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Full Length Research Paper

Synthesis and *in vitro* nematicidal activity of new chalcones vectorised by imidazopyridine

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A series of 3-(3-Arylpropenoyl)imidazopyridine (5a to z) was synthesized by crotonization reaction of 2-methyl-3-acetylimidazopyridine with arylaldehyde derivatives. Structural determination of these new chalcones was done by ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR and electrospray ionization (ESI) mass spectroscopy. All compounds have been evaluated *in vitro* for their anthelmintic activities against *Haemonchus contortus*. Compounds 5n, 5s, 5t and 5w showed a great nematicidal activity (LC_{100}) ranging between 0.0005 and 0.002 µg/ml. The activity of these four chalcones was equivalent to that of fenbendazole and ivermectin which were reference anthelmintic drugs. This study has shown that imidazopyridine-chalcone derivatives are promising candidates for the development of new anthelmintic agents.

Key words: *Haemonchus contortus*, imidazopyridine, chalcone, nematicidal activity.

INTRODUCTION

The chalcone derivatives or 1,3-diphenyl-2-propen-1-ones are known for their multiple anti-infective activities (Dimmock et al., 1999; Zdzislawa, 2007). Several studies have shown that these compounds are active on infectious germs by inhibiting certain enzymes having thiol function, such as glutathione S-transferase (Li et al., 1995; Awasthi et al., 2009). They may prevent or delay inactivation, degradation and excretion of anti-infective drugs (Coles and Kadlubar, 2003; Awasthi et al., 2009). Moreover, their action could also delay or even prevent emergence of new drug-resistant strains of parasites (Kotze et al., 2006; Robinson et al., 2004). Such property could be exploited in the design, the synthesis and the development of novel anthelmintic agents. Indeed, despite the diversity of chalcones anti-infective properties, their anthelmintic activity was rarely reported. Moreover resistance to anthelmintic agents observed in some parasites, in particular *Haemonchus contortus* (Roos et al., 1990) was the principal cause of the appearance of several veterinary and economic problems (Geerts and Gryseels, 2000; Waller, 2003; Hassan et al., 2011). It is now a real threat to food security, especially in tropical and subtropical regions where its prevalence may reach 100% (Kaplan, 2004; CEDEAO, 2008; Kaboré et al., 2009). The main reason for this is related to the current misuse of usual anthelmintic drugs. Owing of their therapeutic efficacy, fight against *Haemonchus* was confined to the systematic use of various drugs especially those with benzimidazole structure (albendazole, mebendazole, fenbendazole, etc.) (Reynold, 1993). This led to the emergence of resistant parasite strains to these benzimidazole anthelmintics. The search for new molecules that can fight effectively against *Haemonchus*

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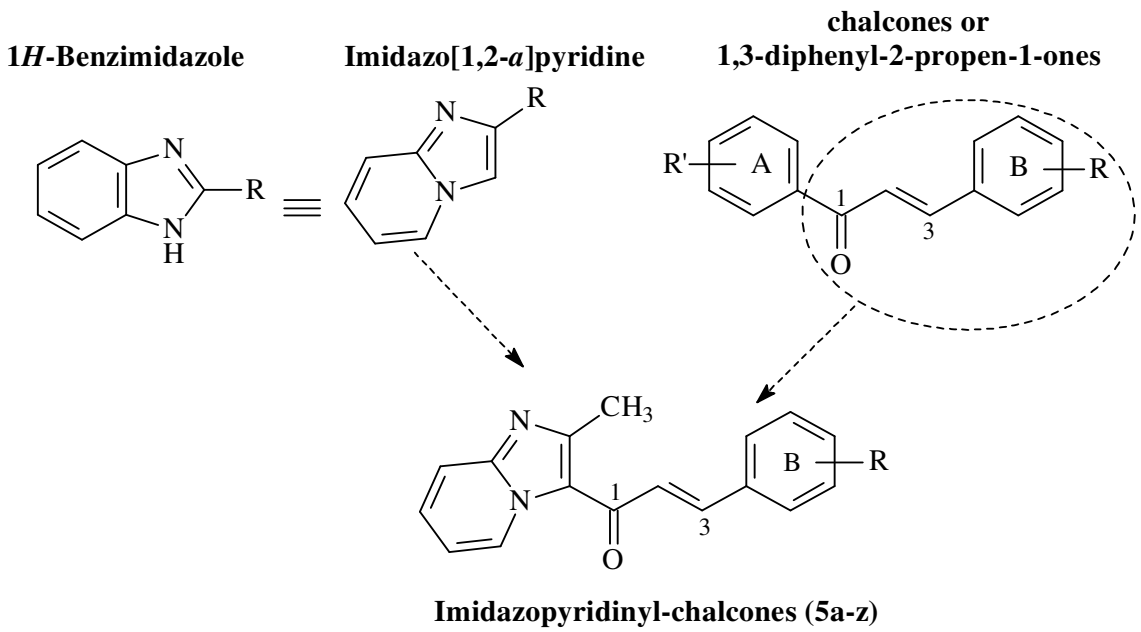


