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Research article

# DFT studies on global parameters, antioxidant mechanism and molecular docking of amlodipine besylate

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ABSTRACT

Amlodipine besylate (AMB) is a synthetic dihydropyridine calcium channel blocker with antihypertensive and anti-anginal effects. Quantum computational investigations on AMB were done using DFT/B3LYP/6-311++G (d, p) level of theory, to study the molecular structural properties, nonlinear properties and antioxidant properties of AMB. The electrophilic and nucleophilic sites along with complete NBO analysis helps to locate the intermolecular electronic interactions and their stabilization energies. Complete NBO analysis was additionally done to locate the intermolecular electronic interactions and their stabilization energies. Charge distributions of Mulliken population, NBO and MEP are correlated. Also, the antioxidant properties of AMB were assessed to check whether these antioxidant effects contribute to the effects of antioxidant therapy. Further, the molecular docking studies of these compounds demonstrated a good selectivity profile with Monoamine oxidase B with better binding affinity and confirms AMB is a potent antioxidant.

## 1. Introduction

Dihydropyridines (DHP) is a significant class of calcium channel blockers, which are derived from the molecule dihydropyridine, usually used to reduce arterial pressure and vascular system resistance. The heterocyclic ring in DHP made it unique by inhibiting the influx of extracellular $Ca^{+2}$ through L-type voltage-dependent calcium channels. DHPs has broad application in medicinal industry for the treatment of hypertension and other calcium-dependent processes including muscle contraction, hormone or neurotransmitter release, gene expression, cell motility, cell division, cell death, etc., (Shaldam et al., 2014). Amlodipine is one of the recent developed vaso-selective dihydropyridine calcium antagonists which give rise to long-lasting (L-type) calcium currents (Nayler, 1997). Its remarkable pharmaco-kinetics and dynamics made its rationale from commercially available DHPs like nifedipine, phenylalkylamines, verapamil, and benzothiazepines (Shaldam et al., 2014).The unique chemical structure of amlodipine was derived from the DHP, nifedipine, with an omission of a nitro substituent group and incorporation of an essential amino acid side chain in the $C_2$ position of the dihydropyridine ring as shown in Fig. 1 (Nayler, 1997). Amlodipine besylate (AMB) is the besylate salt of amlodipine, that act as a long-acting calcium channel blocker (K.P. Safna Hussan et al., 2018a, b).The differentiating feature of AMB and its radical scavenging activity appealed the experimentalists to biological significance.

To our knowledge, computational studies based on frontier molecular orbitals and its antioxidant properties were not yet be done on AMB widely, while a joint experimental (FT-IR, FT-Raman, NMR) and theoretical DFT study on amlodipine besylate were reported by Szabó et al. (Leopold et al., 2009) and its pharmacokinetics and dynamics were experimentally explored extensively (Lee et al., 2015; Maheswari et al., 2014; Prasad et al., 1998; Ramya Deepthi and Kumar, 2016; K.P. Safna Hussan et al., 2018a, b; Suresh et al., 2015; Vishal et al., 2010). In this work, we present a detailed discussion on quantum computational calculations and predictions based on its structural geometry, frontier molecular orbitals; natural bond orbital analysis (NBO) and non-linear optical properties (NLO), of the title compound using B3LYP/6-311G+(d,p) level of theory. In addition, the electronic properties such as Highest occupied molecular orbital (HOMO) and Lowest unoccupied molecular orbital (LUMO), bond dissociation enthalpy (BDE),

*Abbreviations:* AMB, Amlodipine besylate; PA, proton affinity; EA, electron affinity; DFT, density function theory; χ, electronegativity; η, Hardness; S, Softness; μ, Chemical potential; ω, Electrophilicity index; MEP, molecular electrostatic potential maps; NBO, natural bond orbital; FMO, frontier molecular orbital; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; H, Enthalpy; S, Entropy; G, Gibbs free energy; IP, ionization potential; BDE, Bond Dissociation Energies; HAT, Hydrogen atom transfer; MAO, B- Monoamine oxidase B

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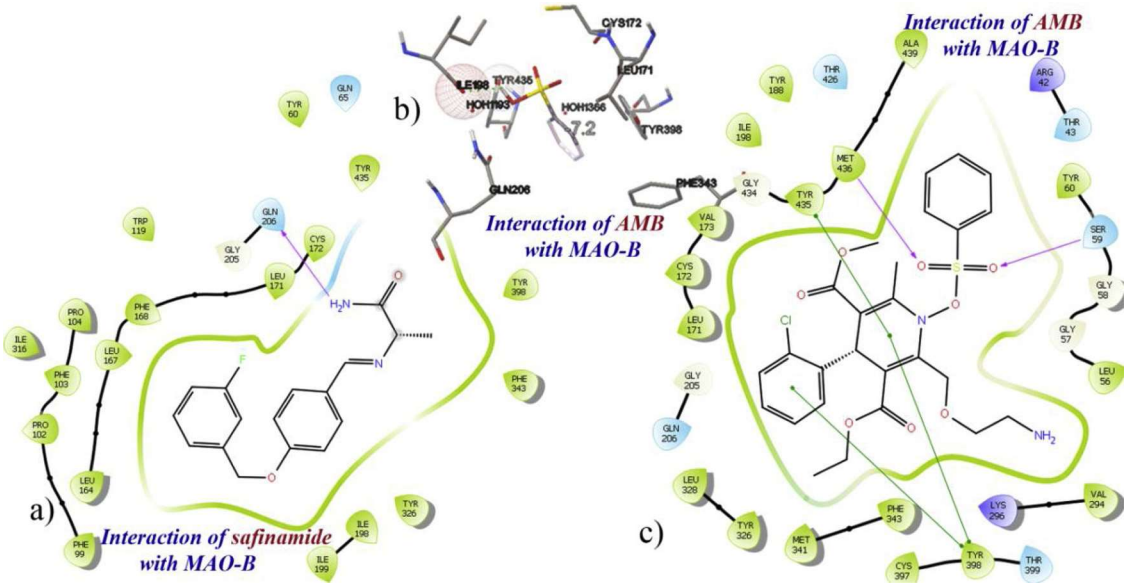


**Fig. 6.** Schematic representation of ligand protein interaction and binding interaction using stick mode. a) safinamide with MAO-B using Schrodinger, b) AMB with MAO-B using AutoDock Vina c) AMB with MAO-B using Schrodinger software.

these compounds demonstrats a good selectivity profile with Monoamine oxidase B with suitable binding affinity and confirms AMB is a potent antioxidant. The docking results from Schrodinger is found to be more accurate than Autodock Vina Software.

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