Bioorganic & Medicinal Chemistry Letters 26 (2016) 1310–1313

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and herbicidal activity evaluation of novel α-amino phosphonate derivatives containing a uracil moiety

Jian-yi Che [a], Xiao-yun Xu [a], Zi-long Tang [b], Yu-cheng Gu [c], De-qing Shi [a,*]

[a] Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, Hubei 430079, People's Republic of China
[b] College of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan, Hunan 411201, People's Republic of China
[c] Syngenta Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, UK

ARTICLE INFO

Article history:
Received 29 October 2015
Revised 23 December 2015
Accepted 6 January 2016
Available online 7 January 2016

Keywords:
α-Amino phosphonate
Uracil
Herbicidal activity
Structure–activity relationship

ABSTRACT

A series of novel α-amino phosphonate derivatives containing a uracil moiety **3a–3l** were designed and synthesized by a Lewis acid (magnesium perchlorate) catalyzed the Kabachnik-Fields reaction. The bioassays {in vitro, in vivo [Glass House 1 (GH1) and Glass House 2 (GH2)]} showed that most of compounds **3** exhibited excellent and selective herbicidal activities; for example, in GH1 test, compounds **3b**, **3d**, **3f**, **3h** and **3j** showed excellent and wide spectrum herbicidal activities at the dose of 1000 g/ha, and compounds **3b** and **3j** exhibited 100% inhibition activities against the four plants in both post- and pre-emergence treatments. Moreover, most of compounds **3** showed higher inhibition against *Amaranthus retroflexus* and *Digitaria sanguinalis* than Glyphosate did in pre-emergence treatment. In GH2 test, the four compounds (**3b**, **3d**, **3h** and **3j**) exhibited 100% inhibition against *Solanum nigrum*, *Amaranthus retroflexus* and *Ipomoea hederacea* in post-emergence treatment and displayed 100% inhibition against *Solanum nigrum*, *Amaranthus retroflexus* in pre-emergence treatment at the rate of 250 g/ha, and compound **3b** showed the best and broad spectrum herbicidal activities against the six test plants. However, the four compounds displayed weaker herbicidal activities against *Lolium perenne* and *Echinochloa crus-galli* than the other four plants at the rate of 250 g/ha in both pre- and post-emergence treatments. So, compounds **3** can be used as a lead compound for further structure optimization for developing potential selective herbicidal agent. Their preliminary structure–activity relationships were also investigated.

Phosphonates possess more lipophilic character and cell permeability along with physiological stability because phosphorus–carbon bond is not susceptible to enzymatic degradation by phosphatases.[1,2] α-Amino phosphonic acid and its ester derivatives are the bio-isosteres of natural amino acid, when the carboxylic group is replaced by a phosphonic moiety, they resemble the tetrahedral transition state of several enzymatic reactions, particularly in amide bond formation and hydrolysis; however, they are significant differences such as molecular dimension, group shape (flat CO_2H vs tetrahedral PO_3H_2) and acidity between amino acids and phosphonic counterparts. Therefore, several enzymes are unable to discriminate between carboxylic and phosphonic function for what concerns binding to active sites. The structural antagonism between amino acids and the phosphonic counterparts results in inhibition of a variety of enzyme activities.[3,4] Since Horiguchi and Kandatsu first described the isolation of β-aminoethylphosphonic acid from *Celiate protozoa* in 1959,[5] amino phosphonate derivatives attracted more and more attention due to their versatile biological activities in pharmaceuticals and agrochemicals.[6–11] Biologically relevant α-amino phosphonate derivatives include the antibacterial agent such as alafosfalin,[12] transition-state analog inhibitors of proteolytic enzymes **A**,[13,14] and haptens for the generation of catalytic antibodies **B** (Fig. 1).[15] Furthermore, (*R*)-phosphotyrosine occurs naturally as a component of two hypotensive tripeptides (Fig. 1),[16] and glyphosate, with structural similar with a naturally occurring glutamate analog, phosphinothricin (**PPT**), as synthetic inhibitor of the shikimate pathway enzyme 5-*enol*-pyruvyl-shikimate-3-phosphate (EPSP) synthase (EC 2.5.1.19), is used worldwide as the non-selective herbicide,[17–19] and *O*,*O*′-diethyl *N*-(4-methylbenzothiazol-2-yl)α-amino-α-(2-fluorophenyl)methylphosphonate (**Dufulin**, Fig. 1) is a commercial anti-TMV (tobacco mosaic virus) agent.[20,21] It also should be mentioned that some of heterocyclic aminomethylenebisphosphonic acid derivatives were evaluated as potential inhibitors of plant δ^1-pyrroline-5-carboxylate reductase (P5CR, EC 1.5.1.2), which catalyzes the last step in proline biosynthesis and can be functioned as a novel potential herbicide target.[22,23] On the other hand, uracil

