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Synthesis, Biological Evaluation and Theoretical Studies of Hydrazone Derivatives

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Abstract: The aim of this work is to synthesize, characterize and evaluate the biological activity of a series of hydrazone derivatives. These compounds were characterized by elemental analysis, IR spectroscopy, mass spectrometry, UV-Vis Spectroscopy, ^{1}HNMR spectra. In vitro, their antibacterial and antifungal activities were screened against bacterial species (*Staphylococcus aureus*, *Pseudomonas aeruginosa and Escherichia coli*) and fungi (*Candida sp).* Amikacin was used as references for antibacterial and antifungal studies. The compounds were optimized at DFT/B3LYP/6-31G (d,p) level of theory. In silico, The Toxicity of the hydrazone derivatives were studied by ADMET(Absorption, distribution, metabolism, excretion, and toxicity) simulations using ADMET lab 2.0 server. The molecular docking studies are carried out to better comprehend the preferential mode of binding of these compounds against biomecular targets such as InhA enzyme characteristic of Mycobacterium Tuberculosis bacteria.

Keywords: Hydrazone derivative, Synthesis, Antibacterial activity, Theoretical study.

Introduction

The Hydrazones possesses some particular properties which make them a potential candidate for designing new moieties. They contain a C=N bond in conjugated form with a functional nitrogen electron pair. They are distinguished from other members of this class (imines, oximes) by the presence of two interlinked nitrogen atoms. These nitrogen atoms are nucleophilic, while the carbon has both an electrophilic and nucleophilic nature and further combining hydrazones with numerous functional groups leads to the formation of products with unique biological properties (Abdullah Shah & Hussain, 2022; Popiolek et al., 2016). Isoniazid is a first-line antitubercular drug and it acts by inhibiting enoyl reductase (InHA) in Mycobacterium Tuberculosis. This drug is a prodrug and needs to be activated by KatG catalase-peroxidase (Al-Khattaf, 2021). A number of hydrazone derivatives have been synthesized from isoniazid and were found to have potentiated activities against various bacterial and fungal strains (Maccari, 2005) including hydrazones with benzohydrazide and menthone (Al-Khattaf, 2021; Krátký, 2017). Furthermore, metal complexes of isonicotinic hydrazones including, copper, zinc, manganese, nickel showed enhanced activities against microbes, tumor and free radicals (Jabeen, 2018).

During the past decades, the human population affected with life-threatening infectious diseases caused by multidrug-resistant Gram-positive and Gram-negative pathogenic bacteria increased at an alarming level around the world . Hence, the development of newer antimicrobial agents is essential to overcome the rapidly developing drug resistance and side effects. In this work , A series of nicotinic acid benzylidene hydrazide derivatives (A-G) was synthesized by condensation of isoniazid with derivatives of aldehydes and tested in vitro for biological evaluations.

Method

Experimental Method

All research chemicals were purchased from Across organics , Sigma-Aldrich and used as such for the reactions. Melting points (mp) were determined on a Veego melting point apparatus (VMP PM, 32/ 1104). Reactions were monitored by thin layer chromatography carried out using pre-coated silica gel plates . Microanalyses were performed on a Thermo Finnigan C, H,N analyser. The mass spectra were obtained on a Hewlett Packard Electron Impact mass spectrometer GCD-1800A (70 eV EI source) using a direct insertion probe and a Quadrapole TOF Mass spectrometer using electrospray ionisation (Positive mode). UV studies were carried out on a UV Visible spectrophotometer (Shimadzu 1700) in acetonitrile . The IR spectra (KBr) were recorded on a FTIR spectrophotometer with Diffuse Reflectance attachment (Shimadzu 8400S).The ^{1} H NMR spectra were obtained on an NMR Spectrophotometer (Bruker Avance II 400 NMR) using dimethyl sulphoxided6 as the solvent. In vitro antimicrobial activities against Gram-positive (Staphylococcus aureus (ATCC 25923) , Gram-negative bacteria (Escherichia coli : (ATCC 25922) et Pseudomonas aeruginosa (ATCC 27853) and fungi (**Levure :** Candida sp) were evaluated.

