Communication

Synthesis and Biological Activity of a Series of Novel *N*-Substituted β-Lactams Derived from Natural Gallic Acid

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A series of novel β-lactams derived from natural gallic acid were conveniently synthesized *via* classical Staudinger ketene-imine cycloaddition reaction. Their structures were confirmed by satisfactory analytical and spectroscopic methods. The preliminary bioassay showed that some of the target compounds exhibited obvious insecticidal activity against *Heliothis armigera* at the dosage of 0.2 mg/mL.

Keywords: β-Lactams; Synthesis; Biological activity.

INTRODUCTION

The β-lactam skeleton is still the essential structural backbone of the widely employed family of natural and unnatural antimicrobial agents to date.[1-4] The most widely used antibiotics such as the penicillins,[5] aztreonam, cephalosporins,[6] carumonam, monobactams and nocardicins (Fig. 1) all contain the azetidine-2-one heterocycle, which is the core structural feature in a number of broad spectrum β-lactams derivatives.[7,8] Nowadays, with the development of resistance of bacteria towards the β-lactam antibiotics, the constant need for novel drugs displaying broader biological activity to combat the microorganisms that have built up a resistance against the most traditional drugs.[9,10] So the extensive interest of chemists into β-lactams have been maintained for decades.

Meanwhile, β-lactams have received wide use as key synthons for many biologically important classes of compounds in organic synthesis.[11-16] Especially, the monocyclic β-lactams namely azetidinones, are an important part of the β-lactams antibiotic scaffold, which are always obtained *via* classical Staudinger ketene-imine cycloaddition reaction[17-22] and are known to exhibit interesting and broad biological activities. A large number of monocyclic β-lactams possess powerful antibacterial, antimicrobial, anti-inflammatory, anti-convulsant, anti-viral and antitubercular activity etc.[23-31]

On the other hand, as we know, natural gallic acid is a strong antioxidant and exhibit potential antifungal, antibacterial, anti-inflammatory and anti-cancer activity.[32,33] Recently, the synthesis and biological evaluation of gallic acid derivatives have attracted considerable attention due to its naturally derived characters, and which are wide prevalence in pesticides and medicinal compounds. More and more derivatives have been demonstrated to present obvious antimicrobial, antitumor, antifungal activity, etc.[34-42]

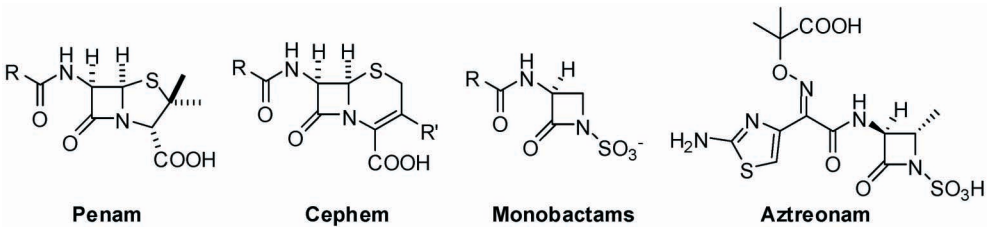

Fig. 1. Representative structures of natural β-lactam antibiotics.

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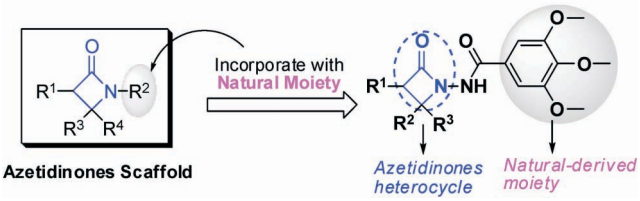


Fig. 2. Design strategy for novel azetidinones derivatives.

Hence, as part of our agrochemistry program aimed at the search for novel natural product-oriented bioactive molecules, based on the aforementioned, we utilized β-lactam scaffold as prototype structural unit and planed for the incorporating natural gallic acid and azetidinone moieties in a single molecular scaffold (Fig. 2). The present work deals with the molecule design, convenient synthesis of novel series of β-lactam derivatives containing natural gallic acid moiety, and evaluated their biological properties as potential agricultural protective plant agents.

