Indian Journal of Chemistry
Vol. 49B, December 2010, pp. 1642-1647

Synthesis and biological screening of novel derivatives of 3-(N-substituted carboxamidoethylthio)-(4*H*)-1,2,4-triazoles

Anil M Manikrao*[a], Ravindra A Fursule[b], K S Rajesh[a], Harish K Kunjwani[a] & Prafulla M Sabale[c]

[a]Department of Pharmaceutical Chemistry, Parul Institute of Pharmacy, Limda, Vadodara 391 760, India
[b]Department of Pharmaceutical Chemistry, H. R. Patel Women's College of Pharmacy, Shirpur, Dhule 425 405, India
[c]Pharmacy Department, Faculty of Technology and Engineering, The M. S. University of Baroda, Vadodara 390 001, India

E-mail: anilmanikrao@rediffmail.com

Received 8 April 2009; accepted (revised) 19 April 2010

3-Mercapto-(4*H*)-1,2,4-triazole has been synthesized from 1-formylthiosemicarbazide. Different N-substituted β-chloropropionamides have been prepared by reacting substituted amines with β-chloropropionylchloride. Different N-substituted β-chloropropionamides have been condensed with 3-mercapto-(4*H*)-1,2,4-triazole in basic medium to obtain various 3-(N-substituted carboxamidoethylthio)-(4*H*)-1,2,4-triazoles. The structure of the synthesized compounds are confirmed by IR, ^{1}H NMR spectra and elemental analysis. All the compounds have been screened for their analgesic, anti-inflammatory and anxiolytic activity.

Keywords: 1-Formylthiosemicarbazide, 1,2,4-triazole, analgesic, anti-inflammatory, anxiolytic

1,2,4-Triazoline-5-thione and their derivatives constitute an important class of organic compounds with diverse biological activities such as tuberculostatic[1-6], anlagesic[7], anti-inflammatory[8-10], antimicrobial[11-17] and can also be used as herbicides[18] or fungicides[19]. It has been well established that introduction of 4-methylmercaptophenyl and 4-methylsulphonyl group to different heterocycles yielded many biologically active compounds endowed with wide spectrum of pharmacological and antimicrobial activities[20,21].

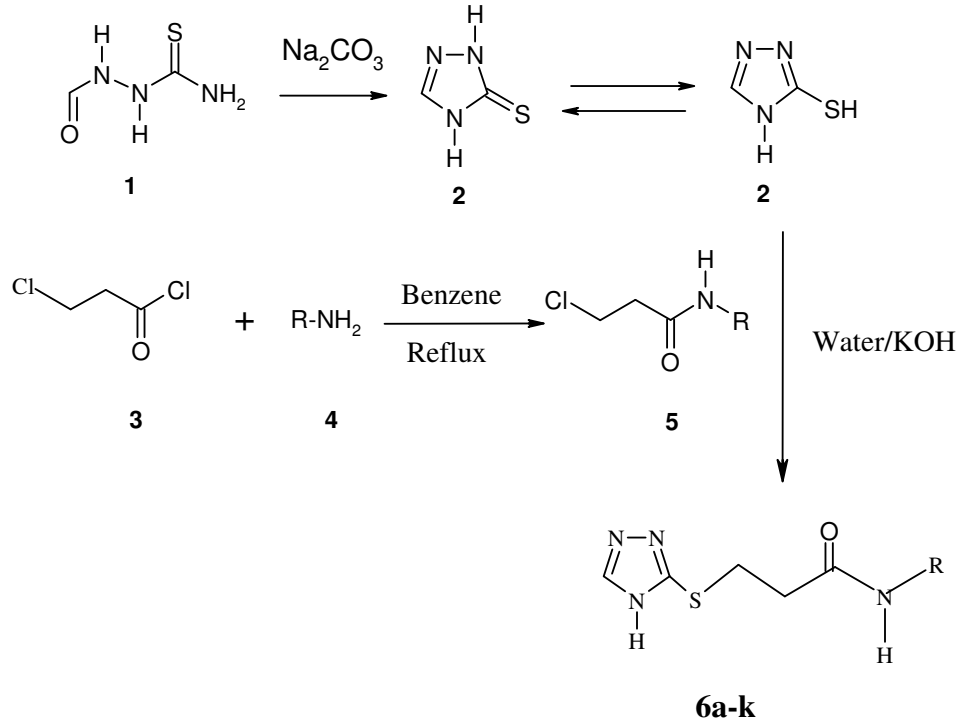
Herein is reported the synthesis of some derivatives of the title structure type containing N-substituted carboxamidoethylthio moiety in an attempt to significantly improve biological spectrum of triazole. All the novel compounds were evaluated for their analgesic, anti-inflammatory and anxiolytic activities.

