Medicinal Chemistry & Drug Discovery

# Design, Synthesis and Biological Evaluation of Tetrahydrodibenzo[b,g][1,8]napthyridinones as Potential Anticancer Agents and Novel Aurora Kinases Inhibitors

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Aurora kinases inhibitors A and B have elucidated a vital role within the carcinogenesis and metastases of assorted sort of cancer. Variety of novel methodologies of drug style and support of potential enzyme inhibitors square measure listed in clinical trials, probably there's no advanced clinical role for kinases because the key targets for developing drug than in cancer medical care until date. Therefore, we have designed and synthesized novel tetrahydrodibenzo[b,g] [1,8] naphthyridinone molecules victimisation L-Proline in ethanol as associate adept organocatalyst for one-pot synthesis. This methodology is delicate, competent, high yielding, and also the product was directly crystallized from hot ethanol, in addition to this synthesized compounds were biologically evaluated for anticancer activity against human respiratory organ cancer (A549), human hepatocellular liver cancer (HepG2) and human cervical cancer animal tissue (HeLa) cells victimisation MTT assay victimisation VX-680 as normal drug, specifically inhibiting Aurora A and Aurora B kinases. The compounds 4 f,4 h and 4k were found to be sensible anticancer agents against the complete selected cancer cell lines. The compound 4k was found to be the foremost potent anticancer compound among the synthesized derivatives with IC50 value 16.22 μM, 20.14 μM and 5.32 μM against A549, HepG2 and Hela cell lines. The potent compounds 4 f,4 h and 4k were specifically inhibiting Aurora A and Aurora B kinases. The compound 4k was found to be potent Aurora kinases substance with IC50 value 24 nM and 58 nM against Aurora A and Aurora B, respectively. The results of Aurora enzymes restrictive activities recommend that the synthesized compounds exert their anticancer activity by inhibiting aurora kinase inhibitors.

## Introduction

Cancer can be a state of disorder where un-manipulate mobile proliferation occurs in body. Over 23-million human beings were recognized with cancer in document published with the aid of most cancers studies UK. Among them, one 0.33 of most cancers patients aren't expected to survive.[1] These numbers make cancer the second most prevalent reason for dying in current scenario. Developing a lead strategies are presently designed for remedy over conventional systemic chemotherapy has been difficult work to conquer this problem. Aurora-kinase inhibitors furthermore played crucial position in improvement of anti-most cancers agents. Recently aurora serine-threonine kinases circle of relatives emerged as key regulators in cell cycle control and mitosis.[2,3] Several structurally various inhibitors of Aurora kinases with top notch anti-tumor hobby are identified, some of which have reached scientific evaluation, like VX-680, PHA-739358, AT9283, MNL8054 (Figure 1).[4–7]

A key challenge among the clinical assessment is to identify the foremost economical combination of enzyme targets then develop treatment mixtures for targeted cancer. The aurora kinases (aurora A, B, and C) area unit a family of threeextremely homologous serine-threonine supermolecule kinases that play a key role in control the cell divisionmethod.[8] The biological roles of Aurora A and B area unitknown, and so the role of Aurora C remains unclear. The expression and activity of Aurora kinases area unit tightly associated with cell cycle.[9] The two major aurora kinases, Aurora A and B, have distinct roles in cell division. Aurora A is said to cytoplasm maturation and separation and thereby regulates spindle assembly and stability.[10] Liberation of cell cycle is seen patentlyonce level of aurora kinases increase and therefore these kinases area unitnecessary targets for researchers to hunt out little molecules to inhibit over expression of Aurora kinases.[11] Aurora-B inhibition ends up in a failure to biorientate chromosomes, flusteredbiological process in cell culture. Because of this inhibition, it creates polyploidization and cell death in p53-proficient additionally as deficient cells.[12–15]

Given the high potential of Aurora enzymes in human cancers and flourishing development of the varied Aurora kinase

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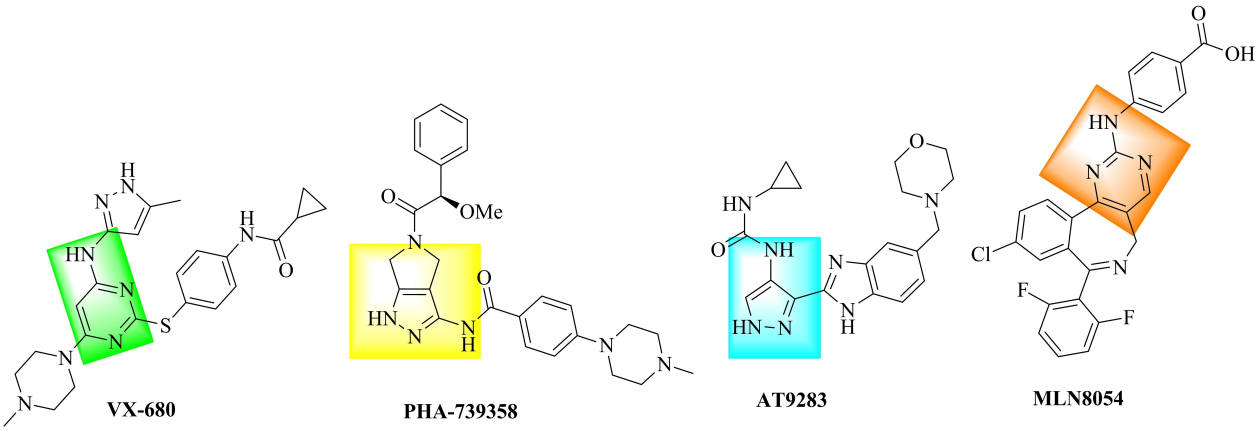



