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# Rational Design, Synthesis and Characterization of Novel Sibutramine Derivatives as Anti-Obesity Activity

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## ABSTRACT

Sibutramine is a medication that is often used orally to treat obesity (marketed under the names Meridia in the US and Reductil in Europe and other countries). It is classed as a Schedule IV prohibited drug in the United States because it is an amphetamine-related centrally acting stimulant. Due to worries that the medication raises the risk of heart attack and stroke in people with a history of heart disease, sibutramine was taken off the market in Canada and the United States in October 2010. To overcome the associated problem, a strategy was developed where selective modification of this drug was performed by chemically re-acting with a substrate (4-aminophenol) to form a new derivative [4-((4-(1-(1-(dimethylamino)-3-methylbutyl)cyclobutyl)phenyl) amino)phenol]. This novel derivative was comprehensively characterized by sophisticated analytical instruments such as FTIR, $^{1}$H-NMR, 13C-NMR, and Mass spectroscopic spectroscopy.

**Keywords:** Antiobesity, Sibutramine, Synthesis, Characterization, Obesity, Discovery

## INTRODUCTION

The process of finding new uses for approved or experimental medications that go beyond the original medical indication is known as drug repurposing. It is also referred to as drug repositioning, reprofiling, or retasking. Compared to developing a whole new medicine for a particular indication, this strategy offers significant advantages. First and foremost, the risk is decreased; the repurposed drug is less likely to fail in upcoming efficacy trials, at least from a safety perspective, because it has already been demonstrated to be sufficiently safe in preclinical animals and humans if early-stage studies have been completed. Second, the time frame for drug development may be decreased even if the majority of preclinical investigations, safety evaluations, and, in some cases, formulation development would already have been completed. Third, fewer assets are required, however depending on the repurposing candidate's stage and development process, this need may differ greatly. Preclinical, Phase-I, and Phase-II costs for a repurposed medicine may be significantly lower than those for a new drug in the same indication, even though regulatory and phase-III costs may be comparable [1].

A drug development programme begins when a disease or clinical condition exists for which there are no adequate medicinal medicines on the market. This unmet clinical need serves as the project's primary driving force. The first study, which frequently takes place in academia, produces information to support a hypothesis that blocking or activating a protein or pathway would have a therapeutic impact in a disease state. In order to justify a drug discovery endeavor, the activity's outcome is the choice of a target that may need more confirmation before moving on to the lead discovery phase. A thorough search is conducted during lead discovery to find a biological or small-molecule therapeutics that is similar to a drug and will advance into preclinical testing and, if successful, clinical testing and eventually become a marketed drug. This type of candidate is known as a development candidate [2].

According to the World Health Organization (WHO), there were about 1.6 billion overweight adults aged 15 years and above and at least 400 million adults are obese worldwide in 2015. Obesity increases the risk of chronic diseases such as diabetes mellitus, cardiovascular disease, stroke and some cancers. It is a serious public health problem that is growing

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in countries with low or middle income. The worldwide prevalence of overweight and obesity has doubled since 1980 to an extent that nearly a third of the world population is now classified as overweight or obese. Obesity adversely affects nearly all physiological functions of the body and comprises a significant public health threat. It increases the risk for developing multiple disease conditions, such as diabetes mellitus, cardiovascular disease, several types of cancers, an array of musculoskeletal disorders, and poor mental health, all of which have negative effects on the quality of life, work productivity, and healthcare costs [3].

In the US, it has been estimated that the health costs incurred by a single obese individual was US$1901 per annum in 2015, extrapolating to US$149.4 billion at the national level. In Europe, the total direct and indirect cost attributable to overweight and obesity was equivalent to 0.47–0.61% of the GDP. The World Health Organization (WHO) defines overweight and obesity as abnormal or excessive fat accumulation that presents a risk to health. The body mass index (BMI), calculated by dividing the body weight in kilograms by the square of height in meters, is a simple metric used to indicate overall body fatness. For adults, current guidelines from the US Centers for Disease Control and Prevention (CDC) and the WHO define a normal BMI range as 18.5 to 24.9, whereas a BMI $\geq$ 25 kg/m$^2$ is considered to be overweight, and a BMI $\geq$ 30 kg/m$^2$ is classified as obese, with severe obesity defined as a BMI $\geq$ 40 kg/m$^2$. Despite this relatively simplistic definition, obesity is a multifactorial disease that results from chronic positive energy balance, i.e. when dietary energy intake exceeds energy expenditure [4].

Excess energy is converted to triglyceride which is stored in adipose tissue depots that expand in size, thereby increasing body fat and causing weight gain. The globalization of food systems that produce more processed and affordable food, and promote passive overconsumption from energy dense, nutrient-poor foods and beverages has been identified as a major driver of the obesity epidemic, although a decrease in physical activity owing to the modernization of lifestyles is also likely involved. Obesity can occur at any age. Previous studies assessing trends in obesity found that its prevalence has increased in both adults and children of all ages, indiscriminate of geographical locality, ethnicity or socioeconomic status. In low-income countries, obesity is generally more prevalent among middle-aged adults from wealthy and urban environments (especially women); whereas, in high-income countries, it affects both sexes and all ages, but its prevalence is disproportionately greater among disadvantaged groups [5].

Sibutramine is a medication that is often used orally to treat obesity (marketed under the names Meridia in the US and Reductil in Europe and other countries). It is classed as a Schedule IV prohibited drug in the United States because it is an amphetamine-related centrally acting stimulant. Due to worries that the medication raises the risk of heart attack and stroke in people with a history of heart disease, sibutramine was taken off the market in Canada and the United States in October 2010 [6].

