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IP LICENSING & COMMERCIALISATION

A2P Care Pharmaceuticals LLP

DIHYDRAZIDE-DIHYDRAZONE COMPOUNDS WITH ADAMANTYL MOIETY AND A PROCESS FOR SYNTHESIS OF THE SAME

Patent Application No.: 202221033544

PCT Patent No.: WO2023237924A1

Google patents:
https://patents.google.com/patent/WO2023237924A1/en?oq=WO2023237924+(A1)

Inventor Profile

DR. RUPA SACHIN PAWAR

Ph.D. in Organic Chemistry

Shri Jagdishprasad Jhabarmal Tibrewala University (JJTU), Rajasthan, India

- **5 years of experience** in Pharma industry and allied teaching.
- **1+ year experience** as an Analytical Data Reviewer in a Pharmaceutical company based in USA.
- **4+ years of teaching experience** in various prestigious institutions.
- Published **four research papers** in UGC-recognized journals, focusing on **dihydrazide-dihydrazone derivatives** with **adamantane moieties**, and their **antifungal/antibacterial properties**.
- Presented original research at **international conferences**.
- Successfully completed Ph.D. **viva voce in December 2023**.

Key Research Contributions

- Focus on **dihydrazide-dihydrazone** derivatives with medicinal properties, including anti-cancer, anti-fungal, and anti-bacterial activities.
- Exploration of adamantane derivatives for **neurological disorders** like Parkinson's and Alzheimer's diseases.
- Extensive testing on anti-diabetic properties, showing promising results for **Type 2 diabetes** treatment.

Notable Publications:

- Synthesis, characterization, and anti-fungal activities of dihydrazide-dihydrazone derivatives with nitro group. IJERA, 2022.
- Antifungal activities of dihydrazide-dihydrazone derivatives with halo group. IJERA, 2022.
- Antibacterial activities of dihydrazide-dihydrazone derivatives with halo group. IJSEDR, 2022.
- Anti-bacterial activities of dihydrazide-dihydrazone derivatives with nitro group. IJETIR, 2022.

OVERVIEW

Our patented compound contains **adamantane** and **dihydrazide-dihydrazone** groups, both of which are known for their **medicinal properties**, as demonstrated in numerous literature reviews. The compound holds promise in the treatment of several diseases, especially **cancer, neurological disorders,** and **diabetes**.

Adamantane Derivatives:

Widely recognized for their efficacy in treating neurological conditions, such as **Parkinson's disease** and **Alzheimer's disease**, adamantane-based compounds are expected to play a pivotal role in the pharmaceutical industry in the near future. According to existing research, adamantane's ability to mitigate neurological complications associated with Type 2 diabetes further strengthens its therapeutic potential.

OVERVIEW

Dihydrazide-Dihydrazone Compounds:

Known for their effectiveness against **hypertension** and **diabetes**, these compounds also exhibit various other pharmacological activities. The literature highlights the specific benefits of **hydrazide/hydrazone** derivatives in inhibiting **alpha-glucosidase**, a key enzyme related to Type 2 diabetes management.

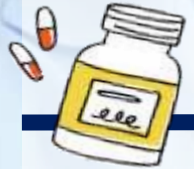
Preclinical Results and Safety

We have conducted comprehensive testing, including both toxicity and anti-diabetic evaluations:

Toxicity Test Results: The compound has been proven non-toxic, with an LD50 value of over 5000 mg/kg, and no mortality has been reported. This ensures the compound is safe for further development and trials.

Anti-Diabetic Activity: The compound has demonstrated significant anti-diabetic effects in preclinical studies when compared to the control group (Streptozotocin). Key observations include:

- A significant decrease in fasting blood glucose levels.
- A notable increase in body weight—a positive indicator, as diabetes often leads to weight loss. It does not even lead to obesity as observed in few cases as per observation.



