Studies on Gastric Antiulcer Active Agents. III. Synthesis of 1-Substituted 4-(5-Tetrazolyl)thio-1-butanones and Related Compounds

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Many 1-substituted 4-(5-tetrazolyl)thio-1-butanones were synthesized and tested for antiulcer activity against acetic acid-induced gastric ulcer in rats. These compounds were prepared by the reaction of 5-mercaptotetrazoles and 4-halogeno-1-butanones. Among them, 1-cyclohexyl-4-(1-phenyl-5-tetrazolyl)thio-1-butanone (VIIIp) was found to have the most potent activity. The structure–activity relationships are discussed.

Keywords 1-substituted 4-(5-tetrazolyl)thio-1-butanone; antiulcer activity; structure–activity relationship; 1-cyclohexyl-4-(1-phenyl-5-tetrazolyl)thio-1-butanone

In the preceding paper,[1] we reported that tetrazole alkanamides showed potent antiulcer activity against acetic acid-induced gastric ulcer in rats, as a model of chronic ulcer. As a continuation of our search for much more active compounds, we report here the synthesis and testing of tetrazoles having a butanone group in their side chain. 1-Cyclohexyl-4-(1-phenyl-5-tetrazolyl)thio-1-butanone (VIIIp) was found to have very potent antiulcer activity. This paper deals with the synthesis, antiulcer activity and structure–activity relationships of 1-substituted 4-(5-tetrazolyl)thio-1-butanones.

Synthesis 1-Substituted 4-halogeno-1-butanones (VI) which are versatile key intermediates in the synthesis of the tetrazolylthiobutanones (VIII), were synthesized by three methods as illustrated in Chart 1.

First, 1-aryl-4-chloro-1-butanones (VIa—h) were prepared by the Friedel–Crafts reaction of aromatic compounds (Ia—h) with 4-chlorobutyryl chloride using aluminum chloride (method A). Secondly, Claisen condensation[2] of the ester derivatives (IIIa—c) with γ-butyrolactone in the presence of sodium alkoxide afforded the corresponding α-acyl-γ-butyrolactones (IVa—c), which were heated in hydrobromic acid or hydrochloric acid to give 1-substituted 4-halogeno-1-butanones (VIi—k) (method B). Finally, 1-substituted 4-chloro-1-butanones (VIl—n) were synthesized by the reaction[3] of Grignard reagents (Va—c) and 4-chlorobutyryl chloride in the presence of ferric chloride (method C). 4-Bromo-1-cyclohexyl-1-butanone (VIi) was also synthesized by method C, but this method did not give a satisfactory yield.

