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Synthesis and anti-inflammatory activities of some thiazolo[3,2-a]pyrimidine derivatives

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Abstract

Sixteen new 2-benzylidene-7-methyl-3-oxo-5-(substituted phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid methyl esters (**1a**–**4d**) have been synthesized by reacting 1,2,3,4-tetrahydropyrimidine-2-thiones (**1**–**4**) with chloroacetic acid and appropriate benzaldehydes in a single step. Their structures have been proved by IR, ^{1}H NMR, mass spectra and elemental analysis. The compounds were tested for their anti-inflammatory activities. Test results revealed that compounds **1b**, **1c**, **4a** and **4c** exerted moderate anti-inflammatory activity at the 100 mg/kg dose level compared with indomethacin.

Keywords: 1,2,3,4-Tetrahydropyrimidine-2-thiones; Thiazolo[3,2-a]pyrimidines; Synthesis; Anti-inflammatory activity

1. Introduction

The chemistry and the synthesis of 1,2,3,4-tetrahydropyrimidine-2-ones(-thiones) have been attracting widespread attention in recent years. The present popularity of these tetrahydropyrimidines is mainly due to their close structural relationship to the clinically important dihydropyridine calcium channel blockers [1–6].

1,2,3,4-Tetrahydropyrimidine-2-thiones are the key intermediate for the synthesis of condensed pyrimidines. Their various condensed derivatives are reported to possess calcium antagonist [7–9], anti-inflammatory [10–12], analgesic [13], antitumor [14,15], antidepressant [16], antibacterial and antifungal effects [17–19].

In our previous study, we synthesized some 2-benzylidene-7-methyl-3-oxo-5-(substituted phenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylic acid methyl esters and investigated their anti-inflammatory activities [20]. Since few of them showed hopeful pharmacological results, we decided to investigate the synthesis and anti-inflammatory activities of new condensed 1,2,3,4-tetrahydropyrimidine derivatives.

In this study, synthesis, structural elucidation and anti-inflammatory activities of a new series of thiazolo[3,2-a]pyrimidine having 4-bromo, 4-methoxy, 4-methyl, 2-fluorophenyl at position 5 and 4-methyl, 4-methoxy, 4-chloro and non-substituted benzylidene at position 2 are reported.

2. Experimental

2.1. Chemistry

All chemicals were from Aldrich Chemical Co. (Steinheim, Germany). Melting points were detected with a Thomas Hoover capillary melting point apparatus (Philadelphia, PA, USA) and are uncorrected. IR spectra (KBr) were recorded on a Perkin–Elmer 1720X FT-IR spectrometer (Beaconsfield, UK). ^{1}H NMR spectra were obtained using a Bruker 200 MHz FT NMR instrument (Karlsruhe, Germany) using $CDCl_3$ or DMSO-d_6 and tetramethylsilane as an internal standard. All chemical shift values were recorded as δ (ppm). Mass spectra were taken on a VG Analytical 70-250S or Finnigan MAT GCQ mass spectrometer with electron ionization (EI) (University of Regensburg or Westfälische Wilhelms–University of Münster, Ger-

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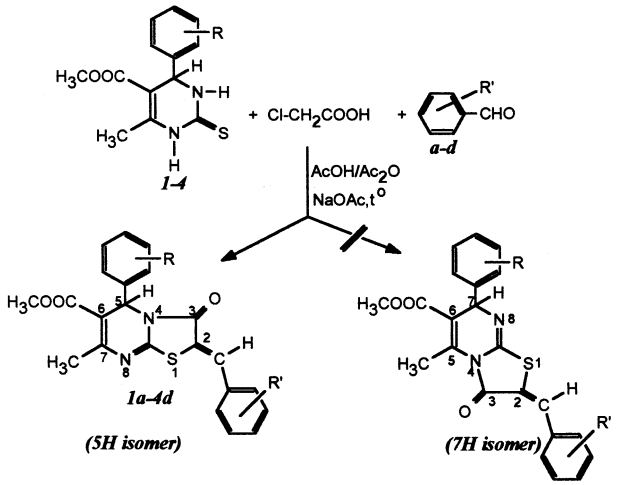


