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SYNTHESIS AND ANTIHYPERTENSIVE ACTIVITY OF SOME NOVEL 2-SUBSTITUTED[1,3,4] THIADIAZOLO[2,3-*b*]-6,7- DISUBSTITUTED THIENO[3,2-*e*]PYRIMIDIN-5(4*H*)-ONES

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Various derivatives of 2-substituted [3,2,4] thiadiazolo [2,3-b]-6,7-disubstituted thieno [3,2-e] pyrimidin-5(4H)-ones have been synthesized by cyclizing 3-Amino-2-mercapto-5,6-disubstituted[2,3-d] pyrimidin-4(3H)- one with a variety of one carbon donors. Preliminary screening of these compounds, for antihypertensive activity was done in spontaneously hypertensive rats (SHR) by tail cuff method, using Harvard Blood Pressure monitor (Kent UK). Compounds II, V, X, XII were found to possess antihypertensive activity more than the standard prazocin.

Keywords: *Thiadiazolo thienopyrmidine; Thienopyrimidine; Antihypertensive*

Introduction

Condensed thienopyrimidines exhibit various biological activities like anlgesic&antiinflammatory (1-3), antibacterial (4), antihistaminic (5-6), and anticonvulsant(7) activity. Various thiadiazolo quinazoline and thiadiazolo thienopyrimidine systems have been synthesized and studied for biological activities(8-17) but the synthesis of [1,3,4]thiadiazolo[2,3-b] quinazolines and [1,3,4]thiadiazolo [2,3-b] thieno[3,2-e]pyrimidines have received only scant attention. Infact, the first report on the synthesis of [1,3,4]thiadiazolo[2,3-b]quinazoline appeared in 1970 and very few reports have appeared since then.

Literature survey reveals antihypertensive activity in [1,3,4]thiadiazolo quinazolines(18-19), their bio isosteric [1,3,4] thiadiazolo [2,3-b] thieno [3,2-e] pyrimidin -5 (4H)-ones is relatively unexplored. The present paper deals with a facile and simple synthesis of 2-substituted[1,3,4] thiadiazolo[2,3-b]-6,7-disubstituted thieno[3,2-*e*] pyrimidin-5(4H)-ones and the pharmacological screening of these compounds for antihypertensive activity . The target compounds (I-XVI) was synthesized by cyclizing 3-Amino-2-mercapto-5,6-disubstituted thieno [2,3-d] pyrimidin -4(3H)-one. 3 with a variety of one carbon donors like triethyl orthoformate, acetic acid, alkyl and aryl isothiocyanates etc. The starting material 3 was synthesized from 2-Amino-3-carbethoxy-4,5-disubstituted thiophene. 1 as depicted scheme-I. All the compounds were obtained in good yield. The compounds synthesized were characterized by IR, NMR and mass spetcra and the purity was ascertained by TLC and microanalysis. Physical data of the compounds synthesized is shown in table 1&2. All the newly synthesized compounds were evaluated for their antihypertensive activity in spontaneously hypertensive rats (SHR) by tail cuff method using Harvard Blood Pressure monitor (Kent UK) (20).

Materials and Methods

Melting points were determined in open capillary tubes on a thomas Hoover melting point apparatus and are uncorrected. Infra red spectra were recorded in potassium bromide discs using

