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Synthesis and Biological Evaluation of Fused Ring Benzomorpholine Monofluoroaniline Derivatives

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ABSTRACT

A novel series of eleven novel 4-(2, 3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluoroaniline derivatives (I e – I o) have been synthesized from commercially available 2-aminophenol 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 ¹HNMR and mass spectral data. 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, Benzomorpholine, Fluoroaniline, Antibacterial, Antifungal Activity.

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INTRODUCTION

Nitrogen and oxygen containing heterocyclic compounds like morpholine¹ and fused ring morpholine²⁻⁵ are very important building blocks in medicinal chemistry⁶ 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 activity⁷ study. After the literature survey that many morpholine derivative molecule are shows very good biological activity in different therapeutic area such as antibacterial⁸, antiviral, anticancer, antimicrobial, antidiabetic, anti-Inflammatory, antimalarial, antifungal⁹, Antiemetic etc.

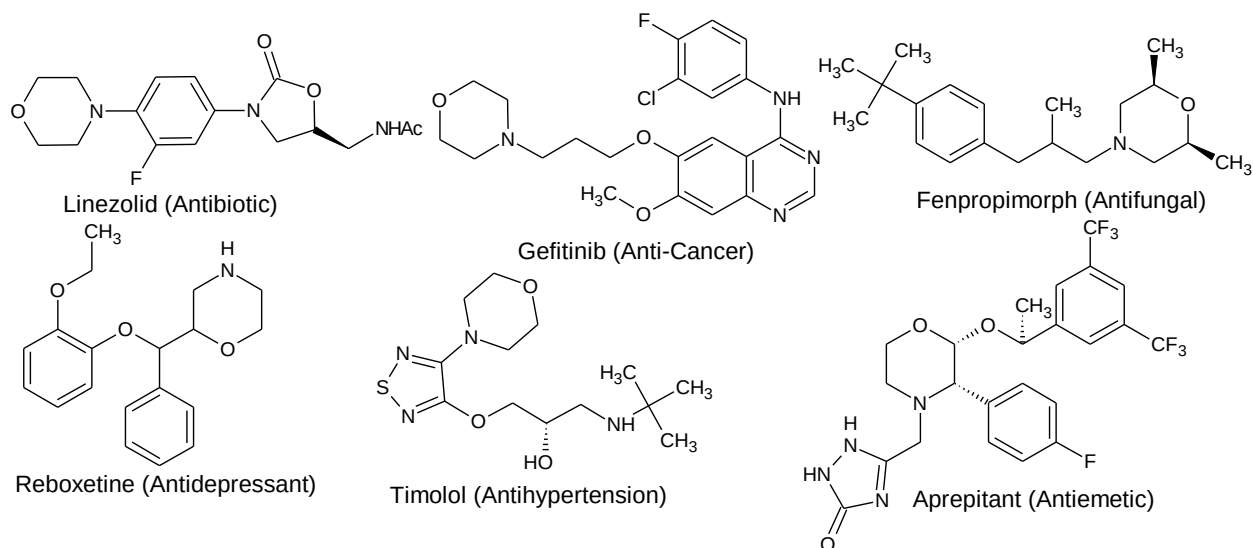


Figure 1: Marketed drugs containing a direct linked morpholine ring.

