Full Paper

Studies on 1,2,4-Triazole Derivatives as Potential Anti-Inflammatory Agents

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The reaction of acetic or propionic acid hydrazides with various aryl/alkyl isothiocyanates gave thiosemicarbazides which furnished the 1,2,4-triazoles by alkali cyclization. The 4-aryl/alkyl-5-(1-phenoxyethyl)-3-[*N*-(substituted)acetamido]thio-4*H*-1,2,4-triazole derivatives were synthesized by reacting the triazoles with 2-chloro-*N*-(substituted)acetamide. The chemical structures of the compounds were elucidated by IR, ^{1}H-NMR, FAB$^+$-MS spectral data and elemental analysis. In the pharmacological studies, anti-inflammatory activities of these compounds have been screened and significant activities were observed.

Keywords: Anti-inflammatory activity / Carrageenan induced oedema / Triazole

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used agents in the treatment of pain, fever, and inflammation, particularly arthritis [1]. The pharmacological activity of NSAIDs arises from their inhibition of the prostaglandin biosynthesis from arachidonic acid by inhibiting the cyclooxygenase enzymes (COXs) [2]. It was discovered that COX exists in two isoforms, COX-1 and COX-2, which are regulated differently [3 – 6]. COX-1 is constitutively expressed and provides cytoprotection in the gastrointestinal tract (GIT) while COX-2 is inducible and mediates inflammation [7 – 8]. The traditional NSAIDs currently in use facilitate non-selective inhibition of COX-1 and COX-2. In fact, most NSAIDs show greater selectivity for COX-1 than COX-2 [9]. Consequently, long-term therapy with non-selective NSAIDs may cause appreciable GI irritation, bleeding, and ulceration. These clinical shortcomings comprise a major challenge confronting medicinal chemists to develop safer agents that spare COX-1 and subsequently its gastric cytoprotective role [10]. For the last many years, there has been a great interest to develop new NSAIDs which could specifically inhibit COX-2, the enzyme responsible for the production of prostaglandins and other mediators which are directly associated with inflammation processes. Some selective inhibitors for COX-2 have already been found and the research in this direction continues with a view to discover new drugs for inhibiting this enzyme [11 – 13].

Understanding the relationship between chemical structure and enzyme activity is crucial for the design of new COX-2-selective inhibitors. Although the active sites of COX-1 and COX-2 are similar, there are differences which have been utilized by medicinal chemists to synthesize molecules which have a selective action on COX-2. Of crucial significance is position 523, which in COX-2 is valine and in COX-1 isoleucine. This difference of a single methyl group is sufficient to allow access of a poten-

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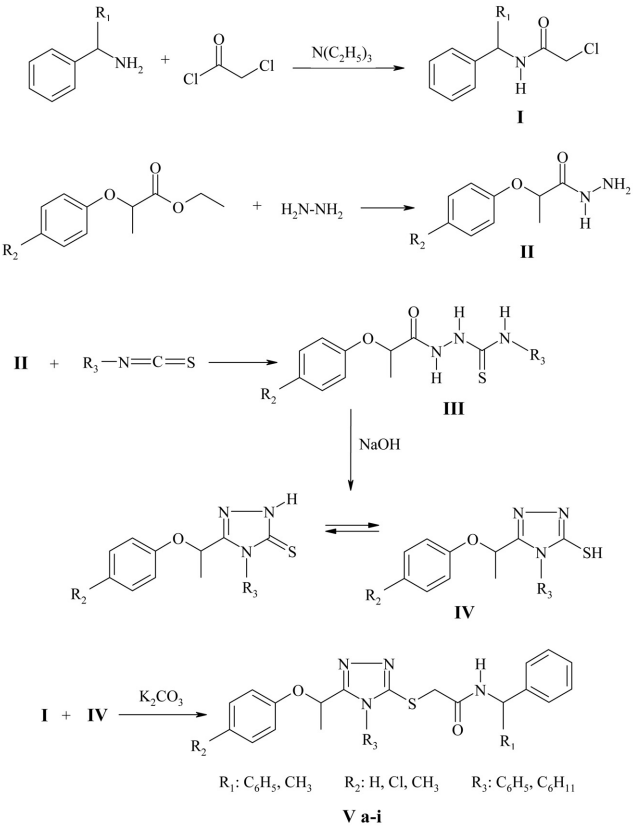
Abbreviations: Nonsteroidal anti-inflammatory drugs (NSAIDs); cyclooxygenase enzymes (COXs); gastrointestinal tract (GIT); structure-activity-relationship (SAR)

