Istanbul J Pharm 52 (1): 47-53
DOI: 10.26650/IstanbulJPharm.2022.958484
Original Article

Synthesis, antifungal activity and *in silico* ADMET studies of benzyl alcohol derivatives

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Cite this article as: Benson Ogala, J., Hassan, J., Samaila, A., Isah Bindawa, M., & Taskin Tok, T. (2022). Synthesis, antifungal activity and in silico admet studies of benzyl alcohol derivatives. *İstanbul Journal of Pharmacy, 52*(1), 47-53. DOI: 10.26650/IstanbulJPharm.2022.958484

ABSTRACT

Background and Aims: Fungal infections continue to pose a serious threat to human well-being due to the increasing cases of resistance against the existing antifungal drugs. Consequently, efforts are increasingly focused towards investigating new moieties with potential activity against different fungal species. The object of this work was to synthesize and evaluate the antifungal activity of five benzyl alcohol derivatives against *Candida albicans* and *Trichophyton rubrum* and also to study the biochemical as well as the ADMET properties of the compounds *in silico*.
Methods: The target compounds were obtained by the reduction of the appropriate aldehyde using sodium borohydride. Subsequently the compounds were tested against the two fungal species using ketoconazole as the positive control. The biochemical activities as well as the ADMET properties were calculated at DFT/B3LYP/6-311G* basis set with the help of Gaussian09 (G09) software.
Results: The findings revealed that some of the compounds exhibited interesting inhibitory action against *C. albicans* while others against *T. rubrum*. However, the MIC and MFC results demonstrated that none of the compounds were fungicidal at the concentrations tested. *In silico* ADMET studies showed that all the compounds have a good cell permeability index, their human intestinal absorption values were within the recommended scale and with good plasma protein binding.
Conclusion: The benzyl alcohol derivatives studied in this work have exhibited some encouraging antifungal activity and favorable biochemical as well as pharmacokinetic properties.

Keywords: ADMET properties, Antifungal activity, Benzyl alcohol, *Candida albicans, Trichophytonrubrum*

INTRODUCTION

Microbial infections, specifically those of fungal origin reportedly account for over 1.5 million deaths *per annum* globally despite the tremendous improvements in the diagnosis and treatment of these infections (Koushlesh et al., 2020). The growing resistance for the existing antimicrobial drugs has been attributed to this unfortunate situation, and this has led to the quest for structurally diverse compounds with a view of discovering alternative drugs (Durante-Mangoni, , Grammatikos, Utili, & Falagas, 2009; Giamarellos-Bourboulis, 2008; Gonzalo-Garijo, Rodriguez-Nevado & de Argila, 2006; Bozdogan & Appelbaum, 2004).

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Submitted: 28.06.2021
Revision Requested: 22.11.2021
Last Revision Received: 03.01.2022
Accepted: 20.01.2022
Published Online: 28.04.2022

Benzyl alcohol (BA) is an aromatic organic compound containing the phenyl methanol moiety. It is used as a local anesthetic, flavor enhancing agent, fragrance in cosmetics, and as a preservative (Almoughrabie et al., 2020; Beata, Anna, & Anna, 2014). BA is naturally found in many plants where it exists as a free molecule and as esters in a variety of essential oils such as hyacinth, ylang-ylang and jasmine (Wei & Shibamoto, 2007). Previously some biological potentials of benzyl alcohol derivatives have been reported, for instance, Wang et al., (2020) reported the use of nitro-benzyl alcohol as a photo-reactive group with amine selectivity which enabled its applications for photo-affinity labeling and cross-linking of biomolecules. Lim et al., (2008) also reported the anti-angiogenic, anti-inflammatory, and anti-nociceptive activities of vanillin. These reports prompted us to further investigate the antifungal activity of some benzyl alcohol derivatives.

MATERIAL AND METHODS

All reagents and solvents were purchased from Sigma-Aldrich (Darmstadt, Germany) and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 spectrometer. FTIR spectra were recorded on a Perkin–Elmer BX spectrophotometer (Bayero University, Kano, Nigeria). Melting points were determined on an Electro-thermal melting point apparatus and are uncorrected.

