World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 4.223

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME 2-NAPHTHYLACETATE MANNICH BASES

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Article Received on 27/05/2017 **Article Revised on 16/06/2017** **Article Accepted on 06/07/2017**

ABSTRACT

Using 2-naphthylacetate as active hydrogen component, the following Mannich bases were synthesized via a general synthesis protocol: 1-hydroxymethyl-1-piperidinomethyl-2-naphthylacetate(I); 1,1-dimorpholinomethyl-2-Naphthylacetate(II) and 1,1-bis-dimethylaminomethyl-2-naphthylacetate(III).The structures of the final products was elucidated by a combination of spectral techniques (UV,IR , ^{1}HNMR and MS). The target molecules were evaluated for antimicrobial activity against six standard human pathogens. Significant activity was exhibited by compound I. It showed antimicrobial activity against all test organisms. Compounds II and III showed significant antifungal activity,

KEYWORDS: Mannich bases, Synthesis, Antimicrobial activity.

INTRODUCTION

The Mannich reaction is a three component condensation in which a compound containing an active hydrogen atom is allowed to react with an aldehyde and an NH-amine derivative. Secondary amines rather than primary amines are usually employed. The resulting product (Mannich Base) is an amine compound having the N atom linking the R substrate through a methylene moiety.[1,2]

Mannich bases have been reported as potential biological agents. They find application as antitubercular,[3] antimalarial,[4] vasorelaxing,[5] anticancer[6] and analgesic drugs.[7] They are also used in the polymer industry as paints and surface active reagents.[8]

Various 1,2,4-triazole derivatives have been reported to possess antibacterial, antifungal, anticancer,[9] antitubercular,[10] analgesic and anti-inflammatory properties.[11]

Phenolic bis-Mannich adducts were identified as IL -2 expression inhibitors in a T cell proliferation screening assay. Providing suitable compounds for further optimization.[12]

Since Mannich bases are known for their potential biological activity, this study was aimed to the evaluation of some Mannich bases for their antimicrobial activity.

MATERIALS AND METHODS

Materials

Chemicals and solvents

Analytical grade reagents were used. They were purchased from Sigma – Aldrich company (UK).

Methods

Synthesis protocols

Synthesis of 2-naphthylacetate

(0.1 mol) of β-naphthol was dissolved in 50 ml of 3M sodium hydroxide solution. (200g) of crushed ice was added followed by (15ml) acetic anhydride. The mixture was shaked vigorously for several minutes. The acetate was separated, dried and the product was recrystallised from 95% ethanol.

Synthesis of the Mannich base: 1-hydroxymethyl-1-piperidinomethyl-2-naphthylacetate

Formalin(1.6g,20mmol), 2-naphthylacetate (3.72g,20mmol) and piperidine hydrochloride (2.45g,20mmol) in a mixture of water and alcohol(1:2,v:v) were refluxed in a water bath for 1 hour and left at room temperature for 48 hours. Removal of

the solvent under reduced pressure gave the Mannich base.

Synthesis of the Mannich base: 1,1-dimorpholinomethyl-2-naphthylacetate

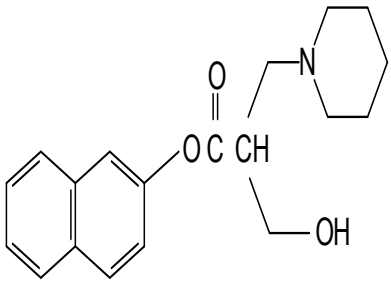
Formalin(1.6g,20mmol), 2-naphthylacetate (3.72g,20mmol) and morpholine (1.74g,20mmol) in a mixture of water and alcohol (1:2,v:v) were refluxed in a water bath for 1 hour and left at room temperature for 72 hours . Removal of the solvent under reduced pressure gave the Mannich base.

