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SYNTHESIS AND BIOLOGICAL ACTIVITY OF IMIDO ESTERS OF 2-ARYL-3-NICOTINAMIDO-4-OXO-1, 3-THIAZOLIDINE-5-YL ETHANOIC ACID

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ABSTRACT

Nicotinic acid hydrazide **(2)** was prepared by the esterification of nicotinic acid **(1)** followed by treatment with hydrazine hydrate, which on condensation with various aldehydes **(3a-e)** gave N'-[arylmethylene]nicotinohydrazide **(4a-e).** These on cyclization with mercaptosuccinic acid, yielded 2-{2-aryl-3-(nicotinamido)-4-oxo-1,3-thiazolidin-5-yl}acetic acid **(5a-e)**. Compounds **(5a-e)** were further converted into acid chloride derivatives **(6a-e)** by reaction with thionyl chloride. Subsequent treatment of **(6a-e)** with N-hydroxyphthalimide in the presence of TEA furnished the title compounds **(7a-e)**. Final compounds have been evaluated for antifungal and antibacterial activity. Some of the compounds have shown significant inhibition towards bacterial and fungal growth.

Key words: Nicotinic acid (Niacin), Nicotinic acid hydrazide, Thiazolidine, N-hydroxyphthalimide and Biological activity.

INTRODUCTION

Niacin is a B-group vitamin and is known as nicotinic acid, of which occur in minutes quantities in all living cells. It is used therapeutically for the prevention, treatment of pellagra like disease in dogs and as a vitamin in animal feeds. It is freely soluble in boiling water and is converted to NAD in vivo. This is an important coenzyme in oxidation-reduction reactions to obtain energy[1-3]. Niacin has been found to prevent cellular injury[4], and also to reduce lung injury induced by parquet[5], or bleomycin[6]. Similarly thiazolidinones are considered as one of the most important pharmacophores in the drug chemistry and their extensive uses as antimicrobial[7,8], anti-inflammatory[9] and anticonvulsant agents.[10] have been well elaborated in the literature. Several derivatives of

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alkoxyphthalimides have been synthesized[11-13] and reported to demonstrate a wide range of pharmacological activities viz. anticancer, antimalarial[14-15], antiepileptic[16], antimicrobial[17] etc. Thus, with an effort to capitalize the pharmacological potential of the above heterocyclic nucleus and our work on phthalimidoxy containing heterocycles, it was considered worthwhile to synthesize new chemical entities incorporating the three active pharmaphores namely niacin, thiazolidine and N-hydroxyphthalimide in a single molecular framework.

EXPERIMENTAL

All melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded on Perkin-Elmer-1800 spectrometer. The ^{1}H NMR spectra (DMSO-d_6) were scanned on a DRX-300 (300 MHz) spectrometer using TMS as internal standard and chemical shifts are expressed in δ ppm. The mass spectra were recorded on Jeol SX-102 (FAB) spectrometer. Purity of synthesized compounds was checked by element analysis and also by TLC using silica gel-G, as adsorbent and visualization was accomplished by iodine. Compounds nicotinic acid 18(a), ethyl nicotinate 18(b), and N-hydroxyphthalimide[19] were synthesized by literature methods. Physical and analytical data of the synthesized compounds are given in Table I.

Synthesis of nicotinic acid hydrazide (2)

A mixture of ethyl nicotinate (0.05 mole) in ethanol (25 mL) and hydrazine hydrate (0.05 mole) is refluxed for 10-12 hrs. After cooling, the solid product obtained is filtered, washed, dried and recrystallized from ethanol. White needle shaped crystals of **(2)** are obtained, M.P.:162◦C, yield 65%.

Synthesis of N'-[arylmethylene]nicotinohydrazide (4a-e):

A mixture of nicotinicacid hydrazide **(2)** (0.01 mole) in ethanol (20 mL), arylaldehyde **(3a-e)** (0.01 mole) and glacial acetic acid (0.5 mL) was refluxed on water bath for 9-11 hrs. After cooling, solvent was distilled under reduced pressure and the residue left is filtered, dried and crystallized from ethanol.

