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Synthesis of novel highly functionalized biologically active polycyclic caged amides

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Abstract—The synthesis of novel polycyclic amides has been achieved through the reaction of bishalomethyl pentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane diones with acyclic and cyclic secondary amines in the presence of an ionic liquid. Three of the compounds prepared have been found to possess antituberculosis activity.

The chemistry of polycyclic cage compounds has intrigued many researchers over the past few decades but only recently have they investigated their pharmacological properties.[1] Many of these compounds have important pharmaceutical applications, ranging from the symptomatic and proposed curative treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's, to anti-viral agents against influenza and the immunodeficiency virus (HIV)[2] as well as antituberculosis drugs.[3] Nearly two million people die each year due to the lack of adequate treatment as well as due to the emergence of resistant strains of *Mycobacterium tuberculosis*.[4] Recently a series of antimicrobial diaminated compounds were reported to be active against resistant *M. tuberculosis* strains.[5] Of these, SQ109, a diaminated cage compound (Fig. 1), was found to be effective even on multidrug resistant (MDR) strains of *M. tuberculosis*.[6]

Interest in the pharmacology of polycyclic cage amines was stimulated by the early findings of Davis et al.[7] that 1-aminoadamantane, commonly known as amantadine, had antiviral activity against a range of viruses causing influenza, hepatitis C, and herpes zoster neuralgia (Fig. 1). Later Schwab et al.[8] reported that amantadine was beneficial to patients with Parkinson's disease and that the hydrophobicity of the hydrocarbon cage enabled this molecule to cross the blood brain barrier and enter the central nervous system.

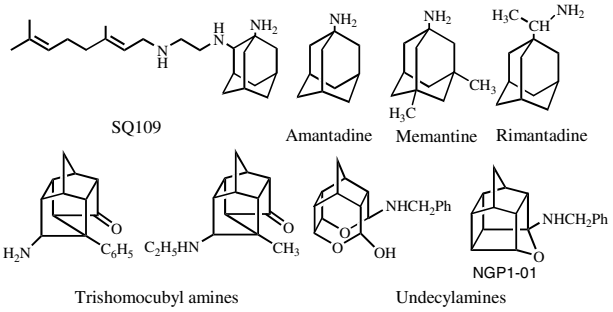

Figure 1. Examples of biologically active amino cage systems.

In addition, memantine (Fig. 1) was found to be a clinically well-tolerated NMDA receptor antagonist.[9] These compounds show promise as neuroprotective drugs by preventing excessive influx of calcium ions into neuronal cells.[10] Earlier Oliver et al.[11] reported that amino-(D_3)-trishomocubanes and pentacycloundecyl amines (Fig. 1) possessed anti-viral activity against Herpes simplex I and II influenza A2/Taiwan and Rhino 1A virus. NGP1-01 (Fig. 1) and related compounds were found to be potential lead structures for the development of neuroprotective compounds having anti-Parkinsonian activity.[12,13] Moreover, derivatives of polycyclic compounds have been used as antidepressants, analgesics,[14]

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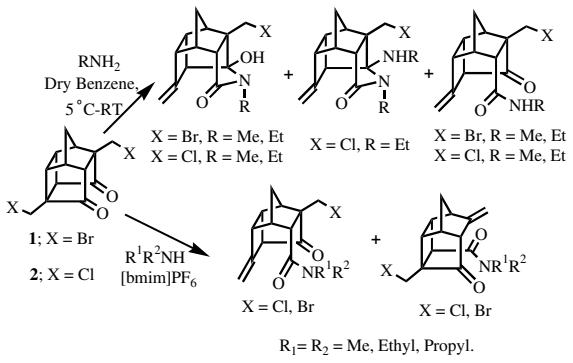
anti-inflammatory,[14] and anti-tumor agents as well as in the inhibition of proteases in a number of different diseases.[15]

These novel applications of polycyclic cage compounds encouraged us to synthesize and study the chemistry of new cage systems bearing nitrogen functionalities. The activity profile of cage amines can be effectively manipulated by means of structural modification, either within the polycyclic cage moiety or by side chain substitution.

