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Development and Synthesis of Novel Heterocyclic Compounds as Potential Pharmaceutical Agents

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Abstract- ***Since they display diverse molecular structure, novel electron system, and unique reactivity at target binding site, heterocyclic compounds are the most important and versatile class of organic molecules used for therapeutic agents in medicinal chemistry because the fundamental core motifs of heterocyclic systems are referred to as "pharmacophore" which plays a major role in the design of different classes of therapeutic drugs like antibacterial, anticancer, antiviral, anti-inflammatory, neurological diseases agents, etc... But since there is rise in resistance of microbials, increase in disease incidents, side effects and limitations by the usage of existing drugs which are low in potency and selectivity with less favorable side effects and poor performance in efficacy and safety, the needs of the new pharmaceutical drug candidates with better biological activity and good performance required immediately. Therefore, this conceptual research article provides an explicit methodological design toward new heterocyclic compounds and design, synthesis, biological and pharmaceutical evaluation strategies of such new molecules using basic knowledge in terms of organic synthesis, molecular modification, SAR analysis, theoretical study and pharmaceutical chemistry, that will ultimately yield high biologically active new molecular structure. This study involves an explicit methodological framework focusing on logical selecting of important biologically important core heterocyclic structures which have nitrogen, oxygen, sulfur atoms at them followed modification in to functional groups and functional molecule followed development in a synthetic route and prediction of relevant physicochemical properties, which enhances good interaction with a specific biologic target for an activity. The conceptual paradigm focuses more on usage of analytical chemistry's advanced characterization techniques in order to describe of molecule such as IR spectroscopy, NMR spectroscopy, mass spectrometry...; and at the same time uses theoretical study such as molecular docking, ADMET prediction study to study of molecules behavior with specific biologic entity and within body. This investigation tends to build up a relevant platform in selecting potential new heterocyclic derivatives through exploration of best candidates with higher potency, excellent selectivity profile compared to existing drug compounds, higher metabolic stability along with less or no toxicity. This research could be a new steppingstone toward the design and creation of new relevant therapeutic candidates which are innovative based on heterocycles and to advance on field of medicinal organic chemistry by providing great insight into molecular structure and its biological interaction, toward a goal of more innovative drugs and healthier living environment.***

Keywords: Heterocyclic compounds, Medicinal chemistry, Drug discovery, Organic synthesis, Structure–activity relationship (SAR), Pharmaceutical agents, Bioactive molecules

I. INTRODUCTION AND BACKGROUND RELATED TO THE STUDY

One of the most important and widely studied subjects in the organic and medical chemistry is heterogeneous chemical structures. Heterocyclic compounds being the simplest structure (cycle organic molecule that contains minimum of heteroatom like nitrogen(N), oxygen(O) and sulfur(S)) but most significant and effective due to their wide array of structural variety, immense biological significance and vast pharmaceutical value. The heteroatom in such heterogeneous ring impart electronic attributes that lead topolarity, hydrogen-bonding capability, conformational property that significantly influence the molecular recognition, its interaction and its overall biological activities that has led to their recognition as key part of structural core of many natural products, bio-active molecules and synthetic therapeutic agents (Joule & Mills, 2010; Katritzky et al., 2010). Many important naturally occurring heterogeneous molecules like alkaloids, flavonoid, nucleic acids base, etc. Possess various unique biological activities whereas synthetically derived heterogeneous scaffolds serve as important building blocks for drug discovery and lead to modulations of various biological targets that lead to the development

of various potential molecules and clinical applications. Important pharmaceutical application of several prominent heterogeneity are: pyridine based molecules possess antimicrobial and anti-cancer agents; imidazole based molecules were evaluated for antifungal and antiviral agent; thiazole based molecules found to possess antibiotic, anticancer and herbicidal activities whereas quinazoline derivatives has been found to be most selective kinase inhibitor and indole based compounds play role for treatment in CNS therapy, and anti- cancer applications (Eicher et al., 2012; Vitaku et al., 2014). Hence, such valuable heterogeneity structures are critically contributing toward advancement of pharmaceutical industry in terms of obtaining better aqueous solubility, molecular interactivity with the desired receptors, enhance solubility and better biological selectivity via simple rational functionalization. Medicinal chemist can able to modulate physicochemical parameters and pharmacokinetic aspect of these heterogeneous compounds and hence enable the synthesis of better and desired drug. Current challenges of existence of resistant pathogen strain with reduced effect of medicines that leads to drug development, toxicity and narrow spectrum of biological activity of available drug in the existing market. There is the urge for identifying novel compound which can overcome the existing limitations. So, heterocyclic designing by taking the help of structure-based design, structure–activity relation and quantitative structure–activity relation and predicted pharmacological evaluation using in silico method helps the medicinal chemist to develop an effective medicine and potential target. Aim of present design study will be to present the strategies on heterocyclic molecule design and synthesis with pharmaceutical perspective that encompasses in silico design, synthetic procedures, SAR and probable in vivo application for their efficacy. Overall goal of present strategy will be to design and synthesize potential candidates that will act as drugs for diseases like infectious disorder, inflammation, cancer etc.

