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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-SUBSTITUDE ETHANAMIDO-5-ALKYL-1, 3, 4-THIADIAZOLES – PART III

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Fourteen novel 2-substituted ethanamido-5-(n-propyl/n-butyl)-1,3,4-thiadiazoles were synthesized and screened for their biological activities. Two of compounds, namely AH-5 and AH-7, showed anti-inflammatory activities comparable to phenylbutazone while compounds AH-1, AH-4, AH-6 and AH-13 showed weak anti-inflammatory activity. Diuretic activity of AH-1 at a dose of 90 mg.kg^{-1} p.o. was 1.5 fold higher when compared to 75 mg kg^{-1} p.o of acetazolamide whilst that of AH-5 and AH-6 were approximately equal to that of acetazolamide. The compound AH-3 showed concentration dependent decrease of blood pressure in the cat. All the synthesized compounds showed weak spasmolytic activity in vitro.

Keywords: 1,3,4- Thiadiazoles; Diuretic; Anti-inflammatory agents; CNS depressant; Spasmolytic agent

Introduction

The multifaceted biological properties of 1,3,4-thiadiazoles which include anti-inflammatory (1), diuretic (2), CNS stimulant (3), anticholinergic (4), hypoglycemic (5) and anticonvulsant activities (6) have been well documented. Anti-inflammatory CNS depressant activities of 1,3,4-thiadiazoles derivatives have been reported from this laboratory (7).

While screening for pharmacological activities of 2-substituted acetylamino-5-alkyl-1, 3, 4-thiadiazole were observed CNS depressant, anti-inflammatory and diuretic activities addition to spasmolytic activity (8, 9). The present paper reports the synthesis, characterization and pharmacological screening of the 2-[substituted ethanamido]- 5-*n*-propyl/*n*-butyl-1, 3, 4- thiadiazoles.

Experimental

Chemistry

The reaction of thiosemicarbazide with aliphatic carboxylic acid in the presence of concentrated sulfuric acid gave the 2-amino-5-alkyl-1,3,4-thiadiazole **[1]**. Compound **1** was then acetylated with chloroacetyl chloride. The chloroacetyl derivative **[2]** on reaction with secondary amines gave 2-substituted ethanamido-5 alkyl-1, 3, 4-thiadiazoles **[3, AH1-AH14]** (Fig.1).

The melting points were determined in open capillary tubes with melting point determination apparatus (Toshniwal, India) and were uncorrected. The purity of the synthesized compounds were checked on TLC (precoated silica gel 60 G254 plates, Merck) using ethanol-water (8:2 v/v) as the solvent system.

^{1}H-NMR spectra were recorder in $CDC1_3$ on a Varian EM-390 [90 MHz] spectrometer, and chemical shifts were given in δ ppm with tetramethylsilane [TMS]. IR spectra were recorded on Shimadzu IR-470 spectrophotometer using KBr pellets. Microanalysis were performed using Carlo-Erba 1106 instrument.

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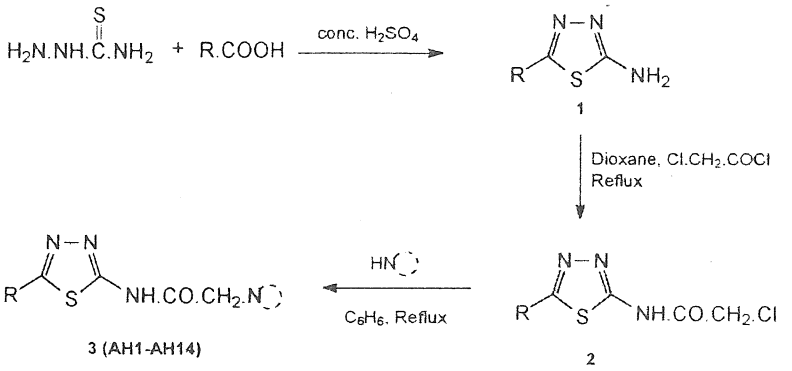
Fig. 1.



Synthesis of 2-amino-5-alkyl-1,3,4-thia-diazole [1]

These were prepared in good yield following the method of Funatsukuri and Ueda (10).