A survey of the literature showed that while the reactions of amines with unsubstituted pentacyclic cage diones had been probed by Marchand et al.,[16] no further developments had been made since. Later, the synthesis and pharmacological properties of several trishomocubylamines and pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecylamines were reported by Oliver et al. in 1991.[11] In an earlier study,[17] we observed that pentacyclic cage compounds **1**, (1,9-bis(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione),[18] and **2**, (1,9-bis(chloromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undeca-8,11-dione),[17] react with primary amines to give ring opened products as shown in Scheme 1. Since this constitutes a rapid and easy method for obtaining various novel cage compounds that would be difficult to synthesize through direct synthetic methods, we initiated a study to obtain a large number of these compounds with higher heteroatom content to study their biological activity. The observation that rimantadine (Fig. 1) had fewer side effects than amantadine was also taken into consideration. The most straightforward method appeared to be the reaction of diones **1** and **2** with secondary amines. However, the secondary amines did not react under the same conditions and alternative reaction conditions were explored. As ionic liquids are known to facilitate many reactions,[19] we explored the reactivity of secondary amines with the above mentioned diones in the presence of the ionic liquid [bmim]PF_6 (1-butyl-3-methylimidazolium hexafluorophosphate). As envisaged, this led to smooth ring cleavage of the pentacyclic system with subsequent formation of novel tetracyclic amides, the details of which are given below.

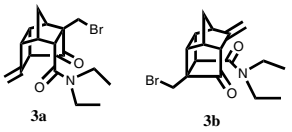
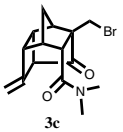
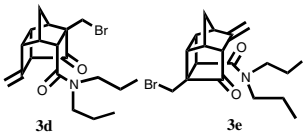
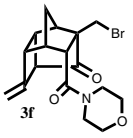
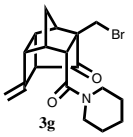
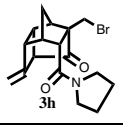
The study was initiated by treatment of 1,9-bis-(bromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **1** and 1,9-bis(chloromomethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione **2** with dialkylamines in the presence of [bmim]PF_6 (Scheme 1). The reaction provided novel ring opened products.



Scheme 1.

The reaction of **1** with diethylamine provided two novel compounds, **3a** and **3b** in 49% and 38% yields. While this result could be expected due to attack of the amine at two different carbonyl centers, the lack of selectivity observed was not disappointing since it paved the way for obtaining such unusual ring structures. Structural details of the products were confirmed through spectroscopic analysis. Compound **3a** was obtained as colorless crystals from an ethyl acetate–petroleum ether mixture (1:2). The IR spectrum showed strong sharp peaks at 1723 cm^{-1} (ring C=O) and 1636 cm^{-1} (amide C=O). The ^{1}H NMR spectrum contained the following characteristic signals: (i) two singlets at δ 4.89 and 4.71 (exocyclic methylene group), (ii) a quartet at δ 3.77 (–CH_2Br), and (iii) two triplets at δ 1.24 and δ 1.03 (methyls of the ethyl substituent). Salient features in the ^{13}C NMR spectrum include signals at (i) δ 209.7 due to the carbonyl group, (ii) δ 168.4 due to the lactam carbonyl, (iii) δ 140.9 and δ 109.7 due to the exocyclic double bond, and (iv) δ 14.4 and δ 12.6 due to the methyl carbons of each ethyl substituent. The HRMS ion at 351.0823 for [M$^+$] indicated the addition of one equivalent of the amine and loss of one bromine atom. All the above data suggested the structure as **3a** (Table 1). This

