# ANNUAL REPORTS IN MEDICINAL CHEMISTRY Volume 7

Sponsored by the Division of Medicinal Chemistry of the American Chemical Society

Editor-in-Chief: RICHARD V. HEINZELMAN

# ANNUAL REPORTS IN MEDICINAL CHEMISTRY Volume 7

Sponsored by the Division of Medicinal Chemistry of the American Chemical Society

Editor-in-Chief: RICHARD V. HEINZELMAN

THE UPJOHN COMPANY KALAMAZOO, MICHIGAN

### **SECTION EDITORS**

EDWARD ENGELHARDT • JOHN TOPLISE TENNETH BUTLER
IRWIN PACHTER • WILLIAM WECHTER ROBERTH ROBERT



# COPYRIGHT © 1972, BY ACADEMIC PRESS, INC.

ALL RIGHTS RESERVED

NO PART OF THIS BOOK MAY BE REPRODUCED IN ANY FORM,
BY PHOTOSTAT, MICROPILM, RETRIEVAL SYSTEM, OR ANY
OTHER MEANS, WITHOUT WRITTEN PERMISSION FROM
THE PUBLISHERS.

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by ACADEMIC PRESS, INC. (LONDON) LTD. 24/28 Oval Road, London NW1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 66-26843

PRINTED IN THE UNITED STATES OF AMERICA

### PREFACE

When a new editor takes over the reins there is a natural tendency to make visible changes in the new volume of a series. After consultation with many of our "customers," the new editor concluded that the volume in its present form is admirably serving its purpose. Consequently the reader will find only minor changes in format.

There is a growing tendency to cover certain very active areas yearly, while at the same time treating more mature fields on an every-two- or -three-year basis. This leaves room for the introduction of new topics on perhaps a one-time basis. In fact, just half of the present twenty-eight chapters deal with topics not included in the previous volume.

The sections, Topics in Chemistry and Topics in Biology contain chapters which are often more provocative and less drug oriented than the rest. In the latter section the emphasis on the rapidly maturing field of immunology is deliberate; some of these chapter topics will be developed in a planned way over the next two or three years.

The many dedicated hours devoted to the volume by authors and section editors are gratefully acknowledged by the editor and will become apparent to the reader as soon as he begins to read.

Suggestions for improvement and for new fields to cover are always welcome.

Kalamazoo, Michigan June, 1972 Richard V. Heinzelman

Pretace
AWARD ADDRESS
Third Award Address - Medicinal Chemistry
Inhibitors of Folate Biosynthesis and Utilization Evolutionary Changes as a Basis for Chemotherapy
I. CNS AGENTS
Section Editor: Edward L. Engelhardt, Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486
<ol> <li>Antipsychotic and Anti-anxiety Agents</li></ol>
2. Antidepressives and Stimulants
3. Analgesics and Narcotic Antagonists
4. Sedatives, Hypnotics, Anticonvulsants and General Anesthetics
5. Recent Developments Relating Serotonin and Behavior 47 Albert Weissman and Charles A. Harbert, Pfizer Inc., Groton, Conn.

# II. PHARMACODYNAMIC AGENTS

Sect	ion Editor: John G. Topliss, Schering Corp., Bloomfield, N. J.
6.	Antihypertensive Agents
7.	Antianginal Agents
8.	Antithrombotic Agents
9. •	Pulmonary and Antiallengy Agents
	III. CHEMOTHERAPEUTIC AGENTS
Secti	on Editor: Kenneth Butler, Pfizer Inc., Groton Connecticut
10.	Antibiotics
11.	Antifungal Agents
12.	Antiviral Agents
13.	Antineoplastic Agents

