



# Structure Based Drug Discovery, Docking, Modelling, Synthesis and Anticancer Screening of Some Novel Quinoline Derivatives

**Bharat Shivaji Honde<sup>a\*</sup> and Rahul Rajendra Kunkulol<sup>a</sup>**

<sup>a</sup> Department of Pharmacology, Pravara Institute of Medical Sciences (Deemed University),  
Loni, 413736, District Ahmednagar, (M.S.), India.

## Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

## Article Information

DOI: 10.9734/JPRI/2022/v34i3A35384

## Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here:  
<https://www.sdiarticle5.com/review-history/81022>

**Original Research Article**

**Received 15 November 2021**

**Accepted 20 January 2022**

**Published 21 January 2022**

## ABSTRACT

A new series of (2-(substituted-phenyl) quinoline-4-yl) (3-(substituted phenyl)-5-phenyl-1H-pyrazol-1-yl) methanone derivatives was carried out docking modelling and synthesized. Purity was checked by TLC and chemical structures of synthesized compounds were elucidated by their IR, <sup>1</sup>HNMR, MS analysis data. The synthesized compounds were screened for anticancer activity by using cell line MCF-7 (Human breast cancer cell line) correlate with docking modelling.

**Keywords:** IR; MS; <sup>1</sup>HNMR; auto dock vina software; docking; modelling; quinoline; MCF-7; anticancer.

## ABBREVIATIONS

MCF-7 : Michigan Cancer Foundatio-7  
TLC : Thin Layer Chromatography  
IR : Infra red  
MS : Mass Spectrum  
<sup>1</sup>HNMR : Proton Nuclear Magnetic Resonance

JASCO FTIR : Fourier Transfer Infra red  
KBR : Potassium Bromide  
TMS : Tetramethylsilane  
CO<sub>2</sub> : Carbon Dioxide  
USP : United State Pharmacopeia.  
DMEM : Dulbecco's Modified Eagle Medium  
DMSOn : Dimethylsulfoxide

\*Corresponding author: E-mail: D.bharat\_honde11@rediffmail.com;

*Bcl-2* : *B-cell lymphoma 2*  
*Bcl-xL* : *B-cell lymphoma-extra large*

## 1. INTRODUCTION

Cancer is an abnormal uncontrollable cell cycle disease characterized by the rapid proliferation of normal cells. Cancer has been ranked as the second leading cause of death all over the world, preceded only by cardiovascular diseases [1,2]. Chalcone moieties and quinoline play an important role in medicinal chemistry, especially in the identification and development of potential anticancer agents. The multi target approach or hybridization is considered as a promising strategy in drug design and discovery. Hybridization may improve the affinity and potency while simultaneously decreasing the resistance and or side effects. The conjugation of quinolines with chalcones has been a promising approach to the identification of potential anticancer agents. In this article, the quinolone chalcone hybrids with potential anticancer activity have been reviewed. This class of compounds might be helpful for the design, discovery and development of new and potential multi-target anticancer agents or drug [3]. The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay is based on the conversion of MTT into formazan crystals by living cells, which determines mitochondrial activity. Since for most cell populations the total mitochondrial activity is related to the number of viable cells, this assay is broadly used to measure the in vitro cytotoxic effects of drugs on cell lines or primary patient cells. In this chapter the protocol of the assay is described including important considerations relevant for each step of the assay as well as its limitations and possible applications [4]. In medicinal chemistry quinoline and pyrazole derivatives have been very well known for their therapeutic applications. The development of a new synthetic methodology for synthesis of compounds containing quinoline and pyrazole continues to be an active and exciting area of research in pharmaceutical chemistry. Quinoline compounds play an important role in designing new classes of structural entities of medicinal importance with potentially new mechanisms of action. Quinoline is nitrogen containing heterocyclic compound [5]. The biological activity of these quinoline derivatives depends not only on the bicyclic hetero-aromatic pharmacophore but, also on the

nature of the peripheral substituent and their spatial relationship. Various quinoline compounds can be prepared by *Skraup* synthesis using series of different oxidizing agents [6]. The pyrazole function is quite stable and has inspired chemist to utilize this stable fragment in bioactive moieties to synthesize new compounds possessing biological activity [6,7].

## 2. EXPERIMENTAL

In this research work, the melting points of the synthesized organic compounds were determined by open capillary tube and are uncorrected. Purity of the compounds was checked by thin layer chromatography using silica gel G as stationary phase and a combination of benzene: chloroform as mobile phase. The IR spectra of intermediate as well as final derivatives were recorded on Fourier Transform Infrared Spectrophotometer on JASCO FTIR 4100 spectrophotometer by using KBR powder. The (<sup>1</sup>H NMR) spectra of the representative compounds were recorded at on Varian NMR 300 MHz spectrophotometer using TMS as an internal standard and chloroform as a solvent.

### 2.1 Synthesis of 2-Phenylquinolin-4 Carboxylic Acid

The mixture of substituted aromatic aldehydes (0.01mole), aniline (0,01mole) and pyruvic acid (0.01 mole) in methanol (100ml) was refluxed in a 250 ml of round bottom flask for 1-3 hours. Reaction was monitored by TLC using ethyl acetate: acetone (2:1) as solvent and iodine vapours as visualising agent, after completion of reaction 50 ml of warm water was added and solution was allowed to cool. The precipitated solid was filtered washed with aqueous methanol (10ml) and recrystallized from methanol [5,6].

### 2.2 Synthesis of 2-Phenylquinolin-4-Carboxylate (A)

2-Phenylquinolin-4 carboxylic acid added ethanol for was refluxed in a 250 ml of round bottom flask for 1-2 hours Reaction was monitored by TLC using ethyl acetate: acetone (2:1) as solvent and iodine vapours as visualising agent, after completion of reaction the solid was filtered washed with aqueous methanol (10ml) and recrystallized from methanol, dried.

