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Computational Studies of Melatonin Analogues

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Abstract

Computational Studies of Melatonin Analogues

Melatonin (MLT, N-Acetyl-5-methoxytryptamine), a naturally occurring hormone produced by the pineal gland, plays a crucial role in the regulation of circadian rhythms. Melatonin supplements are utilized in treating various sleep disorders, but detrimental side effects currently discourages its use in space. Computer generated molecular models of MLT analogues were studied with the purpose of resolving the deficiencies within existing therapeutic agents by constructing an enhanced MLT analogue. The MT receptor binding data for each analogue was obtained from the literature and Sybyl 6.9 was used to perform 3-D quantitative structure-activity relationship (QSAR) studies on eight data sets, using the comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) methods. The predictive capabilities of each mathematical model were tested and structural changes, which most effectively increased the predicted activities for each set, were noted. The models consistently indicated that a steric increase of the methoxy group would improve the activity of MLT.

I. Introduction

3…2…1…Blast-off! With a deafening roar, a space shuttle is launched for its mission in space. Such an event captures the attention of thousands of people and their eyes become glued to the scene as they wait with breathless anticipation to see another successful space take-off. Outer space has been an intriguing unknown throughout the ages. Each space probe sent out and mission undertaken gives scientists new pieces of data that serve to increase their knowledge of the vast expanse that we label outer space.

However, space exploration is constrained by the limited amount of time that astronauts are able to spend in space during one space mission. One reason that longer space missions are currently not practical is that astronauts have difficulty sleeping in space. When they do sleep, it is not a deep, restful sleep. Lack of sleep, in addition to a reduction in the total amount of time slept, is a source of concern in space and rightfully so. It is a well-known fact that adequate sleep is essential for optimal mental and physical performance, both of which are high priorities on a space mission. Fatigue is a serious problem because it affects performance by causing increased irritability, diminished concentration, slower reaction time and an increased risk of accidents.

Melatonin and its derivatives have been proposed as a potential solution to help alleviate this major health problem. A naturally occurring neurohormone, melatonin (N-acetyl-5-methosyindolamine) is produced by the pineal gland.[1-17] The synthesis and release of melatonin is triggered by darkness and suppressed by light.[4] Melatonin has several functions, including control of the function of the adrenocortical and thyroid glands, testes, and ovaries, oxidant/antioxidant regulation, free radical scavenging, thermoregulation, and support of the immune response against viral infections.[18-19] Nevertheless, the most

important property of melatonin, in regards to this research project, is the sleep-inducing effect it has on the body.[10] Melatonin plays a crucial role in the daily regulation of circadian rhythms.[14] Our body's master clock naturally produces cycles that are slightly longer than earth's day.[20] A daily adjustment is necessary to prevent our body's biological night and day from getting out of sync with the environment. On earth, it simply resets itself after exposure to the brightness of daytime sunlight.[20] However, in space, astronauts are subjected to irregular light and dark hours which interfere with their bodies' biological clocks.[20] Consequently, astronauts sleep poorly in space, and when they do sleep, it is not a refreshing sleep.

Melatonin supplements are presently used to minimize jet-lag, regulate delayed sleep-phase syndrome, control seasonal depression, and also to treat disorders resulting from shift work disturbances.[2] But its use in space is currently prevented on account of its short biological half-life, lack of selectivity, poor oral bioavailability, and detrimental side-effects such as drowsiness, headaches, stomach cramps, dizziness, irritability, depression, and slower reaction times.[18, 21]

Through previous research, it has been discovered that the actions of melatonin are the consequence of high affinity bonding receptors located in the brain, kidneys, adipocytes, retina, blood vessels, and gastrointestinal tract.[7] Three distinct melatonin receptor subtypes, classified as MT_1, MT_2, and MT_3, have been identified.[6] The MT_1 receptor is localized in the suprachiasmatic nucleus (SCN) of the hypothalamus and the MT_2 receptor is found in the SCN and retina.[3] MT_1 and MT_2 have both been found in mammal tissues and are both G-protein-coupled receptors; MT_3 has been identified as being a homologue of the human quinine reductase 2.[12] Each of the receptors performs a

different function. MT_1 is believed to control melatonin's circadian and reproductive actions, while MT_2 modulates circadian rhythms and visual functions.[5] The function of MT_3 has not been as thoroughly investigated, but it is thought to be involved with detoxifying processes.[12] Although previous studies have provided insights into the molecular requirements of melatonin's specific interaction with MT_1 and MT_2 receptors, the results have not led to a solution for sleep-related problems in space. The goal is a new, effective melatonin analogue able to activate all the necessary physiological processes required for a healthy, wakeful state in astronauts, with minimal side effects.

In this study, molecular models were computer-generated for melatonin with the purpose of resolving the deficiencies of existing therapeutic agents for sleep disorders and designing measures against the harmful effects resulting from insufficient sleep of astronauts during space missions. Operating under the assumption that changes in biological activities are related to the physicochemical properties of the compound, the mathematical nature of the relationship was examined. The specific goals of this project were to: 1) Create databases of melatonin analogues containing indicators of biological and physicochemical properties by retrieving data from the literature. 2) Derive mathematical models relating to biological activity and changes in molecular properties using Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA). 3) Test the predictive capabilities of the mathematical models, with the intent that, after careful analysis of these models, modifications that would enhance the activity of melatonin could be suggested.

II. Materials and Methods

This research was performed using Silicon Graphics Inc. (SGI) work stations, as well as Dell 650n work stations, to run Sybyl 6.9 (TRIPOS Associates Inc., St. Louis, MO), a Linux-based molecular modeling program. In order to discover new insights into the structural requirements for melatonin's biological activity, 3-D quantitative structure-activity relationships (QSAR) were determined using the comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) methods. These methods are useful because they generate 3-D models that graphically represent the structure-activity relationship among a given series of compounds. Both of these QSAR methods are based on the assumption that changes in binding affinities of compounds are related to changes in molecular properties which are represented by fields.[22] The two methods differ only in the implementation of the fields. The goal of this molecular modeling research was to first gain an understanding of the fundamental relationship between the chemical and physical properties of a molecule, its chemical structure, and the 3-D structure it adopts. By relating these properties to the biological function of a molecule, this new understanding was used to logically design molecules of altered, or enhanced, function.

For this research project, information from the literature was gathered on eight unique data sets of melatonin analogues. The names and structures used to generate the QSARs are shown in Figures 1-8. Each compound was represented by a single molecular model. Based on the information in the literature, models were manually sketched and minimized using the standard Tripos force field.[23] The purpose of minimization is to reduce the internal strain energy of a compound by adjusting its bond angles and torsions.

Once minimized, the Gasteiger-Huckel atomic partial charges of each compound were computed. After these initial steps were completed, MOPAC, which stands for molecular orbital package, was run on each compound.[23] MOPAC is a general-purpose semiempirical molecular orbital package for the study of molecular structures. It obtains molecular orbitals, as well as the heat of formation and its derivatives, for a compound; it then uses these results for the calculations. The two functions of MOPAC are to apply an external electric field and to optimize the geometry of a compound. MOPAC starts with the approximation of the desired geometry previously found by minimization and, by calculating the forces acting on the system, changes the geometry of a compound until the energy is at a minimum. MOPAC-determined atomic charges and the new geometries were applied to the compounds. The MOPAC setup was as follows: Method – AM1, State – singlet, Net Charge – 0 u.e., Time Limit – 7200 s, Convergence – Normal and Precise, Optimization – Full, and Keyword – mmok. AM1 (Austin Model 1) is parameterized to be especially useful for hydrocarbons and other polar structures that have appreciable hydrogen bonding interactions. The singlet setting constrains the choice of energy states to singlets only. All of the compounds studied had a net charge of 0; however, when the system being studied is an ion, a charge must be supplied. The full optimization setting optimizes all bonds, angles, and torsion angles. The MOPAC keyword mmok uses molecular mechanics correction to carbon, oxygen, nitrogen, and hydrogen bonds.

Next, the compounds in each database were aligned with a chosen reference compound. The idea underlying CoMFA and CoMSIA is that differences in a target property are related to the differences in the shapes of the non-covalent fields surrounding the tested molecules. The magnitudes of each compound's steric and electrostatic fields are

sampled at regular intervals throughout a defined region. The positioning of a molecular model with a fixed lattice is the most important input variable because the relative interaction energies depend strongly on relative molecular positions.[25] Without close alignment, accurate comparisons of their molecular properties cannot be made. If, after the initial run, the results were not satisfactory, then closer alignment was achieved by twisting or turning the side chains of each individual compound. After modification, each compound was manually realigned to the reference compound. MOPAC was rerun on these modified compounds, but only the atomic charges were applied the second time. Finally, the aligned compounds containing MOPAC charges were put into a database.

For each database, a CoMFA spreadsheet and a CoMSIA spreadsheet were created for each data set of property variables. The experimentally determined biological activities, which were obtained from the literature, were entered in the first column of the spreadsheets. CoMFA and CoMSIA columns were then generated; the settings were left on default. The CoMFA setup was as follows: CoMFA Field Class – Tripos Standard, Field Values – Type(s): Both, Dielectric: Distance, Smoothing: None, Drop Electrostatics: Within Steric Cutoff for Each Row, Cutoffs – Steric: 30.0 kcal/mol, Electrostatic: 30.0 kcal/mol, Transition: Smooth, and Region: Create Automatically. The CoMSIA setup was as follows: Field Parameters – Attenuation Factor: 0.3 and Region: Create Automatically. Each CoMFA/CoMSIA row in the column corresponds directly to the field of the corresponding molecule. CoMFA generates a column containing information about sterics, or bulk, a column containing information about electrostatics, or charge, and a column containing information on both sterics and electrostatics. CoMSIA is slightly different and generates a column containing steric and electrostatic field information, a hydrogen donor

and acceptor column, and a hydrophobic column, which indicates where interactions with water would be negative or favorable.[24] Both of these methods use probe atoms to analyze the shapes of the fields surrounding the tested compounds to find similarities and differences among the compounds of interest which can be related to biological activity.

QSAR Partial Least Squares (PLS) was run on each spreadsheet using the CoMFA or CoMSIA information. Although the rationale behind computing CoMFA and CoMSIA fields is different, they are technically of equivalent form, so the subsequent PLS analyses are identically performed.[25] Column One, containing the biological activities, was designated as being the dependent column. The PLS method in Sybyl 6.9 was used to extract a QSAR relationship from the data tables; this method attempts to determine the relationship between the CoMFA/CoMSIA values and the known experimental activity of each molecule. Least Squares, or linear regression, is commonly used to draw the best straight line between many data points. Partial Least Squares is the same idea, but it involves fitting many x's, all the molecular properties, to one y, which is the biological activity.[24] The ultimate goal of QSAR analyses is the prediction of biological activities of molecules not yet synthesized.

The first step in QSAR PLS was conducting a Leave-One-Out cross-validation run. The number of components was set to 6; these were selected by the standard PLS algorithm and then cross-validated in order of their correlation with the dependent variable.[25] During this run, the computer leaves out one compound and uses a model created by the remaining compounds to predict the activity of the left-out compound. It then compares the predicted activity to the known activity to see how accurate the prediction was. Cross-validation evaluates a model not by how well it fits data, but by how

well it predicts data.[24] When finished, the optimum number of components for the best model, the model which had the smallest difference between the predicted and actual dependent property values, and the corresponding correlation coefficient, or Q^2 value, were displayed and recorded. Q^2 indicates how well the model was able to predict the activities of the left out compounds. Q^2 values range from 0 to plus or minus 1. A Q^2 of plus 1 would indicate a model with perfect positive correlation, meaning that high and low field values are observed at corresponding spatial locations, while a Q^2 of 0 would indicate a model with dissimilar fields and therefore lacking any type of predictive power.[26] Negative values signify that the biological property values are better estimated by the mean of all values than by the model under consideration.

Next, a No Validation PLS run was conducted using the optimum number of components as previously determined by the cross-validation analysis. The No Validation PLS runs reported explanatory R^2 values, standard error of estimate, F values, and the probability of R^2 equaling 0. R^2 gives the fraction of the variance that is explained by the regression line; it is the correlation coefficient that indicates how accurately the model containing all the compounds was able to predict the activity of the compounds. The more scattered the data points, the lower R^2 will be. Just like Q^2, the R^2 values also range from 0 to plus or minus 1. The residuals are one way to quantify the error in the estimate for individual values calculated by the regression equation in a data set. The standard error of estimate for the residuals is calculated by taking the root-mean-square of the residuals. The F value indicates the probability of a true relationship, or the significance level of a multiple linear regression model; it is the ratio between explained and unexplained variance for a given number of degrees of freedom. The larger the F value, the greater the

probability that the QSAR equation is significant. All of these numbers were recorded for each of the different analyses.

Once a PLS analysis has been completed, the QSAR results are visually represented by a three-dimensional model using a specific coloring scheme to indicate the different fields and a scatter plot showing the residuals between the experimental activities and the predicted activities. The visualization of the results of the comparative analyses in terms of field contributions was performed by means of computer graphics enclosing the volumes above and below particular field values with colored polyhedra.[23] Evaluation of the field values indicates in which spatial areas significant variations among the compounds occur that correlate with the dependent property variable. In general, the colored polyhedra in each map surround all lattice points where the QSAR strongly associates changes in field values with changes in biological activity, indicating areas where appropriate alterations of the field values will enhance or reduce the value of the dependent property variable. Color is used to code the direction and magnitude of these different interactions; CoMFA and CoMSIA models both use the same coloring scheme for steric and electrostatic fields. Green polyhedra on a model indicate where increasing bulk would lead to a favorable change in a compound's activity (binding is expected to increase with increases in steric bulk), while yellow polyhedra indicate where bulk is unfavorable. Red polyhedra on a model indicate where increasing charge would lead to a favorable change in a compounds activity, while blue polyhedra indicate where charge is unfavorable. The colored-coded polyhedra are particularly useful because they allow the QSAR maps to easily be interpreted.

After a model has been created, the next step is to refine it. The goal of refining a model is to maximize the Q^2 and R^2 values. To do this, major outliers, or compounds with large residual values, were deleted. A residual is the difference between the actual and predicted activities of a compound. A large residual value indicates that a compound is not modeled well by the QSAR and theory predicts that that the expected prediction error for such compounds is large. A good method for outlier elimination should ultimately decrease the root mean squared error of prediction. However, as few compounds as possible should be eliminated. Elimination of prediction outliers leads to substantial improvement of prediction errors if extreme outliers are present, but improvement is only modest for typical QSAR data sets containing similar compounds. Once major outliers were removed, Partial Least Squares QSAR was run again using the modified spreadsheet, generating a new and improved model.

The two uses for QSAR 3-D models are to enable the design of new compounds based on examination of the displays of the CoMFA and CoMSIA results and also to be able to predict the target property values of the newly designed compounds. The most important characteristic of QSAR models is their predictive power. The predictive power of a model indicates how reliable the model is and how well it predicts the activities of unknown compounds. To test this, a compound, or several compounds, with a high activity were chosen from each dataset and modified according to the information given by the model. All of the previously mentioned guidelines were used in constructing and aligning them. These new compounds were then added to the corresponding spreadsheet and the biological activities of each were predicted using the patterns established from the original set of compounds. It was thus determined whether or not the modifications affected the

activity in the way that the model indicated. Then, an attempt was made to integrate the information learned from each of the models in order to identify the key areas for melatonin binding activity and to also make suggestions about structural changes in these specific areas that would enhance melatonin's biological activity, as well as decrease its side effects.

III. Results & Discussion

During this research project, eight different sets of melatonin analogues were studied. The compounds outlined in Tables 1–8 were submitted to comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) in order to devise quantitative models for identifying relationships between structural features and biological activity. The CoMFA and CoMSIA results for each data set, including the predicted activities and residuals, are reported in Tables 1A – 8A.

Set 1

Set 1 is composed of sixteen 2-substituted indole compounds (Table 1).[9] This set contained biological activity information about the MT_1, MT_2, pRA_1, and pRA_2 binding affinities for the indolic analogues. CoMFA/CoMSIA was run on this set of compounds four times, using each set of binding affinities as the dependent variable once. QSAR 3-D models were generated for each CoMFA/CoMSIA run and the results are listed in Table 1A.

Although four different sets of numbers were used as the dependent variables, the 3-D models show nearly identical regions which affected the activity. The maps of steric activities indicate that increasing the bulk at the 2-position will enhance activity (Set 1 figures). They also signify that increasing the bulk at the end of the indolic chain will lead

to enhanced activity; however, the models also indicate that past a certain point, bulk will become detrimental to the activity of a compound. Electrostatically, the models show a region between the indolic chain and the 2-position chain where occupancy of an electronegative group enhances activity. The models containing information about both sterics and electrostatics reinforce the findings of the separate steric and electrostatic models; the field contributions can be seen in the Set 1 models.

Test compounds were modified according to the insight gained by the 3-D graphs and the compounds with their predicted activities are listed in Tables 1a – 1h. The most successfully modified compounds, according to predicted activities, were those that were modified by increasing the charge, and correspondingly the bulk, of the 2-substituted side chain in the region indicated by the models. Slightly increasing the bulk of the methoxy group to an ethoxy group was also favorable.

Set 2

Set 2 consists of a series of sixteen substituted oxygenated heterocycles and thio-analogues of melatonin (Table 2).[13] The ovine pars tuberalis membrane binding affinities for these melatonin analogues was used as the dependent variable for the CoMFA and CoMSIA analyses; the QSAR results for the models built by PLS analysis are reported in Table 2A.

The CoMFA and CoMSIA analyses indicated similar regions surrounding the side chain, close to the ring attachment, where occupancy with sterically demanding groups enhances activity (Set 2 figures). The 3-D maps containing electrostatic property information also show areas, at the beginning and towards the end, on the side chain where increased electronegative groups enhance activity. A region to be avoided by

electronegative groups is indicated at the end of the methoxy group, while a yellow polyhedron to the left of the oxygen on the methoxy group shows a region to be avoided by sterically demanding groups.

Test compounds were built in accordance with the information displayed by the CoMFA and CoMSIA 3-D maps and the activities for each were predicted (Tables 2a – 2c). The initial activities of the substituted oxygenated heterocycles and thio-analogues of melatonin were all lower than that of unmodified melatonin and although the predicted activities increased for the modified test compounds, they still did not surpass the binding affinity of melatonin. Increasing the charge towards the end of the side chain and increasing the bulk towards the beginning of the side chain led to the most successfully modified compounds according to predicted activities.

Set 3

Set 3 contains a series of forty-six naphthalenic analogues of melatonin (Table 3).[21] The original series was composed of fifty derivatives, but binding studies only provided useful 1-state (site) model receptor binding information for forty-six of the compounds.[21] The compounds were analyzed as a global set, and then three subsets were analyzed individually. The three subsets were composed of compounds 10-38, 10-47, and 48-60. Comparable results were obtained for all four runs; the QSAR results for the models built by PLS analysis using ovine pars tuberalis membrane binding affinities as the dependent variable are reported in Table 3A.

The CoMFA and CoMSIA 3-D maps for all four runs had a red region surrounding the oxygen of the methoxy group, signifying its importance in binding activity (Set 3 figures). Sterically, green polyhedra indicated that increasing the length of the methoxy

group would be beneficial. While the 3-D graphs showed that adding bulk to the side chain can increase binding affinity, predicted activities indicate that additional bulk is only beneficial to a certain point and then it becomes detrimental. Key areas for adding electronegative elements to the side chain were also identified.

Test compounds were modified according to the insight gained by the 3-D graphs and the compounds with their predicted activities are listed in Tables 3a – 3e. The test compounds with the most favorable increase in predicted activities were those modified by changing the methoxy group to either an ethoxy or isopropoxy group.

Set 4

Set 4 includes a series of twenty-seven benzocycloalkene derivatives using indan, tetraline, and benzocycloheptene as the base structures (Table 4).[5] Human MT_1 and hamster MT_3 binding affinities were used as the dependent variables for CoMFA and CoMSIA analyses (Table 4A).[5]

The CoMFA and CoMSIA steric analyses using the human MT_1 binding affinities indicate that increasing the length of the methoxy chain will result in a favorable increase in binding affinity. The MT_1 3-D maps also show regions along the side chain where increasing the sterics and the charge will enhance binding affinity (Set 4 MT_1 figures). However, they indicate that increasing the length of the side chain will result in a loss of binding affinity.

The hamster MT_3 CoMSIA and CoMFA results are very similar to the MT_1 maps. The MT_3 3-D maps also indicate that increasing the length of the methoxy chain will result in increased binding affinity (Set 4 MT_3 figures). Additionally, a green polyhedron on the CoMSIA 3-D map indicates that increasing the bulk at the indolic nitrogen would be

beneficial. The electrostatic map and the map containing both static and electrostatic MT_3 information show that an increase of charge in a region around the ester group will result in a favorable increase in binding affinity.

Test compounds were built in an attempt to maximize binding potential based on the CoMFA/CoMSIA indicators and the predicted activities are reported in Tables 4a – 4c. The most successfully modified compounds, according to the predicted activities for both MT_1 and MT_3, were those modified by changing the methoxy group to either an ethoxy or propoxy group. The MT_3 test compounds with bulk added to the indolic nitrogen had favorable increases in predicted binding affinity as well.

Set 5

Set 5 is made up of a series of thirty-five N-naphthylethyl amide derivatives (Table 5).[18] These compounds were previously synthesized and evaluated as melatonin receptor ligands in the hope of designing new compounds which would be metabolically more stable than melatonin.[18] Set 5 was evaluated as a global set and then two subsets, each containing compounds built from mutual base structures, were analyzed. The ovine pars tuberalis membrane binding affinities were used as the dependent variables, and the QSAR results for the models created by PLS analysis are listed in Table 5A.

The CoMFA and CoMSIA analyses of these melatonin analogues containing steric information indicated two main areas where increasing the bulk has a favorable effect on binding affinity (Set 5 figures). These two regions are found at the end of the methoxy group and the end of the side chain. The CoMSIA map created using all of the compounds and the steric CoMFA map created using compounds 95-105 both showed that increasing bulk at the nitrogen on the side chain enhanced binding affinity. Electrostatic

polyhedra indicated the importance of the electronegative oxygen in the methoxy group and the indolic nitrogen; several regions along the side chain were also identified as favorable locations for increased electronegative atoms, particularly toward the end of the chain.

The areas targeted for building modified test compounds, and the ones that gave the best results, occur toward the end of the side chain and at the methoxy group. The predicted activities for these compounds are reported in Tables 5a – 5f.

Set 6

Set 6 includes thirty-nine melatonin agonists and antagonists derived from 6H-isoindolo[2,1-a]indoles, 5,6-dihydroindolo[2,1-a]isoquinolines, and 6,7-dihydro-5H-benzo[c]azepino[2,1-a]indoles (Table 6_i – 6_{iii}).[10] The 6H-isoindolo[2,1-a]indole, 5,6-dihydroindolo[2,1-a]isoquinoline, and 6,7-dihydro-5H-benzo[c]azepino[2,1-a]indole analogue groups were first analyzed separately and then as a global set. The QSAR results for the best models built by PLS analysis using Human MT_1 and MT_2 binding affinities as the dependent variables are listed in Table 6A. The Table 6_{iii} subset did not yield satisfactory QSAR results, so it was excluded.

Green polyhedra shown by the CoMFA and CoMSIA results for the MT_1 binding affinity analyses indicated that increasing the bulk of the methoxy group would lead to a favorable increase in activity; however, the close proximity of a yellow polyhedron limits how far the methoxy group can be extended before increased sterics would lead to unfavorable changes in binding affinity (Set 6 figures). Another key steric region for MT_1 binding lies to the right of the side chain, where increased bulk is shown to be favorable. Red polyhedra surrounding the methoxy group indicate the importance of the

electronegative oxygen atom to binding strength, and other regions along the side chain indicate where activity may be enhanced by increasing electronegativity in those areas. Several blue regions seen on the MT_1 3-D activity maps illustrate where electronegative atoms need to be avoided if binding affinity is to be maximized.

Like the MT_1 analyses, MT_2 analyses reveal almost identical regions of steric and electrostatic importance around the methoxy group. The MT_2 CoMSIA and CoMFA 3-D maps generated from the global set of compounds contain green polyhedra to the right of the side chain in the same location as the MT_1 maps. However, unlike the MT_1 maps, multiple blue and yellow polyhedra on the MT_2 maps depict many more areas where care must be taken to avoid excess bulk and charge.

Test compounds were built in an attempt to maximize binding potential based on the CoMFA/CoMSIA indicators and the predicted activities are reported in Tables 6a – 6l. The most successfully modified compounds, according to the predicted activities, were those altered by increasing the electronegativity of the R substituent group.

Set 7

Set 7 is composed of fifty-six melatonin agonists and antagonists derived from tetrahydrocyclopent[b]indoles, tetrahydrocarbazoles, and hexahydrocyclohept[b]indoles (Table 7).[10] Analysis of the individual subsets did not yield satisfactory results, so the compounds shown in the four tables were analyzed together as a global set. Table 7A lists the QSAR results for the models created by PLS analysis.

Green polyhedra on the 3-D maps containing steric property information indicate that increasing the bulk of the methoxy group will lead to an increase in activity; they also show that increasing the length of the side chain, up to a certain point indicated by a

yellow polyhedron, will increase activity (Set 7 figures). The CoMFA map containing both electrostatics and sterics indicates that increasing bulk on the indolic nitrogen will have a favorable effect. Electrostatically, red polyhedra indicate the importance of the oxygen in the methoxy chain, as well as two regions on the side chain where increased electronegativity is favorable.

Test compounds were built in an attempt to maximize binding potential based on the CoMFA/CoMSIA indicators, and the predicted activities are reported in Tables 7a – 7b. Adding increased bulk to the indolic nitrogen and changing the methoxy group to an ethoxy group led to increased predicted activities of the modified compounds.

Set 8

Set 8 contains thirty-nine benzoxazole derivatives, which are reported in Table 13.[2] The benzoxazole melatonin analogues were chosen because they possess high binding affinity toward human MT_1 and MT_2 receptor subtypes, comparable to or higher than the affinity of melatonin itself.[2] The QSAR results for the best models built by PLS analysis of the global set using Human MT_1 and MT_2 binding affinities as the dependent variables are listed in Table 8A.

Although the MT_2 3-D maps contain more colored polyhedra indicating areas of importance, the CoMFA and CoMSIA analyses for both human MT_1 binding affinities and MT_2 binding affinities yielded very similar results. Green polyhedra indicate that increasing the bulk on the end of the R chain will have a favorable effect; the CoMFA analyses also show that increasing the bulk on the side of the R_1 chain toward the end should lead to an increase in binding affinity. Electrostatically, red polyhedra indicate the importance of the double-bonded oxygen on the R_1 chain; in addition, the 3-D maps show

an area on the R chain where increasing the electronegativity is favorable for binding interaction.

Test compounds were built in an attempt to maximize binding affinity based on the CoMFA/CoMSIA indicators and the predicted activities are reported in Tables 8a – 8d. Increasing the electronegativity of an atom attached to the ring or increasing the sterics of the R_1 substituent led to slightly higher predicted activities.

IV. Conclusions

The CoMFA and CoMSIA methodology was applied to many structurally different melatonin analogues in order to derive 3-D QSAR models correlating the differences in biological activity with the variation of the 3-D fields within selected series of compounds. For each set of compounds in which the melatonin analogues were grouped, a 3-D QSAR model with reasonably good predictive and descriptive power was obtained. The models gave useful information about the structure-activity relationships within the eight data sets.

According to these models, the methoxy group on melatonin is consistently a critical component with respect to the strength of its binding affinity. Increasing the sterics in this region, such as altering the methoxy group to a larger ethoxy group is predicted to correspond with increased activity. The side chain also plays an important role in binding affinity; the QSAR results indicate that proper modification of the steric and electrostatic properties is key for optimal binding potential. Several of these melatonin analogue sets already possess promising melatonin receptor binding affinity initially and, if modified according to the QSAR results, may prove to be even more powerful melatonin agonists.

The models obtained in this study are reasonably predictive and provide useful structural information, which can be used to suggest where and how known structures can

be modified in order to develop compounds with higher affinity. Additional 3-D quantitative structure-activity studies may lead to a better understanding of the molecular features required for a compound to exhibit increased melatonergic binding affinity. However, further investigation by synthesizing and testing the activity of compounds structurally modified in areas according to the information given by the models is needed to confirm the reliability of these models and the extent of their predictability.

