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Research Article

Anti-Amyloid Aggregation Activity of Isatin Derivatives: An Implication for Alzheimer's Drug Discovery

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ABSTRACT

Alzheimer's disease (AD) is marked by the aggregation of amyloid-beta (Aβ) peptides into plaques, which are key contributors to neurodegeneration and cognitive decline. The search for effective inhibitors of Aβ aggregation is critical for AD drug discovery, and isatin derivatives have emerged as promising candidates due to their diverse biological activities. This study explores the anti-amyloid aggregation potential of various isatin derivatives using a suite of computational tools. Molecular docking studies performed using PyRx software revealed significant binding interactions between the isatin derivatives and Aβ peptides, identifying compounds with high binding affinities. SwissADME was employed to evaluate the pharmacokinetic properties of the derivatives, ensuring their drug-likeness and oral bioavailability. PASS (Prediction of Activity Spectra for Substances) analysis predicted these derivatives to be strong inhibitors of Aβ aggregation. Molinspiration was used to assess molecular properties such as bioactivity scores, further validating their potential as drug-like compounds. The results of these computational analyses highlight several isatin derivatives with potent anti-amyloid activity, supported by favorable docking scores and optimal pharmacokinetic profiles. Structure-activity relationship (SAR) analysis identified key functional groups that enhance the anti-aggregation activity, with some derivatives demonstrating maximum inhibition of Aβ fibril formation. This study suggests that isatin derivatives are strong candidates for Alzheimer's drug discovery, offering a promising avenue for the development of novel anti-amyloid agents based on in silico evaluation. Among the three Isatin derivatives, 3-[2-(4-fluorophenyl) hydrazinyl]indol-2-one obtained the best docking score and hence it can be considered as a promising compound for Alzheimer's treatment.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the gradual loss of cognitive functions, particularly memory, and is the most common form of dementia. It affects millions of people worldwide and places a significant emotional and financial burden on families and healthcare systems.

Causes and Risk Factors

- **Genetic Factors**: Family history and specific genes, such as APOE-e4, increase the risk.
- **Lifestyle Factors**: Poor cardiovascular health, obesity, diabetes, smoking, and lack of physical activity are associated with higher risk.
- **Head Injuries**: Severe or repeated head trauma can elevate the risk.

Symptoms

- **Early Symptoms**: Memory loss, trouble completing familiar tasks, difficulty finding words, disorientation. And mood changes.
- Progressive Symptoms: Increased confusion, significant memory loss, difficulty recognizing loved ones, impaired reasoning, and language difficulties.
- Diagnosis
- Medical History: Evaluation of family and personal medical history.
- Cognitive Tests: Assessments to evaluate memory, attention, problem-solving, and language.
- Neurological Exams: Imaging tests like MRI and CT scans to exclude other conditions.
- Biomarker Tests: Advanced tests for amyloid and tau proteins in cerebrospinal fluid or PET scans.

Treatment and Management

- **Medications**: Cholinesterase inhibitors (e.g., Donepezil) and NMDA receptor antagonists (e.g., Memantine) to manage symptoms.
- **Lifestyle Changes**: Regular exercise, a healthy diet, mental stimulation, and social interaction.
- **Supportive Care**: Essential role of caregivers, with support groups and respite care available.

Pathophysiology

Alzheimer's disease (AD) is characterized by complex pathological processes leading to progressive neurodegeneration. The disease's hallmark features include the accumulation of amyloid-beta plaques, the formation of neurofibrillary tangles composed of hyperphosphorylated tau protein, and widespread neuronal loss.

Amyloid-Beta Plaques

- **Production**: Amyloid-beta (Aβ) is a fragment of the amyloid precursor protein (APP), which is cleaved by enzymes β-secretase and γ-secretase. Normally, these fragments are cleared away, but in AD, they accumulate.
- **Aggregation**: Aβ monomers aggregate to form oligomers, which further assemble into fibrils and eventually deposit as extracellular plaques in the brain.
- **Toxicity**: Aβ oligomers are particularly toxic to neurons. They disrupt synaptic function, induce oxidative stress, and trigger inflammatory responses.

