Article

Antibacterial Activity of Novel 18*β*-Glycyrrhetinic Hydrazide or Amide Derivatives

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Through a facile structural modification on the natural bioactive ingredient 18β-glycyrrhetinic acid(GA), a series of novel GA hydrazide or amide derivatives was obtained, and their final molecular frameworks were characterized by NMR and HRMS analysis. Antibacterial bioassays revealed that some of the GA hydrazide or amide derivatives were able to suppress the growth of three tested plant pathogens. Particularly, compound **3**c exhibited excellent *in vitro* activity against *Xanthomonas oryzae* pv. *Oryzae* (*Xoo*), *Pseudomonas syringae* pv. *actinidiae*(*Psa*), and *Xanthomonas axonopodis* pv. *citri*(*Xac*), providing the EC_{50} values of 5.89, 16.1, and 3.64 μg/mL, respectively. The data were better than those of the positive controls thiodiazole copper(92.7, 77.8, and 89.9 μg/mL, respectively) and bismerthiazol(31.1, 125.6, and 77.4 μg/mL, respectively). In addition, *in vivo* experiments suggested that, compared with thiodiazole copper(41.93% and 39.73%, respectively), compound **3**c exerted prominently curative and protective activities against rice bacterial leaf blight at 200 μg/mL with the control effects of 52.36% and 51.40%, respectively. Given these obtained results, GA hydrazide or amide derivatives could serve as the feasible leads for exploring highly bioactive substrates.

Keywords 18*β*-Glycyrrhetinic; Hydrazide or amide derivative; Synthesis; Antibacterial activity

1 Introduction

Plant pathogens, such as the most destructive *Xanthomonas oryzae* pv. *oryzae*(*Xoo*), *Pseudomonas syringae* pv. *actinidiae*(*Psa*), and *Xanthomonas axonopodis* pv. *citri*(*Xac*), that can attack and infect more than 200 plant species, especially the rice, kiwifruit, grapefruit and citrus are greatly hard to manage in agriculture[1−3]. As one of the most harmful plant bacterial pathogens, *Xoo* is a notorious pathogen in rice and causes rice bacterial leaf blight with typical symptoms including thin and white plant leaves[4,5]. Normally, these plant diseases cause seriously reduced food production and economic losses that prompt significant concerns in every country, especially in Asia and Western Africa[6]. Even though there are a limited number of bactericides including copper preparations and bismerthiazol that can plausibly control this bacterial disease, the lower control effectiveness cannot meet the modern demands because of the extensive use and abuse of these pesticides and the emergence of resistant bacterial strains[7,8]. In this case, there is an urgent demand for discovering and developing novel agrochemicals targeting plant bacterial diseases, especially the progressive diseases caused by the aforementioned three pathogens[9,10].

Natural product was an extremely valuable source for creating fresh bioactive ingredients for their privileged features, such as natural molecular skeletons, good biocompatibility, and capturing multiple targets of adversaries[11,12]. 18*β*-Glycyrrhetinic acid(GA), discovered and separated from a traditional Chinese medicine *Glycyrrhiza* sp., is a natural pentacyclic triterpene[13]. Currently, GA is a successfully commercialized product with the mature technology and a relatively lower price. This popular structure has been reported to have a wide range of bioactivities, including anti-cancer[14,15], antibacterial[16−18], antiviral[19], anti-inflammatory[20], and hepatic protective effects[21,22]. However, GA displays some disagreeable physicochemical properties, especially the high hydrophobicity and low water solubility and penetrability[23], thus seriously blocking its broader applications. To make up for these deficiencies, extensive efforts have been attempted, such as developing different formulations, fabrication of biocompatible nano-inclusions or nano-capsules, and chemical modification[24,25]. Among them, chemical modification has achieved great advances because the decorated GA derivatives normally possess improved bioactivities and augmented biological silhouettes. Consequently, a lot of 18*β*-glycyrrhetinic derivatives mainly modified at the C—OH and C30 were developed and displayed improved biological activities[26,27]. For example, Cai and co-workers[28] reported a series of amide-linked GA derivatives mainly modified at the C30, which exhibited noteworthy anticancer activity against Karpas299, A549, HepG2, MCF-7 and PC-3 cells. Liu *et al.*[29] have evaluated the antitumor activities of a series of GA derivatives, which were

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modified at the C30, and found that the designed target compounds exhibited significant antiproliferative activities against all the tested MDR cell lines(A549, MCF-7, Bel-7402, K562, L-O2).

