Journal of Fluorine Chemistry 185 (2016) 173–180

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Discovery of flufenoxystrobin: Novel fluorine-containing strobilurin fungicide and acaricide

Lin Li[a,b], Miao Li[c], Huiwei Chi[c], Jichun Yang[c], Zhinian Li[c], Changling Liu[c,*]

[a] State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian, China
[b] Department of Pharmaceutical Chemistry, Hebei Medical University, Shijiazhuang, China
[c] State Key Laboratory of the Discovery and Development of Novel Pesticides, Shenyang sinochem agrochemicals R&D Co., Ltd., Shenyang, China

ARTICLE INFO

Article history:
Received 19 February 2016
Received in revised form 24 March 2016
Accepted 24 March 2016
Available online 24 March 2016

Keywords:
Flufenoxystrobin
Strobilurin derivatives
Fungicidal activity
Acaricidal activity
Structure-activity relationship
Intermediate derivatization methods

ABSTRACT

To discover new strobilurin analogues with high activity, a series of new fluorine-containing strobilurin derivatives were synthesized utilizing intermediate derivatization methods (IDM). The compounds were identified by ^{1}H and ^{19}F nuclear magnetic resonance (NMR), IR and elemental analysis. Preliminary bioassays in greenhouse indicated that compounds **2a** (SYP-3759, flufenoxystrobin) and **2c** exhibited excellent fungicidal activities against *Erysiphe graminis* protecting wheat at 1.56 mg L^{-1} concentration and compounds **2a** showed a moderately high acaricidal activity at 10 mg L^{-1}. Field trials showed the fungicidal activities of compounds **2a** and **2c** is almost equivalent to that of pyraclostrobin, higher than that of triadimefon and the acaricidal activity of compound **2a** is almost equivalent to that of pyidaben, but lower than that of fluacrypyrim. The preliminary mammalian toxicology results showed compound **2a** was a low-toxicity compound. In conclusion compound **2a** is a promising candidate for further development; mammalian toxicology and ecotoxicology with compound **2a** are in progress.

1. Introduction

The strobilurins are known as one of the most important classes of agricultural fungicides with broad fungicidal spectrum, lower toxicity towards mammalian cells and environmentally benign characteristics. Although many strobilurin fungicides have already been commercialized, we postulated that new strobilurin analogues could be discovered using the Intermediate Derivatization Methods (IDM), a useful three-pronged approach for agrochemical discovery that includes the Common Intermediate Method (CIM), Terminal Group Replacement Method (TRM), and the Active Compound Derivatization Method (ADM) [1–16]. In this paper, we present our results from the application of TRM to generate new strobilurin derivatives.

The strobilurin derivatives containing *meta*-trifluoromethyl substituted phenyl, pyridine and pyrimidine in the side chain display excellent fungicidal and acaricidal activity, such as fungicides picoxystrobin [17] and acaricide fluacrypyrim [18]. In order to discover new strobilurin analogues with higher biological activity, we initially designed general structure (**1**) by combining structural components taken from highly potent picoxystrobin and acaricidal fluacrypyrim as shown in Fig. 1. The candidate structure (**1**) encompasses the strobilurin moieties, "methyl *(E)*-β-methoxyacrylate", "methyl (*E*)-methoxyiminoacetate", "*N*-methyl (*E*)-methoxyiminoacetamide" and "methyl *N*-methoxycarbamate", and the *meta*-trifluoromethyl substituted phenol in the side chain.

3-Trifluoromethylphenol is also an important intermediate in synthesis of herbicides picolinafen and diflufenican. Therefore, we hypothesized that the 3-trifluoromethyl phenol moiety and the strobilurin moieties are two critical components in their activities and by replacing the pyridine or pyrimidine moiety in picoxystrobin and fluacrypyrim with 3-trifluoromethylphenol would improve their biological activities further (see Fig. 1). Using this approach, we synthesized a number of compounds of the type **1** and screened them for fungicidal activity.

In order to further optimize our lead compound (**1**), we observed that the diphenyl ether herbicides fomesafen, oxyfluorfen, lactofen, acifluorfen, ethoxyfen-ethyl and fluoroglycofen-ethyl each share the 2-chloro-4-(trifluoromethyl)phenol (**7a**) moiety which is by-product in synthesis process of oxyfluorfen (Figs. 2 and 3). Our next step was to replace the 3-trifluoromethylphenol moiety in the designed structure (**1**) with the 2-chloro-4-(trifluoromethyl)phenol moiety, common to the above listed herbicides, to obtain compounds shown as design structure (**2**) [19]. We also prepared similar analogues with pyridine as shown in design structure (**3**).

