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# 2,4-Disubstituted Oxazoles and Thiazoles as Latent Pharmacophores for Diacylhydrazine of SC-51089, a Potent $PGE_2$ Antagonist

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**Abstract**—8-Chlorodibenz[b,f][1,4]oxazepine-10(11H)-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.[1,2] Analogues of SC-51089, in which the diacylhydrazine moiety has been replaced with 2,4-disubstituted-oxazoles and-thiazoles, are described.


## Introduction

SC-51089 illustrated in Figure 1, a functional $PGE_2$ antagonist with an excellent analgesic profile,[1,2] contains a 1,2-diacylhydrazine moiety which releases hydrazine during metabolism in cultured rat hepatocytes.[3] Although hydrazine is known to be carcinogenic in rodents,[4] its release had not been seen in **4**, [3] an earlier member of this structural class. It should be noted that this phenomenon has not been seen in human hepatocytes.[3] Identifying a pharmacophore that could replace the diacylhydrazine and, yet, would retain the desirable analgesic-$PGE_2$ antagonism profile of SC-51089 became the focus of our research.

As described in earlier reports,[1,5,6] 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. Analgesia based on $PGE_2$ antagonism would preclude the problems associated with inhibition of prostanoid biosynthesis.

Although research on this class of compounds has exhaustively explored the exocyclic chain appended to the hydrazine[1,5,6] and more recently the 8-chlorodibenzoxazepine (**5**), current efforts have been directed towards an alternative for the diacylhydrazine group. The amino acetyl moiety[6] has been shown to have some promise as a replacement for the diacylhydrazine. Having identified the pyridylpropionyl group, among others of the extended chain, and the 8-chlorodibenzoxazepine, **5**, as desirable structural fragments in the $PGE_2$ antagonist-analgesics, this report describes research on identifying possible pharmacophores for the diacylhydrazine moiety.

Earlier studies on the conformation of diacylhydrazines by X-ray crystallography have shown that 1,2-diformylhydrazine and 1,2-diacetylhydrazine are planar molecules with *Z-E-Z* geometry.[7] A series of $^1H$ NMR studies by Sutherland[8] suggested that there was hindered rotation about the N−N bond of the diacylhydrazine in nonpolar solvent. Anthoni et al.[9] found monoacylhydrazines to exist in an all *trans* conformation in nonpolar solvents. However, with increasing solvent dielectric constant, isomerism shifted from all *trans* to a *cis-trans*/*trans-trans* mixture. Bouchet et al.[10] studied rotation about NCO bonds of 1,2-diacylhydrazine and the influences of solvent on geometric isomerism. They found in polar solvents such as dimethylsulfoxide-$d_6$ (DMSO-$d_6$) equilibrium shifts the NCO bond from *E* to *Z*. The NMR studies on **4** reveal two distinct conformers, the most stable having no NOE interactions between the hydrazide hydrogens, the less stable having complex interactions between these hydrogens.[11]

Since MM2 calculations[12] and NMR data have indicated that a number of low energy conformations are available

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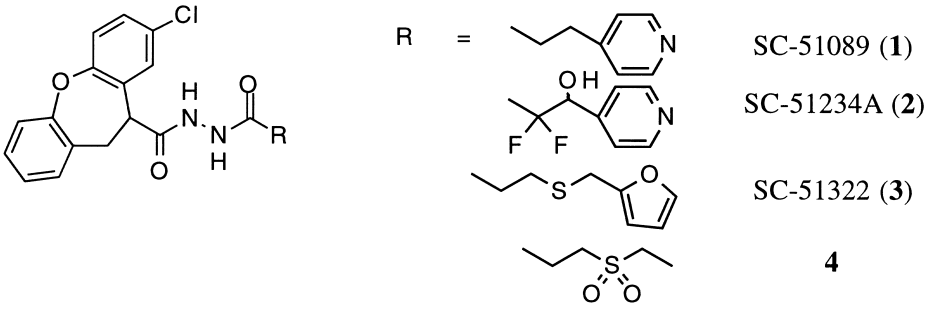



**Figure 1.**

to the 1,2-diacylhydrazine, few structural constraints can be imposed, a priori, on choices of isosteres (as seen in Figure 3).

