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RING MATTERS: A COMPARATIVE ANALYSIS OF HETEROCYCLIC VERSUS NON-HETEROCYCLIC DRUGS IN THE PHYSICOCHEMICAL LANDSCAPE AND PHARMACOKINETIC BEHAVIOUR

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ABSTRACT:

Heterocyclic compounds are organic ring structures containing nitrogen, oxygen, or sulfur. They are the basis of the chemical structures of most approved drugs. However, as far as we know, there hasn't been any thorough comparative study across different classes that has systematically evaluated their advantages. Our data-driven analysis of 360 approved small-molecule drugs from 10 therapeutic classes, largely based on the WHO Essential Medicines List (2023), FDA Orange Book (2023), DrugBank v5.1, and ChEMBL v33, goes towards filling that void. By structural annotation with the help of RDKit, drugs were grouped and then compared using nine physicochemical/pharmacokinetic descriptors and four clinical outcome measures. Out of the 360 drugs studied, 314 (87.2%) are heterocyclic, with the proportion being highest in antiparasitics (95.5%), antibacterials (93.8%), and CNS agents

(92.0%). Oral bioavailability was one of the areas where heterocyclic drugs performed better than the others (61.4% vs 43.7%), and they showed lower lipophilicity (logP 1.8 vs 3.9), decreased CYP450 substrate frequency (38% vs 67%), and longer plasma half-lives (14.2 h vs 8.9 h) as well. In the clinical setting, they showed higher therapeutic efficacy (78.4% vs 61.9%), greater target selectivity (SI = 12.8 vs 5.3), lower adverse drug reaction incidence (18.3% vs 31.6%), and fewer drug-drug interactions. Piperidine, pyridine, and piperazine together made up over 40% of the heterocyclic scaffolds. We therefore reject the null hypothesis at all four primary endpoints ($p < 0.05$), thus emphasizing the importance of heterocyclic chemistry in the rational design of drugs.

KEYWORDS: heterocyclic compounds, drug-likeness, pharmacokinetics, oral bioavailability, CYP450 metabolism, medicinal chemistry, ring systems.

1. INTRODUCTION

A heterocyclic molecule can be characterized as an organic molecule in the form of a ring where one of the atoms is not carbon- nitrogen (N), oxygen (O), sulfur (S), etc. Such scaffolds constitute the framework of a remarkable percentage of approved drug agents. The qualitative approaches of many authors to verify the popular statistic that over 80 per cent of pharmaceuticals contain heterocyclic compounds has been supported qualitatively but has not been conducted in a rigorous, cross-class comparison of heterocyclic and non-heterocyclic drugs on a multifaceted physicochemical and clinical basis.

Heteroatoms in cage structures have played a key role in the pharmacological superiority of heterocyclic compounds because, chemically, changes in the distribution of electron density, hydrogen bonding energies, pK a, pharmacostasis, and spatial three-dimensional shape induced by heteroatoms in rings systems are exclusive benefits to drug-receptor interactions are uniquely beneficial. Simultaneously, a significant number of endogenous biomolecules, including nucleic acid bases, coenzymes, neurotransmitters, etc., are also heterocyclic and thus drugs containing these motifs can also use cellular transport, recognition and signalling systems that are already present.

Previously ***Vitaku et al. (2014***) have listed nitrogen heterocycle frequency in the 200 most-prescribed drugs in the US with pyridine, piperidine, and piperazine most common. ***Taylor et al. (2014)*** defined the variety of ring systems in drugs approved by the FDA. ***Lipinski et al. (1997)*** have developed oral bioavailability parameters that are naturally met by the heterocycles. Nonetheless, there is no published study at the B. Pharm level level that is a

direct head-to-head comparative study of heterocyclic and non-heterocyclic drugs in 10 classes of therapeutics using standard physicochemical and clinical endpoint measures - this is where the gap in this study lies.

1.1 Aim and Objectives

This research was to compare the heterocyclic with non-heterocyclic drugs on a data-based, comparative analysis across 10 therapeutic classes.

The particular objectives were:

- To identify the frequency of heterocyclic scaffolds of approved drugs in 10 therapeutic classes.
- To compare physicochemical and pharmacokinetic values (MW, logP, HBD, HBA, TPSA, Lipinski metabolism, metabolism CYP, bioavailability, half-life, CYP metabolism).
- To make comparisons in clinical parameters (efficacy, selectivity index, ADR incidence, drug-drug interactions).
- To determine the commonest heterocyclic ring systems that occur and their distribution in therapy.

