British Journal of Pharmaceutical Research
11(4): 1-7, 2016, Article no.BJPR.25645
ISSN: 2231-2919, NLM ID: 101631759

SCIENCEDOMAIN *international*
www.sciencedomain.org

Synthesis, Characterization of Novel Furan Based Imidazolones and Their Boilogical Studies

Dakshayini Chandrashekarachar[1*], M. Chaitramallu[2], N. D. Rekha[3], Devaraju Kesagudu[4] and P. Ranjini[5]

[1]Department of Chemistry, Faculty of Government College for Women, Mandya and Research Scholar at Yuvaraja's College, University of Mysore, Mysuru-5, India.
[2]Department of Chemistry, Research Scholar at Yuvaraja's College, Mysuru-5, India.
[3]Department of Biotechnology, Faculty of JSS College, Ooty Road, Mysuru, India.
[4]Department of Chemistry, Faculty of Yuvaraja's College, University of Mysore, Mysuru-5, India.
[5]Department of Biotechnology, Faculty of Maharani's Science College, Mysuru-6, India.

Authors' contributions

This work was carried out in collaboration between all authors. Authors DC and DK designed the research. Author DC performed the research. Authors DC, MC and DK analysed spectral data. Authors NDR and PR analyzed the biological data. Authors DC and NDR wrote the paper. All the authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJPR/2016/25645
Editor(s):
(1) Rafik Karaman, Bioorganic Chemistry, College of Pharmacy, Al-Quds University, USA.
Reviewers:
(1) Maurizio D'Auria, Uiversità della Basilicata, Italy.
(2) Claudia Araceli Contreras Celedon, Universidad Michoacana de San Niciolas de Hidalgo, Michoacan, Mexico.
(3) Volodymyr Chernyshenko, Palladin Institute of Biochemistry NAS of Ukraine, Ukraine.
(4) Awatef Mohamed Elmaghraby, South Valley University, Egypt.
Complete Peer review History: http://sciencedomain.org/review-history/14306

Original Research Article

Received 13th March 2016
Accepted 15th April 2016
Published 23rd April 2016

ABSTRACT

Background: Heterocyclic derivatives are of various pharmacological activities. The five membered rings, imidazole moiety is present in wide range of naturally occurring molecules, for example furan is a five membered heterocyclic nucleus which contain oxygen atom as heteroatom having broad spectrum of antimicrobial activities against microbes and fungal strains.
Results: We prepared a series of 3-(4-Acetyl-phenyl)-5-arylidene-2-furan-2-yl-3, 5-dihydro-imidazol-4-one with different aldehydes through Erlenmeyer reaction and condensation methods. The newly synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}C NMR and mass spectral

**Corresponding author: E-mail: Iladevi.N@gmail.com;*

studies. All final compounds are screened for their antimicrobial activities done by Gram-negative bacteria *Proteus,* Gram-positive bacteria *Bacillus subtili* and one yeast type fungi, *C. albicans*. Anti oxidant assay through DPPH radical scavenging, Nitric oxide assay.