Thromboxane $A_2$ ($TXA_2$) antagonists described by Squibb researchers as illustrated in Figure 2 suggested possible insight into potential pharmacophores.[13] An acyl hydrazone functionality incorporated into the omega chain of the thromboxane skeleton, **6**, evolved into amino acetyl group, **7**, and, subsequently, 2,4-disubstituted-oxazole, **8**.

This observation begged the question as to whether an analogy could be drawn between $TXA_2$ antagonists and the $PGE_2$ antagonists-analgesics. A parallelism between

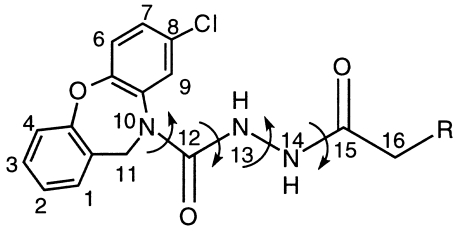
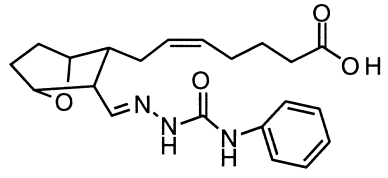


**Figure 2.**

$TXA_2$ antagonists, **6**–**8**, and $PGE_2$ antagonists-analgesics as illustrated by **9** and **10** shown in Figure 4,[6] suggested 2,4-substituted oxazoles as a potential pharmacophore for the diacylhydrazine. Having surmised that five-membered aromatic heterocycles are possible pharmacophores, syntheses of **15**–**26** have been undertaken and are illustrated below.

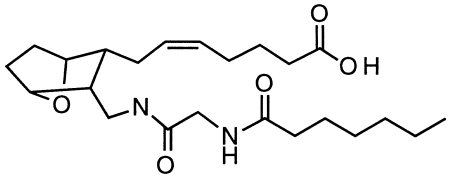
## Results

Ethyl 2-methyl-4-oxazolecarboxylate, **11**, described by Cornforth,[14] is brominated using NBS catalyzed by AIBN with or without light. Ethyl 2-bromomethyl-4-oxazolecarboxylate, **13**, as well as all possible combinations of brominated products including ring bromination, are isolated. With minor modifications, a rhodium catalyzed cycloaddition of ethyl 2-diazo-3-oxo-propanoate to bromoacetonitrile as reported by Helquist[15] was employed to generate **13**. With **13** in hand, alkylation of **5** proceeds uneventfully to give **15** as illustrated in Scheme 1. Hydrolysis of the ester provides intermediate acid **17** that is coupled to the appropriate amine or alcohol to obtain **19**–**21** as shown in Scheme 2. Alternatively, amidation of **15** using Weinreb conditions lead to **22**–**24** as illustrated in Scheme 2.



SQ 27,825,

**6**



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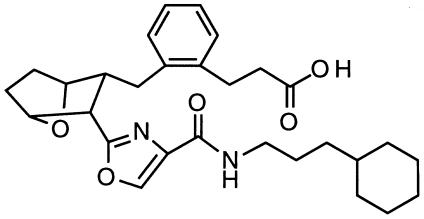
**7**



