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Dihydropyrimidin-2(1*H*)-one and its analogues as a platform for the design and synthesis of new biologically active compounds

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The data published mainly over two past decades on various types of biological activity of 5-functionally substituted 3,4-dihydropyrimidin-2-ones and their analogues, 2-thiones and 2-imines, and more complex dihydropyrimidine derivatives are summarized. Apart from medicinal chemistry issues, including structure – activity relationships, the pharmacological profiles of the most promising derivatives and the routes for further structural modification of known chemical compounds are discussed in general terms. Examples of potential uses of new compounds in medicine as single pharmaceutical agents and as parts of compositions are given.
The bibliography includes 334 references.

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I. Introduction

The role of pyrimidine derivatives in vital processes in the human body is well-known; the most important of these processes is the transfer of hereditary information. The pyrimidine ring and its oxohydrogenated forms constitute the core of the nitrogenous bases of nucleic acids and some natural and synthetic pharmaceutical drugs. Chemists' and pharmacologists' attention has long been concentrated on the synthesis of uracil and barbituric acid derivatives and their thio analogues and also substituted aminopyrimidines, which resulted in the development of a number of demanded drugs. In the recent decades, researchers have become interested in the biological activities of hydrogenated pyrimidine derivatives.

This review focuses, with rare exceptions, only on compounds based on 5-substituted 3,4-dihydropyrimidin-2(1*H*)-ones and their S- and N-analogues. The vast majority of these dihydropyrimidines (DHPMs) were prepared using a three-component condensation of aldehydes, CH-active carbonyl compounds and ureas (thioureas, guanidines), which was discovered by Biginelli more than a hundred years ago and was named after him. By chemical transformations of simpler products of the Biginelli reaction, complex DHPM derivatives were prepared. The study of the proper Biginelli reaction and the dihydropyrimidine synthesis and chemical modification are the subjects of several comprehensive reviews;[1–14] therefore, the problem of DHPM synthesis is fully beyond the scope of our review.

The biological activity of dihydropyrimidine derivatives has been considered in quite a few of diversified publications of the last two decades in chemical, biological and medical periodicals and in patent literature. In some of them, the range of known biologically active compounds was extended and new derivatives with improved pharmacological profiles as compared with certified drugs were obtained. Other publications describe in-depth pharmacological investigations, and some papers present data on specific sorts of activity or on new structural types of biologically active compounds discovered among hydrogenated pyrimidine derivatives and their S- and N-analogues. A certain part of such papers have been surveyd in reviews,[1, 15–27] but, most often, only brief descriptions are

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given, while some other papers have not been surveyed at all. Furthermore, some publications that deserve close attention appeared lately.

Here we made at attempt to give an extensive survey of the biological activities of promising compounds of this class and to compare the results of studies performed by different research teams. Our review is based on the structure-chemical principle, *i.e.*, a particular type of activity is discussed for chemically similar 5-functionalized DHPMs and topologically related dihydroquinazolines.

The review starts with a discussion of the data for the most abundant and best studied class of derivatives with an ester group in position 5 of the heterocycle. This is followed by sections dealing with the corresponding ketones, amides, nitriles and nitro derivatives. Data for the closest analogues — dihydropyrimidine-2-ones and -2-thiones — are discussed together, whereas the N-analogues have some specific features in both the chemical behaviour and biological activity and, hence, they are considered separately.

II. 5-Functionally substituted 3,4-dihydropyrimidine-2(1*H*)-ones(thiones)

II.1. 5-Alkoxycarbonyl derivatives

Back in 1930 it was found that some cyclic molecules in which the thiourea residue is incorporated into the dihydropyrimidine system, for example, 4-chlorophenyl 5-ethoxycarbonyl-3,4-dihydropyrimidine-2-thione **1** and analogous compounds, can serve as agents protecting wool and furs from textile pests [28] (see †). Some time later, oxygen analogues — aryl dihydropyrimidin-2-ones **2** — were found to exhibit antiviral activity against murine poliomyelitis virus,[29] and the nitrofuryl derivative Nitractin **3** showed rather high antiviral activities against ornithosis, lymphogranuloma inguinale and trachoma, while having very low toxicity.[30, 31]

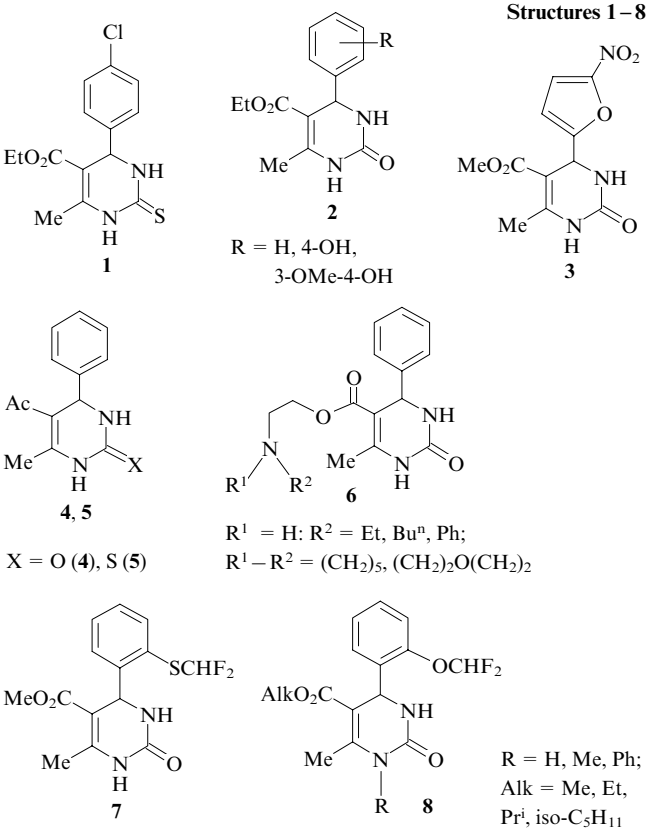
A decade later, Latvian researchers [32, 33] reported an antitumour action for 5-ethoxycarbonyl derivative **2** (R = H) and 5-acetyl derivatives **4** and **5**. Interest was also aroused by the first mentions of the hypotensive and coronary vasodilator properties of ester derivative **6**.[34, 35] Compounds **7** and **8** were shown to be quite good vasodilating agents.[36, 37]

However, studies along this line lacked proper development for a long period of time, and only 15 – 20 years later was there a revival in the interest in the biological activities of DHPMs, the heterocyclic skeleton of which is structurally similar to 1,4-dihydropyridines (DHPs) functioning as modulators of the calcium transport across cell membranes. Compounds of the latter type [*e.g.*, Nifedipine (**9**), Amlodipine (**10**), Nitrendipine (**11**), Nicardipine (**12**), Isradipine (**13**) and so on] started to be used in the clinical practice for prevention and treatment of some cardiovascular diseases.[38, 39]

The presence of an urea moiety in the pyrimidine derivatives and the molecular core topology, the same as in the biologically active DHPs, provides the formation of a special group of cardioactive agents with pharmacological action also based on calcium channel blockade. It was noted

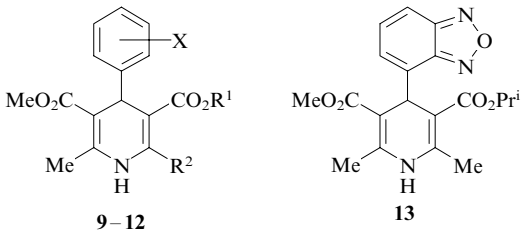
† See also *Fortschritte der Teerfarbenfabrikation und Verwandter Industriezweige* Teil 18 (Berlin: Springer-Verlag, 1933) S. 2590

Structures 1 – 8



that 2-thiones differ little from oxygen analogues **7** and **8** in the action on the cardiovascular systems of test animals.[36]

Structures 9 – 13



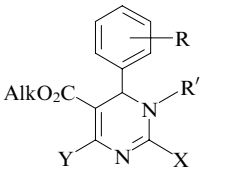
Compound	X	R^1	R^2
Nifedipine (**9**)	2-NO_2	Me	Me
Amlodipine (**10**)	2-Cl	Et	$CH_2O(CH_2)_2NH_2$
Nitrendipine (**11**)	3-NO_2	Et	Me
Isradipine (**12**)	3-NO_2	$(CH_2)_2NMeBn$	Me

II.1.a. Antihypertensive and vasodilating agents

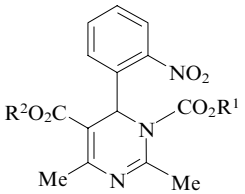
5-Alkoxycarbonyl-3,4-dihydropyrimidines with the general formula **14** were among the first compounds mimicking the structure of biologically active dihydropyridines to be studied in detail.[40]

The early biological testing of N-unsubstituted analogues **14** as vasodilators did not show any activity. Meanwhile, the corresponding N(3)-alkylated derivatives had a low activity, which increased upon variation of substituents R in the benzene ring in the series 3-NO_2 < 2-Br < 2-Cl < 2-NO_2. The replacement of the N(3)-alkyl group by an alkoxycarbonyl group gives compounds with two

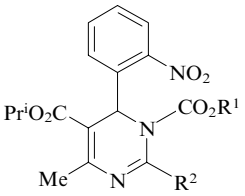
Structures 14 – 18



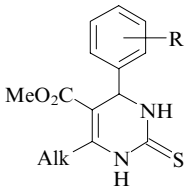
14 (R′ = H, Alk)



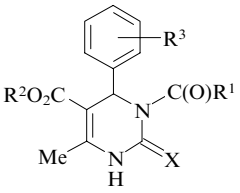
15



16



17



18

15: R^1 = Et, Hept, $(CH_2)_2$NMeBn, $(CH_2)_2$NPhBn, $(CH_2)_2NBn_2$, $(CH_2)_2$N(Bn)CH_2Naph-2; R^2 = Et, Pr^i, Bu^n, Hept, $(CH_2)_2$NMeBn, $CH_2C_3H_5$-cyclo;
16: R^1 = Et, $(CH_2)_2NBn_2$, $(CH_2)_2NBnCH_2$Naph-2; R^2 = H, Et, Pr^i, CF_3, NMe_2, SMe;
17: Alk = Me: R = H, 4-Me, 2-OMe, 4-OMe, 4-NHC(O)Me, 2-Cl, 3-Cl, 4-Cl, 4-Br, 2-NO_2, 3-NO_2, 4-NO_2;
18: R^1 = Me, OEt, NH_2, NHMe, NHEt, $NHPr^i$, NHBn, NMe_2; R^2 = Me, Et, Pr^i; R^3 = H, 2-Cl, 3-Cl, 4-Cl, 2-CF_3, 3-CF_3, 2-NO_2, 3-NO_2, 4-OMe; X = O, S; Hept is n-heptyl, Naph is naphthyl

ester groups in the heterocycle [at the N(3) and C(5) atoms], which reproduce the structure of dihydropyridine calcium channel blockers — Nifedipine (**9**) and its analogues, and this enhances the vasodilator activity of the corresponding dihydropyrimidines **15** and **16**. Furthermore, dihydropyrimidines proved to be less toxic than the pyridine analogues. The series of compounds **15** included only 2,6-dimethyldihydropyrimidine derivatives, while in series **16**, the substituent in position 2 of the heterocycle varied, which enabled conducting the first structure – activity relationship analysis.[40] A study of the vasodilator and antihypertensive activities of these agents upon intravenous injection in dogs identified a number of promising compounds.[40] To illustrate the dependence of the biological activity of some of these products on the structure, ED_{30} values are given (Table 1).

A study into the nature of this effect by monitoring the degree of displacement of labelled Nitrendipine[^{3}H] (**11**) from biological specimens prepared from rat cerebral cortex under the action of dilute solutions of test compounds showed a similar behaviour of compound **15** [$R^1 = (CH_2)_2NBnCH_2$Naph-2, $R^2 = Pr^i$] with other Ca-channel blockers such as Nifedipine or Nicardipine.[40]

A similar procedure was used to determine the degree of displacement of another labelled Ca-channel blocker, Isradipine[^{3}H] (**13**), from microsomal membranes prepared from rat skeletal muscle on treatment with solutions of

Table 1. Observed vasodilator effect of compounds **15** and **16** on dog blood vessels at 30% level relative to the control (ED_{30}) upon intravenous injection.[40]

Compound	R^1	R^2	ED_{30} /μg kg^{-1}
15	Et	Et	3.0
15	Hept	Et	3.2
15	Et	Hept	23.0
15	Hept	Hept	180
15	$(CH_2)_2$NMeBn	Et	0.75
15	$(CH_2)_2$NMeBn	$CH_2C_3H_5$-cyclo	0.5
15	Et	$(CH_2)_2$N(Me)Bn	13.0
15	$(CH_2)_2$NPhBn	Pr^i	0.74
15	$(CH_2)_2NBn_2$	Pr^i	2.8
15	$(CH_2)_2$N(Bn)CH_2Naph-2	Pr^i	1.8
16	Et	Et	8.0
16	Et	CF_3	8.3
16	$(CH_2)_2$N(Bn)CH_2Naph-2	H	> 100
16	$(CH_2)_2$N(Bn)CH_2Naph-2	Et	27
16	$(CH_2)_2$N(Bn)CH_2Naph-2	Pr^i	> 100
16	$(CH_2)_2$N(Bn)CH_2Naph-2	NMe_2	> 100
16	$(CH_2)_2$N(Bn)CH_2Naph-2	SMe	> 100
9 (Nifedipine)			0.5
11 (Nitrendipine)			1.2
12 (Nicardipine)			3.0

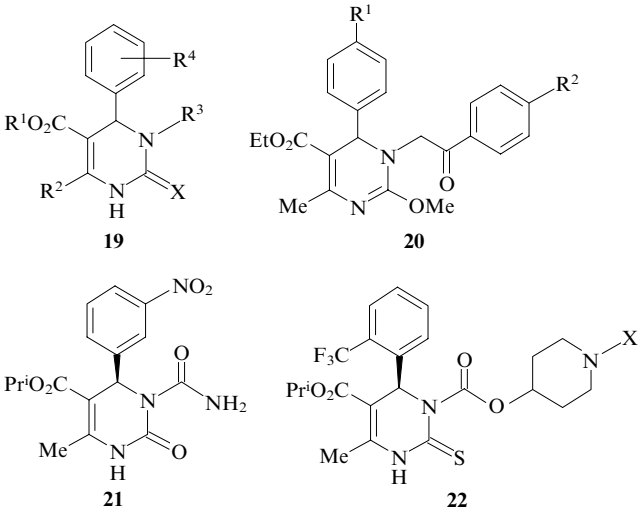
several dihydropyrimidinethiones **17**; this also revealed their inhibitory effect and allowed the test compounds to be ranked in terms of the effective concentration at 50% Isradipine displacement level (inhibition constant K_i in the range of $2 \times 10^{-3} - 4.7 \times 10^{-6}$ mol litre^{-1}).[41,42] Upon the comparison of these values with $K_i = 10^{-8}$ mol litre^{-1} for Nifedipine taken as the reference, the authors draw the conclusion of weak inhibitory action of dihydropyrimidinethiones as Ca antagonists, as opposed to their oxygen analogues. The same compounds show anti-aggregatory activity, which is not correlated with their Ca^{2+}-antagonism.[42]

The general conclusions about the dependence of Ca-exchange modulating activity of DHPMs on their molecular structures follow from data on the activity of N(3)-carbonyl derivatives **18**.[43–45] A moderate Ca-channel blocker activity was found[43] for a small series of N(3)-acetyl derivatives **18** (R^1 = Me; R^2 = Et; R^3 = H, 4-Cl, 4-OMe; Y = O, S). Testing of N(3)-carbamoyl derivatives **18** ($R^1 = NH_2$, NHMe, NHBn, NMe_2; $R^2 = Pr^i$; Y = O, S) showed that compounds with the monosubstituted carbamoyl group were most active *in vivo*, being only slightly inferior in the antihypertensive activity to Nifedipine or Amlodipine.[44]

Cardiovascular agents promising as antihypertensive drugs were found among a large series of N(3)-alkyl- and N(3)-carbonyl dihydropyrimidinone(thione) derivatives represented by general formula **19**. The efficiency of the these agents varies appreciably depending on the type of heteroatom X, substituents R^2 and R^3 and aryl (hetaryl) moiety in the dihydropyrimidine core, but depends little on the nature of substituent R^1 in the ester group.[40,44–49] It was also demonstrated that the Ca-blocking activity of the *R*-enantiomer is 2 – 3 orders of magnitude higher than that of the *S*-form.[44,49] The replacement of the 6-methyl group in the 5-methoxycarbonyldihydropyrimidine molecule by an ethyl group does not bring about a substantial activity

change. Compounds with a similar topology but existing as other tautomers of the dihydropyrimidine core (*e.g.*, series of compounds **20**) do not lose the biological activity in some cases.[50] However, on going to S- and N-analogues (2-SMe and 2-NMe_2 derivatives), the activity largely decreases (see Table 1).[40]

Structures 19 – 22



19: R^1, R^2 = H, Alk, cyclo-Alk, $(CH_2)_2NHAlk$, $(CH_2)_2OAlk$, $(CH_2)_2SAlk$, Ar, *etc.*; R^3 = H, Alk, $CH_2C(O)Alk$, $CH_2C(O)Ar$, $CH_2C(O)NAlk_2$, C(O)Alk, CO_2Alk, SO_2Alk, SO_2Ar, *etc.*; R^4 = H, Alk, Hal, OH, OAlk, SAlk, SO_2Alk, CF_3, CN, NO_2, *etc.*; X = O, S;
20: R^1 = H, Cl, OMe, OH, Me; R^2 = H, Cl, OMe;
22: X = $CH_2C_6H_4F$-4

Pharmacological investigations demonstrated that administration of some agents in animals with hypertension in the doses of 1 – 50 mg per kg of body weight reduces blood pressure. It was assumed that these compounds as Ca^{2+}-exchange blockers can not only act as hypotensive drugs but also serve as anti-arrhythmic, anti-anginal, anti-asthmatic and antifibrillatory agents.[44, 46 – 49]

Testing of a number of N(3)-substituted dihydropyrimidines such as compounds **20** revealed anti-inflammatory and antihypertensive activities, which have different levels for the same compound. For example, an antihypertensive activity comparable with that of Nifedipine (**9**) was displayed by compounds with a definite set of substituents in both benzene rings (Table 2),[50] while high anti-inflammatory activity at the Ibuprofen level was found for N(3)-phenacyl derivatives with a different set of these substituents (compounds **20**: R^1 = Me, OMe; R^2 = H, Cl, OMe).[50]

In a study of the activities of N(3)-carbonyl dihydropyrimidinone and -thione derivatives with variation of single substituents in the molecules, a group of compounds was found to demonstrate a noticeable capability for vasodilatation in isolated rabbit thoracic aorta samples. Most promising among them were compounds **21** (SQ 32926) and **22** (SQ 32547), which were comparable with Nifedipine (**9**) and Amlodipine (**10**) in the vasodilator and antihypertensive effects.[2, 44, 45, 51] In isolated rat aorta, IC_{50} (half-maximal inhibitory concentration) was 5.5 nmol litre^{-1} for compound **21** and 8.1 nmol litre^{-1} for thione **22**, which is comparable with the Nifedipine value of 2.9 nmol litre^{-1}.[52]

Table 2. Antihypertensive activity of compounds **20** in 10 mg kg^{-1} dose.[50]

Compounds **20**	Decrease in the systolic blood pressure (mm Hg) in rats after specified periods of time (min)			
R^1, R^2	0	60	180	400
H, Cl	226	193	161	125
H, OMe	226	193	161	125
Cl, Cl	225	195	160	125
OMe, Cl	226	193	161	125
OH, Cl	226	190	160	125
Me, Cl	226	193	161	125
Me, OMe	225	191	161	125
OMe, H	222	193	161	123
OMe, Cl	228	183	161	113
OMe, OMe	226	190	160	120
Control	225	224	224	224
Nifedipine (**9**)	225	195	168	122

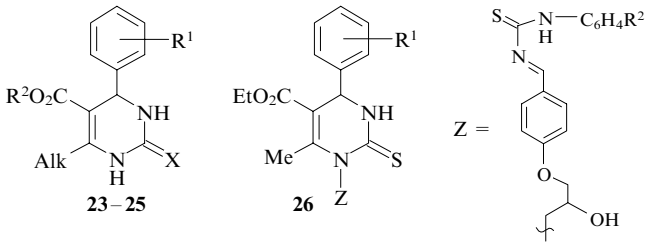
In testing on isolated rat ileum, compound **23** (R^1 = 2-Cl) in 10^{-5} mol litre^{-1} concentration proved to be more efficient than Nicardipine (**12**). When tested on carotid artery, other compounds **23** (R^1 = 2-Me, 2-Br, 3-Br) were active in concentrations of $10^{-6} – 10^{-5}$ mol litre^{-1} (Ref. 53).

In a study of the action of analogous 4-aryl-6-ethyl-5-methoxycarbonyldihydropyrimidinethiones **24** on a rat ileum section, the most pronounced relaxant effect, somewhat inferior to that of Nicardipine, was demonstrated by *ortho*-aryl-substituted compounds (R^1 = 2-Me, 2-OEt, 2-Cl, 2-NO_2), whereas in thoracic aorta experiments, a noticeable efficiency was found only for the *ortho*-ethoxyphenyl derivative (R^1 = 2-OEt).[54]

The DHPM interaction with β-adrenergic blocker and Ca-channel blocker was studied using a specially selected group of 4-aryl-5-ethoxycarbonyldihydropyrimidinones **25**.[55] The cardiovascular effects studied on isolated frog heart were manifested as the dose-dependent inotropic action, either positive or negative depending on the nature of substituent R in the aryl group.

Methoxy- and hydroxyphenyl derivatives **25** (R^1 = 3-OH, 4-OH, 4-OMe) increased the force of heart contraction (positive inotropic effect) with a simultaneous

Structures 23 – 26



23: R^1 = H, 2-Me, 3-Me, 2-OMe, 3-OMe, 2-Cl, 3-Cl, 2-Br, 3-Br, 2-CF_3; R^2 = Me; Alk = Et; X = O;
24: R^1 = H, 2-Me, 3-Me, 4-Me, 2-OMe, 2-OEt, 2-F, 3-F, 2-Cl, 3-Cl, 4-Cl, 3-Br, 4-Br, 2-NO_2, 3-NO_2; R^2 = Me; Alk = Et; X = S;
25: R^1 = 3-OH, 4-OH, 4-OMe, 2-Cl, 2-NO_2; R^2 = Et; Alk = Me; X = O;
26: R^1 = 2-NO_2, 3-NO_2; R^2 = H, 2-OMe, 4-OMe, 4-Cl, 4-CO_2H

decrease in the contraction rate (negative chronotropic effect) and an increase in the cardiac output; the effects were comparable with or higher than those of the cardiotropic agent Digoxin. Replacement of the ethyl group in the dihydropyrimidinone ester moiety by a phenyl group did not change the observed trends. Since the cardiotonic action of these compounds was found to be blocked by Verapamil (Ca-channel blocker), the researchers concluded that the test compounds participate in the opening of slow Ca-channels.

