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Research Article

Microwave-assisted synthesis and biological screening of some novel phenyl Morpholine Benzene sulfonamide schiff bases.

Loganathan velupillai[1], Prashant P Dixit[2], M.S. Shingare[1], Choudhari B R[3] and D.V.Mane*[1].

[1] Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India- 431004.

[2] Department of Microbiology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Sub campus, Osmanabad, Maharashtra, India- 413501.

[3] Department of Chemistry, Jaihind College, Dhule, Maharastra, India-424002.

ABSTRACT

A new effective approach to the synthesis of novel schiff base compounds (9 E – 9 M) of 2-amino-*N*-[4-(morpholin-4-yl) phenyl]benzenesulfonamide have been synthesized from commercially available 1-Chloro-4-nitrobenzene as a starting material. The reaction conducted with help of microwave irradiated organic synthesis. The Schiff base formation reaction consumes 12-18 hour in normal conventional heating methods, but using microwave irradiation the reaction was more fast and dramatically reducing the time 4–6 min. The more yield and good quality of the synthesized product was shows that there is no side reaction and by product while the organic synthesis. The structure confirmation of the synthesized molecules was confirmed by means of proton nuclear magnetic resonance spectroscopy and LC-MS spectroscopy. The synthesized NCE's were further tested for their antibacterial and antifungal studies. Some of the molecules were identified to show better antibacterial and antifulgul activity.

Keywords: Benzenesulfonamide, Schiff base, Microwave, Antibacterial, Antifungal Activity.

INTRODUCTION

The use of microwave irradiation[1-5] for the synthesis of organic compounds showed to be a simple & efficient, low pollution, simple work-up, safe, eco-friendly technique, with shorter reaction time and high yields. Additionally, Microwave synthesis gives organic chemists more time to expand their scientific creativity in medicinal chemistry. Instead of spending hours or even days synthesizing a single compound, chemists can now perform that same reaction in minutes.

Microwave oven is a tool for synthetic chemistry for rapid growing medicinal research field. Since the first studies of microwave assisted synthesis in 1986. As a result, modern scientific microwave apparatus is the ability to control reaction conditions very specifically, monitoring temperature, pressure and reaction times. Several methods have been developed for performing reactions using microwaves including solvent free conditions. In case the reaction conducted in a solvent, the media should have high dielectric constant which to take advantage effect on micro wave heating reaction. To this conclusion, solvents like ethanol (ϵ=24.3) were employed as better solvent for conducting the reaction. Microwave

irradiation has been used extensively and successfully with homogeneous solution-phase reactions include standard organic reactions in which all reagents are dissolved in the solvent [6].

Hugo Schiff was discovered the Schiff base [7], Schiff base is the compound which containing an azomethazine (imine) group (-CH=N-) in their structure, these are usually resulted by reacting primary amine with active carbonyl compound [8]. The presence of Schiff bases in chemical moiety are produces better biological activity. Sulfonamides are compound contain sulfur in a (-SO_2NH-) moiety directly attached to a benzene ring. The sulfonamide drugs were developed in 1930 for effective medications against the bacterial infections. It seems as miracle drug at a time of large number of people dead because of common[9] bacterial disease like pneumonia and blood poisoning. The sulfonamide derivatives widely used in variety of biological actions[10], including for antibacterial, antitumour, diuretic and antithyroid activities. From these ideas it is well known that the introduction of azomethine (imine) and sulfonamide functional group into organic molecule causes dramatic changes in its biological profile.

The heterocyclic compounds like morpholine[11] and fused ring morphline[12-15] are very essential building blocks in medicinal chemistry[16] field. So the morpholine derivatives are extensively very important in the new drug discovery research, which induce research activity in the field of the broad spectrum of biological activity [17] study. The different literature survey says that the molecule containing the morpholine moiety shows better biological profile in verity of therapeutic field like antiviral, antimicrobial, antimalarial, antibacterial[18], anticancer, antifungal[19], anti-Inflammatory, antidiabetic etc.