tial inhibitor to a side pocket in COX-2. In addition, proximity to an arginine residue at position 513 (histidine in COX-1) is important, which provides hydrogen bonding for an inhibitor of a structure that enables it to extend into the side pocket. Another significant difference between COX-2 and COX-1 is at position 503, which is the aromatic amino acid phenylalanine in COX-1 but the relatively small, non-aromatic leucine in COX-2; this allows leucine at position 384 to re-orient its methyl side chain away from the enzymatic site of the COX-2 enzyme [14, 15]. The final result of these differences is an approximate 20% increase in the active site of COX-2 compared to COX-1. In the light of these findings, it could be speculated that acetic or propionic acids act non-selectively, probably because of their relatively small size tolerated by both COX-1 and COX-2. It appears that bulkier structures are more likely to confer selectivity to COX-2 due to its wider active site [16, 17].

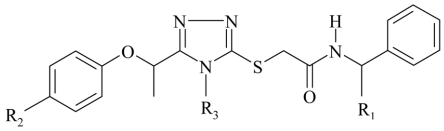
It has been reported that modification of the carboxyl function of representative NSAIDs results in retained anti-inflammatory activity with minimized ulcerogenic potential along with reduced lipid peroxidation [18 – 22].

In addition, several examples of NSAIDs having a triazole structure have been noted in the medicinal chemistry literature. Among them, 1,2,4-triazol-3-thiol derivatives are of particular interest and have been studied and patented in recent years [23 – 25]. In this study, we were interested in replacing the carboxyl function of acetic and propionic acids by selected bulkier moieties with the goal of improving the safety profile of these agents while retaining anti-inflammatory activity.



Scheme 1. The general synthesis route of presented compounds.

Table 1. Some characteristics of the compounds.



Compound	R_1	R_2	R_3	Mp. (°C)	Yield (%)	Mol. Formula
Va	C_6H_5	H	C_6H_5	156 – 158	80	$C_{31}H_{28}N_4O_2S$
Vb	C_6H_5	Cl	C_6H_5	145 – 147	76	$C_{31}H_{27}ClN_4O_2S$
Vc	CH_3	Cl	C_6H_5	48 – 50	81	$C_{26}H_{25}ClN_4O_2S$
Vd	CH_3	CH_3	C_6H_5	82 – 84	78	$C_{27}H_{28}N_4O_2S$
Ve	C_6H_5	H	C_6H_{11}	148 – 150	75	$C_{31}H_{34}N_4O_2S$
Vf	C_6H_5	CH_3	C_6H_{11}	160 – 162	80	$C_{32}H_{36}N_4O_2S$
Vg	CH_3	H	C_6H_{11}	54 – 56	72	$C_{26}H_{32}N_4O_2S$
Vh	CH_3	Cl	C_6H_{11}	20 – 21	77	$C_{26}H_{31}ClN_4O_2S$
Vi	CH_3	CH_3	C_6H_{11}	110 – 112	81	$C_{27}H_{34}N_4O_2S$

Results and discussion

Chemistry

In the present work, nine new compounds (**Va – i**) which are thioether derivatives of 1,2,4-triazol-3-thiol, were synthesized (Table 1, Scheme 1). The structures of the obtained compounds were elucidated by spectral analyses. According to the spectroscopic data of the final compounds the IR showed characteristic C=O (amide) stretching bands in the 1699 – 1665 cm^{-1} region.

In the ^{1}H-NMR spectra of the compounds, the signal due to the S-CH_2 methylene protons present in all compounds appeared at 3.95 – 4.15 ppm, as singlets. NH proton was observed at 8.65 – 9.20 ppm as a doublet band. All the other aromatic and aliphatic protons were observed at the expected regions. Mass spectra (MS (FAB)) of the compounds showed a [M+1] peak, in agreement with their molecular formula.

