IJISET - International Journal of Innovative Science, Engineering & Technology, Vol. 8 Issue 4, April 2021
ISSN (Online) 2348 – 7968 | Impact Factor (2020) – 6.72
www.ijiset.com

# *In Silico* designing, QSAR analysis and receptor –ligand interaction studies of some potential IRAK4 inhibitors

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**Abstract**

Interleukin-1 receptor (IL-1R)-associated kinase-4 (IRAK-4) plays a pivotal role in alleviating chronic inflammatory and autoimmune disorders. IRAK4 [EC:2.7.11.1] involves in pathways like MAPK signaling pathway, NF-kappa B signaling pathway, Toll-like receptor signaling pathway, NOD-like receptor signaling pathway, Toll and Imd signaling pathway, Neurotrophin signaling pathway, Pathogenic Escherichia coli infection, Salmonella infection, Pertussis, Yersinia infection, Leishmaniasis, Chagas disease (American trypanosomiasis), Toxoplasmosis, Tuberculosis, Hepatitis B, Measles, Influenza A, Herpes simplex virus 1 infection, Epstein-Barr virus infection, Human immunodeficiency virus 1 infection, based on KEGG pathway. QSAR studies was shown that Ledipasvir is less soluble in water and more harder than Coumarin, [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy]-7-methoxyisoquinoline-6-carboxamide and 5-Azaquinazoline. Ledipasvir and Coumarin has shown hydrophobic in nature and [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy]-7-methoxyisoquinoline-6-carboxamide and 5-Azaquinazoline has shown hydrophilic nature. Molecules like 5-Azaquinazolines (-163.21 Kcal/mol), Ledipasvir (-111.92 Kcal/mol) and [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (-108.38 Kcal/mol) is observed more effective on IRAK4 inhibition than molecules like Coumarin (-66.48 Kcal/mol) as anti-inflammatory compounds. 5-Azaquinazolines was found better activity compared to other selected compounds after simulation at 300K. Further research is to be conducted in the understanding of the temporal features of virus -induced inflammatory response in relation to the timing of therapeutic interventions.

***Keywords:*** *IRAK-4, potential IRAK4 inhibitors, QSAR, Docking*

## 1. Introduction

Interleukin-1 receptor (IL-1R)-associated kinase-4 (IRAK-4) belongs to a mammalian IRAKs family that plays a pivotal role in alleviating chronic inflammatory diseases and autoimmune disorders [1,2,3]. IRAK4 is a threonine/serine protein kinase that contains 460 amino acids, which contains a kinase domain and a death domain, that functions downstream of a Toll receptor [4,5].

The IRAK family has key signaling component in downstream of Toll like receptor (TIR) family that includes IL-1R, IL-18R, LBP, CD14 and TLR (Toll-like receptors) genes [6]. The Inhibition of IRAK4 blocks the production of several inflammatory cytokines in the human monocytes that includes IL-1, IL-6, IL-12, type I interferon's, and tumor necrosis factor, which are the key drivers of inflammatory and autoimmune diseases in response to the immune complex activation. Modulation of IRAK-4 function due to kinase inhibition may provide an attractive and novel therapeutic approach by reducing the responses for oncogens and inflammatory diseases [7]. Nevertheless, the current targets that are available did not offer any sufficient relief in some of the patients and have a broad spectrum of some adverse events in the subjects. Hence, emphasis has been laid on highlighting development of small molecule inhibitors that are targeting the kinase activity of IRAK-4 and prediction of protein/inhibitor interactions to develop potent targets having no adverse effects.

Table 1 shows the candidate innate immunity genes.

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**Table 1: Candidate innate immunity genes**

| Group | Gene | Other names | | Group | Gene | Other names |
|---|---|---|---|---|---|---|
| IL1/IL18 related | *IL1A* | IL1-alpha | | Toll/IL1 receptor (TIR) adaptors | *MYD88* | -- |
| | *IL1B* | IL1-beta | | | *TIRAP* | MAL |
| | *IL1R1* | IL1RA, IL1R | | | *TICAM1* | TRIF |
| | *IL1R2* | IL1RB | | | *IRAK1* | IRAK |
| | *IL1RL1* | ST2 | | | *IRAK2* | -- |
| | *IL1RN* | IL1RA | | | *IRAK4* | REN64 |
| | *IL18* | IGIF | | | *TOLLIP* | -- |
| | *IL18R1* | IL18RA, IL1RRP | | | *TRAF6* | -- |
| | *IL18RAP* | IL18RB, ACPL | | NFκB related | *CHUK* | IKBKA, NFKBIKA, IKKA, IKK1 |
| | *IL18BP* | -- | | | *NFKB1* | -- |
| TLRs | *TLR1* | TIL | | | *NFKB2* | LYT10 |
| | *TLR2* | TIL4 | | | *NFKBIA* | NFKBI, IKBA |
| | *TLR3* | -- | | | *NFKBIB* | IKBB, TRIP9 |
| | *TLR4* | TOLL | | | *NFKBIE* | IKBE |
| | *TLR5* | TIL3 | | | *IKBKB* | NFKBIKB, IKKB, IKK2 |
| | *TLR6* | -- | | Others | *LBP* | -- |
| | *TLR7* | -- | | | *CD14* | -- |
| | *TLR8* | -- | | | | |
| | *TLR9* | -- | | | | |
| | *TLR10* | -- | | | | |

