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SYNTHESIS AND BIOLOGICAL EVALUATION OF (3S)-3-[4-METHOXYMETHOXY) BENZYL] MORPHOLINE DERIVATIVES FROM L-TYROSINE

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Abstract:

Morpholine backbone is essential in different pharmacologically active synthetic compounds. Present work is synthesis of novel morpholine nucleus based compounds such as (3S)-3-[4-(methoxymethoxy) benzyl] morpholine and their derivatives (3 I – 3 O). The compounds were synthesized in multistep reaction with more efficient process starting from L-Tyrosine as key starting material. The moiety L-Tyrosine is commercially available and is also available from Sigma-Aldrich. The chemical structures of the synthesized compounds were confirmed by means of ^{1}HNMR and mass spectral data. High yield and high purity indicates lack of side reaction and by product. The synthesized compounds were then examined for their antibacterial and antifungal activities. Some of them were found to possess good antibacterial and antifungal activity.

Keywords: *Morpholine, Tyrosine, Antibacterial, Antifungal Activity.*

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INTRODUCTION

Though there are many of active compounds developed for functionalized morpholine. Still there is scope for synthesis of new compounds to built morpholine ring system & it found to be among the most efficient for achieving useful transformations in to morpholine backbone and their derivatives later on. Nitrogen and oxygen containing heterocyclic compounds like morpholine [1] and substituted morpholine [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.

Hence, in the present study, some new substituted morpholine like (3S)-3-[4-(methoxymethoxy) benzyl] morpholine and their derivatives have been synthesized. The prepared substituted morpholine and three derivatives are very useful building blocks in medicinal chemistry. After the preparation of derivatives, the deprotection of methoxy methyl (MOM) [10] group will give phenolic hydroxyl which is also very useful building blocks in drug discovery synthesis. The chemical structures of the synthesized compounds were confirmed by spectroscopic methods like ^{1}HNMR and mass spectral data.

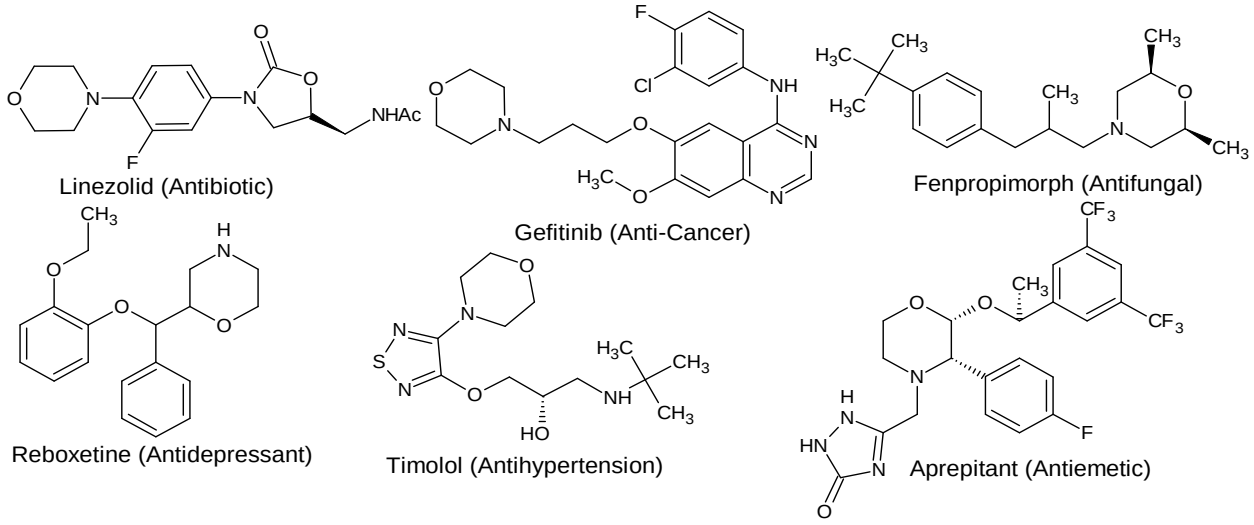


Figure 1: Marketed drugs containing a direct linked morpholine ring.

