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# ANTI-CANCER DOCKING INVESTIGATIONS, ANTI-OXIDANT PROPERTIES AND MICROWAVE-ASSISTED SYNTHESIS OF 1-(4-((2-((7-HYDROXY-1, 8-NAPHTHYRIDIN-2-YL) AMINO)-6-PHENYLPYRIMIDIN-4-YL) AMINO)PHENYL)-3-ARYLPROP-2-EN-1-ONES

**B. Srinivasa Reddy[1], M. Rajeshwari[2], P. Bhaskar[3], D. Ramesh[4] and E. Laxminarayana[5]***

*[1]Mahatma Gandhi Institute of Technology, Kokapet, Gandipet, Hyderabad - 500075 Telangana Indi*
*Kukatpally, Hyderabad, Telangana, India – 500085*
*[2]Telangana University Dichpally, Nizamabad-503322 Telagana India.*
*[3]Nalla Narasimha Reddy Education Society's Group of Institutions Integrated Campus, Korremula 'X' Road, Chowdariguda (Vill), Ghatkesar (Mandal), Medchal (Dist), Hyderabad. – 500088*
*[4]Department of Chemistry and Pharmaceutical Sciences, Mahatma Gandhi University, Nalgonda-508544, India..*
*[5]Sreenidhi Institute of Science and Technology (Autonomous), Ghatkesar, Hyderabad-501 301 Telangana India.*
*Corresponding author: elxnkits@yahoo.co.in*

**Abstract:**
*This study discuss a reliable, convenient an energy-efficient and environmentally benign synthesis of 2-substituted 1,8-Naphthyridine derivatives under microwave synthesis with excellent yields. This is atom economical method, presented in this communication. The advantages of this protocol are green, clean and efficient, less reaction time, easy workup and high yields, further the compounds tested for antioxidant activity, the compounds* ***5b, 5c, 5d*** *exhibited significant activity.*

**Keywords:** Microwave, Chalcones, Pyrimidine 1, 8-Naphthyridine anti-oxidant activity,

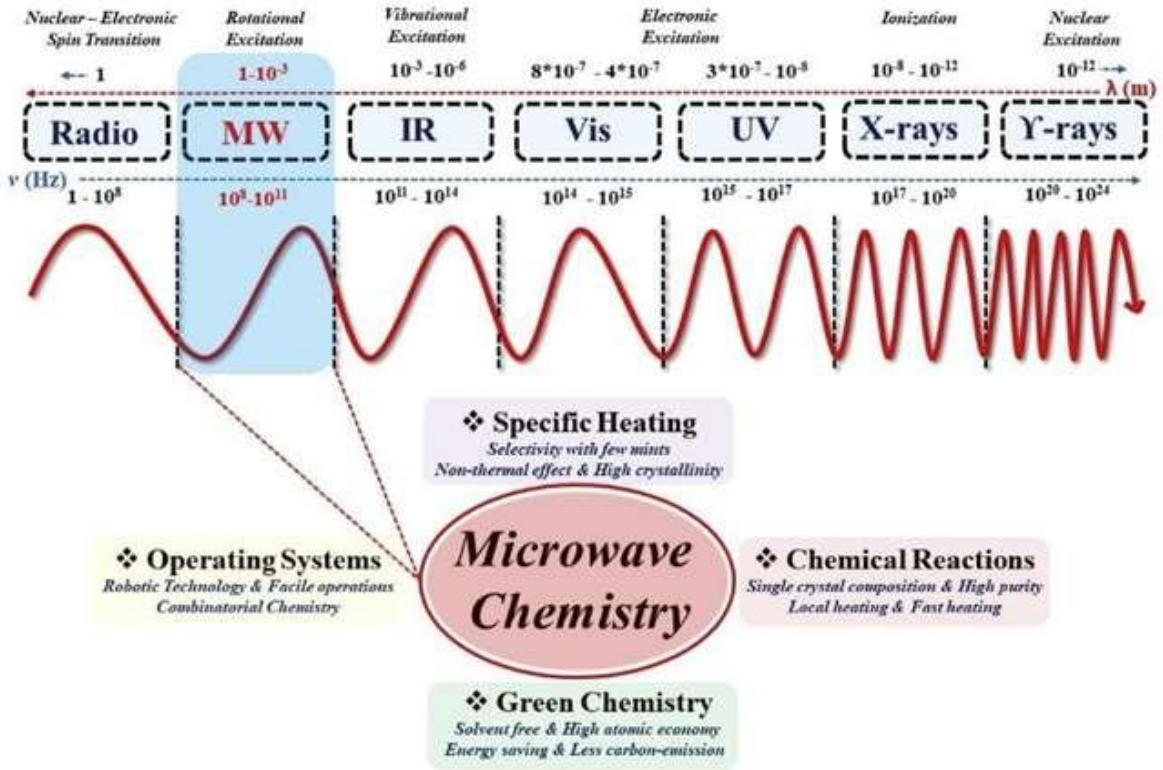
## Introduction:

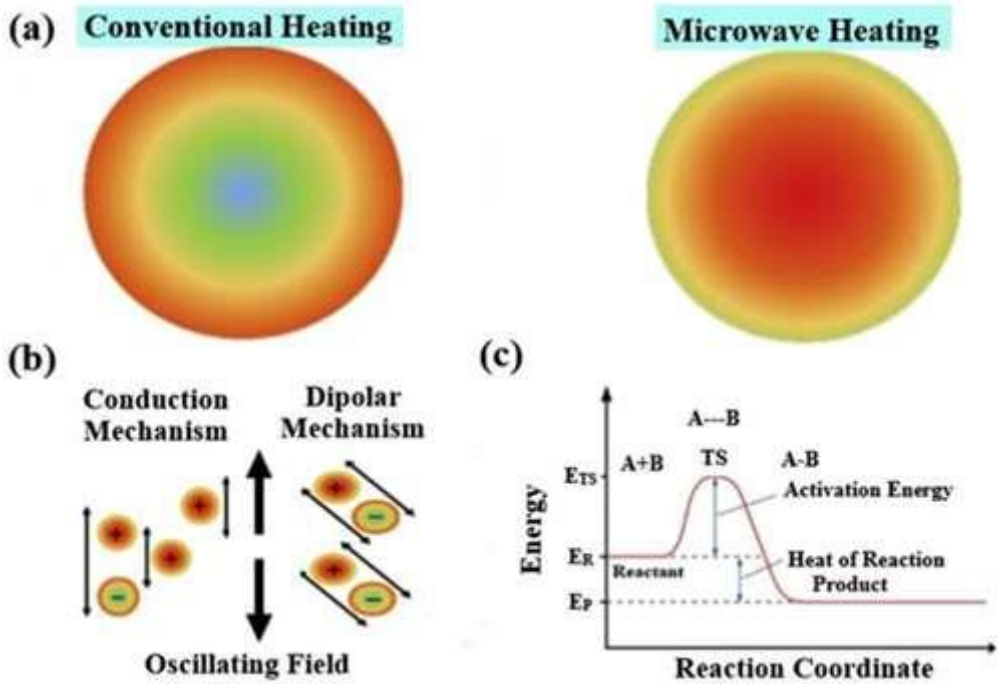
In organic synthesis microwave (MW)[i-iii] applications are widely used in synthetic chemistry advantages of MW assisted synthesis are good product yield, less energy consumes, simple processing and handling. In addition, due to high reaction rates, greater selectivity during the reaction[iv-vii], microwave-assisted synthesis attracted interest. However, under solvent-free conditions, chemical reactions exclude a need for hazardous organic solvents causes environmental pollution[viii-xiv].

Heterocyclic compounds such as amino pyrimidine, chalcone have played an important role in organic chemistry, the presence of reactive α, β-unsaturated carbonyl compounds. Chalcones possess analgesic[xv], antimicrobial[xvi], antioxidant[xvii], antitubercular[xviii], and antihistaminic[xix], anticancer[xx], antidepressant[xxi], etc.

The pyrimidine nucleus present in nucleotides, nucleic acids and alkaloids obtained from tea, cocona and coffee. The Genetic materials are made up of heterocycle rings like cytosine, adenine, uracil thymine and guanine. Six member pyrimidine ring show various properties like anti inflammatory[xxii,xxiii], antimicrobial activity[xxiv], anti plasmodial activity[xxv], antitumor[xxvi], antibacterial[xxvii] and antiviral[xxviii]. But pyrimidine derivatives synthesized using organic solvents and basic catalysts. There are also a number of disadvantages, such as long response time, the need for a high temperature, more complicated recovery, and complex reaction conditions. Organic solvents have toxicity issues, in addition to all of these drawbacks, and these catalysts are more difficult to reuse and recover. A new set of criteria is therefore necessary to prevent any of these drawbacks. Microwave synthesis[xxix] is a new technique that has been established over the last few years. It focuses on the safety of the environment through chemical process engineering that minimises or eliminates the production of hazardous substances. Our interest is synthesis of pyrimidine under microwave with good yields.