**Figure 1.** Aurora kinases inhibitors currently under clinical evaluation.

inhibitors, to spotlittle molecular lead compounds. Functionalized heterocyclic building blocks area unit of monumental implication for each organic and healthful chemists and their synthesis continues to represent a challenge from the artificial perspective.[16] Recently Morteza Shiri and coworkers reported the synthesis of novel functionalized pyrazolo-pyranoquinoline and tetrahydrodibenzo-[1,8]naphthyridinone derivatives.[17] 1,8-Naphthyridines and pyrano[2,3-b]quinolines area unit of interest as a result ofthey arenecessary subunits of the varied natural and artificial compounds.1,8-Naphthyridine derivatives have shown a broad vary of fascinating biological activities, like analgesic,[18] antiaggressive,[19] antiinflammatory,[20] antitumour,[21] medication,[22] antineoplastic,[23] medication,[24] antiallergitic,[25] and antimalarial drug properties.[26] Furthermore, 1,8-naphthyridine derivatives documented as fluorescent dyes,[27] and sensors,[28] thanks to their optical properties. It's anticipated that the mixing of the 1,8-naphthyridines and pyrazolone moieties resulting intetrahydrodibenzo[b,g] [1,8]naphthyridinone scaffolds might be fascinating and useful from the biological purpose of read by molecular crossing approach. It's stunning that there's no compound possessing such a molecular skeleton accordinginside the literature to date and in continuation of our recent work aiming at the synthesis of a range of heterocyclic systems with exceptional biological importance.[29]

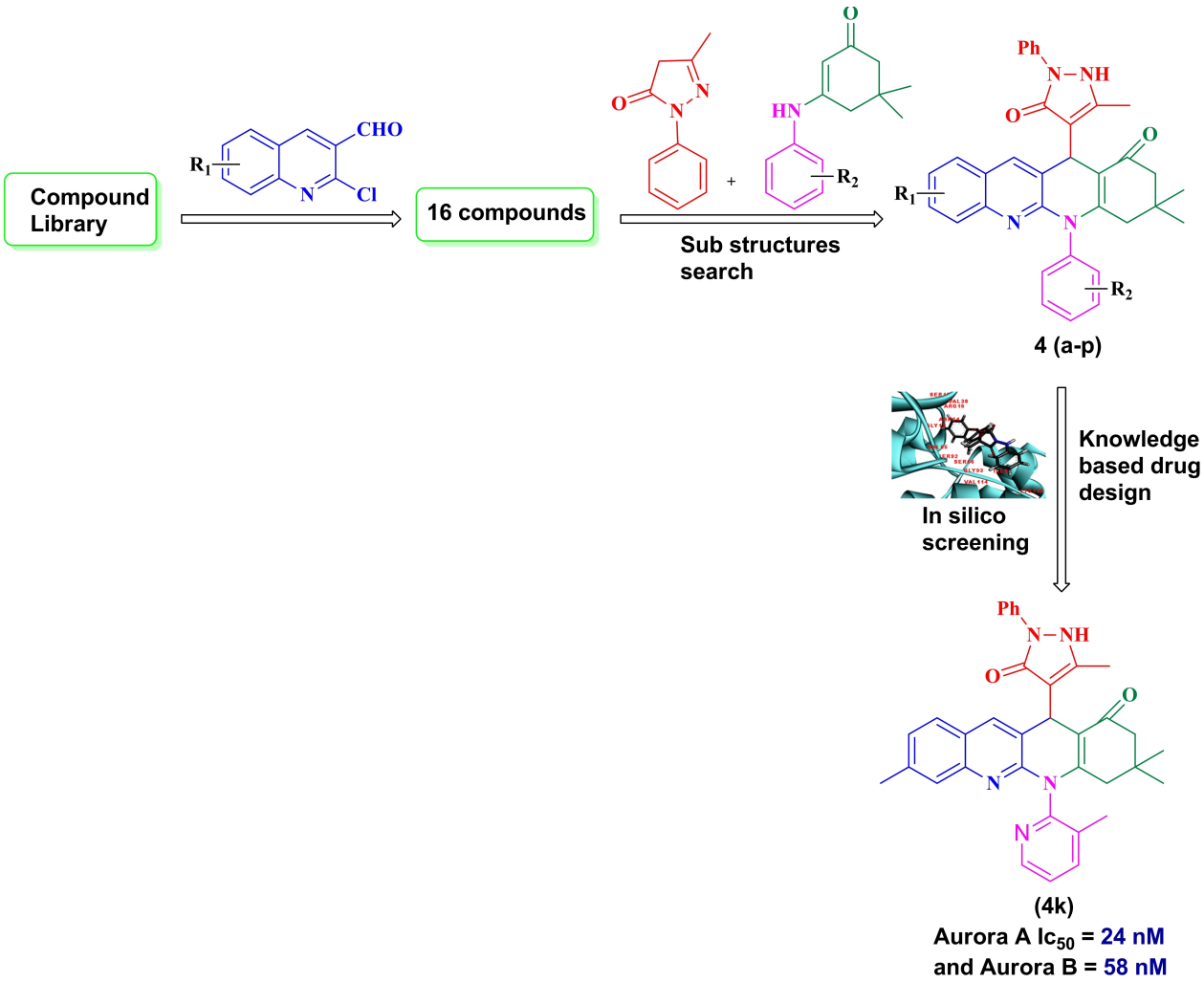
In this paper, we have a tendency to exemplify the finding of a new series of tetrahydrodibenzo[b,g] [1,8]naphthyridinone derivatives with use of L-Proline as associate degreeskilled organocatalyst by exploitationone in every ofthe foremost promising approaches to the presentform ofeconomical synthesis depends on multicomponent reactions (MCRs) which might be accustomed generate a library of compounds with a minimum variety of steps and high atom economy,[30] and as novel Aurora enzyme inhibitors A and B exploitation knowledge-based style and in silico molecular mooragearist9.1 exploitation Glide v. 6.8 (Schrodinger LLC). Screening of our observational, known compound **4k**, its restrictive effects of cell growth and skill to inhibit Aurora A and Aurora B enzyme activity exploitation cell-based assays with IC50 value24 nM and 58 nM against Aurora A and Aurora B, respectivally (Scheme 1).