Computational Method

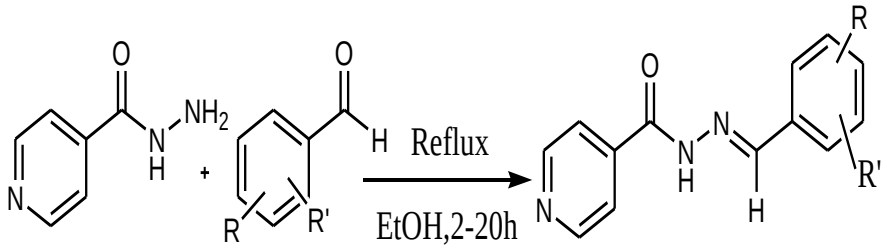
The compounds were optimized at DFT/B3LYP/6-31G (d,p) level of theory. The minimized structures of the investigated molecules were docked with the target protein using MOE 2015.10 software (Chemical Computing Group, 2015). The starting point of the docking simulation was the X-ray structure of ethenoylacyl carrier protein reductase “InhA” with PDB ID **4TZK** obtained through the protein data bank (PDB) and imported to MOE interface. The structure of the protein was prepared with MOEQuikPreptool at default parameters, wherethe ligand and all water molecules that are farther than 4.5 Å from the proteinwere removed, except the co-factor NAD^{+}(Angelova et al., 2017) all necessary hydrogen atoms were added to the structure, followed by its energy optimization.

The preparedInhAstructureand the investigated moleculeswere subject to a number of docking runs. The bestbinding conformation was selected based by following to “standard” docking solutions considered as typical in docking analysis i.e., (1) the minimalbinding energy (ΔG),that reflects the best docking pose, (2) the lowest with lowest root mean square deviation (RMSD) value that validate the docking process(Shawn, 2016) For each investigated molecule, a protein-ligand interactions diagram was constructed based on the best binding pose, using Ligand interactions entry in MOE software.The interactions werein the maximum distance of 4.5 Å; between heavy atoms of the ligand and the receptor residues, and their nature was identified according to the diagram legend given in Ligand interactions entry.

In silico predictive models are frequently applied to get an early estimation of the ADMET profile (Absorption, distribution, metabolism, excretion, and toxicity), this estimation has become a standard step nowadays in drug discovery.Thus, ADMETlab 2.0 server (Xiong et al., 2021)was used to predict the ADMET profile of the tested compounds.

Synthesis

In a 250 ml flask, an equimolar mixture of isoniazid (isonicotinic hydrazide acid, INH) and aldehyde was introduced in 10 ml of ethanol. The reaction mixture was refluxed with stirring for (2 to 20 hours), and after cooling, a solid formed. This solid was then recovered by filtration and purified by washing with ethanol.



1 **2** **3A-G**

A: R= H, R'=H, **B:** R= H, R'= 4-OH, **C:** R= H, R'= 4-Cl, **D** : R= H, R'=4-N$(CH_3)_2$, **E:**R= H, R'= 4-NO_2, **F:** R= H, R'= 4-OCH_3, **H :** R= H, R'= 4-CH_3

Figure 1. Condensation of isoniazid with derivatives of aldehydes

Results and Discussion

Caracterization

The compounds 3 A-G were prepared in excellent yields in a one-step reaction of isonocotinylhydrazone (1) with various substituted aryl aldehydes 2A-G in ethanol . yields of reactions are influenced by the nature of the electron-donating or electron-withdrawing substituents on the benzaldehydes (Table 1). The structures of the synthesised compounds were further confirmed by mass spectra and elemental analysis (Table 2). The UV-Visible spectra of compounds 3A-G reveal two absorptions, with the most intense one attributed to the π→π* transition, and the weaker one characterizing the n→π* electronic transition(Table 3).

The IR spectra of derivatives of compounds 3A-G show the appearance of characteristic bands at 3100-3500 cm^{-1}, 1712-1789 cm-1 and 1550-1650 cm-1 (Thomas, 2016) which correspond respectively to the elongation vibrations of the -NH group, of the C=O carbonyl group and of the C=N imine group. The Table 4 summarizes the main vibration bands corresponding to the different functional groups of compounds 3A-G. Another piece of evidence for condensation isoniazid with derivatives of aldehydes of is the appearance of a singulet signal equivalent to 1 proton in1HNMR spectrum between 7.4 and 8.4 ppm (signal of N=CH) and a equivalent to 1 proton between 8 and 8.35 ppm (signal of NH)(Table 5).

