

Brain penetration in CNS and non-CNS drugs using molecular electronic parameters

C. Ergul, S. Kurumoglu*, Y. Yalcin Gurkan

Tekirdag Namik Kemal University, Department of Chemistry, Tekirdag, Turkey

Accepted: July 28, 2026

The blood-brain barrier (BBB) is a selective biological filter that protects the central nervous system, and it is important for some drugs to enter the brain while others do not. BBB permeability is conventionally predicted on the basis of physicochemical parameters, including logP, molecular weight, and total polar surface area (TPSA). However, research in this area is still in its early stages, with only a limited number of studies conducted thus far investigating the impact of these structural and reactive properties on the aforementioned process. The objective of this research endeavour was to ascertain the correlation between BBB penetration, as determined by DFT calculations, and global reactivity descriptors (i.e. η , ω , dipole moment, polarizability). A comparison with classical ADMET descriptors was also carried out. Four small molecules that have been clinically approved were selected for further investigation: Diazepam and carbamazepine exhibit high BBB permeability, while atenolol and metformin demonstrate low BBB permeability. The molecules were optimised at the B3LYP/6-311++G(d,p) DFT level, and parameters such as the HOMO-LUMO energy difference, chemical hardness, softness, electrophilic index, dipole moment, and polarizability were calculated. BBB parameters were evaluated using SwissADME via logBB, logP, and TPSA. The objective of this study was to establish a comparison that would reveal the reactivity and classical parameter differences between molecules that successfully pass the BBB and those that do not. Preliminary analyses indicate that molecules with high BBB passage exhibit reduced dipole moments and enhanced polarizability. Furthermore, it is hypothesised that the energy range and electrophilic indices may offer a superior explanation for BBB passage in comparison to classical logP and TPSA. The present study demonstrates that BBB permeability can be evaluated as a potential additional marker alongside reactivity parameters in molecular electronic parameter-based reactivity assessments and as a criterion in CNS drug design.

Keywords: ADMET, Blood-brain barrier, CNS drugs, DFT, Electronic reactivity, LogBB

INTRODUCTION

The blood-brain barrier (BBB) is a selectively permeable and highly dynamic interface that maintains homeostasis within the central nervous system (CNS) [1, 2]. This structure is vital for protecting the integrity of the nervous system by isolating the brain from potential pathogens and toxic molecules in the bloodstream. The integrity of the barrier is subject to regulation by a complex cellular network comprising endothelial cells, neurons, pericytes, and the basal laminae that tightly bind these components together. This microstructure is important for the global balance of the CNS [3]. One of the major problems in the management of CNS disorders is the low permeability of active substances through the BBB [4]. Poor pharmacokinetic behavior and undesirable safety features of potential drugs can impede the development of new pharmaceuticals [5].

The exposure of a particular compound in the brain depends on the physical characteristics of the compound [6]. In traditional literature, logBB value, the ratio between the total concentration of drug in

the brain and that in the blood stream, has been used as permeability standard [7, 8]. However, it is necessary to expand the scope beyond the consideration of concentration as the standardization of geometric factors like the polar surface area (PSA) of the molecule is critical [9].

Advanced computational approaches are used in modern drug discovery to overcome the limitations of experimental methods. Hybrid techniques such as the extreme parallel graph convolutional network (XP-GCN) are employed for analyzing molecular graph data, yielding highly accurate results without the need for backpropagation techniques [10]. Artificial neural networks were also proved to be a feasible approach to predict chemical absorption using the logBB scale [11].

Density functional theory (DFT) and time-dependent density-functional theory (TD-DFT) are used to calculate the optimal coordinates of the atoms inside the molecules and the energy band analysis [12, 13]. Information obtained from such computations such as the adiabatic ionization potential (AIP), the bond dissociation enthalpy (BDE), and molecular electrostatic potential (ESP) give detailed information regarding the interaction

* To whom all correspondence should be sent:

E-mail: skurumoglu@nku.edu.tr

of the molecule with biological entities [14, 15]. The Boiled-Egg approach is a method of *in silico* analysis that has been developed for the purpose of evaluating the absorption properties of drugs across both the gastrointestinal tract (GIT) and the blood-brain barrier (BBB). Nevertheless, the precision of such methodologies is subject to constant enhancement, in view of the challenges posed by imbalanced data sets and elevated false positive values [16].

