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**Original Article**

# Lead Optimization Studies on Novel Quinolones Derivatives as CYP-450 Inhibitor by using *In-Silico* Modulation

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## ABSTRACT

The *In-silico* studies considered as complementary to in vivo and in vitro biological studies are performed by using a computer and are playing increase larger and more important role in drug discovery and development. We describe here in *In-silico* study of various hypothetical Quinolines and their interactions with CYP450 enzymes by computational methods including chem draw ultra, Avogadro and ochem database software methods. We worked on a chemical reaction scheme of Quinolines and we prepared different 20 Quinolines derivatives. The CYP450 super family of heme enzymes plays an important role in the metabolism of a large number of endogenous and exogenous compounds including most of the drugs currently on the market. Comprehensive studies of the quantum approaches on the quinolines derivatives like QD1, QD8 and QD13 was found to be CYP450 enzymes inhibitors interactions. The quantum approaches by lead optimization will require further studies; the data reported in this work may be helpful guide for medicinal chemist who is working in this area.

**Keywords:** *In-silico,* Quinolone, CYP450 inhibitor

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## INTRODUCTION

Quinolines agents exhibit a bicyclic aromatic core, containing a carbon at the 8th position, yielding a true quinolones, or nitrogen, and provide a ring system technically termed as naphthyridone. In common usage, both quinoline and naphthyridone structures are encompassed in the class descriptor quinolones antibacterial agents [1].

The first generation quinolones compounds generally displayed increased Gram-negative activity over nalidixic acid, but lacked useful activity against Gram-positive cocci, pseudomonas aeruginosa, and anaerobes. They were, however, generally well absorbed after oral administration and attained high concentrations in the urinary tract, making them useful therapeutically for treatment of urinary tract infections. In the second-generation quinolones, the piperazine ring remains relatively undisturbed, except for alkylation on the distal nitrogen or, less frequently, on the ring carbons.

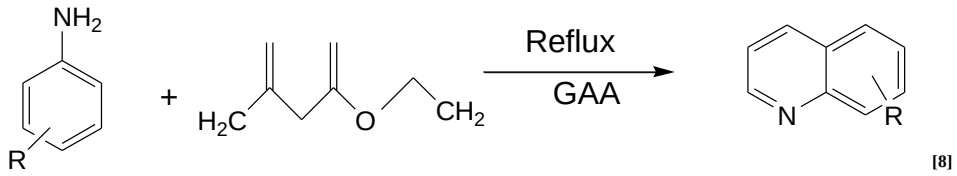
The second-generation compounds are characterized by good to excellent Gram-negative activity, with ciprofloxacin exhibiting the strongest Gram-negative spectrum. The third- and fourth-generation quinolones are characterized by increased structural novelty and complexity, which has resulted in new and useful characteristics [2, 3]. *In-silico* literally Latin for "in silicon", alluding to the mass use of silicon for semiconductor computer chips is an expression used to mean performed on computer or via computer simulation. The phrase was coined in 1989 as an allusion to the Latin phrases in vivo, in vitro, and in situ, which are commonly used in biology and refer to experiments done in living organisms, outside of living organisms, and where they are found in nature, respectively [4]. Computer-aided drug design is the use of computer systems to aid in the creation, modification, analysis, or optimization of a design. CADD software is used to increase the productivity of the designer, improve the quality of design, improve communications through documentation, and to create a database for manufacturing [5].

CADD output is often in the form of electronic files for print, machining, or other manufacturing operations. The term CADD is also used. Its use in designing electronic systems is known as electronic design automation. In mechanical design it is known as mechanical design automation or computer-aided drafting, which includes the process of creating a technical drawing with the use of computer software [6]. Inhibitors of the CYP450 enzymes have more important role in the treatment of several disease conditions such as numerous cancers and anti fungal interactions in addition to their critical role in drug-drug interaction. Understanding the key structure features of inhibitors responsible for their inhibition potency has been essential for CYP450 inhibitors design and development [7].

## MATERIAL AND METHODS

**Software used for lead optimization:** Chem Draw Ultra8.0, Avogadro, OCHEM database.

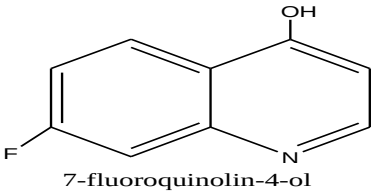
**Chemical Reaction:**




[8]

**20 novel quinolones derivatives with elemental analysis:**

**QD1.**




7-fluoroquinolin-4-ol

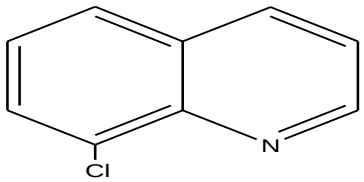
$C_9H_6FNO$
Exact Mass: 163.0433
Mol. Wt.: 163.1484
m/e:
C, 66.26; H, 3.71; F, 11.64; N, 8.59; O, 9.81

**QD2.**


6-chloroquinolin-4-ol

$C_9H_6ClNO$
Exact Mass: 179.01379
Mol. Wt.: 179.60304
m/e:
C, 60.19; H, 3.37; Cl, 19.74; N, 7.80; O, 8.91

