Whites Science
A Scientific Erudition

Utilization of β3 Adrenergic Receptors as Targets for Treating Diabesity - Mirabegron and Beyond ''- A Systematic Review

Kulvinder Kochar Kaur[1*], Gautam Allahbadia[2] and Mandeep Singh[3]

[*1]Dr. Kulvinder Kaur Centre of Human Reproduction, Jalandhar, Punjab, Pin code: 144001, India
[2]Ex-Rotunda-A Centre for Human reproduction, Mumbai, Pin Code: 400040, India
[3]Swami Satyanand Hospital, Jalandhar, Punjab, Pin code: 144001, India

ABSTRACT

The incidence of obesity along with its comorbidities are increasing markedly so much so that the term diabesity got coined. Hence the need of trying to treat the two conditions together. We have been reviewing how to get a better antiobesity drug helping in medical treatment that is preferable over the more expensive bariatric surgery (BS). Here we have further extended our previous publications on utilizing BAT/WAT As targets for introducing antiobesity therpy. In view of brown adipose tissue (BAT) hardly present in adult human beings the importance of beiging was highlighted earlier. Hence the accidental discovery of Mirabegron that has been used in OAB for long was detected to be a special β3 adrenergic receptor agonist having actions besides bladder on Adipose tissue (AT) lipolysis and beiging of white adipose tissue (WAT) along with increasing uncoupling protein 1 (UCP1) induction in WAT helped in trying to use it as the treatment of patients having diabesity in preference to BS. The only problem is recent some doubts that have arisen regarding safety profile of Mirabegron with upper airway angioedema along with rise in BP and prolongation of QT c interval on ECG, newer compounds are being studied on the basis of Comparative molecular field analysis (CoMFA) and Comparative molecular similarity index analysis (CoMSIA) studies and formation of contour maps. On the basis of quantitative structure – activity relationship (QSAR) 41 Aryloxy Propanol-Amine Agonists in a serial basis, were evaluated and validated certain drugs having antiobesity andantidiabetic effects for further evaluation for developing newer β3 adrenergic receptor agonists to replace Mirabegron.

Keywords: β3 adrenergic receptor agonist, Mirabegron, WAT Beiging, CoMFA, CoMSIA, UCP1

INTRODUCTION

Obesity is increasing worldwide with increasing comorbidities, and need is to develop medical therapies with earlier efforts failing to give any effective long term therapy. Thus earlier we have tried to find various medical methods of treating obesity medically, and find any updates of medical treatment, reviewing, roles Qsymia (topiramate/phentermine), Contrave(naltrexone/bupropion), liraglutide for both obesity and diabetes mellitus (DM), role of thylakoids , Glucagon like peptide 1 (GLP1) and different glucagon combinations but other than or list at till now no drug is found to have long term maintenance effects other than bariatric surgery (BS) [1-7] which can't be used for all obese subjects in view of cost and comorbidities associated with morbid obesity like DM, hyperlipidemia etc. Here we have emphasized on how white adipose tissue (WAT)/ Brown adipose tissue (BAT) metabolism can be exploited using the β3 adrenergic receptor agonist Mirabegron that was initially

***Corresponding Author:**
kulvinder.dr[at]gmaildotcom

Receiving Date: December 4, 2018
Acceptance Date: December 18, 2018
Publication Date: December 25, 2018

ISSN 2047-9093

approved for treating Overactive bladder (OAB), but has been found to be effective in increasing energy expenditure (EE), along with weight loss by increasing beiging in WAT and hence can be used to treat diabesity simultaneously [8]. Thus efforts have continued to look for newer therapies although lot of newer drugs showed promise like rimonabant and had to be stopped in clinical Trials in view of psychiatric side effects.

Initially subcutaneous (s/c) white adipose tissue (WAT) acts to store fat in unilocular adipocytes. But on cold exposure /that of β adrenergic agonists, those adipocytes that express uncoupling protein 1 (UCP1) develop in WAT depots [9]. These adipocytes have been also referred to as beige adipocytes in view of their special characteristics, location as per anatomy, along with from the formation point [10-13]. These beige adipocytes have functional correlation with brown adipocytes that liberate energy as heat. Besides thermogenesis, energy used causes brown adipose tissue (BAT) to protect from obesity in rodents [14]. This action of beige /brown adipocytes in energy liberation can be used for antiobesity therapy is still not clear [15]. Besides thermogenesis along with energy liberation, both beige/brown adipocytes are correlated with enhanced glucose along with lipid metabolism, with better insulin sensitivity, in humans along with mice [16,17]. Thus lot of attraction is there regarding approaches to recruit along with activate these beige/brown adipocytes for counteracting the deleterious effects on metabolism resulting from obesity [9,13].

METHODS

Thus we decided to carry out a systematic approach utilizing the pubmed engine regarding the use of β3 adrenergic receptor agonists for developing any therapies on the basis of β3 adrenergic receptor agonist in the treatment of obesity utilizing the MeSH terms like β3 adrenergic receptor agonist; Mirabegron; other β3 adrenergic receptor agonists;

RESULTS AND DISCUSSION

We found a total of 200 articles relating to this topic from 1975 to 2018 out of which we selected 93 articles for this article. No meta-analysis was done.

β3 adrenergic receptor

Initial β3 adrenergic receptor agonists were identified following > lipolytic activity in AT versus contraction of the atrium in contrast to tracheal or relaxation of uterus [18]. Thus β3 adreno receptors were thought of being a target for a variety of drug companies for developing anti-obesity and anti-DM drug. But these efforts did not materialise during clinical trials ,since although BRL 37344 was found to possess activity at the rodent β3 adreno receptor, it did not act in human receptor, in view of little separations in the ligand pocket of rodent vs human β3 adreno receptor, no bioavailability along with separate ways that β3 adreno receptor were expressed among rodents and humans. Besides at this β3 adreno receptor has shown actions in brain (memory, learning and control of appetite), heart (protection of heart) along with genital and urinary tract (control of bladder function) for roles of the β3 adreno receptor along with structure, both agonism and antagonism structure. Later human active β3 adreno receptor agonists revealed, with maximum work carried out in transfected cell lines that reveal β3 adreno receptor for finding the potency along with binding capacity of Mirabegron which represents a very selective β3 adreno receptor agonist [19].

ISSN 2047-9093

Role of cold and Mirabegron in Beiging

Rodent research has suggested that cold markedly stimulates beige adipocytes in s/c WAT depots, with current workers trying this induction of beige adipocytes in humans with the utilization of a number of stimuli [9,13,20,21]. The expression of mRNA of UCP1 along with the marker of beige adipose tissue (AT) TMEM26 get inducted by acute cold along with seasonal exposure along with inhibition of this induction by obesity and inflammation as reported by the group of Finlin et al. [20,21]. This is same as the publications showing that BAT found by positron emission tomography-computed tomography (PET CT) is <in obese individuals [22,23]. Chandronika et al. documented that the expression of UCP1 protein in abdominal s/c WAT is > in the subjects who were involved in this study where BAT was demonstrated by PET CT scans [16]. Exercise might stimulate beiging in humans [24].But maximum beiging of human WAT takes place in human WAT in certain disease conditions like severe burns or in cancer patients having cachexia or phaeochromocytoma [25-27]. From these studies it is clear that human s/c WAT has the potential for beiging. But approaches for induction of beige AT in humans presenting with metabolic diseases for enhancing glucose and lipid metabolism are absent at present.

