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Synthesis, Characterization, and Study the Lipophilicity Properties of Some Imine Compounds and Their Starting Materials

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Abstract:

Some Imines were prepared by condensation of 4-aminoantipyrole with benzil or vanillin. The prepared compounds were identified by FT-IR and ^{1}H-NMR spectroscopy. The prepared compounds and the starting materials were studied their lipophilicity properties and the Log P (logarithm of partition coefficient) values were determined by four theoretical methods and two practical methods, and the antifungal activity was determined. The correlation coefficients between the methods was estimated, there are good agreement between the theoretical methods except Hyperchem. The practical methods showed best correlation between TLC (thin layer chromatography) and theoretical method Marvin. On the other hand, the antifungal activity enhanced the lipophilicity values that calculated from the theoretical and practical methods.

Keyword: Lipophilicity, Imine, TLC and Shake Flask.

1. Introduction

Imines/Schiff bases were first discovered by Hugo (ugo) Schiff more than a century ago. Since then Schiff bases constitute one of the most widely used families of organic compounds. Compounds which posses R-CH=N-R' as a general formula of Imines or Schiff bases and can be efficiently prepared by condensation of an aromatic aldehyde or ketone with an appropriate aromatic amine at an optimum pH of 4-6 using dry alcohol as a solvent**[1,2]**. Schiff bases were reported to possess antifungal, antibacterial, anti-*T. cruzi*, estrogenic and cytotoxic activities **[3,4]**. Hearn and co-workers demonstrated structural variant of Isoniazid (INH) i.e., INH Schiff base that displayed strong activity, low toxicity and excellent bioavailability**[5]**. Shi and co-workers studied Structural Activity Relationship (SAR) of some Schiff bases derived from 5-chlorosalicyladehyde and concluded that the hydrophilicity and aromaticity are important parameters for antimicrobial activity**[6]**. Paula and co-workers verified SAR considering the lipophilicity potential maps and calculated logP values for the set of novel 5-nitro-heterocyclic Schiff bases and concluded that chlorine substitution on furfuryliden indicated optimum lipophilicity value and hence had better biological effect**[7]**.

The most popular scale to measure the lipophilicity of organic compounds is the logarithm of the partition coefficient of compound (called the log *P* parameter) between 1-n-octanol and water,**[8,9]**. Log *P* is a frequently used molecular descriptor in

QSAR analysis **[10,11]**. It is a quantitative descriptor of lipophilicity, one of the key determinants of pharmacokinetic properties. The lipophilicity modifies the penetration of bioactive molecules through the non-polar cell membranes. This property is usually characterized by the partition coefficient, which is essentially determined from distribution studies of the compound between an immiscible polar and non-polar solvent pair. By knowing exact values for this parameter, it is possible to predict the inhibitory activity of a drug.**[12]**

The hydrophobic interactions of drugs with their receptors, pharmacokinetic behavior of drug molecules and toxicological properties as well as pharmaceutical aspects like solubility are examples of a steadily increasing number of topics in which lipophilicity plays an important role.**[13]**

The determination of the partition coefficient by direct measurement using the shake-flask method faces problems such as poor reproducibility, length of time for experiment, it needs a reasonable quantity of compound and it needs very pure compound because impurity influence the partition coefficient value. The lipophilicity of the compounds also were determined in the reverse phase and normal phase TLC and this is the alternative to shake-flask partition coefficient method. The advantage of TLC method are purity of the compound is immaterial, requires very less quantity and short time.**[14-16]**

In the present work, two imine compounds have been synthesized and identified by FT-IR and H-NMR, the lipophilicity properties (Log P) of these compounds and their starting materials have been studied by practical methods (Shake Flask and TLC) and by theoretical methods (ALOGPS, Chemoffice, MarvinSketch, and HyperChem). Also, the antifungal activity of the compounds was studied. The results of lipophilicity by these different methods were correlated and the correlation coefficient were estimated and compared with antifungal activity.

2. Experimental Part

Melting points were determined by open capillary and are uncorrected. The purity of the compounds was checked using precoated TLC plates (MERCK, 60F) using n-Hexane: Ethyl acetate solvent system with a gradient of polarity 8:2. The plates were visualized under UV light (254 nm). IR spectra were recorded using KBr on Shimadzu FT-IR model 8400 Spectrophotometer (Central Laboratories, Petrochemical Company, Basra, Iraq), ^{1}H NMR spectra was performed in DMSO (D6) on a BRUKER FT-NMR instrument using TMS as internal standard (Tarbiat Mudaresi University, Tehran, Iran).

LogP values of synthesized compounds and starting materials were obtained from two practical methods, Shake-flask and TLC, and four theoretical methods, MarvinSketch 4.1.6 (2007), Chemoffice 11.0(2007), HyperChem 7.52 (2002) and ALOGPS online version 2.1 (2007) Clog P.

Preparation of compounds AMB and AMV[17]

To the mixture of 0.01mole (2.1g benzil or 1.5g vanillin) dissolved in 50ml ethanol and few drops of glacial acetic acid, 0.01mole (2.03g) 4-aminoantipyrine in 15ml ethanol was added. The mixture was refluxed for 3hrs. The resulting solution was cooled to room temperature, the precipitate was filtered off and washed with chloroform to remove the not reacted materials. The product was crystallized from ethanol and dried at room temperature. As shown in Scheme 1. The characterizations of the prepared compounds and the starting materials were listed in Table 1.

