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SYNTHESIS AND POTENTIAL ANTIMICROBIAL ACTIVITY AND EVALUATION OF NAPHTHA [2, 3-D] IMIDAZOLES DERIVATIVES

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ABSTRACT

A new series of some naphtho[2,3-d]imidazoles derivatives have been synthesized. Thestructures of the synthesized compounds were confirmed by IR, 1H NMR and Mass spectralanalysis and they were evaluated for their antibacterial activities by disc diffusion method.All of the synthesized compounds showed good antibacterial activity. However theantibacterial activity was observed for all the compounds using four strains of Gram (+ ve)and Gram (-ve) bacteria. The strains used were *Staphylococcus aureus, Bacillus pumilis*,*Proteus mirabilis* (+ve) and *Escherchia coli* (-ve) activity of the synthesized compoundsagainst the tested organisms was found to be less than that of respective standard drug attested dose level.

Keywords:*Napthalenediamine*,Antibacterial activity, NMR

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INTRODUCTION

The structural and therapeutic diversity coupled with commercial capability of smallmoleculeshas enthralledorganicandmedicinalchemists.Therehasbeensignificantinterestinthe chemistryof heterocyclic systems whichisa corestructureinvarioussyntheticpharmaceuticals displaying broadspectrumof biological activity.In thepastfewyears,researchfor new antibacterial, antifungal inflammatoryagentshas beenreportedthatmany compoundshavinga imidazole ring with substituents like 1,3,4-oxadiazole and azetidinederivativesareknownfortheirantifungal and antibacterial activity. Therefore it was enabled that compounds containing naphtho[2,3-d]imidazoles would result in interesting of biological activities. In the present study substituted naphtho[2,3-d]imidazoles were synthesized by treating 2,3 Naphthalene diamine with 4 amino carboxylic acids to get 5-amino 2-substituted naphtho[2,3-d]imidazoles derivatives then this derivatives treated with different types of substituted aromatic benzaldehydes gives (E)-N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)3-4 substituted phenyl)enamine thenfinally their thiazolidiones and azetidionesderivatives were synthesized.

MATERIALS AND METHODS

All used chemicals were purchased from Spectrochem and Alfa acerCompany. Melting points were determined on open capillary tube and are uncorrected. The NMR spectra were recorded on a Bruker (300 MHz) spectrometer. Chemical shifts (ppm) were referred to the internal standard tetramethylsilane (TMS).Themass Spectrawererecordedona JEOLJMS-D300spectrometeroperatingat70eV. Reactions were monitored by thin layer chromatography using silica gel F254 aluminum sheets (ethyl acetate/ n-nexane, 3:1).

Experimental

SynthesisofComp 2 (4-(1H-naphtho[2,3-d]imidazol-2-yl)aniline)

The synthetic strategy leading to the target compounds 1 are illustrated inscheme1 .synthesized byequimolar quantities (0.01mol) of *2,3*napthalenediamine,p-aminobenzoicacid(0.01mol) in polyphospheric acid (PPA) (20ml)wasrefluxed at 170^{o} C for2 hrs.Themixtureiscooled anddiluted with water and quenched by 10% NaOH, aqueous layer was extracted by EtOAc, organic layer was separated dried over $Na_2SO_4$and concentrated to afford desired compound as brown colored free flow solid. Obtained compound was purified by column chromatography as 4-(1H-naphtho[2,3-d]imidazol-2-yl)anilineYield59%; mp209-212^0 c DM-259+1

General methodof Synthesisof Compound (3a-3e)

(E)-N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)enamine

A compound 24-(1H-naphtho[2,3-d]imidazol-2-yl)aniline(0.01mol) and ofand aromatic benzaldehyde**(a –e)** was refluxed for16hrs In20 ml ofethanol. Thereaction mixture wascooledand concentrated obtained solid was recrystallized from ether: pentane.The crystals foundwasfiltered andobtained as desired comp (3a-3e).

General methodof synthesis of azetidinones(4a-4e)

Compound 3 (3a-3e) (0.001mol) andtriethylamine(0.003mol)wasdissolvedin1,4 –Dioxan(25ml), stirred and cooled to 0^{o}C thissolution ofchloroacetyl chloride (0.0012mol) in dioxane was added drop wise and reaction was stirred at rate for 16 hrs. Reaction was monitored by TLC after consumption of starting material reaction was concentrated to half of solvent separated and yield comp 1-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-3-chloro-4-(4-substituted phenyl) azetidin-2-one, recrystallized from chloroform.

General method of synthesis of thiazolidinones(5a-5e)

A Compound 3 (3a-3e)(0.001mol) and thioglycollic acid(0.001mol) dissolved in1,4dioxane (20 ml), anhydrous zinc chloride (0.5mg)was added and refluxed at 900C for16h.The reaction was then cooled and the resulting solid was washed with sodiumbicarbonate solution and final compound as 3-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-(4-substitutedphenylthiazolidin-4-one(5a-5e) recrystallizedfromabsoluteethanol.

