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Synthesis and biological evaluation of some novel 2-mercaptobenzothiazoles carrying 2-pyrazoline

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This study presents synthesis of several 2-mercaptobenzothiazole derivatives **6a-s** bearing 2-pyrazoline at the second position. Compounds **6h**, **6i**, **6j** and **6n** exhibited significant antimicrobial activity (inhibition zone 30-35 mm) against *Pseudomonas aeruginosa*. Compounds **6i**, **6j** and **6n** showed significant analgesic and anti-inflammatory activities. Compounds **6i** and **6n** showed significant gastrointestinal protection compared to the standard drug diclofenac sodium.

Keywords: Anti-inflammatory activity, Antimicrobial activity, 2-Mercaptobenzothiazoles, 2-Pyrazolines, Ulcerogenic action

Introduction

Use of anti-inflammatory therapy may lessen immunological response to bacterial infections[1] and as such while confounding the progression of disease by suppressing inflammation, fever and pain, they could actually be enhancing progression of bacterial infection. Moreover, this also increases the risk for developing NSAIDs-related complications especially in elderly, patients with prior history of peptic ulcer disease and patients with impaired liver or kidney functions and patients taking anticoagulants, corticosteroids, etc. concurrently. Hence, there is a pressing need for drugs having both antimicrobial and analgesic-anti-inflammatory activities with minimum adverse effects. Substances containing 2-pyrazoline[2,3] moieties have occupied a unique position in the design and synthesis of novel biologically active agents with remarkable antimicrobial, analgesic and anti-inflammatory activities. In addition, 2-mercaptobenzothiazoles are known to possess antimicrobial[4] and anti-inflammatory[5] properties. Studies on 2-mercaptobenzothiazole[6,7] prompted authors to link 2-mercaptobenzothiazole nucleus at the second position to some 2-pyrazoline ring system to bring them in the same matrix to serve as a new scaffold.

In present study, 2-pyrazoline incorporated 2-mercaptobenzothiazoles **6a-s** were synthesized and evaluated for antimicrobial, analgesic, anti-inflammatory and ulcerogenic effects.

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Experimental Section

Melting points were determined in open glass capillaries and were uncorrected. Reaction progress was routinely monitored by thin layer chromatography (TLC) on silica gel plates. Infrared (IR) spectra were recorded on KBr disks, using a Shimadzu 8400S FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker AV-III 400 spectrometer with DMSO-d_6 as the solvent. Chemical shifts are reported in ppm, using solvent or TMS as internal standard. LC-MS and EI-MS were obtained on Shimadzu 2010A and Jeol GC Mate II instruments, respectively. Elemental analyses were carried out on a Flash EA 1112 series instrument.

Intermediate chalcones (**5a-s**) were prepared[8] by the base catalyzed Claisen-Schmidt condensation of aromatic ketones (**3a-c**) with different aromatic aldehydes (**4a-g**).

