Summary

I have synthesized 27 novel drivatives of piperidine-indole with amide and urea linkage in the 1st chapter of this thesis. All compounds are characterized at NIH US in total 60 cell lines. In which Compound **9c**, **11d**, **13b**, and **13e** had noteworthy anticancer effects against kidney cancer (UO-31). Compound **11f** demonstrated noteworthy anticancer action against breast cancer (MDA-MB-468) and leukemia (RPMI-8286), with inhibition levels indicating their potential for therapeutic use. While compound **9j** (SNB-75) had efficacy against CNS cancer. All 27 compounds are characterised by TLC, LC-MS, ^{1}H NMR, ^{13}C NMR, IR, Elimental analysis and Melting point.

I have synthesized 14 novel drivatives of piprazine-benzoxazole with amide linkage in the 2nd chapter of this thesis. All novel compounds are characterized by antimicrobial activity. In which Compounds **9b** and **9f** shows highest active in both gram positive and gram negetive pathogens in antimicrobial activity. All compounds are characterised by TLC, LC-MS, ^{1}H NMR, ^{13}C NMR, IR, Elemental analysis and melting point. Compounds **9b** and **9f**, which shows the highest docking scores of -7.7 kcal/mol and -7.8 kcal/mol respectively. With the exception of compounds **9k** and **9l**, which had molecular weights more than 500, all produced compounds adhered to Lipinski's rule of five. Interestingly, the lipophilicity ratings of all benzoxazole derivatives ranged from 1.94 to 4.31. Using SwissADME, the computational analysis was carried out.

A series of hybrid naphthalene-imidazole derivatives was synthesized in the 3rd chapter of this thesis. All novel compounds are characterized by antimicrobial activity. In which compounds **9k** and **9p** shows highest active in both gram positive and gram negetive pathogens in antimicrobial activity. All Compounds are characterised by TLC, LC-MS, ^{1}H NMR, ^{13}C NMR, IR, Elemental analysis and melting point. Also compounds **9k** and **9p** both had significant antibacterial action, achieving the highest docking scores of -8.7 kJ/mol and -8.5 kJ/mol, respectively.

A series of hybrid furan-indoline and pyrrole-indoline derivatives were synthesized in the 4th chapter of this thesis. All compounds are characterized by TLC, LC-MS, ^{1}H NMR, ^{13}C NMR, IR and Elemental analysis. Compound **6k** possesses the greatest binding affinity (-8.4 kcal/mol) in the **6a-k** series. While compound **13e** possesses the greatest binding affinity (-9.8 kcal/mol) in the **13a-k** series. Also these both compounds are more active in gram-positive and gram-nagetive pathogens.

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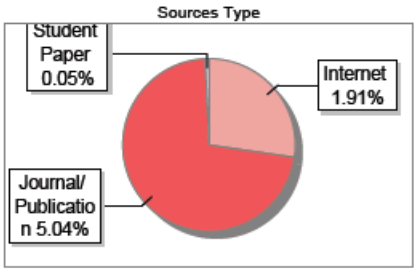

