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Synthesis and Biological Evaluation of Substituted Imidazo [2,1-b]-1,3,4-Thiadiazole Derivatives as Anti-Inflammatory Agents

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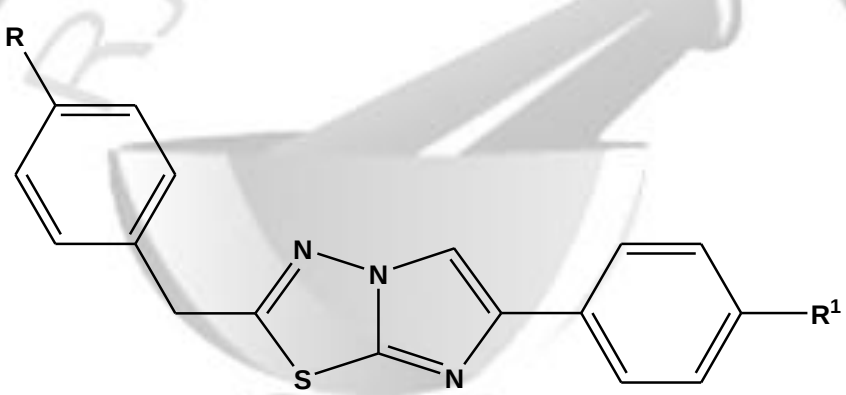
ABSTRACT

The reaction of 2-amino-5-benzyl-1,3,4-thiadiazoles with appropriate 4-substituted/unsubstituted phenacyl bromides yielded substituted imidazothiadiazoles in good yields. The investigations for anti-inflammatory activity revealed a better anti-inflammatory activity. Compounds RUS-06, RUS-01 were capable of showing better anti-inflammatory activity compared to the standard Ibuprofen.



R=Cl,NO_2. R^1=H,Cl,OCH_3,CH_3,NO_2.

Keywords: 2-amino-5-benzyl-1,3,4-thiadiazoles, phenacyl bromides, imidazothiadiazoles, anti-inflammatory activity.

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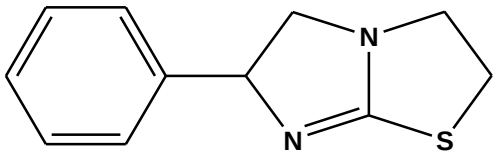
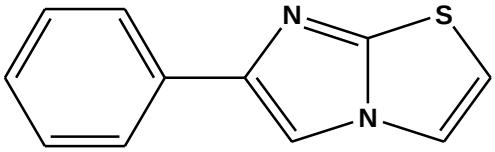
INTRODUCTION

Levamisole [A] an anthelmintic agent was found to be an immunostimulant by Renoux in 1972.It appears to be most effective in patients with small tumour antigens.[1] Further, the imidazo(2,1-b) thiazole [B] derivatives have been reported as potential antitumor agents.[2]

In view of the above and in continuation of our search for novel biological active molecules, we report synthesis and biological evaluation of substituted imidazo[2,1-b]-1,3,4-thiadiazole derivatives [C] as anti-inflammatory agents.



Levamisole [A]



Imidazo (2,1-b) thiazole [B]

2,6-Substituted imidazo[2,1-b]-1,3,4-thiadiazole [c]

MATERIAL AND METHODS

Synthesis of 2-amino-5-(4-substituted/unsubstituted benzyl)-1,3,4-thiadiazole[3]

Substituted acetic acid (0.3M), concentrated sulphuric acid (31.5ml) and thiosemicarbazide (0.25M) were taken in two necked round bottom flask and slowly heated to 70-80°c and maintained at that temperature for 7-8 hours. After cooling poured into ice water and made basic with concentrated ammonia. The product obtained was filtered, washed with water and recrystallised from ethanol.