Potential for Oral Drug Development

In compliance with **Lipinski's 'Rule of Five',** which guides the development of orally active compounds, our compound meets all criteria, making it suitable for further exploration as an **oral drug**. Specifically:

- It has fewer than 5 hydrogen bond donors.
- It has fewer than 10 hydrogen bond acceptors.
- Its molecular weight is below 500.
- Its calculated Log P (cLogP) falls within acceptable limits.

Market Potential and Strategic Fit

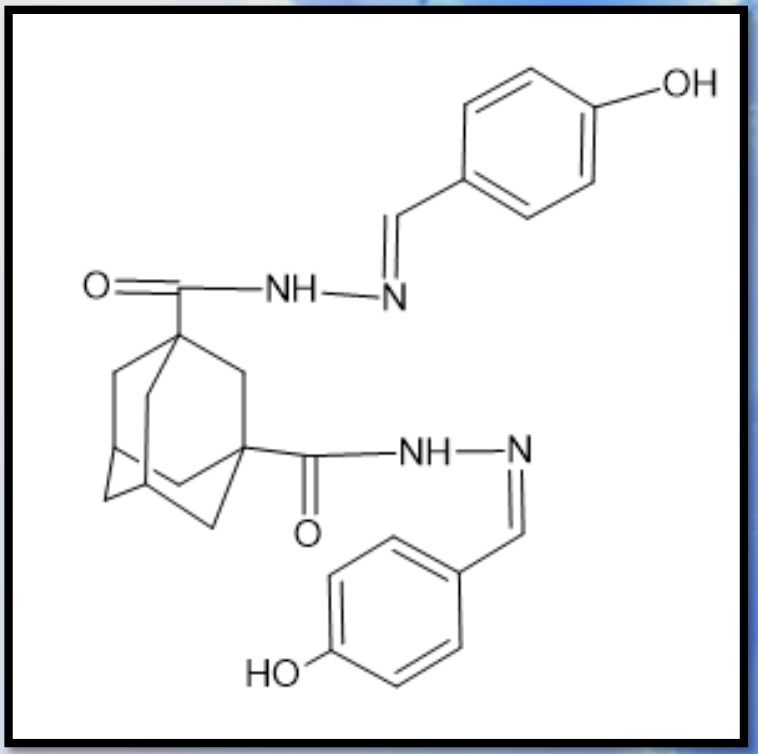
Pharmaceutical Impact:

Given the rising incidence of neurological disorders and diabetes globally, this compound addresses multiple therapeutic areas with high unmet need. Its dual action—on both **Type 2 diabetes** and **neurological side effects**—makes it particularly valuable in treating the growing population of diabetic patients experiencing cognitive impairments.

Licensing Opportunity:

We are seeking strategic partners to advance this compound through the next phases of development, including preclinical and clinical trials. By licensing this patent, you will have access to a scientifically sound, non-toxic, and potentially breakthrough compound with robust data supporting its therapeutic claims.