14	Antiparasitic Agents
	IV. METABOLIC DISEASES AND ENDOCRINE FUNCTION
Section	on Editor: I. J. Pachter, Bristol Laboratories, Syracuse, New York
15.	Prostaglandins and Related Compounds
16.	Atherosclerosis
17.	Steroids and Biologically Related Compounds
18.	Peptide Hormones of the Hypothalamus and Pituitary 194 Roger Burgus, The Salk Institute, La Jolla, Calif.
19.	Non-steroidal Antiinflammatory Agents
	V. TOPICS IN BIOLOGY
Sectio	on Editor: William J. Wechter, The Upjohn Company, Kalamazoo, Michigan
20.	Mechanisms of Resistance to Antibiotics

21.	The Serum Complement System	228
22.	Immediate Hypersensitivity: Laboratory Models and Experimental Findings	238
23.	Transition State Analogs as Enzyme Inhibitors	249
	VI. TOPICS IN CHEMISTRY	
Secti	on Editor: Robert A. Wiley, University of Kansas, Lawrence, Kans	sas
24.	Biopharmaceutics and Pharmacokinetics	259
25.	Reactions of Interest in Medicinal Chemistry	269
26.	Intramolecular Catalysis in Medinical Chemistry Richard D. Gandour and Richard L. Schowen, Department of Chemistry, University of Kansas, Lawrence, Kansas	279
27.	Peptide Synthesis	289
28.	Preparation of Radioisotope-Labeled Drugs	296

### AWARD ADDRESS

Inhibitors of Folate Biosynthesis and Utilization --Evolutionary Changes As a Basis for Chemotherapy

George H. Hitchings Wellcome Research Laboratories, Research Triangle Park, N. C.

Fourth Award in Medicinal Chemistry, Thirteenth National Medicinal Chemistry Symposium of the American Chemical Society, Iowa City, Iowa, June 18-22, 1972

The exploration of enzymes and metabolic pathways by means of antimetabolites has been productive of both new medicinal agents and advances in fundamental knowledge.

One of the implications of such an approach to chemotherapy is that it is necessarily uncommitted with respect to specific targets. It feeds on the knowledge that it itself generates, and takes full advantage of the new discoveries arising from basic work elsewhere. Its goal is the unveiling of biochemical differences that can be exploited for the development of new medicinal agents. The program with which your Medalist has been associated has been involved with diverse categories: leukemia, protozoal and bacterial infections, gout and organ transplantation. All of these comprise a single package of applications from studies of nucleic acid metabolism.

This essay will attempt to describe the method of working primarily through one example, selective inhibitors of the biogenesis and utilization of folates and their application to anti-microbial chemotherapy<sup>2</sup>. Specifically, the combination of trimethoprim and sulfamethoxazole is now available in some 60 countries of the world (with the notable exception of the United States) and has been used in some 25 x 10<sup>6</sup> courses of therapy with highly satisfactory results<sup>3,4</sup>.

Its origins can be traced to early findings of the present program, to the detection of antimetabolites that possess selective effects<sup>5</sup>. Substances were found that exhibited a consistent pattern of antimetabolic

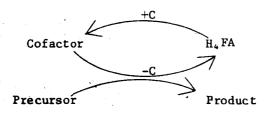
effects in microbial systems. Some were unusable as chemotherapeutic agents because of metabolic destruction or pharmacodynamic actions when they were tested in chemotherapeutic trials. Among them, however, was a sizable group that have "similar but distinct effects in different organisms" and it was felt that substances with such selective action could be regarded as leads to chemotherapeutic agents. Several possible modes of selective action were recognized:

"(1) The compound may possess several active centers which allow it to block, more or less independently, different biochemical reactions in different tissues; (2) a single reaction may be blocked in all organisms but this reaction may be of relatively greater importance to one organism than another; (3) the dissociation of the inhibitor-cell receptor complex may vary widely from organism to organism; or (4) the reaction blocked may be one which occurs only sporadically in nature as an obligate biochemical mechanism".

