Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is © The Royal Society of Chemistry 2012

Supporting Information for

Synthesis, biological evaluation and structure activity relationships of new estrogen receptor ligands based on a bridged oxabicyclic core embellished with arylsulfonamides

Manghong Zhu,[a] Chen Zhang,[a] Jerome C. Nwachukwu,[c] Sathish Srinivasan, [c] Valerie Cavett,[c] Yangfan Zheng,[a] Kathryn E. Carlson,[b] Chune Dong,[a] John A. Katzenellenbogen,[b]* Kendall W. Nettles,[c] Hai-Bing Zhou[a]*

TABLE OF CONTENTS

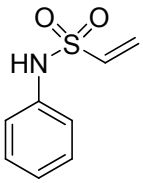
This journal is © The Royal Society of Chemistry 2012

PART I. SYNTHETIC PROCEDURES AND CHARACTERIZATION OF COMPOUNDS 7- 9 AND 11

Materials and Methods. Unless otherwise noted, reagents and materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and toluene were dried over Na and distilled prior to use. Dichloromethane was dried over CaH_2 and distilled prior to use. Glassware was oven-dried, assembled while hot, and cooled under an inert atmosphere. Unless otherwise noted, all reactions were conducted in an inert atmosphere. Reaction progress was monitored using analytical thin-layer chromatography (TLC). Visualization was achieved by UV light (254 nm). ^{1}H NMR and ^{13}C NMR spectra were obtain on Bruker Biospin AV400 (400 MHz) instrument. The chemical shifts are reported in ppm and are referenced to either tetramethylsilane or the solvent. Mass spectra were recorded under electron impact conditions at 70 eV. Melting points were obtained on SGW X-4 melting point apparatus and are uncorrected. Flash chromatography was performed with silica gel (0.040-0.063 mm) packing.

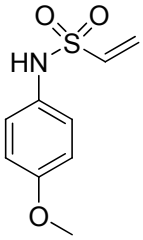
General synthesis of dienophiles 7. 2-Chloroethanesulfonyl chloride (1.2 equiv) was added slowly to a solution of aniline (0.5 equiv) in acetone at 0 °C. The mixture was stirred overnight at 0~10 °C, the evaporated *in vacuum*, extracted with CH_2Cl_2 and water for 3 times. The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4, filtered and evaporated *in vacuum*. The product was purified by column chromatography (EtOAc/ petroleum ether = 1:2).

***N*-Phenylethenesulfonamide (7a).** White solid (34% yield; mp 123-125°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.17 (dd, *J* = 16.6, 8.2 Hz, 3H), 7.01 (s, 1H), 6.57 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.28 (d, *J* = 16.5 Hz, 1H), 5.95 (d, *J* = 9.9 Hz, 1H); MS (EI): *m*/*z* 183 (M^+).



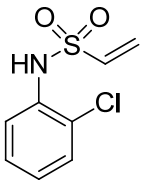
7a

***N*-(4-methoxyphenyl)ethenesulfonamide (7b).** Colorless oil (30% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.52 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.18 (d, *J* = 16.5 Hz, 1H), 5.99 (d, *J* = 9.9 Hz, 1H), 3.80 (s, 3H); MS (EI): *m*/*z* 213 (M^+).



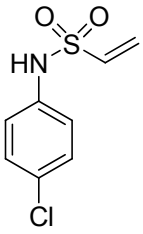
7b

***N*-(2-chlorophenyl)ethenesulfonamide (7c).** Light brown oil (35% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.39 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.11 (td, *J* = 7.8, 1.3 Hz, 1H), 6.56 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.28 (d, *J* = 16.5 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 1H); MS (EI): *m*/*z* 217 (M^+).



7c

***N*-(4-Chlorophenyl)ethenesulfonamide (7d).** Colorless oil (38% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.19 – 7.12 (m, 2H), 6.58 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.28 (d, *J* = 16.5 Hz, 1H), 6.00 (d, *J* = 9.9 Hz, 1H); MS (EI): *m*/*z* 217 (M^+).



