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Determining the Dual Effect of Mirabegron on Anticancer Mechanism and Brown Adipose Tissue Activation - An *in-silico* Approach

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Abstract

Mirabegron, a β3-adrenoceptor agonist first developed for treating overactive bladder, has shown unexpected impacts on cancer and metabolic processes. Initially targeting the bladder's detrusor muscle, new research has revealed its potential in cancer therapy and brown adipose tissue (BAT) activation. This work employs silico approaches to evaluate how Mirabegron impacts critical cellular pathways such as AMPK, mTOR, and UCP, which are important for cancer and metabolic regulation. Docking studies show that Mirabegron binds effectively to several targets, with high affinities indicating a meaningful interaction. Specifically, it binds to AMPK at -7.0 kcal/mol, mTOR at -5.4 kcal/mol, and UCP at -7.4 kcal/mol. These interactions contain key residues, indicating that Mirabegron's influence extends beyond its original usage, potentially affecting cancer progression and metabolism.

Keywords: *AMPK, β3-Adrenoreceptor Agonist, Brown Adipose Tissue (BAT), Cancer Therapy, Docking Studies, Glucose Uptake, in silico, mTOR, Mirabegron, Molecular Interactions, Uncoupling Proteins (UCPs).*

Introduction

Mirabegron, previously used to treat overactive bladder, has gained attention in biomedical research for its pharmacological effects beyond its original purpose. By targeting the β3-adrenoreceptor, Mirabegron was initially intended to relax bladder smooth muscle and alleviate urinary symptoms in patients with overactive bladder [1]. However, further exploration has revealed its wider range of pharmacological impacts, particularly in cancer therapy and metabolic regulation through the activation of brown adipose tissue (BAT) [2]. The β3-adrenoreceptor, which Mirabegron primarily targets, is now known to be involved in various cellular processes beyond bladder function, such as proliferation, apoptosis, and migration in different types of cancer [3]. The smooth muscular layer that causes bladder contractions, the detrusor muscle, relaxes in response to mirabegron's activation of these receptors, this relaxation raises bladder capacity, which is important for controlling symptoms of OAB and NDO such as urgency, frequency, and incontinence [4, 5].

The findings are additionally backed by computational modelling and molecular dynamics simulations, which unveil the molecular interactions linking Mirabegron with cancer-related signalling pathways like PI3K-Akt and MAPK pathways [4]. In addition, preclinical studies have shown that Mirabegron can boost immune responses to combat tumors. It has been noted to stimulate anti-tumor immune function in melanoma models, indicating a comprehensive strategy for treating cancer that goes beyond just direct cytotoxic

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effects similar to the hesperidin [6, 7]. However, some research indicates that because mirabegron interacts with beta-3 receptors in other parts of the body, it may raise blood pressure and heart rate, especially at larger doses. As a result, those who already have cardiovascular disease should use mirabegron with caution [8].

According to recent research, mirabegron significantly reduces the risk of some cancers, such as hepatocellular carcinoma (HCC) and pancreatic ductal adenocarcinoma (PDAC). Treatment with mirabegron decreased tumor growth rates and extended the survival of tumor-bearing animals in preclinical settings. The capacity of mirabegron to cause browning of adipose tissues—which includes both brown adipose tissue (BAT) and white adipose tissue (WAT)—is closely associated with its anticancer activity [9]. There are different micorRNA is involved in the neuroblatoma activity [10]. The anticancer effect of mirabegron was found to be dose-dependent, with even low doses (as low as 3.2 mg/kg) effectively inhibiting tumor growth. Mechanistically, the antitumor activity of mirabegron is closely linked to its ability to induce the browning of both brown adipose tissue (BAT) and white adipose tissue (WAT) [11].

BAT, or brown adipose tissue, is a unique form of adipose tissue that is essential for regulating body temperature and energy expenditure in mammals, especially in maintaining metabolic balance [12]. Contrary to white adipose tissue (WAT) which stores energy as triglycerides, BAT contains a high density of mitochondria and has a heightened metabolic rate, attributed to the presence of uncoupling protein 1 (UCP1). UCP1 disrupts oxidative phosphorylation from ATP production, releasing energy as heat through mitochondrial respiration. BAT's thermogenic function is mainly controlled by β3-adrenoreceptors, which are highly present in brown adipocytes [13].

