

# 2D QSAR Approach to Develop Newer Analogs as Melatonin Receptor Agonist

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**ABSTRACT:** QSAR analysis was performed using 20 MT1 agonist and 18 MT2 agonist. MODI was 0.6373 in case of MT1 agonist and 0.6299 in case of MT2 agonist. QSAR model for MT1 receptor agonist was  $pK_d = 16.24793(+/-0.93539) + 1.0924(+/-0.18831) ALogP - 0.11399(+/-0.01383) apol + 0.59876(+/-0.16599) C2SP3 - 10.29435(+/-2.81413) E3p$  and for MT2 receptor agonist was  $pK_d = 6.38692(+/-0.91098) + 0.87139(+/-0.20258) ALogP - 0.0351(+/-0.00542) AMR + 3.33079 (+/-0.80377) SpMin6\_Bhm + 146.76208(+/-28.14492) VE2\_Dt$  with statistical parameter as  $Q^2:0.79167, r^2 :0.88878, |r^2-r^2|:0.04633, k:1.03159, [(r^2-r^2)/r^2]:0.01013, k':0.96695, [(r^2-r^2)/r^2]:0.06226$  and  $Q^2:0.81401, r^2:0.97384, |r^2-r^2|:0.1039, k:0.98543, [(r^2-r^2)/r^2]:0.08048, k':1.01351, [(r^2-r^2)/r^2]:0.18717$  respectively; comply with the Golbraikh and Tropsha acceptable model criteria. The results from MLR Y Randomization test in case of MT1 agonist was  $cRp^2: 0.7665$  and MT2 agonist was  $cRp^2: 0.7284$ . Applicability domain were identified by Euclidean and Mahalanobis Distance Method. Finally it was clear that all the predicted data are inside the area of observed data points and also some data are purely overlapped.

**Key words:** Melatonin, MODelability index, golbraikh and tropsha acceptable model, MLR Y randomization, euclidean and mahalanobis distance

## INTRODUCTION

Presently barbiturates, benzodiazepines are being used as sedative hypnotics for the treatment of insomnia. However these drugs have side effects like high abuse potential, cognitive impairment, psychomotor impairment, dependence, tolerance, hangover, rebound insomnia, and so on.<sup>1</sup> A thirst for the discovery of newer hypnotics remains relevant till to date. Circadian rhythm is the term used to describe the physiological and behavioral twenty four hour cycle that most organisms experience. The mammalian biological clock is situated in the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus.<sup>2</sup> After seeing relation between sleep and release of melatonin there has been a focus on the development of hypnotic agents

that selectively target melatonin receptors. Melatonin (*N*-acetyl-5-methoxytryptamine), the hormone normally secreted from the pineal gland at night, serves as the signal of darkness in the organism and as such plays a pivotal role in the physiological regulation of circadian rhythms, including sleep.<sup>3</sup> Small number of melatonin receptor agonist like melatonin, ramelteon, tasimelteon, agomelatine are available in the market. Putative melatonin receptors are initially classified into MT1 and MT2, based on the kinetic and pharmacological differences in 2-[<sup>125</sup>I] iodomelatonin binding. Melatonin is believed to exert these effects via two specific high affinity guanine nucleotide binding protein (G protein coupled receptors) in the SCN, MT1 and MT2.<sup>4</sup> Exogenous melatonin treatment has a phase shifting effect on circadian rhythms. The influence of an external agent on the biological clock is referred to as the chronobiotic effect. The chronobiotic effect of

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melatonin is due to the presence of MT1 and MT2 receptors in the SCN. MT1 receptors inhibit multiunit activity, while MT2 receptors are responsible for phase shifting responses. It seems likely from *in vivo* studies that the chronobiotic effect of exogenous melatonin is due to the concerted actions of MT2 resetting the circadian clock and MT1 suppressing neuronal firing at the SCN. Ramelteon has been shown to improve sleep disorders in patients suffering from transient and chronic insomnia without causing significant adverse events. In addition, Ramelteon has a low abuse potential and does not appear to be associated with a withdrawal syndrome or with rebound insomnia. Agomelatine received marketing authorization in the European Union in 2009, for the treatment of depression. In patients with major depression, agomelatine was similarly as effective as paroxetine, sertraline, venlafaxine and fluoxetine, with a lower relapse rate (23.9%) compared to the placebo (50.0%). Tasimelteon has been developed for the treatment of circadian rhythms sleep disorders and approved in the USA in 2014 for the treatment of non-24 h sleep-wake disorder in the blind.<sup>5</sup> Moreover, it has been suggested that melatonin receptor agonists have opportunities to cure various diseases, like Alzheimer disease, bipolar disorder, cancer, hypertension, urinary incontinence, and so on.

In present study we have been develop a QSAR model for the future synthesis of melatonin receptor agonist using melatonin receptor agonist affinity data as biological activity.

## MATERIALS AND METHODS

QSAR model was conducted by using a set of theoretical and constructive descriptors. QSAR Model was constructed by use of MLR Plus Validation Tool. More than 1800 descriptors include Ghose-Crippen Log Ko/w, Ghose-Crippen molar refractivity, Sum of the atomic polarizabilities (including implicit hydrogens), Wildman- Crippen LogP and MR, Wildman-Crippen MR, Eccentric Connectivity Index: topological descriptor combining distance and adjacency information, H Bond

Acceptor Count Number of hydrogen bond acceptors, McGowan characteristic volume, Wiener Polarity Number, Kappa shape indices, Electrotopochemical atom were calculated by PADEL and ToMoCoMD software. All the explanations of relevant descriptors were enlisted in (Table 1). A descriptor represents a quantitative property depends on the molecular structure. Theoretical descriptors were advantageous due to its free from uncertainty of experimental measurement and can be calculated for compounds before synthesis. Theoretical descriptors were employed in this QSAR study to model as melatonin (MT1 & MT2) receptor agonist.