Tau Protein and Neurofibrillary Tangles

- **Normal Function**: Tau is a microtubule-associated protein that stabilizes microtubules, which are essential for intracellular transport and neuronal structure.
- **Hyperphosphorylation**: In AD, tau becomes abnormally hyperphosphorylated, losing its ability to bind to microtubules effectively.
- **Tangle Formation**: Hyperphosphorylated tau forms insoluble paired helical filaments and straight filaments, which aggregate into neurofibrillary tangles within neurons.
- **Neuronal Damage**: These tangles disrupt cellular transport, leading to cell death.

Synaptic Dysfunction and Neuronal Loss

- **Synaptic Loss**: Aβ and tau pathology lead to synaptic dysfunction and loss, which correlates with cognitive decline in AD.
- **Neuronal Death**: Progressive accumulation of Aβ and tau pathology results in widespread neuronal death, particularly in the hippocampus and cortex, which are critical for memory and cognitive functions.

Inflammatory Responses

- **Microglial Activation**: Microglia, the brain's resident immune cells, become activated in response to Aβ plaques and tau tangles.
- **Neuroinflammation**: Activated microglia release pro-inflammatory cytokines, which can exacerbate neuronal damage and contribute to disease progression.
- **Astrocytes**: These glial cells also become reactive, contributing to the inflammatory milieu and further disrupting neuronal function.

Oxidative Stress

- **Reactive Oxygen Species (ROS)**: Aβ plaques and tau tangles induce the production of ROS, leading to oxidative damage to proteins, lipids, and DNA.
- **Mitochondrial Dysfunction**: Oxidative stress impairs mitochondrial function, reducing the energy supply to neurons and promoting cell death.

Vascular Contributions

- **Cerebral Amyloid Angiopathy (CAA)**: Aβ can accumulate in the walls of cerebral blood vessels, leading to CAA, which contributes to blood-brain barrier disruption and cerebral blood flow alterations.
- **Vascular Pathology**: Impaired cerebral perfusion and vascular integrity further exacerbate neuronal damage and cognitive decline.

Genetic Factors

- **Familial AD**: Mutations in genes such as APP, PSEN1, and PSEN2 lead to early-onset familial AD by increasing the production of pathogenic Aβ.
- **Apolipoprotein E (APOE)**: The APOE-e4 allele is a major genetic risk factor for sporadic AD, influencing Aβ aggregation and clearance.

Cellular and Molecular Pathways

- **Calcium Dysregulation**: Disruption of calcium homeostasis is linked to Aβ and tau pathology, contributing to synaptic dysfunction and cell death.
- **Protein Misfolding and Degradation**: Impaired proteostasis, including dysfunction in the ubiquitin-proteasome system and autophagy, leads to the accumulation of misfolded proteins.

Disease Progression

- **Preclinical Stage**: Aβ accumulation begins years before clinical symptoms, with initial deposition in the entorhinal cortex and hippocampus.
- **Mild Cognitive Impairment (MCI)**: Early clinical symptoms appear, including mild memory loss and cognitive decline, with significant Aβ and tau pathology.

Alzheimer's Dementia: As the disease progresses, extensive Aβ plaques and tau tangles are found throughout the cortex, leading to severe cognitive and functional impairments.

Unlocking The Potential of Isatin

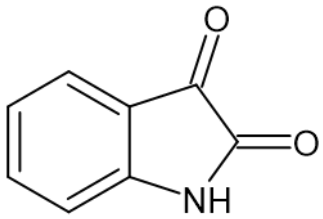


Figure 1: Structure of Isatin

Isatin (indole-2,3-dione) is a unique and structurally versatile organic compound. Here's a detailed look at its structure and the structure-

activity relationship (SAR) in Alzheimer's disease (AD):

Structural Characteristics

- Chemical Formula: C8H5NO2
- Molecular Weight: 147.13 g/mol
- Structural Formula: Isatin consists of an indole ring fused to a two-carbon lactam (keto) group at the 2,3-positions.

