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DEIGNED SYNTHESIS AND BIOEVLUATION OF 4-ARYL BENZELIDENE-2-((5-FLUORO-1H-INDOL-1-YL) METHYL) OXAZOL-5(4H)-ONE PROMOTED BY KIO_4.

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ABSTRACT

A great deal of work has been done on the series of five series of 4-arylbenzelidene-2-((5-fluoro-1H-indol-1-yl) methyl) oxazol-5(4H)-ones. These derivatives were prepared from the condensation of 2-(2-(5-fluoro-1H-indol-1-yl) acetamides) aceticacd, substituted aromatic aldehydes with acetic anhydride sodium acetate and sodium acetate in the presence ofKIO_4 under reflux. Five series novel new derivatives. 2-(2-(5-fluoro-1H-indol-1-yl) acetamides) acetic acid was obtained from 2-(5-fluoro-1H-indol-1-yl) acetyl chloride with lysine in the presence of NaOH and HCl in the ice cold solution. 2-(5-fluoro-1H-indol-1-yl) acetyl chloride can be synthesized from 5-fluoro indole with chloroacetyl chloride in triethylamine and dichloromethane. The structures of the compounds were confirmed by advanced spectroscopic data based on ^{1}H-NMR, ^{13}CNMR and LCMS and by elemental analysis. This compound was screened by anti-microbial activity.

KEYWORDS: 2-(5-fluoro-1H-indol-1-yl) acetyl chloride, 2-(2-(5-fluoro-1H-indol-1-yl) acetoamide) acetic acid, 4-aryl Benzelidene-2-((5-fluoro-1H-indol-1-yl) methyl) oxazol-5(4H)-one, anti-microbial activity, KIO4.

INTRODUCTION

Active Five membered heterocyclic compounds are one of the important topic of interest for the synthetic organic chemistry and medicinal chemistry which showed a number of pharmacological properties. A five membered heterocyclic compounds containing nitrogen, sulphur, oxygen having occupied most important significant field in the organic chemistry as well as medicinally chemistry.[1] Oxazalones are five member heterocyclic compounds having nitrogen and oxygen as hetero atoms. The C-2 and C-4 positions of Oxazalones are responsible for their various biological activities such as analgesic1, anti-inflammatory, antidepressant, anticancer, antimicrobial, and antidiabetic and anti obesity. Oxazalones are heterocyclic compounds which perform an important role in the synthesis of several organic molecules including amino acids[2], amino alcohols, thiamine[3], amides[4], peptides[5-7] and polyfunctional compounds[8], Certain natural and synthetic Oxazalones also including benzoxazolone[9-13], derivatives possess important biological activities; such as antimicrobial[14, -16], anti-inflammatory[17, 18], anticancer[19, 20], anti-HIV[21-23], antiangiogenic[24], anticonvulsant[25], antitumor, antagonistic, sedative[26-28], and cardio tonic activity[29], These are used as synthons for the construction of various alkaloid skeletons, immunomodulator and biosensors.[30-32]

The number of drug moiety was developed against bacterial infections. The present work done the Oxazalones from 5-fluoro indole molecules and also examined the bioevaluation.

METHODS AND MATERIALS

All reagents, solvents and chemicals were purchased from Sigma Aldrich. Organic solvent used was absolute alcohol. The melting points of 4-aryl Benzelidene-2-((5-fluoro-1H-indol-1-yl) methyl) oxazol-5(4H)-one were determined in open glass capillaries on a Mettler FP51 melting point apparatus and are uncorrected. The NMR spectra of selective compounds were recorded on a Bruker for 400 MHz ^{1}H NMR spectra and 100 MHz for ^{13}C NMR spectra in $CDCl_3$ solvent using TMS as internal standard. Elemental analysis was obtained using Perkin Elmer (USA) 2400, series II CHN-analyser. Reactions were monitored by TLC, using silica gel as an adsorbent and ethyl acetate-hexane in different ratios as eluent.

Experimental

Synthesis of 2-(5-fluoro-1H-indol-1-yl) acetyl chloride (3)

5-fluoroindole is dissolved in a base such as triethylamine and dichloromethane taken in a 50mLfour neck RB flask. The chloroacetyl chloride added to the above mixture with using dropping funnel by portion wise in fume cupboard in a cooling condition. The RB flask fitted on the magnetic stirrer under reflux condition and the reaction was monitored by TLC (7:3, n-hexane: ethylacetate). After all the reactants were consumed, the product poured in a ethylacetate and neutralizes with

sodium bicarbonate solution. Final compound was recrystallized from ethanol.

