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Synthesis of batracylin and its *N*-sulfonamido analogues in [b-3C-im][NTf_2] ionic liquid

Ming-Chung Tseng [a,†], Peng-Yeh Lai [b,†], Lin Shi [a,‡], Hsin-Yi Li [a], Min-Jen Tseng [b], Yen-Ho Chu [a,*]

[a] Department of Chemistry and Biochemistry, National Chung Cheng University, 168 University Road, Minhsiung, Chiayi 62102, Taiwan, ROC
[b] Institute of Molecular Biology, National Chung Cheng University, 168 University Road, Minhsiung, Chiayi 62102, Taiwan, ROC

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ABSTRACT

Starting with commercial and inexpensive reagents, a high-yielding chemical process carried out in [b-3C-im][NTf_2] ionic liquid was achieved to afford the synthesis of batracylin and its *N*-sulfonamido analogues. Among all compounds synthesized, compounds **1**, **11**, and **14** exhibit potent inhibitory activity against human topoisomerase 1 (hTop1).

1. Introduction

This paper reports a high-yielding synthesis of batracylin **1** and its *N*-sulfonamido analogues in [b-3C-im][NTf_2] ionic liquid **2**. Ionic liquids are low-melting molten salts composed entirely of ions, and many of them are liquid at room temperature.[1–5] This class of ionic solvents are known to carry numerous desirable properties, such as negligible vapor pressure, good thermal and chemical stability, high conductivity, and attractive recyclability that are suited for a myriad of applications, including excellent reaction media for organic synthesis, remarkable affinity separation of biomolecules, outstanding electrolytes for rechargeable lithium ion batteries, and unique solvents for cellulose dissolution.[1–5]

Many natural and unnatural products have quinazoline ring embedded in their structures and batracylin **1** carries such structural motif (Fig. 1).[6–8] A good number of quinazoline and quinoline products have been sold as drugs in market[9] and many others are currently under different phases of clinical trial.[10] This quinazoline core has attracted great attention to chemists due primarily to its diverse biological activities.[11]

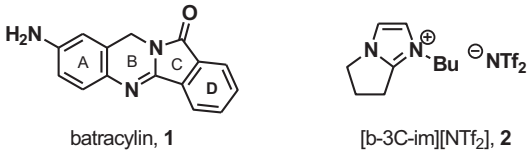

Fig. 1. Structures of batracylin **1** and [b-3C-im][NTf_2] ionic liquid **2**.

In our laboratory, we have been interested in developing new ionic liquids and have an ongoing program to evaluate ionic liquids as novel and stable media for organic syntheses[1,5,12–14] and biochemistry applications.[15,16] Also, our group recently reported syntheses of quinazolin-4-one containing natural products, such as luotonin A,[17] asperlicin C,[18] circumdatin F,[18,19] sclerotigenin,[18,19] and rutaecarpine,[20] and their derivatives.[19,21] We therefore envisaged that ionic liquids, such as the chemically stable [b-3C-im][NTf_2] **2** previously developed in our laboratory,[1,5] are non-volatile and should be excellent reaction media for other quinazoline alkaloid synthesis and, for exactly this reason, specifically targeted batracylin **1** and its analogues. In this work, we report a synthetic strategy for simultaneous construction of quinazoline and isoindolinone cores (BC rings) applied to the total synthesis of **1**. This synthesis of batracylin **1** completed in ionic liquid, to our knowledge, has not been reported in the literature and its approach may potentially be of use for the synthesis of other complex natural products.

* Corresponding author. Tel.: +886 52428148; fax: +886 52721040; e-mail address: cheyhc@ccu.edu.tw (Y.-H. Chu).
† These authors contributed equally to this work.
‡ On leave from the Shenyang Agricultural University, Shenyang 110161, Liaoning, PR China.

