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# *N*-Cyano sulfilimine functional group as a nonclassical amide bond bioisostere in the design of a potent analogue to anthranilic diamide insecticide†

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To explore the potential of the *N*-cyano sulfilimine group as an amide bond isostere, a derivative of the blockbuster anthranilic diamide, chlorantramiliprole, was synthesized and evaluated with regard to its physicochemical properties, permeability, and biological activity. Given the combination of *N*-cyano sulfilimine chlorantraniliprole **1** and its strong hydrogen bond acceptor character, high permeability, and excellent insecticidal activity, the *N*-cyano sulfilimine functional group could be considered as an amide bond isostere.

## Introduction

The introduction of a bioisostere, a functional group with similar physicochemical and biological properties, is a common strategy for the enhancing the properties of biologically active compounds, such as their potency, selectivity and suitable pharmacokinetic (PK) or pharmacodynamic (PD) parameters.[1,2] A representative example of such a strategy is replacement of an amide bond with a surrogate structure.[3–5] Indeed, amide bonds are one of the most important functional groups in medicinal chemistry and play a crucial role in the composition of numerous biologically active molecules.[6,7] However, amide bonds have a permeation problem arising from hydrolysis and polarity.[3,4] In addition, resonance stabilization of amides, mainly caused by differences in electronegativity between oxygen and nitrogen, can leads to their inertness. Consequently, the carbonyl functional group of amides is less electrophilic than the carbonyl of other carboxylic acid derivatives (Fig. 1A).[8,9] Under such circumstances, attempting to replace the amide moiety with a surrogate structure may be valuable. Among the most commonly applied isosteres of the amide group, sulfonamides are known to be useful for increasing water solubility and providing additional hydrogen bond acceptors (HBAs).[3] Sulfonamides, the most common S(VI) functional groups, have attracted considerable attention, and intensified research activities with regard to crop science and pharmaceutical industry studies have resulted in many marketed products.[10–12] Distinguishing features of the sulfur–nitrogen (S–N) bond, such as its polarized character[13,14] and the ability to adopt a wide variety of oxidation states of sulfur, has led to important breakthroughs in many areas.[15–19]

Recently, exploration of sulfilimidoyl S(IV) and sulfonimidoyl S(VI) functional groups, such as sulfilimines[25–30] (Fig. 1B) and sulfoximines,[31–34] has facilitated the discovery of important agrochemicals[25–30,35–38] as well as clinical candidates of the kinase inhibitors.[39,40] The unique hydrogen bond donor and

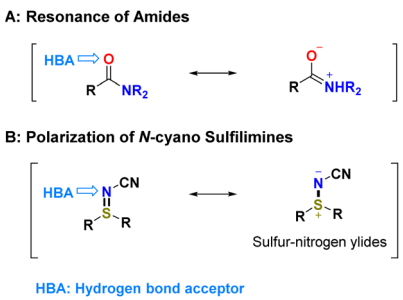


Fig. 1 (A) Resonance forms of amides,[8,9] (B) polarized forms of *N*-cyano sulfilimines[20–24].

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acceptor properties of the sulfonimidoyl groups have led to their widespread application in drug design as bioisosteres for carboxylic acids, alcohols and sulfones.[41–45]

*N*-Cyano sulfilimines have generally been applied as building blocks in the synthesis of biologically active *N*-cyano and NH-sulfoximines.[25–28,30,46–54] The S=N bond of S(IV) functional group is stabilized by electron-withdrawing groups and can be considered as a sulfur–nitrogen ylide in its ionic form (Fig. 1B).[20–24] Furthermore, there has been increased application with regard to drug development[46,53–55] and agrochemical research.[25–28] For a particular example, researchers at Pfizer studied the discovery of new types of clinically useful β-lactam drugs, such as penicillin an *N*-cyano sulfilimine. The resulting introduction of an *N*-cyano sulfilimine moiety led to formation of intramolecular N–H···N hydrogen bonding (Fig. 2A).[46] Intramolecular hydrogen bonds (IHBs) play crucial role in absorption, distribution, metabolism, and excretion (ADME)-toxicology profiles.[56,57] It has been suggested that IHB can improve intrinsic membrane permeability and intestinal absorption beyond the rule of five chemical space.[58,59]

In this context, introduction of an *N*-cyano sulfilimine group, as a suitably positioned HBA functionality, seemed to be attractive based on the possible role of IHB in facilitating permeability (Fig. 1B). Consequently, we reasoned that *N*-cyano sulfilimines may hold considerable promise as non-classical amide isosteres.