Synthesis of the Mannich base: 1,1-bis-dimethylaminomethyl-2-naphthylacetate

Formalin(1.6g,20mmol), 2-naphthyl acetate (3.72g,20mmol) and dimethylamine (0.90g,20mmol) in a mixture of water and alcohol (1:2,v:v) were refluxed in a water bath for 2 hours and left at room temperature for 48 hours. Removal of the solvent under reduced pressure gave the Mannich base.

RESULTS AND DISCUSSION

Synthesis of: 1-hydroxymethyl-1-piperidinomethyl-2-naphthylacetate (I)



I

The Mannich base I was synthesized by refluxing a mixture of formalin, 2-naphylacetate and piperidine in aqueous ethanol for one hour.

The UV spectum of compound I (Fig.1) showed λ_{max} (MeOH) 219,274,317nm. The IR spectrum (Fig.2) showed ν(KBr) 761,823,925(C-H, Ar., bending), 1215(C-O), 1460,1508, 1591(C=C,Ar), 1755(C=O),2948(C-H,aliph.). The ^{1}H NMR spectrum (Fig.3) revealed the following signals:

δ 1.64	doublet	2H
δ 2.32	singlet	6H
δ 2.40	singlet	6H
δ 3.11	singlet	1H
δ 7.29	doublet	1H
δ 7.55	doublet	2H
δ 7.62	doublet	2H
δ 7.96	doublet	2H

The signal at δ 1.64(2H) was assigned for a methylene moiety-(-CH_2-OH). The resonance at δ 2.32(6H) is characteristic of three methylenes of piperidine moiety , while the signal at δ2.40(6H) accounts for three methylenes moieties shifted downfield by nitrogen electron-withdrawal effect. The methine proton resonates as singlet at δ 3.11ppm.The resonances at δ 7.29,7.55 δ 7.62 and δ 7.96ppm account for the aromatic protons. The mass spectrum (Fig.4) gave m/z315 for (M^++3H). On the basis of such evidence structure I above was assigned for the Mannich base I.

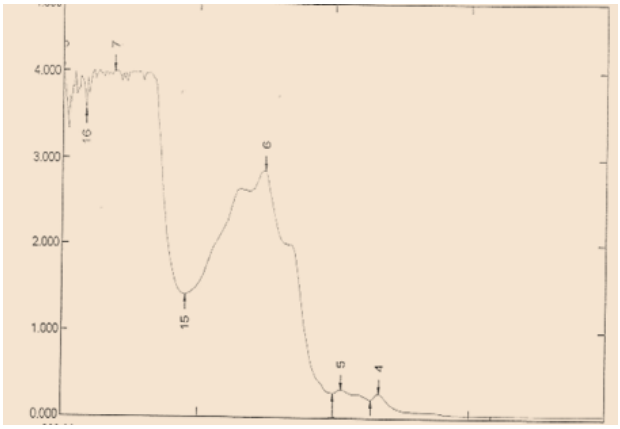


Fig. 1: UV spectrum of compound I.

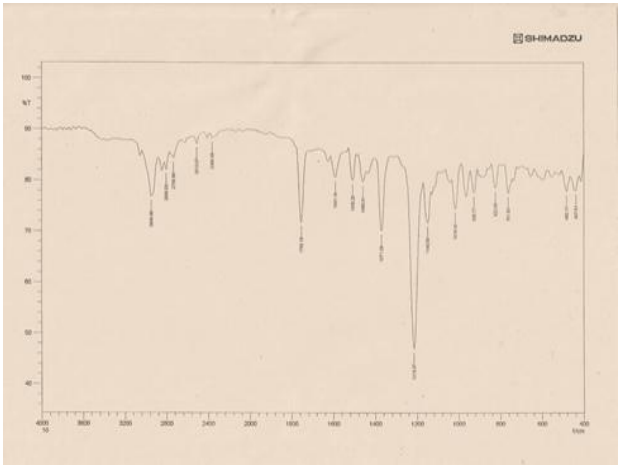


Fig. 2: IR spectrum of compound I.

