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Target-Based Drug Discovery: Discovery and Synthesis of G-Protein Biased Agonists Towards the 5-Hydroxytryptamine$_{2A}$ Receptor

By Angela Long

AUTHOR BIOGRAPHY

Angela Long is an upcoming Canadian Grade 12 student attending St. Mildred's-Lightbourn School. Her interest in drug discovery and pharmaceutical research actually stems from her passion for biochemistry which her grandparents and cousin inspired her to chase. She hopes to major in chemistry and pursue pharmacology in her higher education to improve representation and quality of care in healthcare.

ABSTRACT

Creating a novel, purposeful medicine through the drug discovery pipeline requires three major considerations: *in vitro* potency and selectivity, pharmacokinetics and pharmacodynamics (PK & PD), and safety. Typically, novel drug research begins with the identification of a healthcare gap or unmet need: for example, neuropsychiatric disorders such as depression or PTSD have become increasingly prevalent in the population, and even with current technology and medicine, there are still concerns that must be addressed. A relatively unexplored treatment angle in this particular field is the harnessing of the therapeutic properties of psychoactive compounds such as LSD or psilocybin while divorcing these benefits from their well-known hallucinogenic effects. The key aims in this review paper cover the discovery and synthesis of novel agonists towards the serotonin receptor 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) inspired by psychoactive drugs and within this context, the different signaling pathways (G-protein vs. β-arrestin) of G-protein coupled-receptors (GPCRs) and the critical concept of biased agonism are discussed as playing a significant role in the discovery of potent and selective ligands (R)-69 and (R)-70. Additionally, screening methodologies to discover hit compounds and the importance of structural motifs including nitrogen heterocycles such as tetrahydropyridines (THPs) in drugs are discussed. Finally, the results of lead candidates (R)-69 and (R)-70 in animal behavioural models such as the Head Twitch Response (HTR) test and Tail Suspension Test (TST) to evaluate the efficacy and safety of the compounds are explored in this review. Although (R)-69 and (R)-70 have not undergone clinical trials, the current findings show an optimistic future perspective for the expansion of neuropsychiatric treatments in a novel direction, and this project represents an interesting case study highlighting the critical components of the drug discovery process.

SCHOLARLY REVIEW JOURNAL

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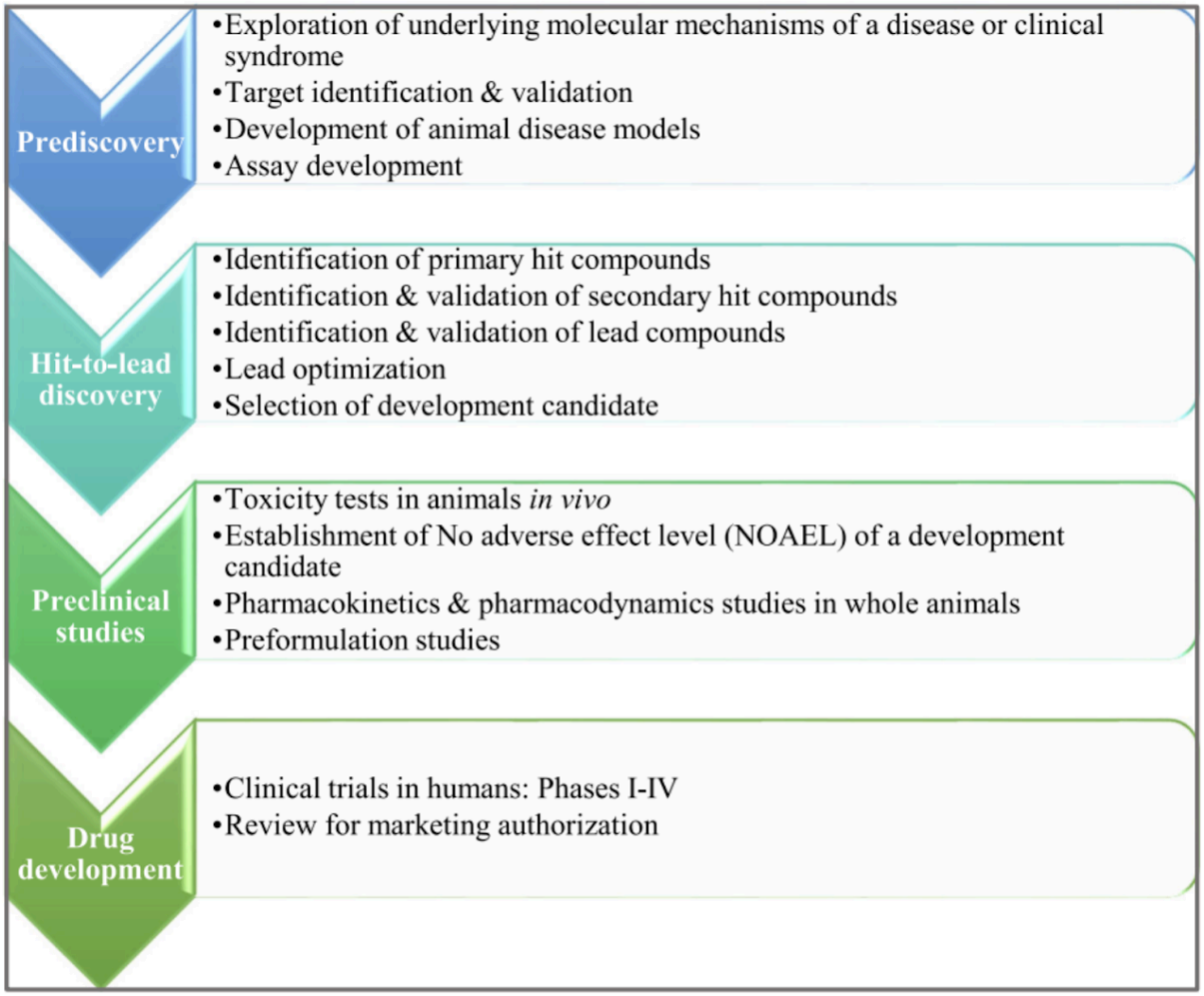

