4. RESULT AND DISCUSSION

4.1. Computational

4.1.1. Selection of Dataset

A set of thirty one agonists of PPARα as well as PPARγ receptor subtypes including eighteen α-alkoxy propanoic acid based, five α-aryloxy propanoic acid based, and eight tyrosine based compounds with their activities of single enantiomer (Table C1) for building the 3D QSAR (Comparative Molecular Similarity Indices Analysis) models was selected from the literature by an exhaustive survey as there is limited activity data available for PPAR ligands with pure configurations. Still dataset molecules were so chosen that they fall in a wide range of PPAR activities (Figure C5) so as to build significant predictive models that could be effectively used for designing novel PPAR activators.

These molecules are composed of three major fragments: (i) the left hand side heterocycle, (ii) the linker and (iii) the right hand side N-substituted tyrosine or α-alkoxy/aryloxy-3-phenyl propanoic acid which constitute the general pharmacophore of PPARα/γ dual agonists.

Farglitazar, a highly potent PPARα/γ dual agonist, also a member of the dataset (training set) was used as the template (Figure C7). The X-ray crystal structure of PPARγ LBD co-crystallised with farglitazar is available in the RCSB PDB. The X-ray crystal structure of PPARα LBD co-crystallised with GW409544, an analog of farglitazar (Figure C7) is also available in the RCSB PDB. The second was also used for docking studies of various designed molecules at PPARα.

4.1.2. Generation of Significant CoMSIA Models

Proper and appreciable structural alignment for the training and test set molecules were performed (as evident in the Figures C8 and C9). Lower and higher column filtering
values than 2.0 kcal/mol; i.e. 0.5, 1.0, 1.5 and 2.5 kcal/mol, respectively, were investigated, but all led to a decrease in the q2 value. So, column filtering value was set to 2.0 kcal/mol for generating the final models.

The best PPARγ model was derived by using all the five descriptors afforded by CoMSIA (Table C2), which possesses the best predictive power (q2 = 0.868). From the comparison of those several PLS analysis results (Table C2) for the different combinations of the descriptors, it is likely that the properties considered are intercorrelated in a complicated way. The intercorrelations of those numerically intensive grid fields are difficult to determine whether some kind of descriptor is more important over the other or not. The advantages of using five different fields of well defined molecular properties have to be noticed in the straightforward partitioning of these properties into spatial locations where they take a determining role on receptor binding. The same descriptors were employed to build the α- and dual models (Tables C3, C4 respectively) despite the combination of steric, electrostatic, hydrophobic and hydrogen bond donor fields resulted in a little better but comparable q2 values in these cases. The relative contributions of the descriptors to the models are of the order: α-model H>E>D>A>S; γ-model H>A>D>E>S and dual-model H>E=A>D>S. In the CoMSIA models, steric, electrostatic, hydrophobic, hydrogen bond donor and hydrogen bond acceptor fields contribute to the QSAR equations by 14.1, 23.8, 27.3, 18.6 and 16.3 in case of α-model; 14.8, 18.0, 29.7, 16.9 and 20.6 in case of γ-model; and 14.6, 18.7, 32.1, 15.8 and 18.7 in case of dual model, respectively, in terms of percent relative contribution. The standard error of estimate (SEE) values of the three models were also fairly less indicating the development of significant models.

4.1.3. Validation of the Generated Models

Validation should be done for establishing reliability and good predictive ability of a model. A test set has been predicted. The PPARγ pEC50 of the test set molecules were predicted with reasonable accuracy (Table C6). Even fair accuracy can be noticed in the prediction of the PPARα activities of the test set molecules except in case of T1. The PPAR dual activities were predicted with appreciable accuracy except T1. The large residual for T1
in the dual model seems to be the contribution of large residual of the $\alpha$-model. The reasons for the deviation have been discussed after the contour analysis.

It is observed in the scatter plots for the predicted vs experimental (reported) activities ($pEC_{50}$ values) for each of the CoMFA models that the predicted activities of the training set molecules (blue diamonds) follow the linearity and the predicted activities of the test set molecules (pink squares) are close to the regression line of linearity except one in each of PPAR$\alpha$ and PPAR$\gamma$ models and two in the PPAR dual model (Figure C10) as discussed above.

The QSAR produced by the CoMSIA models, which are usually represented as 3D ‘coefficient contour maps’, are shown in figures C11-20. The molecular structure of compound 20 (GI 262570) is displayed inside the contour maps as the reference structure. Careful observation of the contour maps indicates some partial and individual contributions of the physicochemical features of the PPAR$\alpha$ and PPAR$\gamma$ models to the PPAR dual model (Figure C21).

4.1.4. Contour analysis (CoMFA)

Comparison of the steric maps

A green contour can be observed covering half of the phenyl ring (C2–C3–C4 region) of the left-hand side phenyl oxazole moiety from the front side in all the three models which indicates steric bulk in this part of the molecule is favourable for PPAR$\alpha$, PPAR$\gamma$ as well as PPAR dual activities (Figure C13). Whereas, the lower part of the large yellow contour on the backside of the same phenyl ring in the dual model is a contribution from the $\alpha$-model. So, sterically large groups are disfavoured in this region for better PPAR$\alpha$ and PPARdual activity. The upper part of the large yellow polyhedra around the nitrogen and oxygen of the oxazole ring in the dual model seems to be contributed by both the $\alpha$- and $\gamma$-models, indicating less steric interactions are favourable for better activity in these regions also, though the green thin contour around the oxygen of the oxazole ring in the a-model disappears in case of the dual model. However, the small yellow map away from the oxazole ring towards the inverse ‘U’ cavity of the molecule is retained in the dual model. A green
A pyramidal red contour can be observed just in front of the C3 position of the phenyl ring of the phenyl oxazole moiety on the left-hand side in the α-model (Figure C14a). In the γ-model, a red polyhedron is seen covering the C2–C3 of the same ring as the former (Figure C14b). In the dual model, a red contour similar to the α-model can be seen (Figure C14c). Again a red contour is observed covering the oxygen atom of the oxazole ring in the a-model, whereas in the γ-model there is a small red contour near to the same oxygen. The resultant effect could be noticed in case of the dual model with a medium-sized red polyhedron covering the same oxygen atom; thereby indicating greater electron density requirement for activity enhancement in these regions. One additional red map is present around the sp³ oxygen of the acid group in the a-model, this disappear in the γ-model and similar red contour again appear in the dual model in similar position but with a diminished size supporting the fact that acid group is necessary at this site for the activities. A blue contour is observed in front of the C2 and the bond linking the phenyl and oxazole ring on the left-hand side in the a-model. In the c-model, a blue contour appears just behind the phenyl ring near to C1–C6–C5 bonds.

Finally, a blue medium-sized pyramidal contour is observed shifted towards the cavity of the molecule and is close to the C1 position of the same phenyl ring and the bond connecting the phenyl and oxazole rings in the dual model. A second blue polyhedron is
observed around the bond attaching the phenyl oxazole moiety and the linker unit of the molecule in the α-model. A large irregular polyhedron can be noticed in case of the γ-model covering the methyl substituent on the phenyl oxazole unit. The combined effect is evident in the dual model in the form of a medium-sized irregular polyhedron around the same methyl group and the same connecting bond indicating positive potential is favoured in these regions for the activities. One additional irregular polyhedron can be seen in the γ-model around the nitrogen atom on the right-hand side, which is absent in the other cases, indicating a less significant feature for the activities.

Comparison of the hydrophobic maps

There is a large irregular white polyhedron near to the oxazole ring towards the cavity of the molecule on the left hand side in the α-model. A second large white contour is seen around the bond connecting the phenyl ring and the oxazole ring and a third white contour is observed near the oxazole ring on the opposite side of the cavity. Two more white 3D maps are seen away from the same ring on the same side. Another white contour can be noticed away from the C4–C5 bond of the phenyl ring on the back side (Figure C15a, C16a). These all 3D maps indicate the incorporation of hydrophilic character in these regions of the template molecule for the improvement of the activity. In the γ-model, a large white contour devours almost the whole oxazole ring except the nitrogen atom and a white polyhedron can also be seen near to the oxazole ring nitrogen on the back side. Three more white contours are observed around the oxazole ring; the first towards the cavity of the molecule, second in front and the third on the opposite side of the cavity (Figure C15b, C16b). Finally, the resultant effect of the white 3D maps around the oxazole ring in the individual models is quite evident in the dual model in the form of a continuous voluminous contour fencing the oxazole ring from all sides (Figure C15c, C16c). Almost the entire ring except the nitrogen atom on the backside is covered by the large white contour. Hydrophobic character is disfavoured in these regions of the molecule for better dual activity which is also supported by the red and blue electrostatic contours discussed previously. There is also a white canopy over the α- and β-carbon to the acid function and close to the acid group on the right-hand part of the molecule in the α-model. This feature is absent in the γ-model, though similar contour appears again in case of the dual model indicating the necessity of the propanoic acid
unit in that region for the PPARα and PPAR dual activity, supported too by the electrostatic red contours. A purple contour in each of the three models is covering the bottom half of the phenyl ring of the phenyl oxazole unit, as a common feature, on the left-hand side of the template indicating hydrophobic groups in this region are favourable for all the three kinds of activities which is in agreement with the green steric contours in this region, combined indicating large hydrophobic groups will enhance the activity. A purple polyhedron is seen away from the oxygen atom of the oxazole ring towards the cavity of the molecule in the α-model. This is absent in case of the c-model and again it appears in the dual model at the same position but with a smaller size than in the first. Another purple contour is observed close to the C4–C5 bond of the first benzene ring on the back side of the benzophenone moiety in the α-model. A purple map is seen near to the NH–C1–C2 bonds in the c-model and finally a purple map is observed near to the C1–C2 bond of the first benzene ring indicating hydrophobic groups are favourable in this region for improved PPARγ and PPAR dual activities though not a need for better PPARα activity. The purple contour on the backside of the first benzene ring in the α-model is absent in the γ- and dual models indicating non-significant contribution of this particular contour to the dual model, though this feature combined with the steric feature at this region of the a-model indicate small hydrophobic substitution at this region will improve PPARα activity. Generation of relatively more number of contours for this property in all the models than the other properties is also in agreement with the result of maximum relative contribution by the hydrophobic descriptor in all the three cases.

Comparison of the hydrogen bond donor maps

A magenta pyramidal contour, seen away from the acid carbonyl oxygen on the opposite side of the molecular cavity in the α-model (Figure C19a), is contributing to the magenta contour of similar shape but of relatively smaller size and more far away from the acid carbonyl oxygen on the right hand side of the molecule in the γ-model (Figure C19b). A magenta stick is also visible just over the carbon atom of the acid function in the a-model. A magenta rhombohedral 3D contour map (not visible, being inside the hollow cavity of the yellow–brown mushroom-shaped 3D contour) can be observed away from the acid hydroxyl oxygen on the front side in the γ-model (Figure C19b) which has very little contribution to the dual
model (Figure C19c) in the form of a tiny magenta polyhedron almost at the same position. The features are in agreement with the importance of hydrogen bond donor groups at these sites for the activities. A small yellow brown contour is noticed near to the acid hydroxyl oxygen in the amodel. A huge yellow–brown mushroom-shaped contour just in front of the acid hydroxyl oxygen atom is observed in the γ-model. The voluminous contour covers the continuous area in front of the acid hydroxyl oxygen atom, the α-carbon, attached nitrogen atom and the β-carbon atom and is away from the ketonic oxygen atom of the benzophenone moiety. The magenta contour is rested just inside the cavity of the hollow contour map. In the dual model, a yellow–brown contour towards the molecular cavity and very near to the ketonic oxygen of the benzophenone moiety and away from the nitrogen atom on the right-hand side of the molecule is observed showing the hydrogen bond donor character disfavoured regions for the PPAR dual activity. It can be inferred by studying the electrostatic and hydrogen bond donor contours that acid function is suitable for the activities but large hydrogen bond donor groups that penetrate the mushroom-shaped yellow–brown contour could be detrimental particularly for the PPARγ activity that will in turn reduce the PPAR dual activity too.

Comparison of the hydrogen bond acceptor maps

In the α-model, two large orange polyhedra are observed. The first is on the left-hand side devouring half of the oxazole ring (except the oxygen atom), the bond between oxazole and phenyl rings and C1–C6 bond of the phenyl ring and the second is on the right-hand side of the molecule devouring the carbonyl oxygen atom of the acid group (Figure C20a). In the γ-model, a large orange polyhedron can be noticed near and behind the phenyl oxazole moiety ranging from nitrogen atom of the oxazole ring to C6 of the phenyl ring (Figure C20b). The contours in the α- and γ-models on the left hand side of the template contribute substantially to the contours of the dual model (Figure C20c) giving rise to a large orange contour very near to the same part of the template as stated in the γ-model and covering the C6 atom of the phenyl ring indicating hydrogen bond acceptor groups in these regions is favourable for PPARα, PPARγ as well as PPAR dual activities. The orange contour on the right hand side in the α-model is absent in the c- and dual models indicating that the feature is not contributing to the dual model and is not important for PPARγ activity though the need of acid group for
PPAR dual activity is already supported by the hydrogen bond donor maps. A cyan contour is seen on the right-hand side at equal distances from the nitrogen atom and the ketonic oxygen atom of the benzophenone moiety on the front side in the α-model. A sleek cyan contour is observed in case of the γ-model almost at the similar position as that in the α-model. The contribution of these is clearly noticed in the dual model resulting in a medium-sized elongated cyan contour at the same position pointing the hydrogen bond acceptor disfavoured regions in the improvement of activities. The results of hydrogen bond acceptor contours agree with the results of the hydrogen bond donor contours.

These results are in accordance with the CoMSIA study that the statistical outcome of the S + E + D + H combination of descriptors is comparable to the statistical outcome of the S + E + D + A + H combination of descriptors for all the models (Tables C2, C3 and C4). When the test set molecules T1 was taken into the molecular areas, no unfavourable overlap was noticed for the electrostatic, hydrophobic, hydrogen bond donor and hydrogen bond acceptor contours. Due to isopropyl group that is less bulky than a substituted aryl group as α-alkoxy substitution on the right hand side of the molecule, it favours the PPARα activity as evident from the steric contours of the α-model. The isopropyl group also fits well for the hydrophobic contours of the α-model. A destabilising overlap can be observed on the back side of the phenyl ring of the phenyl oxadiazole moiety on the left-hand side of the molecule with the large yellow steric map in the PPARα model. Similar destabilising overlap was noticed with the contours of the PPAR dual model. Although, only this reason cannot solely explain such large residual values for the PPARα and PPAR dual pEC50 predictions. There are several other reasons that may account for the greater residual value, for example, an incorrectly measured experimental value, a different binding conformation, a significant difference in the physicochemical properties or structural uniqueness which are not a rare instance for the PPAR ligands.

### 4.1.5. Generation of CoMFA Models

Comparative Molecular Field Analysis was performed with the same training set molecules (employed for developing CoMSIA models) using Sybyl 7.3. CoMSIA models
were generated in a similar way as is stated for the generation of the CoMSIA models (Experimental section) and the three CoMFA models (PPARα, PPARγ and PPAR dual) were found to be significant and robust ($q^2$ values for all the three models greater than or close to 0.6). The steric and electrostatic contours of the PPARα and PPARγ models helped in designing of the partial agonists (Figure C21a and C21b).

The steric and electrostatic contours of the CoMSIA and CoMFA models and the additional contours generated in CoMSIA that indicate the required hydrogen bond donor and hydrogen bond acceptor features for enhancement of activities provided a great deal of assistance in designing the right hand side hydrogen bonding part to be introduced in the designed partial agonists. The steric and electrostatic contours also helped in designing the left hand side heterocyclic moieties to be incorporated in the designed partial agonists.

4.1.6. Failure of Dual Agonists and Preference of Partial Agonists

As increasing number of cases of discontinuation and withdrawal of the PPARα/γ dual agonists owing to their unwanted side effects, sometimes severe began to come forward during the period of research; according to the demand of the changing scenario of the PPAR research, the work was planned for the design of partial PPARα/γ ligands and, synthesis of the selected molecules predicted as the best partial PPARα/γ ligands based on the hypothesis that partial agonism at both PPARα and PPARγ receptors by dual partial activators may provide a solution resulting in the desirable responses and reducing the adverse effects caused by the individual and dual agonists for the treatment of T2DM.

4.1.7. Design and Activity Prediction of NCEs with Standard Fragment

The aim of the work was to design novel dual PPARα/γ partial agonists. PPARα/γ dual agonists mainly the tyrosine and propanoic acid derivatives usually possess essential pharmacophoric elements $^{545,554,555}$ i.e.; an acidic group or a hydrogen bonding part attached to a central flat aromatic ring, a linker and a large hydrophobic fragment and adopts
a bioactive U-shapped conformation for receptor binding (Figure C6a-c). It was planned to select and design left hand side hydrophobic heterocyclic fragment and right hand side hydrogen bonding fragment keeping the central flat aromatic ring intact which will ultimately impart partial agonistic character to the designed molecules based on the general pharmacophore of the PPARα/γ dual activators.