Meanwhile, two other compounds of series **25** (R^1 = 2-Cl, 2-NO_2) blocked the effect of adrenalin by acting as β-adrenergic receptor antagonists and also induced a negative inotropic effect and reduced the cardiac output.[55]

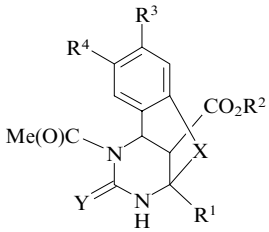
A series of hybrid structures **26** comprising an arylthiourea moiety and an aryloxypropanol spacer were prepared in order to enhance the action of β-adrenergic receptor blockers.[56] Most compounds of this series demonstrated negative inotropic and chronotropic effects when compared with the action of adrenalin in isolated frog heart experiments. It was concluded that the hypotensive and antihypertensive effects of these compounds can be due to Ca^{2+} entry blockade and β-adrenergic receptor blockade caused by the action of two different chemical groups.[56]

Compounds **27** and **28** with O- and S-bridges that additionally link the aryl substituent to the pyrimidine heterocycle are formed intramolecularly from 4-(2-hydroxyphenyl)- and 4-(2-sulfanylphenyl)dihydropyrimidinones; they are fully isomeric to the latter and could be biologically active. However, data on the activity are limited only to a statement about these compounds being used as prolonged-action Ca-channel blockers with anti-arrhythmic and anti-anginal action on the cardiac muscle, antihypertensive and spasmolytic effects on the brain vessels and on the vessels of respiratory and urogenital systems.[57]

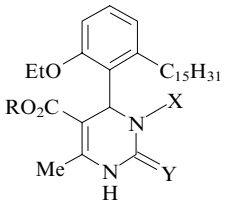
In an early stage, the development of the methods for the synthesis of DHPM derivatives was mainly aimed at investigation of these compounds as modulators of calcium transport across cell membranes. These modulators regulate important physiological properties, including muscle contraction, hormone secretion, nerve impulse transmission, enzyme activity and gene expression. In conformity with diverse physiological processes in the body, the calcium channels are subdivided into five types: L (or Ca_v1), P/Q (or $Ca_v2.1$), N (or $Ca_v2.2$), R (or $Ca_v2.3$) and T (or Ca_v3). Some chemical compounds were found to act not only specifically on a particular channel, for example, L- or T-channel, but also simultaneously on both channels. L-Channel blockers play a crucial role in the treatment of arterial hypertension and cardiac angina, whereas the agents that act only or predominantly as T-channel blockers are useful against sleep disorder, depression, brain impairment and other neurodegenerative processes.[58] As a rule, substituted dihydropyrimidinones act as L-channel blockers, and there are still few examples of their ability to act on T-channels. Meanwhile, calcium T-channel blockers were found to play some role in arresting epileptic seizures and Parkinson's disease tremor. Furthermore, pharmacological data attest to a role of these blockers in the therapy of pulmonary hypertension in animals.

An extensive range of dihydropyridine and -pyrimidine derivatives have been studied as Ca-channel blockers; these compounds are topologically related structures, which comprise a heterocyclic core and the disubstituted aryl moiety

Structures 27 – 30



27, **28**



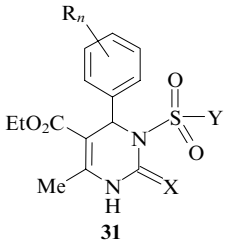
29, **30**

27: R^1 = H, Me; R^2 = Me, Et, $CH_2CH{=}CH_2$; R^3 = H, SMe; R^4 = H, NO_2; X = O; Y = O;
28: R^1 = Me; R^2 = Me, Et; R^3 = H, CN; R^4 = H, NO_2; X = O; Y = S;
29: R = Et; X = C(O)Et; Y = S;
30: R = Pr^i; X = CO_2Et; Y = O

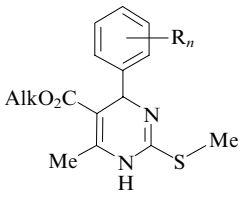
with an alkoxy group and a long-chain alkyl or alkenyl substituent (*e.g.*, compound **29**). A number of these products were found to inhibit T-type and/or L-type channels depending on the particular chemical structure.[59] Unexpectedly, *in vitro* experiments on human embryonic kidney (HEK) cells showed a slow onset of the activity for the selected group of compounds, for example 10 min for compound **30** *versus* 12 s for Mibefradil, a standard T-blocker, and more prolonged action. The dose required for 50% T-channel blockade (ED_{50}) was in the range of 25 – 1000 nmol litre^{-1} (Ref. 59).

Testing of these compounds on isolated rat thoracic aorta specimens and on cell lines expressing cloned human T- and L-type calcium channel genes demonstrated the efficiency of test compounds and the possibility of using them for treating a number of diseases, including hypertension, ischemia, renal failure, diabetes, endotoxemia, hemorrhagic shock and central nervous system (CNS) disorders and for alleviation of pain of various etiology. These compounds could also find use as anti-arrhythmic, anti-

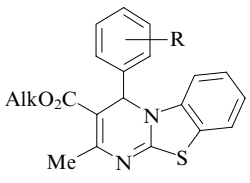
Structures 31 – 34



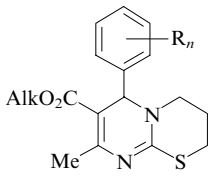
31



32



33



34

31: R_n = 2,3-Cl_2, 2-NO_2, 3-NO_2, 2-Cl-3-NO_2, *etc.*; X = O, S; Y = Me, Bu^n, $(CH_2)_3NMe_2$, Ph;
32: Alk = Me, Et; R_n = 4-Cl, 4-NO_2;
33: Alk = Me, Et; R = 2-Cl, 3-Cl, 4-F, 2-OH, 4-OH, 4-OMe, 3-NO_2, 4-NO_2, 4-NMe_2;
34: Alk = Me, Et; R_n = 2-F-4-Cl, 4-Cl-3-NO_2, 3,4-Cl_2, 4-OMe, 3,4,5-$(OMe)_3$

asthmatic, anti-arteriosclerotic agents and drugs against radiation and chemotherapeutic injury.[58]

N(3)-Sulfonyl DHPMs **31** are also cardiovascular agents. They act as Ca^{2+} entry blockers and can be used as hypotensive agents. When used in combination with other hypotensive agents, they have anti-arrhythmic, anti-anginal, anti-fibrillatory and anti-asthmatic properties.[48]

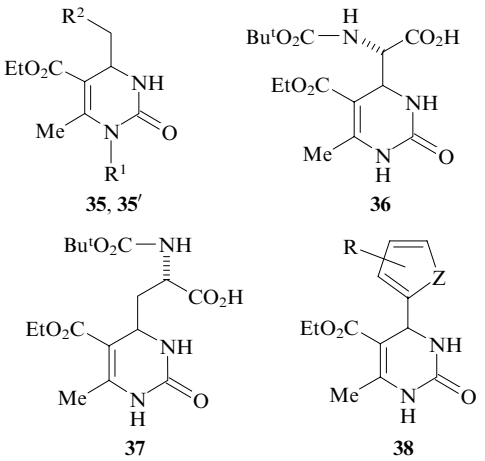
As the sulfur atom in dihydropyrimidinethione is alkylated to give an open-chain (compound **32**) or ring side group (compound **33**), the antihypertensive activity of the derivatives acting as selective L-type Ca-channel blockers is retained at a high level.[60, 61]

Anti-anginal and anti-inflammatory properties are inherent in alkyl 4-aryl-3,4-dihydropyrimidine-5-carboxylates **34** containing a saturated N,S-heterocycle.[62]

In the course of screening of biologically active compounds and elucidation of the role of particular structural groups of the dihydropyrimidine molecule, an attempt was made to replace the aromatic group by a simple or functionalized alkyl substituent. A series of N(1)-methyl- and 4-methyl-substituted dihydropyrimidinones **35** and **35′** were synthesized and tested for the ability to restore the shrinkage of the cell membrane, which depends only on the influx of extracellular calcium. It was found that compounds **35** (IC_{50} = 100 – 300 μmol litre^{-1}) are 10 – 30 times less efficient than Nifedipine (IC_{50} = 10 μmol litre^{-1}) in *in vitro* experiments using KCl.[63] The N(1)-alkylated derivatives of the same series and 4-phenyl derivatives are also inferior to Nifedipine in the observable Ca-channel blocking ability.[64]

Some heterocyclic α-amino acid derivatives, in particular, esters of 4-(α-glycyl)- (**36**) and 4-(α-alanyl)dihydropyrimidin-2-one (**37**) were prepared; they did not show a noticeable activity but could still be of interest as components for the further design of biologically active oligopeptides.[65, 66]

Structures 35 – 38



35, **35′** **36** **37** **38**

35: R^1 = H: R^2 = H, Me, Et, Pr^n, Pr^i, Bu^n, C_9H_{19}, $C_{10}H_{21}$, CH=CH_2, CN, $C(O)CH_2CO_2Me$, $C(O)CH_2CO_2Et$, SO_2Ph;
35′: R^1 = Me: R^2 = H, Ac, Bz, SO_2Ph, $C(O)CH_2CO_2Et$;
38: R = H, 3-Me, 5-Me; Z = O, S, NMe

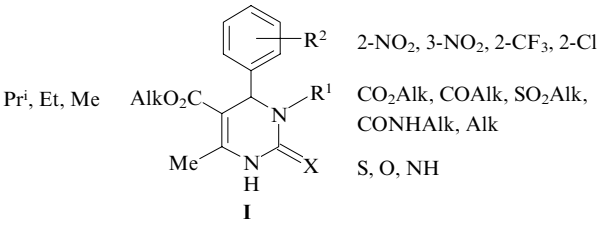
The experimental data gained even in early stages of research revealed the structural requirements to dihydropyrimidinones as cellular Ca^{2+} transport blockers. It was shown that N(3)-substituted derivatives with electron-withdrawing groups reproduce qualitatively the trends we found for 1,4-dihydropyridines.[45, 67] Meanwhile, N(1)-substituted dihydropyrimidinones show rather low activity.[63]

The dihydropyrimidinone activity is boosted by electron-withdrawing substituents in the *ortho*- or *meta*-position of the benzene ring.[45, 49] Note that similar trends were found in the series of analogous 4-aryl-substituted dihydropyrimidinethiones. It was shown that isopropyl ester has a more pronounced effect than methyl or ethyl ester. However, further branching or elongation of the alkyl chain in the ester group does not increase the activity.[68]

A comparative *in vitro* investigation of the antihypertensive and Ca-channel blocking activity of Nifedipine and DHPMs with a five-membered heterocyclic substituent (furyl, thienyl, 1-methylpyrrolyl; compounds **38**) instead of the phenyl group showed that the activity is retained, including the case where there is no ester group in the pyrimidine ring.[69]

The relationships between the chemical structure and Ca-channel blocking activity noted above can be represented in a general form (structure **I**; the substituents and functional groups are listed in the order of decreasing DHPM activity).[11, 17]

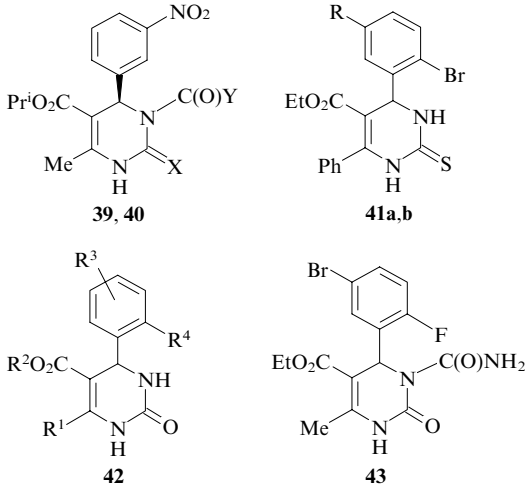
Structure I



I

High activity of the 4*R*-enantiomers and low activity of the 4*S*-counterparts was found in a comparative *in vitro* and *in vivo* studies of some model dihydropyrimidin-2-ones and -2-thiones, for instance, **39** and **40**, for vasodilator activity on rabbit thoracic aorta specimens and antihypertensive activity on rats.[44, 45, 49, 70] This relationship also holds for other structures.[4]

Structures 39 – 43

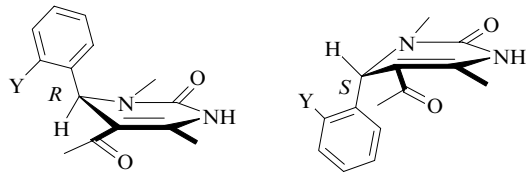


39, **40** **41a,b** **42** **43**

39: X = O, Y = NH_2; **40**: X = S, Y = OEt; **41**: R = H (**a**), OH (**b**);
42: R^1 = Me, R^2 = Et, R^3 = 4-OC(O)Hex, R^4 = H (**a**); R^1 = H, Me; R^2 = Et, P^n, Bu^i; R^3 = 5-F, 5-Cl, 5-Br, 5-CN; R^4 = H, OH;
Hex is n-hexyl

The conformational and structural characteristics responsible for Ca-channel modulation were considered by Rovnyak *et al.*[71] The Ca-channel modulation effect of DHPMs was found to depend on the absolute configuration of the molecule and binding of the agent with the *R*- or *S*-configuration at C(4) to a particular receptor. The receptor-linked agent acts as a molecular switch, which is different for the antagonist (the aryl-substituted group points upward, *R*-configuration) and the agonist (the aryl-substituted group points downward, *S*-configuration) (structures **II** and **III**). The substituent Y in the aryl group should preferably have *syn*-periplanar orientation [relative to the C(4)–H bond]. Furthermore, for the optimal modulating activity of DHPM, the ester carbonyl group should be *cis*-oriented relative to the C(5)–C(6) double bond of the dihydropyrimidine ring.[71]

Structures II, III



II **III**

In a study of the inhibitory activities of a large series of dihydropyrimidinones and -thiones towards non-selective Ca-channels, several compounds were distunguished, *e.g.*, **41a** ($IC_{50} \leqslant 5.0$ nmol litre^{-1}) and **41b** ($IC_{50} \leqslant 1.0$ nmol litre^{-1}), promising as parts of compositions for pain alleviation.[72]

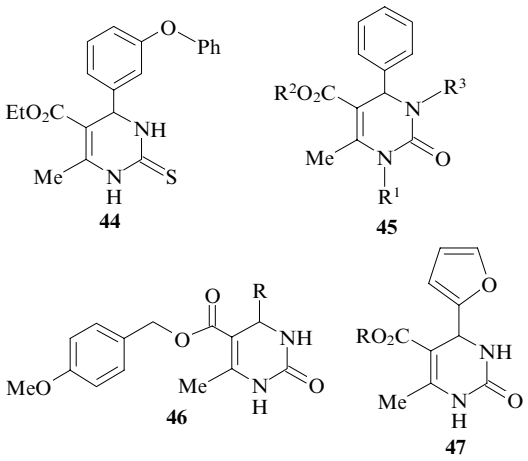
Recently it was found that 5-alkoxycarbonyldihydropyrimidinones behave as inducible NO-synthase inhibitors. Nitric oxide is enzymatically synthesized in cell structures from L-arginine, the synthesis involving different synthase (NOS) isoforms — endothelial (eNOS) and neuronal (nNOS) synthases — which act selectively and depend on the state of the calcium/calmodulin system. These synthases play an important role in the regulation of cardiovascular homeostasis, nerve impulse transmission, regulation of intracellular calcium levels, gastrointestinal tract and bronchus functioning, platelet aggregation inhibition and thermal regulation.[73] In particular, heptanoyloxyphenyl derivative **42a** showed anti-aggregatory activity in *in vivo* and *in vitro* experiments.[74]

The third isoform, inducible NO-synthase (iNOS), is a Ca-independent enzyme, which is absent from normal cells, but is rapidly formed in response to appearance of endotoxins or cytokines. The key function of iNOS is to synthesize nitric oxide as a cytotoxic and anti-inflammatory agent and to provide immune protection. However, an increased nitric oxide level in inflamed tissues causes local pain and enhances the action of irritants on the central and peripheral nervous systems. In this situation, it is necessary to utilize specific inhibitors to reduce nitric oxide production. The search for NO-synthase inhibitors among dihydropyrimidinones revealed the range of most promising agents (*e.g.*, **42** and **43**) that had effective iNOS inhibition concentrations EC_{50} of $\leqslant 5$ μmol litre^{-1} (Ref. 73).

3-Phenoxyphenyl-3,4-dihydropyrimidinethione **44** exhibits anti-inflammatory properties in microglial cells. It reduces the effect of several factors such as nitric oxide, prostaglandin and interleukin and suppresses the expression of inducible NO-synthase and cyclooxygenase. This compound also inhibits the activation of mitogen-activated protein kinases. The authors indicate the possibility to utilize these properties for treating neurodegenerative diseases.[75]

Worth noting is also the ability of DHPMs to inhibit sodium iodide transport from blood to the thyroid gland and thus to affect the biosynthesis of thyroid hormones, which are vital components of regulation of natural metabolism and functioning of the central nervous systems of vertebrates and humans. A modern biochemical analysis identified the key role of sodium iodide transport in the case of thyroid gland diseases and some autoimmune diseases. Screening of chemical compounds resulted in the discovery of new agents blocking iodide entry into the human embryonic kidney (HEK) cells; among these, quite a reasonable activity was found for dihydropyrimidinone **45a**.[76]

Structures 44 – 47



44 **45** **46** **47**

45: $R^2 = CH_2C_6H_4OMe$-4: $R^1 = R^3 = H$ (**a**), Me (**b**); R^1 = Me, Bu^i, Bn; R^3 = H, Me;
46: R = 3-FC_6H_4 (**a**); R = H, Et, Bn, cyclo-C_3H_5, cyclo-C_5H_9, Cy, Bz, 2-Naph, 2-Fu, 3-Fu, 2-Th, 3-Th, 2-Ind, 3-Ind, 4-Py, 4-Quin, $C_6H_{5-n}R'_n$ (R'_n = 2-Br, 3-Br, 4-Br, 3-Cl, 4-Cl, 2-F, 3-F, 4-F, 2-I, 4-CF_3, 3-CN, 4-NO_2, 2-OH, 3-OH, 4-OH, 2-OMe, 4-OMe, 4-OAc, 4-NHAc, 4-NMe_2, 4-Bz, 3-OBn, 4-OBn, 3,4-$(OH)_2$, 2,5-$(OMe)_2$, 2,4,5-$(OMe)_3$ *etc.*), *etc.*;
47: R = $CH_2C_6H_4OMe$-4; Cy is cyclohexyl, Fu is furyl, Th is thienyl, Ind is indolyl, Quin is quinolinyl, Py is pyridyl

The subsequent chemical modification and testing of more than a hundred of synthesized compounds of types **45** and **46** resulted in a series of the most efficient sodium iodide transport inhibitors (NIS inhibitors).[76] The IC_{50} values of dihydropyrimidinones (65 nmol litre^{-1} for **45b**; 75 nmol litre^{-1} for **46a**), which characterize the inhibitory action on the iodide insertion into rat thyroid FRTL-5 cells, show that the activity is enhanced compared with N(1),N(3)-unsubstituted compound **45a** (89 nmol litre^{-1}). The inhibitory activity was especially pronounced for compound **47** (3.2 nmol litre^{-1}).[76]

II.1.b. Receptor blockers and modulators

The keen attention of pharmacologists was also drawn to the search for selective adrenergic receptor antagonists, in view of the vital role they play in a living organism by regulating a variety of physiological processes in norm and pathology. In terms of their structure, they are G-protein-

coupled receptors and are classified into several types and subtypes depending on their location in the body and the sort of performed functions. For instance, the α_{1a} receptor subtype is a signal mediator for urinary tract and prostate smooth muscle contraction, while functioning disorder is responsible for prostatic hyperplasia. Currently, some natural alkaloids and some synthetic α_1-adrenergic receptor antagonists are used for treating and preventing prostate diseases; a drawback of these agents is low selectivity.[77, 78] Therefore, efforts on the search for new, more efficient and selective agents are quite justified. In this respect, worthy of note is the series of studies on the synthesis and pharmacological behaviour of N(3)-substituted 4-aryl-3,4-dihydropyrimidines and dihydropyrimidin-2-ones performed in the late 20th and early 21st century by several research teams.[79 – 90]

The selection of suitable dihydropyrimidines was based on analysis of data on the activity of various α_1-adrenergic receptor antagonists and the role of particular structural moieties and functional groups in the molecules of known agents.[77, 78] The analogy with pyridine α-adrenergic blockers, compounds **48** [(*S*)-Niguldipin] and **49** (SNAP 5089), which contain an ester or amide group with an alkyl chain linked to the piperidine ring, seemed to be most appropriate.[77]

4-Aryl-2,6-dimethyl-3,4-dihydropyrimidine-5-carboxylates with a piperidinoalkyl or piperazinoalkyl chain at N(3) (compounds **50** and **51**)[87] and the corresponding N(3)-carbamoyl derivatives **52** were considered to be close analogues of these dihydropyridine derivatives.[83 – 86] (For compounds **52** and similar situations below, various combinations of two or three out of the listed substituents R are supposed to be possible). The deliberately synthesized N(3)-carbamoyl derivatives **52** proved indeed to be α_{1a}-antagonists; some of them had high selectivity and were able to block prostatic smooth muscle contraction, without affecting the blood pressure. Moreover, they were more stable to metabolic oxidation than compounds **50** and **51**.

Conversely, the known α_1-antagonist drugs Terazosin and Doxazosin showed low selectivity in model experiments on dogs; therefore, blood pressure decreased together with suppression of the prostate contraction. This low drug selectivity may cause orthostatic hypotension, dizziness, asthenia and other adverse effects in patients.[84]

Study of the pharmacological profile of dihydropyrimidines pertaining to series **50** and **51** revealed lead compound **50a**.[87] It is able to efficiently bind to proteins incorporated in the receptor structure (in the concentration of 1.0 nmol litre^{-1}) and has high α_{1a} receptor selectivity (> 1000-fold) over the α_{1b} and α_{1d} receptors; this resembles the action of close analogues — the corresponding substituted dihydropyrimidinone (0.1 nmol litre^{-1}) and dihydropyridine derivative **49** (0.2 nmol litre^{-1}) — on the same receptors. Note that the receptor affinity level and binding selectivity of racemic **50a** are mainly dictated by the (+)-enantiomer, which has a suitable spatial organization and, conversely, the (−)-enantiomer of **50a** has a lower affinity and low selectivity in binding to the α_{1a}, α_{1b}, α_{1d} and α_2 receptors. This is in agreement with similar data for compounds of the dihydropyridine series.[87]

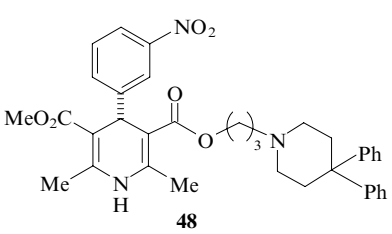
The crucial role of the ester function in these structures was noted; replacement of this group by a primary or secondary amide group reduces the binding affinity and selectivity.[87]

Despite the high activity and selectivity of lead compound (+)-**50a**, investigation of its metabolism *in vitro* and *in vivo* indicated that (+)-**50a** is N-dealkylated to give 4-methoxycarbonyl-4-phenylpiperidine, which is an opiate receptor agonist.[87] Therefore, the search for adrenergic blockers among these dihydropyrimidines was not further developed.

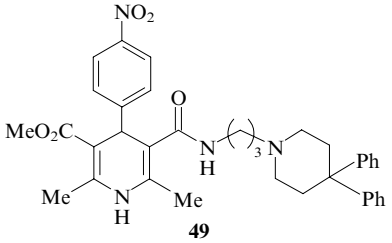
Among the studied N(3)-carbamoyldihydropyrimidinones, compounds **53**–**55** showed good activity and high selectivity *in vitro* and *in vivo*. The (+)-forms of these agents were found to have higher selectivity to α_{1a}-receptors (> 1500) over α_{1b}- and α_{1d}-receptors.[84, 85, 90] Compounds **55** were found to be highly selective to L-type Ca-channels.[90] The reported data can serve as a guiding point for the development of new efficient adrenergic blockers (Table 3).