Preparation of phenacyl bromide: [4]

To a solution of various acetophenones (0.02M) in acetic acid 4ml was added drop wise bromine (0.02M) in acetic acid (3.5ml) with stirring at 0-10°c during 1hr. It was further stirred for 2hr at room temperature and poured in to crushed ice (25gm).The solid that separated was

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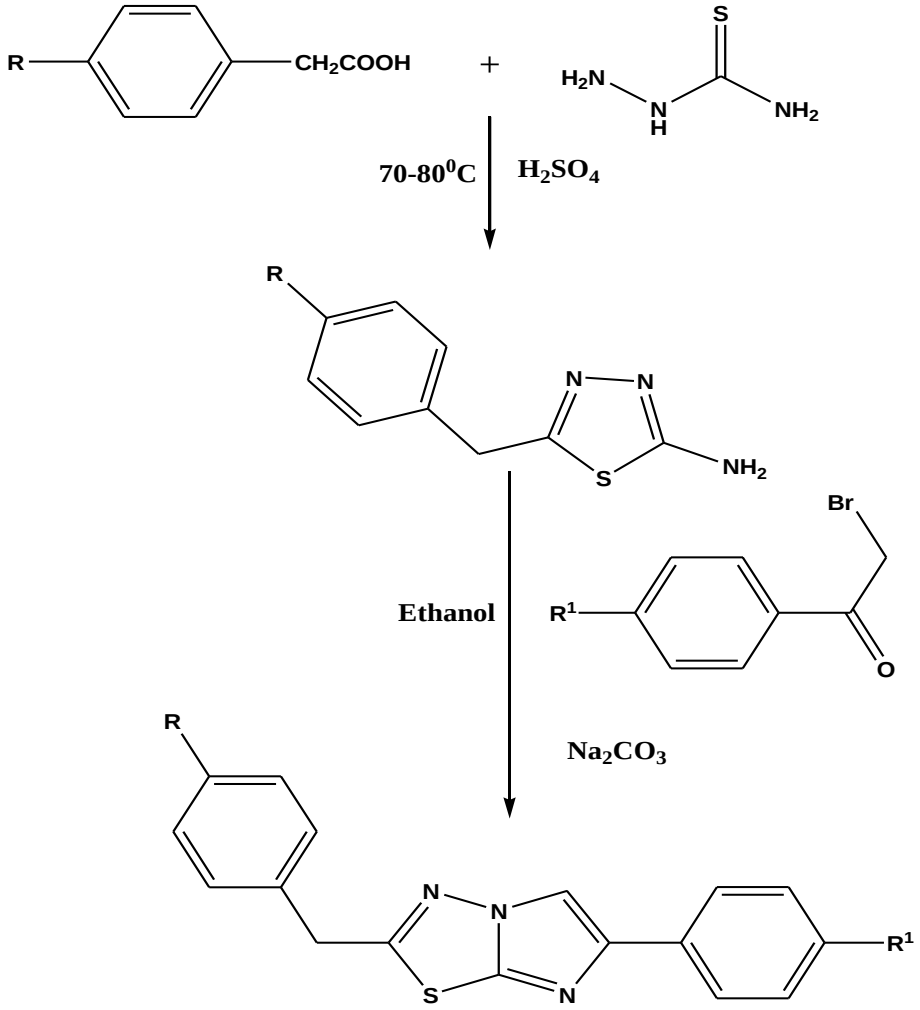
filtered, washed with water and dried. The different crude phenacyl bromides were purified by recrystallisation from methanol.



(RUS-01,RUS-02,RUS-03,RUS-04,RUS-05,RUS-06)

Fig: 1: Scheme for synthesis

Synthesis of 2-(4-substituted/unsubstituted benzyl)-6-(4-substituted phenyl)imidazo[2,1-b][1,3,4] thiadiazole [4,5]

A mixture of 2-amino-5-substituted[1,3,4-]thiadiazole (0.02 M) and appropriate phenacyl bromide (0.02M) in ethanol (50ml) was refluxed on water bath for 10-12hrs. Excess of solvent was removed under reduced pressure and the solid hydrobromide that separated was filtered, washed with cold ethanol and dried. Neutralization of the above hydrobromide salts were done with cold aqueous solution of sodium carbonate (pH-7) to get corresponding bases. All free bases were purified by recrystallisation from ethanol.

