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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-(2,3-DIHYDRO-4H-PYRIDO[3,2-B][1,4]OXAZIN-4-YL)-3-FLUOROANILINE DERIVATIVES

Loganathan Velupillai*[1], Prashant P Dixit[2], M.S. Shingare[1], D.V.Mane[1], Choudhari B R[3]

[1.] Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India- 431004.

[2.] Department of Microbiology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Sub campus, Osmanabad, Maharashtra, India- 413501.

[3.] Department of Chemistry, Jaihind College, Dhule, Maharastra, India-424002.

Abstract:

A series of seven compounds 4-(2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-yl)-3-fluoroaniline derivatives (5I e – 5I k) was prepared from commercially available 2-Amino-3-Hdroxy Pyridine. The morpholine, pyridine, fluorine, aniline and amides were introduced in our moiety considering the better biological results in vaster range of therapeutic area. The compound bearing such moieties gives good bio-active data. The more yield and good quality of the synthesized product was shows that there is no side reaction and by product while the organic synthesis. The structure confirmation of the synthesized molecules was confirmed by means of proton nuclear magnetic resonance spectroscopy and LC-MS spectroscopy. The synthesized NCE's were further tested for their antibacterial and antifungal studies. Some of the molecules were identified to show better antibacterial and antifulgul activity.

Keywords: *Pyridine morpholine, Morpholine, Fluoroaniline, Antibacterial, Antifungal.*

Corresponding Author:

Loganathan velupillai,

Department of Chemistry,

Dr. Babasaheb Ambedkar Marathwada University,

Aurangabad, Maharashtra, India- 431004.

**Telephone: +910240-2471399;*

Email: vloganathan007@gmail.com

QR code

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INTRODUCTION

The heterocyclic compounds like morpholine [1] and fused ring morpholine [2-5] are very essential building blocks in medicinal chemistry [6] field. So the morpholine derivatives are extensively very important in the new drug discovery research, which induce 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, Antimalarials, and antifungal [9], Antiemetic etc.

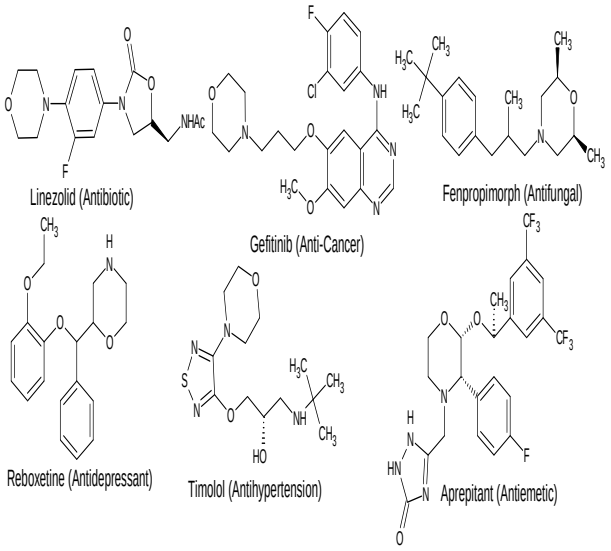


Fig 1: Marketed Drugs Containing A Direct Linked Morpholine Ring.

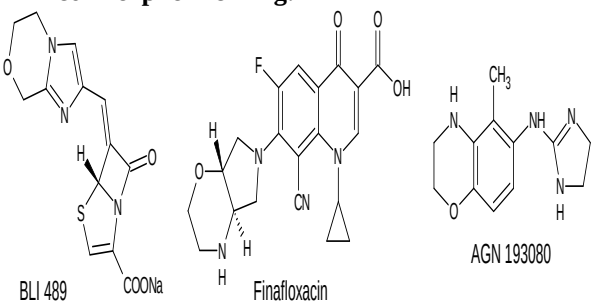


Fig 2: Clinical and Preclinical Drugs Having A Fused Morpholine Ring.