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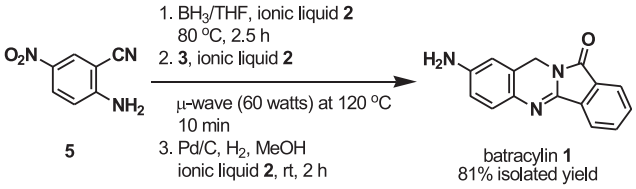
Batracylin **1** is a cytostatic and experimental anticancer agent, not only displays potent antitumor activity in vivo against murine solid tumors but is also effective against murine leukemia P-388 and colon adenocarcinoma 38 cell lines with acquired resistance to adriamycin, cisplatin, and methotrexate.[22–24] Batracylin **1** has been tested and evaluated in phase I clinical trial, and the studies were completed in 2011 and the data are currently being analyzed.[22] It was also demonstrated that **1** acted as a dual inhibitor of topoisomerases 1 and 2 to stabilize DNA/enzyme binary complexes, induced unscheduled DNA synthesis of nonproliferating cells in rat hepatocytes, and displayed growth inhibition in HT29 colon carcinoma cells with a GI_{50} value of 10 μM.[25,26] Albeit it is far from being potent enough for cancer chemotherapy, **1** is nevertheless a lead compound and has been the subject of a number of synthetic investigations.[27–34] These reported syntheses of **1**, however, often required long hours in reactions, low to moderate yields in key steps, and harsh experimental conditions.[27–34] Thus, further development of practical and efficient synthesis of **1** and its derivatives, such as *N*-sulfonamido analogues would be of immense value for the structure-and-activity relationship (SAR) study.

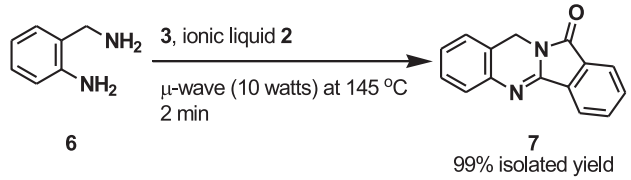
2. Results and discussion

In literature, the most common approach in synthesis of **1** was by using intermediate construction with either phthalic anhydride or phathalimide and substituted benzyl halides or benzyl amine.[27–34] Scheme 1 outlines our one-pot synthesis of batracylin **1**, of which the key BC rings were assembled from phathalic anhydride **3** and the intermediate 2-amino-5-nitrobenzylamine **4** obtained from very inexpensive 2-amino-5-nitrobenzonitrile **5** ($1/g, Aldrich) by reduction with borane. We envisioned that the concomitant formation of BC rings, when formed, would require heated conditions to drive two consecutive dehydrative cyclizations to completion and, moreover, ionic liquids are non-volatile, polar, ionic, and can be efficiently heated by microwaves,[35] we therefore decided to employ microwaves to deliberately promote such cyclodehydration reactions in the water immiscible, hydrophobic [b-3C-im][NTf_2] ionic liquid **2**.



Scheme 1. One-pot synthesis of batracylin **1** in [b-3C-im][NTf_2] **2**.

To validate this key second step (Scheme 1), we selected 8-desaminobatracylin **7** as the model compound for **1** and examined the double cyclodehydrative reaction of commercial *o*-aminobenzylamine **6** with phathalic anhydride **3** in ionic solvent **2** under microwave condition. The result is summarized in Scheme 2. To our delight, this microwave-assisted double cyclization in ionic liquid **2** proved to be highly effective and the synthesis of **7** was obtained with 99% excellent isolated yield at 145 °C after only 2 min of microwaves (10 W). Under identical experimental condition, if the same reaction was performed in molecular solvent, such as the polar DMF, incomplete reaction was resulted and the product **7** was obtained only with marginal 9% yield after column chromatography.[36] This result of the dehydrocyclization formation of **7** in ionic liquid **2** is consistent with our recent reports on the Lewis acidic nature of ionic liquid, which likely activates phathalic anhydride **3** as well as the corresponding imide intermediate.[13] We also found that a moderate 34% isolated yield of **7** was resulted if carried out in the hydrophilic, water-soluble [b-3C-im][Br] ionic liquid. This may be understood by the fact that the use of the water immiscible, hydrophobic [b-3C-im][NTf_2] ionic liquid **2** potentially inhibit the reverse hydrolysis of product formed and the water, once produced, became immiscible with the ionic liquid solvent and, in the end, likely was carried away by microwave heating. If this reaction was performed at ambient temperature, trace of **7** was not at all detected.



