Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Structure-Activity Relationships of Thiophene Derivatives of Biological Interest

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To cite this Article Drehsen, G. and Engel, J.(1983) 'Structure-Activity Relationships of Thiophene Derivatives of Biological Interest', Journal of Sulfur Chemistry, 3: 5, 171 — 207
To link to this Article: DOI: 10.1080/01961778308082453
URL: http://dx.doi.org/10.1080/01961778308082453

Sulfur Reports
Volume 3(5), August 1983, pp. 171–214
0196-1772/83/0305–0171/$12.00/0

Printed in the United States of America

STRUCTURE-ACTIVITY RELATIONSHIPS OF THIOPHENE DERIVATIVES OF BIOLOGICAL INTEREST

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Literature data on thiophene structure-activity relationships of the last 10 years are reviewed. With regard to the broad spectrum of molecular structures the investigated compounds have been arranged according to their various therapeutic properties as indicated by the specific biological test systems. The interchange with the thiophene ring included mainly the following aromatic ring systems: benzene naphthalene, furan, pyridine, thiazole, pyrrole, and the respective indole, benzofuran, and benzthiazole analogs. Summarizing these findings it can be concluded that no general activity pattern can be given. Neither the exchange of the 2-thienyl moiety by the 3-thienyl nor the replacement of the thiophene ring by various aromatic rings resulted in a consistent superiority of any of the molecular structures.

INTRODUCTION

Recently, thiophene derivatives, marketed drugs as well as agents under clinical investigation, have been reviewed comprehensively, however, excluding aspects of structure-activity relationship.[1,2]

A summary of physiological activities of thiophene derivatives in relationship to replacement of the aromatic thiophene nucleus by various heterocycles or the phenyl group comprises literature up to the early sixties.[3] In conclusion, this review showed a general biological similarity of the phenyl and thienyl groups. While quantitative differences could be observed the respective isomers seemed to display some unique biological activity, too.

The investigation of sympathomimetic agents with a phenylethyl structure demonstrated that the biological activity did not depend on the phenyl ring. Replacement of the latter by the 2- or 3-thienyl moiety led to no significant decrease of potency.[4]

The studies of Campaigne and co-workers were designed to elucidate the biological effects after a 2-thienyl group had been replaced by a 3-thienyl one. The anticonvulsant activity of hydantoin derivatives was found to be more pronounced in the 3-thienyl compounds than in the 2-thienyl ones. The toxicity of the latter was even higher by a factor of 3.[5]

In the first instance, this report is meant to update results in the field of structure-activity relationships of thiophenes, especially those of the last 10 years. Patent literature was not included since exact data on pharmacological findings are often missing. Secondly, the comparison of findings with a broad range of molecular structures and physiological activities should allow conclusions for further designs in the research for

potent drugs. In this review only results of self-consistent pharmacological tests were cited because of the well-known reproducibility problems arising from different animal species as well as from changing test conditions. Thus this review reports on the biological consequences of the replacement of the thiophene moiety by various aromatic ring systems (e.g. phenyl, naphthyl, heterocycles). Because of the heterogeneity of the molecular structures involved the agents have been grouped according to their medical indications.

List of Agents Groups Investigated

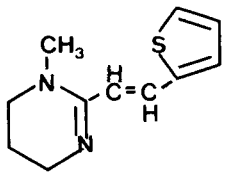
1. Chemotherapeutics
1.1 Agents against parasitic diseases
1.1.1 Anthelmintics
1.1.2 Antiprotozoals
1.1.2.1 Agents against trypanosomiasis
1.1.2.2 Agents against schistosomiasis
1.2 Antimicrobial agents
1.2.1 Tuberculostatics
1.2.2 Cephalosporins
1.2.3 Penicillins
1.2.4 Miscellaneous antibacterial agents
1.2.5 Antifungal agents
1.2.6 Antiviral agents
2. Insecticides
3. Hypolipidemic agents
4. Diuretics
5. Analgesic-antipyretics, anti-inflammatory agents
6. Psychoactive agents
7. Amines, biogenic amines
8. Vasoactive agents
9. Agents acting at synaptic and neuroeffector functional sites
10. Amino acid analogs
11. Retinoids
12. Bradykinin analogs
13. Pancreozymine analogs
14. Inhibitors of arginine-specific esteroproteases

1. CHEMOTHERAPEUTICS

1.1 Agents against parasitic diseases

1.1.1 Anthelmintics The anthelmintic compounds pyrantel and morantel belong to the well-known examples of structure variations among thiophene derivatives.[6]

Pyrantel pamoate was introduced into veterinary practice as a broad-spectrum anthelmintic effective against pinworm, roundworm, and hookworm.



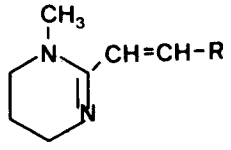
1 Pyrantel

The aromatic ring is essential for non-negligible activity. The potency decreases in the sequence 2-thienyl- > 3-thienyl- > phenyl- > 2-furyl-, whereas pyrryl, pyrrazolyl, or thiazolyl analogs are inactive.[7]

More recently, pyrantel analogs have been tested against whipworm (*Trichuris muris*) though it is well-known that pyrantel itself is inactive against adult whipworms. As can be seen from Table I the phenyl derivative is inferior to the thienyl one when investigated in mice.[8] Additionally, this study revealed a significant increase in potency depending upon the methyl substitution in the ortho, meta, and para positions of the phenyl ring.

TABLE I

Activity of Pyrantel Analogs against *Trichuris Muris* in Mice[8]



R	ED_{90} mg/kg
Pyrantel = 2-thienyl	> 100
phenyl	200
o-toly	> 31
m-tolyl	> 200
p-tolyl	> 250

1.1.2 Antiprotozoals

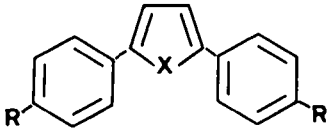
1.1.2.1 Antiprotozoals against trypanosomiasis Substituted thiophenes and *N*-methylpyrroles have been tested against *Trypanosoma rhodesiense* in mice, see Table II.[9] The aromatic diamidine derivative Pentamidine, a compound introduced into therapy a number of years ago, was used as the reference substance. On the one hand, furan, which had been tested previously, thiophene, and *N*-methylpyrrole showed comparable activity. On the other hand, the compounds exhibited comparable levels of activity to the standard diamidines, e.g. Pentamidine. Thus the authors concluded that the role of the 5-membered heterocycle could be nothing more than that of a relatively inert spacer for the guanylphenyl functions.[9]

Similar results were obtained in mice with trypanocidal diamidines containing three isolated ring systems,[10] see Table III. Both compounds, the benzothiophene and the indole, are virtually equipotent.

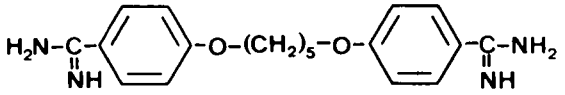
1.1.2.2 Antiprotozoals against schistosomiasis Substituted nitrofurans and nitrothiophenes have been tested in mice infected with *Schistosoma mansoni* (Tables IV, V).

TABLE II

Activities of Thiophenes and *N*-Methylpyrroles in Mice[9]



3



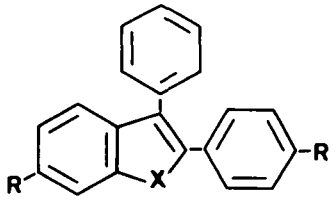
4

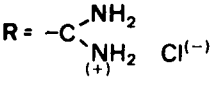
X	Cures[a] at Dosage			
	1.25 (mg/kg)	2.5 (mg/kg)	5.0 (mg/kg)	10 (mg/kg)
S	2	3	4	5
NCH_3	1	2	4	5
Pentamidine	1	4	5	5

[a] a cure is defined as a 30 day increase in survival time of 5 treated mice over the controls, pentamidine serving as the reference compound

TABLE III

Comparison of the Trypanocidal Activity of Diamidines in Mice[10]





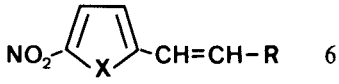
5

X	[a]Curative activity after infection with		
	T. gambiense	*T. rhodesiense*	*T. congolense*
S	+ +	+ +	+ +
NH	+ +	+ +	+

[a] minimal curative dose
+ + = 10–100 mg/kg
+ = >100 mg/kg

TABLE IV

Antischistosomal Activity in Mice[11]