Figure 1. Design of chemical profile of imidazopyridinyl-chalcone derivatives.

becomes crucial. In this context we are interested in chalcones and the imidazo[1,2-a]pyridine heterocyclic. The latter is known as a bioisostere of benzimidazole which is the fundamental heterocyclic of principal anthelmintic drugs. In addition, the imidazopyridine ring like chalcone derivatives possesses many anti-infective properties including antibacterial (Ertepinarl et al., 1995; Gui-Bai et al., 2007), antiviral (Chafiq et al., 1999; Kristjan and Brian, 2007), antiprotozoal (Tesfaye et al., 2006) and anthelmintic, especially (Fisher and Lusi, 1972; Richard et al., 1981). Therefore, the imidazopyridine ring could replace the benzimidazole ring in the design and the development of new anthelmintic agents. Also, base on the medicinal chemistry concepts of juxtaposition of bioactive entities, we have undertaken the synthesis of new chalcones carrying this imidazopyridine heterocyclic as vector (Figure 1). The imidazopyridinyl-chalcone derivatives obtained for the first time have been evaluated for their anthelmintic properties especially nematicidal activities against *H. contortus*. The other aspect of this study is to establish some structural elements which have led to induction and increased anthelmintic properties of imidazopyridinyl-chalcone derivatives.

MATERIALS AND METHODS

Chemistry

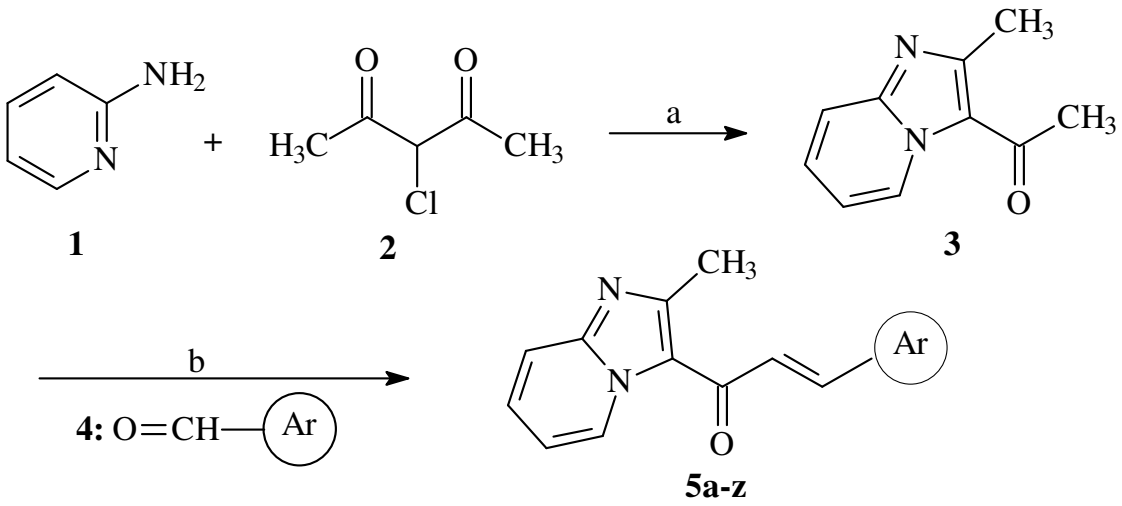
Synthesis of imidazopyridinyl-chalcones was made from 3-acetyl-2-methylimidazopyridine 3. This compound was obtained in one step from 2-amino pyridine 1 and 3-chloro-pentan-2,4-dione 2 (Starrett et al., 1989). Compound 3 undergoes a Claisen-Schmidt condensation with aromatic aldehydes (Figure 2). Specifically, the report of the general method for the synthesis of our chalcones is as follows: 1.5 g (8.62 mmol) of 3-acetyl-2-methyl imidazopyridine 3 was dissolved in ethanol solution of sodium hydroxide (64.6 mmol sodium in 40 ml of ethanol) and 8.62 mmol of benzaldehyde derivatives 4 was added. The mixture was left at room temperature and stirred for 5 h. After neutralizing with a solution of 30% acetic acid, the precipitate obtained was dried and then recrystallized to give compounds 5a to z.

