Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 2699–2704

BIOORGANIC &
MEDICINAL CHEMISTRY
LETTERS

NEW CLASS OF BIPHENYLENE DIBENZAZOCINONES AS POTENT LIGANDS FOR THE HUMAN EP_1 PROSTANOID RECEPTOR

Réjean Ruel,* Patrick Lacombe, Mark Abramovitz, Claude Godbout, Sonia Lamontagne, Chantal Rochette, Nicole Sawyer, Rino Stocco, Nathalie M. Tremblay, Kathleen M. Metters, and Marc Labelle

Merck Frosst Centre for Therapeutic Research P.O.Box 1005
Pointe Claire - Dorval, Québec, Canada H9R 4P8

Received 22 June 1999; accepted 12 August 1999

Abstract: A new class of potent and selective ligands for the human EP_1 prostanoid receptor is described. SAR studies reported herein allowed the identification of several potent dibenzazocinones bearing an acylsulfonamide side chain. The binding affinity of these compounds on all eight human prostanoid receptors is reported. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Introduction

Prostanoid receptors are members of the G-protein coupled receptor superfamily. Recently, eight prostanoid receptors have been cloned and characterized.[1] The molecular characterization of these receptors·has resulted in renewed interest in the field because selectivity of compounds on human prostanoid receptors can now be determined. Consequently, the correlation of a specific receptor or set of receptors with various pathologies can be established. In fact, to this date, most prostanoids which have been marketed as drugs are potent but poorly-selective agonists.[2–4] A few antagonists[5–8] such as SC-51089 and its back-up compounds SC-56551 and SC-55602 as well as ZD-4953 have entered clinical trial for indications related to hyperalgesia.

Our search for a selective EP_1 receptor ligand was initiated by screening a large number of compounds from our sample collection in our in vitro binding assays.[9] Biphenylene dibenzazocinone **1** (Figure 1) was the lead compound identified from this screening effort with a K_i value of 100 nM on EP_1 and >2 μM on EP_2, EP_3 and EP_4.[10]

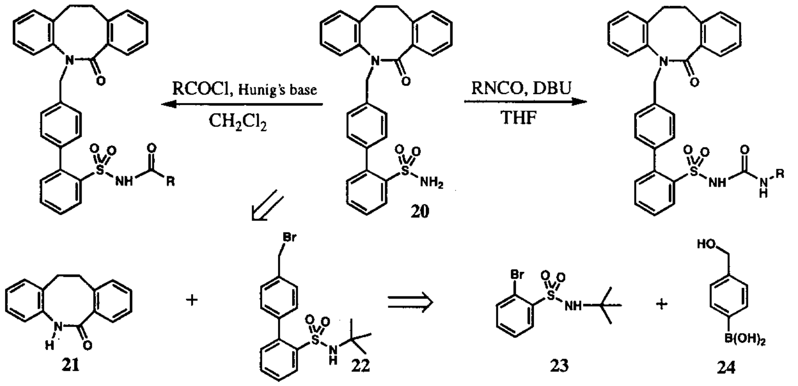
Chemistry

Sulfonylureas described in Tables 1 and 2, with the exception of N-methyl urea **10c**, were prepared from the reaction of common intermediate **20** with the corresponding isocyanate in the presence of DBU. Typically, the reactions were run in refluxing THF and were complete after 12 h. In the case of **10c**, sulfonamide **20** was reacted with the N-methyl chlorocarbamate derivative obtained by treating N-methyl phenethylamine and phosgene (toluene, NaOH 0.05 M at 0 °C). Also, non-acidic analogues **10a** and **10b** were obtained by direct alkylation using standard procedures. On the other hand, acylsulfonamides and sulfonylcarbamate **11** described in Table 3 were obtained by treating **20** with the corresponding acyl chloride and benzyl chloroformate, respectively (Scheme 1).

PII: S0960-894X(99)00465-5

The common sulfonamide intermediate **20** was obtained by treatment of commercially available 5,6,11,12-tetrahydrodibenz[*b,f*]azocine-6-one (**21**) with benzyl bromide **22** and sodium hydride in DMF followed by removal of the *tert*-butyl group with TFA. In turn, bromide **22** was obtained from **23** and **24** using a Suzuki cross-coupling reaction[11] then subsequent bromination using DiPHOS/CBr_4.