6

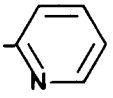
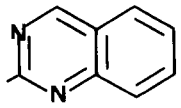
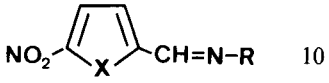
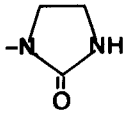
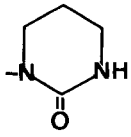
X	R		Dose mg/kg	Short-term effects: % Damage to female worm reproductive system	Long-term effects: % reduction of worms
O		7	250	97	91
S			200	50	19
O		8	250	18	0
S			200	15	10
O		9	200	71	21
S			200	17	0

TABLE V

Antischistosomal Activity in Mice[12]



10

X	R		% Kill of worms[a]
O		11	0
S			12
O		12	0
S			84

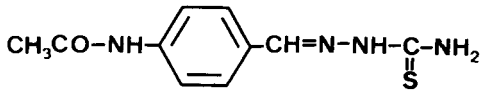
[a] the compounds were dosed once per day on 4 consecutive days—250 mg/kg orally on the first 2 days and 25 mg/kg intraperitoneally on the third and fourth day

Among the many types of drugs that have shown potentially useful antischistosomal activity the nitroheterocycles have demonstrated unusual promise. As can be seen from Table 4 the furan derivatives exhibit clearly superior activity compared to the respective thiophene compounds.[11] Furthermore, when R is a monocyclic heterocycle, the potency is increased in comparison with the benzopyrimidine analog.

However, the investigation of a different series of nitrofurans and nitrothiophenes (Table V) demonstrated the ineffectiveness of the furan derivatives whereas the thiophene analogs were effective.[12]

1.2 Antimicrobial agents

1.2.1 Tuberculostatics Thiosemicarbazones, e.g. the drug thiacetazone found by Domagk, have a potential tuberculostatic effect.[13]



13

(thiacetazone, conteben, tebethion)

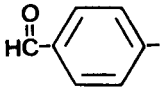
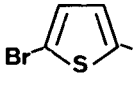
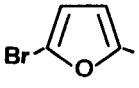
Thiacetazone has been under experimental clinical investigation in different countries. Thus a series of new thiosemicarbazone derivatives have been investigated in infected mice, see Table VI.

The results of the investigation[13] can be summarized as follows: The furan and thiophene compounds can be considered as equipotent. However, compared with the known efficacy of thiacetazone, these new compounds must be regarded as weak agents and therefore were not specifically tested against the standard drug. In addition, bromo substitution in the 5-position of the thiophene and furan ring increases the activity.

TABLE VI

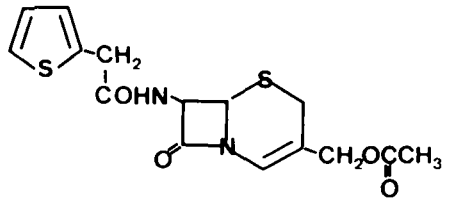
Tuberculostatic Activity in Mice[13]

R—CH=N—NH—CS—NH_2

R		Oral dose mg/kg	Q[a]
	14	250	1.09
		500	1.14
	15	37.5	0.96
		75.0	1.05
	16	12.5	0.96
		25.0	0.91
	17	10.0	0.98
		20.0	0.93

[a] Q = therapeutic potency defined as the ratio of the pathological index in the test divided by that of the control

1.2.2 Cephalosporins (β-lactam antibiotics) Cephalotin is a semisynthetic derivative of cephalosporin C

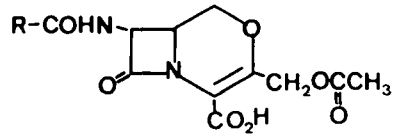


18 Cephalotin

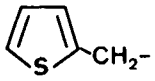
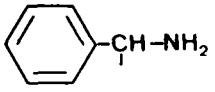
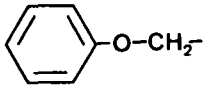
A series of compounds of isocephalosporins has been synthesized and tested *in vitro*, cephalotin being the reference drug.[14] The initial goal of the study was first to examine whether or not it was necessary to retain the sulfur atom in position 1 of the cephalosporin ring of cephalotin and secondly if the heteroatom could be moved to position 2. The *in vitro* results (Table VII) show that the thiophene derivative has a broad-spectrum antibacterial activity which is definitely better than that of the phenylderivatives.[14] It must be stressed that in this case the thiophene moiety was not replaced by the respective phenyl rest. However, the examples cited here are of special interest. According to the intentions of this investigation it could be proved that the thiophene compound (isocephalotin) is highly active against *Staphyloccus aureus*, cephalotin being only slightly

TABLE VII

In vitro Activities of Some Isocephalosporins Against Gram-Positive and -Negative Bacteria[14]



19

		Minimum inhibitory concentrations (MIC) μg/ml										
R		*S. pyogenes*	*S. aurens* Smit	BX 1633	*E. coli* Juhl	9675	*K. pneumania* 9977	1530	*Proteus mirabilis*	*morganii*	*Enterobacter doacae*
	20	0.03	0.50	2	8	63	1	63	1	> 125	16
	21	0.06	1	8	1	4	1	8	0.5	32	2
	22	0.13	1	125	16	125	16	> 125	4.0	> 125	63
Cephalotin		0.06	0.13	0.25	16	63	0.25	16	0.5	> 125	2

better, whereas it is even superior to cephalotin against *S. pyogenes*. The *in vivo* blood levels in mice after both agents were essentially equivalent with high protection especially against *S. pyogenes*, the thiophene derivative being slightly superior to cephalotin.[14]

1.2.3 Semi-synthetic penicillins—Ampicillin analogs Ampicillin has a broad spectrum of antimicrobial activity. A variety of ampicillin analogs containing heterocyclic groups instead of phenyl have been synthesized and tested *in vitro*.[15] The results are shown in Table VIII.

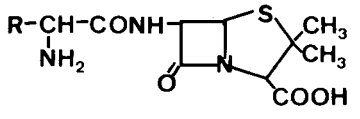
The diastereoisomeric compounds showed all high broad-spectrum antibacterial activity similar to ampicillin. The 3-thienyl derivative was slightly less active than ampicillin and the 2-thienyl compound.[15] The thiazole and isothiazole agents exhibited equipotent activities comparable to those of the 2-thienyl derivative.

1.2.4 Miscellaneous antibacterial agents

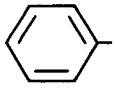
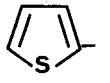
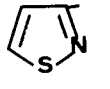
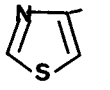
1.2.4.1 Nalidixic acid type compounds Nalidixic acid possesses activity against Gram-positive and -negative bacteria. The isostere with the thienyl ring proved to have the same

TABLE VIII

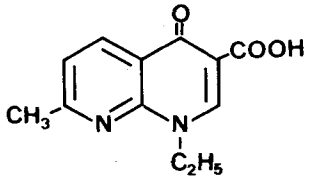
Antimicrobioal Activity of Ampicillin Analogs[27]



23

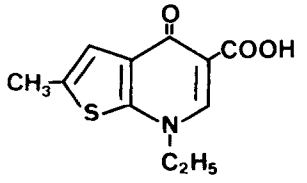
R		Minimum inhibitory concentrations (MIC) μg/ml					
		S. aureus	*S. epidermis*	*B. subtilis*	*E. coli*	*Sal. enteritidis*	*Shig. dysenteriae*
	24	0.037	1.25	0.037	2.5	10	0.3
(= Ampicillin)							
	25	0.075	0.62	0.15	5	5	1.25
	26	0.32	1.25	0.075	5	10	1.25
	27	0.07	0.15	0.31	10	2.5	0.65
	28	0.075	0.62	0.03	10	5	1.25

antibacterial potency. It could be demonstrated that the carboxylic acid group is essential for the antibacterial activity.[16]



29

nalidixic acid



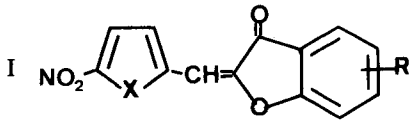
30

thienyl analog

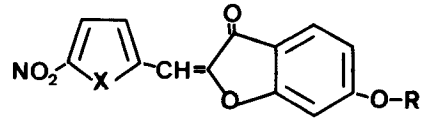
1.2.4.2 Nitroheterocycles 2-(5-Nitro-2-furfurylidene) compounds, derived from cyclic ketones, often exhibit interesting antimicrobial activities. Thus some nitrofurfural, -thiophene and -pyrrole analogs have been synthesized. Some of these compounds and their *in vitro* activities are listed in Table IX. They were tested against Gram-positive and -negative bacteria, mycobacteria, fungi, and trichomonades. No compound was active against *Entamoeba histolytica*. On the basis of these results the authors came to the