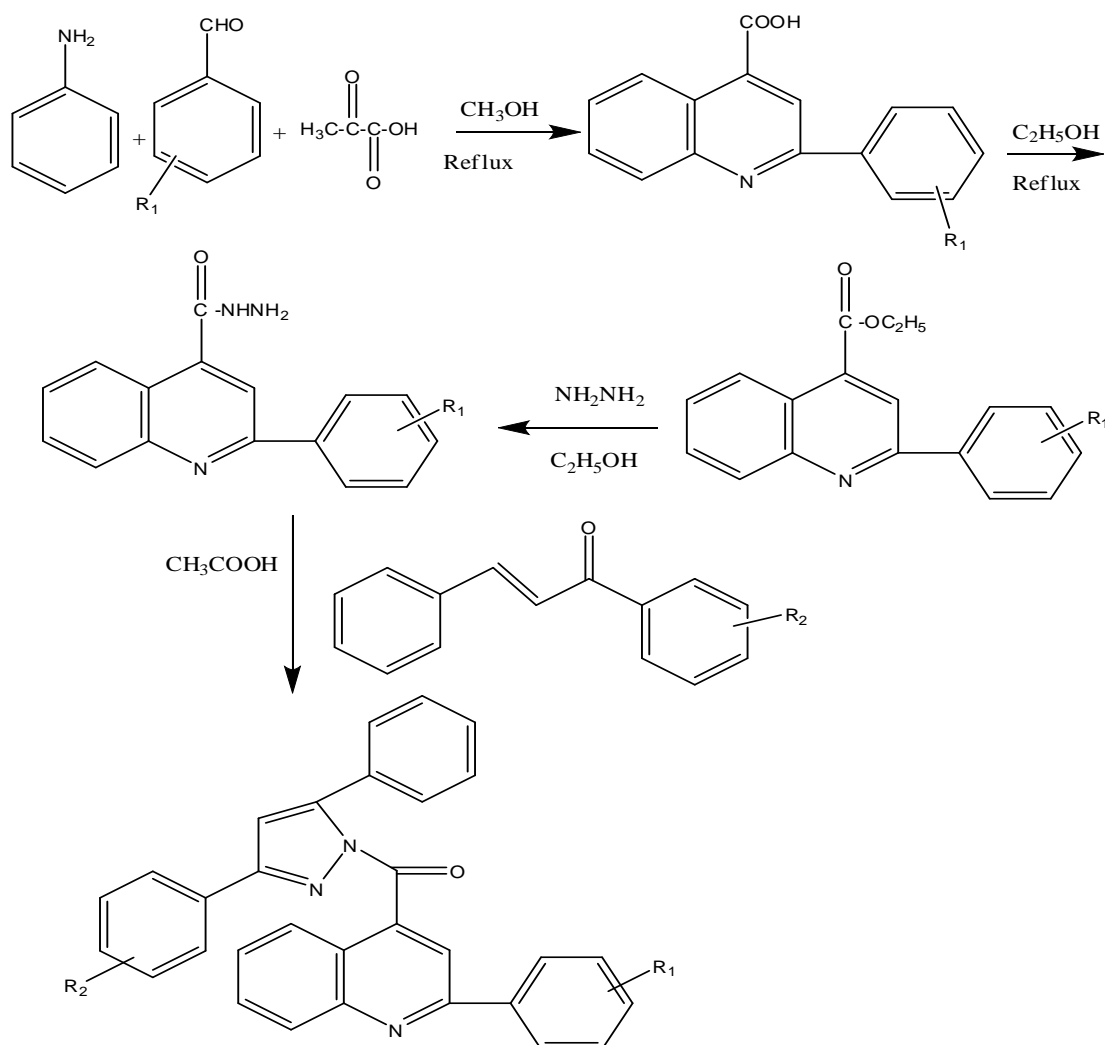


Image 1. Scheme of synthesis

### 2.3 Synthesis of 2-Phenylquinolin-4-Carbohydrazide(B)

2-Phenylquinolin-4-carboxylic acid and hydrazine hydrate in 1:1 portion was mixed in methanol (30ml) and refluxed for 4-6 hours. Reaction was monitored by TLC using ethyl acetate: acetone (2:1) as solvent. The excess of methanol was removed by distillation on cooling the product, the acid hydrazide separated out; it was filtered, dried and recrystallized from methanol, dried.

### 2.4 Synthesis of Chalcones or 1-phenyl-3-Substituted Phenyl Propene 1-one (c)

A solution of 10% NaOH and rectified spirit was taken in Erlenmeyer flask provided with mechanical stirrer. The flask was immersed in a bath of crushed ice, acetophenone (0.83ml, 0.43mol) was poured and stirring was started,

substituted aromatic aldehydes (0.43mol) was then added. Temperature of the mixture was kept within 15 to 30°C. Stirring was continued until the mixture becomes so thick that stirring is no longer effective and then reaction mixture was left in a refrigerator overnight. The product was filtered, washed with cold water until the washing are neutral to litmus and recrystallized from methanol. This substance should be handled with great care.

### 2.5 Synthesis of (2-(substituted-phenyl)quinoline-4-yl) (3-(substituted phenyl)-5-phenyl-1H-pyrazol-1-yl) methanone derivatives(d)

A mixture of substituted chalcone (0.01mol) and 2-Phenylquinolin-4-carbohydrazide (0.01mol) was refluxed in acetic acid (20 ml) for 8-16 hours. The reaction mixture was monitored by TLC using benzene: chloroform (2:1) as solvent. After

completion of reaction, the mixture was cooled and obtained solid was filtered, recrystallized from methanol, n-hexane, Chloroform, pet.ether.

