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SYNTHESIS AND BIOLOGICAL EVALUATION OF MORPHOLINE AND SALICYLAMIDE NUCLEUS BASED DERIVATIVES.

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ABSTRACT

Morpholine backbone is essential in different pharmacologically active synthetic compounds. Present work is synthesis of novel morpholine and salicylamide nucleus based compounds such as 3-amino-2, 2-dimethylpropyl 2-(2-(2-morpholinoethylcarbomyl)phenoxy)acetate and their derivatives (6 L – 6 R). The compounds were synthesized in multistep reaction with more efficient process. Starting materials are 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, Salicylamide, Salicylic acid, Antibacterial, Antifungal Activity.

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.

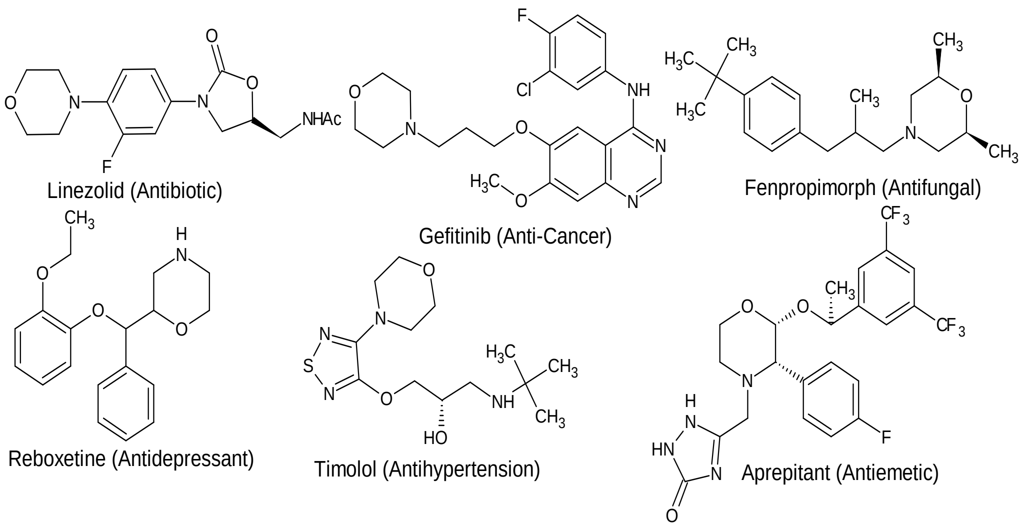


Figure 1: Marketed drugs containing a direct linked morpholine ring.

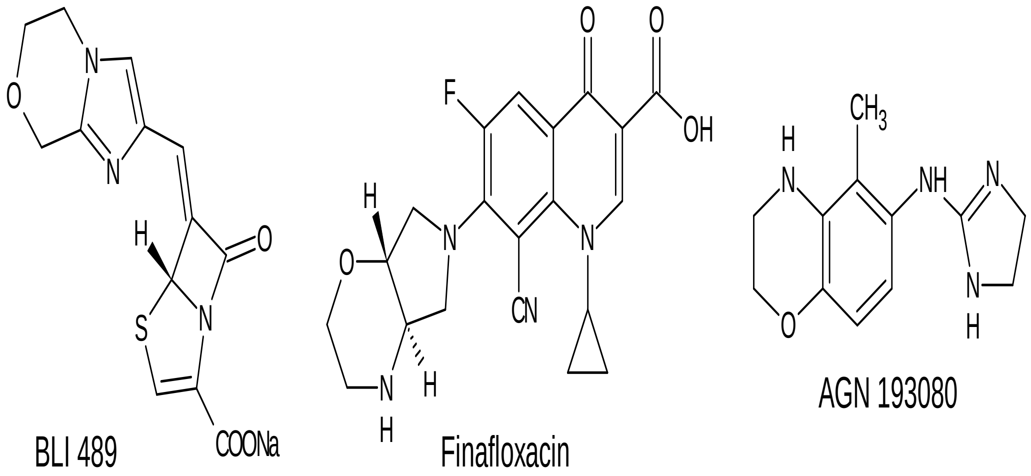


Figure 2: Clinical and preclinical drugs having a fused morpholine ring.

