Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2015, 4 (5): 1456-1461

(International Peer Reviewed Journal)

Synthesis, Characterization and Biological Evaluation of Novel Imidazolones Derived from Azlactones

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Accepted on 8th September 2015

ABSTRACT

*A series of novel 1-(4-(1H-benzo imidazol-2-yl)phenyl)- 4-arylidene -2-phenyl-1-1H-imidazol-5(4H)-one **3(a-j)** were prepared starting from Azlactones **(1)** with 4-(1H-benzo[d]imidazol-2-yl)aniline **(2)**. We developed a simple, efficient method for the synthesis of imidazolones **(3a-j)**. The structural confirmation of the newly synthesized compounds was carried out on the basis of IR, ^{1}H NMR and Mass spectral studies. All these synthesized compounds were screened for their activity against bacterial and fungal organisms.*

Keywords: Phenyloxazolone, p-aminobenzoic acid, Anti-bacterial activity, imidazolones.

INTRODUCTION

The necessity to design new compounds to overcome the resistance over available drugs has become one of the most important areas of research today. The synthesis of heterocyclic compounds has always drawn the attention of chemists over the years mainly because of their important biological properties. Heterocyclic compounds [1, 2, 3] particularly Imidazolones have unique structure and diverse biological activities. Imidazole belongs to the class of azole antifungal agents like ketoconazole, miconazole, clotrimazole. Many imidazoles have been prepared as pharmacological agents like Azomycine, Clotrimazole, Miconazole**,** Ergothionine, Clonidine and Moxonidine. Most important applications of imidazole derivatives are Anti-bacterial activity [4-8], Antifungal activity [9], Anti-inflammatory activity [10], Analgesic activity [11], Anti-tubercular activity [12], Anti-depressant activity [13], Anti-cancer activity, Anti-viral activity, Antileishmanial activity. In view of the above, Imidazolones have been prepared by the condensation of different 5-oxazolones (Azlactones) [14] with 4-(1*H*- benzo[d]imidazol-2-yl) aniline.

MATERIALS AND METHODS

Materials: All reagents and solvents used were of analytical grade, purchased from Aldrich and SD fine-Chem- limited and were used without further purification. The purity of synthesized compounds was checked by TLC on silica gel GF254 plates using UV/Iodine as visualizing agents. Melting points have been measured in open capillaries using the electrical melting point apparatus and are reported

uncorrected. Infrared spectra were recorded on a Fourier Transform Infra-Red (FTIR) Perkin–Elmer spectrophotometer using potassium bromide optics, Tensor 27 model spectrophotometer, stretching vibration frequencies are given in cm^{-1}. ^1H NMR (400MHz) spectra were recorded on a Bruker WM-400 spectrometer in DMSO-d_6 with TMS as an internal standard. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrometer.