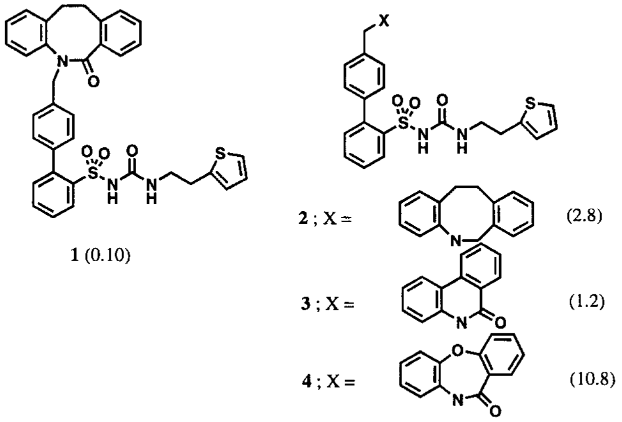
Scheme 1. General preparation of acylsulfonamides and sulfonylureas



Discussion

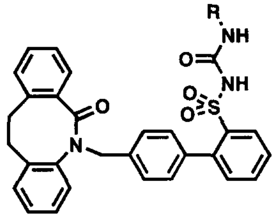
Our first effort in modifying the lead structure **1** started with examining possible replacements for the dibenzazocinone moiety. The eight-membered ring amide was first replaced by the corresponding tertiary amine **2** which resulted in a 28-fold loss of potency on the human EP_1 receptor. Also detrimental to binding affinity on EP_1, by at least 10-fold, were modifications leading to the 6- and 7-membered ring analogs **3** and **4**. We therefore focused our attention on modifications of the side chain and left the dibenzazocinone moiety intact.

Figure 1. (Value in parentheses indicate K_i value on EP_1 in μM).



We then determined the optimal side chain length for potency on EP_1 of urea analogs of lead compound **1**. The results are shown in Table 1 which also includes binding affinity for the other EP receptors.

Table 1. K_i values of sulfonylurea analogs of 1 on EP receptors.[12]

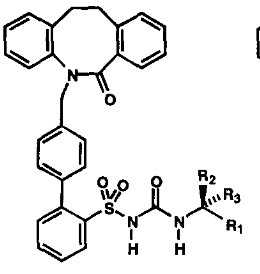


Compd	R	K_i (μM) EP_1	K_i (μM) EP_2	K_i (μM) EP_3	K_i (μM) EP_4
1	CH_2CH_2-(2-thiophene)	0.10±0.03	>100	2.2	>100
5	CH_2CH_2Ph	0.12±0.03	>100	51.2	>100
6	$CH_2CH_2CH_2Ph$	0.40±0.04	>100	>100	>100
7	CH_2Ph	0.20±0.02	>100	13±6	>100
8	Ph	21±15	16±7	4.6	19±15

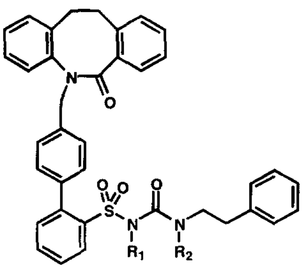
The side chain part of the molecule was explored as the thiophene was replaced by phenyl analogs. The potency on EP_1 of phenyl analogue **5** was found to be similar to that of the thiophene lead compound. The homologue **6**, however, was about three fold less potent while N-benzyl derivative **7** was two fold more potent than **6**. The aniline derivative **8** was, on the other hand, inactive on EP_1. From this study, one and two carbon atom-long chains were selected as optimum lenght for potency on EP_1. It is noteworthy that EP_1 selectivity of compounds **5**-**7**, with one to three carbon atoms between the nitrogen atom and the phenyl, was improved. We therefore set out to further modify the best compounds **5** and **7**.

The terminal phenyl group of N-benzyl analogue **7** was removed and replaced by three aliphatic carbons to give rise to compound **9a**. This *n*-butyl derivative **9a** showed similar in *vitro* profile compared to **7** both in terms of potency and selectivity, but the corresponding *t*-butyl analogue **9b** was less potent and much less selective with a ratio of K_i's of EP_3/EP_1 of only 1.7. Substitution at the alpha position of the nitrogen in compound **7** provided **9c** with slightly improved EP_1 affinity. Conversely, alkylation of the acidic proton of the lead compound affording the methyl and benzyl analogues **10a** and **10b,** respectively, though these compounds possessed lower potency on EP_1. It is interesting to note, however, that the non-acidic analogue **10a** still showed some activity on the EP_1 receptor while the bulkier analogue **10b** was inactive. By far the best modification in this series was the addition of a methyl group on the other nitrogen atom and the resulting compound **10c** was potent on EP_1(K_i = 17 nM) and quite selective.

