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# DFT and QSAR study of Catechol-O-methyltransferase (COMT) as inhibitors for Parkinson's disease treatment

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## Abstract

Parkinson's disease is characterized by a lack of the neurotransmitter or cell-signaling molecule dopamine. Levodopa is a well-known drug for Parkinson's disease since it induces dopamine. Catechol-O-methyltransferase (COMT) are enzymes that break down levodopa, limiting the amount delivered to the brain. COMT inhibitors act by extending the duration of action of levodopa, thus improving the amount of time benefit from levodopa. There are several FDA-approved COMT inhibitors used, such as Entacapone and Tolcapone. Tolcapone can penetrate blood-brain barrier (BBB), but most of the drug stays in the plasma because its high protein bound, and it has severe side effects, while Entacapone cannot penetrate BBB, which reduces drug efficiency. This study aims to design higher-efficiency drug inhibitors by investigating the physical properties in terms of total energy, total dipole moment and HOMO/LUMO band gap at DFT: B3LYP level using the LAN2DZ basis set, in addition to quantitative structure activity relationship (QSAR) calculations to test the biological activity of these drug inhibitors for the treatment of Parkinson's disease.

**Keywords** Parkinson's Disease · COMT inhibitors · DFT · Total dipole moment · HOMO/LUMO · QSAR

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## 1 Introduction

Parkinson's disease (PD) is a prevalent neurological disorder that significantly influences people's daily lives (Jankovic 2008). Recent research indicates that PD affects 2–4% of the over-65 populations (Jankovic 2008; Latif et al. 2021). PD is a neurodegenerative condition characterized by the selective degradation of dopaminergic neurons in the compact substantia nigra pars (Latif et al. 2021). This causes a significant drop in striatal dopamine (DA) levels, which in turn causes the hallmark motor symptoms of PD: muscle rigidity, hypo- and bradykinesia, and resting tremor (Katsaiti and Nixon 2018). Current medications rely on the treatment of physical motor symptoms by providing DA replacement therapy (Bloem et al. 2021). Levodopa, the precursor of DA, remains the most effective pharmacological medication for the symptomatic treatment of PD even after 50 years of use (Katsaiti and Nixon 2018; Jenner et al. 2021). Levodopa crosses the blood-brain barrier (BBB) and converts to DA in both the CNS and periphery (Gandhi and Saadabadi 2023). Despite levodopa's status as the standard gold treatment for PD, several supplementary levodopa treatments and studies aimed to improve the delivery method developed due to shortcomings in the pharmacological profile, particularly oral administration and the resulting incidence of motor complications (Tambasco et al. 2017). Such enhancement of PD treatment involves the inhibition of Catechol O-methyl transferase (COMT). COMT is a member of the large and diverse family of S-adenosyl-L-methionine transferases that is responsible for methylation reactions of neurotransmitters such as DA. Subsequently, it is used to treat PD by identifying it as a drug target (Salamon et al. 2022). Drug design for COMT inhibition passed through three generations (Cruz-Vicente et al. 2022). First generation involved catechol/pyrogallol derivatives which showed low bioavailability and high toxicity. Therefore, there was a need to design new inhibitors to overcome the limitations of the first generation. Di-substituted catechol with a nitro group at 5-position was designed, which was more potent and selective, and this was the second generation. From the second generation, two drugs were FDA approved, entacapone and tolcapone (Cruz-Vicente et al. 2022; Kiss and Soares-da-Silva 2014). Entacapone inhibits COMT peripherally, while tolcapone crosses the blood-brain barrier (BBB), which increases levodopa bioavailability (Cruz-Vicente et al. 2022; Bonifácio et al. 2007). However, tolcapone is associated with liver failure and increased risk of dyskinesia, which limits its use clinically. Additionally, they largely fail to influence the fluctuations in the levodopa plasma profile, which reflects the fact that neither inhibitor completely blocks all COMT activity on a continuous basis (Jenner et al. 2021; Cruz-Vicente et al. 2022; Moschovou et al. 2020; Müller 2015; Lanier et al. 2014). The third-generation inhibitors showed low toxicity and more effectiveness, yet it does not cross BBB (i.e., opicapone) (Salamon et al. 2022; Cruz-Vicente et al. 2022; Caldas et al. 2018).