Activation of brown adipose tissue (BAT) is mainly induced by the sympathetic nervous system (SNS). Exposure to cold or specific drugs leads to the release of norepinephrine by the SNS, which then attaches to β3-adrenergic receptors on brown fat cells [14]. This attachment initiates a series of internal processes that result in the activation of UCP1 and the subsequent production of heat [15, 2, 9].

There is more to the investigation of this connection than just scientific interest. It could be revolutionary to comprehend how Mirabegron induces BAT activation and how this activation translates into possible anticancer effects. This information may open the door to completely new cancer treatment approaches [16]. Consider drugs or therapies that go after the BAT activation pathway set off by mirabegron, or even techniques that alter BAT activity directly to fight cancer. In comparison to conventional cancer treatments, this may result in more focused therapy with fewer side effects [9].

Targeting the detrusor muscle in the bladder wall, mirabegron is known to help treat overactive bladder syndrome (OAB) by increasing relaxation and lowering symptoms including frequency and urgency. Nevertheless, research by Liu et al. (2023) that was published in Nature suggests an unexpected side effect: in animal models, mirabegron appears to activate brown adipose tissue (BAT). BAT specializes in thermogenesis, which is the mechanism by which the body burns calories to produce heat, as opposed to normal white adipose tissue, which is used to store fat. The fact that medications that target beta-3 adrenergic receptors, like Mirabegron, and cold exposure are recognized activators of BAT makes Mirabegron's capacity to activate BAT all the more intriguing [17].

Researchers may be able to develop completely new therapeutic approaches for the treatment of cancer if they can unravel the connection between mirabegron-induced BAT

activation and its anticancer effects seen in animal studies. To battle cancer, this may entail creating medications that target the same pathway or even directly influencing BAT function [9], [18].

AMP-activated protein kinase (AMPK) is a key regulator of cellular energy levels in eukaryotes, responding to low ATP by promoting energy production and inhibiting energy consumption to maintain metabolic balance [19]. The protein mechanistic target of rapamycin (mTOR) in animals is a key regulator of cell growth and metabolism. It receives signals from both nutrients and growth factors as well as information regarding energy levels to coordinate actions like protein synthesis with those throughout lipid synthesis [20]. These proteins, named uncoupling proteins (UCPs), are situated in mitochondria where their activity breaks the link between transporting electrons from food through ATP forming oxidation (partial process) and synthesising energy [21,22,23].

The study aims to use computational tools to explore Mirabegron's surprising dual effects: anticancer mechanisms and brown adipose tissue (BAT) activation. It will focus on identifying the molecular pathways Mirabegron interacts within cancer cells and BAT to achieve these effects. By analyzing these interactions, the study hopes to predict potential mechanisms for Mirabegron's anticancer activity and BAT activation.

Materials and Methods

Protein Target Preparation

From the Protein Data Bank (PDB), the protein targets AMPK(4cff), m-TOR (4jsv) and UCP(8j1n) were acquired. The Discovery Studio Visualizer 2020 was used to build the protein. The water molecules that were present in the protein molecules were checked and removed if needed. Additionally, the linked ligands and ions were eliminated. PDB proteins often don't include hydrogen atoms. To change the protein into a conventional protein, hydrogen atoms were added. Additionally, docking research uses hydrogen atoms. The synthesis of proteins was accomplished through the application of optimization and minimization strategies [24].

Ligand Preparation

The PubChem database provided the source of Mirabegron. Compound modifications were created using the Discovery Studio Visualizer 2020, and to guarantee the ligand's lowest energy isomer. Molecular docking tests were performed on the ligand molecules after they had their energy reduced [25].

Molecular Docking

Molecular docking of protein and ligand has been done [26]. To cover all active site residues shown on the site map, the grid size was selected at roughly 60 angstroms. Initially, the default value for the van der Waals radii of the nonpolar atoms in the ligand and receptor was 0.50. Hydrophobic contacts, hydrogen bonding, glide energy, and docking score were among the variables used to determine the optimal structural location [27, 28].