Synthesis of 2-chloroacetylamino-5-alkyl-1,3,4-thiadiazole [2]

Chloroacetylchloride (0.20 mole) was added dropwise to compound **1** (0.20 mole) dissolved in dioxane (250 mL). The reaction mixture was refluxed for 3 hours, then cooled by pouring on crushed ice. The precipitate was filtered and washed repeatedly with aqueous potassium carbonate (1% w/v) and washed with ice cold water. The product was recrystallised from absolute alcohol. 5-*n*-proply : yield 95%, mp 202- 4°C; 5-*n*-butyl : 87%, 195-8°C.

Synthesis of 2-subsituted ethanamido-5-alkyl-1,3,4-thiadiazole [3, AH1–AH14]

To a stirred suspension of 0.05 mole of **2** in 100 mL of benzene, appropriate amount of amine (0.075 mole) was added dropwise and this mixture was then refluxed for 5-6 hours. After cooling, the benzene layer was washed several times with water. The organic phase was freed from water using desiccated sodium sulfate. Removal of the organic phase under vacuum gave the product which was recrystallised from suitable solvent.

Yield, melting points, recrystallization solvents and elemental analysis and ^{1}HNMR and IR spectral data are given in Tables 1 and 2.

Pharmacology

For the pharmacological studies, adult cats (2.0-3.5 kg), guinea pig (300-400 g), albino rats (150-170 g) and albino mice (20-25 g) of either sex were used. Hydrochloride salts of the compounds were used after dissolving in either distilled water or saline depending upon the requirement. The control group received only the vehicle.

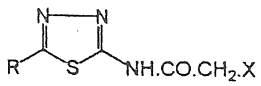
Approximate Lethal Dose [ALD 50]

The albino mice were divided into groups of four animals. The were then administered 215, 464, 1000 and 2150 mg.kg^{-1} (i.p.) of the drugs intra-peritoneally and mortality was observed up to 24 hours. In cases where per cent mortality was observed even at a dose of 215 mg kg^{-1}, further studies were undertaken with 10% of the above doses to find the acute toxicity. The lethal dose was then taken from the Horn's Table (11).

Anti-inflammatory activity

0.05 ml of freshly prepared 1% suspension of carrageenin in saline was injected under the subplanter aponeurosis of the right paw of albino rats by the method of Winter et al. (1962) (12). The animals were kept at 27°C and food and water allowed ad. libitum. One group (5 rats) was kept as control and the animals of the other groups were divided in randomized order and pretreated with the test drug (dose 1/10th of ALD_{50}) orally 30 min prior to the carregeenin injection. One group received standard drug phenylbutazone (30 mg kg^{-1} p.o.). Volume of the paw was measured plethysmographically immediately and after 3 hours of injection of carrageenin. percent anti-inflammatory activity was calculated and the p-values determined according to the Student's t-test using Graphpad Instat Program. The study was done under blind condition.

