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DESIGNED AND AN EFFICIENT SYNTHESIS OF NOVEL DERIVATIVES OF (E)-4-BENZYLIDINE-2-(4-(4, 5-DIPHENYL-1H-IMIDAZOL-2-YL) PHENYL) OXAZOLE-5 (4H)-ONE

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ABSTRACT

A great deal of work has been done on the series of six Synthesis of (E)-4-benzylidine-2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazole-5(4H)-one (8a-8e) can be obtained by (4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl) glycine and aryl aldehyde in the presence of CSA. The compound (6) can be synthesized from compound (4) with glycine. The Synthesis 4-1 H-benzo [d] imidazole-2-yl benzoyl chlorides (5) is obtained by compound (4) with thionyl chloride and 4-(1H-benzimidazol-2-yl) benzoic acid (3) can be prepared from the reaction of benzil with carboxy benzaldehyde, ammonium acetate in the presence of silver triflate. The structures of the compounds were evaluated based on ^{1}H-NMR, ^{13}CNMR and LCMS and by elemental analysis. This compound was screened by anti-bacterial activity.

KEYWORDS

4-benzylidine-2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazole-5(4H)-one, Silver triflate, 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl) glycine, 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl chloride, 4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoic acid, Benzil, Carboxyl benzaldehyde, Ammonium acetate, CSA and Antibacterial activity.

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INTRODUCTON

Active heterocyclic compounds are one of the important topics of interest for the organic chemistry and medicinal chemistry which was elaborates a number of pharmacological properties. A five and six membered heterocyclic compounds containing nitrogen, sulphur, oxygen and they was occupied numerous significant in the field in the organic chemistry as well as medicinally chemistry[1]. Oxazolones are five member heterocyclic moieties containing nitrogen and

oxygen as hetero atoms. The C-2 and C-4 positions of Oxazolones are responsible for their different biological activities such as analgesic[1], anti-inflammatory, antidepressant, anticancer, antimicrobial and antidiabetic and anti-obesity. Oxazolones are the heterocyclic compounds which perform an significant 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 Oxazolones 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 synthon for the construction of various alkaloid skeletons, immunomodulatory and biosensors[30-32].

The main focus on the (E)-4-benzylidine-2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazole-5(4H)-one derivatives are interest moieties in the organic chemistry in recent time and also applied in area of medicinally chemistry as well as pharmaceutical area of chemistry. These derivatives are used as intermediate in drug design in medicinally chemistry. Our continuous program, the synthesis of Oxazalones molecules formed with the various intermediates followed by Scheme No.1 in the presence dehydrating reagent such as CSA.

EXPERIMENTAL METHODS

The synthetic grade reagents, solvents, chemicals and desired raw materials are procured from Merck chemical PVLTd and also used for without purification. The melting points of the newly obtained derivatives were measured by a Thermo Scientific Fluke 51 II, melting point instrument and uncorrected was reported. The newly synthesized derivatives were evaluated by advanced spectroscopic methods such as 1H NMR (400 MHz) and 13C NMR (100MHz) spectra of the synthesized compounds were recorded values by an instrument Bruker Ultra Shield at room temperature Ultra Shield using tetramethylsilane (TMS) as the internal standard and deuterated chloroform (CDCl3) as the solvent. Chemical shift values were recorded in δ (ppm) and multiplicities are expressed as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). The molecular weights of the derivatives were measured by LCMS instrument were run on a Shimadzu spectrometer instrument, which was operating at 70 eV in positive mode. The progress of the reactions was examined by thin layer chromatography (TLC) analyses using (Merck 60 F254 silica gel).

General Procedure for the Synthesis Preparation of 4-(1H-benzimidazol-2-yl) benzoic acid (3)

The take clean and dry 50mL four neck RBF. 25mL ethanol was introduced into RBF and the mixture of benzil with carboxy benzaldehyde, ammonium acetate and ethanol was dissolved in the above solvent. The catalyst silver triflates is added gradually into RBF. The total arrangement fitted on the magnetic stirrer and reaction was continued for appropriate time at 70^{o}C. The reaction was checked by TLC as mobile phase (4:6 = EtOAc: petroleum ether). After completion of the reaction, we observed TLC and stop the reaction. The reaction mixture was cooled at room temperature and filtered the catalyst, poured in ethylacetae solvent. The organic layer is neutralized with saturated solution of sodium by carbonate and separated ethylacetae layer. This organic layer washed with water in TWO times and separated ethylacetae layer. The organic layer distilled of under vacuum and recrystallized from ethanol.

