A Review on Synthesis and SAR of Anti-Obesity Drugs

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

School of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "A Review on Synthesis and SAR of Anti-Obesity Drugs" submitted by Faisal Hasan (19346002), of Summer'19, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.).

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Ethics Statement

This project does not involve any kind of animal and human trials.

Abstract

Obesity is considered as a chronic metabolic disorder when there is excessive accumulation of body fat in a person. It can cause such risks of type 2 diabetes, cardiovascular disease and even certain cancers. The most suggested anti-obesity drugs are Orlistat, Semaglutide, Liraglutide, Topiramate, Phentermine, Naltrexone-Bupropion. The mechanism of action of these drugs are different. Some inhibit lipid absorption; some suppress the appetite by serotonergic or adrenergic pathways. Structure-Activity Relationship (SAR) is important for rational drug design because even very small changes in the functional groups can cause significant changes in the receptor affinity, metabolic stability, selectivity etc. So, the study of SAR plays a vital role in increasing the efficacy, potency and minimizing the side effects. Continuous invention of the novel targets and proper refinements of the SAR data will help in the development of the next generation anti-obesity drugs that will have improved efficacy with minimal side effects.

Keywords: Anti-obesity drugs; Structure activity Relationship; Mechanism of Action; Orlistat; Semaglutide; Naltrexone-Bupropion.

Dedication

The project was dedicated to my parents and teachers.

Acknowledgement

First and foremost, I want to express my gratitude to Allah the Almighty for providing me with the perseverance and strength to finish this project with the knowledge and wisdom that I hope my project will demonstrate. Working on my project, having amazing experience and getting the help of many individuals, who are gratefully acknowledged here.

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Chapter 1

Introduction to Obesity, its Prevalence, Causes and Harmful Effects

Obesity can be defined as a chronic, progressive, and multifactorial disease which can be characterized by excessive accumulation of fat, which presents health complications and is associated with increased mortality. Obesity is declared by the World Health Organization (WHO) as one of the largest public health concerns worldwide and has identified it as the fifth biggest cause of death worldwide (Song, Ko, & Kim, 2024). Obesity also significantly contributes to the global burden of non-communicable diseases (NCDs), including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), metabolic syndrome, various cancer types, and musculoskeletal disorders. Psychiatric consequences of obesity including depression, anxiety, and social stigma, are similarly severe, while the economic burdens of obesity are increasingly staggering for healthcare systems in both the developed and developing world.

1.1 Prevalence of Obesity

In the last 50 years, global cases of overweight and obesity have more than doubled along with increased prevalence of obesity among adolescents, and adults even in children in nearly every country. It is thought that 40% of the world's adult population is currently overweight (30-34.9) and 10-15% of the world's adult population is classified as obese. It is predicted that over 2.16 billion individuals will be overweight and over 1.12 billion will be obese by the year of 2030 which indicate that over 1,000 genetic loci are associated with BMI, though they only explain around 20% of the variance in BMI. Genes can impact weight by altering metabolism, food preference, and the amount of energy expended, but none of these mechanisms can account for the rapid rise in obesity.

While some genetic and epigenetic factors can't usually be modified, new awareness of aural and gut microbiome, hormonal pathways, and epigenetic modifications provide clues into the mechanisms underlying the relationship between genetics, epigenetics and obesity. For example, epigenetic mechanisms that might alter obesity risk could be nutrient exposure to the mother during pregnancy or immediately after birth, while factors in the aural or gut microbiome can be altered or reversed either as a protective factor from obesity or as an effective treatment. Several studies have demonstrated that a caloric and primarily plant-based diet can alter the aural and gut microbiome through the fiber and water proportions while gut health, nutrition and types of specific bacteria are associated with obesity.

1.2 Causes of Obesity

There are so many causes that are thought to be responsible for the obesity problem in humans. Academic research has increasingly recognized and documented the relationship between foods and clear weight gain. Some other factors are also responsible such as genetic factors, lifestyle factors, environmental factors etc. (Safaei et al.,2021).

Genetic and Epigenetic Factors: Genetic factors have a significant effect on individual risk of obesity. Twin siblings and family studies have estimated the range of BMI heritability to be 40--70%. Genome--wide association studies (GWAS) have found that more than 100 obesity trait loci, including well--known genes: FTO (fat mass and obesity associated gene), MC4R (melanocortin 4 receptor), and LEPR (leptin receptor) as essential contributors to appetite regulation and balance in energy in the hypothalamic melanocortin pathway (Singh, Kumar, & Mahalingam, 2017). In addition, epigenetic changes like DNA methylation and histone modification can regulate genes without changing the DNA itself, allowing individuals' obesogenic risk to relate to environmental exposures.

Environmental and Lifestyle Factors: Individuals' risk of obesity, and the obesity epidemic as a whole, has been vastly related to individual and societal shifts towards higher-energy, nutrient-poor foods, reduced physical activity, stationary jobs, and urban communities, poor sleep habits, and also psychosocial stress (Masood & Moorthy, 2023). Aggressive marketing of energy-dense, palatable foods, especially directed at children has also been noted as a factor related to unhealthy food choices. An "obesogenic environment" would incorporate all these factors and represent society's overall environmental signature shift to convenience-themed and health damaging behaviors.

Developmental and Early-life Predictors: Early-life experiences, including prenatal nutrition, birth weight, infant feeding habits, and early weight gain all can affect the obesity risk. Maternal obesity, excessive gestational weight gain, and maternal smoking during pregnancy have been linked to higher childhood BMI (Han, Lawlor, & Kimm, 2010). Several reports indicate that breastfeeding for at least 4-6 months may have a protective effect against obesity, but the patterns are not always uniform. Also, early exposure to unhealthy, energy-dense foods, and insufficient fruits and vegetables, can create taste preferences and eating behaviors that may carry into the later life of the children.

