ION EXCHANGE AND ADSORPTION
ISSN: 1001-5493
Vol. 23, Issue-02, 2023
pp.142-150

SYNTHESIS, CHARACTERISATION AND ANTIMICROBIAL STUDIES OF SOME NOVEL ISOXAZOLINE DERIVATIVES FROM FLUORINATED CHALCONES

Sandip U Agare[1], Mahesh P. More[2] and Tanuja V Kadre[3]*
[1,2,3]Department of Chemistry, Dr. A.P.J. Abdul Kalam University, Indore, Madhya Pradesh-452016, India.
***Correspondence author: Tanuja Kadre**
Department of Chemistry, Dr. A.P.J. Abdul Kalam University, Indore, Madhya Pradesh-452016, India, Email ID: tanujakadre45@gmail.com

Abstract:
In the present investigation, a set of novel fluorine containing isoxazoline derivatives 3(a-i) were synthesized by refluxing fluorinated chalcones 2(a-i) with hydroxylamine hydrochloride under basic condition. The synthesized isoxazoline derivatives were confirmed by using spectroscopic techniques such as FT-IR, NMR, CHN and HRMS. Synthesized derivatives 3(a-i) evaluated for in-vitro antimicrobial studies. Antimicrobial study reveals that compounds 3(c-d) for S. aureus, 3(b, c and f) for B. subtilis, 3(a-e, and i) for E. coli, 3(b-d, and g) for P. aeruginosa exhibited excellent antimicrobial activity respectively as compared with standard streptomycin.

Keywords: Chalcone, Isoxazoline, Fluorinated, Antibacterial, gram-positive and negative microorganisms.

Introduction:

The specified derivatives synthesizing using traditional method by condensation of substituted aldehydes with aromatic ketones, resulting in α-β unsaturated ketones (chalcones)1-5. This derivative further cyclization in alkaline medium by treating with hydroxylamine hydrochloride produces the desired isoxazoline derivatives 6. In recent times, growing interest in preparing isoxazoline Derivatives due to its potential sources of antibacterial agents7. The synthesis isoxazoline derivatives to be a primary attention in research due to their reported antifungal 8,9,10, antibacterial 11, anticonvulsant 12, anti-inflammatory 13, and analgesic15,16, Anti-oxidant 17, Anticancer 18,19 activities.

Fluorinated acetophenones, particularly in drugs like ciprofloxacin, have gained significance importance in recent years, with the incorporation of fluorine influencing both the reaction pathways and biological activities19-20. Additionally, isoxazoline derivatives are find extensive applications in organic synthesis21.

Isoxazole and isooxazoline derivatives due is potent biological activities motivated to synthesize a new novel series of fluorine-containing derivatives 3(a-i) Figure 2. This approach aims to combine both biologically active Derivatives in a single molecule and subsequently assess the antibacterial activities of the newly synthesized molecules.

The known isoxazoline and oxazole containing clinical drugs and biological importance are showed in Figure 1.

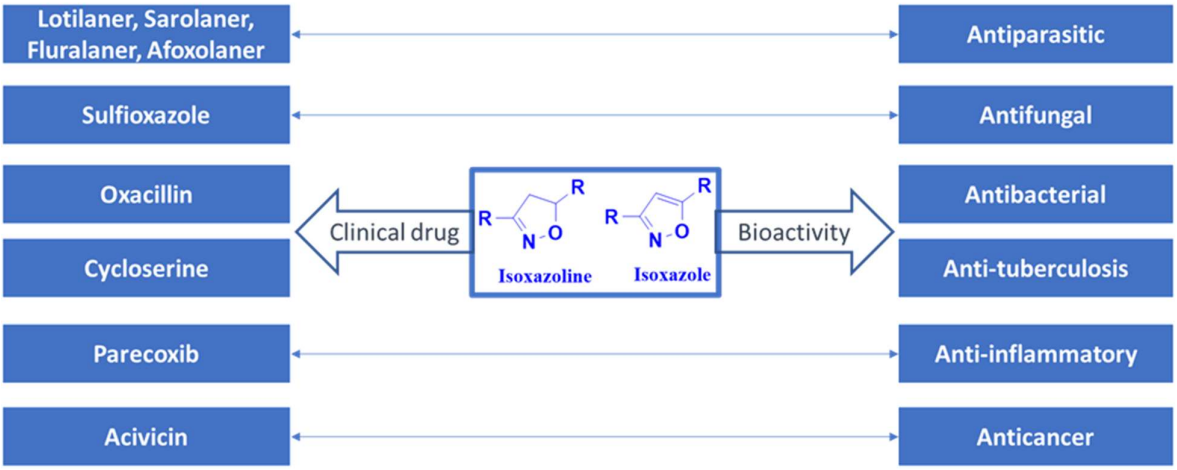


Figure 1: Biological importance of Isoxazoline and isoxazole derivatives

Experimental:

Method and discussion:

Melting points recorded without correction using an open capillary on Mettler FP51. Elemental analysis was carried out by CIF at Pune University, with results falling within range of ±0.5% calculated numbers. Infrared spectra were recorded on a Brucker FT-IR spectrometer using KBr pellet and stretching frequency. NMR spectra were obtained on a Bruker Avance dpx-400 spectrometer (400 MHz) and TMS as an standard. All analytical grade reagents were used to synthesize the specified derivatives. Chemical shifts are denoted in ppm relative to the internal standard. Reaction progress were monitored by TLC. The synthesized Derivatives were purified by column using silica gel and eluted product with 10-20% methanol in dichloromethane as an eluent. The fractions were collected by visualised under UV (254 nm) cabinet or iodine stain to assess compound purity.