RESULTS AND DISCUSSION

Synthesis of *N*-substituted β-lactams derived from natural gallic acid

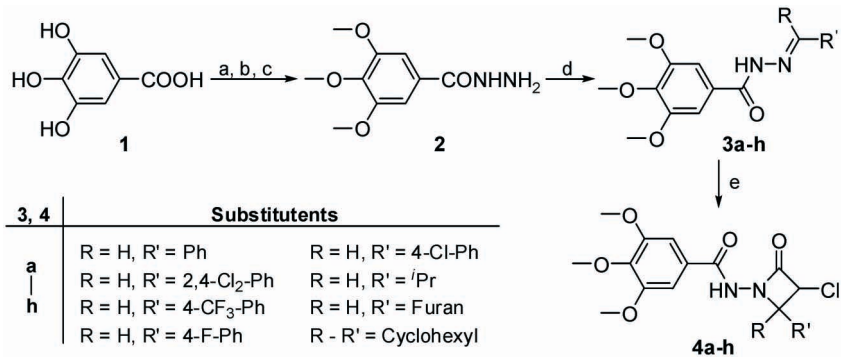
In the present study, a series of novel β-lactams derivatives were designed and synthesized by reacting functionalized acylhydrazones with 2-chloroacetyl chloride. The general method for the preparation of β-lactams derivatives containing natural gallic acid moiety **4a-h** are outlined in Scheme I.

The natural gallic acid **1** was selected as starting materials, which were routinely transferred to the corresponding 3,4,5-trimethoxybenzohydrazide **2** *via* sequence steps including *O*-alkylation, esterification and hydrazinolysis reaction. The synthesized benzoates were treated with hydrazine hydrate in EtOH to afford the hydrazides **2**. The following condensation reaction between hydrazides **2** and various aldehyde or ketone led to the important substrates, substituted benzoylhydrazone **3a-h**. Then the various benzoylhydrazone derivatives **3a-h** were treated with ketenes, generated *in-situ* from 2-chloroacetyl chloride in the presence of triethylamine to give desired multi-substituted monocyclic β-lactams derivatives **4a-h**. All the target compounds **4a-h** gave satisfactory chemical analyses. ^{1}H NMR, ESI-MS spectra and elemental analyses were consistent with the assigned structures.

The ketene-imine heterocyclization reaction is most probably initiated by a nucleophilic attack of the imino hydrazone nitrogen to the carbonyl carbon of *in-situ* generated ketene leading to an intermediate, with subsequent intramolecular reaction leading to the formation of target compounds. The possible mechanism of cycloaddition reaction to form target compounds is illustrated below in Scheme II.

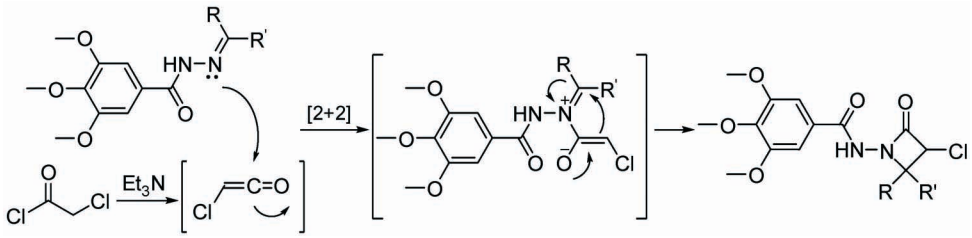
In the above-described experimental conditions, the heterocyclization reaction reached completion with a moderate yields and shorter time for target β-lactams derived from gallic acid. The obtained novel β-lactams derivatives were screened for insecticidal activity. The commercial insecticide spirodiclofen was tested as a reference compound under the same conditions as the synthesized β-lactams derivatives.

