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

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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.
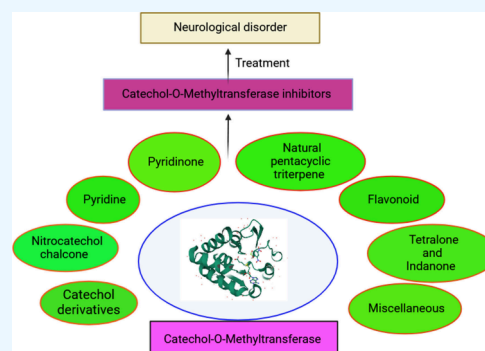
1. INTRODUCTION

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
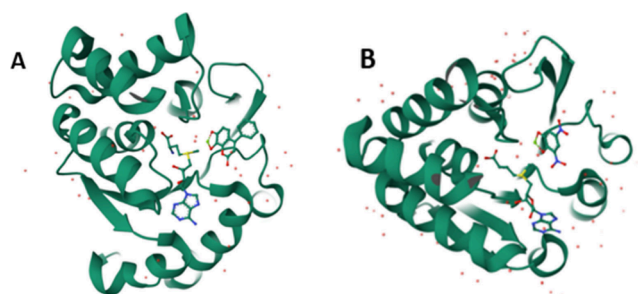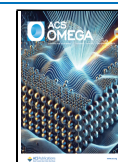

Figure 1. (A) Crystal structure of rat COMT in complex with *S*-adenosyl-methionine (SAM), dinitrocatechol (DNC), and Mg^{2+}. (B) Crystal structure of human COMT in complex with *S*-adenosyl-methionine (SAM), 7,8-dihydroxy-4-phenyl-2*H*-chromen-2-one, and Mg^{2+}.
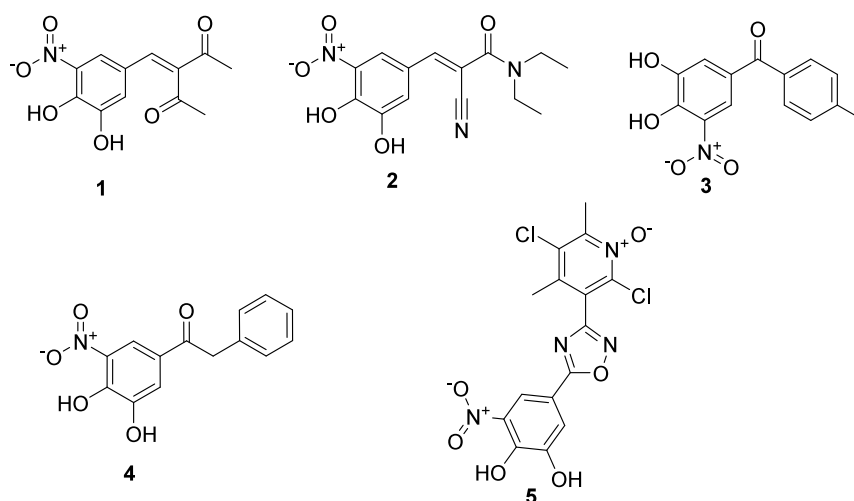
Figure 2. Structures of clinically used COMT inhibitors: nitecapone (**1**), entacapone (**2**), tolcapone (**3**), nebicapone (**4**), and opicapone (**5**).

similarity.[8] Specifically, the COMT enzyme is made up of two sets of α-helices (helices $\alpha1-\alpha5$ on one side and helices $\alpha6-\alpha8$ on the other) sandwiched around a seven-stranded β-sheet core (ordered in an order of 3, 2, 1, 4, 5, 7, 6). Strand 7 is antiparallel to the others in the β-sheet. Along the first half of the core β-sheet ($\beta1-\beta4$), the cofactor SAM interacts with conserved residues.[9] E90 ($\beta2$) makes hydrogen bonds with SAM's ribose hydroxyl groups. SAM's adenine ring interacts via van der Waals interactions with residues I91 ($\beta2$), A118 ($\beta3-\alpha6$ loop), and W143 ($\beta4-\alpha7$ loop) and forms hydrogen bonds with S119 and Q120 ($\alpha6$). The coordination of methionine in SAM is achieved through hydrophobic contacts with M40, V42, and Y68, and hydrogen bonds with residues V42 ($\alpha2-\alpha3$ loop), S72 ($\alpha4$), and D141 ($\beta4$). The methyl group (CH_3) of the SAM methionine sulfur atom is orientated toward the substrate binding site, more precisely toward the catechol oxygen atom that has to be methylated. The "gatekeeper" residues W38 and P174, together with M40, L198, and W143, define the shallow pocket that serves as the substrate-binding site. All of these residues being hydrophobic implies that van der Waals interactions are the primary mechanisms underlying ligand binding. Every single crystal structure of COMT complexed with a ligand contains the magnesium ion (Mg^{2+}), a cofactor essential for methylation.[10] The side chains of D141, D169, and N170, the two hydroxyl groups of the catechol substrate, and a water molecule all work together to coordinate the Mg^{2+} ion octahedrally in the active site. This is unambiguous evidence that Mg^{2+} aids in the enzymatic activity by making the substrate more soluble. This explains why the ion is necessary for catalysis mediated by COMT. It is noteworthy that the pK_a of the catechol hydroxyl is lowered by the Mg^{2+} ion, causing it to be more ionized.[11] In general, human COMT has lower K_m (Michaelis constant) values for catechol substrate methylation than rat COMT.[12] An analysis comparing the human and rat active sites explains why the K_m values of these two proteins and other kinetic characteristics differ. Human COMT has shorter Mg^{2+} ligand distances in its crystal structure than rat COMT, suggesting that substrate binding is more robust (lower K_m value) in the human protein.[9] The majority of residues in the sites are identical, though three residues are found to differ in the SAM binding sites of these two proteins: M89, M91, and Y95 in the rat protein and I89, I91, and C95 in the human protein. In

comparison to the human protein, the rat protein residues are larger and interact with SAM more intimately. Additionally, two changes in charge (R201 and E202 in humans compared to M201 and K202 in rats) are present at the substrate-binding site. It seems unlikely that the two residues will interact directly with the substrate. However, because of their position at the pocket entry, they might have an impact on V_{max} in addition to substrate binding and release.

