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Synthesis and Evaluation of 4-(1h-Benzimidazol-2-Yl)-6-(2 Chloroquinolin-3-Yl) Pyrimidin-2-Amine as Potent Anthelmintic Agents

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ABSTRACT

A new series of 4-(1H-benzimidazol-2-yl)-6-(2-chloroquinolin-3-yl)pyrimidin-2-amine (Va-k) derivatives were prepared and characterized by their IR, 1H NMR and Mass spectral studies. The synthesized compounds were evaluated for their anthelmintic activity by in-vitro method, against south Indian adult earth worms Pheretima posthuma using Albendazole as a standard drug. The mean paralysis time and mean death time were calculated for each tested concentrations of the compounds. Among all the compounds synthesized, Vb, Vc and Vd were found to be the most active compounds.

Keywords: Benzimidazoles; Chalcones; Pyrimidines; Albendazole; Anthelmintic activity

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INTRODUCTION

Heterocyclic compounds are widely dispersed in nature and are essential for life in a variety of ways. In particular, these compounds are important due to the wide range of physiological activities associated with these class substances. Heterocyclic rings are present in a variety of compounds, e.g., most of the members of the vitamin B complex, drugs, dyes, enzymes, the genetic material DNA etc [1].

Among the wide variety of heterocyclics investigated to develop pharmaceutically important molecules, benzimidazoles have played an important role in medicinal chemistry [2]. Compounds carrying benzimidazole nucleus are reported to elicit certain biological activities such as antihypertensives [3], analgesics [4], antiviral [5], antimicrobial [6], antitumour agents [7], antihelminthic [8], antiamoebic [9], anti-inflammatory [10] etc.

The greatest importance of heterocycles in nature product chemistry and pharmacology constantly drive the search for new methods for the construction of heterocyclic unit viz., Pyrimidines. These Pyrimidines were synthesized from chalcones which are vital intermediate compounds and they also possess biological and pharmacological activities.

Pyrimidines can be considered as a cyclic amine and also be known as m-diazone (or) 1,3-diazine. It is a major component of a large group of heterocyclic compounds and plays a vital role in many biological processes as found in nucleic acids, several vitamins, co-enzymes and purines. Pyrimidine is the most significant member of all

the diazines as this ring occurs widely in living organisms. Pyrimidine itself is not found in nature however substituted Pyrimidines and compounds containing the Pyrimidine ring are widely distributed in nature. Derivatives of barbituric acid, widely used in medicines, for example veronal, Pentothiol, Luminol are used as hyphotics while is employed as anesthetic. Purines, Uric acid, alkoxan, barbuturic acid and a mixture of amtimalarial and antibacterial drug additionally contain the Pyrimidine ring. Substances containing un-fused Pyrimidine rings occur in free stage as in Uracil, Thymine, Orotic acid, Cytosine, the glycosides, Vitamin B (thiamine), amicetin and numerous others.

Various methods have been used in literature for the preparation of Pyrimidines. Uracils (or) dehydrouracils are often synthesized from urea and α, β – unsaturated acids (or) their esters. When S-benzyl (or) S-methyl thiourea is condensed with ethyl ψ - bromo acetoacetate, the product is a pyrimidine. In the synthesis of orotic acid from urea and oxalacetic ester, the first formed hydantoin is rearranged to pyrimidine in presence of alkali. Preclinical data from the literature study show that together with pyrimidine, heterocycles exhibit good antimicrobial [11], antioxidant [12], anti-inflammatory [13], analgesic and antipyretic [14], anti-tumor activities [15].