### 3. DOCKING MODELLING

The rational design of new chemical entities intended for use as drugs can be based on several methods. For the optimization of binding to the molecular target, structure based design has been very successful. However, a good drug has not only high and selective affinity for its target; it should also have appropriate pharmacokinetic and bio pharmaceuticals properties [8]. The computational process of searching for a ligand that is able to fit both geometrically and energetically into the binding site of a protein is called molecular docking. Molecular docking is an efficient tool for investigating receptor-ligand interactions and for virtual screening which plays a key role in rational drug design, especially when the crystal structure of a receptor or enzyme is available. It is widely accepted that drug activity is obtained through the molecular binding of ligand to receptor which is commonly a protein. In their binding conformations, the molecules exhibit geometric and chemical complementarity, both of which are essential for successful drug activity [9]. The grid based docking is a rigid and exhaustive docking method. In this method, after unique conformers of the ligand are generated, the receptor cavity of interest is chosen by the user and a grid is generated around the cavity (default grid interval size 1 Å). Cavity points are found and the centre of mass of the ligand is moved to each cavity point. All rotations of ligand are scanned at each cavity point where ligand is placed (step size of rotation could be typically 100-150 as an example). For each rotation a pose of the ligand is generated and the corresponding bumps are checked for each pose of ligand. The dock score is calculated for each valid pose (determined by the cut off criteria fed by user in terms of max no of allowed bumps) and the pose of the ligand with the best score is given as output to user [10-16]. Docking study of the title compounds was done on Auto dock Vina and then this enzyme structure was used further for docking purpose.

#### 3.1 MTT Assay Experimental Procedure

##### 3.1.1 Cell line: MCF-7 (Human breast cancer cell line)

1. CO<sub>2</sub> Incubator- Thermo Fisher, USP

2. Multimode micro plate reader- Bene Sphera E21 Avantor USP.
3. Refrigerated centrifuge- Eppendorf Germany.
4. Cell : MCF-7 (Human breast cancer cell line) NCCS Pune.
5. MTT.(3-(4,5-dimethyl thiazol-2-yl)-2,5-diphenyltetrazoliumbromide)).
6. Fetabovineserum (Gibco, Invitrogen) (CatNo.-10270106)
7. Trypsin.
8. Penicillin.
9. DMEM With high glucose (CatNo.-11965-092).
10. Antibiotic- Antimycotic 100X solution (Thermo fisher scientific)- (CatNo.-1524006)

Cells were incubated at a concentration of  $1 \times 10^4$  cells/ml in culture medium for 24h at 37 °C and 5% CO<sub>2</sub>. Cells were seeded at a concentration (70 microml)  $10^4$  cells/well in 100 µl culture medium and 100 µl sample of 1 to 10 (1000 µg/ml) in to micro plates respectively (tissue culture grade and 96 wells). Control wells were incubated with DMSO (0.2% in PBS) and cell line. All samples were incubated in triplicate. Controls were maintained to determine the control cell survival and the percentage of live cells after culture. Cell cultures were incubated for 24h at 37 °C and 5% CO<sub>2</sub> in CO<sub>2</sub> incubator (Thermo scientific BB150). After incubation, the medium was completely removed and added 20 µl of MTT reagent (5mg/min PBS). After addition of MTT, cells incubated for 4hrs at 37 °C in CO<sub>2</sub> incubator. Observed the wells for formazan crystal formation under microscope. The yellowish MTT was reduced to dark coloured formazan by visible cells only. After removing the medium completely. Added 200 µl of DMSO (kept for 10min.) and incubate at 37 °C (wrapped with aluminium foil). Triplicate samples were analyzed by measuring the absorbance of each sample by a microplate reader (Benesphera E21) at wavelength 550 nm.

### 4. RESULTS AND DISCUSSION

**4a) IR(KBr) cm<sup>-1</sup>: 3244(N-H); 3144,2975(Ar-C-H); 1730(C=O); 1644(Ar-C=C); 773(C-H-Ar).**

**4b) IR(KBr) cm<sup>-1</sup>: 3338(N-H); 2924(Ar-C-H); 1623(N=C); 1646(C=O); 1677(Ar-C=C); 1317(C-N); 1233(Ar-O-C):**

**4c) IR(KBr) cm<sup>-1</sup>: 3388(N-H); 3067(Ar-C-H); 1592(C=O); 924(C-H-Ar).**

**4d) IR(KBr)  $\text{cm}^{-1}$ :** 3319(O-H); 2924(Ar-C-H); 1617.02(N=C)1641(C=O); 1671.02(Ar-C=C); 1113(C-N):754(C-H-Ar).

**4e) IR(KBr)  $\text{cm}^{-1}$ :** 3250(N-H); 3120,2982(Ar-C-H); 1730(C=O); 1644(Ar-C=C);N):780(C-H-Ar).

**4f) IR(KBr)  $\text{cm}^{-1}$ :** . 3237, 3126 (N-H); 2982(Ar-CH); 1724(C=O); 1644(NH-C=O); 826(C-Cl).

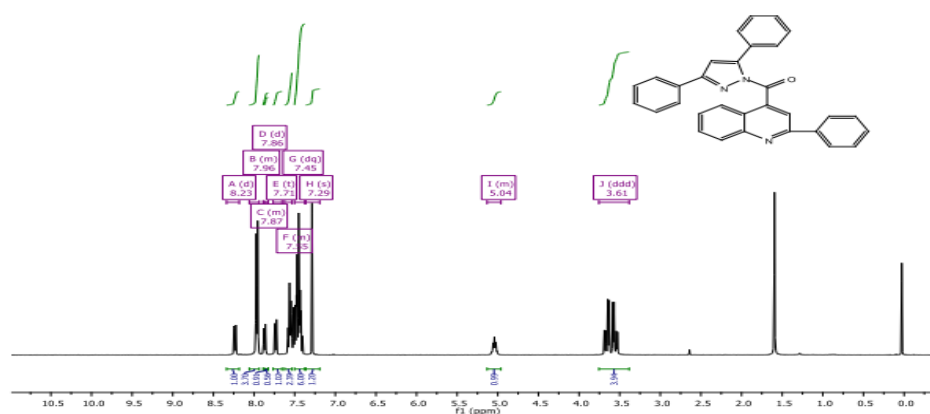
**4g) IR(KBr)  $\text{cm}^{-1}$ :** 3215(N-H); 3113 (=C-H); 2982(C-H); 1703(C=O); 1651(C=N); 1088 (C-N): 773(C-H-Ar).