Results and Discussion

3-Mercapto-(4*H*)-1,2,4-triazole **2** was synthesized by cyclization of 1-formylthio semicarbazide **1** as the essential pharmacophore for targeted compounds. Various N-substituted β-chloropropionamides **5** were synthesized using an appropriate method given in the literature[22] by condensing different amines **4** using β-chloropropionylchloride **3** as acylating agent. These compounds were characterized by TLC, melting point and IR spectra that showed characteristic absorption bands at 3250 and 1650 cm^{-1} of N-H and C=O respectively. The different N-substituted β-chloropropionamides **5** were condensed with triazole pharmacophore **2** to obtain various 3-(N-substituted carboxamidoethylthio)-(4*H*)-1,2,4-triazole derivatives **6 (Scheme I, Table I)**. The infrared spectra of the 3-mercapto-(4*H*)-1,2,4-triazole showed one characteristic absorption band at 2585 cm^{-1} attributed to SH, which disappeared by the formation of 3-(N-substituted carboxamidoethylthio)-(4*H*)-1,2,4-triazoles. Similarly the ^{1}H NMR spectra of the synthesized triazole showed one characteristic signal at δ 13.8-13.95, which was absent in the ^{1}H NMR spectra of substituted triazoles. The absence of these absorptions due to SH established that the triazoles were converted to 3-(N-substituted carboxamidoethylthio)-(4*H*)-1,2,4-triazoles by reacting with N-substituted β-chloropropionamides. The structure of the various synthesized compounds was established by IR, ^{1}H NMR and elemental analysis.

Data of anti-inflammatory activity was expressed as mean ±SEM, and the student's t-test was applied to determine the significance of the difference between the control group and rats treated with the test compounds. The anti-inflammatory activity of the newly synthesized compounds **6a-k** was compared

* Present address: Sahyadri College of Pharmacy, Methwade, Sangola, Solapur 413 307, India



Scheme I

Table I — Physico-chemical data of synthesized compounds

Compd	R	Mol.Wt.	Mol. formula	Yield %	m.p. ºC	Elemental analysis Found % (Calcd)		
						C	H	N
6a	C_6H_5	248.3	$C_{11}H_{12}N_4OS$	30	110-12	53.12	4.85	22.50
						(53.21	4.87	22.56)
6b	*p*-Cl-C_6H_4	282.75	$C_{11}H_{11}ClN_4OS$	32	97-99	46.65	3.85	19.85
						(46.73	3.92	19.81)
6c	*p*-NO_2-C_6H_4	293.3	$C_{11}H_{11}N_5O_3S$	28	142-45	45.10	3.73	23.48
						(45.05	3.78	23.88)
6d	*m*-Cl-C_6H_4	282.75	$C_{11}H_{11}ClN_4OS$	35	108-10	46.68	3.80	20.05
						(46.73	3.92	19.81)
6e	*m*-NO_2-C_6H_4	293.31	$C_{11}H_{11}N_5O_3S$	31	96-98	45.10	3.58	23.60
						(45.05	3.78	23.88)
6f	*o*-CH_3-C_6H_4	262.34	$C_{12}H_{14}N_4OS$	24	94-97	54.65	5.22	21.15
						(54.94	5.38	21.36)
6g	*p*-CH_3-C_6H_4	262.34	$C_{12}H_{14}N_4OS$	27	116-18	54.80	5.20	21.54
						(54.94	5.38	21.36)
6h	*o*-NO_2-C_6H_4	293.31	$C_{11}H_{11}N_5O_3S$	29	188-90	45.22	3.55	23.98
						(45.05	3.78	23.88)
6i	*p*-OCH_3-C_6H_4	278.33	$C_{12}H_{14}N_4O_2S$	32	178-80	51.59	5.30	20.35
						(51.78	5.07	20.13)
6j	$CH_2C_6H_5$	262.34	$C_{12}H_{14}N_4OS$	45	108-10	54.60	5.44	21.55
						(54.94	5.38	21.36)
6k	*o*-Cl-C_6H_4	282.75	$C_{11}H_{11}ClN_4OS$	33	90-93	46.71	3.82	20.05
						(46.73	3.92	19.81)

