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SYNTHESIS, ANTIFUNGAL ACTIVITY AND MOLECULAR DOCKING STUDIES OF AROMATIC ACYLALS

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Abstract: There is an urgent need to explore alternative compounds in order to develop new antifungal medications due to the rise of fungal infections and the attending resistance to some of the existing drugs. Thus, the object of this work was to synthesize and evaluate, for the first time the antifungal activity of eight known aromatic acylals against *Aspergillus niger*, *Aspergillus flavus* and *Trichophyton rubrum*. The aromatic acylals were obtained by the reaction of aromatic aldehydes with acetic anhydride using H_2SO_4-silica as a catalyst. *In vitro* evaluation of the compounds against *A. niger*, *A. flavus* and *T. rubrum*, along with ketoconazole as the positive control was then performed. The results showed that all of the compounds were active against *A. flavus*. Compound **2a** demonstrated interesting antifungal potential showing the lowest MIC value among the tested compounds.

***Keywords*:** Aromatic acylals, Antifungal activity, Docking studies, MIC, MFC

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Introduction

Fungal infections also termed mycoses are described as one of the overlooked emerging diseases which are responsible for approximately 1.7 million deaths annually.[1] Globally, more than 1 billion people are affected by fungal infections in which over 150 million accounts for severe and life-threatening cases.[2] The current mainstay for the treatment of antifungal infections relies heavily on four classes of drugs, namely the polyenes, azoles, echinocandins and the pyrimidine analogue flucytosine (5-fluorocytosine).[3] However, novel resistant variants of previously susceptible pathogens such as *Aspergillus fumigatus*,[4] as well as entirely new emerging species like *Candida auris* that are resistant to multiple antifungal drugs have been reported.[5] When a fungal pathogen develops resistance to one class of antifungal agent, research has shown that the remaining alternatives may be less successful as well.[6] Looking at the few numbers of antifungal medications that are now licensed for use in the treatment of fungal infections where most of them have drawbacks such high toxicity and limited efficacy.[7] The urgent option is to vigorously search for novel antifungal agents in order to tame the unfolding public health crises. Meldrum's acid can be structurally considered as a cyclic diacetate in which the two carboxylate groups are connected by a methylene and quaternary carbons (Figure 1a). Derivatives of Meldrum's acid have been reported to have a wide spectrum of biological activities which includes anticancer, antifungal, and antibacterial properties.[8] Thus, this continued to attract the attention of medicinal chemists in drug design. In continuation of our search for biologically active small molecules,[9-13] we decided to explore the antifungal property of simple aromatic acylals which coincidentally contains the acyclic core structural motif of Meldrum's acid (Figure 1b). Hence in this work, some known aromatic acylals were synthesized and for the first time evaluated their activity against three fungal species *in vitro*.

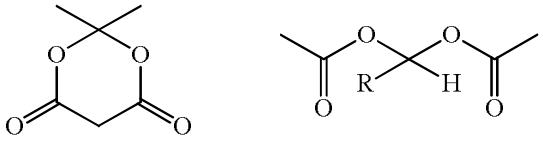
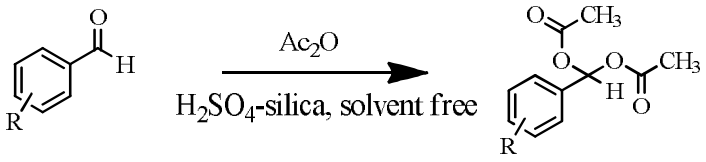


Figure 1. Structures of (a) Meldrum's acid (b) Core acylal motif.