It is better concept that the introduction of fluorine [10-13] atom into organic compound makes spectacular changes in its biological activity, mainly because of more electro negativity of fluorine causes increase lipid solubility. Hence, in the present paper, reports the remarkable fast synthesis of some new derivatives of Pyridine morpholine-3-fluroaniline have been prepared. Their structure confirmation of the synthesized compounds was confirmed by proton NMR spectroscopy and LC-MS spectroscopy spectrum. Anti-bacterial and antifungal activities of these derivatives have been studied. The synthesized compounds were further tested for their antibacterial and antifungal studies. Some of the molecules were identified to show good antibacterial and antifungal activity, the results were summarized in table-2.

MATERIALS AND METHODS

All the organic reagents, chemicals and solvents were used as obtained from the supplier or recrystallized/redistilled as necessary. The moiety 2-Amino-3-Hdroxy Pyridine [14-15] and 3,4-Difluoronitrobenzene[16-21] is commercially available and is also available in Sigma Aldrich. This can be also prepared 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 (5I e – 5I 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 Dimethyl sulphoxide 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 Poloxamer 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 dimethyl sulphoxide (positive control) and without dimethyl sulphoxide (negative control) were also included in the test. The Petri plates were put in the dark conditions at 37^0C 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 (5I e – 5I 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 Poloxamer 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 (Fluconazole), 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

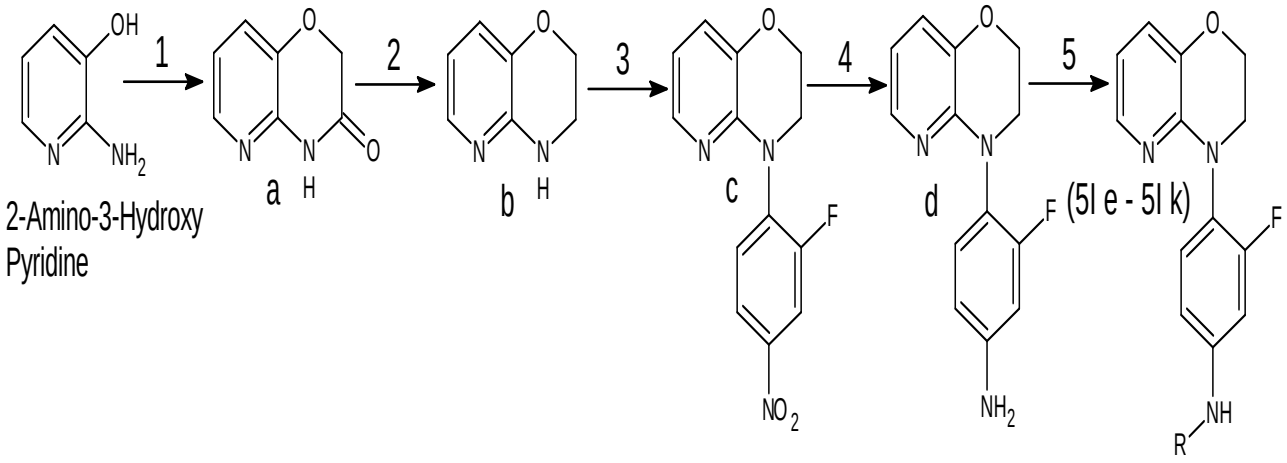
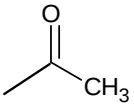
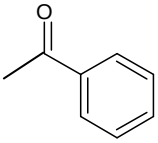
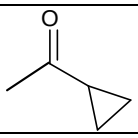
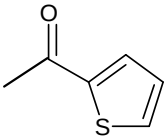
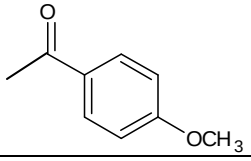
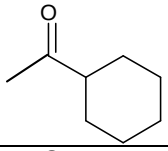
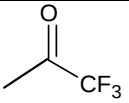


Fig 3: Synthesis of 4-(2,3-dihydro-4H-Pyrido[3,2-b][1,4]oxazin-4-yl)-3-Fluoroaniline and Their Derivatives.

Table1: Physical Data of Synthesized Compounds (5I e – 5I k).