Research Objectives related to the study

1. To identify biologically active heterocyclic scaffolds.
2. To design new derivatives through structural modification.
3. To propose synthetic pathways for target compounds.
4. To predict pharmaceutical potential using computational and biological approaches.
5. To establish possible structure–activity relationships.

Literature Review

The history of heterocyclic drugs clearly proves a marvelous evolution in the field of medicinal chemistry starting from the understanding that cyclic molecules containing a heteroatom namely, N, O, and S have distinct chemical properties and can strongly interact with biological systems; Throughout the growth of organic chemistry heterocyclic structures have progressed to form the backbone of today's drug research and an essential pharmacophore of most of the present drugs. Historically early efforts in nineteen and early twentieth century exploring this field laid an idea of their formation, and modification, thereby generating knowledge over ring formation reactions, insertion of hetero atoms and alteration to make them suitable for exploring biological activity followed by discovery of numerous biologically active entities; Early success on drug discovery in connection with heterocyclic chemistry were penicillin derivatives having a stressed nitrogen containing ring i.e., a six membered ring where the beta-lactam ring itself acts as an active structure inhibiting cell wall synthesis by its attack to a penicillin binding protein to produce an active mechanism, modification of its basic structure led to improved drugs (Kong et al. 2010). Sulfanilamide drugs followed in the decade 1930's that were the first truly effective systematic synthetic drugs against antibacterial activity and were a precursor for the synthesis and usage of nitro and aromatic heterocyclic systems that work in the system of bacteria to degrade a vital compound called folate. Azole derivatives derived from the imidazole and triazole ring namely Ketoconazole, fluconazole and Itraconazole in nineties have an anti-fungal action that works by interfering the action of fungal cyto-P450 that helps in the steroid metabolism preventing further growth and development (Sheehan et al 1999). Quinoline base antimalarial drugs have an enormous contribution in the entire world and their history can be seen to originate from naturally occurring quinine which was modified by synthesizing drugs such as chloroquine and its analogues based on the quinoline

system; Though quite a few of these have generated resistance now, that is why research is continuing to find novel heterocyclic based antiparasitic compounds (Wells 2011). Overall, it is very apparent that the growth and evolution of these compounds came due to constant integration of synthesis, pharmacology, and study of their relations among structure and biological activity.

Historical Development of Heterocyclic Drugs

Heterocyclic chemistry has also made a cornerstone contribution to the field of medicinal chemistry, by showing that heterocycles composed of ring systems that include heteroatoms like nitrogen, oxygen or sulfur, demonstrate unique electronic and biological properties that are amenable for use in therapy development. Starting from basic discovery of heterocyclic frameworks then followed by various molecular modification techniques combined with analysis of structure-activity relationship, leading into logical design of drug substances. Amongst some of the major breakthroughs of history involving heterocyclic compound includes those based on l-lactam heterocyclic skeleton. Penicillin is an antibiotic produced by a mold that involves the b-lactam ring of the heterocyclic compound. Modifications from penicillin resulted in the invention of various penicillins that improved stability, activity, broadened spectrum of antimicrobial activity as well as reduced adverse effects (Kong et al., 2010). Sulphonamide derivatives of 1930 is another example; it was one of the earliest successfully synthetically developed antibiotics to inhibit bacterial folate biosynthesis. Heterocyclic aromatic compounds with an active nitrogen within them became significant part of new discovery and development (Lombardino & Lowe, 2004). Subsequently azole antifungals that included imidazole and triazole derivatives like fluconazole and itraconazole were important breakthrough by inhibiting specifically fungal sterol synthesis (Sheehan et al., 1999). Quinine and Chloroquine were a significant step in antiparasitic development based on quinoline structures for antimalarial therapy but due to the emergence of resistance to existing drugs, new efforts were made in development of heterocyclic antimalarials (Wells, 2011).

