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Inhibition of Adhesion Molecule Expression by *N*-Alkylthiopyridine-benzo[*b*]thiophene-2-carboxamides

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Abstract—The surface levels of ICAM-1 and E-selectin on activated endothelial cells can be reduced by 3-alkoxybenzo[*b*]thiophene-2-carboxamides. This property is shared by several *N*-alkylthiopyridine substituted imides. Combining structural elements of these two diverse series lead to a new class of small molecule inhibitors of adhesion molecule expression. Copyright © 1996 Elsevier Science Ltd

Introduction

In response to injury or infection, neutrophils migrate from the vasculature into the tissue. This process is a cascade of events wherein the neutrophils adhere transiently then firmly to the endothelial cells lining the blood vessels, followed by diapedesis through the vessel wall. The interactions of specific cell surface proteins termed adhesion molecules mediate the various steps in this sequence.[1–3] ICAM-1 (intercellular adhesion molecule-1)[4] and E-selectin (ELAM-1, endothelial leukocyte adhesion molecule-1)[5] are adhesion molecules that appear on the surface of endothelial cells several hours after stimulation with inflammatory mediators. The ligands on the neutrophils for these two adhesion molecules are the β2 integrins, which recognize ICAM-1, and carbohydrate epitopes, such as sialyl Lewis X (sLe^x), which recognize E-selectin. The inhibition of cell adhesion as a therapeutic strategy for the treatment of inflammatory diseases was validated by the activity of an antibody to ICAM-1 in a clinical trial of rheumatoid arthritis.[6] In addition, there are numerous reports of the effectiveness of sLe^x and related carbohydrates,[7,8] and also of antagonists of β2 integrin mediated adhesion[9–11] in animal models where monoclonal antibodies to adhesion molecules were efficacious.[12,13]

We previously reported a series of benzo[*b*]thiophene-2-carboxamides and related heterocycles of structure **A** that inhibited the adhesion of neutrophils to TNF-α (tumor necrosis factor-α) activated HUVECs (human umbilical vein endothelial cells).[14,15] The parent compound **1** had an IC_{50} of 3.8 μM in this assay and ELISAs demonstrated that **1** modulated the surface expression of both ICAM-1 (IC_{50} = 0.39 μM) and E-selectin (IC_{50} = 0.70 μM). The sulfoxide analogue of **1**, PD 144795 (**2**), while less potent than **1** in vitro, was orally active in several animal models of inflammation.[15] The only other report of small molecule inhibitors of adhesion molecule expression is a patent application from Takeda which claimed a series of *N*-alkylthiopyridine imides as antiinflammatory and analgesic agents.[16] Some of these compounds, including **3** and **4**, inhibited the expression of ICAM-1 and E-selectin (Table 1) as measured by ELISA. Combining structural elements of **1** and those of the Takeda compounds lead to the design of compounds of structure **B**.

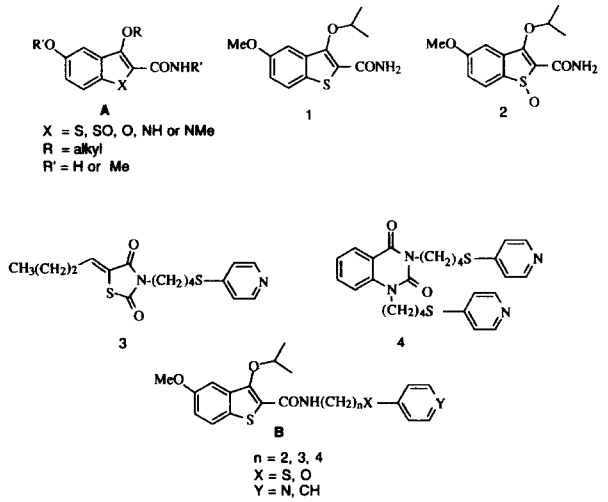
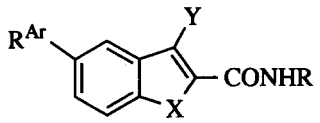


Figure 1.