Table 1. Melting points Mp and yields of compounds A- G

Compound	Mp (°C)	y(%)	Coulour
A	192-200	75	White
B	264-268	93	Yellow
C	218-221	85	White crystals
D	104-106	88	Yellow
E	225-257	75	Yellow
F	170-173	90	White
G	198-201	80	white

Table 2. Elemental analysis and mass spectrometry data

Compound	m/z $(M+H)^{+.}$	Anal. Calcd C% H% N%	Found C% H% N%
B	242.5	$C_{13}H_{11}N_3O_2$(241.25) 64.72 4.60 17.42	C, 64.57; H, 4.52; N, 17.36 %.
C	260.4	$C_{13}H_{10}ClN_3O$ (259.69) 60.12, 3.88, 16.18.	60.34 , 3.76 , 16.13
D	269.5	$C_{15}H_{16}N_4O$ (268.31) 67.15, 6.01; 20.88	67.58, 6.12, 21.13
E	271.4	$C_{13}H_{10}N_4O_3$ (270.24) 57.78, 3.73, 20.73	58.07, 3.68, N, 20.51
F	256.5	$C_{14}H_{13}N_3O_2$ (255.27) 65.87, 5.13, 16.46.	65.43, 5.64, 16.80

Table 3. UV-vis spectral analysis

Compounds	λ(nm)	Transition
A	240	π→π*
B	242	π→π*
	322	n→π*
C	242	π→π*
	295	n→π*
D	358	π→π*
E	277	π→π*
	325	n→π*
F	277	π→π*
	325	n→π*
G	312	π→π*

Table 4. IR *bands for the compounds A-G as* KBr *pellets*

Fonction Compound	ν(NH)	ν C=O	υC=N	υC=C	νC-H	νOH	νC-Cl	υ -NO_2
A	3653	1691	1565	1538	3184-3194	/	/	/
B	3231	1657	1555	1647-1670	3018-3227	/ 3340	/	/
C	3510	1667	1592	/	/	/	698	/
D	3415	1665	1592	1647	/	/	/	/
E	3510	1791	1693	1647	/	/	/	1512 1334
F	3510	1791	1611	1611-1619	3166-3228	/	/	/

Table 5. ^{1}H NMR data of hydrazone derivatives

Chemical shift δ (ppm)	**B**	**C**	**D**	**E**	**F**
(d, Pyridine 2H)	8.8-8.5	8.88-8.91	8.73 8.72	9.32 9.25	8.75 8.85
	8.4-8.3		7.82 7.84	8.51 8.55	7.63 7.70
(s, N=CH)	7.8	8.32	8.35	8.1	.4
(s, NH),	8	8.65	8.65	8.34	8.35
(d, Aromatic 2H),	7.0-6.8	7.0-7.5	7.62 7.6	7.89 7.93	7.63 7.70
	7.5-7.3		6.69 6.66	7.6 7.62	6.84 6.89
(s, OH)	11.5	/	/	/	/
(s, CH_3, - 6H)	/	/	3.07	/	/
(s, O-CH_3,3H)	/	/	/	/	3.78

Biological Evaluation

Table 6. Antimicrobil activity via disc diffusion method

Compounds	E.coli ATCC 25922	P.aeruginosa ATCC 27853	S.aureus ATCC 25923	Candida sp
	Zone of Inhibition (mm) (mm)			
A	6	9	11	11
B	8	8	15	13
C	12	13	15	14
D	11	8	10,5	13
E	12	11	14	15
F	8	11	6	15
Amikacin	22	24	33	25

The antibacterial sensitivities of test compounds were assayed using the paper disc. Diffusion method using Amikacin for comparison, as shown in Table 6. From the screening, it was concluded that compounds show

varied responses against the bacteria . The presence of electron withdrawing NO_2 and Cl groups in the molecular structure leads to a steep increase in antibacterial activity. Regarding the antifungal activity, all the compounds exhibit moderate activity

Molecular Docking

Isonicotinohydrazideis one of the drugs routinelyused against Mycobacterium Tuberculosis, a bacterium that causes Tuberculosis disease. This bacterium can affect all age groups (Carren, 2011) representing a global health problem that induced the death of two millions of people each year With the resistance of Mycobacterium Tuberculosisto Isonicotinohydrazide,molecular docking studies were extensively conductedin the last years toproposederivatives that had better interaction with Mycobactarium tuberculosis enoyl-acyl carrier protein reductase (InhA) enzyme than isonicotinohydrazide Abdullah Shah & Hussain, 2022 ; Dogan et al ., 2020).

In this study, molecular docking study was performedin an effort to evaluate the binding interactions of the investigated N-benzoylisonicotinohydrazidederivatives withInhA, and predict the best InhA inhibitor among them. The molecules were docked in the active site of InhA and the results are summarized in table 7.

As sen from Table 7, all N-benzoylisonicotinohydrazide derivatives (**B- G**) fitted well in the active site of InhAand showedmore negative binding energy values than N-benzoylisonicotinohydrazidemolecule (M^1), which is indicating a better enzyme inhibition, with the molecule **D** ranking by the docking as the top score, and predicted as the best inhibitor.

