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"Synthesis of Novel Heterocyclic 4 – Thiazolidinone Derivatives and their Antibacterial Activity"

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Abstract

4-Thiazolidinones have been prepared by the reaction of various substituted Schiff bases 3 with Thioglycolic acid and Thiolactic acid. The intermediate Schiff bases 3 were synthesized by the condensation of various substituted 2- amino benzothiazole 1 with 1-(4-methyl Phenyl)-3-methyl-5- pyrazolone 2. The starting compound substituted 2-amino benzothiazoles were prepared from various substituted amines via substituted phenyl thiourea. The structures of the compounds have been confirmed by elemental analysis and spectral analysis. The antibacterial activity of the compounds has also been screened against Staphylococcus aureus and Escherichia coli.

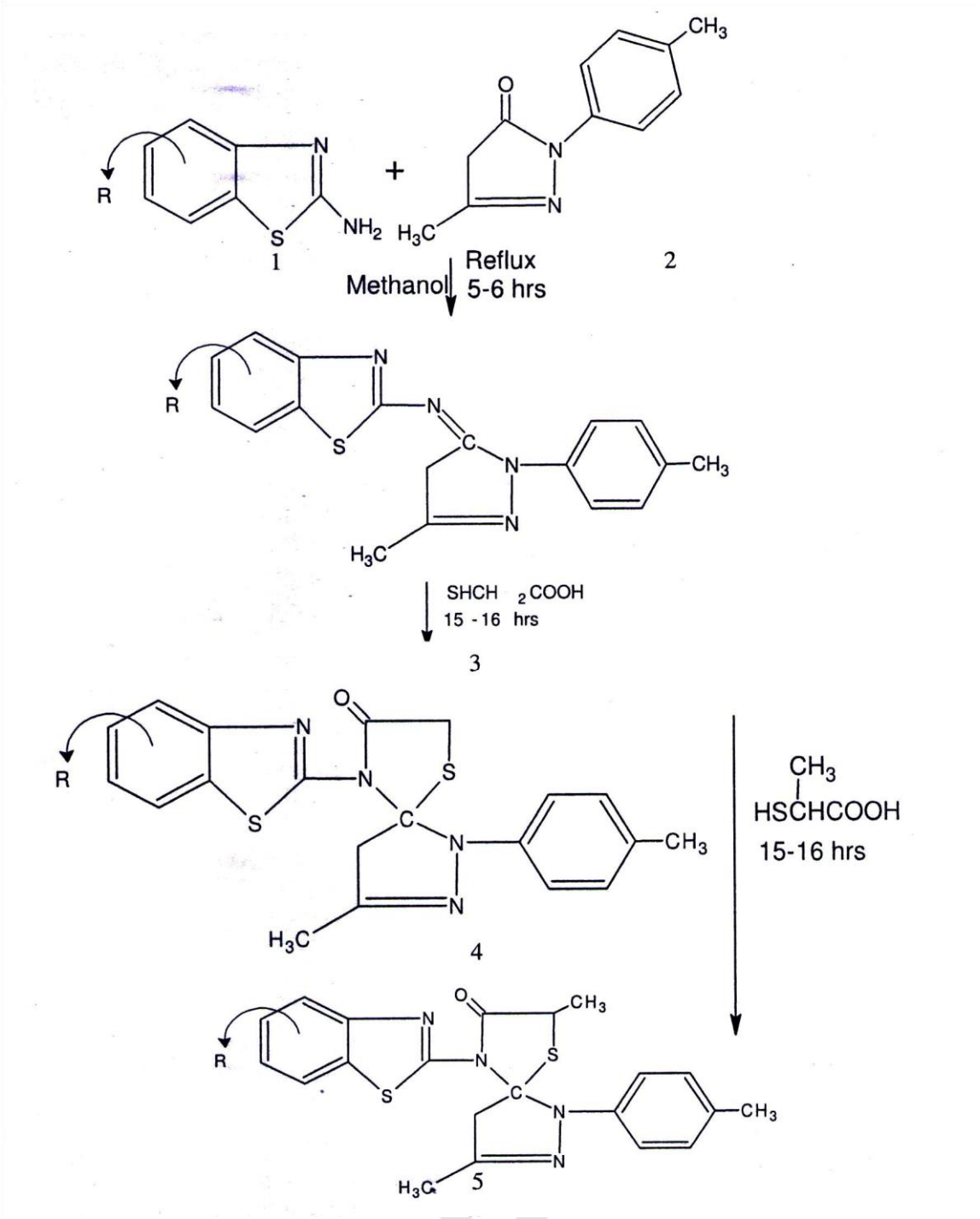
Introduction

Benzothiazole derivatives were prepared and known to exhibit various biological activities as anti-tuberculotic[1], anti-allergic[2]. Pyrazole ring system is of some practical importance, because many drugs and medicines contain a pyrazole ring system. As early as 1884 Knorr discovered the antipyretic (temperature reducing) action of a pyrazole derivative in human beings and due to its antipyretic property, he named the compound "Antipyrine". Schiff Base gives good antimicrobial activity and pharmacological applications[3] and it can be prepared by the acid catalyzed reaction of amines & ketones or aldehydes. It gives a good fungicidal activity[4]. 4-Thiazolidinones gives good pharmacological properties[5]. 4-Thiazolidinones are known to exhibit antitubercular6, antibacterial[6,7], anticonvulsant8, antifungal[8,9], antithyroid activities.

