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Syntheses of Three Mono-Brominated Enamide Analogs of Natural Alkaloids Isolated from the Tasmanian Marine Bryozoan *Amathia Wilson*

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Abstract. Synthesis of three brominated enamides, analogs of natural alkaloids isolated from the Tasmanian marine bryozoan *Amathia Wilson*, were prepared by a sequence of reactions starting from 3-hydroxybenzaldehyde.
Keywords: brominated enamides, amathamides.

Resumen. Síntesis de tres enamidas bromadas, análogas a los alcaloides naturales aislados del briozoo *Amathia Wilson* de los mares de Tasmania. Esta síntesis se llevo a cabo a través de una secuencia de reacciones que parten del 3-hidroxibenzaldehído.
Palabras clave: enamidas bromadas, amathamidas.

Introduction

The enamides form an important group of naturally occurring compounds which have been isolated from a number of different sources, including terrestrial plants [1-3], microorganisms [4-6] and marine organisms [7-11]. In general, compounds belonging to this class of enamides show an array of biological effects including antibiotic [4], protein kinase inhibition [5] and antitumor activity [12].

Marine invertebrates are currently the focus of an intense worldwide search for new pharmacologically activity cytotoxic and antineoplastic agents. The amathamides are brominated proline-derived alkaloids which differ from each other by the degree of bromination or methylation and by their double bond geometry (Figure 1) [13-15].

Biological activity of this type of enamide alkaloids has not been fully studied and only a limited biological activities such as, nematocidal, antifungal, and antibacterial activity has been described for amathamides A, B, G, H, and I isolated from *A. wilsoni* and *A. convolute* species [16-17]

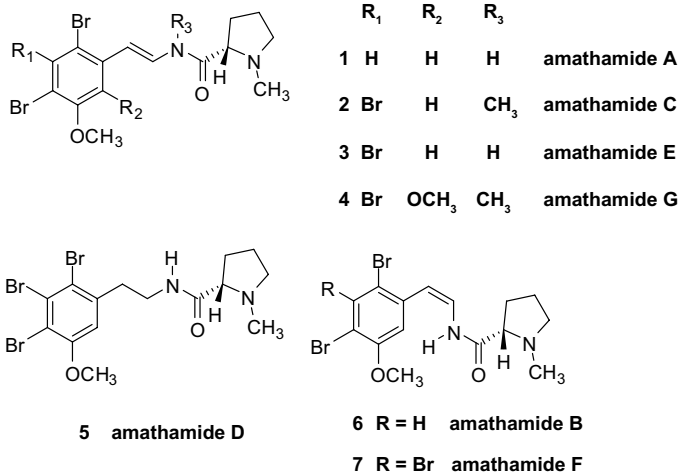


Fig. 1. Structures of amathamides A, B, C, D, E, F and G.

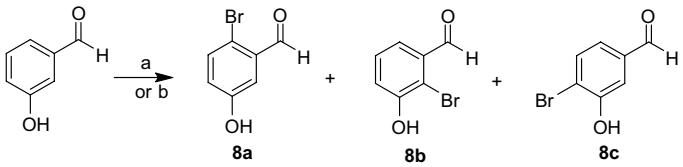
Our previous studies relating to the synthesis of two natural amathamides (A and B), prompted us to investigate the synthesis of analogous of amathamides using the same general synthetic route [18], Additionally, we developed a simple route to making a library of enamides. Testing the library of compounds revealed that the brominated and fluorinated enamides had good insecticidal properties [19].

Results and discussion

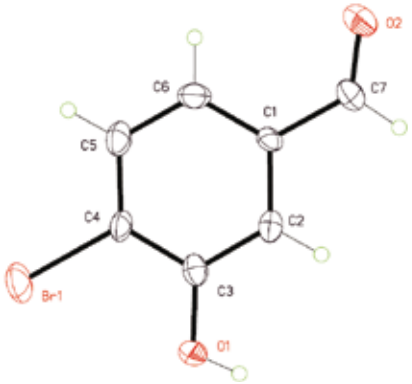
Bromination of 3-hydroxybenzaldehyde (Scheme 1), gave a mixture of **8a-c** (Br_2 in $CHCl_3$, rt) in a ratio of 87:3:10. Recrystallization of the mixture from acetic acid gave pure **8a** in 65% yield.

