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Research Article

Synthesis and Analgesic, Anti-inflammatory Activities of Some Novel Thiadiazole Derivatives

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ABSTRACT

A series of novel 1,3,4-thiadiaoles was synthesized and investigated for *in vivo* analgesic and *in vivo* anti-inflammatory activity. All synthesized compounds' structures were confirmed by means of elemental analysis, IR, ^{1}H NMR, and LCMS. All compounds were evaluated for their analgesic and anti-inflammatory activities by tail-flick method and carrageenan-induced rat paw edema test, respectively. Among all the synthesized compounds, compounds 3d and 3e exhibited the most prominent and consistent anti-inflammatory activity. In acute ulcerogenic study, it can be concluded that these compounds are devoid of deadlier gastrointestinal toxicities.

Introduction

Inflammation is a common state during infections and many diseases from hay fever, periodontitis, atherosclerosis, and rheumatoid arthritis to cancer.[1-4] The mediators of inflammation, discomfort and swelling are well known as prostaglandins (PGs). Prostaglandins are produced by the action of the cyclooxygenase (COX) enzyme on arachidonic acid. Metabolites of the COX pathway are widely accepted as mediators of the inflammatory response.[5-8] Pain intensity is influenced by the meaning of the pain to the patient and its expected duration.[9] Pain is rarely caused by psychological factors but is associated with psychological and emotional effects such as fear, anxiety and depression. Acute or chronic pain can lead to varying degrees of altered behaviour, dysfunction or disability.[10-11] The most widely used medications in inflammatory disorders are nonsteroidal anti-inflammatory drugs (NSAIDs) since they are effective in treating pain, fever, redness, edema resulting as a result of the release of inflammatory mediators.[12-16]

1,3,4-thiadiazole derivatives have been of interest to the medicinal chemists for many years because of their anti-cancer,[17] antitubercular,[18] antibacterial,[19] anti-fungal,[20] anticonvulsant,[21] analgesic-anti-inflammatory,[22] cardiotonic[23] and diuretic[24] activities.

We planned to synthesize novel 1,3,4-Thiadiazole derivatives as powerful and non-ulcerogenic analgesic, anti-inflammatory lead-candidates in the present work.

Material and Methods

The synthetic route used to synthesize title compounds is outlined in Fig. 1. MPs of the synthesized compounds were determined in open capillary tubes and are uncorrected. IR absorption spectra were recorded on Bruker alpha.

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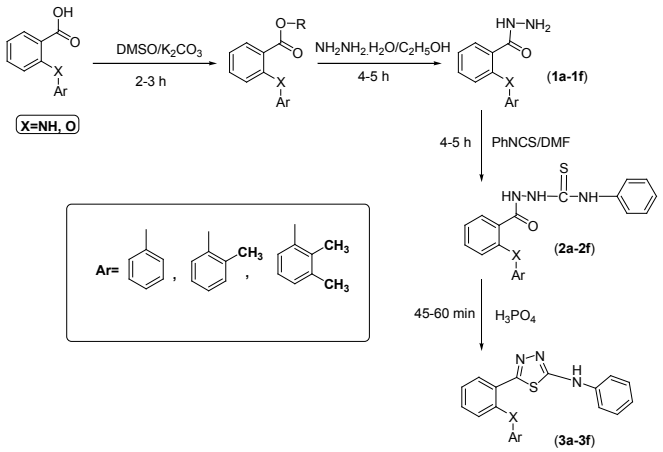

Fig. 1: Synthetic scheme of 1,3,4-thiadiaoles (3a-3f)

Elemental analysis (C, H, and N) was undertaken with a Perkin-Elmer model 240C analyzer. ^{1}H NMR spectra were recorded on the Bruker DPX-400 instrument at 400 MHz. The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer.

The compounds (1a-1f) was prepared by earlier reported literature.[25]

4-Phenyl-1-(2-(phenylamino)benzoyl) thiosemicarbazide (2a)

Equimolar amount of 2-(Phenylamino) benzohydrazide 1a and Phenyl isothiocyanate were refluxed for 4 h a mixture of 20 mL DMF and 40 mL ethanol. The reaction mixture was allowed to cool and then poured into ice-cold water. The solid precipitated was filtered off and recrystallized.

