Design and Synthesis of Small Organic Molecules having Potential Biological Activity

Thesis Presented by

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Click and Release: SO_2 Prodrugs with Tunable Release Rates

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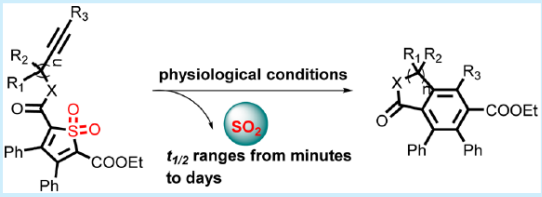
Supporting Information

ABSTRACT: Employing an intramolecular cycloaddition reaction, we have developed a series of SO_2 prodrugs with tunable release rates with half-lives ranging from minutes to days.



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List of Abbreviation

3-MST	3-Mercaptopyruvate sulfurtransferase
AC	Adenylyl cyclase
Akt	Protein kinase B (PKB), also known as Akt
ATP	Adenosine triphosphate
bax	Apoptosis regulator BAX, also known as bcl-2-like protein
Bcl-2	(B-cell lymphoma 2
BCN	Bicyclo-[6.1.0]nonyne
BH4	6R-5,6,7,8-Tetrahydro-L-biopterin
BK_{Ca}	Big-conductance calcium sensitive K channels
Boc	Tert-butyloxycarbonyl
BTS	Benzothiazole sulfinate
cAMP	Cyclic adenosine monophosphate
cAMP	3′–5′-cyclic adenosine monophosphate;
CAT	Cysteine aminotransferase
CBS	Cystathionine-β- synthase
CDO	Cysteine dioxygenase
cGMP	Cyclic guanosine monophosphate
CL	Cysteine lyase
CO-RM	Carbon monoxide releasing molecules
c-Raf	Rapidly accelerated fibrosarcoma (isoform c)
CSE	Cystathionine-γ- lyase
CVDs	Cardiovascular diseases
DAPI	4',6-Diamidino-2-phenylindole
DAR_{INV}	Inverse electron Demand Diel Alders reaction
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DCU	Dicyclohexylurea
DI	Deionized
DIC	N,N'-Diisopropylcarbodimide
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMD	Dimethyl dioxirane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DTNB	5,5′-Dithiobis(2-nitrobenzoic acid)
EDC	N-Ethyl-N'- (3-dimethylaminopropyl)carbodiimide
EDRF	Endothelium-derived relaxing factor

eNOS	Endothelial nitric oxide synthase
EPC	Endothelial progenitor cells
Erk/MAPK	Extracellular signal-regulated kinases/mitogen-activated protein kinase
Et_3N	Triethylamine
ET-CO-RMs	Enzyme triggered carbon monoxide releasing molecules
Fmoc	Fluorenylmethyloxycarbonyl
GSH	Reduced glutathione
GSH- Px	Glutathione peroxidase
GSSG	Oxidized glutathione
GTP	Guanosine triphosphate
HIF1α	Hypoxia-inducible factor 1α
HL-60	Human promyelocytic leukemia cells
HO-1	Heme oxygenase-1
HOAt	Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
HOMO	Highest occupied molecular orbital
HONB	Hydroxy-5-norbornene-endo-2,3-dicarboxyimide
HPLC	High performance liquid chromatography
HRMS (ESI)	High resolution mass spectrometry (electron spray ionization)
IBD	Inflammatory bowel diseases
ICAM-1	Intercellular Adhesion Molecule 1, also known as Cluster of Differentiation 54
IK_{Ca}	Intermediate-conductance calcium sensitive K channels
IL	Interleukin
iNOS	Inducable Nitric Oxide Synthase
LPS	Lipopolysaccharide
LUMO	Lowest unoccupied molecular orbital
mCPBA	m-Chloroperbenzoic acid
MeCN	Acetonitrile
MEK-1	Mitogen-activated protein kinase 1
MERK	Extracellular signal-regulated kinases
MOPS	(3-(N-morpholino)propanesulfonic acid
MPO	Myeloperoxidase
MPTP	Mitochondrial permeability transition pore
MSBT	Methyl sulfonyl benzothiazole
NADPH	Nicotinamide-adenine-dinucleotide phosphate
NBS	N-bromosuccinimide
NF-E2	Nuclear factor erythroid 2 related factor 2
NF-κB	Nuclear factor κB;