Code	-R	Molecular Formula	M.Wt	M.P (°C)	% Yield
5I e		$C_{15}H_{14}FN_3O_2$	287.28	193-195	94
5I f		$C_{20}H_{16}FN_3O_2$	349.35	181-183	91
5I g		$C_{17}H_{16}FN_3O_2$	313.32	172-174	89
5I h		$C_{18}H_{14}FN_3O_2S$	355.38	203-205	96
5I i		$C_{21}H_{18}FN_3O_3$	379.38	187-189	98
5I j		$C_{20}H_{22}FN_3O_2$	355.40	162-164	86
5I k		$C_{15}H_{11}F_4N_3O_2$	341.26	184-186	88

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-(2-fluoro-4-nitrophenyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (c): The 3,4-Difluoronitrobenzene (6g, 52 mmole) was added slowly to the solution of compound (b) (6 g, 44 mmole), Triethylamine (6.7 g, 66 mmole) in Chloroform (60 ml) and the mixture was stirred for 16 hr at reflux. After completion of reaction, the solution was evaporated in vacuum and the residue was suspended in water (60 ml) and the suspension

was stirred for 2 hr at room temperature. Filtered and washed with water (20 ml), 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-yl)-3-fluoroaniline (d): The Methanol (60 ml), compound (c) (6 g, 21 mmole) and 10% Pd-C catalyst (0.6 g) was added charged 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 (12 ml). The filtrate was evaporated under vacuum. Yielded the titled product (d) as brown solid.

General method for the synthesis of compounds (5I e – 5I k): The corresponding carboxylic acid (1mol.Eq) was taken in water (10volume). Followed by charged EDC.HCl (1.2 mol.Eq), HOBT (1 mol.Eq), N-Methyl morpholine (1.5 mol.Eq) and compound (d) (1mol.Eq). Then the mixture was continued to stir for 5hr at room temperature. After completion of reaction, the solids were observed in reaction mass, filtered and washed with water, after drying yielded the titled product as crude white solid. The crude solid further purified by column chromatography using 60-120 mesh silica column chromatography and eluted with 30% acetone in hexane. After evaporation of product fractions in rotavapor gives the titled product (5I e – 5I 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-(2-fluoro-4-nitrophenyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (c): Yellow solid; Yield 92%; M.W: 275.23; Mol.For: $C_{13}H_{10}FN_3O_3$; LC-MS (m/z): 276.1(M+1); ^{1}HNMR (400MHz, $DMSOd_6$): δ 8.66-8.69 (1H, m), 8.33-8.35 (2H, m), 7.38-7.43 (1H, m), 6.56-6.58 (2H, m), 4.47 (2H, t, J=4.4 Hz), 3.87 (2H, t, J=3.6 Hz).

4-(2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-yl)-3-fluoroaniline (d): A white solid; Yield 89%; M.W: 245.25; Mol.For: $C_{13}H_{12}FN_3O$; LC-MS (m/z): 246.2(M+1); ^{1}HNMR (400MHz, $DMSOd_6$): δ 7.50-7.52 (1H, m), 6.96-7.02 (2H, m), 6.54-6.57 (1H, m), 6.36-6.38 (2H, m), 5.34 (2H, s), 4.27 (2H, t, J=4.4 Hz), 3.67 (2H, t, J=3.6 Hz).

***N*-[4-(2,3-dihydro-4*H*-pyrido[3,2-*b*][1,4]oxazin-4-yl)-3-fluorophenyl]acetamide (5I e):** A white crystalline solid; Yield 94%; M.W: 287.28; Mol.For: $C_{15}H_{14}FN_3O_2$; LC-MS (m/z): 288.2 (M+1); ^{1}HNMR (400MHz, $DMSOd_6$): δ 10.13 (1H, s), 7.54-7.63 (2H, m), 7.26-7.32 (1H, m), 7.06-7.08 (2H, m), 6.61-6.64 (1H, m), 4.31 (2H, t, J=4.0 Hz), 3.76 (2H, t, J=3.6 Hz), 2.06 (3H, s).