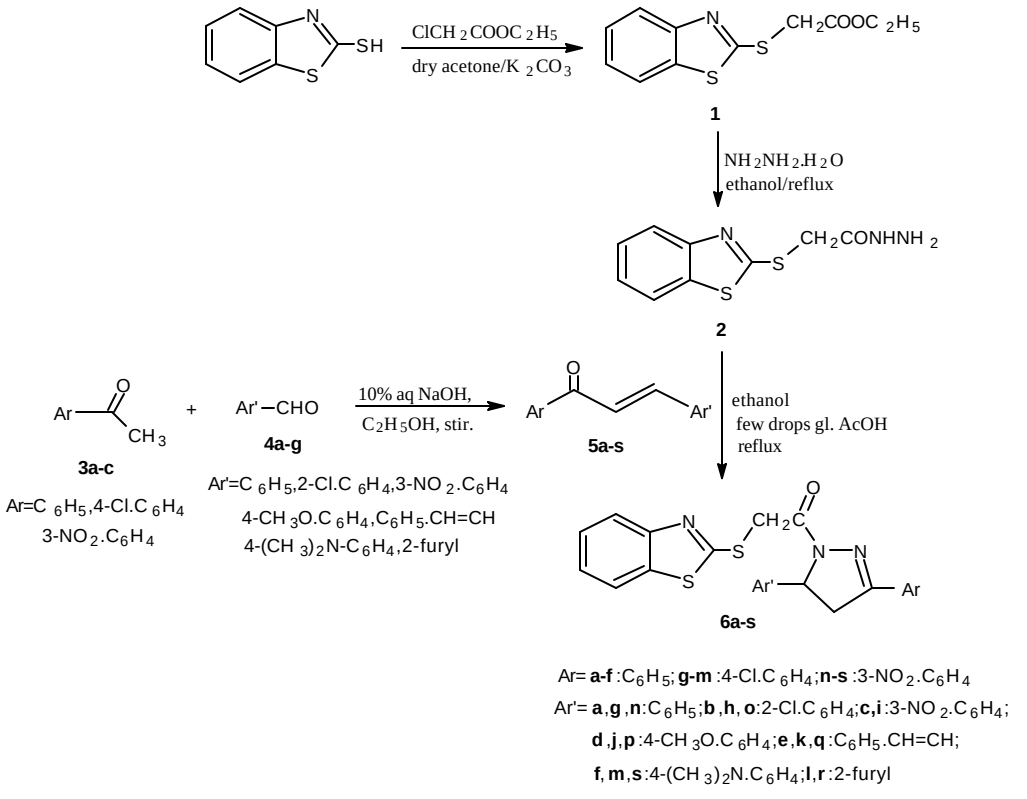
Synthesis of 2-(1,3-benzothiazol-2-ylsulfanyl)-1-(3,5-disubstituted-4,5-dihydro-1H-pyrazol-1-yl)ethanones (6a-s)

To a solution of appropriately substituted chalcone (**5a-s**, 10 mmol) in absolute ethanol (75 ml), benzothiazol-2-ylthio acetic acid hydrazide (**2**, 10 mmol) and few drops of glacial acetic acid were added. Reaction mixture was refluxed for 14-16 h on a water bath. After completion of reaction, content of flask was reduced under vacuum, cooled and poured onto crushed ice and kept overnight. Separated solid was filtered, washed several times with water, dried and recrystallized from suitable solvent to

Table 1—Characterization data of synthesized compounds **6a-s**

Compd.	Ar	Ar2	Solv. Cryst.	M.p. (°C)	[a]Yield (%)	C=O/C=N (cm^{-1})
6a	C_6H_5	C_6H_5	acetone	168	57	1689/1640
6b	C_6H_5	2-Cl.C_6H_4	DMSO:ethanol (1:1)	200	69	1681/1618
6c	C_6H_5	4-NO_2.C_6H_4	methanol	178	56	1674/1640
6d	C_6H_5	4-CH_3O.C_6H_4	dichloromethane:acetone (1:1)	162	67	1668/1658
6e	C_6H_5	CH=CH.C_6H_5	ethanol	170	56	1680/1647
6f	C_6H_5	4-$(CH_3)_2$N.C_6H_4	DMF:ethanol (1:1)	210	47	1666/1642
6g	4-Cl.C_6H_4	C_6H_5	acetone	194	59	1683/1645
6h	4-Cl.C_6H_4	2-Cl.C_6H_4	THF	222	64	1681/1618
6i	4-Cl.C_6H_4	3-NO_2.C_6H_4	THF	210	72	1668/1622
6j	4-Cl.C_6H_4	4-CH_3O.C_6H_4	ethanol	184	66	1681/1622
6k	4-Cl.C_6H_4	CH=CH.C_6H_5	acetone	192	49	1683/1649
6l	4-Cl.C_6H_4	2-furyl	ethanol	168	64	1654/1647
6m	4-Cl.C_6H_4	4-$(CH_3)_2$N.C_6H_4	ethanol	210	61	1666/1647
6n	3-NO_2.C_6H_4	C_6H_5	ethanol	122	74	1683/1618
6o	3-NO_2.C_6H_4	2-Cl.C_6H_4	ethanol	102	69	1685/1647
6p	3-NO_2.C_6H_4	4-CH_3O.C_6H_4	ethanol	140	66	1670/1625
6q	3-NO_2.C_6H_4	CH=CH.C_6H_5	ethanol	206	70	1666/1612
6r	3-NO_2.C_6H_4	2-furyl	ethylacetate	136	66	1680/1618
6s	3-NO_2.C_6H_4	4-$(CH_3)_2$N.C_6H_4	ethylacetate	110	57	1683/1654

[a]Isolated yield; All compounds showed satisfactory elemental analysis.



