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Full Length Original Research Paper

# *In-Silico* search of Tailored Cox-2 Inhibitors: Screening of Quinazolinone derivatives via molecular modeling Tools

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## Abstract:

Novel Quinazoline derivatives were designed through *in silico* studies including Molecular properties prediction, Toxicity risk prediction and by Molecular Docking approaches. The hypothetically designed molecules were studied for Lipinski rule of 5 properties. The successful molecules were subjected to toxicity risk prediction by Osiris property calculator.The docking methodology applied in the study was first validated by redocking the celecoxib in cox-2 domain with the co-crystallized one. Cox-2 protein was explored for the residues imperative for activity by analyzing the binding pattern of celecoxib and selected compounds of quinazolinone derivatives in the active domain. All the selected molecules passed Lipinski rule of five successfully and they were safe. The docking results explored that compound IQ1, IQ2, IQ5, IQ8 and IQ12 have binding affinity -9.3, which indicated that these compounds may prove successful anti-inflammatory oral candidates.

**Keywords**: Cox-2, Quinazolinone, Molecular docking, Pymolautodock/vina plugin, Molecular properties



## Introduction

Inflammation is the response of the tissue against endogenous or exogenous stimuli such as infection, irritation or foreign substance intrusion. It is a part of the host defense mechanisms that is known to be involved in the inflammatory reactions associated with the release of histamine, bradykinin& prostaglandins. Cornelius Celsus of Rome reported 2000 years ago that inflammation is characterized by rubor (redness) or calor (heat) and /or dolar (pain) at the affected region because of a complex biological response of vascular tissues to harmful stimuli including pathogens, irritants or damaged cells[1,2].

Cyclooxygenases (COX) or prostaglandin endoperoxide synthases (PGHS) are the key enzymes in the synthesis of prostaglandins, the main mediators of inflammation, pain and increased body temperature (hyperpyrexia). The body produces two main isoforms COX proteins i.e., cyclooxygenases –1 (COX-1) and cyclooxygenases-2 (COX-2). The COX-1 is responsible for formation of important biological mediators such as prostanoids, including prostaglandins, prostacyclin and thromboxane and involved in pain causing, blood clotting and protecting the stomach [3] whereas COX-2 involved in the pain by inflammation and plays a major role in prostaglandin biosynthesis in inflammatory cells and central nervous system[4]. When COX-1 is inhibited, inflammation is reduced,

but the protection of the lining of the stomach is also lost. This can cause stomach upset as well as ulceration and bleeding from the stomach and even the intestines. Whereas, COX-2 is usually specific to inflamed tissue, there is much less gastric irritation associated with COX-2 inhibition together with the decreased risk of peptic ulceration [5]. Therefore, selective COX-2 inhibitors such as celecoxib and rofecoxib had been developed for ease of inflammation associated with COX[6]. The use of coxib drugs such as rofecoxib and valdecoxib were withdrawn from the market in 2004 and 2005, respectively, because of increased risk of heart attacks and strokes with long term use[7]. On the other hand, some studies have suggested that rofecoxib's adverse cardiac events may not be a class effect but rather an intrinsic chemical property related to its metabolism [8]. At present, Celecoxib is the only COX-2 inhibitor available in the United States. Hence, there is a need for COX-2 inhibitor with no adverse effects.

Anti-inflammatory function associated with COX-2 can be anticipated based on docking analysis. This approach is adopted as evaluation of biological function of any compound especially associated with human trials which is a long term process and always risky. In this context, molecular docking continues to hold great promise in the field of computer based drug design, which screens small molecules by orienting and scoring them in the binding site of a protein as a result, novel ligands for receptors of known structure were designed and their interaction energies were calculated using the scoring functions.

The quinazolinone moiety is an important pharmacophore showing many types of pharmacological activities [9]. The quinazolinones are considered to be a "privileged structure" for drug development [10]. In view of the above, the present investigation merits in understanding the imperative role of Quinazoline derivatives for anti-inflammatory properties against COX-2 protein based on fitness score, type of binding pattern, energy values etc. Before carrying out the docking studies, attempts were made to rationalize the selection of molecules to be docked by screening the series of molecules by "*Lipinski's Rule of Five*", so that successful oral candidates could be discovered out.