Thus Finlin et al. tried exposing both thin and obese subjects to cold (application of cold ice pack for 30 min/day for 10 days on the upper thigh) or treated these subjects with β3 agonist Mirabegron. They checked the beige AT marker utilizing immune histochemistry (IHC) and quantitative polymerase chain reaction (qPCR), along with evaluating mitochondrial biogenetics and UCP activity using the Oxytherm System. They found that cold significantly stimulated UCP1 and TMEM 26 protein in both thin and obese subjects, with the effect having no correlation with age. These proteins escalated to the same degree in s/c WAT of the nonice contralateral leg that suggested that there was a crossover action. Further evaluation of bioenergetics of the mitochondria that had been purified from the abdominal s/c WAT of cold treated participants and observed that continuous application of ice markedly enhanced uncoupled respiration, that validated UCP1 protein development and getting activated following that, cold further enhanced State 3 and maximum respiration, and action of mitochondrial biogenetics was > in summer than in winter. Chronic treatment (10 wks; 50 mg/day) with the Mirabegron stimulated UCP1, TMEM26, cell death – inducing fragmentation factor alpha like effector A (CIDEA), and phosphorylastion of HSL on serine 660 in obese individuals. Thus concluding that cold or β3 agonists induce beige adipocytes in human s/c WAT depots; and this process might be utilized for enhancing beige AT in older insulin resistance (IR) obese persons [28].

Role of Mast cells in response to cold and Mirabegron in Beiging

Besides β3 adrenergic signalling along with sympathetic nervous system (SNS), the immune system has been demonstrated to modulate adipocytes beiging [29]. Experiments conducted in mice implied that there is a role of macrophages, eosinophils, type 2 innate lymphoid cells, and iNKT cells in human s/c WAT beiging [29]. Further the group of Finlin et al. demonstrated the role of mast cells in the seasonal regulation of UCP1 [20]. They observed that mast cells act as cold sensors, which liberate histamine that further activates lipolysis along with inducing UCP1 in adipocyte [20]. There is a complex interaction among the immune cells between each other, with adipocytes, along with nerves to affect catecholamine amounts, innervations and formation of a variety of substances which help in adipocytes beiging [29-36]. Conversely retention of macrophages in AT has been demonstrated in mice to prevent beiging [37], and in vitro studies demonstrate that macrophage conditioned medium along with cytokines that are inflammatory prevent UCP1 expression within adipocytes [21,38-40]. Finlin et al recently in 2018 tried cold application stimulated beiging in subcutaneous WAT of humans again independent of body mass index (BMI). For detecting causes that help or prevent beiging they undertook multiplex evaluation of gene expression utilizing the Nanostring nCounter system (probe set

ISSN 2047-9093

had genes for particular immune cell markers ,cytokines as well as chemokines on the s/c WAT through lean individuals. Multiple association analysis found mast cell tryptases and CCL26, a chemokine for mast cells, as genes ,that on change had a positive association with the alteration in UCP1 in s/c WAT, suggesting a posit that mast cells help in s/c WAT beiging in response to cold. Quantification of mast cells recruited into s/c WAT and degranulation was performed. An increase in mast cell numbers s/c WAT occurred in lean individuals, and enhancement of degranulated mast cells was observed in both lean individuals along with obese individuals. They checked that norepinephrine had a stimulatory effect on mast cells degranulation along with histamine liberation *in vitro*. Thus concluding that cold stimulated at recruitment of mast cells in lean individuals and mast cells degranulation in s/c WAT of all research subjects that was independent of BMI, pointing that mast cells stimulate adipocytes beiging via liberation of histamine or other products [41].

Role of Treg induction in response to cold and Mirabegron in Beiging

Obesity and metabolic syndrome (MetS) are on the rise and have become crucial problems in the modern societies.A differential correlation with local fat depots with visceral WAT (VAT) is present in metabolic diseases and this VAT has > susceptibility to obesity associated inflammation [42]. Besides their key part in immune suppression, regulatory Tcells (Tregs) are crucial in regulating tissue homeostasis and function that includes local fat depots. Expression of CD4CD25 along with the transcription factor FOXP3 that acts as the master controller of their function as well as formation are the main characteristics of Tregs [43]. Autoimmunity with severe inflammatory phenotypes in both mice (scurfy ones) along with humans (IPEX-immuno dysregulation, polyendocrinopathy, X-linked syndrome, enteropathy), results due to mutations in Foxp3 gene have emphasized the critical role of Foxp3 for Treg function [44]. Activated T cells can show low levels of FOXP3 [45], in humans, in contrast to high expression of FOXP3are characteristics of immunosuppressive Tregs, associated with low level of expression of CD127 [46]. In this scenario FOXP3 gives depressive ability by making sure that the following immunosuppressive molecules like CTLA4, LAG3 and IL-10 get expressed [47].

In the peripheral immune system, Tregs can get induced, that is called Treg conversion or induction [48]. From naive $CD4^+$ Tcells effective Tregs induction can be obtained utilizing antigenic stimulation in the sub immunogenic circumstances preventing the activation of antigenic presenting and T cells [49]. Conversely immunogenic stimulation with good costimulatory signals result in phosphoinositide 3 kinase (PI3K)/Akt/mechanistic target of the rapamycin (mTOR) pathway activation and thus affecting the Tregs induction [48-50].

For seeing to it that local homeostasis is assured, Tregs go and stay in VAT, and subsequently cause tissue particular adaptations of their functions like expressing the transcription factor Peroxisome proliferator-activated receptor gamma(PPARy) [51]. Various immune cell types are present around adipocytes and these immune cell types, their amounts and action changes markedly after over nutrition. Tregs present in the fat modulate local inflammatory processes. Particularly on finding hypercaloric challenge marked decrease in Tregs frequencies in VAT occur along with enhanced inflammation [52]. Notably Tregs have the capacity to act as per environmental and metabolic signals. This is being clarified that interference with these interactions amongst immune along with environmental- metabolic actions crucially => metabolic diseases origin.

