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Research Article

SYNTHESIS AND SCREENING OF SOME NEW BENZIMIDAZOLE DERIVATIVES

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INTRODUCTION

The benzimidazoles are the largest chemical family to treat endoparasitic diseases in domestic animals. They are characterized by a broad spectrum of activity and a wide safety margin. Their high degree of efficiency is related both to their pharmacodynamic and pharmaco kinetic characters. Benimidazoles are low use-rate, broad spectrum fungicide that have been used commercially for the control of plant diseases since the late 1960's.at the time of their introduction, they represented a ground-breaking class of fungicide with unique properties including systemic and curative activity that allowed extended spray intervals. World-wide, benzimidazole fungicides are registered in many countries on more than 70crops including cereals, grapes, fruits and vegetables currently commercially available include the following active ingradients: benomyl, carbendazim, thiabendazole, thiophanate, thiophanate-methyl and fuberidazole. The group includes thiabendazole analogs and benzimidazole carbamates; substitution of various side chains and radicals on the parent benzimidazole nucleus produces the individual members. Benzimidazoles bind to the ß-tubulin, a structural protein and block polymerization of tubulin into microtubules. This damages the integrity and transport functions of cells within parasite. The antiparasitic effect in a lethal, but relatively tardy process. Binding of benzimidazoles to ß-tubulin is reversible and saturable.

Resistance status

Resistance developed after a long period of use, e.g., more than 10 years for cereal eyespot caused by tapesia spp.nevertheless, benzimidazoles are still used widely and continue to be valuable fungicide in global agricultural production. Since commercialization at least 100 species of fungi have developed some degree of resistance to benzimidazoles.

Site of action

Benzimidazoles are potent inhibitors of ß-tubulin seem to be the predominant inhibitory process for this chemical class, interactions with other forms of tubulin as well as differential interactions with tubulin in the free and polymerized states also have been reported. Benzimide fungicide selectively affects tubulin and microtubule interactions in oomycetes without significant inhibitory effects in true fungi.

Mechanism of resistance

Studies have demonstrated that fungicidal activity and resistance are determined by affinity of specific inhibitors for target sites on ß-tubulin. Resistance to benzimidazole fungicide is related primarily to specific binding sites on ß-tubulin protein. Approximately 10 mutations conferring resistance to benzimidazoles have been identified in the ß-tubulin gene in laboratory studies with a wide range of different fungi. at codon 200, resistant isolates are characterized by a single substitution of phenyl amine by tyrosine. Not only are these mutants resistant to benzimidazole inhibitors, but they are mostly fit and fully capable of survival in the absence of fungicide.

Cross resistance with other fungicide

For practical applications, fungi isolates to the benzimidazole fungicide usually are resistant to other members of the chemical class. Therefore combinations of various benzimidazole fungisude cannot be used a résistance management tool. The usual phenomenon of negative cross resistance has been reported between benzimidazole fungicide and two other chemical classes, n-phynylcarbamates and n-phynylformamidixes.This phenomenon allows

mixtures of these two classes to be used commercially for resistance management in botrytis cinerea.

Benzimidazoles

- Action: bind to nematode dimeric tubulin to prevent polymerization of tubulin during microtubule assembly.
- No side effects observed when demonstrated to young, sick, or deabilited animals.
- Wide margin of safety with regards to dose when used on sheep and goats, most effective on full feed.
- Thiabendazole (treasaderm-merial; tbz-the oral anthelimenthic product is no longer being manufactured.
- Mebendazole (mbz, telmin, telmentic)-withdrawn cambendazole (cbz)-withdraw.
- Fenbendazole(pancer,safeguard-hoechst roussel and many other products)

➢ Mode of action: inhibits parasitic energy metabolism
➢ Horses
➢ Anthelimenthic spectrum: adult small and large stronglyes, oxyuris, parascaris, fourth stage stronglus vulgaris
➢ Supplied as a paste, suspension or granules for top-dressing.

Doses

1.5mg/kg orally in one dose can be repeated every 8 weeks.
2. for treatment of S vulgaris larvae, 4.6mg/kg
3. for parascaris, 10 mg/kg.

- Can be used with trichlofrm for gastrophilus.
- No known containdications
- Not for use in horses intended for food.

Dogs (also lions, tigers, cheetahs, pumas, jagrs, leopards, panthers, grizzly bears, polar bear and black bears)
Anthelimenthic spectrem
toxocara spp, ancylostoma, uncinaria, trichuris, taenia.
Dose:50mg/kg daily for 3 days
1. for felidae and ursidae: 10mg/kg daily dose for 3 days
2. May need retreatment after 4 to 6 weeks.