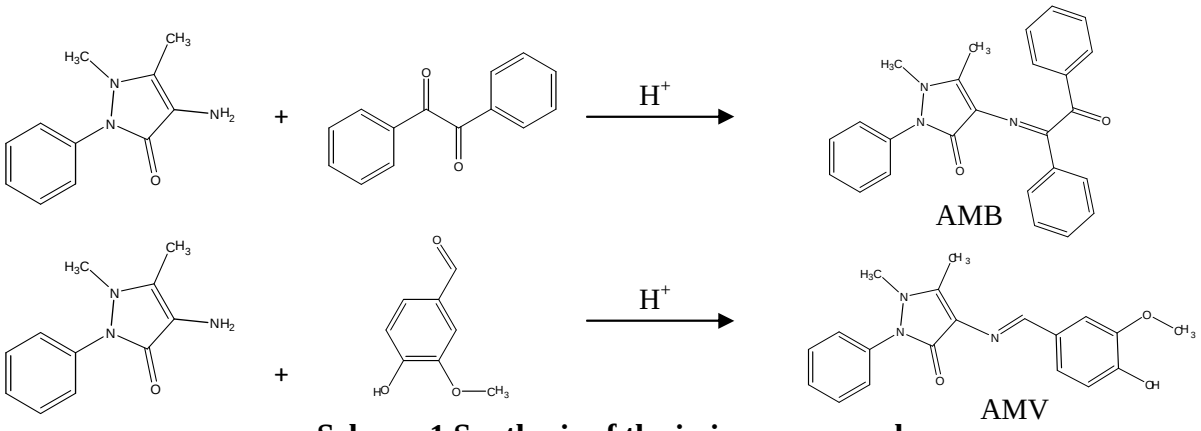
AM = 4-Aminoantipyrine.

B = Benzil.

V = Vanillin.

AMB = 1,5-dimethyl-4-(2-oxo-1,2-diphenylethylideneamino)-2-phenyl-1H-pyrazol-3(2H)-one.

AMV = E-4-(4-hydroxy-3-methoxybenzyl ideneamino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one



Scheme 1 Synthesis of the imine compounds

Table 1 The characterization of the compounds

Compd.	Molecular formula	Molecular weight (g/mole)	Crystal color and shape	m.p. (^{o}C)	Yield (%)	R_f value
AM	$C_{11}H_{13}N_3O$	203.24	Pale yellow crystal	109	-	0.25
B	$C_{14}H_{10}O_2$	210.23	Yellow powder	95	-	0.71
V	$C_8H_8O_3$	152.15	White crystal	81-83	-	0.27
AMB	$C_{25}H_{21}N_3O$	395.45	Yellow platted crystal	125-127	81	0.78
AMV	$C_{19}H_{19}N_3O_3$	337.37	Brown crystal	136-138	74	0.62

Shake flask method[9,18]

Each compound from the five was dissolved in 5ml of n-octanol by magnetic stirrer at room temperature for 1/2 hr then diluted by 5ml of cyclohexane. The solutions of each compound in different concentration ($3.125x10^{-4}$-10^{-2}M) were used in the calibration curve (Abs. in λ_{max} vs. concentration), as shown in Figure 1.

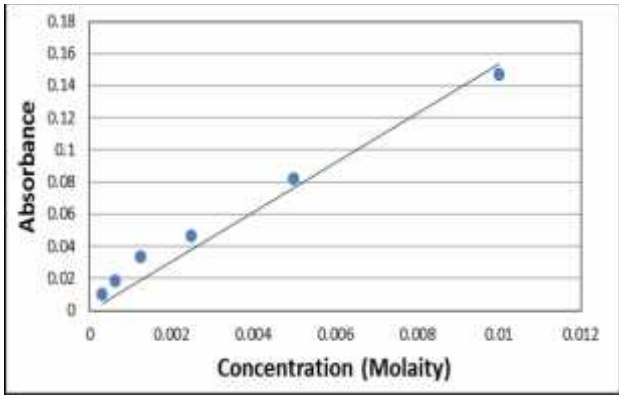


Figure 1 Calibration curve of AM compound

The concentration of 10^{-2}M from each compound prepared in 5ml octanol by magnetic stirrer at room temperature for 1/2 hr, after that 25ml of water was added. The mixture was shaken by mechanical shaker for 1hr, centrifuged for 20min to afford complete phase separation, and the octanol phase was removed by Pasteur pipette. Absorbance of 2ml of octanol phase diluted with 5ml of cyclohexane was measured and the concentration of each compound was determined by calibration curve. The lipophilicity logP was determined by using equation 1.

$$\log P = \log\left(\frac{C_{oct}}{C_{aq}}\right) \quad \text{- - - - - - - 1}$$

C_{oct}=concentration of substance in octanol layer

C_{aq}=concentration of substance in aqueous layer

TLC method[14,19]

Ethanolic solution for each compound was prepared and the TLC plate with 90x30mm dimensions was used to determine the R_f value for each compound. The spotting was done with class capillary tube from each solution and the mobile phase was different concentrations of ethylacetate and petroleum ether. The R_f values for each compound was recorded in Table 2.

Antifungal activity[20]

The antifungal activity of the compounds was tested against the fungus *Aspergillus niger* at a concentration of 1000 µg/ml in dimethyl sulfoxide solvent using agar diffusion method .The medium used in this respect was Sabouraud dextrose agar .

Wells (6mm in diameter) were cut using stainless sterile cutting device (cork borer) and 100 µl of each compound was added to each well. Plates were incubated at 25^{o}C for 5-7 days , inhibition zone diameters in mm were measured and recorded in Table 9.

Table 2 R_f values of the compounds

V/V% ethylacetate	AM	B	V	AMB	AMV
20	0.25	0.71	0.27	0.78	0.62
30	0.31	0.64	0.31	0.73	0.58
40	0.34	0.59	0.35	0.70	0.51
50	0.41	0.56	0.38	0.64	0.47
60	0.46	0.52	0.42	0.58	0.44

1. Result and Discussion

^{1}H-NMR spectra

^{1}H-NMR spectra of the prepared compounds AMB and AMV were performed in deuterated dimethyl sulfoxide solutions with tetramethylsaline as an internal standard. Figures 2 and 3 represent the ^{1}H-NMR spectra of the AMB and AMV, respectively. These spectra showed signals at 2.5 ppm which was due to DMSO solvent and at 3.33 ppm due to dissolved water in DMSO[21].

