Aminoacetyl Moiety as a Potential Surrogate for Diacylhydrazine Group of SC-51089, a Potent PGE_2 Antagonist, and Its Analogs

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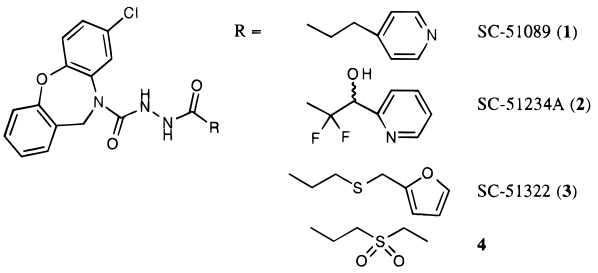
Received June 20, 1995[⊗]

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic acid, 2-[1-oxo-3-(4-pyridinyl)propyl]hydrazide, monohydrochloride (**1**, SC-51089) is a functional PGE_2 antagonist selective for the EP_1 receptor subtype with antinociceptive activity. During metabolism in cultured rat hepatocytes, SC-51089, which contains a diacylhydrazine moiety, has been shown to release hydrazine. Analogs of SC-51089, in which the diacylhydrazine functionality has been replaced by isosteric and isoelectronic groups, have been synthesized and have been shown to be analgesics and PGE_2 antagonists of the EP_1 subtype. This report discusses the structure−activity relationships within these series.

Introduction

SC-51089, a functional PGE_2 antagonist with an excellent analgesic profile,[1,2] contains a diacylhydrazine moiety, which, during metabolism in cultured rat hepatocytes, releases hydrazine.[3] Although hydrazine was known to be carcinogenic in rodents,[4] its release had not been seen in an earlier member of this structural class, **4**.[3] This phenomenon necessitates identifying a pharmacophore that can replace the diacylhydrazine and, yet, will retain the desirable pharmacological profile of SC-51089.



Pain on exposure to noxious stimuli is thought to occur through the intermediacy of several autacoids, among them prostaglandin E_2 (PGE_2), that are released at the site of injury.[5] Relief of mild to moderate pain is attained with over-the-counter and prescription nonsteroidal antiinflammatory drugs (NSAIDs). The antinociceptive action of NSAIDs is believed to occur through the inhibition of the action of cyclooxygenase on arachidonic acid.[6] Ferreira suggested that the effectiveness of NSAIDs against the pain accompanying inflammation and tissue injury is due specifically to the inhibition of PGE_2 formation from arachidonate.[6b] More particularly, NSAIDs block the production of PGE_2, a prostanoid, which causes pain and hyperalgesia and potentiates the action of bradykinin in pain transmission.[6] Two decades of research by several research groups have provided evidence supporting this view.[7]

While NSAIDs are considered generally safe, untoward effects do accompany their administration. The most notable and most prevalent are the gastric side effects including dyspepsia and heartburn.[8] Chronic use of NSAIDs often results in severe damage to gastric and intestinal mucosa that can lead to frank bleeding requiring emergency intervention.

The rationale of our analgesia program is based on the hypothesis that PGE_2-induced hyperalgesia occurring in inflamed tissue would be attenuated by selective blockade of PGE_2 receptors.[6,7] Analgesia based on PGE_2 antagonism would preclude the problems associated with inhibition of prostanoid biosynthesis.

Although research on the SC-51089 class of compounds has exhaustively explored the extended chain[1,9,10] and more recently the 8-chlorodibenzoxazepine,[11] little effort has been directed toward identifying an alternative for the diacylhydrazine functionality. Our initial strategy examined the need for hydrogen-bonding properties of the diacylhydrazine group. This was accomplished by a systematic replacement of each nitrogen of hydrazine with a methylene. Although conceptually basic, this is key to understanding the requirement for the hydrogen bond acceptor−hydrogen bond donor properties of the diacylhydrazine. Using the extended chains of four exceedingly effective analgesic-PGE_2 antagonists,[1,10,12] the diacylhydrazine group of compounds **1**−**4** has been substituted by an aminoacetyl moiety as illustrated by analogs **11**−**13**, **15**, **21**, and **22**.