The template (Figure C7) used for the design is a highly potent agonist to both PPARα and PPARγ. If the disfavored steric, electronic, hydrogen bond donor and acceptor features, or the contradictory of the favorable features are considered for the structural modification of the template to design the partial agonists; the direction towards designing obtained from the resulted four types of contours from the CoMFA and CoMSIA models can be effectively employed for the design of the partial agonists. Therefore, it was planned to first select and design left hand side hydrophobic heterocyclic fragment and right hand side hydrogen bonding fragment and secondly, to validate and establish the effectiveness of the lhs and rhs fragments (to be incorporated in the designed NCEs) to impart partial agonistic features in the designed NCEs. So, after obtaining the required fragments they were to be introduced into some known standard dual activators in place of their respective lhs and rhs fragments and the subsequent activity predictions of the resulted molecules by the generated CoMFA models and analysis of the results would help to be more particular in selecting more suitable fragments among the designed for the purpose of final designing of the partial dual agonists. This operation resulted in the five series of NCEs with Standard Fragment (Tables C7-C11).

From the analysis of the steric and electrostatic contours resulted from the QSAR models, it was understood that reducing the extension length (vertical) of the hydrophobic heterocyclic part on the left hand side of the template will lead to reduction of PPAR α and γ activities (Figure C21a and C21b). Likewise, it was understood that reducing the bulk (downwards/vertical) of the hydrogen bonding part on the right hand side of the template will lead to reduction of PPARα as well as PPARγ activities (Figure C21a and C21b). Fusion of the five and six membered rings of the hydrophobic part of farglitazar to get a benz fused heterocycle would result in reduction of the extending length of the hydrophobic unit. Two
benzfused heterocycles namely; benzimidazole and indole, popular for their versatile pharmacological potential, were taken according to design guided by the analysis and requirement of steric and electrostatic features of the contours (Figure C21d and C21e). Benz fused heterocycles (benzimidazole/indole) would remain away from the green contours on the lhs of the template (Figure C21f) and effect reduction of activities, i.e.; would favor partial agonistic activities at both the receptors. The site around the oxygen atom present at the oxazole ring (left hand side of the template), if rendered electron deficient (red rhombohedral contour, discussed previously) will disfavor enhancement of activities (Figure C21a and C21b). Placing N-Me at the site satisfied the requirement. The heteroatom (nitrogen) of the heterocycles with methyl group substitution was desirable to suppress electron richness (red rhombohedral contour on the left hand side of the PPARα and PPARγ models) simultaneously rendering less bulk in the region (yellow contour on the left hand side of PPARγ model) as found from observation and analysis of the contours (Figure C14, C21a and C21b) and also keeping in view the housability of the ligands at the receptor site.

The selection of benzimidazole and indole heterocycles as part of the lhs fragments is also supported chemical structure analysis of the known standard PPAR molecules. To reduce the extending length of the hydrophobic unit unlike a phenyl oxazole in farglitar or muraglitazar; thiophenyl oxazole in LY 510929 etc (Figure C21d and C21e); benzfused heterocyles were incorporated in the designed molecules. The heterocyclic left hand side part of full agonist rosiglitazone can also be structurally modified by joining the heteroatom of the N-methyl pyridyl moiety to the carbon atom adjacent to the N-Me group of the spacer to obtain a benzfused heterocycle benzimidazole with one heteroatom substituted with a methyl group (Figure C21d). The bioisosteric replacement of the unsubstituted nitrogen with a ‘CH’ group gives rise to other benzfused heterocycle indole with the heteroatom substituted with a methyl group (Figure C21e).

A tricyclic moiety, acridone, was taken as it would extend from front to back and not upto the said green contours so it gives two advantages in the design; firstly it would remain away from the green contours and secondly, as the tricyclic ring extends from front to rear in a horizontal manner it exerts a negative effect on the steric requirements of the yellow
contours (around the oxazole moiety of the template, figures C13, C21a-b) which indicates less steric bulk in the region is beneficial for enhancing the activity, on the lhs of the both PPARα and PPARγ models.

These heterocycles were incorporated as the left hand side hydrophobic part of the series I and II NCEs in place of the existing phenyl oxazole moiety (Tables C7 and C8). Such heterocyclic scaffolds contributed to the reduction of PPARα and PPARγ activities compared to the previously known molecules (Tables C7 and C8). Reduction of the individual activities decreased the overall dual activities too as the PPAR dual model incorporates contributed features from the individual models (PPARα and PPARγ) which has been previously discussed.

It could be concluded from the analysis of the hydrogen bond donor acceptor CoMSIA contours that hydrogen bond acceptor group close to the secondary amino nitrogen (small cyan triangle), on the rhs of the template, is disfavored for activity (Figure C21c) and hydrogen bond acceptor group near to the same also diminishes activity (yellow brown contour) (Figure C21c). To optimize these requirements in such a way so that the designed molecules should have lesser activity and the general pharmacophore of PPAR agonists, it was decided to use α-alkoxy propanoic acid as the hydrogen bonding moiety for the design of the molecules. An oxygen atom at that place would oppose the requirements of the cyan region on the right hand side (Figure C20) thereby, was expected to result in desired moderate extent of activity of the designed molecules (Figure C21e). The replacement of the secondary amino group on the rhs of the template with an oxygen atom for satisfying the less bulk and electrostatic requirements and requirements of hydrogen bond- acceptor features also suggest the choice of ether-oxygen at the said position in the designed molecules (Tables C9-C11). To understand the effect of bulk of the rhs fragment (hydrogen bonding unit) on the activity three different alkyl groups with different bulk (large to moderate) were incorporated in the α-alkoxy acid or β-ketoester unit of the designed molecules with standard fragment in place of the existing fragment (Tables C9-C11).
The effect of length of the alkyloxy spacer on the activities was also examined by varying the length (ethyleneoxy and methylenoxy for benzimidazole/indole containing molecules). The length of the two carbon linker (as reported in farglitazar, ragaglitazar, tesaglitazar etc.) if decreased to one carbon would impart further constraint to the designed molecules and help in satisfying the steric requirement of the heterocyclic hydrophobic fragment for partial agonism (i.e., keeping away from the green contours on the lhs, Figure C21f). A special type of linker ‘N-methyl amino ethanol’ was incorporated for the NCEs containing chromone, reported in the literature for PPARγ agonists like rosiglitazone to understand the effect of this kind of linker on activity. Ethyleneoxy or propyleneoxy linker was taken in the NCEs containing acridone in stead of methylenoxy or ethyleneoxy as in case of benzimidazole/indole containing molecules because the former linker is equivalent to the later in distance from heteroatom (nitrogen) of heterocycle to the ethereal oxygen of the linker.

The predicted activities of the five series of molecules with standard fragments were comparatively studied (Tables C7-C11) and the results supported the design of the lhs and rhs fragments.

The predicted PPARα, PPARγ and PPAR dual activities of the first two series of NCEs with standard fragment (Tables C7, C8) help to select the more suitable heterocycles for the design of PPARα/γ partial agonists and also indicated the more suitable length of linker to be used for the same purpose.

It was found from the comparison of activities that the series I NCEs containing benzimidazole, indole or acridone heterocycle that benzimidazolyl/indolyl linked NCEs with shorter linker (methyleneoxy) show lesser activities compared to that of most of the the standard molecules (Table C7). The ethyleneoxy analogs of the NCEs exhibit predicted activities greater or near to that of some of the standard molecules. The predicted activities of the acridonyl linked NCEs with propyleneoxy analogs were near to that of the ethyleneoxy analogs. Moreover, the NCEs with shorter linker (methyleneoxy in case of benzimidazole/indole containing NCEs and ethyleneoxy in case of acridone containing NCEs) were found to have lesser activities than their analogs with longer linker (ethyleneoxy
in case of benzimidazole/indole containing NCEs and propyloxy in case of acridone containing NCEs) (Table C7).

It was found from the comparison of activities that the series II NCEs containing benzimidazole, indole or acridone heterocycle that benzimidazolyl/indolyl linked NCEs with shorter linker (methyleneoxy) show lesser activities compared to that of most of the the standard molecules (Table C8). The ethyleneoxy analogs of the NCEs exhibit predicted activities greater or near to that some of the standard molecules. The predicted activities of the acridonyl linked NCEs with propyleneoxy analogs were near to that of the ethyleneoxy analogs. Moreover, the NCEs with shorter linker (methyleneoxy in case of benzimidazole/indole containing NCEs and ethyleneoxy in case of acridone containing NCEs) were found to have lesser activities than their analogs with longer linker (ethyleneoxy in case of benzimidazole/indole containing NCEs and propyloxy in case of acridone containing NCEs) (Table C8). The results were in compliance with that of the results obtained in case of series I NCEs.

The results strongly indicate the incorporation of the discussed three heterocycles and a shorter spacer, which further help in imparting constraint into the molecules, for the design of the partial agonists. The results were as expected according to contour analysis and structure analysis of the standard molecules as discussed earlier (Figure C21d and C21e).

To investigate the effects of the designed rhs hydrogen bonding fragments on PPAR activities; the PPAR activities of series III, IV and V NCEs with standard fragment were predicted and studied.

It was observed from the comparison of the activities that the NCEs with $\alpha$-alkoxy acid moiety of lesser bulk (isobutyloxy, isopropyloxy) shows lesser activities compared to the analogs with $\alpha$-alkoxy acid moiety of greater bulk ($p$-isopropyl benzyloxy) in series III NCEs with standard fragment (Table C9). $\alpha$-methyl group increases the PPAR$\alpha$ activity compared to the analogs in which $\alpha$-methyl group is absent. The results were according to the expectation and previous discussion and can be attributed to lesser bulk of the isobutyloxy
and isopropyloxy with respect to the \( p \)-isopropylbenzyloxy moiety (Figures C21 a, b and d). The predicted PPAR activities of the NCEs were lesser than the standard molecules in most of the cases. The results indicated the incorporation of \( \alpha \)-isobutyloxy and \( \alpha \)-isopropyloxy propanoic acid moiety as the hydrogen bonding acidic unit for the design of the partial agonists.

To be more precise for the selection of rhs fragments and also the suitable length of the spacer/linker for the design of partial agonists two more series of molecules were predicted for their PPAR \( \alpha \), \( \gamma \) and dual activities with the developed CoMSIA models and the results were analyzed.

Analyzing the predicted PPAR activities of the series IV NCEs (Table C10) similar results were obtained as in case of the series III NCEs. The isobutyloxy and isopropyloxy propanoic acid based molecules show lesser activities with respect to the \( p \)-isopropylbenzyloxy propanoic acid based molecules (Table C10). The NCEs with methyleneoxy linker were found to have lesser activities than their ethyleneoxy analogs. The predicted PPAR activities of the NCEs were lesser than the standard molecules in most of the cases.

To understand the effect of the linker (\( N \)-methyl amino ethanol/\( N \)-methyl amino methanol) other series of NCEs (Series V) derived from series IV molecules were predicted for their PPAR activities and the results were comparatively studied with the previous results (Table C11).

Form the comparison of order of predicted PPAR\( \alpha \),\( \gamma \) and dual activities of the series V NCEs with standard fragment (Table C10) it is found that the NCEs containing isopropyloxy and isobutyloxy group show lesser PPAR activities compared to their \( p \)-isopropylbenzyloxy analogs. The NCEs containing methyleneoxy linker were found to have lesser activities than their ethyleneoxy analogs. The predicted PPAR activities of the NCEs were lesser than the standard molecules in most of the cases. Interestingly, the activities of this series of NCEs (that are without \( N \)-Me group as a part of the linker) exhibit lesser PPAR...
activities than the previous series of molecules (Series IV NCEs with N-Me group as a part of the linker). The results recommended the use of methyleneoxy linker over ethyleneoxy and not N-Me containing linker to impart lesser activities to the NCEs in the design of PPARα/γ partial ligands.

The above discussion lead to the pharmacophore shown in (figure C21d) for the design of the novel PPAR α/γ partial agonists.

From the above discussion following points were concluded for the design of PPARα/γ partial ligands;

- Benzimidazole, indole, acridone heterocycle to be incorporated.
- Methyleneoxy linker is preferred over ethyleneoxy as alkyloxy linker in case of benzimidazole and indole containing molecules.
- α-alcoxy acids with less bulk as isobutyloxy, isopropyloxy and even of lesser bulk as the rhs hydrogen bonding part.

**Designed partial agonists**

Based on the above points the benzimidazol/indol/acridone-yl linked based α-alcoxy propanoic acid based NCEs were designed (Tables C12-C14). Though shorter linker was preferred for the aimed purpose, NCEs with both ethyleneoxy and methyleneoxy linker in case of benzimidazole/indole containing molecules and; propyloxy and ethyleneoxy linker in case of acridone containing molecules were kept for the design to be more precise about the final selection of the appropriate molecules. α-alcoxy propanoic acid of moderate to smaller bulk like α-isobutyloxy, α-isopropyloxy, α-ethylxy, α-methoxy as well as α-alcoxy propanoic acid of larger bulk like α- (isopropyl benzyl)oxy propanoic acid (Figure C21d, Tables 12-14) were incorporated for the design of the NCEs to better understand the effect of bulk on PPARα and PPARγ activities and receptor binding thereby understanding optimum bulk requirement for the ligands to bind partially to both PPARα and PPARγ receptors. As the benzylidene and benzyl thiazolidenediones and, benzylidene and benzyl 1,3-diesters and
their analogs are also reported to be PPAR active agents; the benzylidene and benzyl thiazolidenediones, and benzylidene and benzyl diethyl malonates containing benzimidazole and indole were also designed for synthesis as additional PPAR molecules.

Benzimidazolyl, indolyl and acridonyl linked α-alkoxy propanoic acid based NCEs were built to obtain total three series of designed NCEs.

The predicted activities (PPARα, PPARγ and PPAR dual in terms of pEC50) and binding affinities (Surflex dock score) of the designed NCEs were compared among themselves as well as with that of the selected standard molecules (Tables C12a-e, C13a-e, C14a-e and C15) for the selection of best PPARα/γ partial agonists from each series. Docking studies of the designed molecules were carried out separately for the individual receptors to predict the binding interactions of the ligands at the active sites of PPARα and PPARγ. The criteria for the selection of best partial ligands from each series was set (Experimental, Computational, Final selection of designed NCEs) in such a manner so as to take into account the three predicted PPAR activities and the total scores for docking at the two receptors which calculate the resultant of several types of interaction energies of the ligand with the receptor at active site of the receptor. As the ranking for each predicted parameter was done in a descending order so the greater the sum of the parameters (for each criterion) for a designed molecule the lesser is its activities and binding affinities and consequently the better it is as a partial PPARα/γ agonist. The proper housability (accommodation) of the ligands at the target receptor active site is an important factor for receptor activation. The more a ligand tends to bulge out or penetrate out of the generated docking cavity the more is the possibility of undesired interactions with other amino acid residues of the active site that may lead to unwanted adverse effects. Therefore, along with the above discussed criteria crash values, which indicate how properly the docked ligands are housed inside the generated docking cavity, of the designed ligands for docking at individual receptors were also recorded and molecules with predicted crash values lesser than -5.00 (crash values nearer to zero indicate better fit inside the cavity, negative values indicate bulging out of the docking cavity) were ignored even if they may fall into selection by the previously discussed criteria. The maximum crash value found from the docking results of the selected standard molecules was -4.03 (Table C15). Thus, to be completely unbiased
during the selection procedure of the designed molecules to be synthesized the limit of crash value for each molecule to be considered was taken as $-4.03 + 1 = -5.03 \approx -5.00$. The molecules showing crash values lesser than $-5.00$ were rejected even if they have greater sum preferences and the molecules with next higher sum and within crash limit were preferred over the former. It was expected that the designed NCEs containing $p$-isopropylbenzyl oxy acid would give rise to greater crash values than the other four types of $\alpha$-aloxy acid containing NCEs containing molecules. This is the part of the NCEs which is supposed to dock at the ‘Y’ shaped cavity of PPARγ and the greater crash values of the molecules containing $\alpha$-($p$-isopropylbenzyl oxy) can be explained on the basis of the steric bulk of alkoxy acid units. The calculated molar volumes of the alkoxy fragments for the said hydrogen bonding units were found to be 153.3, 92.4, 75.9, 59.0 and 42.5 respectively with a deviation of ±3 cm$^3$ and the molar volumes of the entire $\alpha$-alkoxy propanoic acids were calculated to be 189.8, 128.9, 112.4, 95.5 and 79.3 respectively with a deviation of ±3 cm$^3$ (Figure C21d). It can be observed that the first $\alpha$-alkoxy propanoic acid has a calculated molar volume near to the hydrogen bonding acidic part of farglitazar (Figure C21d) and is therefore, not preferable to be a part of partial activators which is further validated by the following results.