Scheme 2. Synthesis of 8-desaminobatracylin **7** in [b-3C-im][NTf_2] **2**.

The proposed reaction sequence shown in Scheme 1 did occur in a one-pot fashion under our optimized experimental conditions. This one-pot synthesis of batracylin **1** started from inexpensive 2-amino-5-nitrobenzonitrile **5**. Upon reacting first with borane/THF in [b-3C-im][NTf_2] ionic liquid **2** at 80 °C for 2.5 h, compound **5** was readily converted to 2-amino-5-nitrobenzylamine **4**. After removing THF and excessive reagent in vacuo, microwaves (60 W) of **4** in ionic liquid **2** with phthalic anhydride **3** at 120 °C for 10 min furnished 8-nitroisoindolo[1,2-*b*]quinazolin-12(10*H*)-one as the 8-nitro substituted **7** followed by catalytic hydrogenation at ambient temperature for 2 h to finally afford the desired fluorescent product, batracylin **1**, with an excellent 81% overall isolated yield after column chromatography. In our hands, a slightly stringent microwave heating condition (60 W, 120 °C, 10 min) was needed and used in the second step for the synthesis of **1**. This is entirely reasonable due primarily to the presence of a nitro substituent in **4** making this intermediate significantly less nucleophilic. This sequence of reactions performed in ionic liquid **2** was remarkably facile and the reactions required no special precautions.

The success of the synthesis of batracylin **1** using microwaves in ionic liquid **2** further prompted us to prepare its derivatives with greater diversity. In this work, we focused on the preparation of the A-ring, *N*-sulfonamide analogues containing alkyl and aromatic groups on the batracylin pharmacophore (**8**–**16**, Fig. 2).

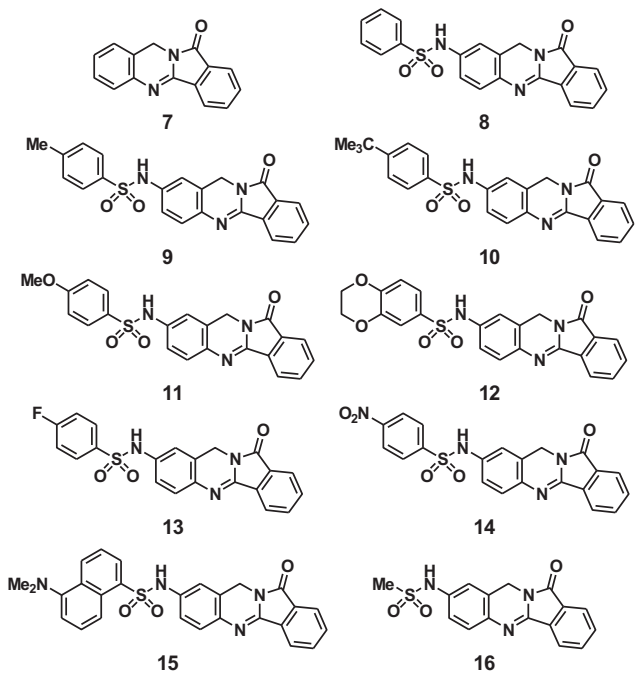
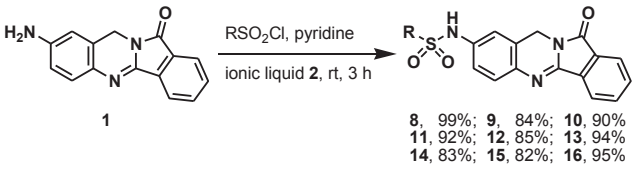


Fig. 2. Structures of batracylin analogues **7**–**16**.

