Synthesis, Chemistry and Anti-Hypertensive Activity of Some New Thiazole-Thiadiazole Derivatives

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ABSTRACT :
This present work deals with the synthesis, characterization and anti-inflammatory activity of some novel thiazole-thiadiazole derivatives. 2-amino 4-phenyl thiazole (I) was readied by triturating thiourea and iodine and mixed with substituted acetophenone. Equal mole of (I) & phenylisothiocyanate in the presence of potassium hydroxide, at room temperature afforded 1-phenyl-3-(4-phenylthiazol-2-yl)thiourea(II). When (II) was directly reacting with hydrazonoyl chloride in refluxing ethanol in the presence of triethylamine afforded 4-substituted phenyl tiazol-2-imine-3,5-diphenyl thiadiazole derivatives(III). The CS synthesized compounds are confirmed by MASS, FTIR and ^{1}H-NMR spectral studies. The SC is (50µgm/kg) screen for anti-hypertensive activity by Tail Cuff method.
Keywords: Anti-hypertensive activity, Tail Cuff method, Thiazole, Thiadiazole.

I.INTRODUCTION

The importance of thiazole and thiadiazole nucleus is entrenched in the field of pharmaceutical science. This class of mixes has played a pivotal role in organic and medicinal chemistry. Various pharmacological activities such as antihypertensive, antidiabetic and anti bacterial are associated with compounds having thiazole and thiadiazole nucleus. On the basis of predicted biological activity spectra, new lead structures were discovered with antimicrobial, antifungal, antiviral and anti-diabetic, anti-inflammatory activities. Once all the values are displayed the recorder is switched off and for next measurement. Some procedures are allowed once when sufficient pulse level is attained.

II. EXPERIMENTAL WORK

The melting range of the synthesized compounds was performed by LAB-INDIA MS-VIS Visual melting point apparatus and is uncorrected.

STEP-1: General procedure for the synthesis of Substituted 2-amino-4-phenyl thiazole derivatives (I).
Substituted 2-amino 4-phenyl thiazole (I) was prepared by triturating thiourea (0.2 mol) and iodine (0.1) and mixed with substituted (0.1mol) acetophenone. The blend was warmed on a water shower with periodic mixing for 8 hrs to get the item. The got strong was washed with diethyl ether to evacuate unreacted substituted acetophenone. The rough item was broken up in boiling hot water and sifted to evacuate the sulphone,the sulphone. Substituted 2-amino-4-phenylthiazole substituted derivatives were precipitated by the addition of ammonia to the above filtrate and re-crystallized from ethanol has resulted white solid, yield 70% m.p 238ºC. It purified by column chromatography on silica gel (toluene: ethyl acetate: formic acid) to give the required 2-amino-4-phenyl thiazole.
STEP-2: Synthesis of substituted 1-phenyl-3-(4-phenylthiazol-2-yl)thiourea(II)
Reaction of 4-phenyl 1,3-thiazol-2-amine derivative(I) with phenylisothiocyanate in dimethylformamide, in the presence of potassium hydroxide, at room temperature afforded 1-phenyl-3-(4-phenylthiazol-2-yl)thiourea(II)
STEP-3: Synthesis of substituted 4-substituted phenyl tiazol-2-imine-3,5-diphenyl thiadiazole derivatives(III)
The reactivity of the disubstituted thiourea derivative II with various types of hydrazonoyl chlorides was

evaluated. Thus, treatment of the disubstituted thiourea derivative II with the hydrazonoyl chloride in refluxing ethanol in the presence of triethylamine afforded 4-substituted phenyl tiazol-2-imine-3,5-diphenyl thiadiazole derivatives(III).

The IRS studies of the synthesized compound were recorded by pressed-pellet technique. IR spectra were recorded in KBr press (Shimadzu). H-NMR-Bruker avance 300MHz using TMS as internal standard. Phenylisothiocyanate in the presence of potassium hydroxide, at room temperature afforded 1-phenyl-3-(4-phenylthiazol-2-yl)thiourea(II). When (II) was directly reacting with hydrazonoyl chloride in refluxing ethanol in the presence of triethylamine afforded 4-substituted phenyl tiazol-2-imine-3,5-diphenyl thiadiazole derivatives(III). The CS synthesized compounds are confirmed by MASS, FTIR and ^{1}H-NMR spectral studies. The SC is (50µgm/kg) screen for anti-hypertensive activity by Tail Cuff method.

