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Synthesis And In Vitro Microbial Evaluation Of Some Novel Imidozol-5-one Derivatives

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Abstract : 3-bromo benzaldehyde (I) was allowed to react with N-acetyl glycine to give in presence of acetic anhydride to get 1,3-oxazol-5-ones (II). These oxazolones were treated with aromatic amines to get various imidazol-5-ones (3a-j). The structures of the newly synthesized compounds were confirmed on the basis of spectral data and physical data. All the synthesized compounds have been screened for their invitro antibacterial and antifungal activities.
Keywords: 1,3 oxazolone, imidazol-5-one, antibacterial activity, antifungal activity.

Introduction

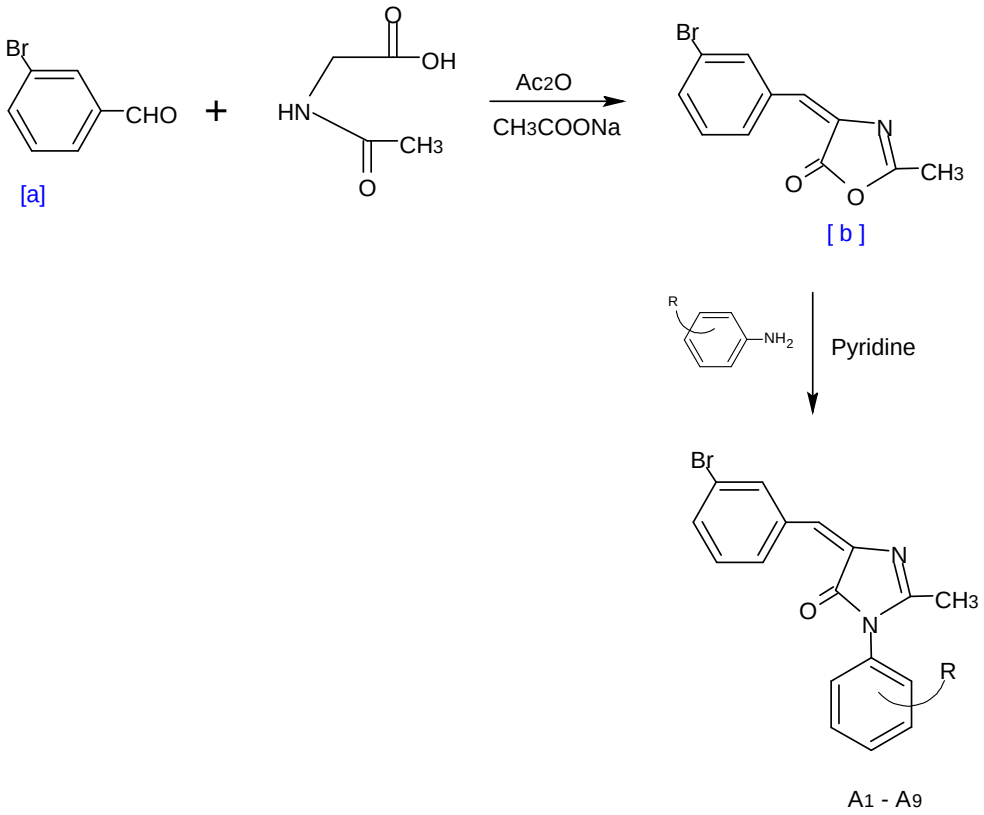
The exploitation of a simple molecule with different functionalities for the synthesis of heterocycles is a worth-while contribution in the chemistry of heterocycles. Imidazolones have been found to be associated with several pharmacological activities[1-4].Imidazolidinones have been reported to possess potent CNS depressant activity. Some imidazoles and substituted imidazolones have been reported to possess monoamine oxidase (MAO) inhibitory and anticonvulsant activities.[5-7] Benzylidene derivatives are also reported to possess anticonvulsant and MAO inhibitory activity.

