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STUDIES ON SYNTHESIS, CHARACTERIZATION, AND ANTIMICROBIAL ACTIVITY OF NOVEL (E)-3-(((4-(BIS(2-CHLOROETHYL)AMINO)NAPHTHALEN-1-YL)IMINO)METHYL)-4-CHLORO-2H-CHROMEN-2-ONE DERIVATIVES

Krushnakumar J. Jilariya *[1], Jayesh S. Babariya[2]

[1]*SMT. J.A. Patel Mahila College, Patel Kanya Chhatralaya Campus, Morbi, Gujarat, India*

[2]*Shree H.N. Shukla College of Science, Bhichari, Rajkot, Gujarat, India*

**Corresponding author: jilariyakishan25891@yahoo.com*

ABSTRACT

In our present research we synthesized novel (E)-3-(((4-(bis(2-chloroethyl)amino)naphthalen-1-yl)imino)methyl)-4-chloro-2H-chromen-2-one derivatives possessing coumarine as basic nucleus and N1,N1-bis(2-chloroethyl)naphthalene-1,4-diamine attached through Schiff base. Characterizations of synthesized compounds were carried by IR, NMR and mass spectral analysis. All synthesized compounds were tested for antimicrobial using cup plate method against standard drug. All the compounds showed moderate to good antimicrobial activity and anti-fungal activity compared to standard.

Keywords: Coumarine, N1,N1-bis(2-chloroethyl)naphthalene-1,4-diamine,Schiff base, Antimicrobial activity

1. INTRODUCTION

Schiff bases or imines, products of the condensation of carbonyl compound and primary amines, are important molecules that have been widely considered owing to their broad range of industrial and biomedical applications [1]. The relation effortlessness of their research, as well as the facile modification of the electronic and steric factor of the ligands; together with their chelating properties toward different metals, has made them attractive targets in the field of medicinal chemistry. Their rising significance stems from their varied pharmacological properties: antibacterial, antifungal, antimalarial, antiinflammatory and antiviral [2-4]. Imines have also been found to possess cytotoxic and antiproliferative activity towards several cancer cell lines like leukemia, colorectal adenocarcinoma (Caco-2), and pancreatic cancer (Panc-1) [5-7], where the presence of the azomethine bond (CH=N) is believe to be critical to biological activity [1, 2, 8]. Inspired by the aforementioned and continuing our work on Schiff base compounds and their applications [9-12], the pyrazole nucleus was incorporated into the design and architecture of the imine ligand, with the objective of finding compounds that elicit and enhance bioactivity. The synthesis of two homologous families of NNN-bis(imino)pyridine and NN-bis(imino) benzene compounds derived from 3-aminopyrazole was reported, as well as their biological activity was evaluated.

In the present work, we report the synthesis of (E)-3-(((4-(bis(2-chloroethyl)amino)naphthalen-1-yl)imino) methyl)-4-chloro-2H-chromen-2-one and their antimicrobial activity against fungi, gram positive and gram negative bacteria. The main importance of the effort is it will provide synthesized and more potent stable molecule for biological response as most of coumarin derivatives has important biological activity. As we mentioned above, the significance and biological profile of this class of molecule so our continue efforts towards the synthesis of potential heterocyclic molecules.

2. EXPERIMENTAL

All chemicals and solvents were of AR grade and used without further purification and purchased from Spectrochem Pvt. Ltd., Mumbai. Melting points were taken in open capillary and are uncorrected. IR spectra were recorded on FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan), using DRS probe KBr pallet. ^{1}H-NMR spectra of the synthesized compounds were recorded on a Bruker-Avance-II (400 MHz) DMSO-*d6* solvent. Chemical shifts are expressed in terms of δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan). Physical constants of the synthesized compounds V-1a to V-1j are shown in Table 1. The method for the synthesis is described in the Experimental section.