For all compounds, melting points were determined on a Köpfler bench and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Brucker Avance 300 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS, δ = 0) used as internal reference in dimethyl sulfoxide (DMSO)-*d6*. Splitting patterns have been designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; qt, quintuplet; m, multiplet. Mass spectra were recorded on a JEOL JMS DX300 spectrometer on mode ESI. The thin layer chromatography (TLC) was performed on silica plates Macherey-Nagel or alumina G/UV254 Macherey-Nagel ALOX N/UV254. Solvents and reagents including arylaldehyde derivatives used were from Aldrich (France).

Nematicidal activity

The anti-haemonchus activities of compounds 5a to z were evaluated on larvae of *H. contortus* and their efficacy as compared to standard anthelmintic drugs (ivermectin and fenbendazole). Furthermore, we have evaluated the nematicidal activity of reference chalcone for the purpose of highlighting some important structural elements for anthelmintic activity. Nematicidal concentrations or larvicidal concentrations (LC_{100}) of all compounds were expressed in micrograms per milliliter (µg/ml).

The method for determining nematicidal activity or larval development assay required *H. contortus* eggs. Their preparation consists in an experimental infection of farmed sheep from 3000 to



Conditions and reagents: (a) EtOH, reflux, (b) $NaHCO_3$ 10%; (b) NaOH/EtOH, 25°C, AcOH 30%.

Figure 2. General procedure for synthesizing imidazopyridinyl chalcones 5a to z.

6000 infective larvae of *H. contortus* L3. After a period of 21 days, the faeces of sheep are infested with parasite eggs. A number of 3000 eggs per gram of faeces have been considered reasonable to perform the anthelmintic tests. The eggs were extracted after grinding, filtration and centrifugation of faeces collected. The suspension was then adjusted with distilled water to a concentration of 80 eggs per 20 ml. The standard anthelmintic drugs (fenbendazole and ivermectin from Sigma Chemical Co, USA) and compounds 5a to z were provided as pure powder. The reference chalcone or 1,3-diphenylpropenone was synthesized in our laboratory according to the classical Claisen-Schmidt using acetophenone and benzaldehyde. All tested compounds (5a to z) including anthelmintic standards drugs (7.5 mg) were, respectively dissolved in 1 ml DMSO and diluted with distilled water to obtain a serial dilution in 96 wells microtitration plates. Agar (l40 µl) at 45 to 50°C containing 2% amphotericin B was added to each well. In the prepared well, 80 eggs freshly harvested were added. The microplates were kept at a humid atmosphere (90%) for 6 days at 27°C. The normal larval development in the absence of test products was also performed in wells containing distilled water to serve as an experiment control. The number of hatched eggs and larvae were counted; stages of development and mobility of larvae were recorded. For a development rate between 0 and 5%, the tested compound was considered active. The tests were repeated three times with all compounds that showed nematicidal activity. The larvicidal concentration (LC_{100}) determined, was the lowest concentration that completely blocked the normal larval development (no hatching eggs, paralysis or death of the larvae).

RESULTS

We have designed, synthesized and characterized 26 new chalcones vectorised by imidazopyridine ring (5a to z). Phenyl group of these chalcones was substituted by different modulating electron donating, such as alkyl, hydroxy, alkoxy, aminoalkyl and halide. Furthermore, we also substituted the phenyl by electron repelling group, such as nitro. For one derivative from imidazopyridinyl-chalcones, phenyl group was replaced by a 3-pyridinyl ring (Figure 3).

Physicochemical data, especially characteristic groups (-C=N, $-CH_3$, -CO-CH=CH-) of all compounds 5a to z and their yields are reported in Table 1.

The results showed that four compounds (5n, 5s, 5t and 5w) had a high nematicidal activity ranging between 0.0005 and 0.002 µg/ml (Table 1). For the other compounds, the nematicidal concentrations are weak and range from 424.5 to 2.87 µg/ml.