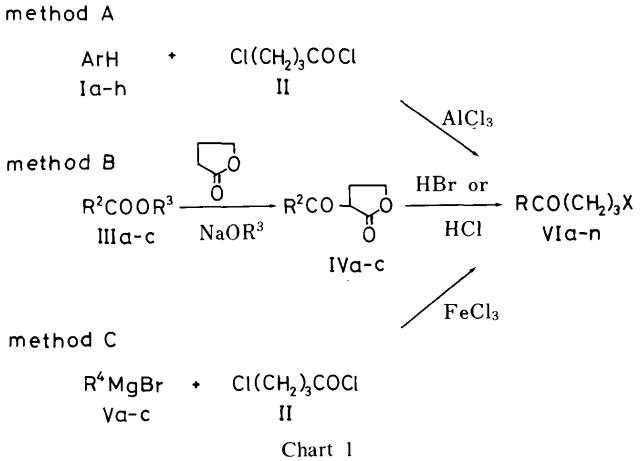


Chart 1

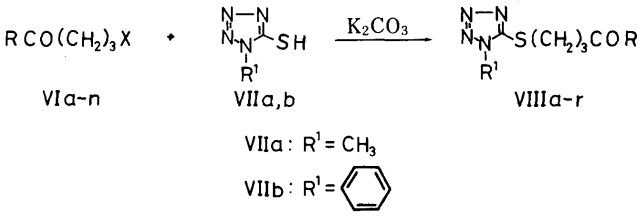


Chart 2

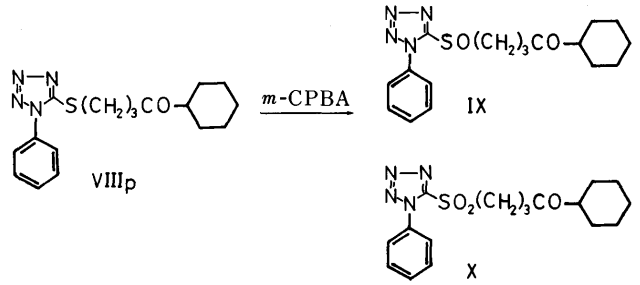


Chart 3

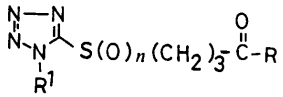
Condensation of 1-methyl-5-mercaptotetrazole (VIIa) or 1-phenyl-5-mercaptotetrazole (VIIb) with 1-substituted 4-halogeno-1-butanones (VIa—n) in the presence of potassium carbonate afforded the corresponding 1-substituted 4-(5-tetrazolyl)thio-1-butanones (VIIIa—r) in good yield (Chart 2, Table I). Oxidation of VIIIp with *m*-chloroperbenzoic acid (*m*-CPBA) gave the sulfinyl and sulfonyl compounds (IX, X) (Chart 3).

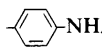
Structure–Activity Relationships The antiulcer activities of synthesized compounds against acetic acid-induced gastric ulcer are summarized in Table I. The structure–activity relationships are discussed below.

First, the effect of the substituent (R) of 1-butanone -$S(CH_2)_3CO$-R was examined; it was found that phenyl and cyclohexyl derivatives (VIIIa, p) showed high potency and benzyl and cyclopentyl derivatives (VIIIn, r) were less active. As regards the other aromatic ring, naphthyl and furyl compounds (VIIIo, h) showed high activity. The compounds substituted on the phenyl ring were less active than the non-substituted compound (VIIIa).

Next, when the effect of the substituent on the tetrazole

TABLE I. 1-Substituted 1-[4-(5-Tetrazolyl)thio]butanones



Compd. No.	R^1	R	n	Yield (%)	Activity[a]	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
VIIIa	CH_3		0	64	33.7	Colorless needles ($MeOH-H_2O$)	57.5—58	$C_{12}H_{14}N_4OS$	54.94 (54.81)	5.38 5.39	21.38 21.59)
VIIIb	CH_3		0	58	12.4	Colorless flakes (AcOEt–hexane)	107—108	$C_{13}H_{16}N_4O_2S$	53.41 (53.21	5.52 5.47	19.16 19.46)
VIIIc	CH_3		0	59	23.2	Colorless needles (Et_2O–hexane)	68—69	$C_{14}H_{18}N_4OS$	57.91 (57.68	6.25 6.20	19.90 19.41)
VIIId	CH_3		0	24	18.5	Colorless prisms ($MeOH-H_2O$)	139—140	$C_{12}H_{13}ClN_4OS$	48.56 (48.07	4.41 4.43	18.88 18.91)
VIIIe	CH_3		0	63	28.4	Colorless needles (EtOH)	170—172	$C_{14}H_{17}N_5O_2S$	52.65 (52.78	5.37 5.46	21.93 21.53)
VIIIf	CH_3		0	62	28.7	Colorless prisms (AcOEt–hexane)	86—87	$C_{14}H_{18}N_4O_3S$	52.16 (51.88	5.63 5.52	17.38 17.36)
VIIIg	CH_3		0	20	15.3	Colorless needles (Et_2O–hexane)	73—75	$C_{11}H_{13}N_5OS$	50.17 (50.12	4.97 4.97	26.60 26.90)
VIIIh	CH_3		0	32	36.6	Colorless needles (Et_2O–hexane)	41—42	$C_{10}H_{12}N_4O_2S$	47.61 (47.40	4.80 4.73	22.21 22.48)
VIIIi	CH_3		0	48	16.7	Colorless needles (Et_2O–hexane)	55—56	$C_{10}H_{12}N_4OS_2$	44.76 (44.65	4.51 4.56	20.88 20.59)
VIIIj	CH_3		0	55	15.1	Pale yellow prisms (AcOEt–hexane)	94—96	$C_{10}H_{12}N_5OS$	47.99 (47.76	4.80 5.28	27.98 28.05)
VIIIk	CH_3		0	50	11.2	Colorless needles (Et_2O–hexane)	64—65	$C_{10}H_{13}N_5OS_2$	42.38 (42.21	4.62 4.56	24.71 24.96)
VIIIl	CH_3	CH_3	0	40	11.6	Colorless oil		$C_7H_{12}N_4OS$	200.0732[b] (200.0791)		
VIIIm	CH_3		0	58	33.1	Colorless oil		$C_{12}H_{20}N_4OS$	268.1358[b] (268.1396)		
VIIIn	CH_3		0	55	21.0	Colorless oil		$C_{13}H_{16}N_4OS$	276.1045[b] (276.1054)		
VIIIo	CH_3		0	50	38.1	Colorless prisms (EtOH)	118—120	$C_{16}H_{16}N_4OS$	61.52 (61.75	5.16 5.15	17.94 18.09)
VIIIp			0	43	38.7	Colorless granules ($MeOH-H_2O$)	57.5—58.5	$C_{17}H_{22}N_4OS$	61.79 (62.13	6.71 6.71	16.96 16.98)
VIIIq			0	15	15.4	Colorless granules ($MeOH-H_2O$)	71—72	$C_{17}H_{16}N_4OS$	62.94 (62.76	4.97 5.04	17.27 17.32)
VIIIr			0	30	26.4	White powder ($MeOH-H_2O$)	56.5—57.5	$C_{16}H_{20}N_4OS$	60.73 (60.78	6.37 6.15	17.71 17.79)
IX			1	78	10.2	Colorless oil		$C_{17}H_{22}N_4O_2S$	330.1514[b] (330.1457)		
X			2	64	16.2	Colorless needles (MeOH)	68.5—69.5	$C_{17}H_{22}N_4O_3S$	56.34 (56.19	6.12 6.09	15.46 15.46)