## MATERIAL AND METHODS

### Molecular Properties Calculations and Molecular Docking

Molecular properties, mainly hydrophobicity, molecular size, flexibility and the presence of various pharmacophoric features influence the Pharmacokinetic and pharmacodynamics behaviour of molecules in the living organism, including bioavailability. Thus in order to achieve good bioavailable drugs, we have subjected a series of quinazolinone derivatives **(IQ1-IQ14)** for the prediction of some basic pharmacokinetic properties under the Lipinski's ``Rule of Five''.

#### *Lipophilicity*

All the compounds were subjected to computational study in order to filter the drugs for biological screening. For good membrane permeability logP value should be ≤5 [11]. All the title compounds **(IQ1-IQ14)** were found to have logP values in the range of 1.62–3.15.

#### *Absorption, Polar surface area, and ''rule of five'' properties*

High oral bioavailability is an important factor for the development of bioactive molecules as therapeutic agents. Good intestinal absorption, reduced molecular flexibility (measured by the



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number of rotatable bonds), low polar surface area or total hydrogen bond count (sum of donors and acceptors), are important predictors of good oral bioavailability[12].Molecular properties such asmembrane permeability and bioavailability is always associated with some basic molecular descriptors such as logP (partition coefficient), molecular weight (MW), or hydrogen bond acceptors and donors counts in a molecule[13]. Lipinski[14] used these molecular properties in formulating his ``Rule of Five". The rule states that most molecules with good membrane permeability have logP ≤ 5, molecular weight ≤500, number of hydrogen bond acceptors ≤10, and number of hydrogen bond donors ≤ 5. This rule is widely used as a filter for drug-like properties. Table 1 contains calculated percentage of absorption (%ABS), molecular polar surface area (TPSA) and Lipinski parameters of the investigated compounds of the series (IQ1-IQ14). Magnitude of absorption is expressed by the percentage of absorption. Absorption percent was calculated[15] using the expression: %ABS =109 - 0.345 PSA. Polar surface area (PSA) was determined by the fragment-based method of Ertl and coworkers [16-17]. A poor permeation or absorption is more likely when there are more than 5 H bond donors, 10 H-bond acceptors. Hydrogen-bonding capacity has been also identified as an important parameter for describing drug permeability[18]. The series (IQ1-IQ14) under investigation had all compounds having hydrogen bond donor and acceptors in considerable range as shown in Table 1.

Number of rotatable bond is important for conformational changes of molecules under study and ultimately for the binding of receptors or channels. It is revealed that for passing oral bioavailability criteria number of rotatable bond should be ≤10. The compounds in this series (IQ1-IQ14)possess lower range of `number of rotatable bonds' i.e. (3-5) and therefore, exhibit low conformational flexibility.

Molecular polar surface area (TPSA) is a very useful parameter for the prediction of drug transport properties. TPSA is a sum of surfaces of polar atoms (usually oxygen, nitrogen and attached hydrogen) in a molecule. TPSA and volume is inversely proportional to % ABS. All the compounds under study have exhibited good %ABS except D6 having 26% Abs, But all the title compounds (IQ1-IQ14) followed the Lipinski ``Rule of Five''. The pharmacokinetic parameters were calculated online from Molinspiration Chemoinformatics (http://www.molinspiration.com/cgibin/properties ) and are given in Table 1.

### *Osiris Calculations*

Structure based drug design is now very routine work as many drug fail to reach clinical phases because of ADME/TOX problem encountered. Therefore prediction of these problems before synthesis is rational approach to minimize cost production of expensive chemicals. The Osiris calculations are tabulated in Table 2. Toxicity risks (mutagenicity, tumorogenicity, irritation, reproduction) and physicochemical properties (cLogP, solubility, drug likeness and drug score) of compounds (IQ1-IQ14)were calculated by the methodology developed by Osiris[19]. The toxicity risk predictor locates fragments within a molecule, which indicate a potential toxicity risk. Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the risk category specified. The logP value of a compound, which is the logarithm of its partition coefficient between n-octanol and water, is a well-established measurement of the compound's hydrophilicity.

Low hydrophilicities and therefore high logP values may cause poor absorption or permeation. It has been shown that for compounds to have a reasonable probability of good absorption, their logP value must not be greater than 5.0. On this basis, all the compounds IQ1-IQ10 possessed logP values in the acceptable range.

