsoldos, Z.; Szabo, I.; Szabo, Z.; A.P.J. "Software Tools for Structure based Rational Drug Design," *J. Mol. Struct. (THEOCHEM).*,2003, 666-667, 659-665.
[56] Guido, R.V.; Oliva, G.; Andricopulo, A.D. "Virtual Screening and its Integration with Modern Drug Design Technologies," *Curr. Med. Chem.*, 2008, 15, (1), 37-46.
[57] K. M. De Cock, "The Eradication of Smallpox: Edward Jenner and the First and Only Eradication of a Human Infectious Disease," *Nature Medicine*, (2001) vol. 7, pp. 15–16.
[58] F. Brown, "Chemoinformatics: What is it and How Does it Impact Drug Discovery," *Annual Reports in Medicinal Chemistry*, (1998) vol. 33, pp. 375–384.
[59] Moitessier N, Englebienne P, Lee D, Lawandi J, Corbeil CR. Towards the Development of Universal, Fast and Highly Accurate Docking/Scoring Methods: A Long Way To Go," *Br J Pharmacol*. (2008),153 (Suppl 1):S7–26.
[60] Shoichet BK, McGovern SL, Wei B, Irwin JJ., "Hits, Leads and Artifacts From Virtual and High Throughput Screening," *Molecular Informatics: Confronting Complexity*, (2002).
[61] Shoichet BK, McGovern SL, Wei B, Irwin JJ, "Lead Discovery Using Molecular Docking," (2002), 6: 439-446.
[62] Gschwend DA, Good AC, Kuntz ID, "Molecular Docking Towards Drug discovery," *J Mol Recognit*, (1996), 9: 175-186.
[63] Ferreira LG, dos Santos RN, Oliva G, Andricopulo AD "Molecular Docking and Structure-Based Drug Design Strategies Molecules," (2015), 20: 13384-13421
[64] Agarwal S, Jangir DK, Mehrotra R, Lohani N, Rajeswari M, "A Structural Insight into Major Groove Directed Binding of Nitrosourea Derivative Nimustine with DNA: A Spectroscopic Study," *PLoS ONE*, (2014), 9: 104-115.
[65] Mehrotra R, Jangir DK, Agarwal S, Ray B, Singh P, et al., "Interaction Studies of Anticancer Drug Lomustine with Calf Thymus DNA Using Surface Enhanced Raman Spectroscopy," *MAPAN*, (2013) 28: 273-277.
[66] Holt PA, Chaires JB, Trent JO, "Molecular Docking of Intercalators and Groove-Binders to Nucleic Acids Using Autodock and Surflex," *J Chem Inf Model*, (2008), 48: 1602-1615.
[67] Falgout, B., Pethel, M., Zhang, Y. M., and Lai, C. J., "Both Nonstructural Proteins NS2B and NS3 are Required for the Proteolytic Processing of Dengue Virus Nonstructural Proteins," *J. Virol*, 65, (1991), 2467−2475.
[68] Rice, C.M., Lenches, E.M., Eddy, S.R., Shin, S.J., Sheets, R.L., Strauss, J.H., "Nucleotide Sequence of Yellow Fever Virus: Implications for *Flavivirus* Gene Expression and Evolution," *Science*, (1985) 229, 726–733.
[69] Cleaves, G.R., Dubin, D.T., "Methylation Status of Intracellular Dengue Type 2 40 S RNA," *Virology*, (1979), 96, 159–165.
[70] Bressanelli, S., Stiasny, K., Allison, S.L., Stura, E.A., Duquerroy, S., Lescar, J., Heinz, F.X., Rey, F.A., "Structure of a *Flavivirus* Envelope Glycoprotein in its Low-pH-induced Membrane Fusion Conformation," *EMBO J*., (2004) 23, 728–738.
[71] Guirakhoo F., Bolin R.A., Roehrig J.T., "The Murray Valley: Encephalitis Virus prM Protein Confers Acid Resistance to Virus Particles and Alters the Expression of Epitopes within the R2 Domain of E Glycoprotein," *Virology*, (1992) 191, 921–931.
[72] Erbel P., Schiering N., D'Arcy A., Renatus M., Kroemer M., Lim S., Yin Z., Keller T., Vasudevan S., Hommel U., "Structural Basis for the Activation of Flaviviral NS3 Proteases from Dengue and West Nile virus," *Nat. Struct. Mol. Biol*., (2006) 13, 372–373.