In order to apply the aforementioned approach in our discovery program, we decided to study the *N*-cyano sulfilimine group-substituted chlorantraniliprole analog **1** based on our previous research.[49–52] As the reference molecule, chlorantraniliprole has captured a significant market share in the insect control business. This insecticide belong to the anthranilic diamide class of chemistry and provides excellent crop protection.[60] To determine the changes in physicochemical properties caused by the presence of IHB, the amide group was replaced with an *N*-cyano sulfilimine moiety (Fig. 2). We assumed that the formation of a sulfur–nitrogen ylide ionic form of *N*-cyano-substituted sulfilimine **1** could increase the strength of N–H···N–CN hydrogen bonding, and provide enhanced permeability *via* IHB while maintaining potency.

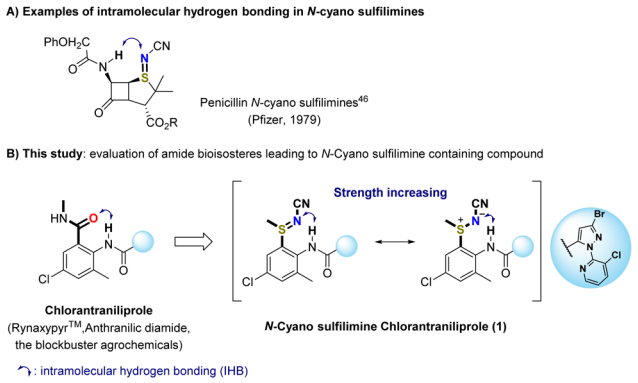



Fig. 2 (A) Penicillin *N*-cyano sulfilimine,[46] (B) *N*-cyano sulfilimine chlorantraniliprole **1**: example of this study.

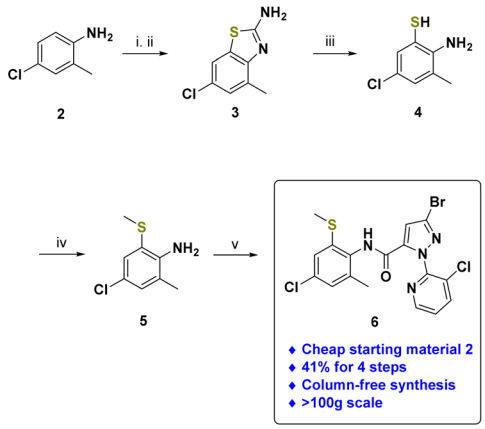
## Results and discussion

### Synthesis

Referring to the previous observation that it was better to perform sulfoximination of sulfide at the late-stage,[61] chlorantraniliprole sulfide **6** was prepared (Scheme 1). Starting from the commercially available 4-chloro-2-methylaniline **2**, 6-chloro-4-methylbenzo[*d*]thiazol-2-amine **3** was formed through reaction with ammonium thiocyanate ($NH_4SCN$) in the presence of bromine in acetic acid. 2-Aminothiophenol **4** was successfully prepared by the reaction of benzothiazole **3** with hydrazine monohydrate[62] and was readily converted to thiomethylated aniline **5** by alkylation with methyl iodide.[63] Then, aniline **5** was coupled with 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid to give the desired chlorantraniliprole sulfide **6** with an excellent yield (41% for 4 steps).[49,50,64] Impressively, the synthesis of the sulfide **6** relied only on recrystallization and did not require column chromatography methods. This protocol could be readily scaled up to the 100 g scale and applied to production of organosulfur-substituted chlorantraniliprole analogs.