Good pharmacological profile of the agents presented above together with their high selectivity to α_{1a}-receptors stimulated some modification of these molecules. Some compounds of series **56** and **57** and related bases [for example, enantiomer (*S*)-L-771668 (**58**)] in the form of hydrochlorides, acetates, tartrates, benzoates, maleates and other salts were recommended for treating prostatic hyperplasia.[82, 83] The recommended daily therapeutic doses of these agents can vary in the range from 0.0002 to 20 mg

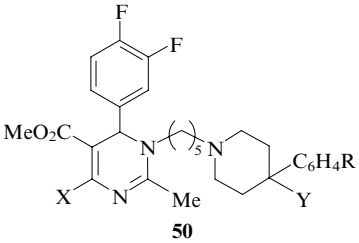
Structures 48 – 52



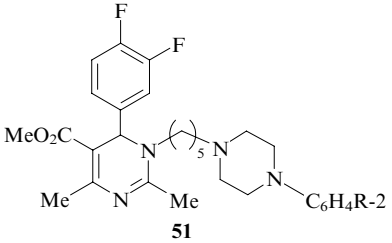
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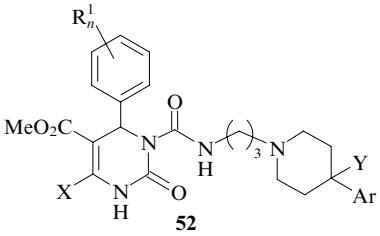
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50



51



52

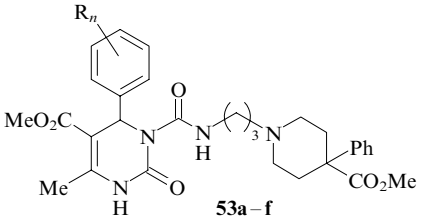
50: R = H, X = Me, Y = CO_2Me (**a**); R = H, Me, CF_3, OMe; X = Me, CH_2OMe; Y = H, Ph, CN, CO_2Me;
51: R = OMe, CO_2Me, $C(O)NH_2$;
52: R^1_n = 3-Me, 3-Cl, 3-F, 4-F, 2,4-F_2, 3,4-F_2, 4-NO_2; Ar = $C_6H_{5-n}R^2_n$ (n = 1–3; R^2 = H, Alk (C_1-C_4), CF_3, OAlk (C_1-C_4), OCF_3, F, CN, *etc.*); X = Me, Et, CH_2OMe; Y = H, Me, Ph, OH, CN, CO_2Me

Table 3. Affinity binding of 5-methoxycarbonyl dihydropyridine and dihydropyrimidine derivatives to recombinant human α_1-adrenergic receptors.[a]

Compound	K_i /nmol litre^{-1}			Ref.
	α_{1a}	α_{1b}	α_{1d}	
Niguldipin (**48**)				
(+)-(*S*)-enantiomer	0.16	55	100	77
(−)-(*R*)-enantiomer	4.7	56	170	77
SNAP 5089 (**49**)	0.35	220	540	77
50a	1.0	480	680	87
(+)-enantiomer	0.1	190	180	87
(−)-enantiomer	13	700	550	87
53a	0.5	28	100	84
(+)-enantiomer	0.4	81	180	84
(−)-enantiomer	2.1	19	80	84
53b	1.1	50	180	84
53c	1.5	67	150	84
53d	1.2	78	180	84
53e	0.2	88	180	84
53f	0.1	45	140	84, 85
(+)-**54**	0.5	440	640	85
(+)-**55**	0.4	500	230	90
(−)-**55**	1.6	250	130	90

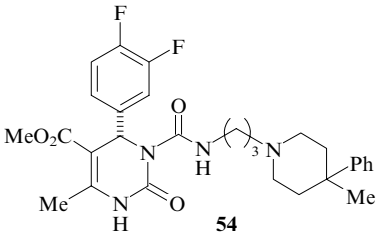
[a] K_i corresponds to displacement of prazosin[^{3}H] from appropriate recombinant human receptors.

Structures 53, 54



53a – f

53: R_n = 4-NO_2 (**a**), 3-Cl (**b**), 3-F (**c**), 4-F (**d**), 2,4-F_2 (**e**), 3,4-F_2 (**f**)



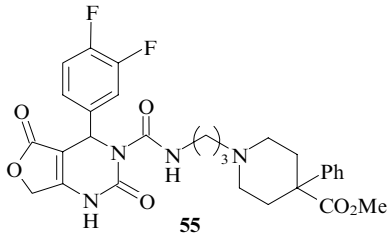
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per kg of human body weight depending on the type of substance.

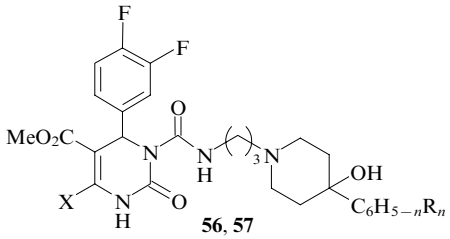
The replacement of the alkyl side chain by a cyclopentane moiety gave rise to a number of stereoisomeric compounds active towards adrenergic receptors, of which isomer **59** with the *R*,*R*-configuration of the cyclopentane moiety proved to be most selective.[88]

The recently synthesized 2-oxotetrahydropyrimidine-5-carboxylic acids **60** and **61**, which showed high affinity for the PPAR-γ receptor (IC_{50} in the range of 0.6 – 1.0 μmol litre^{-1}) involved in the regulation of lipogenesis, homeostasis and insulin dependence, started to be considered as potential competitors to antidiabetic the drugs Pioglitazone and Rosiglitazone (IC_{50} = 0.8 μmol litre^{-1}).[91] Apparently, this issue holds good promise, since

Structures 55 – 57



55

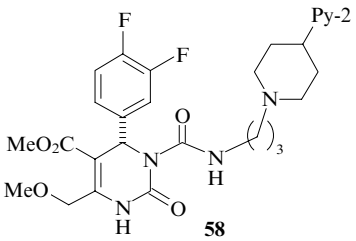


56, **57**

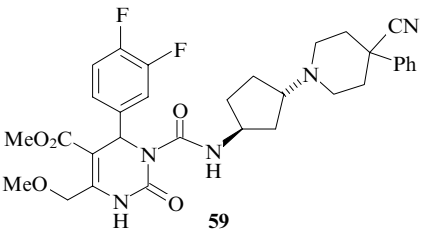
56: X = H: R = H, Hal, CN, CF_3, OCF_3, Alk (C_1-C_4), OAlk (C_1-C_4), $(CH_2)_mCF_3$, $(CH_2)_mOCF_3$ (m = 1 – 3); n = 1 – 3;
57: X = Me: R = H, Alk (C_1-C_4), CF_3, OAlk (C_1-C_4), OCF_3, F, CN, *etc.*; n = 1 – 3

the application of these drugs to treat diabetes has now come into question because of complications in the cardiac function and the urinary system. Quite lately, it has been shown that a few 4-aryl-5-ethoxycarbonyldihydropyrimidinones **2** (R = 4-F, 4-NO_2) and analogous dihydropyrimidinethiones (R = H, 4-OMe) also hold a therapeutic potential as antidiabetic agents; they inhibit the α-amylase activity *in vitro* by 64% – 97% when present in the concentration of 300 μg ml^{-1} (see Ref. 92).

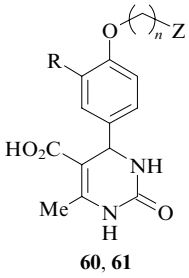
Structures 58 – 61



58



59



60, **61**

60: R = H, OMe; Z = OHet (OHet is carbazol-4-yloxy, 2-methylquinolin-2-yloxy, 2-methylquinolin-4-yloxy, *etc.*); n = 2, 3;
61: R = H, OMe; Z = Het (Het is carbazolo, 4-acetylcarbazolo, pyrrolo[2,3-*b*]pyridin-1-yl); n = 2, 3

The introduction of a terminal dimethylamino group into the ester alkyl group of tetrahydropyrimidine-5-carboxylic acid resulted in compounds **62** exhibiting antimuscarinic activity. Considering preliminary results on their ability to inhibit muscarinic acetyl choline receptors (mAChRs), these compounds can be regarded as alterna-

tives to atropine for neutralization of the toxic action of organophosphorus pesticides and poisons.[93]

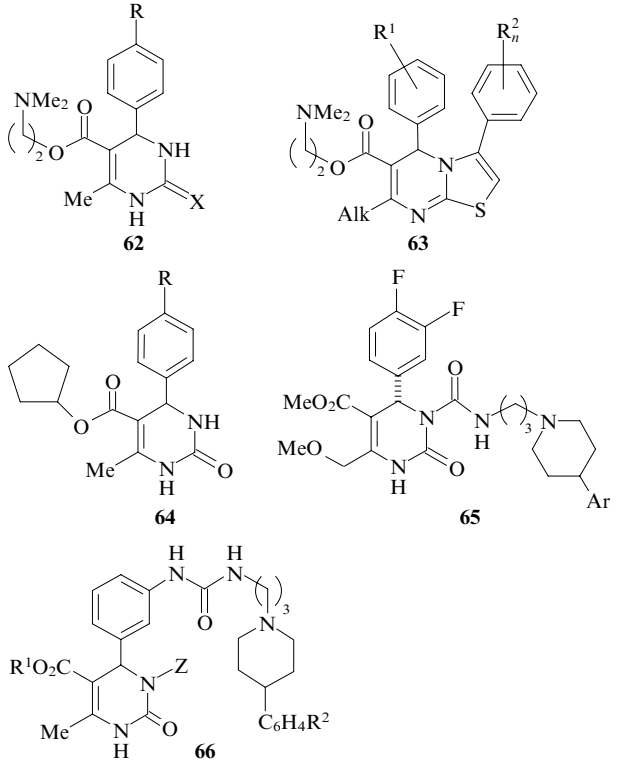
The search for selective antagonists of metabotropic glutamate receptors mGluR, which perform numerous functions in the central and peripheral nervous systems, resulted in the synthesis of diaryl-substituted 5*H*-thiazolo[3,2-*a*]pyrimidines **63**. In a primary pharmacological investigation of their activities on rat cell cultures, a group of the most active compounds was identified and the inhibition constants for the receptor in question were determined.[94] Aryldihydropyrimidinones containing a lipophilic ester group were identified as inhibitors of specific proteins that transport fatty acids from the intestine to the enterocytes. The most clear-cut inhibitory properties were found for esters with a cyclopentyl moiety (compounds **64**) and a benzene moiety with an electron-withdrawing substituent, *e.g.*, NO_2 or CF_3. It was noted that these properties are mainly inherent in *S*-enantiomers.[95]

The (+)-enantiomer of **65** (SNAP 7941) was found to behave as a selective and highly efficient antagonist of the melanin-concentrating hormone receptor MCHR1, which is important for regulation of the energy balance of the body; in *in vivo* experiments, upon long-term administration with food, this enantiomer reduced the overweight in rats. A study of SNAP[^{3}H]-7941 location in the rat brain and behavioural experiments in rats led the authors to conclusion that this drug acts as an antidepressant and anxiolytic, similarly to clinically applied antidepressants.[96] However, other behavioural experiments on mice with non-labelled compound **65** and other related MCHR1 receptor antagonists[97] did not support the results of the above-cited researchers. Moreover, doubt was cast on the applicability of MCHR1 receptor antagonists as potential antidepressant drugs. Positron emission tomography with radioactively labelled agents appears to be quite useful for the monitoring of *in vivo* pathologies related to MCHR1 receptors. Hence, two labelled molecules, SNAP[^{11}C]-7941 (the ^{11}C half-life is $t_{1/2}$ = 20 min) and SNAP[^{18}F]-7941 (the ^{18}F half-life is $t_{1/2}$ = 110 min), were recently synthesized.[98]

5-Alkoxycarbonyldihydropyrimidinones with a different position of the amide moiety (compounds **66**), which have a very low affinity for the α_{1a}-adrenergic receptors and Ca-channels, proved to be non-peptide antagonists of neuropeptide receptors with high binding selectivity to Y_1-receptors (IC_{50} in the range of 1 – 0.1 μmol litre^{-1} in the human neuroblastoma cell membrane test).[99] This type of agents could find use in clinical indications characterized by enhanced content of neuropeptide Y, which causes functional disorders of many organs — heart, blood vessels, lungs and sympathetic and central nervous systems. Presumably, these agents can function as effective anorexiants for weight normalization.[99]

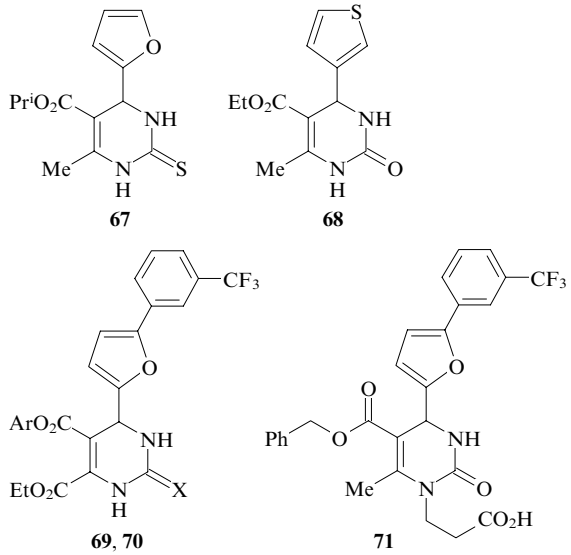
It was found that DHPM esters of a simple structure containing five-membered heterocyclic residues as the 4-aryl substituent can act as selective adenosine A_{2B}-receptor antagonists. These antagonists are used in medicine for the therapy of diabetes, asthma and chronic pulmonary diseases. In *in vitro* experiments on labelled ligand displacement from the HEK-293 cells by the test compounds, the highest A_{2B}-receptor selectivity was found for (2-furyl)dihydropyrimidinethione **67** [K_i (hA_{2B}) = 10.2 μmol litre^{-1}] and (3-thienyl)dihydropyrimidinone **68** [K_i(hA_{2B}) = 23.6 μmol litre^{-1}].[100]

Structures 62 – 66



62: R = OMe, NMe_2; X = O, S;
63: Alk = Me, Et, Pr^i, Bn; R^1 = 2-Me, 2-F, 2-Cl, 2-OMe, 3-OMe, 4-OMe, 2-OEt, 2-OPr^i; R^2_n = 4-Cl, 2,4-Cl_2, 2,6-Cl_2;
64: R = H, Me, F, Cl, Br, OH, OMe, OPr^i, OCF_3, CF_3, CN, NH_2, NMe_2, NO_2, SMe, SO_2Me;
65: Ar = C_6H_4NHAc-3;
66: R^1 = Alk (C_1-C_3); R^2 = H, OMe; Z = H, Alk (C_1-C_3), CO_2Alk

Structures 67 – 71



69, 70: Ar = C_6H_4OMe-4: X = S (**69**), O (**70**)

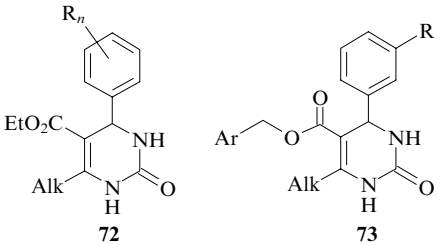
4-Aryl(hetaryl)dihydropyrimidinones and -thiones also aroused interest as potential non-steroidal anti-inflammatory agents. These agents were tested as blockers of microsomal prostaglandin E_2-synthase-1 (mPGES-1), which stim-

ulates an inflammatory process. Prostaglandin synthase blockade is assumed to be an alternative way of treating chronic inflammations. In order to elucidate the optimal structure of the agent, a number of 5-ethoxycarbonyl and 5-benzoyl dihydropyrimidinones were tested *in silico*.[101] By molecular docking of the selected structures into the mPGES-1 receptor cavity, the key role of particular moieties and substituents in the molecule was elucidated and then the predicted trends were confirmed experimentally. The experiments on mPGES-1 inhibition by structurally identical 5-benzoyl-substituted thiones **69** and O-analogues **70** showed the latter to be more active.[101] On further optimization of structure **70** (IC_{50} = 4.16 μmol litre^{-1}), lead compound **71** was identified (IC_{50} = 0.41 μmol litre^{-1}).[102]

Calcitonin, a polypeptide hormone produced by the thyroid gland and thymus, is actively involved in bone tissue resorption inhibition. Owing to retardation of bone resorption and renal excretion of calcium, calcitonin finds therapeutic use in the treatment of a number of diseases, including osteoporosis- and osteodistrophy- (Paget's disease) associated hypercalcemia. Although calcitonin isolated from salmon (s-CT) is effective, upon parenteral administration, for reducing bone resorption, extensive use of this agent is hampered by a short period of action in the body and the necessity of multiple injections.[103] The search for selective calcitonin mimetics among various synthetic derivatives led to investigation of the biological activities of ethyl (**72**) and benzyl 2-oxotetrahydropyrimidine-5-carboxylates (**73**).[103] The selective activity of the tested compounds in experiments on human embryonic kidney cells HEK-293 was estimated by the degree of accumulation of cyclic adenosine monophosphate (c-AMP) in the calcitonin receptor CTR-2 compared with the action of calcitonin s-CT.

Although compounds like ester **73** appeared to be several orders of magnitude less efficient than calcitonin, they were found to exhibit dose-dependent retardation of the loss of ^{45}Ca-labelled bone tissue in mice. In particular, methoxybenzyl ester **73a** (Alk = Pr^i, R = Me, Ar = C_6H_4OMe-4) was also active as a calcitonin mimetic in *in vivo* tests upon subcutaneous injection in rats (EC_{50} = 6 μmol litre^{-1}).[103]

Structures 72, 73



72: Alk = Pr^n, n-C_5H_{11}; R_n = 3-Me, 3-Cl, 3,5-Me_2;
73: Alk = Pr^i, R = Me, Ar = C_6H_4OMe-4 (**a**); Alk = Me, Pr^n, Pr^i; R = H, Me; Ar = Ph, C_6H_4OMe-4, $C_6H_4CO_2$H-4, $C_6H_4CO_2$Me-4

All of the chemical structures considered above are based on a dihydrogenated pyrimidine ring, which can lose two hydrogen atoms and be aromatized under the action of organic and inorganic oxidants;[11, 15] therefore, DHPMs belong to the type of organic reducing agents and can behave as antioxidants. The antioxidant behaviour depends on the nature of substituents and functional groups present in the molecule and on the methods of activity testing.[104 – 107] In relation to a selected group of phenyl-substituted ethyl 2-oxotetrahydropyrimidine-5-carboxylates — close structural analogues of esters **25** with R^1 = H, 4-OH, 4-OMe, 3-NO_2, 4-NO_2 — and the corresponding thiones, it was shown that the presence of a hydroxyl group in the molecule boosts the antioxidant and antiradical activities.[104] In turn, thiones show higher activities than oxygen analogues.[105] A high antioxidant activity was noted for 4-(2-furyl)-substituted thione **67** with an isopropyloxycarbonyl group in comparison with other esters (ethyl, *tert*-butyl and benzyl ones).[106] Thione S-alkylation with simultaneous intramolecular acylation at the ring nitrogen atom gives rise to the dihydrothiazolo[3,2-*a*]pyrimidine system, the derivatives of which also exhibit antioxidant properties.[108]

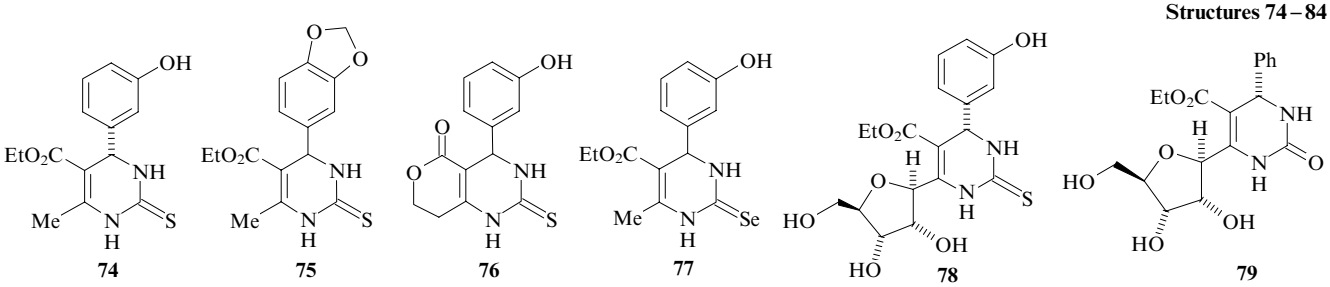
II.1.c. Antiproliferative and cytotoxic activities

We have already noted early publications of Latvian researchers[32, 33] who discovered a moderate antitumour activity for a series of 5-carbonyl DHPMs, *e.g.*, for compound **4**. Examples of more effective agents are (*S*)-Monastrol (**74**) and its structural analogues belonging to 5-carbonyl DHPMs — (*S*)-Enastron and (*S*)-Dimethylenastron (see below, Section II.2) — which possess a noticeable antiproliferative activity towards cancer cells.[109 – 113] A higher activity was noted for the Monastrol *S*-enantiomer as compared with the *R*-enantiomer or the racemate.[109, 114 – 123] Monastrol (**74**) and its analogues inhibit the mitotic kinesin Eg5, which plays a vital role in the cell division process. However, the antimitotic effect of Monastrol is too low (IC_{50} > 14 μmol litre^{-1} *in vitro*) for this agent to be practically used as a cancerostatic.[119] The O-analogue is somewhat less active than Monastrol.[110] The methylenedioxyphenyl derivative **75** (Refs 111 and 112) and cyclic ester **76** (Ref 120) are an order of magnitude more active than Monastrol. The replacement of sulfur in the Monastrol molecule by selenium (compound **77**) reduces the inhibitory activity approximately twofold.[121] Nevertheless, (*S*)-Monastrol, being the first specific inhibitor of the motor activity of the human mitotic kinesin Eg5, has started to be used as a model compound to study the interaction of analogous derivatives with the kinesin Eg5.[109, 122]

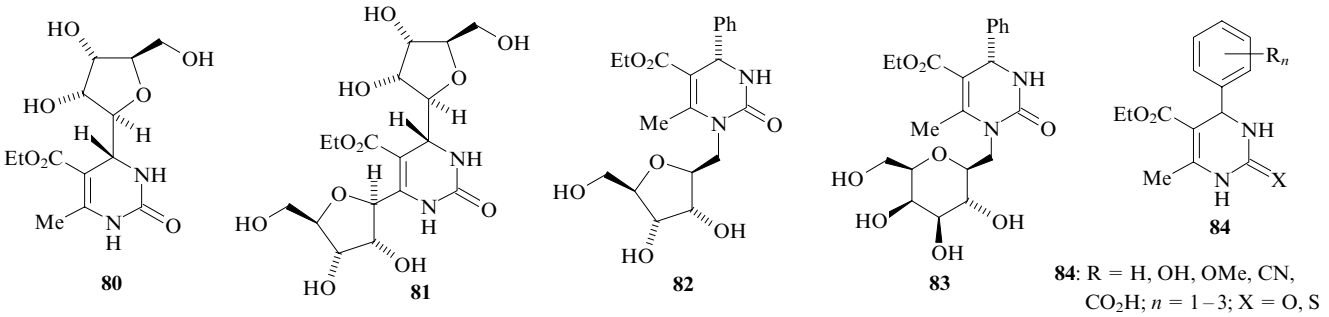
A comparative study of the inhibitory activities of (*S*)-Monastrol (**74**), diastereomers of 6-(β-D-ribofuranosyl)-substituted Monastrol (**78**) and some other C- and N-glycosylated dihydropyrimidinones **79** – **83** towards mitotic kinesin Eg5 demonstrated that *S*-stereomer of **78**, which is most efficient among them, is half as active as Monastrol.[65, 66]

The activity has been studied for a broad range of analogous compounds of the same structural type containing electron-donating and electron-withdrawing substituents in the benzene ring (compounds **84**; various patterns of mono-, di- and trisubstitution in the benzene ring were considered); the cytotoxicity level towards tumour cells was found to depend on the nature of the aryl substituent.[123 – 125] It appears pertinent to study the antitumour activities of boron-containing 4-aryl(hetaryl)dihydropyrimidinones, similar to compound **85**. The antitumour therapy implies selective insertion of a ^{10}B-labelled agent into the tumour and subsequent irradiation of the tumour with slow neutrons.[126]