Figures 2 and 3 show a characteristic highfield singlet signals which attributed to the protons of aliphatic systems, the compound AMB gave two singlet signals at 2.45 and 3.13 ppm related to protons of C-CH_3 and N-CH_3 groups ,respectively, of aminoantipyrine fragment. The second compound AMV exhibited three singlet signals at 2.43, 3.12 and 3.83 ppm. The first two signals related to the protons of C-CH_3 and N-CH_3 groups, respectively, of aminoantipyrine fragment, whereas the third signal attributed to protons of O-CH_3 group of vanillin fragment, as shown in Table 3.

The second type of signals are attributed to protons of aromatic systems in the two compounds. The compound AMB exhibited multiplet signals in the range 7.14-7.69 ppm related to the 15 protons of aromatic systems of benzyl and aminoantipyrine fragments. The compound AMV exhibiter multiplet signals between 6.83-7.53 ppm which attributed to the 8 protons of vanillin and aminoantipyrine fragments.

The compound AMV showed two singlet signals at downfield 9.45 ppm attributed to the proton of azomethine group –N=CH- which absence in AMB compound, and at 9.50 ppm due to intramolecular hydrogen bonded proton of –OH group of vanillin fragment, as shown in Figure 3 and Table 3.

Table 3 ^{1}H-NMR data of compounds AMB and AMV

Compd.	¢ ppm					
	C-CH_3	**N-CH_3**	**-O-CH_3**	**Aromatic system**	**-N=CH-**	**-OH**
AMB	2.45 (s)	3.13 (s)	-	7.14-7.69 (m)	-	-
AMV	2.43 (s)	3.12 (s)	3.83 (s)	6.83-7.53 (m)	9.45 (s)	9.50 (s)