Molecular modeling is a computational tool for elucidating chemical, physical and biological properties of many systems and compounds (El-Mansy et al. 2021, 2023; Hegazy et al. 2022; Badry et al. 2022; Ebied et al. 2022; Degheidy and Elkenany 2012, 2016). It is always the tool for novel therapeutic candidates, so that, modeling represents computational efforts which have been crucial in the ease of identification of leads for experimental in vitro and in vivo testing (Hu et al. 2021; Jin et al. 2020). Molecular modeling could be described as an essential tool for understanding fundamental concepts in many areas, especially in drug structure as well as activity (Carvalho et al. 2005). It is recommended as the first tool

in medicinal chemistry educations (Candela et al. 2021; Yang et al. 2021). Modelling PD was reported by Yates (2020).

The goal of the current research is to identify new COMT competitive fragments that could be more effective for the treatment of PD and can penetrate BBB by inhibiting COMT peripherally and ventrally. The proposed potential COMT inhibitors were studied using density functional theory (DFT) molecular modeling calculations. Quantitative structure activity relationship (QSAR) analysis was also conducted to identify the promising lead compounds and compare them with a well-known peripherally COMT inhibitor called DNC.

## 2 Computational details

### 2.1 Choosing chemical compounds

The chemical compounds were chosen based upon two factors. The first is to be all catechol/pyrogallol derivatives to assure competitive inhibition for COMT. Secondly, pharmacophores were generated based on DNC inhibitor from the PDP structure 3BWY using Pharmit (Sunseri and Koes 2016). Using the generated pharmacophores, it was searched in the MCULE database to find the candidate compounds. Then, the compounds were library-filtered using the DataWarrior platform according to the drug-likeness properties of the software (Sander et al. 2015; Openmolecules 2023).

### 2.2 Calculation details

All the studied models were subjected to DFT quantum mechanical calculations using GAUSSIAN 09 softcode (Frisch et al. 2010) at Molecular Modeling and Spectroscopy Laboratory, Centre of Excellence for Advanced Science, National Research Centre, Egypt. Geometry optimization was done at B3LYP (Becke 1993; Lee et al. 1988; Miehlich et al. 1989) level using LAN2DZ basis set, at which the values of the total energy (E), total dipole moment (TDM), and HOMO/LUMO bandgap energy (ΔE) were also calculated. QSAR analysis was performed at PM6 level using SCIGRESS 3.0 molecular modeling software (Stewart 2009) at Spectroscopy Department, National Research Centre, Egypt.

## 3 Results and discussions

The models between a well-known drug (DNC) and COMT pocket were built as between the candidate drugs and COMT active site. QSAR analysis was carried out on the previous models to analyze the biological activity of such molecules with their structures (descriptors). There were many descriptors, which can be examined, but this research focused on the most beneficial ones for our aim. The calculated electronic descriptors for the previous models were total energy E, TDM, ΔE, and molecular polarizability (P). Additionally, the hydrophobic descriptors, such as partition coefficient (Log P), were calculated, as well as steric descriptors like molar refractivity (MR), surface area (SA), and volume (V).

### 3.1 Proposed Drugs

The generated pharmacophores were two hydrogen bond donors, six hydrogen bond acceptors, one aromatic ring, and one hydrophobic. These findings are similar to the reported pharmacophores generated from all the known COMT inhibitors by Petal and his colleagues, except the number of hydrogen bond acceptors was two rather than six (Patel et al. 2017). After the filtration of the compound library, the following five candidate drugs (Fig. 1) were obtained. The presence of enantiomers was observed, which are natural compounds from the flavonoids family (Drugs 3 and 6).