7d

General synthesis of dienophiles 8. The corresponding anhydride (2.0 equiv) was added to a solution of aniline (1.0 equiv) and DMAP (0.2 equiv) in CH_2Cl_2 (10 mL) at 0 °C. After the addition, the temperature was allowed to raise to room temperature. The reaction was quenched with water and stirred for 2h, extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with 1N HCl, dried over Na_2SO_4, filtered and evaporated *in vacuum*. The crude amide **3** was used for next reaction without separation.

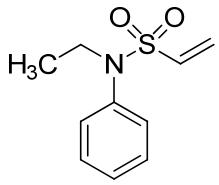
The BH_3 (1 M in THF) (6.0 equiv) was added to a solution of amide **3** in THF under Ar_2 atmosphere at room temperature. After the addition, the temperature was raised to 65 °C. The mixture was stirred for 4h, then cooled to the room temperature. The mixture was quenched with

This journal is © The Royal Society of Chemistry 2012

MeOH at 0 °C, then evaporated *in vacuum*. The residue was dissolved into a mixture of Et_2O and aq. NH_4Cl and extracted with Et_2O (3 × 30 mL). The combined organic phase was washed with saturated NaCl, dried over Na_2SO_4, filtered and evaporated *in vacuum*. The aniline **4** was purified by column chromatography (EtOAc/ petroleum ether = 1:10) to get colorless to light yellow oil.

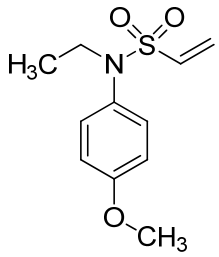
2-Chloroethanesulfonyl chloride (1.2 equiv) and 25% NaOH (2.5 mL for 1mmol 2-chloroethanesulfonyl chloride) was added together slowly to a solution of aniline **4** (1.0 equiv) in CH_2Cl_2 at 0 °C. The adding process should be very slow. After the addition, the temperature was allowed to raise to room temperature and stirred over night. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The conbimed organic layers was washed with saturated NaCl, dried over Na_2SO_4, filtered and evaporated *in vacuum*. The product **8** was purified by column chromatography (EtOAc/ petroleum ether = 1:5).

***N*-Ethyl-*N*-phenylethenesulfonamide (8a).** Colorless oil (20% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.4 Hz, 2H), 7.27 – 7.18 (m, 3H), 6.46 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.07 (d, *J* = 16.6 Hz, 1H), 5.87 (d, *J* = 9.9 Hz, 1H), 3.56 (q, *J* = 7.1 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); MS (EI): *m*/*z* 211 (M^+).



8a

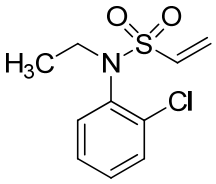
***N*-Ethyl-*N*-(4-methoxyphenyl)ethenesulfonamide (8b).** Colorless oil (20% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H), 6.92 – 6.86 (m, 2H), 6.54 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.15 (d, *J* = 16.6 Hz, 1H), 5.94 (d, *J* = 9.9 Hz, 1H), 3.81 (s, 3H), 3.59 (q, *J* = 7.1 Hz, 2H), 1.12 (t, *J* = 7.1 Hz, 3H); MS (EI): *m*/*z* 241 (M^+).



8b

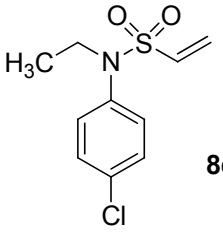
***N*-(2-Chlorophenyl)-*N*-ethylethenesulfonamide (8c).** Colorless oil (18% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 1H), 7.36 – 7.31 (m, 1H), 7.26 – 7.21 (m, 2H), 6.57 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.14 (d, *J* = 16.5 Hz, 1H), 5.88 (d, *J* = 9.9 Hz, 1H), 3.56 (q, *J* = 7.2 Hz, 2H), 1.08 (t, *J* = 7.2

Hz, 3H); MS (EI): *m*/*z* 245 (M^+).