Scheme 1. Synthesis of 2-pyrazoline incorporated 2-mercaptobenzothiazoles

give **6a-s**. Characterization (Table 1), ^{1}H NMR (Table 2), Mass and ^{13}C NMR data (Table 3) are presented.

Results and Discussion

For synthesis of **6a-s** (Scheme 1), ethyl (benzothiazol-2-ylthio) acetate (**1**) and benzothiazol-2-ylthio acetic acid

Table 2—^{1}H NMR data of synthesized compounds **6a-s**

Compounds	^{1}H NMR (DMSO-d_6)/*d* ppm	MS *m/z*
6a	8.01-7.53 (m, 4H, ArH), 7.51-7.23 (m, 10H, ArH), 6.30 (t, 1H, CH pyrazoline), 4.73 (s, 2H, SCH_2CO), 4.21 (d, 2H, CH_2 pyrazoline)	430 (M^++1)
6b	8.15-7.68 (m, 4H, ArH), 7.57-7.37 (m, 9H, ArH), 7.12 (t, 1H, CH pyrazoline), 4.70 (s, 2H, SCH_2CO), 4.44 (d, 2H CH_2 of pyrazoline)	465 (M^++1)
6c	8.33-7.72 (m, 5H, ArH), 7.62-7.27 (m, 8H, ArH), 6.48 (t, 1H, CH pyrazoline), 4.75 (s, 2H, SCH_2CO), 4.23 (d, 2H, CH_2 pyrazoline)	474 (M^+)
6d	8.02-7.57 (m, 6H, ArH), 7.53-6.94 (m, 7H, ArH), 6.75 (t, 1H, CH pyrazoline), 4.82 (s, 2H, SCH_2CO), 4.47 (d, 2H, pyrazoline), 3.78 (s, 3H, OCH_3)	459 (M^+)
6e	8.12-7.86 (m, 4H, ArH), 7.78-7.42 (m, 10H, ArH), 6.96 (m, 2H, CH=CH), 6.71-6.65 (m, 1H, CH pyrazoline), 4.76 (s, 2H, SCH_2CO), 4.34-4.25 (m, 2H, CH_2 pyrazoline)	455 (M^+)
6f	8.02-7.61 (m, 4H, ArH), 7.59-7.13 (m, 9H, ArH), 6.73 (t, 1H, CH pyrazoline), 4.71 (s, 2H, SCH_2CO), 4.36 (d, 2H, CH_2 pyrazoline), 2.17 (s, 6H, 2xCH_3)	473 (M^+)
6g	8.01-7.57 (m, 6H, ArH), 7.48-7.17 (m, 7H, ArH), 6.83 (t, 1H, CH pyrazoline), 4.73 (s, 2H, SCH_2CO), 4.28 (d, 2H, CH_2 pyrazoline)	464 (M^+)
6h	8.05-7.74 (m, 4H, ArH), 7.62-7.37 (m, 8H, ArH), 6.72 (t, 1H, CH pyrazoline), 4.69 (s, 2H, SCH_2CO), 4.39 (d, 2H, CH_2, pyrazoline)	499 (M^++1)
