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Short communication

2-Amino-5-sulfanyl-1,3,4-thiadiazoles: A new series of selective cyclooxygenase-2 inhibitors

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A new series of cyclooxygenase-2 inhibitors with 2-amino--5-sulfanyl-1,3,4-thiadiazole as the central scaffold unit has been synthesized. The newly synthesized compounds were characterized by analytical and spectral methods. Compounds were screened for cyclooxygenase inhibitory activity by the colorimetric COX (ovine) inhibitor screening assay, anti-inflammatory activity by the carrageenean induced rat paw oedema test and analgesic activity by the tail flick method. Some compounds exhibited significant biological activity.

Keywords: 2-amino-5-sulfanyl-1,3,4-thiadiazoles, cyclooxygenase-1, cyclooxygenase-2, anti-inflammatory activity, analgesic activity

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Suppression of pain and inflammation still continues to be a challenge despite the availability of a number of non-steroidal anti-inflammatory drugs (NSAIDs). This is because NSAIDs do not only exhibit a different spectrum of analgesic, anti-pyretic and anti-inflammatory effects but also cause gastrointestinal (GI) complications ranging from dyspepsia to fatal upper GI tract bleeding and perforation (1). Efforts to improve the adverse effect profile of the current NSAIDs have been focused on developing prodrugs (2) or modifications of marketed formulations (3). These approaches have been only partially successful. A recent approach is development of selective cyclooxygenase (COX)-2 inhibitors (4–6). COX is the key enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and thromboxans. There are two types of cyclooxygenase enzymes, COX-1 and COX-2. Currently available NSAIDs inhibit both COX-1 and COX-2 enzymes. Inhibition of COX-1 reduces basal production of cytoprotective prostaglandins (PGs) PGE2 and PGI2 and hence causes ulceration while inhibition of COX-2 inhibits inflammation. Complete inhibition of COX-1 is therefore not preferred and drugs that inhibit the COX-2 enzyme are better anti-inflammatory agents (7, 8).

Owing to the continuous efforts in exploring the structural insights to aid the design (9, 10) and synthesis of safer novel anti-inflammatory agents, 2-amino-5-sulfanyl--1,3,4-thiadiazole was identified as the central nucleus. To date, 2-amino-5-sulfanyl--1,3,4-thiadiazole derivatives have not been reported to exhibit anti-inflammatory and

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analgesic activity. For this reason, it was thought worthwhile to synthesize a series of diaryl substituted 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives, and perform their pharmacological testing.

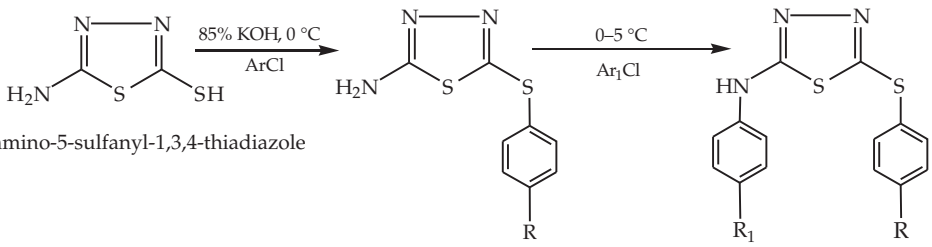
EXPERIMENTAL

Melting points were determined in an open capillary tube and were uncorrected. Purity of the compounds was checked on pre-coated silica gel G plates (0.2 mm thickness, Merck, India) using iodine vapor as visualizing agent. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 IR spectrometer (USA) and ^{1}H spectra were obtained on a Bruker DRX-300 MHz FT NMR spectrometer (USA). Mass spectra were recorded on a Jeol SX-102 mass spectrometer (Japan). Elemental analyses of the synthesized compounds were obtained on an Elemental Vario EL II /Carlo N 1108 (Italy). All the reagents used in the present work were of synthetic grade (Aldrich, Germany, Lancaster, UK).

The synthetic pathway is given in Scheme I (11) and characterization data of compounds are given in Table I.

