



RESEARCH ARTICLE

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# Topological Polar Surface Area, Molecular Weight, and Rotatable Bond Count Account for the Variations in the Inhibitory Potency of Antimycotics against *Microsporium canis*

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## Abstract

Multivariate statistical models were utilized to identify the interaction between the inhibitory activity and the molecular properties of the different antimycotics against *Microsporium canis*. Information on the inhibitory potency against *M. canis* and molecular properties of antifungal agents were obtained from literature. The relationship between the inhibitory potency and the molecular properties of the different antimycotics against *M. canis* was established using multiple linear regression analysis (MLRA) and principal component analysis (PCA). Three major descriptors: topological polar surface area, molecular weight, and rotatable bond count of the antimycotics were identified to confer inhibitory action against *M. canis* using MLRA ( $r^2=0.8968$ ,  $p<0.0001$ ) and PCA (95.86% total contribution rate). Both MLRA and PCA as statistical approaches demonstrate their potential as tools in computational structure design and for possible synthesis of next generation antimycotics as more effective treatments of fungal infections.

**Keywords:** Dermatophytes, fungal infections, molecular descriptors, multivariate data analysis, regression equation

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## INTRODUCTION

Superficial fungal infections, which are commonly caused by dermatophytes including *Microsporum canis*, are treated with topical antimycotics, but resistance to these topical agents was observed in cases of tinea unguium and tinea capitis which necessitate the use of systemic antifungal drugs.<sup>1-3</sup> Molecular properties such as topological polar surface area, heavy atom count, hydrogen bond acceptor and donor counts, rotatable bond count, complexity, lipophilicity, and molecular weight were important descriptors in assessing the inhibitory effect of drugs. Since statistical modelling is a very important tool in predicting biological activities of compounds<sup>4</sup>, antifungal drugs against *M. canis* were statistically evaluated using multiple linear regression analysis (MLRA) and principal component analysis (PCA). In drug design, establishing the relationship between the activity and the properties of a compound is of utmost importance.<sup>5</sup> The generated relationship will likewise unveil the relevant molecular properties of the existing antifungal drugs that would account for their inhibitory action against *M. canis*. Findings of the investigation would offer additional insights relevant to the synthesis of new derivatives of antimycotics as more effective treatments of dermatophytoses.

## MATERIALS & METHODS

### Inhibitory Potency of Antifungal Drugs

The biological activity of 16 different antifungal drugs against *M. canis* was obtained from literature.<sup>6</sup> Six of these agents which are systemic drugs include voriconazole, terbinafine, ketoconazole, griseofulvine, fluconazole, and itraconazole. The 10 topical agents were amorolfine, butenafine, clotrimazole, econazole, miconazole, naftifine, tioconazole, tolciolate, tolnaftate, and undecylenic acid.

### Molecular Descriptors of Antifungal Drugs

Information on the molecular descriptors of the 16 drugs (Table 1) were retrieved from NCBI (National Center for Biotechnology Information) databases<sup>7-22</sup>, and these include topological polar surface area (tpsa), logarithm of molecular weight (logmw), heavy atom count (hac), lipophilicity (xlogp), logarithm of complexity (logcomp), hydrogen bond acceptor count (hbac), rotatable bond count (rbc), and hydrogen bond donor count (hbdc).

### Multiple Linear Regression Analysis and Principal Component Analysis

For the model construction, quantitative relationship between the inhibitory activity of antimycotics and their molecular properties was established using MLRA. This multivariate statistical approach is a computational method

