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# STUDIES IN DESIGNING OF SUBSTITUTED 4H-PYRANO [3,2-H]QUINOLINE-3-CARBONITRILE DERIVATIVES AS POTENTIAL NEURAMINIDASE INHIBITORS OF SWINE FLU IN SILICO APPROACH

**Prasanna B. Ranade[1]*, Dinesh N. Navale[1], Pramod P. Gaikwad[1] , Usama A. Anware[1] , Santosh W. Zote[2], Dnyaneshwar K. Kulal[3], Swapnil J. Wagh[4], Vaijayanti Ghase[5]**

*[1]Department of Chemistry, Vivekanand Education Society's College of Arts, Science and Commerce, (Autonomous), Chembur, Mumbai 400 071 INDIA.*
*[2]Department of Chemistry, PTVA's Sathaye College (Autonomous), Dixit Road, Vile Parle (East), Mumbai-400 057, Maharashtra, INDIA.*
*[3]Department of Chemistry, Ramnarain Ruia Autonomous College, L. N. Road, Matunga, Mumbai-400 019, Maharashtra, INDIA.*
*[4]Department of Chemistry, R.S.S. Prasarak Mandal's Nanasaheb Yashvantrao Narayanrao Chavan, Arts, Science & Commerce College Chalisgaon, Jalgaon-424101Maharashtra, INDIA.*
*[5]Department of Chemistry, S.K. Somaiya College Vidyavihar, Ghatkopar Mumbai, INDIA*
*Corresponding author: prasannabranade@gmail.com*

**Keywords:** Neuraminidase Inhibitors, Swine Flu, Blind docking, 3TI6, 4H-Pyrano[3,2-h] quinoline-3-Carbonitrile derivatives, ADME.

**Abstract**: The present work describes the docking between 4H-Pyrano [3,2-h] quinoline-3-Carbonitrile derivatives against neuraminidase of swine flu. The dock score of Oseltamivir, Zanamivir is found to be comparable with 4H-Pyrano[3,2-h] quinoline-3-Carbonitrile derivatives. The hydrogen bonding, hydrophilic interactions, Van der waals forces, were found between designed 4H-Pyrano[3,2-h] quinoline-3-Carbonitrile derivatives with Glu119, Asp 151, Arg152, Trp178, Ser179, Ile222, Arg224, Glu227, Ser246 Glu276, Glu277, Arg292, Asn294, Arg371, Tyr406. ADME properties of 4H-Pyrano[3,2-h]quinoline-3-carbonitrile derivatives are in range.

**Introduction:** Swine flu [i], also known as the H1N1 influenza virus [ii], emerged as a global health concern during the pandemic of 2009. The H1N1 influenza virus belongs to *orthomyxoviridae* [iii] family and is characterized by its unique genetic composition, resulting from a combination of avian, swine, and human influenza viruses.[iv] This strain of the influenza virus was quickly spread across international borders. The World Health Organization (WHO)declared the H1N1 pandemic a public health emergency of international concern, because of the serious fatal rate [v]. The H1N1 virus possesses the ability to infect

humans, leading to a range of respiratory symptoms from mild to severe illness. Its transmission primarily occurs through respiratory droplets expelled from infected individuals during coughing, sneezing, or close contact.[vi] Additionally, the virus can survive on surfaces for a limited period, contributingto its potential for rapid dissemination.

Swine flu virus contains envelope proteins hemagglutinin (HA), neuraminidase (NA), viral RNA polymerases, nonstructural proteins NS1 and NS2, which are crucial for efficient pathogenesis and viral replication. [vii-x] Neuraminidase cleaves terminal sialic acid residues from carbohydrate moieties on the surfaces of host cells and influenza virus envelopes; this process promotes the release of progeny viruses from infected cells.[xi-xiii]The function of neuraminidase is to help new viruses to get released from infected cells, and so, its inhibition will disrupt further infection of the host's cells.[xiv-xv]

Currently Zanamivir, Oseltamivir, Peramivir and Laninamivir were used to combat swine flu.[xvi-xviii]. Consequently, concerted efforts were made to develop vaccines [xix] and distribute them to protect vulnerable populations. Antiviral medications were also employed to treat those infected and reduce the severity of symptoms. Quinoline derivatives known for their antimalarials[xx-xxiv], antiHIV [xxv-xxvii], antidengue[xxviii-xxix], anti covid [xxx]. Pyran derivatives are knownfor different biological acitivties. [xxxi-xxxii].Combination of quinoline and 4H-pyran derivatives may have potential biological acitivites against viral diseases. Therefore, in present work we have studied docking of 4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives [xxxiii] as potential neuraminidase inhibitors.

