The Synthesis of Difluoro[1]benzothieno[2,3-*c*]quinolines and Their *N*-Methyl Quaternary Salts

Jiann-Kuan Luo, Steven L. Castle and Raymond N. Castle* [1]

Department of Chemistry, University of South Florida,
Tampa, FL 33620 USA

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A series of difluoro[1]benzothieno[2,3-*c*]quinolines has been prepared by photocyclization of the appropriate carboxamides. The lactams obtained were converted into the corresponding chloro derivatives which were catalytically dechlorinated into the difluoro[1] benzothieno[2,3-*c*]quinolines. The latter compounds were transformed into the *N*-methyl quaternary salts.

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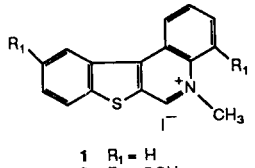
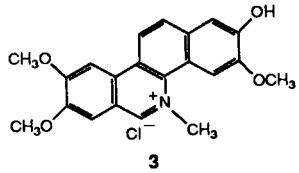
We have been interested in the synthesis of polycyclic nitrogen and sulfur containing heterocycles *via* photocyclization of the appropriate anilides [2-6]. This led us to the discovery of the antileukemic activity against L-1210 of 5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide **1** [4,7] and its 4,10-dimethoxy-substituted derivative **2** [2,7] as sulfur-containing analogs of the naturally occurring antileukemic alkaloids fagaronine **3** [8] and nitidine **4** [9]. This



1 R_1 = H
2 R_1 = OCH_3



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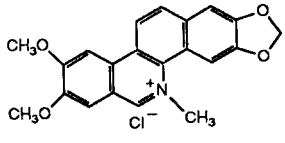

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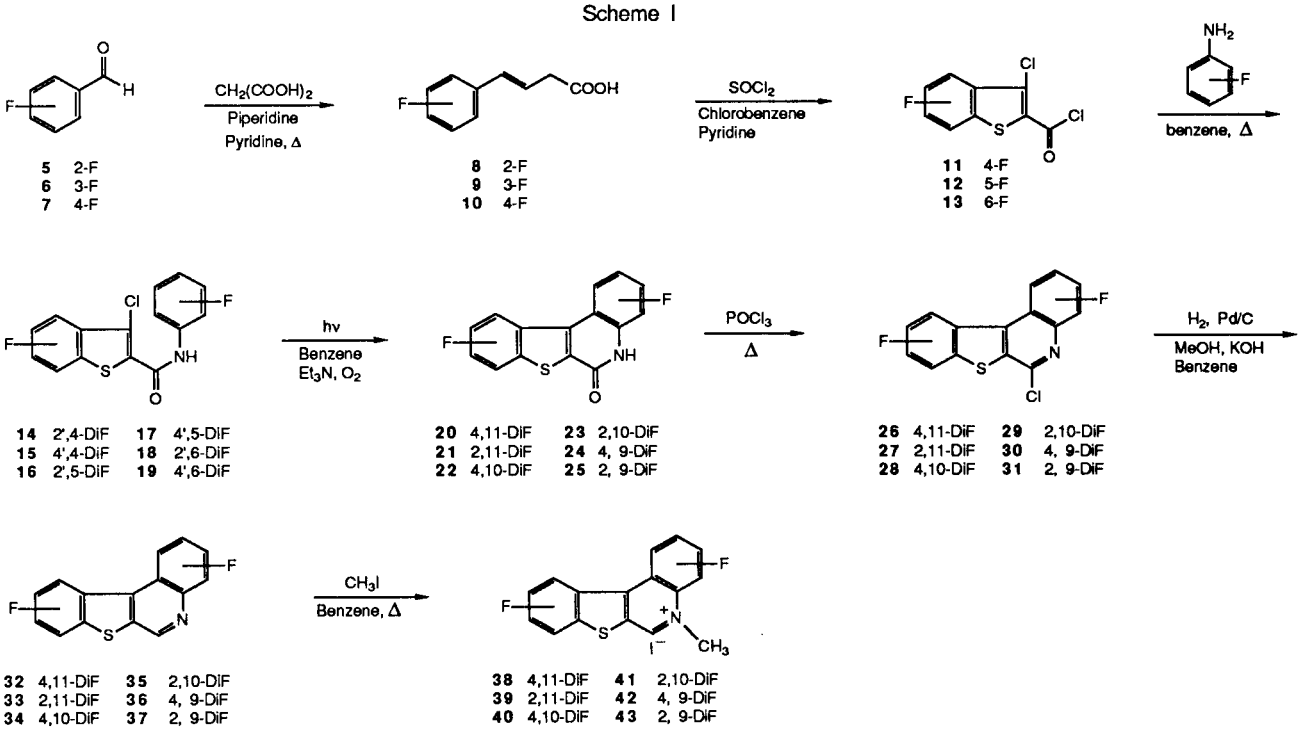
finding prompted us to report the synthesis of a series of difluoro[1]benzothieno[2,3-*c*]quinolines **32-37** and their *N*-methyl quaternary salts **38-43** for biological evaluation since the introduction of a fluorine atom into an organic compound has frequently produced a change in biological activity due to the stability of the C-F bond, the strong electronegativity of the fluorine atom, and the size of the fluorine atom similar to that of the size of the hydrogen atom.

