

Synthesis and Pharmacological Evaluation of Azetidin-2-ones and Thiazolidin-4-ones Encompassing Benzothiazole

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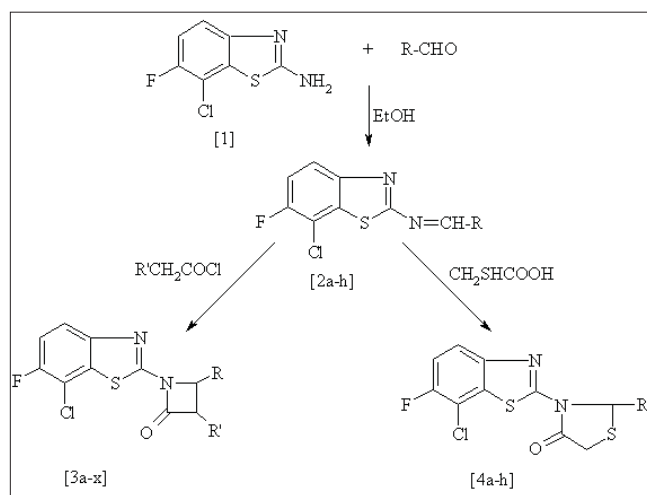
Various 7-chloro-6-fluoro-2-arylidénylaminobenzo(1,3)thiazole (2a-h) have been synthesized by the condensation of 7-chloro-6-fluoro-2-aminobenzo(1,3)thiazole (1) with different aromatic aldehydes. The Schiff's bases on reaction with acetyl chloride, chloroacetyl chloride and phenyl acetyl chloride yielded 1-(7-chloro-6-fluorobenzothiazol-2-yl)-3,4-substituted-aryl-azetidin-2-ones (3a-x). Similarly, cyclization of Schiff's base with thioglycolic acid furnished 3-(7-chloro-6-fluoro-benzothiazol-2-yl)-2-substituted-arylthiazolidin-4-ones (4a-h). The structures of the newly synthesized compounds have been established on the basis of their spectral data and elemental analysis. Some selected compounds were evaluated for antiinflammatory, analgesic, CNS depressant and skeletal muscle relaxant activity.

Key words: Benzothiazole, azetidinones, thiazolidinones, pharmacological activity

The β -lactam antibiotics are extensively used for bacterial infections. The cephalosporins¹ have withstood the onslaught of microorganisms and have come to be physician's arsenal in combating a wide range of microbial infections. Moreover various β -lactams are associated with antitumor², antitubercular³, antiinflammatory⁴ activities. Similarly, thiazolidinones have attracted considerable attention as they are also enrolled with wide range of pharmacological activities like anticonvulsant⁵, analgesic⁶ and antiinflammatory⁷ activities. In continuation of our studies on benzothiazole^{8,9}, we have synthesized benzothiazole moiety linked to bioactive β -lactam and thiazolidinone rings, to analyse their biological profile.

The starting material for the synthesis of desired compounds is 7-chloro-6-fluoro-2-aminobenzo(1,3)thiazole¹⁰ (1), which on treatment with different aromatic aldehydes in concentrated sulphuric acid yields the respective Schiff bases (2a-h). The Schiff bases were separately reacted with substituted acetyl chloride and mercaptoacetic acid produced 1-(7-

chloro-6-fluorobenzothiazol-2-yl)-3,4-substituted-arylazetidin-2-ones (3a-x) and 3-(7-chloro-6-fluoro-benzothiazol-2-yl)-2-substituted-arylthiazolidin-4-ones (4a-h) respectively (Scheme 1). The newly synthesized compounds were characterized by spectroscopic data and elemental analysis and were screened for their antiinflammatory, analgesic, CNS depressant and



Scheme 1: Synthetic scheme of Schiff's bases, azetidine-2-ones and thiazolidin-4-ones
 R = C₆H₅, C₆H₄-4-OCH₃, C₆H₄-2-OH, C₆H₄-3-OCH₃, C₆H₄-4-N(CH₃)₂, C₆H₄-2-NO₂, C₆H₄-3Cl and C₄H₃O (2-furyl). R' = H, Cl and C₆H₅.

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skeletal muscle relaxant activities.