The present paper, reports the remarkable fast synthesis method of Schiff base formation in presence of ethanol as solvent under microwave irradiation. The synthesis were carried out by the simple mixing of equimolar amounts of 2-amino-*N*-[4-(morpholin-4-yl) phenyl]benzenesulfonamide and aldehyde in minimum quantity of ethanol (2 volume), were irradiated in a microwave oven at 320W for 4–6 min at 65°C. The results were summarized in Table-1. Their characterization was done by spectroscopic methods like ^{1}HNMR and mass spectral data. Further, antibacterial and antifungal activities of these derivatives have been studied, the results were summarized in Table-2.

MATERIALS AND METHODS

All the reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as necessary. The moiety 4-Nitrochlorobenzene [20-25] is commercially available and is also in Sigma Aldrich. This can be also synthesized as per reported literature. Melting points were recorded on open capillary melting point apparatus and are uncorrected. Mass spectra were recorded on 'LCMS-QP2010s' instrument by direct injection method. Nuclear Magnetic Resonance spectra (^{1}HNMR) Were recorded in DMSO-d_6 & $CDCl_3$ on Bruker advance spectrometer at 400MHz using Tetramethylsilane (TMS) as internal standard and the chemical shift (δ) are reported in parts per million. The purity of the synthesized compounds was checked by Thin Layer Chromatography, Merck pre-coated plates (silica gel 60 F254) were visualized with UV light. Fungus Culture: Candida sp. Gram-positive microorganisms: Staphylococcus aureus, Staphylococcus albus, Streptococcus faecalis, Bacillus sp and Gram-negative microorganisms: Klebsiella pnuemoniae, Escherichia coli, Pseudomonas sp, Proteus sp were used for biological activity.

Antimicrobial Activity: The antimicrobial activity of all synthesized compounds (9 E- 9 M) was examined by standard literature procedure using agar diffusion method by finding the zone of inhibition of the drug sample against the standard drugs. Compounds were taken as test samples along with a standard drug Ciprofloxacin sample. 10 mg of each test compound was dissolved in 1 ml of Dimethylsulphoxide for preparing stock solution of standard drugs. The organisms employed in the in vitro testing of the compounds were gram-positive and gram-negative. Procedure for the preparation of inoculum for all the organisms was same. The inoculum was prepared from a 24-hours old growth of organism on Nutrient agar slant. With the help of sterile nichrome wire loop, the growth of the organism on slant was aseptically transferred to a tube containing sterile distilled water. The contents of the tube were then shaken properly so as to get uniform cell suspension of the organism. Optical density the innoculum was adjusted to 0.6 on the photoelectric colorimeter by using sterile distilled water, before using it as an inoculum.

The medium, 1.5 g of Nutrient agar (Microbiology grade, Hi Media) was dissolved in 100 ml of sterile distilled water. 3 g of Poloxomer 182 was added as a surfactant to the media to prevent the drug precipitation. 20 ml of this stock solution was

transferred to each Petri plate. On to each Petri plate containing 20 ml of sterile Nutrient agar 0.1 ml of an authentic culture (corresponding to 5 X 10^{15} CFU/ml.) of test organisms was spread. Four bore wells were bored on each Petri plate and 5-20 µl of the stock solution was added to it. This corresponds to concentration range of 30 µg/ml of the test compound. The tests were carried out in duplicate. Apart from putting the controls of standard drug (Ciprofloxacin), controls with dimethylsulphoxide (positive control) and without dimethylsulphoxide (negative control) were also included in the test. The Petri plates were put in the dark conditions at 37^0C for 24 hours. At the end of incubation period, the results were interpreted by finding the zone of inhibition.

Antifungal Activity: The antifungal activity of all synthesized compounds (9 E- 9 M) screened against Candida sp in dimethylsulfoxide. Fluconazole was employed as standard drug during the test procedures as references. 10 mg of each test compound was dissolved in 1 ml of Dimethylsulphoxide. 3 gm of Saboraud`s dextrose agar (microbiology grade, Hi Media LABORATORY) was dissolved in 100 ml of sterile distilled water. 3 g of Poloxomer 182 was added as a surfactant to the media to prevent the drug precipitation.