Pharmacology

In the acute inflammation model, compounds **Va**, **Vc**, **Vg**, and **Vh** showed maximum inhibition of carrageenan-induced rat paw oedema. Carrageenan-induced hind paw oedema is the standard experimental model of acute inflammation. Carrageenan is the phlogistic agent of

choice for testing anti-inflammatory drugs as it is not known to be antigenic and is devoid of apparent systemic effects. Moreover, the experimental model exhibits a high degree of reproducibility. Carrageenan-induced oedema is a biphasic response. The first phase is mediated through the release of histamine, serotonin, and kinins, whereas the second phase is related to the release of prostaglandin and other slow-reacting substances [26]. The compounds **Va**, **Vc**, **Vg**, and **Vh** exhibited maximum inhibition values of 70.5%, 73.1%, 73.8%, 72.1%, respectively, while the standard drug indomethacin showed an inhibition of 67.3% in the carrageenan-induced rat paw oedema (acute) model. Thus, we may conclude that the tested compounds **Va**, **Vc**, **Vg**, and **Vh** showed higher anti-inflammatory activity than the standard drug indomethacin. Compounds **Vb** and **Vd** showed notable activity (57.2% and 57.6%, respectively) compared with the standard drug. **Ve**, **Vf**, and **Vi** also showed interesting activity (43.2%, 20.2%, and 37.6%).

The SAR (structure-activity-relationship) observations show that the substitution on the phenoxy moiety has an interesting role on the activity. The unsubstituted phenoxy and *p*-Cl-substituted phenoxy derivatives are the more active than the *p*-methyl derivatives. The modifications on R_1 and R_3 do not play a remarkable role on the activity.

The authors have declared no conflict of interest.

Experimental

Chemistry

All reagents were used as purchased from commercial suppliers without further purification. Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected (Electrothermal, Essex, UK). The compounds were checked for purity by TLC on silica gel 60 F_{254}. Spectroscopic data were recorded on the following instruments: IR, Shimadzu 435 IR spectrophotometer (Shimadzu, Tokyo, Japan); ^{1}H-NMR, Bruker 250 MHz NMR spectrometer (Bruker Bioscience, Billerica, MA, USA) in DMSO-d_6 using TMS as internal standard; MS-FAB, VG Quattro mass spectrometer (Fisons Instruments Vertriebs GmbH, Mainz, Germany); Elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyser (Perkin-Elmer, Norwalk, CT, USA).

General procedure for synthesis of the compounds 2-Chloro-N-(substituted)acetamides I

Chloroacetylchloride (20 mmol) and triethylamine (20 mmol) were added to a solution of amine (20 mmol) in anhydrous benzene and the mixture was treated as described in the literature [27].

2-Phenoxypropionic acid hydrazides II

These compounds were prepared according to the reported method, by reacting ethyl 2-phenoxypropionates with hydrazine hydrate [28, 29].

1-(2-Phenoxypropionyl)-4-phenyl/cyclohexyl-3-thiosemicarbazides III

Equimolar quantities of acid hydrazide (30 mmol) and phenyl/cyclohexyl isothiocyanate in 25 mL of absolute ethanol were refluxed for 3–5 h. The resulting solid was filtered and recrystallized from ethanol [30, 31].

4-Phenyl/cyclohexy-5-(1-phenoxyethyl)-2,4-dihydro-3H-1,2,4-triazol-3-thione IV

Suitable substituted thiosemicarbazides **III** (20 mmol) were dissolved in 2 N sodium hydroxide and the resulting solution was heated under reflux for 3 h. The solution was cooled and acidified to pH 2–3 with hydrochloric acid solution and recrystallized from ethanol [30, 31].

*4-Phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[N-(substituted)acetamido]thio-4H-1,2,4-triazole **Va–i***

A mixture of the acetamide **I** (10 mmol), appropriate triazoles **IV** and anhydrous potassium carbonate in acetone was mixed at room temperature for 6 h. The mixture was filtered; the filtrate was evaporated until dryness. The residue was washed with water and recrystallized from ethanol.