MP: 206-208°C; Yield: 83 %; R_f value: 0.78; IR (υ_{max}, cm^{-1}): 3438, 3326 (NH), 2957, 2929 (Ar-CH), 1652 (C=O), 1436, 1415 (Ar. C=C), 1258 (C=S).

The similar procedure was adopted to synthesize the remaining thiosemicarbazide derivatives (2b-2f) by using corresponding hydrazides (1b-1f).

1-(2-(*o*-Toluidino)benzoyl)-4-phenylthiosemicarbazide (2b)

MP: 210-212°C; Yield: 79 %; R_f value: 0.73; IR (υ_{max}, cm^{-1}): 3423, 3342 (NH), 2942, 2918 (Ar-CH), 1634 (C=O), 1452, 1429 (Ar. C=C), 1227 (C=S).

1-(2-(2,3-Dimethylphenylamino)benzoyl)-4-phenylthiosemicarbazide (2c)

MP: 222-224°C; Yield: 75 %; R_f value: 0.64; IR (υ_{max}, cm^{-1}): 3459, 3336 (NH), 2958, 2934 (Ar-CH), 1626 (C=O), 1447, 1412 (Ar. C=C), 1245 (C=S).

1-(2-Phenoxybenzoyl)-4-phenylthiosemicarbazide (2d)

MP: 216-218°C; Yield: 78 %; R_f value: 0.77; IR (υ_{max}, cm^{-1}): 3462, 3399 (NH), 2958, 2942 (Ar-CH), 1617 (C=O), 1329 (C–O-C), 1451, 1427 (Ar. C=C), 1207 (C=S).

4-Phenyl-1-(2-(*o*-tolyloxy)benzoyl) thiosemicarbazide (2e)

MP: 218-220°C; Yield: 72 %; R_f value: 0.72; IR (υ_{max}, cm^{-1}): 3418, 3387 (NH), 2948, 2916 (Ar-CH), 1631 (C=O), 1343 (C–O-C), 1452, 1437 (Ar. C=C), 1249 (C=S).

1-(2-(2,3-Dimethylphenoxy)benzoyl)-4-phenylthiosemicarbazide (2f)

MP: 222-224°C; Yield: 74 %; R_f value: 0.62; IR (υ_{max}, cm^{-1}): 3456, 3393 (NH), 2935, 2903 (Ar-CH), 1662 (C=O), 1357 (C–O-C), 1446, 1417 (Ar. C=C), 1228 (C=S).

N-Phenyl-5-(2-(phenylamino)phenyl)-1,3,4-thiadiazol-2-amine (3a)

About 1 mmol 4-Phenyl-1-(2-(phenylamino)benzoyl) thiosemicarbazide (2a) derivative was added in small quantity of orthophosphoric acid at 95–100°C by continuous stirring for 30 min. After addition is finished, the reaction mixture was further heated for 45 minutes and later poured into ice water. The solid precipitated so obtained was filtered off and recrystallized from appropriate solvents. The completion of reaction was monitored by running TLC using mobile phase Benzene: Ethyl acetate.[26]

MP: 192-194°C; Yield: 80 %; R_f value: 0.86; Anal. Calcd. for $C_{20}H_{16}N_4S$ (344.43): C, 69.74; H, 4.68; N,16.27. Found: C, 69.45; H, 4.38; N, 15.95. IR (υ_{max}, cm^{-1}): 3343 (NH), 2948, 2912 (Ar-CH), 1574 (C=N), 1453, 1424 (Ar. C=C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 3.91 (s, 1H, NH), 6.86-7.58 (m, 14H, Ar-H), 7.96 (s, 1H, NH). LCMS (m/z): $[M]^+$; 344.11

The similar procedure was adopted to synthesize thiosemicarbazide derivatives (3b-3f) by using corresponding semicarbazides (2b-2f).

