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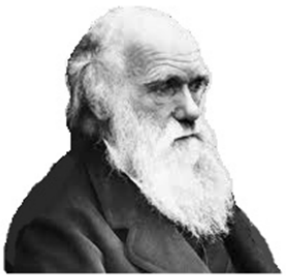

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Design, Synthesis, Characterization and Antimicrobial Screening of Newly Synthesized Isoxazole of Vanillin Analogues

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ABSTRACT

Several 3-(Aryl)-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole derivatives (1a-1h) have been synthesized by refluxing various 3-Methoxy-4-(2,4-dichlorophenylmethoxy) chalcones with hydroxylamine hydrochloride and catalytic amount of acetic acid results good to moderate yield. 3-Methoxy-4-(2,4-dichlorophenylmethoxy) chalcones were synthesized by constant stirring of 3-Methoxy-4-(2,4-dichlorophenylmethoxy)benzaldehyde with different substituted acetophenones. The analytical and physical data of all the synthesized compounds (1a-1h) were observed and reported. The structures of each newly synthesized isoxazole derivative have been characterized by various methods like Elemental analysis, Infrared spectroscopy, ^{1}H-NMR spectroscopy, and Mass spectroscopy. Furthermore, each compound was screened for its *in-vitro* antibacterial activity towards *Gram-positive* and *Gram-negative* bacterial strains and antifungal towards fungi *Aspergillus niger (A. niger)* and *Candida albicans (C. albicans)* with the concentration of 40µg/ml and data was collected.

***Keywords*:** Heterocycle, Isoxazole, Chalcone, Vanillin, Anti-microbial

1. INTRODUCTION

In the world of chemistry, heterocyclic compounds are an important class of organic compounds. The different types of heterocycles have key importance in a wide range of areas, among pharmaceuticals and cosmetics are very well known. Isoxazoles and isoxazolines are

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five-membered most popular heterocyclic compounds (Fig. 1) for developing novel drug candidates.[1]

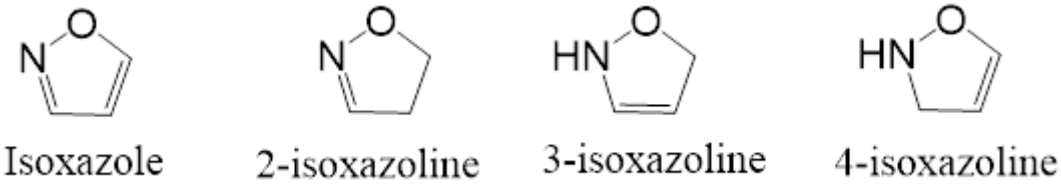


Fig. 1. Structure of isoxazole and isoxazilines

Evidently, the core structure of isoxazole and isoxazoline has been found in many natural products and reported drugs like Valdecoxib (Fig. 2), Flucloxacillin, Cloxacillin, Danazol, Dicloxacillin, Fluralaner (Fig. 3) and Afoxolaner[2]. Valdecoxib is a well-known nonsteroidal anti-inflammatory drug used in the treatment of various symptoms and it was patented in 1995[3-4]