MATERIALS AND METHODS

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on FTIR Shimadzu 1400S and NMR spectra were recorded on AMX-400 in $\text{CDCl}_3/\text{DMSO}-d_6$ using TMS as internal standard (chemical shifts in δ ppm). Mass spectra were recorded on FT VG-7070H Mass spectrophotometer using the EI technique at 70 eV. Satisfactory elemental analyses were obtained for all the compounds and were within $\pm 0.4\%$ of the theoretical values. The reactions were monitored on TLC with solvents of varying polarity and the spots were located by iodine vapors. For antiinflammatory and analgesic activities, adult healthy rats of Wistar strain of either sex weighing between 150-200 g were used. For CNS depressant and skeletal muscle relaxant activity studies, adult, healthy mice of Wistar strain of either sex weighing 20-25 g were used. All animals were maintained under standard conditions and had access to pelleted animal feed and water *ad libitum*. The study protocols were carried out as approved by the Institutional Ethics Committee (CPCSEA Reg. No. 144).

To a mixture of 7-chloro-6-fluoro-2-aminobenzo(1,3)thiazole (1) (0.1 mol) and benzaldehyde (0.1 mol), was added two drops of concentrated sulphuric acid and the reaction mixture was refluxed in ethanol (25 ml) for 3 h. The contents were poured into cold water. The Schiff's base (2a) thus formed was filtered off and recrystallised from hot ethanol to give 7-chloro-6-fluoro-(2-hydroxy-benzylidene)-benzo(1,3)thiazole. IR (ν_{max}): 1650(C=N) and 3480 (Ar-OH). $^1\text{H NMR}(\text{CDCl}_3)$: 9.25 (s, 1H, -N=CH), 12.1 (s, 1H, Ar-OH), 7.0-8.0 (m, 6H, Ar-H). Mass: m/z 306 and fragment ion peaks at 289, 202, 175 and 140. Similarly, the other Schiff's bases (2b-h) were prepared.

The mixture of Schiff's base (2a) (2.90 g, 0.01 mol) and triethylamine (1.02 ml, 0.01 mol) was dissolved in dioxane (40 ml) and kept in an ice bath. To this, cold solution of acetyl chloride (0.72 ml, 0.01 mol) was added slowly at 0° , stirred for 10-12 h and left over night. The precipitated triethylammonium chloride was filtered off and dioxane was removed by distillation. Residue was poured into cold water; the resulting solid was dried and crystallized from ethanol

to give 3a. The Schiff's bases (2b-h) were treated separately with acetyl chloride to get 3b-h. Similarly, 3i-p and 3q-x were prepared by treating 2a-h with chloroacetyl chloride and phenyl acetyl chloride separately. 3i IR (ν_{max}): 1650(C=O). $^1\text{H NMR}(\text{CDCl}_3)$: 3.7(d, 1H, -NCH), 3.9 (d, 1H, CHCl), 7.2-7.9 (m, 6H, Ar-H); 3q IR(ν_{max}): 1660 (C=O stretch) azetidinone ring, $^1\text{H NMR}(\text{CDCl}_3)$: 3.1 (d, 1H, -NCH), 3.7 (d, 1H, CH-Ar), 7.0-7.8 (m, 12H, Ar-H).

A mixture of Schiff's base 2a (2.90 g, 0.01 mol) and mercaptoacetic acid (1.19 ml, 0.01 mol) was dissolved in dioxane (20 ml). A pinch of anhydrous zinc chloride was added and then refluxed for 8 h. Separated solid was filtered, washed with sodium bicarbonate solution and then recrystallised from ethanol. Similarly, the other compounds (4b-h) were prepared. 4a IR (ν_{max}): 1660 (C=O) thiazolidine ring. $^1\text{H NMR}(\text{CDCl}_3)$: 3.8 (s, 2H, CH_2), 3.6 (s, 1H, -NCH), 7.2-7.6 (m, 7H, Ar-H). Mass: m/z 364 and fragment ions peak at 289, 202, 175, 101, 81 and 69. Physical data of the compounds is given in Table 1.