with the standard, showing 23.14% inhibition of rat paw edema whereas the tested compounds showed inhibition ranging from 25.94-44.44% after 90 min. The compound **6a** showed equipotent activity compared to standard drug, whereas the incorporation of chloro, nitro, methyl and methoxy groups into phenyl ring and replacement of phenyl nucleus by benzyl enhanced the anti-inflammatory activity considerably. Among these triazole derivatives **6b** and **6d** showed the maximum anti-inflammatory activity. It was also observed that the substitution at *para* position is more potent than the *ortho* and *meta* positions.

All the compounds were tested for their analgesic activity and exhibited percent inhibition in the range of 0.3-303%. The compound **6a** showed highly potent analgesic activity compared to standard drug Tramadol (TMD), whereas rest of the tested compounds did not show significant analgesic activity in the model used. It was interesting to note that the compound **6a** manifested both anti-inflammatory and analgesic activities.

All the compounds were tested for their anxiolytic activity and it was observed that the control does not show any entry in open arm, and spent total time in enclosed arm. After the treatment with the standard drug Diazepam, there was significant increase in the time spent as well as percent number of entries in the open arm. After the treatment with triazole derivatives there was increase in percent time spent and number of entries in the open arm but the anxiolytic activity was found to be very less as compared to the standard drug.

Materials and Methods

Anti-inflammatory activity

All the synthesized compounds were tested for their anti-inflammatory activity using carragenan induced rat hind paw edema method of Winter *et al.*[23]. Albino rats (Wistar strain) of either sex, weighing between 150-200 g were used for the experiment. The animals were divided into various groups, consisting of six animals each. One group served as control and received 0.1 mL of normal saline i.p. and group II served as standard and received Diclofenac sodium at the dose of 100 mg/kg i.p. 30 min after the administration of test compounds at the dose of 40 mg/kg i.p. in distilled water, 0.1 mL of 1% formalin in normal saline was given i.p. to the subplantar region of right hind paw. The rat paw volume was measured after 30 min, 60 min and 90 min respectively after formalin induction by using Plethysmometer. The difference between the paw volume at 90 min and 0 hr measurement was calculated and taken as edema volume. Percentage inhibition in the paw edema was calculated by using the formula, percent inhibition = $100(1-V_t/V_c)$, where the V_t represents mean increase in paw volume of test and V_c represents mean increase in paw volume of control. Percentage inhibition shown by tested compounds is recorded in **Table II**.