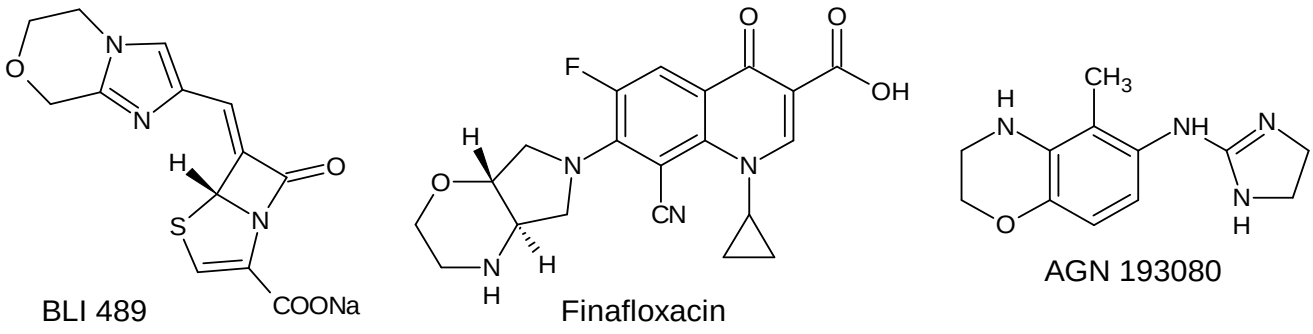


Figure 2: Clinical and preclinical drugs having a fused morpholine ring.

MATERIALS AND METHODS

All the reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as necessary. The moiety L-Tyrosine [11-15] 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 $DMSOD_6$ & $CDCl_3$ 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 (3 I – 3 O) were screened against different standard organism obtained from the American type of cell culture collection, including Staphylococcus aureus, Escherichia coli and Pseudomonas sp. Agar diffusion technique at the concentration level of 5µg molar was applied. Ciprofloxacin was used as reference compounds for antibacterial activities.

The antimicrobial activity of all the newly synthesized compounds were determined by well plate method in nutrient agar (Hi-media) was used for antibacterial activity. The antibacterial activity of the test compounds was assayed against gram-positive and gram-negative by Cup plate method. The compounds were tested at a concentration of a 100 µg/ml were prepared in dimethylforamide (DMF). The Petri dishes used for antibacterial screening were incubated at 37±1 for 24h; the diameters of zone of inhibition (mm) surroundings each of the wells recorded. The results were compared Ciprofloxacin of a 100µg/ml concentration (cacic, M et al., 2006).

Antifungal Activity:

The antifungal activity of all synthesized compounds (3 I – 3 O) screened against Candida sp in DMF by poisoned food technique. Fluconazole was employed as standard drug during the test procedures as references. Potato dextrose agar (PDA) Media were prepared and about 15ml of PDA was poured into each Petri plate allowed to solidify 5mm disc of seven-day-old culture of the test fungi was placed at the centre of the Petri plates and incubated at 26°C for 7 days. After incubation, the percentage inhibition was measured and three replicates were maintained for each treatment.