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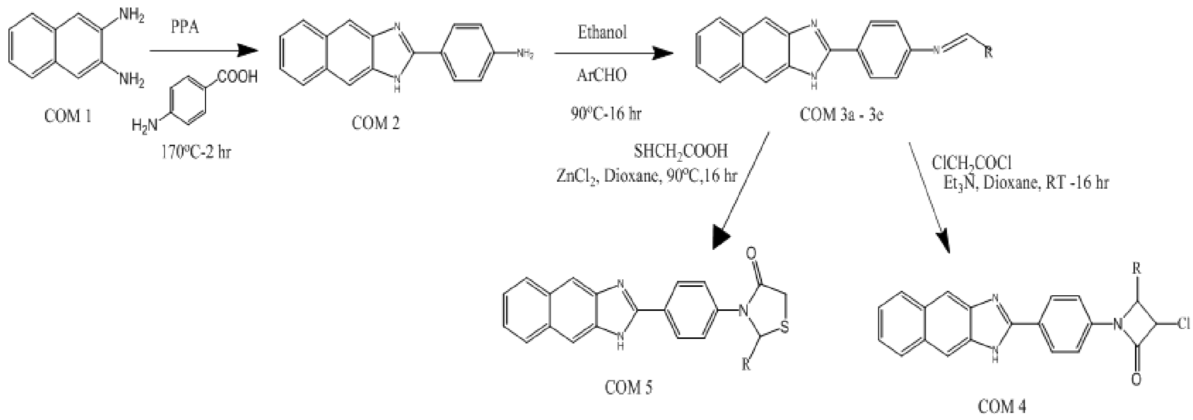
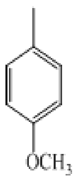
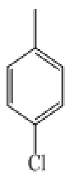
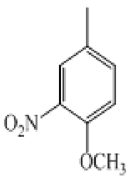
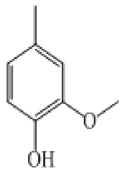
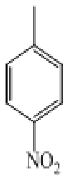
Scheme 1



Compound COD		R1	Compound COD		R1
3a , 4a ,5a	a		3d , 4d ,5d	d	
3b , 4b ,5b	b		3e , 4a ,5e	e	
3c , 4c ,5c	C				

Analytical Data

4-(1H-naphtho[2,3-d]imidazol-2-yl)aniline(2)

Brown Solid :- Yield59%;m.p.:209-212;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.70-7.75(s,2H), 8.11-8.15(d,2H),7.69-7.70(d,2H), 7.90-7.92(dd,2H),6.70-6.71(dd, 2H), NH 12.56 (bs , 1H),NH_2 5.24(s,2H) ; MS:m/z259(M^+)

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3a-3e

(E)-N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-1-(4-methoxyphenyl)methanimine (3a)

Reddish colour Solid Yield49%;m.p.:221-223;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 7.90-7.92(dd,2H),6.70-6.71(dd, 2H), 7.85-7.92(dd,2H),7.05-7.06(dd, 2H), NH 12.56 (bs , 1H), CH 8.65(s,1H), OCH_3 3.81(s,3H) ; MS:m/z 377(M^+)

(E)-N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-1-(4-methoxy-3-nitrophenyl)methanimine (3b)

White Solid Yield39%;m.p.:222-223;^{1}HNMRdata(DMSO)δ(ppm)aromaticcprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 7.90-7.92(dd,2H),6.70-6.71(dd, 2H), 8.55-8.52(d,1H),8.20-8.25(dd, 1H), 7.58-7.60(dd, 1H), NH 12.56 (bs , 1H), CH - 8.54 (s,1H), OCH_{3-} 4.02 (s,3H) ; MS:m/z422(M^{+1})

(E)-N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-1-(3-nitrophenyl)methanimine (3c)

OFF White Solid Yield62%;m.p.:221-223;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 7.76-7.81(dd,2H),7.65-7.71(dd, 2H), 8.15-8.19(dd,2H),8.34 -8.39(dd, 2H), NH 12.56 (bs , 1H), CH 8.58(s,1H),; MS:m/z 393(M^+)

(E)-N-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-1-(4chlorophenyl)methanimine (3d)

OFF white Yield52%;m.p.:221-223;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 7.76-7.81(dd,2H),7.65-7.71(dd, 2H), 7.59-7.61(dd,2H),7.94 -7.99(dd, 2H), NH 12.56 (bs , 1H), CH 8.68(s,1H),;

MS:m/z 382(M^{+1})