DISCUSSION

The analysis of results in a structure-activity correlation study shows that the replacement of phenyl group in the reference chalcone or 1,3-diphenylprop-2-en-1-one by imidazopyridine ring (Figure 1) inhibits emergence of nematicidal activity. Indeed, compound 5a (LC_{100} = 424.5 µg/ml) is 35 times less active than the reference chalcone (LC_{100} = 12.0 µg/ml). To improve the expected activity, we introduced various substituents on the phenyl group. Thus, maintaining the imidazopyridine with the substitution of phenyl group by electron donating alkyl, such as methyl compounds (5b to d) causes a loss of nematicidal activity as compared to reference chalcone. However, this loss of activity is relatively low when the methyl is in isomeric position 3 (LC_{100} = 212.3 µg/ml) than position 2 and 4 (LC_{100} = 424.5 µg/ml). Furthermore, substitution with a substituent electron donating group having higher lipophilicity as isopropyl in position 4 (compound 5e), did not improve the larvicidal activity (LC_{100} = 424.5 µg/ml) . When phenyl group of

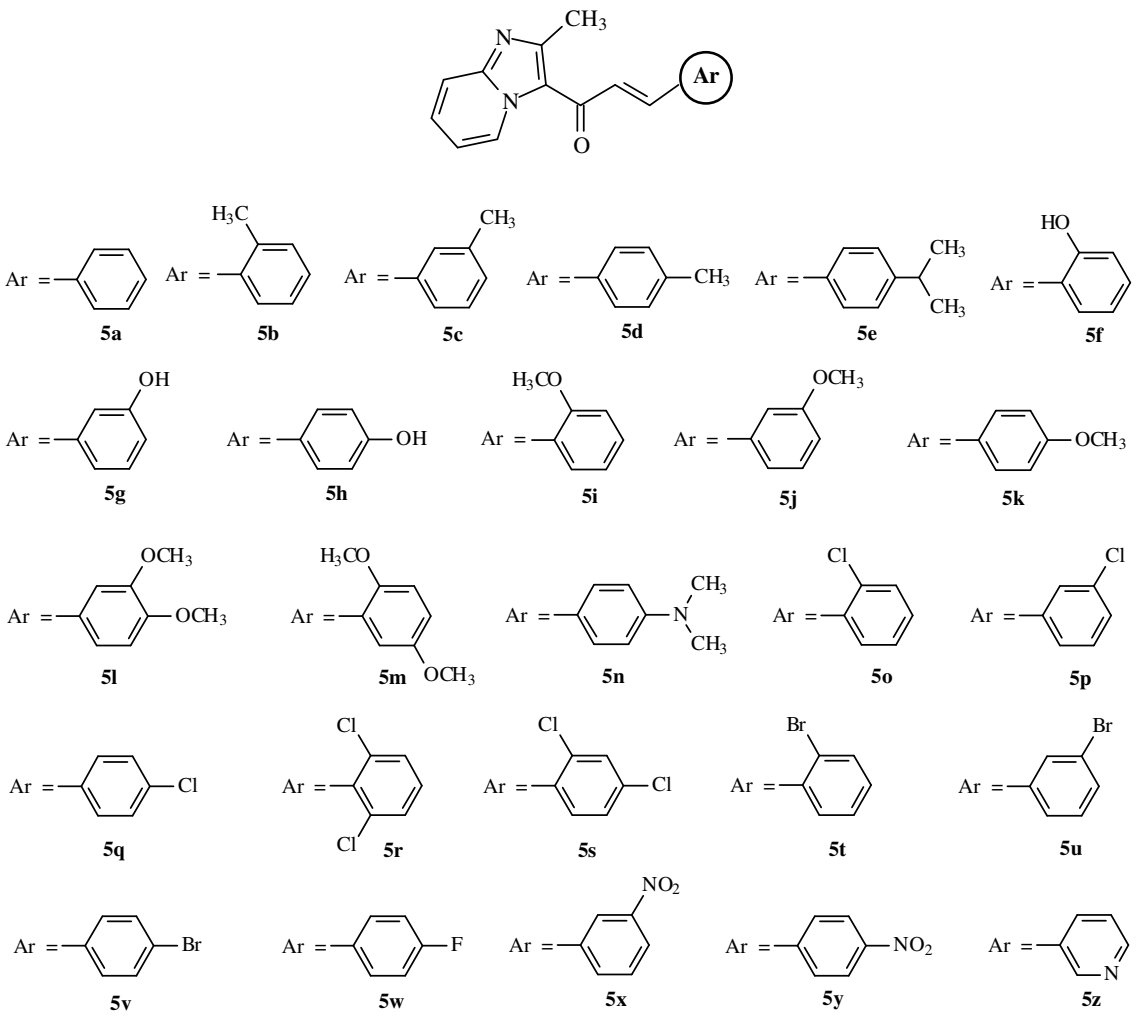


Figure 3. Structures of imidazopyridinyl-chalcone compounds (5a to z).