However, similar bromination of 3-hydroxybenzaldehyde (Br_2 in silica gel/CH_2Cl_2, rt) (Scheme 1), gave **8a-c** in ratio (68:7:25). Compounds were separated by column chromatography and recrystallization of **8c** from acetic acid gave a single crystal X-ray structure (figure 2), confirming the position of bromine atom in **8c** [20]**.** Mono-brominated compounds **8b** and **8c** were separated by chromatography in 7% and 25% yields respectively.

Aldehydes **8a-c** were treated with methyl iodide in DMF in the presence of K_2CO_3 to give methyl ethers **9a-c** respectively (Scheme 2). Subsequent condensation with nitromethane in the presence of ammonium acetate gave the nitroolefins **10a-c** in 80-85% yields. Michael addition of thiophenol with a catalytic amount of *N*-isopropylcyclohexylamine to each nitroolefin gave adducts **11a-c** in 85-92% yields. Reduction of the nitro



Scheme 1. Reagents and conditions: a) $Br_2/CHCl_3$, b) silica gel/Br_2/CH_2Cl_2.



Scheme 2. Reagents and conditions: a) CH_3I, DMF, K_2CO_3. b) CH_3NO_2, AcOH, $AcONH_4$ c) PhSH, *N*-isopropylcyclo hexylamine, CH_2Cl_2 d) Zn, HCl, AcOH e) PhCOCl, DMAP, CH_2Cl_2 f) i. $NaIO_4$, MeOH; ii.Toluene K_2CO_3 Reflux.

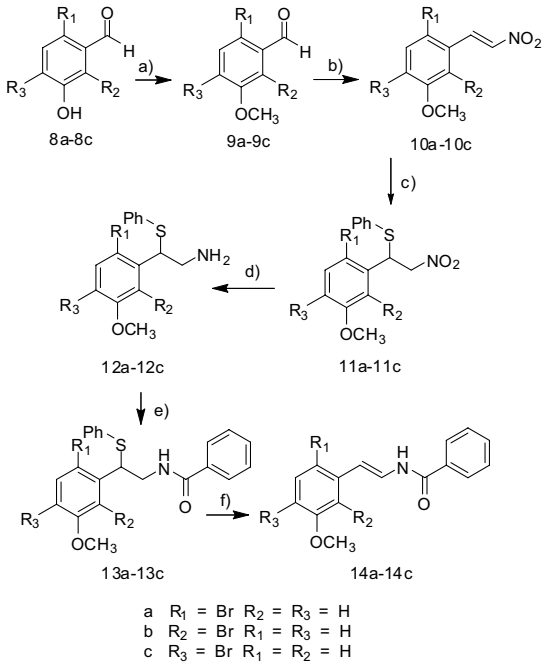


Fig. 2. X-ray crystal structure of 4-bromo-3-hydroxybenzaldehyde **8c** [20].

compounds **11a-c**, with Zn in acid conditions gave amines **12a-c** in 33-47% yields. We previously made the reduction with samarium diodide (SmI_2), however is a very expensive reagent and used 10 equivalents [18]. Acylation of amines with benzoyl chloride gave the products **13a-c** in 81-95% yields. Oxidation of **13a-c** with sodium periodate and subsequent elimination of thiophenol led to the desired enamides **14a-c** in 36-56% yields.

Conclusion

In conclusion using specific bromination techniques we have synthesized three monobromobenzadehydes, which were subsequently converted via a series of reactions involving, nitrolefin formation, followed by Michael addition of thiophenol, reduction, acylation and elimination of sulfoxide to give the desired enamides (**14a-c**). Future work towards the synthesis of amathamides C, E and F are under progress.

Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. IR Spectra were taken on a Perkin Elmer FT-IR 1600 spectrometer. ^{1}H-(200 MHz) spectra were recorded on a Varian Oxford 200 MHz spectrometer. Spectra were recorded in $CDCl_3$ with tetramethylsilane (TMS) used as internal standard. The EIMS data were obtained on a Finnigan MAT-90 instrument and all experiments were performed in the electron-impact mode (EI) at 70 eV using a direct insertion probe. All starting materials were research grade chemical, commercially available and used witthout further purification. Silica gel 60 F_{254} was used for TLC. Compound visualization was effected by UV light (252 nm).

