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SYNTHESIS AND BIOLOGICAL SCREENING OF SOME NOVEL BENZOXAZOLE DERIVATIVES

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ABSTRACT

Molecules containing the benzoxazole moiety have gained a lot of momentum now-a-days owing to their remarkable biological activities like anti-inflammatory, antihistaminic, antimicrobial, anti-cancer and psychotrophic activities. In the present work, we have taken up the synthesis and pharmacological evaluation of some new 2-mercapto benzoxazoles containing more potent pharmacophores at side chain of the benzoxazole moiety. Synthesis of (Benzoxazole-2-yl) thioacetic acid arylidine hydrazide derivatives with biologically important organic compounds by adopting appropriate synthetic routes was carried out. Further, purification, characterization and toxicity evaluation were carried out for all the new compounds including those of intermediates. Preliminary investigation for their Gross behavioural changes, Locomotor activity and Analgesic activity was also taken up. The biological screening confirmed development of pharmacologically significant molecules with potentially therapeutic activity in vivo.

KEY WORDS

Benzoxazole, 2-mercapto benzoxazole, Analgesic, Behavioural study, Locomotor activity

1. INTRODUCTION

Molecules containing the benzoxazole moiety, either isolated from plants or obtained by total synthesis, possess remarkable biological activities [1]. Some of the examples being, gram-positive antibacterials [2,3], polycyclic antibiotics [4,5], antiparasitics [6,7], anti-inflammatories [8-11], elastase inhibitors [12-14] and H2-antagonists [15,16] that contain benzoxazole moiety. Moreover, benzoxazoles possess a number of optical applications like photoluminescents 17], whitening agents [18] and dye laser [19]. By synthetic methods calcymicin [20], an antibiotic and benzoxaprofen [21], an anti-inflammatory agent was also obtained, which contained benzoxazole ring system (Fig 1).

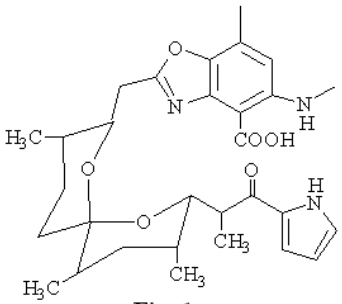
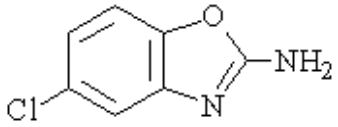


Fig. 1

Zoxazolamine, an α-amino-5-chlorobenzoxazole possessing muscle relexant, sedative activity and uricosuric effect was also reported [22]. These examples highlight the level of interest in new synthetic approaches to benzoxazole derivatives. Because of the varied pharmacological properties possessed by the benzoxazoles, they are considered to be important.



It is evident from literature that the presence of the benzoxazole nucleus is found to have various pharmacological activities like anti-inflammatory, antihistaminics, antimicrobial, anti-cancer and psychotrophic activities. We have taken up the synthesis and pharmacological evaluation of some new 2-mercapto benzoxazoles containing more potent pharmacophores at side chain of the benzoxazole moiety.

2. Methods

2.1. Synthesis of compounds

2.1.1. Synthesis of 4-Carbomethoxy-2-nitrophenol (II)

To a solution of aluminium nitrate (40g) in acetic acid and acetic anhydride (1:1) mixture (160ml) was added an appropriate phenol i.e. methyl 4-hydroxybenzoate (I, 40g) in small portions, while cooling and shaking occasionally. The reaction mixture was left at room temperature for 1.5 hours while shaking the content intermittently to complete the nitration. The resulting brown solution was diluted with ice cold water (500ml) and acidified with concentrated nitric acid (40ml) to get a yellow bulky precipitate. It was filtered, washed with small quantity of methanol and purified by recrystallization from alcohol to get yellow crystalline solid (44g, 85%), m.p. 73°C (lit.m.p.73°C).

2.1.2. Synthesis of Methyl-3-amino-4-hydroxy benzoate (III)

4-Carbomethoxy-2-nitrophenol (II,10g) was dissolved in boiling alcohol (50%,100ml) and sodium dithionite was added to this boiling alcohol solution until it becomes almost colorless. Then the alcohol was reduced to one-third of its volume by distillation and the residual liquid triturated with ice cold water. The resulting colorless, shiny product was filtered, washed with cold water and dried. It was purified by recrystallizing from benzene to get colorless, shiny scales (5.1g, 60%), m.p.143°C (lit. m.p. 143°C).