6i	8.20-7.60 (m, 8H, ArH), 7.52-7.33 (m, 4H, ArH), 7.01 (t, 1H, CH pyrazoline), 4.71 (s, 2H, SCH_2CO), 4.48 (d, 2H, CH_2 pyrazoline)	509 (M^+)
6j	8.00-7.59 (m, 5H, ArH), 7.56-6.95 (m, 7H, ArH), 6.76 (t, 1H, CH pyrazoline), 4.74 (s, 2H, SCH_2CO), 4.45 (d, 2H, CH_2 pyrazoline), 3.78 (s, 3H, OCH_3)	495 (M^++1)
6k	8.27-7.52 (m, 8H, ArH), 7.46-7.12 (m, 5H, ArH), 6.92 (m, 2H, CH=CH), 6.72-6.67 (m, 1H, CH pyrazoline), 4.70 (s, 2H, SCH_2CO), 4.42-4.34 (m, 2H, CH_2 pyrazoline)	491 (M^++1)
6l	8.11-7.76 (m, 4H, ArH), 7.45-6.85 (m, 7H, ArH), 6.68 (t, 1H, CH pyrazoline), 4.78 (s, 2H, SCH_2CO), 4.49 (d, 2H, CH_2 pyrazoline)	454 (M^+)
6m	8.02-7.54 (m, 6H, ArH), 7.50-6.94 (m, 6H, ArH), 6.76 (t, 1H, CH pyrazoline), 4.77 (s, 2H, SCH_2CO), 4.42 (d, 2H, CH_2 pyrazoline), 2.16 (s, 6H, 2x CH_3)	507 (M^+)
6n	8.21-7.78 (m, 4H, ArH), 7.72-7.37 (m, 9H, ArH), 6.81 (t, 1H, CH pyrazoline), 4.81 (s, 2H, SCH_2CO), 4.47 (d, 2H, CH_2 pyrazoline)	474 (M^+)
6o	8.09-7.54 (m, 6H, ArH), 7.49-7.16 (m, 6H, ArH), 6.79 (t, 1H, CH pyrazoline), 4.75 (s, 2H, SCH_2CO), 4.44 (d, 2H, CH_2 pyrazoline)	510 (M^++1)
6p	8.12-7.59 (m, 4H, ArH), 7.46-7.21 (m, 8H, ArH), 6.78 (t, 1H, CH pyrazoline), 4.71 (s, 2H, SCH_2CO), 4.48 (d, 2H, CH_2 pyrazoline), 3.78 (s, 3H, OCH_3)	504 (M^+)
6q	8.34-7.43 (m, 8H, ArH), 7.41-7.18 (m, 5H, ArH), 7.09-6.88 (m, 2H, CH=CH), 6.68-6.64 (m, 1H, CH pyrazoline), 4.69 (s, 2H, SCH_2CO), 4.44-4.40 (m, 2H, CH_2 pyrazoline)	501 (M^+)
6r	8.09-7.74 (m, 4H, ArH), 7.66-6.89 (m, 7H, ArH), 6.72 (t, 1H, CH pyrazoline), 4.80 (s, 2H, SCH_2CO), 4.49 (d, 2H, CH_2 pyrazoline)	464 (M^+)
6s	8.11-7.59 (m, 4H, ArH), 7.47-7.16 (m, 8H, ArH), 6.76 (t, 1H, CH pyrazoline), 4.76 (s, 2H, SCH_2CO), 4.47 (d, 2H, CH_2 pyrazoline), 2.18 (s, 6H, 2xCH_3)	518 (M^+)

