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Synthesis, Molecular Docking and in Silico ADME Prediction of 2-Benzoylamino-*N*-Phenyl-Benzamide Derivatives

Karima Ighilahriz
Mouloud Mammerie University of Tizi-Ouzou

Amina Benazzouz –Touami
Mouloud Mammerie University of Tizi-Ouzou

Malika Makhloufi-Chebli
Mouloud Mammerie University of Tizi-Ouzou

Noura Kichou
Mouloud Mammerie University of Tizi-Ouzou

Abstract: 2-Benzoylamino-*N*-phenyl-benzamide derivatives (3a–h) were synthesized starting from 2-phenyl-3,1-(4*H*)-benzoxazin-4-one and substituted anilines in the presence of acid as catalysts. The reaction were conducted without under solvent-free condition and microwave irradiation, offering an efficient and environmentally friendly synthetic approache. The compound structures were established by NMR (including extensive 2D NMR analysis). Additionally, structure–activity relationship study was performed to establish correlation between the chemical structures and their potential biological activities. Physicochemical properties of the compounds were analized, and their pharmacokinetic profiles ADME were predicted using in silico tools. these assessment included predictions of bioavailability drug-likeness levels, showing that several of the derivatives exhibited acceptable and favorable properties for pharmaceutical application. The drug-likness further supported suitability as drug candidates. Finally, molecular docking was studies were carried out to investigate the interactions of these compounds with biological targets. The docking results highlighted promising binding for certain derivatives, suggesting their potential as effective therapeutic agents. Overall, this study demonstates the successful design and synthesis of novel benzamide derivatives with encouraging pharmacological profiles for future drug development.

Keywords: Benzoylamino-*N*-phenyl-benzamides, ADME, Molecular docking

Introduction

In December 2019, the SARS-CoV-2-caused coronavirus illness 2019 (COVID-19) outbreak sparked a global health concern. It is a member of the coronavirus family of single-stranded positive-sense RNAs (Lo et al., 2020). Its genome consists of different regions including a spike protein (S) gene, an envelope protein (E) gene, a membrane protein (M) gene, and a nucleocapsid protein (N) gene (Zhu et al., 2020). ,e sequence of SARS-CoV-2 showed more than 50% identity to SARS-CoV and MERS-CoVandcloserrelationto bat-SL-CoVZC45 (Chan et al., 2020).

SARS-CoV produces several functional proteins while its main protease is emerging as a promising therapeutic target as it is responsible for the processing of translated polyprotein. ,us, inhibition of the main protease was confirmed to affect the viral replication (Yamamoto et al., 2020). Its high sequence conservation with SARS-CoV main protease suggests the effectiveness of HIV-1 protease in hibitors such as nelfinavir against it (Wu &

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McGoogan, 2020). SARS-CoV-2 shares the mode of transmission with SARS-CoV and MERS-CoV, after which it binds to ACE2 on the surface of host cells via the receptor-binding domain (RBD) in its spike proteins (Li, 2016). Blocking the ACE2 and RBD interaction by antibodies and inhibitors would be an effective way to stop the virus infection (Chung et al., 2004).

Symptoms of COVID-19 greatly resembled viral pneumonia ranging from mild to more severe eventually ending in several organ malfunction (Wu & McGoogan, 2020). Discovery of effi cacious drugs for this deadly disease could be achieved by one of the three options: testing the existing antiviral drugs which are already used to treat viral infections, secondly, screening of different existing drugs, and finally, discovery of new specific drugs based on the individual coronavirus genome (Lu et al., 2020). Chloroquine, HIV protease inhibitors, ACE-2 inhibitors, and many other drugs were predicted to be COVID-19 drug candidates (Maxmen et al., 2020).

