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N-Substituted-3-chloro-2-azetidinones: Synthesis and characterization of novel anthelmintic agents

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#### **ABSTRACT**

Various substituted 4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'-substituted (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloro azetidin—2—one containing different functional groups have been synthesized by treating fluorochloroaniline with KSCN in presence of bromine in glacial acetic acid and ammonia to get 2-amino-6-fluoro-7-chloro-(1,3)-benzothiazole, which was treated with anthranillic acid in presence of dry pyridine to get 2-amino-N-(6-fluoro-7-chloro-(1,3)-benzothiazol-2-yl) benzamide. To the above, refluxed with vanillin and alcohol in presence of Conc. HCl to get 2-(3-hydroxy-4-methoxy benzylidene amino phenyl amido)-6-fluoro-7-chloro-(1, 3)-benzothiazole or Schiff's base. A Solution of Schiff's base in 1, 4-dioxane was added to well-stirred mixture of chloroacetyl chloride and triethylamine to get Azetidinone. To the above product different primary and secondary aromatic amines in presence of DMF were treated to get newly targeted compound through replacing at 7<sup>th</sup> position chlorine. The lead compounds were characterized by melting point, TLC, calculated elemental analysis, UV, IR, <sup>1</sup>HNMR and MASS spectral studies. The compounds were tested for anthelmintic activity against earthworms, Perituma posthuma and showed significant activity at low and high concentration compared to standard; still further studies are requested.

Keywords: Anthelmintic activity, Azetidinone, Benzothiazole, Fluorine,

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#### INTRODUCTION

We report here in the new and unreported yet the synthesis of fluoro benzothiazoles [1] comprising azetidinone derivatives. The chemistry and pharmacology of azetidinone have been of great interest because, of its various biological activities in the areas of antimicrobial [2], anti-tuburcular [3], carbonic anhydrase inhibitors [4], local anaesthatics [5], anti-inflammatory [6], anthelmintic [7], anticonvulsant [8], hypoglycemic agents [9] etc, so that the biological and pharmacological activity of thiazolidinone with fluoro benzothiazoles may be taken into account for synergism [10].

It is well known that the introduction of fluorine atom [11] into an organic molecule causes dramatic changes in its biological profile, mainly due to high electro negativity of fluorine, the strong carbon-fluorine bond and increased solubility in lipids. Therefore it was thought worthwhile to synthesize better kinds of drugs by incorporating azetidinone in benzothiazole moiety.

In search for new biodynamic potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in the  $\beta$ -lactam nucleus and study their biological and pharmacological activity [12], the review of literature reveal prompted us to synthesize substituted fluorobenzothiazole, azetidinone targeted compounds and those will be screened for anthelmintic activity against earthworms, Perituma posthuma.

#### MATERIALS AND METHODS

# Chemicals and Reagents

4-fluoro-3-chloro aniline, Potassium thiocyanate, Glacial acetic acid, Bromine, Anthranillic acid, Pyridine, Vanillin, Ethanol, Conc. Hydrochloric acid, Chloroacetyl chloride, Triethylamine, N,N-dimethyl formamide (DMF), various substituted aniline, morpholine, piperazine and diphenylamine.

### **Experimental Section**

Step I: 4-fluoro-3-chloro aniline was treated with potassium thiocyanate (KSCN) in presence of glacial acetic acid and bromine to get 2-amino-6-fluoro-7-chloro-benzothiazole.

Step II: 2-amino-6-fluoro-7-chloro-benzothiazole treated with Anthranillic acid in presence of Pyridine to get 2 (o-amino phenyl amido) 6–fluoro -7-chloro (1,3) benzothiazole.

Step III: 2 (o-amino phenyl amido) 6—fluoro -7-chloro (1,3) benzothiazole reflexed with vanillin and alcohol in presence of Conc.HCl to get 2 (3-hydroxy-4-methoxy benzylidene amino phenyl amido) 6-fluoro-7-chloro-(1,3) benzothiazole or Schiff's base.