NHS	N-hydroxy succinimde
NMR	Nuclear magnetic resonance
nNOS	Neuronal Nitric Oxide Synthase
NOS	Nitric Oxide Synthase
Nrf-2	Nuclear factor (erythroid-derived 2)-like 2, also known as NFE2L2 or Nrf2,
NSAID	Non-steroidal anti-inflammatory drug
PBS	Phosphate buffered saline
PDE-5	Phosphodiesterase-5
PDGF-BB	Platelet-derived growth factor (PDGF)- BETA BETA CHAIN
PFP	Pentafluorophenol
pERK,	Phosphorylated ERK
PGI_2	Prostacyclin
PI3K	Phosphatidylinositol 3-kinase
PK	Protein kinase
PNP	p-nitrophenol
Ppm	Part per million
RM	Releasing molecules
sGC	Soluble guanyl cyclase
SH,	Thiol
SK_{Ca}	Small-conductance calcium sensitive K channels
SMC	Smooth muscle cells
SNP	Sodium nitroprusside
SO	Sulfite oxidase
SOD	Superoxide dismutase
SSH	Hydropersulfide
STAT3	Signal transducer and activator of transcription 3
$t_{1/2}$	Half life
TAE	Trisaminomethane, acetic acid, EDTA buffer system
TFA	Trifloroacetic acid
THF	Tetrahydrofuran
TIMP1	Tissue inhibitor of metalloproteinases 1
TPCPD	Tetraphenylcyclopentadiene-1-one
Tris–Cl	Trisaminomethane or THAM $(HOCH_2)_3CNH_2$
TRVP	Transient receptor potential vanilloid
TsCl	Tosyl chloride
TSMT	Thiol S-methyltransferase.
UV-Vis	Ultraviolet -Visible
VEGF	Vascular endothelial growth factor
VSMC	Vascular smooth muscle cells

Abstract

Signaling molecules come in all sizes and chemical dispositions, ranging from relatively large proteins, lipids, and peptides through biogenic amines and amino acids, to gaseous molecules. Endogenously generated gaseous molecules involved in signaling process are called "Gasotransmitters". Gasotransmitters are endogenously generated in mammalian cells with specific substrates and enzymes; their production is regulated to fulfill signaling messenger functions. They are involved in signal transduction and have specific cellular and molecular targets. Nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S) are powerful signaling molecules that play a variety of roles in mammalian biology. Recently, cumulative evidences present sulfur dioxide (SO_2) as another potential gasotransmitters.

SO_2 is a lipid soluble, membrane permeable gas molecule. SO_2 can be generated endogenously during the metabolism of sulfur-containing amino acids such as L-cysteine. Endogenous SO_2 was reported to exert a negative regulation on vascular smooth muscle cell proliferation by suppressing the Erk/MAPK pathway. Its sulfite and bisulfite derivatives also showed endothelium-independent vasorelaxation effect partially by the PGI (2)-AC-cAMP-PKA signal pathway. In addition to its physiological effects in the cardiovascular system, SO_2 also showed potentials as a therapeutic agent with a variety of pathophysiological effects, including anti-hypertensive, anti-atherosclerotic, anti-oxidative, and anti-mycobacterial effects, as well as protective effects against cardiac ischemia-reperfusion (I/R) injury.

Different investigations are required to explore the potentials of SO_2 as gasotransmitter. These investigations include: exploration of the difference between the toxic and therapeutic effects of SO_2, expanding the knowledge of physiological and therapeutic effects of SO_2 in different organs and systems, studying the possible interactions between SO_2 and other gasotransmitters and exploration of the therapeutic potential of new SO_2 donors and their possible clinical utilization. Since most the biological effects observed for SO_2 was obtained by using gaseous SO_2 or its sulfite and bisulfite (3:1) derivatives. Neither of these methods could provide controlled release of SO_2 to imitate the process of endogenous production of SO_2. Thus, there is a need for the development of prodrugs or SO_2 donors that can controllably release SO_2 under