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LIST OF ABBREVIATIONS

Abbreviations	Full forms
Akt	Protein kinase b
BBB	Blood-brain barrier
BCSC	Breast cancer stem cell
C-SH2	C-terminal Src homology-2 domain
DiFMUP	6,8-Difluoro-4-methylumbelliferyl phosphate
DGC	Differentiated glioma cells
DNMT1	DNA (cytosine-5)-methyltransferase 1
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EGFRvIII	Epidermal growth factor receptor variant III
ER	Estrogen receptor
ERK	Extracellular signal-regulated/activated kinase
HER2	Human epidermal growth factor receptor 2
GBM	Glioblastoma multiforme
GOF	Gain-of-function
GRB2	Growth factor receptor-bound protein 2
GSC	Glioma stem cells/GBM stem-like cells
GSH	Glutathione
HIF1α	Hypoxia inducible factor 1 alpha
HIF1αi	HIF1α inhibitors
JAK	Janus kinase
MAPK	Mitogen-activated protein kinase
MEK	mAPK/ERK kinase
MOE	Molecular Operating Environment
mTOR	Mammalian target of rapamycin
N-SH2	N-Terminal Src homology-2 domain
$p21^{Cip1}$	Cyclin-dependent kinase interacting protein 1
p53	Tumor protein 53

PAINS	Pan assay interference
PARP	Poly-ADP ribose polymerase
PBVS	Pharmacophore based virtual screening
PCa	Prostate cancer
PDK1	Phosphoinositide-dependent kinase-1
PI3K	Phosphoinositide-3-Kinase
PR	Progesterone receptor
PTEN	Phosphatase and tensin homolog
pTyr	Phosphotyrosines
PTP	Protein tyrosine phosphatase
PTPN	Non-receptor protein tyrosine phosphatase
PUMA	p53 upregulated modulator of apoptosis
RAF	Rapidly accelerated fibrosarcoma kinase
RAS	Rat sarcoma small GTPase
RMSD	Root mean square deviation
RTK	Receptor tyrosine kinase
ROS	Reactive oxygen species
SHP2	Src homology-2 (SH2) domain-containing phosphatase-2
STAT3	Signal transducer and activator of transcription 3
TME	Tumor microenvironment
TMZ	Temozolomide
TNBC	Triple negative breast cancer
TPC	Tumor propagating cells
USFDA	United States Food and Drug Administration
VEGF	Vascular endothelial growth factor

LIST OF SYMBOLS

Symbol	Meaning
α	Alpha
β	Beta
Δ	Delta
λ	Lambda
ºC	Degree celsius
Å	Angstrom
mg	milligram
µg	Microgram
µM	Micromolar
mM	Millimolar
mL	Millilitre
µL	Microlitre
h	Hour
nm	Nanometer
ppm	Parts per million
rpm	Revolutions per minute
kcal	Kilocalories
MHz	Megahertz
J	Coupling constant
d	Doublet
t	Triplet
m	Multiplet
dd	Doublet of doublet
m/z	Mass-to-charge ratio
%	Percent
pH	Potential of hydrogen
<	Less than
>	More than
±	Plus, or minus

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.