3. Objectives and plan of work

3.1. Importance of proposed research investigation

- Fused pyrimidines have potential application in several therapeutic areas which include oncology as potentiators of antimetabolic agents. Synthetic studies of fused pyrimidines have been documented extensively because of their structural diversity and association with a wide spectrum of biological activities.

- Although 5-flourouracil was introduced into the anticancer chemotherapy in 1958, it is still the gold standard in colorectal cancer treatment. But, different types of cancer either did not respond to 5-florouracil or developed resistance to it. Because of the cytotoxic effect of rapidly proliferating tissues, the drug frequently causes myelosuppression with a risk of hemorrhage, gastrointestinal toxicity, bone marrow suppression, head ache, somnolence and dermatitis. Significant increases in survival will occur only when the selectivity of present day anticancer agents can be increased or new class of more selective agents can be discovered. Therefore, there is a insistent need to design novel analogues as potential TS and DHFR inhibitors and as anticancer agents.

- The folate analogues with a 6-5 fused ring system could bind to folate related enzymes and it could explain the inhibitory effects of the aimed compounds against TS and DHFR.

- Pyrimidopyridine derivatives increase the cytotoxicity and reduce its own toxicity.

- The prepared schemes includes, simpler methodology like, microwave irradiation. Therefore, it is very time saving. Moreover, these processes consist of only a few steps by making use of easily available chemicals at lesser cost.
In view of variegated importance associated with these compounds, it was thought worthwhile to synthesis a series of structurally novel and potentially very important anticancer and antiinflammatory agents.

3.2. Plan of work

3.2.1. To synthesize fused pyrimidin-4(3H)-ones

3.2.1a. Synthesis of fused benzopyrimidin-4(3H)-ones (BP 1-28)
- 2-(chloromethyl)-3-substituted quinazolin-4(3H)-ones (BP 1-3)
- 2-phenyl-3-substituted quinazolin-4(3H)-ones (BP 4-6)
- 6-chloro-3-substituted-2-phenylquinazolin-4(3H)-ones (BP 7-14)
- 6,7-dimethoxy-2-phenyl-3-substituted quinazolin-4(3H)-ones (BP 15-22)
- 2-(4-fluorophenyl)-3-substituted quinazolin-4(3H)-ones (BP 23-28)

3.2.1b. Synthesis of fused pyridopyrimidin-4(3H)-ones (PP 1-16)
- 2-(chloromethyl)-3-substituted pyrido[2,3-d]pyrimidin-4(3H)-ones (PP 1-8)
- 2-phenyl-3-substituted pyrido[2,3-d]pyrimidin-4(3H)-one (PP 9-16)


3.2.2. To study the physical characteristics of the synthesized compounds

3.2.3. To characterize the synthesized compounds by the following spectral analysis
- UV absorption spectroscopy
Objectives and Plan of work...

- Infrared spectroscopy
- $^1$H Nuclear magnetic resonance spectroscopy
- $^{13}$C Nuclear magnetic resonance spectroscopy
- Mass spectroscopy

3.2.4. Docking studies on the following enzymes using MVD docker
- Dihydrofolate reductase inhibition
- Thymidylate synthase inhibition

3.2.5. Biological evaluation
- *In vitro* antioxidant activity by DiphenylPicrylhydrazyl radical scavenging method (DPPH$^*$)
- Acute toxicity studies on Wistar rats by up and down staircase method
- *In vivo* antiinflammatory activity by carrageenan induced rat paw oedema model
- *In vitro* anticancer activity
  - MTT assay
  - DNA ladder assay
- Acute toxicity studies on Swiss albino mice by up and down staircase method
- *In vivo* anticancer activity by Liquid tumor model on Ehrlich Ascites Carcinoma cells bearing mice