## Result and discussion

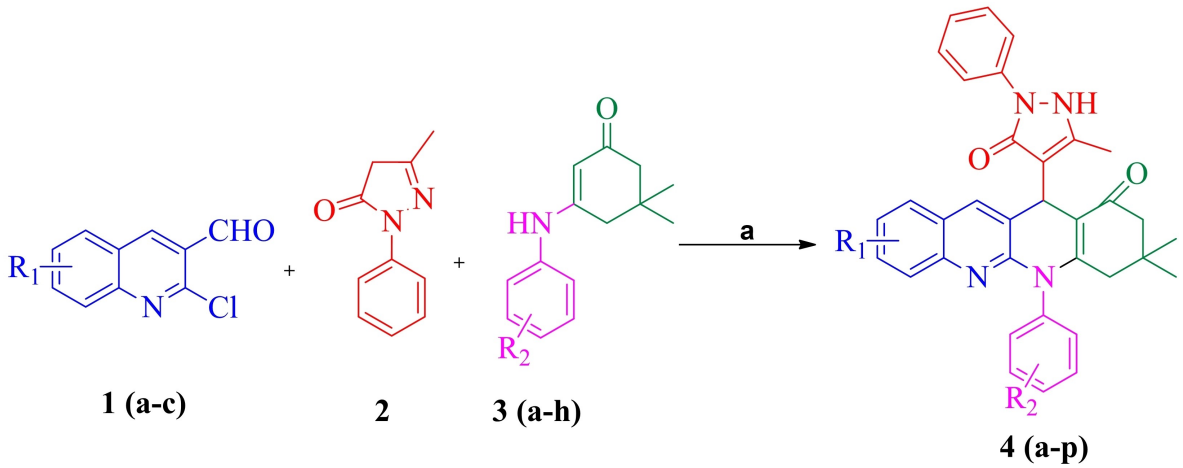
### Chemistry

The general synthetic route for these new functionalized tetrahydrodibenzo[b,g] [1,8]naphthyridinone derivatives is illustrated in (Scheme 2). The 2-Chloroquinoline-3-carbaldehydes, are key moieties used for the formation of various heterocyclic molecules. The treatment of dimedone with aryl amines generated amine**3** **(a–h)** via nucleophilic substitution of dimedone within the presence of variedphenylamine,[31] afterward, the reaction of 2-chloroquinoline-3-carbaldehydes **1 (a–c)**, phenyl pyrazolone **(2)** compounds with the **3 (a–h)** afforded tetrahydrodibenzo[b,g] [1,8]naphthyridinone derivatives withL-proline as a organocatalyst in ethanolbelow reflux condition. Initially 2-Chloroquinoline-3-carbaldehyde **(1 a)**, phenyl pyrazolone **(2)**, and enaminone **(3 a)** were designated as model substrates and evaluated belowvaried conditions (Scheme 2). The impact of solvent and catalysts were evaluated for this reaction, and results were summarized in (Table 1). It had been found that fermentation alcohol as solvent provided highest yield those found than the alternative organic solvents like $CH_3CN$, DMF, THF, Toulene, and $CHCl_3$ (Table 1, entries 6–10). To extend the yields, we have a tendency to explore this reaction mistreatmentvaried catalysts. Some bases like $Cs_2CO_3$, $K_2CO_3$, $Et_3N$ and Lewis acid like $AlCl_3$ were ineffective (Table 1, entries 1–4). Remarkably, L-proline was recognized because theoptimum catalyst for the synthesis of **4 a** (Table 1, entry 11). What is more, we have a tendency to test the amount of L-proline required for this reaction. The results incontestable that 15 mol% of L-proline at reflux in fermentation alcoholis perfectto hold out this reaction in higher yields.

We have studied the electronic result of the substituent on the reaction. It had beenascertained that 2-chloroquinoline-3-carbaldehydes either electron-withdrawing or electron-donating teams on aldehyde ring were tolerated beneath the

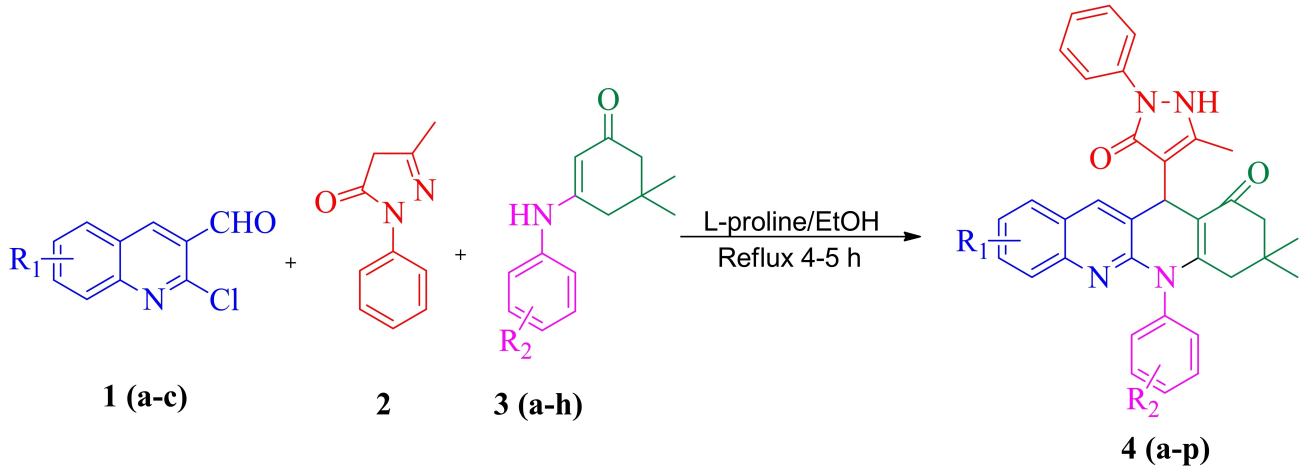


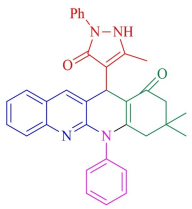

**Scheme 1.** Flowchart depicting the process of discovery of novel tetrahydrodibenzo[b,g] [1,8]naphthyridinone-based Aurora kinase inhibitor Aurora A and Aurora B, **4 k**.