Benzamides and their derivatives have garnered considerable attention due to their significant biological activities. A wide array of benzamide derivatives, often incorporated into clinically relevant drug candidates, exhibit notable pharmacological properties. These include anticonvulsant (Foster et al., 1999), Anti-inflammatory (Caliendo et al., 2001), Analgesic (Carnson et al., 2004), Antitumor (Xu et al., 2006) Antimicrobial (Sener et al., 2002) and antiviral activity (Chen et al., 2013). Particularly, *N*-phenylbenzamide derivatives have demonstrated a variety of applications, with several showing promising antiviral properties (Ji, X.Y., et al., 2013). It is therefore imperative to test their effectiveness in COVID-19.

Computational methods are commonly used for structure-based drug discovery (SBDD) and ligand-based drug discovery (LBDD) (Wakui et al., 2018). Since they accelerate the lengthy drug discovery and development process, recently, they have been extensively used for lead discovery against COVID-19 by virtually screening compounds with potential biological activity (Elmezayen et al., 2020). However, few studies were directed towards the discovery of multitarget drugs (Joshi et al., 2020). The present study computationally assesses the inhibitory effects of Benzoylamino-*N*-phenyl-benzamides on two potential SARS-CoV-2 drug targets and predicts their pharmacokinetics identifying promising candidates against COVID-19.

Method

Experimental Method

The melting points were take ninan open capillary tube using an Electrothermal melting point apparatus (Electrotermal, Rochford, GreatBritain). Thevaluesare reportedin Candareuncorrected. 1H and 13C NMR spectra were recorded in DMSO-d6 solutions on Bruker Avance 300 (300.13 MHz for 1H and 75.47 MHz for 13C) spectrometer. Chemical shifts are reported in parts per million (d, ppm) using TMS as internal reference and coupling constants (J) are given in hertz (Hz). 13C assignments were made using NOESY, HSQC, and HMBC (delays for one bond and long-range JC/H couplings were optimized for 145 and 7 Hz, respectively) experiments.

Computational Method

The crystal structure of the target protein for the COVID-19 study (PDB ID: 6LU7) was retrieved from the Protein Data Bank (PDB) in its 3D format. Protein structure refinement was carried out using Discovery Studio software. Prior to molecular docking, both the target proteins and the synthesized ligands were prepared using AutoDock Tools. This preparation process included energy minimization, addition of charges, incorporation of polar hydrogens, and the generation of a grid box. A grid-based docking approach was employed, with carefully defined dimensions and spacing to accurately model the active sites. The docking grid was centered at the coordinates X = -10.712, Y = 12.411, and Z = 68.831, with a grid spacing of 0.375 Å, enabling detailed exploration of the binding domain.

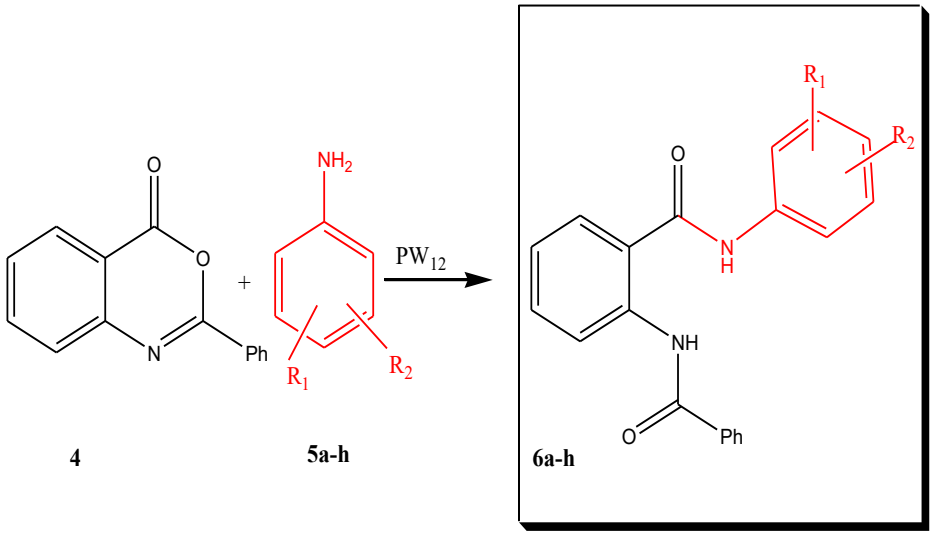
In Silico ADME Prediction

In silico predictive models play a crucial role in modern drug discovery by providing early estimations of the ADME (Absorption, Distribution, Metabolism and Excretion) profiles of compounds. These predictions help researchers evaluate the potential safety and efficacy of new drugs before they enter costly and time-consuming