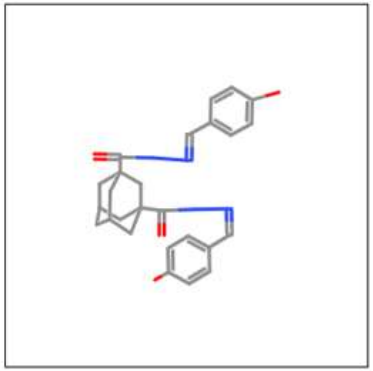
Structure



$C_{28}H_{28}N_4O_4$ M_{av} : 460.5249 Da

Computerized Toxicity Report

Oral toxicity prediction results for input compound



Predicted LD50: 698mg/kg

Predicted Toxicity Class: 4

1 2 3 4 5 6

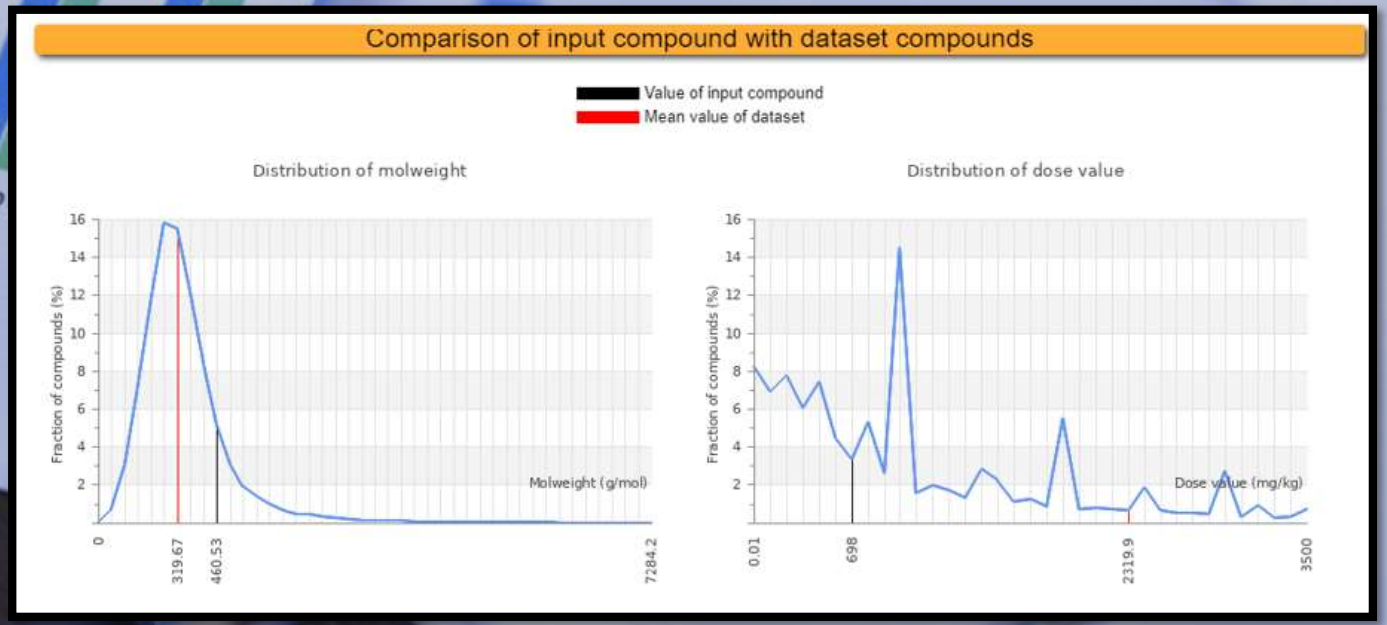
Average similarity: 58.97%

Prediction accuracy: 67.38%

20% 40% 60% 80%

Name	User defined
Molweight	460.53
Number of hydrogen bond acceptors	36
Number of hydrogen bond donors	4
Number of atoms	62
Number of bonds	66
Number of rotable bonds	8
Molecular refractivity	128.94
Topological Polar Surface Area	123.38
octanol/water partition coefficient(logP)	4.07

Computerized Toxicity Report



Computerized Toxicity Report

+ Similar compounds

Toxicity Model Report

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.51
Toxicity end points	Carcinogenicity	carcino	Active	0.54
Toxicity end points	Immunotoxicity	immuno	Inactive	0.92
Toxicity end points	Mutagenicity	mutagen	Inactive	0.52
Toxicity end points	Cytotoxicity	cyto	Inactive	0.73
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.73
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.87
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.75
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.96
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.96
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.91
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.91
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.56
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.86
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.92

The toxicity radar chart is intended to quickly illustrate the confidence of positive toxicity results compared to the average of its class.
Click the thumbnail to access the plot once it has finished loading.