More recently, we successfully developed a practical and scalable method for introduction of an *N*-cyano sulfilimine moiety into reactive functional group-substituted thioanisols.[51,52] Following our thionium-mediated reaction method, the desired *N*-cyano sulfilimine chlorantraniliprole **1** was successfully synthesized (Scheme 2).[65] It should be highlighted that this practical synthetic method of *N*-cyano sulfilimine **1** is column chromatography-free, with high yield, and performed on a 10 g scale.

To study the effect of IHB by means of introducing different functional groups, organosulfur group-substituted chlorantraniliprole derivatives (**7**–**9**) were also prepared (Scheme 2). For synthesis of 2-sulfoxide **7** and -sulfone **8**, oxidation methods using *m*CPBA and MonoPeroxyPhthalate hexahydrate (MMPP·$6H_2O$) easily provided the desired compounds **7** and **8**, respectively. Oxidation of sulfilimine **1** readily produced the *N*-




Scheme 1 Reagents and conditions: (i) $NH_4SCN$, AcOH, RT, 0.5 h, (ii) $Br_2$, AcOH, RT, 24 h, (iii) hydrazine monohydrate, 2-methoxyethanol, (iv) *t*BuOK, MeI, THF, RT, 2 h, (v) 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid, 3-picoline, MsCl, MeCN, RT, 24 h.

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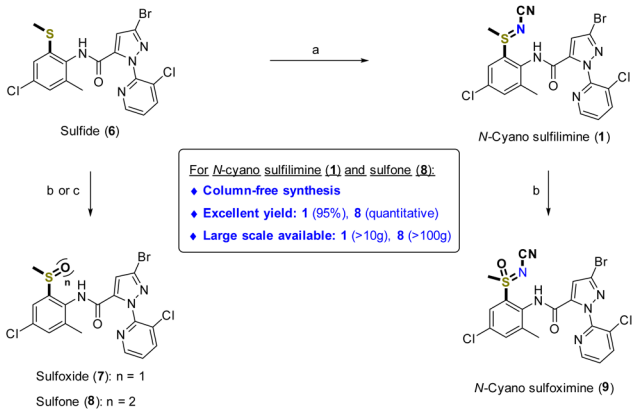


Scheme 2 (a) Thionium-mediated synthesis of *N*-cyano sulfilimine chlorantraniliprole **1**, reagents and conditions: $PhI(OAc)_2$, $H_2NCN$, DMF, 0 °C, 1 h; (b) synthesis of sulfoxide **7** and sulfoximine **9**, reagents and conditions: *m*CPBA, $K_2CO_3$, MeOH; (c) synthesis of sulfone **8**, reagents and conditions: MMPP·$6H_2O$, MeOH/$CH_2Cl_2$.

cyano sulfoximine **9** with an excellent yield. The column chromatography-free strategy was also successfully applied to prepare sulfone-substituted derivative **8**. In addition, oxidation of sulfide **1** with MMPP·$6H_2O$ was suitable to manufacture a large amount of highly pure compound **8**.

### Intramolecular hydrogen bonding

$^1$H NMR analysis and p$K_a$ value measurements were employed to investigate IHBs in *N*-cyano sulfilimine chlorantraniliprole **1** and a series of organo sulfur-substituted chlorantraniliprole derivatives **7–9**. To determine the intramolecular interactions between organosulfur functionalities and the amide moiety, CO–NH (amide) proton chemical shift of each compound were divided by the corresponding p$K_a$ value.[66] As shown in Fig. 3,

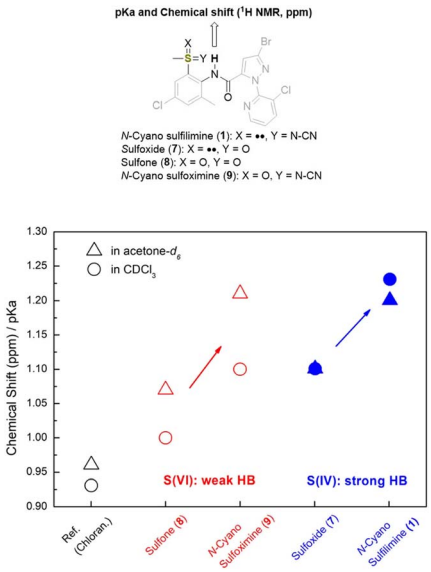


Fig. 3 $^1$H NMR and p$K_a$ analyses of organosulfur compounds **1** and **7–9**.