Synthesis of Isoxazoline Derivatives 3(a-i):

The chalcone derivatives synthesis involved the treating the 1-(4-Fluoro-3-methylphenyl) ethanone (1) with substituted benzaldehydes (a-i) in the presence of base through the Claisen-Schmidt condensation method, resulting in the formation of fluorinated chalcones 2(a-i). [22]

The novel isoxazoline derivatives were synthesized as per the standard protocol with minor modifications. A mixture of Chalcone 2(a-i) (1.0 eq.), hydroxylamine hydrochloride (1.0 eq.), and 2N aq. sodium hydroxide (0.5 ml) in ethanol (30 mL). The resulting solution was then refluxed for a duration of 5-6 hours. After refluxing, the solution was poured into ice-cold water and subsequently filtered. The obtained precipitate was collected by filtration and washed with water. The obtained crude derivatives were recrystallized using ethanol or silica gel column chromatography. Obtained pure derivatives dried in rotary evaporator under vacuum to get isoxazoline derivatives 3(a-i).

Scheme 01: Synthesis of Isoxazoline Derivatives 3(a-i)

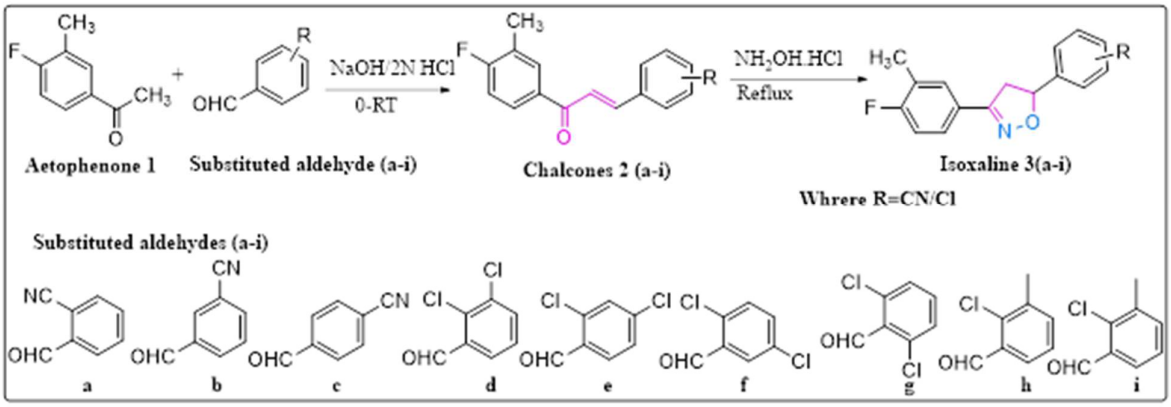


Table 01: Physical and chemical properties of 3(a-i)

Derivative 3(a-i)	Appearance	M.W.	Formula	M.P. (°C)	Yield (% mole)
3(a)	Off white colour solid	280.30	$C_{17}H_{13}FNO$	183-185	70.0
3(b)	Off white colour solid	280.30	$C_{17}H_{13}FNO$	177-179	75.0
3(c)	Off white colour solid	280.30	$C_{17}H_{13}FNO$	182-184	84.6
3(d)	Pale yellow solid	324.18	$C_{16}H_{12}FCl_2ON$	180-182	67.5
3(e)	Pale yellow solid	324.18	$C_{16}H_{12}FCl_2ON$	187-189	70.0
3(f)	Pale yellow solid	324.18	$C_{16}H_{12}FCl_2ON$	181-182	71.9
3(g)	Pale yellow solid	324.18	$C_{16}H_{12}FCl_2ON$	183-185	67.5
3(h)	Pale yellow solid	324.18	$C_{16}H_{12}FCl_2ON$	190-192	82.1
3(i)	Yellow solid	358.62	$C_{16}H_{11}FCl_2N$	196-199	73.5

Preparation of Microbiology Culture Media:

In a clean and dry autoclave dissolved charged the nutrient agar (0.028 kg) in distilled water (1.0 L), heated at 121°C and maintained for 15 minutes under 15 lbs pressure. Subsequently, at 37°C, pour the prepared media into Petri dishes, suitable for bacterial streaking. The pathogens used in this study included B. subtilis, P. aeruginosa, Escherichia coli, and Staphylococcus aureus. Solutions for the investigated Derivatives (0.02 g of each compound in 5 mL of dimethylformamide) were prepared using dimethylformamide (DMF) as a solvent. Subsequently, all derivatives were tested for inhibitory zones. The bacterial cultures were incubated for 24 hours at 37 °C and the plates were inspected for inhibitory effects.23

Results and Discussion:

FT(IR) Spectra:

The infrared spectrum data for derivatives 3(a-i) revealed distinct bands in specific regions. The frequency bands in the range of 1582-1672 cm-1 signified the existence of (C=N) isoxazole functional group. Additionally, bands in the range 3280-3284 cm-1 signified the existence of (Ar-H) aromatic hydrogen groups, while bands at 2887-2971 cm-1 pointed to the presence of (-CH2-) methine groups. The presence of chloro (C-Cl) groups was suggested by bands at 840-846 cm-1, and bands range 3055-3338 cm-1 signified the existence of (C-H) groups in the (CH3) methyl group. Bands range 1283-1362 cm-1 were observed, signified the existence of (C-F) groups, and bands at 1450-1596 cm-1 signified the existence of aromatic (C=C) bonds. Finally, bands at 1141-1452 cm-1 signified the existence of (C-O) bonds within the isoxazole ring.

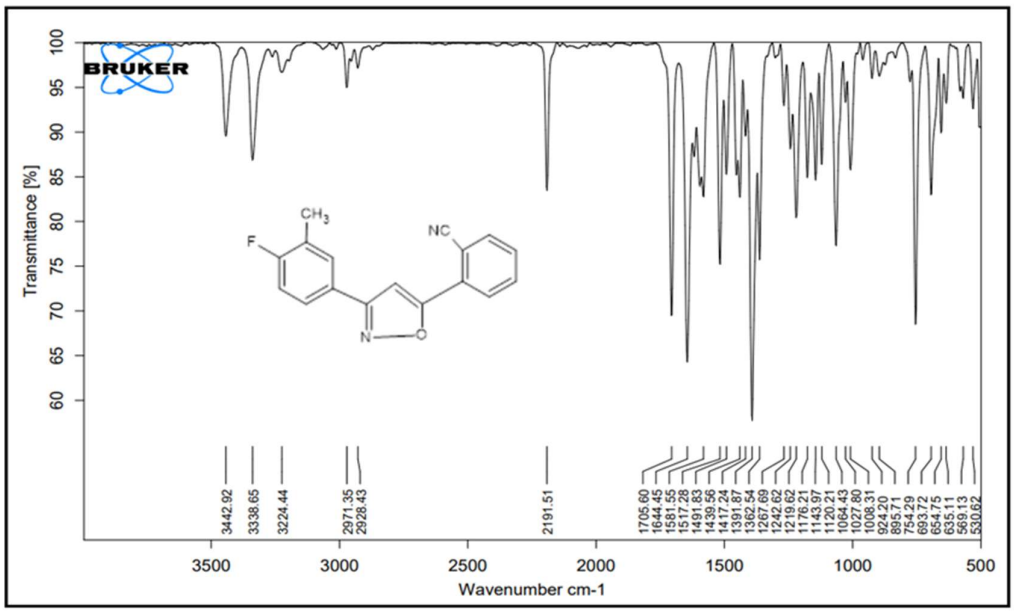


Figure-2: IR data of derivative 3(a)

1H NMR Spectra:

The 1H NMR (DMSO and CDCl3) spectra of derivatives 3(a-i) showed the following characteristics peaks in NMR: multiplate in the range of 7.05-8.04 ppm for 7-5H for Ar-H, a multiplate or doublet due to adjacent fluorine and methyl groups in the range of ~2.30 C ppm for 3H of CH3, a doublet of doublet of 1H of -CH2 of isoxaline ring at 2.95 to 3.02 ppm, A doublet of doublet of 1H of -CH2 of isoxaline ring at 3.51 to 3.57 ppm, A triplet of 1H of O-CH at 4.97 to 5.02 ppm

