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# DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL FUSED RING PYRIDINE MORPHOLINE BENZENE SULPHONAMIDE DERIVATIVES

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## ABSTRACT

A novel series of seven novel 4-(2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-ylsulfonyl)aniline derivatives (4II e – 4II k) have been synthesized from commercially available 2-Amino-3-Hdroxy Pyridine as a starting material. High yield and high purity indicates lack of side reaction and by product. The chemical structures of the synthesized compounds were confirmed by means of $^{1}$HNMR and mass spectral data. The synthesized compounds were then examined for their antibacterial and antifungal activities. Some of them were found to possess good activity.

**KEYWORDS:** Fused Ring, Morpholine, Benzenesulphonamide, Antibacterial, Antifungal Activity.

## INTRODUCTION

Nitrogen and oxygen containing heterocyclic compounds like morpholine.[1] and fused ring morphline.[2-5] are very important building blocks in medicinal chemistry.[6] field. So the morpholine derivatives are extensively very essential in the drug discovery research, which stimulate research activity in the field of the broad spectrum of biological activity.[7] study. After the literature survey that many morpholine derivative molecule are shows very good

biological activity in different therapeutic area such as antibacterial.[8] antiviral, anticancer, antimicrobial, antidiabetic, anti-Inflammatory, antimalarial, antifungal,[9] Antiemetic etc.