**Experimental functions:**

**Materials and Methods**

Hardware Molecular docking studies described herein were performed on Acer ASPIRE Lite i3 Laptop (Intel® Core™ i3-processor) running Windows 11 Operating System.

**Docking studies:**

Docking[xxxiv,xxxv]between 4H-Pyrano[3,2-h] quinoline-3-Carbonitrile derivatives and neuraminidase protein were performed on CB Dock web server.[xxxvi] neuraminidase proteins were downloaded from www.rcsb.org PDB ID 3TI6 used for docking.[xxxvii]

**Ligands Preparation**

Chemdraw software used to draw different pyran derivatives and saved in *.sdf* file format. SWISS ADME Web server [xxxviii] used to calculate ADME properties.

**Results and Discussions**:

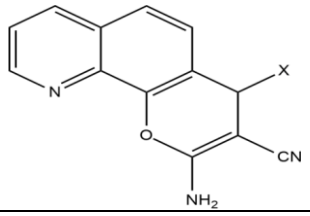
Standard drugs such as oseltamivir and zanamivir were docked against swine flu neuraminidase (PDB ID 3TI6). The dock score observed for oseltamivir and zanamivir were -6.5 and -8.2 respectively. Oseltamivir and Zanamivir found to interact with the Arg118, Glu119, Ile149, Asp151, Arg152, Trp178, Ser179, Ile222, Arg224, Glu227, Ser246, Glu276, Glu277, Arg292, Asn294, Gly348, Arg371, Tyr406.[xxxviii-xxxix]

In the current study, we did docking of Oseltamivir, Zanamivir against neuraminidase using PDB ID 3TI6. Designed 4H-Pyrano[3,2-h] quinoline-3-Carbonitrile derivatives show a comparable dock score with Zanamivir (Table 01). The addition of heterocycle in the designed 4H-Pyrano[3,2-h] Quinoline-3-Carbonitrile molecule results in decrease in docking score whereas addition of substituted phenyl ring at 4H-Pyrano[3,2-h] quinoline-3-Carbonitrile molecule results in increase of dock Score.

The designed 4H-Pyrano[3,2-h] quinoline-3-carbonitrile derivatives show hydrophilic interaction, lipophilic interaction, hydrogen bonding and van der waals forces with Arg118, Glu119, Ile149, Asp151, Arg152, Trp178, Ser179, Ile222, Arg224, Glu227, Ser246, Glu276, Glu277, Arg292, Asn294, Gly348, Arg371, and Tyr406 which are in active site of neuraminidase of swine flu [xl-xli]. This indicates designed compounds have potential neuraminidase inhibiting activity in silico. The ADME properties are in range. (Table 02).

The docking poses are available in supplementary file.

**Table 01**




| Sr No | Name of Compound | X- Group | Dock Score |
|---|---|---|---|
| 1 | Compound 1 | Phenyl | -7.8 |
| 2 | Compound 2 | 2-chloro phenyl | -8.2 |
| 3 | Compound 3 | 3-chloro phenyl | -8.1 |
| 4 | Compound 4 | 4-chloro phenyl | -8.1 |
| 5 | Compound 5 | 2-fluro phenyl | -8.0 |
| 6 | Compound 6 | 3-fluro phenyl | -8.0 |
| 7 | Compound 7 | 4-fluro phenyl | -8.0 |
| 8 | Compound 8 | 2-hydroxy phenyl | -8.0 |
| 9 | Compound 9 | 3-hydroxyphenyl | -8.3 |
| 10 | Compound 10 | 4-hydroxy phenyl | -8.2 |
| 11 | Compound 11 | 2-methoxy Phenyl | -7.2 |
| 12 | Compound 12 | 3-methoxyphenyl | -8.0 |
| 13 | Compound 13 | 4-methoxy phenyl | -8.3 |
| 14 | Compound 14 | 2-Nitro phenyl | -7.6 |
| 15 | Compound 15 | 3-nitro phenyl | -8.0 |
| 16 | Compound 16 | 4-nitro phenyl | -7.7 |
| 17 | Compound 17 | 2-trifluromethylPhenyl | -8.9 |
| 18 | Compound 18 | 3-trifluromethylphenyl | -8.4 |
| 19 | Compound 19 | 4-trifluromethyl phenyl | -8.2 |
| 20 | Compound 20 | 2-methyl phenyl | -7.6 |
| 21 | Compound 21 | 3-methylphenyl | -8.2 |
| 22 | Compound 22 | 4-methylphenyl | -8.1 |
| 23 | Compound 23 | 2-furyl | -7.6 |
| 24 | Compound 24 | 2-azolyl | -7.5 |
| 25 | Compound 25 | 2-thiopheneyl | -7.7 |
| 26 | Oseltamivir | - | -6.5 |
| 27 | Amantadine | - | -6.9 |
| 28 | Rimantadine | - | -5.9 |
| 29 | Remdesivir | - | -6.0 |
| 30 | Zanamivir | - | -8.2 |

