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Mini-Review

Recent Progress in Synthetic and Natural Catechol-*O*-methyltransferase Inhibitors for Neurological Disorders

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Cite This: https://doi.org/10.1021/acsomega.4c06190

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ABSTRACT: Catechol-*O*-methyltransferase (COMT) inhibitors have played a crucial role in the development of potent and selective drugs for the treatment of Parkinson's disease, depression, and anxiety disorders. This review provides a comprehensive analysis of the structure−activity relationship (SAR) of COMT inhibitors, highlighting key structural features and pharmacophoric elements that govern their potency, selectivity, and pharmacokinetic properties. This review also discusses the application of SAR principles in the design and optimization of COMT inhibitors. Our analysis reveals the emergence of novel chemical scaffolds and the potential for COMT inhibitors to address unmet medical needs in neurology and psychiatry. This Perspective serves as a valuable resource for clinicians and researchers, providing insights into the rational design of COMT inhibitors and the development of next-generation therapeutics.

1. INTRODUCTION

Catechol-*O*-methyltransferase (COMT) is a divalent magnesium (Mg^{2+}) dependent enzyme that catalyzes the transfer of a methyl group to catechol substrates by using *S*-adenosyl-L-methionine (SAM) as a methyl donor, producing *O*-methylated catechol and *S*-adenosyl-L-homocysteine as reaction products.[1] Both endogenous and exogenous neurotransmitters, such as epinephrine, noradrenaline, and dopamine, as well as levodopa, the metabolic precursor of dopamine, are examples of COMT substrates.[2] The physiological actions of neurotransmitters are terminated by COMT metabolism, which makes this enzyme relevant for therapeutic purposes. Many central and peripheral nervous system disorders, such as Parkinson's disease (PD), depression, schizophrenia, and other diseases linked to dopamine deficiency, can be treated with drugs that target COMT.[3]

COMT exists in two isoforms that are expressed from two promoters: the membrane-bound form, MB-COMT, which is more frequently found in the brain, and the soluble S-COMT isoform, which is expressed in most tissues, including the liver, blood, and kidneys.[4] MB-COMT is particularly noteworthy to investigate as a target due to its function in controlling extracellular dopamine levels inside the prefrontal cortex.[5] The COMT gene is located on chromosome 22q11.2 and is 27.22 kb long.[6] The 158th amino acid residue of the membrane-bound isoform (or the 108th amino acid of the soluble form) is changed from valine (Val) to methionine (Met) by a frequent nonsynonymous single-nucleotide polymorphism (rs4680). Because the Met variant is more thermolabile at physiological temperature, its presence causes a 4-fold decrease in COMT enzyme activity levels in the prefrontal cortex.[7] There are several crystal structures available for COMTs in rats and humans. Both the human and rat COMTs (Figure 1) are members of the highly structurally conserved SAM-dependent methyltransferase fold family, and they have 81% sequence

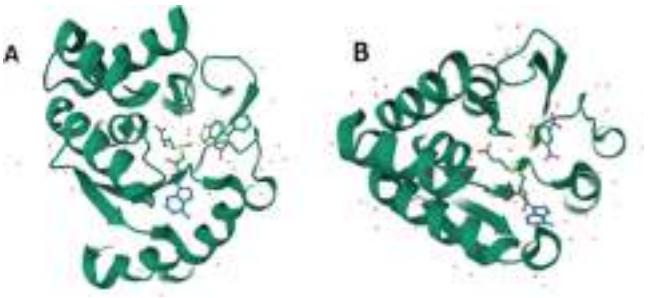

Figure 1. (A) Crystal structure of rat COMT in complex with *S*-adenosyl-methionine (SAM), dinitrocatechol (DNC), and Mg^{2+}. (B) Crystal structure of human COMT in complex with *S*-adenosyl-methionine (SAM), 7,8-dihydroxy-4-phenyl-2*H*-chromen-2-one, and Mg^{2+}.

Received: July 4, 2024
Revised: October 3, 2024
Accepted: October 11, 2024