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Synthesis and antifungal studies of bis-mono and difluorophenacyl azolium compounds

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ABSTRACT

A new series of novel bis-mono and difluorophenacyl triazolium and imidazolium compounds were synthesized starting from mono and difluorophenacyl chloride, 1H-1,2,4-triazole and 1H-imidazole. Similarly, 4-amino mono and difluorophenacyl triazolium compounds were prepared from 4-amino-4H-1,2,4-triazole and mono and difluorophenacyl chloride. A comparative study of these compounds against the fungi (aspergillus niger, aspergillus flavus and penicillium chrysogenum) were screened, while keeping Amphotericin B as standard. The antifungal tests have shown that most of the synthesized azolium compounds exhibit slight to moderate activity against the selected fungi.

Keywords: Azole; synthesis, antifungal activity, triazolium chloride, imidazolium chloride

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INTRODUCTION

It is observed that among the different microbes, fungi have an enormous impact on the immunocompromised patients and emerged as a major infection [1]. Furthermore the growing problem of antimicrobial resistance on prolonged exposure has induced the race for the design and development of new antimicrobial agents. As azoles and their compounds are the important class of the aromatic heterocyclic compounds having a wide range of biological applications especially as an active moieties in first, second and third generation conazoles which acts as an antifungal agents such as miconazole, econazole, fluconazole, itraconazole and voriconazole, we were interested in exploring further possibilities in azoles [2,3]. The actions of these compounds are based on the inhibition of the biosynthesis of ergosterol, the major steroid in the fungal membrane [4-6].

Structural modification have shown that the azole compounds also exhibits properties like antibacterial [7], anticonvulsant [8,9], anticancer [10,11], anti-inflammatory [12,13], antimalarial [14], anti-neoplastic [15], insecticidal and herbicidal [16-18]. Like azoles, azolium salts due to their characteristic behavior found application in many fields. The polyfluoroalkylated and perfluoroalkylated-1,2,4- triazolium compounds with low melting points (< 100^{o}C), thermal stability at higher temperatures, low vapour pressure, and highly polar (non- coordinating) nature attracting them towards the field of catalysis, lubrication, reaction media, and material science [19-23]. The another class of azolium salts termed as ionic liquids, such as [BmIm] PF_6 finding expanded application in the field

of organic synthesis, as efficient nucleophillic catalyst in carbonyl Umpolung reaction [24], redox catalysis [25], transesterification [26], polymerization reactions [27] and ring opening reactions [28]. Some of them are used in Baylis-Hillman reaction [29] and Stetter reaction [30] due the properties like high electrical conductance, high dielectric constant, thermal and chemical stabilities. Gree and his group have reported some of the imidazolium compounds which are used as room temperature ionic liquids in Stetter reaction [31].

As substituent fluorine has considerable impact on the behavior of a molecule in a biological environment due to special properties like small size, high electro negativity and less polarizability of C-F bond [32]. Furthermore, the triazole compounds containing fluorine have been of great interest in the field of medicine, agriculture, material science and in the fluorine chemistry [33].

In consideration of the above facts, we have prepared bis-mono and difluorophenacyl triazolium and imidazolium chloride salts shown in Figure 1. Our present work describes the antifungal activities of these salts towards the fungi such as *aspergillus niger*, *aspergillus flavus and penicillium chrysogenum* against the standard drug Amphotericin B.