Structural Activity Relationship of Isatin

Core Structure

The core structure of isatin is an indole ring fused with a two-carbon lactam (keto) group at the 2,3-positions. This core structure is crucial for its biological activity.

Key Sites for Structural Modifications and Their Effects

Modifications at the Indole Ring

1. N1-Substitution (Position 1)
   - Alkyl and Aryl Groups:
     - Alkyl (e.g., Methyl, Ethyl**)**: Improves lipophilicity and BBB penetration, enhancing central nervous system (CNS) activity.
     - Aryl (e.g., Benzyl, Phenyl**)**: Can enhance binding to targets by increasing π-π interactions and hydrophobicity.
   - Effect on AD: N1-substituted derivatives often show improved neuroprotective effects and better penetration into the CNS.
2. Substitution at Position 5, 6, and 7
   - Electron-Donating Groups (EDGs):
     - Examples: Methoxy (-OCH3), Methyl (-CH3)
     - Effect: Increases electron density on the indole ring, enhancing antioxidant properties and reducing oxidative stress.
   - Electron-Withdrawing Groups (EWGs):
     - Examples: Nitro (-NO2), Halogens (e.g., -Cl, -Br)
     - Effect: Increases electrophilicity of the carbonyl groups, potentially enhancing interactions with amyloid-beta or tau proteins.
   - Effect on AD: Such modifications can enhance anti-amyloid and anti-tau activities, potentially reducing plaque and tangle formation.
3. Modifications at the Carbonyl Groups
1. Schiff Bases (C=N)
   - Formation: Reaction with primary amines.
   - Effect on AD: Schiff bases of isatin can inhibit amyloid-beta aggregation and reduce oxidative stress, showing neuroprotective properties.
2. Hydrazones (C=N-NH)
   - Formation: Reaction with hydrazines.
   - Effect on AD: Hydrazone derivatives are potential inhibitors of tau aggregation and possess neuroprotective effects.
3. Spiro Compounds
   - Formation: Reaction with various nucleophiles to form spirocyclic structures.
   - Effect on AD: Spiro compounds may offer unique interactions with amyloid-beta and tau proteins, enhancing anti-amyloid and anti-tau activities.
4. Specific Examples and Activities
1. N-Mannich Bases
   - Structure: Amino alkyl chains at the nitrogen atom.
   - Activity: Enhanced acetylcholinesterase (AChE) inhibitory activity, beneficial for increasing acetylcholine levels in AD.
2. N-Benzyl Isatin Derivatives
   - Structure: Benzyl groups at the nitrogen atom.
   - Activity: Improved anti-amyloidogenic properties and neuroprotection.
3. 5,7-Dihydroxy Isatin Derivatives
   - Structure: Hydroxy groups at positions 5 and 7.
   - Activity: Increased antioxidant activity and inhibition of amyloid-beta aggregation

MATERIALS AND METHODS

Protein Preparation: The target protein structure (PDB ID: 5TPT) was obtained from the Protein Data Bank.

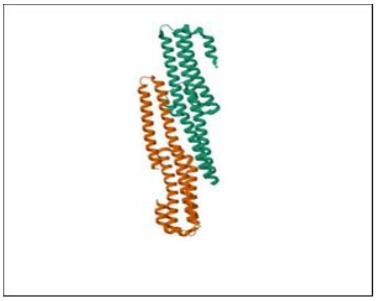


Figure 2: Structure of 5TPT

2.Ligand Preparation: The ligand structure was sourced from PubChem database and some structures were drawn by using Chemsketch.

3.Software and Tools used:

Chemsketch - Used for drawing and optimizing the ligand structure.

Molinspiration - Used for evaluating molecular properties such as LogP, TPSA and Lipinski's rule of five.

PASS Online - Employed to predict the biological activity of spectrum of the ligand.

SWISS ADME - Utilized to assess ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of the ligand.