Analgesic Activity

All the compounds were tested for their analgesic activity by using Eddy's hot plate technique[24]. Mice (Swiss strain) of either sex weighing between 18 and

Table II — Anti-inflammatory activity of synthesized compounds
Paw volume (sec) Mean ± SEM

Compd	30 min	% inhibition	60 min	% inhibition	90 min	% inhibition
Control	0.2±0	0.00	0.283± 0.072	0.00	0.216 ± 0.01667	0.00
Diclofenac Sodium	0.13±0.01	35.00	0.15±0	88.66	0.166 ± 0.01667	23.14
6a	0.2 ± 0.04	0.00	0.2± 0.007	29.32	0.16±0.00128	25.92
6b	0.14 ± 0.06	30.00	0.12 ± 0	57.59	0.12±0.006	44.44
6c	0.1283 ± 0	7.20	0.1283 ± 0.05	54.66	0.1583±0	26.85
6d	0.15 ± 0	5.00	0.14± 0.008	50.33	0.13 ± 0.003	39.81
6e	0.2 ±0.06	0.00	0.23± 0.0083	18.72	0.22±0.007	1.85
6f	0.175±0.0083	12.5	0.15± 0.0083	46.99	0.15±0	30.55
6g	0.1583±0	4.17	0.125±0.008	55.83	0.14±0.0083	35.18
6h	0.18 ±0.09	10.00	0.16±0.006	43.46	0.15 ±0.003	30.55
6i	0.17±0.007	15.00	0.133±0.008	53.00	0.14 ±0.004	35.18
6j	0.133± 0.008	33.50	0.133 ±0.008	53.00	0.14±0.0083	35.18
6k	0.15±0.00166	25.00	0.123±0. 0.0013	56.43	0.15±0	30.55

26 g were used for the experiment. Tramadol at the dose of 20 mg/kg body weight i.p. was used as standard, which showed percentage analgesic activity of 169%. In this method heat is used as a source of pain. Animals were individually placed on hot plate maintained at a temp of 55±1°C. The basal reaction time of all animals towards thermal heat was recorded. The animals which showed fore paw licking or jumping response (whichever appears first) within 6 to 8 sec was selected for the study. Tested compounds at the dose of 40 mg/kg body weight were given i.p. to animals and observed the reaction time of the animals on the hot plate at 30, 60 and 90 min after the compound administration. A cut off time of 15 sec was taken as maximum analgesic response to avoid injuries to the paws. Percentage analgesic activity shown by the tested compounds is recorded in **Table III**.

Anxiolytic Activity

All the compounds were tested for their anxiolytic activity by using Elevated plus maze[25]. The mice of either sex weighing between 18-26 g were used for the study. Diazepam at the dose of 2.0 mg/kg body weight i.p. was used as standard drug. In control groups animals were treated with 0.1 mL of normal saline. Tested compounds at the dose of 40 mg/kg body weight were given i.p. to animals. After 30 min of the administration of tested compounds, standard and normal saline in respective groups, the animals were placed on the elevated plus maze facing the closed arm. The animals were observed for 5 min and time spent in open arm and in enclosed arm was recorded. The time spent in the open arm and closed arm was compared with the control group and recorded in **Table IV**.

Experimental Section

Thin layer chromatography was used to reach the completion of the reaction and homogeneity of the compounds synthesized. Melting points were determined by open capillary and are uncorrected. IR spectra in KBr pellets were recorded on Shimadzu-

Table III — Analgesic activity of synthesized compounds
Latency period (sec) Mean ± SEM

Compd	30 min	% inhibition	60 min	% inhibition	90 min	% inhibition
Control	3.866±0.23	0.00	3.8667±0.23	0.00	3.866± .23	0.00
Tramadol	14±1.73	262.13	15±0	287.93	5.56±2.94	169.4
6a	7.7±1.2	99.17	7.3± 4.1	88.79	6.9±1.6	303.4
6b	4.87±1.19	25.97	6.14± 1.01	58.79	4.59±1.7	72.4
6c	4.66±1.443	20.71	3.91± 1.192	1.12	3.89± 1.19	2.4
6d	3.866±2.091	0.00	5.04± 3.06	30.34	3.87± 1.79	0.4
6e	11.19±3.29	189.53	8.17± 4.629	111.29	4.47± 2.34	60.4
6f	5.39±0.30	39.5	3.89± 0.32	0.6	3.89± 2.14	2.4
6g	3.976±2.59	2.86	4.82± 3.1	246.55	3.91± 0.09	4.4
6h	7.35±6.64	90.11	4.4± 2.42	137.93	3.87± 1.48	0.3
6i	6.233±3.87	61.22	3.87± 0.7	0.086	3.95±0.6	8.4
6j	3.89±1.946	0.6	3.867± 1.01	0.086	3.87± 0.71	0.4
6k	3.87±0.505	0.1	3.89± 1.61	0.6	3.91± 2.02	4.4