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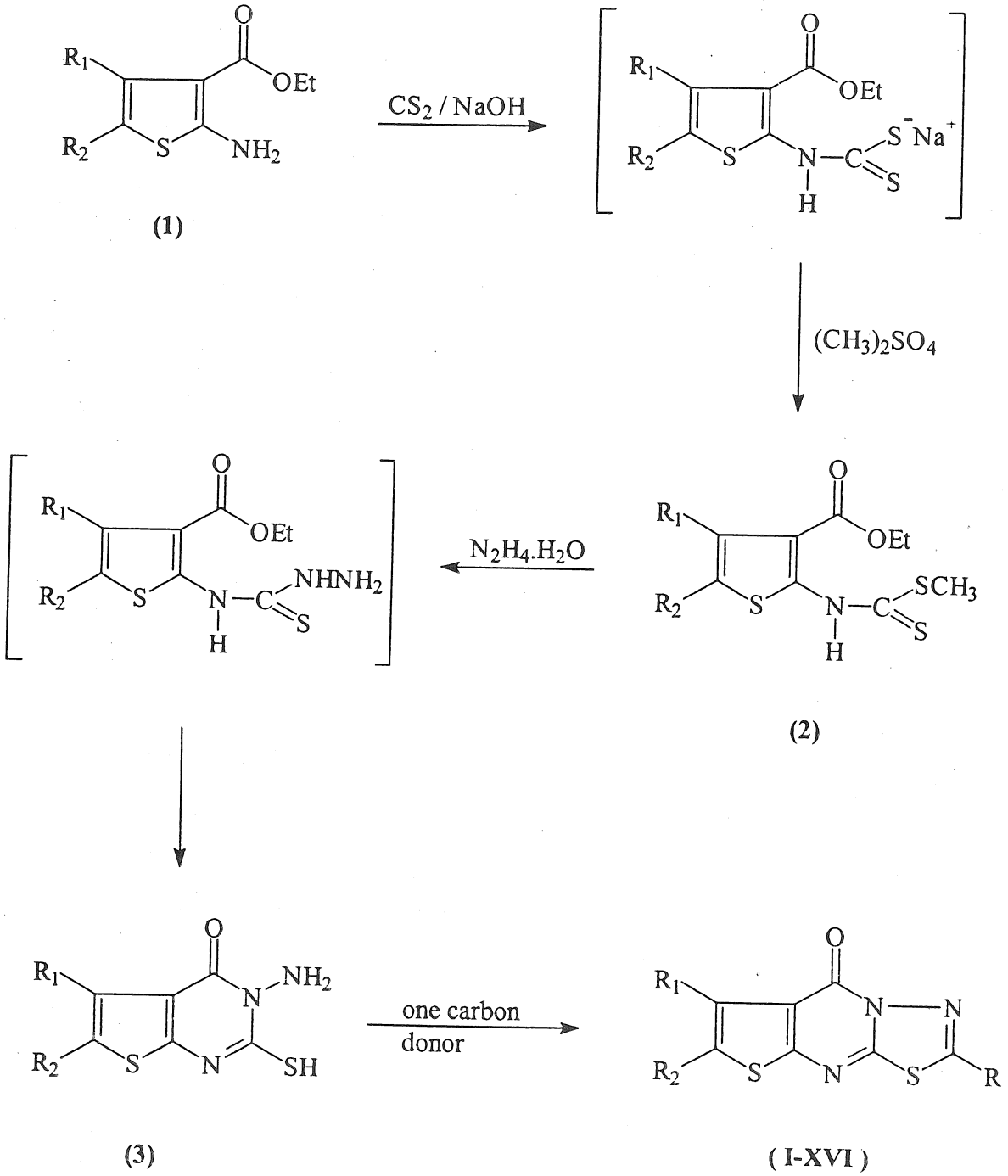

R1
R2
S
NH2
O
OEt
(1)
CS2 / NaOH
S⁻Na⁺
N
C
S
H
(CH3)2SO4
SCH3
(2)
N2H4.H2O
NHNH2
(3)
one carbon
donor
N
SH
R

Scheme-1

Perkin-Elmer mode 1841 grating spectrophotometer. NMR spectra were taken on varian EM-360L spectrometer at 60 MHz and the chemical shifts are given in units as parts per million downfield from Tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on Joel D-300 Electron impact mass spectrometer

The starting material 2-Amino-3-Carbethoxy-4,5-disubstituted thiophene was prepared by the method reported by K. Gewald and E. Schinke(21).

Synthesis of Methyl N-(3-carbethoxy-4,5-dimethylthienyl)dithio carbamate.2

To a vigorously stirred solution of 2-amino-3-carbethoxy-4,5-dimethylthiophene 1[4.18g; 0.02 mol] in dimethylsulphoxide (10 ml) at room temperature, carbondisulphide [1.98 g; 0.026 mol] and 20 Molar aqueous sodium hydroxide solution[1.2 ml] were added dropwise. After 30 minutes, dimethylsulphate [2.5 g; 0.02 mol] was added dropwise under cooling with an ice bath. Stirring was continued for 3 hours, then the reaction, mixture was poured in ice-water mixture (100ml). The precipitated product was filtered, dried and recrystallised from ethanol (95%) to yield the yellow crystalline product 3.6g (89%). M.P. 110-112°C;

IR (KBr) (cm^{-1})-3200 (NH), 2980 (CH), 1680 (C=O), 1060(C=S); **NMR** ($CDCl_3$) δ ppm-1.95(t, 3H, 2-$COOCH_2C\underline{H}_3$), 2.20(s, 3H, 5-$C\underline{H}_3$), 2.30(s, 3H, 6-$C\underline{H}_3$), 4.20(q, 2H, 2-$COOC\underline{H}_2CH_3$), 4.30(s, 3H, 1-$SC\underline{H}_3$), 7.0(s, 1H, 1-N$\underline{H}$ $CSSCH_3$;D_2O exchangeable), Anal ($C_{11}H_{15}NO_2S_3$) C,H,N.