in vitro or in vivo testing phases. Thus, SwissADME server was used to predict the ADME profile of the tested compounds.

Synthesis

A mixture of the appropriate 2-phenyl-1,3-(*4H)*-benzoxazin-4-one 1 and amines (10 mmol) was added the catalyst heteropolyacid (1.2 mol %). This mixture was heated by microwave, initially set to 300 W for 3 min and then it was increased to 450 W for 10 min. The obtained solid was washed by the water to eliminate acid.



Scheme 1. Synthesis of 2-Benzoylamino-*N*-phenyl-benzamide derivatives

Results and Discussion

Caracterization

The 2-Benzoylamino-*N*-phenyl-benzamide derivatives 3a-h were prepared in good yields (65-92 %) (Ighilahriz et al., 2017). It was found that yields of products 3 depend on the nature substituent groupe aniline. the presence of electron donating groups led to a yield increase. se. With methyl and hydroxy groups in C_6H_4, the yields are 85% and 92%, respectively, against 80% for the phenyl. These groups are beneficial because of their high electron density, induced by the aromatic system unlike, the electron chloro, which led to a yield decrease from 80% to 78%. The presence of a second chlorine atom in the aniline also led to a yield decrease from 78% to 65%. Among dichloroanilines, 2,4-dichloro-C_6H_3 gave the better yield (73% against 65–70%). This decrease is attributed to the group steric effect (Table 1).

Table 1. Melting points Mp and yields of compounds 3a-h.

Compounds	ArNH	Yields (%)	Melting points (^{0}C)
3a	C_6H_5	80	281
3b	4-CH_3-C_6H_4	85	123
3c	4-OH-C_6H_4	92	160
3d	4-Cl-C_6H_4	80	161
3e	2,4-Cl_2- C_6H_3	75	140
3f	2,5-Cl_2- C_6H_3	70	167
3g	2,6-Cl_2- C_6H_3	65	162
3h	3,4-Cl_2- C_6H_3	70	192

Structures of all prepared compounds were confirmed by, IR, NMR (including extensive 2D NMR analysis, such as HSQC, HMBC, and NOESY) and elemental analysis analysis. The IR spectrum also confirms the structure of compounds 3a-h by the appearance of two characteristic bands at 1647-1674 cm-1 and 2925-3393 cm-1 corresponding to the carbonyl and imine functions, respectively (Table 2).

Table 2. IR bands for the compounds 3a-h as KBr pellets.

Compounds \ Fonction	ν C=O	υC=N
3a	1647	3280
3b	1650	2935
3c	1698	3010
3d	1660	2925
3e	1667	3293
3f	1647	3286
3g	1674	3300
3h	1647	3273

In order to clarify the structures of the synthesised compounds, 2D NMR (HMBC) analyses of compound (3d) have been selected as examples. The HMBC (heteronuclear multiple bond correlation) spectrum identifies long-range couplings between protons and carbons via two or three chemical bonds. HMBC analysis of compound 3d shows correlations between H-8 and the amide C7, confirming condensation. Additionally, correlations between H-6 and C1, C2, and C7, as well as H-2' and C1', support the proposed structure of compound 3d.

