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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEW BENZOTHIAZOLE EMBEDDED IMIDAZOLINONE DERIVATIVES

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Abstract
A new series of oxazolones **(2a-j)** were prepared by reacting substituted aromatic aldehydes with N-acetylglycine in presence of anhydrous sodium acetate and acetic anhydride as the solvent medium. The respective oxazolones**(2a-j)** were then reacted with 2-Aminobenzothiazole**(1)** in glacial acetic acid medium to yield the title compounds Imidazolinones **(3a-j)**. All the newly synthesized compounds were evaluated for their *in –vitro* antibacterial and antifungal activities. The new compounds were assigned on the basis of ^{1}H-NMR, IR,Mass spectral data and elemental analysis.

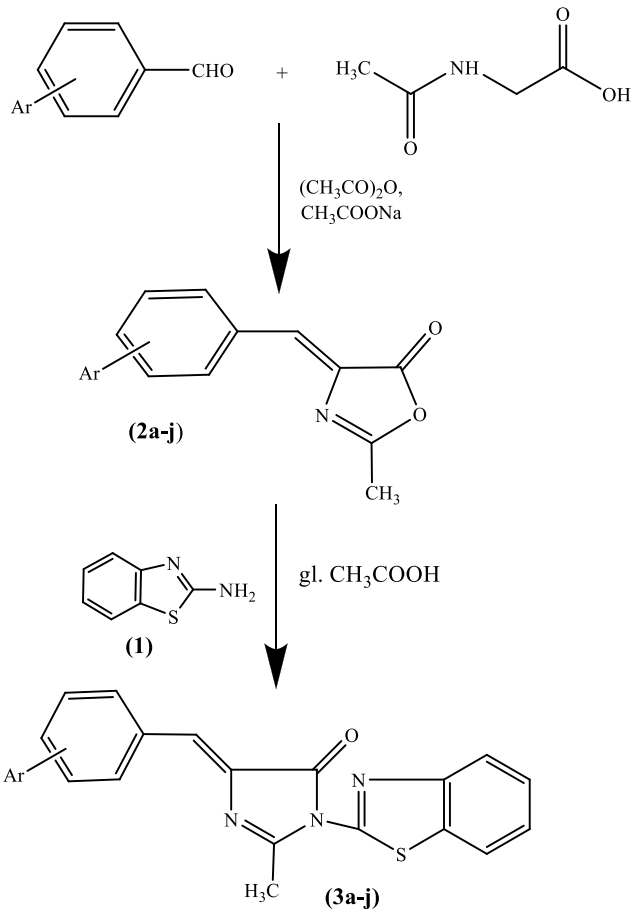
Introduction
The chemistry of nitrogen containing heterocycles have attracted medicinal chemist because of their varied . Imidazolinones and their derivatives are known for their potential biological and pharmacological properties. Naphazoline hydrochloride, Xylometazoline hydrochloride etc. are various Imidazolinones derivatives which have been used as adrenergic stimulants and Tolazoline and Phenotolamine as adrenergic blocking agents. Imidazolinones are reported to possess various activities like anticonvulsant[I], MAO Inhibitor[II], CNS depressant[III], antiparkinsonian[IV], antibacterial[V] etc.,

A variety of benzimidazole are in use, like thiabendazole, mebendazole and flubendazole (anthelmintic), omeprazole and lansoprazole (antiulcerative) and astemizole (antihistaminic), pimobendan (ionodialator). Benzimidazoles and its derivatives possess various biological activities such as antioxidant[VI], antimicrobial[VII], antihelmintic[VIII], anticancer[IX], anti-inflammatory[X].

A new series of oxazolones**(2a-j)** were prepared by reacting substituted aromatic aldehydes with N-acetylglycine in presence of anhydrous sodium acetate and acetic anhydride as solvent medium as per the reported procedure[XI]. The title compounds substituted Imidazolinones **(3a-j)** were prepared by condensation of 2-aminobenzothiazole **(1)**(procured from Himedia) and oxazolones **(2a-j)**in glacial acetic acid medium. All the new compounds were established by

spectral data and elemental analysis. The reaction sequence for the synthesis of title compounds is outlined in **Scheme-01.**

Scheme-01



Experimental

Melting points were determined by open capillary tubes and are uncorrected. The Purity of the synthesized compounds was ascertained by TLC on silica gel plate using iodine vapours as detecting agent. The IR spectrum is recorded by using Alpha Bruker IR Spectrometer using a thin film on KBr pellet technique and frequencies are expressed in $cm^{-1.}$ The PMR spectra were recorded on Bruker Avance II 400 NMR Spectrometer. All spectra were obtained in $CDCl_3$ and DMSO. Chemical shift values are reported as values in ppm relative to TMS (δ=0) as internal standard. Mass spectra were recorded on ESI.

Synthesis of Imidazolinones(3a-j)

A solution of oxazolones**(2a-j)** (0.01 mol) and 2-amino benzothiazole**(1)**(0.01 mol) in glacial acetic acid (25 ml) was refluxed for about 30-38 hr. Excess of solvent was removed under reduced pressure and the reaction mixture was poured into ice cold water. The product which was obtained is filtered, washed with water and recrystallized from ethanol. The physical data of compounds is given in table-1.