2.1.3. Synthesis of 2-mercapto-1,3-benzoxazole-6-carboxylic acid (IV)

Methyl-3-amino-4-hydroxybenzoate (III, 0.01mol) was dissolved in alcoholic potassium hydroxide (0.15 mol) and then refluxed with carbon disulphide (0.15mol) for 4 hours. Then the reaction mixture was cooled to room temperature and the excess potassium hydroxide was neutralized with dilute hydrochloric acid to get the colorless crystals. Then the resultant product was dried and recrystallized from methanol, m.p. 214°C, yield 75%.

2.1.4. Synthesis of Ethyl (benzoxazole-2-yl)-6-carboxy thioacetate (V)

2-Mercapto-1,3-benzoxazole-6-carboxylic acid (IV, 0.1mol) anhydrous potassium carbonate (0.15mol) were dissolved in dry acetone (0.1mol) and ethyl chloroacetate (0.1mol) was added, the resulted solution was refluxed in a 100ml round bottom flask for 18 hours and then concentrated in vacuum. The reaction mixture was poured into crushed ice. The solid product thus separated was washed with cold water and recrystallized from ethanol, m.p. 81°C, yield 70%.

2.1.5. Synthesis of (Benzoxazole-2-yl)-6-carboxy thioacetic acid hydrazide (VI)

Ethyl (benzoxazole-2-yl)-6-carboxy thioacetate (V, 0.1mol) was refluxed with excess of hydrazine hydrate (99%) in methanol (50ml) for 4 hours on a water bath. The excess amount of the solvent was distilled off. The solid thus separated was filtered, washed with cold ethanol and recrystallized from ethanol, m.p. 191°C, yield 80%.

2.1.6. Synthesis of (Benzoxazole-2-yl)-6-carboxy thioacetic acid arylidine hydrazide (VII)

A mixture of the compound (VI) i.e. (Benzoxazole-2-yl)-5-carboxy thioacetic acid hydrazide (0.01mol) and an appropriate aromatic aldehyde (0.01mol) in methanol (50ml) was heated under reflux on a water bath for about 3 hours. The compound thus resulted upon cooling was filtered, washed with small portion of cold methanol and dried. It was purified by recrystallization from suitable solvents.

Twelve compounds were prepared by adopting above prescribed procedure and their physical data are presented in the Table 1.

2.2. Identification and characterization

The identification and characterization of the synthesized compounds were carried out by the following procedures to ascertain that all the synthesized compounds were of different chemical nature than the respective parent compounds.

2.2.1. Melting point determination and solubility

The melting points of the organic compounds were determined by open capillary tube method. Melting point is a valuable criterion of purity for an organic compound, as a pure crystal will have a definite and sharp melting point. The purity should not be assumed but must be established by observation of any changes in the melting point when the compound is subjected to purification by recrystallization. The solubility of synthesized compounds was tested in various solvents.

2.2.3. Elemental Analysis

The Elemental Analysis (C, H and N) of the synthesized compounds were determined by using Carlo Erba EX 1108 elemental analyzer.

2.2.4. Thin Layer Chromatography

Chromatography is an important technique to identify the formulation of new compounds and also to determine the purity of compounds. The R_f value is characteristic for each of the compound. The R_f values of compounds were calculated using the formula.

$$R_f \text{ value} = \frac{\text{Distance travelled by sample}}{\text{Distance travelled by solvent front}}$$

3. Spectral analysis

3.1. Infra-red spectroscopy

The peaks in IR Spectrum gave an idea about the probable structure of the compound. IR region ranges between 4000-650 cm^{-1}. The derivatives including intermediates were recorded on NICOLET FT-IR spectrometer.

3.2. ^{1}H NMR Spectroscopy

NMR spectroscopy enables us to recorded differences in magnetic properties of the various magnetic nuclei present and to deduce in the large measure about the position of theses nuclei within the molecule. We can deduce how many different kinds of environment are there in the molecules and also which atoms are present in neighboring groups. The proton NMR spectra, enables us to know different chemical and magnetic environments corresponding to protons in molecules. ^{1}H NMR of the title compounds were recorded in BRUKER AV-300 MH_z (or) BRUKER AMX-400 MH_z

3.3. Mass Spectroscopy

Mass spectra of title compounds were recorded on micro mass Quatro II Mass Spectrometer.