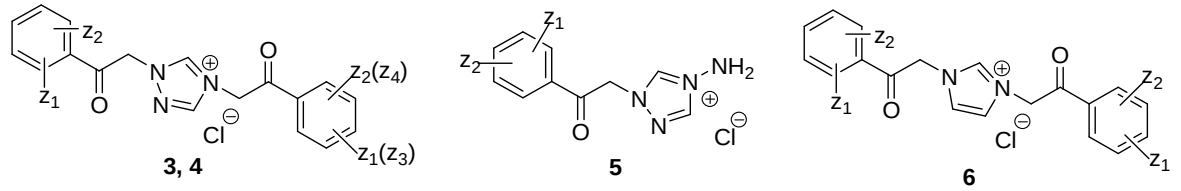
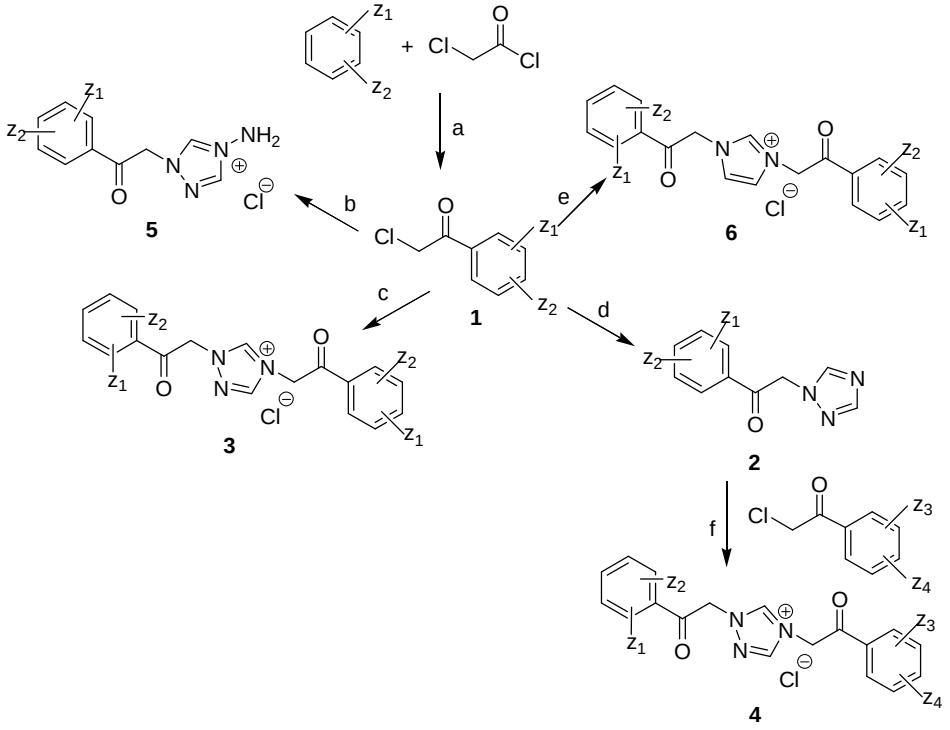


Figure 1. General structure of bis-mono and difluorophenacyl triazolium chloride (3 & 4), 4-amino triazolium chloride (5) and bis-mono and difluorophenacyl imidazolium chloride (6)



Scheme 1. Synthetic route to the target compound 3-6. Reagents and conditions: (a) anhydrous $AlCl_3$, 60 ^oC, dichloromethane (b) 4-amino-4*H*-1,2,4-triazole, 2-propanol, reflux (c) 1*H*-1,2,4-triazole, 2-propanol (d) 4-amino-1,2,4-triazole, 2-propanol, diazotization (e) imidazole, 2-propanol (f) mono and difluoro phenacyl chloride, 2-propanol

MATERIALS AND METHODS

All reagents were obtained commercially and used as received unless otherwise stated without further purification. Melting points were determined on a Reichert thermopan melting point apparatus. ^{1}H NMR spectra were recorded with Bruker Avance 300 MHz and Varian 500 MHz spectrometer using TMS as the internal standard in DMSO-d_6. IR spectra were recorded on a Perkin-Elmer Spectrum One Fourier transform FT-IR spectrophotometer. High-resolution mass spectral analyses were performed using the electrospray ionization (ESI) method on Xevo G2 QTOf mass spectrometer. The intermediate **1a** and **2a** was prepared by the reported procedure and applied the same for the preparation of **1b-d** [34]**. Caution**! The intermediate compounds **1a-d** were highly lachrymatory in nature and should be handled in fuming hoods.

General procedure for the preparation of 3a-3d

To a stirred solution of **1** (34.7 mmol) in 2-propanol (20 mL), 1*H*-1,2,4-triazole (14.4 mmol) was added and stirred at 80 ^{o}C for 11-12 h under nitrogen atmosphere. The reaction mixture was concentrated under vacuum and stirred with dichloromethane (10 mL) for 30 min. The precipitated solid was filtered and washed with dichloromethane (5 mL) to give **3**.