The study of CNS permeability has a direct impact on the therapy of severe disorders such as Alzheimer's disease and epilepsy. For instance, the development of inhibitors that prevent A β peptide deposition and p-Tau protein phosphorylation in Alzheimer's disease requires a balance of physicochemical properties [17]. The drug carbamazepine, used to treat epilepsy, and benzodiazepines, popular due to their effectiveness in treating anxiety and insomnia, act by affecting GABA_A receptors in the brain [18-20]. The lipophilicity of beta-blockers (e.g., atenolol) can enable its penetration through the BBB, which may ultimately result in the appearance of neuropsychiatric side effects [21]. The interaction of metformin, a medication used to treat type 2 diabetes, with transporters at the blood-brain barrier (BBB), and the precise mechanism by which it penetrates the brain, remains a current area of research [22].

The primary novelty of this study is the introduction of an alternative perspective to the existing literature by correlating blood-brain barrier (BBB) permeability not only with classical physicochemical descriptors (logP, TPSA) but also with quantum mechanical-based global reactivity parameters. Although BBB crossing is usually analysed using empirical methods in the current literature, this study has conducted a thorough investigation of the electronic structure of molecules via dynamic indicators such as chemical hardness, polarizability and electrophilic index. These were investigated using DFT calculations performed at the B3LYP/6-311++G(d,p) level. In particular, the correlation of the decisive role of low dipole moment and optimised polarizability in the CNS transition with classical ADMET parameters provides a more precise and predictive set of criteria for central nervous system (CNS) drug design. This approach establishes an innovative evaluation framework for the design of future drug candidate molecules by accounting not only for passive diffusion but also for the molecule's potential for electronic interaction with its biological environment.

MATERIALS AND METHODS

Molecular optimization was performed using the Gaussian 09W software with the DFT/B3LYP method and the 6-311++G(d,p) basis set [23]. The molecular structures, optimized structures, and HOMO and LUMO orbitals of the basic dyes used to calculate quantum chemical parameters have been modeled. The frontier molecular orbital (FMO) has been used to estimate the E_{HOMO} (energy of the highest occupied molecular orbital) and E_{LUMO} (energy of the lowest unoccupied molecular orbital), followed by the values of the HOMO–LUMO energy gap, including global softness (η), global softness (S), electronic chemical potential (μ), electrophilic index (Ψ), electronegativity (χ), ionization energy (IE), and electron affinity (EA) were approximately calculated using the following equations in terms of HOMO and LUMO orbital energies [24].

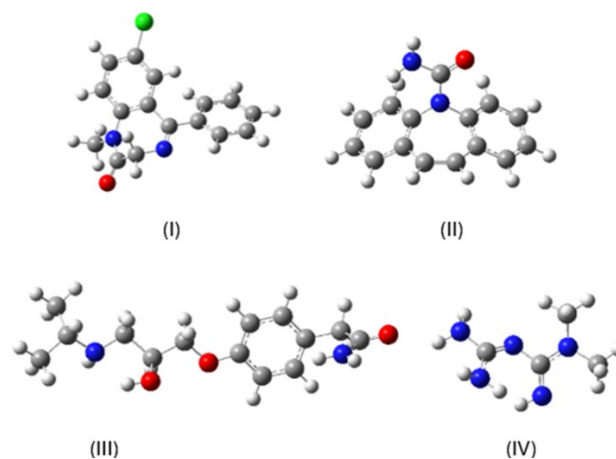


Fig. 1. Optimized structures of (I) diazepam; (II) carbamazepine; (III) atenolol; (IV) metformin (grey, C; white, H; red, O; blue, N; green, Cl)

Following the calculation of quantum chemical parameters, the pharmacokinetic profiles and blood-brain barrier (BBB) permeability potentials of the selected molecules were evaluated *in silico*. Physicochemical parameters (lipophilicity – logP, molecular weight and total polar surface area – TPSA) were obtained using the SwissADME platform (<https://www.swissadme.ch/index.php>). The molecules' central nervous system (CNS) penetration capabilities were validated via numerical logBB and logPS (Permeability-Surface area product) values obtained through the pkCSM (<https://biosig.lab.uq.edu.au/pkcsm/>) databases. In particular, the logPS values obtained from the pkCSM platform were classified based on the critical threshold of -2 for CNS penetration. In the final stage, a correlation analysis was performed between the reactivity indices (η , S , μ , Ψ) from the Gaussian

09W output and *in silico* ADME data to investigate the decisive influence of electronic structure on the BBB crossing mechanism.