Hence, in the present study, we have considered chemical moiety which gives sounder biological profile like salicylic acid[10-12], 3-amino-2,2-dimethylpropan-1-ol[13-15] and 2-chloroethanamine hydrochloride[16-18]. The salicylamide[19-21] was introduced in our moiety considering the better biological activity in vaster range of therapeutic field. Suitable conditions were used for functional group protection[22] and de-protection. Here some new substituted morpholine like 3-amino- 2, 2 - dimethylpropyl 2-(2-(2-

morpholinoethylcarbomyl)phenoxy)acetate and their derivatives have been synthesized. The prepared substituted morpholine and their derivatives are very useful building blocks in medicinal chemistry. The chemical structures of the synthesized compounds were confirmed by spectroscopic methods like ^{1}HNMR and mass spectral data.

MATERIALS AND METHODS

All the reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as necessary. The moiety Ethyl cyanoacetate, salicylic acid, 3-amino-2,2-dimethylpropan-1-ol and 2-chloroethanamine hydrochloride 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 (6 L – 6 R) 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 (6 L – 6 R) 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

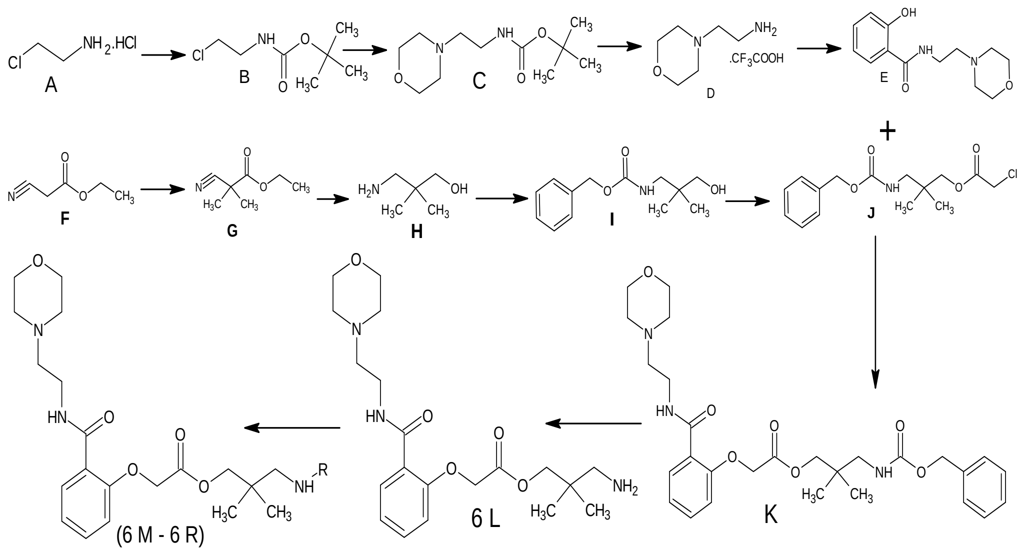
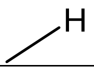
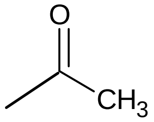
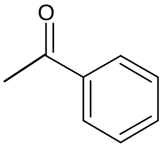
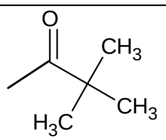
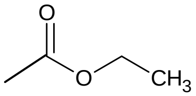
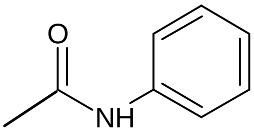
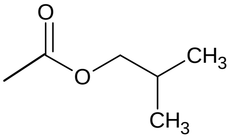


Figure 3: Synthesis of 3-amino-2, 2-dimethylpropyl 2-(2-(2-morpholinoethylcarbomyl) phenoxy)acetate and their derivatives.

Table 1: Physical data of synthesized compounds (6 L – 6 R).

Code	-R	Molecular Formula	M.wt	M.P (°C)	% Yield
6 L		$C_{20}H_{31}N_3O_5$	393.47	72-75	94
6 M		$C_{22}H_{33}N_3O_6$	435.51	146-149	85
6 N		$C_{27}H_{35}N_3O_6$	497.58	175-178	82
6 O		$C_{25}H_{39}N_3O_6$	477.59	137-140	78

6 P		$C_{23}H_{35}N_3O_7$	465.53	121-124	76
6 Q		$C_{27}H_{36}N_4O_6$	512.59	191-194	86
6 R		$C_{25}H_{39}N_3O_7$	493.59	134-137	88

Preparation of tert-butyl 2-chloroethylcarbamate (B): The BOC anhydride (20.7g, 94mmol) was added drop-wise to the solution of sodium hydrogen carbonate (18.1g, 215mmol) and 2-Chloroethylamine hydrochloride (10g, 86mmol) in water (100ml) at room temperature. The resulting suspension was stirred at room temperature for 4hr. After completion of reaction, the reaction was extracted with 2x40ml of ethyl acetate, dried with sodium sulfate and distilled out solvent completely. Yielded the titled product **(B)** as yellow oil.