### 3.2 Building the models

#### 3.2.1 COMT active cite model

COMT pocket site consists of gate keeper residues (TRP38, TRP143, PRO174, LEU198), LYS144 and GLU199, co-enzyme named s-adenosyl-L-methionine (SAM), and magnesium ion (Mg2+). Out of the six amino acids forming the pocket, the main two that form the main interaction with the substrate were chosen according to the literature, which are LYS144

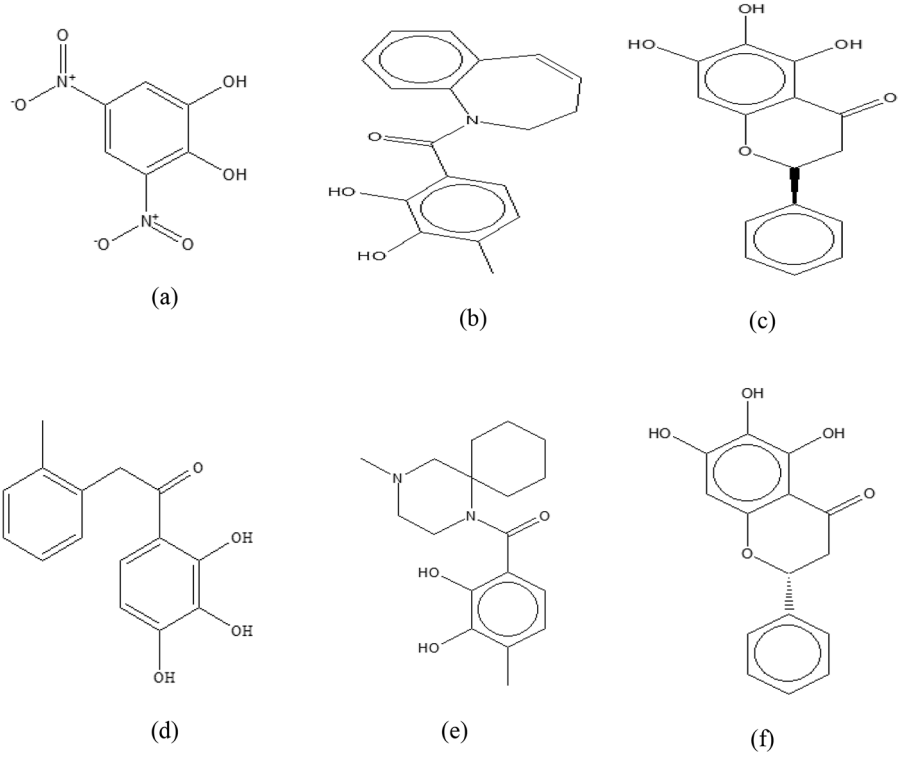


**Fig. 1** (**a**) the well-known DNC inhibitor, (**b**) first proposed drug MCULE-2003405854-0, (**c**) second proposed drug CHEMBL402227 (S isomer) (flavonoids), (**d**) third proposed drug CHEMBL3109029, (**e**) fourth proposed drug MCULE-8507898166-0, (**f**) last proposed drug which is the enantiomer of c MCULE-9153751111-0 (R isomer)

and GLU199. Additionally, magnesium ion forms an octahedral complex by binding with oxygen atoms in the following three residues (Asp141, Asp169, and Asn170) coordinately (Kiss and Soares-da-Silva 2014). Another coordination bond is formed with a molecule of water (400). Figure 2 illustrates the amino acids residues drew to build the model of COMT active site. The final two coordination bonds are formed with two hydroxyl groups of catechol substrate (Fig. 2) (Palma et al. 2006).

### 3.2.2 COMT Pocket interacted with the drugs models

According to the previous statements and findings, the magnesium interaction alongside the catechol/pyrogallol (inhibitors) interactions with LYS144 and GLU199 from their hydroxyl groups via hydrogen bonds was drawn (Fig. 3).

## 3.3 Total energy, total dipole moment and HOMO/LUMO bandgap

All the candidate drugs that interacted with COMT pocket were lower in energy, drug 5 has the lowest energy (-13454.674 eV), than DNC (-12550.274 eV) while the total dipole moment of DNC is the highest (6.507 Debye) followed by drug 5 (4.950 Debye) and drug 2 (4.621 Debye) (Table 1). ΔE for drug 5 (8.447 eV) and drug 2 (8.209 eV) was the highest (Table 1). The proposed drugs form a more stable interaction with COMT pocket than DNC due to their low energy values. Drugs 2 and 5 are less likely to interact with the surrounding since ΔE is higher than that of DNC (Table 1).