Synthesis of 2-{2-aryl-3-(nicotinamido)-4-oxo-1,3-thiazolidin-5-yl}aceticacid (5a-e)

Compound **(4a-e)** (0.01 mole) is dissolved in dry THF (25 mL) and mercaptosuccinic acid (0.01 mole) is added portion wise to it along with a pinch of anhydrous zinc chloride. Reaction mixture is refluxed on water bath for 7-9 hrs, the separated solid was filtered, dried and recrystallized from ethanol.

Synthesis of 2-{2-aryl-3-(nicotinamido)-4-oxo-1,3-thiazolidin-5-yl} acetyl chloride (6a-e)

A solution of **(5a-e)** (0.01 mole) in benzene (20 mL) and thionyl chloride (0.02 mole) is refluxed for 3-5 hrs on water bath. Excess of thionyl chloride is removed by distillation under reduced pressure. On cooling, the solid is filtered, dried and recrystallized from benzene.

Synthesis of 1, 3-dioxoisoindolin-2-yl-2-[3-(nicotinamido)-4-oxo-2-aryl-1, 3-thiazolidin-5-yl] acetate (7a-e)

N-Hydroxyphthalimide (0.01 mole) is added to the solution of **(6a-e)** (0.01 mole) in dry DMF (25 mL) and TEA (0.02 mole) is added as a base. The mixture is stirred at room temperature for 2 hrs and refluxed for 8-10 hrs. Then it is filtered and solvent was distilled off under reduced pressure. Crude so obtained is filtered, dried and recrystallized from ethanol.

Table 1. Characterization data of the newly synthesized compounds

Compd.	m.p.°(C) /(Solvent)	Colour Yield (%)	Mol. formula (Mol. Wt.)	Elemental analysis [Calcd./ Found (%)]		
				C	H	N
4a	112 (EtOH)	Dark brown 74	$C_{13}H_{11}N_3O$ (225.24)	69.32 69.25	4.92 4.89	18.66 18.61
4b	120 (EtOH)	Pale Yellow 78	$C_{13}H_{10}N_3OF$ (243.23)	64.19 64.11	4.14 4.09	17.28 17.22
4c	131 (EtOH)	Yellow 81	$C_{13}H_{10}N_3OCl$ (259.69)	60.12 60.08	3.88 3.90	16.18 16.20
4d	141 (EtOH)	Light Yellow 79	$C_{13}H_{10}N_4O_3$ (270.24)	57.78 57.70	3.73 3.70	20.73 20.68
4e	136 (EtOH)	Brown 83	$C_{14}H_{13}N_3O_2$ (255.27)	65.87 65.81	5.13 5.09	16.46 16.40
5a	185 (EtOH)	Off-white 70	$C_{17}H_{15}N_3O_4S$ (357.38)	57.13 57.11	4.23 4.19	11.76 11.72

Cont…

Compd.	m.p.°(C) /(Solvent)	Colour Yield (%)	Mol. formula (Mol. Wt.)	Elemental analysis [Calcd./ Found (%)]		
				C	H	N
5b	170 (EtOH)	Yellow 72	$C_{17}H_{14}N_3O_4FS$ (375.37)	54.39 54.31	3.76 3.69	11.19 11.22
5c	201 (EtOH)	Brown 77	$C_{17}H_{14}N_3O_4Cl\ S$ (391.83)	52.11 52.01	3.60 3.59	10.72 10.65
5d	189 (EtOH)	Off-white 69	$C_{17}H_{14}N_4O_6S$ (402.38)	50.74 50.76	3.51 3.55	13.92 13.90
5e	196 (EtOH)	Yellow 75	$C_{18}H_{17}N_3O_5S$ (387.41)	55.80 55.78	4.42 4.39	10.85 10.82
6a	161 (Benzene)	Brown 65	$C_{17}H_{14}N_3O_3ClS$ (375.83)	54.33 54.11	3.75 3.69	11.18 11.20
6b	149 (Benzene)	Light Brown 68	$C_{17}H_{13}N_3O_3ClFS$ (393.82)	51.85 51.81	3.33 3.29	10.67 10.62
6c	186 (Benzene)	Dark brown 63	$C_{17}H_{13}N_3O_3Cl_2S$ (410.27)	49.77 49.71	3.19 3.20	10.24 10.22
6d	205 (Benzene)	Dark brown 60	$C_{17}H_{13}N_4O_5ClS$ (420.83)	48.52 48.51	3.11 3.09	13.31 13.26
6e	170 (Benzene)	Brown 61	$C_{18}H_{16}N_3O_4ClS$ (405.85)	53.27 53.21	3.97 3.89	10.35 10.32
7a	250 (EtOH)	Dark Brown 52	$C_{25}H_{18}N_4O_6S$ (502.50)	59.75 59.67	3.61 3.59	11.15 11.20
7b	231 (EtOH)	Brown 56	$C_{25}H_{17}N_4O_6FS$ (520.49)	57.69 57.65	3.29 3.30	10.76 10.72
7c	281 (EtOH)	Dark brown 51	$C_{25}H_{17}N_4O_6ClS$ (536.94)	55.92 55.93	3.19 3.17	10.43 10.42
7d	301 (EtOH)	Dark brown 49	$C_{25}H_{17}N_5O_8S$ (547.49)	54.84 54.81	3.13 3.19	12.79 12.72
7e	243 (EtOH)	Dark brown 55	$C_{26}H_{20}N_4O_7S$ (532.52)	58.64 58.61	3.79 3.76	10.52 10.50