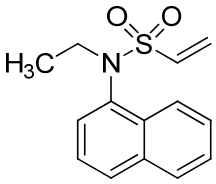
8c

***N*-(4-Chlorophenyl)-*N*-ethylethenesulfonamide (8d).** Colorless oil (17% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.44 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.07 (d, *J* = 16.5 Hz, 1H), 5.90 (d, *J* = 9.9 Hz, 1H), 3.55 (q, *J* = 7.1 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H); MS (EI): *m*/*z* 245 (M^+).



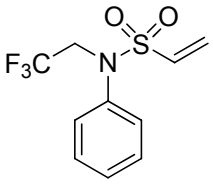
8d

***N*-Ethyl-*N*-(naphthalen-1-yl)ethenesulfonamide (8e).** Colorless oil (10% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.55 (dt, *J* = 24.2, 7.3 Hz, 2H), 7.49 – 7.39 (m, 2H), 6.68 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.22 (d, *J* = 16.5 Hz, 1H), 5.97 (d, *J* = 9.9 Hz, 1H), 3.82 – 3.69 (q, *J* = 7.1 Hz, 2H), 1.13 (t, J = 7.1 Hz, 3H); MS (EI): *m*/*z* 261 (M^+).



8e

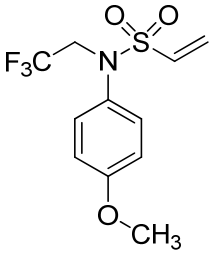
***N*-Phenyl-*N*-(2,2,2-trifluoroethyl)ethenesulfonamide (8f).** Colorless oil (15% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 3H), 7.26 (dd, *J* = 7.8, 1.8 Hz, 2H), 6.53 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.12 (d, *J* = 16.5 Hz, 1H), 5.94 (d, *J* = 9.9 Hz, 1H), 4.17 (q, *J* = 8.4 Hz, 2H); MS (EI): *m*/*z* 265 (M^+).



8f

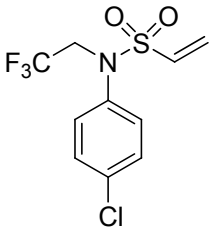
***N*-(4-methoxyphenyl)-*N*-(2,2,2-trifluoroethyl)ethenesulfonamide (8g).** Colorless oil (18% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.50 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.06 (d, *J* = 16.5 Hz, 1H), 5.90 (d, *J* = 9.9 Hz, 1H), 4.09 (q, *J* = 8.4 Hz, 2H), 3.71 (s,

3H); MS (EI): *m*/*z* 295 (M^+).



8g

***N*-(4-Chlorophenyl)-N-(2,2,2-trifluoroethyl)ethenesulfonamide (8h).** Colorless oil (11% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 6.6 Hz, 2H), 6.50 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.12 (d, *J* = 16.5 Hz, 1H), 5.96 (d, *J* = 9.8 Hz, 1H), 4.13 (q, *J* = 8.3 Hz, 2H); MS (EI): *m*/*z* 299 (M^+).



8h

General synthesis of dienophiles 9. The acetic anhydride (2.0 equiv) was added to a solution of aniline (1.0 equiv) and DMAP (0.2 equiv) in CH_2Cl_2 at 0 °C. After the addition, the temperature was allowed to raise to room temperature. The mixture was stirred for 2h, extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with 1N HCl, dried over Na_2SO_4, filtered and evaporated *in vacuum*. The crude amide **3** was used for next reaction without purification.

NaH (1.2 equiv) was added to a solution of amide **3** in THF under Ar_2 atmosphere at 0 °C. Keeping the temperature, the mixture stirred for 0.5h. CH_3I (1.2 equiv) was added dropwise, then the temperature was allowed to raise to room temperature. The mixture was stirred for 6h and quenched with aqueous NH_4Cl (25 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4, filtered and evaporated *in vacuum*. The crude product **5** was used for next reaction without separation.