TABLE IX

In vitro Antimicrobial Activities of Nitroheterocycles[17]



31



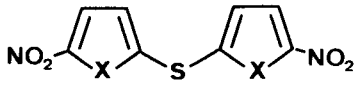
32

			Minimum inhibitory concentrations (MIC) μg/ml								
	X	R	*S. aureus*	*E. coli*	*Prot. vulg.*	*K. pneum.*	*Pseud. aerug.*	*M. tubercul.*	*Cand alb.*	*Trich. ment.*	*Trichom. vag.*
I	a S	6-OH	0.78	6.2	—	—	—	3.1	—	—	0.098
	b NH	6-OH	—	—	—	—	—	—	—	—	6.2
	c O	6-OH	0.012	0.2	0.2	0.39	1.6	—	—	—	0.098
II	d S	COC_3H_7	0.2	—	—	—	—	—	—	—	0.39
	e NH	COC_2H_5	—	—	—	—	—	—	—	—	1.6
	f O	COC_2H_5	0.006	0.2	0.2	0.39	1.6	0.2	3.1	12	0.2
	g O	COC_3H_7	0.012	0.2	0.098	0.20	0.78	0.2	—	12	0.78

following conclusions:[17] The thiophene and pyrrole analogs are less active than the respective nitrofuran compounds. The activity is strongly affected by the ring substitutents, but a propionyl and a butyryl group leads to nearly the same activity (see f, g).

Two series of nitrofuran and nitrothiophene derivatives of 1,3-dioxane-4,6-diones showed considerable activities against bacteria, protozoae, and various dermatophytes.[18] The results are listed in Table X. The activities of the thiophene and furan analogs vary strongly according to the test system so that a general conclusion can hardly be given. While the furans show superior activity against *Trichomonas vaginalis* and *Entamoeba histolytica* the thiophenes of series I and II are more potent against *Shigella flexneri* and *Trichophyton quincleanum* and series I thiophenes are the most effective against *Microsporum canis* and *Candida albicans*.

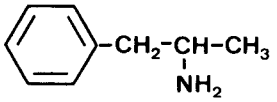
Equal antibacterial activities of *33*(X = O) and *33*(X = S) have been reported in the literature.[19]



X=S, O

33

1.2.4.3. Amphetamine sulfonamides with antimicrobial activity Amphetamine is a psychostimulant with a phenylaminopropane structure.



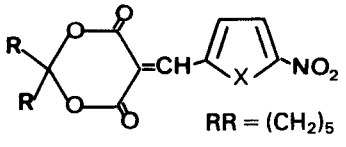
36

Sulfonamide derivatives of amphetamine (e.g. formula in Table XI) generally showed no psychoactive effects, but several of these agents were successfully tested against Gram-

TABLE X

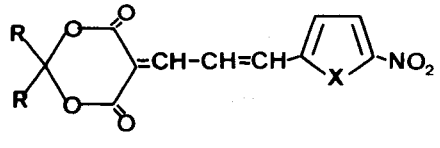
***In vitro* Antimicrobial Activities of Nitrofurans and Nitrothiophenes[10]**

I



34

II



35

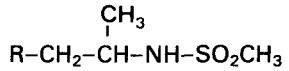
		Minimum inhibitory cooncentrations (μg/ml)					
	X	*Trich. vag.*	*Entamoeba histolytica*	*Shig. flexneri*	*Trichoph. quinck.*	*Microsp. canis*	*Cand. alb.*
I	O	5.0	12.5	> 50	> 100	> 100	> 100
	S	25	25	6.3	25	25	10
II	O	6.3	1.6	> 50	50	25	> 100
	S	> 100	> 100	25	> 100	50	> 100

positive and -negative bacteria, a mold, and a yeast.[20] Appreciable sulfonamide-like activity was observed for most of the compounds, however, without any compound demonstrating a clear superiority in dependence of the nature of the aromatic nucleus, see Table XI.

1.2.4.4 α-Amino γ-keto esters and aroylacrylic Esters β-Amino ketones have been found to possess antibacterial activities.[21] Also derivatives of α-amino γ-ketones and aroylacrylic esters have been synthesized and tested. The *in vitro* results of with regard to the antimicrobial properties of various compounds are listed in Table XII.[21] The most

TABLE XI

Antimicrobial Activities of Some Amphetamine Sulfonamides[20]

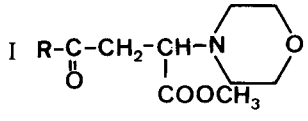


37

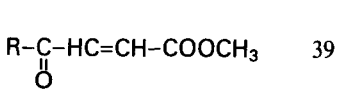
Minimum inhibitory concentrations (1/M)				
R	***S. aureus***	***E. coli***	***Aspergillus niger***	***Cand. alb.***
2-thienyl	< 10.000	< 10.000	< 10.000	< 100.000
3-methyl-2-thienyl	< 10.000	< 10.000	< 10.000	< 10.000
3-pyridyl	< 10.000	< 10.000	< 10.000	< 100.000
4-chlorophenyl	< 10.000	< 10.000	< 10.000	< 10.000

TABLE XII

In vitro Antimicrobial Activities of α-Amino γ-Keto Esters and Aroylacrylic Esters[21]



38



39

Minimum inhibitory concentrations (μg/ml)								
R	***S. oxford***	***S. faecalis***	***Bac. subt.***	***Eber-typh.***	***E. coli***	***Prot. vulg.***	***K. pneum.***	***Pseud. aerug.***
I								
phenyl	4	128	> 1024	128	128	128	512	> 1024
2-thienyl	8	128	> 1024	128	128	64	512	> 1024
2-furyl	16	128	256	256	64	32	256	> 1024
II								
phenyl	8	128	> 1024	128	128	64	256	> 1024
2-thienyl	16	128	> 1024	128	64	64	128	> 1024
2-furyl	16	128	> 1024	128	32	32	512	> 1024

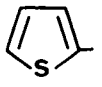
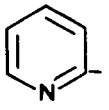
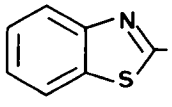
pronounced effects can be seen in the furan derivative of series I, whereas the phenyl and 2-thienyl compounds are equipotent. The three compounds of series II can be regarded as equipotent.

1.2.5 Antifungal agents Heterocyclic sulfonylmethyl thiocyanates proved to have high fungicidal activities in the spore germination test on slides:[22] The replacement of the thiophene moiety by either pyridine or benzthiazole did not significantly change the fungicidal properties (Table XIII).

TABLE XIII

Fungicidal Activity of Heterocyclic Sulfonylmethyl Thiocyanates[22]

R - SO_2CH_2SCN 40

		Minimum inhibitory concentration[a]	
R		*Fusarium culmorum*	*Venturia inaequalis*
	41	5.0	5.9
	42	4.7	5.3
	43	6.2	6.5

[a] neg. log. of the conc.

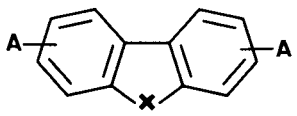
1.2.6 Antiviral agents Reports describing the antiviral activity of bis-(aminoalkyl) esters, ethers, and ketones of fluorene and fluorenone led to the investigation of dibenzofuran and dibenzothiophene analogs. Antiviral activities were determined *in vivo* against encephalomyocarditis (EMC) virus. The activities are expressed as survival time ratios (STR); see Table XIV.[23] In one case the thiophene analog, bearing ester side chains, was the most potent compound within the series. However, generally, the fluorenone nucleus contributed most to the potency, the furan derivatives being the least active. Furthermore, the basic ketone side chain had the greatest positive influence on the antiviral activity relative to basic ester and ether chains.[23]

2. INSECTICIDES

Some chrysanthemates have been tested as insecticides. The insecticidal activity was measured by the dry film method using first instar nymphs of the American cockroach as the test insect and is represented by percent mortality after 24 h, the furan analog being clearly the most potent.