5-(2-(*o*-Toluidino)phenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (3b)

MP: 196-198°C; Yield: 70 %; R_f value: 0.88; Anal. Calcd. for $C_{21}H_{18}N_4S$ (358.46): C, 70.36; H, 5.06; N,15.63; Found: C, 69.98; H, 4.79; N, 15.38. IR (υ_{max}, cm^{-1}): 3316 (NH), 2957, 2932 (Ar-CH), 1568 (C=N), 1436, 1417 (Ar. C=C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.19 (s, 3H, CH_3), 3.21 (s, 1H, NH), 6.71-7.62 (m, 13H, Ar-H), 8.65 (s, 1H, NH). LCMS (m/z): $[M+H]^+$; 359.13.

5-(2-(2,3-Dimethylphenylamino)phenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (3c)

MP: 212-214°C; Yield: 81 %; R_f value: 0.83; Anal. Calcd. for $C_{22}H_{20}N_4S$ (372.49): C, 70.94; H, 5.41; N,15.04. Found: C, 70.68; H, 5.22; N, 14.75. IR (υ_{max}, cm^{-1}): 3324 (NH), 2942, 2923 (Ar-CH), 1559 (C=N), 1463, 1437 (Ar. C=C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.14 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.66 (s, 1H, NH), 6.82-7.53 (m, 12H, Ar-H), 8.74 (s, 1H, NH). LCMS (m/z): $[M]^+$; 372.14.

5-(2-Phenoxyphenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (3d)

MP: 188-190°C; Yield: 75 %; R_f value: 0.83; Anal. Calcd. for $C_{20}H_{15}N_3OS$ (345.42): C, 69.54; H, 4.38; N,12.17. Found: C, 69.34; H, 3.99; N, 11.89. IR (υ_{max}, cm^{-1}): 3372 (NH), 2964, 2936 (Ar-CH), 1565 (C=N), 1352 (C–O-C), 1443,

Table 1: Analgesic activity of title compounds

	Reaction Time (mean ± SEM) Sec				*Relative Analgesic Activity (%)*			
Compounds	*30 min*	*60 min*	*90 min*	*120 min*	*30 min*	*60 min*	*90 min*	*120 min*
Control	2.680 ± 0.082	2.813 ± 0.055	3.055 ± 0.210	4.192 ± 0.172	-	-	-	-
Mefenamic acid	3.860 ± 0.028**	5.643 ± 0.101**	5.657 ± 0.104**	6.682 ± 0.097**	100	100	100	100
3a	2.752 ± 0.053^{ns}	3.597 ± 0.070**	3.622 ± 0.094*	4.902 ± 0.019**	6.07	27.70	21.79	28.51
3b	2.765 ± 0.048^{ns}	3.188 ± 0.214^{ns}	3.623 ± 0.082*	4.503 ± 0.071^{ns}	7.20	13.25	21.83	12.49
3c	2.813 ± 0.027^{ns}	4.479 ± 0.108**	4.762 ± 0.086**	5.797 ± 0.092**	11.30	58.87	65.60	64.46
3d	3.667 ± 0.088**	4.532 ± 0.092**	5.440 ± 0.101**	6.463 ± 0.103**	83.62	60.74	91.66	91.20
3e	3.758 ± 0.053**	4.712 ± 0.073**	5.368 ± 0.102**	5.711 ± 0.058**	91.38	67.10	88.89	61.00
3f	3.632 ± 0.076**	4.748 ± 0.079**	5.365 ± 0.093**	5.698 ± 0.048**	80.65	68.37	88.78	60.48

"Data analyzed by one-way ANOVA followed by Dunnett's '*t*' test, (n = 6), *P< 0.05, **P< 0.01 significant from control; ns, not significant".

