Chapter-10

Summary

Chapter-1 deals with the introduction of related to adenosine, adenosine receptors and various classes of adenosine receptor ligands. The adenosine receptors have been a well-explored field of research over the years. The therapeutic potential that is on offer by being able to manipulate these receptors is immense because the distribution of the receptors is so wide-spread in the physiological system. As there is great and extensive roles of adenosine receptor subtypes in both physiological and pathophysiological events, these receptors are becoming important drug targets in the treatment of a variety of diseases like cardiovascular disorders (A\textsubscript{1} adenosine receptor antagonist), Parkinson disease (A\textsubscript{2A} adenosine receptor antagonist), inflammation (A\textsubscript{2B}/A\textsubscript{3} adenosine receptor antagonist) etc. With all the studies it has emerged that adenosine receptors can be safely targeted by various ligands and various highly specific agonists and antagonists of adenosine receptors can be generated. As a result, increasing numbers of clinical trials testing of novel molecules in various indications have been initiated during the past decade.

Chapter-2 deals with rationale behind the molecules designed in the work. Fragment based drug design approach was used for the design of molecule. Considering the good affinity of the two fragments 2-aminothiazole and 2-aminothiophene towards adenosine receptors, they were clubbed into one molecule for the design of the molecule. Further modification of the design was done to come up at good adenosine receptor antagonists. Novel synthetic methodology was also developed for the synthesis of new 2-amino 1,3,4-thiadiazines and 2-cyclicamino 1,3,4-thiadiazines.

Chapter-3 deals with the validation study of the designed thiophenyl-thiazole carboxamides by docking study. After docking validation, series of thiophenyl-thiazole carboxamides were synthesized and the synthetic methodology was further converted modified into one-pot synthetic methodology. Library of molecules were synthesized and all the molecules were tested into radio ligand binding assay for adenosine receptors.
Most of the molecules were found to show affinity towards adenosine receptors particularly towards $A_3$ adenosine receptor. Particularly the molecules PMCDP-3, PMCDP-4, PMCDP-12 and PMCDP-19 showed good affinity towards $A_1$, $A_{2A}$ and $A_3$ adenosine receptor subtypes. From this the molecules PMCDP-3, PMCDP-4 and PMCDP-19 were selective towards $A_3$ adenosine receptor (Figure 10.1).

![Active and selective adenosine receptor thiophenyl-thiazole carboxamides](image)

Figure 10.1: Active and selective adenosine receptor thiophenyl-thiazole carboxamides

In the chapter 4 we have modified the previous series of molecule in to $N$-cycloamino/disubstituted/diamino thiazoles coupled with thiophenes. Library of compounds were synthesized and all the molecules were tested into radio ligand binding assay for adenosine receptors. The molecules were found to show moderate to good activity. The compounds PMCDP-24, PMCDP-29 and PMCDP-41 found to show affinity towards $A_1$, $A_{2A}$ and $A_3$ adenosine receptors. PMCDP-29 was nonselective whereas PMCDP-24 and PMCDP-41 were selective towards $A_3$ adenosine receptor. From SAR it was found that the molecules with 4th position phenyl or furyl group were found to be active where as the molecules with 4th position hydrogen was found to deleterious in the activity against adenosine receptors (Figure 10.2).
In the Chapter-5 we modified our design from thiophenyl-thiazole carboxamides into thiophenyl-thiophene carboxamides for adenosine receptors. The substituted 2-chloroacetamido thiophene derivatives were coupled with wilgerodt kindler substituted 1-morpholino-2-arylprop-2-ene-1-thione adducts to generate library of thiophenyl-thiophene carboxamide derivatives. The compounds were characterized and they were screened for radio ligand binding assay for adenosine receptors. Particularly the compounds PMCDP-BTP-4, PMCDP-BTP-8 and PMCDP-BTP-13 found to show affinity towards A1, A2A and A3 adenosine receptors. The compound PMCDP-BTP-13 was non selective whereas the compounds PMCDP-BTP-4 and PMCDP-BTP-8 were selective towards A3 adenosine receptor (Figure 10.3).

Chapter-6 discusses the synthesis novel di/tri substituted N-cyclicamino thiazoles and their biological activity against adenosine receptor. Here we designed new N-cyclicamino
thiazole based on our previous active trisubstituted \( N \)-cyclicamino thiophenes. The new disubstituted thaizoles were synthesized by new route of synthesis. These molecules were further confirmed by various spectral techniques and they were further evaluated for their binding affinity against adenosine receptor. The molecules PMCDP-TZA9 PMCDP-TZ\( 14 \) and PMCDP-TZA16 were found to be active. Here the molecule PMCDP-TZA14 was the most selective molecule against \( A_3 \) adenosine receptor, where as PMCDP-TZA16 was the most active compound with good affinity towards \( A_1 \), \( A_{2A} \) and \( A_3 \) adenosine receptors (Figure 10.4).