**Table 1.** Descriptors of the different antimycotics.

Antimycotic	Properties								Reference
	tpsa	logmw	hac	xlogp	logcomp	hbac	hbdc	rbc	
Amorolfine	12.5	2.502	23	5.7	2.526	2	0	6	7
Butenafine	3.2	2.502	24	6.3	2.573	1	0	5	8
Clotrimazole	17.8	2.538	25	5.0	2.598	1	0	4	9
Econazole	27.0	2.582	24	5.3	2.579	2	0	6	10
Fluconazole	81.6	2.486	22	0.4	2.554	7	1	5	11
Griseofulvin	71.1	2.547	24	2.2	2.760	6	0	3	12
Itraconazole	101.0	2.849	49	5.7	3.049	9	0	11	13
Ketoconazole	69.1	2.725	36	4.3	2.866	6	0	7	14
Miconazole	27.0	2.619	25	5.3	2.620	2	0	6	15
Naftifine	3.2	2.458	22	5.1	2.534	1	0	5	16
Terbinafine	3.2	2.465	22	5.6	2.631	1	0	5	17
Tioconazole	55.3	2.588	23	5.3	2.579	3	0	6	18
Tolciolate	44.6	2.510	23	5.5	2.656	2	0	3	19
Tolnaftate	44.6	2.488	22	5.5	2.587	2	0	3	20
Undecylenic acid	37.3	2.265	13	3.9	2.149	2	1	9	21
Voriconazole	76.7	2.543	25	1.5	2.651	8	1	5	22

frequently utilized in drug design owing to its simplicity and reproducibility.<sup>23</sup> In variable selection, backward elimination was employed in the construction of the regression model. The adequacy of the obtained regression model was evaluated using the computed  $r^2$ , squared correlation coefficient<sup>24</sup>. In addition, bivariate correlation studies examined the presence of outliers, linearity, normality, independence, homoskedasticity, and multicollinearity among the significant molecular predictors.

To assess the similarity among the antimycotics and to identify possible correlations in the different drug properties, principal component analysis was employed. Using this multivariate statistical approach, information regarding the data set is summarized into principal components where each component contains uncorrelated linear combinations of variables having the maximum variance.<sup>25</sup> Among correlated variables, linear transformation was performed and these transformed variables were then sorted in order of decreasing variance. In the present study, principal components with loading eigenvalues greater than 1.0 were included. An absolute value correlation coefficient of at least 0.39 between the index and its principal component retains the molecular property within the given component. Data analyses were performed using STATA® V12.0 at 0.05 significance level.

## RESULTS

The computed loading values of the three principal components have contribution rates of 50.30%, 32.55%, and 13.01% (Table 2). Complexity, heavy atom and hydrogen bond acceptor counts, molecular weight, and topological polar surface area were in the 1<sup>st</sup> principal component. Lipophilicity and hydrogen bond donor count were in the 2<sup>nd</sup> component, while rotatable bond count was in the 3<sup>rd</sup> principal component. When PCA technique was used in assessing the inhibitory effect of the 16 antimycotics, comprehensive scores (range: 6.62-34.93) were obtained (Table 3). Relatively higher comprehensive scores were

**Table 2.** Principal component loading values and eigenvectors.

Antimycotic Property	1 <sup>st</sup> Component	2 <sup>nd</sup> Component	3 <sup>rd</sup> Component
logmw	0.4470	-0.2337	-0.0616
xlogp	-0.0860	-0.5646	0.2922
logcomp	0.4369	-0.2103	-0.2980
hbac	0.4218	0.3192	-0.0534
hbdc	-0.0401	0.5843	0.2351
rbc	0.2284	0.0147	0.8643
tpsa	0.3966	0.3152	-0.0775
hac	0.4615	-0.1988	0.1043
Proportion	0.5030	0.3255	0.1301
Cumulative	0.5030	0.8285	0.9586
Eigenvalue	4.0242	2.6041	1.0408

**Table 3.** Comprehensive scores of the antimycotics using principal component analysis.

Antimycotic	Comprehensive evaluation			Comprehensive Score	Rank
	1 <sup>st</sup> Component	2 <sup>nd</sup> Component	3 <sup>rd</sup> Component		
Itraconazole	69.07	-3.22	9.51	34.93	1
Fluconazole	47.70	0.36	4.32	24.67	2
Ketoconazole	49.02	-2.43	6.05	24.65	3
Voriconazole	47.63	-0.26	4.32	24.43	4
Griseofulvin	44.15	-1.24	2.59	22.14	5
Tioconazole	36.10	-2.99	5.19	17.86	6
Tolciclate	31.43	-3.11	2.59	15.14	7
Tolnaftate	30.93	-3.11	2.59	14.88	8
Miconazole	25.40	-2.99	5.19	12.48	9
Undecylenic acid	23.59	-1.62	7.78	12.35	10
Econazole	24.91	-2.99	5.19	12.23	11
Clotrimazole	21.29	-2.82	3.46	10.24	12
Amorolfine	18.64	-3.22	5.19	9.00	13
Butenafine	15.01	-3.56	4.32	6.95	14
Naftifine	14.05	-2.88	4.32	6.69	15
Terbinafine	14.10	-3.16	4.32	6.62	16

observed in systemic antifungal drugs compared with topical antimycotics.