Several COMT inhibitors have been developed to treat neurodegenerative disorders to date. The early developed COMT inhibitors, often referred to as "first-generation" inhibitors, inhibited COMT from extending the physiological action of endogenous neurotransmitters, albeit their effectiveness on noradrenergic, adrenergic, and dopaminergic pathways was limited.[13] The derivatives of pyrogallol and catechols, such as gallic acid, caffeic acid, U-0521, 2-hydroxy estrogens, or flavonoids like quercetin or rutin are examples of first-generation COMT inhibitors. Moreover, it was questioned how "first-generation" COMT inhibitors affected the inactivation of neurotransmitters at receptor sites. During the 1970s, there was escalating interest in COMT following the discovery that the enzyme was involved in the metabolic breakdown of the popular antiparkinsonian medication L-DOPA (levodopa). PD is a chronic degenerative neurological disorder caused by the reduction of dopamine levels due to the death of dopaminergic cells in the substantia nigra pars compacta. It is possible to control the levels of this neurotransmitter in the brain by using L-DOPA, a biological precursor of dopamine.[14] L-DOPA's short *in vivo* half-life is one of its main disadvantages, despite its advantageous capacity to regulate dopamine levels in the brain. COMT inhibitors prolong the pharmacological impact of L-DOPA and reduce the therapeutic dose by inhibiting COMT from converting L-DOPA to 3-O-methyl-L-DOPA (3-OMD) in peripheral tissues. In order to target COMT and provide a more continuous and prolonged distribution of dopamine to the striatum, various research groups from academia and the pharmaceutical industry have been working in the last 30 years to optimize L-DOPA therapy. In the process of finding novel COMT inhibitors, "second-generation" inhibitors were discovered, which had better pharmacokinetic characteristics than their "first-generation" predecessors. Second generation inhibitor examples of clinically relevant COMT inhibitors for
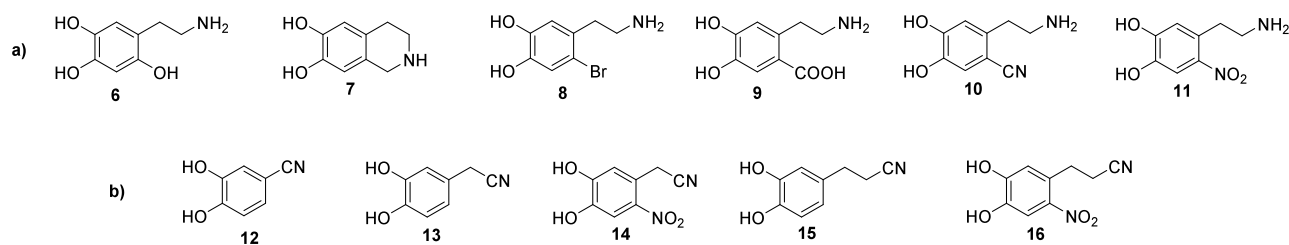
Figure 3. Designed and synthesized (a) dopamine and (b) catechol derivatives.
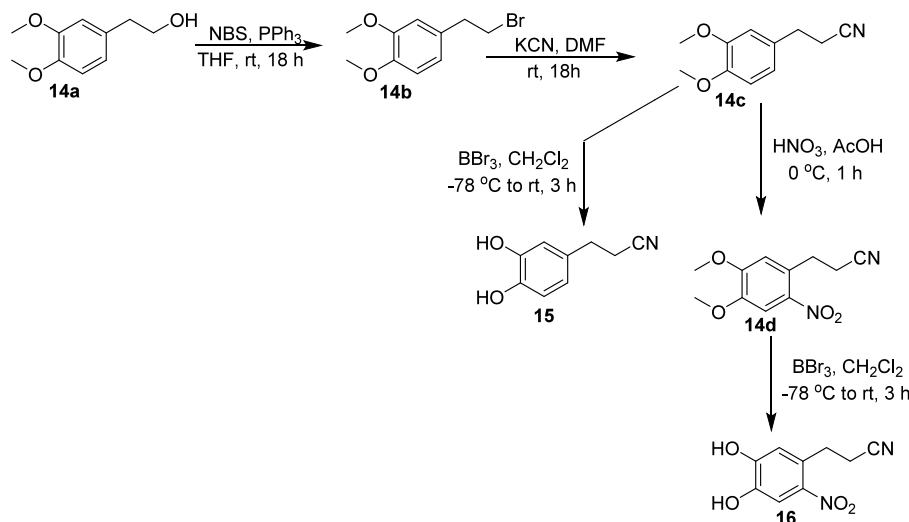
Figure 4. Synthesis of the catechol derivatives.

the adjunctive therapy of Parkinson's disease (PD) are nitecapone **1** (OR-462), entacapone **2** (OR-611), tolcapone **3** (Ro40-7592), and nebicapone **4** (BIA 3-202) (Figure 2), while opicapone **5** (BIA 9-1067) (Figure 2) is an example of a third-generation COMT inhibitor having lower toxicity and higher inhibitory activity. Recently, Akhtar et al. summarized the last 50 years of research on COMT inhibitors from 2019 as a review article.[15] A timely update is necessary for the further design and development of the novel COMT inhibitors. Therefore, in this review, we cover the COMT inhibitors published from 2019 to 2024.

2. COMT INHIBITOR STRUCTURE BASED DESIGN

2.1. Catechol Derivatives. Several FDA-approved drugs, for example, entacapone, as COMT inhibitors for the treatment of Parkinson's disease showed poor performance due to various pharmacokinetic and pharmacodynamics reasons such as their low bioavailability and low metabolic stability that have resulted in increased and repeated doses throughout the day. Also, some side effects, such as hepatitis, make therapy less efficient. Therefore, continuous efforts have been made to deliver a good therapeutic drug molecule. Recently, Peterson et al. designed and synthesized six substituted dopamine analogues (**6−11**) and five catechol derivatives (**12−16**) (Figure 3) for their COMT inhibition studies.[16] The authors undertook the work based on an ab initio study of the designed compounds' binding energies in the enzyme's active site.[17]

Dopamine derivatives were synthesized by methods previously reported by the authors,[16] and the catechol derivatives were achieved from the corresponding commercially available starting materials by nitration and deprotection

of hydroxyl groups by BBr_3. The side chain −CN group was introduced from corresponding 2-phenyl ethanol to 2-phenyl ethyl bromide by the Apple reaction and subsequent conversion to nitrile by KCN. Finally, the deprotection of methoxy groups afforded the catechol derivatives (Figure 4).

The synthesized compounds were checked for their stability under the assay conditions in a phosphate buffer at pH 7.4 for 1 h and then analyzed by HPLC before the inhibition study, revealing that all of the compounds experienced little to no degradation over the time except 5-(2-aminoethyl)benzene-1,2,4-triol (**6**), 1,2,3,4-tetrahydroisoquinoline-6,7-diol (**7**), 2-(4,5-dihydroxy-2-nitrophenyl)acetonitrile (**14**), and 3-(3,4-dihydroxyphenyl)propanenitrile (PCN) (**15**). The in vitro S-COMT inhibition by the synthesized dopamine derivatives (**6−11**) was tested at two concentrations, 10 and 100 μM, with reference to 3,5-dinitrocatechol (DNC) as a positive control. The authors did not report the IC_{50} values for the compounds. Dopamine derivatives (**6−11**) did not show any inhibition effect at 10 μM. At 100 μM, the catechols 2-(2-aminoethyl)-4,5-dihydroxybenzonitrile (**10**) and 4-(2-aminoethyl)-5-nitro-benzene-1,2-diol (**11**) exhibited about 30% to 50% COMT inhibitory activity. At 10 μM, only 2-(4,5-dihydroxy-2-nitrophenyl)acetonitrile (**14**) showed a significant decrease in the COMT activity. However, at 100 μM, all the nitrile derivatives inhibited COMT activity to some degree with 2-(4,5-dihydroxy-2-nitrophenyl)acetonitrile (**14**) and 3-(4,5-dihydroxy-2-nitrophenyl)propanenitrile (**16**) demonstrating complete inhibition of COMT. The pK_a values and docking studies supported trends of the COMT inhibition effect of these compounds. The compounds with an electron-with-drawing nitro group help to lower the pK_a, but the neutral
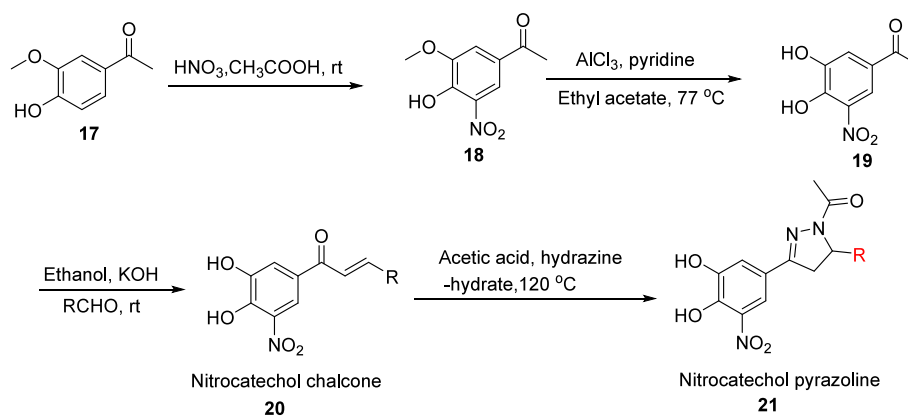
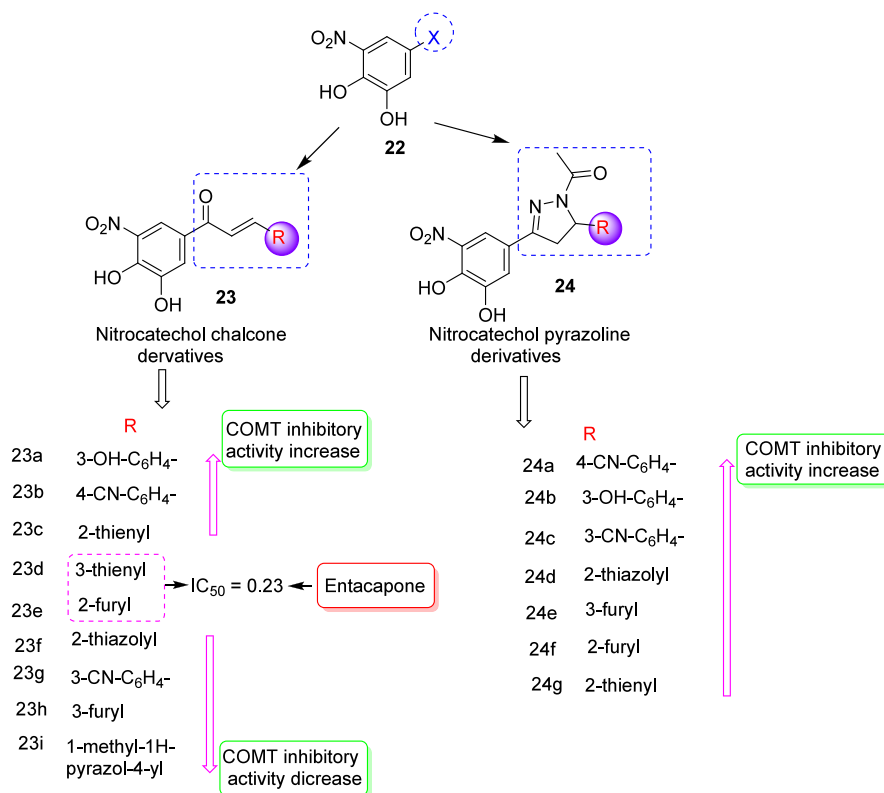**Figure 5.** Synthesis of nitrocatechol chalcone derivatives.