4. Biological screening

In the present investigation, having synthesized such new compounds it has been considered meaningful to screen, preliminarily all of them for their Toxicity studies, Gross behavioral changes, Locomotor activity and Analgesic activity.

4.1. Acute toxicity study

Healthy and adult male albino swiss mice weighing between 20-25g were used in the investigation. Animals were fasted for 24 hours and divided into groups of six animals each. The test compounds, suspended in sodium carboxymethyl cellulose (0.1%) were administered, intraperitonelly, in doses of 5mg to 500mg per kg (b.w.). The control group of received only the vehicle (0.1% sodium CMC). The animals were observed for 48 hours from the time of administration of test compound to record the mortality.

4.2. Gross Behavioural studies

All the compounds tested for acute toxicity studies were also observed for gross behavioural changes, continuously for 3 hours starting from the administration of the compounds and for 48 hours, intermittently and compared with that of control groups of mice. In the behavioral profile, the animals have been observed for changes in their awareness (alertness, visual placing, stereotype and passitivity), mood (grooming, vocalization, restlessness, irritability and fearfulness), Motor Activity (reactivity, touch response and pain response).

4.3. Locomotor activity

The Locomotor activity was studied with actophotometer after half an hour of administration of the test compounds.

5. Results and discussion

5.1. Characterization

The synthesized compounds showed minute changes in melting point after recrystallization respectively. The melting points of the compounds are reported in the physical data table (Table 1). The solubility of

synthesized compounds was tested in various solvents. All the synthesized compounds were soluble in Dimethyl sulphoxide, Dimethyl Formamide, Chloroform and Methanol. The R_f values of all the samples were found to be different from that of the parent compound spotted along with it. This conformed that the compounds formed were entirely different from that of the parent compound. Moreover, since the entire sample gave a single spot, the compounds were taken to be free from impurities. The characteristic absorption bands (FT IR), proton NMR spectra and Mass spectra of the few synthesized compounds are presented in Table 2.

Table 1: Physical data of (Benzoxazole-2-yl)-5-carboxy thioacetic acid arylidine hydrazides (VII)

S.No.	Compound	Ar	Mol. formula	M.P. (°C)	Mol. Wt.	Yield (%)
1	VIIa	Phenyl	$C_{17}H_{13}N_3O_4S$	231-232	355	61
2	VIIb	2-Hydroxyphenyl	$C_{17}H_{13}N_3O_5S$	258-260	371	65
3	VIIc	4-Dimethylaminophenyl	$C_{19}H_{18}N_4O_4S$	240-241	398	68
4	VIId	4-Methoxyphenyl	$C_{18}H_{15}N_3O_5S$	209-211	385	59
5	VIIe	2-Bromophenyl	$C_{17}H_{12}BrN_3O_4S$	272-273	434	52
6	VIIf	2,6-Dichlorophenyl	$C_{17}H_{11}Cl_2N_3O_4S$	251-252	424	57
7	VIIg	4-Chlorophenyl	$C_{17}H_{12}ClN_3O_4S$	243-244	389.5	54
8	VIIh	3,4-Dimethoxyphenyl	$C_{19}H_{17}N_3O_6S$	239-241	415	56
9	VIIi	4-Hydroxy-3-methoxyphenyl	$C_{18}H_{15}N_3O_6S$	248-249	401	51
10	VIIj	2-Chlorophenyl	$C_{17}H_{12}ClN_3O_4S$	249-251	389.5	55
11	VIIk	4-Flourophenyl	$C_{17}H_{12}FN_3O_4S$	284-286	373	48
12	VII l	2-Nitrophenyl	$C_{17}H_{12}N_4O_6S$	241-243	400	69