2-Bromo-5-hydroxybenzaldehyde 8a

To a solution of 3-hidroxybenzaldehyde (5.00 g, 40.94 mmol) in $CHCl_3$ (50 mL) was added bromine (2.05 mL, 40.94 mmol) in $CHCl_3$ (30 mL). The resulting solution was stirred at rt for 1 h. The excess bromine was removed with a saturated solution of sodium thiosulfate (20 mL), the organic phase was washed with water and dried over anhydrous Na_2SO_4. Removal of solvent gave a brown solid, which was recrystallized from acetic acid (7.16 g, 87%); mp 132-134 ºC. IR (film): 3325, 3064, 1682, 1592 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.30 (s, 1H), 7.50 (d, 8.7 Hz, 1H), 7.44 (d, 3.0 Hz, 1H), 7.03 (dd, 8.7, 3.17 Hz, 1H), 5.93 (bs, 1H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 192.5, 155.8, 135.1, 134.2, 123.6, 118.0, 115.9. ppm. MS (EI) m/z (%) 200 (M^+, 96); 202 (M^++2, 100).

Monobromo-3-hydroxybenzaldehydes 8b, c

To a solution of 3-hidroxybenzaldehyde (10.00 g, 81.88 mmol) in CH_2Cl_2 (100 mL). was added silica gel (10.00 g) and bromine (4.10 mL, 81.88 mmol) in CH_2Cl_2 (30 mL). The resulting solution was stirred at rt for 1 h. The excess bromine was removed with a saturated solution of sodium thiosulfate (30 mL), and filtered. The organic phase was washed with water and dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica, eluting with CH_2Cl_2:Hexane (1:1).

2-Bromo-3-hydroxybenzaldehyde 8b

Obtained from 3-hidroxybenzaldehyde as white solid which was recrystallized from acetic acid (1.15 g, 7%); mp 147-148 ºC. IR (film): 3143, 3064, 1654, 1566 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.29 (s, 1H), 7.51 (dd, 7.4, 2 Hz, 1H), 7.36 (t,

7.4 Hz, 1H), 7.28 (dd, 7.32, 2.01 Hz, 1H), 5.97 (s, 1H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 191.4, 153.2, 134.7, 129.1, 122.9, 121.9, 114.2 ppm. MS (EI) m/z (%) 200 (M^+, 86); 202 (M^++2, 100).

4-Bromo-3-hydroxybenzaldehyde 8c

Obtained from 3-hidroxybenzaldehyde as white solid which was recrystallized from acetic acid (4.11 g, 25%); mp 127-128 °C. IR (film): 3281, 3064, 1684, 1585 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.93 (s, 1H), 7.66 (d, 8.2 Hz, 1H), 7.50 (d, 1.8 Hz, 1H), 7.34 (dd, 8.19, 1.7 Hz, 1H), 5.97 (s, 1H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 192.3, 153.3, 137.5, 133.2, 122.9, 117.6, 116.5 ppm. MS (EI) m/z (%) 200 (M^+, 57); 202 (M^++2, 63), 63 (100).

General procedure to obtained compounds 9a-c

To a solution of **8a** (2.00 g, 9.95 mmol), **8b** (1.50 g, 7.46 mmol), or **8c** (1.50 g, 7.46 mmol), and K_2CO_3 (2.67 g) in dry DMF (30 mL) was added methyl iodide (19.9 mmol, 1.23 mL) and the mixture was stirred for 3 h at rt. The reaction mixture was quenched with water (50 mL) and the organic phase extracted into diethyl ether, dried over anhydrous sodium sulfate and the solvent removed to give a white solid.

2-Bromo-5-methoxybenzaldehyde 9a

Obtained from **8a** as white crystal (1.93 g, 90%); mp 70-71 °C (CH_2Cl_2). IR (film): 3004, 2072, 1673, 1597 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.28 (s, 1H), 7.47 (d, 8.8 Hz, 1H), 7.35 (d, 3.2 Hz, 1H), 7.01 (dd, 8.8, 3.2 Hz, 1H), 3.81 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 191.5, 159.2, 134.5, 133.8, 122.9, 117.8, 112.6, 55.6 ppm. MS (EI) m/z (%) 214 (M^+, 93); 216 (M^++2,100).