Statistical evaluation of the molecular descriptors of the antifungal drugs showed that molecular weight exhibited a positive correlation with heavy atom count, hydrogen bond acceptor count, and topological polar surface area (Table 4). Topological polar surface area and heavy atom count were directly correlated with hydrogen bond acceptor count. Among the antifungal agents,

positive correlation between the numbers of heavy atom and rotatable bond exists. Complexity of the antimycotics was positively correlated with hydrogen bond acceptor and heavy atom counts, topological polar surface area, and molecular weight. However, lipophilicity of the antimycotics was negatively correlated with hydrogen bond donor count, hydrogen bond acceptor count, and topological polar surface area.

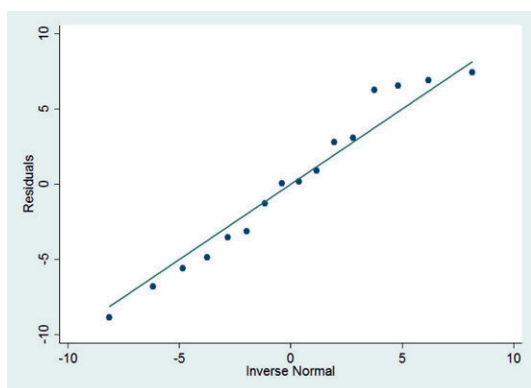
**Table 4.** Correlational analysis on the molecular descriptors of antimycotics.

	logmw	xlogp	logcomp	rbc	hbac	hbdc	tpsa	hac
logmw	1.0000	0.1561	0.9165**	0.3466	0.5547*	-0.4352	0.5127*	0.9323**
xlogp	0.1561	1.0000	0.0621	0.1431	-0.6285**	-0.7601**	-0.5768*	0.1609
hbdc	-0.4352	-0.7601**	-0.4498	0.1797	0.4013	1.0000	0.3674	-0.3298
hbac	0.5547*	-0.6285**	0.5891*	0.3531	1.0000	0.4013	0.9294**	0.6122*
rbc	0.3466	0.1431	0.1261	1.0000	0.3531	0.1797	0.2996	0.5033*
tpsa	0.5127*	-0.5768*	0.5190*	0.2996	0.9294**	0.3674	1.0000	0.5368
hac	0.9323**	0.1609	0.9007**	0.5033*	0.6122*	-0.3298	0.5368	1.0000
logcomp	0.9165**	0.0621	1.0000	0.1261	0.5891*	-0.4498	0.5190*	0.9007**

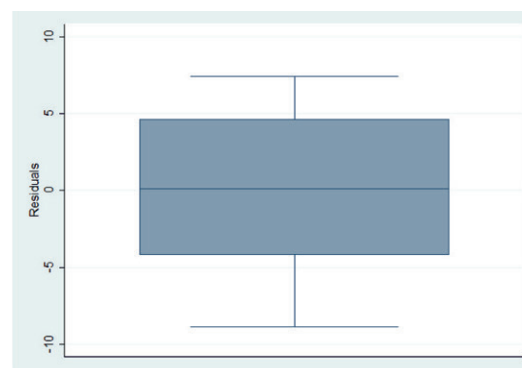
\*\*significant at 1%; \*significant at 5%