hydrazide (**2**) were prepared according to reported procedures[4,5]. Intermediate chalcones (**5a-q**) were prepared[8] by base catalyzed Claisen-Schmidt condensation of aromatic ketones (**3a-c**) with different aromatic aldehydes (**4a-g**) Cyclo-condensation of prepared chalcones with hydrazide (**2**) in absolute ethanol in presence of few drops of glacial acetic acid furnished the corresponding novel 2-(1,3-benzothiazol-2-ylsulfanyl)-

Tables 3—^{13}C NMR data of the synthesized compounds **6a-s**

Compd.	^{13}C NMR (DMSO-d_6)/*d* ppm
6a	169.07, 166.14, 163.46, 159.19, 152.53, 136.86, 135.58, 130.91, 129.20, 129.02, 128.72, 128.31, 126.97, 126.28, 124.52, 121.74, 121.10, 65.04, 55.78, 35.62
6b	169.45, 166.34, 163.75, 152.58, 149.10, 136.77, 134.70, 133.43, 133.14, 130.80, 129.67, 129.29, 128.97, 128.39, 127.58, 126.33, 124.42, 121.50, 121.09, 63.28, 55.24, 35.66
6c	169.18, 166.38, 163.49, 152.56, 150.06, 139.73, 139.47, 137.10, 134.66, 129.49, 129.35, 128.98, 128.28, 128.17, 126.26, 124.48, 124.34, 121.70, 121.03, 65.54, 55.25, 35.73
6d	168.98, 166.42, 163.67, 160.02, 156.23, 153.20, 136.25, 135.42, 131.22, 129.53, 129.23, 128.24, 126.41, 124.91, 121.53, 121.02, 120.52, 64.78, 55.21, 54.25, 35.86.
6e	169.15, 166.35, 162.98, 154.55, 152.78, 139.23, 137.21, 136.26, 134.87, 132.45, 131.72, 131.28, 129.68, 129.23, 128.68, 128.57, 128.32, 127.45, 125.45, 63.75, 54.98, 34.75.
6f	168.78, 165.92, 164.05, 153.47, 150.59, 138.23, 137.57, 134.52, 130.11, 129.62, 129.22, 128.54, 128.32, 127.92, 121.87, 121.63, 118.68, 63.21, 54.78, 36.27, 34.98, 31.13.
6g	169.52, 166.44, 164.35, 153.78, 147.12, 138.20, 137.25, 136.25, 134.95, 133.45, 130.07, 129.25, 129.22, 128.73, 128.23, 121.85, 121.07, 63.16, 54.57, 34.62.
6h	169.32, 165.72, 163.22, 155.21, 146.22, 137.18, 136.20, 134.72, 134.25, 132.98, 130.45, 130.21, 129.11, 128.54, 128.16, 121.65, 121.23, 64.31, 55.23, 33.18.
6i	169.18, 166.01, 163.52, 152.52, 148.25, 147.59, 137.57, 137.22, 135.47, 134.68, 134.35, 133.93, 130.66, 130.06, 128.46, 126.30, 124.40, 123.53, 121.89, 64.16, 55.22, 35.57.
6j	168.97, 165.78, 164.21, 160.13, 153.87, 152.27, 137.24, 136.20, 135.28, 134.95, 132.21, 130.21, 129.78, 128.21, 121.32, 121.10, 120.51, 64.28, 55.37, 54.17, 34.82.
6k	169.23, 166.31, 163.74, 152.95, 152.57, 137.73, 136.20, 135.70, 134.71, 130.62, 128.88, 128.61, 128.03, 126.81, 126.33, 124.43, 121.78, 121.28, 121.09, 62.42, 55.34, 35.66.
6l	169.12, 166.41, 163.78, 154.28, 152.12, 146.72, 142.34, 138.21, 135.37, 130.26, 129.18, 128.45, 128.32, 121.22, 121.07, 118.45, 112.79, 63.28, 55.53, 34.28.
6m	168.86, 166.52, 164.12, 153.78, 151.58, 150.56, 136.98, 134.22, 133.52, 130.21, 129.12, 128.75, 126.22, 125.23, 121.67, 121.12, 118.21, 64.72, 56.21, 36.23, 34.78, 31.07.
6n	169.62, 166.21, 163.52, 155.23, 151.11, 148.23, 137.21, 135.42, 130.33, 129.45, 128.37, 128.21, 128.11, 127.21, 126.63, 123.72, 123.52, 121.32, 121.10, 63.97, 55.45, 34.78.
6o	168.92, 165.72, 163.31, 154.68, 152.22, 148.62, 136.63, 135.72, 135.32, 133.12, 132.45, 130.15, 129.87, 129.65, 128.88, 128.56, 126.22, 123.71, 123.45, 121.21, 121.11, 65.12, 55.78, 34.92.
6p	168.85, 165.92, 163.22, 160.25, 154.17, 148.52, 138.23, 136.72, 136.12, 133.55, 130.77, 130.12, 129.68, 128.68, 128.55, 124.21, 123.72, 121.75, 121.13, 63.01, 55.22, 34.72.
6q	169.39, 166.20, 163.96, 152.54, 151.69, 147.86, 138.46 137.99, 136.12, 135.25, 130.04, 128.68, 128.00, 126.90, 126.38, 124.59, 123.78, 121.91, 121.75, 121.09, 120.94, 62.52, 55.74, 35.63.
6r	169.21, 166.07, 164.12, 154.77, 151.31, 148.23, 146.54, 142.23, 137.15, 136.23, 130.21, 129.55, 128.21, 124.62, 123.12, 121.24, 121.02, 118.33, 113.23, 63.78, 56.12, 34.92.
6s	169.20, 165.97, 164.11, 154.72, 152.22, 151.57, 148.46, 136.88, 135.32, 133.14, 130.25, 129.62, 129.54, 128.21, 125.21, 123.12, 121.63, 121.14, 116.45, 64.21, 55.45, 36.21, 34.72, 31.43.

