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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME AZETIDINONE DERIVATIVES WITH THE β-NAPHTHOL

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ABSTRACT

Azetidinone derivatives were synthesized from β-naphthol in two steps. First the Schiff's bases were prepared by reacting the hydrazine of a naphthalene derivative with different aromatic aldehydes.Cyclocondensation of the Schiff's bases with chloroacetyl chloride in the presence of triethylamine resulted in the formation of corresponding azetidinone analogues. The structures of the newly synthesized compounds were confirmed by IR,[1]H NMR, and Mass spectroscopic analysis The in vitro antibacterial and antifungal activity of compound have been evaluated by paper disc diffusion method.

Keywords: Azetidinone, Naphthalene, Antimicrobial.

INTRODUCTION

Naphthalene containing drugs are available, such as Nafacillin, Naftifine, Tolnaftate, Terbinafine, etc. which play vital role in the control of microbial infection[1]. Naphthalene and its derivative have shown a large spectrum of antimicrobial activity .several research has been done and has proved β-naphthol as an excellent lead moiety for designing a synthetic derivative, which would posses good biologically activity[(1-5)].

A large number of 3-chloro monocyclic β-lactams having substitution at position 1 and 4 posses' powerful antimicrobial, anticonvosant, and anti-tubercular activity [(6-12)]

In the present study synthetic derivatives, simultaneously containing naphthalene and azetidine-2-one have been prepared and it is speculated to get a combined effect of both the moieties.

EXPERIMENTAL

The solvent and reagents used in the synthetic work were of laboratory grade and were purified by distillation or crystallization where necessary and their melting points were compared with the available literature values. Purity of the compounds was checked by TLC on silica gel G.1H NMR spectrum was recorded on Varian Mercury Plus 300MHz.The IR spectrum was recorded on Perkin Elmer PSEN60825,The mass spectrum was recorded on Varian pro star 500ms. The antibacterial activity of different samples done in Paper disc diffusion method

Ethyl (naphthalene-2-yloxy) acetate (1)

A mixture of 2-naphthol (0.1mol), ethylchloroacetate (0.1mol), and anhydrous potassium carbonate (19.5gm, 0.15mol) in dry acetone were refluxed on a water bath for 24 hrs at 70 ^{0}c. The resultant reaction mixture was cooled and filtered. From the filtrate excess of acetone was removed by distillation. This reaction mixture of filtrate was than poured on to the ice cold water and stirred well. The organic layer was extracted with ether and further the ether layer was washed with 5% HCl and dried over anhydrous sodium sulphate. Ether layer was evaporated by drying on water bath. The resultant collected liquid was purified under reduced pressure to yield pure Ethyl (naphthalene-2-yloxy) acetate.

2-(Naphthalen-2-yloxy) acetohydrazide (2)

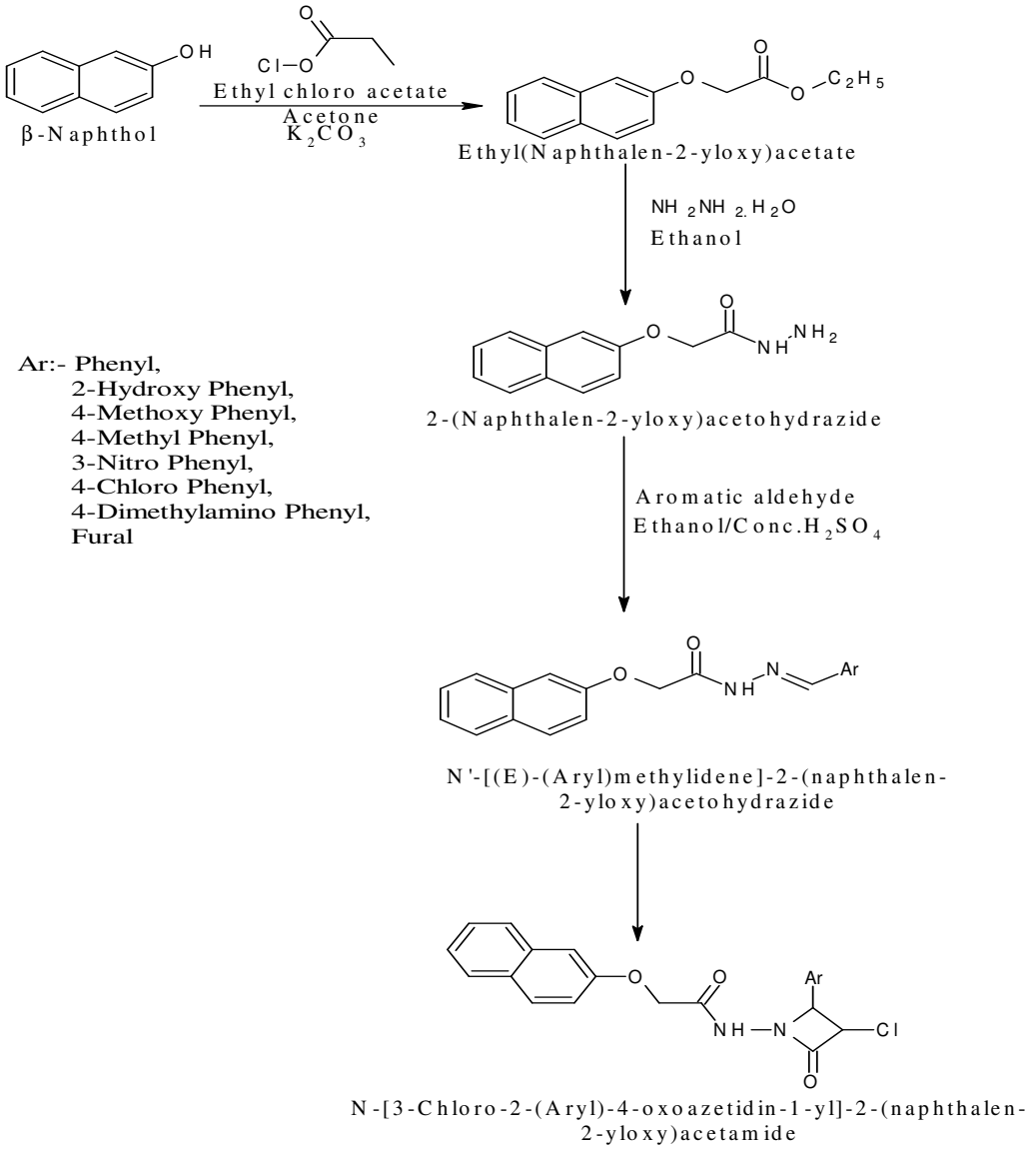
A mixture of Ethyl (naphthalene-2-yloxy) acetate (0.05mol), hydrazine hydrate (99% 0.07mol) in ethanol (100ml) was refluxed for 6 hrs. From the resultant mixture excess of ethanol was removed by distillation. On cooling, from the resultant mixture, yellow crystal of 2-(Naphthalen-2-yloxy) acetohydrazide began to separate. It was collected and then recrystallized from ethanol.