**Table 1. List of relevant descriptor with explanation.**

Abbreviation descriptors	Explanation of descriptors
AlogP	Ghose-Crippen LogKow
SpMin3_Bhv	Burden modified eigenvalues
ntN	Total number of Nitrogen Atoms
ETA_Beta_ns	A measure of electron-richness of the molecule
Crippen MR	Crippen's molar refractivity
McGowan volume	McGowan characteristic volume
VABC	Van der Waals volume calculated
nRing	No of ring
nRotb	No of rotatable bonds
Phia Kappa	flexibility index
Bac	Balaban centric index
AlogP	Ghose-Crippen LogKow
Crippen LogP	Crippen's LogP
XLogP	XLogP
AMR	Molar refractivity
TopoPSA	Topological polar surface area
Wpol	Weiner polarity number
MW	Molecular weight
ETA	Electro topochemical descriptor

**Dataset and descriptor calculation.** Dataset of 20 melatonin receptor MT1 agonist and 18 MT2 agonist were extracted.<sup>6-20</sup> All the molecules SMILE format were transferred into .mol format by ACDLABS and structures were optimized. 2D and 3D descriptors were calculated using PADEL descriptor<sup>21</sup> and ToMoCoMD<sup>22</sup> software.

**MO Delability index calculation.** MODELability index<sup>23</sup> was a way to estimate for every compound present in a dataset with the smallest Euclidean distance in the entire descriptor space belongs to

same or different activity class. The number of nearest neighbor pairs that were not activity cliff was counted for each class of compounds using proper threshold value.

**Descriptor pretreatment.** Inter correlated descriptor was cut off using V-WSP<sup>24</sup> as variance cut off 0.0001 and correlation coefficient value 0.99.

**Dataset division.** Dataset of 20 molecules as MT1 agonist was divided into 14 molecules in training and 6 molecules in Test set using Kennard Stone method and Dataset of 18 molecules as MT2 agonist was divided into 12 molecules in training and 6 molecules in test set using Kennard Stone method.

**Suitable descriptor selection.** Suitable descriptor selection was performed using stepwise MLR as F values 3.9 to 4.0. Then best subset was selected using 4 descriptor combination and r<sup>2</sup> cut off value 0.6.

**The chemometric tool.** The development of QSAR equation was implemented two methods (1) Stepwise regression (2) multiple linear regressions with factor analysis as pre processing factor analysis for variable selection (FA-MLR).

**Stepwise regression.** Multi step linear equation, a multistep equation was built by step by step. The basic procedure involved: (i) Identifying an initial model (ii) Repeating the previous step by altering descriptor or variable combination to achieve better F and r<sup>2</sup> value. (iii) Calibrate the equation by justify the values in between observed and predicted values. The stepwise MLR was performed using statistical software SPSS and it was judged by parameters as explained variance (r<sup>2</sup>a), correlation coefficient (r), standard error of estimate (s) and variance ratio (F) at a specified degree of freedom (DF). All accepted MLR equation had regression level significant at 95 and 99% levels. The generated QSAR equation was validated by leave one out or LOO method using Minitab software and different parameters like cross validation r<sup>2</sup> (q<sup>2</sup>), standard deviation based on press (S<sub>PRESS</sub>) and standard deviation of error of prediction (SDEP).<sup>25</sup>

**FA-MLR.** In this case a final statistical tool was used to develop a QSAR relation, factor analysis as a

data pre processing step to identify the important factor to identify the important variables contributing the response variable by avoiding co linear value. The data matrix is first standardized and correlation matrix and subsequently reduced correlation matrix. An eigen value problem is then solved and the factor pattern can be obtained from the corresponding eigen vectors. The main objectives are to display multidimensional data in space of lower dimensionality with minimum loss of information (explaining > 95% of variance of data matrix) and to extract the basic features behind the data with ultimate goal of interpretation.<sup>26</sup>

**QSAR equation development.** MLR plus valid software was used to developed QSAR equation, where pKd value was used as biological effect.<sup>27,28</sup>

**QSAR equation validation.** Golbraikh and Tropsha acceptable model criteria<sup>29-31</sup> to validate a QSAR equation:

1. Q<sup>2</sup> value is passed (Threshold value Q<sup>2</sup>>0.5).
2. r<sup>2</sup> value is passed (Threshold value r<sup>2</sup>>0.6).
3. |r<sup>0</sup><sup>2</sup>-r<sup>0</sup><sup>2</sup>| value is passed (Threshold value |r<sup>0</sup><sup>2</sup>-r<sup>0</sup><sup>2</sup>|<0.3).

**QSAR equation cross validation.** The model was cross validated using Leave-One-Out (LOO) process.<sup>32</sup> Applicability domain of the developed QSAR equation was checked based on the response and chemical structure space in which the QSAR model makes predictions with a given reliability. Euclidean distance<sup>33</sup> and Mahalanobis<sup>34</sup> distance method. The distance of a test compound to its nearest neighbor in the training set is compared to the predefined applicability domain threshold.