1.3 Harmful Effect of Obesity

The health effects of obesity are numerous, complex, and often co-varying. Obesity dramatically levels up the chances of metabolic disturbances such as T2DM and dyslipidemia, cardiovascular diseases such as hypertension and atherosclerosis, NAFLD, osteoarthritis, obstructive sleep apnea, and sometimes various cancers. In addition to the physiological considerations, obesity is associated with a low-quality life and an increased risk of development of adverse mental health conditions, such as depression, especially for the teenager and young adults (Pei et al., 2013).

The health outcomes of obesity can have a quick onset in children. Children who are obese will encounter negative health events such as insulin resistance, early onset puberty, Orthopedic disruptions and overall distress related to body image. Importantly, childhood obesity is a precursor of obesity in adult life which can increase the likelihood of further harmful health events.

1.4 The need for Pharmacological Intervention

While lifestyle changes continue to be the first line of defense to treat obesity, many find it challenging to sustain prolonged weight loss due to the body's natural compensatory physiological responses to weight loss, including decrease in basal metabolic rate, increased appetite and hormonal adjustments that prioritize energy conservation. These barriers highlight the need for adjunct pharmacological interventions (Sauer, 2023).

Anti-obesity medications aim to offer treatment options by targeting specific mechanisms such as appetite suppression, blocking fat absorption, or increasing energy expenditure. Agents such as phentermine, liraglutide, and naltrexone/bupropion have shown preliminary positive outcomes in producing 5–10% of weight loss, a target weight loss range which can result in noteworthy improvements in blood glucose, blood pressure, and lipid concentrations. Nevertheless, the long-term efficacy of the anti-obesity drugs and safety of anti-obesity drugs are contingent on understanding how to design and synthesize the pharmacophore through structure-activity relationship (SAR) analysis. Some examples are to produce specific pharmacokinetic properties in terms of efficacy and manage unwanted effects.

As such, it is clear through the obesity epidemic and its health and economic impact, research on the design and SAR of anti-obesity compounds is an important contribution. In this review, it will

highlight the aspects of the design process related to SAR and develop a better foundation for generating more useful therapeutic agents in the future.

Figure: 1. Factors often leading to adult overweightness/obesity (Safaei et al., 2021).

Chapter 2

Methodology

This thesis titled “A review on Structure and SAR of Anti-obesity Drugs” is based on the structured review of the existing scientific literature and research. The data for the thesis were collected from the renowned online databases such as PubMed, Google Scholar and Scopus. These platforms provide a wide range of access to the reliable and also peer-reviewed articles. That is why these platforms were chosen. Articles about medicines, pharmacology and drug development are easily available in these databases.

Specific keywords were used while searching about the articles which were relevant to the topic. Obesity, cardiovascular disease, mechanism of action, structure-activity relationship (SAR) novel targets these words were used as the keywords. The most relevant studies were easier to find out because of these keywords and also, they helped to narrow down the search.

Articles published between 2000-2025 had the most priority. The selected studies focused on anti-obesity drugs, how they exert their work, their chemical structure, their effectiveness and potency and any known limitations.

Important information was collected and irrelevant information were excluded. Also, emerging treatment as well as the existing ones were focused mostly. This method provided a clear overview that helped to catch the main theme of the thesis which is understanding the structure and SAR of the anti-obesity drugs.

Chapter 3

Standard Anti-obesity Drugs: Structures, mechanism and limitations

Obesity is a chronic multifactorial disease necessitating integrated approaches to management. The use of pharmacotherapy is indicated for individuals with obesity who meet certain clinical recommendations, if non-pharmacological approaches are insufficient. Very few medications are approved following clinical trials for long-term use in management of obesity, with some commonalities including all medications provide varying sets of efficacy, safety and accessibility limits to the patients as well as the differing chemical structures and mechanisms and clinical profiles (Mukherjee, Baranwal, & Schade, 2016).

3.1 Orlistat

Structure & Mechanism: Orlistat is a β-lactone that is a derivative of lipstatin that binds irreversibly to the active serine site of gastric and pancreatic lipase. This binding ultimately impedes the hydrolysis of the dietary triglycerides into individual fatty acids to result in ~30% less fat absorbed from food sources.

Efficacy & Limits: Provides a modest placebo adjusted weight loss (~2.8–3.2% at 1–4 years) and improved lipid profiles and insulin sensitivity. Adverse events include steatorrhea, oily stools, fecal urgency, and flatulence. Long term use is associated with fat soluble vitamin deficiencies requiring supplementation. Orlistat does not usually modulate appetite regulation (Henderson, Lewis, Sloan, Bessesen, & Arterburn, 2024).

3.2 Phentermine-Topiramate extended release

Structure & Mechanism: Phentermine is a sympathomimetic amine that acts centrally at the hypothalamus by increasing norepinephrine release to suppress appetite. Topiramate is a monosaccharide that replaces one of the lipid moles with a sulfamate. This also has a GABA-modulating mechanism added to appetite suppression with additional anticonvulsant effects as well as flavor and altered taste perceptions.

3.3 Naltrexone-Bupropion: Sustained Release

Structure and Mechanism: Naltrexone is an opioid receptor antagonist that inhibits the autoinhibition of hypothalamic pro-opiomelanocortin (POMC) neurons mediated by β-endorphin, and bupropion is a norepinephrine-dopamine reuptake inhibitor that stimulates POMC neurons and modulates activity in reward circuits to reduce craving.