The ACS recommended under Green Chemistry the use of 'MW irradiation' or 'catalysts' to decrease the energy needed for the synthesis process. Disadvantages of 'synthetic chemistry' are 'trial-and-error time-consuming' experiments. MW technology advantages are solvent-free reactions, non-toxic, eco-friendly, high purity, reproducibility, high yield.

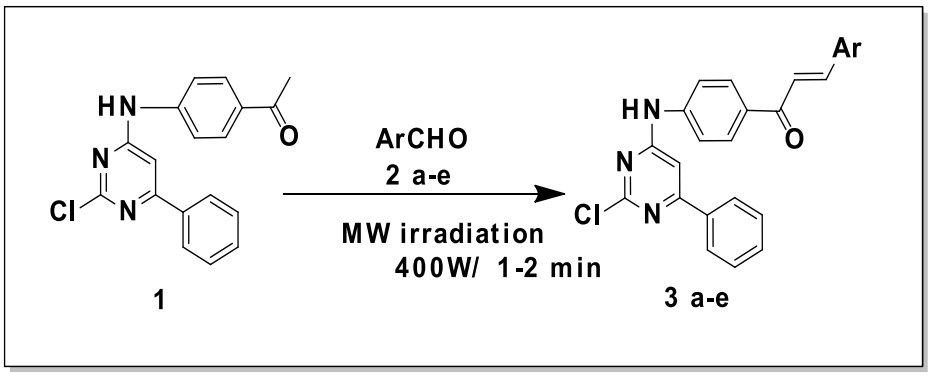





**Results and Discussion:**

In the current study, a series of 2-substituted 1,8-Naphthyridine derivatives we are reported, all the compounds were prepared under microwave irradiation, which configurated in Scheme 1. 1-(4-((2-chloro-6-phenylpyrimidin-4-yl)amino)phenyl)ethanone (**1)** and aromatic benzaldehydes **(2 a-e)** under solvent free conditions gave a series of compound those are **3 a-e** gave in excellent yield.

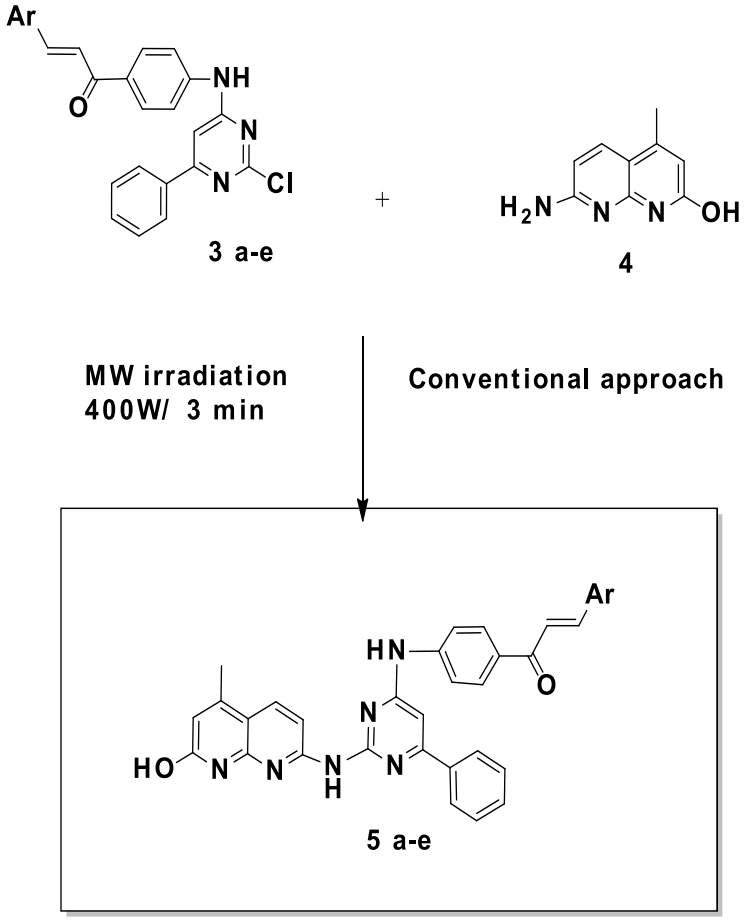
**Scheme-1**




For the synthesis of titled compound **5,** we tried different two methods those are microwave and conventional approaches using different solvents and different temperature, in the conventional method first we have tried with tetrahydrofuran as a solvent and as a base potassium carbonate in the reaction mass, after 9 hr reaction progress was not observed, same in the case of acetonitrile solvent no reaction was observed, when the same method was applied to the in the methanol solvent, reaction progress observed around 10% yield isolated, we have tried in another solvent DMF and potassium carbonate as a base no convincing conversion observed. Further, same compounds were put under MW irradiation to 390 W at 130 $^{0}$C in ethanol and DMF, in the microwave vial, we observed significant progress in the reaction observed in entry 5, 6. When we tried in the solvent free condition potassium carbonate as a base, surprisingly we observed good yields, so in this study revealed that

