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Original article

Azopyridine-imidacloprid derivatives as photoresponsive neonicotinoids

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ABSTRACT

A series of imidacloprid derivatives containing an azopyridine motif as a photoswitchable functional group were designed and synthesized. The new version of photoresponsive imidacloprid analogues showed improved solubility in comparison with their azobenzene analogues. 1.2 to 2-fold activity difference was observed for these azopyridine-imidacloprids against house fly (*Musca domestica*) and cowpea aphid (*Aphis craccivora*) upon irradiation.

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1. Introduction

The development of photoswitches provides enormous potential for applications in chemistry, biology and material science [1–7]. With an increasing number of examples, photopharmacology is rapidly developing recently [8,9]. The photocontrol of the bioactivity has many advantages over the conventional method, such as precise manipulation of activity of interest, antiresistance and avoidance of side effects. Thus, many photoswitchable pharmaceuticals have been elaborately designed and achieved by attaching a light-responsive moiety to a bioactive molecules, such as using an optical mechanism to control antibacterial activity [10], coupling a photoswitch with the propofol analogue [11,12], optical control of insulin release with photoswitchable sulfonylurea [13], photoswitchable acetylcholinesterase inhibitors [14], nociception regulators [15], mast cell activation inhibitors [16] and microtubule formation inhibitors [17].

The optical control of activity was well addressed in the pharmaceutical area but seldom used in pesticide design. We recently reported a first example of photoswitchable neonicotinoids by merging imidacloprid (IMI) with azobenzene, which facilitated the remote regulation of insecticide performance with light [18]. Activity variation upon irradiation was achieved in the above examples, but the difference was not large enough and the relatively poor solubility limited their applications.

The azobenzene is a most commonly used photoswitched motif, but it has poor solubility in water. The recently developed azopyridines (**AP**) revealed a novel type of photoswitchable molecules with excellent properties, such as quantitative rates of photoisomerization, good water solubility and slow thermal isomerization [19,20].

Enlightened by the above descriptions, therefore, to develop a novel photoswitchable version of imidacloprid, our strategy here is trying to replace the chloropyrindyl part with **AP** by sharing a common pyridine fragments, generating the target compounds (Fig. 1). Besides, we hope the introduction of the **AP** fragment would lead to the improvement of the water solubility and insecticidal activity.

2. Experimental

2.1. Chemicals and instrumentations

Melting points were recorded on a Büchi B540 apparatus (Büchi Labortechnik AG, Flawil, Switzerland) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. Electrospray ionization (ESI) mass spectrometry was performed in an HP 1100 LC-MS spectrometer.

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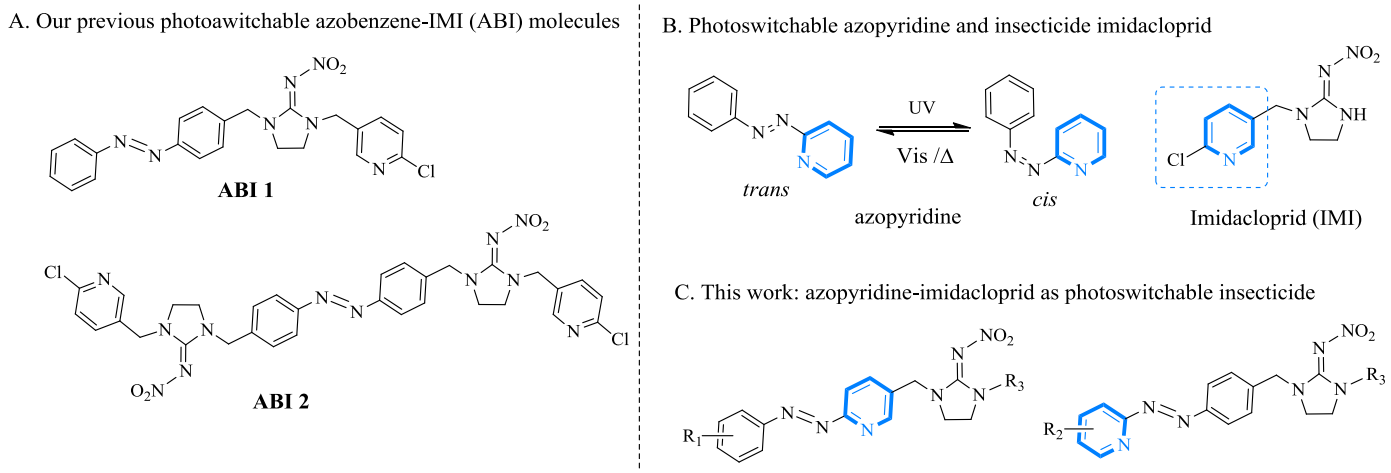


Fig. 1. Molecular design of azopyridine-imidacloprid as photoswitchable neonicotinoids.