The influence of the substituentsin the p-position of the benzene ringon the binding with InhA is clearly demonstrated in here, the order based on the substituents was found to be: **D**(benzene-$N(CH_3)_2$>**E**(benzene-NO_2)> **F**(benzene-OCH_3) > **C** (benzene-Cl)> **G** (benzene-CH_3)> **B** (benzene-OH) > **A**(benzene-H). The substitution with electron withdrawing groups (NO_2), and (Cl)seems to be favorable in enhancing the binding affinity between the substituted molecules and InhA enzyme, although (Cl) group is a weak electron withdrawing group (Sun, 2017) the binding still better than withM^1. Meanwhile, molecules with electron donating substituents like (OH),(OCH_3) and (CH_3) showed moderate binding energy values. The OCH_3 and CH_3 groups, being weak electron donating groups(Sun, 2017),slightly improved the binding affinity compared with OH.

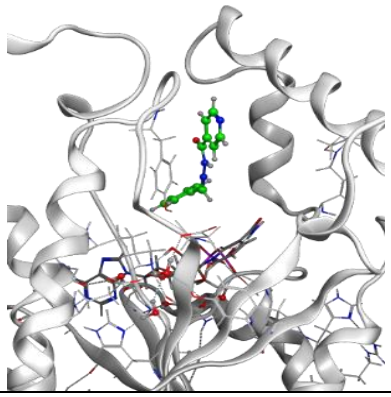
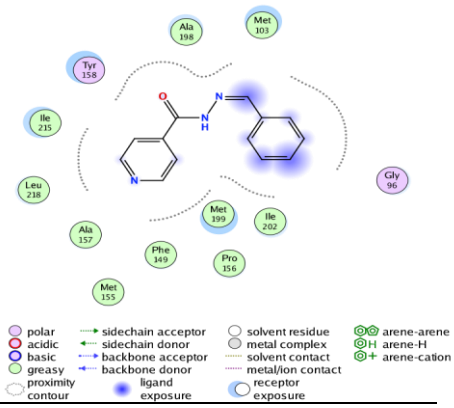
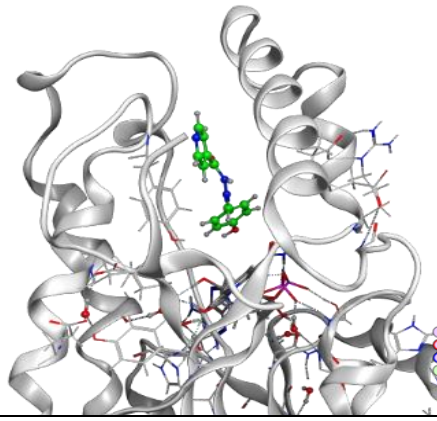
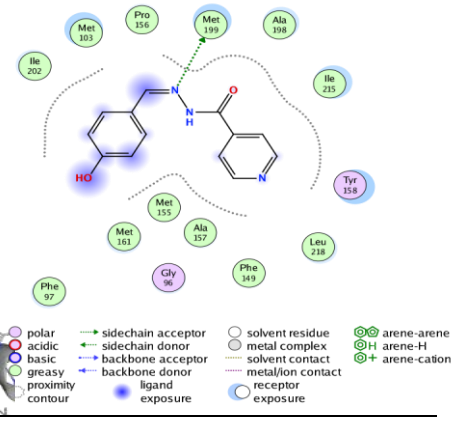
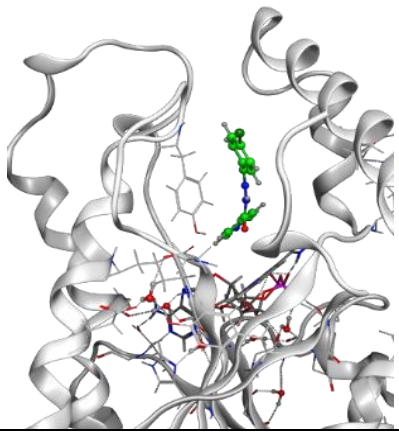
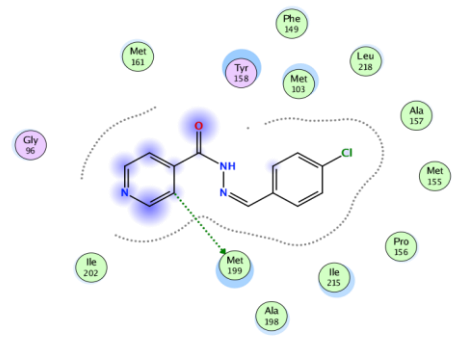
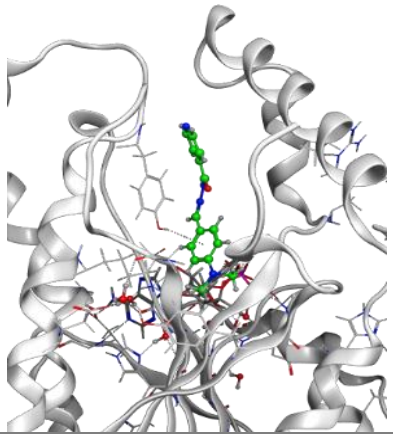
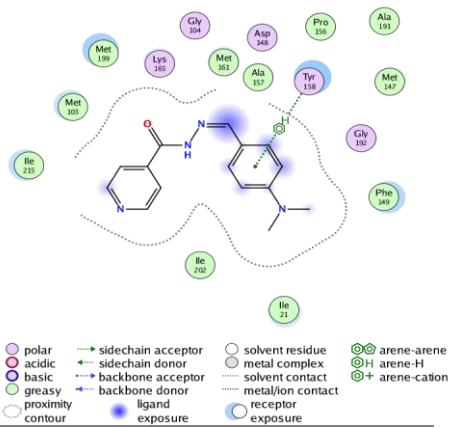
To sum, the substitution with powerful electron withdrawing groupswas favored, particularly with (NO_2) group. In contrast, substitution with strong electron donating groups such as (OH) was disfavored. Besides, the substituents that are weak electron withdrawing group as (Cl) and weak electron donating such as (OCH_3), (CH_3) had almost the same influence, molecules containing those groups showedclose binding energies values and hencenearbinding affinity with InhA.