Characterization of the product

Pale red solid; Yield-84%, m.p-247-249^{o}C; Rf-0.40 (petroleum ether: EtOAc- 6:4); 1HNMR (400MHz, CDCl3) ppm: 10.982 (acid, 1H, s),9.664 (N-Himidazole, 1H, s,) 8.182-8.095 (Ar-H,2H, m), 7.857-7.718 (Ar-H, 4H, m), 7.298-7.268 (Ar-H, 2H, m); 13CNMR (100MHz, $CDCl_3$) δppm: 167.29, 145.76, 139.62, 135.73, 129.64, 128.74, 128.32, 127.96, 122.66, 121.45, 115.63; LCMS (m/z): 239.37 (M+H); Molecular formulae: $C_{14}H_{10}N_2O_2$: Elemental analysis: Calculated: C- 70.58, H-4.23, N-11.76; found: C- 70.52, H- 4.22, N-11.83.

4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl chloride: General Procedure for the Synthesis 4-(1H-benzo[d]imidazole-2-yl)-benzoyl chloride (4)

The take clean and dry 50mL four neck RBF. 25 mL DCM was introduced into RBF and the compound (3) was added with thionyl chloride slowly by using addition funnel into RBF. The total arrangement fitted on the magnetic stirrer and reaction was continued for appropriate time at 400C.The reaction was monitored by TLC as mobile phase (4: 8 = EtOAc: petroleum ether). After completion of the reaction, we observed TLC and stop the reaction. The solvent was evaporated under heating at 40^{o}C.

Characterization of the product

Palered compound: Yield-84%, m.p-221-223^{o}C; Rf-0.45 (petroleumether: EtOAc-5: 5); ^{1}HNMR (400 MHz, $CDCl_3$) ppm: 9.574 (N-Himidazole, 1H, s,), 8.216 (Ar-H, 2H, d, J=7.2Hz), 7.924 (Ar-H, 2H, d, J=6.4Hz), 7.638 (Ar-H, 2H, d, J=9.0Hz), 7.294 (Ar-H, 2H, t, J=5.4Hz); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 168.94, 148.35, 137.86, 131.32, 129.04, 128.85, 128.31, 122.28, 115.74. LCMS (m/z): 258.31 (M+2); Molecular formulae: $C_{14}H_9ClN_2O$. Elemental analysis: Calculated: C- 65.51, H-3.53, N-10.91; found: C- 65.47, H- 3.51, N- 10.99.

(4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl) glycine

0.10mol of glycine was dissolved in 25ml of 10% KOH solution taken in conical flask and 4-(1H-benzo [d] imidazole-2-yl)-benzoyl chloride was added 2 or 3 portions gradually to the solution. The flask was shaken vigorously of each addition till all 4-(1H-benzo [d] imidazole-2-yl)-benzoyl chlorides reacted. The solution was transfer to 50ml beaker and conical flask was rinsed with small amount of water. Some amount of crushed ice was added to the solution and concentrated HCl was gradually added drop by drop with constant stirring, till the mixture acidic to pale Congo red paper. The resulting crystalline compound was filtered upon a Buchner funnel, washed with cold water and drained well. The desired product is recrystallized from ethanol.

Palered compound

Yield-87%, m.p-221-223^{o}C; Rf-0.46 (petroleum ether: EtOAc-5: 5); 1HNMR (400 MHz, CDCl3) ppm:, 8.216 (Ar-H, 2H, d, J=7.2Hz), 7.924 (Ar-H, 2H, d, J=6.4Hz), 7.638 (Ar-H, 2H, d, J=9.0Hz), 7.294 (Ar-H, 2H, t, J=5.4Hz); 13CNMR (100MHz, CDCl3) δppm: 165.94, 147.35, 136.86, 132.32, 129.58, 128.82, 128.34, 121.28, 116.74.; LCMS(m/z): 258.31(M+2); Molecular formulae: C14H9ClN2O. Elemental analysis: Calculated: C- 65.51, H-3.53, N-10.91; found: C- 65.47, H- 3.51, N- 10.99.