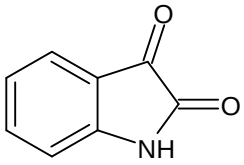
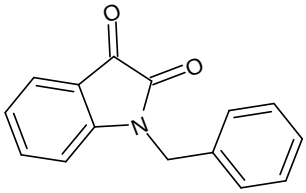
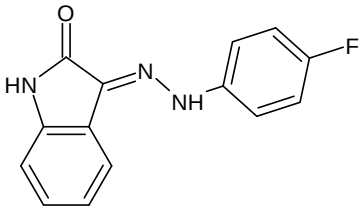
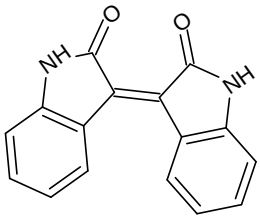
4.Molecular Docking - Docking studies was were carried out using PyRx, an open software for virtual screening. The protein was prepared by removing water molecules and adding polar hydrogens. The receptor-ligand interaction was analyzed through Biovia Discovery Studio Visualizer.

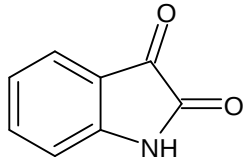
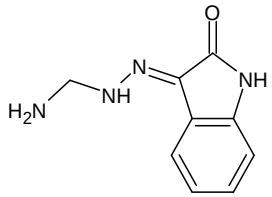
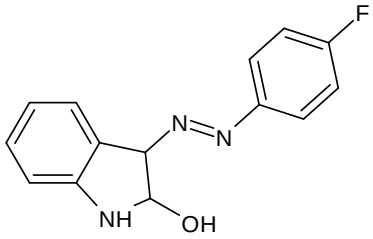
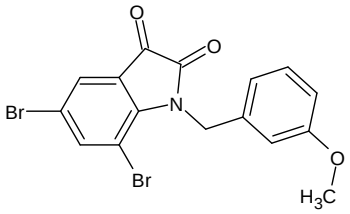
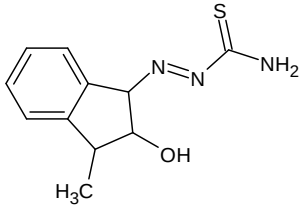
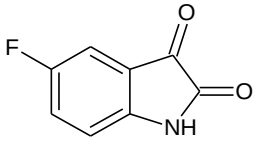
5.Analysis – The results were evaluated to identify ligands with significant binding affinity and their interaction with the active site of the protein.

RESULT AND DISCUSSIONS

In the present study, various isatin derivatives were selected and analyzed to evaluate their potential as Anti-Alzheimer's agents. These derivatives were drawn using *Chem Sketch*.

Table 1: Structure of isatin derivatives using Chem Sketch

Isatin		O=C1Nc2ccccc2C1=O
N-Benzyl isatin		O=C1N(Cc2ccccc2)c2ccc cc2C1=O
Isatin-3-(4-fluorophenyl) hydrazone		O=C/1Nc2ccccc2\C\1=N/N c1ccc(F)cc1
3-(2-oxoindolin-3-yldiene) indoline-2-one		O=C\1Nc2ccccc2/C/1=C1\c 2ccccc2NC1=O

Isatin		O=C1Nc2ccccc2C1=O
Isatin-3-thiosemicarbazone		O=C/1Nc2ccccc2\C\1=N/NCN
3-[2-(4-fluorophenyl) hydrazinyl] indol-2-one		OC1Nc2ccccc2C1\N=N\c1ccc(F)cc1
5,7-Dibromo-n-(p-methoxybenzyl) isatin		O=C1N(Cc2cc(ccc2)OC)c2c(Br)cc(Br)cc2C1=O
N-Methylisatin-3-thiosemicarbazone		S=C(N)\N=N\C1c2ccccc2C(C)C1O
5-Fluoroisatin		Fc1cc2C(=O)C(=O)Nc2cc1

Among all the compounds, three compound showed best docking score. Docking helps to predict how small molecules, like drugs, bind to a target protein and it was carried out by using ***PyRx*** software.