Thus *o*-fluorobenzaldehyde **5**, *m*-fluorobenzaldehyde **6** or *p*-fluorobenzaldehyde **7** were allowed to react with malonic acid under Knoevenagel condensation conditions [10] to give 2-, 3-, or 4-fluorocinnamic acids **8** (73%), **9** (80%), or **10** (73%), respectively. Preparation of the fluorine-substituted 3-chlorobenzo[*b*]thiophene-2-carbonyl chlorides **11**, **12**, and **13** was carried out in a similar manner to that described by Wright and Brabander [11] starting with fluorocinnamic acids **8**, **9** and **10**. When 3-chloro-4-fluorobenzo[*b*]thiophene-2-carbonyl chloride **11** was treated with *o*- or *p*-fluoroaniline, the corresponding carboxamides **14** (92%) and **15** (92%) were isolated. Likewise, treatment of **12** or **13** with *o*- or *p*-fluoroaniline in benzene solution afforded carboxamides **16** (88%), **17** (91%), **18** (83%), and **19** (85%), respectively.

Oxidative photocyclization of the above carboxamides was accomplished by irradiating a mixture of equimolar amounts of the carboxamide and triethylamine with a 450 watt medium pressure mercury vapor lamp using benzene as the solvent to yield the corresponding difluoro[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-ones **20** (93%), **21** (98%), **22** (86%), **23** (70%), **24** (52%), and **25** (48%), respectively. The lactams were chlorinated in refluxing phosphorus oxychloride to provide difluoro-6-chloro[1]benzothieno-[2,3-*c*]quinolines **26** (37%), **27** (83%), **28** (84%), **29** (67%), **30** (74%), and **31** (60%).

Catalytic dechlorination of **26-31** with hydrogen and 10% Pd-C as the catalyst in 1:1 benzene-methanol solution in the presence of potassium hydroxide resulted in difluoro[1]benzothieno[2,3-*c*]quinolines **32** (78%), **33** (74%), **34** (82%), **35** (82%), **36** (83%), and **37** (89%). When **32-37** were allowed to react with iodomethane in benzene in a sealed tube at 100-110°, the difluoro-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodides **38** (68%), **39** (71%), **40** (24%), **41** (74%), **42** (55%), and **43** (73%) were obtained. Interestingly, the ^1H nmr spectra of compounds **38**, **40** and **42** exhibited a doublet centered at *ca.* δ 4.84 ppm with J = 10 Hz for the *N*-methyl group. The relative magnitudes of the ^1H-^{19}F coupling constants of fluorinated aromatic compounds are remarkably constant [12]. We observe (Table 1) that the heteronuclear coupling constants between the H1 resonance and the fluorine at the 11-position are larger in every case than the corresponding vicinal coupling between H1 and a fluorine in the 2-position. In light of this, it is difficult to believe that a scalar coupling through six bonds would be larger than the corresponding coupling through three bonds when the latter is contained wholly within the same aromatic ring. Given this, coupled with the fact that H1 and the 11-^{19}F substituent are in proximity in a bay-region, it seems logical to conclude that these substituents may be coupled through space rather than through bonds as would normally be the case.

Scheme I



5 2-F
6 3-F
7 4-F

8 2-F
9 3-F
10 4-F

11 4-F
12 5-F
13 6-F

14 2',4-DiF 17 4',5-DiF
15 4',4-DiF 18 2',6-DiF
16 2',5-DiF 19 4',6-DiF

20 4,11-DiF 23 2,10-DiF
21 2,11-DiF 24 4, 9-DiF
22 4,10-DiF 25 2, 9-DiF

26 4,11-DiF 29 2,10-DiF
27 2,11-DiF 30 4, 9-DiF
28 4,10-DiF 31 2, 9-DiF

32 4,11-DiF 35 2,10-DiF
33 2,11-DiF 36 4, 9-DiF
34 4,10-DiF 37 2, 9-DiF

38 4,11-DiF 41 2,10-DiF
39 2,11-DiF 42 4, 9-DiF
40 4,10-DiF 43 2, 9-DiF

These quaternary salts will be submitted for biological screening and these data will be reported elsewhere.

Table 1
Coupling Constants of $J_{1,F_{11}}$ and J_{1,F_2} for Compounds **21**, **27** and **33**

Compound Number	$J_{1,F_{11}}$ in Hz	J_{1,F_2} in Hz
21	11.7	9.0
27	12.0	9.3
33	12.2	10.5

EXPERIMENTAL

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Beckman FT 1100 spectrometer as potassium bromide pellets and frequencies are expressed in cm^{-1}. The ^1H nmr spectra were obtained on a JEOL FX-90Q spectrometer in the solvent indicated with TMS as the internal standard. Chemical shifts are reported in ppm (δ) and J values in Hz. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

2-Fluorocinnamic Acid (**8**).

A mixture of 100.0 g (0.81 mole) of 2-fluorobenzaldehyde (**5**), 109.1 g (1.05 moles) of malonic acid, 15 ml of piperidine, and 1000 ml of pyridine was heated at 100° for 20 hours. After cooling to room temperature, the solution was poured into *ca.* 3000 ml of ice water and acidified to *p*H 3-4 with *ca.* 900 ml of concentrated hydrochloric acid. The precipitate was collected by filtration and washed with water and then recrystallized from 95% ethanol with charcoal as a decolorizing agent to give 98.5 g (0.59 mole, 73%) of **8**, mp 178-179°; lit 175° [13,14], 177-178° [15]; ^1H nmr (DMSO-d_6): δ 6.52 (d, J = 16.1 Hz, 1H, $CH\text{-}CO_2H$), 6.97-7.66 (m, 4H, ArH), 7.80 (d, J = 16.1 Hz, 1H, $CH{=}CHCO_2H$), 10.29 (br s, 1H, CO_2H).

3-Fluorocinnamic Acid (**9**).