- No known contraindications
- Safe no-reported toxic reactions to high doses, no known icompatabilities with other drugs.
- Supplied as 22.2% granules for topdressings
- Do not use for 14 days before or during hunting season

Birds

- Anthelimenthic spectrem: syngamus trachea, heterakis, ascardia, capillaria
- Dose: 60ppm for 6 days.

Cattle

- Anthelimenthic spectrem: dictyocalaus, haemonchus, ostertagia, trichostrongly, bunostomum, nematodirus, cooperia, trichostrongylus, oesophagostomum, moieties
- **Dose:**5mg/kg:may be administred at 10mg/kg for ostertagia arrested L4
- Withdrawal: 8 days before slaughter, no milk withdrawal for paste
- Some products approved for use in dairy cattle of breeding age and during lactation.

Albendazole (valben-pfizer)

- Anthelimenthic spectrem: fasciola, heads and segments of monienzia spp, adults and fourth stage larvae of ostertagia ,haemonchus, trichostrongylus, nematodirus, cooperia ,dictyocaulus, adult bunostomum, oesophagostomum
- **Dose:** 10 mg/kg
- **Withdrawal:** 27 days before slaughter
- Not for use in dairy cattle of breeding age, or if any cattle during the first 45 days of pregnancy.

Oxfenbendazole (synthetic, benzelmin-fort dodge, equicide- equi-labs)

Horses

- Anthelimenthic spectrem: ascarids .large and small strongles, pinworms. round warms
- Dose: 10mg/kg orally retreatment if needed in 6-8 weeks.
- Formulations
- Single entity as reconstitubale powder, paste or suspension
- Wide margin of safety
- Symptoms of overdose are ataxia, colic and diarrhea
- Antidote: atropine
- Not for use in sick/ debilitated horses or mares in last month of pregnancy
- Not for use in horses intended for food.

Cattle

- **Anthelimenthic spectrem**
- dictyocaulus, Haemonchus, ostertagia, oesophagostomum, cooperia, moniezia.
- **Dose:**2.05 mg/kg orally or injected directly into the rumen with synthetic rumen injector
- Available as paste and suspension
- No known contraindications
- Withdrawal:1 days before slaughter
- Not for use in dairy cattle of breeding age

Oxybendazole

- Dogs (see de above)
- Horses
- **A**nthelimenthic spectrem**:** large and small strongyles, parascaris, oxyuris, strongloudies
- Dose: 10mg/kg every 6 to 8 weeks if reinfection is likely.
- can be used with carbon disulfide for gastrophilus
- contraindications: not for severely debilitated horses, or those with colic toxemia nor infectious disease
- Not for use in horses intended for food.

Probenzimidazoles

- **Mode of action** metabolized in liver to fenbendazole and oxfenbendazole blocks energy metabolism parasites resistant to benzimidazoles are also resistant to probenzimidazoles
- Wide safety margin
- No known contraindications except in pregnant dogs or cats**.**

Horses

- **Anthelimenthic spectrem**: small and large stronglus, parascaris, oxyuris
- Safe for any age horses and any breeding status
- Dose:6mg/kg orally
- Available as a suspension ,paste or top dressing
- Can be combined with trichloform for gasterophilus.

Dogs and cats

- **Anthelimenthic spectrem**
- Dogs: ancylostoma, toxocora toxascaris trichuris
- Cats: ancylostoma toxoscor toxoscaris
- Dose:
- Dogs and cats over 6 months :10mg/kg daily for 3 days
- Puppies and kittens under 6 months: 15mg/kg daily for 3 days.
- Use on fill stomach for puppies and kittens under 6 months
- Safe effects: transient loose stool is possible
- Toxicity: repeated overdose caused 2 of 4 dogs to die, no adverse reaction in otherwise healthy cats, but overdose caused death in cats with pre-existing kidney and liver dysfunction.

Experimental section

Step 1: synthesis of 2- glycyl- 1 – H-isoindole -1,3(2H)-dione (A) (yield_95%)

0.5gm of glycine and 1.0gm of phthalic anhydrate were taken in a test tube and immersed in a previously heated sand bath. The mixture was stirred occasionally during the first 10 mins and any phthalic anhydrate which sublimed was pushed down into the reaction mixture till there was complete fusion. The mixture was kept undisturbed for 5min when the liquid mass solidified. The solid obtained wast then recrystallised from 10%ethanol.

Step 2: synthesis of 2-methyl (benzimidazolyl)-1H-isoindole- 1,3,2(H) dione.(B)

0.1mol of A and 0.1 mol of O-phynylene diamine were refluxed in 30ml of 4 N Hcl for 2hrs.the solution on cooling gave a precipitate which was filtered, dried and recrystallised from ethanol.