**Table 02 : ADME Data**

| Compound | H-bond acceptors | H-bond donors | Consensus Log P | GI absorption | BBB permeant | log Kp (cm/s) | Lipinski violations |
|---|---|---|---|---|---|---|---|
| Compound 1 | 3 | 1 | 2.91 | High | Yes | -5.6 | 0 |
| Compound 2 | 3 | 1 | 3.44 | High | Yes | -5.36 | 0 |
| Compound 3 | 3 | 1 | 3.45 | High | Yes | -5.36 | 0 |
| Compound 4 | 3 | 1 | 3.45 | High | Yes | -5.36 | 0 |
| Compound 5 | 4 | 1 | 3.23 | High | Yes | -5.64 | 0 |
| Compound 6 | 4 | 1 | 3.22 | High | Yes | -5.64 | 0 |
| Compound 7 | 4 | 1 | 3.22 | High | Yes | -5.64 | 0 |
| Compound 8 | 4 | 2 | 2.52 | High | No | -5.94 | 0 |
| Compound 9 | 4 | 2 | 2.51 | High | No | -5.94 | 0 |
| Compound 10 | 4 | 2 | 2.5 | High | No | -5.94 | 0 |
| Compound 11 | 4 | 1 | 2.91 | High | No | -5.8 | 0 |
| Compound 12 | 4 | 1 | 2.91 | High | No | -5.8 | 0 |
| Compound 13 | 4 | 1 | 2.9 | High | No | -5.8 | 0 |
| Compound 14 | 5 | 1 | 2.16 | High | No | -5.99 | 0 |
| Compound 15 | 5 | 1 | 2.16 | High | No | -5.99 | 0 |
| Compound 16 | 5 | 1 | 2.15 | High | No | -5.99 | 0 |
| Compound 17 | 6 | 1 | 3.94 | High | No | -5.38 | 0 |
| Compound 18 | 6 | 1 | 3.96 | High | No | -5.38 | 0 |
| Compound 19 | 6 | 1 | 3.96 | High | No | -5.38 | 0 |
| Compound 20 | 3 | 1 | 3.24 | High | Yes | -5.42 | 0 |
| Compound 21 | 3 | 1 | 3.25 | High | Yes | -5.42 | 0 |
| Compound 22 | 3 | 1 | 3.26 | High | Yes | -5.42 | 0 |
| Compound 23 | 4 | 1 | 2.24 | High | No | -6.18 | 0 |
| Compound 24 | 3 | 2 | 2.14 | High | No | -6.36 | 0 |
| Compound 25 | 3 | 1 | 2.92 | High | No | -5.83 | 0 |
| Oseltamivir | 5 | 2 | 1.43 | High | No | -7.42 | 0 |
| Amantadine | 8 | 7 | -2.55 | Low | No | -10.59 | 2 |
| Rimantadine | 1 | 1 | 2.18 | High | Yes | -5.49 | 0 |
| Remdesivir | 1 | 1 | 2.62 | High | Yes | -5.53 | 0 |
| Zanamivir | 12 | 4 | 1.5 | Low | No | -8.62 | 2 |

**Conclusion:** The docking study of designed 4H-pyran derivatives show hydrogen bonding, hydrophilic interaction, lipophilic interaction or van der Waals forces with neuraminidase. This indicates designed pyran derivatives have potential characteristics in silico against swine flu. The ADME properties reveal the drug likeness properties for designed compounds.

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**Conflict of interest:** All authors declare no conflict of interest.

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