Figure 1. Generic outline of the drug discovery and development process. Reprinted from Exploring different approaches to improve the success of drug discovery and development projects: a review. (Kiriiri et al., 2020)

PROCESS OF DRUG DEVELOPMENT

Drug discovery describes the process in which a medication or novel treatment option is developed to address a current disease or disorder. The journey can be complex and long, but for a molecule to become a drug, there are three broad requirements: in vitro potency and selectivity, pharmacokinetics and

SCHOLARLY REVIEW

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pharmacodynamics (PK & PD), and safety. Potency explains the measure of sensitivity of a drug to a target receptor or organ while selectivity generally describes the degree to which the drug will interact with the target site versus other sites or targets. PK & PD studies focus on the interactions between the drug candidate and body: how does the body process the drug (PK) and what therapeutic effects does the drug have on the body (PD). Safety requires a potential drug candidate to deliver its therapeutic effect while doing limited harm to the patient.

There are two different outlooks to drug development: phenotypic and target-based drug discovery (PDD/TDD). The TDD process begins with the recognition of an unmet clinical need and a clear understanding of the disease's biological mechanism. This initial pre-discovery phase shapes the approach to the rest of the project and depends on the complexity of the condition and of existing knowledge and equipment. Then, potential therapeutic candidates are identified through a range of screening methods, and evaluated for early signs of efficacy, safety, and drug-like behavior. After significant optimization, promising compounds move into preclinical testing, where pharmacokinetics, pharmacodynamics, and toxicity are assessed through assays and animal models. If successful, this leads to clinical trial planning and testing in human control groups.

Target-based drug discovery (TDD) has been the primary process used in the pharmaceutical industry since the 1980s in discovering and developing novel drugs. Although there has been debate over this form of drug discovery and its effectiveness over phenotypic drug discovery (PDD), TDD has been highly effective, as 70% of US FDA-approved first-in-class drugs were developed through TDD over the last three decades (Croston, 2017). While PDD is more serendipitous, relying less on understanding the target and mechanism of action, TDD analyzes the mechanism and biological targets as the reference for creating a novel drug. Unfortunately, while both PDD and TDD procedures can help the development of successful drugs, not every research and development project will succeed—in fact, they rarely do: only around 1 in 20,000–30,000 projects come to fruition after going through the entire TDD process (Yamaguchi et al., 2021). Adding in that the typical successful innovative drug development projects take on average 9.1 years (Brown et al., 2021), it is clear that the creation of novel drugs is difficult and strenuous. As a result, it's important to understand what has made previous clinical development projects successful and find ways to increase the success of a project. This review will analyze the general principles of the drug discovery pipeline. The discovery and synthesis of novel biased agonists towards the serotonin receptor 5-HT_{2A} for the treatment of neuropsychiatric disorders will be discussed as a case study to demonstrate crucial areas of this drug discovery pipeline, and in doing so, the importance of GPCR signaling pathways and nitrogen heterocycles in drug discovery will be detailed.

TDD FOR NEUROPSYCHIATRIC INDICATIONS AND GPCR SIGNALING

To kickstart the target based drug discovery process, an unmet or insufficiently met need must be identified, which becomes the motivation behind developing a drug or treatment. In the context of this project, the treatment of neuropsychiatric disorders—which includes schizophrenia, PTSD, anxiety, and depression—represents the focus of this research. These are all conditions that have been reported to have substantially risen in these past few decades: anxiety and depression increasing by 25% in 2019, the global

SCHOLARLY REVIEW JOURNAL

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prevalence of PTSD increasing from 3.4% (2017-2018) to 7.5% (2021-2022), and schizophrenia cases rising from 13.1 million in 1990 to 20.9 million in 2016 (World Health Organization et al., 2022; Zhai & Du, 2024; Charlson et al., 2018). Despite current technology and medicine, these conditions have become more common within the population, creating a critical medical need that still must be addressed.