2.1. Synthesis of 2,2'-((4-nitronaphthalen-1-yl)azanediyl) diethanol (Int a)

N,N-bis ethanolamine (350 m mole) were added in RBF containing 1-bromo-4-nitronaphthalene (300 m mole) and heated for 6-8 hr. at 90°C. After the end of the reaction, the reaction mixture was cooled to room temperature and poured in to crushed ice. Separated solid was filtered and wash with water and dried to afford int-a. This compound was used in next step not including further purification.

2.2. Synthesis of N,N-bis(2-chloroethyl)-4-nitronaphthalen-1-amine (Int-b)

Thionyl chloride (250 m mole) was added drop wise to a well stirred and cooled solution of 2,2'-((4-nitrophenyl)azanediyl)diethanol (200 m mole) in 50 ml DMF. After addition Reaction mixture was heated at 70-80°C for 3hr. After the completion of reaction, mixture was poured in to ice. Separated solid was filtered, washed with water and dried to afford Int-b.

2.3. Synthesis of N1, N1-bis(2-chloroethyl) naphthalene-1,4-diamine (Int-c)

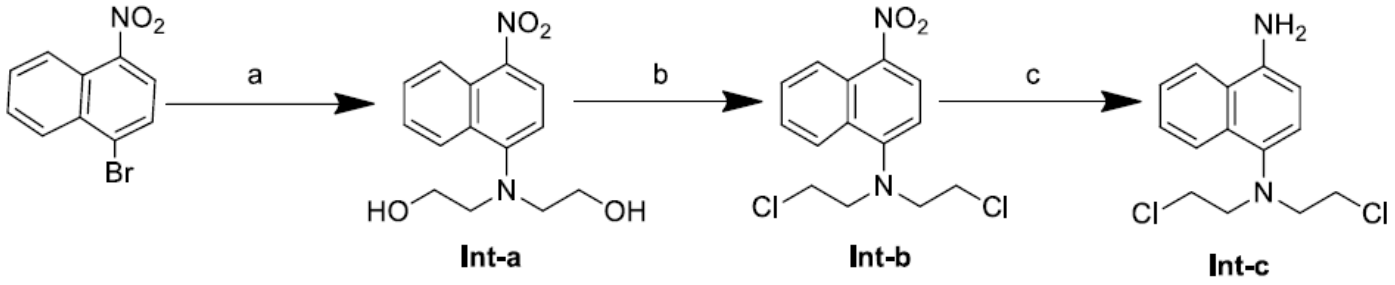
Tin metal (200 m mole) was added in the mixture of Int-b (50 m mole) and 50 ml con. HCl at room temperature in RBF. Then the reaction mixture was refluxed for 6 hr till the all tin metal desolved and clear solution obtained. After completion of the Reaction, mixture was filtered off and basified with NaOH solution by keeping temperature below 10°C. After neutralization, solution was extracted with ethyl acetate. After separated organic layer, combined organic layer was dried over sodium sulphate and acidified with ethyl acetate HCl. Precipitated hydrochloride salt was filtered and washed with ethyl acetate to afford Int-c.

2.4. Synthesis of 4-hydroxy coumarin(int-1)

Anhydrous zinc chloride (30 gm) which was preheated to get rid of any moisture added to Various Substituted phenols (0.1 mole), malonic acid and phosphorus oxychloride (40 ml). After the addition reaction mixture was heated on a water bath at 70°C for 8-10 hr. It was cooled and poured into ice and water to afford buff-yellow coloured solid. The solid was then filtered and washed thoroughly with water. It was then triturated with 10% sodium carbonate solution and filtered. The filtrate was gradually acidified with dilute HCl till the effervescence ceased. The product was filtered, dried and recrystallized with methanol.