This has been exemplified by Kalin et al.regarding how environmental- metabolic stimuli interfere with functional interaction between Tregs and AT [53]. Particularly emphasizing on the key role of cold exposure in altering the metabolic changes in obesity, they demonstrated that short-term cold exposure or β3 adrenergic activation induce murine Tregs both *in vitro* along with *in vivo* [53]. Similarly another

ISSN 2047-9093

study had illustrated the effect of cold exposure on BAT Tregs [54]. Utilizing $CD4^+$ Tcells proteomes they demonstrated the mechanism that causes > protein expression of Foxp3 regulatory networks after cold exposure or β3 adrenergic activation [53]. With the use of loss-and-gain-of-function studies they emphasized that a Tcell specific Stat6/Pten axis accommodates $Foxp3^+$ Tregs induction and AT function as per the sympathetic tone and environmental temperature [53]. As compared to WAT ,that mainly acts for storing lipids, BAT crucially adds to non shivering thermogenesis (NST), by burning energy it expels heat. This is helped by the expression of UCP1 whose function is to uncouple mitochondrial respiration from adenosine triphosphate (ATP) Synthesis [52]. On exposure to cold or β3 adrenergic activation WAT undergo a process of browning by which they express UCP1 in WAT [55].

Cold inducible BAT in adults has been discovered [56]. Increasing BAT burning energy with > EE(energy expulsion) via β3 adrenergic activation (ADRB3), that is expressed by human adipocytes along with other tissues like human peripheral blood mononuclear cells (PBMC) [46] could also be attained by Mirabegron, that is ADRB3 agonist [57]. Further cold exposure gave benefits to whole body along with enhance skeletal muscle insulin sensitivity in cases of obesity and Type2 diabetes mellitus (T2DM) [58]. Thus Mirabegron was demonstrated to activate human BAT thermogenesis and thus might be a future option for therapy of metabolic diseases [59]. Inspite of these understanding regarding Tregs AT crosstalk in murine species along with concentration on metabolic readout on cold exposure in humans the effect of human Tregs in helping out in the functional immunometabolic interaction in relation to cold exposure in vivo remains unclear.

Thus Becker et al. utilized combined methods of next generation mouse types along with in vitro and in vivo studies together with β3 adrenergic activation to explore the basic mechanisms of human Tregs stimulation on exposure to environmental stimuli like cold. For finding the translational importance of their results they evaluated samples from the FREECE study, where human subjects got exposure to cooling protocols on individual basis. These samples were evaluated exvivo and following in vitro Tregs induction with the utilization of qRT-PCR, immunoflourescence, along with multicolour flow cytometry and cell sorting. They observed that in vitro β3 adrenergic agonist, Mirabegron application in humanized mice stimulated thermogenesis along with improving Tregs induction capability of naive Tcells removed from these animals. Utilizing samples of the human FREECE study, they showed that a small time cold stimulus helped in human Tregs induction both in vitro and *in vivo*. From the point of mechanism of action, they noticed BORCS6 encoded the Ragulator interacting protein C17 orf 59 got significantly induced by within the human $CD4^+$ Tcells on small time cold exposure. Marked mTOR signalling limits Tregs induction successfully and possibly by causing alteration of mTOR activation at the surface of lysosomes, C17 orf 59 increases the Tregs induction ability of human naive Tcells on cold exposure. Thus concluding that these novel ways of understanding the molecular methods of human Tregs induction point to a significant role of Tregs in connecting environmental stimuli with AT function and metabolic diseases. Further these new findings throw light on probable methods regarding anti-inflammatory approaches which promote human AT homeostasis by inducing Tregs [60].

Different doses of Mirabegron on BAT Thermogenesis

Loh e al. tried to find the acute energy liberated, supraclavicular temperature of the skin and the cardiovascular (CVS) effect following 4 doses of Mirabegron. They included 17 subjects (n=11 male, n=6 female) in this gradually increasing dose study, giving single 50-, 100-, 150- and 200 mg doses of Mirabegron on 4 different days having a 3-14 days washout among every dose. All variables were checked at every visit from baseline to 180 min after Mirabegron therapy. For checking BAT thermogenic effectivity of every dose, EE and supraclavicular temperature of the skin were contrasted from baseline to 180 min after Mirabegron therapy. For checking safety, variations in CVS variables at

ISSN 2047-9093

100, 150 and 200 mg were compared with usual clinical dose of 50 mg. Significant enhancement of EE, following the 100 (35.6±5.4Kj/H) and 200 mg (35.6 ±13.1kj/h) doses ($p \leq 0.05$), and tended to rise following 150 mg (24.1±13.6kj/h). An increase in supraclavicular temperature of the skin following 50(0.22 ±0.1^{0}C), 100 (0.30±0.1^{0}C), and 150 mg Mirabegron dosage (0.29±0.1^{0}C,$p \leq 0.05$). Change in systolic blood pressure (BP) was higher following 150- (7.1±1.3 mm Hg) and 200mg dosage (9.3±1.9 mm Hg)as compared to that following 50 mg dosage (2.2±1.3 mm Hg; ($p \leq 0.05$). Alteration in heart rate (HR) was more following 200 mg dosage (9±2.2 bpm) in contrast to 50 mg (2.9±1.4 bpm; $p \leq 0.05$). Thus concluding that 100 mg Mirabegron enhances EE along with supraclavicular temperature of the skin in a β3 adrenoceptor–particular way, without the off target escalations of BP and HR seen at higher dosages [61].

Role of Mirabegron in obesity

Hao et al. tried to evaluate whether Mirabegron used in both in vitro and in vivo models could help in decreasing obesity. They utilized mouse preadipocytes and 3T3-L1 cells and gave them separate concentrations of Mirabegron (0.03-3μg/ml) and then evaluated the effect on expression of genes that were related to brown fat by utilizing quantitative real time polymerase chain reaction (qRT-PCR). Moreover, male C57BL/6J mice were given a high fat diet (HFD) for 10 weeks and Mirabegron (2mg/kg body weight) or a vehicle control was deposited in the interscapular BAT (iBAT) utilizing ALZET osmotic pumps from 7 to 10 wks. Examination of metabolic factors and tissues was done. Mirabegron stimulated UCP1 in both mouse preadipocytes and 3T3 L1 cells. In the animal experiments mice that had received Mirabegron showed lower body weight along with adiposity. In the mice that had received Mirabegron much less and shorter sized lipid droplets were found in the iBAT in contrast to vehicle-treated mice. Following haematoxylin (H) & eosin (E) staining along with immunochemistry suggested that Mirabegron enhanced the amount of beige cells in inguinal WAT (iWAT). In contrast to vehicle treated mice, mice that had received Mirabegron displayed a > UCP1 gene expression (14 times) along with cell death-inducing fragmentation factor alpha like effector A (CIDEA) (4 times) in iWAT. Moreover > glucose tolerance and insulin sensitivity was observed in those receiving Mirabegron therapy. Thus in all Mirabegron escalates UCP1 expression and helps in browning of iWAT, that are associated with a better glucose tolerance and insulin sensitivity along with not allowing HFD diet induced obesity (DIO) [62].