(Z)-1-(benzo[d]thiazol-2-yl)-4-benzylidene-2-methyl-1H-imidazol-5(4H)-one (3a): IR :1551 (C=C),1599 (C=N),1673 (C=O),3047 (C-H). **NMR (δ) in ppm:**2.91 (s, CH_3, 3H), 6.89-7.59 (m, Ar-H, 9H), 8.26 (s, C=CH, 1H).**Mass: m/z** 319 (M+).

(Z)-1-(benzo[d]thiazol-2-yl)-4-(4-fluorobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (3b) :IR :725 (C-F), 1442 (C=C), 1551 (C=N), 1673 (C=O), 2965 (C-H). **NMR (δ) in ppm:** 1.25 (s, CH_3, 3H), 6.91-7.53 (m, Ar-H, C=CH, 9H)
(Z)-1-(benzo[d]thiazol-2-yl)-2-methyl-4-(4-nitrobenzylidene)-1H-imidazol-5(4H)-one (3c) :IR :1550 (C=C), 1639 (C=N), 1673 (C=O), 3047 (C-H).**NMR (δ) in ppm:** 2.17 (s, CH_3, 3H), 6.79-8.27 (m, Ar-H, C=CH, 9H)
(Z)-1-(benzo[d]thiazol-2-yl)-4-(4-chlorobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (3d) :IR 766 (C-Cl), 1552 (C=C), 1639 (C=N), 1673 (C=O), 2965 (C-H).**NMR (δ) in ppm:** 2.17 (s, CH_3, 3H), 6.89-7.69 (m, Ar-H, C=CH, 9H) .**Mass: m/z** 353 (M+)

Table-1:Physical data of Imidazolinones (3a-j)

Comp	Ar-CHO	Molecular formula	Molecular weight	MP (°C)	Yield (%)
3a	C_6H_5	$C_{18}H_{13}N_3OS$	319	148-50	69
3b	4-F	$C_{18}H_{12}FN_3OS$	337	134-36	62
3c	4-NO_2	$C_{18}H_{12}N_4O_3S$	364	112-14	61
3d	2-Cl	$C_{18}H_{12}ClN_3OS$	353	85-87	65
3e	4-Cl	$C_{18}H_{12}ClN_3OS$	353	96-98	63
3f	4-OH	$C_{18}H_{13}N_3O_2S$	335	105-07	69
3g	2-OH	$C_{18}H_{13}N_3O_2S$	335	155-57	66
3h	4-OCH_3	$C_{19}H_{15}N_3O_2S$	349	126-28	65
3i	3,4-$(OCH_3)_2$	$C_{20}H_{17}N_3O_3S$	379	162-64	71
3j	3,4,5-$(OCH_3)_3$	$C_{21}H_{19}N_3O_4S$	409	140-42	63

Antimicrobial activity

Compounds of the series **(3a-j)** were evaluated for antibacterial activity against Gram Positive bacteria *B.subtilis, S.aureus*, and Gram Negative bacteria *E.coli, P.aeruginosa* using agar plate diffusion technique[XII] at 100 µg/ml conc. The antifungal activity was carried out against *C.albicans* and *A.fumigatus*. Standard drugs like Ciprofloxacin and Flucanazole were used for comparison purpose. DMF was used as solvent control. The antimicrobial data of the compounds is given in table -2.

In the antibacterial activity, all the tested compounds showed moderate activity against the gram positive organisms and weak to moderate activity against gram negative organisms. None of the tested compound was found to be potent when compared to the standard drug Ciprofloxacin.

In the antifungal activity, all the tested compounds showed moderate activity against both the fungal organisms *A.flavus* and *A.fumigatus*. The compounds with electron withdrawing groups like F, NO_2 showed weak activity against *A.flavus*. The compounds with phenyl and -F group showed good activity against *A.fumigatus*.

Table 2:**Data of Antimicrobial activity of Compounds (3a-j)**

Comp	Diameter of Zone of Inhibition(mm)					
	B.subtilis	***E.coli***	***P.aeruginosa***	***S.aureus***	***A.flavus***	***A.fumigatus***
3a	13	08	08	13	13	19

3b	13	08	08	13	08	19
3c	13	13	13	12	08	13
3d	13	13	13	12	13	13
3e	12	12	11	12	13	13
3f	12	12	12	13	12	13
3g	11	11	13	12	13	12
3h	13	12	12	11	12	13
3i	12	13	10	10	12	12
3j	13	12	11	12	11	12
Ciprofloxacin	24	24	23	24	-	-
Flucanazole	-	-	-	-	24	24
Control (DMF)	-	-	-	-	-	-

Conclusion

A new series of Imidazolinone derivatives embedded with aninobenzothiazole moiety were synthesized. All the compounds were characterized by spectral data and physical data. Some of the tested compounds exhibited good antifungal activity, but in case of antibacterial activity most of the synthesized compounds showed very weak activity.

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