Efficacy and limitations: ~4–6% placebo-adjusted weight loss with decreases in hedonic eating. Common adverse effects include nausea, constipation, headache, and insomnia. Also, the possible increases in blood pressure are typically transient. Contraindicated in persons with seizure disorders, uncontrolled hypertension, chronic opioid use (Falk et al., 2023).

3.4 Liraglutide (3.0 mg): A GLP-1 receptor agonist with an additional C16 fatty acid side chain that allows the compound to bind to albumin, resulting in a longer half-life, which only requires a once daily injection, compared to the less potent forms of GLP-1 that require multiple injections. Liraglutide activates GLP-1 receptors located in the hypothalamus and brainstem, while promoting a delayed rate of gastric emptying and increased glucose-dependent insulin secretion.

Efficacy and Mechanism: About Mean ~5–8% weight loss calculating the adjusted placebo effect with positive cardiometabolic risk factors. Adverse effects may include nausea, vomiting, diarrhea, pancreatitis, and gallbladder disease (both rates are <0.1% of those studied). Cost and daily injections were significant barriers to patient adherence. This medicine is normally contraindicated in the patients with a family history including medullary thyroid carcinoma or Multiple Endocrine Neoplasia (MEN2) type 2 (Correia & Haynes, 2006).

3.5 Semaglutide (2.4 mg)

Structure and Mechanism: A GLP-1 analogue derived through a C18 fatty diacid modification that extends the half-life of Semaglutide, allowing for a weekly dosing schedule and for multiple preclinical and clinical related studies using its pathophysiological GLP-1 receptor affinity much higher than Liraglutide.

Efficacy and limitations: Within STEP trials mean weight loss was between 14–17% with personalized psychology and healthy eating plans with or without high-intensity exercise incorporation. An average of ~1.0 KG, similar to Phentermine, lost during the prevention period is relevant to the SEMAGLUTIDE weight loss framework starting point of integrated weight loss distraction.

3.6 Tirzepatide

Structure and mechanism: A dual agonist of the GLP-1 and a Glucose-dependent Insulinotropic Peptide (GIP) receptor that increases satiety, delays gastric emptying, and improves insulin sensitivity.

Efficacy and limitations: In SURMOUNT trials, the mean weight loss is 15-21% with tirzepatide,

similar with outcomes of bariatric surgery. GI tolerability is an issue with tirzepatide and cardiovascular safety data is expanding. The high cost and lack of third-party payors limits its greater utilization (Mark, 2009).

3.7 Setmelanotide: A melancortin-4 receptor agonist indicated for rare syndromes in monogenic obesity (deficiencies in POMC, PCSK1, and LEPR, Bardet-Biedl syndrome), restoring appetite regulation.

Structure and mechanism: Highly efficacious in the targeted populations, but may cause increased blood pressure and heart rate potential requiring monitoring of the cardiovascular systems (Son & Kim, 2020), (Hofbauer, Nicholson, & Boss, 2007).

3.8 Rimonabant

Structure and Mechanism: It is a cannabinoid receptor type 1 (CB1) inverse which has some anti-obesity properties. It blocks the work of the CB1 receptor balancing the appetite and energy balance.

Efficacy and limitations: Although this drug showed efficacy in the role of an anti-obesity drug it was withdrawn from market as it showed psychiatric effects among the patients.

3.9 Lorcaserin

Structure and mechanism: Lorcaserin is a selective serotonin 2C (5-HT2C) receptor agonist which also has anti-obesity properties. It works by activating the 5-HT2C receptors in the brain where appetite control is done. So, people feel fullness in the stomach.

Efficacy and limitations: It also showed efficacy in the anti-obesity management but like rimonabant it was also withdrawn from the market as it has possible risk of creating cancer in the patients. So, the FDA proposed a market withdrawal.

3.10 Crotadihydrofuran

Structure and mechanism: This drug is an isoflavonoid, which is a natural organic compound. This drug is thought to have anti-obesity effects as the research is still going on. It works as a Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) antagonist. It has a vital role in the regulation of fat cells, glucose metabolism and lipid storage. It blocks the activity of PPARγ activity thus acting as an anti-obesity agent.

Efficacy and limitations: Although it shows promising results in the role of an anti-obesity agent, it is still in the early stage. So, the results of the clinical trials are needed properly.

Table 1: Characteristics of the Enrolled Patients Before They Commenced the Use of Anti-obesity Medications. (Song et al., 2024)

	Phentermine	**Phentermine/Top-iramate**	**Liraglutide**	**Naltrexone/Bupro-pion**	**Lorcaserin**	**Orlistat**	P value
Age (years)	34.0 ± 10.4	42.5 ± 12.6	38.7 ± 13.9	41.6 ± 13.6	41.5 ± 9.4	38.6 7 ± 12.7	.035
Body Weight	108.5 ± 30.6	93.42 ± 26.03	87.5 ± 22.0	91.0 ± 19.3	94.9 ± 31.4	91.2 ± 34.8	.015
Body Mass Index (BMI)	38.8 ± 9.2	34.3 ± 7.9	33.1 ± 6.7	33.9 ± 7.2	33.4 ± 7.6	32.7 ± 8.7	.018
Percentage body fat	44.8 ± 6.6	41.5 ± 7.6	42.5 ± 6.9	43.0 ± 4.6	39.8 ±4.0	40.2 ± 5.0	.041

Hypertension	20 (51.3)	17 (33.3)	19 (30.6)	5 (29.4)	6 (25)	5 (41.7)	.249
Type 2 Diabetes	6 (15.4)	13 (25.5)	10 (16.1)	0 (0)	4 (16.7)	2 (16.7)	.424
Current smoker	9 (23.1)	10 (19.6)	11 (17.7)	2 (11.8)	5 (20.8)	3 (25.0)	.876
Regular exercise	19 (48.7)	26 (51.0)	42 (67.7)	12 (70.6)	19 (79.2)	8 (66.7)	.076

Mechanistic Categories of approved anti-obesity Agents:

1. Appetite Suppression- modulation of neurotransmitter (phentermine/topiramate, naltrexone/bupropion).

2. Hormonal Modulation- satiety and delay gastric emptying (liraglutide, semaglutide, tirzepatide).

3. Nutrient absorption Inhibition- gastrointestinal inhibition of lipase (orlistat) *(Kim et al., 2013).*

General Limitations Across All Agents

• Efficacy Gap: No drug alone will achieve sustained weight loss similar to patients undergoing bariatric surgery.

