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Note

Synthesis and biological activity of 4′-oxathiazolidinyl benzopyrazoles

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New 3-methyl-1-[(2′-substituted phenyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted-benzopyrazoles **3** and 3-methyl-1-[(2′-substituted-phenyl-5′-methyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted-benzopyrazoles **4** are synthesized, characterized and evaluated for their antimicrobial and antitubercular activity.

Keywords: Benzopyrazoles, antimicrobial activity, antitubercular activity

IPC: **Int.Cl.[8] C 07 D**

In pharmacological studies of benzopyrazoles and their derivatives they have been shown to possess a variety of activities including antimicrobial and antiinflammatory[1]. 4-Oxathizolidines and their 5-arylmethylene derivatives also possess a variety of therapeutic activities[2-4]. Therefore, it was thought to combine benzopyrazole and oxathiazolidine rings together in a molecular framework to see the additive effects of these rings towards the biological activities.

In this paper we report the synthesis of 3-methyl-1-[(2′-substituted phenyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted-benzopyrazoles **3** and 3-methyl-1-[(2′-substituted-phenyl-5′-methyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted benzopyrazoles **4** (**Scheme I**). These new compounds are evaluated for their antimicrobial and antitubercular activity.

5,6-Substituted-3-methylbenzopyrazole-1-acetic acid hydrazides **1** were prepared from 5,6-substituted-3-methylbenzopyrazoles. The reaction of compound **1** and substituted benzaldehydes in methanol as solvent and a few drops of acetic acid as a catalyst under reflux, afforded 5,6-substituted-3-methyl-1-(substituted benzalhydrazinocarbonylmethyl)benzopyrazoles **2** in good yields. The reaction of **2** with thioglycolic acid and thiolactic acid in dry benzene and after a convenient work-up, gave the corresponding compounds 3-methyl-1-[(2′-substituted-phenyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted-benzopyrazoles **3** and 3-methyl-1-[(2′-substituted-phenyl-5′-methyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted-benzopyrazoles **4**, respectively (**Scheme I**, **Table I)**.

Antimicrobial activity

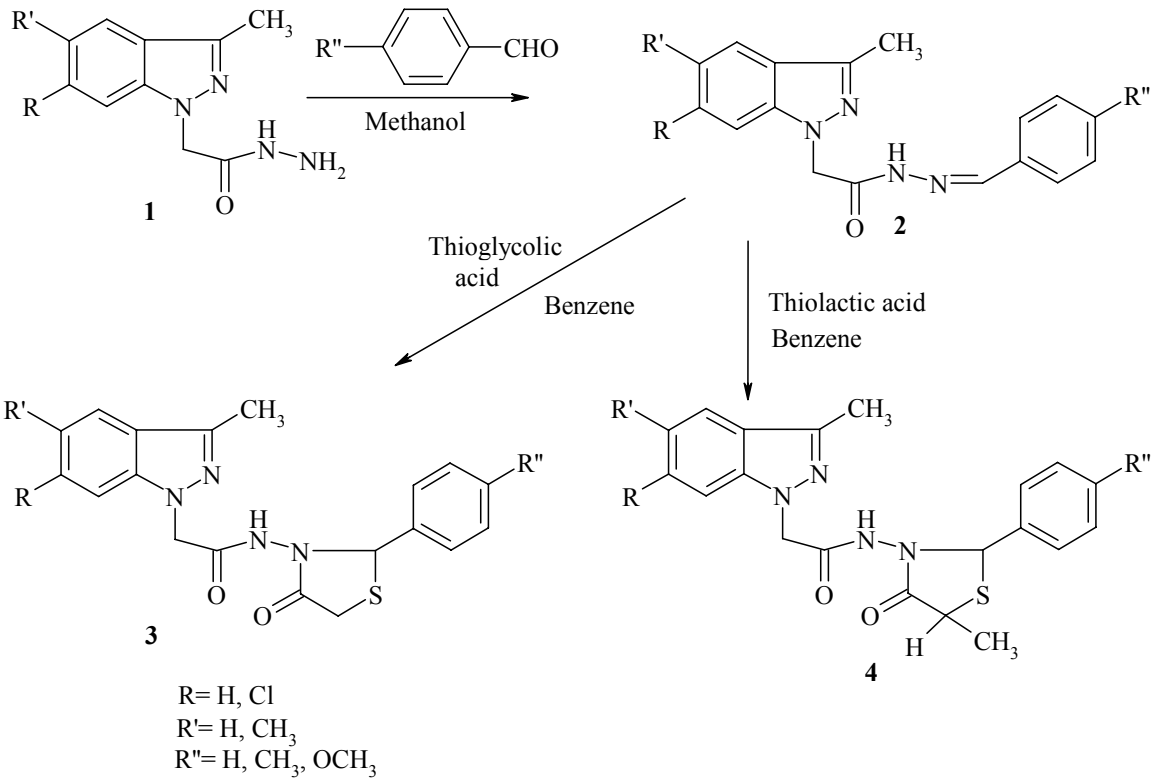
The compounds were screened[5-6] for their antibacterial activity against pathogenic organisms *E.coli, P.aureus, S.aureus, S.typhi, B.subtilis* and antifungal activity against *C.albicans, A.niger* and *A.fumigatus* by single disc method at different concentrations. The compounds were also screened for their *in vitro* antitubercular[7] activity against $H_{37}R_V$ strain of *Mycobacterium tuberculosis*. The screening results exhibited the minimum inhibitory concentration (MIC) against the microorganisms in the range 25-250 μg/mL and are given in **Table II**. A commercial antibacterial Ampicillin and antifungal Micanozole were used as standards for comparison.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer FTIR-1600 Spectrophotometer; ^{1}H and ^{13}C NMR spectra on Bruker AM X (500 MHz) spectrometer using TMS as an internal standard (chemical shifts in δ, ppm); and mass spectra on a Jeol JMS-D300 spectrometer. TLC was run on silica gel-G plates and spots were located by iodine vapours and ultra violet lamp with frequency 560 and 252 nm. Satisfactory C, H, N results were obtained for all the compounds.