Methods

General procedure for the preparation of benzyl alcohol derivatives (A-E)

In a round bottom flask, aldehyde (26.6mmol) was dissolved in ethanol (8 mL), and the mixture placed on an ice-bath to cool. Using a small vial, $NaBH_4$ (26.4 mmol) was dissolved in 1M NaOH (7.6mL), and the resulting solution was then added slowly to the solution of the aldehyde over a period of 10 min. The mixture was stirred at room temperature for 10 min, and then cooled down. While stirring, HCl solution (6 M) was added dropwise, this led to the precipitation of the respective product. The addition continued until the evolution of H_2 gas stopped. Then, the *p*H was checked to ensure that the solution was acidic. The product was collected by filtration, washed twice with ice-cold water, transferred to a dry piece of filter paper and air dried. However in the case of compound **E,** after the addition of HCl solution (6 M), the resulting mixture was treated with chloroform (30 mL), and then separated. The chloroform layer was evaporated to afford the corresponding solid product.

Characterization

4-Bromobenzyl alcohol, **Compound A**

White powder; 95% yield; mp 212-215 °C; ^{1}HNMR (400MHz, $DMSO_4$-d_6) δ ppm 4.46 (2H, s, CH_2), 5.38 (1H, s, OH), 7.27 (2H, d, *J* = 8.0 Hz, Ar-H), 7.48 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C-NMR (100MHz, $DMSO_4$-d_6) δ ppm 62.40 (CH_2), 119.81 (Ar-C), 128.79 (2×ArCH), 131.12 (2×ArCH), 142.06 (Ar-CBr); FTIR cm^{-1} 3272 (OH), 1002 (C-O).

4-Nitrobenzyl alcohol, **Compound B**

Yellow powder, 93% yield, mp 131-134 °C. ^{1}HNMR (400MHz, $DMSO_4$-d_6) δ ppm 3.56 (2H, s, CH_2), 5.61 (1H, s, OH), 7.57 (2H, d, *J* = 8.0 Hz, Ar-H), 8.17 (2H, d, *J* = 4.0 Hz, Ar-H); ^{13}CNMR (100MHz, $DMSO_4$-d_6) δ ppm 62.21 (CH_2), 123.49 (2×ArCH), 127.25 (2×ArCH), 148.50 (Ar-C), 150.89 (Ar-CNO_2); FTIR cm^{-1} 3503 (OH), 1054 (C-O).

4-Hydroxybenzyl alcohol, **Compound C**

White powder, 87% yield, mp 260-265 °C; ^{1}HNMR (400MHz, $DMSO_4$-d_6) δ ppm 4.37 (2H, s, CH_2), 5.07 (1H, s, OH), 6.71 (2H, d, *J* = 8.0 Hz, Ar-H), 7.11 (2H, d, *J* = 8.0 Hz, Ar-H), 9.36 (1H, s, Ar-OH); ^{13}CNMR (100MHz, $DMSO_4$-d_6) δ ppm 63.09 (CH_2), 115.10 (2×ArCH), 128.43 (2×ArCH), 132.94 (Ar-C), 156.41 (Ar-COH); FTIR cm^{-1} 3377 (OH), 1207 (C-O).

4-Hydroxy-3-methoxybenzyl alcohol **Compound D**

White powder, 93% yield, mp 112-114 °C. ^{1}HNMR (400MHz, $DMSO_4$-d_6) δ ppm 3.74 (3H, s, OCH_3), 4.37 (2H, s, CH_2), 5.14 (1H, s, OH), 6.70 (2H, s, 2×Ar-H), 6.88 (1H, s, Ar-H), 8.88 (1H, s, ArOH); ^{13}CNMR (100MHz, $DMSO_4$-d_6) δ ppm 55.80 (OCH_3), 63.36 (CH_2), 111.32 (Ar-C), 115.35 (Ar-CH), 119.51 (Ar-CH), 133.72 (Ar-CH), 145.54 (ArC-OCH_3), 147.67 (Ar-COH); FTIR cm^{-1} 3503 (OH), 1121 (C-O).