Figure 6. SAR of nitrocatechol chalcone and pyrazoline derivatives.

nitrile tail interacts more favorably with the residues at the back of the active site.

2.1.1. Nitrocatechol Chalcone Derivatives. Hitge et al. (2020) designed and synthesized a series of novel nitrocatechol chalcone and nitrocatechol pyrazoline derivatives as COMT inhibitors.[18] The designed compounds were synthesized by nitration of 4-hydroxy-3-methoxyacetophenone (apocynin, **17**) with nitric acid in the presence of acetic acid to form the nitro derivative (5-nitro-apocynin; **18**). Demethylation of nitro derivative **18** in the presence of AlCl₃ in pyridine and ethyl acetate gave 5-acetyl-3-nitrocatechol (**19**), which on Claisen−Schmidt condensation reaction with an appropriate aldehyde in the presence of KOH in ethanol formed nitrocatechol chalcones (**20**). The nitrocatechol pyrazoline derivatives (**21**) were synthesized by reacting compounds **20** with hydrazine hydrate in the presence of acetic acid at 120 °C (Figure 5).[19]

Rat liver tissue was used as an enzyme source to determine the COMT inhibitory activity of the synthesized compounds.[20] Among the synthesized derivatives, nitrocatechol pyrazoline derivatives were found to be more potent than nitrocatechol chalcone derivatives. In a series of nitrocatechol pyrazoline derivatives, all the designed compounds demonstrated effective COMT inhibitory activity (IC$_{50}$ = 0.048 to 0.21 μM) compared to the standard molecule entacapone (IC$_{50}$ = 0.23 μM). In this series, compound **24a** was found to be the most active COMT inhibitor with an IC$_{50}$ value of 0.048 μM. The presence of the −CN group at the fourth position of the spacer phenyl, which attached to the R position, was responsible for the COMT inhibitory activity of compound **24a**. Substitution of the −CN group at the third position of spacer phenyl resulted in a slight decrease in COMT inhibitory activity. The replacement of the −CN group with the −OH group at the spacer phenyl also causes a decline in COMT inhibitory

activity. In this series, among the heterocyclic derivatives (**24d–24g**), compound **24d** (2-thiazolyl substituted) was found to be the most active compound with an IC$_{50}$ value of 0.16 μM. Substitution of 2-furyl, 3-furyl, and 2-thienyl at the R position resulted in a slight decrease in COMT inhibitory activity.

In a series of nitrocatechol derivatives, compound **23a** showed the highest COMT inhibitory activity with an IC$_{50}$ value of 0.14 μM. Substitution of the −OH group at the third position of spacer phenyl, which attached to the R position, was responsible for the highest COMT inhibitory activity. Substitution of the −CN group at the fourth position of spacer phenyl retains the COMT inhibitory activity, while substitution of the −CN group at the third position of spacer phenyl results in a decrease in inhibitory activity. The substitution of heterocyclic moieties such as 3-thienyl and 2-furyl at the R position showed similar inhibitory activity compared to that of standard molecule entacapone. Substitution of 2-thiazolyl at the R position resulted in a slight decrease in COMT inhibitory activity; further substitution with 1-methyl-1*H*-pyrazol-4-yl at the R position resulted in the least potent COMT inhibitor **23i** with an IC$_{50}$ value of 0.29 μM (Figure 6).

2.2. Pyridine Derivatives. de Beer et al. (2021) introduced the design and synthesis of various non-nitro-catechol 3-hydroxypridin-4-ones as COMT inhibitors.[21] The designed compounds were synthesized by refluxing maltol with suitable primary amines in an acidified water/ethanol (0.9:0.1) mixture as a solvent to afford the 3-hydroxypyridine-4-ones (Figure 7).
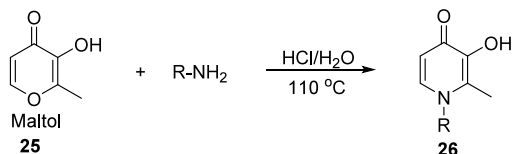

Figure 7. Synthesis of 3-hydroxypyridin-4-ones.

The COMT from porcine liver was used in the study, and (−)-norepinephrine was used as the enzyme substrate. Among the synthesized derivatives, compounds **27a** and **27i** were identified as active COMT inhibitors with IC$_{50}$ values of 4.55 μM and 5.76 μM, respectively, but not as active as the

reference inhibitors, entacapone and tolcapone. The spacer between the phenyl group and pyridone moiety by one to four carbon atoms significantly affected the COMT inhibitory activity. The spacers with 1- and 4-carbon atoms showed increased inhibitory effect; however, the spacer with 1-carbon, benzyl, showed the highest COMT inhibitory effect (Figure 8). The methyl substituent at the 4-position of the benzyl group exhibited slightly decreased inhibitory activity. The −Cl substitution at the 4-position of the phenyl group showed a slight increase in inhibition, and the same substitution at the 3-position made no appreciable change in the activity. Docking of compound **27a** indicated proper positioning for coordination with Mg^{2+}.

2.3. Pyridinone Derivatives. Ernst et al. (2019)[22] designed and synthesized a series of fused bicyclic pyridinone derivatives and evaluated their inhibitory activity against COMT. The synthesis of the target molecules was started with −OH protection of the hydroxyl group of kojic acid (5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one (**28**), to form compound **29**. The N atom was installed in the kojic acid ring by ethylenediamine at 90 °C in ethanol through replacing the ring O atom of kojic acid (**30**). The cyclization to a fused heterocyclic system was then achieved by oxidation of the hydroxymethyl group and imine formation in one pot (**31**). The reduction of the imine with NaBH$_4$ yielded a pyridopyrazine fused bicyclic ring (**32**). Then functionalization of the N−H group (**33**) and successive deprotection of the benzyl group lead to the target molecules (**34**) as shown in Figure 9.