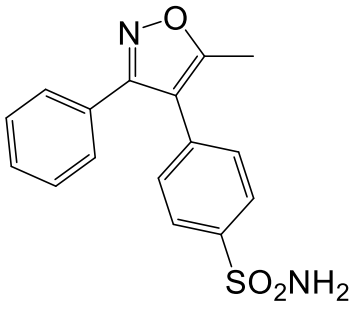


Fig 2 Structure of Valdecoxib

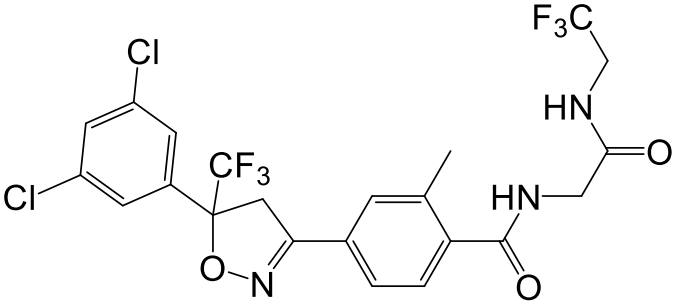


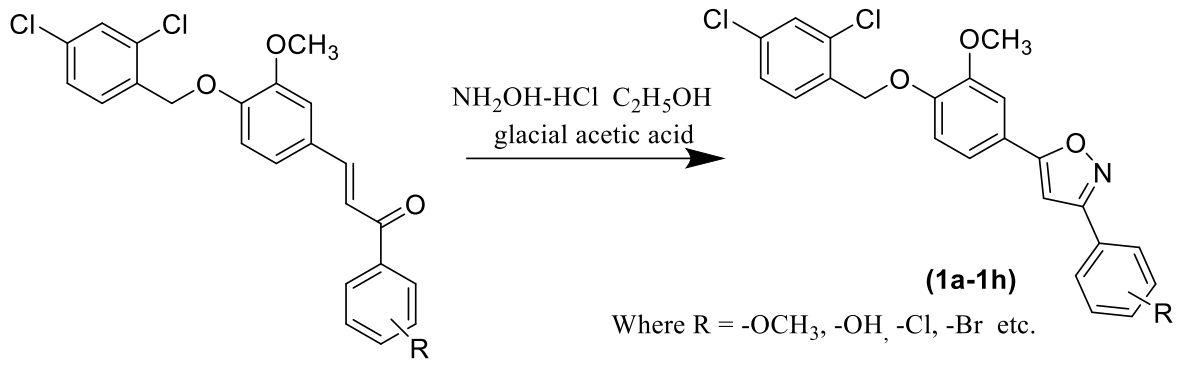
Fig 3 Structure of Fluralaner

As a unique building block, isoxazole derivatives have various applications in medicine and agriculture area due to its unique structural features and physicochemical properties.[5] Owing to its good chemotherapeutic profile, isoxazole has taken a dominant position in the agrochemical industry and medicinal chemistry. Isoxazole scaffolds show a wide variety of biological activities like antifungal, anti-inflammatory, anti-HIV, anti-platelet, Alzheimer, and analgesic.[6-18] Isoxazole also works against autoimmune lymphocyte properties.[19-20]

In literature, there are so many methods for the synthesis of isoxazole. Furthermore, the multi-component reaction of active methylene compounds, aldehydes, and hydroxylamine derivatives was well studied under different conditions.[21-25]

In the framework of this research we decided to synthesize the isoxazole by cyclocondensation of α, β-unsaturated carbonyl compounds with hydroxylamine hydrochloride (Scheme 1) and anti-microbial screening of each synthesized compound was also performed.

The synthesis of isoxazole and isoxazoline is a regioselective and stereoselective [3+2] cycloaddition (32CA) reaction involving benzonitrile N-Oxide, nitrile oxide and diarylnitryl imine analogs in different condition are repoted.[26-44]



Scheme 1. Synthesis of Vanillin Analogues

2. MATERIALS AND METHODS

All required chemicals and solvents were purchased from Merck Chemical, Finar, and Spectrochem. The progress of the reaction and purity of each compound was monitored by thin-layer chromatography with silica gel as the stationary phase and a mixture of ethyl acetoacetate and hexane in different proportions as mobile phage. Visualization was achieved with UV light using a UV chamber. The melting points determined by electrothermal apparatus using open capillary tubes and uncorrected. IR spectra were recorded on a Shimadzu 8400 FTIR instrument in a KBr disc, and only significant absorbance levels (cm^{-1}) are listed. ^{1}H-NMR spectra (400 MHz) were recorded on a "Bruker AVANCE III spectrometer" using different solvents with TMS as an internal standard, and chemical shifts were recorded in δ ppm. Mass spectra were determined using a direct inlet probe on a GCMS-QP2010 mass spectrometer (Shimadzu, Kyoto, Japan). Elemental analysis was performed on Carlo Erba EA1108 elemental analyzer.

3. EXPERIMENT

3. 1. General synthesis of isoxazole derivatives

Several [3-(Aryl)-5-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]isoxazoles (1a-1h) were synthesized by reaction of 3-Methoxy-4-(2,4-dichlorophenylmethoxy)-(aryl)-chalcone (0.01 mol) in methanol (25mL) with solution of hydroxylamine hydrochloride (1.40g, 0.02 mol) in methanol (20 mL) and anhydrous sodium acetate (1.46g, 0.02 mol). In this mixture catalytic amount of glacial acetic acid was added and the final mixture was refluxed in the water bath for 10-12 hours and poured onto crushed ice. The solid product was isolated and crystallized from methanol. The melting point and elemental data of each synthesized compound collected and are recorded in **Table 1.**

