Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 3, pp. 509-514, 1994

0960-894X/94 $6.00+0.00

0960-894X(93)E0115-H

8-CHLORODIBENZ[B,F][1,4]OXAZEPINE-10(11H)-CARBOXYLIC ACID, 2-[3-[2-(FURANYLMETHYL)THIO]-1-OXOPROPYL]HYDRAZIDE (SC-51322): A POTENT PGE_2 ANTAGONIST AND ANALGESIC

E. Ann Hallinan,* Awilda Stapelfeld, Michael A. Savage, Melvin Reichman

Department of Chemistry
Searle
4901 Searle Parkway
Skokie, Illinois 60077

Abstract

SC-51322 is the most potent PGE_2 antagonist (pA_2 = 8.1) and analgesic (ED_{50} = 0.9 mg/kg) that has been seen in this series of N-substituted dibenzoxazepines.

Introduction

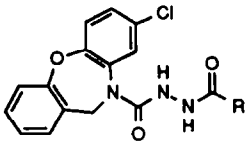
Prostaglandin E_2 (PGE_2), a product of arachidonic acid metabolism, is one mediator of the nociceptive process. PGE_2 has been shown to elicit pain and hyperalgesia in humans and to potentiate the action of bradykinin in the transmission of pain.[1] Ferreira and Vane have postulated that the alleviation of pain with NSAIDs (non-steroidal antiinflammatory drugs) occurs by the inhibition of cyclooxygenase's action on arachidonic acid.[2] In particular, the inhibition of cyclooxygenase prevents the formation of PGE_2.

Sanner and others have observed that SC-19220 (1) is a functional antagonist of PGE_2-elicited contractions in select tissues in vitro;[3] while Hammond et al. have shown that antagonists of PGE_2 such as SC-19220 and pinadoline (2) are analgesic.[4] 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 of the EP1 subtype in the periphery and in the CNS. Additionally, analgesics based on PGE_2 antagonism would preclude the problems associated with NSAIDs, particularly their gastric side effects.[5]

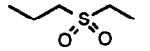
Chemistry

We sought a clinical replacement for the PGE_2 antagonist-analgesic, pinadoline.[6] A synthetic effort led to the identification of **3**[7] as a clinical candidate which had PGE_2 antagonism and analgesic activity quite similar to pinadoline. To exploit this lead and to identify a more potent analgesic-PGE_2 antagonist, structural modifications of the alkylsulfonylalkyl moiety of **3** were explored.



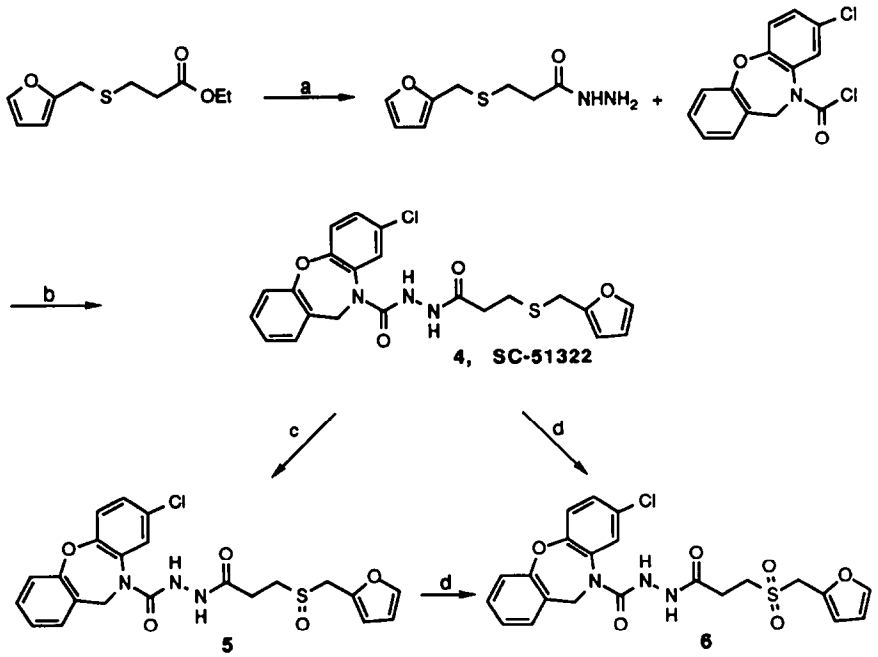
R = Me **1**, SC-19220

=  **2**, pinadoline

=  **3**

Previous research on the alkyl chain of the N-substituted dibenzoxazepines had shown that introduction of heteroaromatic functionality could produce PGE_2 antagonists-analgesics.[8] The impact of a heteroaromatic group on the alkylthioalkyl moiety had not been investigated. (The oxidation state of sulfur of **3** and its congeners was not crucial for biological activity.) Initial research involved replacement of the terminal methyl of the ethylsulfonylpropionyl functionality of **3** with a furanyl ring. As illustrated in Scheme 1, the syntheses of **4-6** employed techniques reported previously.[8,9,10]

SCHEME 1



a) NH_2NH_2, EtOH, Δ, 24 h, 69% b) TEA, DCM, 16 h, 79% c) 30% H_2O_2, HOAc, 1 h, rt, 79% d) 30% H_2O_2, HOAc, 24 h, 55°, 22%.

