WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 20, 875-889. Research Article ISSN 2277–7105

SYNTHESIS AND CHARACTERIZATION OF SOME NEW ISOXAZOLES IN SEARCH FOR NEW THERAPEUTIC AGENTS

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Article Received on
02 September 2024,

Revised on 22 Sept. 2024,
Accepted on 12 October 2024

DOI: 10.20959/wjpr202420-34303

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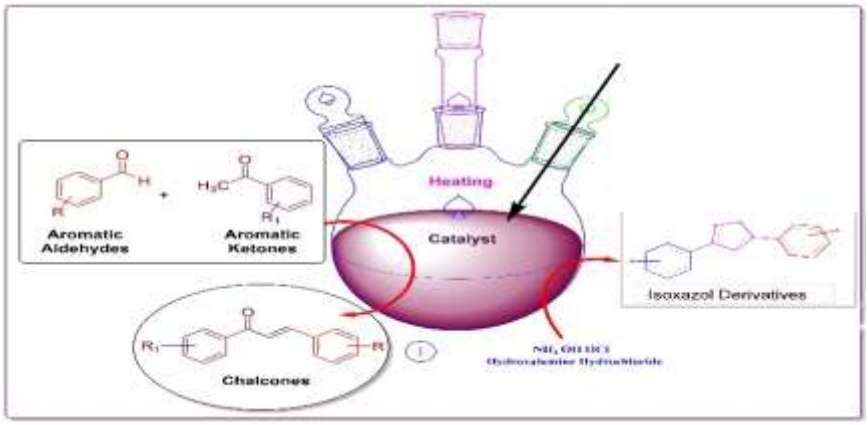
ABSTRACT

The Clasien-Schmidt condensation of substituted acetophenones and substituted benzaldehydes were used to synthesize chalcones such as, (E)-3-(2,3-dichlorophenyl)-1-arylprop-2-en-1-one, (E)-3-phenyl-1-(3-(aryl) prop-2-en-1-one and (E)-1-(aryl)-3-(quinolin-6-yl) prop-2-en-1-one. The resulting chalcones were get converted to 3-(2,3-dichlorophenyl)-5-(aryl) isoxazole, 5-(aryl)-3-phenylisoxazole and 5-aryl-3-(quinolin-6-yl) isoxazole derivatives. All the synthesized compounds are characterized by spectroscopic data. Using standard as the reference medication, all of the synthesized compounds were evaluated for them in vitro antibacterial and antifungal activity. BCB-R_1-2-CF_3& JT-R_3-4-OMe found to be a promising compound in their antimicrobial activity as compared to other synthesized molecules.

KEYWORDS: Isoxazole, Chalcones, Antibacterial, Antifungal.

GRAPHICAL ABSRACT



INTRODUCTION

The advancement of organic chemistry is a constant factor in the advancement of many other scientific disciplines. The heterocyclic rings with contiguous oxygen and nitrogen atoms make up the five-membered hetero aromatic ring known as an isoxazole.[1-4] It serves as both a crucial pharmacophore and foundation for biological activity. The isoxazole ring exhibits desirable pharmacological activity because its two adjacent electronegative heteroatoms facilitate hydrogen donor-acceptor interactions with a variety of target enzymes and receptors that other ring systems are unable to access. There is clearly a considerable deal of interest in the synthesis of functional isoxazoles, as evidenced by the fact that the isoxazole ring ranks 33rd in frequency among the 351 ring systems included in currently marketed pharmaceuticals.[5]

Because of their many biological actions, including antibacterial, antifungal, antiviral, anti-tubercular, anti-epileptic, anti-diabetic, anticancer, anthelmintic, antioxidant, antipsychotic, antimalarial, analgesic, and anti-inflammatory properties, isoxazole derivatives are essential.

Many pharmacological compounds, including the antirheumatic Leflunomide[6], the non-steroidal anti-inflammatory medication Valdecoxib[7], and the anticonvulsant zonisamide[8,9], contain isoxazole scaffold. Analogously, compounds derived from isoxazoles, such as Isocarboxazid[10], function as inhibitors of monoamine oxidase. It is used to treat depressive symptoms, such as anxiety, panic attacks, and phobias. On the other hand, the clinical usage of isoxazole derivatives, such as Sulfamethoxazole[11], Sulfisoxazole[12], and Oxacillin[13], is limited to treating bacterial infections. Antibiotics that are resistant to β-lactamase also contain isoxazole pharmacophore such as Cloxacillin[14], Dicloxacillin, and Flucloxacillin.[15] Suvorexantore[16] is approved for the treatment of insomnia. Risperidone[17] is used in the treatment of bipolar mania. A naturally occurring antibiotic with an isoxazole moiety and anti-tubercular properties is Cyclorine.[18] There are many isoxazoles derivatives which shows anti-HIV, and anticancer activities such as. Acivicin[19], and Maytansine.[20,24]