After identifying a major gap in healthcare, an appropriate target must be identified and validated for the treatment of the condition. For the case of many drug candidates, this refers to the receptor that a drug molecule can bind to potently and selectively to provide a therapeutic benefit. Effective drug targets must be disease-relevant, druggable, and safe to affect with therapeutic compounds.

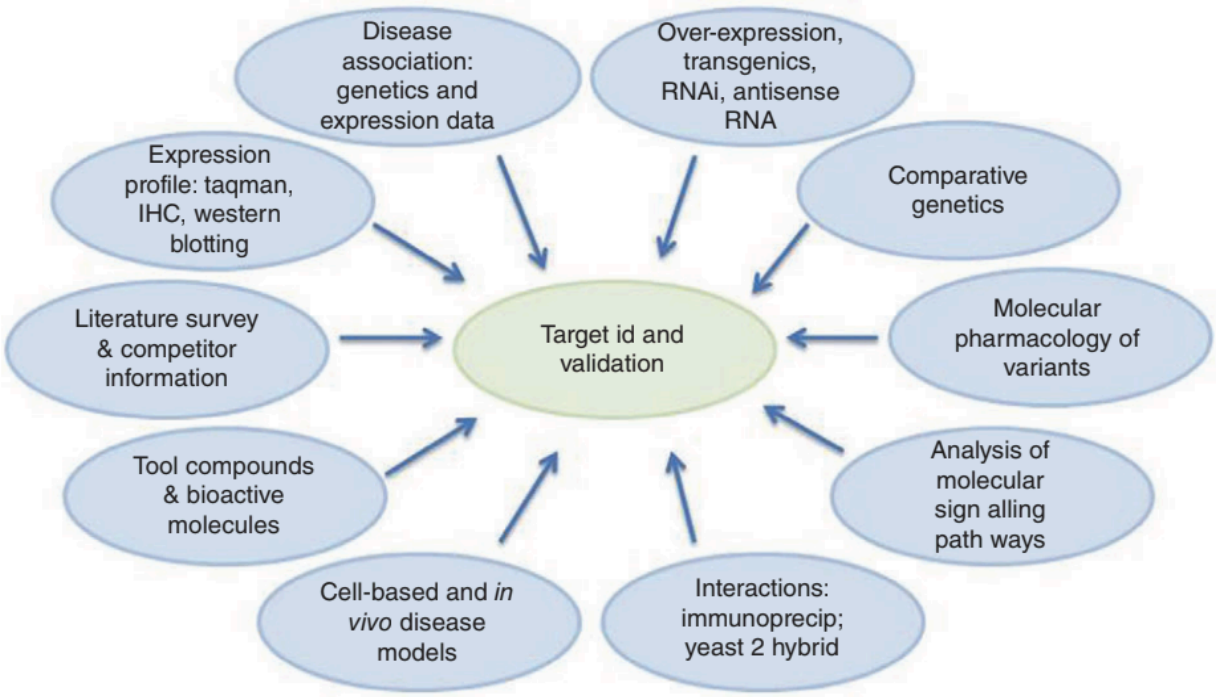

Figure 2. Target ID and validation is a multifunctional process. Reprinted from "Principles of early drug discovery". (Hughes et al., 2010)

GPCRs are the most common class of druggable targets, due to being both the largest family of membrane receptors in humans and regulating many core human processes from cognition to emotional regulation (Wootten et al., 2018). To date, an approximate 34% of US Food and Drug Administration (FDA)-approved drugs are targeted to GPCRs (Zhang et al., 2024). GPCRs are involved in a wide range of physiological processes and are highly "druggable" due to their accessible extracellular binding pockets and their ability to activate intracellular signaling cascades.

SCHOLARLY REVIEW

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GPCRs are seven unit transmembrane proteins that mediate cellular responses to diverse stimuli via two main signaling pathways: the G-protein mediated pathway and the β-arrestin pathway. Ligand binding changes the shape of the receptor—like what happens when LSD binds to 5-HT_{2A}—which then decides what signals are sent inside the cell. These conformational changes help the receptor choose which pathway to activate, such as the G-protein or β-arrestin pathway.

In the G-protein mediated pathway, the ligand-GPCR complex will then bind to a G-protein, which are proteins composed of 3 subunits, the alpha subunit (Gα) and beta-gamma subunits (Gβɣ) (Professor G - Pharmacology, 2024). When the receptor is not bound to any receptor (inactive), the Gα subunit is bound to GDP. However, when an agonist does bind, it initiates guanylyl exchange where the GDP molecule on the Gα subunit is exchanged for GTP—this causes the subunits to disassociate from the receptor and interact with their own individual targets, which can subsequently affect different signaling cascades. Depending on which cascade, this could result in the stimulation or inhibition of activities. Kinases are enzymes that catalyze the transfer of phosphate groups, also known as phosphorylation; critical to regulating signaling pathways and cellular processes, the transfer of a phosphate group can activate or deactivate the target protein. Phosphorylation occurring also leads to receptor desensitization (Professor G - Pharmacology, 2024).