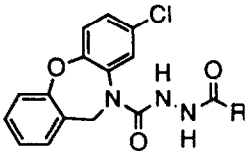
Pharmacology

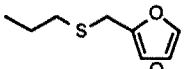
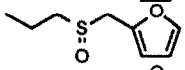
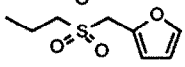
To determine the effectiveness of **4-6** as analgesics and PGE_2 antagonists, they were tested in the mouse writhing assay[11] and PGE_2 antagonism assay.[8] Analog **6** was found to have in vitro activity comparable to **3**; but, it had only marginal analgesic activity and **5** had activity similar to **6**. The penultimate precursor of **6**, **4** (SC-51322), was the most active PGE_2 antagonist that has been seen in this chemical series. To confirm that the analgesic activity was due to PGE_2 antagonism and not inhibition of cyclooxygenase, SC-51322 was screened by Panlabs in its cyclooxygenase inhibition assay. Also to ensure that SC-51322 was a selective PGE_2

antagonist, it was screened in Panlabs general pharmacology screen which found no other biological activity.[12]

Modification of **3** has yielded SC-51322, the most potent PGE_2 antagonist seen in this structural class. SC-51322 will be a powerful tool in further elucidating the role of PGE_2 in the nociceptive process and other PGE_2 mediated disorders.

Table 1: Bioassay Data for PGE_2 Antagonists



No.	R	PGE_2 Antagonsim Assay in GPI[a]	Mouse Writhing Assay (i.g.[c] at 30 mg/kg)
		pA_2[b]	ED_{50}[d]
2	$(CH_2)_4Cl$	6.2±0.2	9.8
4		8.1±0.2	0.9 (0.6-1.5)
5		6.2	5/10
6		6.6	5/10

a. guinea pig ileum. b. pA_2 determined based on the dose ratio at 3 μM. c. intra gastric. d. The initial screening dose of test compound is 30 mg/kg. Values in parentheses are confidence limits determined at 95% ($P<0.05$).

Acknowledgements

The authors would like to thank Dr. Michael F. Rafferty for his enthusiastic support of this project. We would like to thank Professor Donna L. Hammond of the University of Chicago for her insights on the mechanisms of pain and the need for new mechanism based treatment of

pain. EAH would particularly like to thank Dr. Barnett S. Pitzele and Dr. Robert H. Mazur for their many helpful ideas and thoughts on this project.

References

1. (a) Taiwo, Y. O.; Levine, J. D. *Brain Research*, *458*, **1988**, 402-406. (b) Taiwo, Y. O.; Goetzl, E. J.; Levine, J. D. *Brain Research*, **1987**, *423*, 333-337. (c) Lamotte, R. H.; Thalhammer, J. G.; Torebjork, H. E.; Robinson, C. J. *J. of Neurosci*, **1982**, *2*, 765-782. (d) Lembeck, F.; Popper, H.; Juan, H. *Naunyn Arch. Pharmacol*, **1976**, *294*, 69-73.5. (e) Abramson, S. B.; Weissmann, G. *Arthritis & Rheumatism*, **1989**, *32*, 1-9. (f) Gelgor, L.; Butkow, N., Mitchell, D. *Br. J. Pharmacol.*, **1992**, *105*, 412-416.

2. (a) Vane, J. R. *Nature*, **1971**, *231*, 232-235 (b) Ferreira, S. H. *Nature*, **1972**, *240*, 200-203. (c) Ferreira, S. H.; Moncada, S.; Vane, J. R. *Br. J. Pharmacol.*, **1973**, *49*, 86-97

3 (a) Sanner, J. H. *Arch. Int. Pharmacodyn. Ther.*, **1969**, *180*, 46-56. (b) Coleman, R. A.; Kennedy, I.; Sheldrick, R. L. G. *Br. J. Pharmacol.*, **1987**, *91*, 323P. (c) Lawrence, R. A.; Jones, R. L.; Wilson, N. H. *Br. J. Pharmacol.*, **1992**, *105*, 271-278.

4. Drower, E. J.; Stapelfeld, A.; Mueller, R. A.; Hammond, D. L. *Europ. J. of Pharmacol.*, **1987**, *133*, 249-256.

5. (a) Isselbacher, K. J. *Drugs*,**1987**,*33* (Suppl. 1), 38-46. (b) Whittle, B. J. R. *ISI Atlas of Science: Pharmacology*,**1987**, 168-172. (c) Miller, T. A. *Am J. Physiol.*,**1983**, *245*, G601-23. (d) Konturek, S. J. *Scand. J. Gastroenterol.*, **1985**, *20*, 543 - 553. (e) ed. Cohen, M. M. Biological Protection with Prostaglandins. vol II, CRC Press, Boca Raton, **1986**.

6. *Clin. Pharmacol. Ther.* **1984**, *36*, 145.