2.5. Synthesis of 4-chloro-3-formayl coumarin (int-2)

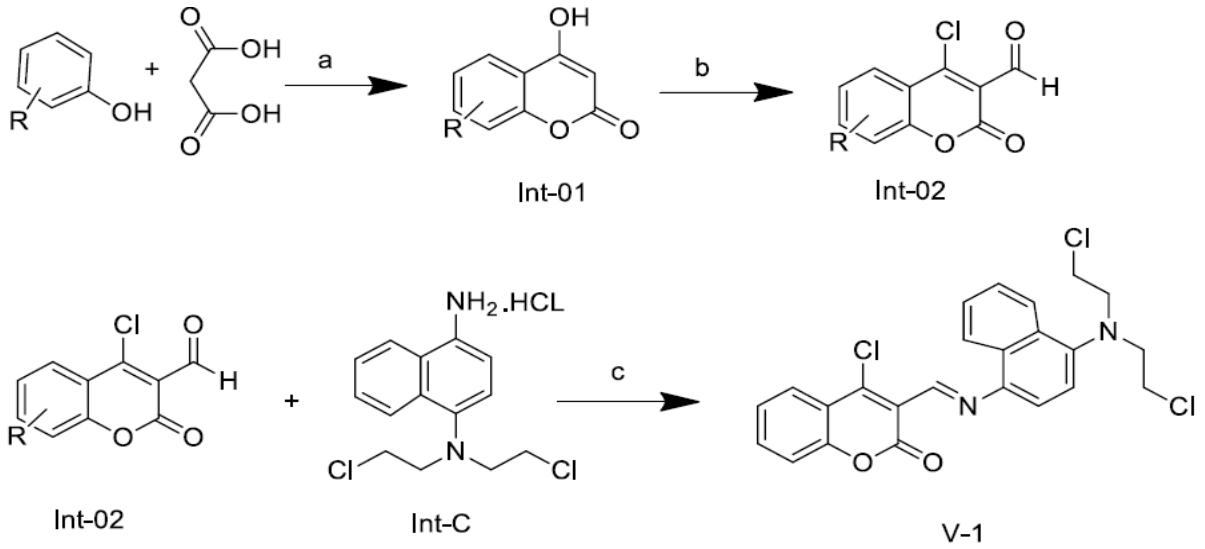
$POCl_3$ (0.18 mole) were added to a stirred mixture of 4-hydroxycoumarin (0.06 mole) in anhydrous DMF (0.6 mole) at 10°C to 5°C. The reaction mixture was allowed to stir furthermore 1 hr at room temperature and later than heated and stirred for 2 hr at 60°C. After the reaction completed, the mixture was poured on to crushed ice under vigorous and continue stirring. Separated pale yellow solid was collect by filtration and washed consecutively with Na_2CO_3 (5%) and water, and then was air–dried. Recrystallization from acetone gave 87% of 4-chloro-3-formyl coumarin (INT-2) as a pale yellow powder with m.p. 115-120°C.



Scheme 1:(a) Diethanol amine, 80°C, 6hr, (b) $SOCl_2$, DMF,70°C, 4hr (c) Sn, HCl, 90°C, Ethyl acetate

2.6. General synthesis of Schiff base of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde with naphthalen-1-amine mustard (V-1a to V-1j)

To a solution of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde (2gm, 0.0090mmole) and methanol (10 ml, 5v), Aniline mustard was added at room temperature. After addition, reaction mixture was heated at reflux temperature for 30 min. After completion of reaction, mixture was cooled. The obtained solid was filtered, wash with methanol and dried it in oven.



Scheme 2: (a) $POCl_3$, Anhy $ZnCl_2$, 80°C, 5-6hr (b)DMF, $POCl_3$, 0-60°C (c) Gly.CH_3COOH, CH_3OH

3. RESULTS AND DISCUSSION

In our present work we have prepared a series of novel (E)-3-(((4-(bis(2-chloroethyl)amino)naphthalen-1-yl) imino)methyl)-4-chloro-2H-chromen-2-one containing different coumarin derivatives by formation of Schiff base. The formation by this method was first developed by us. All synthesized compounds were obtained in good to moderate yield.