Benzimidazolyl linked $\alpha$-alkoxy propanoic acid based designed NCEs (B1-B10) were arranged according to decreasing order of their predicted PPAR activities (Tables C12a-c) and then ranked. They were also arranged in decreasing order of their surflex dock scores for the two proteins (PPARα and PPARγ) (Tables C12d-e) and then ranked. When the criteria for selection of molecules was considered it was found that only B4 (containing $\alpha$-isobutyloxy propanoic acid), B6 (containing $\alpha$-isopropoxy propanoic acid), B8 (containing $\alpha$-ethoxy propanoic acid) and B10 (with $\alpha$-methoxy propanoic acid) (Table C16, highlighted in green) were selected by both the criteria. The selected showed lesser activities and docking score compared to most of the selected standard molecules. The NCEs selected as the best four partial agonists of this series which can be taken forward for synthesis were according to the expectation as discussed above. This can be well explained by critical observation of the adjustment of the NCEs with the steric, electronic and hydrogen bond donor and acceptor requirements of the resulted contours from the generated CoMSIA models (Figures C25-27). When all the designed NCEs with methyleneoxy linker of this series (B2, B4, B6, B8 and
B10) are displayed in molecular areas within the steric and electrostatic contours (transparent) of the PPARα model it can be observed that the NCEs with p-isopropyl benzyl group (B2, shown in violet) as a part of the hydrogen bonding unit extend beyond the green steric contour on the right hand side (rhs) (Figure C25a) but the NCEs with isobutyl group (B4, shown in blue), isopropyl (B6, shown in red), ethyl (B8, shown in yellow) or methyl (B10, shown in green) group remain within and away from the said contour and satisfy the steric requirements for partial agonistic character of the molecules as discussed earlier and indicated in (figures C21a, C25, C26 and C27). The molecules with alkoxy moieties of lesser bulk (isobutyloxy, isoprpyloxy, ethoxy and methoxy) comply better with hydrophobic contours compared to p-isopropyl benzyloxy containing NCE (Figures C25b, C26b and C27b). When all the designed NCEs with methyleneoxy linker of this series are displayed in molecular areas within the hydrogen bond donor and acceptor contours (transparent) of the PPARα CoMSIA model the molecules with larger alkoxy group do not exert much significant effect to be disqualified as partial agonists according to the hydrogen bond donor and acceptor requirements (Figures C25c, C26c and C27c), they are mainly rejected on the basis of steric requirements for partial agonism. However, the molecules due to the presence of benzimidazole heterocycle satisfy the requirements of hydrogen bond acceptor feature for partial activity as discussed earlier. Since the NCEs with bulky alkoxy moiety (B2) favors the features of the contours (CoMSIA and CoMFA) they show greater activities and, the NCEs with smaller alkoxy moiety (B4, B8, B6 and B10) optimize and sometimes disfavor the features which can be reasoned for their predicted lesser activities. If the selected NCEs with methyleneoxy linker (B4, B6, B8 and B10 shown in green) are compared with their ethyleneoxy analogs (B3, B5, B7 and B9 shown in red) within the contours of PPARα model; the hydrophobic heterocyclic moiety of the NCEs with the longer linker penetrate the green contour on the left hand side (lhs) due to longer linker while the hydrophobic heterocyclic moiety of the NCEs with the shorter linker remain away from the said contour (Figure C26a) satisfying the requirements for partial agonism as discussed before. B4, B6, B8 and B10 (shown in green) can also be noticed within the hydrogen bond donor and acceptor contours fulfilling the requirements to show lesser activities at the target receptors, according to the discussed required features, hence partial agonism better compared to B3, B5, B7, B9 (shown in red) in figure C26c. As the NCEs with ethyleneoxy linker (B3, B5, B7 and B9) favor the
features of the contours they show greater activities compared to the NCEs with methyleneoxy linker (B4, B6, B8 and B10) which optimize and sometimes disfavor the features (which can be reasoned for their predicted lesser activities) and therefore show lesser activities than the former and are preferred as partial agonists of PPARα. The benzimidazolyl linked molecules with methyleneoxy linker and hydrogen bonding moieties of less bulk (isobutyloxy, isopropyloxy, ethoxy and methoxy containing α-alkoxy acids), the selected four NCEs lie within the contours (steric-electrostatic, hydrophobic and hydrogen bond donor-acceptor) with all the favorable features for PPARα partial agonism (Figure C27). When all the designed NCEs with methyleneoxy linker of this series (B2, B4, B6, B8 and B10) are displayed in molecular areas within the steric and electrostatic contours (transparent) of the PPARγ model it can be observed that the NCEs with p-isopropyl benzyloxy group (B2, shown in violet) as a part of the alkoxy acid moiety extend beyond the green steric contour on the right hand side (rhs) (Figure C28a) but the NCEs with α-isobutyloxy (B4), isopropyloxy (B6), ethyl or methyl group remain within the said contour and satisfy the steric requirements for partial agonistic character of the molecules as discussed earlier and indicated in figures C21a, C21b and C21e. The selected NCEs fit well into the hydrophobic contours too (Figure C28b, C29b and C30b) in such a manner that favors partial activity. The hydrophobic heterocyclic moieties of the designed molecules are observed away from the purple contours (hydrophobicity favored) on the lhs thereby diminishing the activity as compared to the template (Figure C27b). The position of the alkoxy (isobutyloxy, isopropyloxy, ethoxy and methoxy) groups near the white contours on the rhs oppose the feature of the hydrophilicity demanded by the contours and cause reduction of activities with respect to the standard molecule. When all the designed NCEs with methyleneoxy linker of this series are displayed in molecular areas within the hydrogen bond donor and acceptor contours (transparent) of the PPARγ CoMSIA model the molecules with larger alkoxy acid group do not exert much significant effect to be disqualified as partial agonists according to the hydrogen bond donor and acceptor requirements (Figures C28c and C29c), they are mainly rejected on the basis of steric requirements for partial agonism. Since the NCE with bulky alkoxy acid moiety (B2) favors the features of the contours (CoMSIA models) they show greater activities and, the NCEs with smaller alkoxy acid moiety (B4, B6, B8 and B10) optimize and sometimes disfavor the features which can be reasoned for their
predicted lesser activities. If the selected NCEs with methyleneoxy linker (B4, B6, B8 and B10 shown in green) are compared with their ethyleneoxy analogs (B3, B5, B7 and B9 shown in red) within the contours of PPARγ CoMSIA model; the hydrophobic heterocyclic moiety of the NCEs with the later linker (B3, B5, B7, B9; shown in red) penetrate the green contour on the left hand side (lhs) due to longer linker while the hydrophobic heterocyclic moiety of the NCEs with the former linker remain away from the said contour (Figure C29a) satisfying the requirements for partial agonism as discussed before (Figures C21a, C21b and C21e). B4, B6, B8 and B10 (shown in green) is also observed within the hydrogen bond donor and acceptor contours fulfilling the requirements to show lesser activities at the target receptors, according to the discussed required features, hence partial agonism better compared to B3, B5, B7, B9 (shown in red), in (figure C29c). As the NCEs with ethyleneoxy linker (B3, B5, B7 and B9) favor the features of the contours they show greater activities compared to the NCEs with methyleneoxy linker (B4, B6, B8 and B10) which optimize and sometimes disfavor the features (which can be reasoned for their predicted lesser activities) and therefore show lesser activities than the former and are preferred as partial agonists for PPARγ. The benzimidazolyl linked molecules with methyleneoxy linker and hydrogen bonding moieties of less bulk (isobutyl, isopropyl, ethyl and methyl containing α-alkoxy acids); the selected α-alkoxy acids lie within the contours (steric, electrostatic and hydrogen bond donor-acceptor) with all the favorable features for PPARγ partial agonism (Figure C30). As B4, B6, B8 and B10 (of benzimidazolyl linked alkoxy acid series) contain the best steric, electrostatic and hydrogen bond donor-acceptor features for showing partial activities at PPARα and PPARγ according to the steric, electrostatic and hydrogen bond donor-acceptor contours of the developed PPARα and PPARγ CoMSIA and CoMFA models discussed earlier it was expected that the NCEs will also satisfy the steric, electrostatic, hydrophobic and hydrogen bond donor-acceptor feature requirements of the PPAR dual models as the dual models include the contribution from the individual PPARα and PPARγ models (discussed earlier). The results were in accordance with the expectations and are reflected in the figures C31-C33 similarly as discussed in case of PPARα and PPARγ models and therefore justify the selection of molecules B4, B6, B8 and B10 of this series for synthesis.
Indolyl linked α-alkoxy propanoic acid based designed NCEs (I1-I10) were arranged according to decreasing order of their predicted PPAR activities (Tables C13a-c) and then ranked. They were also arranged in decreasing order of their surflex dock scores for the two proteins (PPARα and PPARγ) (Tables C13d-e) and then ranked. When the sum criterion for selection of molecules were considered it was found that only I4 (with methyleneoxy linker and isobutyloxy acid moiety), I6 (with methyleneoxy linker and isopropyloxy acid moiety), I10 (with methyleneoxy linker and methoxy acid moiety) (highlighted in green, Table C17) and also I9 (with ethyleneoxy linker and methoxy acid moiety) were selected by the criterion. The molecules I9 though came under selection but was not selected for synthesis as the NCEs with ethyleneoxy linker were found to show generally greater activities and binding than their methyleneoxy analogs. The NCEs selected as the best partial agonists of this series which can be taken forward for synthesis were according to the expectation as discussed above. This can be well explained by critical observation of the adjustment of the NCEs with the steric, electronic, hydrophobic and hydrogen bond donor and acceptor requirements of the resulted contours from the generated CoMSIA models (Figures C34-42). When all the designed NCEs with methyleneoxy linker of this series (I2, I4, I6, I8 and I10) are displayed in molecular areas within the steric and electrostatic contours (transparent) of the PPARα CoMSIA model it can be observed that the NCEs with p-isopropyl benzyloxy group (I2, shown in violet) as a part of the α-alkoxy acid moiety extend beyond the green steric contour on the right hand side (rhs) (Figure C34a) but the NCEs with isopropyl (I6, shown in red), ethyl or methyl group remain within and away from the said contour and satisfy the steric requirements for partial agonistic character of the molecules as discussed earlier. The selected NCEs fit well into the hydrophobic contours too (Figure C34b, C35b and C35c) in such a manner that favors partial activity. The hydrophobic heterocyclic moieties of the designed molecules are observed away from the purple contours (hydrophobicity favored) on the lhs thereby diminishing the activity as compared to the template (Figure C34b). The postion of the alkoxy (isobutyloxy, isopropyloxy, ethoxy and methoxy) groups near the white contours on the rhs oppose the feature of the hydrophilicity demanded by the contours and cause reduction of activities with respect to the standard molecule. When all the designed NCEs with methyleneoxy linker of this series are displayed in molecular areas within the hydrogen bond donor and acceptor contours (transparent) of the PPARα CoMSIA model the
molecules with larger alkoxy group do not exert much significant effect to be disqualified as partial agonists according to the hydrogen bond donor and acceptor requirements (Figure C34a), they are mainly rejected on the basis of steric requirements for partial agonism. However, the molecules due to the presence of indole heterocycle satisfy the requirements of hydrogen bond acceptor feature for partial activity as discussed earlier. Since the NCEs with the large alkoxy moiety (I2) favors the features of the contours (CoMSIA and CoMFA) therefore, show greater activities and, the NCEs with smaller alkoxy moiety (I4, I6, I8 and I10) optimize and sometimes disfavor the features which can be reasoned for their predicted lesser activities. If the selected NCEs with methyleneoxy linker (I4, I6, I8 and I10 shown in green) are compared with their ethyleneoxy analogs (I3, I5, I7 and I9 shown in red) within the contours of PPARα CoMSIA model; the hydrophobic heterocyclic moiety of the NCEs with the later linker (I3, I5, I7, I9: shown in red) penetrate the green contour on the left hand side (lhs) due to longer linker while the heterocyclic moiety of the NCEs with the former linker remain away from the said contour (Figure C35a) satisfying the requirements for partial agonism as discussed before. I4, I6, I8 and I10 (shown in green) can also be noticed within the hydrogen bond donor and acceptor contours fulfilling the requirements to show lesser activities at the target receptors, according to the discussed required features, hence partial agonism better compared to I3, I5, I7, I9 (shown in red) in figure C35c. As the NCEs with ethyleneoxy linker (I3, I5, I7 and I9) favors the features of the contours they show greater activities compared to the NCEs with methyleneoxy linker (I4, I6, I8 and I10) which optimize and sometimes disfavor the features (which can be reasoned for their predicted lesser activities) and therefore show lesser activities than the former and are preferred as partial agonists of PPARα. The indolyl linked molecules with methyleneoxy linker and hydrogen bonding moieties of less bulk (isobutyloxy, isopropyloxy, ethoxy and methoxy containing β-ketoester), the selected α-alkoxy acids lie within the contours (steric-electrostatic and hydrogen bond donor-acceptor) with all the favorable features for PPARα partial agonism (Figure C36). When all the designed NCEs with methyleneoxy linker of this series (I2, I4, I6, I8 and I10) are displayed in molecular areas within the steric and electrostatic contours (transparent) of the PPARγ model it can be observed that the NCEs with p-isopropyl benzyluxy group (I2, shown in violet), as a part of the α-alkoxy propanoic acid moiety, extend beyond the green steric contour on the right hand side (rhs) (Figure 37a)
but the NCEs with alkoxy group of lesser bulk (I4, shown in blue; I6, shown in red), ethyl (I8, shown in yellow) or methyl group (I10, shown in green) remain within the said contour and satisfy the steric requirements for partial agonistic character of the molecules as discussed earlier and indicated in figures C38 and C39. The selected NCEs fit well into the hydrophobic contours too (Figure C25b, C26b and C27b) in such a manner that favors partial activity. The hydrophobic heterocyclic moieties of the designed molecules are observed away from the purple contours (hydrophobicity favored) on the lhs thereby diminishing the activity as compared to the template (Figure C38b and C39b). When all the designed NCEs with methyleneoxy linker of this series are displayed in molecular areas within the hydrogen bond donor and acceptor contours (solid and transparent) of the PPARγ CoMSIA model the molecule with larger alkoxy acid group does not exert much significant effect to be disqualified as partial agonists according to the hydrogen bond donor and acceptor requirements (Figures C37c), it is mainly rejected on the basis of steric requirements for partial agonism. Since the NCE with bulky alkoxy acid moiety (I2) favors the features of the contours (CoMSIA) show greater activities and, the NCEs with smaller alkoxy acid moiety (I6, I8, I10 and I12) optimize and sometimes disfavor the features which can be reasoned for their predicted lesser activities. When the selected NCEs with methyleneoxy linker (I6, I8, I10 and I12 shown in green) are compared with their ethyleneoxy analogs (I5, I7, I9 and I11 shown in red) within the contours of PPARγ model; the hydrophobic heterocyclic moiety of the NCEs with the later linker (I5, I7, I9, I11: shown in red) penetrate the green contour on the left hand side (lhs) due to longer linker while the hydrophobic heterocyclic moiety of the NCEs with the former linker remain away from the said contour (Figure C38a) satisfying the requirements for partial agonism as discussed before. I4, I6, I8 and I10 (shown in green) can also be seen within the hydrogen bond donor and acceptor contours fulfilling the requirements to show lesser activities at the target receptors, according to the discussed required features, hence partial agonism better compared to I3, I5, I7, I9 (shown in red) in figure C38c. As the NCEs with ethyleneoxy linker (I5, I7, I9 and I11) favors the features of the contours they show greater activities compared to the NCEs with methyleneoxy linker (I6, I8, I10 and I12) which optimize and sometimes disfavor the features (which can be reasoned for their predicted lesser activities) and therefore show lesser activities than the former and are preferred as partial agonists for PPARγ. The indolyl linked molecules with
methyleneoxy linker and hydrogen bonding moieties of less bulk (isobutyloxy/isopropyloxy/ethoxy/methoxy acids); the selected α-alkoxy acids lie within the contours (steric, electrostatic, hydrophobic and hydrogen bond donor-acceptor) with the favorable features for PPARγ partial agonism (Figure C39). As I4, I6, I10 (of indolyl linked α-alkoxy carboxylic acid series) contain the best steric, electrostatic, hydrophobic and hydrogen bond donor-acceptor features for showing partial activities at PPARα and PPARγ according to the steric, electrostatic, hydrophobic and hydrogen bond donor-acceptor contours of the developed PPARα and PPARγ CoMSIA models discussed earlier it was expected that the NCEs will also satisfy the steric, electrostatic and hydrogen bond donor-acceptor feature requirements of the PPAR dual models as the dual models include the contribution from the individual PPARα and PPARγ models (discussed earlier). The results were in accordance with the expectations and are reflected in the figures C40-C42 similarly as discussed in case of PPARα and PPARγ models.

