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1-ARYLSULFONYL-3-(α-HYDROXYBENZYL)-1*H*-PYRROLES, A NOVEL CLASS OF ANTI-HIV-1 REVERSE TRANSCRIPTASE INHIBITORS

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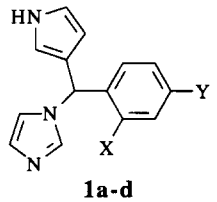
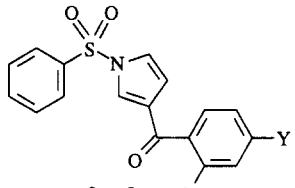
Abstract. Various 1-arylsulfonyl-3-(α-hydroxybenzyl)-1*H*-pyrroles were prepared by Friedel-Crafts reaction of 1-arylsulfonyl-1*H*-pyrroles with aroylchlorides in the presence of aluminum trichloride, followed by reduction of the ketones to the required carbinols. Title compounds were identified as a novel class of non-nucleoside HIV-1 reverse transcriptase inhibitors characterized by the presence of a diarylcarbinol moiety, a chemical feature that strictly correlates with the anti-HIV-1 activity. © 1997 Elsevier Science Ltd.

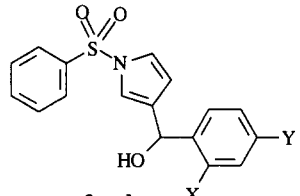
During research aimed at synthesizing novel imidazole derivatives related to clotrimazole we required (1*H*-pyrrol-1-yl)(1*H*-imidazol-1-yl)arylmethanes (**1a-d**) as intermediate compounds. The synthetic pathway leading to **1a-d** involved sulfones **2a-d** - **4a-d** as intermediates. Since the latter contained a diaryl sulfone moiety, they were selected as potential anti-HIV-1 agents and tested in MT-4 infected cells. In fact, diaryl and pyrrolyl aryl sulfones such as **5** (NPPS)[1] and **6** (a member of the very recently discovered pyrrolyl aryl sulfone (PAS) family[2]) have been reported as potent anti-HIV-1 agents targeted at the reverse transcriptase (RT).[3]



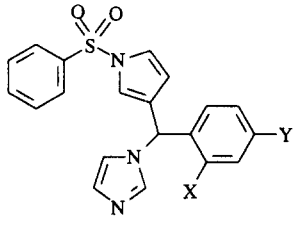
1a-d



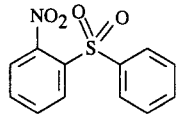
2a-d



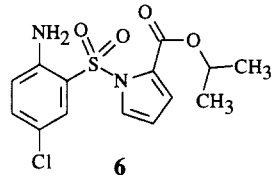
3a-d



4a-d



5



6

X = Y = H (**a**); X = H, Y = CH_3 (**b**); X = H, Y = Cl (**c**); X = Y = Cl (**d**)

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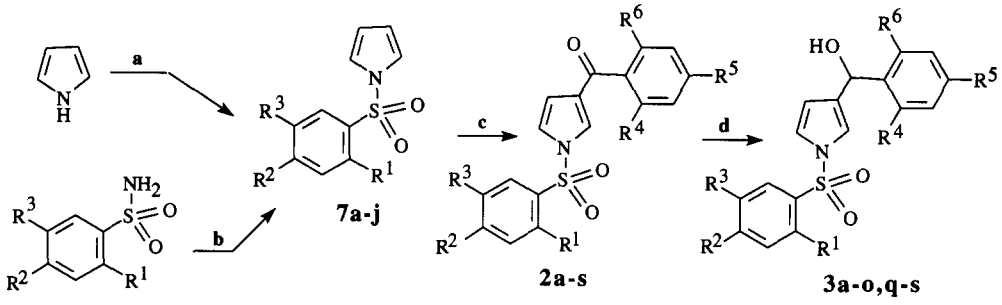
SCHEME 1