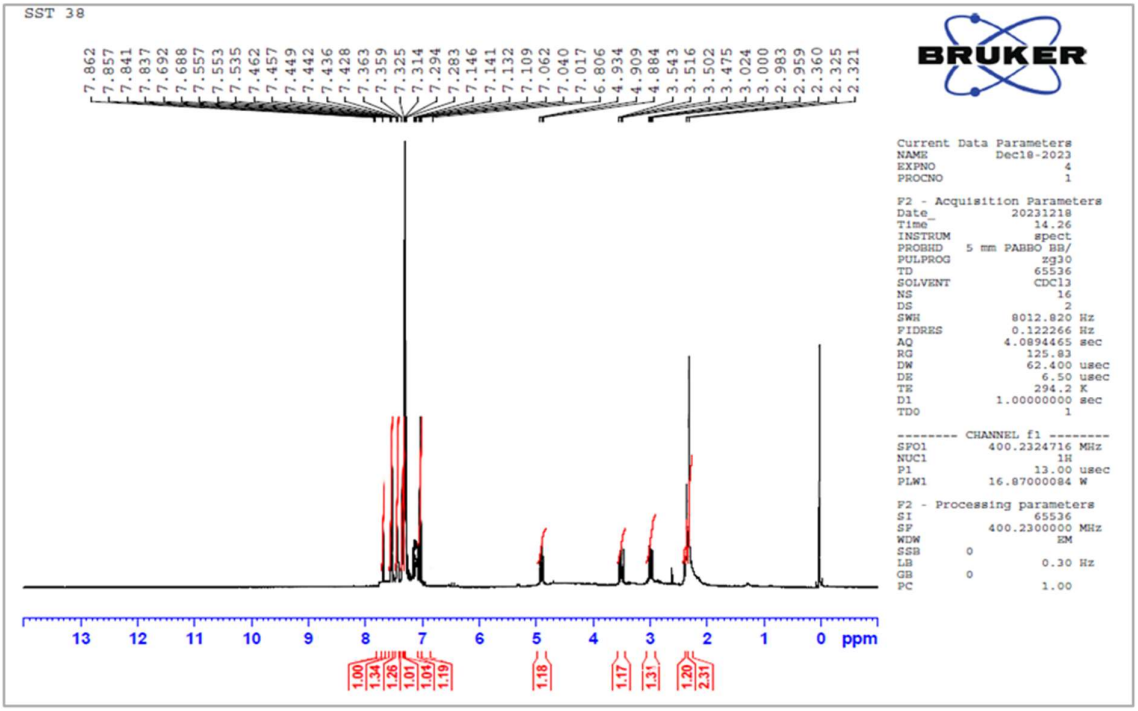
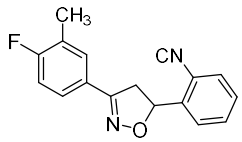
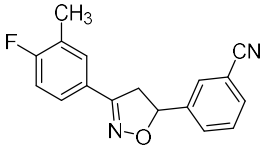
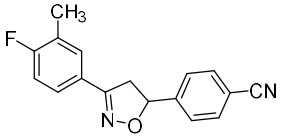
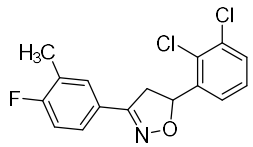
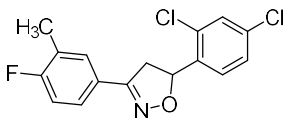
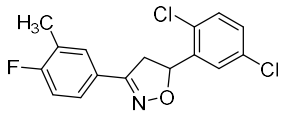
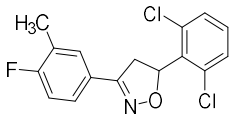
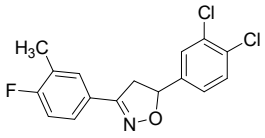
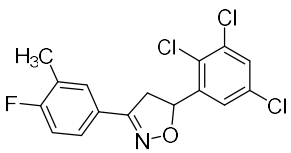


Figure 2: 1H NMR of derivative 3(h)

Table 2: Structure and spectroscopic data 3(a-i)