This compound was prepared from 3-fluorobenzaldehyde (**6**) (50.8 g, 0.41 mole) and malonic acid (54.0 g, 0.52 mole) in piperidine (7.5 ml) and pyridine (500 ml) in a manner similar to that described for the synthesis of **8**, thus 55.0 g (0.33 mole, 80%) of **9** was obtained, mp 166-167°, lit [16-17] 166.5°; ^1H nmr (DMSO-d_6): δ 6.42 (d, J = 16.2 Hz, 1H, $CH\text{-}CO_2H$), 6.95-7.50 (m, 4H, ArH), 7.61 (d, J = 16.2 Hz, 1H, $CH{=}CHCO_2H$), 9.05 (br s, 1H, CO_2H).

4-Fluorocinnamic Acid (**10**).

This compound was prepared from 4-fluorobenzaldehyde (**7**) (101.4 g, 0.82 mole) and malonic acid (108.4 g, 1.04 moles) in piperidine (15 ml) and pyridine (1000 ml) in a manner similar to that described for the synthesis of **8**; 98.9 g (0.60 mole, 73%) of **10** was obtained, mp 206-208°, lit 203° [18], 206-207° [19]; ^1H nmr (DMSO-d_6): δ 6.26 (d, J = 15.9 Hz, 1H, $CHCO_2H$), 6.89-7.60 (m, 5H, ArH and $CH{=}CHCO_2H$), 9.05 (br s, 1H, CO_2H).

3-Chloro-4-fluorobenzo[*b*]thiophene-2-carbonyl Chloride (**11**) [11].

To a suspension of 94.0 g (0.57 mole) of **8** in 500 ml of chlorobenzene containing 4.26 ml of pyridine in an ice bath was added dropwise 200 ml (2.74 moles) of thionyl chloride. The mixture was gradually warmed to room temperature and then heated under reflux for 80 hours. The solvent and the excess thionyl chloride were removed by distillation under reduced pressure and the residue was triturated with hexanes (350 ml). The solid was collected by filtration and recrystallized from hexanes to give 32.0 g (0.13 mole, 23%) of **11** as yellow crystals, mp 126.5-128°; ^1H nmr (deuteriochloroform): δ 7.03-7.26 (m, 1H, H-6), 7.42-7.67 (m, 2H, H-5 and H-7).

3-Chloro-5-fluorobenzo[*b*]thiophene-2-carbonyl Chloride (**12**) [11].

This compound was prepared from **9** (53.0 g, 0.32 mole), thionyl chloride (110 ml, 1.51 moles) in chlorobenzene (300 ml) and pyridine (2.4 ml) in a manner similar to that described for the synthesis of **11**; 21.0 g (84 mmoles, 26%) of **12** was obtained as yellow crystals, mp 104-106° lit [11] 108-110°; ^{1}H nmr (deuteriochloroform): δ 7.26-7.48 (m, 1H, H-6), 7.63 (dd, $J_{4,F}$ = 8.8 Hz, $J_{4,6}$ = 2.4 Hz, 1H, H-4), 7.80 (dd, $J_{6,7}$ = 8.8 Hz, $J_{F,7}$ = 4.6 Hz, 1H, H-7).

3-Chloro-6-fluorobenzo[*b*]thiophene-2-carbonyl Chloride (**13**) [11].

This compound was prepared from **10** (98.9 g, 0.60 mole), thionyl chloride (215 ml, 2.95 moles) in chlorobenzene (500 ml) and pyridine (5 ml) in a manner similar to that described for the synthesis of 11, thus 49.2 g (0.20 mole, 33%) of **13** was obtained as yellow needles, mp 106-108° lit [11] 109-111°; ^{1}H nmr (deuteriochloroform): δ 7.16-7.39 (m, 1H, H-5), 7.50 (dd, $J_{F,7}$ = 8.1 Hz, $J_{5,7}$ = 2.4 Hz, 1H, H-7), 7.96 (dd, $J_{4,5}$ = 9.0 Hz, $J_{4,F}$ = 5.1 Hz, 1H, H-4).

3-Chloro-4-fluoro-*N*-(2′-fluorophenyl)benzo[*b*]thiophene-2-carboxamide (**14**).

A mixture of 6.0 g (24 mmoles) of **11**, 2.68 g (24 mmoles) of *o*-fluoroaniline in 85 ml of benzene was heated under reflux for two hours. After cooling to room temperature the solvent was removed under reduced pressure and the residue was recrystallized from 95% ethanol to give 7.09 g (22 mmoles, 92%) of **14** as off-white needles, mp 150-152°; ir (potassium bromide): 3394 (NH stretching), 1669 (C=O stretching); ^{1}H nmr (DMSO-d_6): δ 7.14-7.67 (m, 5H, ArH), 7.76-7.97 (m, 2H, ArH), 9.92 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_8ClF_2NOS$: C, 55.65; H, 2.49; N, 4.33; S, 9.90. Found: C, 55.68; H, 2.46; N, 4.33; S, 9.89.

3-Chloro-4-fluoro-*N*-(4′-fluorophenyl)benzo[*b*]thiophene-2-carboxamide (**15**).

This compound was prepared from **11** (6.0 g, 24 mmoles) and *p*-fluoroaniline (2.68 g, 24 mmoles) in benzene (85 ml) in a manner similar to that described for the synthesis of **14**, and 7.05 g (22 mmoles, 92%) of **15** was obtained from 95% ethanol as off-white needles, mp 168-170°; ir (potassium bromide): 3302 (NH stretching), 1640 (C=O stretching); ^{1}H nmr (DMSO-d_6): δ 7.13-7.85 (m, 6H, ArH), 7.98 (dd, $J_{6,7}$ = 8.0 Hz, $J_{5,7}$ = 1.3 Hz, 1H, H-7), 10.67 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_8ClF_2NOS$: C, 55.65; H, 2.49; N, 4.33; S, 9.90. Found: C, 55.49; H, 2.50; N, 4.29; S, 10.00.