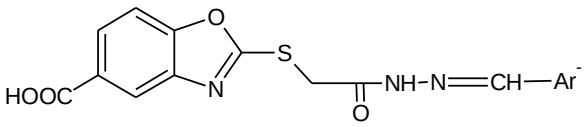
5.2. Biological screening

The toxicity studies of the test compounds revealed that they are quite safe even up to a dose of 2000 mg/kg, intraperitoneally. The gross behavioural studies showed that all the compounds could exhibit CNS depressant effect (Table 3). Table 4 pertaining to the results of the effect of the (Benzoxazole-2-yl) thioacetic acid arylidine hydrazide (VII) derivatives on locomotor activity of the mice shows that all the test compounds reduce the locomotor activity. The compounds VII g (Ar=4-ClC6H4), VII j (Ar=2-ClC6H4), VII k (Ar=4-FC6H4) and VII l (Ar=2-NO2C6H4) exhibited more effect among all the compounds with more than 70% in reduction in activity as compared to the control, where as the standard drug (Diazepam) showed 81.4% in reduction in activity. This is followed by the compounds VII f (Ar=2,6-Cl2C6H3), VII e (Ar=2-BrC6H4), VII i (Ar=3-OCH34OHC6H3), VII h (Ar=3,4-(OCH3)2C6H3), VII c (Ar=4-N(CH3)2C6H4), VII b (Ar=2-OHC6H4), VII d (Ar=4-OCH3C6H4) and VII a (Ar= C6H5) were next in the order of reduction of locomotor activity respectively.

6. CONCLUSIONS

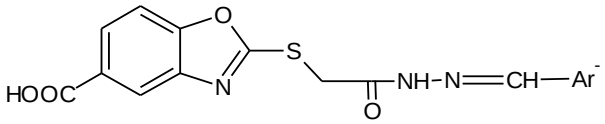
Some new 2-mercapto benzoxazoles containing more potent pharmacophores at side chain of the benzoxazole moiety were synthesized successfully and characterized. The biological screening confirmed development of pharmacologically significant molecules with potentially therapeutic activity in vivo. Further screening of the molecules for other potential activities will be taken up in future.

Table 2: Infra-Red, ^{1}H NMR and FAB-Mass Spectral data of (Benzoxazole-2-yl)-5-carboxy thioacetic acid arylidine hydrazides (VII)



Compound	IR		PMR		Mass
	(cm^{-1}) in KBr	Type of vibrations	Values in PPM	No. Of Protons	
VII b	3032.10 2837.69 1692.77 1572.29 1469.96 678.71	– NH – str –Ar–CH str C=O str –N–N=C str –C=C– str –CS str	11.26 10.486 8.464 6.893 – 7.915 3.870	s, 1H, OH, phenolic s, 1H, CONH– s, 1H, benzylidienimino of –CH m, 7H, Ar –H s, 2H, $–CH_2–$	(m) at m/z 371.1
VII c	3033.79 2897.59 1693.02 1514.83 1494.72 707.69	– NH – str –Ar–CH str C=O str –N–N=C str –C=C– str –CS str	10.582 8.145 7.014 – 7.902 4.620 3.812 – 3.869	s, 1H, CONH– s, 1H, benzylidienimino of –CH m, 7H, Ar –H s, 2H, $–CH_2–$ s, 6H, $–CH_3$	(m) at m/z 398.2
VII d	3034.12 2895.46 1696.68 1531.51 1491.25 700.96	– NH – str –Ar–CH str C=O str –N–N=C str –C=C– str –CS str	10.564 8.057 6.750 – 7.879 4.642 3.866	s, 1H, CONH– s, 1H, benzylidienimino of –CH m, 7H, Ar –H s, 2H, $–CH_2–$ s, 6H, $–CH_3$	(m) at m/z 385.3
VII j	2896.10 1676.87 1600.39 1480.67 670.13	–Ar–CH–str C=O str –N–N=C str –C=C– str –CS str	10.473 8.586 7.439 – 8.032 3.871	s, 1H, CONH– s, 1H, benzylidienimino of –CH m, 7H, Ar –H s, 2H, $–CH_2–$	(m) at m/z 389.1
VII k	3039.61 2849.61 1698.41 1605.49 690.51	– NH – str –Ar–CH str C=O str –C=C– str –CS str	12.201 10.345 8.206 7.284 – 7.921 3.870	s, 1H, –COOH s, 1H, CONH– s, 1H, benzylidienimino of –CH m, 7H, Ar –H s, 2H, $–CH_2–$	(m) at m/z 373.2
VII l	3235.47 2892.1 1693.11 1585.50 693.88	– NH – str –Ar–CH str C=O str –C=C– str –CS str	12.54 11.12 8.631 7.657 – 8.145 3.873	s, 1H, –COOH s, 1H, CONH– s, 1H, benzylidienimino of –CH m, 7H, Ar –H s, 2H, $–CH_2–$	(m) at m/z 400.1
VI	3193.46 3015.76 1660.32 1593.51 1438.77	$– NH_2$ – str –NH – str C=O str –N=C – str –C=C – str	9.075 7.47 – 7.778 4.614 3.846	s,1H, CONH– m,3H, Ar – H s,2H, $– NH_2$ s, 2H, $– CH_2–$	(m) at m/z 267.1