## MATERIALS AND METHODS

### Procurement of chemicals, reagents, and solvents

Chemicals, reagents, and solvents will be procured from standard vendors like HiMedia Ltd., Sigma Aldrich Ltd., etc.

### Pharmacokinetics, Bioavailability, and Drug-likeliness studies

The computational studies will be performed as per the procedure put forward by Deokar and Shaikh, 2022 [19]. A pharmacokinetics prediction study, namely one looking at ADME, bioavailability, and the drug-likeness of ligands, will be carried out using the Swiss ADME online tool. The method calculates bioavailability radar based on six physicochemical characteristics, including lipophilicity, size, polarity, insolubility, flexibility, and insaturation, to determine drug-likeness. The ADME features, including blood-brain barrier (BBB) penetration and passive human gastrointestinal absorption (HIA), as well as substrate or non-substrate of the permeability glycoprotein (P-gp), were found positively or negatively in the tool's BOILED-Egg model. The generalized-born and solvent accessible surface area (GB/SA) model was used to calculate the free energies of solvation in n-octanol and water. The lipophilicity estimation (Log p/w) parameters include iLOGP on these results, XLOGP3 is an atomistic method with corrective factors and a knowledge-based library, WLOGP is an implementation of a purely atomistic method, and MLOGP is an archetype of The first rule-of-five to be integrated into a tool is the Lipinski (Pfizer) filter, which will be used to forecast drug-likeness. Based on a number of physicochemical properties, the bioavailability radar was utilized to forecast oral bioavailability. The ranges of each parameter will be mentioned as LIPO = lipophilicity as -0.7 < XLOGP3 < +5.0; SIZE = size as molecular weight 150 g/mol < MV < 500 g/mol; POLAR = polarity as 20Å$^2$ < TPSA (topological polar surface area) < 130Å$^2$; INSOLU = insoluble in water by log S scale 0 < Logs (ESOL) < 6; INSATU = insaturation or saturation as per fraction of carbons in the sp$^3$ hybridization 0.3 < Fraction Csp$^3$ < 1 and FLEX = flexibility as per rotatable bonds 0 < Number of rotatable bonds < 9.

### Synthesis of molecules

Place 2 mL (2.08 g) of aniline 30 mL of 10% NaOH solution in 250 mL conical flask, then add 0.002 M (0.75 g) of

sibutramine slowly with vigorous shaking. Reflux the content for 4-5 hrs. Dilute the reaction mixture with cold water, filter the crude content with suction on a Buchner funnel, wash with cold water, and crystallize from hot alcohol. Dry the product and calculate the percentage yield [20] (**Figure 1**).

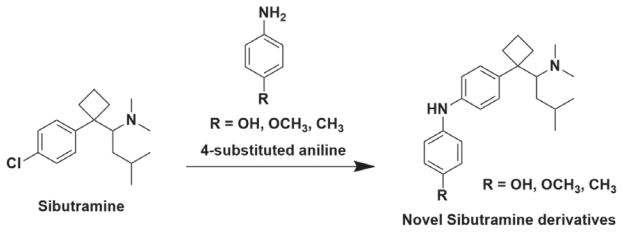


**Figure 1:** Synthesis of novel sibutramine derivatives.

## Characterization of compounds using laboratory techniques

The synthesized molecules will be characterized in terms of Yield (from the formula; Practically obtained weight / Theoretically calculated weight × 100), Appearance (color and state), Melting point (calculated using Thiele's tube method), and Retention factor (based on optimized chromatographic solvent system).

## Characterization of compounds using sophisticated analytical techniques

The synthesized molecules will be comprehensively characterized using sophisticated analytical techniques such as Fourier-transformed Infrared (FT-IR) Spectroscopy, Proton-Nuclear Magnetic Resonance ($^{1}$H-NMR) Spectroscopy, Carbon-Nuclear Magnetic Resonance ($^{13}$C-NMR) Spectroscopy, and Mass Spectroscopy; where specific peaks will be studied to establish the chemical structures of the newly synthesized molecules. CHN-Elemental Analysis will be used to determine Carbon, Hydrogen, and Nitrogen compositions (in %) in the molecules and compare with the theoretically calculated values.

## Statistical analysis of the results

All the data will be represented in Mean ± SD. Data will be analyzed using one-way ANOVA followed by Dunnett's multiple comparison tests using Sigmastat® software. The group means will be considered significantly significant when p-value is $< 0.05$.

# RESULTS AND DISCUSSION

## Pharmacokinetics, Bioavailability, and Drug-likeliness studies

### Compound-1

**Table 1** describes the predictive values for pharmacokinetics, bioavailability and drug-likeness data on novel sibutramine derivative. The molecule showed high absorption rate. Good blood-brain permeability was obtained based on LogP value while low negative value indicated less skin permeation. In case of metabolism, the molecule did not prove to be a p-glycoprotein substrate. It acts as $CYP_{450}$ inhibitors and specifically inhibits CYP1A2 and CYP2D6 isoforms. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score was obtained. Poor water soluble characteristics were obtained for the novel sibutramine derivative.

### Compound-2

The molecule showed high absorption rate. Good blood-brain permeability was obtained based on LogP value while moderate negative value indicated less skin permeation. In case of metabolism, the molecule did prove to be a p-glycoprotein substrate. It acts as $CYP_{450}$ inhibitors and specifically inhibits CYP2D6 isoform. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score (0.55) was obtained. Poor to moderate water soluble characteristics were obtained for this novel sibutramine derivative.