Synthesis of derivatives of (E)-4-benzylidine-2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazole-5(4H)-one

A mixture of 0.25mol on substituted aryl aldehydes, 0.25mol of (4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl) glycine, 0.75mol of acetic anhydride and 0.25mol of anhydrous sodium acetate taken in 100ml of RB flask. The small amount of camphorsulphonicacid as catalyst was added into the flask. The flask was heated on steam bath with constant shaking and small amount of camphorsulphonicacid was added to the above mixture in RB flask. The reaction carried on the magnetic stirrer and reflux using water condenser and guard tube. As soon as solid dissolve, reflux was continued for 2 hours and allowed the mixture to stand overnight. Filter the crystallized product with suction and wash with hot water and then with a little volume of 1:1 ethanol. Recrystallized from ethanol and the purity of the compounds was checked using TLC.

(E)-4-benzylidine-2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazole-5(4H)-one (8a)

Pale red Solid; Yield-85; m.p.217-219°C. Rf=0.45 (EtOAc; n-hexane =5:5); ^{1}H NMR (400MHz, $CDCl_3$): 12.564 (s, 1H, NHimidazole), 7.892-7.564 (m, 6H, Ar-H), 7.485-7.384 (m, 8H, Ar-H), 7.363-(s, 1H, =C-H), 7.284-7.256 (m, 4H, Ar-H). ^{13}CNMR (100MHz, $CDCl_3$) ppm: 176.75, 167.66, 161.44, 139.88137.45, 135.37, 132.26, 129.78, 129.36, 128.93, 128.66, 128.31, 128.07, 127.81, 127.33, 126.34, 126.55, 112.64; LCMS (m/z): 468.33 [M+ H]: Molecular formula: $C_{31}H_{21}N_3O_2$.

Elemental analysis: Calculated: C-79.64; H-4.53; N- 8.99; Obtained: C,-79.56, H-4.51; N-9.08.

(E)-4-(4hydroxybenzylidene)-2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazol-5(4H)-one (8b)

Pale red Solid; Yield-94; m.p.242–244°C. Rf=0.48 (EtOAc; n-hexane =5:5); 1H NMR (400MHz, $CDCl_3$): 12.487 (s, 1H, NHimidazole), 9.473 (s, 1H, -OH); 7.924-7.884 (m, 2H, Ar-H), 7.494-7.382 (m, 8H, Ar-H), 7.352 (s, 1H, =CH), 7.294-7.265 (m, 4H, Ar-H), 7.057-6.915 (m, 2H, Ar-H); ^{13}CNMR (100MHz, CDCl3) ppm: LCMS (m/z): 484.03 [M+H]: Molecular formule: $C_{31}H_{21}N_2O_2$. Elemental analysis: Calculated: C-77.01; H-4.38; N- 8.69; Obtained: C,-76.94, H-4.36; N-

(E)-4-(4-chlorobenzylidene)-2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazol-5(4H)-one (8c)

Orange red Solid; Yield-88; m.p.241–243°C. Rf=0.42 (EtOAc; n-hexane = 4:6); 1H NMR (400MHz, $CDCl_3$): 12.874 (s, 1H, NHimidazole), 7.815 (d, J=7.6Hz, 2H, Ar-H), 7.653-7.564 (m, 6H, Ar-H), 7.387 (s, 1H, =C-H), 7.376-7.284 (m, 10, Ar-H). 13CNMR (100MHz, $CDCl_3$) ppm: 178. 39, 167.26, 158.48, 137.45, 135.74, 133.57, 131.64, 130.04, 129.73, 129.18, 128.94, 128.65, 128.36, 128.14, 127.78, 127.09, 126.66, 113.75. LCMS (m/z): 503.23 [M + 2]: Molecular formula: $C_{31}H_{20}ClN_3O_2$. Elemental analysis: Calculated: C-74.18; H-4.02; N- 8.37; Obtained: C,-74.11, H-4.00; N-8.45.

