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Design and synthesis of benzo-lipoxin A_4 analogs with enhanced stability and potent anti-inflammatory properties

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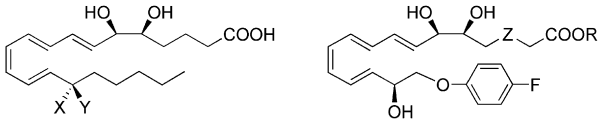
Abstract—A new class of chemically and metabolically stable lipoxin analogs featuring a replacement of the tetraene unit of native LXA_4 with a substituted benzo-fused ring system have been designed and studied. These molecules were readily synthesized via a convergent synthetic route involving iterative palladium-mediated cross-coupling, and exhibit enhanced chemical stability, as well as resistance to metabolic inactivation via eicosanoid oxido-reductase. These new LX analogs were evaluated in a model of acute inflammation and were shown to exhibit potent anti-inflammatory properties, significantly decreasing neutrophil infiltration in vivo. The most potent among these was compound **9** (*o*-[9,12]-benzo-15-epi-LXA_4 methyl ester. Taken together, these findings help identify a new class of stable and easily prepared LX analogs that may serve as novel tools and as promising leads for new anti-inflammatory agents with improved therapeutic profile.

The conventional strategy for the development of anti-inflammatory therapeutics has been the inhibition of pathways related to the biosynthesis and actions of pro-inflammatory mediators, such as the prostaglandins (PGs) and the leukotrienes (LTs) that are derived from arachidonic acid (AA) and help amplify the inflammatory response.[1,2] An alternative approach for the discovery of effective anti-inflammatory agents without the usual adverse side-effects has been suggested from recent investigations initiated in our laboratories[3,4] based on promoting the resolution of inflammation.[5,6] Rather than interfering with the biosynthesis and actions of pro-inflammatory PGs and LTs, this novel strategy is based on mimicking the actions of endogenous *anti-inflammatory* and *pro-resolution lipid mediators*. The first class of such compounds to be discovered were the lipoxins (LX), which feature a unique trihydroxy-*E*,*E*,*Z*,*E*-tetraene structure and are generated from AA via lipoxygenase-mediated transcellular biosynthesis. Lipoxin A_4 (LXA_4, **1**) (Scheme 1) was shown to potently suppress inflammation upon binding to its receptor (ALXR or hFPRL1), a G-protein-coupled receptor known to play a key role in modulating inflammation that belongs to a phylogenetic cluster that includes known receptors for other lipid mediators.[7] Notably, in a manner common to other eicosanoids, LXA_4 is rapidly inactivated in vivo (>60% in 30 s),[8] via a metabolic enzyme system consisting of 15-prostaglandin dehydrogenase (15-PGDH) and eicosanoid oxido-reductase (EOR). The stereoselectivity of this inactivation was further validated with the discovery of 15-epi-LXA_4 (**2**), which is generated via an alternative biosynthetic path-



1, X=OH, Y=H, Lipoxin A_4 (LXA_4)
2, X=H, Y=OH, 15-epi LXA_4

3, Z=CH_2, R=Me, ATLa
4, Z=O, R=Na, ZK-142

Scheme 1.

Keywords: Lipoxin analogs; Benzo-analogs; Palladium; Suzuki coupling; Heck reaction; Anti-inflammatory agents; Inflammation; Eicosanoid oxido-reductase; Neutrophil infiltration; Lipid mediators.
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way originating in endothelial or epithelial cells that involves the initial mono-oxygenation of AA via the action of COX-2 in the presence of aspirin.[9] The aspirin-triggered lipoxin (ATL) **2** retains the potent biological actions of LXA_4, but exhibits a longer half-life in vivo,[10] apparently because it is a less effective substrate for the metabolizing enzymes, due to its 15(*R*) configuration. The ATL pathway was recently shown to operate in humans taking low dose aspirin[11] and provides a novel mechanism for aspirin's many health benefits.[12]

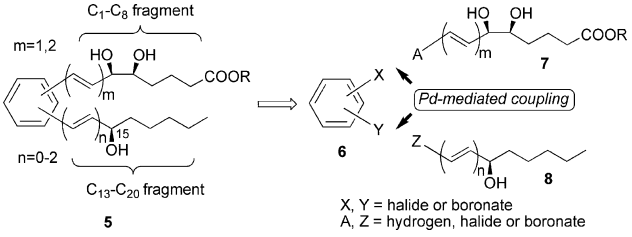
In order to increase the half-life of LX, we have previously developed[4,10] the first metabolically stable LXA_4 analogs that retain all of the potent actions of LX but are not susceptible to enzymatic inactivation. The initial LX analogs[10] were based on modifying the C_{15}–C_{20} portion of LX, thereby suppressing EOR-mediated metabolic inactivation. Using such long acting synthetic molecules we were able to systematically investigate a number of important biological actions of LX, and have demonstrated their potential anti-inflammatory role.[3,4] Among the several LXA_4 analogs designed, synthesized, and studied, the aspirin-triggered lipoxin analog (ATLa) 16-*p*-fluorophenoxy-15-epi-LXA_4 methyl ester (**3**) turned out to be the most effective,[13] and has served as the gold standard for studying a wide range of LX-associated actions.[3,4] Compound **3** also led to the discovery of the 3-oxa LX analog ZK-142 (**4**) and its 11-dehydro analog ZK-994, which are topically and orally active anti-inflammatory agents currently under development.[14,15]