code	Structure	Spectroscopic data
3(a)	 3-(4-fluoro-3-methylphenyl)-5-(2-isocyanophenyl)-4,5-dihydroisoxazole	**IR (KBr):** -CH_3 (3338 cm^{-1}), -CH_2- (2971 cm^{-1}), **-CN (nitrile, 2191 cm^{-1}),** C=C str. (1581/1491 cm^{-1}), C–F str. (1362 cm^{-1}), C=N (isoxazoline ring, 1644 cm^{-1}), –C–O–C– (sym, 1391 cm^{-1}). **^{1}H NMR ($CDCl_3$):** δ 7.975-7.946 (m, 2H), 7.894-7.817 (m, 1H), 7.778-7.722 (m, 2H), 7.615-7.580 (m, 1H), 7,129-6.776 (m, 1H), 5.764-5.746 (d, 1H), 3,353 (m, 1H), 3,353-3.333 (d, 1H), 2.339-2.330 (dd, 3H). **HRMS**: m/z 281.1094. Elemental analysis for $C_{17}H_{13}FN_2O$: C: 71.99; H: 4.59; N: 9.98%
3(b)	 3-(3-(4-fluoro-3-methylphenyl)-4,5-dihydroisoxazol-5-yl)benzonitrile	**IR (KBr)**: -CH_3 (3328 cm^{-1}), -CH_2- (2923 cm^{-1}), **-CN (Nitrile, 2229 cm^{-1}),** C=C str. (1583/1490 cm^{-1}), C–F str. (1283 cm^{-1}), C=N (isoxazoline ring, 1664 cm^{-1}), –O–C– (sym, 1415 cm^{-1}). **^{1}H NMR** ($CDCl_3$): δ 7.846-7.803 (t, 2H), 7.624-7.246 (m, 4H), 7.106-7.061 (m, 1H), 4.155-4.121 (t, 1H), 3.543-3.483 (t, 1H), 3.358-3.324 (t, 1H), 2.340-2.261 (dd, 3H). **HRMS (m/z)**: 279.0841, Elemental analysis for $C_{17}H_{13}FN_2O$: C: 71.97; H: 4.58; N: 9.97%.
3(c)	 4-(3-(4-fluoro-3-methylphenyl)-4,5-dihydroisoxazol-5-yl)benzonitrile	**IR (KBr)**: -CH_3 (3284 cm^{-1}), -CH_2- (2919 cm^{-1}), **-CN (nitrile, 2221 cm^{-1})**, C=C str. (1596/1450 cm^{-1}), C–F str. (1329 cm^{-1}), C=N (isoxazoline ring, 1663 cm^{-1}), –C–O–C– (sym, 1410 cm^{-1}). **^{1}H NMR** ($CDCl_3$): δ 7.636-7.618 (m, 1H), 7.558-7.537 (m, 1H), 7.330-7.291 (m, 1H), 7.103- 7.040 (m, 2H), 6.988-6.926 (m,1H), 5.629-5.588 (t, 1H), 3.797-3.723 (m, 1H), 3.210-3.110 (m, 1H), 2.465-2.350 (dd, 3H). **HRMS (m/z)**: 279.9840, Elemental analysis for $C_{17}H_{13}FN_2O$: C: 72.66; H: 4.66; N: 9.90%.
3(d)	 5-(2,3-dichlorophenyl)-3-(4-fluoro-3-methylphenyl)-4,5-dihydroisoxazole	**IR (KBr)**: -CH_3 (3070cm^{-1}), -CH_2- (2971 cm^{-1}), C=C str. (1584/1498 cm^{-1}), C–F str. (1305 cm^{-1}), C=N (isoxazoline ring, 1672 cm^{-1}), –C–O–C– (sym, 1393 cm^{-1}), **C–Cl (859 cm^{-1})**. ^{1}H NMR ($CDCl_3$): δ 7.792-7.787 (m, 1H), 7.614-7.599 (m, 1H) 7.545-7.531 (m, 1H), 7.518-7.400 (m, 2H), 7.095-7.051 (m, 1H), 6.947-6.926 (m, 1H), 5.861-5.819 (m, 1H), 3.897-3.832 (m, 1H), 3.033-2.999 (m,1H), 2.504-2.345 (m, 3H). **HRMS (m/z)**: 325.2278. Elemental analysis for $C_{16}H_{12}$ Cl_2FNO: C: 59.19; H: 3.72; N: 4.31%
3(e)	 5-(2,4-dichlorophenyl)-3-(4-fluoro-3-methylphenyl)-4,5-dihydroisoxazole	**IR (KBr):**-CH_3 (3235cm^{-1}), -CH_2- (2921cm^{-1}), C=C str. (1501/1466cm^{-1}), C–F str. (1320 cm^{-1}), C=N (isoxazoline ring, 1582 cm^{-1}), –C–O–C– (sym, 1382 cm^{-1}), **C–Cl (862 cm^{-1}).** ^{1}H NMR ($CDCl_3$): **^{1}H NMR** ($CDCl_3$): δ ppm 7.726-7.368 (m, 4H), 7.223-7.296 (m, 1H), 7.065-7.020 (m,1H), 5.764-5.746 (d, 1H), 3.353 (S, 1H), 3.353-3.333 (d, 1H), 2.339-2.330 (dd, 3H), **HRMS**