a) Results are given as healing ratio (%) of acetic acid-induced gastric ulcer in rats 10 mg/kg/d × 2 *p.o.* For comparison purposes: cimetidine healing ratio at 100 mg/kg/d × 2 *p.o.*, 24.0%; sucralfate healing ratio at 1 g/kg/d × 2 *p.o.*, 34.5%. *b*) Determined by high-resolution mass spectrometry. Upper figure, calculated for M^+ (IX; $M^+ - 16$) and lower figure, found.

at the 1-position was compared, the phenyl group (VIIIp) was as effective as the methyl group (VIIIm). But compound VIIIq, having the 1-phenyl-1-butanone structure, showed decreased activity. The effect of the linking group between the nucleus and side chain was also examined, and sulfinyl and sulfonyl derivatives (IX, X) were less active than the sulfur derivative (VIIIp). Thus, the sulfur group is essential for potent activity.

Among the compounds listed in Table I, VIIIa, h, m, o, p, especially 1-cyclohexyl-4-(1-phenyl-5-tetrazolyl)thio-1-butanone (VIIIp, OPC-12182), showed good antiulcer activity. Compound VIIIp therefore seems worthy of further pharmacological evaluation as a new type of antiulcer agent.

Experimental

All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on Varian EM-390 and Bruker AC-200 NMR spectrometers in $CDCl_3$. Chemical shifts are given in ppm with tetramethylsilane as an internal standard. Infrared (IR) spectra were taken on a JASCO IRA-2 spectrometer. Mass spectra (MS) were obtained on a Varian MAT-312 instrument.

Preparation of 1-Substituted 4-Halogeno-1-butanones (VIa—n), Method

A $AlCl_3$ (0.45 mol) was added in small portions to a stirred solution of Ia—h (0.15 mol) and 4-chlorobutyryl chloride (0.27 mol) in carbon disulfide (110 ml) at room temperature, and the mixture was stirred at 40—50 °C for 30 min, then poured into ice-water. The resulting precipitate was collected by filtration and recrystallized from a suitable solvent. The oily compounds were purified by column chromatography. The following compounds were synthesized.