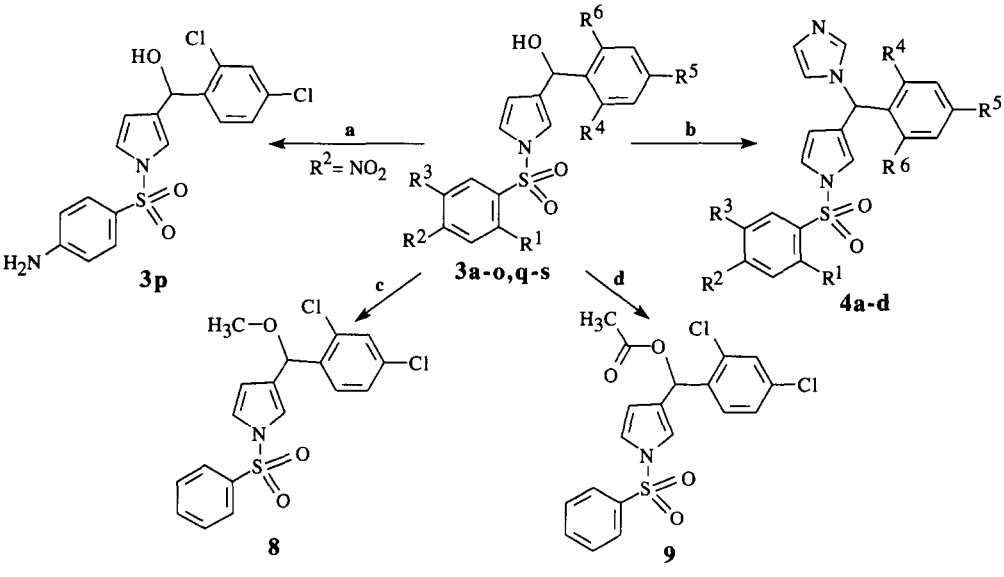


Legenda: **a**: $ArSO_2Cl$, NaOH; **b**: 2,5-dimethoxytetrahydrofuran, AcOH; **c**: ArCOCl, $AlCl_3$; **d**: $NaBH_4$, THF.

R^1 = H, CH_3, NO_2, NH_2; R^2 = H, CH_3, C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$, Cl, NO_2, NH_2; R^3 = H, Cl; R^4 = H, F; R^5 = H, CH_3, OCH_3, Cl; R^6 = H, Cl, F.

When tested in MT-4 cells acutely infected with HIV-1, carbinols **3a-d** showed activity, whereas the related ketones **2a-d** and imidazoles **4a-d** were totally inactive. Since 1-benzenesulfonyl-3-(α-hydroxy-2,4-dichlorobenzyl)pyrrole (**3d**) showed the highest activity (CC_{50} = 57 μM, EC_{50} = 5 μM and S.I. = 11), it was chosen as a lead for the development of further compounds.

SCHEME 2



Legenda: **a**: Fe, AcOH; **b**: $(imidazolyl)_2CO$; **c**: ICH_3, KOH; **d**: Ac_2O, DMAP.

R^1 = H, CH_3, NO_2, NH_2; R^2 = H, CH_3, C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$, Cl, NO_2, NH_2; R^3 = H, Cl; R^4 = H, F; R^5 = H, CH_3, OCH_3, Cl; R^6 = H, Cl, F.

As a first attempt at optimizing the activity of such compounds, derivatives bearing substituents in the aromatic portion of the α-hydroxy benzyl moiety (**3e-g**) were prepared. Substituents were also introduced in

the benzenesulfonyl group (**3h-s**) and the free carbinol **3h** was transformed into methoxy and acetoxy derivatives **8** and **9**, respectively.

Table 1. Chemical and Physical Data,[a] Cytotoxicity and anti-HIV-1 Activity of Derivatives **2a-d**, **3a-s** and **4a-d**[b]