Synthesis of 5,6-substituted-3-methyl-1-(substituted-benzalhydrazinocarbonylmethyl)benzopyrazoles 2. **General procedure**. A solution of compound **1** (0.1 mole) in dry methanol (200 mL) and benzaldehyde (0.1 mole) was refluxed on a water-bath for 5-6 hr. The reaction mixture was cooled; separated solid was filtered, washed with cold methanol and recrystallized from ethanol; yield 70-80%. The characterization data of **2** are given in **Table I**.

Synthesis of 3-methyl-1-[(2′-substituted-phenyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted-



Scheme I

Table I — Characterization data of compounds **2, 3** and **4**

Compd	R	R′	R″	m.p.°C	Spectral data
2a	Cl	H	OCH_3	120-21	^{1}HNMR($CDCl_3$): δ 2.5 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.2 (s, 2H, CH_2), 6.9-7.8 (m, 7H, ArH), 8.4 (s, 1H, N=CH), 13.0 (s, 1H, NH). ^{13}C NMR: δ14.127(CH_3), 55.341(CH_2), 63.914 (OCH_3), 108.6-132.7 (12 Ar-C), 159.1 & 159.9 (2×C=N), 168.7 (C=O carbons). MS (EI): M^+ 356.5 and M^{+2} peak at 358.6.
2b	Cl	H	CH_3	235-36	^{1}HNMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 6.9-7.8 (m, 7H, ArH), 8.4 (s, 1H, N=CH), 13.0 (s, 1H, NH)
2c	Cl	H	H	154-55	^{1}HNMR ($CDCl_3$): δ 2.2 (s, 3 H, CH_3), 4.2 (s, 2H, CH_2), 6.7-7.1 (m, 8H, ArH), 8.2 (s, 1H, N=CH), 13.1 (s, 1H, NH)
2d	H	H	OCH_3	220-22	^{1}HNMR (DMSO-d_6): δ 2.2 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.2 (s, 2H, CH_2), 6.8-7.9 (m, 8H, ArH), 8.7 (s, 1H, N=CH), 12.8 (s, 1H, NH).
2e	H	H	CH_3	110-11	^{1}HNMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 6.7-7.6 (m, 8H, ArH), 8.0 (s, 1H, N=CH), 13.2 (s, 1H, NH).
2f	H	H	H	180-81	^{1}HNMR ($CDCl_3$): δ 2.6 (s, 3H, CH_3), 4.1 (s, 2H, CH_2), 6.7-7.8 (m, 9H, ArH), 8.7 (s, 1H, N=CH),13.5 (s, 1H, NH).
2g	Cl	CH_3	OCH_3	80	
2h	Cl	CH_3	CH_3	178-79	
2i	Cl	CH_3	H	280-81	^{1}HNMR (DMSO-d_6): δ 2.1 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 6.9-7.8 (m, 8H, ArH), 8.7 (s, 1H, N=CH), 13.3 (s, 1H, NH).
3a	Cl	H	OCH_3	189-90	^{1}HNMR ($CDCl_3$): δ 2.5 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 4.2 (s, 2H, CH_2), 5.0 (s, 2H, CH_2), 6.9-7.3 (m, 8H, ArH), 13.0 (s, 1H, NH). ^{13}C NMR: δ15.3 (CH_3), 55.8 (CH_2), 63.8 (OCH_3), 79.8 (CH_2), 118.7-131.8 (13 Ar-C), 159.5 (C=N), 167.9 and 174.0 (2×C=O).
3b	Cl	H	CH_3	210-12	^{1}HNMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.1 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 6.8-7.4 (m, 7H, ArH), 13.2 (s, 1H, NH). MS (E1): M^+ peak at 414.8 and M^{+2} peak at 416.9.