Results and Discussion

It was envisioned that the desired substituted amides could be obtained by treatment of the imidazolide of acid **5**[17] with the appropriate amine or by alkylation of the primary carboxamide group of **1** with the appropriate alkyl halide. The required amines or halides were prepared, as shown in Scheme 1, using the routes described by Takeda. In general, the amines were

Table 1. Inhibition of adhesion molecule expression by *N*-alkylthiopyridine-benzo[*b*]thiophene-2-carboxamides



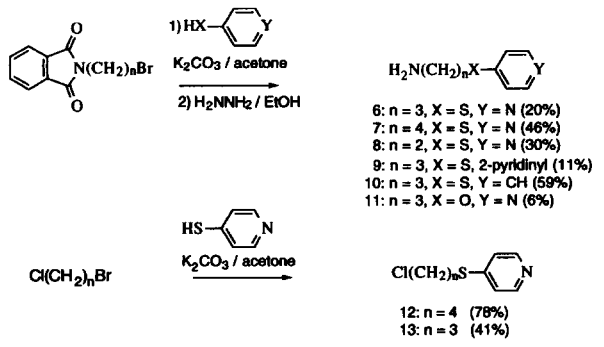
Compd	X	Y	R	R^{Ar}	ICAM/ESEL[a]
1	S	O-*i*-Pr	H	OMe	0.39/0.70
3	Takada				75%/94% at 13 μM[16]
4	Takada				83%/96% at 13 μM[16]
14	S	O-*i*-Pr	$(CH_2)_3$-S-4-pyr	OMe	5.7/8.4
15	S	O-*i*-Pr	$(CH_2)_4$-S-4-pyr	OMe	8.6/9.3
16	S	O-*i*-Pr	$(CH_2)_2$-S-4-pyr	OMe	6.9/9.8
17	S	O-*i*-Pr	$(CH_2)_3$-S-2-pyr	OMe	8.8/7.4
18	S	O-*i*-Pr	$(CH_2)_3$-S-phenyl	OMe	48%/32% at 30 μM
19	S	O-*i*-Pr	$(CH_2)_3$-O-4-pyr	OMe	68%/81% at 30 μM
22	O	O-*i*-Pr	$(CH_2)_3$-S-4-pyr	OMe	25/26
23	NH	O-*i*-Pr	$(CH_2)_3$-S-4-pyr	OMe	54%/47% at 30 μM
25	N $(CH_2)_3$-S-4-pyr	O-*i*-Pr	H	OMe	18%/NA[b] at 30 μM
28	S	H	$(CH_2)_3$-S-4-pyr	OMe	18%/6% at 30 μM
29	S	H	$(CH_2)_3$-S-4-pyr	H	NA[b]/NA[b] at 30 μM
30	1C-homologue at C-2 of **14**				18%/6% at 30 μM
31	ester analogue of **15**				22%/29% at 30 μM

[a]Inhibition of ICAM-1 or E-selectin surface expression reported as the IC_{50} (μM) or the percent inhibition at the stated concentration. The details of this assay have been reported.[15] Data shown is the average of two assays each performed in triplicate. The mean standard error is less than 10%.
[b]NA-less than 4% inhibition of adhesion molecule expression at the stated concentration.

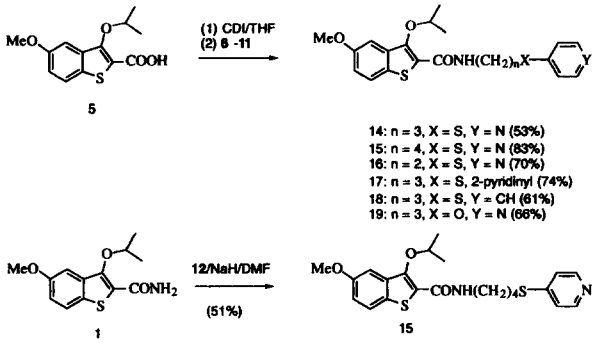
prepared by the reaction of 4-mercaptopyridine, or an analogue, with a *N*-bromoalkyl-phthalimide derivative in the presence of potassium carbonate. Anhydrous hydrazine was then used to remove the protecting group providing the desired primary amines **6–11**. The chloro derivatives **12** and **13** were prepared by the reaction of 1-bromo-4-chlorobutane and 1-bromo-3-chloropropane, respectively, with 4-mercaptopyridine and potassium carbonate.

