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Contemporary trends in development of active substances possessing the pesticidal properties: ryanodine-receptor targeting insecticides

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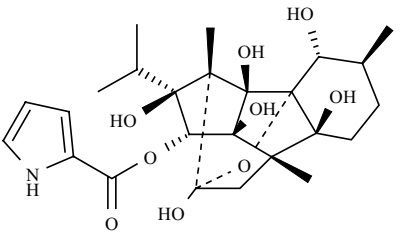
Abstract: The latest developed classes of synthetic insecticides – phthalic acid diamides and antranilic diamides, acting as ryanodine receptor modulators, are discussed. The mode of their activity, the insecticidal properties and characteristics of their representatives is reviewed.

Keywords: ryania, ryanodine, ryanodine-receptors, calcium channels, phthalic acid diamides, anthranilic diamides, flubendiamide, chlorantraniliprole, Cyazypyr

INTRODUCTION

The insecticidal properties of *Ryania speciosa* stem extract have been described and published in 1945 [1]. The extract (ryania) was served as a natural botanical insecticide by SB Penick & Co. In the early 1940s the plants of *Ryania* species were used for euthanasia and rats intoxication. The formulates comprising ryania extract, manufactured by AgroSystems International, were present at the market under the trade-marks of Natur-Gro R-50 and Natur-Gro Triple Plus. In turn, Dunhill Chemical produced a preparate trade-marked Ryan 50. However, in 1997 the use of these formulates was finished.

The extract from *Ryania* displays a limited insecticidal activity, although it is effective against some of selected insect species. The main component of ryania extract is an alkaloid ryanodine (I), which affects the ligand-gated calcium channels – called ryanodine receptors RyRs.



(I)

The latter plays an important role in controlling the release of calcium ions Ca^{2+} – universal intracellular transmitters, from intracellular stores. The flow of calcium ions is regulated by ryanodine receptors, which mediate in several metabolic and physiological cellular processes, as neurotransmission, hormones secretion, muscles excitation-contraction coupling [1]. Ryanodine works as a specific blocker of releasing the calcium ions from the sarcoendoplazmic reticulum [2, 3].

It is worth to mention, that in 1990s there were conducted research investigations on ryanodine structural modifications to increase its insecticidal activity [4].

Until recently the ryanodine receptors have not been entertained as a target in searching the new synthetic structures with insecticidal properties. This *status quo* can undergo an alteration in regard of the works done within the last years on the field of chemistry of insecticides by research teams at Nihon Nohyaku Co., Ltd. (Japan), Bayer CropScience AG (Germany) and DuPont (USA).

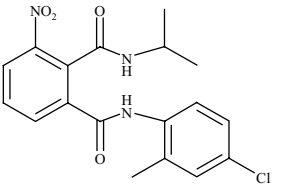
Nihon Nohyaku and Bayer CropScience AG jointly developed and marketed Flubendiamide, a first example of the phthalic acid diamides – a novel class of insecticides working as activators of the ryanodine receptor.

DuPont is developing another group of compounds that affect this receptor, called anthranilic diamides, with representatives – chloranthraniliprole (common name) and Cyazypyr™, already registered in many countries.

PHTHALIC ACID DIAMIDES. FLUBENDIAMIDE

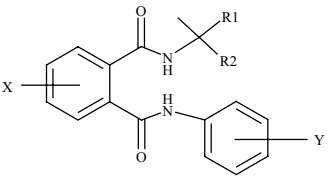
Diamides of phthalic acid and their representative – flubendiamide, were synthesized in the laboratories of previously mentioned Japanese company Nihon Nohyaku [5-9]. After, Nihon Nohyaku and Bayer CropScience have ruled to join the efforts over the commercialization of flubendiamide.

Since many years at Nihon Nohyaku research center have been carried out the wide-ranging studies in the domain of chemistry of insecticidally active substances. They resulted in the discovery of a new, benzenedicarboxyamide compound (II) displaying the insecticidal properties.



(II)

Although the level of its insecticidal activity was not satisfactory, (II) has attracted the attention of Japanese scientists because of its structure novelty and intriguing symptoms of its biological mode of action. Thus, the intensive investigations to increase the activity of the finding compound have been continued, and many compounds with the general structure (III) have been synthesized. They are, in general, derivatives of phthalic acid diamide.