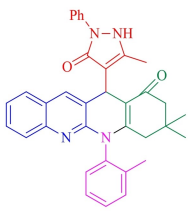


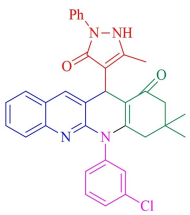

**Scheme 2.** Reaction conditions: a) L-proline/EtOH; Reflux 4–5 h.

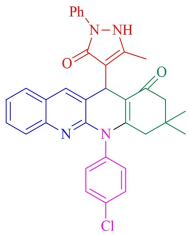
**Table 1.** One-pot multicomponent synthesis of new tetrahydrodibenzo[ b,g][1,8]naphthyridinone derivatives **4 (a–p).**

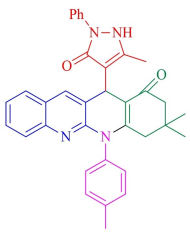


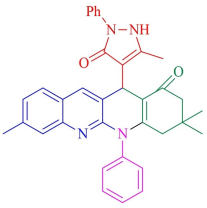


4a (4-5 h, 95%)
M.P. >300 °C

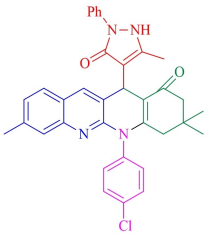

4b (4-5 h, 84%)
M.P. 284-286 °C

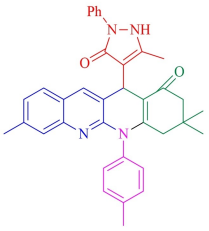

4c (4-5 h, 90%)
M.P. 280-282 °C

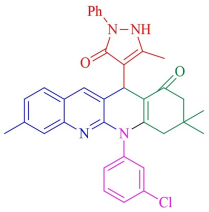

4d (4-5 h, 92%)
M.P. 292-294 °C

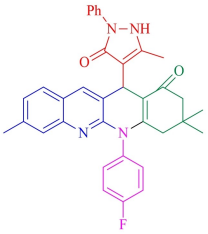

4e (4-5 h, 96%)
M.P. >300 °C

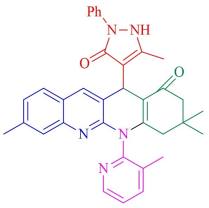

4f (4-5 h, 90%)
M.P. >300 °C

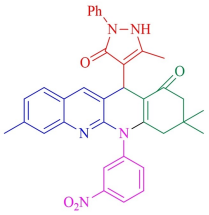

4g (4-5 h, 78%)
M.P. >300 °C

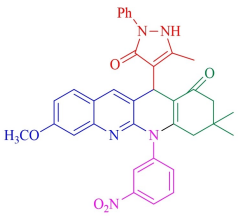

4h (4-5 h,70%)
M.P. 286-288 °C

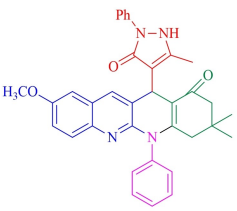

4i (4-5 h, 86%)
M.P. >300 °C

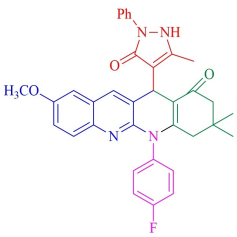

4j (4-5 h, 78%)
M.P. >300 °C

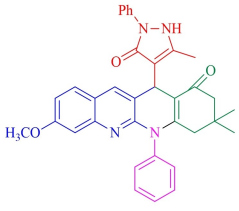

4k (4-5 h, 88%)
M.P. 290-292 °C


4l (4-5 h, 86%)
M.P. 298-300 °C


4m (4-5 h, 76%)
M.P. 280-282 °C


4n (4-5 h, 86%)
M.P. 296-298 °C


4o (5-10 h,
No Product)


4p (5-9 h, 76%)
M.P. >300 °C

reaction conditions affording the specified compounds in sensible yields (Table 2). Here we tend to tried to judge the one-pot four element reaction of 2-Chloroquinoline-3-carbaldehyde (**1 a**), phenyl pyrazolone (**2**), dimedone (**3**) and 4-methyl aminoalkane(**4**)within the presence of L-proline in EtOH under reflux conditions, howeverthe specified product **4 a** was obtained in only just65 % yield (Scheme 3).

## Reaction Mechanism

A proposed mechanism supported the proposal of Fu and colleagues et. al.[32] was shown in (Scheme 4). it wasplanned that L-proline mediates the production of iminium **A**in a very reversible reaction with the 2-chloroquinoline-3-carbaldehyde (**1 a**), the higher reactivity of the iminium ion compared with the carbonyl species may improve knoevenagel reaction with

**Table 2.** Examination of various conditions for the reaction of2-Chloroquinoline-3-carbaldehyde (**1 a**), phenyl pyrazolone (**2**), dimedone (**3**), enaminone (**3 a**), p-Cl-aniline (**4**).[a]

| Entry | Catalyst | Solvent | Yield[b] (%) |
|---|---|---|---|
| 1. | None | EtOH | 30 |
| 2. | $K_2CO_3$ | $CH_3CN$ | 60 |
| 3. | $Cs_2CO_3$ | DMF | 65 |
| 4. | $Et_3N$ | EtOH | 62 |
| 5. | $AlCl_3$ | EtOH | 67 |
| 6. | L-proline (15%) | $CH_3CN$ | 63 |
| 7. | L-proline (15%) | DMF | 60 |
| 8. | L-proline (15%) | THF | 45 |
| 9. | L-proline (15%) | Toulene | 55 |
| 10. | L-proline (15%) | $CHCl_3$ | 51 |
| 11. | L-proline (5%) | EtOH | 62 |
| 12. | L-proline (10%) | EtOH | 80 |
| 13. | L-proline (15%) | EtOH | 92 |