2-(Naphthalen-2-yloxy)-N′[Substituted phenyl methylidene] acetohydrazide(3a)

Mixture of 2-(Naphthalen-2-yloxy)acetohydrazide (0.01mol) (dissolved in minimum quantity of ethanol)and benzaldehyde (0.01mol,dissolved in minimum quantity of ethanol) was refluxed together employing Sulphuric acid about 0.01 mol as catalyst in a round bottom flask on a water bath for 6h. The precipitate was filtered, washed with ice cold water and recrystalized from ethanol.

N-(3-chloro-2oxo-4phenylazetidin-1-yl)-2(naphthalene-2-yloxy)acetamide(4a). [7]

Chloroacetyl chloride was added drop wise to Schiff's base of2-(Naphthalen-2-yloxy)-N′ [(E)-phenyl methylidene] acetohydrazide (0.01 mol)and triethylamine (0.02 mol) in dioxane (25ml)at 5-10^{0}c.the mixture was stirred for 20 h and left at room temperature for 3d.the mixture were filtered, dried and recrystlized from ethanol .



Scheme-1

RESULTS AND DISCUSSION

Synthesis of the azetidinone derivatives by the described method resulted in good yields of the products, as can be seen from Table I, which also lists the physical data of compounds 4a-h.

Table-1:Physical data of the synthesized azetidinone compounds (4a-4h)

Compound No.	Physical state	Melting point^{0}c	Molecular formula	%yield
4a	Brown Color	210-212^{0}c	$C_{21}H_{17}ClN_2O_3$	85%
4b	Pale Buff Crystal	232-234^{0}c	$C_{21}H_{17}ClN_2O_4$	80%
4c	Brownish Yellow Crystal	212-214^{0}c	$C_{22}H_{19}ClN_2O_4$	83%
4d	Dark red Crystal	256-258^{0}c	$C_{22}H_{19}ClN_2O_3$	58%
4e	Brownish Crystal	224-226^{0}c	$C_{22}H_{19}ClN_2O_4$	60%
4f	Buff Crystal	232-234^{0}c	$C_{22}H_{19}ClN_2O_4$	74%
4g	Redish Crystal	220-222^{0}c	$C_{23}H_{22}ClN_3O_3$	72%
4h	Grey Crystal	202-204^{0}c	$C_{22}H_{19}ClN_2O_4$	60%

(2a) ;IR (KBr,cm^{-1}): 2853 (C-H str.of methylene); 1626, 1513(N-H bending of NH_2); 1463 (C-H deformation of CH_2, aromatic C=C str. of benzene); 1377,1254 (C-N str. of amide); 1217, 1065 (C-O str. of >C=O); 1184 (C-O str. of C-O-C); (C-O stretching in C=C-O-C; 731, 594 (N-H out of plane deformation).

(4a): IR (KBr, cm^{-1}): 2853(C-H str. of methylene); 1463(C-H deformation in CH_2, aromatic C=C str. of benzene); 1377(C-N str. of amide); 1044(C-O str.of C=C-O-C); 722(N-H out plane of deformation); 612(C-Cl str.)