Colourless, yields-77%. **^{1}HNMR(400Mz, $CDCl_3$)ppm**:7. 632(s, 1H, Ar-H), 7. 541(d, J=8. 8Hz, Ar-H), 7. 279(d, J=7. 6Hz, 1H, Ar-H), 7. 117(d, J=9. 2Hz, Ar-H), 6. 803(d, J=8. 4Hz, Ar-H), 1. 935(s, 2H, -CH2-). **^{13}CNMR(100MHz, $CDCl_3$)ppm:**190. 38, 136. 42, 128. 35, 125. 59, 122. 07, 121. 18, 119. 26, 113. 36, 104. 72, 73. 45. **LCMS**(m/z):210. 89(M-H). **Molecularformule**:$C_{10}H_7ClFNO$,. **Elemental Analysis**: Calculated C-56. 76, H-3. 33, N-6. 62. Obtained: C-56. 72, H-3. 32, N-6. 69.

Synthesis of 2-(2-(5-fluoro-1H-indol-1-yl) acetoamide) acetic acid (6)

The glycine introduced in a 50 mL RB flask and it dissolved in sodiumhydraoxide and added few drops of conc HCl with shaking vigorously in ice cold solution. The 2-(5-fluoro-1H-indol-1-yl) acetyl chloride added to above the mixture in RT condition. After completion of the reaction, the reaction mixture was taken with ethyl acetate and neutralized with base. The desired product can be obtained when recrystallized from ethanol.

Colourless, yields-75%, **^{1}HNMR(400Mz, CDCl3)ppm**:11. 346(s, 1H, -COOH), 8. 894(s, 1H, N-H, amide), 7. 608(s, 1H, Ar-H), 7. 451(d, J=9. 2Hz, Ar-H), 7. 392(d, J=8. 4Hz, Ar-H), 7. 250 (d, J=8. 4Hz, Ar-H), 7. 172(d, J=8. 4Hz, Ar-H), 1. 882(s, 2H, -CH2-), 1. 486(s, 2H, Ar-H). **^{13}CNMR(100Mz, $CDCl_3$) ppm:**172. 65, 166. 72, 136. 08, 128. 36, 127. 94, 125. 82, 121. 48, 119. 77, 112. 49103. 81, 42. 23, 40. 75. **LCMS** (m/z): 250. 08. **Molecularformulae**:$C_{12}H_{11}FN_2O_3$,. **Elemental Analysis**: Calculated:C-57. 60, H-4. 43, N-11. 20. Obtained: C-57. 55, H-4. 41, N-11. 28.

Preparation of derivatives of 4-Benzylidine-2((5-fluoro-1H-indolyl-1-yl) methyl) oxazol-5(4H)-one (8)

A mixture of 2-(2-(5-fluoro-1H-indol-1-yl) acetoamide) acetic acid with substituted aromatic aldehydes, acetcianhydride. sodium acetate taken in a 50mL conical flask. The small amount of KIO_4 added above the mixture under reaction condition. When 1mol of KIO_4 added the above mixture. The reaction mixture continued on the magnetic stirrer and reflux condition. The reaction was check with TLC (6:4, n-hexane: ethylacetae) when the all the reactants were consumed and after completion of the reaction, the crude was poured in ice cold solution and addition with ethyl acetate. The compound can be separated from crude by column chromatography (5:5, n-hexane:ethylacetate).

1)4-Benzylidine-2((5-fluoro-1H-indolyl-1-yl) methyl) oxazol-5(4H)-one (6a)

Corourless, yeilds-85%. **^{1}HNMR(400Mz, $CDCl_3$)ppm**:7. 658-7. 352(m, 7H, Ar-H), 7. 326(t, J= 8. 4Hz, 2H, Ar-H), 7. 124(d, J=7. 6HzAr-H), 6. 684(d, J=8. 0Hz, 1H-indole), 1. 892(s, 2H, CH_3). **^{13}CNMR (100Mz, $CDCl_3$)ppm:** 165. 84, 162. 74, 134. 57, 129. 43, 128. 75, 128. 88, 127. 48, 127. 32, 125. 54, 124. 74, 121. 90, 119. 57, 115. 79, 112. 87, 106. 87, 56. 42. **LCMS**(m/z):319. 88. **Molecularformulae**: $C_{19}H_{13}FN_2O_2$. **Elemental Analysis**: Calculated:C-71. 24, H-4. 04, N-8. 75. Obtained: C-71. 20, H-4. 03, N-8. 81.