4-Methoxybenzyl alcohol, **Compound E**

White solid; 94% yield; mp 212-215 °C; ^{1}HNMR (400MHz, $DMSO_4$-d_6) δ ppm 3.71 (3H, s, OCH_3), 4.40 (2H, s, CH_2), 5.15 (1H, s, OH), 6.87 (2H, d, *J* = 8.0 Hz, Ar-H), 7.22 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}CNMR (100MHz, $DMSO_4$-d_6) δ ppm 55.22 (OCH_3), 62.79 (CH_2), 113.67 (Ar-C), 128.21 (2×ArCH), 128.82 (2×ArCH), 158.36 (Ar-$COCH_3$), FTIR cm^{-1} 3326 (OH), 1244 (C-O).

Antifungal activity

Test microorganisms

The test microorganisms used in this study were clinical isolates of *Candida albicans* and *trichophyton rubrum* obtained from the Department of Microbiology, Umaru Musa Yar'adua University, Katsina, Nigeria.

In vitro assay of the activity of the synthesized compounds on *Candida albicans* and *Trichophyton rubrum*

An 80 mg/mL solution of each of the compounds including the positive control, ketoconazole was prepared by dissolving 0.2 g each in 2.5 mL of 50% DMSO in separate test tubes. Sterilized discs were made from filter paper and 100 discs were transferred into each tube so that each disc absorbed 100 µL (equivalent to 800 µg of the compound). After the disc preparation, each of the fungal isolates was separately inoculated on the freshly prepared SDA plates using a streak plate method. Four (4) discs impregnated with a compound, standard drug or 50% DMSO were then introduced into each of the inoculated plates using an aseptic technique. The plates were inoculated at room temperature for 7 days after which the zones of inhibition were recorded for each plate (Singh, Dar, & Sharma, 2012). This process was repeated three (3) times.

Preparation of different concentrations of the compounds for MIC and MFC

About 0.1 g of each compound was dissolved in 100 mL DMSO to obtain a stock solution of 1000µg/mL. Dilution was carried out using sterile syringes to obtain concentrations of 1000, 800, 600, 400, 200, 100 and 50 µg/mL.

Determination of minimum inhibitory concentration (MIC)

The MIC of the compounds was determined using the tube dilution method. Serial dilutions of the solutions of the compounds were carried out in well labeled test tubes using Muller-Hinton broth as diluents. The tubes were then inoculated with 0.1 mL of standard inoculums and incubated for 72h until turbidity was observed. The least concentration showing no visible sign of growth, which gave no turbidity of the medium, was taken as the MIC. Broth with no inoculum, broth containing the test organism and ketoconazole and broth with test organisms only, were included as controls (EUCAST, 2003).

Determination of the minimum fungicidal concentration (MFC)

The contents of the tubes used for the MIC determination study were streaked onto SDA plates using a wire-loop and the plates were incubated aerobically at 37˚C for 3 days. The MFC values were read as the least concentrations that killed the test organisms, which was indicated by the absence of growth (Imanirampa & Alele, 2016).

Statistical analysis

Data were statistically analyzed using SPSS 16.0 software by comparison of means (one-way ANOVA) using the Tukey post hoc test, at the significance level of $p < 0.05$.