Viruses like SARS CoV- 2 shows response to Innate Immunity [8] via IRAK4 (Figure 1).

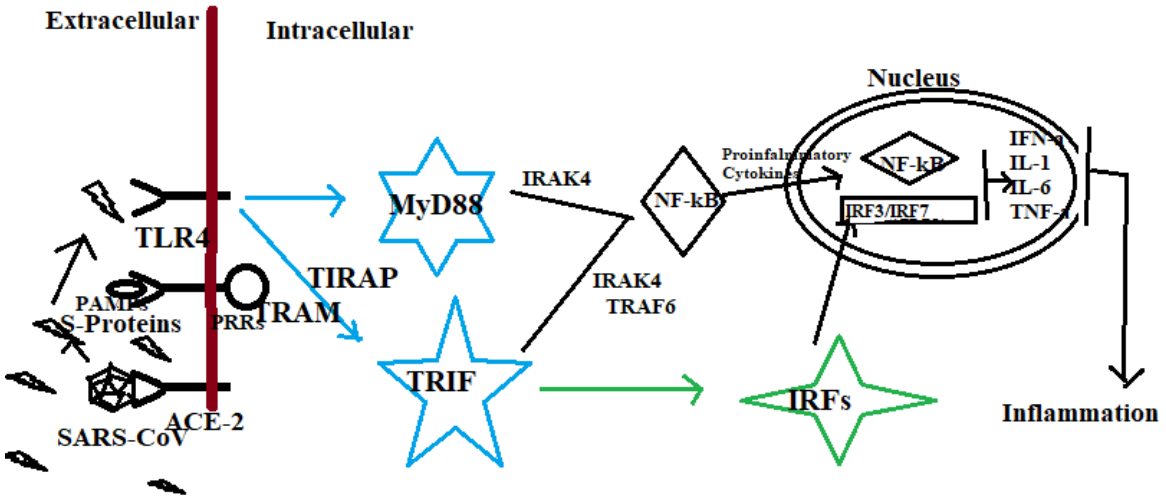


**Figure 1: SARS CoV-2 showing innate Immunity response**

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Some special/significant features of each IRAK family member:

1. There is some evidence that IRAK-1 functions in regulating the other signaling cascades leading to NF-κB gene activation. Thesignaling pathway that is particularly to nerve growth factor (NGF) may be dependent on IRAK-1 function in its signaling pathway for its cell survival and signaling activation.
2. IRAK-2 has 4 different isoforms like IRAK-2a, IRAK-2b, IRAK-2c, and IRAK-2d. IRAK-2a and IRAK-2b are positively activate the NF-κB/TLR pathway by stimulating LPS (Lipopolysaccharide). IRAK-2c and IRAK-2d have negative feedback inhibition in the TLR signaling pathways.
3. IRAK-M is unambiguous to monomyeloic cells (like macrophages and monocytes) while the other types of IRAKs are ubiquitously expressed. IRAK-M negatively regulates TLR signaling by inhibiting the IRAK-4/IRAK-1 complex.
4. IRAK-4 has been found to be critical for the recruitment of IRAK-1 and for its degradation /activation. IL-1 stimulates the IRAK-4 to the IL-1R complex that leads to initiating the Toll/IL-1 receptor signaling cascade upstream of IRAKs, hence the deletion of IRAK-1 is not abolish in the activation of NF-κB and mitogen-activated protein kinase pathways.