N-Sulfonamido analogues of **1** were selected for the reasons that the sulfonamide group plays an important role in the topoisomerase inhibitory activity of amsacrine[37,38] and compounds, such as sulfonamide derivatives of epipodophyllotoxin (etoposide, VP-16) and chloroquinoxaline have been reported to be more potent inhibitors than VP-16 to human topoisomerase 2.[39,40] The synthesis of the *N*-sulfonamido analogues from the requisite **1** is depicted in Scheme 3. Results show that regardless of the nature of sulfonyl substituents, target compounds **8**–**16** were all prepared in the presence of pyridine in ionic liquid **2** at ambient temperature (3 h) with high to excellent isolated yields (Scheme 3). In our hands, batracylin analogues **8** and **15** gave the highest (99%) and lowest (82%) isolated yields, respectively. The successful application of our one-pot protocol to access the core isoindolo[1,2-*b*]quinazolin-12(10*H*)-one structure and its sulfonamide derivatives demonstrates the utility of our synthetic method. With an ultimate goal of developing new and more potent anticancer agents, the SAR of batracylin **1**, 8-desaminobatracylin **7** and *N*-sulfonamido batracylins **8**–**16** was then studied.



Scheme 3. Synthesis of *N*-sulfonamido batracylins **8**–**16** in [b-3C-im][NTf_2] **2**.

All compounds synthesized in this work were assayed for biological activities (Fig. 3). In literature, no *N*-sulfonamido batracylins were reported and showed promising biological activities. Inhibitory activities of compounds **1** and **7**–**16** to human topoisomerase 1 (hTop1) were measured by assaying the relaxation of a supercoiled pHOT-1 plasmid DNA.[41]

3. Conclusions

We have developed a one-pot protocol for the synthesis of batracylin **1** in the chemically stable, water immiscible [b-3C-im][NTf_2] ionic liquid **2**. Our method avoids the need for harsh conditions and allows concomitant construction of BC ring structure. This is the shortest synthesis of batracylin.

Compared with previously reported syntheses, our ionic liquid approach presents the advantages of a short synthesis route, high isolated yield, and no need for the isolation and purification of any intermediates. The chemistry presented in this work efficiently achieves the synthesis of batracylin as well as the preparation of its *N*-sulfonamido analogues and should contribute to the SAR study in this family of antitumor agents to further identify batracylin analogues with more potent anticancer activity.

4. Experimental section

4.1. General

Microwave irradiation experiments were performed using a CEM Discover microwave reactor from CEM Corporation (North Carolina, USA). Flash chromatography was performed on silica gel (230–400 mesh). TLC was carried out on aluminum-backed silica plates precoated with silica (0.2 mm), which were developed using standard visualizing agents, such as UV fluorescence and iodine. Unless otherwise indicated, all reactions were carried out without the aid of dry nitrogen or argon. NMR spectra were recorded on a Bruker AVANCE DPX 400 at 400 MHz (^{1}H) and 100.6 MHz (^{13}C) both in $CDCl_3$ unless otherwise stated. Chemical shifts were quoted in parts per million (ppm). Melting points were determined on a Fargo MP-2D apparatus (Taiwan, ROC) and are uncorrected. Solvents and reagents were obtained from commercial sources and were used without further purification.