Synthesis of 4-[5-chlorophenylamino)-1,3,4-thiadiazole-2-yl-sulphanyl]-benzene sulphonamide (1)

2-Amino-5-sulfanyl-1,3,4-thiadiazole (0.01 mol, 1.31 g) was suspended in a minimum quantity of water and a sufficient quantity of 85% KOH solution was added under stirring at room temperature. After a few minutes (5–10), the solution was brought to 0 °C in an ice bath and 4-chlorobenzene sulfonamide (ArCl) (0.01 mol, 1.92 g) was added under vigorous stirring. The reaction mixture was checked by thin layer chromatography.



2-amino-5-sulfanyl-1,3,4-thiadiazole

1-15

ArCl: 4-chlorobenzene sulfonamide (**1**, **3**, **5**, **7**, **9**, **11**, **14**, **15**) or 4-chlorobenzene sulfonylchloride (**2**, **4**, **6**, **8**, **10**, **12**, **13**). Ar_1Cl: 1,4-disubstituted benzene [1,4-dichlorobenzene (**1**, **2**), 1-bromo-4-chlorobenzene (**3**, **4**), 1-chloro-4-flurobenzene (**5**, **6**), 1-chloro-4-methylbenzene (**7**, **8**), 1-chloro-4-trifluromethylbenzene (**9**, **10**), 1-chloro-4-trichloromethylbenzene (**11**, **12**), 4-chlorobenzene sulfonylchloride (**13**, **14**), 4-chlorobenzene sulfonamide (**15**)

Scheme I

Table I. Characterization data of synthesized compounds ***1–15***

Compd.	Formula (M_r)	Yield (%)	M.p. (°C)	IR (KBr) (ν cm^{-1})						^{1}H NMR ($CDCl_3$) (δ, ppm)			MS (*m/z*, %)
				NH_2	NH	CH	C=N	SO_2	C-X	NH_2	NH	H_{ar}	
1	$C_{14}H_{11}ClN_4O_2S_3$ (398.9)	75	146–148	3334 3241	3285	3100	1637	1331 1165	540	2.5, s	4.4, s	7.47, s, 4H; 7.66, d, 2H; 7.85, d, 2H	398 M^+ (15) 400 M+2 (5), 274 (100), 156 (5), 111 (25)
2	$C_{14}H_9Cl_2N_3O_2S_3$ (418.3)	78	136–138	3285 3118	3240	3096	1656	1331 1176	560	–	3.4, s	7.48, 2H, 7.65, 2H, 7.75, 2H, 7.85, 2H	418 M^+ (5), 422 M+4 (5), 420 M+2 (10), 274 (100), 111 (18)
3	$C_{14}H_{11}BrN_4O_2S_3$ (443.4)	67	145–147	3500 3390	3280	3050	1640	1300 1120	560	2.0, s	3.4, s	7.48, s, 4H; 7.66, 2H, 7.84, 2H	443 M^+ (24), 445 M+2 (8), 274 (100)
4	$C_{14}H_9ClBrN_3O_2S_3$ (462.8)	69	192–194	3350 3185	3210	3050	1590		550 580	–	3.4, s	6.85, 2H, 7.18, 2H, 7.41, 2H, 7.78, 2H	462 M^+ (10), 464 M+2 (20), 466 M+4 (70)
5	$C_{14}H_{11}FN_4O_2S_3$ (382.5)	80	138–140	3289 3150	3241	3100	1656	1386 1176	1022	2.5, s	3.5, s	7.48, s, 4H; 7.67, 2H, 7.83, 2H,	382 M^+ (27), 384 M+2 (9), 274 (100)
6	$C_{15}H_9ClFN_3O_2S_3$ (401.9)	72	220–222	3340 3215			1660		980 580	–	4.0, s	6.44, d, 2H; 6.72, d, 2H; 7.41, d, 2H; 7.78 d, 2H;	401 M^+ (87), 403 M+2 (16), 405 M+4 (8)
7	$C_{15}H_{14}N_4O_2S_3$ (378.5)	70	144–146	3333 3240	3286	3090	1634	1329 1167	760	–	3.43, s	7.48, s, H; 7.67, 2H; 7.84, 2H;	378 M^+ (25), 274 (100), 91 (45)
8	$C_{15}H_{12}ClN_3O_2S_3$ (397.9)	68	130–132	–	3270	3070	1630	1350 1140	550	–	3.43, s	6.34, d, 2H; 6.81, d, 2H; 7.41, d, 2H; 7.78, d, 2H;	397 M^+ (18), 399 M+2 (6), 91 (40)