[73] Luo D., Xu T., Hunke C., Gruber G., Vasudevan S.G., Lescar J., "Crystal Structure of the NS3 Protease-helicase from Dengue Virus," *J. Virol*., (2008) 82, 173–183.
[74] Aleshin A., Shiryaev S., Strongin A., Liddington R., "Structural Evidence for Regulation and Specificity of Flaviviral Proteases and Evolution of the Flaviviridae," *fold. Pro. Sci*., (2007) 16, 795–806.
[75] Brecher M., Zhang J., Li H., "The *Flavivirus* Protease as a Target for Drug Discovery," *Virol. Sin.*, (2013) 28, 326–336.
[76] Chambers T.J., Hahn C.S., Galler R., Ric, C.M., "*Flavivirus* Genome Organization, Expression, and Replication," *Annu. Rev. Microbiol*., (1990) 44, 649–688.
[77] Ahmad F Eweas, Owayyed M Al-Muqati, Rayid S Al-Osaimi, Mohammed D Al-Juaid, "Virtual Screening and Molecular Docking of 4,6,7-Tri Substituted Quinazoline Derivatives as Potential EGFR Inhibitors," *Der Pharma Chemica*, (2017), 9(9):76-96.
[78] Su Hui Yang, Daulat Bikram Khadka, Suk Hee Cho, Hye-Kyung Ju, Kwang Youl Lee, Ho Jae Han,Kyung-Tae Lee, Won-Jea Cho, "Virtual Screening and Synthesis of Quinazolines as Novel JAK2 Inhibitors," *Bioorganic & Medicinal Chemistry*, 19 (2011) 968–977.
[79] Vinay Sonawane, Mohd Usman Mohd Siddique, Surender Singh Jadav, Barij Nayan Sinha, Venkatesan Jayaprakash, Bhabatosh Chaudhuri, "Cink4T, a Quinazolinone-based Dual Inhibitor of Cdk4 and Tubulin Polymerization, Identified via Ligand-based Virtual Screening, for Efficient Anticancer Therapy," *European Journal of Medicinal Chemistry*, 165, (2019), 115-132.
[80] Marko Juki ˇc, Martina Hrast, Delphine Patin, Eva Ogorevc, Hélène Barreteau, Stanislav Gobec, "Virtual Screening Approach and Biochemical Evaluation on MurB," *Chemical Data Collections*, 24 (2019) 100276,
[81] Anita Puspa Widiyana, Galih Satrio Putra, Luthfi Ahmad Muchlashi, Mellany Ika Sulistyowaty & Tutuk Budiati, "Design and Molecular Docking Studies of Quinazoline Derivatives as Antiproliferation," *Jurnal Farmasi Dan Ilmu Kefarmasian Indonesia*, Vol. 3 No. 2, December 2016.
[82] Mohamed F. Zayed, Sahar Ahmed, Saleh Ihmaid, Hany E. A. Ahmed, Heba S. Rateb and Sabrin R. M. Ibrahim, "Design, Synthesis, Cytotoxic Evaluation and Molecular Docking of New Fluoroquinazolinones as Potent Anticancer Agents with Dual EGFR Kinase and Tubulin Polymerization Inhibitory Effects," *Int. J. Mol. Sci*. 2018, 19, 1731.
[83] Shinky Mehta, Sanjiv Kumar, Rakesh Kumar Marwaha, Balasubramanian Narasimhan, Kalavathy Ramasamy, Siong Meng Lim, Syed Adnan Ali Shan and Vasudevan Mani, "Synthesis, Molecular Docking and Biological Potentials of New 2‑(4‑(2‑chloroacetyl) piperazin‑1‑yl)‑N‑(2‑(4‑chlorophenyl)‑4‑oxoquinazolin‑3(4H)‑yl) Acetamide derivatives," *BMC Chemistry*, (2019) 13:113.
[84] Rashad Al‑Salahi, Hatem A. Abuelizz, Hazem A. Ghabbour, Rabab El‑Dib and Mohamed Marzouk, "Molecular Docking Study and Antiviral Evaluation of 2-thioxo-benzo[*g*] Quinazolin-4(3*H*)-one derivatives," *Chemistry Central Journal (2016) 10:21.*
[85] Jasper Fuk-Woo Chan, Kenn Ka-Heng Chik, Shuofeng Yuan, Cyril Chik-Yan Yip, Zheng Zhu, Kah-Meng Tee, Jessica Oi-Ling Tsang, Chris Chung-Sing Chan, Vincent Kwok-Man Poon, Gang Lu, Anna Jinxia Zhang, Kin-Kui Lai, Kwok-Hung Chan, Richard Yi-Tsun Kao, Kwok-Yung Yuen, "Novel Antiviral Activity and Mechanism of Bromocriptine as a Zika virus NS2B-NS3 Protease Inhibitor," *Antiviral Research*, 141 (2017) 29-37.