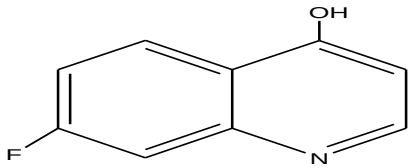
**QD3.**




8-chloroquinoline

$C_9H_6ClN$
Exact Mass: 163.01888
Mol. Wt.: 163.60364
m/e:
C, 66.07; H, 3.70; Cl, 21.67; N, 8.56

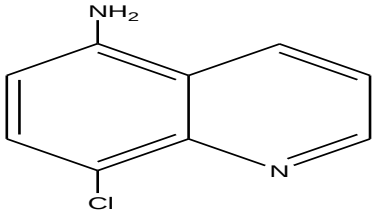
**QD4.**




7-fluoroquinolin-4-ol

$C_{10}H_6ClNO_2$
Exact Mass: 207.0087
Mol. Wt.: 207.6131
m/e:
C, 57.85; H, 2.91; Cl, 17.08; N, 6.75; O, 15.41

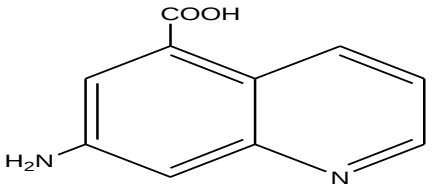
**QD5.**




8-chloroquinolin-5-amine

$C_9H_7ClN_2$
Exact Mass: 178.0298
Mol. Wt.: 178.6183
m/e:
C, 60.52; H, 3.95; Cl, 19.85; N, 15.68

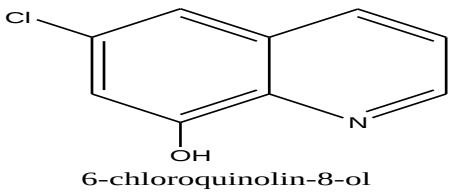
**QD6.**




7-aminoquinoline-5-carboxylic acid

$C_{10}H_8N_2O_2$
Exact Mass: 188.05858
Mol. Wt.: 188.18272
m/e:
C, 63.82; H, 4.28; N, 14.89; O, 17.00

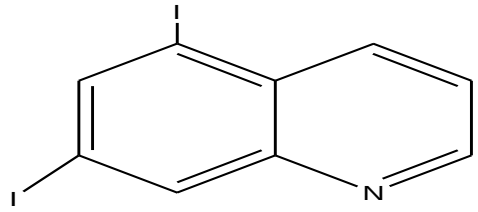
**QD7.**




6-chloroquinolin-8-ol

$C_9H_6ClNO$
Exact Mass: 179.01379
Mol. Wt.: 179.60304
m/e:
C, 60.19; H, 3.37; Cl, 19.74; N, 7.80; O, 8.91

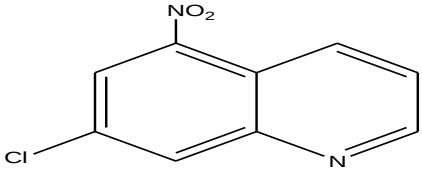
**QD8.**




5,7-diiodoquinoline

$C_9H_5I_2N$
Exact Mass: 380.8511
Mol. Wt.: 380.9516
m/e: 380.8511 (100.0%), 381.8545 (9.7%)
C, 28.38; H, 1.32; I, 66.62; N, 3.68

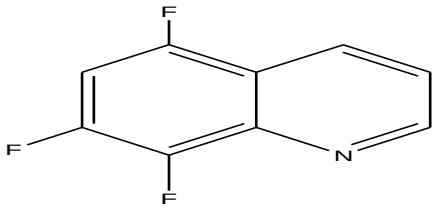
**QD9.**




7-chloro-5-nitroquinoline

$C_9H_5ClN_2O_2$
Exact Mass: 208.004
Mol. Wt.: 208.6012
m/e:
C, 51.82; H, 2.42; Cl, 17.00; N, 13.43; O, 15.34

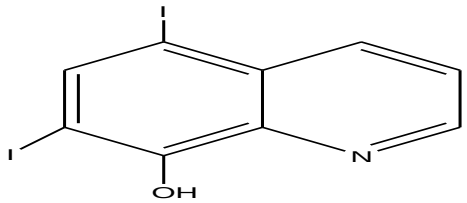
**QD10.**




5,7,8-trifluoroquinoline

$C_9H_4F_3N$
Exact Mass: 183.0296
Mol. Wt.: 183.13
m/e: 183.0296 (100.0%), 184.0329 (9.7%)
C, 59.03; H, 2.20; F, 31.12; N, 7.65

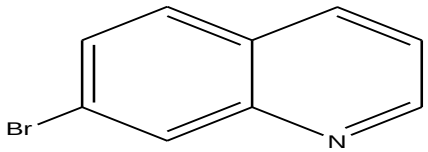
**QD11.**




5,7-diiodoquinolin-8-ol

$C_9H_5I_2NO$
Exact Mass: 396.846
Mol. Wt.: 396.951
m/e: 396.8460 (100.0%), 397.8494 (9.7%)
C, 27.23; H, 1.27; I, 63.94; N, 3.53; O, 4.03