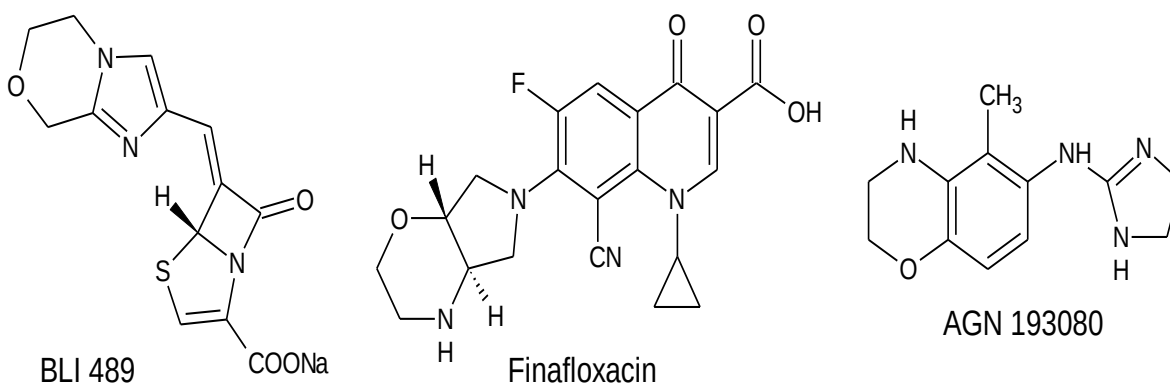


Figure 2: Clinical and preclinical drugs having a fused morpholine ring.

It is well known that the introduction of fluorine¹⁰⁻¹³ atom into organic molecule causes dramatic changes in its biological profile, mainly due to high electro negativity of fluorine causes increase lipid solubility. Hence, in the present study, some new derivatives of Benzomorpholine-3-fluoroaniline have been synthesized. Their characterization was done by spectroscopic methods like

¹HNMR and mass spectral data. Further, antibacterial and antifungal activities of these derivatives have been studied.

MATERIALS AND METHOD

All the reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as necessary. The moiety 2-Aminophenol¹⁴⁻¹⁶ 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 (¹HNMR) Were recorded in DMSO-d₆ & CDCl₃ 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 pneumoniae*, *Escherichia coli*, *Pseudomonas* sp, *Proteus* sp were used for biological activity.

Antimicrobial Activity:

The antimicrobial activity of all synthesized compounds (I e – I 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 dimethylformamide (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 (I e – I 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

Preparation of 2H -1,4-benzoxazin -3(4H)-one (a):

The chloroacetyl chloride (36.18g, 320mmol) was added drop wise to the solution of 2-aminophenol (25.4g, 232mmol), potassium carbonate (93.36g, 688mmol) 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.

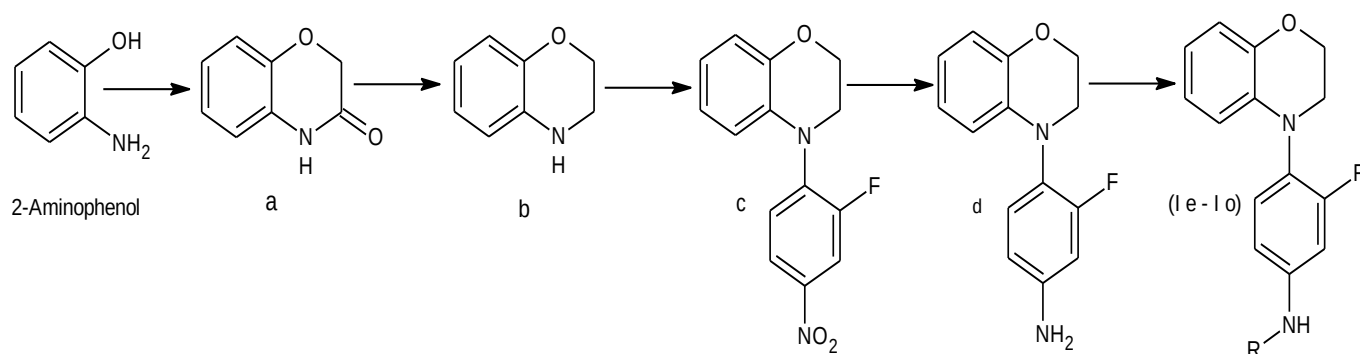
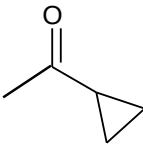
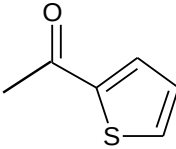
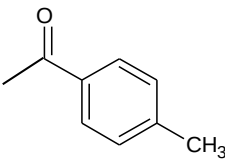
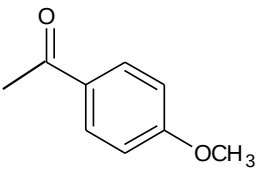
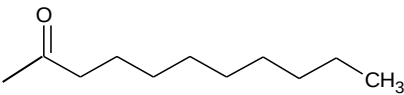
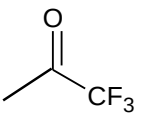
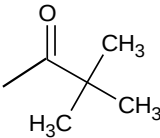
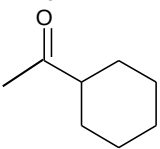