[86] Maheswata Sahoo, Lingaraja Jena, Sangeeta Daf, Satish Kumar, "Virtual Screening for Potential Inhibitors of NS3 Protein of Zika Virus," *Genomics Inform*, (2016);14(3):104-111.

[87] Wolfgang Dohle, Fabrice L. Jourdan, Grégory Menchon, Andrea E. Prota, Paul A. Foster, Pascoe Mannion, Ernest Hamel, Mark P. Thomas, Philip G. Kasprzyk, Eric Ferrandis, Michel O. Steinmetz, Mathew P. Leese and Barry V. L. Potter: Quinazolinone Based Anticancer Agents, "Synthesis, Antiproliferative SAR, Antitubulin Activity, and Tubulin Co-crystal Structure," *Journal of Medicinal Chemistry* (2018), 61, 1031−1044.

[88] Yahia Nasser Mabkhot, "Synthesis, Anti-microbial and Molecular Docking Studies of Quinazolin-4(3H)-one Derivatives**,"** *Central Journal Science Chemistry*, (2014) **,**vol.2 pg.no-455.

[89] Sukanya Nara, Achaiah Garlapati, "Design, Synthesis and Molecular Docking Study of Hybrids of Quinazolin-4(3H)-one as Anticancer Agents," *Medicinal Chemistry Research Lab, University College of Pharmaceutical Sciences*, (2018), vol.59 (3), pg.no-121-13.

[90] S.K. Krishnan, S. Ganguly, R. Veerasamy, B. Jan, "Synthesis, Antiviral and Cytotoxic Investigation of 2-phenyl-3-substituted Quinazolin-4(3H)-ones," *European Review for Medical and Pharmacological Sciences*, (2011), 15: 673-681

[91] V.D.Gupta, Joginder Singh, Mayank Kinger, Avnish Kumar Arora and Vivek Sheel, "Synthesis and Antiviral Activities of Some 2,3-Disubstituted Quinazolines," *Asian Journal of Chemistry*, (2015), Vol. 27, No. 124379-4382.

[92] Pandey V. K., Tusi S., Tusi Z., Raghubir R., Dixit M., Joshi M. N., Bajpai S. K., "Thiadiazolyl Quinazolones as Potential Antiviral and Antihypertensive Agents," *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* 43 (2004) 1, 180-183.

[93] Periyasamy Selvam, Paulchamy Vijayalakshimi, Donald F Smee, Brian B Gowen, Justin G Julander, Craig W Day and Dale L Barnard, "Novel 3-sulphonamido-quinazolin-4(3*H*)-one Derivatives: Microwave-assisted Synthesis and Evaluation of Antiviral Activities Against Respiratory and Biodefense Viruses," *Antiviral Chemistry & Chemotherapy* (2007) 18:301–305.

[94] Samir Y. Abbas, Khairy A. M. El-Bayouki, Wahid M. Basyouni, Eslam A. Mostafa, "New Series of 4(3H) Quinazolinone Derivatives: Syntheses and Evaluation of Antitumor and Antiviral activities," *Medicinal Chemistry Research*, (2017), 17-2083-7.

[95] Krishnan Suresh Kumar, Swastika Ganguly, Ravichandran Veerasamy, Erik De Clercq, "Synthesis, Antiviral Activity and Cytotoxicity Evaluation of Schiff Bases of some 2-phenyl Quinazoline-4(3)H-ones," *European Journal of Medicinal Chemistry*, 45 (2010) 5474-5479.