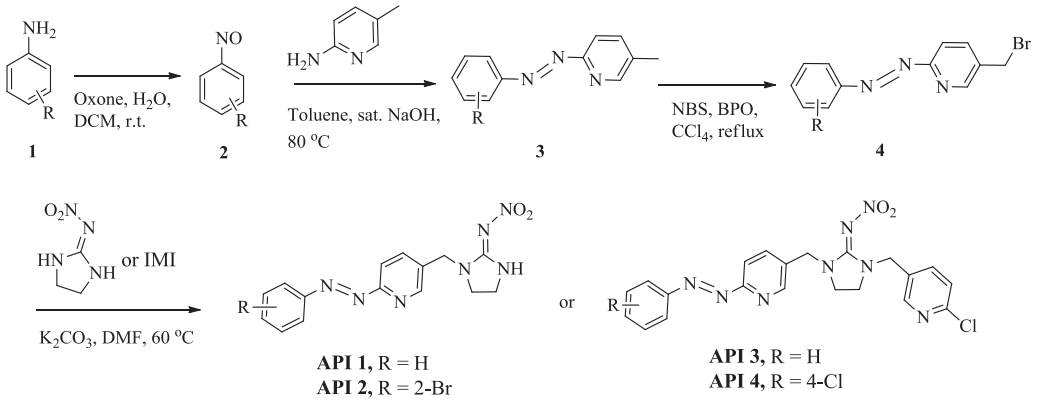
Analytical thinlayer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized under ultraviolet (UV) light. Column chromatography was performed using 200–300 mesh silica gel (Hailang, Qingdao). The water solubility of the compounds was determined by SiriusT3 (Sirius Analytical Ltd, UK). Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Yields were not optimized. All reactions were carried out under a protective atmosphere of drying nitrogen or utilizing a calcium chloride tube.

2.2. Synthesis the target compounds

Compounds **API 1–API 4** were synthesized starting from anilines (Scheme 1). Oxidation of anilines by Oxone generated nitrosobenzenes, which then reacted with 2-amino-5-methylpyridine to construct the corresponding azopyridine. Bromination of azopyridine by NBS/BPO afforded bromomethyl-intermediate, which coupled with *N*-(imidazolidin-2-ylidene)nitramide or IMI to provide the final products (Scheme 1). **API 5** was prepared by the similar procedure from *p*-toluidine and 2-amino-5-chloropyridine (Scheme 2). The synthetic procedure of **API 1** as representative is given as follow and the detailed syntheses for **API 2–5** are provided in the Supporting information.

Synthesis of methyl-2-phenyldiazenylpyridine (**3a**): Aniline (**1a**) (33.1 mmol, 1.0 equiv.) was dissolved in 100 mL of dichloromethane. To this solution was added potassium peroxymonosulfate (Oxone) (66.2 mmol, 2.0 equiv.) in 400 mL of water. The solution was stirred under nitrogen at room temperature until TLC monitoring indicated the complete consumption of the starting material (0.5 h). After separation of the layers, the aqueous layer was extracted with dichloromethane twice. The combined organic layers were washed with 1 mol/L HCl, saturated sodium bicarbonate solution, water, brine, dried (magnesium sulfate) and evaporated to dryness affording the crude nitrosobenzene (**2a**). Nitrosobenzene is directly used for the next step without further purification. Crude nitrosobenzene (3.49 mmol, 1.2 equiv.) was dissolved in 25 mL of toluene. To this solution was added 2-amino-5-methylpyridine (2.9 mmol, 1.0 equiv.). Then to this solution was added saturated aqueous solution of sodium hydroxide (12 mmol, 4.0 equiv.). The resulting mixture was stirred at 60 °C for 30 min. Then 15 mL of water was added in the mixture, after separation of the layers, the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried (magnesium sulfate) and evaporated to dryness. Purification by chromatography (petroleum ether/ethyl acetate = 10:1, silica gel) yielded the product as an orange solid. Yield 43%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, 1H, J = 2.0 Hz), 8.08–8.01 (m, 2H), 7.87 (dd, 1H, J = 8.2, 2.3 Hz), 7.72 (d, 1H, J = 8.2 Hz), 7.57–7.52 (m, 3H), 2.54 (s, 2H).

Synthesis of 5-bromomethyl-phenyldiazenylpyridine (**4a**): **3a** (10 mmol, 1.0 equiv.) was dissolved in 25 mL of carbon tetrachloride. To this solution was added benzoyl peroxide (BPO) (1 mmol, 0.1 equiv.). Then *N*-bromosuccinimide (NBS) (11 mmol, 1.1 equiv.) was partially added to this solution. The solution was stirred under nitrogen at 70 °C for 12 h. The precipitate was separated by filtration; the filtrate was washed with brine, dried (magnesium sulfate) and evaporated to dryness. Purification by chromatography



Scheme 1. Synthesis of **API 1–API 4**.

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