Figure 3: Synthesis of 4-(2,3-dihydro-4H-1-benzoxazin-4-yl)- 3-fluoroaniline and their derivatives.

Table1: Physical data of synthesized compounds (I e – I o).

Code	-R	Molecular Formula	M.wt	M.P (°C)	% Yield
I e		C ₁₆ H ₁₅ FN ₂ O ₂	286.30	180-182	90
I f		C ₂₁ H ₁₇ FN ₂ O ₂	348.37	164-166	95
I g		C ₂₄ H ₂₃ FN ₂ O ₂	390.45	193-195	89

I h		$C_{18}H_{17}FN_2O_2$	312.38	174-176	86
I i		$C_{19}H_{15}FN_2O_2S$	354.39	210-212	72
I j		$C_{22}H_{19}FN_2O_2$	362.39	168-170	81
I k		$C_{22}H_{19}FN_2O_3$	378.39	188-190	86
I l		$C_{24}H_{31}FN_2O_2$	398.51	144-146	71
I m		$C_{16}H_{12}F_4N_2O_2$	340.27	175-177	70
I n		$C_{19}H_{21}FN_2O_2$	328.38	171-173	86
I o		$C_{21}H_{23}FN_2O_2$	354.41	155-157	84

Preparation of 3,4-dihydro-2H-1, 4-benzoxazine (b):

The compound (a) (26.49g, 177mmole) in tetrahydrofuran (130ml) was added slowly to the solution of lithium aluminium hydride (10.11g, 266mmol) in tetrahydrofuran (130ml) at 0°C and the mixture was stirred for 16hr at room temperature. After completion of reaction, the reaction was quenched with wet sodium sulfate. The reaction mass filtered through high-low bed washed with tetrahydrofuran 25ml. The filtrate was distilled out completely. Yielding the titled product (b) as light green solid.

Preparation of 4-(2-fluoro-4-nitrophenyl)-3,4-dihydro-2H-1,4-benzoxazine (c):

The 3,4-difluoronitrobenzene (30.81g, 193mmole) was added to the solution of compound (b) (21.82g, 161mmole), potassium tert-butoxide (19.92g, 177mmole) in N,N-Dimethylformamide (130ml) and the mixture was stirred for 16 hr at 80°C. After completion of reaction, the reaction

mass slowly poured into cold water (800ml) and stirred for 2hr at room temperature. Filtered and washed with water (40 ml), after drying yielded the titled product (c) as yellow solid.

Preparation of 4-(2,3-dihydro-4H-1,4-Benzoxzin-4-yl)-3-fluroaniline (d):

The methanol (120ml), compound (c) (20g, 72mmole) and 10% palladium on carbon catalyst (2g) 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 (40ml). The filtrate was evaporated under vacuum. Yielded the titled product (d) as brown solid.

General method for the synthesis of compounds (I e - I o):

The Acid chloride (1mol.Eq) was added to the solution of compound (d) (1mol.Eq), N,N-Diisopropyl ethylamine (1.1mol.Eq) in Dichloromethane (10volume) at 0°C and the mixture was stirred for 15minute at 0°C . After completion of reaction of reaction, the solution was evaporated in vacuum and the residue was suspended in 10volume of ethyl acetate and washed with 2×4 volume of 10% sodium bicarbonate solution. The organic layer dried with sodium sulfate and slowly poured into 10 volume of hexane at room temperature. Stirred for 2hr at room temperature. Filtered and washed with hexane (2volume) to get pure crystalline white product (I e – I o).

