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Research Article
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Synthesis of Bioactive Molecule Fluoro Benzothiazole Comprising Potent Heterocyclic Moieties for Anthelmentic Activity

Sreenivasa G.M., Jayachandran E.,* Shivakumar, B., Jayaraj Kumar K, Vijay Kumar M.M.J.

P. G. Department of Pharmaceutical Chemistry, S. C. S. College of Pharmacy, Harapanahalli - 583 131

Fluorobenzothiazole comprising sulfonamido pyrazole derivatives have been synthesized and evaluated for their anthelmentic activity. Structures of these products have been established by IR, ^{1}HNMR data. Significant anthelmentic activities were observed for members of this series.

Key Words: Anthelmintic activity, Fluorobenzothiazole, Pyrazole, Sulfonamido.

INTRODUCTION

The sulfonamide[1-5] drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and cure of bacterial infection in human beings. The introduction of trimethaprim and sulphamethoxazole has resulted in increased use of sulfonamide for the treatment of specific microbial infection. Benzothiazoles with sulphonyl group and pyrazolone etc were reported to posses various pharmacological activity of clinical importance.

However, little is known about substituted benzothiazoles having sulphonamido moiety and pyrazole with sulphonamido group. Therefore in present work we have sulphonamido group incorporated with benzothiazole ring with pyrazolone group to get good biodynamic leads.

Pyrazoles[6-8] are well known to have number of biological and anti-microbial activities. This includes anti-inflammatory, anti-bacterial, anti-neoplastic and anti-allergic activity. Therefore in present work we have prepared pyrazoles incorporated with substituted Benzothiazole ring.

EXPERIMENTAL

Condensation of 2-amino-6-fluoro-7-chloro-benzothiazole and *p*-acetamido benzene sulphonyl chloride:

2-amino-6-fluoro-7-chloro (1,3) benzothiazole (0.013 mol) was taken in pyridine (4 ml) and acetic anhydride (20 ml), to this *p*-acetamido benzene sulphonyl chloride (0.01 mol) were added and the mixture was kept in water bath for 2 hrs. The reaction mixture then poured in to 20 ml of ice cold water. The solid obtained was filtered and recrystallized from dil. ethanol (80%) to get pure compound 6-fluoro-7-chloro-2- (*p*-acetamido benzene sulphonamido) (1,3)- benzothiazole.

Corresponding Author

Srinivasa G.M.
E-mail : gms_2006@rediffmail.com

Synthesis of 6-fluoro-7-substituted-2-(*p*-acetamido benzene sulphonamido) (1,3) benzothiazoles:

The 0.01mol of 6-fluoro-7-chloro-2-(*p*-acetamido benzene sulphonamido) (1,3) benzothiazole was treated with equimolar quantity of various substituted anilines, PABA, morpholine, piperazine, dimethylamine, diphenylamine and refluxed for 2 hrs. in presence of DMF (dimethylformamide) then the mixture was cooled and poured in to crushed ice. The solid separated was filtered off, dried and recrystallised from benzene and super dry alcohol (1:1).

Hydrolysis of the 6-fluoro-7-substituted-2-(*p*-acetamido benzene sulphonamido) (1,3) benzothiazoles:

The derivatives obtained were hydrolyzed by boiling them in 50 ml of 80% acetic acid for 4 to 5 hrs. and the contents were poured into crushed ice. The obtained hydrolyzed derivatives were filtered at suction and dried.

Synthesis of 6-fluoro-7-substituted-2-(*p*-hydrazino benzene sulphonamido) (1,3) benzothiazole:

10 ml of conc. HCl was added drop wise with stirring to hydrazine hydrate (12ml, 0.2 mol) at 5-10°C followed by ethylene glycol 40 ml. To the above solution 0.1 mol of 6-fluoro-7-substituted-2-(*p*-amino benzene sulphonamido)

(1,3) benzothiazoles in portion were added and the resulting mixture was refluxed for 2 hrs., cooled, poured into crushed ice. The solid separated, was filtered, dried and recrystallised from ethanol.