Role of UCP1 Induction in WAT for improving glucose uptake

BAT helps mammals to regulate their temperature via NST. It is markedly present in newborns and is necessary for ensuring their life in the lack of any separate thermogenesis methods [63]. It is also observed in adults, in correlation with lesser body weight [23]. BAT activation helps in improving systemic metabolism, other than controlling body temperature and energy homeostasis [64]. Increased glucose tolerance and insulin sensitivity along with reduction in body weight and dyslipidemia [64]. Thus, at present, BAT is considered a target for therapy of obesity along with obesity related diseases [65]. The main part that modulates thermogenesis is UCP1. UCP1 is situated in the inner mitochondrial membrane, and there it affects dissociation of cellular respiration from ATP formation. With particular stimuli like cold exposure, sympathetically released norepinephrine acts on β3 adrenergic receptors in brown adipocytes that increases free fatty acids (FFA) release and ultimate activation of UCP1 [63]. But BAT is not preserved in adults from neonates. Hence inducing beige/brite adipocytes in human WAT is another method for management of increased nutrient energy. In mice, cold induced WAT browning helps in better glucose and lipid metabolism [66]. Mirabegron, that has been approved by food and drug administration of US (FDA) for overactive bladder, in humans induces a complicated network for controlling thermogenesis, that includes a lot of browning genes like UCP1, TMEM 26, CIDEA, etc [22,28].

ISSN 2047-9093

In vitro experimental data reveals that glucose uptake and glycolysis are needed stringently needed for adrenergically induced oxidative metabolism of murine brown adipocytes [67]. If UCP1 is expressed ectopically in mice WAT it decreases plasma glucose levels [68]. In fact, uptake of glucose has been utilized mostly to find BAT action in mice as well as humans in basal along with cold exposed circumstances utilizing ^{18}F-FDG-PET/CT, considered the gold standard of finding BAT and its activity checking [69]. The reason behind this is the finding that BAT has > metabolic action in contrast to other tissues. From this it can be interpreted that BAT utilizes more glucose as compared to WAT. But UCP1 knockdown in mice is not seen to reduce glucose uptake, pointing that thermogenesis and glucose movement get dissociated in BAT, whose molecular cause of increased glucose uptake has to be found [70]. Thus Tews et al. showed that in human white adipocytes both basal along with resting glucose uptake is influenced by just increasing UCP1 protein amounts. Developing human white Simpson – Golabi – Behmel syndrome (SGBS) adipocytes utilizing a stable knockout along with over expression of UCP1 they observed that UCP1 overexpression in adipocytes increased glucose uptake markedly by 40%. The basic cause found for this was a > glucose movement, that led to > Oxygen (O2) utilization, extracellular acidification and lactate liberation rates. This enhancement of glucose consumption can be compared to white to brown conversions, the way it is tested for 1st time, by direct comparison of in vitro differentiated mouse brown adipocytes vis a vis white ones. Though no adipogenic, metabolic and mitochondrial gene expressions got affected in any significant manner in SGBS cells, inhibiting GLUT1 by pharmacological means completely ameliorated the separation among UCP1+ and control cells thus unravelling GLUT1-modulated uptake acting as a watchdog permissively. Together their results show that enhancing UCP1 amounts is enough for enhancing human white adipocytes acting in the form of a glucose dumper that did not cause any cellular side effects, and thus not needing the adrenergically controlled, complex network of browning that mostly interferes with translational actions [71].

Role of SAR for finding newer β3 Adreno receptors, other than Mirabegron

The β3 adrenergic receptors represents a transmembrane protein belonging to the superfamily of Gprotein coupled receptor (GPCR) [72]. Three kinds of β3 adrenergic receptors exist. β1 adrenergic receptors, that is present in the CVS chiefly,at a place it is the target of specific blockers, like atenolol or bisoprolol, that are chiefly utilized for treating hypertension [73]. β2 adrenergic receptors is distributed in smooth muscles mostly, in which salbutamol or salmeterol the β2 adrenergic receptor agonists are useful for treating asthma [74]. While the B3 adrenergic receptors is present in body having a broader presence in the human being. It is seen in CVS [75], colon,bladder and AT [76]. Hence it might be used to treat a variety of diseases like depression [77], hypertension [78], overactive bladder (OAB) syndrome [79], cancer of colon [80] MetS along with obesity [81].

Till now for designing and synthesizing of newer β3 adrenergic receptors ligands ethanolamine chain has been utilized.Maximum of such agents are phenyl ethanolamine or aryl oxy propranolol – amine type. For getting β3 adrenergic selective agent ,adding a bulky group on the right hand part of the molecule help but since Mirabegron got approved in 2012, very few agents that have selectivity for β3 adrenergic receptors have been documented [82]. These drugs are CL-316,243 [83], amibegron (SR58611A), Mirabegron (YM-178) [79] and vibegron [RVT 901) [84]. CL-316, 243 posesses both antiobesity and anti DM actions [85]. Amibegron has antidepressant action in experimental animals [86]. Currently only Mirabegron is the only one of these group having selectivity for β3 adrenergic receptors that has approval from US FDA for therapy of OAB syndrome [87], but recently it has been documented that upper airway angioedema following Mirabegron intake occurs [88]. Further it has also been noted that Mirabegron increases BP and increases the QT c interval in the Electrocardiogram (ECG) [89]. Thus can Mirabegron be continued, Merck came up with vibegron in 2016, i.e a newer agonist that has effective along with having selectivity for β3 adrenergic receptors, and is right now undergoing clinical

ISSN 2047-9093

trials for therapy of OAB [84]. Comparative molecular field analysis (CoMFA) and Comparative molecular similarity index analysis (CoMSIA) developed using the research done by Cramer and Klebe [90,91] are helpful methods for getting insight into the pharmacological characteristics of a number of agents,Contour maps formed via CoMFA and CoMSIA display areas of the molecular formula in which changes in the steric, hydrophobic as well as H-bond characteristics develop a good or not helpful change in the biological action. Thus these maps help in:

i) getting insight into the type of ligands - receptor interactions
ii) forecast how much is the biological action and
iii) help in a proper designing of newer agents

In the past decade, only 2 publications on quantitative structure – activity relationship (QSAR) have been reported on particular agents regarding β3 adrenergic receptors [92]. One of these was conducted by the same researcher group as reported by Apablaza et al. [92]. In both studies were done on phenyl ethanolamine – type compounds. No further work on QSAR experiments on aryl oxy propanolamines have been there. Hence Lorca et al. conducted an elaborate structure activity relationship (SAR) of 41 Aryloxy Propanol-Amine Agonists in a serial basis, on the basis of 3-dimensional quantitative SAR (3D-QSAR) methods. This was supposedly the 1st combined relative molecular field analysis(CoMFA)and relative Molecular similarity in an index analysis in a comparative fashion study in number of Aryloxy Propanol-Amine in a serial manner that exhibited antidiabetic along with antiobesity structures in pharmacological manner. Best CoMFA and CoMSIA models gave results of r^2_{ncv}=0.993 and 0.984 and reports of r^2_{test}=0.865 and o.918 respectively. These data were further validated extensively utilizing external methods (q^2,$r^2r^2_m$,etc) and an ultimate series of agents were fashioned and their biological function was anticipated (best EC_{50}=8.561 [93].