Classification of Pharmaceutical Heterocycles

Pharmaceutical heterocycles have generally been categorized based upon the heteroatom contained within their respective ring systems; among these, nitrogen-, oxygen- and sulfur-containing heterocycles hold the foremost places in medicinal chemistry owing to their myriad biological activities as well as their structural rigidity and ease of manipulation for increasing drug-like characteristics. Nitrogen-containing heterocycles are largely prominent within therapeutically viable drugs; pyridine derivatives have shown promising antimicrobial, anticancer and receptor targeting potential (Mahmood and Saei, 2014; Hassan et al., 2011), pyrimidine structures are building blocks to nucleic acid analogs and kinase inhibitors (Lidmila et al., 2012), imidazoles affect their antifungal, antibacterial and antiviral characteristics through biological enzymes (Silva et al., 2014), and the indole class has been established for its diverse neurological and cancer therapeutic effects (El-Dien et al., 2014). Oxygen containing heterocycles; furan and coumarin derivatives, also bear important health functions ranging from antioxidation, anticlotting, antibacterial activity, to anticancer activity stemming from their novel electronic character and molecular interaction (Murray et al., 2013). Sulfur-containing heterocycles including thiophenes and thiazoles were considered prime targets in medicinal chemistry for anti-microbial and inflammatory properties, anticancer treatment and Enzyme Inhibition (Joule and Mills, 2010). These frameworks have thus been crucial platforms for the rational design and synthesis of the next generation of therapeutics.

Biological Activities of Heterocyclic Compounds

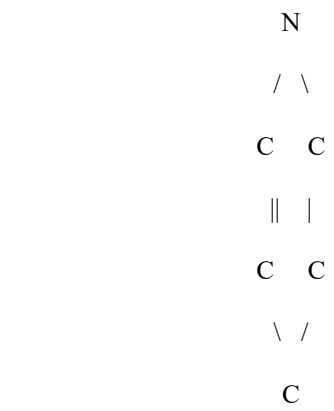
Heterocyclic compounds' wide scope of activities is credited to their diverse molecular structure enabling specificity to important targets inside the cells, thus showing their applicability in development of pharmaceutical drugs. Among them, activities such as Antimicrobial activities are highly studied due to the various strategies which heterocyclic drugs use to stop proliferation such as through suppression of essential enzymes in a metabolic cascade and altering cell membrane integrity in microbes, inhibition of nucleic acids necessary for multiplication and survival (Mandal et al., 2019); in development of Cancer treatment, it has attracted much attention as it affects

crucial targets such as tyrosine kinases, cell cycle checkpoints' replication mechanisms and the programmed death pathways to alter cancerous cells' behavior on multiplication, death and differentiation (Murray et al., 2014); many such derivatives are found to possess anti-inflammatory behavior as they control inflammatory mediators through inhibition of COX enzymes that lead to the creation of Prostaglandins, and also cytokine pathways in inflammatory disorders (Gilroy et al., 2004); the multifarious characteristics of heterogeneous molecules present a fundamental characteristic for developing novel and more potent drugs against microbial infections, cancer, inflammation with enhanced pharmacological traits.

Conceptual Research Methodology

The molecular design is the starting point of the proposed conceptual research methodology designed for the synthesis and evaluation of novel heterocyclic derivatives as potential pharmaceutical agents, the main biological-significance heterocycles are chosen and optimized using rational medicinal chemistry processes (structural analyzing, modification of structure as well as prediction of pharmaceutical characters), because heteroatoms involved in these heterocyclic frameworks including nitrogen, oxygen, sulfur; which provide favorable electronic characteristics, capability for hydrogen bonding, polarity and receptor-binding possibility and affect biological performance and pharmacokinetics features of molecular. From above, it focused on those nitrogen-containing heterocycles like pyridine, pyrimidine, imidazole and indole due to their extensive use as the scaffold building for developing antimicrobial, anti-cancer, anti-virus and anti-inflammatory drugs, meanwhile the heterocyclic parent as pyridine is particularly described in which the basic nitrogen atom at the structure improve interaction with receptor molecule, basicity, and capability for coordination with biological system. Thus, the suggested design process relies on using of a chosen parent heterocycle which is matched the biological requirement, related drug effects and synthetization feasibility; then a variety of functional groups including hydroxyl, methoxy, amino, halogen, trifluoromethyl, and alkyl group substituted on the parent scaffold structure to improve molecular properties like characteristic of molecules, targeting, chemical stability and biological activity. Evaluate the designed molecules through those drug-likeness parameters predicted from Lipinski's rule of five, including MW, donors of H-bond, acceptor of H-bond, lipophilicity and molecular flexibility, to estimate the absorption, distribution, metabolization and drug suitable of molecule; Additionally apply structure-activity relationship (SAR) to analyze how these electronic, steric, hydrophobic effect and molecular conformation affect the biological activity, and optimized these lead molecule; finally, propose docking study and ADMET study to explore the interactions between design heterocyclic molecule and related bio-molecules, e.g. Microbial enzymes, tyrosine kinase, DNA repair proteins, cyclooxygenase and inflammatory factors, such as binding affinity, stability of molecule and ADMET characters etc.. At last, explore those lead compound possessing excellent features that is applied for chemical synthesis, structure confirmation, biological characterization etc.