Results and Discussion

Chemistry

Acylals, **2a-h** were synthesized (Scheme 1) by reacting the appropriate aldehyde with acetic anhydride using H_2SO_4-silica as a catalyst. The obtained products were characterized using NMR and FTIR spectroscopic techniques. According to the NMR data of compound **2a**, the ^{1}H NMR spectrum (Figure 2) of the compound gave a signal at 2.13 ppm assigned to the six protons of the methyl groups of the diacetoxy groups, $(OCOCH_3)_2$. The two aromatic protons closer to the carbon of the ring bonded to the carbon attached to diacetoxy group appeared at 7.41 ppm, while the signal at 7.52 ppm was assigned to the other three aromatic protons on the benzene ring. The signal at 7.6 ppm was assigned to the proton from the methine group (–CH) attached to the diacetoxy group $(OCOCH_3)_2$. The ^{13}C NMR spectrum (Figure 3) gave a signal at 20.8 ppm for the two methyl carbons, $(–CH_3)$, and the signal from 89.7 ppm was assigned to the methine carbon (–CH) bonded to the diacetoxy groups, $(OCOCH_3)_2$. The signals from the range 126.7 ppm – 135.5 ppm were designated for the aromatic carbons. Lastly, the signal at 168.8 ppm was assigned to the two carbonyl carbons of the diacetoxy group, $(OCOCH_3)_2$. The FTIR spectrum indicated the absorption band for C–O group at 1498 cm^{-1}, the absorption band for C-H group at 3064 cm^{-1}, while the absorption at 1752 cm^{-1} confirmed the presence of carbonyl groups C=O.



1a-h **2a-h**

	R
a	H
b	4-Cl
c	4-OH
d	4-CF_3
e	4-CH_3
f	3-NO_2
g	4-OCH_3
h	4-OH, 3-OCH_3

Scheme 1. Synthesis of aromatic acylals.

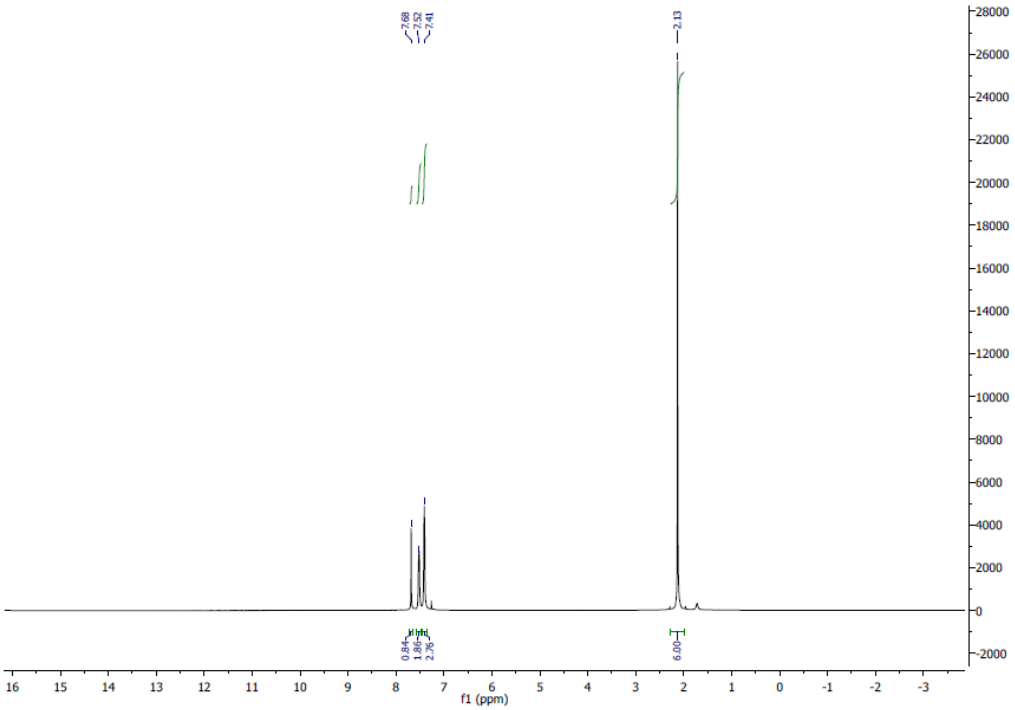


Figure 2. ^{1}H NMR spectrum of compound **2a**.