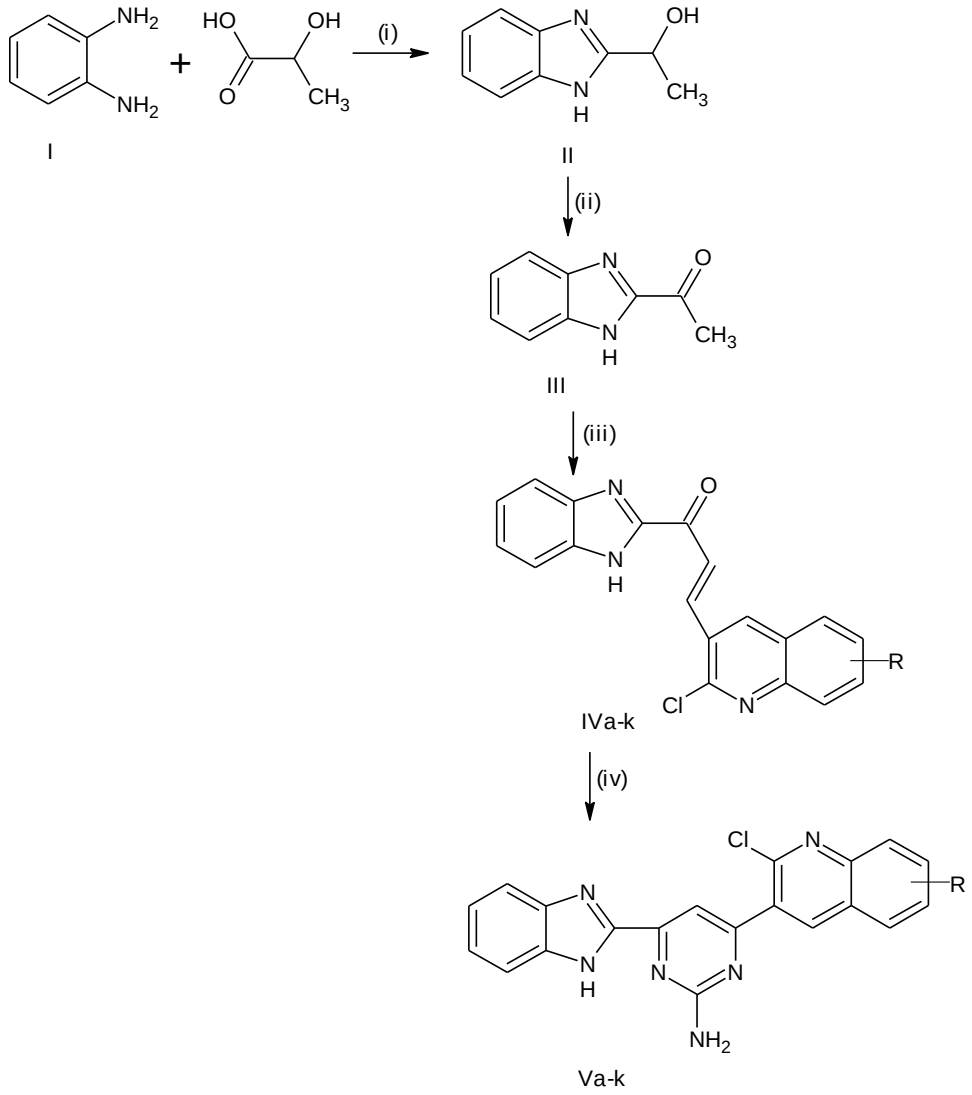
Compound bearing benzimidazole nucleus have been of great interest to synthetic and medicinal chemists from a long time due to their unique chemical and biological properties which are identical to traditional anthelmintics like Albendazole and Oxibendazole. Albendazole, a benzimidazole carbamate (methyl-5-propylthio-1H-benzimidazole-2-yl-carbamate) with widespread clinical use as an anthelmintic drug can also inhibit hepatocellular carcinoma cell proliferation under both in vitro and in vivo experimental conditions [16].

The anthelmintic activity of the benzimidazole-2-carbamates relates to their selective antimitotic activity due to their preferential binding to the helminthic tubulin over mammalian tubulin [17].

Human and animal diseases caused by helminthes parasites have great impact on public health. Toxocariasis is an infection caused by the nematode Toxocara commonly found in the intestines of puppies and older dogs (*Toxocara canis*) and cats (*Toxocara cati*). Humans become infected either by ingesting embryonated eggs accidentally or eating contaminated food with soil containing the eggs (such as unwashed raw vegetables). Hymenolepiasis is caused by (*Hymenolepis nana* or *Hymenolepis diminuta*) the dwarf tapeworm that is the most typical reason behind all intestinal cestode infections. In an infected person the worms can remain encysted in tissue so infection can persist for years.