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ANTI-INFLAMMATORY ACTIVITY:

Model: Carragenan induced paw edema model
Dose : Standard Ibuprofen-100mg/kg
Test Drug (RUS-01,RUS-02,RUS-03,RUS-04,RUS-05,RUS-06)-100mg/kg

The anti-inflammatory activity was evaluated by using carragenan- induced paw edema model.[6] The method involves injection of Standard carrageenan (prepared freshly in normal saline) into the subplanatar region of left hind paw 0.1ml in rats. In the control group animals, only vehicle is injected. Test drug is administered orally or intraperitoneally according to body weight,;lk immediately or half an hour before carrageenan challenge. A mark is made at the ankle point of each rodent. Paw volume up to the ankle joint is measured in drug treated and untreated groups before and up to 6 hours after carrageenan challenge using a Plethysmograph filled with mercury. The % edema rate (ER) was calculated using the formula:

$$\%ER = \frac{V_C - V_t}{V_t} \times 100$$

V_C =volume of paw before injection
V_t = volume of paw after 't' time
From this data the % inhibition of edema is calculated using the formula:

$$\%IE = \frac{E_C - E_t}{E_t} \times 100$$

E_C = oedema rate of pathogenic control
E_t = oedema rate of compound treated group

RESULTS AND DISCUSSION

We have synthesized a series of six derivatives of Imidazo(2,1-b)-1,3,4-thiadiazole containing substituted benzyl at 2nd position and substituted phenyl at the 6th position by reacting 2-amino-5-benzyl-1,3,4-thiadiazoles and an appropriate 4-substituted/unsubstituted phenacyl bromides as depicted in Scheme. Structures of synthesized compounds were synthesized were confirmed by IR, NMR, MS.

Further compounds (RUS-01, RUS-02, RUS-03, RUS-04,RUS-05,RUS-06) and Ibuprofen as standard were evaluated for anti-inflammatory activity by using carragenan- induced paw edema model. The results are presented by Fig:2,Fig:3,Fig:4,Fig:5.

The test compounds were statistically compared with standard Ibuprofen by Newman-Keuls Multiple comparison Test. All the test compounds showed anti-inflammatory activity.Compounds RUS-06, RUS-01 were capable of showing better anti-inflammatory activity compared to the standard.

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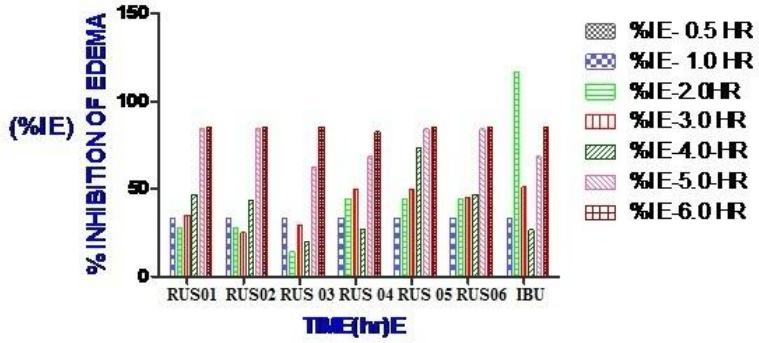
Fig. 2 : Physicochemical data of the synthesized compounds

Comp Code	R	R^1	Mol.Formula	Yield (%)	M.P(^{0}c)
RUS-01	Cl	H	$C_{17}H_{12}ClN_3S$	60	135-137^{0}c
RUS-02	Cl	Cl	$C_{17}H_{11}Cl_2N_3S$	50	121-125^{0}c
RUS-03	Cl	OCH_3	$C_{18}H_{14}ClN_3OS$	63	130-132^{0}c
RUS-04	Cl	CH_3	$C_{18}H_{14}ClN_3S$	65	142-145^{0}c
RUS-05	Cl	NO_2	$C_{17}H_{11}ClN_4O_2S$	64	216-219^{0}c
RUS-06	NO_2	H	$C_{17}H_{12}N_4O_2S$	58	135-137^{0}c