**4h) IR(KBr)  $\text{cm}^{-1}$ :** . 3402(N-H); 3055 (=C-H); 1700(C=O); 1574(C=C); 705(C-H-Ar).

In the mid-2000s, Abbott Laboratories developed a novel inhibitor of Bcl-2, Bcl-xL and Bcl-w, known as ABT-737. This compound is part of a

group of  $\text{BH}_3$  mimetic small molecule inhibitors (SMI) that target these Bcl-2 family proteins.. *In vitro* studies showed that primary cells from patients with B-cell malignancies are sensitive to 5FU, ABT-737.ABT-737 does not directly induce apoptosis; it enhances the effects of apoptotic signals.

In the mid-2000s, Abbott Laboratories developed a novel inhibitor of Bcl-2, Bcl-xL and Bcl-w, known as ABT-737. This compound is part of a group of  $\text{BH}_3$  mimetic small molecule inhibitors (SMI) that target these Bcl-2 family proteins.. *In vitro* studies showed that primary cells from patients with B-cell malignancies are sensitive to 5FU, ABT-737.ABT-737 does not directly induce apoptosis; it enhances the effects of apoptotic signals.

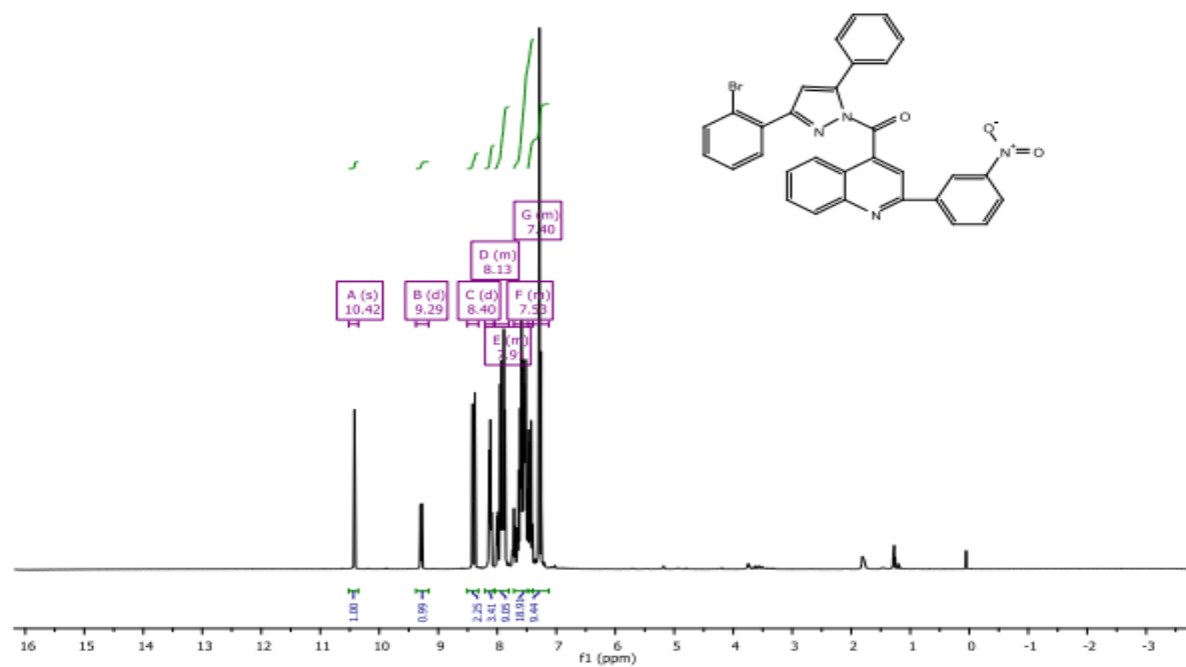


<sup>1</sup>H NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.23 (d,  $J$  = 8.4 Hz, 1H), 8.06 – 7.92 (m, 4H), 7.92 – 7.78 (m, 1H), 7.73 (d,  $J$  = 8.1 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.49 – 7.39 (m, 6H), 7.29 (s, 1H), 5.14 – 4.96 (m, 1H), 3.61 (ddd,  $J$  = 23.3, 17.0, 6.8 Hz, 4H).

