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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL SCREENING OF SOME NEWLY SYNTHESIZED ISOXAZOLINE DERIVATIVES

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Abstract:

Isoxazolines are important class of nitrogen and oxygen containing heterocycles belong to the azoles family which have gained much importance in the medicinal, industrial and agricultural fields. They are also used as important precursor for the synthesis of many organic molecules widely used in the industries. The importance of five-member heterocyclic rings possessing nitrogen and oxygen as hetero atoms are also known for their utility in drug discovery. Antibiotics such as cloxacillin, dicloxacillin, flucloxacillin and oxacillin possesses the 3-arylisoxazole moiety in their side chain. Perhaps the most commonly encountered products containing isoxazoline moiety are some veterinary medicines *viz.* Fluralaner, Afoxolaner and Sarolaner used to prevent flea infections in dogs. Considering its applicability in various sector which manufacturing drug for human and animals. So, we have synthesized some analogues of 3-(4-subtituted phenyl)-5-substituted isoxazoline form 1-(4-substitutedphenyl)-3-substitutedchalcones. The newly synthesized compounds were assayed for their antimicrobial activity against some bacteria *viz. Staphylococcus aureus, Enterococci, Escherichia coli, Pseudomonas aeruginosa* some fungi *viz. Candida albicans, Aspergillus niger.*

Keywords: Chalcones, chloro substituted isoxazoline, nitro substituted isoxazoline and antimicrobial activity etc.

Introduction:

The synthesis of the isooxazoline involves the base-catalyzed condensation of substituted aromatic ketones and substituted aldehydes to give α-β-unsaturated ketones (chalcones), which on cyclization with hydroxylamine hydrochloride in alkaline medium give the corresponding isoxazoline derivatives. In recent years, attention has increasingly been given to the synthesis of isoxazoline derivatives as a source of new antibacterial agents. The synthesis of novel isoxazoline derivatives remains a main focus of medicinal research. Isoxazolines are an important class of nitrogen- and oxygen- containing heterocycles which are belong to the azoles family and have gained great importance in the field of medicinal chemistry as anticancer agents [I, II]. Isoxazoline derivatives have found applications as antituberculosis agents [III],

antifungal agents [IV], anti-inflammatory agents [V], antibacterial agents [VI], anticonvulsant agents [VII], antiviral agents [VIII], and analgesic [IX] agents. They are also found to possess mesogenic core exhibiting liquid crystalline properties, [XI].

Kadnor V.A. *et al* [XII] synthesized fluorine substituted isooxazoline from the reaction of fluoro chalcones and hydroxylamine in acetic acid medium under reflux conditions and reported their antibacterial activities. By introducing fluorine atom into specific position of organic molecule may cause significant changes in the stability, lipophilicity and biological activities of the resulting molecules [XIII].

Desai *et al* [XIV] reported a series of 3-[3-(2,4-dichloro-5-fluorophenyl)-5-(2-furyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-5-(substituted phenyl/2-thienyl) isoxazolines possessing antibacterial properties. Motegaonkar in 2020 [XV] synthesized some of isoxazoline derivatives prepared by refluxing chalcone and hydroxylamine hydrochloride and in presence of sodium acetate in ethanol solvent and also report their antibacterial efficacy. Sailu *et al* [XVI] synthesized chalcone form base-catalyzed cyclization of 2-hydroxyacetonaphthanone with substituted vanillin which on further treatment with $NH_2OH.HCl$ in alkaline medium in EtOH provide corresponding isoxazoline derivatives. Isoxazoline-containing cyclolignan derivatives display potent antiviral, immunosuppressive and cytotoxic activities [XVII].

Literature survey reveals that, nitrogen and oxygen containing chloro substituted heterocycles were found to be very instrumental in controlling the diseases in the field of agriculture. The present study has been undertaken to synthesis some new isoxazoline analogues and test them for their antimicrobial efficacy.

Experimental:

The structure of all the newly synthesized compounds was characterized on the basis IR, NMR and Mass spectroscopy. The IR spectra were recorded on Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance-II 400 NMR spectrophotometer in DMSO using TMS as an internal standard.

Preparation of 1-(4-chlorophenyl)-3-(4-methoxyphenyl) chalcone(1a)

To a cooled solution of NaOH (40%) and ethanol, 4-chloroacetophenone (0.01 M) was added followed by addition of substituted 4-methoxy benzaldehyde (0.01 M), the reaction mixture was stirred for 2-3 hours till the mixture become viscous and then the mixture was kept overnight in a refrigerator. The product, thus separated, was filtered and washed with cold water. Then it was crystallized in rectified spirit to yield the compound 1a.