Lipoxins and their stable analogs were recently shown to simultaneously dampen the adverse effects of inflammation in addition to promoting its resolution.[3,4] Moreover, the therapeutic potential of these molecules was demonstrated for a number of major inflammatory disorders, including: vascular injury,[15,16] dermal inflammation,[14,15,17] gastrointestinal disease,[18] colitis,[19] asthma,[20] arthritis,[21] ocular inflammation,[22] kidney disease,[23] periodontal disease,[24] and cystic fibrosis.[25] The development of pharmacologically active stable LX analogs that mimic the actions of LX, therefore, is of great interest for the development of new anti-inflammatory therapeutics for a variety of applications.

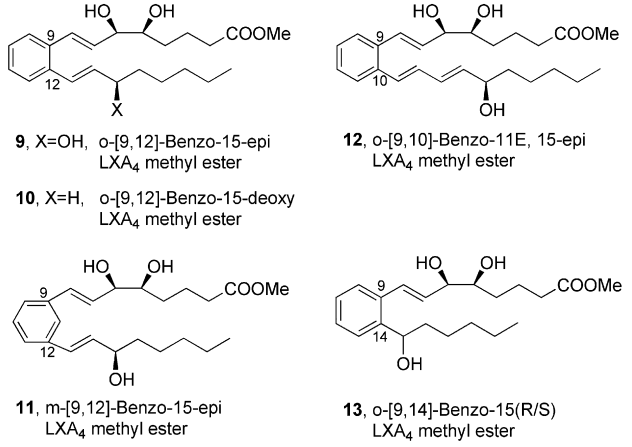
Herein, we report the design, synthesis, and evaluation of several benzo-LXA_4 analogs that involve the modification of the tetraene portion of the LX molecule. In addition to enhanced chemical stability, these new LX analogs are much easier to synthesize through a highly convergent and efficient strategy, and exhibit potent anti-inflammatory actions in vivo, while resisting metabolic inactivation by eicosanoid oxido-reductase.

Since the detailed three-dimensional molecular structure of ALXR is not known, the design of LX analogs has been substrate-driven and guided by considerations linked to LX biological function. Based on known structure–function studies of LX and LX analogs to date, it can be concluded that the most active and longer acting LX analogs have the following minimum structural features: (a) a free acid, carboxylate salt, or ester at C_1, (b) a diol moiety at C_5–C_6 having the native 5(*S*),6(*R*) configuration, and (c) a hydroxyl group at C_{15} having the 15(*R*) configuration (15-epi). It is also known that the LX isomer with an all-trans tetraene moiety is much less active than molecules having the native 7*E*,9*E*,11*Z*,13*E* stereochemistry, suggesting the critical importance of the 11*Z* C=C bond. Since this bond can be readily isomerized to the corresponding *E*-isomer under a variety of chemical or biological conditions,[26] this limits the overall chemical and in vivo stability of LX analogs. Moreover, the synthesis of LX analogs containing a *Z*-alkene is more challenging, because this must be done in a stereospecific manner and at a later stage of the synthesis in order to avoid pre-mature isomerization. Therefore, it would be preferable to replace the native tetraene unit with an equivalent moiety that is more stable and easier to synthesize, while retaining the other desired structural characteristics needed for bioactivity.

Using the above principles, we designed a new series of benzo-LXA_4 analogs[27] of the general structure **5** (Scheme 2) and explored the potential use of such compounds as anti-inflammatory agents. Herein, we present the synthesis and study of selected examples shown in Scheme 3. An added advantage of molecules of this type is that they can be readily prepared in large scale from three readily available building blocks (**6**–**8**) using iterative Pd-mediated coupling processes. Overall, therefore, such benzo-LXA_4 analogs could benefit both from enhanced chemical and biological stability as well as sim-



Scheme 2. Strategy for the design and synthesis of benzo-LXA_4 analogs.



