



DESIGN AND PHARMACOCHEMICAL DEVELOPMENT OF NEW ANTHELMINTICS WITH BENZIMIDAZOLYL ARYLPROPENONE PROFILE: STRUCTURE-ACTIVITY RELATIONSHIP

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ARTICLE INFO

Received:
08 Aug 2019
Received in revised form:
14 Jan 2020
Accepted:
22 Jan 2020
Available online:
28 Feb 2020

Keywords: Benzimidazole.
Arylpropenone. Arylcyclohexenone.
Arylacrylonitrile. α -Cyano
arylpropénone. Structure-activity
relationships. Anthelmintic.
Haemonchus contortus

ABSTRACT

On the basis of our previous study, which had demonstrated the strong anthelmintic potential of benzimidazole-2-arylpropenones, we proposed to extend the anthelmintic evaluation by testing a novel series of benzimidazole against *Haemonchus contortus*. The aim of this work is to appreciate the impact of the bioisoteric replacement of arylpropenone by arylacrylonitrile. Furthermore, we have established the structural elements necessary to get good anthelmintic activities in series of 2-substituted benzimidazoles. The structure-activity relationship studies made after all biological evaluations gathered, revealed that in series benzimidazolyl-phenylpropenones, excellent anthelmintic activities similar to those of Ivermectin have been achieved with the unsubstituted phenyl derivative, with the *meta*hydroxyphenyl derivative, and by replacing the benzene homocycle with a heterocycle like pyridine or furan. Of all the variations made around the benzimidazole heterocycle, it appears that the introduction of a chlorine atom on one of the potential sites of metabolism of benzimidazole (C-5), coupled with the non-substitution of pyrrolic nitrogen, is favorable for obtaining powerful anthelmintic activities superior to those of Ivermectin and similar to those of fenbendazole. The isosteres of the arylpropenone chain, namely arylacrylonitrile and aryl- α -cyanopropenone or even its cyclized derivative (arylcyclohexenone), did not allow the enhancement of anthelmintic activities expected.

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To Cite This Article: Ouattara Mahama, N'Guessan Deto Jean-Paul, Coulibaly Songuigama, Sissouma Drissa, Koné W Mamidou, (2020), "Design and Pharmacochemical Development of New Anthelmintics with Benzimidazolyl Arylpropenone Profile: Structure-Activity Relationship", *Pharmacophore*, **11(1)**, 58-66.

Introduction

Both human and veterinary helminthiasis continues to be a growing issue in health care and at the socio-economic level. Different antiparasitic compounds have been used until now [1, 2]. In fact, with the resurgence of the resistance of antiparasitic drugs [3-5], we are witnessing a significant increase in morbidity and mortality associated with helminth infections. The medication currently used for these parasitic diseases is limited by the upsurge of drug resistance to anthelmintics (Figure 1) [6-10]. Therefore, there is considerable interest in the development of new anthelmintic compounds that are more effective and better tolerated. Interestingly, our previous pharmacochemistry studies established the promising anthelmintic efficiency of benzimidazole-based arylpropenones against *Haemonchus contortus* [11]. This greatly comforts us to pursue with particular interest the investigations of biological activities around the benzimidazoles heterocycle. Herein, we designed by a conformational blockage of propenone, cyclohexenones linked to the benzimidazole ring, to mimic the cyclic structure of flavonoids from which chalcones are derived (Figure 2) [12]. Moreover, the advent of Closantel in 1977 followed by Monépantel in 2008 in human antiparasitic therapy, highlighted the interest of the acetonitrile group as a modulator of

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anthelmintic activity [13-16]. The addition of this group to the pharmacophore styryl present in tetrahydropyrimidines anthelminticslike Pyrantel [17], has led us to new modulators of activity namely acrylonitrile and α -cyano propenones. (**Figure 2**). Thus, in this work we prepared and evaluated activities of these four chemical profiles with benzimidazole supports namely 2-arylpropenone, 2-cyclohexenone, 2-arylacrylonitrile, and 2- α -cyanoarylpropenone (**Figure 3**). By grouping all the results of anthelmintic activities of 2-substituted benzimidazole derivatives against *Haemonchus contortus*, we aimed to seek new benzimidazole anthelmintic modulators such as methylcarbamate, thiomethyl or thiazolyl. Precisely, we highlighted in a structure-activity relationship study, structural elements favorable to the induction and improvement of anthelmintic activities, both in series of 2-arylpropenone benzimidazoles and in series of 2-arylacrylonitrile benzimidazoles.