Fig.3: % Edema rate of prepared compounds in comparison to standard Ibuprofen

S. No.	Compound Name	% edema rate						
		0.5h	1h	2h	3h	4h	5h	6h
1	RUS-01	0.0±0.0	16.67± 0.0	33.33± 0.0	77.78± 5.555	44.44± 3.514	16.67± 0.0	16.67± 0.0
2	RUS-02	0.0±0.0	16.67± 0.0	33.33± 0.0	83.34± 7.453	47.22± 2.778	16.67± 0.0	16.67± 0.0
3	RUS-03	0.0±0.0	22.22± 3.512	52.78± 2.778	86.11± 5.122	66.67± 4.303	36.11± 5.122	16.67± 0.0
4	RUS-04	0.0±0.0	33.33± 0.0	61.11± 5.557	100.0± 0.0	61.11± 5.557	33.33± 0.0	19.45± 2.777
5	RUS-05	0.0±0.0	33.33± 0.0	66.67± 0.0	33.33± 0.0	22.22± 0.0	16.67± 0.0	16.67± 0.0
6	RUS-06	0.0±0.0	33.33± 0.0	66.67± 0.0	66.67± 0.0	44.44± 7.029	16.67± 0.0	16.67± 0.0
7	Control	0.0±0.0	27.78± 3.512	47.22± 2.778	66.67± 0.0	83.33± 0.0	105.5± 3.500	113.9± 5.114
8	Standard Ibuprofen	0.0±0.0	33.33± 0.0	100±0.0	66.67± 0.0	61.05± 5.550	33.33± 0.0	16.67± 0.0



IBU- Standard Ibuprofen

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S.No.	Compound code	% inhibition rate						
		0.5h	1h	2h	3h	4h	5h	6h
1	RUS-01	0.0±0	33.31±21.07*	44.46±11.12**	50.0±0.0**	43.33±4.214***	84.12±0.4996***	85.21±0.6580***
2	RUS-02	0.0±0	33.32±10.54***	27.78±5.557***	34.896±5.557ns	46.67±4.216***	84.12±0.4996***	85.21±0.6580***
3	RUS-03	0.0±0	33.31±21.07*	44.46±11.12*	49.99±0.0**	26.66±6.668ns	68.25±0.9993***	82.48±3.218***
4	RUS-04	0.0±0	33.32±10.54**	27.78±5.557*	25.00±11.18**	43.33±3.333***	84.12±0.4996***	85.21±0.6580***
5	RUS-05	0.0±0	33.31±21.07*	44.46±11.12*	45.23±6.667**	46.66±8.435*	84.12±0.4996***	85.21±0.6580***
6	RUS-06	0.0±0	33.32±10.54**	13.89±9.046ns	29.16±7.682*	19.99±5.164ns	62.69±4.106**	85.21±0.6580***
7	STANDARD IBUPROFEN	0.0±0	33.31±21.07ns	116.7±16.72***	50.89±6.667**	26.67±6.667ns	68.26±1.006**	85.21±0.6411***