Microbial interactions are primarily initiates thae complex network interactions between the host and the pathogen [9, 10]. For the survival and pathogenecity, several pathogens express the signature molecules called PAMPs (Pathogen Associated Molecular Patterns). PAMPs are recognized by Toll -Pike receptors (TLRs) through lipids, lipoproteins, and nucleic acids of the bacterial, parasite, viral, and fungal origins [11]. The recognition of PAMPs by TLRs also occurs in cell membranes, lysosomes, endosomes, endocytolysosomes and other locations in cells. Different TLRs can induce different types of biological responses via subsequent activation of varied adapter proteins, such as MyD88, TIRAP, TRIP, TRIF and TRAM. MyD88 is the first identified TIR family member, which acts as an adapter protein by almost all TLRs except the TLR3. MyD88 mainly activates the transcription factor NF -kB to induc expression. TRIF is also an adapter protein of TLR3 and TLR4, which activates the transcription factors IRF3, IRF7 and NF -kB to induce the expression of type I interferon and immune - inflammatory formation of IL -1, IL-6, IFN. The receptor 6 (Extra cellular proximal IRAK family member that includes IRAK1 and IRAK4, are known to play a pivotal role in the process of inflammation mediated by IL-1/IL-18/TLR ligands [12]. Hence IRAK4 was selected as potential drug target for the present work.

## 2. Materials and Methods

Virtual screening (Figure 2) to identify the potential IRAK4 Inhibitors: Ligand and Structure based pharmacophore modeling is well known approach for hit identification process [13,14]. In our current study, ligand and structure pharmacophore model will be generated using known IRAK4 inhibitors.

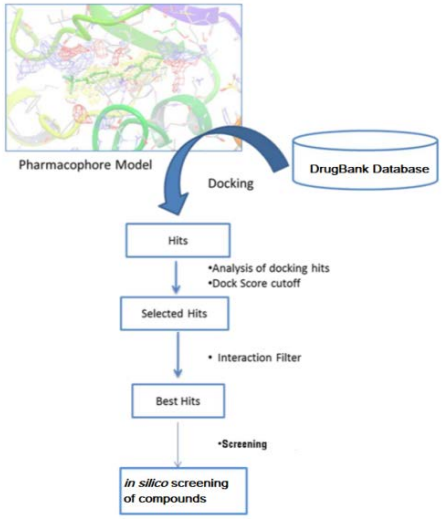


**Figure 2: Virtual screening of anti-inflammatory drugs**

A pharmacophore model showing 3D arrangement for the collection of features is necessary for the biological activity of the ligands. The features in pharmacophore are associated with location constraints, displayed as colored spheres, which allow a certain spherical tolerance surrounding the ideal position of a particular feature in 3D space. Ligand and structure based pharmacophore models were generated for known inhibitors of IRAK4 using iGEMDOCK.

**System Properties**
Intel ® Celeron ® CPU N3350 1.10Ghz processor with 4Gb RAM and 64 bit operating system of x64-based processor.

**KEGG**
KEGG (Kyoto Encyclopedia of Genes and Genomes) provides the mechanism for the understanding of activity of IRAK4

**String v11.0b**
String v11.0b database provides the protein-Protein Interactions (PPI) studies for the proteins based on the KEGG database and aggregated other (primary) databases. The functionary mechanism will be understood based on the string database and the protein 3D molecule is retrieved for *in silico* interaction with anti-inflammatory compounds.

**Hyperchem v8.0.5**
HyperChem v8.0.5 software used to study QSAR properties of the selected anti-inflammatory compounds

**iGEMDOCK v2.1**
iGEMDOCK v2.1 docking software is used to dock compounds to the active site of protein. Typically, this selected set of anti-inflammatory compounds is screened using the virtual screening (VS) mode of iGEMDOCK. Usually, structure-based virtual screening uses a high-resolution co-crystallized protein structure to define the binding site for docking. The selected ligands are docked with the IRAK4 receptor.

## 3. Results and Discussion

Members of interleukin-1 receptor (IL-1R) and the Toll-like receptor (TLR) superfamily share an intracytoplasmic Toll-IL-1 receptor (TLR) domain that mediates recruitment of the interleukin-1 receptor-associated kinase (IRAK) complex via TIR (Toll/IL-1 receptor) -containing adapter molecules. The TIR-IRAK signaling pathway emerges to be a crucial for protective immunity against specific bacteria or viruses but is redundant against most other microorganisms. IRAK4 is considered as the “master IRAK” in the mammalian IRAK family that is mostly crucial to its functioning. One of these pathways is stimulated, the cell is triggered to release proinflammatory signals and trigger innate immune actions via microbial infections. The loss of IRAK4, or its intrinsic kinase activity, can entirely stop signaling through these pathways [16]. The mechanism involved in IRAK-4 based on KEGG is shown in Figure 3.