• Adverse Events: GI distress (GLP-1 drugs, orlistat), stimulation of the cardiovascular (phentermine/topiramate), or psychiatric (naltrexone/bupropion).

• Long-Term Safety: Many other drugs have been withdrawn due to long-term safety concerns which require ongoing monitoring.

• Adherence Issues: Discontinuation and adherence can be challenging, especially due to side effects, financial costs or not feeling benefits.

• Cost & Access: Incretin-based therapies (e.g., semaglutide, tirzepatide) are expensive, often not reimbursed by insurance (Müller et al., 2022). (Al Roomy et al., 2024).

Chapter 4

Synthetic Strategies for Anti-Obesity Drugs: Approaches, Advantages, and Challenges

The design and synthesis of anti-obesity drugs are an intersection of medicinal chemistry, processes improvements, and therapeutic innovation. These agents target multiple biological pathways (endocannabinoid system; serotonin receptors (sub-types 5-HT1B, 5-HT2C); PPARγ; pancreatic lipase; GLP-1 receptors etc.) requiring many ways in their synthesis. Now some of the synthesis procedures of currently marketed anti-obesity drugs and their advantages and challenges are discussed below. Also, some investigational leads will be also discussed.

4.1 Peptide-Based Therapies – GLP-1 Analogues:

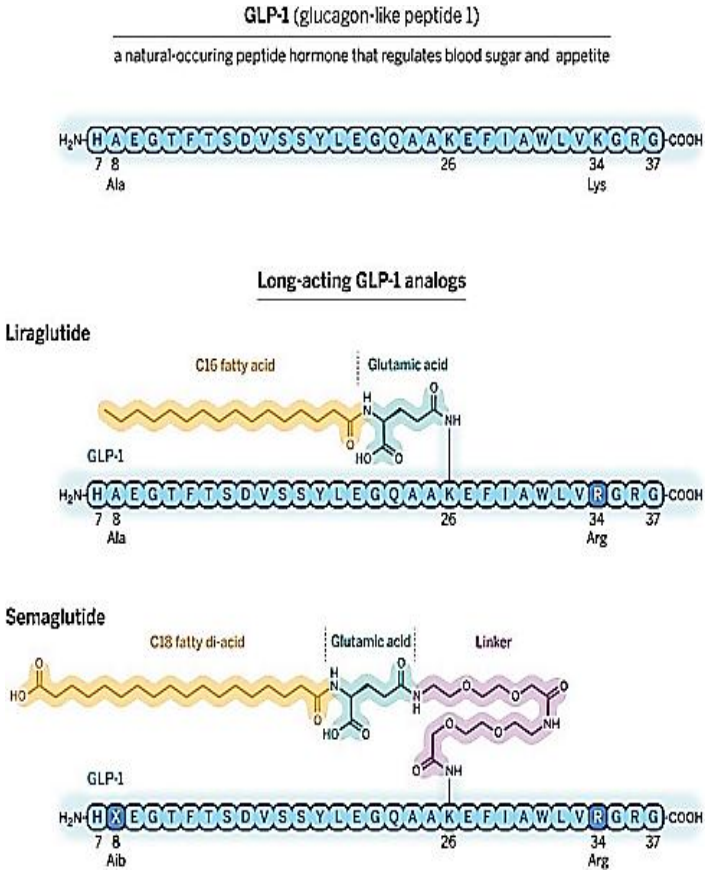

Figure: 2. GLP-1 serves as the active agents in the two long-acting anti-obesity drugs, Liraglutide (middle) and semaglutide (bottom). (Friedman, 2024)

GLP-1 receptor agonist peptides such as liraglutide and semaglutide are effective agents for weight and metabolic regulation. Their preparation typically involves solid-phase, solid-phase peptide synthesis (SPPS), with further modifications such as fatty acid acylation for half-life extension via albumin binding. For liraglutide, pseudoproline incorporation and BAL resin were employed to minimize aggregation and enhance synthesis efficiency (Carbajo et al., 2019). SPPS is best for mid-sized peptides, automation, and high yield. Longer sequences or complex modifications may require native chemical ligation (NCL). Peptide drugs encounter challenges like liability to enzymatic breakdown and requirement of cold-chain logistics (Friedman, 2024).

Advantages:

• Once-weekly dosing with beneficial weight loss.

• Scalable SPPS with improved yield and purity.

Challenges:

• Costly production and synthesis time.

• Poor oral bioavailability and formulation stability.

4.2 Opioid Antagonist – Naltrexone

(-)-Naltrexone, a non-peptide medication used in combination treatment of obesity, was traditionally derived semi-synthetically from thebaine. A more recent asymmetric total synthesis route avoids this reliance by starting from achiral precursors. The key steps include Sharpless dihydroxylation, Rh(I)-catalyzed alkenylation, and torque-selective electrocyclization producing the desired scaffold in 17 steps with precise stereo-control. This strategy facilitates analogue development but is limited by the requirement for several transition-metal catalysts and a long process (Dongbang, Pedersen, & Ellman,

2019).