* Corresponding author.
E-mail address: liuchangling@vip.163.com (C. Liu).

http://dx.doi.org/10.1016/j.jfluchem.2016.03.013
0022-1139/

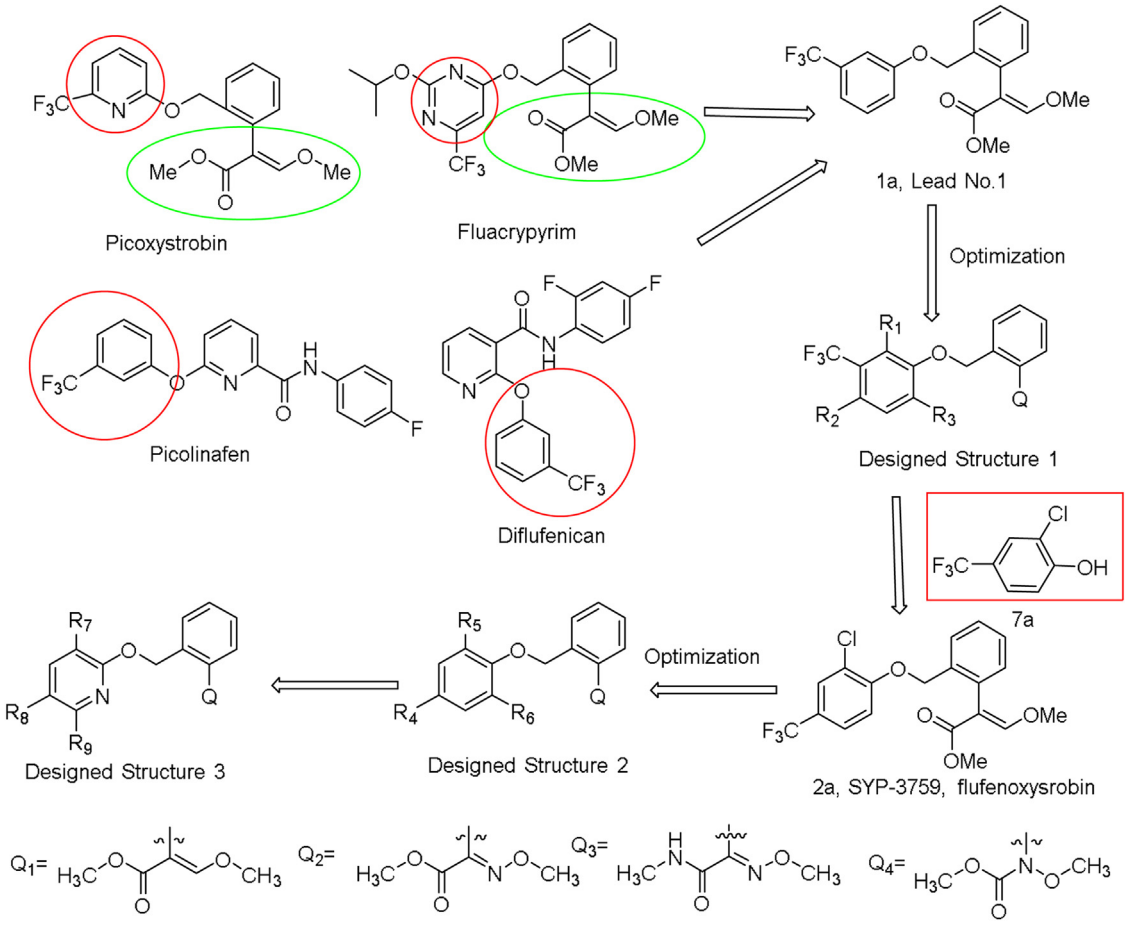

Fig. 1. Design of skeleton.

A series of new strobilurin derivatives containing phenyl and pyridine in the side chain were synthesized and bioassayed. We have found that some compounds display an excellent fungicidal activity against *Erysiphe graminis* (*E. graminis*) protecting respective crops as compared to such standard fungicides as azoxystrobin, kresoxim-methyl and pyraclostrobin (Fig. 4). In addition to its strong fungicidal activity, compound **2a** (SYP-3759, flufenoxystrobin) exhibits an acaricidal activity against *Tetranychus*

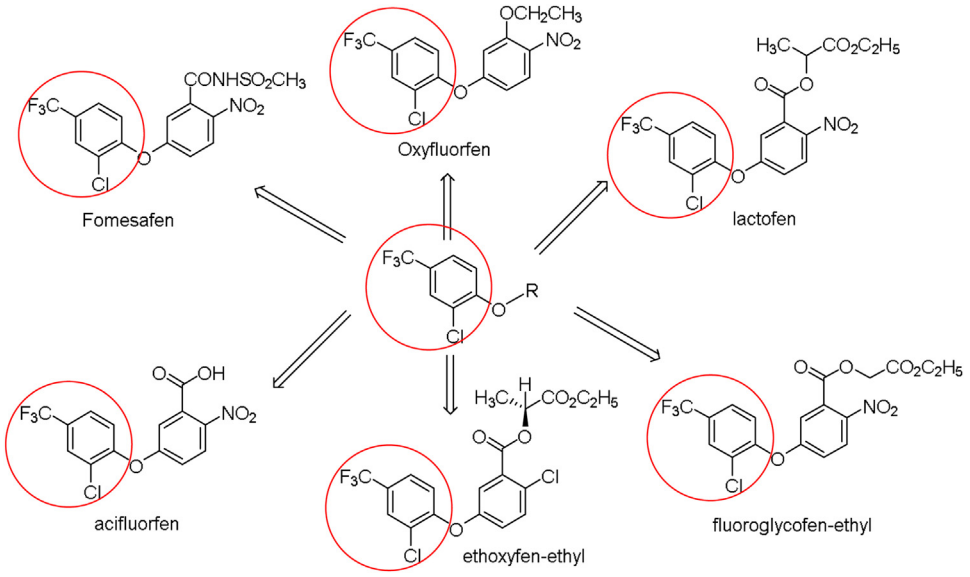

Fig. 2. Agrochemicals containing 2-chloro-4-trifluoromethylphenol.