Preparation of tert-butyl 2- morpholino ethylcarbamate (C): The morpholine (6.4g, 73mmol) was added to the solution of compound (B) (12g, 66mmol) Triethylamine (8.09g, 88mmol), Potassium iodide (1.1g, 6mmol) in $CHCl_3$ (60ml) and the mixture was stirred for 8hr at reflux. After completion of reaction, the reaction mass cooled to room temperature and washed with water (2x40ml), dried with sodium sulfate and distilled out solvent completely. The residue was suspended in hexane (60ml), stirred for 1hr, filtered and washed with hexane (20ml), after drying yielded the titled product (C) as white solid.

Preparation of 2-morpholinoethanamine trifluoroacetic acid salt (D): The trifluoroaceticacid (24ml) was added slowly to the solution of compound (C) (12g, 52mmol) in dichloromethane (60ml) at 0°C and the mixture was stirred for 2 hour at 0°C. After completion of reaction, the solution was evaporated in vacuum and the residue was suspended in acetone (60ml), stirred for 1hr, filtered and washed with hexane (20ml), after drying Yielded the titled product (D) Trifluoroacetic acid salt as off-white solid.

Preparation of 2-hydroxy–N-(2-Morpholinoethyl) benzamide (E): The compound (D) (11g, 45mmol), salicylic acid (5.27g, 40 mmol), EDC.HCl (11.18g, 58mmol), HOBT (6.08g, 45mmol) and N, N-Diisopropylethylamine (14.55g 112mmol) was added to the DMF (100ml). The mixture was stirred for 4 hour at room temperature. After completion of reaction, the reaction mass poured into cold water (400ml), stirred at room temperature for 2hr. Filtered and washed with water (20ml), after drying yielded the titled product (E) as off-white solid.

Preparation of Ethyl-2-cyano-2-methyl propanoate (G): The methyl iodide (56.47g, 0.39mol) was added slowly to the solution of cesium carbonate (95g, 0.29mol), Ethyl cyanoacetate (F) (15g, 0.13mol), in N,N –Dimethylforamide (45ml) at 0°C and the mixture was stirred for 4hr at room temperature. After completion of reaction, the reaction mass poured into 200ml of cold water extracted with 2x50 ml of ethyl acetate, dried with sodium sulfate. Distilled out solvent completely. Pure product isolated by doing high vacuum (10mm) distillation, vapor temperature 50-60°C, oil bath temperature 75°C yielded the titled product (G) as colorless oil.

Preparation of 3-amino-2,2-dimethyl propan-1-ol (H): The compound (G) (9g, 63mmol) in 45ml of tetrahydrofuran was added to the solution of Lithium Aluminium Hydride (3.63g, 95mmol) in tetrayhydrofuran (45ml) at 0°C and the mixture was stirred for 6 hour 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 20 ml. The filrtrate was distilled out completely. Yielded the titled product (H) as white solid.

Preparation of Benzyl (3-hydroxy-2,2-dimethylpropyl)carbamate (I)

The benzylchloroformate (50% in Toluene) (17.82 ml, 53mmol) was added to the solution of compound (H) (5g, 48mmol), sodium bicarbonate (6.1g, 72mmol) in water (50ml) and the mixture was stirred for 1 hour at room temperature. After completion of reaction, the reaction was extracted with 2x20ml of ethyl acetate, dried with sodium sulfate and distilled out completely. The solid was re-crystallized by n-Pentane (20ml). Yielded the titled product (I) as off-white solid.

Preparation of Benzyl 3-(2-chloroacetoyloxy)-2,2-dimethylpropylcarbamate (J): The chloroacetyl chloride (4.53g, 40mmol) was added to the solution compound (I) (8g, 33mmol) and triethylamine (5.06g, 50mmol) in dichloromethane (80ml) at 0°C. The mixture was stirred for 4 hr at 0°C. After completion of reaction, the solution was evaporated in vacuum and the residue was suspended in 120ml of ethyl acetate and washed with 2x40ml of 10% sodium bicarbonate solution. The organic layer dried with sodium sulfate and evaporated the solvent. Pure product isolated by flash column chromatography eluted with 10% ethyl acetate in hexane yielded the titled product (**J**) as light brown solid.