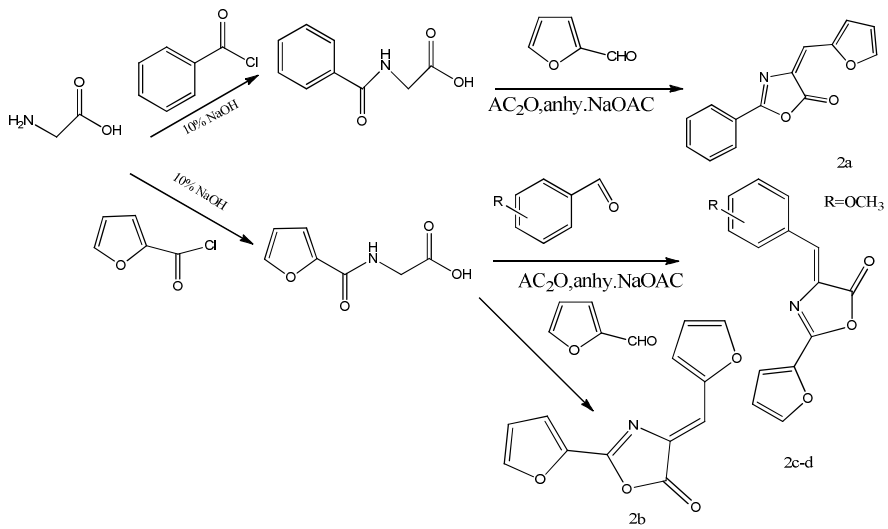
Conclusion: Furan based compounds having greater importance in medicinal chemistry. This research work is an attempt to highlight some compounds shows good potency against microbial activity. Of all the compounds 3d appear to be a potent molecule. 3a, 3c killed all micro organism and there by showing their non-specificity in recognising the micro organism. 3e appears to be less potent molecule as, it is not acting on Gram-negative bacteria's and *B. subtilis* (Gram-positive) bacteria and it's killing Micrococcus with MIC of 92 µg. Among all 3f compound shows good potent against DPPH and nitric oxide radical scavenging assay.

Keywords: 2-furyl-4-arylidene-5(4H)-oxazolones; celite545; erlenmeyer reaction; antibacterial/ antifungal activity; anti oxidant assay.