Toxicity targets

Exemplary Study for Oral Toxicity

Study Title: Acute Oral Toxicity of XXXX in Rats- Acute Toxic Class Method (OECD Guideline No. 423)

Study Number : SB/TOX/24-55

Study Director : Reniguntla Kumar

Client : Rupa Pawar Pune

Client Representative : Rupa Pawar

ABBREVIATIONS & SYMBOLS:

CMC : Carboxy Methyl Cellulose

H : Hour

Ml : Milliliter

Mg : Milligram

Mg/kg : Milligram per kilogram

Min : Minutes

M : Males

NA : Not applicable

NAD : No abnormality Detected

% : Percent

< : Less than

& : and

Exemplary Study for Oral Toxicity

Mortality & Morbidity: The results for mortality and morbidity, along with the experimental procedures followed during the study, are summarized in **Table 1**.

Body Weights: The body weights of each animal were recorded before the administration of the test compound (Day 0) and subsequently on Days 7 and 14 of the study. These data are presented in **Table 2**.

Clinical Observations: All animals were monitored for clinical signs throughout the study, and the observed signs are detailed in **Table 1**.

Gross Pathology: The gross pathology findings from the animals at various stages of the study are also documented in **Table 1**.

Conclusion

Based on the results obtained from the study, the test compound RP-TOX is classified as Category 5 or unclassified according to the Globally Harmonized System (GHS) for the classification of chemicals. The LD50 value is determined to be greater than 5000 mg/kg, indicating that the compound is non-toxic and safe for further development.

Exemplary Study for Oral Toxicity

Table 1: Results of Mortality & Morbidity; Clinical signs and Gross pathology

Steps	Dose	Animal No.	Clinical Signs	Mortality & Morbidity	Gross Pathology
1	300 mg/kg	1	All animals were apparently normal following test item administration on day 0.	Nil	NAD
		2			NAD
		3			NAD
2	300 mg/kg	4	All animals were apparently normal following test item administration on day 0.	Nil	NAD
		5			NAD
		6			NAD
3	2000 mg/kg	7	All animals were apparently normal following test item administration on day 0.	Nil	NAD
		8			NAD
		9			NAD
4	2000 mg/kg	10	All animals were apparently normal following test item administration on day 0.	Nil	NAD
		11			NAD
		12			NAD

Exemplary Study for Oral Toxicity

Table 2: Individual Animal Body weights (g)