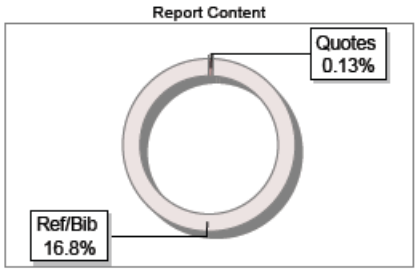

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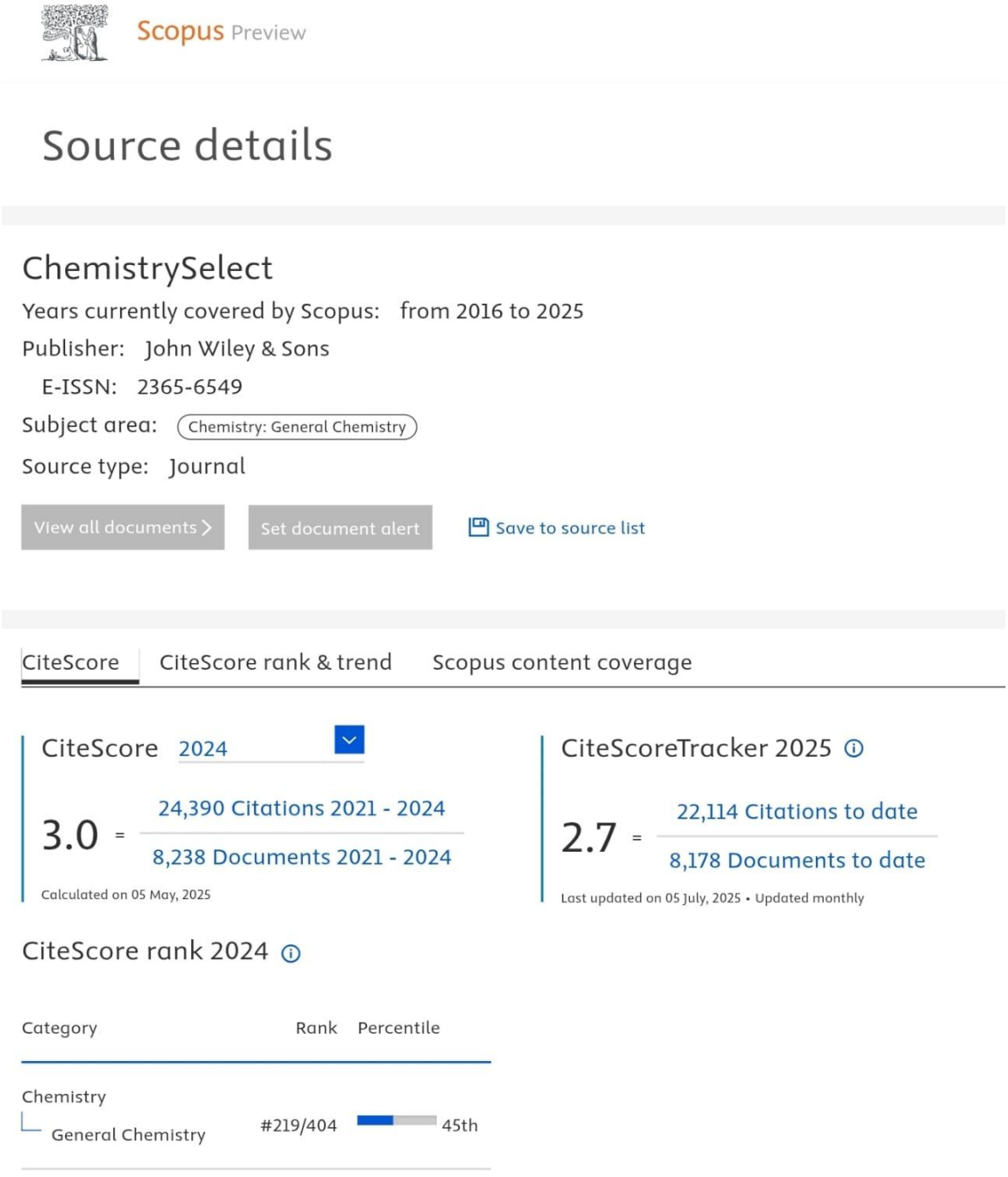

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Synthesis, In Vitro Antiproliferative Activity, and In Silico Studies of Indole–Piperidine Hybrids Bearing Amide and Urea Linkages

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The present study described the synthesis and anticancer activity of new indole–piperidine hybrids functionalized with piperidin-4-yl-benzamide (**9a–n**) and piperidin-4-yl-urea (**11a–g**, **13a–f**) moieties. All the newly synthesized compounds were purified by reverse phase flash chromatography and characterized by FTIR, ^{1}H and ^{13}C NMR, LC–MS, and elemental analysis. Their in vitro anticancer activity was tested against the NCI-60 human tumor cell lines (National Cancer Institute, USA). The results revealed that compounds **9c**, **11d**, **13b**, and **13e** were found active against UO-31 (renal cancer) having growth (%) as −22.98%, −49.98%, −83.76%, and −82.75%, respectively. While compound **11f** exhibited notable activity against RPMI-8226 (leukemia) and MDA-MB-468 (breast cancer). Moreover, in silico docking studies revealed effective VEGFR-2 binding with the receptor and formed stable protein–ligand complex with low docking scores. Additionally, drug-likeness and ADMET predictions indicated favorable pharmacokinetic profiles with no associated toxicity concerns.

