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Quino[8,1-*bc*][1,4]benzoxazepinones – HIV-1 Reverse Transcriptase Inhibitors

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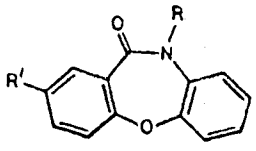
A series of quinobenzoxazepinones showed activity against the reverse transcriptase of HIV-1. The most potent one was 13 with an amino and methyl substitution. Active compounds 5, 12 and 13 inhibited both AZT-sensitive and AZT- resistant strains of HIV-1 but were inactive against 'pyridone-resistant' HIV-1 and HIV-2. The tricyclic dibenzoxazepine derivative 23 also showed activity against HIV-1 RT.

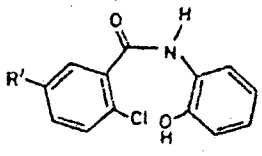
The period 1950-1975 can be considered to be the most productive phase of Prof. T. R. Govindachari's professional life and falls into two neat segments—1950-1962 when he was Chief Professor of Chemistry, Presidency College, Madras and 1963-1975 when he was Director of Ciba Research Centre, Goregaon, Bombay. The Research Centre was unique at that time, being the single largest institution in the private sector devoted to the development of new drugs. One of the earliest drugs to come out of the Centre was the tricyclic antidepressant, nitroxazepine hydrochloride 1 (Sintamil^{R})[1,2] which is registered and sold in this country. The synthesis of 1 started from 2-aminophenol. Its 2-chloro-5-nitrobenzamide (2) underwent facile cyclization in aqueous sodium hydroxide to afford the dibenzoxazepinone (3). Treatment of a suspension of 3 in acetone with dimethylaminopropyl chloride in aqueous alkali led to 1[3]. Amide analogs of 2, not having an activating group *para* to the chlorine atom could be cyclized by heating their sodium salts in DMF. The chemistry was extended to the cyclization of 2-chlorobenzamides of 8-hydroxy-1,2,3,4-tetrahydroquinolines of the type 4 to yield quino[8,1-*bc*][1,4]benzoxazepines* of type 5[4]. Extensive biological evaluation of a large number of these and related molecules disclosed analgesic, CNS depressant[5] and anticonvulsant[6] activities. It is interesting to record in this article that nearly two decades after their synthesis, some of the quinobenzoxazepine derivatives have been found to have inhibitory activity of the Reverse Transcriptase (RT) of the Human Immunodeficiency Virus (HIV) that has been identified as the cause of the contemporary and deadly AIDS disease.

Since the start of the AIDS pandemic, more than 13 million people have been infected with HIV. A significant percentage of the infected have progressed to full-blown AIDS leading to high mortality[7,8]. India with 1.5 million sero-positive population has the largest incidence of HIV infection in the Asia-Pacific region. By the turn of the century, six out of thousand Indians are expected to be affected[9]. The terrifying global dimension of the disease has forced countries to allocate large resources to fight and contain the scourge if not to conquer it. The attack against HIV is being targeted at various vulnerable sites—RT inhibitors, protease inhibitors, 'Tat' inhibitors etc. Some of the earliest RT inhibitors were from the class of nucleosides exemplified by azidothymidine (AZT). This has been followed by didanosine, D4T, 3TC and FTC[7].

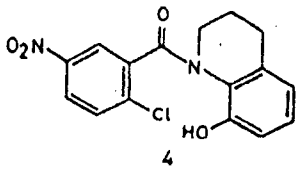
Development of resistance to nucleoside inhibitors of RT impelled investigators to look for leads among nonnucleoside compounds. The search threw up several of these, such as tetrahydroimidazobenzodiazepinone (TIBO), pyridone L-697661 and nevirapine (6)[7], the last one arising by optimization of RT inhibiting activity among sev-



1. R = $(CH_2)_3$ NMe_2·HCl ; R′ = NO_2
3. R = H ; R′ = NO_2
21. R = $(CH_2)_3$ NMe_2 ; R′ = NH_2
22. R = $(CH_2)_2$ CO_2H ; R′ = NO_2
23. R = $(CH_2)_2$ CO_2H ; R′ = NH_2



2. R′ = NO_2



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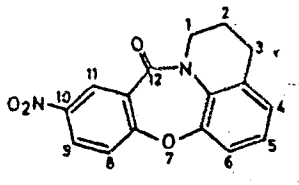

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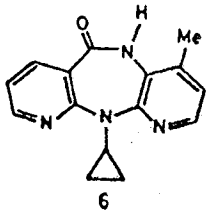

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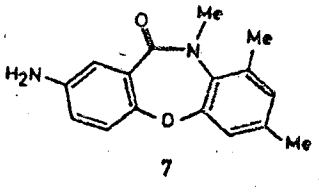

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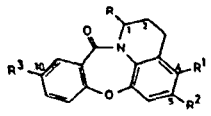
*These had been named pyrido[3,2,1-*de*]dibenz[*b,f*][1,4]oxazepines earlier[4].