Table 2: Anti-inflammatory activity of title compounds

	Volume of edema (mean) ± SEM (ml)				*Anti-inflammatory activity (% inhibition)*			
Compounds	*1h*	*2h*	*3h*	*4h*	*1h*	*2h*	*3h*	*4h*
Control	0.034 ± 0.001	0.036 ± 0.001	0.056 ± 0.001	0.037 ± 0.001	-	-	-	-
Mefenamic acid	0.026 ± 0.001*	0.017 ± 0.001**	0.007 ± 0.001**	0.005 ± 0.001**	24.03	53.25	88.39	86.49
3a	0.016 ± 0.001*	0.024 ± 0.001*	0.035 ± 0.001*	0.026 ± 0.002**	51.97	34.25	37.20	29.73
3b	0.016 ± 0.001*	0.026 ± 0.002*	0.026 ± 0.001**	0.027 ± 0.002**	52.94	27.31	53.57	27.03
3c	0.026 ± 0.001^{ns}	0.013 ± 0.001**	0.016 ± 0.001**	0.006 ± 0.001**	23.03	63.42	71.73	83.78
3d	0.027 ± 0.001^{ns}	0.015 ± 0.001**	0.020 ± 0.002**	0.007 ± 0.001**	21.09	57.42	64.88	81.08
3e	0.020 ± 0.002^{ns}	0.017 ± 0.001**	0.025 ± 0.001**	0.005 ± 0.001**	41.18	54.17	55.05	85.68
3f	0.021 ± 0.002^{ns}	0.014 ± 0.001**	0.022 ± 0.008**	0.011 ± 0.001**	37.74	62.03	61.30	72.97

"Data analyzed by one-way ANOVA followed by Dunnett's '*t*' test, (n = 6), *P< 0.05, **P< 0.01 significant from control; ns, not significant".

1416 (Ar. C=C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 3.53 (s, 1H, NH), 6.77-7.49 (m, 14H, Ar-H). LCMS (m/z): $[M]^+$; 345.09.

5-(2-(*o*-Toluidino)phenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (3e)

MP: 196-198°C; Yield: 73 %; R_f value: 0.71; Anal. Calcd. for $C_{21}H_{17}N_3OS$ (359.44): C, 70.17; H, 4.77; N,11.69. Found: C, 69.89; H, 4.48; N, 11.45. IR (υ_{max}, cm^{-1}): 3395 (NH), 2932, 2908 (Ar-CH), 1553 (C=N), 1368 (C–O-C), 1463, 1437 (Ar. C=C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.29 (s, 3H, CH_3), 3.76 (s, 1H, NH), 6.84-7.93 (m, 13H, Ar-H). LCMS (m/z): $[M+H]^+$; 360.11.

5-(2-(2,3-Dimethylphenoxy)phenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (3f)

MP: 202-204°C; Yield: 79 %; R_f value: 0.78; Solvent system: Benzene: Ethylacetate (8:2)

Anal. Calcd. for $C_{22}H_{19}N_3OS$ (373.47): C, 70.75; H, 5.13; N,11.25. Found: C, 70.49; H, 4.92; N, 10.97. IR (υ_{max}, cm^{-1}): 3362 (NH), 2954, 2927 (Ar-CH), 1566 (C=N), 1334 (C–O-C), 1458, 1429 (Ar. C=C). ^{1}H NMR (400 MHz, DMSO-d_6); δ: 2.23 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.59 (s, 1H, NH), 6.89-7.69 (m, 12H, Ar-H). LCMS (m/z): $[M]^+$; 373.12.

Table 3: Ulcerogenic profile of 3d and 3e

Compounds	*Ulcer Score (mean ± SEM)*	*Ulcer Index*
Control	0.326 ± 0.013	-
Mefenamic acid	1.931 ± 0.051**	1.605
3d	0.657 ± 0.057^{ns}	0.331
3e	1.249 ± 0.233^{ns}	0.923

"Data analyzed by one-way ANOVA followed by Dunnett's '*t*' test, (n = 6), *P< 0.05, **P< 0.01 significant from control; ns, not significant".

Acute Toxicity Study

Wistar rats weighing 150-200 g were used for acute toxicity study. The animals were housed in colony cages, conditions of constant temperature (22 ± 2°C), a 12 h light/dark schedule, and allowed free access to standard diet and tap water except during the experiment. The animals were allowed to habituate to the laboratory environment for 2 h before the experiments were initiated. Institutional Animal Ethical Committee approved the study's protocol (Registration no. 126/CSS/BNCP-17/IAEC).