Treatment with Praziquantel or Albendazole is currently being sought as an alternative to these drugs. The continuous and longterm 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 many side effects are reported in hosts like gastrointestinal symptoms (epigastric pain, diarrhea, nausea, vomiting); nervous system symptoms (headache, dizziness) and allergic phenomena (edema, rashes, urticaria). Some anthelmintic medications like Praziquantel and Albendazole are contraindicated for certain groups of patients like pregnant and lactating woman. The global burden of both, human and domestic animal parasitic diseases coupled with the emergence of drug resistance has made the development of new chemotherapy a critical need.

By seeing impressive biological profile of benzimidazoles and pyrimidines and also with respect to our work in synthesis and evaluation of biologically active new heterocycles, we planned to synthesize the new series of 4-(1*H*-benzimidazol-2-yl)-6-(2-chloroquinolin-3-yl)pyrimidin-2-amine as potent anthelmintic agents.



Scheme

R= (a)-H; (b)-6-CH_3; (c)-7-CH_3; (d)-8-CH_3; (e)-6-Meo; (f)-7-Meo; (g)-8-Meo; (h)-6-Cl; (i)-7-Cl; (j)-6-Br; (k)- 6-F.

Reagents and conditions: (i) Lactic acid, 4N HCl, reflux for 4 to 6 hrs, (ii) $K_2Cr_2O_7$, H_2SO_4 (25% v/v) 2 hrs, (iii) 10% NaOH, 2-chloroquinoline-3-carbaldehydes, Ethanol, 0.5 hrs, (iv) Guanidine nitrate, Ethanol, NaOH (40%), 10 hrs.

EXPERIMENTAL SECTION

By open capillary tube method, melting points were checked and are uncorrected. By using TLC plates, TLC analysis was performed. By using KBr method, on a Shimadzu FTIR 8400S spectrometer IR spectra were recorded.

On Bruker Avance II of 400 MHz NMR spectrometer, NMR spectra and Mass spectra on a Waters, Q-TOF Microma SS spectrometer.

Synthesis of 1-(1H-benzimidazol-2-yl)ethanol (II)

o-phenylenediamine (0.01,mole) (I) was mixed with Lactic acid (0.01 mole) and 4N hydrochloric acid under Phillips conditions and refluxed for 4 to 6 hrs. TLC was monitored, after completion of reaction period; cooled mixture was neutralized by sodium bi carbonate. The solid was separated, filtered and recrystallization was carried out from absolute alcohol. m.p-180-82ċ [18-20].

Synthesis of 1-(1H-benzimidazol-2-yl)ethanone (III)

To a solution of 1-(1H-benzimidazol-2-yl)ethanol (II) (9.8 g, 50 mmole) in dilute H2SO4 (5%, 40 ml) was added a solution of K2Cr2O7 (44g, 150 mmole) in dilute H2SO4 (25%, 80 ml) with constant stirring, drop wise for 20 minutes at an ambient temperature. The stirring further continued for 2 hours. On completion of reaction period (TLC monitered), separated solid (a chromium complex) dispersed in water and adjusted a pH up to 6 to 6.5 with aqueous ammonia (1:1). Solid product then washed, dried and recrystallized by ethyl acetate to obtain a purified compound. m.p- 191-93ċ [21-22].

Synthesis of 1-(1H-benzimidazol-2-yl)-3-(2-chloroquinolin-3-yl)prop-2-en-1-one (IVa-k)

1-(1H-benzimidazol-2-yl)ethanone (III) (10 mmole, 1.6g) and substituted 2-chloroquinoline-3-carbaldehydes (10 mmole, 1.91g) were mixed in 30 ml of aqueous NaOH (10%). Continuing stirring up to 30 minutes, TLC was checked for completion of reaction. Solid filtered was dried. In addition, purified by recrystallization from a suitable solvent [23-29].