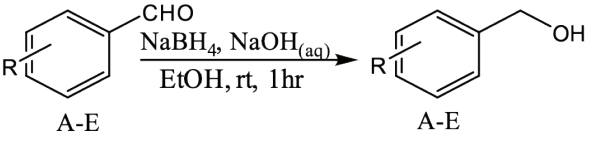
Biochemical activity and *in silico* ADMET analysis

All compounds (A-E and ketoconazole as positive control) were optimized and the vibrational frequencies of the benzene's derivatives were calculated at DFT/B3LYP/6-311G* basis set with the help of Gaussian 09 (G09) software (Gaussian et al., 2009) to investigate the chemical and biochemical activities of the benzene's derivatives. Afterwards, the eigenvalues of HOMO and LUMO, the global hardness (η), the chemical potential (μ), electrophilicity index (ω) and dipole moments (DM) on each compound were calculated at same level of theory. Further, Lipinski (Lipinski et al., 2001) and Veber rules (Veber et al., 2002) were performed using Discovery Studio (DS) 3.5 for the compounds. Then in silico, an ADMET (Absorption, Distribution, Metabolism, Extraction and Toxicity) analysis for the compounds was predicted by using the sub-protocol of DS 3.5 software and pkCSM server (Cheng et al., 2012) in order to elucidate the pharmaco informatic information of the compounds examined. Human intestinal absorption (HIA), Caco2 permeability for the prediction of oral drug absorption, skin permeability, blood brain barrier penetration (BBB), Human ether-a-go-go related gene (hERG) inhibition, Cytochrome P450 (CYP1A2, CYP1C19, CYP2C9, CYP2D6, CYP3A4) inhibition, AMES toxicity, Tetrahymena Pyriformis Toxicity and plasma protein binding (PPB) descriptors were calculated.

RESULTS

Chemistry

The benzyl alcohol derivatives, **A-E** were obtained by reducing the appropriate aldehyde with $NaBH_4$ as shown in Scheme 1, and their structures were confirmed by the ^{1}H and ^{13}C NMR, and FTIR spectroscopie techniques.



	R
A	4-Br
B	4-NO_2
C	4-OH
D	4-OH, 3-OCH_3
E	4-OCH_3

Scheme 1. Synthesis of benzyl alcohol derivatives.

Antifungal activity

The synthesized compounds were screened for *in vitro* antifungal activity against *C. albicans* and *T. rubrum* using a disc diffusion method. Generally, both fungi were sensitive to all the compounds except C which had no activity on *C. albicans* (Table 1).

The MIC and MFC of the compounds against both organisms are given in Tables 2 and 3 respectively.

Biochemical activity and *in silico* ADMET analysis

In the present study, we firstly investigated the five compounds and selected a positive control (ketoconazole) based on quantum chemical parameters. The obtained direct and indirect parameters for each compound are summarized in Table 4 and Figure 1.

The five compounds were examined according to both the Lipinski and Veber rules, and the result is presented in Table 5.

Table 1. Comparative activities of the compounds against *C. albicans* and *T. rubrum at* 800 µg/dis*c.*

		Ketoconazole	Compound A	Compound B	Compound C	Compound D	Compound E	Negative control
C. albicans	Mean ZI (mm)	22.98±4.13	13.74±3.4^{a}	18.56±1.3^{b}	06.93±5.2^{c}	14.62±3.7^{ab}	10.66±1.8^{ac}	07.15±0.3^{c}
T. rubrum	Mean ZI (mm)	25.84±6.18^{b}	13.52±3.3^{a}	21.48±5.1^{b}	12.23±3.5^{a}	10.55±1.0^{ac}	07.20 ±2.58^{c}	00.00

Values are expressed as mean ± standard deviation of three experiments conducted in quadruplicates. Those with the same superscript are not significantly different statistically ($p>0.05$)

Table 2. MIC of the compounds against *C. albicans* and *T. rubrum*.

C. albicans							
Compound	1000 µg/ml	800 µg/ml	600 µg/ml	400 µg/ml	200 µg/ml	100 µg/ml	50 µg/ml
A	-	+	+	+	+	+	+
B	+	-	+	+	+	+	+
C	+	+	+	+	+	+	+
D	-	+	+	+	+	+	+
E	+	+	+	+	+	+	+
T. rubrum							
Compound	1000 µg/ml	800 µg/ml	600 µg/ml	400 µg/ml	200 µg/ml	100 µg/ml	50 µg/ml
A	-	+	+	+	+	+	+
B	-	+	+	+	+	+	+
C	+	+	+	+	+	+	+
D	+	+	+	+	+	+	+
E	+	+	+	+	+	+	+

+ = Presence of growth; – = Absence of growth; Ketoconazole = 50 µg/ml for both organisms

Table 3. MFC of the compounds against *C. albicans* and *T. rubrum*.