Table 2. K_i values of sulfonylurea analogs of 5 and 7 on EP receptors.[12]



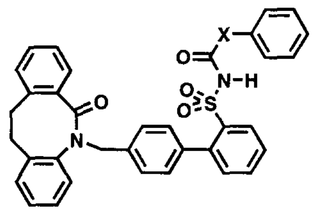
9



10

Compd	**R_1**	**R_2**	**R_3**	**K_i (μM) EP_1**	**K_i (μM) EP_2**	**K_i (μM) EP_3**	**K_i (μM) EP_4**
9a	n-C_3H_7	H	H	0.22±0.02	>100	6.0	>100
9b	Me	Me	Me	0.77±0.12	>100	1.2	4.7±1.3
9c	Ph	Me	H	0.14±0.03	21±5	4.7±0.3	6.9±2.1
10a	Me	H	-	0.36	>100	>100	>100
10b	CH_2Ph	H	-	51.0	>100	>100	>100
10c	H	Me	-	0.017±0.001	23±3	5±3	1.1±0.5

Table 3. K_i values of sulfonylcarbamate and acylsulfonamide analogs on EP receptors.[12]



Compd	**X**	**K_i (μM) EP_1**	**K_i (μM) EP_2**	**K_i (μM) EP_3**	**K_i (μM) EP_4**
11	OCH_2	0.15±0.03	11±1	2.4	6±4
12	CH_2CH_2	0.047±0.007	>100	3.6	13±7
13	CH_2O	0.14±0.03	22±5	4.7±0.3	7±2
14	$C(CH_3)_2CH_2$	0.018±0.006	>100	16±6	2.4±0.1
15	CH_2	0.057±0.001	14±2	2.8±0.3	>100
16	$CH(CH_3)$	0.016±0.001	>100	5±3	20±14
17	$C(CH_3)_2$	0.010±0.003	23±6	4±4	5±3
18	(R)-$C(OMe)CF_3$	0.050±0.007	13±1	1.6±0.1	3±2
19	(S)-$C(OMe)CF_3$	0.012±0.002	11±1	1.3±0.4	4±1

Oxygen and carbon analogs of urea **7** were also studied (Table 3). Unlike carbamate **11**, acylsulfonamide **12** was about three-fold more potent than the corresponding nitrogen analog. The presence of an electron-withdrawing group in **13** reduced the potency on EP_1 and the best compounds were those obtained by substitution on phenethyl and benzyl analogs **12** and **15**, respectively. The binding affinity on EP_1 of these compounds (**14**, **16**, **17**, and **19**) was very near that of the endogenous ligand PGE_2 in the EP_1 assay (ca. 10 nM).

The best EP_1 compounds described herein are therefore selective over the other EP receptors but also, as indicated in Table 4, with respect to the other four human prostanoid receptors. Table 4 includes the secondary binding[9] results for these compounds.

Table 4. Secondary binding affinity of the best EP_1 compounds[9]

Compd	**K_i (μM) DP**	**K_i (μM) FP**	**K_i (μM) IP**	**K_i (μM) TP**
10c	2.87±0.01	6.2±0.1	52±3	2.1±0.7
14	4.0	1.3	21±13	1.1
16	2.8±0.2	5.3±0.4	28.3	2.8
17	2.4±0.8	5±3	21±3	3±1
19	2.0±0.9	3.8±0.6	13±2	1.5±0.2

Publications[5–7] and patents[8] have appeared in recent years on selective EP_1 antagonists. The vast majority of structures reported so far are dibenzoxapines or *ortho* disubstituted aromatic ethers. The dibenzazocinones reported herein therefore constitute a novel series of EP_1 antagonists, demonstrated by our Aequorin luminescence-based functional calcium assay[13], with high affinity and selectivity on all human prostanoid receptors.

Conclusion

We have reported a new class of dibenzazocinones that are potent prostanoid receptor antagonists[13] which show good selectivity for the EP_1 receptor[14]. SAR indicated that substitution of the non-acidic NH functionality in the urea-like series provide the best compound in this series. The acylsulfonamides, in turn, were more potent than the corresponding urea analogues and SAR reported in this series indicates that substitution on the acylsulfonamide side chain increases binding affinity on EP_1 by up to five fold. We have reported herein the structures of five selective new compounds with K_i values in the 10–20 nM range, which is comparable to that of the endogenous agonist PGE_2 on EP1. Studies on the pharmacology of these compounds will be reported in the near future.