Table 2. Spectra of the newly synthesized compounds

Comp.	Spectra
4a	IR (KBr)cm^{-1}:3454 (N-H,CONH),1655 (C=O,CONH),1599 (C=N),1199 (N-N)
4b	IR (KBr)cm^{-1}:3450 (N-H,CONH),1670 (C=O,CONH),1560 (C=N),1190 (N-N)
4c	IR (KBr)cm^{-1}:3461 (N-H,CONH),1663 (C=O,CONH),1581 (C=N),1180 (N-N)
4d	IR (KBr)cm^{-1}:3445 (N-H,CONH),1680 (C=O,CONH),1570 (C=N),1173 (N-N)
4e	IR (KBr)cm^{-1}:3430 (N-H, CONH),1657 (C=O,CONH),1545 (C=N),1160 (N-N)
5a	IR (KBr)cm^{-1}:3409 (N-H,CONH),3226-2850 (OH,COOH),1710 & 1656 (C=O), 1180 (N-N),761 (C-S-C) δ_H (ppm):12.01 (s,1H,COOH),9.07 (s,1H,CONH),8.77-7.46 (m,9H,ArH),6.55 (s,1H,CH-Ar),3.54 (t,1H,CH-CH_2),3.14 (d,2H,CH-CH_2)
5b	IR (KBr)cm^{-1}:3445 (N-H,CONH),3190-880 (OH,COOH),1735&1625 (C=O),1175 (N-N),780 (C-S-C) δ_H (ppm):11.91 (s,1H,COOH),9.12 (s,1H,CONH),8.43-.10 (m,8H,ArH),6.32 (s,1H, CH-Ar),3.60 (t,1H,CH-CH_2),3.08 (d,2H,CH-CH_2)
5c	IR (KBr)cm^{-1}:3426 (N-H,CONH),3250- 855 (OH,COOH),1731&1624 (C=O),1176 (N-N),771 (C-S-C) δ_H (ppm):12.10 (s,1H,COOH),8.98 (s,1H,CONH),8.62-7.32 (m,8H,ArH), 6.52 (s, 1H, CH-Ar),3.48 (t,1H,CH-CH_2),3.18 (d,2H,CH-CH_2)
5d	IR (KBr)cm^{-1}:3390 (N-H,CONH),3210-2848 (OH,COOH),1728&1621 (C=O), 1195 (N-N),782 (C-S-C) δ_H (ppm):12.07 (s,1H,COOH),9.08 (s,1H,CONH),8.43-.21 (m,8H,ArH),6.61 (s,1H, CH-Ar),3.61 (t,1H,CH-CH_2),3.21 (d,2H,CH-CH_2)
5e	IR (KBr)cm^{-1}:3465 (N-H,CONH),3220-2882 (OH,COOH),1715 (C=O,COOH), 1620 (C=O,cyclic),1150 (N-N),777 (C-S-C) δ_H (ppm):12.20 (s,1H,COOH),9.14 (s,1H,CONH),8.91-7.48 (m,8H,ArH),5.98 (s, 1H,CH-Ar),3.80 (s,3H,OCH_3),3.51 (t,1H,CH-CH_2),3.30 (d,2H,CH-CH_2)