— Contd

Table I — Characterization data of compounds **2, 3** and **4** — *Contd*

Compd	R	R′	R″	m.p.°C	Spectral data
3c	Cl	H	H	250-51	
3d	H	H	OCH_3	156-57	^{1}HNMR (DMSO-d_6): δ 2.4 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.1 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 6.7-7.8 (m, 8H, ArH), 12.9 (s, 1H, NH). MS (El): M^+ ion peak at m/z 396
3e	H	H	CH_3	251-52	^{1}HNMR ($CDCl_3$): δ 2.6 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 6.7-7.5(m, 8H, ArH), 12.9 (s, 1H, NH)
3f	H	H	H	123-24	^{1}HNMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 4.1 (s, 2H, CH_2), 5.2 (s, 2H, CH_2), 6.6 - 7.7 (m, 8H, ArH), 12.8 (s, 1H, NH).
3g	Cl	CH_3	OCH_3	174-75	^{1}HNMR (DMSO-d_6): δ 2.5 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.1 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 6.6-7.7 (m, 7H, ArH), 12.9 (s, 1H, NH).
3h	Cl	CH_3	CH_3	190-92	^{1}HNMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 6.7-7.5 (m, 7H, ArH), 13.2 (s, 1H, NH).
3i	Cl	CH_3	H	210-12	^{1}HNMR (DMSO-d_6): δ 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 5.1 (s, 2H, CH_2), 6.7-7.5 (m, 7H, ArH), 13.5 (s, 1H, NH).
4a	Cl	H	OCH_3	262-63	^{1}HNMR ($CDCl_3$): δ 2.5 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 4.2 (s, 2H, CH_2), 5.0 (s, 1H, CH), 5.7 (s, 1H, CH), 6.8-7.8 (m, 8H, 1H & 7ArH), 12.9 (s, 1H, NH). ^{13}C NMR: 14.1 and 17.3 (2 -CH_3), 55.3 (CH_2), 64.0 (OCH_3), 83.570(tetrahedral carbon), 92.1 (ring tetrahedral carbon), 119.1 -133.4 (13 Ar-C), 157.2 (C=N), 168.7 and 173.8 (2 × C=O carbons).
4b	Cl	H	CH_3	214-15	^{1}HNMR (DMSO-d_6): δ 2.2 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 5.2 (s, 1H, CH), 5.8 (s, 1H, CH), 6.8-7.7 (m, 7H, ArH), 13.0 (s, 1H, NH). ^{13}C NMR: δ14.6, 16.9 & 17.8 (3 -CH_3), 57.6 (CH_2), 82.8 (tetrahedral carbon), 92.7 (ring tetrahedral carbon), 221.0-131.8 (12 Ar-C), 157.7 (C=N), 168.9 and 174.7 (2×C=O carbons).
4c	Cl	H	H	181-82	^{1}HNMR (DMSO-d_6): δ 2.2 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 5.2 (s, 1H, CH), 5.8 (s, 1H, CH), 6.8-7.8 (m, 7H, ArH), 13.0 (s, 1H, NH).
4d	H	H	OCH_3	215-16	^{1}H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.3 (s, 2H, CH_2), 5.2 (s, 1H, CH), 5.8 (s, 1H, CH), 6.8-7.7(m, 8H, ArH), 13.0 (s, 1H, NH).
4e	H	H	CH_3	148-50	^{1}H NMR:δ 2.2 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 5.2 (s, 1H, CH), 5.8 (s, 1H, CH), 6.6-7.8(m, 8H, ArH), 13.0 (s, 1H, NH).
4f	H	H	H	287-88	
4g	Cl	CH_3	OCH_3	193-95	^{1}H NMR (DMSO-d_6): δ 2.2 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.3 (s, 2H, CH_2), 5.2 (s, 1H, CH), 5.8 (s, 1H, CH), 6.8-7.7 (m, 7H, ArH), 13.0 (s, 1H, NH).
4h	Cl	CH_3	CH_3	204-05	^{1}H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 5.2 (s, 1H, CH), 5.8 (s, 1H, CH), 6.5 - 7.8 (m, 7H, ArH), 13.0 (s, 1H, NH).
4i	Cl	CH_3	H	106-07	^{1}H NMR (DMSO-d_6): δ 2.2 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 4.4 (s, 2H, CH_2), 5.6 (s, 1H, CH), 5.9 (s, 1H, CH), 6.8 - 7.8 (m, 7H, ArH), 12.8 (s, 1H, NH).