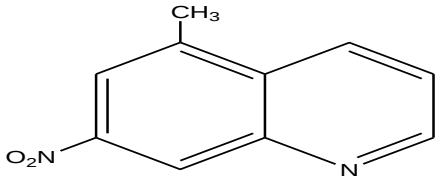
**QD12.**




7-bromoquinoline

$C_9H_6BrN$
Exact Mass: 206.9684
Mol. Wt.: 208.0546
m/e:
C, 51.96; H, 2.91; Br, 38.41; N, 6.73

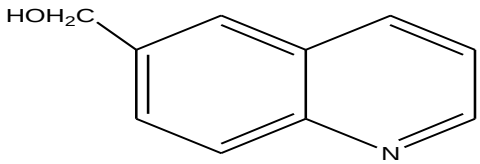
**QD13.**




5-methyl-7-nitroquinoline

$C_{10}H_8N_2O_2$
Exact Mass: 188.0586
Mol. Wt.: 188.1827
m/e:
C, 63.82; H, 4.28; N, 14.89; O, 17.00

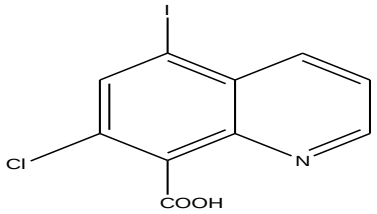
**QD14.**




(quinolin-6-yl)methanol

$C_{10}H_9NO$
Exact Mass: 159.0684
Mol. Wt.: 159.1846
m/e: 159.0684 (100.0%), 160.0718 (10.8%)
C, 75.45; H, 5.70; N, 8.80; O, 10.05

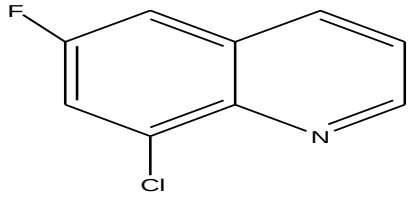
**QD15.**




7-chloro-5-iodoquinoline-8-carboxylic acid

$C_{10}H_5ClINO_2$
Exact Mass: 332.9053
Mol. Wt.: 333.5097
m/e:
C, 36.01; H, 1.51; Cl, 10.63; I, 38.05; N, 4.20; O, 9.59

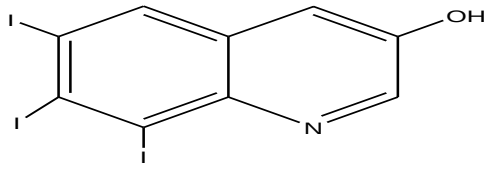
**QD16.**




8-chloro-6-fluoroquinoline

$C_9H_5ClFN$
Exact Mass: 181.0095
Mol. Wt.: 181.5941
m/e:
C, 59.53; H, 2.78; Cl, 19.52; F, 10.46; N, 7.71

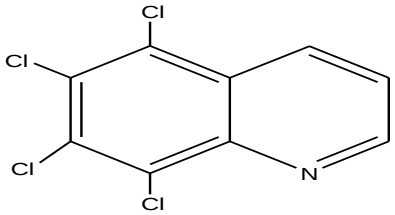
**QD17.**




6,7,8-triiodoquinolin-3-ol

$C_9H_4I_3NO$
Exact Mass: 522.7427
Mol. Wt.: 522.8476
m/e: 522.7427 (100.0%), 523.7460 (9.7%)
C, 20.67; H, 0.77; I, 72.82; N, 2.68; O, 3.06

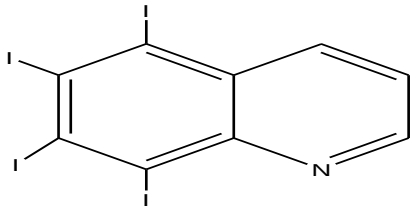
**QD18.**




5,6,7,8-tetrachloroquinoline

$C_9H_3Cl_4N$
Exact Mass: 264.902
Mol. Wt.: 266.9388
m/e: 266.8990 (100.0%), 264.9020 (78.2%), 268.8961 (47.9%), 270.8931 (10.2%), 267.9024 (9.7%), 265.9053 (7.6%), 269.8994 (4.7%)
C, 40.49; H, 1.13; Cl, 53.13; N, 5.25

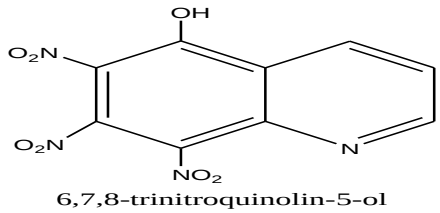
**QD19.**




5,6,7,8-tetraiodoquinoline

$C_9H_3I_4N$
Exact Mass: 632.6444
Mol. Wt.: 632.7447
m/e: 632.6444 (100.0%), 633.6478 (9.7%)
C, 17.08; H, 0.48; I, 80.22; N, 2.21