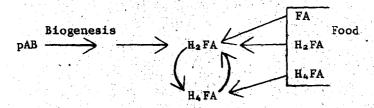
Trimethoprim is an outstanding example of the third mechanism stated above. It inhibits the dihydrofolate reductase of Escherichia coli at a concentration of ca. 10 %, while a concentration of nearly 10 % is required for a comparable inhibition of human liver dihydrofolate reductase 6.

The rationale for its use in combination with a sulfonamide is quite simply stated. The target is the microbial pool of tetrahydrofolate cofactors that are essential to the metabolism and multiplication of the microbial cell. Such cofactors occur ubiquitously and perform essential functions in all cells: in the biosynthesis of purines and thymine, the synthesis of serine and the methylation of homocysteine to form methione. Microorganisms employ similar reactions in the biosynthesis of riboflavin, pantothenate, thiamin and dihydrofolate itself. All of these latter metabolites have become "vitamins," i.e., the mechanisms for their biogenesis have been lost during the course of evolution, and higher organisms must have them preformed from food. Perhaps this in itself makes the microorganism the more sensitive to interference with the capabilities of the tetrahydrofolate pool. At some point, for example, reduction of the tetrahydrofolate pool results in inhibition of folate biosynthesis, a vicious cycle effect.

### COFACTOR ACTIVITY

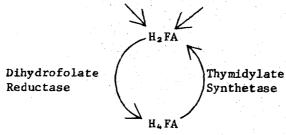


The selective effects of sulfonamides rest on a similar base. Sulfanilamide, and its relatives, act as antagonists of p-aminobenzoic acid, a building block of the folate molecule, and thus inhibit the biogenesis of dihydrofolate — the primary product of the biosynthetic reaction. Since man requires preformed folate, this antimetabolic effect is directed at a reaction that is present in the parasite and absent from the host. This, however, is only half the explanation of the chemotherapeutic activity of sulfonamides. Their action is contingent also on the inability of pathogenic microorganisms to incorporate preformed folates from the environment and so to by-pass the sulfonamide block. The ability to use preformed folates in evolution must have preceded the deletion of the biosynthetic route. Pathogens continue to synthesize folates de novo because they have failed to develop the ability to take advantage of the ample supplies of folates in body fluids?



The effect produced by a sulfonamide on the microorganism's tetrahydrofolate pools is a depletion contingent on slow attrition and dilution through cellular division. Eventually, the pool falls to a level that will no longer permit multiplication, and the organism passes into a resting phase. The sulfonamide is thus bacteriostatic in its action.

Trimethoprim, by blocking the reduction of dihydrofolate, reduces the tetrahydrofolate pool more rapidly. In part, the attrition of the tetrahydrofolate pool is assisted by the activity of thymidylate synthetase, since in this reaction the cofactor not only transfers a one-carbon fragment (methylene) but contributes to the reduction of the methylene group to methyl, and is itself oxidized to dihydrofolate. The effect of trimethoprim is thus to trap folates in the dihydro-state, and the functional tetrahydrofolate pool is depleted.



Trimethoprim, however, is a competitive inhibitor of dihydrofolate reductase 10. The accumulation of dihydrofolate, through continuing biosynthesis and reoxidation of tetrahydrofolate, tends to increase the metabolite: antimetabolite ratio and diminishes the effectiveness of the blockade. Conjoint application of a sulfonamide, however, removes the source of new dihydrofolate and improves the effectiveness of the inhibition. In practice the simultaneous use of the 2 inhibitors results in a 5-10-fold potentiation, broadening of the spectrum of action, a decreased liability to the development of resistance, and a conversion of bacteriostatic to bactericidal effects?

Trimethoprim emerged from a group of diaminopyrimidine derivatives which were viewed "as structural analogues of folinic acid of a remote sort" that were selective because they could have a "differential affinity...for the receptors of the parasite..." In the beginning they were characterized as substances that interfered with the utilization of folic acid by lactic acid bacteria. With the isolation and characterization of dihydrofolate reductase, their target was identified. The application of a spectrum of inhibitors to a selection of partially purified reductases documented their mechanism of action, and revealed with clarity the magnitude of their differential affinities for the reductases of different species. Trimethoprim represents the culmination of an effort to tailor a molecule for maximum binding to bacterial reductases with minimum binding to mammalian reductases "12".