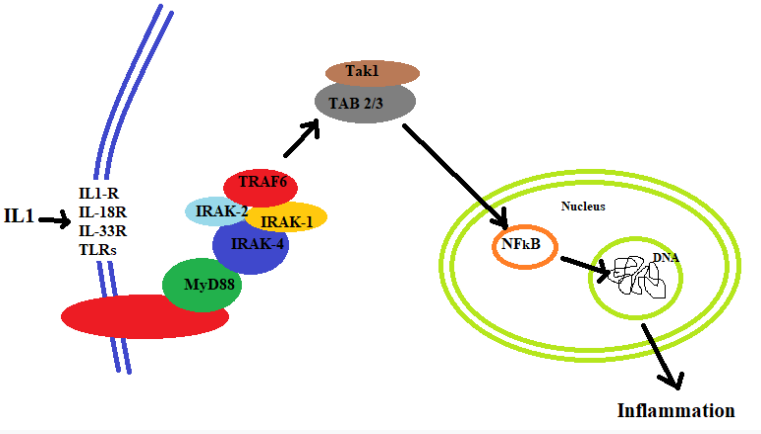


**Figure 3: Signaling pathway through IRAK4 and the myddosome complex**

IRAK-4 [EC:2.7.11.1] involves in pathways like MAPK signaling pathway, NF-kappa B signaling pathway, Toll-like receptor signaling pathway, NOD-like receptor signaling pathway, Toll and Imd signaling pathway, Neurotrophin signaling pathway, Pathogenic Escherichia coli infection, Salmonella infection, Pertussis, Yersinia infection, Leishmaniasis, Chagas disease (American trypanosomiasis), Toxoplasmosis, Tuberculosis, Hepatitis B, Measles, Influenza A, Herpes simplex virus 1 infection, Epstein-Barr virus infection, Human immunodeficiency virus 1 infection based on KEGG pathway. Figure 4 shows mechanism involved in IRAK-4 based on KEGG.

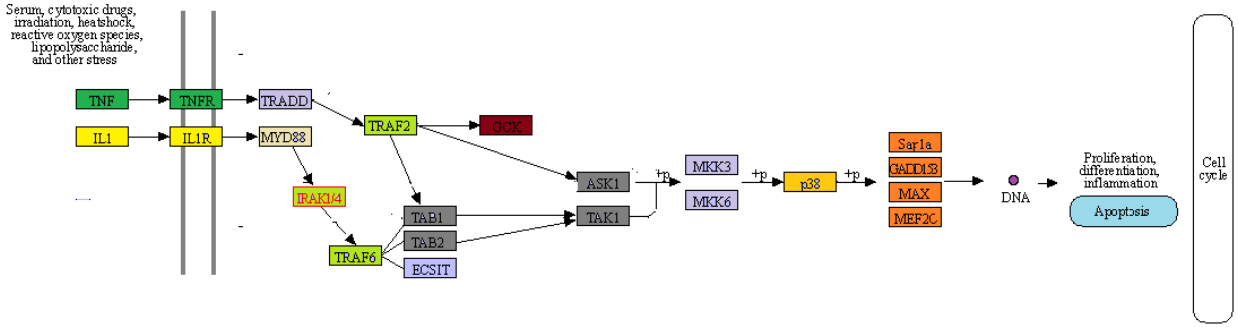


**Figure 4: IRAK4 signalling Pathway**

The protein- protein interaction for IRAK4 in homo sapiens result was shown in Figure 5. The IRAK4 has interactions with IRAK1. IRAK2, IRAK3, IRF7, TLR4, TRAF6,IL1R1, MyD88, TIRAP and IKBKG proteins

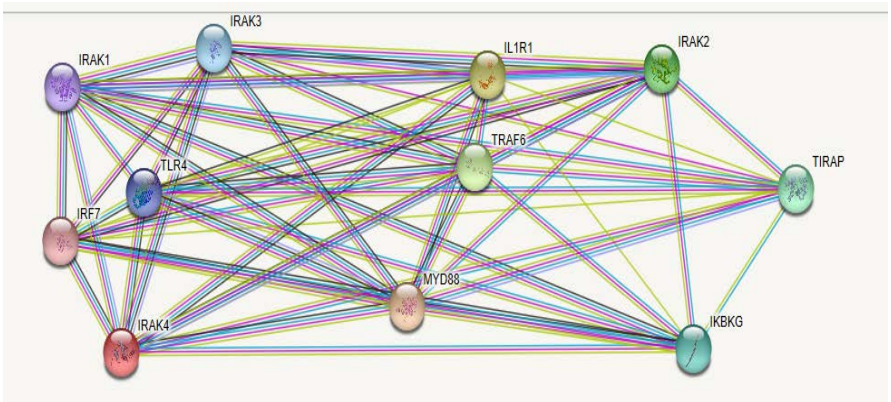


**Figure 5: Protein- Protein interaction for IRAK4 in homo sapiens**

Human IRAK4 maps to 12q12 chromosome that contains 12 exons. The 3D structure of IRAK4 from sequence of string and result of swissmodel swissmodel was shown in Figure 6.

