Synthesis, antimicrobial activity and molecular docking study of (e)-4-(4-((3-benzylidene-2-oxoindolin-1-yl) methyl)-1h-1,2,3-triazol-1-yl)benzoic acid derivatives

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Abstract

A series of (E)-1-((1-aryl-1H-1,2,3-triazol-4-yl) methyl)-3-(arylmethylene)indolin-2-ones was synthesised starting from commercially available indolin-2-one by the reaction with aldehydes, propargyl bromide and finally benzoic acid azides. All the synthesized 1,2,3-triazole derivatives structure were characterized by IR, ^{1}HNMR, ^{13}CNMR and mass spectrometry.

The synthesized compounds were evaluated for their in vitro antimicrobial activity and their molecular docking studied with comparison of Oseltamivir drug into the active pocket of neuraminidase.

Keywords: 1,2,3-triazole, oxaindole, chalcone, benzoic acid and antimicrobial activity.

Introduction

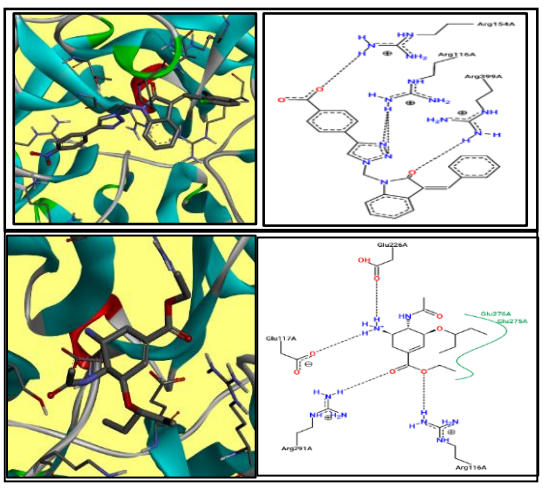
Oxindole has emerged as a valuable scaffold in medicinal chemistry possessing diverse range of pharmacological activities. Its value has further been increased by its natural occurrence as alkaloids in variety of plants. Oxindoles are possessing wide range of applications including antiviral[19], antifungal[1], antibacterial[17], antiproliferative[5], anticancer[2], anti- inflammatory[12], antihypertensive[8] and anticonvulsant[14] activities. Oxindole moieties have been investigated in the development of new efficient bioactive molecules with diverse pharmacological properties[3].

In addition, triazole nucleus has been incorporated into a wide variety of therapeutically interesting drug candidates[13]. Some of the modern day drugs having fused heterocycles with a triazole moiety are: alprazolam[16], triazolam[11], estazolam[18](hypnotic, sedative, tranquilizer), trazodone[4] (antidepressant, anxiolytic), trapidil[10] (hypotensive), terconazole[4] (antifungal), hexaconazole[7] (antifungal), etizolam[15] (amnesic, anxiolytic, anticonvulsant, hypnotic, sedative and skeletal muscle relaxant), rilmazafon[9] (hypnotic, anxiolytic) and rizatriptan[6] (antimigrane agent).

It was considered worthwhile that active pharmacophores in a single molecular frame evidenced that which one enhanced biological potency, hence we have taken up synthesize of two active pharmacophores such as oxaindole and 1,2,3-triazole entities in single molecular frame work to evaluate for their antimicrobial activity.

Material and Methods

Melting points are uncorrected and were find out in open capillary tubes in sulphuric acid bath. TLC was carried out on silica gel-G and spotting was done using UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr phase. The 1 H NMR spectra were record on a Varian as 400 MHz instrument in $CDCl_3$, chemical shifts are given in ppm relative to TMS and coupling constants (J) are expressed in Hertz (Hz). Combinations of the following abbreviations are used to describe NMR spectra: s-singlet; d-doublet; t-triplet; m-multiplet.



Graphical Abstract

^{13}C NMR spectra were recorded with a Bruker Advance 400 (100 MHz) spectrometer. Mass spectra on Agilent LCMS instrument gave only (M+H) values.

