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Synthesis and antiviral, insecticidal, and fungicidal activities of gossypol derivatives containing alkylimine, oxime or hydrazine moiety

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ABSTRACT

Gossypol is a part of the cotton plant's defense system against pathogens and herbivorous insects. To discover gossypol analogs with broad spectrum and high activity, a series of gossypol alkylamine Schiff base, oxime and hydrazone derivatives were synthesised and bioassayed. The biological results indicated that most of these derivatives exhibited higher anti-TMV activity than gossypol. Interestingly, the activities of compounds **10**, **15**, **18**, **20**, **23** and **26** were much higher than that of ribavirin. Furthermore, compound **26**, which was low toxicity to rat, showed better activity than control plant virus inhibitors in the field. Additionally, allyl amine Schiff base (**9**) displayed remarkable insecticidal activities against *Mythimna separata*, *Helicoverpa armigera* and *Ostrinia nubilalis*, whereas (pyridin-3-yl)methanamine Schiff base (**13**) showed excellent activity against *Culex pipiens pallens*. The fungicidal results revealed that all of compounds exhibited good activity against *Physalospora piricola*.

1. Introduction

Botanical pesticides refer to the plants, crude plant extracts or the derivatives of the active ingredients for the protection of crops and stored products from insect pests. It can be recommended as an ecochemical and sustainable strategy for the management of agricultural pests, due to their biodegradable nature, systemicity after application, capacity to alter the behavior of target pests and favorable safety profile.[1] Naturally active substances are featured by structural diversity and complexity, more stereogenic centers, but some deficiencies, such as the limited quantity available, being too complex to synthesize and being easy to decompose, inevitably limit the widespread use. Therefore, they usually are good lead compounds, and unlikely meet the demands as pesticides.[2] So, it is necessary to modify and optimize these structural frameworks.

Gossypol is the secondary metabolite of Gossypium and mainly embedded in the cottonseed pigment glands. The investigations on gossypol and its derivatives have been given considerable attention since the discovery of its impressive application in antifertility activity. It is also well known that gossypol displays great medical activities, providing an opportunity in struggling with the diseases such as cancer, HIV, and malaria.[3] Moreover, as a part of the plant's defense system against pathogenic fungi and insects,[4] gossypol is also endowed with great agricultural implication. However, the research based on gossypol as botanical pesticide is still rare.

Additionally, Schiff bases, usually synthesized by the condensation of amines with active carbonyl groups, exhibit a broad range of biological activities, including antifungal,[5] insecticidal,[6] antiviral[7] and herbicidal[8] activities. Significantly, it is expected that various natural products with the different imine groups could demonstrate distinctly pharmacological efficacy.[9] Taking our previous work[10] as an example, the anti-TMV activities of aromatic gossypol Schiff bases revealed the substituent groups of amine had great effect on the anti-TMV activities. As a continuous exploitation of the concept of the SAR, a series of gossypol alkylamine Schiff bases (Fig. 1) with the modification of the functional groups have been synthesized. Some compounds that displayed promising antiviral activity against TMV were identified. Further field trials showed that compound **26** displayed higher anti-TMV activity than did the control plant virus inhibitors.

It is also reported that oximes[11] and hydrazones[12] frequently exhibit satisfactory insecticidal, fungicidal, herbicidal and antiviral activity. And the majority of these compounds have characteristics of low toxicity and residue. As a result, the study on molecular design, synthesis and biological activity of oximes and hydrazones has attracted more and more attention in recent years. It is well

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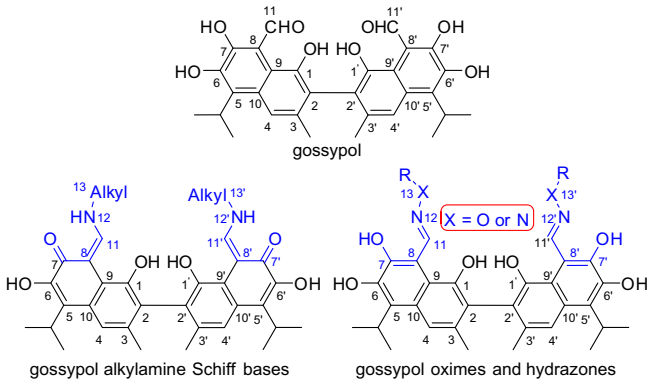


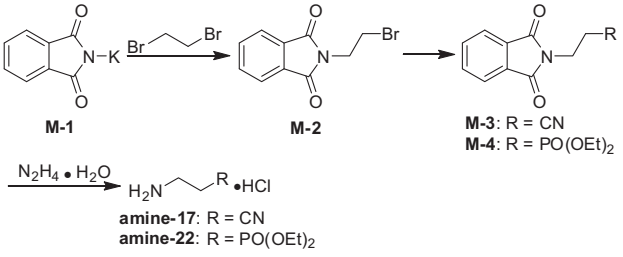
Figure 1. The structure of gossypol and its derivatives.

known that gossypol can exist in three symmetrical tautomeric forms: aldehyde–aldehyde, lactol–lactol, and ketol–ketol whereas oximes or hydrazones and amine Schiff bases of gossypol can be present in the two tautomeric forms that are analogous to the aldehyde–aldehyde and ketol–ketol tautomeric forms of gossypol.[9] As a further investigation on the influence of biological activity by the form of oximes and hydrazones and the improvement of their biological activities, a series of gossypol oxime and hydrazone derivatives (Fig. 1) have been synthesized and characterized in detail. Their biological activities in the field of pesticides have been performed as well.