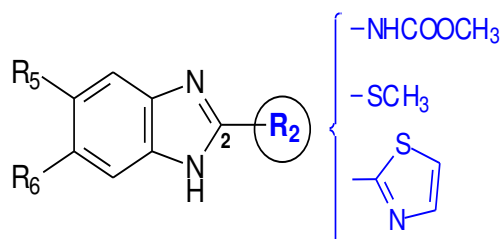


Figure 1: Old anthelmintic benzimidazoles and their pharmacophores in position 2.

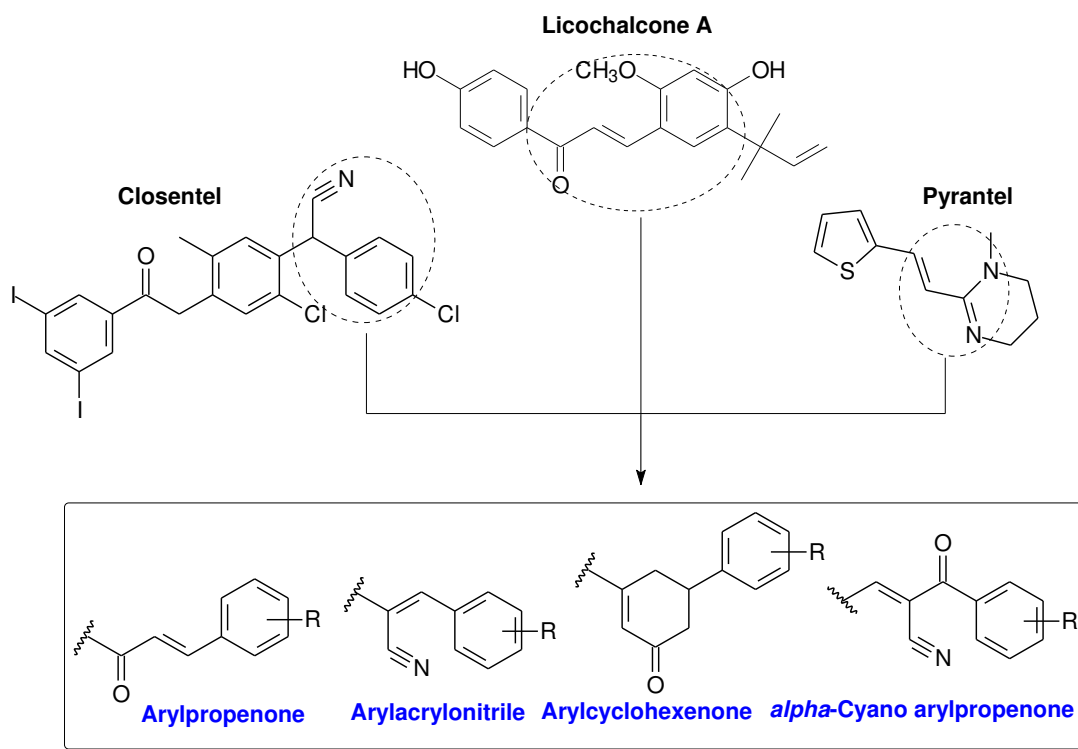


Figure 2: Design of potential anthelmintic pharmacophores.

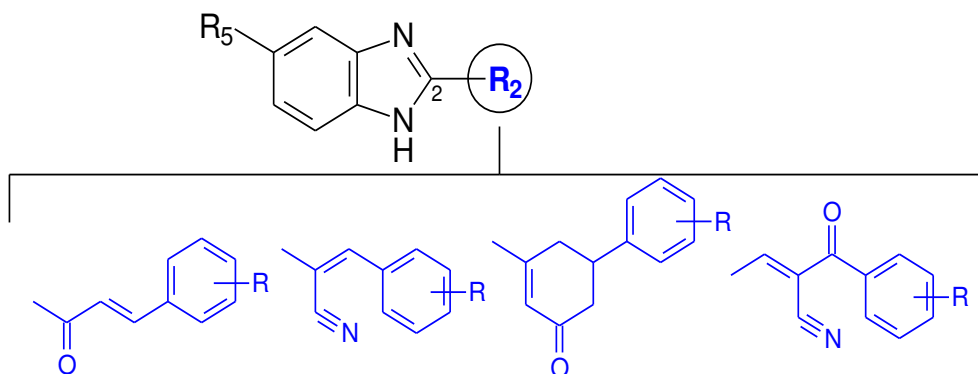


Figure 3: New potential anthelmintic benzimidazoles and their new pharmacophores in position 2.