***Aqueous solubility***

The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. In general a low solubility goes along with a poor absorption and therefore the general aim is to avoid poorly soluble compounds. Our estimated logS value is a unit stripped logarithm (base 10) of a compound's solubility measured in mol/liter. There are more than 80% of the drugs on the market have a (estimated) logS value greater than -4. In present series the values of logS are around -5. Further, Table-2 shows drug likeness of compounds (IQ1-IQ14) which is in the acceptable zone to be drug like when compared with standard drug. We have calculated overall drug score (DS) for the compounds IQ1-IQ14 and compared with that of standard drug ciprofloxacin. The drug score combines drug likeness, cLogP, logS, molecular weight and toxicity risks in one handy value than may be used to judge the Compound's overall potential to qualify for a drug. This value is calculated by multiplying contributions of the individual properties with the equation (1):

$DS = \prod (1/2+1/2Si) \prod ti$

Where S; $(1/1+e^{ap+b})$

DS is the drug score, Si is the contributions calculated directly from miLogP; logS, molecular weight and drug likeness (pi) via the second equation, which describes a spline curve. Parameters a andb are (1,-5), (1, 5), (0.012, -6) and (1, 0) for cLogP, logS, molecular weight and drug likeness, respectively. The ti is the contributions taken from the four toxicity risk types and the values are 1.0, 0.8 and 0.6 for no risk, medium risk and high risk, respectively. The reported compounds IQ1-IQ14showed moderate to good drug score as compared with standard drug used.

***Molecular docking studies of the compounds using Pymol/Autodockvina Plugin:***

The compounds in the study were subjected to dock in the active domain of COX-2 protein by using Pymol/Autodockvina Pluginsoftware**.** Crystal structures of COX-2 protein in complex with celecoxib (PDB ID: 3LN1) with resolution 2.4 Å was downloaded from RCSB Protein Data Bank to serve as the docking template[20]. The crystallographic water and ligand molecules were removed from the protein complex.

PymolAutoDockvina plugin developed by Seeliger [21] was used on Linux ubuntu 12.0 installed on Pentium i3workstation. ChemDraw ultra 8.0 software (Chemical Structure Drawing Standard; Cambridge Soft corporation, USA (2003)) was used for construction of compounds which were converted to 3D structures using Chem3D ultra 8.0 software and the constructed 3D structures were energetically minimized by using MOPAC (semi-empirical quantum mechanics) with AM1 mozyme geometry, 100 iterations and minimum RMS gradient of 0.10.

They were ranked according to their docking score as shown in Table-3. The redocked pose of the ligand celecoxib with the co-crystallized structure of the same has been shown in Fig-1. The docked structure of all the compounds has been shown in Fig-2.

## Results and Discussion:

Low hydrophilicities and therefore high logP values may cause poor absorption or permeation. It has been shown that for compounds to have a reasonable probability of good absorption, their logP value must not be greater than 5.0. On this basis, most of our compounds possess acceptable logP values and can be considered as drugs. All the title compounds (IQ1-IQ14) were found to have logP values in the range of 3.33 to 3.94 except compound IQ 2 and IQ 14 having 5.36 and 6.33 respectively.

According to Veber's rule number of rotatable bonds is important for conformational changes of molecules under study and ultimately for the binding of receptors or channels. It is revealed that for passing oral bioavailability criteria, number of rotatable bond should be <10.The compounds in this series (IQ1-IQ14) possess lower range of 'number of rotatable bonds' i.e. (3-5) and therefore, exhibit low conformational flexibility.

Molecular polar surface area (PSA) is a very useful parameter for the prediction of drug transport properties. PSA is a sum of surfaces of polar atoms (usually oxygen, nitrogen and attached hydrogen) in a molecule. PSA and volume is inversely proportional to %ABS (Remko 2009).All the title compounds (IQ1-IQ14) were found to have PSA values in the range of 2 to 5. PSA and volume is inversely proportional to % ABS. All the compounds under study have exhibited good %absorption ranging from 88 % to 99 %. All the designation compounds (IQ1-IQ14) passed the Lipinski ``Rule of Five''.