		(m/z): 328.2318. Elemental analysis for $C_{16}H_{12}Cl_2FNO$: C: 59.22; H: 3.70; N: 4.31%
3(f)	 5-(2,5-dichlorophenyl)-3-(4-fluoro-3-methylphenyl)-4,5-dihydroisoxazole	**IR (KBr):** -CH_3 (3055cm^{-1}), -CH_2- (2919 cm^{-1}), C=C str. (1586/1496 cm^{-1}), C–F str. (1304 cm^{-1}), C=N (isoxazoline ring, 1655 cm^{-1}), –C–O–C– (sym, 1414 cm^{-1}), **C–Cl (851 cm^{-1})**. **^{1}H NMR** ($CDCl_3$): δ 7.865-7.432 (m, 3H), 7.316-7.298 (m, 2H), 7.103-7.040 (m, 1H), 6.988-6.926 (m,1H), 5.629-5.588 (t, 1H), 3.797-3.723 (m, 1H), 3.210-3.110 (m, 1H), 2.465-2.350 (dd, 3H). **HRMS (m/z)**: 328.3742. Elemental analysis for $C_{16}H_{12}Cl_2FNO$: C: 59.00; H: 3.70; N: 4.31%.
3(g)	 5-(2,6-dichlorophenyl)-3-(4-fluoro-3-methylphenyl)-4,5-dihydroisoxazole	**IR (KBr):** -CH_3 (3177cm^{-1}), -CH_2- (2887 cm^{-1}), C=C str. (1591/1500 cm^{-1}), C–F str. (1316 cm^{-1}), C=N (isoxazoline ring, 1666 cm^{-1}), –C–O–C– (sym, 1422 cm^{-1}), **C–Cl (854 cm^{-1}). ^{1}H NMR** ($CDCl_3$): δ 7.599-7.570 (m, 3H). 7.503-7.498 (m, 1H), 7.091-7.056 (m, 2H), 4.934-4.884 (dd, 1H), 3.543-3.475 (m, 1H), 3.024-3.000 (d, 1H), 2.454-2.357 (dd, 3H). **HRMS (m/z)**: 324.0366. Elemental analysis for $C_{16}H_{12}Cl_2FNO$: C: 58.89; H: 3.72; N: 4.30%.
3(h)	 5-(3,4-dichlorophenyl)-3-(4-fluoro-3-methylphenyl)-4,5-dihydroisoxazole	**IR (KBr)**: -CH_3 (3243 cm^{-1}), -CH_2- (2921 cm^{-1}), C=C str. (1560/1500 cm^{-1}), C–F str. (1327 cm^{-1}), C=N (isoxazoline ring, 1583 cm^{-1}), –C–O–C– (sym, 1327 cm^{-1}), **C–Cl (847 cm^{-1}).** ^{1}H NMR ($CDCl_3$): δ 7.8627.688 (m, 1H), 7.557-7.457 (m, 1H), 7.442-7.428 (m, 1H), 7.363-7.314 (m, 1H), 7.283-7.146 (m, 1H), 7.141-7.132 (m, 1H), 7.132-6.806 (m, 1H), 4.934-4.884 (m, 1H), 3.543-3.475 (m, 1H), 2.360-2.321 (m, 3H), **HRMS (m/z)**: 325.5578. Elemental analysis for $C_{16}H_{12}Cl_2FNO$: C: 59.22; H: 3.72; N: 4.31%.
3(i)	 3-(4-fluoro-3-methylphenyl)-5-(2,3,5-trichlorophenyl)-4,5-dihydroisoxazole	**IR (KBr):** -CH_3 (3070 cm^{-1}), -CH_2- (2971 cm^{-1}), C=C str. (1684/1498 cm^{-1}), C–F str. (1305 cm^{-1}), C=N (isoxazoline ring, 1672 cm^{-1}), –C–O–C– (sym, 1393 cm^{-1}), **C–Cl (859 cm^{-1})**. ^{1}H NMR ($CDCl_3$): **^{1}H NMR** (DMSO-d6): δ 7.744-7.726 (d, 1H), 7.662-7.648 (m, 1H), 7.634-7.578 (m, 1H) , 7.309-7.258 (m, 2H), 5.646-5.603 (m, 1H), 3.914-3.838 (m, 1H), 3.269-3.210 (m, 1H), 2.316-2.219 (dd, 3H). **HRMS (m/z)**: 359.0783. Elemental analysis for $C_{16}H_{12}Cl_2FNO$: C: 53.01; H: 3.00; N: 4.89%.

Antibacterial activity:

The targeted molecules were tested for antibacterial activities against various test organism, including S. aureus (Staphylococcus aureus) and B. subtilis (Bascules subtilis) gram-positive microorganism and E. coli (Escherichia coli) and P. aeruginosa (Pseudomonas aeruginosa) gram-negative microorganism. The results reveal that derivatives 3(a-d) exhibit high activity, while derivatives 3(e-i) demonstrate poor activity against E. coli. Against P. aeruginosa.

In the case of S. aureus and B. subtilis, derivative 3(c and d) demonstrate high activity, whereas other derivative display modest to poor activity. Furthermore, derivatives 3(c), 3(d), and 3f exhibit high activity against B. subtilis, while derivatives 3(g) and 3(h) show low activity.

Table 3: Antimicrobial studies of compound 3(a-i)

Compound	Antibacterial Activity (zone of inhibition)			
	S. aureus	***B. subtilis***	***E. coli***	***P. aeruginosa***
3 (a)	7	8	17	8
3 (b)	7	12	30	10
3 (c)	12	10	32	13
3 (d)	11	8	33	11
3 (e)	7	7	12	8
3 (f)	0	12	8	7
3 (g)	0	6	0	12
3 (h)	8	0	9	6
3 (i)	8	7	13	0
Streptomycin	8	7	13	7