Synthesis

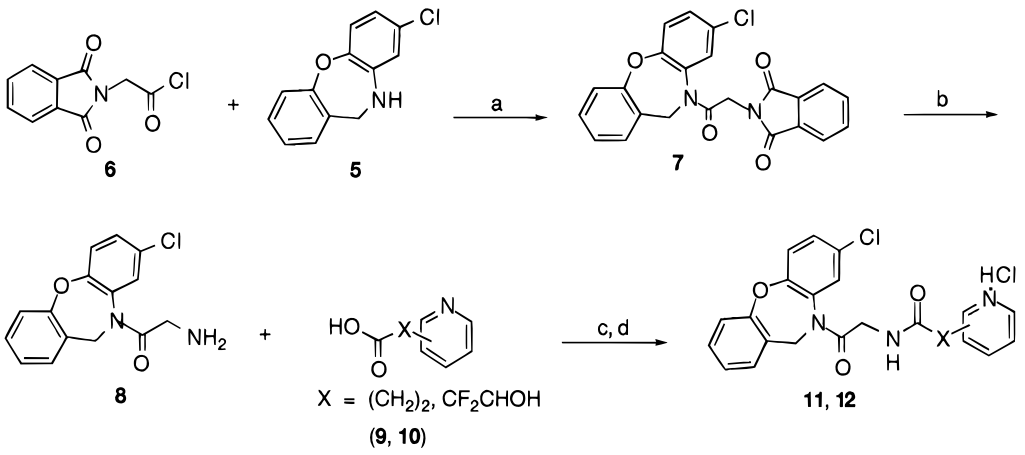
Syntheses of the diamide analogs, where the nitrogen proximal to the 8-chlorodibenzoxazepine ring is replaced with a methylene, are illustrated in Schemes 1 and 2. Acylation of 8-chlorodibenzoxazepine (**5**) with activated Boc-Gly (e.g. symmetrical anhydride, mixed anhydride, and carbodiimide with and without additives) was unsuccessful. With Phth-Gly-Cl, acylation of **5** was effected, yielding **7**. Subsequent transformations of **7** including removal of the phthaloyl protecting group and acylation of the resultant amine gave analogs **11**−**14**. Oxidation of **14** with H_2O_2 resulted in sulfone **15**.

The methods for assembling the urea−ketone analogs, in which the nitrogen distal to 8-chlorodibenzoxazepine is replaced with methylene, are illustrated in Scheme 3. Installation of the aminoacetyl group was accomplished by acylating **5** with ethyl isocyanoacetate.

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1995.

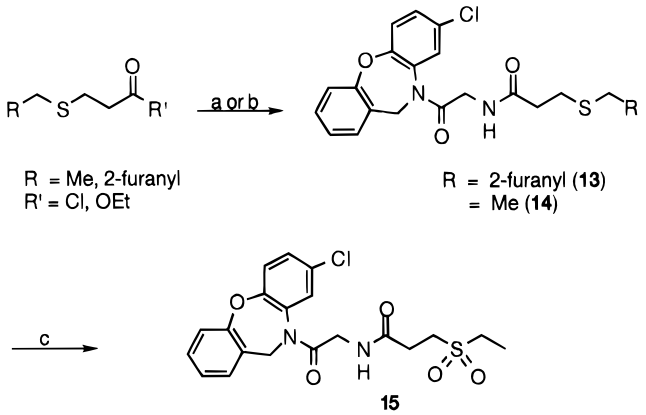
0022-2623/96/1839-0609$12.00/0

Scheme 1[a]



[a] (a) toluene, TEA, Δ, 3h; (b) NH_2NH_2, EtOH, Δ, 4 h; (c) $Me_2N(CH_2)_3N{=}C{=}NCH_2CH_3$, Et_3N, DMF, 5−20 °C, 16 h; (d) HCl/EtOH or 1 N HCl.

Scheme 2[a]



[a] (a) **8**, $AlMe_3$, toluene; (b) **8**, TEA, DCM, 5 °C; (c) 30% H_2O_2, HOAc, 72 °C.