(E)-4-(4-Bromobenzylidene)-2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazol-5(4H)-one (8d)

Red compound; Yield-90; m.p. 245-247°C. Rf=0.47 (EtOAc; n-hexane = 4:6); 1H NMR (400MHz, CDCl3): 12.891 (s, 1H, NHimidazole), 7.845-7.642 (m, 8H, Ar-H), 7.484-7.394 (m, 6H, Ar-H), 7.352 (s, 1H, =C-H), 7.294-7.271 (m, 4H, Ar-H). 13CNMR (100MHz, $CDCl_3$) ppm: 178.78, 168.12, 158.79, 138.04, 136.34, 132.89, 131.19, 130.55, 129.66, 129.05, 128.84, 128.41, 128.14, 128.04, 127.86, 127.22, 112.36. LCMS (m/z): 547.11 [M+ 2]: Molecular formula: $C_{31}H_{20}BrN_3O_2$. Elemental analysis: Calculated: C-68.14; H-3.69; N- 7.69; Obtained: C-68.05, H-3.68; N-7.78.

(E)-4-(2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazol-5(4H)-ylidine) methyl) benzonitrile (8e)

Palered compound; Yield-88; m.p.251-253°C. Rf=0.40 (EtOAc; n-hexane = 5:5); 1H NMR (400MHz, $CDCl_3$): 12.124 (s, 1H, NHimidazole), 7.942 (d, J-8.8Hz, 2H, Ar-H), 7.824 (d, J=7.6HJz, 2H, Ar-H), 7.567 (d, J=8.0Hz, 2H, Ar-H), 7.520 (d, J=8.0Hz, 2H, Ar-H), 7.510-7.372 (m, 6H, Ar-H), 7.360 (s, 1H, =C-H), 7.313-7.274 (m, 2H, Ar-H). ^{13}CNMR (100MHz, $CDCl_3$) ppm: 178.24, 164.48, 160.24, 138.21, 132.74, 130.75, 130.05, 129.89, 129.21, 128.88, 128.40, 128.12, 127.57, 126.38, 119.89, 111.96, 110.27; LCMS (m/z): 492.39 [M+]: Molecular formula: $C_{32}H_{20}N_4O_2$. Elemental analysis: Calculated: C-78.03; H-4.09; N- 11.36 Obtained: C-77.95, H-4.07; N-11.45.

RESULTS AND DISCUSSION

Chemistry

A great deal of work has been done on the series of six Synthesis of (E)-4-benzylidine-2-(4-(4, 5-diphenyl-1H-imidazol-2-yl) phenyl) oxazole-5(4H)-one can be obtained by (4-(4, 5-diphenyl-1H-imidazol-2-yl) benzoyl) glycine and aryl aldehyde in the presence of CSA .The compound (5) can be synthesized from compound (4) with glycine. The Synthesis 4-1 H-benzo [d] imidazole-2-yl benzoyl chlorides (4) is obtained by compound (3) with thionyl chloride and4-(1H-benzimidazol-2-yl) benzoic acid (3) can be prepared from the reaction of benzil with carboxy benzaldehyde, ammonium acetate in the presence of silver . The ^{1}H-NMR spectrums showed characteristic pattern of peaks. The methoxy protons appeared in the region of 3.754 pm, whereas the aromatic protons appeared at 7.278-7.984ppm. The electron ionization mass spectrometric fragmentation patterns of the compounds were the same. The complete analytic and spectral data of the obtained products are given in the Supplementary material to this paper. The yields of the compounds varies from the electron donating as well as electron withdrawing groups and halogen substituted compounds having disubstituted electron donating groups and also got

more yields compare the monosubstituted electron donating groups.

ANTIBACTERIAL ASSAY

The cup plate method is simple and measurement of inhibition of microorganisms is also easy. Here, we have use this method for antibacterial screening of the test compounds. The media was prepared from nutrient agar 2%, peptone 1%, beef extract 1%, sodium chloride 0.5%, and distilled water up to 100mL. All the ingredients were weighed and added to water. This solution was heated on water bath for about one and half-hour till it became clear. This nutrient media was sterilized by autoclave. The antibacterial activity was evaluated against Gram positive: Streptococcus pneumonia, Bacilli's subtilis and Gram negative i.e Pseudomonas aeruginosa, Escherichia coli. While ampicillin was the standard used for the evaluation of anti-bacterial activity against gram positive bacteria and gen tamicin was used as a standard in assessing the activity of the tested compounds against gram negative bacteria. The results expressed as the mean zone of inhibition in mm ± standard deviation beyond well diameter (6mm) produced on the microorganisms using (10mg/ml) con- centration of tested samples, shown in Table No.1.