1,4-bis[2,4-difluorophenacyl]-1*H*-1,2,4-triazol-4-ium chloride (3a); 3.20 g, Light brown solid; IR (KBr) 3091, 3043, 2974, 2927, 1694, 1611, 1575, 1072, 876, 758 cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6) δ 6.11 (s, 2H, CH_2), 6.27 (s, 2H, CH_2), 7.34-7.42 (m, 2H, 2CH), 7.57-7.64 (m, 2H, 2CH), 8.08-8.14 (m, 2H, 2CH), 9.29 (s, 1H, CH, triazole), 10.16 (s, 1H, CH, triazole); HRMS (ESI, QTOF) for $C_{18}H_{12}ClF_4N_3O_2$ [M^+ - Cl] : *m/z* calcd: 378.0866; found: 378.0894.

1,4-bis[3,4-difluorophenacyl]-1*H*-1,2,4-triazol-4-ium chloride (3b); 2.51 g, Pink solid; IR(KBr) 3144, 3065, 2931, 2909, 1688, 1610, 1576, 1086, 896, 745 cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6) δ 6.25 (s, 2H, CH_2), 6.45 (s, 2H, 2CH), 7.75- 7.78 (m, 2H), 8.00-8.02 (br m, 2H), 8.17-8.23 (m, 2H, 2CH), 9.30 (s, 1H, CH, triazole), 10.17 (s, 1H, CH, triazole); HRMS (ESI, QTOF) for $C_{18}H_{12}ClF_4N_3O_2$ [M^+ - Cl] : *m/z* calcd: 378.0866; found: 378.0891.

1,4-bis[2,5-difluorophenacyl]-1*H*-1,2,4-triazol-4-ium chloride (3c); 3.33 g, Cream solid; IR (KBr) 3119, 3063, 2928, 1701, 1621, 1581, 1075, 843, 733 cm^{-1}; ^{1}H-NMR (300MHz, DMSO-d_6) δ 6.11 (s, 2H, CH_2), 6.29 (s, 2H), 7.59-7.64 (m, 2H, 2CH) 7.72-7.82 (m, 4H, 4CH), 9.27 (s, 1H, CH, triazole), 10.11 (s, 1H, CH, triazole); HRMS (ESI, QTOF) for $C_{18}H_{12}ClF_4N_3O_2$ [M^+ - Cl] : *m/z* calcd: 378.0866; found: 378.0888.

1,4-bis[4-fluorophenacyl]-1*H*-1,2,4-triazol-4-ium chloride (3d); 2.69 g, Off white solid; IR (KBr) 3077, 2985, 3038, 1693, 1600, 1575, 1073, 837, 751 cm^{-1}; ^{1}H NMR (300MHz, DMSO-d_6) δ 6.36 (s, 2H, CH_2), 6.52 (s, 2H, CH_2), 7.49-7.55 (br s, 4H, 4CH), 8.20 (s, 4H, 4CH), 9.39 (s, 1H, CH, triazole), 10.31 (s, 1H, CH, triazole); HRMS (ESI, QTOF) for $C_{18}H_{14}ClF_2N_3O_2$ [M^+ - Cl] : *m/z* calcd: 342.1054; found: 342.1051.

General Procedure for the Preparation of 4a-4b

To a stirred solution of **2** (4.48 mmol) in 2-propanol (20 mL), **1** (5.38 mmol) was added and stirred at 80 ^{o}C for 8-9 h under nitrogen atmosphere. The reaction mixture was concentrated under vacuum. The residue was stirred with dichloromethane (10 mL) for 30 min. The precipitated solid was filtered and washed with dichloromethane (5 mL) to obtain **4**.

1-(2,4-difluorophenacyl)-4-(3,4-difluorophenacyl)-1*H*-1,2,4-triazol-4-ium chloride (4a); 1.50 g, Tan brown solid; IR (KBr) 3083, 3031, 2929, 1705, 1693, 1614, 1574, 834, 751cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.26 (s, 4H, 4CH), 7.37 (t, 1H, CH), 7.61-7.62 (q, 1H, CH), 7.76-7.80 (q, 1H, CH), 8.00-8.02 (br s, 1H), 8.10-8.20 (m, 2H), 9.27 (s, 1H, CH, triazole); 10.10 (s, 1H, CH, triazole); HRMS (ESI, QTOF) for $C_{18}H_{12}ClF_4N_3O_2$ [M^+ - Cl] : *m/z* calcd: 378.0866; found: 378.0894.

