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SYNTHESIS OF DIBENZO[a,d]CYCLOHEPTANES AS CYTOKINE BIOSYNTHESIS INHIBITORS

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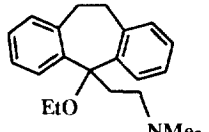
Abstract: 2-[10,11-Dihydro-5-ethoxy-5H-dibenzo[a,d]cyclohepten-5-yl]-N,N-dimethyl-ethanamine (**1**) has been found to possess anticytokine activity. The synthesis and structure-activity relationship study of a series of analogues are reported.

The regulation of cytokine function as an approach towards the treatment of immunological and inflammatory disorders is an area of growing interest.[1] Screening of selected compounds from our corporate database identified 2-[10,11-dihydro-5-ethoxy-5H-dibenzo[a,d]cyclohepten-5-yl]-N,N-dimethyl-ethanamine (**1**) as an inhibitor of the synthesis or release of tumor necrosis factor-α (TNF-α) from a murine monocytic cell line stimulated with lipopolysaccharide (LPS)[2] with an IC_{50} = 1.7 ± 0.6 μM. Subsequently, we found that **1** and related analogues inhibit the accumulation of the inflammatory cytokines interleukin-1α (IL-1α), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and γ-interferon (γ-IFN) in the serum of *C. parvum*-primed mice.[3] We now report our initial findings from the structure-activity relationship study of **1**. Since the ethoxy group in **1** was cleaved in 1 N HCl within 1 h at room temperature to produce the corresponding inactive hydroxy derivative **15a** (IC_{50} > 10 μM for *in vitro* TNF-α), one objective of our study was to find an acid-stable replacement for this potential site of metabolism.



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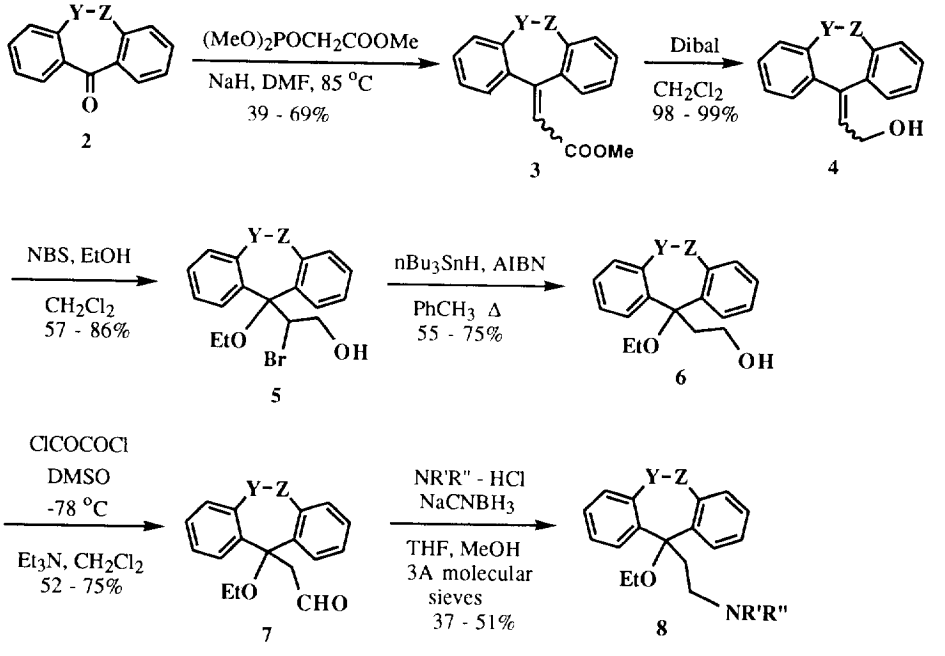
Chemistry

The compounds[4,5] evaluated in our investigation were synthesized as shown in Schemes 1 and 2. The 10,11-dihydro-5-ethoxy-5H-dibenzo[a,d]cycloheptene derivatives **8** were prepared