2) Benzylidine-2((5-fluoro-1H-indolyl-1-yl) methyl)-4-(4-hydroybenzylidine) oxazol-5(4H)-one (6b)

Colourless, yields-88%;**^{1}HNMR(400Mz, $CDCl_3$)ppm**:9. 354(s, 1H, -OH), 7. 597-7. 288(m, 5H, Ar-H), 7. 189(d, J=7. 6Hz, Ar-H), 6. 884(d=7. 2Hz, 1H, Ar-H), 5. 547(s, 1H, =C-H), 1. 478(s, 3H, CH_2). **^{13}CNMR(100Mz, $CDCl_3$)ppm:**165. 54, 162. 38, 136. 74, 129. 87, 128. 96, 128. 54, 127. 85, 126. 65, 123. 45, 121. 87, 120. 02, 119. 55, 112. 98, 109. 87, 56. 87. **LCMS**(m/z):337. 12(M+H). Molecular formulae: $C_{19}H_{13}FN_2O_3$. ElementalAnalaysis: Calculated: C-67. 84, H-3. 90, N-8. 34. Obtained: C-67. 80, H-3. 88, N-8. 39.

3) Benzylidine-2((5-fluoro-1H-indolyl-1-yl) methyl)-4-(4-methylbenzylidine) oxazol-5(4H)-one (6c)

Pale-yellow, yields-86%;**^{1}HNMR(400Mz, $CDCl_3$)ppm**:7. 778(d, J=8. 0Hz, Ar-H), 7. 214(d, J=8. 0Hz, Ar-H), 7. 124(d, J=8. 0Hz, 1H, Ar-H), 5. 547(s, 1H, =C-H), 1. 984(s, 3H, -CH_3);. **^{13}CNMR(100Mz, $CDCl_3$)pm:**165. 25, 162. 88, 138. 98, 131. 78, 129. 47, 128. 95, 128. 24, 127. 54, 125. 12, 123. 54, 120. 88, 119. 47, 112. 85, 108. 54, 104. 21, 55. 98, 21. 76. **LCMS**(m/z):335. 25. Molefor:$C_{20}H_{15}FN_2O_2$. **Elemental analysis**: Calculated: C-71. 84, H-4. 52, N-8. 37. Obtained: C-71. 80, H-4. 51, N-8. 43.

4) Benzylidine-2((5-fluoro-1H-indolyl-1-yl) methyl)-4-(4-methoxybenzylidine) oxazol-5(4H)-one (6d)

pale-yellow, yields-87%. **^{1}HNMR(400Mz, $CDCl_3$)ppm:**7. 735-7. 324(m, 7H, Ar-H), 7. 245(d, J=8. 4 Hz, 1H, Ar-H), 6. 896(d, J=7. 2Hz, 1H, Ar-H), 5. 345(s, 1H, =C-H), 1. 984(s, 2H, -CH_2). **^{13}CNMR (100Mz, $CDCl_3$)ppm:**166. 22, 162. 87, 137. 74, 129. 55, 128. 77, 128. 54, 127. 88, 127. 12, 126. 91, 125. 65, 124. 24, 120. 02, 118. 28, 115. 09, 112. 36, 102. 93, 57. 49, 53. 12. **LCMS**(m/z):349. 76(M-H). Molecular formulae: $C_{20}H_{15}FN_2O_3$. **ElementalAnalaysis**: Calculated: C-68. 56, H-4. 31, N-8. 01. Obtained: C-68. 50, H-4. 30, and N-8. 09.