Table 1. Reaction of secondary amines with **1**

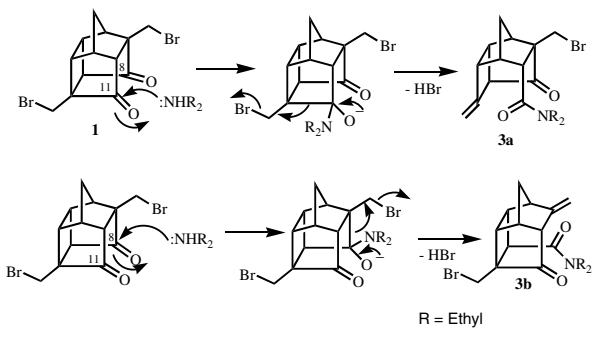
Entry	Reaction conditions	Product	Yield (%)
1	Diethylamine rt, 5 h	 **3a** **3b**	**3a**: 49 **3b**: 38
2	Dimethylamine rt, 3 h	 **3c**	**3c**: 60
3	Dipropylamine rt, 5 h	 **3d** **3e**	**3d**: 48 **3e**: 36
4	Morphline rt, 3 h	 **3f**	**3f**: 58
5	Piperidine rt, 6 h	 **3g**	**3g**: 56
6	Pyrrolidine rt, 5 h	 **3h**	**3h**: 59

structure was based on a mechanism analogous to that proposed earlier for the reaction of **1** with primary amines, viz., attack of the nucleophile on the carbonyl carbon followed by rearrangement and elimination of HBr resulting in the formation of a pentacyclo[5.4.1.0.^{2,6}.0^{5,9}.0^{8,11}]dodecane system as confirmed earlier by single crystal X-ray crystallography.[17]

The second product **3b** was obtained in 38% yield and crystallised from ethyl acetate–petroleum ether mixture (1:3). Comparison of the spectra of **3b** with those of **3a** showed some similarities including the presence of two different carbonyl peaks at 1631 cm^{-1} (amide C=O) and 1741 cm^{-1} (ring C=O) in the IR spectrum. The ^{1}H NMR spectrum indicated the presence of the following characteristic signals: (i) two singlets at δ 4.94 and δ 4.92 (exocyclic methylene group), (ii) two doublets at δ 3.85 and δ 3.62 with coupling constants of 10.6 Hz (–CH_2Br), (iii) two triplets at δ 1.20 and δ 1.05 with coupling constants of 7.1 Hz (methyl groups of the ethyl substituents). The ^{13}C NMR spectrum confirmed the presence of a carbonyl group, an amide group and an exocyclic double bond demonstrating signals at δ 209.6, 168.6, 145.9 and 110.5, respectively. The two methyl carbons resonated at δ 13.9 and δ 12.6 in the ^{13}C NMR spectrum. The HRMS mass ion at 351.0840, which was the same as that of compound **3a**, lent additional support to the compound being identified as **3b**.

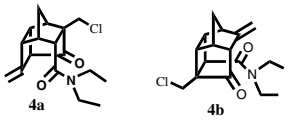
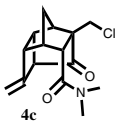
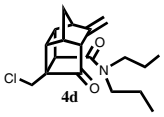
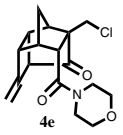
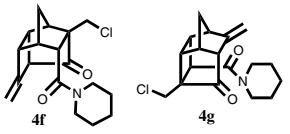
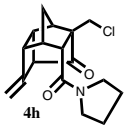
The mechanism proposed for the formation of these novel cage amides **3a** and **3b** involves initial nucleophilic attack of the nitrogen lone pair of the amine on either of the carbonyl carbons of the pentacyclic dione. In the first scenario, cleavage of a five-membered ring followed by elimination of the halogen atom leads to an exocyclic double bond. Displacement of HBr is probably facilitated by the excess amine present in the reaction mixture (Scheme 2).

The reaction of bisbromomethyl cage dione **1** with dimethylamine, morpholine, piperidine and pyrrolidine yielded only one product selectively through attack of the amine at the C11 carbonyl carbon only (Table 1). The structures of these products were assigned on the basis of spectral comparison with the pentacyclo-[5.4.1.0.^{2,6}.0^{5,9}.0^{8,11}]dodecane system.[17] In the cases of diethyl and dipropylamine, the reaction provided both



Scheme 2.