Materials and Methods

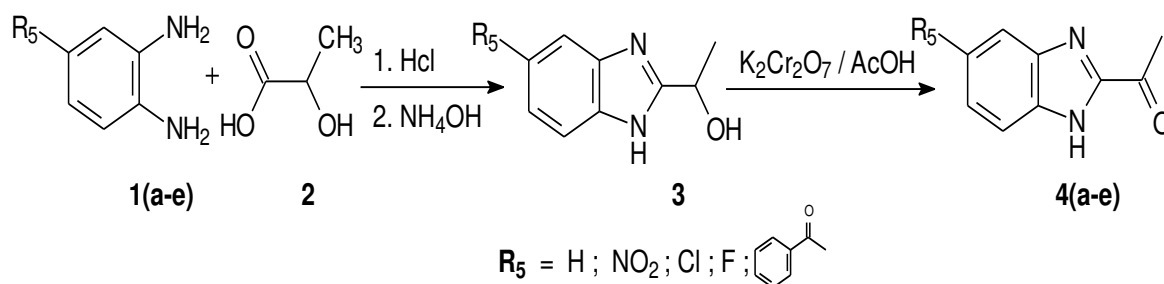
Chemistry

The descriptions of the NMR spectra, mass spectra, and melting points for all compounds were described in previous studies [11, 18-20]. The thin layer chromatographies (TLC) were performed on silica plates Macherey-Nagel Sil G/UV254 or aluminaMacherey-Nagel ALOX N/UV254. Revelation of products was performed under a UV light source (254 nm). The solvents and reagents including benzaldehydes used were purchased from Acros Organics (France) or Aldrich (France). Standard antiparasitic drugs, Fenbendazole, and Ivermectin were purchased from SIGMA Chemical Co. (USA).

General method for synthesis of compounds: Formation of benzimidazolyl-arylpropenones and its cyclohexenone derivatives (7a to 7u)

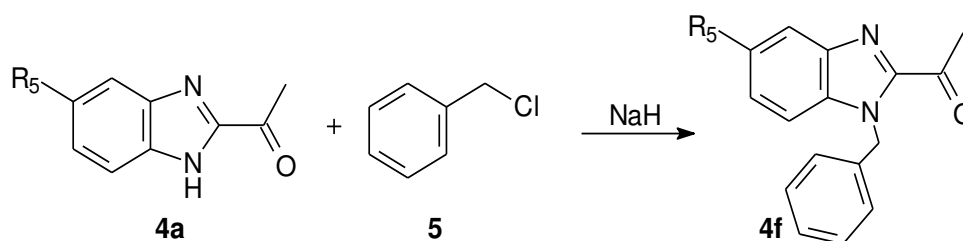
Step1: Formation of the 2-acetylbenzimidazoles **4a-e**.

A mixture of orthophenylenediamine suitably chosen **1a-e** (42 mmol), and lactic acid (**2**) (60 mmol) was stirred in 4N hydrochloric acid (50 mL), then heated at reflux for 45 mins. After the completion of the reaction (monitored by TLC), the cooled reaction mixture was alkalized using ammonia. The solid obtained was filtered off, washed with water, and recrystallized with water. The desired product 2- hydroxyethylbenzimidazole (**3**) was isolated in high yields in the essentially pure form. To a solution of 2- hydroxyethylbenzimidazole (22 mmol) in 30 mL of acetic acid was added 10 mL of an aqueous solution of potassium dichromate (11 mmol). The reaction mixture was heated under reflux for 45 min. The precipitate afforded after cooling and neutralization with ammonia was filtered off and then taken up in chloroform. The organic layer was then washed with water, dried over magnesium sulfate and then evaporated under reduced pressure. The solid of 2-acetylbenzimidazole and its derivatives **4a-e** were obtained in an overall yield of 72% after recrystallization in water/Ethanol (1:1) [19] (**Scheme 1**).



