

PREFACE

The Src homology-2 (SH2) domain-containing phosphatase-2 (SHP2) is the first proto-oncogenic protein tyrosine phosphatase (PTP) mediating carcinogenesis by regulating nearly all the signalling pathways through a kind of “master control”. Several allosteric sites and an orthosteric site have been identified in SHP2. Yet, there is a dearth of clinically approved SHP2 inhibitors due to inherent challenges like the polar nature of the catalytic site and sequence homology between catalytic domains of PTPN paralogues. We have applied pharmacophore-based virtual screening and ligand-guided lead optimization approaches to identify and develop novel heterocyclic pharmacophoric scaffolds bearing 1,3,4-thiadiazole core as small-molecule SHP2 inhibitors and evaluated them pharmacologically.

The present study is divided into five chapters and are as follows.

Chapter 1 initiates a comprehensive exploration of glioblastoma multiforme (GBM) and breast cancer, encompassing their background, pathophysiology, and the current therapeutic landscape. It also deals with SHP2 as a target of GBM and breast cancer and an exhaustive literature review on reported small-molecule SHP2 inhibitory scaffolds and the research objectives.

Chapter 2 deals with virtual screening-guided design, synthesis, and biological evaluation of thioacetamide tethered thiadiazole-1,2,4-triazole hybrids (**STT series**)

Chapter 3 deals with the design, synthesis, and biological evaluation of 5-(substituted phenyl)-1,3,4-thiadiazole-2-amine derived sulphur-linked acetamides (**STS series**)

Chapter 4 deals with the design, synthesis, characterization and biological evaluation of S-acetohydrazones of 5-methyl-1,3,4-thiadiazole-2-thiol (**TEH series**)

Chapter 5 presents the concluding remarks and future prospective

An appendix of additional supporting information, spectral data of representative compounds, and a list of publications from the course of the Ph.D. work are included.