**QD20.**

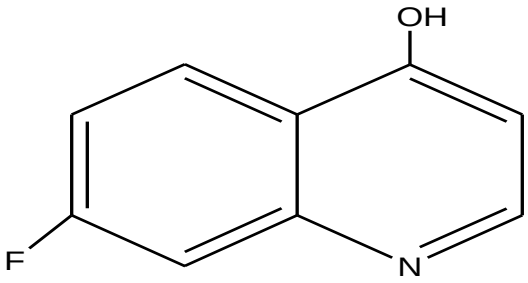



6,7,8-trinitroquinolin-5-ol

$C_9H_4N_4O_7$
Exact Mass: 280.008
Mol. Wt.: 280.1507
m/e: 280.0080 (100.0%), 281.0114 (9.7%), 281.0050 (1.5%), 282.0122 (1.4%)
C, 38.59; H, 1.44; N, 20.00; O, 39.98

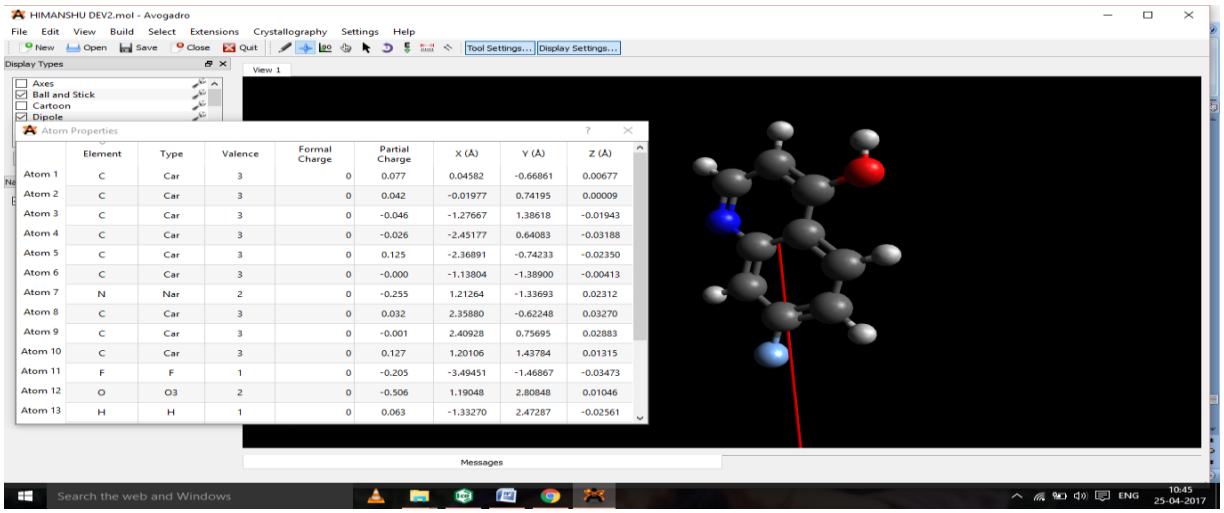
## RESULT AND DISCUSSION

### QD1.

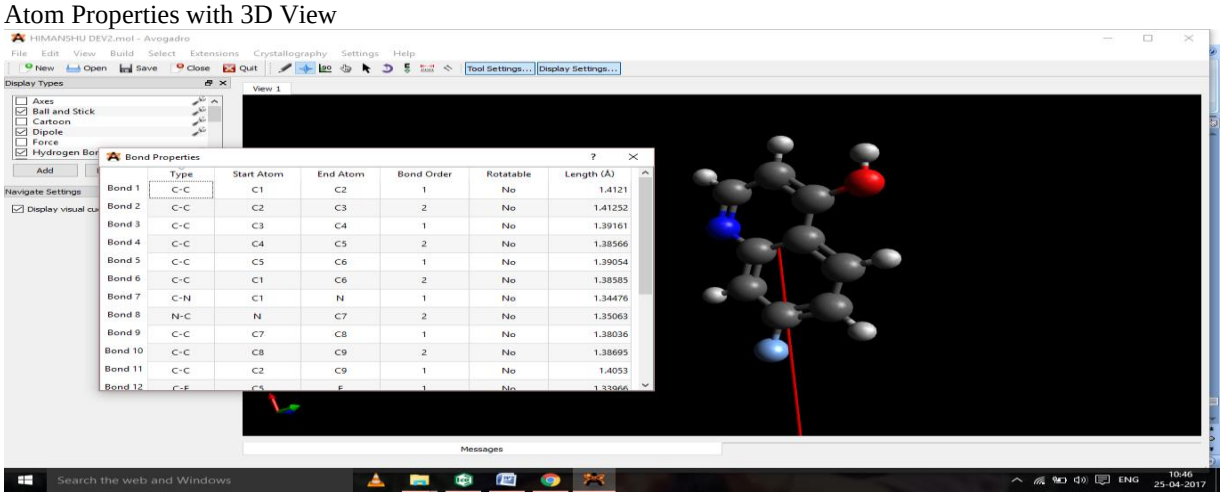



7-fluoroquinolin-4-ol

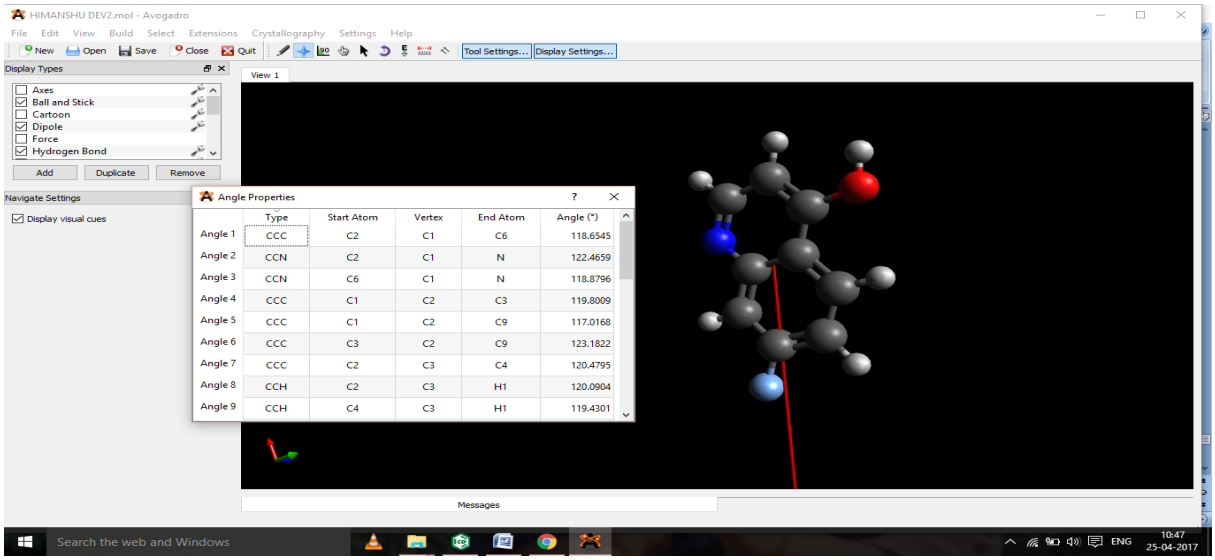
Boiling Point: 589.75 [K]
Melting Point: 446.18 [K]
Critical Temp: 798.81 [K]
Critical Pres: 49.87 [Bar]
Critical Vol: 436.5 [cm3/mol]
Gibbs Energy: -38.05 [kJ/mol]
Log P: 1.89
MR: 42.18 [cm3/mol]
Henry's Law: 8.47
Heat of Form: -153.59 [kJ/mol]
CLogP: 2.55581
CMR: 4.3341




Atom Properties with 3D View




