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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 1-(4-CHLOROPHENYL)-2-(3-SULPHOXYPHENYL-4-(4-SUBSTITUTED BENZYLIDENE)-5-IMIDAZOLONES

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ABSTRACT

Imidazolones are believed to be associated with several pharmacological activities. Their significance lies in the fact that they show diverse biological activities. Which include anticancer, anticonvulsant, antiparkinsonian, CNS depressant, antimicrobial, antihelmintic, anti HIV, anti-inflammatory etc.However no work is reported on imidazolone from substituted benzoyl glycine.Therefore it was thought interesting to attempt synthesis of imidazolones containing new substituent and study there antimicrobial activity In the proposed work, we have reported eight newly synthesized sulphoxy substituted imidazolones from oxazolones and 4-chloroaniline in presence of zeolite as a catalyst. The oxazolones were obtained from 3-sulphoxy benzoyl glycine and variedly substituted aromatic aldehydes in presence of anhydrous sodium acetate and acetic anhydride. The characterisation of these compounds was made by chemical properties, elemental analysis and spectral data like IR, ^{1}H-NMR.In order to know antimicrobial property these compounds were assayed for their antimicrobial activity against the test organisms E.coli, K.pheumoniae, S.aureus. S.epidermis. Out of eight samples tested, sample 2g and 2c each. The compound containing –OH group showed antimicrobial activity against maximum number of organisms followed by sample 2h containing -OCH_3 along with -OH group. Thus it may be concluded that -OH group present on benzylidene moiety irrespective of its position shows antimicrobial property.

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INTRODUCTION

Imidazolones form an important class of heterocyclic compounds since they can be converted into amino acid [1-2],used in drugs[3],pigments and electrodes[4].They have also shown diverse bioactivities including anticancer[5], anti HIV[6], antiparkinsonian[7-8], CNS depressant[9], antihelmintics[10]. Gabillet S, et al reported A Phosphine-Catalyzed Preparation of 4-Arylidene-5-imidazolones [11]. Snehalatha P and Subhashini N. J. P carried out, "Synthesis, characterization and biological evaluation of novel imidazolones derived from azlactones[12].Ming and coworkers[13] synthesized 2-alkoxy 4H-imidazole-4-ones.from aza-witting reaction of iminophosphorane with phenyl isocyanate to form carbodiimide which on subsequent reaction with ROH in presence of RONA gave the target compounds. Kedar and Dehmukh[14]reported "synthesis of 1-(-4-methyl phenyl)-2-(3-bromo phenyl) -4-(4-substituted benzylidene) -5-imidazolones. Chopra et al [15] carried out Microwave assisted synthesis of some 5-substituted imidazolone analogues as a new class of nonpurine xanthine oxidase inhibitors. However no work is reported on imidazolones synthesized from substituted benzoyl glycine. Thus, due to their diverse applications and also part of our study, it was thought interesting to synthesize some new imidazolones containing different substituent's and to screen some of them for their antimicrobial activity.

MATERIALS AND METHOD

Aromatic aldehydes, benzoylglycine, 4-chloroaniline,sodium acetate, acetic anhydride and zeolite are required chemicals purchased from sd fine chemicals. All the chemicals used were of AR grade. Melting points were measured in open capillary tube. The purity of the compounds were checked by TLC on silica gel in petroleum ether and ethyl acetate (80:20).The IR spectra were recorded on Agilent Technologies cary 630 FTIR.^{1}H-NMRspectra were recorded on Brucker AVANCE 400MHz spectrometer using TMS as internal standard. This work involved condensation of 3-sulphoxy benzoyl glycine with substituted aldehyde in acetic anhydride in presence of anhydrous sodium acetate to obtain variedly substituted oxazolones.Oxazolones were further reacted with 4-chloro aniline in presence of zeolite as a catalyst to obtain the target compounds 1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-(4-substituted benzylidene)-5-imidazolones.In order to know their antimicrobial activity, these compounds were than tested for antimicrobial activity against four test organisms, Klebsiella pneumonie , Staphylococcus aureus, E.Coli and Staphylococcus epidermis.

METHOD

Step-I: Synthesis of 2-(3-sulphoxyphenyl)-4-(4-methoxybenzylidene)-5-oxazolone.

To the solution of 3-sulphoxy benzoyl glycine 2.14gm(0.01mol)in acetic anhydride ,added 1.36gms of anisaldehyde(0.01mol)and then .0.7gms anhydrous sodium acetate (0.01mol).The contents were dissolved in ethyl alcohol .The solution was refluxed under water condenser for 3-hours It was poured to ice cold water when an yellowish solid was obtained. Washed it 2-3times with ice cold water and recrystallised from ethanol.