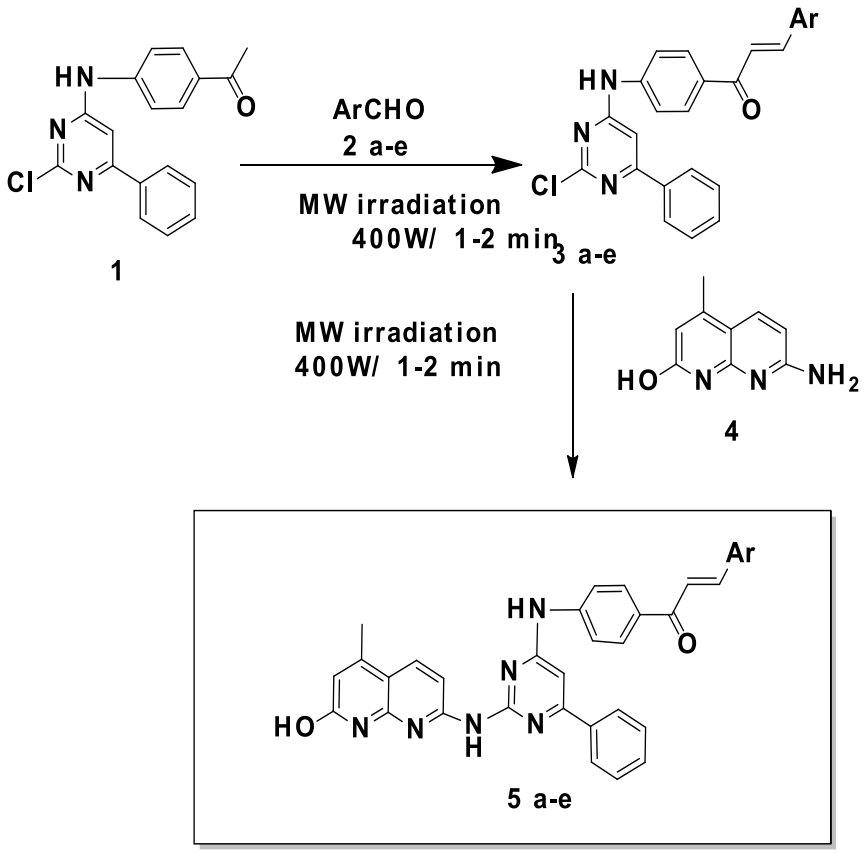
solvent free, neat conditions under MW approaches found to be preferred over conventional method. All the prepared compounds were characterised by, ESI-MS, IR, 1H-NMR.

**Scheme-2**




| Entry | Method | Condition | T(°C) | Time | Yield% |
|---|---|---|---|---|---|
| 1 | Conventional | $K_2CO_3$, THF | 80 | 9 h | No reaction |
| 2 | Conventional | $K_2CO_3$, MeCN | 85 | 8 h | No reaction |
| 3 | Conventional | $K_2CO_3$, EtOH | 95 | 6 h | 10 |
| 4 | Conventional | $K_2CO_3$, DMF | 100 | 4 h | 14 |
| 5 | Microwave | $K_2CO_3$, EtOH | 130 | 3 min | 45 |
| 6 | Microwave | $K_2CO_3$, DMF | 130 | 3 min | 55 |
| 7 | Microwave | $K_2CO_3$, Neat | 130 | 3 min | 78 |

All the reactions, **Scheme-1, Scheme-2**




**Ar = phenyl, 4-bromophenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-hydroxyphenyl,**

**Experimental:**

Solvents and Chemicals were reagent grade and used. M.P were determined on a capillary melting point apparatus. The $^{1}$H NMR were recorded on a Varian 300 MHz spectrometer. Mass spectra were measured on a Jeol JMS D-300 spectrometer. IR were recorded in KBr on Brucher-IFS-66 FTIR spectrophotometer.