Initially, the COMT inhibition was assessed for the parent and seven N-functionalized compounds (Figure 10). Among them, the *N*-benzylated derivative exhibited COMT inhibition in the submicromolar range with an IC$_{50}$ value of 220 nM. Others showed many fold loss in COMT inhibition. The group subsequently investigated COMT inhibition with *N*-benzylated compounds by modifying the electron-withdrawing groups (EWGs) and electron-releasing groups (ERGs) at the *ortho*- and *para*-positions. The result clearly showed that the EWGs and ERGs at the *ortho*-position had higher potency than the groups placed at the *para*- position. Among them, the −CH$_3$ group and −Cl group at the *ortho*-position (**36d,e**) exhibited excellent inhibition effects with IC$_{50}$ values of 50 and 40 nM, respectively (Figure 11).
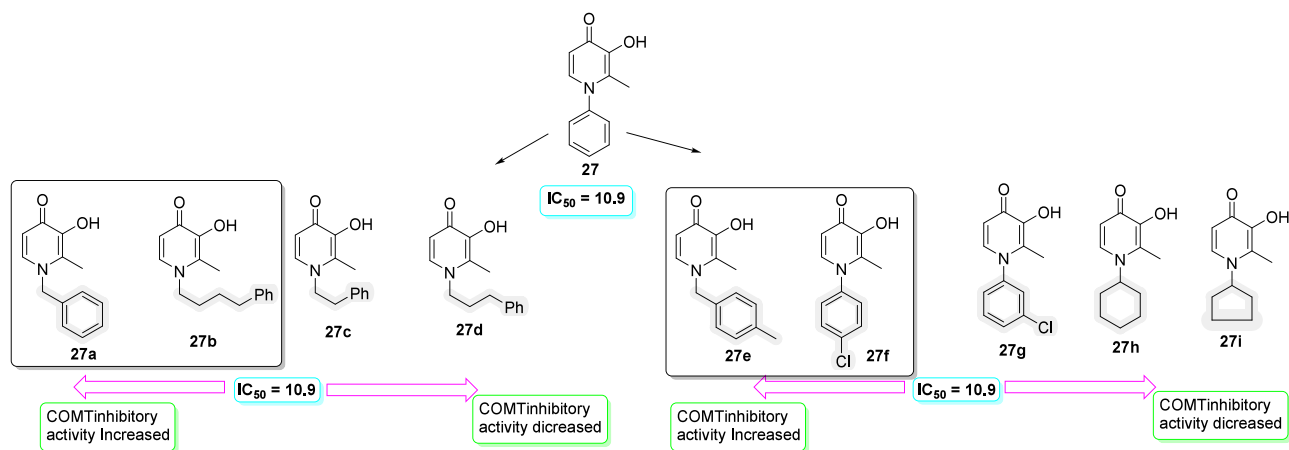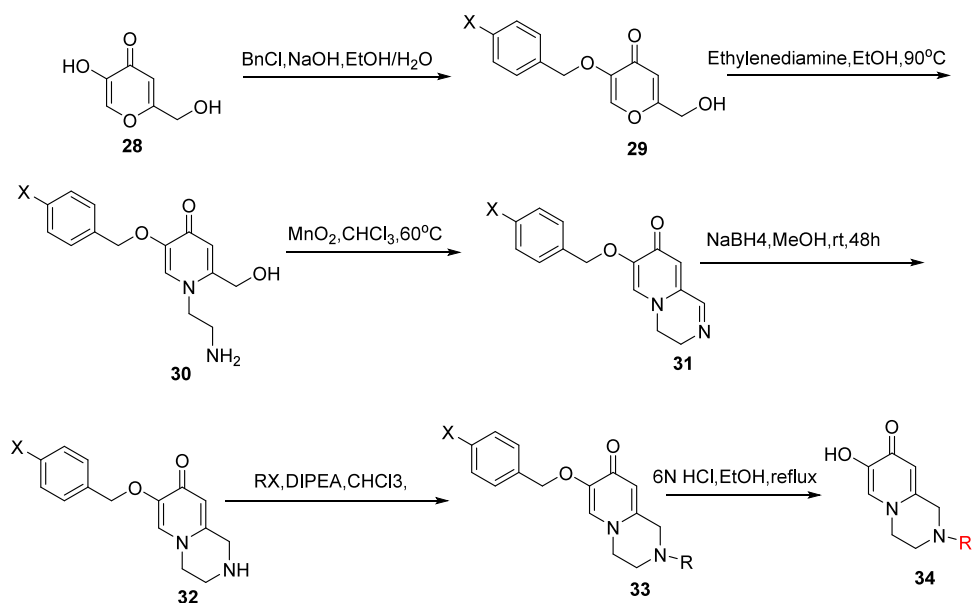

Figure 8. SAR of pyridin-4-one derivatives.

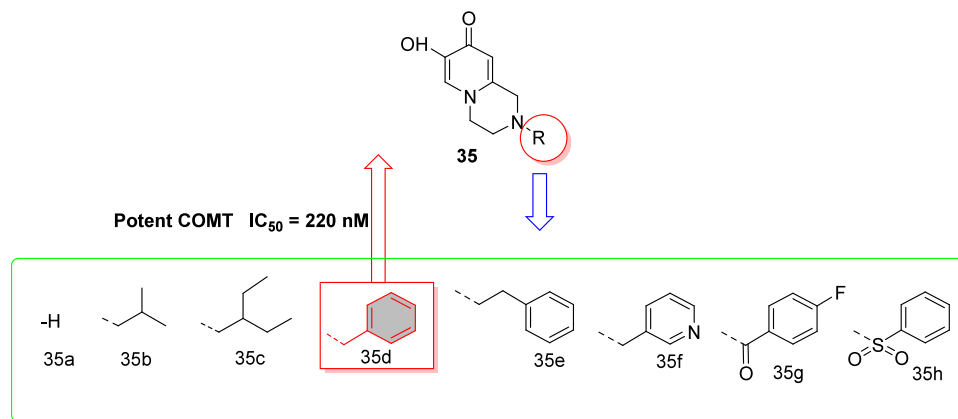**Figure 9.** Synthetic route for fused bicyclic hydroxypyridones.
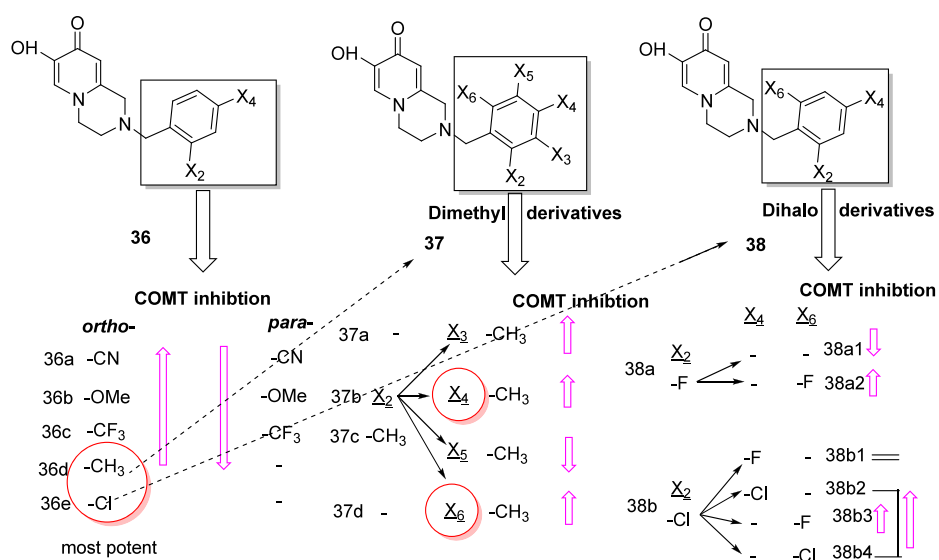

Figure 10. SAR of pyridinone derivatives.

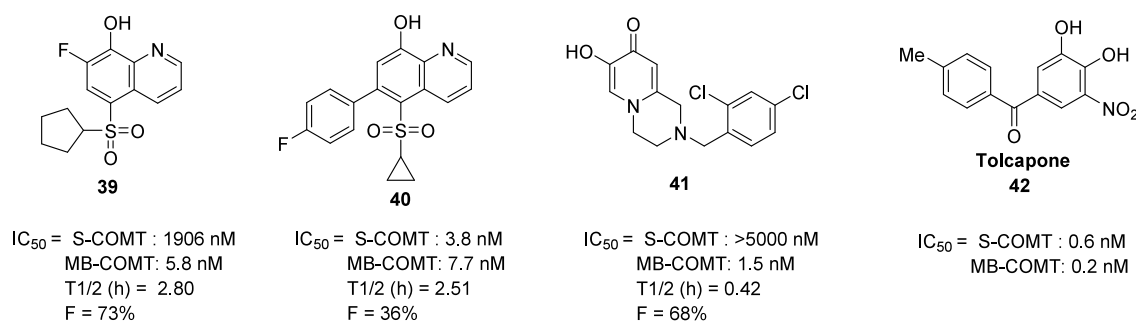**Figure 11.** SAR of pyridinone derivatives.

Figure 12. Selected potent inhibitors for *in vivo* COMT evaluations.

The −CH$_3$ and −Cl substituents were further taken to explore the inhibition effect at different positions of the benzyl group by keeping one at the *ortho*-position and another at all available positions. (Figure 11). Among the di −CH$_3$ derivatives 37, methyl groups at the 2,4- (37b) and 2,6-positions (37d) exhibited excellent inhibitory effects with IC$_{50}$ values of 13 and 6.3 nM, respectively.

Similarly, halogen substituents, −F and −Cl (38), were explored for COMT inhibition and 2-F 38a had a slight loss in potency compared to 2-Cl 38b. Among the dihalo derivatives, 2,4-dichloro- (38b2) and 2,6-dichloro- (38b4) exhibited a further increase in potency, with an IC$_{50}$ value of 10 nM, compared with chloro and fluoro substituted derivatives (Figure 11).

