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Research Article

ANTI-PYRETIC ACTIVITY OF SOME SYNTHESIZED NOVEL L-ARGININE ANALOGUES (PEPTIDES)

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ABSTRACT

Objective: The objective of the study is to synthesize, characterize and evaluate for anti-pyretic activity of some novel L-arginine analogues.

Method: A series of novel L-arginine analogues were synthesized, characterized and screened for anti-pyretic activity by brewer's yeast induced pyrexia modelin rats using paracetamol as the standard drug for comparing the test results. The purity of the synthesized compounds has been characterized by various analytical techniques such as UV, FTIR and TLC.

Results and Conclusion: The study concluded that the compound 1, 4, 7, 8 and 11were found to exhibit significant anti-pyretic action.

Keywords: Substituted L-Arginine analogues, Anti-pyretic activity, Brewer's yeast induced pyrexia model, Paracetamol.

INTRODUCTION

Fever is the most common symptom of sickness which is caused by increase in body temperature of an individual at a particular time [1].In humans, cutaneous blood vessels are controlled by both neurogenic reflexes and local factors [2].

In nonglabrous or hairy skin, reflex control of the cutaneous vasculature is mediated by two sympathetic pathways: a noradrenergic vasoconstrictor system and active vasodilator system that involves cholinergic transmission [3].Nitric oxide (NO) production is involved in cutaneous vasodilation [4].

The observation that Nitric oxide synthase production plays a significant role in the cutaneous vasculature and also suggest**s** that NO could be involved in the cutaneous vasodilation that caused an increase in the temperature of the skin [5].

Identification of N-methyl-L-Arginine (L-NMA) as the first inhibitor ofNO biosynthesis led to the design of selective iNOS inhibitors [6]. Hence the present study was planned to synthesize some novel substituted L-arginine analogues and to evaluate for itsanti-pyretic activity.

MATERIALS AND METHODS

Synthetic Chemistry

STEP-I

Synthesis of 4-benzylidine-2-phenyl oxazole – 5- ones

A mixture of benzoyl glycine, redistilled benzaldehyde, acetic acid and anhydrous sodium acetate was heated on an electric hot plate with stirring. On liquefaction it was heated for 2hrs and ethanol was added slowly and the mixture was allowed to stand overnight. The product obtained is washed with boiling water and dried at 100°C. The product obtained in step-I was used in step-2 for further synthesis.

STEP-II

Synthesis of substituted L-arginine analogues

The product obtained in step-I was reacted with unsubstituted L-Arginine and some substituted L-Arginine in alkali like NaOH and acetone which results in clear solution after 2-3hrs of reaction. The solution thus obtained was acidified by the addition of HCl. The products separated were unsubstituted and some substituted L-arginine analogues. L-Arginine analogues were washed with cold water and dried. The compounds thus obtained were used for screening the anti-pyretic activity after purification and characterization. The %yield, melting points, Rfvalues and molecular formula of various substituted L-arginine analogues are tabulated in Table 1

Table 1: Physical data of substituted L-arginine analogues (1-11)

Compound name	R	Melting point (°C)	Rf value	% yield	Molecular formula
1	H	205	0.62	76	$C_{22}H_{25}N_5O_4$
2	4-Cl	180 – 185	0.76	66	$C_{22}H_{24}N_5O_4Cl$
3	4-OCH_3	210	0.48	65	$C_{23}H_{27}N_5O_5$
4	4-OH	190	0.66	45	$C_{22}H_{25}N_5O_5$
5	4-OH, 3-OCH_3	175 – 177	0.82	47	$C_{23}H_{27}N_5O_6$
6	5-Br, 4-OH, 3-OCH_3	170 – 172	0.72	46	$C_{23}H_{26}N_5O_6Br$
7	4-$N(CH_3)_2$	198 – 200	0.56	79	$C_{24}H_{30}N_6O_4$
8	4–$(CH_3)_2$	190	0.692	55	$C_{25}H_{31}N_5O_4$
9	4-NO_2	195	0.833	51	$C_{22}H_{24}N_6O_6$
10	4-CH_3	205	0.44	53	$C_{23}H_{27}N_5O_4$
11	5-I, 4-OH, 3-OCH_3	207	0.51	45	$C_{23}H_{26}N_5O_6I$

Preparation of the test and standard drug

The synthesized L-arginine analogues were insoluble in water. So, the test compounds and standard drug were suspended 1% carboxy methyl cellulose and prepared in the concentration of 100mg.kg body weight.