Inspired by the above-mentioned investigations and trying to improve the solubility and biological effects of GA, in this work, we exploited a facile structural modification strategy to prepare a series of novel 18*β*-glycyrrhetinic hydrazide or amide derivatives(Fig.1). Within these title molecules, a valuable hydrazide or amide pattern was placed at the C30 position of GA. The *in vitro* antibacterial activities toward three above-mentioned plant bacterial strains of all the title molecules were examined. Meanwhile, the *in vivo* experiments against rice bacterial blight of the highly bioactive target compound **3**c would be carried out.

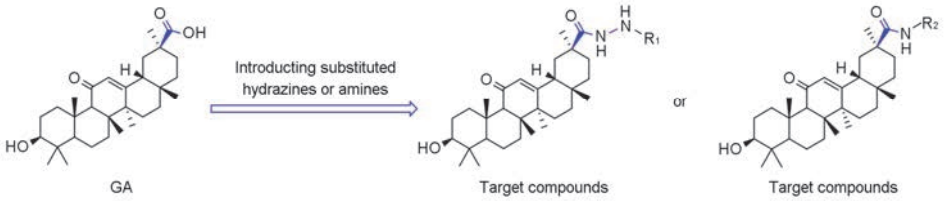


Fig.1 Design route of a series of 18*β*-glycyrrhetinic hydrazide or amide derivatives

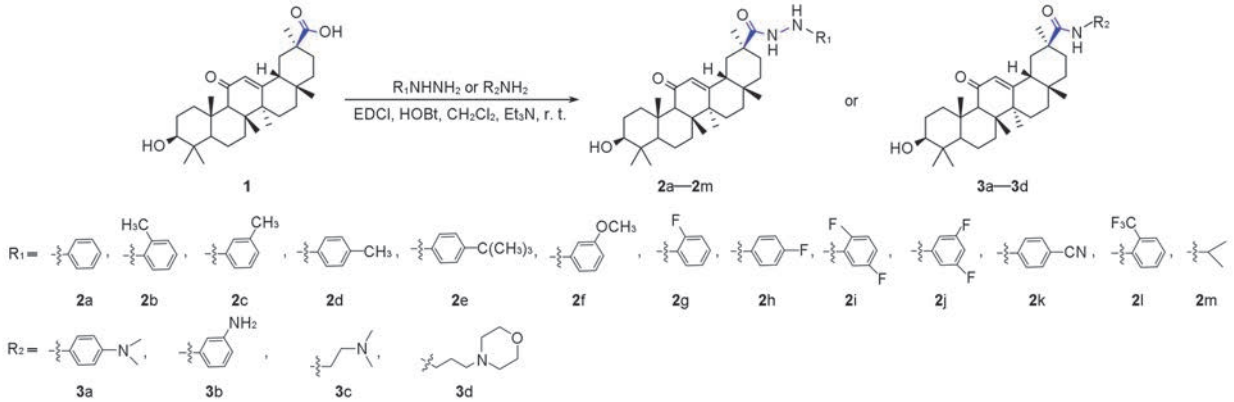
2 Experimental

2.1 General Information

Instruments: NMR, JEOL-ECX-500 and Bruker Biospin AG-400 apparatuses; melting point apparatus, SGW® X-4B, Shanghai Yidian Physical Optical Instrument Co., Ltd.; high resolution mass spectrometer, UItiMate 3000, Thermo SCIENTIFIC; contact angle apparatus, JC2000D1, Shanghai Zhongchen Digital Tchnic Apparatus Co., Ltd. All statistical analyses were executed by the analysis of variance(ANOVA) with software SPSS 20.0.

