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MICROWAVE ASSISTED SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4-((4-SUBSTITUTEDPHENYL)SULFONYL)MORPHOLINES

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ABSTRACT: A series of 4-((4-substitutedphenyl)sufonyl)morpholines have been synthesized from 4-substitutedbenzenesulfonohydrazides and morpholine under microwave irradiation and conventional heating methods. All the compounds tested for their in vitro antimicrobial activity against bacterial and fungal organisms and they were characterized on the basis of spectral data such as IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.

KEYWORD: Morpholine, arylsulfonohydrazides, antimicrobial activity, microwave irradiation

INTRODUCTION

Morpholine is an important building block in the field of medicinal chemistry field [I-II] and its derivatives plays very essential role in the drug discovery process [III]. The morpholine and its derivatives shows various biological activities such as antimicrobial [IV], anticancer [V], anti-parasitic [VI] and analgesic, anti-inflammatory [VII] ect. Some of the morpholine scaffold drugs Linezolid [VIII] is a antibiotic, Aprepitantis is neurokinin 1 (NK1) receptor antagonist, Timolol is used for ocular hypertension and glaucoma, Moclobemide [IX] is a reversible inhibitor of monoamine oxidase A (RIMA) drug primarily used to treat depression and social anxiety, Emorfazone is anti-inflammatory drug and analgesic [X], Phenadoxone is analgesic agent, Reboxetine [XI] is norepinephrine reuptake inhibitor (NRI) and Gefitinib [XII] is used in cancer treatment, Phenmetrazine is appetite suppressant, Canertinib is an irreversible tyrosine-kinase inhibitor with activity against EGFR, Fenpropimorph is a fungicide [XIII], and Finafloxacin & Levofloxacin are antibacterial drugs [XIV].

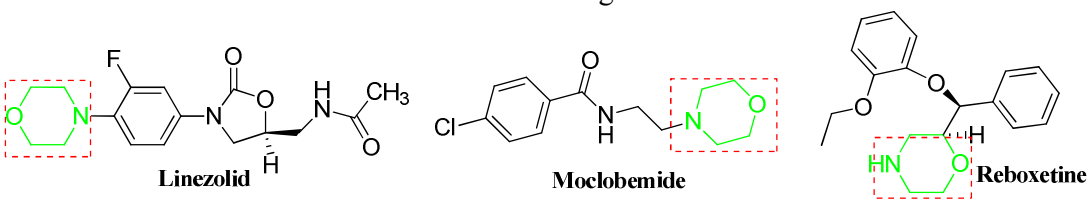

Figure-1: Drugs containing morpholine scaffold.

Sulfonamides are very significant class of compounds modern organic chemistry and synthetic and medicinal chemistry.[XV] Sulfonamides are ubiquitous motif seen in many of natural products and pharmaceutically active compounds. Sulfonamide derivatives play various biological activities such as antibacterial, anticancer, antiviral, anticonvulsant, anti-inflamatory, antiviral, antitumor and HIV protease inhibitor [XVI-XVII] ect.

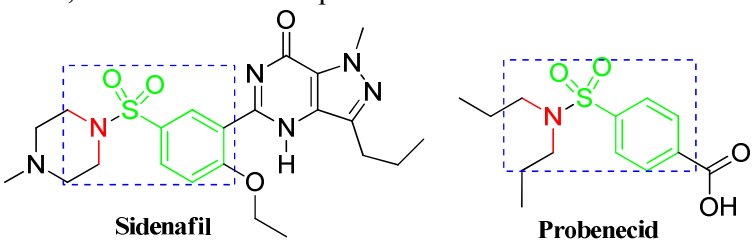

Figure-2: Arylsulfonamides scaffold in drugs.