Synthesis of 6-fluoro-7-substituted-2-[(3'-amino-4'-carboxamido-5'-s-methyl-pyrazolidin-1'-yl)-*p*-benzene sulphonamido] (1,3)- benzothiazole:

A mixture of 6-fluoro-7-substituted-2-(*p*-hydrazino benzene sulphonamido)-(1,3)-benzothiazole and bis-s-methyl ethylene cyanoacetamide were refluxed in ethanol for 2 hrs., and later excess of ethanol was distilled off and poured into crushed ice. The product obtained was filtered and recrystallised from ethanol.

Anilino-s-methyl ethylene cyanoacetamide:

0.1mol of bis-s-methyl ethylene cyanoacetamide and 0.11mol of aniline were placed in round bottomed flask and refluxed for 3hrs. in the presence of ethanol as a solvent. Then the reaction mixture was allowed to cool and poured into crushed ice. The obtained was filtered and washed with water.

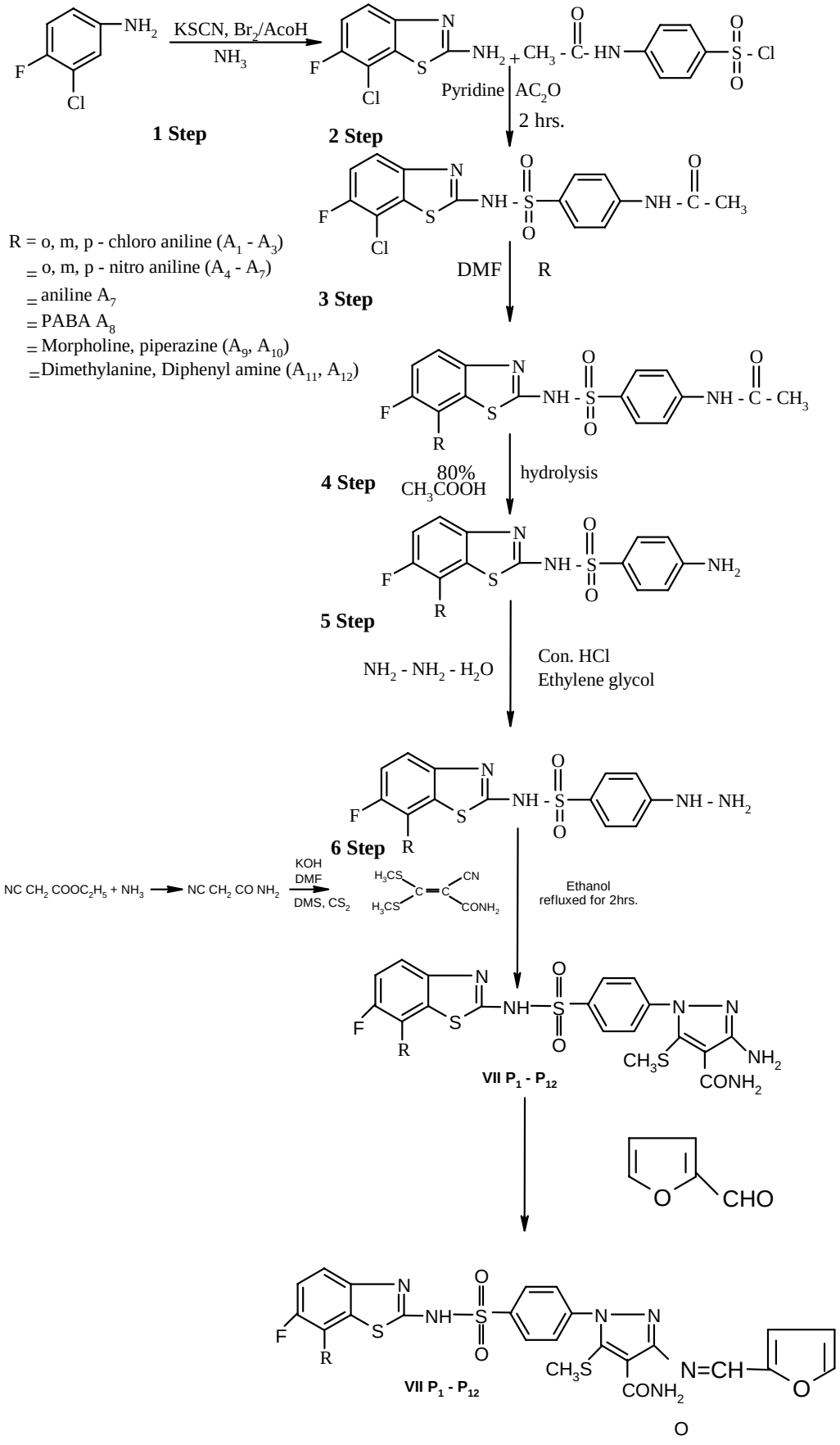
Synthesis of 6-fluoro-7-substituted-2-[(3'-amino-4'-carboxamido-5'-s-methyl-pyrazolidin-1'-yl)-*p*-benzene sulphonamido] (1,3)- benzothiazole:

A mixture of 6-fluoro-7-substituted-2-(*p*-hydrazino benzene sulphonamido)-(1,3)-benzothiazole and anilino-s-methyl ethylene cyanoacetamide were refluxed in ethanol for 2 hrs., and later excess of ethanol was distilled off and poured into crushed ice. The obtained was filtered and was recrystallised from ethanol.

A mixture of 6-fluoro-7-substituted-2-(*p*-hydrazino benzene sulphonamido) (1,3)-benzothiazole with a solution of aldehyde (furfuraldehyde) in refluxing flask. Then add 20 ml of ethanol and 3-4 drops of HCl and refluxed for 2-3 hours. Then the mixture in concentrated to remove ethanol. The remaining solution is cooled and poured into crushed ice in small portions.

The solid separated was filtered off. Dried and recrystallized with benzene and ethanol.

SCHEME - I


KSCN, Br2/AcoH
NH3
1 Step
2 Step
Pyridine
AC2O
2 hrs.
R = o, m, p - chloro aniline (A1 - A3)
= o, m, p - nitro aniline (A4 - A7)
= aniline A7
= PABA A8
= Morpholine, piperazine (A9, A10)
= Dimethylanine, Diphenyl amine (A11, A12)
DMF
R
3 Step
4 Step
80%
CH3COOH
hydrolysis
5 Step
NH2 - NH2 - H2O
Con. HCl
Ethylene glycol
6 Step
KOH
DMF
DMS, CS2
Ethanol
refluxed for 2hrs.
VII P1 - P12
VII P1 - P12