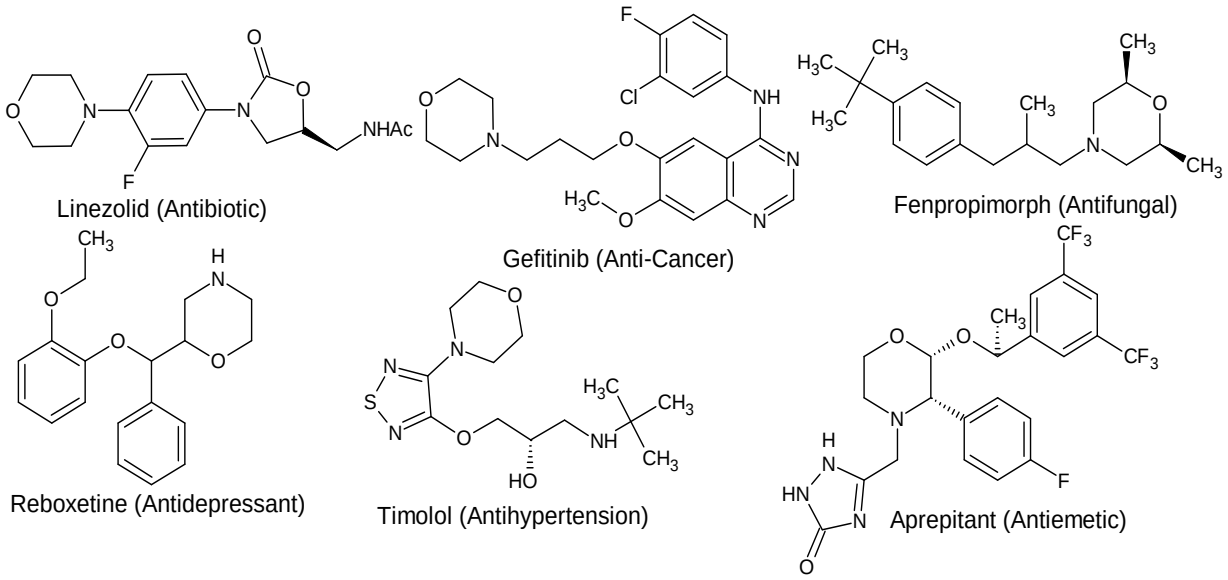



**Figure 1: Marketed drugs containing a direct linked morpholine ring.**

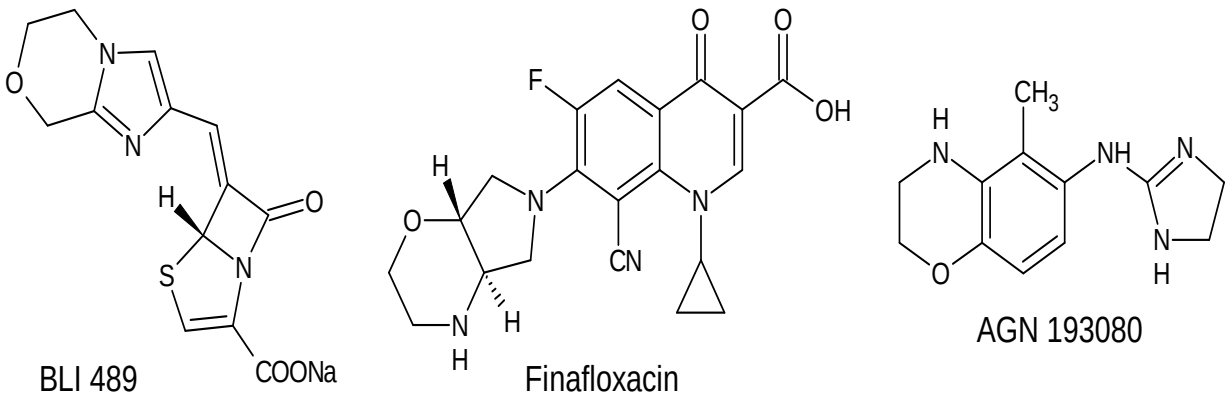



**Figure 2: Clinical and preclinical drugs having a fused morpholine ring.**

It is well known that the introduction of sulfonamide.[10-14] moiety into organic molecule causes dramatic changes in its biological profile. Sulfonamides are compound contain sulfur in a (-$SO_2$N-) moiety directly attached to a benzene ring. Sulfa drugs, developed in the 1930s, were the first medications effective against bacterial disease. They appeared as the first "miracle drugs" at a time when death from bacterial infections such as pneumonia and blood poisoning were common. The sulfonamide derivatives widely used in variety of biological actions, including for antibacterial, antitumour, diuretic and antithyroid activities. Hence, in the present study, some new derivatives of 4-(2,3-dihydro-4H-pyrido[3,2-b] [1,4]oxazin-4-ylsulfonyl)aniline have been synthesized. 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.

## MATERIALS AND METHODS

All the reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as necessary. The moiety 2-Amino-3-Hdroxy Pyridine [15-16] 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 (4II e - 4II k) 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 $37^0$C 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 (4II e - 4II k) 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.

## EXPERIMENTAL

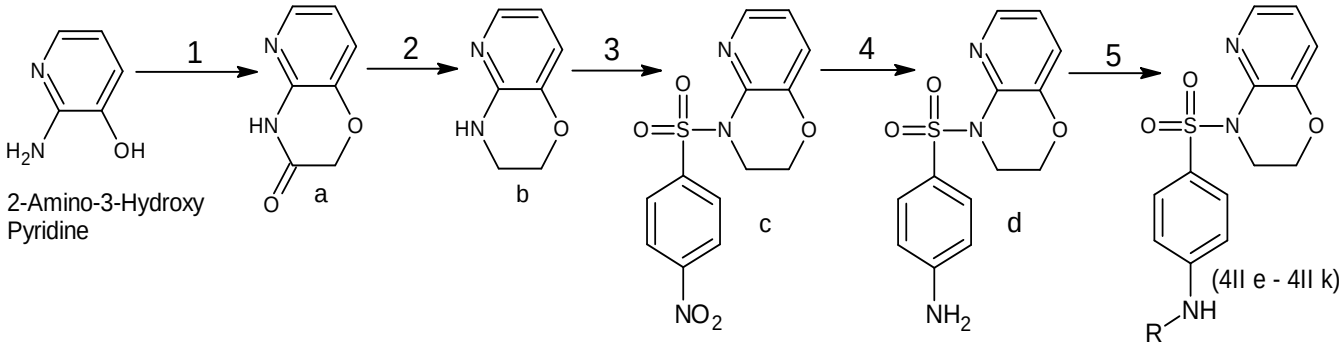
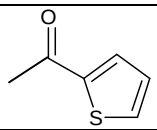
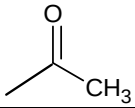
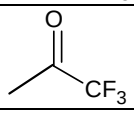
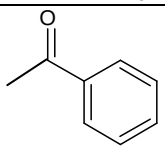
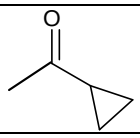
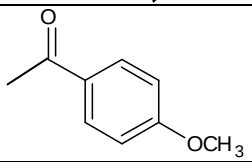
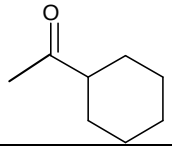