Scheme 1: Synthesis of 2-acetylbenzimidazole and its derivatives C5 substituted

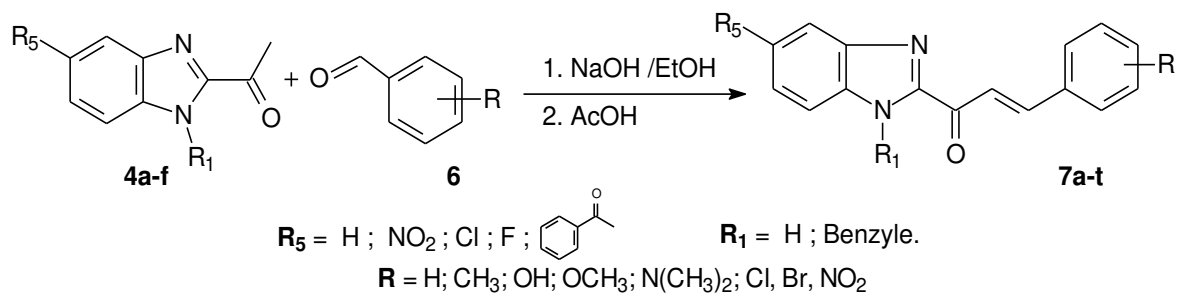
Then, from methyl ketone **4a**, we carried out an *N*-benzylation reaction using benzyl chloride and sodium hydride. As a result of purification by recrystallization, the benzyl derivative **4f** was isolated in 71% yield (**Scheme 2**) [18, 19].



Scheme 2: Synthesis of *N*-benzyl 2-acetylbenzimidazole.

Step 2: Formation of benzimidazolyl arylpropenones C-5 substituted **7a-t**.

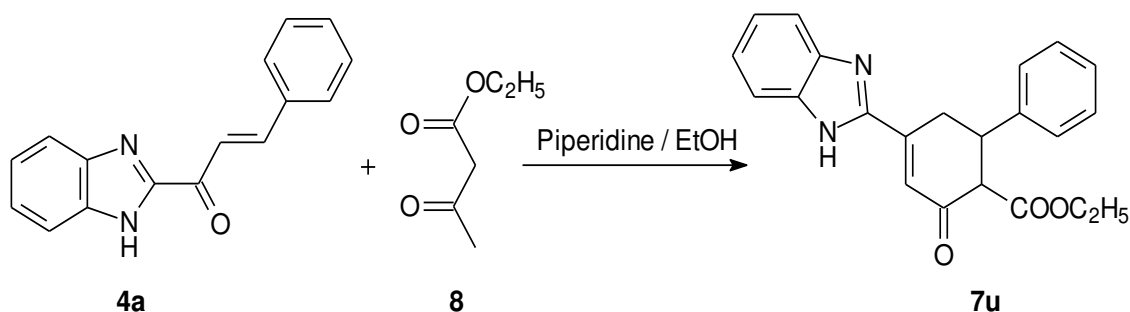
To 2-acetylbenzimidazoles **4a-f** (10 mmol), was added arylaldehyde **6a-m** (10.1 mmol) properly chosen and the mixture was stirred in an ethanolic solution of sodium hydroxide (75 mmol of sodium hydroxide in 40 mL of ethanol) at room temperature for 3 to 5 hours. The alkalization of the middle using a solution of acetic acid to 30% afforded a precipitate. The achieved precipitate was filtered, dried, and recrystallized to yield benzimidazolyl arylpropenones **7a-t** (50-86%) as crystals (**Scheme 3**) [11, 18, 19].



Scheme 3: Synthesis of the benzimidazolyl arylpropenones C-5 substituted.

Step 3: Formation of benzimidazolyl arylcyclohexenone **7u**.

Benzimidazolyl arylpropenone **7a** and ethyl acetoacetate **8** in the 1:1,2 ratio in 15 mL of ethanol were maintained in a crushed ice bath at -10°C for 2 h. Then, 0.1 mL piperidine was added and the reaction mixture was kept overnight at room temperature. The precipitate was filtered off and recrystallized from ethanol/toluene mixture (1:4) to yield a pure solid of cyclohexenone **7u** as diastereoisomeric mixture with 83% yield (Scheme 4) [19].