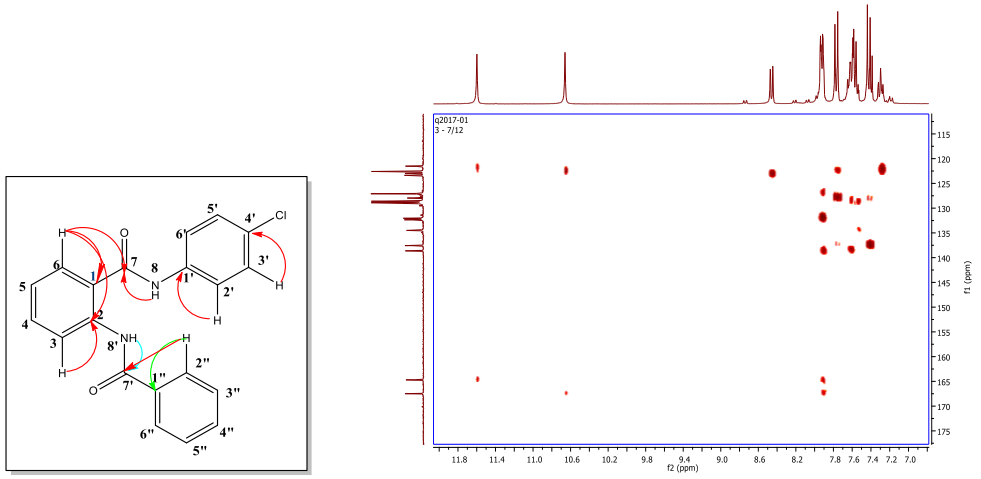


Figure 1. The HMBC spectra and connectivities of 3d

The structures of the synthesised compounds 3a-d were further confirmed by and elemental analysis (Table 3).

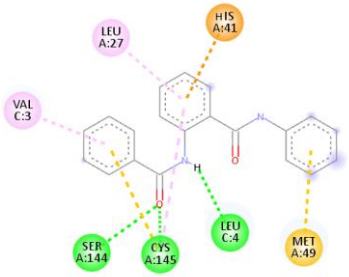
Table 3. Elemental analysis data for the compounds 3a-h.

Compounds	Chemical formula	Elemental analysis Calcd. %	Elemental analysis Found%
3a	$C_{20}H_{16}N_2O_2$	C 76.13, H 5.25, N 8.98, O 9.63	C 75.93, H 5.10, N 8.86, O 10.11
3b	$C_{21}H_{18}N_2O_2$	C 76.55, H 5.60, N 8.53, O 9.31	C 76.43, H 5.49, N 8.48, O 9.69
3c	$C_{20}H_{16}N_2O_3$	C 72.50, H 4.96, N 8.49, O 14.04	C 72.28, H 4.85, N 8.43, O 14.44
3d	$C_{20}H_{15}ClN_2O_2$	C 68.55, H 4.36, Cl 10.13, N 7.39, O 9.57	C 68.48; H 4.31, Cl 10.11, N 7.99, O 9.12
3e	$C_{20}H_{14}Cl_2N_2O_2$	C 62.50, H 3.71, Cl 18.48, N 7.37, O 7.94	C 62.34, H 3.66, Cl 18.41, N 7.27, O 8.31
3f	$C_{20}H_{14}Cl_2N_2O_2$	C 62.50, H 3.71, Cl 18.48, N 7.37, O 7.94	C 62.34, H 3.66, Cl 18.41, N 7.27, O 8.31
3g	$C_{20}H_{14}Cl_2N_2O_2$	C 62.50, H 3.71, Cl 18.48, N 7.37, O 7.94	C 62.34, H 3.66, Cl 18.41, N 7.27, O 8.31
3h	$C_{20}H_{14}Cl_2N_2O_2$	C 62.50, H 3.71, Cl 18.48, N 7.37, O 7.94	C 62.34, H 3.66, Cl 18.41, N 7.27, O 8.31