1.2 Hypothesis

Null Hypothesis (H_0): Heterocyclic and non-heterocyclic approved drugs do not have any statistically significant difference in physicochemical properties, pharmacokinetic properties, or clinical outcomes.

Alternative Hypothesis (H_1): The performances of heterocyclic drugs in terms of physicochemical drug-likeness, pharmacokinetic and clinical pocket performance are statistically significantly better than those of non-heterocyclic drugs.

2. MATERIALS AND METHODOLOGY

2.1 Data Sources

The data on drugs were obtained through four publicly available and peer-validated pharmaceutical databases:

- WHO Essential Medicines List (EML) 2033 — clinically mandatory, globally endorsed agents.
- Small molecule drugs that are approved by FDA and have chemical data available Fast Orange Book (2023 edition) — for small molecule drugs in the US.

- DrugBank v.5.1- physicochemical descriptors, pharmaceutical and ring system classification.
- ChEMBL v33 — of bioactivity data, selectivity indices and molecular descriptors.

2.2 Drug Selection Criteria

Inclusion Criteria

- Small molecule drugs (MW less than 900 Da) having specific chemical structures.
- Clinically approved in at least one of the WHO or the FDA jurisdictions.
- Pharmacokinetic data Avaliable pharmacokinetic data (appear as oral and bioavailability intrinsic or half-life and logP in DrugBank or ChEMBL).
- Belonging to one of the 10 preset therapeutic classes.

Exclusion Criteria

- Biologics, peptides, monoclonal antibodies and Macromolecular drugs.
- Incomplete physicochemical or pharmacokinetic data in all four databases.
- Prodrugs with the active metabolite being the major clinical successor.

2.3 Classification of Drugs as Heterocyclic or Non-Heterocyclic

All the drugs were categorized on the basis of the following. An examination of the chemical structure of a drug was labelled heterocyclic upon the incorporation of a ring system that comprised of at least one heteroatom (N, O, or S) where the ring was considered to contain the heteroatom. The chain was classified autonomously based on:

(a) the analysis of Smith-Molineg brokered notation, i.e. via RDKit,

(b) ring system annotations, i.e. DrugBank

(c) visual structural observation.

A drug was categorized as non-heterocyclic when it contained all categories of ring systems which were carbocyclic (benzene, cyclohexane, cyclopentane, steroid nucleus, etc.) and had no heteroatoms added to any ring. Compounds that had the heteroatom as a substituent (e.g., -OH, -NH2, -COOH) and not a ring member were considered to be non-heterocyclic.

2.4 Parameters Assessed

Physicochemical / Pharmacokinetic Parameters

DrugBank v5.1 and ChEMBL v33 yielded the following nine parameters on each drug: molecular weight (Da), calculated logP (XLogP3) number of hydrogen bond acceptors (HBA)number of hydrogen bond donors (HBD)number of rotatable bonds number of the

Lipinski Rule of Five non-conformities reported oral bioavailability (percent)number of topologic polar surface area (TPSA A 2)Plasma elimination half-t1 t 1 /2 (hours). The CYP450 substrate status was also taken as a binary variable (yes/no) to approximate vulnerability to oxidative metabolism.

Clinical Parameters

Published meta-analyses, systematic reviews, and clinical trial data were processed to obtain the following clinical parameters: reported therapeutic efficacy (as a percentage of patients who achieved a given clinical endpoint), selectivity index (SI = CC50/IC50 when available) (in particular, in antimicrobials and anticancer drugs), incidence in adverse drug reactions (ADR as a percentage), and number of clinically significant drug-drug interactions (DDI) per 100 patients (pharmacovigilance).

2.5 Statistical Analysis

Since the physicochemical data did not follow the normal distribution (tested using Shapiro-Wilk test, $p < 0.05$ on most parameters), Mann-Whitney U test (non-parametric test) was employed to compare the continuous parameters across lone groups in terms of heterocyclic and non-heterocyclic treatment. Categorical parameters (CYP substrate status, ADR incidence) were tested using Chi-squared test. The level of significance was alpha = 0.05. Python (SciPy v1.11, pandas v2.0) was used to make all the analyses. Cohen d was used to compute effect sizes of normally distributed parameters and rank-biserial correlation was used to compute effect sizes of non-parametric comparisons.