Structural representation:



Pyridine molecular formula:

$$C_5H_5N$$

The nitrogen atom contributes:

- ✓ Basicity
- ✓ Coordination ability
- ✓ Enhanced receptor interaction

Drug-Likeness Evaluation

After selection of the heterocyclic core, molecular properties are optimized according to established

pharmaceutical criteria. The proposed compounds should satisfy drug-like characteristics such as:

Lipinski's Rule of Five

Parameter	Recommended criteria
Molecular weight	≤500 Da
Hydrogen bond donors	≤5
Hydrogen bond acceptors	≤10
LogP value	≤5
Rotatable bonds	Controlled flexibility

Characterization Methods

Structural and Physicochemical Characterization of Novel Heterocyclic Derivatives: Structure verification and physicochemical characterization of novel heterocyclic compound(s) of interest will be key steps to organic synthesis geared towards pharmaceutical sciences; various advanced spectroscopic and analytical techniques are herein suggested for establishing structural identity and functional group incorporation, purity and integrity of the synthesized derivatives; FTIR will provide a significant pre-analytical tool that is important to indicate presence or absence of a particular functional group on structure by providing specific vibrational frequencies that are related to each functional group on heterocyclic compound; Fourier transform infra-red technique will identify the absorption peaks corresponding to C=N stretching vibration for imine or heteroaromatic system, C=O stretching vibrations for carbonyl functionalized heterocycles, N-H stretching for aminos or amides on the produced derivatives as evidence to chemical reaction and functionalization, and finally, a confirmation test has been established (Silverstein et al., 2014); Proton nuclear magnetic resonance (1H NMR) has been proposed to elucidate detail chemical environment, connectivity and position of hydrogens at specific chemical framework, a confirmation test will have been developed on chemical shift, coupling reaction and signal integration as information; Carbon-13 nuclear magnetic resonance (13C NMR) will give the structural framework, atom surroundings, and substitution patterns of compounds and mass spectrometry is a very helpful technique in accurately determine the molecular masses, possible fragmentation behavior and verifying the proposed pharmaceutical structure (Pavia et al., 2015).

Significance of the Research

It can be envisioned that investigation of the synthesis, development, and structure of novel heterocyclic molecules as therapeutic agents will greatly impact the areas of science, pharmaceutics and industry by acting as a basis for interdisciplinary advancement of medicinal chemistry and drug discovery through different aspects. First from a scientific aspect, the research investigation would benefit the exploration and extension of knowledge in the field of medicinal organic chemistry by expanding fundamental insights into the contexture of heterocyclic architecture of molecules to reactivity, biological activity and structure-activity relationship. In addition, it introduces potential new synthetic pathways to facilitate synthesis of diversified heterogeneous systems with improved pharmacological attributes, which is important for understanding molecular designs, reactions optimization and new potential approaches to realize the formation of biologically active species (Lombardino & Lowe, 2004); second from pharmaceutical view, it will be used as one foundation of discovering valuable lead molecules against major clinical issues including infectious disease, tumors and inflammatory illness, which could also offer improved activities, targets and other pharmaceutical implications such as efficacy, targeting, and safety. Thus, it will also strengthen the relentless search for new types of drugs to address clinical needs (Harvey et al., 2015); finally, from an industry stand point, the research can also provide useful candidates for the further preclinical experiments, drug optimization and pharmaceutical development thereby support contemporary drug discovery pipeline and integrate chemistry, computation science and bio-screening into the development. In a word, the investigation is considered to be an achievement toward novel heterocyclic medicine drugs discovery and pharmaceutical technology in future.