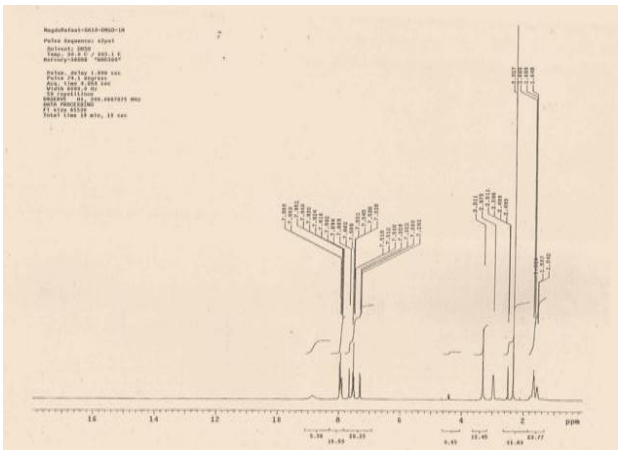


Fig. 3: ^{1}H NMR spectrum of compound I.

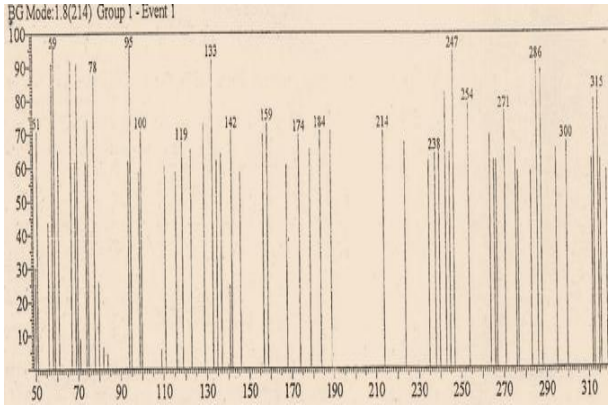


Fig. 4: Mass spectrum of compound I.

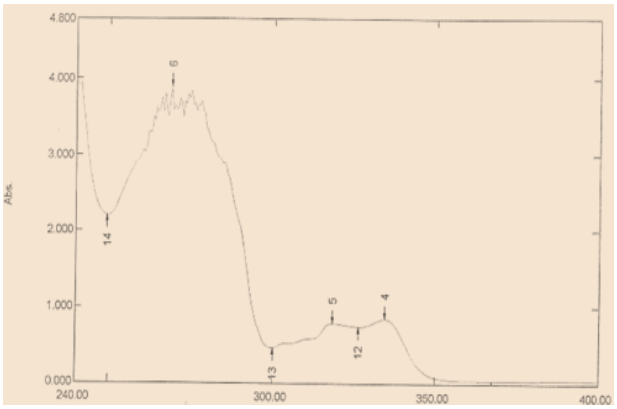
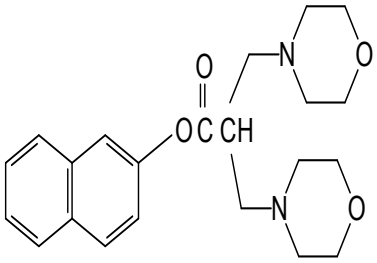


Fig. 5: UV spectrum of compound II.

Synthesis of Mannich base: 1,1-dimorpholinomethyl-2-naphthylactate(compound II)



II

The Mannich base II was synthesized by refluxing a mixture of formalin, 2-naphylacetate and morpholine in aqueous ethanol for one hour.