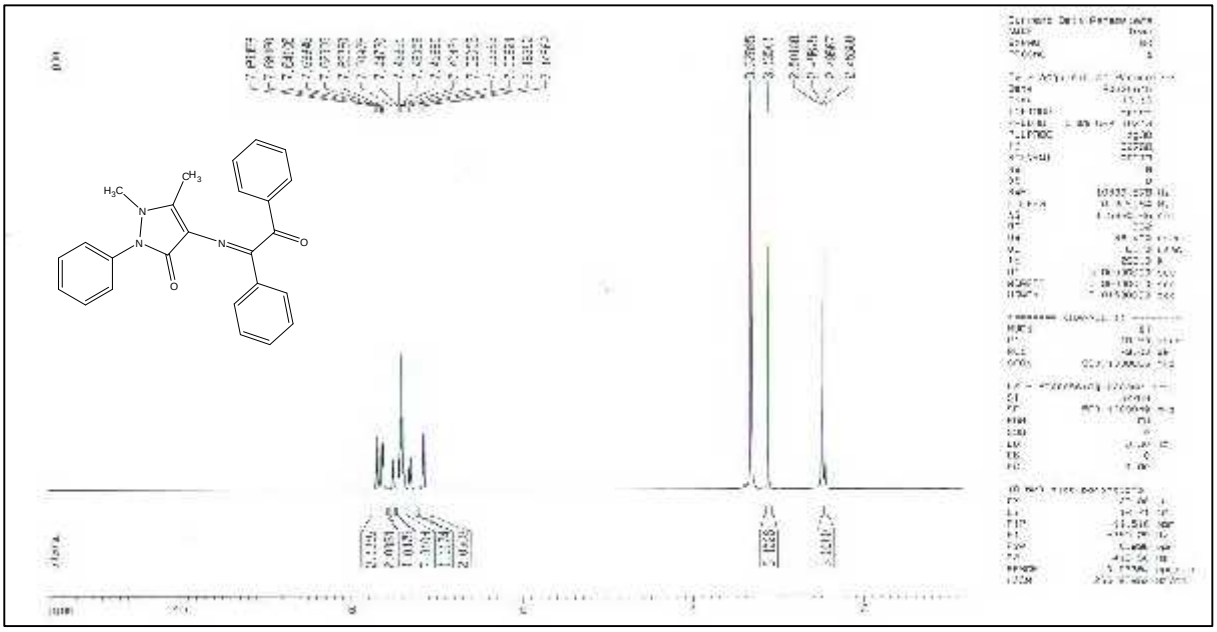


Figure 2 ^{1}H-NMR spectrum of the compound AMB

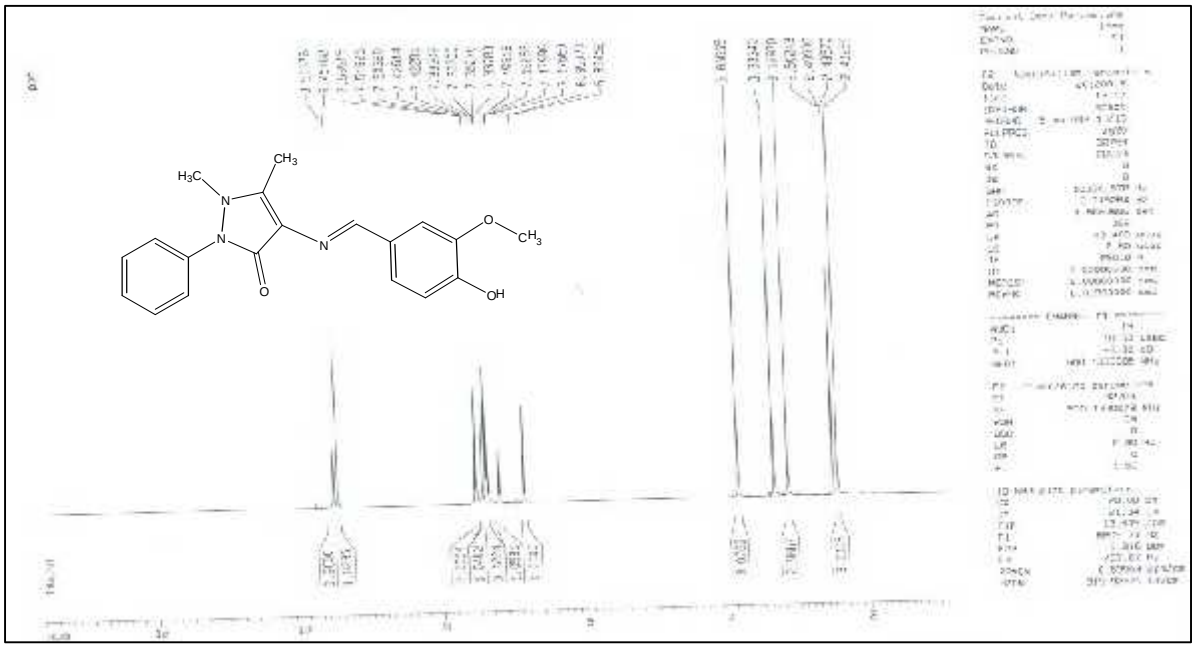


Figure 3 ^{1}H-NMR spectrum of the compound AMV

FT-IR Spectra

The IR spectra for AMB and AMV compounds were performed by the KBr disc method. Table 4 represents the data of the important bands of the IR spectra of these compounds.

These compounds exhibited common bands, 1640 and 1658 cm^{-1} attributed to the $\nu_{C=O}$ bond of carbonyl group, absorption bands in the 1593 and 1600 cm^{-1} are assigned to the existence of $\nu_{C=N}$ of the azomethine group. Medium bands in the range 1570-1478 cm^{-1} and 1217-1207 cm^{-1} which attributed $\nu_{C=C}$ stretching of aromatic ring and ν_{C-N} stretching of pyrazole ring, respectively. The compound AMV exhibited a broad band at 3210 cm^{-1} attributed to ν_{O-H} stretching of vanillin fragment which at the lower frequency due to intramolecular H-bonding[22] with $–O-CH_3$ group. As shown in Table 4.

Table 4 IR spectra data of compounds AMB and AMV

AMB	AMV	Assignment
	3210 br	O-H stretching
3056 w	3075 w	C-H stretching aromatic
2918 w	2927 w	C-H stretching aliphatic
1658 s	1640 s	C=O stretching
1593 m	1600 m	C=N stretching
1560 m 1492 m	1570 m 1478 m	C=C stretching of aromatic ring
1417 m 1319 m	1428 m 1327 m	C-H bending aliphatic
1217 m	1207 m	C-N stretching
	1150 m	C-O stretching
910 s 690 s	790 s 720 s	C-H bending aromatic

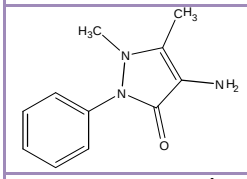
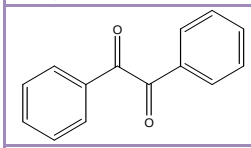
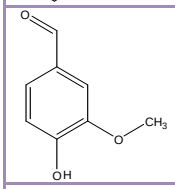
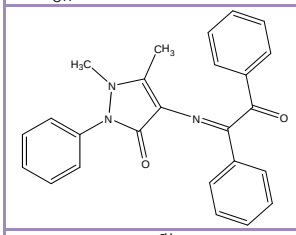
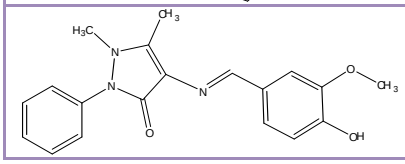
br = broad, s = strong, m = medium, w = weak

Lipophilicity study

1- Theoretical methods[15,23]

Four programs were used in the calculation of Log P by the theoretical method, Table 5 represents the lipophilicity of these compounds by these different theoretical methods.

Table 5 Lipophilicity of the five compounds by theoretical methods

COMPOUND	Sym.	Log P (Thr.)			
		ALOGPS 2.1	MarvinSkectch 4.1.6	ChemOffice 11	HyperChem 7.52
	AM	0.47(±0.75)	0.83	-0.53	-1.19
	B	3.06(±0.4)	2.8	2.78	3.15
	V	1.18(±0.16)	1.18	1.26	-1.79
	AMB	3.83(±0.59)	4.66	3.36	2.19
	AMV	2.34(±0.49)	3.04	1.84	-2.41

2- Shake flask method

The absorbance of octanol layer is measured before and after the shaking process. The absorbance for each compound is converted to concentration by calibration curve. Equation 1 is used to calculate the log P by this method. Table 6 shows the lipophilicity of the compounds.

Table 6 Lipophilicity of the five compounds by shake flask method

Compound	AM	B	V	AMB	AMV
Log P	0.719	1.44	0.32	1.28	0.837

3- TLC method

The lipophilicity (R_{MO}) is obtained from R_f values by equations 2 and 3. The R_M value is calculated from R_f value by equation 2. The lipophilicity value is obtained by the extrapolation to zero concentration of polar component in the graph drawn between R_M and concentration of polar component in mobile phase. The C in equation 3 is the

concentration of the polar component in the mobile phase. The b in equation 3 is called as specific hydrophobic surface area of compound. The lipophilicity determined in TLC are being correlated with theoretically calculated log P and the biological activity of the compounds.

$$R_M = \log(\frac{1}{R_f} - 1) \text{ - - - - - - - } 2$$

$$R_M = R_{MO} + bC \text{ - - - - - - - } 3$$

R_M value of the compounds are determined in TLC method using ethylacetate and petroleum ether as mobile phase. The R_f values are taken in the duplicate and the average value is taken for R_M value calculation. The R_f values for each compound is determined in five different composition of mobile phase (as shown in Table 2) and the R_M of the five compounds are shown in Table 7. The R_f in Table 2 are converted to R_M by equation 2.