1. Introduction

Cancer, a disease characterized by pathological proliferation of malignant cells, is the second leading cause of death worldwide.[1] Despite the development of numerous anticancer agents, drug resistance and adverse side effects remain significant challenges.[2] Amongst the various cancer types, leukemia, renal cancer, and breast cancer are categorized into major molecular subtypes based on hormone and growth factor receptor expression.[3] The limitations of current treatments contribute to the high mortality rate associated with breast cancer, highlighting the need for novel antineoplastic drugs to address these challenges.[4] Although several cancer therapies have been approved globally, the emergence of resistance underscores the ongoing demand for medications that can overcome this obstacle.

In anticancer drug discovery, heterocyclic compounds are key constituents of numerous pharmacological active molecules and are present in over 80% of FDA-approved medications.[5] These compounds exert their bioactivity by inhibiting specific genes, enzymes, and receptors to provide protection against cancer. Based on their biochemical modes of action and suitability for cancer therapy, the FDA approved several heterocyclic derivatives in 2024 that exhibit physiological activity against various types of cancer growths.[6] Particularly, hybrid heterocycles containing two active pharmacophores are being increasingly explored due to their ability to interact with multiple receptors with high affinity. These hybrid structures are frequently found in various pharmacologically active compounds. Among them, indole based heterocycles are considered one of the most significant structural classes in drug development.[7,8] In medicinal chemistry, indole and its analogs are being rapidly identified, because of diverse synthetic methodologies and abundant natural sources.[9] Several indole derivatives containing a piperidine moiety have shown promising biological activities, including antidepressant (Indalpine, **1**),[10] antiviral (Ajmalicine, **2**),[11] anti-inflammatory (**3**), antitubercular (**4**),[12] anticancer (Mitraphylline, **5**),[13] antioxidant (**6**), antidiabetic (**7**),[14] antidepressants (Mitragynine, **8**),[15] anti-HIV (Atevirdine, **9**,[16] Delavirdine, **10**[17]), antitumorigenic (Brivanib, **11**)[18] activities. Notably, in recent years, several indole-based molecules such as Tadalafil (**12**),[19] Alectinib (**13**),[20] Apaziquinone (**14**), and Panobinostat (**15**),[21] (Figure 1) have been approved for the treatment of various cancers, demonstrating their potential as leads for new anticancer drug development.

Indole derivatives featuring various functional groups and amide linkages have been well reported as histamine H_1-receptor antagonists,[22] enzyme inhibitors,[23] and agents with antiproliferative activity.[24] Moreover, inspired from the structural for-