EXPERIMENTAL

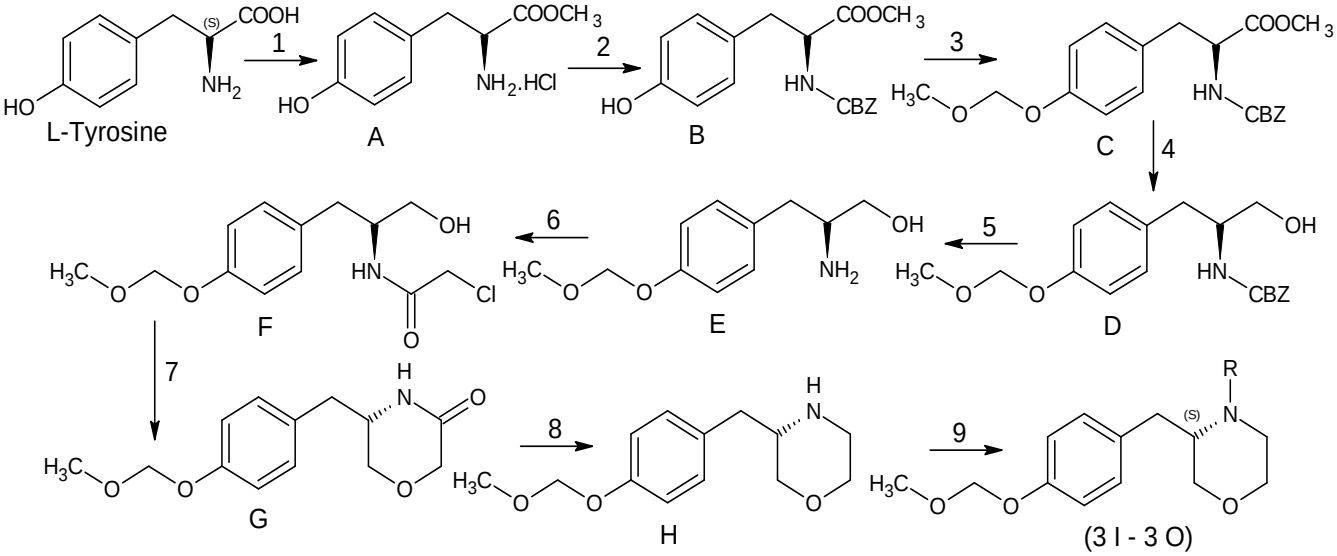
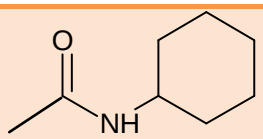
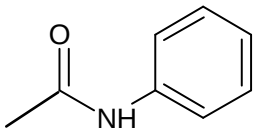
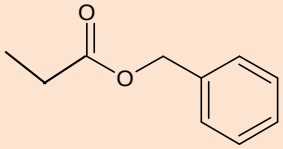
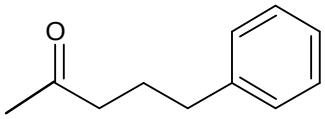
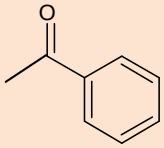
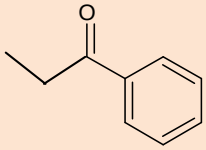


Fig 3: Synthesis of (3S) -3-[4-methoxymethoxy) benzyl] morpholine and their derivatives.

Table 1: Physical Data of Synthesized Compounds (3 I – 3 O).

Code	-R	Molecular Formula	M.wt	M.P (°C)	% Yield
3 I		$C_{20}H_{30}N_2O_4$	362.4	67-69	83
3 J		$C_{20}H_{24}N_2O_4$	356.4	73-74	80
3 K		$C_{22}H_{27}NO_5$	385.4	55-57	87
3 L		$C_{23}H_{29}NO_4$	383.4	79-81	92
3 M		$C_{20}H_{23}NO_4$	341.4	47-49	80
3 N		$C_{15}H_{20}N_2O_3$	276.3	36-37	78
3 O		$C_{21}H_{25}NO_4$	355.4	44-46	86

Preparation of methyl (2S)-2-amino-3-(4-hydroxyphenyl) propionate Hydrochloride (A): The thionylchloride (14.44g, 121mmol) was added to the solution of L-Tyrosine (20gm, 110mmol) in methanol (120ml) at 0°C and the mixture was stirred for 16 hr at room temperature. After completion of reaction, the solution was evaporated in vacuum and residue was suspended in 200ml acetone, stirred for 30 mints. Filtered and dried. Yielded the titled product (A) as white solid.

Preparation of Methyl (2S)- 2-{[Benzyloxy)carbonyl]amino}-3-(4-hydroxyphenyl) propanoate (B): The Benzyl chloroformate (19.22g, 112mmol) was added to the solution of compound (A) (20gm, 102mmol), sodium bicarbonate (17.21g, 204mmol) in water (120ml) at 10°C and the mixture was stirred for 2hr at room temperature. After completion of reaction, the reaction mass extracted with twice with 100ml of ethyl acetate, dried with sodium sulfate and distilled out completely. The crude was suspended in n-Hexane (200ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with n-Hexane (40ml), after drying yielded the titled product (B) as white solid.