3. 2. Antimicrobial screening

All the synthesized compounds (**1a-1h**) were screened for their antibacterial activity using the cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hours old subcultures of *Gram-positive* bacteria *Staphylococcus aureus (S. aureus)* and *Bacillus subtilis (B. subtilis)*, *Gram-negative* bacteria *Pseudomonas aeruginosa (P. aeruginosa)* and *Escherichia coli (E. coli)* in separate conical

flasks at 40-50 °C and mixed well by gentle shaking. About 25 ml content of the flask was poured and evenly spread in a Petri dish (13 cm diameter) and allowed to set for 2 hours. The cups (10 mm diameter) were formed with the help of a borer in agar medium and filled with 0.04 ml (40 µg) solution of the sample in DMF. The plates were incubated at 37 °C for 24 hours and the control was also maintained with 0.04 ml of DMF similarly and the zone of inhibition of the bacterial growth was measured in *millimeters* and recorded in **Table 2**.

Aspergillus niger (A. niger) and *Candida albicans (C. albicans)* were employed for testing antifungal activity using the cup-plate method. The culture was maintained on *subouraud's agar slants*. Sterilized *sabouraud's agar* medium was inoculated for 72 hours and an old 0.5 ml suspension of fungal spores in a separate flask. About 25 ml of inoculated medium was evenly spread in a Petri dish and allowed to be set for two hours. The plates were incubated at 30 °C for 48 hours. After the completion of the incubation period, the zone of inhibition of growth in the form of diameter in *millimeters* was measured and recorded in **Table 2**. The collected data were compared with the standard drugs Fluconazole (an antifungal drug).

Table1. Physical and Analytical data
of 3-(Aryl)-5-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]isoxazoles (1a-1h)

Comp. Code	-R	Mol. Formula	Mol. Wt.	M.P. (°C)	% Yield
1a	$-C_6H_5$	$C_{23}H_{17}Cl_2NO_3$	426	201	59
1b	$-4-Br-C_6H_4$	$C_{23}H_{16}BrCl_2NO_3$	505	179	72
1c	$-4-Cl-C_6H_4$	$C_{23}H_{16}Cl_3NO_3$	460	217	76
1d	$-2-Cl-C_6H_4$	$C_{23}H_{16}Cl_3NO_3$	460	98	68
1e	$-2,4-Cl_2-C_6H_3$	$C_{23}H_{15}Cl_4NO_3$	495	126	64
1f	$-4-OH-C_6H_4$	$C_{23}H_{17}Cl_2NO_4$	442	138	53
1g	$-2-OH-C_6H_4$	$C_{23}H_{17}Cl_2NO_4$	442	185	72
1h	$-4-OCH_3-C_6H_4$	$C_{24}H_{19}Cl_2NO_4$	456	153	78

Aspergillus niger (A. niger) and *Candida albicans (C albicans)* were employed for testing antifungal activity using the cup-plate method. The culture was maintained on *subouraud's agar slants*. Sterilized *sabouraud's agar* medium was inoculated for 72 hours and an old 0.5 ml suspension of fungal spores in a separate flask. About 25 ml of inoculated medium was evenly spread in a Petri dish and allowed to be set for two hours. The plates were incubated at 30 °C for 48 hours. After the completion of the incubation period, the zone of inhibition of growth in the form of diameter in *millimeters* was measured and recorded in **Table 2**. The collected data were compared with the standard drugs Fluconazole (an antifungal drug).

Table 2. Antimicrobial Screening results of 3-(aryl)-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole (1a-1h)

Comp	-R	Molecular Formula	Antibacterial activity (zone of inhibition in mm)				Antifungal activity (zone of inhibition in mm)	
			S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*A. niger*	*C. albicans*
1a	-C_6H_5	$C_{23}H_{17}Cl_2NO_3$	10	09	07	13	09	11
1b	-4-Br-C_6H_4	$C_{23}H_{16}BrCl_2NO_3$	12	09	11	14	06	13
1c	-4-Cl-C_6H_4	$C_{23}H_{16}Cl_3NO_3$	11	10	06	09	11	07
1d	-2-Cl-C_6H_4	$C_{23}H_{16}Cl_3NO_3$	15	12	11	12	04	05
1e	-2,4-Cl_2-C_6H_3	$C_{23}H_{15}Cl_4NO_3$	12	10	12	11	15	12
1f	-4-OH-C_6H_4	$C_{23}H_{17}Cl_2NO_4$	09	06	10	12	12	09
1g	-2-OH-C_6H_4	$C_{23}H_{17}Cl_2NO_4$	06	08	09	07	14	16
1h	-4-OCH_3-C_6H_4	$C_{24}H_{19}Cl_2NO_4$	08	12	13	11	09	14
	Sparfloxacin		24	25	25	22	-	-
	Benzylpenicillin		18	17	16	16	-	-
	Fluconazole		-	-	-	-	22	20