Along with potent compounds, such as 2-chloro 36e, 2,4-dichloro 38b2, and 2,6-dimethyl derivative 37d, the parent and 2-chloro-6-fluoro derivative 38b3 were examined for physicochemical and drug metabolism and pharmacokinetics (DMPK) properties, both *in vitro* and *in vivo*. Interestingly, these potent compounds have extraordinarily low levels of protein and tissue binding, which increase the availability of circulating compounds to interact with the target of interest.

The same group subsequently published the *in vivo* activity of novel COMT inhibitors to identify a COMT inhibitor with good oral bioavailability and significant effects on neurochemical biomarkers and behavior in rats along with tolcapone as a reference drug.[23] The selected previously described potent inhibitors (Figure 12) exhibited good *in vivo* COMT inhibitory activity by significantly decreasing homovanillic acid (HVA) and increasing 3,4-dihydroxyphenylacetic acid (DOPAC) at the tested time points. Then the cognitive function was measured as performance in the ASST. These novel inhibitors produced qualitatively similar effects compared to tolcapone.

2.4. Natural Pentacyclic Triterpene Derivatives. Wang et al. (2021) isolated and determined the structure−activity relationship of various series of natural pentacyclic triterpenes such as oleananes, lupanes, friedelanes, and ursanes as COMT inhibitors.[24] A two-photon fluorescent probe was used to determine the COMT inhibitory activity. The reaction was carried out in an incubation mixture containing recombinant human S-COMT (2.0 µg/mL), MgCl$_2$ (5 mM), DTT (1 mM), SAM (200 µM), 3-BTD (2 µM), and varying concentrations (from 0.125 to 20 µM) of tested compounds in a final volume of 200 µL in PBS buffer (50 mM, pH 7.4) in order to determine the IC$_{50}$ values of COMT inhibition. In a series of oleanane derivatives, compound 43a was found as the most active COMT inhibitor with an IC$_{50}$ value of 4.7 µM. The substituent −COOH group at R$_1$ and −CH$_3$ group at R$_3$ and R$_4$ positions was responsible for the COMT inhibitory activity of compound 43a. On replacement of the −CH$_3$ group

at the R$_4$ position of compound 43a with the CH$_2$OH group, the derivative retains the COMT inhibitory activity. The substituent −COOH group at R$_1$, −CH$_3$ group at R$_3$ and R$_4$ positions, and −OH group at R$_5$ position effect a decrease in COMT inhibitory activity with respect to standard drug epicatechin having an IC$_{50}$ value of 9.5 µM. The substituents −CH$_3$ at R$_1$ and R$_3$ positions and −COOH at R$_4$ position effect a further decrease in COMT inhibitory activity. The substituent −CH$_3$ at R$_1$, R$_3$, and R$_4$ positions led to the least potent molecule of this series, 43e, with an IC$_{50}$ value of 114.9 µM. The substituents −COOH at R$_1$, −OH at R$_2$, −CH$_2$OH at R$_3$, −CH$_3$ at R$_4$, and −OH at R$_5$ position (43f) led to loss of COMT inhibitory activity (Figure 13).

	R$_1$	R$_2$	R$_3$	R$_4$	R$_5$
43a	-COOH	-H	-CH$_3$	-CH$_3$	-----
43b	-COOH	-H	-CH$_3$	-CH$_2$OH	-----
43c	-COOH	-H	-CH$_3$	-CH$_3$	OH
43d	-CH$_3$	-H	-CH$_3$	-COOH	-----
43e	-CH$_3$	-H	-CH$_3$	-CH$_3$	-----
43f	-COOH	-OH	-CH$_2$OH	-CH$_3$	OH

COMT inhibitory activity increases

Epicatechin IC$_{50}$ = 9.5
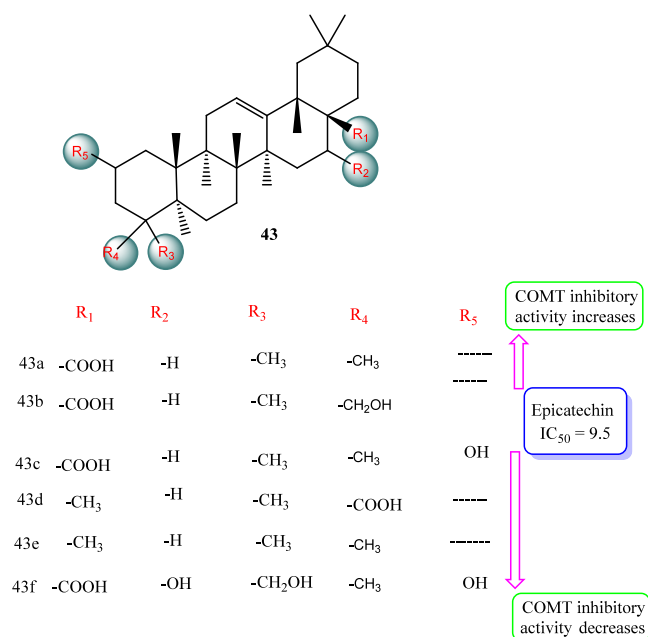
COMT inhibitory activity decreases

Figure 13. SAR of oleanane derivatives.

In the series of ursane derivatives, all compounds show less activity as compared to the standard drug epicatechin having an IC$_{50}$ value of 9.5 µM. Among all these derivatives, compound 44a was found as the most effective COMT inhibitor. The substituents −COOH at R$_2$, −OH at R$_4$, and −CH$_3$ at R$_3$, R$_7$, and R$_8$ positions were responsible for the highest COMT inhibition of compound 44a. The substituents −COOH at R$_1$, −OH at R$_4$, and CH$_3$ at R$_3$, R$_7$, and R$_8$ positions led to a decrease in COMT inhibitory activity. The substituents −COOH at R$_1$, −CH$_2$OH at R$_3$, −OH at R$_4$ and R$_5$ positions, and −CH$_3$ at R$_2$, and R$_8$ position led to the least

potent molecule of this series with IC_{50} value 43.1 μM. With substituents −COOH at R_2, −OH at R_4, =O at R_6, and −CH$_3$ at R_3 and R_8 positions, **44d** exhibited loss of COMT inhibitory activity (Figure 14).
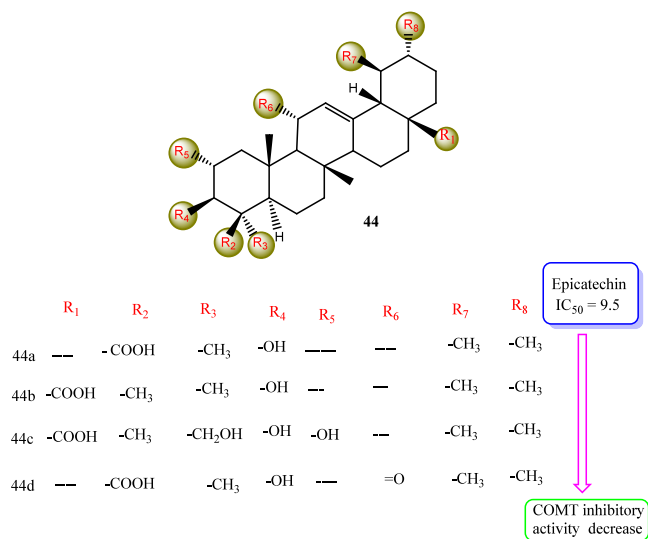

Figure 14. SAR of the ursane derivatives.

Figure 15. SAR of the lupane derivatives.

In the series of lupane derivatives, the substituent −COOH at R_1, −CH$_3$ at R_2 and R_3 positions, and −OH at R_4 position conferred the highest efficacy for COMT inhibition within this series, with an IC_{50} value of 5.07 μM. The substituents −CH$_2$OH at R_1, −CH$_3$ at R_2 and R_3 positions, and −OH at R_4 position produced a slight increase in COMT inhibitory activity with respect to standard drug epicatechin. The substituents −CH$_3$ at R_1, R_2, and R_3 positions and −OH at R_4 position further increased COMT inhibitory activity. The substituents −C=O at R_1, −CH$_3$ at R_2 and R_3 positions, and −OH at the R_4 position slightly decreased COMT inhibitory activity. Substituents −COOH at R_1, −CH$_3$ at R_2 and R_3 positions, and =O at R_4 position further decreased COMT inhibitory activity. Substituents −CH$_3$ and COOH at R_1, −CH$_2$OH at R_2, −CH$_3$ at R_3, and −OH at R_4 produced the least potent molecule (**45f**) of this series with an IC_{50} value of 31.42 μM (Figure 15).