Subsequent manipulations, including saponication of **16** and acylation of *N*,*O*-dimethylhydroxylamine with **17**, resulted in the Weinreb amide **18**. Metalation of **18** with vinylmagnesium bromide yielded α,β-unsaturated ketone, **19**. Michael addition to **19** with ethyl mercaptan and furfuryl mercaptan produced **20** and **21**. Oxidation of **20** with H_2O_2 resulted in the sulfone **22**.

Pharmacology

The phenylbenzoquinone (PBQ) writhing assay in mouse was used to evaluate the antinociceptive effectiveness of these compounds.[1] PGE_2 antagonism was confirmed in PGE_2-stimulated guinea pig ileum muscle strip assay.[1]

Results and Discussion

As seen in Table 1, the urea−ketones, **21** and **22**, show a reduction in analgesic efficacy as compared to parents, **3** and **4**, respectively. A loss in PGE_2 antagonism activity is also seen with **21**. Given the uninteresting activity in these urea−ketones, no attempts were made to synthesize the urea−ketone analogs of **1** and **2**.

A disparate picture emerges with the diamide congeners of the PGE_2 antagonists−analgesics as can be seen in Table 1. Diamide **15** has a biological profile that parallels its parent, **4**, in that it has comparable analgesic and PGE_2 antagonism activity. Analog **13** disappointingly is a significantly less efficacious analgesic and PGE_2 antagonist than its parent, **3**.[10] As with **13**, uninteresting analgesic and PGE_2 antagonism activity is noted with **11**. None of the desirable properties of its parent, **1**, is seen with **11**. Analog **12** parallels its parent, **2**, in its analgesic potency.[1]

Conclusion

PGE_2 antagonism is observed in all compounds of this series that have been tested; however, this series of compounds shows a trend toward attenuation of PGE_2 antagonism. That PGE_2 antagonism is observed suggests that the hydrogen-bonding properties of the hydrazine NH's are not essential in eliciting PGE_2 antagonism in this class of compounds.

Observing the desired analgesic activity in diamides **12** and **15** indicates that modification of the diacylhydrazine is allowed without a concomitant loss of analgesic efficacy. However, methylene substitution for NH is not universally tolerated as **11** and **13** are poorly active.

Experimental Section[1]

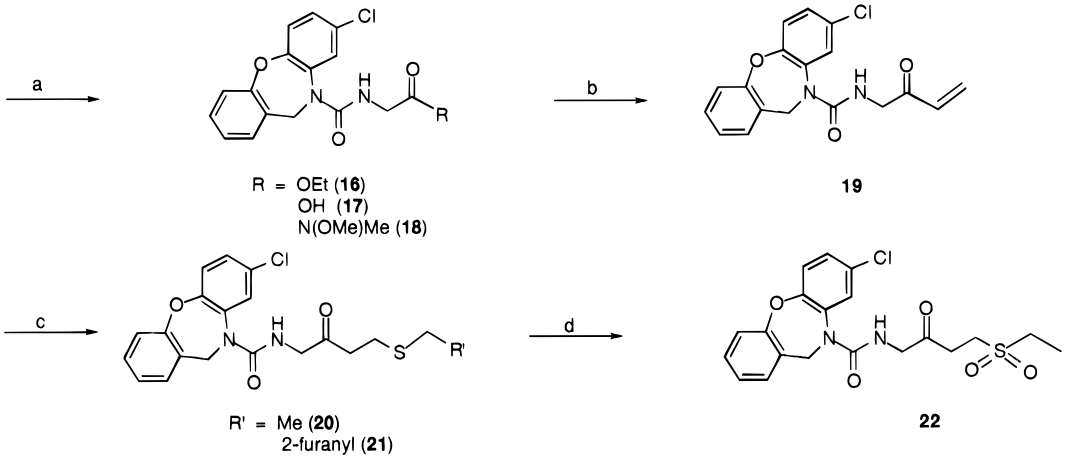
1,3-Dihydro-1,3-dioxo-2*H*-isoindole-2-acetyl Chloride (6). A solution of 1,3-dihydro-1,3-dioxo-2*H*-isoindole-2-acetic acid (Phth-Gly) (7.00 g, 34.1 mmol) and thionyl chloride (12 mL, 165 mmol) was heated at reflux for 1 h. Thionyl chloride was distilled from the reaction, and the resulting crude product was further purified by distillation at 160−180 °C (10 Torr) to yield 6.88 g (90%).