General procedure for preparation of (E)-4-(4-((3-benzylidene-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid derivatives (6a-l): A mixture of (E)-3-benzylidene-1-(prop-2-yn-1-yl)indolin-2-one (4a-d) (1 mmol), azido benzoic acid (5a-c) (1.2 mmol) and copper sulphate (2 mmol) and sodium ascorbate (2 mmol) in DMF: water (3 ml) was stirred at room temperature for 6 hr. Progress of the reaction was monitored by TLC. Upon completion of the process, the reaction mixture was poured into ice cold water. The solid precipitate formed slowly. It was filtered off, washed with water, dried and purified by column chromatography using chloroform: methanol (8:2) as an eluent to give the corresponding pure 6a-l compounds.

Spectral data

(E)-4-(4-((3-benzylidene-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6a): IR spectrum, *v*, cm^{-1}: 1500, 1596 and 1654; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.14 (s, 2H, NCH_2), 6.48 (s, 1H, Ar-H), 6.87 (m, 1H, Ar-H), 7.23-8.14 (m, 11H, Ar-H), 8.40 (s, 1H, Ar-H), 9.07 (s, 1H, Ar-H), 13.04 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 53.0, 109.7, 115.0, 119.7, 121.7, 122.0, 122.3, 122.8, 124.9, 125.9, 130.8, 122.0, 133.7, 139.3, 143.1, 158.0, 160.5, 166.5; Mass spectrum, *m/z* (I_{rel}, %): 423 $(M+H)^+$.

(E)-3-(4-((3-benzylidene-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6b): IR spectrum, *v*, cm^{-1}: 1502, 1597 and 1652; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.14 (s, 2H, NCH_2), 6.48 (s, 1H, Ar-H), 6.87 (m, 1H, Ar-H), 7.22-7.54 (m, 5H, Ar-H), 7.85-8.08 (m, 6H, Ar-H), 8.35 (s, 1H, Ar-H), 9.00 (s, 1H, Ar-H), 13.04 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 53.3, 109.3, 115.8, 116.0, 120.6, 122.5, 123.0, 123.3, 129.9, 130.0, 130.2, 130.7, 131.9, 133.4, 143.2, 157.8, 161.4, 163.9, 166.8; Mass spectrum, *m/z* (I_{rel}, %): 423 $(M+H)^+$.

(E)-2-(4-((3-benzylidene-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6c): IR spectrum, *v*, cm^{-1}: 15030, 1595 and 1656; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.13 (s, 2H, NCH_2), 6.84-6.93 (m, 2H, Ar-H), 7.06-7.16 (m, 4H, Ar-H), 7.22-7.38 (m, 6H, Ar-H), 7.58-7.60 (d, *J* = 4.8 Hz, 1H, Ar-H), 8.36 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 13.02 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 53.6, 109.4, 114.2, 120.8, 121.4, 122.4, 123.3, 123.8, 124.0, 124.7, 125.3, 129.5, 130.0, 130.4, 132.2, 135.0, 142.9, 158.5, 161.6, 165.9; Mass spectrum, *m/z* (I_{rel}, %): 423 $(M+H)^+$.

(E)-4-(4-((3-(4-fluorobenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6d): IR spectrum, *v*, cm^{-1}: 1502, 1597 and 1652; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.11 (s, 2H, NCH_2), 6.48 (s, 1H, Ar-H), 6.85 (m, 1H, Ar-H), 7.18-8.10 (m, 10H, Ar-H), 8.35 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 13.01 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 52.6, 109.5, 115.2, 121.5, 122.2, 123.5, 124.5, 125.2, 125.9, 130.7, 132.0, 133.8, 135.4, 137.2, 143.2, 158.0, 160.5, 165.9; Mass spectrum, *m/z* (I_{rel}, %): 441 $(M+H)^+$.

(E)-3-(4-((3-(4-fluorobenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6e): IR spectrum, *v*, cm^{-1}: 1502, 1597 and 1652; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.11 (s, 2H, NCH_2), 6.48 (s, 1H, Ar-H), 6.85 (m, 1H, Ar-H), 7.18-8.10 (m, 10H, Ar-H), 8.35 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 13.01 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 52.6, 109.5, 115.2, 119.5, 121.5, 122.2, 122.5, 123.5, 124.5, 125.2, 125.9, 130.7, 132.0, 133.8, 135.4, 137.2, 143.2, 158.0, 160.5, 165.9, 166.5; Mass spectrum, *m/z* (I_{rel}, %): 441 $(M+H)^+$.