Compd.	Formula (M_r)	Yield (%)	M.p. (°C)	IR (KBr) (ν cm^{-1})						^{1}H NMR ($CDCl_3$) (δ, ppm)			MS (*m/z*, %)
				NH_2	NH	CH	C=N	SO_2	C-X	NH_2	NH	H_{ar}	
9	$C_{15}H_{11}ClF_3N_4O_2S_3$ (432.5)	65	134–136	3333 3151	3241	3070	1633		1151	2.5, s	3.41, s	6.39, d, 2H; 7.20, d, 2H; 7.46, d, 2H; 7.77, d, 2H	432 M^+ (4), 434 M+2 (12), 436 M+4 (12), 430 M+6 (4)
10	$C_{15}H_9ClF_3N_3O_2S_3$ (451.9)	78	116–118	–	3245	3075	1640	1336 1152	1090 580		4.0, s	6.39, d, 2H; 7.20, d, 2H; 7.41, d, 2H; 7.78 d, 2H;	452 M^+ (8)
11	$C_{15}H_{11}Cl_3N_4O_2S_3$ (481.8)	58	137–139	3334 3151	3240	3050	1651	1328 1176	1014	2.5, s	3.49, s	7.56, d, 2H; 7.65, d 2H; 7.83,d 2H; 7.94 d, 2H;	482 M^+ (8)
12	$C_{15}H_9Cl_4N_3O_2S_3$ (501.3)	71	125–127	–	3250	3040	1650	1333 1150	550		3.49, s	6.39, d, 2H; 7.56, d, 2H; 7.41, d, 2H; 7.75, d, 2H;	501 M^+ (12)
13	$C_{14}H_9Cl_2N_3O_4S_4$ (482.4)	82	152–154	–	3285	3070	1640	1340 1145	575	–	3.53, s	6.69 d ,2H; 7.69, d, 2H; 7.41, d, 2H;	482 M^+ (5)
14	$C_{14}H_{11}ClN_4O_4S_4$ (463)	68	126–128	3271 3185		3087	1638	1336 1139		2.5, s	3.53, s	7.48 d, 2H; 7.65 d, 2H; 7.68 d, 2H; 7.83 d, 2H;	463 M^+ (24), 465 M+2 (8), 274 (100), 175 (40)
15	$C_{14}H_{13}N_5O_2S_4$ (443.5)	60	146–148	3310 3250			1640	1345 1150		2.5, s	3.46, s	7.37 d, 2H; 7.54 d, 2H; 7.65, d, 2H; 7.86 d, 2H	443 M^+ (25), 274 (100), 156 (45)

The solution was neutralized upon completion of the reaction. The precipitate of 4-[5--amino-(1,3,4)thiadiazole-2-yl-sulphanyl]-benzene sulphonamide formed slowly. It was filtered, washed with distilled water and crystallized using ether as a solvent. The purity of the synthesized intermediate was ascertained by thin layer chromatography using a methanol and xylene mixture (4:6, *V*/*V*). The intermediate (0.01 mol; 2.88 g) was dissolved in ether and 1,4-dichlorobenzene (0.01 mol, 1.48 g) was added under stirring while maintaining the temperature between 0–5 °C. After 30 minutes, water was added, and a precipitate was formed. Filtration of the compound and recrystallization from ether yielded compound **1**. Compounds **2–15** were synthesized in a similar way.

Colorimetric COX (ovine) inhibitor screening assay

All synthesized compounds were evaluated for COX-1 and COX-2 inhibitory activity by the colorimetric COX (ovine) inhibitor screening assay (13). It utilizes the peroxidase component of cyclooxygenase. The peroxidase activity was assayed colorimetrically by monitoring the appearance of oxidized *N,N,N,N*-tetramethyl-*p*-phenylenediamine (TMPD) at 590 nm. This assay measures the heme-catalyzed hydroperoxidase activity of ovine cyclooxygenase. The percentage of COX-1 and COX-2 inhibition is reported in Table II.