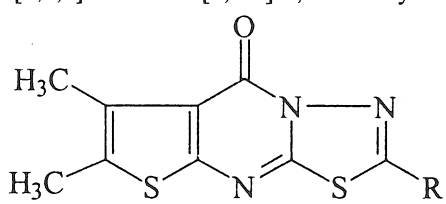
Synthesis of 3-Amino-2-mercapto-5,6-dimethylthi-eno [2,3-d]pyrimidin- 4(3H)-one.3

To solution of methyl N-(3-carbethoxy-4,5-dimethylthienyl)dithiocarbamate 2 [3.0 g; 0.01 mol] in ethanol (95%; 30 ml)was treated with hydrazine hydrate [99%; 4.3 g; 0.1 mol] and refluxed on a water bath until the methylmercaptan evolution ceases (6 hours). After cooling, the solid obtained was filtered dried and recrystallized from ethanol (95%)-acetone mixture to yield 2.4 g (80%) of white crystalline product. M.P. 269-271°C; **IR** (KBr) (cm^{-1})-3330, 3240 (NH_2), 1680(C=O), 1600, 1080 (C=S); **NMR** (DMSO-d_6) δ ppm –2.12 (s, 3H, 5-$C\underline{H}_3$), 2.19 (s, 3H, 6-$C\underline{H}_3$), 3.10 (s, 1H, 2-S$\underline{H}$), 5.20(s, 2H, 3-$N\underline{H}_2$, D_2O exchangeable); Anal ($C_8H_9N_3OS_2$) C, H, N.

Synthesis of 2-Allylamino-1,3,4-thiadiazolo [2,3-b]-6,7-dimethylthieno-[3,2-e]pyrimidin-5(4H)-one (V).

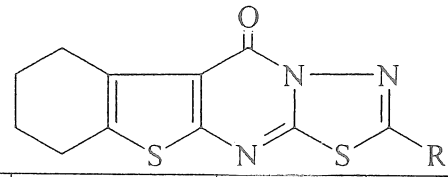
A mixture of 3-amino-2-mercapto-5,6-dimethyl-thieno [2,3-d]pyrimidin-4(3H)-one 3 (4.5 gm; 0.02 mol) a pinch of potassium carbonate (anhydrous) and allylisothiocyanate (1.98 g; 0.02 mol) in DMF 20 ml was refluxed in an oil bath maintaining the temperature at 153°C for thirty six hours. The solvent was removed by distillation under reduced pressure. The solid obtained was recrystallised form alcohol (95%)-chloroform mixture to yield 4.06 gm (62%) of colourless crystalline product. M.P. 255-257°C

Table1. Physical data of 2-substituted[1,3,4]thiadiazolo[2,3-b]-6,7-dimethylthieno[3,2-e]pyrimidine-5(4H)-ones.



Compd. No.	R	Molecular Formula	Molecular weight	MP°C	Yield %	RF Value
I	–H	$C_9H_7N_3OS_2$	237	210-11	75	0.50
II	$-CH_3$	$C_9H_7N_3OS_2$	251	194-96	80	0.60
III	$-CH_2CH_2CH_3$	$C_{12}H_{13}N_3OS_2$	279	165	88	0.80
IV	$-NHCH_3$	$C_{10}H_{11}N_4OS_2$	266	250	40	0.59
V	$-NHCH_2-CH=CH_2$	$C_{13}H_{13}N_4OS_2$	292	255-57	62	0.61
IV	$-NHC_6H_5$	$C_{15}H_{12}N_4OS_2$	328	>300	73	0.65
VII	$-NH(-3CH_3C_6H_4)$	$C_{16}H_{14}N_4OS_2$	342	250-53	67	0.72
VIII	$-NH(4-OCH_3C_6H_4)$	$C_{16}H_{14}N_4O_2S_2$	358	235-237	66	0.85

Table 2. Physical data of 2-substituted [1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)-thieno[3,2-e]-pyrimidin-5(4H)-ones.