During the past decade a large number of imidazolone containing compounds have been in the market with diverse pharmacological properties e.g. clonidine, phentolamine for the treatment of hypertension, cimetidine as antiulcer, dacarbazine as anticancer, metronidazole as antiprotozoal drug , ketoconazole, econazole as antifungal agents[8] and two imidazolines priscol and privine are vasodilating and vasoconstricting drugs[9]. This observation prompted us to synthesize new imidazolones and evaluate their antimicrobial activity.

Materials and methods

All chemicals were of analytical grade and used directly. All melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. The purity of all dyes was determined by thin-layer chromatography (TLC) using silica gel-G coated Al-plates (0.5 mm thickness, Merck). Infrared spectra were recorded on a Shimadzu FT-IR 8400S model using KBr pellets. ^{1}H NMR spectra were acquired on a Varian 400 MHz model spectrophotometer using DMSO as a solvent and TMS as internal reference (chemical shifts in δ, ppm). Elemental analysis carried on Carlo Erba 1108 instrument.

Reaction Scheme



Preparation of 4-(3'-bromo benzylidene)-2-methyl-1,3-oxazol-5-one (b)

A mixture of 3-bromo benzaldehyde (0.01 mole), N-acetyl glycine (0.007mol) acetic anhydride (0.017 mole) and sodium acetate (0.003 mole) was heated on electric hot plate with constant shaking in a conical flask. As soon as the mixture was liquified completely, the flask heated on water bath for two hours. Ethanol (5 mL) was added slowly to the contents of flask, the mixture was allowed to stand overnight. The separated crystalline solid was filtered, washed with ice-cold alcohol and hot water successively to obtain **(b)**.

Preparation of1-(substituted phenyl)-2-methyl-4-(3'-bromobenzylidene)-imidazol-5-one (3a-j)

A mixture of 4-(3'-bromo benzylidene)-2-methyl-1,3-oxazol-5-one (0.01 mol) and different substituted aromatic amines (0.01 mol) , Acetone (15ml), pyridine (2 ml) and 1-2 pellets of KOH were taken in a round bottom flask and refluxed for 4 h on sand bath. After that the reaction mixture was a poured into crushed ice and neutralized with conc. HCl. The solid separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give (**A1-A9)**.

Compound (A_1): Yield: 71%; m.p. 220^{0}C (dec.); **NMR DMSO**: 2.46 (s, 3H, Me), 7.43-8.91 (m, 10H, Ar-H), **IR (KBr)/cm^{-1}** : 1328 (C-N), 1548 (C=N), 1685 (C=O), 3198 cm^{-1} (-NH-), 3032-3059 cm^{-1} (-C-H) stretching of aromatic rings, 2821-2997 cm^{-1} (-C-H) stretching of methyl group; Anal. Calcd. for $C_{17}H_{13}BrN_2O$ (341.20): C, 59.84%; H, 3.84%; N, 8.21%; found: 59.78%; H, 3.87%; N, 8.25%.

Compound (A_2): Yield: 76%; m.p. 220^{0}C (dec.); **NMR DMSO**: 2.46 (s, 3H, Me), 2.69 (s, 3H, Me), 7.43-8.91 (m, 9H, Ar-H), **IR (KBr)/cm^{-1}** : 1328 (C-N), 1548 (C=N), 1685 (C=O), 3198 cm^{-1} (-NH-), 3032-3059 cm^{-1} (-C-H) stretching of aromatic rings, 2821-2997 cm^{-1} (-C-H) stretching of methyl group; Anal. Calcd. for $C_{18}H_{15}BrN_2O$ (355.22): C, 60.86%; H, 34.26%; N, 7.89%; found: 60.80%; H, 34.19%; N, 7.93%.

Compound (A_3): Yield: 82%; m.p. 220^{0}C (dec.); **NMR DMSO**: 2.46 (s, 3H, Me), 2.69 (s, 3H, Me), 7.43-8.91 (m, 9H, Ar-H), **IR (KBr)/cm^{-1}**: 1328 (C-N), 1548 (C=N), 1685 (C=O), 3198 cm^{-1} (-NH-), 3032-3059 cm^{-1} (-C-H) stretching of aromatic rings, 2821-2997 cm^{-1} (-C-H) stretching of methyl group; Anal. Calcd. for $C_{18}H_{15}BrN_2O$ (355.22): C, 60.86%; H, 34.26%; N, 7.89%; found: 60.80%; H, 34.19%; N, 7.93%.