2.2 Synthetic Procedures of Target Compounds (2a—2m and 3a—3d)

A simple structural modification way towards GA was shown in Scheme 1. The starting material 18*β*-glycyrrhetinic acid(1.06 mmol) was added to a mixture containing EDCI (1.59 mmol), HOBt(0.53 mmol) and triethylamine(3.39 mmol) in 8 mL of CH_2Cl_2. After stirring for 10 min at 25 °C, the related substituted hydrazines or substituted anilines(2.12 mmol) were added, and the mixture was stirred for another 24 h at 25 °C. After that, the organic matter was extracted with CH_2Cl_2, washed twice with purified water, and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. Finally, target compounds **2**a—**2**m and **3**a—**3**d were obtained by silica gel column chromatography using CH_2Cl_2/CH_3OH(50/1, volume ratio) as the eluent[30]. All these molecular structures were detected by NMR and HRMS spectra. All the spectral data and physical properties of the target compounds are presented in the Electronic Supplementary Material of this paper.



Scheme 1 Synthetic route of target compounds(2a—2m and 3a—3d)

3 Results and Discussion

3.1 Chemistry

A simple structural modification way towards GA was shown in Scheme 1. Briefly, GA was treated with various substituted hydrazines or substituted amines under typically condensating agents to provide the target compounds **2**a—**2**m and **3**a—**3**d with the yields of 55.3%—86.9%. All these molecular structures were detected by NMR and HRMS spectra(see the

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Electronic Supplementary Material of this paper).

3.2 Bioactivities

3.2.1 *In vitro* Antibacterial Activity

The antibacterial activity of all the title compounds toward *Xoo*, *Psa* and *Xac* was evaluated by the classical turbidimeter test[31,32]. As indicated in Table 1, most of the title compounds exhibited better inhibitory effects on the bacterial growth compared to that of GA at 200 or 100 μg/mL. Distinctively, compound **2**f provided a strong inhibitory effect toward *Xoo* with a rate of 61.5% at 200 μg/mL. This outcome was better than that of GA(15.1%). For the hydrazide series(**2**a—**2**m), although most of the target compounds showed slightly ameliorative antibacterial bioactivity compared to the parent compound GA, the values were quite lower than that of positive controls(BT and TC). By contrast, compounds **3**c and **3**d afforded excellent inhibition rates of 100% at 200 and 100 μg/mL. These data were quite better than those of the parent structure GA(15.2% and 9.34%, respectively) and commercial agent TC(77.2% and 61.7%, respectively), and were comparable to those of BT(100% and 100%, respectively). The structure-activity relationship(SAR) was summarized according to the obtained molecular structures and properties and preliminary biological data. The water solubility and dispersion of compounds **2**a—**2**m(concentration of 200 μg/mL) are presented in Fig.S1(see the Electronic Supplementary Material of this paper). The result showed that the relatively good bioactive compound **2**f(a strong electron-donating group 3-OCH_3 on the benzene ring) displayed improved water solubility than other target compounds and the parent compound GA, which was in accordance with the predictive *AlgP* value of compound **2**f(*AlgP* value is 0.816, while *AlgP* value for GA is 1.683, Table S1, see the Electronic Supplementary Material of this paper). Meanwhile, introducing the hydrophobic groups[such as $-CH_3$, $-C(CH_3)_3$, $-CF_3$] on the benzene ring along with high *AlgP* values(1.966—3.185) could not endow the target compounds with significant bioactivity. On the other hand, these hydrazide derivatives showed little improved surface wettability towards rice leaves from the contact angles detection(concentration of 200 μg/mL, Fig.S2, see the Electronic Supplementary Material of this paper), providing the contact angles within 96.5°—108.5°(the parent compound GA gives 103°). This outcome suggested that the hydrazide series showed relatively weak interactions with the surface of rice leaves, which might affect the bioavailability. For the amide series(**3**a—**3**d), the highly bioactive compound **3**c displayed the best water solubility than other target compounds and GA(Fig.S1). The predictive *AlgP* value indicated that compound **3**c performed ameliorative hydrophilicity compared to the parent compound GA. The increase(compound **3**a) and the decrease(compounds **3**b and **3**d) of the *AlgP* values of the target compounds would reduce the bioactivity(Table S1). Moreover, compound **3**c showed significantly improved surface wettability towards rice leaves from the contact angles detection(Fig.S2), providing the contact angles of 85.5°(GA gives 103°). This outcome suggested that the designed compound **3**c might improve the bioavailability.