**Figure 3: Synthesis of 4-(2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-ylsulfonyl)aniline and their derivatives.**

**Table1: Physical data of synthesized compounds (4II e – 4II k).**

| Code | -R | Molecular Formula | M.Wt | M.P (°C) | % Yield |
|---|---|---|---|---|---|
| 4II e |  | $C_{18}H_{15}N_3O_4S_2$ | 401.45 | 212-214 | 86 |
| 4II f |  | $C_{15}H_{15}N_3O_4S$ | 333.36 | 192-194 | 93 |
| 4II g |  | $C_{15}H_{12}F_3N_3O_4S$ | 387.33 | 178-180 | 86 |
| 4II h |  | $C_{20}H_{17}N_3O_4S$ | 395.43 | 197-199 | 92 |
| 4II i |  | $C_{17}H_{17}N_3O_4S$ | 359.39 | 166-168 | 82 |
| 4II j |  | $C_{21}H_{19}N_3O_5S$ | 425.45 | 183-185 | 96 |
| 4II k |  | $C_{20}H_{23}N_3O_4S$ | 401.47 | 176-178 | 85 |

**Preparation of 2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (a)**

The chloroacetyl chloride (33.33g, 295mmol) was added drop-wise to the solution of potassium carbonate (95.5g, 692mmol) and 2-amino-3-Hydroxy pyridine (25g, 227mmol) in THF (250ml) at 0°C. The resulting suspension was stirred at room temperature for 1hr. Then

the reaction mixture heated to reflux and maintained for 4h. After completion of reaction, the reaction was cooled to room temperature and the inorganic solids were removed by filtration washed with THF (25ml), the filtrate solvent was concentrated under vacuum to give a crude solid. The crude was suspended in water (250ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with water (25ml), after drying yielded the titled product (a) as off-white solid.

**Preparation of 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (b)**

The compound (a) (8g, 53mmol) in tetrahydrofuran (40ml) was added slowly to the solution of lithium aluminium hydride (3g, 79mmol) in tetrahydrofuran (40ml) at 0°C and the mixture was stirred for 6 hr at room temperature. After completion of reaction, the reaction was quenched with wet sodium sulfate. The reaction mass filtered through celite bed washed with tetrahydrofuran (16ml). The filtrate was distilled out completely. Yielded the titled product (b) as off-white solid.

**Preparation of 4-[(4-nitrophenyl)sulfonyl]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (c)**

The 4-Nitrobenzenesulphonyl chloride (12.53g, 56mmol) in 70ml of DCM was added to the solution of compound (b) (7g, 51mmol), Triethylamine (7.78g, 77mmol) in Dichloromethane (70ml) at 0°C and the mixture was stirred for 4 hr at room temperature. After completion of reaction, the solution was evaporated in vacuum and the residue was suspended in water (70 ml) and the suspension was stirred for 2hr at room temperature. Filtered and washed with water (15ml), after drying yielded the titled product (c) as yellow solid.

**Preparation of 4-(2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-ylsulfonyl)aniline (d)**

The Methanol (200ml), compound (c) (10g, 31mmole) and 10% Pd-C catalyst (3g) was added 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 methanol (20ml). The filtrate was evaporated under vacuum. Yielded the titled product (d) as white solid.

**General method for the synthesis of compounds (4II e – 4II k)**

The corresponding carboxylic acid (1mol.Eq) was dissolved in dry DMF (10volume). Followed by charged HATU (1mol.Eq), DIPEA (1.1mol.Eq) and compound (d) (1mol.Eq). Then the mixture was continued to stir for 5hr room temperature. After completion of reaction, the reaction mass poured into cold water and the suspension was stirred for 2hr at

room temperature. Filtered and washed with water, after drying yielded the titled product as crude white solid. The crude solid further recrystallized by using ethyl acetate gives the titled product (4II e – 4II k) as white crystalline solid.

## RESULTS AND DISCUSSION

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

**2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (a)**

Off-white solid; Yield 97%; M.W: 150.13; Mol. For: $C_7H_6N_2O_2$; LC-MS (m/z): 151.1(M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 11.23 (1H, s), 7.88-7.90 (1H, m), 7.33 (1H, d, J=8.0 Hz), 6.95-6.98 (1H, m), 4.64 (2H, s).