1-(2,4-difluorophenacyl)-4-(4-fluorophenacyl)-1*H*-1,2,4-triazol-4-ium chloride (4b); 1.43 g, Off white solid; IR (KBr) 3040, 3012, 2933, 1708, 1692, 1616, 1578, 1073, 833, 758 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.29-6.32 (d, 4H, 2CH_2), 7.35-7.66 (m, 4H, 4CH), 8.11-8.21 (m, 3H, 3CH), 9.34 (s, 1H, CH, triazole), 10.20 (s, 1H, CH, trioazole); HRMS (ESI, QTOF) for $C_{18}H_{13}ClF_3N_3O_2$ [M^+ - Cl] : *m/z* calcd: 360.0960; found: 360.0986.

General Procedure for the Preparation of 5a-5c

To a stirred solution of **1** (15.5 mmol) in 2-propanol (20 mL), 4-amino-4*H*-1,2,4-triazole (11.9 mmol) was added.

The reaction was stirred at 80 ^{o}C for 18-20 h and concentrated under vacuum to remove the solvent. The residue was diluted with dichloromethane (10 mL) and stirred for 30 min at 10-15 ^{o}C. The precipitated solid was filtered and washed with pre-cooled dichloromethane (5 mL) to furnish **5**.

4-amino-1-[2,4-difluorophenacyl]-1*H*-1,2,4-triazolium chloride (5a); 2.88 g, Tan brown solid; IR (KBr) 3077, 2983, 2943, 1697, 1610, 1567, 1434, 1146, 1077, 872, 753 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.14 (s, 2H, CH_2), 7.35-7.39 (m, 3H, NH_2 and CH), 7.57-7.62 (m, 1H, CH), 8.08-8.10 (m, 1H, CH), 9.35 (s, 1H, CH, triazole), 10.28 (s, 1H, CH, triazole); HRMS (ESI, QTOF) for $C_{10}H_9ClF_2N_4O$ [M^+ - Cl] : *m/z* calcd: 239.0739; found: 239.0749.

4-amino-1-[3,4-difluorophenacyl]-1*H*-1,2,4-triazolium chloride (5b); 2.74 g, Pink solid; IR (KBr) 3106, 2999, 2954, 1701, 1610, 1563, 1441, 1167, 1071, 896, 739 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ 6.36 (s, 2H, CH_2), 7.34-7.44 (br s, 2H, NH_2), 7.72-7.77 (m, 1H), 7.98-8.01 (m, 1H, CH), 8.16-8.20 (m, 1H, CH), 9.36 (s, 1H, CH, triazole), 10.38 (s, 1H, CH, triazole); HRMS (ESI, QTOF) for $C_{10}H_9ClF_2N_4O$ [M^+ - Cl] : *m/z* calcd: 239.0739; found: 239.0747.

4-amino-1-[4-fluorophenacyl]-1*H*-1,2,4-triazolium chloride (5c); 2.76 g, Light brown solid; IR (KBr) 3017, 2951, 2757, 1697, 1598, 1510, 1162, 1070, 843, 746 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ 6.32 (s, 2H, CH_2), 7.34 (br s, 2H, NH_2), 7.47-7.50 (m, 2H, 2CH), 8.15-8.18 (m, 2H, 2CH), 9.34 (s, 1H, CH, triazole), 10.30 (s, 1H, CH, triazole); HRMS (ESI, QTOF) for $C_{10}H_{10}ClFN_4O$ [M^+ - Cl] : *m/z* calcd: 221.0839; found: 221.0844.

General Procedure for the Preparation of 6a-6c

To a stirred solution of **1** (32.4 mmol) in 2-propanol (20 mL), 1*H*-imidazole (14.7 mmol) was added. The reaction was stirred at 80 ^{o}C for 14-16 h and concentrated under reduced pressure to remove the solvent. To the residue dichloromethane (10 mL) was added and stirred for 30 min at 10-15 ^{o}C. The precipitated solid was filtered and washed with dichloromethane (5 mL) to obtain **6**.