On to each Petri plate containing 20 ml of sterile Saboraud`s dextrose agar (microbiology grade, Hi Media LABORATORY) 0.1 ml of an authentic culture (corresponding to 5 X 10^{15} CFU/ml.) of test organisms was spread. Four bore wells were bored on each Petri plate and 5-20 µl of the stock solution was added to it. This corresponds to concentration range of 30 µg/ml of the test compound. The tests were carried out in duplicate. Apart from putting the controls of standard drug (Fuconazole), controls with dimethyl sulphoxide (positive control) and without dimethyl sulphoxide (negative control) were also included in the test. The test tubes were put in the dark conditions at room temperature for 48 hours. At the end of incubation period, the results were interpreted by finding the zone of inhibition.

Preparation of 4-Morpholinonitrobenzene (A): The 4-Nitrochlorobenzene (8g, 50mmole) was added to the solution of Morpholine (5.3g, 60mmole), Triethylamine (7.7g, 76mmole) in Chloroform (80ml) and the mixture was stirred for 16 hr at reflux. After completion of reaction, the solution was evaporated in vacuum and the residue was suspended in water (80ml). Stirred for 2hr at room temperature. Filtered and washed with water (16ml), after drying yielded the titled product (A) as yellow color solid.

EXPERIMENTAL

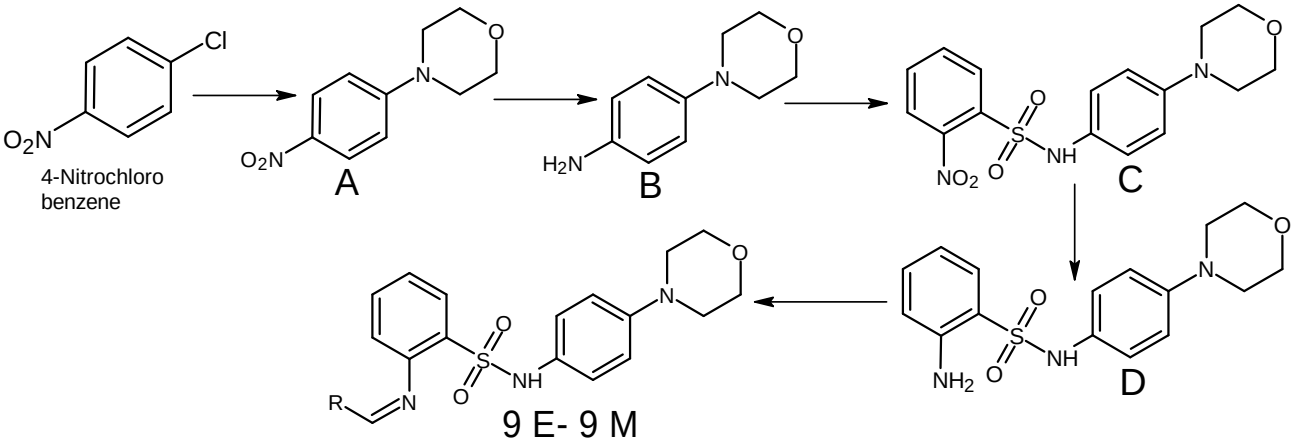
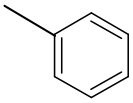
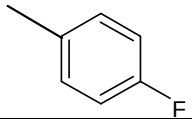
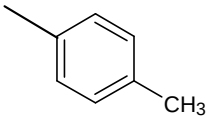
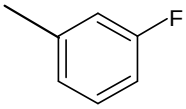
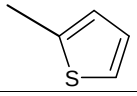
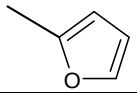
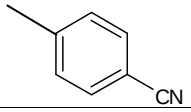
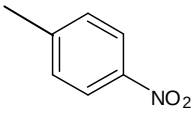
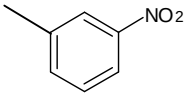


Figure 1: Synthesis of 2-amino-*N*-[4-(morpholin-4-yl) phenyl] benzenesulfonamide and their derivatives.