Va: IR (KBr, cm^{-1}): 3115 (NH), 1675 (C=O), 1590–1415 (C=C and C=N), 1265–1051 (C–O). ^{1}H-NMR (250 MHz) (DMSO-d_6) δ (ppm): 1.60 (3H, d [*J* = 6.47 Hz], CH–*CH*$_3$), 4.15 (2H, s, S–*CH*$_2$), 5.55 (1H, q, *CH*–CH$_3$), 6.10 (1H, d [*J* = 8.38 Hz], N-*CH*), 6.75–7.55 (20H, m, aromatic protons), 9.20 (1H, d [*J* = 8.48 Hz], *NH*). MS (FAB) [M+1]: *m*/*z* 521, Anal. Calc. for $C_{31}H_{28}N_4O_2S$: C, 71.51; H, 5.42; N, 10.76. Found: C, 71.55; H, 5.40; N, 10.77.

Vb: IR (KBr, cm^{-1}): 3105 (NH), 1695 (C=O), 1560–1403 (C=C and C=N), 1275–1025 (C–O). ^{1}H-NMR (250 MHz) (DMSO-d_6) δ (ppm): 1.55 (3H, d, *J* = 6.45 Hz, CH–*CH*$_3$), 4.05 (2H, s, S–*CH*$_2$), 5.45 (1H, q, *CH*–CH$_3$), 6.05 (1H, d, *J* = 8.45 Hz, N-*CH*), 6.70–7.50 (19H, m, aromatic protons), 9.15 (1H, d, *J* = 8.53 Hz, *NH*). MS (FAB) [M+1]: *m*/*z* 555; Anal. Calc. for $C_{31}H_{27}ClN_4O_2S$: C, 67.08; H, 4.90; N, 10.09. Found: C, 67.10; H, 4.94; N, 10.10.

Vc: IR (KBr, cm^{-1}): 3095 (NH), 1672 (C=O), 1520–1425 (C=C and C=N), 1225–1015 (C–O). ^{1}H-NMR (250 MHz) (DMSO-d_6) δ (ppm): 1.30 (3H, d, *J* = 6.99 Hz, N-CH–*CH*$_3$), 1.55 (3H, d, *J* = 6.45 Hz, O-CH–*CH*$_3$), 3.95 (2H, s, S–*CH*$_2$), 4.90 (1H, q, *CH*–CH$_3$), 5.50 (1H, d, *J* = 6.30 Hz, N-*CH*), 6.70–7.40 (14H, m, aromatic protons), 8.70 (1H, d, *J* = 8.13 Hz, *NH*). MS (FAB) [M+1]: *m*/*z* 493. Anal. Calc. for $C_{26}H_{25}ClN_4O_2S$: C, 63.34; H, 5.11; N, 11.36. Found: C, 63.30; H, 5.11; N, 11.38.

Vd: IR (KBr, cm^{-1}): 3157 (NH), 1685 (C=O), 1505–1402 (C=C and C=N), 1295–1095 (C–O). ^{1}H-NMR (250 MHz) (DMSO-d_6) δ (ppm): 1.35 (3H, d, *J* = 7.00 Hz, N-CH–*CH*$_3$), 1.55 (3H, d, *J* = 6.44 Hz, O-CH–*CH*$_3$), 2,30 (3H, s, phenyl-*CH*$_3$), 4.00 (2H, s, S–*CH*$_2$), 4.85 (1H, q, *CH*–CH$_3$), 5.45 (1H, d, *J* = 6.43 Hz, N-*CH*), 6.60 and 7.00 (4H, two d, *J* = 8.48 and 8.41 Hz, 1,4-disubstituted phenyl protons), 7.30–7.60 (10H, m, aromatic protons), 8.75 (1H, d, *J* = 8,09 Hz, *NH*). MS (FAB) [M+1]: *m*/*z* 473. Anal. Calc. for $C_{27}H_{28}N_4O_2S$: C, 68.62; H, 5.97; N, 11.85. Found: C, 68.60; H, 6.00; N, 11.83.

