Molecular Design and Synthesis of Benzoheterocyclic Compounds with Anticipated Anticancer Activity

Thesis

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Synthesis, ADMET Properties, and Biological Evaluation of Benzothiazole Compounds Targeting Chemokine Receptor 2 (CXCR2)

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Herein we describe the synthesis and biological evaluation of a series of novel benzothiazoles based on a diaryl urea scaffold previously reported in some allosteric chemokine receptor 2 (CXCR2) inhibitors. From a library of 41 new compounds, 17 showed significant inhibition of CXCR2, with IC_{50} values less than 10 μM and selectivity over CXCR4. Our ADMET simulations suggest favorable drug-like properties for the active compounds. Importantly, we developed a predictive model that can distinguish active from inactive compounds; this will serve as a valuable tool to guide the design of optimized compounds to be evaluated in preclinical models.

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ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity

Arg: Arginine

Asp: Aspartic acid

BRAK: Breast and Kidney-expressed chemokine

CADD: Computer-aided drug design

cAMP: Cyclic adenosine monophosphate

CF: Cystic fibrosis

COPD: Chronic obstructive pulmonary disease

COX2: Cyclooxygenase 2

CXCL: Chemokine CXC ligand

CXCR: Chemokine CXC receptor

DCM: Dichloromethane

DIPEA: *N*,*N*-Diisopropylethylamine

DMAP: 4-Dimethylaminopyridine

DMB: 2,4-Dimethoxybenzyl

DMF: Dimethylformamide

DMSO: Dimethyl sulfoxide

2D: Two-dimensional

3D: Three-dimensional

ENA-78: Epithelial-derived neutrophil-activating peptide 78

equiv: Equivalent

ESI: Electrospray ionization

EtOAc: Ethyl acetate

FACS: Fluorescence-activated cell sorting

FDA: Food and drug administration

FRET: Fluorescence resonance energy transfer

GA: Genetic algorithm

GCP-2: Granulocyte chemotactic protein 2

Glu: Glutamic acid

GOLD: Genetic Optimization for Ligand Docking

GPCR: G-protein coupled receptor

Gro: Growth-regulated oncogene

GTPase: Guanosine triphosphate hydrolase enzyme

h: Hour

H-bond: Hydrogen bond

HCC: Hepatocellular carcinoma

HIF1α: Hypoxia-inducible factor 1-alpha

HIV: Human immunodeficiency virus

HTS: High throughput screening

^{1}H NMR: Proton Nuclear Magnetic Resonance

IBD: Inflammatory bowel disease

IC_{50}: Half maximal inhibitory concentration

IL-8: Interleukin 8

IP-10: Interferon gamma-induced protein 10

I-TAC: Interferon-inducible T-cell alpha chemoattractant

kDa: Kilodalton

LC/MS: Liquid chromatography–mass spectrometry

Leu: Leucine

LPS: Lipopolysaccharide

MAPK: Mitogen-activated protein kinase

MHz: Mega hertz

Mig: Monokine induced by gamma interferon

min: Minute

mL: Milliliter

mmol: Millimole

MS: Mass spectrometry

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide

m/z: Mass-to-charge ratio

µM: Micromole

NAP-2: Neutrophil activating peptide 2

NEAA: Nonessential amino acids

NF-κB: Nuclear factor-κB

NMR: Nuclear magnetic resonance

nm: Nanometer

nM: Nanomole

PDB: Protein data bank

Pd-C: Palladium on carbon

PDGF: platelet-derived growth factor receptor

PF-4: Platelet factor 4

PI3K: Phosphoinositide 3-kinase

PLC: Phospholipase C

PMB: p-Methoxybenzyl

ppm: Part per million

t_R: Retention time

Raf : Rapidly growing fibrosarcoma

ROCS: Rapid Overlay of Chemical Structures

SDF-1: Stromal cell-derived factor 1

STAT3: Signal transducer and activator of transcription 3

TEA: Triethylamine

THF: Tetrahydrofuran

TLC: Thin-layer chromatography

Tyr: Tyrosine

UV: Ultraviolet

VEGF: Vascular endothelial growth factor

WHO: World Health Organization

Abstract

Cancer is a term for a wide scope of diseases that can affect any part of the body. Other terms used are malignant tumors and neoplasms. One distinctive attribute of cancer is the expeditious formation of aberrant cells that grow beyond their usual boundaries, and which can then invade neighboring parts of the body and spread to other organs, the latter process is recognized as metastasizing. Metastasis is a significant cause of death from cancer.

Recently, multiple studies indicate that CXCR2 and its associated ligands have universally important roles in cancer cell biology and that CXCR2 inhibition offers a promising therapeutic avenue for a number of different diseases, including cancer.

In this study, guided by SAR studies and molecular modeling, two new series of diaryl urea compounds based on a benzothiazole scaffold were designed and synthesized.

The synthesized compounds were purified and structurally confirmed by different analytical and spectral techniques.

In vitro characterization and SAR analysis to assess selectivity of the compounds for CXCR2 over CXCR4 was accomplished using a Tango assay.

Out of 41 compounds, 17 showed significant inhibition of CXCR2 with IC_{50} values less than 10 μM and selectivity against CXCR2 over CXCR4.

Finally, a thorough molecular docking studies were performed using the GOLD (Genetic Optimization for Ligand Docking) software package, version 5.2. Morever, ADMET properties and associated risk values were calculated using ADMET Predictor 8.0 from Simulation Plus, Inc.

The synthesized compounds have reasonable calculated ADMET properties and are suitable candidates for further optimization.