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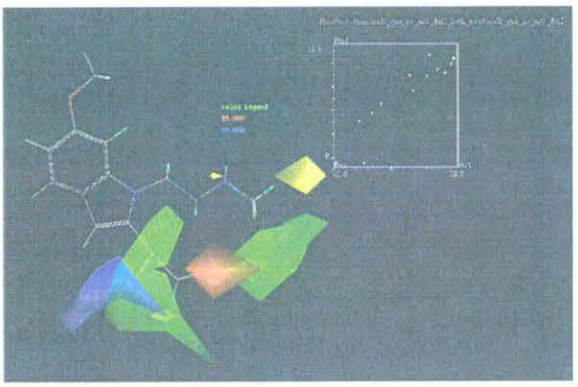
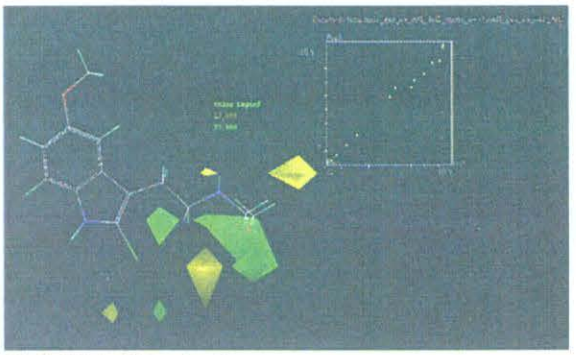
Set 1 Human MT_1 Binding 3-D QSAR Maps



CoMFA (Both)



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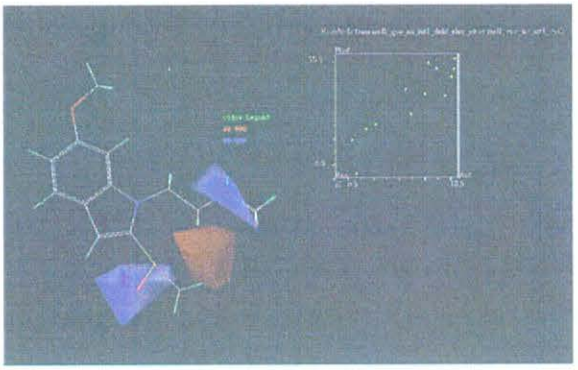

CoMFA (Electrostatics)

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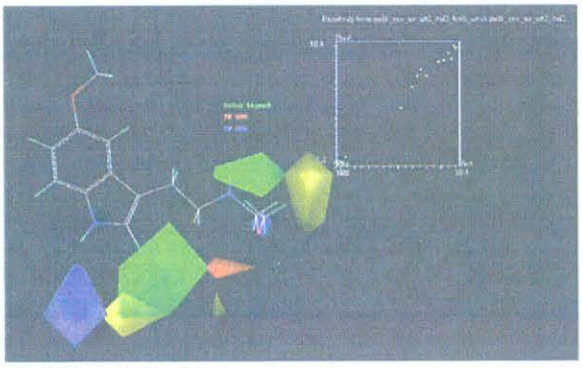

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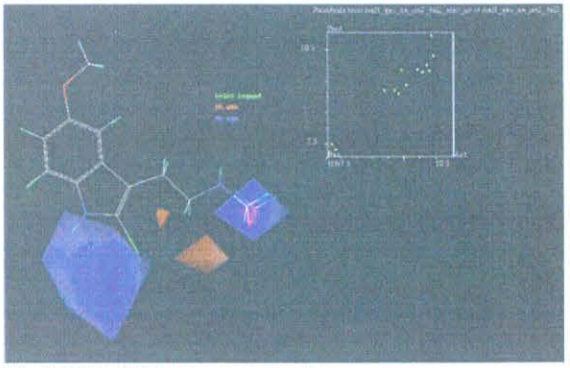

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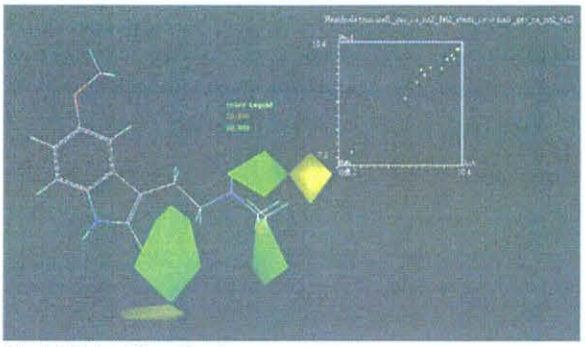

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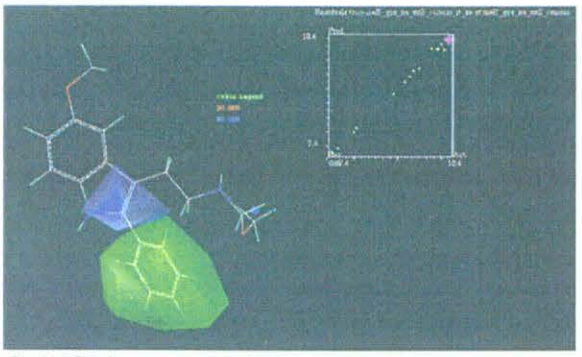
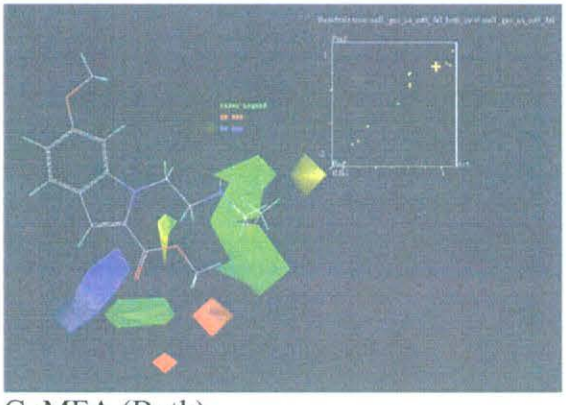


CoMSIA

Set 1 pRA_1 Binding 3-D QSAR Maps



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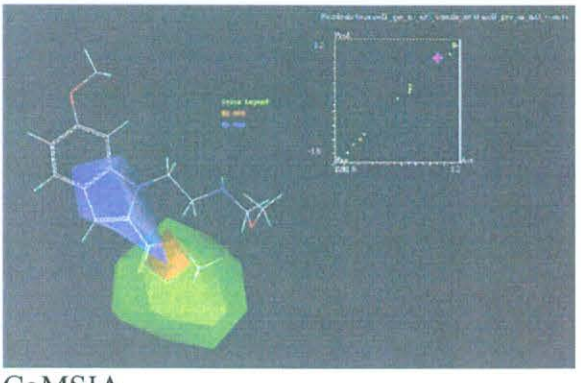

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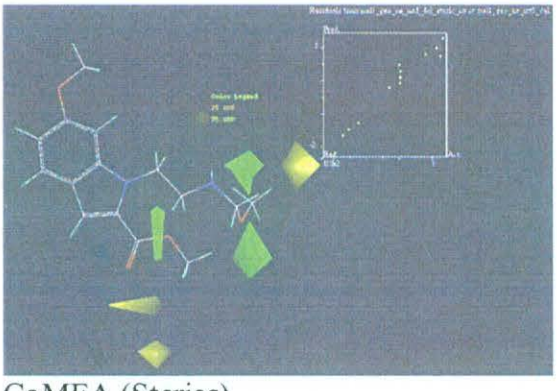

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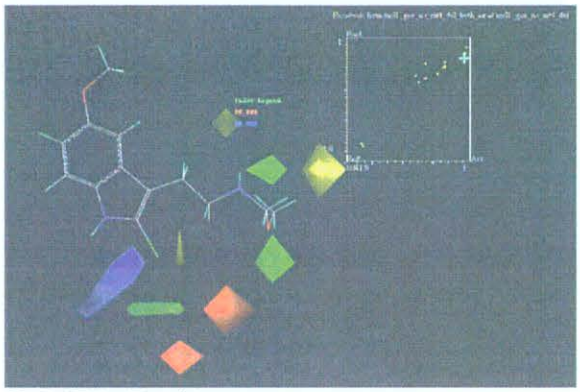

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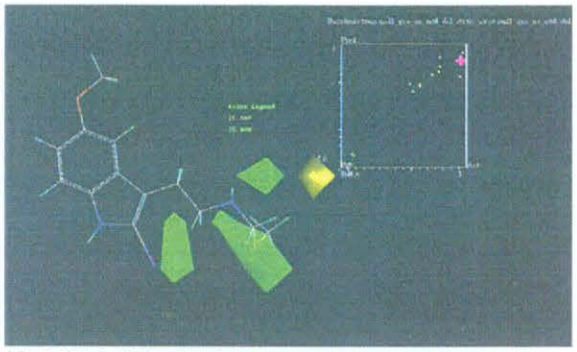

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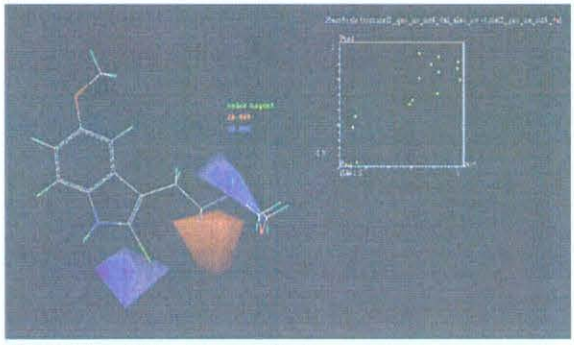

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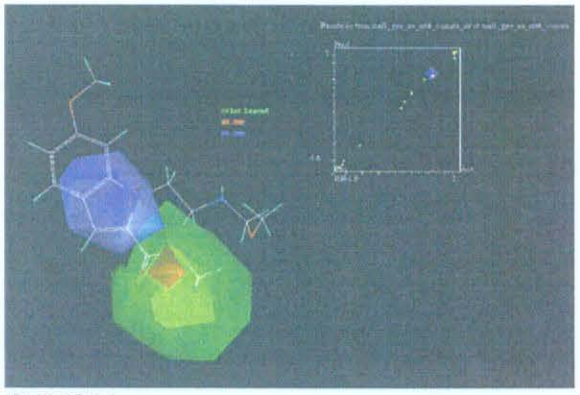

CoMSIA

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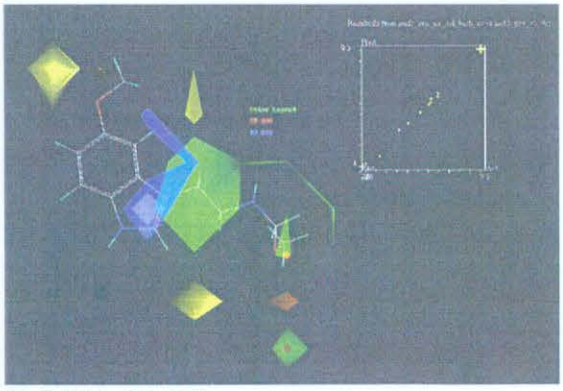

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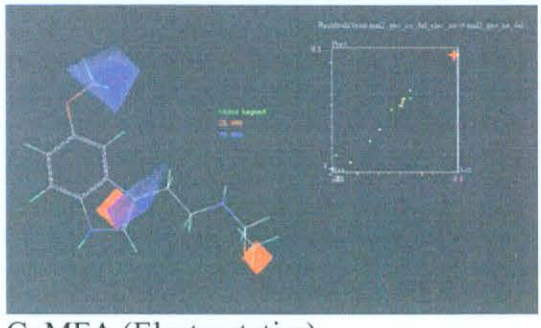

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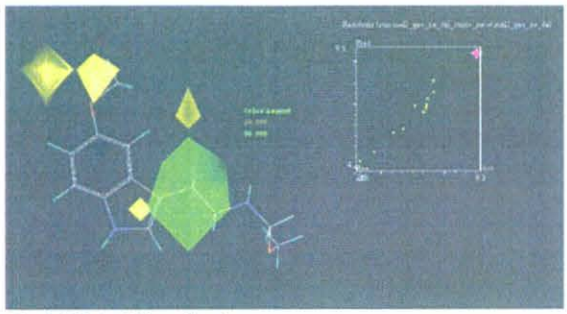
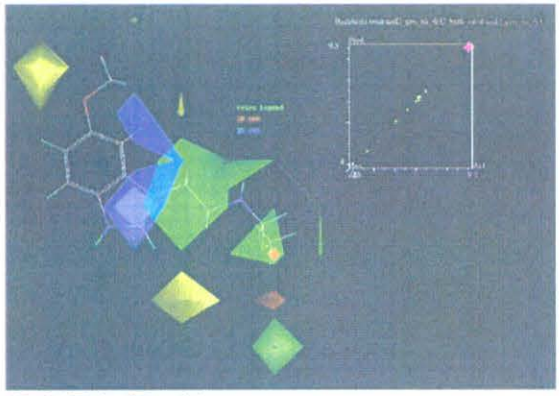


CoMFA (Sterics)

Set 2 Ovine Pars Tuberalis Membrane Binding CoMFA[c] and CoMSIA[d] 3-D QSAR Maps



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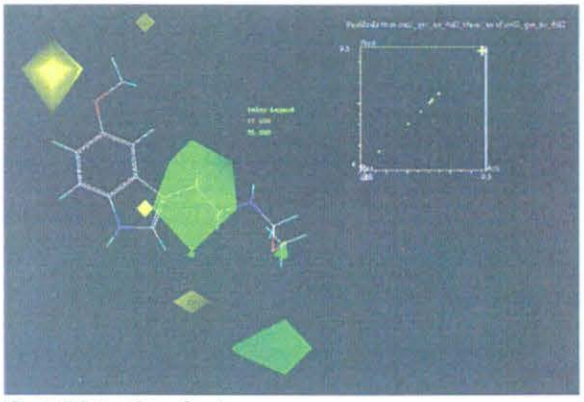

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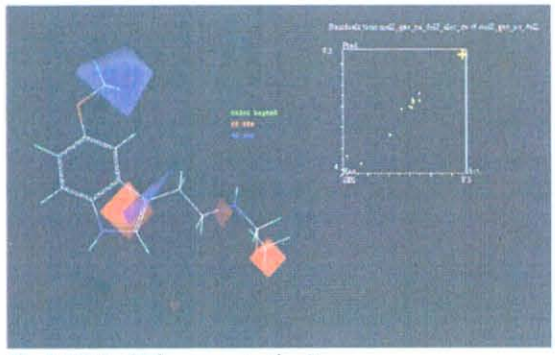

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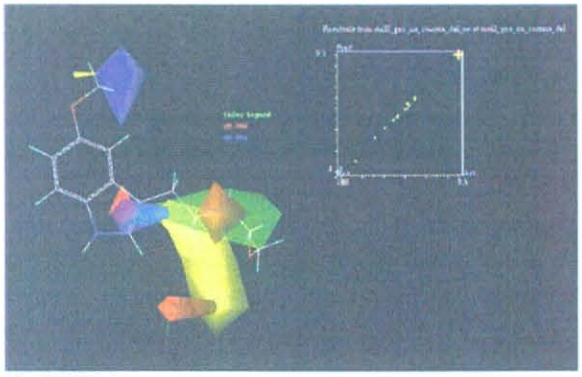
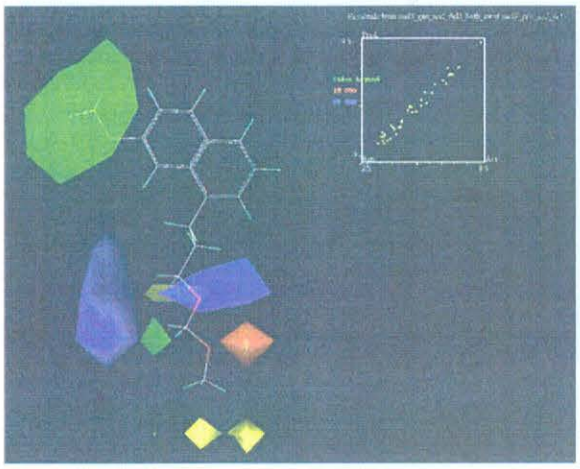


CoMSIA

Set 3 Ovine Pars Tuberalis Membrane Binding 3-D QSAR Maps – All Cmpds



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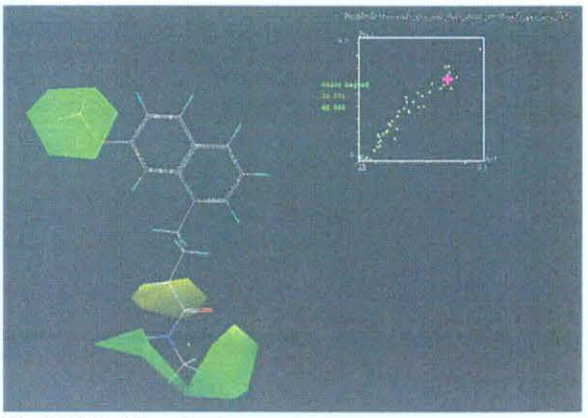

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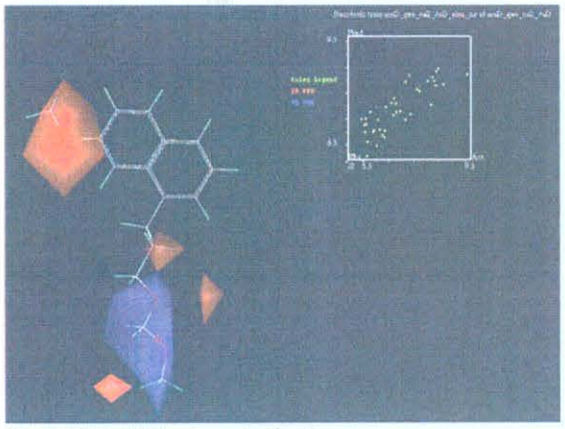
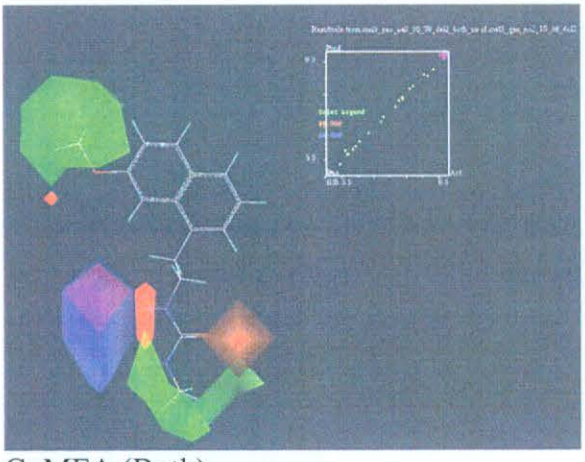


CoMFA (Electrostatics)

Set 3 Ovine Pars Tuberalis Membrane Binding 3-D QSAR Maps – Cmpds 10-38



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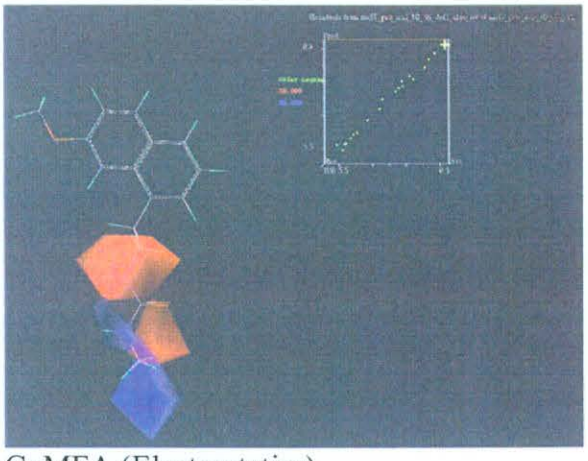

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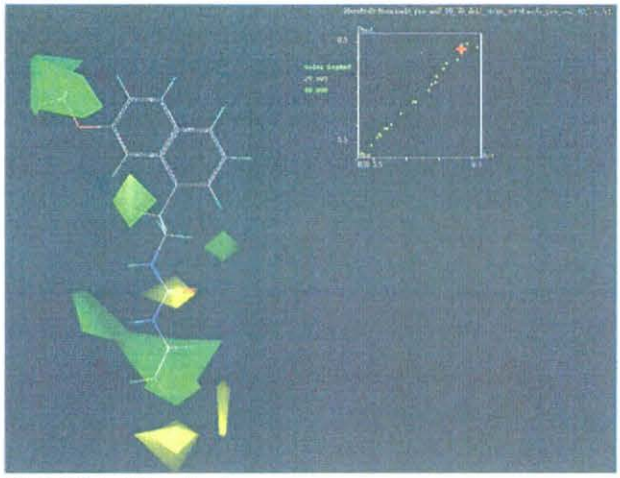

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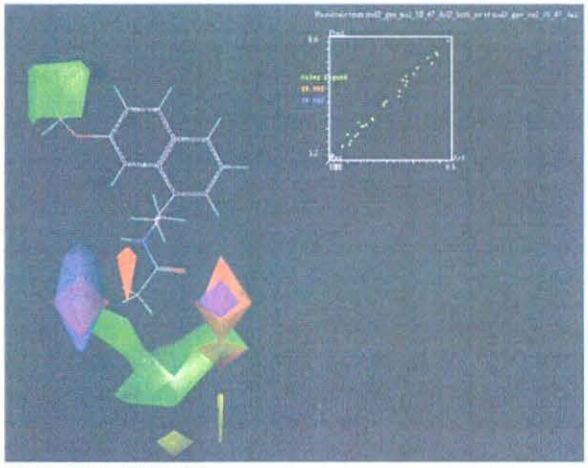

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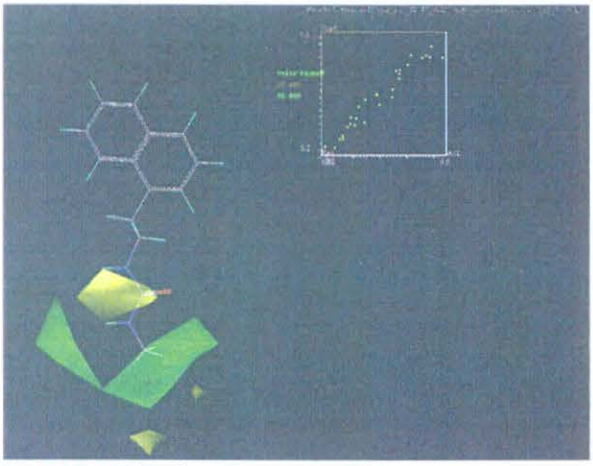

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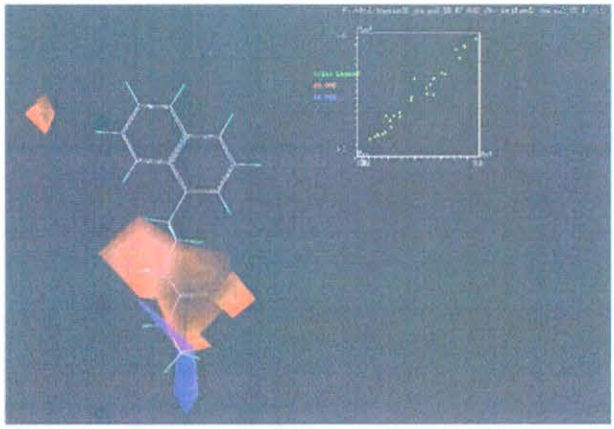

CoMFA (Electrostatics)

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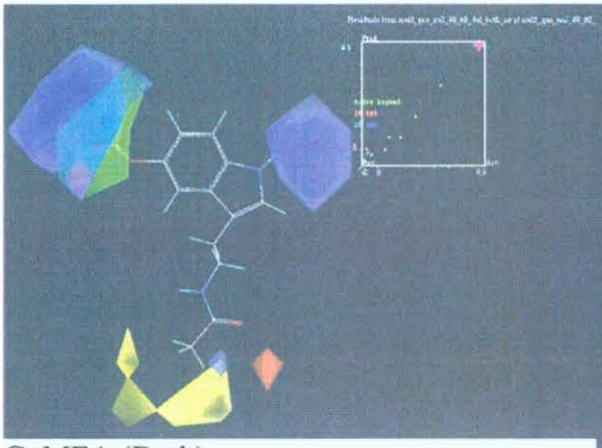

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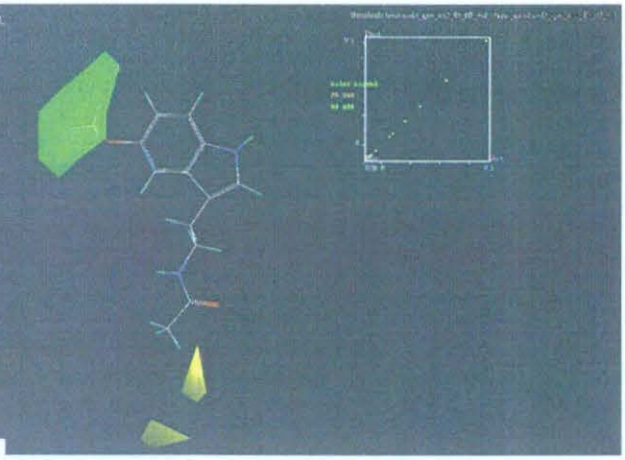

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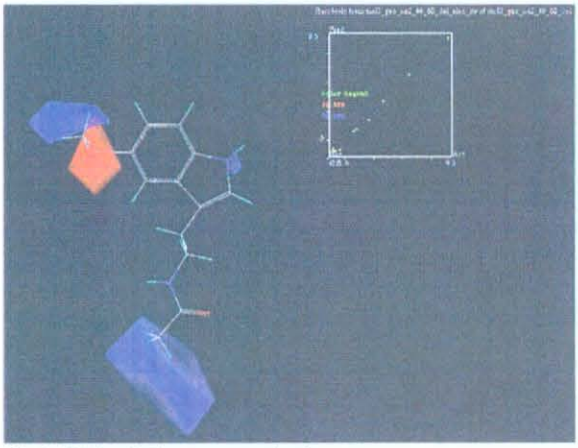
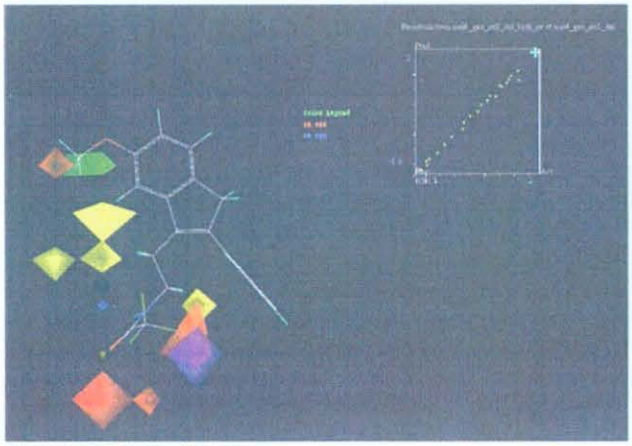


CoMFA (Electrostatics)

Set 4 Human MT_1 Binding 3-D QSAR Maps



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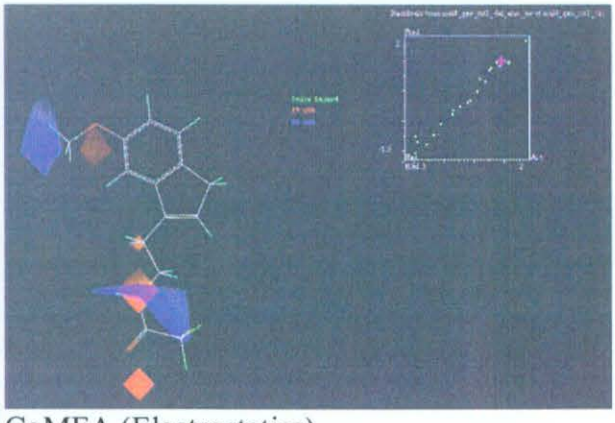

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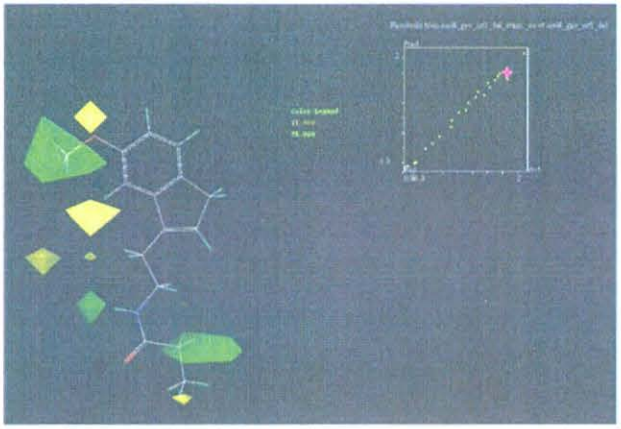

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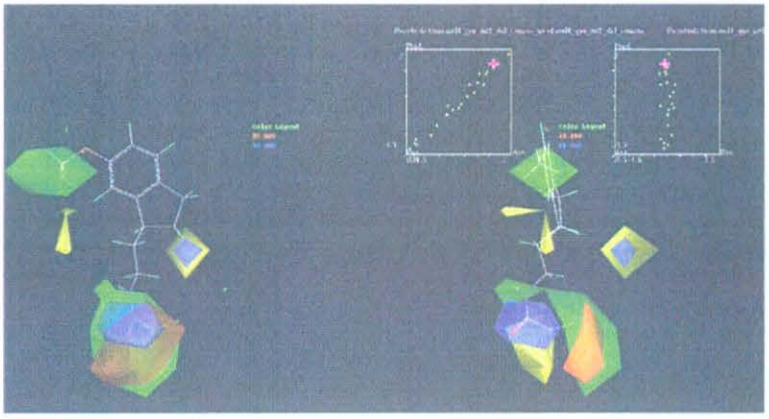

CoMSIA

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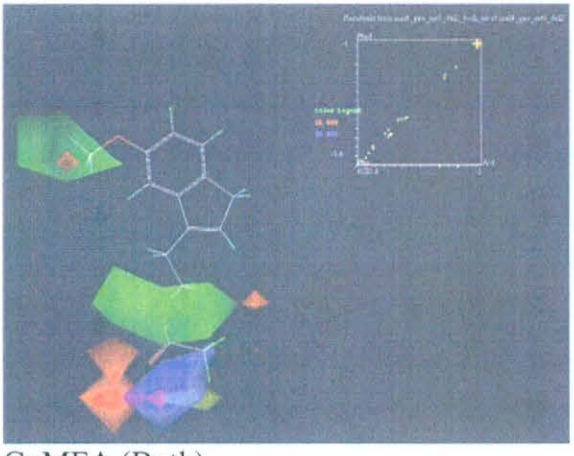

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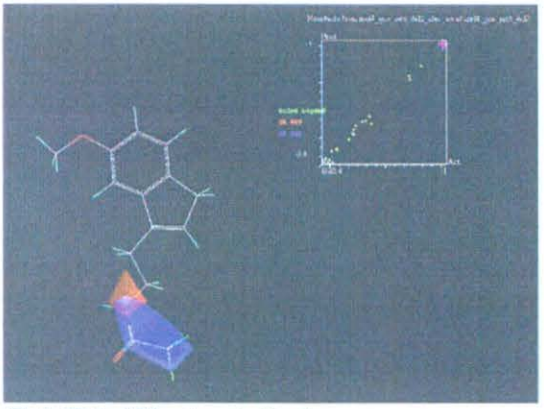
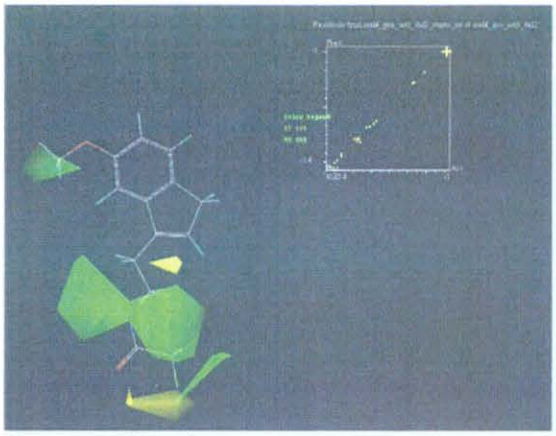
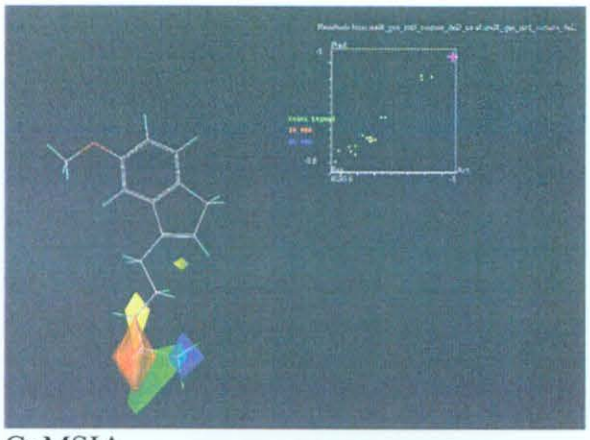