4. RESULTS AND DISCUSSION

The purity of all compounds **(1a-1h)** is checked by thin layer chromatography and their characterization is carried out through elemental analysis, Infrared spectroscopy, ^{1}H-NMR spectroscopy, and further supported by Mass spectroscopy. The band observed in IR at 1591-98 cm^{-1} is due to the aromatic C=C stretching vibration of the isoxazole ring. Also the bands observed at 1248-57 cm^{-1} and 822-27 cm^{-1} are due to C-N stretching and N-O stretching frequency of isoxazole scaffold present in each isoxazole derivative. The disappearance of strong absorption bands in the range of 1653-56 cm^{-1} for carbonyl group ν(C=O str) of α, β-unsaturated ketone of chalcone also supports the formation of isoxazole moiety. The ^{1}H-NMR also supports the isoxazole moiety by chemical shift for one of the protons in the aromatic

region (6.5-6.9δ) which supports the formation of isoxazole rather than isoxazoline. The molecular ion peak (m/z) is equivalent to the molecular weight of proposed compounds and the fragmentation pattern of synthesized compounds matched with the typical fragmentation pattern of the isoxazole moiety further confirms the structures of the compounds. M and M+4 pecks were also observed in each compound due to the presence of two chlorine atoms in the basic moiety. The elemental analysis (% of C, H, and O) data found is equivalent to their calculated value. The antimicrobial screening data of synthesized isoxazole directives show that the compounds (**1i-1h)** have comparatively low antibacterial activity against *S .aureus, and B. subtilis* (Gram-positive bacteria) compared to Benzylpenicillin. Similarly, they have no antibacterial activity against *P. aeruginosa* and *E. coli* (Gram-negative bacteria) respectively compare to Benzylpenicillin. Antifungal activity data shows that no single compound haswell to moderate antifungal activity.

5. SPECTROSCOPIC DATA OF EACH SYNTHESIZED COMPOUND

1.3-phenyl-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole(1a)

Yield 59%; m.p. 201-204 °C; IR (KBr) cm^{-1}: 2938 (C-H), 3227 (Ar C-H), 1593(C=N), 1258 (Ar-O-C), 1630 (N-O), 690 (C-Cl), ^{1}H-NMR ($CDCl_3$): 5.23 (s, 2H, -O-CH_2-), 3.91 (s, 3H, -OCH_3), 6.79-7.56 (17H, m, Ar-H); Mass (m/z): 425(M+).Anal. Cal. for $C_{23}H_{17}Cl_2NO_3$, Required: C, 64.80; H, 4.25; N, 3.27%; Found: C, 64.67; H, 4.51; N, 3.25%

2.3-(4-bromo-phenyl)-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole (1b)

Yield 72%; m.p. 179-181 °C; IR (KBr) cm^{-1}: 2936 (C-H), 3225 (Ar C-H), 1591(C=N), 1261 (Ar-O-C), 1630 (N-O), 691 (C-Cl), ^{1}H-NMR ($CDCl_3$): 5.19 (s, 2H, -O-CH_2-), 3.90 (s, 3H, -OCH_3), 6.87-7.51 (16H, m, Ar-H); Mass (m/z): 503(M+), 505(M+2).1b, Anal. Cal.for $C_{23}H_{16}BrCl_2NO_3$, Required: C, 54.68; H, 3.19; N, 2.77%; Found: C, 54.59; H, 3.60; N, 2.77%

3.3-(4-chloro-phenyl)-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole (1c)

Yield 76%; m.p. 217-219 °C; IR (KBr) cm^{-1}: 2932 (C-H), 3219 (Ar C-H), 1597(C=N), 1265 (Ar-O-C), 1631 (N-O), 696 (C-Cl), ^{1}H-NMR ($CDCl_3$): 5.18 (s, 2H, -O-CH_2-), 3.91 (s, 3H, -OCH_3), 6.78-7.57 (16H, m, Ar-H); Mass (m/z): 459(M+).Anal. Cal. for $C_{23}H_{16}Cl_3NO_3$, Required: C, 59.96; H, 3.50; N, 3.04%; Found: C, 59.83; H, 3.89; N, 3.09%

4.3-(2-chloro-phenyl)-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole (1d)