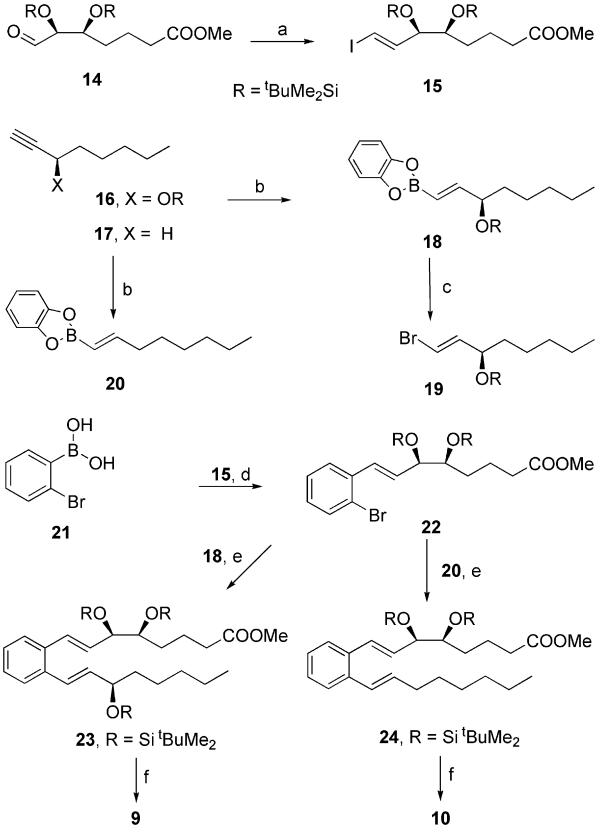
Scheme 3. Selected benzo-LXA_4 analogs synthesized and studied.

plified synthesis, while having structures that can mimic ATL and their actions.

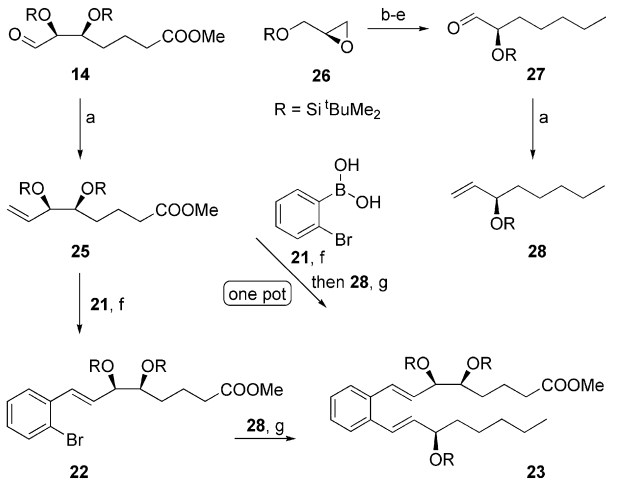
The naming of these analogs, shown in Scheme 3, was based on the native LXA_4 structure and the incorporation of a fused *o*- or *m*-substituted benzo-ring between two positions of the tetraene. This naming suggests a more direct co-relation between the analogs and the native LX structure. Among these, LX analogs **9**, **10**, **12**, and **13** have the two key LX fragments in a proximal *o*-orientation, while LX analog **11** has a more angular *m*-configuration. The 15-deoxy analog **10** lacking a third hydroxyl group at C_{15} would constitute a negative control for LX actions, since the corresponding 15-deoxy-LXA_4 analog is generally inactive. The more extended LX analog **12** was designed to provide an insight into the acceptable length of LX agonists, while analog **13** has a more condensed structure, generated simply by joining atoms C_9 and C_{14} of the tetraene.

As outlined in Scheme 2, our synthetic strategy for all of these LX analogs was based on Pd-mediated coupling procedures.[28] The detailed syntheses of compounds **9**–**13** are shown in Schemes 4–8.

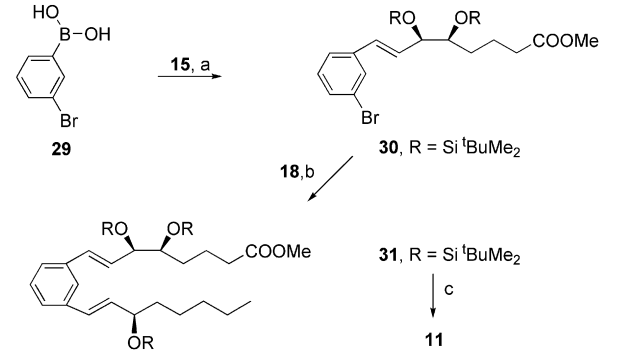
For the synthesis of the *o*-analog **9** we investigated two alternative strategies starting with *o*-bromophenyl boronic acid **21**, one relying on the Suzuki–Miyaura coupling