Step IV: A Solution of Schiff's base (0.01 mol) in 1,4-dioxane (50ml) was added to well-stirred mixture of Chloroacetyl Chloride (0.95 ml, 0.012 mol) and Triethylamine (1.08 ml, 0.02 mol) at  $0^{\circ}$  C. The reaction mixture was then stirred for 18 - 20 hrs and kept aside for 3 days at room temperature. The product was recrystallised from N,N' Dimethyl formamide (DMF).

Step V: Azetidine were treated with double the quantities of various substituted aniline, piperazine, diphenyl amine, refluxed for 2 hours in presence of N,N-dimethyl formamide (DMF). The mixture was cooled and poured in to crushed ice. The solid separated was filtered off, dried and crystallized from alcohol and benzene.





# Scheme

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#### Identification and Characterization

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr pellet technique) were recorded using a Perkin-Elmer 237 spectrophotometer. <sup>1</sup>H NMR spectra were recorded on Bruker AM 400 instrument (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO-d6 as a solvent. Chemical shifts are given in parts per million (ppm). Splitting patterns are designated as follows: s- singlet, d-doublet, t- triplet, q- quartet and m-multiplet. Mass spectra (MS) were recorded on Shimadzu GC-MS operating at 70eV. All the synthesized compounds were purified by recrystallization. The reactions were followed up and the purity of compounds was monitored on pre-coated TLC plates and visualizing the spots in ultraviolet light.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'-o-nitroanilino (1, 3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloro azetidin–2–one (A<sub>1</sub>). Yield 78%; mp 190°C; IR (KBr) v (cm<sup>-1</sup>); 3350 (Ar-NH); 1750 (C=0); 1550 (C=N); 1710 (C=C); 1450 (NO<sub>2</sub>); 1130 (C-F); 720 (C–S); 1300 (Sec.Ar.Amine); 840 (C–Cl); 1250 (C-O-C); 1390 (Ar-OH);  $^1$ H NMR (CDCl<sub>3</sub>) δ 9.5 (s, 1H, -NH-); 9.2 (s, 1H, -NH-); 8.4 (s, 1H, -OH); 7.0 to 8.0 (m, 13H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.7 (s, 3H, -OCH<sub>3</sub>); Analysis Calcd. for C<sub>30</sub>H<sub>21</sub>O<sub>6</sub>SN<sub>5</sub>FCl; C, 56.83%; H, 3.34%; N, 11.05%; Found; C, 56.81%; H, 3.33%; N, 11.01%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'-m-nitroanilino (1, 3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloro azetidin–2–one ( $A_2$ ). Yield 82%; mp 178°C; IR (KBr) v (cm<sup>-1</sup>); 3370 (Ar-NH); 1710 (C=0); 1525 (C=N); 1680 (C=C); 1450 (NO<sub>2</sub>); 1160 (C-F); 720 (C–S); 1340 (Sec.Ar.Amine); 840 (C–Cl); 1250 (C-O-C); 1390 (Ar-OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.6 (s, 1H, -NH-); 9.4 (s, 1H, -NH-); 8.2 (s, 1H, -OH); 7.0 to 8.0 (m, 13H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.6 (s, 3H, -OCH<sub>3</sub>); Analysis Calcd. for  $C_{30}H_{21}O_6SN_5FCl$ ; C, 56.83%; H, 3.34%; N, 11.05%; Found; C, 56.82%; H, 3.32%; N, 11.04%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'-p-nitroanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloro azetidin–2–one (A<sub>3</sub>). Yield 75%; mp 183°C; IR (KBr) v (cm<sup>-1</sup>); 3370 (Ar-NH); 1700 (C=0); 1540 (C=N); 1660 (C=C); 1420 (NO<sub>2</sub>); 1160 (C-F); 725 (C–S); 1310 (Sec.Ar.Amine); 850 (C–Cl); 1255 (C-O-C); 1380 (Ar-OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.6 (s, 1H, -NH-); 9.3 (s, 1H, -NH-); 8.6 (s, 1H, -OH); 7.2 to 8.0 (m, 13H, Ar-H); 7.0 (d, β lactum 2H – Proton); 3.6 (s, 3H, -OCH<sub>3</sub>); MS (m/z) 634 (M<sup>†</sup>) 517.5, 379.4, 201.3, Analysis Calcd. for  $C_{30}H_{21}O_6SN_5FCl$ ; C, 56.83%; H, 3.34%; N, 11.05%; Found; C, 56.81%; H, 3.32%; N, 11.01%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'-o-chloroanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloro azetidin–2-one (A<sub>4</sub>). Yield 72%; mp 164°C; IR (KBr) v (cm<sup>-1</sup>); 3380 (Ar-NH); 1730 (C=0); 1540 (C=N); 1680 (C=C); 1155 (C-F); 720 (C–S); 1300 (Sec.Ar.Amine); 850 (C–Cl); 1250 (C-O-C); 1380 (Ar-OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.6 (s, 1H, -NH-); 9.4 (s, 1H, -NH-); 8.6 (s, 1H, -OH); 7.0 to 7.8 (m, 13H, Ar-H); 6.9 (d, β lactum 2H – Proton); 3.8 (s, 3H, -OCH<sub>3</sub>); Analysis Calcd. for  $C_{30}H_{22}O_4S_2N_4FCl$ ; C, 57.79%; H, 3.39%; N, 8.99%; Found; C, 57.73%; H, 3.35%; N, 8.92%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'-m-chloroanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloro azetidin–2–one (A<sub>5</sub>). Yield 74%; mp 132°C; IR (KBr) v (cm<sup>-1</sup>); 3400 (Ar-NH); 1765 (C=0); 1540 (C=N); 1690 (C=C); 1170 (C-F); 725 (C–S); 1310 (Sec.Ar.Amine); 820 (C–Cl); 1250 (C-O-C); 1380 (Ar-OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.3 (s, 1H, -NH-); 9.0 (s, 1H, -NH-); 8.6 (s, 1H, -OH); 7.2 to 8.0 (m, 13H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.8 (s, 3H, -OCH<sub>3</sub>); Analysis Calcd. for  $C_{30}H_{22}O_4S_2N_4FCl$ ; C, 57.79%; H, 3.39%; N, 8.99%; Found; C, 57.72%; H, 3.33%; N, 8.96%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'-p-chloroanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloro azetidin–2–one (A<sub>6</sub>). Yield 73%; mp 126°C; IR (KBr) v (cm<sup>-1</sup>); 3290 (Ar-NH); 1720 (C=0); 1530 (C=N); 1680 (C=C); 1160 (C-F); 725 (C–S); 1300 (Sec.Ar.Amine); 840 (C–Cl); 1250 (C-O-C); 1380 (Ar-OH);  $^1$ H NMR (CDCl<sub>3</sub>) δ 9.5 (s, 1H, -NH-); 9.2 (s, 1H, -NH-); 8.4 (s, 1H, -OH); 7.0 to 8.0 (m, 13H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.7 (s, 3H, -OCH<sub>3</sub>); MS (m/z) 634 (M<sup>†</sup>) 613.9, 454.7, 369.8, 203.8; Analysis Calcd. for  $C_{30}H_{22}O_4S_2N_4FCl$ ; C, 57.79%; H, 3.39%; N, 8.99%; Found; C, 57.74%; H, 3.36%; N, 8.94%.