3-Chloro-5-fluoro-*N*-(2′-fluorophenyl)benzo[*b*]thiophene-2-carboxamide (**16**).

This compound was prepared from **12** (4.0 g, 16 mmoles) and *o*-fluoroaniline (1.78 g, 16 mmoles) in benzene (60 ml) in a manner similar to that described for the synthesis of **14**, therefore 4.57 g (14 mmoles, 88%) of **16** was obtained from cyclohexane as colorless crystals, mp 162-163°; ir (potassium bromide): 3394 (NH stretching), 1671 (C=O stretching); ^{1}H nmr (DMSO-d_6): 100° δ 7.18-8.00 (m, 6H, ArH), 8.14 (dd, $J_{6,7}$ = 9.2 Hz, $J_{F,7}$ = 4.8 Hz, 1H, H-7), 9.87 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_8ClF_2NOS$: C, 55.65; H, 2.49; N, 4.33; S, 9.90. Found: C, 55.88; H, 2.74; N, 4.35; S, 10.01.

3-Chloro-5-fluoro-*N*-(4′-fluorophenyl)benzo[*b*]thiophene-2-carboxamide (**17**).

This compound was prepared from **12** (4.0 g, 16 mmoles) and *p*-fluoroaniline (1.78 g, 16 mmoles) in benzene (60 ml) in a manner similar to that described for the synthesis of **14**; 4.73 g (14.6 mmoles, 91%) of **17** was obtained from benzene as fine colorless needles, mp 180-182°; ir (potassium bromide): 3296 (NH stretching), 1640 (C=O stretching); ^{1}H nmr (DMSO-d_6): δ 7.11-7.84 (m, 6H, ArH), 8.19 (dd, $J_{6,7}$ = 9.0 Hz, $J_{F,7}$ = 4.8 Hz, 1H, H-7), 10.60 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_8ClF_2NOS$: C, 55.65; H, 2.49; N, 4.33; S, 9.90. Found: C, 55.50; H, 2.70; N, 4.16; S, 9.79.

3-Chloro-6-fluoro-*N*-(2′-fluorophenyl)benzo[*b*]thiophene-2-carboxamide (**18**).

This compound was prepared from **13** (5.0 g, 20 mmoles) and *o*-fluoroaniline (2.23 g, 20 mmoles) in benzene (72 ml) in a manner similar to that described for the synthesis of **14**, and 5.34 g (16.5 mmoles, 83%) of **18** was obtained from 95% ethanol as off-white needles, mp 170-172°; ir (potassium bromide): 3386 (NH stretching), 1661 (C=O stretching); ^{1}H nmr (DMSO-d_6): δ 7.20-7.60 (m, 4H, ArH), 7.74-7.99 (m, 2H, ArH), 8.09 (dd, $J_{F,7}$ = 9.0 Hz, $J_{5,7}$ = 2.2 Hz, 1H, H-7), 10.13 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_8ClF_2NOS$: C, 55.65; H, 2.49; N, 4.33; S, 9.90. Found: C, 55.74; H, 2.65; N, 4.35; S, 9.83.

3-Chloro-6-fluoro-*N*-(4′-fluorophenyl)benzo[*b*]thiophene-2-carboxamide (**19**).

This compound was prepared from **13** (5.0 g, 20 mmoles) and *p*-fluoroaniline (2.23 g) in benzene (72 ml) in a manner similar to that described for the synthesis of **14**, thus 5.52 g (17 mmoles, 85%) of **19** was obtained from benzene as off-white needles, mp 178-181°; ir (potassium bromide): 3317 (NH stretching), 1643 (C=O stretching); ^{1}H nmr (DMSO-d_6): δ 7.12-7.99 (m, 6H, ArH), 8.10 (dd, $J_{F,7}$ = 9.0 Hz, $J_{5,7}$ = 2.2 Hz, 1H, H-7), 10.55 (br s, 1H, NH).

Anal. Calcd. for $C_{15}H_8ClF_2NOS$: C, 55.65; H, 2.49; N, 4.33; S, 9.90. Found: C, 55.68; H, 2.54; N, 4.33; S, 9.86.

4,11-Difluoro[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**20**).

A solution of 0.5 g (1.54 mmoles) of **14** in 500 ml of benzene containing 0.15 g of triethylamine was irradiated with a 450 watt Hanovia medium pressure mercury vapor lamp for 4 hours. A slow stream of air was passed through the solution during the course of the reaction. The solid was collected by filtration and washed with water to give 0.41 g (1.43 mmoles, 93%) of **20** as an off-white powder, mp >280°; ir (potassium bromdie): 3142 (NH stretching), 1666 (C=O stretching): ^{1}H nmr (DMSO-d_6): 140° δ 7.25-7.78 (m, 4H, ArH), 8.01 (dd, $J_{8,9}$ = 7.9 Hz, $J_{8,10}$ = 1.0 Hz, 1H, H-8), 8.47 (m, 1H, H-1), 11.50 (br s, 1H, NH). This compound was used without further purification in the next reaction because of low solubility.

2,11-Difluoro[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**21**).

This compound was obtained in 98% yield from **15** in a manner similar to that described for the synthesis of **20**, mp >280°; ir (potassium bromide): 3137 (NH stretching), 1669 (C=O stretching); ^{1}H nmr (DMSO-d_6): 150° δ 7.28-7.77 (m, 4H, ArH), 8.01 (dd, $J_{8,9}$ = 8.0 Hz, $J_{8,10}$ = 0.9 Hz, 1H, H-8), 8.39 (ddd, $J_{1,F11}$ = 11.7 Hz, $J_{1,F2}$ = 9.0 Hz, $J_{1,3}$ = 2.7 Hz, 1H, H-1), 11.84 (br s, 1H, NH). This compound was used without further purification in the next

reaction due to its low solubility.