Number of hydrogen bond acceptor and donors were calculated for all the molecules in the series. The number of hydrogen bond acceptorsand donors were in the range of 3-6 and 0-1 respectively, thus none of the compound violated the Lipinski's rule in this regard.

Further the molecular weights of the compounds taken for the screening were less than 500, thereby passing the Lipinski's rule.

The molecules to be synthesized were subjected for prediction of drug score and drug likeness along with the prediction of toxicity risk evaluation. For toxicity risk assessment, Tumorogenicity, Mutagenicity, Irritation and reproductive effect were taken into consideration.From the data evaluated from Osiris calculations it is obvious that among the series IQ1-14, only the group with N,N-dimethyl derivative (IQ 8) has shown mild mutagenic toxicity risk or else all the compounds in the series were safe and do possess acceptable drug likeness and drug score. The compounds IQ1-IQ14 showed moderate to good drug score as compared with standard drug used.

While screening for Cox-2; docking method was validated by redocking the celecoxib with the cox-2 protein and the interactions obtained were considered as the standard, to compare with the docking of the other compounds. Redocked structure of celecoxib in 3LN1 receptor, as shown in Fig.1 revealed that the original cocrystallized and docked celecoxib are overlapping to each other, thereby validating to our docking methodology. The results of cox-2 docking have been summarized in Table-3. Interestingly compounds IQ1, IQ2, IQ5, IQ8 and IQ12 has shown binding affinity -9.3, the maximum in the series. Compound IQ7 was found to have binding affinity -8.1, the minimum in the series.

Thus by and large, it can be concluded that the designed molecules pass the Lipinski's rule of 5

and veber's rule. Thereby they are expected to be good oral candidates with low toxicity profile. Further these designed compounds are also having good affinity with active domain of COX-2 protein, which forecast the good expected Anti-inflammatory activity of these compounds. Finally in large this is worthwhile to go for the wet lab synthesis of these rationally designed compounds.

**Table 1:** Pharmacokinetic Properties important for good oral bioavailability for the compounds of IQ series.

| Compds | %ABS | Vol (A3) | TPSA (A2) | NROTB | HBA | HBD | Log*P* | M W | Lipinski's Violations |
|---|---|---|---|---|---|---|---|---|---|
| **Rule** | - | - | - | - | <10 | <5 | ≤5 | <500 | ≤1 |
| **IQ1** | 97.0182 | 304.64 | 34.73 | 2 | 3 | 0 | 3.85 | 389 | 0 |
| **IQ2** | 97.0182 | 336.57 | 34.73 | 2 | 3 | 0 | 5.36 | 456.92 | 1 |
| **IQ3** | 88.6485 | 399.92 | 58.99 | 5 | 6 | 0 | 3.48 | 479.03 | 0 |
| **IQ4** | 94.272 | 336.24 | 42.69 | 3 | 4 | 0 | 3.91 | 419.01 | 0 |
| **IQ5** | 91.0635 | 315.18 | 51.99 | 2 | 4 | 1 | 3.339 | 405 | 0 |
| **IQ6** | 88.266 | 348.08 | 60.1 | 3 | 5 | 1 | 3.34 | 435.01 | 0 |
| **IQ7** | 88.6312 | 400.39 | 59.04 | 5 | 6 | 0 | 3.87 | 479.03 | 0 |
| **IQ8** | 96.2661 | 354.19 | 36.91 | 3 | 3 | 0 | 3.98 | 432.04 | 0 |
| **IQ9** | 88.7175 | 399.76 | 58.79 | 5 | 6 | 0 | 3.73 | 479.03 | 0 |
| **IQ10** | 91.0704 | 316.25 | 51.97 | 2 | 4 | 1 | 3.59 | 405 | 0 |
| **IQ11** | 97.0182 | 325.58 | 34.73 | 3 | 3 | 0 | 3.94 | 403.02 | 0 |
| **IQ12** | 94.1271 | 315.18 | 43.11 | 3 | 4 | 0 | 3.39 | 405 | 0 |
| **IQ14** | 99.99 | 352.65 | 13.03 | 3 | 1 | 0 | 6.33 | 414 | 1 |

%ABS, percentage of absorption; TPSA, topological polar surface area; NROTB, number of rotatable bonds; MW, molecular weight; Log*P*, logarithm of compound partition coefficient between n-octanol and water; HBA, number of hydrogen bond acceptors; HBD, number of hydrogen bond donors.