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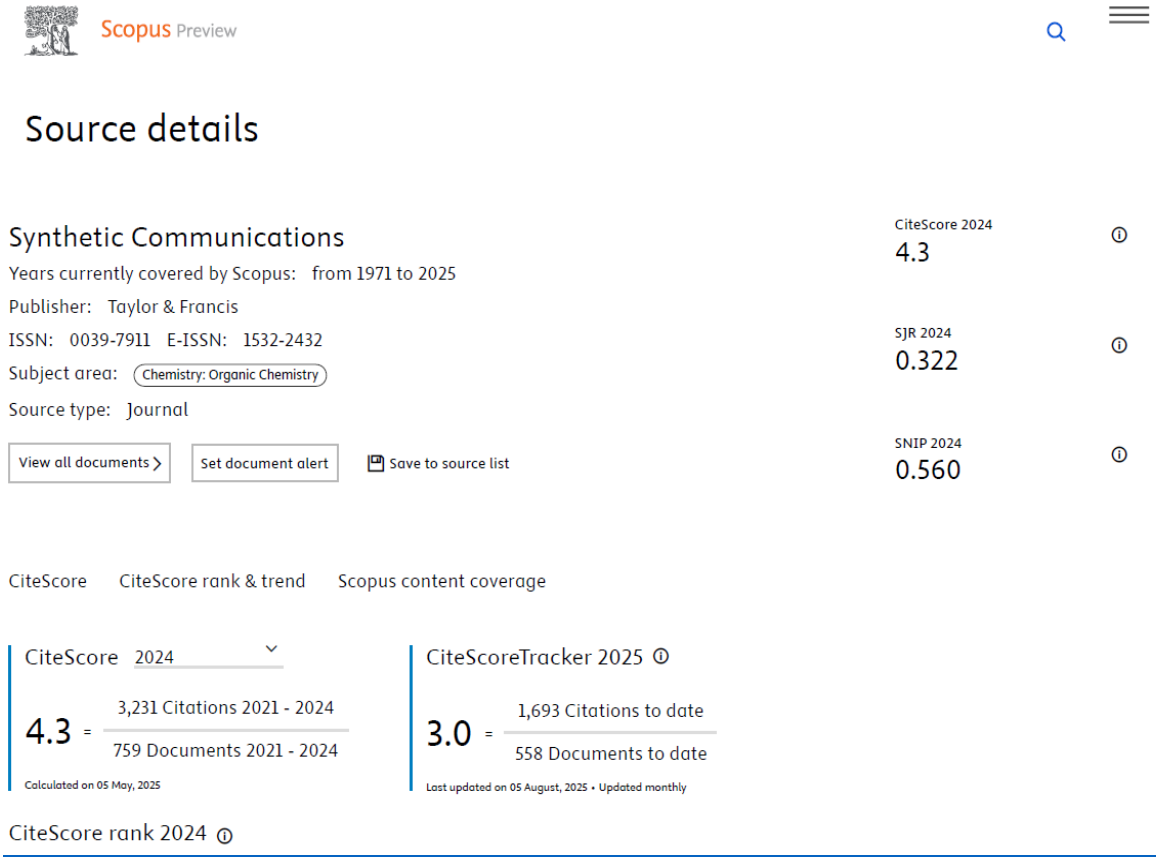

