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Derivatives of 1-chloromethyl naphthalene: Synthesis and microbiological evaluation as potential antifungal agents

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ABSTRACT

The present research work was undertaken to evaluate the in vitro antifungal activity of a series of 1-chloromethyl naphthalene derivatives. A series of 1-chloromethyl naphthalene derivatives was synthesized by condensing 1-chloromethyl naphthalene with various substituted anilines and heteroaryls. All the derivatives were characterized by IR, ^{1}H NMR and elemental analysis. The antifungal activity was evaluated by their MIC and zone of inhibition of synthesized compounds. The microbiological assay revealed that the compound ***2h,*** *3-chloro-4-fluoro-N-(naphthalen-1-yl methyl)aniline and* ***2j*** *N-(naphthalen-1-ylmethyl)-4H-1,2,4-triazol-4-amine showed better antifungal profile.*

Keywords: Terbinafine, 1-chloromethyl naphthalene, antifungal activity.

INTRODUCTION

The incidence of systemic fungal infections has been increasing dramatically over the past 25 years due to an increase in the number of immunocompromised hosts. Patients undergoing anticancer chemotherapy, organ transplants or long treatment with antimicrobial agents and patients with AIDS are immunosuppressed and very susceptible to life threatening systemic fungal infections like candidiasis, cryptococcosis and aspergillosis [1]. The knowledge of fungal cell structure, function and metabolism gave the opportunity to synthesize new agents. The search for new, potent and broadly active antimycotics, new targets in fungal cell, modification of currently known agents was of a big interest during the past decades [2].

Antifungals are those agents that destroy or inhibit the growth of pathogenic fungi. A host of antifungal drugs act by inhibiting various enzymes along the biosynthetic pathway to ergosterol.

Squalene epoxidase (SE) enzyme present in fungal and mammalian cell systems is important in ergosterol biosynthesis. SE is involved in the conversion of squalene to squalene 2, 3-epoxide, which is subsequently converted into lanosterol and then into ergosterol. SE, which is a membrane bound enzyme, has been proposed as a target for the action of the allylamine class of antifungal agents [3]. The antifungal activity of allylamines has been attributed exclusively to the inhibition of the SE enzyme system in the ergosterol biosynthetic pathway. The allylamine class of antifungal agents was discovered as a result of a chemical inventory for antifungal activity. Investigation of the mechanism of action of allylamines revealed that they interfere with fungal ergosterol biosynthesis at an early stage namely the epoxidation of squalene catalyzed by the enzyme squalene epoxidase. Mammalian squalene epoxidase is very weakly inhibited by the allylamines, which do not appear to significantly affect cholesterol biosynthesis.The spectrum of activity of naftifine and terbinafine extends to numerous fungi pathogenic for humans, among which dermatophytes are recognized as being extremely sensitive both *in vitro* and *in vivo* [4]. Since these marketed antifungals are having naphthalene as basic skeleton which was found to possess marked antifungal activity, 1-chloromethylnaphthalene has been chosen as a basic nucleus.

MATERIALS AND METHODS

Chemistry

All the chemicals and solvents used were of synthetic grade. The melting points were determined by open capillary method on Veego VMP-D digital melting point apparatus and are uncorrected. The IR spectrum of synthesized compounds was recorded on Jasco FT-IR 4100 in potassium bromide. The ^{1}H NMR spectra was recorded using NMR Varian Mercury plus 300 MHz using tetramethyl silane (TMS) as internal standard. The completion of reaction was monitored by thin layer chromatography performed on Merck precoated silica gel F_{254} plates. Results of elemental analysis are within ± 0.4 % range of theoretical values for all the compounds. The various derivatives synthesized are illustrated in Table 1.

1-chloromethyl naphthalene **1**

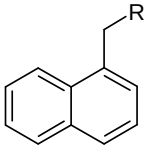
1-chloromethyl naphthalene was synthesized using the method available in the literature. In a three-necked flask, fitted with a reflux condenser and mechanical stirrer were placed 25g (0.19mol) naphthalene, 9g (0.27mol) of paraformaldehyde, 30ml of conc. hydrochloric acid and 14ml of O-phosphoric acid, heated the mixture in a water bath at 80-85^0 C and vigorously stirred for 9-10 hours. After the reaction mixture has been cooled to 15-20^{0}C, it was poured into cold water 200ml, decanted the water from oily layer and washed 3 times with 200ml portions of cold water by decantation. Dried organic layer over little anhydrous sodium sulphate filtered and extracted with ether. Then the reaction mixture was distilled out under reduced pressure to yield 1-chloromethyl naphthalene. The spectral data matched with that reported in the reference [5-8].