* Corresponding author. Tel.: +86 27 6786 7958; fax: +86 27 6786 2041.
E-mail address: chshidq@mail.ccnu.edu.cn (D.-q. Shi).

http://dx.doi.org/10.1016/j.bmcl.2016.01.010
0960-894X/

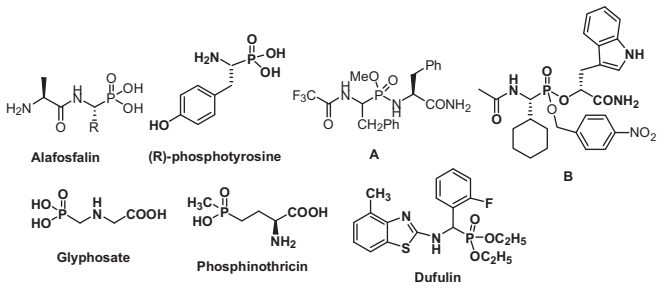


Figure 1. Structures of some amino phosphonic acid derivatives with versatile biological activities.

derivatives acted as the inhibitors of protoporphyrinogen oxidase (PPO, E.C. 1.3.3.4), an enzyme in the chlorophyll and heme biosynthetic pathway. To date, several uracil derivatives have been commercialized (Fig. 2), among them, bromacil and isocil were firstly developed as commercial herbicides by DuPont corporation in 1962.[24] Butafenacil, benzfendizone and saflufenacil were subsequently commercialized by Syngenta, FMC and BASF, respectively.[25–27] These high active uracil-type herbicides usually possess the following structural features: (i) a central 1*H*-pyrimidine-2,4-dione moiety; (ii) a methyl group linked at N(1) position, and trifluoromethyl at C(6) and substituted phenyl at N(3) position of uracil; (iii) the phenyl substitution at N(3) position, the one, with Cl or F introduced into the C(2), or/and C(4), and an ester or amide moiety introduced into the C(5) of the benzene ring, always displays good herbicidal activities. It is well known that there are more than 300 commercial herbicides used in the world, however, only 20 herbicidal modes of action are involved and more than a half of them are belonged to PSII, AHAS, ACCase and PPO enzyme inhibitors. Due to the persistent and large doses application of these high selective herbicides, the number of resistant biotypes against these herbicides increases greatly. For example, the biotypes resistant against AHAS, Triazines and ACCase inhibitors keep increasing seriously.[28] On the other hand, significant increases in weed resistance to glyphosate have been aroused due to rapidly increasing cultivation of glyphosate resistant crops.[29,30] So, in order to reduce the resistance risk of resistant biotypes of weeds against herbicides, the development of novel herbicides with novel mode of action remains in high demand. As mentioned above, α-aminoalkylphosphonic acids and its ester derivatives have attracted increasing interest for the development of new herbicides due to their high susceptibility to degradation by soil microorganisms, low toxicity to mammalian as well as diverse modes of action.[31,32] In attempt to develop α-amino alkyl phosphonates containing of heterocycle moieties as selective herbicide candidates with novel mode of action,[33] in this Letter, we designed and synthesized a series of novel α-amino alkyl phosphonate derivatives containing a uracil moiety via a Lewis acid (magnesium perchlorate) catalyzed the Kabachnik–Fields reaction of 2,4-disubstituted-5-[3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl]anilines **1**, aromatic aldehydes **2**, and diethyl phosphite using the commercial herbicide butafenacil as a lead compound (Schemes 1 and 2), the target compounds **3** were evaluated for herbicidal activities in vitro and in vivo, and their preliminary structure–activity relationship were also studied.