RESULTS AND DISCUSSION

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

2H -1,4-benzoxazin -3(4H)-one (a): Off-white color solid; Yield 96%; M.W: 149.1; Mol. For: C₈H₇NO₂; LC-MS(m/z): 150.1(M+1); ¹HNMR (400MHz, CDCl₃): δ 8.89 (s, 1H), 6.94-6.97 (m, 3H), 6.81-6.84 (m, 1H), 4.62 (s, 2H).

3,4-dihydro-2H-I, 4-benzoxazine (b): Light green solid; Yield 93%; M.W: 135.1; Mol. For: C₈H₉NO; LC-MS(m/z): 136.0(M+1); ¹HNMR (400MHz, CDCl₃): δ 6.58-6.79 (m, 4H), 4.24-4.26 (t, 2H), 3.72 (s, 1H), 3.41-3.43 (t, 2H).

4-(2-fluoro-4-nitrophenyl)-3,4-dihydro-2H-1,4-benzoxazine (c): Yellow solid; Yield 84%; M.W: 274.24; Mol. For: C₁₄H₁₁FN₂O₃; ¹HNMR (400MHz, CDCl₃): δ 7.98-8.05 (m, 2H), 7.39-7.41 (t, 1H), 6.81-6.94 (m, 4H), 4.29-4.31 (t, 2H), 3.77-3.79 (t, 2H).

4-(2,3-dihydro-4H-1,4-Benzoxzin-4-yl)-3-fluroaniline (d): Brown solid; Yield 95%; M.W: 244.2; Mol For: C₁₄H₁₃FN₂O; LC-MS(m/z): 245.2(M+1); ¹HNMR (400MHz, DMSOd₆): δ 6.97-7.02 (t, 1H), 6.41-6.73 (m, 5H), 6.18-6.20 (d, 1H), 5.44 (s, 2H), 4.24-4.26 (t, 2H), 3.50-3.52 (t, 2H).

N-[4-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluorophenyl]acetamide (I e): A white color solid; yield 90%; M.P: 180-182°C; M.W: 286.3; Mol. For: C₁₆H₁₅FN₂O₂; LC-MS(m/z): 287.1(M+1); ¹HNMR (400MHz, DMSOd₆): δ 10.17 (s, 1H), 7.68-7.71 (d, 1H), 7.30-7.31 (d, 2H), 6.62-6.78 (m, 3H), 6.28-6.30 (d, 1H), 4.26-4.28 (t, 2H), 3.58-3.61 (t, 2H), 2.06 (s, 3H).

N-[4-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluorophenyl]benzamide (I f): A white color solid; yield 95%; M.P: 164-166°C; M.W: 348.3; Mol. For: C₂₁H₁₇FN₂O₂; LC MS(m/z): 349.3(M+1); ¹HNMR (400MHz, DMSOd₆): δ 10.47 (s, 1H), 7.86-7.97 (m, 2H), 7.53-7.62 (m, 3H), 7.38-7.40 (t, 1H), 6.78-6.80 (d, 1H), 6.64-6.68 (m, 2H), 6.34-6.36 (d, 1H), 4.29-4.30 (t, 2H), 3.62-3.64 (t, 2H).