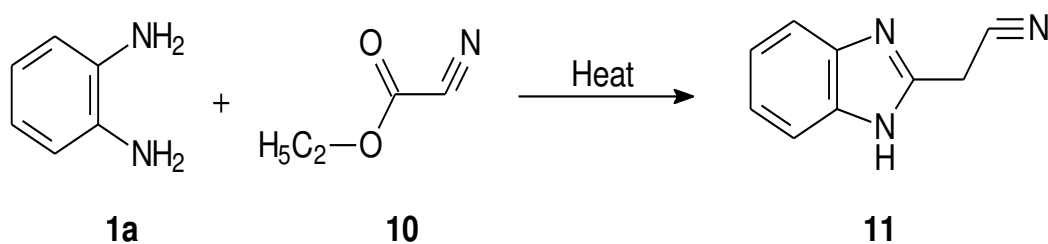


Scheme 4: Synthesis of benzimidazolyl arylcyclohexenone.

General method for synthesis of 1H-Benzimidazol-2-ylacrylonitrile (12a-h) and its analog phenyl α -cyanopropenone (14a)

Step 1: Synthesis of 1H-Benzimidazole-2-acetonitrile **11**.

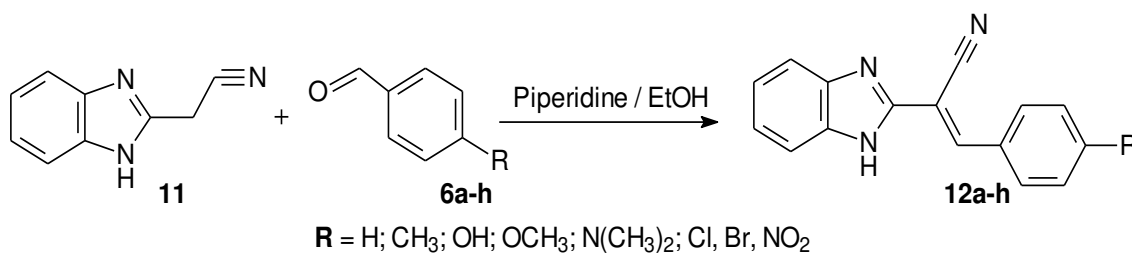
The mixture of *o*-phenylenediamines **1a** (4.2 mmol) and ethylcyanoacetate **10** (7 mmol) was heated for 2 h at 200°C . After cooling, the residue was extracted with chloroform and purified by column chromatography using EtOAc/*n*-hexane (1:1) as eluant and decolorized with activated carbon. 1H-Benzimidazole-2-acetonitrile **11** was afforded with an acceptable yield (35%) (Scheme 5) [20].



Scheme 5: Synthesis of 1H-benzimidazol-2-ylacrylonitrile.

Step 2: Synthesis of the 1H-Benzimidazolyl-2-acrylonitriles **12a-h**.

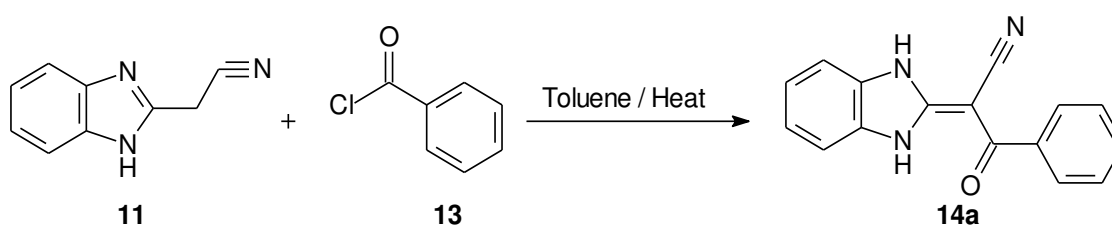
To a solution of 2-cyanomethyl benzimidazole in absolute ethanol (20 mL), equimolar suitable chosen benzaldehyde derivative and few drops of piperidine were added. The reaction mixture was heated under reflux for 2–6 h. Then cooled to room temperature and excess of ethanol was evaporated at reduced pressure. Freshly distilled water was added to the crude mixture and the precipitated product was filtered and dried. The pure product **12a-h** was obtained by recrystallization from methanol (Scheme 6) [20].



Scheme 6: Synthesis of the 1*H*-Benzimidazolyl-2-acrylonitriles

Step 3: Synthesis of 1H-Benzimidazolyl-2-phenyl α-cyanopropenone 14a.

A suspension of 2-cyanomethyl benzimidazole **11** (1.5 mmol.) and benzoyl chloride **13** (3 mmol) in dry toluene (20 mL) was heated under reflux for 5 h. The reaction mixture was cooled to 20°C before filtration. The residue was then washed with water (3 x 5 mL), then crystallized from acetic acid and dried yielding benzimidazolyl phenyl α-cyanopropenone **14a** (60%) (Scheme 7) [20].