### Compound-3

The molecule showed low absorption rate. Poor blood-brain permeability was obtained based on LogP value while low negative value indicated less skin permeation. In case of metabolism, the molecule did prove to be a p-glycoprotein substrate. It acts as $CYP_{450}$ inhibitors and specifically inhibits CYP2C19 and CYP2D6 isoforms. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score (0.55) was obtained. Poor water soluble characteristics were obtained for the novel sibutramine derivative.

**Table 1: Pharmacokinetics and physicochemical properties of novel sibutramine derivatives.**

| PROPERTIES | 1 | 2 | 3 |
|---|---|---|---|
| Physicochemical Properties | | | |
| Formula | $C_{23}H_{32}N_2O$ | $C_{24}H_{34}N_2O$ | $C_{24}H_{34}N_2$ |
| Molecular weight (g/mol) | 329.04 | 366.54 | 350.54 |
| Number of heavy atoms | 26 | 27 | 26 |
| Number of aromatic heavy atoms | 12 | 12 | 12 |
| Fraction $Csp^3$ | 0.48 | 0.50 | 0.50 |

**Table 1:** ***(Continued)***

| | | | |
|---|---|---|---|
| Number of rotatable bonds | 7 | 8 | 7 |
| Number of H-bond acceptors | 2 | 2 | 1 |
| Number of H-bond donors | 2 | 1 | 1 |
| Molar Refractivity | 111.71 | 116.18 | 114.65 |
| TPSA ($A^2$) | 35.05 | 24.50 | 15.27 |
| Lipophilicity | | | |
| Log Po/w (iLOGP) | 3.67 | 4.42 | 4.40 |
| Log Po/w ($XLOGP_3$) | 5.99 | 6.32 | 6.71 |
| Log Po/w (WLOGP) | 5.53 | 5.84 | 6.14 |
| Log Po/w (MLOGP) | 4.05 | 4.26 | 4.87 |
| Log Po/w (SILICOS-IT) | 4.65 | 5.20 | 5.66 |
| Consensus Log Po/w | 4.78 | 5.21 | 5.56 |
| Water Solubility | | | |
| Log S (ESOL) | -5.68 | -5.90 | -6.12 |
| Solubility | 7.39e-04 mg/ml ; 2.09e-06 mol/l | 4.67e-04 mg/ml ; 1.27e-06 mol/l | 2.66e-04 mg/ml ; 7.58e-07 mol/l |
| Class | Moderate Soluble | Moderate Soluble | Poorly Soluble |
| Log S (Ali) | -6.51 | -6.62 | -6.83 |
| Solubility | 1.08e-04 mg/ml ; 3.07e-07 mol/l | 8.71e-05 mg/ml ; 2.38e-07 mol/l | 5.13e-05 mg/ml ; 1.46e-07 mol/l |
| Class | Poorly Soluble | Poorly Soluble | Poorly Soluble |
| Log S (SILICOS-IT) | -6.83 | -7.53 | -7.80 |
| Solubility | 5.17e-05 mg/ml ; 1.47e-07 mol/l | 1.09e-05 mg/ml ; 2.97e-08 mol/l | 5.58e-06 mg/ml ; 1.59e-08 mol/l |
| Class | Poorly Soluble | Poorly Soluble | Poorly Soluble |
| Pharmacokinetics | | | |
| GI absorption | High | High | Low |
| BBB permeant | Yes | Yes | No |
| P-gp substrate | No | Yes | Yes |
| CYP1A2 inhibitor | Yes | No | No |
| CYP2C19 inhibitor | No | No | Yes |
| CYP2C9 inhibitor | No | No | No |
| CYP2D6 inhibitor | Yes | Yes | Yes |
| CYP3A4 inhibitor | No | No | No |
| Log Kp (skin permeation) (cm/s) | -4.20 | -4.05 | -3.67 |
| Drug-likeness | | | |
| Lipinski | Yes; 0 violation | Yes; 1 violation: MLOGP>4.15 | Yes; 1 violation: MLOGP>4.15 |
| Ghose | Yes | No; 1 violation: WLOGP>5.6 | No; 1 violation: WLOGP>5.6 |
| Veber | Yes | Yes | Yes |
| Egan | Yes | Yes | No; 1 violation: WLOGP>5.88 |
| Muegge | No; 1 violation: XLOGP3>5 | No; 1 violation: XLOGP3>5 | No; 1 violation: XLOGP3>5 |
| Bioavailability Score | 0.55 | 0.55 | 0.55 |
| Medicinal Chemistry | | | |
| PAINS | 0 alert | 0 alert | 0 alert |
| Brenk | 1 alert: hydroquinone | 0 alert | 0 alert |
| Lead-likeness | No; 2 violations: MW>350, XLOGP3>3.5 | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | No; 2 violations: MW>350, XLOGP3>3.5 |
| Synthetic accessibility | 3.19 | 3.30 | 3.28 |

## Bioavailability Radar Plot

### Compound-1

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per $Csp^3$ as 0.48, FLEX as per number of rotable bond 7, INSOLU Logs (ESOL) as -5.68 (insoluble), SIZE as molecular weight (g/mol) of 329.04, POLAR as TPSA (Å²) 35.05, and LIPO as XLOGP3 value of 5.99 (**Figure 2A**).