Table 1 Inhibition effects of target compounds(2a—2m, 3a—3d) against *Xoo*

Compd.	Inhibition rate(%)	
	200 μg/mL	100 μg/mL
2a	18.6±1.6	8.54±0.82
2b	15.2±3.1	0
2c	28.1±1.9	9.69±1.07
2d	0	0
2e	12.6±2.8	8.14±0.45
2f	**61.5±3.7**	18.1±2.1
2g	0	0
2h	15.6±2.3	8.27±1.79
2i	11.9±0.9	0
2j	19.7±1.3	12.4±0.9
2k	14.8±1.7	0
2l	18.1±2.9	0
2m	38.7±2.9	16.2±3.1
3a	9.64±1.89	0
3b	31.4±1.5	11.8±0.8
3c	**100**	**100**
3d	**100**	**100**
GA	15.1±2.2	9.34±1.53
BT	100	100
TC	77.2±2.7	61.7±1.4

For the anti-*Psa* activity(Table 2), compounds **2**e—**2**h, **2**k and **3**d displayed certain biological effects with inhibition rates of 36.4%, 34.7%, 37.5%, 38.9%, 40.2% and 63.7% at 200 μg/mL. As decreasing the dosage to 100 μg/mL, compounds **2**k and **3**d afforded better antibacterial ability(38.1% and 53.5%) than that of BT(33.4%). Compounds **2**f, **2**j, **2**l, and **3**a showed better bioactivities(within 23.5%—26.6%) compared to that of GA(0%). Especially, compound **3**c showed a significant inhibitory effect toward *Psa* with a rate of 100% even at 100 μg/mL. SAR showed that the introduction of strong electron-withdrawing group 2-CF_3(**2**l, 31,7%) or 4-CN(**2**k, 40.2%) on the benzene ring could improve the anti-*Psa* activity by comparing to compound **2**a(—H, 26.8%). The position of substituted groups on the phenyl ring also affected the anti-*Psa* capacity, illustrated by the contrastive inhibition rates of compounds **2**c(3-CH_3, 29.2%)>**2**d(4-CH_3, 26.9%)>**2**b(2-CH_3, 19.9%).

For the anti-*Xac* activity, most of the compounds exhibited lower antibacterial effects(Table 3). Among them, compounds **2**l and **3**b gave the inhibition rates of 22.1% and 20.5%, respectively, which exceeded that of GA(9.36%). Meanwhile,

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Table 2 Inhibition effects of target compounds(2a—2m, 3a—3d) against *Psa*

Compd.	Inhibition rate(%)	
	200 μg/mL	100 μg/mL
2a	26.8±0.9	12.1±3.3
2b	19.9±1.2	0
2c	29.2±3.1	17.3±1.5
2d	26.9±2.3	16.5±0.6
2e	36.4±2.4	19.7±2.4
2f	34.7±3.2	23.5±3.2
2g	37.5±2.7	15.1±1.2
2h	38.9±1.5	16.3±1.6
2i	9.94±1.44	0
2j	30.3±0.3	25.4±1.7
2k	40.2±1.6	38.1±0.3
2l	31.7±1.6	24.6±3.6
2m	0	0
3a	30.8±2.6	26.6±1.7
3b	24.1±2.7	19.5±1.4
3c	**100**	**100**
3d	63.7±3.1	53.5±2.5
GA	21.3±1.6	0
BT	84.5±3.4	33.4±1.8
TC	89.4±1.9	58.0±1.5

Table 3 Inhibition effects of target compounds(2a—2m, 3a—3d) against *Xac*

Compd.	Inhibition rate(%)	
	200 μg/mL	100 μg/mL
2a	7.94±0.52	0
2b	0	0
2c	0	0
2d	19.1±1.6	11.2±3.5
2e	12.7±2.8	11.5±3.7
2f	8.86±0.81	0
2g	9.11±2.56	0
2h	18.9±2.1	10.6±0.5
2i	0	0
2j	0	0
2k	11.1±1.3	0
2l	22.1±3.3	13.6±2.6
2m	13.9±2.5	0
3a	0	0
3b	20.5±3.6	9.61±2.11
3c	**100**	**100**
3d	82.9±2.6	73.4±1.9
GA	9.36±1.18	0
BT	95.4±1.5	63.1±3.5
TC	91.0±1.1	55.9±3.2

compound **3**d displayed a better inhibitory effect toward *Xac* with the rates of 82.9% and 73.4% at 200 and 100 μg/mL, respectively. Particularly, compound **3**c exerted the strongest inhibition rate of 100% at the concentrations of 200 or 100 μg/mL.

