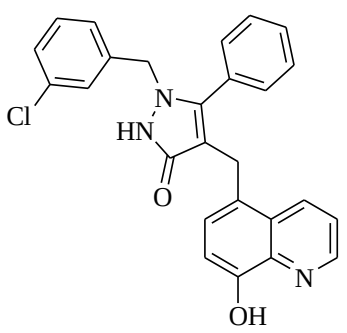
6. Conclusion

In an effort to design and develop novel therapeutics for Alzheimer's disease, derivatives based on 8-hydroxyquinoline-pyrazolone **(66-121)** and 8-hydroxyquinoline-pyrimidinone **(122-150)** scaffolds were synthesized and evaluated for their anti-Alzheimer's activity. The goal was to develop compounds that could potentially inhibit cholinesterase (ChEs) and monoamine oxidase B (MAO-B), key enzymes involved in Alzheimer's pathology. The presence of nitrogen-containing pyrazolone, pyrimidinone, and quinoline heterocycles in these compounds was intended to control their basicity, which could facilitate blood-brain barrier (BBB) penetration. Among the synthesized compounds, several compounds exhibited dual inhibition, indicating their potential for multi-target therapy. Compound **83** demonstrated moderate inhibition of both **AChE (50.9%)** and **MAO-B (38.66%)**, while compound **72** also showed dual activity against **AChE (51.4%)** and **MAO-B (31.2%)**. Compound **102** displayed significant dual inhibition of **AChE (68.7%)** and **MAO-B (80.34%)**, highlighting its potential for multi-target applications. Compound **107** combined strong **MAO-B** inhibition **(99.22%)** with moderate **AChE** activity **(56.4%)**, whereas compound **105** showed a balanced inhibitory profile against **AChE (67.2%)** and **MAO-B (69.58%)**. Compound **100** was notable for its moderate dual inhibition of **AChE (42.7%)** and **BuChE (44.9%)**, while compound **149** exhibited dual activity against **AChE (48%)** and **MAO-B (70.43%)**, suggesting its potential applicability in multi-target approaches. In contrast, compound **138** demonstrated high selectivity for **MAO-B (100%)**, whereas compound **150** displayed weak dual inhibition of **AChE (35%)** and **BuChE (30%)**.

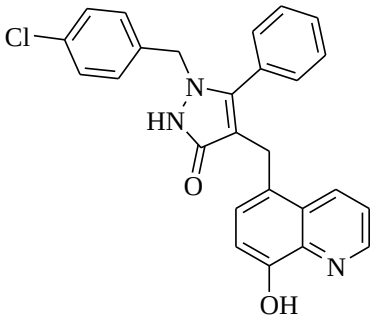
Among all the synthesized compounds, four most effective compounds **(106, 107, 118** and **138)** selected for IC_{50} analysis. Compound **(118)** was the most potent, showing an IC_{50} value of **15.11 ± 8.41 nM**. Compounds **(106)** and **(107)** also exhibited significant activity, with IC_{50} values of **26.23 ± 10.56 nM** and **16.02 ± 4.48 nM**, respectively **(Figure 6.1)**. Additionally, compound **(75)** from this series displayed strong BuChE inhibitory activity, achieving **94.07 ± 0.19** % inhibition.

Among the pyrimidinone based series, compound **(138)** exhibited the strongest MAO-B inhibitory activity, with an IC_{50} value of **19.14 ± 11.21 nM (Figure 6.1)**. Other compounds in the series demonstrated good to moderate levels of activity. Additionally, Compound **(118)**

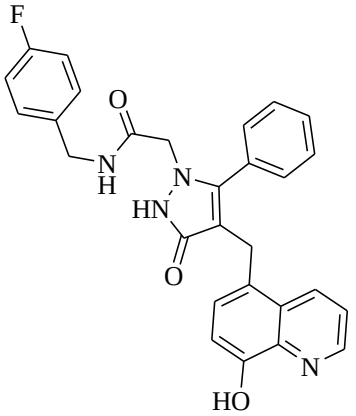
was found to possess best antioxidant property with % radical scavenging of **5.19%** and metal chelating activity with **21.39 ± 4.30 %** at 10 µM.



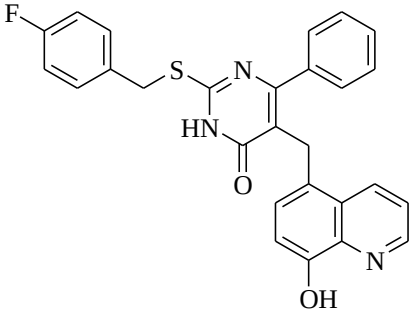
(106)
IC_{50}= 26.23 ± 10.56 nM;



(107)
IC_{50}= 16.02 ± 4.48 nM;



(118)
IC_{50}= 15.11 ± 8.41 nM;
%MCA = 21.39 ± 4.30 %;
%RSA = 5.191 ± 1.205 %;



(138)
IC_{50}= 19.14 ± 11.21 nM;

Figure 6.1: IC_{50} against MAO-B inhibition of most active compounds **(106, 107, 118** and **138).**

Moreover, all the active compounds showed strong binding interactions with the active sites of both AChE and MAO-B enzymes. In conclusion, the 8-hydroxyquinoline-pyrazolone and 8-hydroxyquinoline-pyrimidinone based compounds have demonstrated potential as lead molecules and should be further explored for development as small molecule therapies for Alzheimer's disease.