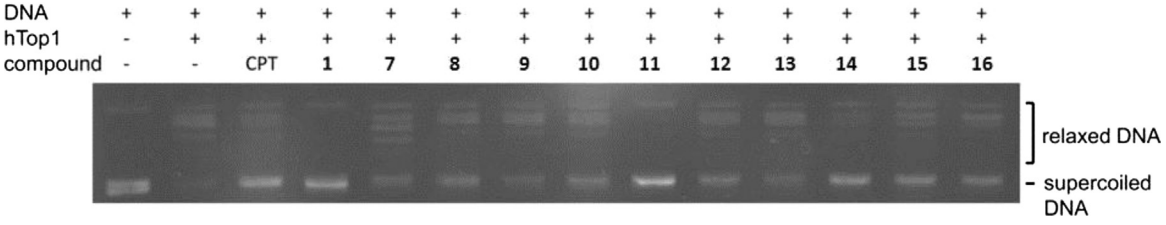


Fig. 3. Analysis of hTop1 inhibition by batracylin **1** and its analogues **7**–**16**.

The assay result showed in Fig. 3 demonstrated that among all compounds synthesized (100 μM), compounds **1**, **11**, and **14** exhibited more potent inhibitory activities than the control compound camptothecin (CPT) against hTop1: 92%, 91%, 82%, and 75% inhibition, respectively. Others showed moderate inhibitory activity against hTop1 (Fig. 3). It is also noted that compounds **1** and **11** showed lower intensity of the migrating bands (corresponding to nicked DNA) than CPT, suggesting that **1** and **11** may be potent inducer of hTopo1-mediated DNA cleavage than CPT.[42] Because of their planar aromatic structure, these hTop1 inhibitors likely bind at the interface of the hTop1-DNA complex by intercalating at the cleavage site and π–π stacking between base pairs.[26] This preliminary activity assay data shown in Fig. 3 could serve as a useful starting point for hit identification in hTop inhibitor discovery. Using the synthetic method developed in this work, a combinatorial approach on the design and synthesis of focused batracylin-templated libraries is in progress and the result on the identification of potent inhibitors will be reported in due course.

4.2. Procedure for the synthesis of batracylin 1

To a microwave reaction vessel containing 2-amino-5-nitrobenzonitrile **5** (30 mg, 0.18 mmol) and [b-3-C-im][NTf_2] ionic liquid **2** (0.1 mL) was carefully added borane (0.2 mL, 2 M in THF). The resulting solution was allowed to react at 80 °C in a sand bath for 2.5 h. After cooling down, the unreacted borane was quenched with MeOH (0.5 mL) and then solvent was removed. Subsequently, the vessel was added phthalic anhydride **3** (30 mg, 0.20 mmol) and placed inside the CEM Discover single-mode microwave synthesizer, where it was exposed to microwaves at 120 °C (60 W) for 10 min. Finally, the reaction vessel was added catalytic amount of Pd/C and methanol (2 mL). The resulting mixture was bubbled with hydrogen at ambient temperature for 2 h. After completion of the reduction reaction, Pd/C was filtered off, and the solvent was removed under reducing pressure to give the crude product and then purified by flash column chromatography (ethyl acetate/hexane=1:1) to afford batracylin **1** (37 mg, 81% yield).[43]

Fluorescent yellow solid; mp 227 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.80 (s, 2H, CH_2), 6.46 (s, 1H, aryl H), 6.51 (dd, J=8.4, 2.1 Hz, 1H, aryl H), 7.12 (d, J=8.4 Hz, 1H, aryl H), 7.69 (t, J=7.2 Hz, 1H, aryl H), 7.76 (t, J=7.2 Hz, 1H, aryl H), 7.84 (d, J=7.4 Hz, 1H, aryl H), 7.94 (d, J=7.3 Hz, 1H, aryl H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.6, 111.9, 113.4, 121.4, 123.0, 129.0, 129.8, 131.5, 133.0, 134.4, 144.0, 148.9, 166.2. ESI-HRMS m/z [M+H$^+$] calcd for $C_{15}H_{12}N_3O$ 250.0980, found 250.0980.