Compound (A_4): Yield: 79%; m.p. 220^{0}C (dec.); **NMR DMSO**: 2.46 (s, 3H, Me), 7.43-8.91 (m, 9H, Ar-H), **IR (KBr)/cm^{-1}**: 1328 (C-N), 1548 (C=N), 1685 (C=O), 3198 cm^{-1} (-NH-), 3032-3059 cm^{-1} (-C-H) stretching of aromatic rings, 2821-2997 cm^{-1} (-C-H) stretching of methyl group, 762 cm^{-1} (Ar-Cl) stretching of chlorine group; Anal. Calcd. for $C_{17}H_{12}BrClN_2O$ (375.64): C, 54.35%; H, 3.22%; N, 7.46%; found: C, 54.41%; H, 3.27%; N, 7.51%.

Compound (A_5): Yield: 79%; m.p. 278^{0}C (dec.); **NMR DMSO**: 2.46 (s, 3H, Me), 7.43-8.91 (m, 9H, Ar-H), **IR (KBr)/cm^{-1}**: 1328 (C-N), 1548 (C=N), 1685 (C=O), 3198 cm^{-1} (-NH-), 3032-3059 cm^{-1} (-C-H) stretching of aromatic rings, 2821-2997 cm^{-1} (-C-H) stretching of methyl group, 762 cm^{-1} (Ar-Cl) stretching of chlorine group; Anal. Calcd. for $C_{17}H_{12}BrClN_2O$ (375.64): C, 54.35%; H, 3.22%; N, 7.46%; found: C, 54.41%; H, 3.27%; N, 7.51%.

Compound (A_6): Yield: 79%; m.p. 254^{0}C (dec.); **NMR DMSO**: 2.46 (s, 3H, Me), 7.43-8.91 (m, 9H, Ar-H), **IR (KBr)/cm^{-1}**: 1328 (C-N), 1548 (C=N), 1685 (C=O), 3198 cm^{-1} (-NH-), 3032-3059 cm^{-1} (-C-H) stretching of aromatic rings, 2821-2997 cm^{-1} (-C-H) stretching of methyl group, 762 cm^{-1} (Ar-Cl) stretching of chlorine group; Anal. Calcd. for $C_{17}H_{12}BrClN_2O$ (375.64): C, 54.35%; H, 3.22%; N, 7.46%; found: C, 54.41%; H, 3.27%; N, 7.51%.

Compound (A_7): Yield: 79%; m.p. 254^{0}C (dec.); **NMR DMSO**: 2.46 (s, 3H, Me), 7.43-8.91 (m, 9H, Ar-H), **IR (KBr)/cm^{-1}**: 1328 (C-N), 1548 (C=N), 1685 (C=O), 3198 cm^{-1} (-NH-), 3032-3059 cm^{-1} (-C-H) stretching of aromatic rings, 2821-2997 cm^{-1} (-C-H) stretching of methyl group, 1036 & 1322 cm^{-1} (NO_2); Anal. Calcd. for $C_{17}H_{12}BrN_3O_3$ (386.19): C, 52.87%; H, 3.13%; N, 10.88%; found: C, 52.82%; H, 3.17%; N, 10.82%.

Compound (A_8): Yield: 79%; m.p. 254^{0}C (dec.); **NMR DMSO**: 2.46 (s, 3H, Me), 7.43-8.91 (m, 9H, Ar-H), **IR (KBr)/cm^{-1}**: 1328 (C-N), 1548 (C=N), 1685 (C=O), 3198 cm^{-1} (-NH-), 3032-3059 cm^{-1} (-C-H) stretching of aromatic rings, 2821-2997 cm^{-1} (-C-H) stretching of methyl group, 1036 & 1322 cm^{-1} (NO_2); Anal. Calcd. for $C_{17}H_{12}BrN_3O_3$ (386.19): C, 52.87%; H, 3.13%; N, 10.88%; found: C, 52.82%; H, 3.17%; N, 10.82%.

