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SYNTHESIS, CHARACTERIZATION, AND ANTI-HIV ACTIVITY OF SOME 2-*p* -X-PHENYL-1,3-N,N'-DIPHENYL-AMIDINES

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Abstract. A series of six 2-*p*-X-phenyl-1,3-N,N'-diphenyl-amidines, in which X = H, Br, Cl, CH_3, NO_2 and OCH_3 has been prepared and fully characterized by IR, ^1H and ^{13}C NMR, and GC-MS. Their anti-HIV activity and cytotoxicity varied greatly with different substitutions. The most active was the *p*-chloro compound, having a selectivity index of 125. All of the compounds with H, CH_3 and OCH_3 groups were essentially inactive. Copyright © 1996 Elsevier Science Ltd

The amidines are interesting nitrogen analogues of carboxylic acids and esters combining an azomethine-like C=N double bond with an amide-like C-N single bond with partial double bond character.[1] The synthesis of amidines proceeds usually through transformation of nitriles by addition of amines,[2,3] metal amides[4,5] or by condensation reactions of amides or their derivatives with amines in the presence of halogenating reagents.[6,7]

Amidines are much used in synthesis. In some cases for the preparation of acyclic compounds,[8,9] but mostly for the synthesis of heterocyclic compounds such as aziridines,[10] pyrroles,[11] oxazoles,[12] oxadiazoles and thiadiazoles,[13] pyridines,[14] pyrimidines,[15] imidazoles,[16] and triazines[17] *inter alia*.

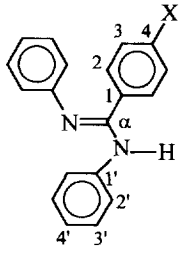
Many amidine derivatives possess useful biological activity. It has been suggested that this is in part due to the resemblace of the amidine function to the biologically important pyrimidines and purines sistems. Formamidines feature in the biochemical pathways associated with the biosynthesis of imidazoles, purines, and in the catabolism of histidine.[18]

The wide-ranging biological activity includes, for example, antiviral activity of some naturally occurring amidines[19,20] interfering with the reverse transcription process. Distamycin derivatives have also been examined for reverse transcription inhibitory properties.

Antibacterial, antifungal, and antiprotozoal activity has been shown for benzamidine derivatives. Pentamidine is used in the treatment of pneumonia due to *Pneumocystis carinii.* This is a serious disease in patients receiving inmunosuppressive therapy for leukaemia, lymphoma, or transplant rejection. N-substituted heteroaromatic cyanoamidines possess good vasodilating[21] and antihypertensive[22] activity by opening the potassium channel. More recently pentamidine has been used in leishmaniasis therapy,[23] a dangerous tropical disease, in substitution of arsenic derivatives and in combating collateral infections in AIDS treatment. Anti-neoplasic activity has also been reported. Terephtanilide derivatives showed significant activity[24] against P388 lymphocytic leukaemia cells in culture, mouse leukaemia L1210.

In the present work, we have prepared a series of triarylamidines; specifically six 2-*p*-X-phenyl-1,3-N,N'-diphenyl-amidines, where X = H, OCH_3, CH_3, Br, Cl and NO_2. They have been characterized by the usual spectroscopic methods and their in vitro anti-HIV activity evaluated.

The amidine derivatives, Figure 1, were prepared essentially by a method described in the literature.[25] *p*-Benzanilides were prepared from benzoic acids and converted to *p*-benzimidoyl chlorides in situ by treatment with halogenating reagents ($SOCl_2$ or PCl_5). Reaction with aniline furnished the target compounds in good yields and with high purity after recrystallization. The amidines were fully characterized by ^1H and ^{13}C NMR, IR, and GC-MS. Physical and spectral data are listed in Table 1.



X = OCH_3, CH_3, H, Br, Cl and NO_2

Figure 1

Triarylamidines were tested for their ability to inhibit the replication of HIV-1 in C8166 cells, as previously described,[26] and the results are shown in the Table 2.

The anti-HIV activity and cytotoxicity of the derivatives varied considerably with simple variation in the position 4 (X, Figure 1). The triarylamidines with H, CH_3 and OCH_3 groups showed varying toxicity, but they were inactive, whereas substitutions with Cl, NO_2 and Br exhibited significant anti-HIV selectivity with EC_{50} values of 8, 20, and 100 μm respectively. The selectivity index of 125 was highest for *p*-chloro derivative, whereas substitution with Br and NO_2 increased toxicity, which led to decreased anti-viral selectivity. These are unusual compounds that can be prepared with relative facility in a pure state and have high stability, showing interesting structure/activity relationship which should be studied further.

Table 1. Physical and spectral data for 2-*p*-X-phenyl-1,3-N,N'-diphenyl-amidines.

X	M.p. (°C)	$M^{+\cdot}$ (%)[a]	$\nu_{C=N}$[b] (cm^{-1})	ν_{C-NH} (cm^{-1})	^{13}C-NMR δC (ppm)
OCH_3	118-120	302 (8.4)	1625	1531	C-α(154.2), C-1(124.1), C-2(130.4), C-3(113.8), C-4(160.6), C-1'(n.o.)[d], C-2'(120.2), C-3'(128.8), C-4'(122.5).
CH_3	163-166	286 (8.4)	1629	1534	C-α(154.4), C-1(132.0), C-2(128.9), C-3(113.8), C-4(145.0), C-1'(139.5), C-2'(121.1), C-3'(128.2), C-4'(122.4).
H	148-149	272 (10)	1627	1533	C-α(154.7), C-1(134.9), C-2(128.3), C-3(128.0), C-4 (n.o.), C-1'(141.5), C-2'(119.6), C-3'(128.9), C-4'(122.3).
Cl	162-165	306 (10) 308 (3.5)	1627	1537	C-α(153.5), C-1(133.5), C-2(130.3), C-3(129.0), C-4(144.7), C-1'(135.8), C-2'(121.4), C-3'(128.6), C-4'(123.0).
Br	142-145	352 (8.7) 354 (9.1)	1628	1535	C-α(155.2), C-1(133.7), C-2(129.2), C-3(131.7), C-4(143.6), C-1'(144.9), C-2'(122.1), C-3'(128.9), C-4'(123.2).
NO_2	142-145	317 (15.4)	1644	1533	C-α(155.9), C-1(142.8), C-2(131.6), C-3(124.1), C-4(149.4), C-1'(137.9), C-2'(122.9), C-3'(129.7), C-4'(124.0).

[a]M/z value with relative intensity in parentheses.
[b]In KBr pellets.
[c]Measured in DMSO-d_6; 200 MHz spectrometer.
[d]n.o. - no observed.

Table 2. Effects of triarylamidines in antigen production, viability of unifected cells and selectivity index.

Compound (X)	EC_{50} (μm)[b]	TC_{50} (μm)[b]	SI[c]
H	> 400	400	< 1
OCH_3	> 80	80	< 1
CH_3	> 500	> 500	< 1
Cl	8	1000	125
Br	100	200	2
NO_2	20	80	4
AZT	0.016	> 1000	$>6 \times 10^4$

[a]EC_{50} represents the drug concentration which reduces viral antigen prduction by 50%.
[b]TC_{50} is concentration of drug which reduces the viability of unifected cells by 50%.
[c]SI (selectivity index) is the ratio of TC_{50} to EC_{50}.

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