C. albicans							
Compound	1000 µg/ml	800 µg/ml	600 µg/ml	400 µg/ml	200 µg/ml	100 µg/ml	50 µg/ml
A	+	+	+	+	+	+	+
B	+	+	+	+	+	+	+
C	+	+	+	+	+	+	+
D	+	+	+	+	+	+	+
E	+	+	+	+	+	+	+
T. rubrum							
Compound	1000 µg/ml	800 µg/ml	600 µg/ml	400 µg/ml	200 µg/ml	100 µg/ml	50 µg/ml
A	+	+	+	+	+	+	+
B	+	+	+	+	+	+	+
C	+	+	+	+	+	+	+
D	+	+	+	+	+	+	+
E	+	+	+	+	+	+	+

+ = Presence of growth; – = Absence of growth Ketoconazole; = <50 µg/ml for both organisms

Table 4. Biochemical activity analysis of the compounds and the positive control (ketoconazole).

Name	εHOMO (eV)	εLUMO (eV)	Dipole M (Debye)	Hardness (η)	Chem. Pot. (µ)	Electrophilicity index (ω)
A	-6.536	-0.583	3.692	5.953	-3.559	1.064
B	-7.437	-2.455	6.529	4.982	-4.946	2.455
C	-5.953	-0.194	1.587	5.759	-3.074	0.820
D	-5.841	-0.048	2.774	5.793	-2.944	0.748
E	-6.040	-0.205	1.702	5.835	-3.122	0.835
Ketoconazole	-5.167	-1.277	5.039	3.890	-3.222	1.334

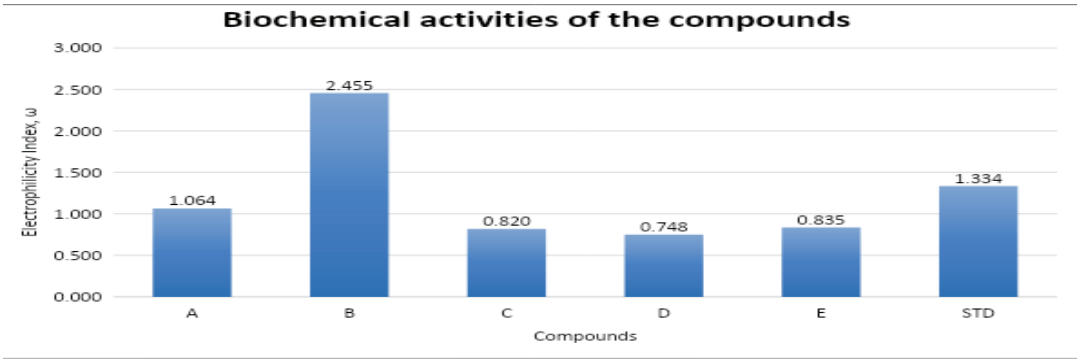


Figure 1. Biochemical activity plot.

The ADMET analysis was also exerted for the same structures to estimate their pharmacokinetic and toxicological properties in the biological system. Thus, the ADMET plots was built for all the compounds and ketoconazole (Tables 6 and 7).

in the aromatic region and was assigned to the two aromatic protons closer to the methylene group, while the signal at 8.18 ppm was assigned to the aromatic protons closer to the nitro group,(-NO_2).

Table 5. The Lipinski and Veber rules analysis of the compounds and positive control (ketoconazole).