## 3.4 QSAR calculations

Table 2 lists the obtained values of the studies QSAR descriptors. Log P is a measure of the partitioning of a molecule in both water and octanol. The optimal Log *P* value for drugs lies in the range of 0 and 3. As Log *P* value increases in the positive direction, the lipophilicity

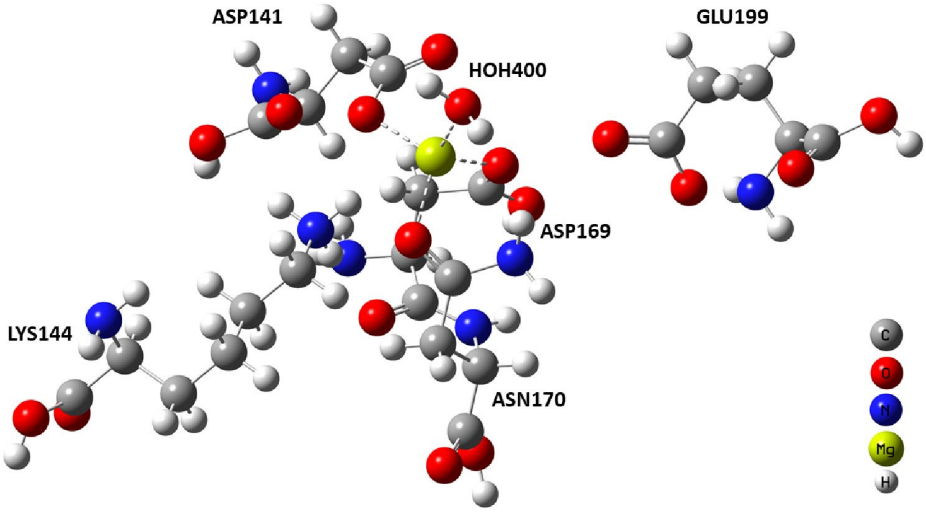


**Fig. 2** Amino acid residues drew to build the model of COMT active site

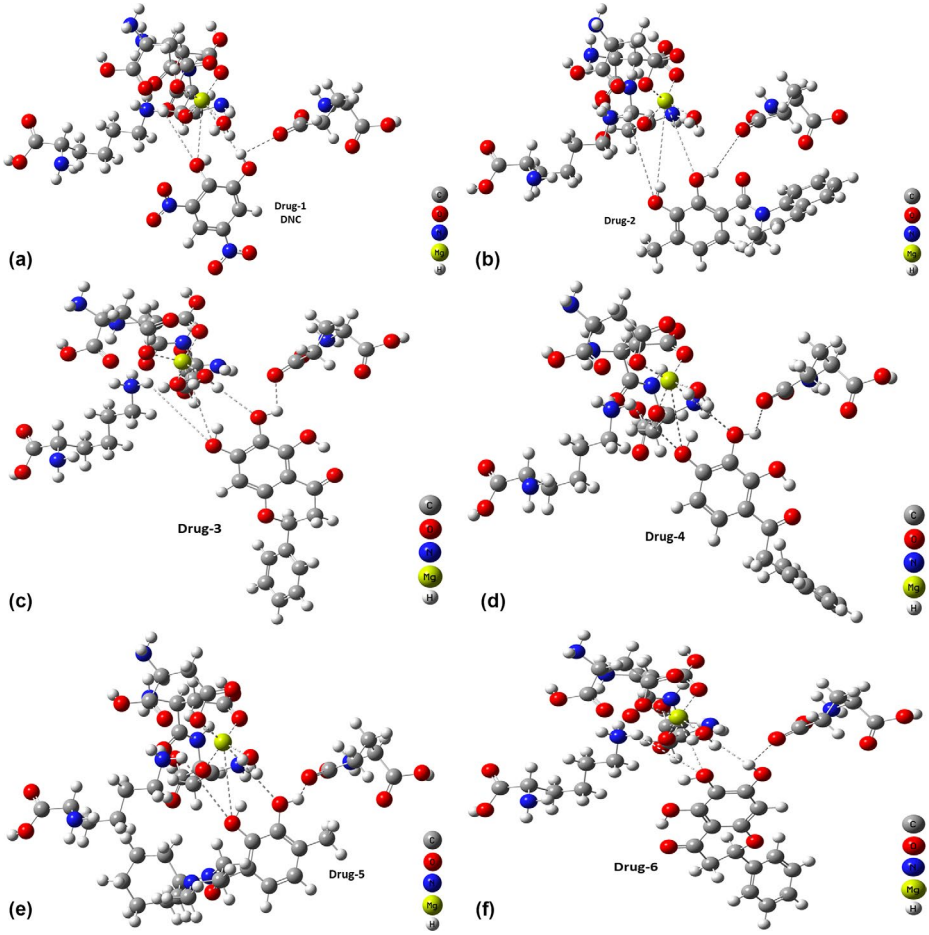


**Fig. 3** The different drugs interaction with COMT pocket: (**a**) DNC (the original ligand) interaction with COMT pocket residues, (**b**) MCULE-2003405854-0 interaction with COMT pocket residues, (**c**) CHEMBL402227 interaction with COMT pocket residues, (**d**) CHEMBL3109029 interaction with COMT pocket residues, (**e**) MCULE-8507898166-0 interaction with COMT pocket residues, (**f**) MCULE-9153751111-0 interaction with COMT pocket residues

is also increasing (more hydrophobic), which facilitates the movement of the drug across the lipid cell membrane (Arnott and Planey 2012). As the Log *P* value becomes closer to 0, it provides an equal distribution along the phospholipid membrane. The proposed drugs are more lipophilic than DNC which assures they can cross lipid membrane more easily than DNC. Additionally, they are qualified to penetrate the blood-brain barrier which is required to increase the efficiency of COMT inhibitors (Banks 2009). All the drugs have Lop *P* values in a range of 1 and 3.5 which is still less than 5 and it is still acceptable as drug-like according to Lipinski's rule of five. As shown in the table, the partition coefficient (Log P) values indicated that the highest drug in lipophilicity is drug 2 (3.467) while the lowest is DNC (1.385).

**Table 1** Calculated total energy (E) as eV, total dipole moment (TDM) as Debye and HOMO/LUMO band-gap energy (ΔE) as eV for COMT Pocket, different drugs (D1, D2, D3, D4, D5, D6) and its interactions with COMT Pocket at PM6 theoretical level

| Structure | E (eV) | TDM (Debye) | ΔE (eV) |
