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NOTE

Synthesis and Evaluation of Antibacterial Activity of 2-Acetamido-4-acet(4′-aryl-3′-chloro-2′-oxo-azetidinyl)amino thiazole

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Arylidene derivatives of ethyl 2-acetamidothiazole-4-acetate were synthesized by condensing an ester of ethyl 2-acetamidothiazole-4-acetate and hydrazine hydrate followed by reaction with the respective aldehydes. These were characterized on the basis of IR, NMR and mass spectral data. Final compounds were evaluated for antibacterial activity against the organisms *Pseudomonas aeruginosa, Bacillus subtilis, Escherichia coli* and *Staphylococcus aureus.*

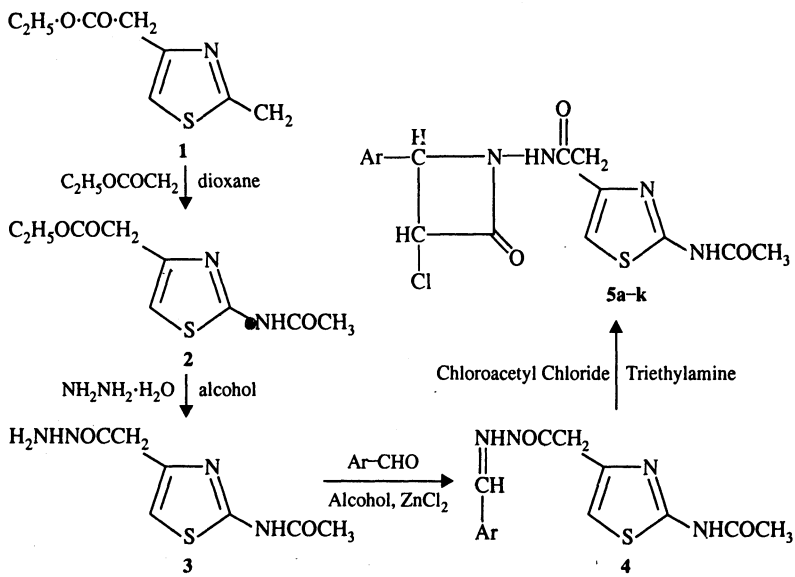
Key Words: Ethyl 2-acetamidothiazole-4-acetate, Arylidene derivatives, Antibacterial activity.

Thiazoles and their substituted ring systems have been shown to possess good antimicrobial, analgesic and antiinflammatory activities[1–3]. Arylidene derivatives show an array of biological activities such as antimicrobial, antiinflammatory and antitubercular activities[4–6]. Azetidinones also have shown good antifungal and antibacterial[7, 8] activities. With these observations, it was attempted to combine the two moieties with the hope of designing a new series of antimicrobial compounds.

Synthesis of ethyl 2-aminothiazole-4-acetate (1): Ethyl bromo acetoacetate, prepared by treating ethyl acetoacetate and bromine, was reacted with thiourea in ice-cold water with vigorous stirring for 1 h. The unreacted ester was extracted with diethyl ether and the aqueous layer was separated out. To the aqueous layer, solid sodium bicarbonate was added till neutralization. At the end point, ethyl 2-aminothiazole-4-acetate was obtained as white coloured solid. It was filtered, washed several times with water and dried. On recrystallization from benzene-pet ether, the pure product was obtained, yield 88.7%.

Synthesis of ethyl 2-acetamidothiazole-4-acetate (2): Compound **1**, dioxan, acetic anhydride were refluxed for 1 h and then it was poured into ice- cold water with vigorous stirring. The mixture was then heated to decompose the excess of acetic anhydride. The solution was then cooled. On cooling, ethyl 2-aminothiazole-4-acetate separate out. It was then filtered, washed with water and dried. It was recrystallized with water giving pure crystals; yield 87.8%.

Synthesis of 2-acetamidothiazole-4-acetic acid hydrazide (3): Compound **2** and hydrazine hydrate were mixed and refluxed for 10 min. Ethanol was added to make both layers miscible. The solvent was distilled out and contents poured into the beaker. The solid product was obtained and recrystallized with water to get pure crystals of 2-acetamidothiazole-4-acetic acid hydrazide; yield 92%.