Name	MW (≤500 g/mol)	AlogP (≤5)	MPSA (≤140 A²)	NRB (≤10)	HA_Lipinski (≤10)	HD_Lipinski (≤5)	HA_Veber (≤12)	HD_Veber (≤12)
A	153.135	1.119	66.05	2	4	1	3	1
B	187.034	1.973	20.23	1	1	1	1	1
C	124.137	0.983	40.46	1	2	2	2	2
D	138.164	1.209	29.46	2	2	1	2	1
E	154.163	0.967	49.69	2	3	2	3	2
Ketoconazole	531.431	3.61	69.06	7	8	0	6	0

Abbreviations: ALogP, octanol/water partition coefficient, a measure for lipophilicity; MW, molecular weight; MPSA, molecular polar surface area; Num_H_Acceptors_Lipinski, Number of hydrogen bond acceptors; Num_H_Donors_Lipinski, Number of hydrogen bond donors;NRB, Number of Rotatable bonds; Num_H_Acceptors, Number of hydrogen bond acceptors based on Veber; Num_H_Donors, Number of hydrogen bond donors based on Veber.

Table 6. ADMET analysis of the compounds and positive control (ketoconazole).

Comp.	PSA_2D(< 140 Å²)	AlogP98(< 5)	HIA	Solubility	BBB	PPB
A	20.815	1.973	0(good)	4(optimal solubility)	1(good)	-2.6545
B	63.638	1.119	0(good)	4(optimal solubility)	3(low)	-4.1726
C	41.631	0.983	0(good)	4(optimal solubility)	2(medium)	-6.351
D	50.561	0.967	0(good)	4(optimal solubility)	3(low)	-4.4769
E	29.745	1.209	0(good)	4(optimal solubility)	2(medium)	-1.9019
Ketoconazole	67.405	3.61	0(good)	2(low)	2(medium)	46.479

Abbreviations: PSA, polar surface area; AlogP98, the logarithm of the partition coefficient between n-octanol and water; BBB blood brain barrier; CYP2D6 cytochrome P450 2D6 binding; PPB plasma protein binding, more than 90% for PPB : Chemicals strongly bound. Less than 90% for PPB: Chemicals weakly bound.

Table 7. ADMET analysis of the compounds and positive control (ketoconazole).

Name	hERG-inhibition	CYP1A2 inhibitor	CYP1C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
A	No	No	No	No	No	No
B	No	Yes	No	No	No	No
C	No	No	No	No	No	No
D	No	No	No	No	No	No
E	No	No	No	No	No	No
Ketoconazole	Yes	Yes	Yes	Yes	Yes	Yes

DISCUSSION

Typically the ^{1}H NMR spectrum of compound **B** gave a signal at 4.62 ppm which was assigned to the two protons of the methylene group (-CH_2). The hydroxyl proton was found at 5.62 ppm. Further down, the signal at 7.57 ppm appeared

The ^{13}C NMR spectrum gave the signal for the methylene carbon at 62.21 ppm, and the signal at 123.49 ppm was assigned to the aromatic carbon to which the methylene group is attached. The signals at 123.49 ppm and 127.25 ppm were assigned to the four carbon atoms further away. Lastly, the signal at 150.89 ppm was assigned to the carbon atom attached to the nitro group (NO_2).

The FTIR spectrum gave the hydroxyl (-OH) band at 3503 cm^{-1}, while the C-O stretch was found at 1054 cm^{-1}.

The antifungal activity (Table 1) revealed that for *Candida albicans*, compound **B** showed very good activity with an inhibition zone of 18.56±1.32 mm compared to the standard antifungal ketoconazole (ZI = 22.98±4.13mm), followed by compound D (ZI = 14.62 ±3.76), A (ZI = 13.74±3.44), E (ZI=10.66±1.81) and the least being compound C that showed no significant activity. In the case of *T. rubrum*, compound **B** gave an excellent inhibition zone of 21.48±5.18 mm quite comparable to the 25.84±6.18mm exerted by the control drug. Compounds **A, C, D** and **E** gave ZI of 13.52±3.31, 12.23±3.53, 10.55± 1.06 and 07.20± 2.58 zones of inhibition respectively. In the case of MIC (Table 2) against *Candida albicans*, Compounds **A** and **D** were both found to show inhibition at concentrations of 1000µg/mL while compound **B** showed an MIC of 800µg/mL. On the other hand, compounds **C** and **E** exhibited no inhibitory actions at all the concentrations tested. For *Trichophyton rubrum,* its MIC showed that only compounds **A** and **B** at 1000µg had inhibitory actions on the fungus. This implied that their activities were concentration-dependent. Compounds **C, D and E** showed no inhibitory effect at all on the concentrations tested. The MFC results (Table 3) indicated that none of the compounds were fungicidal against any of the pathogens at all on the concentrations tested. This showed that the compounds **A, B and D** only succeeded in inhibiting the growth of the organisms but could not kill them. They were therefore, fungistatic and not fungicidal.