Structures 74 – 84



74 **75** **76** **77** **78** **79**



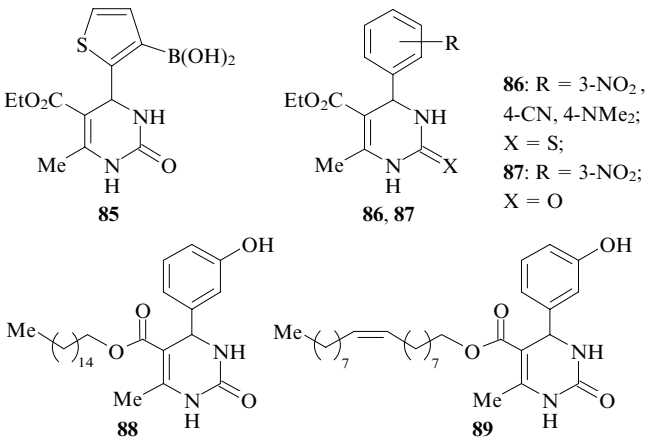
80 **81** **82** **83** **84**

84: R = H, OH, OMe, CN, CO_2H; n = 1 – 3; X = O, S

The first study of the cytotoxic activity of Monastrol (**74**) and related compounds **86** and **87**, which was carried out *in vitro* on human and rat glioma cell lines, showed a high antiproliferative activity.[112,113] The highest activity, which was twice as high as the Monastrol activity, was found for oxygen analogue **87**.[112]

Monastrol modification aimed at increasing the lipophilicity of its molecule by the synthesis of long-chain esters containing hydrocarbon moieties of natural aliphatic acids may provide the way for overcoming the blood – brain barrier in the brain blood circulation and thus increase the efficiency of such synthetic agents in brain tumour chemotherapy. Study of the antitumour activities of this type of hybrid structures on human glioma cells revealed the highest antiproliferative activity for Monastrol O-analogues — esters of cetyl (**88**) and oleyl (**89**) alcohols, which reduced the survival rate of U-138-MG glioma cells by 50% when present in concentrations of 10 μmol litre^{-1}, without affecting the nerve cells.[127]

Structures 85 – 89



85 **86, 87**

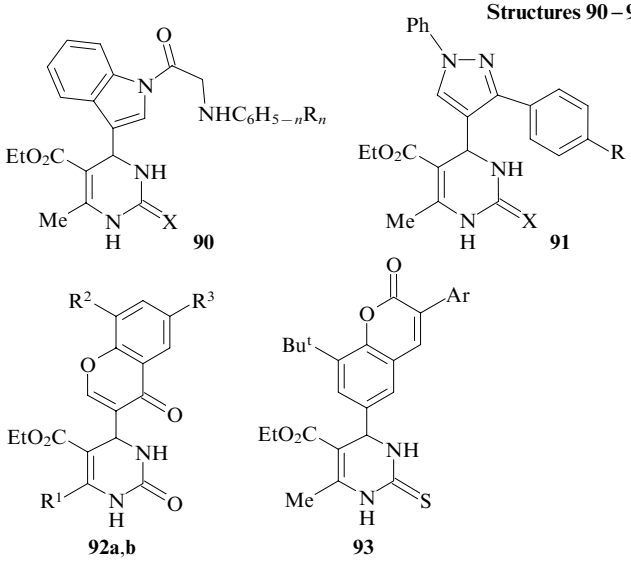
86: R = 3-NO_2, 4-CN, 4-NMe_2; X = S;
87: R = 3-NO_2; X = O

88 **89**

Replacing the benzene ring in compounds **84** by a 3-indolyl ring (compounds **90**) gives rise to fairly active antimicrobial and anticancer agents. N-Nitrophenyl thione **90** (X = S, R_n = 4-NO_2) is not inferior to Norfloxacin in the action on *Escherichia coli*, while a close analogue, nitrochlorophenyl dihydropyrimidinone derivative **90** (X = O, R_n = 3-Cl-4-NO_2) is not inferior to 5-fluorouracil in the anticancer activity, as shown by *in vitro* experiments on HCT-116 colon cancer cells.[128]

Testing of arylpyrazolyl derivatives **91** identified two compounds (X = S; R = H, Cl) exhibiting antituberculosis activity (against the $H_{37}Rv$ mycobacteria) and noticeable anticancer activity towards MCF-7.[129] Comparison of anticancer properties of O- and S-analogues **91** showed the latter to be preferable.[129] However, O-analogues of this series showed a higher antituberculosis activity than thiones.[130] It is noteworthy that 2-methoxy DHPMs **20** were also efficient against $H_{37}Rv$ mycobacteria.[131]

Structures 90 – 93

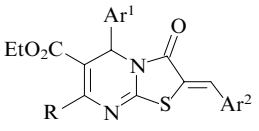


90 **91** **92a,b** **93**

90: R = H, 2-Me, 2-Cl, 3-Cl, 2-NH_2, 2-NO_2, 3-NO_2, 4-NO_2; X = O, S; n = 1, 2;
91: R = H, Cl, F, NO_2; X = O, S;
92: R^1 = Me, R^2 = NO_2, R^3 = H (**a**); R^1 = CF_3, R^2 = H, R^3 = Ph (**b**);
93: Ar = $C_6H_2(OMe)_3$-3,4,5

A similar picture was found for 4-chromon-3-yl DHPMs, among which the most pronounced anticancer activity was inherent in compound **92a** and the highest antituberculosis activity was observed for compound **92b**.[132] Hybrid DHPM with a coumarin moiety (compound **93**) exhibited a high anticancer activity, while acting selectively only on breast cancer cells without affecting proliferation of other cancer cells.[133]

Structures 94 – 96



94 – 96

94: R = Me, Ar^1 = 2-Th, Ar^2 = C_6H_2OH-4-Br_2-3,5;
95: R = Me, Ar^1 = C_6H_4Cl-4, Ar^2 = $C_6H_3(OH)_2$-3,4;
96: R = Ph, Ar^1 = C_6H_4Hal-4 (Hal = F, Cl), Ar^2 is 5-(3-carboxyphenyl)furan-2-yl

Bicyclic compounds **94 – 96**, which should be considered as N(3)-acyl *S*-alkyldihydropyrimidine analogues, do not lose the biological activity inherent in the similar monocyclic derivatives. Indeed, 4-(2-thienyl) derivative **94** exhibited a noticeable activity against *plasmodium malariae* and tuberculosis mycobacteria,[134] while 4-(4-chlorophenyl) derivative **95** showed antiproliferative and apoptotic action on liver and gastric cancer cell lines with good selectivity and cell permeability.[135] High cytostatic activity was detected in analogous compounds while they were tested on 60 leukemia, melanoma and lung, ovarian and breast cancer cell lines.[136] Some carboxyphenyl analogues (*e.g.*, compound **96**) showed high antibacterial activity against staphylococcus.[137]

At a certain investigation stage, it seemed attractive to prepare and test derivatives that would contain several DHPM moieties in order to improve pharmacological characteristics of the agents. Compound **97** with a phenylene bridge connecting two pyrimidine moieties proved to be synthetically the most available. A study of the cytotoxic activity of three structurally identical analogues (X = O, S, NH) carried out *in vitro* on five human cancer cell lines attested to their weak or moderate activity.[138]

Compounds **98** and **99**, each containing two Monastrol moieties connected by a long and flexible spacer, were tested *in vitro* for antiproliferative activity towards several human cancer cell lines, namely, breast (MCF-7), colon (Colo-305), skin (A431) and lung (A549) cancer cells.[139] The results are summarized in Table 4.

Table 4. Antiproliferative activity (IC_{50}, μg ml^{-1}) of Monastrol (**74**) and its dimeric analogues.[139]

Compound	*n*	Cell lines			
		MCF-7	A431	Colo-205	A549
74		45	53	164	118
98	3	16	76	144	120
98	4	186	> 200	> 200	> 200
98	5	178	74	190	> 200
99	3	175	190	> 200	175
99	4	128	146	154	> 200
99	5	34	159	71	184

Note. The data for compounds **98** and **99** are referred to one structural moiety of Monastrol.

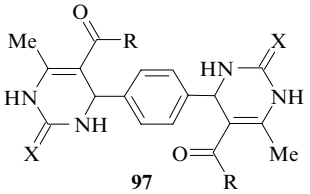
The above-mentioned dihydropyrimidinones **79 – 83** with C- and N-glycoside moieties in the molecule are also of interest for pharmacologists as a starting material for the search of new low-toxicity anticancer agents.

It has been noted above that the antimitotic effect of Monastrol is not sufficiently high for this compound to be practically used as a cancerostatic. 6-Aryl-5-benzoyl-substituted Monastrol analogues, which are discussed in Section II.2, may be more advantageous for this purpose.

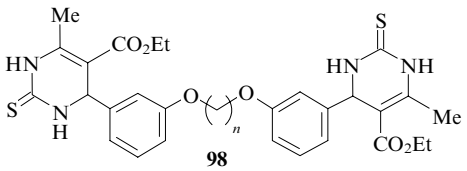
It was assumed that the introduction of a lipophilic CF_3 group into a Monastrol molecule would promote a better penetration of the agent across biological membranes and enhance its antimitotic effect. Indeed, compounds **100** and **101** showed good antiproliferative activity towards colon cancer cells (the IC_{50} value was 12.2 and 8.1 μmol $litre^{-1}$, respectively).[140]

The idea of introducing a highly polar group into the dihydropyrimidinone molecule to facilitate passage of the agent across the membranes was implemented in relation to the synthesis of a small series of *N*(3)-[2-(diethoxyphosphorylmethoxy)ethyl]dihydropyrimidinones tested for cytotoxicity towards cancer cells.[141] A high activity was found for 4-hydroxyphenyl derivative **102**, which induces apoptosis of

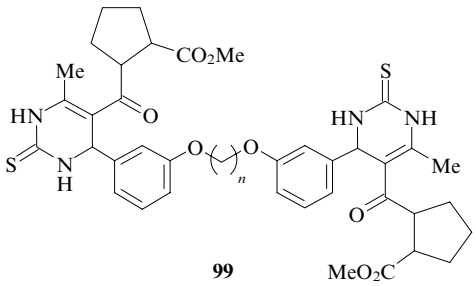
Structures 97 – 102



97

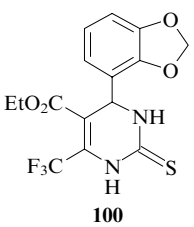


98

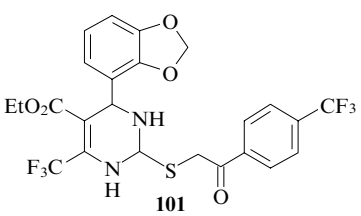


99

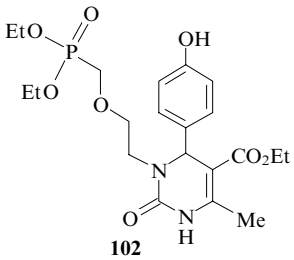
97: X = O, S, NH; R = Me, Ph, OEt; **98**, **99**: *n* = 3 – 5



100



101



102

breast adenocarcinoma cells when present in concentration of $\geqslant 50$ μg ml^{-1}.

A number of DHPMs showed themselves as selective isoforms of $GABA_A$ receptors containing δ-subunits, mutations in which may be associated with heritable epilepsy. Out of this series, Monastrol (**74**) and some 4-aryldihydropyrimidines showed encouraging results, which gives grounds for the search for new agents possessing higher selectivity.[142]

More intricate DHPM derivatives were tested as modulators of endogenous thermal shock proteins (chaperones), Hsp70 and Hsp40, the function of which is to restore the damaged proteins and protein complexes. It was demonstrated that DHPMs with long alkyl chains at N(1) [for example, compound **103** (SW02)] are able to stimulate the activity of chaperones, increase the anti-aggregatory activity and retard cell proliferation.[143, 144]

Compounds of this type, MAL2-213 (**104**) and MAL2-215 (**105**), were presented as a new class of antimalarial agents able to inhibit replication of malarial plasmodia in human red blood cells (*via* inhibition of the plasmodial chaperone Hsp70) causing tropical malaria.[145]

More complex molecules that modulate the chaperone activity arouse interest as targeted cytoprotective agents in the therapy of malignant tumours and specific viral infections such as hepatitis B, herpes or papilloma.[146] Compounds **106** (MAL3-39), **107** (MAL3-90) and **108** (MAL3-101) were found to be most promising chaperone Hsp70 modulators. Compound **108** induces apoptosis of breast cancer cells with $ED_{50} < 10$ μmol litre^{-1} (Ref. 147).

In order to improve the physicochemical properties and enhance the cellular activity of this agent, a series of modified structures were prepared. Modification of molecule **108** (MAL3-101) consisted in the variation of substituents both in the pyrimidine ring and in the dipeptide moiety. Antiproliferative activity testing demonstrated that a number of these compounds inhibit the cancer cell growth; derivatives **109** (DMT003088), **110** (DMT003132) and **111** (DMT003052) surpass compound **108** in the efficiency (Table 5).[147]

Table 5. Inhibition of SK-BR-3 and MCF-7 breast cancer cell and HT29 colon cancer cell growth.[147]

Compound	GI_{50} /μmol litre^{-1}		
	SK-BR-3	MCF7	HT29
108	27	14.7	> 50
109	6.5	2.4	4.8
110	6.2	6.3	5.3
111	8.8	7.8	3.1

Note. GI_{50} is the half-maximal growth inhibition concentration.

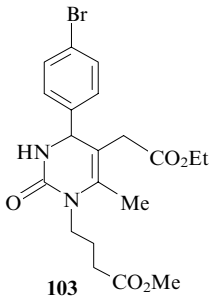
Among other properties of Monastrol as a mitotic kinesin Eg5 inhibitor, when present in concentration of 10 μmol litre^{-1} (IC_{50}), it was found to inhibit proliferation of amastigotes in microphage cultures infected with *Leishmania donovani*; no cytotoxicity to other cells was noted. The *in vivo* experiments on syrian hamsters showed that oral administration of Monastrol in a dose of 5 mg kg^{-1} every 2 days inhibits the growth of leishmania parasites by 50%.[148]

II.1.d. Anti-inflammatory, antimicrobial and antiviral activities

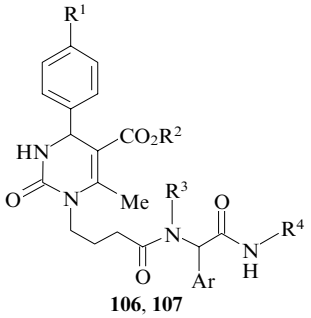
Compounds possessing anti-aggregatory[42] and anti-inflammatory [149] activities were found among dihydropyrimidinethiones **17** (Alk = Et) and bicyclic derivatives **112**. For example, compounds **17** (R = 2-OMe) and **112** (R = 2-Me) showed an anti-inflammatory effect in carrageen mice experiments when administered in 100 mg kg^{-1} dose, the effect being comparable with the action of 10 mg kg^{-1} of Indomethacin. Unlike Indomethacin, these compounds did not affect stomach or kidneys.[149]

The search for non-steroidal anti-inflammatory agents of the same type resulted in the synthesis of two new series of dihydropyrimidinethione derivatives **113** containing an urea (X = O) or thiourea (X = S) moiety in the benzene

Structures 103 – 111

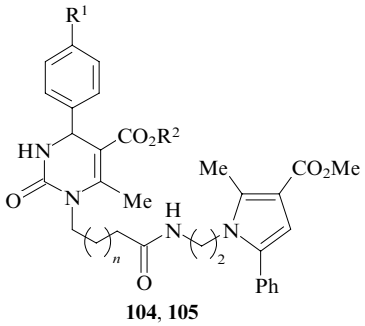


103



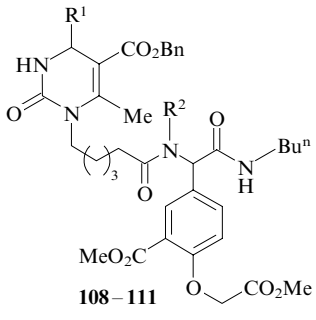
106, **107**

Compound	R^1	R^2	R^3	R^4	Ar
106	NO_2	Bn	2-morpholinoethyl	Bu^t	C_6H_4Ph-4
107	Br	Et	Bn	Bu^n	$C_6H_3(OCH_2O)$-3,4



104, **105**

104: $R^1 = NO_2$, $R^2 = Et$, $n = 1$;
105: $R^1 = Ph$, $R^2 = Bn$, $n = 3$



108 – 111

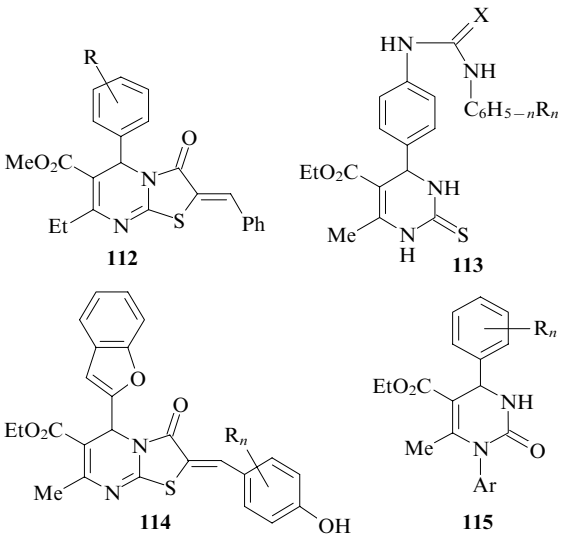
Compound	R^1	R^2
108	C_6H_4Ph-4	Hex
109	Ph	Hex
110	cyclo-C_3H_5	Hex
111	C_6H_4Ph-4	$(CH_2)_2OMe$

ring.[150, 151] All compounds **113** were tested for the action on proinflammatory cytokines, α-tumour necrosis factor (TNF-α) and interleukin (IL-6), which perform signalling functions in cell structures during inflammation processes, cardiovascular diseases and cancer. The inhibitory effects of two compounds with the urea moiety (X = O; R_n = 2-Cl-4-CF_3, 3,5-F_2) and all compounds **113** with the thiourea moiety (X = S) were found to be fairly high, being only slightly inferior to the Dexamethasone effect on cytokines.[150, 151]

The biological activities of complex hybrid structures are often multiple. Examples of accompanying types of activity exhibited by some compounds or groups of compounds have already been presented above. In particular, compounds **20** exhibiting antihypertensive and anti-inflammatory properties[50] were also found to have antituberculosis activity.[131] Antituberculosis activity was also detected in compounds **91** and **92b** in addition to anticancer activity;[129, 132] hybrid DHPMs with a thienyl (compound **94**) or benzofuryl substituent (compound **114**) exhibit both antituberculosis and antimalarial activities.[134] A higher activity against mycobateria was observed for pyrimidinones **91** as compared with the -thiones; two O-compounds (R = F, NO_2) were more active *in vitro* [minimal inhibitory concentration (MIC) of 0.02 μg ml^{-1}] than Isoniazid (MIC = 0.03 μg ml^{-1}).[130] The ability of MAL2-213 (**104**) and MAL2-215 (**105**) to inhibit the replication of malarial plasmodia in red blood cells has been mentioned above.[145]

The quest for new antituberculosis and antimalarial drugs led to investigation of the already mentioned compounds **112**. Preliminary data on the inhibition of IspF enzymes specific to tuberculosis mycobaterium and malarial plasmodium were reported.[134]

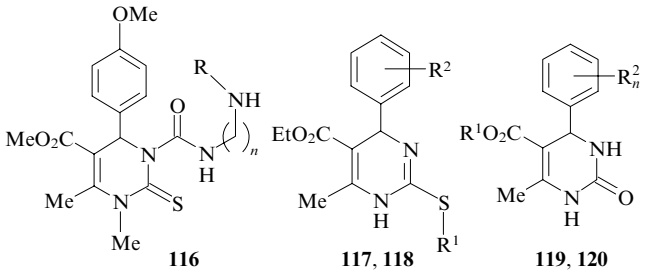
Structures 112 – 115



112: R = 2-Me, 3-Me, 2-OMe, 3-OMe;
113: R_n = 4-Pr^i, 2-OCF_3, 3,5-F_2, 2-Cl-6-F, 2-Cl-6-Me, 2-Cl-4-CF_3, 2-Cl-5-CF_3, 2-Cl-6-CF_3; X = O, S;
114: R_n = H, 3-Br, 3,5-Br_2, 3,5-Cl_2;
115: R_n = H, 4-OH, 4-OMe, 3,4-$(OMe)_2$, 2-Cl, 3-Cl, 4-F, 2-NO_2, 3-NO_2; Ar = C_6H_3Cl-3-F-4

Upon N(1)-arylation of ethyl esters of DHPM-based acids, moderate antimycobacterial activity is retained: indeed, compounds **115** present in concentrations of > 6.25 μg ml^{-1} suppress the growth of H_{37}Rv mycobacteria by 20% – 70%.[152] A high antimalarial activity comparable with that of Chloroquine was found for citrates of N(3)-carbamoyl dihydropyrimidinethiones **116** containing a 7-chloroquinolin-4-yl moiety.[153]

Structures 116 – 120



116: R is 7-chloroquinolin-4-yl, *n* = 2 – 4;
117: R^1 = n-C_5H_{11}, R^2 = 4-F;
118: R^1 = $(CH_2)_2CO_2H$; R^2 = H, 2-OMe, 3-OH;
119: R^1 = $(CH_2)_2$NPhBn; R^2_n = H, 3-NO_2;
120: R^1 = Et; R^2_n = 2-OH-5-Br

Compounds like S-pentyl derivative **117** and some of its analogues possessing antifilarial activity can be useful in the search for effective agents for the therapy of parasite invasion of human lymphatic vessels.[154] Potential effective agents for the control of protozoa parasites that cause toxoplasmosis are S-carboxyethyl derivatives **118**, which demonstrated high inhibitory activity against dihydrofolate reductase (IC_{50} of 0.027 – 0.075 μmol $litre^{-1}$). Furthermore, experiments on infected mice revealed only minor histopathological changes of the liver, spleen and lungs, as compared with other drugs.[155]

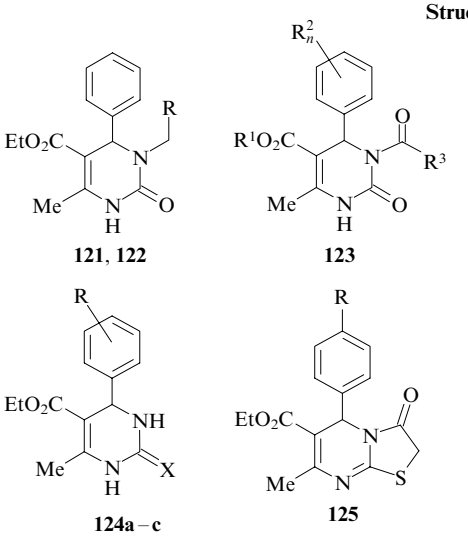
Analogous S-methyl derivatives **32** [Alk = Me, Et; R_n = H, 4-OMe, 4-Cl, 4-NO_2, 4-NMe_2, 3,4,5-$(OMe)_3$] possess analgesic properties at the level of Diclofenac.[156]

Compounds **119**,[157] **120** and **121**[158, 159] exhibit noticeable antioxidative properties. Like compounds **122**, they also possess antimicrobial activity against gram-positive and gram-negative bacteria.[160]

On the basis of QSAR analysis of the electronic and steric factors affecting the antibacterial activity of N(3)-formyl and N(3)-benzoyl derivatives **123**, requirements to the structure of potential agents exhibiting a definite type of activity were formulated.[161, 162] Testing of four synthesized methoxyphenyl derivatives **123** [R^2_n = 3,4,5-$(OMe)_3$] for the action on the gram-positive bacteria *Staphylococcus aureus* demonstrated a close correspondence between the predicted and experimentally found activities.[161] Out of 4-aryl-5-ethoxycarbonyldihydropyrimidinones and -thiones, products **124a**,**b** proved to be the most active fungicides towards the fungi *Trichoderma hammatum*, *Trichoderma koningii* and *Aspergillus niger*.[163, 164] A similar result was obtained for the antifungal activity of two compounds **124c** as well as of bi- and polycyclic acylated analogues **125 – 128** towards *A. niger* and *A. ocharactus niger*.[165]

Other halo-substituted DHPMs with the same molecular core (*e.g.*, some compounds of series **127**) demonstrated high fungicidal, antibacterial and antimicrobial activities, which are not inferior to the activities of Fluconazole and Ciprofloxacine, respectively.[166] Many derivatives of series **20** and **126** also possess antibacterial activity (from moder-

Structures 121 – 125



121, **122** **123**

124a – c **125**

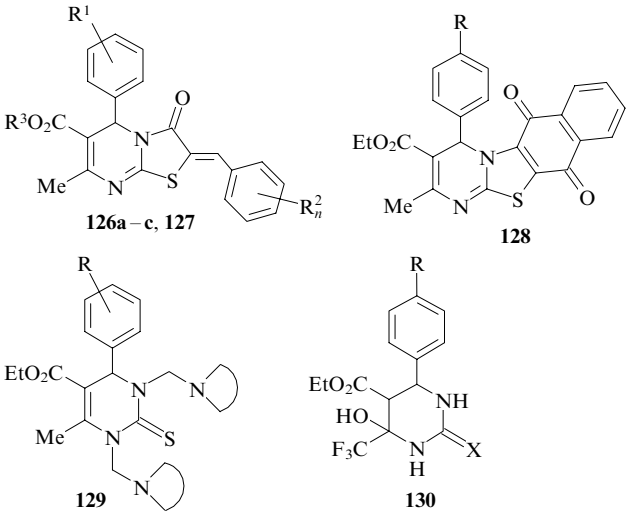
121: R = cyclo-$CHCH_2O$;
122: R = $CH(OH)CH_2NHR'$ (R′ = Me, Bu^t, Ph);
123: R^1 = Me, Et; R^2_n = H, 2-OH, 4-OMe, 4-NMe_2, 4-$CH{=}CH_2$, 2-Fu, 3,4,5-$(OMe)_3$; R^3 = H, Ph;
124: R = H, 2-OH, 4-NMe_2; X = O (**a**); R = H, 2-OH, 4-NMe_2; X = S (**b**); R = 4-Cl, 4-NMe_2; X = S (**c**);
125: R = Cl, NMe_2

ate to high) towards gram-positive and gram-negative bacteria.[108, 131, 167, 168]

The biological testing of several DHPMs **129** demonstrated that they possess strong antimicrobial action comparable with the action of streptomycin on *E. coli*.[169] It is noteworthy that compounds **130**, which formally belong to tetrahydropyrimidinones and their thio analogues, were found to exhibit high antimicrobial activity comparable with or exceeding the activity of tetracycline.[170] These compounds can actually be considered as resulting from double bond hydration in the dihydropyrimidine ring; hence, regarding the activity, they can be compared with dihydropyrimidinones. Some recent publications provide the conclusion that highly diverse compounds incorporating a dihydropyrimidine ring in the molecule can exhibit antimicrobial, antibacterial and fungicidal properties to one or another extent.[171 – 184]

Targeted agents were designed by introducing particular groups, not necessarily pharmacophoric, into a DHPM molecule. For example, a series of 1,4-diaryldihydropyrimidinones with electron-withdrawing substituents, such as CN and CF_3, in the aryl groups were shown to inhibit human neutrophil elastase (HNE); this can be utilized in the preparation of drugs for treating inflammatory processes, including rheumatoid arthritis, pneumonia, chronic bronchitis, atherosclerosis, myocardial infarction and so on.[185 – 187] Table 6 presents examples of chemical compounds **131 – 135** that exhibit the highest inhibitory activities.