All synthesized compounds were characterized by IR, NMR and Mass spectrometry. We describe the results of antimicrobial evaluation of novel synthesized entities which shows significant biological activity. However, when comparing our results to those of older studies, it must be pointed out that biological activity can be increasing by certain groups.

Table-1: Synthesized coumarin based aniline nitrogen mustard analogues

Code	Molecular Formula	R	Molecular Weight	Melting Point °C	Yield %
V-1a	$C_{24}H_{19}Cl_3N_2O_2$	H	422	190	78
V-1b	$C_{25}H_{21}Cl_3N_2O_2$	2-CH_3	487	183	67
V-1c	$C_{25}H_{21}Cl_3N_2O_2$	3-CH_3	487	148	69
V-1d	$C_{25}H_{21}Cl_3N_2O_2$	4-CH_3	487	204	65
V-1e	$C_{26}H_{23}Cl_3N_2O_2$	2,3-diCH_3	502	174	63
V-1f	$C_{26}H_{23}Cl_3N_2O_2$	3,4-diCH_3	502	176	71
V-1g	$C_{26}H_{23}Cl_3N_2O_2$	3,5-diCH_3	502	196	64
V-1h	$C_{26}H_{23}Cl_3N_2O_2$	2,5-diCH_3	502	189	57
V-1i	$C_{24}H_{18}BrCl_3N_2O_2$	4-Br	550	192	62
V-1j	$C_{24}H_{18}Cl_3FN_2O_2$	4-F	491	214	68

3.1. (E)-3-(((4-(bis(2-chloroethyl)amino)naphtha -len-1-yl)imino)methyl)-4-chloro-2H-chromen-2-one (V-1a)

Brown solid; R_f 0.42 (8:2 MDC-hexane); **MP**190°C; ***IR (KBr, cm^{-1}):*** 3278, 1686, 1608, 1557, 1516, 1482, 1376, 1318, 1243, 1063,845, 753, 695, 625 cm^{-1}; ***^{1}H NMR δ PPM***: 8.610 to 8.340(m, 4H, Ar-H), 7.730(tri, 1H, Ar-H), 7.440(s, 2H, Ar-H), 7.085(s, 2H, Ar-H), 6.785(s, 2H, Ar-H), 6.672(s, H, -CH), 3.748(s, 8H, (-CH_2CH_2-)$_2$). ***^{13}C NMR (400 MHz, DMSO):*** 41.06, 52.08, 111.65, 114.55, 116.35, 117.35, 124.56, 125.16, 126.75, 134.10, 145.15, 151.35, 155.35. ***MS (m/z):*** 422 (M^+); Anal. Calcd for: $C_{24}H_{19}Cl_3N_2O_2$: C, 57.62; H, 4.37; Cl, 24.30; N, 6.40; Found: C, 54.12; H, 4.02; N, 9.9.

3.2. (E)-3-(((4-(bis(2-chloroethyl)amino)phenyl) imino)methyl)-4-chloro-8-methyl-2H-chromen-2-one (V-1b)

Brown solid; R_f 0.40 (8:2 MDC-hexane); **MP** 183°C; ***IR (KBr, cm^{-1}):*** 3298, 1681, 1610, 1510, 1490, 1315, 1203, 1105, 868, 787, 724, 645 cm^{-1}; ***MS (m/z):*** 436 (M^+); Anal. Calcd for: $C_{25}H_{21}Cl_3N_2O_2$: C, 57.62; H, 4.37; Cl, 24.30; N, 6.40; Found: C, 55.14; H, 4.21; N, 9.40.

3.3. (E)-3-(((4-(bis(2-chloroethyl)amino)phenyl) imino)methyl)-4-chloro-7-methyl-2H-chromen-2-one (V-1c)

Brown solid; R_f 0.46 (8:2 MDC-hexane); **MP**148°C; ***IR (KBr, cm^{-1}):*** 3295, 1685, 1605, 1515, 1315, 1205, 1105, 868, 825, 785, 725, 645 cm^{-1}; ***MS (m/z):*** 437 (M^+); Anal. Calcd for: $C_{25}H_{21}Cl_3N_2O_2$: C, 57.62; H, 4.37; Cl, 24.30; N, 6.40; Found: C, 55.14; H, 4.21; N, 9.40.