4-(Chloro-1-(4-methoxyphenyl)-1-butanone (VIa): Yield 95%, colorless flakes (from AcOEt–petroleum ether), mp 31 °C. NMR δ: 1.90—2.40 (2H, m), 3.06 (2H, t, J=7 Hz), 3.59 (2H, t, J=6 Hz), 3.78 (3H, s), 6.81 (2H, d, J=8 Hz), 7.80 (2H, d, J=8 Hz). IR ν(KBr): 1670, 1595, 1250, 1170 cm^{-1}. *Anal.* Calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16. Found: C, 61.82; H, 6.12.

4-Chloro-1-(4-ethylphenyl)-1-butanone (VIb): Yield 81%, a pale yellow oil, bp 141—148 °C (0.9 mmHg). NMR δ: 1.23 (3H, t, J=7 Hz), 1.90—2.90 (4H, m), 3.13 (2H, t, J=7 Hz), 3.62 (2H, t, J=6 Hz), 7.18 (2H, d, J=8 Hz), 7.85 (2H, d, J=8 Hz). IR ν(neat): 1675, 1600, 1410, 1230, 1180 cm^{-1}. MS *m/z*: 79 (9%), 105 (13), 133 (100), 134 (11), 148 (20), 181 (8), 210 (M^+, 0.4), 211 (2).

4-Chloro-1-(4-chlorophenyl)-1-butanone (VIc): Yield 24%, a pale yellow oil. NMR δ: 2.20—3.30 (4H, m), 3.57 (2H, t, J=7 Hz), 6.90—7.50 (4H, m). IR ν(KBr): 1680, 1580, 1395, 1220, 1090, 810 cm^{-1}. MS *m/z*: 75 (27%), 111 (28), 139 (100), 141 (33), 154 (28), 156 (9), 181 (6), 217 (M^+, 4).

1-(4-Acetylaminophenyl)-4-chloro-1-butanone (VId): Yield 28%, colorless granules (from EtOH), mp 157—163 °C. NMR δ (DMSO-d_6): 1.90—2.30 (2H, m), 2.10 (3H, s), 3.05 (2H, m), 3.60 (2H, t, J=6 Hz), 7.56 (2H, d, J=8 Hz), 7.75 (2H, d, J=8 Hz), 9.90 (1H, br s). IR ν (KBr): 3300, 3250, 1680, 1670, 1590, 1540, 1230, 830 cm^{-1}. *Anal.* Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 59.94; H, 5.82; N, 5.79.

4-Chloro-1-(3,4-dimethoxyphenyl)-1-butanone (VIe): Yield 53%, pale yellow prisms (from ligroin), mp 90—92 °C. NMR δ: 1.90—2.40 (2H, m), 3.07 (2H, t, J=7 Hz), 3.58 (2H, t, J=6 Hz), 3.87 (6H, s), 6.68 (1H, d, J=8 Hz), 7.43 (1H, d, J=2 Hz), 7.48 (1H, dd, J=8, 2 Hz). IR ν (KBr): 1670, 1590, 1510, 1270, 1210, 1120, 1010, 780 cm^{-1}. *Anal.* Calcd for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.23. Found: C, 59.32; H, 6.09.

4-Chloro-1-(2-furyl)-1-butanone (VIf): Yield 23%, a pale yellow oil. NMR δ: 1.90—2.40 (2H, m), 3.01 (2H, t, J=7 Hz), 3.62 (2H, t, J=6 Hz), 6.47 (1H, dd, J=4, 2 Hz), 7.13 (1H, d, J=4 Hz), 7.59 (1H, d, J=2 Hz). IR ν (neat): 1670, 1570, 1470, 760 cm^{-1}. MS *m/z*: 41 (18%), 95 (100), 110 (79), 173 (M^+, 2).

4-Chloro-1-(2-naphthyl)-1-butanone (VIg): Yield 18%, colorless flakes (from hexane–petroleum ether), mp 43—44 °C. NMR δ: 2.00—2.50 (2H, m), 3.23 (2H, t, J=7 Hz), 3.65 (2H, t, J=6 Hz), 7.30—8.40 (7H, m). IR ν (KBr): 1670, 1615, 1310, 1170, 820, 750 cm^{-1}. *Anal.* Calcd for $C_{14}H_{13}ClO$: C, 72.26; H, 5.63. Found: C, 72.16; H, 5.69.