1,3-bis[2,4-difluorophenacyl]-1*H*-imidazolium chloride (6a); 3.74 g, Off white solid; IR (KBr) 3097, 2855, 1701, 1611, 1566, 1487, 1045, 876, 759 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.00 (s, 4H, $4CH_2$), 7.35-7.39 (m, 2H, 2CH), 7.60 (m, 2H, 2CH), 7.76 (s, 2H, 2CH, imidazole)), 8.11 (m, 2H, 2CH), 9.09 (s, 1H, CH, imidazole); HRMS (ESI, QTOF) for $C_{19}H_{13}ClF_4Cl_3N_2O_2$ [M^+ - Cl] : *m/z* calcd: 377.0908; found: 377.0910.

1,3-bis[3,4-difluorophenacyl]-1*H*-imidazolium chloride (6b); 3.17 g, Off white solid; IR (KBr) 3051, 2833, 1694, 1610, 1572, 1462, 1039, 861, 752 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ 6.14 (s, 4H, $4CH_2$), 7.73-7.78 (m, 4H, $4CH_2$), 7.98-8.00 (br s, 2H, 2CH, imidazole), 8.15-8.19 (m, 2H, 2CH), 9.11 (s, 1H, CH, imidazole); HRMS (ESI, QTOF) for $C_{19}H_{13}ClF_4Cl_3N_2O_2$ [M^+ - Cl] : *m/z* calcd: 377.0913; found: 377.0914.

1,3-bis[4-fluorophenacyl]-1*H*-imidazoliumchloride (6c); 3.27 g, Pink solid; IR (KBr) 3073, 2900, 2848, 1696, 1596, 1445, 1035, 851, 776 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.16 (s, 4H, $2CH_2$), 7.48-7.52 (t, 4H, 4CH), 7.79 (s, 2H, 2CH, imidazole), 8.15-8.18 (m, 4H), 9.10 (s, 1H, CH, imidazole); HRMS (ESI, QTOF) for $C_{19}H_{15}ClF_2N_2O_2$ [M^+ - Cl] : *m/z* calcd: 341.1102; found: 341.1106.

RESULTS AND DISCUSSION

As shown in the Scheme 1, the targeted compounds were readily synthesized. Compound **3a-d** were prepared by the reaction of 1*H*-1,2,4-triazole with excess mono and difluorophenacyl chloride in 2-propanol. It was inferred from the yield that the formation of quaternary ammonium salt needs a higher temperature for the salt formation. Hence we have chosen reflux temperature (80 ^{o}C) for the preparation of target compounds. To study the positional effect of fluorine atom towards the targeted fungi we have prepared the azolium compounds **4a-b** by the reaction of **2** with the differently substituted fluorine atom of **1**, in an equimolar ratio. As both the triazole and imidazole compounds were reported to have the biological application, we have prepared imidazolium compounds in addition to triazolium compounds. The imidazolium compounds, **6a-c** were prepared by the reaction of imidazole with an excess bis-mononddifluorophenacyl chloride in 2-propanol. Furthermore we have prepared the another series of triazolium compounds, **5a-c** using 4-amino-4*H*-1,2,4-triazole and bis-mononddifluorophenacyl chloride. The melting points of all the prepared compounds were recorded as shown in Table 1 and were found to be very high (<100 ^{o}C). Due to the higher melting points, further studies on their physical behavior and application as an ionic liquid were not investigated.

The probability of alkylation at N_2 position was theoretically explained by Schmidt-Gordon and Boatz [35]. The 1,2 disubstituted triazolium compounds were assumed to be higher in energy compared to 1,4- disubstituted compounds and thus those are less favorable. In addition to the above 1,2-disubstituted triazolium compounds because of the symmetry, believe to shows only one signal in proton NMR corresponds to the triazole protons (3*H* and 5*H*), however two signals confirmed the formation of 1,4- disubstituted compounds. The chemical shift values of triazole protons (3*H* and 5*H*) for **3-5** were found to be nearly same as the 1,4-disubstituted triazolium compounds. This difference in chemical shift values for 3*H* and 5*H* were due to the positive charge at N_4 position and this was further confirmed by the data provided by Pirotte *et al* [36]. Similarly for the 1,3-disubstituted imidazolium compounds (**6a-c**) the chemical shift value for the 2*H* proton in imidazole were nearly same as the 3*H* proton for 1,4-disubstituted triazolium. This closeness was observed due to the similar chemical environment of the protons flanked by the two nitrogen atoms of azole.