4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'- anilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloro azetidin–2–one ( $A_7$ ). Yield 76%; mp 112°C; IR (KBr) ν (cm<sup>-1</sup>); 3390 (Ar-NH); 1755 (C=0); 1510 (C=N); 1690 (C=C); 1150 (C-F); 720 (C–S); 1255 (Sec.Ar.Amine); 840 (C–Cl); 1220 (C-O-C); 1380 (Ar-OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.6 (s, 1H, -NH-); 9.2 (s, 1H, -NH-); 8.2 (s, 1H, -OH); 7.4 to 8.2 (m, 14H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.6 (s, 3H, -OCH<sub>3</sub>); Analysis Calcd. for  $C_{30}H_{22}O_4S_2N_4FCl$ ; C, 61.17%; H, 3.76%; N, 9.51%; Found; C, 61.14%; H, 3.72%; N, 9.46%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'- o-methoxyanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloroazetidin–2–one ( $A_8$ ). Yield 65%; mp 124°C; IR (KBr) v (cm<sup>-1</sup>); 3350 (Ar-NH); 1720 (C=0); 1540 (C=N); 1685 (C=C); 1165 (C-F); 725 (C–S); 1310 (Sec.Ar.Amine); 830 (C–Cl); 1250 (C-O-C); 1390 (Ar-OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.5 (s, 1H, -NH-); 9.2 (s, 1H, -NH-); 8.4 (s, 1H, -OH); 7.0 to 8.0 (m, 13H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.8 (s, 3H, -OCH<sub>3</sub>); 3.6 (s, 3H, -OCH<sub>3</sub>); Analysis Calcd. for  $C_{31}H_{24}O_5SN_4FCl$ ; C, 60.14%; H, 3.91%; N, 9.05%; Found; C, 60.13%; H, 3.87%; N, 9.01%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'- m - methoxyanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloroazetidin–2-one (A<sub>9</sub>). Yield 69%; mp 118°C; IR (KBr) v (cm<sup>-1</sup>); 3310 (Ar-NH); 1730 (C=0); 1550 (C=N); 1650 (C=C); 1130 (C-F); 725 (C–S); 1310 (Sec.Ar.Amine); 840 (C–Cl); 1245 (C-O-C); 1380 (Ar-OH);  $^1$ H NMR (CDCl<sub>3</sub>) δ 9.5 (s, 1H,-NH-); 9.2 (s, 1H, -NH-); 8.4 (s, 1H, -OH); 7.0 to 8.0 (m, 13H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.8 (s, 3H, -OCH<sub>3</sub>); 3.6 (s, 3H, -OCH<sub>3</sub>); 6.4 (d, β lactum 2H – Proton); Analysis Calcd. For C<sub>31</sub>H<sub>24</sub>O<sub>5</sub>SN<sub>4</sub>FCl; C, 60.14%; H, 3.91%; N, 9.05%; Found; C, 60.12%; H, 3.88%; N, 9.02%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'- p - methoxyanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloroazetidin–2-one (A<sub>10</sub>). Yield 83%; mp 158°C; IR (KBr) v (cm<sup>-1</sup>); 3400 (Ar-NH); 1750 (C=0); 1560 (C=N); 1660 (C=C); 1170 (C-F); 730 (C–S); 1300 (Sec.Ar.Amine); 850 (C–Cl); 1230 (C-O-C); 1385 (Ar-OH);  $^1$ H NMR (CDCl<sub>3</sub>) δ 9.5 (s, 1H, -NH-); 9.2 (s, 1H, -NH-); 8.4 (s, 1H, -OH); 7.0 to 8.0 (m, 13H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.8 (s, 3H, -OCH<sub>3</sub>); 3.6 (s, 3H, -OCH<sub>3</sub>); Analysis Calcd. for C<sub>31</sub>H<sub>22</sub>O<sub>6</sub>SN<sub>4</sub>FCl;C, 60.14%; H, 3.91%; N, 9.05%; Found; C, 60.11%; H, 3.89%; N, 9.01%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'- p – carboxyanilino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloroazetidin–2–one ( $A_{11}$ ). Yield 77%; mp 260°C; IR (KBr) v (cm<sup>-1</sup>); 3320 (Ar-NH); 1700 (C=0); 1530 (C=N); 1640 (C=C); 1165 (C-F); 730 (C=S); 1310 (Sec.Ar.Amine); 840 (C–Cl); 1270 (C-O-C); 1380 (Ar-OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.2 ( s, 1H, -COOH); 9.5 (s, 1H, -NH-); 9.2 (s, 1H, -NH-); 8.4 (s, 1H, -OH); 7.0 to 8.0 (m, 13H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.8 (s, 3H, -OCH<sub>3</sub>); 3.6 (s, 3H, -OCH<sub>3</sub>); Analysis Calcd. for  $C_{31}H_{22}O_6SN_4FCl$ ; C, 58.82%; H, 3.50%; N, 8.85%; Found; C, 58.77%; H, 3.47%; N, 8.82%.