Structures 126 – 130



126a – c, **127** **128**

129 **130**

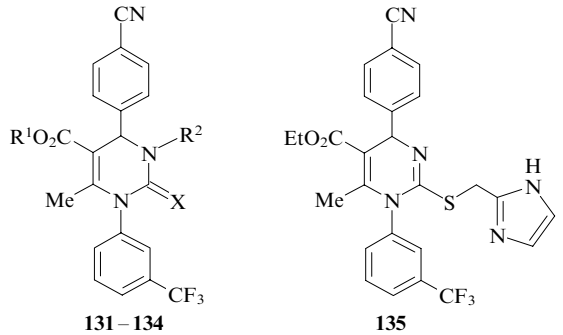
126: R^1 = 4-SMe, R^3 = Et: R^2_n = 4-Cl, 4-F, 4-OH, 4-OMe, 4-SMe, 2,4-Cl_2, 4-F-3-OPh, 4-OH-3-OMe, 3,4-OCH_2O (**a**); R^1 = 4-($C_6H_4CO_2$Et-3): R^2_n = Bu^t, Pr^i, Br, Cl, NMe_2, NO_2 (**b**); R^1 = 4-NHC(O)NHPh: R^2_n = Et, F, Cl, OMe, NO_2 (**c**);
127: R^1 = 4-Br, 4-OMe; R^2_n = 4-OMe, 2-F-4-OMe, 2-Cl-6-F, 3,4-F_2, 4-F-2-CN, 4-Cl-3-CF_3; R^3 = Me;
128: R = Cl, NMe_2;
129: R = H, 2-OH, 4-OMe, 3-OMe-4-OH; N◯ is morpholino, phthalimido, benzimidazolo, 1,2,3-benzotriazol-1-yl, *etc.*;
130: R = H, Me, OH, OMe, Cl, F, NMe_2, NO_2; X = O, S

Table 6. Neutrophil elastase inhibition by dihydropyrimidines **131 – 135**.

Compound	IC_{50}/nmol litre^{-1}	Ref.
131	6	185
132	5	185
133	5	185
134	9	186
135	5	186

In recent years, the search for new antiviral agents resulted in the discovery of antiviral activities in a variety of heterocyclic compounds, including dihydropyrimidine derivatives. Of most importance are agents for prevention and treatment of infections dangerous for humans that are caused by polyomaviruses, herpesviruses and immunodeficiency viruses.

Structures 131 – 135



131 – 134 **135**

Compound	R^1	R^2	X
131	$(CH_2)_2OH$	H	O
132	Et	Me	O
133	Et	$CH_2C(O)N(CH_2CH_2)_2NMe$	O
134	Et	H	S

Polyomaviruses and herpesviruses are carried by the majority of population all over the world. Although they exist in the latent state in the host organism, they may become pathogenic upon decrease in the immunity and cause severe diseases of various organs. Furthermore, polyomaviruses are customarily regarded as tumourigenic viruses for humans and animals. Out of the six known polyomaviruses, there are two main similar viruses — the Simian virus 40 (SV40) and the BK virus, leading to respiratory infections and damage of kidneys. Testing of the antiviral properties among the DHPM – peptide hybrid molecules revealed a noticeable inhibition of the replication of SV40 and BK viruses *via* a targeted change in the chaperone Hsp70 activity ($IC_{50} \approx 50$ μmol litre^{-1}) by the compound MAL2-11B (**136**).[188] Later, the chemical structure of this compound was modified to study the structure – activity relationship. The replacement of the terminal carboxyl group in the N(1)-pentamethylene chain by a tetrazole ring gave DHPM **137** ($IC_{50} \approx 20$ μmol litre^{-1}) and then a series of similar derivatives with variation of the alkyl chain length and flexibility and the natures of aryl and ester groups.[189] The elucidated relationships were used to prepare hybrid compound **138** with the optimal structure, improved physicochemical properties and high ability to inhibit replication of both viruses — SV40 and BK — in a renal cell culture ($IC_{50} \approx 5$ μmol litre^{-1}).[189]

Most attempts to reveal an inhibitory activity towards herpes simplex virus (HSV-1) among dihydropyrimidinones **139** were unsuccessful, except for the bromophenyl derivative (R^1 = Me, R^2 = 4-Br). This compound, which showed a high inhibitory activity (IC_{50} = 0.9 μmol litre^{-1}) and low toxicity (CC_{50} = 100 μ mol litre^{-1}, CC_{50} is the cytotoxic concentration at which the cell survival decreases by 50%) *in vitro* on Vero cells, may become a drug candidate to be used as an antiherpetic agent.[190] Among the DHPM S-analogues, a high inhibitory activity was found for thienyl derivative **140** (Alk = Bu^i) with good pharmacological characteristics (IC_{50} = 1.8 μmol litre^{-1}, CC_{50} = 87.5 μmol litre^{-1}).[190]

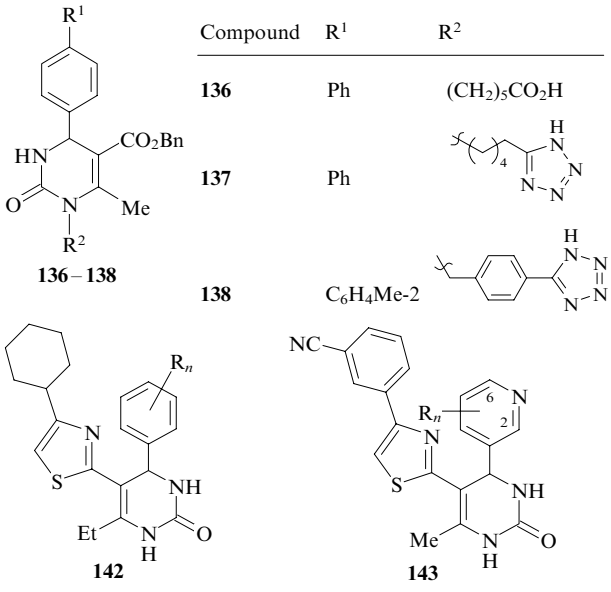
Several hundred dihydropyrimidinones of diverse structures were screened for anti-HIV activity using appropriate virological procedures and reference antiviral drugs — Azidothymidine (AZT) and Nevirapine. A group of most efficient compounds, 4-aryl-5-(cycloalkyl)methyloxycarbonyl derivatives **141**, was thus identified.[191 – 193] The activity of compounds **141** was found to increase with increasing size of the cycloalkyl moiety and to be completely lost as this moiety is replaced by an aromatic ring. In infected cell culture experiments, compounds **141a – d** (EC_{50} of 0.031 – 0.087 μmol litre^{-1}) surpassed Nevirapine (EC_{50} = 0.087 μmol litre^{-1}) in the antiviral activity.[192] Typically, the activity of the 4*S*-enantiomer of **141b** (EC_{50} = 0.038 μmol litre^{-1}) is many orders of magnitude greater than the activity of its 4*R*-enantiomer (EC_{50} > 10 μmol litre^{-1}).[192]

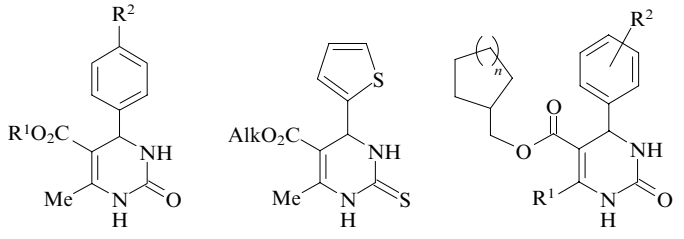
Since both enantiomers showed insufficient stability to metabolism in the human body (elimination half-time $t_{1/2}$ = 11 min), the ester function in the dihydropyrimidine ring was replaced by a thiazolyl moiety (compounds **142**). Although the antiviral activity somewhat decreased, the metabolic stability increased by a large factor; this can be seen for compound **142a** (EC_{50} = 0.078 μmol litre^{-1}, $t_{1/2}$ = 682 min).[193]

Further optimization of this structure consisted in replacement of the cyclohexyl group by an aromatic ring. An extensive series of derivatives was synthesized and tested for the cytotoxicity and the degree of HIV replication inhibition in cell culture experiments.[194] The best results on the antiviral activity (IC_{50} < 1 μmol litre^{-1}) and cytotoxicity (the toxic concentration reducing the cell growth by 50%, TC_{50} > 100 μmol litre^{-1}) were observed for cyanophenylthiazolyl derivatives **143** (for comparison, AZT has IC_{50} = 0.08 μmol litre^{-1} and TC_{50} > 100 μmol litre^{-1}).[194]

As the C=O moiety in the heterocycle position 2 is replaced by an alkyl or hetaryl group, the resulting compounds generally retain the biological activity, but the activity profile changes. Indeed, 6-methyl-4-phenyl-1,4-dihydropyrimidines **144 – 146**[195 – 199] and 6-aminomethyl analogues **147**[200] formed a new group of efficient

Structures 136 – 143





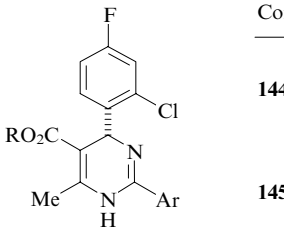
139: R^1 = Me, Et, Bu^t, Ph; R^2 = H, F, Br;
140: Alk = Me, Et, Pr^i, Bu^i;
141: R^1 = Me, Et, Pr^n, CH=CHMe, CH_2Cl; R^2 = H, 3-OH, 4-OH, 3-OAc, 4-OAc, 3-NH_2, 4-NH_2, 3-NHAlk, 4-NHAlk, 4-$NAlk_2$, 4-NHAc, 3-NO_2, 4-NO_2, 4-CN, 4-CO_2Alk; n = 1 – 3;
R^1 = Et, n = 2: R^2 = 4-F (**a**), 3-OH (**b**), 4-OH (**c**), 4-NHAc (**d**);
142: R_n = 3-Cl-4-OH (**a**), R_n = 3,5-$(CF_3)_2$, 3-NH_2, 4-NH_2, 4-NHAlk, 4-Ac, 4-NO_2, 3-CO_2Alk, 4-CO_2Alk;
143: R_n = 2-F, 5-F, 2,6-Cl_2, 6-Br, 6-CF_3, 6-OMe, 6-OPh, 6-NMe_2

Table 7. Efficiency (IC_{50}) against hepatitis B virus and toxicity (TC_{50}) of compounds **144** – **146**.[199]

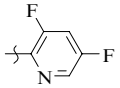
Compound	IC_{50} /μmol litre^{-1}	TC_{50} /μmol litre^{-1}
144	0.05	7
145	0.15	50
146	0.03	25

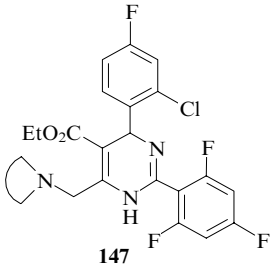
non-nucleoside inhibitors of hepatitis B virus (HBV) genome replication. Highly specific antiviral activity of compound **144** (Bay 41-4109) was demonstrated *in vitro* on cell cultures and *in vivo* on HBV-transgenic mice who were orally administered the agent in 3 – 30 mg kg^{-1} doses for 28 days. The agent induced dose-dependent decrease in the liver and plasma levels of viral DNA comparable with the action of the nucleoside drug Lamivudine.[198] According to the cell culture experiments, the antiviral activity is inherent only in the (−)-enantiomer (*R*-enantiomer) of compound **144**. A pharmacokinetic investigation in mice showed fast absorption and 30% bioavailability. Analogous products **145** (Bay 38-7690) and **146** (Bay 39-5493) also demonstrated a similar antiviral activity. Table 7 shows characteristics of the efficiency of these agents in relation to hepatitis B virus and toxicity characteristics.[199]

Structures 144 – 147



144 – 146

Compound	R	Ar
144	Me	
145	Et	
146	Et	



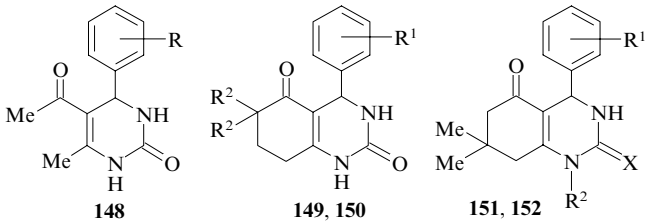
147

147: N = $N(CH_2)_4$, $N(CH_2)_5$, $N(CH_2CH_2)_2NH$, $N(CH_2CH_2)_2NMe$, $N(CH_2CH_2)_2NEt$, $N(CH_2CH_2)_2O$, $N(CH_2CH_2)_2S$

II.2. 5-Acyldihydropyrimidinones and related carbonyl derivatives

5-Acetyl-4-phenyl-substituted dihydropyrimidinones **148** and bicyclic analogues **149**, **150** as Ca^{2+} antagonists were studied *in vitro* on rat ileum samples pretreated with a solution of $BaCl_2$. However, their relaxant effect proved to be low in comparison with the drug Nicardipine (**12**).[201 – 203] Meanwhile, isomers **151** and **152** with a different arrangement of methyl groups in the cycloacyl moiety were found to be more potent Ca^{2+} antagonists, while *N*(1)-methyl-4-(3-chlorophenyl) derivative **152a** (R^1 = 3-Cl, R^2 = Me) surpassed Nicardipine in the activity.[204 – 206]

Structures 148 – 152



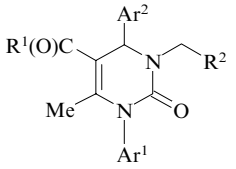
148 **149**, **150** **151**, **152**

148: R = H, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br;
149: R^1 = H, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 3-NO_2, 4-NO_2; R^2 = H;
150: R^1 = 3-Me, 4-Me, 3-OMe, 3-Cl, 4-Cl, 4-Br; R^2 = Me;
151: R^1 = H, 4-Me, 2-OMe, 3-OMe, 4-OMe, 3-Cl, 4-Cl, 4-Br; R^2 = H; X = S;
152: R^1 = H, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br; R^2 = H, Me; X = O

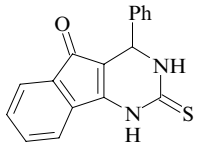
Some N(1),N(3)-disubstituted dihydropyrimidinones (*e.g.*, compounds **153**) are efficient neutrophil elastase inhibitors (IC_{50} of 8 – 30 nmol litre^{-1}) suitable for treating chronic pulmonary diseases, acute coronary insufficiency and myocardial infarction.[178]

5-Carbonyl derivatives of 4-aryl(hetaryl)dihydropyrimidinones and -thiones can be of interest, together with the above-mentioned 5-alkoxycarbonyl analogues, as potential non-steroidal anti-inflammatory drugs. These compounds were found to block microsomal prostaglandin E_2-synthase-1 (mPGES-1), which stimulates inflammatory processes. The *in silico* molecular docking of some structures into the cavity of the mPGES-1 receptor resulted in selection of the optimal chemical structures, which were tested experimentally to reveal the key roles of particular molecular moieties in the appearance of the activity. The *in vitro* experiments on mPGES-1 inhibition by structurally similar 5-benzoyl-substituted dihydropyrimidinethione **69** and dihydropyrimidinone **70** showed that the latter is more active.[101]

Structures 153 – 155

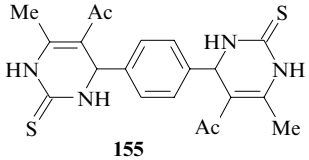


153



154

153: R^1 = Me, 2-Fu, 3-Py, OH, OAlk, NH_2; R^2 = CO_2H, CO_2Alk, $C_6H_4CO_2H$, $C_6H_4CO_2Alk$; Ar^1 = $C_6H_4CF_3$-3; Ar^2 = C_6H_4CN-4, 3-Py



155

In the initial stage of investigation of various types of DHPM activity, there appeared a brief communication about discovery of the antitumour properties in a series of 5-acetyl dihydropyrimidinone derivatives and the corresponding thiones.[32, 33] Further development of synthetic methods and investigation of antitumour activities of new

Table 8. Inhibition of the ATPase activity of kinesin Eg5 by Monastrol (**74**) and its analogues.[119]

Compound	Monastrol (**74**)	**156**	**157**	**158**	**159a**	**159b**	**159c**	**159d**	**159e**
IC_{50} /μmol litre^{-1}	16.0	0.51	0.15	0.8	0.25	0.82	0.50	0.50	1.1
Maximal inhibition (%)	⩾90	⩾90	⩾90	85	⩾90	87	⩾90	⩾90	⩾90

carbonyl DHPMs adhered to this trend. Compound **154** was claimed to inhibit the intracellular Wnt/β-catenin signalling system affecting proliferation of cellular entities, including melanoma and benign nevi.[207] Compound **155** showed moderate cytotoxic activity towards several human cancer cell lines; the authors attributed this activity to the presence of a thiourea moiety in the molecules.[138] Also, it was ascertained that the *R*-enantiomer of **154** is an effective antagonist of the transient receptor potential (TRPA1) channel, which is involved in various inflammatory and pain processes. The action of this agent on the rat and human TRPA1 receptors was detected at a concentration of 10 nmol litre^{-1} (Ref. 208).