8-Chloro-10,11-dihydro-10-[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)acetyl]dibenz[*b*,*f*] [1,4]oxazepine (7). After heating 3 h at reflux, the reaction mixture of **5** (4.00 g, 17.9 mmol), **6** (4.16 g, 18.0 mmol), and triethylamine (TEA) (2.8 mL, 20.1 mmol) in toluene solution (100 mL) was poured onto 1 N HCl at 0 °C. The insoluble product was collected by filtration, washed with toluene and Et_2O, and dried *in vacuo* to yield 6.36 g (85%) of shiny white crystals: mp 184−185 °C.

10-(Aminoacetyl)-8-chloro-10,11-dihydrodibenz[*b*,*f*][1,4]-oxazepine (8). After a solution of hydrazine monohydrate (1.25 mL) and **7** (5.00 g, 11.9 mmol) in absolute ethanol (125 mL) was heated at reflux for 4 h, the reaction mixture was filtered hot and rinsed with EtOH and then with hot DCM. The filtrate and rinses were combined, evaporated *in vacuo*, and purified by chromatography to give 2.91 g (84%) of a light yellow solid: mp 110−112 °C.

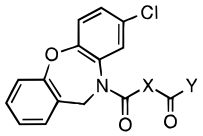
3-(4-Pyridyl)propanoic Acid (9). After stirring for 3 h at ambient temperature, the reaction mixture of methyl 3-(4-pyridyl)propanoate[1] (1.00 g, 6.1 mmol) and sodium hydroxide

Scheme 3[a]



[a] (a) (i) **5**, $OCNCH_2COOEt$, toluene, Δ; (ii) 1 N NaOH, MeOH; (iii) 1,1′-carbonyldiimidazole, NH(OMe)Me·HCl, TEA, THF, 5′-20 °C; (b) CH_2═CHMgBr, THF, −70 °C; (c) HSR, piperidine, $BzlMe_3N^+OH^-$, DCM/MeOH (4:1); (d) 30% H_2O_2, HOAC, 60 °C.

Table 1. Phenylbenzoquinone Writhing Assay in Mouse and PGE_2 Antagonism in Guinea Ileum for Aminoacetyl Analogs



no.	X	ED_{50} (mg/kg)[a]	pA_2[b]	no.	X	Y	ED_{50} (mg/kg)	pA_2
1	NHNH	6.8[c]	6.5[c]	**11**	CH_2NH	$(CH_2)_2$-4-pyridyl	5/10	5.7 ± 0.05
2	NHNH	9.1[c]	7.5[c]	**12**	CH_2NH	CF_2CHOH-2-pyridyl	8.1 (0.88−29.6)	nt[f]
3	NHNH	0.9[d]	8.1[d]	**13**	CH_2NH	$(CH_2)_2SCH_2$-2-furanyl	13.5 (4.7−199)	7.4 ± 0.13
				21	$NHCH_2$	$(CH_2)_2SCH_2$-2-furanyl	5/10	7.2 ± 0.10
4	NHNH	7.4[e]	5.8[e]	**15**	CH_2NH	$(CH_2)_2SO_2CH_2CH_3$	5.9 (3.9−16.6)	5.7 ± 0.12
				22	$NHCH_2$	$(CH_2)_2SO_2CH_2CH_3$	5/10	5.6 ± 0.10

[a] The initial screening dose of test compound is 30 mg/kg. ED_{50}'s are determined for compounds in which seven out of ten animals respond. Values in parentheses are confidence limits determined at 95% ($p < 0.05$). [b] pA_2's are determined based on the dose ratio at 3 μM.[9a,13] [c] Reference 1. [d] Reference 10. [e] Reference 11. [f] Not tested.

(0.42g, 10.5 mmol) in 8 mL of methanol−H_2O (5:3) was treated with 6 N HCl. After the reaction mixture was concentrated, the residue was treated with absolute EtOH (10 mL), heated at reflux, filtered, and rinsed with hot EtOH. The filtrates were evaporated *in vacuo*. The residue was treated with Et_2O, and the product was collected by filtration, washed with Et_2O, and dried *in vacuo* to yield 0.52 g (46%) of a white solid: mp 204−207 °C.