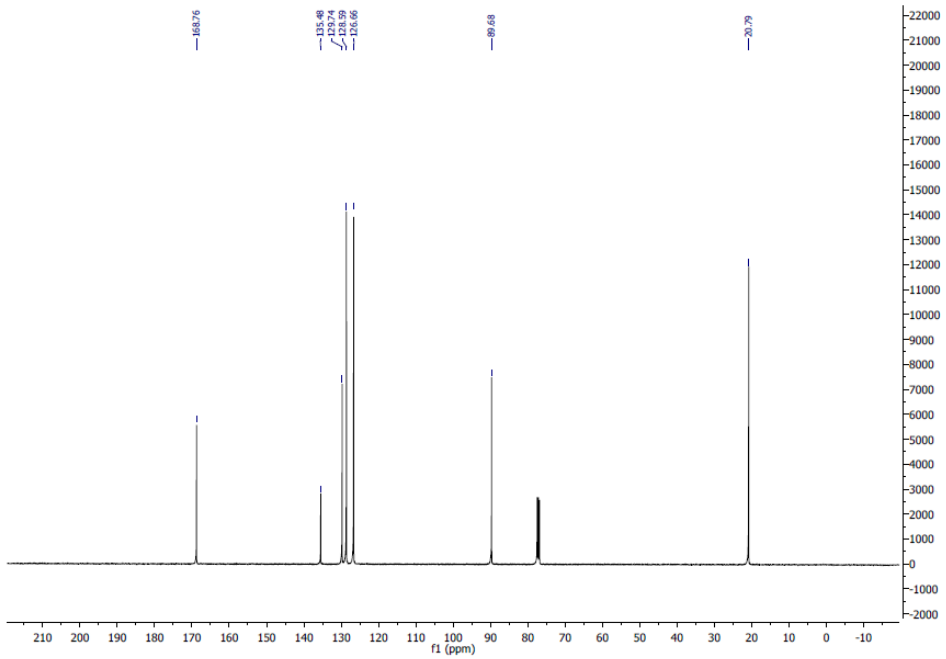


Figure 3. ^{13}C NMR spectrum of compound **2a**.

Antifungal activity

The compounds were screened for antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, and *Trichophyton rubrum* following a disc diffusion method. All of the fungi were found to be sensitive to the compounds except **2b** which showed no activity against *A. niger* and *T. rubrum* (Table 1). Compounds **2a**, **2c**, **2d**, and **2e** demonstrated substantial inhibition zones, particularly against *A. niger* at 13 mm, 21 mm, 15 mm and 17 mm respectively. While, compounds **2b**, **2g**, and **2h** did not showed activities against this fungal strain. However, compounds **2a**, **2c**, and **2d** were most effective, against *A. flavus* with zones of inhibition of 19 mm, 26 mm and 19 mm respectively. This was followed by compound **2g** at 11 mm. Compounds **2b**, **2e**, **2f**, and **2h** were less effective with similar zones of inhibition of 9 mm. As for *T. rubrum*, compound **2d** exhibited the highest activity at 24 mm followed by compound **2a** with 18 mm.

Compound **2e** was less effective with 8 mm zone of inhibition, while compounds **2b**, **2c**, **2f** and **2h** were inactive against this strain. This suggested that structural variations among the compounds may significantly influence their antifungal properties. The results indicated that while all compounds showed activity against *A. flavus*, but sensitivity towards *A. niger* and *T. rubrum* was selective. The absence of activity in compounds **2b**, **2c**, **2g**, and **2h** against specific strains highlights the need for further structural modifications to enhance their antifungal efficacy.

Table 1. Zone of inhibition of aromatic acylals against fungi.

Compound 1,000 *µg/mL*	**Fungi Zone of Inhibition (mm)[a]**		
	Aspergillus niger	***Aspergillus flavus***	***Trichophyton rubrum***
2a	13	19	18
2b	ND	9	ND
2c	21	26	ND
2d	15	19	24
2e	17	9	8
2f	11	9	ND
2g	ND	11	11
2h	ND	9	ND
Ketoconazole	41	32	36

[a] = mean values of triplicate tests; ND = not determined

The active compounds were further evaluated for Minimum inhibitory concentration. It was found that compounds **2a** demonstrated the lowest concentration of 10 µg/mL against *T. rubrum*. While compounds **2a**, **2d**, **2e** inhibited *A. flavus* at 15 µg/mL. Compound **2e** was the only one with a lowest inhibitory activity of 15 µg/mL against *A. niger* (Table 2).

Table 2. Minimum inhibitory concentration of aromatic acylals against Fungi.

Compound	Concentration (µg/mL)		
	Aspergillus niger	***Aspergillus flavus***	***Trichophyton rubrum***
2a	30	15	10
2c	25	20	ND
2d	25	15	20
2e	15	15	ND
2f	25	ND	ND
2g	ND	ND	20
Ketoconazole	2.5	5	5

ND = not determined

Investigation of the minimum fungicidal concentration showed that compound **2a**, **2d**, and **2g** were fungicidal at 25 µg/mL against *T. rubrum*. Compound **2d** exhibited the lowest fungicidal effect against *A. flavus* at 15 µg/mL but the compound was not found to be fungicidal against *A. niger*. Compounds **2c** and **2f** demonstrated a fungicidal effect of 25 µg/mL against *A. niger* (Table 3). Generally, compound **2a** which contains none of activating or deactivating groups appeared to exhibit the most interesting potency in this study.