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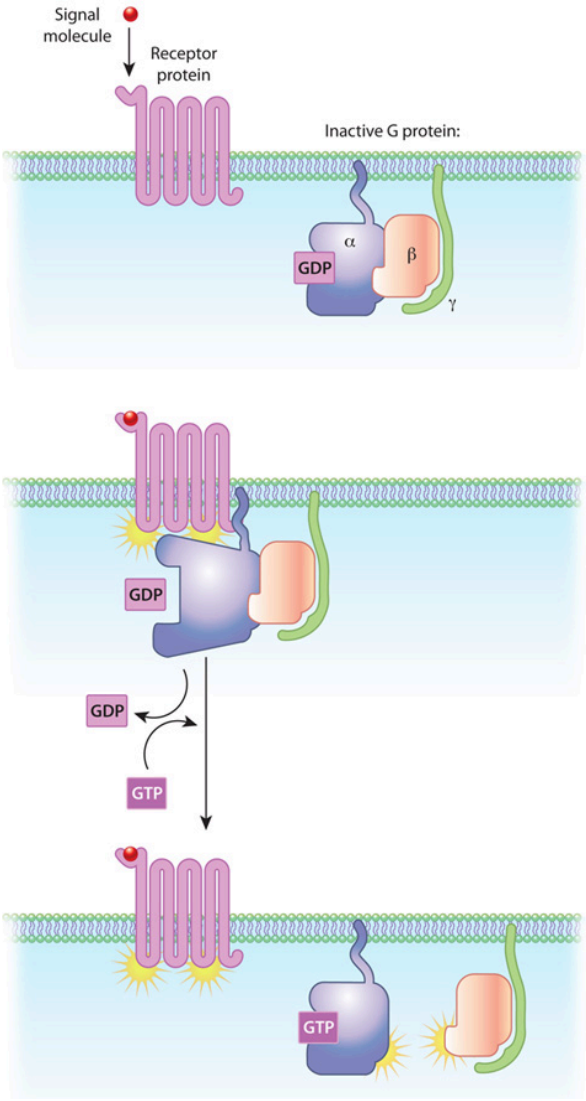

Figure 3. Illustration of GDP and GTP exchange after a compound binds to a GPCR receptor that results in the dissociation of the G-protein subunits. Reprinted from GPCR. (*GPCR | Learn Science at SciTable*, n.d.)

In the beta-arrestin pathway of GPCRs, the understanding originally was that the β-arrestin pathway binds to the phosphorylated receptor, blocks G-protein pathway signaling, and prepares the receptor for clathrin-mediated endocytosis which removes the receptor from the membrane and brings it inside the cell in an endosome—however this is only the understanding of GPCRs from only 20 years ago. Knowledge of GPCR pathways is much more intricate now: β-arrestin interacts and affects pathways that contribute to the effects of a GPCR ligand which are independent to the Gα and Gβɣ subunits (Professor G - Pharmacology, 2024). This differs from the classical thinking that β-arrestin pathways are not involved in similar cascades such as the G-protein subunits and only reacts to a phosphorylated GPCR.

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Importantly, this dual signaling nature of GPCRs introduces an opportunity for pathway-selective pharmacology also known as biased agonism. Some ligands are biased agonists that can activate the G-protein mediated pathway without activating the β-arrestin signaling, or vice versa. This is the concept of biased agonism, in which drugs are engineered to selectively activate only one pathway by preferentially stabilizing different conformational states of the GPCR complex. An example of G-protein activity biased agonists is oliceridine, a μ-opioid receptor used to treat pain. The therapeutic effects are caused by the G-protein mediated signaling cascade while the β-arrestin pathway is responsible for the negative effects such as nausea or constipation (Professor G - Pharmacology, 2024). As a result, it's clear that a drug biased towards the 'positive' therapeutic pathway without activating the other signaling pathway would provide a more useful medication. This concept is also well known as functional selectivity.