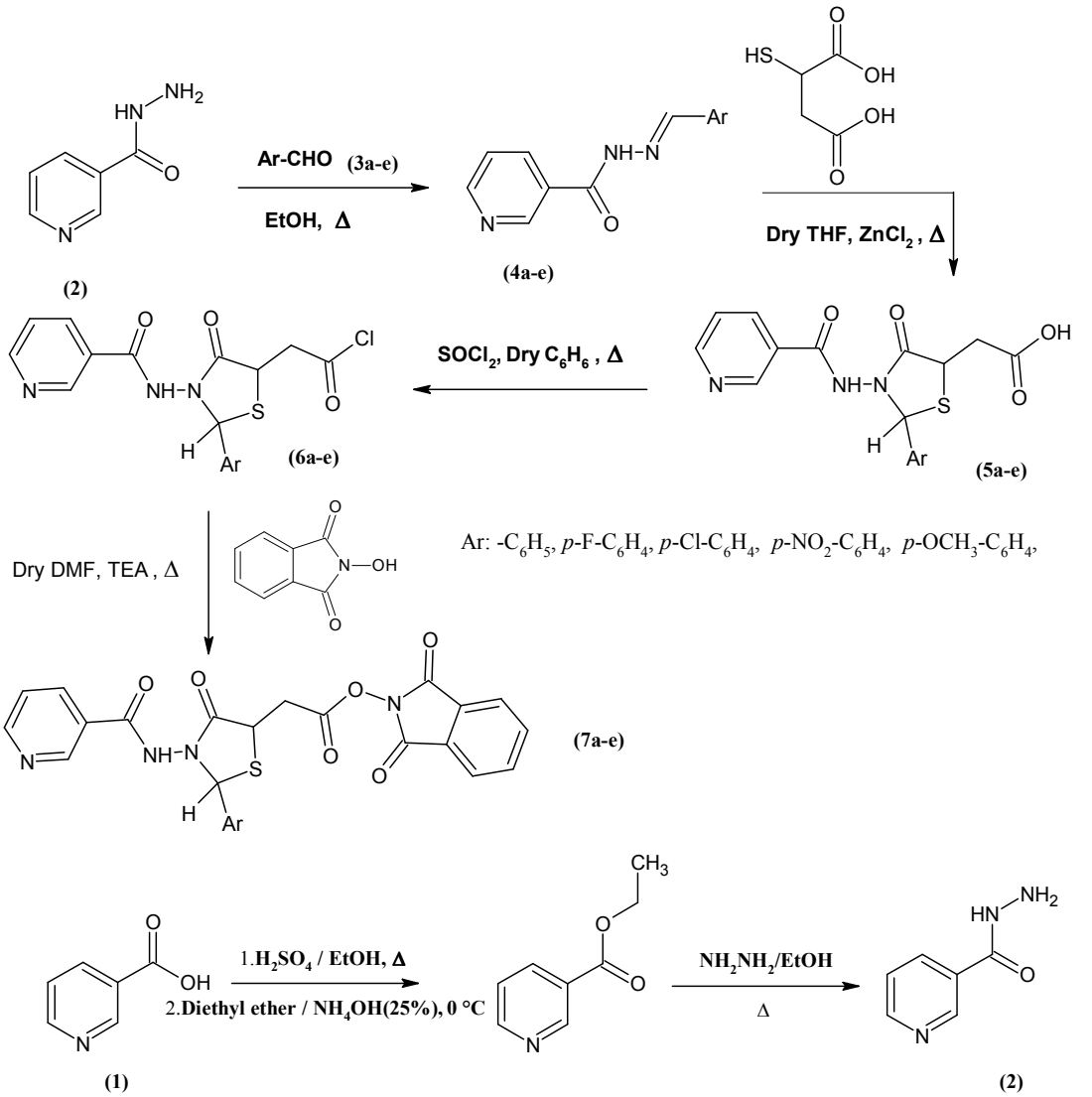
Comp.	Spectra
6a	IR (KBr)cm^{-1}:3448-3245 (N-H,CONH),3085 (C-H,ArH),1750 (C=O,COCl),1670 (C=O,Cyclic),1295 (C-N),1180 (N-N),764 (C-Cl,COCl) δ_H (ppm): 9.01 (s,1H,CONH),8.89-7.17 (m,9H,Ar-H),5.80 (s,1H,CH-Ar),3.44 (t,1H, CH-CH_2),3.03 (d,2H,CH-CH_2)
6b	IR (KBr)cm^{-1}:3430-3250 (N-H,CONH), 3070 (C-H,ArH),1770 (C=O,COCl),1651 (C=O,Cyclic),1290 (C-N),1183 (N-N),758 (C-Cl,COCl) δ_H (ppm): 9.09 (s,1H,CONH),8.85-7.24 (m,8H,Ar-H),5.88 (s,1H,CH-Ar),3.60 (t,1H, CH-CH_2),3.08 (d,2H,CH-CH_2)
6c	IR (KBr)cm^{-1}:3435-3240 (N-H,CONH), 3091 (C-H,ArH),1767 (C=O,COCl),1658 (C=O,Cyclic),1275 (C-N),1172 (N-N),766 (C-Cl,COCl) δ_H (ppm): 9.10 (s,1H,CONH),8.84-7.26 (m,8H,Ar-H),5.85 (s,1H,CH-Ar),3.48 (t,1H, CH-CH_2),3.18 (d,2H,CH-CH_2)
6d	IR (KBr)cm^{-1}:3415-3251 (N-H,CONH),3064 (C-H,ArH),1748 (C=O,COCl),1688 (C=O,Cyclic),1290 (C-N),1164 (N-N), 775 (C-Cl,COCl) δ_H (ppm): 9.08 (s,1H,CONH),8.43-7.28 (m,8H,Ar-H),5.91 (s,1H,CH-Ar),3.61 (t,1H, CH-CH_2),3.21 (d,2H,CH-CH_2)