Results

The molecular docking scores of Mirabegron with AMPK (PDB ID:4cff), m-TOR (PDB ID:4jsv), and UCP (PDB ID:8j1n) reveal significant interactions that highlight the potential therapeutic efficacy of this compound. The binding affinities were determined using AutoDock 1.5.7 and visualized with Discovery Studio software.

Molecular Docking Analysis for Mirabegron and AMPK

Mirabegron demonstrated the binding affinity with AMPK, exhibiting a docking score of -7.0 kcal/mol which is represented in Table 1. It formed conventional hydrogen bonds with ARG E:269, and Pi-sigma with VAL E:297, as well as Pi-alkyl & alkyl bond with PHE E:273 and Pi-Alkyl PRO E:365 from fig.1. AMPK illustrates visualizations of the amino acid site

with 3D image structures and represented in fig.
2.

Table 1: The Log Table Illustrates The Affinity and RMSD Rates of AMPK with Mirabegron

Mode	Affinity(kcal/mol)	Dist from rmsd l.b	Best mode rmsd u.b.
1	-7.0	0.000	0.000
2	-6.8	1.365	3.160
3	-6.8	2.499	4.109
4	-6.7	2.769	4.935
5	-6.7	4.498	7.985
6	-6.7	3.453	7.352
7	-6.7	4.371	7.170
8	-6.6	17.298	21.240
9	-6.6	1.988	3.622

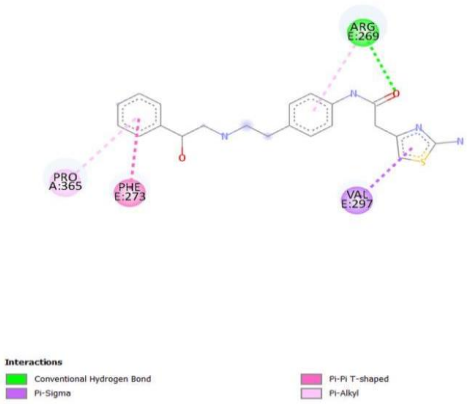

Figure 1: Mirabegron Interacts with AMPK in a 2D Structure.

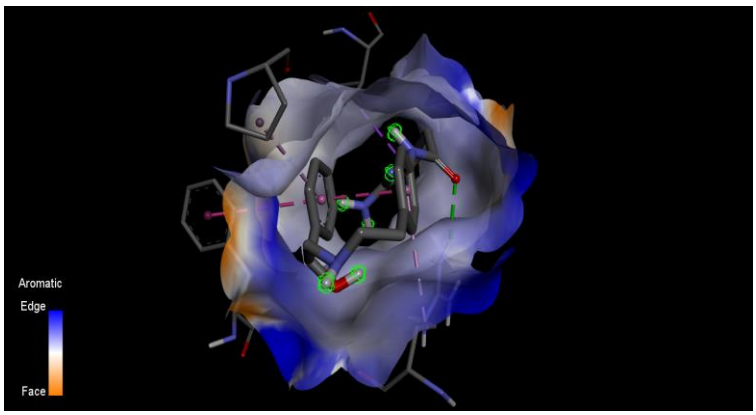

Figure 2: Mirabegron Interacts with AMPK in a 3D Structure.

Molecular Docking Analysis for Mirabegron and m-TOR

Mirabegron displayed a binding affinity for m-TOR, with a docking score of -5.4 kcal/mol which is represented in table 2. It established conventional hydrogen bonds with ASP A:2252 and LYS A:2306, as well as Pi-alkyl bonds with LEU A:2302 and LEU A:2305, as shown in fig. 3. Mirabegron and mTor provide docking score visualisations and protein interaction site in 3D picture structures in fig. 4.

Table 2. The log table illustrates the affinity and RMSD rates of mTOR with Mirabegron.