Table 1
Physical data of synthesized compounds (9 E – 9 M).

S.No	Code	-R	Molecular Formula	M.wt	M.P (°C)	% Yield
1	9 E		$C_{23}H_{23}N_3O_3S$	421.51	186-189	91
2	9 F		$C_{23}H_{22}FN_3O_3S$	439.50	192-195	94
3	9 G		$C_{24}H_{25}N_3O_3S$	435.53	177-180	89
4	9 H		$C_{23}H_{22}FN_3O_3S$	439.50	184-187	93
5	9 I		$C_{21}H_{21}N_3O_3S_2$	427.53	201-204	86
6	9 J		$C_{21}H_{21}N_3O_4S$	411.47	194-197	91
7	9 K		$C_{24}H_{22}N_4O_3S$	446.52	181-184	95
8	9 L		$C_{23}H_{22}N_4O_5S$	466.51	213-216	96
9	9 M		$C_{23}H_{22}N_4O_5S$	466.51	202-205	87

Preparation of *N*-[4-(morpholin-4-yl)phenyl]-2-nitrobenzenesulfonamide (C): The 2-Nitrobenzenesulfonyl Chloride (10.4g, 46mmole) in Dichloromethane (40ml) was added to the solution of compound (B) (8g, 44mmole), Triethylamine (5.9g, 58mmole) in Dichloromehane (40ml) at 0°C and the mixture was stirred for 1hr at 0°C. After completion of reaction, the solution was evaporated in vacuum and the residue was suspended in water (80ml). Stirred for 2hr at room temperature. Filtered and washed with water (16ml), after drying yielded the titled product (C) as white color solid.

Preparation of 2-amino-*N*-[4-(morpholin-4-yl)phenyl]benzenesulfonamide (D): The N,N-Dimethylformamide (40ml), Dichloromethane (40ml), compound (C) (10g, 27mmole) and 10% palladium on carbon catalyst (2g) was charged into the hydrogenation parr shaker reactor, 30 PSI hydrogen gas pressure applied and the mixture was stirred for 5 hr at room temperature. After completion of reaction, the reaction mass filtered through celited bed washed with Dichloromethane (20ml). The filtrate was evaporated under vacuum and the residue was suspended in Diethylether (80ml). Stirred for 2hr at room temperature. Filtered and washed with

diethylether (20ml), after drying yielded the titled product (D) as white color solid.

General method for the synthesis of compounds (9 E – 9 M): The equimolar amounts of compound (D) (1mol.Eq) and benzaldehyde (1mol.Eq) in minimum quantity of ethanol (2volume) were taken in small single neck round bottom flask. The reaction mixture was irradiated at 320W for 4–6 min in microwave at 65°C. The progress of reaction was monitored on TLC. After completion of reaction, allowed to cool, the crude solid product was collected through filtration and washed ethanol then dried using a vacuum. The product was re-dissolved in ethanol for recrystallization and after drying yielded the titled product (9 E – 9 M) as white color solid.

RESULTS AND DISCUSSION

The results are obtained from various spectral data are results discussed below.

4-Morpholinonitrobenzene (A): Yellow color solid; Yield 96%; M.W: 208.2; Mol. For: $C_{10}H_{12}N_2O_3$; LC-MS (m/z): 209.2 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 8.05 (2H, d, J=9.2 Hz), 7.04 (2H, d, J=9.2 Hz), 3.73 (4H, t, J=5.6 Hz), 3.41 (4H, t, J=5.2 Hz).

4-Morpholinoaniline (B): Brown solid; Yield 98%; M.W: 178.23; Mol. For: $C_{10}H_{14}N_2O$; LC-MS (m/z): 179.2 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 6.68 (2H, d, J=8.4 Hz), 6.49 (2H, d, J=8.4 Hz), 4.56 (2H, s), 3.69 (4H, t, J=4.8 Hz), 2.86 (4H, t, J=4.4 Hz).