4-(m-hydroxy-p-methoxy phenyl)-1-[(6'-fluoro-7'-piperzino (1,3)-benzothiazol-2'-yl) amido-2-phenyl]-3-chloroazetidin–2–one ( $A_{12}$ ). Yield 85%; mp 308°C; IR (KBr) v (cm<sup>-1</sup>); 3300 (Ar-NH); 1650 (C=0); 1550 (C=N); 1650 (C=C); 1190 (C-F); 740 (C–S); 1290 (Sec.Ar.Amine); 850 (C–Cl); 1290 (C-O-C); 1380 (Ar-OH); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.5 (s, 1H, -NH-); 8.4 (s, 1H, -OH); 7.0 to 8.0 (m, 9H, Ar-H); 6.8 (d, β lactum 2H – Proton); 3.8 (s, 3H, -OCH<sub>3</sub>); 2.6 (t, 4H, (CH<sub>2</sub>)<sub>2</sub>); 2.4 (t, 4H, (CH<sub>2</sub>)<sub>2</sub>); Analysis Calcd. for  $C_{30}H_{22}O_4S_2N_4FCl$ ; C, 57.78%; H, 4.33%; N, 12.03%; Found; C, 57.74%; H, 4.30%; N, 12.81%.

# In- vitro anthelmintic study

The synthesized compounds are screened for anthelmintic activity by using earthworms, Perituma posthuma [13]. Six 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 [14]. 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. 1).

Table No-1. Anthelmintic activity

SI. No.	Name	Time in Minutes					
		For Paralysis			For Death		
		% of Concentration			% of Concentration		
		0.1	0.2	0.5	0.1	0.2	0.5
01	Control (0.9 % Concentration)						
02	Albendazole	9.0	9.0	4.0	10.0	10.0	8.0
03	A <sub>1</sub>	9.0	9.0	7.0	13.0	15.0	16.0
04	A <sub>2</sub>	9.0	8.0	4.0	16.0	15.0	9.0
05	A <sub>3</sub>	2.0	1.0	1.0	13.0	13.0	11.0
06	A <sub>4</sub>	9.0	9.0	5.0	16.0	14.0	9.0
07	A <sub>5</sub>	8.0	8.0	7.0	23.0	20.0	15.0
08	A <sub>6</sub>	8.0	7.0	5.0	19.0	17.0	12.0
09	A <sub>7</sub>	6.0	5.0	4.0	17.0	15.0	8.0
10	A <sub>8</sub>	12.0	6.0	5.0	17.0	15.0	12.0
11	A <sub>9</sub>	8.0	6.0	5.0	18.0	14.0	7.0
12	A <sub>10</sub>	9.0	8.0	4.0	13.0	12.0	8.0
13	A <sub>11</sub>	2.0	2.0	1.0	9.0	8.0	3.0
14	A <sub>12</sub>	11.0	11.0	6.0	21.0	17.0	13.0

Activity Index = Test Compound / Standard compound

#### RESULTS AND DISCUSSION

Synthesized compounds of 4(m-hydroxy-p-methoxy phenyl)-1[(6'-fluoro-7'-substituted (1,3)-benzothiazol-2'-yl) amido-2-phenyl] 3-chloro azetidin–2–one were tested for anthelmintic activity against earthworms, Perituma posthuma compared to standard albendazole.  $A_3$ ,  $A_7$ ,  $A_9$  and  $A_{11}$  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 azetidinone to get targeted molecules were synthesized and evaluated for anthelmintic 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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