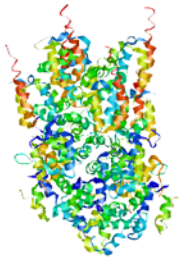

**Figure 6: PDB id : 3MOP for IRAK4 from string database**

**Amino acid sequence: 460 aa**

MNKPITPSTYVRCLNVGLIRKLSDFIDPQEGWKKLAVAIKKPSGDDRYNQFHIRRFEALL
QTGKSPTSELLFDWGTTNCTVGDLVDLLIQNEFFAPASLLLPDAVPKTANTLPSKEAITV
QQKQMPFCDKDRTLMTPVQNLEQSYMPPDSSSPENKSLEVSDTRFHSFSFYELKNVTNNF
DERPISVGGNKMGEGGFGVVYKGYVNNTTVAVKKLAAMVDITTEELKQQFDQEIKVMAKC
QHENLVELLGFSSDGDDLCLVYVYMPNGSLLDRLSCLDGTPPLSWHMRCKIAQGAANGIN
FLHENHHIHRDIKSANILLDEAFTAKISDFGLARASEKFAQTVMTSRIVGTTAYMAPEAL
RGEITPKSDIYSFGVVLLEIITGLPAVDEHREPQLLLDIKEEIEDEEKTIEDYIDKKMND
ADSTSVEAMYSVASQCLHEKKNKRPDIKKVQQLLQEMTAS

Previous studies for selective inhibitors/ anti-inflammatory drugs with models were provided in figure 7.

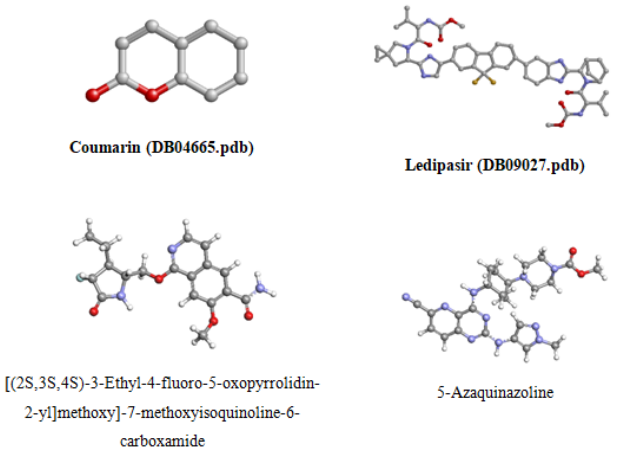


**Figure 7: Ligands selected (Before Simulation)**

Selective inhibitors/ anti-inflammatory drugs with models after simulation were provided in figure 8.

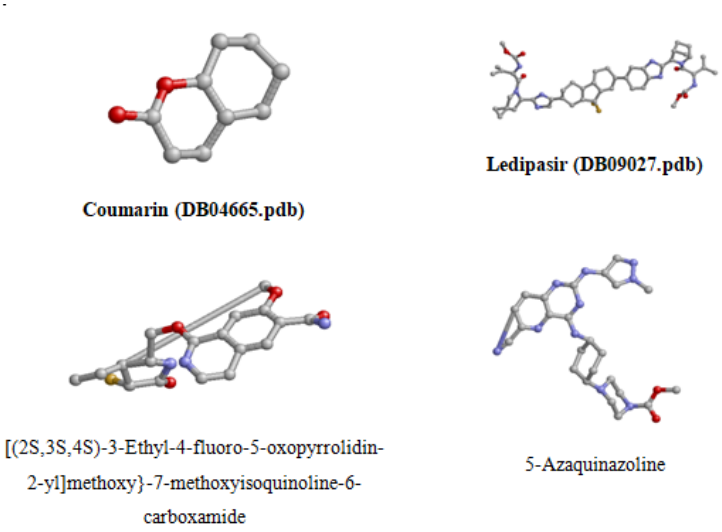


**Figure 8: Selective inhibitors/ anti-inflammatory drugs with models after simulation**

Ledipasvir ( Synonym: methyl [(2S)-1-{(6S)-6-[4-(9,9-difluoro-7-{2-[(1R,3S,4S)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-azabicyclo[2.2.1]hept-3-yl]-1H-benzimidazol-5-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate) is a direct acting antiviral (DAA) medication used as part of combination therapy to treat chronic Hepatitis C, an infectious liver disease caused by infection with Hepatitis C Virus (HCV). Coumarins are found at high levels in some essential oils, particularly cinnamon bark oil (7,000 ppm), cassia leaf oil (up to 87,300 ppm) and lavender oil. Coumarin is also present in fruits (e.g. bilberry, cloudberry), green tea and other foods such as chicory.