Yield: 65% **Melting point: 145^{0}C**
Molecular formula $C_{17}H_{12}NO_5$ **Molecular weight: 342**

IR (KBr) in cm^{-1}:3045 (Ar,C-Hstr);2937(Aliph,C-Hstr);1787(C=Ostr);1651(C=Nstr);1596(C=Cstr);1311(C-O bend);1263(C-N bend);1028(S-O Asymmetric str);981(S-O symmetric str).
^{1}H-NMR(∂) : 8.27(d,2H,Ar-H);8.11(d,2H,Ar-H);7.66-7.68(t,1H,Ph-CH);7.58-7.61(t,2H,Ar-H);7.60(d,2H,Ar-H);3.87(s,3H,-OCH_3).
Elemental analysis for $C_{17}H_{12}NO_5$ (342)

Calculated	**%C=59.64**	**%H=3.50**	**%N=4.09**	**%S=9.35**
Found	**%C=59.60**	**%H=3.48**	**%N=4.02**	**%S=9.30**

Step-II :- Synthesis of 1-(4-clorophenyl)-2-(3-sulphoxyphenyl)-4-(4-methoxybenzylidene)-5-imidazolone

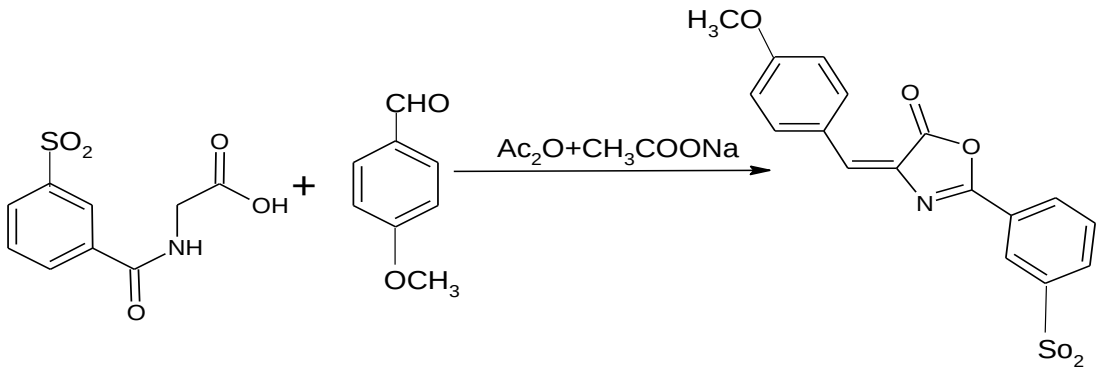
To the ethanolic solution of oxazolone(3.42gm,0.01M) obtained in step-I, added 4chloro aniline (1.27gm,0.01M)and zeolite (1gm) as a catalyst followed by 1ml of 2%aq NaOH solution. The reaction mixture was reflux under water condenser for two and half hours it was allowed to cool and poured to ice cold water obtained colourless solid on acidification with dil HCl Washed it 2-3times with cold water and recrytalised from ethanol

Yield: 60% **Melting point: 235^{0}C**
Molecular formula $C_{23}H_{16}N_2SClO_4$ **Molecular weight: 451**

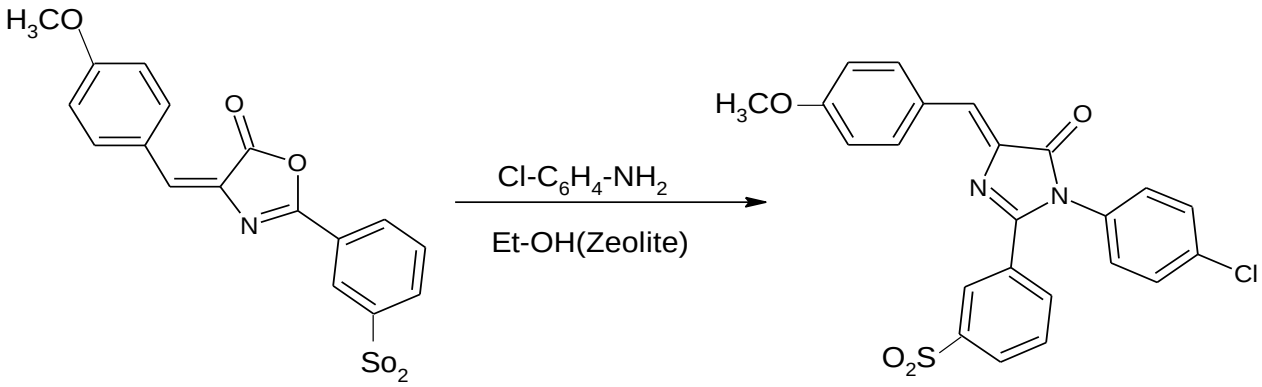
IR (KBr) :3030cm^{-1}(Ar,C-Hstr);2925cm^{-1}(Aliph,C-Hstr)1710cm^{-1}(C=Ostr);1639cm^{-1}(C=Nstr);1599cm^{-1}(C=Cstr);1305cm^{-1}(C-Obend);1258cm^{-1}(C-Nbend);1035cm^{-1}(S-OAsymmstric str);1020cm^{-1}(S-O symmstric str)
^{1}H-NMR(∂) : 8.04(d,2H,Ar-H);7.74(d,2H,Ar-H);7.56-7.61(m,3H,Ar-H);7.48.-7.52(t,1H,Ph-CH);7.29(d,2H,Ar-H); 7.14(S,1H,Ar-H);6.92(d,2H,Ar-H);3.78(S,3H,OCH3)
Elemental analysis for $C_{23}H_{16}N_2SClO_4$ (451.5)