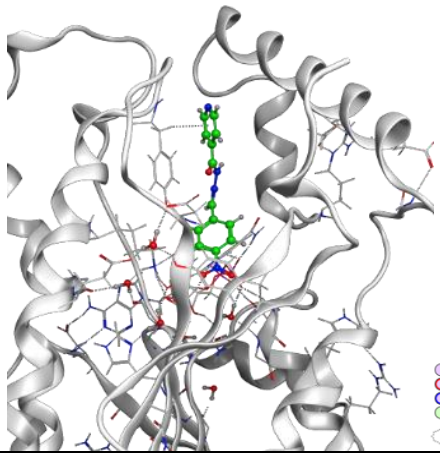
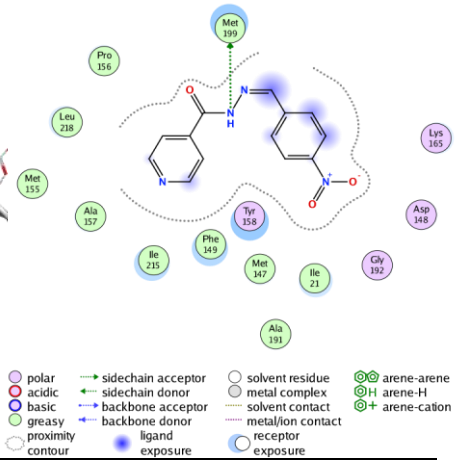
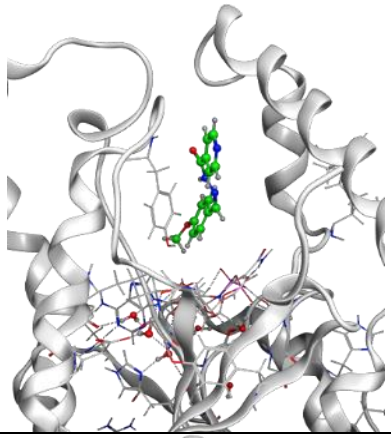
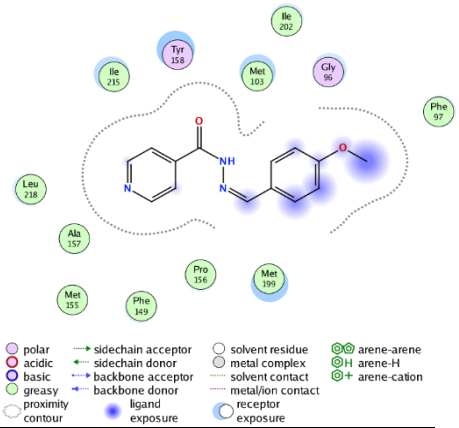
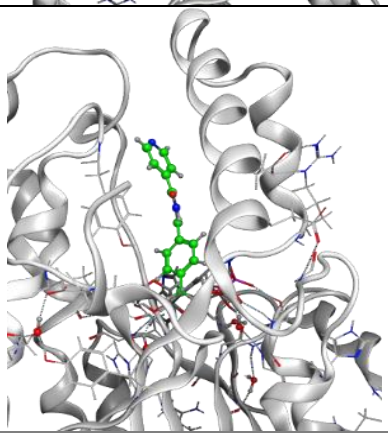
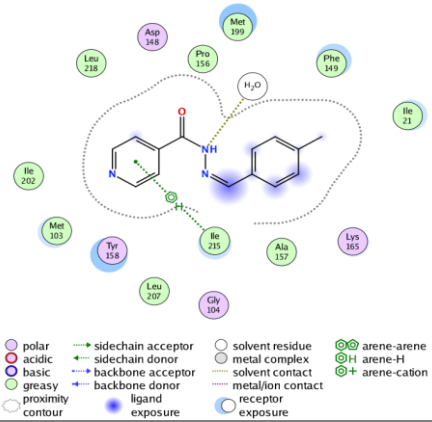
However, although **D** molecule have an electron donating substituent ($N(CH_3)_2$), it was ranked by the best docking score (-6.46 Kcal/mol). This is probably due to the nature of the interactions involved in the binding with amino-acids residue , which will be detailed in the following paragraph.