Preparation of Methyl (2S)-2-{[benzyloxy)carbonyl]amino}-3-[4-(methoxymethoxy)phenyl]propanoate (C): The chloromethyl methyl ether (5.28g, 65mmol) was added to the solution of compound (B) (18gm, 54mmol), N,N-Diisopropyl ethylamine (14.12g, 109mmol) in dichloromethane (108ml) at 0°C and the mixture was stirred for overnight at room temperature. After completion of reaction, the

solution was evaporated in vacuum and the residue was suspended in 180ml of ethyl acetate and washed with 2×100 of water. The organic layer dried with sodium sulfate and distilled out completely. Yielded the titled product (C) as oily mass.

Preparation of benzyl{ (2S)-1-hydroxy-3-[4-(methoxymethoxy)phenyl]propan-2-yl} carbamate (D):

The compound (C) (15g, 40mmol) in 50ml of tetrahydrofuran was added slowly to the solution of lithium borohydride (1.3gm, 60mmol) in tetrahydrofuran (100ml) at 0°C and the mixture was stirred for 5hr at 0°C. After completion of reaction, the reaction was quenched with wet sodium sulfate. The reaction mass filtered through celite bed washed with tetrahydrofuran (15ml).The filtrate was distilled out completely. Yielded the titled product (D) as white solid.

Preparation of (2S)-2-amino-3-[4-(methoxymethoxy) phenyl] propan-1-ol (E):

The methanol (80ml), compound (D) (10g, 28mmol) and Pd-C (1gm) catalyst was added into the hydrogenation Parr-shaker reactor. 30 PSI of hydrogen gas applied and the mixture was shaken for 5hr. After completion of reaction, the reaction mass filtered through celite bed washed with methanol 20ml. The filtrate was distilled out completely. Yielded the titled product (E) as white solid.

Preparation of 2-chloro-N-{(2S)- 1-hydroxy-3-[4-(methoxymethoxy)phenyl]propan-2-yl} acetamide (F):

The chloroacetyl chloride (4.49g, 39mmol) was added to the solution of compound (E) (8gm, 37mmol), sodium bicarbonate (84g, 41mmol) in tetrahydrofuran (64ml) at 0°C and the mixture was stirred for 1hr at 0°C. After completion of reaction, the reaction filtered and removed the sodium bicarbonate. The filtrate concentrated completely. The crude was suspended in n-Hexane (80ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with n-Hexane (20ml), after drying yielded the titled product (F) as light brown solid.

Preparation of (5S)-5-[4-(methoxymethoxy) benzyl] morpholin-3-one (G):

The potassium tert-butoxide (2.63gm, 23mmol) was added to the solution of compound (F) (4.5gm, 15mmol) in N,N-Dimethylformamide (45ml) and the mixture was stirred for 5hr at room temperature. After completion of reaction, the reaction mass poured into cold water (200ml). The reaction mass pH was neutralized with 5% AcOH solution. The reaction mass was stirred at room temperature for 3hr. Filtered and washed with water (20ml), after drying yielded the titled product (G) as white solid.

Preparation of (3S)-3-[4-(methoxymethoxy) benzyl] morpholine (H):

The compound (G) (3gm, 11mmol), in 15ml of tetrahydrafuran was added slowly to the solution of lithium aluminium hydride (0.68g, 17mmol) in tetrahydrafuran (15ml) at 0°C and the mixture was stirred for 4hr 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 15ml. The filtrate was distilled out completely. Yielded the titled product (H) as oily mass.

Preparation of (3S)-3-[4-(methoxymethoxy) benzyl]–N-cyclohexylmorpholine-4-carboxamide (3 I):

The cyclohexyl isocyanate (0.42g, 3 mmol) was added to the solution of compound (H) (0.8gm, 3mmol) in tetrahydrofuran (8ml) at 0°C and the mixture was stirred for 1hr at 0°C. After completion of reaction, the reaction mass evaporated in vacuum and the residue was suspended in ethyl acetate (8ml) and washed with 2×4ml of water. The organic layer dried with sodium sulfate and distilled out completely. The crude was suspended in n-pentane (8ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with n-pentane (2ml), after drying yielded the titled product (3I) as white solid.