In the series of friedelane derivatives, they found three derivatives, namely, known as celastrol, hydrocelastrol, and friedelin. Among these compounds, celastrol demonstrates the most significant inhibitory efficacy against COMT, evidenced by an IC_{50} value of 3.89 μM; conversely, hydrocelastrol exhibits a comparatively diminished COMT inhibitory efficacy relative to the reference compound epicatechin, which has an IC_{50} value of 9.5 μM, whereas friedelin manifests no observable COMT inhibitory activity (Figure 16).

2.5. Flavonoid Derivatives. Zhao et al. (2021) isolated and characterized naturally occurring potent COMT inhibitors from the medicinally active plant Scutellariae radix.[25] A Triple TOF 5600 mass spectrometer (AB SCIEX) running in negative ion mode was coupled to a UPLC system (Shimazu) for the analysis of the samples, and mixed standards were used to determine the composition. To determine the COMT inhibitory activity, 3-(benzo[*d*]thiazol-2-yl)-7,8-dihydroxy-2*H*-chromen-2-one (3-BTD), an extremely selective optical probe substrate specifically designed for measuring the residual activities of human catechol-*O*-methyltransferase (hCOMT)
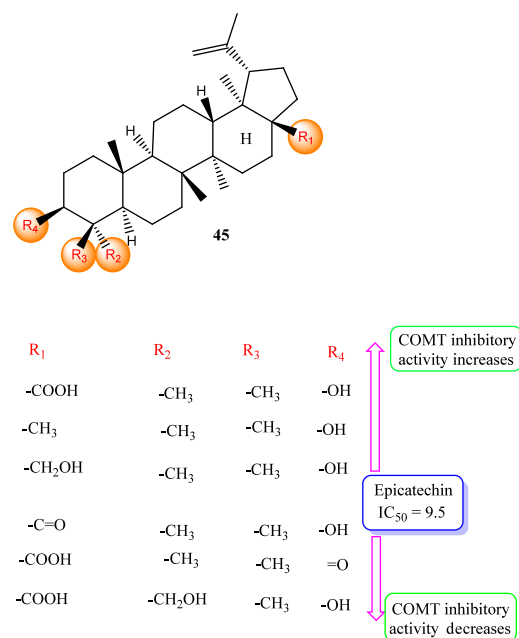
in the presence or absence of inhibitors, was used. Among the isolated derivatives, compound **49a** was found to be the most active molecule against COMT having an IC_{50} value of 0.018 μM. The substituent −OCH$_3$ at R_2 position was responsible for the highest significant COMT inhibitory activity of compound **49a**. Substituents (1*S*,2*R*,3*S*,4*S*,5*R*)-2,3,4-trihydroxy-5-(*λ*-oxidaneyl)cyclohexane-1-carboxylic acid at Ar$_2$ and −OCH$_3$ at R_5 position (**51a**) increased COMT inhibitory activity with respect to entacapone, having IC_{50} value 0.23 μM. The substituent −OH group at the R_1 and R_2 positions conferred a further increase in COMT inhibitory activity. Substituent −OH at the R_2 position slightly decreased the COMT inhibitory activity. Furthermore, the substitution −OCH$_3$ at the R_3 position resulted in a decrease in the COMT inhibitory activity. The substituent (1*S*,2*R*,3*S*,4*S*,5*R*)-2,3,4-trihydroxy-5-(*λ*-oxidaneyl)cyclohexane-1-carboxylic acid at Ar$_2$ position produced the least active compound (**51b**) against COMT with IC_{50} value greater than 100 μM (Figure 17).

Zhao et al. further isolated and characterized flavonoid derivatives from vine tea as COMT inhibitors in 2021.[26] A Triple TOF 5600 Mass Spectrometer system (AB SCIEX, Foster City, USA) in conjunction with a UPLC system (Agilent, California, USA) was used to carefully analyze the main ingredients of the bioactive fractions of vine tea. A highly selective optical probe substrate called 3-BTD was utilized to measure the COMT inhibitory activity in the presence or absence of inhibitors. For comparison of the COMT activity, quercetin was used as a standard. Among the isolated flavonoid derivatives, compound **53a** exhibited the highest level of potency with an IC_{50} value of 0.96 μM. Substituents benzene-1,2,3-triol at the Ar$_2$ position and −OH group at R_1 position were responsible for the highest COMT inhibitory activity of compound **53a**. Substituents benzene-1,2,3-triol at the Ar$_2$ position and (2*S*,3*R*,4*S*,5*S*,6*R*)-2-methyl-6-(oxidaneyl) tetrahydro-2*H*-pyran-3,4,5-triol at R_1 position slightly decreased COMT inhibitory activity with respect to standard molecule quercetin. Removal of the double bond from a core molecule of flavonoid at the second position of ring A results in a
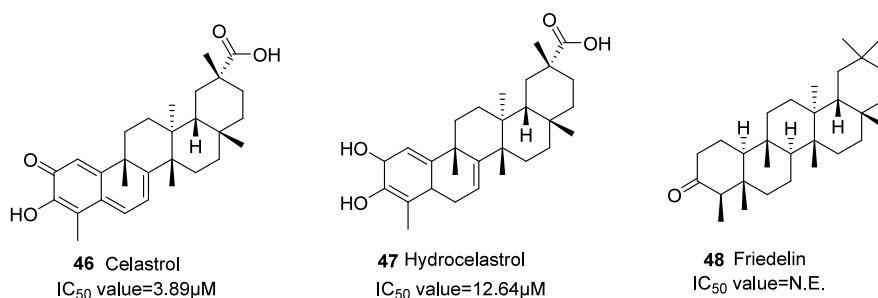
46 Celastrol
IC$_{50}$ value=3.89μM

47 Hydrocelastrol
IC$_{50}$ value=12.64μM

48 Friedelin
IC$_{50}$ value=N.E.

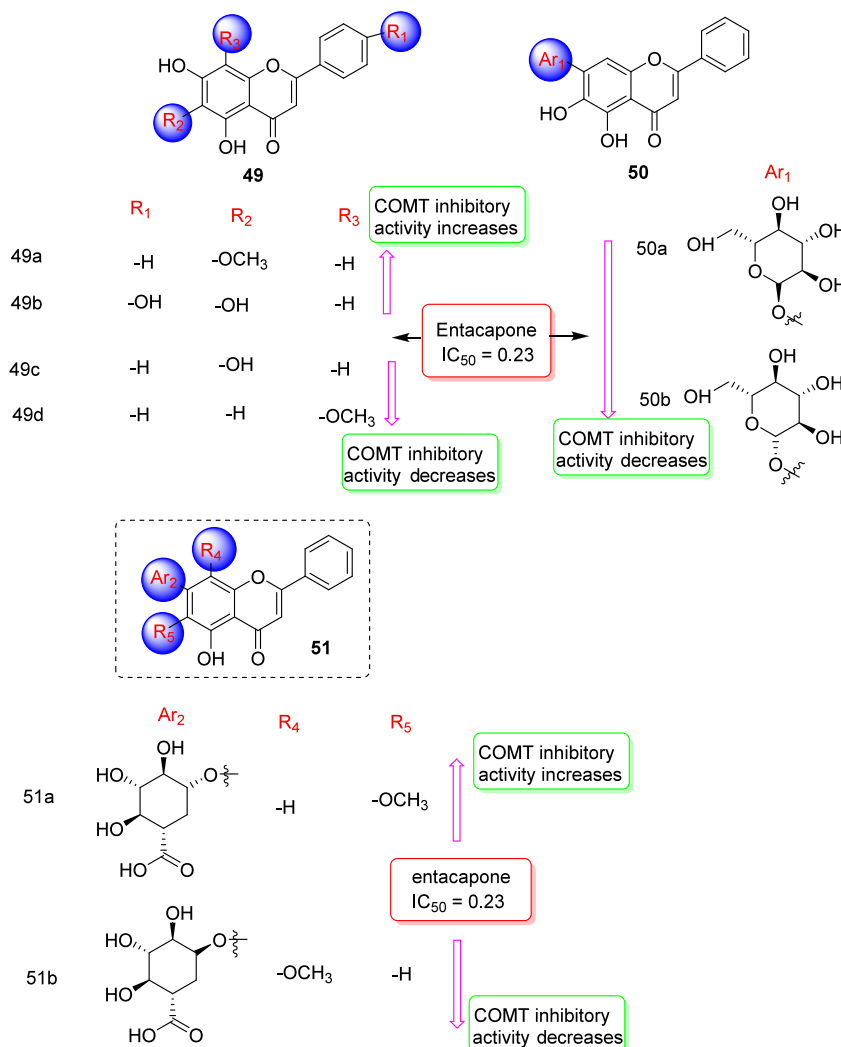**Figure 16.** SAR of friedelane derivatives.