General procedure for synthesis of derivatives **2a-2j**

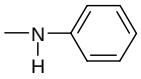
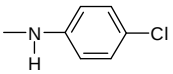
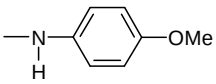
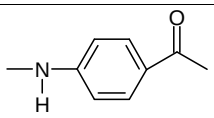
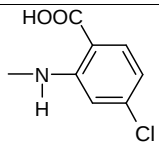
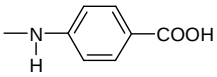
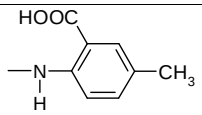
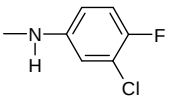
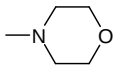
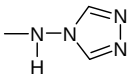
In a 250 ml RBF equipped with reflux condenser, stirrer and calcium chloride guard tube, a mixture of 1-chloromethyl naphthalene (0.01mol), aniline (0.01mol) and potassium carbonate (0.01mol) in appropriate solvent was refluxed for 17 hours. Reaction was monitored by TLC. After completion of the reaction, reaction mixture was cooled, product extracted with

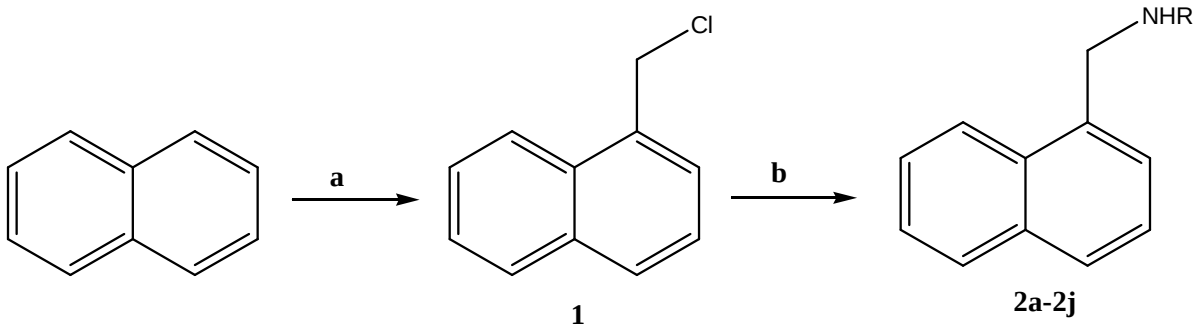
chloroform, organic layer separated and dried over anhydrous sodium sulphate. Solvent was evaporated under vacuum to obtain the crude product which was recrystallized from methanol.

Table 1. Physicochemical data with antifungal activity of the synthesized compounds



Where R is substituted aryl amine

Comd.	R	Molecular formula	% Yield	M.P.* (^{0}C)	Zone of Inhibition	MIC (µg/ml)
2a		$C_{17}H_{15}N$	47	156-158	21	100
2b		$C_{17}H_{14}ClN$	59	199-201	30	50
2c		$C_{18}H_{17}NO$	68	306-308	24	25
2d		$C_{19}H_{17}NO$	84	178-180	25	50
2e		$C_{18}H_{14}ClNO_2$	65	122-124	34	25
2f		$C_{18}H_{15}NO_2$	60	102-104	29	25
2g		$C_{19}H_{17}NO_2$	58	190-192	23	100
2h		$C_{17}H_{13}ClFN$	59	110-112	35	12.5
2i		$C_{15}H_{17}NO$	44	131-133	30	50
2j		$C_{13}H_{12}N_4$	80	153-155	35	12.5
Standard	Terbinafine				37	



Scheme 1 Synthetic protocol of title compounds a. Formaldehyde, HCl, H_3PO_4, CH_3COOH; b. Primary aromatic amines/ heteroaryls, K_2CO_3, CH_3CN/ DMF/Toluene.

Following compounds were synthesized using above method:

1-chloromethyl naphthalene (1-Naphthylmethyl chloride) (1)
Yield: 50%, mp: 32°C. IRν_{max} (cm^{-1}) (KBr): 3049, 2964, 1626, 775. ^{1}H NMR (δ ppm; $CDCl_3$): 7.22-8.10 (m, 7H, C-H in naphthalene ring), 4.92(s, 2H, -CH_2-). Elemental analysis Calcd. (Found): C, 74.79 (74.85); H, 5.14(5.08); Cl, 20.7(20.01).

***N*-((naphthalene-1-yl)methyl) benzenamine (2a)**
Yield: 47%, mp: 110-112°C. IRν_{max} (cm^{-1}) (KBr): 3367, 3049, 2951, 1480-1536. ^{1}H NMR (δ ppm; $CDCl_3$): 6.98-8.62(m, 12H, C-H in aromatic ring), 4.73(s, 2H, -CH_2-), 3.91(s, 1H, N-H). Elemental analysis Calcd. (Found): C, 87.52(87.37); H, 6.48(6.61); N, 6.00(6.02).