4,10-Difluoro[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**22**).

This compound was obtained in 86% yield from **16** in a manner similar to that described for the synthesis of **20**, mp >280°; ir (potassium bromide): 3145 (NH stretching), 1664 (C=O stretching); ^{1}H nmr (DMSO-d$_6$): 150° δ 7.30-7.61 (m, 3H, ArH), 8.22 (dd, $J_{8,9}$ = 9.0 Hz, $J_{8,F}$ = 5.3 Hz, 1H, H-8), 8.34-8.58 (m, 2H, H-1 and H-11), 11.81 (br s, 1H, NH). This compound was used without further purification in the next reaction due to its low solubility.

2,10-Difluoro[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**23**).

This compound was obtained in 70% yield from **17** in a manner similar to that described for the synthesis of **20**, mp >280°; ir (potassium bromide): 3137 (NH stretching), 1653 (C=O stretching): ^{1}H nmr (DMSO-d$_6$): 150° δ 7.25-7.67 (m, 3H, ArH), 8.20 (dd, $J_{8,9}$ = 8.7 Hz, $J_{8,F}$ = 5.4 Hz, 1H, H-8), 8.28 (dd, $J_{1,F}$ = 10.3 Hz, $J_{1,3}$ = 2.6 Hz, 1H, H-1), 8.50 (dd, $J_{F,11}$ = 10.8 Hz, $J_{9,11}$ = 2.3 Hz, 1H, H-11), 11.85 (br s, 1H, NH). This compound was used without further purification in the next reaction due to its low solubility.

4,9-Difluoro[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**24**).

This compound was obtained in 52% yield from **18** in a manner similar to that described for the synthesis of **20**, mp >280°; ir (potassium bromide): 3145 (NH stretching), 1643 (C=O stretching); ^{1}H nmr (DMSO-d$_6$): 120° δ 7.28-7.58 (m, 3H, ArH), 8.05 (dd, $J_{8,F}$ = 9.0 Hz, $J_{8,10}$ = 2.6 Hz, 1H, H-8), 8.42 (m, 1H, H-1), 8.80 (dd, $J_{10,11}$ = 9.3 Hz, $J_{F,11}$ = 5.1 Hz, 1H, H-11), 11.77 (br s, 1H, NH). This compound was used without further purification in the next reaction due to its low solubility.

2,9-Difluoro[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**25**).

This compound was obtained in 48% yield from **19** in a manner similar to that described for the synthesis of **20**, mp >280°; ir (potassium bromide): 3137 (NH stretching), 1653 (C=O stretching); ^{1}H nmr (DMSO-d$_6$): 150° δ 7.25-7.67 (m, 3H, ArH), 8.01 (dd, $J_{8,F}$ = 8.9 Hz, $J_{8,10}$ = 2.5 Hz, 1H, H-8), 8.30 (dd, $J_{1,F}$ = 10.4 Hz, $J_{1,3}$ = 2.5 Hz, 1H, H-1), 8.78 (dd, $J_{10,11}$ = 9.1 Hz, $J_{F,11}$ = 5.0 Hz, 1H, H-11), 11.68 (br s, 1H, NH). This compound was used without further purification in the next reaction due to its low solubility.

6-Chloro-4,11-difluoro[1]benzothieno[2,3-*c*]quinoline (**26**).

A mixture of 2.03 g (7.07 mmoles) of lactam **20** and 45 ml of phosphorus oxychloride was heated at 100-110° for four hours. After cooling in an ice bath, the mixture was poured into 300 ml of ice water with great caution keeping the temperature of the solution below 60°. The solid thus obtained was collected by filtration and washed with plenty of water and dried. The solid was recrystallized from benzene to give 0.81 g (2.65 mmoles, 37%) of **26** as a yellowish powder, mp 240-242°; ir (potassium bromide): 3080 (aromatic CH stretching); ^{1}H nmr (DMSO-d$_6$): 130° δ 7.26-7.82 (m, 4H, ArH), 7.96 (dd, $J_{8,9}$ = 7.8 Hz, $J_{8,10}$ = 1.2 Hz, 1H, H-8), 8.67-8.88 (m, 1H, H-1).

Anal. Calcd. for $C_{15}H_6ClF_2NS$: C, 58.93; H, 1.98; N, 4.58; S, 10.49. Found: C, 58.81; H, 1.80; N, 4.72; S, 10.48.

6-Chloro-2,11-difluoro[1]benzothieno[2,3-*c*]quinoline (**27**).

This compound was obtained from benzene in 83% yield from the corresponding lactam **21** in a manner similar to that described for the synthesis of **26**, mp 224-225°; ir (potassium bromide): 3065 (aromatic CH stretching); ^{1}H nmr (DMSO-d$_6$): 135° δ 7.35-7.88 (m, 3H, ArH), 8.02-8.23 (m, 2H, ArH), 8.58 (ddd, $J_{1,F11}$ = 12.0 Hz, $J_{1,F2}$ = 9.3 Hz, $J_{1,3}$ = 2.7 Hz, 1H, H-1).

Anal. Calcd. for $C_{15}H_6ClF_2NS$: C, 58.93; H, 1.98; N, 4.58; S, 10.49. Found: C, 58.82; H, 1.83; N, 4.41; S, 10.63.

6-Chloro-4,10-difluoro[1]benzothieno[2,3-*c*]quinoline (**28**).

This compound was obtained from benzene in 84% yield from the corresponding lactam **22** in a manner similar to that described for the synthesis of **26**, mp 246-247°; ir (potassium bromide): 3086 (aromatic CH stretching); ^{1}H nmr (DMSO-d$_6$): 100° δ 7.42-8.02 (m, 3H, ArH), 8.20 (dd, $J_{8,9}$ = 9.1 Hz, $J_{8,F}$ = 5.3 Hz, 1H, H-8), 8.49-8.66 (m, 2H, H-1 and H-11).