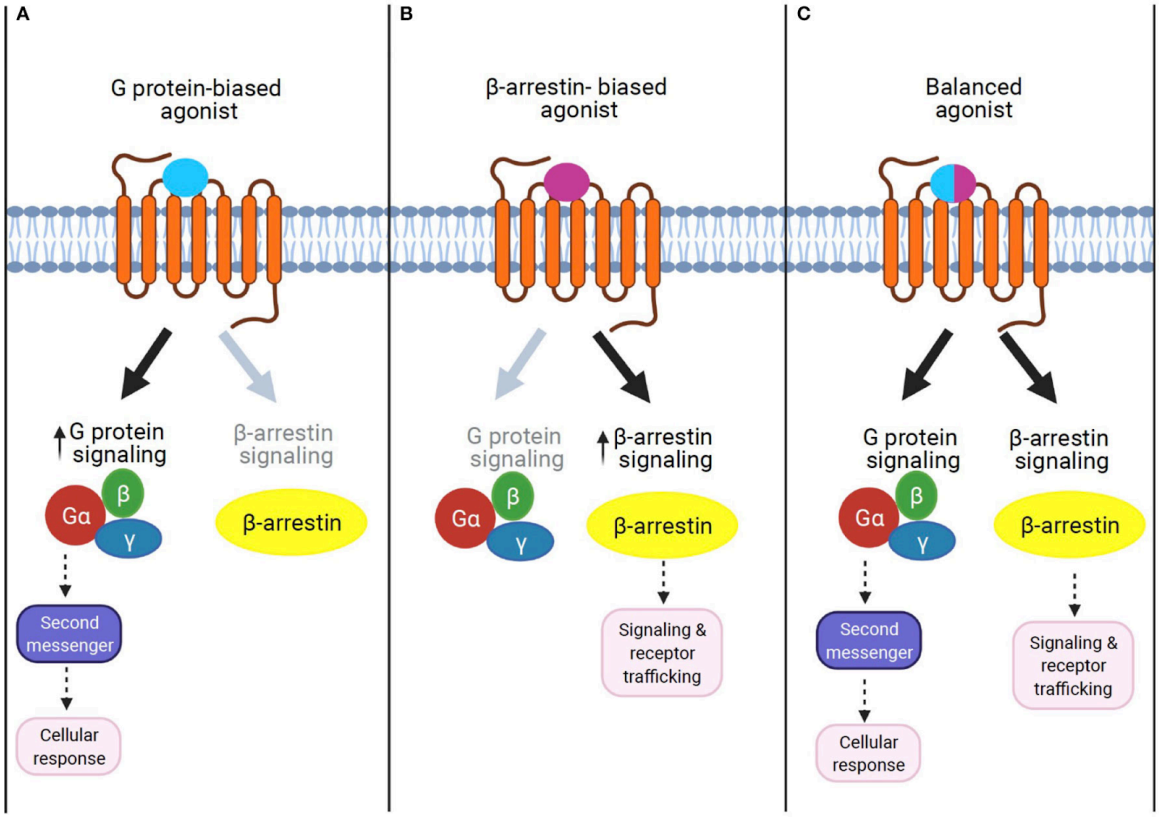

Figure 4. Diagram displaying biased agonism behaviour when an agonist prefers a G-protein pathway, β-arrestin pathway, or triggers both. Reprinted from Metabolic functions of G Protein-Coupled receptors and β-arrestin-Mediated signaling pathways in the pathophysiology of type 2 diabetes and obesity. (De Souza et al., 2021)

SCHOLARLY REVIEW

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For the 5-HT_{2A} project, harnessing the advantages of biased agonism and functional selectivity was the goal in discovering a novel drug which would retain the beneficial unique antidepressant, anxiolytic, and anti-addictive effects of psychoactive drugs while eliminating their more harmful, psychoactive side effects.

In the case of 5-HT_{2A}, LSD activates both pathways: the G-protein mediated pathway is associated with the aforementioned therapeutic effects, while the β-arrestin pathway is linked to undesirable hallucinogenic effects. The hope was to create a drug that would produce the good effects through the preferentially selected pathway and get rid of the bad. If such a drug could be produced, then this has the potential of redesigning and creating novel drugs that have never been produced before and expanding the range of treatments for neuropsychiatric conditions.

PREDISCOVERY → HIT TO LEAD

Challenges in target identification include distinguishing between primary disease drivers and secondary effects, as well as predicting off-target interactions. Validation also requires robust disease models, often involving cell-based or animal models, which may or may not reflect the same effects on human physiology. Ultimately, target selection must and should be validated in multiple different ways for confidence in the target itself.

Hit-to-lead discovery is a critical process where initial hit compounds identified through primary screening are optimized into lead candidates with improved potency, selectivity, and pharmacokinetic (PK) properties. This process begins with validating primary hits to confirm target engagement utilizing screening strategies such as high-throughput (HTS) or virtual screening (VS). Promising hits then undergo iterative chemical modification and *in vitro/in vivo* assays to test their efficacy, selectivity, and drug characteristics. Beginning with protein-based assays and cellular models, the testing builds up into experiments using whole organisms such as mice or rats.

HTS is the traditional screening method and requires a large, real library of compounds. These libraries can hold up to millions of potential molecules and are analysed in assays—this approach relies on brute-force experimental testing of all compounds. HTS is still relatively slower than VS even with the automation of the process. Although HTS requires significant resources such as cost, time, and infrastructure, it is an unbiased exploration of chemical space that can uncover novel properties. Additionally, HTS' weakness compared to VS is that the approach is limited to what is available (often in the millions) while VS can run through billions of potential targets.

