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Review

Successful fluorine-containing herbicide agrochemicals☆

Tomoya Fujiwara [a,b], David O'Hagan [a,*]

[a] School of Chemistry and Centre for Biomolecular Sciences, University of St Andrews, St Andrews, KY16 9ST, UK
[b] Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Sugitani, Toyama 930-0194, Japan

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ABSTRACT

Of the herbicides licensed worldwide, currently around 25% contain at least one fluorine atom and many contain multiple fluorines in the form of difluoro- and trifluoromethyl groups. Fluorine-containing compounds have made a significant contribution to the development of products for the agrochemicals industry and many organofluorine entities have found stable market positions. In this review we highlight the most important fluorinated herbicides in terms of their global use. The compounds are grouped by mode of action. A synthesis route is described for each compound although the synthesis presented may not actually be the industrial process.

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1. Introduction

The population of the world is growing at a steady pace with estimates suggesting up to a 30% increase over the next decade and the global population rising from 7 billion at present to 9.6 billion by 2050 [1a]. Also there is a significant shift occurring from the current dependence on plant based (4.6 billion) to more intensively produced meat based (2.3 billion) diets as populations move from the countryside to urbanised conurbations. Meat production is estimated to double by 2050 [1b,c]. With this backdrop the requirement to maximise crop production from the available arable land is ever more pressing. Agrochemical products are recognised now as increasingly as significant in terms of meeting societal demands as

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* Corresponding author. Tel.: +44 1334 467176; fax: +44 1334 463808.
E-mail address: do1@st-andrews.ac.uk (D. O'Hagan).

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pharmaceutical products have been in the past. The challenges are for increased efficacy (lower g/ha), and reduced environmental impact. Innovation and discovery in the agrochemicals sector is extremely active. In this regard fluorine is an important tool. The element finds its way into all classes of performance organic compounds extending from pharmaceuticals to organic materials [2], and it has had no less of an impact in agrochemicals. Indeed organic fluorine products have a particularly high frequency in agrochemical products [3]. A recent survey of the licensed herbicides reveals that almost ~25% (56 compounds from 229) contain at least one fluorine atom, most often present as aryl-F, aryl-CF_3 and aryl-OCF_3 substituents, although aliphatic fluorinated motifs are also represented [4]. The impact that the highly electronegative fluorine and fluorinated substituents can have on the behaviour and properties of agrochemical ingredients and bioactives more generally such as pharmaceuticals, has been widely articulated and is covered in other reviews [5–7]. In summary the C–F bond is the strongest in organic chemistry, and fluorine in the next smallest atom that can be covalently bonded to carbon, so exchanging F for H has a minimal steric perturbation, and leads to stable derivatives. Multiply fluorinated substituents (*eg.* XCF_3) typically increase lipophilicity and thus bioavailability of molecules traversing cellular membranes, and site specific location of a fluorine or fluorinated group can be used to protect against or suppress *in vivo* metabolism *eg.* P_{450} oxidations. Additionally the polarity associated with the C–F [8,9] bond will induce dipoles, and influence conformational changes relative to the hydrogen analogue, and this can lead to improved target binding. The electron withdrawing effect of fluorine incorporation can be used to tune the acidity (*eg.* H-bonding capacity) of adjacent protic functional groups (*eg.* OH, NRH, CO_2H, *etc.*). Thus the inclusion of fluorine into a molecular framework can have a variety of impacts which assist in the development of lead compounds to result in a substantial improvement in efficacy. This review aims to highlight the more important fluorinated products that are present in the current herbicides market. The compounds are classed by their modes of action and a focus of the review is structure and consideration of a representative synthesis route for each of the products presented.