SAR showed that whether placing the electron-donating groups or electron-withdrawing groups on the benzene ring had weak effects on the anti-*Xac* activity by comparing to compound **2**a(7.94%) without a substituent. The alkylamine substitutions(**3**c and **3**d) at C30 of GA afforded better antibacterial ability by comparing to the aromatic substituents (**3**a and **3**b) at 200 or 100 μg/mL.

To have a deeper study for the antibacterial activity of compound **3**c, the EC_{50} values against *Xoo*, *Psa* and *Xac* were obtained as 5.89, 16.1, and 3.64 μg/mL, respectively, and presented in Table 4, which were better than those of the antibacterial drugs TC(92.7, 77.8, and 89.9 μg/mL) and BT(31.1, 125.6, and 77.4 μg/mL). In comparison, compound **3**d could achieve certain improvement effects against *Xoo* and *Xac* with EC_{50} values of 36.5 and 29.1 μg/mL, respectively, suggesting that the presence of an amide pattern could benefit more interactions with the receptors of tested pathogens. Given the above results, compound **3**c could be considered as the leading compound for exploring highly bioactive antibacterial agents.

3.2.2 *In vivo* Antibacterial Activity

Because compound **3**c performed the considerable anti-*Xoo* activity and was swiftly synthesized, the antibacterial activity *in vivo* triggered by compound **3**c against rice bacterial blight under greenhouse conditions was studied.

As indicated in Table 5 and Fig.2, 14 days after inoculation, compared with the commercial agent TC(41.93%), compound **3**c exerted prominent *in vivo* curative activity(52.36%) at 200 μg/mL. Moreover, Table 5 and Fig.3 showed that compound **3**c demonstrated good *in vivo* protective activity with the control effect of 51.40% at 200 μg/mL, which was better than that of TC(39.73%). This finding suggested that compound **3**c can be considered as a new antibacterial lead.

Table 4 EC_{50} values of compounds 3c and 3d against pathogen *Xoo*, *Psa* and *Xac*

Compd.	*Xoo*		*Psa*		*Xac*	
	Regression equation	EC_{50}/(μg·mL^{-1})	Regression equation	EC_{50}/(μg·mL^{-1})	Regression equation	EC_{50}/(μg·mL^{-1})
3c	y=6.486x+0.005	5.89±0.11	y=1.075x+3.704	16.1±0.1	y=5.240x+2.060	3.64±0.03
3d	y=0.6489x+3.9858	36.5±0.3	y=1.840x+1.215	114.1±8.4	y=1.8818x+2.2463	29.1±2.4
GA	—	>100	—	>100	—	>100
BT	y=4.174x–1.229	31.1±0.9	y=4.739x−4.947	125.6±4.9	y=3.948x–2.456	77.4±1.7
TC	y=2.555x–0.026	92.7±3.4	y=2.907x–0.498	77.8±3.1	y=3.828x–2.480	89.9±2.7

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Table 5 *In vivo* bioactivities of compound 3c against rice bacterial blight at 200 μg/mL(14 days after spraying)

Compd.	Curative activity			Protective activity		
	Morbidity(%)	Index(%)	Control efficiency(%)[b]	Morbidity(%)	Index(%)	Control efficiency(%)[b]
3c	100	38.51	52.36 A	100	39.29	51.40 A
TC	100	46.94	41.93 B	100	48.72	39.73 B
CK[a]	100	80.84	——	100	80.84	——

a. Negative control; *b.* statistical analysis was executed by the ANOVA method under the condition of equal variances assumed(P>0.05) and equal variances not assumed(P<0.05). Different uppercase letters indicate the control efficiencies with sigrificant differences among different treatment groups.