CoMFA (Electrostatics)

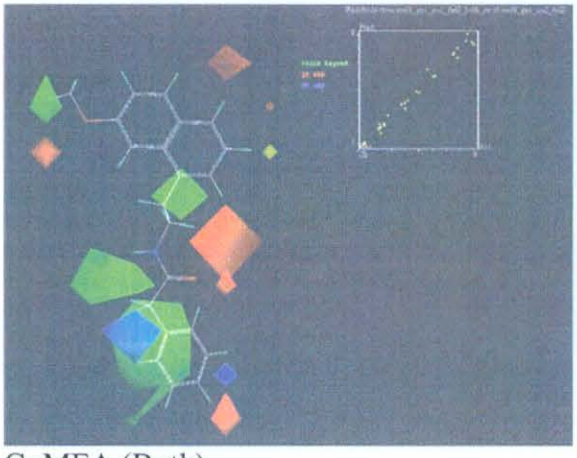


CoMFA (Sterics)

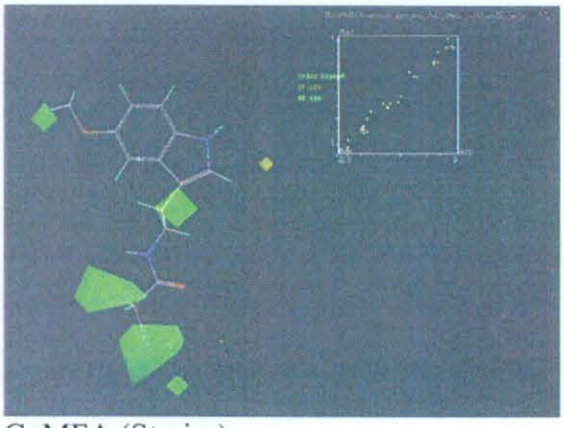


CoMSIA

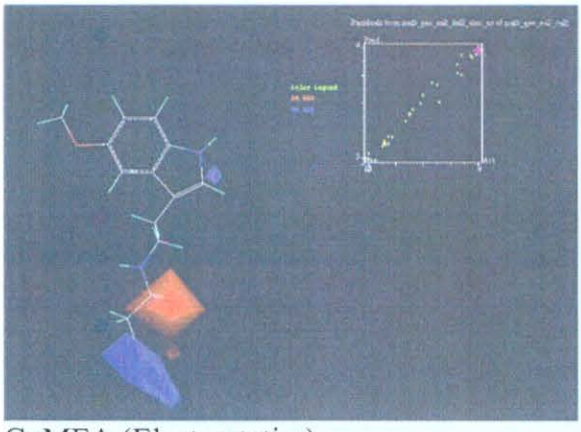
Set 5 Ovine Pars Tuberalis Membrane Binding 3-D QSAR Maps – All Cmpds



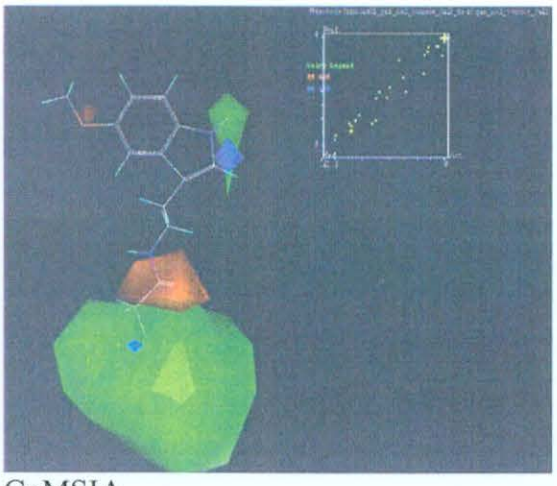
CoMFA (Both)



CoMFA (Sterics)

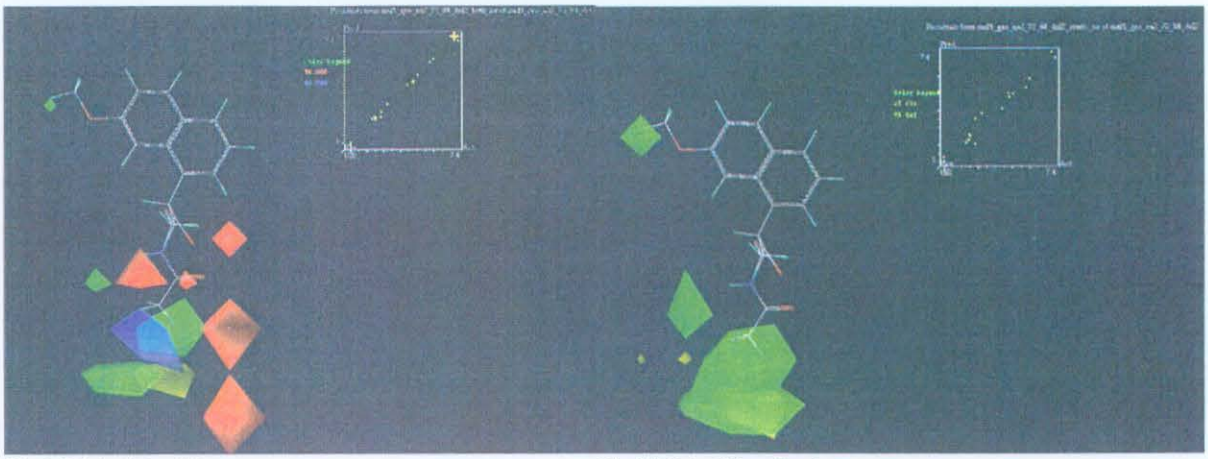


CoMFA (Electrostatics)



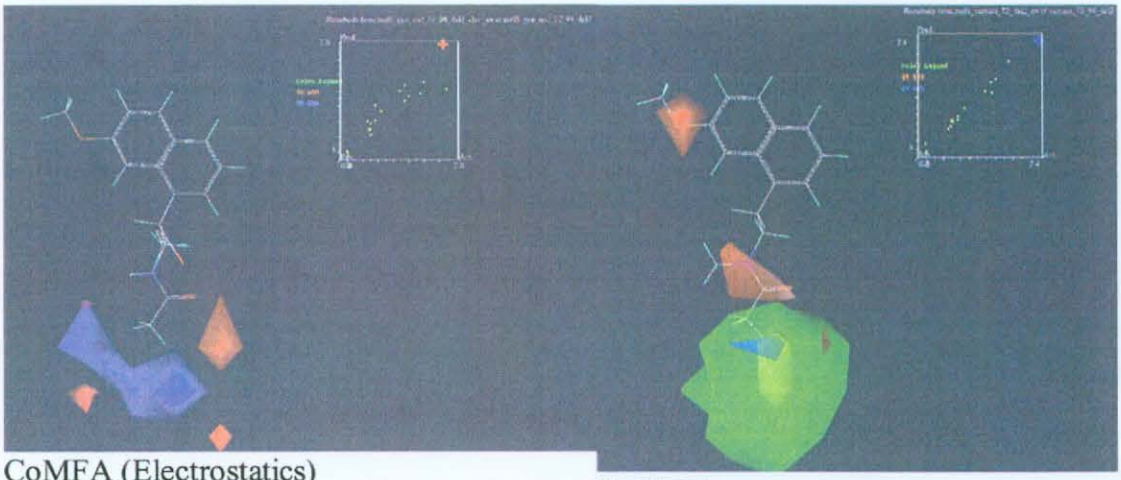
CoMSIA

Set 5 Ovine Pars Tuberalis Membrane Binding 3-D QSAR Maps – Cmpds 72-94



CoMFA (Both)

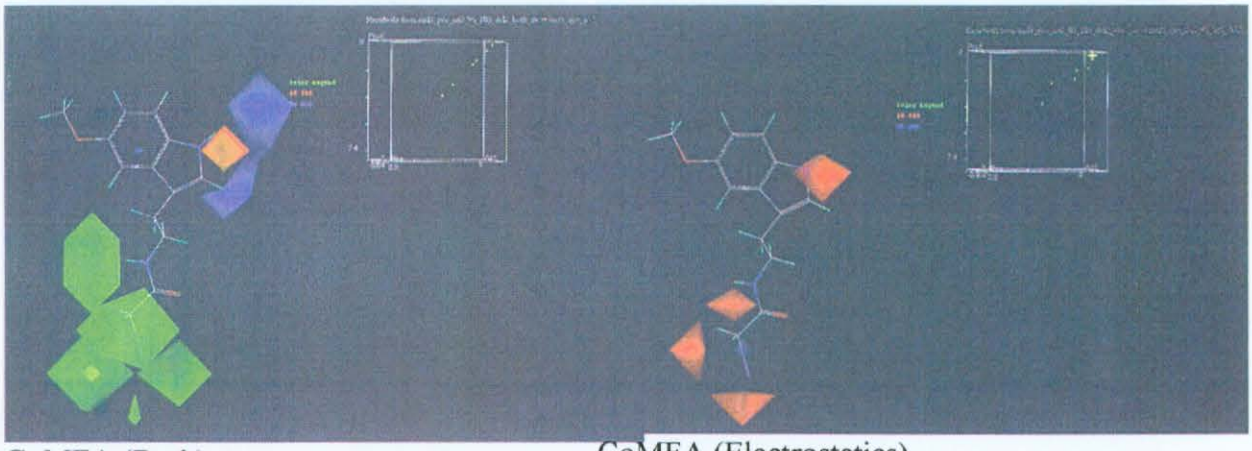
CoMFA (Sterics)



CoMFA (Electrostatics)

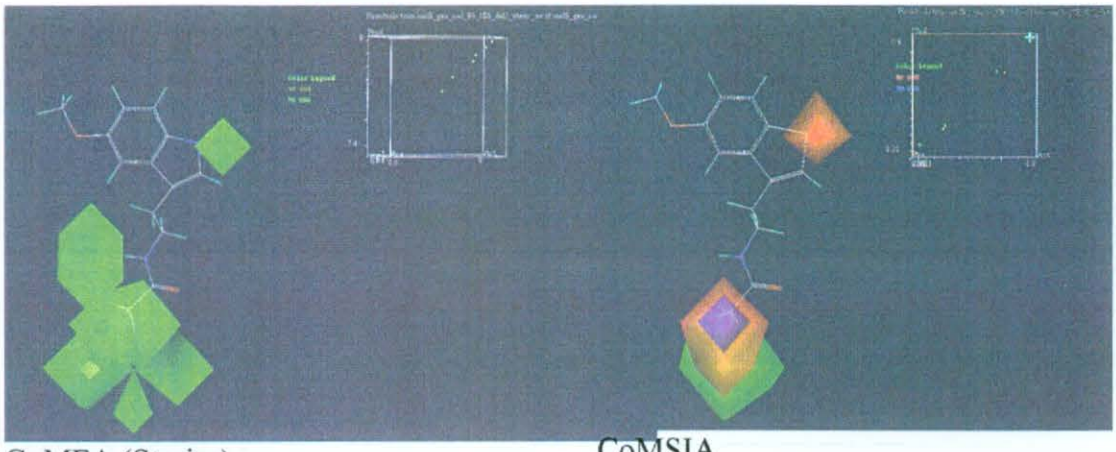
CoMSIA

Set 5 Ovine Pars Tuberalis Membrane Binding 3-D QSAR Maps – Cmpds 95-105



CoMFA (Both)

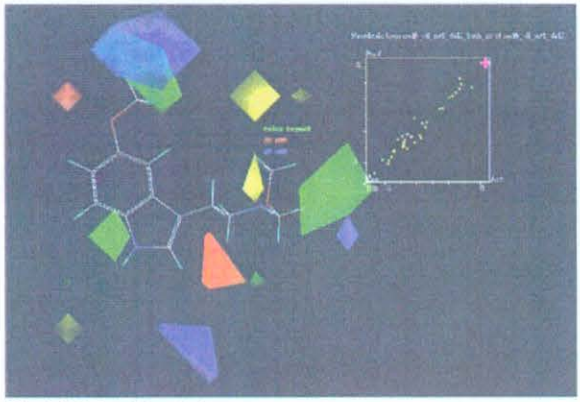
CoMFA (Electrostatics)



CoMFA (Sterics)

CoMSIA

Set 6 Human MT_1 Binding 3-D QSAR Maps – All



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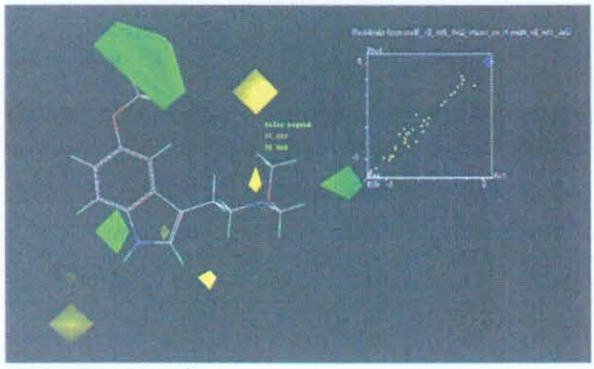

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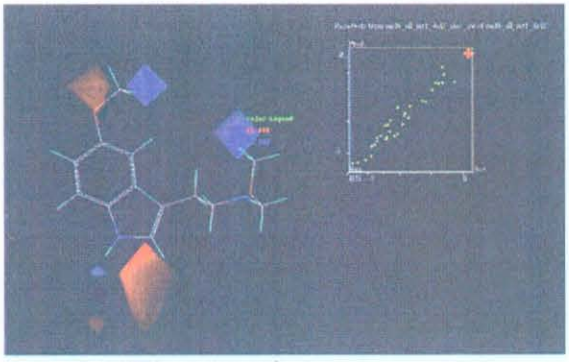
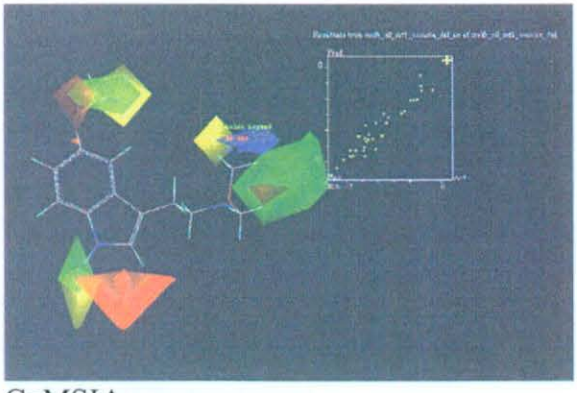
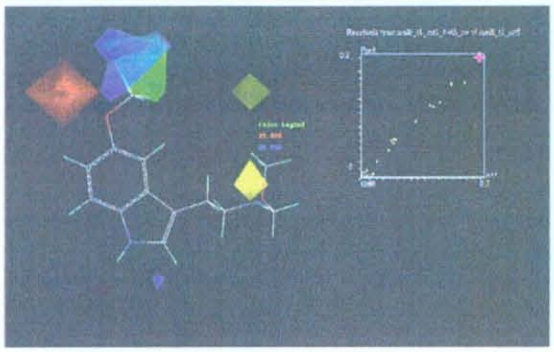


CoMFA (Electrostatics)

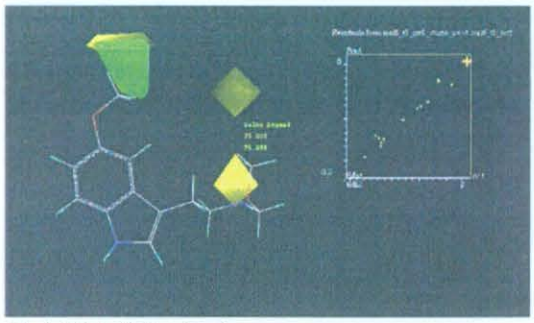


CoMSIA

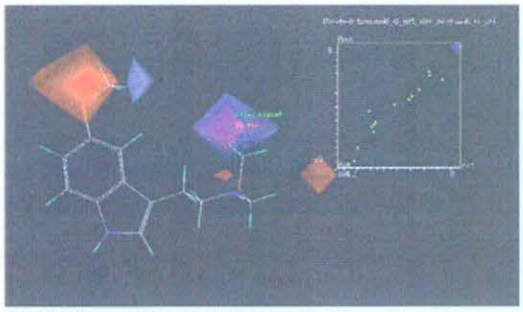
Set 6 Human MT_1 Binding 3-D QSAR Maps – Table 6_i



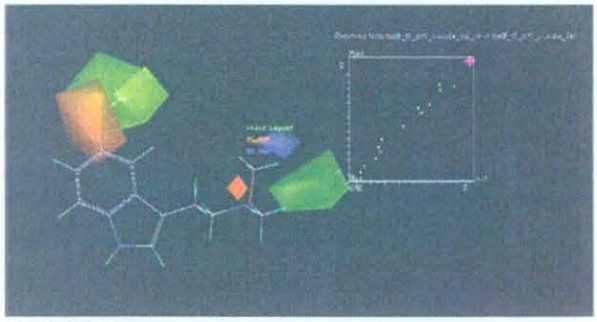
CoMFA (Both)



CoMFA (Sterics)

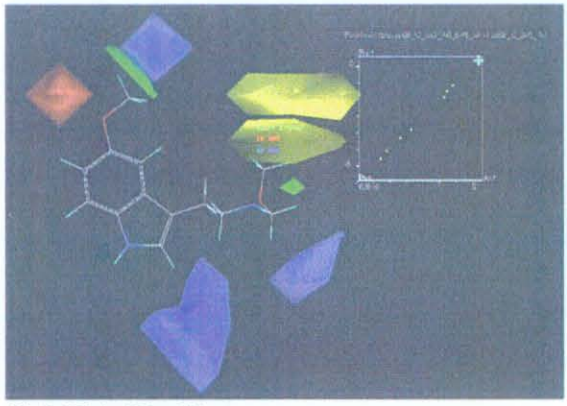


CoMFA (Electrostatics)

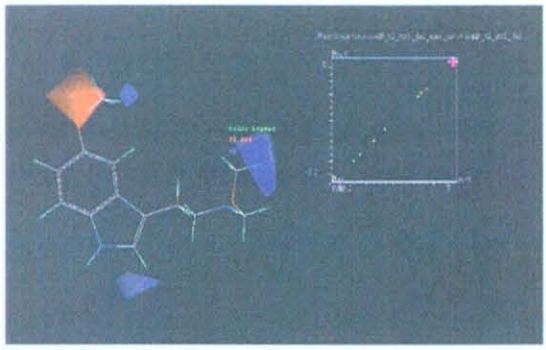


CoMSIA

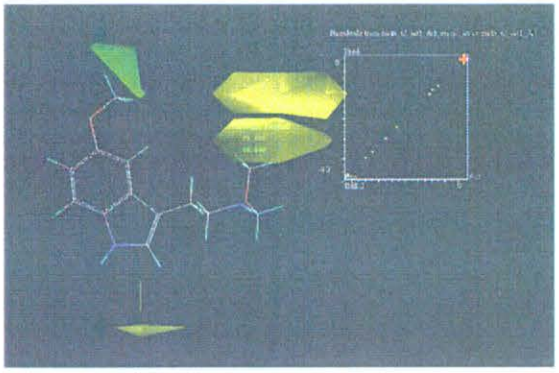
Set 6 Human MT_1 Binding 3-D QSAR Maps – Table 6_{ii}



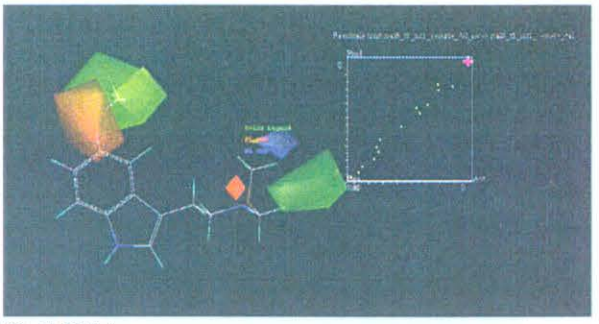
CoMFA (Both)



CoMFA (Electrostatics)

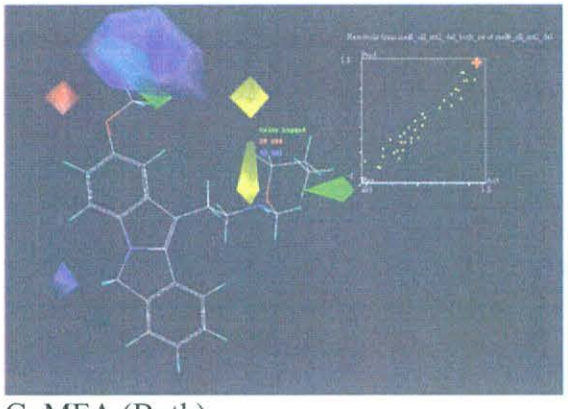


CoMFA (Sterics)

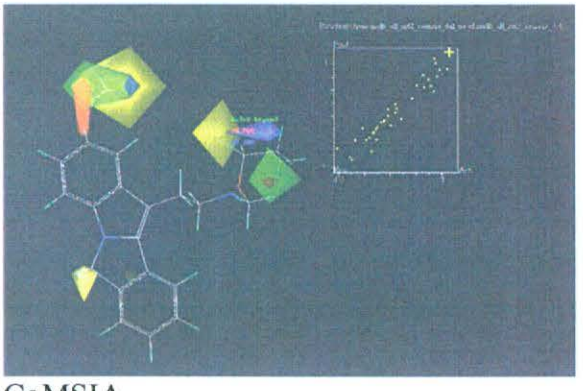


CoMSIA

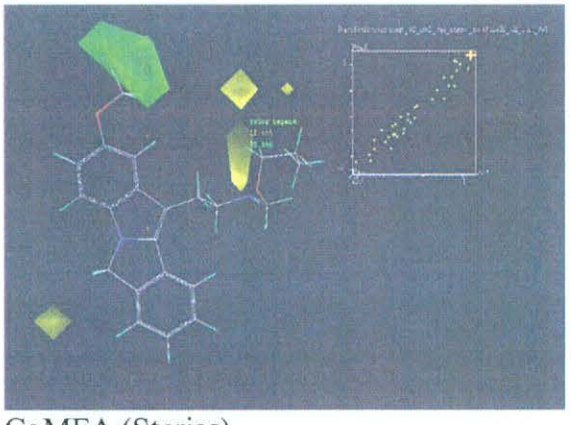
Set 6 Human MT_2 Binding 3-D QSAR Maps – All



CoMFA (Both)

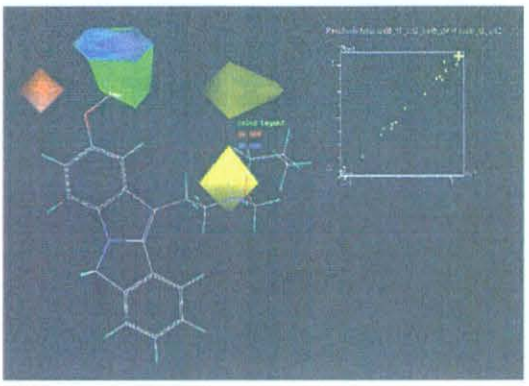


CoMSIA

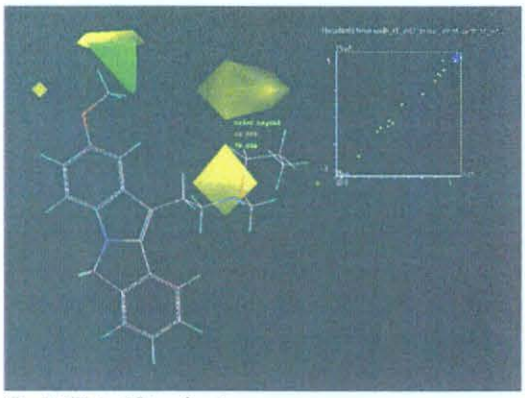


CoMFA (Sterics)

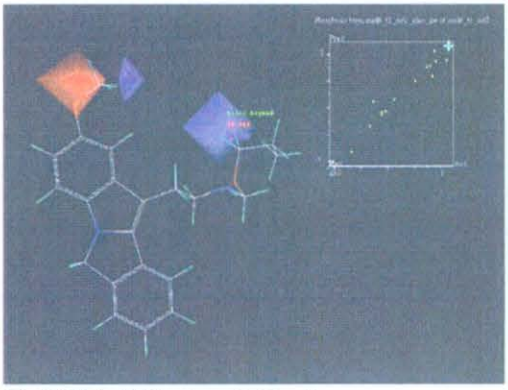
Set 6 Human MT_2 Binding 3-D QSAR Maps – Table 6_i



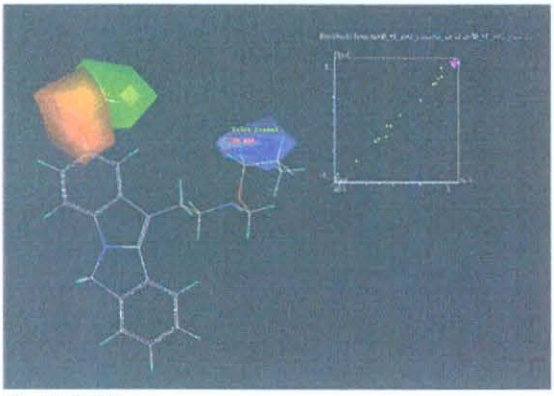
CoMFA (Both)



CoMFA (Sterics)

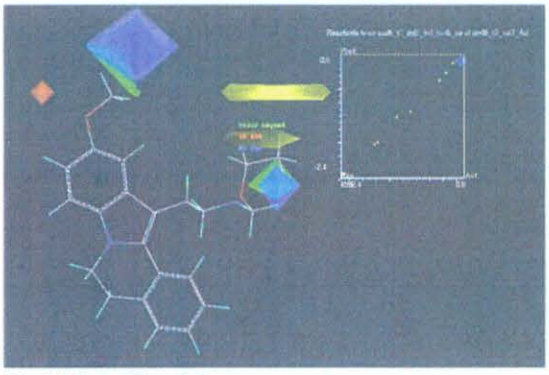


CoMFA (Electrostatics)

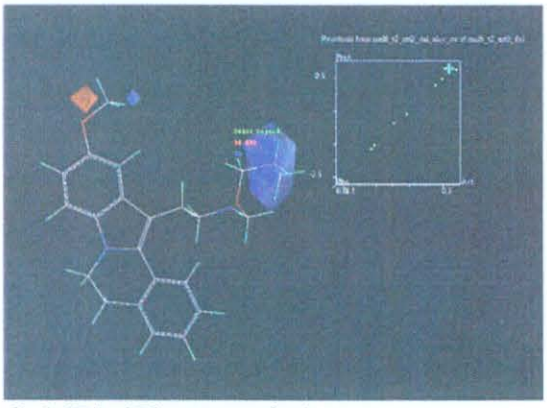


CoMSIA

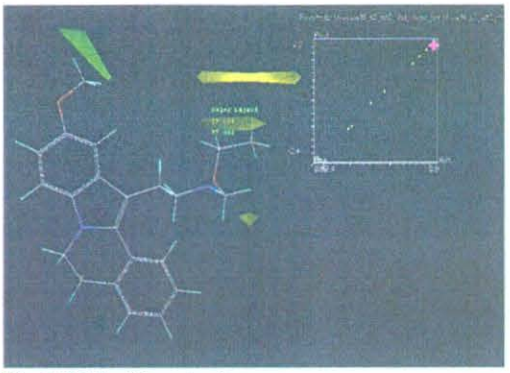
Set 6 Human MT_2 Binding 3-D QSAR Maps – Table 6_{ii}



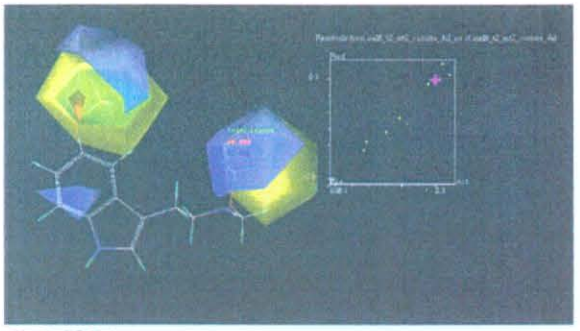
CoMFA (Both)



CoMFA (Electrostatics)

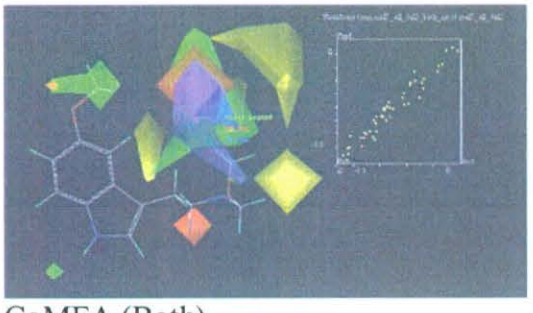


CoMFA (Sterics)

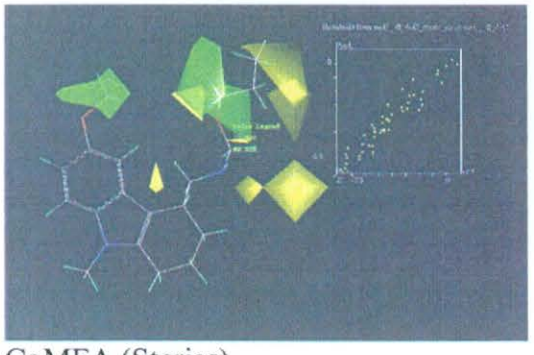


CoMSIA

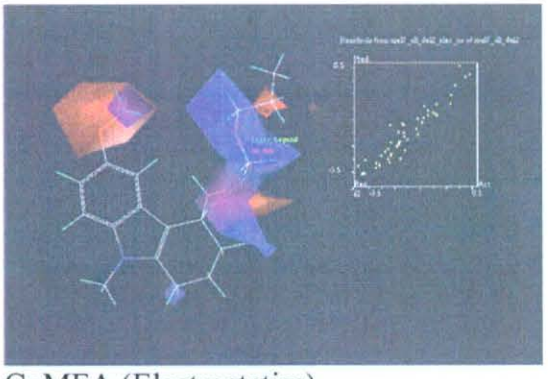
Set 7 Ovine Pars Tuberalis Membrane Binding 3-D QSAR Maps