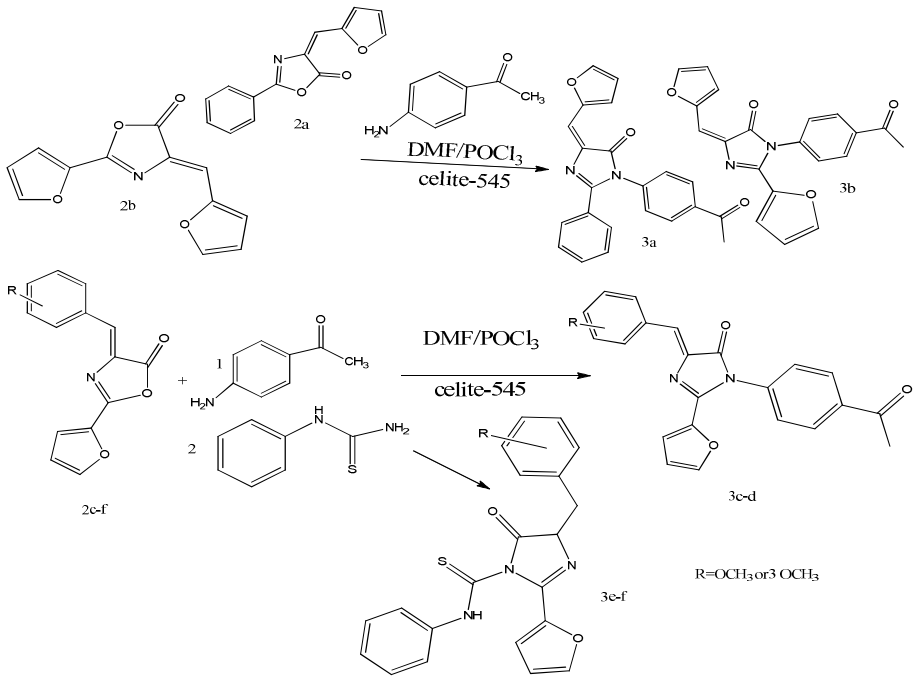
1. INTRODUCTION

In the field of medicinal chemistry, the furan derivatives occupied the unique place. The incorporation of furan nucleus is to enhance the high therapeutic properties. The numerous methods for the synthesis of furans are employed, the series of compounds com prising reactions were completed in fewer minutes by microwave method with minimal use of solvents, high yield and screened against phyto-pathogenic and nitrifying bacteria [1]. Oxazolone molecules exhibit their therapeutic use mainly functional group substituent at the C-4 and C-2 position. It plays a vital role in the reactivity and greatly influences the immune suppressive activity [2-4]. Oxazol-5-ones inhibit the activity of *thyrosinase enzyme* with maximum inhibition by the derivative which bears a cinnamoyl residue at C-4 oxazolone moiety. 3,4-diaryloxazolones showed inhibition of *cyclooxygynese-2*(COX2), *in vivo* anti-inflammatory and excellent activities in arthritis and hyperalgesia [5-7]. Some of the Oxadiaryl proved as fungicides as iprodione that controlled the brown patch (*Rhizactonia solani*) [8]. Also, oxazolone and imidazolone derivatives are used as antioxidant and anticorrosive additives for lubricant oils [9-11]. The chemical stability and potency of the oxazolones can be turned by choosing substituent which influences the reactivity of the carbonyl by electronic and steric effects. Here we synthesis a series of 3-(4-Acetyl-phenyl)-5-arylidene-2-furan-2-yl-3,5-dihydro-imidazol-4-one with different aldehydes through condensation methods. The newly synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}C NMR and mass spectral studies.

1.1 Experimental: Scheme-1



1.2 Scheme-2



2. MATERIALS AND METHODS

All the chemicals were purchased from sigma and SD fine chemicals. They were used without further purification; Melting points were taken in open capillary tubes and are uncorrected. The reactions are monitored by TLC using pre coated silica gel plates, theIR,NMR,^{13}CNMR and Mass spectral studies were obtained from IOE, University of Mysore,Mysuru.

2.1 Synthesis

2.1.1 Procedure for the preparation of substituted Oxazolone (2a-f)

A mixture of substituted aromatic aldehyde (0.01 mole) furoyl glycine or benzoyl glycine (0.01 mol) acetic anhydride (0.04 mol) and anhydrous acetate (0.01 mol) was taken in 350 ml round bottom flask and refluxed for 2 hours. Upon completion of the reaction 25 ml of ethanol was added and the precipitate obtained was recrystallized from benzene.

2.1.2 Procedure for the preparation of substituted imidazlone (3a-f)

DMF/$POCl_3$ mixture was prepared by slow addition of DMF to $POCl_3$ (1.96 mol) with constant stirring at 0-5℃ for 30 minutes in 250 ml round bottom flask. To this substituted oxazolones (2a-f) (0.01 mol),p-amino acetophenone or 1-phenyl thiourea, catalytic amounts of Celite-545 were added and refluxed for 2-hours for maintaining 0℃. The reactions were monitored by precoated silica gel plates. The mixture was poured in to crushed ice and kept for few minutes to settle down the products. The solid was filtered, washed with ice cold water; purification of the compounds was done by column chromatography.

(Z)-1-(4-acetylphenyl)-4-benzylidene-2-(furan-yl)-1H-imidazol-5(4H)-one(3a)

Colour;Yellowsolid,Yield:81%;Mp.,98℃;IR(KBr, cm-^{1});3130(ArHStr),2089(alipha-CHstr),1759 (C=O),1068(CNStr);^{1}HNMR(400MHz,dmso .δ/ppm);3.15(S,3H,CH_3),6.8(S,1H,Fu-H),7.25-7.8(m.10H,Ar-H,Fu-H,-CH=),7.65(t,1H,Fu-H) 8.17(m,1H,Fu-H),^{13}CNMR;(100MHz.$CDCl_3$,δ/ppm),26.5,56,109,113,124,128,129.7,130.5 132.2, 135,136.5, 142,144.5, 197.5;ESIMS(M/Z); 356$(M)^+$Anal.calcd.for$C_{22}H_{16},N_2O_3$;C,71.1: H,4.49 found:C,74;H,4.45

(Z)-1-(4-acetylphenyl)-2-(furan-2-yl)-4(furan-2-yl-methylene)-1H-imidazol-5(4H)-one(3b)

Colour:Yellowsolid,Yield:75%,Mp.,210℃ IR(KBr,cm^{-1});3160(Ar-HStr),2890(alipha-CHstr)