2-Bromo-3-methoxybenzaldehyde 9b

Obtained from **8b** as white crystal (1.41 g, 88%); mp 64-65 °C (CH_2Cl_2). IR (film): 3040, 2846, 1684, 1561 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.43 (s, 1H), 7.51 (dd, 7.5, 2.0 Hz, 1H), 7.38 (t, 7.8 Hz, 1H), 7.13 (dd, 7.2, 2.0 Hz, 1H), 3.95 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 192.4, 156.4, 134.9, 128.5, 121.5, 117.2, 117.1, 56.8 ppm. MS (EI) m/z (%) 214 (M^+, 48); 216 (M^++2, 48), 63 (100).

4-Bromo-3-methoxybenzaldehyde 9c

Obtained from **8c** as white crystal (1.44 g, 90%); mp 126-127 °C (CH_2Cl_2). IR (film): 3281, 3064, 1684, 1585 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.93 (s, 1H), 7.70 (d, 7.6 Hz, 1H), 7.36 (d, 1.4 Hz, 1H), 7.30 (dd, 7.6, 1.4 Hz, 1H), 3.95 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 191.0, 156.5, 136.7, 133.9, 124.4, 119.4, 109.8, 56.3 ppm. MS (EI) m/z (%) 200 (M^+, 57); 202 (M^++2, 63), 63 (100).

General procedure to obtained nitroolefins of 10a-c

To a solution of **9a, 9b or 9c** (1.00 g, 4.65 mmol) in glacial AcOH (10 mL) was added $AcONH_4$ (0.36 g, 4.65 mmol) and nitromethane (1.73 mL). The solution was heated under reflux for 1 h. The mixture was cooled to rt. and treated with water (20 mL). A precipitate was formed wich was collected by filtration. The solid was dissolved with methylene chloride, filtered through a plug of silica gel and dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a yellowish solid which was recrystallized with methylene chloride.

(E)-1-bromo-4-methoxy-2-(2-nitrovinyl)benzene 10a

Obtained from **9a** as with crystals (956 mg, 80%); mp 104-105 °C. IR (film): 3105, 2837, 1589, 1510 cm^{-1}; ^{1}H-NMR: δ 8.33 (d, 14.0 Hz, 1H), 7.55 (d, 8.8 Hz, 1H), 7.51 (d, 14.0 Hz, 1H), 7.05 (d, 3.0 Hz, 1H), 6.91(dd, 8.8, 3.0 Hz, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 159.3, 139.1, 137.9, 134.8, 131.1, 119.4, 117.1, 113.5, 55.9 ppm. MS (EI) m/z (%) 257 (M^+, 45); 259 (M^++2, 48), 63 (100).

(E)-2-bromo-1-methoxy-3-(2-nitrovinyl)benzene 10b

Obtained from **9b** as with crystals (991 mg, 83%); mp 106-107 °C. IR (film): 3111, 2838, 1632, 1512 cm^{-1}; ^{1}H-NMR: δ 8.45 (d, 14.0, 1H), 7.51 (d, 14.0 Hz, 1H), 7.34 (t, 8.0 Hz, 1H), 7.16 (dd, 7.7, 2.0 Hz, 1H), 7.01 (dd, 7.5, 2.0 Hz, 1H), 3.94 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 156.9, 139.2, 138.2, 129.2, 128.7, 120.4, 116.1, 114.4, 56.7 ppm. MS (EI) m/z (%) 257 (M^+, 24); 259 (M^++2, 23), 63 (100).

(E)-1-bromo-2-methoxy-4-(2-nitrovinyl)benzene 10c

Obtained from **9c** as with crystals (1015 mg, 85%); mp 166-167 °C. IR (film): 3116, 2942, 1629, 1502 cm^{-1}; ^{1}H-NMR: δ 7.95 (d, 13.8 Hz, 1H), 7.62 (d, 7.8 Hz, 1H), 7.58 (d, 13.4 Hz, 1H), 7.04 (dd, 8, 1.8 Hz, 1H), 6.99 (d, 1.6 Hz, 1H), 3.95 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 156.5, 138.4, 137.7, 135.1, 134.5, 122.7, 121.4, 111.6, 56.4 ppm. MS (EI) m/z (%) 257 (M^+, 15); 259 (M^++2, 14), 63 (100).