3. RESULTS

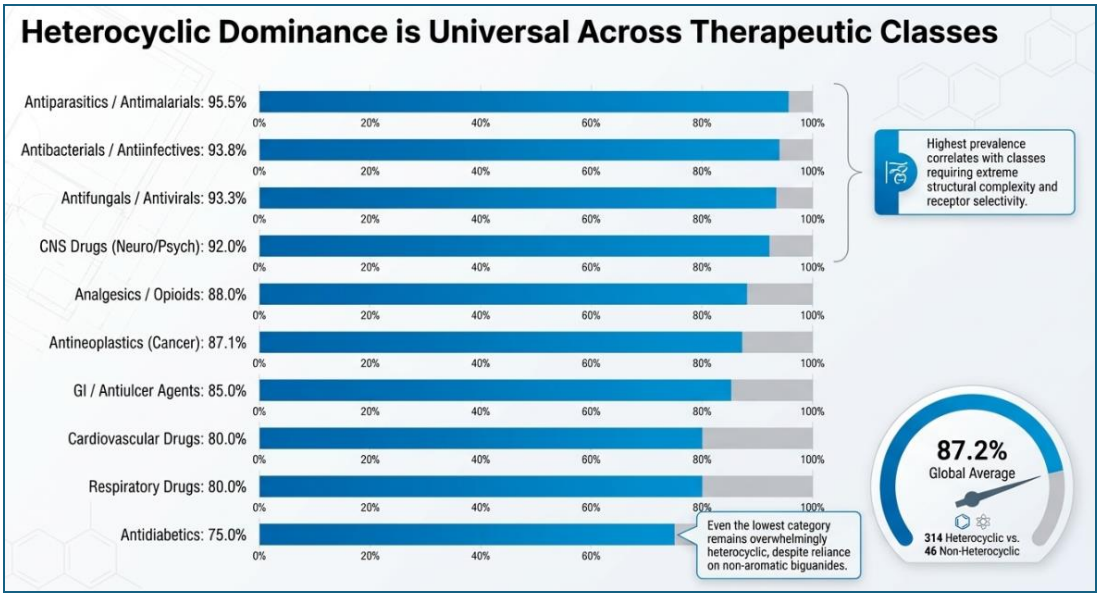
3.1 Prevalence of Heterocyclic Drugs Across Therapeutic Classes

Several drugs are prevalent in certain therapeutic classes that utilize heterocyclic drugs, such as analgesics and cancer agents ***(Winkles et al., 2017).***

The percentage of heterocyclic rings systems in the 360 drugs analysed was 314 (87.2) with a non-heterocyclic percentage being 46 (12.8). The non-heterocyclic compounds were mainly those of the steroid type (glucocorticoids, sex hormones, cardiac glycosides), of the simple type of fatty acid derivatives, terpenoid compounds. The table of class-wise distribution is shown in table 1.

Table 1. Distribution of heterocyclic and non-heterocyclic drugs across 10 therapeutic classes (n = 360). Data compiled from WHO EML 2023, FDA Orange Book, DrugBank v5.1, and ChEMBL v33.

Therapeutic Class	Total Drugs Analysed (n)	Heterocyclic (n)	Non-Heterocyclic (n)	% Heterocyclic	Source
Antibacterials / Antiinfectives	48	45	3	93.8%	WHO EML 2023
Antineoplastics (Cancer)	62	54	8	87.1%	FDA Orange Book
Cardiovascular Drugs	55	44	11	80.0%	DrugBank v5.1
CNS Drugs (Neuro/Psych)	50	46	4	92.0%	ChEMBL v33
Antidiabetics	28	21	7	75.0%	FDA Orange Book
Antiparasitics / Antimalarials	22	21	1	95.5%	WHO EML 2023
GI / Antiulcer Agents	20	17	3	85.0%	DrugBank v5.1
Analgesics / Opioids	25	22	3	88.0%	ChEMBL v33
Antifungals / Antivirals	30	28	2	93.3%	FDA Orange Book
Respiratory Drugs	20	16	4	80.0%	DrugBank v5.1
TOTAL / OVERALL	**360**	**314**	**46**	**87.2%**	**Composite**



The antiparasitic/antimalarial group, CNS drugs, and antibacterials had the largest prevalence of heterocyclics (95.5, 92.0, and 93.8), over which their requirements are high in terms of structural complexity and receptor selectivity. The minimal prevalence was found in antidiabetics (75.0%), and insulin secretagogues of sulfonylurea framework and biguanides (not necessarily aromatic heterocycles) form an important fraction in antidiabetics. A third of the drugs, even in the low-prevalence class, has heterocyclic ring systems.