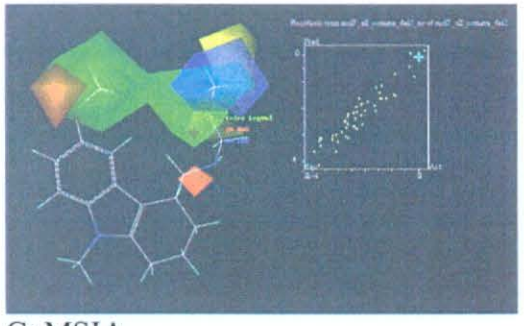
CoMFA (Both)



CoMFA (Sterics)

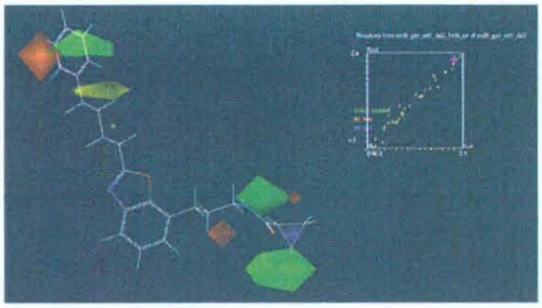


CoMFA (Electrostatics)

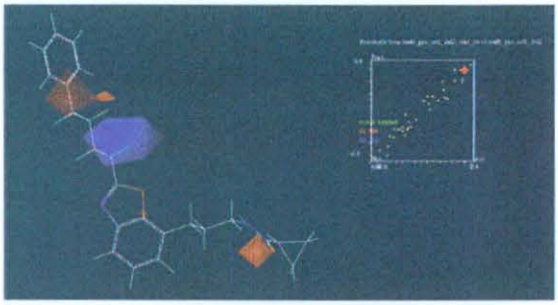


CoMSIA

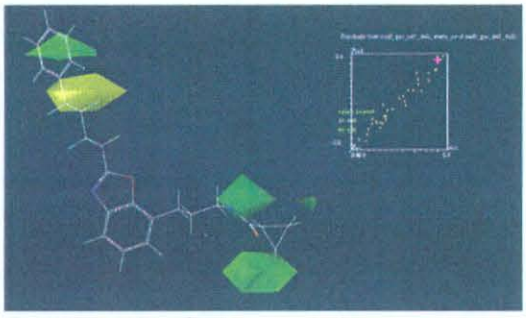
Set 8 Human MT_1 Binding 3-D QSAR Maps



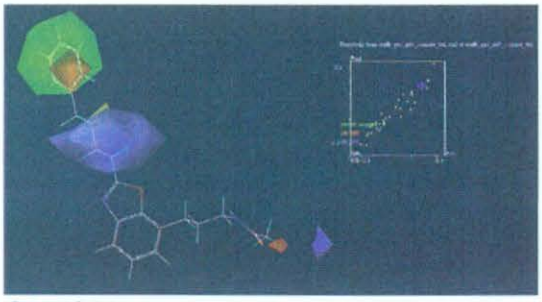
CoMFA (Both)



CoMFA (Electrostatics)

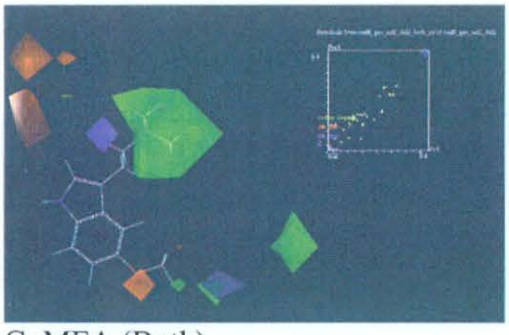


CoMFA (Sterics)

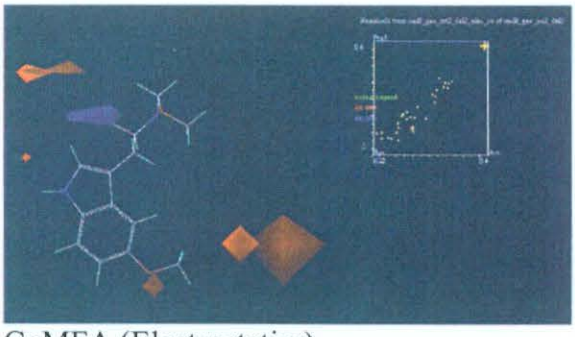


CoMSIA

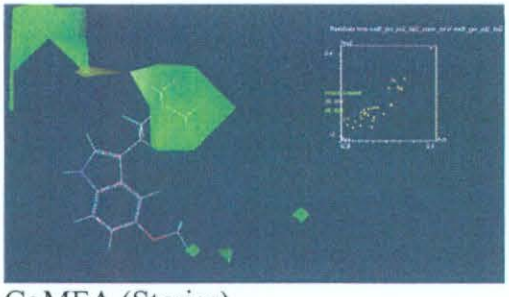
Set 8 Human MT_2 Binding 3-D QSAR Maps



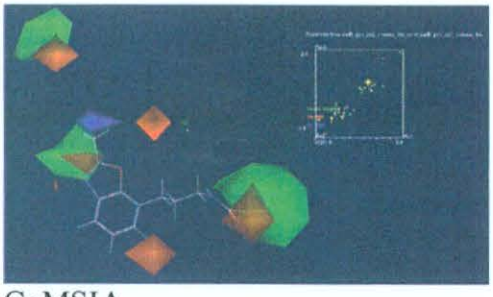
CoMFA (Both)



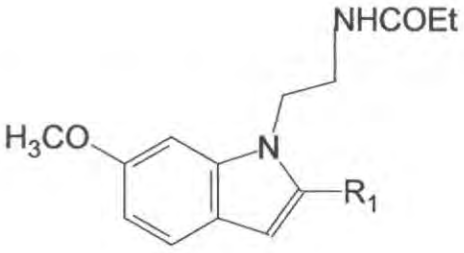
CoMFA (Electrostatics)



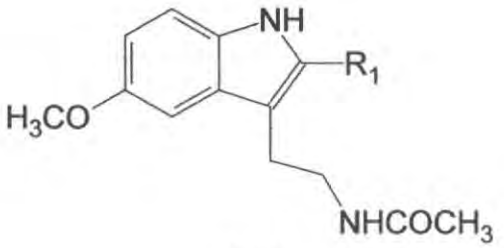
CoMFA (Sterics)



CoMSIA



01-11



12-16

Table 1 Set 1 Compounds

		bio. act.	
Compound	R_1	MT_1	MT_2
cmpd01	COOMe	9.82	10.12
cmpd02	CF_3	9.52	10.08
cmpd03	SO_2Me	6.83	7.34
cmpd04	CHO	8.95	9.34
cmpd05	CH_2CH_2Ph	7.20	8.88
cmpd06	$CONH_2$	7.57	7.79
cmpd07	$NHCONH_2$	6.65	7.21
cmpd08	CH_2OH	7.46	7.87
cmpd09	H	8.77	9.21
cmpd10	Ph	9.97	10.36
cmpd11	Br	10.28	10.21
cmpd12	H	6.93	9.43
cmpd13	Br	10.54	9.94
cmpd14	Ph	10.66	10.42
cmpd15	I	10.64	10.29
cmpd16	CH_2Ph	7.50	9.60

Test	Original	Modification(s)
cmpd17	cmpd14	OCH_3
cmpd18	cmpd14	naphthalene
cmpd19	cmpd13	$N\text{-}NH_2$
cmpd20	cmpd13	$CH_2\text{-}Br$
cmpd21	cmpd13	$C(CH_3)_2\text{-}Br$
cmpd22	cmpd15	$CH_2\text{-}I$
cmpd23	cmpd16	CH-BrPh
cmpd24	cmpd13	$C(Br)_3$
cmpd25	cmpd16	$C(Br_2Ph$
cmpd26	cmpd16	OCH_3
cmpd27	cmpd02	CH_2CF_3
cmpd28	cmpd02	$C^{10}HOH$
cmpd29	cmpd02	$C^{10}HCH_3$
cmpd30	cmpd02	CBr_3, OCH_2CH_2Br
cmpd31	cmpd02	CBr_3, OCH_2CH_3
cmpd32	cmpd10	OCH_3
cmpd33	cmpd10	$C^{13}HCH_2CH_3$
cmpd34	cmpd10	$OCH(CH_3)_2$
cmpd35	cmpd11	$CH_2CH_2CBr_3$
cmpd36	cmpd10	$N\text{-}CH_3$

[a] MLT

Table 1A

Set 1: Summary of the Statistical Results for the PLS Analyses [9,a]

	Human MT_1				Human MT_2			
	CoMFA[b]			CoMSIA	CoMFA[c]			CoMSIA
	B	E	S		B	E	S	
Q^2	0.462	0.411	0.406	0.455	0.584	0.468	0.134	0.684
no. comp	1	1	5	6	3	2	4	6
s	0.694	0.684	0.222	0.062	0.177	0.340	0.214	0.091
R^2	0.801	0.807	0.987	0.999	0.979	0.915	0.973	0.996
F	44.350	45.936	106.449	1388.633	141.605	53.655	71.657	374.138
Prob. R^2=0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

	pRA_1				pRA_2			
	CoMFA[d]			CoMSIA	CoMFA[e]			CoMSIA
	B	E	S		B	E	S	
Q^2	0.257	-0.021	0.421	0.646	0.298	0.227	0.321	0.758
no. comp	3	1	4	6	3	1	3	6
s	0.313	0.730	0.271	0.087	0.282	0.591	0.302	0.067
R^2	0.938	0.596	0.958	0.996	0.938	0.675	0.929	0.997
F	50.624	17.712	51.602	418.412	50.694	24.977	43.833	577.121
Prob. R^2=0	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000

[a] Alignment using MLT as the basic molecule [b] Outliers: 1, 8,16 [c] Outliers: 1, 6, 8 [d] Outliers: 8, 11 [e] Outliers: 8, 11

Table 1a CoMFA Human MT1

	MT_1	PA B	RES B	PA E	RES E	PA S	RES S
CMPD02 (5B)	9.52	9.44	0.08	9.24	0.28	9.30	0.22
CMPD03 (5C)	6.83	5.75	1.08	6.15	0.68	6.84	-0.01
CMPD04 (5D)	8.95	8.82	0.13	8.46	0.49	9.28	-0.33
CMPD05 (5E)	7.20	7.89	-0.69	7.88	-0.68	7.21	-0.01
CMPD06 (5F)	7.57	8.28	-0.71	8.06	-0.49	7.57	0.00
CMPD07 (5G)	6.65	7.55	-0.90	7.47	-0.82	6.63	0.03
CMPD09 (51)	8.77	9.47	-0.70	9.43	-0.66	8.95	-0.18
CMPD10 (5J)	9.97	9.72	0.25	10.22	-0.25	9.80	0.17
CMPD11	10.28	9.58	0.70	9.18	1.10	10.20	0.08
CMPD12	9.63	10.35	-0.72	10.44	-0.81	9.57	0.06
CMPD13	10.54	9.96	0.58	9.90	0.64	10.28	0.26
CMPD14	10.66	10.18	0.48	10.59	0.07	10.84	-0.18
CMPD15	10.64	10.22	0.43	10.20	0.44	10.76	-0.12

Table 1a CoMFA Human MT1 cont.

Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD17	?	10.11	-0.07	10.33	-0.25	10.78	-0.06
CMPD18	?	9.57	-0.61	9.67	-0.91	9.45	-1.39
CMPD19	?	10.28	0.32	9.83	-0.06	10.65	0.38
CMPD20	?	10.13	0.17	10.48	0.58	9.90	-0.94
CMPD21	?	9.79	-0.17	9.95	0.05	9.39	-1.38
CMPD22	?	10.36	0.14	10.25	0.05	11.66	0.89
CMPD23	?	9.93	0.86	10.47	1.58	10.02	1.13
CMPD24	?	9.46	-0.50	9.95	0.05	9.07	-0.39
CMPD25	?	9.76	0.68	10.21	1.32	9.96	1.07
CMPD26	?	9.67	0.60	9.78	0.89	9.94	1.05
CMPD27	?	9.36	-0.08	9.29	0.05	9.44	0.14
CMPD28	?	8.57	-0.87	8.38	-0.86	8.64	-0.66
CMPD29	?	9.50	0.05	9.36	0.12	9.40	0.10
CMPD30	?	9.67	0.22	9.74	0.49	10.01	0.71
CMPD31	?	9.47	0.02	9.51	0.27	9.43	0.13
CMPD32	?	9.52	-0.20	9.44	-0.79	9.44	-0.36
CMPD33	?	9.27	-0.44	9.80	-0.42	10.17	0.37
CMPD34	?	9.38	-0.34	9.41	-0.81	10.56	0.76

Table 1b CoMSIA Human MT_1

	MT_1	PA	RES
CMPD01 (SA)	9.82	9.85	-0.03
CMPD02 (5B)	9.52	9.51	0.01
CMPD03 (5C)	6.83	6.83	0.00
CMPD04 (5D)	8.95	8.94	0.01
CMPD05 (5E)	7.20	7.22	-0.02
CMPD06 (5F)	7.57	7.54	0.03
CMPD07 (5G)	6.65	6.65	0.00
CMPD08 (5H)	7.46	7.44	0.02
CMPD09 (51)	8.77	8.79	-0.02
CMPD10 (5J)	9.97	10.00	-0.03
CMPD11 (5K)	10.28	10.25	0.03
CMPD12	9.63	9.70	-0.06
CMPD13	10.54	10.64	-0.10
CMPD14	10.66	10.62	0.04
CMPD15	10.64	10.52	0.12
CMPD16	7.50	7.50	0.00

Table 1b CoMSIA Human MT_1

Modified		PA	Δ
CMPD17	?	10.19	-0.43
CMPD18	?	9.02	-1.60
CMPD19	?	9.34	-1.29
CMPD20	?	9.92	-0.72
CMPD21	?	9.33	-1.31
CMPD22	?	9.61	-0.91
CMPD23	?	8.61	1.11
CMPD24	?	10.50	-0.14
CMPD25	?	9.20	1.70
CMPD26	?	8.90	1.40
CMPD27	?	8.59	-0.93
CMPD28	?	10.02	0.51
CMPD29	?	9.62	0.11
CMPD30	?	9.77	0.25
CMPD31	?	9.69	0.17
CMPD32	?	9.26	-0.74
CMPD33	?	10.11	0.11
CMPD34	?	10.00	0.00

Table 1c Set 1 CoMFA Human MT_2

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD02 (5B)	10.08	9.99	0.09	9.78	0.30	10.01	0.07
CMPD03 (5C)	7.34	7.36	-0.02	7.33	0.01	7.37	-0.03
CMPD04 (5D)	9.34	9.57	-0.23	9.10	0.24	9.72	-0.38
CMPD05 (5E)	8.88	8.70	0.18	9.20	-0.32	8.90	-0.02
CMPD07 (5G)	7.21	7.20	0.01	7.49	-0.28	7.07	0.14
CMPD09 (51)	9.21	9.26	-0.05	9.22	-0.01	9.37	-0.16
CMPD10 (5J)	10.36	10.40	-0.04	10.94	-0.58	10.31	0.05
CMPD11 (5K)	10.21	10.19	0.02	10.02	0.19	10.13	0.08
CMPD12	9.43	9.76	-0.33	9.84	-0.41	9.57	-0.14
CMPD13	9.94	9.96	-0.02	9.88	0.06	9.75	0.19
CMPD14	10.42	10.34	0.08	10.31	0.11	10.31	0.11
CMPD15	10.29	10.03	0.26	9.82	0.47	10.04	0.26
CMPD16	9.60	9.56	0.04	9.37	0.23	9.78	-0.18
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD17	?	10.24	-0.10	10.15	-0.16	10.29	-0.02
CMPD18	?	10.13	-0.21	9.87	-0.45	9.51	-0.81
CMPD19	?	9.98	0.02	9.66	-0.22	10.34	0.58
CMPD20	?	10.22	0.26	10.41	0.53	10.06	0.31
CMPD21	?	10.15	0.19	10.22	0.34	9.55	-0.20
CMPD22	?	10.39	0.36	9.98	0.16	10.91	0.88
CMPD23	?	9.82	0.26	9.88	0.50	9.80	0.02
CMPD24	?	9.76	-0.20	9.89	0.02	9.52	-0.23
CMPD25	?	9.81	0.24	9.69	0.31	9.91	0.13
CMPD26	?	9.75	0.19	9.42	0.04	9.92	0.14
CMPD27	?	10.07	0.07	10.03	0.25	9.72	-0.29
CMPD28	?	9.78	-0.21	9.78	0.00	9.44	-0.57
CMPD29	?	9.91	-0.09	9.91	0.13	10.12	0.11
CMPD30	?	10.01	0.01	10.21	0.43	10.13	0.11
CMPD31	?	9.74	-0.25	9.80	0.02	9.82	-0.19
CMPD32	?	10.38	-0.02	10.20	-0.73	10.08	-0.23
CMPD33	?	10.01	-0.39	10.66	-0.28	10.33	0.02
CMPD34	?	10.14	-0.26	10.47	-0.47	10.58	0.27
CMPD35	?	10.31	-0.09	10.64	-0.30	10.32	0.02
CMPD36	?	10.46	0.06	10.85	-0.09	10.51	0.20

Table 1d Set 1 CoMSIA Human MT_2

	EA	PA	RES
CMPD01 (5A)	10.12	10.15	-0.03
CMPD02 (5B)	10.08	10.11	-0.03
CMPD03 (5C)	7.34	7.36	-0.02
CMPD04 (5D)	9.34	9.31	0.03
CMPD05 (5E)	8.88	8.88	0.00
CMPD06 (5F)	7.79	7.75	0.04
CMPD07 (5G)	7.21	7.18	0.03
CMPD07 (5H)	7.87	7.89	-0.02
CMPD09 (51)	9.21	9.22	-0.01
CMPD10 (5J)	10.36	10.34	0.02
CMPD11 (5K)	10.21	10.24	-0.03
CMPD12	9.43	9.50	-0.07
CMPD13	9.94	10.06	-0.12
CMPD14	10.42	10.37	0.06
CMPD15	10.29	10.08	0.21
CMPD16	9.60	9.65	-0.05
Modified		PA	Δ
CMPD17	?	10.36	0.00
CMPD18	?	10.06	-0.30
CMPD19	?	9.92	-0.14
CMPD20	?	9.78	-0.28
CMPD21	?	9.56	-0.50
CMPD22	?	9.76	-0.32
CMPD23	?	10.10	0.46
CMPD24	?	10.30	0.24
CMPD25	?	10.55	0.90
CMPD26	?	10.59	0.94
CMPD27	?	9.46	-0.65
CMPD28	?	10.21	0.10
CMPD29	?	10.27	0.15
CMPD30	?	10.51	0.40
CMPD31	?	10.32	0.21
CMPD32	?	10.11	-0.23
CMPD33	?	10.45	0.12
CMPD34	?	10.35	0.02

Table 1e Set 1 CoMFA pRA_1

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01 (5A)	0.82	0.72	0.10	0.05	0.77	0.80	0.02
CMPD02 (5B)	1.34	1.18	0.16	0.18	1.16	1.29	0.05
CMPD03 (5C)	-1.54	-1.56	0.02	-2.11	0.56	-1.47	-0.07
CMPD04 (5D)	0.02	0.48	-0.46	-0.45	0.47	0.50	-0.48
CMPD05 (5E)	-1.24	-1.10	-0.14	-1.00	-0.24	-1.26	0.02
CMPD06 (5F)	-1.71	-1.66	-0.05	-0.98	-0.73	-1.63	-0.08
CMPD07 (5G)	-1.95	-2.21	0.26	-1.01	-0.94	-2.18	0.23
CMPD09 (51)	0.05	0.18	-0.13	0.14	-0.09	0.28	-0.23
CMPD10 (5J)	0.04	0.11	-0.07	0.07	-0.03	-0.05	0.09
CMPD12	0.05	0.52	-0.47	0.84	-0.79	0.10	-0.05
CMPD13	1.26	0.75	0.51	0.49	0.77	0.75	0.51
CMPD14	0.04	0.18	-0.14	0.67	-0.63	0.11	-0.07
CMPD15	1.15	0.82	0.33	0.66	0.49	1.00	0.15
CMPD16	-0.31	-0.40	0.09	0.46	-0.77	-0.20	-0.11
Modified		PA B	Δ		Δ		Δ
CMPD19	?	0.86	0.11	0.47	-0.02	0.97	0.22
CMPD20	?	0.80	0.05	0.83	0.33	1.15	0.40
CMPD21	?	0.35	-0.41	0.42	-0.07	0.31	-0.44
CMPD22	?	0.73	-0.09	0.68	0.01	1.29	0.29
CMPD23	?	0.02	0.42	0.80	0.34	0.21	0.41
CMPD24	?	0.46	-0.29	0.56	0.06	0.32	-0.43
CMPD25	?	-0.04	0.36	0.66	0.20	-0.15	0.05
CMPD26	?	-0.01	0.39	0.47	0.01	-0.18	0.02
CMPD27	?	-0.03	-1.21	-0.07	-0.25	0.40	-0.89
CMPD28	?	-0.13	-1.32	-0.78	-0.97	-0.01	-1.31
CMPD29	?	1.17	-0.02	0.25	0.07	1.32	0.02
CMPD30	?	0.91	-0.27	0.42	0.24	1.25	-0.04
CMPD31	?	0.41	-0.77	0.21	0.03	0.89	-0.40

Table 1f Set 1 CoMSIA pRA_1

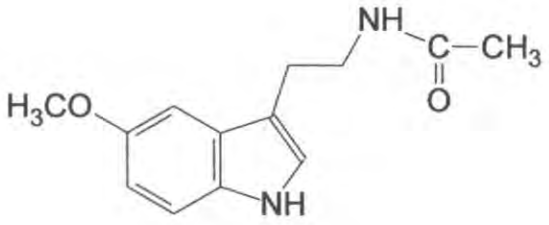
	EA	PA	RES
CMPD01 (5A)	0.82	0.91	-0.09
CMPD02 (5B)	1.34	1.26	0.08
CMPD03 (5C)	-1.54	-1.54	-0.01
CMPD04 (5D)	0.02	-0.06	0.08
CMPD05 (5E)	-1.24	-1 .238	0.00
CMPD06 (5F)	-1.71	-1.77	0.06
CMPD07 (5G)	-1.95	-1.92	-0.03
CMPD08	-1.35	-1.39	0.04
CMPD09 (51)	0.05	0.14	-0.09
CMPD10 (5J)	0.04	0.02	0.02
CMPD11 (5K)	1.26	1.31	-0.05
CMPD12	0.05	0.15	-0.10
CMPD13	1.26	1.24	0.02
CMPD14	0.04	0.05	-0.01
CMPD15	1.15	1.02	0.13
CMPD16	-0.31	-0.25	-0.06

Table 1g Set 1 CoMFA pRA_2

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	0.49	0.41	0.09	-0.18	0.67	0.47	0.02
CMPD02 (5B)	1.09	0.94	0.15	0.20	0.89	0.95	0.14
CMPD03 (5C)	-1.65	-1.67	0.02	-1.99	0.34	-1.67	0.02
CMPD04 (5D)	-0.25	0.18	-0.43	-0.44	0.19	0.15	-0.40
CMPD05 (5E)	-0.16	0.01	-0.17	-0.34	0.17	-0.03	-0.13
CMPD06 (5F)	-1.69	-1.61	-0.08	-0.76	-0.93	-1.64	-0.05
CMPD07 (5G)	-1.75	-1.97	0.22	-1.06	-0.69	-1.88	0.12
CMPD09 (51)	0.01	0.11	-0.10	0.24	-0.23	0.11	-0.10
CMPD10 (5J)	0.52	0.43	0.09	0.39	0.13	0.60	-0.08
CMPD12	0.01	0.509 .	-0.50	0.90	-0.89	0.15	-0.14
CMPD13	1.03	0.64	0.39	0.50	0.53	0.34	0.69
CMPD14	0.52	0.54	-0.02	0.79	-0.27	0.83	-0.31
CMPD15	1.04	0.78	0.26	0.68	0.36	0.75	0.29
CMPD16	0.32	0.23	0.09	0.60	-0.28	0.38	-0.06
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD19	?	0.81	0.17	0.56	0.06	0.90	0.55
CMPD20	?	0.78	0.14	0.85	0.35	0.79	0.45
CMPD21	?	0.60	-0.04	0.45	-0.05	0.37	0.03
CMPD22	?	0.75	-0.04	0.70	0.02	1.30	0.55
CMPD23	?	0.44	0.21	0.81	0.21	0.58	0.19
CMPD24	?	0.56	-0.09	0.48	-0.02	0.32	-0.02
CMPD25	?	0.47	0.24	0.68	0.08	0.48	0.10
CMPD26	?	0.51	0.28	0.48	-0.12	0.48	0.09
CMPD27	?	0.09	-0.85	0.08	-0.12	0.28	-0.67
CMPD28	?	-0.23	-1.17	-0.51	-0.71	-0.34	-1.29
CMPD29	?	0.95	0.01	0.27	0.07	1.04	0.09
CMPD30	?	0.92	-0.02	0.43	0.24	1.14	0.19
CMPD31	?	0.49	-0.44	0.25	0.05	0.84	-0.11

Table 1h Set 1 CoMSIA pRA_2

	EA	PA	RES
CMPD01	0.49	0.54	-0.04
CMPD02 (5B)	1.09	1.08	0.01
CMPD03 (5C)	-1.65	-1.62	-0.03
CMPD04 (5D)	-0.25	-0.31	0.06
CMPD05 (5E)	-0.16	-0.15	-0.01
CMPD06 (5F)	-1.69	-1.71	0.02
CMPD07 (5G)	-1.75	-1.79	0.04
CMPD08 (5H)	-1.26	-1.24	-0.02
CMPD09 (51)	0.01	0.05	-0.04
CMPD10 (5J)	0.52	0.47	0.05
CMPD11 (5K)	1.03	1.08	-0.05
CMPD12	0.01	0.07	-0.06
CMPD13	1.03	1.03	0.00
CMPD14	0.52	0.50	0.02
CMPD15	1.04	0.92	0.12
CMPD16	0.32	0.39	-0.07



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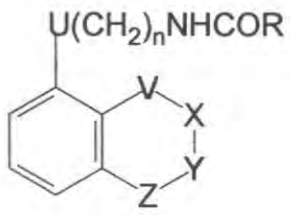

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Table 2 Set 2 Compounds

Compound	U	V	Z	X-Y	n	R	bio. act.
cmpd01	-	-	-	-	-	-	9.52
cmpd02	CH_2	O	O	CH_2-CH_2	0	CH_3	3.70
cmpd03	CH_2	O	O	CH_2-CH_2	1	CH_3	6.62
cmpd04	CH_2	O	O	CH_2-CH_2	2	n-Pr	7.11
cmpd05	CH_2	O	O	CH_2-CH_2	2	CH_3	7.46
cmpd06	CH_2	O	O	CH_2-CH_2	3	CH_3	7.12
cmpd07	CH_2	S	O	CH_2-CH_2	2	CH_3	7.02
cmpd08	CH_2	S	O	CH_2-CH_2	3	CH_3	7.14
cmpd09	CH_2	S	O	CH_2-CH_2	4	CH_3	6.66
cmpd10	CH_2	O	O	CH=CH	2	CH_3	7.20
cmpd11	CH_2	O	O	CH=CH	2	n-Pr	7.48
cmpd12	O	O	O	CH_2-CH_2	2	CH_3	5.60
cmpd13	O	O	O	CH_2-CH_2	3	CH_3	6.45
cmpd14	O	O	O	CH_2-CH_2	4	CH_3	6.05
cmpd15	O	O	CH_2	CH_2-CH_2	2	CH_3	4.68
cmpd16	O	S	CH_2	CH_2-CH_2	2	CH_3	4.00

Test	Original	Modification(s)
cmpd17	cmpd04	$C^{34}H_2CH_3$
cmpd18	cmpd04	$C^{10}(CH_3)_2$-
cmpd19	cmpd04	C^{11}HOH-
cmpd20	cmpd04	$C^{11}Br_2$-
cmpd21	cmpd04	$C^{11}(OH)_2$
cmpd22	cmpd05	$C^{34}HCH_3$-
cmpd23	cmpd04	$C^{34}H_2F$

[a] MLT

Table 2A

Set 2: Summary of the Statistical Results for the PLS Analyses [13,a]

Ovine Pars Tuberalis Membrane Binding

	CoMFA[b]			CoMFA[c]			CoMSIA[d]
	B	E	S	B	E	S	
Q^2	0.390	0.253	0.395	0.406	0.197	0.545	0.471
no. comp	4	2	2	6	2	6	6
s	0.130	0.292	0.317	0.064	0.314	0.023	0.129
R^2	0.994	0.963	0.956	0.999	0.959	1.000	0.994
F	339.936	130.066	109.371	896.319	105.535	6769.902	229.905
Prob. R^2=0	0.000	0.000	0.000	0.000	0.000	0.000	0.000

[a] Alignment using MLT as the basic molecule [b] Outliers: 2, 9, 13 [c] Outliers: 2, 9, 12, 13 [d] Outlier: 2

Table 2a Set 2 Predicted Activities: CoMFA[b]