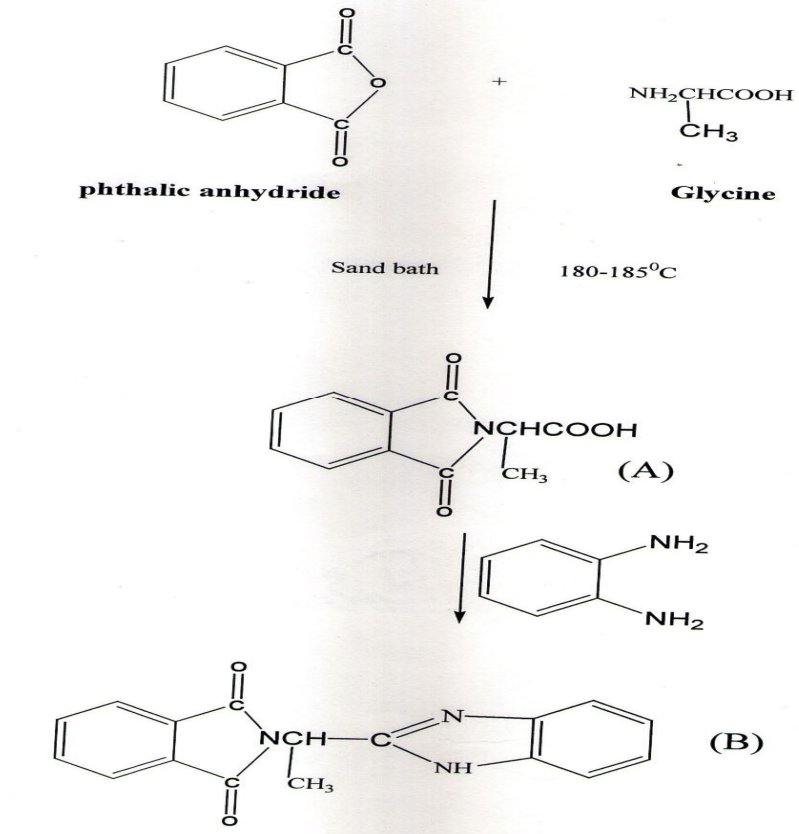
Step 3: synthesis of 2- methyl (1H-aminomethyl-sulfanilic –benzimidazolyl)1H-isoindole 1,3(2H)-dione.(C) (yield-60%)

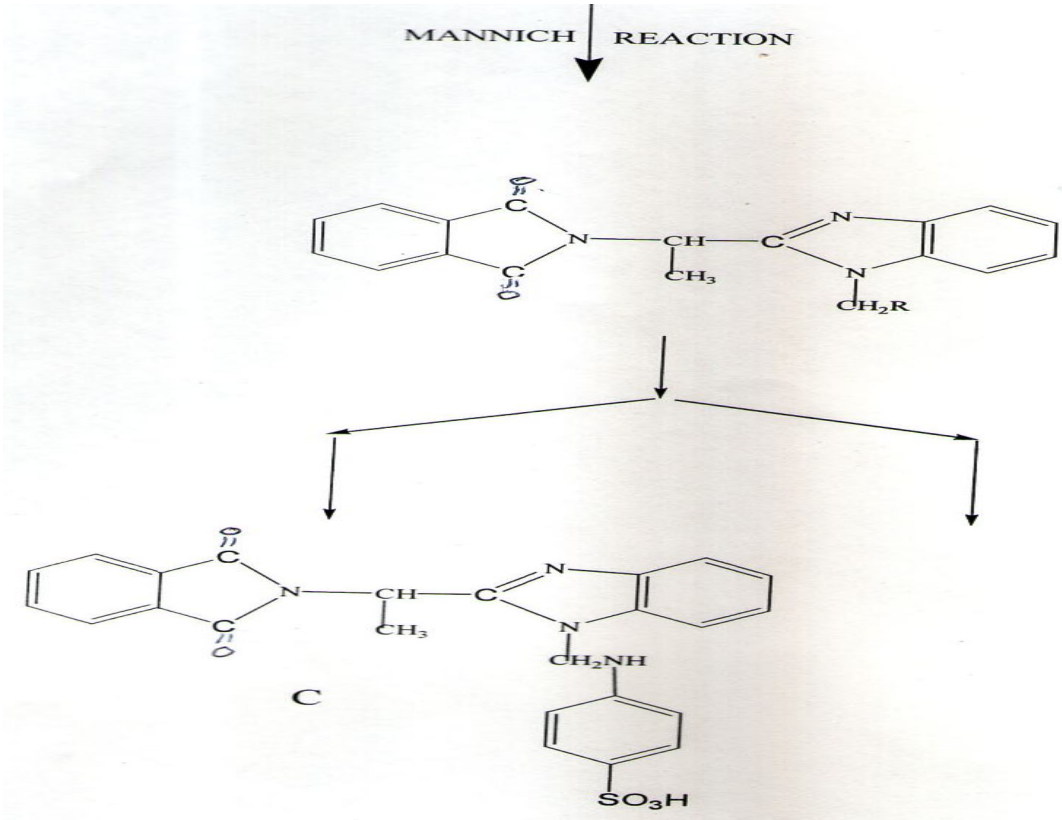
0.1 Mol of B was dissolved in 0.2 ml of 35% formaldehyde mixed in ethanol. To this was added 0.2 ml of sulfanilic acid and mixture was refluxed for 4-5 hrs on a water bath. The solution was left over night in a freezer. The solid obtained was filtered, dried and recrystallised from ethanol.