TABLE XIV

Antiviral Activities of Dibenzofurans and -Thiophenes, Fluorenes, and Fluorenones[23]



44

$A_1 = —CO_2—(CH_2)_3—N(C_2H_5)_2$

$A_2 = —O—(CH_2)_2—N(C_2H_5)_2$

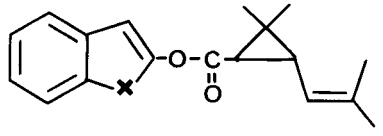
$A_3 = —CO—(CH_2)_3—N(C_2H_5)_2$

	STR values[a]		
X	A_1	A_2	A_3
CH_2	1.09	1.22	2.08
C=O	1.63	1.95	2.19
O	1.19	1.31	1.49
S	1.77	1.12	1.90

[a] STR is defined as the mean day of death of the treated group of mice divided by the mean day of death of the control group (= mean survival time ratio) after 50 mg/kg of test compound (administered subcutaneously)

TABLE XV

Insecticidal Activity of Some Chrysanthemates[24]



45

	Mortality in % at μg per dose		
X	100	10	1
O	100	100	75
S	100	100	25
CH_2	100	95	0

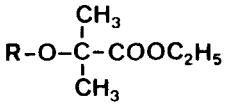
3. HYPOLIPIDEMIC AGENTS

3.1 Clofibrate analogs

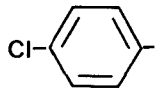
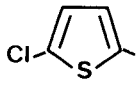
The hypolipidemic effects of clofibrate analogs, clofibrate being a marketed lipid-lowering drug, have been investigated *in vivo* in rats[25] and in mice.[26] The thiophene analog of clofibrate showed only weak hypolipidemic activity in hyperlipidemic rats, Table XVI.[25] In a further series of experiments it could be demonstrated that the analogs

TABLE XVI

Hypolipidemic Activity in Rats of the Thiophene Analog of Clofibrate[25]



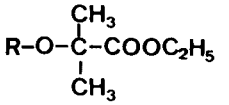
46

R[a]		% Reduction of plasma	
		Cholesterol	Triglycerides
 = clofibrate	47	27	25
	48	8	19

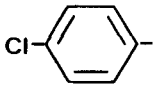
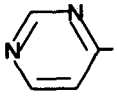
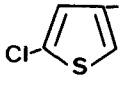
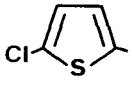
[a] the compounds were supplemented to the diet at a level of 0.3 %

TABLE XVII

Hypolipidemic Activities in Mice of Clofibrate Analogs[26]



49

R[a]		% Reduction of plasma	
		Cholesterol	Triglycerides
 clofibrate	50	−10	47
	51	12	21
	52	31	41
	53	−12	−13

[a] the compounds were supplemented to the diet at a level of 0.3 %. The percentage of reduction represents values obtained versus untreated control animals. Negative values represent an increase.

were inferior to clofibrate, but the 2-thienyl compound showed an interesting cholesterol reducing effect, Table XVII.[26] However, a clear superiority of the 2-thienyl over the 3-thienyl derivative could be established.

3.2 γ-Aroyl-β-methylbutyric acids and δ-aroyl-β-methylvaleric acids

Several *p*-biphenylyl substituted acids have been reported to exhibit hypocholesterolemic activity in both animal and human studies.[27] Therefore, hypolipidemic effects of aromatic substituted acids were assessed in rats. Table XVIII indicates the degree of serum lipid (Cholesterol and triglycerides) reduction.[27]

The biphenylyl group can be replaced by the ring system of dibenzofuran and -thiophene, thus resulting in a slight additional lowering of serum triglyceride levels. The furan and thiophene analogs, however, are equipotent.

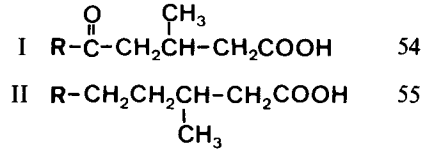
3.3 Substituted carboxylic acids

The research for agents against atherosclerosis led to substituted benzoic acids. A significant reduction of plasma lipids in rats was also obtained with substituted heterocycles,[28] Table XIX.

Replacement of the benzene ring—with a carboxylic acid group in the para position—by furan or thiophene enhanced the potency of the hypolipidemic agents; on the other hand, the two heterocylic compounds were equipotent.

TABLE XVIII

Hypolipidemic Activities in Rats[27]



I $R-\overset{O}{\overset{\|}{C}}-CH_2\overset{CH_3}{\overset{|}{C}}H-CH_2COOH$ 54

II $R-CH_2CH_2\overset{CH_3}{\overset{|}{C}}H-CH_2COOH$ 55

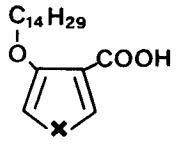
R[a]	Serum lipid reduction			
	Cholesterol		Triglycerides	
	I	II	I	II
2-Dibenzofuryl	O	++	++	+++
2-Dibenzothienyl	+	O	++	+++
4-Biphenylyl	++	+	+	++

ranges of reduction relative to control values
O = NS 15 %
\+ = significant reduction of 16–25 %
++ = significant reduction of 26–35 %
+++ = significant reduction of > 36 %

[a] the compounds were added to the diet at a level of 0.2 %.

TABLE XIX

Hypolipidemic Effects in Rats of Substituted Carboxylic Acids[28]



56

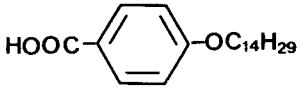
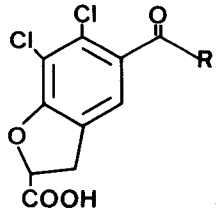
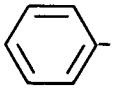
X	% Reduction of plasma		
	μmol/kg/4 days	Cholesterol	Triglycerides
O	410	40	75
S	441	54	83
 57	407	31	39

TABLE XX

Oral Natriuretic Activity in the Rat[29]



59

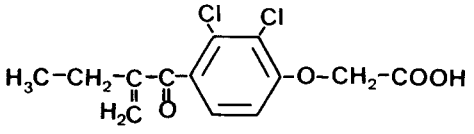
R		m equiv. of $Na^+ \times 100$/cage[a] at doses of			
		3	9	27	81 (mg/kg)
	60	175	191	257	310
	61	69	150	218	322
	62	38	82	230	284
	63	59	85	117	119
$-CH_3$	64	13	26	76	161

[a] rat per cage

4. DIURETICS

4.1 2,3-Dihydro-5-acyl-2-benzofurancarboxylic acids

Ethacrynic acid, many years ago introduced as a diuretic, has been used as a model compound for the synthesis of new diuretic agents.



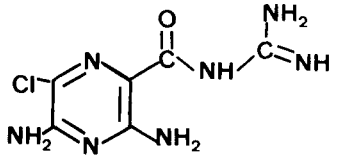
58

ethacrynic acid

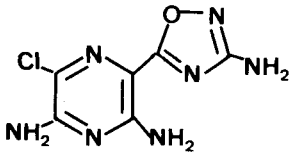
Several compounds have been tested in the rat for natriuretic activity, Table XX.[29] The thiophene derivative was superior to all other ones investigated, the heterocycles furan and isothiadiazole, as well as the phenyl and methyl compound.

4.2 3-Amino-5-aryl-1,2,4-oxadiazoles

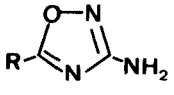
While the 1,2,4-oxadiazolyl analog derivative of amiloride, a potassium sparing diuretic, showed similar potency in the rat and dog, no significant activity was obtained when the pyrazine moiety was replaced by 2- and 3-thienyl and 3-pyridyl.[30]



amiloride 65



amiloride analog 66



inactive analogs 67

R=2-thienyl
3-thienyl
3-pyridyl

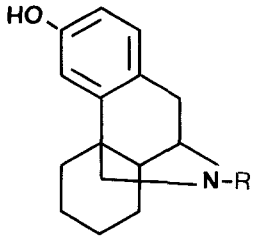
5. ANALGESICS-ANTIPYRETICS, ANTIINFLAMMATORY AGENTS

5.1 Morphinan derivatives

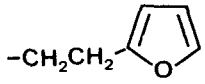
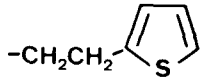
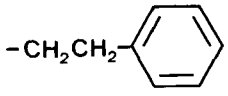
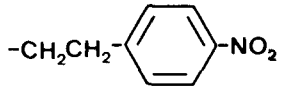
The analgesic activities of morphinan derivatives have been determined in mice using levorphanol as reference substance.[31] β-Arylethyl substituents increase the potency considerably, the most pronounced effect was recorded for the furan derivative. The replacement of furan by thiophene caused a decrease in potency of about 50 %, whereas phenyl substitution decreased it again to only one tenth of the highest value (Table XXI).