VS is a computational target filtering strategy using online chemical libraries that select potential hit compounds by simulating their interactions with a target's 3D structure. Using molecular docking algorithms, VS predicts how small molecules fit into the target's binding site such as the 5-HT_{2A} pocket. These docking simulations are designed to estimate how well a compound would perform in real *in vitro* assays, providing an early assessment of potency and binding before physical testing. This approach relies on structural data such as

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crystal structures and cryogenic electron microscopy (cryo-EM) and can screen ultra-large libraries at significantly lower costs than HTS. While VS is resource-efficient, its accuracy depends on the quality of the target model and hits typically require experimental validation. Although the effects of compounds in *in vitro* and *in vivo* testing may be predicted, this can only be validated through empirical trials. For the discovery of potent and selective ligands towards 5-HT_{2A}, although VS was able to filter through billions of molecules in a chemical library to ultimately end up with 17 potential hit-compounds, empirical testing revealed that only 4 were hits towards the actual receptor. Through further optimization and testing, two lead candidates in the project *(R)-69* and *(R)-70* were discovered.

IMPORTANCE OF NITROGEN HETEROCYCLES

Within this process, another important consideration within screening is that there are often structural motifs that are searched for and prioritized when selecting target-compounds. In the case of the LSD-inspired antidepressant drug candidates, N-heterocycles were a key molecular structure searched for within the target-compounds. Why nitrogen heterocycles? Virtual screening was used to search for initial hit compounds toward the target receptor 5-HT_{2A} and focused specifically on searches through molecules containing nitrogen heterocycles. N-heterocycles are prevalent within approximately 60% of all FDA approved drugs because of a multitude of reasons (Dongbang et al., 2021): nitrogen is capable of the strongest intermolecular force—hydrogen bonding—as well as salt bridges which are critical in binding a drug to a target site (Bosshard et al., 2004). Additionally, in a ring structure, the nitrogen atom is less mobile compared to a free nitrogen which facilitates more stable intermolecular force (IMF) interactions.

A strong understanding of molecular structure is key to understanding and manipulating a compound's selectivity and potency. Two key molecules that potently and selectively bind to the target site 5-HT_{2A} are serotonin and LSD and a structural motif within these two molecules are nitrogen heterocycles.

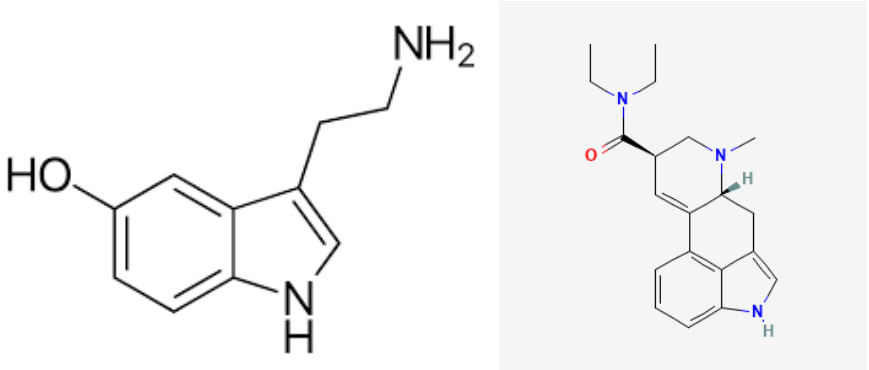

Figure 5. Compound drawings of Serotonin ($C_{10}H_{12}N_{20}$) also known as 5-hydroxytryptamine and LSD (Lysergide, $C_{20}H_{25}N_{30}$).

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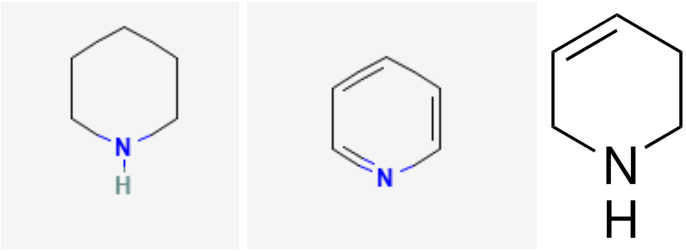

Figure 6. Compound drawings of three n-heterocycles from the left to the right being piperidine, pyridine, tetrahydropyridine (THP).

Taking all of this into consideration, within the case study project, tetrahydropyridine (THP) was chosen as a key structure that should appear in the hit-compound in VS. Why THP rather than piperidine or pyridine? Piperidine and pyridine are both common structures within FDA-approved drugs, while THP is much more underrepresented, which offers more unique opportunities to form novel drugs. This also decreases the chances of producing a drug with a clinical and commercial use that is too similar to any other approved drug already existing in the market. After identifying key structural motifs that should exist within the target compound and conducting VS and real assays, lead optimisation follows. Specifically, structure activity relationship (SAR) and empirical studies are conducted to improve potency, selectivity, and other favourable drug properties.