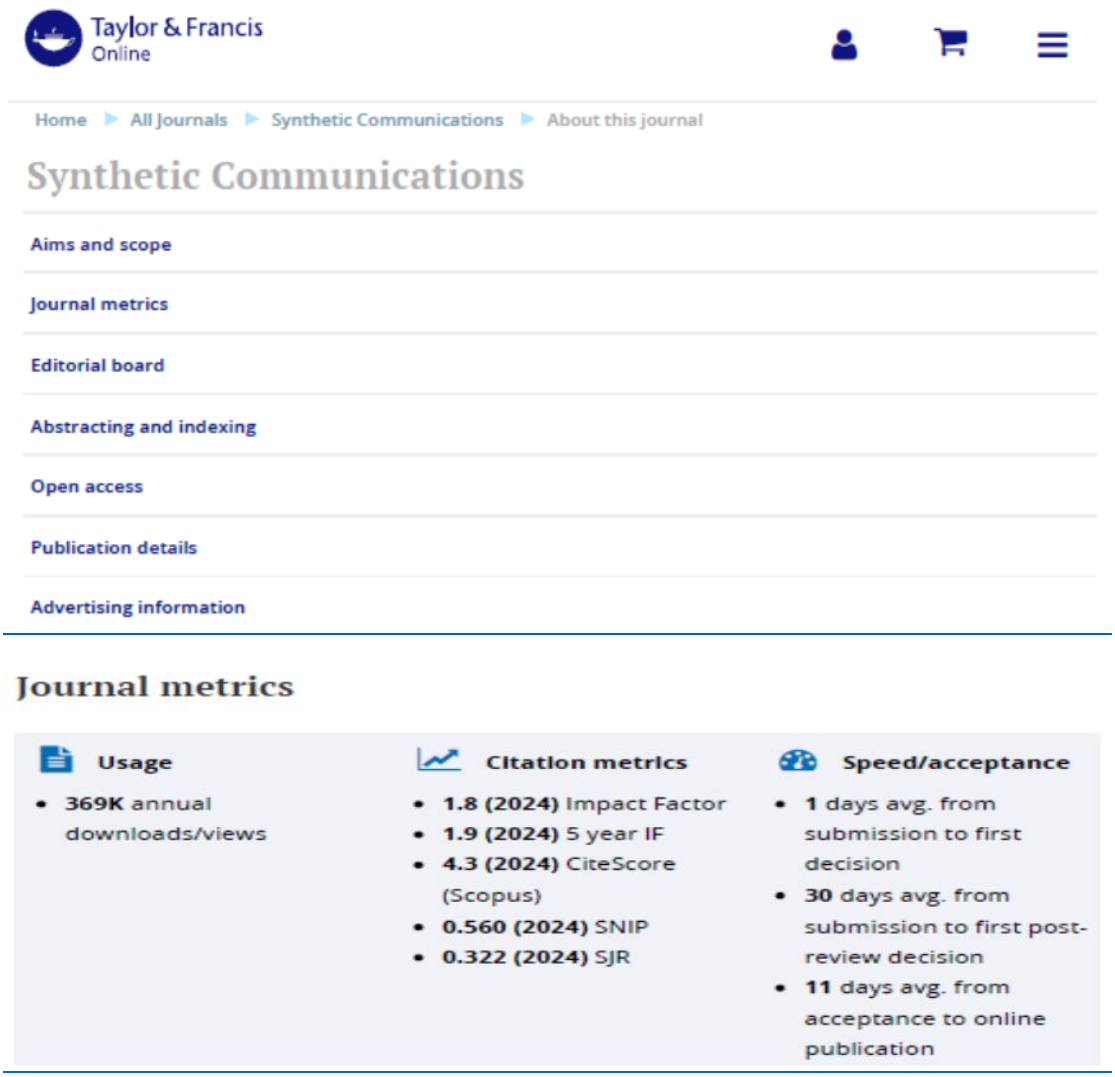
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Design, synthesis, antimicrobial evaluation, in-silico molecular docking, and ADME-T evaluation of novel benzoxazole-piperazine hybrids with amide linkage

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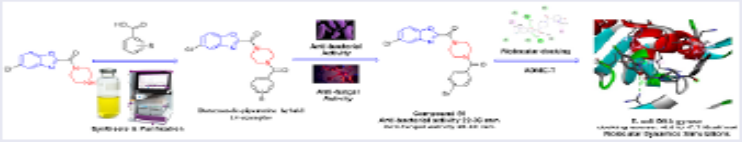
ABSTRACT

A series of benzoxazole-piperazine hybrids (**9a–n**) has been synthesized via a multistep approach incorporating the Mitsunobu reaction. These compounds were obtained in good yields using cost-effective and readily available starting materials under mild reaction conditions. Structural characterization was performed using ^{1}H NMR,^{13}C NMR, LCMS, elemental analysis, and FTIR spectroscopy. The antimicrobial potential of **9a–n** was assessed against bacterial strains *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa,* and *Escherichia coli* and fungal strains *Aspergillus niger,* and *Candida albicans*. Notably, compounds **9b**, **9c** and **9f** exhibited potent antibacterial activity, comparable to chloramphenicol and gentamicin, and antifungal activity similar to nystatin. Molecular docking and dynamics simulations suggested that **9f** inhibits *E. coli* DNA gyrase, forming a stable protein-ligand complex with strong binding interactions and low docking scores. Furthermore, in silico ADMET analysis indicated favorable pharmacokinetic properties with no significant toxicity concerns, highlighting their potential as promising antimicrobial agents.