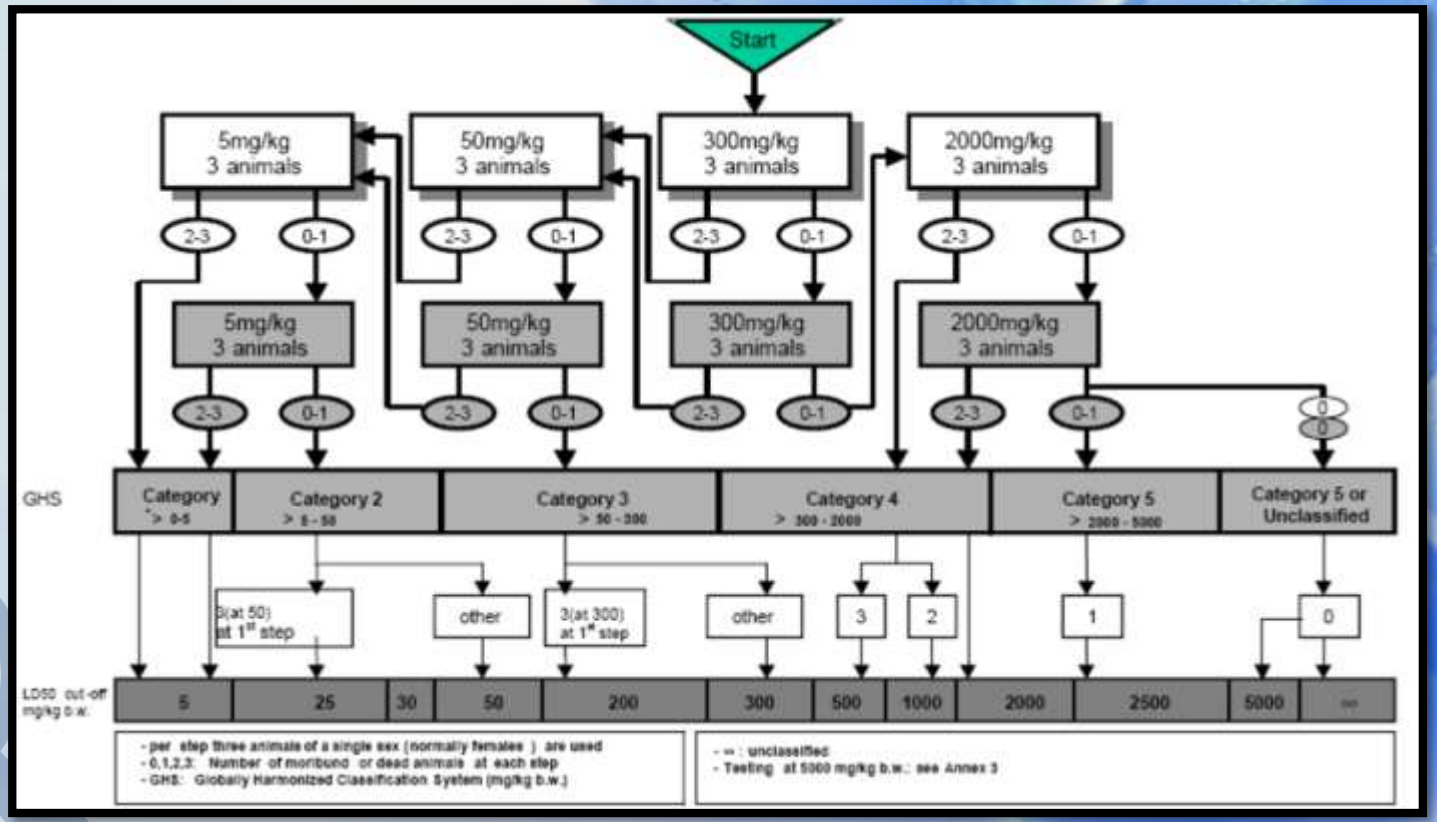
Step (mg/Kg b.w.)	A.No.	Day 0	Day 7	Day 14	Increase in body weight at the end of the experiment
1 (300)	1	130.0	138.4	145.8	12.2
	2	127.5	134.0	140.2	10.0
	3	124.2	131.1	143.4	15.5
2 (3000	4	130.3	136.9	143.9	10.4
	5	134.8	141.0	151.0	12.0
	6	133.6	140.8	148.6	11.2
3 (2000)	7	131.1	138.3	145.4	10.9
	8	125.7	133.4	140.1	11.5
	9	130.4	136.9	143.7	10.2
4 (2000)	10	133.8	140.2	148.9	11.3
	11	130.2	137.8	143.4	10.1
	12	128.9	135.2	142.9	10.9

Exemplary Study for Oral Toxicity

Table 2: Individual Dose volume administered (mL)

Step (mg/Kg b.w.)	A.No.	Individual Dose volume administered (mL)
1 (300)	1	1.3
	2	1.3
	3	1.2
2 (3000	4	1.3
	5	1.3
	6	1.3
3 (2000)	7	1.3
	8	1.3
	9	1.3
4 (2000)	10	1.3
	11	1.3
	12	1.3

Test Procedure With A Starting Dose Of 300 Mg/Kg Body Weight



Exemplary Study for Anti-diabetes

Study Title: Assessment of Anti-diabetic Potential of RP-AD in Streptozotocin-Nicotinamide Induced type 2 diabetic Rat model

Study Number : SB"MD/24-58

Study Director : Reniguntla Kumar

Client : Rupa Pawar

Client Representative : Rupa Pawar

Exemplary Study for Anti-diabetes

Mortality & Morbidity

The mortality and morbidity results, as well as the experimental procedures used in this study, are detailed in **Table 1.**