Bond Properties with 3D View

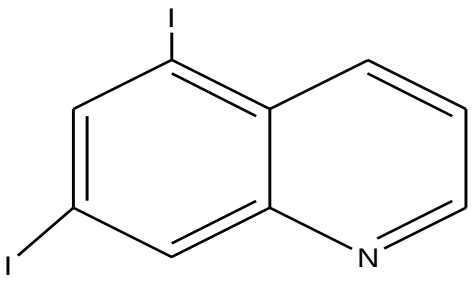



Angle Properties with 3D View

**Ochem database prediction results as CYP450 inhibitor:**

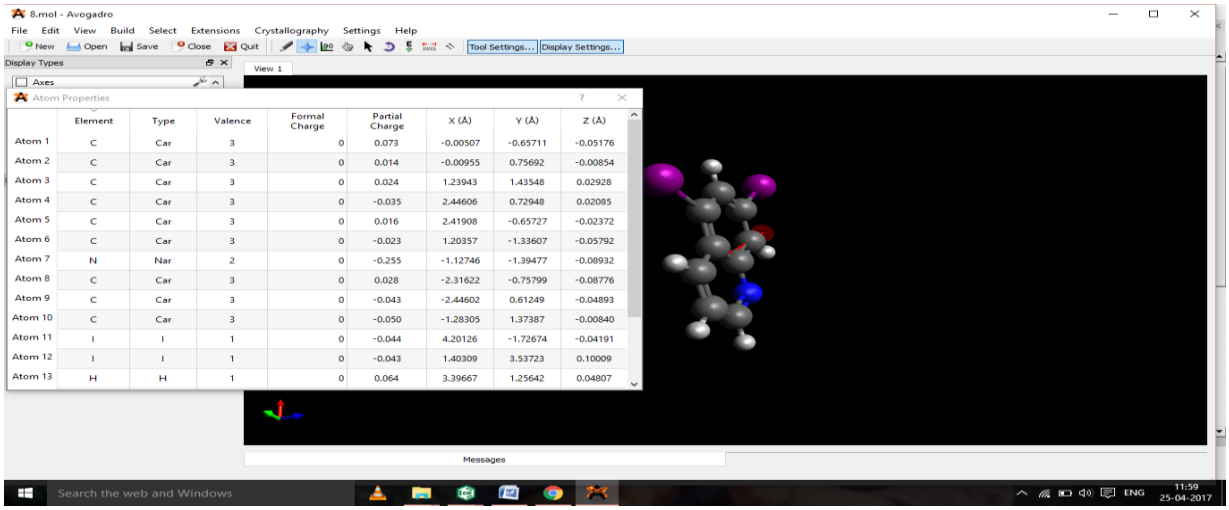
LogPow (ALogPS 3.0) = 1.9 Log unit ± 0.77 (ASNN-STDEV = 0.14, estimated RMSE = 0.39)
Aqueous Solubility (ALogPS 3.0) = 2.1 –log (mol/L) ± 1.41 (ASNN-STDEV = 0.30, estimated RMSE = 0.72)
Log (IGC50-1) (Toxicity against T. Pyriformis) = 0.48 –log (mmol/L) ± 1.07 (ASNN-STDEV = 0.57, estimated RMSE = 0.55)
CYP450 modulation= inhibitor (94.0% accuracy)
Melting Point (Melting Point prediction (best Estate)) = 170 °C
Aqueous Solubility (ALOGPS 2.1 logS) = -1.7 log (mol/L)
LogPow (ALOGPS 2.1 logP) = 2.2 Log unit