We observed the microbial activity of titled moiety, the compound '3b', 3c 3i and 3j showed maximum active potent against E.coli. The compound '3c', 3d showed maximum active potent against P.aeruginosa. The compound, 3e showed moderate active potent against S. pneumonia. The compound, 3e showed good active potent against B.substills. The rest of the compounds exhibit poor to moderate active potent. All the reported showed above Table No.1.

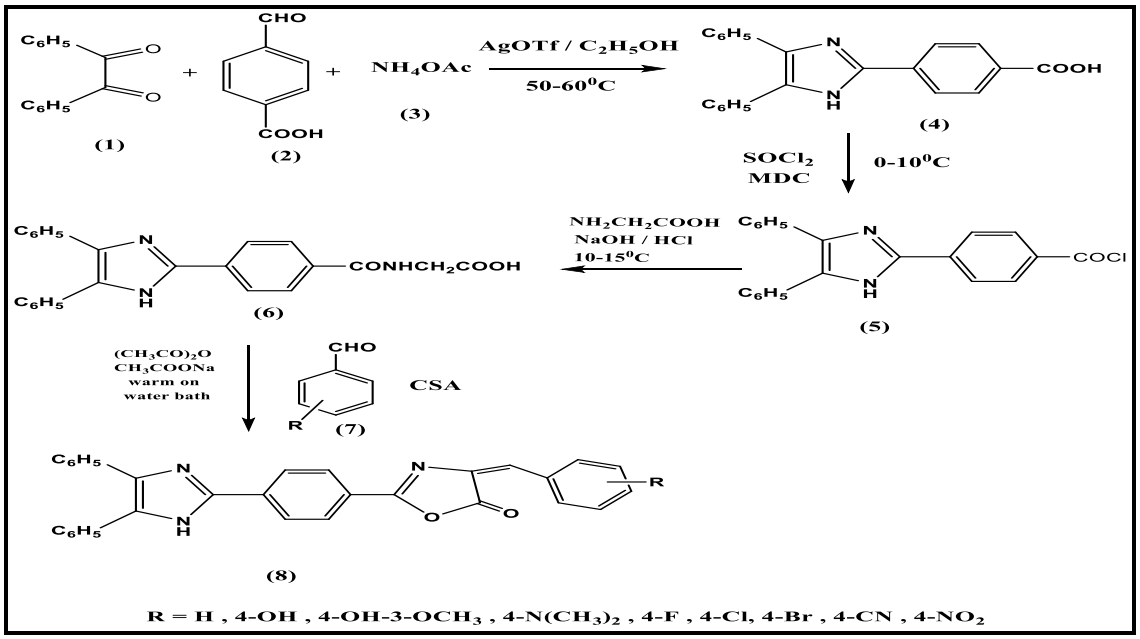

Table No.1: Anti-bacterial activity of titled derivatives

S.No	Compound Code	*Zone of inhibition in (mm)			
		Bacteria			
		P.aeruginosa	***E.coli***	***S. pneumonia***	***B.substills***
1	8a	08	07	06	04
2	8b	19	24	11	15
3	8c	21	26	19	19
4	8d	24	20	21	20
5	8e	16	10	19	21
6	gentamicin	30	30	---	---
7	ampicillin	---	---	30	30
8	DMSO	10	10	10	10

CONCLUSION

The reaction condition carried at reflux for all titled compounds. The yield of the desired compounds obtained from 84-95%. The derivatives possesses electron donating group gives maximum yield than that of the compound possesses electron withdrawing group. The rate of reaction was accelerated by using camphor Sulphonic acid. All the compounds was tested by anti-microbial activity against gram positive, gram negative and fungal. The compound having electron donating group showed excellent active potential. Other 6 wise the compounds having halogens which showed better active potential than that of the electron withdrawing group.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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