Table IV — Anxiolytic activity of synthesized compounds

Compd	Total time spent in open arm (sec) (Mean± SEM)	% time spent in open arm	No. of entries in open arm	% of entries in open arm
Control	0±5.774	0.00	0.00	0.00
Diazepam	61±9.074	20.30	25.00	83.33
6a	21.33±6.984	7.11	4.00	44.44
6b	11±5.568	3.66	2.00	20.00
6c	4.33±2.186	1.44	1.00	10.00
6d	48.33±21.279	16.11	7.00	58.33
6e	20±5.774	6.66	6.00	46.15
6f	11.33±3.18	3.77	3.00	30.00
6g	29.33±23.835	9.77	7.00	53.84
6h	43.33±6.009	14.44	8.00	61.53
6i	31.22±8.09	10.4	5.00	50.00
6j	32.33±4.91	10.77	6.00	54.54
6k	30.33±8.667	10.11	7.00	58.33

8400 FTIR spectrophotometer, ^{1}H NMR spectra were recorded on Bruker spectrometer (400 MHz) in DMSO-d_6/$CDCl_3$ using TMS as an internal standard (Chemical shifts are expressed in δ, ppm). The mass spectra were recorded on Shimadzu LCMS 2010 spectrometer. The homogeneity of the compounds were checked on Silica gel-G coated plates by using chloroform and methanol (8:2) as the eluent and observed in UV light. All the synthesized compounds gave satisfactory elemental analysis.

Preparation of 3-mercapto-(4*H*)-1,2,4-triazole, 2

This was prepared by cyclization of 1-formyl-thiosemicarbazide in a 2M sodium carbonate solution as per the procedure reported in literature[26]. The reaction yield was 63%, m.p. 220°C.

General method for the synthesis of N-substituted β-chloropropionamides, 5

Method A. For primary aromatic amines

m-Nitro aniline (1.45 g, 0.00105 mole) was suspended in solution of β-chloropropionyl chloride (1.50 g, 0.00118 mole) in benzene and boiled under reflux until hydrogen chloride evolution ceased. The solvent was then removed under diminished pressure. The residual material which solidified on cooling was purified by recrystallization from methanol.

Method B. For benzyl amines

β-Chloropropionyl chloride (10.7 g, 0.1 mole) was added drop wise with stirring and cooling, to a solution of benzyl amine (25.2 g, 0.2 mole) in benzene. After completion of the reaction, the mixture was diluted with water and the benzene was removed by distillation under reduced pressure. The water insoluble amide was purified by recrystallization from benzene[22].

General method for the synthesis of N-substituted carboxamidoethylthio-(4*H*)-1,2,4-triazoles, 6

3-Mercapto-(4*H*)-1,2,4-triazole (0.01 mole) was dissolved in aqueous potassium hydroxide solution (0.06 g in 100 mL water) till a clear solution was obtained and filtered to remove insoluble impurities. To this aqueous solution N-substituted β-chloro-propionamides (0.01 mole) was added in small portion with stirring at RT over a period of 3 hr. If some solid remained in the mixture, a few mL of ethanol was added to obtain clear solution. The reaction mixture was stirred for 36 hr at 70-80ºC. Then the reaction mixture was left for 24 hr and the product that separated was filtered, dried and purified by recrystallization from 50% ethanol[27]. The completion of the reaction was monitored by TLC using silica gel-G coated plates in chloroform and methanol (8:2) as the mobile phase and observed in UV light. The physico-chemical data of synthesized compounds were reported in **Table I**.