1-(3,5-disubstituted-4,5-dihydro-1*H*-pyrazol-1-yl) ethanones (**6a-s**).

IR spectra of **6a-s** showed carbonyl (C=O) frequency at 1689-1654 cm^{-1}. Shift in frequency to lower values could be explained on the basis of mesomeric effect. C=N stretching observed at 1658-1612 cm^{-1} is due to ring closure, which confirm formation of desired pyrazoline ring in all prepared compounds. Compounds **6e**, **6k** and **6q** showed additional sharp bands at 1605-1622 cm^{-1} due to aliphatic C=C stretching. ^{1}H NMR spectra[3] of **6a-d**, **6f-j**, **6l-p, 6r** and **6s** showed broad triplet signal at *d* 7.12-6.30 ppm for CH proton at 5th position and doublet signal at *d d* 4.52-4.21 ppm for CH_2 protons at 3rd position of pyrazoline ring. In **6e**, **6k** and **6q**, multiplet signals were observed at *d* 6.72-6.63 and ´ 4.45-4.25 ppm, respectively for CH and CH_2 protons of pyrazoline ring. Protons belonging to aromatic rings and substitutent groups were observed within the expected chemical shift values. ^{13}C NMR spectra were recorded for **6a-s**. ^{13}C NMR spectrum of **6i** showed two signals

Table 4—Antimicrobial screening of synthesized compounds **6a-s** by cup plate method

	Zone of inhibition (mm)[a,b]					
Compd.	*S.a.*	*B.s.*	*E. c.*	*P. a.*	*C.a.*	*A.n.*
6a	13	14	-	-	-	-
6b	26	24	14	15	-	-
6c	13	12	-	-	-	-
6d	21	23	33	27	-	-
6e	22	23	22	24	-	-
6f	27	22	21	26	-	-
6g	13	13	-	-	-	-
6h	23	24	25	30	-	-
6i	23	21	27	34	-	-
6j	22	24	29	33	-	-
6k	13	12	-	-	-	-
6l	14	12	-	-	-	-
6m	27	26	19	20	-	-
6n	24	23	28	35	-	-
6o	14	15	-	-	-	-
6p	12	14	-	-	-	-
6q	29	28	22	28	-	-
6r	23	22	13	14	-	-
6s	13	12	14	16	-	-
DMSO	-	-	-	-	-	-
Ciprofloxacin	34	34	40	35	-	-
Ketoconazole	-	-	-	-	32	28

Test compounds, ciprofloxacin and ketoconazole were tested at 100, 10 and 20 µg/ml concentrations, respectively. [a]Average of three readings; [b]indicates no activity; *S.a.-Staphylococcus aureus; B.s.-Bacillus subtilis; E.c.- Escherichia coli*; *P.a.- Pseudomonas aeruginosa*; *C. a. - Candida albicans*; *A. n.- Aspergillus niger*

Table 5—Analgesic activity of some selected 2-pyrazoline incorporated2-mercaptobenzothiazoles in mice by tail immersion method