CONCLUSIONS

Here we have emphasized on how WAT/BAT metabolism can be exploited using the β3 adrenergic receptor agonist Mirabegron was initially approved for treating OAB, but has been found to be effective in increasing EE, along with weight loss by increasing beiging in WAT and hence can be used to treat diabesity simultaneously [19]. Besides that Mirabegron can be used for several other off target effects like heart failure. But with recent problems encountered with Mirabegron with regards to some CVS side effects and angioedema, newer β3 adrenergic receptor agonist are being developed with QSAR being done to find safer ABEG drugs like the introduction of virabegron .Thus here a comprehensive review of how Mirabegron acts through recruiting Tregs in WAT, its efficacy in glucose metabolism, role of mast cells in their action besides that of cold exposure has been conducted to pave the way for a safer beta 3 adrenergic agonist of the newer drugs getting tested although Mirabegron is still being used for OAB having approval in Japan, USA and many other countries.

REFERENCES

1. Kulvinder Kochar Kaur, Gautam Allahbadia, and Mandeep Singh.Current Management of Obesity in an Infertile Female-Recent Advances and Future Prospective Drugs.J Pharm Nutr Sci[Internet].; 2013;3:1-13.
2. Kulvinder Kochar Kaur, Gautam Allahbadia, and Mandeep Singh. An Update on a Etiopathogenesis and Management of Obesity. Obes Control Ther [Internet].; 2016 Nov 21; 3(1): 1-17.
3. Kulvinder Kochar Kaur, Gautam Allahbadia, and Mandeep Singh.Further update on the management o f Obesity with Emphasis on Genetic Perspective.BAOJ Obe Weigt Manage[Internet].; 2017 Jan 11;3:1:010(1-11).

ISSN 2047-9093

4. Kulvinder Kochar Kaur, Allahbadia G and Singh M. Existing and prospective pathways for intervention in treatment of obesity in a novel way–a review. MOJ Drug Des Develop Ther[Internet]. 2018 May 23 ;2(3):95–105. Available from https://doi.org/.10.15406/mojddt.2018.02.00035
5. Kulvinder Kochar Kaur, Allahbadia G and Singh M. ''An update on Bariatric Surgery with long term efficacy and its utilization for medical therapy development from the different mechanism of action and other shortcomes to be outcome''. BAOJ Surgery[Internet] 2018 June 6, 4: 2 4: 038
6. Kulvinder Kochar Kaur, Allahbadia G and Singh M. Can Thylakoids Replace Bariatric Surgery for Long Term Maintenance of Weight Loss in Obesity Giving A More Physiological Approach . Obes Control Ther [Internet].;2018 July 31; 5(1): 1-10.
7. Kulvinder Kochar Kaur, Allahbadia G and Singh M. Are we at the verge of finding a new efficacious pharmacotherapy for obesity in the form of agonism at triple drug receptors: glucagon, Glucagon like peptide1 (GLP1), glucose dependent insulin tropic peptide (GIP). *Int* Phys Med Rehab J[Internet]. 2019 Feb 18 ;3(1):22–27. Available from https://doi.org/ 10.15406/mojddt.2019.03.0007.
8. Kulvinder Kochar Kaur, Allahbadia G and Singh M. Importance of simultaneous treatment of obesity and diabetes mellitus: A sequelae to the understanding of diabesity-A review.Obes Res Open J[Internet].; 2019 Mar 14; 6(1): 1-10. Available from https://doi.org/ 10.17140/OROJ-6-136
9. Kajimura S,Spiegelman BM,Seale P.Brown and BiegeFat:Physiological roles beyond heat generation. Cell Metab[Internet].;2015 Oct 6;22(4):546-59.Available from https://doi.org/10.1016/j.cmet.2015.09.007.
10. Kulvinder Kochar Kaur ,Allahbadia GN,Singh M. An Update on MicroRNA's and Metabolic Regulation with Future Potentials Regarding Diagnosis and treatment of Obesity,Metabolic Syndromeand other related Disorders.J Health Med Informa [Internet]. *2015 Apr 13*;6(2):1000184. Available from http://dx.doi.org/10.4172/2157-7420.1000184
11. Kulvinder Kochar Kaur ,Allahbadia GN,Singh M. *Advances in BAT physiology for understanding and translating into Pharmacotherapies for obesity and comorbidities. MOJ Drug Des Develop Ther[* Internet].. 2018 Sept 12 ;2(5):166–176.
12. Wu J,etal. Biege adipocytes are a distinct type of thermogenic fat cell in mouse and humans .Cell [Internet]. 2012;150(2):366-76.
13. Sidossis L, Kajimura S. Brown and BiegeFat in humans:thermogenic adipocytes that control energy and glucose homeostasis.J Clin Investig [[Internet] 2015Feb 2 ;125(2):478-86. Available from https://doi.org/10.1172/JCI78362.
14. Feldmann HM,Golozoubova V,CannonB,Nedergaard J.UCP1 ablation induces obesity and abolishes diet induced thermogenesis in mice exempt from thermal stress by living in thermoneutrality.Cell Metab Internet]. 2009;9(2):203-209.
15. Porter C,Chondronikola M , Sidossis L.The therapeutic potential of brown adipocytes in humans.Front Endocrinol(Lausanne) [[Internet].; 2015 Oct 13;6:156. Available from http:// doi.org: 10.3389/fendo.2015.00156. eCollection
16. Chondronikola M ,Volpi E,Borsheim E, Porter C ,Annamalai P,Even pack Setal.Brown adipocyte tissue improves whole body glucose homeostasis and insulin sensitivity in humans.Diabetes Internet].; 2014 Dec online nov 13;63(12):4089-99 Available from https://doi.org/10.2337/db14-0746.
17. Min SY,Kady J,Nam M,Rojas-Rodriques R,Berkenwald A ,Kim JH,Noh HLetal.Human brite/beige adipocytes develop from capillary networks and their implantation improves metabolic homeostasis in mice .Nature Medicine Internet]. 2016 Jan 25;22(3):312-18. Available from https://doi.org/10.1038/nm.4031.
18. Arch JR,Kaumann AJ. β3 and atypical adreno receptors.Med Res Rev Internet]. 1993Nov;13(6):663-729. Available from PMID 8258999
19. Dehvari N,Dantas da Siva E Jr,Bengtsson T,Hutchinson DS. Mirabegron:potential off target effects and uses beyond the bladder.Br J Pharmacol Internet]. 2018 Nov 16 ;175:4072. Available from https://doi.org/10.1111/bph.14121,
20. Finlin BS, Memetimin M,Confides AS,Kasza I,Zhu P,Vekaria HJ, etal.Mast cells promote seasonal white Adipose Beiging in Human . Diabetes [Internet]. 2017 Aug 9 ;66(5):1237-1246 Available from https://doi.org/10.2337/ db16-1057 .
21. Kern PA, Finlin Brian S., Zhu Beibei, Rasouli Neda, McGehee Robert E., Westgate PhilipM, etal.The effects of temperature and seasons in subcutaneous white Adipose tissue in humans:evidence for thermogenic

ISSN 2047-9093

gene induction.J Clin Endocrinol Metab[Internet]. 2014 99(12):E2772-E2779.Available at https://doi.org/10.1210/jc.2014-; 2440.