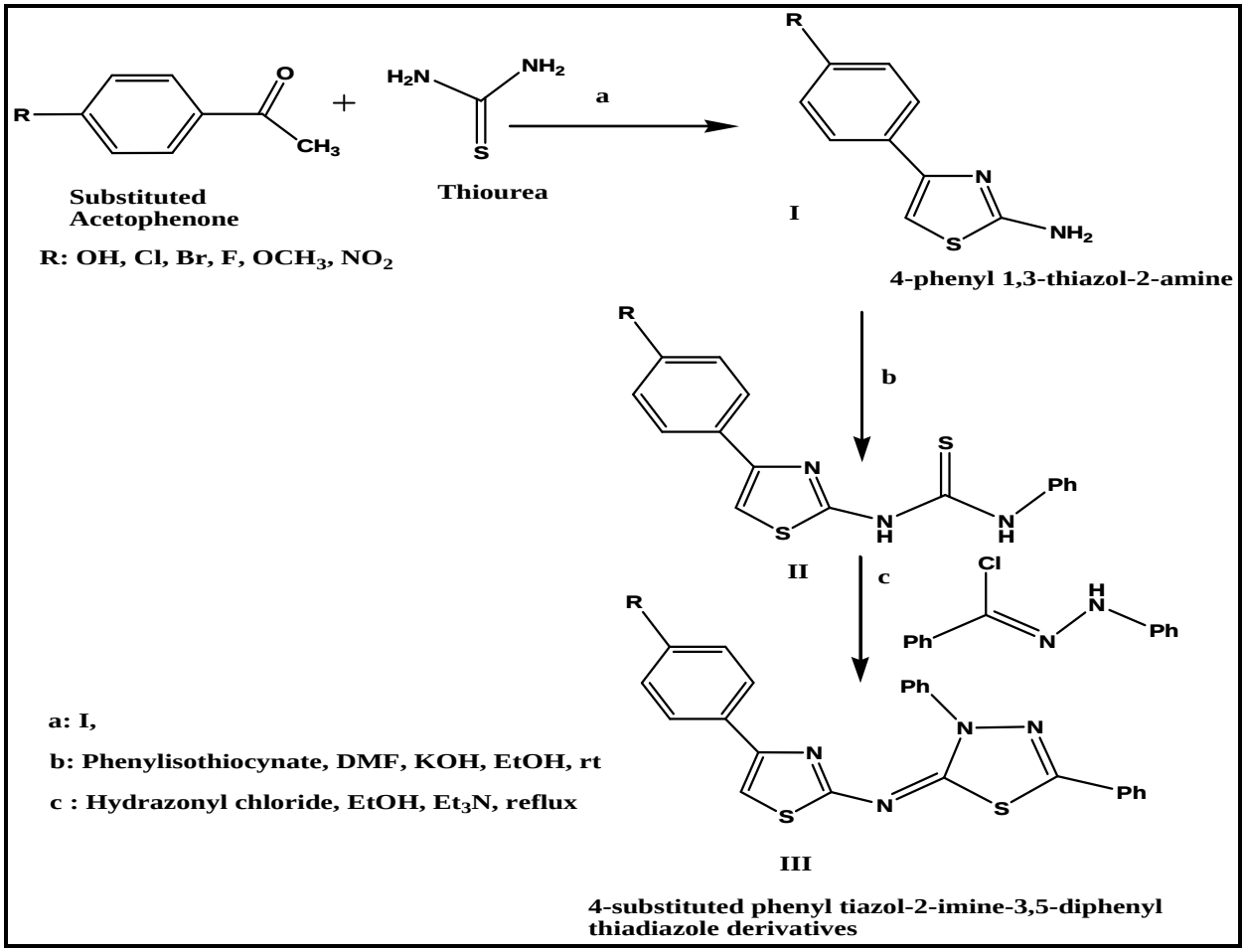

Fig.1. LAB-INDIA MS-VIS Visual melting point apparatus and is uncorrected.

III.RESULTS AND DISCUSSION

The synthesized compounds were screened for anti-hypertensive activity on Albino normotensive rats (Wistar Strain) by Tail Cuff method.

Pharmacological evaluation:Pharmacological Investigation of Thaiazole-thaidiazole Derivatives for anti-hypertensive activities

Procedure For Development Of Hypertention For Normotensive Rats (Tail Cuff Method)

1. Albino normotensive rats (Wistar Strain) were taken and they were hypertensized by cholinomimetic agents for screening of all the synthesized benzimidazole derivatives for their anti-hypertensive activity. Suspension of test compounds was prepared in 1% w/v sodium carboxy methyl cellulose (sodium CMC) and was administered at dose level of 50 and 100 microgram/kg animal body weight to different groups of

five rats each. After administration of dose to animal blood pressure was measured by normotensive tail and cuff method using LE-5001 pressure meter. Measurement were done after one hour and three hours interval in step-wise manner as follows:

2. One hour after administration of drug sample, animal was shifted to the restrainer, which restricts the movement of animal.
3. The tail was cleaned with moist cotton to remove the dirty matter and talcum powder was sprayed on tail to make its surface smooth.
4. A tail cuff and pulse transducer was fixed around the tail.
5. Initially animal shows particular pulse level, when the pulse rate is within the normal range. 'STRAT' switch is put on and the recorder records the blood pressure as SBP(systolic blood pressure). DBP(Diastolic blood pressure) and MABP (mean arterial blood pressure), which is displayed on monitor. The pressure can be easily read from the pre-calibrated monitor. Once all the values are displayed the recorder is switched off and for next measurement. Some procedures are allowed once when sufficient pulse level is attained.