The starting compound substituted 2-amino benzothiazole 1 have been synthesized from various substituted amines[10]. Different substituted 2-amino benzothiazoles were condensed with 1-(4-methyl Phenyl)-3-methyl-5-pyrazolone to yield Schiff Base 3. The Schiff bases 3 were further reacted with Thioglycolic acid and Thiolactic acid to yield 4-Thiazolidinone derivatives 4a-j & 5a-j respectively.

Experimental

All the melting points were determined in open capillary and are uncorrected. The purity of compounds was checked by TLC on silica gel coated glass plates. IR spectra were recorded with KBr on Shimatzu FT-IR 8300 spectrophotometer, 1H NMR spectra on a Varian Geminy 200 MHz spectrometer using tetramethylsilane as an internal standard.



Scheme 1 Synthesis of 1-(4-Methyl phenyl)-3-methyl-5-(2-imino substituted benzothiazole)- pyrazole.

Procedure

In a 250 mL R. B. F. mixture of 1-(4-methyl Phenyl)-3-methyl-5-pyrazolone

(0.01 mole) and substituted 2-amino benzothiazole (0.01 mole) were taken. About 20 mL methanol was added to it and refluxed for 5 - 6 hrs. After the completion of reaction, the solvent was removed by vaccum distillation. The solid product was filtered, dried and recrystalised from absolute alcohol. All substituted Schiff bases were prepared in the similar manner.

Synthesis of 2-[spiro-{1-(4-methyl phenyl)-3-methyl}-pyrazole]-3-(6-nitro benzothiazole)-4-thiazolidinone. (4a)

In a 250 mL R. B. F. schiff base 3a (0.01 mole, 3.65 g) in benzene was taken, Dean stark apparatus was attached to it and thioglycolic acid (0.01 mole, 0.92 g) in benzene was added slowly. Then it was refluxed for 15 - 16 h, during the course of the reaction the water was removed continuously. The benzene was distilled off to get the thiazolidinone 4a. The solid product was filtered, dried and recrystalised from absolute alcohol. m.p. 145oC, yield 80%. The compounds 4b-j were prepared by the same procedure. Their characterization data are shown in Table 1.

Synthesis of 2-[spiro-{1-(4-methyl phenyl)-3-methyl}-pyrazole]-3-(6-nitro benzothiazole)-5-methyl-4-thiazolidinone. (5a)

In a 250 mL R. B. F. Schiff base 3a (0.01 mole, 3.65 g) in benzene was taken, Dean stark apparatus was attached to it and thiolactic acid (0.01 mole, 1.06 g) in benzene was added slowly. Then it was refluxed for 15 - 16 hrs, during the course of the reaction the water was 192 K. R. DESAI *et al.* removed continuously. The benzene was distilled off to get the thiazolidinone 5a. The solid product was filtered, dried and recrystalised from absolute alcohol. m.p.156^{o}C, yield 72%. The compounds 5b-j were prepared by the same procedure.Their characterization data are shown in Table 2.

Table : 1 - Characterization data of compounds 4a-j

No.	R	M.F. (M.W.)	Yield, %	M.P,.^{0}C	% Analysis Calc.(Found)		
					C	H	N
4a	6‴-NO_2	$C_{20}H_{17}N_5O_3S_2$ (439.0)	80	145	54.66 (54.69)	3.87 (3.88)	15.94 (15.96)
4b	6‴-SO_3H	$C_{20}H_{18}N_4O_4S_3$ (474.0)	77	165	50.63 (50.65)	3.79 (3.82)	11.81 (11.79)
4c	6‴-CH_3	$C_{21}H_{20}N_4OS_2$ (408.0)	75	112	61.76 (61.73)	4.90 (4.87)	13.72 (13.75)
4d	6‴-OH	$C_{20}H_{18}N_4O_2S_2$ (410.0)	76	142	58.53 (58.52)	4.39 (4.43)	13.65 (13.68)
4e	4‴-OCH_3	$C_{21}H_{20}N_4O_2S_2$ (424.0)	72	103	59.43 (59.46)	4.71 (4.73)	13.20 (13.24)
4f	6‴-Cl	$C_{20}H_{17}N_4OS_2Cl$ (428.5)	77	138	56.00 (56.04)	3.97 (3.95)	13.06 (13.09)
4g	4‴,6‴-$(NO_2)_2$	$C_{20}H_{16}N_6O_5S_2$ (484.0)	68	133	49.58 (49.61)	3.30 (3.29)	17.35 (17.36)
4h	6‴-OCH_3	$C_{21}H_{20}N_4O_2S_2$ (424.0)	73	101	59.43 (59.57)	4.71 (4.75)	13.20 (13.18)
4i	4‴-NO_2	$C_{20}H_{17}N_5O_3S_2$ (439.0)	70	118	54.66 (54.62)	3.87 (3.91)	15.94 (15.97)
4j	6‴-$NHCOCH_3$	$C_{22}H_{21}N_5O_2S_2$ (451.0)	71	157	58.53 (58.55)	4.65 (4.67)	15.52 (15.50)