Table 3. Minimum fungicidal concentration of aromatic acylals against fungi.

Compound	Concentration (µg/mL)		
	Aspergillus niger	***Aspergillus flavus***	***Trichophyton rubrum***
2a	35	25	25
2c	25	25	ND
2d	ND	15	25
2e	30	20	ND
2f	25	ND	ND
2g	ND	ND	25
Ketoconazole	5	10	10

ND = not determined

Molecular docking studies

Uridine 5′-diphospho-N-acetylglucosamine, (UDP-GlcNAc) is an essential building block in the fungal and bacterial cell walls. The enzyme responsible for the catalysis of first and rate-limiting step in hexosamine biosynthesis which produced UDP-GlcNAc is called glucosamine-6-phosphate synthase, GlcN-6-P), hence it becomes an interesting target for antifungal and antibacterial drug discovery[14-17]. All the eight compounds have demonstrated a number of favorable interactions with various residues of the enzyme (Table 4). Generally, the compounds can be grouped into two in terms of the binding energies; compounds **2d**, **2e**, **2f** and **2h** appeared to have lower energies than compounds **2a**, **2b**, **2c** and **2g**. Specifically, compound **2d** which exhibited broad spectrum low MIC values for the three fungal species appeared to have a binding energy of -6.1 kcal/mol for a total of six interactions (Figure 4).

Table 4. Binding Interactions of GlcN-6-P with Compounds 2a-h.

Protein	Ligand	Binding Site Residues	Interaction Types	Distance (Å)	Binding Affinity (kcal/mol)
GlcN-6-P	**2a**	LEU;145, LEU;43	Hydrophobic Hydrophobic	5.71, 4.25	- 5.7
	2b	SER;99, HIS;69	Carbon H-Bond	4.29, 6.63	- 5.9
	2c	LEU;145, TYR;149	Hydrophobic Donor-Donor	6.07, 5.49	- 5.8
	2d	HIS;69, PRO;66, VAL;89	H-Bond, Carbon H-Bond, Hydrophobic	5.66, 4.77, 4.55	- 6.1
	2e	PRO;66, LEU;132	Hydrophobic, Hydrophobic	4.89, 4.23	-6.1
	2f	ARG;113, VAL;142 VAL;106	H-Bond, Hydrophobic	6.46, 3.48 4.31	- 6.3
	2g	CYS;158, LEU;145	H-Bond, Hydrophobic	5.06, 6.16	- 5.8
	2h	VAL;106, LEU;145	H-Bond, Hydrophobic	3.01 5.66	- 6.1