Advantages:

• Access to new analogs and both enantiomers

• Completely synthetic, bypassing plant-based intermediates

Challenges:

• Time-consuming and costly due to metal-catalyzed steps

• Scalability remains limited

4.3 PPARγ Antagonists Derived from Natural Products and Hybrids

Crotadihydrofuran C (CC):

A natural product PPARγ antagonist, CC was produced enantio-selectively as a product of a 16-step synthesis using Suzuki couplings with green reactants. It enabled in vivo studies demonstrating increased insulin sensitivity and regulation of lipid metabolism in a mouse model of obesity. While it shows great promise biologically, the length of this synthesis limits the scale of production in large quantities (Sun et al., 2017).

Topiramate-phenolic acid conjugates:

Using an innovative hybrid strategy, topiramate was conjugated with phenolic acids, including caffeic acid, utilizing either esterification or condensation reactions to develop new PPARγ antagonists. One compound (T3) was the most active weight of the novel compounds - it showed docking affinity as well as biological activity. Computational docking models directed by the synthetic process provided guidance for SAR studies. The challenge in conducting this work lied in modifying the available sites on the phenolic moiety that would not cause isomerization (Padhy et al., 2024).

Advantages:

• Enantioselectivity and SAR flexibility

• Combination of green chemistry and modular chemistry

Challenges:

• Multi-step process

• Stability of the core natural products during synthetic process

4.4 Pancreatic Lipase Inhibition – Pyrazole-Benzimidazole Derivatives

A novel series of lipase inhibitors based on an N5-(1H-pyrazol-3-yl)-3H-benzo[d]imidazole 2,5-diamine template exhibited strong enzymatic inhibition (93%) and better binding orlistat. The synthetic route involved sequential condensation and amination reactions. Although the approach gave lead compounds with good potency, the polarity and functional complexity created serious purification and scalability problems.

Advantages:

• Displays high bioactivity towards pancreatic lipase

• Rational design enhances lead efficiency

Challenges:

• Purification is difficult due to polar intermediates

• Multistep complex synthesis

4.5 Cannabinoid Receptor Antagonist – Rimonabant

Rimonabant was originally produced as a CB1 antagonist via a lengthy six-step route using hazardous reagents such as thionyl chloride and cryogenic reaction conditions. Condensed this process to a three-

step synthesis utilizing safer ("greener") methods, employing DCC-mediated amidation and acid hydrolysis for the toxic reagent. The modifications resulted in greater yield and less reagent use, while no longer relying on cryogenic set-ups, allowing for industrial implementation. These updates reduced operating procedures and increased efficiency. However, it is still a challenge to maintain acceptable high enantiomeric purity and improve environment for greener solvents (Kotagiri et al., 2007).

Advantages:

• Fewer steps and safer reagents

• Higher yield and more cost effective

Challenges:

• Controlling purity at scale

• Managing solvent/salts/waste

4.6 Serotonin Agonist – Lorcaserin

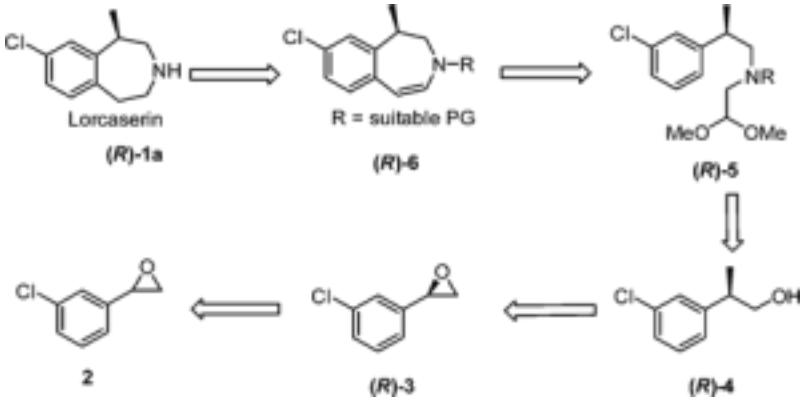

Figure: 3. Retrosynthesis of Lorcaserin (Ghotekar et al., 2019)

Lorcaserin would be a 5-HT2C receptor agonist and actively has multiple process improvements. A six-step synthesis that involved allylation, N-protection, Friedel–Crafts alkylation, and chiral resolution with L-(+)-tartaric acid, generating >99.8% enantiomeric excess but only a 23.1% overall yield [3]. Developed an even better enantioselective approach that involved hydrolytic kinetic resolution of 3-

chlorostyrene oxide using Mitsunobu coupling, avoiding any chromatographic purification and applying regioselective transformations to give greater stereo-control (Zhu et al., 2015).

Advantages:

• Excellent enantioselectivity and stereospecificity

• Potential for scale up and operational simplicity

Challenges:

• Length and complexity of the isolation and protect/deprotect processes

• Availability and price of some uniquely valuable catalysts (Ghotekar et al., 2019).

4.7 Broader Considerations in Synthetic Strategy

Throughout all methods, synthetic routes have to compromise between chemical efficiency, stereoselectivity, environmental footprint, and scalability. For small molecules, developments such as green solvents and organo-catalysis are being used. In peptide synthesis, SPPS and chemical ligation are mainstream but are required by long reaction times and cost inefficiencies. Peptidomimetics and chemical stabilization (e.g., PEGylation, cyclization) are being investigated to bypass pharmacokinetic limitations.