6e	IR (KBr)cm^{-1}:3490-3278 (N-H,CONH),3062 (C-H,ArH),1743 (C=O,COCl),1655 (C=O,Cyclic),1270 (C-N),1172 (N-N),778 (C-Cl, COCl) δ_H (ppm): 9.01 (s,1H,CONH),8.83-7.24 (m,8H,Ar-H),5.80 (s,1H,CH-Ar),3.44 (t,1H,CH-CH_2),3.03 (d,2H,CH-CH_2), 3.73 (s, 3H, OCH_3)
7a	IR (KBr)cm^{-1}:3419 (N-H,CONH),3069 (C-H,ArH),1739 (C=O),1694 (C=O,Cyclic),1421 (N-O),1288 (C-N),1203 (N-N),1117 (C-O),703 (C-S-C) δ_H (ppm): 9.13 (s,1H,CONH),8.66-7.21 (m,13H,Ar-H),6.48 (s,1H,CH-Ar),3.62 (t, 1H, CH-CH_2),3.12 (d,2H,CH-CH_2) Mass m/z: 502$[M]^+$, 474, 425, 204, 190, 162, 146, 132, 121.
7b	IR (KBr)cm^{-1}:3455 (N-H,CONH),3094 (C-H,ArH),1755 (C=O),1710 (C=O, Cyclic), 1428 (N-O),1290 (C-N),1200 (N-N),1121 (C-O),746 (C-S-C) δ_H (ppm): 9.18 (s,1H,CONH),8.69-7.24 (m,12H,Ar-H),6.46 (s,1H,CH-Ar),3.63 (t,1H, CH-CH_2),3.04 (d,2H,CH-CH_2) Mass m/z: 520$[M]^+$, 492,443,399,374,316,190,162,132.