Over the last several years many endeavors have been made for the synthesis of sulfonamides by using various reagents and catalyst, the most of them suffer from harsh and complex reaction conditions, slow reactivity, poor functional group tolerability, tedious purification procedures and usage of transition metals which may cause contamination in pharmaceutical industry. Hence, we plan to synthesize 4-((4-substitutedphenyl)sufonyl)morpholines from 4-substitutedbenzenesulfonohydrazides and morpholine by using iodine under microwave irradiation method. The microwave assisted organic synthesis reaction condition is promising alternative to conventional methods as these reactions represent clean, effective, safe, economical and eco-friendly procedure and is believed to be a step towards green chemistry.

Scheme-1: Synthesis of 4-((4-Substitutedphenyl)sulfonyl)morpholines

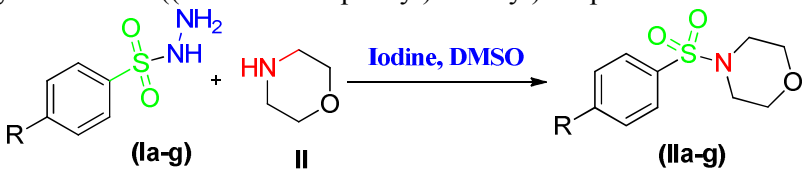

Table-1: Physical data of 4-((4-Substitutedphenyl)sulfonyl)morpholines **(3a-g)**

Compound	Reaction time		Yield (%)	
	Conventional (hr)	MWI (min)	Conventional	MWI
3a. hydrogen	3	1	88	98
3b. 4-methyl	3	1	90	99
3c. 4-methoxy	3	1	92	100
3d. 4-bromo	3	1	91	96
3e. 4-chloro	3	1	86	95
3f. 4-nitro	3	1	88	96
3g. naphthyl	3	1	90	99

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC using precoated silica gel plates 60_{254}(Merck). Microwave reactions were carried out in milestone multi SYNTH microwave system. IR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer. Elemental analysis was determined by using a Thermo Finnigan CHNS analyzer.

ANTIMICROBIAL ACTIVITY

Antibacterial activity:

All the compounds were screened for their in vitro antibacterial activity against *Escherichia coli,* and *Staphylococcus aureus* using ampicillin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm. The compounds were screened at the concentrations of 25, 50 and 100µg/ml in DMSO. From the screening studies it is evident that the synthesized compounds **3a** and **3e** showed good antibacterial activity against all the tested organisms.

Antifungal activity:

All the compounds were screened for their antifungal activity in vitro against *Aspergillus niger* and *Candida metapsilosis* using Grieseofulvin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm. The compounds were screened at the concentrations of 25, 50 and 100µg/ml in DMSO. From the screening studies it is evident that the synthesized compounds **3d** and **3e** showed good antifungal activity against all the tested organisms.

General Synthetic procedure for 4-((4-Substitutedphenyl)sulfonyl)morpholines (3a-g)

1) Microwave irradiation method

To a mixture of arylsulfonohydrazide (**1a-g**) and morpholine (**2**) was added DMSO followed by iodine catalytic amount. Then the reaction mixture irradiated under microwave at 160 w for 3 min. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with Chloroform, and quenched with saturated sodium thiosulfate solution and extracted with Chloroform. The compound washed with ice cold water and dried over anhyd. Sodium sulfate. The solvent was evaporated and the residue was subjected to column chromatography to afford pure 4-((4-Substitutedphenyl)sulfonyl)morpholines **(3a-g)**.

2) Conventional heating method

To a mixture of arylsulfonohydrazide (**1a-g**) and morpholine (**2**) was added DMSO followed by iodine catalytic amount. Then the reaction mixture was heated at 80 °C for 1 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with chloroform, and quenched with saturated sodium thiosulfate solution and extracted with chloroform. The compound was washed with icecold water and dried over anhyd. sodium sulfate. The solvent was evaporated and the residue was subjected to column chromatography to afford pure 4-((4-Substitutedphenyl)sulfonyl)morpholines **(3a-g)**.