Scheme 7: Synthesis of 1*H*-Benzimidazolyl-2-phenyl α-cyanopropenone

Anthelmintic activities

The *in vitro* screening of anthelmintic activities of 21 arylpropenones derivatives, 9 arylacrylonitriles derivatives, and structural analogs was carried out on a helminthic strain of *Haemonchus contortus* furnished by Swiss Center for Scientific Research in Côte d'Ivoire by the Larval Development Assay (LDA) [21-23]. The tests were conducted in triplicate with all the products that showed activity. The tests were performed compared to two reference drugs namely Fenbendazole and Ivermectin.

Results and Discussion

The results obtained at the end of the evaluation of antilarval activity against *H. contortus* of the new benzimidazole derivatives, the Fenbendazole and Ivermectin gathered in **Tables 1, 2, and 3**. The activity of each product is given by its larvicidal concentration 100 (LC₁₀₀) expressed in micromolar (μM).

Table 1: *In vitro* anthelmintic activities of reference substances against *Haemonchus contortus*.

Reference substances' names	LC ₁₀₀ (μM)
1,3-diphenylpropenone (Chalcone)	57.210
Fenbendazole	0.002
Ivermectin	0.010

Table 2: *In vitro* anthelmintic activities of benzimidazolyl-arylpropenones and structural analogs (**7a-u**) against *Haemonchus contortus*.

Chemical structure	Compound code	R	LC ₁₀₀ (μM)
	7a	H	0.007
	7b	2-CH ₃	43.220
	7c	3-CH ₃	10.310
	7d	4-CH ₃	0.574
	7e	2-OH	10.240
	7f	3-OH	0.007
	7g	4-OCH ₃	2.310
	7h	2-Cl	0.535
	7i	4-Cl	40.260

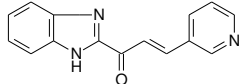
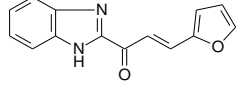
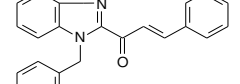
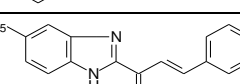

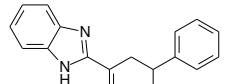
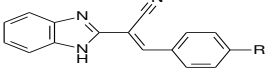
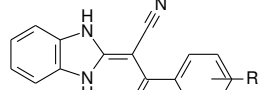
	7j	3-Br	0.466
	7k	4-F	42.610
	7l	3-NO ₂	0.030
	7m	4-NO ₂	9.278
	7n	-	0.007
	7o	-	0.008
	7p	H	>33.940
	7q	Cl	0.002
	7r	F	0.566
	7s		8.144
	7t	NO ₂	>41.02
	7u	H	32.130

Table 3: *In vitro* anthelmintic activities of benzimidazolyl-arylacrylonitriles and structural analog against *Haemonchus contortus* (**12a-h**, **14a**).

Chemical structure	Compound code	R	LC ₁₀₀ (μM)
	12a	H	46.39
	12b	CH ₃	>44.01
	12c	OH	>43.69
	12d	OCH ₃	>41.58
	12e	N(CH ₃) ₂	>39.78
	12f	Cl	>40.95
	12g	Br	35.57
	12h	NO ₂	>39.53
	14a	H	43.69

The results of the relationship between structure and activity revealed that the introduction in position 2 of the benzimidazole nucleus of the arylpropenone functional chain of chalcones to obtain a benzimidazolyl-phenylpropenone **7a** allowed to induce anthelmintic activities of 0.007 μM. It appears that our design undertaken, made possible to obtain a remarkable anthelmintic compound.

The arylpropenone group can, therefore, be considered as a new anthelmintic performance modulator, like the methylcarbamate, thiomethyl or thiazole of traditional benzimidazole anthelmintic [24]. This result corroborates the intrinsic anti-infectious (antiviral, antibacterial, antifungal, and antiparasitic) potentials of the benzimidazole ring and the arylpropenone group of chalcones [25-27]. Moreover, the anthelmintic activity of some compounds derived from benzimidazole 2-phenylpropenone **7a** was found to be dependent on the substitution at different levels of its structure (**Figure 4**).