Table II. Structure and in vitro *inhibition of COX-1 and COX-2 by compounds **1** to **15***

Compd. No.	R	R_1	Inhibition (%)	
			COX-1[b]	COX-2[a,b]
1	$-SO_2NH_2$	–Cl	97.17 ± 0.01	3.43 ± 0.02
2	$-SO_2Cl$	–Cl	100.00 ± 0.03	87.85 ± 0.04
3	$-SO_2NH_2$	–Br	56.50 ± 0.03	12.15 ± 0.02
4	$-SO_2Cl$	–Br	70.12 ± 0.01	60.74 ± 0.01
5	$-SO_2NH_2$	–F	–41.24 ± 0.03	14.95 ± 0.04
6	$-SO_2Cl$	–F	100.00 ± 0.02	100.00 ± 0.01
7	$-SO_2NH_2$	$-CH_3$	–91.52 ± 0.01	22.74 ± 0.03
8	$-SO_2Cl$	$-CH_3$	100.00 ± 0.01	100.00 ± 0.01
9	$-SO_2NH_2$	$-CF_3$	–119.25 ± 0.02	8.10 ± 0.01
10	$-SO_2Cl$	$-CF_3$	100.00 ± 0.03	100.00 ± 0.02
11	$-SO_2NH_2$	$-CCl_3$	–85.87 ± 0.03	–20.87 ± 0.02
12	$-SO_2Cl$	$-CCl_3$	100.00 ± 0.04	100.00 ± 0.03
13	$-SO_2Cl$	$-SO_2Cl$	100.00 ± 0.03	100.00 ± 0.02
14	$-SO_2NH_2$	$-SO_2Cl$	–110.17 ± 0.03	42.36 ± 0.01
15	$-SO_2NH_2$	$-SO_2NH_2$	100.00 ± 0.01	100.00 ± 0.02
Indomethacin	–	–	100.00 ± 0.02	97.00 ± 0.01
Celecoxib	–	–	0.00	100.00 ± 0.01

[a] 0.1 nmol applied
[b] Mean ± SEM, $n = 3$.

The inhibitory activity was measured on a Bio Rad 550 (India) plate reader, on a plate consisting of ninety wells. First, three wells were marked as background wells, then three wells were marked as 100% initial activity wells and the remaining fifty-one wells were marked as inhibitor wells. To the background wells, 160 μL buffer (0.1 mol L^{-1} Tris HCl, pH 8), 10 μL heme and 10 μL DMSO were added; 150 μL buffer, 10 μL heme, 10 μL DMSO and 10 μL of COX-1 enzyme were added to 100% initial activity wells; 150 μL buffer, 10 μL heme, 10 μL of COX-1 and 10 μL of 10 m mol L^{-1} solution of test compound **1** in DMSO were added to the other three wells. In the same manner, the remaining forty-eight wells were prepared for test compounds 2 to 15, indomethacin and celecoxib, respectively. The plate was carefully shaken for a few seconds and incubated for 5 minutes at 25 °C. Finally, 20 μL TMPD and 20 μL arachidonic acid were added to all fifty-seven wells. The plate was shaken again and incubated for 5 minutes at 25 °C. The absorbance was noted at 590 nm and percentage inhibition was calculated. The procedure was repeated three times.

The COX-2 inhibitory activity was determined as discussed above; here COX-2 enzyme was used instead of COX-1 enzyme.

Anti-inflammatory activity

Anti-inflammatory activity of all synthesized compounds was determined by the carrageenean-induced rat paw oedema test as described by Winter *et al*. (14). Albino rats of Wistar strain (150–200 g) of both sexes were divided into different groups (control, test and standard) containing six animals each. The animals were housed in standard polypropylene cages under standard laboratory conditions (12:12 hour light/dark cycle at 25 ± 2 °C). They had free access to standard commercial diet and water. Ethical guidelines for the investigations of animals used in experiments were followed in all tests and the institutional Ethical Committee Approval was provided. The test and standard compounds were suspended in 1% carboxymethyl cellulose and administered orally to each animal using a gastric gavage needle. The control group animals, however, received the same volume of vehicle (1% carboxymethyl cellulose). One hour after the compounds were administered, carrageenean was injected into the subplantar surface of the right hind paw of animals. In this study, the animals were administered a 56 mg kg^{-1} (body mass) dose of the test drug and 10 mg kg^{-1} (body mass) dose of the standard drug indomethacin. The paw volume was measured immediately using a plethysmometer (initial paw volume) and thereafter the paw volume was measured 3 hours and 6 hours after the administration of carrageenean. Percent paw oedema inhibition is reported in Table III.