[a]All reactions were carried out using 2-Chloroquinoline-3-carbaldehyde (**1 a**)(1 mmol), phenyl pyrazolone (**2**)(1 mmol), and enaminone (**3 a**) (1 mmol) and EtOH as a solvent under reflux condition,[b]Isolated yield

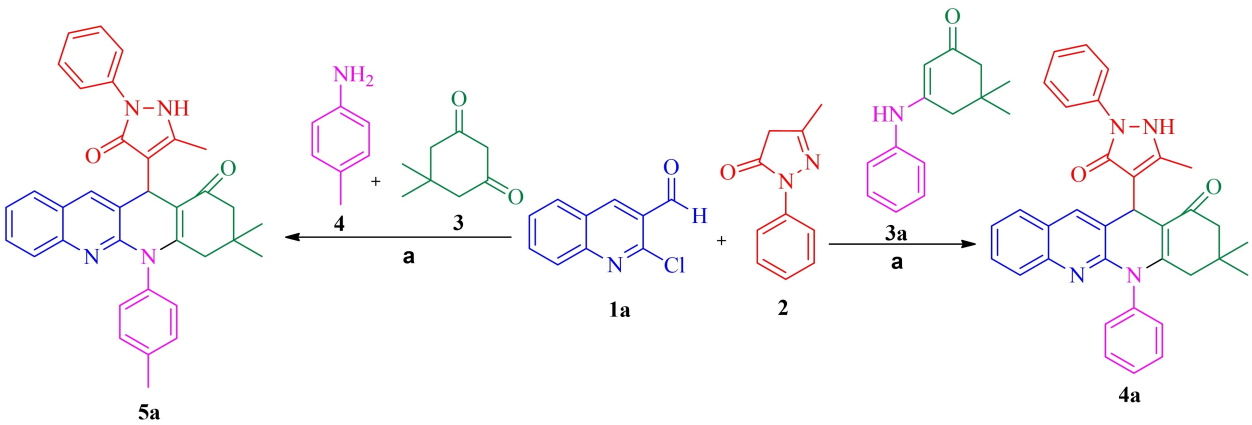
3-methyl-1phenyl-1*H*-pyrazol-5(4*H*)-one (**2**), through intermediate **B**, and once the elimination of L-roline, C can be provided as Associate in Nursing intermediate. The addition of **C** to enaminone (**3 a**) then may accomplish the intermediate **D** that after intramolecular cyclization formed product (**4 a**).

### Molecular Docking Study into Aurora Kinase Enzymes

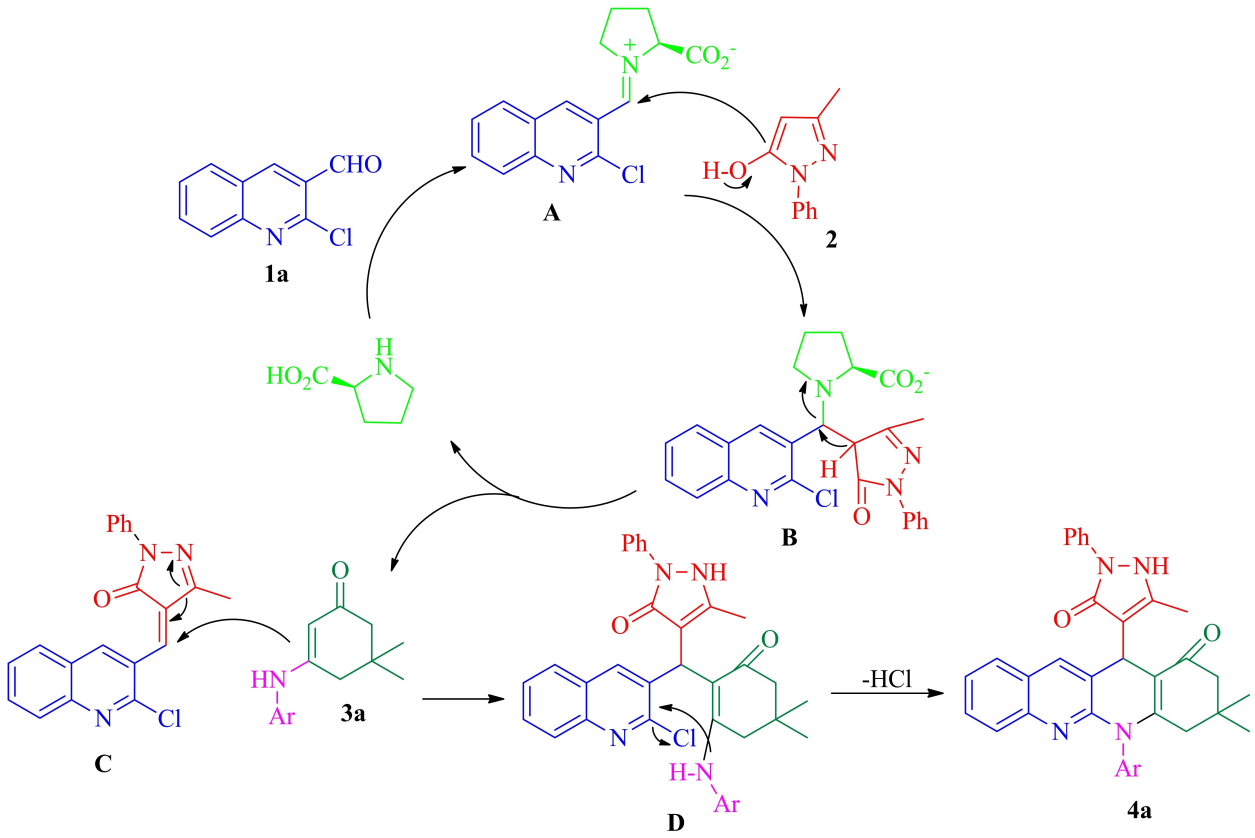
Molecular docking study was performed in Maestro 9.1 using Glide v. 6.8 (Schrodinger LLC). All compounds were built using maestro build panel and optimized to lower energy conformers using Ligprep v3.5 (Schrodinger, Inc., New York, NY, USA). The coordinates for EGFR enzyme were taken from RCSB protininformation Bank and ready for prepared for docking using 'protein preparation wizard' in maestro v10.3. The bond orders and formal charges were extra for hetero-groups and hydrogen's were extrato any or all atoms within the structure. Aspect chains that aren'ton the brink of the binding cavity and don't participate in salt bridges were neutral and termini were capped by adding ACE and NMA residue. Once preparation, the structure was refined to optimize the bond network victimisation OPLS_2005 field. The diminution was terminated once the energy converged or the RMSD reached a most cutoff of zero.30 Å. the extra precision (XP) docking mode for all compounds was performed on generated grid of macromolecule structure.[33] The ultimateanalysis of ligand-protein binding was finished Glide score.[34]