The QSAR studies were conducted on Ledipasir, Coumarin [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide and 5-Azaquinazoline.

**Table 2: QSAR Properties of Ledipasvir and Coumarin**

| **Property** | **Ledipasvir** | **Coumarin** | [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide | 5-Azaquinazoline |
|---|---|---|---|---|
| Partial Charge | 0 | 0 | 0 | 0 |
| Surface Area (Apprx) A2 | 926.54 | 409.52 | 509.84 | 614.11 |
| Surface Area (Grid) A2 | 1111.10 | 304.66 | 596.25 | 730.27 |
| Volume A3 | 2063.78 | 461.39 | 1000.38 | 1305.54 |
| Hydration energy kcal/mol | -12.63 | -5.17 | -9.69 | -10.64 |
| LogP | 10.43 | 2.66 | -1.58 | -0.37 |
| Refractivity A3 | 96.24 | 29.25 | 94.28 | 138.03 |
| Polarizability A3 | 68.63 | 12.93 | 35.71 | 51.60 |
| Mass amu | 834.59 | 140.10 | 361.37 | 490.57 |

The analysis of QSAR properties (Gasteiger charges, surface area, volume, hydration energy, log p refractivity, sum of bond polarizabilities, mass) provided better understanding of the molecules. If Log P increases, solubility in water decreases so absorption decreases. Ledipasvir is less soluble in water than Coumarin, [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide and 5-Azaquinazoline. According to 'Lipinski's Rule of 5', the logP of a compound intended for oral administration should be <5. LogP is negative it means that the molecule is hydrophilic. Hence [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide and 5-Azaquinazoline has shown hydrophilic nature (Table 2).

Antiviral molecule like Ledipasvir (-111.92 Kcal/mol) is observed more effective than natural molecule like Coumarin (-66.48 Kcal/mol) as anti-inflammatory compounds. Ledipasvir, Coumarin, [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide and 5-Azaquinazoline are selected for activity on IRAK4 protein. 5-Azaquinazoline has shown better activity followed by Ledipasvir, [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-

yl]methoxy}-7-methoxyisoquinoline-6-carboxamide and Coumarin . Further analysis with large scale or Highthroughput methods provide better molecules in control of diseases like SARS-CoV-2, cancer, etc that acts as anti-inflammatory molecules. The results obtained that Ledipasvir is interacting at the lowest energy level with all the amino acids in the potential active site (Table 3,4 and Figure 9).

The drug molecules are computed with molecular dynamics at 300k simulation temperature at 1time steps. The molecules are docked with IRAK4.

**Table 3: Docking studies with IRAK4**

| **Ligand** | **Energy value (in Kcal/Mole)** | **Energy value (in Kcal/Mole) (Molecular dynamics at 300K (26.85°C) simulation temperature at 1time steps)** |
|---|---|---|
| Ledipasvir | -119.92 | -113.38 |
| Coumarin | -66.48 | -68.4 |
| [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide | -108.38 | -95.8 |
| 5-Azaquinazolines | -163.21 | -118.61 |

**Table 4: Docking studies with IRAK4**

| **Ligand (without simulation)** | **Active site** |
|---|---|
| Ledipasvir | H-M-ASP-55-H-S-GLU-60-H-S-ARG-81-H-M-GLY-3-V-M-ASP-55-V-S-ASP-55-V-M-PHE-56-V-S-ARG-81-V-M-GLY-3-V-S-ASN-15 |
| Coumarin | H-M-TYR-58-H-M-CYS-13-H-M-LEU-14-V-M-PHE-56-V-M-GLU-57-V-S-ASN-15 |
| [(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide | H-S-ARG-28-H-S-GLU-52-H-M-PHE-56-H-S-GLU-57-H-S-ASN-26-V-M-ASP-55-V-M-PHE-56-V-M-GLU-57-V-S-GLU-57-V-S-ASN-26-V-M-LYS-115-V-S-LYS-115-V-M-ALA-119-V-M-ALA-120 |
| 5-Azaquinazolines | H-S-SER-23-H-S-ASP-24-H-S-ASP-27-H-S-SER-65-H-M-ARG-54-V-S-ARG-40-V-S-GLN-42-V-S-ARG-20-V-M-ASP-24-V-S-ASP-24-V-S-ASP-27-V-S-PRO-28-V-M-GLY-63-V-M-LYS-64-V-M-SER-65-V-S-ARG-54-V-M-ARG-55-V-S-ARG-55-V-M-ALA-58-V-S-LEU-59 |