TABLE XXI

Analgesic Potency of Morphinan Derivatives[31] in the Hot-Plate Test as Determined from ED_{50} Values After Subcutaneous Application



68

R		Analgesic potency in mice
$-CH_3$ (levorphanol)	69	1
	70	30
	71	16
	72	3
	73	9

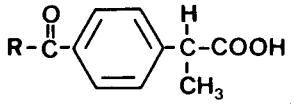
5.2 Substituted thiophene derivatives

5.2.1 Suprofen analogs Suprofen (α-methyl-4-(2-thienyl-carbonyl)benzeneacetic acid is a new drug, marketed as a potent inhibitor of prostaglandin biosynthesis. A series of suprofen analogs has been synthesized and screened pharmacologically. The writhing test was used for the determination of the analgesic potency in rats.[32] As can be seen from Table XXII the thiophene derivative is more potent than the most active reference compound ketoprofen. Indometacin and aspirin belong to the most widely used therapeutics against rheumatic diseases, whereas tolmetin and ketoprofen were introduced only recently. Replacement of the thiophene ring by 3-pyridyl and 4-thiazolyl results in a marked loss of activity.

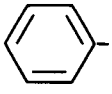
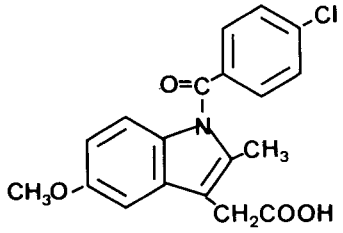
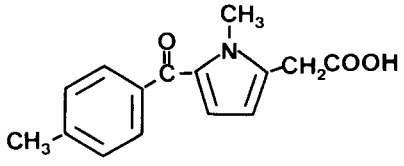
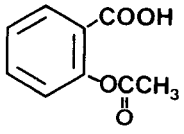
5.2.2. Thienylacetic acid derivatives Thiophene derivatives have been tested for analgesic (acetic acid test) and antiinflammatory (carrageenin edema) activity in mice.[33] The results are summarized in Table XXIII. The median active dose, which results in a protection of 50 %, respectively 40 %, shows that phenyl and α-thienyl substitution

TABLE XXII

Analgesic Activity of Suprofen Analogs as Determined by the Writhing Test in Rats[32]



74

	R	ED_{50} mg/kg p.o.
	2-thienyl=suprofen	0.074
	3-pyridinyl	2.5
	4-thiazolyl	5.0
75	 =ketoprofen	0.45
76	 =indometacin	1.1
77	 =tolmetin	2.2
78	 =aspirin	15.2

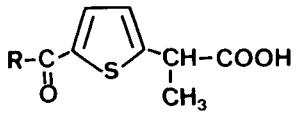
cause equipotency, replacement by α-naphthyl, however, leads to a considerable loss of activity. The furyl derivative showed different activities in both test systems, but in the same range as was found for the 2-thienyl one.

5.3 Substituted benzothiazines

Antiinflammatory activity of substituted benzothiazines was assessed in the rat foot carrageenin edema as the mean percent wise inhibition of the edema compared to untreated controls[34], Table XXIV.

TABLE XXIII

Analgesic (Acetic Acid Test) and Antiinflammatory (Carrageenin Edema) Activity of Thiophene Derivatives in Mice[33]



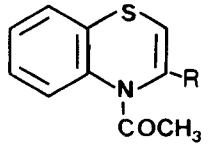
79

R	Acetic acid test [a]DA_{50} s.c.	Carrageenin edema [b]DA_{40} i.p.
phenyl	10	10
2-thienyl	10	12
2-furyl	15	8
2-naphthyl	100	100

[a] DA 50 = active dose at the 50 % level
[b] DA 40 = active dose at the 40 % level

TABLE XXIV

Antiinflammatory Activity of Substituted Benzothiazines[34]



80

R[a]	Mean inhibition (%) of Carrageenin edema in rats
p-chlorophenyl	13
p-bromophenyl	22
p-iodophenyl	42
β-naphthyl	26
α-furyl	26
α-thienyl	2
indometacin	58

[a] the compounds were administered orally at 20 mg/kg

While the furyl derivative showed slight inhibition its thiophene analog was ineffective. The β-naphthyl compound was equipotent with the α-furyl one. The activity increased as a function of halogen substitution (Cl < Br < I) of the phenyl ring.

6. PSYCHOACTIVE AGENTS

6.1 Phencyclidines

Phencyclidines were originally developed because of their advantages as analgesic-anesthetic agents. However, soon it became known that they exhibited behavioral and subjective effects in man with a certain abuse potential. Nevertheless, the pharmacological properties of phencyclidines are still under investigation.

Phencyclidine (PCP) analogs have been tested in rats in comparison to PCP.[35] The potency of PCP to produce discriminative stimuli in the rat was defined = 1. Replacement of the phenolic moiety by the thienyl group or replacement of the piperidine moiety by a pyrrolidine residue changed the relative potencies of these compounds only slightly. The effects of the morpholino derivatives were significantly poorer than those of PCP, TCP, PCPY, and TCPY (Table XXV).

A comparison of the *in vitro* activity of PCP and TCP, using the oxidation of pyruvate by brain mitochondria, revealed that the thienyl group increased the activity by 10 %.[36]

Another series of phencyclidine derivatives has been investigated with the special intention of elucidating the relationship between conformation and biological activity.[37] A clear correlation could be demonstrated (Table XXVI).

The *trans* isomer of the thienyl derivative is more than 25 times more potent in both tests than the *cis* isomer. Conformational studies have proved that in the *trans* isomer the aromatic group is more axial than in the *cis* isomer.[37]

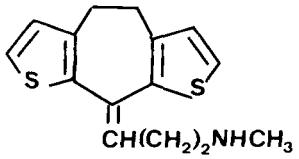
6.2 Antidepressant agents

6.2.1 10,11-Dihydrodibenzocycloheptene Thiophene analogs of the antidepressant drugs amitriptyline and nortriptyline have been investigated. The inhibition of amine uptake and their reserpine antagonism were taken as measures to quantify the potencies of the compounds.[38] The results are summarized in Table XXVII. According to *in vivo* and *in vitro* studies the new compounds are very weak inhibitors of NA (noradrenaline) and 5-HT (5-hyroxytryptamine), although they have effects similar to those of the parent compounds. The results indicate that in the future special designs could provide the starting point for the development of more selective agents.

Other investigators[39] determined the influence of the conformation of the 7-membered central ring of tricyclic antidepressants, e.g. nortriptyline and imipramine. The studies revealed that the thiophene compound is considerably less active than e.g. nortriptyline.

nortriptyline

89

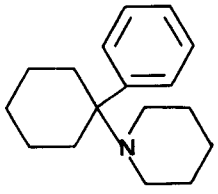
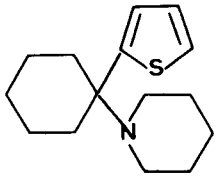
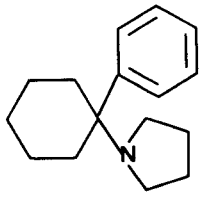
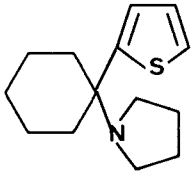
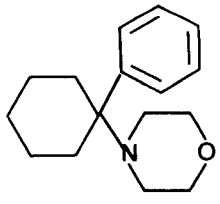
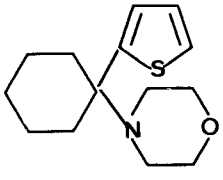


thiophene analog

90

TABLE XXV

Potency of Phencyclidine (PCP) Analogs in Producing PCP-like Discriminative Stimuli in the Rat[35]

	Analog		Relative potencies[a]
81		PCP	1.0
82		TCP	1.31
83		PCPY	0.97
84		TCPY	0.87
85		PCM	0.10
86		TCM	0.07

[a] the relative potency indicates mg of PCP equivalent to 1 mg of the listed drug

TABLE XXVI

Relative Potencies of Phencyclidine Derivatives in A (the Rotarod Test *in vivo*) and in B (Specific Receptor Binding *in vitro* in Rat Brain Membranes) PCP = 1[37]

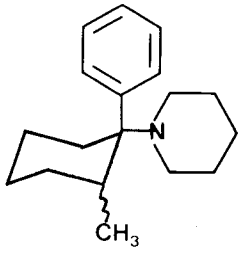
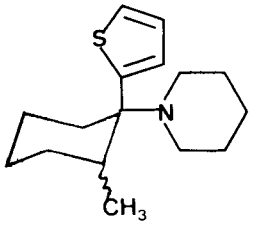
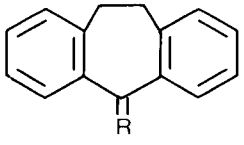
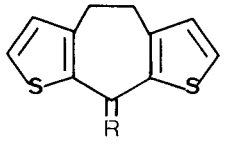
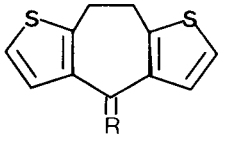
Compound		A	B
	87	*cis* 0.03 *trans* 0.54	0.16 2.08
	88	*cis* < 0.03 *trans* 1.14	0.25 6.25