The designed acridonyl linked alkoxy carboxylic acid based NCEs (A1-A10, Table C14) when arranged in order of their three types of activities (Tables C14a-c), surflex dock scores (Tables C14a-c) for docking at the crystal structures of the two proteins and compared by the criterion in a similar way as discussed previously for the designed benzimidazolyl/indolyl linked α-alkoxy propanoic acid based NCEs; A3 (containing propyloxy linker and isobutyloxy group) was selected by the selection criterion as the best partial PPARα/γ dual agonists (highest sum in this series) (Table C18). Moreover, A5 (containing propyloxy linker and isopropyloxy group) was found to have highest binding affinity for PPARγ (Table C14e) and lowest for PPARα (Table C14d) and therefore, selected as a selective PPARγ partial agonist. A3 and A5 from the series of acridonyl linked NCEs were put forward for synthesis. Interestingly, in case of acridonyl linked molecules an NCE with a longer linker (A3) came into selection, over the NCEs with shorter linker, as best partial molecule. This may be attributed to the flexibility of a longer linker (propyloxy) which may have rendered the heterocyclic moieties of the molecules in such a geometric orientation so that they optimize/disfavor the features for enhancement of activities as required by the contours, therefore show lesser activities. The selection of a NCE containing an alkoxy group of moderate bulk (A3 containing isobutyloxy) over a NCE containing a
bulky alkoxy group (A1, A2), as best partial agonist was expected as discussed in case of the previous two series of molecules. A3 satisfy the required steric, electrostatic, hydrophobic and hydrogen bond donor-acceptor features (for the three models) for partial agonism better than A1/A2 (and also the other NCEs of this series), hence the best partial agonist (Figures C43, C46 and C49). The propyloxy linker helps the heterocyclic moiety of the NCEs to keep away from the green contour (steric) on the lhs of the three models whereas the heterocyclic moiety of the NCEs having ethyleneoxy linker (due to less flexibility of the spacer) enters into the green region favoring the feature of greater bulk in the region and resulting in higher predicted activities of the later class of NCEs (Figures C44b, C47b and C50b). When the NCEs containing alkoxy acid moieties of lesser bulk (isobutyloxy/ isopropyloxy/ ethoxy/ methoxy propanoic acid) and having ethyleneoxy spacer are compared to their propyloxy analogs within the steric contours of the three models the former is found to favor the features of the contours and the later optimize/disfavor the steric feature and therefore, exhibit lesser activities i.e., better partial agonism (Figures C44a, C47a and C50a). The NCEs containing alkoxy acid moieties of lesser bulk (isobutyloxy/ isopropyloxy/ ethoxy/ methoxy propanoic acid) and having propyloxy spacer fit into the contours of the three models favoring the features for partial agonism (Figures C45, C49 and C51).

The activities and docking scores of the benzimidazolyl/indolyl linked bezylidene/benzyl thiazolidenedione based NCEs (Table C19) were found lesser in most of the cases compared to the standard molecules (Table C15) approving the NCEs of this class as partial PPARα/γ ligands.

The activities and docking scores of the benzimidazolyl/indolyl linked bezylidene/benzyl diethyl malonate based NCEs (Table C20) were found lesser in most of the cases compared to the standard molecules (Table C15) approving the NCEs of this class as partial PPARα/γ ligands.

To justify the selection procedure of the benzimidazolyl, indolyl and acridonyl linked NCEs, as partial PPARα and PPARγ activators, from each series and to verify and validate the appropriateness of the selected molecules the hydrogen bonding interactions and other
details of scores resulted from the docking studies at PPARα and PPARγ separately were explored for the selected NCEs and compared with that of the selected standard molecules.

The results of the docking experiment of the selected standard molecules at the active site of PPARα show that GW409544, among the selected standard molecules shows maximum number of hydrogen bonds (four) interacting with the active site of PPARα (1k7l) followed by fradlitazar (Table C21). From the docking experiment of the selected benzimidazolyl/ indolyl/acridonyl linked alkoxy acid based NCEs it was found that B4, B6, B8, B10 and I4, I6, I8, I10 interact with the active site by partial binding as evident from the lesser values of the other scores resulted from docking studies (G score, D score, PMF score and CHEM score) compared to the standard molecules in most of the cases (Table C22-23). The NCEs also form lesser number of hydrogen bonds compared to the standard molecules indicating lesser binding to the active site compared to the standard molecules. B6, B8, B10, I4, I6 interact with the PPARα active site with one H-bond each, whereas B4 forms three and I10 two H-bonds and I8 show no H-bonding interaction (Figure C52a-d, C54a-c, C55a-c and Table 22). A5 and A7 interact with the active site of 1k7l with two H-bonds each whereas A9 with one and A3 shows no hydrogen bonding interaction at the site (Figure C56a-c and Table 23). All the selected benzimidazolyl/ indolyl/acridonyl linked alkoxy acid based NCEs were found well housed inside the generated docking cavity which is desirable to avoid unwanted interactions with the active site (Figure C54b, C55b and C56b). The H-bond distances of the NCEs were found to be in a similar range as that found in case of the standard molecules (Tables C22 and C23). Generally, the carbonyl oxygen or the hydroxyl oxygen of the acid group of the NCEs, are found to be involved interacting with the amino acid (AA) residues of the active site of PPARα (MET220/ THR279/ SER280/THR283/ GLU286/ ALA333/Tyr334/Tyr464). The oxygen atom of the linker also found to be interacting with THR279 in case of B8. Some of the AA residues were found common to that of the standard molecules and also three interactions which are not present in case of the standard molecules were also recorded (as with AA residues THR279, THR283 and GLU286 for B8, B4, B6 respectively). The results indicated partial binding of the said NCEs with the active site of PPARα.
The benzimidazolyl/indolyl linked benzyldiene and benzyl thiazolidenedione based NCEs exhibit no H-bonding interactions at the PPARα active site (Table C24) which is expected. The lesser score values compared to the standard molecules also indicate much less affinities of these ligands to the active site (Tables C24 and C21). Lesser score values for docking and lesser number of H-bonds are found in case of the benzimidazolyl/indolyl linked benzyldiene and benzyl diethylmalonate based NCEs compared to the selected standard molecules also, indicating partial binding which would lead to partial activation of the receptor by this class of NCEs (Tables C24 and C21).

The results of the docking experiment of the selected standard molecules at the active site of PPARγ show that farglitazar and GW409544 interact forming four H-bonds each and NND9, DRF2725 and LY510929 interact forming three H-bonds each with the active site of PPARγ (1fm9) involving the acidic part of their skeleton (Table C25). From the results of the docking studies of the designed NCEs at PPARγ, it was found that among the selected benzimidazolyl/indolyl linked alkoxy acid based NCEs that I4 forms four H-bonds involving two AA residues; B8, B10, I10 form three H-bonds each with three AA residues of the active site; I8 forms two hydrogen bonds; B4 and B6 interacts with one AA residue each and B6 show no hydrogen bonding interaction with the active site. So, though the number of H-bonds formed is similar to some of the standard molecules lesser binding to the active site is expected which is supported by the lesser G score values of these compared to some of the standard molecules (Tables C26 and C25). The H-bond distances of the NCEs were found to be in a similar range as that found in case of the standard molecules (Tables C26 and C25, Figures C57a-C58c). A5, A7 and A9 form three H-bonds each involving three AA residues whereas A3 interact with the active site with only one H-bond (Table C27 and Figures C59a-C59c). All the selected benzimidazolyl/indolyl/acridonyl linked α-alkoxy propanoic acid based NCEs were found well housed inside the generated docking cavity which is desirable to avoid unwanted interactions with the active site (Figures C57b, C58b and C59b). The best predicted partial agonist of the acridone series, NCE A3 (highest sum criterion) interact with the active site of PPARγ involving the sp³ oxygen atom of the acid group forming one H-bond (AA residue: SER 289) (Figure C59c). The interacting AA residues of the active site were found common to that in case of the standard molecules (Tables C25, C26 and C27).
The lesser number of H-bonds and lesser score values of the NCEs (Tables C26 and C27) indicate partial agonism to the receptor which further supports the selection procedure of the NCEs for synthesis.

The benzimidazolyl/indolyl linked benzylidene and benzyl thiazolidenedione based NCEs exhibit H-bonding interactions with the AA residues found in common to that in case of the standard molecules for docking at the PPARγ active site (Table C28). The benzimidazolyl/indolyl linked benzyl thiazolidenediones (1BT and 1IT respectively) interact with five H-bonds each involving four AA residues of the active site, whereas the benzylidene analogs of the said molecules (1BTd and 1ITd respectively) interact with three H-bonds each involving two AA residues. The lesser score values compared to the standard molecules indicate lesser affinities of these ligands to the active site (Tables C28 and C25). Lesser score values for docking are found in case of the benzimidazolyl/indolyl linked benzylidene and benzyl diethylmalonate based NCEs compared to the selected standard molecules also, indicating partial binding which would lead to partial activation of the receptor by this class of NCEs (Tables C29 and C24). The benzimidazolyl/indolyl linked benzylidene and benzyl diethylmalonate based NCEs exhibit H-bonding interactions with the AA residues almost common to that found in case of the standard molecules for docking at the PPARγ active site (Table C29). The benzimidazolyl/indolyl linked benzyl/benzylidene diethylmalonates (7B, 7I and 7Bd, 7Id respectively) interact with four H-bonds each involving three AA residues of the active site, except in case of 7Bd which interacts with two AA residues. The diester moiety (hydrogen bonding part) of the NCEs is involved in hydrogen bond formation involving the carbonyl oxygen or the ethoxy oxygen (Table C29).
4.2 Synthesis

The synthetic strategy designed for the synthesis of Heterocyclyl Linked α-Alkoxy Carboxylic Acids based targeted NCEs (F1a-d, F2c-d and F3c-d) involved the preparation of the Heterocyclyl Linked Methoxy Vinyl derivatives (L7, L9 and L11) from the corresponding Heterocyclyl Linked Benzaldehydes (L1, L2 and L3). These methoxy vinyl derivatives were then converted to corresponding Dialkoxy: Acetal derivatives (L7a-d, L9c-d and L11c-d) by simply refluxing with the Alcohol concerned in the presence of catalytic amount of p-toluenesulphonic acid. The acetals upon treatment with trimethylsilylcyanide in the presence of boron trifluoride gave the required Heterocyclyl Linked α-Alkoxy Propionitriles (L8a-d, L10c-d and L12c-d) and which upon subsequent alkaline hydrolysis while using sodium hydroxide gave the Desired and Targeted NCEs (F1a-d, F2c-d and F3c-d) - Synthetic Scheme: 6 and 6a-c.

The Heterocyclyl Linked Benzaldehydes (L1 and L2) required in this synthetic sequence in turn were prepared by treating N-methyl-2-hydroxymethyl benzimidazole or N-methyl-2-hydroxymethyl indole respectively with 4-fluorobenzaldehyde while the acridone linked benzaldehyde (L3) was prepared by the Microwave irradiation of acridone and 4-bromopropoxy benzaldehyde - Synthetic Scheme: 1-3.

The Heterocyclyl Linked Benzaldehydes (L1 and L2) were subjected to undergo coupling with the thiazolidine-2,4-dione and diethyl malonate respectively in the presence of piperidinium acetate for the synthesis of Heterocyclyl Linked Benzylidene based other NCEs (F4a, F5a and F6a, F7a) as our own internal standard molecules - Synthetic Scheme: 7a and 7c.

The catalytic reduction of the Heterocyclyl Linked Benzylidene Diethyl Malonate based ONCEs (F6a and F7a) gave the corresponding Heterocyclyl Linked Benzyl Diethyl Malonate based ONCEs (F6b and F7b) - Synthetic Scheme: 7a and 7c.
The desired benzimidazolyl linked benzyl based thiazolidine-2,4-dione (F4b) were synthesized through the acidic hydrolysis of the corresponding 2-Iminothiazolidine-4-one (L13a) - Synthetic Scheme: 7b. The indolyl linked benzyl based thiazolidine-2,4-dione (F5b) on the other hand was synthesized via Mitsunobu coupling of the 4-hydroxybenzylthiazolidine-2,4-dione (R1) and N-methyl-2-hydroxy methyl indole (L2b) - Synthetic Scheme: 7d. The 4-substituted 2-iminothiazolidine-4-one (L13a and R1b) required in turn were prepared by reacting the corresponding α-bromo esters (L13 and R1a) with thiourea in the presence of sodium acetate - Synthetic Scheme: 7b and 7d. The α-bromo esters thus required in turn were prepared from the correspondingly 4-substituted aniline (L4 and p-anisidine) respectively - Synthetic Scheme: 7b and 7d.

The N-methyl benzimidazolyl linked aniline (L4) required in this case and other heterocyclyl linked anilines (L5 and L6) were prepared through the catalytic reduction of corresponding Nitro derivatives (L4a, L5a and L6a) respectively. The nitro derivatives required in turn were prepared as per procedure used for the preparation of corresponding Heterocyclyl Linked Benzaldehydes while using 4-chloronitrobenzene in case of (L4a and L5a) and using 4-bromopropoxy nitrobenzene in case of (L6a) - Synthetic Scheme: 4 and 5. The N-methyl-2-hydroxy methyl benzimidazole and N-methyl-2-chloromethyl benzimidazole and N-methyl-2-hydroxy methyl indole required in these synthetic sequences were prepared as per Synthetic Schemes: 1 and 2.
Left Hand Side (LHS) Moieties and Related Intermediates (L1a – L3)
The L1: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzaldehyde and L2: 4-[(1-methyl-1H-indol-2-yl)methoxy]benzaldehyde required were prepared\(^5\) by the drop wise addition of a solution of 4-fluorobenzaldehyde (1.3mmol) in 5 ml of dry DMF to a stirred suspension of sodium hydride (1.4mmol, 60% w/w dispersion) in 20 ml dry DMF containing 1.2mmol L1a: (1-Methyl-1H-benzoimidazol-2-yl)-methanol and L2b: (1-Methyl-1H-indol-2-yl)-methanol respectively at 0°C followed by 24 hour stirring at room temperature and subsequent workup involving quenching in water and ethyl acetate extraction and column chromatography of the residue thus obtained using methanol and dichloromethane (1:10) as eluent (TABLE S1 and Scheme 1-2).

Alternatively L1: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzaldehyde was also prepared following similar procedure\(^5\) while adding a solution of L1b: 2-Chloromethyl-1methyl-1H-benzoimidazole in DMF to a stirred suspension of sodium hydride in dry DMF containing 4-hydroxybenzaldehyde at 4-8°C followed by 24 hour stirring at room temperature and addition of crushed ice to the contents (TABLE S1 and Scheme 1).

The presence of two weak bands representing the coupled doublet characteristic of aldehydic C-H stretch at 2820 and 2732 cm\(^{-1}\) and at 2822 and 2732 cm\(^{-1}\) along with aldehydic C=O stretch at 1697 cm\(^{-1}\) in both these molecules and also the presence of antisymmetric and symmetric C-O stretch establishing the formation of the ether linkage at 1247 and 1005 cm\(^{-1}\) and 1244 and 995 cm\(^{-1}\) respectively in the IR spectrum of both the molecules confirm the structure assigned. Additional presence of bands corresponding the out of plane C-H bending for the two and four adjacent aromatic hydrogens at 827 and 749 cm\(^{-1}\) and at 789 and 753 cm\(^{-1}\) respectively further support their structure. Further support to the structure assigned is indicated by the presence of IH singlet at 9.88 and 9.90 ppm for the aldehydic proton and additional presence of 2H singlet for the –CH\(_2\)-O- at 5.52 and 5.29 ppm along with a 3H singlet representing the –N-CH\(_3\) present in both these molecules at 3.91 ppm and 3.82 ppm respectively in their PMR spectrum. The aromatic protons in case of L1 appeared as two 3H multiplets at 7.84 and 7.38 and one 2H doublet at 7.24 ppm respectively. The aromatic protons in case of L2 appeared as a set of two 2H doublets at 7.86 and 7.13 ppm showing a
coupling constant $J = 8.76 \text{ Hz}$ for the p-disubstituted benzene moiety, the characteristic indolyl proton at position 3 appeared as a 1H singlet at 6.63 ppm along with other aromatic protons in the region 7.62 – 7.26 ppm in the PMR spectrum. The structure assigned to both these molecules was further confirmed from the presence of $[M+1]^+$ peak at m/z 267 (8) and at m/z 266 (100) in the Mass spectrum of L1 and L2 respectively along with base peak at 146 (100) in the Mass spectrum of L1 (PLATES: IR 1 and IR 3; PMR 2 and PMR 5; MS 1 - CHART1 and MS 2).

The L1a: (1-Methyl-1H-benzoimidazol-2-yl)-methanol and L1b: 2-Chloromethyl-1methyl-1H-benzoimidazole thus required for the synthesis of L1 were prepared$^{557}$ refluxing a mixture solution of N-methyl-1, 2-phenylenediamine dihydrochloride containing glycolic acid and chloroacetic acid respectively in water for about 90 minutes followed by basification with dilute ammonia solution under ice cold conditions and subsequent filtration and recrystallization (TABLE S1 and Scheme 1-2).