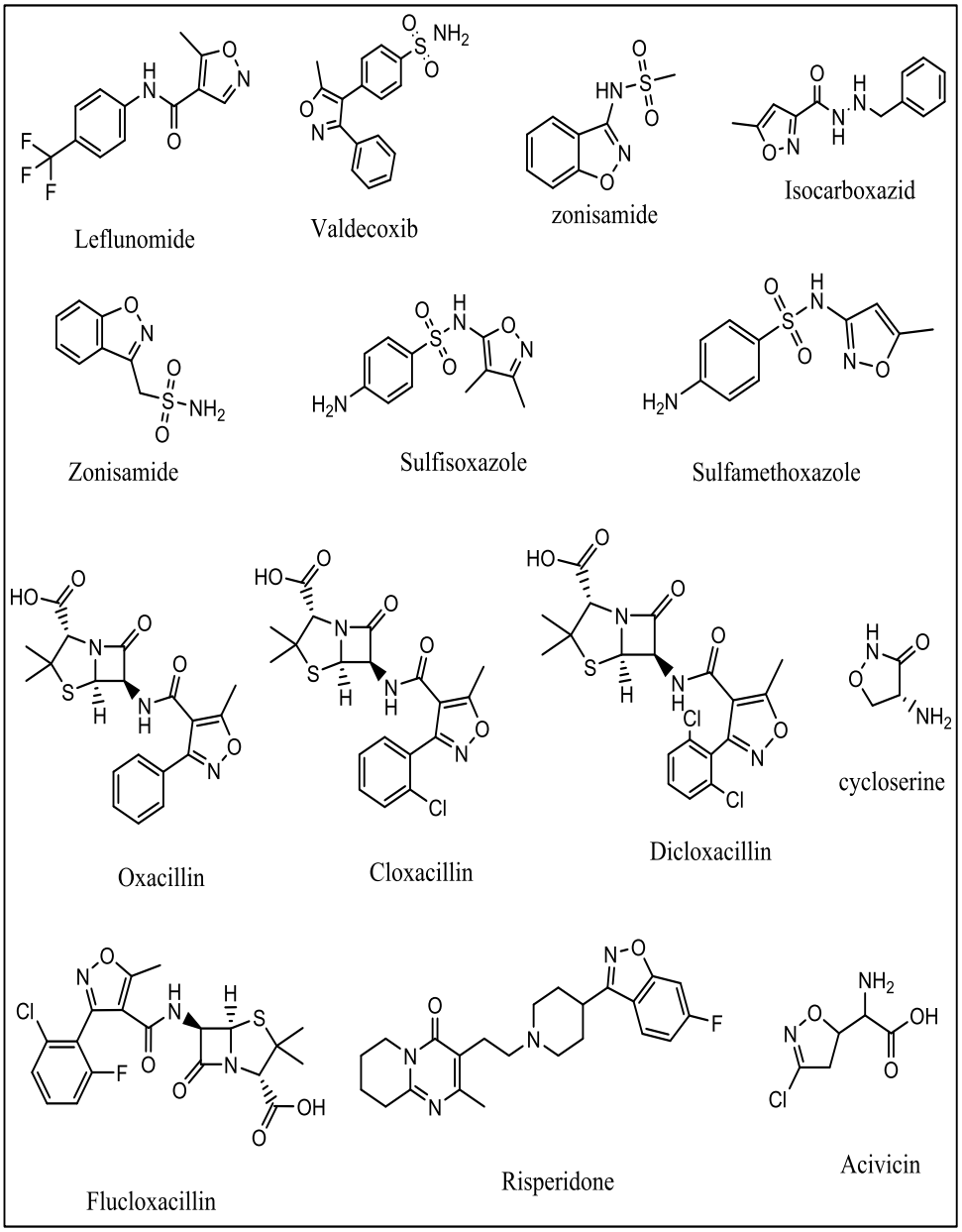


Fig. 1: Some of the commercially used isoxazoline compounds for therapeutic uses.