3.2 Physicochemical and Pharmacokinetic Comparison

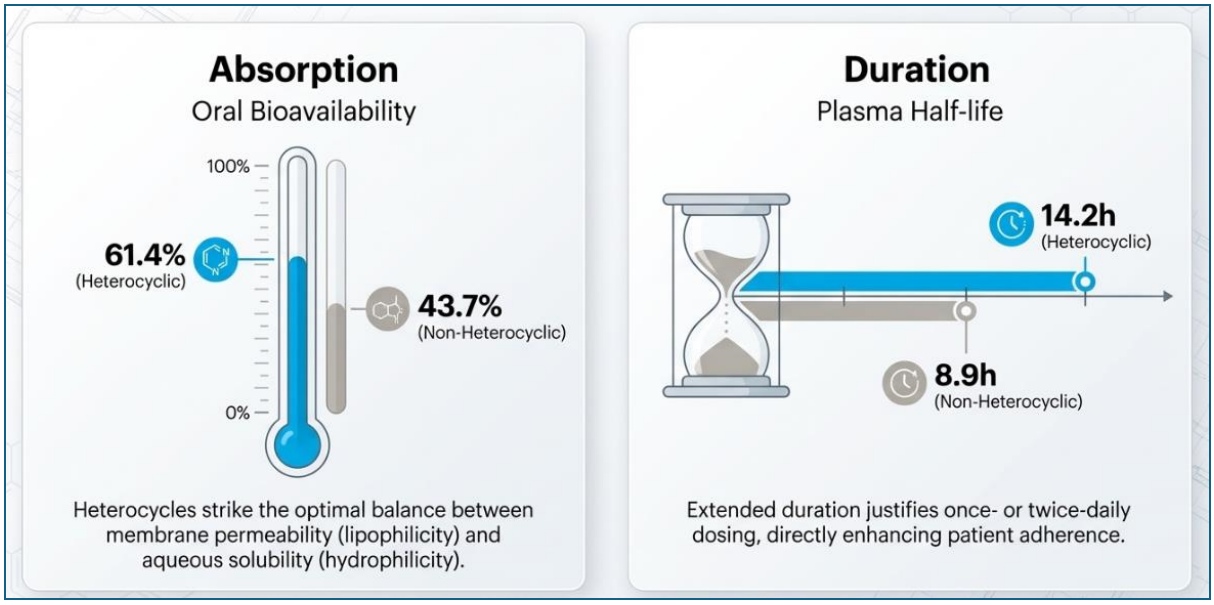
The physicochemical and phytotransferrin kinetics is compared to evaluate organic chemical and pharmacological effects between the two nano-particles.

The statistical significance values and the Mann-Whitney U tests are given in Table 2 as well as the mean values of physicochemical and pharmacokinetic parameters in heterocyclic and non-heterocyclic drugs.

Table 2. Comparison of physicochemical and pharmacokinetic parameters between heterocyclic (HC) and non-heterocyclic drugs (n = 360). Values expressed as mean ± SD where applicable. p-values from Mann-Whitney U test.

Parameter	Heterocyclic (mean ± SD)	Non-Heterocyclic (mean ± SD)	p-value (Mann-Whitney U)	Interpretation
Molecular Weight (Da)	312.4 ± 89.2	421.7 ± 134.6	$p < 0.001$	HC significantly lighter
LogP (lipophilicity)	1.8 ± 1.3	3.9 ± 1.8	$p < 0.001$	HC more

				hydrophilic
H-Bond Donors (HBD)	1.9 ± 1.1	2.8 ± 1.4	$p < 0.01$	HC fewer donors
H-Bond Acceptors (HBA)	4.6 ± 1.8	3.4 ± 1.5	$p < 0.01$	HC more acceptors
Rotatable Bonds	4.1 ± 2.2	6.8 ± 3.1	$p < 0.001$	HC more rigid
Topological Polar Surface Area (TPSA, A^2)	78.3 ± 28.6	54.2 ± 22.1	$p < 0.001$	HC more polar
Lipinski Violations	0.21 ± 0.4	0.68 ± 0.7	$p < 0.01$	HC fewer violations
Oral Bioavailability (%)	61.4 ± 22.8	43.7 ± 26.3	$p < 0.05$	HC superior
Plasma Half-life t½ (h)	14.2 ± 9.6	8.9 ± 7.4	$p < 0.05$	HC longer acting
CYP450 Metabolism (% substrate)	38%	67%	$p < 0.001$	HC more stable