References and Notes

1. $\underline{EP_1}$: Funk, C. D.; Furci, L.; FitzGerald, G. A.; Grygorczyk, R.; Rochette, C.; Bayne, M. A.; Abramovitz, M.; Adam, M.; Metters, K. M. *J. Biol. Chem.* **1993**, *268*, 26767. $\underline{EP_2}$: Regan, J. W.; Bailey, T. J.; Pepperl, D. J.; Pierce, K. L.; Bogardus, A. M.; Donello, J. E.; Fairbairn, C. E.; Kedzie, K. M.; Woodward, D. F.; Gil, D. W. *Mol. Pharmacol.* **1994**, *46*, 213. $\underline{EP_3}$: Adam, M.; Boie, Y.; Rushmore, T. H.; Muller, G.; Bastien,

L.; McKee, K. T.; Metters, K. M.; Abramovitz, M. *FEBS Lett.* **1994**, *338*, 170. EP$_4$: Bastien, L.; Sawyer, N.; Grygorczyk, R.; Metters, K. M.; Adam, M. *J. Biol. Chem.* **1994**, *269*, 11873. DP: Boie, Y.; Sawyer, N.; Slipetz, D. M.; Metters, K. M.; Abramovitz, M. *J. Biol. Chem.* **1995**, *270*, 18910. FP: Abramovitz, M.; Boie, Y.; Nguyen, T.; Rushmore, T. H.; Bayne, M. A.; Metters, K. M.; Slipetz, D. M.; Grygorczyk, R. *J. Biol. Chem.* **1994**, *269*, 2632. IP: Boie, Y.; Rushmore, T. H.; Darmon-Goodwin, A.; Grygorczyk, R.; Slipetz, D. M.; Metters, K. M.; Abramovitz, M.; *J. Biol. Chem.* **1994**, *269*, 12173. TP: Hirata, M.; Hayashi, Y.; Ushikubi, F.; Yokota, Y.; Kageyama, R.; Nakanishi, S.; Narumiya, S. *Nature* **1991**, *349*, 617.

2. Abramovitz, M.; Metters, K. M. *Annu. Rep. Med. Chem.* **1998**, *33*, 223.
3. Coleman, R. A. *in Eicosanoids: From Biotechnology to Therapeutic Applications* Folco, Samuelsson, Maclouf, and Velo Eds; Plenum Press, New-York, **1996**, Chap 14. 137.
4. Ichikawa, A.; Sugimoto, Y.; Negishi, M. *J. Lipid Mediators Cell Signaling* **1996**, *14*, 83.
5. Hallinan, E. A.; Hagen, T. J.; Husa, R. K.; Tsymbalov, S., Rao, S. N.; vanHoeck, J.-P.; Rafferty, M. F.; Stappelfeld, A.; Savage, M. A.; Reichman, M. *J. Med. Chem.* **1993**, *36*, 3293.
6. Hallinan, E. A.; Staplefeld, A.; Savage, M. A.; Reichman, M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 509.
7. Hallinan, E. A.; Hagen, T. J.; Tsymbalov, S.; Husa, R. K.; Lee, A. C.; Stapelfeld, A.; Savage, M. A. *J. Med. Chem.* **1996**, *39*, 609.
8. (a) Ohuchida, S.; Nagao. **WO 98/27053**; (b) Breault, G. A. **WO 97/00864**; (c) Breault, G. A. **WO 97/00863**; (d) Breault, G. A.; Oldfield, J.; Tucker, H.; Warner, P. **EP 0 752 421 A1**; (e) Breault, G. A.; Oldfield, J.; Tucker, H.; Warner, P. **WO 9603380A1**; (f) Breault, G. A.; Oldfield, J.; Tucker, H.; Warner, P. **WO 9606822**; (g) Oldfield, J.; Tucker, H. **EP 0 534 667 A1**; (h) Oldfield, J.; Tucker, H. **EP 0 480 641 A1**.
9. Abramovitz, M.; Adam, A.; Boie, Y.; Godbout, C.; Lamontagne, S.; Rochette, C.; Sawyer, N.; Tremblay, N. M.; Belley, M.; Gallant, M.; Dufresne, C.; Gareau, Y.; Ruel, R.; Juteau, H.; Labelle, M.; Ouimet, N.; Metters, K. M. *Biochim. Biophys. Acta.* **1999** *In Press.*
10. All new compounds reported herein were characterized (^{1}H NMR, MS) and gave satisfactory elemental analyses.
11. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 53.
12. EP receptor filtration binding assays were performed using radioligand PGE$_2$. K$_i$ values represent the mean from three independent determinations performed in duplicate, where standard deviation is report.
13. Ungrin, M. D.; Singh, L. M. R.; Stocco, R.; Sas, D. E.; Abramovitz, M. *Anal. Biochem.* **1999**, *272*, 34.
14. For comparaison, SC51089 profil is: EP$_1$ 1,3 μM EP$_2$ >96,5 μM EP$_3$ 1,8 μM EP$_4$ >49,5 μM.