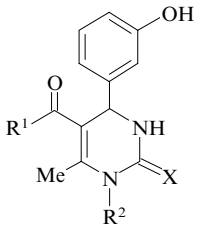
Compounds **156** – **158**, **159a** – **e** and **160** are structural varieties of Monastrol (**74**); they showed a noticeable antiproliferative activity towards several types of cancer cells. The N(1)-methylation and replacement of the ethoxycarbonyl group in the Monastrol molecule by a benzoyl group furnished Monastrol-97 (**157**). A study of the ability of these compounds to inhibit the kinesin Eg5 ATPase activity *in vitro* identified a group of quite promising antimitotic agents several orders of magnitude more potent than Monastrol, which allows these compounds to be used as cancerostatics (Table 8).[119] Note that many other 4-aryl(hetaryl)-5-aroyldihydropyrimidines exhibit some antiproliferative activity.[209]

The replacement of the methyl group in the dihydropyrimidine ring by the electron-withdrawing CF_3 group often affords a stable hydrated species like **130**; compounds of this type were found to exhibit cytotoxic properties against COLO-320 cancer cells (the minimal IC_{50} values were 9.3 and 11.5 μmol litre^{-1}).[140]

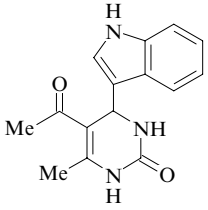
The simultaneous presence of the indole moiety and the acetyl group in the heterocycle (compound **161**) gives rise to high antiproliferative activity, which was identified in relation to hepatocarcinoma HepG2 cells (IC_{50} = 17.9 nmol litre^{-1}, which exceeds the action on normal liver cells, IC_{50} = 136.9 nmol litre^{-1}).[210] Study of the activity of compound **161** by *in silico* molecular docking demonstrated its effective interaction with the PPAR-g receptor, which was consistent with the *in vitro* experiment.[210]

The structure – inhibitory activity relationship in a dihydropyrimidinethione series was studied *in silico* on a mitotic kinesin Eg5 receptor model; the obtained trends were compared with experimental data.[110, 211, 212] The molecular docking of these molecules with the receptor was performed by the GOLD v.4.0.1 program. The authors investigated the hydrophobic cavity of the receptor into which they placed various Eg5 inhibitors, including the 5-benzoyl Monastrol analogue — Monastrol-97 (**157**), for which the crystal structure of the complex with the Eg5 receptor had already been determined and the protein amino acid residues responsible for interaction with the ligand had been identified.[122, 211] Note that *R*-**157** binds at the receptor active sites more efficiently than the *S*-enantiomer, whereas the *in vitro* inhibitory activity of the Monastrol *S*-enantiomer is higher than that of the *R*-enantiomer. Experiments determining the inhibitory properties *in vitro* also attest to better kinesin Eg5 binding of *R*-enantiomers than *S*-enantiomers for both compound **157** and another modified structure — Fluorastrol (**162**).[122]

Structures 156 – 161



156 – 158, 159a – e, 160



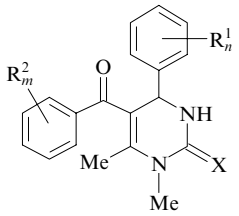
161

Compound	R^1	R^2	X	Compound	R^1	R^2	X
156	Me	H	S	**159c**	3-ClC_6H_4	H	S
157	Ph	Me	S	**159d**	3-MeC_6H_4	H	S
158	Ph	Me	O	**159e**	3-$MeOC_6H_4$	H	S
159a	Ph	H	S	**160**	3,4-$F_2C_6H_3$	H	O
156b	3-FC_6H_4	H	S				

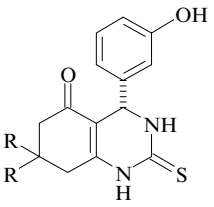
The process of enhancing the inhibiting properties of DHPMs towards Eg5 was optimized by combining *in vitro* biological activity testing and molecular docking.[122] Although 2-oxo derivatives of Monastrol are less active than the S-analogues, O-analogues with an alkyl group at N(1) were synthesized; the resulting compounds **163a** – **c**, **164** demonstrated indeed improved Eg5 ATPase-activity inhibition (IC_{50} of 7.2 – 12.2 μmol litre^{-1}). The Fluorastrol O-analogue devoid of methyl group at heterocycle N(1) atom (compound **160**) was most active (IC_{50} = 12.1 μmol litre^{-1}).[122] According to docking data, upon replacement of N-methyl group in molecule **164** by the N-ethyl group, the affinity of both molecules towards the receptor is similar, because the longer ethyl chain protrudes from the receptor cavity towards the solvent and does not interact with the protein. Therefore, and increase in the substituent bulk is admissible at either N(1) or C(6), but combination of two bulky substituents can lead to steric repulsion and disrupt an efficient interaction with the protein.[122]

Relying on the molecular docking results, a series of 4-aryl-5-acyldihydropyrimidines with a hydroxyl group in the benzene moiety was synthesized and tested for the ability to inhibit the ATPase activity of Eg5.[122] In active compound **165** containing two fluorine atoms in the benzoyl moiety, the IC_{50} value decreases to 1.3 μmol litre^{-1}. The decrease in the IC_{50} values of DHPMs down to micromolar concentrations stimulated the synthesis of 2-thio analogues, out of which (*S*)-Enastron (**166**) and (*S*)-Dimethylenastron (**167**) proved to be efficient inhibitors.[110, 111, 122]

Structures 162 – 167



162, **163a – c**, **164**, **165**



166, **167**

R = H (**166**), Me (**167**)

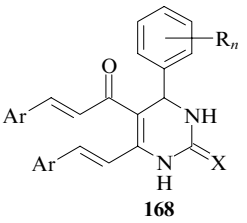
Compound	R^1_n	R^2_m	X	Compound	R^1_n	R^2_m	X
162	3-OH	3,4-F_2	S	**163c**	H	3,4-F_2	O
163a	H	3-F	O	**164**	3,4-F_2	3,4-F_2	O
163b	H	4-F	O	**165**	3-OH	3,4-F_2	O

(*R*)-Fluorastrol (**162**) was the most potent inhibitor with IC_{50} = 0.48 μmol litre^{-1}; it was approximately three times more active than the corresponding 2-oxo analogue. The authors cited also noted that compounds with an additional methyl group at N(1) are always more active than similar compounds without the methyl group.[122]

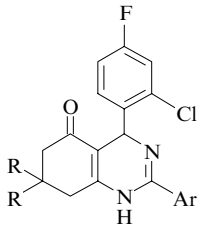
A hybrid DHPM has been synthesized on the basis of curcumin in order to extend the pharmacological profile of the products, as curcumin and its derivatives possess a variety of pharmacological activities.[213, 214] In both publications cited, the cytotoxicity was tested for roughly the same set of these hybrid derivatives **168**.[213, 214] In one study, *in vitro* experiments on lung, liver and colon cancer cells demonstrated that 4-hydroxyphenyl DHPMs **168** possess the highest cytostatic activity in this series.[213] A synergistic effect of the DHPM and curcumin moieties was noted for compounds **168**, which exhibited not only anticancer activity but also antimicrobial and fungicidal properties.[213] In a later extended research, chloro and methoxy dihydropyrimidinone derivatives showed moderate anticancer activity towards leukemia and breast, kidney, colon and prostate cancers.[214]

Relying on the antiviral activity data for alkyl 2-hetaryl-1,4-dihydropyrimidine-5-carboxylates **144 – 147**, which formed a new group of efficient non-nucleoside hepatitis B virus (HBV) genome replication inhibitors, Zhu *et al.*[215] investigated a series of compounds of the same type containing a carbonyl group in the annulated cyclohexene moiety (compounds **169 – 172** and their analogues). By determining the degrees of inhibition of HBV genome replication upon variation of heterocyclic substituents in the dihydropyrimidine molecule, the authors identified the most active compounds: **169b** (IC_{50} = 1.10 nmol litre^{-1}), **171** (IC_{50} = 1.05 nmol litre^{-1}) and **172** (IC_{50} = 0.44 nmol litre^{-1}) comparable in the action with Bay 41-4109 (**144**, IC_{50} = 0.78 nmol litre^{-1}). Other compounds, including **169a** and **170**, demonstrated moderate or low activity.[215] It is noteworthy that many compounds of this series of dihydropyrimidines have relatively low cytotoxicity, which accounts for rather good values for the therapeutic index.[215]

Structures 168 – 172

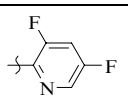


168

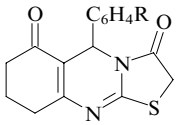


169a,**b**, **170 – 172**

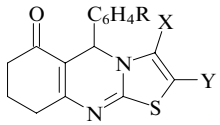
168: Ar = C_6H_3OH-4-OMe-3; X = O: R_n = H, 4-Me, 2-OH, 4-OH, 4-F, 4-Cl, 4-OMe, 4-NO_2, 4-OH-3-OMe, 3,4-$(OMe)_2$; X = S: R_n = H, 4-F, 4-Cl, 4-OH, 4-OMe, 4-NO_2, 4-OH-3-OMe

Compound	R	Ar	Compound	R	Ar
169a	H		**171**	Me	
169b	H		**172**	Me	
170	H				

Structures 173 – 175



173



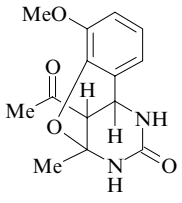
174, **175**

173 – 175: R = H, 4-Me, 2-OH, 4-OH, 4-Cl, 4-OMe, 4-NMe_2;
174: X = Ph, Y = H;
175: X = NH_2, Y = CN

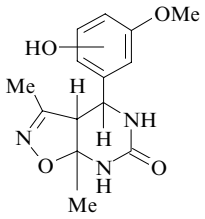
After the formation of the second annulated five-membered thiazole ring in the DHPM molecule, the type of biological activity changes: compounds **173 – 175** proved to be active fungicides towards the fungi *T. hamatum, T. koningii* and *A. niger*.[164]

It was noted above that if the dihydropyrimidinone (or thione) molecule contains an aryl substituent with an *ortho*-hydroxyl group, O-bridged structures can be formed (see, for example, compounds **27** and **28**). El-Hamouly *et al.*[216] prepared O-bridged compounds of the same type with an acetyl group in the pyrimidine ring and studied them for the antihypertensive activity. A marked activity was found for

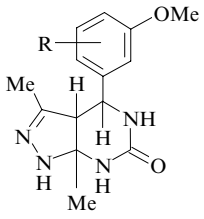
Structures 176 – 180



176



177, **178**



179, **180**

177: 4-OH; **178**: 2-OH: **179**: R = 4-OMe; **180**: R = 2-OH

methoxyphenyl derivative **176**. Furthermore, the presence of the reactive carbonyl group made it possible to modify some 5-acetyldihydropyrimidinones by treatment with hydroxylamine and hydrazine to give heteroannulated structures **177** – **180**.

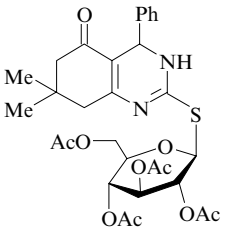
Testing of these compounds for antihypertensive activity in a 5 mg kg^{-1} dose administered subcutaneously in rat models of hypertension showed a noticeable decrease in the blood pressure; for compound **176**, this value was comparable with that of Nifedipine (**9**) (Table 9).[216]

Table 9. Average blood pressure values for hypertensive rats 2 h after injection of the agents (5 mg kg^{-1}).[216]

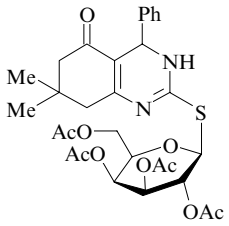
Compound	Blood pressure /mm Hg	Compound	Blood pressure /mm Hg
176	107.8	**180**	113.8
177	114.0	Nifedipine (**9**)	109.0
178	111.8	Normal	104.0
179	112.5	Control	132.17

Structural analogues of Dimethylenastron **151** demonstrated a considerable anti-inflammatory activity, which was higher for S-glycosylated derivatives **181** – **183**.[217]

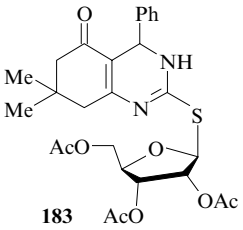
Structures 181 – 183



181



182

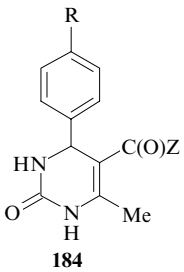


183

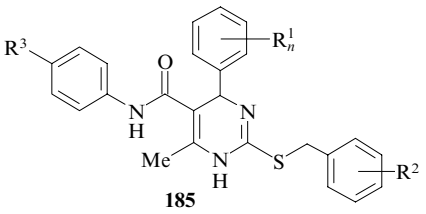
II.3. 5-Carbamoyl-substituted dihydropyrimidines

Upon replacement of the ester group in position 5 of the hydrogenated pyrimidine ring by an amide group, the biological activity is generally retained, although the interaction of one or other derivative with particular receptors may bring about different effects. 4-Aryl-5-carboxamides **184**, like the carbonyl analogues considered above, were found to be Ca^{2+} antagonists exhibiting antihypertensive activity.[218] In testing of these compounds for Ca-channel blocking behaviour in isolated rat colon, the highest blocking activity was inherent in 5-diethylaminocarbonyl derivative **184a** (IC_{50} = 19.8 μg ml^{-1}), which was comparable with the action of Nifedipine (**9**) (IC_{50} = 20 μg ml^{-1}). In rat experiments, the same compounds induced a decrease in blood pressure to different extents, the most pronounced antihypertensive effect, comparable with that of Nifedipine, being observed for 5-morpholinocarbonyl derivative **184b**.[218]

Structures 184, 185



184



185

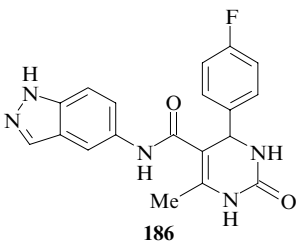
184: R = Cl, Z = NEt_2 (**a**); R = H, Z = $N(CH_2CH_2)_2O$-cyclo (**b**); R = H, Cl; Z = NMe_2, NEt_2, $N(CH_2)_5$-cyclo, $N(CH_2CH_2)_2O$-cyclo; **185**: R^1_n = 2,4-Cl_2, 4-Br, 3-NO_2, 4-NO_2, 3,4-$(OMe)_2$, 4-OMe; R^2 = H, 2-Cl, 3-Cl, 4-Cl, 4-F; R^3 = F, Br, NO_2

Quite recently, a series of 4-aryl-5-arylaminocarbonyldihydropyrimidinethiones were synthesized and then converted to S-benzyl derivatives **185**; the latter showed a stable decrease in the systolic blood pressure in rats at desoxycorticosterone acetate-induced hypertension. Moreover, the antihypertensive effect observed for quite a number of these compounds markedly surpassed the action of Nifedipine. Other compounds of this series also exhibited an antihypertensive effect, but it was moderate and short-term.[219]

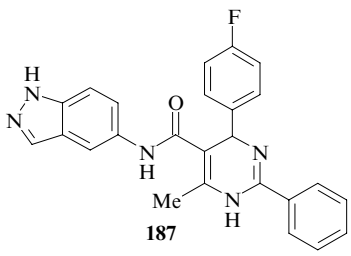
Alam *et al.*[219] analyzed the structure – activity relationship and drew a number of conclusions about the influence of substituents R^1 and R^2 on the antihypertensive activity of compounds. Electron-donating groups R^1 were shown to increase the activity, so do chlorine atoms relative to other halogen atoms. Meanwhile, varying the substituents R^3 in the benzene ring of the amide moiety does not have any effect on the activity.[219]

Amide **186** with a similar molecular core topology was found to act as a selective inhibitor of serine threonine kinase (ROCK1), which is involved in a number of cellular processes, including vascular smooth muscle contraction, which affects the course of hypertension.[220] The subsequent structure optimization of amide **186** culminated in the

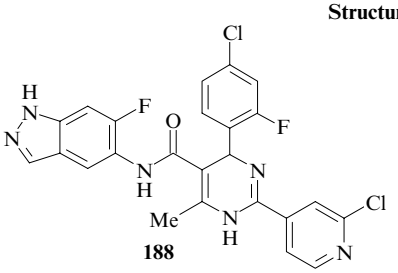
Structures 186 – 188



186



187



188

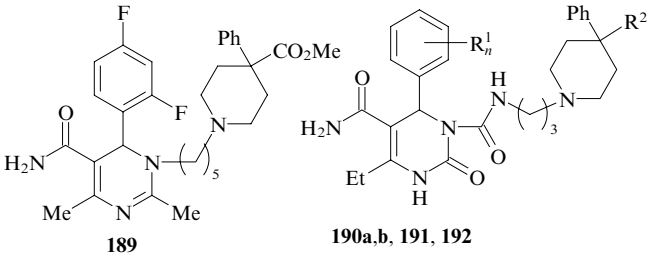
Table 10. Serine threonine kinase ROCK1 inhibition by compounds **186** – **188**.[221]

Compound	IC_{50} /nmol litre^{-1}	
	ROCK1	rat aorta
186	14	760
187	105	1300
188	6	256

synthesis of modified ROCK1 inhibitors — 2-aryl-1,4-dihydropyrimidines **187** and **188**.[221] The replacement of the urea moiety [NHC(=O)NH] in the pyrimidine ring of amide **186** by an amidine ring [NHC(Ar)=N], giving compound **187**, decreased the ROCK1 inhibiting activity but improved pharmacokinetic characteristics (Table 10). Single-dose oral administration of 30 mg kg^{-1} of modified inhibitor **188** in rats induced a clear-cut decrease in the blood pressure by 25 mm Hg. Furthermore, compound **187** showed a high selectivity to other kinases.[221]

A few publications were devoted to 5-carbamoyl DHPMs as adrenergic receptor antagonists. A characteristic structural feature of these adrenergic blockers is the presence, in their molecules, of N(3)-alkyl (compound **189**) or alkylcarbamoyl (compounds **190a**,**b**, **191**, **192**) chains ending with a phenylpiperidine moiety, which makes them similar to pyridine and pyrimidine adrenergic blockers.[84 – 87, 89] The structures of these highly active and selective antagonists in the series of alkyl dihydropyrimidinecarboxylates are given above in Section II.1.b. However, 4-methoxycarbonyl-4-phenylpiperidine, which is a μ-opioid agonist, was detected among the metabolites of compound **190a** in a pharmacokinetic investigation of its transformations in a living organism.[85]

Structures 189 – 192



189

190a,**b**, **191**, **192**

190: R^2 = CO_2Me: R^1_n = 2,4-F_2 (**a**), 3,4-F_2 (**b**);
191: R^1_n = 2,4-F_2, R^2 = CN;
192: R^1_n = 4-NO_2, R^2 = CO_2Me

In order to eliminate the formation of opioid agonists in the body, compounds with modified structures were synthesized. Modification of the linker between the piperidine moiety and the N(3) atom of DHPM furnished a series of compounds with efficient binding to α_{1a} receptor G-proteins (binding affinity K_i < 1 nmol litre^{-1}) and high selectivity (K_i value 300 times higher than those for α_{1b}- and α_{1d}-receptors). A microsomal assay in *in vitro* experiments demonstrated that these compounds do not give undesirable piperidine derivatives in the body.[85]

The second approach to chemical structure modification implied the change of the piperidine moiety itself in such a way that metabolites no longer showed a noticeable μ-opiate activity. Some of these compounds retained high selectivity and high α_{1a}-adrenergic receptor affinity, and the piperidine moiety (4-cyano-4-phenylpiperidine group in compound **191**) affected weakly the μ-opiate receptor (IC_{50} > 30 μmol litre^{-1} *vs.* 3 μmol litre^{-1} for 4-methoxycarbonyl-4-phenylpiperidine).[85]

(+)-Enantiomers of amide **191** and cyclic ester **55** were subjected to thorough pharmacological investigation *in vitro* and *in vivo*. Apart from high selectivity to α_{1a}-receptors (> 880-fold higher affinity compared with α_{1b} or α_{1d}), both compounds also showed good selectivity to other human recombinant G-protein-coupled receptors. These compounds demonstrated a good functional activity on isolated human prostate tissues, comparable with the activity observed in the *in vitro* experiments mentioned above. Furthermore, the (+)-enantiomer of amide **191** showed fairly high uroselectivity in experiments on dogs.[85]

A comparison of the biological testing results for substituted amides and related esters of the same type made it possible to identify some aspects of similarity and difference in the effect of these compounds on the α_{1a}-adrenergic receptors. We have already discussed above (Section II.1.2) the dependence of the activity of DHPMs and dihydropyrimidinone 5-alkylcarboxylates on structural changes of the molecules, in particular, replacement of the ester function by the amide one. Among 2,6-dialkyl-4-aryl-3,4-dihydropyrimidines, replacement of the ester function by a primary or secondary amide group in position 5 of the heterocycle reduces the selectivity and α_{1a}-receptor affinity of the products. However, in the series of dihydropyrimidinones, both functional groups in position 5 of the heterocycle are comparable in efficiency (for example, cyclic ester **55** *vs.* amide **190b** with a similar structure).[84]

The affinity and selectivity of compounds are mainly dictated by (+)-enantiomers, while (−)-enantiomers show poorer affinity and selectivity to α_{1a} receptor over α_{1b}, α_{1d} and α_2 receptors (Table 11).

The subsequent structural modification of the above adrenergic blockers consisted in the transfer of the phenylpiperidylalkyl moiety from the N(3)-carbamoyl group to the 5-carbamoyl group (compounds **193** – **198**). The resulting 5-carbamoyl dihydropyrimidinones isomeric to the compounds described above are also effective α_{1a}-receptor antagonists, their action exceeding the α_{1b}- and α_{1d}-receptor

Table 11. Binding affinity of 5-carbamoyldihydropyrimidinones to recombinant human α_1-adrenergic receptors.[a]

Compound	K_i /nmol litre^{-1}			Ref.
	α_{1a}	α_{1b}	α_{1d}	
189	4.2	410	690	87
190a	0.2	220	340	85
(+)-**190a**	0.2	340	440	84
(+)-**190b**	0.2	260	350	84
(+)-**191**	0.7	610	1280	85
192	0.5	160	290	84
(+)-**192**	0.2	360	740	84
(−)-**192**	1.9	130	420	84
(+)-**55**	0.4	500	230	90

[a] K_i corresponds to replacement of prazosin[^{3}H] from recombinant human receptors.

Table 12. Selectivity of adrenergic blockers **193** – **198** *in vitro*.[89]

Compound	K_i /nmol litre^{-1}		
	α_{1a}	α_{1b}	α_{1d}
193	0.24	41	260
194	0.17	24	68
(+)-**195**	0.18	120	590
(−)-**195**	20	110	600
(+)-**196**	0.18	20	200
(−)-**196**	11	85	410
197	0.75	25	170
198	0.45	235	495

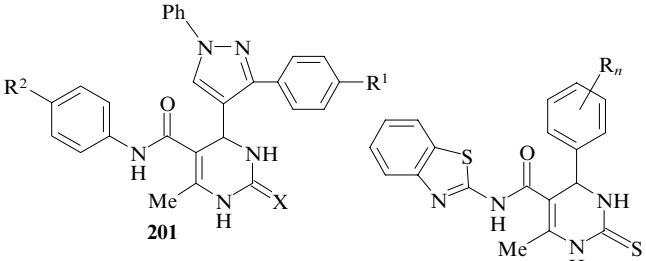
antagonism by a large factor (Table 12). In *in vivo* experiments on rats and dogs, prospective compound **193** showed adequate bioavailability and a suitable pharmacokinetic profile, indicating a decrease in hyperplasia symptoms without noticeable influence on the cardiovascular system.[89] The reported data attest to higher activity and selectivity of (+)-enantiomers of adrenergic blockers **195** and **196** compared with the (−)-enantiomers. The replacement of the fluorophenyl moiety in the piperidine ring of carbamoyl dihydropyrimidinones **193** and **194** by other aryl or hetaryl groups resulted in the synthesis of a series of compounds that also possessed a reasonably good selectivity to α_{1a}-adrenergic receptors but were less active than the compounds mentioned above, except for compound **198** with a pyridyl substituent in the piperidine ring (see Table 12).[79, 85, 89]

Further modification of the structures by varying substituents in the benzene rings and heterocycle and the length and branching degree of the linker connecting the amide function and the piperidine ring has markedly extended the set of α_{1a}-adrenergic receptor blockers of this type with K_i < 30 nmol litre^{-1} and with an order of magnitude higher selectivity to α_{1a}-receptors over α_{1b}- and α_{1d}-receptors. These compounds can be used in combination with human 5α-reductase inhibitors for the therapy of acute and chronic benign prostatic hyperplasia.[79, 222]

Compounds with two dihydropyrimidine moieties of the same type (such as **199** and **200**), in which the spacer incorporated amine, amide, guanidine and other moieties, inhibited neutrophil elastase over a very broad concentration range (IC_{50} of 1 – 1000 nmol litre^{-1}).[223]

Owing to the presence of the diarylpyrazolyl moiety and the lipophilic carbamoyl group, some compounds **201** exhibit anticancer and antituberculosis activities.[129] This conclusion is consistent with the above-presented data for the chemical precursors of these structures — the corresponding ethyl carboxylates (compounds **91**), which also have antituberculosis properties. Among benzothiazolylcarboxamides **202**, some compounds (R = H, 4-F, 4-CF_3, 4-NMe_2) functioned *in vitro* as antituberculosis agents (MIC 0.08 – 0.09 μmol litre^{-1}) more potent than Isoniazid (MIC = 0.2 μmol litre^{-1}).[224] Pharmacokinetics of these agents upon intravenous and oral administration in rats (10 and 20 mg kg^{-1}, respectively) showed a 50% bioavailability.[224]

Structures 201, 202



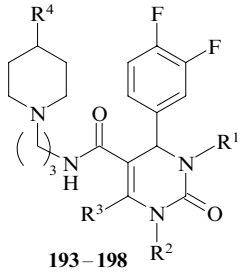
201

202

201: R^1 = H, Cl; R^2 = H, Me, OMe, Cl, NO_2; X = O, S;
202: R_n = H, 2-Cl, 4-Cl, 2,4-Cl_2, 4-F, 4-CF_3, 4-Br, 2-OMe, 4-OMe, 2-OH, 4-OH, 2-NO_2, 3-NO_2, 4-NO_2, 4-NMe_2, 2-OH-3-OMe, 3-OH-2-OMe, 4-CO_2Me, 4-OBn

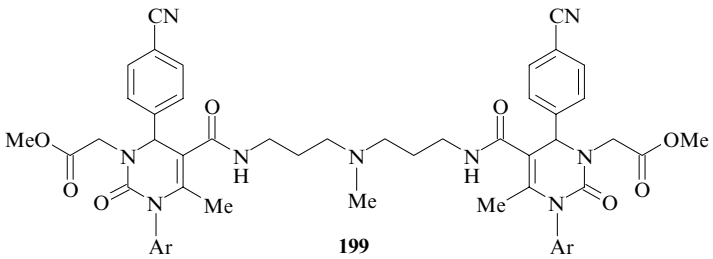
Encouraging results concerning the antiviral activity of the esters of dihydropyrimidinone- and -thione-based carboxylic acids against herpes simplex virus (HSV) have been already mentioned.[190] It was shown in the same study that some arylamides of the acids based on halo-substituted