General procedure to obtained compounds 11a-c

To a solution of **10a, 10b or 10c** (1.0 g, 3.87 mmol) in CH_2Cl_2 (20 mL) was added thiophenol (5.25 mmol, 0.54 mL) and 4 drops of *N*-isopropylcyclo hexylamine. The resulting mixture was stirred for 1 h at rt. The mixture was concentrated and subjected to flash chromatography on silica gel using hexane/ CH_2Cl_2 (80:20) as eluting solvent to give a brownish oil.

2-(2-Bromo-5-methoxyphenyl)-2-(thiophenyl)-1-nitroethane 11a

Obtained from **10a** (1207 mg, 85%). IR (film): 3005, 2936, 1593 cm^{-1}; ^{1}H-NMR: δ 7.50-7.20 (m, 6H), 6.72 (bs, 2H), 5.35 (t, 7.4 Hz, 1H), 4.88 (dd, 13.0, 8.8 Hz, 1H), 4.71 (dd, 13.0, 7.0

Hz, 1H), 3.71 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 159.2, 136.3, 134.3, 134.1, 131.5, 129.5, 129.1, 115.5, 114.8, 114.1, 77.4, 55.6, 48.9 ppm. MS (EI) m/z (%) 367 (M^+, 30); 369 (M^++2, 32), 212 (100).

2-(2-Bromo-3-methoxyphenyl)-2-(thiophenyl)-1-nitroethane 11b

Obtained from **10b** (1235 mg, 87%). IR (film): 3074, 2839, 1552, 1512 cm^{-1}; ^{1}H-NMR: δ 7.45-7.27 (m, 5H), 7.24 (t, 8.4 Hz, 1H), 6.84 (dd, 8.6, 2.0 Hz, 1H), 6.82 (dd, 8.6, 2 Hz, 1H), 5.51 (dd, 8.8, 7.0 Hz, 1H), 4.91 (dd, 13.6, 8.8 Hz, 1H), 4.71 (dd, 13.6, 7.0 Hz, 1H), 3.90 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 156.6, 137.0, 133.9, 132.0, 129.5, 129.0, 128.5, 119.8, 114.4, 111.9, 77.6, 56.6, 49.0 ppm. MS (EI) m/z (%) 367 (M^+, 30); 369 (M^++2, 32), 212 (100).

2-(4-Bromo-3-methoxyphenyl)-2-(thiophenyl)-1-nitroethane 11c

Obtained from **10c** (1306 mg, 92%). IR (film): 3059, 3007, 2942, 1582, 1547 cm^{-1}; ^{1}H-NMR: δ 7.47 (d, 8.6 Hz, 1H), 7.45-7.31 (m, 5H), 6.75 (m, 2H), 4.86-4.77 (m, 3H), 3.84 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 156.3, 137.3, 134.1, 133.7, 131.4, 129.5, 129.1, 120.7, 111.9, 111.4, 78.3, 56.3, 49.6 ppm. MS (EI) m/z (%) 367 (M^+, 8); 369 (M^++2, 8), 212 (100).

General procedure to obtained amines 11a-c

To solution of **11a, 11b or 11c** (0.50 g, 1.48 mmol) in AcOH (10 mL) and Zn powder (14.8 mmol, 0.967 g) was added dropwise a conc. HCl (5 mL). The mixture was stirred for 1 h at 5 °C and quenched with 50 mL of water. The solution was neutralized with 2 N NH_4OH. The residue was extracted into with methylene chloride (3 × 30 mL) and organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give amines **12a, 12b or 12c** as pale brown oil.

2-(2-bromo-5-methoxyphenyl)-2-(phenylthio) ethanamine 12a

Obtained from **11a** (165.3 mg, 33%). IR (film): 3372, 3057, 2936 cm^{-1}. ^{1}H-NMR: δ 7.44 (d, 8.8 Hz, 1H), 7.34-7.20 (m, 5H), 6.98 (d, 3.0 Hz 1H), 6.68 (dd, 8.83 Hz, 1H), 4.72 (t, 6.6 Hz, 1H), 3.75 (s, 3H), 3.09 (bs, 2H), 1.70 (bs, 2H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 159.3, 140.2, 134.0, 133.6, 132.0, 129.1, 127.4, 115.3, 115.0, 114.6, 55.6, 55.6, 46.9 ppm. MS (EI) m/z (%) 337 (M^+, 5); 369 (M^++2, 5), 258 (100).

