ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Short Communication

SYNTHESIS AND CHARACTERIZATION OF NOVEL SCHIFF BASE OF QUINOLIN ALDEHYDE WITH 4-(4-AMINOPHENYL) MORPHOLIN-3-ONE DERIVATIVES AND ITS ANTIMICROBIAL ACTIVITY

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ABSTRACT

A highly functionalized heterocyclic library were synthesized, characterized and tested for biological evaluation against bacteria and fungus. This novel synthetic rout involves Schiff base of Quinolin aldehyde with 4-(4-aminophenyl) morpholin-3-one in the presence of base and methanol as a solvent in good yield and high purity. All the synthesized compound of libraries characterized using ^{1}H NMR, Mass, and IR spectroscopic technique. Also all compound screened for antimicrobial activity against standard drugs.

Keywords: 4-(4-aminophenyl) morpholin-3-one, Antimicrobial activity, Quinolin

1. INTRODUCTION

The six membered nitrogen containing heterocycles, quinoline (benzazine or 1-azanapthalene or benzo[*b*]pyridine) **(1)** is one of the very important heterocyclic compounds featuring a nitrogen atom as part of the ring system. The quinoline nucleus constitutes an important core among pharmacologically active synthetic and natural compounds with widespread prevelance [1]. A prominent example is quinine, an alkaloid found in plants. 4-Hydroxy-2-alkylquinolines (HAQs) are involved in antibiotic resistance. Quinoline has slight solubility in cold water, complete solubility in hot water and in most organic solvents. Quinoline exhibits both electrophilic and nucleophilic substitution reactions analogous to those of pyridine and benzene. Its oral absorption and inhalation is not dangerous to human beings. Quinoline **(1)** has a property to undergo degradation in presence of micro-organisms like *Rhodococcus* species strain Q_1 [2].

Quinolines and related heterocyclic systems represent an important class of alkaloids and are also found as structural frameworks in a large number of biologically active natural products and pharmaceuticals [3]. These nitrogen-containing heterocycles possess broad applications in drug development such as treatment of MCH (Melanin Concentrating Hormone) receptor related disorder [4], cell proliferative disease [5], Melting points were taken in open capillary method and are uncorrected. IR spectra were recorded on FTIR-8400 transmissible spongiform encephalopathies [6], malignant tumor, stomach cancer, brain tumor, and large intestine cancer [7] and bacterial infections in mammals [8]. Substituted quinolines are historically among the most important antimalarial and their immense use in 20th century provided well founded hopes for malaria eradication [9]. Pharmaceutically important quinoline containing molecules such as chloroquine **(2)** and amidoquine **(3)** are found as an anti-malarial marketed drug in which a chlorine atom is attached at the C-7 position according to quinoline ring.

In the present work, we report the synthesis of Schiff base of Quinolin aldehyde with 4-(4-aminophenyl) morpholin-3-one and their antimicrobial activity against fungi, gram positive and gram negative bacteria. The main significance of the work is it will provide synthesized and more potent stable molecule for biological response as most of Quinolin derivatives has significant 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 used to synthesised library were purchased from CDH chemical, Delhi of AR grade and were used without further purification. spectrophotometer (Shimadzu, Kyoto, Japan), using DRS probe KBr pallet. 1H-NMR spectra of the synthesized

compounds were recorded on a Bruker-Avance-II (400 MHz) DMSO-*d*6 solvent.

Chemical shifts are expressed in 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 are shown in Table 1.

2.1. Synthesis of int-01

Dimethyl formamide (0.0125 mol) was charged in a three necked round bottom flask equipped with a thermometer, a dry tube and mechanical stirrer and cooled to 0°C. to it Phosphorous oxychloride (0.035 mol) was added drop wise with stirring at 0-10°C.To the solution, corresponding substituted acetanilide (0.05 mol) was added and mixture was refluxed for 3hr at 80°C.after completion reaction mass was poured into crushed ice solid separated was filtered and washed with water and re-crystalized from ethyl acetate.

