CHAPTER - 5

CONCLUSION
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The results of spectral analysis revealed the confirmation of structure of all synthesized derivatives. The characteristic peaks around 1300 and 1100 cm\(^{-1}\) were present at FT/IR spectra of each final compound of scheme, suggested the presence of sulfonyl group in structure which were completed by the characteristic NMR peaks for urea amine groups. These data helped to conclude the presence of sulfonyleurea group in the structure. The characteristic peaks for secondary amine got absent in the carbamate intermediate (4a-e) of scheme-I, suggested the successful formation of trisubstituted amine group in the structure which were converted to trisubstituted sulfonylurea in the later steps. There were different heterocyclic rings present in corresponding schemes were confirmed by their respective peaks in individual spectrum. Further the completion of reaction and purity were well established by the physicochemical data i.e. melting point study, thin layer chromatography (TLC) study, UV spectroscopic study etc.

In the biological evaluation, all the compounds were shown inhibitory activity in the rise of blood glucose level in diabetes induced rates. The objective of study and rational of preparation of trisubstituted sulfonylurea were well supported by the results of antidiabetic evaluation. Here the trisubstituted sulfonylurea (5a-o, 6i-v) derivatives were found to be more active than the bisubstituted sulfonylurea compounds as the trisubstituted sulfonylurea derivatives were showing a dominant data for percentage of inhibition in blood glucose lowering effect.

The trisubstitution in sulfonylurea was successful attempt with phenyl (5a-e) as well as with 2-pyridyl (5k-o, 6i-v). But the pyridyl heteroaryl group containing derivatives
were more effective than the phenyl (aromatic) group present as third substituent. This conclusion made due to the most active compound 1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfonyl)-3-phenyl-1-(pyridin-2-yl) urea (5k) was belonging pyridyl (scheme-I) group even with thiazolidinedione containing derivatives (6i-v, scheme-II).

From results of study, it was seen the substitution on distal phenyl ring were also affected the antidiabetic profile of derivatives. The unsubstituted phenyl ring containing trisubstituted molecules (5a, 5k, 6i) were the more active than the substituted. On the other hand, out of the other substituent, hydroxyl (-OH) group was more significant for enhancement of activity of lead than rest of the substituent groups. This hydroxyl substitution was found most active for antidiabetic effect in bisubstituted sulfonylurea series (5c, 6c, 6iii, 7iii, 7viii, 3iv).

On the study for the effect of different heterocyclic ring associated with sulfonylurea in scheme-I, scheme-II and scheme-III, it was concluded that the thiazine heterocyclic ring (scheme-I) was well complimented the activity of sulfonylurea pharmacophore than thiazolidinedione (scheme-II) and pyrazole (scheme-III).

In bisubstituted compound there were two pharmacophore sulfonylurea and sulfonylthiourea were prepared and studies. The bioisosteric replacement of oxygen with sulphur atom to prepare sulfonylthiourea derivatives (6g-l, 7vi-x) was not so effective for blood glucose lowering effect. The other effort was done in scheme-III to find the effect of heterocyclic ring (3vii, 3viii) instead of aryl ring was not given satisfactory results that helped to conclude the suitability of phenyl ring at this site.

The result of oral glucose tolerance test (OGTT) was suggested that all the active compounds were effective to utilize normal insulin level of rats because they cleared glucose from the blood at faster rate than control. The most active compound 5k was
studied at two different dose levels, 10 and 50 mg/kg body weight. The curve of this study was suggested that the compound was given faster response at the dose of 50 mg/kg than 10 mg/kg body weight. This result was supported by area under curve (AUC) graph where the glucose concentration was least at the dose of 50 mg/kg body weight. The insulin resistance condition can be treated by the synthesized active compound as these were utilized normal insulin for glucose clearance at faster rate which was shown in OGTT study. This result was supported the treatment of insulin resistant activity which can be followed by the mechanism of glycogen synthase kinase (GSK3β) inhibition. This interpretation of results for inhibition was assured by the in silico (molecular docking) study where the compound form hydrogen bond and settled effectively on the protein cascade (binding site) with effective docking energy of \(-12.49\) kcal/mol (5k).

After the anticonvulsant study of synthesized compounds, activity was found against both maximal electroshock method (MES) and subcutaneous pentylentetrazole (scPTZ) induced seizure. The bisubstituted sulfonylurea series were found more active than trisubstituted sulfonylurea derivatives. Out of all the derivatives the compound thiazine containing \(6b, 6c, 6a\), thiazolidinedione containing \(7iii, 7iv\) and pyrazole containing \(3iii, 3iv\) were more active than rest of the compounds. From the active substituents, compound \(1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfonyl)-3-(4-hydroxyphenyl)urea \((6c)\) was found to be the most active.

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\begin{align*}
\text{(6c)}
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The effect of substituent on distal phenyl ring was very significant to discuss. The electronegative groups viz. –OH, -Cl, -OCH₃, containing phenyl ring derivatives were more active than the electron donating methyl (–CH₃) group containing derivatives. Out of these substituents, hydroxyl group was contributed more to enhance the anticonvulsant activity of sulfonylurea viz. \(1-(4-(4,6-dimethyl-6H-1,3-thiazin-2-yl)phenylsulfonyl)-3-(4-hydroxyphenyl)urea \((6c)\), \(1-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenylsulfonyl)-3-(4-hydroxyphenyl)-1-(pyridin-2-yl)urea \((6iii)\), \(4-(3,5-dimethyl-1H-pyrazol-1-yl)-N-(4-
hydroxyphenylcarbamoyl) benzenesulfonamide (3iv). The order of electron withdrawing substituent found for anticonvulsant activity was $-\text{OH} > -\text{Cl} > -\text{OCH}_3$. The sulfonylthiourea structural analog compound 6i of most active compound (6c) was not showing significant anticonvulsant activity as sulfonylurea analogs were given.

Thus the above comparison helped to conclude that the sulfonylurea was more effective than the sulfonylthiourea. This could be due to sulfonylurea was a more close structural analog of arylurea (hydantoin) structure present in well established anticonvulsant drug phenytoin. The closeness of structure was rationalized by similarity in their mechanism of action. To support this assumption in silico study were performed by using open form of voltage-gated sodium channel pore as protein target. The active compounds were well bound in the active site by a hydrogen bond and hydrophobic interactions shown in their solid surface structure with docking energy $-13.20$ kcal/mol (6c).

At the end of the study it was concluded that the thiazine heterocyclic ring is most suitable to associate with the sulfonylurea. While the trisubstitution in sulfonylurea is favorable for antidiabetic activity and the bisubstituted sulfonylurea can be a suitable candidate for the anticonvulsant activity.