The UV sepectum (Fig.5) showed λ_{max} (MeOH) 275,332nm. The IR spectrum (Fig.6) showed ν(KBr) 705,817(C-H, Ar., bending), 1114(C-O), 1417,1458, 1593(C=C,Ar), 1757(C=O) 2850 cm^{-1} (C-H, aliphatic). The ^{1}H NMR spectrum (Fig.7) revealed the following signals:

δ 2.33	singlet	12H
δ 2.52	singlet	8H
δ 3.56	singlet	1H
δ 7.07	doublet	1H
δ 7.27	doublet	1H
δ 7.43	doublet	1H
δ 7.67	doublet	1H
δ 8.00	m	3H

The signal at δ 2.33(12H) was assigned to six methylene moieties in (-CH_2-N (CH_2)$_2$), while the resonance at δ2.52(8H) accounts for the other four methylenes of the morpholine moiety . The methine proton resonates as singlet at δ 3.56ppm. The resonances at δ 7.07, δ 7.27, δ 7.43 , δ7.67 and δ 8.00 ppm account for the aromatic protons. The mass spectrum (Fig.8) gave m/z282 for (M^{+}+H).

On the basis of such cumulative data structure II above was assigned for compound II.

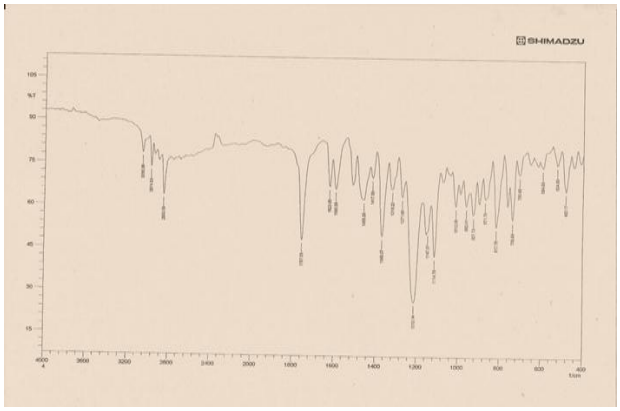


Fig. 6: IR spectrum of compound II.

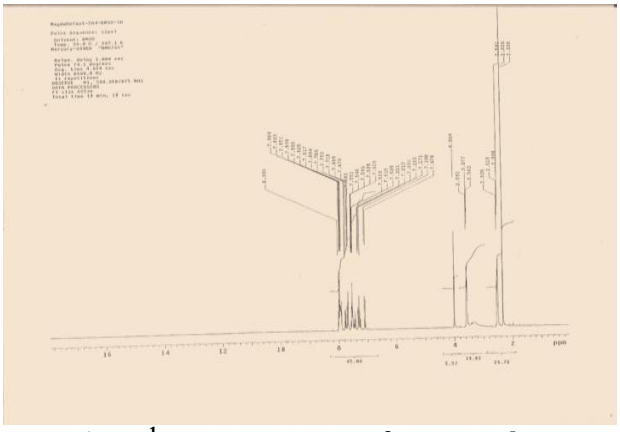


Fig. 7: ^{1}H NMR spectrum of compound II.

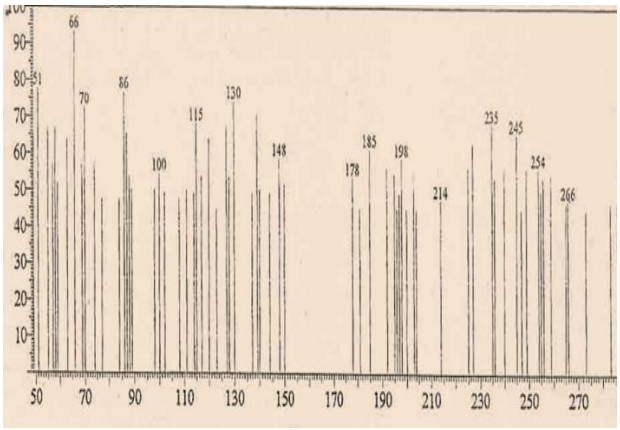
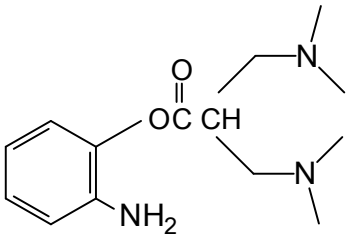


Fig. 8: Mass spectrum of compound II.

