Pesticide Biochemistry and Physiology 107 (2013) 1–7

Contents lists available at SciVerse ScienceDirect

Pesticide Biochemistry and Physiology

journal homepage: www.elsevier.com/locate/pest

Mini Review

Sulfoxaflor and the sulfoximine insecticides: Chemistry, mode of action and basis for efficacy on resistant insects ☆

Thomas C. Sparks *, Gerald B. Watson, Michael R. Loso, Chaoxian Geng, Jon M. Babcock, James D. Thomas

Dow AgroSciences, 9330 Zionsville Road, Indianapolis, IN 46268, United States

ARTICLE INFO

Article history:
Received 17 March 2013
Accepted 31 May 2013
Available online 13 June 2013

Keywords:
Sulfoxaflor
Sulfoximines
Mode of action
Cross-resistance
Structure activity relationships
Neonicotinoid resistance

ABSTRACT

The sulfoximines, as exemplified by sulfoxaflor ([*N*-[methyloxido[1-[6-(trifluoromethyl)-3-pyridinyl]ethyl]-λ^4-sulfanylidene] cyanamide] represent a new class of insecticides. Sulfoxaflor exhibits a high degree of efficacy against a wide range of sap-feeding insects, including those resistant to neonicotinoids and other insecticides. Sulfoxaflor is an agonist at insect nicotinic acetylcholine receptors (nAChRs) and functions in a manner distinct from other insecticides acting at nAChRs. The sulfoximines also exhibit structure activity relationships (SAR) that are different from other nAChR agonists such as the neonicotinoids. This review summarizes the sulfoximine SAR, mode of action and the biochemistry underlying the observed efficacy on resistant insect pests, with a particular focus on sulfoxaflor.

1. Introduction

Resistance to existing insecticides is an on-going problem [1] that requires the development of new insect control tools. A number of sap-feeding insects including *Myzus persicae* (green peach aphid; GPA), *Aphis gossypii* (cotton aphid), *Bemisia tabaci* (sweet potato whitefly) and *Nilaparvata lugens* (brown plant hopper), have a history of developing resistance to available insecticides [1]. Although initially slow to develop, many of these same sap-feeding insect pests have now developed resistance to the neonicotinoid insecticides [2–4] that are currently the mainstay for their control in a wide range of crops [2,3].

The sulfoximines are a new class of insecticides targeting sap-feeding insects [5–7]. Sulfoxaflor (Fig. 1) is the initial compound in this new sulfoximine insecticide class to be selected for commercial development. The sulfoximines, as exemplified by sulfoxaflor, exhibit several unique characteristics. The members of this class contain a unique chemical moiety, a sulfoximine, the first for a commercial agrochemical, and one which confers a unique set of structure activity relationships (SAR) compared to other insecticides. Like several chemically diverse classes of insecticides (spinosyns, neonicotinoids, nereistoxin analogs), sulfoxaflor acts on insect nicotinic receptors (nAChRs). However, as discussed below, there are aspects of the sulfoxaflor – nAChR interaction that distinguish it from the other nAChR acting insecticides. The sulfoximines are also effective against a wide range of sap-feeding insect pests that are resistant to other classes of insecticides, including many that are resistant to the neonicotinoids. Associated with this lack of cross-resistance, the sulfoximines such as sulfoxaflor are poor substrates for the metabolic enzymes involved in resistance to other classes of insecticides. This review examines each of these aspects and how it applies to insecticide resistance management (IRM) for this novel class of chemistry.

2. Chemistry

2.1. Discovery

The sulfoximine insecticides (SFI), including sulfoxaflor, emerged from exploration of unusual and underrepresented chemical moieties for pesticidal activity an example of which is the sulfoximine moiety (Fig. 1) [6]. Early sulfoximine analogs (Fig. 1, strucuture A) exhibited weak fungicidal activity [6]. Continued exploration led to *N*-nitro substituted sulfoximines (Fig. 1, structure B), which evolved to a chloropyridine analog (SFI-1 Fig. 1) that

Abbreviations: GPA, green peach aphid (*Myzus persicae*); IRM, insecticide resistance management; IRAC, Insecticide Resistance Action Committee; MTH, 2-CH_3-thiazole; nAChR, nicotinic acetylcholine receptors; SAR, structure activity relationships; SFI, sulfoximine insecticide; SFX, sulfoxaflor; TFT, tertrahydrofuran.

* Corresponding author. Address: Discovery Research, Dow AgroSciences, 9330 Zionsville Road, Bldg. 306/G1, Indianapolis, IN 46268, United States.
E-mail address: tcsparks@dow.com (T.C. Sparks).

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http://dx.doi.org/10.1016/j.pestbp.2013.05.014