(E)-2-(4-((3-(4-fluorobenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6f): IR spectrum, *v*, cm^{-1}: 1502, 1590 and 1650; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.10 (s, 2H, NCH_2), 6.50 (s, 1H, Ar-H), 6.89-8.04 (m, 11H, Ar-H), 8.32 (s, 1H, Ar-H), 9.01 (s, 1H, Ar-H), 13.03 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 53.3, 109.3, 115.8, 116.0, 120.7, 122.5, 123.3, 128.7, 130.0, 130.5, 130.8, 131.3, 132.2, 133.0, 142.7, 157.2, 161.6, 164.1, 166.9; Mass spectrum, *m/z* (I_{rel}, %): 441 $(M+H)^+$.

(E)-4-(4-((3-(4-bromobenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6g): IR spectrum, *v*, cm^{-1}: 1503, 1595 and 1657; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.09 (s, 2H, NCH_2), 6.84-6.93 (m, 2H, Ar-H), 7.18-8.05 (m, 10H, Ar-H), 8.29 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 13.01 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 52.5, 109.4, 114.2, 115.8, 120.8, 121.4, 122.4, 123.3, 124.7, 125.3, 129.5, 130.0, 131.1, 132.2, 135.0, 143.2, 158.5, 161.0, 166.5; Mass spectrum, *m/z* (I_{rel}, %): 501 $(M+H)^+$.

(E)-3-(4-((3-(4-bromobenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6h): IR spectrum, *v*, cm^{-1}: 1500, 1596 and 1655; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.08 (s, 2H, NCH_2), 6.92-6.95 (m, 2H, Ar-H), 7.16-8.01 (m, 10H, Ar-H), 8.25 (s, 1H, Ar-H), 9.00 (s, 1H, Ar-H), 13.02 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 52.6, 109.4, 114.2, 120.8, 121.4, 122.4, 123.3, 124.0, 124.7, 125.3, 129.5, 130.0, 130.8, 132.2, 135.0, 142.9, 158.5, 161.6, 165.9; Mass spectrum, *m/z* (I_{rel}, %): 501 $(M+H)^+$.

(E)-2-(4-((3-(4-bromobenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6i): IR spectrum, *v*, cm^{-1}: 1503, 1595 and 1656; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.09 (s, 2H, NCH_2), 6.99-7.02 (m, 2H, Ar-H), 7.25-8.05 (m, 10H, Ar-H), 8.27 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 13.03 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 52.6, 109.4, 114.2, 120.8, 121.8, 122.7, 123.8, 124.0, 124.7, 125.5, 129.5, 130.0, 130.4, 131.0, 135.5, 142.7, 158.5, 161.0, 166.4; Mass spectrum, *m/z* (I_{rel}, %): 501 $(M+H)^+$.

(E)-4-(4-((3-(4-chlorobenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6j): IR spectrum, *v*, cm^{-1}: 1240, 1503, 1593 and 1652; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.10 (s, 2H, NCH_2), 6.86-6.90 (m, 2H, Ar-H),

7.02-8.01 (m, 10H, Ar-H), 8.34 (s, 1H, Ar-H), 9.04 (s, 1H, Ar-H), 13.01 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 52.3, 109.6, 114.9, 120.5, 122.8, 123.5, 125.5, 127.4, 129.5, 130.2, 130.4, 131.2, 133.1, 135.4, 135.8, 142.5, 161.4, 165.8; Mass spectrum, *m/z* (I_{rel}, %): 457 $(M+H)^+$.