**QD8.**

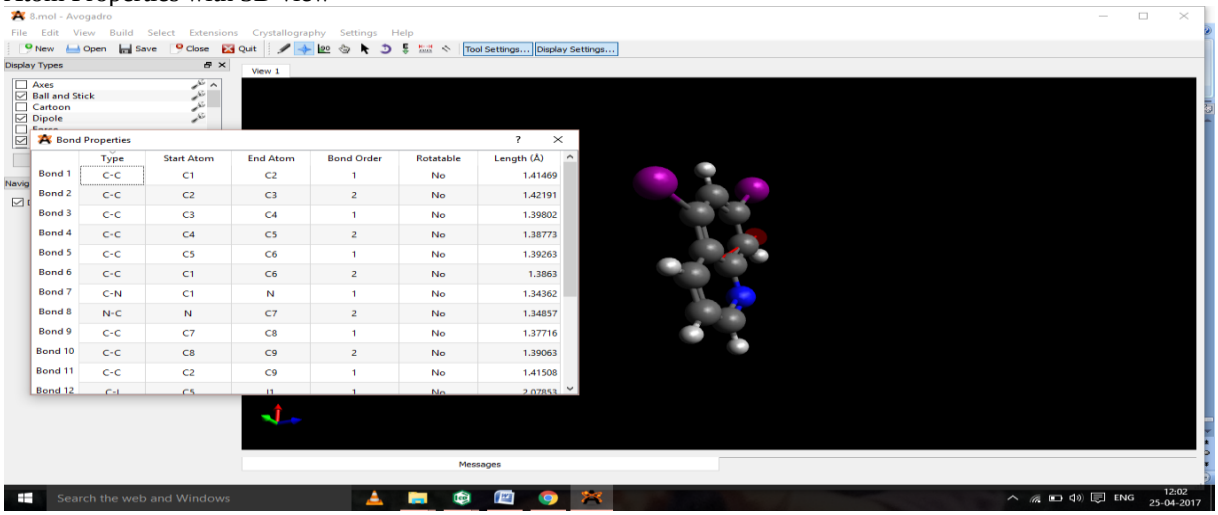



5,7-diiodoquinoline

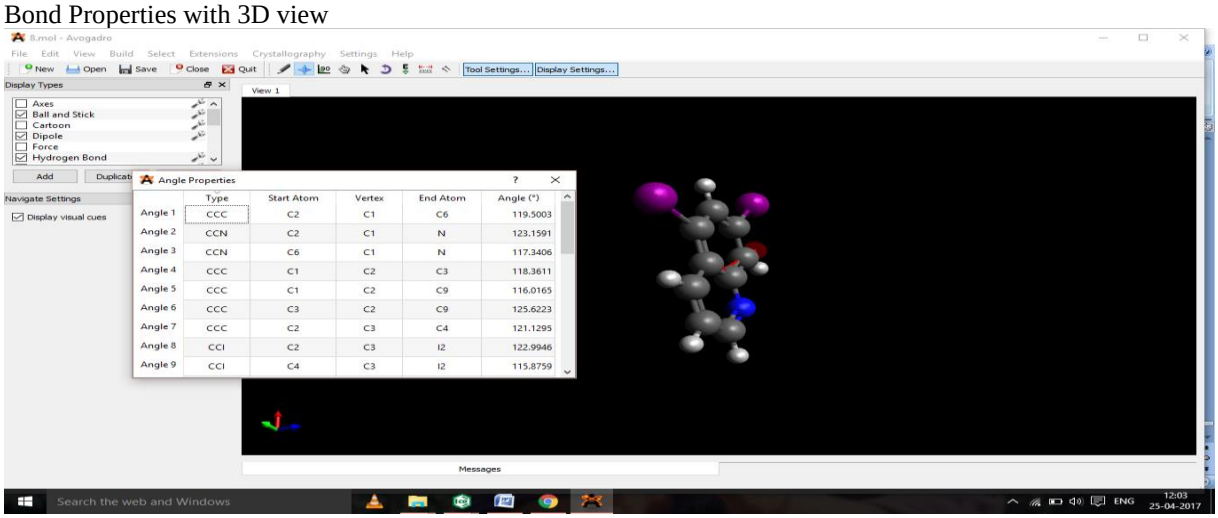
Boiling Point: 701.12 [K]
Melting Point: 462.51 [K]
Critical Temp: 924.56 [K]
Critical Pres: 40.11 [Bar]
Critical Vol: 578.5 [cm3/mol]
Gibbs Energy: 417.99 [kJ/mol]
Log P: 4.83
MR: 64.95 [cm3/mol]
Henry's Law: 5.82
Heat of Form: 362.1 [kJ/mol]
CLogP: 4.36005
CMR: 6.7783



