



SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF 6-NITRO-2-[4-FORMYL-3-(SUBSTITUTED PHENYL) PYRAZOL-1-YL] BENZOTHIAZOLES

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ABSTRACT

Various 6-nitro-2-[4-formyl-3-(substituted phenyl) pyrazol-1-yl] benzothiazoles were synthesized and screened for antitubercular activity against H37Rv strain of *Mycobacterium tuberculosis* by proportion method on Lowenstein Jensen (LJ) media. Synthesis of 6-nitro-2-[4-formyl-3-(substituted phenyl) pyrazol-1-yl] benzothiazoles reported in this study provides a novel example of Vilsmeier Haack reagent mediated heterocyclic synthesis. 6-Nitro-2-[4-formyl-3-(substituted phenyl) pyrazol-1-yl] benzothiazoles exhibit a range of activities in the antitubercular screens. Compounds **IVh** and **IVj** emerged as the most promising active compounds comparable to that of standards.

Key words: Formylated pyrazole benzothiazole, Antitubercular, Vilsmeier Haack reaction, Lowenstein Jensen (LJ) media.

INTRODUCTION

Benzothiazole derivatives have fascinating field of investigation in medicinal chemistry as they have been found to possess wide spectrum of biodynamic properties. Many of them have been reported as antimicrobial^{1,2}, anti-inflammatory³, antitumour⁴, anticonvulsant⁵, antitubercular⁶, muscle relaxant and CNS depressant. Therefore, it was considered worthwhile to explore the synthesis of compound built upon benzothiazole skeleton incorporating pyrazolyl moiety with hope of potentiating the activity of two such units in the same compound.

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For present investigation, we have prepared 6-nitro-2-[4-formyl-3-(substituted phenyl) pyrazol-1-yl] benzothiazoles (**IVa-j**) by treating 6-nitro-2-benzothiazolamine (**I**) with hydrazine hydrate to give 6-nitrobenzothiazol-2-yl-hydrazine (**II**), which on condensation with appropriate phenyl methyl ketones gives rise to 6-nitrobenzothiazol-2-yl-hydrazones (**IIIa-j**), followed by its cyclization using Vilsmeier Haack reaction.(Scheme 1)

All the synthesized compounds were screened for their *in vitro* antitubercular activity against H37Rv strain of *Mycobacterium tuberculosis* by proportion method on LJ media.

EXPERIMENTAL

Melting points were taken on Thiele's tube apparatus and are uncorrected. Thin layer chromatography was used to assess the course of reaction and the purity of the intermediates and the final compounds, giving a single spot on TLC plate (Silica gel G), using various solvent systems. Visualization of the compounds on chromatographic plates was done by exposure to iodine vapors.

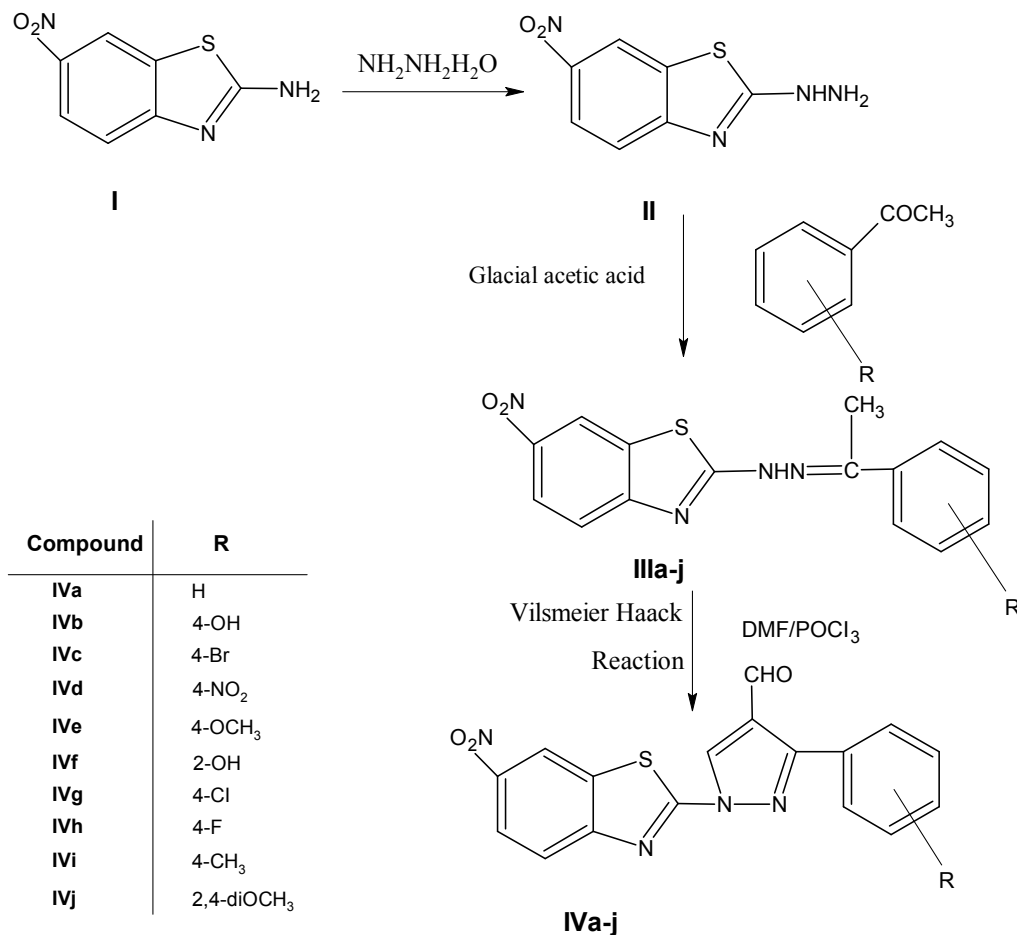
IR spectra were recorded using KBR disc on a Jasco FTIR-410. ¹H NMR spectra were recorded in CDCl₃ solution on FT-NMR Varian mercury 300 MHz spectrometer using tetramethylsilane as internal standard.