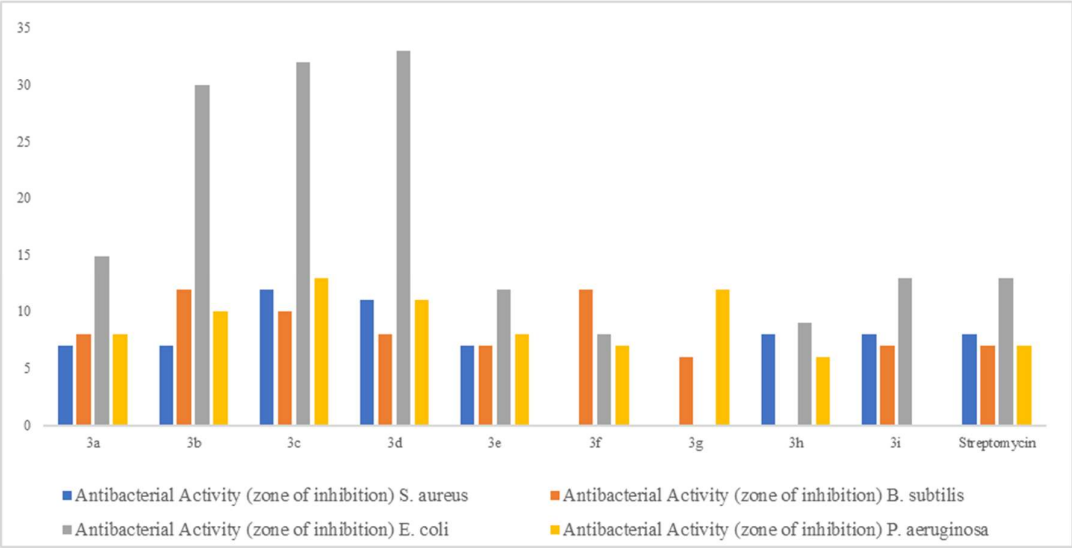


Figure-3: Antimicrobial activity of derivatives 3(a-i)

Conclusion:

This study presents the synthesis of novel series of 5-(substituted phenyl)-3-(4-fluoro-3-3methylphenyl)-4,5-dihydro-1,2-oxzole derivatives 3(a-i) and structure confirmed by mass, IR and NMR. The antimicrobial activities of all 9 derivatives were evaluated and found some 3(b-d) are good antibacterial activity 3(a and i) having moderate and 3(e-g) least activity. The findings from this study aim to contribute to the design and synthesis of more effective yet safe antimicrobial drugs. The novel series derivatives may be the new lead and research area for researcher to develop the more potent and safer biological active drugs.

References:

1. Bandeira P. N., Lemos T. L.G., Santos S. H. et al. Synthesis, structural characterization, and cytotoxic evaluation of chalcone derivatives. Med Chem Res. 2019, 28,2 037–2049 https://doi.org/10.1007/s00044-019-02434-1

2. Sreevidya T. V., Narayana B., & Yathirajan H. S. Synthesis and characterization of some chalcones and their cyclohexenone derivatives. Central European Journal of Chemistry, 2019, 8(1), 174-181.https://doi.org/10.2478/s11532-009-0124-x

3. Almeida L. R., Anjos M. M., Ribeiro G. C., Valverde C., Machado D. F., Oliveira G. R., ... & de Oliveira H. C. Synthesis, structural characterization and computational study of a novel amino chalcone: a potential nonlinear optical material. New Journal of Chemistry, 2017, 41(4), 1744-1754. https://doi.org/10.1039/C5NJ03214H

4. Shaik A. B., Bhandare R. R., Nissankararao S., Edis Z., Tangirala N. R., Shahanaaz S., & Rahman M. M. Design, facile synthesis and characterization of dichloro substituted chalcones and dihydropyrazole derivatives for their antifungal, antitubercular and antiproliferative activities. Molecules. 2020, 25 (14), 3188. https://doi.org/10.3390/molecules25143188

5. Suyambulingam A., Nair, S., & Chellapandian K. Synthesis, spectral characterization of novel chalcones based oxazines derivatives and screening of their antimicrobial and antioxidant activity. Journal of Molecular Structure. 2022, 1268, 133708. DOI:10.1016/j.molstruc.2022.133708

6. Bommagani M. B., Yerrabelly J. R., Chitneni M., Thalari G., Vadiyala N. R., Boda S. K., & Chitneni P. R. Synthesis and antibacterial activity of novel cinnoline-isoxazole derivatives. Chemical Data Collections, 2021, 31, 100629. https://doi.org/10.1016/j.cdc.2020.100629

7. Phanumartwiwath A., Kesornpun C., Sureram S., Hongmanee P., Pungpo P., Kamsri P., ... & Ruchirawat S. Antitubercular and antibacterial activities of isoxazolines derived from natural products: Isoxazolines as inhibitors of Mycobacterium tuberculosis Inh A. Journal of Chemical Research, 2021,45(11-12),1003-1015. https://repository.li.mahidol.ac.th/handle/123456789/76580

8. Zhang T., Dong, M., Zhao J., Zhang X., & Mei X. Synthesis and antifungal activity of novel pyrazolines and isoxazolines derived from cuminaldehyde. Journal of Pesticide Science, 2019, 44(3), 181-185. doi:10.1584/jpestics.D19-028