,1750(C=O),1060(CNStr);^{1}HNMR(400,MHz,dmso .δ/ppm);2.2(S,3H,CH_3),6.7-6.83(m,2H,Fu-H),7.1 (S,1H,Furan),7.47.5(m,4H,Ar-H,Fu-H),7.99(S,-CH=),8-8.1(3H,Fu-H,Ar-H,);^{13}CNMR(100MHz. $CDCl_3$,δ/ppm),26.6,109.9,112,124.6,129.8,132.5, 136.7,141.4,142.2,143,153.93,169.6,198.5;ESIM S(M/Z);343$(M)^+$.Anal.cald.for$C_{20}H_{14}N_2O_4$; C, 69.36: H, 4.04, found: C, 69.32: H, 4.01.

(Z)-1-(4-acetylphenyl)-2-(furan-2y)-4(3, 4, 5-trimethoxybenzylidene)-1H-*imidizol-*5(4H)-one(3c)

Colour:brightyellowsolid,Yield:80%,Mp.,170℃,IR (KBr,cm^{-1});3134(Ar-HStr),2894(alipha-CHstr) ,1760(C=O),1060(CNStr);^{1}HNMR(400,MHz,dmso .δ/ppm);2.2(S,3H,CH3),3.8-3.9(m,9H,OCH_3) ,6.8 (S,1H,Furan),7.25-7.5(m,4H,Ar-H),7.5-8.1(5H, Fu-H,Ar-H,CH=);^{13}CNMR(100MHz.$CDCl_3$, δ/ppm),27.5,56,104,109,116.8,120.5,125.7,127.4 ,132.21,142,155.9,160.6,198.5;ESIMS(M/Z);431($M)^+$.Anal.cald.for$C_{25}H_{22}N_2O_6$;C,67.26:H,4.9,found :C,67.23 :H,4.6.

(Z)-1-(4-acetylphenyl)-2-(furan-2-yl)-4-(4-methoxybezylidene)-1H-imidazole-5(4H)-one(3d)

Colour:yellowsolid,Yield:81%,Mp.,145℃,IR(KBr, cm^{-1});3160(Ar-HStr),2900(alipha-CHstr),1760 (C=O),1098(CNStr);^{1}HNMR(400,MHz,dmso.δ/pp m);2.2(S,3H,CH_3),3.9(S,3H,OCH3),6.8(S,1H,Fu-H),6.95-7.2,(m,4H,Ar-H),7.85-8.1(7H,Fu-H,Ar-H,-CH=);^{13}CNMR(100MHz.$CDCl_3$,δ/ppm)27.5, 56.3,104,109,116,120.5,124.7,127.5,132,142,15 5.9,160.6,199.5;ESIMS(M/Z);373$(M)^+$.Anal.cald. for:$C_{23}H_{18}N_2O_4$;C,71.42:H,4.65,found:C,71.12: H,4.63

(Z)-4-(furan-2-yl methylene)-5-oxo-N,-2-diphenyl-4,5-dihydro-1H-imidazole-1-carbothiomide(3e)

Colour:yellowsolid,Yield:71%,Mp., 130℃ IR(KBr,cm^{-1});1395(N-C=S),3130(Ar-H-Str) 2894 (aliphaCHstr),1759(C=O),1068(CNStr),1470 (C=S);^{1}HNMR(400,MHz,dmso.δ/ppm);3.15(S,3H, CH_3),6.8-6.82(m,2H,Fu-H,Ar-H),7.25-7.8 (m.7H,ArH,CH=),7.65(m,1H,Fu-H)8.17(m,1H,Fu-H),^{13}CNMR;(100MHz.$CDCl_3$,δ/ppm),109,113,124 126,128,129.7,130.5,132.2,136,138,144,152,157 159,168,191;ESIMS(M/Z);262$(M)^+$.Anal.cald.for: $C_{21}H_{15}N_3O_3S$;C,70.52:H,3.91:O13.44:N,10.found; C,70.53:H,3.5:O,13.4.