Mode	Affinity(kcal/mol)	Dist from rmsd l.b.	Best mode rmsd u.b.
1	-5.4	0.000	0.000
2	-5.4	26.695	28.706
3	-5.3	22.342	26.091
4	-5.3	21.960	25.684
5	-5.2	26.851	29.093
6	-5.0	14.331	17.141
7	-5.0	18.986	21.110
8	-4.9	29.497	31.750
9	-4.9	26.170	28.201

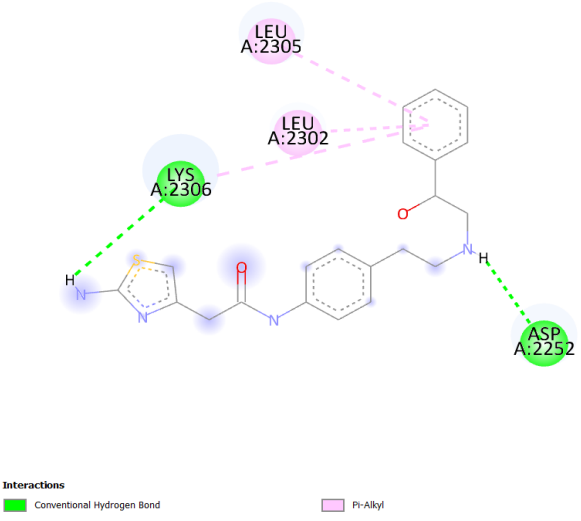

Figure 3: Mirabegron interacts with mTOR in a 2D structure.

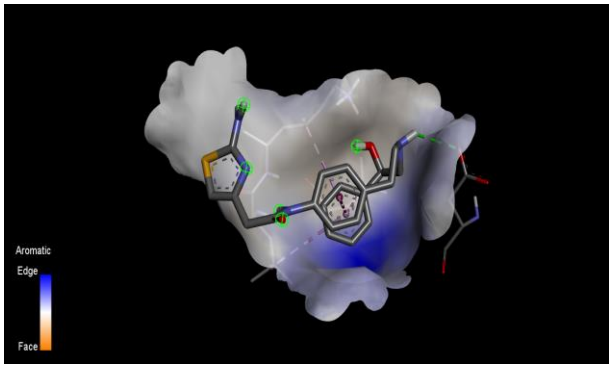

Figure 4: Mirabegron interacts with mTOR in a 3D structure.

Molecular Docking Analysis for Mirabegron and UCP

Mirabegron demonstrated the highest binding affinity with UCP, exhibiting a docking score of -7.4 kcal/mol represented in table 3. Mirabegron is associated with the Unfavorable Donar-Donar bond with THR A:177, Pi-Donor Hydrogen bond with PHE A:266, Pi-Sulfur bond with MET A:255, Pi-Pi Stacked bond with PHE A:258 and Pi-Alkyl bond with ALA A:254, VAL A:235 , VAL A:232 ,PRO A:178, VAL A:250 from fig. 5. Fig. 6, has UCP which illustrates visualizations 3D image structures with amino acid interactions.

Table 3: The log table illustrates the affinity and RMSD rates of UCP with Mirabegron.

Mode	Affinity(kcal/mol)	Dist from rmsd l.b.	Best mode rmsd u.b.
1	-7.4	0.000	0.000
2	-7.3	2.169	3.462
3	-7.1	17.202	19.363
4	-7.0	2.454	3.794
5	-7.0	1.967	3.284
6	-6.9	2.448	4.110
7	-6.8	5.025	9.995
8	-6.8	25.636	28.834
9	-6.8	9.524	15.949

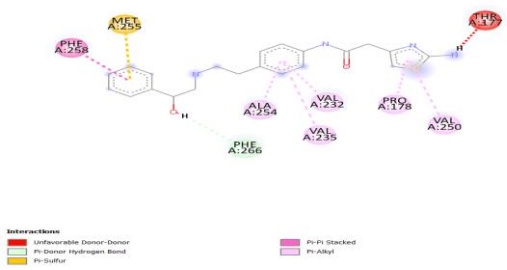

Figure 5: Mirabegron interacts with UCP in a 2D structure.