Synthesis of: 1,1-bis-dimethylaminomethyl-2-naphthylactate (III)



III

The Mannich base III was synthesized by refluxing a mixture of formalin, 2-aminophenylacetate and dimethylamine in aqueous ethanol for 2 hours.

The UV sepectum (Fig.9) showed λ_{max} (MeOH) 243,386nm. The IR spectrum (Fig.10) showed ν(KBr) 661,785,842(C-H, Ar., bending), 1282(C-O) ,1450,1541(C=C,Ar), 1658(C=O) 2881 cm^{-1} (C-H, aliphatic). The ^{1}HNMR spectrum (Fig.11) revealed the following signals:

δ 2.08	singlet	16H
δ 2.50	singlet	4H
δ 6.72-6.86	multiplet	5H
δ 6.93	singlet	1H

The signal at δ 2.08(s,16H) was assigned for four methyls and two methylene functions. The multiplet at δ6.72-6.86ppm(5H) is characteristic of aromatic protons and methine moiety(shifted downfield by electron-withdrawal effect of the neighboring carbonyl function) . The protons of the amino function resonated well downfield as a singlet at δ 6.93ppm. The Mass spectrum (Fig.12) gave m/z263 for (M^{+} + 2H).

On the basis of such spectral data structure III above was assigned for this Mannich base.

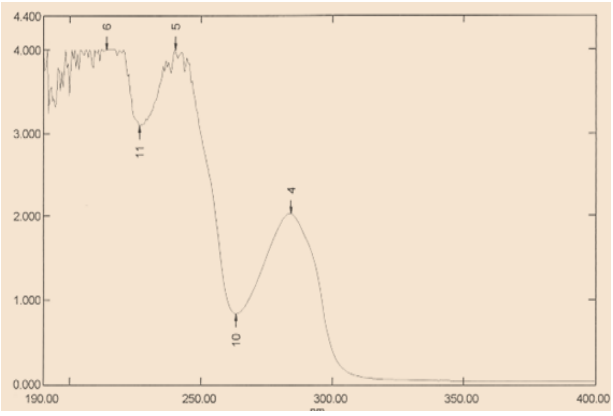


Fig. 9: UV spectrum of compound III.

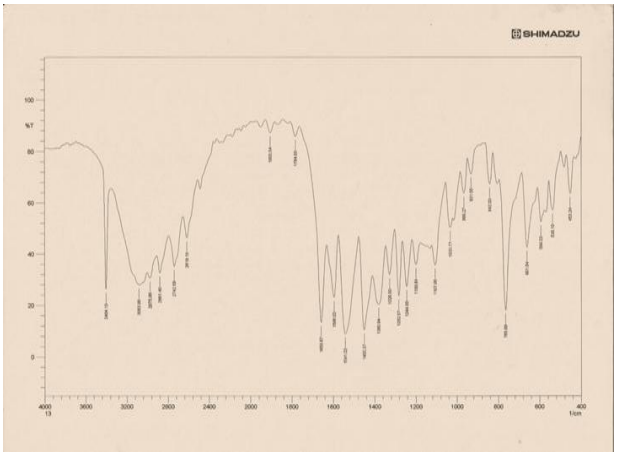


Fig. 10: IR spectrum of compound III.

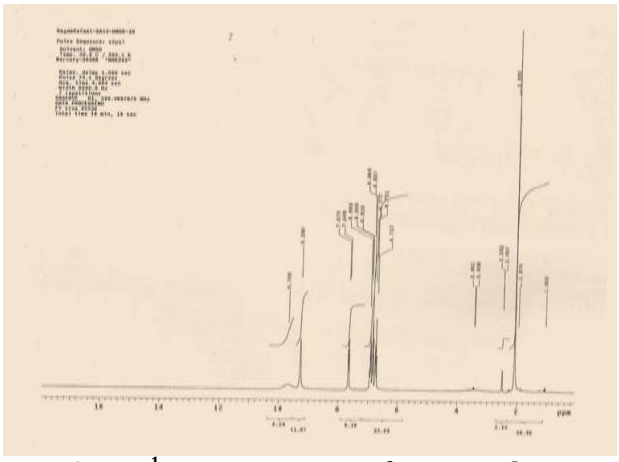


Fig. 11: ^{1}H NMR spectrum of compound III.