Table 7 The R_M value of the compounds

v/v% ethylacetate	AM	B	V	AMB	AMV
20	0.477	-0.388	0.431	-0.549	-0.212
30	0.347	-0.249	0.347	-0.431	-0.140
40	0.288	-0.158	0.268	-0.367	-0.017
50	0.158	-0.104	0.212	-0.249	0.052
60	0.069	-0.034	0.140	-0.104	0.104

The lipophilicity R_{MO} of the five compounds is determined by equation 3 via the graphical method, as shown in Table 8.

Table 8 The lipophilicity R_{MO} of the compounds

Compound	AM	B	V	AMB	AMV
R_{MO}	-0.01	0.008	-0.007	0.01	0.008

Antifungal method

Antifungal activity for the five compounds are shown in Figure 5 and inhibition zones are shown in Table 9 and Figure 4. The inhibition zone of the compounds gave good activity as compared with the control (the solvent DMSO) reflected that these compounds have different lipophilicity behaviors, where the inhibition zone was in the rank, AMB>AMV>B>V>AM. The antifungal activity was due to the blocking the ergosterol biosynthetic pathway, the main steroid found in fungal cell membranes[24,25].

Table 9 Inhibition zone of the five compounds at 1000 «g/ml against *Aspergillus niger*

Compound	AM	B	V	AMB	AMV
Inhibition Zone (mm)	7	11	9	18	16

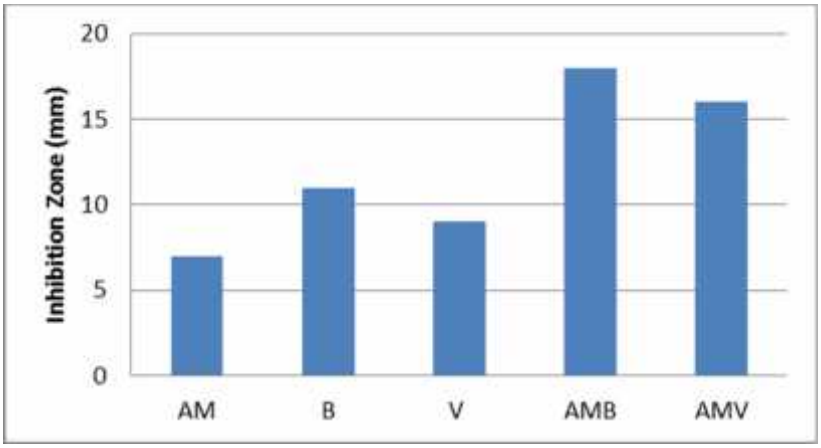


Figure 4 Inhibition zone of the compounds against *Aspergillus niger*

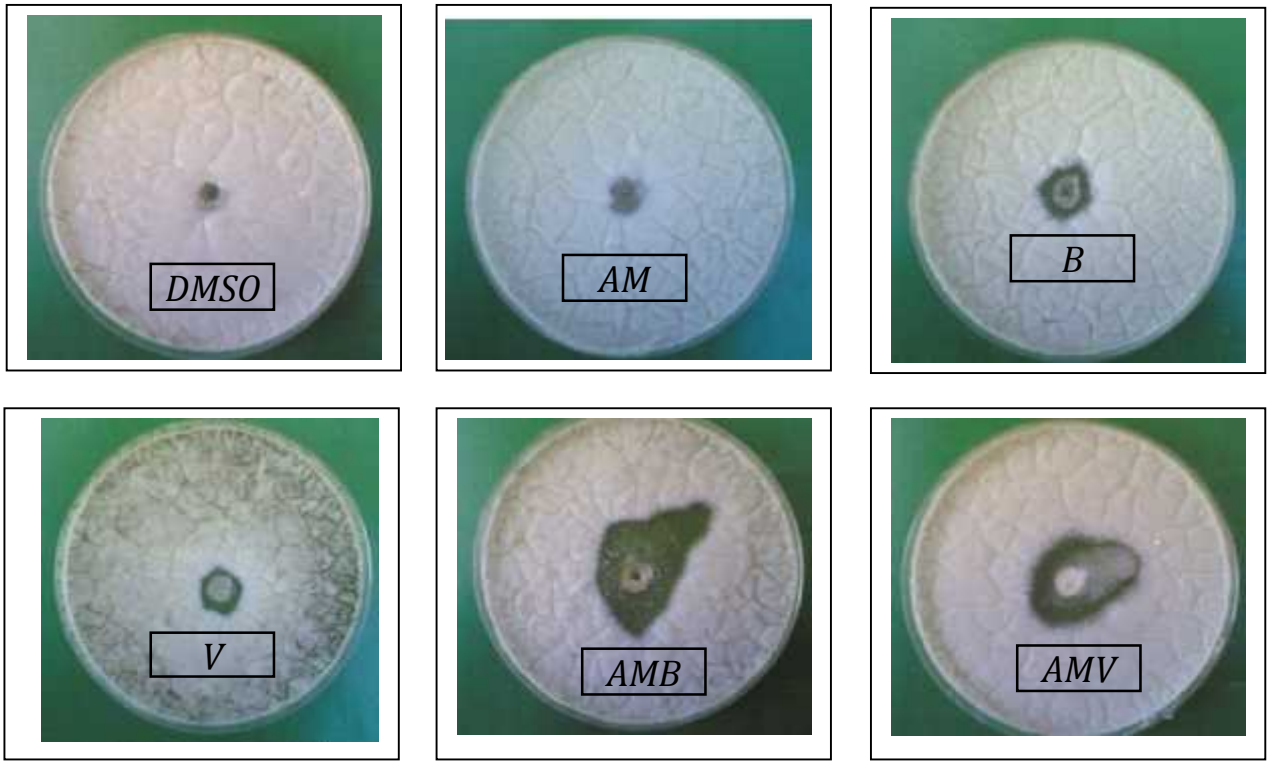


Figure 5 Antifungal activity of the compounds and DMSO against *Aspergillus niger*

Correlation Study

The lipophilicity values determined by the previous methods were correlated graphically to obtain the best correlation coefficient between these values.

a- The correlation between the theoretical methods:

Figure 6 show the correlation between MarvinSketch , Chemoffice, HyperChem and ALOGPS methods. We show that there

are different values of correlation coefficients between these methods, and the best correlated methods that may used to determine the lipophilicity is 0.936 which between ALOGPS and Chemoffice, and correlation coefficient between ALOGPS and Marvin is 0.917. whereas, there is not good correlation between Hyperchem and the other methods. Therefore, the ALOGPS, chemoffice and Marvin methods are good method to show the lipophilicity of the compounds.