(Z)-2-(furan-2-yl)-5-oxo-N-phenyl-4-(3,4,5-trimethoxybenzylidine)-4,5dihydro-1H-(imidazole-1-carbothiomide(3f)

Colour:Yellowsolid,yield:74%,Mp.,180℃,IR(KBr, cm^{-1});940,1390,(N-C=S),3130(Ar-HStr),2894 (alipha -CHstr),1759(C=O),1068(CNStr),1470 (C=S);^{1}HNMR(400,MHz,dmso.δ/ppm);3.83(m,9H ,OCH_3),6.8(m,1H,Fu-H),7.24(m,3H,Ar-H),7.4 (m,3H,Ar-H,Fu-H),7.7(m,3H,Fu-H,Ar-H),7.8 (S,1H,-CH=);^{13}CNMR;(100MHz.$CDCl_3$,δ/ppm), 26.5,56,103,109,126,128,129.7,130.5,141,153, 159,192;ESIMS(M/Z);362$(M)^+$.Anal.cald.for: $C_{24}H_{21}N_3O_5S$;C,62.20:H,4.4:N,9:O,17.2.found: C,62.18:H,4.3:N,8.9:O,17.1.

2.2 Biological Activity

2.2.1 Antimicrobial activity

The newly synthesized compounds 3a-3f were screened for antimicrobial assay through disc diffusion method using Muller-Hinton medium for bacteria and the same medium with 4% glucose for *fungi* [12]. Compounds were tested in vitro for their antimicrobial activity against two gram positive and two gram-negative bacteria stains and one Yeast type *fungi*,*Candida albicans*. Commercial antibiotics such as *gentamycin* and *flucanzole* were used as reference drugs. The result was compared with reference drugs as depicted in Table 1. All the compounds under study showed very good activity on *P.fluroscence* which is the Gram negative bacteria with MIC ranging from 7-14 µg however the compound 3e did not show any activity on *P. fluroscence* and *Proteus*. Among them 5 micro organism which were used *C. albicans* which is a yeast type *fungi* was susceptible for all the compounds under study -followed by *Micrococcus*.

2.2.2 Antioxidant assay

2.2.2.1 DPPH radical scavenging assay

DPPH radical scavenging activity was done by the method of Shone et al., (1998) with little modifications. Briefly, one ml of DPPH solution (0.1 mM in methanol) was incubated with gradient concentrations (20 µg/ml to 100 µg/ml) of the synthetic Imidazolone compounds, shaken and incubated for 30 min at room temperature and absorbance was read at 517 nm against a blank. BHT was used as reference compound. The radical scavenging activity was measured as decreases in the absorbance of DPPH and

calculated by using the following equation. Radical scavenging potential was expressed as IC_{50} value, which represents the sample concentration at which 50% of the DPPH radical were scavenged.

Scavenging effect = [1-sample absorbance (517 nm)/control absorbance (517 nm) ×100]

2.2.2.2 Nitric oxide radical scavenging assay

Nitric oxide radical scavenging activity was performed by the method of (Marcoci et.al, 1994), with minor modifications. Nitric oxide was generated from Sodium nitroprusside, in aqueous solution at 7.3 $_{P}$H, spontaneously generated nitric oxide reacts with oxygen to produce nitrite ions that can be estimated by the Griess reagent Scavengers of nitric oxide compete with oxygen leading to reduced production of nitric oxide. Sodium Nitroprusside (5mM) in Phosphate buffer saline was mixed with the synthetic imidazolone compounds are incubated at room temperature for 60 min. The sample from the above was reacted with Griess reagent (1% sulphanilamide, 2%H_3PO_4 and 1% naphthalene diamine dihydrochloride). The absorbance of the chromophore formed during the diazotization of nitrite with sulphanilamide and coupling with naphthalene diamine was read at 546 nm and referred to the absorbance of BHT treated into the same way with Griess reagent. The radical scavenging activity was measured using the equation described for DPPH radical scavenging activity.