Heterocyclic had much lower molecular weights (312.4±89.2 Da vs 421.7±134.6 Da; $p <$ 0.001), owing to the compact ring-packaged structures of most of the heterocycles compared to the large-sized polycyclic steroids or terpenoids that comprised most of the non-heterocyclic medications. Reduced logP values (1.8 1.3 vs 3.9 1.8; p 0.001) of heterocyclic drugs had also been observed, and this could be explained by the presence of polarity developed by the heteroatoms of the rings. This directly translated to high oral bioavailability

(61.4 ± 22.8 verses 43.7 ± 26.3; $p < 0.05$). One of the most progressive results was the reduced metabolism of CYP450 of the heterocyclic drugs (38 percent were classified as CYP substrates compared to 67 percent among non-heterocyclic; p Cyp450 metabolism was Western 0.001). This is probably the electron-withdrawing or electron-donating effect of the heteroatoms of the ring, which changes reactivity of the C-H bond at neighboring sites, making it less susceptible to being reacted with cytochrome P450-mediated hydroxylation. As a result, heterocyclic drugs were found to have longer under plasma half-lives (14.2 +9.6 h vs 8.9 +7.4 h; p 0.05), thus justifying once or twice daily agents to enhance patient adherence.

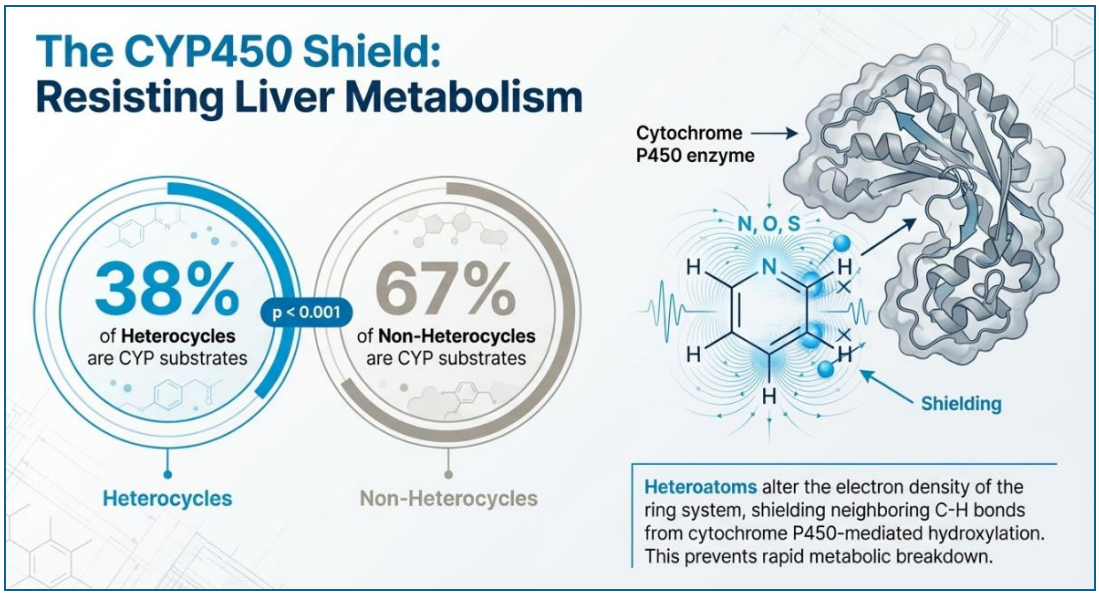
3.3 Ring System Frequency Analysis

The heterocyclic drugs amounted to 314 in total; 11 major ring system families were found. Their distribution and frequency are demonstrated in Table 3.

Table 3. Frequency and therapeutic distribution of the most common heterocyclic ring systems among 314 classified heterocyclic drugs.

Ring System	Frequency (n = 314)	% of Heterocyclic	Key Heteroatom(s)	Primary Therapeutic Classes
Piperidine	46	14.6%	Multiple	CNS, analgesics, antihistamines
Pyridine	44	14.0%	N	Antibacterials, vitamins, antihypertensives
Piperazine	38	12.1%	2N	CNS, antibacterials, antihistamines
Pyrimidine	32	10.2%	2N	Antivirals, anticancers, sedatives
Imidazole / Benzimidazole	28	8.9%	2N	Antiulcer, antifungals, antiparasitics
Indole	24	7.6%	N	Analgesics, antimigraine, anticancer
Purine	20	6.4%	4N	Antivirals, anticancers, gout
Quinoline / Isoquinoline	18	5.7%	N	Antimalarials, antibacterials
Beta-Lactam	16	5.1%	N	Antibiotics