(E)-3-(4-((3-(4-chlorobenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6k): IR spectrum, *v*, cm^{-1}: 1237, 1499, 1593 and 1650; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.08 (s, 2H, NCH_2), 6.86-6.94 (m, 2H, Ar-H), 7.03-8.06 (m, 10H, Ar-H), 8.30 (s, 1H, Ar-H), 9.00 (s, 1H, Ar-H), 13.00 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 52.5, 109.2, 114.9, 120.7, 122.1, 122.5, 123.5, 127.3, 128.9, 129.3, 130.2, 133.1, 136.6, 142.7, 161.6, 165.1; Mass spectrum, *m/z* (I_{rel}, %): 457 $(M+H)^+$.

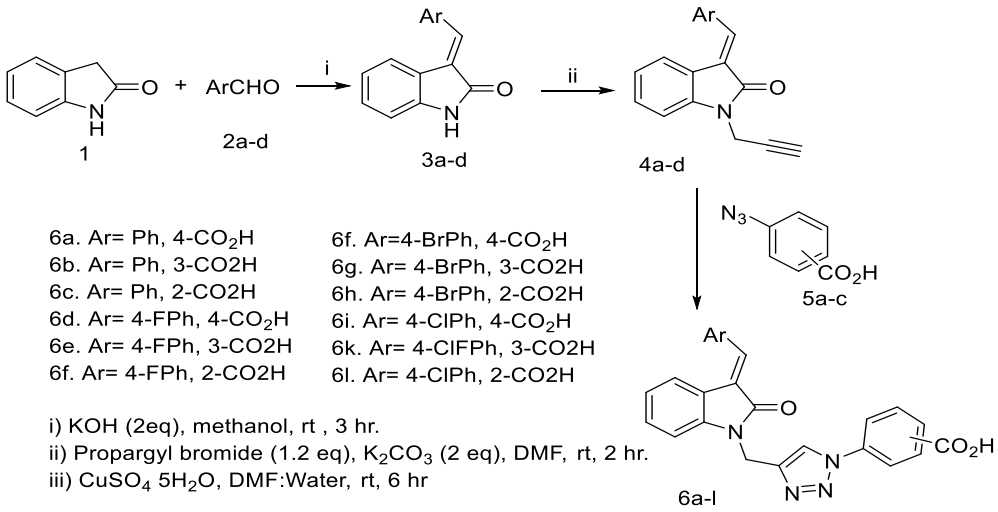
(E)-2-(4-((3-(4-chlorobenzylidene)-2-oxoindolin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (6l): IR spectrum, *v*, cm^{-1}: 1241, 1502, 1596 and 1652; ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.06 (s, 2H, nCH_2), 6.86-6.90 (m, 1H, Ar-H), 7.02-8.06 (m, 10H, Ar-H), 8.27 (s, 1H, Ar-H), 9.02 (s, 1H, Ar-H), 13.02 (s, 1H, OH); ^{13}C NMR spectrum, δ, ppm: 52.5, 109.3, 114.9, 120.2, 122.1, 122.6, 123.6, 127.3, 128.4, 129.3, 130.1, 133.1, 135.5, 142.7, 161.4, 165.1,; Mass spectrum, *m/z* (I_{rel}, %): 457 $(M+H)^+$.

Results and Discussion

Chemistry: The title derivatives (E)-1-((1-aryl-1H-1,2,3-triazol-4-yl)methyl)-3-(arylmethylene)indolin-2-ones (6a-l) have been synthesised starting from commercially indolin-2-one (1). Initially, the indolin-2-one (1) was reacted with five different aryl aldehydes (2a-d) using potassium hydroxide in methanol medium to afford corresponding five 3-(arylmethylene)indolin-2-one derivatives (3a-c) respectively.

The formation of the derivatives was confirmed by previous literature data. Then, the five 3-(arylmethylene)indolin-2-ones (3a-c) reacted with propargyl bromide using potassium carbonate as base in DMF medium to give desired N-propargylated derivatives such as four 3-(arylmethylene)-1-(prop-2-yn-1-yl)indolin-2-ones (4a-d) quantitatively.

Finally, the 1,2,3-triazole ring was developed by using click reaction condition using five 3-(arylmethylene)-1-(prop-2-yn-1-yl)indolin-2-ones (4a-d) and three different benzoic acid azides (5a-c) in the presence of copper catalyst (Table 3).