Comp.	Spectra
7c	IR (KBr)cm^{-1}:3450 (N-H,CONH),3072 (C-H,ArH),1746 (C=O),1700 (C=O,cyclic),1419 (N-O),1301 (C-N),1195 (N-N),1113 (C-O),715 (C-S-C) δ_H (ppm): 9.19 (s,1H,CONH),8.74-7.22 (m,12H,Ar-H),6.51 (s,1H,CH-Ar),3.69 (t,1H, CH-CH_2),3.18 (d,2H,CH-CH_2) Mass m/z: 536$[M]^+$,538$[M+2]^+$,508,459,415,390,332,190,162,132.
7e	IR (KBr)cm^{-1}:3400 (N-H,CONH),3020 (C-H,ArH),1715 (C=O),1688 (C=O,cyclic),1435 (N-O),1275 (C-N),1208 (N-N),1125 (C-O),755 (C-S-C) δ_H (ppm): 9.14 (s,1H,CONH),8.76-7.30 (m,12H,Ar-H),6.55 (s,1H,CH-Ar),3.68 (t,1H, CH-CH_2),3.25 (d,2H,CH-CH_2),3.80 (s, 3H, OCH_3) Mass m/z: 532$[M]^+$,504,455,421,386,328,190,162,132.

Table: 3 Antimicrobial activity of some synthesized compounds Zone of inhibition (mm) (activity index)*

	B. subtilis	*E. coli*	*P. aeruginesa*	*S. typhi*	*C. albicans*	*A. fumigatus*
7a	18 (0.90)	17 (0.81)	18 (0.90)	18 (0.95)	15 (0.88)	17 (0.89)
7b	19 (0.95)	26 (1.24)	25 (1.25)	22 (1.16)	19 (1.12)	23 (1.21)
7c	18 (0.90)	18 (0.86)	18 (0.90)	22 (1.16)	17 (1.00)	18 (0.95)
7d	14 (0.70)	16 (0.76)	17 (0.85)	17 (0.89)	16 (0.94)	13 (0.68)
7e	13 (0.65)	16 (0.76)	18 (0.85)	18 (0.95)	14 (0.82)	18 (0.95)
C_1	20	21	20	19	-	-
C_2	-	-	-	-	17	19

***Activity index = Inhibition area of the sample/ inhibition area of the standard**
C_1 = Ciprofloxacin, C_2 = Amphotericin-B.



RESULTS AND DISCUSSION

In order to synthesize the titled compounds, nicotinic acid **(1)** is converted to corresponding hydrazide derivative **(2)** by its esterification followed by reaction with hydrazine hydrate. Schiff's bases **(4a-e)** of **(2)** are allowed to react with mercaptosuccinic acid in the presence of anhydrous $ZnCl_2$ to furnish 2-{2-aryl-3-(nicotinamido)-4-oxo-1,3-thiazolidin-5-yl}aceticacid **(5a-e).**

Ring formation is confirmed by the appearance of signals in 1H NMR spectra of **(5a)** at δ 12.01, 6.10, 3.54 and 3.13 for –COOH, -CH-Ar, -CH-CH_2, -CH-CH_2 protons in the form of singlet, singlet, triplet and doublet, respectively. The chemoselective reaction of -COOH group of **(5a-e)** with thionyl chloride lead to the formation of corresponding chloride derivatives **(6a-e).** Disappearance of singlet at δ 12.01 for –COOH proton in ^{1}H NMR spectra confirmed its formation that was present in its precursor compound. Synthesis of 1,3-dioxoisoindolin-2-yl-2-[3-(nicotinamido)-4-oxo-2-aryl-1,3-thiazolidin-5-yl]acetate **(7a-e)** is achieved by substitution reaction of **(6a-e)** with N- hydroxyphthalimide in the presence of TEA as a base. IR displays intense bands at 1421 cm^{-1} and 1117 cm^{-1} corresponding to the N-O and C-O bond stretching, respectively.

Biological activity

Preliminary antibacterial and antifungal susceptibility tests for all the synthesized **(7a-e)** were preformed by using cup and well method[20,21] at a concentration of 500 ppm against some selected pathogenic strains viz. *B. subtilis, E. coli, S. typhi* and *P. aeruginosa* for antibacterial and *A. fumigatus* and *C. albicans* for antifungal inhibition. Commercial antibacterial ciprofloxacin and antifungal amphotericin-B were also screened under similar conditions for a comparison. The results have been tabulated in the form of inhibition zones and activity index in Table 3.

From the data presented in Table 3, it is clear that compound **(7b)** possesses good activity against *E. coli, P. aeruginosa* but shows only moderate activity against *B. subtilis*, *S. typhi*, while other compounds show poor inhibition towards antibacterial activity against all the tested microbes.

On the other hand, it was observed that almost all the compounds show significant activity against both the fungal strains as compared to standard drug Amphotericin-B. Hence, the conclusion can be drawn that synthesized compounds are better antibacterial agents than antifungal.

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