(E)-4-(((4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)imino)methyl)-2-methoxyphenol (3e)

Brown colourYield50%;m.p.:200-203;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 7.76-7.81(dd,2H),7.65-7.71(dd, 2H), 7.36(s,1H),7.34(d, 1H),6.88(d, 1H), NH 12.56 (bs , 1H), CH 8.63(s,1H), OH 9.95(s,1H) OCH_3 3.83(s,3H) ; MS:m/z 394(M^{+1})

4a-4e

1-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-3-chloro-4-(4-methoxyphenyl)azetidin-2-one (4a)

White solid Yield79%;m.p.:230-233;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H),8.10(dd,2H),7.45(dd, 2H), 7.22(dd,2H),6.88(dd, 2H), aliphatic CH -5.16 (d,1H), 5.23 (d,1H), NH 12.56 (bs , 1H), OCH_3 3.81(s,3H) MS:m/z 454(M^{+1})

1-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-3-chloro-4-(3-methoxy-4-nitrophenyl)azetidin-2-one (4b)

Off white yellowish –Yield39%;m.p.:222-223;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons --7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 8.10(dd,2H),7.45(dd, 2H), 8.22(d,1H),7.28(d, 1H) ,7.24(d, 1H), aliphatic CH -5.16 (d,1H), 5.23 (d,1H), NH 12.56 (bs , 1H), OCH_3 3.87(s,3H) ; MS:m/z 499(M^{+1}).

1-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-3-chloro-4-(4-nitrophenyl)azetidin-2-one (4c)

Yellow Yield65%;m.p.:240-243;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 8.10(dd,2H),7.45(dd, 2H), 7.65(dd,2H),8.18(dd, 2H), aliphatic CH -5.26 (d,1H), 5.43 (d,1H), NH 12.56 (bs , 1H), MS:m/z 469(M^{+1})

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1-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-3-chloro-4-(4chlorophenyl)azetidin-2-one (4d)

White solidYield65%;m.p.:240-243;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 8.10(dd,2H),7.45(dd, 2H), 7.48(dd,2H),7.50(dd, 2H), aliphatic CH -5.26 (d,1H), 5.43 (d,1H), NH 12.56 (bs , 1H), MS:m/z 458(M^{+1})

1-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-3-chloro-4-(4-hydroxy-3-methoxyphenyl)azetidin-2-one (4e)

Pinkish white –Yield39%;m.p.:232-223;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons --7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 8.10(dd,2H),7.45(dd, 2H), 6.81(d,1H),6.73(d, 1H) , 6.95(d, 1H), aliphatic CH -5.16 (d,1H), 5.43 (d,1H), NH 12.56 (bs , 1H), OCH_3 3.77(s,3H), OH 9.96(s,1H) ; MS:m/z 499(M^{+1}).

<u>5a-5e</u>

3-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-(4-methoxyphenyl)thiazolidin-4-one (5a)

Off white –Yield35%;m.p.:210-212;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 8.0(dd,2H),7.43(dd, 2H), 7.83(dd,2H),6.83(dd, 2H), NH 12.56 (bs , 1H), CH 6.44(s,1H), CH_2 4.02(s,2H), OCH_3 3.81(s,3H) ; MS:m/z 452(M^{+})

3-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-(4-methoxy-3-nitrophenyl)thiazolidin-4-one (5b)

Yellowish solidYield35%;m.p.:210-212;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 8.00-8.12(dd,2H),7.43(dd, 2H), 8.23(d,1H),7.25(s, 1H), 7.20(d,1H), NH 12.56 (bs , 1H), CH 6.44(s,1H), CH_2 4.02(s,2H), OCH_3 3.87(s,3H) ;

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MS:m/z 497(M^+)

3-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-(4-nitrophenyl)thiazolidin-4-one (5c)

Yellow Solid –Yield40%;m.p.:205-207;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 8.0(dd,2H),7.43(dd, 2H), 7.54(dd,2H),8.21(dd, 2H), NH 12.56 (bs , 1H), CH 6.44(s,1H), CH_2 4.02(s,2H);

MS:m/z 467(M^+)

3-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-(4-chlorophenyl)thiazolidin-4-one (5d)

White Solid :-Yield40%;m.p.:205-207;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 8.0(dd,2H),7.43(dd, 2H), 7.20(dd,2H),7.38(dd, 2H), NH 12.56 (bs , 1H), CH 6.44(s,1H), CH_2 4.02(s,2H);

MS:m/z 456(M^+)

3-(4-(1H-naphtho[2,3-d]imidazol-2-yl)phenyl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (5e)