Preparation of Benzyl 3-(2-(2-(2-morpholinoethylcarbamoyl)phenoxy)acetoyloxy)-2,2-dimethyl propylcarbamate (K): The Compound (J) (5g, 19mmol) was added to the solution compound of potassium tert butoxide (3.36g, 29mmol) in N,N-Dimethylforamide (40ml) and the mixture was stirred for 15 minutes at room temperature. Then charged compound (h) (6.26g, 19mmol) lot wise and the mixture was stirred for 4 hour at room temperature. After completion of reaction, the reaction mass slowly poured into 200ml of cold water and stirred for 2 hr. Filtered and washed with water (20ml) after drying yielded the titled product (K) as off-white solid.

Preparation of 3-amino-2,2-dimethylpropyl 2-(2-(2-morpholinoethylcarbomyl) phenoxy)acetate (6 L): The methanol (60ml), Compound (K) (6g, 11mmol) and 10% Pd-C (0.6gm) catalyst was added into the hydrogenation Parr shaker reactor. 30 PSI of hydrogen gas applied and the mixture was shaken for 6 hour. 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 (6 L) as white solid.

Preparation of 3-acetamido-2,2-dimethylpropyl 2-(2-2-morpholinoethylcarbamoyl) phenoxy) acetate (6 M): The Acetyl chloride (79.79mg, 1.01mol) was added to the solution of compound (6 L) (400mg, 1.01mol), N,N-Diisopropyl ethylamine (144.52mg, 1.11mol) in dichloromethane (4ml) at 0°C and the mixture was stirred for 2 hour at 0°C. After completion of reaction, , the solution was evaporated in vacuum and the residue was suspended in 4ml of ethyl acetate and washed with 2x4ml of 10% sodium bicarbonate solution. The organic layer dried with sodium sulfate and slowly poured into 8 ml of hexane at room temperature, stirred for 2 hr at room temperature. Filtered and washed with hexane (2ml), after drying yielded the titled product (6 M) as white solid.

Preparation of 3-(benzamido)-2,2-dimethylpropyl 2-(2-(2-morpholinoethylcarbamoyl) phenoxy) acetate (6 N): The Benzoyl chloride (142.9mg, 1.01mol) was added to the solution of compound (6 L) (400g, 1.01mole), N,N-Diisopropyl ethylamine (144.52mg, 1.11mol) in dichloromethane (4ml) at 0°C and the mixture was stirred for 2 hour at 0°C. After completion of reaction, , the solution was evaporated in vacuum and the residue was suspended in 4ml of ethyl acetate and washed with 2x4ml of 10% sodium bicarbonate solution. The organic layer dried with sodium sulfate and slowly poured into 8 ml of hexane at room temperature. Stirred for 2 hr at room temperature. Filtered and washed with hexane (2ml), after drying yielded the titled product (6 N) as white solid.

Preparation of 2,2-dimethyl-3-(pivalamido)propyl 2-(2-(2-morpholinoethylcarbamoyl) phenoxy) acetate (6 O): The pivaloyl chloride (122.58mg, 1.01mol) was added to the solution of compound (6 L) (400mg, 1.01mol), N,N-Diisopropyl ethylamine (144.52mg, 1.11mol) in dichloromethane (4ml) at 0°C and the mixture was stirred for 2 hour at 0°C. After completion of reaction, , the solution was evaporated in vacuum and the residue was suspended in 4ml of ethyl acetate and washed with 2x4ml of 10% sodium bicarbonate solution. The organic layer dried with sodium sulfate and slowly poured into 8 ml of hexane at room temperature. Stirred for 2 hr at room temperature. Filtered and washed with hexane (2ml), after drying yielded the titled product (6 O) as white solid.