Body Weights

The body weights of each animal were recorded before administering the test compound (Day 0) and again on Days 7 and 14 of the experiment. The data is presented in **Table 2.**

Clinical Observations

Clinical signs were recorded throughout the study. These observations are also summarized in **Table 1.**

Gross Pathology

Gross pathology findings from the animals during different stages of the study are detailed in **Table 1.**

Exemplary Study for Anti-diabetes

Conclusion

The test compound **RP AD** (administered at 300 mg/kg, PO for 28 days) demonstrated a **statistically significant increase in body weights** on Days 14, 21, and 28 when compared to the Streptozotocin G1 control group. Moreover, a **statistically significant decrease in fasting blood glucose levels** was observed on Days 14, 21, and 28 in the RP AD test compound group compared to the Streptozotocin G1 group.

These results suggest that **RP AD** shows promising potential as an effective treatment for diabetes, with beneficial effects on both body weight and blood glucose regulation.

Exemplary Study for Anti-diabetes

TABLE 1: SUMMARY OF CLINICAL SIGNS AND MORTALITY OBSERVATIONS OF ANIMALS

Group	Clinical signs on days				Mortality & Morbidity
	Day 1-8	Day 9-15	Day 16-22	Day 23-28	
G1-Streptozotocin (STZ) Control, (60 mg/kg, i.p., single dose)+Vehicle PO, uid, 28 days)	Normal	Normal	Normal	Normal	0/5
G2-Streptozotocin (60 mg/kg) + Metformin (100 mg/kg, PO, uid, 28 days)	Normal	Normal	Normal	Normal	0/5
G3-Streptozotocin (60 mg/kg) + RP AD (300 mg/kg, PO, uid, 28 days)	Normal	Normal	Normal	Normal	0/5

Exemplary Study for Anti-diabetes

TABLE 2: SUMMARY OF BODY WEIGHTS

Group	Body weights (g) (Mean ± SD)				
	Day 1	Day 8	Day 15	Day 21	Day 28
G1-Streptozotocin (STZ) Control, (60 mg/kg, i.p., single dose)+Vehicle PO, uid, 28 days)	167.1 ± 2.6	161.8 ± 2.6	146.3 ± 2.5	121.5 ± 3.8	109.0 ± 6.1
G2-Streptozotocin (60 mg/kg) + Metformin (100 mg/kg, PO, uid, 28 days)	165.4 ± 5.9[ns]	160.8 ± 5.7[ns]	159.5 ± 6.2***	165.7 ± 6.1***	172.1 ± 5.0***
G3-Streptozotocin (60 mg/kg) + RP AD (300 mg/kg, PO, uid, 28 days)	164.4 ± 3.1[ns]	158.8 ± 3.1[ns]	154.6 ± 3.4*	151.4 ± 3.6***	149.1 ± 4.6***

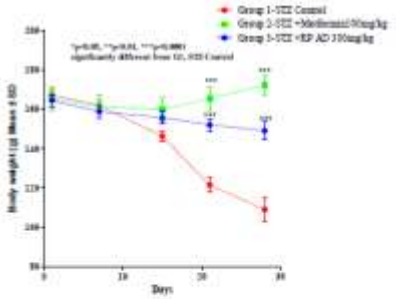


Figure 1: Body weights during study following treatment. Error bars are the Mean ± SD. The legend for each group is shown below the axis. Data expressed as Mean ± SD; *p < 0.05, **p < 0.01 & ***p < 0.0001 significantly different from G1, STZ control group; ns: non-significant.

Exemplary Study for Anti-diabetes

9.3 Glucose Readings

The summary of clinical signs and mortality observations of animals was presented in Table-3.

The RP AD test compound (300 mg/kg, uid, PO, 28 days) demonstrated a statistically significant decrease in fasting blood glucose levels on days 14, 21, and 28 in the RP AD test compound group compared to the Streptozotocin G1 group.