4-Chloro-1-(2-pyrrolyl)-1-butanone (VIh): Yield 3%, colorless needles (from AcOEt–petroleum ether), mp 69.5—71.5 °C. NMR δ: 1.90—2.60 (2H, m), 2.98 (2H, t, J=7 Hz), 3.63 (2H, t, J=6 Hz), 6.20—6.40 (1H, m), 6.80—7.20 (2H, m). IR ν (neat): 3280, 1630, 1390, 1105 cm^{-1}. *Anal.* Calcd for $C_8H_{10}ClNO$: C, 55.99; H, 5.87; N, 8.16. Found: C, 55.97; H, 5.84; N, 8.13.

Preparation of IVa—c, Method B α-Cyclohexylcarbonyl-γ-butyrolactone (IVa): Sodium ethoxide (2.4 kg, 35.2 mol) was added to a mixture of methyl cyclohexane carboxylate (2.0 kg, 14.1 mol) and γ-butyrolactone (1.8 kg, 21.1 mol) in dioxane (8.0 l) and dimethyl sulfoxide (DMSO) (1.2 l). The mixture was heated at 100 °C for 6.5 h, then ice-water and acetic acid were added under chilling and the whole was extracted with CH_2Cl_2. The extract was washed with water, $NaHCO_3$ aqueous solution and saturated NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was distilled *in vacuo* to give IVa (1.97 kg, 71%) as a colorless oil, bp 154—168 °C (7 mmHg). NMR δ: 1.05—2.10 (10H, m), 2.10—3.00 (3H, m), 3.81 (1H, dd, J=6, 9 Hz), 4.30 (2H, m). IR ν (neat): 1770, 1715, 1380, 1170 cm^{-1}. MS *m/z*: 55 (40%), 83 (100), 86 (44), 111 (30), 113 (8), 196 (M^+, 4). The following compounds were synthesized by the same procedure as described for IVa.

α-[(2-Pyridinyl)carbonyl]-γ-butyrolactone (IVb): Yield 33%, a pale yellow oil. NMR δ: 2.50—3.00 (2H, m), 4.30—4.80 (2H, m), 5.13 (1H, dd, J=8.5, 8 Hz), 7.20—8.10 (3H, m), 8.50—8.70 (1H, m). IR ν (neat): 1760, 1690, 1580, 1370, 1250, 1230, 1160, 1020, 990 cm^{-1}. MS *m/z*: 41 (67%), 51