Analgesic activity

The analgesic activity was measured by the tail flick method (15), using a radiant type analgesiometer. The basal reaction time to radiant heat was taken by placing the tip of the tail on the radiant heat source. Swiss albino mice (25–30 g) of either sex were divided into seventeen groups containing six animals each. Animals were housed in standard polypropylene cages under standard laboratory conditions (12:12 hour light/dark cycle at 25 ± 2 °C). They had free access to standard commercial diet and water. For each animal, the tail flick reaction time was obtained thrice before drug administration and

*Table III. Anti-inflammatory activity of synthesized compounds **1** to **15** on carrageenen induced rat paw edema*

Compd. No.	Inhibition of paw oedema after 3 hours (%)[a,b]	Inhibition of paw oedema after 6 hours (%)[b]
Control	–	–
1	15.11 ± 0.02	10.41 ± 0.01
2	46.51 ± 0.01	34.37 ± 0.01
3	23.25 ± 0.01	16.66 ± 0.02
4	38.37 ± 0.02	31.25 ± 0.01
5	26.74 ± 0.02	20.83 ± 0.02
6	61.62 ± 0.02	47.91 ± 0.02
7	41.86 ± 0.01	34.37 ± 0.02
8	65.11 ± 0.01	44.79 ± 0.02
9	18.60 ± 0.02	13.54 ± 0.02
10	61.62 ± 0.01	52.08 ± 0.02
11	00.00	–4.16 ± 0.01
12	65.11 ± 0.01	44.79 ± 0.01
13	61.62 ± 0.02	41.66 ± 0.02
14	53.48 ± 0.02	47.91 ± 0.03
15	63.95 ± 0.01	50.00 ± 0.01
Indomethacin	76.74 ± 0.01	58.33 ± 0.02

[a] Dose for **1–15**: 56 mg kg^{-1} b.m.
Dose for indomethacin 10 mg kg^{-1} b.m.
[b] Mean ± SEM, $n = 6$.

the mean was used as the pre-drug reaction time. After administration of the drug, the tail flick reaction times were measured after 30, 60, 90 and 180 minutes. The first group served as control and the animals were administered the vehicle (10% Tween 20). The second group of animals was administered 22.8 mg kg^{-1} (body mass) standard drug (tramadol hydrochloride). The animals of the third to seventeenth group were treated with 30 mg kg^{-1} (body mass) dose of the test drugs **1–15**. Increase in the tail flick reaction time after the administration of test drugs and standard drug were calculated for 30, 60, 90 and 180 minutes (Fig. 1).

RESULTS AND DISCUSSION

2-Amino-5-sulfanyl-1,3,4-thiadiazole reacted with potassium hydroxide to afford a water soluble weak salt with an electron rich center and reacted with electron deficient 4-chlorobenzene sulphonamide to yield the intermediate 4-(5-amino-[1,3,4]-thiadiazole-

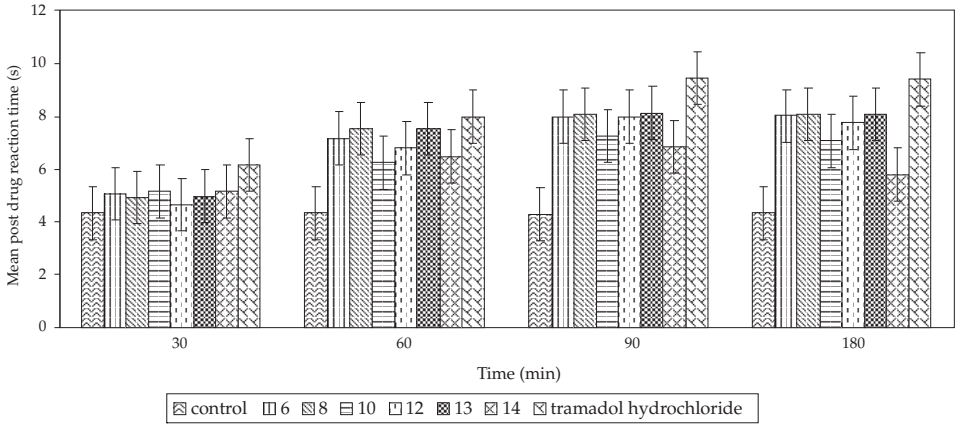


Fig. 1. Analgesic activity (tail flick) (mean post drug reaction ± SEM, $n = 6$).