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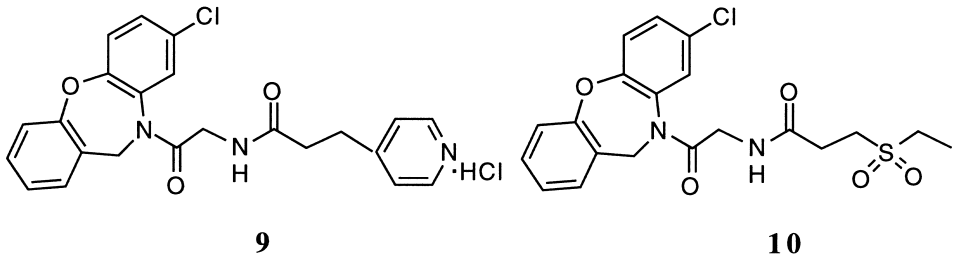
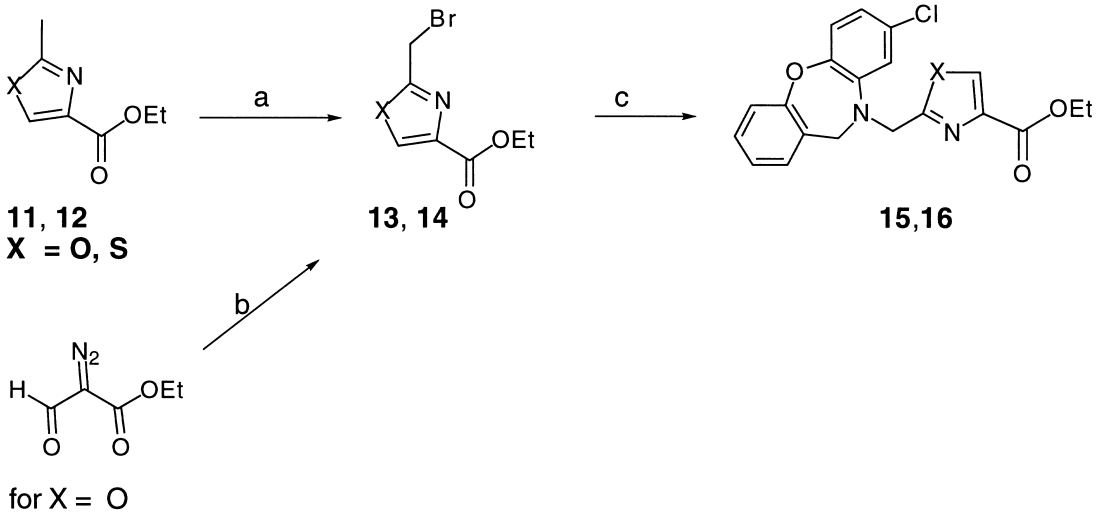
**8**