Table 1. Physical data of 2-substituted ethanamido –5-alkyl-1,3,4-thiadiazoles



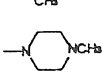
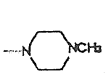
Compound No	R	X	Molecular Formula	Elemental Analysis (%) Found (Calculated) C	H	N	Yield (%)	Melting Point° °C	Recryst. Solvent
AH-1	*n*-C_3H_7		$C_{12}H_{22}N_4OS$	53.20 (53.34)	8.06 (8.14)	20.63 (20.74)	70	69	Ethanol (95%)
AH-2	*n*-C_4H_9		$C_{13}H_{24}N_4OS$	53.81 (54.93)	8.40 (8.45)	19.67 (19.72)	55	70	Ethanol (95%)
AH-3	*n*-C_3H_7		$C_{11}H_{18}N_4OS$	51.73 (51.97)	7.00 (7.09)	21.96 (22.50)	72	102	Methanol
AH-4	*n*-C_4H_9		$C_{12}H_{20}N_4OS$	53.60 (53.73)	7.33 (7.46)	20.78 (20.90)	75	97	Methanol
AH-5	*n*-C_3H_7		$C_{12}H_{20}N_4OS$	53.61 (53.73)	7.37 (7.46)	20.76 (20.90)	50	120	Methanol
AH-6	*n*-C_4H_9		$C_{13}H_{22}N_4OS$	55.27 (55.32)	7.75 (7.80)	19.81 (19.86)	65	110	Methanol
AH-7	*n*-C_3H_7		$C_{13}H_{22}N_4OS$	55.23 (55.32)	7.69 (7.80)	19.70 (19.86)	50	80	Ethanol (95%)
AH-8	*n*-C_4H_9		$C_{14}H_{24}N_4OS$	56.69 (56.76)	8.18 (8.11)	18.99 (18.92)	59	110	Ethanol (95%)
AH-9	*n*-C_3H_7		$C_{12}H_{21}N_5OS$	50.68 (50.88)	7.35 (7.42)	24.67 (24.73)	45	151	Ethanol (95%)
AH-10	*n*-C_4H_9		$C_{13}H_{23}N_5OS$	52.45 (52.53)	7.71 (7.74)	23.53 (23.57)	40	110	Ethanol (95%)
AH-11	*n*-C_3H_7		$C_{11}H_{16}N_4O_2S$	49.20 (49.25)	5.91 (5.97)	20.95 (20.89)	59	150	Ethanol (95%)
AH-12	*n*-C_4H_9		$C_{12}H_{18}N_4O_2S$	51.23 (51.06)	6.41 (6.38)	19.79 (19.86)	40	140	Absolute Ethanol
AH-13	*n*-C_3H_7		$C_{11}H_{19}N_5OS$	48.97 (49.07)	7.00 (7.06)	25.86 (26.02)	60	87-90	Absolute Ethanol
AH-14	*n*-C_4H_9		$C_{12}H_{21}N_5OS$	50.79 (50.88)	7.39 (7.42)	24.65 (24.73)	52	135	Absolute Ethanol