|---|---|---|---|
| D1: DNC | -2890.391 | 6.507 | 8.198 |
| D2: mcule-2,003,405,854 | -3488.565 | 4.621 | 8.209 |
| D3: chembl402227 | -3456.917 | 3.275 | 7.965 |
| D4: chembl3109029 | -3192.858 | 1.988 | 8.172 |
| D5: mcule-8,507,898,166 | -3792.230 | 4.950 | 8.447 |
| D6: mcule-9,153,751,111 | -3456.922 | 3.107 | 7.974 |
| COMT Pocket | -9659.256 | 9.517 | 4.600 |
| COMT Pocket-D1 | -12550.274 | 13.452 | 3.981 |
| COMT Pocket-D2 | -13148.379 | 12.489 | 4.743 |
| COMT Pocket-D3 | -13118.830 | 7.837 | 2.381 |
| COMT Pocket-D4 | -12853.559 | 3.752 | 3.978 |
| COMT Pocket-D5 | -13454.674 | 6.553 | 2.835 |
| COMT Pocket-D6 | -13119.347 | 7.996 | 2.229 |

**Table 2** QSAR parameters including Log P, heat of formation (HF) as kcal/mol, ionization potential (IP) as eV, molar refractivity (MR) as $m^3$/mol for COMT Pocket, different drugs (D1, D2, D3, D4, D5, D6) and its interactions with COMT Pocket calculated at PM6 theoretical level

| Structure | Log P | HF (kcal/mol) | IP (eV) | MR ($m^3$/mol) |
|---|---|---|---|---|
| D1: DNC | 1.385 | -62.959 | 10.364 | 44.096 |
| D2: mcule-2,003,405,854 | 3.467 | -68.713 | 8.769 | 86.267 |
| D3: chembl402227 | 1.987 | -163.962 | 8.822 | 70.429 |
| D4: chembl3109029 | 2.814 | -132.558 | 9.111 | 71.306 |
| D5: mcule-8,507,898,166 | 2.394 | -120.662 | 8.714 | 89.815 |
| D6: mcule-9,153,751,111 | 1.987 | -164.099 | 8.839 | 70.429 |
| COMT Pocket | -6.539 | -860.613 | 9.879 | 145.761 |
| COMT Pocket-D1 | -5.972 | -938.037 | 9.864 | 190.334 |
| COMT Pocket-D2 | -2.738 | -942.193 | 10.015 | 234.057 |
| COMT Pocket-D3 | -4.369 | -1086.273 | 6.950 | 215.639 |
| COMT Pocket-D4 | -5.008 | -1026.656 | 9.316 | 216.281 |
| COMT Pocket-D5 | -5.452 | -1055.118 | 7.490 | 236.589 |
| COMT Pocket-D6 | -5.858 | -1098.026 | 7.659 | 217.204 |