Scheme 1.

many). The purity of the compounds was controlled by thin layer chromatography (Merck, silicagel, $HF_{254-361}$, type 60, 0.25 mm, Darmstadt, Germany). The elementary analyses were performed by Westfälische Wilhelms–University of Münster, Germany. Elementary analyses for C, H, N were within $\pm 0.4\%$ of theoretical values.

2.1.1. Methyl 6-methyl-4-(substituted phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates ***(1–4)***

A mixture of thiourea (0.05 mol), substituted benzaldehyde (0.05 mol), methyl acetoacetate (0.075 mol), dry ethanol (20 ml) and 37% HCl (eight drops) was heated under reflux for an appropriate period and the reaction solution was allowed to cool. The product, which appeared as a precipitate, was filtered off and washed with 50% ethanol. It was then recrystallized from ethanol. The synthesis and the structural data of compounds **1–3** were reported previously [5,6]. Compound **4** was newly synthesized and its structure was proved by IR, ^{1}H NMR and elementary analysis.

2.1.2. Methyl 6-methyl-4-(2-fluorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***(4)***

M.p. 215–216°C (EtOH). IR (KBr): $\nu = 3186$ cm^{-1} (NH), 1665 (C=O), 1573, 1490, 1456 (C=C), 1347, 1285, 1271 (C–O, C–N), 1196 (C=S). ^{1}H NMR (DMSO-d_6): $\delta = 2.30$ (s, 3H, $-CH_3$), 3.50 (s, 3H, $-OCH_3$), 5.50 (d, $J = 3.68$ Hz, 1H, H-4), 6.90–7.40 (m, 4H, arom. H), 9.60 (s, 1H, N_1–H), 10.40 (s, 1H, N_3–H). *Anal.* ($C_{13}H_{13}FN_2O_2S$) C, H, N.

2.1.3. Methyl 2-benzylidene-7-methyl-3-oxo-5-phenyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylates ***(1a–4d)***

These were obtained by reacting 1,2,3,4-tetrahydropyrimidine-2-thiones (**1–4**) with chloroacetic acid and the appropriate benzaldehydes as reported in Ref. [20].

2.2. Pharmacology

Local breed albino mice of both sexes (Refik Saydam Hıfzıssıhha Institute, Animal Care Unit, Ankara, Turkey) weighing approximately 20–25 g were used. Six randomly chosen mice were housed for 2 days for acclimatization to room conditions and were main-

Table 1
Some characteristics of the compounds **1a–4d**

Comp. no.	R	R′	M.p. (°C)	Yield (%)	Formula (MW)	Analysis [a]
1a	4-Br	-H	143–144	63.10	$C_{22}H_{17}BrN_2O_3S$	C, H, N
1b		4-CH_3	204–205	53.79	$C_{23}H_{19}BrN_2O_3S$	C, H, N
1c		4-OCH_3	161–162	66.88	$C_{23}H_{19}BrN_2O_4S$	C, H, N
1d		4-Cl	197–198	58.55	$C_{22}H_{16}BrClN_2O_3S$	C, H, N
2a	4-OCH_3	-H	171–172	62.43	$C_{23}H_{20}N_2O_4S$	C, H, N
2b		4-CH_3	194–195	63.29	$C_{24}H_{22}N_2O_4S$	C, H, N
2c		4-OCH_3	184–186	61.60	$C_{24}H_{22}N_2O_5S$	C, H, N
2d		4-Cl	217–218	50.56	$C_{23}H_{19}ClN_2O_4S$	C, H, N
3a	4-CH_3	-H	167–168	50.20	$C_{23}H_{20}N_2O_3S$	C, H, N
3b		4-CH_3	218–219	39.13	$C_{24}H_{22}N_2O_3S$	C, H, N
3c		4-OCH_3	167–168	44.13	$C_{24}H_{22}N_2O_4S$	C, H, N
3d		4-Cl	198–199	55.93	$C_{23}H_{19}ClN_2O_3S$	C, H, N
4a	2-F	-H	192–193	52.64	$C_{22}H_{17}FN_2O_3S$	C, H, N
4b		4-CH_3	132–133	74.56	$C_{23}H_{19}FN_2O_3S$	C, H, N
4c		4-OCH_3	213–214	45.61	$C_{23}H_{19}FN_2O_4S$	C, H, N
4d		4-Cl	133–134	62.09	$C_{22}H_{16}ClFN_2O_3S$	C, H, N