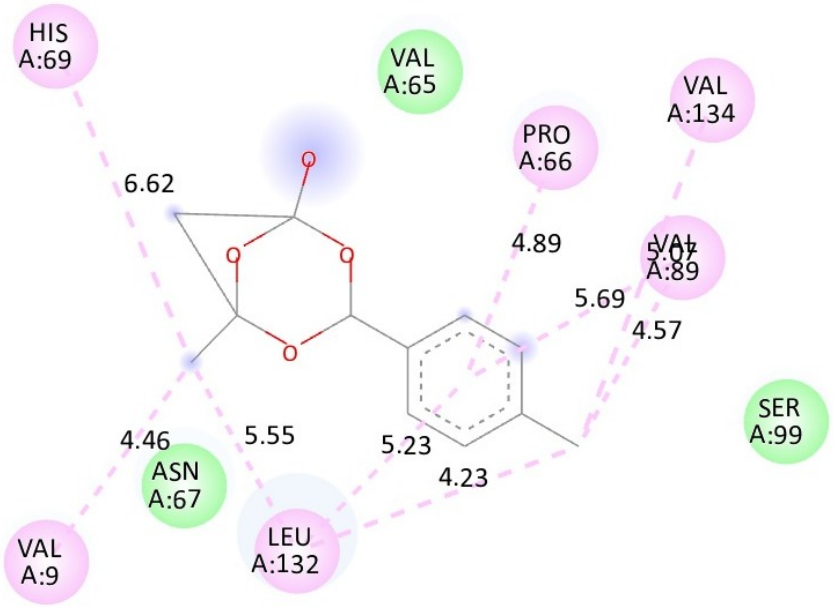


Figure 4. Docking pose of GlcN-6-P with compound **2d.**

Experimental

All reagents and solvents used in this work were obtained from Sigma-Aldrich (Darmstadt, Germany). NMR spectroscopic analysis was recorded on Bruker AVANCE 400 MHz and chemical shifts (δ) are reported in ppm, while FTIR spectra were recorded on a Perkin–Elmer BX spectrophotometer and the position of the absorption bands are reported in cm^{-1}. Melting points were determined on electrothermal IA 9100.

General Procedure for the Preparation of Acylals 2a-h

A mixture of aldehyde (10 mmol), acetic anhydride (40 mmol), and powdered H_2SO_4-silica as catalyst (3 mg, 1 mol %) was stirred at room temperature. The reaction was monitored by TL C until completion. After completion, the catalyst was filtered by washing with ethyl acetate. The collected organic layers were further treated with saturated $NaHCO_3$

solution (3 × 10 mL), water (10 mL), and finally dried with anhydrous Na_2SO_4. The solvents were removed *in vacuo* and the products recrystallized from ethyl acetate/hexane mixture (1:1) to afford the pure compounds, **2a**-**2b**,[18] **2c**,[19] **2d-e**,[20] **2f**-g,[18] **2h**.[21]

Phenylmethylene diacetate (**2a)**

White crystals; 92% yield; mp 45-46 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.13 (6H, s, CH_3), 7.41 (3H, m, Ar-H), 7.52 (2H, m, Ar-H), 7.68 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 20.8, 89.7, 126.7, 128.6, 129.7, 135.5, 168.8; FTIR (ν): 3064, 1752, 1499, 1237 cm^{-1}.

4–Chlorophenyl)methylene diacetate (**2b)**

White crystals; 94% yield; mp 83-84 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.12 (6H, s, CH_3), 7.37 (2H, d, *J* = 8.0 Hz, Ar-H), 7.45 (2H, d, *J* = 8.0 Hz, Ar-H), 7.63 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 20.9, 89.2, 128.3, 128.9, 134.1, 135.8, 168.8 ; FTIR (ν): 3050, 1737, 1416, 1059 cm^{-1}.

4-Hydroxyphenyl)methylene diacetate (**2c)**

White crystals; 96% yield; mp 63-64 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.12 (6H, s, CH_3), 5.30 (s, –OH), 6.98 (2H, d, *J* = 8.0 Hz, Ar-H), 7.63 (1H, s, CH), 7.89 (2H, d, *J* = 8.0 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 20.9, 89.0, 116.0, 127.2, 128.6, 160.0, 168.8; FTIR (ν): 3355, 3035, 1737, 1506, 1059 cm^{-1}.

4-(Trifluoromethyl)phenyl)methylene diacetate (**2d)**

White crystals; 93% yield; mp 52-53 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.12 (6H, s, CH_3), 7.37 (2H, d, *J* = 8.0 Hz, Ar-H), 7.45 (2H, d, *J* = 8.0 Hz, Ar-H), 7.63 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 21.0, 21.4, 89.9, 126.7, 129.3, 132.7, 139.9, 169.0; FTIR (ν): 3055, 1759, 1521, 1327, 1118 cm^{-1}.

***4-Methylphenyl)methylene diacetate* (2e)**

White crystals; 95% yield; mp 62-63 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.12 (6H, s, CH_3), 2.37 (3H, s, CH_3), 7.22 (2H, d, *J* = 8.0 Hz, Ar-H), 7.41 (2H, d, *J* = 8.0 Hz, Ar-H), 7.64 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$), δ(ppm): 21.0, 21.4, 89.9, 126.7, 129.4, 132.7, 139.9, 169.0; FTIR (ν): 3047, 1737, 1565, 1059 cm^{-1}.