Similarly, 1-(1H-benzimidazol-2-yl)-3-(2-chloroquinolin-3-yl)prop-2-en-1-one (IVa-k) were synthesized.

IVb: yield 77%, m.p-250-52ċ; IR (KBr): 3250, 3150, 2800, 1650, 1575, 1425, 1225, 730 cm-1; 1H NMR (CDCl3, 400 MHz): δ 2.75 (s, 3H, CH3), 5.29 (s, 1H, NH-benzimidazole), 6.63 (d, 1H, 1-ethylene), 7.34 (d, 1H, 1-ethylene), 7.39-7.86 (m, 4H, Benzimidazole), 7.90-8.90 (m, 4H, Quinoline). MS: m/z 347.70 (M+•).

IVd: yield 86%, m.p-262-64ċ; IR (KBr): 3300, 3100, 2750, 1650, 1525, 1200, 740 cm-1; 1H NMR (CDCl3, 400 MHz): δ 2.27 (s, 3H, CH3), 5.19 (s, 1H, NH-benzimidazole), 6.87 (d, 1H, 1-ethylene), 7.51 (d, 1H, 1-ethylene), 7.65-7.97 (m, 4H, Benzimidazole), 8.21-8.69 (m, 4H, Quinoline). MS: m/z 347.71 (M+•).

IVe: yield 88%, m.p-278-80ċ; IR (KBr): 3300, 2850, 1670, 1550, 1425, 1325, 725 cm-1; 1H NMR (CDCl3, 400 MHz): δ 3.91 (s, 3H, OCH3), 4.95 (s, 1H, NH-benzimidazole), 6.98 (d, 1H, 1-ethylene), 7.73 (d, 1H, 1-ethylene), 7.18-7.50 (m, 4H, Benzimidazole), 7.51-7.95 (m, 4H, Quinoline). MS: m/z 363.74 (M+•).

Synthesis of 4-(1H-benzimidazol-2-yl)-6-(2-chloroquinolin-3-yl)pyrimidin-2-amine (Va-k)

In ethanol (25 ml), add a 1-(1H-benzimidazol-2-yl)-3-(2-chloroquinolin-3-yl)prop-2-en-1-one (IV) (3.33g, 0.01 mole) and guanidine nitrate (1.80 g, 0.01 mole). An aqueous solution of sodium hydroxide (40%, 5 ml) was added portion wise during a period of 3 hours. Refluxing was continued further for 7 hours. The solvent portion reduced so that only half of the volume remains. The compound with crystalline form was separated on cooling. The collected compound was filtered and dried. The purification was done to obtain a pure product [30-31].

Similarly, 4-(1H-benzimidazol-2-yl)-6-(2-chloroquinolin-3-yl)pyrimidin-2-amine (Va-k) were synthesized.

Vb : Yellow solid, yield 57%, m.p-166-168ċ; IR (KBr): 3321, 3196, 1600, 1550, 1429, 1224, 738 cm-1; 1H NMR(CDCl3, 400 MHz): δ 2.68 (s, 3H, CH3), 4.64 (d, 2H, aromatic C-NH), 5.32 (s, 1H, NH-benzimidazole), 7.24 (s, 1H, 2-Pyrimidine) 7.28-7.60 (m, 4H, Benzimidazole), 7.86-8.62 (m, 4H, Quinoline). MS: m/z 386.80 (M+•).

Vd: Yellow solid, yield 61%, mp 176-178ċ; IR (KBr): 3321, 3196, 1602, 1548, 1431, 1222, 740, cm-1; 1H NMR(CDCl3, 400 MHz): δ 2.76 (s, 3H, CH3), 4.65 (d, 2H, aromatic C-NH), 5.33 (s, 1H, NH-benzimidazole), 7.19 (s, 1H, 2-Pyrimidine) 7.36-8.01 (m, 4H, Benzimidazole), 8.09-8.62 (m, 4H, Quinoline). MS: m/z 386.82 (M+•).