3. RESULTS AND DISCUSSION

All the compounds are synthesized through Erlenmeyer reaction and condensation reaction The spectral data of IR absorption band between, 1020-1090 cm^{-1}, 1600-1790 cm^{-1}, 2770-2900 cm^{-1}, 3130-3314 cm^{-1}due to C=N,C=O,CH aliphatic and Aromatic C-H stretchings.^{1}HNMR shows that the shift δ2.2-2.5,-CH_3,shiftδ3.2-3.9 shows-OCH_3 shift,δ6.5-8.1 shows Ar-H,Furan-H shift. Mass spectral showed agreeable value for proposed structures.

3.1 Biological Activity

3.1.1 Antimicrobial activity

Of all the compounds 3d appear to be a potent molecule. 3a, 3c killed above mentioned microorganism and there by showing their non-specificity in recognising the micro organism. 3e appears to be a less potent molecule, as it is not acting on Gram-negative bacteria's and *B. Subtilis* (Gram-positive) bacteria and it's killing Micrococcus with MIC of 92 µg.

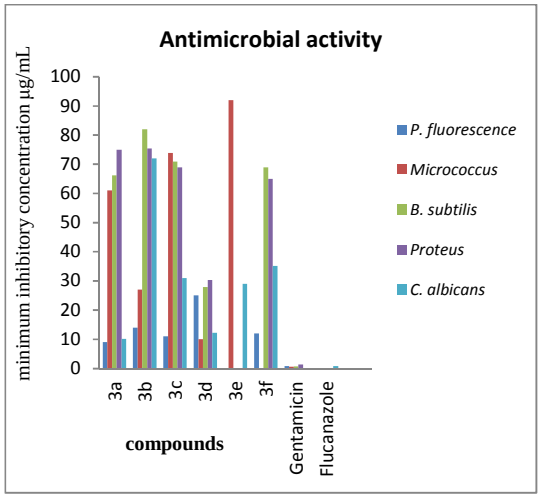


Fig. 1. Antibacterial study of compounds 3a-3f

3.2 Antioxidant Assay

3.2.1 DPPH radical scavenging assay

The DPPH radical scavenging activity of imidazolone compounds such as 3f is showing better scavenging activity with reference to BHT with an IC_{50} value of ranging from 18.1µg/mL to 19.9 µg/mL on the contrary BHT scavenged the protons with and IC $_{50}$ value of 20.29 µg/ml due to the presence of proton donating groups like CH_3, OCH_3 and imidazolone moiety are responsible for the activity.

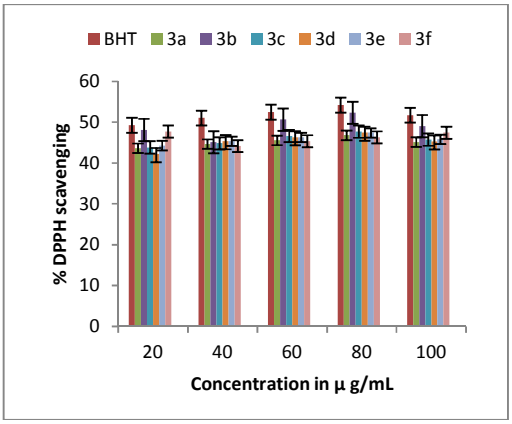


Fig. 2. DPPH radical scavenging assay of compounds 3a-3f

3.2.2 Nitric oxide radical scavenging assay

The compound 3c, 3f showed the significant NO radical scavenging activity. This is attributed to the presence of reducing groups like electron donating group $S.OCH_3$ among them.

As above in the antioxidant activity, the 3f showed good potent molecule containing tri-methoxy group on the substituted phenyl ring at Para and the meta position displayed the considerable activity, this is due to steric hindrance between the methoxy groups.