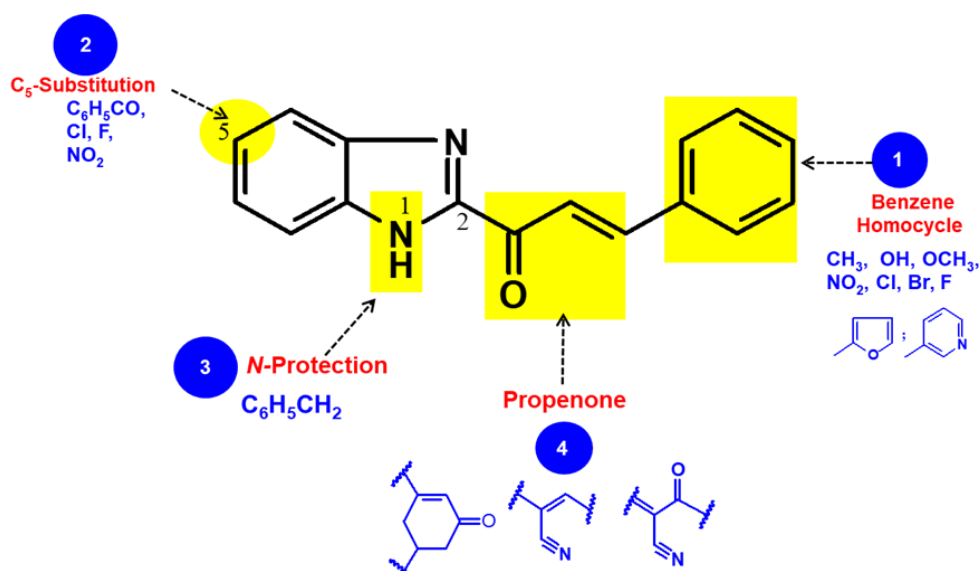


Figure 4. Pharmacomodulation sites of benzimidazolyl arylpropenone.

Structural variations of the benzene homocycle.

The structural variations around the benzene homocycle of **compound 7a** led to the following findings: the substitution of a homocyclic ring with a methyl group leads to a decrease of the anthelmintic activities observed with **compound 1a** ($LC_{100} = 0.0075 \mu M$) whatever the isomeric position of this group is. In addition, the larvicidal activities of all methylated derivatives remain insufficient compared to those of references namely Ivermectin ($LC_{100} = 0.0103 \mu M$) and Fenbendazole ($LC_{100} = 0.0017 \mu M$).

The orientation of the hydroxyl group proved to be important, as when it is in the *meta* position. Indeed, only the *meta* hydroxylated derivative **7f**, with an activity of $0.007 \mu M$ showed anthelmintic activity similar to those of benzimidazolyl phenylpropenone **7a**. In contrast, the *O*-methylated derivative in the *para* position **7g** did not achieve an anthelmintic activity as good as its *m*-hydroxy analog. The chlorination in *ortho* or *para* position of benzene homocycle of **7a** (**7h** and **7i** respectively) led to fewer contacts to residues in the binding pocket with a decrease in the larvicidal activity of up to $40 \mu M$. Replacing the chlorine in *para* position **7i** with a fluorine **7k** maintains activity around $40 \mu M$. With an anthelmintic activity at $0.5 \mu M$, the *meta*-brominated derivative **7j** seems to fit in the target pocket, suggesting that the electro-attractive effect of the halogen group is likely to have a positive influence in the *ortho* or *meta* position of the benzene homocycle.

Likewise, the electron attractive property of the nitro group (**7l** and **7m**), is most likely to have relevance in improving biological activity in the *meta* position of the benzene ring ($LC_{100} = 0.03 \mu M$). This activity, remain beneath those of the non substituted derivative. Finally, the replacement of the benzene homocycle with a heterocycle of pyridine **7n** or furanic **7o** led to the maintenance of anthelmintic activity around $0.007 \mu M$. Such efficiencies are indeed superimposable with those of benzimidazolyl-phenylpropenone (about $7 nM$). It emerges from all the aforementioned modulations carried out around benzene homocycle that obtaining excellent anthelmintic activities superimposable on those of Ivermectin is based either on non-substitution of the benzene homocycle, or on the presence of a *meta* hydroxyl group on the benzene homocycle, or on replacement of the benzene homocycle with a pyridine or furanic heterocycle.

Structural variations of the benzimidazole heterocycle.