22. Cypess AM,Lehman S,Williams G,Tal I,Rodman D,Goldfine AB, etal,.Identification and importance of brown adipose tissue in adult humans.N Engl J Med[Internet]. 2009 Apr 9;360(15):1509-17. Available at https://doi.org/. 10.1056/NEJMoa0810780.
23. Van Marken Lichtenbelt WD,Vanhommrig JW,Smulders NM etal.Cold activated brown adipose tissue in healthy men.N Engl J Med[Internet].; 2009 ; 360;1500-508.Available at https://doi.org/10 1056/NEJMoa0808718 360/15/1500 [pii].[3].
24. Stanford KI,Goodyear LJ.Exercise regulation of adipocyte tissue .Adipocyte 2016;5(2);153-62.
25. Sidossis LS, Porter C ,Saraf MK,Borsheim E,Radhakrishnan RS,etal.Browning of subcutaneous white Adipose tissue in humans after severe Adrenergic Stress. Cell Metab[Internet]. 2015 Aug 4;22(2):219-27. https://doi.org/10.1016/j.cmet.2015.06.022
26. Petruzzelli M,etal.A switch from white to brown fat increases energy expenditure in cancer associated cachexia. Cell Metab[Internet].2014;20(3):433-47. Available at https://doi.org/10.1016/j.cmet.2014.06.011
27. Kir S,White JP,Kleiner S,Kazak L,Cohen P,Baracos VE,Spiegelman BM.Tumor derived PTH –related protein triggers adipocyte tissue browning and cancer cachexia.Nature[Internet]. 2014;513(7516):100-104. Available from https://doi.org/10.1038/nature13528.
28. Finlin BS,Memetimin H,Confides AL,Kasza I,Zhu B,Vekaria HJ,etal.Human Adipose Beiging in response to cold and Mirabegron.JCI Insight[Internet]. 2018 Aug 9;3(15). 10.1172/jci.insight.121510.eCollection;3(15):e121510 Available from. https://doi.org/10.1172/jci. insight.121510.
29. Villaroya F,Cereijo R, Villaroya J,Gavalda-Navarro A,Giralt M.Toward an understanding of how Immune cells Control Brown and Biege Adipobiology. Cell Metab[Internet]. 2018;27:954-61. Available from https://doi.org/10.1016/j.cmet.2018.04.006.
30. Ruiz de Azua I,Mancini G,Srivastava RK,Ray AA,Caedinal P,Tedesco L,etal. Adipocyte cannabinoid receptor CB1 regulates energy homeostasis and alternatively activated macrophages. J Clin Investig[Internet]. 2017 Oct 16;127:4148-62. Available from https://doi.org/10.1172/JCI83626.
31. Nguyen KD,Qiu Y,Cui X,Sharon Goh YP,Mawangi J,David T,etal. Alternatively activated macrophages Produce catecholamines to sustain adaptive thermogenesis.Nature[Internet]. 2011 Nov 20;480:104-108.
32. Rao RR,Long JZ,White JP,Svensson KJ,Lou J,Lokurkar I, etal.Meteorin –like is a hormone that regulates Immune –Adipose interactions to increase beige fat thermogenesis.Cell [Internet]. 2014 June 5;157:1279-91. Available from https://doi.org/10.1016/j.cell.2014.03.065.
33. Lee MW,Odegaard JI,Mukundan L,Qiu Y,Molofsky AB,Nussbaum JC etal. Activated type 2 innate lymphoid cells regulate beige fat biogenesis .Cell [Internet]. 2015 Dec 24;160:74-87. Available from https://doi.org/10.1016/j. cell.2014.12.01
34. Brestoff JR,Kim BS,Saenz SA,Stine RR,Monticelli JA,Sonnenberg LA, etal. Group2 Innate innate lymphoid cells promote beiging of white Adipose tissue and limit obesity. Nature[Internet]. 2015 Mar 12;519:242-46. Available from https://doi.org/10.1038/nature14115.
35. Fischer K,Rhuz HH,Jhun K,Finan B,Oberlin DK,Van der Vid Vetal. Alternatively activated macrophages do not synthesize catecholamines or contribute to adipose tissue adaptive thermogenesis.Nat Med[Internet]. 2017 Apr 17;23:623-30. Available from https://doi.org/10.1038/nm.4316.
36. Camell CD,Sander J,Spadaro O,LeeA,Nguyen KY,Wing A,etal.Inflassome driven catecholamines catabolism in microphages blunts lipolysis during ageing. Nature[Internet]. 2017 Sept 27;550:119-23. Available from https://doi.org/10.1038/nature24022.
37. Chung KJ, Chatzigeorgiou A, EconomopoulouM,Garcia-Martin R.Alexai V,Mitroulis I, etal.A self sustained loop of inflammation driven inhibition of beige adipogenesis in obesity.Nat Immuunol [Internet]. 2017 Apr 17;18:654-664. Available from https://doi.org/10.1038/ni.3728.
38. Goto T,etal.Pro inflammatory cytokine interleukin-1 beta suppresses cold induced thermogenesis in adipocytes .Cytokines[Internet]. 2016;77:107-14. Available from
39. Sakamoto T ,etal. Macrophage infiltration into obese adipose tissue suppresses the induction of UCP1expression in mice .Am J Physiol Rndocrinol Metab[Internet]. 2016;ajpendo 0002802015. Available from https://doi.org/10.1016/j.cyto.2015.11.001.