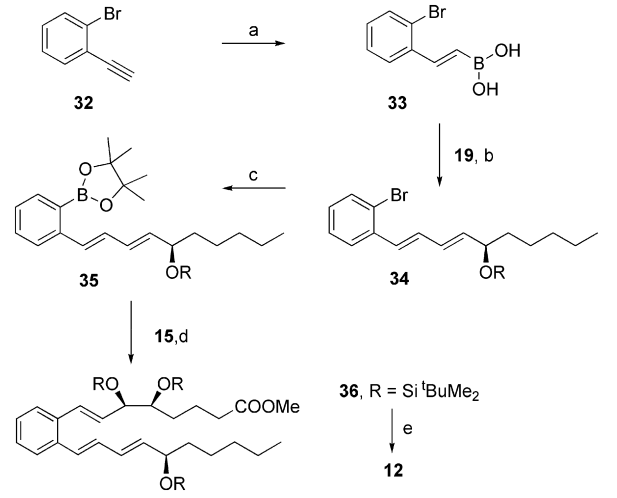
Scheme 4. Reagents and conditions: (a) CHI_3, $CrCl_2$, THF, 0 °C to rt (40%); (b) catecholborane, 60 °C; (c) *N*-bromosuccinimide, rt (80%); (d) $Pd(PPh_3)_4$, K_2CO_3, dioxane, 60 °C (70%); (e) $Pd(PPh_3)_4$, K_2CO_3, dioxane/H_2O, 80 °C (40–45%); (f) Bu_4NF, THF (95–97%).



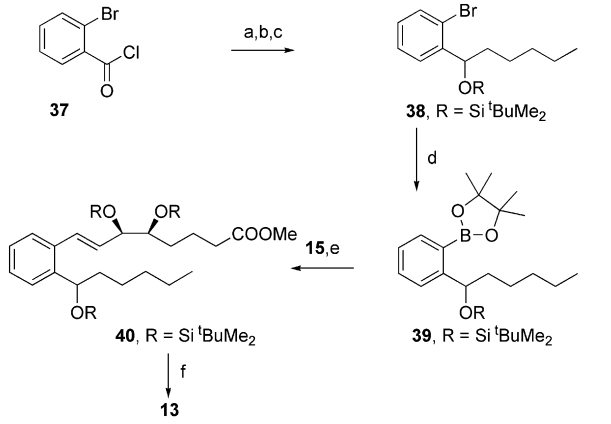
Scheme 5. Reagents and conditions: (a) Cp_2TiMe_2, THF, 80 °C (67–72%); (b) ^nBuLi, CuI, THF (70%); (c) $^tBuMe_2SiCl$, imidazole, DMAP, CH_2Cl_2 (86%); (d) CSA, MeOH/CH_2Cl_2 (97%); (e) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2 (75%); (f) $Pd(OAc)_2$, Cs_2CO_3, MeCN, 85 °C (62%); (g) $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, PPh_3, MeCN, 60 °C (47%).



Scheme 6. Reagents and conditions: (a) $Pd(PPh_3)_4$, K_2CO_3, dioxane, 60 °C (70%); (b) $Pd(PPh_3)_4$, K_2CO_3, dioxane/H_2O, 80 °C (44%); (c) Bu_4NF, THF (95%).



Scheme 7. Reagents and conditions: (a) BCl_3, Et_3SiH, 0 °C, then NaOH, then HCl (50%); (b) $Pd(PPh_3)_4$, K_2CO_3, dioxane, 60 °C (65%); (c) bis-pinacolato diboron, $PdCl_2$(dppf), dppf, AcOK, DMSO, 80 °C (40%); (d) $PdCl_2$(dppf), K_3PO_4, DMF, 60 °C (45%); (e) Bu_4NF, THF (96%).



Scheme 8. Reagents and conditions: (a) MeNHOMe·HCl, Et_3N, CH_2Cl_2, then $C_5H_{11}MgBr$, THF (70%); (b) $NaBH_4$, MeOH (90%); (c) $^tBuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2 (95%); (d) bis-pinacolato diboron, $PdCl_2$(dppf), dppf, AcOK, DMSO, 80 °C (40%); (e) $PdCl_2$(dppf), K_3PO_4, DMF, 60 °C (46%); (f) Bu_4NF, THF (95%).

(Scheme 4), and one featuring a novel boronic acid Heck-type coupling (Scheme 5). The first approach involves the Suzuki–Miyaura coupling between **21** and iodide **15**, which is readily prepared by Takai olefination[29] of aldehyde **14** (Scheme 4). A subsequent Suzuki–Miyaura coupling of **22** with boronate **18** gave after deprotection the *o*-[9,12]-benzo LX analog **9**. The 15-deoxy analog **10** was prepared similarly via the coupling of **22** with the corresponding boronate **20**. Interestingly, we have also shown that *it is possible to construct these benzo-LX analogs in one-pot*, in somewhat lower yields, by using iterative Pd-mediated couplings between **21** and the required alkenyl fragments (**15**, **19**) without intermittent isolation steps.