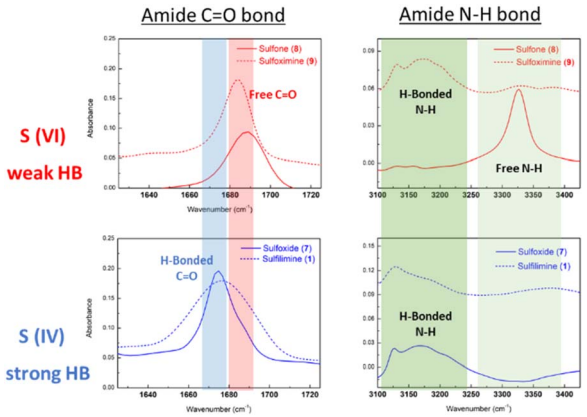


Fig. 4 FT-IR spectra of the organosulfur derivatives **1** and **7–9**.

organosulfur derivatives **1** and **7–9** appeared to have stronger interaction than the diamide compound chlorantraniliprole. In particular, S(IV) compounds **1** and **7** (highlighted in blue) exhibited superior hydrogen bonding interactions to the S(VI) compounds **8** and **9** (highlighted in red) and were slightly affected by the polarity of NMR solvents. These results clearly imply that sulfoxide **7** and sulfilimine **1** had a strong hydrogen bonding properties.

The FT-IR spectra of organosulfur compounds **1** and **7–9** were illustrated in Fig. 4. The spectrum of each compound showed different spectroscopic characteristics at 1660–1700 cm$^{-1}$ (amide C=O bond) and 3100–3400 cm$^{-1}$ (amide N–H bond). If strong hydrogen bonding was present, the absorbance peaks of the C=O and N–H bonds tended to appear at small wavenumbers (cm$^{-1}$).[67] Consequently, the FT-IR study suggested that S(IV) compounds **1** and **7** were the best moieties for the formation of IHB.

### Permeability

The synthesized organosulfur compounds **1** and **7–9** were evaluated for their permeability using parallel artificial membrane permeability assay (PAMPA). Interestingly, a similar trend was observed that the S(IV) compounds possessed superior properties to S(VI) compounds. As shown in Fig. 5, *N*-cyano sulfilimine **1**, S(IV) compound, displayed

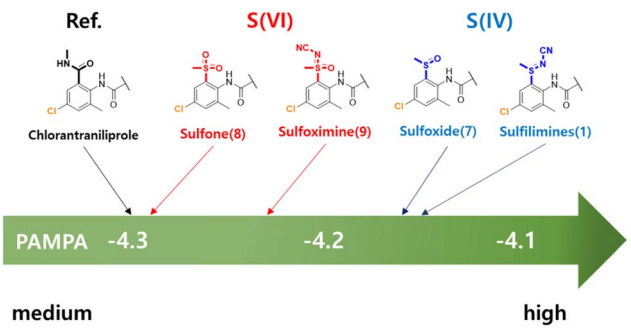


Fig. 5 Comparison of experimental PAMPA permeability values of organosulfur compounds **1** and **7–9**, and chlorantraniliprole.