As shown in Scheme 2, amide **14** was obtained in 53% yield via treatment of **5** with 1,1′-carbonyldiimidazole followed by the addition of **6**. The corresponding 1-carbon homologue **15** was obtained in 83% yield by this route and in 51% yield via alkylation of amide **1** with **12**. Due to the better yield obtained via the acid, this route was chosen for the preparation of the additional analogues **16–19**. As shown in Table 1, **14** inhibited the expression of both ICAM-1 ($IC_{50} = 5.7$ μM) and E-selectin ($IC_{50} = 8.4$ μM). This finding contrasts with the SAR of series **A** where secondary amides showed reduced activity when compared with **1**, with the activity decreasing with the increasing size of the N-substituent.[15] The length of the N-alkyl chain of **14** could be increased or decreased by one methylene group, **15** and **16**, and the potency retained. The pyridine nitrogen of **14** could also be moved from the *para* to the *ortho* position, **17**, without reduction in activity. However, replacement of the pyridine ring of **14** with a phenyl group, **18**, or of the exocyclic sulfur of **14** with oxygen, **19**, was detrimental to the activity.

The benzofuran and indole analogues of **14**, **22**, and **23**, were prepared via conversion of the corresponding acid **20**[17] or **21**[18] to the imidazolide followed by addition of **6** (Scheme 3). Both these heterocyclic derviatives were less potent than **14**, in divergence from the SAR



Scheme 1.



Scheme 2.

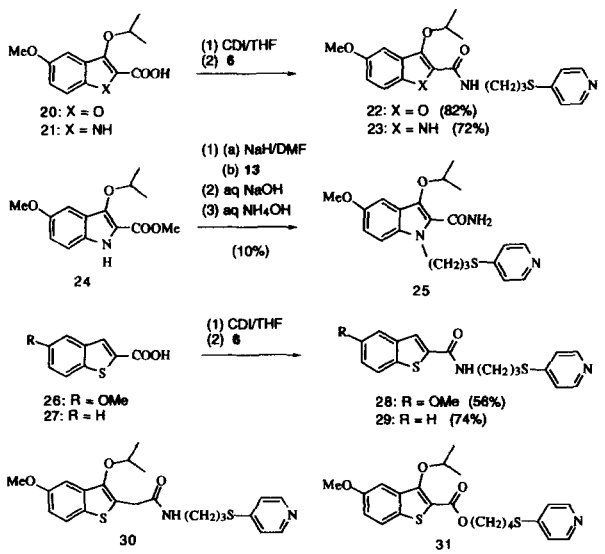
observed in series **A**, where variation of the heteroatom from sulfur to nitrogen or oxygen was not detrimental.[15] Indole **25**, which is isomeric to **23**, was obtained by alkylation of the indole nitrogen of **24**[19] with **13**, followed by conversion of the ester to the primary carboxamide. This introduction of the propylthiopyridine group onto the indole nitrogen while retaining the primary carboxamide at C-2, resulted in reduced activity when compared to the isomeric indole **23**. This decrease in activity parallels that seen in series **A** with indole-N substituents larger than methyl.[15]

Analogues of **14** lacking the 3-alkoxy group or both the 3- and the 5-alkoxy groups, **28** and **29**, were prepared from the known acids **26**[20] and **27**[21] by the above method. Compound **28**, which lacks the 3-isopropoxy group of **14**, showed marked reduction in activity, while the analogue lacking both the 3-isopropoxy and the 5-methoxy substituents, **29**, was inactive. These results demonstrated that the alkoxy substituents contribute to the activity of the compounds as was seen previously for the primary carboxamides.[15] The inactivity of **30**, the 1-carbon C-2 homologue of **14**, and of **31**, the ester corresponding to amide **15**, demonstrates that the amide functionality is crucial and must be directly attached to the heterocyclic ring.