3.4. (E)-3-(((4-(bis(2-chloroethyl)amino)phenyl) imino)methyl)-4-chloro-6-methyl-2H-chromen-2-one (V-1d)

Yellowish solid; R_f 0.42 (8:2 MDC-hexane); **MP**204°C; ***IR (KBr,cm^{-1}):*** 3305, 1685, 1605, 1515, 1455, 1316, 1205, 1105, 1065, 865, 789, 725, 645 cm^{-1}; ***^{1}H NMR (δ PPM)***: 8.285(s, 4H, Ar-H), 7.556(d, J=7.0 Hz, 1H, Ar-H), 7.321(d, J=7.01 Hz, 1H, Ar-H), 7.062(d, J=6.5 Hz, 2H, Ar-H) 6.750(d, J=6.3 Hz, 2H, Ar-H), 6.650(s, H, -CH), 3.745(s, 8H, (-CH_2CH_2-)$_2$), 2.405(s, 3H, -CH_3). ***^{13}C NMR(400 MHz, DMSO):*** 20.52, 41.06, 52.13, 111.63, 114.03, 116.33, 117.10, 124. 15, 125.05, 126.78, 134.00, 134.85, 145.15, 145.37,149.38, 155.52. ***MS (m/z):*** 436 (M^+); Anal. Calcd for $C_{25}H_{21}Cl_3N_2O_2$: C, 57.62; H, 4.37; Cl, 24.30; N, 6.40; Found: C, 55.14; H, 4.21; N, 9.40

3.5. (E)-3-(((4-(bis(2-chloroethyl)amino)phenyl) imino)methyl)-4-chloro-7,8-dimethyl-2H chromen-2-one (V-1e)

Brown solid; R_f 0.44 (8:2 MDC-hexane); **MP**174°C; ***IR (KBr, cm^{-1}):*** 3307, 1677, 1607, 1536, 1487, 1336, 1207, 1106, 1066, 897, 777, 726, 648 cm^{-1}; ***^{1}H NMR (δ PPM):*** 8.161(d, J=8.2Hz, 1H, Ar-H), 7.252(d, J=8.6Hz, 1H, Ar-H), 7.053(d, J=8.3Hz, 4H, Ar-H), 6.730(d, J=8.3Hz, 2H, Ar-H), 6.672(s, H, -CH), 3.740(s, 8H, (-CH_2CH_2-)$_2$), 2.360(s, -CH_3), 2.260(s, -CH_3). ***^{13}C NMR (400 MHz, DMSO):*** 11.45, 19.93, 41.06, 52.12, 111. 66, 111.96, 115.85, 121.29, 124.39, 125.02, 125.72, 127.05, 143.52, 145. 06, 146.08, 149.29, 155.39. ***MS (m/z):*** 451 (M^+); Anal. Calcd for $C_{26}H_{23}Cl_3N_2O_2$: C, 58.49; H, 4.69; Cl, 23.54; N, 6.20; Found: C, 56.12; H, 4.54; N, 9.12.

3.6. (E)-3-(((4-(bis(2-chloroethyl)amino)phenyl) imino)methyl)-4-chloro-6,7-dimethyl-2H-chromen-2-one (V-1f)