Table 2. Reaction of secondary amines with **2**

Entry	Reaction conditions	Product	Yield (%)
1	Diethylamine rt, 5 h	 **4a** **4b**	**4a**: 37 **4b**: 49
2	Dimethylamine rt, 3 h	 **4c**	**4c**: 58
3	Dipropylamine rt, 5 h	 **4d**	**4d**: 61
4	Morphline rt, 3 h	 **4e**	**4e**: 59
5	Piperidine rt, 6 h	 **4f** **4g**	**4f**: 36 **4g**: 54
6	Pyrrolidine rt, 5 h	 **4h**	**4h**: 56

possible products formed via attack of the amine at both carbonyl carbons of cage dione **1** (C8 and C11).

Analogous products were obtained upon the reaction of **2** with various cyclic and acyclic secondary amines and the results are summarized in Table 2. The structures of the products were assigned on the basis of spectroscopic data. Reaction of **2** with dimethylamine, dipropylamine, morpholine and pyrrolidine gave only one product, whereas the reaction with diethylamine and piperidine gave both possible products.

The structures of compounds **3b** and **3e** (Table 1) and **4b**, **4d** and **4g** (Table 2) were determined based on spectral comparison with the tetracyclo[4.2.1.1^{3,8}.0^{2,5}]decane system, the structure of which in turn had been confirmed by single crystal X-ray crystallography.[20]

We have studied the antibacterial and antituberculosis activity of these cage amides on *M. tuberculosis*.[21,22] The results indicated that compounds **4b** and **4h** possess anti TB activity at concentrations of 10 μg per ml, whilst compound **3d** showed activity at 50 μg per ml.

In conclusion, we have shown that several highly functionalized novel polycyclic cage amides with antibacterial activity against *M. tuberculosis* with potential for

further development could be synthesized readily through the reaction of secondary amines with bis(halomethyl)-substituted pentacycloundecane diones in the presence of [bmim]PF_6.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.125.

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21. *Antimycobacterial activity screening by Resazurin Assay*: *M. tuberculosis* H37Rv was grown in Middlebrook 7H9 broth (Difco BBL, Sparks, MD, USA) supplemented with 10% OADC (Becton Dickinson, Sparks, MD, USA). The culture was diluted to McFarland 1 standard with the same medium. From this, 50 μl of this culture was added to 450 μl of fresh medium in 2 ml microcentrifuge tubes. Stock solutions (2 mg/ml) of the test compounds were prepared in dimethylformamide (DMF). The compounds were tested at 1, 10 and 50 μg/ml concentrations. Control tubes had the same volumes of DMF without any substrate. After incubation at 37 °C for 7 days, 20 μl of 0.01% Resazurin (Sigma, St. Louis. MO, USA) in water was added to each tube. Resazurin, a redox dye, is blue in the oxidized state and turns pink when reduced by the growth of viable cells. The control tubes showed a colour change from blue to pink after 24 h at 37 °C. Compounds which prevented the change of colour of the dye were considered to be inhibitory to *M. tuberculosis*.
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General procedure for the reaction of the pentacyclic compounds with dialkylamines: Compound **1** or **2** (100 mg) was taken in 3 ml of ionic liquid, bmim[PF_6] and stirred well at room temperature for 0.5 h. To this homogenous solution, the secondary amine was added dropwise and stirring was continued (3–14 h). (Dimethylamine gas or diethylamine gas (produced by heating an aqueous solution of the amine in a water bath) was passed through the ice cooled reaction mixture for 0.5 h and then the reaction mixture was allowed to warm to room temperature and stirred for 3–8 h.) Next, the reaction was worked up by extraction with diethyl ether (5 × 10 ml) until the ether layer gave no spots on TLC corresponding to the products. Ether was removed, and the crude compound was purified on a silica gel column. The products obtained after purification were crystallized from dichloromethane–petroleum ether mixture.
Spectral data for selected compounds:
7-Bromomethyl-8-(N-diethyl-carbamoyl)tetracyclo[4.2.1.1^{4,7}.0^{2,5}]dec-3(11)-ene-10-one (**3a**): Crystallised from ethyl acetate–petroleum ether (1:2). Melting point: 117–119 °C;