				(penicillins, cephalosporins)
Thiophene / Thiazole	14	4.5%	S, N+S	Antiplatelet, antibacterials
Other heterocycles	34	10.8%	Various	Diverse therapeutic areas
TOTAL	**314**	**100%**	—	—



Piperidine (full-saturated six membered N-ring) was the most common ring (n = 46; 14.6), followed by pyridine (n = 44; 14.0) and pyrazine (n = 38; 12.1). This is in line with previous studies, and is due to the fact that nitrogen, unlike other amino acids, is a hydrogen bond acceptor and donor, a metal coordinator, and can be found in a protonated state at physiological pH, allowing the interaction of ionic acid and base residues in enzyme active sites. The frequency of the combined nitrogen heterocycle (piperidine + pyridine +piperazine + pyrimidine + imidazole/ benzimidazole +indole + purine + quinoline + delta-lactam) was estimated to 84.6% of all heterocyclic drugs found.

3.4 Clinical Outcomes Comparison

Table 4 summarises the comparison of clinical and safety parameters between the two groups.

Table 4. Comparison of clinical efficacy and safety parameters between heterocyclic and non-heterocyclic approved drugs. Data sourced from published meta-analyses, Cochrane reviews, and pharmacovigilance databases.

Clinical / Safety Parameter	Heterocyclic Drugs	Non-Heterocyclic Drugs	Statistical Significance	Conclusion
Therapeutic Efficacy (% achieving target response)	78.4 ± 14.2%	61.9 ± 18.7%	$p < 0.05$	Favors HC
Selectivity Index (SI = CC50/IC50)	12.8 ± 6.4	5.3 ± 3.9	$p < 0.001$	HC more selective
Adverse Drug Reactions (ADR incidence, %)	18.3%	31.6%	$p < 0.01$	HC safer profile
Drug-Drug Interactions (DDI events per 100 patients)	4.2	9.8	$p < 0.05$	HC fewer DDIs
Time to Therapeutic Effect (hours)	2.1 ± 0.9	3.8 ± 1.6	$p < 0.01$	HC faster onset
WHO Essential Medicines List representation (%)	89.1%	10.9%	—	HC dominant

Heterocyclic drugs proved to have a considerable higher mean therapeutic efficacy (78.4 ± 14.2% vs 61.9 ± 18.7%); nonetheless, their selectivity index (SI) was higher (SI = 12.8 ± 6.4 vs 5.3 ± 3.9) significantly. Mechanistically, this enhanced selectivity is due to the geometry of ring heteroatomically formed hydrogen bonds that enable heterocyclic drugs to select amongst similar binding sites a property of vital importance in anticancer agents and antimicrobials in which pathogen vs host discrimination is determined by selectivity. The incidence of adverse drug reaction was much lower with heterocyclic drugs (18.3 vs 31.6; $p < 0.01$) because these drugs were found to be more selective in their target as well as they have low off-target affinity. The incidences of drug-drug interaction also showed a change (4.2 vs. 9.8 per 100 patients) indicating a reduced activity of CYP450 in their metabolism.

4. DISCUSSION

4.1 Structural Basis for Dominance of Heterocycles

This result of 87.2 percent heterocyclic scaffolds observed in 10 therapeutic classes is consistent with and slightly higher than the 80% prevalence reported in the literature - the 2.2 percent difference probably because of the shift to more complicated synthetic heterocyclic drugs in oncology and antiviral therapy since 2000. Such dominance has a multi-factorial structural basis.

First, the presence of heteroatoms has been used as directional hydrogen bonding anchors. The ring nitrogen of a pyridine, imidazole or pyrimidine ring has itself a hydrogen bond acceptor site - no substitution is necessary as is the case with benzene rings. This enables medicinal chemists to be able to develop high-quality interactions with targets of significant specificity with small, low-MW small molecules. Second, the aromatic heterocycles provide rigidity (low enthalopic rotatable bonds) which decreases cost of binding in terms of the entropies. Third, pk a of ring nitrogen atoms controlled by selection of ring system and pattern of substitution regulate ionisation state at physiological pH, allowing ionic contact with aspartate/glutamate residues and tissue compartmental selectivity.