The heat of formation for all drugs is an exothermic process, which does not need any energy but instead, it releases it. The ionization potential of DNC is the highest with a value of 10.364 eV which assures its low reactivity.

All the drugs, including DNC, have a small surface area and volume compared to COMT pocket as indicated in Table 3. However, the proposed drugs have larger volume than that of DNC, so their molecular polarizability values are the highest as listed in Table 3.

There is a clear relationship between surface area, volume, and polarizability. The polarizability of drugs is directly proportional to their volume and, consequently, surface area. The MR and polarizability increased as the volume and molecular weight of drugs increased, which is convenient with the Lorentz–Lorenz formula that relates polarizability, refractive

**Table 3** Calculated surface area (SA) as $A^2$, volume (V) as $A^3$ and polarizability (P) as $A^3$ for COMT Pocket and different drugs (D1, D2, D3, D4, D5, D6) calculated at PM6 theoretical level

| Structure | SA ($A^2$) | V ($A^3$) | P ($A^3$) | MW (Da) |
|---|---|---|---|---|
| D1: DNC | 192.149 | 190.164 | 14.889 | 200.11 |
| D2: mcule-2,003,405,854 | 304.879 | 343.641 | 26.661 | 295.2017 |
| D3: chembl402227 | 274.092 | 296.719 | 23.364 | 272.2534 |
| D4: chembl3109029 | 276.176 | 300.282 | 22.124 | 258.27 |
| D5: mcule-8,507,898,166 | 331.689 | 395.907 | 24.943 | 318.2084 |
| D6: mcule-9,153,751,111 | 273.589 | 297.255 | 23.184 | 272.2534 |
| COMT Pocket | 532.728 | 795.378 | - | |

index, and molecular weight (Mignani et al. 2014). DNC has the lowest molecular weight (200.11 Da) and volume (190.164 $A^3$) and consequently lowest MR (44.096 $m^3$/mol), while drug 5 has the highest molecular weight (318.2084 Da), volume (395.907 $A^3$), and consequently highest MR (89.815 $m^3$/mol). The volume of all drugs assures that they can fit into the COMT pocket since they all have smaller volume than the pocket itself (< 532.728).

All the studied compounds achieved Lipinski's rule of 5 (number of hydrogen bond donor atoms < 5, number of hydrogen bond acceptors < 10, Log $P$ < 5, molecular mass < 500 Da). They also follow the Ghose filter and Egan rule.

## 4 Conclusion

Designing new drugs for Parkinson's disease is mandatory to minimize the side effects of the approved drugs and achieve better effectiveness (Cruz-Vicente et al. 2022). The proposed drugs are considering promising judged by their hydrophobic characteristics, which make them more sophisticated and spontaneously pass the blood-brain barrier (BBB), in addition to their stable interaction with COMT, which was more favorable than DNC. They are also compatible with the COMT pocket due to their size. Moreover, drug 2 and 5 specifically exhibit low reactivity toward the surrounding media due to the large difference in energy between HOMO and LUMO, which give them an advantage over the other proposed drugs. The current trend is to design drugs with dual inhibition effects on COMT and MAO-B, the proposed candidate drugs are promising for inhibiting both due to the similarity in the structure with other dual inhibitors such as Fisetin (Engelbrecht et al. 2019). Further research is needed to compare them with the FDA-approved drugs that penetrate BBB (tolcapone) to achieve a better counteract against these proteins which cause such a disease.

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**Data availability** The data will be available upon request. Contact Ahmed Refaat: am.refaat@nrc.sci.eg.

## Declarations

**Ethical approval** This work is not applicable to both human and/or animal studies.

**Competing interests** The authors declare no competing interests.



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