An alternative and potentially more versatile strategy for the synthesis of **23** (Scheme 5) involves the consecutive Heck-type coupling of **21** with alkenes **25** and **28**, which were prepared via the titanium-mediated methylenation[30] of aldehydes **14** and **27**. Interestingly, the first Heck coupling of *o*-bromophenyl boronic acid **21** with **25** proceeded selectively at the boronic acid position,[31] affording the corresponding bromide **22**, which was subjected to a second Heck-type coupling under the Jeffery conditions[32] to give **23**. A novel one-pot iterative coupling of **21** with **25** and **28** was also shown to afford **23**, without isolation of **22**.

The *m*-[9,12]-benzo LX analog **11** was prepared similarly by starting with *m*-bromophenyl boronic acid **29** (Scheme 6). The extended benzo-LX analog **12** was prepared as shown in Scheme 7 from 2-bromo styryl boronic acid **33**, which was synthesized from 2-bromo-phenyl acetylene **32** using the hydroboration procedure reported by Matteson.[33] Suzuki–Miyaura coupling of **33** with bromide **19**, prepared via the stereospecific bromination[34] of boronate **18** (Scheme 4), gave bromide **34** which was converted to the corresponding pinacol boronate **35** under a Pd-catalyzed reaction with bis-pinacolato diboron.[35] Coupling of **35** with iodide **15** (Scheme 4) formed, after desilylation, the *o*-[9,10]-benzo-LX analog **12** (Scheme 7). Finally, as shown in Scheme 8, the condensed analog **13** was prepared from racemic bromide **38**, which was prepared from acyl chloride **37**. Conversion of **38** to the boronate **39** using bis-pinacolato diboron under Pd-catalysis,[35] followed by Suzuki–Miyaura Pd-mediated coupling[28] with iodide **15** and a final desilylation, gave LX analog **13**.

In order to determine whether these new LX analogs were resistant to rapid enzymatic catalysis,[10] each of these compounds (~15 μM) was incubated with recombinant EOR (0.05 μg) and their rates of conversion were calculated by monitoring formation of NADH, an essential cofactor in this process (Table 1). Native LXA_4 (**1**) was converted most readily (3.1 μM/min), while the 15-epi-LXA_4 methyl ester **2-Me** (ATL-Me), used here as a positive control, as well as the benzo-LX analogs (**9**–**13**) were not readily converted, in comparison with LXA_4. As expected, the initial rate of conversion for the deoxy LX analog **10**, used as a negative control, was the slowest.

For a side-by-side comparison of the anti-inflammatory action of the LX analogs, a dose of 15 μg kg^{-1} or ~300 ng/mouse was used since it was most efficacious in previous studies. As shown in Table 2, the *o*-[9,12]-benzo analog **9**, and *m*-[9,12]-benzo analog **11** were most effective, both exhibiting a statistically significant ~32% inhibition of PMN infiltration ($n = 5$–10, $P < 0.005$ and $P < 0.05$, respectively, compared to control). The *o*-[9,14]-benzo analog **13** was the least effective, decreasing PMN infiltration by ~22% compared to control (one-tailed *t*-test), while mice treated with the *o*-[9,10]-benzo analog **12** failed to inhibit PMN numbers in a statistically significant manner. Interestingly, the 15-deoxy *o*-[9,12]-benzo analog **10** did show some activity in this model (~24%), despite lacking the 15-OH group.

These results indicate that the new benzo-LXA_4 analogs are: (a) readily prepared via short and efficient synthetic pathways, (b) are resistant to enzymatic catalysis relatively to LXA_4, and (c) exhibit potent LX-like anti-inflammatory actions in vivo. While the analogs of this series share a common benzo-fused backbone and 5*S*,6*R*-vicinal hydroxyl groups, there are subtle differ-

Table 1. Metabolic conversion of benzo-LXA_4 analogs by recombinant eicosanoid oxido-reductase (EOR)

Compound	EOR conversion rate (μM/min)	EOR relative conversion rate (%)
1 (LXA_4)	2.42	100
2-Me (ATLa)	0.21	9
9 (*o*-[9,12]-Benzo)	0.19	8
10 (*o*-[9,12]-Benzo, 15 deoxy)	0.04	2
11 (*m*-[9,12]-Benzo)	0.45	19
12 (*o*-[9,10]-Benzo)	0.14	6
13 (*o*-[9,14]-Benzo)	0.09	4

Each compound was incubated with 50 ng of recombinant EOR at 37 °C (0.1 M Tris–HCl, pH 9.0, 1 mM NAD^+, 100 μL total volume) for 25 min and the rate of NADH formation was monitored. Initial reaction velocities were calculated using linear regression analysis of the linear phase of conversion. Rate values represent means ± SEM, $n = 3$.