A protein-ligand interactions diagram of InhA amino-acids residues with all investigated molecules (**A-G**) was provided by molecular docking analysis, in the main to elucidate the nature and number of the interactions involved in the binding. The results areshowing that residues Met 103, Tyr 158, Met 199 and Ile 215 demonstrated an exposure to all the molecules, these residues were explicitly mentioned as very important since they are located in the binding site of InhA enzyme. Molecule A did not demonstrate any interaction with amino-acids residues.

Whereas, almost all the derivatives molecules exhibited one or more interactions. MoleculeM^4 displayed one hydrogen bond interaction with Tyr 158 (between OH group of tyrosine 158 and benzene ring), this type of interaction is known to play important roles in protein–ligand complex formation and stability (Andersson et al ., 2020; Moreno Fuquen, 2022) which enhances the binding affinity, reflected in here by the highest binding score (-6.46 Kcal/mol).Molecule **G** exhibited also one hydrogen bond interaction via the benzene ring but with another amino-acid residue namely Isoleucine 215 (Ile 215), while Tyr 158 is in total exposure, the molecule showed a second hydrogen bond with H_2O solvent. The rest of the molecules showed VDW interactions withMethionine 199 (Met199) through the azote atom of the hydrazide part. Although, **F** molecule did not show any interactions, the docking ranking was quite good and the residues mentioned before as important residues were still close.

Table 7. Binding energy and RMSD values of N-benzoylisonicotinohydrazide and its derivatives best poses along with their corresponding 2D and 3D representations.

Mol.	ΔG (Kcal/mol)	RMSD (Å)	3D representation of the best Binding conformations	2D diagram of ligand-protein interactions
A	-5.53	0.81		
B	-5.58	0.72		
C	-5.90	1.33		
D	-6.46	1.27		

E	-6.10	1.21		
F	-6.01	1.02		
G	-5.87	0.99		

ADMET Analysis

ADMET properties of the investigated molecules A-G were reported in Table 8. All the tested molecules were predicted as non-carcinogenic; don't induce cancer to humans, and non hERG channel blockers. It worth mentioning that hERG channel is known for its role in coordinate the heart's beating (Angelova et al., 2017) any blockage causes sudden death (Shawn, 2016). Additionally, almost all molecules demonstrated a non-AMES Toxicity, except for **D** and **E**, that were predicted to be AMES Toxic which means that they can induce changes and damages in DNA (Carren, 2011) However, all the investigated molecules were predicted to cause eye irritation and skin sensitization. Additionally, D presented a high probability of respiratory toxicity. Concerning the intestinal absorption, all the investigated molecules presented Caco-2 Permeability indices higher than -5, expressing their good permeability across the human carcinoma intestinal cells (Gabriela, 2022). In contrast, the same molecules showed a poor human intestinal absorption rate (HIA% < 30%) . All the studiedmolecules are non-inhibitors and non-substrates of Permeability-GlycoProtein (Pgp) that is localized in the intestine, hepatocytes and renal tubules. Therefore, besides of its localisation, Pgp appears to be not involved in limiting the intestinal absorption or enhancing the excretion of the tested moleculesfrom out of the human