TABLE XXVII

Inhibition of Amine Uptake (^{3}H—NA and ^{3}H—5—HT) and Antagonism Against Reserpine Produced Hypothermia in Mice[38]

a) R = $CHCH_2CH_2N(CH_3)_2$ b) R = $CHCH_2CH_2NHCH_3$

Compound		EC_{50} μM *in vitro* NA	EC_{50} μM *in vitro* 5-HT	ED_{50} mg/kg i.p. *in vivo* NA	ED_{50} mg/kg i.p. *in vivo* 5-HT	ED_{50} mg/kg i.p. *in vivo* antagonism
	91					
amitriptyline	a	3	3	7	36	2.5
nortriptyline	b	0.3	7	20	> 40	1.0
	92					
R	a	2	—	20	> 20	> 20
	b	0.5	23	13	> 40	5
	93					
R—	a	6	—	16	> 40	> 20
	b	5	2	> 20	> 40	5

6.2.2 Bicyclic phthalanes and thiophthalanes In the assessment of norepinephrine uptake into the adrenergic nerves of rabbit aorta and into crude rat hypothalamus synaptosomal preparations the relative potencies of a phthalane and a thiophthalane compound were compared to those of desipramine, a 10,11-dihydrodibenzazepine derivative, Table XXVIII.[40] The orientation of the propylamine side chain with respect to the benzene rings is very similar to the orientation seen in desipramine. The methyl groups of the bicyclic ring system are involved in binding to the receptors.[40]

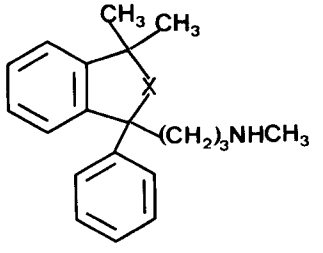
7. AMINES, BIOGENIC AMINES

7.1 Indole and benzo[b]thiophenes

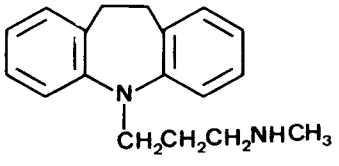
The activity of indole and benzo[b]thiophene derivatives has been determined in rat stomach fundus preparations[41]. As can be seen from Table XXIX the replacement of the indole nucleus by benzo[b]thiophene does not markedly alter their biological activity.

TABLE XXVIII

Relative Potencies of Bicyclic Phthalanes and Thiophthalanes Determined as the Uptake of Norepinephrine into the Adrenergic Nerves of Rabbit Aorta and into Crude Rat Hypothalamic Synaptosomal Preparations[40]



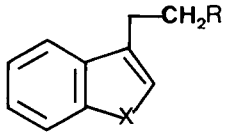
94

Compound	[a] Relative potencies	
	aorta	Hypothalamus
X=O	210	255
X=S	480	522
 95	300	363
=desipramine		

[a] relative potencies (IC_{50} standard/IC_{50} test compound) standard compound: IC_{50} for aorta = 4.10^{-6}M; IC_{50} for hypothalamus = $1.2.10^{-6}$ M

TABLE XXIX

Activity of Amines in Rat Stomach Fundus Preparations, Expressed as pD_2 Values[41]

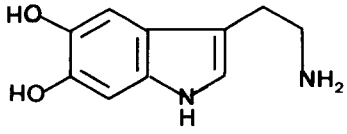


96

R	X	pD_2 values
NH_2	NH	5.84
NH_2	S	4.78
NMe_2	NH	3.52
NMe_2	S	4.07

7.2 Biogenic amine analogs

5,6-Dihydroxytryptamine (5,6-DHT) is considered as a selective depletor of brain 5-HT (serotonine) and is therefore used as reference substance for the assessment of monoaminergic activity.[42]



5,6-DHT 97

Replacement of the indolic nitrogen by sulfur abolishes the 5-HT depleting activity in spleen and in brain, but does not alter the NE (norepinephrine) depleting activity in the heart, spleen, or brain.[42]

Isosteres of 5-HT (5-hydroxytryptamine = serotonine) have been investigated as agonists and for their degree of blockade by phenoxybenzamine in the rat stomach fundus strip.[43] Table XXX summarizes the results and from this it is obvious that the three isosteres are less potent than 5-HT in producing contractions of the fundus strip. The rank order is as follows: 5-HT > indene > thiophene > furan.

However, substitution of the indolic moiety of 5-HT by O, S, CH_2 has little effect on the relative intrinsic activities.

8. VASOACTIVE AGENTS

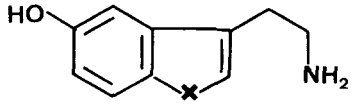
8.1 Coronary vasodilators

The pharmacological screening of dipyridyl- and diphenylalkane derivatives demonstrated the dependency of the biological activities upon the aromatic nucleus.[44] Therefore, corresponding thienylalkane derivatives were synthesized and tested. They showed coronary vasodilator activities in the guinea pig, using the Langendorff heart as

test model.[44] Table XXXI enlists the results. Among the ω,ω-diaryl-ω-hydroxypropylamine compounds the one with two phenyl groups was most potent, whereas this finding could not be confirmed in the ω,ω-diaryl-ω-propenylamine series. In the latter unsymmetrical substitution with a phenyl and a 2-thienyl group proved to be most advantageous.

TABLE XXX

Activity of 5-HT and its Isosteres as Agonists and Degree of Blockade by Phenoxybenzamine in the Rat Stomach Fundus Strip[43]

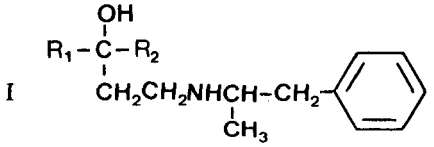


98

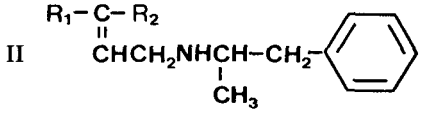
X	Rel. intrinsic agonist activity	% Blockade of agonist response	Molar conc. of agonist
NH=5-HT	1.0	95.67	3.5×10^{-6}
O	0.84	67.66	1.8×10^{-2}
S	1.08	70.60	7.8×10^{-4}
CH_2	0.96	78.00	7.5×10^{-4}

TABLE XXXI

Coronary Vasodilator Activity of Thienylalkane Derivatives in the Guinea Pig (Langendorff heart), Expressed as Per Cent Increase of Coronary Flow (Dose 10 γ per Heart)[44]



I 99

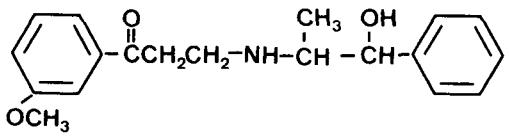


II 100

	R_1	R_2	% Increase
I	2-thienyl	phenyl	80
	2-thienyl	2-thienyl	96
	phenyl	phenyl	144
II	2-thienyl	phenyl	145
	2-thienyl	2-thienyl	122
	phenyl	phenyl	117

8.2 Cerebral vasoactive compounds

Oxyfedrin is a marketed drug, established in the therapy of coronary diseases since years.



101

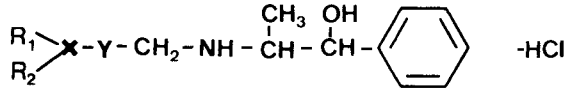
oxyfedrin

In further research for new potent agents in the field of heart and circulatory therapeutics β-amino ketones of the oxyfedrin type were used as the starting point for the synthesis of heteroalkane derivatives.[4,5]

A series of compounds were investigated for their cerebral vasoactivities with special respect to structure-activity relationships. The percent increase of A. vertebralis blood flow in the anesthetized dog was determined as listed in Table XXXII. Consistent superiority was noted for the compounds containing two 3-thienyl groups.[4,5]

TABLE XXXII

Increase of A. Vertebralis Blood Flow in the Anesthetized Dog after Administration of Various Heteroalkane Derivatives[4,5]



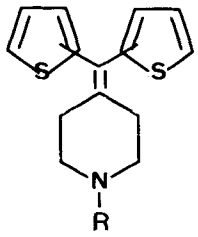
102

R_1	R_2	X–Y[a]	% Increase
phenyl	3-thienyl	OH | C—CH_2	23
2-thienyl	3-thienyl	OH | C—CH_2	29
3-thienyl	3-thienyl	OH | C—CH_2	63
phenyl	phenyl	C=CH	13
phenyl	3-thienyl	C=CH	48
2-thienyl	3-thienyl	C=CH	59
3-thienyl	3-thienyl	C=CH	81

[a] the compounds were administered intravenously at 0.3 mg/kg

8.3 Antiischemic agents

A series of new dithienylpiperidines of the following general structure have been synthesized.