In summary, a series of *N*-alkylthiopyridine-5-methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxamides, exemplified by **14**, reduced the surface levels of ICAM-1 and E-selectin on activated endothelial cells. In addition, **14** blocked the adhesion of neutrophils to TNF-α activated HUVECs ($IC_{50} = 18$ μM). These compounds are undergoing further evaluation.

Experimental

Reactions were performed under an atmosphere of nitrogen or argon. Flash chromatography was performed with E. Merck silica gel 60, 230–400 mesh. Melting points were recorded on a Mel-Temp melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker AM 250 or Varian Unity 400 NMR spectrometer, with chemical shifts reported in δ units relative to TMS. IR spectra were recorded on a Nicolet MX-1 or Mattson Cygnus 100 FTIR spectrometer. Mass spectra were recorded on a VG Masslab Trio-2A, a Finnigan 4500, or a VG Analytical 7070E/HF mass spectrometer. All new compounds yielded satisfactory NMR, IR, and MS data. Elemental analyses were performed by the Parke-Davis Analytical Chemistry staff and were within ±0.4% of the theoretical values.



Scheme 3.

3-(4-Pyridinylthio)-1-propanamine (6). To a solution of 4-mercaptopyridine (983 mg, 8.39 mmol) in 30 mL of acetone was added potassium carbonate (2.5 g, 18.1 mmol) followed by *N*-(3-bromopropyl)phthalimide (2.51 g, 9.39 mmol). The soln was heated at reflux for 20 min then cooled to rt. The resulting solid was collected by filtration, and washed with ethyl acetate to provide 857 mg (34%) of 2-[3-(4-pyridinylthio)propyl]-1*H*-isoindole-1,3(2*H*)-dione, mp 128–130 °C; ^{1}H NMR (DMSO-d_6): δ 1.96 (m, $J = 7$ Hz, 2H), 3.12 (d, $J = 7$ Hz, 2H), 3.73 (d, $J = 7$ Hz, 2H), 7.26 (d, $J = 6$ Hz, 2H), 7.85 (m, 4H), 8.35 (d, $J = 6$ Hz, 2H). Anal. calcd for $C_{16}H_{14}N_2O_2S \cdot 25\ H_2O$: C, 63.44; H, 4.83; N, 9.25; found: C, 63.58; H, 4.66; N, 9.22.

To a suspension of 2-[3-(4-pyridinylthio)propyl]-1*H*-isoindole-1,3(2*H*)-dione (443 mg, 1.48 mmol) in 7 mL of ethanol was added hydrazine (60 μL, 1.91 mmol). After stirring at rt overnight, 1 mL conc HCl was added. The precipitate was removed by filtration and the filtrate concd in vacuo. The residue was dissolved in ethyl acetate and washed with a weakly basic aqueous NaOH soln. The organic layer was dried over $MgSO_4$, filtered and concd in vacuo to provide 148 mg (60%) of **6** that was not purified.

5-Methoxy-3-(1-methylethoxy)-*N*-[3-(4-pyridinylthio)-propyl]benzo[*b*]thiophene-2-carboxamide (14). To a soln of **5**[17](247 mg, 0.93 mmol) in 10 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (166 mg, 1.02 mmol). The soln was heated at reflux for 1.5 h then cooled to rt and a soln of triethylamine (280 μL, 2.00 mmol) and **6** (188 mg, 1.12 mmol) in 10 mL of tetrahydrofuran was added. The soln was heated at reflux for 8.5 h then stirred at rt overnight. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered and concd in vacuo. Flash chromatography eluting with a gradient of 2:1 ethyl acetate:hexane to all ethyl acetate gave 198 mg (53%) of **14**, mp 74–76 °C; ^{1}H NMR (DMSO-d_6): δ 1.34 (d, $J = 6$ Hz, 6H), 1.93 (m, 2H), 3.13 (t, $J = 7$ Hz, 2H), 3.47 (m, 2H), 3.85 (s, 3H), 4.71 (heptet, $J = 6$ Hz, 1H), 7.13 (dd, $J = 9$, 2.5 Hz, 1H), 7.19 (d, $J = 2.5$ Hz, 1H), 7.28 (d, $J = 6$ Hz, 2H), 7.84 (d, $J = 9$ Hz, 1H), 8.03 (t, $J = 5.5$ Hz, 1H-NH), 8.37 (d, $J = 6$ Hz, 2H). Anal. calcd for