Table 2. Spectral data of the synthesized compounds

Compound No.	IR (cm^{-1}, KBr)	^{1}HNMR (δ, $CDCl_3$)
AH 1	3500-3300, 2900, 1715, 1615, 1505, 1440, 1205, 1085, 975, 815	0.82 (t, 3H, J=7.0 Hz, $-CH_2CH_2C\underline{H}_3$); 1.10 (t, 3H, J=6.0 Hz, $-(CH_2)_3C\underline{H}_3$); 1.20-1.80 (br/m, 8H, $-C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$ fused with $-CH_2C\underline{H}_2CH_3$); 2.65 (s, 3H, $-N-CH_3$); 3.00 (t, 2H, J=7.0 Hz, $-C\underline{H}_2CH_2CH_3$); 3.85 (s, 2H, $-COCH_2-$); 7.60 (br, 1H, NH, D_2O exchangeable)
AH 2	3305, 2915, 1700, 1625, 1520, 1425, 1220, 1080, 967, 820	0.95-1.10 (br/m, 6H, $-(CH_2)_3-C\underline{H}_3$), 1.30-1.80 (br, 8H, $-CH_2(C\underline{H}_2)_2CH_3$); 2.00-2.60 (br/m, 4H, $C\underline{H}_2(CH_2)_2CH_3$); 2.75 (s, 3H, $-N-CH_3$); 3.60 (s, 2H, $-COCH_2-$); 6.25-8.00 (br, 1H, NH, D_2O exchangeable)
AH 3	3340, 2910, 1705, 1627, 1500, 1420, 1205, 1085, 957, 865	1.02 (t, 3H, J=6.5Hz, $-CH_2CH_2C\underline{H}_3$); 1.60-2.10 (m, 6H, $-CH_2CH_2-$ of pyrro. fused with $-CH_2C\underline{H}_2CH_3$); 2.55-2.87 (m, 4H, $-CH_2-N-CH_2-$); 3.07 (t, 2H, J=7.0 Hz, $-C\underline{H}_2CH_2CH_3$); 3.38 (s, 2H, $-COCH_2-$); 7.00-8.50 (br, 1H, NH)
AH 4	3250, 2905, 1700, 1605, 1517, 1425, 1215, 1100, 970, 840	0.95 (t, 3H, J=7.0Hz, $-(CH_2)_3-C\underline{H}_3$), 1.15-1.60 (m, 2H, $-CH_2C\underline{H}_2CH_2CH_3$); 1.70-2.10 (m, 6H, $-CH_2CH_2-$ of pyrro. fused with $-CH_2CH_2C\underline{H}_2CH_3$); 2.50-2.85 (m, 4H, $-CH_2-N-CH_2$); 3.00 (t, 2H, J=6.5 Hz, $-C\underline{H}_2(CH_2)_2CH_3$); 3.40 (s, 2H, $-COCH_2-$); 6.00-7.20 (br, 1H, NH)
AH 5	3400, 2975, 1700, 1600, 1540, 1460, 1200, 1130, 980, 840	0.95 (t, 3H, J=8.0Hz, $-CH_2CH_2C\underline{H}_3$); 1.30-1.95 (m, 8H, $-(CH_2)_3-$ of pipd. fused with $-CH_2C\underline{H}_2CH_3$); 2.30-2.65 (m, 4H, $-CH_2-N-CH_2-$, pipd); 2.95(t, 2H, J=6.0Hz, $-C\underline{H}_2CH_2CH_3$); 3.10 (s, 2H, $-COCH_2-$); 3.30-4.00 (br, 1H, NH, D_2O exchangeable)
AH 6	3450, 2955, 1700, 1610, 1525, 1430, 1225, 1150, 1080, 975, 835	0.94 (t, 3H, J=7.0Hz, $-(CH_2)_3C\underline{H}_3$), 1.10-2.00 (m, 10H, $-(CH_2)_3-$ of pipd. fused with $-CH_2C\underline{H}_2C\underline{H}_2CH_3$); 2.32-2.65 (br, 4H, $-CH_2-N-CH_2-$, pipd); 2.94(t, 2H, J=5.5Hz, $-C\underline{H}_2(CH_2)_2CH_3$); 3.20 (s, 2H, $-COCH_2-$); 8.50-9.30 (br, 1H, NH, D_2O exchangeable)
AH 7	3220, 2900, 1680, 1605, 1570, 1450, 1200, 1105, 960, 825	0.90-1.15 (br/m, 6H, 2 $-C\underline{H}_3$ groups); 1.20-2.10 (br, 8H, $-(CH_2)_3-$ of pipd. fused with $-CH_2C\underline{H}_2CH_3$); 2.15-2.80 (br, 3H, $-CH_2-N-CH<$, pipd.); 2.95 (t, 2H, J=6.0Hz, $-C\underline{H}_2CH_2CH_3$); 3.20 & 3.40 (d, H_a & H_b, J=18.0Hz, $-COCH_2-$); 8.10-9.00 (br, 1H, NH)
AH 8	3300, 2900, 1690, 1620, 1550, 1465, 1200, 1080, 960, 820	0.90-1.15 (br/m, 6H, 2 $-CH_3$ groups), 1.20-2.05 (br, 10H, $-(CH_2)_3-$ of pipd. fused with $-CH_2C\underline{H}_2C\underline{H}_2CH_3$); 2.15-2.85 (br, 3H, $-CH_2-N-CH<$, pipd); 3.00 (t, 2H, J=6.0Hz, $-C\underline{H}_2(CH_2)_2CH_3$); 3.15 & 3.35 (d, H_a & H_b, $-COCH_2-$); 6.75-8.00 (br, 1H, NH)