Anthelmintic screening of derivatives resulting from the C5 modulation of benzimidazole suggested that the presence of a benzoyl group (**7s**) as in the Mebendazole molecule, or a nitro **7t**, leads to a decrease or even a total loss of anthelmintic efficacy. Indeed, with LC_{100} respective of about 8 and up to $41 \mu M$, the anthelmintic performance of these derivatives was much lower than those of benzimidazolyl phenylpropenone. In addition, it appears that the chlorine atom at the 5-position of the benzimidazole ring **7q** has increased by about 4 times the anthelmintic activity of that of its non-chlorinated analog **7a**. This modulator in the molecule of Triclabendazole [28] induced remarkable activity (up to $1.7 nM$). This anthelmintic efficacy is superimposable to that of Fenbendazole and is about 5 times more active than Ivermectin. Notwithstanding, the replacement of chlorine by Fluorine **7r** did not enhance the anthelmintic activity.

Considering only the difference in *N1*, it would be able to deduce that bulky groups like the benzyl group in the pyrrole nitrogen of benzimidazole nucleus (**7p**) are unfavorable to the activity ($LC_{100} > 34 \mu M$). This absence of activity confirms that free pyrrole nitrogen is essential to induce good activity in a series of anthelmintic benzimidazole drugs [24]. Based on all the foregoing variations, it appears that the introduction of a chlorine atom on one of the potential sites of metabolism of benzimidazole, coupled with the non-substitution of pyrrolic nitrogen, is favorable to obtain powerful anthelmintic activities superior to those of Ivermectin and superimposable to those of Fenbendazole.

Structural variations of propénone.

In the first place, it was cyclized to cyclohexenone **7u** like ethyl 4-(3-bromophenyl)-6-(6-methoxy-2-naphthyl)-2-oxocyclohex-3-ene-1-carboxylate which has shown interesting anti-infectious activities *in vitro* [27]. Such a variation, which introduces a conformational restriction, has not been shown to be appropriate for improving the anthelmintic activities of the cyclohexenone derivative, whose concentration is 32 μ M. In a second modulation, we replaced propenone with acrylonitrile through the bioisosteric substitution of $-\text{CO}$ by $-\text{CN}$, while maintaining the previously introduced modulators of benzimidazolyl arylpropenones [28]. Since all the tested acrylonitrile derivatives **12a-h** showed no-to-moderate anthelmintic activity against *Haemonchus contortus*, it can be inferred that the addition of additional carbon on the α,β -ethylenic chain is unfavorable to the interaction with the biological target. As far as we know that some α,β -unsaturated nitrile-containing drugs are conjugated with additional electron-withdrawing groups to facilitate Michael additions as in entacapone [26], we further designed the α -cyanopropenone resulting from the introduction of the nitrile adjacent to a hydrogen bond acceptor, a ketone group. Surprisingly, This derivative was less effective than propenone isostere. Like previously, this suggests that the concept of bioisostery did not ameliorate anthelmintic properties. As a result of the previous modulations around propenone, the cyclization thereof in cyclohexenone or its replacement by acrylonitrile or an α -cyanopropenone is not propitious to the improvement of anthelmintic activities.

Conclusion

Interesting trends have been observed in structure-activity relationship studies carried out from the anthelmintic activities of 2-substituted benzimidazole derivatives against *Haemonchus contortus*. These findings can be summarized in three major points. Firstly, the presence of chlorine-type halogen at position 5 on the benzimidazole nucleus, doubled with the presence of pyrrole nitrogen of a secondary nature, may be considered a real scaffold for anthelmintic activities. The substitution of the $-\text{NH}-$ group in the benzimidazole ring by a hydrophobic benzyl group drastically decreased the anthelmintic activity. Secondly, the arylpropenone functional group at the 2-position of benzimidazole would be an excellent modulator of anthelmintic activities such as methylcarbamates and thiomethyls of anthelmintic benzimidazoles used therapeutically. Finally, nitrile does not function as a ketone bioisostere, which proves that the ketone group in the arylpropenone chain is likely to be involved in specific, non-polar interactions with the target. Similarly, aryl- α -cyanopropenones or aryl cyclohexenone derivatives exhibited very weak larvicidal activity against *Haemonchus contortus*.

Acknowledgments

The authors thank the Swiss Center for Scientific Research in Ivory Coast (CSRS-CI) for carrying out anthelmintic tests, and the CEISAM Laboratory of the University of Nantes for NMR and MS spectra.

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