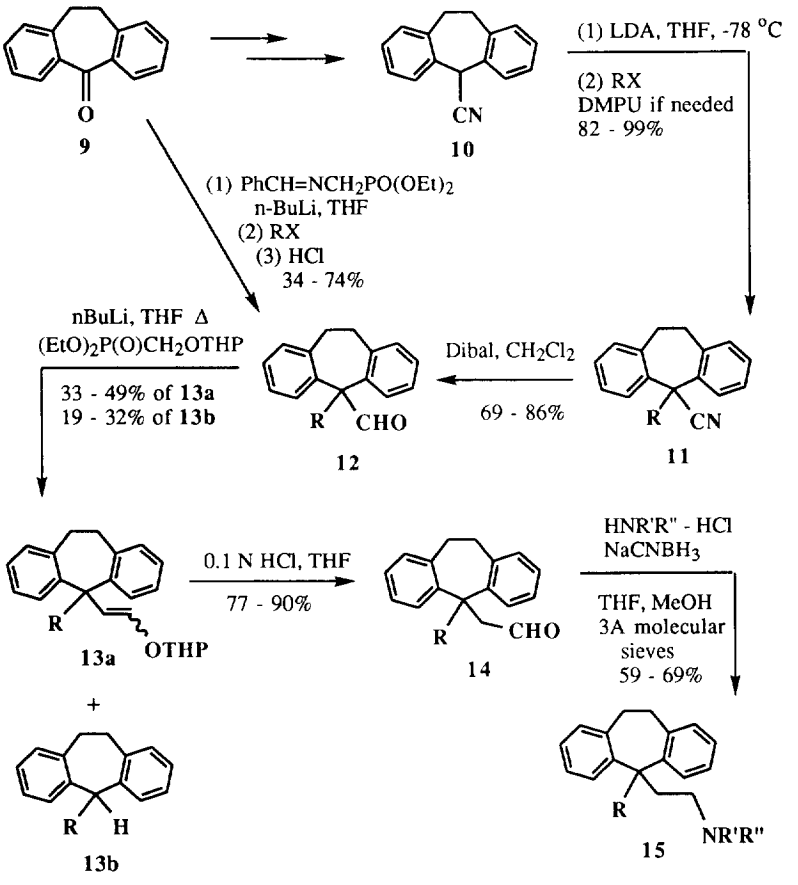
by a Horner-Emmons reaction[6] on ketone **2**,[7] followed by Dibal reduction[8] of the resulting ester **3** to the corresponding alcohol **4**. N-Bromosuccinimide[9] promoted Markovnikov addition of ethanol to the double bond gave the bromoether intermediate **5**. Radical reduction[10] to remove the bromide and Swern oxidation[11] of primary alcohol **6** provided the key aldehyde **7**. Various analogues **8** were obtained by reductive amination[12] of aldehyde **7**.

Scheme 1



Two synthetic routes were used to construct the 5-alkyl-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene compounds **15**. The 5-alkyl substituent could be introduced by alkylation of the known nitrile **10**.[13] Alkylated nitrile **11** was transformed into the corresponding aldehyde **12** by Dibal reduction.[8] Alternatively, a metalloenamine reaction[14] was employed to form the quaternary center of aldehyde **12** directly from ketone **9**.[7] A one carbon homologation was accomplished with the Kluge phosphonate reagent[15] which produced the enol ether **13a** and afforded aldehyde **14** after mild acid hydrolysis. An undesired component of the Kluge phosphonate reaction was the retro-aldol type product **13b**. Reductive amination[12] of aldehyde **14** yielded the target analogues **15**.

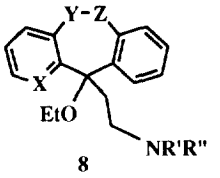
Scheme 2



Biology and Structure-Activity Relationships

Following oral administration, lead compound **1** inhibited the synthesis or release of IL-1α, IL-6, TNF-α and γ-IFN in *C. parvum*-primed mice treated with LPS (Table 1).[3] Replacement of an aromatic carbon atom in the tricyclic portion of **1** with a nitrogen atom to obtain **8a** resulted in the loss of inhibitory activity against all the cytokines investigated. Introduction of unsaturation into the cycloheptane ring resulted in analogue **8b**, which exhibited reduced cytokine inhibitory potency relative to **1**. The dimethylamino group in **1** could be replaced by a pyrrolidine ring as in **8c** with retention of anticytokine activity albeit with reduced

potency against IL-1α and γ-IFN. However, rendering the amino group nonbasic by the formation of an amide bond to produce **8d** completely removed cytokine inhibitory activity.



8

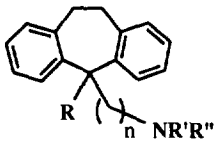
Table 1

Compound	X	Y-Z	NR'R"	Inhibition of Serum Cytokine Levels ED_{50} (mg / kg), p.o.			
				IL-1α	IL-6	TNF-α	γ-IFN
1	C	C-C	NMe_2	2.4 (0.97-4.3)	8.0 (4.8-14.0)	17.6 (9.9-41)	1.3 (0.43-2.4)
8a	N	C-C	NMe_2	>25	>25	>25	>25
8b	C	C=C	NMe_2	>6.25	>25	>25	13.2
8c	C	C-C	pyrrolidine	11.1	ND	16.1	11.3
8d	C	C-C	NMeAc	>25	>25	>25	>25

ND not determined

Values in parentheses are confidence intervals determined at 95%, $p = 0.05$.