Figure 17. SAR of flavonoid derivatives by Zhao et al. (2021).[25]

decrease in COMT inhibitory activity. Substitution of benzene-1,2,3-triol at the Ar$_1$ position of saturated ring A of the flavonoid molecule results in a further decrease in COMT inhibitory activity. Substitution of 4-methylbenzene-1,2-diol at the Ar$_1$ position of saturated ring A of the flavonoid molecule resulted in the least active molecule against COMT with an IC$_{50}$ value of 42 μM (Figure 18).

2.6. Tetralone and Indanone Derivatives. de Beer et al. (2021) designed and synthesized a series of novel tetralone and indanone derivatives as COMT inhibitors.[27] The designed compounds were synthesized from 5-nitrovanillin (**54**), treated with aluminum trichloride (AlCl$_3$) in the presence of pyridine

to give intermediate 3,4-dihydroxy-5-nitrobenzaldehyde (**55**), which was reacted in acidic medium with appropriate 1-indanone (**56**) and 1-tetralone (**57**) derivatives to give the corresponding indanone derivatives (**58**) and tetralone derivatives (**59**) (Figure 19).

The soluble fractions from homogenates of rat liver tissue were used as an enzyme source for the COMT inhibition investigations.[28] Among the synthesized compounds, indanone derivatives were found to be more potent inhibitors as compared to tetralone derivatives. In a series of indanone derivatives, the one with a substituent −CH$_2$O− group at the R$_1$ position (**61a**) showed the highest COMT inhibitory
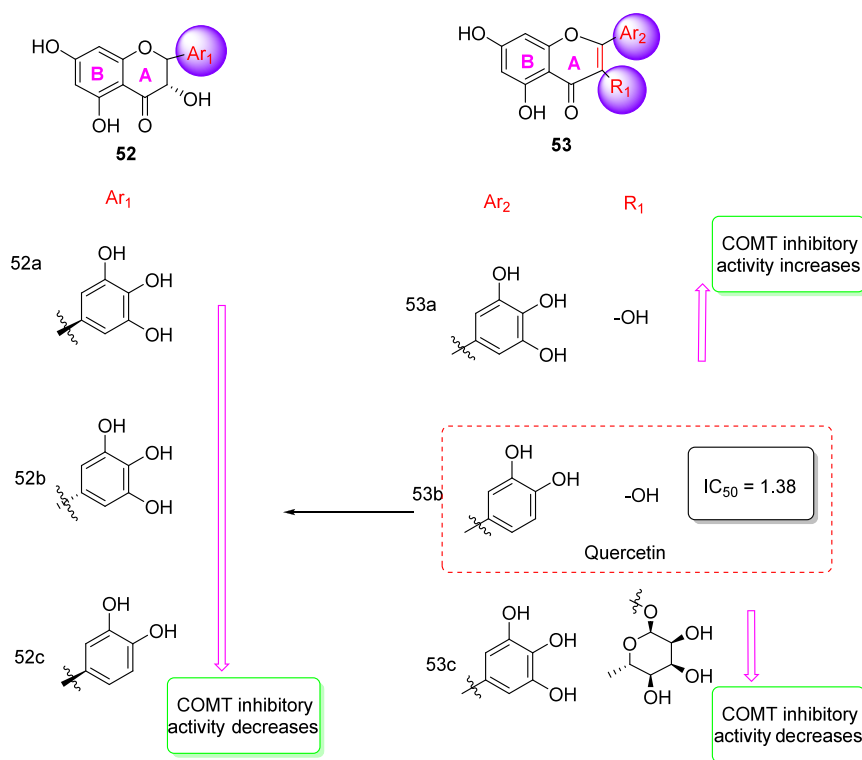
Figure 18. SAR of flavonoid derivatives.

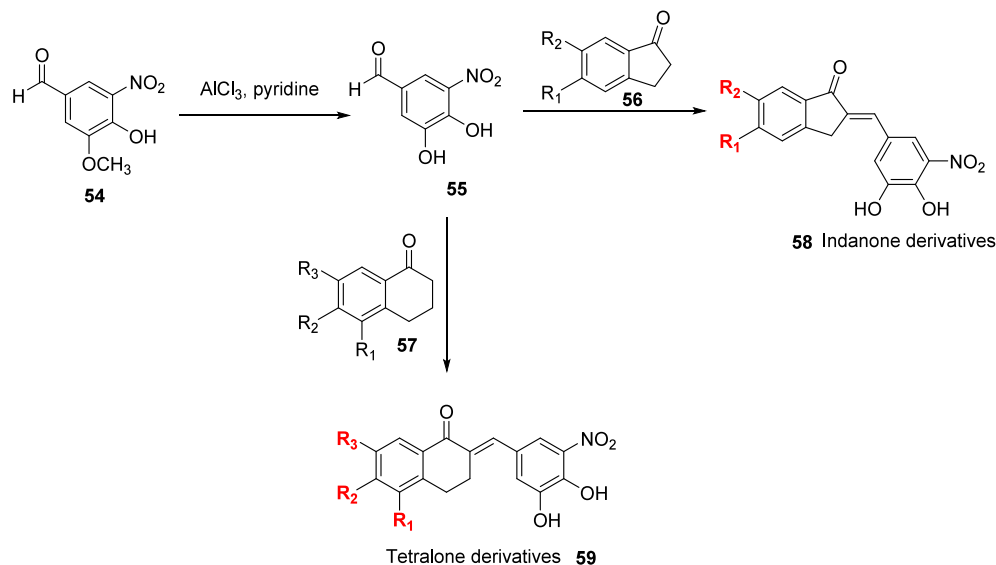**Figure 19.** Synthesis of tetralone and indanone derivatives.

activity with IC_{50} value of 0.16 μM. The substituent $-OCH_3$ at the R_1 position slightly increased COMT inhibitory activity as compared to the standard molecule entacapone (IC_{50} = 0.23 μM). Substitution of hydrogen and $-OCH_3$ at R_1 and R_2 positions simultaneously results in a decrease in COMT inhibitory activity. Substitution of the hydroxy ($-OH$) group at the R_1 position, **61e**, results in the least potent COMT inhibitor of this series with an IC_{50} value of 0.38 μM.

In the series of tetralone derivatives, all molecules were found to be less potent COMT inhibitors compared to entacapone. In this series, the substitution of electron donating groups ($-NH_2$, $-OCH_3$) and hydrogen resulted in a decrease in COMT inhibitory activity as compared to entacapone.