**Figure 3.**

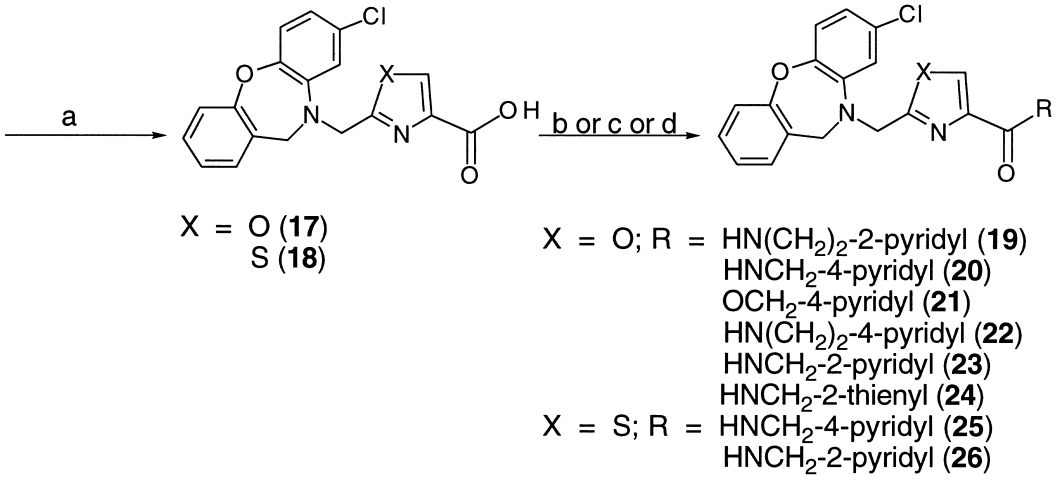


**9** **10**

**Figure 4.**



**Scheme 1.** (a) NBS, $CCl_4$, AlBN, hv, Δ. (b) $BrCH_2CN$, $Rh_2(OAc)_4$, 70 °C. (c) **5**, i-$Pr_2EtN$, toluene, Δ.



**Scheme 2.** (a) **15** or **16**, 1 N NaOH, MeOH:THF (1:1). (b) i. **15,** $Me_2N(CH_2)_3N{=}C{=}NCH_2CH_3$, $RNH_2$, $Et_3N$, DMAc, 5–20 °C, 16 h. ii. HCl/dioxane, $Et_2O$. (c) i. **15** or **16**, $H_2NR$, $AlMe_3$, DCM, Δ, 5 h. ii. 1 N HCl. (d) **16**, $H_2NR$, 110 °C, 1 h.

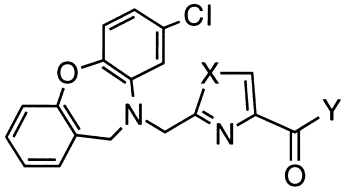
Synthesis of the thiazole analogues requires the pivotal intermediate, ethyl 2-methyl-4-thiazolecarboxylate, **12**, which is synthesized as described previously.[16] Bromination using NBS proceeds in good yield to afford **14**. Chemistry analogous to that used to synthesize the oxazoles is employed to assemble thiazole analogues **25** and **26**.

The phenylbenzylquinone 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 strips assay.[1]

## Discussion

In the oxazole series, **15**, **17** and **19**–**24** are $PGE_2$ antagonists with observed $pA_2$'s in the range of 6.1–7.4 (shown in Table 1). The analgesic activity seen among

**Table 1.** Phenylbenzoquinone writhing assay in mouse and $PGE_2$ antagonism in guinea pig ileum for oxazolyl and thiazolyl analogues




| No. | X | Y | PBQ writhing assay[a] | $pA_2$[b] |
|---|---|---|---|---|
| **15** | O | OEt | 9/10 | 6.1 |
| **17** | O | OH | 1/10 | 7.4±0.01 |
| **19** | O | $HN(CH_2)_2$-2-Pyridyl | 7/10 | 7.3±0.07 |
| **23** | O | $HNCH_2$-2-Pyridyl | 2/10 | 7.5± 0.01 |
| **20** | O | $HNCH_2$-4-Pyridyl | 9/10 | 7.4±0.17 |
| **22** | O | $HN(CH_2)_2$-4-Pyridyl | 6/10 | nt[c] |
| **21** | O | $OCH_2$-4-Pyridyl | 4/10 | nt[c] |
| **24** | O | $HNCH_2$-2-Thienyl | 7/10 | 6.9±0.35 |
| **16** | S | OEt | 1/10 | 5.9±0.15 |
| **18** | S | OH | 5/10 | 8.1±0.11 |
| **25** | S | $HNCH_2$-4-Pyridyl | 4/9 | nt[c] |
| **26** | S | $HNCH_2$-2-Pyridyl | 7/10 | 6.0±0.10 |

[a]The initial screening dose of test compound is 30 mg/kg. The data are reported as number of animals positively responding out of the ten aminals tested.
[b]$pA_2$ determined based on the dose ratio at 3 μM.
[c]Not tested.

the oxazoles does not correlate with its $PGE_2$ antagonism. Illustrative of this are **17** and **23**, which are potent $PGE_2$ antagonists but have minimal analgesic activity, while **15**, **19**, **20**, **21** and **24** are both effective analgesics and $PGE_2$ antagonists.

## Conclusions

2,4-Substituted-oxazoles as potential isosteres for diacylhydrazines have been identified. However, a one to one correlation does not seem to exist between the $PGE_2$ antagonism and analgesia in the oxazole and thiazole series. At present, it is unknown whether this is due to bioavailability, metabolism, or a separation of activity in this structural class. On a larger issue, we do not know at this time whether or not there has been a dissociation of $PGE_2$ antagonism and analgesia or the lack of analgesic action is due to metabolism or bioavailability.