imidazopyridinyl-chalcone carries a hydroxy, strongly electron donating, we observed no increase in helminthicidal activity regardless of its isomeric position (5f to h: LC_{100} = 424.5 µg/ml). The replacement of hydroxy by methoxy, less electron donating increases nematicidal activities, especially when the methoxy was in position 3 (5j: LC_{100} = 2.87 µg/ml) and to a lesser extent in position 4 (5k: LC_{100} = 50.5 µg/ml). However, these activities remained significantly lower than those of ivermectin (LC_{100} = 0.00920 µg/ml) and fenbendazole (LC_{100} = 0.0005 µg/ml). As for 2-methoxy derivative, it had no nematicidal activity (5i: LC_{100} = 424.5 µg/ml) as compared to reference chalcone. Duplication of methoxy at positions 3 and 4 (5l) or 2 and 5 (5m) did not enhance the larvicidal activity (LC_{100} = 424.5 to 212.3 µg/ml). When phenyl was substituted in position 4 by dimethylamine (5n, LC_{100} = 0.0005 µg/ml), more electron donating than hydroxyl, we had an exaltation of the larvicidal activity. This was 24000 times higher than the reference chalcone. Moreover, this product had a nematicidal activity 18 times greater than that of ivermectin and equal to that of fenbendazole. The introduction of halogen on phenyl induced larvicidal activities depends on the type of halogen and its isomeric position on the phenyl. Thus, single substitution by chlorine did not induce good larvicidal activity as compared to the reference chalcone. However, substitution at positions 3 and 4 (5p and 5q) gave better larvicidal activities (LC_{100} = 50.5 µg/ml) than the 2-chloro isomer (5o, LC_{100} = 424.5 µg/ml). Surprisingly, duplication of chlorine atoms in positions 2 and 4 (5s) generated an exaltation of anti-haemonchus activity. As the derivative 5n, this compound exhibited a larvicidal concentration (LC_{100} = 0.0005 µg/ml) 24000 times lower than the reference chalcone. It also showed a larvicidal activity 18 times greater than ivermectin and equal to fenbendazole. However, the change of chlorine atoms positions in 2 and 6, has caused a total loss of nematicidal activity (LC_{100} = 424.5 µg/ml). The substitution of phenyl group by a bromine atom induced an effective larvicidal activity when the atom is fixed in

Table 1. Physicochemical data for characteristic groups and *in vitro* nematicidal activity of compounds 5a to z against *H. contortus*