Compd. No.	R	Molecular Formula	Molecular weight	MP°C	Yield %	RF Value
IX	$-H$	$C_{11}H_9N_3OS_2$	263	285	72	0.55
X	$-CH_3$	$C_{12}H_{11}N_3OS_2$	277	275	80	0.62
XI	$-CH_2CH_2CH_3$	$C_{14}H_{15}N_3OS_2$	305	157-59	85	0.81
XII	$-NHCH_3$	$C_{12}H_{13}N_4OS_2$	292	265	45	0.59
XIII	$-NHCH_2-CH=CH_2$	$C_{14}H_{15}N_4OS_2$	292	271-72	65	0.61
XIV	$-NHC_6H_5$	$C_{17}H_{14}N_4OS_2$	354	295	70	0.67
XV	$-NH(-3CH_3C_6H_4)$	$C_{18}H_{16}N_4OS_2$	368	296	69	0.70
XVI	$-NH(4-OCH_3C_6H_4)$	$C_{18}H_{16}N_4O_2S_2$	384	310	67	0.81

$$\%\text{Reduction in BP} = \frac{\text{BP of SHR before drug treatment} - \text{BP of SHR after drug treatment}}{\text{BP of SHR before drug treatment}} \times 100$$

Percentage decrease in systolic BP is shown in Table 3.

Table 3. Antihypertensive activityy of compounds (I-XVI).

Percent decrease in systolic Blood pressure					
Compd. No.	Ist hour	IInd hour	IIIrd hour	IVth hour	Vth hour
II	15.8	28.7	30.7	17.9	17.0
V	30.1	38.1	29.3	25.2	21.9
X	27.5	31.0	34.5	33.6	17.3
XIII	28.0	24.3	28.0	16.3	16.3
Prazocin	28.0	21.7	13.6	11.7	10.6

257°C; IR (KBr) (cm^{-1}) 3280 (NH), 1690 (C=O), 1510, 1180; NMR ($CDCl_3$) δppm-1.4(s, 6H, $C\underline{H}_3$ at 6&7), 2.1 (m, 5H, $-C\underline{H}_2-C\underline{H}=C\underline{H}_2$), 4.1 (s, 1H, at N$\underline{H}$); Anal ($C_{12}H_{13}N_4OS_2$) C, H, N.

The compounds IV-VIII and XII-XVI were also prepared similarly.

The compound II was prepared by refluxing the 3-amino-2-mercapto-5,6-dimethylthione[2,3-d]pyr-imidin-4(3H)-one 3 with glacial acetic acid for 8 hours.

Similarly the compounds I,III, XI-XI were prepared.

Antihypertensive activity

In vivo antihypertensive activity of compounds (I-XVI) was determined in spontaneously hypertensive rats (SHR) by tail cuff method using Harvard Blood Pressure Monitor (Kent, UK).

Conscious spontaneously hypertensive rats weighing 190 to 200 g. were placed in restraining cages for 15 minutes. The rat was put into a restrainer and its tail was introduced into the cuff. Initial gain set was established by means of a pulse sensor in order to get a minor deflection. The pressure was then raised to 250 mm Hg and slowly released by means of a screw attachment. During this decline of pressure, the point at which the amplitude of the deflection became the maximum, was considered as systolic pressure of the rat. At this point, the heart rate was measured by increasing the chart speed and recording the beats per minute . In each group five rats were taken. Compounds (I-XVI) and standard Prazocin were administered in suspension from (sodium CMC suspension) at a dose of 50 mg/kg oral route. Measurements were recorded before and after the drug treatment at the interval of 1hr. for 5hrs.

Percentage decrease in blood pressure was calculated as follows.

Results and Discussion

Among the compounds (I-XVI) tested for their antihypertensive activity, compounds II, V, X, XII were found to reduce the systolic BP significantly. However there was no significant effect on heart rate. Other compounds did not exhibited any significant antyhypertensive activity. From the unaffected heart rate by the test compounds and the reports of

the earlier work, we can conclude that these compounds may be acting by blocking α_1, recepter, hence we have compared the antihypertensive activity of the test compounds with the standard α_1, blocker prazocin. Compounds II, V, X, XII exhibited better antihypertensive activity than the standard prazocin at the same dose level.

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