***3-Nitrophenyl)methylene diacetate* (2f)**

Yellowish crystals; 97% yield; mp 66-67 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.16 (6H, s, CH_3), 7.62 (1H, t, *J* = 8.0 Hz, Ar-H), 7.72 (1H, s, CH) 7.83 (1H, d, *J* = 8.0 Hz, Ar-H), 8.27 (1H, d, *J* = 8.0 Hz, Ar-H), 8.39 (1H, s, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 20.8, 88.4, 122.0, 124.6, 129.9, 133.0, 137.6, 148.4, 168.7; FTIR (ν): 3040, 1752, 1528, 1349, 1193 cm^{-1}.

***4-Methoxyphenyl)methylene diacetate* (2g)**

Pale yellow oily; 95% yield; mp 63-64 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.08 (6H, s, CH_3), 3.71 (3H, s, OCH_3), 6.86 (2H, d, *J* = 8.0 Hz, Ar-H), 7.4 (2H, d, *J* = 8.0 Hz, Ar-H), 7.5 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 20.4, 55.1, 89.4, 113.9, 127.5, 129.6, 131.5, 169.0; FTIR (ν): 3060, 1767, 1513, 11155, 1021 cm^{-1}.

***4-Hydroxy-3-methoxyphenyl)methylene diacetate* (2h)**

White powder; 96% yield; mp 64-65 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.12 (6H, s, CH_3), 2.32 (3H, s, OCH_3), 3.86 (1H, OH), 7.02 (1H, d, *J* = 8.0 Hz, Ar-H), 7.06 (1H, d, *J* = 8.0 Hz, Ar-H) 7.12, (1H.s, Ar-H) 7.65 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 21.0, 55.1, 89.4, 110.9, 119.3, 123.0, 134.3, 140.8, 151.2, 164.3; FTIR (ν): 3045, 1744, 1513, 1200 cm^{-1}.

Antifungal activity

Sourcing of fungal species

Clinical isolates of *Aspergillus niger*, *Aspergillus flavus*, and *Trichophyton rubrum* were sourced from the Department of Microbiology, Umaru Musa Yar'adua University, Katsina, Nigeria.

Fungal susceptibility test

All compounds were evaluated for antifungal activity by disc diffusion method against the clinical isolates of *A. niger*, *A. flavus*, and *T. rubrum*. Sterilized Whatman filter discs with 6 mm diameter were impregnated with 1.00 µg/mL DMSO solution of the compounds and standard drug (ketoconazole) in separate test tubes. The isolates were inoculated on the freshly prepared SDA plates using a streak plate method. Then four discs impregnated with each compound and standard drug were introduced into the plates by aseptic technique. Finally, the plates were inoculated for 7 days at room temperature, and the zones of inhibition were recorded. This process was repeated three (3) times[22].

Determination of minimum inhibitory/fungicidal concentrations (MIC/MFC)

These were done as previously reported in our work[10].

Molecular docking studies

AutoDock program was implored to investigate the binding within the active site of the model structure of glucosamine-6-phosphate synthase, GlcN-6-P, ID: 4AG9, downloaded from the protein data bank. The full set of compounds **2a-h** was drawn using Chem. 3D pro. (v. 12), and the binding conformation was visualized on PyMOL tool software. The grid size was placed in the active site pocket centre set to 40 × 40 × 40 xyz points designated at dimensions (x = 27.610, y = 17.684, z = 16.621 with the

spacing of 0.375 Å for 4AG9. This ensured that the grid boxes comprised the whole binding site of the enzyme and offered enough space for the translational and rotational walk of the ligands. AutoDock was executed and different ligand conformations in a complex with the receptor were obtained which were ranked based on binding energy. The results were then analyzed using Biovia Discovery Studio (BDS, v. 24.1.0) software and expressed in terms of binding affinity (kcal/mol) of protein-ligand binding.[23]

Conclusions

Some known aromatic acylals were synthesized following a standard procedure and their structures fully characterized using NMR and FTIR spectroscopic techniques. Those acylals were evaluated for the first time against three species of fungi, namely *A. niger*, *A. flavus*, and *T. rubrum* in the presence of ketoconazole as standard drug. It was found that all the compounds were active against *A. flavus*, but selective against the other two fungal species. Further screening revealed that compound **2a** exhibited the lowest minimum inhibitory activity against *T. rubrum*, which demonstrated fungicidal activity against the same fungi at 25 µg/mL. Although none of the compounds possess superior activity over the control drug, but the tested fungal species were established to be sensitive to the aromatic acylals, and thus provided proof–Of–Concept for further studies.

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