N-(3-fluoro-4-(2,3-dihydrobenzo[b][1,4]oxazin-4-yl)phenyl)-4-phenylbutanamide (I g): A white color solid; yield 89%; M.P: 193-195°C; M.W: 390.4; Mol. For: C₂₄H₂₃FN₂O₂; LC MS(m/z): 391.3(M+1); ¹HNMR (400MHz, DMSOd₆): δ 10.13 (s, 1H), 7.69-7.73 (d, 1H), 7.19-7.32 (m, 5H), 6.62-6.78 (m, 3H), 6.28-6.30 (d, 1H), 4.26-4.28 (t, 2H), 3.58-3.60 (t, 2H), 2.61-2.64 (t, 2H), 2.32-2.35 (t, 2H), 1.88-1.92 (m, 2H).

N-[4-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluorophenyl]cyclopropanecarboxamide (I h): A white color solid; yield 86%; M.P: 174-176°C; M.W: 312.3; Mol. For: C₁₈H₁₇FN₂O₂; LC MS(m/z): 313.2(M+1); ¹HNMR (400MHz, DMSOd₆): δ 10.43 (s, 1H), 7.69-7.72 (d, 1H), 7.31-7.32 (m, 2H), 6.76-6.78 (d, 1H), 6.62-6.66 (m, 2H), 6.29-6.31 (d, 1H), 4.26-4.29 (t, 2H), 3.59-3.61 (t, 2H), 1.75-1.78 (m, 1H), 0.81-0.83 (d, 4H).

N-[4-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluorophenyl]Thiophene-2-carboxamide (I i): A white solid; yield 72%; M.P: 210-212°C; M.W: 354.3; Mol. For: C₁₉H₁₅FN₂O₂S; LC MS(m/z): 355.2(M+1); ¹HNMR (400MHz, DMSOd₆): δ 10.42 (s, 1H), 8.02-8.03 (d, 1H), 7.79-7.90 (m, 2H), 7.54-7.57 (d, 1H), 7.35-7.40 (t, 1H), 7.24-7.26 (t, 1H), 6.64-6.80 (m, 3H), 6.34-6.36 (d, 1H), 4.28-4.30 (t, 2H), 3.62-3.64 (t, 2H).

N-[4-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluorophenyl]-4-methylbenzamide (I j): A white solid; yield 81%; M.P: 168-170°C; M.W: 362.3; Mol. For: C₂₂H₁₉FN₂O₂; LC MS(m/z): 363.3(M+1); ¹HNMR (400MHz, DMSOd₆): δ 10.37 (s, 1H), 7.86-7.89 (d, 3H), 7.60-7.62 (d, 1H), 7.34-7.39 (t, 3H), 6.78-6.80 (d, 1H), 6.64-6.68 (m, 2H), 6.33-6.64 (d, 1H), 4.28-4.30 (t, 2H), 3.62-3.64 (t, 2H), 2.39 (s, 3H).

N-[4-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluorophenyl]-4-methoxybenzamide (I k): A white solid; yield 86%; M.P: 188-190°C; M.W: 378.3; Mol. For: C₂₂H₁₉FN₂O₃; LC MS(m/z): 379.3(M+1); ¹HNMR (400MHz, DMSOd₆): δ 10.30 (s, 1H), 7.85-7.97 (m, 3H), 7.59-7.61 (d, 1H),

7.34-7.38 (t, 3H), 7.07-7.09 (d, 1H), 6.64-6.80 (m, 2H), 6.33-6.35 (d, 1H), 4.28-4.30 (t, 2H), 3.84 (s, 3H), 3.62-3.64 (t, 2H).

N-(3-Fluoro-4-(2,3-dihydrobenzo[b][1,4]oxazin-4-yl)phenyl)decanamide (I l): A white solid; yield 71%; M.P: 144-146°C; M.W: 398.5; Mol. For: C₂₄H₃₁FN₂O₂; LC MS(m/z): 399.4(M+1); ¹HNMR (400MHz, DMSOd₆): δ 10.13 (s, 1H), 7.70-7.73 (d, 1H), 7.30-7.33 (m, 2H), 6.76-6.78 (d, 1H), 6.62-6.66 (m, 2H), 6.28-6.62 (d, 1H), 4.26-4.29 (t, 2H), 3.58-3.60 (t, 2H), 2.29-2.33 (t, 2H), 1.57-1.60 (t, 2H), 1.25-1.29 (m, 12H), 0.83-0.87 (m, 3H).