2.2. Synthesis of Schiff base of 2-chloroquinolone 3-carbaldehyde with 4-(4-aminophenyl) morpholin-3-one

Into the RBF, Methanol and substituted 2-chloroquinoline 3-carbaldehyde (0.02 mol) was cooled to 0°C and 2-3 drops of glacial acetic acid was added as catalyst. To this mixture 4-(4-aminophenyl) morpholin-3-one (0.02 mol) was added and Completion of reaction was checked over TLC. After completion of the reaction, mixture was poured into crushed ice, filtered and washed with water. Crystallization from chloroform gives Schiff base Yield 68-86%.

2.3. Reaction Scheme

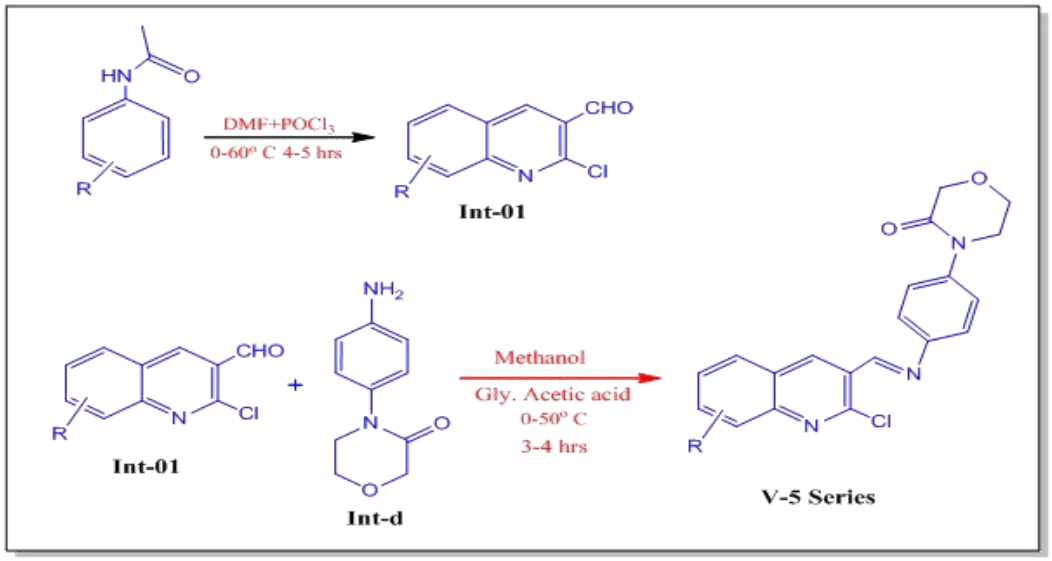

Fig.1 Reaction Scheme

3. RESULTS AND DISCUSSION

All the synthesized compounds confirmed by spectroscopic techniques such as ^{1}H- NMR and mass spectroscopy. Molecular ion peak was observed in agreement with a molecular weight of the respective compound.

3.1. Spectral data of synthesized compound (E)-4-(4-(((2-chloroquinolin-3- yl) methylene) amino) phenyl) morpholin-3-one (V-5a)

Yellow solid, Rf Value 0.44 (Ethyl acetate 8:Hexane 2), M.P-150-152°C; ***IR (KBR pallet) in cm^{-1}***, 2904.51(C-H Str. In alkane), 3058.46 (C-H Str. In aromatic), 1644.77 (C=O Str. In amide), 1124.37 (C-O Str. In ethers), 740.25 (o-disub. Aromatic), 860.22 (p-disub. Aromatic), 819.74 (C-Cl Str.); ***^{1}H NMR(CDCl$_3$) in δ ppm***: 7.30-8.10 (multiplet, 9H aromatic), 3.80-3.90 (Triplet, 2H –CH_2), 4.0-4.10 (Triplet, 2H –CH_2), 4.40 (Singlet, 2H –CH_2); ***MS (m/z):*** 365 (M^+); Anal. calculated for Molecular formula $C_{20}H_{16}ClN_3O_2$ is C; 65.67%, H; 4.41%, N; 11.49 % found C; 65.62%, H; 4.35%, N; 11.44 %

3.2.(E)-4[-(4-(((6-bromo-2-chloroquinolin-3-yl)methylene)amino)phenyl)morpholin-3-one(V-5b)