ISSN 2047-9093

40. Sakamoto T ,Takahashi N, Sawaragi Y,NaknunooI S.Yu R,Goto T,etal.Inflammation induced by a RAW macrophages suppresses UCP1 mRNA induction via ERK activation in 10 T1/2 adipocytes . Am J Physiol Cell Physiol[Internet]. 2013 Jan 9;304:C729-C738. Available from https://doi.org/10.1152/ajpendo.00028.2015.
41. Finlin BS, Confides AL ,Zhu B,Boulanger MC,Memetimin H,Taylor KW,et al. Adipose tissue Mast cells Promote Human Adipose beiging in response to cold .Scientific Reports[Internet]. 2019 2019 Jun 17;9(1):8658. Available from https:// doi.org/ 10.1038/s41598-019-45136-9.
42. Rosen ED, Spiegelman BM.What we talk about when we talk about fat.Cell[Internet]. 2014;156(1-2):20-44. Available from
43. Fontenot JD,Gavin MA ,Rudensky AY.Foxp3 programs the development and function of CD4+CD25+regulatory Tcells.Nat Immunol[Internet]. 2003;4(4):330-336. Available from
44. Brunkow ME,Jeffery EW,Hjerrlid KA,Paeper B,Clark LB,Yasayko SA,etal..Disruption of a new forkhead/winged –helix protein ,scurfin ,results in the fatal lymphoproliferative disorders of the scurfy mouse .Nat Genet[Internet]. 2001;27(1):68-73. Available from
45. Morgan ME,Van Bilsen JH,Bakker AM,Heemskerk B,Schilham MW,Hartgers FC,etal.Expression of FOXP3 mRNA is not confined to CD4+CD25+regulatory Tcells in humans .Human Immunol [Internet]. 2005;66(1):13-20.
46. Liu W,Putnam AL,Xu-Yu Z,Szot GL,Lee MR,Zhu S,etal.CD127 expression inversely correlates with Foxp3 and suppressive function of human CD4+Treg cells.J Exper Med[Internet]. 2006;203(7):1701-11.
47. Wing JB,Tanaka A,Sakaguchi S,.Human FOXP3+ regulatory Tcells heterogeneity and function in autoimmunity and cancer .Immunity[Internet]. 2019;50(2):302-16.
48. Von Boehmer H,Daniel C.Therapeutic opportunities for manipulating T(Reg) cells in autoimmunity and cancer .Nat Rev Drug Discov[Internet]. 2013;12(1):51-63.
49. Daniel C,Weigman B.Bronson R,Boehmer HV.Prevention of type1 diabetes in mice by tolerogenic vaccination with a strong agonist insulin mimetope. J Exper Med [Internet]. 2011;208(7):1501-10.
50. Sauer S,Bruno L,Hertweck A,Finlay D,Leleu M,Spivakov M,etal.Tcell receptor signaling controls Foxp3 expressions via PI3K,Akt and mTOR.Proceedings of the National Academy of the United States of America 2008;105(22):7797-7802.
51. Cipoletta D,Fuerer M,Li A,Kamel N,LeeJ,Shoelson SE,etal.PPAR-gamma is a major driver of of the accumulation and phenotype of Adipose tissue Treg cells.Nature[Internet]. 2012;486(7404):549-53.
52. Fuerer M,Herrero l, Cipoletta D,Naaz A,Wong J,Nayer A,etal.Lean,but not obese ,fat is enriched for a unique population of regulatory Tcells that affect metabolic parameters .Nat Med [Internet]. 2009;15(8):930-939.
53. Kalin S,Becker M,Ott VB,Serr L,Hosp F,Mollah MMH,etal.A Stat6/pten Axis links regulatory Tcells with Adipose tissue function.Cell Metab[Internet]. 2017;26(3):475-92.e7.
54. Medrikova T,Sijmonsma TP,Sowodniok K,Richards DM,Delacher M,Sticht C,etal.Brown Adipose tissue harbours a distinct sub population of regulatory Tcells.PLoSOne[Internet]. 2015;10(2):e0118534.
55. Wu J,Bostrom P,Sparks LM,Li Y,Choi JH,Giang AH,Khandekar M et al(2012).Beige adipocytes are a distinct type of thermogenic fat cell in use and humans.Cell[Internet]. 2012 ;150(2):366-376.
56. Cypess AM,White AP,Vernochen C,Schultz TZJ,Xue R,Sass CA et al .Anatomical localization,gene expression profiling and functional characterization of adult human neck brown fat.Nat Med[Internet]. 2013 May;19(5):635-9. Available from https://doi.org/10.1016/j.cmet.2014.12.009. .
57. Malik M,Van Gelderen EM,LeeJH,Kowalski DL,Yen M,Goldwater R,etal.Proarrythmic study of frepeat doses of Mirabegron in healthy subjects:a randomized,double blind ,placebo ,and active controlled through QT study.Clin Pharmac Therap[Internet]. 2012;92(6):696-706.
58. Hanssen MJ,Hoeks J,Brans B,Van der Lans AA,Schart G, Van derDriessche JJ,etal.Short term cold acclimation improves insulin sensitivity in patients with type 2 Diabetes Mellitus. Nat Med[Internet]. 2015;21(8):863-65.
59. Cypess AM,Weiner LS,Roberts-Toler C,Franquet-Elia E,Kessler SH,etal.Activation of human Brown Adipose tissue by a β3 adrenergic receptor agonist . Cell Metab[Internet]. 2015 Jan 6;21(1):33-8. Available from https://doi.org/ 10.1016/j.cmet.2014.12.009.

ISSN 2047-9093

60. Becker M,Serr I,Salb VX, Ott VB,Mengel L,Bluher M,etal.Short-term exposure supports human Treg induction in vivo.Mol Metabol[Internet]. 2019;28:73-82. Available from https://doi.org/ 10.1016/molmet.2019.08.02.
61. Loh RKC,Formosa MF,La Gerche A,RAeuters AT,Kingwell BA,Carey AL.Acute metabolic and cardiovascular effects of Mirabegron in healthy individuals . Diabetes Obes Metab[Internet]. 2019 june ,online apr2;21(2):276-84. Available from https://doi.org/10.1124/jpet.118.255778
62. Hao L,Scott S,Abbasi M,Zu Y,Khan MSH,Yang Y,Wu D,Zhao L,Wang S.Beneficial metabolic effects of Mirabegron in vitro and in high fat diet –induced obese Mice.J Pharmacol Exp Ther [Internet]. 2019Feb online sep 24 2018;369(3):419-27. Available from https://doi.org/10.1111/dom.13515
63. CannonB,Nedergaard J(2004).Brown adipose tissue:Function and physiological significance.Physiol Rev[Internet]. ;84:277-359. Available from https://doi.org/10.1152/physrev. 00015.2003.
64. Stanford KI,Middlebeek RJW,Townsend KL,An D,Nygaard EB,Hitchcox KM. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity .J Clin Invest[Internet]. 2013;123:215-223. Available from https://doi.org/10.1172/JCI62308.
65. Chouchani ET,Kazak L,Spiegelman bm.New advances in adaptive thermogenesis :UCP1 and beyond. Cell Metab[Internet]. 2019;29:27-37. Available from https://doi.org/10. 1016/j.cmet.2018.11.002.
66. Cohen P,Levy JD,Yingying Z,Frontini A,Kolodin DP,Svensson KJ,Lo JC et al(2014).Ablation of PRDM 16 and Beige Adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch.Cell [Internet]. 2014;156:304-316. Available from , https://doi.org/10.1016/j.cell.2013.12.021
67. Skjjoldborg N,Isidor MS,Cheung A,Winther S,Hansen JB,Quistoff B,BasseeAL.Restricting glycolysis impairs brown adipocytes glucose and oxygen consumption. Am J Physiol Rndocrinol Metab[Internet]. 2017;314:E214-E223. Available from https://doi.org/10. 1152/ajpendo.00218.2017
68. Yamada T,Katagiri H,Ishigaki Y,Oghira T.Imai J,Uno Y,etal.Signals from intra-abdominal fat modulate insulin and leptin sensitivity through different mechanisms :neuronal involvement in food intake regulation. Cell Metab[Internet]. 2006;3:223-29 Available from https://doi.org/10.1016/j.cmet.2006.02.001
69. Chen KY,Cypess AM,Laughlin MR,Haft CR,Hu HH,Bredella MA,etal. Brown adipose reporting criteria in imaging Studies(BARCIST 1.0)recommendations for standardized FDG-PET/CT experiments in humans . Cell Metab[Internet]. 2016;24:210-22. Available from https://doi.org/10.1016/j.cmet.2016. 07.014.
70. Hankir MK,Krantz M,Keipert S,Weiner J,Andreasen SG,Kern M,etal.Dissociation beween Brown adipose effects ^{18}F-FDG uptake and thermogenesis in uncoupling protein 1 deficient mice.JNucl Med[Internet]. 2017;58:1526-31. Available from https://doi.org/10. 2967/jnumed.116.186460.
71. Tews D,Pula T,Funcke JB,Jastroch M,Keuper M ,Debatin KM,etal.Elevated UCP1 levels are sufficient to improve glucose uptake in human white adipocytes.Redox Biology[Internet]. 2019 July 27;26:101286. Available from https://doi.org/10.1016/j.redox.2019.101286