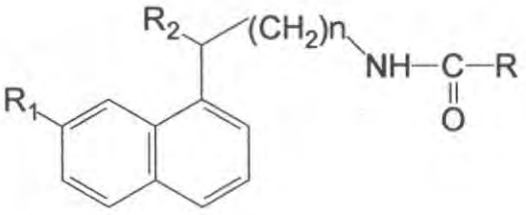
	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01 (ML T)	9.52	9.56	-0.04	9.34	0.18	9.37	0.15
CMPD03 (1 B)	6.62	6.58	0.04	6.80	-0.18	6.93	-0.31
CMPD04 (1 CA)	7.11	7.05	0.06	7.00	0.11	6.77	0.34
CMPD05 (1CB)	7.46	7.33	0.13	7.34	0.12	7.59	-0.13
CMPD06 (1 D)	7.12	7.23	-0.11	7.28	-0.16	6.98	0.14
CMPD07 (1 E)	7.02	6.95	0.07	6.99	0.03	6.64	0.38
CMPD08 (1 F)	7.14	7.20	-0.06	7.16	-0.02	6.90	0.24
CMPD10 (1HA)	7.20	7.21	-0.01	7.31	-0.11	7.27	-0.07
CMPD11 (1 HB)	7.48	7.46	0.02	7.71	-0.23	8.10	-0.62
CMPD12 (11)	5.60	5.75	-0.15	5.32	0.28	5.64	-0.04
CMPD14 (1 K)	6.05	6.06	-0.01	5.85	0.20	5.81	0.24
CMPD15 (1 L)	4.68	4.47	0.21	4.29	0.39	4.72	-0.04
CMPD16 (1M)	4.00	4.15	-0.15	4.63	-0.63	4.29	-0.29
Modified	EA	PA B	Δ	PA E	Δ	PA S	Δ
CMPD17	?	7.00	-0.05	6.90	-0.10	6.84	0.07
CMPD18	?	7.30	0.25	6.61	-0.39	7.38	0.61
CMPD19	?	7.34	0.29	7.23	0.23	6.82	0.05
CMPD20	?	6.68	-0.36	8.57	1.57	6.29	-0.48
CMPD21	?	6.96	-0.09	8.68	1.68	6.38	-0.39
CMPD22	?	7.45	0.12	7.51	0.17	7.54	-0.05
CMPD23	?	6.71	-0.34	7.16	0.16	6.79	0.02

Table 2b Set 2 Predicted Activities: CoMFA[c]

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01 (MLT)	9.52	9.53	-0.01	9.44	0.08	9.52	0.00
CMPD03 (1B)	6.62	6.61	0.01	6.87	-0.25	6.62	0.00
CMPD04 (1CA)	7.11	7.16	-0.05	6.94	0.17	7.10	0.01
CMPD05 (1CB)	7.46	7.47	-0.01	7.26	0.20	7.47	-0.01
CMPD06 (1D)	7.12	7.18	-0.06	7.31	-0.19	7.15	-0.03
CMPD07 (1E)	7.02	6.98	0.04	6.99	0.03	7.03	-0.01
CMPD08 (1F)	7.14	7.07	0.07	7.18	-0.04	7.11	0.03
CMPD10 (1HA)	7.20	7.21	-0.01	7.24	-0.04	7.21	-0.01
CMPD11 (1HB)	7.48	7.46	0.02	7.61	-0.13	7.48	0.00
CMPD14 (1K)	6.05	6.05	0.00	5.64	0.41	6.05	0.00
CMPD15 (1L)	4.68	4.62	0.06	4.30	0.38	4.70	-0.02
CMPD16 (1M)	4.00	4.06	-0.06	4.62	-0.62	3.99	0.01
Modified	EA	PA B	Δ	PA E	Δ	PA S	Δ
CMPD17	?	7.16	0.00	6.88	-0.06	7.27	0.17
CMPD18	?	7.42	0.26	6.62	-0.32	7.69	0.59
CMPD19	?	7.33	0.17	7.21	0.27	6.94	-0.17
CMPD20	?	6.40	-0.77	8.36	1.42	5.88	-1.22
CMPD21	?	6.66	-0.50	8.52	1.58	6.08	-1.02
CMPD22	?	7.33	-0.15	7.24	-0.02	7.18	-0.28
CMPD23	?	6.84	-0.32	7.15	0.21	7.13	0.02

Table 2c Set 2 Predicted Activities: CoMSIA

	EA	PA	RES
CMPD01 (MLT)	9.52	9.53	-0.01
CMPD03 (1B)	6.62	6.58	0.04
CMPD04 (1CA)	7.11	7.22	-0.11
CMPD05 (1CB)	7.46	7.52	-0.06
CMPD06 (1D)	7.12	7.25	-0.13
CMPD07 (1E)	7.02	6.97	0.05
CMPD08 (1F)	7.14	7.00	0.14
CMPD09 (1G)	6.66	6.66	0.00
CMPD10 (1HA)	7.20	7.14	0.06
CMPD11 (1HB)	7.48	7.44	0.04
CMPD12 (1I)	5.60	5.61	-0.01
CMPD13 (1J)	6.45	6.44	0.01
CMPD14 (1K)	6.05	6.08	-0.03
CMPD15 (1 L)	4.68	4.49	0.19
CMPD16 (1M)	4.00	4.19	-0.19
Modified	EA	PA	Δ
CMPD17	?	7.27	0.05
CMPD18	?	6.48	-0.74
CMPD19	?	6.23	-0.99
CMPD20	?	6.60	-0.62
CMPD21	?	6.38	-0.84
CMPD22	?	6.61	-0.91
CMPD23	?	7.33	0.11



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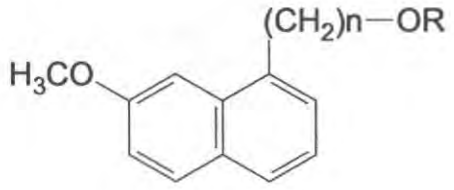

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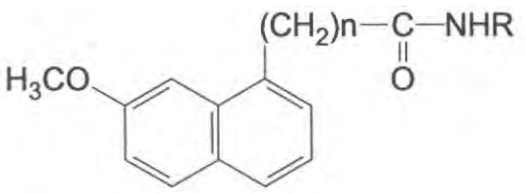

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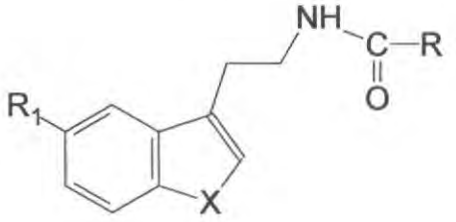

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Table 3 Set 3 Compounds

Compound	R_1	R_2	n	X	R	bio. act.
cmpd01	OCH_3	H	-	NH	CH_3	9.57
cmpd10	H	H	1	O	CH_3	8.40
cmpd11	H	H	1	O	C_3H_5	7.38
cmpd12	H	H	1	O	C_4H_7	7.40
cmpd13	H	H	1	O	CF_3	7.18
cmpd14	H	H	1	O	CH_2-C_6H_5	5.67
cmpd15	H	H	1	O	$(CH_2)_3C_6H_5$	5.84
cmpd16	H	$COOCH_3$	1	O	C_3H_5	6.04
cmpd17	H	$COOCH_3$	1	O	C_4H_7	5.16
cmpd18	OCH_3	H	0	O	CH_3	6.34
cmpd19	OCH_3	H	2	O	CH_3	8.34
cmpd20	OCH_3	H	2	O	nC_4H_9	6.71
cmpd21	OCH_3	H	2	O	C_3H_5	7.62
cmpd22	OCH_3	H	1	O	OCH_3	7.72
cmpd24	OCH_3	H	1	O	NH_2	8.45
cmpd25	OCH_3	H	1	O	$NHCH_3$	8.66
cmpd26	OCH_3	H	1	O	NHC_2H_5	8.17
cmpd28	OCH_3	H	1	O	$NHnC_4H_9$	5.61
cmpd29	OCH_3	H	1	O	$NHCH_2CH_2MN$	5.92
cmpd30	H	H	1	O	NH_2	6.62
cmpd31	H	H	1	O	$NHCH_3$	6.97
cmpd32	OCH_3	H	0	O	$NHnC_3H_7$	7.28
cmpd33	OCH_3	H	0	O	$NHnC_4H_9$	5.70
cmpd34	OCH_3	H	2	O	$NHnC_3H_7$	6.79

Table 3 Set 3 Compounds cont.

Compound	R_1	R_2	n	X	R	bio. act.
cmpd35	OCH_3	H	1	S	$NHCH_3$	8.05
cmpd38	OCH_3	H	1	S	$NHnC_4H_9$	5.44
cmpd39	-	-	2	-	CH_3	5.94
cmpd40	-	-	2	-	C_2H_5	6.09
cmpd41	-	-	3	-	$COCH_3$	6.70
cmpd42	-	-	2	-	$COCH_3$	6.16
cmpd43	-	-	2	-	H	6.36
cmpd44	-	-	2	-	CH_3	8.15
cmpd45	-	-	3	-	CH_3	8.29
cmpd46	-	-	3	-	nC_3H_7	7.37
cmpd47	-	-	1	-	$CH_2CH_2CH_2C_6H_5$	7.16
cmpd48	H	-	-	NH	nC_4H_9	5.60
cmpd49	H	-	-	NH	C_3H_5	6.81
cmpd50	H	-	-	NH	C_4H_7	5.65
cmpd51	H	-	-	NH	C_5H_9	5.57
cmpd53	OCH_3	-	-	NH	$NHCH_2CH_2MI$	6.40
cmpd54	OCH_3	-	-	O	$NHCH_3$	8.22
cmpd55	OCH_3	-	-	O	NHC_2H_5	8.37
cmpd56	OCH_3	-	-	O	$NHnC_3H_7$	7.33
cmpd57	H	-	-	O	C_4H_7	5.80
cmpd59	H	-	-	S	C_3H_5	7.53
cmpd60	H	-	-	S	C_4H_7	6.27

Test	Original	Modification(s)
cmpd61	cmpd19	n=3
cmpd62	cmpd19	OCH_2CH_3
cmpd63	cmpd20	n=3
cmpd64	cmpd21	n=3
cmpd65	cmpd25	OCH_2CH_3
cmpd66	cmpd10	OCH3
cmpd67	cmpd10	OCH_2CH_3
cmpd68	cmpd23	R=NHnC3H7
cmpd130	cmpd55	$C^{31}H_2F$
cmpd131	cmpd55	$C^{11}F_2$-
cmpd132	cmpd55	$NHCH(CH_3)_2$
cmpd133	cmpd55	OCH_2CH_3
cmpd134	cmpd55	$OCH(CH_3)_2$
cmpd135	cmpd01	$C^{14}H_2F$
cmpd136	cmpd01	$C^{14}H_2F$
cmpd137	cmpd01	OCH_2CH_3
cmpd138	cmpd01	$OCH(CH_3)_2$
cmpd139	cmpd24	$NHCH_3$
cmpd140	cmpd24	OCH_2CH_3
cmpd141	cmpd24	$OCH(CH_3)_2$
cmpd142	cmpd35	$C^{26}H_2F$
cmpd143	cmpd35	OCH_2CH_3

Table 3 Set 3 Compounds cont.

Test	Original	Modification(s)
cmpd44	cmpd35	$OCH(CH_3)_2$
cmpd145	cmpd25	$C^{26}H_2CH_3$
cmpd146	cmpd25	replace =O with F
cmpd147	cmpd25	OCH_2CH_3
cmpd148	cmpd19	$C^{12}H_2F$
cmpd149	cmpd19	OCH_2CH_3
cmpd150	cmpd25	$OCH(CH_3)_2$
cmpd151	cmpd25	$OC(CH_3)_3$
cmpd152	cmpd25	$OCH(CH_3)_2$
cmpd153	cmpd19	$OCH(CH_3)_2$
cmpd154	cmpd54	OCH_2CH_3
cmpd155	cmpd54	OCH_2CH_3, $C^{16}H_2F$

[a] MLT [b] MN: 7-Methoxy-1-naphthyl [c] MI: 5-Methoxy-3-indolyl

Table 3A

Set 3: Summary of the Statistical Results for the PLS Analyses [21,a]

Ovine Pars Tuberalis Membrane Binding

	All CoMFA[b]			All CoMSIA[c]	Cmpds 10-38 CoMFA[d]		
	B	E	S		B	E	S
Q^2	0.548	0.420	0.399	0.621	0.689	0.657	0.631
no. comp	6	2	5	4	6	6	6
s	0.202	0.599	0.326	0.413	0.074	0.106	0.120
R^2	0.972	0.721	0.924	0.882	0.997	0.993	0.991
F	184.638	46.621	80.469	59.861	698.533	338.734	259.474
Prob. R^2=0	0.000	0.000	0.000	0.000	0.000	0.000	0.000

	Cmpds 10-47 CoMFA[e]			Cmpds 48-60 CoMFA[f]		
	B	E	S	B	E	S
Q^2	0.651	0.379	0.547	0.679	0.545	0.660
no. comp	6	6	5	3	6	2
s	0.128	0.214	0.266	0.282	0.138	0.000
R^2	0.987	0.963	0.940	0.970	0.996	1.000
F	276.302	95.567	72.480	63.715	135.907	
Prob. R^2=0	0.000	0.000	0.000	0.000	0.001	

[a] Alignment using cmpd18 as the basic molecule [b] Outliers: 10, 11, 12, 15, 32, 44, 59 [c] Outliers: 10, 11, 12, 15, 30, 32, 41, 44, 59 [d] Outliers: 10, 24, 30, 31 [e] Outliers: 10, 24, 30, 31, 44 f Outliers: 55, 59

Table 3a Set 3 CoMFA All

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	9.57	9.54	0.03	8.22	1.35	9.26	0.31
CMPD13	7.18	7.01	0.17	6.48	0.71	6.98	0.20
CMPD14	5.67	5.50	0.17	5.07	0.60	5.44	0.23
CMPD16	6.04	6.15	-0.11	5.45	0.59	6.32	-0.28
CMPD17	5.16	4.92	0.24	5.12	0.04	4.99	0.17
CMPD18	6.34	6.19	0.15	5.79	0.55	6.11	0.23
CMPD19	8.34	8.25	0.09	7.79	0.55	8.59	-0.25
CMPD20	6.71	7.01	-0.30	7.30	-0.59	7.19	-0.48
CMPD21	7.62	7.52	0.10	7.64	-0.02	7.55	0.07
CMPD22	7.72	7.86	-0.14	7.57	0.15	7.89	-0.17
CMPD24	8.45	8.26	0.19	8.44	0.01	7.72	0.73
CMPD25	8.66	8.53	0.13	7.84	0.82	8.15	0.51
CMPD26	8.17	7.89	0.28	7.04	1.13	7.84	0.33
CMPD28	5.61	5.61	0.00	6.51	-0.90	5.56	0.05
CMPD29	5.92	5.70	0.22	6.00	-0.08	5.99	-0.07
CMPD30	6.62	6.84	-0.22	7.12	-0.50	6.92	-0.30
CMPD31	6.97	6.78	0.19	6.80	0.17	7.18	-0.21
CMPD33	5.70	5.88	-0.18	5.60	0.10	5.65	0.05
CMPD34	6.79	6.95	-0.16	7.09	-0.30	6.81	-0.02
CMPD35	8.05	8.01	0.04	7.96	0.09	7.72	0.33
CMPD38	5.44	5.51	-0.07	6.49	-1.05	5.25	0.19
CMPD39	5.94	6.24	-0.30	6.07	-0.13	6.03	-0.09
CMPD40	6.09	6.08	0.01	6.48	-0.39	6.23	-0.14
CMPD41	6.70	6.96	-0.26	6.64	0.06	7.35	-0.65
CMPD42	6.16	5.86	0.30	6.10	0.06	6.42	-0.26
CMPD43	6.36	6.36	0.00	6.04	0.32	6.62	-0.26
CMPD45	8.29	8.24	0.05	7.96	0.33	8.06	0.23
CMPD46	7.37	7.12	0.25	6.70	0.68	6.99	0.38
CMPD47	7.16	7.25	-0.09	7.95	-0.79	7.53	-0.37
CMPD48	5.60	5.94	-0.34	5.99	-0.39	5.87	-0.26
CMPD49	6.81	6.74	0.07	6.76	0.05	6.76	0.05
CMPD50	5.65	5.78	-0.13	6.29	-0.64	5.79	-0.14
CMPD51	5.57	5.78	-0.21	6.26	-0.69	5.40	0.17
CMPD53	6.40	6.42	-0.02	6.96	-0.56	6.78	-0.38
CMPD54	8.22	8.53	-0.30	8.12	0.10	8.56	-0.34
CMPD55	8.37	8.29	0.08	8.35	0.02	8.32	0.05
CMPD56	7.33	7.56	-0.23	8.19	-0.86	7.41	-0.08
CMPD57	5.80	5.62	0.18	6.77	-0.97	5.91	-0.11
CMPD60	6.27	6.16	0.11	5.87	0.40	5.71	0.56
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD61	?	5.59	-2.66	6.55	-1.24	7.00	-1.60
CMPD62	?	8.25	0.00	7.85	0.06	8.82	0.23
CMPD63	?	5.03	-1.98	6.07	-1.24	6.23	-0.96
CMPD64	?	6.54	-0.98	6.33	-1.31	7.76	0.21
CMPD65	?	8.22	-0.31	7.72	-0.12	8.80	0.65
CMPD130	?	9.09	0.80	8.64	0.29	8.30	-0.02
CMPD131	?	8.88	0.59	8.76	0.41	8.32	0.00
CMPD132	?	8.43	0.14	7.71	-0.64	8.55	0.23
CMPD133	?	8.49	0.20	7.88	-0.48	8.88	0.56
CMPD134	?	8.49	0.20	7.68	-0.67	9.54	1.22
CMPD135	?	8.88	-0.65	7.75	-0.47	9.40	0.15
CMPD136	?	9.79	0.25	7.85	-0.37	7.95	-1.31
CMPD137	?	9.28	-0.25	7.76	-0.46	8.19	-1.07
CMPD138	?	9.54	0.00	8.23	0.01	8.72	-0.54
CMPD139	?	7.73	-0.53	7.23	-1.21	7.63	-0.08
CMPD140	?	8.48	0.22	7.89	-0.54	8.29	0.57
CMPD141	?	7.49	-0.77	6.88	-1.56	7.66	-0.05
CMPD142	?	8.42	0.40	6.44	-1.53	7.08	-0.65
CMPD143	?	7.96	-0.05	6.67	-1.29	7.59	-0.14
CMPD144	?	8.04	0.03	6.49	-1.47	7.76	0.04

Table 3b Set 3 CoMSIA All

	EA	PA	RES
CMPD01	9.57	8.65	0.92
CMPD13	7.18	7.02	0.16
CMPD14	5.67	5.41	0.26
CMPD16	6.04	5.70	0.34
CMPD17	5.16	5.26	-0.10
CMPD18	6.34	6.62	-0.28
CMPD19	8.34	8.39	-0.05
CMPD20	6.71	6.74	-0.03
CMPD21	7.62	7.77	-0.15
CMPD22	7.72	8.01	-0.29
CMPD24	8.45	8.71	-0.25
CMPD25	8.66	8.70	-0.04
CMPD26	8.17	7.34	0.83
CMPD28	5.61	6.16	-0.55
CMPD29	5.92	5.69	0.23
CMPD31	6.97	7.43	-0.46
CMPD33	5.70	5.37	0.33
CMPD34	6.79	7.42	-0.62
CMPD35	8.05	7.65	0.40
CMPD38	5.44	5.16	0.28
CMPD39	5.94	6.56	-0.62
CMPD40	6.09	6.34	-0.25
CMPD42	6.16	5.94	0.22
CMPD43	6.36	6.56	-0.20
CMPD45	8.29	8.40	-0.11
CMPD46	7.37	6.89	0.48
CMPD47	7.16	6.61	0.55
CMPD48	5.60	5.76	-0.16
CMPD49	6.81	6.44	0.37
CMPD50	5.65	6.34	-0.69
CMPD51	5.57	5.93	-0.36
CMPD53	6.40	6.42	-0.02
CMPD54	8.22	8.31	-0.09
CMPD55	8.37	8.15	0.22
CMPD56	7.33	7.45	-0.12

Table 3c Set 3 CoMFA Cmpds 10-38

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD11	7.38	7.42	-0.04	7.52	-0.13	7.31	0.07
CMPD12	7.40	7.35	0.05	7.36	0.04	7.48	-0.08
CMPD13	7.18	7.11	0.07	7.21	-0.03	7.07	0.12
CMPD14	5.67	5.66	0.01	5.64	0.03	5.73	-0.06
CMPD15	5.84	5.83	0.01	5.81	0.03	5.91	-0.07
CMPD16	6.04	6.06	-0.02	5.98	0.06	6.03	0.01
CMPD17	5.16	5.13	0.03	5.16	0.00	5.14	0.02
CMPD18	6.34	6.32	0.02	6.36	-0.02	6.37	-0.03
CMPD19	8.34	8.26	0.08	8.36	-0.02	8.45	-0.11
CMPD20	6.71	6.68	0.03	6.69	0.02	6.71	0.00
CMPD21	7.62	7.68	-0.06	7.67	-0.05	7.72	-0.09
CMPD22	7.72	7.75	-0.03	7.59	0.13	7.87	-0.15
CMPD25	8.66	8.70	-0.04	8.60	0.06	8.36	0.30
CMPD26	8.17	8.07	0.10	8.19	-0.02	8.31	-0.14
CMPD28	5.61	5.79	-0.18	5.47	0.14	5.63	-0.02
CMPD29	5.92	5.92	0.00	5.93	-0.01	5.91	0.01
CMPD32	7.28	7.32	-0.04	7.30	-0.02	7.24	0.04
CMPD33	5.70	5.68	0.02	5.66	0.04	5.69	0.01
CMPD34	6.79	6.82	-0.03	6.98	-0.19	6.71	0.08
CMPD35	8.05	8.10	-0.05	7.93	0.12	7.98	0.07
CMPD38	5.44	5.37	0.07	5.62	-0.18	5.40	0.04
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD145	?	8.33	-0.37	8.08	-0.53	7.96	-0.40
CMPD146	?	7.73	-0.98	7.36	-1.25	7.53	-0.83
CMPD147	?	8.72	0.02	8.58	-0.02	8.35	-0.01
CMPD148	?	7.89	-0.37	8.22	-0.13	8.39	-0.06
CMPD149	?	8.28	0.02	8.29	-0.07	8.43	-0.01

Table 3d Set 3 CoMFA Cmpds 10-47

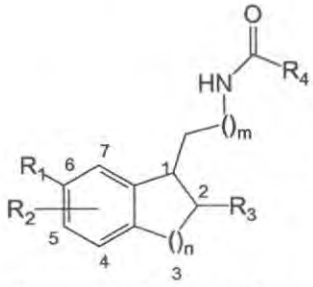
	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD11	7.38	7.57	-0.19	7.38	0.00	7.50	-0.12
CMPD12	7.40	7.42	-0.02	7.41	-0.01	7.61	-0.21
CMPD13	7.18	7.13	0.05	6.94	0.24	7.03	0.15
CMPD14	5.67	5.52	0.15	5.73	-0.06	5.62	0.05
CMPD15	5.84	5.79	0.06	5.73	0.11	5.90	-0.06
CMPD16	6.04	6.07	-0.03	6.14	-0.10	5.95	0.09
CMPD17	5.16	5.21	-0.05	5.19	-0.03	5.31	-0.15
CMPD18	6.34	6.30	0.04	6.36	-0.02	6.04	0.30
CMPD19	8.34	8.21	0.13	8.34	0.00	8.34	0.00
CMPD20	6.71	6.78	-0.07	6.83	-0.12	6.87	-0.16
CMPD21	7.62	7.65	-0.03	7.56	0.06	7.77	-0.15
CMPD22	7.72	7.82	-0.10	7.52	0.20	8.07	-0.35
CMPD25	8.66	8.65	0.01	8.58	0.08	7.98	0.68
CMPD26	8.17	7.97	0.20	8.01	0.16	8.05	0.12
CMPD28	5.61	5.83	-0.22	5.65	-0.04	5.54	0.07
CMPD29	5.92	5.83	0.09	5.79	0.14	5.99	-0.07
CMPD32	7.28	7.46	-0.18	. 7.208	0.07	7.59	-0.31
CMPD33	5.70	5.62	0.08	5.67	0.03	5.55	0.15

Table 3d Set 3 CoMFA Cmpds 10-47 cont.

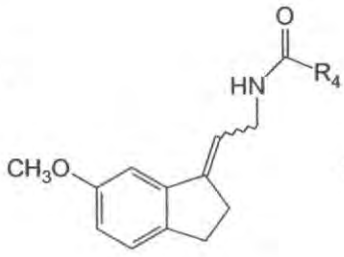
CMPD34	6.79	6.82	-0.03	7.39	-0.60	6.56	0.23
CMPD35	8.05	8.12	-0.07	8.26	-0.21	7.99	0.06
CMPD38	5.44	5.48	-0.03	5.57	-0.13	5.26	0.18
CMPD39	5.94	6.18	-0.24	6.26	-0.32	6.20	-0.26
CMPD40	6.09	6.08	0.01	5.94	0.15	6.14	-0.05
CMPD41	6.70	6.69	0.01	6.74	-0.04	6.87	-0.17
CMPD42	6.16	6.12	0.04	6.27	-0.11	6.51	-0.35
CMPD43	6.36	6.26	0.10	6.25	0.11	6.71	-0.35
CMPD45	8.29	8.27	0.02	8.38	-0.09	8.01	0.28
CMPD46	7.37	7.30	0.07	6.90	0.48	7.36	0.01
CMPD47	7.16	6.97	0.19	7.11	0.05	6.79	0.37
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD147	?	8.71	0.05	8.57	-0.01	8.04	0.06
CMPD149	?	8.26	0.05	8.23	-0.12	8.42	0.08
CMPD150	?	8.75	0.10	8.51	-0.07	8.13	0.16
CMPD151	?	7.72	-0.93	8.00	-0.58	8.00	0.02
CMPD152	?	7.67	-0.98	6.91	-1.67	7.59	-0.39
CMPD153	?	8.26	0.05	7.93	-0.41	8.44	0.11

Table 3e Set 3 CoMFA Cmpds 48-60

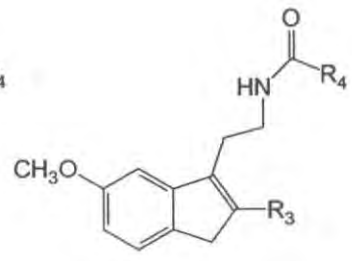
	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	9.57	9.66	-0.09	9.54	0.03	9.57	0
CMPD48	5.60	6.01	-0.41	5.64	-0.04	5.60	0
CMPD49	6.81	6.43	0.38	6.69	0.12	6.81	0
CMPD50	5.65	5.88	-0.23	5.63	0.02	5.65	0
CMPD51	5.57	5.58	-0.01	5.70	-0.13	5.57	0
CMPD53	6.40	6.43	-0.03	6.38	0.02	6.40	0
CMPD54	8.22	8.25	-0.03	8.29	-0.07	8.22	0
CMPD56	7.33	7.16	0.17	7.35	-0.01	7.33	0
CMPD57	5.80	5.81	-0.01	5.68	0.12	5.80	0
CMPD60	6.27	6.01	0.26	6.32	-0.05	6.27	0
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD154	?	8.45	0.20	7.73	-0.56	8.52	0.30
CMPD155	?	8.49	0.24	8.18	-0.11	8.46	0.24



8a-n, 13, 19, 20, 21a-c



(E)-9a, (Z)-9a



10a-d

Table 4 Set 4 Compounds

Compound	R_1	R_2	R_3	R_4	n	m	bio. act.
comp01	-	-	-	-	-	1	1.08
cmpd08a	CH_3O	H	H	CF_3	3	1	-0.22
cmpd08b	CH_3O	H	H	CF_3	2	1	1.33
cmpd08c	CH_3O	H	H	CH_3	1	1	0.88
cmpd08d	CH_3O	H	H	C_2H_5	1	1	1.14
cmpd08e	CH_3O	H	H	$(CH_2)_2CH_3$	1	1	1.26
cmpd08f	CH_3O	H	H	$(CH_2)_3CH_3$	1	1	-0.12
cmpd08g	CH_3O	H	H	$CH(CH_3)_2$	1	1	0.60
cmpd08h	CH_3O	H	H	CF_3	1	1	1.65
cmpd08i	CH_3O	7-CH_3	H	CF_3	1	1	-1.45
cmpd08j	CH_3O	5-CH_3	H	CF_3	1	1	1.01
cmpd08k	CH_3O	7-CH_3O	H	CF_3	1	1	-1.67
cmpd08l	CH_3O	5-CH_3O	H	CF_3	1	1	-0.61
cmpd08m	CH_3O	H	C_6H_5	CF_3	1	1	-0.20
cmpd08n	H	H	H	CF_3	1	1	-1.09
cmpd09a(E)	-	-	-	C_2H_5	-	-	0.68
cmpd09a(Z)	-	-	-	C_2H_5	-	-	0.03
cmpd10a	-	-	H	C_2H_5	-	-	1.64
cmpd10b	-	-	H	CF_3	-	-	1.39
cmpd10c	-	-	C_6H_5	CF_3	-	-	2.22
cmpd10d	-	-	$CH_2C_6H_5$	CF_3	-	-	-0.84
cmpd13	CH_3O	H	H	CF_3	1	0	-1.46
cmpd19	CH_3O	H	H	CF_3	1	2	0.28
cmpd20	OH	H	H	C_2H_5	1	1	-1.38
cmpd21a	C_2H_5O	H	H	C_2H_5	1	1	1.00
cmpd21b	$CH_3(CH_2)_2O$	H	H	C_2H_5	1	1	0.37
cmpd21c	$(CH_3)_2CHO$	H	H	C_2H_5	1	1	-0.16

Test	Original	Modification(s)
cmpd22	cmpd10c	OCH_2CH_3
cmpd23	cmpd10c	delete =O
cmpd24	cmpd10a	OCH_2CH_3
cmpd25	cmpd08h	OCH_2CH_3
cmpd26	cmpd10c	$OCH_2CH(CH_3)_2$
cmpd27	cmpd10c	$OCH_2CH_2CH_3$
cmpd28	cmpd10c	$CH_2CH_2CH_3$

Table 4 Set 4 Compounds cont.