Table 2. Continued

AH 9	3270, 2900, 1720, 1637, 1585, 1470, 1235, 1080, 985, 865	0.92 (t, 3H, J=7.0 Hz, $-CH_2CH_2C\underline{H}_3$); 1.20-1.65 (m, 2H, $-CH_2C\underline{H}_2CH_3$); 2.25 (s, 3H, $-N-CH_3$); 2.30-2.85 (br, 8H, pipz.); 3.05 (t, 2H, J= 6.5 Hz, $-C\underline{H}_2CH_2CH_3$); 3.25 (s, 2H, $-COCH_2-$); 5.40-7.10 (br, 1H, NH)
AH 10	3310, 2890, 1705, 1605, 1545, 1435, 1210, 1180, 960, 840	0.90 (t, 3H, J=7.5 Hz, $-CH_2(CH_2)_2-C\underline{H}_3$); 1.15-1.50 (m, 2H, $-CH_2C\underline{H}_2CH_2CH_3$); 1.55-1.90 (m, 2H, $-(CH_2)_2-C\underline{H}_2CH_3$); 2.25 (s, 3H, $-N-CH_3$); 2.35-2.80 (br, 8H, pipz.); 3.00 (t, 2H, J=7.0Hz $-C\underline{H}_2(CH_2)_2CH_3$); 3.22 (s, 2H, $-COCH_2-$); 3.40-3.80(br, 1H, NH)
AH 11	3400, 2975, 1700, 1685, 1610, 1545, 1460, 1217, 1095, 945	0.90 (t, 3H, J=7.5 Hz, $-CH_2CH_2C\underline{H}_3$); 1.20-1.85 (br, 8H, $-(CH_2)_3-$ of pyrro. fused with $-CH_2C\underline{H}_2CH_3$); 2.80 (t, 2H, J=6.0Hz, $-C\underline{H}_2CH_2CH_3$); 3.20 (s, 2H, $-COCH_2-$); 5.00-6.50 (br, 1H, NH)
AH 12	3400, 2950, 1725, 1700, 1610, 1525, 1440, 1210, 1105, 960, 840	0.95 (t, 3H, J=7.5Hz, $-CH_2(CH_2)_2C\underline{H}_3$); 1.20-2.20 (br, 10H, $-(CH_2)_3-$ of pyrro. fused with $-CH_2(C\underline{H}_2)_2CH_3$); 3.00 (t, 2H, J=6.0Hz, $-C\underline{H}_2(CH_2)_2CH_3$); 3.20 (s, 2H, $-COCH_2-$); 8.00-9.20 (br, 1H, NH)
AH 13	3310, 2950, 1685, 1625, 1500, 1367, 1205, 1095, 960, 850	1.05 (t, 3H, J=7.5 Hz, $-CH_2CH_2C\underline{H}_3$); 1.80 (m, 2H, J=4.0 Hz, $-CH_2C\underline{H}_2CH_3$); 2.40-2.78 (br, 4H, $-CH_2-N-CH_2-$, pipz); 2.80-3.15 (br, 6H, $-C\underline{H}_2-NH-C\underline{H}_2-$ of pipz. fused with $-C\underline{H}_2CH_2CH_3$); 3.22 (s, 2H, $-COCH_2-$); 3.80-4.50(br, 2H, NH)
AH 14	3300, 2965, 1690, 1632, 1520, 1340, 1200, 1105, 900, 845	0.95 (t, 3H, J=8.0 Hz, $-CH_2(CH_2)_2C\underline{H}_3$); 2.25-2.60 (br, 8H, $-CH_2-N-CH_2-$ of pipz. fused with $-CH_2(C\underline{H}_2)_2-CH_2$); 2.70-3.10 (br, 6H, $-C\underline{H}_2-NH-C\underline{H}_2-$ of pipz. fused with $-C\underline{H}_2(CH_2)_2CH_3$); 3.25 (s, 2H, $-COCH_2-$); 4.50-6.00 (br, 2H, NH)

Diuretic activity

This was determined in male adult rats weighing 175-200g of Sprague Dawley strain of Central Drug Research Institute, Lucknow, according to the method of Kau *et al.* (1984) (13). Rats were fasted overnight with free access to water and were given 5 mL/100g body weight saline orally by using a feeding cannula. Immediately after saline loading, each animal was placed in an individual hanging metabolic cage and urine was collected into a measuring cylinder at hourly intervals over a period of 5 hours. Osmolality, Na^+ and K^+ levels of urine were measured. Animals whose osmolality, urine volume or electrolyte output were not within normal range during initial screening were discarded. Suitable rats were paired to obtain similar cumulative urine volume, osmolality and electrode levels. They were weighed, color coded and administered orally with test agents or standard drug. The urinary bladder was emptied by gentle compression of the pelvic area and by gentle pull of the tail and left in metabolic cages. After 5 hours the bladders were again emptied as before and urine volume determined. Acetazolamide (75 mg kg^{-1}) was used as the standard. The results were expressed in terms of per cent urine volume excretion taking acetazolamide activity as 100%. One group of rats served as control.

