Asian Journal of Chemistry; Vol. 23, No. 11 (2011), 5159-5160

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

NOTE

Antitubercular Evaluation of Some Novel 2-Imino-3-(4'-carboxamidopyridyl)-5-arylidene-4-Thiazolidinones and Their Brominated Derivatives

SUSHIL K. KASHAW[1,*], VARSHA KASHAW[2], PRADEEP MISHRA[1] and AJAY KUMAR[3]

[1]Pharmaceutical Chemistry Division, Department of Pharmaceutical Sciences, Dr. H.S. Gour University, Sagar-470 003, India
[2]Sagar Institute of Pharmaceutical Sciences, Sagar-470 228, India
[3]Institute of Pharmacy, C.S.J.M. University, Kanpur-208 024, India

*Corresponding author: E-mail: sushilkashaw@dhsgsu.ac.in

(*Received*: 30 September 2010; *Accepted*: 30 July 2011) AJC-10235

Antitubercular activities of some new 2-imino-3-(4'-carboxamido pyridyl)-5-arylidene-4-thiazolidinones and their brominated products, structurally related to isoniazid were evaluated. Structure of the synthesized compounds was confirmed by means of elemental analysis, IR spectra and ^{1}H NMR spectral data and were consistent with the chemical structure. Antitubercular activities of compounds were done by liquid dilution method where MIC (minimum inhibitory concentration) were determined. Isoniazid was used as the standard drug for reference. Minimum inhibitory concentration of the compounds ranged between 11-23 µg/mL and some of the synthesized compounds showed significant inhibitory activities. It was concluded that arylidene nuclei at position 5 of the 4-thiazolidinone nucleus improved the antitubercular activity.

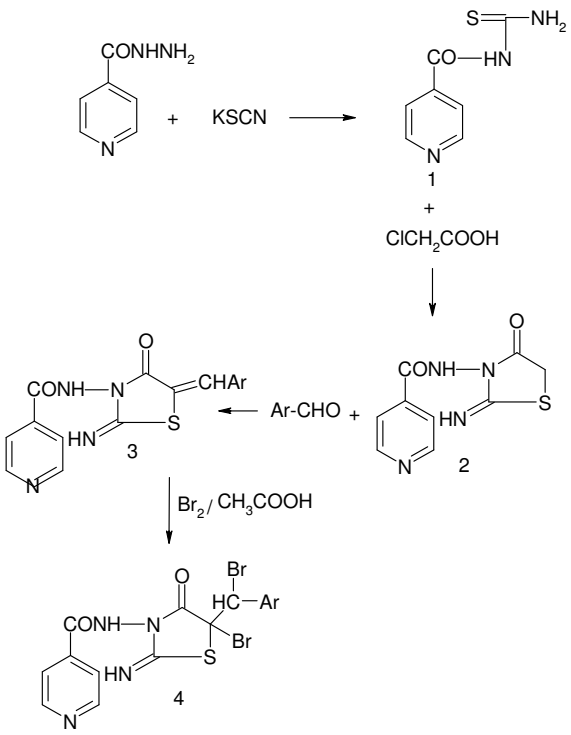
Key Words: 4-Thiazolidinones, Antitubercular activity, Minimum inhibitory concentration.

Evaluation of synthetic compounds for potential antimicrobial activity continues to be an important field for the identification of NCEs with clinical values. Literature survey show the potential of 4-thiazolidinones as promising fungitoxic agents[1], bactericidal[2-8] and fungitoxic compounds[9]. Isoniazid is a clinical established anti-tubercular drug and in continuation of our search for potent and novel antibacterial compounds[10,11] we report here the antitubercular activities of a few new chemical entities with 4-thiazolidinone skeleton generated from isoniazid.

Detailed synthesis of the titled compounds *via* **Scheme-I** is already published[12].

Bromination of compounds (4): A mixture of **3** (0.005 mol) in glacial acetic acid and bromine (0.005 mol) in acetic acid in cold (0-3º) was kept overnight. The crude product obtained was washed with ether and dried. TLC was performed on silica gel-G plate using benzene: DMF (2:1) as solvent system.