Test	Original	Modification(s)
cmpd29	cmpd10c	$CH_2C(CH_3)_3$
cmpd30	cmpd10c	$OC(CH_3)_3$
cmpd31	cmpd10c	O-Ph
cmpd32	cmpd10c	delete F
cmpd33	cmpd10c	delete Ph group
cmpd34	cmpd10c	$OCH(CH_3)_2$
cmpd35	cmpd10c	OCH_2CH_3
cmpd36	cmpd10a	replace N with O
cmpd37	cmpd10c	$C^{16}(CH_3)_3$
cmpd38	cmpd08h	$C^{16}H(CF_3)_2$
cmpd39	cmpd10a	replace C^{16} with O
cmpd40	cmpd10a	OCH_2CH_3
cmpd41	cmpd10a	$OCH(CH_3)_2$
cmpd42	cmpd10a	OCH_2CH_3, $C^{16}(CH_3)_3$
cmpd43	cmpd10a	C^2Br
cmpd44	cmpd10a	OCH_2CH_3, $C^{16}(CH_3)_3$, C^2Br
cmpd45	cmpd10b	C^2Br
cmpd46	cmpd10b	OCH_2CH_3, C^2Br
cmpd47	cmpd10b	$C^{11}(CH_3)_2$-
cmpd48	cmpd10b	N-CH_3
cmpd49	cmpd10b	OCH_2CH_3
cmpd50	cmpd10b	CH_2CF_3
cmpd51	cmpd10b	N-$C(CH_3)_3$
cmpd52	cmpd10a	N-$CH(CH_3)_2$
cmpd53	cmpd10a	OCH_2CH_3, N-$CH(CH_3)_2$
cmpd54	cmpd10b	N-$CH(CH_3)_2$
cmpd55	cmpd10b	OCH_2CH_3, N-$CH(CH_3)_2$
cmpd56	cmpd01	N-CH_3
cmpd57	cmpd10b	replace F with H
cmpd58	cmpd10b	replace =O with Br and CH3
cmpd59	cmpd01	$C^{13}(CH_3)_2$-
cmpd60	cmpd01	C^{13}HBr-
cmpd61	cmpd10a	OCH_2CH_3

[a] MLT

Table 4A

Set 4: Summary of the Statistical Results for the PLS Analyses [5,a]

	Human MT_1			Hamster MT_3			
	CoMFA[b]			CoMFA[c]			CoMSIA[d]
	B	E	S	B	E	S	
Q^2	0.541	0.346	0.611	0.706	0.794	0.696	0.642
no. comp	6	4	6	6	5	6	3
s	0.116	0.186	0.144	0.065	0.078	0.051	0.187
R^2	0.993	0.979	0.989	0.995	0.991	0.997	0.947
F	363.027	209.191	236.837	362.749	300.282	576.504	95.831
Prob. R^2=0	0.000	0.000	0.000	0.000	0.000	0.000	0.000

[a] Alignment using cmpd08c as the basic molecule [b] Outliers: 8d, 8f, 21a, 21c [c] Outliers: 8b, 8j, 9ae, 9az, 10d, 21c [d] Outliers: 8c, 8h, 8k, 9az, 10d

Table 4a Set 4 CoMFA Human MT_1

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	1.08	1.10	-0.02	1.27	-0.19	1.02	0.06
CMPD08A	-0.22	-0.31	0.09	-0.27	0.05	-0.31	0.09
CMPD08B	1.33	1.34	-0.01	1.32	0.01	1.40	-0.07
CMPD08C	0.88	0.76	0.12	0.81	0.07	0.76	0.12
CMPD08E	1.26	1.22	0.04	1.42	-0.16	1.25	0.01
CMPD08G	0.60	0.64	-0.04	0.48	0.12	0.70	-0.10
CMPD08H	1.65	1.32	0.33	1.41	0.24	1.30	0.35
CMPD081	-1.45	-1.55	0.10	-1.01	-0.44	-1.51	0.06
CMPD08J	1.01	1.15	-0.14	1.20	-0.19	1.16	-0.15
CMPD08K	-1.67	-1.71	0.04	-1.63	-0.04	-1.61	-0.06
CMPD08L	-0.61	-0.58	-0.03	-0.61	0.00	-0.63	0.02
CMPD08M	-0.20	-0.10	-0.10	-0.15	-0.05	-0.08	-0.12
CMPD08N	-1.09	-1.12	0.03	-1.29	0.20	-1.03	-0.06
CMPD09AE	0.68	0.79	-0.11	0.89	-0.21	0.87	-0.19
CMPD09AZ	0.03	0.12	-0.09	-0.02	0.05	0.17	-0.14
CMPD10A	1.64	1.61	0.03	1.48	0.16	1.52	0.12
CMPD10B	1.39	1.44	-0.04	1.50	-0.10	1.48	-0.09
CMPD10C	2.22	2.25	-0.03	2.17	0.06	2.15	0.07
CMPD10D	-0.84	-0.85	0.01	-0.97	0.13	-0.86	0.02
CMPD13	-1.46	-1.42	-0.04	-1.57	0.11	-1.53	0.07
CMPD19	0.28	0.25	0.03	0.12	0.16	0.27	0.01
CMPD20	-1.38	-1.33	-0.05	-1.20	-0.18	-1.49	0.11
CMPD21B	0.37	0.48	-0.11	0.18	0.19	0.50	-0.13
Modified	EA	PA B	Δ	PA E	Δ	PA S	Δ
CMPD22	?	2.28	0.03	0.95	-1.22	2.39	0.24
CMPD23	?	1.53	-0.72	2.23	0.07	2.16	0.01
CMPD24	?	1.70	0.08	0.42	-1.06	1.75	0.23
CMPD25	?	1.39	0.07	0.34	-1.07	1.54	0.24
CMPD26	?	2.13	-0.12	0.75	-1.42	2.44	0.29
CMPD27	?	2.26	0.01	0.88	-1.29	2.37	0.22
CMPD28	?	1.74	-0.51	-0.61	-2.78	2.36	0.21
CMPD29	?	1.43	-0.82	-0.56	-2.72	1.78	-0.37

Table 4a Set 4 CoMFA Human MT_1 cont.

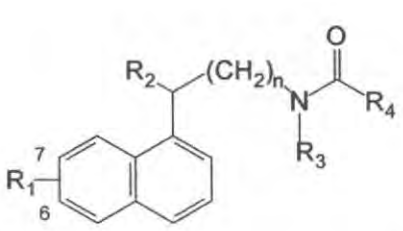
Modified	EA	PA B	Δ	PA E	Δ	PA S	Δ
CMPD30	?	1.81	-0.44	1.41	-0.75	1.77	-0.38
CMPD31	?	1.52	-0.73	0.67	-1.50	2.00	-0.15
CMPD32	?	2.53	0.28	2.09	-0.08	2.16	0.01
CMPD33	?	1.40	-0.85	1.21	-0.96	1.59	-0.56
CMPD34	?	2.17	-0.08	1.28	-0.88	2.39	0.24
CMPD35	?	1.76	-0.49	0.62	-1.55	2.36	0.21
CMPD36	?	1.80	0.19	1.87	0.39	1.95	0.43
CMPD37	?	1.83	-0.42	1.50	-0.66	1.68	-0.47
CMPD38	?	1.23	-0.09	1.45	0.05	1.46	0.16

Table 4b Set 4 CoMFA Human MT_3

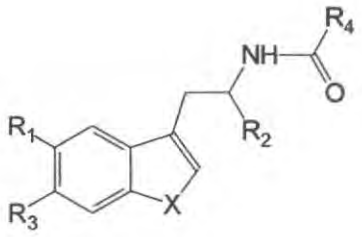
	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	-1.44	-1.47	0.03	-1.43	-0.01	-1.45	0.01
CMPD08C	-2.50	-2.56	0.05	-2.70	0.20	-2.51	0.01
CMPD08D	-2.84	-2.92	0.08	-2.74	-0.10	-2.97	0.13
CMPD08E	-2.98	-2.91	-0.07	-3.04	0.06	-2.90	-0.08
CMPD08F	-2.92	-2.98	0.06	-2.91	-0.01	-2.95	0.03
CMPD08G	-3.36	-3.33	-0.03	-3.29	-0.07	-3.36	0.00
CMPD08H	-2.70	-2.60	-0.10	-2.66	-0.04	-2.64	-0.06
CMPD081	-3.41	-3.46	0.05	-3.48	0.07	-3.42	0.01
CMPD08K	-3.50	-3.52	0.02	-3.45	-0.05	-3.50	0.00
CMPD08L	-2.89	-2.93	0.04	-2.82	-0.07	-2.89	0.00
CMPD08M	-3.25	-3.24	-0.01	-3.27	0.01	-3.27	0.02
CMPD10A	-1.69	-1.71	0.02	-1.65	-0.04	-1.69	0.00
CMPD10B	-0.96	-0.96	0.00	-0.97	0.01	-0.99	0.03
CMPD10C	-1.68	-1.64	-0.04	-1.72	0.04	-1.66	-0.02
CMPD13	-2.63	-2.60	-0.03	-2.63	0.00	-2.62	-0.01
CMPD19	-2.55	-2.59	0.04	-2.53	-0.02	-2.55	0.00
CMPD20	-3.26	-3.19	-0.07	-3.24	-0.02	-3.22	-0.04
CMPD21A	-2.88	-2.92	0.04	-2.92	0.04	-2.89	0.01
CMPD218	-2.91	-2.83	-0.08	-2.91	0.00	-2.89	-0.03
Modified	EA	PA B	Δ	PA E	Δ	PA S	Δ
CMPD24	?	-1.53	0.19	-1.76	-0.11	-1.52	0.17
CMPD47	?	-1.25	-0.29	-1.15	-0.18	1.40	2.39
CMPD48	?	-0.90	0.06	-1.01	-0.04	-0.93	0.05
CMPD49	?	-0.81	0.15	-0.99	-0.02	-0.83	0.16
CMPD50	?	-1.26	-0.30	-1.27	-0.30	-1.37	-0.38
CMPD51	?	-0.97	-0.01	-0.91	0.06	-0.96	0.02
CMPD52	?	-1.55	0.16	-1.25	0.40	-1.58	0.11
CMPD53	?	-1.38	0.33	-1.34	0.31	-1.39	0.30
CMPD54	?	-0.93	0.03	-0.95	0.02	-0.94	0.05
CMPD55	?	-0.80	0.16	-0.99	-0.02	-0.83	0.15
CMPD56	?	-1.40	0.31	-1.34	0.31	-1.42	0.27

Table 4c Set 4 CoMSIA MT_3

	EA	PA	RES
CMPD01	-1 .44	-1.54	0.10
CMPD08B	-2.78	-3.05	0.27
CMPD08D	-2.84	-3.05	0.21
CMPD08E	-2.98	-3.01	0.03
CMPD08F	-2.92	-3.00	0.08
CMPD08G	-3.36	-3.32	-0.04
CMPD081	-3.41	-3.21	-0.20
CMPD08J	-3.66	-3.32	-0.34
CMPD08L	-2.89	-2.99	0.10
CMPD08M	-3.25	-3.40	0.15
CMPD09AE	-3.08	-2.93	-0.15
CMPD10A	-1.69	-1.51	-0.18
CMPD10B	-0.96	-1.05	0.09
CMPD10C	-1.68	-1.60	-0.08
CMPD13	-2.63	-2.51	-0.12
CMPD19	-2.55	-2.50	-0.05
CMPD20	-3.26	-3.20	-0.06
CMPD21A	-2.88	-3.10	0.22
CMPD21B	-2.91	-3.06	0.15
CMPD21C	-3.74	-3.57	-0.17
Modified	EA	PA	Δ
CMPD45	?	-1.01	0.04
CMPD46	?	-1.02	0.03
CMPD48	?	-1.63	-0.58
CMPD49	?	-1.09	-0.04
CMPD54	?	-1.75	-0.70
CMPD55	?	-1.75	-0.70
CMPD57	?	-1.06	-0.01
CMPD58	?	-1.58	-0.53
CMPD59	?	-1.61	-0.07
CMPD60	?	-1.71	-0.17



72-94



95-104

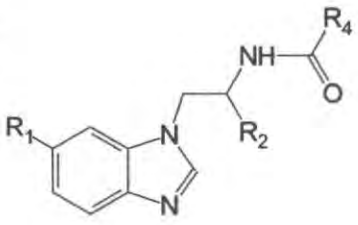


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Table 5 Set 5 Compounds

Compound	R_1	R_2	n or x	R_3	R_4	bio. act.
cmpd01	OCH_3	H	-	NH	CH_3	9.57
cmpd72	7-OCH_3	H	1	H	CH_3	10.12
cmpd73	7-OCH_3	H	1	H	n-C_3H_7	11.46
cmpd74	7-OCH_3	H	1	H	C_5H_9	6.51
cmpd75	7-OCH_3	H	1	H	C_6H_{11}	6.36
cmpd76	7-OCH_3	H	1	H	CH_2Br	11.93
cmpd77	7-OCH_3	H	1	H	n-C_3H_6Cl	10.82
cmpd78	7-OCH_3	H	1	H	C_6H_5	5.60
cmpd79	7-OCH_3	H	1	H	(3,5-diClC_6H_3)	5.00
cmpd80	7-OCH_3	H	1	H	(2-indolyl)	5.57
cmpd81	7-OCH_3	H	1	H	$CH_2C_6H_5$	5.01
cmpd82	7-OCH_3	H	1	H	$CH(C_6H_5)_2$	4.99
cmpd83	7-OCH_3	H	1	H	$(CH_2)_2C_6H_5$	5.58
cmpd85	7-OCH_3	H	1	H	CH_2-4-morph	6.50
cmpd86	7-OCH_3	H	1	H	CH_2-TMZ	5.52
cmpd87	7-OCH_3	H	1	NR_3R_4 = 2-pyrr		7.00
cmpd88	7-OCH_3	H	1	CH_3	CH_3	7.59
cmpd89	7-OCH_3	H	1	CH_3	C_4H_7	5.88
cmpd90	6-OCH_3	H	1	H	CH_3	6.91
cmpd91	6-OCH_3	H	1	H	C_4H_7	5.73
cmpd92	6-OCH_3	H	1	H	CF_3	5.73
cmpd93	7-OCH_3	H	1	H	CH_3	6.61
cmpd94	7-OCH_3	$COOCH_3$	1	H	CH_3	7.50
cmpd95	OCH_3	H	NH	H	C_3H_5	13.30
cmpd96	OCH_3	H	NH	H	CH_2I	9.01
cmpd97	OCH_3	H	NH	F	C_3H_5	8.72
cmpd98	OCH_3	H	O	H	CH_3	8.77
cmpd99	OCH_3	H	O	H	n-C_4H_9	8.24
cmpd100	OCH_3	H	O	H	C_3H_5	8.26
cmpd101	OCH_3	H	S	H	CH_3	8.92
cmpd102	OCH_3	H	S	H	C_3H_5	8.40
cmpd103	OCH_3	H	S	H	C_4H_7	7.33
cmpd104	OCH_3	H	S	H	CH_2I	8.41
cmpd105	OCH_3	H	-	H	CH_3	5.28

Table 5 Set 5 Compounds cont.

Test	Original	Modification(s)
cmpd106	cmpd81	OCH_2CH_3
cmpd107	cmpd81	$C^{16}F$
cmpd108	cmpd81	$C^{17}F$
cmpd109	cmpd81	$C^{16}F$, $C^{17}F$
cmpd110	cmpd81	$C^{43}(CH_3)_2$-
cmpd111	cmpd81	$C^{26}CH_3$
cmpd112	cmpd94	$C^{31}CH_3$
cmpd113	cmpd94	OCH_2CH_3
cmpd114	cmpd94	$C^{14}F$
cmpd115	cmpd96	$C^{14}(CH_3)_2$-
cmpd116	cmpd96	N-NH_2
cmpd117	cmpd96	$C^{14}I_3$
cmpd118	cmpd96	replace =O with F
cmpd119	cmpd96	remove I
cmpd120	cmpd96	replace I with CH_3
cmpd121	cmpd97	OCH_2CH_3
cmpd122	cmpd97	$C^{26}CH_3$
cmpd123	cmpd97	$C^{14}CH_3$
cmpd124	cmpd97	$C^{11}F$
cmpd125	cmpd99	OCH_2CH_3
cmpd126	cmpd99	$C^{14}CH_3$
cmpd127	cmpd99	$C^{26}CH_3$
cmpd128	cmpd99	$C^{38}CH_3$
cmpd129	cmpd99	$C^{11}F_2$

[a] MLT [b] morph: morpholino [c] TMZ: 1-(2',3',4'-trimethoxybenzyl) [d] 2-pyrr: 2-pyrrolidinone

Table 5A

Set 5: Summary of the Statistical Results for the PLS Analyses [18,a]

Ovine Pars Tuberalis Membrane Binding

	All				Cmpds 72-94			
	CoMFA[b]			CoMSIA[c]	CoMFA[d]			CoMSIA[e]
	B	E	S		B	E	S	
Q^2	0.835	0.843	0.823	0.841	0.780	0.418	0.592	0.583
no. comp	5	5	5	2	6	4	5	6
s	0.173	0.229	0.219	0.358	0.070	0.352	0.163	0.108
R^2	0.986	0.976	0.978	0.934	0.995	0.850	0.970	0.986
F	320.871	181.258	197.153	176.599	396.785	19.864	84.248	116.376
Prob. R^2=0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

	Cmpds 95-105			
	CoMFA[f]			CoMSIA[g]
	B	E	S	
Q^2	0.357	0.615	0.411	0.798
no. comp	5	3	4	3
s	0.003	0.123	0.042	0.032
R^2	1.000	0.977	0.998	0.992
F	34293.898	42.791	280.345	124.651
Prob. R^2=0	0.004	0.006	0.004	0.001

[a] Alignment using cmpd18[(21)] as the basic molecule [b] Outliers: 72, 73, 76, 77, 76, 105 [c] Outliers: 72, 73, 76, 77, 95, 105 [d] Outliers: 72, 73, 76, 77 [e] Outliers: 72, 73, 76, 77, 87, 94 [f] Outliers: 102, 105 [g] Outliers: 95, 96, 103, 105

Table 5a Set 5 CoMFA All

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD74	6.51	6.30	0.22	6.55	-0.04	6.41	0.10
CMPD75	6.36	6.45	-0.09	6.34	0.02	6.58	-0.22
CMPD78	5.60	5.63	-0.03	5.49	0.11	5.70	-0.10
CMPD79	5.00	5.04	-0.04	4.98	0.02	4.90	0.10
CMPD80	5.57	5.73	-0.16	5.54	0.04	5.67	-0.10
CMPD81	5.01	5.06	-0.05	5.18	-0.17	5.18	-0.17
CMPD82	4.99	4.95	0.04	5.17	-0.18	4.80	0.19
CMPD83	5.58	5.57	0.01	5.62	-0.04	5.57	0.01
CMPD84	5.61	5.40	0.21	5.55	0.06	5.44	0.17
CMPD85	6.50	6.51	-0.01	6.64	-0.13	6.46	0.04
CMPD86	5.52	5.56	-0.04	5.43	0.09	5.57	-0.05
CMPD87	7.00	6.88	0.12	7.29	-0.29	6.85	0.15
CMPD88	7.59	7.50	0.09	7.02	0.57	7.60	0.00
CMPD89	5.88	6.06	-0.18	5.77	0.11	6.27	-0.39
CMPD90	6.91	6.92	-0.01	6.98	-0.07	6.64	0.27
CMPD91	5.73	5.75	-0.02	5.80	-0.07	5.49	0.24
CMPD92	5.73	5.67	0.06	5.53	0.20	5.99	-0.26
CMPD93	6.61	6.60	0.01	6.76	-0.15	6.57	0.04
CMPD94	7.50	7.48	0.02	7.67	-0.17	7.62	-0.12

Table 5a Set 5 CoMFA All cont.

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD96	9.01	8.67	0.34	8.89	0.12	8.70	0.31
CMPD97	8.72	8.78	-0.06	8.72	0.00	8.71	0.01
CMPD98	8.77	9.03	-0.26	8.64	0.13	9.03	-0.26
CMPD99	8.24	8.27	-0.03	8.39	-0.15	8.10	0.14
CMPD100	8.26	8.34	-0.08	8.09	0.17	8.19	0.07
CMPD101	8.92	8.74	0.18	8.76	0.16	8.77	0.15
CMPD102	8.40	8.15	0.25	8.01	0.39	8.15	0.25
CMPD103	7.33	7.73	-0.40	7.72	-0.39	7.77	-0.44
CMPD104	8.41	8.52	-0.11	8.74	-0.33	8.54	-0.13
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD106	?	5.69	0.63	5.75	0.57	5.78	0.60
CMPD107	?	5.40	0.34	5.33	0.15	5.16	-0.01
CMPD108	?	5.43	0.37	5.55	0.37	5.10	-0.07
CMPD109	?	5.78	0.72	5.82	0.64	5.09	-0.08
CMPD110	?	4.78	-0.28	4.70	-0.48	4.79	-0.39
CMPD111	?	4.76	-0.30	4.91	-0.27	4.97	-0.21
CMPD112	?	6.65	-0.83	7.39	-0.28	6.61	-1.01
CMPD113	?	7.29	-0.18	7.40	-0.28	7.45	-0.17
CMPD114	?	7.52	0.04	7.70	0.03	7.62	0.00
CMPD115	?	7.87	-0.79	8.77	-0.12	7.78	-0.93
CMPD116	?	8.30	-0.37	9.15	0.25	8.20	-0.51
CMPD117	?	7.07	-1.59	8.23	-0.66	6.77	-1.93
CMPD118	?	7.96	-0.71	8.11	-0.78	8.33	-0.37
CMPD119	?	8.87	0.20	8.83	-0.07	8.98	0.28
CMPD120	?	8.87	0.20	8.77	-0.12	8.89	0.19
CMPD121	?	8.82	0.04	8.65	-0.07	8.79	0.08
CMPD122	?	8.41	-0.37	8.94	0.23	8.37	-0.33
CMPD123	?	8.46	-0.33	8.73	0.01	8.40	-0.31
CMPD124	?	9.05	0.26	9.10	0.39	8.69	-0.02
CMPD125	?	8.33	0.06	8.32	-0.07	8.20	0.09
CMPD126	?	7.94	-0.33	8.31	-0.08	7.78	-0.32
CMPD127	?	8.58	0.31	8.38	-0.01	8.50	0.40

Table 5b Set 5 CoMSIA All

	EA	PA	RES
CMPD74	6.51	5.93	0.58
CMPD75	6.36	5.82	0.55
CMPD78	5.60	5.72	-0.12
CMPD79	5.00	5.22	-0.22
CMPD80	5.57	5.52	0.05
CMPD81	5.01	5.38	-0.37
CMPD82	4.99	4.71	0.29
CMPD83	5.58	5.58	0.00
CMPD84	5.61	5.54	0.07
CMPD85	6.50	6.75	-0.25
CMPD86	5.52	5.81	-0.29
CMPD87	7.00	7.15	-0.15
CMPD88	7.59	6.99	0.60

Table 5b Set 5 CoMSIA All

	EA	PA	RES
CMPD89	5.88	6.13	-0.25
CMPD90	6.91	6.78	0.13
CMPD91	5.73	5.93	-0.20
CMPD92	5.73	5.92	-0.19
CMPD93	6.61	7.00	-0.39
CMPD94	7.50	7.52	-0.02
CMPD96	9.01	8.97	0.04
CMPD97	8.72	8.67	0.05
CMPD98	8.77	8.66	0.11
CMPD99	8.24	7.65	0.59
CMPD100	8.26	8.35	-0.09
CMPD101	8.92	8.33	0.59
CMPD102	8.40	8.47	-0.07
CMPD103	7.33	8.15	-0.82
CMPD104	8.41	8.63	-0.22
Modified		PA	Δ
CMPD106	?	5.57	0.19
CMPD107	?	5.45	0.07
CMPD108	?	5.45	0.07
CMPD109	?	5.54	0.17
CMPD110	?	5.12	-0.26
CMPD111	?	5.09	-0.29
CMPD112	?	7.08	-0.44
CMPD113	?	7.51	-0.01
CMPD114	?	7.46	-0.06
CMPD115	?	8.84	-0.13
CMPD116	?	8.33	-0.64
CMPD117	?	9.10	0.13
CMPD118	?	8.24	-0.73
CMPD119	?	9.14	0.18
CMPD120	?	8.85	-0.12
CMPD121	?	9.33	0.66
CMPD122	?	8.80	0.13
CMPD123	?	9.14	0.47
CMPD124	?	9.31	0.64
CMPD125	?	7.68	0.03

Table 5c Set 5 CoMFA 72-94

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD74	6.51	6.50	0.01	6.75	-0.24	6.53	-0.02
CMPD75	6.36	6.40	-0.04	6.60	-0.24	6.25	0.11
CMPD78	5.60	5.60	0.00	5.45	0.15	5.65	-0.05
CMPD79	5.00	5.02	-0.02	4.97	0.03	5.01	-0.01
CMPD80	5.57	5.56	0.01	5.62	-0.05	5.51	0.06
CMPD81	5.01	4.93	0.08	4.90	0.11	5.01	0.00
CMPD82	4.99	4.97	0.02	5.03	-0.04	5.12	-0.13
CMPD83	5.58	5.63	-0.05	5.57	0.01	5.52	0.06
CMPD84	5.61	5.62	-0.01	5.75	-0.14	5.60	0.01
CMPD85	6.50	6.45	0.05	6.35	0.15	6.61	-0.11
CMPD86	5.52	5.59	-0.07	5.80	-0.28	5.46	0.06

Table 5c Set 5 CoMFA 72-94 cont.

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD87	7.00	7.02	-0.02	6.84	0.16	6.97	0.04
CMPD88	7.59	7.45	0.14	6.65	0.94	7.45	0.14
CMPD89	5.88	5.93	-0.05	6.08	-0.20	6.14	-0.26
CMPD90	6.91	6.95	-0.04	6.53	0.38	6.75	0.16
CMPD91	5.73	5.63	0.10	6.23	-0.50	5.43	0.30
CMPD92	5.73	5.76	-0.03	5.83	-0.10	6.01	-0.28
CMPD93	6.61	6.63	-0.02	6.47	0.14	6.60	0.01
CMPD94	7.50	7.56	-0.06	7.80	-0.30	7.59	-0.09
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD106	?	5.58	0.65	4.96	0.06	5.64	0.63
CMPD107	?	5.12	0.19	5.20	0.31	5.01	0.00
CMPD108	?	5.30	0.37	5.34	0.44	4.98	-0.03
CMPD109	?	5.52	0.59	5.78	0.88	4.98	-0.03
CMPD110	?	4.79	-0.14	5.38	0.48	4.81	-0.21
CMPD111	?	4.94	0.01	5.07	0.18	5.18	0.17
CMPD112	?	6.54	-1.02	7.83	0.03	6.26	-1.33
CMPD113	?	7.48	-0.08	7.85	0.05	7.42	-0.17
CMPD114	?	7.58	0.02	7.87	0.07	7.59	0.00

Table 5d Set 5 CoMSIA 72-94

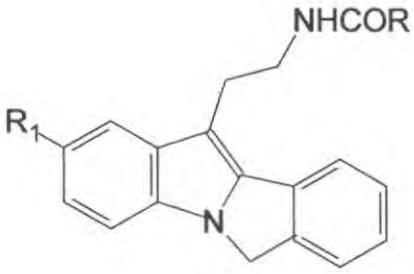
	EA	PA	RES
CMPD74	6.51	6.32	0.19
CMPD75	6.36	6.34	0.02
CMPD78	5.60	5.69	-0.09
CMPD79	5.00	4.95	0.05
CMPD80	5.57	5.53	0.04
CMPD81	5.01	4.90	0.11
CMPD82	4.99	5.13	-0.14
CMPD83	5.58	5.64	-0.06
CMPD84	5.61	5.63	-0.02
CMPD85	6.50	6.55	-0.05
CMPD86	5.52	5.47	0.05
CMPD88	7.59	7.50	0.09
CMPD89	5.88	5.95	-0.07
CMPD90	6.91	7.03	-0.12
CMPD91	5.73	5.69	0.04
CMPD92	5.73	5.76	-0.03
CMPD93	6.61	6.63	-0.02
Modified		PA	Δ
CMPD106	?	5.43	0.53
CMPD107	?	5.07	0.17
CMPD108	?	5.03	0.13
CMPD109	?	5.22	0.32
CMPD110	?	4.62	-0.28
CMPD111	?	4.70	-0.20
CMPD112	?	7.25	-0.25
CMPD113	?	8.07	0.57
CMPD114	?	8.10	0.60

Table 5e Set 5 CoMFA 95-105

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD96	9.01	9.01	0.00	9.01	0.00	9.00	0.01
CMPD97	8.72	8.72	0.00	8.64	0.08	8.69	0.03
CMPD98	8.77	8.77	0.00	8.79	-0.01	8.79	-0.02
CMPD99	8.24	8.24	0.00	8.27	-0.03	8.24	0.00
CMPD101	8.92	8.92	0.00	8.82	0.10	8.91	0.01
CMPD103	7.33	7.33	0.00	7.30	0.03	7.32	0.01
CMPD104	8.41	8.41	0.00	8.58	-0.16	8.46	-0.05
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD116	?	8.91	-0.11	9.07	0.06	8.93	-0.07
CMPD117	?	8.47	-0.54	8.98	-0.03	8.40	-0.60

Table 5f Set 5 CoMSIA 95-105

	EA	PA	RES
CMPD97	8.72	8.73	-0.01
CMPD98	8.77	8.73	0.04
CMPD99	8.24	8.24	0.00
CMPD100	8.26	8.29	-0.03
CMPD101	8.92	8.94	-0.02
CMPD102	8.40	8.39	0.01
CMPD104	8.41	8.41	0.00



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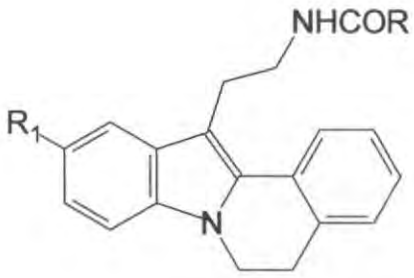


20a-21d

Table 6$_i$ Set 6 - Group 1 Compounds

Compound	R_1	R	MT_1	MT_2
cmpd01	-	-	0.18	0.48
cmpd02	-	-	-2.78	-1.65
cmpd05a	H	Me	-2.29	-1.23
cmpd05b	H	Et	-2.31	-1.24
cmpd05c	H	Pr	-2.24	-1.08
cmpd05d	H	c-C_3H_5	-2.89	-2.35
cmpd05e	H	c-C_4H_7	-3.08	-3.05
cmpd07a	OMe	Me	-0.26	1.22
cmpd07b	OMe	Et	-0.64	0.77
cmpd07c	OMe	Pr	-0.65	1.30
cmpd07d	OMe	c-C_3H_5	-1.67	0.02
cmpd10a	OEt	Me	-1.26	0.68
cmpd10b	OEt	Et	-1.16	0.59
cmpd10c	OEt	Pr	-0.95	0.80
cmpd10d	OEt	c-C_3H_5	-2.37	-0.74
cmpd13	Cl	Me	-2.45	-1.53