Step:4 synthesis of 2-methyl (1-H amino methyl p-amino benzoic aid-benzimidazolyl)1Hisoindole 1,3,2(H)-dione(D)

It was synthesized in the same manner as C instead of sulfanilic acid PABA was used. (yield-60%)

REACTIONS


phthalic anhydride
Glycine
Sand bath
180-185°C
(A)
(B)
MANNICH REACTION


C

Section 2

Synthesis of benzimidazole-2-one (E)

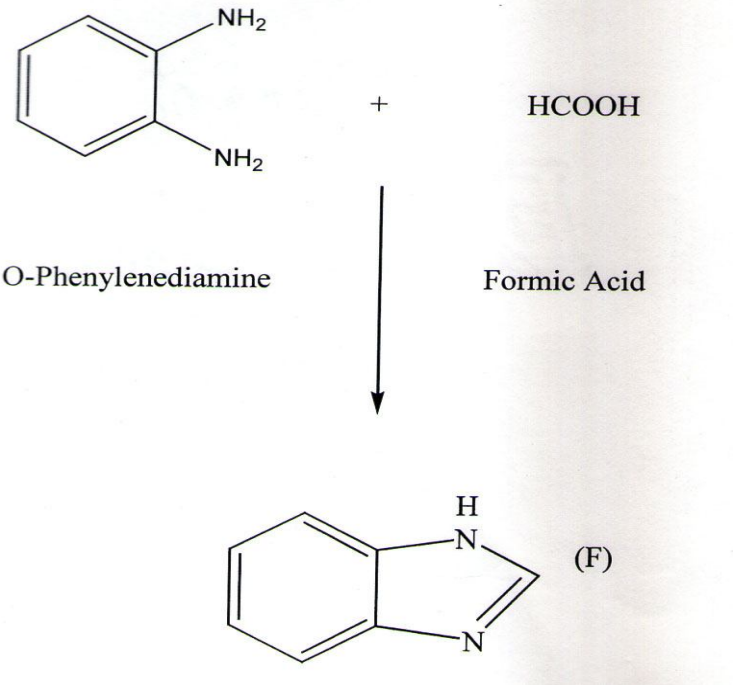
To a solution of O-phynylene diamine (5g) in DMF was added urea used (5.25g) and the mixture heated to 135-140 c for 12 hrs. when reaction was complete, the separated solid was washed with water and then dissolved in 10% NaOH solution .the aqueous alkaline solution was aq Hcl (35%).the separated product was filtered washed and dried to obtain pure product.(yield-94%)

Section 3

Synthesis of benzimidazole (F)

2grms of orthophynylene diamine was taken in a round bottom flask and to that 10ml of formic acid was added. The mixture was refluxed for 15 INS, it was cooled and 10% NaOH sol was added slowly until benzimidazole precipitate out. The precipitate was filtered washed and dried.

REACTIONS



Section 4

Synthesis of methyl benzimidazole (G)

2grms of orthophylline diamine was taken in a round bottom flask and to that 10ml of acetic acid was added. The mixture was refluxed for 15 mins, it was cooled and 10% NaOH sol was slowly until methyl benzimidazole precipitates out. The precipitate was filtered washed and dried.

RESULTS AND DISCUSSIONS

The biological screening data show that compounds a,b,c,d were found to moderately active to active against all the species with the zone of inhibition between 8mm and 12mm.rest of the compounds were ineffective. regarding antifungal activity compounds C and D were found to be moderately active against the two strains used. Remaining compounds were ineffective.

ACKNOWLEDGEMENTS

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Table 1: Anti microbial activity of the synthesized compounds

S.NO	compound	Staphylococcus auries	Protious vulgaris	E.coli	Bacillus Subtilis
1	A	±	±	±	±
2	B	±	±	±	±
3	C	±	±	++	±
4	D	±	±	++	++
5	E	-	-	±	++
6	F	-	-	-	±
7	G	-	-	-	±

(-) inactive (+) moderately active (++) most active

Table 2: Antifungal activity of synthesized compounds

S.NO	compound	Candida albicam	Aspergillus niger
1	A	-	-
2	B	-	-
3	C	±	±
4	D	±	±
5	E	-	-
6	F	-	-
7	g	-	-

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