Preparation of Ethyl 3-(2,(2-(2-morpholinoethylcarbamoyl) phenoxy) acetoyloxy)-2,2-dimethyl propylcarbamate (6 P): The Ethyl chloroformate (108.52mg, 1.01mol) was added to the solution of compound (6 L) (400mg, 1.01mol), N,N-Diisopropyl ethylamine (144.52mg, 1.11mole) in dichloromethane (4ml) at 0°C and the mixture was stirred for 2 hour at 0°C. After completion of reaction, the solution was evaporated in vacuum and the residue was suspended in 4ml of ethyl acetate and washed with 2x4ml of 10% sodium bicarbonate solution. The organic layer dried with sodium sulfate and slowly poured into 8 ml of hexane at room temperature. Stirred for 2 hr at room temperature. Filtered and washed with hexane (2ml), after drying yielded the titled product (6 P) as white solid.

Preparation of 2,2-dimethyl-3-(3-Phenylureido)propyl 2-(2-(2-morpholinoethylcarbamoyl) phenoxy) acetate (6 Q): The phenyl isocyanate (121.09mg, 1.01mol) was added slowly to the solution of compound (6 L) (400mg, 4mol) in dichloromethane (4ml) at 0°C and the mixture was stirred for 1 hour. After completion of reaction, the reaction was evaporated in vacuum and the residue was suspended in 4ml of ethyl acetate and washed with 2x4ml of water. The organic layer dried with sodium sulfate and distilled out completely. Yielded the titled product (6 Q) as white solid.

Preparation of Isobutyl 3-(2-(2-(2-morpholinoethylcarbamoyl) phenoxy) acetoyloxy)-2,2-dimethylpropylcarbamate (6 R): The Isobutyl chloroformate (138.84 mg, 1.01mol) was added to the solution of compound (6 L) (400mg, 1.01 mol), N,N-Diisopropyl ethylamine

(144.52mg, 1.11mol) in dichloromethane (4ml) at 0°C and the mixture was stirred for 2 hour at 0°C. After completion of reaction, the solution was evaporated in vacuum and the residue was suspended in 4ml of ethyl acetate and washed with 2x4ml of 10% sodium bicarbonate solution. The organic layer dried with sodium sulfate and slowly poured into 8 ml of hexane at room temperature. Stirred for 2 hr at room temperature. Filtered and washed with hexane (2ml), after drying yielded the titled product (6 R) as white solid.

RESULTS AND DISCUSSION

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

Preparation of tert-butyl 2-chloroethylcarbamate (B): A oily mass 13.5g (Yield 87%). M.W: 179.6; Mol For: $C_7H_{14}ClNO_2$; LC-MS (m/z): 180.1 (M+1); ^{1}HNMR (400MHz, $CDCl_3$): δ 7.62 (s, 1H), 3.71-3-3.73 (t, 2H), 3.32-3.35 (t, 2H), 1.36 (s, 9H).

Preparation of tert-butyl 2- morpholino ethylcarbamate (C): A white solid 14g (Yield 91%). M.W: 230.3; Mol For: $C_{11}H_{22}N_2O_3$; LC-MS (m/z): 231.2 (M+1); ^{1}HNMR (400MHz, DMSO-d_6): δ 6.65 (s, 1H), 3.53-3.55 (t, 4H), 3.00-3.05 (m, 2H), 2.27-2.34 (m, 6H), 1.37 (s, 9H).

Preparation of 2-morpholinoethanamine trifluoroacetic acid salt (D): A off-white solid 12g (Yield 94%). M.W: 244.21; Mol For: $C_8H_{15}F_3N_2O_3$; LC-MS (m/z): 131.1 (M+1); ^{1}HNMR (400MHz, DMSO-d_6): δ 3.54-3.56 (t, 4H), 2.58-2.61 (t, 2H), 2.33 (s, 4H), 2.25-2.28 (t, 2H), 1.22-1.68 (bs, 2H).

Preparation of 2-hydroxy–N-(2-Morpholinoethyl) benzamide (E): A off-white solid 9g (Yield 80%). M.W: 250.29; Mol For: $C_{13}H_{18}N_2O_3$; LC-MS (m/z): 251.2 (M+1); ^{1}HNMR (400MHz, DMSO-d_6): δ 12.42 (s, 1H), 8.82 (s, 1H), 7.81-7.84 (d, 1H), 7.37-7.41 (t, 1H), 6.87-6.91 (t, 2H), 3.58-3.60 (t, 4H), 3.41-3.46 (m, 2H), 2.55-2.26 (t, 2H).