Microbiological evaluation: In the present study, liquid dilution method was used for the determination of minimum inhibitory concentration of the synthesized compounds. The MIC was taken as the lowest concentration (highest dilution) without visible growth. Nutrient broth (beef extract-1.0 g, yeast extract-2.0 g, peptone-5.0 g, sodium chloride-5.0 g, distilled



Scheme-I: Synthesis of title compounds

TABLE-2
CONCENTRATION OF THE COMPOUNDS USED TO DETERMINE MINIMUM INHIBITORY CONCENTRATION

Test tube No.	1	2	3	4	5	6	7	8
Test compound (0.5 mg/mL)	0.1 mL	0.2 mL	0.3 mL	0.4 mL	0.5 mL	–	–	1 mL
Inoculum	0.1 mL	0.1 mL	0.1 mL	0.1 mL	0.1 mL	0.1 mL	–	–
Broth	9.8 mL	9.7 mL	9.6 mL	9.5 mL	9.4 mL	9.4 mL	10 mL	9 mL
Final concentration of test compound (µg/mL)	5	10	15	20	25	–	–	50
Solvent blank	–	–	–	–	–	0.5 mL	–	–

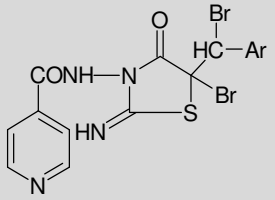
water q.s to 1000 mL) was used as the growth medium for the bacteria. Culture was incubated in electrically heated incubator at 37 ºC for 24 h.

Preparation of solution of synthesized compounds: A stock solution of each synthesized compound (1 µg/mL) was prepared in 0.1N HCl. Required concentrations were prepared by appropriate dilution of stock solution with distilled water. In the same way solution of the standard drug was prepared. A loopful of the original lyophilized microbial strain was transferred into the required medium aseptically and incubated at 37 ºC for 48 h. These were used as stock culture. All the culture medium, culture tubes and other materials was sterilized by autoclaving at 15 lb/inch^2 pressure for 20 min.

Determination of minimum inhibitory concentration (MIC): A set of 8 sterilized test tubes were taken and different solutions were transferred aseptically to each test tubes as per the quantities given in Table-2. Test tube 6, 7 and 8 were controls. Test tube 6 contained no inhibitor (40 % formalin) and confirmed that the culture was viable. Test tube 7 contained neither inhibitor nor organism, which confirmed the sterility of the culture. Test tube 8 contained high concentration of inhibitor but no organisms to detect the precipitation caused by interaction of broth constituents and test compound. All the test tubes were incubated for the period as mentioned above and examined for growth of the test organism. The MIC of the test compound was between the lowest concentration inhibiting growth and the highest concentration allowing growth. These two concentrations for each synthesized were noted. The exact MIC of the each synthesized compound was determined by repeating the experiment, using a range of concentrations between these two concentrations.

The structure of the compounds was confirmed on the basis of m.p., elemental (nitrogen and bromine) analyses, IR and ^{1}H NMR spectra. Structures of the final compounds are given (**3a-g** and **4a-g**) Table-1. Compound (**2**) showed absorption bands at 3450, 1580, 1500 cm^{-1} for -NH, 1640 cm^{-1} for >C=O, 1460 for -C=N of imino group, 1240 for -C-N and 683 for -C-S stretching. The ^{1}H NMR spectral studies showed chemical shift at δ 7.84, 8.70 ppm (pyridyl) 7.87 (-CONH) and 3.45 (-CH_2-). Compound (**3**) showed spectral data as compound (**2**) to indicate the presence of the 4-thiazolidinone nuclei. Observation in Table-2 shows that the MIC of the synthesised compounds ranged between 11-22 µg/mL A closer look at the Table-2 shows that the introduction of a arylidene nuclei at position 5 of the 4-thiazolidinone nucleus improved the antituberdcular activity namely **3g**, **3a** and **3f** as against **2**. Bromination of the compounds has resulted into **4** with practically no change in their bactericidal potency. In the prepared series of compounds the most active compounds were **3b** and **4a**. However bromination gave some improvement in their bactericidal effect. Most active compounds in brominated series were **4a** and **4b**. Presence of *p*-NO_2 or *p*-Cl in the phenyl ring group at position 5 showed good bactericidal effects.

TABLE-1
PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS (**3a-g** AND **4a-g**)



Compound No.	Ar	MIC (µg/mL)
3a	*p*-Nitro phenyl	23
3b	Phenyl	12
3c	3-Methoxy 4-hydroxy phenyl	17
3d	*p*-Methyl phenyl	13
3e	Furfuryl	16
3f	*p*-(Trimethyl amino)phenyl	22
3g	*p*-Chloro phenyl	19
4a	*p*-Nitro phenyl	11
4b	Phenyl	13
4c	3-Methoxy 4-hydroxy phenyl	17
4d	*p*-Methyl phenyl	14
4e	Furfuryl	16
4f	*p*-(Trimethyl amino)phenyl	22
4g	*p*-Chloro phenyl	18
	Isoniazid	0.08

ACKNOWLEDGEMENTS

The authors are thankful to RSIC, CDRI Lucknow and Sophisticated Instruments Division of NIPER, Chandigarh for spectral and nitrogen analysis, respectively.

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