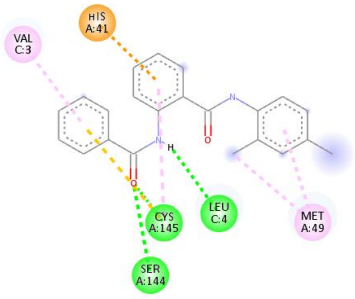
Binding Mode of Studied Compounds

The active site of the enzyme is formed by His41, Met49, Phe140, Leu141, Asn142, Gly143, His163, His164, Met165, Glu166, Leu167, Pro168, His172, Gln189, Thr190, and Ala191. The amino acid residues His41 and

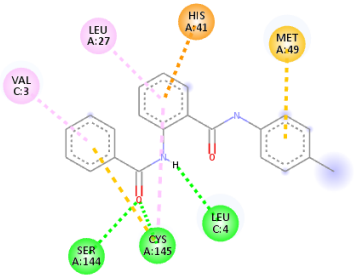
Cys145 constitute a catalytic dyad within the active site, located between domain I and domain II (Pratama et al., 2020). The docking results demonstrate that all ligands are anchored within the catalytic site, engaging specifically with the dyad formed by His41 and Cys145, with binding energies ranging from -8.4 kcal/mol to -6.5 kcal/mol. Stabilization of the ligand–protein complexes is primarily mediated by hydrogen bonds involving Cys145, Leu4, and Ser144 for compounds 3a, 3b, 3d, 3f, and 3g; Phe140 for compound 3c; and Thr26 for compound 3h.



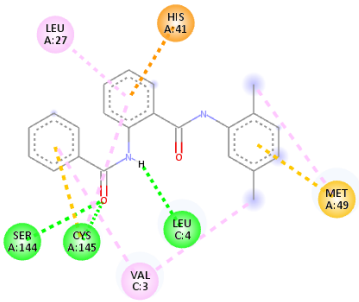
3a, *E=-8.1 Kcal/mol*



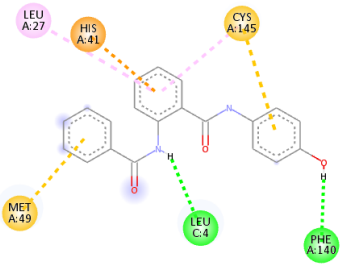
3e, *E=-8.3 Kcal/mol*



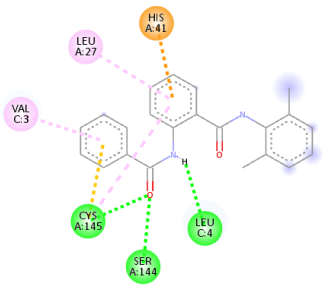
3b, *E=-8.2Kcal/mol*



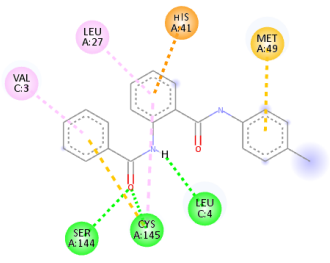
3f, *E=-8.3 Kcal/mol*



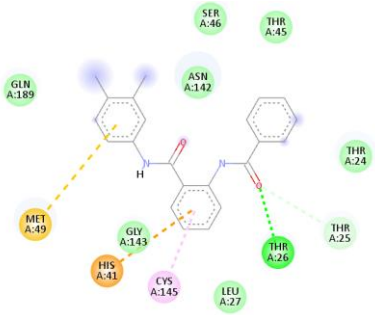
3c, *E=-7.5Kcal/mol*



3g, *E=-7.9Kcal/mol*



3d, *E=-8.1Kcal/mol*



3h, *E=-6.5 Kcal/mol*

Figure 2. Promising 2-Benzoylamino-*N*-phenyl-benzamide derivatives in the active site of SARS-CoV-2 main protease (PDB ID: 6LU7).

Importantly, for all evaluated ligands, both residues of the catalytic dyad (His41 and Cys145) participate in multiples types of non-covalent interactions, including hydrophobic contacts and electrostatic interactions, underscoring their critical role in ligand binding.