72. Tan S,Curtiz –Prior PB.Characterization of the beta-adrenoceptor of the adipose cell of the rat .Int J Obese[Internet]. 1983;7:409-414.
73. Heel RC.Brodgen RN,Speight TM.Avery GS.Atenolol:a review of the pharmacological properties and therapeutic efficacy in angina pectoris and hypertension.Drugs[Internet]. 1979;17:425-60.
74. Paterson JW ,Evans RJ,Prime FJ.Selectivity of bronchodilator action of salbutamol in asthmatic patients .Br J Dis Chest[Internet]. 1971;65:21-38.
75. Gauthier C,Tavernier G,Carpentier F,Lamgin D,LeMarc H.Functional β3 Adreno receptors in the human heart. J Clin Invest[Internet]. 1996;98:556-62.
76. Krief S,Lonqvist F,Raimbult S,Baude B,Van Spronsen A,Arner P,etal.Tissue distribution of β3 adrenergic receptor mRNA in man. J Clin Invest[Internet]. 1993;91:344-49.
77. Stemmelin J,Cohen C,Terranova JP,Lopez-Grancha M,Pichat P,Bergis O.etal.Stimulation of the β3 Adreno receptor as a novel strategy for anxiety and depressive disorders.Neuropsychopharmacology[Internet]. 2008;33:574-87.
78. Gauthier C,Rozee B,Manoury B,Balligand JL. β3 Adreno receptors as a new therapeutic targets for cardiovascular pathologies .Curr Heart Fail Rep[Internet]. 2011;8:184-92.

ISSN 2047-9093

79. Takasu T,Ukai M ,Sato S,Matsui T,Nagase I,Maruyama T,etal.Effect of (R)-2-(2-aminothiazol=4-yl)-4'-[2[-(2-hydroxy-2-phenyl ethyl)aminoethyl]acetanilide)YM-178,anovel selective β3 Adreno receptor agonist ,on bladder function.J Pharmacol Exp Therm[Internet]. 2007;321:642-47.
80. Perrone MG ,Notarmocola M,Caruso MG.Tutino V,Scilimati A.Upregulation of β3 Adrenergic receptor mRNA in human colon cancer :A preliminary study.Oncology[Internet]. 2008;75:224-29.
81. Van Bak MA,Hul GB,Toubro S,Astrup A,Gottediener KM,DeSmet M,etal.Acute effect of L-796568,anovel β3 Adrenergic receptor agonist ,on energy expenditure in obese men.Clin Pharmacol Ther[Internet]. 2002;71:272-79.
82. Hertzberg R,Monreal-Santiago G,Moberg C.Synthesis of β3 Adrenergic receptor agonist solabegron and analogous N-(2-ethylamino)-beta amino alcohols from O-acylated cyanohydrins-expanding the scope of minor enantiomer recycling .J Org Chem[Internet]. 2015;80:2937-41.
83. Bloom JD,Dutia MD,Johnson BD,Wissner A,Burns MG,Largis EE,etal.Disodium(R,R)-5[2-[(3-Chlorophenyl)-2 hydroxy ethyl-amino]propyl]-1,3 benzodioxole -2,2 dicarboxylate(CL-316,243).A potent β3 Adrenergic receptor agonist virtually specific for beta 3 receptors.A promising antidiabetic and antiobesity agent.J Med Chemv 1992;35:3081-84.
84. Edmondson SD,Zhu C,Kar NF,Di Salvo J,Nagabukuro H,et al.Discovery of Vibegron :A potent and selective β3 Adrenergic receptor agonist for the treatment of overactive bladder. J Med Chem[Internet]. 2016;59:609-23.
85. Collins S,Daniel KW,,Petro AE,Surwit RS.Strain specific response to β3 Adrenergic receptor agonist treatment of diet –induced obesity in mice.Endocrinology[Internet]. 1997;138:405-13.
86. Overstreet DH,Stemmelin J,Griebel G.Confirmation of antidepressant potential of the selective β3 Adreno receptor agonist amibegron in an animal model of depression.Pharmacol Biochem Behav[Internet]. 2008;89:623-26.
87. Gras J. Mirabegron for the treatment of overactive bladder.Drugs Today[Internet]. 2012;48:25-32.
88. Myrbetriq.Available online:http:www.myrbetriq,hcp.com/accessed on may 10,2018.
89. Van Geldersen M,Stolzel M,Meijer K,Kerbusch C,Collins C,Korstanje C.An Exploratory Study in Healthy Male Subjects of the Mechanisms of Mirabegron-Induced cardiovascular effects.J Clin Pharmacol[Internet]. 2017;57:1534-44.
90. Cramer RD,,Patterson DE,Bunce JD,.Comparative molecular field analysis (CoMFA).1.Effect of shape on binding of steroids to carrier proteins .J Am Chem Soc[Internet]. 1988;110:5959-67.
91. Klebe G,Abraham U,Mietzner T.Molecular similarity in a comparative analysis (CoMSIA)of drug molecules to correlate and predict their biological activity. J Med Chem[Internet]. 1994;37:4130-46.
92. Apablaza G,Montoya L,Morales-Verdejo C,Mellado M,Cuellar M,Lagos CF,etal.2D-QSAR and 3D QSAR/ CoMSIA Studies on a series of (R)-2-((2-(1H—Indol-2-yl)amino)-1-Phenylethan-1-ol with Human beta(3)-Adrenergic Activity.Molecules[Internet]. 2017 22:404.
93. Lorca M, Morales-Verdejo C,Vasquez-Velasquez D,Andrades-LagosJ,Campanini-Salinas J,Soto-Delgado J,etal.Structure Activity Relationships Based on 3D-QSAR CoMFA / CoMSIA and Design of Aryloxy Propanol-Amine Agonists with Selectivity for the Human β3 adrenergic receptor and Anti-Obesity and Anti –Diabetic Profiles.Molecules[Internet]. 2018 May 16;23:1191.Available from https://doi.org/10.3390/molecules23051191.

ISSN 2047-9093