Aurora kinase are a category of serine/threonine protin kinase family that helps within themethod of cell division for healthy cell proliferation. The Aurora A enzyme is related tocytoplasm maturation and separation and thereby regulates spindle assembly and stability. The Aurora B enzymeis a chromosome passenger protein and regulates body segregation and organic process. As Aurora kinase thought to be potential targets for novel tiny molecule inhibitors we have studied docking of designed aurora kinase inhibitors on Aurora A and B kinase enzymes respectively.

The docking studies were performed on Aurora kinase A (PDB ID: 1MQ4) and Aurora kinase B (PDB ID: 4B8 M) respectively. It was observed that the inhibitor molecules were attached into the pocket of the receptor enzyme through different hydrogen and hydrophobic interactions. The binding affinity and pose of compounds **4 f**, **4 h** and **4 k**were found to be correlating with that of the standard molecule pose VX-680 in Aurora A kinase. However, the observations and results of molecular docking with Aurora B kinase was not found satisfactory, hence its results were not taken into consideration. The main amino acid residues of Aurora A kinase which were involved in the hydrogen bonding and Pi- Pi stacking interactions were Lys 141, Phe 144 and Lys 258 respectively. The compound **4 k** was found to be highly potent among the others in the series. It was also observed that the compound **4 k** showed the salt bridge interaction and metal co-ordinate bonding with $Mg^{2+}$ ions which possessed highest binding affinity with good docking score in Aurora A kinase. Figure 2 represents the 2D image of highly potent compound **4 k** whereas Figure 3 represents the 2D image of standard VX-680 docked on Aurora A kinase.




**Scheme 3.** Reaction conditions: a) L-proline/EtOH; reflux 4–5 h.




**Scheme 4.** Proposed mechanism for the synthesis of **4a.**

### In vitro anticancer activity

The synthesized compounds were tested against human lung carcinoma A549 cells, human hepatocellular liver carcinoma HepG2 cells and human cervical carcinoma epithelial HeLa cells using MTT assay. The VX-680 was been used as standard drug. The obtained for the anticancer screening study are as revealed in (Table 3).

**Table 3.** In vitro anti-cancer screening data of compounds **4 (a–n)**[a]

| Sr. No. | Product | Yield (%) | M. P. (°C) | $IC_{50}$ μM A549 | HePG2 | HeLa |
|---|---|---|---|---|---|---|
| 1. | **4a** | 92 | >300 | 34.97±1.2 | 31.06±2.8 | 15.16±3.6 |
| 2. | **4b** | 84 | 284–286 | 32.16±2.4 | 29.88±2.6 | 11.79±1.4 |
| 3. | **4c** | 90 | 280–282 | 34.18±1.8 | 31.33±2.6 | 14.96±1.6 |
| 4. | **4d** | 92 | 292–294 | 33.76±0.9 | 30.12±1.4 | 13.08±2.8 |
| 5. | **4e** | 96 | >300 | 31.14±1.4 | 29.11±3.3 | 12.45±0.2 |
| 6. | **4f** | 90 | >300 | **24.92**±2.2 | **22.44**±2.8 | **7.18**±3.4 |
| 7. | **4g** | 78 | >300 | 26.62±0.8 | 27.24±3.2 | **9.86**±1.8 |
| 8. | **4h** | 70 | 286-288 | **20.08**±3.2 | **21.66**±2.8 | **6.94**±3.4 |
| 9. | **4i** | 86 | >300 | 30.77±1.8 | 28.38±0.7 | 10.98±2.0 |
| 10. | **4j** | 78 | >300 | 27.34±2.6 | 26.72±2.2 | 10.54±3.2 |
| 11. | **4k** | 88 | 290–292 | **16.22**±1.2 | **20.14**±2.6 | **5.32**±3.8 |
| 12. | **4l** | 86 | 298–300 | 25.06±0.2 | 25.82±0.4 | **7.88**±0.6 |
| 13. | **4m** | 76 | 280–282 | 25.98±1.8 | 26.12±1.6 | **8.44**±1.8 |
| 14. | **4n** | 86 | 296–298 | 30.56±0.4 | 27.99±0.8 | 10.76±0.8 |
| 15. | **4o** | NP[c] | NP[c] | – | – | – |
| 16. | **4p** | NP[c] | NP[c] | – | – | – |
| VX-680 | - | – | – | 14.82±1.8 | 18.24±0.6 | 7.99±2.4 |

[a]All reactions were carried out using 2-Chloroquinoline-3-carbaldehyde **1 (a–c)**(1 mmol), phenyl pyrazolone (**2**)(1 mmol), and enaminone **3 (a–h)**(1 mmol) and EtOH as a solvent under reflux condition,[b]Isolated yield, [c]No product