***N*-[4-(2,3-dihydro-4*H*-pyrido[3,2-*b*][1,4]oxazin-4-yl)-3-fluorophenyl]benzamide (5I f):** A white crystalline solid; Yield 91%; M.W: 349.35; Mol.For: $C_{20}H_{16}FN_3O_2$; LC-MS (m/z): 350.2 (M+1); ^{1}HNMR (400MHz, $DMSOd_6$): δ 10.27 (1H, s), 7.86-7.97 (2H, m), 7.53-7.62 (5H, m), 7.38-7.40 (1H, m), 6.78-6.80 (1H, m), 6.64-6.68 (2H, m), 4.32 (2H, t, J=4.1 Hz), 3.72 (2H, t, J=3.7 Hz).

***N*-[4-(2,3-dihydro-4*H*-pyrido[3,2-*b*][1,4]oxazin-4-yl)-3-fluorophenyl]cyclopropane carboxamide (5I g):** A white crystalline solid; Yield 89%; M.W: 313.32; Mol.For: $C_{17}H_{16}FN_3O_2$; LC-MS (m/z): 314.1 (M+1); ^{1}HNMR (400MHz, $DMSOd_6$): δ 10.23 (s, 1H), 7.89-7.92 (1H, m), 7.51-7.52 (2H, m), 6.76-6.78 (1H, m), 6.62-6.66 (2H, m), 6.29-6.31 (1H, m), 4.36 (2H, t, J=4.4 Hz), 3.79 (2H, t, J=3.6 Hz), 1.75-1.78 (1H, m), 0.82-0.84 (4H, m).

***N*-[4-(2,3-dihydro-4*H*-pyrido[3,2-*b*][1,4]oxazin-4-yl)-3-fluorophenyl]thiophene-2-carboxamide (5I h):** A white crystalline solid; Yield 96%; M.W: 355.3; Mol.For: $C_{18}H_{14}FN_3O_2S$; LC-MS (m/z): 355.1 (M+1); ^{1}HNMR (400MHz, $DMSOd_6$): δ 10.22 (1H, s), 8.02-8.04 (1H, m), 7.92-7.99 (2H, m), 7.51-7.54 (1H, m), 7.35-7.40 (1H, m), 7.24-7.26 (1H, m), 6.64-6.76 (2H, m), 4.35 (2H, t, J=3.4 Hz), 3.72 (2H, t, J=3.6 Hz).

***N*-[4-(2,3-dihydro-4*H*-pyrido[3,2-*b*][1,4]oxazin-4-yl)-3-fluorophenyl]-4-methoxybenzamide (5I i):** A white crystalline solid; Yield 98%; M.W: 379.3; Mol.For: $C_{21}H_{18}FN_3O_3$; LC-MS (m/z): 380.1 (M+1); ^{1}HNMR (400MHz, $DMSOd_6$): δ 10.20 (1H, s), 7.85-

7.97 (2H, m), 7.59-7.61 (1H, m), 7.34-7.38 (3H, m), 7.07-7.09 (1H, m), 6.64-6.76 (2H, m), 6.33-6.35 (1H, m), 4.36 (2H, t, J=3.6 Hz), 3.84 (3H, s), 3.73 (2H, t, J=3.6 Hz).

***N*-[4-(2,3-dihydro-4*H*-pyrido[3,2-*b*][1,4]oxazin-4-yl)-3-fluorophenyl]cyclohexane carboxamide (5I j):** A white crystalline solid; Yield 86%; M.W: 355.4; Mol.For: $C_{20}H_{22}FN_3O_2$; LC-MS (m/z): 356.2 (M+1); ^{1}HNMR (400MHz, $DMSOd_6$): δ 10.22 (1H, s), 7.82-7.89 (1H, d), 7.35-7.38 (2H, m), 6.73-6.76 (1H, m), 6.59-6.63 (2H, m), 6.20-6.26 (1H, m), 4.35 (2H, t, J=4.0 Hz), 3.87 (2H, t, J=3.7 Hz), 2.29 (1H, m), 1.62-1.79 (5H, m), 1.20-1.39 (5H, m).