Anal. Calcd. for $C_{15}H_6ClF_2NS$: C, 58.93; H, 1.98; N, 4.58; S, 10.49. Found: C, 58.81; H, 1.80; N, 4.72; S, 10.48.

6-Chloro-2,10-difluoro[1]benzothieno[2,3-*c*]quinoline (**29**).

This compound was obtained from cyclohexane in 67% yield from lactam **23** in a manner similar to that described for the synthesis of **26**, mp 272-273°; ir (potassium bromide): 3068 (aromatic CH stretching); ^{1}H nmr (DMSO-d$_6$): 150° δ 7.46-7.79 (m, 2H, H-3 and H-9), 8.18 (dd, $J_{3,4}$ = 8.7 Hz, $J_{F,4}$ = 5.9 Hz, 1H, H-4), 8.27 (dd, $J_{8,9}$ = 9.0 Hz, $J_{8,F}$ = 5.1 Hz, 1H, H-8), 8.53 (dd, $J_{1,F}$ = 7.9 Hz, $J_{1,3}$ = 2.6 Hz, 1H, H-1), 8.65 (dd, $J_{F,11}$ = 7.7 Hz, $J_{9,11}$ = 2.3 Hz, 1H, H-11).

Anal. Calcd. for $C_{15}H_6ClF_2NS$: C, 58.93; H, 1.98; N, 4.58; S, 10.49. Found: C, 59.08; H, 1.84; N, 4.61; S, 10.38.

6-Chloro-4,9-difluoro[1]benzothieno[2,3-*c*]quinoline (**30**).

This compound was obtained from benzene as colorless needles in 74% yield from the lactam **24** in a manner similar to that described for the synthesis of **26**, mp 278-279°; ir (potassium bromide): 3080 (aromatic CH stretching); ^{1}H nmr (DMSO-d$_6$): 150° δ 7.40-7.92 (m, 3H, ArH), 8.09 (dd, $J_{8,F}$ = 9.0 Hz, $J_{8,10}$ = 2.6 Hz, 1H, H-8), 8.68 (br d, $J_{1,2}$ = 8.2 Hz, 1H, H-1), 8.9 (dd, $J_{10,11}$ = 9.1 Hz, $J_{F,11}$ = 5.0 Hz, 1H, H-11).

Anal. Calcd. for $C_{15}H_6ClF_2NS$: C, 58.93; H, 1.98; N, 4.58; S, 10.49. Found: C, 59.13; H, 1.78; N, 4.68; S, 10.29.

6-Chloro-2,9-difluoro[1]benzothieno[2,3-*c*]quinoline (**31**).

This compound was obtained from benzene in 60% yield from the lactam **25** in manner similar to that described for the synthesis of **26**, mp 260-262°; ir (potassium bromide): 3065 (aromatic CH stretching); ^{1}H nmr (DMSO-d$_6$): 120° δ 7.39-7.80 (m, 2H, H-3 and H-10), 8.04-8.25 (m, 2H, H-4 and H-8), 8.54 (dd, $J_{1,F}$ = 10.4 Hz, $J_{1,3}$ = 2.4 Hz, 1H, H-1), 8.91 (dd, $J_{10,11}$ = 9.1 Hz, $J_{F,11}$ = 5.0 Hz, 1H, H-11).

Anal. Calcd. for $C_{15}H_6ClF_2NS$: C, 58.93; H, 1.98; N, 4.58; S, 10.49. Found: C, 58.93; H, 1.74; N, 4.64; S, 10.36.

4,11-Difluoro[1]benzothieno[2,3-*c*]quinoline (**32**).

A mixture of 0.72 g (2.36 mmoles) of **26**, 0.132 g (2.36 mmoles) of potassium hydroxide, 0.1 g of 10% Pd-C, 80 ml of benzene and 80 ml of methanol was stirred under a hydrogen atmosphere at atmospheric pressure and room temperature until the uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residual solid was recrystallized from cyclohexane to afford 0.50 g (1.84 mmoles, 78%) of **32** as an off-white powder, mp 175-176°; ir (potassium bromide): 3047 (aromatic CH stretching); ^{1}H nmr (DMSO-d$_6$): 100° δ 7.36-7.88 (m, 4H, ArH), 8.12 (dd, $J_{8,9}$ = 7.6 Hz, $J_{8,10}$ = 1.2 Hz, 1H, H-8), 8.69-8.90 (m, 1H, H-1), 9.54 (s, 1H, H-6).

Anal. Calcd. for $C_{15}H_7F_2NS$: C, 66.41; H, 2.60; N, 5.16; S, 11.82. Found: C, 66.36; H, 2.89; N, 4.83; S, 11.50.

2,11-Difluoro[1]benzothieno[2,3-*c*]quinoline (**33**).

This compound was obtained from cyclohexane as colorless crystals in 74% yield from **27** in a manner similar to that described for the synthesis of **32**, mp 175-176°; ir (potassium bromide): 3078) aromatic CH stretching); ^{1}H nmr (deuteriochloroform): δ 7.19-7.71 (m, 3H, ArH), 7.82 (dd, $J_{8,9}$ = 7.8 Hz, $J_{8,10}$ = 1.2 Hz, 1H, H-8), 8.26 (dd, $J_{3,4}$ = 9.0 Hz, $J_{F,4}$ = 6.0 Hz, 1H, H-4), 8.78 (ddd, $J_{1,F11}$ = 12.2 Hz, $J_{1,F2}$ = 10.3 Hz, $J_{1,3}$ = 2.7 Hz, 1H, H-1), 9.24 (s, 1H, H-6).