***N*-[4-(morpholin-4-yl)phenyl]-2-nitrobenzenesulfonamide (C):** white color solid; Yield 91%; M.W: 363.3; Mol. For: $C_{16}H_{17}N_3O_5S$; LC-MS (m/z): 364.2 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 10.23 (1H, s), 7.78-7.95 (4H, m), 6.97 (2H, d, J=8.8 Hz), 6.83 (2H, d, J=9.2 Hz), 3.68 (4H, t, J=5.2 Hz), 3.01 (4H, t, J=4.4 Hz).

2-amino-*N*-[4-(morpholin-4-yl)phenyl]benzenesulfonamide (D): white color solid; Yield 96%; M.W: 333.40; Mol. For: $C_{16}H_{19}N_3O_3S$; LC-MS (m/z): 334.2 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 9.74 (1H, s), 7.37 (1H, d, J=6.4 Hz), 7.18 (1H, d, J=7.6 Hz), 6.90 (2H, d, J=9.2 Hz), 6.72-6.78 (3H, m), 6.50 (1H, t, J=7.2 Hz), 5.93 (2H, s), 3.67 (4H, t, J=4.8 Hz), 2.98 (4H, t, J=4.8 Hz).

***N*-(4-morpholinophenyl)-2-[benzylideneamino]benzenesulfonamide (9 E):** white color solid; Yield 91%; M.W: 421.51; Mol. For: $C_{23}H_{23}N_3O_3S$; LC-MS (m/z): 322.3 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 7.81 (1H, s), 7.30-7.54 (6H, m), 7.12-7.15 (1H, m), 6.69-6.89 (4H, m), 6.56 (1H, m), 3.65 (4H, t, J=4.8 Hz), 3.00 (4H, t, J=4.4 Hz).

***N*-(4-morpholinophenyl)-2-[(4-fluorobenzylidene)amino]benzenesulfonamide (9 F):** white color solid; Yield 94%; M.W: 439.50; Mol. For: $C_{23}H_{22}FN_3O_3S$; LC-MS (m/z): 440.4 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 8.15 (1H, s), 7.11-7.81 (7H, m), 6.57-6.96 (5H, m), 3.66 (4H, s), 3.01 (4H, s).

***N*-(4-morpholinophenyl)-2-[(4-methylbenzylidene)amino]benzenesulfonamide (9 G):** white color solid; Yield 89%; M.W: 435.5; Mol. For: $C_{24}H_{25}N_3O_3S$; LC-MS (m/z): 436.4 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 9.95 (1H, s), 7.07-7.74 (8H, m), 6.50-6.84 (5H, m), 3.64 (4H, s), 2.99 (4H, s), 2.23 (3H, s).

***N*-(4-morpholinophenyl)-2-[(3-fluorobenzylidene)amino]benzenesulfonamide (9 H):** white color solid; Yield 93%; M.W: 439.50; Mol. For: $C_{23}H_{22}FN_3O_3S$; LC-MS (m/z): 440.3 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 7.84 (1H, s), 7.07-7.54 (7H, m), 6.59-6.90 (6H, m), 3.66 (4H, t, J=4.8 Hz), 3.02 (4H, t, J=4.8 Hz).

***N*-(4-morpholinophenyl)-2-[(thiophen-2-ylmethylidene)amino]benzenesulfonamide (9 I):** white color solid; Yield 86%; M.W: 427.53; Mol. For: $C_{21}H_{21}N_3O_3S_2$; LC-MS (m/z): 428.3 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 8.79 (1H, s), 6.74-7.95 (12H, m), 3.66 (4H, s), 2.96-3.04 (4H, m).

***N*-(4-morpholinophenyl)-2-[(furan-2-ylmethylidene)amino]benzenesulfonamide (9 J):** white color solid; Yield 91%; M.W: 411.47; Mol. For: $C_{21}H_{21}N_3O_4S$; LC-MS (m/z): 412.3 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 8.95 (1H, s), 8.41 (1H, s), 6.36-7.81 (11H, m), 3.66 (4H, t, J=4.8 Hz), 2.96-3.04 (4H, m).