Synthesis of 6-nitrobenzothiazol-2-yl-hydrazine (**II**)

Conc. HCl (6 mL) was added drop wise with stirring to hydrazine hydrate (6 mL) at 5-10⁰C. Then, ethylene glycol (24 mL) and 6-nitrobenzothiazolamine (**I**) (0.03 mol) were added and refluxed for 3 hr. On cooling, it gives 6-nitrobenzothiazol-2-yl-hydrazine (**II**), which was filtered, washed with water and recrystallized from ethanol. The compound was dried in oven. m.p. 220-224 ⁰C :IR (KBr) (Cun⁻¹): 3320, 3221, 1650, 1460 (C=N), 1192, 1157 and 820.

Synthesis of 6-nitrobenzothiazol-2-yl-substitutedacetophenone hydrazone (**III_{a-j}**)

Compound (**II**) (1.5 mmol), appropriate acetophenone (2.2 mmol) and glacial acetic acid (2-3 drops) were taken in absolute ethanol (20 mL) and refluxed on water bath for 5-13 hr. On cooling, it gives corresponding hydrazone, which was recrystallized from ethanol and dried under oven. **III_a**: IR (KBr) (Cun⁻¹): 3136, 3051, 2918, 1571, 1449 (NHNH=C), 1339, 1128, 925 and 940.



Scheme 1: Synthetic route to 6-nitro-2-[4-formyl-3-(substituted phenyl) pyrazol-1-yl] benzothiazoles

Synthesis of 6-nitro-2-[4-formyl-3-(substituted phenyl) pyrazol-1-yl] Benzothiazoles (IVa-j)

Compound (**IIIa-j**) (5 mmol) was dissolved in Vilsmeier Haack reagent [DMF] (6 mL) in POCl₃ (1.5 mL) and stirred at room temperature for 4 hr. Then the contents were poured over crushed ice (previously neutralized with NaHCO₃). A solid separated out, which was filtered, washed with water, dried and crystallized from ethanol.

IVa: IR (KBr) (Cun⁻¹); 3095, 1648, 1126 (C-S), 1332, 1535, 1697 (CHO). ¹H NMR (CDCl₃) (δ): 8.74 (1H, s, ArH), 8.55 (1H, d, ArH), 8.44 (1H, d, ArH), 7.54 (1H, s,

pyrazole), 9.91 (1H, s, CHO), 7.41(4H, m, ArH) and 7.24 (1H, m, ArH).

Antitubercular activity

The screening was carried out by using proportion media on LJ media on the H37 Rv strain of *Mycobacterium tuberculosis*⁷. The synthesized derivatives were dissolved in dimethyl sulfoxide to get concentration of 100 µg/mL. Rifampicin and isoniazid were used as standard drugs, which inhibit the growth of *Mycobacterium tuberculosis* at a concentration of 40 µg/mL and 0.2 µg/mL, respectively.

Table 1: Antitubercular activity of formylated pyrazol benzothiazoles

Compound	% Growth observed after 42 days		
	I	II	III
Control	+++	+++	+++
Standard (Rifampicin 40 µg/mL)	-	-	-
Standard (Isoniazid 0.2 µg/mL)	-	-	-
IVa	+	+	+
IVb	+	+	+
IVc	++	++	++
IVd	+	+	+
IVe	+	+	+
IVf	+	+	+
IVg	++	++	++
IVh	-	-	-
IVi	+	+	+
IVj	-	-	-

Key to symbols:

No growth : - (below 1%); Mild growth: + (1-50%);

Moderate growth: ++ (50%-100%); Severe growth: +++ (above 100%)

The results were read for the first time on the 28th day. The colonies were counted only on the slopes seeded with the inoculum that has produced exact readable counts, the results, which are “sensitive” at the 28th day a second reading was made on the 42nd day to get the definitive result and data are presented in Table 1.

RESULTS AND DISCUSSION

The antitubercular activity tests results for the synthesized compound are reported in Table 1. Compounds **IVh** and **IVj** show the activity comparable to that of standard used for assessment of antitubercular activity. Compound **IVa**, **IVb**, **IVd**, **IVe**, **IVf** and **IVi** have mild activity against the *Mycobacterium tuberculosis*. Compound **IVc** and **IVg** are resistant to tubercular bacterium.

CONCLUSION

The synthesis of 6-nitro-2-[4-formyl-3-(substituted phenyl) pyrazol-1-yl] benzothiazoles reported in this study provides a novel example of Vilsmeier Haack reagent mediated heterocyclic synthesis.

The present results revealed that a number of 6-nitro-2-[4-formyl-3-(substituted phenyl) pyrazol-1-yl] benzothiazoles exhibit a range of activities in the antitubercular screens, with compound **IVh** and **IVj** showing activity comparable to that of standards.

ACKNOWLEDGEMENT

The authors are thankful to Mr. D. D. Chougule, Principal, A. B. College of Pharmacy, Sangli for providing the necessary research facilities during the course of present investigation. Thanks are due to Pune University for providing spectral data.

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Accepted : 15.03.2008