Scheme 1: Synthesis of (E)-1-((1-aryl-1H-1,2,3-triazol-4-yl)methyl)-3-(arylmethylene)indolin-2-ones (6a-l)

Table 1
Optimization reaction conditions of the compound 6a

Entry	Solvent	Reaction time	Yield (%)[a]
1	Water	8 hr	64
2	*t*-BuOH	8 hr	58
3	DMF	8 hr	55
4	DMSO	8 hr	42
5	TEA	8 hr	38
6	*t*-buOH	8 hr	47
7	DMF:water(1:2)	8 hr	74
8	DMF:water (1:1)	6 hr	78
9	DMF:water(2:1)	6 hr	92
10	*t*-buOH:water	6 hr	82

[a] isolated yield

Table 2
Reaction time and yield comparison data of compound 6a-l.

Entry	Compound	M.P. (°C)	Reaction time(hr)	Yield (%)
1	6a	125-127	6	92
2	6b	121-123	6	90
3	6c	122-124	6	91
4	6d	130-132	6	90
5	6e	127-129	6	92
6	6f	133-135	6	93
7	6g	151-153	6	88
8	6h	142-144	6	92
9	6i	147-149	6	89
10	6j	144-146	6	90
11	6k	140-142	6	90
12	6l	138-140	6	87

Here, a model reaction was carried out for preparation of compound 6a by the reaction of compound 4a with 4-benzoic acid azide 5a using copper sulphate and sodium ascorbate in different solvent mediums like TEA, DIPEA, DMF and DMSO. The maximum yield of product 6a was obtained in DMF: water (2:1) medium at room temperature.

3-(arylmethylene)-1-(prop-2-yn-1-yl)indolin-2-ones (4a-d) reacted with three different azides 5a-c under the optimized reaction conditions. The structure of the compounds was confirmed by different analytical method such as IR, ^{1}HNMR and mass spectrometry. In IR spectrum, the compounds show two characteristics stretching frequencies at1596 and 1654 cm^{-1} corresponding to C=N and carbonyl C=O bond bonds respectively. The ^{1}H NMR spectrum of the compound (6a) showed two characteristic peaks at 5.14 ppm integrated for two protons assigned to N-methylene group and a peak shown at 13.01 ppm as a broad singlet integrated for one proton was assigned to acid group respectively.

In the ^{13}C NMR spectrum, the compound 6a-l showed three characteristic peaks at 53 and 166.5 ppm assigned to N-methylene and cyclic amide carbonyl carbons respectively and the spectrum showed required number of carbon peaks. The LCMS spectrum of the compound exhibited the peak at 423 *m/z* value as [M+H]+.

Antimicrobial activity: The *in vitro* antibacterial activity was performed against a series of Gram-positive bacteria and Gram-negative bacteria such as *Mycobacterium tuberculosis (M. tub), Micrococcus luteus (M. lut), Methicillin-resistant Staphylococcus aureus (MRSA), Bacillus subtilis (B. sub)* and *Bacillus cereus (B. cer)* such as *Pseudomonas aeruginosa (P. aer), Klebsiella pneumonia (K. pne), Escherichia coli (E. col), Proteus vulgaris (P. vul), Salmonella typhi (S. typ)*. Ciprofloxacin was used as standard reference drug and the activity was screened using agar well diffusion technique. Among all synthesized derivatives, the compounds 6c, 6d and 6e have shown good inhibition activity against almost all stains. All compounds were screened for their antifungal activity against four pathogenic fungi such as *Aspergillus niger Candida albicansusing, Fusarium oxysporum and Fusarium solan*.

Nystatin was used as standard reference drug and the activity was screened using agar well diffusion technique. All the compounds showed moderate antifungal activity against the tested fungal organism. The derivatives 6c, 6e, 6g and 6k have shown good inhibition activity against fungal organism.