[a] Analytical results for C, H, N were within $\pm 0.4\%$ of the calculated values.

Table 2
IR and ^{1}H NMR data of the compounds **1a–4d**

Comp. no.	IR (KBr): ν (cm^{-1})	^{1}H NMR ($CDCl_3$): δ (ppm) (J in Hz)
1a	1708 (C=O), 1603 (C=N)	2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 6.15 (s, 1H, H-5), 7.20–7.50 (m, 9H, arom.H), 7.70 (s, 1H, =C–H)
1b	1708, (C=O), 1598 (C=N)	2.40 (s, 3H, =CH–C_6H_4–CH_3), 2.55 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 6.15 (s, 1H, H-5), 7.20–7.50 (m, 8H, arom.H), 7.75 (s, 1H, =C–H)
1c	1714 (C=O), 1588 (C=N)	2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 3.85 (s, 3H, =CH–C_6H_4–OCH_3), 6.15 (s, 1H, H-5), 6.95 (d, $J = 8.70$ Hz, 2H, arom.H), 7.30 (d, $J = 8.70$ Hz, 2H, arom.H), 7.40–7.50 (m, 4H, arom.H), 7.70 (s, 1H, =C–H)
1d	1717 (C=O), 1608 (C=N)	2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 6.15 (s, 1H, H-5), 7.20–7.50 (m, 9H, arom.H), 7.70 (s, 1H, =C–H)
2a	1706 (C=O), 1622 (C=N)	2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-C_6H_4$–OCH_3), 6.15 (s, 1H, H-5), 6.82 (d, $J = 8.50$ Hz, 2H, arom.H), 7.25–7.50 (m, 7H, arom.H), 7.75 (s, 1H, =C–H)
2b	1703 (C=O), 1599 (C=N).	2.40 (s, 3H, =CH–C_6H_4–CH_3), 2.55 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-C_6H_4$–OCH_3), 6.15 (s, 1H, H-5), 6.80 (d, $J = 8.50$ Hz, 2H, arom.H), 7.20–7.40 (m, 6H, arom.H), 7.75 (s, 1H, =C–H)
2c	1710 (C=O), 1596 (C=N)	2.55 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-C_6H_4$–OCH_3), 3.85 (s, 3H, =CH–C_6H_4–OCH_3), 6.15 (s, 1H, H-5), 6.80 (d, $J = 8.50$ Hz, 2H, arom.H), 6.95 (d, $J = 8.50$ Hz, 2H, arom.H), 7.25–7.45 (m, 4H, arom.H), 7.70 (s, 1H, =C–H)