**MLR Y randomization test.** In this test, random MLR models were generated by randomly shuffling the dependent variable while keeping the independent variables as it is. The new QSAR models were expected to have significantly high R<sup>2</sup> and Q<sup>2</sup> values for several trials, which confirm that the developed QSAR models were robust. Another parameter, cRp<sup>2</sup> was also calculated which should be more than 0.5 for passing this test.<sup>35</sup>

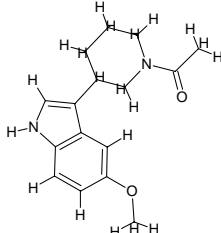
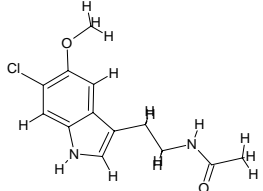
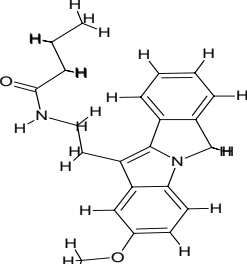
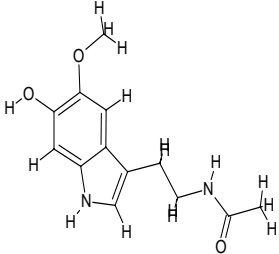
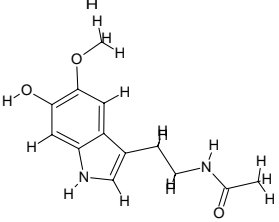
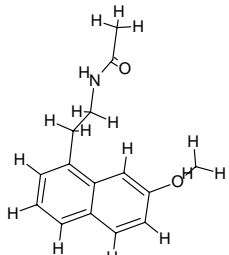
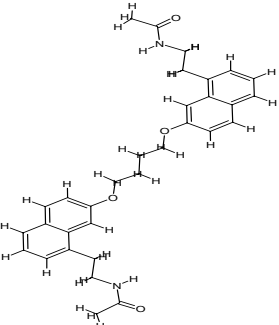
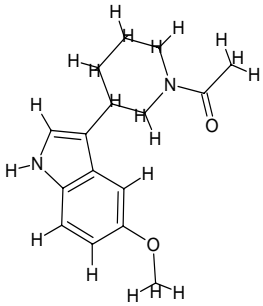
$$cRp^2 = R * (R^2 - (\text{Average } R_r)^2)^{1/2}$$
 where, Average R<sub>r</sub> = average 'R' of random models.

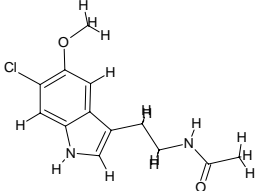
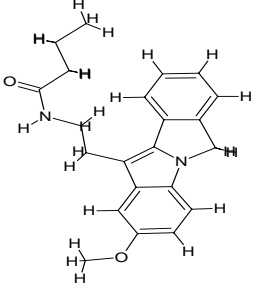
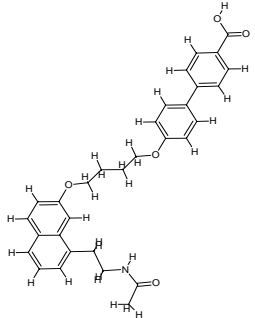
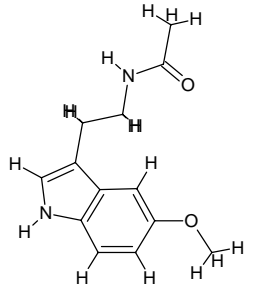
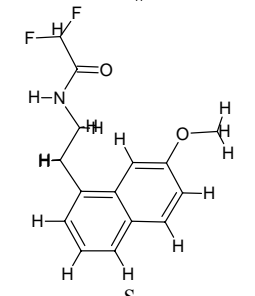
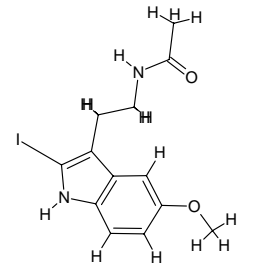
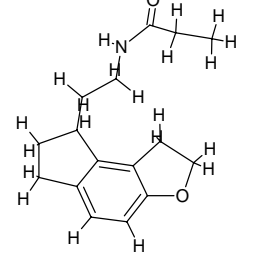
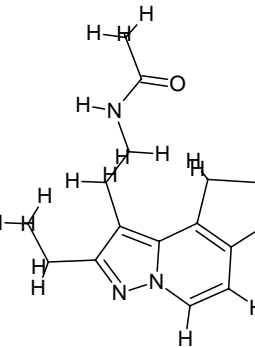
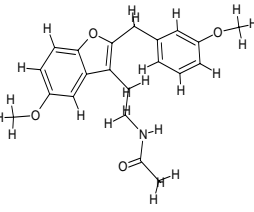
## RESULTS AND DISCUSSION