body. After the intestinal absorption, molecules are distribute through the body's blood into tissues. To evaluate the distribution, protein plasma binding rate (PPB%), volume of distribution (VD) and blood-brain barrier (BBB) penetrationwere predicted. Interestingly, almost all thetested molecules werepredicted to be permeable into the blood–brain barrier (BBB) except for **A**, **B**, **E**.. It should be noted that penetrating the blood-brain barrier is critical for molecules targeting central nervous system, such as antidepressants, however for non-target molecules it can cause neurotoxicity. All molecules showed high rates (>90%) for binding to plasma proteins, including serum albumin, hemoglobin and α-acid glycoproteins. As only unboundmoleculecan be distribute into tissues, the distribution of the studied molecules may fail (Sun, 2017). It is well-known that that molecules that are extensively bound to plasma proteins will have a low volume of distribution (VD), and have low clearance (CL) by both liver (hepatic) and kidney (Renal) routes. This was confirmed here by low values of volume of distribution (VD) ranging between 0.54 and 0.89 L/ kg. It should be noted that the acceptable range is between 0.04-20 L /Kg. Moreover, the clearance index for almost all the tested molecules was low (CL < 5 mL/min/Kg)and quite moderate (CL >5 mL/min/Kg) for **B**, **D** et **F** molecules. Remember that, for a better clearance, CL index should be higher than 15 mL/min/Kg.A part from direct elimination of a molecule by hepatic and Renal routes, a molecule can be inactivated through biotransformation to allow clearance from the body, this is facilitated by metabolizing enzymes i.e.,CYP450 cytochromes such as CYP2D6 (Shoombuotang et al., 2017). Among the tested molecules, **D** and **F** can be metabolized by CYP2D6. While, **C** and **F**are predicted to be significant inhibitors of CYP2D6, leading to a decrease in the metabolism of CYP2D6substrates (Shoombuotang et al., 2017).

Table 8. ADMET properties of the molecules A-G

Absorption	A	B	C	D	E	F	G
Caco-2 Permeability	-4.37	-4.55	-4.38	-4.39	-4.43	-4.44	-4.40
HIA (%)	< 30	< 30	< 30	< 30	< 30	< 30	< 30
Pgp-inhibitor	No	No	No	No	No	No	No
Pgp-substrate	No	No	No	No	No	No	No
Distribution PPB (%)	95.70	94.35	97.05	95.11	95.51	95.79	96.17
VD (L/Kg)	0.68	0.54	0.82	0.89	0.64	0.67	0.82
BBB Penetration Metabolism	No	No	Yes	Yes	No	Yes	Yes
CYP2D6inhibitor	No	No	Yes	No	No	Yes	No
CYP2D6substrat	No	No	No	Yes	No	Yes	No
Excretion CL(mL/min/Kg) Toxicity	4.26	6.98	3.07	6.23	2.42	5.65	3.86
AMES Toxicity	No	No	No	Yes	Yes	No	No
Carcinogencity	No	No	No	No	No	No	No
hERG Blockers	No	No	No	No	No	No	No
Eye Irritation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Skin Sensitization	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Respiratory Toxicity	No	No	No	Yes	No	No	No
Absorption	A	B	C	D	E	F	G
Caco-2 Permeability	-4.37	-4.55	-4.38	-4.39	-4.43	-4.44	-4.40
HIA (%)	< 30	< 30	< 30	< 30	< 30	< 30	< 30
Pgp-inhibitor Distribution	No	No	No	No	No	No	No
PPB (%)	95.70	94.35	97.05	95.11	95.51	95.79	96.17
VD (L/Kg)	0.68	0.54	0.82	0.89	0.64	0.67	0.82
BBB Penetration Metabolism	No	No	Yes	Yes	No	Yes	Yes
CYP2D6inhibitor	No	No	Yes	No	No	Yes	No
CYP2D6substrat Excretion	No	No	No	Yes	No	Yes	No
CL (mL/min/Kg) Toxicity	4.26	6.98	3.07	6.23	2.42	5.65	3.86
AMES Toxicity	No	No	No	Yes	Yes	No	No
Carcinogencity	No	No	No	No	No	No	No
hERG Blockers	No	No	No	No	No	No	No
Eye Irritation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Skin Sensitization	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Respiratory Toxicity	No	No	No	Yes	No	No	No

Conclusion

In the present study, the synthesis and activity of benzylidene isonicotinohydrazide derivatives have been described. It was observed that the tested compounds containing electron withdrawing (nitro, halogen and dimethoxy) moiety on phenyl ring of the compounds were found to have significant in vivo. In silico, The molecule **E** : N-(4-methoxybenzylidene) isonicotinohydrazide is a better candidate for the treatment against Mycobacterium Tuberculosis, the molecule presented a better ADMET profile and a good binding energy with InhA enzyme of Mycobacterium Tuberculosis.

Scientific Ethics Declaration

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

Acknowledgements or Notes

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References

Abdullah Shah, M., & Hussain, H. (2022). Synthesis and characterization of novel hydrazone derivatives of is nicotinic hydrazide and their evaluation for antibacterial and cytotoxic potential. *Molecules, 27,* 6770-6782.