2d	1704 (C=O), 1625 (C=N)	2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-C_6H_4$–OCH_3), 6.15 (s, 1H, H-5), 6.80 (d, $J = 8.30$ Hz, 2H, arom.H), 7.25–7.50 (m, 6H, arom.H), 7.70 (s, 1H, =C–H)
3a	1710 (C=O), 1604 (C=N)	2.30 (s, 3H, $-C_6H_4$–CH_3), 2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 6.15 (s, 1H, H-5), 7.10–7.50 (m, 9H, arom.H), 7.70 (s, 1H, =C–H)
3b	1714 (C=O), 1601 (C=N)	2.30 (s, 3H, $-C_6H_4$–CH_3), 2.40 (s, 3H, =CH–C_6H_4–CH_3), 2.55 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 6.15 (s, 1H, H-5), 7.05–7.40 (m, 8H, arom.H), 7.70 (s, 1H, =C–H)
3c	1708 (C=O), 1595 (C=N)	2.30 (s, 3H, $-C_6H_4$–CH_3), 2.55 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 3.85 (s, 3H, =CH–C_6H_4–OCH_3), 6.15 (s, 1H, H-5), 6.95 (d, $J = 8.20$ Hz, 2H, arom.H), 7.10 (d, $J = 8.20$ Hz, 2H, arom.H), 7.30 (d, $J = 8.20$, 2H, arom.H), 7.40 (d, $J = 8.20$ Hz, 2H, arom.H), 7.70 (s, 1H, =C–H)
3d	1715 (C=O), 1621 (C=N)	2.30 (s, 3H, $-C_6H_4$–CH_3), 2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 6.15 (s, 1H, H-5), 7.10 (d, $J = 8.50$ Hz, 2H, arom.H), 7.30 (d, $J = 8.50$ Hz, 2H, arom.H), 7.35–7.50 (m, 4H, arom.H), 7.65 (s, 1H, =C–H)
4a	1718 (C=O), 1604 (C=N)	2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 6.40 (s, 1H, H-5), 6.95–7.50 (m, 9H, arom.H), 7.75 (s, 1H, =C–H)
4b	1714 (C=O), 1602 (C=N)	2.40 (s, 3H, =CH–C_6H_4–CH_3), 2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 6.40 (s, 1H, H-5), 6.95–7.45 (m, 8H, arom.H), 7.70 (s, 1H, =C–H)
4c	1713 (C=O), 1595 (C=N)	2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 3.85 (s, 3H, =CH–C_6H_4–OCH_3), 6.40 (s, 1H, H-5), 6.90–7.45 (m, 8H, arom.H), 7.70 (s, 1H, =C–H)
4d	1713 (C=O), 1607 (C=N)	2.50 (s, 3H, $-CH_3$), 3.65 (s, 3H, $-OCH_3$), 6.40 (s, 1H, H-5), 6.95–7.50 (m, 8H, arom.H), 7.65 (s, 1H, =C–H)