Its selectivity has important implications for both chemotherapy and for evolution. The most probable interpretation of its action is that it is bound partly within and partly outside the active center of the enzyme. It thus differs in locus of binding from a structural analogue of folic acid, such as methotrexate, which has all the binding groups of the substrate and would thus be expected to bind in proportion to the substrate binding. The implication of selective binding in regions of the enzyme near to, but not in, the active center, is that evolutionary changes have been much more active in these supporting structures than in the active center itself. Dihydrofolate reductase thus falls in line, with hemoglobins and other proteins, now known to exist in manifold variants that retain, in the main, the function of the primitive protein. It is being recognized that mutational changes are occurring at rates that would have been regarded as improbably enormous only 5 years ago, out that the bulk of such mutations are neutral<sup>19</sup>. An exciting chapter in the history of dihydrofolate reductase still lies ahead when studies on the sequence and conformation of the enzyme from different sources will permit comparative studies.

For chemotherapy, trimethoprim and its relatives carry the implication that selective inhibition of any function may be possible, and that the most probable access to selective effects may lie in the supportive structures of the cellular receptors.

### References

- 1. G. H. Hitchings, Cancer Res., 29, 1895 (1969).
- 2. G. H. Hitchings and J. J. Burchall, Adv. in Enzymol., 27, 417 (1965).
  - 3. L. P. Garrod, Drugs, 1, 3 (1971).

1;

- 4. Editorial, Drugs, 1, 7 (1971).
- G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood and H. VanderWerff, J. Biol. Chem., 183, 1 (1950).
- 6. J. J. Burchall and G. H. Hitchings, Mol. Pharmacol., 1, 126 (1965).
- 7. G. H. Hitchings, Ann. N. Y. Acad. Sci., 186, 444 (1971).
- 8. G. M. Brown, J. Biol. Chem., 237, 536 (1962).
- 9. G. H. Hitchings, Postgrad. Med. J. suppl., 45, 7 (1969).
- 10. J. J. Burchall, Postgrad. Med. J. suppl., 45, 29 (1969).
- 11. G. H. Hitchings, E. A. Falco, H. VanderWerff, P. B. Russell, and G. B. Elion, J. Biol. Chem., 199, 43 (1952).
- 12. J. J. Burchall, Ann. N. Y. Acad. Sci., 186, 143 (1971).
- 13. T. Ohta and M. Kimira, Nature, 233, 118 (1971).

### Section I - CNS Agents

Editor: Edward L. Engelhardt

Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486

Chapter 1. Antipsychotic and Anti-anxiety Agents

Charles L. Zirkle and Carl Kaiser Smith Kline & French Laboratories, Philadelphia, Pa. 19101

Introduction - Despite continuation of the extensive research efforts in this field, no fundamentally new antipsychotics and anti-anxiety agents emerged in 1971. However, the ever expanding investigations of the monoaminergic, particularly catecholaminergic, pathways in the brain and of the effects of drugs upon them suggest that this approach, which was so successful in setting the stage for the discovery of L-dopa for the treatment of parkinsonism, will eventually lead to a better understanding of the presently available drugs and to more effective or selective psychotropic agents. An important clinical development was announced - the resolution of the controversy over the use of Li<sub>2</sub>CO<sub>3</sub> as prophylactic treatment of manic-depression. Results of an extensive 4 year study to be reported by NIMH have confirmed the belief long held by some clinicians that daily use of the drug is effective in preventing broad swings in mood in patients with this disorder. A number of books and reviews treating the biochemical, 2 mb pharmacological, 3 mb clinical, 4 and structure-activity 110 aspects of the antipsychotics and anti-anxiety agents have been published.