Calculated	**%C=61.12**	**%H=3.54**	**%N=6.20**	**%S=7.08**	**% Cl =7.86**
Found	**% C=61.05**	**%H=3.50**	**% N=6.18**	**%S=7.02**	**% Cl =7 .78**

REACTION



1a



2a

RESULTS AND DISCUSSION

The oxazolones required for the synthesis of imidazolones were prepared by condensation of newly synthesied 3-sulphoxy benzoyl glycine with variedly substituted aldehydes in presence of anhydrous sodium acetate in acetic anhydride Their formation was confirmed by physical and chemical tests. Thus eight variedly substituted oxazolones were obtained from different aldehyde and 3-sulphoxy benzoyl glycine. The target compounds 1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-substituted arylidene)-5-Imidazolones were synthesized by reacting each of these oxazolones with p-chloroaniline in ethanolic medium in presence of zeolite as a catalyst. It offered easy to workout methodology and also reduced reflux time to two and half hours. The compound (2a) gave positive test (orange colour)with ethanolic solution of 2,4dinitrophenyl hydrazine in presence of cone H_2SO_4 confirming the presence of (2a). It showed absorption bands at 2925cm-1due to Aliphatic ,C-H str;1710cm^{-1}due to C=Ostr;1639cm^{-1} C=N str;1035-1025cm^{-1}S-O Asymmetric str and symmetric str 690 C-Cl str similarly ^{1}H-NMR spectrum of 2 (a) showed the following chemical shift(∂)8.04(d,2H,Ar-H);7.74(S,1H,Ar-H);7.56-7.61(m,3H,Ar-H);7.48-7.52(t,1H,Ph-CH);7.29(d,2H,Ar-H);7.14(S,1H,Ar-H);6.92(d,2H,Ar-H);3.78(s,3H,O-CH_3) Which tallies with Molecular formula of target compound 2a $C_{23}H_{16}N_2SClO_4$ Elemental analysis also supported this formula experimental value of which are comparable with calculated ones all these evidences support the formation of 2(a) similarly other target compound (2b-2h)were synthesized by employing above mentioned procedure.

Table-1: List of synthesized compounds, their % yield and melting points.

Sr. No.	Compound	%Yield	Melting Point (in ^{0}C)
1	1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-(4-methoxy benzylidene)-5-Imidazolone.(2a)	60	235
2	1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-(4-nitrobenzylidene)-5-Imidazolone.(2b)	65	290
3	1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-(4-hydroxybenzylidene)-5-Imidazolone.(2c)	68	220
4	1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-(4-dimethylaminobenzylidene)-5-Imidazolone.(2d)	62	310
5	1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-(3,4,5tri methoxybenzylidene)-5-Imidazolone.(2e)	64	170
6	1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-(4-chlrobenzylidene)-5-Imidazolone.(2f)	69	230
7	1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-(2-hydroxy benzylidene)-5-Imidazolone.(2g)	69	210
8	1-(4-chlorophenyl)-2-(3-sulphoxyphenyl)-4-(4-hydroxy3-methoxybenzylidene)-5-Imidazolone.(2h)	70	160

ANTIMICROBIAL ACTIVITY

Method for the determination of antimicrobial activity

The newly synthesized eight compounds 2(a-h) were screened for their antimicrobial activity against E.coli(gram -ve), K.pneumoniae(gram -ve) ,S. aureus (gram +ve)and S. epidermis(gram +ve) by using agar disc diffusion method [16] at concentration of 100 **µ**gm/ml in DMF as a solvent. Each standardized test organism (0.1ml)was spread on the solidified sterile agar plates.

Table 2 : Antimicrobial activity of imidazolones.