Atom Properties with 3D view




Bond Properties with 3D view

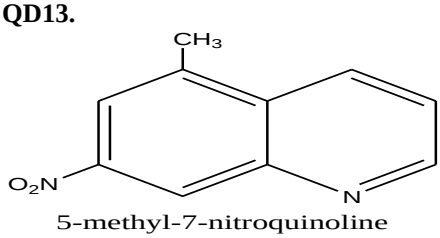



Angle Properties with 3D view

**Ochem database prediction results as CYP450 inhibitor:**

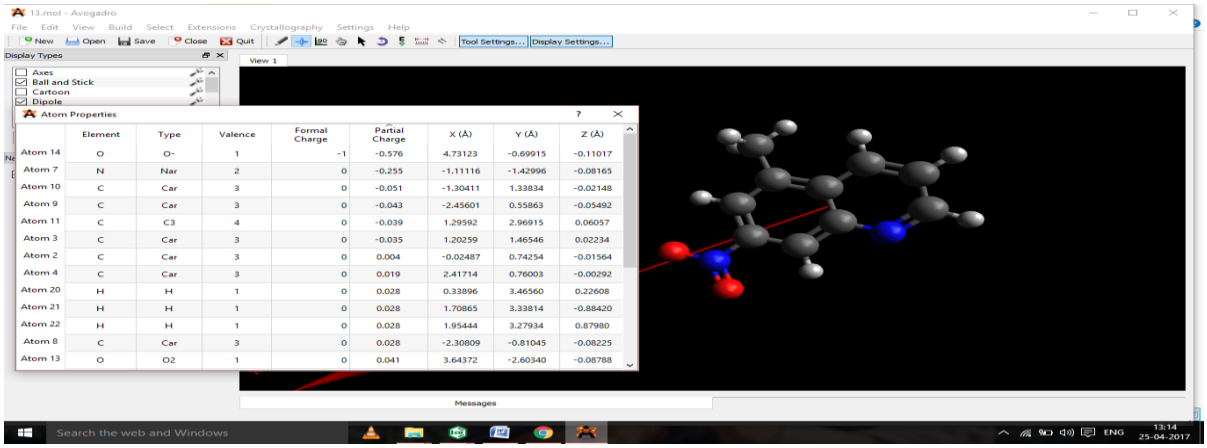
LogPow (ALogPS 3.0) = 4.6 Log unit ± 1.50 (ASNN-STDEV = 0.87, estimated RMSE = 0.76)
Aqueous Solubility (ALogPS 3.0) = 5 –log (mol/L) ± 1.41 (ASNN-STDEV = 0.81, estimated RMSE = 0.72)
Log (IGC50-1) (Toxicity against T. Pyriformis) = 1.1 –log (mmol/L) ± 1.07 (ASNN-STDEV = 1.05, estimated RMSE = 0.55)
CYP450 modulation = inhibitor (83.0% accuracy)
Melting Point (Melting Point prediction (best Estate)) = 150 °C
Aqueous Solubility (ALOGPS 2.1 logS) = -4.3 log (mol/L)