**General procedure for the preparation of 1-(4-(2-chloro-6-phenylpyrimidin-4-ylamino)phenyl)-3-arylprop-2-en-1-ones 3a-e**

1 µ moles of compound 1, 1 µ moles of different substituted aromatic aldehydes (**2a-e**), solvent-free condition under microwave irradiation. The microwave oven was programmed at 390 W at 120°C for 2 min. After completion of the reaction as indicated by T.L.C. The solvent distilled under vacuum evaporated and added water. The ppt solid was collected by filtration

**1-(4-(2-chloro-6-phenylpyrimidin-4-ylamino)phenyl)-3-phenylprop-2-en-1-one (3a)**

IR ( KBr, cm$^{-1}$): 1600 (C=N), 1750 (C=O), 3300 (N-H), 3118; $^{1}$H-NMR: 8.30 (1H, broad, -NH-), 7.89 (1H, doublet, -CH-), 7.60 (1H, doublet, -CH-), 7.20-7.60 (12H, multiplet, Ar-H), 6.29-6.69 (3H, multiplet, Ar-H); ESI-MS: *m/z*, 412 (M+H).

**1-(4-(2-chloro-6-phenylpyrimidin-4-ylamino)phenyl)-3-(4-bromophenyl)prop-2-en-1-one (3b)**

$^{1}$H-NMR: 8.40 (1H, broad, -NH-), 7.89 (1H, doublet, -CH-), 7.59 (1H, doublet, -CH-), 7.20-7.60 (11H, multiplet, Ar-H), 6.40-6.59 (3H, multiplet, Ar-H); ESI-MS: *m/z*, 491 (M+H).

**1-(4-(2-chloro-6-phenylpyrimidin-4-ylamino)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (3c)**

$^{1}$H-NMR: 8.35 (1H, broad, -NH-), 7.92 (1H, doublet, -CH-), 7.66 (1H, doublet, -CH-), 7.19 -7.56 (11H, multiplet, Ar-H), 6.35-6.65 (3H, multiplet, Ar-H); ESI-MS: *m/z*, 447 (M+H).

**1-(4-(2-chloro-6-phenylpyrimidin-4-ylamino)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (3d)** $^1$H-NMR: 8.29 (1H, broad, -NH-), 7.89 (1H, doublet, -CH-), 7.59 (1H, doublet, -CH-), 7.20 -7.49 (9H, multiplet, Ar-H), 6.29-6.69 (5H, multiplet, Ar-H), 3.69 (3H, singlet, -$OCH_3$); ESI-MS: *m/z*, 442 (M+H).

**1-(4-(2-chloro-6-phenylpyrimidin-4-ylamino)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (3e)** $^1$H-NMR: 9.09 (1H, broad, -OH), 8.29 (1H, broad, -NH-), 7.89 (1H, doublet, -CH), 7.59 (1H, doublet, -CH-), 7.20 -7.49 (9H, multiplet, Ar-H), 6.29-6.80 (5H, multiplet, Ar-H); ESI-MS: *m/z*, 428 (M+H).

**General procedure for the preparation of 5a by Conventional method**

1 µ moles of compound **3 a**, 1 µ moles of 7-amino-4-methyl-1,8-naphthyridin-2-ol, were taken in Tetra hydro furan (THF) in the presence of potassium carbonate. After every 1 hr progress of reaction was monitored by TLC. The solvent distilled under vacuum evaporated and added water. The ppt solid was collected by filtration. The same procedure was repeated other solvents like MeCN, EtOH and DMF).

**General procedure for the preparation of 1-(4-((2-((7-hydroxy-5-methyl-1,8-naphthyridin-2-yl)amino)-6-phenylpyrimidin-4-yl)amino)phenyl)-3-arylprop-2-en-1-ones 5a-e**

1 µ moles of compound **3 a-e**, 1 µ moles of 7-amino-4-methyl-1,8-naphthyridin-2-ol, were taken in microwave vial . The microwave oven was programmed at 390 W at 120°C for 2 min. After completion of the reaction as indicated by T.L.C. The solvent distilled under vacuum evaporated and added water. The ppt solid was collected by filtration. The same protocol was applied to the remaining other compounds **(5b-e).**

**1-(4-((2-((7-hydroxy-5-methyl-1,8-naphthyridin-2-yl)amino)-6-phenylpyrimidin-4-yl)amino)phenyl)-3-phenylprop-2-en-1-one (5a)**

IR ( KBr, $cm^{-1}$): 1600 (C=N), 1750 (C=O), 3100 (C-H), 3265 (N-H), 3410 (OH); $^1$H-NMR : 9.09(1H, -OH), 8.19 (2H, -NH-), 7.89 (1H, -CH-), 7.49 (1H, -CH-), 7.11 -7.79 (13H, Ar-H), 5.79-6.69 (5H, Ar-H), 2.40 (3H, -$CH_3$); ESI-MS: *m/z*, 551 (M+H).