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Table 1 Insecticidal activities of *N*-cyano sulfilimine chlorantraniliprole **1** and a series of organo sulfur-substituted chlorantraniliprole derivatives **7–9** against the 3rd instar larvae of *Spodoptera litura*

| | Derivatives | Against the 3rd instar larvae of *Spodoptera litura* | | | |
|---|---|---|---|---|---|
| | | Larvicidal activity (%) | | | Eating area (%) |
| | | | At time (h) | | |
| Entry | Functionality | Concentration (ppm) | 72 h | 96 h | 96 h |
| 1 | *N*-Cyano sulfilimine (**1**) | 12.5 | 100 | 100 | 0–5 |
| | | 6.25 | 100 | 100 | 0–5 |
| 2 | Sulfoxide (**7**) | 50 | 93.3 | 100 | 5–10 |
| 3 | Sulfone (**8**) | 12.5 | 96.7 | 100 | 0–5 |
| | | 6.25 | 96.7 | 100 | 0–5 |
| 4 | *N*-Cyano sulfoximine (**9**) | 50 | 10 | 16.7 | 10–30 |
| 5 | Chlorantraniliprole | 12.5 | 96.7 | 100 | 0–5 |
| | | 6.25 | 90 | 100 | 0–5 |

the highest permeability. It was clearly demonstrated that the presence of a sulfur–nitrogen ylide in the ionic form of *N*-cyano sulfilimine could increase the permeability of the molecule. For physicochemical properties of organosulfur compounds (**1**, **7–9**) such as equilibrium solubility, p$K_a$, logP, and PAMPA values are reported in supplemental Table S1.†

### Potency

*N*-Cyano sulfilimine chlorantraniliprole **1** and a series of organosulfur-substituted chlorantraniliprole derivatives **7–9** were measured for their insecticidal activities against the third instar larvae of *Spodoptera litura* according to the reported leaf-dip method.[68] Importantly, an *N*-cyano sulfilimine **1** showed excellent activity with a high inhibition of feeding behavior (eating area: 0–5%, ref.: 0–5%, Table 1) (for images, please see the ESI†). According to the data in Table 1, the *N*-cyano sulfilimine group could be considered an amide bioisostere.

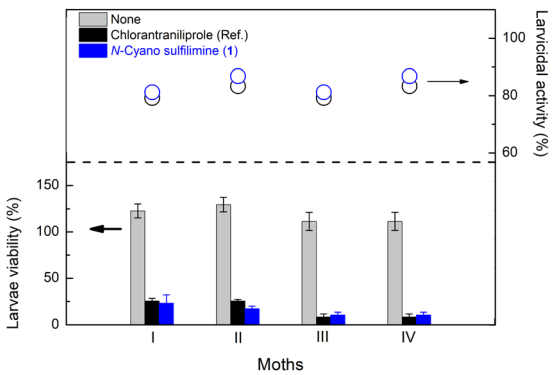


Fig. 6 An open-field test with *N*-cyano sulfilimine chlorantraniliprole **1** [(I) *Diamondback moth* (after 3 days), (II) *Diamondback moth* (after 7 days), (III) *Spodoptera litura* (after 3 days), (IV) *Spodoptera litura* (after 7 days)].

### Field test

An open-field test was conducted to evaluate the efficacy of *N*-cyano sulfilimine chlorantraniliprole **1** against *Spodoptera litura* and *Diamondback moth* (Fig. 6, for a description of the tests, please see the ESI†). High control of pests was observed at least 3 days after treatment. The consistent high activity of *N*-cyano sulfilimine **1** was assumed to be due to its high permeability, good water solubility and relatively low logP, leading to high systemicity in plants and good distribution in the soil.[69]

## Conclusions

In summary, the studies described here demonstrated that the *N*-cyano sulfilimine group comprised a viable new surrogate for the amide moiety with potential applications in bioactive molecule design. The replacement of an amide bond with an *N*-cyano sulfilimine moiety could successfully produce the compound **1** which showed the permeability enhancement with an increase in hydrogen bond strength. *N*-Cyano sulfilimine chlorantraniliprole **1** displayed high activity against a range of insects in the laboratory and in open-field tests. As a result, the *N*-cyano sulfilimine could be considered as a valuable addition to the existing amide bond isosteres.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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