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SYNTHESIS AND CHARACTERIZATION OF NOVEL SULFONAMIDES DERIVATIVES OF 4-(4-AMINOPHENYL)MORPHOLIN-3-ONE AND ITS ANTIMICROBIAL ACTIVITY

AHIR VALJI MAHADEVABHAI

Dr. KRUSHNAKUMAR J. JILARIYA

Assistant professor GES - II ,

R.R.LALAN COLLAGE - BHUJ

Abstract

A highly functionalized heterocyclic library were synthesized, characterized and tested for biological evaluation against bacteria and fungus. This novel synthetic rout involves sulfonamides derivatives of 4-(4-aminophenyl)morpholin-3-one 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

1. Introduction.

Sulfonamides constitute an important class of antimicrobial agents in the world owing to their low cost, low toxicity, and excellent activity against bacterial diseases. Sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthase in bacteria, and catalyze the conversion of p-aminobenzoic acid into an essential nutrient for some bacteria[1]. After the introduction of penicillin and other antibiotics, the popularity of sulfonamides decreased. However, they are still considered to be useful in certain therapeutic fields, especially in the case of ophthalmic infection in urinary and gastrointestinal tract. Besides, sulfa drugs are till today among the drugs of first selection (together with ampicillin and gentamycin) as chemotherapeutic agents in bacterial infections by E. coli in human. The potentially active sulfonamide derivatives deserve more detailed experimental and systematic theoretical studies using updated computer programs and recently available knowledge on structure activity relations.

The sulfonamide functionality is much more widespread in pharmaceuticals than just in an early class of antibiotics. Sulfonamides have been the subject of pharmaceutical interest as a result of their potent biological activities[2-6]

In the present work, we report the synthesis of sulfonamides derivatives of 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 sulfonamides derivatives has significant biological activity.

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. Melting points were taken in open capillary method and are uncorrected. IR spectra were recorded on FTIR-8400 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.

General Procedure for the synthesis of INT-01

To a previous cooled solution of Chlorosulphonic acid (0.02 mol), Substituted aromatic compounds (0.01mol) was added in portion wise. Further allowed to stir at room temperature for 3 hrs. carefully poured reaction mass in to crushed ice after completion of the reaction. Filter the reaction and wash with water to yield INT-01

General synthesis of V-1

In to a 100ml RBF DMF and K_2CO_3 (0.01 mol) was stirred at room temperature. To this Product of INT-01(0.01 mol) was added portion wise and allow to stir for further 3 hr. completion of reaction was checked on TLC. After completion of the reaction, reaction mass was poured into crushed ice and filter the separated product. Wash with water to yield INT-01

