

## Research Article



## Synthesis, Characterization and Biological Activity of Substituted Cinnoline Benzimidazole Derivatives

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### ABSTRACT

In the present study we have made an attempt to synthesize novel cinnoline benzimidazoles and evaluate them as potential therapeutic agent for their Anthelmintic activity. Substituted Cinnoline benzimidazole were synthesized by four steps: firstly preparation of diazonium salt by the reaction of substituted anilines with mixture of conc. HCl and cold saturated solution of sodium nitrite at 0-5°C, then synthesis of 3- chlorophenyl hydrazono (cyno) acetamide (2a-g) by the reaction of cyano acetamide with 10 gm CH<sub>3</sub>COONa and 15 ml alcohol. In the third step 7-chloro 4-aminocinnoline-3- carboxamide (3a-g) is synthesized by the treatment of 3-chlorophenylhydrazono(cyno)acetamide with anhydrous AlCl<sub>3</sub> and chlorobenzene and nitrogen gas was passed for half an hour and finally synthesis of substituted 4-(p-amino benzimidazole) Cinnoline -3-carboxamide was done with the reaction of Substituted 4-amino cinnoline -3-carboxamide in DMF and *o*-chloro Benzimidazole. The synthesized compounds were analyzed by physical and analytical data. The synthesized compounds were evaluated for their Anthelmintic activity. All the synthesized substituted cinnoline benzimidazole has shown moderate to good Anthelmintic activity.

**Keywords:** Anthelmintic, Benzimidazole, Japp-Klingemann reaction, Mebendazole.

### INTRODUCTION

Anthelmintics or antihelminthics are drugs that expel helminth parasitic worms (helminths) from the body, either by stunning or killing them. They may also be called vermifuges (stunning) or vermicides (killing). However they have shown the development of resistance to some broad spectrum Anthelmintics (benzimidazoles, levamisole, avermectins) and also some narrow spectrum dewormers such as the salicylanilides (closantel). Some type of dangerous helminthes infections like filariasis has only a few therapeutic modalities at present.<sup>1</sup> The continuous and long-term reliance on a small range of compounds has led to the development of drug resistance in many helminthic strains. In addition, after treatment with albendazole or mebendazole, several side effects have been reported in hosts such as gastrointestinal symptoms (epigastric pain, diarrhea, nausea, vomiting), nervous system symptoms (headache, dizziness), and allergic phenomena (edema, rashes, urticaria). Some Anthelmintic drugs, such as praziquantel and Albendazole are contraindicated for certain groups of patients like pregnant and lactating woman. These drugs have also to be used with caution in hepatitis patients and in children below 2 years of age.<sup>2</sup> To overcome the development of drug resistance it is crucial to synthesize a new class of compounds possessing different chemical properties from those of used commonly.

A survey of literature reveals that some of the cinnoline derivatives possess various biological activities like anthelmintic<sup>3-5</sup>, antiantimalarial<sup>6</sup>, antibacterial<sup>7-9</sup>, antitumor and antifungal<sup>10</sup>, anti-inflammatory<sup>11</sup> activities. In the present study, an attempt was made towards the incorporation of cinnoline derivative moiety, to probe

how this moiety will influence the Anthelmintic activity along with benzimidazole derivatives. In view of these valid observations in our present study, we reported the synthesis of new benzimidazole derivatives and the synthesized compounds were screened for their Anthelmintic activity.