Yellow solid, Rf Value 0.40 (Ethyl Acetate : Hexane-(8:2), M.P-168-170°C; ***IR (KBR pallet) in cm^{-1}***, 2965.22(C-H Str. In alkane), 3032.56 (C-H Str. In aromatic), 1648.15 (C=O Str. In amide), 1118.13 (C-O Str. In ethers), 735.15 (o-disub. Aromatic), 850.69 (p-disub. Aromatic), 811.04 (C-Cl Str.), 695.22 (C-Br Str.) ***^{1}H NMR (CDCl$_3$) in δ ppm***: 7.20-8.10 (multiplet, 8H aromatic), 3.60-3.80 (Triplet, 2H –CH_2), 4.0-4.20 (Triplet, 2H –CH_2), 4.30 (Singlet, 2H –CH_2); ***MS (m/z)***: 444 (M^+); Anal. calculated for Molecular formula $C_{20}H_{15}BrClN_3O_2$ is C; 54.02%, H; 3.40%, N; 9.45% found C; 54.00%, H; 3.35%, N; 9.41%.

Table 1: Physical constant of synthesized library

Code	Molecular formula	Substitution	Molecular Weight	M.P. °C	Percentage of Yield
V-5a	$C_{20}H_{16}ClN_3O_2$	H	365	150-152	72
V-5b	$C_{20}H_{15}BrClN_3O_2$	4-Br	444	168-170	85
V-5c	$C_{20}H_{15}Cl_2N_3O_2$	4-Cl	400	144-146	69
V-5d	$C_{21}H_{18}ClN_3O_3$	4-OMe	395	164-166	81
V-5e	$C_{21}H_{18}ClN_3O_2$	4-Me	379	178-180	88
V-5f	$C_{22}H_{20}ClN_3O_2$	2,4- Di Me	393	182-184	73
V-5g	$C_{20}H_{15}ClN_4O_4$	4-NO_2	410	154-156	76
V-5h	$C_{20}H_{15}C_{l2}N_3O_2$	2-Cl	400	146-148	79
V-5i	$C_{21}H_{18}ClN_3O_2$	2-Me	379	182-184	84
V-5j	$C_{21}H_{18}ClN_3O_3$	2-OMe	395	186-188	80

Antimicrobial activity is the process of killing or inhibiting the pathogenic microbes causing disease [10]. An antimicrobial is an agent that kills microorganisms or stops their growth [11]. Antimicrobial can be anti-bacterial, anti-fungal or antiviral [12]. Agents that kill microbes are called microbicidal, while those that inhibit their growth are called microbistatic [13]. All agents have different modes of action by which they act against infection. The use of antimicrobial medicines to treat infection is known as antimicrobial chemotherapy.

In our current study antibacterial and antifungal activity was tested by standard agar cup method [14]. All the synthesized compound were tested for their in vitro antimicrobial activity against Gram +*ve (Bacillus megaterium, Micrococcus spp.*), Gram -*ve (E.coli, S. typi) and fungal spps. (Ganoderma spp., A. niger, A. flavus and Penicillium spp.*), taking streptomycin, ciprofloxacin, and nystatin as standard drugs. Suspension of 24 to 48 hrs grown fresh bacteria and fungal culture was prepared in N- broth and potato dextrose broth respectively. All the bacterial and fungal suspension was equally spreaded on to the sterile Muller Hinton and PDA plates respectively with the help of sterile swabs. Wells were made in the plates (1 cm) with the help of sterile cork borer.

The standard antibiotics were dissolved in sterile distilled water to make the final concentration of 200µg/ml.

The synthesized compounds to be tested were dissolved in DMSO up to the final concentration of 1 mg/ml and 0.1 ml of it was loaded in the well. The plate was incubated at 4°C for 20 minutes for proper diffusion of compound in agar and then the plates were incubated in upward position for 24 hrs at 37°C for bacterial culture and 48 hrs at 25°C for fungal cultures. The control activity against DMSO was also performed. After incubation zone of inhibition was observed and measured.