### Compound-2

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per $Csp^3$ as 0.50, FLEX as per number of rotable bond 8, INSOLU Logs (ESOL) as -5.90 (insoluble), SIZE as molecular weight (g/mol) of 366.54, POLAR as TPSA (Å²) 24.50, and LIPO as XLOGP3 value of 6.32 (**Figure 2B**).

### Compound-3

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per $Csp^3$ as 0.50, FLEX as per number of rotable bond 7, INSOLU Logs (ESOL) as -6.12 (insoluble), SIZE as molecular weight (g/mol) of 350.54, POLAR as TPSA (Å²) 15.27, and LIPO as XLOGP3 value of 6.71 (**Figure 2C**).

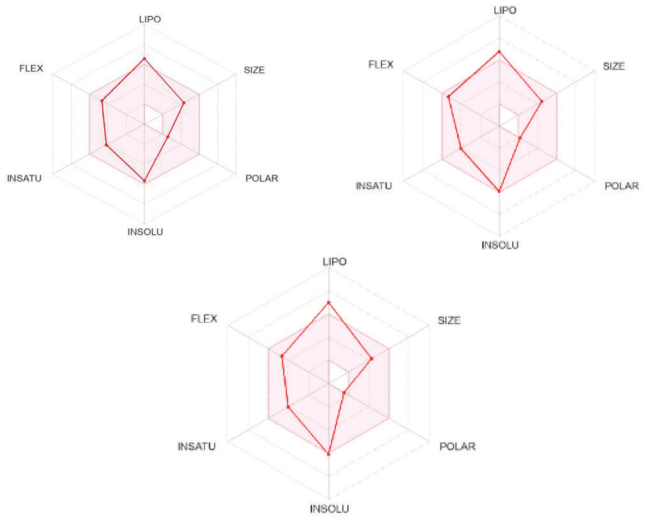


**Figure 2:** Bioavailability Radar Plot (A) Compound-1, (B) Compound-2, and (C) Compound-3.

## Boiled Egg Plot

In case of BOILED-Egg model (**Figure 3**), it was obtained that novel sibutramine derivative **(1)** has limited capability of blood-brain barrier penetration as well as it also showed low gastrointestinal absorption. The molecule was found to be PGP positive as non-substrate in predictive model. In contrast to it, compound (2-3) has interestingly, the Brain OrIntestinaLEstimateD permeation method (BOILED-Egg) has already been proposed as an accurate predictive model, which helps by computational prediction of the lipophilicity and polarity of small molecules. In overall predictive results, novel sibutramine derivative can be suitable drug candidate as per bioavailability radar and BOILED-Egg representation.

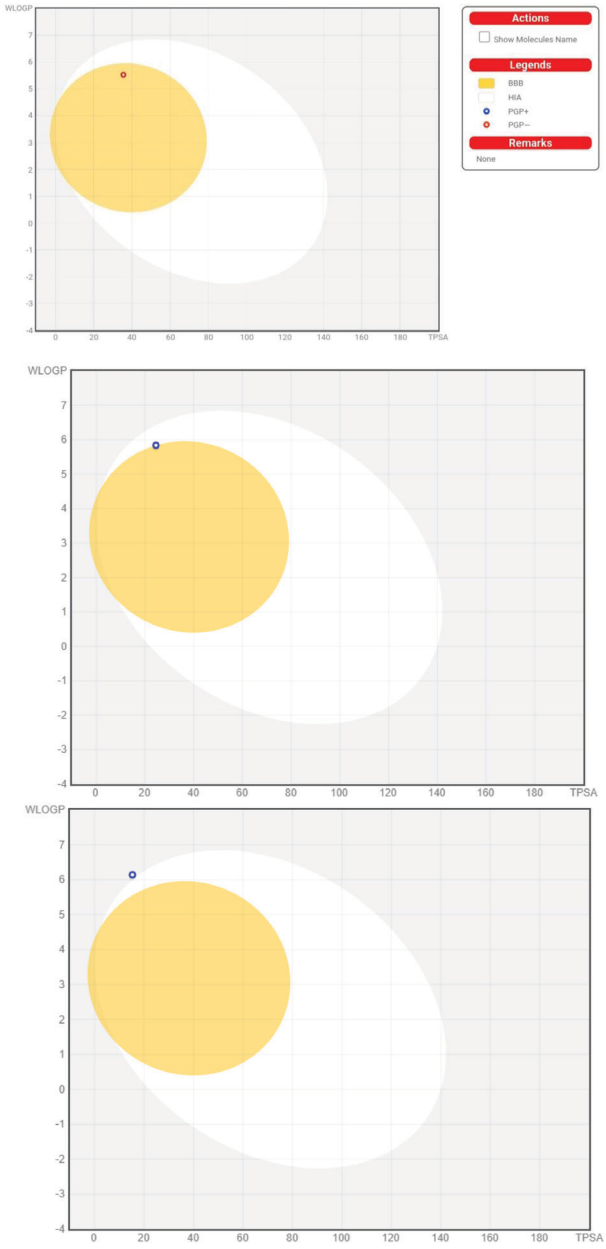


**Figure 3:** Boiled Egg Plot (A) Compound-1, (B) Compound-2, and (C) Compound-3.

## Physical characterization of novel sibutramine derivatives

### Appearance

The final compound was found to be solid, white in color, and crystalline in nature **(Table 2)**.