TABLE 1–ANTI-HIV-1 RT INHIBITORY ACTIVITY OF



Compd.	R	R^1	R^2	R^3	EC_{50} (μM)
5	H	H	H	NO_2	116 ± 64
8	Me	H	H	NO_2	ϕ
9	H	Cl	H	NO_2	ϕ
10	H	H	H	H	31 ± 19
11	H	Cl	NO_2	NO_2	ϕ
12	H	H	H	NH_2	2.0 ± 0.7
13	Me	H	H	NH_2	1.3 ± 0.4
14	H	Cl	H	NH_2	6.9 ± 4.1
15	H	H	NH_2	H	82 ± 48
16	Me	H	NH_2	H	25 ± 12
17	Me	H	H	$NHCOCH_2Cl$	ϕ
18	Me	H	H	NHC(=S)NHPh	ϕ
19	Me	H	H	$NHC(=S)NHCH_2CH=CH_2$	ϕ
20	H	H	$NHCH=C(CO_2Et)_2$	H	ϕ

eral classes of tricyclic molecules[10–12]. Among these, dibenzoxazepinone (7) was also a potent anti-HIV agent[11].

Inspired by the activity of 7, we considered it worthwhile to have available members of our tetracyclic series of type 5 screened for RT inhibitory activity (Table 1). The synthesis of compounds of Table 1 has already been reported[4]. Briefly, 5, 8, and 9 were obtained by aqueous alkali cyclization of 2-chloro-5-nitrobenzamides of the appropriate 8-hydroxy-1,2,3,4-tetrahydroquinolines of type 4, while 10 was obtained by heating the dry sodium salt of *N*-(2-chlorobenzoyl)-8-hydroxy-1,2,3,4-tetrahydroquinoline. Catalytic reduction of 5, 8, and 9 afforded respectively, 12,13, and 14. Nitration of 9 led to the dinitro compound (11). Similar nitration of 10 and its 1-methyl analog followed by catalytic reduction yielded the amines 15 and 16. Suitable derivatisation of 13 gave compounds 17, 18, and 19. Compound 20 likewise was obtained from 15.

The compounds were subjected to primary screening by the National Cancer Institute, Bethesda, Maryland, U.S.A., using the procedure of Weislow *et al.*[13]. The candidate agent was dissolved in dimethyl sulphoxide, then diluted 1 : 100 in cell culture medium. T4 lymphocites (CEM cell line) were added and after a brief interval HIV-1 was added resulting in a 1 : 200 final dilution of the compound. Uninfected cells with the compound served as a toxicity control and infected and uninfected cells as basic controls. Cultures were incubated at 37° in a 5% carbon dioxide atmosphere for 6 days. Tetrazolium salt XTT was added to all wells and cultures were incubated to allow formazan color development by viable cells. Individual wells were analyzed spectrophotometrically to quantitate formazan production and in addition viewed microscopically for detection of viable cells and confirmation of protective activity. The percentage of surviving HIV-infected cells treated with the candidate compound relative to uninfected, untreated controls was plotted against the $\log_{10}$ of sample concentration and a 50% effective concentration (EC_{50}) was obtained. The results are presented in Table 1.

Quinobenzoxazepinone 10, the prototype of this series, showed RT inhibitory activity with an EC_{50} of around 31 μM. The introduction of a NO_2 group at position-10 (5) resulted in a four-fold decrease in this activity while further substitution at position-1 with a methyl group (8) or a chlorine atom at position-4 without a NO_2 group at position-5 (9) or with one (11) caused a total loss of activity. When the NO_2 group in 5 was reduced to an amine (12), the activity increased dramatically fifteen-fold (EC_{50} 2 μm); 13 with an extra methyl group at position-1 was the most active compound of the study (EC_{50} 1.3 μm), having approximately one-fifteenth potency of 6. Compound 14 with a chlorine substitution was less active. Transfer of the NH_2 group in 12 and 13 from position 10 to 5 afforded 15 and 16 respectively, and led to diminution of activity. Derivatisation of the NH_2 group in 13 (17, 18, 19) or in 15 (20) gave inactive compounds. In general, addition of a lipophilic group appeared to contribute to the activity.

Three active compounds from this study were chosen for extended evaluation. Compounds 12 and 13 were active against AZT-resistant HIV strains with an EC_{50} of 3.2 and 3.3 μM respectively, but were inactive against the 'pyridone-resistant' HIV strain A17 and HIV-2. Compound 5 was moderately active against HIV-1 (IIIB) strain (EC_{50}, 71 μm), HIV (6S) AZT strain (EC_{50}, 38 μm) and HIV-1 (6R) AZT resistant strain (EC_{50},51μm) but was inactive against the pyridone-resistant strain HIV (A-17) MER-RT and HIV-2 (ROD) strain.

It was of interest for us to check whether nitroxazepine hydrochloride (1) and its metabolites (21, 22, and 23)[14] had any activity. In the primary screen (HIV-1 RT), 1, 21, and 22 were found inactive but 23 had good activity with an EC_{50} of 8.9 + 2.1 μM.

In conclusion, aminoquinobenzoxazepinones of the type 12 have good inhibitory activity against the Reverse Transcriptase of HIV-1, both AZT-sensitive and AZT-resistant, but are inactive against 'pyridone-resistant' HIV. However, as has been pointed out by Goldman[15] it may be possible by suitable molecular manipulation of 12 to identify a second generation of analogs which can overcome the resistance of the first generation.

Acknowledgement

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