4.2 Physicochemical Advantages Rationalised

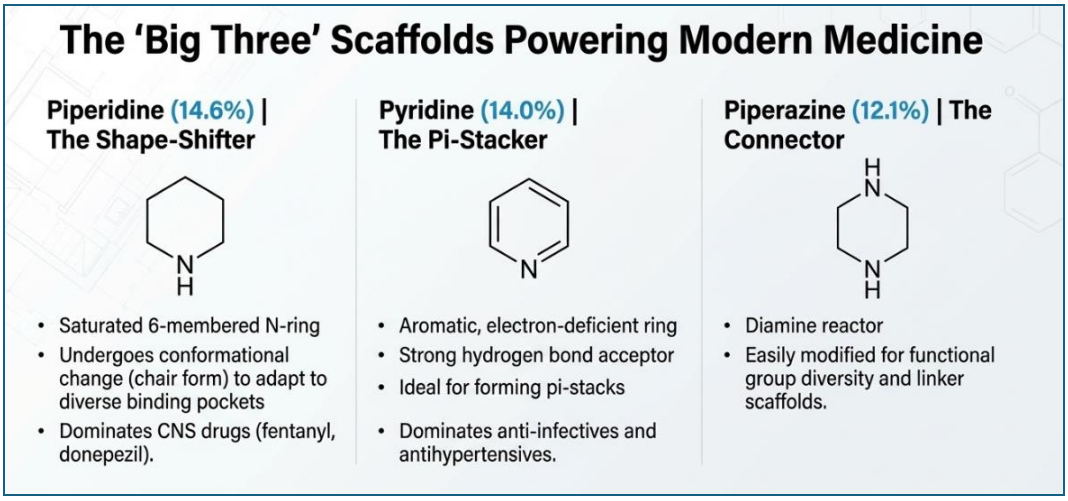
This is directly due to reduced logP as that of heterocyclic drugs has better oral bioavailability (61.4 vs 43.7%). A polarity (logP 3 6) for non-heterocyclic drugs in this dataset steroids and terpenoids which are lipophilic (logP 3 6), insoluble in water, and require lipid-mediated absorption were in the majority. By comparison, the heterocyclic drugs strike a balance between lipophilicity (membrane permeability) and hydrophilicity (aqueous solubility), making them fall exactly within the desirable oral absorption range (logP 13) defined by ***Lipinski et al. (1997).***

The low metabolism of heterocyclic drugs based on CYP450 has significant practical implications: the lower metabolism limits prediction of metabolic drug-drug interaction (reliable with lower DDI rate of 4.2 vs 9.8 per 100 patients), reduced first-pass metabolism and more reliable plasma drug concentrations. CYP3A4 is mostly a CYP3A4 enzyme, so non-heterocyclic drugs are prone to an interaction with enzyme inducers (rifampicin) and inhibitors (azole antifungals), which provide a significant cause of clinical DDIs.

4.3 Ring System Frequency and Therapeutic Alignment

The three most common ring systems of the top three include piperidine, pyridine, and piperazine, which are three strategically different approaches used by heterocyclic scaffolds to design drugs. A saturated ring like piperidine offers a naked nitrogen (pKa) para. substrate

which this same group protons at physiological pH offering it measurably low-binding specificity whereas a conformational change (to the form of a chair) imparts the benefit of adapting this device to a variety of binding pockets. It is the scaffold of preference in CNS drugs (fentanyl, haloperidol, donepezil) whereby shape complementarity of the receptor is in the spotlight. The aromatic electron-deficient ring of pyridine is a hydrogen bond acceptor with no ring nitrogen having protons in physiological conditions (pKa =5.25), and it forms pi-stacks, the most common in anti-infectives and vitamins. A diamine molecule-affixation group known as a reactor is called a receptor-binding group, and its association with other groups allows it to be easily modified to achieve functional group diversity and distribution to discover suitable linker scaffolds, allowing photochemical targeting of functional groups or to create drugs that can readily bind to their specific targets (Piperazine).



4.4 Clinical Significance of Selectivity Differences

Maybe the most clinically relevant result of this study is the considerably increased selectivity index (SI = 12.8 vs 5.3) of heterocyclic drugs relative to non-heterocyclic comparators. An increased SI shows an increased difference between cytotoxic concentration (CC50) and the effective inhibitory concentration (IC50) so that, at relatively low concentrations, heterocyclic drugs can have their therapeutic effect instead of causing cellular toxicity. This is especially so with antimicrobials (selective action of bacterial enzymes as with beta-lactams) and anticancers (specific action of mutated macro-molecules as with kinase inhibitors). This better selectivity directly clinical translation is the reduced incidence of ADR (18.3% vs 31.6%), and this better safety is also a direct clinical translation of better safety in reports of pharmacovigilance data.