Within the field of medicinal chemistry, Chalcone scaffolds are preferred chemical structures. They are found in α, β-unsaturated forms, which have a more thermodynamically stable trans-conformation between two aryl groups.[25] They are secondary metabolites of plants. Chalcone and its derivatives are the building blocks of many biologically intriguing substances, and they have often been extracted from a variety of medicinal plants, including Angelica keiskei, Medicago sativa, and Dracaena cincinabari.

Chalcones can be readily synthesized chemically by utilizing a variety of reaction techniques and approaches. One popular technique to create the title compound through carbonyl

derivative condensation in the presence of base is the named reaction, known as Claisen-Schmidt condensation. In addition, there are known solid acid catalyst-mediated reactions, the Suzuki−Miyaura coupling reaction, Heck coupling reaction, the Sonogashira isomerization coupling reaction, and the continuous flow deuteration reaction.[26-31]

Chalcones, which are the precursors of flavonoids and isoflavones, offer a promising scaffold for the synthesis of pharmacologically active chemicals when combined with other heterocyclic moieties. which are crucial to the medical field's efforts to enhance pharmaceuticals and prepare candidates for drug research.[32]

MATERIALS AND METHODS

We obtained AR-grade chemicals for this experiment from reliable vendors. Strict industry-standard drying or purification procedures were applied to these materials to guarantee their quality and suitability for use in experiments. As a baseline measurement for their thermal properties, the unaltered melting points of the synthesized compounds were determined via open capillary tubes.

We used thin-layer chromatography (TLC) to evaluate the course of reactions and the conversion of products. The substances were able to flow through the chromatographic process by employment of ethyl acetate and hexane as the mobile phases and silica gel as the stationary phase. This procedure played a critical role in verifying the successful progression of reaction and the synthesis of the intended products.

Brucker 400 MHz spectrometer for nuclear magnetic resonance (NMR) spectra and FT-IR spectrometer for infrared spectra were two of the sophisticated instruments used in the structural analysis phase. GC-MS was used to carry out the mass analysis of the compounds. These cutting-edge tools were essential in providing comprehensive details regarding the molecular makeup and structure of the produced compounds, providing important insights into their chemical properties. The meticulous implementation of these approaches demonstrates our commitment to accuracy and thoroughness in the experimental processes carried out for this investigation.

Reaction scheme

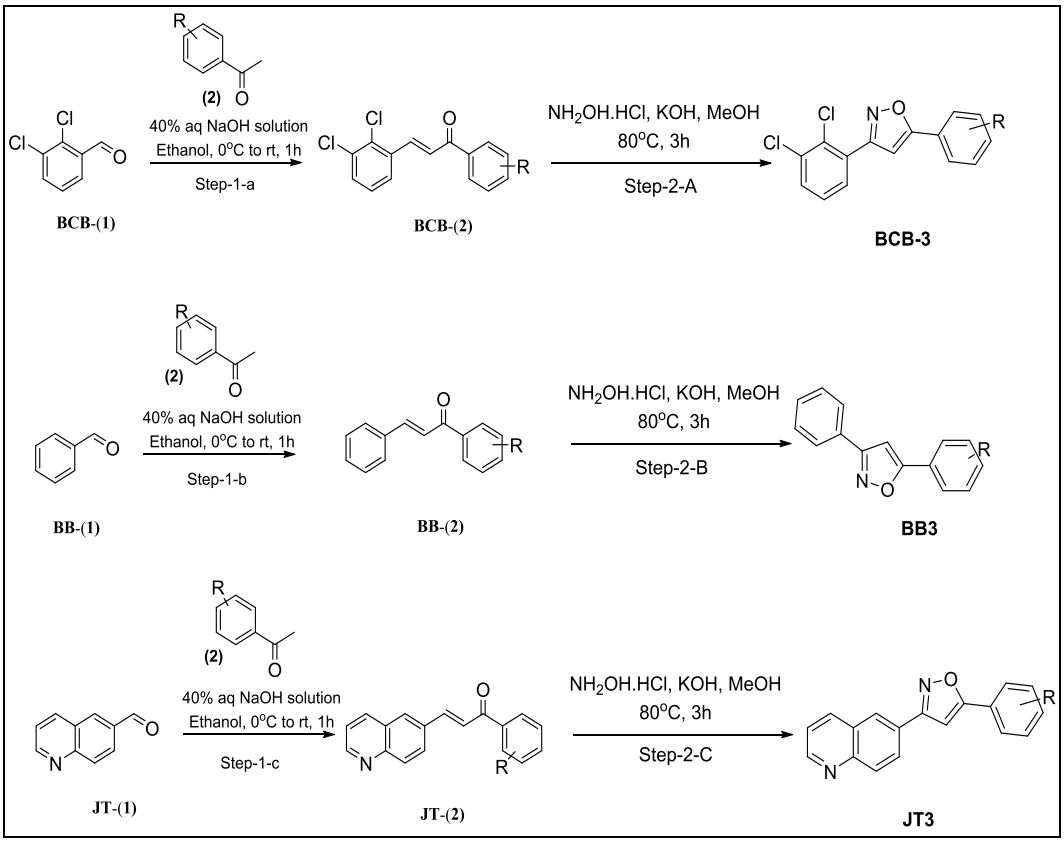
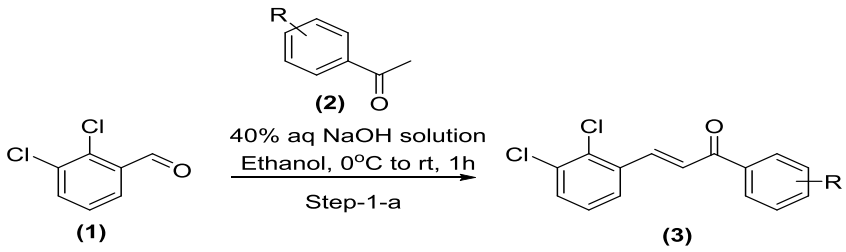