Mol. Formula $C_{16}H_{13}ClO_2$(1a): White amorphous solid, m.p. 112^{o}C, yield 79%, **Elemental analysis (%): C** 70.41/70.46**; H** 40.78/40.80**; Cl** 12.95/13.00; **O** 11.71/11.73. **IR (KBr cm^{-1})** 1654 (=C-C=O), 1566 (Ar ring), 1440 (Ar C=C), 1332 (C-O), 1262 (C-OCH_3),686(C-Cl).**ESI-MS** $[M^+H]^+$ Calculated for $C_{16}H_{14}ClO_2$: m/z 273.06, found 273.03, **^{1}H-NMR (500 MHz, DMSO)** δ 8.14 (d, *J* = 7.9 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 15.6 Hz,1H), 7.72 (d, *J* = 15.5 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H).

Preparation of 1-(4-chlorophenyl)-3-(2-chlorophenyl) chalcone(1b)

To a cooled solution of NaOH (40%) and ethanol, 4-chloroacetophenone (0.01 M) was added followed by addition of substituted 2-chlorobenzaldehyde (0.01 M), the reaction mixture was stirred for 2-3 hours till the mixture become viscous and then the mixture was kept overnight in a refrigerator. The product, thus separated, was filtered and washed with cold water. Then it was crystallized in rectified spirit to yield the compound 1b.

Mol. Formula$C_{15}H_{10}Cl_2O$ (1b): Pale yellow crystalline Solid, m.p. 87^oC, yield 78%,**Elemental analysis (%): C** 65.00/65.01 **; H** 3.62/3.64 **; Cl** 25.55/25.58; **O** 5.73/5.77**, IR (KBr cm^{-1})** 1685 (=C-C=O), 1560 (Ar ring), 1440 (Ar C=C), 1332 (C-O), 627 (C-Cl)**, ESI-MS**$[M+H]^+$ Calculated for $C_{15}H_{11}Cl_2O$: *m/z* 277.01, found 276.97**, ^{1}H-NMR (500 MHz, DMSO)** δ 8.19 (m, 3H), 8.06 (d, *J* = 15.5 Hz, 1H), 7.96 (d, *J* = 15.7 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.52 – 7.44 (m, 2H).

Preparation of 1-(4-hydroxyphenyl)-3-(4-methoxyphenyl) chalcone(1c)

To a cooled solution of NaOH (40%) and ethanol, 4-hydroxyacetophenone (0.01 M) was added followed by addition of substituted 4-methoxybenzaldehyde (0.01 M), the reaction mixture was stirred for 2-3 hours till the mixture become viscous and then the mixture was kept overnight in a refrigerator. The product, thus separated, was filtered and washed with cold water. Then it was crystallized from rectified spirit to yield the compound 1c.

Mol. Formula $C_{16}H_{14}O_3$(1c): Yellow crystalline Solid, m.p. 108^oC, yield 79%, **Elemental analysis (%): C** 75.55/75.57**; H** 5.52/5.55**; O** 18.84/18.88.

Preparation of 1-(4-hydroxyphenyl)-3-(2-chlorophenyl) chalcone(1d)

To a cooled solution of NaOH (40%) and ethanol, 4-hydroxyacetophenone (0.01 M) was added followed by addition of substituted 2-chlorobenzaldehyde (0.01 M), the reaction mixture was stirred for 2-3 hours till the mixture become viscous and then the mixture was kept overnight in a refrigerator. The product, thus separated, was filtered and washed with cold water. Then it was crystallized from rectified spirit to yield the compound 1d.

Mol. Formula $C_{15}H_{11}ClO_2$ (1d) : Cream amorphous solid, m.p. 80^oC, yield 74%, **Elemental analysis (%): C** 69.62/69.64 **; H** 4.27/4.29 **; Cl** 13.67/13.70; **O** 12.34/12.37; **IR (KBr cm^{-1})** 3209 (OH), 1651 (=C-C=O), 1616 (Ar ring), 1438 (Ar C=C), 1317 (C-O); **ESI-MS**$[M+H]^+$ Calculated for $C_{15}H_{12}ClO_2$: *m/z* 259.05, found 259.01; **^{1}H-NMR (500 MHz, DMSO)** δ 10.69 (s, 1H), 8.18 (d, *J* = 6.9 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 15.5 Hz, 1H), 7.95 (d, *J* = 15.6 Hz, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.51 – 7.42 (m, 2H), 6.93 (d, *J* = 8.2 Hz, 2H).