SCHEME - II

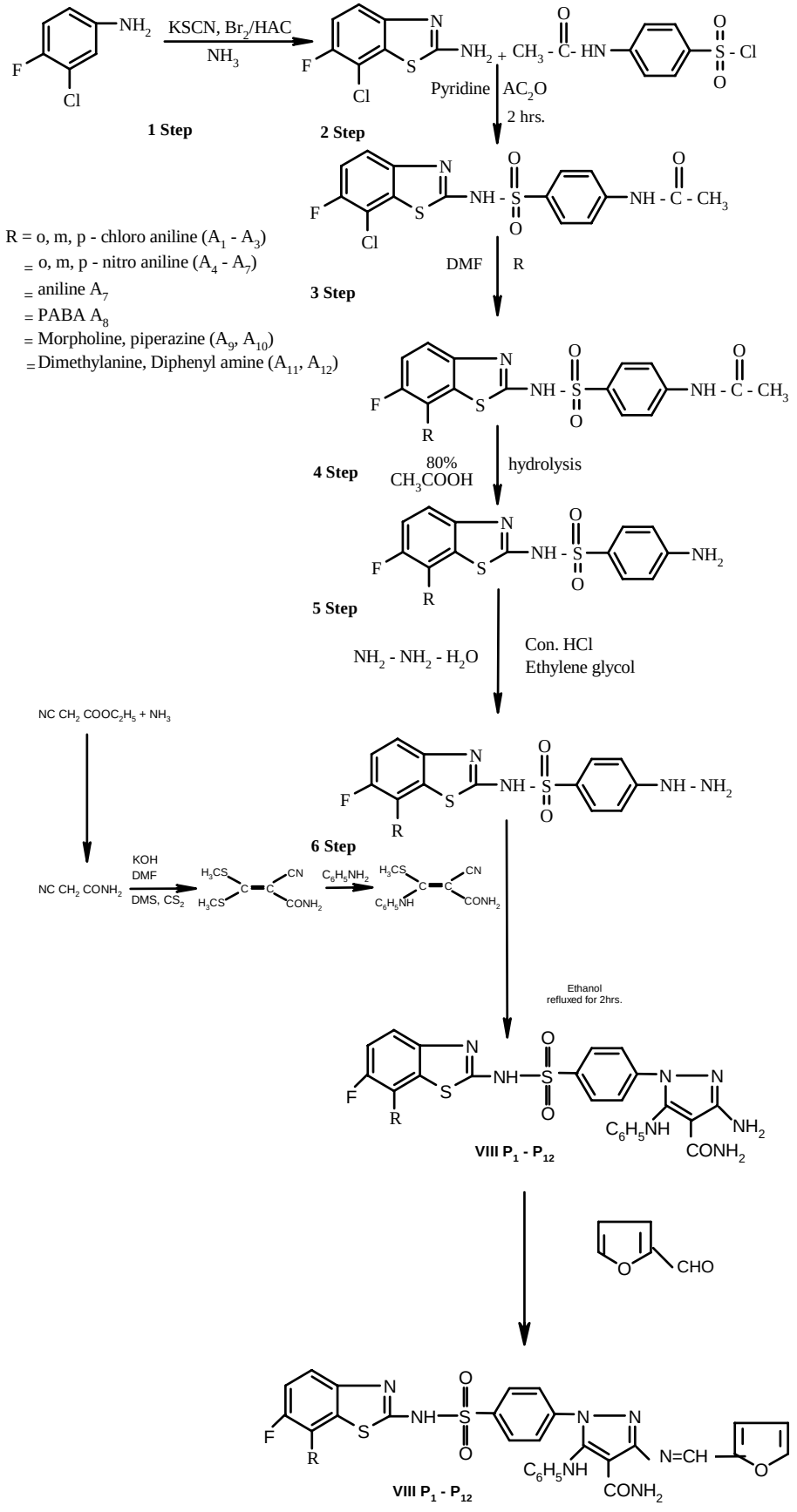

KSCN, Br2/HAC
NH3
1 Step
Pyridine
AC2O
2 hrs.
2 Step
R = o, m, p - chloro aniline (A1 - A3)
= o, m, p - nitro aniline (A4 - A7)
= aniline A7
= PABA A8
= Morpholine, piperazine (A9, A10)
= Dimethylanine, Diphenyl amine (A11, A12)
DMF
R
3 Step
80%
CH3COOH
hydrolysis
4 Step
NH2 - NH2 - H2O
Con. HCl
Ethylene glycol
5 Step
NC CH2 COOC2H5 + NH3
NC CH2 CONH2
KOH
DMF
DMS, CS2
6 Step
Ethanol
refluxed for 2hrs.
VIII P1 - P12
CHO
VIII P1 - P12