Scheme I



Synthetic route for azetidinones derivatives. Reagents and conditions: a. Me_2SO_4, NaOH, then HCl; b. EtOH, Conc. H_2SO_4; c. 5 equiv. $NH_2NH_2{\cdot}H_2O$, reflux for 5-7 h; d. 1.1 equiv. Ketone/aldehyde, EtOH, reflux for 6-8 h; e. 1.2 equiv. $ClCH_2COCl$, $CHCl_3$, Et_3N, r.t. to 40 °C for 2-5 h.

Scheme II The possible mechanism of cyclcondenation reaction to afford β-lactams

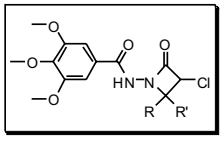


Biological activity evaluation for β-lactams derivatives 4a-h

The bioactivity of synthesized β-lactams derivatives containing gallic acid moiety **4a-h** against *Heliothis armigera* and *Plutella xylostella* were performed according to the modified method described in literature.[43] Unfortunately, none of the title compounds were found to be active against the *Plutella xylostella*, however, four compounds exhibited obvious insecticidal activity against *Heliothis armigera* at the dosage of 0.2 mg/mL, which are presented in Table 1.

The results listed in Table 1, indicated that some of target molecules (such as compounds **4a**, **4f**, **4g**, and **4h**) displayed obviously selective insecticidal activity against *Heliothis armigera* at the dosage of 200 μg/mL. Especially, compound **4a** and **4f** bearing phenyl and isopropyl, respectively, which indicate moderate activity at the relative low concentration of 100 μg/mL. In addition, the introduction of electron-withdrawing groups (such as halogen and trifluoromethyl) lead to the striking contrast, compounds containing these groups almost lost activities at the same concentration level (Entry 2-5, Table 1).

Table 1. Insecticidal activities of target compounds **4a-h** against *Heliothis armigera*



Entry	Compd. No.	Substituents		Insecticidal activity at different Concentration (%, μg/mL)					
		R	R′	200	100	50	25	12.5	6.25
1	**4a**	H	Ph	80	50	40	30	30	0
2	**4b**	H	4-Cl-Ph	0	0	0	0	0	0
3	**4c**	H	2,4-Cl_2-Ph	0	0	0	0	0	0
4	**4d**	H	4-F-Ph	0	0	0	0	0	0
5	**4e**	H	4-CF_3-Ph	0	0	0	0	0	0
6	**4f**	H	^{i}Propyl	90	70	30	30	0	0
7	**4g**	H	Furan-2-yl	50	50	30	0	0	0
8	**4h**	Cyclohexyl		100	50	30	0	0	0
9	Spirodiclofen			30	30	0	0	0	0

CONCLUSIONS

In summary, we have described the molecular design, synthesis, and biological evaluation of a series of novel monocyclic β-lactams derived from natural gallic acid. Eight novel β-lactams derivatives have been conveniently synthesized, and characterized by analytical and spectroscopic methods. The preliminary bioassay results indicated that some of target compounds exhibited obviously insecticidal activity compared commercial spirodiclofen. To our best knowledge, this is the first report about the syntheses and insecticidal activity of gallic acid-based β-lactams derivatives. Further structural optimization and activity profiles about the designed novel β-lactams derivatives are well under way.

EXPERIMENTAL

Instrumentation and chemicals

All melting points were taken on a digital model X-5 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker spectrometer (500 MHz) with $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values. Coupling constants ^{n}J are reported in Hz. Mass spectra were performed on a MicroMass Quattro microTM API instrument. Elemental analyses were performed on a Vario EL III elemental analysis instrument. Analytical thin-layer chromatography (TLC) was carried out on precoated plates, and spots were visualized with ultraviolet light. All chemicals or reagents were purchased from standard commercial supplies. Anhydrous $CHCl_3$ was dried according to standard methods.[44] All other solvents and reagents were analytical reagent and used directly without purification.