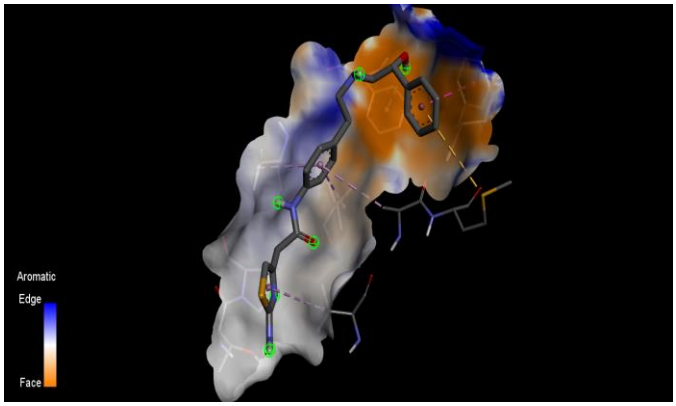

Figure 6: Mirabegron interacts with UCP in a 3D structure.

Table 4: (I), (II) and (III) overall analysis of molecular docking of Mirabegron on AMPK (4cff), m-TOR (4jsv) and UCP (8j1n).

RESULT ANALYSIS	VISUALISATION SOFTWARE	PROTEIN	LIGAND	DOCKING SCORE	AMINO ACID RESIDUE
Auto dock 1.5.7	Discovery software	AMPK (4cff)	Mirabegron CID: 9865528	-7.0	Conventional hydrogen bond; ARG E:269; Pi-Sigma: VAL E:297; Pi-Pi T-shaped: PHE E:273; Pi-Alkyl PRO: E:365
		mTOR (4jsv)	Mirabegron CID: 9865528	-5.4	Conventional hydrogen bond: ASP A:2252 LYS A:2306; Pi-AlkylL: LEU A:2302; LEU: A:2305

		UCP (8j1n)	Mirabegron CID: 9865528	-7.4	Unfavorable Donar-Donar: THR A:177; Pi-Donor Hydrogen bond: PHE A:266; Pi-Sulfur MET A:255; Pi-Pi Stacked PHE A:258; Pi-Alkyl ALA A:254; VAL A:235; VAL A:232; PRO A:178; VAL A:250

Discussion

Mirabegron, a selective β3-adrenergic receptor agonist, has been studied for its effects on metabolism and cardiovascular health. It primarily activates AMP-activated protein kinase. This activation is critical for increasing energy expenditure and glucose metabolism. Mirabegron has been shown in studies to improve whole-body oxygen consumption and boost glucose uptake in brown and white adipose tissues, potentially enhancing metabolic health and weight management. For example, one study found that mirabegron significantly improved glucose tolerance and insulin sensitivity in obese mice fed a high-fat diet, which was linked to increased expression of uncoupling protein 1 (UCP1) in brown adipose tissue, indicating increased thermogenic activity and browning of white adipose tissue. Furthermore, mirabegron has been proven to provide cardioprotective benefits by decreasing right ventricular, in animal models of pulmonary hypertension, hypertrophy and fibrosis are induced by processes involving Drp1 inhibition and AMPK activation. This dual action underlines mirabegron's metabolic benefits as well as its potential therapeutic applications in the treatment of obesity and cardiovascular disease. Furthermore, combining mirabegron with other metabolic medications, such as metformin, has shown cumulative effects on weight loss and metabolic improvements, indicating a promising route for obesity treatment techniques. Overall, mirabegron represents a novel strategy to improve metabolic health due to its distinct mechanisms of action, particularly in the context of obesity, other metabolic disorders and cancer [29]. Similarly, miRNA-20a: would have a dual regulation in both cell migration and apoptosis in the OSCCC conditions [30]. Mirabegron showed a docking score of -7.0 kcal/mol, indicating a binding affinity with AMPK in Table 1. Conventional hydrogen bonds were established, Pi-sigma, Pi-alkyl & alkyl bond and Pi-Alkyl from fig. 1, and docking score visualisations for 2D and 3D picture structures are shown in Figures 1 and 2 for AMPK.