Test	Original	Modification(s)
cmpd31	cmpd07c	R_1: O-iPr
cmpd32	cmpd07c	R_1: O-tBu
cmpd33	cmpd07c	R: OH
cmpd34	cmpd07c	R: F
cmpd35	cmpd07c	R_1: O-tBu, R: OH
cmpd36	cmpd07c	R_1: O-tBu, R: F
cmpd37	cmpd07c	OCH_2CH_3
cmpd38	cmpd07c	$C^{44}H_2CH_3$
cmpd39	cmpd07c	$C^{44}CH_2CH_3$

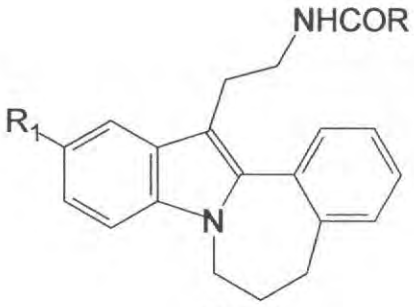
[a] MLT [b] Luzindole

Table 6$_{ii}$ Set 6 - Group 2 Compounds

Compound	R_1	R	MT_1	MT_2
cmpd01	-	-	0.18	0.48
cmpd02	-	-	-2.78	-1.65
cmpd20a	H	Me	-2.59	-1.56
cmpd20b	H	Et	-2.17	-0.97
cmpd20c	H	Pr	-1.85	-0.57
cmpd20d	H	c-C_4H_7	-3.31	-2.55
cmpd21a	OMe	Me	-0.86	0.29
cmpd21b	OMe	Et	-0.77	0.92
cmpd21c	OMe	Pr	-0.61	0.70
cmpd21d	OMe	c-C_4H_7	-2.64	-2.51

Test	Original	Modification(s)
cmpd41	cmpd21c	R: n-Bu (up)
cmpd42	cmpd21c	R: n-Bu (down)
cmpd43	cmpd21b	R_1: OEt
cmpd44	cmpd21b	R_1: OPr
cmpd45	cmpd21b	R_1: O-iPr
cmpd46	cmpd21b	R_1: OMeOH
cmpd57	cmpd21b	R_1: O-tBu
cmpd48	cmpd21c	R: n-Bu (up), R_1: OMeOH

[a] MLT [b] Luzindole



23a-30

Table 6_{iii} Set 6 - Group 3 Compounds

Compound	R_1	R	MT_1	MT_2
cmpd01[a]	-	-	0.18	0.48
cmpd02[b]	-	-	-2.78	-1.65
cmpd23a	H	Me	-2.38	-2.35
cmpd23b	H	Et	-2.06	-1.66
cmpd23c	H	Pr	-1.90	-1.80
cmpd23d	H	c-C_3H_5	-2.07	-1.72
cmpd23e	H	c-C_4H_7	-2.40	-2.49
cmpd25a	OMe	Me	-2.44	-0.80
cmpd25b	OMe	Et	-1.72	-0.15
cmpd25c	OMe	Pr	-1.82	0.30
cmpd25d	OMe	c-C_3H_5	-2.70	-1.08
cmpd25e	OMe	c-C_4H_7	-2.88	-1.50
cmpd27a	OEt	Me	-2.71	-2.07
cmpd27b	OEt	Et	-2.43	-1.34
cmpd27c	OEt	Pr	-2.41	-0.81
cmpd27d	OEt	c-C_3H_5	-3.47	-1.93
cmpd30	Cl	Me	-2.46	-0.70

[a] MLT [b] Luzindole

Table 6A

Set 6: Summary of the Statistical Results for the PLS Analyses [10,a]

	Human MT_1 All				Human MT_1 Table 6_i			
	CoMFA[b]			CoMSIA[c]	CoMFA			CoMSIA[d]
	B	E	S		B	E	S	
Q^2	0.724	0.781	0.735	0.764	0.719	0.698	0.693	0.708
no. comp	6	6	6	6	6	3	4	5
s	0.208	0.235	0.215	0.283	0.165	0.302	0.213	0.166
R^2	0.959	0.947	0.956	0.920	0.984	0.929	0.968	0.984
F	104.292	80.293	97.267	55.388	93.225	52.215	82.019	107.820
Prob. R^2=0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

	Human MT_1 Table 6_{ii}				Human MT_2 All			
	CoMFA[e]			CoMSIA[f]	CoMFA[g]			CoMSIA[h]
	B	E	S		B	E	S	
Q^2	0.661	0.708	0.716	0.722	0.818	0.719	0.813	0.809
no. comp	6	6	6	5	5	4	6	6
s	0.069	0.024	0.026	0.119	0.342	0.390	0.322	0.371
R^2	0.999	1.000	1.000	0.996	0.933	0.910	0.943	0.921
F	385.602	3203.643	2824.707	155.024	83.423	78.310	79.442	58.375
Prob. R^2=0	0.003	0.000	0.000	0.001	0.000	0.000	0.000	0.000

	Human MT_2 Table 6_i				Human MT_2 Table 6_{ii}			
	CoMFA			CoMSIA	CoMFA[i]			CoMSIA[j]
	B	E	S		B	E	S	
Q^2	0.859	0.809	0.862	0.929	0.694	0.768	0.737	0.671
no. comp	5	4	5	6	6	5	6	4
s	0.187	0.338	0.182	0.164	0.151	0.125	0.092	0.235
R^2	0.987	0.953	0.988	0.991	0.996	0.996	0.999	0.981
F	152.489	56.311	160.930	166.798	86.123	152.798	234.353	52.793
Prob. R^2=0	0.000	0.000	0.000	0.000	0.012	0.001	0.004	0.001

[a] Alignment using MLT as the basic molecule [b] Outliers: 23a, 25a [c] Outliers: 5c, 25a, 30 [d] Outlier: 5c [e] Outlier: 21d [f] Outlier: 21d [g] Outliers: 20c, 21d, 30 [h] Outliers: 21d, 30 [i] Outliers: 21d [j] Outliers: 21d

Table 6a Set 6 CoMFA MT_1 All

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	0.18	0.14	0.04	0.11	0.07	0.06	0.12
CMPD02	-2.78	-2.81	0.03	-2.73	-0.05	-2.90	0.12
CMPD05A	-2.29	-2.10	-0.19	-1.97	-0.32	-2.17	-0.12
CMPD05B	-2.31	-2.55	0.24	-2.32	0.01	-2.61	0.30
CMPD05D	-2.89	-3.03	0.14	-3.09	0.20	-3.03	0.14
CMPD05E	-3.08	-2.90	-0.18	-3.21	0.13	-2.96	-0.12
CMPD07A	-0.26	-0.64	0.38	-0.77	0.51	-0.69	0.43
CMPD07B	-0.64	-0.67	0.03	-0.80	0.16	-0.66	0.02
CMPD07C	-0.65	-0.35	-0.30	-0.31	-0.34	-0.40	-0.25
CMPD07D	-1.67	-1.73	0.06	-1.52	-0.15	-1.70	0.03

Table 6a Set 6 CoMFA MT_1 All cont.

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD10A	-1.26	-1.30	0.04	-1.36	0.10	-1.30	0.04
CMPD10B	-1.16	-1.27	0.11	-1.38	0.22	-1.21	0.05
CMPD10C	-0.96	-0.95	-0.01	-1.02	0.06	-0.97	0.01
CMPD10D	-2.37	-2.27	-0.10	-2.11	-0.26	-2.22	-0.15
CMPD13	-2.45	-2.16	-0.29	-2.13	-0.32	-2.05	-0.40
CMPD20A	-2.59	-2.26	-0.33	-2.45	-0.14	-2.21	-0.38
CMPD20B	-2.17	-2.17	0.00	-2.46	0.29	-2.07	-0.10
CMPD20C	-1.85	-2.21	0.36	-1.84	0.01	-2.13	0.28
CMPD20D	-3.31	-3.31	0.00	-3.28	-0.03	-3.30	-0.01
CMPD21A	-0.86	-0.91	0.05	-0.80	-0.06	-0.91	0.05
CMPD21B	-0.77	-0.80	0.03	-0.81	0.04	-0.74	-0.03
CMPD21C	-0.61	-0.54	-0.07	-0.53	-0.08	-0.52	-0.09
CMPD23B	-2.06	-1.59	-0.47	-1.56	-0.50	-1.61	-0.45
CMPD23C	-1.90	-2.14	0.24	-2.09	0.19	-1.94	0.04
CMPD23D	-2.07	-2.35	0.28	-2.40	0.33	-2.44	0.37
CMPD23E	-2.40	-2.44	0.04	-2.55	0.15	-2.48	0.08
CMPD25B	-1.72	-1.87	0.15	-1.90	0.18	-1.90	0.18
CMPD25C	-1.82	-1.74	-0.08	-1.76	-0.06	-1.80	-0.02
CMPD25D	-2.70	-2.60	-0.10	-2.51	-0.19	-2.63	-0.07
CMPD25E	-2.88	-2.93	0.05	-2.78	-0.10	-2.93	0.05
CMPD27A	-2.71	-2.64	-0.07	-2.62	-0.09	-2.68	-0.03
CMPD27B	-2.43	-2.50	0.07	-2.57	0.14	-2.48	0.05
CMPD27C	-2.41	-2.35	-0.06	-2.50	0.09	-2.36	-0.05
CMPD27D	-3.47	-3.40	-0.07	-3.31	-0.16	-3.38	-0.09
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD33	?	-0.30	0.05	-0.45	-0.13	-0.40	0.01
CMPD34	?	-0.29	0.06	-0.78	-0.46	-0.38	0.02

[a] MLT [b] Luzindole

Table 6b Set 6 CoMSIA MT_1 All

	EA	PA	RES
CMPD01	0.18	0.24	-0.06
CMPD02	-2.78	-2.81	0.02
CMPD05A	-2.29	-2.13	-0.16
CMPD05B	-2.31	-2.29	-0.02
CMPD05D	-2.89	-2.66	-0.23
CMPD05E	-3.08	-2.93	-0.15
CMPD07A	-0.26	-0.72	0.45
CMPD07B	-0.64	-0.59	-0.05
CMPD07C	-0.65	-0.24	-0.41
CMPD07D	-1.67	-1.61	-0.06
CMPD10A	-1.26	-1.46	0.20
CMPD10B	-1.16	-1.40	0.24
CMPD10C	-0.96	-1.04	0.08
CMPD10D	-2.37	-2.35	-0.02
CMPD13	-2.45	-2.64	0.19
CMPD20A	-2.59	-2.19	-0.40
CMPD20B	-2.17	-2.29	0.12
CMPD20C	-1.85	-2.17	0.32
CMPD20D	-3.31	-3.20	-0.11

Table 6b Set 6 CoMSIA MT_1 All

	EA	PA	RES
CMPD21A	-0.86	-1.04	0.18
CMPD21B	-0.77	-1.02	0.25
CMPD21C	-0.61	-0.74	0.13
CMPD21D	-2.64	-2.21	-0.43
CMPD23A	-2.38	-1.85	-0.53
CMPD23B	-2.06	-1.76	-0.30
CMPD23C	-1.90	-2.19	0.28
CMPD23D	-2.07	-2.60	0.53
CMPD23E	-2.40	-2.84	0.44
CMPD25B	-1.72	-1.77	0.05
CMPD25C	-1.82	-1.47	-0.35
CMPD25D	-2.70	-2.65	-0.05
CMPD25E	-2.88	-2.83	-0.05
CMPD27A	-2.71	-2.64	-0.07
CMPD27B	-2.43	-2.55	0.12
CMPD27C	-2.41	-2.26	-0.15
CMPD27D	-3.47	-3.44	-0.03
Modified		PA	Δ
CMPD34	?	-0.17	0.07
CMPD35	?	-1.36	-1.12
CMPD36	?	-0.71	-0.47
CMPD37	?	-0.50	-0.26
CMPD38	?	-0.07	0.17
CMPD39	?	-0.22	0.02

Table 6c Set 6 CoMFA MT_1 6_i

	EA	PA B	RES B	PA E	RES_E	PA S	RES S
CMPD01	0.18	0.20	-0.02	0.17	0.01	0.09	0.10
CMPD02	-2.78	-2.79	0.01	-2.80	0.02	-2.70	-0.08
CMPD05A	-2.29	-2.15	-0.14	-2.13	-0.16	-2.29	0.00
CMPD05B	-2.31	-2.28	-0.03	-2.34	0.03	-2.37	0.06
CMPD05C	-2.24	-2.15	-0.09	-2.06	-0.18	-2.17	-0.07
CMPD05D	-2.89	-3.14	0.25	-3.20	0.31	-3.20	0.31
CMPD05E	-3.08	-3.06	-0.02	-3.28	0.20	-3.16	0.08
CMPD07 A	-0.26	-0.53	0.27	-0.78	0.52	-0.59	0.33
CMPD07B	-0.64	-0.54	-0.10	-0.68	0.03	-0.50	-0.14
CMPD07C	-0.65	-0.59	-0.06	-0.55	-0.10	-0.46	-0.19
CMPD07D	-1.67	-1.63	-0.04	-1.52	-0.15	-1.62	-0.05
CMPD10A	-1.26	-1.18	-0.09	-1.37	0.11	-1.28	0.02
CMPD10B	-1.16	-1.21	0.05	-1.28	0.12	-1.22	0.06
CMPD10C	-0.95	-1.11	0.16	-1.09	0.14	-1.10	0.15
CMPD10D	-2.37	-2.20	-0.17	-2.19	-0.18	-2.15	-0.22
CMPD13	-2.45	-2.48	0.03	-1.73	-0.72	-2.09	-0.37
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD31	?	-1.43	-0.84	-0.51	0.04	-1.36	-0.90
CMPD38	?	-0.47	0.12	-0.61	-0.06	-0.43	0.04
CMPD39	?	-0.50	0.08	-0.46	0.09	-0.51	-0.05

Table 6d Set 6 CoMSIA MT_1 6_i

	EA	PA	RES
CMPD01	0.18	0.19	-0.01
CMPD02	-2.78	-2.78	0.00
CMPD05A	-2.29	-2.03	-0.26
CMPD05B	-2.31	-2.37	0.06
CMPD05D	-2.89	-2.96	0.07
CMPD05E	-3.08	-3.09	0.01
CMPD07 A	-0.26	-0.52	0.26
CMPD07B	-0.64	-0.64	0.00
CMPD07C	-0.65	-0.47	-0.18
CMPD07D	-1.67	-1.65	-0.02
CMPD10A	-1.26	-1 .127	-0.13
CMPD10B	-1.16	-1.28	0.12
CMPD10C	-0.95	-1.04	0.09
CMPD10D	-2.37	-2.24	-0.13
CMPD13	-2.45	-2.57	0.12
Modified		PA	Δ
CMPD39	?	-0.30	0.18

Table 6f Set 6 CoMSIA MT_1 6_{ii}

	EA	PA	RES
CMPD01	0.18	0.19	0.00
CMPD02	-2.78	-2.78	0.00
CMPD20A	-2.59	-2.49	-0.10
CMPD20B	-2.17	-2.23	0.06
CMPD20C	-1.85	-1.86	0.01
CMPD20D	-3.31	-3.32	0.01
CMPD21 A	-0.86	-0.99	0.13
CMPD21 B	-0.77	-0.78	0.01
CMPD21 C	-0.61	-0.50	-0.11
Modified		PA	Δ
CMPD41	?	-0.38	0.12
CMPD42	?	-0.42	0.09
CMPD43	?	-0.59	0.19
CMPD44	?	-0.62	0.16
CMPD45	?	-0.56	0.22
CMPD46	?	-0.87	-0.08
CMPD47	?	-0.29	0.49
CMPD48	?	-0.47	0.03

Table 6e Set 6 CoMFA MT_1 6_{ii}

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	0.18	0.19	-0.01	0.18	0.00	0.18	0.00
CMPD02	-2.78	-2.78	0.00	-2.78	0.00	-2.78	0.00
CMPD20A	-2.59	-2.55	-0.04	-2.59	0.00	-2.59	0.00
CMPD20B	-2.17	-2.16	-0.01	-2.18	0.01	-2.18	0.01
CMPD20C	-1.85	-1.90	0.05	-1.84	-0.01	-1.87	0.01
CMPD20D	-3.31	-3.32	0.01	-3.31	0.00	-3.30	-0.01
CMPD21 A	-0.86	-0.92	0.06	-0.86	0.00	-0.87	0.01
CMPD21 B	-0.77	-0.74	-0.03	-0.75	-0.02	-0.74	-0.03
CMPD21 C	-0.61	-0.58	-0.03	-0.63	0.02	-0.61	0.00
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD41	?	-0.47	0.11	-0.94	-0.31	-0.46	0.16
CMPD42	?	-0.52	0.06	-0.90	-0.27	-0.50	0.11
CMPD43	?	-0.74	0.00	-0.80	-0.05	-0.59	0.15
CMPD44	?	-0.77	-0.02	-0.80	-0.05	-0.59	0.15
CMPD45	?	-0.78	-0.04	-1.42	-0.67	-0.61	0.13
CMPD46	?	-0.61	0.13	-0.49	0.26	-0.61	0.13
CMPD47	?	-0.74	0.00	-1.83	-1.08	-0.54	0.20
CMPD48	?	-0.34	0.24	-0.73	-0.10	-0.33	0.28

Table 6g Set 6 CoMFA MT_2 All

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	0.48	0.45	0.03	0.72	-0.24	0.19	0.29
CMPD02	-1.65	-1.61	-0.04	-2.04	0.39	-1.67	0.02
CMPD05A	-1.23	-1.46	0.23	-0.88	-0.35	-1.47	0.23
CMPD05B	-1.24	-1.62	0.38	-1.19	-0.05	-1.64	0.40
CMPD05C	-1.08	-0.79	-0.29	-0.93	-0.15	-0.90	-0.18
CMPD05D	-2.35	-2.17	-0.18	-2.16	-0.19	-2.22	-0.13
CMPD05E	-3.05	-2.34	-0.71	-2.69	-0.36	-2.71	-0.34
CMPD07 A	1.22	0.83	0.39	0.89	0.33	0.85	0.37
CMPD07B	0.77	1.11	-0.34	0.95	-0.18	1.13	-0.36
CMPD07C	1.30	1.50	-0.20	1.42	-0.12	1.36	-0.06
CMPD07D	0.02	0.04	-0.02	0.14	-0.12	0.02	0.00
CMPD10A	0.68	0.11	0.57	0.08	0.60	0.17	0.51
CMPD10B	0.59	0.41	0.18	0.17	0.42	0.53	0.06
CMPD10C	0.80	0.80	0.00	0.49	0.31	0.77	0.03
CMPD10D	-0.74	-0.64	-0.10	-0.69	-0.05	-0.57	-0.17
CMPD13	-1.53	-1.26	-0.27	-0.95	-0.58	-1.28	-0.25
CMPD20A	-1.56	-1.92	0.36	-1.79	0.23	-1.64	0.08
CMPD20B	-0.97	-1.45	0.48	-1.77	0.80	-1.20	0.23
CMPD20D	-2.55	-2.57	0.02	-2.50	-0.05	-2.44	-0.11
CMPD21 A	0.29	0.28	0.01	0.58	-0.29	0.49	-0.20
CMPD21 B	0.92	0.81	0.11	0.61	0.31	1.01	-0.09
CMPD21 C	0.70	1.11	-0.41	0.90	-0.20	1.15	-0.45
CMPD23A	-2.35	-1.86	-0.49	-1.60	-0.75	-1.87	-0.48
CMPD23B	-1.66	-1.38	-0.28	-1.42	-0.24	-1.35	-0.31
CMPD23C	-1.80	-1.94	0.14	-1.71	-0.09	-1.78	-0.02
CMPD23D	-1.72	-2.24	0.52	-2.26	0.54	-2.21	0.49
CMPD23E	-2.49	-2.61	0.12	-2.87	0.38	-2.67	0.18
CMPD25A	-0.80	-0.50	-0.31	-0.40	-0.40	-0.63	-0.17
CMPD25B	-0.15	-0.28	0.13	-0.39	0.24	-0.33	0.18
CMPD25C	0.30	-0.16	0.46	-0.16	0.46	-0.31	0.61
CMPD25D	-1.08	-1 .126	0.05	-0.99	-0.09	-1 .123	0.04
CMPD25E	-1.50	-1.62	0.12	-1 .232	-0.27	-1.76	0.26
CMPD27 A	-2.07	-1.51	-0.56	-1.42	-0.66	-1.50	-0.57
CMPD27B	-1.34	-1 .020	-0.32	-1.29	-0.05	-1.00	-0.34
CMPD27C	-0.81	-0.96	0.15	-1 .139	0.33	-1.04	0.23
CMPD27D	-1.93	-2.01	0.08	-2.06	0.13	-1.95	0.02
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD33	?	1.60	0.10	1.03	-0.39	1.43	0.07
CMPD34	?	1.58	0.08	0.87	-0.55	1.44	0.08
CMPD38	?	1.49	-0.01	0.72	-0.70	1.42	0.05

Table 6h Set 6 CoMSIA MT_2 All

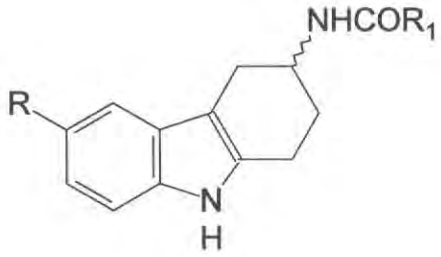
	EA	PA	RES
CMPD01	0.48	0.42	0.06
CMPD02	-1.65	-1.61	-0.04
CMPD05A	-1.23	-1.17	-0.06
CMPD05B	-1.24	-1.23	-0.01
CMPD05C	-1.08	-0.74	-0.34
CMPD05D	-2.35	-1.93	-0.43
CMPD05E	-3.05	-2.27	-0.79
CMPD07 A	1.22	0.83	0.39
CMPD07B	0.77	1.05	-0.28
CMPD07C	1.30	1.48	-0.18
CMPD07D	0.02	0.19	-0.17
CMPD10A	0.68	-0.04	0.72
CMPD10B	0.59	0.16	0.43
CMPD10C	0.80	0.55	0.25
CMPD10D	-0.74	-0.73	-0.01
CMPD13	-1.53	-1.92	0.39
CMPD20A	-1.56	-1.53	-0.03
CMPD20B	-0.97	-1.36	0.39
CMPD20C	-0.57	-1.13	0.55
CMPD20D	-2.55	-2.60	0.05
CMPD21A	0.29	0.59	-0.30
CMPD21B	0.92	0.80	0.12
CMPD21C	0.70	1.23	-0.53
CMPD23A	-2.35	-1.94	-0.42
CMPD23B	-1.66	-1.67	0.01
CMPD23C	-1.80	-1.86	0.06
CMPD23D	-1.72	-2.37	0.65
CMPD23E	-2.49	-2.71	0.22
CMPD25A	-0.80	-0.53	-0.27
CMPD25B	-0.15	-0.30	0.15
CMPD25C	0.30	0.11	0.19
CMPD25D	-1.08	-1.00	-0.08
CMPD25E	-1.50	-1.43	-0.07
CMPD27A	-2.07	-1.48	-0.59
CMPD27B	-1.34	-1.23	-0.11
CMPD27C	-0.81	-0.87	0.06
CMPD27D	-1.93	-1.93	0.00
Modified		PA	Δ
CMPD38	?	1.52	0.04

Table 6i Set 6 CoMFA MT_2 6_i

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	0.48	0.50	-0.02	0.52	-0.04	0.35	0.13
CMPD02	-1.65	-1.63	-0.02	-1.68	0.03	-1.54	-0.11
CMPD05A	-1.23	-1.25	0.02	-1.16	-0.07	-1.13	-0.10
CMPD05B	-1.24	-1.38	0.14	-1.24	0.00	-1.34	0.10
CMPD05C	-1.08	-1 .172	0.09	-1.13	0.05	-1.23	0.15
CMPD05D	-2.35	-2.47	0.12	-2.65	0.30	-2.44	0.09
CMPD05E	-3.05	-2.85	-0.20	-3.00	-0.05	-3.05	0.00
CMPD07 A	1.22	1.04	0.18	0.79	0.43	1.10	0.12
CMPD07B	0.77	1.14	-0.37	1.12	-0.35	1.12	-0.35
CMPD07C	1.30	1.36	-0.06	1.33	-0.03	1.23	0.07
CMPD07D	0.02	-0.09	0.11	0.02	0.00	-0.14	0.16
CMPD10A	0.68	0.45	0.23	0.19	0.49	0.57	0.11
CMPD10B	0.59	0.57	0.02	0.56	0.03	0.61	-0.02
CMPD10C	0.80	0.80	0.00	0.74	0.06	0.76	0.04
CMPD10D	-0.74	-0.63	-0.11	-0.68	-0.06	-0.50	-0.24
CMPD13	-1.53	-1.41	-0.12	-0.76	-0.77	-1.40	-0.14
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD33	?	1.43	0.07	1.02	-0.32	1.11	-0.12
CMPD34	?	1.50	0.13	0.93	-0.40	1.14	-0.09
CMPD39	?	1.15	-0.21	1.44	0.10	1.06	-0.17

Table 6j Set 6 CoMSIA MT_2 6_i

	EA	PA	RES
CMPD01	0.48		
CMPD02	-1.65		
CMPD05A	-1.23		
CMPD05B	-1.24		
CMPD05C	-1.08		
CMPD05D	-2.35		
CMPD05E	-3.05		
CMPD07A	1.22		
CMPD07B	0.77		
CMPD07C	1.30	1.26	0.04
CMPD07D	0.02		
CMPD10A	0.68		
CMPD10B	0.59		
CMPD10C	0.80		
CMPD10D	-0.74		
CMPD13	-1.53		
Modified		PA	Δ
CMPD 38	?	1.41	0.15
CMPD39	?	1.47	0.21
CMPD40	?	1.35	0.09



2f-2q

9a-9w

Table 7$_i$ Set 7 - Group 1 Compounds

Compound	R_1	R	MT_1
cmpd01	-	-	0.23
cmpd02	-	-	-3.21
cmpd03	-	-	-2.75
cmpd02f	H	Me	-3.73
cmpd02g	H	Et	-2.64
cmpd02h	H	Pr	-3.03
cmpd02i	H	CH_2Br	-2.87
cmpd02j	H	CF_3	-3.67
cmpd02l	OMe	Me	-2.34
cmpd02m	OMe	Et	-1.61
cmpd02n	OMe	Pr	-2.75
cmpd02o	OMe	CH_2Br	-0.92
cmpd02p	OMe	CF_3	-2.01
cmpd02q	OMe	c-C_3H_5	-2.16

Test	Original	Modification(s)
cmpd12a	cmpd01	OCH_2CH_3
cmpd12b	cmpd01	$OCH(CH_3)_2$
cmpd12c	cmpd01	$C^{28}H_2CH_3$
cmpd12d	cmpd01	replace O with C=O

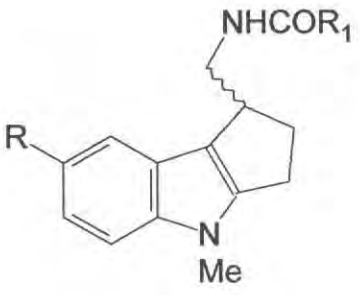
[a] MLT [b] Luzindole [c] N-CBCPT [N-(Cyclobutylcarbonyl)-2-phenyltryptamine]

Table 7$_{ii}$ Set 7 - Group 2 Compounds

Compound	R_1	R	MT_1
cmpd01	-	-	0.23
cmpd02	-	-	-3.21
cmpd03	-	-	-2.75
cmpd09a	H	Me	-2.36
cmpd09b	H	Et	-2.31
cmpd09c	H	Pr	-2.33
cmpd09e	H	c-C_3H_5	-3.65
cmpd09g	OMe	Me	0.01
cmpd09h	OMe	Et	-0.16
cmpd09i	OMe	Pr	0.42
cmpd09j	OMe	C_4H_9	-1.91
cmpd09k	OMe	c-C_3H_5	-1.48
cmpd09l	OMe	c-C_4H_7	-2.43
cmpd09m	OMe	CF3	-0.30
cmpd09n	OCF_3	Me	-2.15
cmpd09o	OCF_3	Et	-1.60
cmpd09p	OCF_3	c-C_4H_7	-3.09
cmpd09q	Me	Me	-1.21
cmpd09r	Me	Et	-0.88
cmpd09s	Me	c-C_4H_7	-2.74
cmpd09t	Cl	Me	-0.33
cmpd09u	Cl	c-C_3H_5	-2.12
cmpd09v	Cl	c-C_4H_7	-2.27
cmpd09w	Et	Et	-1.44

Test	Original	Modification(s)
cmpd13a	cmpd09g	NH_2CH_3
cmpd13b	cmpd09g	$C^{40}H_2CH_3$
cmpd13c	cmpd09g	OCH_2CH_3
cmpd13d	cmpd09g	$OCH(CH_3)_2$
cmpd13e	cmpd09g	OCH_2OH
cmpd14a	cmpd09i	NH_2CH_3
cmpd14b	cmpd09i	$C^{41}H_2CH_3$
cmpd14c	cmpd09i	OCH_2CH_3
cmpd14d	cmpd09i	$OCH(CH_3)_2$
cmpd14e	cmpd09i	OCH_2OH
cmpd14f	cmpd09i	$C^{41}HFCH_3$

[a] MLT [b] Luzindole [c] N-CBCPT

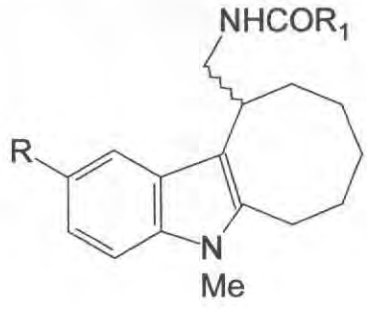


10a-10k

Table 7_{iii} Set 7 - Group 3 Compounds

Compound	R_1	R	MT_1
cmpd01[a]	-	-	0.23
cmpd02[b]	-	-	-3.21
cmpd03[c]	-	-	-2.75
cmpd10a	H	Me	-2.71
cmpd10b	H	Et	-2.43
cmpd10c	H	Pr	-2.38
cmpd10e	H	c-C_3H_5	-3.71
cmpd10f	H	c-C_4H_7	-3.76
cmpd10h	OMe	Me	-2.21
cmpd10i	OMe	Et	-1.20
cmpd10j	OMe	Pr	-1.36
cmpd10k	OMe	c-C_3H_5	-2.66