The biochemical activity analysis (Table 4 and Figure 1) revealed that compound B exhibited the best electrophilicity index value compared to the rest of the compounds including the positive control (ketoconazole). According to the Lipinski and Veber rules, it is suggested that potential lead compounds that conform to their rules of 5 tend to have lower withdrawal rates during phases of clinical trials and have an increased chance of reaching the markets (Leeson & Springthorpe, 2007). As shown in Table 5, all the tested compounds were found to be located within the borders of tests. The ADMET plot (Tables 6 and 7), the two parameters; polar surface area (PSA) and lipophilicity (AlogP98) served as indicators of cell permeability. Any compound with PSA < 140 $Å^2$ and AlogP98 < 5 has optimum cell permeability. In this work, all the studied compounds followed these rules. In addition to these parameters, the human Intestinal absorption (HIA) and Caco-2 permeability presented in Table 6 serve as good indicators for drug absorbance in the intestine and for predicting the gut blood barrier penetration. While for all the studied compounds including the control, the HIA values were found to be good in terms of Caco2 permeability and have permeability coefficient values at the recommended scale (> 0.90 log cm/s), the BBB partition coefficient was estimated to predict the blood brain barrier permeability for each compound. It indicates accessibility of bioactive for the central nervous system. As shown in Tables 6-7, while ketoconazole has a low BBB coefficient, others have a medium BBB value. The PPB coefficient is a prediction of plasma-protein binding. The binding of the compound to the plasma proteins such as lipoprotein, glycoprotein, human serum albumin, a, b, and c globulins can greatly affect the quantity of the drug in blood circulation. In general, the less degree of PPB is desirable for designing drugs with more cell availability and cell membrane traverse/diffusion. The computed values show that all the compounds are in the acceptable range (< 90-chemicals weakly bound) in terms of PPB.

CONCLUSION

Five benzyl alcohol derivatives were successfully obtained *via* $NaBH_4$ reduction of the appropriate aldehyde. For the first time, the antifungal activities of the compounds were evaluated against *Candida albicans* and *Tricophyton rubrum* using disc diffusion method. And it was found that compounds A, B and D exhibited fungistatic effect against *C. albican*, while compounds A and B against *T. rubrum*. However, none of the compounds were fungicidal at the concentrations tested. In terms of a broad spectrum activity, the nitro-substituted compound (compound B) was found to exhibit a promising efficacy almost competing with that of the standard drug (ketoconazole). In order to understand the mode of interaction of the compounds, an *in silico* ADMET analysis was exerted for the same structures to estimate their pharmacokinetic and toxicological properties in the biological system. Fortunately, all the compounds were found to be in the acceptable range of the pharmacokinetics parameters.

Acknowledgement: The authors thank Kabir Yahuza and Mannir Kabir for the antifungal assay.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Y.H.; Data Acquisition- J.B.O., M.I.B., A.S., T.T.T.; Data Analysis/Interpretation- J.B.O., Y.H., M.I.B., A.S., T.T.T.; Drafting Manuscript- J.B.O.; Critical Revision of Manuscript- Y.H., M.I.B., A.S., T.T.T.; Final Approval and Accountability- J.B.O., Y.H., M.I.B., A.S., T.T.T.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: Authors declared no financial support.