Preparation of 1-(4-nitrophenyl)-3-(4-chlorophenyl) chalcone(1e)

To a cooled solution of NaOH (40%) and ethanol, 4-nitroacetophenone (0.01 M) was added followed by addition of substituted 4-chlorobenzaldehyde (0.01 M), the reaction mixture was stirred for 2-3 hours till the mixture become viscous and then the mixture was kept overnight in a refrigerator. The product, thus separated, was filtered and washed with cold water. Then it was crystallized from rectified spirit to yield the compound 1e.

Mol. Formula $C_{15}H_{10}ClNO_3$ (1e): Yellow amorphous solid, m.p. 124^oC, yield 80%, **Elemental analysis (%): C**62.60/62.62 **; H** 3.47/3.50 **; Cl** 12.30/12.32;**N** 4.85/4.87;**O** 16.65/16.68; **IR (KBr cm^{-1})**1664 (=C-C=O), 1616 (Ar ring), 1438 (Ar C=C), 1319 (C-O); **ESI-MS**$[M+H]^+$ $[M+H]^+$ Calculated for $C_{15}H_{11}ClNO_3$: *m/z* 288.04 ; **^{1}H-NMR (500 MHz, DMSO)** δ 8.38 (d, *J* = 8.3 Hz, 2H), 8.34 (d, *J* = 8.5 Hz, 2H), 7.97 – 7.90 (m, 3H), 7.81 (d, *J* = 15.5 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H).

Preparation of 1-(4-chlorophenyl)-3-(4-chlorophenyl) chalcone(1f)

To a cooled solution of NaOH (40%) and ethanol, 4-chloroacetophenone (0.01 M) was added followed by addition of substituted 4-chlorobenzaldehyde (0.01 M), the reaction mixture was stirred for 2-3 hours till the mixture become viscous and then the mixture was kept

overnight in a refrigerator. The product, thus separated, was filtered and washed with cold water. Then it was crystallized from rectified spirit to yield the compound 1*f*.
Mol. Formula $C_{15}H_{10}Cl_2O$ (1f): White amorphous solid, m.p. 86°C, yield 81%, Elemental **analysis (%): C** 65.00/65.01**; H** 3.61/3.64**; Cl** 25.55/25.58; **O** 5.74/5.77.

Preparation of 3-(4-chlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-Δ^2-isoxazoline(2a)
1-(4-Chlorophenyl)-3-(4-methoxyphenyl) chalcone(1a) (0.01M) refluxed with hydroxylamine hydrochloride (0.01M) for 1.5 hours in pyridine solvent. After completion of the reaction, the reaction mixture was cooled to room temperature then poured into ice-cold water containing dilute acetic acid. The product obtained was filtered, washed with water and crystallized from ethanol to get the compound 2a.

Mol. Formula$C_{16}H_{14}ClNO_2$ (2a) : White Crystalline solid, m.p. 154°C, yield 70%, **Elemental analysis (%): C** 66.76/66.79**; H** 4.88/4.90 **; Cl** 12.30/12.32; **N** 4.85/4.87;**O** 11.00/11.12; **IR (KBr cm^{-1})**3016 (=CH), 1614 (C=N), 1438 (Ar C=C), 750 (C-Cl); **ESI-MS**$[M+H]^+$ Calculated for $C_{16}H_{15}ClNO_2$: *m/z* 288.74, found 288.98; **^{1}H-NMR (500 MHz, DMSO)** δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 6.8 Hz, 2H), 7.32 (d, *J* = 11.5 Hz, 2H), 6.93 (t, *J* = 15.9 Hz, 2H), 5.71 – 5.65 (m, 1H), 3.81 (dd, *J* = 17.2, 10.9 Hz, 1H), 3.75 (s, 3H), 3.37 (dd, *J* = 17.2, 9.0 Hz, 1H).

Preparation of 3-(4-chlorophenyl)-5-(2-chlorophenyl)-4,5-dihydro-Δ^2-isoxazoline(2b):
1-(4-Chlorophenyl)-3-(2-chlorophenyl) chalcone(1b) (0.01M) refluxed with hydroxylamine hydrochloride (0.01M) for 1.5 hours in pyridine solvent. After completion of the reaction, the reaction mixture was cooled to room temperature then poured into ice-cold water containing dilute acetic acid. The product obtained was filtered, washed with water and crystallized from ethanol to get the compound 2b.