Anal. Calcd. for $C_{15}H_7F_2NS$: C, 66.41; H, 2.60; N, 5.16; S, 11.82. Found: C, 66.19; H, 2.84; N, 5.19; S, 11.66.

4,10-Difluoro[1]benzothieno[2,3-*c*]quinoline (**34**).

This compound was obtained from cyclohexane as off-white crystals in 82% yield from **28** in a manner similar to that described for the synthesis of **32**, mp 193-195° dec; ir (potassium bromide): 3055 (aromatic CH stretching); ^{1}H nmr (deuteriochloroform): δ 7.23-7.75 (m, 3H, H-2, H-3 and H-9), 7.91 (dd, $J_{8,9}$ = 8.8 Hz, $J_{8,F}$ = 5.1 Hz, 1H, H-8), 8.17-8.36 (m, 2H, H-1 and H-11), 9.25 (s, 1H, H-6).

Anal. Calcd. for $C_{15}H_7F_2NS$: C, 66.41; H, 2.60; N, 5.16; S, 11.82. Found: C, 66.19; H, 2.26; N, 5.09; S, 11.73.

2,10-Difluoro[1]benzothieno[2,3-*c*]quinoline (**35**).

This compound was obtained from cyclohexane as colorless crystals in 82% yield from **29** in a manner similar to that described for the synthesis of **32**, mp 206-208°; ir (potassium bromide): 3068 (aromatic CH stretching); ^{1}H nmr (deuteriochloroform): δ 7.29-7.64 (m, 2H, H-3 and H-9), 7.99 (dd, $J_{3,4}$ = 8.8 Hz, $J_{F,4}$ = 5.1 Hz, 1H, H-4), 8.21-8.43 (m, 3H, H-1, H-8 and H-11), 9.27 (s, 1H, H-6).

Anal. Calcd. for $C_{15}H_7F_2NS$: C, 66.41; H, 2.60; N, 5.16; S, 11.82. Found: C, 66.40; H, 2.71; N, 5.18; S, 11.76.

4,9-Difluoro[1]benzothieno[2,3-*c*]quinoline (**36**).

This compound was obtained from cyclohexane as yellowish crystals in 83% yield from **30** in a manner similar to that described for the synthesis of **32**, mp 198-200° dec; ir (potassium bromide): 3080 (aromatic CH stretching); ^{1}H nmr (deuteriochloroform): δ 7.26-7.81 (m, 4H, ArH), 8.53 (dt, $J_{1,2}$ = 8.3 Hz, $J_{1,3}$ = 1.2 Hz, $J_{1,F}$ = 1.2 Hz, 1H, H-1), 8.73 (dd, $J_{10,11}$ = 9.0 Hz, $J_{F,11}$ = 4.8 Hz, 1H, H-11), 9.33 (s, 1H, H-6).

Anal. Calcd. for $C_{15}H_7F_2NS$: C, 66.41; H, 2.60; N, 5.16; S, 11.82. Found: C, 66.32; H, 2.80; N, 5.21; S, 11.62.

2,9-Difluoro[1]benzothieno[2,3-*c*]quinoline (**37**).

This compound was obtained from cyclohexane as colorless crystals in 89% yield from **31** in a manner similar to that described for the synthesis of **32**, mp 192-194°; ir (potassium bromide): 3060 (aromatic CH stretching); ^{1}H nmr (deuteriochloroform): δ 7.26-7.76 (m, 3H, ArH), 8.19-8.39 (m, 2H, H-1 and H-8), 8.63 (dd, $J_{10,11}$ = 9.2 Hz, $J_{F,11}$ = 5.0 Hz, 1H, H-11), 9.23 (s, 1H, H-6).

Anal. Calcd. for $C_{15}H_7F_2NS$: C, 66.41; H, 2.60; N, 5.16; S, 11.82. Found: C, 66.27; H, 2.81; N, 5.12; S, 11.66.

4,11-Difluoro-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**38**).

A mixture of 0.34 g (1.25 mmoles) of **32**, 2 ml of iodomethane and 25 ml of benzene was heated at 100-110° in a sealed reaction vessel for 24 hours. After cooling the precipitate was collected by filtration and then recrystallized from methanol to afford 0.35 g (0.85 mmole, 68%) of quaternary salt **38** as orange needles, mp 218-220° dec; ir (potassium bromide): 3050 (aromatic CH stretching), 2993 (aliphatic CH stretching), 1378 (CH bending of CH_3); ^{1}H nmr (DMSO-d_6): 90° δ 4.85 (d, J_{F,CH_3} = 9.7 Hz, 3H, CH_3), 7.59-8.21 (m, 4H, ArH), 8.40 (dd, $J_{8,9}$ = 8.0 Hz, $J_{8,10}$ = 1.0 Hz, 1H, H-8), 9.01-9.21 (m, 1H, H-1), 10.35 (s, 1H, H-6).

Anal. Calcd. for $C_{16}H_{10}F_2INS$: C, 46.50; H, 2.44; N, 3.39; S, 7.76. Found: C, 46.62; H, 2.19; N, 3.44; S, 7.70.

2,11-Difluoro-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**39**).

This compound was obtained from methanol as orange needles in 71% yield in a manner similar to that described for the synthesis of **38**, mp 294-295° dec; ir (potassium bromide): 3037 (aromatic CH stretching), 2980, 2954 (aliphatic CH stretching), 1376 (CH bending CH_3): ^{1}H nmr (DMSO-d_6): 100° δ 4.77 (s, 3H, CH_3), 7.56-8.28 (m, 3H, H-3, H-9 and H-10), 8.38 (dd, $J_{8,9}$ = 8.1 Hz, $J_{8,10}$ = 1.0 Hz, 1H, H-8), 8.76 (dd, $J_{3,4}$ = 9.7 Hz, $J_{F,4}$ = 5.1 Hz, 1H, H-4), 8.98 (dt, $J_{1,F2} \simeq J_{1,F11}$ = 10.5 Hz, $J_{1,3}$ = 2.8 Hz, 1H, H-1), 10.44 (s, 1H, H-6).