In vitro antifungal activities of the synthesized compounds **3-6** were investigated against the fungi *aspergillus niger, aspergillus flavus and penicillium chrysogenum*. The minimum inhibitory concentrations (MIC) were determined by the agar diffusion method with a concentration of 0.065, 0.125, 0.25, 0.5, 1.0 and 2.0 mg/mL. The stock solutions were prepared in methanol. Czapek-Dox agar was employed for fungal growth. The stock culture were inoculated in broth media and grown at 27 ^{o}C for 48 h. The agar media were prepared and the wells were made in those plates. Each plates were inoculated with 48 h old culture (10^4 CFUs/100 µL) and spread evenly on the plate. After 20 min the wells were filled with different concentration of compounds whereas the control wells were filled with amphotericin B. The MIC values were determined at the lowest concentration of the antifungal agents at which there was no fungal growth. The MIC values for the different fungi in comparison with the standard amphotericin B are summarized in the Table 1.

Table 1. *In vitro* antifungal activity and MIC of compounds 3, 4, 5 and 6 using agar well diffusion method

Compd.	Position of Fluorine atom				Mp (^{o}C)	Yield (%)	Diameter of inhibition zone in mm (MIC in mg/mL)		
	Z_1	Z_2	Z_3	Z_4			*P.chy.*	*A.niger*	*A.flavus*
3a	2-F	4-F	-	-	204-206	53.5	5 (1.0)	--	--
3b	3-F	4-F	-	-	225-227	42.0	--	--	8 (0.5)
3c	2-F	5-F	-	-	207-209	55.8	--	--	5 (1.0)
3d	4-F	-	-	-	218-220	49.3	5 (0.5)	3 (2.0)	--
4a	2-F	4-F	3-F	4-F	215-217	85.5	3 (2.0)	--	--
4b	2-F	4-F	4-F	-	200-202	74.6	--	2 (2.0)	--
5a	2-F	4-F	-	-	198-200	88.4	4 (2.0)	--	--
5b	3-F	4-F	-	-	223-225	84.2	--	--	--
5c	4-F	-	-	-	208-210	90.6	--	2 (2.0)	--
6a	2-F	4-F	-	-	245-247	61.8	3(1.0)	--	--
6b	3-F	4-F	-	-	235-237	52.4	--	--	8 (2.0)
6c	4-F	-	-		220-222	59.2			4 (1.0)
Amphotericin B	-	-	-	-	-	-	5 (0.4)	7 (0.1)	10 (0.4)

Double hyphens (--) denotes no activity

The results of *in vitro* antifungal activity showed that almost all the compounds were active against fungi, except **5b**. Most of them have shown in vitro antifungal activities against the tested fungi with low MIC values included in the range of 0.5-1.0 mg/mL. Compound **3a**, **3d** and **6a** were the most potent against *penicillium chrysogenum* with MIC value of 0.5-1.0 mg/mL, however posses lesser activity than amphotericin B (MIC = 0.4 mg/mL). Similarly compound **3b**, **3c**, **6b** and **6c** have shown a good inhibition against *aspergillus flavus* with MIC value of 0.5-2.0 mg/mL. The imidazolium compounds have shown no activity towards *aspergillus* niger. It was observed from the study that the 4-amino triazolium compounds were the less active against the tested fungi in comparison with the others.

CONCLUSION

In conclusion the prepared compounds have been identified as a new class of azole antifungal agents. Both the azolium compounds **3a**, **3b, 3c, 3d, 4a, 6a, 6b** and **6c** showed significant *in vitro* antifungal activities towards *P.chrysogenum* and *aspergillus flavus*, whereas **5a-c** were found to be inactive against *aspergillus flavus*. The imidazolium compounds **6a-c** has shown no activity against *aspergillus niger*. As some of these compounds possessed moderate antifungal activity, we would like to focus our future research with a different substitution containing different anions on these new antimicrobial agents.

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