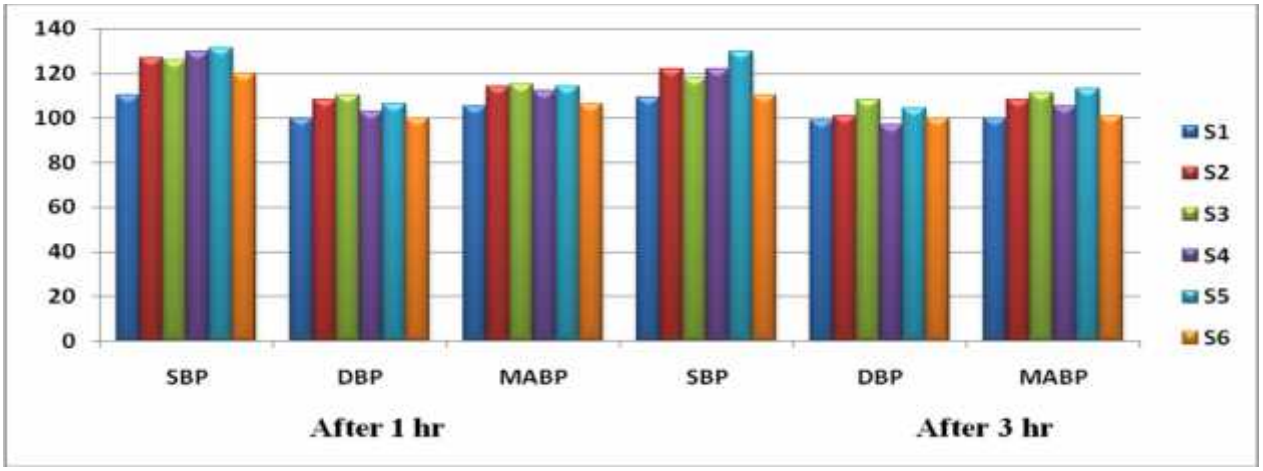

Fig.2: Reduction in blood pressure (mm Hg) at a dose of 50µgm/kg animal body weight.

Table: 1 Hypertension induced in normotensive rat

COMPOUNDS	Exp.Animal albino(wistar) rat	After 1hr			After 3hrs		
		SBP	DBP	MABP	SBP	DBP	MABP
S1	1	140	108	119	136	102	108
	2	138	106	118	140	104	109
	3	140	100	119	141	104	110
	4	139	101	108	140	102	119
	5	140	105	110	139	101	120
S2	1	142	110	122	140	102	108
	2	140	107	120	141	106	122
	3	141	110	121	140	104	120
	4	140	105	111	141	104	122
	5	141	108	119	138	105	121
S3	1	142	112	127	140	110	111
	2	140	110	125	140	112	123
	3	141	114	123	141	115	122
	4	140	113	120	142	114	115
	5	138	110	125	140	109	119
S4	1	142	108	125	158	102	120
	2	140	106	123	140	104	122
	3	138	104	121	139	103	121
	4	140	104	122	141	105	122
	5	141	109	125	140	108	124

S5	1	144	108	120	140	105	118
	2	141	103	119	140	106	117
	3	140	110	124	139	103	118
	4	139	107	120	140	108	122
	5	138	105	121	139	107	121
S6	1	141	109	120	138	100	107
	2	139	107	119	140	102	109
	3	140	100	120	141	104	120
	4	139	101	109	141	104	120
	5	140	105	110	140	102	121

Table: 2 Reduction in blood pressure (mm Hg) at a dose of 50µgm/kg animal body weigh

COMPOUNDS	**Exp. Animal albino (wistar) rat**	**After 1hr**			**After 3hrs**		
		SBP	**DBP**	**MABP**	**SBP**	**DBP**	**MABP**
S1	1	110	100	105	109	99	100
	2	108	99	99	100	100	101
	3	111	100	104	110	101	100
	4	107	98	100	100	100	99
	5	105	100	101	100	101	100
S2	1	127	108	114	122	101	108
	2	126	106	113	125	105	112
	3	127	109	115	123	102	109
	4	125	104	111	124	103	110
	5	126	107	113	122	103	109
S3	1	126	110	115	118	108	111
	2	124	109	114	120	110	113
	3	127	112	117	122	114	117
	4	127	111	116	122	112	115
	5	126	110	117	120	108	112
S4	1	130	103	112	122	97	105
	2	130	105	113	128	100	109
	3	127	99	108	126	99	107
	4	129	102	111	128	102	111
	5	130	105	113	128	103	111
S5	1	131	106	114	130	104	113
	2	128	102	111	130	105	113
	3	134	110	118	128	101	110
	4	131	106	114	133	106	115
	5	130	104	113	131	104	114
S6	1	120	100	106	110	100	101
	2	118	98	100	100	101	100
	3	120	98	105	112	100	101
	4	118	100	100	100	101	100
	5	117	100	101	101	100	101

CONCLUSION

In conclusion, the present study highlights the importance of thiazole-thiadiazole derivatives for rational drug designing for various diseases. And therefore serves as lead molecules for further modification (molecular modeling) to obtain clinically useful entities. On the basis of predicted biological activity spectra, new lead structures were discovered with antimicrobial, antifungal, antiviral and anti-diabetic, anti-inflammatory activities etc.,

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