General synthetic procedure for 3,4,5-trimethoxybenzohydrazide 2

The key synthetic intermediates 3,4,5-trimethoxybenzohydrazide **2** was prepared *via* three general steps including alkylation, esterification and hydrazinolysis reaction following the modified method according to literature. This compound was obtained following the above method as white crystal, yield 74%, m.p. 158-160 °C (Lit.[37] 156-158 °C).

General synthetic procedure for substituted aroylhydrazones 3a-h

Substituted aroylhydrazones **3a-h** were synthesized by condensation reactions between hydrazides **2** and various aldehyde or ketone. Following the brief descriptions: The equal amounts of 3,4,5-trimethoxybenzohydrazide (0.01 mol), appropriate aldehyde/ketone (0.01 mol) were refluxed in absolute alcohol (15 mL) for several hours, which was detected by TLC. Then the solution was concentrated, and the condensation product aroylhydrazone separated out on cooling and was recrystallized from ethanol. Their physico-chemical properties and spectra data are as follows:

***N*′-Benzylidene-3,4,5-trimethoxybenzohydrazide (3a)**

This compound was obtained following the above method as white crystal, yield 83%, m.p. 141-142 °C; ESI-MS: calcd for $C_{17}H_{18}N_2O_4$ *m/z* 314.1; found, 315.6 $(M+H)^+$.

***N*′-(4-Chlorobenzylidene)-3,4,5-trimethoxybenzohydrazide (3b)**

This compound was obtained following the above method as white powder, yield 86%, m.p. 185-187 °C; ESI-MS: calcd for $C_{17}H_{17}ClN_2O_4$ *m/z* 348.1; found, 349.4 $(M+H)^+$.

***N*′-(2,4-Dichlorobenzylidene)-3,4,5-trimethoxybenzohydrazide (3c)**

This compound was obtained following the above method as white powder, yield 90%, m.p. 221-222 °C; ESI-MS: calcd for $C_{17}H_{16}Cl_2N_2O_4$ *m/z* 382.0; found, 383.8 $(M+H)^+$.

***N*′-(4-Fluorobenzylidene)-3,4,5-trimethoxybenzohydrazide (3d)**

This compound was obtained following the above method as white sheet crystal, yield 85%, m.p. 179-180 °C; ESI-MS: calcd for $C_{17}H_{17}FN_2O_4$ *m/z* 332.1; found, 332.9 $(M+H)^+$.

3,4,5-Trimethoxy-*N*′-(4-(trifluoromethyl)benzylidene)-benzohydrazide (3e)

This compound was obtained following the above method as white solid, yield 88%, m.p. 194-195 °C; ESI-MS: calcd for $C_{18}H_{17}F_3N_2O_4$ *m/z* 382.1; found, 383.5 $(M+H)^+$.

3,4,5-Trimethoxy-*N*′-(2-methylpropylidene)benzohydrazide (3f)

This compound was obtained following the above method as white powder, yield 80%, m.p. 142-143 °C; ESI-MS: calcd for $C_{14}H_{20}N_2O_4$ *m/z* 280.1; found, 281.7 $(M+H)^+$.

***N*′-(Furan-2-ylmethylene)-3,4,5-trimethoxybenzohydrazide (3g)**

This compound was obtained following the above method as white powder, yield 76%, m.p. 164-165 °C; ESI-MS: calcd for $C_{15}H_{16}N_2O_5$ *m/z* 304.1; found, 305.4 $(M+H)^+$.

***N*′-Cyclohexylidene-3,4,5-trimethoxybenzohydrazide (3h)**

This compound was obtained following the above method as white powder, yield 80%, m.p. 118-120 °C; ESI-MS: calcd for $C_{16}H_{22}N_2O_4$ *m/z* 306.2; found, 307.8 $(M+H)^+$.