2-(2-bromo-3-methoxyphenyl)-2-(phenylthio) ethanamine 12b

Obtained from **11b** (235.3 mg, 47%). IR (film): 3372, 3057, 2936 cm^{-1}. ^{1}H-NMR: δ 7.34-7.17 (m, 5H), 7.10 (t, 7.6 Hz, 1H), 6.81 (d, 7.6 Hz, 2H), 4.88 (t, 7.0 Hz, 1H), 3.90 (s, 3H), 3.10 (d, 7.0 Hz, 2H), 1.66 (bs, 2H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 156.2, 140.9, 134.6, 131.8, 129.1, 128.3, 127.2, 121.0, 114.66, 110.9, 56.6, 55.4, 47.0 ppm. MS (EI) m/z (%) 337 (M^+, 5); 369 (M^++2, 5), 258 (100).

2-(4-bromo-3-methoxyphenyl)-2-(phenylthio) ethanamine 12c

Obtained from **11c** (200.25 mg, 40%). IR (film): 3372, 3057, 2936 cm^{-1}. ^{1}H-NMR: δ 744 (d, 8.0, 1H), 7.30-7.21 (m, 5H), 6.77-6.72 (m, 2H), 4.12 (t, 6 Hz, 1H), 3.87-382 (m, 2H), 3.82 (s, 3H), 1.99 (bs, 2H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 156.0, 141.3, 133.8, 133.4, 132.9, 129.1, 127.8, 121.4, 111.7 110.8, 56.3, 56.3, 48.0 ppm. MS (EI) m/z (%) 337 (M^+, 5); 369 (M^++2, 5), 258 (100).

General procedure to obtained amides 13a-c

To a solution of **12a, 12b or 12c** (300.0 mg, 0.88 mmol) in CH_2Cl_2 (10 mL) and added a catalytic amount of DMAP and benzoyl chloride (136.23 mg, 0.97 mmol) and stirred for 3 h. The mixture was concentrated in vacuo, and the residue was purified by circular chromatography using hexane/CH_2Cl_2 (1:1) as eluting solvent. Removal of the solvent gave colorless oils

N-(2-(2-bromo-5-methoxyphenyl)-2-(phenylthio)ethyl) benzamide 13a

Obtained from **12a** (372.7 mg, 95%). IR (film): 3329, 3059, 2967, 1639, 1542. cm^{-1}; ^{1}H-NMR: δ 7.66-7.22 (m, 11H), 6.95 (d, 3.0 Hz, 1H), 6.69 (dd, 8.8, 3.0 Hz, 1H), 6.36 (bs, 1H), 5.00 (t, 8.0 Hz, 1H), 3.91 (t, 7.0 Hz, 2H), 3.73 (s, 3H). ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 167.7, 159.4, 139.4, 134.0, 133.8, 132.3, 131.7, 130.3, 129.3, 128.7, 127.8, 127.1, 115.6, 115.2, 114.4, 55.7, 51.1, 44.2 ppm. MS (EI) m/z (%) 441 (M^+, 69); 443 (M^++2, 67), 105 (100).

N-(2-(2-bromo-3-methoxyphenyl)-2-(phenylthio)ethyl) benzamide 13b

Obtained from **12b** (334.8 mg, 86%). IR (film): 3224, 3059, 2932, 1645, 1574 cm^{-1}; ^{1}H-NMR: δ 7.63-7.60 (m, 2H), 7.50-7.35 (m, 5H), 7.29-7.21 (m, 4H), 7.07 (dd, 8.0, 1.4 Hz, 1H), 6.82 (dd, 8.0, 1.4 Hz, 1H), 6.37 (bs, 1H), 5.16 (t, 7.0 Hz, 1H), 3.93 (t, 7.0 Hz, 2H), 3.90 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 167.6, 156.26, 140.2, 133.7, 132.1, 131.7, 130.3, 129.3, 128.7, 128.5, 127.7, 127.1, 120.8, 114.6, 111.3, 56.6, 51.1, 44.3 ppm. MS (EI) m/z (%) 441 (M^+, 35); 443 (M^++2, 64), 105 (100).