α,α-Difluoro-*β*-hydroxy-3-(2-pyridyl)propanoic Acid (10). 10 was synthesized in a similar manner to **9** on a 17 mmol scale starting with ethyl α,α-difluoro-*β*-hydroxy-3-(2-pyridinyl)propanoate[1] to give a quantitative yield of a pale yellow solid.

***N*-[2-(8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepin-10-yl)-2-oxoethyl]-4-pyridinepropanamide, Monohydrochloride (11).** To a stirring solution of **8** (0.77 g, 2.7 mmol), **9** (0.50 g, 2.7 mmol), and TEA (0.8 mL, 5.8 mmol) in 10 mL of dimethylformamide (DMF) at 5 °C was added 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (0.56 g, 2.9 mmol). After stirring at room temperature for 60 h, the reaction was partitioned between saturated $NaHCO_3$ solution (100 mL) and EtOAc (75 mL) and filtered. The filtrate was separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 × 100 mL), H_2O (100 mL), and brine (100 mL) and worked up in the routine manner. The crude product was purified by chromatography. The purified product was taken up in EtOAc and treated with HCl in ethanol. The product was collected by filtration and dried *in vacuo* to yield 0.23 g (19%) of a white solid: ^{1}H NMR (DMSO-d_6) δ 8.74 (d, 2H, J = 6.6 Hz), 8.25 (t, 1H, J = 5.4 Hz), 7.84 (d, 2H, J = 6.6 Hz), 7.49−7.51 (m, 1H), 7.41 (d, 1H, J = 8.5 Hz), 7.17−7.30 (m, 3H), 7.11 (dt, 1H, J = 0.9, 7.7 Hz), 3.03 (t, 2H, J = 7.3 Hz), 2.56 (t, 2H, J = 7.3 Hz). Anal. ($C_{23}H_{20}ClN_3O_3$·HCl) C, H, N, Cl.

***N*-[2-(8-Chlorodibenz[*b,f*][1,4]oxazepin-10(11*H*)-yl)-2-oxoethyl]-α,α-difluoro-*β*-hydroxypyridine-2-propanamide, Monohydrochloride (12). 12** was synthesized in a manner similar to **11** on a 3.8 mmol scale starting with **8** and **10** to give 1.40 g (78%) of the free base which was treated with 1 N HCl to give a white solid hydrochloride salt: ^{1}H NMR (DMSO-d_6) δ 8.69 (d, 1H, J = 4.6 Hz), 8.29 (dt, 1H, J = 1.6, 7.9 Hz), 7.87 (d, 1H, J = 8.0 Hz), 7.76−7.80 (m, 2H), 7.52 (br d, 1H), 7.44 (br d, 1H), 7.27−7.31 (m, 2H), 7.21 (d, 1H, J = 1.1 Hz), 7.19 (d, 1H, J = 1.1 Hz), 7.11 (t, 1H, J = 7.3 Hz), 5.43 (dd, 1H, J = 8.0, 15.2 Hz). Anal. ($C_{23}H_{18}ClN_3O_3F_2$·HCl) C, H, N, Cl.

***N*-[2-(8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepin-10-yl)-2-oxoethyl]-3-[(2-furanylmethyl)thio]propanamide (13).** Trimethylaluminum (2.0 M in toluene; 4.6 mL) was added dropwise to a stirring solution of methyl 3-[(2-furanylmethyl)thio]propanoate (0.75 g, 3.7 mmol) and **8** (1.00 g, 3.5 mmol) in toluene (30 mL) at room temperature. After stirring for 5 h, the reaction was quenched with methanol (14 mL). After concentrating *in vacuo*, the resulting orange residue was partitioned between chloroform (50 mL) and 1 N NaOH (50 mL). The aqueous layer was extracted with chloroform (50 mL). The combined chloroform extracts were washed with 1 N NaOH (50 mL), 1 N HCl (2 × 50 mL), and brine (50 mL) and worked up in the usual manner. The crude product was purified by chromatography followed by recrystallization from cyclohexane/EtOAc to yield 0.63 g (40%) of a tan solid: mp 90−95 °C. Anal. ($C_{23}H_{21}ClN_2O_4S$) C, H, N, Cl, S.