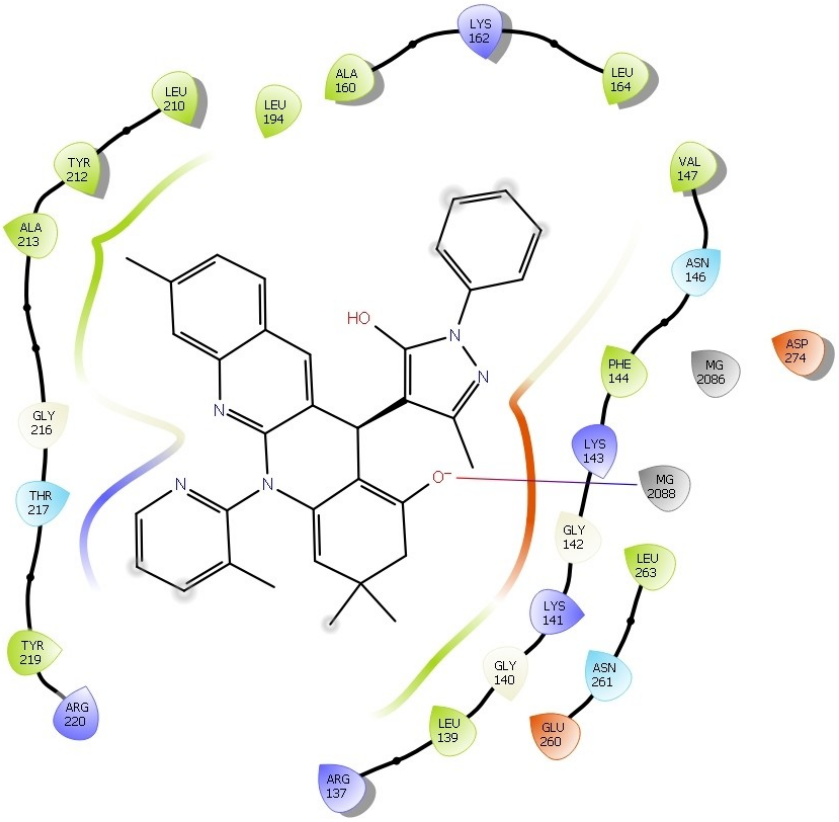



**Figure 2.** 2D image of compound **4**konAurora A kinase.

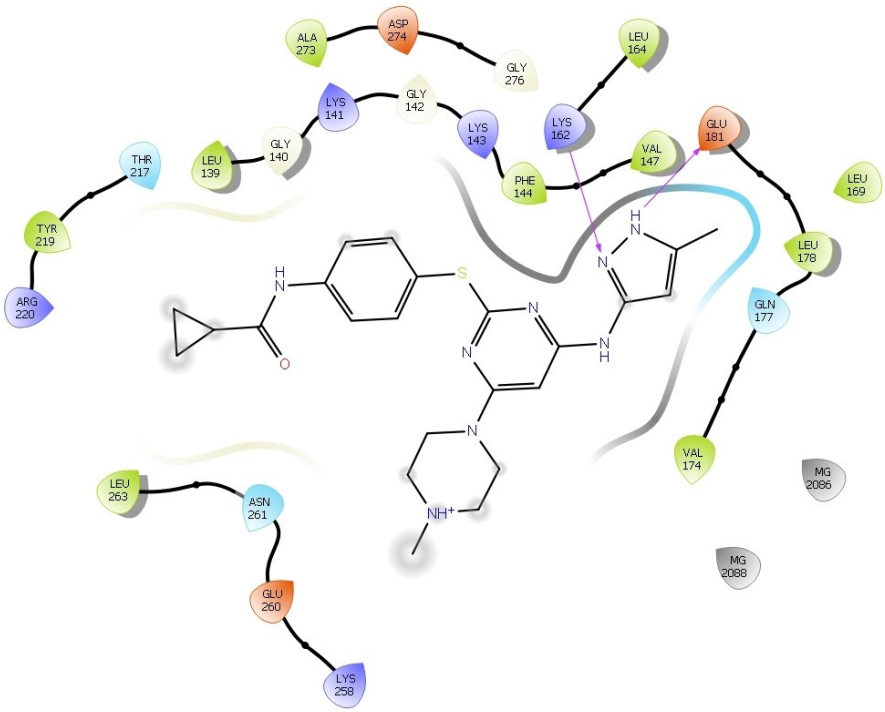



**Figure 3.** 2D image of compound VX-680 on Aurora A kinase.

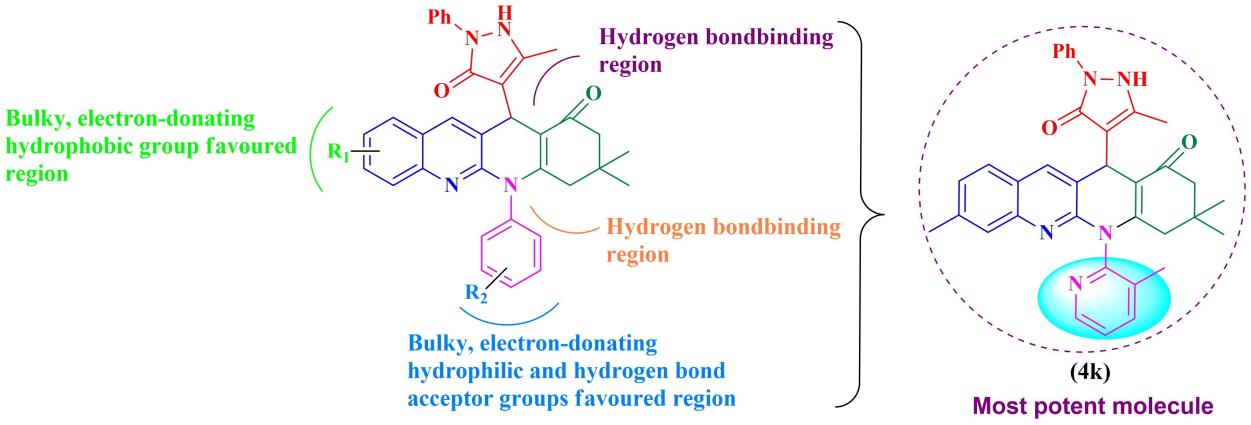



**Figure 4.** Structure-activity relationship taken from present docking studies.

The result of the in vitro anticancer evaluation explains that the synthesized derivatives were found to be good anticancer agents against the HeLa cells when compared to its effect on HepG2 and A549 cells. The compounds **4f**, **4h** and **4k** were found to be good anticancer agents against all the selected cancer cell lines. The compound **4k**i.e. 3,3,8-trimethyl-12-(5-methyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-5-(3-methylpyridin-2-yl)-3,4,5,12 tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2H)-one was found to be the most potent anticancer compound among the synthesized derivatives with $IC_{50}$ value16.22 μM, 20.14 μM and 5.32 μM against A549, HepG2 and HeLa cell lines.

The synthesized derivatives **4f**, **4g**, **4h, 4k, 4l** and **4m** were found to be most active anticancer compounds on HeLa cells. The synthesized derivatives **4h, 4k** and **4l** have shown $IC_{50}$ value6.94 μM, 5.32 μM and 7.88 μM, respectively and were found to be more potent than the standard drug VX-680 ($IC_{50}$ value 7.99 μM) against the HeLa cells.

The compounds **4f**, **4h** and **4k** were found to be good anticancer agents against A549 and HepG2 cell lines. The compound **4h** was found to be second most potent anticancer agents against A549 and HepG2 cell lines with $IC_{50}$ value 20.08 μM and 21.66 μM, respectively.

After delineated study of anticancer evaluation results a structure activity relationship was drawn. (Figure 4). The anticancer activity data helps us to divide the synthesized derivatives into three different series, 5-(substituted phenyl/heteryl)-3,3,8-trimethyl-12-(5-methyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3,4,5,12-tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2H)-one derivatives, 5-(substituted phenyl)-3,3-dimethyl-12-(5-methyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3,4,5,12-tetrahydrodibenzo [b,g][1,8]naphthyridin-1(2H)-one derivatives and 5-(substituted phenyl)-8-methoxy-3,3-dimethyl-12-(5-methyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3,4,5,12-tetrahydrodibenzo[b,g][1,8] naphthyridin-1(2H)-one derivatives. From the above three different series the derivatives of 5-(substituted phenyl/heteryl)-3,3,8-trimethyl-12-(5-methyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3,4,5,12-tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2H)-one were found to be most active than the other two series.

**Table 4.** The kinase inhibitions of selected compounds *in vitro*.

| Compound | $IC_{50}$ nM[a] Aurora A | Aurora B |
|---|---|---|
| **4f** | 24 ± 4.2 | 58 ± 1.2 |
| **4h** | 105 ± 11.1 | 120 ± 8.8 |
| **4k** | 142 ± 1.9 | 96 ± 6.2 |