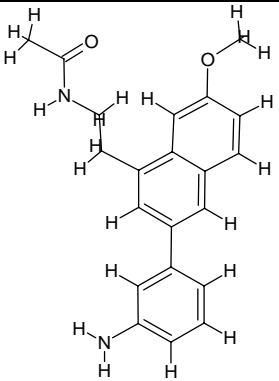
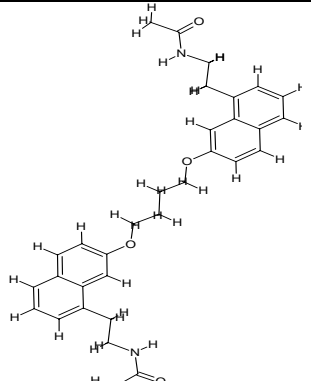
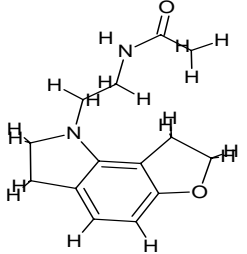
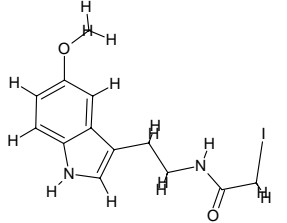
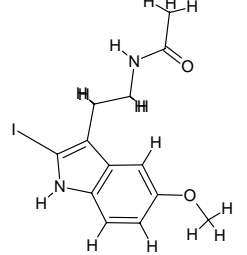
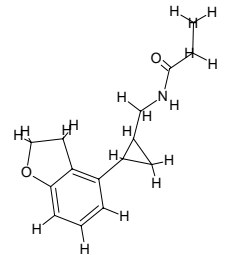
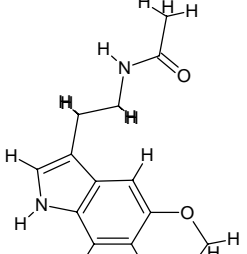
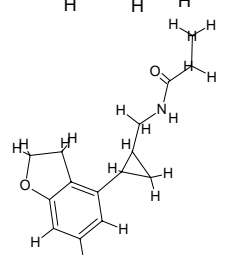
The total dataset of 20 MT1 receptor agonist and 18 MT2 receptor agonist were subdivided into training and test set along with chemical structure and pKd (affinity towards MT1 & MT2 receptor) as biological effect was diagrammatized in (Tables 2 and 3). The outcome from MODELability index was

0.6373 with threshold value 0.65 and total actives/toxic (H): 17.0000 total less actives/less toxic (L): 3.0000 in case of MT1 agonist and 0.6299 with threshold value 0.65 and total actives/toxic (H): 11.0000 total less actives/less toxic (L): 7.0000 in case of MT2 agonist and detail of MODELability Index was diagrammatized in (Table 4). In case of

**Table 2. Detail list of training set molecule with affinity towards MT1 and MT2 receptor.**

Compound name	Structure	pKd value (MT1 affinity)	Compound name	Structure	pKd value (MT2 affinity)
GR 128107		6.9	6-Cl-MLT		8.5
IKK7		8.3	6-hydroxy melatonin		8.6
6-hydroxy-melatonin		9.0	Agomelatine		10.2
S26284		8.9	GR 128107		8.8

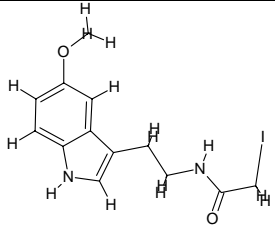
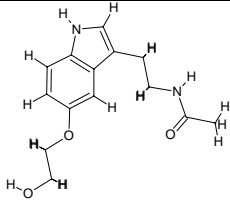
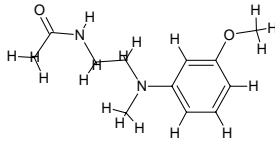
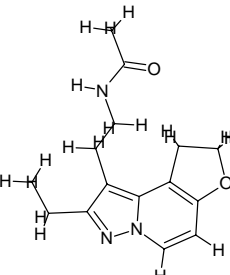
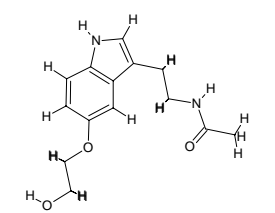
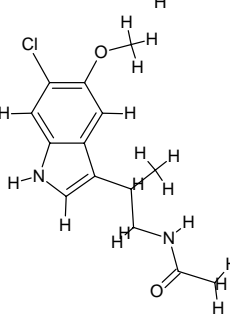
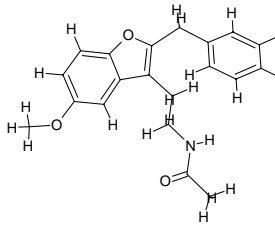
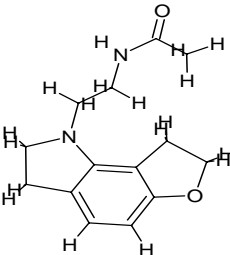
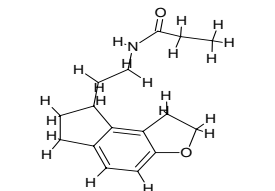
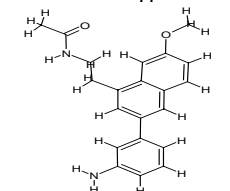
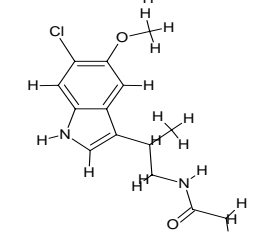
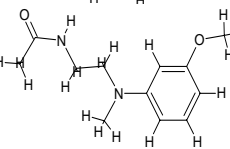
Compound name	Structure	pKd value (MT1 affinity)	Compound name	Structure	pKd value (MT2 affinity)
6-Cl-MLT		9.6	IJK7		10.3
CBOBNEA		9.3	Melatonin		9.3
Difluoroag o-melatine		10.5	MLT		9.9
Agomelatine		10.2	Ramelteon		10.0
EFPPEA		10.2	S24014		9.4