Andersson, B., Mishra,K., Forsgren,N., Ekstrom, F., & Linusson, A. (2020). Physical mechanisms governing substituent effects on arene–arene ınteractions in a protein milieu, The *Journal of Physical Chemistry B, 124*(30), 6529.

Angelova, V. T., Valcheva, V., Pencheva, T., Voynikov, Y., Vassilev,N., Mihaylova, R., Momekov, G., & Shivachev, B. (2017). Synthesis, antimycobacterial activity and docking study of 2-aroyl benzopyrano[4,3-c] pyrazol-4(1H)-one derivatives and related hydrazide-hydrazones, *Bioorganic & Medicinal Chemistry Letters*, *27*(13), 2996–3002.

Chemical Computing Group. (2015). *Molecular operating environment (MOE)*. http://www.chemcomp.com.

Carren, P. (2011). An investigation into pharmaceutically relevant mutagenicity data and the influence on Ames predictive potential. *Journal of Cheminformatics, 3*,51.

Falcón Cano,G. (2022). Reliable prediction of caco-2 ermeability by supervised recursive machine learning approaches. *Pharmaceutics , 14*(10).

Jabeen, M., Mehmood, K., Ain Khan, M., Aslam, N., Zafar, A.M., Noreen, S, Aslam, S., & Ghafoor, A. (2018). Microwave and conventional synthesis of Co (II), Cu (II) and Ni (II) metal complexes of some acid hydrazones with their spectral characterization and biological evaluation. *Pakistan Journal of Pharmaceutical Sciences, 31*, 1003–1011.

Khattaf, F.S., Mani, A., Hatamleh, A.A., & Akbar, I.(2021). Antimicrobial and cytotoxic activities of isoniazid connected menthone derivatives and their investigation of clinical pathogens causing infectious disease. *Journal of Infection and Public Health, 14*, 533–542.

Krátký. M, Bosze. S., Baranyai, Z., Stolarikova, J., & Vinsova, J. (2017). Synthesis and biological evolution of hydrazones derived from 4-(trifluoromethyl) benzohydrazide. *Bioorganic & Medicinal Chemistry Letters, 27,* 5185– 5189.

Maccari, R., Ottanà, R., & Vigorita, M.G. (2005). In vitro advanced antimycobacterial screening of isoniazid-related hydrazones, hydrazides and cyanoboranes: Part 14. *Bioorganic & Medicinal Chemistry Letters, 15*, 2509–2513.

Moreno Fuquen, R., García-Torres,E., Arango Daraviña, K., & Ellena, J . (2022). Structural, theoretical analysis and molecular docking of two benzamide isomers. Halogen bonding and its role in the diverse ways of coupling with protein residues. *Chemical & Pharmaceuticial Bulletin (Tokyo), 70*(11) . 782–790.

Lamothe, S. M. (2016). The human ether-a-go-related gene (hERG) potassium channel represents an unusual target for protease-mediated damage. *The Journal of Biological Chemistry, 39*, 20387-20401.

Popiolek, L., Stefanska, J., Kielczykowska, M., Musik, I., Biernasiuk, A., Malm, A., & Wujec, M. (2016). Al-synthesis, dissociation constants and antimicrobial activity of novel 2, 3-disubstituted-1, 3-thiazolidin-4-one derivatives. *Journal of Heterocyclic Chemistry, 53*, 393–402.

Sun, L. (2017). in silico prediction of compounds binding to human plasma proteins by QSAR models. *ChemMedChem*, 13, 572-581

Soombuatong, W., Prathipati, P., Prachayasittikul, V., Schaduangrat, N., Malik, A. A., Pratiwi, R., Wanwimolruk, S., Wikberg, J. E. S., Gleeson, M. P., Spjuth, O., & Nantasenamat, C. (2017). Towards predicting the cytochrome P450 modulation: from QSAR to proteochemometric modeling. *Current Drug Metabolism,18*(6), 540–555.

Thomas, A.S., & Hamane, S.C. (2016). Synthesis and biological evaluation of Schiff's bases and 2 azetidinones of isonocotinyl hydrazone as potential antidepressant and nootropic agents. *Arabian Journal of Chemistry, 9*, 79-90.

Xiong, G., Wu, Z., Yi, J., Fu, L., Yang, Z., Hsieh, C., Yin, M., Zeng, X., Wu, C., Lu, A., Chen, X., Hou, T., & Cao, D. (2021). ADMETlab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties, *Nucleic Acids Research*, 5–14.

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