5) 4-(4-bromobenzylidine) -2((5-fluoro-1H-indolyl-1-yl) methyl)-oxazol-5(4H)-one (6e)

Red colour, yields-77%. **^{1}HNMR(400Mz, $CDCl_3$)ppm:**7. 847(s, 1H, Ar-H), 7. 650-7. 446(m, 5H, Ar-H), 7. 429(d, J=7. 6Hz, 1H, Ar-H), 7. 371(d, J=8. 8Hz, indole1H), 6. 895(d, J=7. 6Hz, 1H, indol), 5. 366(s. 1H. =C-H), 1. 994(s, 2H, CH_2). **^{13}CNMR(100Mz, $CDCl_3$)ppm:**167. 54, 164. 17, 137. 42, 131. 58, 129. 78, 128. 54, 128. 54, 127. 30, 125. 55, 124. 54, 123. 54, 121. 87, 120. 45, 114. 87, 111. 87, 105. 76, 57. 72. **LCMS**(m/z):399. 07(M+1). Molecularformule:$C_{19}H_{12}BrFN_2O_2$. **ElementalAnalaysis**: Calculated: C-57. 17, H-3. 02, N-7. 01. Obtained: C-57. 11, H-3. 02, N-7. 09.

Biological Activity

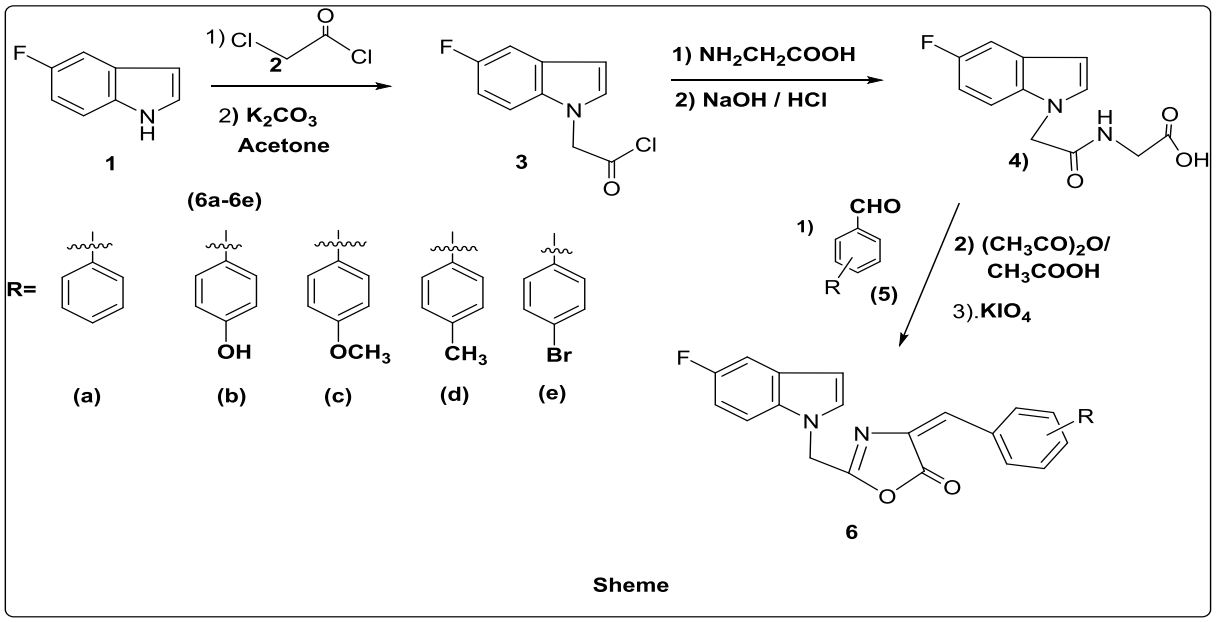
Antibacterial sensitivity assay

All the five derivatives of 4-aryl benzelidene-2-((5-fluoro-1H-indol-1-yl) methyl) oxazol-5(4H)-one compounds were dissolved in DMSO and screened for their antimicrobial activities *in vitro* by disc diffusion method. Bacterial cultures were prepared in Nutrient Agar medium (NAM) and for fungal test Potato Dextrose Agar (PDA) medium was used. 10 mL of distilled water was used to scrape conidia from 10 days culture and the spores were collected after filtration. The spores were resuspended in sterile distilled water and were used as inoculum. For bacterial culture plates a 100 µL of the cell suspension) was used to prepare bacterial lawn. Antimicrobial tests were done by disc diffusion technique. Discs were prepared with Whatman No. 1 filter paper and was impregnated with 100 µg/ disc of each compound and placed on the inoculated microbial plates. And all the plates were subjected to incubation at 37 ºC for 24 hours for bacterial culture and 48-72 hours for fungal culture. Streptomycine was used as standard drug control and was placed in the centre of all the plates for bacterial cultures and Ketoconazole was used as standard drug control for fungal cultures.