General procedure for the synthesis of 1,4-disubstituted-3-chloro-2-azetidinones

Equimolar amounts (0.01 mol) of aroylhydrazones **3a-h** and triethylamine in dry $CHCl_3$ (30 mL) were refluxed for 15 min. The reaction mixture was then cooled, and a solution of chloroacetyl chloride (0.012 mol) in $CHCl_3$ was added dropwise. The reaction mixture was stirred for further 2-5 h and washed with water. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed over silica gel with ethyl acetate/petroleum ether as eluent or recrystallized to give solid or powder. Their physico-chemical properties and the spectra data are as follows:

***N*-(3-Chloro-2-oxo-4-phenylazetidin-1-yl)-3,4,5-trimethoxybenzamide (4a)**

This compound was obtained following the above method as white solid, yield 72%, m.p. 126-128 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.50 (s, 2H, Ph-H), 7.44 (s, 3H, Ph-H), 7.12 (s, 2H, Ph-H), 7.08 (s, 1H, N-H), 5.53 (d, J = 7.8 Hz, 1H, COCH), 4.65 (d, J = 7.8 Hz, 1H, NCH), 3.91 (s, 9H, CH_3O); ESI-MS: calcd for $C_{19}H_{19}ClN_2O_5$ *m/z*

390.1; found, 391.7 $(M+H)^+$; Anal. Calcd for $C_{19}H_{19}ClN_2O_5$: C, 58.39; H, 4.90; N, 7.17. Found: C, 58.23; H, 4.97; N, 7.25.

***N*-(3-Chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-3,4,5-trimethoxybenzamide (4b)**

This compound was obtained following the above method as white flocculus, yield 65%, m.p. 147-149 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.44-7.38 (m, 4H, Ph-H), 7.10 (s, 2H, Ph-H), 7.04 (s, 1H, NH), 5.68 (d, *J* = 7.2 Hz, 1H, COCH), 4.74 (d, *J* = 7.2 Hz, 1H, NCH), 3.92 (s, 9H, CH_3O); Anal. Calcd for $C_{19}H_{18}Cl_2N_2O_5$: C, 53.66; H, 4.27; N, 6.59. Found: C, 53.52; H, 4.34; N, 6.50.

***N*-(3-Chloro-2-(2,4-dichlorophenyl)-4-oxoazetidin-1-yl)-3,4,5-trimethoxybenzamide (4c)**

This compound was obtained following the above method as white powder, yield 76%, m.p. 239-240 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.12 (bs, 1H, NH), 7.29-7.68 (m, 3H, Ph-H), 7.15 (s, 2H, Ph-H), 5.76 (d, *J* = 8 Hz, 1H, COCH), 4.79 (d, *J* = 8 Hz, 1H, NCH), 3.97 (s, 9H, CH_3O); ESI-MS: calcd for $C_{19}H_{17}Cl_3N_2O_5$ *m/z* 458.0; found, 459.8 $(M+H)^+$; Anal. Calcd for $C_{19}H_{17}Cl_3N_2O_5$: C, 49.64; H, 3.73; N, 6.09. Found: C, 49.50; H, 3.80; N, 6.14.

***N*-(3-Chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl)-3,4,5-trimethoxybenzamide (4d)**

This compound was obtained following the above method as white powder, yield 65%, m.p. 139-141 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69 (s, 1H, NH), 7.53-7.47 (m, 1H, Ph-H), 7.11-7.05 (m 5H, Ph-H), 5.72 (d, *J* = 6.8 Hz, 1H, COCH), 4.70 (d, *J* = 6.8 Hz, 1H, NCH), 3.91 (s, 6H, CH_3O), 3.89 (s, 3H, CH_3O); ESI-MS: calcd for $C_{19}H_{18}ClFN_2O_5$ *m/z* 408.1; found, 408.6 $(M+H)^+$; Anal. Calcd for $C_{19}H_{18}ClFN_2O_5$: C, 55.82; H, 4.44; N, 6.85. Found: C, 55.95; H, 4.36; N, 6.93.