103
R_a=alkyl
R_b=$(CH_2)_n$—O—R

The biological screens revealed two distinct activities. When R was alkyl, the compounds showed antiischemic and peripheral vasodilating properties,[46] on the other hand, the presence of an alkoxy group resulted in antihistaminic activities.[47] However, in both screening systems no significant differences in potencies were found between the 2- and 3-thienyl compounds.

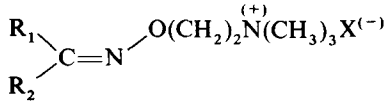
9. AGENTS ACTING AT SYNAPTIC AND NEUROEFFECTOR JUNCTIONAL SITES

9.1 Anticholinergic agents

Selected isomeric oxime ethers have been assayed for anticholinergic activity by measurement of spasmogen induced intestinal contractions in the presence of the spasmolytics.[48] The test tissues consisted of smooth muscle from rat ileum. The results can be seen in Table XXXIII. It is apparent that the muscarinic receptor is stereospecific toward this series of geometric isomers, although the thienyl derivatives are superior to the phenyl ones.

TABLE XXXIII

Anticholinergic Activity of Some Isomeric Oxime Ethers in Smooth Muscle from Rat Ileum *in vitro*[48]



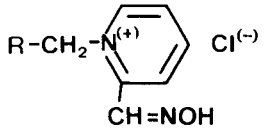
R_1	R_2		General activity pattern
H	phenyl	a	(a) compounds—with (E)—configuration—were uniformely more active than their counterparts (b) with (Z)—configuration-, the thienyl derivatives were more potent than the phenyl derivatives
phenyl	H	b	
H	2-thienyl	a	
2-thienyl	H	b	

9.2 Reactivators of acetylcholinesterase

1-(Hetero)arylmethyl-pyridinium oximes have been investigated as reactivators after inhibition of acetylcholinesterase by tabun.[49] The percentage of reactivation after incubation of 10 μM of several compounds (Table XXXIV) was recorded after 2h and at $t = \infty$ at pH 7.5 and 25 °C. The thienyl derivative was found to be the most potent; the 2-furyl one was essentially equipotent with the 4-thiazolyl compound

TABLE XXXIV

Percentage of Reactivation of Acetylcholinesterase after Incubation of 10 μM of Various 1-(Hetero)arylmethylpyridinium Oxides[49]

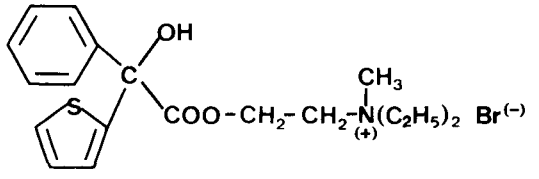


104

R	% Reactivation t = 2h	t = ∞
2-thienyl	38	88
2-furyl	15	73
4-thiazolyl	10	66

9.3 Spasmolytics

Nibitor is a spasmolytic which has been introduced in France.[50]



105

Further search for spasmolytics included variations of this molecule. The reduction of spasms, induced by acetylcholine, was studied *in vitro* in the isolated rabbit duodenum.[50] Table XXXV demonstrates that the hydroxyacetic acid derivatives had weak spasmolytic activity, the phenyl and 2-thienyl compounds being essentially equipotent.

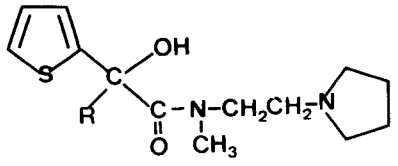
However, the mean lethal doses of both agents indicate that the toxicity of the thienyl derivative is reduced compared to that of the phenyl derivative.

9.4 Sympathicolytics

Basic heteroaryl ethers have been found to possess sympathicolytic activity.[51] They were tested in the isolated seed vesicles of the guinea pig. The pyridyl and thienyl compounds

TABLE XXXV

Spasmolytic Activity of Hydroxyacetic Acid Derivatives in the Isolated Rabbit Duodenum[50]

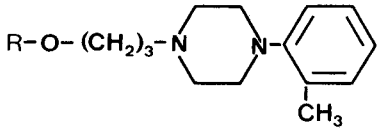


106

R	DL_{50} i.v. mg/kg	DL_{50} i.p. mg/kg	CE_{50} $\mu g/cm^3$
phenyl	16	110	0.1
2-thienyl	22	182	0.1

TABLE XXXVI

Symphaticolytic Activity of Heteroarylethers in the Isolated Seed Vesicles of the Guinea Pig[51]



107

R	ED_{50} $\mu g/50$ ml
2-pyridyl	0.5
2-thienyl	0.5

(Table XXXVI) possessed the highest potency in a series of heteroarylethers. It could be demonstrated that the tolyl group is essential for the sympathicolytic activity.[51]

10. AMINO ACID ANALOGS

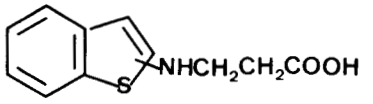
N-Benzoyl-β-2- and 3-thienyl-D,L-alanine have been found to be potent inhibitors in a microbial antitumor screen, see Table XXXVII.
The 2-thienyl derivative showed superior activity compared with the 3-thienyl derivative.

11. RETINOIDS

A comparison for the capacity of retinoids to stimulate the differentiation of embryonal carcinoma cells with their ability to compete for the binding site of the retinoic acid binding protein has been performed.[53] The binding site results are summarized in Table XXXVIII.

TABLE XXXVII

Inhibitory Effect of Equimolar Concentrations of Amino Acid Analogs in a Microbial Antitumor Screen[52]

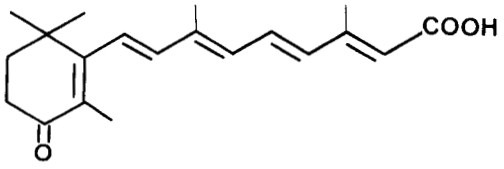
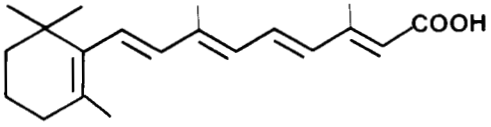
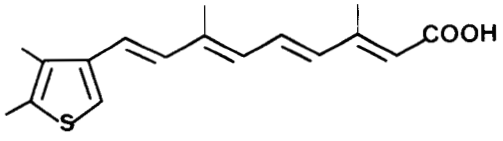
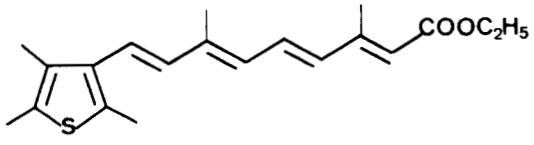
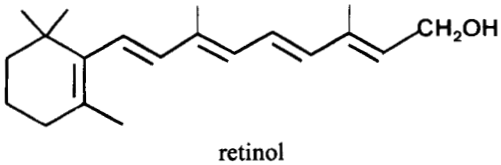


108

Position	% Growth of *L. casei* 7469
2	76
3	56

TABLE XXXVIII

Competition for the Binding Site on Retinoic Acid Binding Protein by Some Retinoids[53]

Compound		Ability to compete for the binding site
	109	+
 retinoic acid	110	+
	111	+
	112	−
 retinol	113	−

Although this example does not follow our general concept of a thiophene replacement by aromatic and heteroaromatic nuclei we think that it is well worthwhile to be cited here.

Replacement of the cyclohexane ring of retinoic acid, e.g. by thiophene, did not interfere with the ability of the analog to compete for the binding site, whereas substitution of the carboxylic acid group affected this activity severely.