RESULTS AND DISCUSSION

The computed thermodynamic properties, which include total electronic energy (ΔE), enthalpy (ΔH), and Gibbs free energy (ΔG), for diazepam, carbamazepine, atenolol, and metformin have been given in Table 1. The calculated energy is found to be significantly negative for all molecules, thereby indicating that the optimized geometry is energetically favorable from a thermodynamic perspective.

Table 1. Gibbs free energy, enthalpy and energy values of optimized molecules

Molecule	ΔE (kcal/mol)	ΔH (kcal/mol)	ΔG (kcal/mol)
Diazepam	-792045.3	-792044.7125	-792083.5
Carbam- azepine	-478999.09	-478998.4994	-479033.15
Atenolol	-553199.19	-553198.5967	-553198.6
Metformin	-271486.21	-271485.6199	-271514.89

The analysis of the molecular structure of the pharmaceutical compound revealed that diazepam exhibited the least significant differences in enthalpy (ΔH), entropy (ΔS), and Gibbs free energy (ΔG). This finding suggests that diazepam possesses enhanced stability in comparison to the other drug molecules that were analyzed in this study. Atenolol demonstrated greater stability and exhibited higher energy levels compared to diazepam. Additionally, carbamazepine and metformin showed elevated energy levels, which can be attributed to differences in molecular size and heteroatom content.

The Gibbs free energies aligned with the trends observed in total electronic energy and enthalpy. The negative ΔG values for the analyzed compounds indicate that their molecular conformations are energetically favored. The minimal difference between ΔE and ΔH values suggests that only minor corrections are necessary when accounting for heat, whereas ΔG values incorporate entropic effects.

The results obtained in this study provide a comprehensive overview of the thermodynamics of the pharmaceutical molecules under investigation. The structural stability is confirmed by these results, which are theoretically supported for studying its further chemical reactivity, interactions with each other, and sorption characteristics.

Table 2 presents the BBB permeability characteristics of logPS, consensus Log Po/w and

topological polar surface area (TPSA), values for selected pharmaceuticals.

Table 2. Prediction results of optimized molecules using SwissADME and pkCSM

Molecule	logPS	Consensus log Po/w	TPSA (Å ²)	BBB permeability
Diazepam	-0.89	2.97	32.67	yes
Carbam- azepine	-0.84	2.40	46.33	yes
Atenolol	-2.19	1.00	84.58	no
Metformin	-3.16	-0.89	91.49	no

Diazepam and carbamazepine exhibited relatively high lipophilicity values, with consensus Log Po/w values of 2.97 and 2.40, respectively. Furthermore, the two substances exhibited low TPSA values (32.67 and 46.33 Å², respectively), which are conducive to passive diffusion. Furthermore, both had elevated logPS values (indicative of reduced negative charge), suggesting effective permeability through the BBB. Consequently, the prediction results indicate that both substances were BBB permeable, thereby aligning with their observed pharmacological effects on the CNS.

Conversely, both atenolol and metformin exhibit comparatively low BBB permeability. Atenolol exhibits intermediate lipophilicity (Log Po/w=1.00) in conjunction with a relatively elevated TPSA value (84.58 Å²). Consequently, the logPS value of the latter was found to be the smallest at -2.19. With regard to metformin, it possesses the lowest lipophilicity (log Po/w: -0.89) and the highest TPSA value (91.49 Å²), indicating that the substance is highly polar and less membrane-permeable. Consequently, both substances are predicted to be unable to pass through the BBB ("no").

The results of the analysis demonstrate a strong correlation between the BBB permeability of the compounds and their lipophilicity and polarity. In general, compounds that exhibit high logP values and low TPSA values tend to demonstrate enhanced penetration into the BBB in comparison to those possessing high TPSA values and low logP values.

The global chemical reactivity descriptors were calculated by utilizing the values for the frontier molecular orbital energies in accordance with Koopmans' theorem. The chemical potential, denoted by μ , is calculated from the average value of the frontier orbital energies, while the global hardness, denoted by η , is calculated from half of the HOMO-LUMO gap energy (ΔE). The remaining parameters, namely the electrophilicity index (ψ), global softness (s), electronegativity (χ), ionization energy (IE), and electron affinity (EA), are derived

from these initial values. The equations, used in the calculations, are given below:

$$\mu = \frac{E_{\{HOMO\}} + E_{\{LUMO\}}}{2} \quad (1)$$

$$\eta = \frac{E_{\{HOMO\}} - E_{\{LUMO\}}}{2} \quad (2)$$

$$\psi = \frac{\mu^2}{2\eta} \quad (3)$$

$$S = \frac{1}{2\eta} \quad (4)$$

$$\chi = -\frac{E_{\{HOMO\}} + E_{\{LUMO\}}}{2} = -\mu \quad (5)$$

$$IE = -E_{\{HOMO\}} \quad (6)$$

$$EA = -E_{\{LUMO\}} \quad (7)$$

The global reactivity indices for diazepam, carbamazepine, atenolol and metformin, as determined using FMO theory, are presented in Table 3 below. The indices are of significance in understanding the electronic stability, reactivity, and electron transfer capability of the compounds.