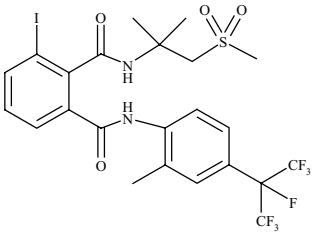


(III)

R^1 = H, CH_3; R^2 = H, $NHCOCH_3$, SO_2CH_3
X = NO_2, H, Cl, F, Br, I
Y = Cl, OCH_3, OCF_3, $CF(CF_3)_2$

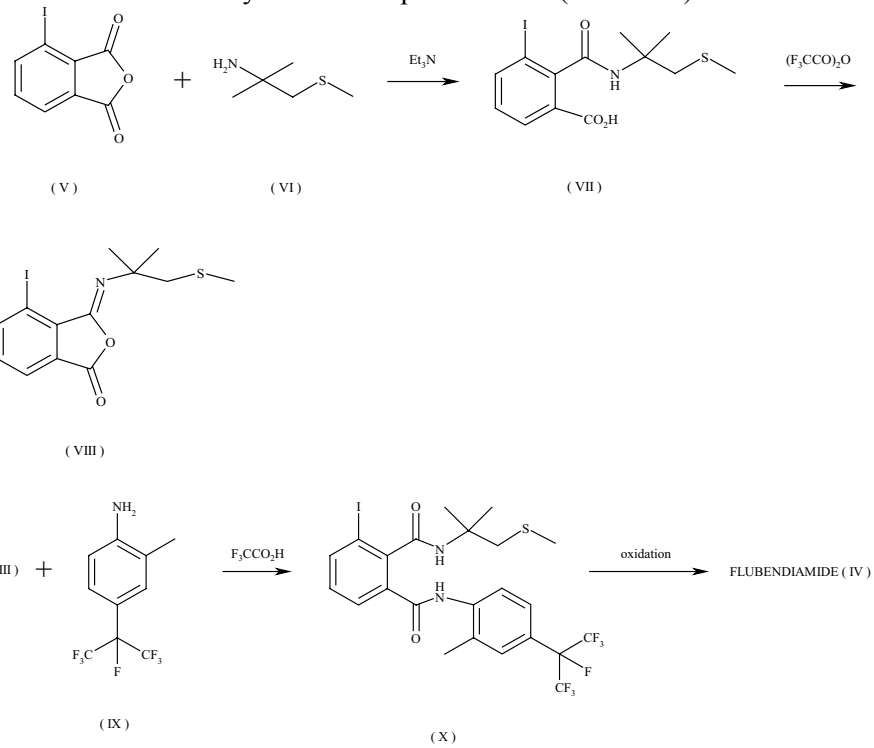
Simultaneusly, the works on the chemistry of their insecticidal action started.

Determination of the insecticidal activity of compounds in line with the formula (III) led to select flubendiamide (IV) (in 1998): N2-[1,1-dimethyl-2-(methylsulfonyl)ethyl]-iodo-N1-[2-methyl-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]phenyl]-1,2-benzenedicarboxyamide, a novel class of insecticide with extremely intensive activity against a range of lepidopteran species.



(IV)

The flubendiamide synthesis is depicted below (Scheme 1):



Scheme 1. Synthesis of flubendiamide.

3-Iodophthalic anhydride (V), when undertaken the reaction with thioalkylamine (VI), was transformed to the phthalamine acid (VII). The latter under the action of trifluoroacetic anhydride underwent the rearrangement to izoimide (VIII), which after subsequent coupling with aniline derivative (IX)

formed diamide (X). Flubendiamide was then consequently obtained by oxidation of (X) with *m*-chloroperoxybenzoic acid (MCPBA) or hydrogen peroxide. The other compounds constitute of the similar structure in agreement with the given above general formula (III) were synthesized in an analogous manner.

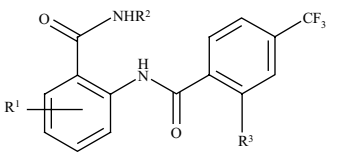
The studies to explain the biological mode of action of phthalic diamides, carried out by researchers from Nihon Nohyaku and Bayer CropScience, exhibited that these compounds activate in insects organisms the ryanodine-sensitive intracellular channels (ryanodine receptors), responsible for the control of calcium ions releasing [10, 11]. Particularly interesting is the lack of any activity of discussed diamides on the mammalian ryanodine receptors of type R_yR1 (present mainly in the skeleton muscles).