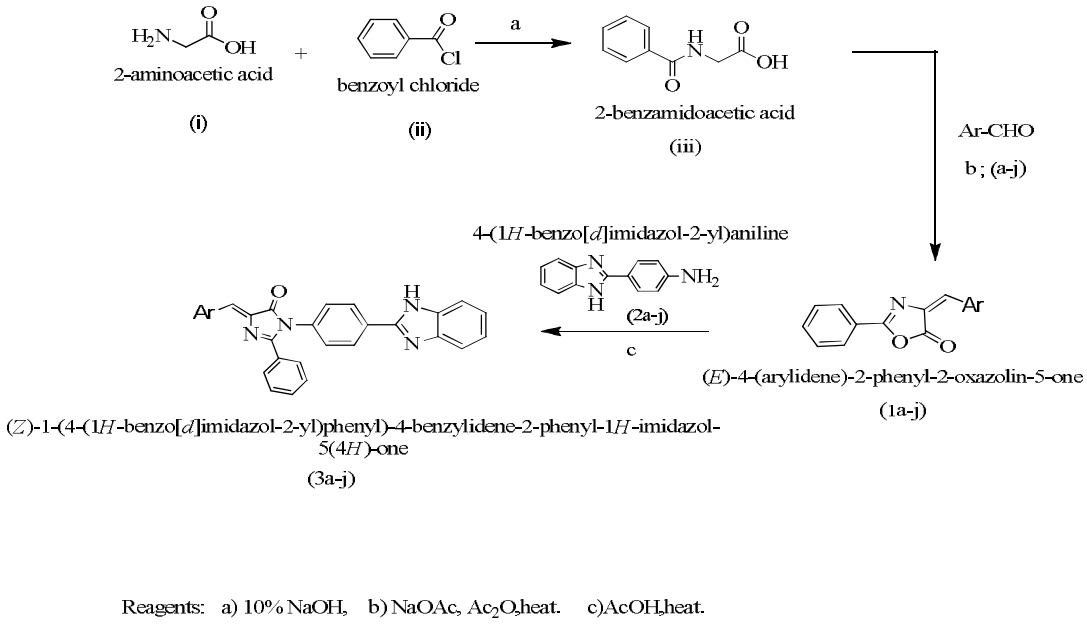
General Procedures

Synthesis of 4-arylidene -2-phenyloxazol -5-one (1a-j): A mixture of aromatic aldehyde (0.25 mol), hippuric acid (0.25 mol), acetic anhydride (0.75 mol), and anhydrous sodium acetate was taken in a 500 mL conical flask and heated on an electric hotplate with constant shaking. As soon as the mixture liquefied completely, transferred the flask to water bath and heated for 2 h. Then added 100 mL of ethanol slowly to the contents of the flask and allowed the mixture to stand overnight. The crystallized product filtered with suction, washed with two 25 mL portions of ice-cold ethanol and then washed with two 25 mL portions of boiling water, dried at 100^0C.The yields of the compounds were 80-85%.

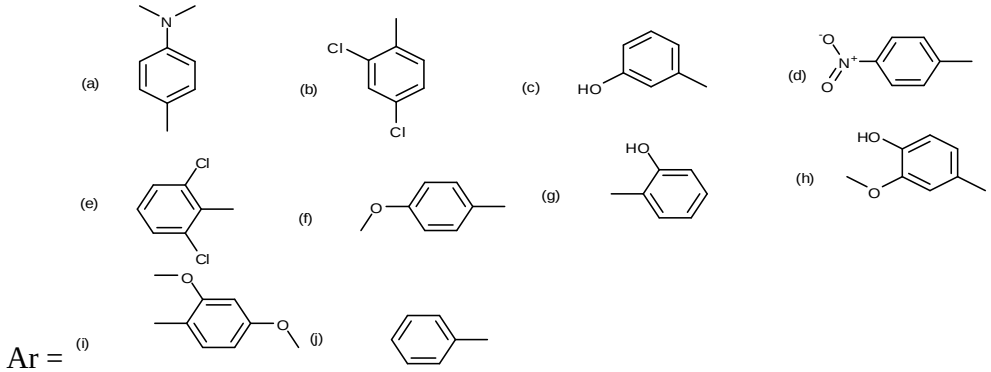
Procedure for 2-(4-amino phenyl) Benzimidazole (2): A mixture of p-amino benzoic acid (4.5g) and o-phenylenediamine (3.8g) were stirred in a syrupy phosphoric acid (45mL) at 200^0c for 2 h. The reaction mixture was cooled and poured in to the crushed ice. The bulky white precipitate obtained was stirred in cold water (400mL) and sodium hydroxide solution (5M) was added until neutralized to the pH 7. The resulting solid was filtered and recrystallized from methanol. The yields of the compounds were 75%.

Synthesis of 4-Benzimidazol-2-yl-4-(4-arylidene)-2-phenyl-imidazolone (3a-j): The equimolar mixture of 4-arylidene -2-phenyl-4H-oxazol-5-one(1) and 2-(4-amino phenyl) benzimidazole(2) was added into the glacial acetic acid (5mL) and few drops of acetic anhydride at 100^0c for 2 h. Reaction mixture was monitored by TLC. Contents of the flask were poured in ice water. The solid was separated, filtered and washed with cold water dried under vacuum pump. The substituted compounds Were synthesized and purified by column chromatographic method. The imidazolones were fully characterized by melting point, IR, ^1H NMR and Mass spectrometry.