The tested compounds were administered intraperitoneally at different dose levels in six groups; each group was consisting of 10 animals. After 24 hours of the

drug administration, the percent mortality in each group was observed; approximate Lethal Dose was calculated by the Karbers Method (~400 mg/kg). [26-27]

In vivo Analgesic Activity

Prescreened animals (reaction time: 3-4 sec) of either sex were assigned to twenty-two groups of six each. Mefenamic acid was used as a standard; 1% CMC was used as a control. Tail-flick latency was assessed with an analgesiometer. The analgesic activity of title compounds (3a-3f, 4a-4f) was evaluated at equimolar doses equivalent to 25 mg/kg (Mefenamic acid) body weight. [25] The strength of the current passing through the naked nichrome wire was kept constant at 6 amps. The reaction time was recorded at 30, 60, 90, and 120 minutes after the treatment, and the cutoff time was set at ten seconds to avoid tissue damage. The difference in reaction time (sec) was calculated by comparing the test compounds/standard drug and the normal controls. The % relative analgesic activity was calculated by using the following formula:

$$\% \text{ Relative analgesic activity} = (DRT_{test} / DRT_{std}) \times 100$$

Where DRT_{test} is the difference in reaction time of the test compound with respect to (w.r.t.) the control and DRT_{std} is the difference in reaction time of the standard drug used w.r.t control.[25]

Statistical Analysis

The results are expressed as the mean ± SEM per group, and the data were statistically analyzed by one-way analysis of Variance (ANOVA) followed by Dunnett's test as a post hoc test. *p*-value <0.05 was considered statistically significant. All statistical calculations were performed using the evaluation version of Graph Pad® Prism 3.0 (USA) statistical software.

In vivo Anti-inflammatory Activity

Anti-inflammatory activity of title compounds (3a-3f, 4a-4f) was evaluated using the well-known Carrageenan induced rat paw edema model of Winter et al. using groups of six animals each. A freshly prepared aqueous suspension of carrageenan (1.0 % w/v, 0.1 mL) was injected in the subplanter region of each rat's right hind paw. One group was kept as control, and the other group's animals were pretreated with the test drugs, 1-hour before the carrageenan treatment. Mefenamic acid was used as a standard, and the anti-inflammatory activity was evaluated at equimolar doses equivalent to 25 mg/kg (Mefenamic acid) body weight. The volume was measured before and after carrageenan treatment at the 1, 2, 3, and 4 hours intervals with the help of a plethysmometer.

Anti-inflammatory activity was expressed as the percent of inhibition of the edema when compared with the control group and was calculated by using the formula:

$$\% \text{ inhibition of edema} = (V_c - V_t / V_c) \times 100$$

where V_t and V_c are the mean paw volumes of the test and control groups, respectively [27].

Statistical Analysis

The results are expressed as the mean ± SEM per group, and the data were statistically analyzed by one-way analysis of Variance (ANOVA) followed by Dunnett's test as a post hoc test. *P* value <0.05 was considered statistically significant. All statistical calculations were performed using the evaluation version of Graph Pad® Prism 3.0 (USA) statistical software.

Acute Ulcerogenesis

Albino rats have been divided into different groups consisting of six animals. In each group. Ulcerogenic activity was evaluated after p.o. Administration of test compounds or standard at the dose of 30 mg/kg. Control rats received p.o. Administration of vehicle (suspension of 1 % carboxy methyl cellulose). Food but not water was removed 24 hours before administration of the test compounds. After the drug treatment, the rats were fed a normal diet for 17 h and then killed. The stomach was removed and opened along the greater curvature, washed with distilled water, and cleaned gently by dipping in saline. The mucosal damage was examined by means of a magnifying glass. For each stomach, the mucosal damage was assessed according to the following scoring system:

0.0 scores were given to normal stomach (no injury, bleeding and latent injury).

0.5 scores were to latent injury or widespread bleeding (below 2 mm).

1.0 was to slight injury (2–3 dotted lines).

2.0 for severe injury (continuous lined injury or 5–6 dotted injuries).