TABLE II. Spectral Data for 1-Substituted [4-(5-Tetrazolyl)thio]butanones

Compd. No.	IR $\nu^{a)}$ cm^{-1} (C=O)	^{1}H-NMR δ ($CDCl_3$), (J, Hz)
VIIIa	1675	2.10—2.50 (2H, m), 3.15 (2H, t, J=6), 3.47 (2H, t, J=7.5), 3.90 (3H, s), 7.30—7.70 (3H, m), 7.80—8.10 (2H, m)
VIIIb	1665	2.00—2.40 (2H, m), 3.10 (2H, t, J=6.5), 3.40 (2H, t, J=7.5), 3.82 (3H, s), 3.85 (3H, s), 6.88 (2H, d, J=9), 7.88 (2H, d, J=9)
VIIIc	1670	1.24 (3H, t, J=6.5), 2.10—2.50 (2H, m), 2.71 (2H, q, J=6.5), 3.13 (2H, t, J=6.5), 3.43 (2H, t, J=6.5), 3.88 (3H, s), 7.27 (2H, d, J=9), 7.87 (2H, d, J=9)
VIIId	1670	2.10—2.50 (2H, m), 3.13 (2H, t, J=6.5), 3.44 (2H, t, J=6.5), 3.90 (3H, s), 7.43 (2H, d, J=9), 7.88 (2H, d, J=9)
VIIIe	1695 1680	1.90—2.30 (2H, m), 2.12 (3H, s), 3.14 (2H, t, J=6), 3.40 (2H, t, J=6), 3.93 (3H, s), 7.73 (2H, d, J=9), 7.92 (2H, d, J=9), 10.20 (1H, br s)[b]
VIIIf	1665	2.10—2.50 (2H, m), 3.12 (2H, t, J=7.5), 3.44 (2H, t, J=7.5), 3.90 (3H, s), 3.92 (6H, s), 6.88 (1H, d, J=6.5), 7.50 (1H, d, J=2), 7.56 (1H, dd, J=7.5, 2)
VIIIg	1700	2.00—2.50 (2H, m), 3.39 (2H, t, J=6), 3.48 (2H, t, J=6), 3.89 (3H, s), 7.30—8.10 (3H, m), 8.50—8.70 (1H, m)
VIIIh	1675	2.00—2.50 (2H, m), 3.02 (2H, t, J=6), 3.42 (2H, t, J=6), 3.90 (3H, s), 6.53 (1H, dd, J=4.5, 1.5), 7.21 (1H, d, J=4.5), 7.58 (1H, d, J=1.5)
VIIIi	1650	2.10—2.50 (2H, m), 3.09 (2H, t, J=6), 3.43 (2H, t, J=6), 3.88 (3H, s), 7.13 (1H, dd, J=4.5, 4.5), 7.63 (1H, d, J=4.5), 7.72 (1H, d, J=4.5)
VIIIj	1645	2.00—2.50 (2H, m), 2.96 (2H, t, J=6), 3.43 (2H, t, J=6), 3.87 (3H, s), 6.20—6.40 (1H, m), 6.80—7.20 (2H, m), 10.10 (1H, br s)
VIIIk	1670	2.20—2.50 (2H, m), 2.75 (3H, s), 3.03 (2H, t, J=6), 3.43 (2H, t, J=6), 3.89 (3H, s), 8.75 (1H, s)
VIIIl	1710	1.90—2.30 (2H, m), 2.18 (3H, s), 2.68 (2H, t, J=6), 3.40 (2H, t, J=7.5), 3.98 (3H, s)
VIIIm	1705	1.00—2.50 (13H, m), 2.63 (2H, t, J=6), 3.33 (2H, t, J=7), 3.90 (3H, s)
VIIIn	1710	1.80—2.20 (2H, m), 2.62 (2H, t, J=7), 3.26 (2H, t, J=6), 3.67 (2H, s), 3.82 (3H, s), 7.10—7.40 (5H, m)
VIIIo	1680	2.10—2.50 (2H, m), 3.25 (2H, t, J=7.5), 3.45 (2H, t, J=7.5), 3.85 (3H, s), 7.50—8.50 (7H, m)
VIIIp	1710	1.20—2.50 (13H, m), 2.61 (2H, t, J=6), 3.38 (2H, t, J=6), 7.57 (5H, s)
VIIIq	1670	2.10—2.50 (2H, m), 3.17 (2H, t, J=6), 3.50 (2H, t, J=7), 7.30—7.65 (3H, m), 7.55 (5H, s), 7.93 (2H, d, J=8)
VIIIr	1710	1.40—2.30 (10H, m), 2.57 (2H, t, J=6), 2.50—2.90 (1H, m), 3.33 (2H, t, J=6), 7.45 (5H, s)
IX	1710	1.00—1.90 (10H, m), 2.05 (2H, m), 2.21 (1H, m), 2.62 (2H, t, J=6), 3.50 (2H, t, J=6), 7.52 (5H, m)
X	1700	1.00—2.00 (10H, m), 2.15 (2H, m), 2.25 (1H, m), 2.63 (2H, t, J=6), 3.68 (2H, t, J=6), 7.52 (5H, m)

a) The spectra of VIIIa—k, o, p and X were taken in KBr. The spectra of VIIIl—m and IX were taken neat. *b*) In $CDCl_3$+DMSO-d_6. MS *m/z*: VIIIl, 45 (100%), 85 (23), 143 (30), 201 (M^+, 9); VIIIm, 41 (100), 83 (73), 268 (M^+, 2), 269 (17); VIIIn, 69 (100), 91 (51), 160 (26), 185 (19), 276 (M^+, 2), 277 (13), IX, 83 (64), 118 (31), 153 (100), 329 (30), 347 (M^++1, 7); X, 41 (55), 55 (71), 65 (23), 83 (100), 363 (M^++1, 7).