When preliminary analysis using stepwise backward elimination of MLRA was employed, heavy atom count, complexity, hydrogen bond acceptor and donor counts, and lipophilicity were removed from the full model. Topological polar surface area, molecular weight, and rotatable bond count were retained as significant independent variables accounting in the variation on the biological activity of these antimycotics against *M. canis*. For every independent variable included in the regression model, a minimum

of five samples is required.<sup>24,26</sup> Since there were only 16 available antimycotics in this study, the constructed regression equation included at most three molecular descriptors. The generated regression model (Eq. 1) has identified three predictors and is adequate ( $r^2=0.8968$ ,  $p=0.0000$ ) in explaining the potency values (MIC, minimum inhibitory concentration) of the antimycotics against *M. canis*. The three descriptors were *tpsa* (topological polar surface area,  $p=0.005$ ), *logmw* (molecular weight,  $p=0.000$ ), and *rbc* (rotatable



**Fig. 1.** Normality assessment of the error term distribution.



**Fig. 2.** Residual box-plot for detection of outliers.

bond count,  $p=0.000$ ), with rotatable bond count and molecular weight accounting to 79.65% of the fluctuations in the response variable (MIC). The negative coefficient of *logmw* suggests that increasing the molecular weight lowers MIC, thus improving the antimycotic potency. The positive coefficients for *tpsa* and *rbc* indicate that MIC increases as topological polar surface area and rotatable bond count increase.

$$\text{MIC} = 301.33(\pm 34.55) - 130.68(\pm 14.31) \logmw + 4.99(\pm 0.76)rbc + 0.19(\pm 0.06)tpsa \quad \dots(\text{Eq.1})$$

After identifying the significant molecular descriptors, various assumptions of MLRA were examined. A large F-value,  $F_{(3,12)}=34.74$  ( $p=0.0000$ ), would indicate that the constructed regression function satisfied the requirement for linearity. Independence of the error terms was likewise met ( $z=-0.52$ ,  $p=0.60$ ). The linear plot obtained between the inverse normal values and the residuals (Fig. 1) suggested normally distributed error terms ( $p=0.482$ ), while test on homoskedasticity identified constant variance ( $p=0.936$ ). The generated boxplot (Fig. 2) showed nonexistence of an outlier. Multicollinearity among significant molecular descriptors was not present since variance inflation factor (VIF) values were all less than 10 (*logmw*, 1.44; *tpsa*, 1.39; *rbc*, 1.16).

The effects of other molecular descriptors obtained from the statistical assessments as regard with the antifungal activity of the drugs were correlated with the included significant properties in the regression equation (Table 4). Apparently, positive correlations exist between molecular weight and hydrogen bond acceptor count ( $r=0.5547$ ,  $p<0.05$ ), heavy atom count ( $r=0.9323$ ,  $p<0.01$ ), and complexity ( $r=0.9165$ ,  $p<0.01$ ). Moreover, rotatable bond count is directly correlated with heavy atom count ( $r=0.5033$ ,  $p<0.05$ ) while topological polar surface area is inversely related with lipophilicity ( $r=-0.5768$ ,  $p<0.05$ ), but directly related with hydrogen bond acceptor count ( $r=0.9294$ ,  $p<0.01$ ) and complexity ( $r=0.5190$ ,  $p<0.05$ ).

## DISCUSSION

Molecular and structural properties of compounds were assessed based on their hydrogen bond acceptor and donor counts, molecular weight, complexity, rotatable bond and

heavy atom counts, lipophilicity, and topological polar surface area. The present study identified molecular weight, rotatable bond count, and topological polar surface area as significant properties of antifungal drugs which confer inhibitory action against dermatophytes particularly caused by *Microsporum canis*. In drug design,  $r^2$  is a useful determinant of model validity<sup>24</sup> and a value of at least 0.6 is considered satisfactory<sup>27</sup>. In the present study, the regression equation is adequate to capture the functional relationship between the inhibitory activity and molecular properties of the antimycotics against *M. canis*.

