3. Aims and objectives

Obesity poses a serious health problem throughout the globe and it cannot be considered as a mere cosmetic issue. It severely affects the quality of life and is associated with several other diseases such as diabetes mellitus, hypertension and certain types of cancers which significantly increases mortality. So, prevention and effective treatment of obesity are the primary challenges with extraordinary urgency for the developed as well as the developing countries.

Very few drugs are available in the market for the treatment of obesity but these drugs are not free from significant side effects. Thus, development of effective therapeutics with lesser/nil side effects is the prime task. CB1 receptor antagonists have shown their potential as effective therapeutic agents for the treatment of obesity. But due to CNS side effects, rimonabant a CB1 receptor antagonist, was withdrawn from the market in 2008. To overcome these side effects, researchers are focusing on the development of peripherally acting selective CB1 receptor antagonists. Generally, polar compounds are poor brain entrants while increasing the lipophilicity enhances brain penetration. Thus, peripherally acting CB1 antagonists can be designed by increasing polar surface area (PSA) and lowering the lipophilicity of the molecules. Hence, development of peripherally acting CB1 antagonists could be a new hope in the treatment of obesity. With the help of molecular modeling, designing of peripherally acting selective CB1 receptor antagonists could be achieved. Modeling studies can suggest the essential structural features required for any compound to exhibit biological activity on the basis of ligand-receptor interaction studies.

1,5-Diaryl pyrazole scaffold has been widely explored for the designing of CB1 receptor antagonists. Rimonabant also contained the same scaffold. After the withdrawl of rimonabant, researchers thought logically to use this already established 1,5-diaryl pyrazole scaffold for the designing of peripherally acting CB1 receptor antagonists. Several reports have appeared in this direction but till date there is no report of 3D-QSAR (CoMFA/CoMSIA) modeling studies using 1,5-diaryl pyrazole containing peripherally acting CB1 receptor antagonists which could identify the structural features required for the peripherally acting compounds. So, development of 3D-QSAR (CoMFA/CoMSIA) models for 1,5-diaryl pyrazole containing compounds could be very useful for the designing of peripherally acting CB1 receptor antagonists.

Along with 1,5-diaryl pyrazole scaffold, some other scaffolds were also reported in the literature showing peripheral CB1 receptor antagonistic activity. So, it was thought to determine the common pharmacophoric features of all these scaffolds for CB1 receptor antagonist activity. The common pharmacophoric features could be used for the designing of peripherally acting CB1 receptor antagonists.

In the literature, it was found that researchers have already worked on the possible scaffolds which could show CB1 receptor antagonistic activity. But unfortunately not even a single compound has been approved as anti-obesity agent till date except rimonabant. So, there is a need to explore new scaffolds which could offer compounds with peripheral CB1 receptor antagonistic activity. This exercise can be tried through virtual screening. Virtual screening can give us some un-explored scaffolds which might offer potential hits as peripherally acting CB1 receptor antagonists.

The newer hits so obtained through virtual screening can be optimized by the molecular modeling techniques. Different types of groups can be introduced into the selected hits which could result into compounds that would have higher PSA and lower lipophilicity. The designed compounds could be synthesized and evaluated for the biological activity.

Thus, the broader aims and objectives of the study are as given below:

1. To determine structural requirements for the peripherally acting 1,5-diaryl pyrazole containing CB1 receptor antagonists used for the treatment of obesity by 3D-QSAR (CoMFA/CoMSIA) studies. The best developed 3D-QSAR model would be used for the designing of some newer compounds having better activity and properties.
2. Development of pharmacophore models and 3D-QSAR (atom-based) models using different scaffolds for the identification of the essential features responsible for CB1 receptor antagonistic activity.
3. To perform virtual screening for the identification of novel scaffolds by using different filters like pharmacophore model, 3D-QSAR (atom-based), molecular docking, Lipinski's rule of five, CNS score and receptor-ligand interactions.
4. Hit optimization through molecular modeling techniques, and synthesis and characterizations of the designed compounds.
5. Pharmacological evaluation/screening of the synthesized compounds as peripherally acting CB1 receptor antagonists for potential treatment of obesity.