### MATERIALS AND METHODS

All the reactions were carried out under prescribed laboratory conditions. The products were purified by recrystallization. Melting points were recorded on capillary melting point apparatus and are uncorrected. <sup>1</sup>H spectra were recorded on Bruker DRX-400 (400 MHz, FT NMR) spectrometer using tetramethylsilane (TMS) as internal standard and the chemical shifts are reported in δ units. Mass spectra were recorded on LC-MS (Schimadzu-2010AT) under Electro Spray Ionization (ESI) technique. IR spectra (λ<sub>max</sub> in cm<sup>-1</sup>) were recorded on Perkin-Elmer infrared-283 FTIR spectrometer. Elemental analyses were recorded on Elementar Vario EL spectrometer. All chromatographic purification was performed with silica gel 60 (230–400 mesh), whereas all TLC (silica gel) development was performed on silica gel coated (Merck Kiesel 60 F254, 0.2 mm thickness). All chemicals were purchased from Aldrich Chemical Ltd (Milwaukee, WI, USA). Solvents used for the chemical synthesis acquired from commercial sources were of analytical grade, and were used without further purification unless otherwise stated.

### Experimental

**General procedure for the preparation of substituted 4-(p-amino benzimidazole) cinnoline -3-carboxamide (2a-g to 4a-g)**



### Synthesis of substituted aniline hydrazone (cyano) acetamide (2a-g)

The substituted aniline (0.195 mole) was dissolved a mixture of conc HCl (7.5ml) and water (7.5ml) and cooled to 0 to 5°C in an ice bath. To this a cold saturated solution of sodium nitrite (0.19 mole) was added slowly. Soon after the addition, the fumes of nitrous acid were liberated; a pinch of sulphamic acid / thiourea is added, stirred till the fumes were ceased. The diazonium salt thus formed was filtered in to a cooled solution of cyano acetamide (0.195 mole) in water (350ml) 10 gm CH<sub>3</sub>COONa and 15 ml alcohol. The mixture was kept stirring up to 6 hrs at room temperature; the solid was collected and recrystallized from methanol.

### Synthesis of substituted aniline 4-amino cinnoline 3-carboxamide (3a-g)

To the anhydrous AlCl<sub>3</sub> (0.11 mole) the chlorobenzene 150 ml was added and nitrogen gas was passed for half an

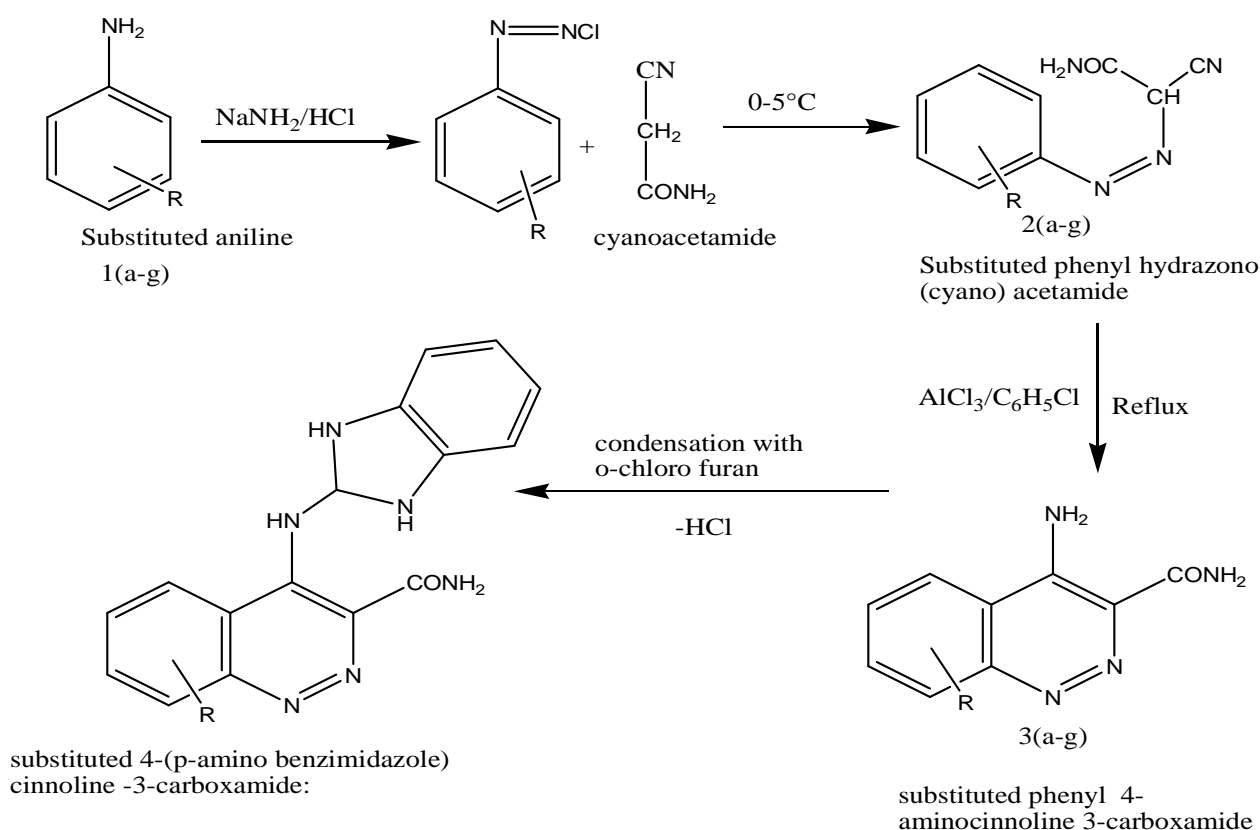
hour. This mixture was added to the substituted phenyl hydrazone cyano acetamide then nitrogen was passed for 10 min, the mixture was then refluxed for 2 hrs. It was cooled; dilute HCl (20ml) was added to it. It was then heated on water bath cooled, filtered, washed twice with dilute NaOH solution and filtered. The product was recrystallized from methanol and water in the ratio of 10:1.