$C_{21}H_{24}N_2O_3S_2 \cdot 75\ H_2O$: C, 58.65; H, 5.98: N, 6.52; found: C, 58.71; H, 5.89; N, 6.47.

5-Methoxy-3-(1-methylethoxy)-*N*-[4-(4-pyridinylthio)-butyl]benzo[*b*]thiophene-2-carboxamide (15). To a soln of **5** (370 mg, 1.39 mmol) in 10 mL of tetrahydrofuran was added 1,1′-carbonyldiimidazole (254 mg, 1.57 mmol). The soln was heated at reflux for 2 h then cooled to rt and a soln of triethylamine (260 μL, 1.87 mmol) and **7** (451 mg, 2.48 mmol) in 6 mL of tetrahydrofuran was added. The soln was heated at reflux for 2 h then partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered and concd in vacuo. Flash chromatography eluting with a gradient of ethyl acetate to 10% methanol in ethyl acetate gave 498 mg (83%) of **15**, mp 105–107 °C; ^{1}H NMR (DMSO-d_6): δ 1.33 (d, J = 6 Hz, 6H), 1.70 (m, 4H), 3.12 (t, J = 6.5 Hz, 2H), 3.37 (m, 2H), 3.85 (s, 3H), 4.73 (heptet, J = 6 Hz, 1H), 7.13 (dd, J = 9, 2.5 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 7.27 (d, J = 6 Hz, 2H), 7.84 (d, J = 9 Hz, 1H), 7.91 (t, J = 6 Hz, 1H-NH), 8.34 (d, J = 6 Hz, 2H). Anal. calcd for $C_{22}H_{26}N_2O_3S_2$: C, 61.37; H, 6.09; N, 6.51; found: C, 61.60; H, 6.12; N, 6.55.

Alternative preparation of 15. To a rt suspension of sodium hydride (70 mg of 60% NaH in oil, 1.82 mmol) in 8 mL of dimethylformamide was added **1**[14] (425 mg, 1.60 mmol). The reaction mixture was stirred at rt for 30 min resulting in a clear yellow soln. A solution of **12** (342 mg, 1.70 mmol) in 4 mL of dimethylformamide was added and the soln was heated at reflux for 3 h then cooled to rt and partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered and concd in vacuo. Flash chromatography eluting with ethyl acetate gave 352 mg (51%) of **15** and 112 mg of recovered **1**.

Compounds 16, 17, 18, 19, 22, 23, 28, 29, and 30. Prepared from carboxylic acids as in the preparation of **14**.

5-Methoxy-3-(1-methylethoxy)-*N*-[2-(4-pyridinylthio)-ethyl]benzo[*b*]thiophene-2-carboxamide (16). (70%) of **16**, mp 108–109 °C; ^{1}H NMR (DMSO-d_6): δ 1.37 (d, J = 6 Hz, 6H), 3.30 (t, J = 6.5 Hz, 2H), 3.62 (q, J = 6.5 Hz, 2H), 3.86 (s, 3H), 4.75 (heptet, J = 6 Hz, 1H), 7.15 (dd, J = 9, 2.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.39 (d, J = 6 Hz, 2H), 7.86 (d, J = 9 Hz, 1H), 8.18 (t, J = 6 Hz, 1H-NH), 8.40 (d, J = 6 Hz, 2H). Anal. calcd for $C_{20}H_{22}N_2O_3S_2$: C, 59.68; H, 5.51; N, 6.96; found: C, 59.79; H, 5.58; N, 6.91.