## Experimental

All experiments were performed under either dry nitrogen or argon. All solvents and reagents were used without further purification unless otherwise noted. The routine work up of the reactions involved the addition of the reaction mixture to a mixture of either neutral, or acidic, or basic aqueous solutions and organic solvent. The aqueous layer was extracted *n* times (×) with the indicated organic solvent. The combined organic extracts were washed *n* times (×) with the indicated aqueous solutions, dried over anhydrous $Na_2SO_4$, filtered, concentrated in vacuo, and purified as indicated. Separations by column chromatography were achieved with conditions described by Still.[17] The hydrochloride salts were made from 1 N HCl, HCl in ethanol (EtOH), or 6 N HCl in dioxane. Thin layer chromatograms were run on 0.25 mm EM precoated plates of silica gel 60 F254. High performance liquid chromatograms (HPLC) were obtained from C-8 or C-18 reverse phase columns which were obtained from several vendors. Analytical samples were dried in an Abderhalden apparatus at either 56 °C or 78 °C. $^1H$ NMR spectra were obtained from either General Electric QE-300 or Varian VXR 400 MHz spectrometers with tetramethylsilane as an internal standard. $^{13}C$ NMR spectra were obtained from a Varian spectrometer at 125.8 MHz with tetramethylsilane as an internal standard. Melting points were obtained by differential scanning calorimetry on a Dupont Model 9900 thermal analysis system.

**Ethyl 2-(bromomethyl)-4-oxazolecarboxylate (13).** To 50 mL of bromoacetonitrile was added 0.12 g of $Rh_2(OAc)_4$. A 50 mL bromoacetonitrile solution of ethyl 2-diazo-3-oxo-propanoate[18] (2.84 g, 20 mmol) was added dropwise via syringe pump at a rate of 5 mL/h to the stirring rhodium acetate solution, which had been heated to 70 °C. Once the addition was complete, the reaction was maintained at 70 °C for an additional 8 h. The excess bromoacetonitrile was removed from the reaction via vacuum distillation. The residue was filtered through a pad of silica gel which was washed with hexanes and DCM. The solvent from the DCM wash was removed in vacuo to yield 3.67 g (78%) of **13**.

**Ethyl 2-[(8-chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-4-oxazole-carboxylic acid (15).** To a stirring solution of **5** (1.16 g, 5 mmol) in 50 mL toluene were added **13** (1.17 g, 5 mmol), *N,N*-diisopropylethylamine (1.7 mL, 10 mmol), and NaI (5 mg). The reaction was heated at reflux for 24 h. The reaction was poured directly onto a column of silica gel and chromatographed to yield **15**, 1.38 g (72%). Anal. calcd for $C_{20}H_{17}N_2O_4Cl{\cdot}0.2\ H_2O$: C, 61.85; H, 4.52; N, 7.21. Found: C, 61.55; H, 4.50; N, 7.19. $^1H$ NMR (DMSO-$d_6$) 8.78 (s, 1H), 7.30–7.33 (m, 2H), 7.09–7.14 (m, 3H), 6.92 (d, 1H, $J=2.4$ Hz), 6.74 (dd, 1H, 2.4, 8.5), 4.74 (s, 2H), 4.61 (s, 2H), 4.28 (q, 2H, 7.1), 1.28 (t, 3H, 7.1).

**2-[(8-Chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-4-oxazolecarboxylic acid (17).** To a stirring solution of **15** (0.56 g, 1.5 mmol) in 10 mL MeOH:THF (1:1) was added 4.5 mL of 1 N NaOH. After 1 h, the reaction was adjusted to pH 3. The organic solvents were removed in vacuo. A white precipitate was filtered, washed with $H_2O$, and dried to yield 0.48 g (89%) of **17**. Anal. calcd for $C_{18}H_{13}N_2O_4Cl$: C, 60.60; H, 3.67; N, 7.85. Found: C, 60.13; H, 4.00; N, 7.82. $^1H$ NMR (DMSO-$d_6$) 8.66 (s, 1H), 7.30–7.33 (m, 2H), 7.19 (d, 1H, $J=7.4$ Hz), 7.09–7.15 (m, 2H), 6.91 (d, 1H, $J=2.0$), 6.73 (dd, 1H, $J=2.5$, 8.5), 4.72 (s, 2H), 4.62 (s, 2H).