7. Mueller, R. A. U.S. patent 4,559,337.

8. Hallinan, E. A.; Hagen, T. J.; Husa, R. K.; Tsymbalov, S.; Rao, S. N.; vanHoeck, J.-P.; Rafferty, M. F.; Stapelfeld, A.; Savage, M. A.; Reichman, M. *J. Med. Chem.*, **1993**, *36*, 3293-3299.

9. Coyne, W. E.; Cusic, J. W. *J. Med. Chem.*, **1968**, *11*,1158-1161.

10. **4:** Analysis calcd. for $C_{22}H_{20}N_3O_4SCl$ (M.W. 457.94): C, 57.70; H, 4.40; N, 9.18; Cl, 7.74; S, 7.00. Found: C, 57.59; H, 4.36; N, 9.01; Cl, 7.95; S, 7.07. Only the peaks of the major rotamer are reported.[8,13] ^1H NMR (DMSO-*d6*.) 9.58 (s, 1H), 8.56 (d, 1H, J = 1 Hz), 7.57 (dd, 1H, J = 0.9, 1.8 Hz),

7.44 (d, 1H, J = 1.8 Hz), 7.20-7.42 (m, 4H), 7.16 (dd, 1H, J = 1.1, 8.2 Hz), 7.06 (dt, 1H, J = 1.3, 7.4 Hz), 6.38 (dd, 1H, J = 1.8, 3.2 Hz), 6.27 (dd, 1H, J = 1.8, 3.2 Hz), 4.84 (s, 2H), 3.77 (s, 2H), 2.63 (t, 2H, J = 7.2 Hz), 2.38 (t, 2H, J = 7.2 Hz). ^{13}C NMR (DMSO-*d6*.) 170.2, 155.4, 153.4, 151.4, 142.4, 134.2, 129.3, 128.8, 128.6, 128.3, 127.7, 126.2, 123.2, 122.9, 120.1, 110.5, 107.6, 48.8, 33.4, 27.1, 26.5. **5**: Analysis calcd. for $C_{22}H_{20}N_3O_5SCl$ (M.W. 473.93): C, 55.76; H, 4.25; N, 8.87; Cl, 7.48; S, 6.77. Found: C, 55.67; H, 4.30; N, 8.79; Cl, 7.47; S, 6.56. ^{1}H NMR (DMSO-*d6*.) 9.73 (s, 1H), 8.58 (s, 1H), 7.68 (s, 1H), 7.15-7.48 (m, 6H), 7.04-7.08 (m, 1H), 6.41-6.47 (m, 2H), 4.85 (s, 2H), 4.25 (d, 1H, J = 4.1 Hz), 4.10 (d, 1H, J = 4.1 Hz), 2.97-3.04 (m, 1H), 2.76-2.82 (m, 1H). ^{13}C NMR (DMSO-*d6*.) 169.7, 155.4, 153.2, 151.4, 145.1, 143.5, 133.9, 129.2, 128.6, 128.5, 128.4, 127.7, 125.9, 123.3, 122.9, 120.1, 111.0, 110.9, 110.8, 49.5, 48.7, 45.6, 20.8. **6**: Analysis calcd. for $C_{22}H_{20}N_3O_6SCl.0.5\ H_2O$ (M.W. 498.95): C, 52.96; H, 4.24; N, 8.42; Cl, 7.11; S, 6.43. Found: C, 52.87; H, 4.03; N, 8.37; Cl, 7.52; S, 6.19. ^{1}H NMR (DMSO-*d6*.) 9.78 (s, 1H), 8.61 (s, 1H), 7.72 (dd, 1H, J = 0.8, 1.8Hz), 7.15-7.44 (m, 6H), 7.04-7.08 (m, 1H), 6.53 (dd, 1H, J = 0.8, 3.2 Hz), 6.50 (dd, 1H, J = 1.8, 3.2 Hz), 4.85 (s, 2H), 4.69 (s, 2H), 3.29 (m, 2H), 2.54 (m, 2H). ^{13}C NMR (DMSO-*d6*.) 168.9, 155.5, 153.2, 151.5, 144.2, 142.6, 133.9, 129.3, 128.7, 127.9, 125.9, 123.4, 123.0, 120.2, 112.2, 111.3, 51.6, 48.8, 47.1, 25.3.

11. Taber, R.I. Predictive Value of Analgesic Assays in Mice and Rats. Advances in Biochemical Psychopharmacology, Bruad, M.C.; Harris, L.S.; May, E.L.; Smith, J.P.; Vilarreal, J.E., Eds.; Raven Press, New York, **1974**, 8, 191-211.

12. Pharmascreen™ and cyclooxygenase inhibition assay, Panlabs Inc., Bothell, Washington 98011.

13. (a) Bouchet, P.; Elguero, J.; Jaquier, R.; Pereillo, J.-M. *Bull. Soc. Chim. Fr*, **1972**, 2264-2271. (b) Bishop, G. J.; Price, B. J.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.*, **1967**, 672-674.

(*Received in USA* 27 *October* 1993; *accepted* 10 *December* 1993)