Animals

Adult albino rats (150-180 gms) were used for the study and kept at the laboratory animal house of SreeDattha Institute of Pharmacy for acclimatization to laboratory environment. They were kept in well cross ventilated room at 27±2°C for 1 week before the

commencement of experiment. Animals were provided with commercial rodent pellet diet and water ad libitum

Anti-pyretic activity

Brewer's yeast induced pyrexia model:

Adult albino rats (150 – 180gms) were fasted for 24hrs but allowed water ad libitum were used for the experiment. They were randomized into groups of six rats each. At zero hour, the basal temperature of the rats was taken using digital clinical thermometer. Therefore each animal was administered subcutaneously with 20% w/v aqueous suspension of yeast at a volume of 10ml/kg [7]. At suitable intervals beginning one hour after yeast injection, rectal temperature of the animals were taken an animals with increase in 1^{o}C were grouped for the study.

The testcompoundsunderstudywere administered i.p. after the pyrogen at the dose of 100 mg/kg to respective groups of rats. The control group received distilled water (10ml/kg) and the reference group was administered with paracetamol (100mg/kg) both intraperitoneally. The rectal temperatures of the groups were taken at 1hr interval for 4hr

Table 2: Anti-pyretic activity of L-Arginine analogues

Groups	Dose (mg/Kg)	Basal temperature	Time interval (h)				
			0hr	1hr	2hr	3hr	4hr
Control	---	35.00 ± 0.19	37.45 ± 0.12	37.65 ± 0.47	39.13 ± 0.33	38.23 ± 0.27	38.18 ± 0.27
Control	--	35.00 ± 0.19	37.45 ± 0.12	37.65 ± 0.47	39.13 ± 0.33	38.23 ± 0.27	38.18 ± 0.27
Paracetamol	100	37.45±0.15	38.17± 0.654	39.29 ± 0.28	38.45 ± 0.51	39.43 ± 0.37	37.90 ± 0.47
				37.17±0.654	37 ± 1.065	39.43 ± 0.37	37.90 ± 0.47
Compound 1	100	38.34 ± 0.07	37.45±0.15	38 ± 0.076	38.17± 0.654	37.78 ± 1.45	*36 ± 0.3651
				37.67±1.202			
Compound 2	100	37.23 ± 0.08	37.85±0.15	37 ± 1.065	36.37± 0.09	36.37± 0.04	37 ± 0.365
Compound 3	100	38.98 ± 0.07	39 ± 0.365	39 ± 0.3651	38.17± 0.654	38.56 ± 0.78	37.76 ± 0.67
Compound 3							
Compound 4	100	38.87 ± 0.09	38.47 ± 0.08	37 ± 1.065	37.37± 0.09	36.67±1.202	*36 ± 0.3651
Compound 5	100	38.97 ± 0.06	38 ± 0.365	37.67±1.202	38.17± 0.654	38.37± 0.09	38.67 ± 0.78
Compound 6	100	37.76 ± 0.87	38 ± 0.365	38 ± 0.23	37 ± 0.365	37.78 ± 0.89	38 ± 0.856
Compound 7	100	38.34 ± 0.05	39 ± 0.3651	38.98 ± 1.34	38.37± 0.09	37 ± 0.856	*36.98 ± 0.087
Compound 8	100	37.28 ± 0.08	38 ± 0.365	37 ± 1.065	37.98 ± 0.87	37.37± 0.09	*36 ± 0.365
Compound 9	100	38.79 ± 0.07	39 ± 0.3651	39 ± 0.3651	39 ± 0.365	38 ± 0.98	39.98 ± 1.98
						39.67±1.202	
Compound 10	100	37.86 ± 0.07	39 ± 0.365	39 ± 0.3651	38.17± 0.654	38.67 ± 0.13	37.67±1.202
Compound 11	100	38.28 ± 0.08	38.2 ± 1.23	37 ± 1.065	37 ± 0.365	36.78 ± .97	*36 ± 0.365

Results are expressed as Mean ± SEM; n=5 in each group; *p<0.05,

RESULTS AND DISCUSSION

All the L-Arginine analogues synthesized have good yield value. The melting points of all the compounds were determined in an open capillary tube using an electro thermal digital meting point apparatus and are uncorrected.

The compounds were characterized using analytical techniques such as UV, TLC and FT-IR. All the Compounds were screened for anti-pyretic activity and the results were compared with that of the standard drug.

The study revealed that Compound 1, 4, 7, 8 and 11 exhibited very significant anti-pyretic action while compound 9 has shown very minimum anti-pyretic action. The compounds can be screened for anti-pyretic action using other screening models to assess their activity on a broader scale which is our future part of the research work.

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