FT-IR (KBr, υ_{max}/cm^{-1}): 2984, 1723, 1636, 1395, 948, 703, 604; ^1H NMR (300 MHz, $CDCl_3$): δ 4.89 (s, 1H), 4.71 (s, 1H), 3.77 (q, $J = 11.3$ Hz, 2H), 3.46–3.29 (m, 6H), 3.11–3.01 (m, 1H), 2.99–2.95 (q, $J = 8.1$ Hz, 1H), 2.86 (s, 1H), 2.58 (d, $J = 4.5$ Hz, 1H), 2.29 (d, $J = 10.5$ Hz, 1H), 1.52 (d, $J = 11.6$ Hz, 1H), 1.24 (t, $J_1 = J_2 = 7.1$ Hz, 3H), 1.03 (t, $J_1 = J_2 = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.7, 168.4, 140.9, 109.7, 56.8, 56.2, 54.4, 50.7, 48.2, 42.8, 42.3, 41.9, 40.5, 38.7, 38.4, 14.4, 12.6; HRMS (M^+): 351.0823, $C_{17}H_{22}NO_2Br$ requires 351.0834.

3-Bromomethyl-4-(N-diethyl-carbamoyl)tetracyclo[4.2.1.1^{3,8}.0^{2,5}]dec-7(11)-ene-10-one (**3b**): Crystallised from ethyl acetate–petroleum ether (1:3). Melting point: 104–106 °C; FT-IR (KBr, υ_{max}/cm^{-1}): 2973, 1741, 1631, 1428, 1362, 687; ^1H NMR (300 MHz, $CDCl_3$): δ 4.94 (s, 1H), 4.92 (s, 1H), 3.85 (d, $J = 10.6$ Hz, 1H), 3.62 (d, $J = 10.6$ Hz, 1H), 3.38-3.33 (m, 2H), 3.27–3.22 (m, 1H), 3.48–3.22 (m, 1H), 3.12–3.10 (m, 2H), 3.07–2.98 (m, 3H), 2.84 (s, 1H), 1.67 (d, $J = 10.2$ Hz, 1H), 1.57 (d, $J = 10.3$ Hz,1H), 1.20 (t, $J_1 = J_2 = 7.1$ Hz, 3H), 1.05 (t, $J_1 = J_2 = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.6, 168.6, 145.9, 110.5, 57.6, 54.9, 47.0, 44.9, 43.5, 41.3, 40.5, 39.9, 39.4, 39.2, 36.4, 13.9, 12.6; HRMS (M^+): 351.0840, $C_{17}H_{22}NO_2Br$ requires 351.0834.

7-Bromomethyl-8-(N-dimethyl-carbamoyl)tetracyclo[4.2.1.1^{4,7}.0^{2,5}]dec-3(11)-ene-10-one (**3c**): Crystallised from ethyl acetate–petroleum ether (1:2). Melting point: 145–147 °C; FT-IR (KBr, υ_{max}/cm^{-1}): 3016, 2930, 1717, 1650, 1276, 816, 706; ^1H NMR (300 MHz, $CDCl_3$): δ 4.88 (s, 1H), 4.72 (s, 1H), 3.77 (q, $J = 11.2$ Hz, 2H), 3.38–3.30 (m, 3H), 3.09 (s, 3H), 3.01–2.95 (m, 2H), 2.79 (s, 3H), 2.60 (d, $J = 5.3$ Hz, 1H), 2.29 (d, $J = 10.5$ Hz, 1H), 1.57 (d, $J = 10.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 169.7, 141.2, 109.4, 56.5, 56.1, 54.5, 50.6, 48.3, 42.5, 41.7, 38.4, 38.2, 37.9, 36.2; HRMS (M^+): 323.0504, $C_{15}H_{18}NO_2Br$ requires 323.0521.