**1-(4-((2-((7-hydroxy-5-methyl-1,8-naphthyridin-2-yl)amino)-6-phenylpyrimidin-4-yl)amino)phenyl)-3-(4-bromophenyl)prop-2-en-1-one (5b)**

$^1$H-NMR: 9.12 (1H, broad,-OH), 8.30 (2H, broad, -NH-), 7.89 (1H, doublet, -CH-), 7.60 (1H, doublet, -CH-), 7.14 -7.79 (12H, multiplet, Ar-H), 5.79-6.80 (5H, multiplet, Ar-H), 2.40 (3H, singlet, -$CH_3$); ESI-MS: *m/z*, 630 (M+H).

**1-(4-((2-((7-hydroxy-5-methyl-1,8-naphthyridin-2-yl)amino)-6-phenylpyrimidin-4-yl)amino)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (5c)**

$^1$H-NMR : 9.9 (1H, broad, -OH), 8.30 (2H, broad, -NH-), 7.89 (1H, doublet, -CH-), 7.60 (1H, doublet, -CH-), 7.09 -7.79 (12H, multiplet, Ar-H), 5.79-6.80 (5H, multiplet, Ar-H), 2.40 (3H, singlet, -$CH_3$); ESI-MS: *m/z*, 586 (M+H).

**1-(4-((2-((7-hydroxy-5-methyl-1,8-naphthyridin-2-yl)amino)-6-phenylpyrimidin-4-yl)amino)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (5d)**

$^1$H-NMR: 9.09(1H, broad, -OH), 8.30 (2H, broad, -NH-), 7.89 (1H, doublet, -CH-), 7.60 (1H, doublet, -CH-), 7.09 –7.79 (10H, multiplet, Ar-H), 5.79-6.80 (7H, multiplet, Ar-H), 3.80 (3H, s, -$OCH_3$), 2.40 (3H,s,-$CH_3$); ESI-MS: *m/z*, 581 (M+H).

**1-(4-((2-((7-hydroxy-5-methyl-1,8-naphthyridin-2-yl)amino)-6-phenylpyrimidin-4-yl)amino)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (5e)**

$^1$H-NMR: 9.09 (2H, broad, -OH), 8.30 (2H, broad, -NH-), 7.89 (1H, doublet, -CH-), 7.60 (1H, doublet, -CH-), 7.09 –7.09 (10H, multiplet, Ar-H), 5.79-6.80 (7H, multiplet, Ar-H), 2.40 (3H, singlet, -$CH_3$); ESI-MS: *m/z*, 567 (M+H).

**Antioxidant activity:** The results of antioxidant activity of the compounds **9a-e** are presented in Table **1** and Fig. **1**. The activity was determined by measuring its electron donating ability

to DPPH which was indicated by changes in absorbance of the solution at 520 nm. The result of the radical scavenging was expressed in terms of half-inhibition concentration ($IC_{50}$) which denotes the concentration required to scavenge 50% of DPPH radicals.

Series of compounds **9a-e** were screened for anti-oxidant activity. Among all the derivatives, bromo substituted compound was found to be more potent with $IC_{50}$ value 19.21 µg/mL. This is due to the formation of a positive charge on the amide's –NH, which is accompanied by a negative inductive effect of these types. Free radical quenching can occur as a result of the positive charge escalation.

**Molecular Docking Studies[xxx]**

The ligands were sketched in chem draw and saved it in mol 2 format. All the sketched molecules were converted to energy minimized 3D structures by using ligprep module for in-silico protein – ligand docking using Schrödinger 11.4. Each molecule was docked separately. Initially the molecule was loaded; torsions were set and saved it in PDB format. All the heteroatoms were removed from the 2R3I. PDB (Structure-guided discovery of cyclin-dependent kinase inhibitors. Cell division protein kinase 2, 5-(2-fluorophenyl)-N-(pyridin-4-ylmethyl)pyrazolo[1,5-a]pyrimidin-7-amine).

CDK2 inhibitors containing the related bicyclic heterocycles pyrazolopyrimidines and imidazopyrazines were discovered through high-throughput screening. where it has been reported as a putative oncogene to make complex receptor free of any ligand before docking . Receptor grid generated using glide module. The best conformation was chosen with the lowest docked energy after the docking search was completed. The interactions of 2R3I protein and ligand conformations, including hydrogen bonds and the bond lengths were analyzed. Molecular docking study was performed by using maestro (Schrödinger 11.4) which was a suite of automated docking tools and was used to predict the affinity, activity, binding orientation of ligand with the target protein and to analyze best conformations, the protein with all the 4 were loaded individually evaluated.