The synthetic landscape for obesity drugs is diverse, driven by target-specific pharmacology and the need for scalable, safe, and inexpensive methods. Whether using natural product scaffolds, hybrid conjugates, or peptides, each approach provides special benefits and intrinsic difficulties. Ongoing optimization of synthetic pathways through greener chemistry, computer-aided design, and biotechnological approaches is key to next-generation anti-obesity therapeutics.

Chapter 5

Structure–Activity Relationships (SAR) of Standard Anti-Obesity Drugs

Understanding the structure–activity relationships (SAR) of the anti-obesity drugs is essential for rational drug design. SAR knowledge optimizes molecular interactions, increases potency, and minimizes side effects. Both synthetic and natural anti-obesity drugs have their own SAR. Modifications in the different functional groups can alter the activity efficacy potency even the toxicity of the drugs. So, it is important to know about the SAR of the anti-obesity drugs (Shaik Mohamed Sayed et al., 2023).

5.1 GLP-1 Receptor Agonists: Semaglutide, Liraglutide

GLP-1 (glucagon-like peptide-1) receptor agonists have been extensively investigated for their strong anti-obesity and antidiabetic effects. SAR investigations have revealed that peptide truncation, certain residue modifications, and conformational constraints critically influence their efficacy. Ultra-short 11 amino acid GLP-1 analogs had retained high potency by maintaining key residues like His^{1}, Gly^{4}, Phe^{6}, Thr^{7}, Asp^{9}, Bip^{10}, and Bip^{11}. Alanine substitutions at these roles generated more than a 100-fold reduction in receptor activity, validating their critical function in receptor activation.

Among the significant changes, substitution of Phe^{6} with 2-fluorophenylalanine ($Phe(2\text{-}F)^{6}$) has increased the potency five times (EC_{50} = 0.1 nM compared to 0.5 nM for parent RXL-100) as a result of tighter hydrophobic packing with receptor residues like L141, L144, L384, and L388. However, over-substitution (e.g., penta-fluorination) can cause decreased activity, which indicates that balance between hydrophobicity and electronic properties is crucial. Lipidation methods such as γ-glutamic acid-linked fatty acids, e.g., semaglutide prolong plasma half-life and albumin binding. In addition, α-methylation of Phe^{6} or substitution with Aib (α-aminoisobutyric acid) at position 2 promotes α-helicity and conformational rigidity, which correlates with enhanced metabolic stability and receptor binding affinity

(Sawyer et al., 2025).

Cap1-Gly-Thr-**α-Me-Phe(2-F)**-Thr-Ser-Asp-**Bip(2′Et, 4′OMe)-hhPhe(3′,5′-Me2)**-NH_2

Cap1 (His-Aib-Glu mimetic):

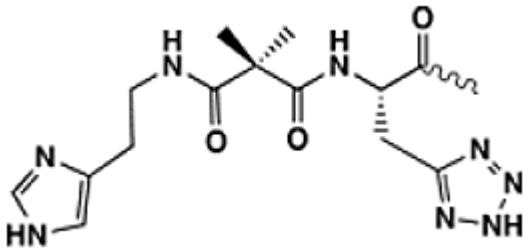

Figure: 4 Sosei Heptares GLP-11–11-NH2 analog (described as truncated peptide agonist or TPA) was used for X-ray studies in complex with GLP-1R (Jazayeri et al. 2017).

5.2 Pancreatic Lipase Inhibitory Flavonoids: Orlistat

Flavonoids are dietary polyphenols found abundantly in food and are known to inhibit pancreatic lipase, thus reducing dietary fat absorption. SAR study of 26 dietary flavonoids demonstrated that flavones were the most active with luteolin being the most potent inhibitor (IC_{50} = 99 μM), followed by quercetin and baicalein.

Several structural features were crucial:

• **C2=C3 double bond** in the C-ring enables π-conjugation, promoting π–π stacking with the active site of lipase.

• **4-keto group** in C-ring is necessary; its absence resulted in decreased activity.

• **Hydroxylation** on A and B rings increased binding through hydrogen bonding

• **Glycosylation** typically reduced activity because of greater steric hindrance and loss of planarity.

Fluorescence titration experiments revealed that active flavones caused blue shifts, suggesting tighter lipase binding. In contrast, flavanones, which lack the C2=C3 bond, showed much weaker inhibitory

effects (Li et al., 2023).

5.3 β3-Adrenergic Receptor Agonists: vibegron, mirabegron

β3-adrenergic receptor (β3-AR) agonists induce thermogenesis and lipolysis and thereby strong candidates for obesity treatment. A QSAR study on imidazolidinone benzene sulfonamides recognized hydrophobic constant (RFR) and molar refractivity (RMR) as significant molecular indicators.

The optimal regression model was:

log EC_{50} = 0.128 RFr – 0.027 RMR – 2.297 with high correlation (r = 0.890), indicating the synergistic effect of lipophilicity and steric bulk. Long alkyl chains (e.g., octyl, cyclohexyl) increased potency as a result of improved receptor interaction and dissociation at a slower rate. Compound 6 with high RFR and RMR values was the most active in the series. Compounds with short chains (e.g., compound 1) showed poor receptor affinity and activity (Kashaw & Mishra, 2003).

5.4 Trifluoromethylated Flavonoid-Based Isoxazoles:

One such promising class of synthetic hybrids trifluoromethylated flavonoid-based isoxazoles exhibits both antidiabetic as well as anti-obesity effects via α-amylase inhibition. α-Amylase inhibition limits carbohydrate digestion, reducing postprandial glucose levels and aiding in weight control (Algethami et al., 2021).

Key features are:

• **Trifluoromethyl group ($–CF_3$)** enhances lipophilicity, metabolic stability, and enzyme affinity.

