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BIARYLCARBOXAMIDE INHIBITORS OF PHOSPHODIESTERASE IV AND TUMOR NECROSIS FACTOR-α

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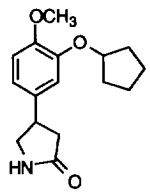
Abstract. Tumor necrosis factor-α (TNF-α) has been implicated as a key mediator in the progression of rheumatoid arthritis. Inhibitors of phosphodiesterase IV (PDE IV) have been shown to inhibit the production of TNF-α by elevating intracellular levels of cyclic adenosine monophosphate (cAMP). Our efforts in a series of biarylcarboxamides have led to the identification of **8j** (CP-353,164) as a potent inhibitor of PDE IV and TNF-α production.

Introduction. Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine produced primarily by monocytes and macrophages, which have been implicated as key mediators in the progression of rheumatoid arthritis.[1] The clinical efficacy of a chimeric monoclonal TNF-α antibody in the treatment of rheumatoid arthritis patients has been demonstrated, thus clinically validating TNF-α as a therapeutic target.[2] Rolipram **1** is a selective inhibitor of phosphodiesterase IV(PDE IV) and has been shown to block TNF-α production by elevating intracellular levels of cyclic adenosine monophosphate (cAMP) and subsequently inhibiting TNF-α mRNA expression.[3] SB-207,499[4] **2** has also been shown to block production of TNF-α by inhibiting PDE IV and is reported to be undergoing clinical evaluation.[5] We would like to report that biarylcarboxamides **8a-n** block the production of TNF-α by inhibiting PDE IV and elevating intracellular levels of cAMP and therefore would be useful therapeutic agents in the treatment of rheumatoid arthritis.

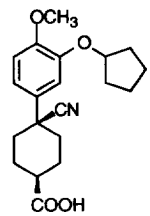
Chemistry. Biarylcarboxamides **8a-n** were prepared in four steps from 5-bromoguaiacol[6] **3** (Scheme I). Etherification[7] of phenol **3** with an appropriately substituted alcohol gave catechol diether **4**. Palladium catalyzed coupling[8] of catechol diether **4** with either an appropriately substituted aryl halide or aryl triflate (Z=I, Br, OTf) **5** yielded esters **6a-n**. Saponification of esters **6a-n** with sodium hydroxide afforded carboxylic acids **7a-n**. Treatment of carboxylic acids **7a-n** with thionyl chloride followed by reaction of the intermediate acid chlorides with ammonia gave carboxamides **8a-n**.

Figure 1



Rolipram

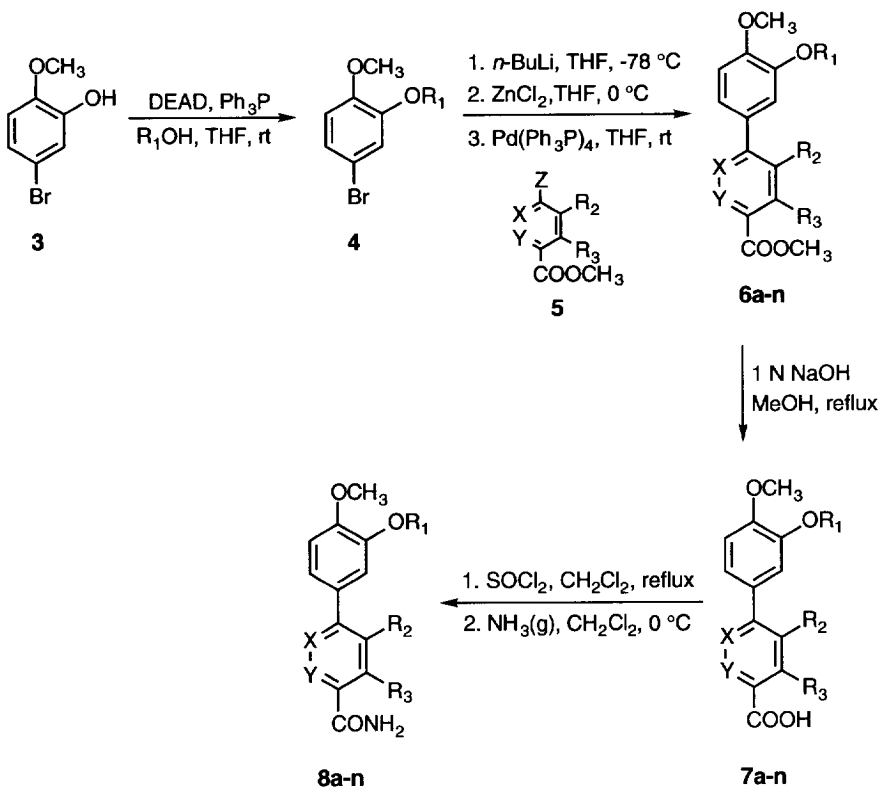
1



SB-207,499

2

Scheme I



Biology. Compounds were evaluated for their ability to block the release of TNF-α in human monocytes.[9] Selected compounds were evaluated for their ability to block the release of TNF-α in human whole blood[10] as well as their ability to inhibit the hydrolysis of cAMP by monocyte cytosol phosphodiesterase[9] and elevate intracellular levels of cAMP in human U937 cells.[11] Compounds **1**, **2**, and **8j** were evaluated for their ability to block murine TNF-α release.[12] Compounds **1** and **2** were dosed po in 0.5% CMC vehicle and **8j** was dosed ip in 30% cremophor EL/10% PEG 400/60% water vehicle.

Table I. TNF-α production in human monocytes.