S24773		7.1	S26284		7.0
GR 196429		9.5	SD6		10.2
MLT		10.3	Tasimelteon		10.2
Melatonin		9.7			
Tasimelteon		9.5			

MT1 receptor agonist, the statistically suitable QSAR model was  $pK_d = 16.24793(\pm 0.93539) + 1.0924(\pm 0.18831) \text{ ALogP} - 0.11399(\pm 0.01383) \text{ apol} + 0.59876(\pm 0.16599) \text{ C2SP3} - 10.29435(\pm 2.81413)$

E3p with statistical information as SEE :0.37938,  $r^2$  :0.91973,  $r^2$  adjusted :0.88405, F :25.77921 (DF :4, 9) and Leave-One-Out (LOO) result was Q2 :0.79167, PRESS :3.3618, SDEP :0.49003 and in case

**Table 3. Detail list of test set molecule with affinity towards MT1 and MT2 receptor.**

Compound name	Structure	pKd value (MT1 affinity)	Compound name	Structure	pKd value (MT2 affinity)
SD6		10.9	5-HEAT		7.1
UCM 793		9.1	EFPEA		9.4
5-HEAT		7.8	LY 156735		10.4
S24014		7.5	GR 196429		9.7
Ramelteon		10.9	S24773		9.4
LY 156735		10.1	UCM 793		9.2

**Table 4. MODELability Index of total dataset for MT1 and MT2 receptor agonist.**

MT1	MT2
True positives: 16.0000	True positives: 6.0000
True negatives: 1.0000	True negatives: 5.0000
Total actives/toxic (H): 17.0000	Total actives/toxic (H): 11.0000
Total less_actives/less toxic (L): 3.0000	Total less_actives/lesstoxic (L): 7.0000
MODELability Index (MODI): 0.6373	MODELability Index (MODI): 0.6299
(Threshold value: MODI:0.65)	(Threshold value: MODI:0.65)

**Table 5. Internal validation parameters and LOO result of QSAR model for MT1 and MT2 agonist.**

MT1	MT2
Internal validation parameters: SEE :0.38624, r <sup>2</sup> :0.90291, r <sup>2</sup> adjusted :0.85976, F :20.92422 (DF :4, 9)	Internal validation parameters: SEE :0.33652, r <sup>2</sup> :0.92765, r <sup>2</sup> adjusted :0.8863, F :22.43744 (DF :4, 7)
Leave-One-Out (LOO) result: Q2 :0.75169, PRESS :3.43374, SDEP :0.49524	Leave-One-Out (LOO) result: Q2 :0.81401 PRESS :2.0378 SDEP :0.41209

**Table 6. Golbraikh and Tropsha acceptable model criteria's of QSAR Model for MT1 and MT2 receptor agonist.**

MT1	MT2
Q <sup>2</sup> : 0.75169 : Passed (Threshold value Q <sup>2</sup> >0.5)	Q <sup>2</sup> :0.81401Passed (Threshold value Q <sup>2</sup> >0.5)
r <sup>2</sup> : 0.81812 : Passed (Threshold value r <sup>2</sup> >0.6)	r <sup>2</sup> :0.97384Passed (Threshold value r <sup>2</sup> >0.6)
r <sup>0</sup> <sup>2</sup> -r <sup>0</sup> <sup>2</sup>   : 0.21411: Passed (Threshold value  r <sup>0</sup> <sup>2</sup> -r <sup>0</sup> <sup>2</sup>  <0.3)	[(r <sup>2</sup> -r <sup>0</sup> <sup>2</sup> )/r <sup>2</sup> ]:0.08048: Passed (Threshold value  r <sup>0</sup> <sup>2</sup> -r <sup>0</sup> <sup>2</sup>  <0.3)
k : 1.01023 k' : 0.98397	K:0.98543, k':1.01351
0.85<k<1.15; 0.85<k'<1.15	0.85<k<1.15; 0.85<k'<1.15
(r <sup>2</sup> -r <sup>0</sup> <sup>2</sup> )/r <sup>2</sup> : 0.09894; (r <sup>2</sup> -r <sup>0</sup> <sup>2</sup> )/r <sup>2</sup> : 0.60511	[(r <sup>2</sup> -r <sup>0</sup> <sup>2</sup> )/r <sup>2</sup> ]:0.08048; [(r <sup>2</sup> -r <sup>0</sup> <sup>2</sup> )/r <sup>2</sup> ]:0.08048
Threshold value: ((r <sup>2</sup> -r <sup>0</sup> <sup>2</sup> )/r <sup>2</sup> )<0.1	Threshold value: ((r <sup>2</sup> -r <sup>0</sup> <sup>2</sup> )/r <sup>2</sup> )<0.1
(r <sup>2</sup> -r <sup>0</sup> <sup>2</sup> )/r <sup>2</sup> <0.1	(r <sup>2</sup> -r <sup>0</sup> <sup>2</sup> )/r <sup>2</sup> <0.1