[a] MLT [b] Luzindole [c] N-CBCPT



11a-11m

Table 7_{iv} Set 7 - Group 4 Compounds

Compound	R_1	R	MT_1
cmpd01[a]	-	-	0.23
cmpd02[b]	-	-	-3.21
cmpd03[c]	-	-	-2.75
cmpd11a	H	Me	-2.63
cmpd11b	H	Et	-2.11
cmpd11c	H	Pr	-1.92
cmpd11d	H	C_4H_9	-3.92
cmpd11e	H	c-C_3H_5	-3.09
cmpd11f	H	c-C_4H_7	-3.23
cmpd11h	OMe	Me	-1.38
cmpd11i	OMe	Et	-0.85
cmpd11j	OMe	Pr	-1.01
cmpd11k	OMe	C_4H_9	-2.67
cmpd11l	OMe	c-C_3H_5	-1.65
cmpd11m	OMe	c-C_4H_7	-2.16

[a] MLT [b] Luzindole [c] N-CBCPT

Table 7A

Set 7: Summary of the Statistical Results for the PLS Analyses [14,a]

Ovine Pars Tuberalis Membrane Binding

	CoMFA[b]			CoMSIA[c]
	B	E	S	
Q^2	0.540	0.678	0.467	0.637
no. comp	6	5	6	6
s	0.286	0.356	0.341	0.371
R^2	0.942	0.908	0.918	0.888
F	116.765	87.223	79.720	57.008
Prob. R^2=0	0.000	0.000	0.000	0.000

[a] Alignment using cmpd10j as the basic molecule [b] Outliers: 2n, 9j, 9k, 9l, 9n, 11c [c] Outliers: 9i, 9n, 9q, 9v, 11c, 11j

Table 7a Set 7 CoMFA

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	0.23	0.23	0.01	0.16	0.07	0.17	0.06
CMPD02	-3.21	-3.48	0.27	-3.33	0.12	-3.54	0.33
CMPD02F	-3.73	-3.56	-0.17	-3.55	-0.19	-3.35	-0.38
CMPD02G	-2.64	-2.93	0.29	-2.86	0.22	-2.49	-0.15
CMPD02H	-3.03	-3.02	-0.01	-2.86	-0.18	-2.64	-0.40
CMPD021	-2.87	-2.92	0.05	-2.71	-0.16	-3.03	0.16
CMPD02J	-3.67	-3.54	-0.13	-3.56	-0.12	-3.47	-0.21
CMPD02L	-2.34	-2.07	-0.27	-1.97	-0.37	-1.94	-0.40
CMPD02M	-1.61	-1.88	0.27	-2.07	0.46	-1.73	0.12
CMPD020	-0.92	-1.08	0.16	-1.28	0.36	-1.31	0.39
CMPD02P	-2.01	-2.07	0.06	-2.28	0.27	-1.86	-0.16
CMPD020	-2.16	-1.83	-0.33	-1.70	-0.46	-1.51	-0.66
CMPD03	-2.75	-3.13	0.38	-2.61	-0.14	-3.03	0.28
CMPD09A	-2.36	-2.07	-0.29	-2.42	0.06	-2.18	-0.18
CMPD09B	-2.31	-2.05	-0.26	-2.32	0.01	-2.41	0.10
CMPD09C	-2.33	-2.11	-0.22	-2.38	0.05	-2.44	0.11
CMPD09E	-3.65	-3.10	-0.55	-3.03	-0.62	-3.12	-0.53
CMPD09G	0.01	0.13	-0.12	0.56	-0.55	-0.08	0.09
CMPD09H	-0.16	-0.41	0.25	-0.19	0.03	-0.69	0.53
CMPD09I	0.42	0.13	0.30	0.24	0.18	-0.01	0.43
CMPD09M	-0.30	-0.45	0.15	-0.54	0.24	-0.24	-0.06
CMPD090	-1.60	-1.47	-0.13	-1.44	-0.16	-0.91	-0.69
CMPD09P	-3.09	-3.17	0.08	-3.21	0.12	-3.25	0.16
CMPD090	-1.21	-0.67	-0.54	-1.31	0.10	-0.55	-0.67
CMPD09R	-0.88	-1.32	0.44	-0.91	0.03	-1.49	0.61
CMPD09S	-2.74	-2.50	-0.24	-3.02	0.28	-2.25	-0.49
CMPD09T	-0.33	-0.67	0.34	-0.86	0.53	-0.38	0.05
CMPD09U	-2.12	-2.01	-0.11	-2.13	0.01	-2.10	-0.02
CMPD09V	-2.27	-2.51	0.24	-3.00	0.73	-2.47	0.20
CMPD09W	-1.44	-1.86	0.42	-1.60	0.16	-1.65	0.21
CMPD10A	-2.71	-3.24	0.53	-3.14	0.43	-3.28	0.57
CMPD10B	-2.43	-2.34	-0.09	-2.52	0.09	-2.54	0.11
CMPD10C	-2.38	-2.36	-0.02	-2.47	0.09	-2.44	0.06
CMPD10E	-3.71	-3.74	0.03	-3.55	-0.16	-3.70	-0.01
CMPD10F	-3.76	-3.98	0.22	-3.58	-0.18	-3.86	0.10
CMPD10H	-2.21	-1.97	-0.24	-1.65	-0.56	-2.03	-0.18
CMPD101	-1.20	-1.00	-0.20	-1.15	-0.05	-1.14	-0.06
CMPD10J	-1.36	-1.08	-0.28	-0.98	-0.38	-1.17	-0.19
CMPD10K	-2.66	-2.63	-0.03	-2.36	-0.30	-2.37	-0.29
CMPD11A	-2.63	-2.35	-0.29	-2.80	0.17	-2.52	-0.11
CMPD11B	-2.11	-2.36	0.25	-2.66	0.55	-2.44	0.33
CMPD11D	-3.92	-3.80	-0.12	-3.27	-0.65	-3.92	0.00
CMPD11E	-3.09	-2.98	-0.12	-3.26	0.17	-2.98	-0.11
CMPD11F	-3.23	-3.17	-0.06	-3.17	-0.06	-3.40	0.17
CMPD11H	-1.38	-1.15	-0.23	-1.43	0.05	-1.44	0.06
CMPD11I	-0.85	-0.95	0.10	-1.31	0.46	-1.03	0.18
CMPD11J	-1.01	-1.64	0.63	-1.22	0.21	-1.70	0.69
CMPD11K	-2.67	-2.59	-0.08	-1.70	-0.98	-2.71	0.04
CMPD11L	-1.65	-1.65	0.00	-1.85	0.20	-1.60	-0.05
CMPD11M	-2.16	-1.83	-0.33	-1.99	-0.17	-2.04	-0.12

Table 7a Set 7 CoMFA cont.

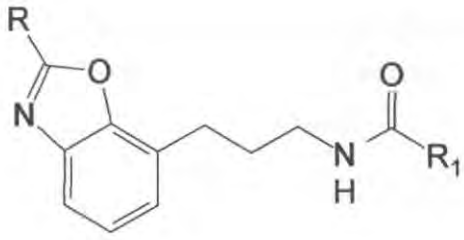
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD12A	?	0.17	-0.06	0.27	0.11	0.19	0.01
CMPD12B	?	0.10	-0.12	-1.08	-1.24	-0.10	-0.28
CMPD12C	?	0.28	0.06	0.30	0.15	0.41	0.24
CMPD12D	?	-0.48	-0.71	-1.04	-1.20	-0.67	-0.84
CMPD13A	?	0.15	0.02	0.72	0.16	-0.06	0.02
CMPD13B	?	-0.35	-0.48	0.54	-0.02	-0.06	0.02
CMPD13C	?	0.00	-0.13	0.67	0.11	-0.20	-0.12
CMPD13D	?	-0.10	-0.23	0.31	-0.25	-0.45	-0.37
CMPD13E	?	0.05	-0.08	0.15	-0.41	-0.19	-0.11
CMPD14A	?	0.17	0.04	0.39	0.14	0.07	0.15
CMPD14B	?	-0.18	-0.30	0.38	0.13	-0.46	-0.38
CMPD14C	?	-0.01	-0.13	0.74	0.50	-0.17	-0.09
CMPD14D	?	-0.02	-0.14	0.79	0.55	-0.43	-0.35
CMPD14E	?	0.19	0.07	0.99	0.75	-0.16	-0.08
CMPD14F	?	0.49	0.37	0.64	0.39	-0.01	0.07

Table 7b Set 7 CoMSIA

	EA	PA	RES
CMPD01	0.23	0.18	0.06
CMPD02	-3.21	-3.03	-0.18
CMPD02F	-3.73	-3.20	-0.54
CMPD02G	-2.64	-3.10	0.46
CMPD02H	-3.03	-3.25	0.22
CMPD021	-2.87	-2.90	0.03
CMPD02J	-3.67	-3.41	-0.26
CMPD02L	-2.34	-1.94	-0.41
CMPD02M	-1.61	-2.08	0.47
CMPD02N	-2.75	-2.46	-0.29
CMPD020	-0.92	-1.49	0.57
CMPD02P	-2.01	-2.10	0.09
CMPD02Q	-2.16	-1.88	-0.28
CMPD03	-2.75	-2.50	-0.25
CMPD09A	-2.36	-2.38	0.02
CMPD09B	-2.31	-2.13	-0.18
CMPD09C	-2.33	-2.77	0.44
CMPD09E	-3.65	-3.13	-0.52
CMPD09G	0.01	-0.08	0.09
CMPD09H	-0.16	-0.80	0.64
CMPD09J	-1.91	-1.75	-0.16
CMPD09K	-1.48	-1.42	-0.06
CMPD09L	-2.43	-2.17	-0.26
CMPD09M	-0.30	0.08	-0.38
CMPD090	-1.60	-1.22	-0.38
CMPD09P	-3.09	-3.63	0.54

Table 7b Set 7 CoMSIA cont.

	EA	PA	RES
CMPD09R	-0.88	-0.69	-0.19
CMPD09S	-2.74	-3.06	0.32
CMPD09T	-0.33	-0.44	0.11
CMPD09U	-2.12	-1.83	-0.29
CMPD09W	-1.44	-1.62	0.18
CMPD10A	-2.71	-2.72	0.01
CMPD10B	-2.43	-2.68	0.25
CMPD10C	-2.38	-2.68	0.30
CMPD10E	-3.71	-3.12	-0.59
CMPD10F	-3.76	-4.14	0.38
CMPD10H	-2.21	-1.62	-0.59
CMPD10I	-1.20	-1.62	0.42
CMPD10J	-1.36	-1.63	0.27
CMPD10K	-2.66	-2.31	-0.35
CMPD11A	-2.63	-2.21	-0.42
CMPD11B	-2.11	-2.60	0.49
CMPD11D	-3.92	-3.63	-0.29
CMPD11E	-3.09	-3.00	-0.09
CMPD11F	-3.23	-3.15	-0.08
CMPD11H	-1.38	-1.14	-0.24
CMPD11I	-0.85	-1.53	0.68
CMPD11K	-2.67	-2.58	-0.09
CMPD11L	-1.65	-1.91	0.26
CMPD11M	-2.16	-2.25	0.09
Modified	EA	PA	Δ
CMPD12A	?	0.37	0.20
CMPD12B	?	0.53	0.35
CMPD12C	?	0.03	-0.14
CMPD12D	?	-0.75	-0.93
CMPD13A	?	-0.08	0.00
CMPD13B	?	-0.36	-0.28
CMPD13C	?	0.12	0.20
CMPD13D	?	0.34	0.42
CMPD13E	?	0.51	0.59
CMPD14A	?	-1.46	-0.01
CMPD14B	?	-1.66	-0.21
CMPD14C	?	-1.21	0.24
CMPD14D	?	-1.01	0.44
CMPD14E	?	-0.63	0.82
CMPD14F	?	-1.19	0.27
CMPD09I	?	-1.45	0.00



7-9 and 13-47

Table 8 Set 8 Compounds

Compound	R_1	R	MT_1	MT_2
cmpd01	-	-	0.40	0.52
cmpd07	H	Me	-1.48	-0.63
cmpd08	H	Et	-0.82	-0.26
cmpd09	H	n-Pr	-1.00	-0.57
cmpd13	Me	Me	-1.38	-0.72
cmpd14	Me	Et	-0.45	-0.45
cmpd15	Me	n-Pr	-0.36	-0.34
cmpd16	Me	i-Pr	-0.48	-0.36
cmpd17	Me	c-Pr	0.15	-0.43
cmpd18	Me	NHEt	-1.70	-1.41
cmpd19	Et	Me	-0.95	-0.36
cmpd20	Et	Et	-0.54	0.00
cmpd21	Et	n-Pr	-0.91	0.00
cmpd22	Et	i-Pr	-1.12	-0.65
cmpd23	Et	c-Pr	-0.65	-0.67
cmpd24	Et	NHEt	-1.88	-1.08
cmpd25	n-Pr	Me	-2.26	-1.54
cmpd26	n-Pr	Et	-1.71	-1.43
cmpd27	n-Pr	n-Pr	-2.22	-1.34
cmpd28	n-Pr	i-Pr	-1.78	-1.46
cmpd29	n-Pr	c-Pr	-1.64	-0.88
cmpd30	n-Pr	NHEt	-2.69	-1.56
cmpd31	i-Pr	Me	-2.06	-1.54
cmpd32	i-Pr	Et	-2.15	-1.18
cmpd33	i-Pr	n-Pr	-2.08	-1.20
cmpd34	i-Pr	i-Pr	-1.60	-1.94
cmpd35	i-Pr	c-Pr	-1.53	-2.06
cmpd36	i-Pr	NHEt	-2.29	-1.72

Table 8 Set 8 Compounds cont.

Compound	R_1	R	MT_1	MT_2
cmpd37	Ph	Me	-1.60	-1.95
cmpd38	Ph	Et	-1.12	-1.00
cmpd39	Ph	n-Pr	-1.78	-1.23
cmpd40	Ph	i-Pr	-1.94	-1.76
cmpd41	Ph	c-Pr	-1.36	-1.58
cmpd42	Ph	NHEt	-2.53	-1.79
cmpd43	$Ph(CH_2)_4$	Me	-0.11	-1.20
cmpd44	$Ph(CH_2)_4$	Et	0.12	-1.15
cmpd45	$Ph(CH_2)_4$	n-Pr	-0.52	-1.46
cmpd46	$Ph(CH_2)_4$	i-Pr	-0.11	-1.26
cmpd47	$Ph(CH_2)_4$	c-Pr	0.20	-1.34

Test	Original	Modification(s)
cmpd48	cmpd47	$C^{25}Br$
cmpd49	cmpd47	$C^{26}Br$
cmpd50	cmpd47	$C^{39}Br$
cmpd51	cmpd47	$C^{38}(CH_3)_2$
cmpd52	cmpd47	$C^{15}CH_3$-
cmpd53	cmpd44	$C^{25}Br$
cmpd54	cmpd44	$C^{26}Br$
cmpd55	cmpd44	$C^{15}OH$-
cmpd56	cmpd44	$C^{38}Br$
cmpd57	cmpd44	$C^{15}CH_3$-
cmpd58	cmpd44	$C^{38}CH_3$-
cmpd59	cmpd14	R: tBu
cmpd60	cmpd14	R_1: $-CBr_2CH_3$
cmpd61	cmpd14	R_1: $-C(CH_3)_3$

[a] MLT

Table 8A

Set 8: Summary of the Statistical Results for the PLS Analyses [2,a]

	Human MT_1				Human MT_2			
	CoMFA[b]			CoMSIA[c]	CoMFA[d]			CoMSIA[e]
	B	E	S		B	E	S	
Q^2	0.765	0.736	0.670	0.786	0.555	0.581	0.561	0.533
no. comp	6	5	5	5	2	3	2	6
s	0.170	0.231	0.211	0.258	0.277	0.224	0.268	0.243
R^2	0.969	0.941	0.950	0.924	0.790	0.868	0.804	0.862
F	139.308	88.605	106.922	73.128	56.598	63.505	61.543	31.116
Prob. R^2=0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

[a] Alignment using cmpd27 as the basic molecule [b] Outliers: 7, 13, 20, 32, 38 [c] Outliers: 7, 13, 38 [d] Outliers: 18, 19, 20, 21, 38, 40 [e] Outlier: 40

Table 8a Set 8 CoMFA MT_1

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	0.40	0.38	0.02	0.34	0.06	0.45	-0.05
CMPD08	-0.82	-0.80	-0.02	-0.70	-0.13	-0.72	-0.10
CMPD09	-1.00	-1.05	0.05	-0.69	-0.31	-0.94	-0.06
CMPD14	-0.45	-0.45	0.00	-0.72	0.27	-0.52	0.07
CMPD15	-0.36	-0.71	0.35	-0.76	0.40	-0.75	0.39
CMPD16	-0.48	-0.35	-0.13	-0.48	0.00	-0.36	-0.12
CMPD17	0.15	0.12	0.03	-0.13	0.28	0.01	0.14
CMPD18	-1.70	-1.35	-0.35	-1.29	-0.41	-1.23	-0.47
CMPD19	-0.95	-1.04	0.09	-0.91	-0.04	-1.13	0.18
CMPD21	-0.91	-1.01	0.10	-1.11	0.20	-1.25	0.34
CMPD22	-1.12	-0.97	-0.15	-0.83	-0.30	-1.00	-0.12
CMPD23	-0.65	-0.74	0.09	-0.82	0.17	-0.74	0.09
CMPD24	-1.88	-1.96	0.08	-1.75	-0.13	-1.88	0.00
CMPD25	-2.26	-2.16	-0.10	-2.31	0.05	-2.27	0.01
CMPD26	-1.71	-1.79	0.08	-1.94	0.23	-1.88	0.17
CMPD27	-2.22	-2.07	-0.15	-1.98	-0.24	-2.07	-0.15
CMPD28	-1.78	-1.93	0.15	-1.70	-0.08	-2.03	0.25
CMPD29	-1.64	-1.60	-0.04	-1.76	0.12	-1.63	-0.01
CMPD30	-2.69	-2.73	0.04	-2.70	0.01	-2.62	-0.07
CMPD31	-2.06	-1.68	-0.38	-1.75	-0.31	-1.72	-0.34
CMPD33	-2.08	-1.96	-0.12	-2.02	-0.06	-1.89	-0.19
CMPD34	-1.60	-1.67	0.07	-1.70	0.10	-1.64	0.04
CMPD35	-1.53		-1.53	-1.68	0.15	-1.43	-0.10
CMPD36	-2.29	-2.64	0.35	-2.63	0.34	-2.49	0.20
CMPD37	-1.60	-1.60	0.00	-1.53	-0.07	-1.73	0.13
CMPD39	-1.78	-1.87	0.09	-1.82	0.04	-1.84	0.06
CMPD40	-1.94	-1.90	-0.04	-1.76	-0.18	-1.82	-0.12
CMPD41	-1.36	-1.36	0.00	-1.45	0.09	-1.39	0.03
CMPD42	-2.53	-2.50	-0.03	-2.45	-0.08	-2.43	-0.10
CMPD43	-0.11	-0.19	0.08	-0.17	0.06	-0.39	0.28
CMPD44	0.12	-0.05	0.17	-0.21	0.33	-0.02	0.14

Table 8a Set 8 CoMFA MT_1

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD45	-0.52	-0.28	-0.24	-0.22	-0.30	-0.12	-0.40
CMPD46	-0.11	-0.17	0.06	0.18	-0.29	-0.13	0.02
CMPD47	0.20	0.26	-0.06	0.16	0.04	0.33	-0.13
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD48	?	0.20	-0.05	0.10	-0.07	0.35	0.02
CMPD49	?	0.22	-0.04	0.28	0.12	0.33	0.00
CMPD50	?	0.32	0.06	0.20	0.03	0.32	-0.01
CMPD51	?	0.25	-0.01	0.14	-0.02	0.22	-0.12
CMPD52	?	0.22	-0.04	0.38	0.21	0.23	-0.10
CMPD53	?	-0.06	0.00	-0.39	-0.19	0.06	0.09
CMPD54	?	-0.06	-0.01	-0.10	0.11	-0.02	0.00
CMPD55	?	-0.14	-0.09	-0.70	-0.50	0.02	0.05
CMPD56	?	0.09	0.14	-0.15	0.05	-0.04	-0.01
CMPD57	?	-0.06	0.00	0.32	0.52	-0.07	-0.04
CMPD58	?	0.25	0.30	0.00	0.21	0.14	0.16
CMPD59	?	-1.31	-0.86	-1.95	-1.22	-1.33	-0.81
CMPD60	?	-0.27	0.18	-0.55	0.17	-0.23	0.30
CMPD61	?	-0.35	0.10	-0.66	0.06	-0.45	0.07

Table 8b Set 8 CoMSIA MT_1

	EA	PA	RES
CMPD01	0.40	0.73	-0.33
CMPD08	-0.82	-0.50	-0.32
CMPD09	-1.00	-0.72	-0.28
CMPD14	-0.45	-0.52	0.07
CMPD15	-0.36	-0.81	0.45
CMPD16	-0.48	-0.42	-0.07
CMPD17	0.15	0.05	0.10
CMPD18	-1.70	-1.27	-0.43
CMPD19	-0.95	-1.05	0.10
CMPD20	-0.54	-1.12	0.58
CMPD21	-0.91	-1.39	0.48
CMPD22	-1.12	-0.99	-0.13
CMPD23	-0.65	-0.79	0.14
CMPD24	-1.88	-1.87	-0.01
CMPD25	-2.26	-2.14	-0.12
CMPD26	-1.71	-1.82	0.11
CMPD27	-2.22	-2.07	-0.16
CMPD28	-1.78	-1.69	-0.09
CMPD29	-1.64	-1.55	-0.09
CMPD30	-2.69	-2.82	0.13
CMPD31	-2.06	-1.71	-0.35
CMPD32	-2.15	-1.81	-0.34
CMPD33	-2.08	-2.04	-0.04
CMPD34	-1.60	-1.69	0.09
CMPD35	-1.53	-1.45	-0.08

Table 8b Set 8 CoMSIA MT_1

	EA	PA	RES
CMPD36	-2.29	-2.54	0.25
CMPD37	-1.60	-1.62	0.02
CMPD39	-1.78	-1.95	0.17
CMPD40	-1.94	-1.61	-0.33
CMPD41	-1.36	-1.38	0.02
CMPD42	-2.53	-2.50	-0.03
CMPD43	-0.11	-0.17	0.06
CMPD44	0.12	-0.25	0.37
CMPD45	-0.52	-0.46	-0.06
CMPD46	-0.11	-0.10	-0.01
CMPD47	0.20	0.08	0.12
Modified		PA	Δ
CMPD48	?	0.32	0.24
CMPD49	?	0.06	-0.02
CMPD50	?	-0.01	-0.09
CMPD51	?	0.11	0.04
CMPD52	?	0.28	0.20
CMPD53	?	0.18	0.43
CMPD54	?	-0.28	-0.03
CMPD55	?	-0.29	-0.04
CMPD56	?	-0.30	-0.05
CMPD57	?	0.03	0.28
CMPD58	?	-0.12	0.13
CMPD59	?	-1.76	-1.25
CMPD60	?	-0.36	0.16
CMPD61	?	-0.92	-0.41

Table 8c Set 8 CoMFA MT_2

	EA	PA B	RES B	PA E	RES E	PA S	RES S
CMPD01	0.52	0.55	-0.03	0.49	0.04	0.59	-0.07
CMPD07	-0.63	-0.42	-0.21	-0.58	-0.05	-0.34	-0.29
CMPD08	-0.26	-0.35	0.09	-0.38	0.12	-0.30	0.04
CMPD09	-0.57	-0.38	-0.19	-0.29	-0.29	-0.37	-0.20
CMPD13	-0.72	-0.63	-0.09	-0.69	-0.03	-0.57	-0.15
CMPD14	-0.45	-0.57	0.12	-0.51	0.06	-0.53	0.08
CMPD15	-0.34	-0.59	0.25	-0.42	0.08	-0.60	0.26
CMPD16	-0.36	-0.59	0.23	-0.54	0.18	-0.58	0.22
CMPD17	-0.43	-0.61	0.18	-0.40	-0.03	-0.59	0.16
CMPD22	-0.65	-1.04	0.39	-0.74	0.09	-1.06	0.41
CMPD23	-0.67	-1.08	0.41	-0.88	0.21	-1.09	0.42
CMPD24	-1.08	-1.20	0.12	-1.00	-0.09	-1.15	0.07
CMPD25	-1.54	-1.26	-0.28	-1.48	-0.06	-1.28	-0.26
CMPD26	-1.43	-1.26	-0.17	-1.17	-0.26	-1.31	-0.13
CMPD27	-1.34	-1.29	-0.05	-1.11	-0.23	-1.38	0.04
CMPD28	-1.46	-1.29	-0.17	-1.21	-0.25	-1.35	-0.11
CMPD29	-0.88	-1.29	0.41	-1.26	0.38	-1.35	0.47
CMPD30	-1.56	-1.38	-0.18	-1.39	-0.18	-1.40	-0.16
CMPD31	-1.54	-1.45	-0.09	-1.79	0.25	-1.48	-0.06
CMPD32	-1.18	-1.41	0.23	-1.59	0.41	-1.46	0.28
CMPD33	-1.20	-1.44	0.24	-1.52	0.32	-1.54	0.34
CMPD34	-1.94	-1.41	-0.53	-1.62	-0.32	-1.47	-0.47
CMPD35	-2.06	-1.43	-0.63	-1.63	-0.43	-1.51	-0.55
CMPD36	-1.72	-1.56	-0.16	-1.75	0.03	-1.56	-0.16
CMPD37	-1.95	-1.82	-0.13	-1.76	-0.19	-1.67	-0.28
CMPD39	-1.23	-1.82	0.59	-1.51	0.28	-1.73	0.50
CMPD41	-1.58	-1.79	0.21	-1.60	0.02	-1.69	0.11
CMPD42	-1.79	-1.91	0.12	-1.73	-0.06	-1.74	-0.05
CMPD43	-1.20	-1.17	-0.03	-1.47	0.27	-1.17	-0.03
CMPD44	-1.15	-1.13	-0.02	-1.25	0.10	-1.15	0.00
CMPD45	-1.46	-1.18	-0.28	-1.20	-0.26	-1.23	-0.23
CMPD46	-1.26	-1.16	-0.10	-1.24	-0.02	-1.20	-0.06
CMPD47	-1.34	-1.14	-0.20	-1.28	-0.07	-1.20	-0.14
Modified		PA B	Δ	PA E	Δ	PA S	Δ
CMPD48	?	-1.14	0.00	-1.29	-0.01	-1.20	0.00
CMPD49	?	-1.16	-0.01	-1.27	0.01	-1.20	0.00
CMPD50	?	-1.12	0.02	-1.24	0.04	-1.20	0.00
CMPD51	?	-1.11	0.03	-1.10	0.17	-1.22	-0.02
CMPD52	?	-1.16	-0.02	-1.19	0.08	-1.20	0.00
CMPD53	?	-1.06	0.07	-1.23	0.01	-1.13	0.03
CMPD54	?	-1.14	-0.01	-1.23	0.02	-1.15	0.00
CMPD55	?	-1.11	0.02	-1.36	-0.12	-1.16	-0.01
CMPD56	?	-1.08	0.05	-1.07	0.18	-1.19	-0.04
CMPD57	?	-1.12	0.01	-1.17	0.08	-1.18	-0.03
CMPD58	?	-1.08	0.05	-1.10	0.15	-1.15	0.00
CMPD59	?	-1.17	-0.61	-1.60	-1.09	-1.20	-0.67
CMPD60	?	-0.58	-0.02	-0.49	0.02	-0.58	-0.05
CMPD61	?	-0.55	0.01	-0.40	0.11	-0.57	-0.04

Table 8d Set 8 CoMSIA MT_2

	EA	PA	RES
CMPD01	0.52	0.52	0.00
CMPD07	-0.63	-0.59	-0.04
CMPD08	-0.26	-0.44	0.18
CMPD09	-0.57	-0.54	-0.03
CMPD13	-0.72	-0.53	-0.19
CMPD14	-0.45	-0.36	-0.09
CMPD15	-0.34	-0.48	0.14
CMPD16	-0.36	-0.59	0.23
CMPD17	-0.43	-0.55	0.12
CMPD18	-1.41	-1.01	-0.40
CMPD19	-0.36	-0.63	0.27
CMPD20	0.00	-0.48	0.48
CMPD21	0.00	0.34	-0.34
CMPD22	-0.65	-0.70	0.05
CMPD23	-0.67	-0.58	-0.09
CMPD24	-1.08	-1.13	0.04
CMPD25	-1.54	-1.48	-0.06
CMPD26	-1.43	-1.08	-0.35
CMPD27	-1.34	-1.19	-0.15
CMPD28	-1.46	-1.33	-0.13
CMPD29	-0.88	-1.21	0.33
CMPD30	-1.56	-1.55	-0.01
CMPD31	-1.54	-1.44	-0.10
CMPD32	-1.18	-1.28	0.10
CMPD33	-1.20	-1.38	0.18
CMPD34	-1.94	-1.52	-0.42
CMPD36	-1.72	-1.92	0.20
CMPD37	-1.95	-1.48	-0.47
CMPD38	-1.00	-1.32	0.32
CMPD39	-1.23	-1.43	0.20
CMPD41	-1.58	-1.44	-0.14
CMPD42	-1.79	-1.93	0.14
CMPD43	-1.20	-1.33	0.13
CMPD44	-1.15	-1.16	0.01
CMPD45	-1.46	-1.27	-0.19
CMPD46	-1.26	-1.40	0.14
CMPD47	-1.34	-1.27	-0.07
Modified		PA	Δ
CMPD48	?	-1.25	0.02
CMPD49	?	-1.40	-0.14
CMPD50	?	-1.12	0.15
CMPD51	?	-1.41	-0.14
CMPD52	?	-1.31	-0.04
CMPD53	?	-0.99	0.17
CMPD54	?	-1.29	-0.13
CMPD55	?	-1.38	-0.22
CMPD56	?	-1.22	-0.06
CMPD57	?	-1.38	-0.21
CMPD58	?	-1.15	0.01