Structures 193 – 200

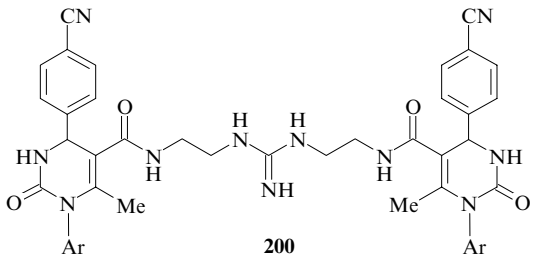


193 – 198

Compound	R^1	R^2	R^3	R^4
193	H	H	CH_2OMe	C_6H_4F-4
194	H	H	H	C_6H_4F-4
195	H	Me	Me	C_6H_4F-4
196	Me	Me	Me	C_6H_4F-4
197	CO_2Me	Me	Me	C_6H_4F-4
198	H	H	CH_2OMe	2-Py



199



200

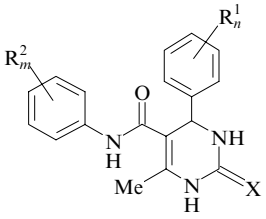
Ar = $C_6H_4CF_3$-3

aryldihydropyrimidinones (or -thiones) out of compounds **203** and **204** possess a noticeable antiherpetic activity. The best pharmacological profile was demonstrated by **204** ($R^1_n = R^2_m$ = 2-Cl) (IC_{25} = 0.7 μmol litre^{-1}) and **203b** (R^2 = 2-Cl; R^1 = 4-Me, 2-Cl, 4-Cl, 3-Br, 4-Br, 3-NO_2) (IC_{25} = 0.08 – 0.16 μmol litre^{-1}), which have low cytotoxicity and high selectivity.[190]

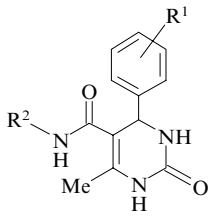
An attempt was made to predict *in silico* the antituberculosis activity of 5-(*N*-phenylcarbamoyl) DHPMs **203a**[225] and the anticancer activity of the O- and S-analogues in series **203b**, **204**[226,227] and **205**[228] and to experimentally determine their efficiency. In a QSAR study of the anticancer activity of a number of these products with some cancer cells, linear correlations were found with the molecular descriptors reflecting the lipophilic, steric and electronic characteristics of the molecules.[228,229] The *in vitro* cytotoxic activity of compounds of this type varies from moderate to weak.[230]

Cyclic amide **206** was found to be an order of magnitude more active than Monastrol. This compound behaves as kinesin Eg5 inhibitor and presents interest for treatment of diseases related to cell proliferation.[120]

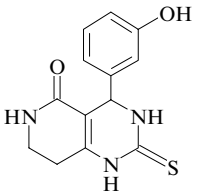
Structures 203 – 207



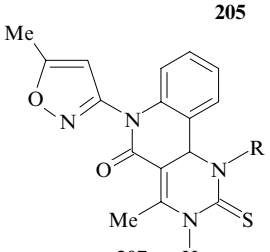
203a,**b**, **204**



205



206



207

203a: R^1_n = 3-Cl, 4-Cl, 4-OH, 4-OMe, 3-OPh, 2-NO_2, 3-NO_2, 4-NO_2; R^2_m = H, 2-Me, 3-Me, 4-Me, 2-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 4-OMe, 3-NO_2; X = O;
203b: R^1_n = H, 4-Me, 4-OH, 2-OMe, 2-Cl, 4-Cl, 2-F, 3-F, 3-NO_2; R^2_m = H, 2-Me, 2-OMe, 2,4-Me_2, 2-Cl; X = O;
204: R^1_n = H, 4-Et, 4-Bu^t, 2-Py, 3-OH, 4-OH, 3-Et-4-OH, 4-OMe, 2,5-$(OMe)_2$, 4,3-$(OMe)_2$, 2-Cl, 4-Cl, 3-F, 3-NO_2; R^2_m = H, 2-Me, 2,4-Me_2, 2-Cl, 4-Cl; X = S;
205: R^1 = H, 4-F, 2-Cl, 4-Cl; R^2 is pyrrolo, piperidino, morpholino;
207: R = Bn, Ph, C_6H_4Me-4, C_6H_4OMe-3, C_6H_4OMe-4, C_6H_4Br-4, C_6H_4Cl-2, C_6H_4Cl-4

5-*N*-Alkyl(aryl)carboxamide DHPMs exhibit anti-inflammatory and analgesic properties,[231] while 5-*N*-arylcarboxamides like **203** and **204** possess noticeable antimicrobial activity.[232 – 235] Some compounds of these series also inhibit efficiently the superoxide-generating ability of liver mitochondria.[236] Similar arylamides with an open-chain amide group proved to be active antimicrobial [175,181,237] and antibacterial [175,184,238] agents as well as insecticides and fungicides.[175,181,237,238] Tricyclic compound **207** with two isoxazole moieties was claimed as a mosquito larvicide.[180]

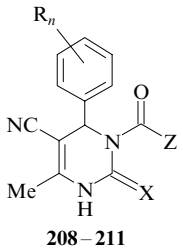
II.4. 5-Carbonitrile dihydropyrimidine derivatives

As follows from the above examples, cardioactive DHPMs typically contain an ester or carboxamide group in position 5 of the pyrimidine ring. While screening potentially biologically active DHPMs, researchers paid attention to 5-carbonitrile derivatives, the cyano group of which can be conventionally considered to be a latent carboxamide group.[239,240] An extensive series of diverse N(3)-carbonyl-4-aryl-6-methyl-5-cyanodihydropyrimidinones (compounds **208 – 211**) were tested.

Pharmacological investigations performed on various cell cultures and cancer cells (breast, prostate, lung, bladder and ovarian) demonstrated the presence of antiproliferative activity for many compounds; the activity was retained for 72 h at IC_{50} < 10 μmol litre^{-1}. A group of promising compounds with high ability to retard tumour cell mitosis and proliferation was identified among N(3)-acyl derivatives **208**.[241,242] The inhibitory activity of N(3)-ethoxycarbonyl derivatives **209** (R′ = H) towards Eg5 proteins, which are involved in cell apoptosis, was studied, and using these compounds in therapy in combination with antitumour agents was proposed.[243] Apart from the broad range of 5-cyanodihydropyrimidinones, a few S-analogues were tested; among them, compound **211** showed antiproliferative activity comparable with that of the best O-analogues.[241 – 243]

Other cyanodihydropyrimidinones displayed the ability to regulate the synthesis of cellular RNA and DNA; this can be used against viral infections such as HIV, papilloma, herpes and so on.

Structures 208 – 211

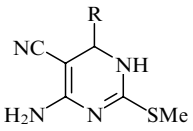


208 – 211

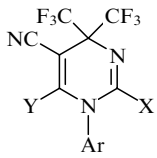
208: Z = Pr^n, Bu^n, 2-Th; R_n = 3-NO_2, 3,5-Cl_2; X = O;
209: Z = OCH_2CH_2R' (R′ = H, OH, Me, NMe_2, $CH_2C_3H_5$-cyclo); R_n = H, 2-Me, 4-Me, 4-C_3H_5-cyclo, 4-Cy, 2-F, 3-F, 4-F, 3-Cl, 4-Cl, 2-Br, 3-Br, 3-CF_3, 3-OMe, 4-OMe, 3-NH_2, 3-NMe_2, 3-NO_2, 3-CN, 3-C(O)NHEt, 2-OBn, 2,5-F_2, 3,5-F_2, 2,3-Cl_2, 3,4-Cl_2, 3,5-Cl_2, 2,5-$(CF_3)_2$, 3,5-$(CF_3)_2$, 3-CN-4-F, 2-Th, thiazol-5-yl, oxazol-4-yl; X = O;
210: Z = NHR′ (R′ = Et, CH_2CF_3, Pr^i, C_3H_5-cyclo, C_4H_7-cyclo, C_5H_9-cyclo, $CH_2C_3H_5$-cyclo); R_n = 3,5-Br_2, 2-OPh, 3-Ph, C_6H_4Cl-3, C_6H_4Cl-4, 3-Th, pyrrol-2-yl, 2-Py, 3-Py, 4-Py and the same as for **209**; X = O;
211: Z = OEt, R^2 = 3-NO_2, X = S

5-Cyano-3,4-dihydropyrimidines containing amino and methylthio groups in the heterocycle, *e.g.*, compounds **212**, possess antibacterial and antifungal activities, comparable with the action of Ampicillin or Chloramphenicol.[244] Several such compounds **213 – 216** containing an amino group and two geminal CF_3 groups were claimed as agents against insects, mites and nematodes — pests of vegetable and grain crops, fruit and ornamental plants.[245]

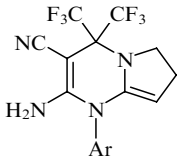
Structures 212 – 216



212



213 – 215

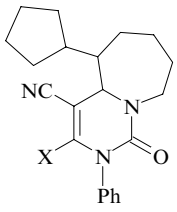


216

212: R = C_6H_4X (X = H, 2-OH, 4-OH, 2-Cl, 4-Cl, 4-OMe, 2-NO_2, 3-NO_2), CH=CHPh;
213: Ar = C_6H_4Br-4, C_6H_4Cl-4, $C_6H_3Cl_2$-2,4, C_6H_3F-2-Cl-4, C_6H_4CN-4; X = H, Me, Et, Pr^n, CH_2OMe, CH_2CH_2OMe, Ph, 2-Th, 3-Th, 2-Fu, 3-Fu, *N*-methylpyrrol-2-yl, 2-Py, 3-Py, *etc.*; Y = NH_2;
214: Ar = C_6H_4Cl-4, $C_6H_3Cl_2$-2,4; X = Me; Y = N=CHPh;
215: Ar = C_6H_4Cl-4, $C_6H_3Cl_2$-2,4; X = Me; Y = N=C$(CH_2)_4$-cyclo;
216: Ar = C_6H_4F-2, C_6H_3F-2-Cl-4, $C_6H_3Cl_2$-2,4;

The replacement of the CF_3 group by a cycloalkyl group changes the activity; for example, compounds **217** and **218** exhibit anti-inflammatory activity comparable with or higher than that of Diclofenac.[246]

Structures 217, 218



217, **218**

217: X = NH_2;
218: X = N=CHPh

II.5. 5-Nitro dihydropyrimidine derivatives

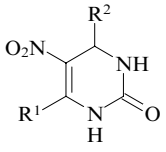
In the light of the foregoing, 5-nitrodihydropyrimidines should be of certain value, as they bear structural similarity to biologically active 5-carbonyl analogues. However, for a long period only a few compounds of this class were known (compounds **219**,[247] **220**,[248] **221 – 223**,[249] **224**[250]) and they were not biologically tested.

The interest in compounds of this structural type, which arouse in the last two decades, was initiated by the discovery of high antihypertensive activity of Bay K 8644 (**225**) with a nitro group in the dihydropyridine ring. However, unlike calcium antagonists, 5-methoxycarbonyl derivatives **7** and **8**, this compound is an agonist with a positive inotropic action and is fairly toxic.[67, 251] In order to find efficient and low-toxic calcium channel blockers among 5-nitrodihydropyrimidinones, aza analogues of the dihydropyridine drug Bay K 8644 were synthesized, namely, N(3)-nitro 5-alkoxycarbonyldihydropyrimidinone derivatives (**226**)[252] and 5-nitro 2-methoxy(phenyl)-1,4-dihydropyrimidine derivatives (**227**, **228**),[253, 254] as well as several 4-aryl-5-nitrodihydropyrimidinones (**229**, **230**).[255 – 257]

According to pharmacological properties, these products can be assigned to the class of regulators of Ca^{2+} transport through the channels.[252, 255, 257] Thus, in experiments on guinea pig ileal longitudinal smooth muscle, N(3)-alkoxycarbonyl derivatives **226** proved to be less potent Ca-channel antagonists (IC_{50} 0.19 – 3.9 μmol litre^{-1}) than Nifedipine (**9**) (IC_{50} = 0.014 μmol litre^{-1}). The *in vitro* experiments on tissue strips from guinea pig atrium showed a weak positive inotropic effect of methyl (Alk = Me) and ethyl (Alk = Et) esters **226**, whereas the other two esters (Alk = Pr^i, Bu^i) did not affect the contractile force of atrium when present in concentrations of 1.61 μmol litre^{-1}.[252]

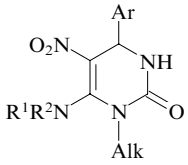
The pharmacological properties of compounds **229a – m** and **230a – f** with chemically different substituents in the aryl moiety have been studied. All these compounds, except for *ortho*-chloro derivative **229f**, reduce blood pressure, thus resembling Nifedipine. They also suppress the contractile activity of myocardium and decrease the cardiac rate to different extents, although no definite trend in the substituent R effect on the cardiac contraction was elucidated. As opposed to the effects of these compounds, chloro derivative **229f** has a positive inotropic action, increases blood pressure and increases the cardiac rate by 14%; the pharmacological profile of **229f** resembles that of the calcium agonist Bay K 8644 (**225**) but the former is much less toxic.[257]

Structures 219 – 234



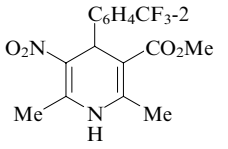
219 – 223

Compound	R^1	R^2
219	Ph	Ph
220	H	morholino
221	H	CH_2Ac
222	H	$CHMeCO_2Et$
223	H	$CHAcCO_2Et$

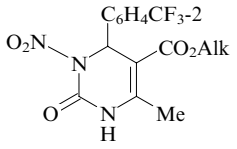


224

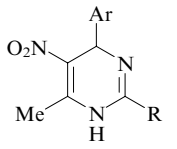
224: Alk = Me, Bn; Ar = Ph, C_6H_4F-2, C_6H_4Br-3, C_6H_4Br-4, $C_6H_4NO_2$-3, $C_6H_4NO_2$-4, $C_6H_3Cl_2$-3,4; R^1 = H: R^2 = Me, Ph, Bn, C_6H_4Cl-4, C_6H_4OMe-4, *etc.*; NR^1R^2 is pyrrolidino, morpholino



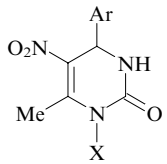
225



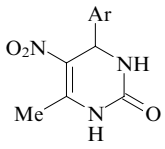
226



227, **228**



229a – m, **230a – f**



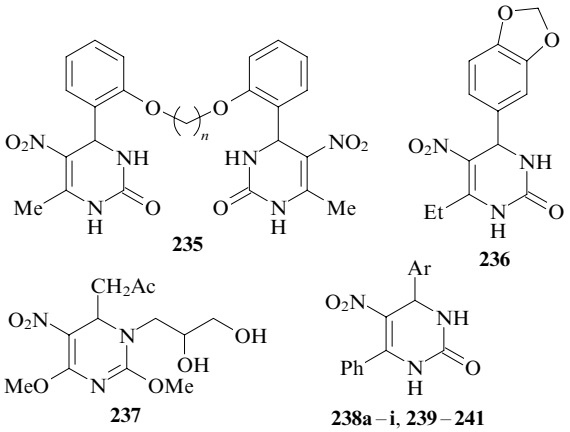
231 – 234

226: Alk = Me, Et, Pr^i, Bu^i; **227**: Ar = Ph, C_6H_4Cl-4, $C_6H_3(OMe)_2$-3,4; R = OMe; **228**: Ar = Ph, C_6H_4Cl-4, $C_6H_3(OMe)_2$-3,4; R = Ph;
229: X = H: Ar = $C_6H_{5-n}R_n$ (R_n = H (**a**), 2-OMe (**b**), 4-OMe (**c**), 3,4,5-$(OMe)_3$ (**d**), 4-OH (**e**), 2-Cl (**f**), 4-Cl (**g**), 2-CF_3 (**h**), 2-$OCHF_2$ (**i**), 2-SCH_2F (**k**), 2-NO_2 (**l**), 3-NO_2 (**m**));
230: X = Me: Ar = $C_6H_{5-n}R_n$ (R_n = H (**a**), 3,4,5-$(OMe)_3$ (**b**), 2-Cl (**c**), 2-CF_3 (**d**), 2-NO_2 (**e**), 3-NO_2 (**f**));
231 – 234: Ar = Ph (**231**), C_6H_4OMe-4 (**232**), C_6H_4OMe-2 (**233**), $C_6H_2(OMe)_3$-3,4,5 (**234**)

Studies of the effects of compounds **231** – **234** in 0.1 mg kg^{-1} doses on the systemic haemodynamics in mice and in 1 μmol litre^{-1} concentration on the contractile activity of myocardium in comparison with Nifedipine (**9**) demonstrated that they cause active vasodilator reaction and, as a result, blood pressure decreases by 5% – 15% and the total peripheral resistance (TPR) decreases by 4% – 40%. Compound **233** with the *ortho*-methoxy group in the benzene moiety, which was inferior to Nifedipine, was found to be most active in this group.[255] The activity of dimeric compound **235** (n = 1) corresponds approximately to those of above-mentioned methoxy derivatives; however, upon elongation of the methylene bridge to n = 3, the cardiovascular activity decreased.[255] When tested on the HEK 293 cell culture (in 25 μmol litre^{-1} concentration), compound **236** with a structure similar to those presented above showed a selective activity towards the calcitonin receptor CTR-2, *i.e.*, it stimulated the accumulation of cyclic adenosine monophosphate (c-AMP) in the cells.[103]

Data on the antiviral activity of a nitro 1,6-dihydropyrimidine derivative (compound **237**), which is an analogue of known acyclic nucleoside antiviral agents, deserve attention.[258] Compound **237** in concentrations of 10 and 50 μg ml^{-1}, like AZT in the same concentrations, was found to inhibit the reverse transcriptase activity in the culture medium by 85% – 90%. Thus, compound **237** is not inferior to AZT in a number of pharmacological characteristics and, furthermore, it is non-toxic in concentrations needed to protect cells from infection.[258]

Structures 235 – 241



235 **236** **237** **238a – i, 239 – 241**

235: n = 1 – 4;
238: Ar = $C_6H_{5-n}R_n$ (R_n = 4-OH (**a**), 4-OMe (**b**), 3-F (**c**), 3-Cl (**d**), 3-NO_2 (**e**), 2-NO_2 (**f**), 2-OH (**g**), 2-OH-5-Me (**h**), 2-OH-5-Br (**i**);
239: Ar = C_6H_2OH-4-Bu^t_2-3,5;
240: Ar = 3-Py;
241: Ar = 2-Th

The replacement of the aliphatic group in position 6 of the pyrimidine ring of the indicated compounds by an aromatic moiety resulted in new derivatives — 4,6-diaryl-5-nitrodihydropyrimidinones **238** – **241**.[259 – 262]

The primary biological testing of compounds of this series showed rather low toxicity and pharmacological behaviour differing from that of other structural types.[259, 260, 263, 264] Without exhibiting antihypertensive properties, some of these compounds showed high anti-arrhythmic activity (Table 13).

Table 13. Anti-arrhythmic activity of 4,6-diaryl-5-nitrodihydropyrimidinones.[260]

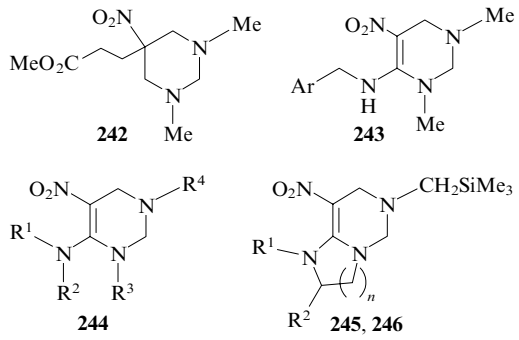
Compound	LD_{50} /mg kg^{-1}	Minimal effective dose /mg kg^{-1}
219	> 5000	3.5×10^{-2}
238a	> 5000	3.5×10^{-2}
238c	> 5000	3.5×10^{-4}
238e	> 1000	4.5×10^{-5}
240	> 1000	3.5×10^{-2}
241	> 1000	3.5
Nifedipine (**9**)	210	3.5
Allapinine		0.3
Verapamil	8.5	1.1 (ED_{50})

The anti-arrhythmic activity was studied upon intravenous injection of the tested agents dissolved in Tween-60 into the femoral vein of narcotized rats. The arrhythmia was induced by single-shot injection, into the same vein, of a 10% solution of $CaCl_2$ (250 mg kg^{-1}) or adrenaline hydrochloride (0.3 mg kg^{-1}) in lethal doses for rats. It was ascertained on the $CaCl_2$ model that preliminary injection of any of the agents fully suppressed the development of arrhythmia. The active dose depended on the structure of agents differing by the nature and position of substituent R in the aryl moiety. The highest activity was found for compounds **238c**,**e** (see Table 13), while derivatives **219**, **238a**, **240** and **241** were less active but still surpassed the reference anti-arrhythmic drugs, Allapinine and Verapamil.[260, 264] Meanwhile, steric shielding of the phenolic hydroxyl group in compound **239** results in complete loss of anti-arrhythmic activity.[261]

It was noted that derivatives **238a**,**c**,**e** are able to improve the myocardial conduction, which is manifested as more clear-cut spikes on an ECG tracing. This effect was not observed for compounds **219** and **240**. One more distinctive feature of derivatives **238a**,**c**,**e** is that they do not affect blood pressure, which distinguishes them from 1,4-dihydropyridine calcium channel blockers.[260, 264]

However, it was found that, when tested on the adrenaline-induced arrhythmia model, none of these agents taken in up to 3.5 mg kg^{-1} doses affected the cardiac electrical

Structures 242 – 246



242 **243** **244** **245, 246**

243: Ar = 3-Py, 6-chloro-3-pyridyl;
244: R^1 = Alk, cyclo-Alk; R^2 = Alk, cyclo-Alk, CH_2Py-3; R^3 = Alk, cyclo-Alk; R^4 = Alk, cyclo-Alk, NMe_2, $NHCO_2Et$;
245, **246**: R^1 = Alk, cyclo-Alk, Bn, CH_2Ar, CH_2Het, *etc.*; R^2 = Me, n = 1 (**245**); R^2 = H, n = 2 (**246**)

conductivity parameters or exhibited anti-arrhythmic effect.[260, 264]

Nevertheless, a nitro group present in the hexahydropyrimidine ring devoid of an urea moiety (compound **242**) still promotes an anti-arrhythmic activity, although it is lower than that of Allapinine.[265] It is noteworthy in this respect that nitrotetrahydropyrimidines with a similar topology (derivatives **243** and **244**) proved to be efficient pesticides, insecticides and nematicides,[266 – 269] while derivatives **245**, **246** were found to be suitable as arthropod control agents.[270]

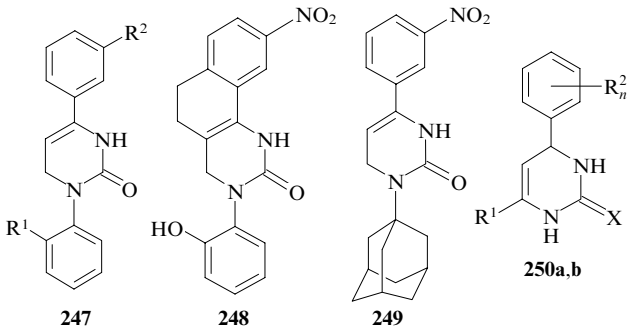
II.6. Other dihydropyrimidine derivatives