of MT2 receptor agonist most valid QSAR model was  $pK_d = 6.38692(+/-0.91098) + 0.87139(+/-0.20258) ALogP - 0.0351(+/-0.00542) AMR + 3.33079(+/-0.80377) SpMin6\_Bhm + 146.76208(+/-28.14492) VE2\_Dt$  with statistical information as SEE :0.33652, r<sup>2</sup> :0.92765, r<sup>2</sup> adjusted :0.8863, F :22.43744 (DF :4, 7) and Leave-One-Out (LOO) result was Q<sup>2</sup> :0.81401, PRESS :2.0378, SDEP :0.41209; all the information were reported in (Table 5). The outcomes from Golbraikh and Tropsha acceptable model criteria in case of MT1 agonist was Q<sup>2</sup>:0.79167, r<sup>2</sup> :0.88878, |r<sup>0</sup><sup>2</sup>-r<sup>0</sup><sup>2</sup>|:0.04633, k:1.03159, [(r<sup>2</sup>-r<sup>0</sup><sup>2</sup>)/r<sup>2</sup>]:0.01013, k':0.96695, [(r<sup>2</sup>-r<sup>0</sup><sup>2</sup>)/r<sup>2</sup>]:0.06226 and in case of MT2 receptor agonist was Q<sup>2</sup>:0.81401, r<sup>2</sup>:0.97384, |r<sup>0</sup><sup>2</sup>-r<sup>0</sup><sup>2</sup>|:0.1039, k:0.98543, [(r<sup>2</sup>-r<sup>0</sup><sup>2</sup>)/r<sup>2</sup>]:0.08048, k':1.01351, [(r<sup>2</sup>-r<sup>0</sup><sup>2</sup>)/r<sup>2</sup>]:0.18717 and all data were

put in (Table 6). The results from MLR Y Randomization test in case of MT1 receptor agonist was Average r: 0.5299; Average r<sup>2</sup>: 0.2997, cRp<sup>2</sup>: 0.7665 and in case of MT2 receptor agonist was Average r: 0.596281; Average r<sup>2</sup>: 0.3705, cRp<sup>2</sup>: 0.7284. after generation of 10 randomized model and cited in (Table 7). The outcomes from applicability domain analysis by Euclidean and Mahalanobis distance methods are quite satisfactory within the normal distribution range and reported at (Tables 8-9). As per the Euclidean Distance method; in case of MT1 receptor agonist in the Training set, GR128107 and melaotnin molecule were with highest and lowest Euclidean distance score and in case of test set SD6 and UCM-793 were responsive for highest score and lowest Euclidean score respectively; and in case of MT2 receptor agonist in the training set; S26284 and



Tasimelteon scored highest and lowest Euclidean distance and in case of test test; Lys15735 & 5-HEAT had lowest Euclidean distance. In case of Mahalanobis distance of MT1 receptor agonist, compound CBOBNEA with highest Mahalanobis distance of 3.12079 and melatonin with lowest Mahalanobis distance of 1.07321 among the training set compounds and compound SD6 with highest

distance score of 2.04131 and ramelteon with 2.04121 lowest distance score among the test compounds as well as in case of MT2 receptor agonist compound S26284 and melatonin with highest and lowest mahalanobis distance respectively present inside the Training set and compound 5-HEAT and EFPPEA with highest and lowest mahalanobis distance respectively present inside the

**Table 7. MLR Y Randomization parameter of QSAR model for MT1 and MT2 receptor agonist.**

Model	MT1			Model	MT2		
	R	R <sup>2</sup>	Q <sup>2</sup>		R	R <sup>2</sup>	Q <sup>2</sup>
Original	0.950215	0.902909	0.751692	Original	0.963145	0.927648	0.814013
Random 1	0.487802	0.23795	-0.6698	Random 1	0.502735	0.252742	-2.65212
Random 2	0.454858	0.206896	-1.78859	Random 2	0.551771	0.304451	-1.92808
Random 3	0.690764	0.477154	-1.28509	Random 3	0.847809	0.718781	-0.07028
Random 4	0.50136	0.251362	-1.08514	Random 4	0.649433	0.421763	-1.10612
Random 5	0.831797	0.691885	-0.37734	Random 5	0.483084	0.23337	-6.76295
Random 6	0.746983	0.557983	-0.98014	Random 6	0.675838	0.456757	-4.07822
Random 7	0.431915	0.186551	-2.44783	Random 7	0.618921	0.383064	-1.92944
Random 8	0.328784	0.108099	-0.55611	Random 8	0.488362	0.238498	-2.2368
Random 9	0.439431	0.193099	-0.87155	Random 9	0.714532	0.510555	-7.33119
Random 10	0.330369	0.109143	-0.77793	Random 10	0.430322	0.185177	-2.85435

Random models parameters:  
Average r: 0.5299; Average r<sup>2</sup>: 0.2997  
cRp<sup>2</sup>: 0.7665.