Table 3. Global reactivity descriptors of optimized molecules

Global reactivity descriptors	Diazepam	Carbamazepine	Atenolol	Metformin
HOMO	-6.26	-5.78	-5.79	-5.40
LUMO	-1.70	-1.36	-0.18	0.56
ΔE	4.56	4.42	5.61	5.96
Chemical potential (μ)	-3.98	-3.57	-2.98	-2.42
Global hardness (η)	-2.28	-2.21	-2.81	-2.98
Global softness (s)	-162.29	-167.50	-131.91	-124.22
Global electrophilicity index (ψ)	-0.01	-0.01	-0.01	-0.02
Electronegativity (χ)	3.98	3.57	2.98	2.42
Ionization energy (IE)	6.26	5.78	5.79	5.40
Electron affinity (EA)	1.70	1.36	0.18	-0.56

The HOMO energies of the studied molecules were found to vary between -6.26 and -5.40 eV. Diazepam has the minimum HOMO energy levels (-6.26 eV) which represents low energy required to remove an electron. Conversely, metformin had the maximum HOMO energy level (-5.40 eV), indicative of the strongest electron donor. LUMO Energies Diazepam and carbamazepine had negative LUMO energy indicating strong propensity to accept electrons. On the other hand, metformin had the highest LUMO energy, which was positive value (0.56 eV).

The energy difference between HOMO and LUMO (denoted by ΔE) is considered as an important parameter for estimating the molecular stability and chemical reactivity. As for the energy gap atom, the result indicates that carbamazepine has the steepest energy gap (4.42 eV), while diazepam has the second largest energy gap just a little higher than carbamazepine (4.56 eV), that means carbamazepine low and so that of diazepam have high chemical reactivity and low kinetic stabilities. The energy difference between the highest occupied and the lowest unoccupied state of metformin is the highest (5.96 eV), implying that metformin is the most kinetically stable and least reactive molecule. Atenolol also had a relatively large ΔE value (5.61 eV), indicating that its electronic structure was more stable relative to others.

The values for the chemical potential (μ) and electronegativity (χ) also supported the electronic nature of these complexes. Among these molecules, diazepam had the maximum electronegativity value (3.98 eV), so it has the strongest pull on electrons. Conversely, the lowest electronegativity value was observed in metformin (2.42 eV), revealing a weakened ability to attract electrons. In addition, the more negative chemical potentials of diazepam and carbamazepine imply greater electronic-structure stabilization relative to atenolol and metformin.

Based on the global hardness values, metformin and atenolol were proposed as more stable molecules with high energy gap between HOMO and LUMO and low reactivity. However, carbamazepine and diazepam exhibited lower global hardness values, indicating a more flexible electronic structure. The same behavior was observed in the context of global softness (s) values of these molecules, with carbamazepine exhibiting the highest value.

The electrophilicity indices obtained are relatively low for all chemicals, thus demonstrating moderate electrophilicity behavior. With regard to the ionization energy, it was established that in order to strip off its electrons, Diazepam requires elevated levels of energy. Conversely, metformin exhibited the lowest ionization energy, thereby demonstrating a pronounced propensity for electron donation. The electron acceptor behavior of diazepam and carbamazepine is also notably higher than that of atenolol and metformin, as evidenced by the electron acceptor values.

In conclusion, from the analysis of the global chemical reactivity descriptors, it is evident that diazepam and carbamazepine exhibit significantly higher levels of reactivity in comparison to atenolol and metformin.

CONCLUSIONS

The permeability of the blood-brain barrier (BBB) to four model compounds (diazepam, carbamazepine, atenolol, and metformin) was studied using quantum chemistry-based reactivity descriptors and *in silico* ADME tools. Compounds that exhibit a higher BBB permeation ability (diazepam, carbamazepine) are associated with a smaller energy difference between HOMO and LUMO levels and a “softer” electronic structure. This facilitates their interaction with membranes. Conversely, BBB impermeable compounds (atenolol, metformin) exhibit a larger gap between electronic levels and higher hardness, which is consistent with increased passivity towards diffusive permeation. The results obtained via our quantum chemical study and virtual pkCSM (logPS) /SwissADME (TPSA) studies were found to be highly congruent. It has been demonstrated that global indices of reactivity can be regarded as potent, high-precision biomarkers for CNS-targeting drug discovery, which can exceed the efficacy of classical descriptors (logP/TPSA).