STRUCTURE-ACTIVITY RELATIONSHIP (SAR)

Structure-activity relationship (SAR) is a key concept describing optimization of the hit compounds in hit-and-lead discovery. SAR explores how modifications to a drug's chemical structure influences biological activity, selectivity, potency, and pharmacokinetic (PK) properties. By systematically altering functional groups or the compound's spatial arrangement, researchers aim to optimize drug candidates until one meets the specific requirements of selectivity and potency. For example, optimizing a compound to bind selectively and strongly to a specific target receptor rather than to multiple other receptors is key to creating an effective target drug. A reasonable example of SAR would be replacing a methyl-group (CH_3) with a chlorine atom (Cl) that is of similar size but makes for a more metabolically stable compound.

In vitro/vivo studies

Preclinical studies evaluate a drug candidate's safety and biological activity before human testing. This stage involves *in vitro* assays such as receptor binding and *in vivo* animal studies to determine toxicity, pharmacokinetics (absorption, metabolism), and pharmacodynamics (mechanism of action). Key outcomes include establishing the No Observed Adverse Effect Level (NOAEL)—the highest dose at which no harmful effects are observed—and optimizing formulation. Only candidates with acceptable safety profiles advance to clinical trials, though ~90% projects fail during this phase due to toxicity or poor drug-like properties (Tagle, 2019).

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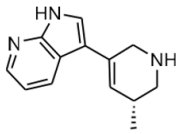
In vitro studies, conducted in controlled environments like cell cultures, allow high-throughput screening of drug candidates and mechanistic exploration of target interactions. These experiments are cost-effective and enable precise manipulation of variables but lack the complexity of living organisms. *In vivo* studies, performed in animal models, bridge this gap by evaluating pharmacokinetics (PK), toxicity, and behavioral outcomes in a whole-organism context. While more resource-intensive, *in vivo* data are essential for validating therapeutic potential and safety before clinical trials. The only issue is that behavioural effects and mechanisms in animal models oftentimes do not translate to the human body. The transition from *in vitro* to *in vivo* is particularly critical for GPCR drugs, where pathway-specific effects (e.g., G-protein vs. β-arrestin bias) may only manifest in intact physiological systems. Advancements in CRISPR technology has made it possible to genetically modify animals to express humanized target proteins or manipulate animals to exhibit a particular trait (such as depression) to show the therapeutic effectiveness of a drug in a potency assay involving animals (Birling et al., 2017).

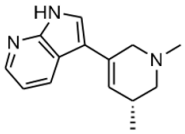
In the context of this project, screening and lead optimization resulted in the identification of two, promising, and selective 5-HT_{2A} agonists—*(R)-69* and *(R)-70* (Kweon, 2022).

(R)-69



MW	213.28 g/mol
cLogP	1.9
tPSA	36
LE	0.64
Brain C_{max} (10 mg/kg, IP)	2510 ng/ml (12 µM)
Plasma:Brain	1.09
Brain $T_{1/2}$	111 min

(R)-70



MW	227.31 g/mol
cLogP	2.2
tPSA	28
LE	0.57
Brain C_{max} (10 mg/kg, IP)	8040 ng/ml (35 µM)
Plasma:Brain	0.11
Brain $T_{1/2}$	28.2 min

Figure 7. Chemical structure and information of *(R)-69* and *(R)-70*. Reprinted from Discovery and Synthesis of N-Heterocyclic Drug-like Compounds by Leveraging Novel Rh(I)-Catalyzed C-H Activation Methods. (Kweon, 2022)

These drug candidates underwent *in vivo* mouse behavioural assays to sufficiently measure the efficiency and success of these molecules. Two standout mice behavioural tests used to identify the antidepressant and lack of psychoactive side effects of the drug candidates are the *Head Twitch Response* (HTR) test and *Tail Suspension Test* (TST).

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The HTR is based on the correlation between mouse head twitches and the psychoactive effect upon them—wherein a lower recorded head movement corresponds with a lower level of recorded psychoactive activity. As seen in *Figure 8.,* neither *(R)-69* nor *(R)-70* produced significant mouse head twitches, which means that these molecules do not appear to produce psychoactive activity. In comparison to the psychoactive drug control LSD, the compounds showed marginal psychoactive activity.