Spectral data of N-substituted carboxamidoethyl-thio-(4*H*)-1,2,4- triazoles, 6a-k

6a: IR (KBr): 3303 (Ar N-H str.), 3096 (Ar C-H str.), 1660 (C=O str.), 1555 (2° N-H), 1445 (C-H bend.), 1175 (C-N str.), 756 cm^{-1} (Ar C-H bend.); ^{1}H NMR ($CDCl_3$): δ 2.8 (t, 2H, CH_2, J = 6.6 Hz), 3.8 (t, 2H, CH_2, J = 6.6 Hz), 7.0-7.6 (m, 5H- Ar), 8.5 (s, 1H, CH), 9.4 (s, 1H, NH); MS: *m/z* $(M+1)^+$ 250.2.

6b: IR (KBr): 3374 (Ar N-H str.), 3078 (Ar C-H str.), 1643 (C=O str.), 1526 (2º N-H), 1462 (C-H bend.), 1180 (C-N str.), 758 cm^{-1} (Ar C-H bend.); ^{1}H NMR ($CDCl_3$): δ 2.7 (t, 2H, CH_2, J = 6.43 Hz), 3.7 (t, 2H, CH_2, J = 6.43 Hz), 7.2-7.8 (m, 4H-Ar), 8.6 (s, 1H, CH), 10.2 (s, 1H, NH); MS: *m/z* $(M+1)^+$ 295.2.

6c: IR (KBr): 3364 (Ar N-H str.), 3082 (Ar C-H str.), 1633 (C=O str.), 1506 (2º N-H), 1472 (C-H bend.), 1183 (C-N str.), 754 cm^{-1} (Ar C-H bend.); ^{1}H NMR ($CDCl_3$): δ 2.9 (t, 2H, CH_2, J = 6.36 Hz), 3.8 (t, 2H, CH_2, J = 6.29 Hz), 7.0-7.8 (m, 4H-Ar), 8.5 (s, 1H, CH), 9.8 (s, 1H, NH); MS: *m/z* $(M+1)^+$ 284.5.

6d: IR (KBr): 3312 (Ar N-H str.), 3088 (Ar C-H str.), 1675 (C=O str.), 1543 (2º N-H), 1427 (C-H bend.), 1151 (C-N str.), 783 cm^{-1} (Ar C-H bend.); ^{1}H NMR ($CDCl_3$): δ 2.8 (t, 2H, CH_2, J = 6.32 Hz), 3.9 (t, 2H, CH_2, J = 6.32 Hz), 7.2-7.6 (m, 4H-Ar), 8.4 (s, 1H, CH), 9.9 (s, 1H, NH).

6e: IR (KBr): 3364 (Ar N-H str.), 3099 (Ar C-H str.), 1695 (C=O str.), 1542 (2º N-H), 1432 (C-H bend.), 1150 (C-N str.), 737 cm^{-1} (Ar C-H bend.); ^{1}H NMR ($CDCl_3$): δ 2.8 (t, 2H, CH_2, J = 6.66 Hz), 3.9 (t, 2H, CH_2, J = 6.48 Hz), 7.2-7.4 (m, 4H-Ar), 8.5 (s, 1H CH), 9.9 (s,1H NH).

6f: IR (KBr): 3233 (Ar N-H str.), 3055 (Ar C-H str.), 1649 (C=O str.), 1544 (2º N-H), 1458 (C-H bend.), 1155 (C-N str.), 753 cm^{-1} (Ar C-H bend.); ^{1}H NMR ($CDCl_3$): δ 2.2 (s, 3H, CH_3), 2.8 (t, 2H, CH_2, J = 6.28 Hz), 3.9 (t, 2H, CH_2, J = 6.30 Hz), 7.1-7.7 (m, 4H-Ar), 8.4 (s, 1H, CH), 10.2 (s, 1H, NH); MS: *m/z* $(M+1)^+$ 264.5.