F l u b e n d i a m i d e in the pure form has the shape of white powder melting at 217.5-220.7 °C. As a representative of a novel class of insecticides it was presented in 2005 at the International Conference on Pesticides in Kuala Lumpur [12] and at BCPC International Congress in Glasgow [13], in 2006 – at the 230th National Meeting of the American Chemical Society [14] and at XIth IUPAC Congress in Kobe (Japan) [15]. It induces a broad spectrum of activity against a range of lepidopteran pests such as diamondback moth (*Plutella xylostella*), cabbage white butterfly (*Pieris ropae crucivora*), tobacco caterpillar (*Spodoptera litura*) and cabbage webworm (*Hellula undalis)*. The insecticide was developed for use to protect fruits, vegetables, tea, maize, rice, and cotton crops. It controls as well juvenile insect stages as the adult forms, acting very fast, mainly by ingestion. Flubendiamide has a favourable ecological, ecotoxicological and environmental profile with low acute mammalian toxicity and no genotoxic, mutagenic or oncogenic properties noted. The exhaustive data concerning the biological characteristics of flubendiamide were presented in the article of Hirooka et al. [16], whereas its ecological interactions were described by Hall [17]. Flubendiamide perfectly matches the guidelines of Integrated Pest Management (IPM) and Insecticide Resistance Management (IRM) programs for different kind of crops, as it displays many favourable profiles, as high and selective activity against a broad range of harmful lepidopteran species, a new mode of action, safety to beneficials, low toxicity against mammals, etc. [15, 18]. For the first time it was registered in the Philippines (trademark Fenos 480SC) to protect cabbage and eggplant crops. In 2007 flubendiamide has been registered in India (under the trademark Fame). Bayer CropScience has intended to introduce flubendiamide to the markets of USA, Canada, Brasil, Australia and UE countries in 2008.

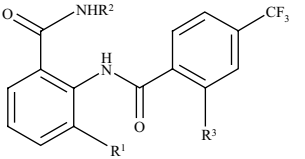
ANTRANILIC DIAMIDES. CHLORANTRANILIPROLE

Antranilic diamides (antranilodiamides) have been developed in the laboratory of plant protection agents of DuPont, by a group of researchers conducted by G. P. Lahm [19, 20]. Similarly as phthalic acid diamides, they act selectively on ryanodine receptors of a broad spectrum of lepidopteran (including caterpillars and potato beetle). When coupled with calcium channels, they induce muscles contraction in a target insect, what quickly results in paralysis and finally – in insect death.

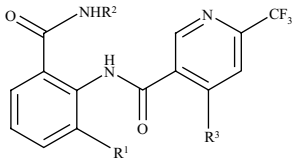
There were synthesized the following groups of the antranilic diamides:



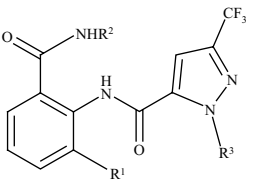
(XI)



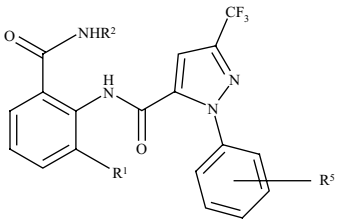
(XII)



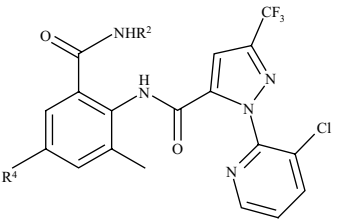
(XIII)



(XIV)

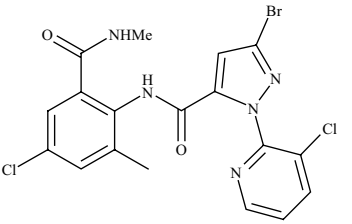


(XV)



(XVI)

The further investigations within the structure (XVI) led to discover a Rynaxypyr™ (XVII), the first antranilic diamide insecticide, selected to the introduction to the world market [24-27]:

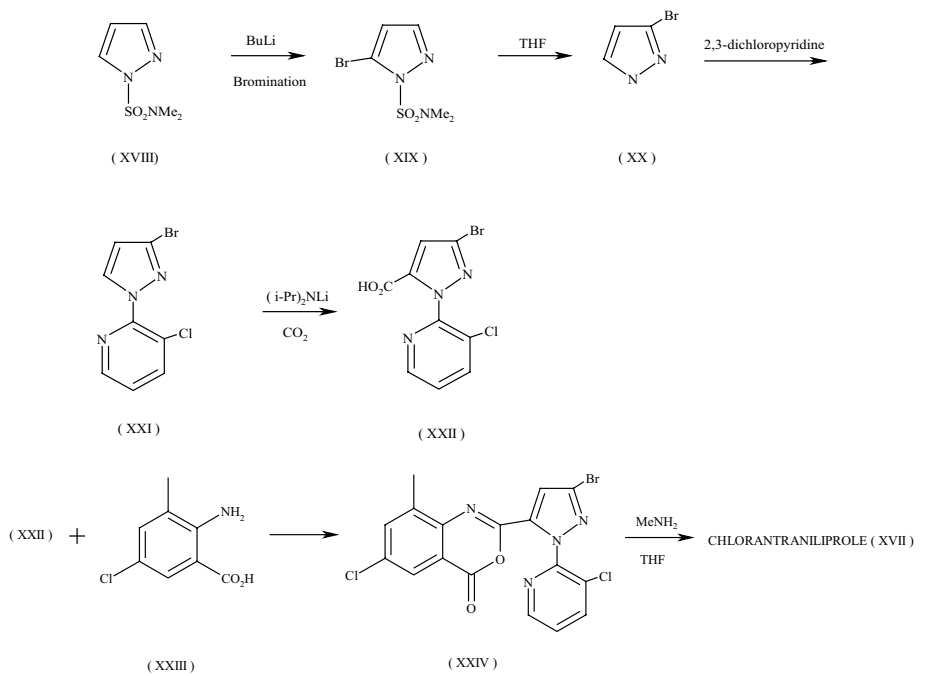


(XVII)

ISO TC (technical committee) on the common names for pesticides and other agrochemicals proposed for (XVII) a common name of chlorantraniliprole [21].

The results of tests concerning antranilic diamides and chlorantraniliprole were presented at BCPC Conference in Glasgow (November 2007) [22] and at XIth IUPAC Congress in Kobe (November 2006), dedicated the chemistry of pesticides [23].

The synthetic pathway to obtain chlorantraniliprole was as follows (Scheme 2):

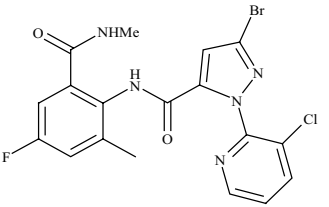


Scheme 2. Synthesis of chlorantraniliprole.

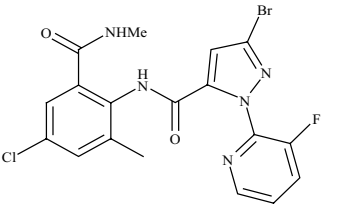
N,N-Dimethylsulfonylpyrazole (XVIII) treated with butyllithium, and subsequently brominated with 1,2-dibromo-1,1,2,2-tetrachloroethane was transformed to the expected 5-bromo-1-*N,N*-dimethylsulfonylpyrazole (XIX). Deprotection of the latter with tetrahydrofurane resulted in 3-bromopyrazole (XX), which coupled with 2,3-dichloropyridine led to 1-pyridyl-3-bromopyrazole (XXI). Deprotonation of (XXI) by use of lithium diisopropylamide, followed by CO_2 addition yielded 3-bromopyrazolocarboxylic acid (XXII). Synthesis of benzoxazinone (XXIV) – a direct precoursor of (XVII), was done from acid (XXII) and 3-chloro-6-methylantranilic acid (XXIII) (antranilic acid, triethylamine, methanesulfonyl chloride). (XXIV) in reaction with methylamine gave chlorantraniliprole (XVII).

In course of doing biological tests it was stated, that chlorantraniliprole exhibits an activity also against hemipteran species, such as sucking insects. It was estimated that level of its activity against aphids and leafhoppers was very much the same as for the other, structurally different preparates already sold at the market.