Vf : Yellow solid, yield 62%, mp 186-188ċ; IR (KBr): 3358, 3196, 1625, 1577, 1496, 1224, 746 cm-1; 1H NMR(CDCl3, 400 MHz): δ 3.60 (s, 3H, OCH3), 4.56 (d, 2H, aromatic C-NH), 5.40 (s, 1H, NH-benzimidazole), 6.97 (d, 1H, 2-Pyrimidine) 7.14-7.45 (m, 4H, Benzimidazole), 7.59-8.53 (m, 4H, Quinoline). MS: m/z 402.80 (M+•).

Vh : Yellow solid, yield 53%, mp 198-200ċ; IR (KBr): 3360, 3186, 1608, 1552, 1437, 1246, 823, 744 cm-1; 1H NMR(CDCl3, 400 MHz): δ 4.46 (d, 2H, aromatic C-NH), 5.26 (s, 1H, NH-benzimidazole), 6.80 (d, 1H, 2-Pyrimidine) 7.32-7.62 (m, 4H, Benzimidazole), 7.67-8.55 (m, 4H, Quinoline). MS: m/z 408.20 (M+ +1).

Table 1. **Physical Characterization of 4-(1*H*-benzimidazol-2-yl)-6-(2-chloroquinolin-3-yl)pyrimidin-2-amine (Va-k)**

Sl. No	Compound Code	R	Molecular formula	Molecular weight	M P Ċ	% Yield
1	Va	H	$C_{20}H_{13}ClN_6$	372.81	160-162	51
2	Vb	6-CH_3	$C_{21}H_{15}ClN_6$	386.83	166-168	57
3	Vc	7-CH_3	$C_{21}H_{15}ClN_6$	386.83	171-173	59
4	Vd	8-CH_3	$C_{21}H_{15}ClN_6$	386.83	176-178	61
5	Ve	6-Ome	$C_{21}H_{15}ClN_6O$	402.83	182-184	65
6	Vf	7-Ome	$C_{21}H_{15}ClN_6O$	402.83	186-188	62
7	Vg	8-Ome	$C_{21}H_{15}ClN_6O$	402.83	190-192	58
8	Vh	6-Cl	$C_{20}H_{12}Cl_2N_6$	407.25	198-200	53
9	Vi	7-Cl	$C_{20}H_{12}Cl_2N_6$	407.25	194-196	55
10	Vj	6-Br	$C_{20}H_{12}BrClN_6$	451.70	208-210	68
11	Vk	6-F	$C_{20}H_{12}FClN_6$	390.80	195-197	62

Anthelmintic activity

The synthesized compounds were tested for anthelmintic activity by in-vitro bioassay method [32-34].

The South Indian adult earthworms *Pheretima posthuma* (earthworms authenticated by the Government Agricultural College, Hitnalli, Vijayapur, Karnataka) with a length of 9-11cm and a width of 0.2-0.3 cm were used for the in vitro anthelmintic bio-assay due to its anatomical and physiological similarity with the intestinal worm parasites of human beings. The nearly equal sized earthworms (9±1cm) were randomly selected, washed thoroughly with normal saline to remove any fecal and adherent materials before being released in to petridishes containing active ingredient in 15 ml of normal saline.

The worms were divided into control, standard and test groups of five earthworms each. All tested compounds and the standard drug solution were freshly prepared before starting the tests. The control group petridish contains 0.5 ml of dimethyl sulfoxide in 14.5 ml of normal saline. The standard drug Albendazole and tested compounds were prepared at a dosage of 30, 50, 100 µg/ml, by dissolving in a minimal amount, about 0.5 ml of dimethyl sulfoxide and the volume was diluted to 15ml with normal saline and then poured into petri dishes.

The five earth worms were placed in each petridish at room temperature and the time for initiation of complete paralysis and the time required for death of individual earthworms was recorded. The time when the worms were motionless and not even used to receive normal saline was found to be the time of paralysis. The death time was determined by external stimuli, unless the individual worms were placed in warm water at 50ċ, which stimulate and induces the movement of worms while they are still alive.

Mean paralysis time and mean dead time was calculated for each concentration of the compounds tested.