Tricyclic compounds with a six-membered central ring - Newer phenothiazine derivatives with clinical antipsychotic efficacy included oxaflumazine (la), 11 a potent cataleptogenic in animals, 12 pipotiazine (lb, RP 19,336), 13 which has a pharmacological profile similar to that of fluphenazine, and a related piperidinol SA 124 (lc). 14 Extensive studies indicated clospirazine (ld, APY-606), 15 116 had clinical antipsychotic activity equivalent to that of chlorpromazine. 17

Several fatty acid esters of alcoholic phenothiazine derivatives, e.g., pipotiazine (1b) undecyclenate and palmitate, fluphenazine enanthate<sup>10</sup> and decanoate,<sup>17</sup> and perphenazine enanthate, as well as the related thioxanthene, flupenthixol decanoate, found clinical utility in antipsychotic maintenance therapy.<sup>20</sup> These esters can afford advantages in absorption to enable attainment of high drug-levels in the CNS<sup>21</sup> and to provide clinical efficacy of 2 to 4 weeks duration following a single injection.<sup>20</sup>

The most effective of a series of phenothiazines having diazabicyclo[4.4.0] decane and -[4.3.0] nonane systems in the side chain was le. In rats le was similar to perphenazine; it blocked conditioned avoidance response (CAR) at 0.5 mg/kg, sc.<sup>22</sup> Imiclopazine (1f), 5014 (1g) and 5023 (1h) were the most potent compounds in a series of imidazolone and oxazolidone derivatives of phenothiazine and 1-azaphenothiazine; they were more potent than perphenazine in tests for sedation and antiaggression in mice and as antiemetics in dogs.23

c) 
$$X=H$$
;  $R=N$  OH

d)  $X=C1$ ;  $R=N$  OH

a)  $X=CF_3$ ;  $R=N$  N( $CH_2$ ) OH

b)  $X=SO_2$  N( $CH_3$ ) 2;  $R=N$  ( $CH_2$ ) OH

f)  $X=C1$ ;  $R=N$  N( $CH_2$ ) 2 N NCH

g)  $X=C1$ ;  $R=N$  N( $CH_2$ ) 2 N NCH

h)  $X=CF_3$ ;  $R=S$  are as in  $g$ 

The most effective member (2a) in a series of amine-altered congeners of unsaturated thioxanthene antipsychotics was nearly equipotent with chlorpromazine in blocking CAR in rats and in depressing spontaneous motor activity (SMA) in mice. $^{24}$  Another thioxanthene ( $\underline{2b}$ , prothixene) decreased SMA in mice only at high doses; however, it caused marked hypocholesteremiain rats.<sup>25</sup> A dihydroanthracene, SK&F 28175 (3a), produced pharmacological responses characteristic of both neuroleptic and antidepressant drugs whereas a demethyl analog, SK&F 25971 (3b), caused only chlorpromazine-like effects.26

a) 
$$X = CCF_3$$
;  $R = N$   $N(CH_2)_2$   $OH$ 

b)  $X = OCH_2$   $C_3$   $R = N$   $CCF_3$ 

a)  $R = CH_3$ 

b)  $R = H$ 

<u>Tricyclic compounds with a seven-membered central ring</u> - A dibenzo-diazepine, clozapine (4, HF-1854), was effective in psychotic patients;<sup>27</sup> however, it produced neither neuroleptic-like (e.g., catalepsy, antiemetic) actions in animals<sup>28</sup> nor parkinsonism-like symptoms in man. A derivative of dibenzthiepin, GP 45795 (5a), was more potent than chlorpromazine in various animal tests for neuroleptic activity and it antagonized amphetamine— and tetrabenazine—induced responses.<sup>29</sup> Clinically, <u>5a</u> improved

chronic schizophrenics.<sup>30</sup> Among a series of related structures, noroctoclothepin (5b), oxometothepin (5c) and oxyprothepin (5d) had neuroleptic-like activity equal to, or greater than, that of octoclothepin in mice.<sup>31</sup> Clinical antipsychotic properties were reported<sup>32</sup> for 5d. Dehydroclothepin (6), one of a series of dibenzthiepins and dibenzoselenopines, was more potent than perphenazine in rotating rod and catalepsy tests in mice; however, toxicity and instability in aqueous acid are possible deterrents to its clinical investigation.<sup>33</sup> Two unsaturated congeners of peradithepin,<sup>15</sup> 7a and 7b, were substantially more potent than the parent in a rat catalepsy test.<sup>34</sup>

