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THROMBOXANE RECEPTOR ANTAGONIST BMS-180291: A NEW PRE-CLINICAL LEAD[1]

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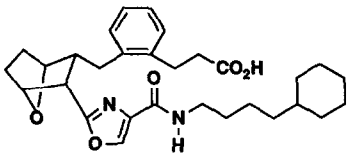
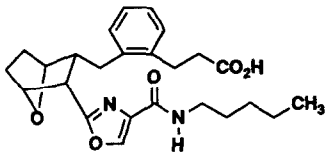
Abstract: The synthesis and initial pharmacology of interphenylene 7-oxabicyclo[2.2.1]heptane oxazole thromboxane (TxA_2) receptor antagonist BMS-180291 is described. BMS-180291 has been characterized as an orally bioavailable, potent and selective TxA_2 antagonist with a long duration of action.

Thromboxane A_2 (TxA_2)[2] is a potent, short-lived endogenous arachidonic acid derived mediator which induces platelet activation/aggregation and vasoconstriction and has been implicated as a contributor in cardiovascular, renal and pulmonary disease.[3] As part of a program to develop selective TxA_2 receptor antagonists[4] with a clinically useful duration of action, we have been involved in the identification of prostanoid-like TxA_2 antagonists with modified carboxyl side chains which would be resistant to β-oxidation (*e.g.* interphenylene[5]), an established route for the metabolic inactivation of prostaglandins. We previously described two series of potent interphenylene 7-oxabicycloheptanes with semicarbazone and 4-amido oxazole omega chains.[6,7] From the 4-amido oxazole series SQ 33,961 was found to be an extremely potent and selective TxA_2 antagonist with a long duration of action and was selected for extensive evaluation.[8] Despite an excellent pharmacological profile,



SQ 33,961



BMS-180291

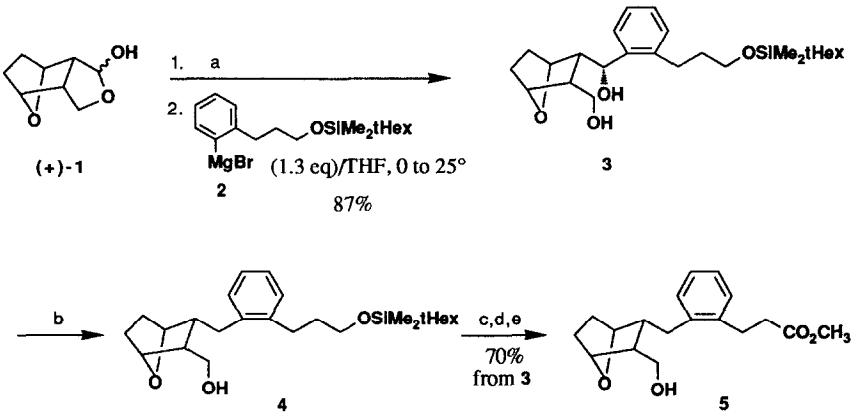
further examination of SQ 33,961 in animal models revealed it was not sufficiently orally bioavailable (<5%) for clinical development. Detailed metabolism studies in monkeys established that the low oral bioavailability of SQ 33,961 was in part a result of extensive first-pass hydroxylation with oxidation localized primarily on the lipophilic cyclohexylbutyl side chain. Based on structure-activity studies,[7] which indicated that substantial structural variability was tolerated in this region of the molecule, a number of related compounds in this series with lipophilic amide side chains less prone to oxidation were examined. From these studies BMS-180291 was identified as a TxA_2 antagonist which showed a pharmacological profile comparable to SQ 33,961 while exhibiting significantly reduced first-pass oxidative metabolism. Further biological evaluation established that BMS-180291 {[(+)1S-(1α,2α,3α,4α)]-2-[[3-[4-[(n-pentylamino)carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid} was an orally bioavailable, potent, selective TxA_2 receptor antagonist with a long duration of action. Based on its pharmacological and metabolic profile, BMS-180291 has been selected for

further development. Disclosed here in preliminary form are the synthesis and a summary of the initial pharmacology of BMS-180291.