• **Isoxazole ring**, created through 1,3-dipolar cycloaddition, facilitates hydrogen bonding and π–π stacking with ASP-206 and GLU-230 in the active site of α-amylase. • **Aryl ring substituents** dictate activity:

Fluorine-substituted analogue 3b was the most potent (IC_{50} = 12.6 μM), on similar with acarbose (IC_{50} = 12.4 μM).

Chlorine (3c) and bromine (3d) analogues also exhibited good activity.

Methoxy-substituted compounds (3h, 3j, 3m) were good performers, maybe because of improved electronic and conformational properties.

The trend of activity was: 3b (F) > 3h ≈ 3j ≈ 3m > 3c > 3d >> unsubstituted analogs.

Docking simulations validated that active analogs interact effectively with ASP-206, GLU-230, and ARG-344.

5.5 SAR of Natural Anti-Obesity Compounds

Natural compounds have anti-obesity actions through various mechanisms, such as thermogenesis induction, appetite suppression, and digestive enzyme inhibition. • **Ephedrine** (from Ephedra Sinica): A β-adrenergic agonist that stimulates

thermogenesis through increased release of norepinephrine. Its basic structure contains a phenyl ring and secondary amine is essential for adrenergic activity.

• **Capsaicin** (from Capsicum annuum): Has a vanillyl group, amide bond, and long hydrophobic tail, which is essential for TRPV1 receptor activation and stimulation of brown adipose tissue (BAT) thermogenesis.

• **Caffeine** (from Coffea arabica): A trimethylated xanthine derivative that stimulates cAMP levels through antagonism of adenosine receptors and phosphodiesterase inhibition leading to augmented energy expenditure.

• **Forskolin** (from Coleus forskohlii): A labdane diterpene with a number of hydroxyl groups and

a strict structure, directly stimulates adenylate cyclase to increase intracellular cAMP and initiate lipolysis.

• **EGCG** (Epigallocatechin gallate from green tea): A polyphenol with potent antioxidant and enzyme inhibitory activity. In spite of poor bioavailability, owing to hydrophilicity, the gallate and catechol groups enable effective inhibition of lipase and amylase in vitro. Key SAR features of natural agents include functional groups that affect lipophilicity (e.g., methyl, methoxy), enhance receptor affinity (e.g., amines, hydroxyls), and enhance bioavailability or metabolic interaction (e.g., unsaturation, aromaticity, polar groups). SAR studies show the crucial part played by structural optimization in strengthening the therapeutic efficacy of anti-obesity agents. Across diverse chemical classes:

• **Aromatic and hydrophobic modifications** (e.g., Phe^{6} analogs, trifluoromethyl enhance receptor binding and bioavailability.

• **Planarity and rigidity** (as in flavones or Aib substitutions) enhance binding affinity.

•**Lipidation and α-helical stabilization** enhance metabolic half-life for peptide-based drugs

•**Functional group modification** (e.g., hydroxyls, halogens) directly influences enzyme inhibition and receptor targeting. Together, these SAR findings constitute a platform for the design of future anti-obesity drugs with improved safety and efficacy profiles.

Chapter 6

Emerging Anti-Obesity Drugs – Future Directions

Obesity is still a worldwide health emergency, necessitating the ongoing creation of pharmacotherapies to augment lifestyle interventions. Existing anti-obesity drugs have been effective but their limitations (moderate weight loss, undesirable effects, and metabolic adaptation) have spurred the quest for more potent and safer agents. Now I will discuss the drug candidates, therapeutic mechanisms, and advancements in the anti-obesity drug development, such as peptide hormones, combination regimens, natural products, and experimental therapies (Kang & Park, 2012).

6.1 Centrally Acting Agents

Histamine H3 Receptor Agonists

Histamine H3 receptor (H3R) agonists such as Imetit have appeared as prospective anti-obesity agents due to their function of suppressing appetite and improving the use of lipids. Chronic imetit administration in diet-induced obese mice has decreased fat mass, leptin, and insulin levels, and increased energy expenditure. Importantly, these effects were absent in H3R knockout mice, validating the receptor-specific action and therapeutic implications for the management of obesity and type 2 diabetes mellitus (T2DM) (Yoshimoto et al., 2006).

Setmelanotide

Setmelanotide, an MC4R (Melanocortin-4-Receptor) agonist, has been promising in the treatment of rare genetic obesity syndromes like Proopiomelanocortin (POMC) deficiencies and Leptin Receptor (LEPR) deficiencies. It bypasses adverse cardiovascular effects which was observed in

previous MC4R agonists by being receptor-specific. Clinical trials have demonstrated significant weight reduction and metabolic enhancement in genetically obese patients.

Tesofensine

Originally researched for neurodegenerative disorders, Tesofensine is a triple monoamine reuptake inhibitor (dopamine, norepinephrine, serotonin). It exhibited ~10% weight loss in clinical trials, with an acceptable side effect profile at less than full doses.

Empatic (Zonisamide/Bupropion)

Empatic combines bupropion (a norepinephrine-dopamine reuptake inhibitor) and zonisamide (an anticonvulsant with serotonergic properties). Phase II trials showed enhanced weight loss over monotherapy, though little nausea and insomnia were common side effects.

6.2 Gut Hormone-Based Therapies

GLP-1 Receptor Agonists: Liraglutide and Semaglutide

Liraglutide, a T2DM drug first, induces satiety and weight loss (~8%) by delaying gastric emptying and regulating energy balance. It also enhances insulin sensitivity and cardiovascular markers.

Semaglutide has established a new standard. STEP 1 trial demonstrated 12.4% mean body weight loss in non-diabetic obese patients. 69% of patients lost over 10% body weight. Apart from weight loss, semaglutide improved cardiometabolic health and is being evaluated in the SELECT trial for cardiovascular outcomes (Martins, Morgado, & Morgado, 2014).