The structure assigned to both these molecules was confirmed from the presence of a broad band for the bonded O-H stretch at 2800 – 3640 cm$^{-1}$ along with free O-H stretch at 3660 cm$^{-1}$ of the alcohol present in L1a and the presence of C-Cl stretch at 751 cm$^{-1}$ in case of L1b in their IR spectrum. The presence of a 2H singlet at 4.89 ppm and 5.07 ppm for the methylene of the CH$_2$-OH and CH$_2$-Cl along with a 3H singlet for the N-CH$_3$ present in both these molecules at 3.91 and 3.44 ppm respectively in their PMR spectrum also support the structure assigned (PLATE: PMR 1).

Whereas L2b: (1-Methyl-1H-indol-2-yl)-methanol required for the synthesis of L2 was prepared$^{556}$ through lithium aluminium hydride reduction of L2a: 1-Methyl-1H-indole-2-carboxylic acid ethyl ester using dry THF as solvent (TABLE S1 and Scheme 2), while L2a in turn was prepared by N-methylation of commercially available Ethyl indoleacetate using iodomethane in the presence of sodium hydride taken in dry DMF as solvent followed by extraction and subsequent column chromatography (TABLE S1 and Scheme 2).
The presence of the ester C=O stretch at 1703 cm\(^{-1}\) in the IR spectrum of \(\text{L2a}\) and the presence of a 3H singlet for the N-CH\(_3\) protons at 4.08 ppm along with a 2H quartet and 3H triplet for the -CH\(_2\)CH\(_3\) group of the ester at 4.37 and 1.41 ppm in the PMR spectrum of this molecules which additionally shows the indole proton at position 3 as a 1H singlet merged in the 2H multiplet in the aromatic region at 7.35 ppm.

The lack of ester carbonyl stretch of \(\text{L2a}\) in the IR spectrum of \(\text{L2b}\) and appearance of a broad band at 3200 – 3550 cm\(^{-1}\) for the alcohol formed not only confirmed the structure assigned but also indicate the completion of reduction leading to its formation. Furhter confirmation of the structure assigned comes from the disappearance of the 2H quartet and 3H triplet representing the ethyl ester and simultaneous appearance of a 2H singlet at 4.81 ppm in the PMR spectrum representing the methylene of –CH\(_2\)-OH thus formed in this molecule. The 3H singlet of the N-CH\(_3\) is present at 3.81 ppm as expected. The upfield shift of the 1H at position 3 of the indole to 6.45 ppm in this molecule is because of loss of the deshielding effect of the ester carbonyl of \(\text{L2a}\) is a further confirmation of the completion of the reduction of the ester of the \(\text{L2a}\) to the –CH\(_2\)OH of \(\text{L2b}\) (PLATES: PMR 4 - 4a).

The preparation of \(\text{L3: 4-[3-(9-oxoacridin-10(9H)-yl)propoxy]benzaldehyde}\) required on the other hand was carried out using microwave irradiation\(^{558}\) of a mixture solution of acridone (0.5mmol) \(\text{L3a: 4-(3-Bromo-propoxy)-benzaldehyde}\) (0.6mmol) and KOH (3.6mmol) in DMF in a microwave oven for 5min at 320W followed by workup involving neutralization extraction and column chromatographic purification (TABLE S1 and Scheme 3).

The structure assigned to this molecule was also confirmed from the presence of two aldehydic C-H stretch as coupled doublet at 2840 and 2724 cm\(^{-1}\) along with two C=O stretching frequencies at 1684 and 1631 cm\(^{-1}\) for the aldehydic and acridione based carbonyl groups respectively in its IR spectrum. Similar informations for the structure assigned were gathered from the presence of a 1H singlet at 9.85 ppm for the aldehydic proton along with two 2H triplets at 4.61 and 4.15 ppm and one 2H quintet at 2.40 ppm respectively characteristic of the propoxy (-N–CH\(_2\)-CH\(_2\)-CH\(_2\)-O-) linkage in the PMR spectrum of this molecule. Additional presence of two 2H doublets at 7.81 and 6.98 ppm with a coupling
constant $J = 8.76$ Hz characteristic of the p-disubstituted benzene ring along with other aromatic protons of the acridone ring present in this molecule as a set of four $2H$ multiplets at $8.54$-$8.52$, $7.64$-$7.62$, $7.60$-$7.53$ and $7.25$-$7.21$ ppm respectively further support the structure assigned. The presence of $[M+1]^+$ peak at $m/z$ $358$ (100) additionally support the structure assigned to this molecule (PLATES: IR 5; PMR 7 - 7a; MS 3).

L3a thus required for this preparation556 in turn was prepared by refluxing a mixture solution of 4-hydroxybenzaldehyde (30mmol), 1,3-dibromopropane (37.5mmol) and anhydrous K$_2$CO$_3$ (40mmol) in 45ml of dry acetone, for 8 hours and subsequent workup of the contents (TABLE S1 and Scheme 3).

The presence of a doublet for the coupled C-H stretch of the aldehydic group at $2828$ and $2740$ cm$^{-1}$ and the aldehydic C=O stretch at $1691$ cm$^{-1}$ along with C-O-C antisymmetric and symmetric stretch of the ether formed at $1252$ and $1025$ cm$^{-1}$ respectively and also the C-Br stretch appearing at $764$ cm$^{-1}$ as expected in the IR spectrum of this molecule confirm the structure assigned. Also the presence of aldehydic proton as $1H$ singlet at $9.89$ ppm along with two $2H$ triplets at $4.20$ and $3.61$ ppm and one $2H$ quintet at $2.36$ ppm for the three methylenes of the bromopropoxy group present in the PMR spectrum of this molecule further confirmed the structure assigned. The mass spectrum of this molecule also shows the presence of $[M]^+$ and $[M+2]^+$ peaks as an isotopic clusture in the ratio $1:1$ at $m/z$ $242$ (9) and $244$ (11) as expected of a mono bromo derivative thereby confirming the formation of the ether linkage (PLATES: IR 4; PMR 6).

Left Hand Side (LHS) Moieties (ONCEs) and Related Intermediates (L4a-L6)

The L4a: 1-Methyl-2-(4-nitro-phenoxy)methyl-1H-benzoimidazole and L5a: 1-Methyl-2-(4-nitro-phenoxy)methyl1H-indole required for the synthesis of desired anilines were prepared556 by the drop wise addition of a solution of 4-chloronitrobenzene (31.25mmol) in 5 ml dry DMF to a stirred suspension of sodium hydride (30mmol, 60% w/w dispersion) in dry DMF containing L1a: (1-Methyl-1H-benzoimidazol-2-yl)-methanol and L2b: (1-Methyl-1H-indol-2-yl)-methanol respectively at $0^\circ$C followed by 24 hour stirring, addition of crushed ice, filtration and recrystallization (TABLE S2 and Scheme 4).
The appearance of the antisymmetric and symmetric N=O stretch of the Nitro group at 1591 and 1324 cm$^{-1}$ and 1591 and 1342 cm$^{-1}$ respectively in the IR spectrum of both these molecules with the simultaneous disappearance of the broad band for the bonded O-H stretch present in L1a and L2b respectively at 2800 – 3640 cm$^{-1}$ and 3200 – 3550 cm$^{-1}$ and additional presence of C-O-C stretch at 1250 cm$^{-1}$ in both cases establishes the formation of the ether linkage and confirmed the structure assigned. Similar informations supporting the structure assigned were obtained from the presence of a 2H singlet and 3H singlet for the -CH$_2$O- linker and N-CH$_3$ group present in these molecules at 5.59 and 3.85 ppm in case of L4a and at 5.31 and 3.80 ppm for L5a. Presence of signals for the p-disubstituted benzene and the heterocycle present in the aromatic region at positions and multiplicities expected were in accordance to the structure assigned. The presence of [M]$^+$ peak at m/z 283 (15) along with a characteristic fragment ion at 145 (100) in the Mass spectrum in case of L4a provide support to the structure assigned to both these molecules (PLATES: IR 6 and IR 7; PMR 8).

Whereas L6b: 10-[3-(4-Nitro-phenoxy)-propy]-10H-acridin-9-one on the other hand was prepared by microwave irradiation$^{558}$ of a mixture solution of acridone and L6a: 1-(3-Bromo-propoxy)-4-nitro-benzene in the presence of KOH taken in DMF under the conditions defined for the preparation of corresponding benzaldehyde L3 (TABLE S2 and Scheme 5).

This molecule like L4a and L5a also shows antisymmetric and symmetric N=O stretch at 1601 and 1330 cm$^{-1}$ in the IR spectrum along with acridone carbonyl stretch at 1634 cm$^{-1}$ confirming the structure assigned. Additional informations for the presence of propoxy (–CH$_2$-CH$_2$-CH$_2$-O-)linker were obtained from the presence of two 2H triplets at 4.68 and 4.23 ppm and one 2H quintet at 2.47 ppm in the PMR spectrum of this molecule (PLATE: IR 9).

The L6a thus required in turn was prepared$^{562}$ following the procedure used for the preparation of corresponding benzaldehyde L3a while using 4-nitrophenol, 1,3-dibromopropane and anhydrous K$_2$CO$_3$ taken in acetone (TABLE S2 and Scheme 5).
Similar information confirming the presence of Nitro group in the IR spectrum and that of propoxy group from the PMR spectrum along with the presence of [M]⁺ and [M+2]⁺ peaks in the mass spectrum of this molecule at m/z 259 (63) and 261(63) in the ratio expected for a mono bromo derivative support the structure assigned (PLATES: IR 8; PMR 9).

All the three heterocyclyl linked nitro compounds L4a, L5a and L6b thus prepared were subjected to catalytic hydrogenation in a Parr bottle with 10% Palladium on charcoal taken in methanol at 20 psi for 2 hours followed by workup involving filtration of the catalyst through diatomaceous earth, vacuum evaporation of the filtrate and tituration of the residue with hexane to obtained the desired anilines L4: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-phenylamine, L5: 4-(1-Methyl-1H-indol-2-ylmethoxy)-phenylamine and L6: 10-[3-(4-Amino-phenoxy)-propy]-10H-acridin-9-one respectively (TABLE S2 and Scheme 4-5).

The successful reduction of the nitro compounds obtained above to corresponding heterocyclyl linked anilines were confirmed from the disappearance of the antisymmetric and symmetric N=O stretch of the nitro group at around 1601-1591 and 1342-1330 cm⁻¹ seen in the IR spectrum of L4a, L5a and L6b and the -NH₂ group thus obtained appeared as antisymmetric and symmetric N-H stretch at 3446 and 3313 cm⁻¹ in case of L4 and as a broad band for the bonded N-H stretch at 3500-3200 cm⁻¹ and 3500-3335 cm⁻¹ in case of L5 and L6 respectively. Presence of 2H and 3H singlets for the -CH₂-O- and N-CH₃ at 5.30 and 3.88 ppm and at 5.10 and 3.80 ppm respectively in the PMR spectrum of L4 and L5. The signals characteristics of the propoxy linker in case of L6 appeared as two 2H triplets at 4.63 and 4.08 ppm and one 2H quintet at 2.38 ppm as expected. All these informations coupled with the presence of [M+1]⁺ peak in the Mass spectrum of these molecules at m/z 254 (100) and 253 (100) in case of L4 and L5 and at m/z 345 (100) in case of L6 provide additional support to the structure assigned and also to the completion of the reduction (PLATES: IR 10 and IR 11 and IR 12; PMR 10; MS 4).

Synthesis of the Targeted NCEs (F1a-d and F2c-d and F3c-d)

Heterocyclyl Based NCEs and Related Intermediates
The Methoxy Vinyls (L7, L9 and L11)
All the three heterocyclyl linked methoxy vinyl derivatives L7: \(2-\{(4-\text{[2-methoxyethenyl]phenoxy}methyl\}-1\text{-methyl-1H-benzimidazole}, \) L9: \(2-\{4-\text{(2-Methoxy-vinyl)-phenoxy}methyl\}-1\text{-methyl-1H-indole} \) and L11: \(10-\{3-\{4-\text{(2-Methoxy-vinyl)-phenoxy}\}\text{-propyl\}-10H-acridine-9-one} \) required for the synthesis of the targeted NCEs as per general synthetic scheme 6 were prepared\(^{559}\) as a mixture of geometric isomers in the 1:2, 1:1 and 1:2 ratio respectively by the addition a solution of corresponding benzaldehydes L1, L2 and L3 in dry THF to a stirred slurry of (methoxymethyl)triphenylphosphonium chloride and LDA (generated \textit{in situ} form diisopropylamine taken in THF and 2.5M \(n\)-butyllithium in hexane), at -10 °C and the contents allowed to warm to room temperature over a period of 2 hours while stirring and subsequent workup involving quenching in water, ether extraction and column chromatographic purification using hexane/ethyl acetate, 4:1 as eluent (TABLE S3-5 and Scheme 6 and 6a-c).

The appearance of characteristic C=C stretch at 1688 - 1645 cm\(^{-1}\) along with a strong symmetric band for the C-O-C stretch of the vinyl ether formed at 1113 -1094 cm\(^{-1}\) in the IR spectrum of all these molecules (L7, L9 and L11) with the simultaneous disappearance of the doublet for the coupled C-H stretch of the aldehydic group at 2840 – 2820 cm\(^{-1}\) and 2732 - 2724 cm\(^{-1}\) and the aldehydic C=O stretch at 1697 - 1684 cm\(^{-1}\) respectively present in the IR spectrum of L1, L2 and L3 not only establishes the completion of the reaction but also confirmed the structure assigned all these molecules.

Similar informations supporting the structure assigned and indication of the presence of the two geometric isomers in each of these compounds in the ratios mentioned above were obtained from the presence of a two isomeric 3H singlet of the methoxy group at 3.75 – 3.71 and 3.65 - 3.61 ppm for the trans and cis isomer respectively and two 1H doublets each at 6.91 -6.90 ppm \((j = 13.00 - 12.96 \text{ Hz})\) and 5.78 – 5.73 ppm \((j = 13.00 - 12.96 \text{ Hz})\) for the trans isomer and at 6.06 – 5.15 ppm \((j = 7.00 - 6.69 \text{ Hz})\) and 3.81 - ppm \((j = 7.04 -7.00 \text{ Hz})\) for the cis isomer respectively in their PMR spectrum in the ratios 2:1, 1:1 and 1:1 respectively for L7, L9 and L11. The presence of two 2H singlet and two 3H singlet for the -
CH$_2$-O- linker and N-CH$_3$ group present in case of L7 and L9 at 3.80 and 3.79 ppm and at 5.16 and 5.17 ppm for the trans and cis geometric isomer along with the signals for the p-disubstituted benzene and the heterocycle present in the aromatic region at positions and multiplicities and ratios expected for both the isomers were in accordance to the structure assigned. The presence of two 4H (2H each) overlapping triplets at 4.58 and 4.06 ppm and one 4H (2H each) overlapping quintet at 2.47 ppm in case of L11 is as expected for the presence of –CH$_2$-CH$_2$-CH$_2$-O- propoxy linker in this molecule.

The presence of [M+1]$^+$ peak at m/z 295 (100), m/z 294 (11) and m/z 286 (22) in the Mass spectrum of L7, L9 and L11 respectively along with other characteristic fragment ion present provide additional support to the structure assigned to all these molecules (PLATES: IR 13 and IR 14 and IR 15; PMR 11 - 11a and PMR 12 and PMR 13; MS 5 - CHART 2 and MS 6 - CHART 3).

The Dialkoxy Derivatives: The Acetals (L7a-d, L9c-d and L11c-d)
A solution of the requisite methoxy vinyl derivative (72.5mmol) L7, L9 and L11 thus prepared$^{559}$ containing and p-toluenesulfonic acid monohydrate (0.026mmol) in iso-Butyl alcohol (7mL) was refluxed overnight followed by in vacuo removal of the solvent and addition of ethyl acetate and subsequent washing, drying and concentration gave the required diisobutoxy acetal L7d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole, L9d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxyethyl]-1-methyl-1H-indole and L11d: 10-{3-[4-(2,2-Diisobutoxy-ethyl)-phenoxy]-propyl}-10H-acridine-9-one (TABLE S3-5 and Scheme 6 and 6a-c).

The absence of band corresponding to the C=C stretch at 1688 - 1645 cm$^{-1}$ characteristic of the vinyl ether in the IR spectrum of all these molecules (L7d, L9d and L11d) and presence of C-O-C stretch at 1119 - 1114 cm$^{-1}$ not only confirmed the structure assigned but also establishes the formation of the diisobutoxy acetal required to be present in these molecules. The PMR spectrum of all these molecules similarly lacks the signals corresponding to two isomeric 3H singlets for the methoxy group present in case of L7, L9 and L11 at around 3.75 – 3.71 and 3.65 - 3.61 ppm for the trans and cis isomer respectively and the presence on
the other hand of 1H triplet and 2H doublet at 4.53 – 4.47 ppm and 2.89 – 2.77 ppm for the methylenic and methynic protons of the ethyl type unit (\(-\text{O-C}_6\text{H}_4\text{-CH}_2\text{CH}\)) thus generated during this reaction along with the presence various signals in the ratio and multiplicities expected for the presence of the required diisobutoxy acetal as two 2H doublet at 3.37 – 3.07 and 3.16 – 3.07 ppm and a 2H (1H each) multiplet at 1.80 – 0.76 ppm and also two 6H doublets (12H multiplet in case of indole) at 1.25 - 0.76 and 0.89 - 0.76 - ppm respectively for the methylenic, methynic and germinal dimethyl based protons of the -O-C_6H_4-CH_2CH[OCH_2CH(CH_3)_2]_2 present in all these molecules confirmed the structure assigned.