Table : 2 - Characterization data of compounds 5a-j

No.	R	M.F. M.W.	Yield %	M.P. ^{0}C	% Analysis Calc.(Found)		
					C	H	N
5a	6‴-NO_2	$C_{21}H_{19}N_5O_3S_2$ (453.0)	72	156	55.61 (55.64)	4.22 (4.25)	15.14 (15.10)
5b	6‴-SO_3H	$C_{21}H_{20}N_4O_4S_3$ (488.0)	71	172	51.62 (51.64)	4.13 (4.16)	11.47 (11.45)
5c	6‴-CH_3	$C_{22}H_{22}N_4OS_2$ (422.0)	70	127	62.53 (62.57)	5.25 (5.26)	13.26 (13.24)
5d	6‴-OH	$C_{21}H_{20}N_4O_2S_2$ (424.0)	78	158	59.41 (59.43)	4.75 (4.73)	13.20 (13.18)
5e	4‴-OCH_3	$C_{22}H_{22}N_4O_2S_2$ (438.0)	65	122	60.25 (60.24)	5.06 (5.09)	12.77 (12.76)
5f	6‴-Cl	$C_{21}H_{19}N_4OS_2Cl$ (443.0)	70	149	56.94 (56.97)	4.32 (4.36)	12.65 (12.67)
5g	4‴,6‴-$(NO_2)_2$	$C_{21}H_{18}N_6O_5S_2$ (498.0)	65	160	50.59 (50.61)	3.64 (3.61)	16.86 (16.88)
5h	6‴-OCH_3	$C_{22}H_{22}N_4O_2S_2$ (438.0)	66	113	60.25 (60.23)	5.06 (5.08)	12.77 (12.79)
5i	4‴-NO_2	$C_{21}H_{19}N_5O_3S_2$ (453.0)	72	131	55.61 (55.62)	4.22 (4.20)	15.14 (15.11)
5j	6‴-$NHCOCH_3$	$C_{23}H_{23}N_5O_2S_2$ (465.0)	64	168	59.33 (59.31)	4.98 (4.95)	15.04 (15.06)

Result and Discussion

Structures of the compounds synthesized have been confirmed by elemental analysis, IR spectra and 1H NMR spectra.

4-Thiazolidinone compound shows IR absorption bands at 1330-1310 cm-1 (Ar-CH3), 800-600 cm-1 (C-S stretching), 1720-1700 cm-1 (C=O stretching) and 1360-1310 cm-1 (C-N stretching), 1690-1640 cm-1 (C=N).

- 1H NMR of compound 4e

2.25 (3H, s, Ar-CH3), 3.13 (4H, s, -CH2), 2.03 (3H, s, -CH3), 6.95 -7.37 (7H, m, Ar-H), 2.70 (3H, s, -OCH3).

- 1H NMR of compound 5a

2.3 (3H, s, Ar-CH3), 3.08 (2H, s, -CH2), 3.70 (1H, s, -CH), 2.10 (6H, s,-CH3), 7.11 - 7.45 (7H, m, Ar-H),

Antibacterial Activity :

The synthesized compounds were tested for their antibacterial activity by measuring the inhibition area on agar plates (diffusimetric method)11 with Staphylococcus aureus and Escherichia coli as test germs.

The results of antibacterial screening indicated that good activity was shown by compounds 4a, 5a, 5h against *Staphylococcus aureus* and compounds 4j, 5d, 5g, 5j shows good activity towards *Escherichia coli*. While the compounds 4i, 5d, 5i have less activity against *Staphylococcus aureus*, and compounds 4f, 5c, 5f have less activity against *Escherichia coli*. Other compounds showed moderate activity against both bacterial strains. (Table 3) **Table : 3 - Antibacterial activity of Newly synthesised compounds, zone of inhibition (mm)**

No.	*S.aureus.*	*E.coli.*	*No.*	*S.aureus.*	*E.coli.*
4a	12.0	9.0	5a	12.0	8.0
4b	11.0	10.0	5b	10.0	11.0
4c	9.0	8.0	5c	9.0	7.0
4d	8.0	11.0	5d	7.0	12.0
4e	8.0	10.0	5e	9.0	11.0
4f	9.0	7.0	5f	11.0	7.0
4g	10.0	11.0	5g	8.0	12.0
4h	11.0	10.0	5h	12.0	9.0
4i	7.0	8.0	5i	7.0	10.0
4j	9.0	12.0	5j	10.0	12.0

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