Synthesis

BMS-180291 was prepared by elaboration of chiral tetrahydrofuranol **1**[9] as shown in Schemes I and II. We have previously described a route for introduction of the interphenylene side chain into **1** by addition of an aryllithium (2.2 eq) affording **3** and *epi*-**3** as an ~1:1 mixture of alcohol epimers.[6] Hydrogenolysis of this mixture resulted in only a 55% yield of desired alcohol **4** and was complicated by the resistance of *epi*-**3** to undergo reduction. In contrast, the stereochemical outcome employing Grignard reagents in this sequence (*i.e.* deprotonation of **1** with ethylmagnesium bromide followed by the addition of arylmagnesium bromide **2**)[10] selectively afforded crystalline diol diastereomer **3** in 87% yield.[11] Subsequent hydrogenolysis of the single epimer **3**

Scheme I: Preparation of Alcohol-Ester Intermediate 5

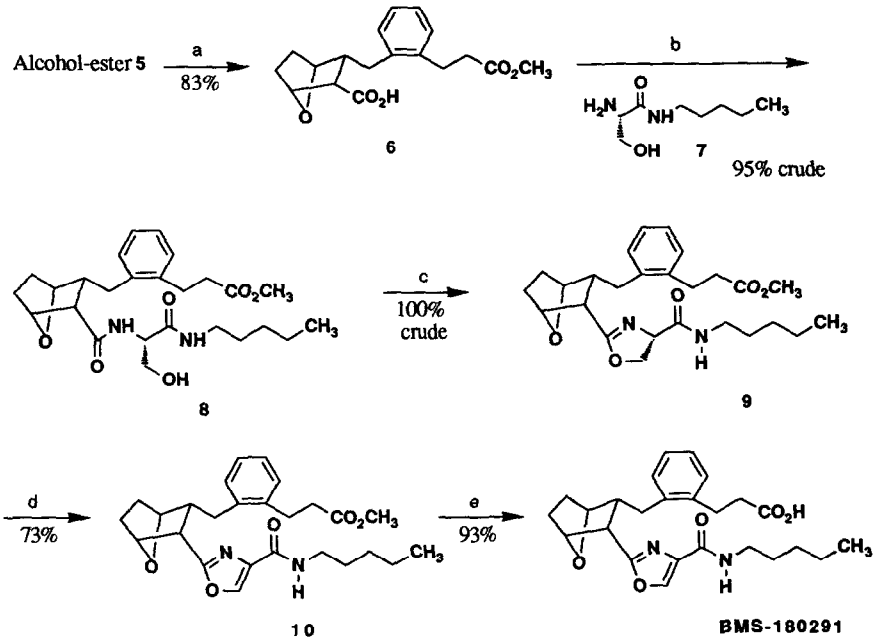


a. EtMgBr (0.95 eq)/THF, 0°; b. 20% $Pd(OH)_2$-C/HOAc/H_2 (1 atm); c. Ac_2O/py, 25°; d. Jones, 25°; e. HCl/MeOH, 25°

proceeded smoothly to give desired alcohol **4**. The protected α-chain alcohol of **4** was then selectively oxidized by a straightforward sequence which involved acetylation and treatment with excess Jones reagent followed by acid catalyzed deacetylation/esterification of the resulting crude acetate-acid product. The overall yield of key intermediate alcohol-ester **5** from **3** was 70%. BMS-180291 was available from **5** by elaboration of the ω-side chain carbinol as shown in Scheme II which began with Jones oxidation to give acid-ester **6**. The carbons required for the 4-amido oxazole substructure were introduced in the form of acyclic serine amide **7**[12] by WS-carbodiimide/HOBT mediated coupling to afford **8**. Diamide **8** was cyclized to oxazoline **9** by mesylation followed by treatment with excess triethylamine. The non-trivial conversion of oxazoline **9** to oxazole **10** was accomplished by a novel copper(II) bromide/DBU oxidation.[13] The procedure involved addition of a $CHCl_3$ solution of oxazoline **9** to a stirred suspension of copper(II) bromide (2 eq) in DBU (4 eq)/ethyl acetate at room temperature under argon. The resulting dark colored reaction mixture was monitored by TLC and additional

portions of copper(II) bromide and DBU were introduced until starting oxazoline was nearly consumed. Generally, 4-6 eq of copper(II) bromide were required and the yields of oxazole were 50-80%. Aqueous base hydrolysis of ester **10** followed by recrystallization gave BMS-180291 as a high melting, stable white solid.[14]

Scheme II: Preparation of BMS-180291 from Alcohol-Ester 5



a. Jones, 25°; b. WSC/4-Methylmorpholine/HOBT/DMF, 0 to 25°; c. MsCl/Et_3N/CH_2Cl_2, 0° then Et_3N/CH_2Cl_2, 25°; d. $CuBr_2$/DBU/EtOAc-$CHCl_3$ (1:1), 25°; e. NaOH/aq THF, 25°.