In the active site of the receptor macromolecule 6LU7, the best binding conformations of compounds 3a–h were observed. The superimposition reveals that all the molecules are located within the active site cavity, indicating their direct interaction with the catalytic residues.

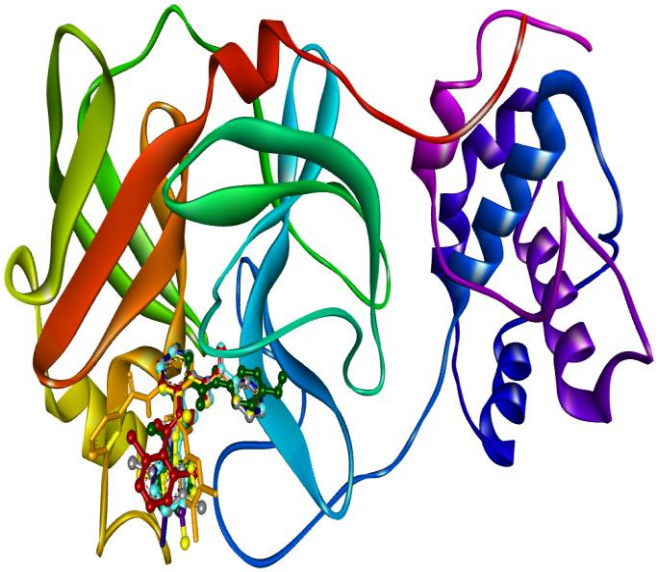


Figure 3. Superimposition of docked conformations of the compounds, **3a-h** on the crystal structure protein 6LU7.

The candidate compounds 3a–h were further evaluated for their predicted pharmacokinetic and physicochemical properties profiles using the freely accessible web-based tool SwissADME. Analyzing the ADME properties (Absorption, Distribution, Metabolism and Excretion) of the target compounds provides crucial information to guide the selection of the most promising drug candidates. The Veber and Lipinski guidelines were applied to predict the oral drug-likeness of the compounds, with all candidates complying except for a single violation of Veber's rule (TPSA > 140 Å²). The bioavailability radar plots showed that, apart from slight deviations in polarity and saturation, the evaluated 2-Benzoylamino-*N*-phenyl-benzamide derivatives (3a–h) fell within the optimal range (pink area) for key parameters including solubility, lipophilicity, flexibility, and molecular size (Fig. 4). These findings provide strong evidence supporting the potential oral bioavailability of the investigated compounds.

In Silico ADME Prediction

Table 3. Calculated physicochemical characteristics of 2-Benzoylamino-*N*-phenyl-benzamide derivatives 3a–h.

Compounds	MW g/mol	TPSA Å²	nRB	nHBA	nHBD	MlogP	Violation
Rule	≤500	≤140	≤10	≤10	≤5	≤4.15	-
3a	316.35	58.20	6	2	2	2.59	yes
3b	330.38	58.2	6	2	2	2.61	yes
3c	332.35	78.43	6	3	3	2.15	yes
3d	350.80	58.20	6	2	2	2.96	yes
3e	385.24	58.20	6	2	2	2.91	yes
3f	385.24	58.20	6	2	2	2.91	yes
3g	385.24	58.20	6	2	2	2.91	yes
3h	385.24	58.20	6	2	2	2.91	yes