-2-yl-sulphanyl)-benzene sulphonamide. The reaction was slow at the initial stage but the formation of KCl enhanced the reaction rate. The intermediate was then subjected to electrophillic substitution reaction with the electron deficient moiety 1,4-dichlorobenzene. It afforded compound **1** and similarly compounds **2–15** (11). Elemental analyses data and spectral data of all the synthesized compounds are in agreement with the assigned structure (Table I).

In vitro inhibition of COX-1 and COX-2 enzyme data (Table II) indicate that compounds **5**, **7**, **9** and **14** were selective inhibitors of COX-2 and potentiated the activity of COX-1 enzyme (16). Among the above four compounds, **14** showed the highest selective inhibitory activity against COX-2 enzyme (42.4%). All the four compounds possess the sulphonamide group, which is in agreement with the established fact that sulphonamide group is a required pharmacophore for selective inhibition of COX-2 enzyme. However, compounds **6**, **8**, **10**, **12**, **13** and **15** showed non-selective COX inhibitory activity; they showed 100% inhibition against COX-1 and COX-2 enzymes. Compounds **1**, **2**, **3** and **4** showed selective inhibitory activity against COX-1 enzymes. The percentage inhibition of COX-1 and COX-2 by compound **2** is comparable to that of the standard drug indomethacin. Most interesting activity was found in compounds **11** and **12**. Compound **11** was found to potentiate the activity of COX-1 and COX-2 enzymes while replacement of $-SO_2NH_2$ in **11** by $-SO_2Cl$ in **12** made it a non-selective COX inhibitor.

Inflammation induced by carrageenean involves three distinct phases of mediator release, including serotonin and histamine in the first phase (0–2 hours), kinins in the second phase (3 hours) and prostaglandin in the third phase (0–4 hours). The results of this study indicate that compounds **6**, **8**, **10**, **12**, **13** and **14** protected the paw oedema in rat by 54 to 65% after 3 hours and 45 to 52% after 6 hours, while other tested compounds showed lower anti-inflammatory activity compared to indomethacin (Table III). This suggests that the presence of $-SO_2Cl$ is also favorable for anti-inflammatory and analgesic activity. The same compounds showed analgesic activity comparable to that of tramadol hydrochloride (Fig. 1).

CONCLUSIONS

Compound **14** {4-[5-(4-sulfamoyl-phenylsulphanyl)-1,3,4-thiadiazole-2-yl-amino]-benzene sulphonyl chloride} can be selected for further studies since it contains sulphonamide as well as sulphonyl group; it showed the highest percentage of COX-2 inhibition and significant anti-inflammatory and analgesic activity compared to indomethacin and tramadol hydrochloride, respectively.

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S A Ž E T A K

2-Amino-5-sulfanil-1,3,4-tiadiazoli: Nova serija selektivnih inhibitora ciklooksigenaze-2

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Sintetizirana je nova serija inhibitora ciklooksigenaze-2 s 2-amino-5-sulfanil-1,3,4-tiadiazolom. Novi spojevi karakterizirani su uobičajenim analitičkim i spektroskopskim metodama. Sintetiziranim spojevima ispitana je sposobnost inhibicije ciklooksigenaze kolorimetrijskim COX testom (goveđi COX), protuupalno djelovanje na edem šape induciran karageninom i analgetsko djelovanje metodom pomicanja repa. Neki su spojevi pokazali značajno biološko djelovanje.

Ključne riječi: 2-amino-5-sulfanil-1,3,4-tiadiazoli, ciklooksigenaza-1, ciklooksigenaza-2, protuupalno djelovanje, analgetsko djelovanje

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