2. Acetolactate synthase (ALS) inhibitors

Acetolactate synthase (ALS) is an enzyme in plant metabolism involved in the biosynthesis of the branched chain amino acids L-valine, L-leucine and L-isoleucine [10,11]. Inhibition of ALS has been an important target in the development of several large classes of herbicides. It is a flavin enzyme that requires thiamine pyrophosphate (TPP) as a co-factor [12]. Fluorinated compounds that have found a significant role as ALS inhibitors are the sulphonamides, flumetsulam (**6**), florasulam (**14**), penoxsulam (**24**) and pyroxsulam (**39**). All of these compounds were introduced by Dow and have triazolopyrimidine sulphonamide structures. They have been used for killing broad leaf weeds associated with wheat and other cereals [13].

Flumetsulam (**6**) was the first of this fluorinated class of herbicide and was introduced in 1992 [14b]. Florasulam (**14**) was introduced in 2000 and is now one of the leading products in this class of herbicides [15]. Synthetic routes from commercially available fluorinated building blocks, 2,6-difluoroaniline (**5**) and 5-fluorouracil (**7**) to these products are outlined in Schemes 1 and 2 [14,16].

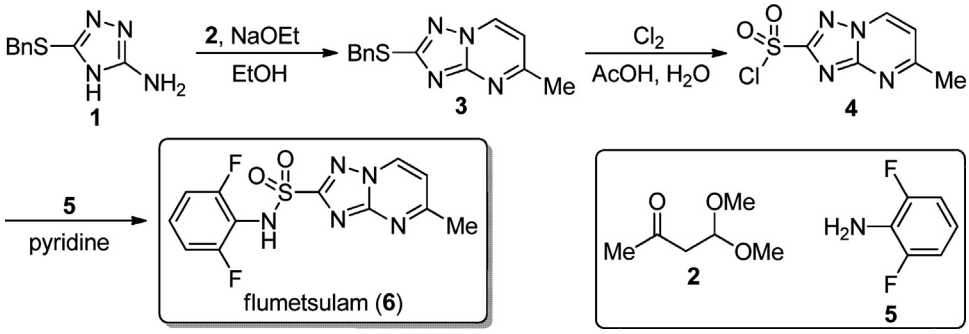
Penoxsulam (**24**) [17] and pyroxsulam (**39**) [18] were introduced in 2005 and 2007, respectively. These compounds have the reversed sulphonamide linkage to **6** and **14**. A synthetic route to **24** shown in Scheme 3 involves alkylation of hydroxyphenyl sulphide **21** derived from 3-(trifluoromethyl)phenol (**18**), with 1,1-difluoro-1-iodoethane [17]. Synthesis of **39** is accomplished *via* the Horner–Wadsworth–Emmons reaction of trifluoromethyl ketone **32** with trimethyl phosphonoacetate (**33**) followed by cyclisation with ammonium acetate (Scheme 4) [18]. Trifluoromethyl ketone **32** is obtained by reaction of ethyl vinyl ether (**31**) with trifluoroacetic anhydride in the presence of pyridine.

The sulfonylurea-containing herbicide, prosulfuron (**45**) was developed by Ciba-Geigy (now Syngenta) around 1995 [19]. This fluorinated compound has been used as a postemergence herbicide for broad-leaved weeds in corn and other cereals. A synthetic route to **45** is shown in Scheme 5 [20]. The key step of this route is the Matsuda–Heck reaction of the diazonium salts obtained by diazotization of 2-aminobenzenesulfonic acid (**40**), with trifluoromethylethylene (**41**).

Flucarbazone (**55**), also of this class is a compound originally developed by Bayer in 2002 [21]. It has broad efficacy being active in controlling a range of grasses and broad leaf weeds. It is now marketed by Arysta. A synthesis is outlined in Scheme 6 and involves fluorination of aryl trichloromethyl ether **51** with HF [22].

3. Acetyl-CoA carboxylase (ACC) inhibitors

Acetyl-CoA carboxylase (ACC) is an enzyme that catalyses the first committed step in plant fatty acid biosynthesis [23]. The enzyme is biotin dependent and it catalyses the conversion of acetyl-CoA to malonyl-CoA, and then malonyl-CoA is the key building block for the assembly of saturated fatty acids, such as palmitate (C_{16}) in the plastid, an organelle unique to plants.



Scheme 1. Synthesis of flumetsulam (**6**).