3.0 for very severe injury (several continuous lined injuries) and

4.0 for widespread lined injury or widened injury.

The mean score of each treated group minus the control group's mean score was regarded as severity index of gastric mucosal damage.

Data are expressed as mean ± SEM; Data analyzed by one-way ANOVA followed by Dunnett's test, the significance of the difference between the control group and rats treated with the test compounds. The difference in results was considered significant when P > 0.01.[27]

Results and Discussion

The title compounds (3a-3f) were synthesized as per the scheme. In the first step, hydrazide derivatives (1a-1f) were synthesized from aromatic acids in two steps *i.e.,* esterification followed by reacting with hydrazine hydrate. IR spectra confirmed the structures with appearance of NH_2 peak. In the second step, thiosemicarbazide derivatives (2a-2f) were synthesized from hydrazides (1a-1f) with phenyl isothiocynate. The structures were confirmed by IR spectra with appearance of C=S peak. In the final step, Thiadiazole (3a-3f) derivatives were synthesized by cyclization of thiosemicarbazide derivatives (2a-2f) by

using phosphoric acid. The structures of title compounds (3a-3f) were confirmed by IR spectra with disappearance of C=O peak and also confirmed by ^{1}H NMR and LCMS. The purity of compounds was also ascertained by Elemental analysis (C, H and N).

In vivo Analgesic Activity

Mefenamic acid was used as a reference standard. The experiments were performed on albino rats of Wistar strain of either sex, weighing 200–250 g (from animal house of BN College of Pharmacy, Udaipur). The animals were maintained at 25 ± 2°C, 50 ± 5 % relative humidity and 12 hours light/dark cycles. The animals were fasted for 24 hours prior to the experiments, and water provided ad libitum. The test compounds were suspended in 1% aqueous carboxy methyl cellulose (CMC) solution and administered orally to experimental animals. The analgesic activity was determined *in vivo* by the abdominal constriction test induced by tail-flick method. The compounds (3a-3f) were screened for analgesic activity. The analgesic activity was evaluated at 30 mg/kg bodyweight. From the results, it was noticed that most of the compounds possess significant analgesic activity. At 30 min, compounds 3d and 3e were shown to possess significant and compounds 3d, 3e and 3f were shown to possess significant activity after 90 min.

In vivo Anti-inflammatory Activity

Carrageenan-induced rat paw edema model evaluated the anti-inflammatory activity of the synthesized compounds (30 mg/kg), subplanter injection of 0.1 mL, 1 % carrageenan produced an increase in paw volume (edema) of all the animals of various groups. The onset of action was evident from 1-hour in various test groups. A significant reduction in rat paw edema was observed by most test compounds at 4 hours compared to the control group. Mefenamic acid was used as reference standard.

From close inspection of the results of *in vivo* experiments, we can conclude that substituted at 3h, compounds 3c exhibited significant anti-inflammatory activity compared to standard drug Mefenamic acid, whereas after 4h, compounds 3c, 3d and 3e showed significant anti-inflammatory activity. [27] From the analgesic and anti-inflammatory activity profile, compounds 3d and 3e were subjected to acute ulcerogenesis test.

Acute Ulcerogenesis Test

The ulcerogenic effect of most active compounds 3d and **3e** was evaluated for gastric ulcerogenic potential in the rat stress model at four times the therapeutic doses. When compared with standard, these compounds showed less ulceration than the standard drugs.

Conclusion

In conclusion, we described some novel 1,3,4-thiadiazole derivatives for *in vivo* analgesic and anti-inflammatory activity. Most of the entitled compounds showed promising analgesic and anti-inflammatory activity. Among all the synthesized compounds, compounds 3d and 3e exhibited most prominent and consistent anti-inflammatory activity. From acute ulcerogenic studies, it can be concluded that compounds 3d and 3e are devoid of deadlier gastrointestinal toxicities. The present investigation suggests that 1,3,4-thiadiazole derivatives are promising templates for the design of new gastric safe anti-inflammatory agents. Further, QSAR research are in progress to study possible descriptors effects on various classes of COX inhibitors.

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