Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 19, pp. 2367-2370, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00427-1

RING-BASED ANALOGUES OF PENTAMIDINE VERSUS *P. CARINII* PNEUMONIA IN CULTURE

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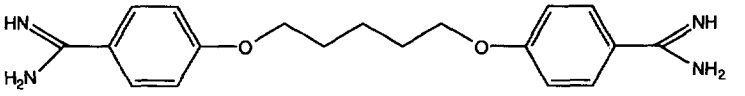
Abstract: The synthesis of aromatic ring-based pentamidine analogues, in which the aliphatic bridge has been replaced by benzene, pyridine, or pyrimidine has been accomplished in two steps. Compounds containing benzene and pyridine as the central core of the molecule have demonstrated activity against PCP in culture.

The struggle against AIDS and related opportunistic infections is being waged on many fronts. While the majority of interest lies in developing inhibitors of HIV, the presumed cause of AIDS, a growing body of knowledge concerning opportunistic infections is developing.

Pneumocystis carinii pneumonia (PCP) is one of the opportunistic infections afflicting many individuals with AIDS. It has been described as the leading cause of death in AIDS patients. Thus, there is an urgency to finding a suitable chemotherapeutic agent that can halt this infection.[1]

At present, only three regimens are approved for treatment of PCP: (1) a combination of trimethoprim and sulfamethoxazole, (2) dapsone, and (3) pentamidine. Since each of these treatments have serious limitations, such as leukopenia, nausea and vomiting, much work is needed to avoid these deleterious side effects. A considerable effort is currently underway to understand and improve the behavior of pentamidine. In related studies, pentamidine has been used effectively, although with undesirable side effects, in the treatment of leishmaniasis.[2]



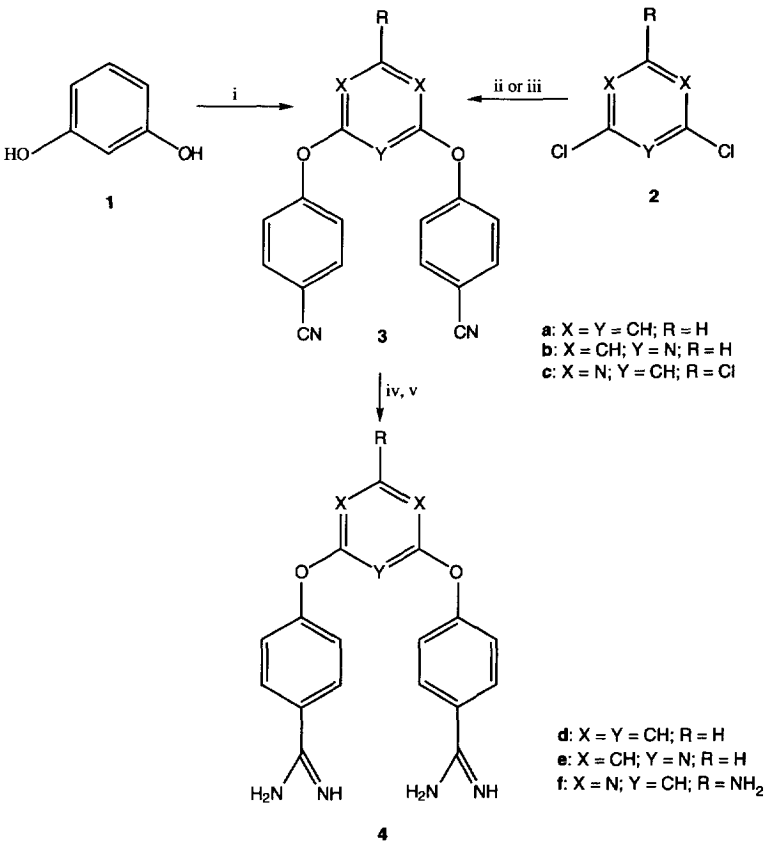
Pentamidine

Analogues of pentamidine were prepared and evaluated in an effort to find a more efficient chemotherapeutic agent for both of these infections. Only recently have these efforts begun to focus on the bridge portion of pentamidine, namely the five carbon chain. Varying the chain length[3-5] has shown that the anti-PCP activity is retained, if not improved. More recently, one double bond has been introduced into the chain[6,7] and anti-PCP activity persists. Stilbamide has been employed against leishmaniasis and analogues