tained on a standard diet and water ad libitum. The food was withdrawn on the day before the experiment, but free access to water was allowed. Mice used in the present study were cared in accordance with the directory of the Refik Saydam Hıfzıssıhha Institute's Animal Care Unit, which applies the guidelines of the National Institutes of Health on laboratory animal welfare.

2.2.1. Anti-inflammatory activity: carrageenan induced edema

The method of Winter et al. [21] was employed with some modifications. All test samples were administered to animals at a 100 mg/kg dosage, as a suspension in 0.5% carboxymethyl cellulose using gastric lavage apparatus. One hour after the oral administration of the test sample, each mouse was injected with 0.01 ml of

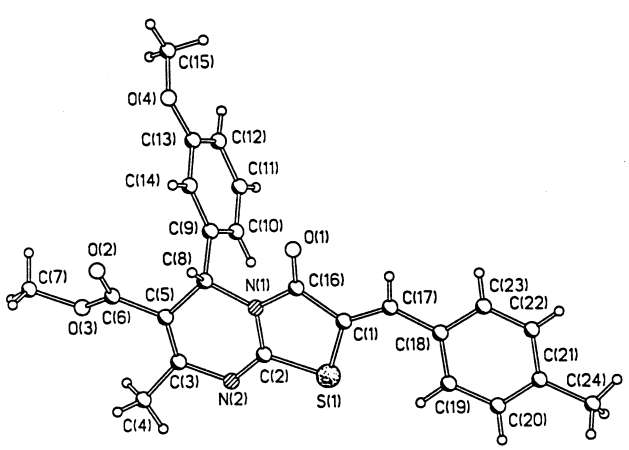
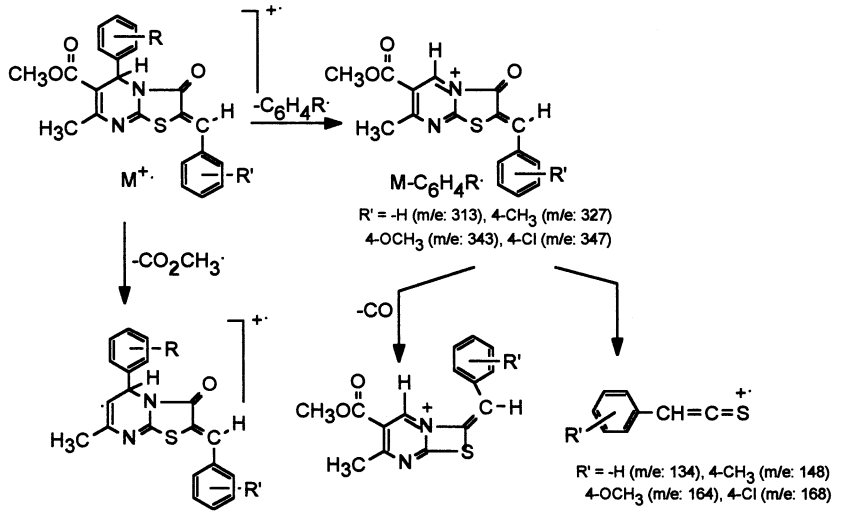


Fig. 1. A view of methyl 2-(4-metylbenzylidene)-7-methyl-3-oxo-5-(3-methoxyphenyl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate [20].



Scheme 2.

2% carrageenan solution into subplantar tissue of the right hind paw. The volume of the paw was measured immediately and again 2 h after the carrageenan injection with a Peacock thickness gauge. The animals in the control group received appropriate volumes of the dosing vehicle only. The percent of inhibitory effects of drugs was calculated according to the following equation:

$$\text{Anti-inflammatory activity } (\%) = [(n - n')/n] \times 100$$

where n is the difference in thickness between the first and second measure of the paw in the control group and n' is the difference in thickness between the first and second measure of the paw in the group treated with the test sample.

Indomethacin (10 mg/kg) was used as a reference compound.

The experiment was repeated at two different dose levels (25 and 50 mg/kg) for the compounds which showed significant statistical differences between the treatments and the control group. ED_{50} values were calculated by using the Lichtfield–Wilcoxon method.

Two-way analysis of variance (ANOVA) was employed as the statistical method.

2.2.2. Gastrointestinal ulceration studies [22]

Mice were fasted for 24 h (with water ad libitum). The compounds were suspended in a carboxymethyl cellulose vehicle and administered orally by lavage at 100 mg/kg/day dose for 5 days in a volume of 0.5 ml/100 g of body weight. The animals were sacrificed with diethyl ether inhalation 4 h after the last dose and their stomachs were removed, opened by cutting along the greater curvature and examined for lesions in the gastrointestinal mucosa under a dissecting microscope. Indomethacin was compared to control groups as a positive control for gastric ulceration.

3. Chemistry

The synthesis of 1,2,3,4-tetrahydropyrimidines (**1**–**4**) was achieved in a one-pot condensation reaction of aromatic aldehyde, thiourea and methyl acetoacetate in ethanolic solution, commonly known as the Biginelli reaction. Reaction of **1**–**4** with chloroacetic acid and appropriate benzaldehydes under the previously given conditions yielded thiazolo[3,2-a]pyrimidines (**1a**–**4d**) (Scheme 1). The melting points, % yields and formulas of the synthesized compounds are given in Table 1. The structures of the compounds were elucidated by IR, ^{1}H NMR, mass spectra and elemental analysis and all spectral data were in accordance with the assigned structures (Table 2).