**Table 2:** Osiris calculation for bioavailability and toxicity prediction forIQ1-IQ14

| BIOAVAILABILITY AND DRUG SCORE[a] | | | | | TOXICITY RISK PREDICTION[b] | | | |
|---|---|---|---|---|---|---|---|---|
| Cmpds | Solubility | Molwt | Drug likeness | Drug score | Mutagenic | Tumorigenic | Irritation | ReproductiveEffect |
| IQ1 | -4.65 | 389 | 4.96 | 0.64 | | | | |
| IQ2 | -6.12 | 457 | 5.96 | 0.39 | | | | |
| IQ3 | -0.47 | 479 | 7.95 | 0.57 | | | | |
| IQ4 | 4.66 | 419 | 512 | 0.62 | | | | |
| IQ5 | -4.35 | 405 | 5.19 | 0.67 | | | | |
| IQ6 | -4.37 | 435 | 5.35 | 0.65 | | | | |
| IQ7 | -0.47 | 479 | 5.53 | 0.57 | | | | |
| IQ8 | 4.68 | 432 | 3.98 | 0.36 | | | | |
| IQ9 | -0.47 | 479 | 5.94 | 0.57 | | | | |
| IQ10 | -4.35 | 405 | 5.19 | 0.67 | | | | |
| IQ11 | -4.99 | 403 | 3.64 | 0.57 | | | | |
| IQ12 | -4.66 | 419 | 5.13 | 0.62 | | | | |
| IQ14 | -4.94 | 415 | 3.86 | 0.57 | | | | |

Colour of circle indicates level of toxicity; Green: low, Yellow: medium, Red: Highly toxic.



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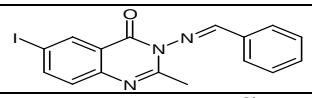
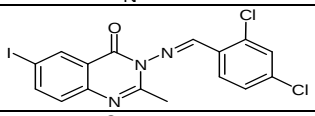
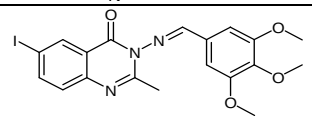
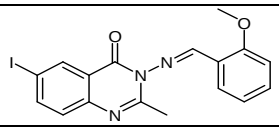
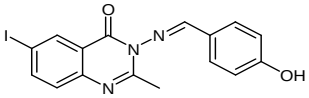
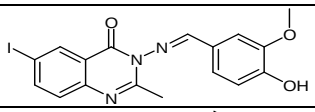
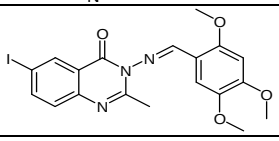
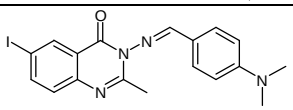
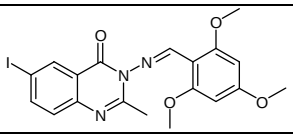
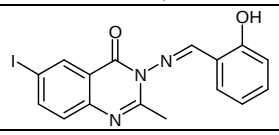
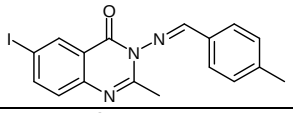
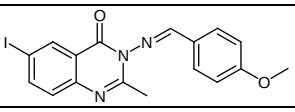
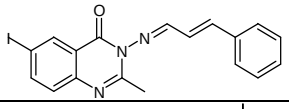
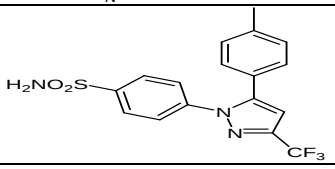
**Table 3:** Scores of all the compounds docked in COX-2 domain

| S. No. | Compd | Structure | Score |
|---|---|---|---|
| 1 | IQ1 |  | -9.3 |
| 2 | IQ12 |  | -9.3 |
| 3 | IQ2 |  | -9.3 |
| 4 | IQ5 |  | -9.3 |
| 5 | IQ8 |  | -9.3 |
| 6 | IQ6 |  | -9.1 |
| 7 | IQ11 |  | -9.0 |
| 8 | IQ10 |  | -8.9 |
| 9 | IQ14 |  | -8.9 |
| 10 | IQ4 |  | -8.8 |
| 11 | IQ9 |  | -8.4 |
| 12 | IQ3 |  | -8.3 |
| 13 | IQ7 |  | -8.1 |
| 14 | CEL |  | -12.6 |