4.3. Procedure for the synthesis of 8-desaminobatracylin 7

To a microwave reaction vessel containing *o*-aminobenzylamine **6** (30 mg, 0.25 mmol) and [b-3-C-im][NTf$_2$] ionic liquid **2** (0.05 mL) was added phthalic anhydride **3** (36 mg, 0.25 mmol) and placed inside the CEM Discover single-mode microwave synthesizer, where it was exposed to microwaves at 145 °C (10 W) for 2 min. After completion of the reaction, the crude product was purified by flash column chromatography (ethyl acetate/hexane=1:6) to afford 8-desaminobatracylin **7** (58 mg, 99% yield). Yellow solid; mp 186–188 °C; ^{1}H NMR (DMSO-d_6, 400 MHz), δ 4.93 (s, 2H, CH_2), 7.26–7.40 (m, 3H, aryl H), 7.40 (d, J=7.5 Hz, 1H, aryl H), 7.75–7.83 (m, 2H, aryl H), 7.89 (d, J=7.0 Hz, 1H, aryl H), 8.01 (d, J=7.5 Hz, 1H, aryl H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.4, 122.2, 123.0, 127.5, 127.5, 127.6, 128.7, 130.4, 132.7, 133.4, 134.3, 140.3, 149.0, 166.4. ESI-HRMS m/z [M+H$^+$] calcd for $C_{15}H_{11}N_2O$ 235.0871, found 235.0869.

4.4. General procedure for the synthesis of *N*-sulfonamido batracylins 8–16

To a stirred solution of batracylin **1** (15 mg, 0.06 mmol) and pyridine (25 μL, 0.32 mmol) in [b-3C-im][NTf$_2$] **2** (100 μL), the corresponding sulfonyl chloride (0.24 mmol) was added portionwise. The resultant mixture was stirred at ambient temperature for 3 h. After completion of the reaction, dichloromethane (2 mL) was added and extracted with 10% citric acid (1 mL×3) and dried over anhydrous sodium sulfate. After filtration, solvent was removed under reduced pressure to give crude product. The residue was then purified by column chromatography (ethyl acetate/hexane=2:3) to afford the desired product as yellow solid (82–99 % isolated yield).

4.4.1. N-Sulfonamido batracylin analogue ***8***. Yellow solid; mp 229 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.83 (s, 2H, CH_2), 7.03 (d, J=10.4 Hz, 1H, aryl H), 7.05 (s, 1H, aryl H), 7.26 (d, J=8.4 Hz, 1H, aryl H), 7.54–7.72 (m, 3H, aryl H), 7.72–7.76 (m, 2H, aryl H), 7.82–7.86 (m, 3H, aryl H), 7.94 (d, J=7.2 Hz, 1H, aryl H), 10.52 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.6, 118.4, 119.6, 122.2, 123.2, 123.4, 127.1, 128.6, 129.7, 130.4, 132.7, 133.4, 133.6, 134.3, 136.6, 137.2, 139.8, 148.3, 166.4. ESI-HRMS m/z [M−H$^-$] calcd for $C_{21}H_{14}N_3O_3S$ 388.0756, found 388.0761.

4.4.2. N-Sulfonamido batracylin analogue ***9***. Yellow solid; mp 237 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.32 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 7.03 (d, J=9.2 Hz, 1H, aryl H), 7.04 (s, 1H, aryl H), 7.36 (d, J=8.4 Hz, 1H, aryl H), 7.51 (d, J=8.0 Hz, 1H, aryl H), 7.70–7.78 (m, 4H, aryl H), 7.84 (d, J=7.2 Hz, 1H, aryl H), 7.93 (d, J=7.2 Hz, 1H, aryl H), 10.46 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.1, 40.4, 118.1, 119.3, 122.0, 123.0, 123.2, 127.0, 128.4, 130.0, 130.2, 132.5, 133.4, 136.4, 136.8, 137.2, 143.6, 148.1, 166.3. ESI-HRMS m/z [M−H$^-$] calcd for $C_{21}H_{14}N_3O_3S$ 402.0912, found 402.0916.