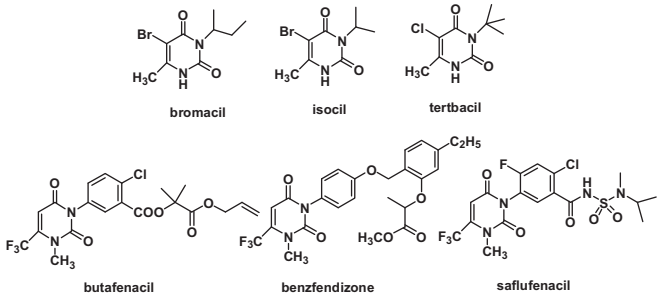
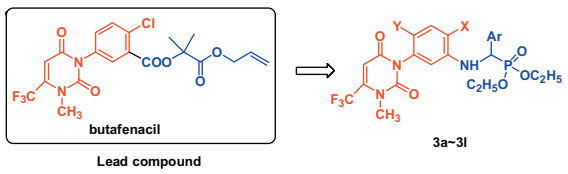


Figure 2. Structures of some commercially uracil herbicides.

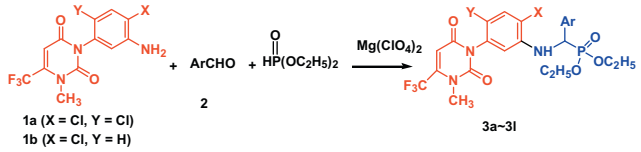
The intermediates 2,4-disubstituted-5-[3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl]anilines **1a–1b** were synthesized via a multi-step reaction according to the reported procedure.[34] A series of α-amino phosphonate derivatives containing a uracil moiety **3** were synthesized by a Lewis acid (magnesium perchlorate) catalyzed the Kabachnik–Fields reaction of 2,4-disubstituted-5-[3-methyl-2,6-dioxo-4-(trifluoromethyl)-2,3-dihydropyrimidin-1(6*H*)-yl]anilines **1**, aromatic aldehydes **2**, and diethyl phosphate in good yields. By exploring a variety of Lewis acids [$FeCl_3$, $Mg(ClO_4)_2$, $Cu(OAc)_2$, $Cu(OTf)_2$] and Brönsted acid *p*-toluenesulfonic acid, it was found that when 5 mol % magnesium perchlorate was used as the catalyst, the reaction gave the highest yield; the optimized conditions were established as follows: $Mg(ClO_4)_2$ as the catalyst, CH_3CN as the solvent, 70–80 °C for 8–12 h (Table 1).

The experimental details and characterization data for compounds **3a–3l** are given in Supplementary materials.[35] The herbicidal activities (in vitro, in vivo) of the synthesized compounds were tested, the bioassays are also included in Supplementary materials.

Herbicidal activity and structure–activity relationships: The results of herbicidal activities of compounds **3** [in vitro and in vivo (GH1, GH2)] are listed in Tables 2–4, respectively. To our



Scheme 1. Molecular design of the title compounds **3a–3l**.



Scheme 2. Synthetic route of the title compounds **3a–3l**.

Table 1
Optimization of the reaction conditions for the synthesis of **3a** via the three-component Kabachnik–Fields reaction[a]

Entry	Catalyst (equiv)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	$FeCl_3$ (0.1)	CH_3CN	75	12	35
2	$Mg(ClO_4)_2$ (0.1)	CH_3CN	75	8	87
3	$Cu(OAc)_2$ (0.1)	CH_3CN	75	12	42
4	$Cu(OTf)_2$ (0.1)	CH_3CN	75	12	48
5	TfOH (0.1)	CH_3CN	75	12	56
6	$Mg(ClO_4)_2$ (0.05)	CH_3CN	75	8	86
7	$Mg(ClO_4)_2$ (0.02)	CH_3CN	75	24	61
8	$Mg(ClO_4)_2$ (0.05)	CH_3CN	25	24	40
9	$Mg(ClO_4)_2$ (0.05)	THF	65	12	70
10	$Mg(ClO_4)_2$ (0.05)	Dioxane	80	12	73
11	$Mg(ClO_4)_2$ (0.05)	DMSO	80	12	58

[a] Reaction conditions (unless otherwise noted): **1a** (1 mmol), **2a** (1.1 mmol), diethyl phosphite (1.1 mmol), catalyst (0.05 mmol), solvent (3.0 mL), stirred at 70–80 °C for 8–12 h until the reaction finished (monitored by TLC).
[b] Isolated yield based on **1a**.