**2-[(8-Chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-*N*-[2-(2-pyridinyl)-ethyl]-4-oxazolecarboxamide, hydrochloride (19).** To a stirring solution of **17** (0.47 g, 1.3 mmol), 2-(2-ethylamino)pyridine (0.17 g, 1.6 mmol), hydroxybenzotriazole (0.22 g, 1.6 mmol), and triethyl-

amine (0.23 mL, 1.6 mmol) in 5 mL dimethylacetamide (DMAc) at 5 °C was added *N,N*-dimethylaminopropylethylcarbodiimide hydrochloride (0.31 g, 1.6 mmol). With warming to ambient temperature, the reaction mixture was stirred for 18 h. The reaction was worked up in the usual manner to yield 0.51 g (85%) of the free base. The residue was dissolved in 100 mL $Et_2O$ to which was added 2 mL 6.8 N HCl/dioxane. The precipitate was filtered, washed with $Et_2O$, and dried. Anal. calcd for $C_{25}H_{21}N_4O_3Cl{\cdot}1.2\ HCl{\cdot}0.3\ H_2O$: C, 58.78; H, 4.51; N, 10.98; Cl, 15.29. Found: C, 58.50; H, 4.44; N, 10.66; Cl, 14.87. $^1$H NMR (DMSO-$d_6$) 8.80 (dd, 1H, $J$ = 1.5, 6.6 Hz), 8.53 (s, 1H), 8.49 (t, 1H, $J$ = 6.1 Hz), 8.43 (dt, 1H, $J$ = 1.6, 7.9 Hz), 7.86–7.89 (m, 2H), 7.28–7.34 (m, 2H), 7.21 (d, 1H, $J$ = 7.9), 7.10–7.14 (m, 2H), 6.89 (d, 1H, $J$ = 2.5 Hz), 6.75 (dd, 1H, $J$ = 2.4, 8.5), 4.69 (s, 2H), 4.60 (s, 2H), 3.71 (dd, 2H, $J$ = 6.6, 6.9), 3.28 (t, 2H, $J$ = 6.6).

**2-[(8-Chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-*N*-(4-pyridinylmethyl)-4-oxazolecarboxamide, monohydrochloride (20).** Compound **20** was prepared in the manner described in example **19** starting with 4-aminomethylpyridine (0.67 mmol) to yield 0.14 g (56%). Anal. calcd for $C_{24}H_{19}N_4O_3Cl{\cdot}HCl{\cdot}1.5\ H_2O$: C, 56.48; H, 4.54; N, 10.98; Cl, 13.89. Found: C, 56.79; H, 4.54; N, 10.70; Cl, 13.59.

**4-Pyridinylmethyl 2-[(8-chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-4-oxazolecarboxylate, hydrochloride (21).** Compound **21** was prepared in the same manner as **19** starting with 4-hydroxymethylpyridine (0.45 g, 0.45 mmol). Anal. calcd for $C_{24}H_{18}N_3O_4Cl{\cdot}1.6\ HCl{\cdot}0.4\ H_2O$: C, 56.15; H, 4.00; N, 8.18. Found: C, 55.99; H, 4.11; N, 8.07. $^1$H NMR (DMSO-$d_6$) 9.03 (s, 1H), 8.89 (d, 2H, $J$ = 6.6 Hz), 7.99 (d, 2H, $J$ = 6.6 Hz), 7.30–7.34 (m, 2H), 7.20 (dd, 1H, $J$ = 1.2, 8.5 Hz), 7.10–7.15 (m, 2H), 6.95 (d, 1H, $J$ = 2.4 Hz), 6.74 (dd, 1H, $J$ = 2.4, 8.5 Hz), 5.61 (s, 2H), 4.79 (s, 2H), 4.64 (s, 2H).