Effects on cardiovascular system

Cats of either sex were anesthetized by injecting pentobarbitone sodium (40 mg kg^{-1} i.p.) (14). The effect of the compound (1.0 and 2.5 mg kg^{-1} i.v. through cannulated femoral vein) on carotid blood pressure, heart rate and respiration were recorded on a polygraph. During the experiment

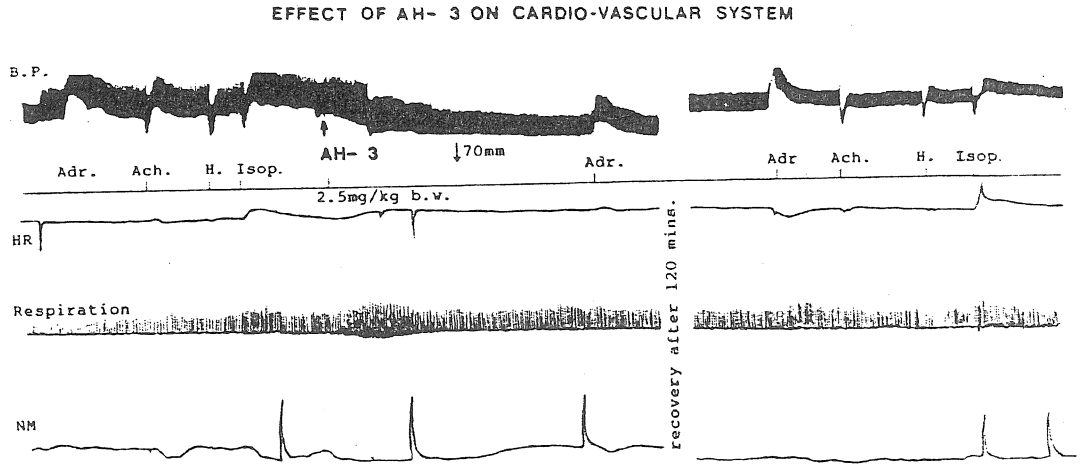


Figure 2. Effects of intravenously administered compound **AH-3**, 2.5 mg kg^{-1} on blood pressure, heart rate, respiration and nictitating membrane of anasthetized cat

the preganglionic sympathetic nerve was also stimulated electrically (10 Hz, 1-5 sec, 5-10v for 5-10sec) (Fig. 2).

In vitro smooth muscle relaxant activity

A 2-3 cm long piece of ileum from a freshly killed guinea pig was suspended in an organ bath containing aerated Tyrode solution (pH 7.4) at 34 C (15). Contrac_tions were recorded on a kymograph though a frontal writing lever. Spasmolytic activities of the compounds were assessed by their abilities to prevent the contraction induced by a submaximal concentrition of acetylcholine ($2.5X10^{-8}$), histamine ($3.0x10^{-7}$) or nicotine ($2.5X10^{-6}$ g ml^{-1}). In all the isolated preparations, graded doses of the spasmolytic compounds were tested against the spasmogen and the IC_{50} was calculated graphically for each experiment.

Results and Discussion

The 2-amino-5-alkyl-1,3,4-thiadiazole **(1)** and 2-chloroacetyl-amino-5-alkyl-1,3,4-thiadiazole **(2)** were prepared according to the reported procedures in this text. 2-Subsituted ethanamido-5-alkyl-1,3,4-thiadiazoles **(3, AH-AH14)** were prepared by refluxing the 2-chloroacetylamino-5-alkyl-1,3,4-thiadiazoles with appropriate amine in benzene for 5-6 hours (Table1).