7-Chloromethyl-8-(N-dimethyl-carbamoyl)tetracyclo[4.2.1.1^{4,7}.0^{2,5}]dec-3(11)-ene-10-one (**4c**): Crystallised from ethyl acetate–petroleum ether (1:2). Melting point: 156–158 °C; FT-IR (KBr, υ_{max}/cm^{-1}): 2892, 1719, 1651, 1422, 1144, 892, 726; ^1H NMR (300 MHz, $CDCl_3$): δ 4.87 (s, 1H), 4.70 (s, 1H), 3.87 (q, $J = 13.7$ Hz, 2H), 3.36—3.33 (m, 3H), 3.09 (s, 3H), 3.01–2.95 (m, 2H), 2.78 (s, 3H), 2.61 (d, $J = 4.8$ Hz, 1H), 2.22 (d, $J = 10.4$ Hz, 1H), 1.58 (d, $J = 10.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 169.6, 141.1, 109.4, 56.0, 55.1, 54.9, 50.5, 48.2, 47.6, 42.6, 41.5, 38.5, 37.8, 36.2; HRMS (M^+): 279.1018, $C_{15}H_{18}NO_2Cl$ requires 279.1026.

7-Chloromethyl-8-(pyrrolidine-carbamoyl)tetracyclo[4.2.1.1^{4,7}.0^{2,5}]dec-3(11)-ene-10-one (**4h**): Crystallised from ethyl acetate–petroleum ether (1:3). Melting point: 154–156 °C; FT-IR (KBr, υ_{max}/cm^{-1}): 2959, 1722, 1631, 1334, 1219, 883, 687; ^1H NMR (300 MHz, $CDCl_3$): δ 4.91 (s, 1H), 4.70 (s, 1H), 3.90 (s, 2H), 3.57–3.44 (m, 2H), 3.38–3.33 (m, 3H), 3.22 (br s, 2H), 3.04–2.95 (m, 2H), 2.62 (d, $J = 5.1$ Hz, 1H),2.19 (d, $J = 10.4$ Hz, 1H), 2.10–1.98 (m, 1H), 1.92–1.90 (m, 2H), 1.75–1.70 (m, 1H), 1.58 (d, $J = 10.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 168.8, 141.1, 109.6, 56.1, 55.9, 55.1, 50.4, 48.2, 47.5, 47.3, 46.6, 42.5, 40.6, 38.4, 26.6, 23.7; HRMS (M^+): 305.1187, $C_{17}H_{20}NO_2Cl$ requires 305.1183.

3-Chloromethyl-4-(N-dipropyl-carbamoyl)tetracyclo[4.2.1.1^{3,8}.0^{2,5}]dec-7(11)-ene-10-one (**4d**): Crystallised from ethyl acetate–petroleum ether (1:3). Melting point: 98–100 °C; FT-IR (KBr, υ_{max}/cm^{-1}): 2873, 1737, 1631, 1464, 1377, 1046, 663; ^1H NMR (300 MHz, $CDCl_3$): δ 4.94 (s, 1H), 4.91 (s, 1H), 3.83 (q, $J = 11.6$ Hz, 2H), 3.54 (d, $J = 7.4$ Hz, 1H), 3.30–3.21 (m, 2H), 3.13–3.06 (m, 2H), 3.01–2.89 (m, 4H), 2.82 (br s, 1H), 1.71 (d, $J = 10.4$ Hz, 1H), 1.64 (d, $J = 7.2$ Hz, 1H), 1.58 (t, $J_1 = 6.8$ Hz, $J_2 = 8.4$ Hz, 2H), 1.48 (m, 2H), 0.94 (t, $J_1 = J_2 = 7.3$ Hz, 3H), 0.83 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.8, 169.2, 146.1, 110.6, 57.7, 55.5, 48.7, 47.6, 47.3, 46.7, 43.4, 42.3, 41.5, 40.3, 39.9, 21.9, 20.6, 11.6, 11.5; HRMS (M^+): 335.1644, $C_{19}H_{26}NO_2Cl$ requires 335.1652.