**Image 2. (3,5-diphenyl-1H-pyrazol-1-yl)(2-phenylquinolin-4-yl)methanone**

**Table 1. Physical properties of synthesized compounds (4a-4v)**

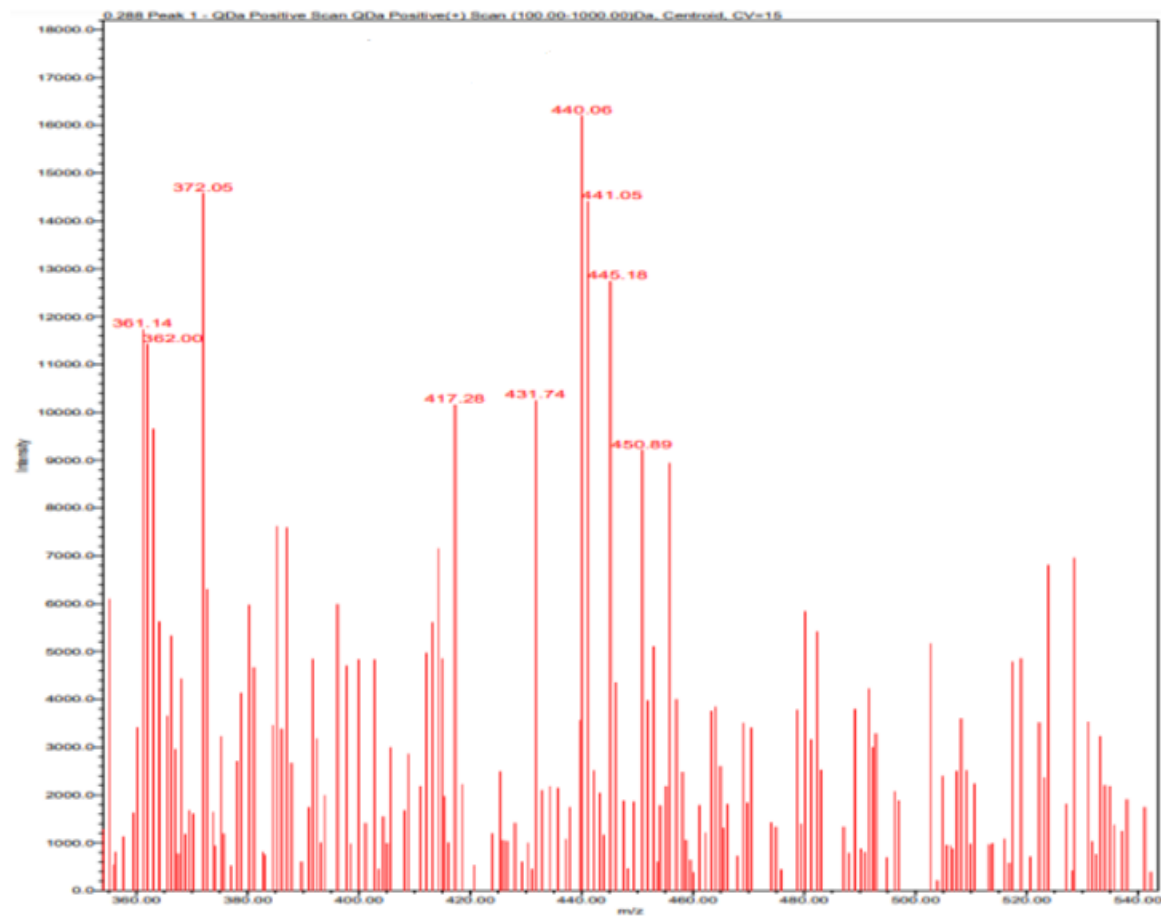
| Sr. No. | Compound | R <sub>1</sub>      | R <sub>2</sub>       | Mol. Formula   | Mol.Wt. (gm) | % yield | M.P. (°C) |
|---------|----------|---------------------|----------------------|--|--------------|---------|-----------|
| 1       | 4a       | Ar-2Cl              | Ar                   | C <sub>31</sub> H <sub>20</sub> N <sub>3</sub> OCl               | 485          | 65      | 151-156   |
| 2       | 4b       | Ar                  | Ar-4OCH <sub>3</sub> | C <sub>32</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>    | 481          | 65      | 163-170   |
| 3       | 4c       | Ar                  | Ar -2Br              | C <sub>31</sub> H <sub>20</sub> ON <sub>3</sub> Br               | 529          | 70      | 166-171   |
| 4       | 4d       | Ar                  | Ar-4OH               | C <sub>31</sub> H <sub>21</sub> O <sub>2</sub> N <sub>3</sub>    | 467          | 68      | 164-170   |
| 5       | 4e       | Ar-3NO <sub>2</sub> | Ar-2Br               | C <sub>31</sub> H <sub>19</sub> N <sub>4</sub> O <sub>3</sub> Br | 575          | 70      | 150-155   |
| 6       | 4f       | Ar-2Cl              | Ar-5Cl               | C <sub>31</sub> H <sub>19</sub> N <sub>3</sub> OCl <sub>2</sub>  | 519          | 69      | 153-158   |
| 7       | 4g       | Ar-2Cl              | Ar-4NH <sub>2</sub>  | C <sub>31</sub> H <sub>21</sub> N <sub>4</sub> OCl               | 500          | 68      | 158-163   |
| 8       | 4h       | Ar                  | Ar                   | C <sub>31</sub> H <sub>21</sub> N <sub>3</sub> O                 | 451          | 70      | 161-166   |



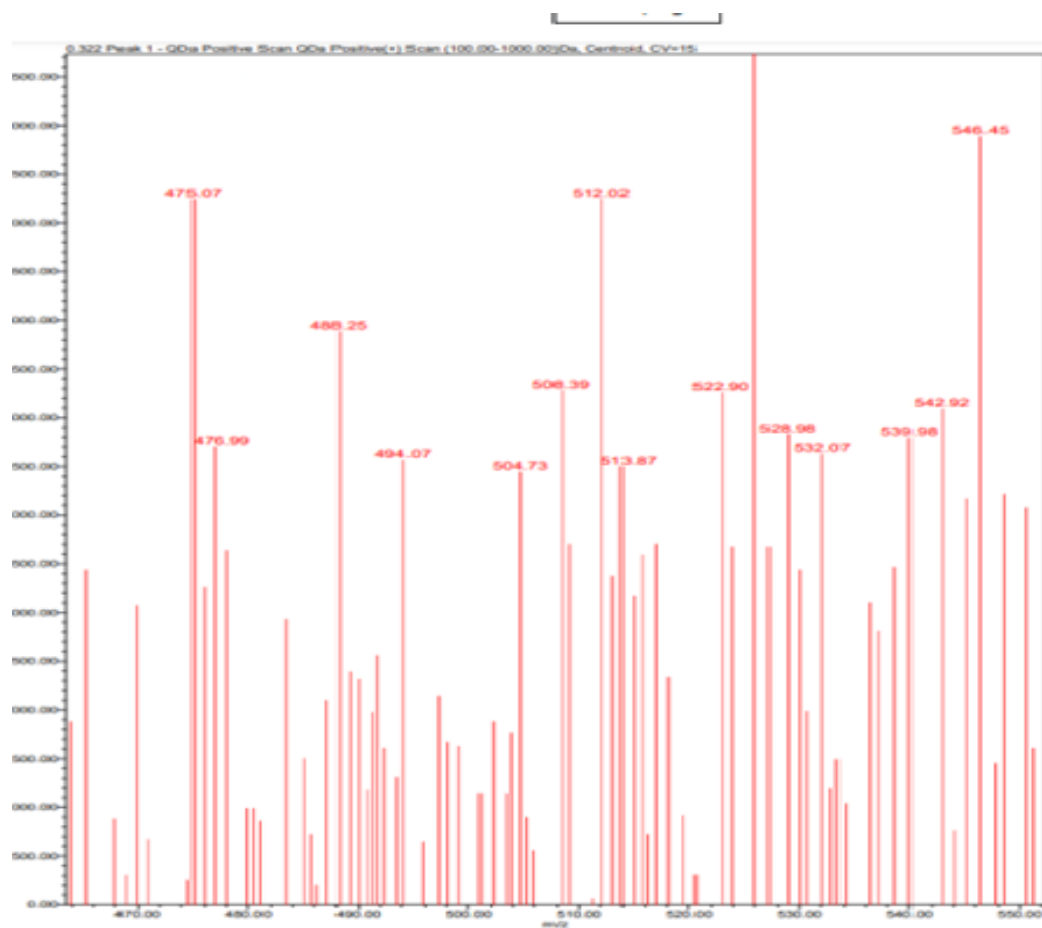
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.42 (s, 5H), 9.29 (d, *J* = 8.6 Hz, 5H), 8.40 (d, *J* = 15.8 Hz, 11H), 8.21 – 8.05 (m, 17H), 8.05 – 7.80 (m, 45H), 7.72 – 7.39 (m, 94H), 7.48 – 7.13 (m, 47H).