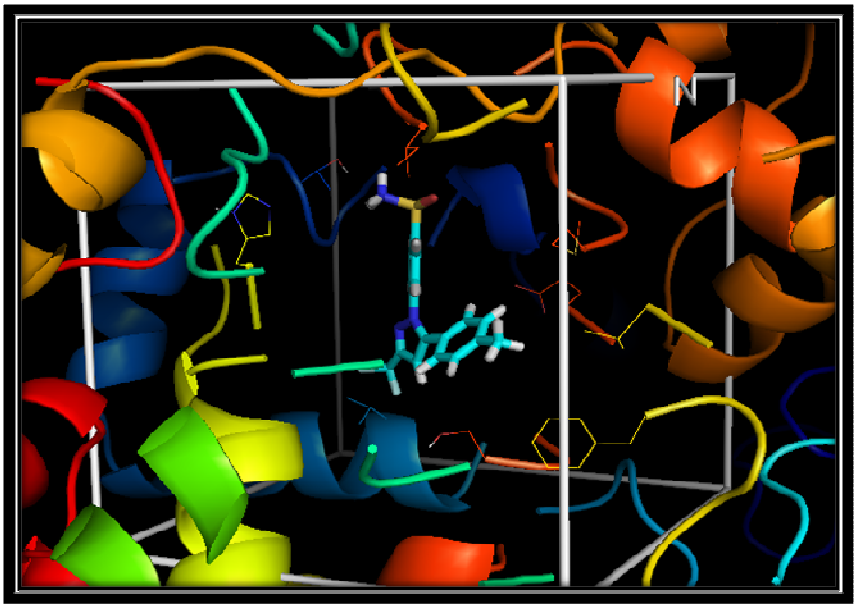



**Fig-1a:** Original Co Crystallized structure of Celecoxib with **COX**-2

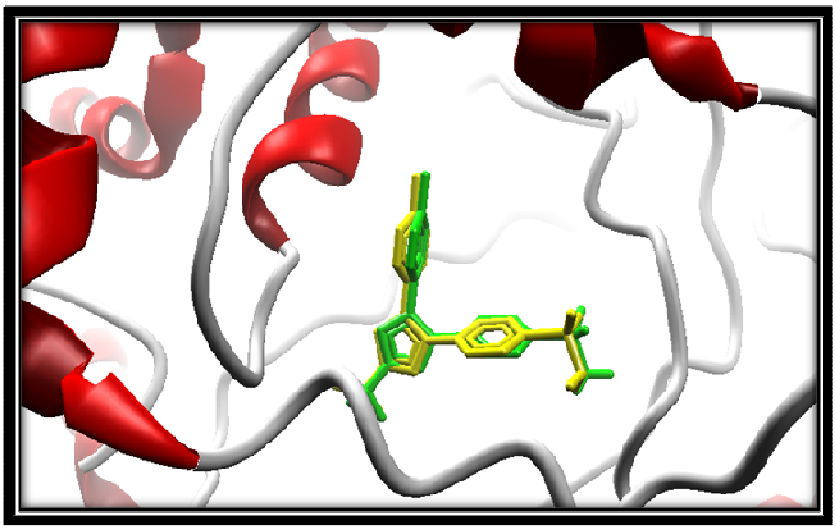


**Fig-1b:** Redocked 3ln1 ribbon view.

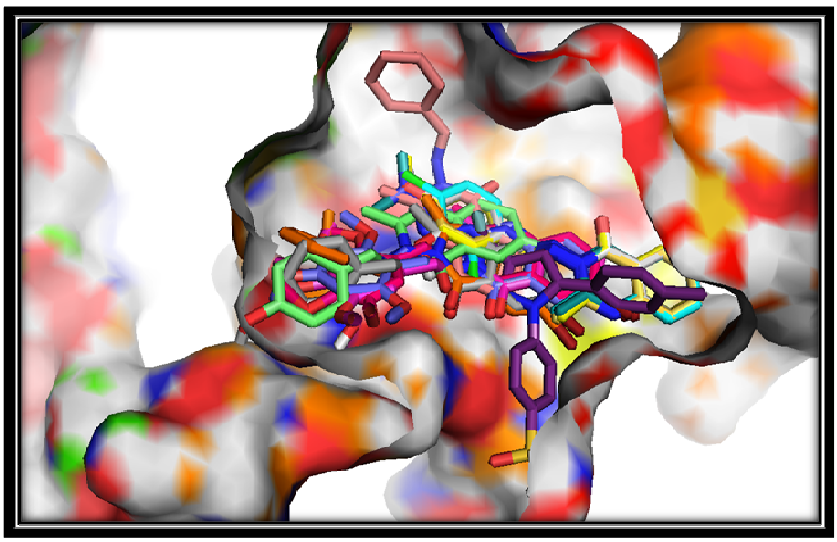


**Fig-2a**: MS view of all the compounds docked in 3ln1

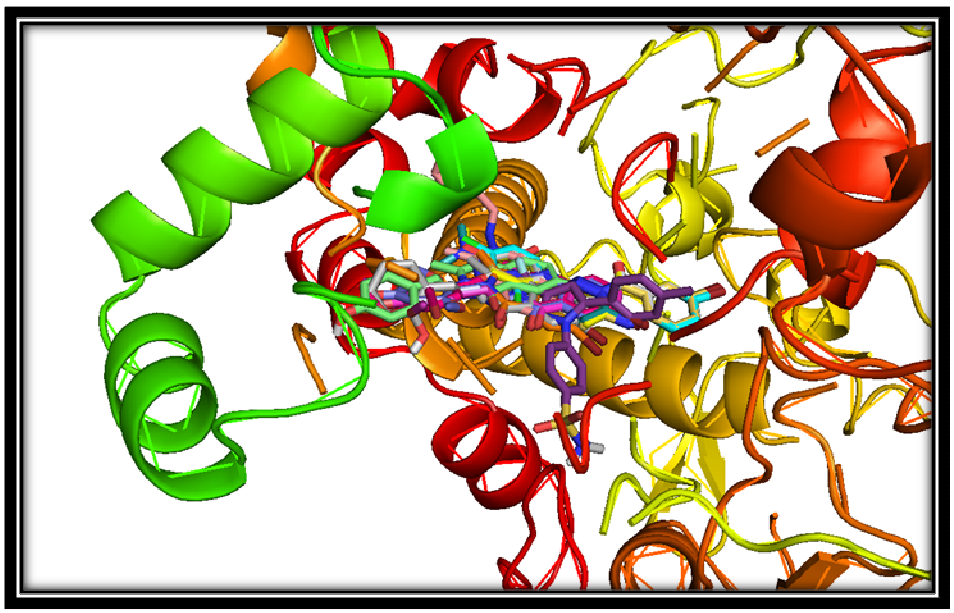


**Fig-2b**: Ribbon view of all the compounds docked in 3ln1

## Conclusion:

The present work was aimed to design few selected Quinazoline derivatives as tailored Cox-2 inhibitors via Molecular properties prediction and Molecular docking studies. Toxicity risk evaluation study was also performed to ensure the safety of the targeted compounds. The compounds designed were first screened for the drug like properties and were filtered on the basis of "Lipinski's rule of 5". They were further subjected to Toxicity risk prediction with the help of Osiris property explorer. The molecular properties were predicted with Molsoft&Molinspirationsoftwares. Henceforward they were subjected to Molecular docking studies with the help of Autodock/ VinaPymol plugin Software to understand the binding mode of the rationally designed compounds with the target receptors. All the *denovo* compounds passed the Lipinski rule of 5, with compounds IQ2 and IQ14 having one violation only. The toxicity prediction ensured that all the compounds were non-mutagenic, non-tumorogenic, non-irritating and no effect on reproductive system except compound IQ8 having medium risk of mutagenicity. Further, docking of the proposed compounds exhibited good binding affinity for compounds IQ1, IQ2, IQ5, IQ8 and IQ12 which anticipated these compounds to be good oral anti-inflammatory compounds. So it is worthwhile to carry out the synthesis of the said compounds.

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