***N*-(3-Chloro-2-oxo-4-(4-(trifluoromethyl)phenyl)-azetidin-1-yl)-3,4,5-trimethoxybenzamide (4e)**

This compound was obtained following the above method as white solid, yield 70%, m.p. 196-197 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.46 (bs, 1H, NH), 7.84 (s, 2H, Ph-H), 7.67-7.60 (m, 2H, Ph-H), 7.15-7.08 (m, 2H, Ph-H), 5.82 (d, *J* = 7 Hz, 1H, COCH), 4.85 (d, *J* = 7 Hz, 1H, NCH), 3.92 (s, 9H, CH_3O); ESI-MS: calcd for $C_{20}H_{18}ClF_3N_2O_5$ *m/z* 458.1; found, 459.8 $(M+H)^+$; Anal. Calcd for $C_{20}H_{18}ClF_3N_2O_5$: C, 52.36; H, 3.95; N, 6.11. Found: C, 52.48; H, 3.87; N, 6.18.

***N*-(3-Chloro-2-isopropyl-4-oxoazetidin-1-yl)-3,4,5-trimethoxybenzamide (4f)**

This compound was obtained following the above method as white powder, yield 77%, m.p. 101-102 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.07 (s, 2H, Ph-H), 6.17 (d, *J* = 2.4 Hz, 1H, N-H), 4.56 (d, *J* = 14 Hz, 1H, COCH), 4.44 (d, *J* = 14 Hz, 1H, NCH), 3.93 (s, 6H, CH_3O), 3.91 (s, 3H, CH_3O), 2.51-2.46 (m, 1H, $\underline{CH}(CH_3)_2$), 1.12 (d, *J* = 7.2 Hz, 3H, $CH(\underline{CH_3})_2$), 0.90 (d, *J* = 6.8 Hz, 3H, $CH(\underline{CH_3})_2$); ESI-MS: calcd for $C_{16}H_{21}ClN_2O_5$ *m/z* 356.1; found, 357.8 $(M+H)^+$; Anal. Calcd for $C_{16}H_{21}ClN_2O_5$: C, 53.86; H, 5.93; N, 7.85. Found: C, 53.70; H, 5.98; N, 7.79.

***N*-(3-Chloro-2-(furan-2-yl)-4-oxoazetidin-1-yl)-3,4,5-trimethoxybenzamide (4g)**

This compound was obtained following the above method as light yellow solid, yield 62%, m.p. 155-156 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.55 (bs, 1H, NH), 7.46 (s, 1H, Furan-H), 7.14 (s, 2H, Ph-H), 6.71 (s, 1H, Furan-H), 6.44 (s, 1H, Furan-H), 5.74 (d, *J* = 7.4 Hz, 1H, COCH), 4.89 (d, *J* = 7.4 Hz, 1H, NCH), 3.88 (s, 9H, CH_3O); ESI-MS: calcd for $C_{17}H_{17}ClN_2O_6$ *m/z* 380.1; found, 381.7 $(M+H)^+$; Anal. Calcd for $C_{17}H_{17}ClN_2O_6$: C, 53.62; H, 4.50; N, 7.36. Found: C, 53.78; H, 4.45; N, 7.41.

***N*-(3-Chloro-2-oxo-1-azaspiro[3.5]nonan-1-yl)-3,4,5-trimethoxybenzamide (4h)**

This compound was obtained following the above method as yellow solid, yield 75%, m.p. 116-118 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.06 (s, 2H, Ph-H), 5.53 (s, 1H, COCH), 3.92 (s, 6H, CH_3O), 3.90 (s, 3H, CH_3O), 2.67-2.60 (m, 2H, Cy-H), 1.91-1.61 (m, 7H, Cy-H), 1.45-1.39 (m, 1H, Cy-H); ESI-MS: calcd for $C_{18}H_{23}ClN_2O_5$ *m/z* 382.1; found, 383.6 $(M+H)^+$; Anal. Calcd for $C_{18}H_{23}ClN_2O_5$: C, 56.47; H, 6.06; N, 7.32. Found: C, 56.33; H, 5.98; N, 7.40.

Biological Evaluation

All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. All compounds were dissolved in EtOH and diluted with distilled water containing Triton X-100 (0.1 μg/mL) to needed concentrations for bioassays. For comparative purposes, spirodiclofen was tested under the same conditions.

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