Limitations of the Study

The presented concept and synthesis of novel heterocycles appear to represent a valuable conceptual framework for the discovery of drug candidates; however, it is important to note some limitations to the described molecular design approaches prior to their success in being classified as successful drugs. While computer modeling, structure-prediction methods and theoretical drug design provide preliminary insights, it is not possible for this approach to perfectly replicate living cells and the physiological environment of humans. Docking, virtual screening and ADMET modeling can predict the molecule and drug target interaction, its bioavailability and the risk for toxicity, but experimental validation of these predicted values is crucial as biological processes may behave differently depending on various biological systems, molecules metabolism and protein-mobility differences, cellular activities etc (Sliwoski et al., 2014). As the predicted potential biological activity is only an initial estimation, actual drugs need to be scientifically verified with regards to their antimicrobial, anti-cancer, anti-inflammatory and other therapeutic effect through a series of biological evaluation tests including cellular systems, enzyme-inhibition assays, susceptibility tests with various microbes and relevant mechanism-based investigations (Patrick, 2017). Not only the biological potential is one important factor as drug molecules with potent activities may exhibit toxicity such as metabolic instability, cell-cytotoxicity or unwanted pharmacological properties leading to different toxicity risk evaluation like liver toxicity, organ specific toxicity etc, therefore extensive investigations regarding toxicity and possible drugs side-effects like cytotoxicity investigation, metabolic evaluation, pharmacokinetic investigations and toxicology testing in animal models have to be conducted (Kola & Landis, 2004). Chemical properties such as synthetic accessibility, up scaling ability to produce vast quantities of molecules, solubility, compound stability and bioavailability with good pharmaceutical formulation ability and absorption is of key importance before further advancement of new drug candidates towards clinical application (Patrick, 2017). Thus, the presented design approach can be regarded as an early-stage design platform which should be strongly supported through experimental validation using synthetic chemistry, computer-design, pharmacology, toxicological aspects and pharmaceutics combined as an integral unit.

Future Perspectives

The future of novel heterocycles is believed to emerge through integrated research of state-of-the-art synthetic techniques, green chemistry tools, computation intelligibility and novel drug delivery system. These tools together pave the way toward overcoming existing drawbacks related to the conventional methods of drug discovery: New synthetic techniques are supposed to augment specificity and structural diversity of heterocycle synthesis in terms of transition-metal catalysis, multicomponent reactions, microwave-assisted synthesis, flow chemistry and selective functionalization of molecules as means for rapid access toward complicated molecular entities with increased biological relevance (Bostrm et al., 2018); Moreover, Green chemistry will constitute an area to focus its increasing utilization as a driving element. Indeed, green chemistry principles are utilized as guidelines during the drug development phase thereby diminishing usages of organic solvents, renewable resource and catalysts, as well as providing efficient atom economy and minimal waste output (Anastas & Warner, 1998); Additionally, AI-enabled drug design and machine learning will likely bring forth revolutionary changes to heterocycle research by way of developing rapid molecular activity prediction methods and optimizing molecular architecture through analysis of large-scale chemical and biological databases for improved efficacy of novel drug candidates (Lavecchia, 2015); The future of these heterocyclic entities is expected to boost by an increase utilization of nanotechnology based drug delivery systems (polymeric nanoparticles, liposomes, dendrimers, nanostructures) to the improvement in overall therapeutic performance in terms of enhancement in solubility, stability, targeted drug delivery, controlled drug release and prevention of undesirable toxic effect at the systemic level (Mitchell et al., 2016). Hence the future of these heterocyclic researches is believed to largely dependent upon integrating synthetic breakthroughs, green chemistry solutions, computations techniques, nanotechnology tool to develop drug with safety, potency and better specificity toward targeting novel illness

CONCLUSION

Since a variety of physical and chemical characteristics plus the ability to respond specifically towards a variety of biological targets can be adjusted, they remain critical components of the drug development process. It has been conceived from the conceptual study of the discovery and design of novel heterocyclic molecules that the logical molecular designs paired with appropriate structural modifications may offer great prospects for better drug candidates with potency, efficacy, stability and pharmacological behavior (Taylor et al., 2014). It can be envisioned that by the systematic incorporation of organic synthesis approaches into computer-aided drug design, including molecular modeling, biological evaluation and pharmacological investigation is possible to be a systematic framework to guide and facilitate drug discovery process thereby diminishing some limitations of conventional discovery techniques (Sliwoski et al., 2014). Additionally, to take advantage of improvement in new synthetic technique and prediction with the assistance of computational methods, a systematic study towards unknown heterocycles and their possible pharmacological evaluation can be performed without further laboratory validation which could result in a decrease in both the efficiency and innovatively of medicinal chemists. Henceforth, the continuous development for the investigation on novel heterocyclic backbones would present a positive direction towards the needs of solving diseases and more drug discovery as well as development, the better, safter and selective drugs with highly specific activity for clinical applications.

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