Scheme



Reagents: a) 10% NaOH, b) NaOAc, Ac_2O,heat. c)AcOH,heat.



RESULTS AND DISCUSSION

The compound 1-(4-(1H-benzimidazol-2-yl)phenyl)-4-benzylidene-2-phenyl-1-1*H*-imidazol-5-(4*H*)-one (3j) was prepared from (1) and (2) refluxing in acetic acid and cooled. The product was collected and recrystallized from ethanol. The yield of the product is 90%.The IR spectrum of 3(j) exhibited a band due to 3061 Ar C=H, 2724 C-H, 1765 C=O, 1643 C=C, 1586 C=N, 872, 857, 834, 752 ,712. Further, in the ^{1}H NMR (DMSO, 400MHz) spectrum shows signals at δ11.13 (s,1H,NH) 8.41-8.38(m,2H), 7.86-7.84(m,4H), 7.59-7.52(m,4H), 7.43-7.41(m,9H) confirms the presence of imidazolinone ring.

Anti-bacterial activity: The compounds **3(a-j)** were screened for their antibacterial activity against *E.coli, salmonella typhi, staphylococcus aureus* and *Bacillus subtilis* by using agar disc diffusion method using penicillin (100µg mL^{-1}) as reference standard. The observed Minimum Inhibitory Concentration (MIC) Values for all the synthesized compounds.

Table 1. Antibacterial screening results of the compounds **(3a-j)**

Compound	*E. coli*	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus Subtilis*
3a	10	19	24	18
3b	12	18	21	17
3c	09	10	20	14
3d	16	20	36	22
3e	12	14	20	19
3f	14	15	34	20
3g	08	10	18	16
3h	13	18	28	24
3i	15	19	32	14
3j	08	10	15	12
Penicillin	18	25	40	27

The investigation of antibacterial screening results indicate that Compounds **3d, 3i, 3f** shows promising activity and compounds **3c, 3g, 3j** poor activity against *E.coli*.Compounds **3a, 3d, 3i** shows good activity against *Salmonella typhi*. Compounds **3d, 3i** show high activity and compounds **3g, 3j** show low activity against *Staphylococcus aureus*. Compounds **3d, 3h** show high activity and compounds **3i, 3j** show low activity against *Bacillus subtilis*.

Anti-fungal activity: The compounds **3(a-j)** were screened for their Anti-fungal activity against *Aspergillus Niger, Aspergillus flavus, Penicillium chrysogenum and Fusurium moneliforme* by using Greseofulvin (100µg/ml) as reference standard. The investigation of antifungal activity data revealed that the new synthesized imidazolones having moderate activity against fungal organisms.

Spectral Data and structure elucidation of compounds

(Z)-1-(4-(1*H*-benzo(d)imidazol-2-yl)phenyl)-4-(4-(dimethylamino)benzylidene)-2-phenyl-1imidazol-5(4*H*)-one (3a):Molecular Formula:$C_{31}H_{25}N_5O$,Physical state : brown Crystalline solid, M.P: 208-210^{0}C.yield:72% .IR Data: υ(cm^{-1})3337C-N, 2922 C-H, 1706 C=O, 1635C=C, 1607N-H,1558C=N, 982,891,778,753C-H. ^{1}H NMR(DMSO,400MHz): δ 10.6(s,1H),7.88-7.86(m, 2H), 7.7-7.68(m,2H), 7.53-7.52 (m, 8H), 7.17-7.15(m, 4H), 6.9-6.6(m, 2H), 2.59-2.56(m, 6H) . ESI-MS, (m/z):484(M+1).