Docking Score

Table 2: Docking score of potent Isatin derivatives using PyRx.

Compound	Binding Affinity (Kcal/Mol)
3-[2-(4-fluorophenyl)hydrazinyl]indol-2-one	-7.4
5,7-dibromo-n-(p-methoxybenzyl)isatin	-7.3
N-Methylisatin-3-thiosemicarbazone	-6.8

Receptor-Ligand Interaction On 2d Diagram from Biovia Discovery Studio Visualizer

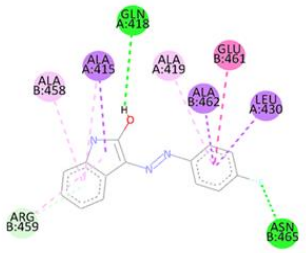


Figure 3: 3-[2-(4-fluorophenyl) hydrazinyl] indol-2-one

Figure 4: 5,7-dibromo-n-(p-methoxybenzyl) isatin

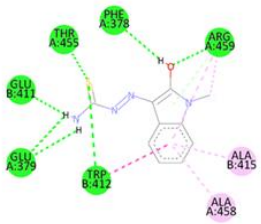
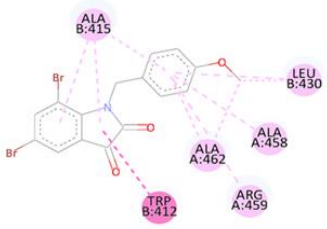


Figure 5: N-Methylisatin-3-thiosemicarbazone



molinspiration

Molinspiration is a cheminformatics software used for calculating molecular properties, bioactivity scores, and predicting drug likeness of chemical compounds. It is widely used in pharmaceutical research and development for its ability to analyse molecular structures and provide insights into their potential as drug candidates.

Analysis of Lipinski's Rules of Standard Drug

Compounds	log P	MW	nON	nOHNH	No. of Rotatable Bonds	Violations
3-[2-(4-Fluorophenyl) hydrazinyl]indol-2-one	2.92	257.27	4	2	2	0
5,7-Dibromo-N-(p-methoxybenzyl) isatin	4.07	425.08	4	0	3	0
N-Methylisatin-3 -thiosemicarbazone	0.84	236.30	5	3	2	0

Table 3: Analysis of Lipinski's rule of five of proposed derivatives

PASS (Prediction of Activity Spectra for Substances) is an online software tool designed for predicting the biological activity of chemical compounds. It uses a large database of known compounds and their activities to predict the potential pharmacological effects, mechanisms of action, toxicity, and interaction with biological targets of new compounds.

In PASS (Prediction of Activity Spectra for Substances), the values Pa and Pi are used to represent the predicted probability of a compound's biological activity. Here's what they mean:

1.Pa (Probability of Activity): This value indicates the likelihood that a compound will show a particular biological activity.

A higher Pa value (closer to 1) meaning that the compound is more likely to exhibit the predicted activity.

A Pa value greater than 0.7 is typically considered highly reliable and indicates a strong prediction.

2. Pi (Probability of Inactivity): This value indicates the likelihood that a compound will not show a particular biological activity.

A lower Pi value (closer to 0) means there is less chance that the compound will be inactive in regard to the predicted activity.

A Pa value closer to 1 combined with a Pi value closer to 0 suggests a strong prediction that the compound will exhibit the activity.

Interpretation:

If Pa > 0.7 and Pi is low, the prediction is more likely to be accurate.

If 0.5 < Pa < 0.7, the prediction is considered less certain but still possible.

If Pa < 0.5, the prediction is less reliable.