Brown solid; R_f 0.42 (8:2 MDC-hexane); **MP** 176°C; ***IR (KBr, cm^{-1}):*** 3310, 1725, 1675, 1515, 1425, 1315, 1205, 1105, 1055, 895, 820, 789, 725, 645 cm^{-1};***^{1}HNMR (δ PPM):*** 8.165(s, 1H, Ar-H), 7.193(s, 1H, Ar-H), 7.045(s, 4H, Ar-H), 6.733(s, 2H, Ar-H), 6.67(s, H, -CH), 2.322(s, 3H, -CH_3), 2.287(s, 3H, -CH_3), 3.745(s, 8H, (-CH_2CH_2-)$_2$). ***^{13}C NMR (400 MHz, DMSO):*** 18.95, 19.56, 41.06, 52.10, 111.62, 116.01, 117.49, 124.25, 124.99, 126.87, 133.21, 144.14, 145.57, 149.59, 155.56. ***MS (m/z):*** 451 (M^+); Anal. Calcd for $C_{26}H_{23}Cl_3N_2O_2$: C, 58.49; H, 4.69; Cl, 23.54; N, 6.20; Found: C, 56.17; H, 4.59; N, 9.19.

3.7. (E)-3-(((4-(bis(2-chloroethyl)amino)phenyl) imino)methyl)-4-chloro-5,7-dimethyl-2H-chromen-2-one (V-1g)

Brown solid; R_f 0.40 (8:2 MDC-hexane); **MP** 196°C; ***IR (KBr, cm^{-1}):*** 3305, 1685, 1605, 1515, 1455, 1320, 1208, 1105, 1065, 869, 789, 725, 645 cm^{-1}; ***MS (m/z):*** 451 (M^+); Anal. Calcd for $C_{26}H_{23}Cl_3N_2O_2$:Elemental Analysis: C, 58.49; H, 4.69; Cl, 23.54; N, 6.20; O, 7.08; Found: C, 57.07; H, 5.09; N, 9.48.

3.8. (E)-3-(((4-(bis(2-chloroethyl)amino)phenyl) imino)methyl)-4-chloro-8,5-dimethyl-2H-chromen-2-one (V-1h)

Brown solid; R_f 0.41 (8:2 MDC-hexane); **MP** 189°C; ***IR (KBr, cm^{-1}):*** 3306, 1725, 1680, 1535, 1485, 1335, 1205, 1105, 1065, 895, 775, 725, 645 cm^{-1}; ***MS (m/z):*** 451 (M^+); Anal. Calcd for $C_{26}H_{23}Cl_3N_2O_2$: C, 58.49; H, 4.69; Cl, 23.54; N, 6.20; Found: C, 56.02; H, 4.37; N, 9.53.

3.9. (E)-3-(((4-(bis(2-chloroethyl)amino)phenyl) imino)methyl)-6-bromo-4-chloro-2H-chromen-2-one (V-1i)

Brown solid; R_f 0.40 (8:2 MDC-hexane); **MP** 192°C; ***IR (KBr, cm^{-1}):*** 3305, 1725, 1605, 1535, 1485, 1335, 1205, 1105, 1065, 895, 775, 725, 645 cm^{-1}; ***MS (m/z):*** 499 (M^+); Anal. Calcd $C_{24}H_{18}BrCl_3N_2O_2$: C, 47.79; H,

3.21; Br, 15.90; Cl, 21.16; N, 5.57; Found: C, 45.34; H, 3.29; N, 8.18.

3.10. *(E)-3-(((4-(bis(2-chloroethyl)amino)phenyl) imino)methyl)-4-chloro-6-fluoro-2H-chromen-2-one (V-1j)*

Brown solid; **R_f** 0.41 (8:2 MDC-hexane); **MP** 214°C; ***IR (KBr, cm^{-1}):*** 3305, 1725, 1605, 1515, 1420, 1315, 1205, 1105, 1060, 895, 820, 785, 725, 645 cm^{-1}; ***MS (m/z):*** 440 (M^+); Anal. Calcd $C_{24}H_{18}Cl_3FN_2O_2$: C, 54.38; H, 3.65; Cl, 24.08; F, 4.30; N, 6.34; Found: C, 50.10; H, 3.80; N, 6.20.