The IR spectra of the compounds characteristic absorption bands at 3300-3100cm^{-1} [N-H], 1720-1680 [C=N], 1215, 1100, 960, 840 [characteristic bands of 1,3,4-thiadiazole ring] (16). In the PMR spectra, the protons of-CO-CH_2-were observed between 3.00-3.90 ppm. In compound **AH 7** and **AH 8** the-CO-CH_2-proton absorbs at 3.20, 3.40 and 3.15, 3.25 as doublet which is due to the non-equivalence nature (designated as H_a and H_b) arising from-CH_3 group of 2-methyl piperidine. The protons of-NH- (D_2O exchangeable) were observed between 3.4 to 9.30 ppm. (Table 2).

Approximate lethal dose [ALD_{50}] of the compounds ranged from 464-100 mg kg^{-1} i.p. Anti-inflammatory activity shown by the compound **AH7** (40.66), **AH5** (21.00) and **AH4** (18.17) were comparable to phenylbutazone (41.33%) (Table 3).

A few of the compounds i.e. **AH1, AH5** and **AH6** showed appreciable diuretic activity comparable to acetazolamide (75 mg kg^{-1} p.o). These results indicate

that the replacement of the $-SO_2NH_2$ group or substitution of acetyl group in the acetazolamide nucleus retained or increased the diuretic activity. However, significant effects were not observed on osmolality, Na^+ or K^+ levels in urine.

All the compounds showed a transient fall in the blood pressure except **AH1, AH3, AH4.** The compound **AH3** produced a concentration dependent decrease of blood pressure. Mild increases in blood pressure (70 mm for 120 min) was observed at dose of 2.5 mg kg^{-1} i.v. (Fig. 2). None of the compounds antagonised the effects of adrenaline, acetylcholine, isoprenaline or histamine *in vivo.*

The compounds under study showed weak non-specific spasmolytic activity *in vitro.* The IC_{50} ($x10^{-7}$ mole L^{-1}) values of the compounds ranged from 10.2 to 35.3 against histamine and 12.5 to 32.1 against acetylcholine.

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Table 3. Pharmacological data of the synthesized compounds (AH-1-AH14)

Compound No	ALD_{50} Mg/kg	Anti-Inflammatory Activity	%Diuretic Activity	Effect CVS (fall in bp)	IC_{50} ($x10^{-7}$, mole/1) Against spasmogen	
	b.wt.i.p.	Dose $1/10^{th}$ of ALD_{50}	Dose $1/5^{th}$ of ALD_{50}	Dose 2.5mg/kg b.w.	Histamine	Acetyl Choline
AH 1	464	17.43	147.3	↓30 (18)	35.3±2.0	12.5±1.0
AH 2	681	-	48.9	↓30 (tr)	26.2±1.2	21.1±1.2
AH 3	825	-	46.9	↓70 (120)	15.7±1.2	22.6±1.5
AH 4	>1000	18.17	40.7	↓46 (35)	14.2±1.1	-
AH 5	464	21.00**	120.6	-	22.4±1.3	32.1±1.17
AH 6	>1000	16.17	87.4	-	20.6±0.9	-
AH 7	464	40.66*	44.8	↓12 (tr)	23.7±1.1	28.5±1.2
AH 8	599	-	39.5	↓20 (tr)	34.5±1.9	17.1±1.0
AH 9	>1000	9.66	38.2	↓10 (tr)	23.2±1.7	28.1±1.3
AH 10	681	-	68.2	↓20 (tr)	19.1±1.9	-
AH 11	825	-	29.9	-	17.5±1.4	-
AH 12	681	-	36.2	↓10 (tr)	10.5±1.1	-
AH 13	681	16.35	47.9	↓25 (tr)	11.8±0.9	13.1±1.0
AH 14	381	-	33.3	↓15 (tr)	10.2±0.8	26.7±1.1
PB 30mg/kg	-	41.33	-	-	-	-
AC 75mg/kg	-	-	100	-	-	-
MP	-	-	-	-	0.09	1.92

PB = Phenylbutazone, AC=Acetazolamide, MP=Mepyramine, p-value=0.001, **p-value=<0,01 tr=transient

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