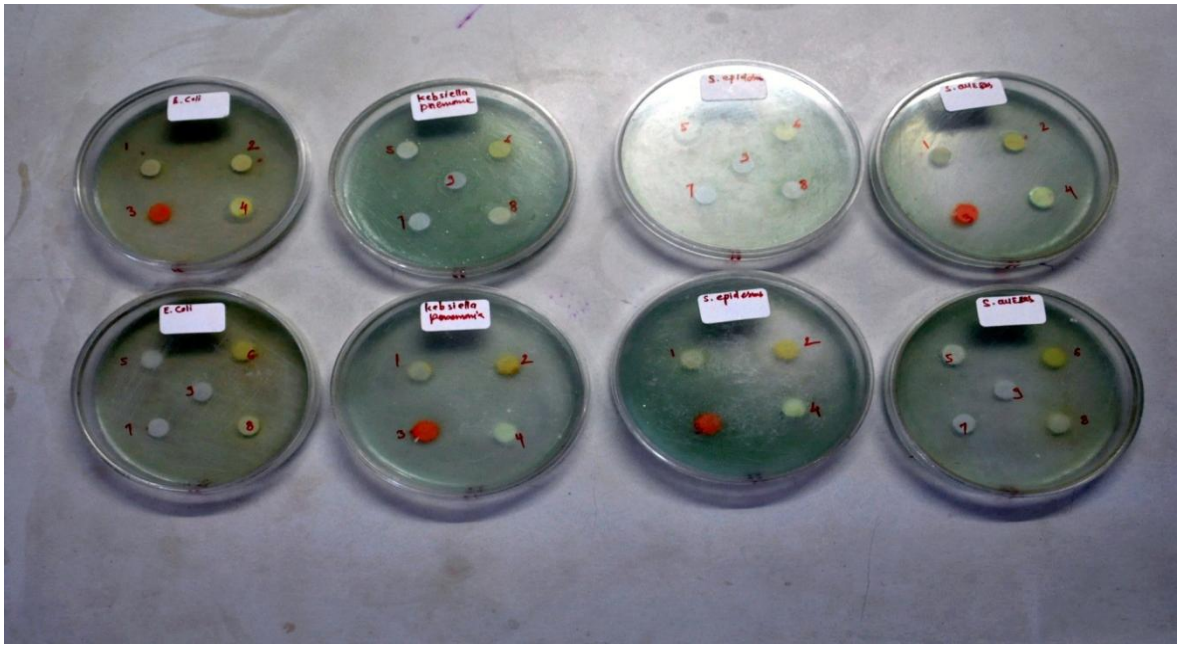
Sr. No	Sample	*E-Coli*	*K. pneumonie*	*S. aurous*	*S. epidermis*
		Zone of inhibition in mm	Zone of inhibition in mm	Zone of inhibition in mm	Zone of inhibition in mm
1.	SACH (2a)	-	6	-	-
2.	SACH (2b)	6	-	-	-
3.	SACH (2c)	10	11	-	13
4.	SACH (2d)	7	-	-	-
5.	SACH (2e)	-	6	-	-
6.	SACH (2f)	-	-	-	-
7.	SACH (2g)	12	13	-	10
8.	SACH (2h)	13	11	-	-

After incubation period of 18 hours at 37^{0}C, the trays were examined for bacterial growth .and zones of inhibition (in mm) were determined and are given in table 2. From these values, it follows that imidazolone containing -OH as substituent(2g and 2c) showed antimicrobial activity against maximum number of organisms followed by 2h ,each of which showed antimicrobial activity against three and two organisms respectively.However, 2a,2d, and 2e showed antimicrobial activity against one organism only.

CONCLUSION

Hence we could synthesize a new series of imidazolones by introducing sulphoxy group as one of the new substituents. Use of zeolite as a catalyst afforded us increase in percent yield and reduction in reflux time. From antimicrobial study it appeared that -OH group(irrespective of its position) as a substituent played a vital role in imparting antimicrobial property to imidazolones, particularly, the substituents like -OH ,-OCH_3attached to benzylidene moiety enhanced the antimicrobial activity of the compounds. Therefore, it may be suggested that more series of compounds are needed to be synthesized by introducing new substituents on benzylidene moiety in order to enhance its value as a drug.

Table 3 : Photoes showing Antimicrobial activity of imidazolones.



DECLARATION OF INTEREST

There is no conflict of interests

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List of abbreviations

A.R -Analytical Reagent
Ac_2O - Acetic anhydride
Et-OH - Ethanol
TLC -Thin layer chromatography
TMS -Tetra methyl silane
Ar -Aromatic
Cl-ph-NH_2 -4-chloro aniline

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