5-Methoxy-3-(1-methylethoxy)-*N*-[3-(2-pyridinylthio)-propyl]benzo[*b*]thiophene-2-carboxamide (17). (74%) of **17**, oil; ^{1}H NMR (DMSO-d_6): δ 1.35 (d, J = 6 Hz, 6H), 1.93 (m, 2H), 3.21 (t, J = 7 Hz, 2H), 3.44 (m, 2H), 3.85 (s, 3H), 4.72 (heptet, J = 6 Hz, 1H), 7.09–7.15 (m, 2H), 7.19 (d, J = 2.5 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.63 (td, J = 8, 2 Hz, 1H), 7.85 (d, J = 9 Hz, 1H), 8.01 (t, J = 6 Hz, 1H-NH), 8.42 (m, 1H). Anal. calcd for $C_{21}H_{24}N_2O_3S_2$: C, 60.55; H, 5.81; N, 6.72; found: C, 60.17; H, 5.91; N, 6.66.

5-Methoxy-3-(1-methylethoxy)-*N*-[3-(phenylthio)propyl]-benzo[*b*]thiophene-2-carboxamide (18). (61%) of **18**, mp 60–62 °C; ^{1}H NMR (DMSO-d_6): δ 1.33 (d, J = 6 Hz, 6H), 1.86 (m, 2H), 3.02 (t, J = 7 Hz, 2H), 3.44 (m, 2H), 3.85 (s, 3H), 4.70 (heptet, J = 6 Hz, 1H), 7.13 (dd, J = 9, 2.5 Hz, 1H), 7.15–7.20 (m, 2H), 7.31–7.38 (m, 4H), 7.84 (d, J = 9 Hz, 1H), 7.99 (t, J = 6 Hz, 1H-NH). Anal. calcd for $C_{22}H_{25}NO_3S_2$: C, 63.59; H, 6.06; N, 3.37; found: C, 63.59; H, 6.02; N, 3.28.

5-Methoxy-3-(1-methylethoxy)-*N*-[3-(4-pyridinyloxo)-propyl]benzo[*b*]thiophene-2-carboxamide (19). (66%) of **19**, mp 92–94 °C; ^{1}H NMR (DMSO-d_6): δ 1.33 (d, J = 6 Hz, 6H), 2.04 (m, 2H), 3.50 (m, 2H), 3.85 (s, 3H), 4.15 (t, J = 6 Hz, 2H), 4.71 (heptet, J = 6 Hz, 1H), 6.97 (d, J = 6 Hz, 2H), 7.13 (dd, J = 9, 2.5 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 7.84 (d, J = 9 Hz, 1H), 8.03 (t, J = 6 Hz, 1H-NH), 8.38 (d, J = 6 Hz, 2H). Anal. calcd for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99; found: C, 63.11; H, 6.28; N, 6.92.

5-Methoxy-3-(1-methylethoxy)-*N*-[3-(4-pyridinylthio)-propyl]-2-benzofuran-carboxamide (22). (82%) of **22**, mp 100–101 °C; ^{1}H NMR (DMSO-d_6): δ 1.31 (d, J = 6 Hz, 6H), 1.89 (m, 2H), 3.11 (t, J = 7 Hz, 2H), 3.42 (m, 2H), 3.82 (s, 3H), 4.92 (heptet, J = 6 Hz, 1H), 7.07 (dd, J = 9, 2.5 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 7.28 (d, J = 6 Hz, 2H), 7.49 (d, J = 9 Hz, 1H), 8.22 (t, J = 6 Hz, 1H-NH), 8.36 (d, J = 6 Hz, 2H). Anal. calcd for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99; found: C, 63.03; H, 6.13; N, 6.89.