Yield 68%; m.p. 98-100 °C; IR (KBr) cm^{-1}: 2902 (C-H), 3234 (Ar C-H), 1593(C=N), 1260 (Ar-O-C), 1633 (N-O), 687 (C-Cl), ^{1}H-NMR ($CDCl_3$): 5.20 (s, 2H, -O-CH_2-), 3.88 (s, 3H, -OCH3), 6.54-7.58 (16H, m, Ar-H); Mass (m/z): 459(M+).Anal. Cal. for $C_{23}H_{16}Cl_3NO_3$, Required: C, 59.96; H, 3.50; N, 3.04%; Found: C, 59.67; H, 3.90; N, 3.02%

5.3-(2, 4-dichloro-phenyl)-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole (1e)

Yield 64%; m.p. 126-128 °C; IR (KBr) cm^{-1}: 2936 (C-H), 3237 (Ar C-H), 1590(C=N), 1264 (Ar-O-C), 1627 (N-O), 679 (C-Cl), ^{1}H-NMR ($CDCl_3$): 5.21 (s, 2H, -O-CH_2-), 3.90 (s, 3H, -OCH_3), 6.70-7.60 (15H, m, Ar-H); Mass (m/z): 492(M+).Anal. Cal. for $C_{23}H_{15}Cl_4NO_3$, Required: C, 55.79; H, 3.05; N, 2.83%; Found: C, 55.83; H, 3.51; N, 2.87%

6.3-(4-hydroxy-phenyl)-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole (1f)

Yield 53%; m.p. 138-140 °C; IR (KBr) cm^{-1}: 3421 (O-H str), 2930 (C-H), 3221 (Ar C-H), 1599(C=N), 1265 (Ar-O-C), 1633 (N-O), 689 (C-Cl), ^{1}H-NMR ($CDCl_3$): 5.20 (s, 2H, -O-CH_2-), 3.92 (s, 3H, -OCH_3), 6.74-7.62 (17H, m, Ar-H); Mass (m/z): 441(M+).Anal. Cal.for $C_{23}H_{17}Cl_2NO_4$, Required: C, 62.46; H, 3.87; N, 3.17%; Found: C, 62.32; H, 4.29; N, 3.19%

7.3-(2-hydroxy-phenyl)-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole (1g)

Yield 72%; m.p. 185-187 °C; IR (KBr) cm^{-1}: 3457 (O-H str), 2927 (C-H), 3232 (Ar C-H), 1592(C=N), 1264 (Ar-O-C), 1630 (N-O), 691 (C-Cl), ^{1}H-NMR ($CDCl_3$): 5.24 (s, 2H, -O-CH_2-), 3.92 (s, 3H, -OCH_3), 6.32-7.52 (17H, m, Ar-H); Mass (m/z): 441(M+).Anal. Cal.for $C_{23}H_{17}Cl_2NO_4$, Required: C, 62.46; H, 3.87; N, 3.17%; Found: C, 62.22; H, 4.28; N, 3.11%

8.3-(4-methoxy-phenyl)-5-[4-(2,4-dichloro-benzyloxy)-3-methoxy-phenyl]-isoxazole (1h)

Yield 78%; m.p. 153-155 °C; IR (KBr) cm^{-1}: 2934 (C-H), 3220 (Ar C-H), 1595(C=N), 1257 (Ar-O-C), 1637 (N-O), 691 (C-Cl), ^{1}H-NMR ($CDCl_3$): 5.18 (s, 2H, -O-CH_2-), 3.93 (s, 3H, -OCH_3), 6.72-7.59 (19H, m, Ar-H); Mass (m/z): 455(M+).Anal. Cal. for $C_{23}H_{19}Cl_2NO_4$, Required: C, 63.17; H, 4.20; N, 3.07%; Found: C, 63.02; H, 4.71; N, 3.02%

6. CONCLUSION

In the present work, a series of 3-(Aryl)-5-[4-(2,4-dichlorophenylmethoxy)-3-methoxyphenyl]isoxazole derivatives (1a-1h) were synthesized and characterized. The antimicrobial activities of synthesized isoxazole compounds show no moderate to good results compared to standard drug data. The green chemistry approach is also applied for synthesis of isoxazole derivative of vanillin analogue. Based on analytical data and spectral data, the structure and geometry of different types of isoxazole derivatives were proposed for each.

Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products. It will be the topic of new research to substitute it with greener reagents, catalyst and solvents, finding more effective anti-fungal and anti-bacterial agents. This work confirms the high importance of heterocyclic compounds in applied fields as reported in many review and research articles.

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