Antimicrobial activity of all the compounds 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 it show in fig. 2 **V-5c** and **V-5d** 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

	V-5a	V-5b	V-5c	V-5d	V-5e	V-5f	V-5g	V-5h	V-5i	V-5j	Streptomycin	Ciprofloxacin	Nystatin
B. megaterium	ND	1.2	ND	1.8	2.6	1.1	2	1.1	0.2	1.1	3	3.8	ND
Micrococcus spp.	1.5	1.4	ND	2.3	0.8	1.2	2	2.1	1.4	ND	2	4	ND
S. typhi	1.1	1.8	0.5	1.1	ND	1.2	1.4	1.7	1.2	1.4	2	4	ND
E. Coli	ND	ND	1	2.8	1.5	1.2	2.2	ND	ND	1	3.2	3	ND
Penicillium spp.	1.4	1.9	2.1	2.4	1.7	ND	1.4	ND	0.7	2	ND	ND	3.2
Ganoderma spp.	ND	1.3	2.2	3.2	0.1	1.3	3	1.4	0.5	2	ND	ND	4
A. niger	1.3	2	1.8	1.9	0.3	0.8	2.8	2	1.3	ND	ND	ND	3.5
A. flavus	0.9	0.9	3.7	1.8	1	2	3.1	3.2	ND	1.4	ND	ND	3.8

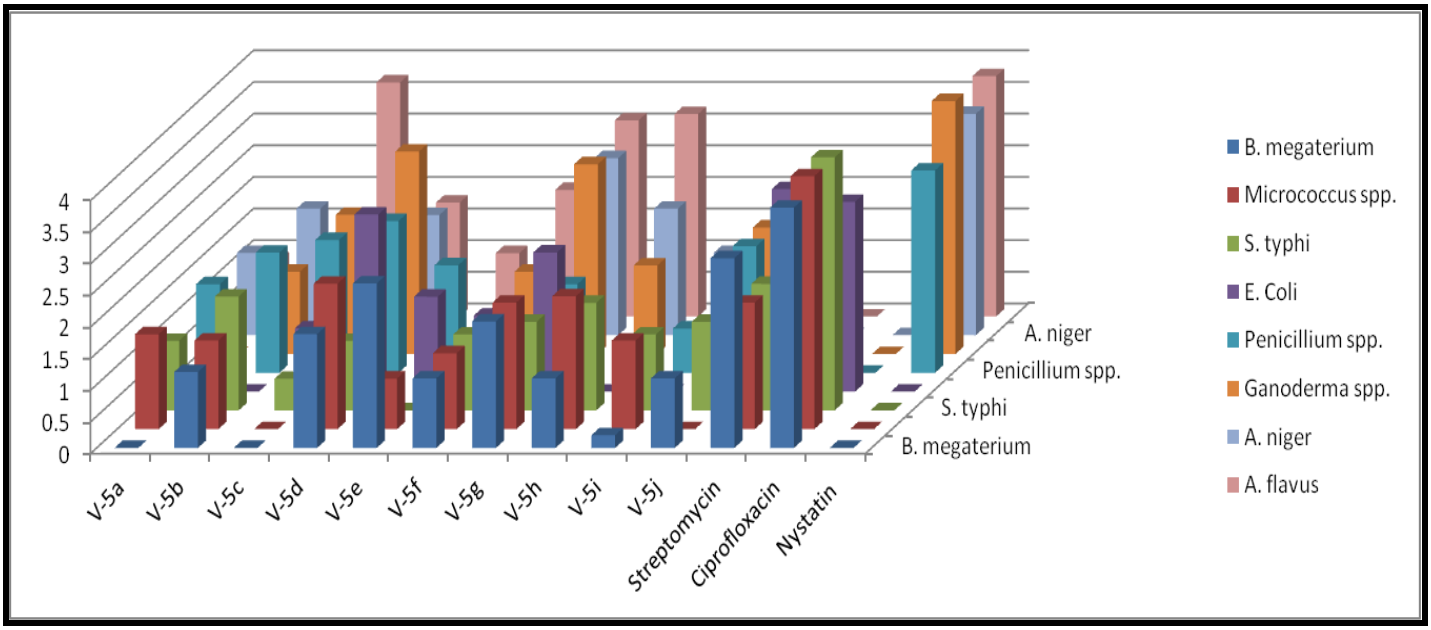

Fig.2: Chart of Antibacterial and antifungal activity

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.

Acknowledgement: None

Conflict of Interest: None declared

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