3. Reaction Scheme

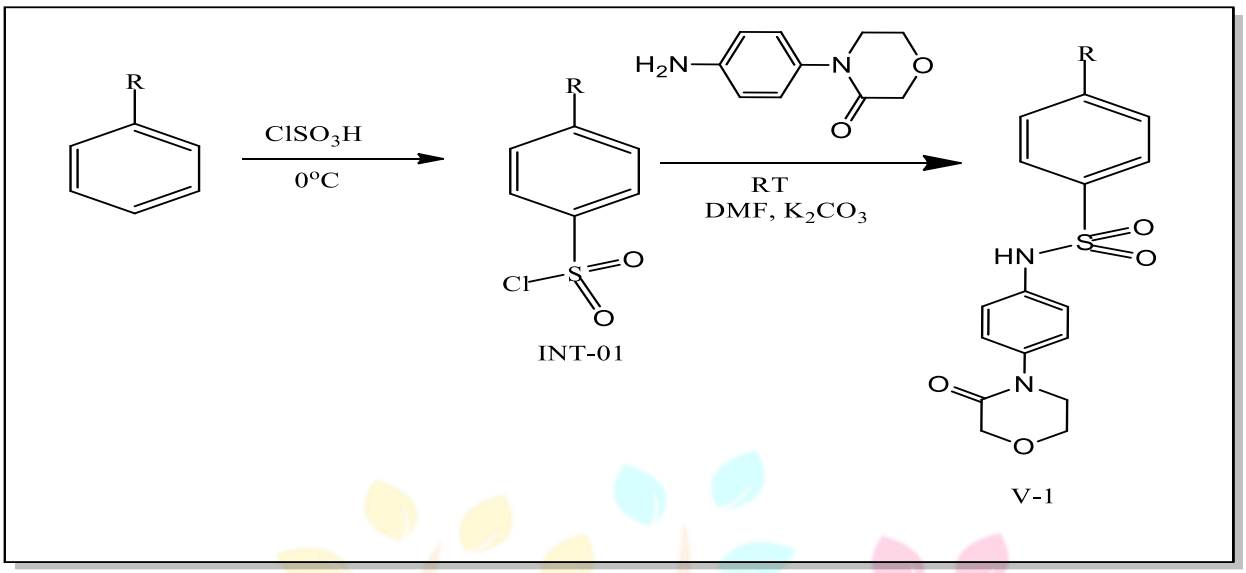

Fig.1 Reaction Scheme

Table-1 physical constant of synthesized library

Code	Molecular formula	Substitution	Molecular Weight	M.P. ^{0}C	Percentage of Yield
V-1a	$C_{17}H_{16}N_2O_7S$	3-COOH,4-OH	392	224-226	82
V-1b	$C_{18}H_{19}N_3O_5S$	4-NHCOMe	389	200-202	70
V-1c	$C_{17}H_{18}N_2O_4S$	4-Me	346	210-212	94
V-1d	$C_{17}H_{18}N_2O_5S$	4-OMe	362	214-216	86
V-1e	$C_{16}H_{15}ClN_2O_4S$	4-Cl	366	206-208	90
V-1f	$C_{19}H_{20}N_2O_7S$	4-COOMe,4-OMe	420	222-224	88
V-1g	$C_{16}H_{15}BrN_2O_4S$	4-Br	409	196-198	84
V-1h	$C_{17}H_{17}N_3O_6S$	2-Me, 5-NO_2	391	184-186	92
V-1i	$C_{18}H_{18}N_2O_6S$	4-OCOMe	390	208-210	90
V-1j	$C_{16}H_{14}ClN_3O_6S$	2-Cl, 5-NO_2	411	192-194	84

4. Spectral data of synthesized compound

2-hydroxy-5-(N-(4-(3-oxomorpholino)phenyl)sulfamoyl)benzoic acid (V-1a)

White solid, Rf Value 0.46 (Ethyl acetate 8:Hexane 2), M.P-224-226^{0}C

IR (KBr pallet) in CM^-, 3045.58 (C-H Str. In aromatic), 2829.31 (C-H Str. In aliphatic), 1644.42 (C=O Str. In amide), 3292.85 (O-H Str. In acid), 3227.42 (O-H Str. In phenol), 2967.45 (N-H Str. In sulphonamide), 1592.02 (C=C Str. In aromatic), 829.22 (p-disub. in Aromatic), 732.77 (o-disub. In aromatic), 1119.17 (C-O Str. In ethers), 1385.21 (S=O Str. In Sulphonamide)

^{1}H NMR($CDCl_3$) in δ_{PPM}: 10.30 (Singlet,1H of –COOH) 3.90 (Singlet, 1H of -OH) 7.10-8.20 (multiplet, 8H aromatic), 3.6-3.7 (Triplet, 2H –CH_2), 3.9-4.0 (Triplet, 2H –CH_2), 4.10-4.20 (Singlet, 2H –CH_2), 2.2-2.4 (Singlet, 1H of -NH)

MS (m/z): 392(M^+)

Ana.calculated for Molecular formula $C_{17}H_{16}N_2O_7S$ is C; 52.04%, H; 4.11%, N; 7.14% found C; 52.30%, H; 4.32%, N; 7.28%

N-(4-(N-(4-(3-oxomorpholino)phenyl)sulfamoyl)phenyl)acetamide (V-1b)

White solid, Rf Value 0.42 (Ethyl acetate 8:Hexane 2), M.P-200-202^{0}C

IR (KBr pallet) in CM^- : 3283.28 (N-H Str. of amide), 3155.51 (C-H Str. In aromatic), 2983.51 (N-H Str. Of sulfonamide), 2899.03 (C-H Str. Of aliphatic), 1686.73 (C=O Str. Of amide),
1599.54, 1520.73 & 1456.30 (C=C Str. of aromatic), 1199.93 (C-O Str. of ether), 825.81 (p-disub. in Aromatic)

^{1}H NMR($CDCl_3$) in δ_{PPM}: 7.07-7.71 (multiplet, 8H aromatic), 3.62-3.64 (Triplet, 2H $–CH_2$), 3.90-3.92 (Triplet, 2H $–CH_2$), 4.14 (Singlet, 2H $–CH_2$)

MS (m/z): 389(M^+)

Ana.calculated for Molecular formula $C_{18}H_{19}N_3O_5S$ is C; 55.52%, H; 4.92%, N; 10.79% found C; 55.59%, H; 4.96%, N; 10.90%

5. Antimicrobial activity:

Antimicrobial activity is the process of killing or inhibiting the pathogenic microbes causing disease[7]. An antimicrobial is an agent that kills microorganisms or stops their growth[8]. Antimicrobial can be anti-bacterial, anti-fungal or antiviral[9]. Agents that kill microbes are called microbicidal, while those that inhibit their growth are called microbistatic[10]. 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[11]. 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 bacterial 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.

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	Streptomycin	Ciprofloxacin	Nystatin
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

6. Conclusion

We have prepared a library of novel 4-(4-aminophenyl) morpholin-3-one containing different Sulfonamides derivatives. 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.

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 **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.

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