Table 3: Gross behavioural studies of (Benzoxazole-2-yl) thioacetic acid arylidine hydrazides.



(VII)

Sl. No.	Comp.	Ar	Time in hrs	Awareness					Mood			
				Alertness	Visual Placing	Stereotypy	Passivity	Writhing	Grooming	Vocalization	Restlessness	Irritability
1	VIIa	C_6H_5	½	+		+	+	+	+		-	-
			1	+		+	+	+	+		-	-
			2	+		+	-	+	+		-	-
			3	-		-	-	-	-		-	-
			4	-		-	-	-	-		-	-
			8	+		+	-	+	+		-	-
			24	+		+	-	+	+		-	-
2	VIIb	2-OHC_6H_4	½	+		+	+	+	+		+	+
			1	+		+	+	+	+		-	-
			2	+		+	-	+	+		-	-
			3	-		-	-	-	-		-	-
			4	-		-	-	-	-		-	-
			8	+		+	-	+	+		-	-
			24	+		+	-	+	+		-	-
3	VIIc	4-$N(CH_3)_2C_6H_4$	½	+		+	+	+	+		-	-
			1	+		+	+	+	+		-	-
			2	+		+	-	+	+		-	-
			3	-		-	-	-	-		-	-
			4	-		-	-	-	-		-	-
			8	+		+	-	+	+		-	-
			24	+		+	-	+	+		-	-

Dose = 200mg/kg bodyweight; + positive response; - negative response

GROSS BEHAVIOURAL STUDIES (continued)

Sl. No.	Comp	Ar	Time in hrs	Awareness					Mood			
				Alertness	Visual Placing	Stereotypy	Passivity	Writhing	Grooming	Vocalization	Restlessness	Irritability
4	VIId	4-$OCH_3C_6H_4$	½	+		+	+	+	+		-	-
			1	+		+	+	+	+		-	-
			2	+		+	-	+	+		-	-
			3	-		-	-	-	-		-	-
			4	-		-	-	-	-		-	-
			8	+		+	-	+	+		-	-
			24	+		+	-	+	+		-	-
5	VIIe	2-BrC_6H_4	½	+		-	+	+	-		-	-
			1	+		-	+	+	-		-	-
			2	-		-	+	-	-		-	-
			3	-		-	-	-	-		-	-
			4	-		-	-	-	-		-	-
			8	+		-	-	+	-		-	-
			24	+		-	-	+	-		-	-
6	VIIf	2,6-$Cl_2C_6H_3$	½	+		-	+	+	+		-	-
			1	+		-	+	+	-		-	-
			2	-		-	+	-	-		-	-
			3	-		-	+	-	-		-	-
			4	-		-	+	-	-		-	-
			8	+		-	-	+	-		-	-
			24	+		-	-	+	-		-	-

Dose = 200mg/kg bodyweight; + positive response; - negative response

GROSS BEHAVIOURAL STUDIES (continued)

Sl. No.	Comp	Ar	Time in hrs	Awareness					Mood			
				Alertness	Visual Placing	Stereotypy	Passivity	Writhing	Grooming	Vocalization	Restlessness	Irritability
7	VIIg	4-ClC_6H_4	½	-		-	+	-	+		-	-
			1	-		-	+	-	-		-	-
			2	-		-	+	-	-		-	-
			3	-		-	+	-	-		-	-
			4	-		-	+	-	-		-	-
			8	+		+	-	+	-		-	-
			24	+		+	-	+	+		-	-
8	VIIh	3,4-$(OCH_3)_2C_6H_3$	½	+		+	+	+	+		-	-
			1	+		+	+	+	+		-	-
			2	+		+	-	-	-		-	-
			3	-		-	-	-	-		-	-
			4	-		-	-	-	-		-	-
			8	+		+	-	+	+		-	-
			24	+		+	-	+	+		-	-
9	VIIi	3-$OCH_3$4OHC_6H_3	½	+		+	+	+	+		+	+
			1	+		+	+	+	+		-	-
			2	-		-	+	-	-		-	-
			3	-		-	-	-	-		-	-
			4	-		-	-	-	-		-	-
			8	+		+	-	+	+		-	-
			24	+		+	-	+	+		-	-