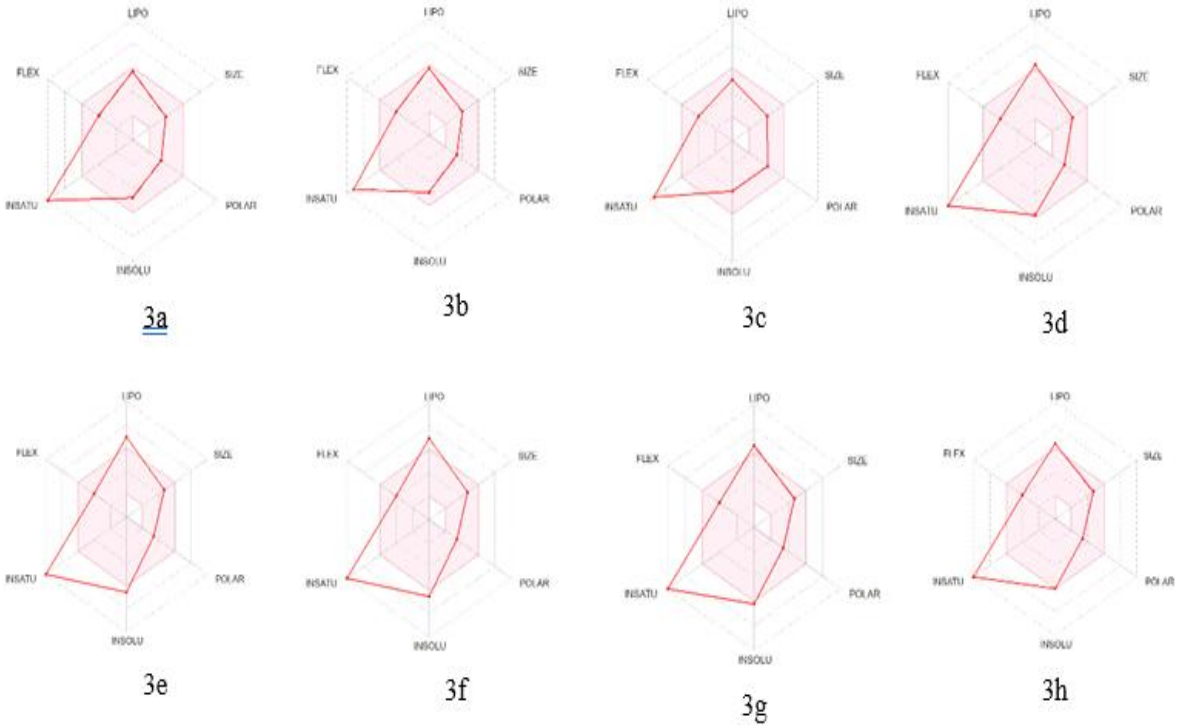


Figure 4. All the eight compounds show in colored zone are the suitable physiochemical space for oral bioavailability and show the LIPO(Lipophilicity), SIZE (Molecular Weight), POLAR (Polarity), INSOLU (Insolubility), INSATU (Instauration) and FLIX (Rotable bond flexibility) parameters

Conclusion

High yields of 2-benzoylamino-*N*-phenylbenzamide derivatives (5a–h) with short reaction times were achieved through microwave irradiation, using Keggin-type heteropolyacids as catalysts under solvent-free conditions. Moreover, all synthesized compounds demonstrated favorable values for the calculated drug similarity parameters, suggesting promising pharmacological profiles. These findings indicate that the 2-benzoylamino-N-phenylbenzamide derivatives could serve as potential candidates for further development as therapeutic agents against COVID-19.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM Journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest

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Notes

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Author Information

Karima Ighilahriz
Laboratory de Physic and Chemistry of Materials LPCM, Departement of Chemistry, Faculty of Sciences, University Mouloud Mammeri, 15000, TiziOuzou, Algeria
Contact e-mail: *karima.boubchir@ummto.com*

Amina Benazzouz-Touami
Laboratory de Physic and Chemistry of Materials LPCM, Departement of Chemistry, Faculty of Sciences, University Mouloud Mammeri, 15000, TiziOuzou, Algeria

Malika Makhloufi-Chebli
Laboratory de Physic and Chemistry of Materials LPCM, Departement of Chemistry, Faculty of Sciences, University Mouloud Mammeri, 15000, TiziOuzou, Algeria

Noura Kichou
Departement of Chemistry, Faculty of Sciences, University Mouloud Mammeri, 15000, TiziOuzou, Algeria

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