6g: IR (KBr): 3288 (Ar N-H str.), 3076 (Ar C-H str.), 1660 (C=O str.), 1543 (2º N-H), 1412 (C-H bend.), 1195 (C-N Str.), 816 cm^{-1} (Ar C-H bend.);

^{1}H NMR ($CDCl_3$): δ 2.3 (s, 3H, CH_3), 2.8 (t, 2H, CH_2, *J* = 6.44 Hz), 3.9 (t, 2H, CH_2, *J* = 6.42 Hz), 7.2-7.4 (m, 4H-Ar), 8.5 (s,1H, CH), 10.1 (s, 1H, NH).

6h: IR (KBr): 3384 (Ar N-H str.), 3078 (Ar C-H str.), 1616 (C=O str.), 1508 (2º N-H), 1429 (C-H bend.), 1175 (C-N str.), 749 cm^{-1} (Ar C-H bend.); ^{1}H NMR ($CDCl_3$): δ 2.8 (t, 2H, CH_2, *J* = 6.52 Hz), 3.8 (t, 2H, CH_2, *J* = 6.48 Hz), 7.2-7.8 (m, 4H-Ar), 8.2 (s, 1H, CH), 10.2 (s, 1H. NH).

6i: IR (KBr): 3338 (Ar N-H str.), 3080 (Ar C-H str.), 1649 (C=O str.), 1545 (2º N-H), 1465 (C-H bend.), 1180 (C-N str.), 802 cm^{-1} (Ar C-H bend); ^{1}H NMR ($CDCl_3$): δ 2.8 (t, 2H, CH_2, *J* = 6.40 Hz), 3.8 (t, 2H, CH_2, *J* = 6.40 Hz), 3.7 (s, 3H, OCH_3), 7.0-7.5 (m, 4H-Ar), 8.2 (s, 1H, CH), 9.4 (s, 1H, NH); MS: *m/z* $(M+1)^+$ 280.2.

6j: IR (KBr): 3291 (Ar N-H str.), 3091 (Ar C-H str.), 1639 (C=O str.), 1558 (2º N-H), 1454 (C-H bend.), 1153 (C-N str.), 728 cm^{-1} (Ar C-H bend.); ^{1}H NMR ($CDCl_3$): δ 2.6 (t, 2H, CH_2, *J* = 6.42 Hz), 3.7 (t, 2H, CH_2, *J* = 6.42 Hz), 4.4 (d, 2H, CH_2, *J* = 5.68 Hz), 7.2-7.4 (m, 5H-Ar), 8.2 (s, 1H, CH), 9.9 (s, 1H, NH); MS: *m/z* $(M+1)^+$ 264.6.

6k: IR (KBr): 3267 (Ar N-H str.), 3046 (Ar C-H str.), 1666 (C=O str.), 1517 (2º N-H), 1440 (C-H bend.), 1163 (C-N str.), 756 cm^{-1} (Ar C-H bend); ^{1}H NMR ($CDCl_3$): δ 2.9 (t, 2H, CH_2, *J* = 6.40 Hz), 3.8 (t, 2H, CH_2, *J* = 6.42 Hz), 7.2-7.4 (m, 4H-Ar), 8.3 (s, 1H, CH), 9.7 (s, 1H, NH).

Conclusion

This study reports the successful synthesis of N-substituted carboxamidoethylthio-(4*H*)-1,2,4-triazoles with moderate yields and all the synthesized triazole derivatives showed potent anti-inflammatory activity but lower analgesic activity. It might be due to increase in distance between aromatic nucleus and side chain nitrogen by one carbon atom as to exhibit analgesic activity, molecule should contain one aromatic nucleus attached to quaternary carbon then ethylene bridge and tertiary nitrogen. N-phenyl carboxamidoethylthio-(4*H*)-1,2,4-triazole **6a** showed equipotent anti-inflammatory as well as analgesic activity as compared to standard drug.