2. Results and discussion

2.1. Chemistry

The synthesis of intermediates **amine-17**, **amine-19**, **amine-20** and **amine-22** was shown in Schemes 1 and 2. Nucleophilic substitution of phthalimide potassium with 1,2-dibromoethane provided **M-2**. And **M-2** further was reacted with sodium cyanide and triethyl phosphate respectively, to give **M-3** and **M-4**. Hydrazinolysis



Scheme 1. Synthetic route for intermediates **amine-17** and **amine-22**.

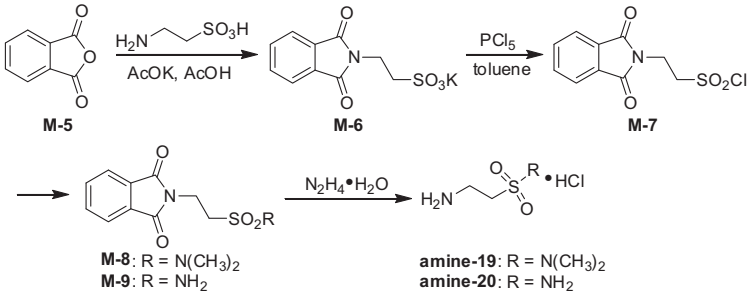
of the N-alkylphthalimide **M-3** or **M-4**, and then acidification could afford **amine-17** or **amine-22**. Ammonolysis of *o*-phthalic anhydride with taurine produced **M-6**, which was converted to sulfonyl chloride **M-7**. Sulfamide **M-8** or **M-9** could be obtained via the reactions of **M-7** and dimethylamine or ammonia. Finally, the same process as **M-3** could provide **amine-19** and **amine-20**.

The derivatives **1**–**33** could be synthesized by condensation of gossypol and corresponding amines in different conditions (Scheme 3). Most of the compounds were prepared by treating gossypol acetic acid with the corresponding amines in ethanol, and then collected by filtration. For the derivatives with sodium salt group (**18**, **25** and **26**), the corresponding amines were firstly prepared from homologous substituted-sulfonic acid and NaOH, which was used 3 equiv of gossypol to ensure the derivatives with sodium salt group. MeOH is employed as the solvent in the preparation of Schiff base **26** due to the poor solubility of sodium aminomethylsulfonate in ethanol. However, the product can be well dissolved in MeOH, making it difficult to be precipitated. Therefore, MeOH should be evaporated before Schiff base is recrystallized from isopropanol. The amine materials of compounds **17**, **19**–**22** and **28** were the hydrochloride salt of corresponding amines, therefore they were deacidized before reaction with gossypol. The oxime **27** could not be well obtained under the above conditions. After screening various conditions, NaOAc was the best base and the yield of oxime reached up to 97.6%.

All of our synthetic gossypol alkylamine Schiff bases exist in the enamine-enamine form, whereas the imine-imine tautomer was observed for oximes and hydrazones of gossypol in solution. Taking compounds **8** and **32** for example, the structures can be interpreted by the ^{1}H NMR spectrum. The signal peaks of symmetrical protons should appear at the same position and have identical coupling constant due to axial symmetry of the structure. For compound **8**, the presence of doublet peaks with the coupling constant of 13.3 Hz in the ^{1}H NMR spectrum can be attributed to the signals of H—C=C proton and H—N—^{t}C proton. This behavior can be rationally explained by the fact that two protons are adjacent and coupled with each other. The signal assigned to H—C_{11} in the ^{1}H NMR spectrum of compound **32** appears as a singlet at 9.64 ppm, indicating the absence of a proton at the ortho N atom. This result suggests the existence of the imine–imine tautomeric form of compound **32** in the solution.

2.2. Antiviral biological assay

The gossypol derivatives of alkylimine, oxime and hydrazone were evaluated for their antiviral activities against TMV in the laboratory (Table 1). Gossypol and ribavirin were used as controls. Overall, compared with gossypol and ribavirin, most of the newly designed compounds exhibited desirable anti-TMV activities. Compounds **10**, **15**, **18**, **20**, **23**, and **26** showed much higher inhibition than that of ribavirin and gossypol both in vitro and in vivo at



Scheme 2. Synthetic route for intermediates **amine-19** and **amine-20**.