Compound	R_1	R_2	R_3	X	Y	TNF-α human monocytes IC_{50} μM (± S.E.M)
1						0.31 ± 0.08
2						0.29 ± 0.02
7a	(*S*)-(+)-exo-norbornyl[b]	H	H	C	C	0.14 ± 0.03
8a	(*S*)-(+)-exo-norbornyl[b]	H	H	C	C	0.024 ± 0.004
8b	cyclopentyl	H	H	C	C	0.026 ± 0.02
8c	2-indanyl	H	H	C	C	0.32 ± 0.22
8d	cyclopentyl	Cl	H	C	C	0.26[a]
8e	cyclopentyl	H	Cl	C	C	0.082 ± 0.14
8f	cyclopentyl	H	CF_3	C	C	1.17 ± 0.66
8g	cyclopentyl	H	CH_3	C	C	0.19 ± 0.11
8h	cyclopentyl	H	H	N	C	0.080 ± 0.03
8i	cyclopentyl	Cl	H	N	C	0.36[a]
8j	cyclopentyl	H	H	C	N	0.037 ± 0.02
8k	(*S*)-(+)-exo-norbornyl[b]	H	H	C	N	0.009 ± 0.006
8l	2-indanyl	H	H	C	N	0.12 ± 0.06
8m	2-phenylethyl	H	H	C	N	0.18[a]
8n	3-phenylpropyl	H	H	C	N	2.31[a]

[a]single determination; [b]e.e. >87%[13]

Results and Discussion. Our efforts in a series of biarylcarboxylic acids that inhibit PDE IV[14] led to the identification of **7a** as a potent inhibitor of TNF-α release by human monocytes (Table I). Conversion of the carboxylic acid in **7a** to a carboxamide led to **8a** with a sixfold increase in potency. Replacement of the *exo*-

norbornyl ring in **8a** with a cyclopentyl ring as in Rolipram **1** and SB-207,499 **2**, gave **8b**, which was equipotent to **8a**. Replacement of the cyclopentyl ring in **8b** with a 2-indanyl ring yielded **8c**, which had reduced potency. Introduction of substituents into the benzamide ring of **8b** proved not to be tolerated and led to a loss in potency (**8d-g**). Replacing the benzamide ring in **8b** with a 2-pyridine-5-carboxamide ring gave **8h**, which had reduced potency in comparison to **8b**. However, substituting the benzamide ring in **8b** with a 5-pyridine-2-carboxamide ring gave **8j**, which was comparable to **8b** in potency. Substituting the cyclopentyl ring in **8j** with an *exo*-norbornyl ring led to **8k** with a fourfold increase in potency. Substituting the cyclopentyl ring in **8j** with either 2-indanyl (**8l**), 2-phenylethyl (**8m**), or 3-phenylpropyl (**8n**) moeities led to a decrease in potency. Thus it would appear that the replacement of the catechol cyclopentyl or exo-norbornyl rings with larger substituents cannot be tolerated, leading to decreased potency.

With analogs **8a-b** and **8j-k** identified as the most potent inhibitors of TNF-α release in human monocytes, we next focused our efforts on demonstrating that these compounds inhibit TNF-α release in human whole blood (Table II). Analogs **8a-b** and **8j-k** showed reduced potency in human whole blood compared to the potency observed in human monocytes, presumably due to serum protein binding of the compounds. However, analogs **8a-b** and **8j-k** proved to be more potent than Rolipram **1** and SB-207,499 **2** in inhibiting TNF-α release in both human monocytes and human whole blood.

Table II. TNF-α inhibition in human whole blood and PDE IV inhibitory activity.

Compound	TNF-α human whole blood IC_{50} μM (± S.E.M.)	PDE human monocytes IC_{50} μM (± S.E.M.)	cAMP human U937 cells IC_{50} μM (± S.E.M)
1	0.66 ± 0.21	4.75 ± 1.42	1.23 ± 0.22
2	6.12 ± 1.43	0.36 ± 0.04	3.63 ± 2.35
8a	0.18 ± 0.09	3.61 ± 2.22	0.022 ± 0.001
8b	0.45 ± 0.02	5.91 ± 1.82	0.081 ± 0.06
8j	0.18 ± 0.08	0.34 ± 0.12	0.046 ± 0.02
8k	0.14 ± 0.04	1.07 ± 0.42	0.049 ± 0.04

We next wanted to show that the mechanism of action by which **8a-b** and **8j-k** blocks TNF-α release is by inhibiting PDE IV and thus elevating intracellular levels of cAMP (Table II). **8j** proved to be the most potent analog in inhibiting the hydrolysis of cAMP by monocyte cytosol phosphodiesterase and was more potent than Rolipram **1** and equipotent to SB-207,499 **2**. Compound **8a** showed the greatest potency in elevating

intracellular levels of cAMP in whole human U937 cells and was more potent than both Rolipram **1** and SB-207,499 **2**. However, **8j** demonstrated the best balance of activities overall.

With **8j** identified as possessing the best activity profile, we turned our attention to demonstrating that **8j** blocks TNF-α release in vivo (Table III). Like Rolipram **1** and SB-207,499 **2**, **8j** proved to be potent in blocking LPS stimulated TNF-α release in mice.

Table III. Inhibition of Murine TNF-α release.

Compound	Murine TNF-α production % Inh. (± S.E.M) @ conc.
1	68.0 ± 2.7% @ 1 mg/kg
2	59.4 ± 7.3% @ 10 mg/kg
8j	65.2 ± 5.3% @ 1 mg/kg

Conclusion. **8j** (CP-353,164) is a potent inhibitor of TNF-α release in vitro, in isolated human monocytes and human whole blood, and in vivo in a murine TNF-α production model. The ability of **8j** to block TNF-α release was found to be due to inhibition of PDE IV and subsequent elevation of intracellular levels of cAMP. **8j** is also significantly more potent in blocking the release of TNF-α than Rolipram **1** and SB-207,499 **2**.

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