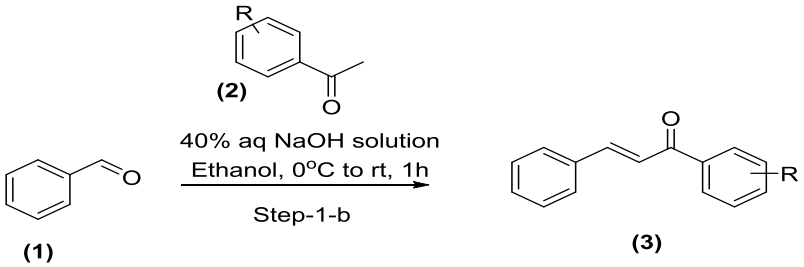
Fig. 2: Reaction Scheme for synthesis of isoxazole derivatives.

Synthesis of (E)-3-(2,3-dichlorophenyl)-1-arylprop-2-en-1-one (Int-3)



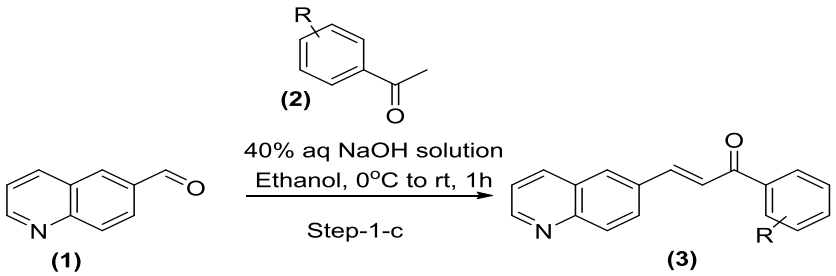
To a solution of compound **1** (7 g, 40.0 mmol, 1.0 eq.) in EtOH (70 mL) was cooled to 0˚ C was added compound **2** (6 g, 40.0 mmol, 1.0 eq.) followed by a 40 % solution of sodium hydroxide in water (2 mL). The Reaction mixture was allowed to warm at room temperature and stirred for 1 h. TLC was used to monitor the progression of the reaction. After completion of the reaction, the formed precipitate was filtered through the Buchner funnel and dried under reduced pressure to get compound **3** (4g).

Synthesis of (E)-3-phenyl-1-(3-(aryl) prop-2-en-1-one



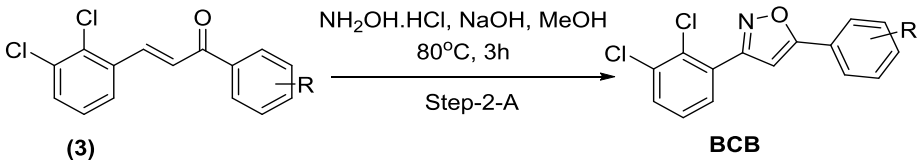
To a solution of compound **1** (4 g, 37.7.0 mmol, 1.0 eq.) in EtOH (50 mL) was cooled to 0˚ C was added compound **2** (7.09 g, 40.0 mmol, 1.0 eq.) followed by 40 % solution of sodium hydroxide in water (2 mL). The Reaction mixture was allowed to warm at room temperature and stirred for 1 h. TLC was used to monitor the progression of the reaction. After completion of the reaction, the formed precipitate was filtered through a Buchner funnel and dried under reduced pressure to get compound **3** (3.0g).