(58), 78 (99), 79 (100), 96 (26), 106 (22), 118 (25), 145 (24), 154 (24), 191 (M^+, 11).

α-[(4-Methyl-5-thiazolyl)carbonyl]-γ-butyrolactone (IVc)[4]: Yield 41%, a pale yellow oil. NMR δ: 2.30—3.10 (2H, m), 2.78 (3H, s), 4.10—4.70 (3H, m), 8.87 (1H, s). IR ν (neat): 1760, 1660, 1490, 1360, 1310, 1150, 1020 cm^{-1}. MS *m/z*: 45 (42%), 99 (37), 126 (100), 211 (M^+, 14).

4-Bromo-1-cyclohexyl-1-butanone (VIi): A mixture of IVa (1.97 kg, 10 mol) and HBr (10 l) was refluxed for 6 h. After being cooled, the reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water, $NaHCO_3$ aqueous solution and saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled *in vacuo* to give VIi (2.15 kg, 92%) as a colorless oil, bp 112—118 °C (1 mmHg). NMR δ: 0.80—2.30 (13H, m), 2.45 (2H, t, J=6 Hz), 3.57 (2H, t, J=6 Hz). IR ν (neat): 1700, 1450, 1370 cm^{-1}. MS *m/z*: 41 (80%), 55 (45), 83 (35), 111 (100), 158 (75), 233 (M^+, 41), 234 (10), 235 (39). The following compounds were synthesized by the same procedure as described for VIi.

4-Chloro-1-(2-pyridinyl)-1-butanone (VIj)[2]: Yield 53%, a pale yellow oil. NMR δ: 2.00—2.60 (2H, m), 3.38 (2H, t, J=7 Hz), 3.65 (2H, t, J=6 Hz), 7.20—8.10 (3H, m), 8.50—8.70 (1H, m). IR ν (neat): 1690, 1580, 1430, 1320, 1220, 990, 750 cm^{-1}. MS *m/z*: 41 (55%), 51 (54), 78 (100), 79 (37), 106 (48), 134 (40), 148 (79), 184 (M^++1, 9).

4-Bromo-1-(4-methyl-5-thiazolyl)-1-butanone Hydrochloride (VIk): Yield 13%, brown powder (from EtOH), mp 175—178 °C. NMR δ: 2.00—2.50 (2H, m), 2.75 (3H, s), 3.04 (2H, t, J=6 Hz), 3.51 (2H, t, J=6 Hz), 8.73 (1H, s). IR ν (KBr): 2450, 1680, 1580, 1230, 865, 695 cm^{-1}. *Anal.* Calcd for $C_8H_{10}BrNOS \cdot HCl \cdot H_2O$: C, 33.56; H, 5.28; N, 4.86. Found: C, 33.56; H, 5.08; N, 4.86.

Preparation of VIl—n, Method C A Grignard reagent was prepared from an alkyl bromide (Va—c, 0.1 mol) and magnesium (0.11 mol) in dry Et_2O (60 ml). The solution of the Gringnard reagent was added to a stirred and cooled solution of 4-chlorobutyryl chloride (0.2 mol) and ferric chloride (3 mmol) in dry Et_2O (80 ml). After being stirred for 1 h at the same temperature, the reaction mixture was poured into ice and ammonium chloride solution, neutralized with K_2CO_3 and extracted with Et_2O. The ether solution was washed with 5% NaOH solution and saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled. The following compounds were synthesized.

1-Butyl-4-chloro-1-butanone (VIl): Yield 37%, a colorless oil, bp 104—106 °C (30 mmHg). NMR δ: 0.91 (3H, t, J=5 Hz), 1.00—2.70 (10H, m), 3.57 (2H, t, J=6 Hz). IR ν (neat): 1710, 1410, 1370, 650 cm^{-1}. MS *m/z*: 41 (100%), 57 (62), 58 (52), 85 (51), 105 (27), 163 (M^+, 9).