5-Methoxy-3-(1-methylethoxy)-*N*-[3-(4-pyridinylthio)-propyl]-1*H*-indole-2-carboxamide (23). (72%) of **23**, mp 133–135 °C; ^{1}H NMR (DMSO-d_6): δ 1.31 (d, J = 6 Hz, 6H), 1.94 (m, 2H), 3.13 (t, J = 7 Hz, 2H), 3.50 (m, 2H), 3.77 (s, 3H), 4.67 (heptet, J = 6 Hz, 1H), 6.85 (dd, J = 9, 2.5 Hz, 1H), 6.98 (d, J = 2.5 Hz, 1H), 7.25–7.29 (m, 3H), 7.63 (t, J = 6 Hz, 1H-NH), 8.36 (d, J = 6 Hz, 2H), 11.05 (s, 1H-NH). Anal. calcd for $C_{21}H_{25}N_3O_3S$: C, 63.13; H, 6.31; N, 10.52; found: C, 62.89; H, 6.28; N, 10.33.

5-Methoxy-*N*-[3-(4-pyridinylthio)propyl]benzo[*b*]thiophene-2-carboxamide (28). (56%) of **28**, mp 163–164 °C; ^{1}H NMR (DMSO-d_6): δ 1.91 (m, 2H), 3.14 (t, J = 7 Hz, 2H), 3.41 (m, 2H), 3.83 (s, 3H), 7.10 (dd, J = 9, 2.5 Hz, 1H), 7.28 (d, J = 6 Hz, 2H), 7.43 (d, J = 2.5 Hz, 1H), 7.88 (d, J = 9 Hz, 1H), 7.98 (s, 1H), 8.36 (d, J = 6 Hz, 2H), 8.83 (t, J = 5.5 Hz, 1H-NH). Anal. calcd for $C_{18}H_{18}N_2O_2S_2$: C, 60.31; H, 5.06; N, 7.81; found: C, 60.06; H, 4.94; N, 7.74.

***N*-[3-(4-Pyridinylthio)propyl]benzo[*b*]thiophene-2-carboxamide (29).** (74%) of **29**, mp 125–127 °C; lit mp[16] 123–124 °C; ^{1}H NMR (DMSO-d_6): δ 1.91 (m, 2H), 3.14

(t, $J = 7$ Hz, 2H), 3.42 (m, 2H), 7.29 (d, $J = 6$ Hz, 2H), 7.41–7.48 (m, 2H), 7.94 (dd, $J = 6$, 2 Hz, 1H), 8.02 (dd, $J = 7$, 2 Hz, 1H), 8.08 (s, 1H), 8.36 (d, $J = 6$ Hz, 2H), 8.85 (t, $J = 6$ Hz, 1H-NH). Anal. calcd for $C_{17}H_{16}N_2OS_2$: C, 62.17; H, 4.91; N, 8.53; found: C, 62.43; H, 5.03; N, 8.52.

5-Methoxy-3-(1-methylethoxy)-*N*-[3-(4-pyridinylthio)-propyl]benzo[*b*]thiophene-2-acetamide (30). (63%) of **30**, mp 93–95 °C; ^{1}H NMR (DMSO-d_6): δ 1.29 (d, $J = 6$ Hz, 6H), 1.78 (m, 2H), 3.07 (t, $J = 7$Hz, 2H), 3.22 (m, 2H), 3.68 (s, 2H), 3.81 (s, 3H), 4.39 (heptet, $J = 6$ Hz, 1H), 6.96 (dd, $J = 9$, 2.5 Hz, 1H), 7.05 (d, $J = 2.5$ Hz, 1H), 7.24 (d, $J = 6$ Hz, 2H), 7.69 (d, $J = 9$ Hz, 1H), 8.27 (t, $J = 5.5$ Hz, 1H-NH), 8.33 (d, $J = 6$ Hz, 2H). Anal. calcd for $C_{22}H_{26}N_2O_3S_2$: C, 61.37; H, 6.09: N, 6.51; found: C, 61.45; H, 6.17; N, 6.51.