Mol. Formula $C_{15}H_{11}Cl_2NO$ (2b): White amorphous solid, m.p. 126°C, yield 78%**, Elemental analysis (%): C** 61.65/61.67 **; H** 3.76/3.79 **; Cl** 24.25/24.27 **N**4.76/4.79;**O**5.46/5.48.**IR (KBr cm^{-1})**3055 (=CH), 1612 (C=N), 1433 (Ar C=C), 750 (C-Cl).**ESI-MS**$[M+H]^+$Calculated for $C_{15}H_{12}C_{l2}NO$: *m/z* 292.02, found 292.87.**^{1}H-NMR (500 MHz, DMSO)** δ 7.98 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.46 (d, *J* = 3.6 Hz, 1H), 7.38 (d, *J* = 5.4 Hz, 2H), 6.03 – 5.97 (m, 1H), 3.99 (m, 1H), 3.33 (dd, *J* = 17.2, 7.4 Hz, 1H).

Preparation of 3-(4-hydroxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-Δ^2-isoxazoline (2c)
1-(4-Hydroxyphenyl)-3-(4-methoxyphenyl) chalcone(1c) (0.01M) refluxed with hydroxylamine hydrochloride (0.01M) for 1.5 hours in pyridine solvent. After completion of the reaction, the reaction mixture was cooled to room temperature then poured into ice-cold water containing dilute acetic acid. The product obtained was filtered, washed with water and crystallized from ethanol to get the compound 2c.

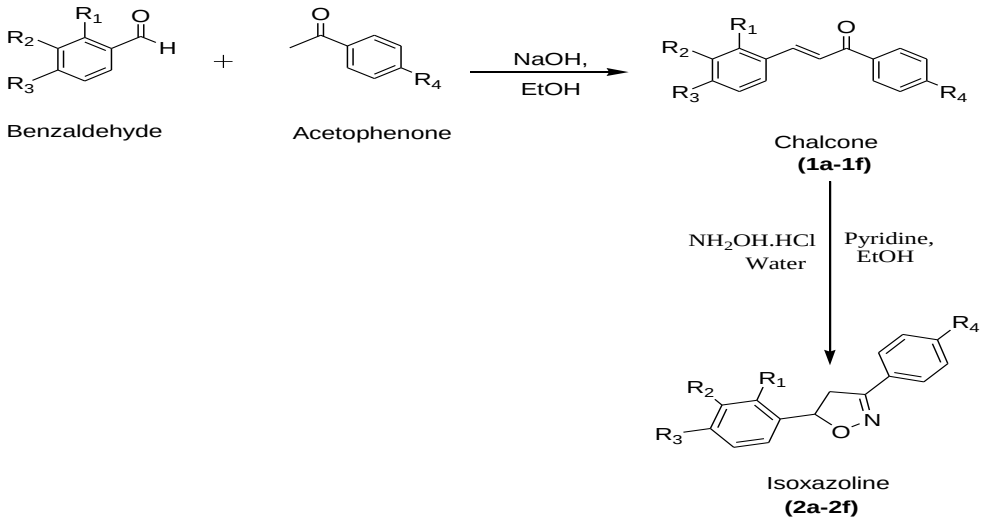
Mol. Formula$C_{16}H_{15}NO_3$ (2c) Cream amorphous solid, m.p. 83°C, yield 75%**,Elemental analysis (%) : C** 71.34/71.36 **; H** 5.00/5.61 **;N**5.17/5.20;**O** 17.00/17.82;**IR (KBr cm^{-1})**3473 (OH), 1608 (C=N), 1448 (Ar C=C).**ESI-MS**[[M+H]+ Calculated for $C_{16}H_{16}NO_3$: m/z 270.30, found 270.88; **^{1}H-NMR (500 MHz, DMSO)** δ 10.12 (s, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 5.58 (m, 1H), 3.82 (s, 3H), 3.76 (m, 1H), 3.28 (dd, *J* = 17.0, 8.6 Hz, 1H).

Preparation of 3-(4-hydroxyphenyl)-5-(2-chlorophenyl)-4,5-dihydro-Δ^2-isoxazoline(2d):
1-(4-Hydroxyphenyl)-3-(2-chlorophenyl) chalcone(1d) (0.01M) refluxed with hydroxylamine hydrochloride (0.01M) for 1.5 hours in pyridine solvent. After completion of the reaction, the reaction mixture was cooled to room temperature then poured into ice-cold water containing dilute acetic acid. The product obtained was filtered, washed with water and crystallized from ethanol to get the compound 2d.
Mol. Formula$C_{15}H_{12}ClNO_2$ (2d) White amorphous solid, m.p. 112^{o}C, yield 69 %**, Elemental analysis (%): C** 65.80/65.82**; H**4.40/4.42**; Cl** 12.93/12.95**; N**5.11/5.12; **O** 11.65/11.69.