12. BRADYKININ ANALOGS

Two analogs of bradykinin, containing β-2-thienyl-L-alanine in the place of phenylalanine have been synthesized and compared biologically.[54] In some assays (Table XXXIX) the analogs showed partly greater bradykinin-like activities, especially in the rat uterus: The presence of the thiophene moiety may allow more effective penetration of the molecule to the site of action, or the molecular conformation of the analog may be favorably altered to allow more effective interaction with receptor sites. Another possibility is that the presence of the thiophene ring may make the peptides resistant to kininases.[54]

TABLE XXXIX

Biological Activity, Compared with Bradykinin Analogs, Based on the Dose Required to Cause a Half-Maximal Isotonic Contraction[54]

Compound	Rat uterus	Guinea pig ileum
bradykinin	1	1
5-thienylalanine-bradykinin	2	0.4
8-thienylalanine-bradykinin	3–5	0.4

13. PANCREOZYMINE ANALOGS

Octa- and tetrapeptides with modified tryptophane residues have tested for their adenylate cyclase activity.[55]

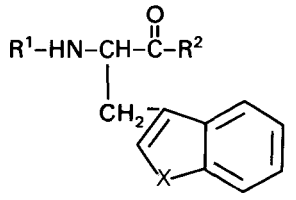
The results in Table XXXX demonstrate that replacement of the nitrogen in the indolyl ring of tryptophan by a sulfur or an oxygen atom leads to a considerable reduction in the affinity of both the octapeptides and the terminal tetrapeptide moieties. The tryptophan residue in the C-terminal part of both gastrin and pancreozymine is essential for the biological function of both peptides.

14. INHIBITORS OF ARGININE SPECIFIC ESTEREOPROTEASES

Dissociation constants of inhibitory diarylamidine derivatives with the enzymes have been determined from rate assays.[56] The Ki values for the enzymes are given in Table XXXXI. Isosteric replacement of the nitrogen by carbon or sulfur resulted in a slight increase in antitrypsin activity while other isosteric modifications caused a

TABLE XXXX

Effects of Pancreozymine Octapeptide (A) ad C-Terminal Tetrapeptide (B) analogs[55]



114

X		Adenylate cyclase activity (pmol · min^{-1} · mg^{-1} protein) A	B
O-(benzofurylalanine)	115	14.0	4.9
S (benzothienylalanine)	116	16.9	5.0
NH (tryptophan)	117	48.0	9.3

decrease. The indene derivative was the strongest trypsin inhibitor and the most potent antithrombin agent. The thiophene compound proved to be the most outstanding kallikrein inhibitor.

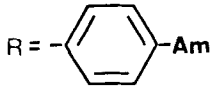
CONCLUSIONS

The literature data, as reviewed in this report, comprise compounds of the most heterogeneic molecular structures as well as a very broad spectrum of biological activities. In the following, the results obtained after replacements of the thiophene moiety are summarized.

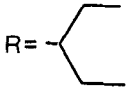
1. Exchange of 2-thienyl versus 3-thienyl:
   When the 2-thienyl substituent of ampicillin analogs was replaced by the 3-thienyl substituent (Table VIII) the antimicrobial activity decreased slightly. A decrease was also found in the hypolipidemic activities of clofibrate analogs (Table IX). However, a consistent superiority of the 3-thienyl derivatives was obtained for cerebral vasoactive compounds (Table XXXII). Our findings with dithienylpiperidines[46,47] support the conclusion that no general pattern can be recognized with regard to the biological activity of 2- and 3-thienyl compounds, since we did not obtain significant differences in potencies.
2. Exchange of thienyl versus phenyl:
   The replacement of the benzene ring or the corresponding phenyl groups by the thiophene nucleus is one of the common variations in structure-activity studies involving thiophenes. Superiority of the thienyl compound was observed in a number of examples (see Tables I, XIX, XX, XXI, XXV, XXXII) whereas the phenyl derivatives were more potent in other cases (see Tables XVI, XVII, XXVII, XXXI).

TABLE XXXXI

Inhibition Constants with Thrombin, Trypsin, and Pancreatic Kallikrein using Amidino Substituted Heterocyclic Compounds as Substrates[56]

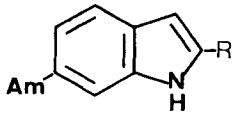
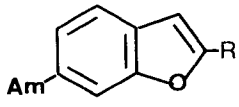
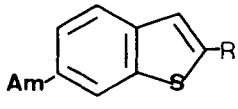
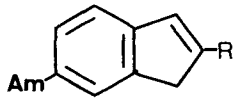
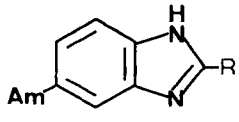


116



Am = —C=NH
|
NH_2

117

	Compound	Ki (μM) Trypsin	Thrombin	Kallikrein
118		5.31	8.37	2.70
119		9.30	53.50	56.20
120		3.94	7.68	0.73
121		3.39	4.73	7.36
122		17.10	24.40	64.50

Furthermore, the study of coronary activity demonstrated superiority for the diphenyl substituted propylamine. On the other hand, substitution with a phenyl and a 2-thienyl group gave the most pronounced effect in the propenylamines (Table XXXI). However, equipotency between the phenyl and thienyl compounds has been observed, too (see Tables XII, XXIII, XXXV).

3. Exchange of the thienyl group versus naphthyl (Table XXIII) resulted in a loss of activity, whereas in a series of benzothiazines (Table XXIV) the thienyl derivative was ineffective.
4. Exchange of the thienyl group versus furyl revealed superior activity for the furans (e.g. Tables IV, IX, XII, XXI, and XXIV), however, inferiority in many other cases (e.g. Tables V, XV, XIX, XX, XXVIII, XXXIV). On the other hand, equipotency has been observed as well (Table VI, reference 19).

5. Exchange of the thiophene ring versus pyridine and thiazole:
   In both cases, the thiophene compounds were in general superior (Tables XXII and XXXIV) or equipotent to the N-heterocyclic ones (Tables XIII, VIII, reference 30).
6. Exchange of the benzothiophene ring versus either benzofuran, indole, or benzothiazole showed mainly equipotency (Tables III, XIII, XVIII, XXIX).

It should be pointed out that only in one of the research reports toxicity data were given. Despite of equipotency of the phenyl and thienyl compound (Table XXXV) the comparison of the mean lethal doses indicates larger toxicity for the phenyl derivative.

Nobles and Blanton concluded in their earlier review[3] that 3-thienyl derivatives were less toxic than their 2-isomers. Nevertheless, neither the metabolism nor the toxicity of thiophenes and their isosteres can be discussed on the basis of the literature cited above. However, the metabolic pathways of substituted furans and thiophenes have been extensively studied in mice and rats, including marketed drugs like furosemide, cephaloridine, and cephalotin. Following metabolic activitation by drug-metabolizing enzymes the animals showed an increase in renal and hepatic necrosis. Organ-specific metabolic transformation by cytochrome P-450 mono-oxygenases seems to lead to toxic intermediates after the administration of both types of heterocycles.[57] Yet further comprehensive studies are necessary before more general conclusions can be drawn.

Within numerous rationally designed synthetic series emphasis has mainly been put on aromatic ring replacements and only secondly on substituent influences. However, the respective findings have more or less been presented in a purely descriptive manner. Thus, theoretical considerations of quantitative structure-activity relationships, e.g. multiple regression analysis, Hammett constants, Hansch parameters, are missing. Reference to such calculations were only made in three research reports,[11,41,43] though without being applicable to a general theoretical discussion in this review. For instance, partition coefficients have been correlated with biological activities only for three furan derivatives.[11]

However, receptor binding studies have been performed with pthalane and thiophthalane compounds[40] as well as with isomeric oximes as anticholinergic agents.[48] On the other hand, a relationship between conformation and biological activity of phencyclidine analogs has been determined.[37]

The above summarizing comparison of the most common and most distinct examples among the reviewed data makes clear that no general scheme can be given for the activity pattern amongst these structure variations. Nevertheless, it could be demonstrated again that isosteric replacements as proposed by Erlenmeyer[58] often result in biosteric compounds. Even the investigation of endogenous compounds and their modified analogs (e.g. retinoids, bradykinins, and pancreozymines) did not reveal actions which could be attributed to a general pathway. In case of 2-and 3-thienyl-alanine containing bradykinins the replacement of the endogeneous phenylalanine resulted in effects superior to those of the original peptide.[54] The reverse was found when the nitrogen atom in the indolyl ring of the tryptophan residue of the C-terminal octapeptide and tetrapeptide of pancreozymin was replaced by sulfur.[55] This latter controversy is in logical coherence according to the variety of e.g. sites of action and receptors which are involved in the development of biological effects. From this point of view it is only natural that this review cannot give a general concept for further drug design.

However, structure activity relationships provide valuable information about the binding to receptors which helps to understand the unique action of an agent and therefore facilitates the search for new therapeutics.

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The authors wish to thank Mrs. C. Krehmer for her conscientious and skillful preparation of the manuscript.