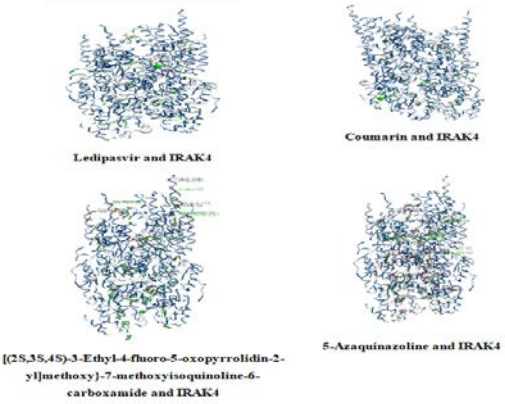


**Figure 9: Docked molecules**

The IRAK4 activation in presence of TIR receptor shows inflammation. In the presence of IRAK4 inhibitors like 5-Azaquinazoline stops the inflammatory responses (Figure 10).

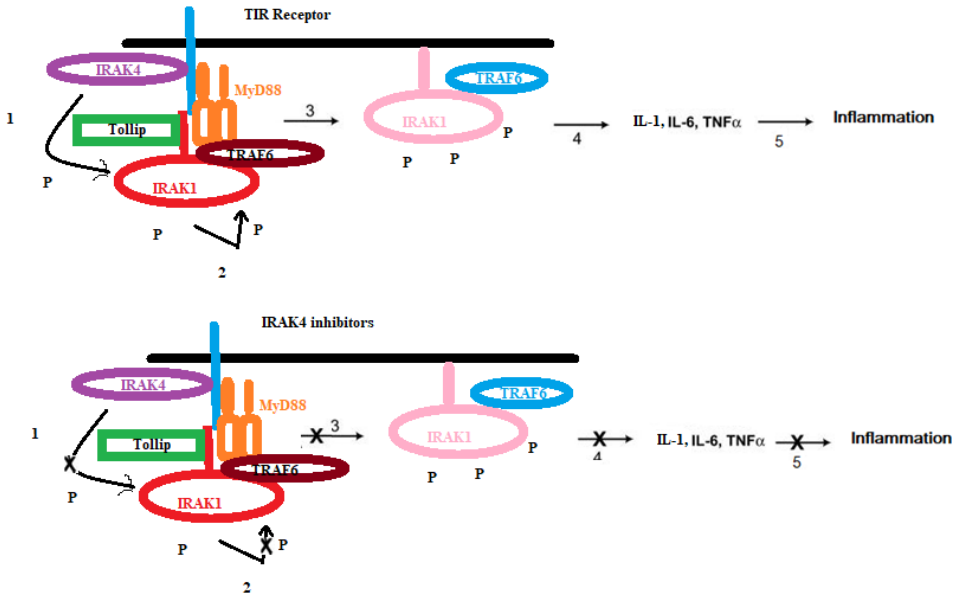


**Figure 10: A model of IRAK1c/ IRAK4 regulation of inflammation**

## 4. Conclusions

There is a need to identify diseased molecules within the human immune system. IRAK4 gene is a member of IL-1R–associated kinase (IRAK) family and has been shown to play an essential role in Toll-like receptor (TLR)–mediated signaling. Animals without IRAK-4 are more susceptible to viruses, bacteria and other diseases. IRAK4 act as sensors of microbial and endogenous danger signals. Antiviral molecule like Ledipasvir (-111.92 Kcal/mol) is observed more effective than natural molecule like Coumarin (-66.48 Kcal/mol) as anti-inflammatory compounds. Further research is to be conducted for the understanding of the temporal features of virus-induced inflammatory response in relation to the therapeutic interventions.

### Acknowledgments

The author likes to thank administration of Atal Bihari Vajpayee University for support and DST-SERB (ECR/2016/001292) for Early career research project for providing financial assistance.

## References

[1] Chaudhary, Divya, Shaughnessy Robinson, and Donna L. Romero. "Recent advances in the discovery of small molecule inhibitors of interleukin-1 receptor-associated kinase 4 (IRAK4) as a therapeutic target for inflammation and oncology disorders: Miniperspective." Journal of medicinal chemistry, Vol. 58, No. 1, 2015,pp. 96-110.
[2] De Nardo, Dominic, Katherine R. Balka, Yamel Cardona Gloria, Vikram R. Rao, Eicke Latz, and Seth L. Masters. "Interleukin-1 receptor–associated kinase 4 (IRAK4) plays a dual role in myddosome formation and Toll-like receptor signaling." Journal of Biological Chemistry, Vol. 293, No. 39, 2018, pp. 15195-15207.
[3] Kaladhar DSVGK. " in silico studies for understanding of IRAK-4 inhibitors as anti-inflammatory and anti-viral agents." Dogo Rangsang Research Journal, Vol. 10, No.8,, 2020, pp. 163-168.