Compound	Physicochemical data: ^{1}H, ^{13}C NMR (DMSO-*d6*, δ ppm) of -C=N, CH_3, -CO-CH=CH- and ESI mass	LC_{100} (µg/ml)
5a	^{1}H: 7.80 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>); 7.50 (1H, d, *J* = 15.6 Hz, C<u>H</u>=CH); 2.89 (3H, s, CH_3). ^{13}C: 179.50 (C=O); 151.98 (C=N), 141.56 (CH=<u>C</u>H); 121.69 (<u>C</u>H=CH); 18.36 (CH_3). ES^+ SM: 263 [$M+H^+$]. Recrystallization from MeCN/H_2O (1:1). Yield: 80%. Mp: 156-158°C	424.5
5b	^{1}H: 7.75 (1H, d, *J* = 16 Hz, CH=C<u>H</u>); 7.48 (1H, d, *J* = 16 Hz, C<u>H</u>=CH); 2.89 (3H, s, CH_3). ^{13}C: 179.35 (C=O); 152.04 (C=N); 141.50 (CH=<u>C</u>H); 121.70 (<u>C</u>H=CH); 18.12 (CH_3). ES^+ SM: 277 [$M+H^+$]. Recrystallization from cyclohexane. Yield: 70%. Mp: 155-157°C	424.5
5c	^{1}H: 7.75 (1H, d, *J* = 16 Hz, CH=C<u>H</u>); 7.54 (1H, d, *J* = 16 Hz, C<u>H</u>=CH); 2.81 (3H, s, CH_3). ^{13}C: 179.22 (C=O); 152.07 (C=N); 141.57 (CH=<u>C</u>H); 121.77 (<u>C</u>H=CH); 18.09 (CH_3). ES^+ SM: 277 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 71%. Mp: 127-130°C	212.3
5d	^{1}H: 7.75 (1H, d, *J* = 16 Hz, CH=C<u>H</u>); 7.48 (1H, d, *J* = 16 Hz, C<u>H</u>=CH); 2.89 (3H, s, CH_3). ^{13}C: 179.36 (C=O); 151.98 (C=N); 141.56 (CH=<u>C</u>H); 121.70 (<u>C</u>H=CH); 18.10 (CH_3). ES^+ SM: 277 [$M+H^+$]. Recrystallization from cyclohexane. Yield: 68%. Mp: 151-153°C	424.5
5e	^{1}H: 7.78 (1H, d, *J* = 15.8 Hz, CH=C<u>H</u>); 7.45 (1H, d, *J* = 15.8 Hz, C<u>H</u>=CH); 2.89 (3H, s, CH_3). ^{13}C: 179.36 (C=O) ; 151.98 (C=N) ;; 141.56 (CH=<u>C</u>H); 121.70 (<u>C</u>H=CH); 18.10 (CH_3). ES^+ SM: 305 [$M+H^+$]. Recrystallization from hexane. Yield: 58%. Mp: 132-135°C	212.3
5f	^{1}H: 7.80 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>); 7.38 (1H, d, *J* = 15.6 Hz, C<u>H</u>=CH); 2.78 (3H, s, CH_3). ^{13}C: 179.50 (C=O); 151.95 (C=N); 141.56 (CH=<u>C</u>H); 120.89 (<u>C</u>H=CH); 18.26 (CH_3). ES^+ SM: 279 [$M+H^+$]. Recrystallization from ethanol. Yield: 56%. Mp: > 260°C	424.5
5g	^{1}H: 7.80 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>); 7.38 (1H, d, *J* = 15.6 Hz, C<u>H</u>=CH); 2.78 (3H, s, CH_3). ^{13}C: 179.17 (C=O); 152.01 (C=N); 141.59 (CH=<u>C</u>H); 120.70 (<u>C</u>H=CH); 18.07 (CH_3). ES^+ SM: 279 [$M+H^+$]. Recrystallization from ethanol. Yield: 70%. Mp: 255-257°C	424.5
5h	^{1}H: 7.80 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>) ; 7.38 (1H, d, *J* = 15.6 Hz, C<u>H</u>=CH); 2.78 (3H, s, CH_3). ^{13}C: 179.39 (C=O); 151.43 (C=N); 141.97 (CH=<u>C</u>H); 121.88 (<u>C</u>H=CH); 18.10 (CH_3). ES^+ SM: 279 [$M+H^+$]. Recrystallization from ethanol. Yield: 57%. Mp: > 260°C	424.5
5i	^{1}H: 7.72 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>); 7.50 (1H, d, *J* = 15.6 Hz, C<u>H</u>=CH); 2.80 (3H, s, CH_3). ^{13}C: 179.30 (C=O); 152.05 (C=N); 141.22 (CH=<u>C</u>H); 120.90 (<u>C</u>H=CH); 18.20 (CH_3). ES^+ SM: 293 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 71%. Mp: 196-198°C	424.5
5j	^{1}H: 7.72 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>); 7.50 (1H, d, *J* = 15.6 Hz, C<u>H</u>=CH); 2.80 (3H, s, CH_3). ^{13}C: 179.30 (C=O); 152.05 (C=N); 141.22 (CH=<u>C</u>H); 120.92 (<u>C</u>H=CH); 18.03 (CH_3). ES^+ SM: 293 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 70%. Mp: 127-130°C	2.87
5k	^{1}H: 7.72 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>); 7.48 (1H, d, *J* = 15.6 Hz, C<u>H</u>=CH); 2.79 (3H, s, CH_3). ^{13}C: 179.41 (C=O); 151.70 (C=N); 141.52 (CH=<u>C</u>H); 121.89 (<u>C</u>H=CH); 18.11 (CH_3). ES^+ SM: 293 [$M+H^+$]. Recrystallization from ethyl acetate. Yield: 73%. Mp: 158-161°C	50.5
5l	^{1}H: 7.66 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>); 7.33 (1H, d, *J* = 15.4 Hz, C<u>H</u>=CH); 2.81 (3H, s, CH_3). ^{13}C: 179.45 (C=O); 148.90 (C=N); 141.92 (CH=<u>C</u>H); 121.89 (<u>C</u>H=CH); 18.0 (CH_3). ES^+ SM: 323 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 70%. Mp: 169-171°C	212.3
5m	^{1}H: 7.66 (1H, d, *J* = 15.6 Hz, CH=CH); 7.35 (1H, d, *J* = 15.4 Hz, C<u>H</u>=CH); 2.80 (3H, s, CH_3). ^{13}C: 179.60 (C=O); 146.49 (C=N); 141.92 (CH=<u>C</u>H); 121.89 (<u>C</u>H=CH); 18.16 (CH_3). ES^+ SM: 323 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 86%. Mp: 165-167°C	424.5