Preparation of 3-(4-nitrophenyl)-5-(4-chlorophenyl)-4,5-dihydro-Δ^2-isoxazoline(2e)
1-(4-Nitrophenyl)-3-(4-Chlorophenyl) chalcone(1e) (0.01M) refluxed with hydroxylamine hydrochloride (0.01M) for 1.5 hours in pyridine solvent. After completion of the reaction, the reaction mixture was cooled to room temperature then poured into ice-cold water containing dilute acetic acid. The product obtained was filtered, washed with water and crystallized from ethanol to get the compound 2e.

Mol. Formula$C_{15}H_{11}ClN_2O_3$ (2e) Orange Crystalline solid, m.p. 162^{o}C, yield 76 %**, Elemental analysis (%): C**59.50/59.52**; H** 3.63/3.66**; Cl** 11.70/11.71**; N** 9.23/9.25; **O** 15.83/15.86.

Preparation of 3-(4-chlorophenyl)-5-(4-chlorophenyl)-4,5-dihydro-Δ^2-isoxazoline(2f)
1-(4-Chlorophenyl)-3-(4-chlorophenyl) chalcone(1f) (0.01M) refluxed with hydroxylamine hydrochloride (0.01M) for 1.5 hours in pyridine solvent. After completion of the reaction, the reaction mixture was cooled to room temperature then poured into ice-cold water containing dilute acetic acid. The product obtained was filtered, washed with water and crystallized from ethanol to get the compound 2f.
Mol. Formula $C_{15}H_{11}Cl_2NO$ (2f) White Crystalline solid, m.p. 137^{o}C, yield 74%**,Elemental analysis (%): C** 61.64/61.67**; H** 3.75/3.79**; Cl** 24.25/24.27; **N**4.77/4.79;**O**5.45/5.48; **IR (KBr cm^{-1})**3060 (=CH), 1595 (C=N), 1431 (Ar C=C), 750 (C-Cl); **ESI-MS**$[M+H]^+$ Calculated for $C_{15}H_{12}Cl_2NO$: *m/z* 292.02, found 292.89; **^{1}H-NMR (500 MHz, DMSO)** δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 5.76 (m, 1H), 3.87 (m, 1H), 3.38 (dd, *J* = 17.2, 8.3 Hz, 1H).
Scheme:



Compounds	**R_1**	**R_2**	**R_3**	**R_4**	**Compounds**	**R_1**	**R_2**	**R_3**	**R_4**
1a	-H	-H	$-OCH_3$	-Cl	**2a**	-H	-H	$-OCH_3$	-Cl
1b	-Cl	-H	-H	-Cl	**2b**	-Cl	-H	-H	-Cl
1c	-H	-H	$-OCH_3$	-OH	**2c**	-H	-H	$-OCH_3$	-OH
1d	-Cl	-H	-H	-OH	**2d**	-Cl	-H	-H	-OH
1e	-H	-H	-Cl	$-NO_2$	**2e**	-H	-H	-Cl	$-NO_2$
1f	-H	-H	-Cl	-Cl	**2f**	-H	-H	-Cl	-Cl

Antimicrobial Screening:

The antimicrobial activities of compounds 1a,1b, 1d, 1e, 2a,2b, 2c, 2f have been assayed at the concentration of 125µg/disc against some pathogens *viz.* bacteria *Staphylococcus aureus, Enterococci, Escherichia coli, Pseudomonas aeruginosa* and some fungi *viz. Candida albicans, Aspergillus niger.* The efficacy of titled compounds is given in following table.

Compound	**Zone of inhibition (mm)**					
	Bacterial pathogens				**Fungal pathogens**	
	Staphylococcus aureus	*Enterococci*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus niger*
1a	12	18	15	20	12	10
1b	10	16	10	17	14	11
1d	13	14	14	18	10	10
1e	12	19	20	11	13	11
2a	13	19	25	22	17	12
2b	24	27	17	20	19	18
2c	13	26	25	21	13	16
2f	12	22	19	26	18	11
Gentamicin	08	08	08	08	--	--
Cabendizum	--	--	--	--	08	08

Result and Discussion

The results of antimicrobial screening indicate that the titled compound shows good to moderate antimicrobial activity against tested bacteria *viz. Staphylococcus aureus, Enterococci, Escherichia coli, Pseudomonas aeruginosa* some fungi *viz. Candida albicans, Aspergillus niger.* The newly synthesized titled compounds are capable to cramp the growth of fungal and bacterial pathogens.

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