Group	Glucose Readings (mg/dL) (Mean ± SD)				
	Day 1	Day 8	Day 15	Day 21	Day 28
G1-Streptozotocin (STZ) Control, (60 mg/kg, i.p., single dose)+Vehicle PO, uid, 28 days)	336.03 ± 50.09	348.17 ± 49.99	364.66 ± 44.87	409.16 ± 48.52	412.62 ± 45.23
G2-Streptozotocin (60 mg/kg) + Metformin (100 mg/kg, PO, uid, 28 days)	342.56 ± 41.08^{ns}	329.66 ± 41.08^{ns}	240.06 ± 41.08***	116.04 ± 14.61***	104.80 ± 18.05***
G3-Streptozotocin (60 mg/kg) + RP AD (300 mg/kg, PO, uid, 28 days)	355.42 ± 37.03^{ns}	339.82 ± 37.03^{ns}	290.14 ± 27.22*	269.54 ± 18.73***	210.94 ± 34.48***

Exemplary Study for Anti-diabetes

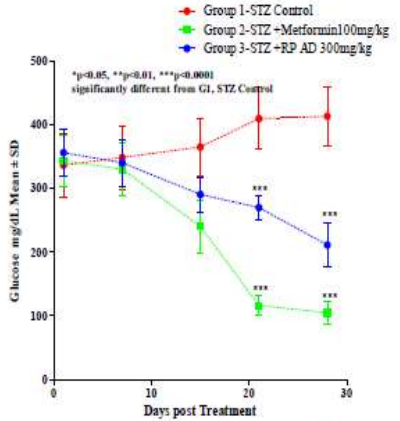


Figure 2: Glucose Readings during study following treatment. Error bars are the Mean ± SD. The legend for each group is shown below the axis. Data expressed as Mean ± SD; *p < 0.05, **p < 0.01 & ***p < 0.0001 significantly different from G1, STZ control group; ns: non-significant.

UNIQUENESS

Novel Chemical Structure:

The invention introduces a **novel combination** of **adamantyl moiety** and **dihydrazide-dihydrazone frameworks**, a structure not previously explored in antimicrobial drug design. This **dual-action mechanism** enhances the compound's effectiveness against a variety of microbes.

Resistance to Microbial Adaptation:

The compounds are designed to **minimize the likelihood of resistance** development by microbes, making them suitable for long-term clinical use. This sets them apart from traditional antibiotics that often lose efficacy over time due to microbial adaptation.

Synthetic Efficiency:

The **two-step synthesis** process is straightforward and efficient, enabling large-scale production with minimal waste. This process allows for customization of the compound's chemical properties, making it versatile for various therapeutic applications.

ABOUT & IT'S ROLE THEREOF

ABOUT

Our innovative drug is based on **dihydrazide-dihydrazone compounds with adamantane moiety**, a unique combination that offers multi-faceted medicinal benefits. The compound is designed primarily for the treatment of **Type 2 diabetes**, leveraging its anti-diabetic properties, while also offering potential benefits in combating neurological disorders and cancer, as identified in various literature reviews.

The drug has undergone initial testing, showing significant promise in terms of **safety** and **efficacy.** It has been tested for toxicity, revealing a high safety profile, and has demonstrated strong **anti-diabetic** effects when compared to standard control treatments. The formulation complies with **Lipinski's Rule of Five**, making it an excellent candidate for oral administration.

ABOUT & IT'S ROLE THEREOF

ROLE

This drug plays a crucial role in addressing **Type 2 diabetes** by targeting several key factors involved in the disease:

1. Blood Glucose Control:

The drug has shown a **statistically significant reduction in fasting blood glucose levels**, outperforming current control treatments in preclinical studies. This makes it a potential game-changer in managing glucose levels for diabetic patients.

2. Weight Management:

Patients treated with the drug also experienced a **notable increase in body weight**, which is important for Type 2 diabetes patients who often suffer from weight loss due to the disease.