Preparation of (3S)-3-(4-methoxymethoxy)benzyl–N-phenylmorpholine-4-carboxamide (3 J):

The phenyl isocyanate (0.35g, 3 mmol) was added to the solution of compound (H) (0.7gm, 3mmol) in tetrahydrofuran (7ml) at 0°C and the mixture was stirred for 1hr 0°C. After completion of reaction, the reaction mass evaporated in vacuum and the residue was suspended in ethyl acetate (7ml) and washed with 2×3ml of water. The organic layer dried with sodium sulfate and distilled out completely. The crude was suspended in n-pentane (7ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with n-pentane (2ml), after drying yielded the titled product (3J) as white solid.

Preparation of benzyl [(3S)-3-(4-methoxymethoxy) benzyl] morpholine-4-acetate (3 K):

The benzyl bromoacetate (0.7g, 3mmol) was added to the solution of compound (H) (0.7gm, 3mmol) and cesium carbonate (1gm, 3mmol) in acetonitrile (7ml) and the mixture was stirred for 3hr at room temperature. After completion of reaction, the reaction mass evaporated in vacuum and the residue was suspended in ethyl acetate (7ml) and washed with 2×4ml of water. The organic layer dried with

sodium sulfate and distilled out completely. The crude was suspended in n-pentane (7ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with n-pentane (2ml), after drying yielded the titled product (3K) as white solid.

Preparation of (3S)-3-[(4-methoxymethoxy) benzyl] morpholine-4-phenylbutan-1-one (3 L): The 4-phenylbutanoyl chloride (0.54g, 3mmol) was added to the solution of compound (H) (0.7gm, 3mmol) and cesium carbonate (1gm, 3mmol) in acetonitrile (7ml) and the mixture was stirred for 3hr at room temperature. After completion of reaction, the reaction mass evaporated in vacuum and the residue was suspended in ethyl acetate (7ml) and washed with 2×4ml of water. The organic layer dried with sodium sulfate and distilled out completely. The crude was suspended in n-pentane (7ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with n-pentane (2ml), after drying yielded the titled product (3L) as white solid.

Preparation of {(3S)-3-[4-(methoxymethoxy) benzyl] morpholin-4-yl}(phenyl)methanone (3 M): The benzoyl chloride (0.41g, 3mmol) was added to the solution of compound (H) (0.7gm, 3mmol) and cesium carbonate (1gm, 3mmol) in acetonitrile (7ml) and the mixture was stirred for 3hr at room temperature. After completion of reaction, the reaction mass evaporated in vacuum and the residue was suspended in ethyl acetate (7ml) and washed with 2×4ml of water. The organic layer dried with sodium sulfate and distilled out completely. The crude was suspended in n-pentane (7ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with n-pentane (2ml), after drying yielded the titled product (3M) as white solid.

Preparation of {(3S)-3-[4-(methoxymethoxy)benzyl] morpholin-4-yl}acetonitrile (3 N): The bromoacetonitrile (0.35g, 3mmol) was added to the solution of compound (H) (0.7gm, 3mmol) and cesium carbonate (1gm, 3mmol) in acetonitrile (7ml) and the mixture was stirred for 3hr at room temperature. After completion of reaction, the reaction mass evaporated in vacuum and the residue was suspended in ethyl acetate (7ml) and washed with 2×4ml of water. The organic layer dried with sodium sulfate and distilled out completely. The crude was suspended in n-pentane (7ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with n-pentane (2ml), after drying yielded the titled product (3N) as white solid.