***N*-[4-(2,3-dihydro-4*H*-pyrido[3,2-*b*][1,4]oxazin-4-yl)-3-fluorophenyl]-2,2,2-trifluoroacetamide (5I k):** A white crystalline solid; Yield 88%; M.W: 341.2; Mol.For: $C_{15}H_{11}F_4N_3O_2$; LC-MS (m/z): 342.1 (M+1); ^{1}HNMR (400MHz, $DMSOd_6$): δ 11.21 (1H, s), 7.69-7.71 (1H, m), 7.51-7.55 (1H, m), 7.40-7.45 (1H, m), 6.78-6.81 (1H, m), 6.66-6.69 (2H, m), 4.78 (2H, t, J=3.6 Hz), 3.85 (2H, t, J=3.6 Hz).

BIOLOGICAL EVALUATION

Some of the synthesized molecules were shows better antimicrobial activity inhibition. Antimicrobial screening results of the tested compounds are displayed 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 (5I e - 5I k)

Compound No.	Inhibition Zone Diameter (mm)								
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**
5I e	10	16	14	15	11	17	14	12	**19**
5I f	13	20	18	21	19	21	18	17	**19**
5I g	14	16	17	22	18	15	14	19	**17**
5I h	14	19	19	15	10	11	15	11	**16**
5I i	16	18	19	16	13	19	15	17	**18**
5I j	16	17	16	14	16	20	21	18	**19**
5I k	14	22	22	19	20	21	23	24	**19**
Control (Solvent)	09	15	17	14	13	15	12	14	**13**
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 s.

CONCLUSION

In this learning, the synthesized compounds of some 4-(2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-yl)-3-fluoroaniline derivatives (5I e – 5I k) was performed and their structures were confirmed by ^{1}HNMR, Mass spectroscopy techniques. In addition, the newly prepared molecules were further screened for their antibacterial and antifungal studies. Some of them were indentified to possess better 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 biologie. 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 chemotheraphy. 1990;34(6),989-93.
10. Diana Gimemez, Cecilia Andreu, Marcel lidel olmo, Tersa 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.Amal Joseph PJ, Priyadarshini S, Lakshmi Kantam M, Maheswaran H. Sulfonic acid resin and copper salts: a novel heterogeneous catalytic system for direct hydroxylation of haloarenes. Catalysis Science & Technology. 2011;1(4),582–85.
15. Behrman E.J. The Persulfate Oxidation of Phenols and Arylamines (The Elbs and the Boyland-Sims Oxidations). Organic Reactions (Hoboken, NJ, United States). 1988;35.
16. A novel method for the nitration of simple aromatic compounds. Smith Keith, Musson Adam, Gareth A DeBoos. J Org Chem. 1998; 63(23): 8448-8454.
17. Aromatic nitration with potassium nitrate or nitric acid and boron trifluoride monohydrate. Olah George A, Wang Qi, Xing-Ya Li, Bucsi Imre. Synthesis. 1992; 11: 1085-6.
18.Elemental fluorine Part 12. Fluorination of 1,4-disubstituted aromatic compounds. Richard D Chambers, John Hutchinson, Matthew E Sparrowhawk, Graham Sandford, John S Moilliet, Julie Thomson. Journal of Fluorine Chemistry. 2000; 102(1-2): 169-173.
19.Synthesis of aromatic fluoro compounds by nucleophilic exchange of nitro groups by fluoride. Effenberger Franz, Streicher Willi. Chemische Berichte. 1991; 124(1): 157-62.
20. Efficient phosphorus catalysts for the halogen-exchange (Halex) reaction. Lacour Marie-Agnes, Zablocka Maria, Duhayon Carine, Majoral Jean-Pierre, Taillefer Marc. Advanced Synthesis & Catalysis. 2008; 350(17): 2677-2682.
21. Continuous flow coupling and decarboxylation reactions promoted by copper tubing. Zhang Yun, Jamison Timothy F, Patel Sejal, Mainolfi Nello. Organic Letters. 2011; 13(2): 280-283.