Acknowledgement

The authors are grateful to Head, SAIF, Punjab University, Chandigarh for ^{1}H NMR, IIT, Powai Mumbai for elemental analysis and Head, O_2h Research Pvt. Ltd. for mass spectroscopic analysis. The authors also thank Dr. Devanshu Patel, Director, Parul Arogya Seva Mandal, Limda, Vadodara for providing research facilities.

References

1 Pancechowska-Ksepko Z, *Acta Polon Pharm*, 50, **1993**, 259.
2 Ppostovskil I & Vereshchagina N N, *Zhur Obshchei Khim*, 26, **1956,** 2583.
3 Hoggarth E & Martin A, *Brit J Pharmacol*, l 6, **1951**, 454.
4 Medne K, Grinsteins V & Cipens G, *Latvijas PSR Zinatnu Akad Vestis*, 7, **1961**, 85.
5 Udupi R H & Puzushottaamachar P, *Indian J Heterocycl Chem*, 9, **2000**, 189.
6 Trzhtsinskaya B V, Aleksandrova V, Apakina V, Vinogradova T I, Shchegoleva R A & Afonin A V, *Pharm Chem J,* 25, **1991**, 171.
7 Ebeid M Y, Ashmawi M, Abbas S & Abu-Kull M M, *Egypt J Pharm Sci,* 30, **1989**, 339.
8 Mekuskiene G, Gaidelis P & Vainilavicius P, *Pharmazie*, 53, **1998**, 94.
9 Sahin G, Palaska E, Kelicen P, Demirdamar R & Altmok G, *Arzneim Forsch,* 51, **2001**, 478.
10 Schenone S, Bruno O, Ranise A, Bondavalli F & Filippelli W, *Il Farmaco,* 53, **1998**, 590.
11 Tozkoparan B, Gokhan N, Aktay G,Yesilada E & Ertan M, *Eur J Med Chem,* 35, **2000**, 743.
12 Talawar M B, Bennur S C, Kankanwadi S K & Patil P A, *Indian J Pharm Sci*, 57, **1995**, 194.
13 Abdou N A, Solman L N & Abou Sier A M, *Bull Fac Pharm,* 28, **1990,** 29.
14 Panasenko O J, Shevchenko J M & Samura B A, *Farm Zh,* 3, **1999**, 44.
15 Udupi R H & Bhatt A R, *Indian J Heterocycl Chem,* 6, **1996**, 41.
16 Eweiss N F, Bahajaj A A & Elsherbini, *J Heterocycl Chem*, 23, **1986**, 1451.
17 Mazzone G, Bonina F, Arrigo Reina R & Blandino G, *Il Farmaco,* 36, **1981**, 181.
18 Holla B S, Sooryanarayana B, Shridlova K & Akberai P M, *Il Farmaco*, 55, **2000,** 338.
19 Abdelal A M, Gineinah M M & Nasr M N, *Boll Chim Farm*, 137, **1998**, 372.
20 Jin L, Chen J, Song B, Chen Z,Yang S, Li Q, Hu D & Xu R, *Bioorg Med Chem Lett*, 16, **2006**, 5036.
21 Kuçukguzel I, Tatar E, Kuçukguzel S G, Rollas S & Clercq E D, *Eur J Med Chem,* 42, **2007**, 893.
22 Harvill E K & Herbst R M, *J Org Chem*, 17, **1952**, 1597.
23 Winter C A, Risley E A & Nuss G W, *Exp Biol Med,* 6k, **1962**, 544.
24 Turner R, *Screening Methods in Pharmacology* (Academic Press, New York, London), **1965,** 100.
25 Vogel H G, *Drug discovery and evaluation*: *Pharmacological assays*, 2nd edn, (Springer-Verlag, Berlin, Heidelberg), **2002,** 759.
26 Orient J, Martinova O, Hrdlicka J & Pacholik J, *Czech*, CS200, **1978**, 559.
27 Khazi I M & Koti R S*, Indian J Heterocycl Chem*, 13, **2003**, 87.