Preparation of 2-{(3S)-3-[4-(methoxymethoxy)benzyl]morpholin-1-phenylethanone (3 O): The phenacyl Bromide (0.58g, 3mmol) was added to the solution of compound (H) (0.7gm, 3mmol) and cesium carbonate (1gm, 3mmol) in acetonitrile (7ml) and the mixture was stirred for 3hr at room temperature. After completion of reaction, the reaction mass evaporated in vacuum and the residue was suspended in ethyl acetate (7ml) and washed with 2×4ml of water. The organic layer dried with sodium sulfate and distilled out completely. The organic layer dried with sodium sulfate and distilled out completely. The crude was suspended in n-pentane (7ml) and the suspension was stirred at room temperature for 1hr. Filtered and washed with n-pentane (2ml), after drying yielded the titled product (3O) as white solid.

RESULTS AND DISCUSSION

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

Preparation of methyl (2S)-2-amino-3-(4-hydroxyphenyl) propionate Hydrochloride (A): A white solid 22g (yield 88%). M.W: 231.6; Mol. For: $C_{10}H_{14}ClNO_3$; LC-MS (m/z): 196.1 (M+1, without HCl); ^{1}HNMR (400MHz, $DMSOD_6$): δ 9.44 (s, 1H), 8.52 (s, 2H), 6.99-7.01 (d, 2H), 6.70-6.73 (d, 2H), 4.16-4.19 (t, 1H), 3.67 (s, 3H), 2.98-3.03 (m, 2H).

Preparation of Methyl (2S)- 2-{[Benzyloxy)carbonyl]amino}-3-(4-hydroxyphenyl) propanoate (B): A white solid 32g (yield 95%). M.W: 329.3; Mol. For: $C_{18}H_{19}NO_5$; LC-MS (m/z): 330.2 (M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 9.23 (s, 1H), 7.76-7.78 (d, 1H), 7.25-7.37 (m, 5H), 7.00-7.02 (d, 2H), 6.64-6.66 (d, 2H), 4.98 (s, 2H), 4.15-4.18 (m, 1H), 3.61 (s, 3H), 2.88-2.91 (m, 1H), 2.73-2.77 (m, 1H).

Preparation of Methyl (2S)-2-{[benzyloxy)carbonyl]amino}-3-[4-(methoxymethoxy)phenyl]propanoate (C): A oily mass 16g (yield 80%). M.W: 373.3; Mol. For: $C_{20}H_{23}NO_6$; LC-MS (m/z): 374.3 (M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 7.79-7.81 (d, 1H), 7.26-7.36 (m, 5H), 7.14-7.16 (d, 2H), 6.91-6.93 (d, 2H), 5.14 (s, 2H), 4.98 (s, 2H), 4.19-4.20 (m, 1H), 3.62 (s, 3H), 3.36 (s, 3H), 2.94-2.98 (m, 1H), 2.8.-2.82 (m, 1H).

Preparation of benzyl{ (2S)-1-hydroxy-3-[4-(methoxymethoxy)phenyl]propan-2-yl} carbamate (D): A white solid 13g (yield 92%). M.W: 345.3; Mol. For: $C_{19}H_{23}NO_5$; LC-MS (m/z): 346.3 (M+1,); ^{1}HNMR (400MHz, $DMSOD_6$): δ 7.10-7.35 (m, 8H), 6.90-6.92 (d, 2H), 5.14 (s, 2H), 4.94 (s, 2H), 4.73-4.76 (t, 1H), 3.59-3.60 (m, 1H), 3.36 (s, 3H), 3.27-3.31 (m, 1H), 2.75-2.80 (m, 1H).

Preparation of (2S)-2-amino-3-[4-(methoxymethoxy)phenyl]propan-1-ol (E): A white solid 5g (yield 83%). M.W: 211.2; Mol. For: $C_{11}H_{17}NO_3$; LC-MS (m/z): 212.2 (M+1); ^{1}HNMR

(400MHz, $DMSOD_6$): δ 7.10-7.12 (d, 2H), 6.91-6.93 (d, 2H), 5.14 (s, 2H), 4.60 (s, 1H), 3.25-3.29 (m, 2H), 3.14-3.18 (m, 2H), 2.80-2.84 (m, 1H), 2.58-2.63 (m, 1H), 2.34-2.39 (m, 2H), 1.90 (bs, 2H).