Table 2. Anti-inflammatory action of benzo-LXA_4 analogs

Compound	Inhibition of PMN infiltration (%)
3 (ATLa)	40.53
9 (*o*-[9,12]-Benzo)	32.21
10 (*o*-[9,12]-Benzo, 15 deoxy)	23.86
11 (*m*-[9,12]-Benzo)	31.97
12 (*o*-[9,10]-Benzo)	17.33
13 (*o*-[9,14]-Benzo)	22.34

Compounds were injected by intravenous bolus injection (15 μg kg^{-1}/100 μL of sterile saline) via the tail vein of 6- to 8-week-old male FVB mice followed by peritoneal injection of zymosan A (1 mg/1 mL). Peritoneal lavages were collected (2 h) and total leukocytes, PMNs, and monocytes were enumerated. Inhibition of PMN infiltration was determined by comparison to inflammation (peritonitis) initiated by zymosan A plus vehicle (100 μL of sterile saline). Values represent means ± SEM, $n = 5–10$.

ences among the analogs studied. Examining the impact of these structural differences in both anti-inflammatory and enzymatic catalysis provided some insights into structure–function relationships.

Earlier generations of LXA_4 analogs were shown to resist inactivation by EOR, mainly through the use of an (*R*)-OH group at C_{15}.[10] In view of this, the benzo LX analogs presented here were synthesized having the (*R*) configuration at this position. In addition, a benzo-fused ring was inserted at various positions of the labile tetraene backbone of LXA_4 because of the inherent chemical instability of the conjugated *E*,*E*,*Z*,*E* tetraene. This modification not only enabled a simplified, highly convergent and stereoselective synthesis, but also provided overall conformational rigidity. All of the benzo LX analogs reported here demonstrated significant resistance to enzymatic dehydrogenation at C_{15} (Table 1), a feature found to enhance bioactivity.[3,4] Comparison among these new LX analogs showed that the 15-deoxy analog **10** was not converted by 15-EOR to an appreciable extent, confirming that EOR acts primarily at the C_{15} (ω-6) OH group and not at the vicinal 5- and 6-hydroxyls of these compounds. While analog **10** was essentially inert to enzymatic catalysis, the other four analogs were inefficiently converted but were not more resistant than ATL-Me. Analog **13** (used as a racemic mixture at C_{15}) was also resistant to 15-EOR, even though half of it had the 15*S* configuration. Presumably, by placing a benzene ring at the site of the 13*E* C=C bond in **13**, which is adjacent to the C_{15} OH, the compound no longer has the preferred allylic alcohol structure,[4] and it is also more hindered. Otherwise, these results suggest that the presence of the benzene ring further away from the C_{15} OH does not confer any additional resistance to EOR inactivation.

The LXA_4 analog ATLa (**3**) has been established as the benchmark of LX analogs, demonstrating potent anti-inflammatory actions as well as resistance to inactivation.[4,13] While other currently available non-steroidal anti-inflammatory drugs (NSAIDs) exhibit similar anti-inflammatory properties, LXs and their analogs are far more potent, requiring two to three orders of magnitude lower concentration for a similar action.[17] In the rank order comparison of these analogs, with ATLa (**3**), the most potent were analogs **9** and **11** reducing PMN infiltration in a statistically significant manner by ~32%, versus 40% for **3**. Earlier results showed that indomethacin, a commonly prescribed NSAID, reduces PMN infiltration by ~35–40% in this model of peritonitis,[36] providing validation of the clinical significance of the degree of activity observed with these new analogs and point to a novel mechanism of action for reducing inflammation which goes beyond the simple inhibition of the production of prostanoids. Our results (Table 2) demonstrate that both the *o*- and *m*-benzo LX analogs blocked PMN infiltration to a similar degree. Since these two analogs differ mainly in the angular orientation between the C_1–C_8 and C_{13}–C_{20} fragments, this suggests that LX-receptor interactions exhibit conformational flexibility. In contrast to the other analogs tested, compound **12** was found to be the least active, suggesting a possible importance of the overall size of the tetraene unit, or more specifically the need for a *cis*-orienting group (*Z*-alkene or benzo-ring) at a more appropriate location of the LX structure.