***N*-(4-Morpholinophenyl)-2-[-(4-cyanobenzylidene)amino]benzenesulfonamide (9 K):** white color solid; Yield 95%; M.W: 446.52; Mol. For: $C_{24}H_{22}N_4O_3S$; LC-MS (m/z): 447.4 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 10.10 (1H, s), 8.08 (2H, s), 7.92 (1H, s), 7.81 (2H, d, J=8 Hz), 7.45-7.55 (3H, m), 7.14 (1H, d, J=8.4 Hz), 6.65-6.90 (4H, m), 3.66 (4H, t, J=4.8 Hz), 3.01 (4H, t, J=4.8 Hz).

***N*-(4-morpholinophenyl)-2-[(4-nitrobenzylidene)amino]benzenesulfonamide (9 L):** white color solid; Yield 96%; M.W: 466.51; Mol.

For: $C_{23}H_{22}N_4O_5S$; LC-MS (m/z): 467.3 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 8.18 (2H, d, J=9.2 Hz), 7.99 (1H, s), 7.48-7.66 (4H, m), 7.16 (2H, d, J=8 Hz), 6.71-6.91 (5H, m), 3.65 (4H, t, J=5.2 Hz), 3.01 (4H, t, J=4.4 Hz).

***N*-(4-morpholinophenyl)-2-[(3-nitrobenzylidene)amino]benzenesulfonamide (9 M):** white color solid; Yield 87%; M.W: 466.51; Mol. For: $C_{23}H_{22}N_4O_5S$; LC-MS (m/z): 467.3 (M+1); ^{1}HNMR (400MHz, DMSO-d_3): δ 8.17 (2H, d, J=8.8 Hz), 8.10 (1H, s), 8.01 (1H, s), 7.47-7.66 (3H, m), 7.16 (2H, d, J=8 Hz), 6.71-6.92 (5H, m), 3.65 (4H, t, J=5.2 Hz), 2.99 (4H, t, J=4.8 Hz).

BIOLOGICAL EVALUATION

Some of the synthesized compounds showed good antimicrobial activity inhibition. Antimicrobial screening results of the tested compounds are shown in Table 2. All the synthesized compounds showed moderate inhibitory activity and some compound showed good antifungal activity inhibition. Antifungal screening results of the tested compounds are shown in Table 2.

CONCLUSION

In this study, the synthesis of some fused ring benzomorpholine derivatives (9 E – 9 M) was performed and their structures were confirmed by ^{1}HNMR, Mass spectroscopy techniques. In addition, the newly synthesized compounds were screened for their antibacterial and antifungal activities. Some of them were found to possess good antifungal and antibacterial activity.

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Table 2
Antibacterial and Antifungal activity data of compounds (9 E – 9 M).

Compound No.	Inhibition Zone Diameter (mm)								
	I	II	III	IV	V	VI	VII	VIII	IX
9 E	16	24	26	21	22	24	20	27	30
9 F	16	24	21	19	17	18	19	26	25
9 G	13	23	26	19	21	17	19	21	25
9 H	14	24	22	18	19	15	19	22	27
9 I	11	26	24	22	23	25	27	29	23
9 J	17	25	24	19	19	17	21	23	22
9 K	14	28	24	17	15	14	16	21	20
9 L	17	17	19	21	23	23	24	19	20
9 M	14	21	21	19	18	21	19	21	25
Control (Solvent)	13	11	15	11	12	14	13	10	13
Ciprofloxacin	---	21	22	15	14	16	17	22	23
Fluconazole	15	---	---	---	---	---	---	---	---

Microbial Cultures Used to test antimicrobial Activity, *Fungus Culture:* I-Candida sp. *Gram Positive Bacteria:* II-Staphylococcus aureus, III-Staphylococcus albus, VIII-Streptococcus faecalis, IX- Bacillus sp. *Gram Negative Bacteria :* IV-Klebsiella pnuemoniae, V-Escherichia coli, VI- Pseudomonas sp, VII- Proteus s.

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