3.11. Antimicrobial activity

Antimicrobial activity of all the synthesized compound were carried out against four bacterial strain (*B. megaterium, S. typi, Micrococcus spp. and E.coli.) four fungal strain (A. niger, A. flavus, Ganoderma spp., and Penicillium spp.*) by agar cup method. The diameter of zone of inhibition of growth was measured in cm. DMSO was used as a solvent to dissolve the compound. The result includes that V-1c, V-1g, & V-1h exhibited potent antibacterial activity against *B. megaterium, S. typi, Micrococcus spp. and E.coli* Hence further investigation can be done, MIC can be identified and such compounds can further be tested and can be used as potent drug in coming time.

Table-2 Antibacterial and antifungal activity of synthesized compounds V-1a to V-1j

	V-1a	V-1b	V-1c	V-1d	V-1e	V-1f	V-1g	V-1h	V-1i	V-1j	SMCN	CFCN	NYSN
B. megaterium	1	1.4	2.2	1.8	ND	0.9	1.4	2.5	ND	1.4	3	3.8	ND
Micrococcus spp.	1.6	1.4	3.2	1.9	ND	1.2	2.2	2.7	1.7	ND	2	4	ND
S. typhi	1.9	ND	2	1.6	1.4	1.2	1.7	1.7	1.2	1.3	2	4	ND
E. Coli	ND	2	2.2	1.1	1.2	1.2	ND	2.3	1.8	1.1	3.2	3	ND
Penicillium spp.	1.2	2	2.2	0.8	0.8	ND	2.2	1.4	0.6	2.1	ND	ND	3.2
Ganoderma spp.	1.1	2.2	2.6	1.2	2.8	1.2	3.2	2.6	0.8	ND	ND	ND	4
A. niger	0.8	2.8	2.1	0.8	0.8	ND	2.6	2	1.6	2.9	ND	ND	3.5
A. flavus	0.2	2.1	3.2	ND	0.5	0.9	3.5	1.8	ND	2.7	ND	ND	3.8

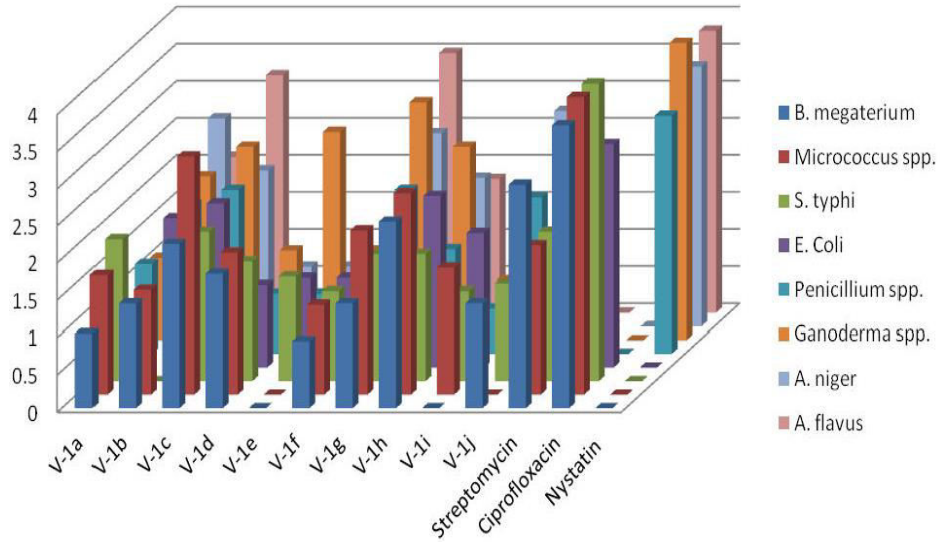


Fig. 1: Antibacterial and antifungal activity

4. CONCLUSION

From activity data we have predicted that some the synthesized compounds shows excellent drug like bioactivity. Out of all compounds some shows remarkable Antibacterial activity and antifungal activity so these compounds would be of better use in drug development against fungal infection and Antibacterial infection.

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