### Synthesis of substituted 4-(p-amino benzimidazole) Cinnoline-3-carboxamide (4a-g)

Substituted 4-amino cinnoline –3-carboxamide (0.05 mole) was taken in 25 ml of DMF and *o*-chloro benzimidazole (0.01 mole) was added and refluxed for 2hrs. The mixture was poured in to the crushed ice and filtered, and recrystallized with alcohol. The data of percentage yield and melting point of the compounds are listed in Table 1.

**Table 1:** Physical data of synthesized compounds (1-7)

Compounds	R	Molecular formula	Molecular Weight	M.P. (°C)	Percentage Yield (%)	R <sub>f</sub> value
1	<i>o</i> -chloro	C <sub>16</sub> H <sub>11</sub> ClN <sub>6</sub> O	338.8	140°-141°C	62.12	0.42
2	<i>p</i> -chloro	C <sub>16</sub> H <sub>11</sub> ClN <sub>6</sub> O	338.8	160°-161°C	61.40	0.76
3	<i>m</i> -chloro	C <sub>16</sub> H <sub>11</sub> ClN <sub>6</sub> O	338.8	160°-161°C	72.42	0.67
4	<i>o</i> -bromo	C <sub>16</sub> H <sub>11</sub> BrN <sub>6</sub> O	383.2	264°-265°C	54.12	0.65
5	<i>p</i> -bromo	C <sub>16</sub> H <sub>11</sub> BrN <sub>6</sub> O	383.2	242°-243°C	60.18	0.45
6	2,4,6 tribromo	C <sub>16</sub> H <sub>10</sub> Br <sub>2</sub> N <sub>6</sub> O	462.1	189°-190°C	64.51	0.56
7	<i>m</i> -bromo	C <sub>16</sub> H <sub>11</sub> BrN <sub>6</sub> O	383.2	143°-145°C	48.54	0.47