Evaluation of the various descriptors of the antimycotics against *M. canis* revealed that molecular weight exhibited a positive correlation with heavy atom count, complexity, topological polar surface area, and hydrogen bond acceptor count. Molecular weight is a very important property especially in small molecule drug discovery<sup>28,29</sup> because it affects several pharmacologic events<sup>30</sup>. Molecular weight of the antimycotics was directly correlated with molecular complexity and these molecular descriptors were identified as significant properties included in the first principal component. Molecular complexity is positively correlated with heavy atom and hydrogen bond acceptor counts, and accounts for various properties such as carbon hybridization, chirality, and aromaticity. Aromaticity is directly related with lipophilicity and albumin affinity.<sup>31</sup> Aromatic molecules with more than three rings had poor compound developability and were associated with increased toxicity risks.<sup>32</sup> In the selection of lead compounds, moderately complex structures are preferred because of their binding specificity<sup>33</sup> and are associated with pharmacologic properties<sup>34</sup> and biological activity<sup>35</sup>. Furthermore, topological polar surface area has been identified as one of the significant molecular descriptors in the regression equation and in the second principal component. This molecular property, defined as the total polar atom surfaces, has correlation with drug transport property, permeability, and absorption.<sup>36</sup> Complexity and hydrogen bond acceptor count are directly related with topological polar surface area. Topological polar surface area and rotatable bond count influence molecular complexity and compound bioavailability.<sup>37</sup>

There are five classes of available antimycotics intended as treatment for fungal infections: allylamines, azoles, echinocandins, nucleoside analogs, and polyenes.<sup>38</sup> In the present study, antimycotics were classified as either a systemic drug or a topical agent. The use of these antifungal drugs depends on the sensitivity profile of species, anatomical site it was found, and the type of infection.<sup>39</sup> Echinocandins such as anidulafungin, caspofungin, and micafungin are considered as a new class of drugs exhibiting fungicidal effects.<sup>40</sup> The mechanism of action of echinocandins prevents glucan synthesis<sup>41</sup> which renders inability of fungal cell wall to withstand osmotic stress<sup>42</sup>. On the other hand, thiocarbamates and allylamines, such as naftifine and terbinafine are antifungals which rupture fungal cell membrane and promote accumulation of squalene which inhibits the synthesis of ergosterol.<sup>41</sup> Terbinafine is the most potent systemic drug against dermatophytoses.<sup>6</sup> In addition, allylamines also restrict sterol derivatives production.<sup>39</sup> Another class of antimycotics are polyenes, which include amphotericin B, which are responsible in the leakage of intracellular constituents including magnesium, sugars, and potassium which disrupt the fungal membrane structure.<sup>43</sup> In spite of its effectivity, amphotericin B has high toxicity restricting its use compared to azoles.

Finally, azoles are semi-synthetic and synthetic compounds with broad spectrum of activity and are classified either as triazoles (itraconazole, fluconazole, and voriconazole) or imidazoles (clotrimazole, econazole, ketoconazole, and miconazole).<sup>39,44</sup> Triazoles are intended for systemic and superficial mycoses.<sup>45</sup> Despite structural differences between triazoles and imidazoles, imidazoles have similar mechanism of action as triazoles.<sup>46</sup> Imidazoles, except for ketoconazole, are used in treating superficial infections.<sup>44</sup> In the present study, azoles intended as systemic drugs against dermatophytoses were classified to have higher comprehensive scores using hierarchical weighted principal component analysis when compared with azoles as topical agents. Azoles affect fungal cell growth and proliferation<sup>41</sup>, but there are limitations on the utility of these antifungal drugs because

of hepatotoxicity and resistance<sup>47</sup>. In general, mucosal or superficial mycoses can usually be successfully treated by imidazole topical agents<sup>48</sup> although triazoles have a broader application in the therapeutic management of both invasive and superficial mycoses<sup>49</sup>.

## CONCLUSION

Computational approach was employed in classifying antimycotics and in establishing functional relationship between their inhibitory activity and molecular properties. Topological polar surface area, molecular weight, and rotatable bond count were identified as significant molecular descriptors of these antifungal drugs conferring their inhibitory action against dermatophytoses caused by *Microsporum canis*. Increase in the molecular weight and decrease in the rotatable bond count and topological polar surface area of the antimycotics will render better potency.

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None.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

## FUNDING

None.

## DATA AVAILABILITY

All datasets analyzed in the study are included in the manuscript and presented as tables.

## ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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