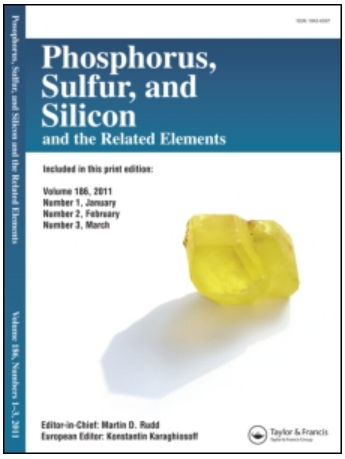

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

A Simple Method of Synthesis of Macrocyclic Amides with one or More Sulfur Atoms in the Ring System Possessing Anti-HIV-1 Activity

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To cite this Article Ramdas, Sukuru R. and Sabina, Jhaumeer B.(1994) 'A Simple Method of Synthesis of Macrocyclic Amides with one or More Sulfur Atoms in the Ring System Possessing Anti-HIV-1 Activity', Phosphorus, Sulfur, and Silicon and the Related Elements, 95: 1, 451 — 452
To link to this Article: DOI: 10.1080/10426509408034273
URL: http://dx.doi.org/10.1080/10426509408034273

Phosphorus, Sulfur, and Silicon, 1994, Vol. 95–96, pp. 451–452
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A SIMPLE METHOD OF SYNTHESIS OF MACROCYCLIC AMIDES WITH ONE OR MORE SULFUR ATOMS IN THE RING SYSTEM POSSESSING ANTI-HIV-1 ACTIVITY.

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Abstract - A series of hitherto unknown macrocyclic amides bearing a phenyl ring with one or two sulfur atoms in the macrocycle have been synthesized in one step starting with the easily available mono and dithioacetic and propionic acids. These macrocycles (I to IV) were found to exhibit anti-HIV-1 activity in a significant way.

INTRODUCTION

The human immuno deficiency virus-1 is well established to be the main causative agent of the acquired immune deficiency syndrome (AIDS)[1]. It is also well-documented that AIDS disease is spreading dramatically in recent years according to the recent WHO report[2]. AZT or Zidovudine (3'-azidothymidine); ddI (2', 3' - didesoxyinosine) and ddC (2', 3'-didesoxycytidine) are the only approved drugs for AIDS disease. But it is also well-understood that these drugs suffer from severe side-effects.

We wish to report here the results we obtained on an entirely new class of macrocyclic amides exhibiting anti-HIV-1 activity. These macrocyclic amides bearing an aromatic/heteroaromatic nucleus with one or two sulfur atoms in the macrocyclic ring were synthesized in a single-step. The method employed involves the condensation of the acid chlorides derived from the easily available monothio and bisthio acetic and propionic acids with 1, 2 -diamino aromatic or 1, 2 -diamino hetero-aromatic or 1, 2-diaminoaliphatic compounds under very high dilution technique using dry benzene as a solvent. The macrocyclic amides synthesized as mentioned above (Ia to d, II, III & IV) (vide scheme) were purified by repeated washing the solids with polar solvents till analytically pure samples were obtained. Condensation of 3, 4-diaminobenzophenone with dithiodisalicyclic acid chloride gave the expected macrocyclic amide (II) in good yield. The structures assigned to these new macrocyclic amides (I, II and III) are based on a careful study of their IR, ^{1}H, & ^{13}C nmr, high resolution mass spectral data coupled with expected micro-analytical results. A comparison of ^{13}C nmr data of (Ia & Id) with

that of the amide obtained from simple adipoyl chloride (If) revealed that carbonyl carbon (i.e γ-carbon) indicated an upfield shift as compared to the carbonyl carbon (γ-carbon) in the non-sulfur macrocyclic amide (If), thereby suggesting that the sulfur atom and the C = O function are in a 'gauche' conformation.

It is also infered that from the study of the ^{13}C nmr spectra as well as the ^{1}H nmr spectra at various temperatures (20°-70°C) that there is no conformational mobility in these systems. Based on the general literature evidence, it is believed that these molecules (I to III) exist in gauche conformation bearing the S-S bond in gauche orientation.

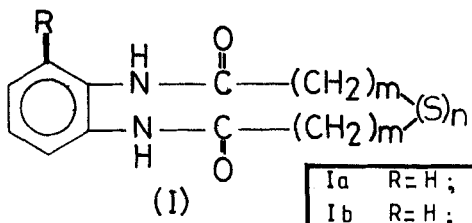
The biological study of these macrocyclic amides (I, II & III) indicated that these compounds exhibited anti-HIV activity to a significant degree. These tests were carried out at Medicinal Research Centre (MRC) London.

ACKNOWLEDGEMENT

Our thanks are due to the Vice-Chancellor of the University of Mauritius and the Air Mauritius for partial financial assistance.

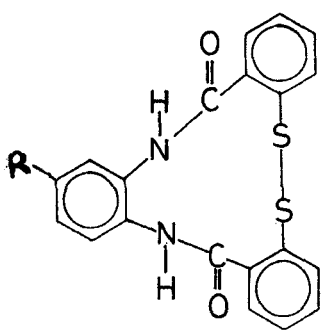
REFERENCES

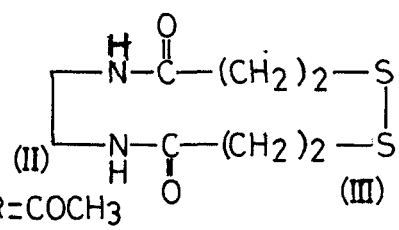
1. Erik De Clerq, Medicinal Research Reviews, Vol 13, No.3, 229 - 258 (1993).
2. WHO (1993) Global Programme on AIDS, July 1992.



(I)

Ia	R=H;	m=1	n=1
Ib	R=H;	m=1	n=2
Ic	R=H;	m=2	n=1
Id	R=H	m=2	n=2
Ie	R=CH3	m=2	n=2
If	R=H	m=2	n=0





(II) (III)

R=COCH3