Compound (A_9): Yield: 79%; m.p. 254^{0}C (dec.); **NMR DMSO**: 2.46 (s, 3H, Me), 7.43-8.91 (m, 8H, Ar-H), **IR (KBr)/cm^{-1}**: 1328 (C-N), 1548 (C=N), 1685 (C=O), 3198 cm^{-1} (-NH-), 3032-3059 cm^{-1} (-C-H) stretching of aromatic rings, 2821-2997 cm^{-1} (-C-H) stretching of methyl group, 1036 & 1322 cm^{-1} (NO_2); Anal. Calcd. for $C_{17}H_{11}BrN_4O_5$ (386.19): C, 47.35%; H, 2.57%; N, 12.99%; found: C, 47.35%; H, 2.57%; N, 12.99%.

Table 1 Physical data of synthesized compounds

Sr. No.	R	Molecular Formula	M.P. ^{o}C	% Yield
A_1	H	$C_{28}H_{22}O_5N_4S_3$	224	71
A_2	3-CH_3	$C_{29}H_{24}O_5N_4S_3$	242	76
A_3	4-CH_3	$C_{29}H_{24}O_5N_4S_3$	235	78
A_4	2-Cl	$C_{28}H_{21}O_5N_4S_3Cl$	285	73
A_5	3-Cl	$C_{28}H_{21}O_5N_4S_3Cl$	288	69
A_6	4-Cl	$C_{28}H_{21}O_5N_4S_3Cl$	279	67
A_7	3-NO_2	$C_{28}H_{21}O_7N_5S_3$	255	70
A_8	4-NO_2	$C_{28}H_{21}O_7N_5S_3$	264	79
A_9	2,4-NO_2	$C_{28}H_{20}O_9N_6S_3$	275	68

Result and Discussion

All the reaction was carried out under conventional methods. 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-*N*-(4-phenyl-thiazol-2-yl)-benzenesulfonamide (5) was key intermediate that required to synthesized target product. Compound 1 was synthesized by the reaction between acetophenone and thiourea on refluxed. Compound 4 was synthesized in three steps. In first step chloro acetic acid and thiourea on reflux gave compound 2 with the removal of one mole of $–H_2O$. In second step above prepared compound 2 condensed with benzaldehyde in presence of toluene and catalytically amount of piperidine gave compound 3. In last step compound 3 on chlorosulphonation gave compound 4. Compound 5 was synthesized by the condensation reaction between compound 1 and compound 4 in presence of pyridine and acetic anhydride. Compound 6 was synthesized by the reaction between various aniline and chloro acetyl chloride in the presence of benzene. Finally compound 5 and compound 6 on condensation gave target compound.

All the synthesized compounds were characterized by IR and ^{1}H NMR spectra. The synthesized compounds in general showed 1340, 1568 cm^{-1} for (C-N) and (C=N) stretching respectively. SO_2 sym & asym showed band in the region of 1144 & 1334 cm^{-1} while (C=O) showed characteristic band at 1668 cm^{-1}, The (C-S) linkage showed banding vibration in the region of 600-800 cm^{-1}. The (-NH-) linkage showed stretching band at 3210 cm^{-1}, 752 cm^{-1} indicates the presence of (Cl) group. The ^{1}H-NMR spectra of all the synthesized compounds shows important signals at their respective positions, confirming the structures.