4. Results and discussion

In the IR spectra no absorption band was detected at about 3152–3380 cm^{-1} and 1187–1196 cm^{-1}. The lack of bands attributable to the N–H and C=S groups, respectively, was the evidence of the ring closure. The lactam C=O and ester C=O stretching bands were seen at the same region (at about 1703–1718 cm^{-1}).

Because of the thiourea moiety, there is a possibility of obtaining two isomeric cyclization products (5H or 7H isomers) in this reaction. The identity of the isolated product has been determined from the ^{1}H NMR data. The signal for the C-4 proton in compounds **1**–**4** appeared at 5.10–5.70 ppm as a doublet. Due to the electronegative effect of the C=O group in position 3 a

Table 3
Anti-inflammatory activity of **1a–4d**

Comp. no.	R	R′	Anti-inflammatory activity (%)[a]	ED_{50}[b]	Ulcer incidence (No./gp.)
1a	4-Br	-H	7		
1b		4-CH_3	41	18.36	6/8
1c		4-OCH_3	38	18.36	6/8
1d		4-Cl	0		
2a	4-OCH_3	-H	5		
2b		4-CH_3	0		
2c		4-OCH_3	0		
2d		4-Cl	0		
3a	4-CH_3	-H	8		
3b		4-CH_3	0		
3c		4-OCH_3	6		
3d		4-Cl	0		
4a	2-F	-H	16	39.68	6/8
4b		4-CH_3	0		
4c		4-OCH_3	28	39.68	6/8
4d		4-Cl	0		
Indomethacin[c]			32	1.98	8/8

[a] 100 mg/kg p.o. ($n = 6$).
[b] Since the result was not significant compared to control ($P > 0.05$) ED_{50} values were not calculated.
[c] 10 mg/kg p.o.

downfield shift of the C-4 proton was observed when the ring closure occurred. Therefore, the fused products **1a–4d** were identified as 5H-thiazolo[3,2-a]pyrimidine and not as 7H-thiazolo[3,2-a]pyrimidine. In our previous study [20], we confirmed the structure of the cyclization product as 5H-thiazolo[3,2-a]pyrimidine for this type of compounds by X-ray crystallographic analysis as illustrated in Fig. 1.

EI-MS spectra of all examined compounds showed molecular ion peaks as expected. The fragmentation patterns (Scheme 2) confirmed the suggested structure. The base peaks were seen at $m/e = 313$ (R′ = -H), $m/e = 327$ (R′ = 4-CH_3), $m/e = 343$ (R′ = 4-OCH_3), $m/e = 347$ (R′ = 4-Cl) resulting from cleavage of the C–C bond adjacent to nitrogen (N-3).

Anti-inflammatory activities of the compounds were screened by the carrageenan induced edema test using indomethacin as a reference compound. The pharmacological results indicated that none of the compounds showed noticeable anti-inflammatory activity (except **1b**, **1c**, **4a** and **4c**) at the 100 mg/kg dose level. Although it has been reported that [20] the introduction of a chlorine atom into the benzylidene group in position 2 of the ring causes an increase in activity, any significant activity for compounds carrying chlorine was not observed. As seen in Table 3, the compounds **1b**, **1c**, **4a** and **4c**, which bear 4-bromo- and 2-fluorophenyl at position 5 of the condensed ring, exhibited some anti-inflammatory activity. On the other hand, whereas the compounds **1b** and **1c** had moderate anti-inflammatory activity at the 100 mg/kg dose, when ED_{50} values were taken into consideration these compounds showed less anti-inflammatory activity than that of indomethacin. It is well known that anti-inflammatory compounds can exhibite ulcerogenic properties. Therefore, the compounds **1b**, **1c**, **4a** and **4c** were screened for their ulcerogenic properties and gastric mucosal erosions were observed at the 100 mg/kg dose level.

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