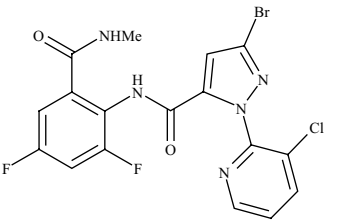
Hemipterans, as having their mouthparts formed into a "rostrum", are quite distinctive when compared with other insects. They are very lively, usually feeding on plant tissues and sucking out the plant tissue sap, so the typical methods for their control involves on principle the insecticides with properties fostering a penetration and systemicity (facile transportation within plant tissues). For this point, as a part of the broaden intentions to modify the physical properties of antranilic diamides towards increase systemic efficacy, there were undertaken attempts to reduce such their feature as lypophilicity. This was done by replacement of halogens in the molecule by fluor atoms [28], and among the others, the following structures of "chlorantraniliprole fluorinated analogs" were synthesized (XXV, XXVI, XXVII):



(XXV)



(XXVI)



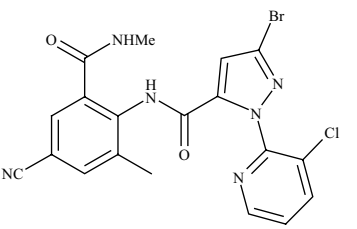
(XXVII)

C h l o r a n t r a n i l i p r o l e (XVII), 3-bromo-*N*-[4-chloro-2-methyl-6-[(methylamino)carbonyl]phenyl]-1-(3-chloro-2-pyridyl)-1*H*-pyrazolo-5-carboxamide (according to CAS nomenclature), occurs in a form of white coloured fine-cristalline powder, melting at 239-240 °C [27]. It exhibits a distinguishing insecticidal activity on the level of 0.01-0.06 ppm, towards the most of species of *Lepidoptera* order. This level is superior than the commonly acknowledged market standards, possessing as well the prominently low mammalian toxicity (LD_{50} p.o for rats > 5000 mg/kg, LC_{50} for fishes 13.8 mh/L, LD_{50} for birds 2250 mg/kg) [27]. For the first time it was registered at Phillippines in 2007 as a preparate Prevathon to protect cabbage, aubergines, beans and rice [29]. The sales in Phillippines, Indonesia, Romania were record. In the wake of these successful events, in 2008 there have been conducted the registration procedures regarding introduction of chloranthraniliprole at the markets of EU, Australia and New Zealand. The US Environmental Protection Agency (EPA) perceives this insecticidide as a first which should be registered globally on the areas of the US and Canada.

DuPont promotes two insecticidal preparates containing chloranthraniliprole: Altacor and Coragen. Altacor is a 35% granulate which is water disperged (WG); it is purposed to protect vineyards, stone and seed fruits, cotton and potatoes crops. The recommended dose of Altacor preparate in the US is 138-311 g/ha (about 48.3-109 g of a.i./ha). For Coragen, which is a concentrated suspension (S.C.) of chloranthraniliprole, containing 200 g a.i./L, and recommended for

protection of vegetable plants, including cabbage, pumpkin, bowl lettuce, tomatoes, pepper, the reccommended dose fits between 148-555 mL/ha (about 29.6-111 g a.i./ha). In Texas the authorities gave a nod for an exceptional use of DuPont insecticidal preparate based on a chlorantraniliprole – Dermacor X, to the rice treatment against the rice water weevil (*Lissorhoptrus oryzophilus)*, despite of the luck of its registration [32].

In the developing planes of DuPont, concerning the new pesticidal a.i. envisioned to marketing within the period of 2010-2015 a next compound from a group of antranilic diamides is an insecticide HGW86, trade-marked as C y a z y p y r ™, common-named cyantraniliprole [29, 32]. It is active against sucking and biting insects. It is predicted for use to control of scaly wings insects (Lepidoptera), beetles (Coleoptera), aphids or shield bugs from the family of Pentatomidae (Hemiptera). The supposed structure of Cyazypyr is depicted below (XXVIII):



(XXVIII)

Cyantraniliprole synthesis can be achieved according to the descriptions published in the patent [33]. HGW86 in 2006 was tested in Brasil for its efficacy to control pests of bean, maize, sugar beetroot, cotton, coffee, citrus fruits, tomatoes, potatoes, oats, melones, rice and wheat.

In June 2008 Syngenta and DuPont announced an agreement concerning the common works to prepare the regulatory studies for DuPont Cyazypyr, for its future global registration and commercialization [35].

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