Preparation of Ethyl-2-cyano-2-methyl propanoate (G): colorless oil 14g (Yield 75%). M.W: 141.16; Mol For: $C_7H_{11}NO_2$; ^{1}HNMR (400MHz, DMSO-d_6): δ 4.39-4.44 (q, 2H), 1.76 (s, 6H), 1.46-1.49 (t, 3H).

Preparation of 3-amino-2,2-dimethyl propan-1-ol (H): A white solid 6.2g (Yield 94%). M.W: 103.16; Mol For: $C_5H_{13}NO$; LC-MS (m/z): 104.0 (M+1); ^{1}HNMR (400MHz, $CDCl_3$): δ 3.51 (s, 2H), 2.73 (s, 2H), 2.68 (s, 2H), 0.90 (s, 6H).

Preparation of Benzyl (3-hydroxy-2,2-dimethylpropyl)carbamate (I): A off-white solid 8.5g (Yield 74%). M.W: 237.29; Mol For: $C_{13}H_{19}NO_3$; LC-MS (m/z): 238.2 (M+1); ^{1}HNMR (400MHz, DMSO-d_6): δ 7.29-7.38 (m, 5H), 7.13-7.16 (t, 1H), 5.02 (s, 2H), 4.42 (s, 1H), 3.08 (s, 2H), 2.87-2.89 (d, 2H), 0.75 (s, 6H).

Preparation of Benzyl 3-(2-chloroacetoyloxy)-2,2-dimethylpropylcarbamate (J): A brown solid 7g (Yield 67%). M.W: 313.77; Mol For: $C_{15}H_{20}CINO_4$; LC-MS (m/z): 314.2 (M+1); ^{1}HNMR (400MHz, $CDCl_3$): δ 7.35 (s, 5H), 5.08 (s, 2H), 4.08 (s, 2H), 3.95 (s, 2H), 3.10-3.11 (d, 2H), 0.94 (s, 6H).

Preparation of Benzyl 3-(2-(2-(2-morpholinoethylcarbamoyl)phenoxy)acetoyloxy)-2,2-dimethyl propylcarbamate (K): A off-white solid 7g (Yield 66%). M.W: 527.60; Mol For: $C_{28}H_{37}N_3O_7$; LC-MS (m/z): 528.5 (M+1); ^{1}HNMR (400MHz, DMSO-d_6): δ 8.49 (s, 1H), 7.87-7.89 (d, 2H), 7.31-7.44 (m, 6H), 7.07-7.15 (m, 2H), 5.01 (s, 4H), 3.85 (s, 2H), 3.54-3.56 (s, 4H), 3.41-3.43 (q, 2H), 2.91-2.92 (d, 2H), 2.46-2.47 (d, 2H), 2.39 (s, 4H), 0.81 (s, 6H).

Preparation of 3-amino-2,2-dimethylpropyl 2-(2-(2-morpholinoethylcarbomyl) phenoxy)acetate (6 L): A white solid 4.2g (Yield 94%). M.W: 393.47; Mol For: $C_{20}H_{31}N_3O_5$; LC-MS (m/z): 394.4 (M+1); ^{1}HNMR (400MHz, DMSO-d_6): δ 8.68 (s, 1H), 7.69-7.71 (d, 1H), 7.43-7.47 (t, 1H), 7.04-7.09 (q, 2H), 4.73 (s, 2H), 4.47-4.50 (t, 2H), 3.55-3.57 (t, 4H), 3.37-3.42 (d, 2H), 3.01-3.06 (dd, 4H), 2.45-2.47 (m, 2H), 2.40 (s, 4H), 0.73 (s, 6H).

Preparation of 3-acetamido-2,2-dimethylpropyl 2-(2-2-morpholinoethylcarbamoyl) phenoxy) acetate (6 M): A white solid 376mg (Yield 85%). M.W: 435.51; Mol For: $C_{22}H_{33}N_3O_6$; LC-MS (m/z): 436.4 (M+1); ^{1}HNMR (400MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.71-7.73 (d, 1H), 7.42-7.46 (t, 1H), 7.09-7.11 (t, 1H), 6.95-6.97 (d, 1H), 4.76 (s, 2H), 3.68-3.84 (m, 6H), 3.55-3.59 (q, 2H), 3.20-3.22 (d, 2H), 2.53-2.63 (d, 6H), 2.03 (s, 2H), 0.86 (s, 6H).