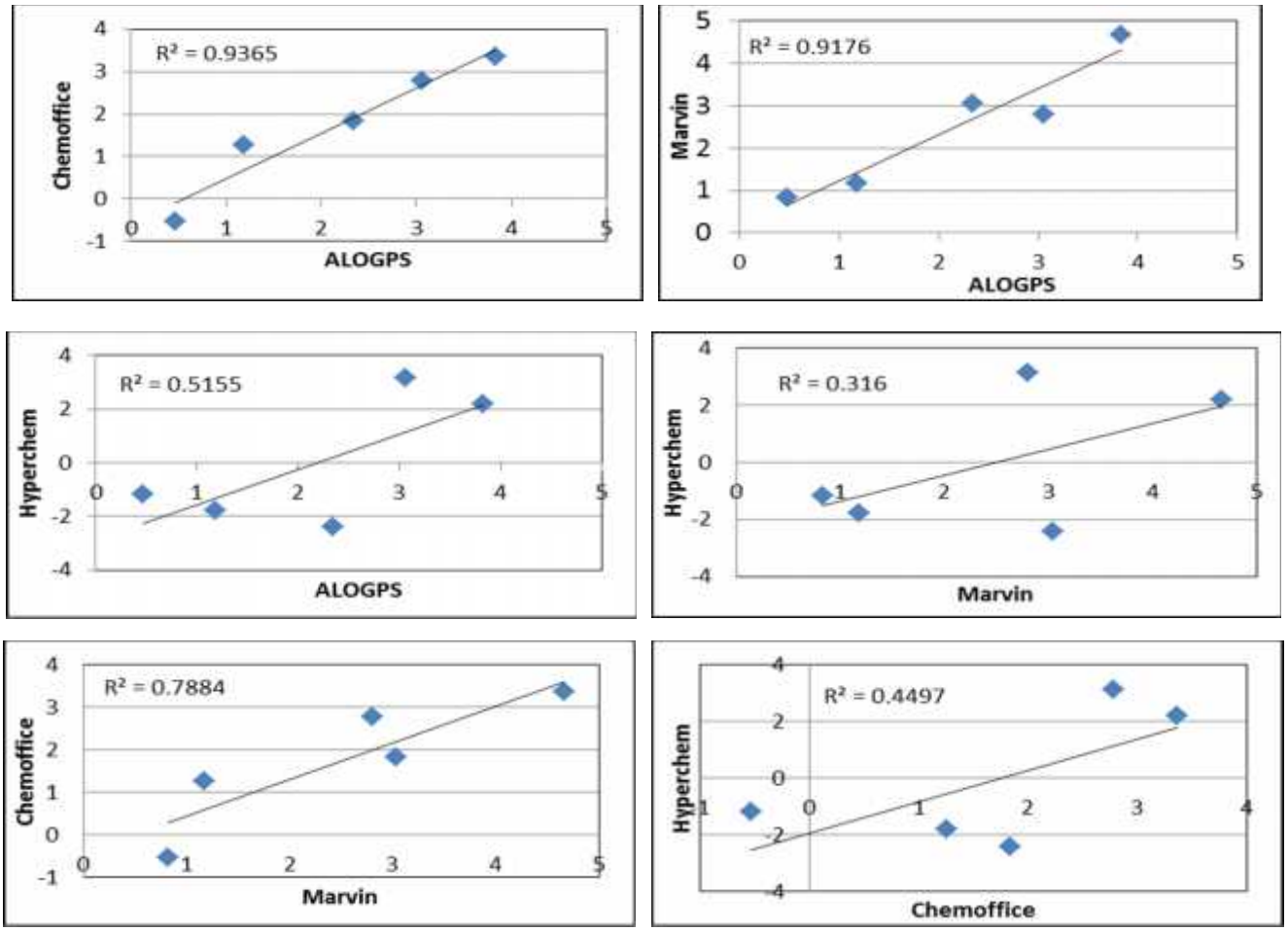


Figure 6 The correlation between the theoretical methods

b- Correlation between Shake Flask and TLC methods with theoretical methods:

We used to practical method to determined Log P, the correlation coefficients gave an idea that there are good agreements between theoretical values and TLC method (0.802-0.892), whereas the agreements is less between the theoretical and Shake Flask methods (0.471-0.653). Therefore, the TLC method may used to show the estimate Log P values and may used in the QSAR study. Figure 7 shows the correlation between the practical and theoretical values of Log P.