Preparation of 2-chloro-N-{(2S)- 1-hydroxy-3-[4-(methoxymethoxy)phenyl]propan-2-yl} acetamide (F): A brown solid 10g (yield 95%). M.W: 287.7; Mol. For: $C_{13}H_{18}ClNO_4$; LC-MS (m/z): 288.2 (M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 8.04-8.06 (d, 1H), 7.10-7.12 (d, 2H), 6.90-6.92 (d, 2H), 5.14 (s, 2H), 4.83 (s, 1H), 4.00 (s, 2H), 3.83-3.85 (1H), 3.35 (s, 3H), 2.74-2.79 (m, 1H), 2.56-2.62 (m, 1H).

Preparation of (5S)-5-[4-(methoxymethoxy) benzyl] morpholin-3-one (G): A white solid 3.7g (yield 96%). M.W: 251.2; Mol. For: $C_{13}H_{17}NO_4$; LC-MS (m/z): 252.2 (M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 8.10 (s, 1H), 7.11-7.13 (d, 2H), 6.94-6.96 (d, 2H), 5.15 (s, 2H), 3.93 (s, 2H), 3.53-3.61 (m, 2H), 3.38-3.41 (m, 1H), 3.36 (s, 3H), 2.67-2.82 (m, 1H), 2.62-2.67 (m, 1H).

Preparation of (3S)-3-[4-(methoxymethoxy) benzyl] morpholine (H): A oily mass 2.7g (yield 96%). M.W: 237.2; Mol. For: $C_{13}H_{19}NO_3$; LC-MS (m/z): 238.1 (M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 7.09-7.11 (d, 2H), 6.92-6.94 (d, 2H), 5.14 (s, 2H), 3.54-3.62 (m, 2H), 3.27-3.33 (m, 2H), 3.00-3.05 (t, 1H), 2.65-2.77 (m, 3H), 2.18-2.44 (t, 2H), 1.35 (s, 1H).

Preparation of (3S)-3-[4-(methoxymethoxy) benzyl]–N-cyclohexylmorpholine-4-carboxamide (3 I): A white solid 1g (Yield 83%). M.W: 362.4; Mol. For: $C_{20}H_{30}N_2O_4$; LC-MS (m/z): 363.3 (M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 7.10-7.12 (d, 2H), 6.92-6.94 (d, 2H), 5.99-6.01 (d, 1H), 5.14 (s, 2H), 3.97 (s, 1H), 3.80-3.83 (d, 1H), 3.50-3.59 (m, 2H), 3.35 (s, 3H), 3.06-3.09 (m, 2H), 2.84-2.90 (m, 1H), 2.60-2.66 (m, 1H), 1.53-1.71 (m, 4H), 1.03-1.22 (m, 4H).

Preparation of (3S)-3-(4-methoxymethoxy) benzyl–N-phenylmorpholine-4-carboxamide (3 J): A white solid 0.8g (Yield 80%). M.W: 356.4; Mol. For: $C_{20}H_{24}N_2O_4$; LC-MS (m/z): 357.3(M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 8.35 (s, 1H), 7.13-7.34 (m, 7H), 6.90-6.93 (d, 2H), 5.09 (s, 2H), 4.21 (s, 1H), 3.88-3.91 (d, 1H), 3.75-3.78 (d, 1H), 3.60-3.63 (d, 1H), 3.37-3.43 (m, 2H), 3.25-3.29 (m, 1H), 2.92-2.96 (m, 1H), 2.80-2.81 (m, 2H).

Preparation of benzyl [(3S)-3-(4-methoxymethoxy) benzyl] morpholine-4-acetate (3 K): A white solid 1g (Yield 88%). M.W: 385.4; Mol. For: $C_{22}H_{27}NO_5$; LC-MS (m/z): 386.4 (M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 7.30-7.39 (m, 5H), 6.99-7.02 (d, 2H), 6.88-6.92 (d, 2H), 5.18 (s, 2H), 4.27-4.29 (d, 1H), 3.88-3.90 (d, 1H), 3.57-3.61 (m, 1H), 3.35 (s, 3H), 3.32 (s, 2H), 3.04-3.08 (t, 1H), 2.66-2.82 (m, 2H), 2.30-2.38 (m, 2H).