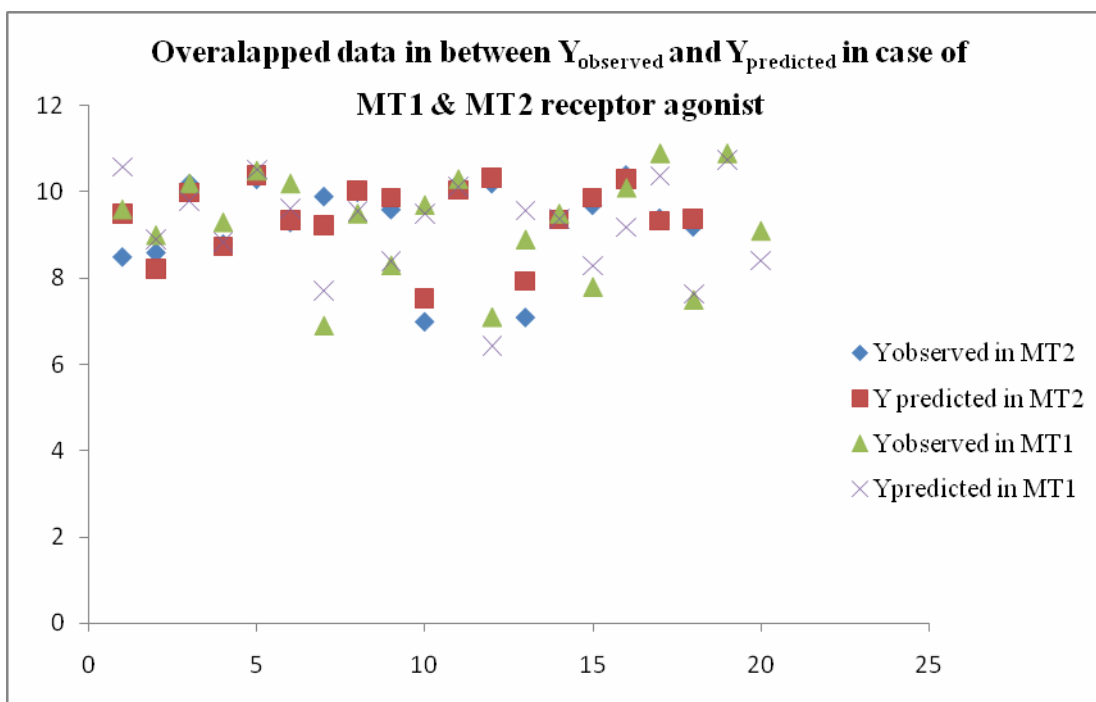
Random models parameters:  
Average r: 0.596281; Average r<sup>2</sup>: 0.3705  
cRp<sup>2</sup>: 0.7284.

**Table 8. Applicability domain analysis by Euclidean distance of QSAR model for MT1 and MT2 receptor agonist.**

For training set	MT1				MT2			
	Comp No	Euclidean Distance	Mean Distance	Norm mean Distance	Comp No	Euclidean Distance	Mean Distance	Norm mean Distance
	1	18.3742	1.4134	0.006461	1	186.906	16.9915	0.016965
	2	29.3515	2.25781	0.387112	2	205.036	18.6396	0.033326
	3	18.5399	1.42614	0.012205	3	257.69	23.4264	0.080841
	4	40.9301	3.14847	0.78861	4	170.522	15.502	0.00218
	5	20.9634	1.61257	0.096242	5	168.782	15.3439	0.00061
	6	18.6995	1.43842	0.01774	6	224.598	20.418	0.050978
	7	47.0262	3.6174	1	7	177.66	16.1509	0.008621
	8	18.477	1.42131	0.010026	8	190.315	17.3014	0.020042
	9	26.4992	2.0384	0.288202	9	168.287	15.2988	0.000163
	10	18.1879	1.39907	0	10	1276.25	116.023	1
	11	20.3548	1.56575	0.07514	11	172.601	15.691	0.004056
	12	20.1491	1.54993	0.068008	12	168.106	15.2824	0
	13	27.5724	2.12096	0.325419				
	14	24.9762	1.92125	0.235392				
For test set	1	11.0276	2.20551	0.449819	1	119.526	23.9053	0
	2	14.0678	2.81356	1	2	122.804	24.5608	0.007491
	3	10.8855	2.1771	0.424111	3	127.894	25.5789	0.019126
	4	11.3875	2.27749	0.514951	4	557.044	111.409	1
	5	8.87877	1.77575	0.060962	5	119.742	23.9483	0.000492
	6	8.5419	1.70838	0	6	121.972	24.3945	0.00559

**Table 9. Applicability domain analysis by Mahalanobis distance of QSAR model for MT1 and MT2 receptor agonist.**

	MT1		MT2	
	Comp no.	Maha distance	Comp no.	Maha distance
For training set	1	2.09035	1	3.00369
	2	2.39464	2	2.26994
	3	1.12236	3	1.12924
	4	3.12079	4	1.92141
	5	2.71822	5	1.97132
	6	1.74566	6	0.916055
	7	2.74391	7	2.35256
	8	1.54564	8	1.57018
	9	2.3087	9	2.33515
	10	1.07321	10	3.13976
	11	1.2857	11	1.75533
	12	1.69115	12	2.17734
	13	2.57867		
	14	2.42869		
For test set	Comp no.	Maha distance	Comp no.	Maha distance
	1	2.04126	1	2.0413
	2	2.04123	2	2.04078
	3	2.04121	3	2.04121
	4	2.04122	4	2.04121
	5	2.04131	5	2.04126
	6	2.04126	6	2.04093

Figure 1. Overlapped data in between  $Y_{\text{Observed}}$  pKd and  $Y_{\text{Predicted}}$  in case of MT1 and MT2 receptor agonist.

test set. Finally the data overlapping was done in between observed and predicted data and the results are reported at (Figure 1). In case of MT1 receptor agonist MODELability Index of the total dataset was 0.6373 with the threshold value 0.65 and in case of MT2 receptor agonist was 0.6299 which reflects that

prediction capacity of the developed QSAR model will have statistical parameters just above the acceptable limit  $r^2:0.6$  and  $q^2 0.5$ . The developed QSAR model for MT1 receptor agonist was  $\text{pKd} = 16.24793(+/-0.93539) + 1.0924(+/-0.18831) \text{ ALogP} - 0.11399(+/-0.01383) \text{ apol} + 0.59876(+/-0.16599)$