N-[4-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluorophenyl]-2,2,2-trifluoroacetamide (I m): A white solid; yield 70%; M.P: 175-177°C; M.W: 340.27; Mol. For: C₁₆H₁₂F₄N₂O₂; LC MS(m/z): 341.3(M+1); ¹HNMR (400MHz, DMSOd₆): δ 11.47 (s, 1H), 7.67-7.71 (d, 1H), 7.53-7.55 (d, 1H), 7.40-7.45 (t, 1H), 6.79-6.81 (m, 1H), 6.67-6.69 (m, 2H), 6.36-6.67 (m, 1H), 4.27-4.29 (t, 2H), 3.62-3.64 (t, 2H).

N-[4-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluorophenyl]-2,2-dimethylpropanamide (I n): A white solid; yield 86%; M.P: 171-173°C; M.W: 328.3; Mol. For: C₁₉H₂₁FN₂O₂; LC MS(m/z): 329.3(M+1); ¹HNMR (400MHz, DMSOd₆): δ 9.41 (s, 1H), 7.74-7.78 (d, 1H), 7.47-7.50 (d, 1H), 7.28-7.32 (t, 1H), 6.76-6.79 (d, 1H), 6.62-6.66 (m, 2H), 6.29-6.31 (d, 1H), 4.27-4.29 (t, 2H), 3.59-3.61 (t, 2H), 1.23 (s, 9H).

N-[4-(2,3-dihydro-4H-1,4-benzoxazin-4-yl)-3-fluorophenyl]cyclohexanecarboxamide (I o): A white solid; yield 84%; M.P: 155-157°C; M.W: 354.4; Mol. For: C₂₁H₂₃FN₂O₂; LC MS(m/z): 355.3(M+1); ¹HNMR (400MHz, DMSOd₆): δ 10.02 (s, 1H), 7.68-7.72 (d, 1H), 7.25-7.34 (m, 2H), 6.73-6.76 (d, 1H), 6.59-6.63 (m, 2H), 6.26-6.59 (d, 1H), 4.24-4.26 (t, 2H), 3.56-3.57 (s, 2H), 2.29 (t, 1H), 1.61-1.79 (m, 5H), 1.20-1.39 (m, 5H).

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 (I k) 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 (I e - I o).

Compound No.	Inhibition Zone Diameter (mm)								
	I	II	III	IV	V	VI	VII	VIII	IX
I e	12	14	12	17	10	14	12	11	16
I f	11	18	16	17	18	19	16	19	15
I g	10	15	15	19	10	14	11	14	14

I h	14	19	19	15	10	11	15	11	16
I i	9	16	14	14	15	16	13	17	13
I j	8	15	15	10	12	15	15	17	12
I k	4	18	19	17	19	10	19	18	13
I l	6	15	15	18	17	17	16	19	12
I m	13	11	10	16	14	15	17	15	16
I n	6	10	11	17	10	12	10	14	18
I o	15	11	19	10	19	10	10	19	14
Control (Solvent)	7	13	12	12	12	11	12	12	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 pneumoniae, V-Escherichia coli, VI- Pseudomonas sp, VII- Proteus s.

CONCLUSION

In this study, the synthesis of some fused ring benzomorpholine derivatives (I e – I o) was performed and their structures were confirmed by ¹HNMR, 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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REFERENCES