Substitution of the $-NH_2$ group at the R_2 position (**60a**) resulted in the highest COMT inhibition in this series with an IC_{50} value of 0.24 μM. The substituents $-OCH_3$ at R_2 and R_3 positions slightly decreased COMT inhibitory activity. The substituent hydrogen at the R_1, R_2, and R_3 positions decreased the COMT inhibitory activity. The substituent $-OCH_3$ at the R_1 or R_3 position further decreased COMT inhibitory activity. The substitution of $-OCH_3$ at the R_2 position (**60f**) resulted in the least potent COMT inhibitor of this series with an IC_{50} value of 0.79 μM. Overall indanone derivatives showed better COMT inhibitory activity than tetralone derivatives (Figure 20).
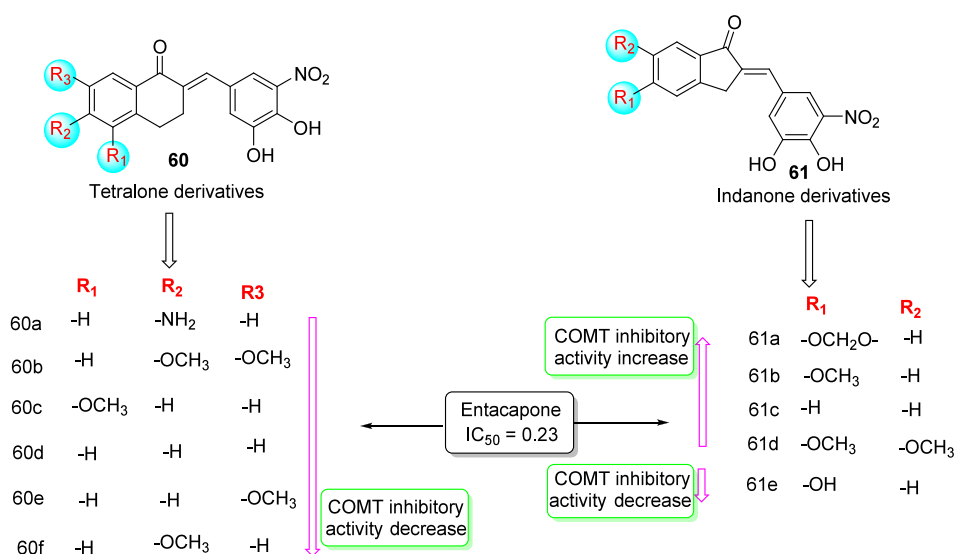
Figure 20. SAR of tetralone and indanone derivatives.
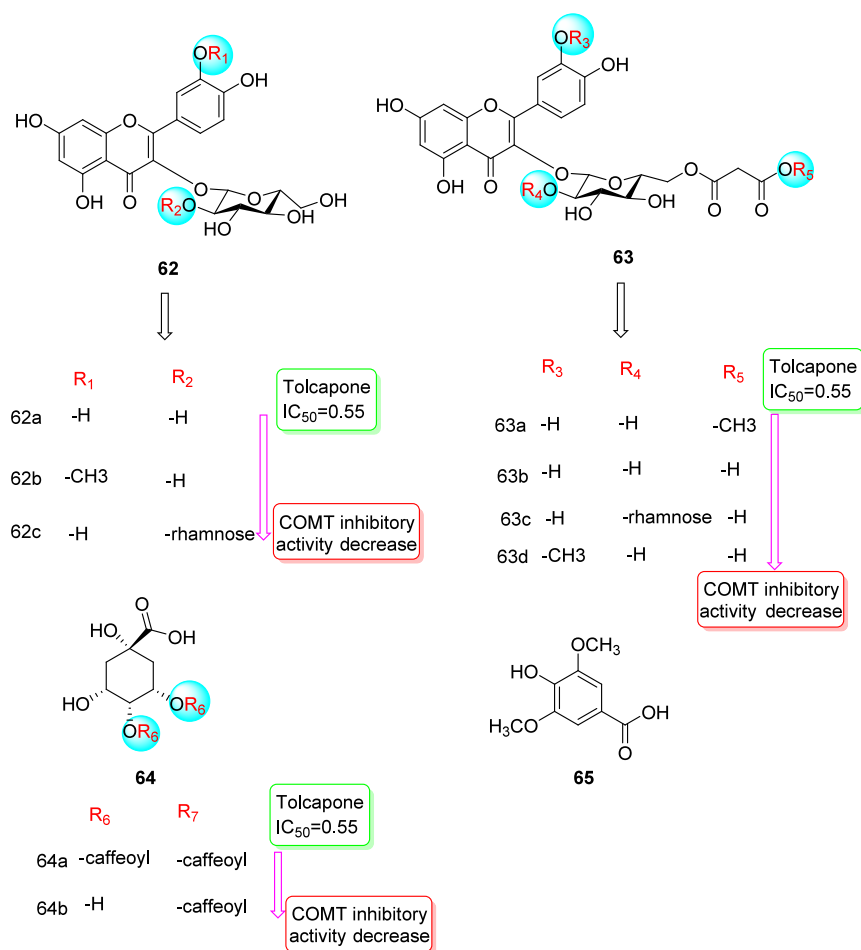
Figure 21. SAR of various COMT inhibitors from *Calendula officinalis* leaf by Kadowaki et al.[29]

2.7. Miscellaneous. Kadowaki et al. (2023) isolated various COMT inhibitors from *Calendula officinalis* leaf.[29] The primary constituents of *Calendula* leaves were determined by isolating ten specific compounds through a variety of chromatographic methods. The isolated compounds were identified by mass spectroscopy (MS) and nuclear magnetic resonance (NMR) spectroscopy to be quercetin 3-O-β-

glucoside (**62a**), isorhamnetin 3-O-β-glucoside (**62b**), quercetin 3-O-β-neohesperidoside (**62c**), quercetin 3-O-6″-O-methylmalonyl)-β-glucoside (**63a**), quercetin 3-O-(6″-O-malonyl)-β-glucoside (**63b**), quercetin 3-O-(2″-O-α-rhamnosyl-6″-O-malonyl)-β-glucoside (**63c**), isorhamnetin 3-O-(6″-O-malonyl)-β-glucoside (**63d**), chlorogenic acid (**64a**), 3,4-dicaffeoyl-quinic acid (**64b**), and syringic acid (**65**). For determining the

COMT inhibitory 3-(benzo[d]thiazol-2-yl)-7,8-dihydroxy-2H-chromen-2-one (3-BTD) was used.[30] For comparison of the COMT inhibitory activity, tolcapone was used as a standard drug. All of the isolated compounds showed less COMT inhibitory activity than the standard drug tolcapone, having an IC$_{50}$ value of 0.55 μM. Among all isolated derivatives, compound **64a** was found to be the most active COMT inhibitor with an IC$_{50}$ value of 21 μM. The substituent caffeoyl at R$_6$ and R$_7$ positions was responsible for the COMT inhibitory activity of compound **64a**. The substituent caffeoyl at the R$_7$ position resulted in a decrease in COMT inhibitory activity. The substituent hydrogen at R$_1$ and R$_2$ positions maintained the COMT inhibitory activity with IC$_{50}$ value 50 μM. Substituents $-$CH$_3$ at the R$_1$ position and rhamnose at the R$_2$ position simultaneously decreased the COMT inhibitory. The substituents hydrogen at the R$_3$ and R$_4$ positions and $-$CH$_3$ at the R$_5$ position produced promising COMT inhibitory activity with an IC$_{50}$ value of 42 μM. Substituent hydrogen at R$_3$, R$_4$ and R$_5$ positions decreased COMT inhibitory activity. The substituents hydrogen at the R$_3$ and R$_5$ positions and rhamnose at the R$_4$ position further decreased in the COMT inhibitory activity. Compound **63d** with substituents $-$CH$_3$ at R$_3$ position and hydrogen at R$_4$ and R$_5$ positions and compound **65** showed the least potent COMT inhibition with an IC$_{50}$ value greater than 100 μM (Figure 21).

3. CONCLUSION

The SAR of COMT inhibitors has emerged as a vital tool in the pursuit of novel therapeutics for Parkinson's disease, depression, and anxiety disorders. In this review, we discussed the synthesis and SAR of various catechol, nitrocatechol, pyridine, pyridinone, flavonoid, tetralone, indanone, and natural pentacyclic triterpene derivatives which have been recently discovered (2019−2024). By elucidating the intricate relationships between chemical structure and biological activity, this review will provide a roadmap for researchers for the design and optimization of next-generation COMT inhibitors. As the field continues to evolve, the insights gleaned from SAR will be crucial in unlocking the full potential of COMT inhibitors and enabling the development of safer, more effective, and personalized treatments for patients in need. Through leveraging the potential of SAR, researchers and clinicians can collaborate to influence the future trajectory of neurology and psychiatry, enhancing lives and improving outcomes.

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Notes

The authors declare no competing financial interest.

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Suraj Mali holds a Ph.D. in Pharmacy and currently serves as an Assistant Professor of Pharmaceutical Chemistry at the School of Pharmacy, DY Patil University, Navi Mumbai, India. A former analytical scientist at Dr. Reddy's Laboratories in Hyderabad, India, Dr. Mali has an M. Pharm. in Pharmaceutical Science and Technology from the Institute of Chemical Technology, Mumbai. He is a distinguished reviewer for 267 scientific journals and was named a Bentham Science Brand Ambassador for 2019−2020. With over 140 international journal publications and an H-index of 27 (Scopus Citations: 1635), Dr. Mali's research focuses on molecular modeling, synthetic chemistry, phytochemistry, pharmacology, and analytics, with a keen interest in drug design and synthesis. His notable achievements include the Institute of Chemical Technology's Masters Best Thesis Aditya Birla Award in 2019. His work has garnered international recognition, including a publication in *Nature Scientific Reports* on identifying antimycobacterial agents through computational methods. Furthermore, Dr. Mali was ranked among the world's top 2% of scientists by Stanford University in both 2023 and 2024, a testament to his outstanding contributions to pharmaceutical science.

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