	Analgesic activity, %			
	30 min	1 h	2 h	3 h
Compd.	%Analgesia ±SEM	%Analgesia ±SEM	%Analgesia ±SEM	%Analgesia ±SEM
6d	10.8±0.3[a]	40.9±0.3[b]	29.8±1.0[b]	17.9±0.6[a]
6e	13.5±0.3[a]	19.3±0.2[a]	56.6±0.7[b]	25.8±0.2[b]
6f	12.7±0.6[b]	19.4±0.5[b]	24.6±0.6[a]	12.5±0.9[b]
6h	14.3±0.8[c]	23.4±1.1[b]	34.6±0.4[a]	12.5±0.4[b]
6i	37.4±0.4[a]	40.2±1.2[c]	69.8±1.3[c]	55.9±1.1[b]
6j	19.2±0.8[c]	25.8±0.7[b]	66.2±0.4[a]	58.0±0.9[b]
6m	19.6±0.5[b]	29.4±0.8[b]	32.6±0.7[a]	15.4±0.9[b]
6n	47.5±0.6[c]	58.6±0.9[b]	57.2±0.5[b]	57.9±0.4[a]
6q	15.1±0.7[c]	17.4±0.3[a]	20.3±0.8[c]	8.3±0.6[c]
Paracetamol	29.2±0.6[c]	44.5±0.7[b]	39.9±0.9[b]	26.1±1.1[c]

Test compounds and paracetamol were tested at 100 and 50 mg/kg, respectively; Results are expressed in mean ± SEM (n=6); Significance levels [a]P<0.05, [b]P<0.01 and [c]P<0.001 compared with respective control

at *d* 166.01 and 163.52 ppm, assigned due to azomethine carbon of benzothiazole and pyrazoline rings, respectively. Carbonyl carbon (amide) displayed a signal at *d* 169.18 ppm while C_5 and C_4 carbons of pyrazoline ring exhibited singlet signals at *d* 55.22 and 35.57 ppm, respectively. Signal observed at *d* 64.16 ppm was assigned to CH_2 fragment of acetyl group. Phenyl carbons appeared within expected chemical shift values. Mass spectrum of **6i** showed molecular ion peak at *m/z* 509, and is in agreement with its molecular formula $C_{24}H_{17}ClN_4O_3S_2$.

Antimicrobial screening[9] displayed variable inhibitory effects on the growth of Gram-positive and Gram-negative bacterial strains, while found inactive against strains of fungi (Table 4). Compounds **6h**, **6i**, **6j** and **6n** showed significant inhibitory activity against *Pseudomonas aeruginosa* (inhibition zone 30-35 mm). Maximum inhibitory activity against *P. aeruginosa* (inhibition zone 35 mm) was observed in **6n** having 3-nitrophenyl and phenyl groups respectively at 3rd and 5th position of pyrazoline ring.

Animals were procured from M/S Venkatesh Enterprises, Bangalore, India and were maintained in colony cages at 23±2°C, relative humidity of 45-50%, under 12 h light and dark cycle and fed with standard rat pellet diet (Hindustan Liver Ltd, Mumbai). Prior approval of Local Animal Ethical Committee was obtained to carry out experimental work on animals. Compounds **6d-f**, **6h**, **6i**, **6j**, **6m**, **6n** and **6q** were evaluated for acute toxicity, analgesic and anti-inflammatory activities. Data were statistically analyzed by one-way analysis of variance (ANOVA) followed by Student's *t*-test. Acute oral toxicity was performed for **6d-f**, **6h**, **6i**, **6j**, **6m**, **6n** and **6q** following Organization of Economic Cooperation and Development (OECD-423) guidelines (acute toxic class method). Swiss albino mice (n=3) of either sex (44-55 g) selected by random sampling were used for the study. In present study, mortality was not observed even at 1000 mg/kg, indicating that compounds are nontoxic to animals.

Analgesic activity of synthesized compounds was evaluated by tail immersion method[10] using mice (Table 5). At 1 h, **6n** showed significant activity (58.6% analgesia), while rest of the compounds were found to be weakly or moderately active (17.4-40.9%). Compounds **6i**, **6j** and **6n** exhibited potent analgesic activity (55.9-69.8%) at 2nd and 3rd h after oral administration, when compared to reference drug

Table 6—Anti-inflammatory activity of some selected 2-pyrazoline incorporated 2-mercaptobenzothiazoles by carrageenan induced rat paw oedema method