Additional presence of 2H and 3H singlets for the -CH_2-O- and N-CH_3 at 5.35 and 3.86 ppm and at 4.58 and 3.71 ppm respectively in the PMR spectrum of L7d and L9d. The signals characteristics of the propoxy linker in case of L11d appeared as two 2H triplets at 4.63 and 4.15 ppm and one 2H quintet at 2.34 ppm as expected. All these informations coupled with the presence of [M+1]^+ peak in the Mass spectrum of L7d at m/z 411 (100) and presence of [M]^+ -73 [- OCH_2CH(CH_3)_2] peak at m/z 336 (84) and base peak at m/z 145 (100) in the Mass spectrum of L9d, L11d on the other hand shows the [M]^+ peak at m/z 501 (7) along with a base peak appearing at m/z 428 (100) corresponding to [M]^+ -73 [- OCH_2CH(CH_3)_2] like those of L7d and L9d provide additional support to the structure assigned (PLATES: IR 16 and IR 17; PMR 14-14b and PMR 15 and PMR 16-16b; MS 7 -CHART 4 and MS 8 - CHART 5 and MS 9 - CHART 6).

Similar procedure was followed for the preparation of diisopropyl acetal L7c: 2-[4-(2,2-Diisoproxy-ethyl)-phenoxy-methyl]-1-methyl-1H-benzimidazole, L9c: 2-[4-(2,2-Diisoproxy-ethyl)-phenoxy-methyl]-1-methyl-1H-indole and L11c: 10-[3-[4-(2,2-Diisoproxy-ethyl)-phenoxy]-propyl]-10H-acridine-9-one while using 7 ml of iso-propyl alcohol (TABLE S3-5 and Scheme 6 and 6a-c).

The absence of band corresponding to the C=C stretch at 1688 - 1645 cm\(^{-1}\) characteristic of the vinyl ether in the IR spectrum of all these molecules and presence of C-O-C stretch at frequencies expected for the formation of corresponding diisoproxy acetal and presence of
various signals in the ratio and multiplicities expected for the presence of the required diisopropoxy acetal in their PMR spectrum as a 2H (1H each) multiplet at 2.20 – 1.60 ppm and two 6H doublets at 1.12 – 0.92 and 1.05 -0.80 ppm respectively for the methyinic and germinal dimethyl based protons of the -O-C₆H₄-CH₂CH(CH(CH₃)₂)₂ present in all these molecules along with the presence 1H triplet and 2H doublet at 4.35 – 4.08 ppm and 3.45 – 2.82 ppm for the methylenic and methylic protons of the ethyl type unit (-O-C₆H₄-CH₂CH-) thus generated during this reaction in all these molecules confirmed the structure assigned. The presence of [M +1]⁺ peak at m/z 473 (30) along with base peak at m/z 430 (100) in case of L11c further support the structure assigned to all these molecules (PLATES: IR 18 and IR 19; PMR 17; MS 10 -CHART 7).

L7b: 2-[4-(2,2-Diethoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole and L7a: 2-[4-(2,2-Dimethoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole were similarly prepared from L7 while using ethyl alcohol and methyl alcohol respectively (TABLE S3-5 and Scheme 6 and 6a-c).

The presence of various signals in the ratio and multiplicities expected for the presence of the required diethoxy acetal in the PMR spectrum of L7b as two 2H overlapping quartets at 3.64 and 3.43 ppm and one 6H (3H each) triplet at 1.15 ppm respectively for the methylinic and methyl based protons -O-C₆H₄-CH₂CH(OCH₂CH₃)₂, while the two methoxy groups of the dimethoxy acetal of L7a appeared as 6H (3H each) singlet at 3.32 ppm in its PMR spectrum. The presence of 1H triplet and 2H doublet at 4.56 and 2.84 ppm and at 4.47 and 2.83 ppm for the methylenic and methylic protons of the ethyl type unit (-O-C₆H₄-CH₂CH-) thus generated during this reaction in case of L7b and L7a respectively support the structure assigned to both molecules. The presence of [M+1]⁺ peak at m/z 355 (100) and at m/z 327 (100) in case of L7b and L7a respectively confirmed the structure assigned beyond doubt (PLATES: IR 20 and IR 21; PMR 18-18a and PMR 19; MS 11 - CHART 8 and MS 12 - CHART 9).

The Alkoxy Propionitriles (L8a-d, L10c-d and L12c-d)
All the dialkoxy acetals thus prepared were converted to corresponding 2-alkoxy propionitriles. L8a-d: 2-methoxy/2-ethoxy/2-Isopropoxy/2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionitrile, L10c-d: 2-Isoproxy/2-Isobutoxy-3-[4-(1-methyl-1H-indol-2-ylmethoxy)-phenyl]-propionitrile and L12c-d: 2-Isoproxy/2-Isobutoxy-3-[4-(3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl]-propionitrile by adding trimethylsilyl cyanide (0.9mmol) and boron trifluoride etherate (0.075mmol) to a solution of the respective dialkoxy acetals L7a-d, L9c-d and L11c-d (0.3mmol) in 8 ml of dichloromethane and subsequent dilution with dichloromethane after 1 hour and work up involving washing, drying and concentration and column chromatographic purification using hexane/ethyl acetate (9:1) as eluent (TABLE S3-5 and Scheme 6 and 6a-c).

The presence of a band at around 2405 – 2362 cm\(^{-1}\) corresponding to the –CN stretching frequency in the IR spectrum of all these molecules along with the presence of the signals characteristic of the alkoxy group present in these molecules in the ratio corresponding to momoalkoxy derivative as two 1H double doublet at 3.49 – 3.15 ppm and 3.17 – 3.05 ppm and a 1H multiplet at 1.86 - 1.82 ppm and a 6H doublets at 0.87 – 0.84 ppm respectively for the methylenic, methynic and germinal dimethyl based protons of the isobutoxy -CH\(_2\)CH(CN)OC\(\text{H}_2\)CH(CH\(_3\))\(_2\) group present in case of L8d, L10d and L12d and as a 1H multiplet at 2.17 - 1.65 ppm and a 6H doublets at 1.20 - 0.78 ppm respectively for the methylenic and germinal dimethyl based protons of the isoproxy -CH\(_2\)-CH(CN)OCH(CH\(_3\))\(_2\) group present in case of L8c, L10c and L12c and as two 1H quartet at 3.81 and 3.49 ppm and a 3H triplet at 1.23 ppm respectively for the methylinic methyl based protons of the ethoxy -CH\(_2\)CH(CN)OCH\(_2\)CH\(_3\) group present in L8b while the methoxy -CH\(_2\)CH(CN)OCH\(_3\) group in case of L8a appeared as 3H singlet at 3.35 ppm in its PMR spectrum. The presence of 1H triplet and 2H doublet at 4.35 – 4.12 ppm and 3.64 – 3.00 ppm for the methylenic and methynic protons of the ethyl type unit (–O-C\(\text{H}_4\)-CH\(_2\)CH-) present in case of all these compounds similarly not only confirm the structure assigned but also support the complete conversion of the dialkoxy acetals to corresponding alkoxy nitriles as expected (PLATES: IR 22 and IR 23 and IR 24 and IR 25; PMR 20-20a and PMR 21-21a and PMR 22 and PMR 23 and PMR 24-24a).
The presence of [M+1]$^+$ peak at m/z 364 (36) along with a base peak at m/z 145 (100) in case L8d and [M+2]$^+$ peak at m/z 364 (100) in case L10d and [M+1]$^+$ peak at m/z 455 (12) in case L12d in their mass spectra provide additional support to the structure assigned to the isobutoxy based compounds. The presence of [M+23]$^+$ peak at m/z 463 (35) in case of L12d containing isopropoxy group while the mass spectra of L8b and L8a on the other hand shows the [M+1]$^+$ peak at m/z 336 (12) and [M+2]$^+$ peak at m/z 323 (7) respectively confirmed the structure assigned beyond doubt (PLATES: MS 13 - CHART 10 and MS 14 - CHART 11 and MS 15 - CHART 12; CHART 13 and CHART 14).

The α-Alkoxy Carboxylic Acids (F1a-d, F2c-d and F3c-d)
All the heterocyclyl linked alkoxy propionitrile L8a-d, L10c-d and L12c-d thus prepared were subjected to alkaline hydrolysis with 6N Sodium hydroxide containing ethanol followed by dilution and acidification of the contents with conc. hydrochloric acid subsequent workup involving ethyl acetate extraction, and purification using recrystallization or column chromatography of the residue concerned to obtain the desired heterocyclyl linked α-alkoxy carboxylic acid based Targeted NCEs 2-alkoxy propionitriles F1a-d: 2-methoxy/2-ethoxy/2-Isopropoxy/2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid, F2c-d: 2-Isopropoxy/2-Isobutoxy-3-[4-(1-methyl-1H-indol-2-ylmethoxy)-phenyl]- propionic acid and F3c-d: 2-Isopropoxy/2-Isobutoxy-3-[4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl]- propionic acid (TABLE S3-5 and Scheme 6 and 6a-c).

The appearance of the a broad band at 34600 – 2400 cm$^{-1}$ and a strong and sharp band at 1728 - 1655 cm$^{-1}$ in the IR spectrum of all these compounds corresponding to the bonded O-H stretch and carbonyl C=O stretch of the carboxyl group present in all these molecules along with simultaneous disappearance of the band at around 2405 – 2362 cm$^{-1}$ corresponding to the –CN stretching the frequency present in the in the IR spectrum corresponding alkoxy nitriles L8a-d, L10c-d and L12c-d confirm the structure assigned to all these molecules and also established the completion of the hydrolysis of the nitriles to the required carboxylic acids. The presence of the signals characteristic of the alkoxy group present in these molecules like that of the nitrile concerned as two 1H double doublet at 3.19
and 2.94 - ppm in case of F1d and as a 2H double doublet at 2.98 ppm and at 2.95 ppm in case of F2d and F3d respectively along with a 1H multiplet at 1.85 – 1.68 ppm and a 6H doublets at 0.87 – 0.72 ppm respectively for the methylenic, methynic and germinal dimethyl based protons of the isobutoxy -CH2CH(COOH) OCH2CH(CH3)2 group present in case of F1d, F2d and F3d and as a 1H multiplet at 2.04 – 1.58 ppm and a 6H doublets at 1.25 - 1.22 ppm respectively for the methynic and germinal dimethyl based protons of the isopropoxy -CH2-CH(COOH)OCH(CH3)2 group present in case of F1c, F2c and F3c and as 2H quartet at 3.76 ppm and a 3H triplet at 1.20 ppm respectively for the methylinic methyl based protons of the ethoxy -CH2CH(COOH)OCH2CH3 group present in F1b while the methoxy -CH2CH(COOH)OCH3 group in case of F1a appeared as 3H singlet at 3.32 ppm in its PMR spectrum. The presence of 1H triplet and 2H doublet at 4.94 - 3.71 ppm and 3.56 -2.75 ppm for the methylenic and methynic protons of the ethyl type unit (-O-C6H4-CH2CH-) present in case of all these compounds not only confirm the structure assigned but also support the complete hydrolysis of the alkoxy nitriles to the desired and targeted alkoxy carboxylic acids (PLATES: IR 26 and IR 27 and IR 28 and IR 29 and IR 30 and IR 31 and IR 32; PMR 25 and PMR 26 and PMR 27 and PMR 28 and PMR 29 - 29a).

The presence of [M+1]+ and [M]+ peak at m/z 383 (30) and at m/z 382 (100) in case of F1d and [M+1]+ peak at m/z 382 (82) in case F2d and [M+1]+ peak at m/z 474 (77) in case F3d in their mass spectra along with other fragments provide additional support to the structure assigned to the isobutoxy based compounds. The presence of [M]+ and [M-1]+ peak at m/z 459 (56) and m/z 458 (100) respectively in case of F3c containing isopropoxy group while the mass spectra of F1a on the other hand shows the [M]+ peak at m/z 340 (9) along with other fragments confirmed the structure assigned to all these molecules beyond doubt (PLATES: MS 16 -CHART 15 and MS 17 - CHART 16 and MS 18 - CHART 17; MS 19 CHART - 18 and MS 20 - CHART 19).

Synthesis of the Other NCEs (F4a-b, F5a-b and F6a-b, F7a-b)
Heterocyclyl Linked Thiazolidinediones/Diethyl malonate Based ONCEs and Related Intermediates
The Benzyldiene-Thiazolidine-2,4-Dione (F4a and F5a)
The benzylidene-1,3-thiazolidine-2,4-dione based other NCEs F4a: 5-{4-(1-methyl-1H-benzimidazol-2-yl)methoxy[benzylidene]-1,3-thiazolidine-2,4-dione and F5a: 5-{4-(1-Methyl-1H-indol-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione were prepared\textsuperscript{560, 561} by refluxing a mixture solution of the corresponding heterocyclyl linked benzaldehyde L1 and L2 respectively and thiazolidine-2,4-dione in the presence of catalytic amount of piperidinium acetate in toluene for 7 hours with continuous removal of water using a Dean-Stark water separator followed by work up and purification involving cooling, filtration and washing (TABLE S6 and Scheme 7a and 7c).

The disappearance of the doublet for the coupled C-H stretch of the aldehydic group at 2828 – 2820 cm\textsuperscript{-1} and 2732 - 2724 cm\textsuperscript{-1} and the aldehydic C=O stretch at 1697 - 1684 cm\textsuperscript{-1} respectively present in the IR spectrum of L1, L2 and simultaneous appearance of the bands corresponding to the N-H and C-S stretch of the thiazolidinedione moiety present in these molecules at 3410 and 3402 cm\textsuperscript{-1} and at 739 and 734 cm\textsuperscript{-1} along with the two carbonyls of the thiazolidinedione appearing at 1725 and 1704 cm\textsuperscript{-1} and at 1732 and 1701 cm\textsuperscript{-1} respectively in the IR spectrum of F4a and F5a as expected confirm their structure. The presence of benzylidene based proton present in both these molecules were also confirmed from the appearance of a 1H singlet at 7.68 ppm and at 7.63 ppm respectively along with the presence of 2H and 3H singlets for the -CH\textsubscript{2}-O- and N-CH\textsubscript{3} at 5.46 and 3.91 ppm and at 5.28 and 3.81 ppm respectively in the PMR spectrum of F4a and F5a.

The presence of [M+1]\textsuperscript{+} peak at m/z 366 (100), m/z 365 (100) in the Mass spectrum of F4a and F5a respectively provide additional support to the structure assigned to these molecules (PLATES: IR 33 and IR 34; PMR 30 - 30a and PMR 31; MS 21 and MS 22).

The Benzyldiene-Malonic Acid Diethyl Esters (F6a and F7a)

The benzyldiene malonic acid diethyl esters F6a: 2-[4-(1-Methyl-1H-benzimidazol-2-ylmethoxy)-benzylidine]-malonic acid diethyl ester and F7a: 2-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzylidine]-malonic acid diethyl ester were similarly prepared\textsuperscript{560} from the corresponding heterocyclyl linked benzaldehyde L1 and L2 respectively while using diethyl malonate and piperidinium acetate and subsequent work up and purification (TABLE S7 and Scheme 7a and 7c).
These molecules also lack the doublet for the coupled C-H stretch of the aldehydic group and the aldehydic C=O stretch present in the IR spectrum of L1, L2 and simultaneous appearance of the bands corresponding to the ester carbonyl C=O stretch at 1723 cm⁻¹ and 1720 cm⁻¹ in their IR spectrum as expected. The presence of benzylidene based proton present in both these molecules as 1H singlet at 7.64 ppm and at 7.67 ppm respectively along with the presence of a 4H (2H each) overlapping quartets at 4.30 ppm and two 3H triplet at 1.31 and 1.29 ppm in the PMR spectrum of F6a for the diethyl malonate based structural units present in this molecule. The diethyl malonate based structural unit in case of F7a on the other hand appeared as two 2H quartets at 4.35 and 4.29 ppm and a 6H (3H each) triplets at 1.32 in its PMR spectrum. The additional presence of 2H and 3H singlets for the -CH₂-O- and N-CH₃ at 5.42 and 3.88 ppm and at 5.22 and 3.79 ppm respectively in the PMR spectrum of in their PMR spectrum confirmed the structure assigned.