Ve: IR (KBr, cm^{-1}): 3162 (NH), 1668 (C=O), 1520–1386 (C=C and C=N), 1233–1042 (C–O). ^{1}H-NMR (250 MHz) (DMSO-d_6) δ (ppm):

0.90 – 1.60 (8H, m, cyclohexyl protons), 1.65 (3H, d, *J* = 6.39 Hz, CH – *CH*$_3$), 1.70 – 2.05 (3H, m, cyclohexyl protons), 4.10 (2H, s, S – *CH*$_2$), 5.85 (1H, q, *CH* – CH$_3$), 6.05 (1H, d, *J* = 8.45 Hz, N-*CH*), 6.90 – 7.40 (15H, m, aromatic protons), 9.15 (1H, d, *J* = 8.45 Hz, *NH*). MS (FAB) [M+1]: *m*/*z* 527. Anal. Calc. for $C_{31}H_{34}N_4O_2S$: C, 70.69; H, 6.51; N, 10.64. Found: C, 70.72; H, 6.54; N, 10.60.

Vf: IR (KBr, cm^{-1}): 3141 (NH), 1699 (C=O), 1495 – 1346 (C=C and C=N), 1243 – 1062 (C – O). ^{1}H-NMR (250 MHz) (DMSO-*d*$_6$) δ (ppm): 1.00 – 1.60 (8H, m, cyclohexyl protons), 1.65 (3H, d, *J* = 6.48 Hz, CH – *CH*$_3$), 1.70 – 2.10 (3H, m, cyclohexyl protons), 2.20 (3H, s, phenyl-*CH*$_3$), 4.15 (2H, s, S – *CH*$_2$), 5.80 (1H, q, *CH* – CH$_3$), 6.10 (1H, d, *J* = 8.47 Hz, N-*CH*), 6.90 and 7.10 (4H, two d, *J* = 8.53 and 8.44 Hz, 1,4-disubstituted phenyl protons), 7.20 – 7.40 (10H, m, aromatic protons), 9.20 (1H, d, *J* = 8.48 Hz, *NH*). MS (FAB) [M+1]: *m*/*z* 541. Anal. Calc. for $C_{32}H_{36}N_4O_2S$: C, 71.08; H, 6.71; N, 10.36. Found: C, 71.11; H, 6.70; N, 10.36.

Vg: IR (KBr, cm^{-1}): 3108 (NH), 1671 (C=O), 1471 – 1337 (C=C and C=N), 1223 – 1101 (C – O). ^{1}H-NMR (250 MHz) (DMSO-*d*$_6$) δ (ppm): 1.00 – 1.30 (4H, m, cyclohexyl protons), 1.35 (3H, d, *J* = 6.93 Hz, N-CH – *CH*$_3$), 1.50 – 1.70 (5H, m, cyclohexyl protons), 1.70 (3H, d, *J* = 6.36 Hz, O-CH – *CH*$_3$), 1.80 – 2.05 (2H, m, cyclohexyl protons), 4.10 (2H, s, S – *CH*$_2$), 4.80 – 5.00 (1H, q, *CH* – CH$_3$), 5.85 – 6.05 (1H, m, N-*CH*), 6.95 – 7.40 (10H, m, aromatic protons), 8.75 (1H, d, *J* = 8.07 Hz, *NH*). MS (FAB) [M+1]: *m*/*z* 465. Anal. Calc. for $C_{26}H_{32}N_4O_2S$: C, 67.21; H, 6.94; N, 12.06. Found: C, 67.20; H, 6.98; N, 12.10.