REFERENCES

- Almoughrabie, S., Ngari, C., Guillier, L., Briandet, R., Poulet, V., & Dubois-Brissonnet, F. (2020). Rapid assessment and prediction of the efficiency of two preservatives against S. aureus in cosmetic products using High Content Screening—Confocal Laser Scanning Microscopy. *PLoS ONE*, *15*, 7, e0236059.
- Beata, Z., Anna, C., & Anna, B. (2014). Development studies on determination of preservatives decomposition products. *Acta Poloniae Pharmaceutica-Drug Research*, *71*(4), 563-573.
- Bozdogan, B., & Appelbaum, P. C. (2004). Oxazolidinones: Activity, Mode of action, and Mechanism of Resistance. *International Journal of Antimicrobial Agents*, *23*(2), 113-119.
- Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., & Tang, Y. (2012). admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. *Journal of Chemical Information and Modeling*, *52*(11), 3099-3105.
- Durante-Mangoni, E., Grammatikos, A., Utili, R., & Falagas M., E. (2009). Do we still need the aminoglycosides? *International Journal of Antimicrobial Agents*, *33*(3), 201-205.

- European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by broth dilution. *EUCAST Discussion Document E.Dis 5.1*, March 2003.
- Gaussian 09, Revision E.01, Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Mennucci, B., & Petersson, G. A. Gaussian, Inc., Wallingford CT, 2009.
- Giamarellos-Bourboulis, E. J. (2008). Macrolides beyond the conventional antimicrobials: A Class of Potent Immunomodulators. *International Journal of Antimicrobial Agents*, *31*(1), 12-20.
- Gonzalo-Garijo, M. A., Rodriguez-Nevado, I., & de Argila, D. (2006). Patch tests for diagnosis of delayed hypersensitivity to cephalosporins. *Allergologia et Immunopathologia*, *34*(1), 39-41.
- Imanirampa, L., & Alele, P. E. (2016). Antifungal activity of *Cleome gynandra* L. aerial parts for topical treatment of *Tinea capitis*: an in vitro evaluation. *BMC Complementary and Alternative Medicine*, 16**,** 1, 1-8
- Koushlesh, K., M., Chanchal, D., K., Anil, K., S., Rajnikant, P., Pankaj, K., Saraswati, P., M., & Shweta, D. (2020). Medicinal Plants Having Antifungal Properties. In Bassam Hassan (Ed.), Medicinal Plants Use in Prevention and Treatment of Diseases. IntechOpen.
- Leeson, P., D., & Springthorpe, B. (2007). The influence of drug-like concepts on decision-making in medicinal chemistry. *Nature Reviews Drugs Discovery*, *6*(11), 881–890.
- Lim, E. J., Kang, H. J., Jung, H. J., Song, Y. S., Lim C. J., & Park, E. H. (2008). Anti-angiogenic, anti-inflammatory and anti-nociceptive activities of vanillin in ICR mice. *Biomolecules and Therapeutics*, *16*, 132-136.
- Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, *46*, 3–26.
- Singh, R., Dar, S. A., & Sharma, P. (2012). Antibacterial Activity and Toxicological Evaluation of Semi Purified Hexane Extract of *Urtica dioica* Leaves. *Research Journal of Medicinal Plants, 6*, 123-135.
- Veber, D. F., Johnson, S. R., Cheng, H.-Y., Smith, B. R., Ward, K. W., & Kopple, K. D. (2002). Molecular properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry*, *45*, 2615–2623.
- Wei, A., & Shibamoto, T. (2007). Antioxidant activities and volatile constituents of various essential oils. *Journal of Agricultural and Food Chemistry*, *55*(5), 1737-1742.
- Wang, C., Liu, Y., Bao, C., Xue, Y., Zhou, Y., Zhang, D., Lin, Q., & Zhu, L. (2020). Phototriggered labeling and crosslinking by 2-nitrobenzyl alcohol derivatives with amine selectivity. *Chemical Communications*, *56(*15), 2264-2267.