**2-[(8-Chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-*N*-[2-(4-pyridinyl)ethyl]-4-oxazolecarboxamide, hydrochloride, acetate (22).** To a stirring solution of **15** (0.19 g, 0.5 mmol) in 5 mL DCM was added 4-(2-aminoethyl)pyridine (0.065 g, 0.6 mmol) and trimethylaluminum (0.3 mL of 2 M solution in toluene). After heating the reaction at reflux for 5 h, the reaction mixture was quenched with MeOH then worked up in the usual manner. The free base was dissolved in acetic acid, treated with 1 N HCl, and lyophilized to yield 0.06 g (26%) of **22**. Anal. calcd for $C_{25}H_{21}N_4O_3Cl{\cdot}1.5{\cdot}HCl{\cdot}1.5\ H_2O{\cdot}0.6$ HOAc: C, 54.38; H, 4.86; N, 9.68; Cl, 15.32. Found: C, 54.78; H, 4.65; N, 9.33; Cl, 15.01. $^1$H NMR (DMSO-$d_6$) 8.76 (br s, 2H), 8.51 (s, 1H), 8.41 (t, 1H, $J$ = 5.7), 7.85 (d, 2H, $J$ = 5.8 Hz), 7.10–7.34 (m, 5H), 6.89 (d, 1H, $J$ = 2.4), 6.75 (dd, 1H, $J$ = 2.5, 8.4), 4.69 (s, 2H), 4.61 (s, 2H), 3.61 (dd, 2H, $J$ = 6.7, 6.9), 3.12 (t, 2H, $J$ = 6.6 Hz).

**2-[(8-Chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-*N*-(2-pyridinylmethyl)-4-oxazolecarboxamide, monohydrochloride (23).** Compound **23** was prepared in the same manner as example **22** using 2-aminomethylpyridine (0.073 g, 0.67 mmol). The yield of **23** was 58%. Anal. calcd for $C_{24}H_{19}N_4O_3Cl{\cdot}0.9\ HCl{\cdot}0.5\ H_2O$: C, 58.98; H, 4.31; N, 11.46; Cl, 13.78. Found: C, 59.13; H, 4.27; N, 11.44; Cl, 13.73. $^1$H NMR (DMSO-$d_6$) 9.02 (t, 1H, $J$ = 5.9 Hz), 8.73–8.75 (m, 1H), 8.65 (s, 1H), 8.29 (dt, 1H, $J$ = 1.3, 7.8 Hz), 7.72–7.75 (m, 2H), 7.30–7.34 (m, 2H), 7.10–7.15 (m, 2H), 6.93 (d, 1H, $J$ = 2.3 Hz), 6.75 (dd, 1H, $J$ = 2.4, 8.5 Hz), 4.73–4.75 (m, 4H), 4.64 (s, 2H).

**2-[(8-Chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-*N*-(2-thienylmethyl)-4-oxazolecarboxamide (24).** Compound **24** was prepared in the same manner as described in example **22** starting with 2-aminomethylthiophene (0.06 g, 0.5 mmol) to yield 0.10 g (45%). Anal. calcd for $C_{23}H_{18}N_3O_3ClS$: C, 61.13; H, 4.01; N, 9.30. Found: C, 60.81; H, 3.93; N, 9.10. $^1$H NMR (DMSO-$d_6$) 8.18 (s, 1H), 7.15–7.28 (m, 3H), 7.13 (dd, 2H, $J$ = 1.2, 3.3 Hz), 7.03–7.06 (m, 3H), 6.98 (dd, 1H, $J$ = 3.5, 5.1 Hz), 6.91 (d, 1H, $J$ = 2.4 Hz), 6.77 (dd, 1H, $J$ = 2.5, 8.5 Hz), 4.78 (d, 2H, $J$ = 5.9 Hz), 4.47 (s, 2H), 4.38 (s, 2H).