**3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine (b)**

Off-white solid; Yield 85%; M.W: 136.15; Mol.For: $C_7H_8N_2O$; LC-MS(m/z): 137.0(M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 7.53 (1H, d, J=4.8 Hz), 6.90 (1H, d, J=8.0 Hz), 6.63 (1H, s), 6.43-6.46 (1H, m), 4.90 (2H, t. J=4.4 Hz), 3.36-3.39 (2H, m).

**4-[(4-nitrophenyl)sulfonyl]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (c)**

Yellow solid; Yield 63%; M.W: 321.30; Mol.For: $C_{13}H_{11}N_3O_5S$; $^1$HNMR (400MHz, $DMSOd_6$): δ 8.19 (2H, d, J=8.8 Hz), 7.77 (1H, d, J=4.4 Hz), 7.67 (2H, d, J=9.2 Hz), 7.26 (1H, d, J=7.6 Hz), 6.91-6.94 (1H, m), 4.35 (2H, t, J=4.4 Hz), 4.00 (2H, t, J=4.0 Hz).

**4-(2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-ylsulfonyl)aniline (d)**

A white solid; Yield 87%; M.W: 291.32; Mol.For: $C_{13}H_{13}N_3O_3S$; LC-MS(m/z): 292.2(M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 7.79-7.80 (1H, m), 7.61 (2H, d, J=8.8), 7.18-7.20 (1H, m), 6.90-6.93 (1H, m), 6.55 (2H, d, J=8.8 Hz), 6.05 (2H, s), 4.24 (2H, t, J=4.8 Hz), 3.98 (2H, t, J=4.0 Hz).

***N*-[4-(2,3-dihydro-4*H*-pyrido[3,2-*b*][1,4]oxazin-4-ylsulfonyl)phenyl]thiophene-2-carboxamide (4II e)**

A white crystalline solid; Yield 86%; M.W: 401.4; Mol. For: $C_{18}H_{15}N_3O_4S_2$; LC MS(m/z): 402.1(M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 10.63 (1H, s), 8.02-8.04 (1H, m), 7.81-7.83 (1H, m), 7.54-7.57 (2H, m), 7.62 (2H, d, J=8.6), 7.19-7.23 (1H, m), 6.91-6.95 (1H, m), 6.56 (2H, d, J=8.6 Hz), 4.25 (2H, t, J=4.8 Hz), 3.99 (2H, t, J=4.4 Hz).

**_N_-[4-(2,3-dihydro-4_H_-pyrido[3,2-_b_][1,4]oxazin-4-ylsulfonyl)phenyl]acetamide (4II f)**

A white crystalline solid; Yield 93%; M.W: 333.3; Mol. For: $C_{15}H_{15}N_3O_4S$; LC MS(m/z): 334.1(M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 10.61 (1H, s), 7.78-7.80 (1H, m), 7.63 (2H, d, J=8.8), 7.19-7.22 (1H, m), 6.89-6.92 (1H, m), 6.55 (2H, d, J=8.8 Hz), 4.23 (2H, t, J=4.4 Hz), 3.98 (2H, t, J=4.0 Hz), 2.08 (3H, s).

**_N_-[4-(2,3-dihydro-4_H_-pyrido[3,2-_b_][1,4]oxazin-4-ylsulfonyl)phenyl]-2,2,2-trifluoroacetamide (4II g)**

A white crystalline solid; Yield 86%; M.W: 387.3; Mol. For: $C_{15}H_{12}F_3N_3O_4S$; LC MS(m/z): 388.2(M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 10.63 (1H, s), 7.79-7.81 (1H, m), 7.63 (2H, d, J=8.6), 7.17-7.20 (1H, m), 6.90-6.94 (1H, m), 6.54 (2H, d, J=8.6 Hz), 4.22 (2H, t, J=4.6 Hz), 3.99 (2H, t, J=4.4 Hz).