Preparation of 3-(benzamido)-2,2-dimethylpropyl 2-(2-(2-morpholinoethylcarbamoyl) phenoxy) acetate (6 N): A white solid 415mg (Yield 82%). M.W: 497.58; Mol For: $C_{27}H_{35}N_3O_6$; LC-MS (m/z): 498.4 (M+1); ^{1}HNMR (400MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.17 (s, 1H), 7.82-7.88 (m, 3H), 7.39-7.43 (t, 2H), 6.93-7.10 (m, 4H), 4.69 (s, 2H), 3.71-3.95 (m, 6H), 3.12-3.19 (m, 4H), 2.81-2.89 (d, 3H), 0.86 (s, 6H).

Preparation of 2,2-dimethyl-3-(pivalamido)propyl 2-(2-(2-morpholinoethylcarbamoyl) phenoxy) acetate (6 O): A white solid 379mg (Yield 78%). M.W: 477.59; Mol For: $C_{25}H_{39}N_3O_6$; LC-MS (m/z): 478.4 (M+1); ^{1}HNMR (400MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.28-7.44 (d, 2H), 7.14-7.18 (t, 1H), 6.79-6.83 (t, 1H), 6.52-6.54 (d, 1H), 4.46 (s, 2H), 3.84-4.02 (m, 4H), 3.44-3.48 (m, 4H), 3.24-3.35 (m, 4H), 2.98-3.02 (s, 2H), 1.00 (s, 9H), 0.86 (s, 6H).

Preparation of Ethyl 3-(2,(2-(2-morpholinoethylcarbamoyl) phenoxy) acetoyloxy)-2,2-dimethyl propylcarbamate (6 P): A white solid 360mg (Yield 76%). M.W: 465.53; Mol For: $C_{23}H_{35}N_3O_7$; LC-MS (m/z): 466.4 (M+1); ^{1}HNMR (400MHz, DMSO-d_6): δ 7.63-7.66 (s, 1H), 7.32-7.43 (m, 2H), 6.99-7.04 (m, 2H), 4.49-4.56 (m, 3H), 3.87-3.96 (m, 4H), 3.51 (s, 4H), 3.01-3.07 (dd, 4H), 2.40 (d, 4H), 0.84-0.87 (t, 3H), 0.73 (s, 6H).

Preparation of 2,2-dimethyl-3-(3-Phenylureido)propyl 2-(2-(2-morpholinoethylcarbamoyl) phenoxy) acetate (6 Q): A white solid 448mg (Yield 86%). M.W: 512.59; Mol For: $C_{27}H_{36}N_4O_6$; LC-MS (m/z): 513.5 (M+1); ^{1}HNMR (400MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.93 (s, 1H), 7.82-7.88 (m, 5H), 7.39-7.43 (t, 2H), 6.43-6.47 (m, 2H), 4.72 (s, 2H), 3.74-3.98 (m, 6H), 3.13-3.20 (m, 4H), 2.83-2.91 (d, 4H), 0.83 (s, 6H).

Preparation of Isobutyl 3-(2-(2-(2-morpholinoethylcarbamoyl) phenoxy) acetoyloxy)-2,2-dimethylpropylcarbamate (6 R): A white solid 442mg (Yield 88%). M.W: 493.59; Mol For: $C_{25}H_{39}N_3O_7$; LC-MS (m/z): 494.5 (M+1); ^{1}HNMR (400MHz, DMSO-d_6): δ 7.65 (s, 1H), 7.35-7.40 (m, 2H), 7.00-7.04 (m, 2H), 4.49-4.56 (m, 3H), 4.05-4.07 (d, 2H), 3.87-3.90 (t, 2H), 3.69-3.72 (s, 4H), 3.01-3.07 (dd, 4H), 2.53-2.55 (d, 2H), 2.40 (s, 4H), 0.87-0.91 (d, 6H), 0.73 (s, 6H).

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 (6 N) 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 (6 L – 6 R).

Compound No.	Inhibition Zone Diameter (mm)								
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**
6 L	13	12	13	40	28	26	16	18	17
6 M	17	10	10	19	12	12	18	10	12
6 N	21	20	21	14	19	14	22	22	21
6 O	19	18	16	11	15	10	15	25	27
6 P	16	10	11	10	13	14	12	20	23
6 Q	18	20	22	31	23	18	22	30	28
6 R	14	22	23	13	12	15	10	10	12
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 synthesis of novel morpholine and salicylamide nucleus based derivatives (6 L – 6 R) 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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