Synthesis of (E)-1-(aryl)-3-(quinolin-6-yl)prop-2-en-1-one (Int-3)



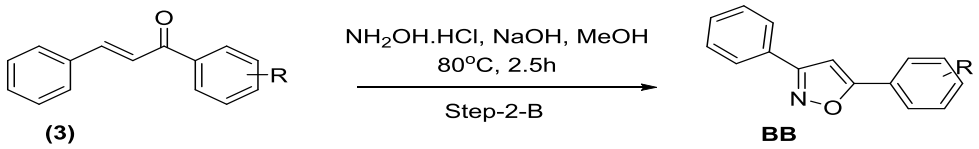
To a solution of compound **1** (5 g, 31.84 mmol, 1.0 eq.) in EtOH (50 mL) was cooled to 0˚ C was added compound **2** (4.8 g, 31.84 mmol, 1.0 eq.) followed by a 40 % solution of sodium hydroxide in water (2 mL). The reaction mixture was allowed to warm at room temperature and stirred for 1 h. TLC was used to monitor the progression of the reaction. After completion of the reaction, the formed precipitate was filtered through the Buchner funnel and dried under reduced pressure to get compound **3** (3.1g).

Synthesis of 3-(2,3-dichlorophenyl)-5-(aryl)isoxazole (BCB)



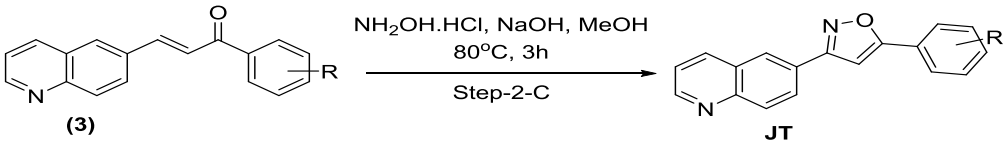
To a solution of compound **3** (0.5 g, 1.6 mmol, 1.0 eq.) in methanol (15 mL) was added hydroxyl amine hydrochloride (0.165 g, 2.4 mmol, 1.5 eq.) followed by sodium hydroxide (0.097 g, 2.4 mmol, 1.5 eq.). The reaction mixture was stirred at 80^{o}C for 3.0 h. Progression of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into water, and the product was extracted with ethyl acetate. The organic layer was washed with brine dried over sodium sulfate and concentrated to afford crude. This was purified by silica gel column chromatography and the product was eluted in 9 % ethyl acetate in hexane to afford pure compound **BCB-03** (Yield: 70-78 %).

Synthesis of 5-(aryl)-3-phenylisoxazole(BB)



To a solution of compound **3** (0.5 g, 1.8 mmol, 1.0 eq) in methanol (15 mL) was added hydroxyl amine hydrochloride (0.186 g, 2.7 mmol, 1.5 eq.) followed by sodium hydroxide (0.108 g, 2.7 mmol, 1.5 eq.). The reaction mixture was stirred at 80^{o}C for 2.5 h. The progression of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into water, and the product was extracted with ethyl acetate. The organic layer was washed with brine dried over sodium sulfate and concentrated to afford crude. This was purified by silica gel column chromatography and the product was eluted in 7% ethyl acetate in hexane to afford pure compound **BB-03** (Yield: 80-83%).

Synthesis of 5-aryl-3-(quinolin-6-yl) isoxazole (JT)



To a solution of compound **3** (0.5 g, 1.7 mmol, 1.0 eq.) in methanol (15 mL) was added hydroxyl amine hydrochloride (0.179 g, 2.6 mmol, 1.5 eq.) followed by sodium hydroxide (0.104 g, 2.6 mmol, 1.5 eq.). The reaction mixture was stirred at 80^{o}C for 3.0h. The progression of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into water, and the product was extracted with ethyl acetate. The organic layer was washed with brine dried over sodium sulfate and concentrated to afford

crude. This was purified by silica gel column chromatography and the product was eluted in 7% ethyl acetate in hexane to afford pure compound **JT-03** (Yield: 60-65 %).

RESULTS AND DISCUSSION

Chemistry

In this study, we initially investigate the synthesis of the title compounds using a diverse range of reagents. The primary goal of this approach is to produce pharmacologically active molecules with improved potency. Consequently, this section aptly demonstrates the successful synthesis of a variety of substituted Chalcone derivatives using a reaction of substituted acetophenone with different aldehydes. The isoxazole derivatives were synthesized by using chalcone derivatives with hydroxyl amine hydrochloride.