**Table 2: Characterization of novel sibutramine derivatives.**

| Characteristics | 1 | 2 | 3 |
|---|---|---|---|
| Appearance | White crystalline solid | Yellow amorphous solid | Yellow crystalline solid |
| Yield (%) | 64 | 73 | 81 |
| Melting point (°C) | 218-219 | 159-161 | 181-182 |
| Rf value | 0.54 | 0.43 | 0.77 |

## Yield

The compounds **(1-3)** were observed to be marginal (64%), moderate (73%), and 81% (significant), respectively. On consecutive purification through column chromatography, the purity of the products were ascertained, however, the quantity was less.

## Melting point

Through digital melting point apparatus, the melting point of the compounds **(1-3)** was detected to be 218-219°C, 159-161°C, and 181-182°C. This study revealed the conversion of intermediate product into the compounds.

## Rf value

Using the mobile phase composition of acetonitrile: ethylacetate (6:4 v/v), the Rf values of the final compound was observed to be 0.54 (for compound-1), 0.43 (for compound-2), and 0.77 (for compound-3). This study revealed the successful formation of all the novel sibutramine derivatives.

## Spectroscopic characterization of final compound

The spectroscopy study supported the formation of the compound. The disappearance of (-Cl) component (655 $cm^{-1}$) and the appearance of NH at 3274 $cm^{-1}$ confirmed the formation of the novel Sibutramine derivative. The C-N component at 1701 $cm^{-1}$ substantiates the presence of the newly added six-membered portion to the parent molecule **(Figure 4)**.

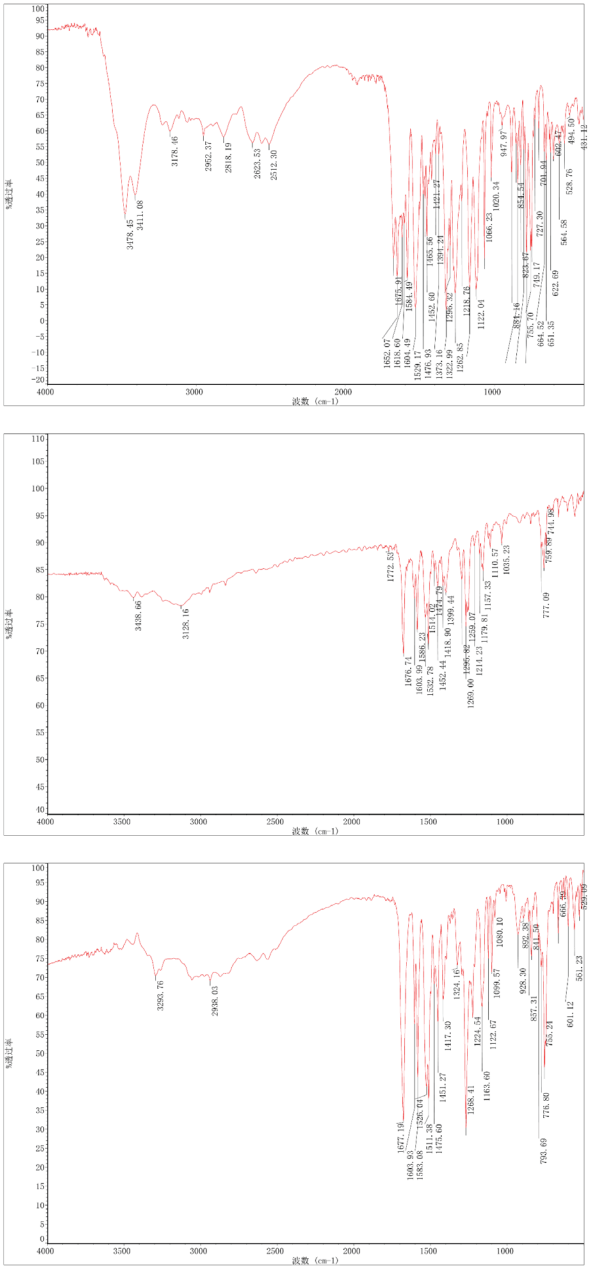

**Figure 4:** FTIR spectrum of novel sibutramine derivatives (A) Compound-1, (B) Compound-2, and (C) Compound-3.

The $^{1}$H-NMR spectra represented few key aspects. The spectral range of 7.0-8.0 ppm emphasizes the presence of protons in the compound. Additionally, the –NH and –OH aspects were located at 10.4 ppm and 3.39 ppm, respectively **(Figure 5)**.