Antiinflammatory activity:

Antiinflammatory activity of some selected compounds was evaluated using carrageenan induced rat hind paw oedema method¹¹. The animals were divided into control, standard and test groups, each consisting of six animals. The first group was treated with Tween-80 (1%) suspension which served as control, second group was administered with a dose of 20 mg/kg suspension of diclofenac sodium intraperitoneally which served as standard and other groups were treated with 30 mg/kg of suspension of test compounds in Tween-80. After 30 min, the rats were injected with 0.1 ml of carrageenan (1% w/v) to the sub plantar region of left paw of the rats. The volume of paw was measured using potassium permanganate solution displacement technique with the help of plethysmograph both in control and animals treated with standard and test compounds at 0, 1, 2 and 3 h after injection of carrageenan. The percentage inhibition of oedema was calculated by using formula, percent inhibition = $(1 - V_t/V_c) \times 100$, where V_t is the mean paw volume of the test drug, V_c is the mean paw volume of the control. The results are recorded in Table 2.

Analgesic activity:

The animals were divided into four groups of six animals each. The animals, which showed reaction

TABLE 1: PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Compd No	R	R ¹	Mp (°)	Yield (%)	Mol. formula*
2a	-	-	165	78	C ₁₄ H ₉ ClFN ₂ S
2b	-	-	160	76	C ₁₅ H ₁₀ ClFN ₂ OS
2c	-	-	175	81	C ₁₄ H ₇ ClFN ₂ OS
2d	-	-	155	69	C ₁₅ H ₁₀ ClFN ₂ O ₂ S
2e	-	-	180	75	C ₁₆ H ₁₃ ClFN ₃ S
2f	-	-	168	72	C ₁₄ H ₇ ClFN ₂ O ₂ S
2g	-	-	170	68	C ₁₄ H ₇ Cl ₂ FN ₂ S
2h	-	-	198	70	C ₁₂ H ₆ ClFN ₂ OS
3a	C ₆ H ₅	H	188	50	C ₁₆ H ₁₀ ClFN ₂ OS
3b	C ₆ H ₄ -4-OCH ₃	H	185	63	C ₁₇ H ₁₂ ClFN ₂ O ₂ S
3c	C ₆ H ₄ -2-OH	H	190	58	C ₁₆ H ₁₀ ClFN ₂ O ₂ S
3d	C ₆ H ₃ -4-OH, 3-OCH ₃	H	170	63	C ₁₇ H ₁₂ ClFN ₂ O ₂ S
3e	C ₆ H ₄ -4-N(CH ₃) ₂	H	195	70	C ₁₈ H ₁₅ ClFN ₂ OS
3f	C ₆ H ₄ -2-NO ₂	H	179	80	C ₁₆ H ₉ ClFN ₃ O ₂ S
3g	C ₆ H ₄ -3-Cl	H	180	73	C ₁₆ H ₉ Cl ₂ FN ₂ OS
3h	C ₄ H ₃ O (2-furyl)	H	205	68	C ₁₅ H ₈ ClFN ₂ O ₂ S
3i	C ₆ H ₅	Cl	150	72	C ₁₅ H ₉ ClFN ₂ OS
3j	C ₆ H ₄ -4-OCH ₃	Cl	200	69	C ₁₇ H ₁₁ Cl ₂ FN ₂ OS
3k	C ₆ H ₄ -2-OH	Cl	194	55	C ₁₆ H ₉ Cl ₂ FN ₂ O ₂ S
3l	C ₆ H ₃ -4-OH, 3-OCH ₃	Cl	187	62	C ₁₇ H ₁₁ Cl ₂ FN ₂ O ₂ S
3m	C ₆ H ₄ -4-N(CH ₃) ₂	Cl	198	65	C ₁₈ H ₁₄ Cl ₂ FN ₂ OS
3n	C ₆ H ₄ -2-NO ₂	Cl	202	71	C ₁₆ H ₈ Cl ₂ FN ₃ OS
3o	C ₆ H ₄ -3-Cl	Cl	170	82	C ₁₆ H ₈ Cl ₃ FN ₂ OS
3p	C ₄ H ₃ O (2-furyl)	Cl	210	72	C ₁₄ H ₇ Cl ₂ FN ₂ O ₂ S
3q	C ₆ H ₅	C ₆ H ₅	215	82	C ₂₂ H ₁₄ ClFN ₂ O ₂ S
3r	C ₆ H ₄ -4-OCH ₃	C ₆ H ₅	216	73	C ₂₃ H ₁₆ Cl ₂ FN ₂ O ₂ S
3s	C ₆ H ₄ -2-OH	C ₆ H ₅	210	54	C ₂₂ H ₁₆ ClFN ₂ O ₂ S
3t	C ₆ H ₃ -4-OH, 3-OCH ₃	C ₆ H ₅	235	63	C ₂₃ H ₁₆ ClFN ₂ O ₂ S
3u	C ₆ H ₄ -4-N(CH ₃) ₂	C ₆ H ₅	208	68	C ₂₄ H ₁₉ ClFN ₃ O ₂ S
3v	C ₆ H ₄ -2-NO ₂	C ₆ H ₅	193	75	C ₂₂ H ₁₃ ClFN ₃ O ₂ S
3w	C ₆ H ₄ -3-Cl	C ₆ H ₅	218	70	C ₂₂ H ₁₃ Cl ₂ FN ₂ OS
3x	C ₄ H ₃ O (2-furyl)	C ₆ H ₅	219	73	C ₂₀ H ₁₂ ClFN ₂ O ₂ S
4a	C ₆ H ₅	-	191	82	C ₁₆ H ₁₀ ClFN ₂ O ₂ S
4b	C ₆ H ₄ -4-OCH ₃	-	118	85	C ₁₇ H ₁₂ ClFN ₂ O ₂ S ₂
4c	C ₆ H ₄ -2-OH	-	180	80	C ₁₆ H ₉ ClFN ₂ O ₂ S ₂
4d	C ₆ H ₃ -4-OH, 3-OCH ₃	-	157	84	C ₁₇ H ₁₂ ClFN ₂ O ₂ S ₂
4e	C ₆ H ₄ -4-N(CH ₃) ₂	-	142	78	C ₁₈ H ₁₅ ClFN ₃ O ₂ S ₂
4f	C ₆ H ₄ -2-NO ₂	-	175	74	C ₁₆ H ₉ ClFN ₃ O ₂ S ₂
4g	C ₆ H ₄ -3-Cl	-	170	70	C ₁₆ H ₉ Cl ₂ FN ₂ O ₂ S ₂
4h	C ₄ H ₃ O (2-furyl)	-	186	65	C ₁₄ H ₈ ClFN ₂ O ₂ S ₂