***N*-[2-(8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylthio)propanamide (14).** To a stirring solution of **8** (1.50 g, 5.2 mmol) and triethylamine (0.84

mL, 5.7 mmol) in DCM (40 mL) at 5 °C was added dropwise 3-(ethylthio)propanoyl chloride (0.87 g, 5.9 mmol) in DCM (10 mL). After stirring for 3 h at ambient temperature, the reaction was diluted with DCM (50 mL) and washed with 50 mL each of 1 N HCl, saturated $NaHCO_3$ solution, and brine. The organic layer was worked up in the usual manner to yield 1.90 g (90%): mp 148−151 °C.

***N*-[2-(8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepin-10-yl)-2-oxoethyl]-3-(ethylsulfonyl)propanamide (15).** To a stirring solution of **14** (1.50 g, 3.7 mmol) in acetic acid (11 mL) at 58 °C was added dropwise H_2O_2 (30 wt % in water; 1.19 mL). After 1 h, the temperature of the oil bath was raised to 72 °C, and additional H_2O_2 (0.8 mL) was added. After 3 h, the reaction was concentrated. The residue was taken up in EtOAc (50 mL) and washed with saturated $NaHCO_3$ solution. The aqueous wash was extracted with EtOAc (50 mL), and the organic extracts were combined and washed with 50 mL each of saturated $NaHCO_3$ solution. The organic layers were worked up in the routine manner and chromatographed. The product was recrystallized from ethanol (3A) to yield 1.30 g (80%) of shiny white crystals: ^{1}H NMR (DMSO-d_6) δ 8.36 (t, 1H, J = 5.7 Hz), 7.83 (br s, 1H), 7.49−7.51 (m, 1H), 7.41 (d, 1H, J = 8.7 Hz), 7.26−7.29 (m, 2H), 7.19 (d, 1H, J = 7.4 Hz), 7.09 (t, 1H, J = 7.4 Hz), 3.21 (t, 2H, J = 7.5 Hz), 3.05 (q, 2H, J = 7.3 Hz), 2.56 (t, 2H, J = 7.5 Hz), 1.17 (t, 2H, J = 7.5 Hz); mp 167−168 °C. Anal. ($C_{20}H_{21}ClN_2O_5S$) C, H, N, Cl, S.

Ethyl [[(8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxaepin-10-yl)carbonyl]amino]acetate (16). After **5** (5.00 g, 21.6 mmol) and ethyl isocyanoacetate (3.07 g, 27.1 mmol) in 50 mL of toluene were heated at reflux for 4 h, additional ethyl isocyanoacetate (1.00 g, 7.7 mmol) was added. The reaction mixture was heated for 16 h. The reaction was worked up in the usual manner to give 7.12 g (91%) of a yellowish oil which solidified on standing.

[[8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxaepin-10-yl)-carbonyl]amino]acetic Acid (17). After stirring for 16 h, a solution of **16** (6.77 g, 18.8 mmol) in methanol (350 mL) and 1 N NaOH (25 mL) was concentrated. The residue taken up in water (300 mL). The solution was washed with Et_2O (2 × 300 mL), acidified with 1 N HCl, and extracted with Et_2O (2 × 350 mL). The combined etheral extracts were worked up in the usual manner to yield 6.29 g (100%).

2-[[(8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepin-10-yl)carbonyl]amino]-*N*-methoxy-*N*-methylacetamide (18). To a stirring solution of 1,1′-carbonyldiimidazole (2.12 g, 14.3 mmol) in THF (60 mL) at 5 °C was added dropwise **17** (4.00 g, 13.7 mmol) in THF (20 mL). After stirring for 1 h at 5 °C and 4 h at room temperature, TEA (1.9 mL, 13.7 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.30 g, 13.3 mmol) were added. After 48 h, the reaction was concentrated and worked up in the usual manner to yield 3.20 g (71%).