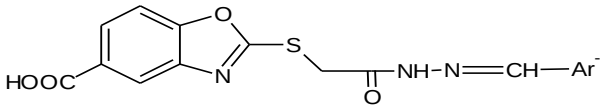
Dose = 200mg/kg bodyweight; + positive response; - negative response

GROSS BEHAVIOURAL STUDIES (continued)

Sl. No.	Comp	Ar	Time in hrs	Awareness					Mood			
				Alertness	Visual Placing	Stereotypy	Passivity	Writhing	Grooming	Vocalization	Restlessness	Irritability
10	VIIj	2-ClC_6H_4	½	-		-	+	-	+		-	-
			1	-		-	+	-	-		-	-
			2	-		-	+	-	-		-	-
			3	-		-	+	-	-		-	-
			4	-		-	-	-	-		-	-
			8	+		+	-	+	-		-	-
			24	+		+	-	+	-		-	-
11	VIIk	4-FC_6H_4	½	-		-	+	-	+		-	-
			1	-		-	+	-	-		-	-
			2	-		-	+	-	-		-	-
			3	-		-	+	-	-		-	-
			4	-		-	+	-	-		-	-
			8	+		-	-	+	-		-	-
			24	+		-	-	+	-		-	-
12	VIII	2-$NO_2C_6H_4$	½	-		-	+	-	+		-	-
			1	-		-	+	-	-		-	-
			2	-		-	+	-	-		-	-
			3	-		-	+	-	-		-	-
			4	-		-	+	-	-		-	-
			8	+		+	-	-	-		-	-
			24	+		+	-	-	-		-	-

Dose = 200mg/kg bodyweight; + positive response; - negative response

Table 4: Locomotor activity of (Benzoxazole-2-yl) thioacetic acid arylidine hydrazides.



(VII)

Groups	Compounds	Ar	Locomotor activity (scores) 10 minutes	% of change in activity
Group I	**Control**	0.5 % CMC	164.8 ± 1.057	
Group II	**Diazepam**	4 mg/kg body wt.	30.6 ± 0.342 [a]	81.4 % ↓se in Activity
	VII a	C_6H_5	117.3 ± 0.661 *	28.8 % ↓se in Activity
	VII b	2-OHC_6H_4	102.3 ± 0.630 *	37.9 % ↓se in Activity
	VII c	4-$N(CH_3)_2C_6H_4$	100.4 ± 0.619 *	39.0 % ↓se in Activity
	VII d	4-$OCH_3C_6H_4$	115.4 ± 0.651 *	29.9 % ↓se in Activity
	VII e	2-BrC_6H_4	80.1 ± 0.571 **	51.3 % ↓se in Activity
Group III	VII f	2,6-$Cl_2C_6H_3$	75.6 ± 0.513 **	54.1 % ↓se in Activity
	VII g	4-ClC_6H_4	33.3 ± 0.415 ***	79.7 % ↓se in Activity
	VII h	3,4-$(OCH_3)_2C_6H_3$	90.4 ± 0.613 **	45.1 % ↓se in Activity
	VII i	3-$OCH_3$4OHC_6H_3	83.6 ± 0.584 **	49.2 % ↓se in Activity
	VII j	2-ClC_6H_4	39.1 ± 0.410 ***	76.2 % ↓se in Activity
	VII k	4-FC_6H_4	43.2 ± 0.476 ***	73.7 % ↓se in Activity
	VII l	2-$NO_2C_6H_4$	36.4 ± 0.348 ***	77.9 % ↓se in Activity

Values expressed as mean ± SEM [a], ***P<0.001, **P<0.01, *P<0.05, ANOVA followed by Dunnet's t-test

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