Brown sticky solid :Yield35%;m.p.:210-212;^{1}HNMRdata(DMSO)δ(ppm)aromaticprotons -7.69-7.70(d,2H), 7.70-7.75(s,2H),8.11-8.15(d,2H), 8.00-8.12(dd,2H),7.43(dd, 2H), 7.34(d,1H),7.45(s, 1H), 6.94(d,1H), NH 12.56 (bs , 1H), CH 6.44(s,1H), CH_2 4.02(s,2H), OCH_3 3.87(s,3H) OH9.96 (s,1H) ; MS:m/z 468(M^+)

BiologicalEvaluation:

Antimicrobial Activity

The synthesized compounds were tested for antimicrobial activity by disc diffusion method. They were dissolved in and sterilized by filtering through 0.45μm Millipore filter. Final into culums of 100μl suspension containing 108CFU/ ml of each bacterium used. Nutrient agar(antibacterial activity) and sabouraud’s dextrose agar medium (antifungal activity) was prepared and sterilized by an autoclave (121^{0}c and 15 Ibs for 20 min) and transferred to previously sterilized petri dishes (9 cm in diameter). After solidification, petri plates were inoculated with bacterial organisms in sterile nutrient agar medium at 45^{0}C, organisms in sterile sabouraud's dextrose agar medium at45^{0}C in aseptic condition. Sterile whatmann filter paper discs (previously sterilized in U.V. lamp) were impregnated with synthesized compounds at a concentration of 300µg/ml and 300µg/ml were placed in the organism-impregnated petri plate sunder sterile condition. The plates were left for 30 min to allow the diffusion of compounds at room temperature. Antibiotic discs of streptomycin (300µg /ml) and 600µg /ml) as standard were used as positive control, while DMSO used as negative control. Then the plates were incubated for 24 hrs at 37 ± 1°C for antibacterial activity and48 h at 37±1°C for antifungal activity. The zone of inhibition was calculated by measuring the minimum dimension of the zone of no microbial growth around the each disc.The synthesized compounds were screened for antimicrobial activity by zone ofinhibition method. Antibacterial activity was observed for all the compounds using fourstrains of Gram (+ ve) and Gram (-ve) bacteria. The strains used were *Staphylococcus aureus*, *Bacillus pumilis*, *Proteus mirabilis* (+ve) and *Escherchia coli* (-ve).The concentrations taken were 300 µg/mL, 600 µg/ml. By the analysis of antimicrobial data found that, compounds 4b and 4c were found to be more active against *Escherchia coli* (-ve) organism and 5b is more active against *Bacillus pumilis*used. 4d and 5d also showing good activity against microorganism at both strengths.The remaining compounds showed moderate and low activity against organisms

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Table 1 Antimicrobial activity of synthesizedcompound Standard as streptomycin

		Zone Of inhibition(in mm)			
Compound	**Conc. (µg/mL)**	***Escherichia coli***	***Bacillus pumilis***	***Proteus mirabilis***	***Staphylococcus Aureus***
4a	300	2.3	5.6	2.9	NA
	600	4.6	10.5	5.9	NA
4b	300	2.9	6.5	9.20	6.32
	600	6.3	13.0	18.3	12.0
4c	300	3.26	6.1	2.12	5.06
	600	6.5	11.2	4.28	10.2
4d	300	2.8	2.26	5.52	5.59
	600	5.3	5.25	10.25	11.2
4e	300	2.26	3.35	4.95	3.02
	600	4.09	6.6	9.01	6.03
5a	300	2.01	4.52	2.21	4.98
	600	3.45	8.6	4.41	5.02
5b	300	2.7	6.92	7.0	6.9
	600	5.4	13.84	14.20	13.12
5c	300	2.6	5.9	5.03	2.9
	600	5.2	10.8	10.06	5.8
5d	300	3.06	7.25	9.24	6.03
	600	6.03	14.02	18.02	12.03
5e	300	1.3	3.5	5.59	4.56
	600	6.85	10.28	11.25	9.06
Std	300	3.27	7.20	12.84	10.34
	600	6.40	14.20	24.50	20.26

RESULTS AND DISCUSSION

Allthesynthesized compoundsexhibited significant antibacterial activity.Azetidinone and thiazolidinone derivatives were found to exhibit most potent antimicrobial activity against all the microbial stains tested. All the compounds were active against all tested microorganism with a range of MIC values for *Staphylococcus aureus*, *Bacillus pumilis*, *Proteus mirabilis* (+ve) and *Escherchia coli* (-ve) Compounds, exhibitedpotentantimicrobial activity againstE-coli andcompounds werefound tobereactive. The datarevealed thatelectronwithdrawing groupslike-NO_2,-Cl,andelectron donating group like -OCH3, -OH were foundto increasetheantimicrobialproperties,whereas electrondonatinggrouplike-CH3group foundtohavemoderate activity.Themostof thesynthesized compounds exhibited significantantibacterialactivity.

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