Compd.	Protection, %			
	30 min % Pretection (Mean % protection ±SEM)	1 h %Protection (Mean % protection ±SEM)	2 h %Protection (Mean % protection ±SEM)	3 h %Protection (Mean % protection ±SEM)
6d	20.5±1.2[b]	31.9±0.6[c]	49.1±0.5[a]	35.7±0.7[b]
6e	35.3±0.8[b]	52.5±0.9[b]	58.4±0.7[c]	53.6±1.1[c]
6f	28.1±0.9[c]	58.0±0.6[b]	48.0±0.5[b]	26.1±0.6[c]
6h	35.0±0.4[b]	70.4±0.7[a]	75.4±0.5[b]	61.2±0.2[a]
6i	43.4±0.6[a]	68.3±0.5[c]	73.7±0.4[b]	65.0±0.6[c]
6j	36.8±0.4[b]	64.4±0.3[b]	72.0±0.7[b]	58.9±0.4[b]
6m	23.4±0.4[c]	45.3±0.8[b]	48.7±0.7[b]	22.3±1.1[c]
6n	46.7±0.7[a]	69.9±0.5[c]	76.9±0.9[b]	69.7±0.6[b]
6q	38.5±0.6[b]	59.3±1.2[c]	61.2±0.5[a]	41.2±0.6[c]
Diclofenac sodium	46.8±1.2[c]	72.3±0.8[b]	72.6±1.1[b]	67.8±0.8[b]

Test compounds and diclofenac sodium were tested at 100 and 20 mg/kg body weight, respectively; Results are expressed in mean ± SEM (n=6); Significance levels [a]P<0.05, [b]P<0.01 and [c]P<0.001 compared with the respective control

Table 7—Ulcerogenic effects of some selected 2-pyrazoline incorporated2-mercaptobenzothiazoles by reported method[12]

Compd.	Control 1% CMC	**6i**	**6j**	**6n**	Diclofenac sodium
Severity Index	0.00±0.2[a]	3.2±0.7[c]	4.0±0.8[b]	2.0±0.3[b]	4.9±0.5[b]

Test compounds and diclofenac sodium were tested at 200 and 20 mg/kg body weight, respectively. Results are expressed in mean ± SEM (n=6); Significance levels [a]P<0.05, [b]P<0.01 and [c]P<0.001 compared with the respective control.

(39.9 and 26.1%, respectively at 50 mg/kg). Moreover, maximum activity (69.8%) was observed at 2nd h in **6i** bearing 4-Cl and 3-NO_2 groups in phenyl rings, respectively at 3rd and 5th position of pyrazoline ring. Acute anti-inflammatory activity results determined using carrageenan-induced paw oedema method[11] in rats (Table 6). At 1 h, **6h-j** and **6n** showed significant protection (64.4-70.4%) against carrageenan induced oedema when compared to reference drug (72.3% at a dose of 20 mg/kg). Whereas at 2nd and 3rd h, same compounds exhibited potent anti-inflammatory activity (58.9-76.9%) and highest activity (76.9%) was observed at 2nd h in **6n**. Compounds **6i**, **6j** and **6n**, evaluated for ulcerogenic potential in rats according to reported method[12], indicated low ulcerogenic activity (2.0±0.3 - 4.0±0.8), whereas standard drug diclofenac sodium showed high severity index of 4.9±0.5. Maximum reduction in ulcerogenic activity was observed in **6i** (3.2±0.7) and **6n** (2.0±0.3). Other tested compounds also exhibited better GI safety profile as compared to standard drug diclofenac sodium (Table 7).

Conclusions

Various 2-mercaptobenzothiazole derivatives were prepared for developing dual acting antimicrobial-anti-inflammatory agents with gastrosparing activity. Derivative 2-(1,3-benzothiazol-2-ylsulfanyl)-1-[3-(3-nitrophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl]

ethanone (**6n**) belonging to sulfanyl series was found to have significant inhibitory activity against Gram-negative bacterial strains. This compound also showed the most prominent and consistent analgesic-anti-inflammatory activity with a significant reduction of gastrointestinal toxicity. Therefore, compound **6n** would represent a fruitful matrix for development of a new class of dual acting antimicrobial-anti-inflammatory agents.

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