C2SP3 -10.29435(+/-2.81413) E3p which suggests that AlogP as Ghose-Crippen LogKow, apol as Sum of the atomic polarizabilities (including implicit hydrogens), C2SP3 as Singly bound carbon bound to two other carbons and E3p as 3rd component accessibility directional WHIM index / weighted by relative polarizabilities are the essential parameters to optimize to improvise the biological activity and in case of MT2 receptor agonist, pKd = 6.38692(+/-0.91098) +0.87139(+/-0.20258) ALogP -0.0351(+/-0.00542) AMR +3.33079(+/-0.80377) SpMin6\_Bhm +146.76208(+/-28.14492) VE2\_Dt which reflects that AlogP as Ghose-Crippen LogKow, AMR as Molar refractivity, SpMin6\_Bhm and VE2\_Dt as Average coefficient sum of the last eigenvector from detour matrix. In case of MT1 receptor agonist Ghose-Crippen LogKow and C2SP3 presence modify the activity profile towards positive direction and in case of MT2 receptor agonist; Ghose-Crippen LogKow and VE2\_Dt give positive response towards biological activity. Among the two QSAR model one parameter as ALogP is common, so we have to emphasize on the partition coefficient value along with molar refractivity, relative polarizability and 2D matrix descriptors.<sup>36,37</sup> The statistical information was SEE: 0.37938,  $r^2$ : 0.91973,  $r^2$  adjusted: 0.88405, F: 25.77921 (DF: 4, 9) and SEE: 0.33652,  $r^2$ : 0.92765,  $r^2$  adjusted: 0.8863, F: 22.43744 (DF: 4, 7) in case of MT1 and MT2 receptor agonist QSAR model reflects that all the parameters are in the acceptable range. In case of MT1 receptor agonist QSAR model: the difference between the  $r^2$  and  $r^2_{adj}$  value is 0.03523 which is less than 0.3 indicates that the number of descriptors involved in the QSAR model is acceptable and F test ratio value 25.77921 also reflects the greater predictability of the QSAR model. In the LOO result the difference between  $r^2$  and  $q^2$  (without scaling) is 0.07149 with accessible limit 0.3 which reflect the good predictability of the QSAR model. The  $rm^2(test)$  value for external validation is 0.80442 which must be greater than 0.5 as a good external predictability parameter. For a QSAR model can be considered acceptable if the values of  $r^2_m$  (overall) and  $r^2_p$  are equal to or above 0.5 (or at least near 0.5); in this developed QSAR

model  $r^2_m$  is 0.80442 and  $r^2_p$  is 0.83739. The results from Golbraikh and Tropsha acceptable model criteria's are  $Q^2$ :0.79167,  $r^2$  :0.88878,  $|r^2 - r'^2|$ :0.04633,  $k$ :1.03159, $[(r^2 - r'^2)/r^2]$ :0.01013,  $k'$ :0.96695, $[(r^2 - r'^2)/r'^2]$ :0.06226 and in case of MT2 receptor agonist was  $Q^2$ :0.81401, $r^2$ :0.97384, $|r^2 - r'^2|$ :0.1039, $k$ :0.98543, $[(r^2 - r'^2)/r^2]$ :0.08048,  $k'$ :1.01351, $[(r^2 - r'^2)/r'^2]$ :0.18717 which also shown that the predictability of the model is quite high and the Y Randomization test result also shown that  $cRp^2$ : 0.7665 which must be greater than 0.5 for good predictability. In case of MT2 receptor agonist QSAR model: the difference between the  $r^2$  and  $r^2_{adj}$  value is 0.04135 which is less than 0.3 indicates that the number of descriptors involved in the QSAR model is acceptable and F test ratio value 22.43744 also reflects the greater predictability of the QSAR model. In the LOO result the difference between  $r^2$  and  $q^2$  (without scaling) is 0.01228 with accessible limit 0.3 which reflect the good predictability of the QSAR model. The  $rm^2(test)$  value for external validation is 0.70121 which must be greater than 0.5 as a good external predictability parameter. For a QSAR model can be considered acceptable if the values of  $r^2_m$  (overall) and  $r^2_p$  are equal to or above 0.5 (or at least near 0.5); in this developed QSAR model  $r^2_m$  is 0.70121 and  $r^2_p$  is 0.88118.<sup>31</sup> The results from Golbraikh and Tropsha acceptable model criteria's are  $Q^2$ :0.79167,  $r^2$  :0.88878,  $|r^2 - r'^2|$ :0.04633,  $k$ :1.03159, $[(r^2 - r'^2)/r^2]$ :0.01013,  $k'$ :0.96695, $[(r^2 - r'^2)/r'^2]$ :0.06226 and in case of MT2 receptor agonist was  $Q^2$ :0.81401, $r^2$ :0.97384, $|r^2 - r'^2|$ :0.1039, $k$ :0.98543, $[(r^2 - r'^2)/r^2]$ :0.08048,  $k'$ :1.01351, $[(r^2 - r'^2)/r'^2]$ :0.18717 which also shown that the predictability of the model is quite high and the Y Randomization test result also shown that  $cRp^2$ : 0.7284 which must be greater than 0.5 for good predictability. As per the data from Applicability Domain analysis not a single molecule is outside the domain. Finally as per the overlapping data, it is quite clear that all the predicted data are inside the area of observed data points and also some data are purely overlapped.

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