(Z)-1-(4-(1*H*-benzimidazol-2-yl)phenyl)-4-(2,4-dichloro benzylidene)-2-phenyl-1*H*-imidazol-5(4*H*)-one(3b): Molecular Formula: $C_{29}H_{18}Cl_2N_4O$, Physical state: Dark brown Solid,M.P:185-192^{0}C, yield52%.IR-Data:υ(cm^{-1}): 3028Ar-C-H, 2896C-H, 1731 C=O, 1656C=C, 1594C=N, 812,770,725,689Ar-C-H. ^{1}H NMR (DMSO,400MHz): δ7.81-7.75 (m,4H), 7.7-7.61(m,3H), 7.53-7.52 (m,6H), 7.17-7.15(m, 4H), 6.9 (s,1H).Mass m/z:509(M+1) $^+$

(Z)-1-(4-(1*H*-benzo(d)imidazol-2-yl)phenyl)-4-(3-hydroxy)benzylidene)-2-phenyl-1*H*-imidazol-5(4*H*)-one(3c): Molecular Formula:$C_{29}H_{20}N_4O_2$, Physical state :yellowish brown Solid, M.P: 185^{0}C**.**yield: 75%.IR: (In cm^{-1}): 3287Presence of OH, 3054Ar –C-H, 2983C-H, 1727 Keto(C=O), 1629C=C, 1512 C=N , 957,903,878,846,813,742,686Ar-CH**.** ^{1}H NMR(DMSO,400MHz): δ 8.29-8.01 (m,6H) 7.8(s,1H), 7.7-7.61(m,3H), 7.53-7.52 (m,6H), 5.46-5.23 (m,3H), 2.25 (s,1H).Mass m/z:457(M+1).

(Z)-1-(4-(1*H*-benzo(d)imidazol-2-yl)phenyl)-4-(4-nitro)benzylidene)-2-phenyl-1*H*-imidazol-5(4*H*)-one(3d):Molecular Formula:$C_{29}H_{19}N_5O_3$, Physical state: yellowish orange solid, M.P : 165^{0}C,yield 62%.IR:υ(cm^{-1}) 3443-3054 Ar–C-H, 2211C-H, 1624(C=O), 1562C=C, 1513N=O, 977, 925, 904, 847, 811, 746, 699Ar-CH. ^{1}H NMR(DMSO,400MHz): δ7.8 (s,1H), 7.7-7.61 (m,3H), 7.53-7.52 (m, 6H), 7.17-7.15 (m, 8H), 6.9 (s,1H).Mass m/z : 486(M+1)+

(Z)-1-(4-(1*H*-benzo(d)imidazol-2-yl)phenyl)-4-(2,6-dichloro)benzylidene)-2-phenyl-1*H*-imidazol-(4*H*) -one(3e): Molecular Formula:$C_{29}H_{18}Cl_2N_4O_2$, Physical state: brown solid, M.P: 220^{0}C,yield 58%. IR-Data:υ(cm^{-1}): 3015 Ar-C-H, 2876C-H, 1681C=O, 1656C=C, 1624C=N, 912,870,775,759Ar-C-H bending. ^{1}H NMR (DMSO, 400MHz): δ8.61-8.25 (m, 4H), 7.7-7.61 (m, 2H), 6.53-6.52 (m, 6H), 5.17-5.15(m, 4H), 3.78 (s, 1H), 2.9 (s,1H).Mass m/z: 509(M+1)

(Z)-1-(4-(1*H*-benzo(d)imidazol-2-yl)phenyl)-4-(4-methoxy)benzylidene)-2-phenyl-1*H*-imidazol-5(4*H*) -one(3f):MolecularFormula:$C_{30}H_{22}N_4O_2$,Physicalstate:Orange-redsolid,M.P:158^{0}C,yield:75%,^{1}HNMR: (DMSO,400MHz)10.39(s,1H,NH),7.97-7.95(m,2H),7.55-7.51(m,9H),7.26-7.03(m,3H),6.96-6.8(m,2H), 4.34 (s, 2H), 3.827(m,3H).Mass m/z:471(M+1).

(Z)-1-(4-(1*H*-benzo(d)imidazol-2-yl)phenyl)-4-(4-(2-hydroxy)benzylidene)-2-phenyl-1*H*-imidazol-5(4*H*) -one(3g):MolecularFormula:$C_{29}H_{20}N_4O_2$, Physical state: darkbrown solid, M.P:180^{0}C. yield:72%, ^{1}HNMR: (DMSO,400MHz): δ11.23 (s,1H,NH)8.38 (s,1H,OH), 8.0-7.9(m,2H), 7.8-7.7(m,3H), 7.4-7.32 (m,6H), 7.30-7.26(m,4H), 7.1-7.0(m,3H). Mass m/z: 457(M+1).