Acknowledgement: The financial support provided by Tekirdag Namik Kemal University BAP unit through Project No. NKUBAP.64.YL.24.546 is gratefully acknowledged.

REFERENCES

1. Y. Zhao, L. Gan, L. Ren, Y. Lin, C. Ma, X. Lin, *Brain Research*, **1788**, 147937 (2022).
2. R. Kumar, A. Sharma, A. Alexiou, A. L. Bilgrami, M. A. Kamal, G. M. Ashraf, *Frontiers in Neuroscience*, **16**, 858126 (2022).
3. Z. F. Gu, Y. D. Hao, T. Y. Wang, P. L. Cai, Y. Zhang, K. J. Deng, H. Lv, *BMC Biology*, **22**(1), 86 (2024).
4. D. J. Begley, *Pharmacology & Therapeutics*, **104**(1), 29 (2004).
5. M. Fridén, Prediction of Drug Exposure in the Brain from the Chemical Structure, in *Drug Delivery to the Brain: Physiological Concepts, Methodologies and Approaches*, Springer New York, New York, NY, 2013, p. 317.
6. M. Fridén, Prediction of Drug Exposure in the Brain from the Chemical Structure, in *Drug Delivery to the Brain: Physiological Concepts, Methodologies and Approaches*, Springer International Publishing, Cham, 2022, p. 437.
7. F. Meng, Y. Xi, J. Huang, P. W. Ayers, *Scientific Data*, **8**(1), 289 (2021).
8. T. Kim, B. H. You, S. Han, H. C. Shin, K. C. Chung, H. Park, *International Journal of Molecular Sciences*, **22**(20), 10995 (2021).
9. C. P. Spielvogel, N. Schindler, C. Schröder, S. L. Stellnberger, W. Wadsak, M. Mitterhauser, C. Vranka, *Journal of Chemical Information and Modeling*, **65**(6), 2773 (2025).
10. M. A. Pala, *Computational Biology and Chemistry*, **120**, 108755 (2026).
11. Q. Zhang, D. Mao, Y. Tu, Y. Y. Wu, *Journal of Chemical Information and Modeling*, **64**(15), 5853 (2024).
12. K. Asokan, S. Sivaraman, K. Nallasamy, J. Subbiah, S. Paranthaman, *Indian Journal of Biochemistry and Biophysics*, **62**(4), 406 (2025).
13. D. Şakar, E. Üstün, *Russian Journal of Inorganic Chemistry*, **68**(9), 1303 (2023).
14. B. T. Ogunyemi, *Communication in Physical Sciences*, **12**(2), 1081 (2025).
15. M. Sönmez Çelebi, M. Çol Ayvaz, D. Şakar, E. Üstün, Ö. Ertürk, *Inorganica Chimica Acta*, **585**, 122752 (2025).
16. S. Şahin, N. Dege, *Polyhedron*, **205**, 115320 (2021).
17. N. Job, V. S. Thimmakondur, K. Thirumoorthy, *Molecules*, **28**(3), 1388 (2023).
18. P. M. Burkat, *The Journal of Clinical Pharmacology*, **62**(10), 1297 (2022).
19. M. Uzzaman, A. Ahsan, M. N. Uddin, *European Journal of Chemistry*, **12**(4), 412 (2021).
20. F. Sotoudegan, M. Amini, M. Sharifzadeh, N. Samadi, F. Sotoudegan, *AAPS Open*, **10**(1), 12 (2024).
21. V. Dahiya, A. Rohilla, S. Jain, S. Rohilla, *Asian Journal of Pharmaceutical and Clinical Research*, **15**(6), 9 (2022).
22. S. Sharma, Y. Zhang, K. A. Akter, S. Nozohouri, S. R. Archie, D. Patel, T. Abbruscato, *Pharmaceutics*, **15**(5), 1357 (2023).
23. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, Gaussian 09, Revision C.01, Gaussian, Inc., Wallingford, CT, USA, 2010.
24. G. Pirinççi, Ş. Kürümoğlu, *Kahramanmaraş Sütçü İmam Üniversitesi Mühendislik Bilimleri Dergisi*, **29**(1), 243 (2026).