Image 3. (3-(2-bromophenyl)-5-phenyl-1H-pyrazol-1-yl)(2-(3-nitrophenyl)quinolin-4-yl) methanone

### Mass Interpretation



**Image 4. Mass spectrum of (3,5-diphenyl-1H-pyrazol-1-yl)(2-phenylquinolin-4-yl)methanone 450.89(100 %, base peak); 445.18(32.85%); 441.05(75.07%); 440.06(45.7%); 431.74(60.0%); 417.28(91.4%); 372.08(37.14%);362:361.14**

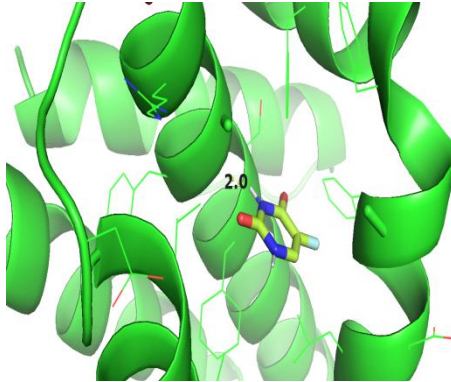


**Image 5. Mass spectrum of (3-(3-chlorophenyl)-5-phenyl-1H-pyrazol-1-yl)(2-(2-chlorophenyl)quinoline-4-yl)methanone  
546.45(100 %, base peak); 542.92(32.85%); 539.98(75.07%); 532.07(45.7%); 528.08(60.0%);  
522.90(91.4%); 513.87(37.14%);512.02:508.39 :504.73:494.07:488.25:476.99:475.07**

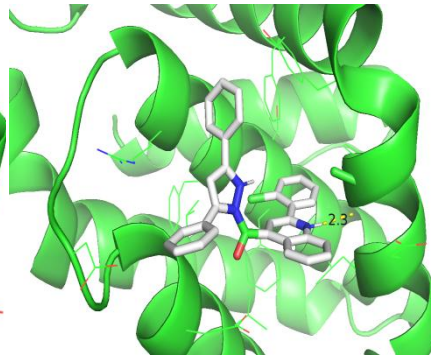
**Table 2. Docking score of substituted quinoline derivatives (pdbcode )**

| <b>Sr. No.</b> | <b>Compound</b> | <b>Binding Affinity (Kcal/mol)</b> |
|----------------|-----------------|------------------------------------|
| 1              | Control         | -                                  |
| 2              | 5FU             | -9.1                               |
| 3              | 4a              | -10.9                              |
| 4              | 4b              | -10.3                              |
| 5              | 4c              | -10.3                              |
| 6              | 4d              | -10.3                              |
| 7              | 4e              | -10.1                              |
| 8              | 4f              | -9.5                               |
| 9              | 4g              | -9.4                               |
| 10             | 4h              | -8.9                               |