**_N_-[4-(2,3-dihydro-4_H_-pyrido[3,2-_b_][1,4]oxazin-4-ylsulfonyl)phenyl]benzamide (4II h)**

A white crystalline solid; Yield 92%; M.W: 395.43; Mol. For: $C_{20}H_{17}N_3O_4S$; LC MS(m/z): 396.1(M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 10.61 (1H, s), 7.80-7.83 (1H, m), 7.62 (2H, d, J=8.8), 7.53-7.60 (5H, m), 7.20-7.25 (1H, m), 6.91-6.94 (1H, m), 6.52 (2H, d, J=8.8 Hz), 4.21 (2H, t, J=4.4 Hz), 3.92 (2H, t, J=4.0 Hz).

**_N_-[4-(2,3-dihydro-4_H_-pyrido[3,2-_b_][1,4]oxazin-4-ylsulfonyl)phenyl]cyclopropane carboxamide (4II i)**

A white crystalline solid; Yield 82%; M.W: 359.3; Mol. For: $C_{17}H_{17}N_3O_4S$; LC MS(m/z): 360.0 (M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 10.59 (1H, s), 7.79-7.80 (1H, m), 7.61 (2H, d, J=8.8), 7.18-7.20 (1H, m), 6.90-6.93 (1H, m), 6.55 (2H, d, J=8.8 Hz), 4.24 (2H, t, J=4.8 Hz), 3.98 (2H, t, J=4.0 Hz), 1.73-1.77 (1H, m), 0.82 (4H, d, J=4.6 Hz).

**_N_-[4-(2,3-dihydro-4_H_-pyrido[3,2-_b_][1,4]oxazin-4-ylsulfonyl)phenyl]-4-methoxybenzamide (4II j)**

A white crystalline solid; Yield 96%; M.W: 425.45; Mol. For: $C_{21}H_{19}N_3O_5S$; LC MS(m/z): 426.2 (M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 10.62 (1H, s), 7.80-7.84 (3H, m), 7.63 (2H, d, J=8.8), 7.19-7.23 (3H, m), 6.91-6.94 (1H, m), 6.52 (2H, d, J=8.6 Hz), 4.23 (2H, t, J=4.4 Hz), 3.99 (2H, t, J=4.2 Hz), 3.82 (3H, s).

***N*-[4-(2,3-dihydro-4*H*-pyrido[3,2-*b*][1,4]oxazin-4-ylsulfonyl)phenyl] cyclohexanecarboxamide (4II k)**

A white crystalline solid; Yield 85%; M.W: 401.47; Mol. For: $C_{20}H_{23}N_3O_4S$; LC MS(m/z): 402.2 (M+1); $^1$HNMR (400MHz, $DMSOd_6$): δ 10.64 (1H, s), 7.80-7.84 (1H, m), 7.60 (2H, d, J=8.8), 7.19-7.24 (1H, m), 6.91-6.95 (1H, m), 6.52 (2H, d, J=8.8 Hz), 4.22 (2H, t, J=4.4 Hz), 3.98 (2H, t, J=4.0 Hz), 2.28 (1H, m), 1.62-1.78 (5H, m), 1.22-1.38 (5H, m).

## 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 compared to other compound. Antifungal screening results of the tested compounds are shown in Table 2.

**Table 2: Antibacterial and Antifungal activity data of compounds (4II e – 4II k)**

| Compound No. | Inhibition Zone Diameter (mm) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **I** | **II** | **III** | **IV** | **V** | **VI** | **VII** | **VIII** | **IX** |
| 4II e | 11 | 10 | 14 | 15 | 08 | 13 | 13 | 12 | 16 |
| 4II f | 12 | 20 | 18 | 18 | 16 | 18 | 16 | 20 | 14 |
| 4II g | 09 | 15 | 14 | 19 | 13 | 17 | 14 | 15 | 15 |
| 4II h | 12 | 21 | 18 | 16 | 12 | 12 | 16 | 12 | 17 |
| 4II i | 11 | 18 | 15 | 16 | 13 | 17 | 15 | 17 | 14 |
| 4II j | 07 | 14 | 18 | 11 | 14 | 16 | 17 | 19 | 13 |
| 4II k | 09 | 15 | 18 | 18 | 19 | 12 | 20 | 22 | 16 |
| Control (Solvent) | 09 | 12 | 13 | 13 | 11 | 13 | 11 | 13 | 10 |
| 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 sp.

## CONCLUSION

In this study, the synthesis of some fused ring benzomorpholine derivatives (4II e – 4II k) 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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