A dibenzazepine, "3-chlorocarpipramine" (8, Y-4153), was effective in assays of neuroleptic activity (0.2-1X chlorpromazine) and it is claimed to lack catoleptogenic properties.<sup>35</sup>

Butyrophenones and related compounds - The butyrophenone <u>9a</u> was effective in the therapy of schizophrenics and caused only mild side effects; it selectively blocked CAR (0.1X trifluperidol) in mice. AHR-2277 (<u>9b</u>) was more potent than chlorpromazine, but less potent than haloperidol, in suppressing CAR in mice and cats in doses below those producing obvious motor defects. A related compound AHR-1900 (<u>9c</u>) elicited neuroleptic-like behavioral effects in mice, rats and squirrel monkeys. In a series of butyrophenones bearing unsaturated amino substituents, most potent CNS depressant activity in mice was noted with <u>9d</u>. Abbott-30360 (<u>9e</u>) combined neuroleptic properties with analgetic potency approximately equal to that of morphine. The most potent compound (<u>10</u>) in a series of methyl-branched aminobutyrophenones was only weakly depressant in mice.

$$F \longrightarrow CO(CH_2)_{\mathfrak{z}} R \qquad \frac{9a}{9b} R = N \longrightarrow CO \longrightarrow F \qquad 9e) \qquad R = N \longrightarrow F$$

$$\frac{9}{9c} R = N \longrightarrow CO_{\mathfrak{z}} H_{\mathfrak{z}} - 2 - OCH_{\mathfrak{z}} \qquad \frac{9e}{H} \qquad R = N \longrightarrow F$$

Other structures with antipsychotic activity - A molindone analog, AL 1612 (11), demonstrated antiemetic and neuroleptic properties in animals;42 however, clinical antipsychotic activity was accompanied by a high incidence of extrapyramidal side effects.43 Combined clinical antipsychotic and antidepressive actions were noted for sulpiride. Sch-12,679 (12) reduced aggressive behavior in mice and monkeys; however, a clinical study indicated it is not a classical neuroleptic. Chronic schizophrenics were improved by <u>D</u>-penicillamine. Prostaglandin E, like chlorpromazine, decreased CAR in both naive and trained rats. [ thieropyridine, EX 11-349 (13), decreased SMA in mice and was effective in a fighting mouse test (ED; 8.9 mg/kg, po).47 Several members of a series of 1-acylated-1,2-dihydroquinolines 14 antagonized amphetamine actions, blocked a CAR, and caused neuroleptic-like effects in mice and rats. 18 The cis-, but not the trans, aminoalcohol (15) was effective in several pharmacological tests for neuroleptic activity. In mice. the benzothiazinone 16 was the most potent of a series of compounds in causing depression, catatonia and decreased SMA.50

Benzoquinolizine-like (short-acting, selective) depletion of central catecholamines was produced by Ro-8-2580  $(\underline{17})^{51}$  and U-20,057  $(\underline{18})$ ,52 compounds causing neuroleptic-like effects in animals.

Benzodiazepines and related compounds - The chemistry and some aspects of the relationship between the structure of 1,4-benzodiazepines and their anti-anxiety activity were reviewed in 1971.<sup>53</sup> In clinical studies, demethdiazepam (19a, Ro-5-2180, A-101) was more effective than diazepam for the treatment of anxiety;<sup>54</sup> however, Ro-5-3350 (19b) was less