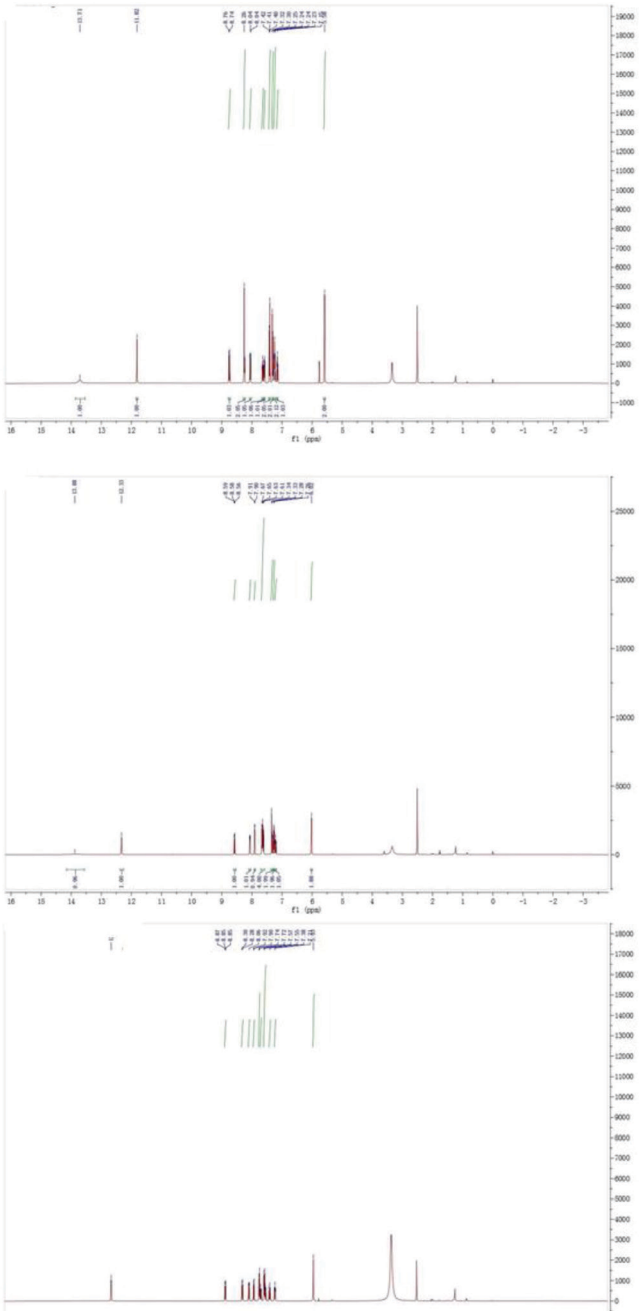

**Figure 5:** $^{1}$H-NMR of novel sibutramine derivatives (A) Compound-1, (B) Compound-2, and (C) Compound-3.

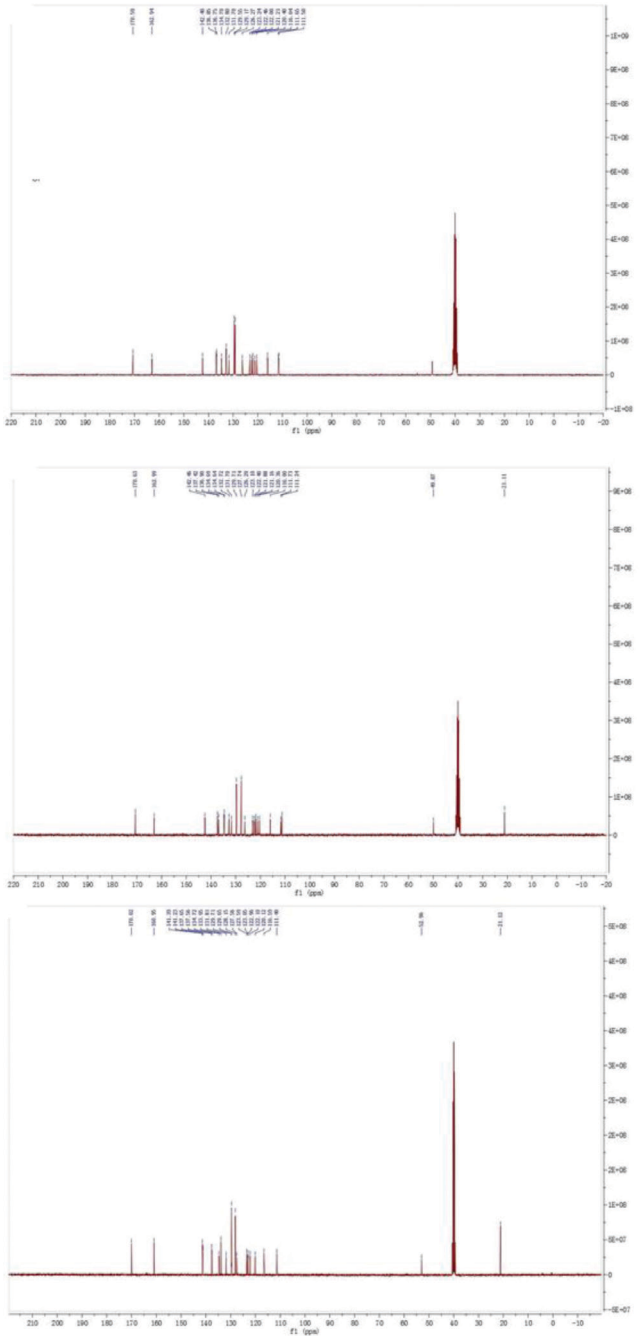

**Figure 6:** $^{13}$C-NMR of novel sibutramine derivatives (A) Compound-1, (B) Compound-2, and (C) Compound-3.

The $^{13}$C-NMR spectrum also confirmed the formation of the novel derivative and showed analogous results to that of proton NMR (**Table 3**). The spectral range of 120.0-140.0 ppm emphasizes the presence of protons in the compound. Additionally, the –NH and –OH aspects were located at 78.2 ppm and 39.6 ppm, respectively **(Figure 6)**.

Furthermore, the mass spectra presented exactly the same molecular weight (m/z 329.04) of the fabricated molecule in the base peak. In addition to that, the fragment peaks (m/z 389.19, 373.19, 321.09, 300.19, 287.19, 256.19, 219.09, 186.19, 173.19, 149.19, 141.19, 127.09, 101.29) also appeared **(Figure 7)**.