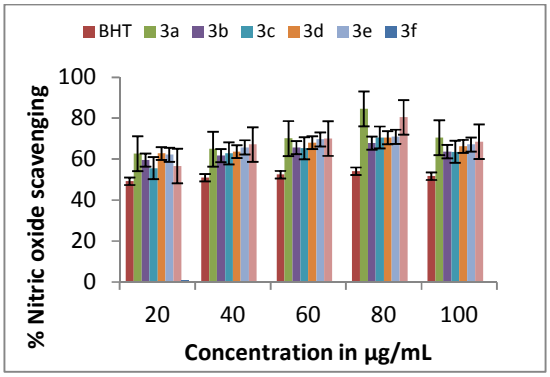


Fig. 3. Nitric oxide radical scavenging assay of compounds 3a-3f

4. CONCLUSION

The hetero cyclic compounds and imidazolone moieties were shown to be potent in antibacterial activity [4-6]. All synthesized compounds are screened for antibacterial assay. In that the compound 3d become good potent molecule, because of having furan and free CH_3 group end. In the case of anti oxidant activity 3f compound showed to be good potent molecule due to steric hindrance of methoxy groups present in that molecule.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

The author thankful to UGC to providing opportunity for FIP facility to do this work and thanks to IOE, university of Mysore, Mysuru for the spectral studies.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Nandakishore S, Thombare Nisha A, Rajesh K, Madhaban G. Synthesis of 2-furyl-4-arylidene-5(4H)-oxazolones as new potent antibacterial agents against phytopathogenic and nitrifying bacteria. Journal of Environmental Science and Health, Part B. 2012;47:326-335.
2. Argade ND, Kalrale BK, Gill CH. Microwave assisted improved method for the synthesis of pyrazole containing 2,4,-disubstituted Oxazole-5-one and their antimicrobial activity. European Journal of Chemistry. 2008;5:120-129.
3. Mesaik NA, Rahat S, Khan KM, Ullah Z, Choudahry MI, Murads S, Ismail Z, Rahman A, Ahmad A. Bioorganic and Medicinal Chemistry. 2004;12:2049-2057.
4. Anitha S, Subhashini NJP. Synthesis, characterization and biological evaluation of novel chalcone derivatives of imidazolones. International. J Pharm Bio Sci. 2014;5(2):433-442.
5. ladva K, Deave V, Parekh H. Imidazolidinones: Part-I: 2, 4-BIS (4'-Arylidene-2'-Methyl/Phenyl-5'-OXO-2'-Imidazolin-1'-YL)-6-Hydroxy pyrimidines. J. Inst. Chem. 1992;64:80.
6. Benedit D, Daniel. Synthesis of 2-Methyl-(Z)-4-(phenylimino) naphthp2,3-d]oxazol-9-one, a monoinime quinoe with selective cytotoxicity toward cancer cells. J. Med. Chem; 1994.
7. Pereira ER, Sancelme M, Voldoire A, Prudhomme M. Synthesis and antimicro-bial activities of 3-N-substituted-4,5-bis(3-indolyl)oxazol-2-ones. Bioorg. Med. Chem. Lett. 1997;7:2503.
8. Viti G, Namnicine R, Ricci R, Pestelline V, Abeli L, Funi M. New antagonists of platelet-activating factor containing 2-oxazolidinone or 2-morpholinone. Eur. J. Med. Chem. 1994;29:401.
9. Gelmi ML, Cleriei F, Melis A. Synyhesis of 2-methyl-(Z)-4-(phenylimino)naphtha-[2,3-d]oxazol-9-one, a monoimine quinone with selective cytotoxicity toward cancer cells. Qu Tetrahedran. 1997;53:1843.

10. El-Mekabaty A. Review erlenmeyer azlactones; Syntheisis, reactions and biological activity. Int. J. Modern Org. Chem. 2013;2(1):40-66.
11. El-Mekabaty A, Osman M, Habib O. Synthesis and evaluation of some novel additives as antioxidants and corrosion inhibitors for petroleum fractions. Pet. Sci. 2014;11:161-173.
12. Amsterdam D. Susceptibility testing of antimicrobials in liquid media. In: Lorion V, (ed). Antibiotics in library medicine, Williams and Wilkins Baltimore. 1996; 4.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/14306