Table II — Antimicrobial activities of compounds **2a-i, 3a-i** and **4a-i**

Compd	Antibacterial activity					Antifungal activity			Antitubercular activity
	E.coli	*P. aureus*	*S. aureus*	*S.typhi*	*B. subtilis*	*C. albicans*	*A. niger*	*A. fumigatus*	$H_{37}R_V$
2a	+++	-	++	-	-	+	++	-	-
2b	++	+	++	-	+++	+	+	+	-
2c	++	++	-	-	++	-	-	-	-
2d	++	++	-	+++	+	-	-	-	-
2e	-	+	-	++	++	++	+	++	-
2f	-	+	++	+++	+	+	+	+++	-
2g	-	+	+	+	+	++	++	-	-
2h	-	++	++	+	++	++	++	+	-
2i	+	++	++	++	++	++	+++	-	-

— *Contd*

Table II — Antimicrobial activities of compounds **2a-i, 3a-i** and **4a-I**—*Contd*

Compd	Antibacterial activity					Antifungal activity			Antitubercular activity
	E.coli	*P. aureus*	*S. aureus*	*S.typhi*	*B. subtilis*	*C. albicans*	*A. niger*	*A. fumigatus*	$H_{37}R_V$
3a	+	+	-	++	-	+	+++	++	-+
3b	++	-	-	+	-	++	-	-	++
3c	++	+	+	++	-	++	+++	-	+
3d	++++	-	+	+	-	+++	+	-	+
3e	+	-	++	+	++	-	+	++	++
3f	+	++	-	-	+	++	-	++	++
3g	+	-	-	++	+	++	-	+	++
3h	-	-	+	++	+	++	-	+	+
3i	-	+	+	++	++	+	-	++	+
4a	-	++	+++	++	++	+	++	++++	++
4b	++	++	++	+	+++	-	++	+++	++
4c	++	++	-	-	+	-	++	++	++
4d	++	++	+	-	+	-	+	-	++
4e	+	+++	-	-	+	+	+	-	+
4f	+++	+++	-	+	-	+	+	-	+
4g	+	+	+	-	-	++	++	+	-
4h	+	+	++	-	-	+	++	+	-
4i	-	+	++	-	-	-	+	+	-

Where; ++++ 50 μg/mL, +++ 100 μg/mL, ++ 200 μg/mL, + 250 μg/mL

benzopyrazoles 3. **General procedure**. A mixture of **2** (0.01 mole) in dry benzene (40 mL) and thioglycolic acid (0.012 mole) was refluxed on a water-bath for 8-9 hr. The excess solvent was removed under vacuum and residue was poured into ice cold water and then neutralized with sodium bicarbonate solution. Solid separated was filtered, dried and recrystallized from aqueous ethanol, yield 65-70%. The characterization data of **3** are given in **Table I**.

Synthesis of 3-methyl-1-[(2′-substituted-phenyl-5′-methyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted-benzopyrazoles 4. **General procedure**. A mixture of **2** (0.01 mole) in dry benzene (40 mL) and thiolatic acid (0.012 mole) was refluxed on a water-bath for 8-9 hr. The excess solvent was removed under vacuum and residue was poured into ice cold water and then neutralized with sodium bicarbonate solution. Solid separated was filtered, dried and recrystallized in aqueous ethanol, yield 65-72%. The characterization data of **4** are given in **Table I**.

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