exploiting this bridge double bond have also been prepared.[8,9] Furthermore, Boykin[10] has succeeded in replacing the entire bridge, including the oxygens, with a furan ring. These results demonstrate that considerable variability in the bridge may be tolerated in such analogues. We wish to report on our initial efforts along these lines.

Our interest in heteroaromatic systems led us to postulate that a ring system in place of the five carbon chain would provide an interesting comparison with the non-cyclic systems reported to have good activity. Indeed, precedence in the field of leishmaniasis suggests that rigid ring systems may very well prove effective.[11,12] The use of an aromatic precursor was envisioned to proceed quite readily, as shown in the Scheme.

SCHEME



i: Na, MeOH, 4-cyanobromobenzene, heat, 1 h
ii: K_2CO_3, 4-cyanophenol, DMF/toluene, heat, 12 h
iii: NaOH, 4-cyanophenol, H_2O/acetone, rt, 3 h
iv: HCl/EtOH/benzene, 0 °C, then rt, 3 h
v: NH_3/EtOH, 60 °C, 6 h

Treatment of 2,6-dichloropyridine **2b** and 2,4,6-trichloropyrimidine **2c** with the anion of 4-cyanophenol led to very good yields of the intermediate 4-cyanophenoxy derivatives (**3b** and **3c**). Because of lower reactivity of halogens on benzene, resorcinol, **1**, was used as the precursor for the benzene analogue. This phenol was converted into the diphenoxide with sodium methoxide and treated with 4-cyanobromobenzene to obtain the corresponding 4-cyanophenoxy derivative **3a**. Subsequent treatment of these intermediates with ethanolic hydrogen chloride, followed by ethanolic ammonia, afforded very good yields of the corresponding amidine products (**4d-f**).[13,14] All compounds had correct elemental analyses and spectral data consistent with the assigned structures.[15]

All three amidines (**4d-f**) were evaluated against PCP in culture. Compounds were evaluated in short term culture inocula from *P. carinii*-infected rat lung and cell cultures of human embryonic lung fibroblasts (HEL cells) as described.[16-19] Both pentamidine (1.65 μM) and trimethoprim/sulfamethoxazole (170/987 μM) were included as positive controls in these experiments. Compounds **4d** and **4e** at 2.4 μM were as effective as pentamidine at 1.65 μM. The third test compound (**4f**) was much less effective with differences from untreated control only appearing at days 5 and 7. We do not have a satisfactory explanation for the failure of the pyrimidine analogue to exhibit the same biological behavior as that of the benzene and pyridine analogues. Full dose response curves would be required to determine the rank order of potency of these compounds relative to pentamidine.

These results demonstrate that rigid structures can also be employed in the development of suitable pentamidine analogues. Investigations in our laboratory continue to explore the role of other rings in lieu of the aliphatic chain of pentamidine.

Acknowledgment: This investigation was supported by a grant from the Research Excellence Fund of the State of Michigan. We thank Ms. Luyi Guo for performing the mass spectral analyses.