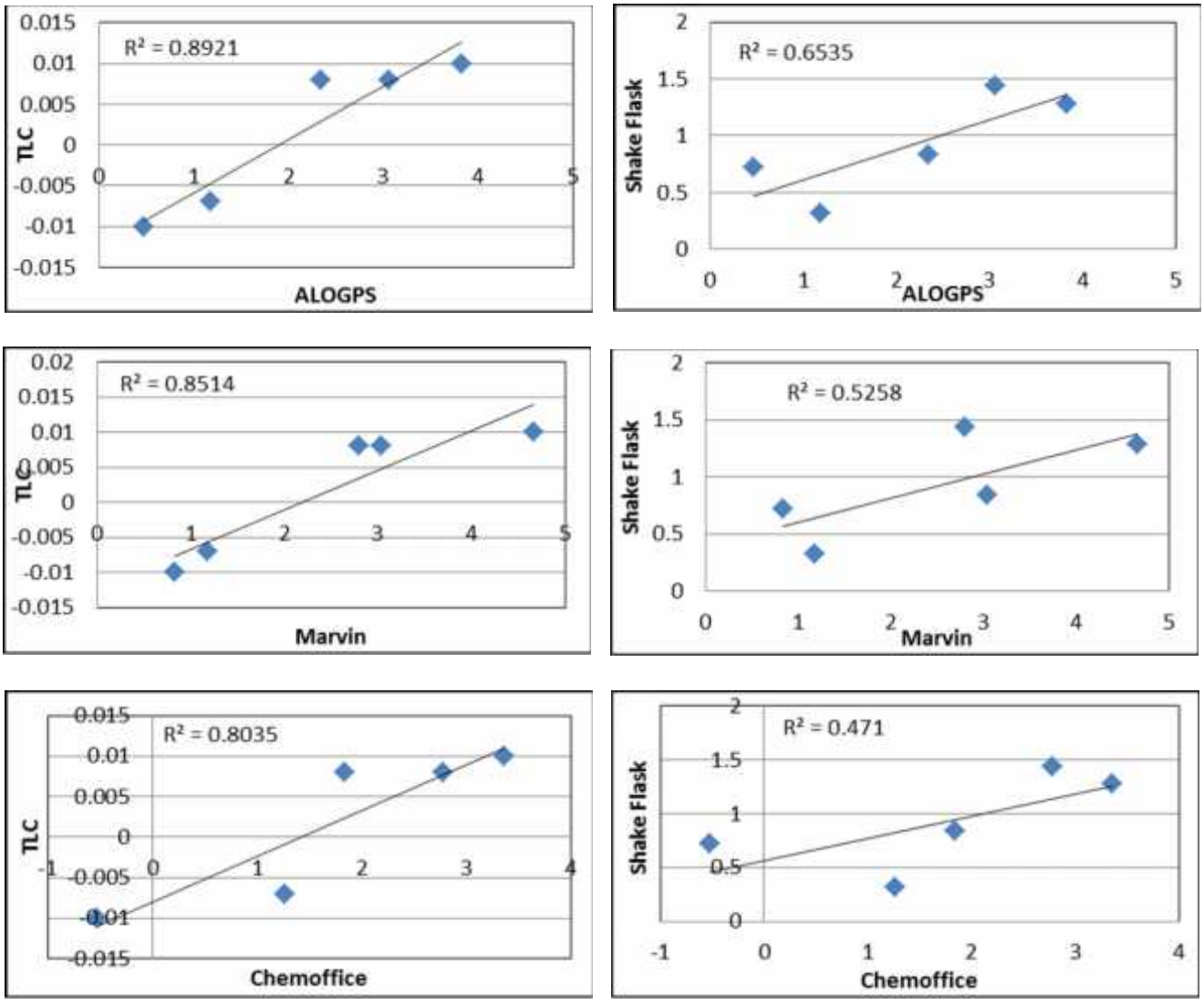


Figure 7 The correlation between the practical and theoretical methods

c- Correlation between antifungal activity with practical and theoretical methods:

The inhibition zone values of the compounds were compared with the lipophilicity values in the best theoretical methods (ALOGPS, Marvin and Chemoffice), as shown in Figure 8.

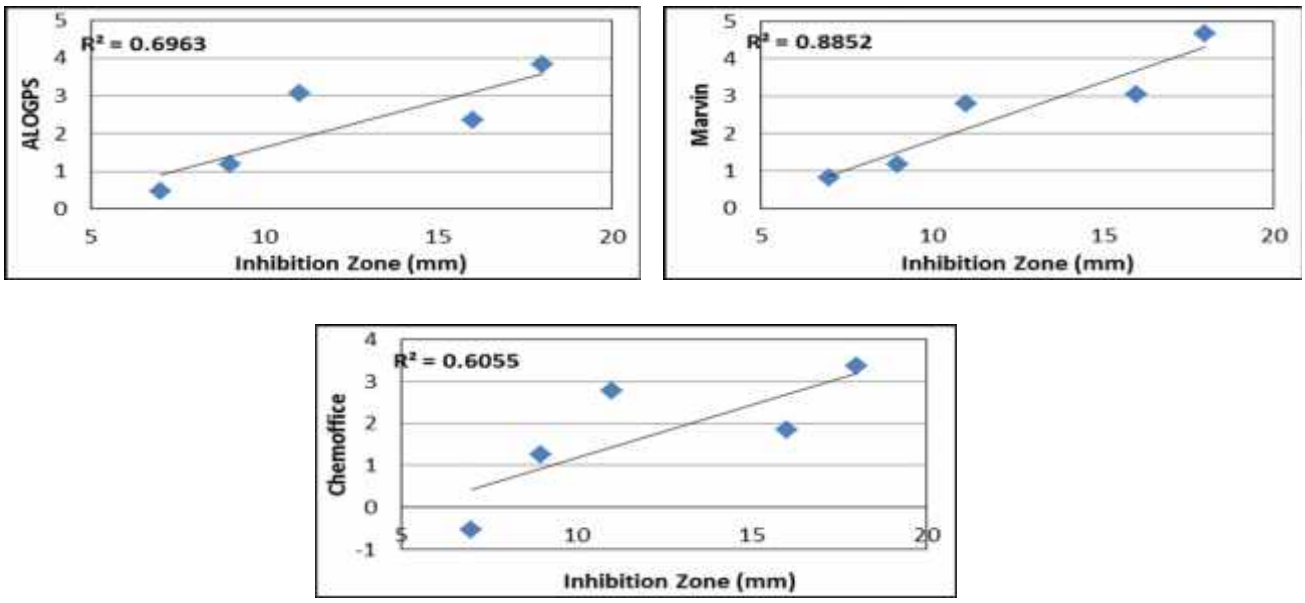


Figure 8 The correlation between the inhibition zone and theoretical methods

We see that there is good agreement between the inhibition zone and lipophilicity by Marvin method of the compounds (0.885), whereas, the other two method gave less values of correlation (0.696 and 0.605). From this method, we see that this method reflected good idea about the penetration of compounds through the membrane of the cell, and the greater lipophilicity the greater antifungal activity.