Antibacterial Activity

The antimicrobial bioassay results presented in Table 2 revealed that, all the tested compounds tended to be more active against gram-positive bacteria, than against gram-negative bacteria. Final *N*-chloro aryl acetamide derivative **A_2** showed excellent activity (MIC, 20 µg/mL, 22 mm of zone of inhibition) against gram–positive strain *S. aureus*. Compounds **A_3, A_4** and **A_1** were found half fold active (MIC, 50 µg/mL) against *S. aureus* as compared to most active analogues **A_2** tested against the same strain. Final *N*-chloro aryl acetamide derivatives **A_2** and **A_5** displayed strong inhibitory action at 20 µg/mL, 24 mm of zone of inhibition against gram–positive *B. subtilis*. Compound **A_5** exhibited similar inhibitory concentration of 20 µg/mL against *S. aureus* with 4 mm of lesser zone of inhibition (20 mm) than **A_2** and **A_3**. Compound **A_4** was found half fold active (MIC, 50 µg/mL) against *B. subtilis* as compared to most active analogues **A_2, A_5** tested against the same strain. Compound **A_5** was found to contribute promising activity (MIC, 50 µg/mL, 20 mm of zone of inhibition) towards gram–negative strain *E. coli*. Compound **A_2** exhibited similar inhibitory concentration of 50 µg/mL against *E. coli* with 1 mm of lesser zone of inhibition (19 mm) than **A_5**. Compound **A_8** was found half fold active (MIC, 100 µg/mL) against *E. coli* as compared to most active analogues **A_5** tested against the same strain. Compound **A_5** appeared with remarkable activity against gram–negative *P. aeruginosa* at 50 µg/mL of MIC, where the half fold activity was observed (MIC, 100 µg/mL) for compounds **A_8** and **A_9** against the same bacteria. All the remaining final *N*-chloro aryl acetamide derivatives exerted good to moderate activity profile at MIC level ranging from 20 to 100 µg/mL, whereas, some derivatives were found to display weak at a higher concentration of 200-500 µg/mL. Moreover, the result showed that the compounds **A_2, A_5** were the best compounds of the series, exhibiting good antibacterial activity against both Gram-positive and Gram-negative bacteria.

Table 2 Antibacterial activity of *N*-chloro aryl acetamide derivatives

Comp. no.	R	Gram negative		Gram positive	
		E.coli	*P.aeruginosa*	*S.aureus*	*B. subtilis*
A_1	H	12 (100)	14 (100)	14 (50)	16 (50)
A_2	3-CH_3	19(50)	18 (50)	22 (20)	24 (20)
A_3	4-CH_3	16 (50)	16(50)	16(50)	16(50)
A_4	2-Cl	17(50)	15(50)	16(50)	18(50)
A_5	3-Cl	20(50)	21(50)	20(20)	24(20)
A_6	4-Cl	12 (100)	11(100)	12(100)	11(100)
A_7	3-NO_2	<10(100)	<10 (100)	14(100)	12(100)
A_8	4-NO_2	16(100)	15(100)	18(50)	20(50)
A_9	2,4-NO_2	18(100)	14(100)	18(50)	14(50)
Ciprofloxacin (100 µg/disc)		30 (≤1)	31 (≤1)	32 (≤1)	33 (≤1)

Conclusion

The results of study of microbial analysis revealed that the synthesized compounds are promisingly significant and possesses good antibacterial activity. We have synthesized some *N*-chloro aryl acetamide analogues combining with different substituted thaizole and thiazolidinedione derivative ring system with a view to get a good antibacterial agent with less toxic effects. We have developed an efficient and potent *N*-chloro aryl acetamide based compounds which are one of the active constituents present in many standard drugs and are well-known for its use to increase pharmacological activity of the molecules. The -NH linkage in the compounds increases the activity of compounds. Screening results clearly indicates the compounds of the scheme exhibit good antibacterial and are equipotent with the standard drugs. This is because of the presence of *N*-chloro aryl acetamide derivatives having electron donating and electron withdrawing groups and heterocyclic system attached to thiazole and thiazolidinedione nucleus. Moreover, *N*-chloro aryl acetamide as coupling component in all compounds increases activity. Hence, there is enough scope for further study in developing such compounds as a good lead activity. Most of the compounds have shown moderate to promising activity as compared to standard drug against all representative panels of bacterial strains. The compounds having *N*-chloro aryl acetamide as coupling components could be useful for derivatization to develop more effective antibacterial agents.

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