1. Review of morpholine and its derivatives, Merck Index, 12th ed. published by Merck & co, Whitehouse Station, NJ, 1996;1074-5.
2. Pushpak Mizar, Bekington Myrboth. Synthesis of substituted 4-(3-alkyl-1,2,4-oxadiazol-5-ylmethyl)-3,4-dihydro-2H-1,4-benzoxazines and 4-(1H-benzimidazol-2-ylmethyl)-3,4-dihydro-2H-1,4-benzoxazines. Tetrahedron Letters. 2006;47(44):7823-26.
3. Satoshi Sakami, Koji Kawai, Masayuki Maeda, Takumi Aoki, Hideaki Fujii, Hiroshi Ohno et al. Design and synthesis of a metabolically stable and potent antitussive agent, a novel δ opioid receptor antagonist, TRK-851. Bioorg Med Chem. 2008;16(17),7956-67.
4. Gang Zhou, Nicolas Zorn , Pauline Ting , Robert Aslanian , Mingxiang Lin , John Cook et al. Development of Novel Benzomorpholine Class of Diacylglycerol Acyltransferase I Inhibitors. Med Chem Lett. 2014;5(5),544-49.

5. Xianhai Huang, Dmitri Pissarnitski, Hongmei Li, Theodros Asberom, Hubert Josien, Xiaohong Zhu et al. Efficient synthesis and reaction pathway studies of novel fused morpholine oxadiazolines for use as gamma secretase modulators. *Tetrahedron Letters*. 2012;53(47),6451-55.
6. Madhu Chopra, VK Ahluwalia. Ane's Student Edition, Text Book of Medicinal Chemistry, 1st ed. New Delhi Published by Ane's Books Pvt. Ltd, 2008.
7. Basudeb Achari, Sukhendu BM, Pradeep Dutta, Chinmay Chowdhury. Perspectives on 1, 4-Benzodioxions, 1, 4-Benzoxazines and Their 2, 3- Dihydro Derivatives. *Synlett*. 2004;14,2449-67.
8. Duhalde V, Lahillie B, camou F, Pedeboscq S, pometan JP. Proper use of antibiotics: a prospective study on the use of linezolid in a French university hospital. *Pathologie biologique*. 2007;55(10),478-81.
9. Marireau C; Guilloton M; kartst F. In vivo effects of fenpropimorph on the yeast *Saccharomyces cerevisiae* and determination of the molecular basis of the antifungal property. *Antimicrobial agents and chemotherapy*. 1990;34(6),989-93.
10. Diana Gimenez, Cecilia Andreu, Marcel lidel olmo, Tera varea, Dolores Diaz, Gregorio Asensio. The introduction of fluorine atoms or trifluoromethyl groups in short cationic peptides enhances their antimicrobial activity. *Bioor Med Chem*. 2006;14(20),6971-78.
11. Böhm HJ, Banner D, Bendels S, Kansy M, Kuhn B, Müller K et al. Fluorine in Medicinal Chemistry. *Chembiochem*. 2004;5(5),637-43.
12. John W Clader. The discovery of ezetimibe: a view from outside the receptor. *J. Med. Chem*. 2004;47,1-9.
13. Massa MA, Spangler DP, Durley RC, Hickory BS, Connolly DT, Witherbee BJ et al. Novel heteroaryl replacements of aromatic 3-tetrafluoroethoxy substituents in trifluoro-3-(tertiaryamino)-2-propanols as potent inhibitors of cholesteryl ester transfer protein. *Bioor Med Chem Lett*, 2001;11,1625-28.
14. Bitu Baghernejad, Majid M. Heravi, Hossein A.Oskooie, Fatemeh F. Bamoharram. Heteropolyacids as an efficient and reusable catalytic system for the regiospecific nitration of phenols with metal nitrates. *Chem Soc Ethiop*. 2012;26(1),145-52.
15. Zhongkui Zhao. Cobalt-modified molybdenum carbide as an efficient catalyst for chemoselective reduction of aromatic nitro compounds. *Green chemistry*. 2014;16(3),1274-81.

16. Weichen Du, Gongzhou Chen, Renfeng Nie, Yingwei Li, Zhaoyin Hou. Highly dispersed Pt in MIL-101: An efficient catalyst for the hydrogenation of nitroarenes. *Catalysis communications*. 2013;41,56-59.

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