Table 2. Anthelmintic activity of 4-(1*H*-benzimidazol-2-yl)-6-(2-chloroquinolin-3-yl)pyrimidin-2-amine (Va-k)

Pyrimidines	Time taken for paralysis (P)			Time taken for Death (D)		
	30 µg/ml	**50 µg/ml**	**100 µg/ml**	**30 µg/ml**	**50 µg/ml**	**100 µg/ml**
Va	56.71 ± 3.56	24.67 ± 1.14	12.52 ± 0.58	82.26 ± 1.40	45.28 ± 1.80	22.74 ± 2.12
Vb	19.21 ± 2.48	15.13 ± 0.70	7.90 ± 0.91	34.49 ± 2.42	25.26 ± 1.72	12.83 ± 0.85
Vc	23.52 ± 3.32	17.52 ± 0.68	8.61 ± 2.14	41.40 ± 2.04	27.82 ± 1.31	14.57 ± 1.07
Vd	20.70 ± 3.22	15.16 ± 1.00	8.16 ± 1.24	38.95 ± 1.66	25.90 ± 1.40	13.84 ± 1.70
Ve	28.18 ± 2.67	18.28 ± 1.33	9.79 ± 1.10	47.92 ± 3.59	32.42 ± 1.27	16.68 ± 1.95
Vf	25.32 ± 2.67	19.47 ± 1.05	9.23 ± 0.96	45.31 ± 3.11	29.01 ± 1.93	15.35 ± 1.78
Vg	53.21 ± 3.86	25.27 ± 0.63	13.23 ± 0.38	76.55 ± 2.94	43.24 ± 1.31	21.56 ± 1.36
Vh	32.06 ± 4.08	19.05 ± 0.96	8.88 ± 1.56	51.10 ± 3.37	34.24 ± 2.08	17.46 ± 3.10
Vi	34.24 ± 3.02	18.81 ± 0.84	9.43 ± 0.74	55.05 ± 2.47	35.22 ± 1.93	16.92 ± 1.83
Vj	40.67 ± 3.68	20.47 ± 1.07	10.71 ± 1.11	60.58 ± 2.95	38.16 ± 1.52	19.58 ± 1.86
Vk	30.94 ± 4.51	18.06 ± 1.26	8.75 ± 0.61	51.94 ± 2.40	33.11 ± 1.16	17.03 ± 1.89
ALZ[a]	15.10 ± 2.84	12.48 ± 0.61	6.93 ± 0.72	26.14 ± 1.87	19.70 ± 1.04	9.80 ± 1.05
Control[b]	-	-	-	-	-	-

Each value represents the Mean ± SEM (n=5).
[a]Standard drug- Albendazole (ALZ)
[b]Control- Normal Saline

RESULT AND DISCUSSIONS

All the newly synthesized 4-(1H-benzimidazol-2-yl)-6-(2-chloroquinolin-3-yl)pyrimidin-2-amine (Va-k) were characterized by IR, 1H NMR and Mass spectral studies. The investigation of all tested groups of compounds at tested concentrations 30, 50 and 100 µg/ml had shown significant activity compared to the standard drug Albendazole.

It was observed that while increasing the concentrations of compounds and Albendazole significantly reduced the time taken for paralysis and death as well. In which Compounds Vb, Vc and Vd showed excellent potent action for time taken to paralysis and death when compared to the standard drug Albendazole. The compounds Ve, Vf and Vk were also registered comparably potent activity to the above mentioned compounds. The compounds Vh,

Vi and Vj were also displayed good anthelmintic activity but compounds Va and Vg possess comparably less potent than other tested compounds.

CONCLUSION

A new series of compounds of 4-(1H-benzimidazol-2-yl)-6-(2-chloroquinolin-3-yl)pyrimidin-2-amine (Va-k) were synthesized. The synthesized compounds were additionally screened for anthelmintic activity. The results of antimicrobial testing revealed the compounds Vb, Vc and Vd have shown promising anthelmintic activity. Therefore, this work would be fruitful matrix for the development of novel class of anthelmintic agents. It is convincing that, derivatives showing significant anthelmintic activity can be further modified to exhibit better potency as that of standard drugs.

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