8-Chloro-*N*-(2-oxo-3-butenyl)dibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxamide (19). To a stirring solution of **18** (3.2 g, 8.5 mmol) in THF (35 mL) at −70 °C was added dropwise a solution of vinylmagnesium bromide (1.0 M THF, 28 mL) in 15 mL of THF. The ice bath was removed, and the reaction mixture was stirred to room temperature for 1 h. The reaction was worked up in the usual manner to yield 2.25 g (77%) of a colorless glass.

8-Chloro-*N*-[4-(ethylthio)-2-oxobutyl]dibenz[*b,f*][1,4]-oxazepine-10(11*H*)-carboxamide (20). A solution of **19** (1.00 g, 2.9 mmol), ethanethiol (0.23 mL, 3.1 mmol), piperidine (0.092 mL), and *N*-benzyltrimethylammonium hydroxide (0.092 mL) in 20 mL of DCM:MeOH (4:1) was stirred for 5 h. The reaction was worked up in the usual manner to yield 0.38 g (32%) of a colorless oil.

8-Chloro-*N*-[4-(ethylsulfonyl)-2-oxobutyl]dibenz[*b,f*]-[1,4]oxazepine-10(11*H*)-carboxamide (22). To a stirring solution of **20** (0.38 g, 0.9 mmol) in HOAc (3 mL) at 60 °C was added 30% H_2O_2 (0.3 mL). After 1 h, an additional 0.1 mL of H_2O_2 was added, and the the reaction was heated for additional 1 h. The reaction mixture was concentrated and worked up in the usual manner to give 0.16 g (39%) of a white solid: ^{1}H NMR (DMSO-d_6) δ 7.47 (d, 1H, J = 2.5 Hz), 7.15−7.42 (m, 5H), 7.06 (dt, 1H, J = 1.1, 7.4 Hz), 6.79 (t, 1H, J = 5.4 Hz), 4.84 (s, 2H), 3.83 (d, 2H, J = 5.5 Hz), 3.23 (t, 2H, J = 7.5 Hz), 3.07 (q, 2H, J = 7.5 Hz), 2.84 (t, 2H, J = 7.4 Hz); mp 140−142 °C. Anal. ($C_{20}H_{21}ClN_2O_5S$) C, H, N, S.

8-Chloro-*N*-[4-[(2-furanylmethyl)thio]-2-oxobutyl]-dibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxamide (21). Conditions described for **20** repeated on a 2.2 mmol scale to yield **21**, a colorless oil: ^{1}H NMR (DMSO-d_6) δ 7.57 (dd, 1H, J = 0.9, 1.8 Hz), 7.47 (d, 1H, J = 2.4 Hz), 7.32−7.41 (m, 2H), 7.15−7.27 (m, 3H), 7.05 (dt, 1H, J = 1.3, 7.4 Hz), 6.72 (t, 1H, J = 5.6), 6.37 (dd, 1H, J = 1.9, 3.2 Hz), 6.24 (dd, 1H, J = 0.8, 3.2 Hz), 4.83 (s, 2H), 3.76 (d, 2H, J = 5.5 Hz), 3.74 (s, 2H), 2.50−2.64 (m, 4H). Anal. ($C_{23}H_{21}ClN_2O_4S$) H, N, Cl, S; C: calcd, 60.46; found, 59.94.

Mouse Writhing Assay.[1] The phenylbenzoquinone (PBQ) writhing assay in mouse was used to evaluate the antinociceptive activity.[1]

PGE_2 Antagonism Assay Utilizing the Guinea Pig Ileum.[1] PGE_2 antagonism was assessed in PGE_2-stimulated guinea pig ileum muscle strip assay.[1]

Acknowledgment. The authors would like to thank Professor Peter Beak of the University of Illinois, Urbana, and Professor A. G. M. Barrett of Imperial College for their many useful conversations about organic chemistry; Professor Lester Mitscher of the University of Kansas for his thoughts concerning medicinal chemistry and pharmacology; Dr. Richard Bitman for his assistance in the statistics calculations of the bioassays; and Dr. Michael F. Rafferty for his support of this project. E.A.H. would particularly like to thank Dr. Barnett S. Pitzele for his many helpful ideas and thoughts on this project.

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JM950454K