**2-Bromomethyl-4-carboxyethyl-thiazole (14).** To a stirring solution of 4-carboxyethyl-2-methyl-thiazole (30.3 g, 179 mmol) in $CCl_4$ (1L) were added NBS (37.7 g, 212 mmol) and AIBN (2.2 g). The resulting mixture was refluxed and irradiated with sun lamp light for 4 h. The mixture was cooled to room temperature and filtered. The solution was chromatographed to yield 36.6 g (95%) of a red oil. This material was used without further purification.

**Ethyl 2-[(8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-yl)-methyl]-4-thiazolecarboxylate (16).** Compound **16** was prepared in the same manner as described for **15** from **14** and **5** on a 17 mmol scale to yield 6.46 g of the crude product as a yellow solid after chromatography. The product was then recrystallized from ethanol to yield 3.4 g of a white solid. Anal. calcd for $C_{20}H_{17}N_2O_3SCl$: C, 59.92; H, 4.27; N, 6.99; Cl, 8.84; S, 8.00. Found: C, 59.78; H, 4.29; N, 6.95; Cl, 8.78; S, 8.63. Mp 151.3 °C. $^1$H NMR ($CDCl_3$) 8.14 (s, 1H), 7.29 (dt, 1H, $J$ = 1.9, 7.8 Hz), 7.06–7.19 (m, 4H), 6.78–6.81 (m, 2H), 4.65 (s, 2H), 4.48 (s, 2H), 4.45 (q, 2H, $J$ = 7.1 Hz), 1.43 (t, 3H, $J$ = 7.1 Hz).

**2-[(8-Chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-4-thiazolecarboxylic acid, sodium salt (18).** Compound **18** was synthesized from **16** using the same conditions described for **17** to give its sodium salt as a white solid. Anal. calcd for $C_{18}H_{12}N_2O_3SClNa{\cdot}0.75\ H_2O$: C, 52.95; H, 3.33; N, 6.86; Cl, 8.68; S, 7.85. Found: C, 53.29; H, 3.11; N, 6.85; Cl, 8.59; S, 7.37.

**2-[(8-Chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-*N*-(4-pyridinylmethyl)-4-thiazolecarboxamide, acetate, hydrochloride (25).** Compound **25** was synthesized in the same manner and scale as described for **22** to give a white foam. Anal. calcd for $C_{24}H_{19}N_4O_2SCl{\cdot}1.66\ HCl{\cdot}1$ HO Ac·0.33 $H_2O$: C, 52.97; H, 4.33; N, 9.50; Cl, 16.00; S, 5.44. Found: C, 52.69; H, 4.14; N, 9.45; Cl, 15.81; S, 5.78.

**2-[(8-Chlorodibenz[b,f][1,4]oxazepin-10(11H)-yl)methyl]-*N*-(2-pyridinylmethyl)-4-thiazolecarboxamide (26).** A mixture of **16** (0.50 g, 1.2 mmol) and 2-aminomethylpyridine (2 mL, 19.5 mmol) was heated at 120 °C for 1 h.

The mixture was cooled to ambient temperature and chromatographed to yield 0.38 g of a yellow foam. Anal. calcd for $C_{24}H_{19}N_4O_2SCl$: C, 62.26; H, 4.14; N, 12.10; Cl, 7.66. Found: C, 62.11; H, 4.52; N, 11.80; Cl, 7.65. $^1H$ NMR (DMSO-$d_6$) 9.32 (m, 1H), 8.86 (d, 2H, $J=6.7$ Hz), 8.26 (s, 1H), 7.96 (d, 2H, $J=2.4$ Hz), 7.33–7.38 (m, 2H), 7.24 (d, 1H, $J=8.0$ Hz), 7.14–7.18 (m, 2H), 6.84 (d, 1H, $J=2.4$), 6.79 (dd, 1H, $J=2.4$, 8.5 Hz), 4.88 (s, 2H), 4.74 (d, 2H, $J=6.1$), 4.71 (s, 2H).

### Mouse writhing assay[1]

The phenylbenzoquinone (PBQ) writhing test was used to assess analgesic efficacy.

### $PGE_2$ antagonism assay utilizing the guinea pig ileum[1]

Evaluation of $PGE_2$ antagonism was performed as described previously.

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