Dual and Triple Agonists

Tirzepatide, which is a dual GLP-1 and GIP receptor agonist, outperformed semaglutide in trials, with up to 13.1% weight loss. Trials in non-diabetic populations are ongoing. Newer agents such as GLP-1/GIP/glucagon co-agonists and oxyntomodulin are being researched for their ability to both decrease appetite and increase the use of energy. A triple co-agonist (GLP-1/GIP/glucagon) called compound 1706 has shown strong preclinical data.

6.3 Therapies Based on Amylin and Leptin

Amylin analogues like davalintide and dual amylin/calcitonin receptor agonists (DACRAs) have synergistic effects when combined with GLP-1 agents, reducing food consumption and enhancing glucose control. Leptin monotherapy was ineffective as a result of resistance and immunogenicity, but therapies in combination using compounds like pramlintide (amylin analogue) and metreleptin (leptin analogue) had additive effects, though here adverse immune responses are an issue.

6.4 Peripheral and New Mechanism Targets

Cetilistat

Cetilistat, a lipase inhibitor structurally different from orlistat, offers a more tolerable side effects profile. In clinical trials with obese patients with T2DM, it improved weight loss and glycemic control with fewer gastrointestinal adverse events. Cetilistat has been approved in Japan and is undergoing evaluation for broader regulatory approval.

Methionine Aminopeptidase 2 (MetAP2) Inhibitors

Beloranib, a MetAP2 inhibitor, promotes fat oxidation and suppresses fat synthesis. Despite its

efficacy, it was withdrawn from the market after pulmonary embolism occurred within trials, highlighting the challenge of risk/benefit balancing.

Fibroblast Growth Factor 21 (FGF21) Analogues

Endocrine analogues are a new endocrine approach. Liver-secreted hormones which increase energy expenditure and insulin sensitivity. In their infancy, in early-phase trials, they offer a new prospect for the design of anti-obesity drugs.

6.5 Combination Therapies

Synergistic benefit is provided by combining agents. Phentermine/topiramate (Qsymia™) offers ~10% weight loss and lowers blood pressure, glucose level in blood and markers of inflammation. Naltrexone/bupropion (Contrave®) targets appetite and reward circuitry, with moderate efficacy and cardiovascular acceptability following Light Study analysis. Semaglutide in combination with cagrilintide (an amylin mimetic) showed up to 17.1% weight loss in earlier-phase studies—more than with semaglutide monotherapy.

6.6 Natural Product-Based Therapeutics

Natural compounds represent a natural, multi-target choice. Major examples are:

• **Garcinia cambogia**: Suppresses hunger by modulating serotonin.

• **Green tea (EGCG)**: Pancreatic lipase inhibition.

• **Chili (capsaicin)**: Controls GLP-1 and ghrelin.

• **Curcumin**: Suppresses inflammation and inhibits adipogenesis. Preclinical evidence is robust, but clinical translation is impaired due to suboptimal standardization and bioavailability. However, these drugs will be useful in new obesity treatments (Karri et al., 2019).

6.7 Vaccines and Experimental Interventions

Next-generation immunotherapies using vaccines targeted against ghrelin, adenovirus-36, and somatostatin are being investigated. These will try to induce long-term control of weight by immunity modulation. Safety concerns and variable immune reactions are still matter of concern *(Müller et al., 2022).*

Future Directions

Emerging strategies revolve around multi-target strategy-based pharmacotherapy, creating mechanisms complementary to one another (e.g., GLP-1 receptor agonism with nicotinic receptor activation), to promote efficacy while minimizing side effects.

There is a growing interest in the activation of brown adipose tissue (BAT), utilizing β3-adrenoceptor agonists like mirabegron, which promotes thermogenesis and energy expenditure. While animal models demonstrate efficacy, the effects in humans are relatively modest, and the cardiovascular safety profile at higher doses is still uncertain (Hainer, 2014).

Chapter 7

Conclusion

Obesity has now become a worldwide matter of concern. More than billions of people are already suffering from obesity and other billions are at the risk of getting affected by obesity. This review article emphasized on the evolution of the anti-obesity drugs, highlighting the shift from centrally acting drugs and the amphetamine-based stimulants which have severe side effects to a more precise approach that focuses on the deeper learning of the more complex neurological and hormonal pathways that regulate our appetite and the metabolism. Anti-obesity pharmacotherapy stands on the edge of a revolutionary era. GLP-1 receptor agonists drugs like liraglutide, semaglutide, tirzepatide, and setmelanotide signal a shift of direction towards multi-pathway targeting, mimicking the metabolic consequences of bariatric surgery. The main success of these medications validates the mechanism of targeting the intricate brain-gut axis and their adoption meeting the growing obesity as a medical situation that requires a long-term pharmacological management. The future of anti-obesity drugs is promising. Next-generation poly-agonists are the drugs that can target the GLP-1, GIP and the glucagon receptors at the same time. They are responsible for greater weight loss as well as improved metabolism, for example, orforglipron which is a novel oral formulation. But in this case long term safety data will be crucial. Individualized medicine, with genetic, metabolic, and microbiome data to inform therapy, will likely be the future (Rodgers, Tschöp, & Wilding, 2012). So the field of anti-obesity drugs is now standing on a crucial inflection point. The present of anti-obesity drugs is defined by GLP-1 agonists. But the future is more promising as it ensures even more accessible and effective medications. As scientific understanding becomes ever more advanced and innovation speeds up, the long-term success will hinge on the balance of efficacy, safety, and patient-specific needs.

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