Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 18, pp. 2143-2146, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00363-0

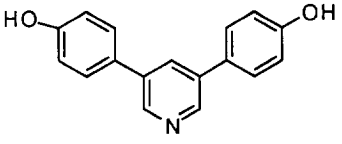
SYNTHETIC INHIBITORS OF INTERLEUKIN-6 II: 3,5-DIARYL PYRIDINES AND META-TERPHENYLS

Jayaram R. Tagat *[a], Stuart W. McCombie [a], Beverly E. Barton *[b], James Jackson [b] and Jennifer Shortall [b]

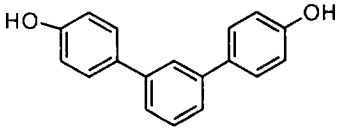
Departments of (a) Chemical Research and (b) Immunology, Schering-Plough Research Institute
2015 Galloping Hill Road, Kenilworth, New Jersey 07033-0539, USA

Abstract : An efficient synthesis of the title compounds using the Ni (II) catalysed coupling of various aryl magnesium bromides with di-halo pyridines and di-halo benzenes is reported. Among the several compounds tested, **1**, **2**, **12** and **17** showed good inhibitory activity against interleukin-6.

Discovering small molecules which modulate the action of cytokines is an area of current therapeutic interest.[1] During a program directed towards finding novel compounds which inhibit the synthesis of interleukin-6, a pleiotropic cytokine involved in several inflammatory and some tumorogenic pathways,[2] we found SCH-21418 (**1**) had good inhibitory activity. Subsequently a systematic synthetic study revealed that the corresponding meta-terphenyls **2** also had comparable activity; the results of this study are reported in this paper.



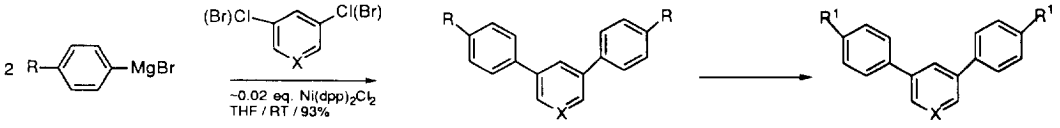
1. Sch-21418



2. Sch-53020

Chemistry: The nickel and palladium catalysed coupling of organometallic reagents to aryl halides is well known.[3] Accordingly, the Grignard reagent **3** derived from p-bromoanisole (2 equivalents) was added to 3,5-dichloropyridine **4** in the presence of a catalytic amount of [1,3-bis(diphenylphosphino) propane] Nickel (II) chloride. The 3,5-dianisylpyridine **5** thus obtained was then demethylated with boron tribromide to furnish **1** in 70% yield (Scheme 1).

Scheme 1: A General Synthesis of the Title Compounds



3. R = OMe

6. R = F

7. R = $CH(OMe)_2$

4. X = N

11. X = CH

5. R = OMe ; X = N

8. R = F ; X = N

9. R = $CH(OMe)_2$; X = N

12. R = OMe ; X = CH

13. R = $CH(OMe)_2$; X = CH

1. R^1 = OH ; X = N

10. R^1 = CHO; X = N

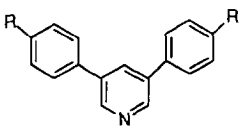
2. R^1 = OH ; X = CH

14. R^1 = CHO; X = CH

15. R^1 = H ; X = N

It is noteworthy that the inexpensive dichloropyridines could be used in this reaction in contrast to most literature procedures which use the more expensive dibromo or diiodo derivatives. Functionalized Grignard reagents **6** and **7** derived from p-fluorobromobenzene and p-bromobenzaldehyde dimethylacetal respectively could be used in this sequence with equal facility to provide targets **8** and **9**. The corresponding meta-terphenyls were prepared by the reaction of the same Grignard reagents with dibromobenzenes mediated by the same Ni(II) catalyst. The bis-aldehydes **10** and **14** had functional handles that could be further elaborated into other targets such as the bis-alcohols, bis-oximes, bis-acids and bis-amines (**16-23**). Similar variations of the heterocyclic component were possible as exemplified by the synthesis of 2,6-dianisyl pyrazine **24** from its dichloro parent (Scheme 2).[4]