Table 4: Prediction of various derivatives using PASS

Compound	Activity	Pa	Pi
3-[2-(4-fluorophenyl) hydrazinyl]indol-2-one	Amyloid beta precursor protein antagonist	0,287	0,025
5,7-dibromo-n-(p-methoxybenzyl)isatin	Dementia	0,379	0,065
N-Methylisatin-3-thiosemicarbazone	Dementia	0,253	0,218

SWISS ADME is an online tool used to predict the pharmacokinetics, drug-likeness, and physicochemical properties of small molecules. Developed by the Swiss Institute of Bioinformatics (SIB), it provides important insights into how a compound might behave in the body, which is essential in drug discovery and development. Here are the key features and components of SWISS ADME:

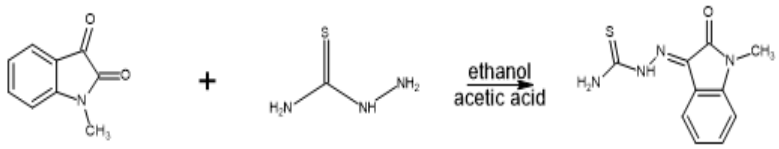
Table 5: Prediction of pharmacokinetic properties using SWISS ADME

Compound	Log p	Log s	GI absorption	BBB permeation	Log Kp	Bioavailability
3-[2-(4-fluorophenyl) hydrazinyl]indol-2-one	2.39	-4.33	High	Yes	-5.09	0.55
5,7-dibromo-n-(p-methoxybenzyl)isatin	2.7	-5.04	High	Yes	-6.23	0.55

N-Methylisatin-3-thiosemicarbazone	1.95	-2.84	High	No	-6.3	0.55

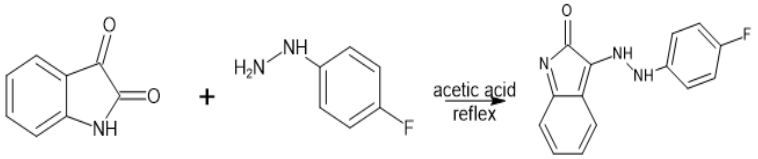
Conventional Synthesis Of Modified Molecules

1.Synthesis of N-Methylisatin-3-thiosemicarbazone



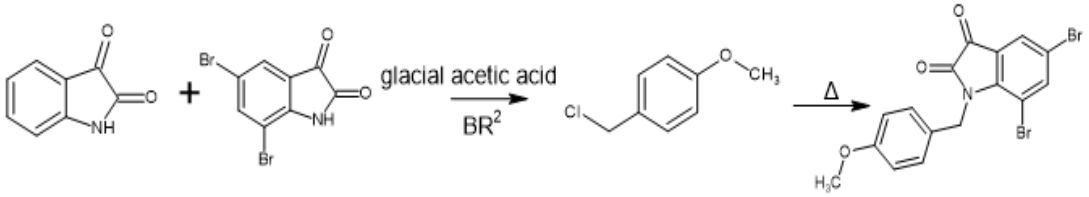
N-Methyl isatin Thiosemicarbazone N-Methylisatin-3-thiosemicarbazone

2.Synthesis of 3-[2-(4-fluorophenyl)hydrazinyl]indol-2-one



Isatin 4-Fluorophenyl hydrazine 3-[2-(4-fluorophenyl)hydrazinyl]-indol-2-one

3.Synthesis of 5,7-dibromo-n-(p-methoxybenzyl) isatin



Isatin 5,7-dibromo isatin p-methoxy Benzyl chloride 5,7-dibromo-n-(p-methoxybenzyl) isatin

CONCLUSION

- The present research work concentrated on rational approach to design and develop isatin derivatives against Alzheimer's disease.
- The work involved in the preliminary insilico screening of various isatin derivatives for their molecular descriptors, drug likeness, ADME profile and analysis of Lipinski rule of five, prediction of biological activities using various software's.
- The good docking score obtained on docking highlights the effectiveness of the derivatives for that particular activity. Prediction of ADME properties using SWISS ADME proved that derivatives can be considered as perspective drug candidate.
- Among the different isatin derivatives, **3-[2-(4-fluorophenyl) hydrazinyl]indol-2-one** obtained the best docking score and hence it can be considered as a promising compound for Alzheimer's treatment.

ACKNOWLEDGEMENT

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