We have meticulously characterized the final compounds through an exhaustive analysis using various spectroscopic techniques, including proton nuclear magnetic resonance (^{1}H NMR), and mass spectrometry. The synthesis process was continuously monitored using Thin Layer Chromatography (TLC), ensuring the progression of reactions.

In our spectroscopic analyses, distinctive peaks corresponding to specific functional groups and structural elements present in the compounds were observed. The ^{1}H NMR spectra provided valuable insights into the synthesized compound's molecular composition and bonding arrangements. Additionally, in the mass spectrometry analysis, molecular ion peaks were identified, aligning precisely with the expected molecular weights for each respective compound. These comprehensive characterizations contribute to a thorough understanding of the chemical identity and structural integrity of the synthesized molecules.

Mass spectral study

The molecular ion peak was observed in agreement with the molecular weight of the respective compound. A systematic fragmentation pattern was observed in mass spectral analysis.

NMR spectral study

In ^{1}H NMR spectra, the one singlet signal at around ~6.7 δ ppm is assigned to the presence of isoxazole's one proton. Signals between ~7.05 δ ppm and ~8.0 δ ppm are assigned to the presence of aromatic protons of synthesized compounds.

Chemical analysis

Melting points were determined by open capillary method and are uncorrected. the 1H NMR spectra were recorded in DMSO-d6 or $CDCl_3$ at room temperature on a Bruker spectrometer using Tetramethylsilane(TMS) as an internal standard, (s = singlet, d = doublet, t = triplet, m = multiplates and br = broad). Coupling constant (J) are given in (Hz). The mass spectra were recorded on GC–MS spectrometer. All reactions were monitored by using thin layer chromatography (TLC) using 0.2 mm silica gel plates. Reaction components were visualized in UV (255 and 365 nm) or iodine.

Table 1: Physical constant for synthesized compounds.

Compound	R	Molecular formula	Molecular Weight	M.P. ^{0}C	% yield
BCB-R_1-H	H	$C_{15}H_9Cl_2NO$	290	259-264	87
BCB-R_1-3-CF_3	3-CF_3	$C_{16}H_8Cl_2F_3NO$	358	288-293	89
BCB-R_1-2-CF_3	2-CF_3	$C_{16}H_8Cl_2F_3NO$	358	288-293	88
BCB-R_1-4-OMe	4-OMe	$C_{16}H_{11}Cl_2NO_2$	320	305-310	79
BCB-R_1-3-OMe	3-OMe	$C_{16}H_{11}Cl_2NO_2$	320	305-310	77
BCB-R_1-2-OMe	2-OMe	$C_{16}H_{11}Cl_2NO_2$	320	305-310	80
BCB-R_1-4-Cl	4-Cl	$C_{15}H_8Cl_3NO$	325	303-308	87
BCB-R_1-2-Cl	2-Cl	$C_{15}H_8Cl_3NO$	325	303-308	86
BCB-R_1-4-Br	4-Br	$C_{15}H_8BrCl_2NO$	369	332-337	76
BCB-R_1-4-CH_3	4-CH_3	$C_{16}H_{11}Cl_2NO$	304	284-289	87
BCB-R_1-3-NO_2	3-NO_2	$C_{15}H_8Cl_2N_2O_3$	335	300-305	92
BCB-R_1-4-NO_2	4-NO_2	$C_{15}H_8Cl_2N_2O_3$	335	300-305	90
BB-R_2-3-CF_3	3-CF_3	$C_{16}H_{10}F_3NO$	289	204-209	85
BB-R_2-2-CF_3	2-CF_3	$C_{16}H_{10}F_3NO$	289	204-209	87
BB-R_2-4-CF_3	4-CF_3	$C_{16}H_{10}F_3NO$	289	204-209	82
JT-R_3-4-OMe	4-OMe	$C_{19}H_{14}N_2O_2$	302	271-276	76
JT-R_3-3-OMe	3-OMe	$C_{19}H_{14}N_2O_2$	302	271-276	79
JT-R_3-4-Me	4-Me	$C_{19}H_{14}N_2O$	286	251-255	76
JT-R_3-4-OH	4-OH	$C_{18}H_{12}N_2O_2$	288	291-295	75

ANTIMICROBIAL ACTIVITY

The effect of various synthetic drugs on the several bacterial strains and fungi were assayed by Agar well diffusion method and further confirmed by Disc diffusion method.[33]

The minimum concentrations of compounds to inhibit the microorganisms were also determined by micro dilution method. We have used the broth dilution method[34] for the evaluation of antimicrobial activity. It is one of the non-automated *in-vitro* microbial susceptibility tests. This classic method technique shows that quantitative result for the number of antimicrobial agents that is needed to inhibit growth of specific microorganisms.