(4b):IR (KBr, cm^{-1}): 3429.46 (O-H Phenolic str.); 2854(C-H str.); 1619(C=O str. of $RCONH_2$); 1459(C-H deformation of CH_2); 1459 (aromatic C=C str. of benzene); 1377(C-N str. of amide); 1075(C-O str.of C=C-O-C); 722 (N-H out plane of deformation); H^1-NMR (DMSO-D_6) 6.9-7.7(m, 11H, Ar-H), 4.7 (s, 1H, Ar-CH), 5.2 (s, 2H, -OCH_2), 9.0 (s, 1H, NH, OH); MS (m/z) 396 (M^-).

(4c):IR (KBr, cm^{-1}): 2853(C-H str.of methylene); 1602(C=O str. of $RCONH_2$); 1463(aromatic C=C str.of benzene, C-H deformation of CH_2); 1377, 1301 (C-N str. of amide); 1250, 1024 (C-O str.of C=C-O-C); 1165(C-O str. of C-O-C); 832(C-Cl str.); 722(N-H out plane of deformation); H^1-NMR (DMSO-D_6) 7.2-7.8(m, 11H, Ar-H), 4.7 (s, 1H, Ar-CH), 5.2 (s, 2H, -OCH_2), 3.8 (s, 3H, -OCH_3), 8.6 (s, 1H, NH)

(4d):IR (KBr, cm^{-1}): 2923.62(C-H)str. Ar-CH_3; 2853(C-H str.of methylene); 1602(C=O str. of $RCONH_2$); 1463(aromatic C=C str.of benzene, C-H deformation of CH_2); 1377, 1301 (C-N str. Of amide); 1250, 1024 (C-O str.of C=C-O-C); 1165(C-O str. of C-O-C); 832(C-Cl str.); 722(N-H out plane of deformation)

(4e): IR (KBr, cm^{-1}): 2853(C-H str.of methylene); 1602(C=O str. of RCONH); 1592(N=O str. Ar-NO_2); 1463(aromatic C=C str.of benzene, C-H deformation of CH_2); 1377, 1301 (C-N str. of amide); 1250, 1024 (C-O str.of C=C-O-C); 1165(C-O str. of C-O-C); 832(C-Cl str.); 722(N-H out plane of deformation);

(4f):IR (KBr, cm^{-1}): 2853(C-H str.of methylene); 1602(C=O str. of $RCONH_2$); 1463(aromatic C=C str.of benzene, C-H deformation of CH_2); 1377, 1301 (C-N str. of amide); 1250, 1024 (C-O str.of C=C-O-C); 1165(C-O str. of C-O-C); 832(C-Cl str.); 705(C-Cl str. aromatic); H^1-NMR (DMSO-D_6) 7.4-7.8(m, 11H, Ar-H), 4.7 (s, 1H, Ar-CH), 5.2 (s, 2H, -OCH_2), 8.7 (s, 1H, NH) ; MS (m/z) 415(M^-).

(4g):IR (KBr, cm^{-1}): 2853(C-H str.of methylene); 1602(C=O str. of $RCONH_2$); 1463(aromatic C=C str.of benzene, C-H deformation of CH_2); 1377, 1301 (C-N str. of amide)1360(C-N str. Aromatic tertiary

amine); 1250, 1024 (C-O str.of C=C-O-C); 1165(C-O str. of C-O-C); 832(C-Cl str.); 722(N-H out plane of deformation)
(4h):IR (KBr, cm^{-1}): 2853(C-H str.of methylene);1686(C-O-Cstr.of furan); 1617(C=O str. of RCONH); 1464(aromatic C=C str.of benzene, C-H deformation of CH_2); 1377, 1297 (C-N str. of amide); 1216, 1019 (C-O str.of C=C-O-C);1156(C-O str.of C-O-C); 838,619(C-Cl str.); 722(N-H out plane of deformation).

Antimicrobial Activity
The Newly Synthesized Compound showed activity against *Escherichia coli, Staphylococcus aureu, Pseudomonas aeruginosa Aspergillus Niger,*using nutrient agar medium (Hi-Media Laboratories, India) Ampicillin and Griesofulvin was used as standard for antibacterial and antifungal activity respectively. The observed zone of inhibition is presented in Table-2

Table-2: Antimicrobial activities of the synthesized compounds

Compound	In-Vitro Antimicrobial Activity- Zone of Inhibition in mm.			
	Escherichia coli	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Aspergillus Niger*
4a	11	10	13	16
4b	10	12	12	14
4c	8	9	11	18
4d	9	11	12	16
4e	8	8	9	17
4f	9	14	13	15
4g	8	9	10	16
4h	7	—	6	—
Ampicillin	14	18	15	—
Griesofulvin	—	6	8	21
DMSO (1% Aq. solution)	—	—	—	—

CONCLUSION

From the biological Investigation it was found that methyl, methoxy and Chloro substituted aromatic substitution gives equipotent antimicrobial activity with standard drug Ampicillin and Griesofulvin while other compounds possess good antimicrobial activities.

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