### Scheme



**Table 2:** Anthelmintic activity of synthesized Compounds

Test Samples	Concentration (mg)	Mean paralyzing time (min) $\pm$ S.E.	Mean death time (min) $\pm$ S.E.
Control	-	No effect	No effect
Mebendazole	100	4.11 $\pm$ 0.32	5.33 $\pm$ 0.24
4a	100	4.10 $\pm$ 0.11*	5.22 $\pm$ 0.10**
4b	100	4.07 $\pm$ 0.16***	5.16 $\pm$ 0.36**
4c	100	4.13 $\pm$ 0.48**	5.38 $\pm$ 0.30**
4d	100	4.14 $\pm$ 0.09*	5.36 $\pm$ 0.42***
4e	100	4.21 $\pm$ 0.11***	5.45 $\pm$ 0.31***
4f	100	4.41 $\pm$ 0.11***	5.89 $\pm$ 0.12***
4g	100	4.23 $\pm$ 0.12***	5.34 $\pm$ 0.65***

'S.E.' represents Standard Error. Values are significantly different from reference standard (Mebendazole);  $p < 0.05$ \*\* ;  $p < 0.001$ \*\*\*.

### Anthelmintic Activity

Anthelmintic activity studies were carried out against Indian earthworms (*Pheretima posthuma*) were collected from the waterlogged areas of soil and identified at Indian Veterinary Research Institute, Izzatnagar and utilized for in-vitro anthelmintic assay as per standard protocol.<sup>13-14</sup>

All the novel benzimidazoles showed moderate to good activity. Suspensions of samples were prepared by triturating the samples with 12.5% tween 80 and distilled water and the resultant mixture were stirred using a mechanical stirrer for 30 minutes. The resulting suspensions were used for the activity studies. The suspensions were diluted to contain 100 mg in 50 ml of the test samples. Standard drug mebendazole was also prepared with the same concentration in a similar way.

The newly synthesized compounds were screened for their Anthelmintic activity. Suspensions of samples were prepared by triturating synthesized compounds (100 mg) with Tween 80 (0.5%) and distilled water and the resulting mixtures were stirred using a mechanical stirrer for 30 min. The suspensions were diluted to contain 0.2% w/v of the test samples. Suspension of reference drug, mebendazole, was prepared with the same concentration in a similar way. Three sets of five earthworms of almost similar sizes (2 inch in length) were placed in Petri plates of 4 inch diameter containing 50ml of suspension of test sample and reference drug at RT. Another set of five earthworms was kept as control in 50 ml suspension of distilled water and Tween 80 (0.5%). The paralyzing and death times were noted and their mean was calculated for triplicate sets. The death time was ascertained by placing the earthworms in warm water (50°C) which stimulated the movement, if the worm was alive. The mean paralyzing time and mean death rate were determined and the results are summarized in Table 2.

#### 6-chloro-4-(*p*-amino benzimidazole) Cinnoline -3-carboxamide (4a C<sub>16</sub>H<sub>11</sub>ClN<sub>6</sub>O)

IR (KBr): 2940 (N-H, ali. str.), 1410 (C-N, ali. Str.), 2450 (N-H, ali. Str.), 1605 (C-C, Ar Str.), 1600 (C=C, Ar Str.), 725 (C-

Cl, Ar Str.), 1575 (N=N, Ar Str.), 1050 (C-N, Ar Str.) 3050 (C-H, Ar Str.), 1640 (CONH<sub>2</sub> Str.) cm<sup>-1</sup>, <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta$  6.21-8.18 (7H,*m*,ArH), 5.97 (2H,*s*,NH<sub>2</sub>), 4.88 (1H,*s*,CH), 3.97 (3H,*s*,Ar C-NH) ppm, MS (ESI) m/z calculated for (C<sub>13</sub>H<sub>15</sub>Cl N<sub>6</sub>O): 340.08 (100%) M<sup>+</sup>.