**Table 1. Antioxidant activity of 1,8-Naphthyridines 9a-e.**

| Compound | $IC_{50}$(µg/mL) |
|---|---|
| 5a | 5.02 |
| 5b | 19.21 |
| 5c | 14.13 |
| 5d | 9.52 |
| 5e | 9.41 |

**Table 2. Docking score of 1,8-Naphthyridines**

| **Molecules** | **Docking score** |
|---|---|
| **2R3I** | |
| 5a | -5.951 |
| 5b | -7.508 |
| **5c*** | **-7.617** |
| 5d | -7.49 |
| **Doxorubicin** | **-6.557** |

% Inhibition of DPPH free radical at different concentrations

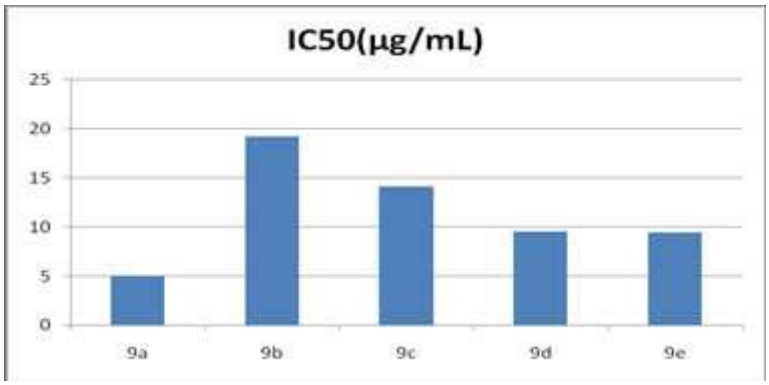
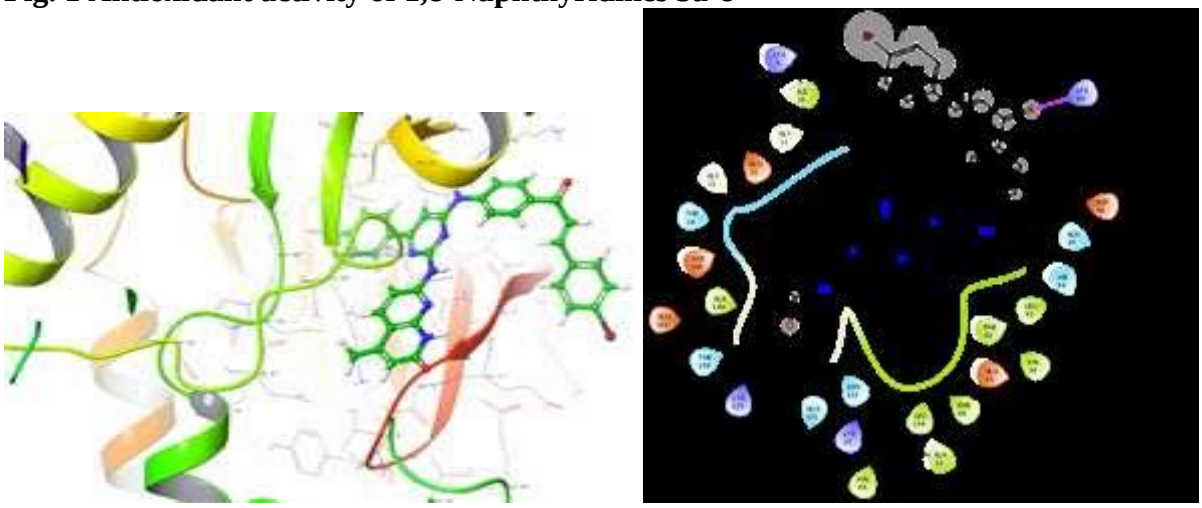
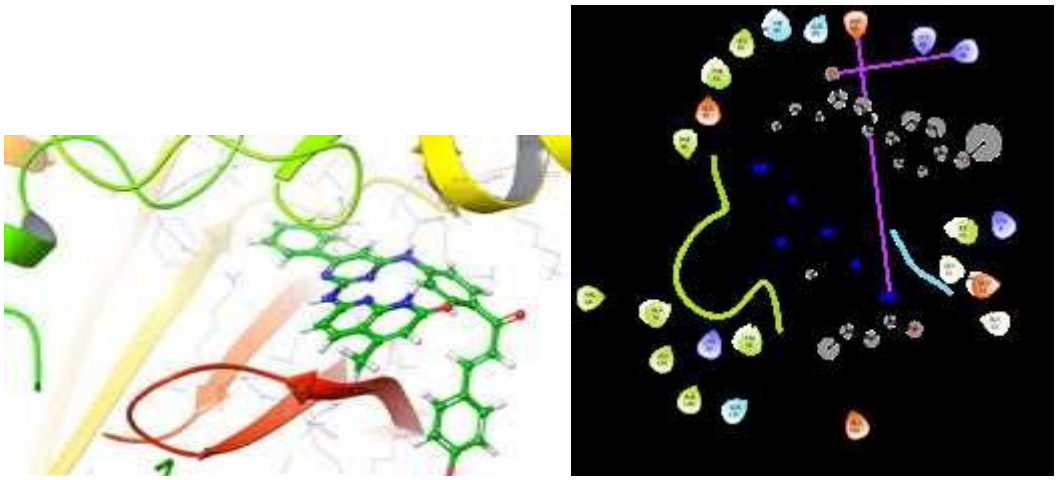