In the present study, a new class of benzo-LX analogs was designed that are resistant to enzymatic catalysis and demonstrated diverse and potent LX-like anti-inflammatory actions. It should be noted that although a related series of benzo-LXA_4 analogs were previously reported,[37] those earlier analogs had the 5,6-diol unit with the unnatural 5*S*,6*S*- and 5*R*,6*S*-configurations, rather than the biologically relevant 5*S*,6*R* configuration of LXA_4 and ATL. Moreover, the previous analogs lacked stereospecificity at the ω-proximal hydroxyl group (i.e., C_{15}), unlike the most active analogs presented here. Also, the 6*S*-isomer of natural LXA_4, denoted 6*S*LXA_4, is essentially devoid of bioactivity.[1] Given the high stereochemical fidelity exhibited by the lipoxins both in terms of their metabolic inactivation by oxido-reductases as well as their receptor-binding actions that are sensitive to hydroxyl group stereochemistry, even relatively small changes in the structures of these molecules can have a dramatic effect on their bioactivities in vivo.

Overall, the new series of LX analogs reported herein have potent anti-inflammatory activities in vivo reducing the infiltration of neutrophils to an inflamed site in vivo, and unlike the native LXA_4, ATL, and earlier generations of LX analogs, they are also characterized by an increased chemical stability, while they can be readily synthesized via stereocontrolled, highly convergent, and efficient synthetic routes. The combined characteristics of these new LX-like molecules,[38,39] therefore, make them appealing candidates for pharmacological applications and for the development of new anti-inflammatory therapeutics.