Nutrient agar plates were seeded separately with 0.1 ml of inoculums (1.5 x 108 cells/ml) containing active growths of test organisms viz., S. aureus, *B. Subtillis*, K. Escherichia coli and *S. Typhi* bacterial specie and *A. Niger*, *A. Clavatus are fungal specie* was distributed by a sterile cotton swab on the surface of the NA medium and left for 5 min in a laminar air flow cabinet to dry. After drying, a well was created by cork borer (9 mm) and the compound in solvents (200 µl) were transferred to the well. In another plate commercial drugs are added to the well as control. The plates were incubated for 24 hrs. at 37 The development of inhibition zone around the well was measured and recorded.

***Primary screen*:** In primary screening 1000 µg/ml, 500 µg/ml and 250 µg/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

***Secondary screen*:** The drugs found active in primary screening were similarly diluted to obtain 200 µg/ml, 100 µg/ml, 50 µg/ml, 25 µg/ml, 12.5 µg/ml, 6.250 µg/ml, and concentrations.

***Reading Result*:** The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculum. The test mixture should contain 10^8 organism/ml. The MIC values of the test compounds are recorded in following Table.

Table 2: Aantibacterial and antifungal Primary screening of synthesised compounds.

Compound	Antibacterial activity				Antifungal activity	
	Zone of inhibition				Zone of inhibition	
	Gram +*ve* Bacteria		Gram –*ve* Bacteria			
	B. Subtillis	*S. Aureus*	*E. Coli*	*S. Typhi*	*A. Niger*	*A. Clavatus*
BCB-R_1-H	12	15	10	12	8	8
BCB-R_1-3-CF_3	20	20	16	17	16	14
BCB-R_1-2-CF_3	24	24	22	23	21	22
BCB-R_1-4-OMe	18	13	14	20	15	13
BCB-R_1-3-OMe	10	11	10	20	14	13
BCB-R_1-2-OMe	11	15	13	20	15	12
BCB-R_1-4-Cl	14	20	15	16	15	10
BCB-R_1-2-Cl	15	22	11	15	14	10
BCB-R_1-4-Br	10	16	10	16	12	16
BCB-R_1-4-CH_3	8	15	8	8	10	10
BCB-R_1-3-NO_2	8	12	8	12	8	9
BCB-R_1-4-NO_2	9	12	8	13	8	8
BB-R_2-3-CF_3	14	14	9	14	15	12

BB-R_2-2-CF_3	15	15	10	14	16	10
BB-R_2-4-CF_3	15	16	10	18	15	13
JT-R_3-4-OMe	24	23	22	24	20	19
JT-R_3-3-OMe	19	18	17	21	17	18
JT-R_3-4-Me	10	16	15	12	8	10
JT-R_3-4-OH	14	15	12	13	10	10
A.	25	24	20	24	-	-
Cl.	24	21	21	20	-	-
C.	26	25	25	22	-	-
N.	25	22	21	26	-	-
G.	22	21	22	25	-	-
N*.	-	-	-	-	24	25
G*.	-	-	-	-	25	25
A: Ampicillin, **Cl**: Chloramphenicol, **C**: Ciprofloxacin, **N**: Norfloxacin **G**: Gentamycin**, N*:** Nystatin, **G*:** Griseofulvin.						

Table 3: Minimum inhibitory concentrations (µg/ml) of synthesised compounds.