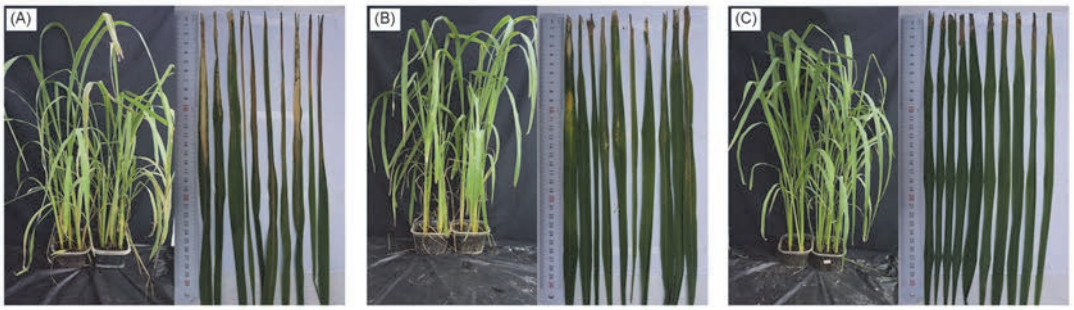

Fig.2 Curative activity of CK(A), TC(B) and compound 3c(C) against rice bacterial blight at 200 μg/mL
In each photograph, the left is the whole inoculated plants without(A) or with[(B) and (C)] drug treatment, the right is the representative leaves obtained from the whole plants.

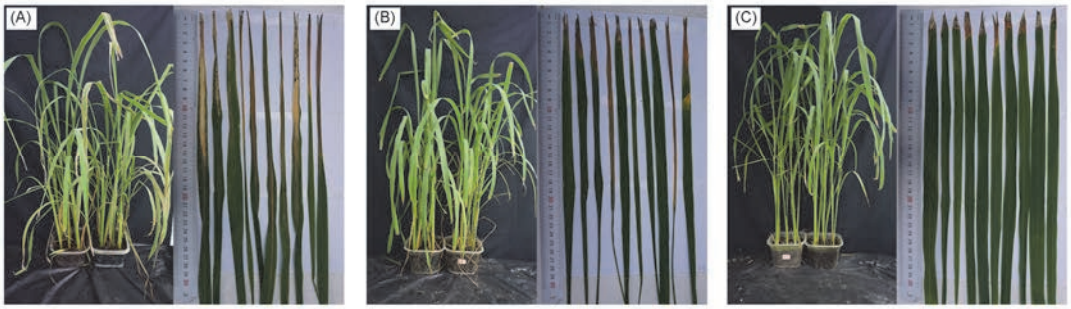

Fig.3 Protective activity of CK(A), TC(B) and compound 3c(C) against rice bacterial blight at 200 μg/mL
In each photograph, the left is the whole inoculated plants without(A) or with[(B) and (C)] drug treatment, the right is the representative leaves obtained from the whole plants.

4 Conclusions

In summary, an array of novel 30-substituted 18β-glycyrrhetinic acid derivatives containing the hydrazine or amide patterns were synthesized based on the natural framework of GA. Subsequently, their antibacterial activities were screened by the typical turbidimeter test. Antibacterial bioassays revealed that compound **3**d exerted prominent inhibitory effects toward *Xoo* and *Xac* with EC_{50} values of 36.5 and 29.1 μg/mL, which was extremely superior to that of the parent structure GA(>100 μg/mL). Especially, compound **3**c afforded excellent bioactivities against *Xoo*, *Psa* and *Xac* with EC_{50} values of 5.89, 16.1 and 3.64 μg/mL, respectively. These data were better than that of the positive controls BT and TC. Additionally, *in vivo* experiments showed that compound **3**c could effectively reduce rice bacterial blight. Moreover, compound **3**c showed significantly improved surface wettability towards rice leaves from the contact angles detection, suggesting that the designed compound **3**c might improve the bioavailability. Given the simple modification on the skeleton of GA, we recommended that this kind of GA hydrazide or amide derivatives could serve as the feasible leads for exploring highly bioactive compounds.

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s40242-021-0370-9.

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Conflicts of Interest

The authors declare no conflicts of interest.

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