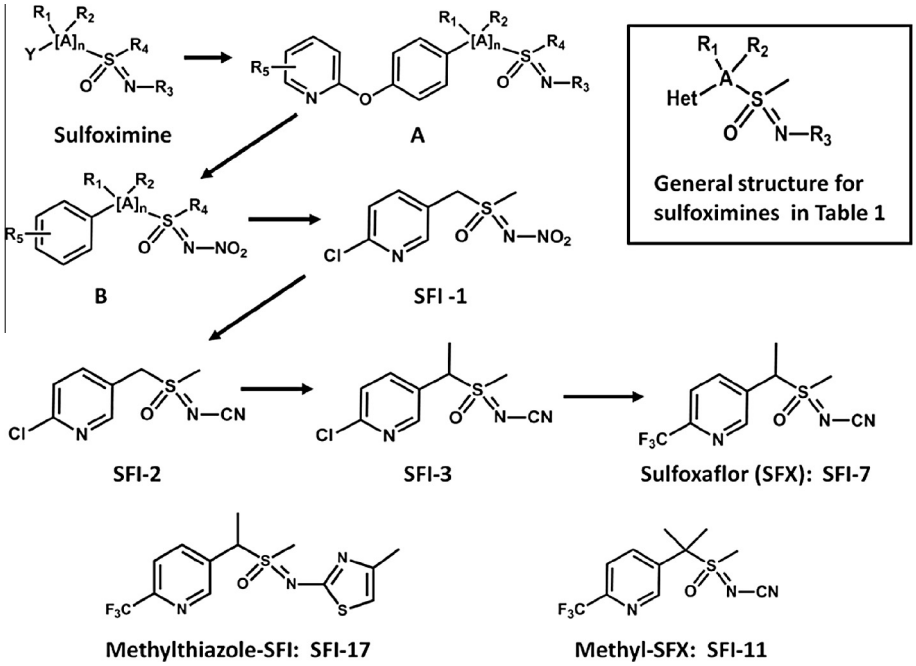

Fig. 1. Evolution of sulfoximine analogs leading to sulfoxaflor, structures of selected sulfoximines and general structure for the sulfoximines in Table 1. Structures A and B represent generalized motifs for early sulfoximine analogs, where R_1-R_5 are substituents and $[A]_n$ = 0-2 atoms.

exhibited a shift in biological activity towards sap-feeding insects [6,8]. Replacement of the nitro substituent on the imine nitrogen with a cyano group improved insecticidal activity (SFI-2; Fig. 1, Table 1), while addition of a methyl group on the methylene bridge between the sulfoximine and the chloropyridine provided a further boost in insecticidal potency (SFI-3, Fig. 1, Table 1). Finally, replacement of the chlorine on the pyridine with a CF_3 resulted in an additional improvement in activity (SF-7; sulfoxaflor, Fig. 1, Table 1).

Table 1
Insecticidal activity of sulfoximine analogs against *Myzus persicae*.

						M. persicae	
SFI[a]	Het	R1	R2	R3	A	LC90[b]	LC50[c]
1	6-Cl-3-pyridyl	H	H	NO2	C	239	–
2	6-Cl-3-pyridyl	H	H	CN	C	11.3	–
3	6-Cl-3-pyridyl	H	CH3	CN	C	1.1	1.4
4	6-Cl-3-pyridyl	H	CH3	NO2	C	12.0	–
5	6-CF3-3-pyridyl	H	H	CN	C	5.0	–
6	6-CF3-3-pyridyl	H	CH3	NO2	C	4.6	>100
7[d]	6-CF3-3-pyridyl	H	CH3	CN	C	0.19	0.08
8	2-Cl-5-thiazoyl	H	H	CN	C	>200	14.4
9	2-CF3-5-thiazoyl	H	H	CN	C	>200	–
10	THF[e]	H	CH3	CN	C	>200	–
11	6-CF3-3-pyridyl	CH3	CH3	CN	C	1.4	0.45
12	6-CF3-3-pyridyl	F	CH3	CN	C	–	4.64
13	6-CF2Cl-3-pyridyl	H	H	CN	C	–	9.6
14	6-Cl-3-pyridyl	H	H	CN	N	>200	–
15	6-Cl-3-pyridyl	H	CH3	CN	N	22.3	–
16	6-CF3-3-pyridyl	H	CH3	CN	N	7.1	–
17	6-CF3-3-pyridyl	H	CH3	MTH[6]	C	3.8	–
Imidacloprid	–	–	–	–	–	0.24	0.1

[a] SFI – sulfoximine insecticide: see Fig. 1 for generic structure of the sulfoximine insecticides.
[b] Watson et al. [23] & unpublished Dow AgroSciences data, LC_{90}, ppm.
[c] [24], ppm.
[d] Sulfoxalfor.
[e] THF = tetrahydrofuran.
[f] MTH = 2-CH_3-thiazole.

The CF_3 analog (sulfoxaflor) was selected for commercial development (Fig. 1).

2.2. Sulfoximines: distinct from the neonicotinoids

Because the sulfoximines and neonicotinoids both function as nAChR agonists, it might be assumed that the SARs and interactions with the insect nAChR of the two chemistries are quite similar. However, the sulfoximines and neonicotinoids are distinct just as other classes of structurally similar insecticides are distinct. For example, the organophosphorus and carbamate insecticides, both of which inhibit acetylcholinesterase, can possess very similar structural elements (Fig. 2), and yet are widely viewed as different classes of insecticides each possessing very individual SARs. These chemistries are defined by the organophosphorus and carbamate functional groups [9–12], not by the presence of a particular aryl or heterocyclic ring system. For instance, methiocarb, MTMC and fenthion, all possess very similar aryl ring systems (Fig. 2), and yet are clearly defined

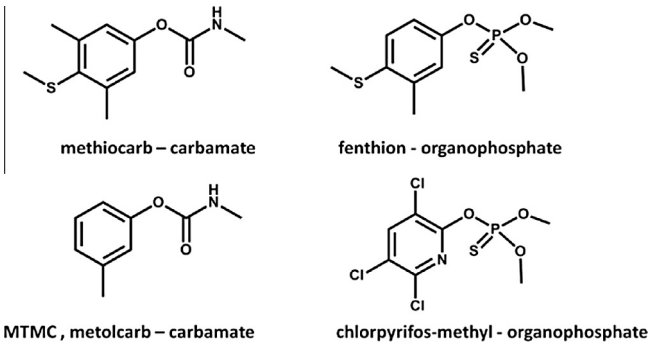

Fig. 2. Structures for selected organophosphorus and carbamates possessing similar aryl moieties or a halopyridine.