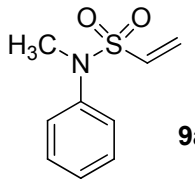
The above obtained crude amide was refluxed in 10% HCl (0.25 mL for 1 mmol amide) and glycol (0.75 mL for 1 mmol amide) for 24h. The mixture was evaporated *in vacuum*, the residue was dissolved into a mixture of EtOAc (25 mL) and aqueous $NaHCO_3$ (25 mL), then extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4, filtered and evaporated in vacuum. The aniline **6** was purified by column chromatography (EtOAc/

This journal is © The Royal Society of Chemistry 2012

petroleum ether = 1:6).

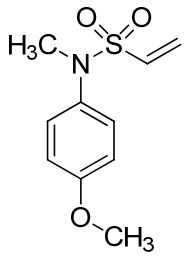
2-Chloroethanesulfonyl chloride (1.2 equiv) and 25% NaOH (2 mL for 1 mmol 2-chloroethanesulfonyl chloride) was added together slowly to a solution of aniline **6** (1.0 equiv) in CH_2Cl_2 at 0 °C. The adding process should be very slow. After the addition, the temperature was allowed to raise to room temperature and stirred over night. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4, filtered and evaporated in vacuum. The product **9** was purified by column chromatography (EtOAc/ petroleum ether = 1:5).

***N*-Methyl-*N*-phenylethenesulfonamide (9a).** Colorless oil (30% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 6.46 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.19 (d, *J* = 16.6 Hz, 1H), 6.02 (d, *J* = 9.9 Hz, 1H), 3.24 (s, 3H); MS (EI): *m*/*z* 197 (M^+).



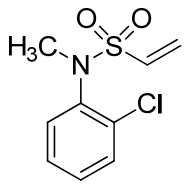
9a

***N*-(4-methoxyphenyl)-*N*-methylethenesulfonamide (9b).** Brown oil (32% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.47 (dd, *J* = 16.6, 10.0 Hz, 1H), 6.17 (d, *J* = 16.6 Hz, 1H), 6.00 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.20 (s, 3H); MS (EI): *m*/*z* 227 (M^+).



9b

***N*-(2-chlorophenyl)-*N*-methylethenesulfonamide (9c).** Colorless oil (28% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 2H), 7.29 (dd, *J* = 6.0, 3.6 Hz, 2H), 6.63 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.24 (d, *J* = 16.5 Hz, 1H), 6.00 (d, *J* = 9.9 Hz, 1H), 3.22 (s, 3H); MS (EI): *m*/*z* 231 (M^+).

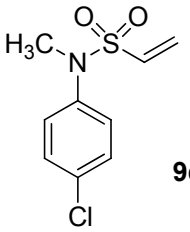


9c

***N*-(4-chlorophenyl)-*N*-methylethenesulfonamide (9d).** Yellow oil (25% yield); ^{1}H NMR (400

This journal is © The Royal Society of Chemistry 2012

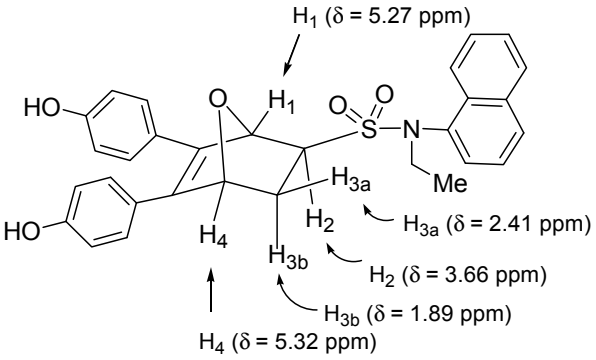
MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 3.4 Hz, 2H), 6.36 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.12 (d, *J* = 16.6 Hz, 1H), 5.96 (d, *J* = 9.9 Hz, 1H), 3.15 (s, 3H); MS (EI): *m*/*z* 231 (M^+).