No of animals per group(n)=6
*** -- P<0.001
**----P<0.01
*-----P<0.01

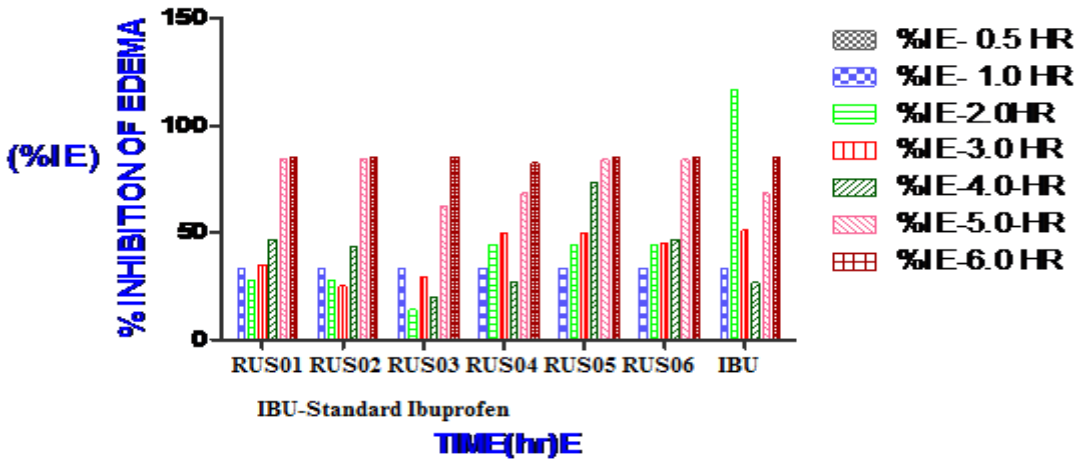

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Table: IV Infrared spectral study of the synthesized compounds.

Compound code	Spectral peaks (cm^{-1})	Molecular nature
RUS-01	3030.59 2915.84 1524.45	Ar. C-H (stretching) Al. C-H (stretching) C=N (stretching)
RUS-02	3076.87 2924.72 1597.73 1508.06	Ar. C-H (stretching) Al. C-H (stretching) C=N (stretching) NO_2 (stretching)
RUS-03	3057.58 2972.73 1524.45	Ar.C-H (stretching) Al.C-H (stretching) C=N (stretching)
RUS-04	3147.26 2921.63 1592.91 1476.24	Ar. C-H (Stretching) Al. C-H (stretching) C=N (stretching) Ar.C=C (stretching)
RUS-05	3129.9 2924.52 1662.34 1596.77 1504.24	Ar. C-H (stretching) Al. C-H (stretching) C=N (stretching) Ar. C=C (stretching) NO_2 (stretching)
RUS-06	3147.26 2921.63 1592.91 1476.24	Ar. C-H (stretching) Al. C-H (stretching) Ar. C=C (stretching) C=N (stretching)

Table : V ^{1}H NMR spectral data of synthesized compounds.

Compound Code	Chemical Shift Value(δ)in ppm	Proton Nature
RUS-01	8.95 8.12-8.30 7.32-7.41 4.45	s,1*H*, C-*H* d,4*H*, Ar-*H* m,5*H*,Ar-*H*, s,2*H*,-CH_2 -
RUS-02	8.55 7.73 7.29-7.41 7.20 4.43 2.30	s,1*H*,C*H* d,2*H*,Ar-*H* m,9*H*, Ar-*H* d,1*H*, C*H* s,2*H*, -CH_2- s,3*H*, CH_3
RUS-03	7.88 7.72-7.74 7.31-7.41 6.95-6.97 4.33 3.8	s,1H,C*H* d,2H,Ar-*H* m,5H, Ar-*H* d,2H,Ar-*H* s,2H,-CH_2- s,3H,OCH_3

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RUS-04	7.94 7.35-7.38 7.27 4.27	s,1*H*, *CH* d,4*H*,Ar-*H* d,2*H*,Ar-*H* s,2*H*,-CH_2-
RUS-05	8.91 8.26 8.09 7.44 4.47	s,1*H*,*CH* d,2*H*,Ar-*H* d,2*H*,Ar-*H* s,4*H*,Ar-*H* s,2*H*,-CH_2-
RUS-06	7.92 7.22-7.69 4.26 2.37	s,1*H*, *CH* d,8*H*, Ar-*H* s,2*H*, -CH_2- s,3*H*, CH_3

Table: VI Mass spectral study of synthesized compounds

Compound code	m/z value
RUS-01	**324.1 (325.4)M^+**
RUS-02	**360.3(360.26)M^+**
RUS-03	**322.3(321.40)M+1**
RUS-04	**304.9(305.40)M-1**
RUS-05	**370.4(370.81)M^+**
RUS-06	**336.1(336.07)M^+**

Values in parenthesis indicate calculated molecular weight of compound.

CONCLUSIONS

Compounds RUS-06, RUS-01 were capable of showing better anti-inflammatory activity compared to the standard.

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