Preparation of (3S)-3-[(4-methoxymethoxy)benzyl] morpholine-4-phenylbutan-1-one (3 L): A white solid 710mg (yield 63%). M.W: 383.4; Mol. For: $C_{23}H_{29}NO_4$; LC-MS (m/z): 384.3(M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 7.03-7.28 (m, 7H), 6.90-6.93 (d, 2H), 5.14 (s, 2H), 4.15-4.18 (d, 1H), 3.81-3.88 (d, 2H), 3.60-3.69 (m, 2H), 3.36 (s, 3H), 3.06-3.09 (m, 1H), 2.90-2.94 (m, 2H), 2.67-2.71 (m, 2H), 2.13-2.18 (t, 2H), 1.57-1.68 (m, 2H).

Preparation of {(3S)-3-[4-(methoxymethoxy) benzyl] morpholin-4-yl}(phenyl)methanone (3 M): A white solid 810mg (Yield 80%). M.W: 341.4; Mol. For: $C_{20}H_{23}NO_4$; LC-MS (m/z): 342.3 (M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 7.48-7.66 (m, 5H), 7.10-7.13 (d, 2H), 6.87-6.90 (d, 2H), 5.15 (s, 2H), 4.23-4.27 (d, 1H), 3.97-4.01 (d, 1H), 3.36 (s, 3H), 3.20-3.25 (m, 1H), 2.91-2.96 (m, 2H), 2.67-2.83 (m, 2H).

Preparation of {(3S)-3-[4-(methoxymethoxy) benzyl] morpholin-4-yl}acetonitrile (3 N):A white solid 0.5mg (yield 62%). M.W: 276.3; Mol. For: $C_{15}H_{20}N_2O_3$; LC-MS (m/z): 277.3 (M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 7.09-7.11 (d, 2H), 6.94-6.96 (d, 2H), 5.15 (s, 2H), 3.83-4.21 (d, 1H), 3.70-3.83 (m, 2H), 3.42-3.49 (m, 2H), 3.36 (s, 3H), 3.10 (t, 1H), 2.94-2.98 (m, 1H), 2.70-2.93 (d, 1H), 2.43-2.48 (m, 2H), 2.27-2.33 (m, 1H).

Preparation of 2-{(3S)-3-[4-(methoxymethoxy) benzyl] morpholin-1-phenylethanone (3 O): A white solid 0.59mg (yield 57%). M.W: 355.4; Mol. For: $C_{21}H_{25}NO_4$; LC-MS (m/z): 356.3(M+1); ^{1}HNMR (400MHz, $DMSOD_6$): δ 7.48-7.65 (m, 5H), 7.10-7.13 (d, 2H), 6.87-6.90 (d, 2H), 5.13 (s, 2H), 4.24-4.28 (d, 1H), 3.97-4.01 (d, 1H), 3.51-3.74 (m, 4H), 3.35 (s, 3H), 3.20-3.25 (m, 1H), 2.91-2.96 (m, 2H), 2.67-2.83 (m, 2H).

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 compound (3 L) 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 (3 I – 3 O).

Compound No.	Inhibition Zone Diameter (mm)								
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**
3 I	10	19	21	11	19	11	10	20	**22**
3 J	12	17	18	10	10	13	13	19	**21**
3 K	13	29	26	22	13	25	19	23	**24**
3 L	17	20	21	10	12	12	12	13	**17**
3 M	09	26	27	16	19	10	15	19	**19**
3 N	11	29	25	18	20	13	18	16	**20**
3 O	12	30	28	20	16	29	19	29	**28**
Control (Solvent)	8	11	17	12	11	14	11	13	**11**
Ciprofloxacin	---	20	22	16	13	17	16	21	**23**
Fluconazole	**14**	---	---	---	---	---	---	---	---

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.

CONCLUSION

In this study, the synthesis of some morpholine derivatives (3 I – 3 O) 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 antibacterial and antifungal activity.

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