Table 1. Contd.

5n	1H: 7.78 (1H, d, J = 16 Hz, CH=CH); 7.45 (1H, d, J = 16 Hz, CH=CH); 2.85 (3H, s, CH3). 13C: 179.36 (C=O); 151.98 (C=N); 141.46 (CH=CH); 121.70 (CH=CH); 18.10 (CH3). ES+ SM: 306 [M+H+]. Precipitation from water. Yield: 30%. Mp: 197-200°C	0.0005
5o	^{1}H: 7.80 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>); 7.43 (1H, d, *J* = 15.9 Hz, C<u>H</u>=CH); 2.83 (3H, s, CH_3). ^{13}C: 179.20 (C=O); 152.68 (C=N); 139.90 (CH=<u>C</u>H); 120.89 (<u>C</u>H=CH); 18.16 (CH_3). ES^+ SM: 297.75 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 65%. Mp: 170-172°C	424.5
5p	^{1}H: 7.88 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>); 7.55 (1H, d, *J* = 15.9 Hz, C<u>H</u>=CH); 2.82 (3H, s, CH_3). ^{13}C: 179.15 (C=O); 152.62 (C=N); 139.85 (CH=<u>C</u>H); 120.89 (<u>C</u>H=CH); 18.16 (CH_3). ES^+ SM: 297.75 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 82%. Mp: 167-170°C	50.5
5q	^{1}H: 7.80 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>) ; 7.51 (1H, d, *J* = 15.9 Hz, C<u>H</u>=CH); 2.79 (3H, s, CH_3). ^{13}C: 180.0 (C=O); 152.62 (C=N); 139.85 (CH=<u>C</u>H); 120.89 (<u>C</u>H=CH); 18.10 (CH_3). ES^+ SM: 297.75 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 72%. Mp: 173-175°C	50.5
5r	^{1}H: 7.86 (1H, d, *J* = 16 Hz, CH=C<u>H</u>); 7.54 (1H, d, *J* = 16 Hz, C<u>H</u>=CH); 2.79 (3H, s, CH_3). ^{13}C: 179.29 (C=O); 152.78 (C=N); 139.91 (CH=<u>C</u>H); 120.89 (<u>C</u>H=CH); 18.16 (CH_3). ES^+ SM: 332 [$M+H^+$]. Recrystallization from ethyl acetate. Yield: 55%. Mp: 180-183°C	424.5
5s	1H: 7.86 (1H, d, J = 16 Hz, CH=CH); 7.54 (1H, d, J = 16 Hz, CH=CH); 2.76 (3H, s, CH3). ^{13}C: 179.29 (C=O); 152.78 (C=N); 139.91 (CH=CH); 120.89 (CH=CH); 18.16 (CH3). ES+ SM: 332 [M+H+]. Recrystallization from hexane/DCM (3:1). Yield: 90%. Mp: 197-200°C	0.0005
5t	^{1}H: 8.15 (1H, d, *J* = 15.3 Hz, CH=C<u>H</u>); 7.90 (1H, d, *J* = 15.3 Hz, <u>C</u>H=CH); 3.04 (3H, s, CH_3). ^{13}C: 178.53 (C=O); 152.67 (C=N); 138.81 (CH=C<u>H</u>); 120.89 (<u>C</u>H=CH); 18.14 (CH_3). ES^+ SM: 342 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 85%. Mp: 177-180°C	0.002
5u	^{1}H: 7.75 (1H, d, *J* = 15.3 Hz, CH=C<u>H</u>); 7.60 (1H, d, *J* = 15.3 Hz, C<u>H</u>=CH); 2.88 (3H, s, CH_3). ^{13}C: 179.13 (C=O); 152.62 (C=N); 139.80 (CH=<u>C</u>H); 121.85 (<u>C</u>H=CH); 18.13 (CH_3). ES^+ SM: 342 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 82%. Mp: 181-183°C	424.5
5v	^{1}H: 7.68 (1H, d, *J* = 15.3 Hz, CH=C<u>H</u>); 7.58 (1H, d, *J* = 15.3 Hz, C<u>H</u>=CH); 2.73 (3H, s, CH_3). ^{13}C: 179.03 (C=O); 152.58 (C=N); 139.84 (CH=<u>C</u>H); 121.85 (<u>C</u>H=CH); 18.13 (CH_3). ES^+ SM: 342 [$M+H^+$]. Recrystallization from ethanol. Yield: 84%. Mp: 207-209°C	424.5
5w	^{1}H: 7.68 (1H, d, *J* = 15.3 Hz, CH=C<u>H</u>); 7.58 (1H, d, *J* = 15.3 Hz, C<u>H</u>=CH); 2.73 (3H, s, CH_3). ^{13}C: 180.03 (C=O); 152.58 (C=N); 139.90 (CH=<u>C</u>H); 121.85 (<u>C</u>H=CH); 18.13 (CH_3). ES^+ SM: 281 [$M+H^+$]. Recrystallization from hexane/DCM (3:1). Yield: 75%. Mp: 192-194°C	0.002
5x	1H: 7.80 (1H, d, J = 15.3 Hz, CH=CH); 7.70 (1H, d, J = 15.3 Hz, CH=CH); 2.85 (3H, s, CH3). 13C: 178.96 (C=O); 152.81 (C=N); 134.16 (CH=CH); 121.88 (CH=CH); 18.13 (CH3). ES+ SM: 308 [M+H+]. Recrystallization from ethanol. Yield: 65%. Mp: 219-221°C	424.5
5y	^{1}H: 7.68 (1H, d, *J* = 15.3 Hz, CH=C<u>H</u>); 7.50 (2H, d, *J* = 15.3 Hz, C<u>H</u>=CH); 2.83 (3H, s, CH_3). ^{13}C: 178.06 (C=O); 153.01 (C=N); 134.34 (CH=<u>C</u>H); 121.0 (<u>C</u>H=CH); 18.20 (CH_3). ES^+ SM: 308 [$M+H^+$]. Recrystallization from butanol. Yield: 80%. Mp: > 260°C	424.5
5z	^{1}H: 7.68 (1H, d, *J* = 15.3 Hz, CH=C<u>H</u>); 7.50 (2H, d, *J* = 15.3 Hz, C<u>H</u>=CH); 2.85 (3H, s, CH_{ar}). ^{13}C: 178.06 (C=O); 153.01 (C=N); 134.34 (CH=<u>C</u>H); 121.0 (<u>C</u>H=CH); 18.0 (CH_3). ES^+ SM: 264 [$M+H^+$]. Recrystallization from acetone/H_2O (1:1). Yield: 44%. Mp: 210-212°C	424.5