9d

This journal is © The Royal Society of Chemistry 2012

PART II. ^{1}H NMR assignments of *exo* **11p**



exo **11p**

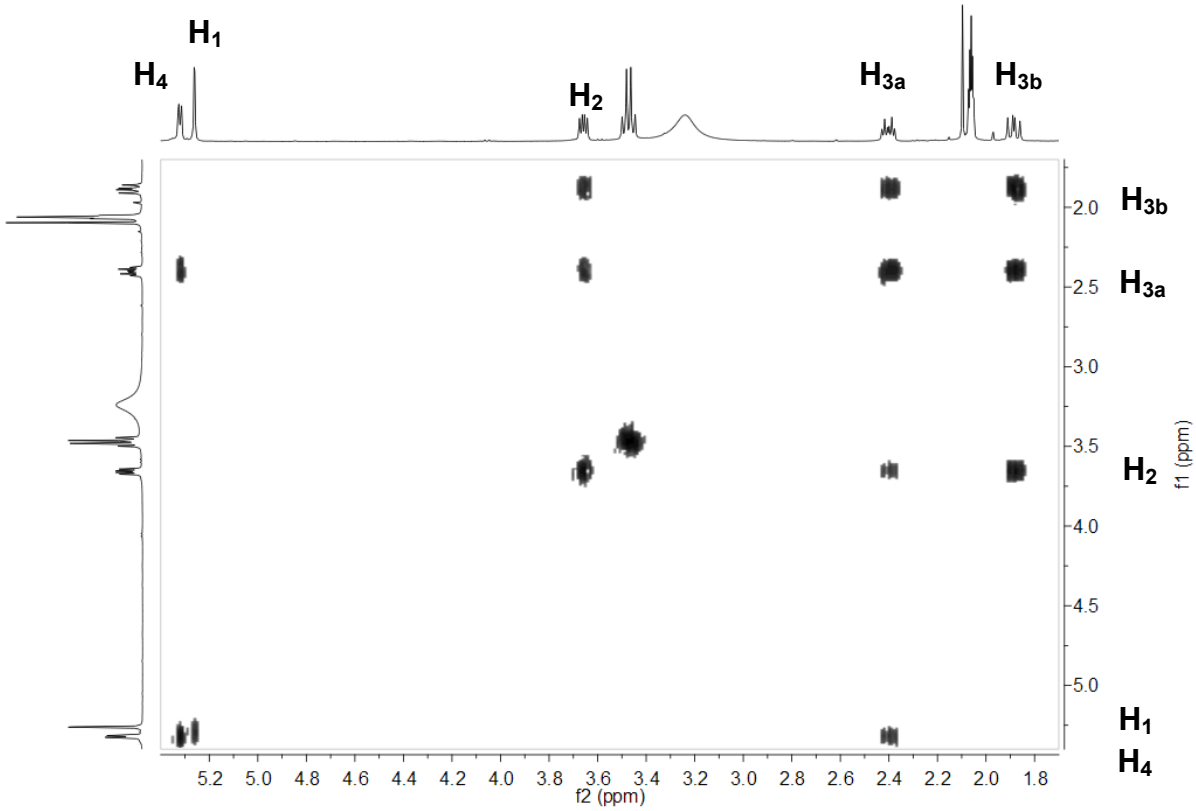


Figure 1. NOSY-NMR of *exo* **11p**. The peaks at 5.27 and 5.23 ppm are the hydrogen atoms on the bridgehead carbons (H_1 and H_4), and the peak at 3.66 ppm is the hydrogen attached to the carbon bearing the sulfonate group (H_2). It is evident that the H_2 doesn't interact with the bridgehead hydrogen. Since the bridgehead hydrogen is necessarily at an *exo* position, this interaction indicates that H_2 is at *endo* position, and, as a result, the sulfonate group is disposed in an *exo* configuration.