compd	R^1	R^2	R^3	R^4	R^5	R^6	m.p. (°C)	recryst.[c] solvent	yield (%)	CC_{50}[d] (μM)	EC_{50}[e] (μM)	IC_{50}[f] (μM)	SI[g]
2a	H	H	H	H	H	H	76-77	a	86	32	>32	-	-
2b	H	H	H	H	CH_3	H	70-72	a	100	30	>30	-	-
2c	H	H	H	H	Cl	H	105-106	b	83	26	>26	-	-
2d	H	H	H	H	Cl	Cl	128-130	c	62	30	>30	-	-
3a	H	H	H	H	H	H	79-80	a	99	124	8	-	15
3b	H	H	H	H	CH_3	H	95-97	a	76	122	15	-	8
3c	H	H	H	H	Cl	H	74-75	a	100	66	9	-	7
3d	H	H	H	H	Cl	Cl	86-88	a	100	57	5	>30	11
3e	H	H	H	H	H	Cl	oil	-	70	113	4.1	29.5	27.5
3f	H	H	H	H	H	F	84-85	a	90	≥200	9.1	-	≥22
3g	H	H	H	F	H	F	103-104	a	100	100	48	-	2
3h	H	CH_3	H	H	Cl	Cl	131-132	a	98	61	0.3	18	203
3i	H	Cl	H	H	Cl	Cl	116-118	a	97	96	4.4	17	21.8
3j	CH_3	H	H	H	Cl	Cl	123-124	c	100	>200	1.7	27	>117
3k	H	C_2H_5	H	H	Cl	Cl	74-75	b	99	71	1.5	22	47
3l	H	$CH(CH_3)_2$	H	H	Cl	Cl	oil	-	100	51	1.8	2.5	28
3m	H	$C(CH_3)_3$	H	H	Cl	Cl	oil	-	95	62	2.5	6.4	24
3n	CH_3	CH_3	H	H	Cl	Cl	oil	-	100	60	0.3	<1.1	200
3o	H	NO_2	H	H	Cl	Cl	94-96	a	67	50	22	-	2.2
3p	H	NH_2	H	H	Cl	Cl	80-82	a	20	74	11	-	6.7
3q	H	CH_3	H	H	CH_3	H	90-92	a	100	96	7.3	4.7	13
3r	H	CH_3	H	H	OCH_3	H	oil	-	100	>200	15.7	-	>12
3s	NH_2	H	Cl	H	H	H	126-127	d	96	109	3.2	>30	34
3t	H	Cl	H	H	Cl	Cl	oil	-	100	28	>28	-	-
3u	H	CH_3	H	H	Cl	Cl	oil	-	100	32	22	-	1.4
3v	H	CH_3	H	H	Cl	Cl	oil	-	100	36	14	-	2.6
3w	NO_2	H	Cl	H	Cl	Cl	95-97	a	53	14	>14	-	-
3x	NH_2	H	Cl	H	Cl	Cl	oil	-	59	29	16	-	1.8
4a	H	H	H	H	H	H	118-120	c	95	25	>25	-	-
4b	H	H	H	H	CH_3	H	-	-	100	26	>26	-	-
4c	H	H	H	H	Cl	H	-	-	78	22	>22	-	-
4d	H	H	H	H	Cl	Cl	114-116	a	21	14	>14	-	-
8	-	-	-	-	-	-	oil	-	87	82	>82	-	-
9	-	-	-	-	-	-	121-122	b	99	100	9.8	-	10
10	-	-	-	-	-	-				95	>95	-	-
HEPT	-	-	-	-	-	-	-	-	-	740	7.0	-	106
AZT	-	-	-	-	-	-	-	-	-	>20	0.01	-	>2000
nevirapine	-	-	-	-	-	-	-	-	-	>200	0.25	0.25	>800

[a] For derivatives **7a-d,i,j** see literature.[2,5-7]
[b] Data represent mean values for three separate experiments. Variation among duplicate samples was less than 10%.
[c] Recrystallization solvents. a: benzene/cyclohexane. b: cyclohexane. c: benzene. d: toluene/ligroin.
[d] Compound concentration required to reduce the viability of mock-infected MT-4 cells by 50%.
[e] Compound concentration required to achieve 50% protection of MT-4 cells against the cytopathic effect of HIV-1.
[f] Compound concentration required to inhibit the HIV-1 recombinant RT (rRT) activity by 50%.
[g] Selectivity index: ratio of CC_{50} to EC_{50}.

Recently, some alkyl derivatives of the diethyl ester of 2-benzyl-1*H*-pyrrole-3,4-dicarboxylic acid have been claimed to be new non-nucleoside reverse transcriptase inhibitors (NNRTIs).[4] In this communication we report a further example of pyrrole derivatives targeted at the RT, which are endowed with anti-HIV-1 activity.

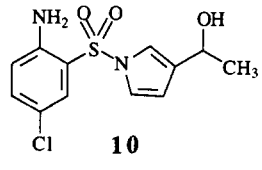
Chemistry

Chemical procedures for the preparation of derivatives **2** , **3** and **4** are depicted in Schemes 1 and 2. 1-Arylsulfonylpyrroles **7**, which were prepared by reacting pyrrole with arylsulfonyl chlorides according to published procedures (**7a-c**)[5] or *via* the Clauson-Kaas method (**7d-j**),[2,6,7] were treated with aroylchlorides under Friedel-Crafts reaction conditions to afford 1-arylsulfonyl-3-aroyl-1*H*-pyrroles **2**. Reduction of ketones to the corresponding carbinols furnished derivatives **3a-s**. Imidazoles **4a-d** were prepared from **3a-d** as reported in previous works[8,9]. Chemical and physical data of the newly synthesized derivatives are reported in Table 1. ^{1}H-NMR spectra ($CDCl_3$, TMS as internal standard, Bruker AC 200 spectrometer) of compounds **2, 3, 4** and related intermediates were in agreement with the proposed structures.

Antiviral Activity and SAR Studies

The cytotoxicity and the capability of derivatives **2a-d, 3a-s** and **4a-d** to inhibit the HIV-1-induced cytopathogenicity were tested in MT-4 cells.[2] In these *in vitro* assays HEPT, AZT and nevirapine were used as reference drugs.