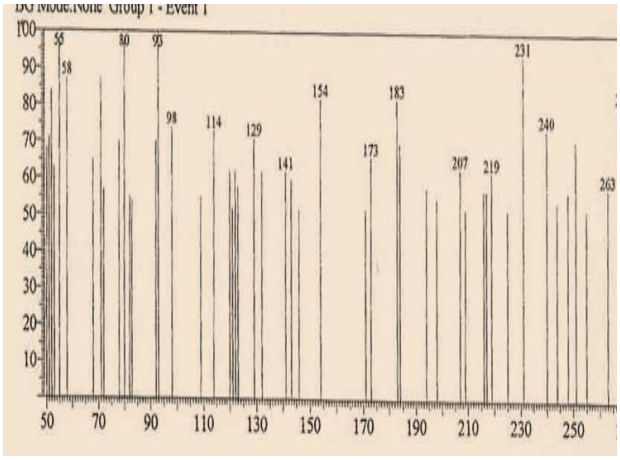


Fig. 12: Mass spectrum of compound III.

Antimicrobial activity

The target Mannich bases were evaluated for their antimicrobial activity against six standard human pathogens, namely, *Staphylococcus aureus* (*S.a.*), *Escherichia coli* (*E.c.*), *Pseudomonas aeruginosa* (Ps.), *proteus vulgaris*(Pv.), *Aspergillus niger(*An.) *and Candida albicans.(*Ca.)-Table 1.

Table 1: Test organisms.

Microorganisms	Type	Source
Staphylococcus aureus	G+ve	ATCC25923
Pseudomonas aeroginosa	G-ve	NCTC 6750
Escherichia coli	G-ve	ATCC 25922
proteus vulgaris	G-ve	ATCC 25925
Aspergillus Niger	Fungi	ATCC 9736
Candida albicans	fungi	NCTC 10716

* NCTC. National collection of type culture, Colindale. England
ATCC. American type culture collection, Maryland, USA

The cup-plate agar diffusion method was adopted with some minor modifications to assess the antimicrobial activity of the synthesized molecules.The diameters of inhibition zones are depicted in Table 2. The results were interpreted in commonly used terms (<9mm: inative;9-12mm:partiallyactive;13-18mm:active;>18mm:very active).

Significant activity was exhibited by compound I. It showed antimicrobial activity against all test organisms. Compounds II and III showed significant antifungal activity . The antibacterial and antifungal activities of standard chemotherapeutic agents are displayed in Tables (3) and (4) respectively.

Table 2: Diameter of inhibition zones of synthesized Mannich bases.

Microorganisms		Comp.	
	I	II	III
Proteus vulgaris	22	16	15
Escherichia coli	21	15	13
Pseudomonas aeruginosa	22	15	16
Staphylococus aureus	19	14	13
Candida albicans	24	21	20
Aspergillus Niger	30	20	21

Table 3: Antibacterial activity of standard chemotherapeutic agents: M.D.I.Z (mm).

Drug	Conc. mg/ml	Bs.	Sa.	Ec.	Ps.
Ampicillin	40	15	30	-	-
	20	14	25	-	-
	10	11	15	-	-
Gentamycin	40	25	19	22	21
	20	22	18	18	15
	10	17	14	15	12

Table 4: Antifungal activity of standard chemotherapeutic agent.

Drug	Conc.mg/ml	An.	Ca.
Clotrimazole	30	22	38
	15	17	31
	7.5	16	29

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