[4] Roy, Anjali, Mansi Srivastava, Uzma Saqib, Dongfang Liu, Syed M. Faisal, Subi Sugathan, Suman Bishnoi, and Mirza S. Baig. "Potential therapeutic targets for inflammation in toll-like receptor 4 (TLR4)-mediated signaling pathways." International Immunopharmacology, Vol. 40, 2016, pp. 79-89.
[5] Gosu, Vijayakumar, Shaherin Basith, Prasannavenkatesh Durai, and Sangdun Choi. "Molecular evolution and structural features of IRAK family members." PLoS One, Vol. 7, No. 11, 2012, pp. e49771.
[6] Meijer, Annemarie H., SF Gabby Krens, Indira A. Medina Rodriguez, Shuning He, Wilbert Bitter, B. Ewa Snaar-Jagalska, and Herman P. Spaink. "Expression analysis of the Toll-like receptor and TIR domain adaptor families of zebrafish." Molecular immunology, Vol. 40, No. 11, 2004, pp. 773-783.
[7] Tartey, Sarang, and Osamu Takeuchi. "Pathogen recognition and Toll-like receptor targeted therapeutics in innate immune cells." International Reviews of Immunology, Vol. 36, No. 2, 2017, pp. 57-73.
[8] Fanny Onodi, Lucie Bonnet-Madin, Laurent Meertens, Léa Karpf, Justine Poirot, Shen-Ying Zhang, Capucine Picard, Anne Puel, Emmanuelle Jouanguy, Qian Zhang, Jérôme Le Goff, Jean-Michel Molina, Constance Delaugerre, Jean-Laurent Casanova, Ali Amara and Vassili Soumelis, “SARS-CoV-2 induces human plasmacytoid predendritic cell diversification via UNC93B and IRAK4.” *J Exp Med* , Vol. 218, No. 4, 2021, pp. e20201387
[9] Von Bodman, Susanne B., W. Dietz Bauer, and David L. Coplin. "Quorum sensing in plant-pathogenic bacteria." Annual review of phytopathology, Vol. 41, No. 1, 2003, pp. 455-482.
[10] Boutin, Sébastien, Louis Bernatchez, Céline Audet, and Nicolas Derôme. "Network analysis highlights complex interactions between pathogen, host and commensal microbiota." PloS one, Vol. 8, No. 12, 2013, pp. e84772.
[11] Li, Geng, Yaohua Fan, Yanni Lai, Tiantian Han, Zonghui Li, Peiwen Zhou, Pan Pan Wang, W., Hu, D., Liu, X. and Zhang, Q. "Coronavirus infections and immune responses." Journal of medical virology, Vol. 92, No. 4, 2020, pp. 424-432.
[12] Rao, Navin, Steven Nguyen, Karen Ngo, and Wai-Ping Fung-Leung. "A novel splice variant of interleukin-1 receptor (IL-1R)-associated kinase 1 plays a negative regulatory role in Toll/IL-1R-induced inflammatory signaling." Molecular and cellular biology, Vol. 25, No. 15, 2005, pp. 6521-6532.
[13] Che, Jinxin, Ruiwei Feng, Jian Gao, Hongyun Yu, Qinjie Weng, Qiaojun He, Xiaowu Dong, Jian Wu, and Bo Yang. "Evaluation of Artificial Intelligence in Participating Structure-Based Virtual Screening for Identifying Novel Interleukin-1 Receptor Associated Kinase-1 Inhibitors." Frontiers in oncology, Vol. 10, 2020, pp. 1769.
[14] Zhong, Liangliang, Lu Zhou, Yahui Tian, and Rong You. "Identification of novel IRAK-4 inhibitors through pharmacophore modeling, atom-based 3D-QSAR, docking strategies and molecular dynamics simulation." Letters in Drug Design & Discovery, Vol. 13, No. 9, 2016, pp. 879-887.
[15] Picard, C., Puel, A., Bonnet, M., Ku, C.L., Bustamante, J., Yang, K., Soudais, C., Dupuis, S., Feinberg, J., Fieschi, C. and Elbim, C.” Pyogenic bacterial infections in humans with IRAK-4 deficiency.” Science, Vol. 299, No.5615, 2003, pp.2076-2079.
[16] Karin, Michael, Toby Lawrence, and Victor Nizet. "Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer." Cell. Vol. 124, No. 4, 2006, pp. 823-835.

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