| VX-680 | 1.5 ± 1.1 | 17.2 ± 0.8 |

[a] The $IC_{50}$ values are the means of at least two experiments.

The compounds bearing the electron donating groups such as methyl **4 (f–l)** or methoxy **4m, 4n** on the naphthyridin ring were found to be more active than those which have unsubstituted naphthyridin ring **4 (a–e)**. The compound **4k**bearing the electron donating group such as methyl on the naphthyridin ring and a pyridine ring which is also been substituted with the electron donating group methyl, which makes this compound most potent anticancer agent from the other derivatives. The compound **4h** which is the second most active anticancer agent consists of methyl group on the naphthyridin ring and a methyl group on the phenyl ring.

In this way we can conclude that the compounds bearing the electron donating group in the structure were found to be more potent than those bearing electron withdrawing groups.

### Aurora kinases inhibitory activities

The potent molecules like **4f, 4h** and **4k** were evaluated for their ability to inhibit aurora enzyme. The VX-680 was been used as drug standard. The inhibition activity against Aurora enzymes was performed by Kinase-Glo luminescent kinase assay in vitro. The results of Aurora kinases inhibitory activities were shown in (Table 4). It may beascertained that the compound 4k was found to be potent Aurora kinases inhibitor with IC50 value 24 nM and 58 nM against Aurora A and Aurora B, respectivally. The oppositetwo tested compounds i.e.**4f** and **4h**even havea capability to inhibit aurora enzyme. The results of Aurora kinase inhibitory activities recommend that the synthesized compounds exert their antitumor activity by inhibiting aurora kinase enzyme.

## Conclusion

We report synthesis and characterization of tetrahydrodibenzo [b,g] [1,8]naphthyridinone derivatives a possibleanticancer agents as a unique Aurora A and Aurora B kinase inhibitors. We offeradditional experimental testimony to support the conclusion that, compound **4k** was found to be potent Aurora kinases inhibitor with IC50 value24 nM and 58 nM against Aurora A and Aurora B, respectively, the foremost molecular target of **4k**in cancer cells. Also, we tend toutilized QSAR and tying upways to explore the structure activity relationship for a series of synthesized tetrahydrodibenzo[b,g] [1,8]naphthyridinone derivatives with wonderful Aurora A and Aurora B kinase inhibitory activities.

## Supporting Information Summary

It contains experiment section including characterization techniques, general procedure for the synthesis of compounds.Spectral data including FT-IR, Mass, $^{1}$H NMR and $^{13}$C NMR spectra.

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## *Conflict of Interest*

The authors declare no conflict of interest.

**Keywords:** Aurora kinases inhibitors · Molecular docking · Multicomponent reaction · Structure activity relationship (SAR) · Tetrahydrodibenzo[b,g] [1,8]naphthyridinone

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