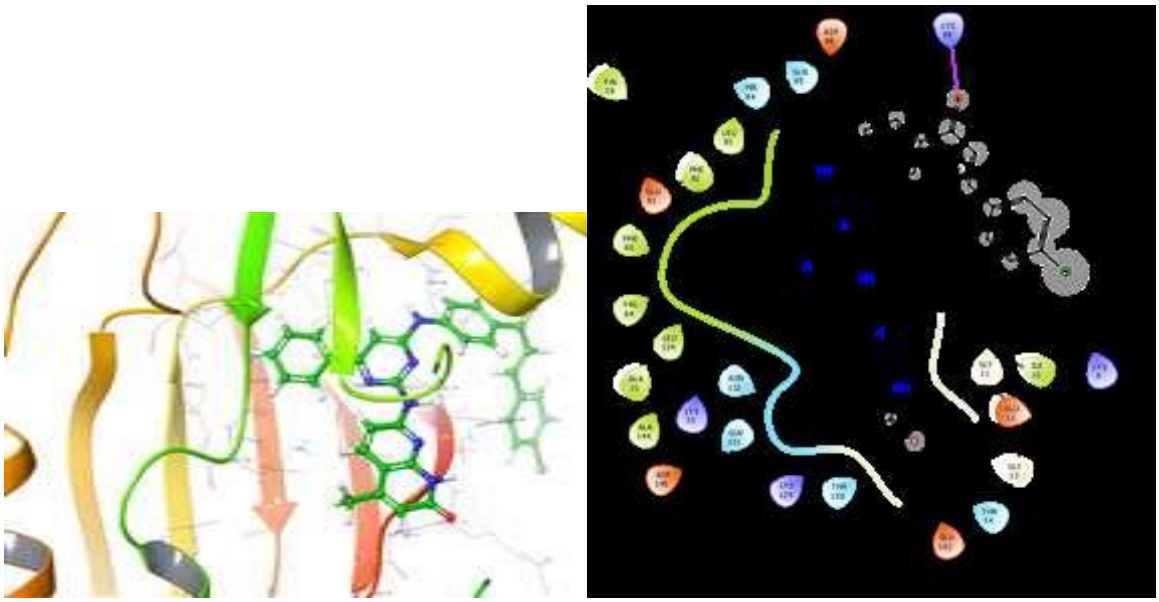

**Fig. 1 Antioxidant activity of 1,8-Naphthyridines 5a-e**



**5b**



**5c**



**5d**

Figure-2. 2D and 3D Interaction study of 1,8-Naphthyridine derivatives with binding domain of target protein

**CONCLUSION:** In conclusion we have developed a facile and efficient method for the synthesis of 1-(4-((2-((7-Hydroxy-1,8-Naphthyridin-2-yl)amino)-6-Phenylpyrimidin-4-yl)amino)Phenyl)-3-Arylprop-2-en-1-ones under both microwave irradiation and conventional conditions, The results in the study shows microwave in solvent-free and potassium carbonate as a catalyst is the best method. The advantages of this protocol are green, clean and efficient, less reaction time, easy workup and high yields, further the compounds tested for antioxidant activity, the compounds 5b, 5c, 5d exhibited significant activity. It is also observed that the compound 5c, 5b, 5d molecule showed best fit and more potent molecules then compared with doxorubicin.

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**CONFLICT OF INTEREST**

The author(s) confirm that this article content has no conflict of interest.

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