Mirabegron, a selective β3-adrenergic receptor agonist, is known to influence the mechanistic target of rapamycin (m-TOR) signalling pathway, which is essential for cell growth, proliferation, and metabolism. Recent research indicates that mirabegron can inhibit mTOR signalling, likely through the activation of AMP-activated protein kinase (AMPK), a critical regulator of cellular energy balance. For instance, in studies involving right ventricular overload, mirabegron was shown to enhance AMPK signalling while simultaneously decreasing the expression of dynamin-related protein 1 (Drp1) and mTOR, suggesting it may protect against cardiac hypertrophy and fibrosis. This interaction implies that

mirabegron could have beneficial effects on both metabolic and cardiovascular health by modulating the mTOR pathway, thus affecting cellular growth and energy metabolism. Additionally, the inhibition of mTOR signalling by mirabegron has been associated with its potential therapeutic uses in conditions like obesity and metabolic syndrome, where m-TOR dysregulation is common. So, we can use this has a therapeutic product for the cancer condition. Similar to the condition how miRNA acts a biomarker for the cancer conditions [31]. These insights underscore mirabegron's diverse role beyond its primary application in treating overactive bladder, indicating its potential as a valuable treatment option for metabolic disorders through its impact on the mTOR pathway and AMPK activation and cancer [32]. Mirabegron demonstrated the binding affinity with m-TOR, exhibiting a docking score of -5.4 kcal/mol Table 2. It formed conventional hydrogen bonds, and Pi-alkyl bonds from fig. 3 and 4 for m-TOR illustrate visualizations of the docking score for 2D and 3D image structures.

Mirabegron, a selective β3-adrenergic receptor agonist, has significant effects on uncoupling proteins (UCPs), particularly UCP1, which is crucial for thermogenesis and energy expenditure in adipose tissues. Research indicates that mirabegron enhances the thermogenic activity of brown adipose tissue (BAT) and promotes the "browning" of white adipose tissue (WAT) by stimulating UCP expression. This process is vital for dissipating energy as heat, which can lead to increased energy expenditure and improved metabolic health. Studies have shown that treatment with mirabegron results in enhanced glucose uptake in brown and beige adipocytes, which contributes to better glucose homeostasis and increased insulin sensitivity. Additionally, mirabegron has been found to stimulate the secretion of adiponectin, an adipokine associated with improved insulin sensitivity, and elevate levels of gastric inhibitory polypeptide (GIP), which is linked to insulin secretion. These findings suggest that mirabegron may offer therapeutic benefits for managing obesity and related metabolic disorders through its effects on UCPs and overall adipose tissue metabolism, highlighting its potential beyond its primary use in treating overactive bladder and cancer [33]. The of microRNA-7-3p and it has a target STAT3, have an important role in the cancer such as HNCC [34]. Mirabegron demonstrated the highest binding affinity with UCP, exhibiting a docking score of -7.4 kcal/mol in Table 3. It formed Unfavorable Donar-Donar bond, Pi-Donor Hydrogen bond, Pi-Sulfur bond, Pi-Pi Stacked bond and Pi-Alkyl bond from Figures 5 and 6 for UCP illustrate visualizations of the docking score for 2D and 3D image structures. Across several fields, the mineralization of synthetic materials like calcium carbonate, PRF, and nano-hydroxyapatite has demonstrated significant clinical value [35-37]. Similar to this Mirabegron we can try with the above materials for this therapeutic applications.

These findings suggest that Mirabegron can effectively bind to these proteins, potentially inhibiting their activity, which could be beneficial in therapeutic applications targeting inflammation and related pathways (Table: 4 (I), (II), (III)).

Conclusion

In conclusion, the in-silico study demonstrates mirabegron's dual therapeutic potential. It activates brown adipose tissue (BAT), increasing thermogenesis and energy expenditure, and interacts with anti-cancer processes via pathways such as AMPK and mTOR. Mirabegron has been shown in studies to greatly increase BAT activity and glucose absorption, both of which are necessary for metabolic homeostasis. The capacity of mirabegron to increase adipose tissue browning and UCP1 expression offers a potential therapeutic approach for focusing on metabolic pathways in the treatment of cancer.

Furthermore, it exhibits promising anticancer properties by increasing adipose tissue browning. These data indicate that mirabegron may provide a multimodal strategy to treatment, targeting both metabolic problems and cancer. This makes mirabegron a promising choice for further research into obesity and cancer-related metabolic dysfunctions. Overall, its potential extends beyond its initial use in treating overactive bladder.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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