4-chloro-*N*-((naphthalene-1-yl) methyl) benzenamine (2b)
Yield: 51%, mp: 114-116°C. IRν_{max} (cm^{-1}) (KBr): 3382, 3041, 2956, 1432-1540. ^{1}H NMR (δ ppm; $CDCl_3$): 6.95-8.57(m, 11H, C-H in aromatic ring), 4.75(s, 2H, -CH_2-), 3.79(s, 1H, N-H). Elemental analysis Calcd. (Found): C, 76.26(76.37); H, 5.27(5.20); N, 5.23(5.17); O, 13.24(13.26).

4-methoxy-*N*-((naphthlen-1-yl) methyl) benzenamine (2c)
Yield: 67%, mp: 127-129°C. IRν_{max}(cm^{-1}) (KBr): 3386, 3047, 2946, 1456-1552. ^{1}H NMR (δ ppm; $CDCl_3$): 6.87-8.34(m, 11H, C-H in aromatic ring), 4.79(s, 2H, -CH_2-), 3.88(s, 3H, -OCH_3), 3.72(s, 1H, N-H). Elemental analysis Calcd. (Found): C, 82.10(82.19); H, 6.51(6.42); N, 5.32(5.26); O, 6.08(6.13).

1-(4-((naphthalen-1-yl) methyl amino) phenyl) ethanone (2d)
Yield: 62%, mp: 139-141°C. IRν_{max} (cm^{-1}) (KBr): 3379, 3042, 2944, 1674, 1465-1561. ^{1}H NMR (δ ppm; $CDCl_3$): 6.89-8.21(m, 11H, CH in aromatic ring), 4.84(s, 2H, -CH_2-), 4.52(s, 1H, N-H), 2.56(s, 3H, -CH_3). Elemental analysis Calcd. (Found): C, 82.88(82.80); H, 6.22(6.26); N, 5.09(5.1); O, 5.81(5.84).

2-((naphthalene-1-yl)methylamino-4-chlorobenzoic acid (2e)
Yield: 65%, mp: 122-124°C. IRν_{max} (cm^{-1}) (KBr): 3422, 3368, 3039, 2948, 1738, 1432-1562. ^{1}H NMR (δ ppm; $CDCl_3$): 10.22(1H, s, -OH), 6.85-8.23(m, 10H, CH in aromatic ring), 4.89(s, 2H, -CH_2), 4.23 (s, 1H, N-H). Elemental analysis Calcd. (Found): C, 69.35(69.47); H, 4.53(4.38); N, 4.49(4.54); Cl, 11.37(11.30); O, 10.26(10.31).

4-((naphthalen-1-yl) methylamino) benzoic acid (2f)
Yield: 60%, mp: 138-140°C. IR ν_{max} (cm^{-1}) (KBr): 3376, 3429, 3042, 2957, 1746, 1445-1554. ^1H NMR (δ ppm; $CDCl_3$): 10.10(1H, s, -OH), 6.92-8.30(m, 11H, CH in aromatic ring), 4.81(s, 2H, -CH_2), 4.23 (s, 1H, N-H). Elemental analysis Calcd. (Found): C, 77.96(77.91); H, 5.45(5.49); N, 5.05(5.03); O, 11.54(11.57).

2-((naphthalene-1-yl) methylamino)-5-methyl benzoic acid (2g)
Yield: 56%. mp: 146-148°C. IRν_{max} (cm^{-1}) (KBr): 3465, 3380, 3044, 2960, 1751, 1442-1557. ^1H NMR (δ ppm; $CDCl_3$): 10.08(1H, s, -OH), 6.98-8.36(m, 10H, CH in aromatic ring), 4.79(s, 2H, -CH_2), 4.26 (s, 1H, N-H), 2.27(s, 3H, -CH_3). Elemental analysis Calcd. (Found): C, 78.33(78.39); H, 5.88(5.81); N, 4.81(4.92); O, 10.98(10.88).

3-chloro-4-fluro-*N*-((naphthalene-1-yl)methyl)benzenamine(2h)
Yield: 59%. mp: 135-137°C. IRν_{max} (cm^{-1}) (KBr): 3374, 3056, 2950, 1442-1548, 1050, 796. ^1H NMR (δ ppm; $CDCl_3$): 6.89-8.31(m, 10H, CH in aromatic ring), 4.77(s, 2H, -CH_2), 4.26(s, 1H, N-H). Elemental analysis Calcd. (Found): C, 71.46(71.40); H, 4.59 (4.61); N, 4.90(4.94); Cl, 12.41(12.45).