4-Chloro-1-cyclopentyl-1-butanone (VIm): Yield 28%, a colorless oil, 92—110 °C (2 mmHg). NMR δ: 0.90—2.20 (11H, m), 2.58 (2H, t, J=4.5 Hz), 3.60 (2H, t, J=6 Hz). IR ν (neat): 2950, 2860, 1710, 1440, 1370, 650 cm^{-1}. MS *m/z*: 41 (100%), 60 (21), 69 (82), 97 (27), 105 (38), 174 (M^+, 3).

1-Benzyl-4-chloro-1-butanone (VIn): Yield 52%, a colorless oil, bp 108—119 °C (0.15 mmHg). NMR δ: 1.70—2.20 (2H, m), 2.58 (2H, t, J=6 Hz), 3.47 (2H, t, J=6 Hz), 3.66 (2H, s), 7.22 (5H, br s). IR ν (neat): 1710, 1450, 730, 690 cm^{-1}. MS *m/z*: 41 (61%), 77 (29), 91 (85), 105 (100), 107 (32), 182 (8), 196 (M^+, 3).

Preparation of VIIIa—r 1-Cyclohexyl-4-(1-phenyl-5-tetrazolyl)thio-1-butanone (VIIIp): A mixture of 1-phenyl-5-mercaptotetrazole (126 g, 0.71 mol), VIi (150 g, 0.64 mol) and K_2CO_3 (107 g, 0.78 mol) in acetone (2 l) was refluxed for 3 h. After the removal of acetone, the residue was poured into water and extracted with $CHCl_3$. The extract was washed with 5% NaOH solution and saturated NaCl solution, and dried over $MgSO_4$. After removal of the solvent, the residue was triturated in Et_2O. The precipitates were collected by filtration. Recrystallization from MeOH–H_2O gave VIIIp (100 g, 50%) as colorless granules, mp 57.5—58.5 °C. IR ν (KBr): 1710, 1490, 1390, 770 cm^{-1}. The elemental analysis and spectra data are shown in Tables I and II.

Compounds VIIIa—o and VIIIq, r were obtained by the same procedure as described for VIIIp; the yields, melting points, NMR and elemental analyses data are given in Tables I and II.

Preparation of 1-Cyclohexyl-4-(1-phenyl-5-tetrazolyl)sulfinyl-1-butanone (IX) A solution of *m*-CPBA (80%, 1.9 g, 11 mmol) in CH_2Cl_2 (40 ml) was added dropwise to a stirred and ice-cooled solution of VIIIp (3.3 g, 10 mmol) in CH_2Cl_2 (60 ml). The reaction mixture was stirred at room temperature for 3 h. The mixture was washed with $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, hexane–AcOEt=2:1) to give IX (2.7 g, 78%) as a colorless oil. IR ν (neat): 1710, 1600, 1500, 1555, 1070 cm^{-1}. The spectral data are given in Table II.

Preparation of 1-Cyclohexyl-4-(1-phenyl-5-tetrazolyl)sulfonyl-1-butanone (X) A solution of *m*-CPBA (4.0 g, 22 mmol) in CH_2Cl_2 (100 ml) was added dropwise to a solution of VIIIp (3.3 g, 10 mmol) in CH_2Cl_2 (70 ml). The reaction mixture was stirred at room temperature for 4 h, then refluxed for 3 h. The CH_2Cl_2 solution was washed with $NaHCO_3$ solution and saturated NaCl solution, and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from MeOH to give X (2.3 g, 64%) as colorless needles, mp 68.5—69.5 °C. IR ν (KBr): 1700, 1590, 1335, 1320, 1150, 780 cm^{-1}. The elemental analysis and spectral data are given in Tables I and II.

Biological Method[5] Gastric ulcer was induced by administration of 30% acetic acid. Sixteen rats were used in each test group. Animals were dosed orally with a suspension of test compound (10 mg/kg) in 0.5% carboxymethylcellulose sodium salt (CMC) solution twice daily for a total of 8 d. Animals were sacrificed at 9 d after ulcer induction. The area of gastric ulcer was measured and used as ulcer index. Healing ratio was calculated by applying the following formula:

$$\text{healing ratio (\%)} = \frac{\text{ulcer index of control group} - \text{ulcer index of drug-treated group}}{\text{ulcer index of control group}} \times 100$$

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