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13. The remaining chlorine in **3c** was replaced by ammonia to give the corresponding amino product, **4f**, in this step.
14. Compound **3a** was previously described; see Ashley, J. N.; Barber, H. J.; Ewins, A. J.; Newberry, G.; Self, A. D. H. *J. Chem. Soc.* **1942**, 103.
15. The chemical data for each of the new compounds reported here are as follows:
3a : Yield 61%; IR (KBr) υ 3101, 2224, 1594, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75 (t, 1H, benzene H_1), 6.88 (m, 2H, Benzene $H_{3,5}$), 7.02 (d, 4H, aromatic CH), 7.40 (t, 1H, benzene H_4), 7.65 (d, 4H, aromatic CH) ppm; ^{13}C NMR ($CDCl_3$) δ 161.1, 156.9, 134.6, 131.8, 118.8, 116.7, 112.5, 106.9 ppm; ms (*m/e*) 312. Anal. calcd for $C_{20}H_{12}N_2O_2$ (found): C, 76.92 (76.88); H, 3.85 (3.97); N, 8.97 (8.85).
3b : Yield 71%; IR (KBr) υ 3075, 2222, 1579, 1503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (d, 2H, pyridine $H_{5,3}$), 7.16 (d, 4H, aromatic CH), 7.58 (d, 4H, aromatic CH), 7.82 (t, 1H, pyridine H_4) ppm; ^{13}C NMR ($CDCl_3$) δ 161.1, 157.8, 143.6, 134.1, 121.7, 118.7, 108.5, 107.2 ppm; ms (*m/e*) 313. Anal. calcd for $C_{19}H_{11}N_3O_2$ (found): C, 72.84 (72.49); H, 3.54 (3.59); N, 13.41 (13.25).
3c : Yield 50%; IR (KBr) υ 3070, 2215, 1579 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.96 (s, 1H, pyrimidine H_5), 7.49 (d, 4H, aromatic CH), 7.98 (d, 4H, aromatic CH), 7.82 ppm; ^{13}C NMR (DMSO-d_6) δ 171.8, 158.8, 156.3, 135.3, 123.3, 118.9, 109.8, 94.8 ppm; ms (*m/e*) 348. Anal. calcd for $C_{18}H_9N_4O_2Cl$ (found): C, 61.98 (61.48); H, 2.58 (2.54); N, 16.07 (15.77).
4d : Yield 90%; IR (KBr) υ 3262, 3070, 1678, 1613, 1590 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.89 (s, 1H, benzene H_1), 6.98 (m, 2H, Benzene $H_{3,5}$), 7.22 (d, 4H, aromatic CH), 7.54 (t, 1H, benzene H_4), 7.90 (d, 4H, aromatic CH), 9.4 (br s, 6H, amidine NH) ppm; ^{13}C NMR (D_2O) δ 166.3, 162.3, 157.0, 132.2, 130.7, 122.8, 118.9, 117.0, 112.4 ppm; ms (*m/e*) 329. Anal. calcd for $C_{20}H_{18}N_4O_2 \cdot 2HCl \cdot H_2O$ (found): C, 54.92 (55.70); H, 5.07(4.82); N, 12.81 (12.59).
4e : Yield 90%; IR (KBr) υ 3270-3090, 1664, 1606, 1578 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.95 (d, 2H, pyridine $H_{5,3}$), 7.90 (d, 4H, aromatic CH), 7.90-8.10 (m, 5H, aromatic CH and pyridine H_4), 9.30 (br s, 6H, amidino NH) ppm; ^{13}C NMR (D_2O) δ 166.4, 161.4, 159.5, 145.5, 130.7, 124.3, 121.7, 108.62 ppm; ms (*m/e*) 331. Anal. calcd for $C_{19}H_{17}N_5O_2 \cdot 2HCl$ (found): C, 54.29 (54.09); H, 4.52 (4.53); N, 16.67 (16.16).
4f : Yield 80%; IR (KBr) υ 3250-3100, 1676, 1582 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.9 (s, 1H, pyrimidine H_5), 7.0–7.2 (m, 4H, aromatic CH), 8.0 (d, 4H, aromatic CH), 9.4–9.6 (br m, 6H, amidino NH) ppm; ^{13}C NMR (DMSO-d_6) δ 171.8, 165.7, 163.7, 157.9, 130.9, 125.1, 122.7, 82.6 ppm; ms (*m/e*) 347. Anal. calcd for $C_{18}H_{17}N_7O_2 \cdot 3HCl \cdot 2H_2O$ (found): C, 42.46 (41.94); H, 4.75 (5.08); N, 19.26 (19.98).
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(*Received in USA* 22 *July* 1996; *accepted* 27 *August* 1996)