(Z)-1-(4-(1*H*-benzo(d)imidazol-2-yl)phenyl)-4-(4-hydroxy-3-methoxy)benzylidene)-2-phenyl-1*H*-imidazol-5(4*H*)-one(3h):Molecular Formula:$C_{30}H_{22}N_4O_3$,Physical state: light yellow solid, M.P :205^{0}C yield:68%. IR**:** υ(cm^{-1})3434 OH, 2918-2849 ArC-H, 1738 C=O,1684C=C,1602C=N,1027O-CH_3, 923, 817, 771,749,698Ar-CH.^{1}H-NMR:(DMSO,400MHz):δ11.7(s,1H,NH),8.15-8.13(m,4H,)7.55-7.4(m,6H),7.21(m, 4H), 6.75-6.73(m,4H), 3.107 (m,3H). Mass m/z: 487(M+1).

(Z)-1-(4-(1*H*-benzo(d)imidazol-2-yl)phenyl)-4-(2,4-dimethoxy)benzylidene)-2-phenyl-1*H*-imidazol-5(4*H*)-one(3i): Molecular Formula:$C_{31}H_{24}N_4O_3$,Physical state: brown solid ,M.P : 182^{0}c, yield : 67% IR Data**:** υ(cm^{-1}) 3061 ArH, 2724 CH, 1740 C=O, 1662 C=C, 1593 C=N, 1095, 1034 (OCH_3), 882, 847, 814,747,702 Ar-CH**,** ^{1}HNMR:(DMSO,400MHz) δ10.13(s,1H,NH) 8.21-8.01(m, 2H),7.81-7.79(m,4H), 7.59-7.54(m,5H), 7.43-7.41(m,6H), 3.379 (m,6H). Mass m/z: 501(M+1).

(Z)-1-(4-(1*H*-benzo[d]imidazol-2-yl)phenyl)-4-benzylidene-2-phenyl-1*H*-imidazol-5(4*H*)-one(3j): Molecular Formula: $C_{29}H_{20}N_4O$, Physical state: brown solid, M.P: 208-210^{0}C, yield:90%**.** IR Data: υ(cm^{-1}) 3061 Ar C=H, 2724 C-H, 1765 C=O, 1643 C=C, 1586 C=N, 872, 857, 834, 752 ,712. ^{1}HNMR**:** (DMSO, 400MHz), δ11.13 (s,1H,NH) 8.41-8.38(m,2H), 7.86-7.84(m,4H), 7.59-7.52(m,4H), 7.43-7.41(m,9H). Mass m/z : 401(M+1)+.

APPLICATIONS

These compounds **(3a-j)** are having good Physico-chemical properties and high penetration into the infective micro-organisms. Because of these qualities these synthesized compounds are very useful for further medication as anti-bacterial agents.

CONCLUSIONS

We developed a simple and efficient method for the preparation of 1-(4-(1*H*-benzo imidazol-2-yl) phenyl)-4-benzylidene-2-phenyl-1-1*H*-imidazol-5(4*H*)-one**(3a-j)** from 4-benzylidene-2-phenyloxazol-5-one **(1a-j).** All are high yield and novel products.The newly synthesized compounds were evaluated for their antimicrobial activity. Compounds of **3(a-j)** showed moderate to excellent anti-bacterial activity. Some derivatives containing methoxy group of **3f, 3h, 3i**, nitro group **3d** showed best antimicrobial activity.

ACKNOWLEDGMENTS

Authors are grateful to The Head, Department of pharmacy, University college of Technology, Osmania University, Hyderabad for providing laboratory facilities and also thankful to Analytical team, CFRD, Osmania University, Hyderabad for providing analytical data. One of the authors (P.S) is thankful to UGC New Delhi for the award of Rajiv Gandhi National Fellowship.

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