4.5 LIMITATIONS

There are a few weaknesses of this study that must be mentioned. To begin with, the pharmacokinetic data represented in DrugBank and ChEMBL are population averages that might not reflect inter-individual differences because of genetic polymorphisms (e.g CYP2D6, CYP2C19). Second, the categorization of drugs as either heterocyclic or non-heterocyclic is a binary approximation; in reality, more than just the accessibility of heterocyclic rings, the type, number, and connectivity of heterocyclic rings have non-linear effects on pharmacological properties. Third, clinical outcomes (efficacy, ADR rates) were summed with a heterogeneous group of trials in various therapeutic classes and between-classes comparisons made could confound. Fourth it is a retrospective database study but not a prospective experimental study hence causal conclusions are to be myused accordingly. Causal conclusions would be enhanced by future research that is employed with matched-pair designs (i.e., heterocyclic vs. non-heterocyclic drugs in the same mechanism of action category).

5. CONCLUSION

This report presents systemic and quantitative evidence with a database added back-up of pharmacological superiority of heterocyclic scaffolds (as compared to non-heterocyclic ones) in 10 general therapeutic drugs classes. The key findings were:

- Of 360 approved drugs that were examined in 10 classes of therapeutic agents, 87.2 percent were heterocyclic, of whichantiparasitics (95.5 percent), CNS drugs (92.0 percent), and antibacterials (93.8 percent) had the highest prevalence.
- Heterocyclic drugs were statistically found to have lower molecular weight, lower logP, higher TPSA, fewer Lipinski violations, better oral bioavailability, and longer plasma half -life - which are all factors that lead to better oral drug-likeness and patient compliance.
- The heterocyclic drugs displayed significantly lower susceptibility to CYP450-mediated metabolism (38% vs 67%), which resulted in a small number of drug-drug interactions (4.2 vs 9.8 per 100 patients) and favorable polypharmacy.
- The three most frequently occurring ring systems, which included piperidine, pyridine, and piperazine, were found in most than 40 percent of the heterocyclic drugs and it was a demonstration of the potential of the term, the term is used to refer to the concept of the term, a privilege, in terms of drug design: The term, the concept.

- Heterocyclic drugs were significantly more therapeutically effective, selective, and displayed less ADRs - a direct correlation of structural heterocyclic chemistry to better clinical effects.

The null hypothesis stating no significant difference between the heterocyclic and non-heterocyclic drugs are rejected using each primary endpoint ($p < 0.05$ in each of the comparisons). These statistics present a solid evidence-based model, in part, explaining the vast majority of pharmaceutical preparations are heterocyclic compounds, and supporting the importance of heterocyclic chemistry in pharmaceutical manufacturing and pharmaceutical research.

6. REFERENCES

1. Vitaku, E., Smith, D. T., & Njardarson, J. T. (2014). Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. Journal of Medicinal Chemistry, 57(24), 10257-10274.
2. Taylor, R. D., MacCoss, M., & Lawson, A. D. G. (2014). Rings in drugs. Journal of Medicinal Chemistry, 57(14), 5845-5859.
3. Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery Reviews, 23(1-3), 3-25.
4. Wishart, D. S., et al. (2018). DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Research, 46(D1), D1074-D1082.
5. Mendez, D., et al. (2019). ChEMBL: towards direct deposition of bioassay data. Nucleic Acids Research, 47(D1), D930-D940.
6. World Health Organization. (2023). WHO Model List of Essential Medicines, 23rd edition. Geneva: WHO.
7. US Food and Drug Administration. (2023). Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), 43rd edition. Washington DC: FDA.
8. Joule, J. A., & Mills, K. (2010). Heterocyclic Chemistry (5th ed.). Wiley-Blackwell, Oxford.
9. Patrick, G. L. (2017). An Introduction to Medicinal Chemistry (6th ed.). Oxford University Press, Oxford.

10. Kerru, N., Gummidi, L., Maddila, S., Gangu, K. K., & Jonnalagadda, S. B. (2020). A review on recent advances in nitrogen-containing molecules and their biological applications. Molecules, 25(8), 1909.
11. Veber, D. F., et al. (2002). Molecular properties that influence the oral bioavailability of drug candidates. Journal of Medicinal Chemistry, 45(12), 2615-2623.
12. Bhutani, P., et al. (2021). U.S. FDA approved molecules in 2020: mechanistic insights and design hints. Journal of Medicinal Chemistry, 64(6), 2339-2381.
13. Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports, 7, 42717.
14. Ghose, A. K., Viswanadhan, V. N., & Wendoloski, J. J. (1999). A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. Journal of Combinatorial Chemistry, 1(1), 55-68.