Molecular docking studies: Newly synthesized molecules and reference drug oseltamivir were docked into the active pocket of neuraminidase. The crystal structure of neuraminidase from a H3N8 influenza virus (PDB ID: 4WA4) isolated from New England harbor seals in complex with oseltamivir carboxylate was downloaded from Protein Data Bank. Initially, the neuraminidase and ligand molecule were loaded into ADT tools. Both were saved in PDBQT file format after removing water and oseltamivir complex from the protein. The grid box was set up with 60 x 60 x 60 $A^{0.}$ Active sites of 4WA4 were determined from the crystalline structure of neuraminidase in which oseltamivir carboxylate was complexed and grid points were assigned along x = 20.407, y = -22.702, z = -18.622 A^{0} centres separated with 0.375 A^{0} spacing.

The docking simulations were run with each individual molecule. The Autodock 4.2 uses a Lamarckian genetic algorithm program to calculate different ligand conformers. Conformations were ranked according to the binding energy obtained from docked procedure and the confirmation with lowest binding energy was considered as the best docking score. The Autodock 4.2 results were visualized by using BIOVIA Discovery Studio Visualizer and Proteins Plus Server.

The docking scores of all newly synthesized compounds (6a-l) are ranging from -7.51 to -9.71 Kcal/mol as shown in table 3 and reference compound oseltamivir scored about -5.48

Kcal/mol. The amino acid residues Arg116, Glu117, Gln134, Arg154, Arg291, Thr323, Tyr344, Arg368, Arg399 and Thr438 of neuraminidase were involved in H-bond interactions. All the newly synthesized ligands molecules showed H-bond interactions with target molecule 4WA4. Hydrophobic interactions were also observed by amino acid residues Gly145, Glu275, Glu276, Tyr344, Ser367, Arg368, Pro431 and Thr438 of 4WA4.

Compound 6f showed highest binding affinity toward neuraminidase of influenza virus with a docking score of -9.71 kcal/mol. It was involved in four H-bond interactions with Arg116(2), Arg154 and Arg399 of 4WA4 and the hydrophobic interactions were absent. The docking pose and 2D interactions of compound 6 with neuraminidase are shown in figure 1.

Compound 2 showed lowest docking score about -7.54 Kcal/mol with neuraminidase among all compounds. Seven H-bond interactions with binding sites Arg116(2), Arg291(2), Tyr344 and Arg368(2) of 4WA4 and one hydrophobic interaction with Gly145 of 4WA4 were observed. The docking pose and 2D interactions of compound 2 with neuraminidase are shown in fig. 2.

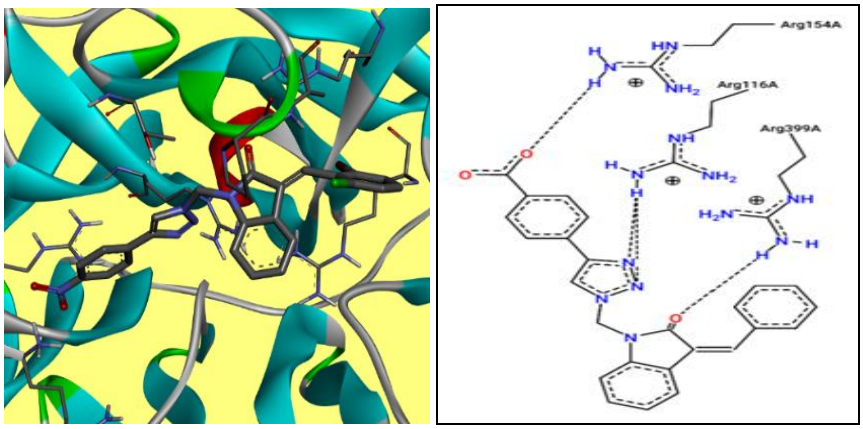


Figure 1: Docking pose and 2D interactions of Compound 1 with neuraminidase (PDB ID:4WA4)