Acknowledgments

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References and notes

1. Samuelsson, B.; Dahlen, S. E.; Lindgren, J. A.; Rouzer, C. A.; Serhan, C. N. *Science* **1987**, *237*, 1171.
2. (a) Funk, C. D. *Science* **2001**, *294*, 1871; (b) Flower, R. J. *Nat. Rev. Drug Discov.* **2003**, *2*, 179.
3. (a) Serhan, C. N. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 141; (b) Serhan, C. N. *Prostaglandins Other Lipid Mediat.* **2002**, *68–69*, 433.
4. Petasis, N. A.; Akritopoulou-Zanze, I.; Fokin, V. V.; Bernasconi, G.; Keledjian, R.; Yang, R.; Uddin, J.; Nagulapalli, K. C.; Serhan, C. N. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 301.
5. (a) Serhan, C. N. *Ann. Rev. Immunol.* **2007**, *25*, 101; (b) Serhan, C. N.; Savill, J. *Nat. Immunol.* **2005**, *6*, 1191.
6. (a) Gilroy, D. W.; Lawrence, T.; Perretti, M.; Rossi, A. G. *Nat. Rev. Drug Discov.* **2004**, *3*, 401; (b) Lawrence, T.; Willoughby, D. A.; Gilroy, D. W. *Nat. Rev. Immunol.* **2002**, *2*, 787.
7. Chiang, N.; Arita, M.; Serhan, C. N. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 163.
8. (a) Serhan, C. N.; Fiore, S.; Brezinski, D. A.; Lynch, S. *Biochemistry* **1993**, *32*, 6313; (b) Clish, C. B.; Levy, B. D.; Chiang, N.; Tai, H. H.; Serhan, C. N. *J. Biol. Chem.* **2000**, *275*, 25372.
9. Clária, J.; Serhan, C. N. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 9475.
10. Serhan, C. N.; Maddox, J. F.; Petasis, N. A.; Akritopoulou-Zanze, I.; Papayianni, A.; Brady, H. R.; Colgan, S. P.; Madara, J. L. *Biochemistry* **1995**, *34*, 14609.
11. Chiang, N.; Bermudez, E. A.; Ridker, P. M.; Hurwitz, S.; Serhan, C. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 15178.
12. Gilroy, D. W. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 203.
13. Clish, C. B.; O'Brien, J. A.; Gronert, K.; Stahl, G. L.; Petasis, N. A.; Serhan, C. N. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 8247.
14. Guilford, W. J.; Bauman, J. G.; Skuballa, W.; Bauer, S.; Wei, G. P.; Davey, D.; Schaefer, C.; Mallari, C.; Terkelsen, J.; Tseng, J.-L.; Shen, J.; Subramanyam, B.; Schottelius, A. J.; Parkinson, J. F. *J. Med. Chem.* **2004**, *47*, 2157.
15. (a) Guilford, W. J.; Parkinson, J. F. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 245; (b) Bannenberg, G.; Moussignac, R.-L.; Gronert, K.; Devchand, P. R.; Schmidt, B. A.; Guilford, W. J.; Bauman, J. G.; Subramanyam, B.; Perez, H. D.; Parkinson, J. F.; Serhan, C. N. *Br. J. Pharmacol.* **2004**, *143*, 43.
16. (a) Takano, T.; Fiore, S.; Maddox, J. F.; Brady, H. R.; Petasis, N. A.; Serhan, C. N. *J. Exp. Med.* **1997**, *185*, 1693; (b) Takano, T.; Clish, C. B.; Gronert, K.; Petasis, N.; Serhan, C. N. *J. Clin. Invest.* **1998**, *101*, 819.
17. Schottelius, A. J.; Giesen, C.; Asadullah, K.; Fierro, I. M.; Colgan, S. P.; Bauman, J.; Guilford, W.; Perez, H. D.; Parkinson, J. F. *J. Immunol.* **2002**, *169*, 7063.
18. (a) Canny, G.; Levy, O.; Furuta, G. T.; Narravula-Alipati, S.; Sisson, R. B.; Serhan, C. N.; Colgan, S. P. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 3902; (b) Wallace, J. L.; Menezes de Lima, O., Jr.; Fiorucci, S. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 251.
19. (a) Gewirtz, A. T.; Collier-Hyams, L. S.; Young, A. N.; Kucharzik, T.; Guilford, W. J.; Parkinson, J. F.; Williams, I. R.; Neish, A. S.; Madara, J. L. *J. Immunol.* **2002**, *168*, 5260; (b) Fiorucci, S.; Wallace, J. L.; Mencarelli, A.; Distrutti, E.; Rizzo, G.; Farneti, S.; Morelli, A.; Tseng, J.-L.; Suramanyam, B.; Guilford, W. J.; Parkinson, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 15736.
20. (a) Levy, B. D.; De Sanctis, G. T.; Devchand, P. R.; Kim, E.; Ackerman, K.; Schmidt, B. A.; Szczeklik, W.; Drazen, J. M.; Serhan, C. N. *Nat. Med.* **2002**, *8*, 1018; (b) Levy, B. D. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 231.
21. (a) Ariel, A.; Chiang, N.; Arita, M.; Petasis, N. A.; Serhan, C. N. *J. Immunol.* **2003**, *170*, 6266; (b) Fiore, S.; Antico, G.; Aloman, M.; Sodin, S. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 189.
22. Gronert, K. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 221.
23. (a) Goh, J.; Baird, A. W.; O'Keane, C.; Watson, R. W. G.; Cottell, D.; Bernasconi, G.; Petasis, N. A.; Godson, C.; Brady, H. R.; MacMathuna, P. *J. Immunol.* **2001**, *167*, 2772; (b) Kieran, N. E.; Maderna, P.; Godson, C. *Kidney Int.* **2004**, *65*, 1145.
24. (a) Serhan, C. N.; Jain, A.; Marleau, S.; Clish, C.; Kantarci, A.; Behbehani, B.; Colgan, S. P.; Stahl, G. L.; Merched, A.; Petasis, N. A.; Chan, L.; Van Dyke, T. E. *J. Immunol.* **2003**, *171*, 6856; (b) Kantarci, A.; Van Dyke, T. E. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 289.
25. (a) Karp, C. L.; Flick, L. M.; Park, K. W.; Softic, S.; Greer, T. M.; Keledjian, R.; Yang, R.; Uddin, J.; Guggino, W. B.; Atabani, S. F.; Belkaid, Y.; Xu, Y.; Whitsett, J. A.; Accurso, F. J.; Wills-Karp, M.; Petasis, N. A. *Nat. Immunol.* **2004**, *5*, 388; (b) Karp, C. L.; Flick, L. M.; Yang, R.; Uddin, J.; Petasis, N. A. *Prostaglandins Leukot. Essent. Fatty Acids* **2005**, *73*, 263.
26. For a review see Dugave, C.; Demange, L. *Chem. Rev.* **2003**, *103*, 2475.
27. Petasis, N. A. U.S. Patent Application 2006/0270734.
28. For reviews see (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
29. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
30. Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
31. Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313.
32. Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.
33. Soundararajan, R.; Matteson, D. S. *J. Org. Chem.* **1990**, *55*, 2274.
34. Petasis, N. A.; Zavialov, I. A. *Tetrahedron Lett.* **1996**, *37*, 567.
35. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
36. Hong, S.; Gronert, K.; Devchand, P. R.; Moussignac, R. L.; Serhan, C. N. *J. Biol. Chem.* **2003**, *278*, 14677.
37. Nokami, J.; Furukawa, A.; Okuda, Y.; Hazato, A.; Kurozumi, S. *Tetrahedron Lett.* **1998**, *39*, 1005.
38. For non-LX agonists of ALXR see Burli, R. W.; Xu, H.; Zou, X.; Muller, K.; Golden, J.; Frohn, M.; Adlam, M.; Plant, M. H.; Wong, M.; McElvain, M.; Regal, K.; Viswanadhan, V. N.; Tagari, P.; Hungate, R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3713.
39. For a related paper that appeared after the reported compounds were disclosed see O'Sullivan, T. P.; Vallin, K. S. A.; AliShah, S. T.; Fakhry, J.; Maderna, P.; Scannell, M.; Sampaio, A. L. F.; Perretti, M.; Godson, C.; Guiry, P. J. *J. Med. Chem.* **2007**, *50*, 5894.