Table 1. Contd.

1,3-diphenylprop-2-en-1-one or chalcone	12.0
Ivermectin	0.0092
Fenbendazole	0.0005

position 2 (5t, LC_{100} = 0.002 µg/ml). Although, this product has a larvicidal concentration higher than fenbendazole, it remains more efficient than ivermectin and the reference chalcone. Equally nematicidal action is found in the 4-fluoro (5w: LC_{100} = 0.002 µg/ml). When we introduced electron repelling group, such as nitro on phenyl of chalcone 5a, no nematicidal activity was observed for compounds 5x and 5y (LC_{100} = 424.5 µg/ml). The only derivative from the replacement of the phenyl group by 3-pyridinyl ring (5z) did not show a good nematicidal activity (LC_{100} = 424.5 µg/ml) as its isostere 3-nitrobenzène (5x).

Conclusion

In this study, we have synthesized 26 imidazopyridinyl-chalcones and evaluated their nematicidal activity against *H. contortus*. This preliminary study has allowed the identification some structural elements of nematicidal activities. It showed that the appearance and the maintenance of nematicidal activity in a series of imidazopyridinyl-chalcones necessarily required introduction of some electron donating group on the phenyl. Finally, this study yielded four molecules (5n, 5s, 5t and 5w) whose activities were comparable to those of references nematicidal, such as ivermectin and fenbendazole. These new chalcones could therefore be promising candidates for the development of novel anthelmintic agents.

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