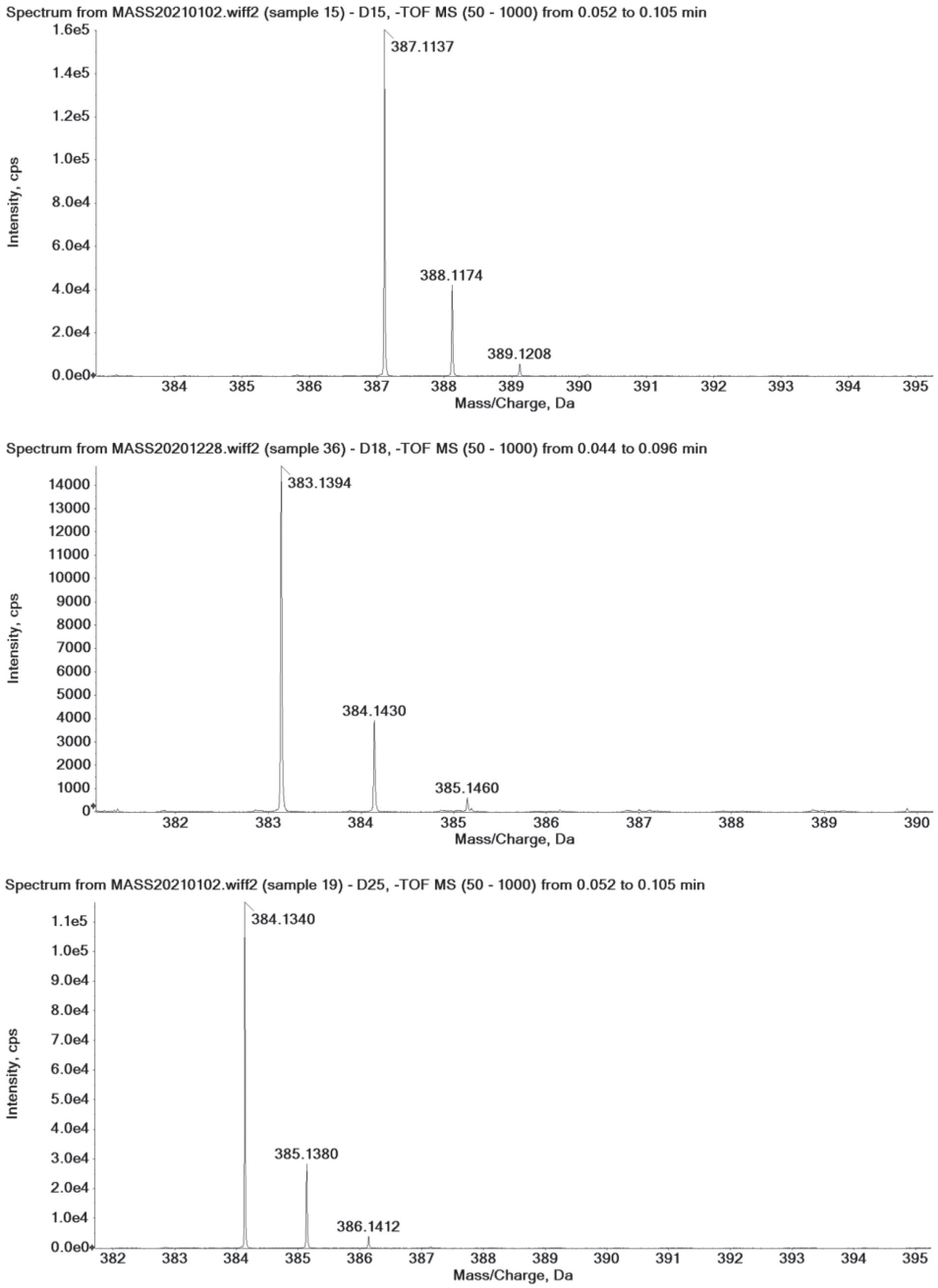


**Figure 7:** Mass spectra of novel sibutramine derivatives (A) Compound-1, (B) Compound-2, and (C) Compound-3.

**Table 3: Spectral data of novel sibutramine derivatives.**

| Tools | Characterization description | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| FT-IR | 3274 (-NH, stretch), 3128 (C-H, aromatic), 1737 (C=O), 1701 (C-N, stretch), 1688 (C=C, aromatic), 1620 (C=C, aromatic), 1562 (-NH, bending), 1488 ($-CH_2$), 1208 (C-O) | 3280 (-NH, stretch), 3168 (C-H, aromatic), 1791 (C=O), 1713 (C-N, stretch), 1681 (C=C, aromatic), 1644 (C=C, aromatic), 1599 (-NH, bending), 1489 ($-CH_2$), 1272 (C-O) | 3299 (-NH, stretch), 3183 (C-H, aromatic), 1754 (C=O), 1734 (C-N, stretch), 1698 (C=C, aromatic), 1667 (C=C, aromatic), 1576 (-NH, bending), 1495 ($-CH_2$), 1213 (C-O) |