9. Huang S.S., Zhu B.B., Wang K.H., Yu M., Wang Z.W., Li, Y.Q., Liu Y.X., Zhang P.L., Li S.J., Li Y.L. et al. Design, synthesis, and insecticidal and fungicidal activities of quaternary

ammonium salt derivatives of a triazolyphenyl isoxazoline insecticide. Pest Manag. Sci. 2022, 78, 2011–2021. DOI 10.1002/ps.6824

10. Zhang, T.; Dong, M.Y.; Zhao, J.J.; Zhang, X.F.; Mei, X.D. Synthesis and antifungal activity of novel pyrazolines and isoxazolines derived from cuminaldehyde. J. Pestic. Sci. 2019, 44, 181–185. doi: 10.1584/jpestics.D19-028

11. Alshamari A., Al-Qudah M., Hamadeh F., Al-Momani L. A., & Abu-Orabi S. Synthesis, antimicrobial, and antioxidant activities of 2-isoxazoline derivatives. Molecules, 2020,25(18), 4271. https://doi.org/10.3390/molecules25184271

12. Chikkula K. V., & Raja S. Isoxazole–a potent pharmacophore. International Journal of Pharmacy and Pharmaceutical Sciences, 2017, 13-24. https://doi.org/10.22159/ijpps.2017.v9i7.19097

13. Rasool J. U., Sawhney G., Shaikh M., Nalli Y., Madishetti S., Ahmed Z., & Ali A. Site-selective synthesis and anti-inflammatory evaluation of Spiro-isoxazoline stitched adducts of arteannuin B. Bioorganic Chemistry, 2021, 117, 105408. https://doi.org/10.1016/j.bioorg.2021.105414

14. Sedenkova K. N., Andriasov K. S., Eremenko M. G., Grishin Y. K., Alferova V. A., Baranova A. A., ... & Averina E. B. Bicyclic Isoxazoline Derivatives: Synthesis and Evaluation of Biological Activity. Molecules, 2022, 27(11), 3546. https://doi.org/10.3390/molecules27113546

15. Sangale S. S., Kale P. S., Lamkane R. B., Gore G. S., Parekar P. B. & Shivpuje S. S. Synthesis of Novel Isoxazole Derivatives as Analgesic Agents by Using Eddy's Hot Plate Method. South Asian Res. J. Pharm. Sci. 2023, 5(1), 18-27. https://sarpublication.com/media/articles/SARJPS_51_18-27.pdf

16. Mota F.V.B., Neta M.S.D., Franco E.D., Bastos I., da Araujo L.C.C. da Silva S.C., de Oliveira T.B., Souza E.K., de Almeida V.M., Ximenes R.M. et. al. Evaluation of anti-inflammatory activity and molecular docking study of new aza-bicyclic isoxazoline acylhydrazone derivatives. Medchemcomm 2019, 10, 1916–1925. https://doi.org/10.1021/jm0101287

17. Gul M., Eryilmaz S. Synthesis, Antioxidant Activity and Theoretical Investigation of Isoxazolines Derivatives of Monoterpenoids. Lett. Org. Chem. 2019, 16, 501–510. DOI: 10.2174/1570178616666181226154540

18. Kaur K., Kumar V., Sharma A.K., Gupta G.K. Isoxazoline containing natural products as anticancer agents: A review. Eur. J. Med. Chem. 2014, 77, 121–133. https://doi.org/10.1016/j.ejmech.2014.02.063

19. Amole K. L., Bello I. A., & Oyewale A. O. Synthesis, characterization and antibacterial activities of new fluorinated chalcones. Chemistry Africa, 2019, 2, 47-55. https://doi.org/10.1007/s42250-019-00043-4

20. Custodio J. M. F., Guimarães-Neto J. J. A., Awad R., Queiroz J. E., Verde G. M. V., Mottin M. & Napolitano, H. B. Molecular modelling and optical properties of a novel fluorinated chalcone. Arabian Journal of Chemistry, 2020, 13(1), 3362-3371. https://doi.org/10.1021/ja01284a011

21. Pandhurnekar C. P., Pandhurnekar H. C., Mungole A. J., Butoliya S. S., & Yadao B. G. A review of recent synthetic strategies and biological activities of isoxazole. Journal of Heterocyclic Chemistry, 2023, 60(4), 537-565. https://doi.org/10.1002/jhet.4586

22. Agare S.U., Tajane S.P., Kadre T.V. Synthesis, characterization, and biological evaluation of cyano and chloro benzaldehyde derivatives of fluorinated chalcones. Eur. Chem. Bull. 2022, 11(Regular Issue 12), 2801-2808 DOI 10.53555/ecb/2022.11.12.2302022.

23. Ngamsurach P., & Praipipat P. Antibacterial activities against Staphylococcus aureus and Escherichia coli of extracted Piper betle leaf materials by disc diffusion assay and batch experiments. RSC advances, 2022, 12(40), 26435-26454. https://doi.org/10.1039/D2RA04611C