![Figure 10.4: Active and selective \( N \)-cyclicamino thiazoles against adenosine receptor](image)

In the Chapter-7 we discussed the design, synthesis and biological activity of new substituted 2-aminothiazoles for adenosine receptors. Based on novartis molecule and our published active molecules against adenosine receptors here we have synthesized new substituted 2-aminothiazoles. The molecules were further confirmed by various spectral techniques and they were further evaluated for their binding affinity against adenosine receptor. This series of molecules were found to be high affinity and selectivity towards adenosine receptors. Particularly the molecules PMCDP-TZ\( B2 \), PMCDP-TZ\( B7 \), PMCDP-TZ\( B16 \), PMCDP-TZ\( B21 \) and PMCDP-TZ\( B22 \) were active in low nanomolar range. The molecules PMCDP-TZ\( B2 \) and PMCDP-TZ\( B22 \) were nonselective whereas the molecules PMCDP-TZ\( B7 \) and PMCDP-TZ\( B16 \) were selective in \( A_3 \); PMCDP-TZ\( B21 \) was selective in \( A_1 \) adenosine receptor. Docking study of the two most active molecules PMCDP-TZ\( B2 \) and PMCDP-TZ\( B22 \) was carried out with \( A_{2A} \) and \( A_3 \).
adenosine receptors respectively to see the possible interaction and the analysis of the
docking justified the biological activity of the two molecules (Figure 10.5).

Figure 10.5: Active and selective 2-amino thiazoles against adenosine receptor

The Chapter-8 deals with the 3D QSAR study of the active molecules against the A_1,
A_2A and A_3 receptor subtypes. The active molecules were taken from the chapter-3, 4, 6
and 7 and aminothiazole was taken as core for alignment. CoMFA was performed and all
the statistical parameters were found to be within the range for good QSAR model. The q^2
and r^2 for a) the A_1: 0.55 & 0.98 respectively, b) the A_2A: 0.45 & 0.96 respectively and
c) the A_3: 0.50 & 0.98 respectively. The CoMFA study generated steric and electrostatic
contour maps which were further analyzed.

Chapter-9 discusses the novel synthetic methodology for the synthesis of new
1,3,4-thiadiazines. Here we report novel synthetic methodology has been developed for
the synthesis of substituted 2-amino 1,3,4-thiadiazines and 2-cycloamino 1,3,4-
thiadiazines from various substituted thiosemicarbazide derivatives and phenacyl bromides (Figure 10.6).

Figure 10.6 : Novel synthetic methodology for the 2-amino/cyclicamino thiadiazines

Overall conclusion of the present work:

- In search of potential antagonist for adenosine receptors here we have adopted a fragment based drug design approach for the design of the new compounds. The designed molecule was further validated with the molecular docking study.
- Synthetic methodology was developed and library of compounds with structural diversification was synthesized from various starting materials. Further all the molecules were characterized by spectral techniques like NMR and Mass.
- All the molecules were screened for their binding affinity to the adenosine receptor subtypes and the molecules were found to be selective and active. Particularly 2-aminothiazoles series were active in low nanomolar range.
- 3D QSAR study of adenosine receptor ligands shown a statistically significant result which is helpful for further modification.
- In conclusion here we are proposing the pharmacophore for lead optimization (Figure 10.7). This suggested that near A, a lipophilic feature with hydrogen-bond donor and acceptor groups like nitrogen heterocycle with an amino function is favourable for better activity. Near B, a bulky and highly lipophilic pi excessive feature such as phenyl ring is favourable. And near C, a lipophilic feature with hydrogen-bond donor and acceptor groups like nitrogen heterocycle with an amino function is favoured.
Figure 10.7: Proposed pharmacophore for lead optimization

**Future Prospects**

- The molecules developed here are the new chemical entity (NCEs) for adenosine receptors.
- Selective and active adenosine receptor antagonist can screened *in vivo* in various diseases like like asthma, parkinson’s disease, alzheimer’s disease, cancer and cardiovascular diseases.
- The molecules can be chemically manipulated to make novel compounds which can be further checked for various biological activities.
- The novel molecules are also having importance as novel synthons.