Scheme 2

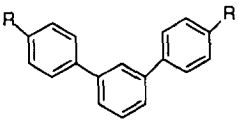


16. R = CH_2OH ($NaBH_4$, 100%)

17. R = COOH ($AgNO_3$-KOH, 68%)

18. R = CH=N-OH (NH_2OH, 79%)

19. R = CH_2NMe_2 (from **16** via chloride, 42%)

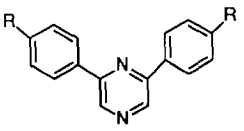


20. R = CH_2OH (70%)

21. R = COOH (60%)

22. R = CH=N-OH (70%)

23. R = CH_2NMe_2 (50%)

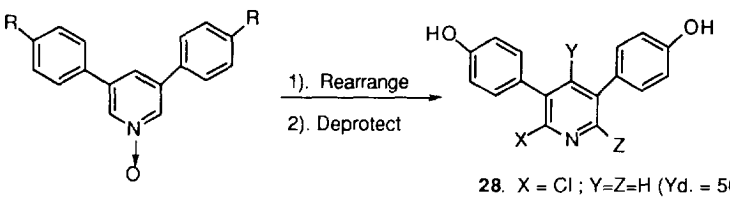


24. R = OMe

25. R = OH (55%)

Substitution on the central pyridine ring was made possible by classical N-oxide chemistry (Scheme 3). Thus, compound **5** was oxidised using m-CPBA to its N-oxide **25** . The latter reacted uneventfully with $POCl_3$, Ac_2O and BzCl-KCN to form the chloro, hydroxy and cyano derivatives.[5]

Scheme 3 : Substitution on the Pyridine Ring



26. R = OMe

27. R = OH (via R=OAc, 70%)

28. X = Cl ; Y=Z=H (Yd. = 56%)

29. Y = Cl ; X=Z=H (Yd. = 30%)

30. X = Z = Cl ; Y=H (Yd. = 49%)

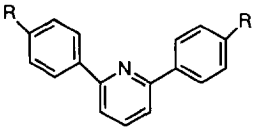
31. X=Y=H ; Z=OH (2-Pyridone)

32. X=Y=H ; Z=CN (Yd. = 70%)

The regioisomeric diarylpyridines **33-38** were similarly prepared by starting with the appropriate dibromopyridines (Scheme 4). Grignard reagents derived from o-bromo and m-bromo anisoles were coupled to 3,5-dichloropyridine and to 1,3-dibromobenzene to provide the ortho-and meta-substituted compounds **39-44**.

The mono-aryl pyridines **45-47** were also included in this study for comparison. IL-6 inhibitory data on these compounds is given in Table 1(SD = Standard Deviation) and discussed in the following section.

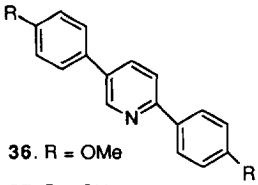
Scheme 4



33. R = OMe

34. R = OH

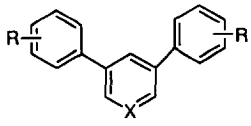
35. R = F



36. R = OMe

37. R = OH

38. R = F



39. X=N ; R=OH (3'-3')

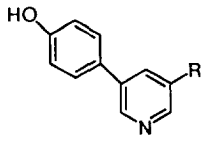
40. X=N ; R=OH (2'-2')

41. X=CH ; R=OMe (3'-3')

42. X=CH ; R=OH (3'-3')

43. X=CH ; R=OMe (2'-2')

44. X=CH ; R=OH (2'-2')



45. R = H

46. R = Cl

47. R = Me

Table 1 : In Vitro IL-6 Inhibitory Activity of Compounds used in this Study

Compd. #	% Inhibition @ 10 μM (±SD)	Compd. #	% Inhibiton @ 10 μM (±SD)	Compd. #	% Inhibition @ 10 μM (±SD)
1	73 (±7)	**22**	46	**36**	30
2	85 (±11)	**23**	cytotoxic !	**37**	27
5	0	**25**	55	**38**	47
8	44	**27**	37	**39**	59
12	75 (±5)	**28**	61	**40**	23
15	8	**29**	60	**41**	24
16	68 (±8)	**30**	52	**42**	21
17	84 (±9)	**31**	49	**43**	22
18	70 (±5)	**32**	40	**44**	21
19	60	**33**	55	**45**	0
20	62	**34**	23	**46**	0
21	50	**35**	44	**47**	7

Biology : All compounds were screened at 10 μM for the inhibition of lipopolysaccharide (LPS)-induced IL-6 production in murine myelomonocytic leukemia (WEHI-265.1) cells. The level of IL-6 was assessed by ELISA.[6] Compounds which exhibited atleast 70% inhibition at 10 μM were then tested several ($\geq$3) times to confirm activity and obtain an IC_{50}; less active compounds were tested $\leq$3 times. Selected compounds were then progressed to an in vivo assay in which they were tested as described in the preceding paper.[2]