Only a few compounds were non cytotoxic for MT-4 cells at doses as high as 200 μM, whereas the majority of derivativesshowed CC_{50} values at concentrations ranging between 14 and 100 μM (Table 1). The most active compounds against HIV-1 were **3h** and **3n**, which showed EC_{50} values (0.3 μM) comparable to that of nevirapine (EC_{50} = 0.25 μM). However, due to their higher cytotoxicity (CC_{50} = 61 and 60 μM, respectively, *versus* >200 μM of nevirapine) the selectivity indexes of **3h** and **3n** (S.I. = 203 and 200, respectively) are about four fold lower than that of nevirapine (S.I. >800).



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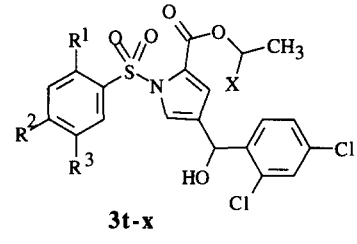
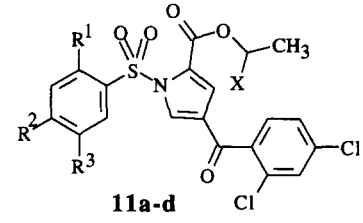
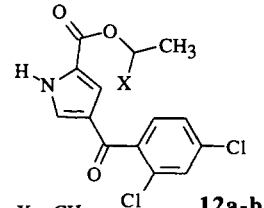


3t-x



11a-d



12a X = CH_3
12b X = H

12a-b

Compd	R^1	R^2	R^3	X
3t , 11a	H	Cl	H	CH_3
3u , 11b	H	CH_3	H	CH_3
3v , 11c	H	CH_3	H	H
3w, 11d	NO_2	H	Cl	H
3x	NH_2	H	Cl	H

The introduction of a *p*-methyl group in the benzene ring of the α-hydroxybenzyl moiety resulted in a slight decrease of activity (compare **3a** and **3b**), whereas the introduction of a *p*-chloro group enhanced the cytotoxicity (compare **3a**, **3c** and **3d**). No substantial variation of activity but a better cytotoxicity profile was observed following *o*-chloro substitution (**3e**). 2,4-Dichlorosubstitution did not lead to improvement of the activity with respect to the 2- and 4-monochloro substitutions, whereas the 2,6-difluorosubstitution was less advantageous than the monosubstitution at position 2. The best results were obtained by substituting the benzenesulfonyl moiety: introduction of a *p*-methyl group resulted in the highest potency, which could not be further increased when one more methyl was introduced at position *ortho*. When the length of the alkyl chain was increased (ethyl or *tert*-butyl) the activity decreased. With the sole exception of **3r**, *para*-derivatives were more cytotoxic than their *ortho*-counterparts (compare **3j** with **3h** and **3k-m**).

The data in Table 1 show that the antiviral activity of derivatives **3a-s** is strongly affected by the presence of the pyrrolylarylcarbinol moiety in the free form. In fact, etherification and esterification of the hydroxyl group led to inactive (**8**) and moderately active (**9**) derivatives, respectively. The inactivity of the ketone derivatives **2a-d** further confirmed the importance of a free hydroxyl group, whose activity, in turn, depends on the presence of two aromatic wings bound to the carbinol group; in fact, replacement of the benzene ring with methyl led to a loss of anti-HIV-1 activity (compare **3s** with **10**[10]). On the other hand, the presence of an alkoxycarbonyl group at position 2 of pyrrole also appears to be deleterious for the activity (see compounds **3t-x**, which were prepared as above from ketones **11a-d**). This result is in evident contrast with those obtained with various arylsulfonylpyrroles described in a previous work[2], the potent anti-HIV-1 activity of which has been found to correlate with the presence of both a *p*-chloroaniline moiety and an ethoxycarbonyl or isopropoxycarbonyl in the position 2 of the pyrrole ring.

Conclusion

The results of anti-HIV-1 activity evaluation suggest that the pyrrolylarylcarbinol moiety is the determinant for the antiviral activity. The ketone counterparts are dramatically less active. These features correlate well with the structural information used by Ding *et al.*[11] for the design of novel NNRTIs. In fact, it can be hypothesized that, unlike ketones, the carbinols assume a tetrahedral spatial arrangement which allows them to mimic the "butterfly-like" conformation of nevirapine and congeners.[12] The fact that the replacement of a hydroxyl by an imidazole group leads to inactive products may be due to the higher steric hindrance exerted by the heterocyclic ring.

In conclusion, 1-arylsulfonyl-3-(α-hydroxybenzyl)pyrroles constitute a novel class of anti-HIV agents targeted at the reverse transcriptase, which need further SAR studies before their potential clinical usefulness can be assessed. In particular, it may be important to study if the antiviral activity of these compounds can be influenced by the shift of the arylsulfonyl moiety from the N-1 to the α and β positions of the pyrrole, and to explore whether the removal of the benzenesulfonyl moiety would abate or enhance the activity. Work is in progress to answer these questions.

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