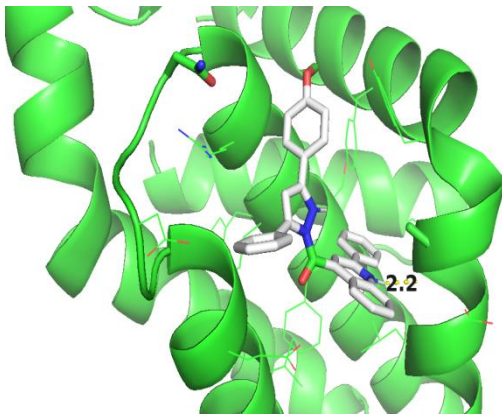
**Docking Modelling Image**



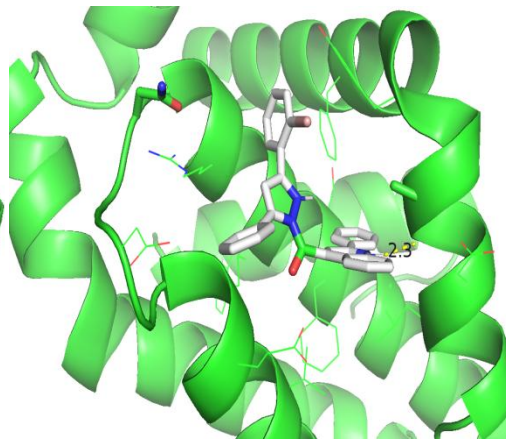
**Image 6. 5-Fluorouracil**



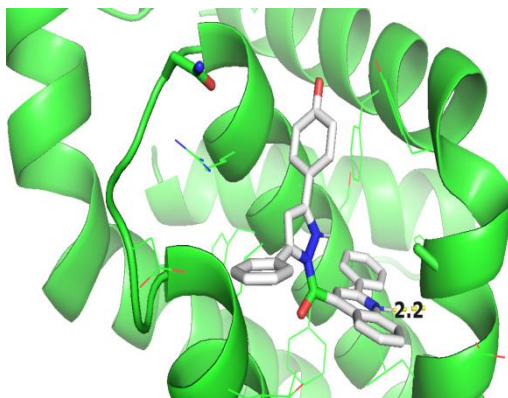
**Image 7. 4a**



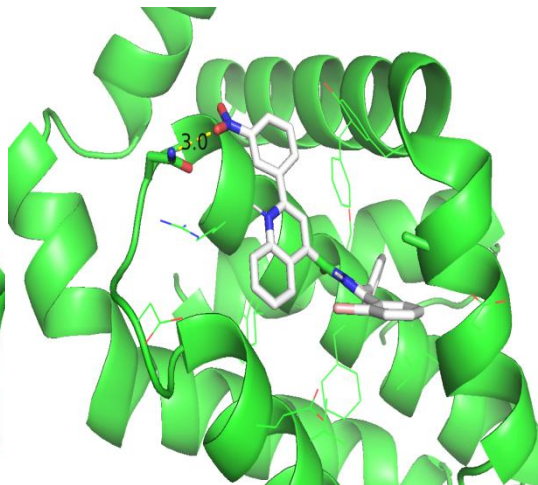
**Image 8. 4b**



**Image 9. 4c**



**Image 10. 4d**



**Image 11. 4e**

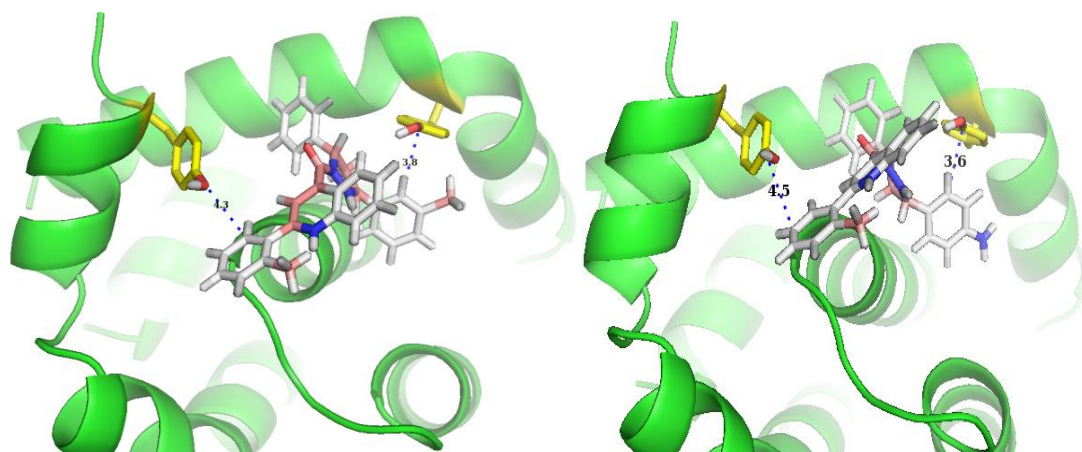


Image 12. 4f

Image 13. 4g

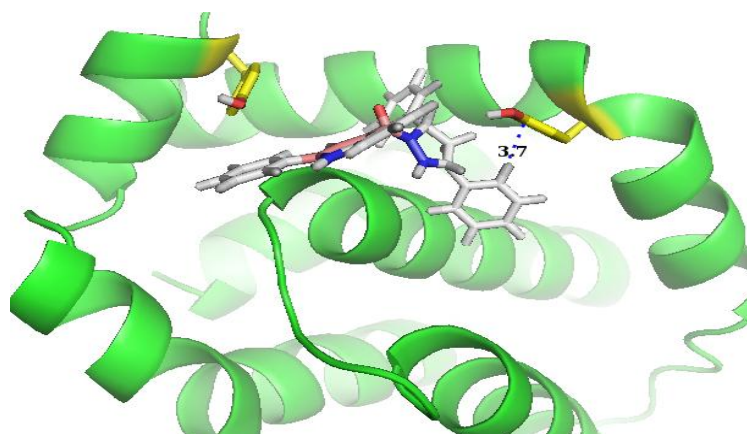


Image 14. 4h

Table 3. Percentage inhibition of synthesized substituted quinoline derivatives

| Sr. No. | Synthesis Compound | Binding Affinity (Kcal/mol) | % Inhibition |       |       |
|---------|--------------------|-----------------------------|--------------|-------|-------|
|         |                    |                             | 10           | 30    | 100   |
| 1       | Control            | -                           | -            | -     | -     |
| 2       | 5FU                | -9.1                        | 62.02        | 68.75 | 75.22 |
| 3       | 4a                 | -10.9                       | 58.62        | 61.80 | 64.05 |
| 4       | 4b                 | -10.3                       | 57.42        | 58.22 | 58.75 |
| 6       | 4c                 | -10.3                       | 46.28        | 51.59 | 57.29 |
| 5       | 4d                 | -10.3                       | 42.83        | 50.13 | 51.98 |
| 7       | 4e                 | -10.1                       | 43.89        | 44.16 | 48.14 |
| 8       | 4f                 | -9.5                        | 40.18        | 42.57 | 46.81 |
| 9       | 4g                 | -9.4                        | 39.52        | 42.70 | 46.00 |
| 10      | 4h                 | -8.9                        | 30.76        | 35.14 | 38.72 |