#### 8-chloro-4-(*p*-amino benzimidazole) Cinnoline -3-carboxamide (4b C<sub>16</sub>H<sub>11</sub>ClN<sub>6</sub>O)

IR (KBr): 2650 (N-H, ali. Str.), 1420(C-N, ali. Str.), 2415 (N-H, ali. Str.), 1600 (C-C, Ar Str.), 1610 (C=C, Ar. Str.) 1555 (N=N, Ar Str) , 1050 (C-N, Ar Str.) cm<sup>-1</sup>, <sup>1</sup>H-NMR( DMSO-d<sub>6</sub>):  $\delta$  6.10-7.98 (7H,*m*,ArH), 5.89 (2H,*s*,NH<sub>2</sub>) 4.59 (1H,*s*,CH) 3.84 (3H,*s*,Ar C-NH) ppm, MS (ESI) m/z calculated for (C<sub>13</sub>H<sub>15</sub>Cl N<sub>6</sub>O): 340.08 (100%)M<sup>+</sup>.

#### 7-chloro-4-(*p*-amino benzimidazole) Cinnoline -3-carboxamide (4c C<sub>16</sub>H<sub>11</sub>ClN<sub>6</sub>O)

IR (KBr): 2630 (N-H, ali. str.), 1430(C-N,ali.-str.), 2420 (N-H aliphatic), 1620 (C-C,Ar), 1620 (C=C,Ar.), 727 (C-Cl,Ar.), 1560 (N=N,Ar), 1035(C-N,Ar,str.) cm<sup>-1</sup>, <sup>1</sup>H- NMR( DMSO-d<sub>6</sub>):  $\delta$  6.19-7.79 (7H,*m*,ArH), 5.79 (2H,*s*,NH<sub>2</sub>) 4.72 (1H,*s*,CH) 3.63 (3H,*s*,Ar C-NH) ppm, MS (ESI) m/z calculated for (C<sub>13</sub>H<sub>15</sub>Cl N<sub>6</sub>O) 342.07 (100%)M<sup>+</sup>.

#### 6-bromo-4-(*p*-amino benzimidazole) Cinnoline -3-carboxamide (4d C<sub>16</sub>H<sub>11</sub>BrN<sub>6</sub>O)

IR (KBr): 2630 (N-H, ali. Str.), 1416(C-N, ali. Str.), 2435 (N-H ali. Str.), 1590 (C-C, Ar Str.), 1616 (C=C, Ar Str.),636 (C-Br, Ar Str.), 1550 (N=N, Ar Str.) , 1053 (C-N Ar, Str.) cm<sup>-1</sup>, <sup>1</sup>H- NMR( DMSO- d<sub>6</sub>):  $\delta$  6.10-7.98 (7H,*m*,ArH), 5.89 (2H,*s*,NH<sub>2</sub>) 4.59 (1H,*s*,CH) 3.84 (3H,*s*,Ar,C-NH),ppm, MS (ESI) m/z calculated for (C<sub>13</sub>H<sub>15</sub>Cl N<sub>6</sub>O) 383.2 (100%)M<sup>+</sup>.

#### 8-bromo-4-(*p*-amino benzimidazole) Cinnoline -3-carboxamide (4e C<sub>16</sub>H<sub>11</sub>BrN<sub>6</sub>O)

IR (KBr): 2680 (N-H, ali. Str.), 1445(C-N, ali. Str.), 2419 (N-H, ali. Str.), 1598 (C-C, Ar Str.), 1645 (C=C, Ar Str.),645 (C-Br, Ar Str.), 1580 (N=N, Ar Str.) , 1060(C-N, Ar, Str.) cm<sup>-1</sup>, <sup>1</sup>H-NMR( DMSO- d<sub>6</sub>):  $\delta$  6.21-7.89 (7H,*m*,ArH), 5.23 (2H,*s*,NH<sub>2</sub>) 4.87 (1H,*s*,CH) 3.90 (3H,*s*,Ar C-NH) ppm, MS (ESI) m/z calculated for (C<sub>13</sub>H<sub>15</sub>Cl N<sub>6</sub>O) 383.2 (100%)M<sup>+</sup>.