Table No. 1 Melting Point

Sl. No	Compound Code	M.P/ B.P^{0}C	% Yield
1	VII P_1	112	95
2	VII P_2	170	98
3	VII P_3	132	97
4	VII P_4	120	85
5	VII P_5	140	90
6	VII P_6	140	92
7	VII P_7	137	91
8	VII P_8	130	86
9	VII P_9	160	93
10	VII P_{10}	95	88
11	VII P_{11}	110	94
12	VII P_{12}	125	89
13	VIII P_1	104	87
14	VIII P_2	97	96
15	VIII P_3	96	94
16	VIII P_4	104	91
17	VIII P_5	103	90
18	VIII P_6	107	92
19	VIII P_7	110	95
20	VIII P_8	93	98
21	VIII P_9	105	86
22	VIII P_{10}	98	91
23	VIII P_{11}	104	92
24	VIII P_{12}	96	90

Identification & Characterization

Melting points was determined by open capillary tube method and are uncorrected (Table No. 1). TLC was run on silica gel G plates using butanol, ethyl acetate and chloroform (1:2:1) as developing solvent for the purity of the compounds. IR Spectra were recorded on Shimadzu FTIR Spectrophotometer by using KBr technique (Table No. 2). Study of anthelmintic activity[9-20]

The synthesized compounds are screened for anthelmintic activity by using earthworms. Five earthworms of nearly equal size were placed in standard drug solution and test compound's solutions at room temperature. Normal saline used as control. The standard drug and test compounds were dissolved in minimum quantity of dimethyl formamide (DMF) and adjusted the volume up to 15 ml with normal saline solution to get the concentration of 0.1 % w/v, 0.2 % w/v and 0.5% w/v. Albendazole was used as a standard drug. The compounds were evaluated by the time taken for complete paralysis and death of earthworms. The mean lethal time for each test compound was recorded and compared with standard drug. The time taken by worms to become motionless was noted as paralysis time. To ascertain the death of the motionless worms were frequently applied with external stimuli, which stimulate and induce movement in the worms, if alive.

The mean lethal time and paralysis time of the earthworms for different test compounds and standard drug are tabulated (Table No. 3).

RESULTS AND DISCUSSION

Synthesized compounds of Fluorobenzothiazole comprising sulfonamido pyrazole derivatives were tested for anthelmintic activity against earthworms, *Perituma posthuma* compared to standard Albendazole.

VII P_8, VIII P_6, VIII P_7, VIII P_8, VIII P_9, VIII P_{10}, VIII P_{11}, VIII P_{12} showed significant activity compared to standard Albendazole.

CONCLUSION

Result of present study demonstrate that, a new class of different aromatic primary and secondary amines encompassing sulfonamido pyrazole to get targeted molecules were synthesized and evaluated for anthelmintic