The presence of [M+1]⁺ peak at m/z 409 (100) and at m/z 408 (100) in the Mass spectrum of F6a and F7a respectively provide additional support to the structure assigned to these molecules (PLATES: IR 35 and IR 36; PMR 32 and PMR 33; MS 23 - CHART 20 and MS 24 - CHART 21).

The Benzyl-Malonic Acid Diethyl Esters (F6b and F7b)
The benzylidene based malonic acid diethyl esters F6a and F7a thus obtained were subjected to catalytic hydrogenation in a Parr bottle with 10% Palladium on charcoal taken in methanol at 20psi for 12 hours followed by workup involving filtration of the catalyst through celite, vacuum evaporation of the filtrate and subsequent recrystallization of the residue with methanol to obtained the desired benzyle malonic acid diethyl esters based other NCEs F6b: 2-[4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzyl]-malonic acid diethyl ester and F7b: 2-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzyl]-malonic acid diethyl ester (TABLE S7 and Scheme 7a and 7c).

The completion of reduction and confirmation of the structure assigned were completely indicated by the presence of a 1H triplet at 3.57 ppm and a 2H doublet at 3.14 ppm in the PMR spectrum of both the molecules and the simultaneous absence of the 1H singlet at 7.64
ppm and at 7.67 ppm respectively present in the PMR spectrum of corresponding benzylidene based molecules F6a and F7a.

The presence of [M+1]$^+$ peak at m/z 411 (100) in the Mass spectrum of F6b and that of [M+2]$^+$ peak at m/z 411 (8) along with other fragment at m/z 162 (14) in the Mass spectrum of F7b provide additional support to the structure assigned to these molecules (PLATES: IR 37 and IR 38; PMR 34 and PMR 35; MS 25 and MS 26 - CHART 22).

The Benzyl-Thiazolidine-2,4-Dione (F4b and F5b)
The desired benzimidazolyl linked benzyl- thiazolidine-2,4-dione F4b: 5-{4-{[1-Methyl-1H-benzimidazol-2-ylmethoxy]-benzyl} - thiazolidine-2,4-dione on the other hand was prepared through acidic hydrolysis$^{561}$ of L13a: 2-Imino-5-[4-(1-methyl-1H-benzimidazol-2-ylmethoxy)-benzyl]-thiazolidine-4-one while refluxing with 2N HCl containing requisite amount of EtOH and subsequent work up involving in vacuo concentration, dilution, neutralized with saturated aqueous NaHCO$_3$ and extraction with CHCl$_3$ (TABLE S6 and Scheme 7b).

The presence of the bands corresponding to the N-H and C-S stretch of the thiazolidinedione moiety at 3450 cm$^{-1}$ and at 740 cm$^{-1}$ along with the two carbonyls of the thiazolidinedione appearing as a broad band at 1717 cm$^{-1}$ respectively in the IR spectrum as expected confirm the structure assigned. The presence of three double doublets 1H each corresponding to one proton of the thiazolidinedione and two benzylic protons present in this molecule at 4.62 ppm and at 3.38 and 3.04 ppm respectively representing an ABX pattern as expected with three coupling constants averaged to (J = 4.12 and 9.22 and 14.12 Hz) for two vicinal and one germinal coupling expected for the set of three protons thus involved further support the structure assigned to this molecule. The presence of [M+1]$^+$ peak at m/z 368 (100) additionally confirmed the structure assigned (PLATES: IR 41; PMR 38 - 38a; MS 28).

L13a thus required was prepared$^{561}$ by refluxing a stirred mixture solution of L13: 2-Bromo-3-[4-(1-methyl-1H-benzoimidazol-2-ylmethoxy)-phenyl]-propionic acid methyl
ester (0.2mmol), thiourea (0.2mol), sodium acetate (0.016g, 0.2mol) in 7 ml of EtOH (7ml) followed by workup of the contents (TABLE S6 and Scheme 7b).

The presence of two N-H stretch corresponding to the N-H and –C=NH of the 2-Iminothiazolidine-4-one moiety thus generate at 3512 and 3119 cm\(^{-1}\) along with the presence of the C=O stretch at 1703 cm\(^{-1}\) in the IR spectrum of this molecule and the similar informations drawn from the presence of two 1H slightly broad singlet at 8.77 and 8.57 ppm corresponding to N-H and =NH of the 2-Iminothiazolidine-4-one in the PMR spectrum of this molecule along with the presence of signals at positions and multiplicities expected like that of F4b explained above are also in accordance to the structure assigned (PLATES: IR 40; PMR 37).

The L13: 2-Bromo-3-[4-(1-methyl-1H-benzoimidazol-2-ylmethoxy)-phenyl]-propionic acid methyl ester thus required in turn was prepared\(^{559, 561}\) via diazotization of L4: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-phenylamine while using 48% aqueous HBr and subsequent treatment with methyl acrylate and then stirring the mixture previously warmed to 38°C and addition of powdered cuprous oxide and subsequent work up involving basification with concentrated aqueous ammonia, and ethyl acetate extraction and column chromatographic purification (TABLE S6 and Scheme 7b).

The structure of L13 was confirmed from the presence of the C-Br stretch at 856 cm\(^{-1}\) along with the ester carbonyl C=O stretch at 1734 cm\(^{-1}\) in the IR spectrum of this molecule with the simultaneous disappearance of the antisymmetric and symmetric –N-H stretch of the –NH\(_2\) at 3446 and 3313 cm\(^{-1}\) present in the IR spectrum of L4: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-phenylamine. Further support to the structure assigned were obtained from the presence of three double doublets 1H each at 4.34 ppm and at 3.40 and 3.18 ppm respectively representing an ABX pattern as expected with three coupling constants averaged to (J = 7.94 and 8.50 and 14.19 Hz) for two vicinal and one germinal coupling expected for the set of three protons thus involved along with a 3H singlet at 3.72 ppm for the –CH\(_3\) of the α-bromo methyl ester. The presence of [M]\(^{+}\) and [M+2]\(^{+}\) peaks as an isotopic cluster in the ration 1:1 at m/z 402 (4) and 404 (4) as expected for a monobromo derivative in the Mass spectrum of...
this molecule additionally confirmed the structure assigned (PLATES: IR 39; PMR 36; MS 27).

The indolyl benzyl-thiazolidine-2,4-dione based other NCE F5b: 5-[(1-Methyl-1H-indol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione was prepared following mitsunobu coupling$^{562}$ of L2b (1-Methyl-1H-indol-2-yl)methanol (0.62mmol) and R1: 5-(4-Hydroxy-benzyl)thiazolidine-2,4-dione (0.94mmol) while using triphenylphosphine (0.935mmol) and diethyl azodicarboxylate (0.93mmol) in dry THF upon stirring at 0°C and then at room temperature followed by work up involving dilution with water and extraction with DCM and subsequent column chromatographic purification of the residue (TABLE S6 and Scheme 7d).

The presence of the bands corresponding to the N-H and C-S stretch of the thiazolidinedione moiety at 3307 cm$^{-1}$ and at 722 cm$^{-1}$ along with the two carbonyls of the thiazolidinedione appearing as a broad band at 1727 and 1684 cm$^{-1}$ respectively in the IR spectrum as expected confirm the structure assigned. The presence of three double doublets 1H each corresponding to one proton of the thiazolidinedione and two benzylic protons present in this molecule at 4.72 ppm and at 3.42 and 3.21 ppm respectively representing an ABX pattern as expected with three coupling constants averaged to (J = 4.08 and 6.56 and 14.00 Hz) for two vicinal and one germinal coupling expected for the set of three protons thus involved like that of F4b further support the structure assigned to this molecule. The indolyl proton at position 3 of this molecule appears as 1H singlet at 6.27 ppm is as expected. The presence of [M]+ peak at m/z 366 (7) in the mass spectrum of this molecule additionally confirmed the structure assigned (PLATES: IR 42; PMR 41-41a; MS 29).

The R1: 5-(4-Hydroxy-benzyl)thiazolidine-2,4-dione required was prepared by the acidic hydrolysis of R1b as per procedure$^{561}$ used for the preparation of F4b.

The structure assigned to this molecule was confirmed from the presence of phenolic O-H stretch at 3208 cm$^{-1}$ in addition to the bands corresponding to the N-H and C-S stretch of the thiazolidinedione moiety at 3412 cm$^{-1}$ and at 727 cm$^{-1}$ along with the two carbonyls of the thiazolidinedione appearing at 1754 and 1697 cm$^{-1}$ respectively in the IR spectrum as
expected along with similar information obtained from the presence of three double doublets 1H each corresponding to one proton of the thiazolidinedione and two benzylic protons present in this molecule at 4.52 ppm and at 3.55 and 3.14 ppm respectively representing an ABX pattern as expected with three coupling constants averaged to \( J = 3.88 \) and \( 9.84 \) and \( 14.08 \) Hz) for two vicinal and one germinal coupling like that of \( F4b \) and \( F5b \) provide further support the structure assigned (PLATE: PMR 40).

The \( R1b \) thus required was prepared from \( R1a: 2\text{-Bromo-3-(4-methoxy-phenyl)-propionic acid methyl ester} \) as per procedure\(^{559, 561}\) reported for the preparation of \( L13a \) (TABLE S6 and Scheme 7d).

The \( R1a: 2\text{-Bromo-3-(4-methoxy-phenyl)-propionic acid methyl ester} \) required in turn was prepared\(^{559}\) from the diazotization of p-anisidine while using \( 48\% \) aqueous HBr and methyl acrylate as per procedure used for the preparation of \( L13 \) (TABLE S6 and Scheme 7d).

The structure of \( R1a \) like that of \( L13 \) was confirmed from the presence of three double doublets 1H each at 4.36 ppm (appeared as triplet) and at 3.41 and 3.18 ppm respectively representing an ABX pattern as expected with three coupling constants \( J = 8.62 \) and \( 6.89 \) and \( 14.14 \) Hz) for two vicinal and one germinal coupling expected for the set of three protons thus involved along with a 3H singlet at 3.73 ppm for the -CH\(_3\) of the α-bromo methyl ester in the PMR spectrum of this molecule very judiciously account for the structure assigned to this molecule (PLATE: PMR 39).
Scheme 1: Synthesis of 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzaldehyde and related Intermediates

\[ \text{N} \quad \text{N} \quad \text{C} \quad \text{H}_3 \quad \text{F} \quad \text{H} \quad \text{O} \quad \text{b} \quad \text{O} \quad \text{H} \quad \text{O} \quad \text{b} \quad \text{OH} \quad \text{NH}_2 \quad \text{NHCH}_3 \cdot 2\text{HCl} \]

a: H\textsubscript{2}O, b: NaH-DMF
Scheme 2: Synthesis of 4-[(1-methyl-1H-indol-2-yl)methoxy]benzaldehyde and related Intermediates

a: CH$_3$I, NaH -DMF,  
b: LAH-THF  
c: NaH-DMF
Scheme 3: *Synthesis of 4-[3-(9-oxoacridin-10(9H)-yl)propoxy]benzaldehyde and related Intermediates*

\[ \text{a: } \text{K}_2\text{CO}_3-\text{Acetone} \text{, b: } \text{KOH-DMF (MW)} \]
Scheme 4: Synthesis of 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-phenylamine and 4-(1-Methyl-1H-indol-2-ylmethoxy)-phenylamine and related Intermediates

\[
\text{a: NaH - DMF, b: Pd/C - H}_2, \text{ MeOH}
\]
Scheme 5: Synthesis of 10-[3-(4-Amino-phenoxy)-propy]-10H-acridin-9-one and related Intermediates

\[ \text{a: } K_2CO_3 \text{- Acetone, b: } \text{KOH - DMF (MW), c: Pd/C - H}_2, \text{MeOH} \]
Scheme 6: General scheme for the synthesis of heterocyclyl linked benzyl based α-alkoxy carboxylic acid as final NCEs and related Intermediates

a: Ph₃P+CH₂OMe Cl-, LDA-THF, (DIPA-nBuLi/THF),
b: ROH, pTSA,
c: TMSCN, BF₃-DCM,
d: NaOH/H₂O-EtOH
Scheme 6a: Synthesis of Benzimidazolyl linked benzyl based α-alkoxy carboxylic acid as final NCEs and related Intermediates

\[ \text{ROH } R = \text{Me, Et, } \text{iPr, iBu} \]

**a:** Ph₃P⁺CH₂OMe Cl⁻, LDA-THF, (DIPA-nBuLi/THF),

**b:** ROH , pTSA,

**c:** TMSCN, BF₃-DCM,

**d:** NaOH/H₂O-EtOH,
Scheme 6b: Synthesis of Indolyl linked benzyl based α-alkoxy carboxylic acid as final NCEs and related Intermediates

\[
\begin{align*}
R &= \text{iPr, iBu} \\
a: \text{Ph}_3\text{P}^+\text{CH}_2\text{OMe Cl}, \text{LDA-THF}, (\text{DIPA-nBuLi/THF}), \\
b: \text{ROH}, \text{pTSA}, \\
c: \text{TMSCN}, \text{BF}_3-\text{DCM}, \\
d: \text{NaOH/H}_2\text{O-EtOH},
\end{align*}
\]
Scheme 6c: Synthesis of acridonyl linked benzyl based α-alkoxy carboxylic acid as final NCEs and related Intermediates

R = \textsuperscript{i}Pr and \textsuperscript{i}Bu
Scheme 7a: Synthesis of Benzimidazolyl linked benzylidene based Thiazolidinediones and Diethyl malonates and benzyl based Diethyl malonates

a: Piperidinium acetate, Toluene
b: H₂-Pd/CH₃OH
Scheme 7b: Synthesis 5-{4-[(1-Methyl-1H-benzimidazol-2-ylmethoxy)-benzyl] - thiazolidine-2,4-dione and related Intermediates

a: HBr, NaNO₂, Methyl acrylate, Cu₂O
b: Thiourea, Sod. acetate/EtOH, c: HCl-EtOH
Scheme 7c: Synthesis of Indoly linked benzyldiene based Thiazolidinediones and Diethyl malonates and benzyl based Diethyl malonates

a: Piperidinium acetate, Toluene
b: H₂-Pd/CH₃OH
Scheme 7d: Synthesis of 5-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione dione and related Intermediates

a: HBr, NaNO\(_2\), Methyl acrylate, Cu\(_2\)O
b: Thiourea, Sod. acetate/EtOH, c: HCl-EtOH, d: Ph\(_3\)P-DEAD/THF
L1: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzaldehyde

PLATE: IR1
L2a: 1-Methyl-1H-indole-2-carboxylic acid ethyl ester
L2: 4-[(1-methyl-1H-indol-2-yl)methoxy]benzaldehyde

PLATE: IR3
L3a: 4-(3-Bromo-propoxy)-benzaldehyde

PLATE: IR4
L3: 4-[3-(9-oxoacridin-10(9H)-yl)propoxy]benzaldehyde

PLATE: IR5
L4a: 1-Methyl-2-(4-nitro-phenoxymethyl)-1H-benzoimidazole

PLATE: IR6
L5a: 1-Methyl-2-(4-nitro-pheoxymethyl)1H-indole
L6a: 1-(3-Bromo-propoxy)-4-nitro-benzene
L6b: 10-[3-(4-Nitro-phenoxy)-propyl]-10H-acridin-9-one

PLATE: IR9
L4: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-phenylamine

PLATE: IR10
L5 : 4-(1-Methyl-1H-indol-2-ylmethoxy)-phenylamine

PLATE: IR11
L6: 10-[3-(4-Amino-phenoxy)-propy]-10H-acridin-9-one

PLATE: IR12
L7: 2-(4-[2-methoxyethenyl]phenoxy)methyl)-1-methyl-1H-benzimidazole

PLATE: IR13
L9: 2-[4-(2-Methoxy-vinyl)-phenoxy-methyl]-1-methyl-1H-indole

PLATE: IR14
L11: 10-[3-[4-(2-Methoxy-vinyl)-phenoxy]-propyl]-10H-acridine-9-one

PLATE: IR15
L7d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole

PLATE: IR16
L9d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxyethyl]-1-methyl-1H-indole

PLATE: IR17
L9c: 2-[4-(2,2-Diispropoxy-ethyl)-phenoxyethyl]-1-methyl-1H-indole
L11c: 10-\{3-[4-(2,2-Diispropoxy-ethyl)-phenoxy]-propyl\}-10H-acridine-9-one
L7b: 2-[4-(2,2-Diethoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole

PLATE: IR20
L7a: 2-[4-(2,2-Dimethoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole

PLATE: IR21
L8d: 2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionitrile
L12d: 2-Isobutoxy-3-[4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl]-propionitrile
L12c: 2-Isopropoxy-3-{4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl}-propionitrile
L8b: 2-Ethoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionitrile
PLATE: IR25

F1d: 2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid
F2d: 2-Isobutoxy-3-[4-(1-methyl-1H-indol-2-ylm ethoxy)-phenyl]-propionic acid
F3d: 2-Isobutoxy-3-[4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl]-propionic acid
**F1c**: 2-Isopropoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid

**PLATE**: IR29
F2c: 2-Isopropoxy-3-[4-(1-methyl-1H-indole-2-ylmethoxy)-phenyl]-propionic acid
F3c: 2-Isopropoxy-3-{4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl}-propionic acid

PLATE: IR31
F1b: *Synthesis of 2-Ethoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid*

PLATE: IR32
F4a: 5-{4-[(1-methyl-1H-benzimidazol-2-yl)methoxy]benzylidene}-1,3-thiazolidine-2,4-dione
F5a: 5-[(1-Methyl-1H-indol-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione

PLATE: IR34
F6a: 2-[4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzylidene]-malonic acid diethyl ester

PLATE: IR35
F7a: 2-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzylidene]-malonic acid diethyl ester
F6b: 2-[4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzyl]-malonic acid diethyl ester

PLATE: IR37
F7b: 2-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzyl]-malonic acid diethyl ester
L13: 2-Bromo-3-[4-(1-methyl-1H-benzoimidazol-2-ylmethoxy)-phenyl]-propionic acid methyl ester
L13a: 2-Imino-5-[4-(1-methyl-1H-benzimidazol-2-ylmethoxy)-benzyl]-thiazolidine-4-one
F4b: 5-[(1-Methyl-1H-benzimidazol-2-ylmethoxy)-benzyl] - thiazolidine-2,4-dione

PLATE: IR41
F5b: 5-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione

PLATE: IR42
L1a: (1-Methyl-1H-benzoimidazol-2-yl)-methanol
L1: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzaldehyde
L2a: 1-Methyl-1H-indole-2-carboxylic acid ethyl ester
L2b: (1-Methyl-1H-indol-2-yl)-methanol

PLATE: PMR 4
L2: 4-[(1-methyl-1H-indol-2-yl)methoxy]benzaldehyde
L3a: 4-(3-Bromo-propoxy)-benzaldehyde

PLATE: PMR 6
L3: 4-[3-(9-oxoacridin-10(9H)-yl)propoxy]benzaldehyde

PLATE: PMR 7
Continued

PLATE: PMR 7a
L4a: 1-Methyl-2-(4-nitro-phenoxy)methyl-1H-benzoimidazole

PLATE: PMR 8
L.6a: 1-(3-Bromo-propoxy)-4-nitro-benzene
L4: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-phenylamine

PLATE: PMR 10
L7: 2-((4-[2-methoxyethenyl]phenoxy)methyl)-1-methyl-1H-benzimidazole

PLATE: PMR 11
L9: 2-[4-(2-Methoxy-vinyl)-phenoxyethyl]-1-methyl-1H-indole

PLATE: PMR 12
L11: 10-{3-[4-(2-Methoxy-vinyl)-phenoxy]-propyl}-10H-acridine-9-one

PLATE: PMR 13
L7d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxy methyl]-1-methyl-1H-benzimidazole

PLATE: PMR 14
Continued

PLATE: PMR 14b
L9d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxyethyl]-1-methyl-1H-indole
L11d: 10-\{3-[4-(2,2-Diisobutoxy-ethyl)-phenoxy]-propyl\}-10H-acridine-9-one

PLATE: PMR 16
Continued

PLATE: PMR 16a
L11c: $10-\{3-[4,2-(Diispropoxy-ethyl)-phenoxy]-propyl\}-10H-acridine-9-one$
L7b: 2-[4-(2,2-Diethoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole
Continued
L7a: 2-[4-(2,2-Dimethoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole

PLATE: PMR 19
L8d: 2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionitrile
PLATE: PMR 20

Continued
L10d: 2-Isobutoxy-3-[4-(1-methyl-1H-indol-2-ylmethoxy)-phenyl]-propionitrile
Continued
L12d: 2-Isobutoxy-3-{4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl}-propionitrile
L12c: 2-Isopropoxy-3-[4-3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl]-propionitrile
L8b: 2-Ethoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionitrile
Continued
F1d: 2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid
F3d: 2-Isobutoxy-3-[4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl]-propionic acid

PLATE: PMR 26
F3c: 2-Isopropoxy-3-[4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl]-propionic acid
F1b: 2-Ethoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid
F1a: 2-Methoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid
F4a: 5-{4-[(1-methyl-1H-benzimidazol-2-yl)methoxy]benzylidene}-1,3-thiazolidine-2,4-dione

PLATE: PMR 30
Continued

PLATE: PMR 30a
F5a: 5-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione

PLATE: PMR 31
F6a: 2-[4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzylidene]-malonic acid diethyl ester

PLATE: PMR 32
F7a: 2-[(4-(1-Methyl-1H-indol-2-ylmethoxy)-benzylidene]-malonic acid diethyl ester

PLATE: PMR 33
F6b: 2-[4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzyl]-malonic acid diethyl ester
F7b: 2-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzyl]-malonic acid diethyl ester

PLATE: PMR 35
L13: 2-Bromo-3-[4-(1-methyl-1H-benzoimidazol-2-ylmethoxy)-phenyl]-propionic acid methyl ester

PLATE: PMR 36
L13a: 2-Imino-5-[(1-methyl-1H-benzimidazol-2-ylmethoxy)-benzyl]-thiazolidine-4-one
PLATE: PMR 37
F4b: 5-{4-[(1-Methyl-1H-benzimidazol-2-ylmethoxy)-benzyl] - thiazolidine-2,4-dione
R1a: 2-Bromo-3-(4-methoxy-phenyl)-propionic acid methyl ester
R1: 5-(4-Hydroxy-benzyl)-thiazolidine-2,4-dione

PLATE: PMR 40
F5b: 5-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione
Continued

PLATE: PMR 41
L1: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzaldehyde

PLATE: MS 1
L2: 4-[(1-methyl-1H-indol-2-yl)methoxy]benzaldehyde
L3: 4-[3-(9-oxoacridin-10(9H)-yl)propoxy]benzaldehyde
L4: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-phenylamine

![Molecular structure of the compound]

**Plate:** MS 4
L7: 2-((4-[2-methoxyethenyl]phenoxy)methyl)-1-methyl-1H-benzimidazole
L9: 2-[4-(2-Methoxy-vinyl)-phenoxyethyl]-1-methyl-1H-indole

PLATE: MS 6
L7d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxy methyl]-1-methyl-1H-benzimidazole

PLATE: MS 7
L9d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxyethyl]-1-methyl-1H-indole

PLATE: MS 8
L11d: 10-{3-[4-(2,2-Diisobutoxy-ethyl)-phenoxy]-propyl}-10H-acridine-9-one

PLATE: MS 9
L11c: 10-{3-[4-(2,2-Diispropoxy-ethyl)-phenoxy]-propyl}-10H-acridine-9-one

PLATE: MS 10
L7b: 2-[4-(2,2-Diethoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole

PLATE: MS 11
L7a: 2-[4-(2,2-Dimethoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole

PLATE: MS 12
L8d: 2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionitrile

PLATE: MS 13
L10d: 2-Isobutoxy-3-[4-(1-methyl-1H-indol-2-ylmethoxy)-pheny]-propionitrile

PLATE: MS 14
L12d: 2-Isobutoxy-3-{4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl}-propionitrile
**F1d:** 2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid
F2d: 2-Isobutoxy-3-[4-(1-methyl-1H-indol-2-ylm ethoxy)-phenyl]-propionic acid

PLATE: MS 17
F3d: 2-Isobutoxy-3-[4-[3-(9-oxo-9H-acridin-10-yl)-propany]-phenyl]-propionic acid

PLATE: MS 18
F3c: 2-Isopropoxy-3-[4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl]-propionic acid

PLATE: MS 19
F1a: 2-Methoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid

PLATE: MS 20
F4a: 5-{4-[(1-methyl-1H-benzimidazol-2-yl)methoxy]benzylidene}-1,3-thiazolidine-2,4-dione

PLATE: MS 21
F5a: 5-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione

PLATE: MS 22
**F6a**: 2-[4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzylidene]-malonic acid diethyl ester

\[
\text{PLATE: MS 23}
\]
F7a: 2-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzylidene]-malonic acid diethyl ester
F6b: 2-[4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzyl]-malonic acid diethyl ester

PLATE: MS 25
F7b: 2-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzyl]-malonic acid diethyl ester
L13: 2-Bromo-3-[4-(1-methyl-1H-benzoimidazol-2-ylmethoxy)-phenyl]-propionic acid methyl ester

PLATE: MS 27
F4b: 5-{4-[1-Methyl-1H-benzimidazol-2-ylmethoxy]-benzyl} - thiazolidine-2,4-dione

PLATE: MS 28
F5b: 5-[4-(1-Methyl-1H-indol-2-ylmethoxy) benzyl]-thiazolidine-2,4-dione
MASS FRAGMENTATION

The Structures of the Plausible Molecular Ions and Some Significant Fragment Ions of Some of the Intermediates and Selected NCEs (Tables S1-S7)

L1: 4-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzaldehyde

LCMS (APCI)

\[
\begin{align*}
\text{N} & \quad \text{N} & \quad \text{O} & \quad \text{C} & \quad \text{H} & \quad \text{O} & \quad + \\
\text{H} & \quad \text{O} & \quad \text{N} & \quad \text{N} & \quad \text{CH} & \quad \text{2} & \quad + \text{H} \\
267 \ (8\%) & \quad + & \quad \text{H} & \quad \rightarrow & \quad 146 \ (100\%) & \quad + \text{H}
\end{align*}
\]

CHART: 1 (PLATE: MS 1)
L7: 2-((4-[2-methoxyethenyl]phenoxy)methyl)-1-methyl-1H-benzimidazole
LCMS (APCI)

CHART: 2 (PLATE: MS 5)
L9: 2-[4-(2-Methoxy-vinyl)-phenoxy methyl]-1-methyl-1H-indole

LCMS (APCI)

![Chemical structure](image)

CHART: 3 (PLATE: MS 6)
L7d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxy-methyl]-1-methyl-1H-benzimidazole

LCMS (APCI)

CHART: 4 (PLATE: MS 7)
L9d: 2-[4-(2,2-Diisobutoxy-ethyl)-phenoxy methyl]-1-methyl-1H-indole

GCMS

CHART: 5 (PLATE: MS 8)
L11d: 10-[3-[4-(2,2-Diisobutoxy-ethyl)-phenoxy]-propyl]-10H-acridine-9-one

LCMS (APCI)

```
\begin{align*}
\text{CHART: 6 (PLATE: MS 9)}
\end{align*}
```
L11c: 10-\{3-[4-(2,2-Diisopropoxy-ethyl)-phenoxy]-propyl\}-10H-acridine-9-one

LCMS (APCI)

CHART: 7 (PLATE: MS 10)
L7b: 2-[4-(2,2-Diethoxy-ethyl)-phenoxyethyl]-1-methyl-1H-benzimidazole

LCMS (APCI)

\[
\text{355 (100\%)} + \text{H} \rightarrow \text{146 (29\%)}
\]

\[
\text{309 (44\%)} \text{ - HOCH}_{2}\text{CH}_{3}
\]

CHART: 8 (PLATE: MS 11)
L7a: 2-[4-(2,2-Dimethoxy-ethyl)-phenoxy-methyl]-1-methyl-IH-benzimidazole

LCMS (APCI)

\[
\begin{align*}
\text{N} & \text{N} \\
\text{C} & \text{H}_3 \\
\text{O} & \text{C} & \text{H}_3 \\
\text{C} & \text{H}_3 & \text{O} & \text{N} & \text{N} & \text{C} & \text{H}_3 \\
\text{O} & \text{C} & \text{H}_3 \\
\text{C} & \text{H}_3 \\
\end{align*}
\]

+ 327 (100%) \\
- HOCH\text{3} \\
\text{N} & \text{N} \\
\text{C} & \text{H}_3 \\
\text{O} & \text{C} & \text{H}_3 \\
\text{C} & \text{H}_3 & \text{O} & \text{N} & \text{N} & \text{C} & \text{H}_3 \\
\text{O} & \text{C} & \text{H}_3 \\
\text{C} & \text{H}_3 \\
\]

+ 295 (27%) \\
\text{N} & \text{N} \\
\text{C} & \text{H}_3 \\
\text{O} & \text{C} & \text{H}_3 \\
\text{C} & \text{H}_3 & \text{O} & \text{N} & \text{N} & \text{C} & \text{H}_3 \\
\text{O} & \text{C} & \text{H}_3 \\
\text{C} & \text{H}_3 \\
\]

+ 146 (51%) \\
\text{N} & \text{N} \\
\text{C} & \text{H}_3 \\
\text{O} & \text{C} & \text{H}_3 \\
\text{C} & \text{H}_3 & \text{O} & \text{N} & \text{N} & \text{C} & \text{H}_3 \\
\text{O} & \text{C} & \text{H}_3 \\
\text{C} & \text{H}_3 \\
\]

CHART: 9 (PLATE: MS 12)
L8d: 2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionitrile

GCMS (APCI)

CHART: 10 (PLATE: MS 13)
L10d: 2-Isobutoxy-3-[4-(1-methyl-1H-indol-2-ylmethoxy)-pheny]-propionitrile

LCMS (APCI)

364 (100%)

337 (10%)

CHART: 11 (PLATE: MS 14)
L12d: 2-Isobutoxy-3-{4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl}-propionitrile

LCMS (ESI)

\[
\begin{align*}
\text{455 (12\%)} & \quad + \quad \text{H} \\
\text{477 (14\%)} & \quad + \quad \text{Na}
\end{align*}
\]

CHART: 12 (PLATE: MS 15)
L12c: 2-Isopropoxy-3-{4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl}-propionitrile

LCMS (ESI)

CHART: 13
L8b: 2-Ethoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionitrile

LCMS (ESI)

\[ \text{Product 336 (12%)} \quad + \quad \text{H} \quad \rightarrow \quad \text{Product 308 (12%)} \quad - \quad \text{HCN} \]

CHART: 14
**F1d:** 2-Isobutoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid

LCMS (APCI)
F2d: 2-Isobutoxy-3-[4-(1-methyl-1H-indol-2-ylm ethoxy)-pheny]-propionic acid

LCMS (APCI)

CHART: 16 (PLATE: MS 17)
**F3d:** 2-Isobutoxy-3-{4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]-phenyl}-propionic acid

**LCMS (ESI)**

[Diagram of molecular structures and reactions]

**CHART: 17 (PLATE: MS 18)**
**F3c: 2-Isopropoxy-3-{4-[3-(9-oxo-9H-acridin-10-yl)-propoxy]phenyl}-propionic acid**

LCMS (APCI)

![Chemical Structure Diagram]

CHART: 18 (PLATE: MS 19)
**F1a:** 2-Methoxy-3-[4-(1-methyl-1H-benzimidazole-2-ylmethoxy)-phenyl]-propionic acid

**LCMS (APCI)**

\[
\begin{align*}
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
& \text{O} \\
\text{O} & \text{H} \\
\text{O} & \text{CH}_3 \\
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
\end{align*}
\]

\[+ \quad + \quad 340(9\%) \quad 279(93\%) \quad + \quad -61\]

\[\begin{align*}
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
& \text{O} \\
\text{O} & \text{H} \\
\text{O} & \text{CH}_3 \\
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
\end{align*}\]

\[\begin{align*}
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
& \text{O} \\
\text{O} & \text{H} \\
\text{O} & \text{CH}_3 \\
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
\end{align*}\]

160 (52%) - 180

\[\begin{align*}
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
& \text{O} \\
\text{O} & \text{H} \\
\text{O} & \text{CH}_3 \\
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
\end{align*}\]

\[\begin{align*}
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
& \text{O} \\
\text{O} & \text{H} \\
\text{O} & \text{CH}_3 \\
\text{N} & \text{N} \\
\text{CH}_3 & \text{O} \\
\text{C} & \text{H}_3 \\
\end{align*}\]

**CHART: 19 (PLATE: MS 20)**
F6a: 2-[(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-benzylidene]-malonic acid diethyl ester

LCMS (APCI)

\[
\begin{align*}
\text{N} & \text{C} \quad \text{H}_3 \\
\text{O} & \text{O} \quad \text{C}_2\text{H}_5 \\
\end{align*}
\]

409 (100%)

\[
\begin{align*}
\text{N} & \text{C} \quad \text{H}_3 \\
\text{O} & \text{O} \quad \text{C}_2\text{H}_5 \\
\end{align*}
\]

+ H

- HOCH\_2CH\_3

363 (3%)

CHART: 20 (PLATE: MS 23)
F7a: 2-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzylidene]-malonic acid diethyl ester

LCMS (APCI)

\[\text{O}^+\text{OC}_2\text{H}_5\text{O}\]

407 (100%) \hspace{1cm} 361 (9%)

\(-\text{HOCH}_2\text{CH}_3\)

CHART: 21 (PLATE: MS 24)
**F7b: 2-[4-(1-Methyl-1H-indol-2-ylmethoxy)-benzyl]-malonic acid diethyl ester**

LCMS (APCI)

![Chemical structure](chart)

**CHART: 22** (PLATE: MS 26)