4-((naphthalen-5-yl) methyl) morpholine (2i)
Yield: 44%. mp: 131-133°C. IRν_{max} (cm^{-1}) (KBr): 3045, 2957, 1436-1551, 1350, 1165. ^1H NMR (δ ppm; $CDCl_3$): 6.93-7.98(m, 7H, CH in aromatic ring), 4.69 (s, 2H, -CH_2), 4.27 (s, 1H, N-H), 3.28(t, 4H, -CH_2-O-CH_2- in morpholine ring), 2.67(t, 4H, -CH_2-N-CH_2- in morpholine ring). Elemental analysis Calcd. (Found): C, 79.26(79.31); H, 7.54(7.50); N, 6.16(6.06); O, 7.04(7.10).

4-((naphthalen-5-yl) methyl)-4-H-1, 2, 4-triazole (2j)
Yield: 80%, mp: 153-155°C. IRν_{max} (cm^{-1}) (KBr): 3020, 2948, 1458-1574, 1380. ^1H NMR (δ ppm; $CDCl_3$): 6.89-8.37(m, 9H, CH in aromatic ring), 4.71(s, 2H, -CH_2), 4.22(s, 1H, N-H), Elemental analysis Calcd. (Found): C, 69.62(69.74); H, 5.39(5.47); N, 24.98(24.80).

Antifungal study
The synthesized compounds (**2a-2j**) were screened for antifungal activity by serial plate dilution method [9-12]. The antifungal activity was carried out against *Candida albicans* strain NCIM 3471. Terbinafine was used as standard drug. Dilutions of the synthesized compounds were prepared in dimethylformamide (DMF) (250µg/ml to 12.5µg/ml). Suspension of the fungi containing approximately 10^7 CFU/ml was seeded on the plates previously prepared using Saubouraud's dextrose agar & incubated at 30-37°C. The plates were observed for growth at the end of 48-72hrs. A set of negative and positive controls of growth was also kept for incubation along with test plates. Minimum inhibitory concentration (MIC) was considered to be the minimum concentration of test compounds exhibiting less or no visible growth of fungi on the plate. The antifungal activity of the synthesized compounds summarized in the Table 1.

RESULTS AND DISCUSSION

The title compounds 1-chloromethyl naphthalene derivatives 2a-2j were synthesized in two step process as per Scheme 1. Naphthalene with paraformaldehyde in hydrochloric acid and *o*-phosphoric acid afforded 1-chloromethyl naphthalene 1. Appearance of -CH aliphatic stretching

at 2964 cm^{-1} in the IR spectrum and appearance of peak at 4.9 δ ppm in the ^1H NMR spectrum and comparison of the melting points confirmed the structure of compound 1. The synthesis of 1-chloromethyl naphthalene derivatives 2a-2j were readily accomplished by refluxing compound 1 with various substituted aniline in presence of potassium carbonate in appropriate solvent. All the synthesized compounds were recrystallized from ethanol. The yields of the final compounds were in the range of 60-70%. Structure confirmation of synthesized compounds was done by IR, ^1H NMR, and elemental analysis. Physical data of all the synthesized compounds is given in Table 1.

The antifungal activity was assessed by the ability of these compounds to inhibit the zone formation induced by *C. albicans*, 2a was selected as a lead compound and substitution was carried out in the phenyl moiety. Majority of the synthesized compounds exhibited considerable antifungal activity as evident from their high zone of inhibition and MIC value (Table 1).

Presence of chloro 2b and acid 2f at forth position of the phenyl ring show significant activity relative to compound 2a, where as substitution at forth position in 2a by methoxy 2c, and acetyl 2d barely enhance the antifungal activity. Further an appreciable increase in activity was observed when acid and chloro were attached to second and fifth position of the aryl ring respectively in di-substituted compound 2e. While substitution by acid and methyl at second and forth position 2g did not increased antifungal activity significantly. The di-halo substituted phenyl ring having fluorine and chlorine at forth and fifth position increased the antifungal activity. Further replacement of substituted anilines with morpholine triazole increases the antifungal activity.

CONCLUSION

In conclusion, several 1-chloromethyl naphthalene derivatives were synthesized and evaluated for their antifungal activity. Mostly all the synthesized compounds exhibited moderate antifungal activity comparable with terbinafine. The 2h 3-chloro-4-fluoro-N-(naphthalen-1-ylmethyl) aniline and 2j N-(naphthalen-1-ylmethyl)-4H-1, 2, 4-triazol-4-amine were found to be most active among all the compounds with impressive antifungal activity.

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