*C, H, N and S are within the limit of ± 0.3%

TABLE 2: RESULTS OF ANTIINFLAMMATORY ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compound No.	Paw volumes ±SEM and% reduction					
	1 h		2 h		3 h	
	Mean±SEM	%RPEV	Mean±SEM	%RPEV	Mean±SEM	%RPEV
3a	1.50 ±0.07	14.60	1.74±0.07	17.14	1.87±0.06*	22.08
3c	1.43±0.03	19.66	1.53±0.05	27.14	1.70±0.04*	29.16
3f	1.40±0.05	21.34	1.45±0.05*	30.95	1.63±0.04*	32.08
3i	1.42±0.03	20.22	1.57±0.11	25.23	1.63±0.10*	32.08
3k	1.38±0.05	22.47	1.40±0.06	33.33	1.43±0.05*	40.41
3n	1.32±0.07	25.84	1.35±0.05	35.71	1.35±0.04*	43.75
3q	1.50±0.04	15.73	1.78±0.05	15.23	1.90±0.02	20.83
3s	1.38±0.05	22.47	1.70±0.05	14.04	1.80±0.05*	25.00
3v	1.30±0.03	26.96	1.65±0.03	21.42	1.75±0.06*	27.08
4a	1.48±0.04	22.00	1.57±0.05*	25.23	1.65±0.06*	31.25
4c	1.45±0.04	18.50	1.53±0.04	27.14	1.63±0.06	32.08
4f	1.28±0.03	28.08	1.42±0.06*	32.38	1.48±0.04*	38.30
Control	1.78±0.05	-	2.10±0.05	-	2.4±0.03	-
Diclofenac Sodium	0.99±0.05	43.24	1.11±0.03*	46.00	1.11±0.05*	54.00