#### 6,7,8-bromo-4-(*p*-amino benzimidazole) Cinnoline -3-carboxamide(4f C<sub>16</sub>H<sub>10</sub>Br<sub>2</sub>N<sub>6</sub>O)

IR (KBr): 2622 (N-H, ali. str.), 1434(C-N,ali. str.), 2432 (N-H ali. Str.), 1586 (C-C Ar Str.), 1615 (C=C, Ar Str.),675 (C-Br, Ar Str.), 1555 (N=N, Ar Str.), 1050(C-N, Ar Str.) cm<sup>-1</sup>, <sup>1</sup>H-NMR( DMSO- d<sub>6</sub>): 6.11-7.21(7H,*m*,ArH), 5.01 (2H,*s*,NH<sub>2</sub>) 4.31 (1H,*s*,CH) 3.31 (3H,*s*,Ar C-NH) ppm, MS (ESI) m/z calculated for (C<sub>13</sub>H<sub>13</sub>Br<sub>3</sub>N<sub>6</sub>O) 262.1 (100%)M<sup>+</sup>, 463.92(70.9%)M<sup>+</sup>2.

#### 7-bromo-4-(*p*-amino benzimidazole) Cinnoline -3-carboxamide(4g C<sub>16</sub>H<sub>11</sub>BrN<sub>6</sub>O)

IR (KBr): 2656 (N-H, ali. Str.), 1424 (C-N, ali.-Str.), 2432 (N-H ali. Str.), 1578 (C-C Ar Str.), 1597 (C=C, Ar Str.), 686 (C-Br, Ar Str.), 1578 (N=N, Ar Str.), 1060(C-N, Ar Str.) cm<sup>-1</sup>, <sup>1</sup>H-NMR( DMSO- d<sub>6</sub>):  $\delta$  6.34-7.80 (7H,*m*,ArH), 5.23



(2H,s,NH<sub>2</sub>) 4.83 (1H,s,CH) 4.19 (3H,s,Ar C-NH) ppm, MS (ESI) m/z calculated for (C<sub>13</sub>H<sub>15</sub>Cl N<sub>6</sub>O) 383.2 (100%)M<sup>+</sup>.

## RESULTS AND CONCLUSION

Structures of all the newly synthesized compounds were confirmed by IR, <sup>1</sup>H NMR and Mass spectral analysis. The IR spectra of the newly synthesized compounds showed the presence of characteristic absorption bands in the region 2940-3000 cm<sup>-1</sup> for N-H aliphatic stretching, 1410 for C-N aliphatic stretching, 3012-3096 cm<sup>-1</sup> for aromatic C-H stretching, 1650-1680 cm<sup>-1</sup> for C=O stretching, 1500-1600 cm<sup>-1</sup> for C=N stretching, 750-600 cm<sup>-1</sup> for C-S stretching. <sup>1</sup>H NMR spectra of synthesized compounds showed the characteristic peaks in the region 5.02-6.54 ppm for –CONH<sub>2</sub> proton and 6.67-7.80 ppm for aromatic protons.

Evaluation of Anthelmintic activity for substituted cinnoline derivatives exhibits potent Anthelmintic activity against earthworm (*Pheretima posthuma*). The two derivatives not only demonstrated significantly shorter paralyzing time, but also caused death of worms in significantly shorter time as compared to reference drug (Mebendazole), while one derivative 4f require longer paralyzing as well as death time, this might be due to the reason that this derivative require more time for absorption. 4b derivative was the most potent followed by 4a and 4c and 4d. Further, it would be suggested that the derivative 4f require improvement in their physicochemical properties in order to get good absorption properties and then further evaluated for shorter paralyzing time in worms. The experimental evidence obtained in the laboratory model could provide a rationale for the clinical use of this as Anthelmintic. It is reported that the Anthelmintic activity of benzimidazole and related compounds had been suggested to be, based on blockage of the response of the worm muscle to acetylcholine, causing a flaccid paralysis in the worm, which is dislodged from the intestinal wall and expelled in the feces.<sup>12</sup>

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