RESULT AND DISCUSSION

Chemistry

All derivatives of 4-aryl benzelidene - 2-((5-fluoro-1H-indol-1-yl) methyl) oxazol-5(4H)-one derivatives were synthesized by the condensation of substituted aromatic aldehydes with 2-(2-(5-fluoro-1H-indol-1-yl) acetamides) acetic acid using KIO_4 catalyst as a catalyst. All the titled compounds were confirmed by different spectroscopic techniques. The ^{1}H-NMR spectrum showed characteristic pattern of peaks. The methoxy protons appeared in the region of 3. 645pm, whereas the aromatic protons appeared at 6. 889–7. 912 ppm. The electron ionization mass spectrometricfragmentation patterns of the compounds were the same. The complete analytic and spectral data of the obtained products are given inthe Supplementary material to this paper. The yeilds of the compounds. The yeilds the compounds varies from the electron donating as well aselectron withdrawing groups and halogensubstituted. Compounds having disubstituted electron donating groups and also got more yeilds compare the monosubstituted electrondonating groups.



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Biological Activity

Anti Bacterial Activity

The anti-bacterial activities of titled derivatives of 4-aryl benzelidene - 2-((5-fluoro-1H-indol-1-yl) methyl) oxazol-5(4H)-one compounds are examined against four pathogenic bacteria strains. The result of antibiotic activity studies for these compounds. The gram negative bacteria screened were Escerichia Coli and S. aureus. The gram positive bacteria screened were S-typhi and Bacillus. The target compounds were used at the concentration of 250 µglml and 500 µglml using DMSO as a solvent the streptomycine 25 µglml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested micro organism.

Anti Fungal Activity

Anti-fungal activity of titled derivatives of 4-aryl benzelidene - 2-((5-fluoro-1H-indol-1-yl) methyl) oxazol-5(4H)-one compounds are evluated by disc diffusion method against the organism of aspergillusniger and Candida ablicans. Compared were treated at the concentrations of 250 µglml and 500 µglml using DMSO as a solvent. The standard drug was used as ketoconazol 22 µglml against both organisms.

All newly titled synthesized compounds can be synthesized under reflux condition. These target compounds can be obtained, we used to KIO_4. This catalyst can be used to improve the reaction conditions

and reaction is completed maximum one hour. The rate of reaction increased by using this catalyst. We used various substituted aromatic aldehydes such as electron donating group of aromatic aldehydes and electron withdrawing group of aldehydes and halogen containing aldehydes.

All the synthesized derivatives of 4-aryl benzelidene - 2-((5-fluoro-1H-indol-1-yl) methyl) oxazol-5(4H)-one compounds were evaluated anti-bacterial activity as well as antifungal. The electron withdrawing groups of compounds show low activities. Other hand electron withdrawing group of compounds exhibited poor activity compared with electron donating groups. All halogen compounds which possess electron donating group shows excellent activity as shown in Table-II.

Table II: Antimicrobial activity screening activity synthesized scaffold.

Entry	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S. aureus	E. coli	S. typhi	B. substills	A. niger	C. albicans
6a	08	09	06	04	09	07
6b	20	17	18	18	15	14
6c	19	18	15	16	10	11
6d	15	17	09	15	20	19
6e	22	21	21	20	12	15
Streptomycin	25	25	25	25	NA	NA
Ketoconazole	NA	NA	NA	NA	22	22
DMSO	---	----	---	---	---	---

CONCLUSION

The reaction condition carried at reflux for all thetitled compounds. The yield of the titled compounds obtained from 85-90%. The compound possesses electron donating group gives maximum yeild than that of the compound possesses electron withdrawing group. The rate of reaction developed by using nano catalyst. All the compounds tested by anti microbial activity against gram positive, gram negitive and fungal. The compound having electron donating group showed excelent active potential. Other wise the compounds having halogens which showed better active potential than that of the electron with drwing group.

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