**Table 3:** ***(Continued)***

| Tools | Characterization description | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| $^{1}$H-NMR | δ 0.99 (3H, t, *J* = 7.4 Hz), 2.65 (2H, q, *J* = 7.4 Hz), 7.10-7.32 (5H, 7.16 (dddd, *J* = 7.8, 1.3, 1.0, 0.5 Hz), 7.20 (tt, *J* = 7.7, 1.3 Hz), 7.26 (tdd, *J* = 7.7, 1.6, 0.5 Hz)) | δ 0.93-1.05 (6H, 0.99 (d, *J* = 6.7 Hz), 0.99 (d, *J* = 6.7 Hz)), 1.18-1.32 (2H, 1.25 (dd, *J* = 7.7, 7.2 Hz), 1.25 (dd, *J* = 7.7, 7.2 Hz)), 1.52 (1H, tsept, *J* = 7.2, 6.6 Hz), 1.70 (1H, dtt, *J* = 14.1, 8.9, 6.7 Hz), 1.85-2.31 (11H, 1.93 (dtt, *J* = 14.1, 6.7, 2.3 Hz), 2.08 (ddd, *J* = 14.6, 6.7, 2.3 Hz), 2.08 (ddd, *J* = 14.5, 6.7, 2.3 Hz), 2.23 (ddd, *J* = 14.6, 8.9, 6.7 Hz), 2.23 (ddd, *J* = 14.5, 8.9, 6.7 Hz), 2.25 (s)), 2.80 (1H, t, *J* = 7.7 Hz), 3.75 (3H, s), 6.29 (2H, ddd, *J* = 8.2, 1.1, 0.5 Hz), 6.67 (2H, ddd, *J* = 8.7, 2.7, 0.5 Hz), 7.04-7.17 (4H, 7.10 (ddd, *J* = 8.7, 1.7, 0.5 Hz), 7.11 (ddd, *J* = 8.2, 1.1, 0.5 Hz)) | δ 0.93-1.05 (6H, 0.99 (d, *J* = 6.7 Hz), 0.99 (d, *J* = 6.7 Hz)), 1.18-1.32 (2H, 1.25 (dd, *J* = 7.7, 7.2 Hz), 1.25 (dd, *J* = 7.7, 7.2 Hz)), 1.52 (1H, tsept, *J* = 7.2, 6.6 Hz), 1.70 (1H, dtt, *J* = 14.1, 8.9, 6.7 Hz), 1.85-2.31 (14H, 1.93 (dtt, *J* = 14.1, 6.7, 2.3 Hz), 2.08 (ddd, *J* = 14.6, 6.7, 2.3 Hz), 2.08 (ddd, *J* = 14.5, 6.7, 2.3 Hz), 2.23 (ddd, *J* = 14.6, 8.9, 6.7 Hz), 2.23 (ddd, *J* = 14.5, 8.9, 6.7 Hz), 2.21 (s), 2.25 (s)), 2.80 (1H, t, *J* = 7.7 Hz), 6.21-6.35 (4H, 6.27 (ddd, *J* = 8.2, 1.4, 0.5 Hz), 6.29 (ddd, *J* = 8.2, 1.1, 0.5 Hz)), 7.06 (2H, ddd, *J* = 8.2, 1.3, 0.5 Hz), 7.21 (2H, ddd, *J* = 8.2, 1.1, 0.5 Hz) |
| $^{13}$C-NMR | δ 11.3 (1C, s), 15.8 (1C, s), 20.3-20.4 (2C, 20.4 (s), 20.4 (s)), 21.3 (1C, s), 26.3-26.4 (2C, 26.4 (s), 26.4 (s)), 29.1 (1C, s), 35.6 (1C, s), 40.6 (1C, s), 41.8 (2C, s), 59.6 (1C, s), 117.9 (2C, s), 119.3 (1C, s), 119.9 (1C, s), 127.1 (1C, s), 129.0 (1C, s), 129.6 (2C, s), 139.4 (1C, s), 141.5 (1C, s), 142.0 (1C, s), 144.9 (1C, s) | δ 15.8 (1C, s), 22.5-22.6 (2C, 22.6 (s), 22.6 (s)), 24.4 (1C, s), 26.3-26.4 (2C, 26.4 (s), 26.4 (s)), 35.1 (1C, s), 40.6 (1C, s), 41.8 (2C, s), 56.0 (1C, s), 60.1 (1C, s), 114.5 (2C, s), 117.9 (2C, s), 120.5 (2C, s), 127.4 (2C, s), 141.9-142.1 (2C, 142.0 (s), 142.0 (s)), 144.9 (1C, s), 159.8 (1C, s) | δ 15.8 (1C, s), 21.3 (1C, s), 22.5-22.6 (2C, 22.6 (s), 22.6 (s)), 24.4 (1C, s), 26.3-26.4 (2C, 26.4 (s), 26.4 (s)), 35.1 (1C, s), 40.6 (1C, s), 41.8 (2C, s), 60.1 (1C, s), 117.9-118.0 (4C, 117.9 (s), 117.9 (s)), 127.4 (2C, s), 129.6 (2C, s), 141.5 (1C, s), 141.9-142.1 (2C, 142.0 (s), 142.0 (s)), 144.9 (1C, s) |
| Mass | m/z 329; Fragments: 389.19, 373.19, 321.09, 300.19, 287.19 | m/z 350; Fragments: 256.19, 186.19, 127.09, 101.29 | m/z 366; Fragments: 219.09, 173.19, 149.19, 141.19 |

## CONCLUSION

This novel derivative [4-((4-(1-(1-(dimethylamino)-3-methylbutyl)cyclobutyl)phenyl)amino)phenol] was synthesized successfully in our laboratory from the parent USFDA approved drug Sibutramine and were comprehensively characterized by sophisticated analytical instruments such as FTIR spectroscopy, $^{1}$H-NMR spectroscopy, $^{13}$C-NMR spectroscopy, and Mass spectroscopic spectroscopy. This drug discovery study has opened new avenues for medicinal chemists by opening the doors for the application of Sibutramine in a new version with complete elimination of its side-effects and associated negative aspects, thereby re-launching the anti-obesity molecule after 13 years.

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