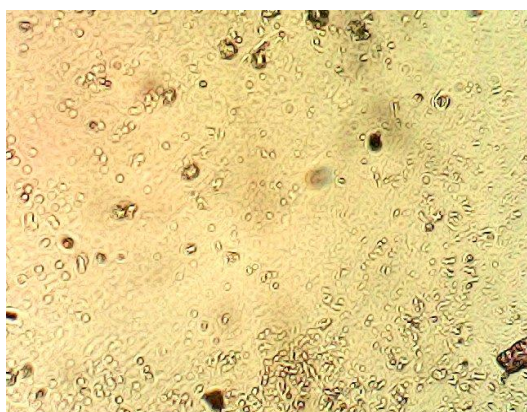


Image . 5-Fluorouracil

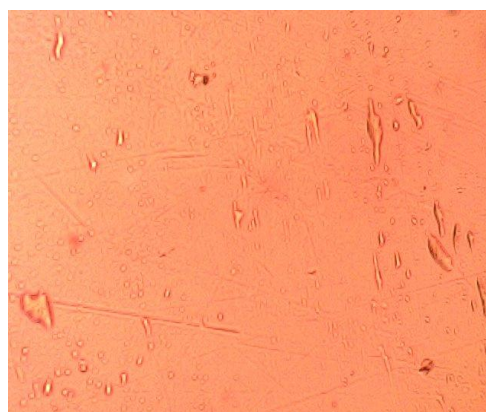


Image 16. 4a

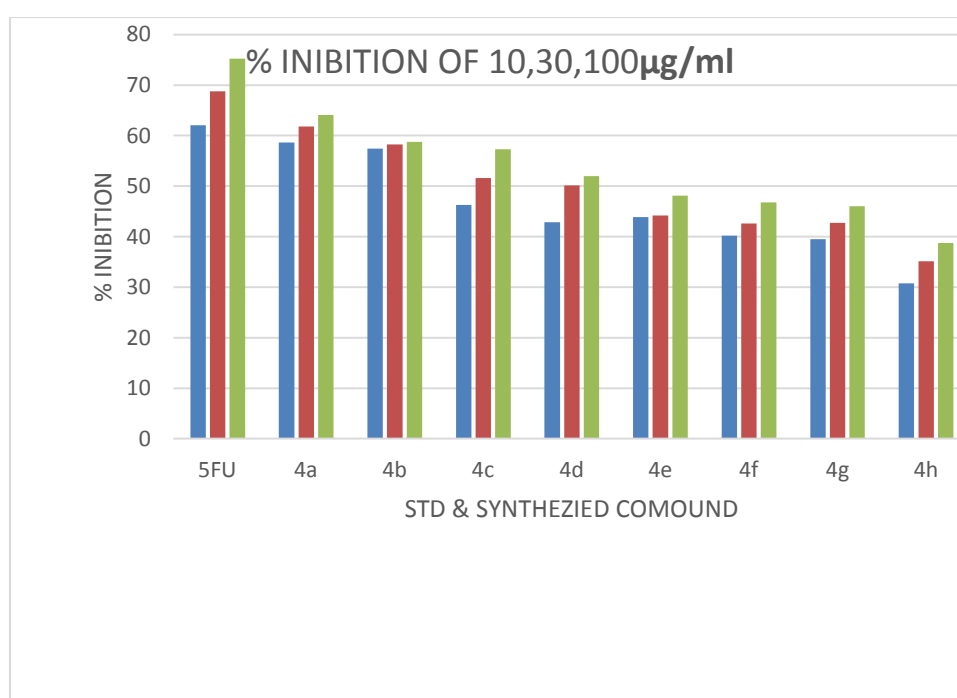


Image 16. Graphical representation of the anticancer activity of synthesized Substituted quinoline derivatives

## 5. CONCLUSION

The synthesized compounds are solids and having melting point in the range 150-200°C. The physical properties of the compounds synthesized are given in Table 1. Among the various synthetic approaches followed in past research works on quinoline the easiest method i.e. three component cyclocondensation of aromatic aldehyde, purvic acid and aniline in presence of ethanol was followed for synthesis of ester. The synthesized quinoline ester was reacted with hydrazine hydrate to obtain the quinoline carbohydrazide. The final quinoline derivatives were synthesized by reaction of

quinoline carbohydrazide with chalcones in acetic acid. The compounds formed were confirmed by physical and spectral data. All the compounds were subjected to anticancer activity by MTT assay. The MCF-7 (Human breast cancer cell line) was tested. Comparison was done with the standard 5FU drug. The results of the anticancer activity are given in Table 3. The compounds correlate with docking, modelling and activity 4a have showed greater as compared to other derivatives. 4b,4c,4d moderate activity and 4e,4f,4g and 4h show good activity according to 30 and 100 µg/ml as compared to std. 5-Fluorouracil drug.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Rashid HU, Muhammad YY, Wangand L, Jiang J. Eur.J.Med.Chem. 2019;161:205–238.
2. Counihan JL, Grossman EA, Nomura DK. Chem. Rev. 2018;118:6893–6923.
3. Mohamed FA. Molecular targets and anticancer activity of quinoline–chalcone hybrids literature review Royal Society of Chemistry, RSC Adv. 2020;10:31139–31155.
4. Johan van Meerloo, Cell Sensitivity Assays, The MTT Assay, Reaserch gate. PubMed. 2015;731:237-247.
5. Wadheretal SJ. Synthesis and biological evaluation of Schiff bases of cinchophen as antimicrobial agents, International Journal of Chem. Tech. Resarch. 2009; 1(4):1297-1302.
6. Ilango K. Design, Synthesis and Biological Screening of 2, 4- Disubstituted Quinolines, Austin Journal of Analytical and Pharmaceutical Chemistry. 2015;2(4): 1-4.
7. Kokare CR. Pharmaceutical Microbiology Experiment and techniques, 2<sup>nd</sup> Edition, Carrier Publication; 2007.
8. Waterbeemd HV, Rose v. Quantitative Approaches to Structure-Activity relationships. The Practice of Medicinal Chemistry. 2003;351.
9. Teodoro ML, Phillips GN, Kaviraki LE. Molecular docking: A problem with thousands of degree of freedom
10. Molecular Design Suite, V Life Technologies, Pune, India.
11. Furniss BS, Hammaford AJ, Smith WG, Tatchell AR. Practical organic chemistry, Vogel's text book. 1168.
12. Gerhard H Vogel, Drug Discovery and Evaluation Pharmacological Assays Second Edition, 487.
13. Indian Pharmacopoeia, Govt. of India, Ministry of Health and Family Welfare, Delhi, Published by Controller of Publication, Delhi. 1996;2.
14. Albert Levai, Jozsef Jeko. Synthesis of carboxylic acid derivatives of 2-pyrazolines, ARKIVOC. 2007;(i):134.
15. Chimmiri A, Gitto R. Heterocycles. 1993; 36:865.
16. Henke BR, Aquino CJ. J Med Chem. 1997; 40:2706.

© 2022 Honde and Kunkulol; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*

*The peer review history for this paper can be accessed here:*  
<https://www.sdiarticle5.com/review-history/81022>