Sr. No.	**Antibacterial activity**				**Antifungal activity**	
	Minimum inhibitory concentration (µg/ml)				**Minimum inhibitory concentration (µg/ml)**	
	Gram +*ve* Bacteria		**Gram -*ve* Bacteria**			
	B. Subtillis	***S. Aureus***	***E. Coli***	***S. Typhi***	***A. Niger***	***A. Clavatus***
BCB-R_1-H	100	100	100	50	-	-
BCB-R_1-3-CF_3	25	25	50	25	25	50
BCB-R_1-2-CF_3	**12.5**	**12.5**	**25**	**12.5**	**12.5**	**12.5**
BCB-R_1-4- OMe	50	100	100	50	100	50
BCB-R_1-3-OMe	200	200	200	50	200	200
BCB-R_1-2-OMe	50	100	100	50	100	100
BCB-R_1-4-Cl	100	50	50	100	100	200
BCB-R_1-2-Cl	100	25	100	100	100	200
BCB-R_1-4-Br	200	100	100	100	100	50
BCB-R_1-4-CH_3	-	100	-	-	200	200
BCB-R_1-3-NO_2	-	200	-	200	-	-
BCB-R_1-4-NO_2	-	200	-	200	-	-
BB-R_2-3-CF_3	100	100	200	100	100	200
BB-R_2-2-CF_3	100	50	200	100	100	200
BB-R_2-4-CF_3	50	50	200	50	100	100
JT-R_3-4- OMe	**12.5**	**25**	**25**	**6.25**	**50**	**100**
JT-R_3-3-OMe	50	100	50	50	100	100
JT-R_3-3-Me	-	100	100	100	-	-
JT-R_3-3-OH	100	100	200	100	200	200
A.	6.25	6.25	12	6.25	-	-
Cl.	6.25	12	12	12	-	-
C.	6.25	6.25	6.25	12	-	-
N.	6.25	12.5	25	6.25	-	-
G.	12.5	12.5	25	6.25	-	-
N*.	-	-	-	-	6.25	6.25
G*.	-	-	-	-	12.5	6.25
A: Ampicillin, **Cl**: Chloramphenicol, **C**: Ciprofloxacin, **N**: Norfloxacin **G**: Gentamycin**, N*:** Nystatin, **G*:** Griseofulvin.						

***Reading Result*:** *The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculum. The test mixture should contain* 10^8 *organism/ml. The MIC values of the test compounds are recorded in the table.*

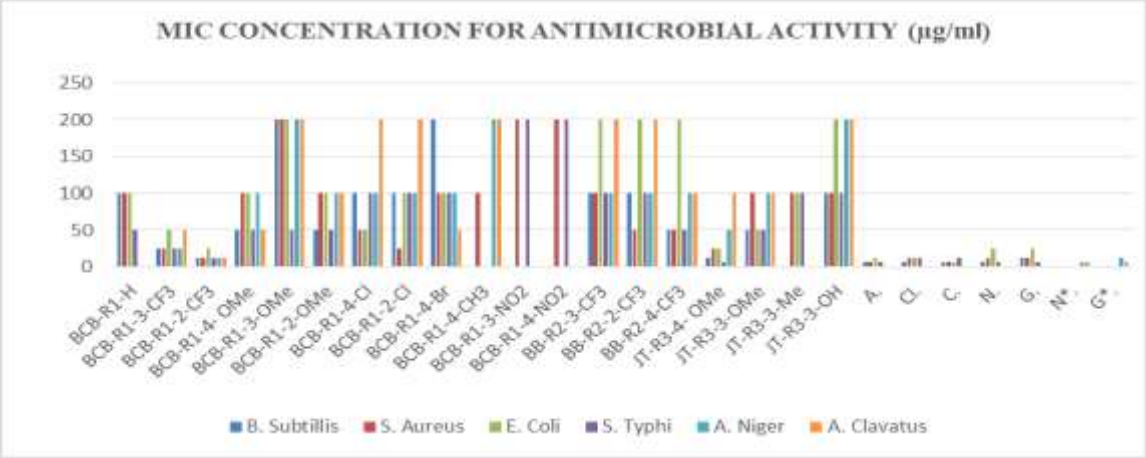


Fig. 3: MIC concentration for antimicrobial activity (µg/ml).

CONCLUSION

The primary goal of this continuing research was the synthesis and characterization of novel derivatives of Isoxazole from chalcones. This research began by converting the original compound—substituted benzaldehydes—into a variety of target chemicals through a synthesis and characterization process. The results of this study demonstrated the utility of isoxazole-based scaffolds as helpful models for additional derivatization or modification to create more potent medicinally active substances. In course of vitro antibacterial and antifungal activity. BCB-R_1-2-CF_3 & JT-R_3-4-OMe are found to be a promising compound in their antimicrobial activity as compared to other synthesized molecules. To determine their broad spectrum of antimicrobial profile, these compounds must be tested further for their antimicrobial activity against different microorganism.

CONFLICT OF INTEREST

The author confirmed that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We are thankful to Department of chemistry, Saurashtra University, Kamani Science college & Prataprai arts college, Amreli and Government polytechnic, Porbandar for providing necessary facilities to carry out the research work and the Special thanks to Commissionerate of Technical Education department, Gujarat for their generous support.

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