4.4.3. N-Sulfonamido batracylin analogue ***10***. Yellow solid; mp 238 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.25 (s, 9H, ^{t}Bu), 4.85 (s, 2H, CH_2), 7.06–7.07 (m, 2H, aryl H), 7.28 (d, J=9.1 Hz, 1H, aryl H), 7.59 (d, J=8.4 Hz, 2H, aryl H), 7.73–7.80 (m, 4H, aryl H), 7.86 (d, J=7.2 Hz, 1H, aryl H), 7.96 (d, J=7.0 Hz, 1H, aryl H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 31.1, 35.2, 40.9, 118.0, 119.2, 122.2, 123.2, 123.5, 126.6, 127.0, 128.6, 130.4, 132.7, 133.6, 134.3, 136.5, 137.1, 137.4, 148.2, 156.4, 166.5. ESI-HRMS m/z [M−H$^-$] calcd for $C_{25}H_{22}N_3O_3S$ 444.1382, found 444.1389.

4.4.4. N-Sulfonamido batracylin analogue ***11***. Yellow solid; mp 228 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.78 (s, 3H, CH_3O), 4.84 (s, 2H, CH_2), 7.02–7.08 (m, 4H, aryl H), 7.27 (d, J=8.4 Hz, 1H, aryl H), 7.72–7.79 (m, 4H, aryl H), 7.86 (d, J=6.8 Hz, 1H, aryl H), 7.95 (d, J=7.2 Hz, 1H, aryl H), 10.39 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.6, 56.0, 114.8, 118.2, 119.4, 122.2, 123.2, 123.4, 128.6, 129.3, 130.4, 131.3, 132.7, 133.6, 134.3, 136.5, 137.5, 148.2, 162.9, 166.5. ESI-HRMS m/z [M−H$^-$] calcd for $C_{22}H_{16}N_3O_4S$ 418.0862, found 418.0868.

4.4.5. N-Sulfonamido batracylin analogue ***12***. Yellow solid; mp 189 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.27 (bd, J=3.2 Hz, 4H, 2×CH_2O), 4.85 (s, 2H, CH_2), 6.99–7.01 (m, 2H, aryl H), 7.27–7.31 (m, 2H, aryl H), 7.75–7.79 (m, 2H, aryl H), 7.87 (d, J=7.2 Hz, 1H, aryl H), 7.97 (d, J=7.2 Hz, 1H, aryl H), 10.41 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.5, 64.2, 64.5, 115.9, 117.8, 118.0, 119.2, 120.6, 122.0, 123.0, 123.3, 128.5, 130.2, 131.9, 132.5, 133.4, 134.2, 136.3, 137.2, 143.5, 147.5, 148.1, 166.3. ESI-HRMS m/z [M−H$^-$] calcd for $C_{23}H_{16}N_3O_3S$ 446.0811, found 446.0810.

4.4.6. N-Sulfonamido batracylin analogue ***13***. Yellow solid; mp 231–233 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.83 (s, 2H, CH_2), 7.01 (d, J=9.2 Hz, 1H, aryl H), 7.04 (s, 1H, aryl H), 7.25 (d, J=8.0 Hz, 1H, aryl H), 7.40 (t, J=8.8 Hz, 2H, aryl H), 7.69–7.73 (m, 2H, aryl H), 7.81 (d, J=6.8 Hz, 1H, aryl H), 7.88–7.91 (m, 3H, aryl H), 10.54 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.4, 116.6, 116.9, 118.5, 119.7, 121.9, 122.9, 123.3, 128.5, 130.0, 130.1, 130.2, 132.5, 133.3, 134.1, 135.9, 136.0, 136.8, 148.2, 163.4, 165.8, 166.2. ESI-HRMS m/z [M−H$^-$] calcd for $C_{21}H_{13}FN_3O_3S$ 406.0662, found 406.0665.