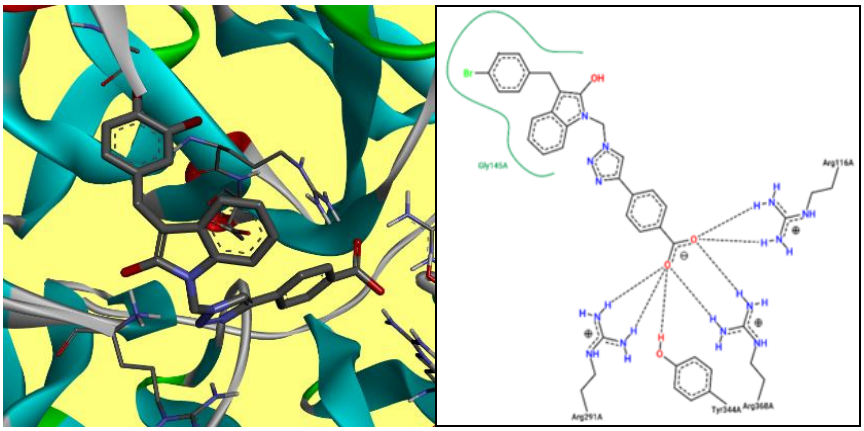


Figure 2: Docking pose and 2D interactions of Compound 7 with neuraminidase (PDB ID: 4WA4)

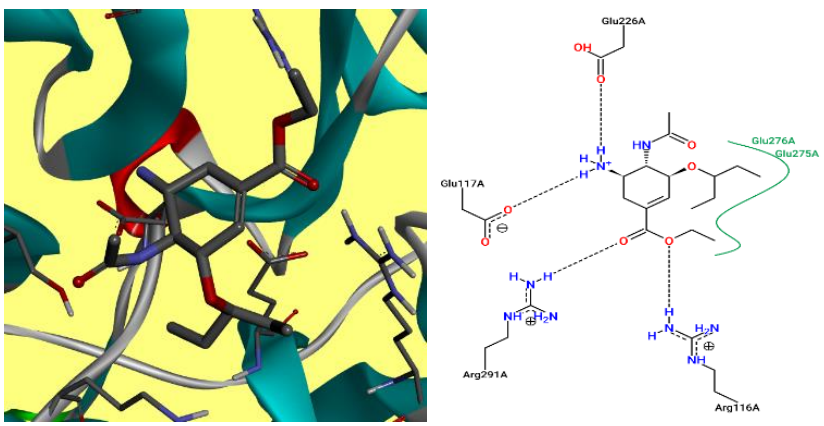


Figure 3: Docking pose and 2D interactions of Oseltamivir with neuraminidase (PDB ID: 4WA4)

Table 3
Molecular docking result of the compound 6a-l

Compound	Binding Energy (Kcal/mol)	Interacting amino acid	
		H-bond	Hydrophobic
6a	-9.71	Arg116(2), Arg154, Arg399	--
6b	-8.32	Arg116, Gln134, Tyr344	Pro431
6c	-9.36	Arg154, Thr438	Tyr344
6d	-9.16	Arg399	Tyr344, Ser367, Arg368, Thr438
6e	-9.38	Arg116(2), Arg154, Arg399	--
6f	-7.51	Arg116(2), Arg291(2), Tyr344, Arg368(2)	Gly145
6g	-9.07	Arg154, Thr323, Tyr344, Arg368	Pro431
6h	-8.25	Arg154, Arg368	Arg368, Pro431
6i	-8.84	Arg116(2), Arg154, Arg399	--
6j	-8.76	Arg116, Arg291(2), Tyr344, Arg368	Gly145
6k	-8.62	Arg116(2), Arg154, Arg399	Ser367
6l	-9.19	Arg116(2), Arg154, Arg399	--
Oseltamivir	-5.48	Arg116, Glu117, Glu226, Arg291	Glu275, Glu276

The reference compound oseltamivir had lowest docking score about -5.61 Kcal/mol than newly synthesized compounds. It was involved in four H-bond interaction with amino acid residues Arg116, Glu117, Glu226 and Arg291 of 4WA4 and two hydrophobic interactions with amino acid residues Glu275 and Glu276 of 4WA4. The docking pose and 2D interactions of Oseltamivir with neuraminidase are shown in figure 3.

The docking results reveal that the newly synthesized molecules are proven to be potent inhibitors of influenza virus. Their docking scores are ranging from -7.54 to -9.71 Kcal/mole higher than that of docking score of oseltamivir (-5.48Kcal/mol).

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