Pharmacology

In human platelet-rich plasma (PRP) BMS-180291 inhibited arachidonic acid-induced (800 μM) and U46,619-induced (10 μM) platelet aggregation with I_{50} values of 6 and 20 nM, respectively.[15] In contrast, at 1 mM BMS-180291 produced no inhibition of ADP-induced (20 μM) platelet aggregation in human PRP, TxA_2 synthase in human PRP, or cyclooxygenase activity in platelets or bovine seminal vesicle microsomes. In human platelets BMS-180291 antagonized the U46,619-induced aggregation response in a non-competitive manner while the shape change response was antagonized in a competitive manner. Radioligand binding studies in human platelet membranes using TxA_2 receptor radioligand [^{3}H]-SQ 29,548 showed a K_d value of 4.03±1.04 nM for BMS-180291 with a slope factor of 1.06 consistent with competitive receptor binding.[16] In rat aortas BMS-180291 competitively inhibited U46,619-induced contractions with a K_B of 0.56 nM. Importantly, BMS-180291 produced no evidence of agonistic activity either *in vitro* or *in vivo*. Duration studies in conscious mice showed that BMS-180291 (0.2 mg/kg, po) provided extended protection (T_{50}=14 hr) from U46,619-induced (2 mg/kg, iv) death.[17] In addition, a single oral dose of BMS-180291 (3 mg/kg) abolished U46,619-induced platelet

aggregation *ex vivo* in African green monkeys for ≥24 hr supporting potential once a day clinical dosing. Finally, preliminary metabolism studies in African green monkeys with [^{3}H] BMS-180291 (1 mg/kg) indicated an oral bioavailability of 20-25%. Detailed SAR, pharmacological and metabolism studies of BMS-180291 will be discussed in future reports.

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   (c) Ogletree, M. L. *Federation Proc.* **1987**, *46* (1), 133-138.
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10. Grignard **2** was prepared from the corresponding aryl bromide[6] (Mg/THF, reflux, cat $I_2/(CH_2Br)_2$).
11. ^{1}H NMR($CDCl_3$) analysis of the crude reaction mixture showed **3**/*epi*-**3** ratio was ~95:5.
12. Serine amide **7** (white solid, mp 77-78°) was prepared in 2 steps from CBZ-L-serine by coupling with amylamine (WSC/HOBT/DMF, 0 to 25°, 69%) followed by CBZ-deprotection (20% $Pd(OH)_2$-C/CH_3OH/H_2 (1 atm), 85%).
13. Similar reaction conditions have been used to α-brominate ketones, see: King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29* (1), 3459-3461 and references cited therein.
14. Characterization of BMS-180291: white solid, mp 148-150° (CH_3CN); IR(KBr): 3406 (broad), 2955, 1726, 1709, 1649, 1603, 1522, 1217 cm^{-1}; 270 MHz ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* =7, 3H), 1.20-1.95 (m, 10H), 2.22 (dd, *J* =5,14, 1H), 2.33 (dd, *J* =14,14, 1H), 2.56 (t, *J* =7, with overlapping 1 H m, 3H total), 2.91 (t, *J* =8, 2H), 3.38 (m, 3H), 4.41 (d, *J* =5, 1H), 4.98 (d, *J* =5, 1H), 7.14 (m, 5H), 8.16 (s, 1H); 67.8 MHz ^{13}C NMR ($CDCl_3$) δ 13.9, 22.3, 27.3, 28.8, 29.0, 29.2, 29.8, 32.5, 34.8, 39.1, 46.9, 49.9, 78.6, 79.7, 126.5, 126.7, 128.9, 129.7, 135.8, 137.7, 138.4, 141.0, 160.8, 163.9, 176.7; MS(CI): *m/z* 441 ($M+H^+$); OR: $[\alpha]_D$ = +23° (c=0.5 in $CHCl_3$).
15. (a) Assay as described by Harris, D. N.; Phillips, M. B.; Michel, I. M.; Goldenberg, H. J.; Heikes, J. E.; Sprague, P. W.; Antonaccio, M. J. *Prostaglandins* **1981**, *22* (2), 295-307; the AAIPA and U-IPA I_{50} of BM13.505 were 730 nM and 1600 nM and those of GR 32,191 were 33 nM and 59 nM, respectively, under identical assay conditions.
    (b) Ogletree, M. L.; Harris, D. N.; Schumacher, W. A.; Hall. S. E.; Brown, B. R.; Misra, R. N. *Circulation*, in press.
16. Assay as described by Hedberg, A.; Hall, S. E.; Ogletree, M. L.; Harris, D. N.; Liu, E. C.-K. *J. Pharmacol. Exp. Ther.* **1988**, *245* (3), 786-792.
17. The T_{50} value is defined as the calculated time from dosing that one half of the population survives U-46,619 challenge. For a description of the assay see: Kohler, C.; Wooding, W.; Ellenbogen, L. *Thromb. Res.* **1976**, *9* (1), 67-80. The T_{50} of BM13.505 was 7.1 hr and that of GR 32,191 was 0.5 hr, under identical assay and dosing conditions.