4.4.7. N-Sulfonamido batracylin analogue ***14***. Yellow solid; mp 189 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.86 (s, 2H, CH_2), 7.03–7.07 (m, 2H, aryl H), 7.29 (d, J=8.4 Hz, 1H, aryl H), 7.75–7.78 (m, 2H, aryl H), 7.86 (d, J=6.8 Hz, 1H, aryl H), 7.95 (d, J=7.2 Hz, 1H, aryl H), 7.05 (d, J=8.8 Hz, 2H, aryl H), 8.37 (d, J=8.8 Hz, 2H, aryl H), 10.82 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.6, 119.2, 120.4, 122.3, 123.2, 123.7, 125.1, 128.7, 130.4, 132.8, 133.6, 134.3, 136.3, 137.3, 145.1, 148.7, 150.3, 166.5. ESI-HRMS m/z [M−H$^-$] calcd for $C_{21}H_{13}N_4O_5S$ 433.0607, found 433.0601.

4.4.8. N-Sulfonamido batracylin analogue ***15***. Yellow solid; mp 209–212 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.80 (s, 6H, 2×CH_3), 4.75 (s, 2H, CH_2), 6.97–6.98 (m, 2H, aryl H), 7.18 (d, J=9.2 Hz, 1H, aryl H), 7.23 (d, J=7.6 Hz, 1H, aryl H), 7.62–7.65 (m, 4H aryl H), 7.78 (d, J=7.2 Hz, 1H, aryl H), 7.88 (d, J=7.2 Hz, 1H, aryl H), 8.30 (d, J=7.2 Hz, 1H, aryl H), 8.37 (d, J=8.6 Hz, 1H, aryl H), 8.44 (d, J=8.4 Hz, 1H, aryl H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.5, 45.3, 115.6, 117.1, 118.3, 118.8, 122.0, 123.0, 123.3, 123.8, 128.4, 128.6, 129.1, 129.2, 130.2, 130.3, 130.5, 133.4, 134.1, 134.8, 136.0, 137.1, 147.9, 151.8, 166.3. ESI-HRMS m/z [M−H$^-$] calcd for $C_{27}H_{21}N_4O_3S$ 481.1334, found 481.1340.

4.4.9. N-Sulfonamido batracylin analogue ***16***. Yellow solid; mp 253 °C (decomp.); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.06 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 7.15 (d, J=8.9 Hz, 2H, aryl H), 7.39 (d, J=8.2 Hz, 1H, aryl H), 7.76–7.82 (m, 2H, aryl H), 7.89 (d, J=7.2 Hz, 1H, aryl H), 7.99 (d, J=7.6 Hz, 1H, aryl H), 9.97 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 40.7, 48.9, 118.2, 119.5, 122.2, 123.2, 123.5, 128.7, 130.4,

132.7, 133.6, 134.4, 136.4, 137.9, 148.2, 166.5. ESI-HRMS m/z [M−H$^-$] calcd for $C_{16}H_{12}N_3O_3S$ 326.0599, found 326.0598.

4.5. DNA relaxation assay

One unit hTop1 (TopoGen, Ohio, USA) was preincubated with 100 μM compound at 37 °C for 2 min followed by adding pHOT1 DNA (15 ng) for another 30 min incubation in a 20 μL reaction solution (10 mM Tris–HCl pH7.9, 1 mM EDTA, 0.15 M NaCl, 0.1% BSA, 0.1 mM spermidine, 5% glycerol) at 37 °C. The reaction was terminated by adding equal volume of phenol/chloroform=1:1. The aqueous phase was loaded onto a 1% agarose gel and electrophoresis was performed in TBE buffer (90 mM Tris–borate and 2 mM EDTA). The gel was stain with ethidium bromide (0.5 μg/mL) for 5–10 min then photographed under transmitted ultraviolet light.

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Supplementary data

These data include ^{1}H and ^{13}C NMR spectra of batracylin **1**, 8-desaminobatracylin **7** and its *N*-sulfonamido analogues **8**–**16** (23 pages). Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.076.

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