The inhibition zone of the tested compounds were correlated with the practical methods (Shake Flask and TLC), as shown in Figure 9. We see that there is good correlation with TLC method and the correlation coefficient is 0.749 as compared with Shake Flask method which gave bad correlation coefficient 0.241.

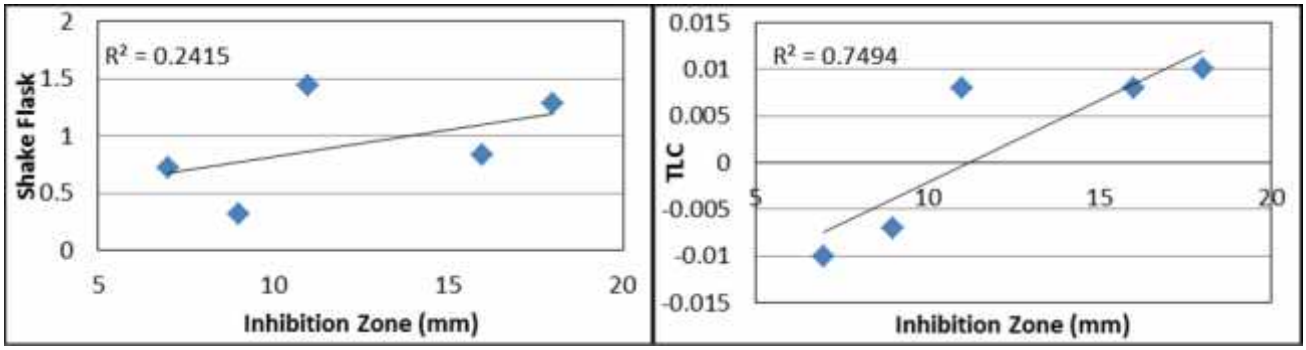


Figure 9 The correlation between the inhibition zone and practical methods

Finally, we can give a picture about the matching of lipophilicity values for each compound using these different methods. We see that the compound AM gave good matching in Log P values, whereas, the compound AMV showed wide gap of Log P values. As shown in Figure 10.

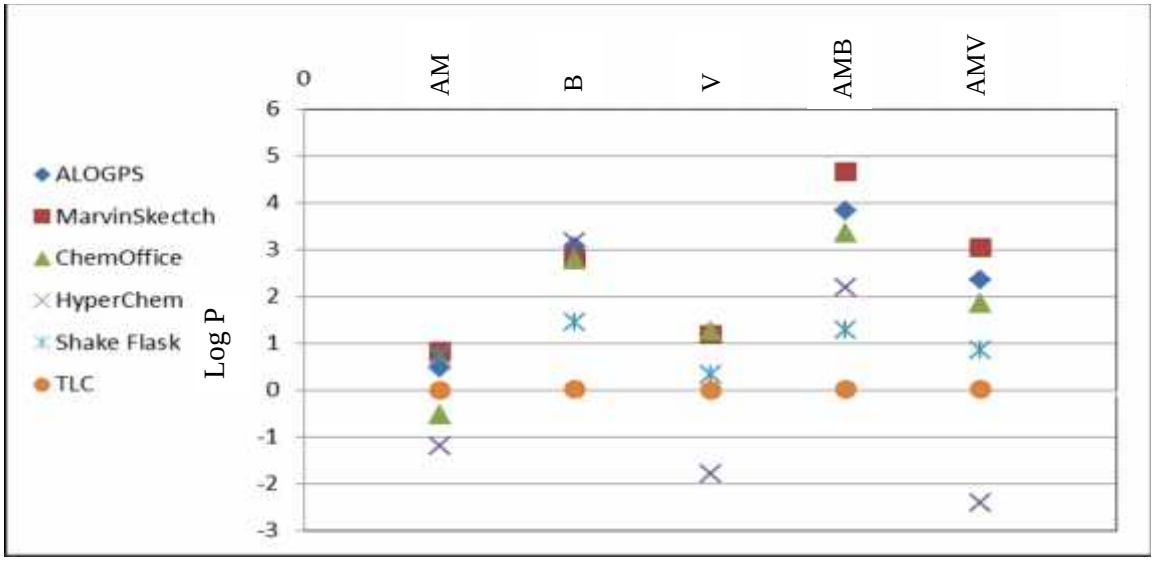


Figure 10 The matching between the Log P values for each compound

2. Conclusion

The lipophilicity determined in TLC have good correlation with theoretical values. Log P values by ALOGPS, Marvin and Chemoffice can be used as descriptor in QSAR and QSPR study in the place of lipophilicity. The lipophilicity of compounds determined in the TLC have good correlation with its antifungal activity. It is understood that the compound having higher lipophilicity is exhibiting higher antifungal activity.

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تحضير وتشخيص ودراسة الصفات المحبة للدهون لبعض مركبات الايمين وموادها الاولية

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الملخص

حضرت بعض مركبات الايمين من تفاعل تكثيف 4-امينو انتي بايرين مع البنزل او الفانيلين.شخصت المركبات المحضرة باستخدام مطياف الاشعة تحت الحمراء والرنين النووي المغناطيسي البروتوني. درست الصفات المحبة للدهون للمركبات المحضرة وموادها الاولية وتم تقدير قيم لوغاريتم معامل التوزيع باستخدام اربع طرق نظرية وطريقتين عملية، وتم تقدير الفعالية ضد الفطريات لهذه المركبات. قدرت معملات الارتباط بين الطرق المستخدمة، وجد توافق جيد بين الطرق النظرية ماعدا هايبركيم. اوضحت الطرق العملية ان هناك توافق جيد بين طريقة كروماتوغرافيا الطبقة الرقيقة وطريقة مارفن النظرية. من جهة اخرى، دعمت الفعالية ضد الفطريات قيم الصفات المحبة للدهون المحسوبة باستخدام الطرق النظرية والعملية.

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