ABOUT & IT'S ROLE THEREOF

3. Neurological Benefits:

The **adamantane moiety** in the compound is well-documented for its efficacy in treating neurological disorders, including **Parkinson's** and **Alzheimer's disease**. This dual-action feature could help manage the neurological side effects that often accompany Type 2 diabetes.

4. Toxicity Profile:

With an **LD50 value greater than 5000 mg/kg**, the drug falls under the "unclassified" category according to the **Globally Harmonized System (GHS)**, indicating a high safety margin for use in humans.

BENEFITS

Broad-Spectrum Application:

The ability to adjust the **substituents** (such as halogen, alkyl, nitro, or hydroxy groups) allows for the compound to be **tailored to target specific pathogens,** which could include not only bacteria but also fungi and viruses. This flexibility increases the compound's application in **multiple therapeutic areas.**

Preclinical Testing Readiness:

Due to the compound's **strong safety profile** and low toxicity, it is ready for **preclinical testing** in a variety of models, potentially speeding up its pathway to **clinical trials.**

Synergistic Drug Combinations:

These compounds could be combined with existing antimicrobial drugs to provide a **synergistic effect**, which may reduce the overall dosage of each drug, minimizing potential side effects while maintaining or enhancing efficacy.

COMMERCIAL VIABILITY

Niche Markets:

Beyond traditional pharmaceutical applications, these compounds have potential use in **biodefense, agriculture**, and **sanitation**, where **antimicrobial resistance** is also a growing problem. This opens up opportunities for licensing beyond healthcare, into industries like **food safety** and **agrochemicals.**

Regulatory Fast-Track Potential:

Given the urgent global need for new antimicrobial agents, this compound might qualify for **regulatory fast-tracking** under programs aimed at combating **antibiotic-resistant infections.** This could speed up the process from **preclinical** to **market**, reducing time to commercialization.

MARKET OPPORTUNITY

The global market for diabetes treatments is expanding rapidly, driven by the rising prevalence of Type 2 diabetes and the need for more effective, multi-functional therapies. Our patented drug, with its unique combination of anti-diabetic and neurological benefits, is positioned to capitalize on several key trends in the healthcare market.

1. Growing Global Diabetes Epidemic

According to the International Diabetes Federation (IDF), the number of people with diabetes worldwide is projected to reach **783 million** by 2045, with **Type 2 diabetes** accounting for 90% of cases.

Current treatments often fail to address the broader complications of diabetes, such as **weight loss** and **neurological issues**. Our drug offers a comprehensive solution by targeting **blood sugar levels** and managing associated side effects.

MARKET OPPORTUNITY

2. Neurological Complications in Diabetic Patients

Neurological disorders, such as **diabetic neuropathy** and cognitive decline, are common complications in patients with Type 2 diabetes.

The **adamantane** component in our drug, recognized for its benefits in treating **neurological disorders** like **Alzheimer's** and **Parkinson's disease**, positions it as a treatment that goes beyond typical glucose management.

3. Shift Towards Oral Therapies

There is an increasing demand for **oral diabetes medications** due to their ease of use, compared to injectable treatments like insulin.

Our drug, which meets the criteria for **oral administration** (as per **Lipinski's Rule of Five**), offers a patient-friendly alternative that could improve **adherence** and **quality of life** for diabetic patients.

MARKET OPPORTUNITY

4. Targeted Market Segments

Developed Markets: North America and Europe, with their high rates of diabetes, will continue to be key regions for advanced therapies.

Emerging Markets: Regions like Asia-Pacific and Latin America are seeing a **rapid increase in diabetes cases** due to lifestyle changes. These markets represent significant growth opportunities for affordable, effective therapies.

5. High Unmet Medical Need

Many existing diabetes treatments focus solely on controlling blood sugar levels without addressing the **broader impact** of the disease on **weight** and **neurological health**.

Our drug's ability to **manage multiple aspects of the disease** makes it highly attractive to physicians and healthcare providers seeking comprehensive solutions for their patients.

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