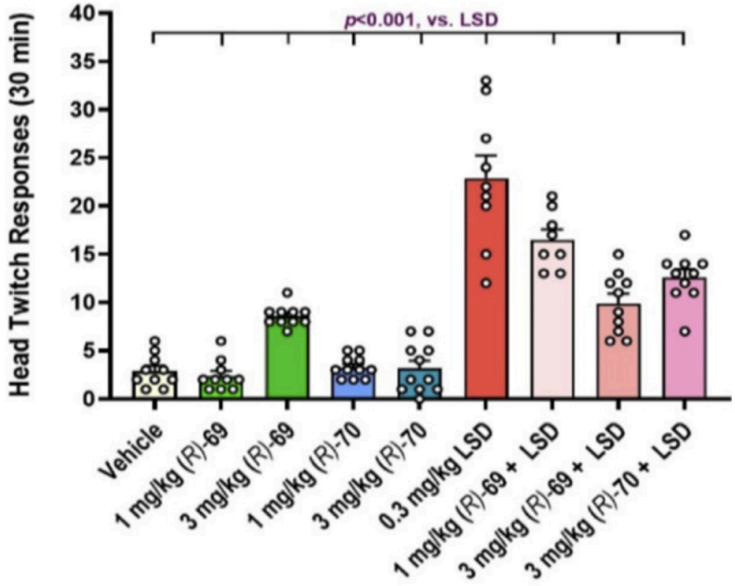

Figure 8. Psychedelic Effects in Mouse Behavioural Studies of Novel 5-HT2AR Agonists. Reprinted from Discovery and Synthesis of N-Heterocyclic Drug-like Compounds by Leveraging Novel Rh(I)-Catalyzed C-H Activation Methods. (Kweon, 2022)

In the Tail Suspension Test, there are two different populations of mice: Wild type (solid bars), and VMAT2-Heterozygous (dashed bars) mice that present with a depressive-like phenotype. Here, the mice are hung by their tails and within a given time frame (480s), the time immobile effectively correlates to the depressive-like behaviour present in mice. *Figure 9.* compares a commercial antidepressant control Fluoxetine (FLX) against the 5-HT_{2A} agonists. While FLX requires 20 mg/kg to provide substantial antidepressant effects, these novel candidates only require 0.5-1 mg/kg to facilitate comparable results (Birling et al., 2017). From these results, it is concluded that these drug candidates do display potent, antidepressant activity.

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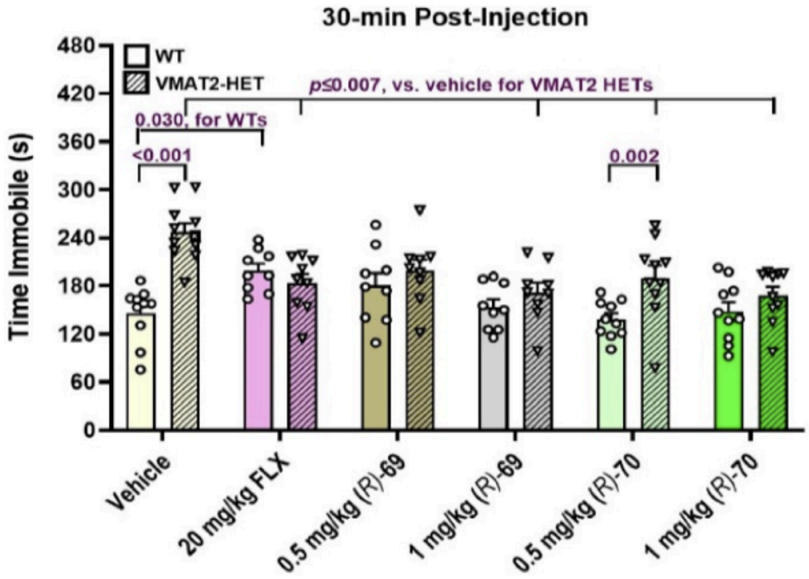

Figure 9. Anti-depressive Effects in Mouse Behavioural Studies of Novel 5-HT2AR Agonists. Reprinted from Discovery and Synthesis of N-Heterocyclic Drug-like Compounds by Leveraging Novel Rh(I)-Catalyzed C-H Activation Methods. (Kweon, 2022)

PREFORMULATION

After significant *in vivo* validation, lead candidates are pushed towards preformulation studies to examine the drug's physical and chemical properties before developing it into a dosage form. Tests evaluate aspects such as solubility in different fluids, stability in different conditions (temperature, light, pH), and drug interactions with excipients.

CLINICAL STUDIES

Drug development involves clinical trials (Phases I–IV) to assess safety, efficacy, and dosing in humans. Phase I tests healthy volunteers for safety (~100 or less), Phase II (up to ~600) evaluates efficacy in patients, and Phase III (thousands) confirms therapeutic benefit in large populations. Successful candidates undergo regulatory review by FDA for market approval. Phase IV monitors long-term safety post-launch (post market surveillance). This process takes 5–10 years, with <10% of candidates ultimately gaining approval due to stringent efficacy and safety requirements.

CONCLUSION

As the pharmaceutical and medical industries advance, so do the possibilities and developments of viable therapies, even from psychoactive drugs. By utilising the drug development process, it has become

possible to produce biased agonists that maximise the unique antidepressant effects while also minimising the deleterious impacts of psychoactive drugs. A great example of this is the discovery of *(R)-69* and *(R)-70,* which both target the 5-HT_{2A} receptor and also show exceptionally potent antidepressant and reduced psychoactive properties. The results yielded during the drug discovery process and animal behavioural assays show a promising future in widening the therapeutic landscape and a solid outlook on clinical trials.

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