Vh: IR (KBr, cm^{-1}): 3128 (NH), 1688 (C=O), 1441 – 1330 (C=C and C=N), 1238 – 1162 (C – O). ^{1}H-NMR (250 MHz) (DMSO-*d*$_6$) δ (ppm): 1.00 – 1.25 (4H, m, cyclohexyl protons), 1.30 (3H, d, *J* = 7.03 Hz, N-CH – *CH*$_3$), 1.40-1.50 (5H, m, cyclohexyl protons), 1.55 (3H, d, *J* = 6.76 Hz, O-CH – *CH*$_3$), 1.70 – 2.00 (2H, m, cyclohexyl protons), 4.15 (2H, s, S – *CH*$_2$), 4.75-5.00 (1H, q, *CH* – CH$_3$), 5.80 – 6.05 (1H, m, N-*CH*), 6.95-7.40 (9H, m, aromatic protons), 8.65 (1H, d *J* = 8.17 Hz, *NH*). MS (FAB) [M+1]: *m*/*z* 499. Anal. Calc. for $C_{26}H_{31}ClN_4O_2S$: C, 62.57; H, 6.26; N, 11.23. Found: C, 62.60; H, 6.28; N, 11.24.

Vi: IR (KBr, cm^{-1}): 3138 (NH), 1679 (C=O), 1441 – 1317 (C=C and C=N), 1201 – 1098 (C – O). ^{1}H-NMR (250 MHz) (DMSO-*d*$_6$) δ (ppm): 0.90-1.20 (4H, m, cyclohexyl protons), 1.35 (3H, d, *J* = 6.85 Hz, N-CH – *CH*$_3$), 1.40 – 1.55 (5H, m, cyclohexyl protons), 1.65 (3H, d, *J* = 6.31 Hz, O-CH – *CH*$_3$), 1.75 – 2.10 (2H, m, cyclohexyl protons), 2.20 (3H, s, phenyl-*CH*$_3$), 4.05 (2H, s, S – *CH*$_2$), 4.85 (1H, q, *CH* – CH$_3$), 5.80 (1H, m, N-*CH*), 6.85 and 7.05 (4H, two d, *J* = 8.48 and 8.20 Hz, 1,4-disubstituted phenyl protons), 7.15 – 7.40 (5H, m, aromatic protons), 8.70 (1H, d, *J* = 8.12 Hz, *NH*). MS (FAB) [M+1]: *m*/*z* 479. Anal. Calc. for $C_{27}H_{34}N_4O_2S$: C, 67.75; H, 7.16; N, 11.70. Found: C, 67.78; H, 7.19; N, 11.71.

Pharmacology

Albino mice of either sex weighing approximately 20-25 g were used. A minimum of six animals was used in each group. The animals were left for two days for acclimatization to animal-room conditions and were maintained on standard pellet diet and water *ad libidum*. The food was withdrawn on the day before the experiment, but free access to water was allowed.

The method of Winter *et al.* was employed with some modifications for anti-inflammatory activity [32]. The activities of the tested compounds are given in Table 2.

Anti-inflammatory activity: Carrageenan-induced oedema

All test samples were administered to animals in a 100 mg/kg dosage as a suspension in 0.5% carboxymethyl cellulose by using a gastric lavage apparatus. One hour after oral administration of test sample, each mouse was injected with 0.01 mL 2% carrageenan solution into the subplantar tissue of the right hind paw. With Peacock-thickness gauge, the volume of the paw was measured immediately and 2 h after the carrageenan injection. The control group of animals received appropriate volumes of the dosing vehicle only. Percent inhibition of the effects of the drugs was calculated according to the following equation:

Anti-inflammatory activity (%) = [(n – n′)/n] × 100

n = difference in thickness between first and second measure of paw in the control group; n′ = difference in thickness between first and second measure of paw in the control group which had been administered the test sample. Indomethacin (100 mg/kg) was used as reference compound.

Table 2. Anti-inflammatory activity.

Compound[a)]	Anti-inflammatory activity (%) (n = 6)[b)]
Va	70.5 ± 1.1*
Vb	57.2 ± 14.3
Vc	73.1 ± 0.8*
Vd	57.6 ± 14.4
Ve	43.2 ± 17.6
Vf	20.2 ± 12.9
Vg	73.8 ± 1.8*
Vh	72.1 ± 0.4*
Vi	37.6 ± 16.2
Indomethacin	67.3 ± 4.6*

a) 100 mg/kg (p.o.).

b) Results are expressed as their mean ± SEM values.

* activity, n = 6, $P < 0.05$.

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