The general trends observed in structure-activity relationship gleaned from the above table can be summarized as follows : Comparison of the activities of compounds **1, 34** and **37** clearly indicates that a 3,5-orientation of the aryl groups with respect to the pyridine nitrogen is preferrred, making 3,5-diaryl pyridine our active pharmacophore; this is also confirmed by the lack of activity of the mono-aryl pyridines **45-47**. An additional nitrogen in the central ring slightly reduces the activity (pyrazine analog **25**). That the higher polarity of the central ring may be deleterious can also be seen in the reduced activities of the chloro pyridines (**28-30**) and of the cyano compound **32** as well as the lack of activity of the N-oxide **27** and the 2-pyridinone **31**. On the other hand, polar groups are preferred on the two aryl rings, the trend being CO_2H > OH~CH_2OH > CH=N-OH > F > OMe ~ H (**1, 5, 8, 16-19**). We also observed that the aryl sustituent exerts its best effect when it is at the para position with respect to the pyridine ring rather than at the ortho or meta positions (**1** vs. **39** and **40**). With the goal of making the central ring non-polar, we initiated the meta-terphenyl series which also exhibited the " para effect " of the peripheral substituents (cf : **2, 12** vs. **41-44**). Interestingly, higher polarity of the substituent in the meta-terphenyls slightly diminishes the activity (**2, 12** vs. **20-23**) in contrast to the diaryl pyridine series. IC_{50} s were determined only for our best compounds : 0.4 μM (**1**) and 1.5 μM (**2**).

Compound **1** showed 63% (i.p) and 71% (p.o) inhibition of serum IL-6 at 25 mpk giving an ED_{50} of 2.8 mpk. The meta terphenyl analog **2** showed 88% inhibition (25 mpk, p.o) of IL-6 in vivo with an ED_{50} of 1.5 mpk. These compounds did not show any inhibition of TNF-α, IL-1 and IL-5. Evaluation of our best IL-6 inhibitors disclosed in this and in the preceding paper in relevant disease models will be reported in due course.

Acknowledgement : We thank Drs. Ashit Ganguly and John Piwinski (SPRI) for discussions.

References and Notes

1. Cooper, K.; Masamune, H. *Ann. Rep. Med. Chem.* **1992**, *27*, 209.
2. Tagat, J. R. ; Nazareno, D. V.; McCombie, S. W.; Barton, B. E.; Shortall, J.; Jackson, J. *Bioorg. Med. Chem. Lett.* previous paper in this issue. See references 5 and 6 therein.
3. (a). Kalinin, V. *Synthesis* **1992**, 413. (b). Jolly, P. W. in *Comp. Org. Met. Chem.*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol 8, 713.
4. All compounds reported herein were fully characterized by spectral and analytical data. Melting Points (°C) : **1**: >290; **2** : 177-179; **5** : 228-229; **8** : 184-186; **10** : 238-240; **12** : 192-194; **16** : 224-225; **17** : >300; **18** : 212-215; **20** : 194-197; **21** : >300; **22** : 186-188; **24** : 125-127; **25** : 280 (dec); **28** : 225-227; **30** : 118-120; **32** : 200 (dec); **33** : 155-157; **34** : 160 (dec); **35** : 69-72; **36** : 217-219; **38** : 190-192; **39** : 275 (dec); **40** : 265 (dec); **41** : 55-57; **42** : 90-92; **43** : 80-82; **44** : 103-105; **45** : 78-80; **46** : 249-250; **47** : 220-223.
5. (a). $POCl_3$ reaction: Bremner, D. H.; Dunn, A. D.; Wilson, K. A. *Synthesis* **1992**, 528.
   (b). Ac_2O reaction: Nagano, H.; Nawata, Y.; Hamana, M. *Chem. Pharm. Bull.* **1987**, *35*, 4068.
   (c). Cyanation: Kobayashi, Y.; Kumadaki, I.; Taguchi, S. *Chem. Pharm. Bull.* **1969**, *17*, 2335.
6. For details of the Enzyme-Linked ImmunoSorbent Assay (ELISA), see : Barton, B. E.; Jakway, J. P.; Smith, S. R. ; Siegel, M. I. *Immunopharm. Immunotox.* **1991**, *13*, 251.

(*Received in USA* 14 *July* 1995; *accepted* 16 *August* 1995)