**QD13.**

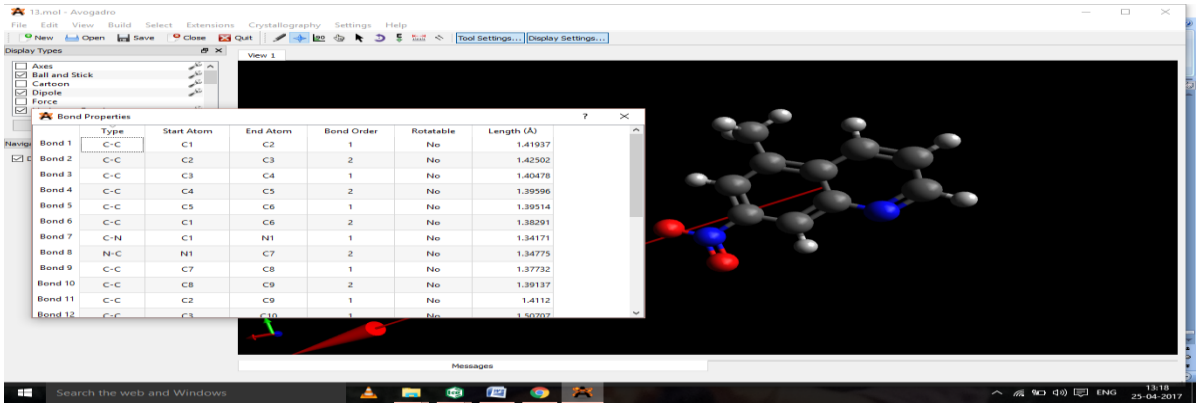



5-methyl-7-nitroquinoline

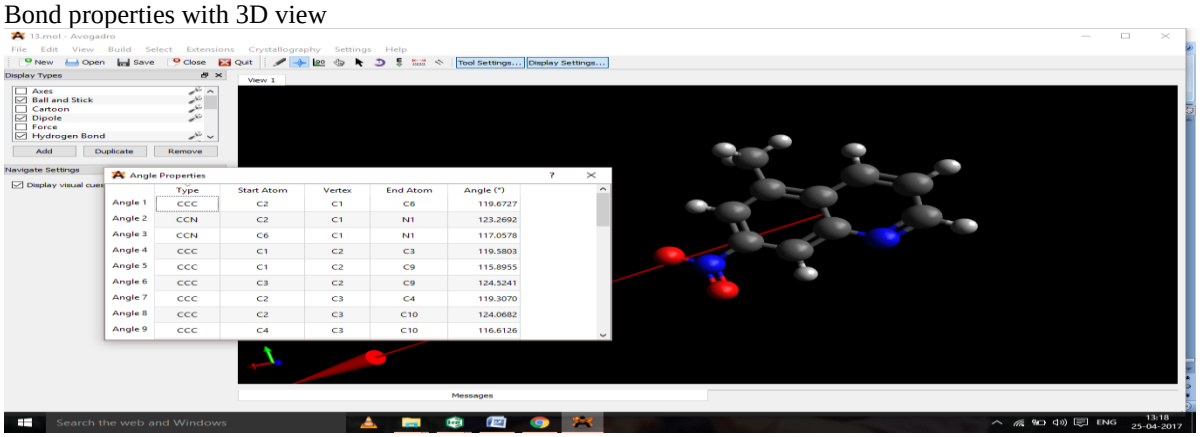
Log P: 2.5
Henry's Law: 3.48
CLogP: 2.406
CMR: 5.2408



Atom properties with 3D view



Bond properties with 3D view



Angle properties with 3D view

**Ochem database results prediction as CYP450 inhibitor:**

LogPow (ALogPS 3.0) = 1.3 Log unit ± 0.77 (ASNN-STDEV = 0.34, estimated RMSE = 0.39)

Aqueous Solubility (ALogPS 3.0) = 2 –log (mol/L) ± 1.41 (ASNN-STDEV = 0.50, estimated RMSE = 0.72)

Log (IGC50-1) (Toxicity against T. Pyriformis) = -0.38 –log (mmol/L) ± 1.07 (ASNN-STDEV = 1.10, estimated RMSE = 0.55)

CYP450 modulation= inhibitor (89.0% accuracy)

Melting Point (Melting Point prediction (best Estate)) = 210 °C

Aqueous Solubility (ALOGPS 2.1 logS) = -2.8 log (mol/L)

LogPow (ALOGPS 2.1 logP) = 2.4 Log unit

We describe here in *In-silico* study of various hypothetical Quinolines and their interactions with CYP450 enzymes by computational methods including CHEM DRAW ULTRA, AVAGARDO, and OCHEM database software methods. We worked on a chemical reaction scheme of Quinolines and I prepared different 20 Quinolines derivatives. A Brief computational study was carried out over 20 designed Quinolines derivatives using various software programmes with the goal of identifying potential and clinically significant molecules that are CYP450 inhibitors. Comprehensive studies of the Quantum

Approaches on the Quinolines derivatives like derivative-1, derivative-8, and derivative-13 were found to be CYP450 enzymes inhibitors interactions. The design and development of potent and selective inhibitors for individual CYP enzymes seems to be an achievable target.

## CONCLUSION

The *In-silico* evaluation conforms that the compound had, "Drug like" properties but did not give information of sufficient value to discriminate between compounds. Lead optimization efforts are produced a fully optimized drug candidate ready for pre-clinical development studies. SAR and 3D-QSAR represent important tools in understanding the interaction of inhibitors with the active sites of the CYP enzymes. Two approaches to QSAR methods used for predicting the metabolism of substrate and inhibitors by CYP have been detailed in this project work. Computational methods including CHEM DRAW ULTRA, for chemical structure drawing, AVAGADRO for molecular editor and visualization tools, and OCHEM DATA BASE for prediction of QSAR based on CYP450 inhibitors studies including other physic-chemical properties of candidate molecules. The recent successes of Quinolines as anti-inflammatory, anti-microbial and anti-cancers have further highlighted the importance of this class in medicinal chemistry. The quantum approaches by lead optimization will require further studies; the data reported in this work may be helpful guide for medicinal chemist who is working in this area.

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