Table No. 2 Infrared Absorption Bands

Sl. No.	Compound Code	Ar-NH2 Stret cm-1	C = N Stret cm-1	Aro. C = C Stret cm-1	C – F Stret cm-1	C – Cl Stret cm-1	NO2 in cm-1	SO2 – NH Stret cm-1	30-Nitrogen cm-1	CH3 Stret cm-1	C-O-C cm-1
1.	VII P1	3385	1620	1450	1190	720	-	1380	3080	1300	-
2.	VII P2	3400	1600	1435	1200	725	-	1385	3100	1290	-
3.	VII P3	3390	1610	1445	1210	718	-	1390	3090	1285	-
4.	VII P4	3395	1590	1440	1195	-	720	1356	3095	1290	-
5.	VII P5	3385	1620	1450	1198	-	725	1385	3080	1295	-
6.	VII P6	3400	1600	1435	1200	-	730	1390	3095	1295	-
7.	VII P7	3390	1610	1445	1210	-	-	1385	3100	1290	-
8.	VII P8	3395	1590	1440	1195	-	-	1380	3110	1300	-
9.	VII P9	3395	1610	1445	1210	-	-	1385	3095	1300	1560
10.	VII P10	3390	1600	1435	1200	-	-	1390	3080	1310	-
11.	VII P11	3400	1620	1450	1198	-	-	1395	3095	1300	-
12.	VII P12	3385	1610	1450	1195	-	-	1380	3085	1310	-
13.	VIII P1	3385	1620	1450	1190	720	-	1380	3080	-	-
14.	VIII P2	3400	1600	1435	1200	725	-	1385	3100	-	-
15.	VIII P3	3390	1610	1445	1210	718	-	1390	3090	-	-
16.	VIII P4	3395	1590	1440	1195	-	720	1356	3095	-	-
17.	VIII P5	3385	1620	1450	1198	-	725	1385	3080	-	-
18.	VIII P6	3400	1600	1435	1200	-	730	1390	3095	-	-
19.	VIII P7	3390	1610	1445	1210	-	-	1385	3100	-	-
20	VIII P8	3395	1590	1440	1195	-	-	1380	3110	-	-
21.	VIII P9	3395	1610	1445	1210	-	-	1385	3095	-	1560
22.	VIII P10	3390	1600	1435	1200	-	-	1390	3080	-	-
23.	VIII P11	3400	1620	1450	1198	-	-	1395	3095	-	-
24.	VIII P12	3385	1610	1450	1195	-	-	1380	3085	-	-

Table No. 3 Anthelmintic Activity

Sl. No	Name	% Concentration	Time in Minutes For Paralysis	For Death
1	Control	0.9%	--	--
2	Albendazole	0.1% 0.2% 0.5%	50 45 40	70 63 55
3	VII P_1	0.1% 0.2% 0.5%	60 50 13	140 120 42
4	VII P_2	0.1% 0.2% 0.5%	55 45 24	100 70 62
5	VII P_3	0.1% 0.2% 0.5%	50 42 16	120 109 44
6	VII P_4	0.1% 0.2% 0.5%	65 55 34	130 75 64
7	VII P_5	0.1% 0.2% 0.5%	40 20 17	100 50 28
8	VII P_6	0.1% 0.2% 0.5%	42 27 12	90 72 22
9	VII P_7	0.1% 0.2% 0.5%	45 31 16	80 49 20
10	VII P_8	0.1% 0.2% 0.5%	35 25 15	68 39 21
11	VII P_9	0.1% 0.2% 0.5%	38 26 14	70 50 20
12	VII P_{10}	0.1% 0.2% 0.5%	32 20 11	70 25 13
13	VII P_{11}	0.1% 0.2% 0.5%	85 70 22	110 90 62
14	VII P_{12}	0.1% 0.2% 0.5%	75 68 37	125 104 73
15	VIII P_1	0.1% 0.2% 0.5%	52 42 19	100 82 62
16	VIII P_2	0.1% 0.2% 0.5%	60 47 23	105 87 65
17	VIII P_3	0.1% 0.2% 0.5%	50 38 33	85 61 48
18	VIII P_4	0.1% 0.2% 0.5%	44 34 24	83 67 44
19	VIII P_5	0.1% 0.2% 0.5%	39 26 15	75 55 46
20	VIII P_6	0.1% 0.2% 0.5%	45 33 17	88 63 47
21	VIII P_7	0.1% 0.2% 0.5%	50 39 21	95 69 54
22	VIII P_8	0.1% 0.2% 0.5%	60 44 35	110 74 59
23	VIII P_9	0.1% 0.2% 0.5%	30 60 10	70 40 35
24	VIII P_{10}	0.1% 0.2% 0.5%	35 20 11	89 55 40
25	VIII P_{11}	0.1% 0.2% 0.5%	28 14 10	70 45 33
26	VIII P_{12}	0.1% 0.2% 0.5%	25 13 10	80 55 50

activity. The newly synthesized heterocyclics exhibited promising anthelmintic activity against earthworms, *Perituma posthuma* at low and high concentration compared to standard Albendazole. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

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