RPEV is reduction in paw edema volume, *Indicates significant difference at p<0.001 when compared to control

time of 2-3 s, were selected for experiment and analgesic activity of some selected compounds was studied by tail flick method¹². The tail received

radiant heat from a wire, which is heated by passing a current of 6 mA. The time taken for the withdrawal of tail was recorded before the

administration of the compounds and for 30, 60, 90 and 120 min after administration of compounds. The cut off time for determination of latent period was taken as 40 s to avoid the injury to the skin and based on our pilot studies. One group served as a standard (pentazocine hydrochloride) with dose of 10 mg/kg body weight and another group served as control (1% Tween-80) and rest of the groups used for the test drugs. The test compounds and pentazocine hydrochloride were suspended in 1% Tween-80 which was used as vehicle for the control group. The tested compounds were administered at the dose of 30 mg/kg in the form of suspension and administered intraperitoneally. The results of analgesic activity are shown in Table 3.

CNS depressant activity:

The CNS depressant activity¹³ of the compounds was studied on mice using actophotometer. Animals of either sex weighing 25-30 g were divided into groups of six each. The actophotometer counts for

10 min were recorded by placing the animals in the actophotometer, which gives the initial reading. The compounds were administered intraperitoneally in the form of suspension prepared in 1% Tween-80 at a dose of 30 mg/kg body weight. Each group served as its own control. Diazepam was administered as standard to one of the test group at a dose of 5 mg/kg body weight. After 30 min and 60 min of administration of test compound, the actophotometer counts were noted for 10 min. Decrease in the number of counts for each group was recorded and finally, the percentage CNS depressant activity was determined. The results of CNS depressant activity are shown in Table 4.

Muscle relaxant activity:

Some of the synthesized compounds were also tested for muscle relaxant activity¹⁴ (muscle grip strength) in mice using rotorod apparatus. The animals were trained to remain on the rotating rod (moving at speed of 25 rpm) for 5 min. The animals which were

TABLE 3: RESULTS OF ANALGESIC ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compound No.	ABRT in sec		ABRT in sec after treatment			
	Pre treatment '0' min	15 min	30 min	45 min	60 min	
3a	3.60±0.08	4.5±0.06*	6.53±0.04*	7.03±0.13*	11.20 ±0.2*	
3c	3.80±0.02	4.5±0.06*	7.05±0.08*	11.40±0.2*	11.40 ±0.2*	
3f	3.60±0.02	4.62±0.10*	4.67±0.06*	5.50±0.14*	5.30±0.03*	
3i	3.20±0.04	5.5±0.22*	5.5±0.22	4.4±0.20	3.40±0.37	
3k	3.40±0.10	3.83±0.31	6.83±0.48*	6.00±0.37*	6.50±0.22*	
3n	2.62±0.04	2.67±0.21	3.33±0.21	4.67±0.21	4.00± 0.37	
3q	3.60±0.10	4.17±0.31*	5.17±0.31	8.0±0.26	9.83±0.31*	
3s	3.20±0.15	4.00±0.26*	5.5±0.34	6.17±0.31*	6.67±0.21*	
3v	3.50±0.02	5.33±0.33*	8.83±0.78*	5.67±0.21*	5.33±0.21*	
4a	3.10±0.06	7.17±0.48*	11.17±0.40*	10.67±0.5*	9.67±0.21*	
4c	3.60±0.06	6.33±0.80*	7.76±0.04	10.33±0.12*	9.25±0.08	
4f	3.60±0.20	3.67±0.21*	3.83±0.31	4.33±0.22	4.33±0.42	
Control	3.60±0.06	3.60±0.10*	3.50±0.15	3.60±0.15	3.40±0.06	
PentazocineHCl	3.60±0.08	4.93±0.18*	8.90±0.15*	10.10±0.2*	12.50±0.1*	

ABRT: Average Basal Reaction Time, *Indicates significant difference at p<0.001 when compared to control