N-(2-(4-bromo-3-methoxyphenyl)-2-(phenylthio)ethyl) benzamide 13c

Obtained from **12c** (315.3 mg, 81%). IR (film): 3342, 3059, 2928, 1639, 1577 cm^{-1}; ^{1}H-NMR: δ 7.66-7.24 (m, 11H), 6.82-6.77 (m, 2H), 6.51 (t, 6.0 Hz, 1H), 4.49 (t, 8.0 Hz, 1H), 3.93-

383 (m, 2H), 3.79 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 167.8, 156.1, 140.5, 133.8, 133.6, 132.5, 131.9, 130.3, 129.3, 128.8, 128.6, 127.0, 121.2, 111.7, 111.1, 56.3, 52.3, 44.7 ppm. MS (EI) m/z (%) 441 (M^+, 14); 443 (M^++2, 17), 105 (100).

General procedure to obtained enamides 14a-c

To a solution of **13a, 13b or 13c** (100.0 mg, 0.22 mmol) in methanol (7 mL) was added a solution of sodium periodate (70.6 mg, 0.33 mmol,) in water (7 mL) and the resulting mixture heated under reflux for 1 h. The methanol was removed *in vacuo* and the aqueous residue was extracted with methylene chloride (3 × 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to give sulfoxide as a brownish oil. The crude product was then used in the next step without purification. The sulfoxide was dissolved in toluene (15 mL), sodium carbonate was added (30 mg) and the mixture heated under reflux for 3 h. The solvent was removed under vacuum, added water (15 ml) and extracted into methylene chloride (3 X10 mL), dried over anhydrous sodium sulfate and the solvent removed to give an oil. The residue was purified by circular chromatography using CH_2Cl_2/MeOH (95:5). to give a brownish oil

(E)-N-(2-bromo-5-methoxystyryl)benzamide 14a

Obtained from **13a** (29.2 g, 40%). IR (film): 3250, 3060, 2929, 1636. cm^{-1}, ^{1}H-NMR: δ 8.18 (d, 11 Hz, 1H), 7.91-7.85 (m, 2H), 7.71 (dd, 14.4, 11.0 Hz, 1H), 7.57-7.44 (m, 3H), 7.41(d, 8.8 Hz, 1H), 7.08 (d, 3.4 Hz, 1H), 6.66 (dd, 8.8, 3.4 Hz, 1H), 6.58 (d, 14.4 Hz, 1H), 3.82 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 164.7, 159.2, 133.6, 133.3, 133.3, 132.5, 129.0, 127.3, 125.2, 115.2, 114.0, 112.5, 110.5, 55.7 ppm. MS (EI) m/z (%) 331 (M^+, 29); 333 (M^++2, 14), 77 (100).

(E)-N-(2-bromo-3-methoxystyryl)benzamide 14b

Obtained from **13b** (40.92 mg, 56%). IR (film): 3249, 3049, 3010, 2942. cm^{-1}; ^{1}H-NMR: δ 8.18 (d, 11.0 Hz, 1H), 7.9-7.8 (m, 2H), 7.72 (dd, 14.0, 11.0 Hz, 1H), 7.60-7.45 (m, 3H), 7.25-7.20 (m, 2H), 6.77 (dd, 7.0, 1.2 Hz, 1H), 6.70 (d, 14.0, Hz 1H), 3.91 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 164.6, 156.3, 137.6, 133.3, 132.5, 129.0, 128.1, 127.3, 125.5, 118.4, 112.7, 109.9, 97.2, 56.5 ppm. (MS (EI) m/z (%) 331 (M^+, 38); 333 (M^++2, 20), 77 (100).

(E)-N-(4-bromo-3-methoxystyryl)benzamide 14c

Obtained from **13c** (26.3 mg, 36%). IR (film): 3059, 3010, 2942, 1592, 1547 cm^{-1}; ^{1}H-NMR: δ 8.04 (d, 11Hz, 1H), 7.88-7.83 (m, 2H), 7.75 (dd, 14.4, 11.0 Hz, 1H), 7.52-7.42 (m, 4H), 6.89 (d, 1.8 Hz, 1H), 6.78 (dd, 8.0, 1.8 Hz, 1H), 6.21 (d, 14.4, Hz 1H) 3.91 (s, 3H) ppm. ^{13}C NMR: ($CDCl_3$, 50 MHz): δ 164.7, 156.1, 133.5, 133.4, 132.5, 129.2, 129.0, 127.3, 128.8, 119.8, 112.9, 110.0, 108.5, 56.4 ppm. MS (EI) m/z (%) 331 (M^+, 29); 333 (M^++2, 22), 77 (100).

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