Anal. Calcd. for $C_{16}H_{10}F_2INS$: C, 46.50; H, 2.44; N, 3.39; S, 7.76. Found: C, 46.65; H, 2.62; N, 3.47; S, 7.61.

4,10-Difluoro-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**40**).

This compound was obtained from methanol as light orange needles in 24% yield in a manner similar to that described for the synthesis of **38**, mp 209-211° dec; ir (potassium bromide): 3044 (aromatic CH stretching), 1363 (CH bending of CH_3); ^{1}H nmr (DMSO-d_6): δ 4.85 (d, J_{F,CH_3} = 10.0 Hz, 3H, CH_3), 7.81-8.21 (m, 3H, H-2, H-3 and H-9), 8.64 (dd, $J_{8,9}$ = 9.0 Hz, $J_{8,F}$ = 5.1 Hz, 1H, H-8), 9.00-9.25 (m, 2H, H-1 and H-11), 10.41 (s, 1H, H-6).

Anal. Calcd. for $C_{16}H_{10}F_2INS$: C, 46.50; H, 2.44; N, 3.99; S, 7.76. Found: C, 46.65; H, 2.19; N, 3.43; S, 7.66.

2,10-Difluoro-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**41**).

This compound was obtained from methanol as orange crystals in 74% yield in a manner similar to that described for the synthesis of **38**, mp 292-293° dec; ir (potassium bromide): 3060 (aromatic CH stretching), 1380 (CH bending of CH_3); ^{1}H nmr (DMSO-d_6): 150° δ 4.77 (s, 3H, CH_3), 7.69-8.22 (m, 2H, H-3 and H-9), 8.53 (dd, $J_{3,4}$ = 9.1 Hz, $J_{F,4}$ = 5.0 Hz, 1H, H-4), 8.75 (dd, $J_{8,9}$ = 9.7 Hz, $J_{8,F}$ = 4.9 Hz, 1H, H-8), 9.00 (br d, 2H, H-1 and H-11), 10.40 (s, 1H, H-6).

Anal. Calcd. for $C_{16}H_{10}F_2INS$: C, 46.50; H, 2.44; N, 3.39; S, 7.76. Found: C, 46.56; H, 2.67; N, 3.40; S, 7.81.

4,9-Difluoro-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**42**).

This compound was obtained from methanol as yellow needles in 55% yield in a manner similar to that described for the synthesis of **38**, mp 217-218° dec; ir (potassium bromide): 3055 (aromatic CH stretching), 1383 (CH bending of CH_3); ^{1}H nmr (DMSO-d_6): δ 4.83 (d, J_{F,CH_3} = 9.7 Hz, 3H, CH_3), 7.77 (td, $J_{10,11}$ = 9.5 Hz, $J_{F,10}$ = 9.0 Hz, $J_{8,10}$ = 2.6 Hz, 1H, H-10), 8.06-8.22 (m, 2H, H-2 and H-3), 8.57 (dd, $J_{8,F}$ = 9.0 Hz, $J_{8,10}$ = 2.6 Hz, 1H, H-8), 9.21 (dd, $J_{1,2}$ = 7.7 Hz, $J_{1,3}$ = 3.0 Hz, 1H, H-1), 9.32 (dd, $J_{10,11}$ = 9.5 Hz, $J_{F,11}$ = 5.1 Hz, 1H, H-11), 10.37 (s, 1H, H-6).

Anal. Calcd. for $C_{16}H_{10}F_2INS$: C, 46.50; H, 2.44; N, 3.39; S, 7.76. Found: C, 46.59; H, 2.34; N, 3.43; S, 7.69.

2,9-Difluoro-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**43**).

This compound was obtained from methanol as yellow crystals in 73% yield in a manner similar to that described for the synthesis of **38**, mp >320°; ir (potassium bromide): 3060 (aromatic CH stretching), 2988 (aliphatic CH stretching), 1368 (CH bending of CH_3); ^1H nmr (DMSO-d_6): 120° δ 4.75 (s, 3H, CH_3), 7.70 (ddd, $J_{10,11}$ = 9.2 Hz, $J_{F,10}$ = 8.7 Hz, $J_{8,10}$ = 2.6 Hz, 1H, H-10), 8.15 (ddd, $J_{3,4}$ = 9.7 Hz, $J_{F,3}$ = 8.0 Hz, $J_{1,3}$ = 2.6 Hz, 1H, H-3), 8.38 (dd, $J_{8,F}$ = 9.1 Hz, $J_{8,10}$ = 2.6 Hz, 1H, H-8), 8.75 (dd, $J_{3,4}$ = 9.7 Hz, $J_{F,4}$ = 5.0 Hz, 1H, H-4), 9.04 (dd, $J_{1,F}$ = 9.7 Hz, $J_{1,3}$ = 2.6 Hz, 1H, H-1), 9.31 (dd, $J_{10,11}$ = 9.2 Hz, $J_{F,11}$ = 4.9 Hz, 1H, H-11), 10.33 (s, 1H, H-6).

Anal. Calcd. for $C_{16}H_{10}F_2INS$: C, 46.50; H, 2.44; N, 3.39; S, 7.76. Found: C, 46.39; H, 2.56; N, 3.39; S, 7.65.

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[1] To whom correspondence should be directed at the Department of Chemistry, University of South Florida, Tampa, FL 33620.

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