Scheme

Synthesis of 2-acetamidothiazole-4-acetic acid arylidene hydrazide (4): Compound **3** and equimolar quantities of the aromatic aldehyde and 40 mL alcohol were refluxed for 3 h. Excess of alcohol was distilled off leaving the residue which was filtered off and dried. The residue was recrystallized using dilute alcohol to get pure compound; yield 60–95%.

Synthesis of 2-acetamido-4-acet(4′-aryl-3′-chloro-2′-oxo-azetidinyl)amino thiazole (5a–k): Compound **4** was added along with dropwise addition of triethylamine followed by dropwise addition of chloroacetyl chloride. The mixture was heated in a microwave oven (BPL-Sanyo microwave system, model BMC-900T, microwave frequency: 2450 MHz) at micro 40 for 40 min 30 s with an interval of 20 s and occasional stirring. The solution was kept overnight. To this, ice-cold water was added to obtain the precipitate. The precipitate was filtered, dried and recrystallized using ethanol; yield 30–97%.

Characterization of 2-acetamido-4-acet(4′-aryl-3′-chloro-2′-oxo-azetidinyl)amino thiazole (5a–d): IR (KBr, cm^{-1}): 3431.1 ν(N—H, str.), 3060.8 ν(C—H, str., aromatic), 2947.0 ν(C—H, str., aliphatic), 1755.1 ν(C=O, str., β-lactam), 1672.2 ν(C=O, str.), 1232.4 ν(C—N, str.), 848.6 ν(Ar—NO_2, str.), 786.9 ν(C—Cl, aliphatic), 651.9 ν(C—S, str.); PMR spectrum ($CDCl_3$) δ: 11.28–11.48 2H (NH), 7.64 1H (thiazole), 7.29–7.96 4H (Ar—H), 4.07–4.10 2H (CH_2), 2.96 1H (CH of azetidinone), 2.86 1H (CH—Cl of azetidinone), 2.18 3H (CH_3), Mass: The *o*-NO_2 azetidinone (GBISB-4) shows the molecular ion peak at 425/427 (Calcd. 423/425). The M + 1 peak is 425/427 (Calcd. 424/426). It also has —CO—CH—Cl with m/e = 76, cleaving the azetidinone ring at m/e = 336. Other fragments are 59, 73, 99, 112.

Antibacterial Activity: Title compounds are evaluated for antibacterial activity by agar diffusion[9] method against the test organisms. The zones of inhibition

were compared with std. amoxicillin (concn. 100 μg/0.1 mL). Results obtained are recorded in Table-1.

TABLE-1
CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY DATA OF 2-ACETAMIDO-4-ACET(4′-ARYL-3′-CHLORO-2′-OXOAZETIDINYL)AMINO THIAZOLE

Compd. No.	R	m.p.	m.f. (m.w.)	*E. coli*	*B. subtilis*	*S. aureus*	*P. aeruginosa*
5a	4-N(Me)$_2$	110	$C_{18}H_{20}N_5O_3SCl$ (421.3)	—	—	—	—
5b	2-OH	125	$C_{16}H_{15}N_4O_4SCl$ (394.3)	12	11	11	—
5c	3-NO$_2$	120	$C_{16}H_{14}N_5O_5SCl$ (423.3)	—	—	—	—
5d	2-NO$_2$	140	$C_{16}H_{14}N_5O_5SCl$ (423.3)	—	—	—	—
5e	5-Br-2-OH	152	$C_{16}H_4N_4O_5SClBr$ (473.2)	—	—	—	—
5f	H	105	$C_{16}H_{15}N_4O_3SCl$ (378.3)	—	—	—	—
5g	4-OH	100	$C_{16}H_{15}N_4O_4SCl$ (394.3)	12	11	11	10
5h	4-OH-3-OMe	95	$C_{17}H_{17}N_4O_5SCl$ (424.3)	—	—	—	—
5i	4-OMe	120	$C_{17}H_{17}N_4O_4SCl$ (408.3)	13	12	10	13
5j	4-Cl	180	$C_{16}H_{14}N_4O_3SCl_2$ (412.7)	14	14	15	12
5k	2-Cl	128	$C_{16}H_{14}N_4O_3SCl_2$ (412.7)	10	13	12	11
Std	Amoxicillin trihydrate			19	15	30	18

Compounds **5i** and **5j** showed good activity against all the organisms. All other compounds had moderate or negligible activity compared to that of the standard.

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