

**THE MEDICINAL CHEMISTRY OF
2-AMINOTETRALIN-DERIVED BENZAMIDES**

A Novel Class of Potential Atypical Antipsychotic Agents

RIJKSUNIVERSITEIT GRONINGEN

**THE MEDICINAL CHEMISTRY OF
2-AMINOTETRALIN-DERIVED BENZAMIDES**

A Novel Class of Potential Atypical Antipsychotic Agents

PROEFSCHRIFT

ter verkrijging van het doctoraat in de
Wiskunde en Natuurwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, Dr. D.F.J. Bosscher,
in het openbaar te verdedigen op
vrijdag 16 oktober 1998
om 16.15 uur

door

Evert Jan Homan

geboren op 17 mei 1970
te Vries

Promotor

Prof. Dr. H.V. Wikström

Co-promotor

Dr. C.J. Grol

Voor mijn ouders

Promotiecommissie

Prof. Dr. U. Hacksell

Prof. Dr. J.P. Snyder

Prof. Dr. J. Zaagsma

Paranimfen

Henk-Frans Kwint

Ruud Timmerman

Colophon

Copyright © 1998 by E.J. Homan. All rights reserved. No part of this book may be reproduced in any manner or by any means without written permission from the publisher.

An electronic version of this thesis is available at <http://www.ub.rug.nl/eldoc/dis/science/e.j.homan>

ISBN 90-367-0953-9

NUGI 746

Printing: Ponsen & Looijen BV, Wageningen, The Netherlands

Cover design: Cor J. Grol

The research project described in this thesis was performed within the framework of the research school GUIDE, and was financially supported by Astra Arcus AB, Södertälje, Sweden.

CONTENTS

1	INTRODUCTION	1
2	2-AMINOTETRALIN-DERIVED SUBSTITUTED BENZAMIDES WITH MIXED DOPAMINE D ₂ , D ₃ , AND SEROTONIN 5-HT _{1A} RECEPTOR BINDING PROPERTIES: A NOVEL CLASS OF POTENTIAL ATYPICAL ANTIPSYCHOTIC AGENTS	57
3	STRUCTURAL ANALOGUES OF 5-OME-BPAT: SYNTHESIS AND INTERACTIONS WITH DOPAMINE D ₂ , D ₃ , AND SEROTONIN 5-HT _{1A} RECEPTORS	81
4	C5-SUBSTITUTED DERIVATIVES OF 5-OME-BPAT: SYNTHESIS AND INTERACTIONS WITH DOPAMINE D ₂ AND SEROTONIN 5-HT _{1A} RECEPTORS	99
5	SYNTHESIS AND <i>IN VITRO</i> PHARMACOLOGICAL EVALUATION OF THE ENANTIOMERS OF 5-OME-BPAT AND 5-OME-(2,6-DI-OME)-BPAT	119
6	<i>IN VIVO</i> PHARMACOLOGICAL EVALUATION OF THE ENANTIOMERS OF 5-OME-BPAT	131
7	MOLECULAR MODELING OF THE DOPAMINE D ₂ AND SEROTONIN 5-HT _{1A} RECEPTOR BINDING MODES OF THE ENANTIOMERS OF 5-OME-BPAT	153
	SUMMARY	179
	SAMENVATTING	183
	ABBREVIATIONS	187
	AMINO ACID CODES AND STRUCTURES	188
	PUBLICATIONS AND PRESENTATIONS	189
	CURRICULUM VITAE	190
	DANKWOORD	191