SPECTRAL DATA

3a) 4-(phenylsulfonyl)morpholine

IR spectrum, ν, cm^{-1} 1346; ^{1}H NMR spectrum, δ, ppm: 7.46-7.48 (d, 2H), 7.35-7.38 (m, 2H), 7.26-7.31 (m, 1H), 3.70-3.72 (t, 4H), 2.95-2.97 (t, 4H); ^{13}C NMR spectrum, δC, ppm: 134.4, 130.4, 128.6, 127.7, 67.5, 55.94; *M* 196 $[M+H]^+$.

3b) 4-(p-tolylsulfonyl)morpholine

IR spectrum, ν, cm^{-1} 1338; ^{1}H NMR spectrum, δ, ppm: 7.38-7.40 (d, 2H), 7.17-7.19 (d, 2H), 3.67-3.69 (t, 4H), 2.87-2.89 (t, 4H), 2.36 (s, 3H); ^{13}C NMR spectrum, δC, ppm: 138.9, 133.0, 129.4, 129.0, 67.6, 55.8, 21.2; *M* 210 $[M+H]^+$.

3c) 4-((4-methoxyphenyl)sulfonyl)morpholine

IR spectrum, ν, cm^{-1} 1336; ^{1}H NMR spectrum, δ, ppm: 7.01-7.03 (d, 2H), 6.88-6.90 (d, 2H), 3.70-3.72 (t, 4H), 2.95-2.97 (t, 4H); ^{13}C NMR spectrum, δC, ppm: 157.1, 133.4, 123.5, 116.7, 67.6, 55.8, 55.3; *M* 216 $[M+H]^+$.

3d) 4-((4-bromophenyl)sulfonyl)morpholine

IR spectrum, ν, cm^{-1} 1338; ^{1}H NMR spectrum, δ, ppm: ^{1}H NMR spectrum, δ, ppm: 7.38-7.40 (d, 2H), 7.21-7.23 (d, 2H), 3.62-3.64 (t, 4H), 2.85-2.87 (t, 4H); ^{13}C NMR spectrum, δC, ppm: 134.2, 131.7, 131.0, 121.6, 67.5, 55.9; *M* 274 $[M+H]^+$.

3e) 4-((4-chlorophenyl)sulfonyl)morpholine

IR spectrum, ν, cm^{-1} 1339; ^{1}H NMR spectrum, δ, ppm: ^{1}H NMR spectrum, δ, ppm: 7.35-7.37 (d, 2H), 7.32-7.30 (d, 2H), 3.68-3.70 (t, 4H), 2.91-2.93 (t, 4H),; ^{13}C NMR spectrum, δC, ppm: 133.7, 133.2, 131.3, 128.8, 67.5, 55.9 *M* 230 $[M+H]^+$.

3f) 4-((4-nitrophenyl)sulfonyl)morpholine

IR spectrum, ν, cm^{-1} 1336; ^{1}H NMR spectrum, δ, ppm: 7.75-7.77 (d, 2H), 7.27-7.29 (d, 2H), 3.72-3.74 (t, 4H), 2.97-2.99 (t, 4H); ^{13}C NMR spectrum, δC, ppm: 155.0, 134.0, 132.7, 126.5, 67.5, 55.94; *M* 241 $[M+H]^+$.

3g) 4-(naphthalen-2-ylsulfonyl)morpholine

IR spectrum, ν, cm^{-1} 1343; ^{1}H NMR spectrum, δ, ppm: 7.96 (s, 1H), 7.82-7.85 (m, 3H), 7.48-7.55 (m, 3H), 3.75-3.77 (t, 4H), 3.04-3.06 (t, 4H); ^{13}C NMR spectrum, δC, ppm: 133.4, 132.7, 132.4, 128.8, 128.2, 127.7, 127.6, 126.5, 126.2, 67.6, 56.1; *M* 246 $[M+H]^+$.

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