GRAPHICAL ABSTRACT



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Introduction

Sixty percent of the earth's biomass is impacted by microbial pathogenic diseases, posing a serious threat to global health.[1] The World Health Organization (WHO) has identified antimicrobial resistance (AMR) as one of the top ten global health threats.[2] Resistant strains of pathogens, such as *Staphylococcus aureus*, *Escherichia coli*, *Bacillus*

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List of Seminar/Conference Participated

1) Online conference on "Research Methodology" by Udemy on 26th May 2021.

2) One week workshop on "copyright, patentfilling and journal indexing" organized by REST Society for Research International (RSRI) Krishnagiri, Tamilnadu, India 7th- 11th June 2021.

3) Online course on "Learning fundamentals of publishing in quality journals" by Elsevier on 26th May 2021.

Researcher Academy On Campus

Certificate of Attendance

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This certifies that

Ajay Jani

has attended the following

Learning fundamentals of publishing in quality journals

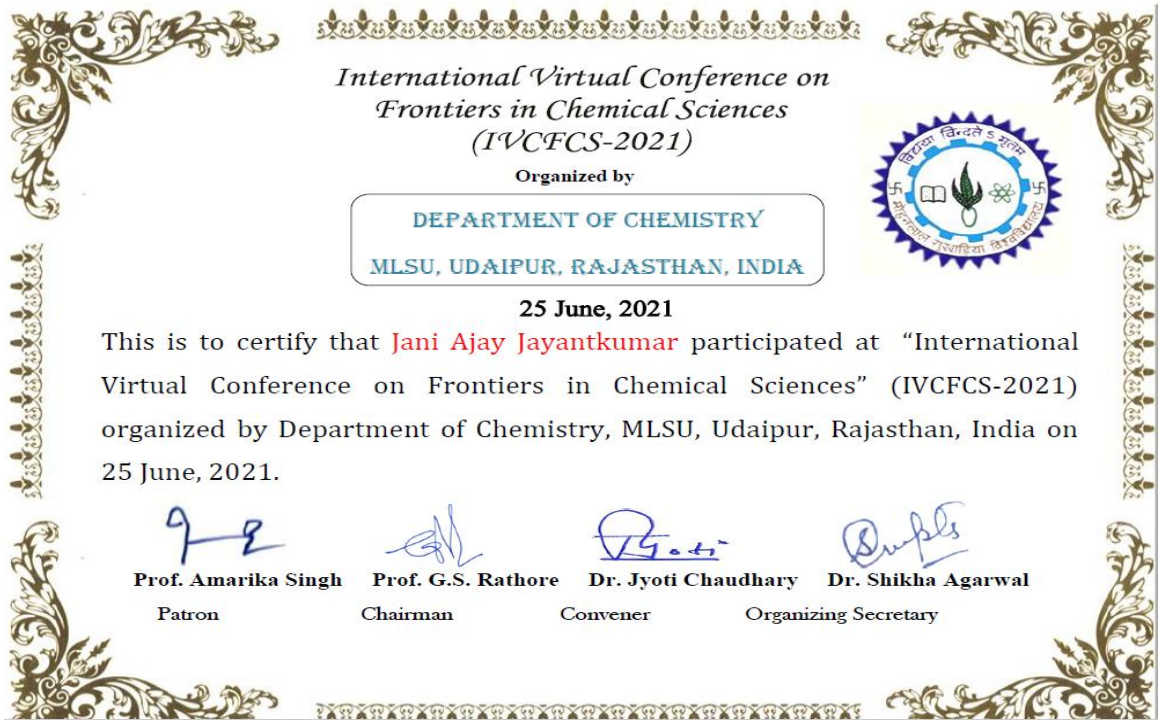
at Sushant University, Gurugram,
on Wednesday 26 May, 2021

Presented by Vishal Gupta Sr. Customer Consultant

Suzanne BeDell
Managing Director, Education
Reference & Continuity Books

Philippe Terheggen
Managing Director, Science,
Technology & Medical Journals

4) Conference: "International virtual conference on frontiers" organised by Department of Chemistry MLSU, Udaipur, Rajasthan, India on 25th June, 2021.



International Virtual Conference on Frontiers in Chemical Sciences (IVCFCS-2021)

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