5-Methoxy-3-(1-methylethoxy)-1-[3-(4-pyridinylthio)-propyl]-1*H*-indole-2-carboxamide (25). To a rt suspension of sodium hydride (210 mg of a 60% NaH in oil) in 10 mL dimethylformamide was added **24**[19] (800 mg, 3.04 mmol). The reaction mixture was stirred at rt for 1 h resulting in a green soln. A soln of **13** (570 mg, 3.04 mmol) in 5 mL of dimethylformamide was added and the orange soln was stirred at rt overnight then partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered and concd in vacuo. Flash chromatography eluting with ethyl acetate gave 442 mg of an oil that was predominately the desired N-alkylation product.

This material was dissolved in 15 mL methanol and treated with 3.5 mL of 1 N NaOH. The soln was heated at reflux for 6 h then cooled and the solvent removed in vacuo. The residue was partitioned between 1 N NaOH and ethyl acetate. The aqueous layer was acidified with concd HCl and the resultant precipitate was extracted into ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concd in vacuo to provide 200 mg of a white solid that was not purified.

This solid was dissolved in 10 mL of tetrahydrofuran and 1,1′-carbonyldiimidazole (105 mg, 0.65 mmol) was added. The solution was heated at reflux for 2 h then allowed to cool slightly and 4 mL of aq ammonium hydroxide was added. The soln was heated at reflux for 6 h then stirred at rt overnight. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was washed with brine then dried over $MgSO_4$, filtered and concd in vacuo. Flash chromatography eluting with 2% methanol in ethyl acetate gave a sticky solid that was triturated with hexane: ethyl acetate (3:1) to provide 94 mg (10% for 3 steps) of **25**, mp 98–100 °C; ^{1}H NMR (DMSO-d_6): δ 1.33 (d, $J = 6$ Hz, 6H), 1.98 (m, 2H), 2.94 (t, $J = 7$ Hz, 2H), 3.79 (s, 3H), 4.63 (m, 3H), 6.93 (dd, $J = 9$, 2.5 Hz, 1H), 7.03 (d, $J = 2.5$ Hz, 1H), 7.12 (d, $J = 6$ Hz, 2H), 7.36 (br s, 1H-NH), 7.50 (d, $J = 9$ Hz, 1H), 7.56 (br s, 1H-NH), 8.30 (d, J = 6 Hz, 2H). Anal. calcd for $C_{21}H_{25}N_3O_3S$: C, 63.13; H, 6.31; N, 10.52; found: C, 63.09; H, 6.21; N, 10.43.

4-(4-Pyridinylthio)butyl 5-methoxy-3-(1-methylethoxy)-benzo[*b*]thiophene-2-carboxylate (31). To a rt suspension of sodium hydride (73 mg of a 60% NaH in oil) in 8 mL of dimethylformamide was added **5** (435 mg, 1.64 mmol). After stirring at rt for 1.5 h the yellow solution became a thick suspension. A solution of **12** (397 mg, 1.97 mmol) in 5 mL of dimethylformamide was added and the reaction mixture was heated at 60–70 °C for 4.5 h then cooled to rt and partitioned between ethyl acetate and brine. The organic layer was dried over $MgSO_4$, filtered and concd in vacuo. Flash chromatography eluting with a gradient of hexane: ethyl acetate (1:1) to all ethyl acetate gave 112 mg of recovered **1** and 449 mg (64%) of **31**, mp 98–99 °C; ^{1}H NMR (DMSO-d_6): δ 1.30 (d, $J = 6$ Hz, 6H), 1.80 (m, 2H), 1.85 (m, 2H), 3.15 (t, $J = 7$ Hz, 2H), 3.85 (s, 3H), 4.31 (t, $J = 6$ Hz, 2H), 4.75 (heptet, $J = 6$ Hz, 1H), 7.25 (m, 2H), 7.28 (d, $J = 6$ Hz, 2H), 7.83 (d, $J = 9$ Hz, 1H), 8.34 (d, $J = 6$ Hz, 2H). Anal. calcd for $C_{22}H_{25}NO_4S_2$: C, 61.23; H, 5.84: N, 3.25; found: C, 61.27; H, 5.91; N, 3.35.

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