TABLE 4: RESULTS OF CNS DEPRESSANT ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compound	Before drug (Mean±SEM)	After drug (Mean±SEM)		CNS depressant activity (%)	
		30 min	60 min	30 min	60 min
3a	835.91±03.63	438.00±07.53	621.50±09.45	46.50	23.60
3c	830.90±03.63	113.17±07.00*	354.33±04.12*	86.20	56.40
3f	804.65±02.60	272.33±14.55*	503.83±04.94	67.00	38.00
3i	877.65±02.50	324.17±05.30*	386.83±06.43*	60.40	52.50
3k	915.63±02.30	384.17±14.28*	453.33±13.24*	53.10	44.30
3n	858.13±05.36	360.50±18.36*	466.17±12.23*	56.00	42.70
3q	766.18±07.21	477.17±07.82*	655.83±12.08	41.70	19.30
3s	811.55±02.20	252.50±16.80*	347.00±17.80*	69.20	57.30
3v	823.37±01.45	608.33±02.23	725.33±02.94	25.70	10.80
4a	811.50±02.00	624.00±07.13	733.50±03.45	23.80	09.80
4c	825.53±02.14	215.00±15.92*	405.00±08.37*	73.70	50.20
4f	815.49±01.93	217.33±08.73*	385.33±12.12*	73.50	52.60
Control	820.23±06.88	818.67±05.93	813.17±07.01	-	-
Diazepam	840.64±09.26	82.17±04.04*	112.50±06.55*	90.00	86.20

*Indicates significant difference at p<0.001 when compared to control

able to remain on the rotating rod for 5 min and above were selected for study and were divided into groups of six each. The compounds were administered intraperitoneally at a dose of 30 mg/kg body weight in the form of suspension in 1% Tween-80 while one group received diazepam as a standard drug at a dose of 4 mg/kg body weight. After 30 min, the mice were placed again on the rotating rod and animal's fall off time was recorded. The percentage muscle relaxant activity was calculated and the results are shown in Table 5.

RESULTS AND DISCUSSION

Two new series of compounds namely substituted azetidines (3a-x) and thiazolidinones (4a-h) possessing fluoro-benzothiazoles have been synthesized by using experimental protocol as shown in Scheme 1. All the derivatives were supported by spectral data. The IR, ¹H-NMR and Mass spectra are in agreement with the proposed structures.

The result of the antiinflammatory activity summarized in Table 2 indicated that 3-chloroazetidines showed better activity among the tested compounds. Further the presence of ortho substituted aryl ring at 4th position of azetidines moiety increased the anti inflammatory activity. Substitution of chloro group with phenyl ring at 3rd position of the azetidone generally causes decrease in the activity. Among the thiazolidinones, 2-nitro phenyl attached to 5th position of thiazolidinone ring showed maximum activity.

TABLE 5: RESULTS OF SKELETAL MUSCLE RELAXANT ACTIVITY OF SYNTHESIZED COMPOUNDS

Compound	Fall of time		% Decrease in time
	Before the drug treatment	After the drug treatment	
3a	43.00±1.37	15.50±0.12*	64.00
3c	23.50±1.52	14.17±1.01*	39.70
3f	26.17±1.19	16.00±0.68*	38.86
3i	38.50±1.38	22.50±1.38*	41.55
3k	26.83±1.47	20.67±0.95	22.95
3n	34.83±1.35	16.67±0.80*	52.13
3q	44.00±1.65	33.67±0.33	23.50
3s	35.67±1.25	30.62±1.01	14.15
3v	42.33±0.76	38.17±1.28	09.30
4a	32.67±0.84	15.33±1.05*	53.07
4c	26.17±1.08	10.83±1.38*	58.61
4f	30.17±0.95	12.00±1.10*	60.22
Control	34.83±1.25	34.67±1.33	-
Diazepam	28.32 ± 0.20	5.75 ± 0.07*	79.69*

*Indicates significant difference at p<0.001 when compared to control

The analgesic activity summarized in Table 3, indicated that 3a and 3c showed maximum analgesic activity. The compounds 4a and 4c exhibited higher analgesic activity than the standard pentazocine at 15, 30 and 45 min interval. However the activity decreases after 60 min suggesting shorter duration of activity for the same.

The CNS depressant activity (Table 4) reveals that 2-hydroxyl phenyl substituted azetidone (3c) and thiazolidinone (4c) showed better depressant activity. However activity decreases after 60 min indicating that the molecules to be short acting CNS depressants. The skeletal muscle relaxant activity (Table 5) indicated that the thiazolidinones (4a, 4c and 4f) and azetidone (3a) showed significant muscle relaxant activity.

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