Since it was demonstrated that the ethoxy group in **1** was susceptible to hydrolysis under acidic conditions resulting in the inactive hydroxy analogue **15a**, effort was directed to identify a surrogate for the ethoxy group that was hydrolytically stable to acid, and maintained anticytokine inhibitory potency. Extension of the ethoxy group in **1** by introduction of a methylene group between oxygen and the tricyclic nucleus reduces cytokine inhibitory potency (Table 2: compare **1** and **15b**). Removal of one of the methyl groups from the amine terminus of ethoxy-extended compound **15b** eliminates the ability of resulting analogue **15c** to inhibit cytokine synthesis or release.



15

Table 2

Cmpd	n	R	NR'R"	Inhibition of Serum Cytokine Levels ED_{50} (mg / kg), p.o.			
				IL-1α	IL-6	TNF-α	γ-IFN
1	2	OEt	NMe_2	2.4	8.0	17.6	1.3
15a	2	OH	NMe_2	>25	>25	>25	>25
15b	2	CH_2OEt	NMe_2	18.1	>25	19.6	13.5
15c	2	CH_2OEt	NHMe	>25	>25	>25	>25
15d	2	propyl	NMe_2	6.25	23.3	ND	10.8
15e	3	propyl	NMe_2	8.7 (4.0-22.8)	15.8 (7.5-55.4)	>25	5.9 (3.0-11.4)
15f	1	propyl	NMe_2	>25	25	>25	3.9
15g	2	hexyl	NMe_2	>25	>25	>25	>25

ND not determined

Values in parentheses are confidence intervals determined at 95%, $p = 0.05$.

Replacement of the oxygen atom in the ethoxy group of **1** with a methylene group resulted in the n-propyl analogue **15d**, which exhibited significant anticytokine activity against IL-1α and γ-IFN, but reduced anticytokine activity against IL-6. Lengthening the chain to the dimethylamino group by one additional carbon atom resulted in **15e** which exhibited anticytokine activity against IL-1α, IL-6, and γ-IFN, but was inactive against TNF-α.

In contrast, shortening the chain to the dimethylamino group by one carbon atom resulted in **15f**, which exhibited cytokine inhibitory potency only against γ-IFN. Replacement of the ethoxy side chain in **1** with the longer n-hexyl substituent incorporated in analog **15g**, completely removed anticytokine activity.

Based on these observations, it may be concluded that the anticytokine activity for this series of 5,5-disubstituted-dibenzo[a,d]cycloheptanes is very sensitive to minor structural

modifications. Nevertheless, the acid-labile ethoxy substituent in our lead compound 2-[10,11-dihydro-5-ethoxy-5H-dibenzo[a,d]cyclohepten-5-yl]-N,N-dimethyl-ethanamine (**1**) could be replaced with the n-propyl group found in compound **15e** with retention of cytokine inhibitory potency against IL-1α, IL-6, and γ-IFN.

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References and Notes:

1. Cooper, K.; Masamune, H. *Ann. Rep. Med. Chem.* **1992**, *27*, 209; and references therein.
2. Inhibition of LPS-induced TNF-α production in vitro was determined in WEHI-265 cells cultured for 24 h at 10^5 cells / mL with 3 μg / mL LPS and analyzed by a TNF-α specific enzyme-linked immunosorbent assay (ELISA). For details of ELISA see: Sheehan, K. C. F.; Ruddle, N. H.; Schreiber, R. D. *J. Immunol.* **1989**, *142*, 3884.
3. Smith, S. R.; Terminelli, C.; Kenworthy-Bott, L.; Calzetta, A.; Donkin, J. *J. Leukoc. Biol.* **1994**, *55*, 711.
4. Satisfactory spectroscopic and analytical data was obtained on all new compounds.
5. For the synthesis of the pyridine compound **8a** see: Villani, F. J.; Daniels, P. J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C.; Wefer, E. A. *J. Med. Chem.* **1972**, *15*, 750. Compound **15e** was prepared as follows: addition of trimethylphosphonoacetate to aldehyde **12**, reduction with lithium aluminum hydride, Swern oxidation, and reductive amination. Compound **15f** was prepared by reduction of nitrile **11** with sodium borohydride and cobalt dichloride to the primary amine followed by methylation with formaldehyde in formic acid.
6. Wadsworth, W. S. *Org. React.* **1977**, *25*, 73.
7. Available from the Aldrich Chemical Company.
8. Winterfeldt, E. *Synthesis* **1975**, 617.
9. Dalton, D. R.; Dutta, V. P.; Jones, D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5498.
10. Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.
11. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
12. Borch, R. F.; Bernstein, M. D.; Dupont Durst, H. *J. Am. Chem. Soc.* **1971**, *93*, 2987.
13. Davis, M. A.; Winthrop, S. O.; Stewart, J.; Sunahara, F. A.; Herr, F. *J. Med. Chem.* **1963**, *6*, 251.
14. Martin, S. F.; Phillips, G. W. ; Puckette, T. A. ; Colapret, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 5866.
15. Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847.

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