The above examples of the diverse biological activities of DHPMs were mainly concerned with derivatives with a 5-functional group. These examples clearly demonstrate, first, that structurally and chemically similar compounds may, nevertheless, exhibit a variety of effects and, second, that the replacement of some pharmacophore group in the pyrimidine ring by some other pharmacophore group may not only markedly affect the activity level but also change the type of activity. Even more substantial changes take place when the functional group is replaced by a neutral alkyl moiety or hydrogen atom. In this regard, it is pertinent to consider 1,4-diaryldihydropyrimidinones **247** and **248** containing no functional groups in the heterocycle. Thus quite long ago compound **247a**, which was called Icilin, was found to exert a pronounced cooling effect in experiments with laboratory animals.[271] Icilin, which behaves as a cold receptor TRPM8 super-agonist, selectively activates this receptor and suppresses the activity of other receptors responsible for pain sensitivity, its therapeutic effect exceeding the action of menthol by a large factor. Therefore, development of new non-opioid analgesics like Icilin arouses interest in medical specialists. A series of compounds **247**, Icilin analogues, were synthesized as potential cold receptor agonists, which can be used as parts of therapeutic compositions to suppress itch and pain of skin, mucosa and stomach.[272] More recently, it was shown that some Icilin analogues can act as cold receptor TRPM8 agonists, substantially less potent than Icilin, while some other analogues act as antagonists of this receptor.[273] Testing of Icilin analogue **248** in which the 4-nitrophenyl group is fixed, so that it cannot rotate, did not show any activity.[273]

Icilin itself was proposed for use in cosmetics and dermatology to reduce hair growth.[274] Moreover, Icilin (**247a**) was found to depress the CNS, while the replacement of the N(1)-aryl moiety by an adamantyl group (compound **249**) brought about the opposite effect by acting as a CNS stimulant.[275]

4-Phenyl-dihydropyrimidinethione (**250a**, R^2_n = H) has anti-inflammatory action comparable with that of prednisolone and analgesic activity exceeding the activity of the drug Valdecoxib.[276] QSAR analysis of the potential biological activity of heterocyclic nitroaryl derivatives indicated the presence of antituberculosis properties.[277] Testing of a series of nitrophenyl-dihydropyrimidinethiones **250b** on $H_{37}Rv$ *Mycobacterium tuberculosis* strain confirmed QSAR data for most of the compounds. Replacement of the methyl group in the structure (series **250a**) by a nitrophenyl group endows compounds **250b** with antimycobacterial properties.[277] It was found that 2-SAlk-derivatives **251** also possess antimicrobial and fungicidal action,[278] while structurally related compound **252** with a quinoline moiety showed also antituberculosis activity comparable with that of Isoniazid.[279] A moderate anti-inflammatory and analgesic action was found for compounds incorporating two 4,4,6-trimethyldihydropyrimidinethione moieties connected by various spacers.[280, 281]

Structures 247 – 250



247 **248** **249** **250a,b**

247: R^1 = OH, R^2 = NO_2 (**a**); R^1 = OH, F, Cl, Alk, CF_3, OAc, OBu^n, OPr^n, OBz; R^2 = NO_2, Alk, CF_3, Br, Cl, I;
250a: R^1 = Me: R^2_n = H, 2-Cl, 4-Cl, 4-Br, 4-F, 4-OMe, 4-NO_2, 4-CF_3, 2,4-Cl_2; X = S;
250b: R^1 = $C_6H_4NO_2$-4: R^2_n = 3-Cl, 4-Cl, 4-Br, 4-F, 3-OMe, 4-OMe, 4-NMe_2, 2,4-Cl_2, 3,4-$(OMe)_2$, 2,5-$(OMe)_2$; X = O, S

According to biological testing of 5-unsubstituted dihydropyrimidinethiones **253** – **256**, compounds **253**, **254** and **256** in 50 mg kg^{-1} oral doses have good anti-inflammatory properties against carrageenin-induced paw oedema in rats. Compounds **255** and **256** showed pain-relieving properties similar to those of Ibuprofen in experimental models of phenylquinone-induced writhing (Table 14).[284, 285]

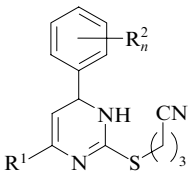
4,6-Diaryldihydropyrimidinethiones containing an acetic (compounds **257**)[286] or propionic (**258**, **259**)[287] acid moiety also demonstrate anti-inflammatory activity when used in 10 and 20 mg kg^{-1} doses in rats.[286]

Compounds with an annulated saturated ring also showed antimycobacterial properties; most noteworthy of them is tetrachloro derivative **260**, which is 2 – 3-fold more

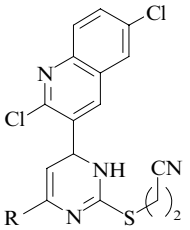
Table 14. Anti-inflammatory and analgesic activities of compounds **253** – **256** in 50 mg kg^{-1} oral doses.[284]

Compound	Anti-inflammatory activity (%)	Analgesic activity (%)
253 (R = 3-CN)	27.9	10
254	34.5	30
255	3.0	50
256	34.3	70
Ibuprofen	38	50

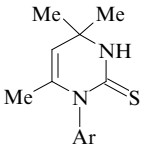
Structures 251 – 259



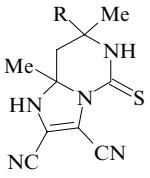
251



252

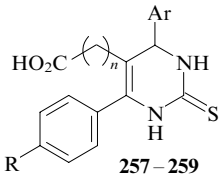


253, **254**



255, **256**

251: $R^1 = C_6H_4NH_2$-4: R_n^2 = H, 4-Me, 4-Cl, 2-OH, 3-OH, 4-OH, 4-OMe, 4-OH-3-OMe, 4-NH_2, 4-NO_2;
252: R = C_6H_4OMe-4;
253: Ar = C_6H_4R (R = 2-NO_2, 3-NO_2, 4-NO_2, 3-CN);
254: Ar is 4-phenyl-1,3-thiazol-2-yl;
255: R = Me; **256**: R = H



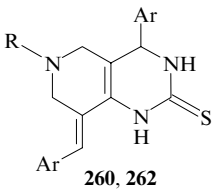
257 – **259**

257: Ar = C_6H_4R' (R′ = H, 4-Cl, 4-OMe); R = H, Cl, Me; *n* = 1;
258: Ar = $C_6H_{5-n}R'_n$ (R'_n = 2-OH, 3,4,5-$(OH)_3$); R = H, Me, OMe; *n* = 2;
259: Ar = 2-Fu; R = H, Me; *n* = 2

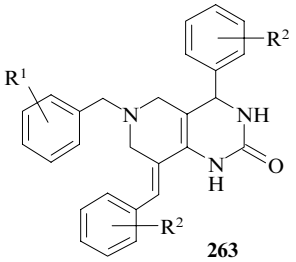
active than Ethambutol but is less active than Rifampicin or Isoniazid.[288]

Dihydropyrimidinethione **261**, which contains two nitrobenzene rings, was found to possess antitumour activity towards various human tumour cells *in vitro*.[289] Antitumour properties towards several types of cancer cells (lung, breast, kidney, colon, prostate and ovarian cancer, leukemia and melanoma) were found for compound **262** in *in vitro* experiments; the GI_{50} values were in the range of 2 – 30 μmol litre^{-1} (Ref. 290). Testing of this compound for anti-HIV-1 activity demonstrated cytotoxic properties against non-infected T4 cells (IC_{50} = 6.8 μmol litre^{-1}) and a minimal antiviral activity in infected cell cultures.[290] A number of halo-substituted dihydropyrimidinones **263** had antiproliferative activity towards liver cancer cells.[291]

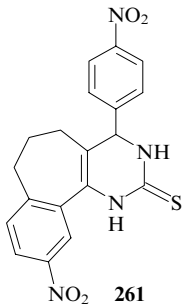
Structures 260 – 263



260, **262**



263



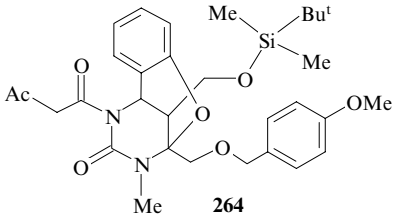
261

260: R = Bn, Ar = $C_6H_3Cl_2$-2,4;
262: R = Me, Ar = C_6H_4OMe-4;
263: R^1 = 2-Me, 2-F, 3-F, 4-F; R^2 = H, 4-Me, 4-Pr^i, 4-OMe, 2-Cl, 4-Cl, 3-F, 4-F

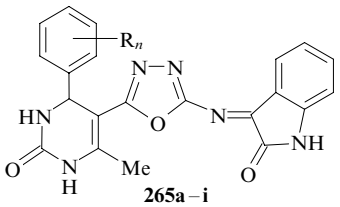
Compound **264** with O-bridged benzene and pyrimidine rings, which is in essence the product of intramolecular transformation of the corresponding 4-(2-hydroxyphenyl)-dihydropyrimidinone, was claimed to inhibit the intracellular Wnt/β-catenin signalling system, regulating cell fate and proliferation for melanoma and benign nevi.[207]

The presence of additional pharmacophore moieties endows this hybrid molecule with a set of new properties and can bring about a synergistic effect in the biological activity. As an example, consider the data on the activities of hybrid molecules composed of potential pharmacophores — substituted dihydropyrimidinone and a heterocycle out of thiazole, oxadiazole, thiadiazole, isatin and imidazole {compound series **142** [R_n = 3,5-$(CF_3)_2$, 3-NH_2, 4-NH_2, 4-NHAlk, 4-Ac, 4-NO_2, 3-CO_2Alk, 4-CO_2Alk], **265** – **269**}. Some compounds of series **142** possess antiviral activity, in particular, against HIV.[191] Testing of compounds **265** and **267** on several types of bacteria and fungi showed them to be potential antibacterial and antifungal agents.[292, 293] Furthermore, chlorophenyl and nitrophenyl derivatives **267** demonstrated anti-inflammatory activity that was somewhat lower than that of Diclofenac,[293] while the antioxidant activity of **265d**,**e**,**h** proved to be close to that of ascorbic acid.[292]

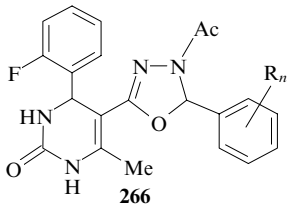
Structures 264 – 266



264



265a – **i**



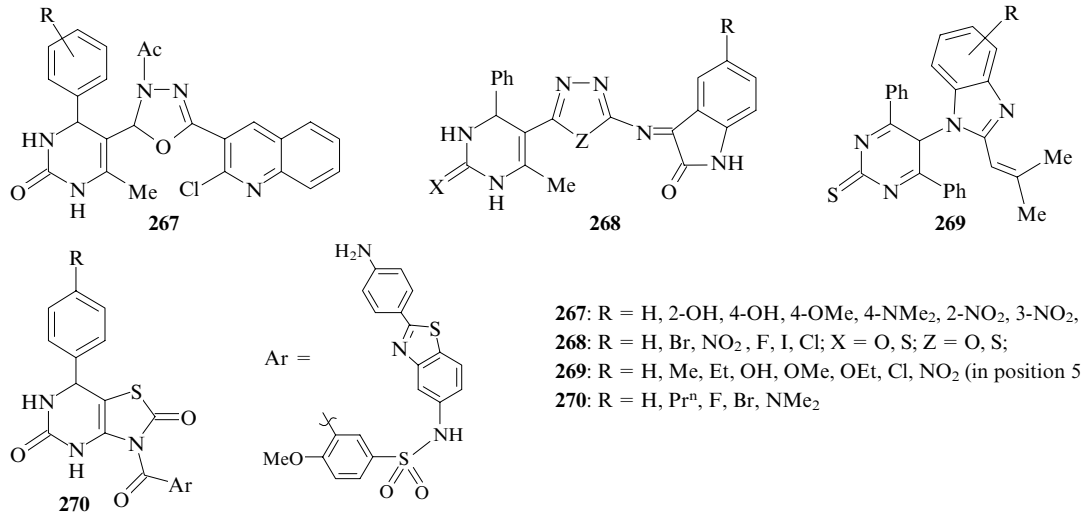
266

265: R_n = H (**a**), 2-Cl (**b**), 2,4-Cl_2 (**c**), 3,4,5-$(OMe)_3$ (**d**), 4-*i*-Pr (**e**), 4-F (**g**), 3-OH-4-OMe (**h**), 4-NMe_2 (**i**);
266: R_n = H, 2-F, 4-F, 4-Cl, 2,6-Cl_2, 2,4-$(OH)_2$, 2,4-$(OMe)_2$, 2-NO_2, 3-NO_2, 4-NO_2

Hybrid compounds of series **268** and **270** were tested for antimicrobial activity; nitro-, amino- and halo-substituted derivatives in a concentration of 6.25 μg ml^{-1} suppress the growth of the H_{37}Rv *M. tuberculesis* strain and are not inferior in efficiency to known drugs such as Ethambutol or Pyrazinamide.[294 – 296] Out of series **266**, the nitro derivative (R = 4-NO_2), which suppresses the growth of mycobacterium to the same extent as Isoniazid, was most active.[297] Moreover, compounds of series **268** demonstrated a noticeable antimalarial activity, and two of them (X = O, Z = O, R^2 = NO_2 and X = S, Z = O, R^2 = Cl) were not inferior to Chloroquine.[295]

All tested compounds **269** showed high bacteriostatic and bactericidal activities (MIC of 3 – 48 μg ml^{-1}) against the bacteria *S. aureus*, *Bacillus subtilis*, *Pseudomonas diminuta* and *E. coli*. It was found that compounds containing electron-withdrawing groups are more active.[298] The

Structures 267 – 270



267: R = H, 2-OH, 4-OH, 4-OMe, 4-NMe_2, 2-NO_2, 3-NO_2, 4-Cl;
268: R = H, Br, NO_2, F, I, Cl; X = O, S; Z = O, S;
269: R = H, Me, Et, OH, OMe, OEt, Cl, NO_2 (in position 5 or 6), 5-Br, 5-CO_2H;
270: R = H, Pr^n, F, Br, NMe_2

attempts of the authors of the cited research to perform QSAR analysis and to establish two- or three-parameter correlations between the compound activity and various structural parameters were unsuccessful. Out of numerous parametric estimates, only the calculated molar refraction showed a satisfactory correlation with the MIC values.[298]

III. 3,4-Dihydroquinazolin-2(1*H*)-ones and analogous thiones

The molecules of 3,4-dihydroquinazolin-2-ones incorporate a dihydropyrimidinone moiety annulated to the benzene ring, which implies the presence of biological activity. Non-peptide inhibitors of Na/Ca exchange in cardiomyocytes, surpassing the tetrapeptide inhibitor Dimethylamiloride, were distinguished in the series of dihydroquinazolinones **271** – **273** (Table 15). Among the presented inhibitors, high activity was observed for compounds **273**, the derivative with R = Bn (SM-15811) being the most active.[299]

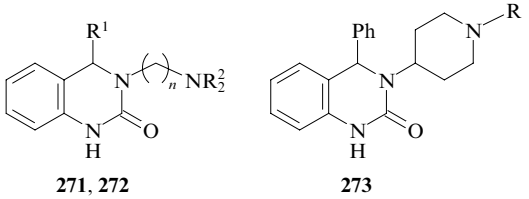
It has already been noted that substituted dihydropyrimidinones behave, most often, as L-type Ca-channel blockers, and only few examples where they affect T-channels are known. It was found that annulation of a benzene ring to the dihydropyrimidine core changes the Ca-channel blocking electrophysiological properties of bioactive molecules, so that they start to better interact with the low-voltage T-channels, which are important for regulation of the peripheral and central nervous systems and the cardiovascular system. For example, various 4,4-disubstituted 3,4-dihydroquinazolinones can act as T-type Ca-channel antagonists.[300 – 303] Initially, T-type calcium channel antagonism was noted for racemic compound **274**. Testing of single enantiomers *in vitro* demonstrated that the racemate activity was wholly due to the *S*-enantiomer. Further optimization of this molecular structure resulted in the preparation of a number of more active compounds; of most interest were 4-alkyl-4-aryl-6-chloro derivatives **275** – **278**, which were investigated *in vitro* and *in vivo* as pure *S*-enantiomers.[300] According to the set of pharmacological and pharmacokinetic characteristics and *in vivo* experiments on rats and dogs, compounds **276** and **278** were the best inhibitors, in particular, for suppression of nervous system disorders such as epileptic seizures, tremor and insomnia.

Study of the pattern of interaction of dihydroquinazolinones **275**, **276** and **278** with Ca-channels by means of [H^3]-labelled ligand displacement demonstrated that these compounds bind at other channel sites than known inhibitors. Therefore, combining two structurally different inhibitors interacting with the allosteric sites of T-type Ca-channels gives rise to a synergistic effect. An increase in the activity and duration of the effect were noted *in vivo* upon oral co-

Table 15. Inhibitory activity of several 3,4-dihydroquinazolin-2(1*H*)-ones towards Na/Ca exchange in rat cardiomyocytes.[299]

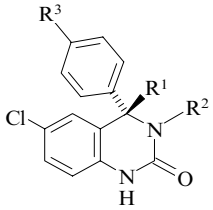
Compound	*n*	R^1	R	IC_{30} /μmol litre^{-1}
271	2	Ph		0.069
271	3	Ph		0.04
271	4	Ph		1.9
272	3	Me		0.51
272	3	Bn		0.57
272	3	Ph		0.46
272	3	2-Fu		3.8
272	3	2-Th		0.69
272	3	2-Py		0.72
273			H	1.1
273			Me	0.087
273			Et	0.053
273			Pr^n	0.093
273 (SM-15811)			Bn	0.017
273			$(CH_2)_2Ph$	3.6
Dimethylamiloride				30

Structures 271 – 273



271: R^1 = Ph, R^2 = Et, *n* = 2 – 4;
272: R^2 = Me, *n* = 3: R^1 = Me, Bn, Ph, 2-Fu, 2-Th, 2-Py;
273: R = H, Me, Et, Pr^n, Bn, $(CH_2)_2Ph$

Structures (*S*)-274 – (*S*)-278



(*S*)-**274** – (*S*)-**278**

Compound	R^1	R^2	R^3
274	Et	Me	H
275	Et	cyclo-C_3H_5	H
276	Et	CH_2CF_3	F
277	cyclo-C_3H_5	CH_2CF_3	F
278	cyclo-C_3H_5	CH_2CF_3	CN

administration of compound **278** and a standard inhibitor in rats (1.0 and 0.3 mg kg^{-1}, respectively).[304]

The broad range of NH-dihydroquinazolinones patented as T-type Ca-channel antagonists[302] was supplemented by the series of N(1)-substituted dihydroquinazolinones with diversified combinations of substituents (compounds **279** – **282**).[303]

Some compounds of this series were reported as potential drugs both as single agents and in compositions with other agents for prevention and treatment or diseases or disorders (neuropathic pain, tremor, sleep disorders, depression, epilepsy, schizophrenia, nervous system disorders, cardiac arrhythmia and hypertension).[302, 303] One strategy for the therapy of schizophrenia involves selective activation of muscarinic acetylcholine receptors. The key role is assigned to M1 and M4 receptor subtypes, the activation of which mitigates the symptoms of schizophrenia. Some N(3)-substituted dihydroquinazolinones proved to be reasonably good agonists of M1 and M4 muscarinic acetylcholine receptors. For example, compound **283** in concentration of 0.3 μmol $litre^{-1}$ showed a high agonistic activity *in vitro*. In *in vivo* experiments on rats, antipsychotic effect (ED_{50}) was achieved upon administration of 3.0 mg kg^{-1} of the agent.[305]

Previously, while searching for effective non-nucleoside HIV reverse transcriptase (RT) inhibitors, pharmacologists paid attention to quinazoline derivatives as an alternative to known drugs used in medicine to stop HIV infection and treat AIDS. The lead agent in the first stage of research was unstable dihydroquinazoline-2-thione **284** (L-608,788),[306] which was modified to obtain compound **285** — the first potent sulfur-free agent of this class. Further studies resulted in the discovery of a line of potential reverse transcriptase inhibitors — 4-alkyl-4-cyclopropyl- (**286**) and 4-cyclopropyl-4-ethynyl derivatives (**287**),[306] suitable both as single agents and as compositions with antiviral agents, immunomodulatory drugs, antibiotics and vaccines for treating AIDS patients.[307] Compounds **286** are good HIV-1 RT inhibitors but their use can be hampered by oxidative metabolic transformations that involve simple 3- and 4-alkyl groups. Compounds **287** (Ref. 306) and **288** (Ref. 308) proved to be free from this shortcoming and able to efficiently inhibit the HIV-1 RT.

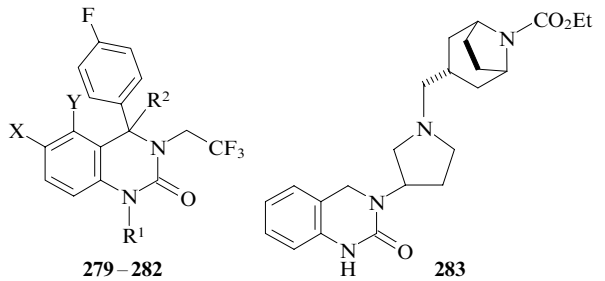
Compounds **287** were evaluated for their ability to inhibit HIV RT. Generally, most of five- and six-membered aryl and hetaryl groups promote potent HIV-1 RT inhibition. The selected compounds were also evaluated as antiviral agents on the HIV-IIIb-infected MT-4 cell culture.[306] Table 16 presents the CIC_{95} values, *i.e.*, concentrations at which the spread of HIV-infection on the MT-4 cells is inhibited by > 95%, for the most active agents. Since compounds **287** showed excellent antiviral and pharmacokinetic profiles, some derivatives were resolved into *R*- and *S*-enantiomers, which were tested for biological activity. In relation to pyridine derivative **287a**, it can be seen that the *S*-enantiomer [(−)-enantiomer] is the active inhibitor, while the *R*-enantiomer [(+)-enantiomer] has low activity.[306]

Table 16. Anti-HIV activities of the most efficient dihydroquinazolinones and -thiones.[306]

Compound	Ar	IC_{50} /nmol $litre^{-1}$	CIC_{95} /nmol $litre^{-1}$ (MT-4 cells)
284		19	50
287	2-Py	23.2	25
287	Ph	17.7	100
287	C_6H_4CN-2	10.8	12
287	Thiazol-2-yl	10.9	12
(*S*)-**287a**	2-Py	12	25
(*R*)-**287a**	2-Py	9300	–
Nevirapine		73	100

Oral administration of compound (*S*)-**287a** in a 10 mg kg^{-1} dose in rhesus monkeys provided peak levels of 12 μmol $litre^{-1}$ within 2 – 4 h, while after 24 h, the agent remained at a > 4 μmol $litre^{-1}$ level. Since enantiomer (*S*)-**287a** possessed an excellent biological activity profile,

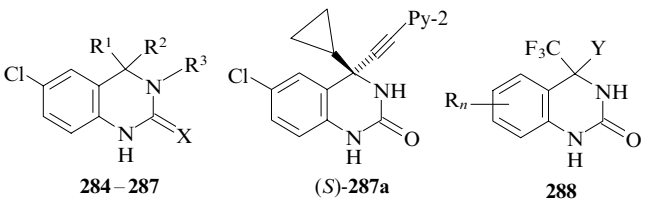
Structures 279 – 283



279 – **282** **283**

Compound	R^1	R^2	X	Y
279	CH_2CN	Et	F	H
280	$(CH_2)_2OMe$	Et	F	F
281	CH_2Py-4	Pr^n	F	F
282	Pyridine-*N*-oxide-4-ylmethyl	cyclo-C_3H_5	Cl	H

Structures 284 – 288



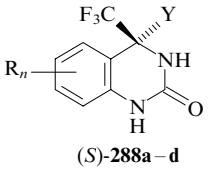
284 – **287** (*S*)-**287a** **288**

284: R^1 = Ph, R^2 = OEt, R^3 = Me, X = S;
285: R^1 = Ph, R^2 = C≡CH, R^3 = Me, X = O;
286: R^1 = cyclo-C_3H_5, R^2 = Alk, C≡CH; R^3 = Me; X = O;
287: R^1 = cyclo-C_3H_5; R^2 = C≡CAr (Ar = Ph, $C_6H_4NO_2$-2, C_6H_4CN-2, 2-Fu, 2-thiazol-2-yl, 2-Py, 3-Py, 4-Py, pyrazin-2-yl, pyrimidin-5-yl); R^3 = H; X = O;
288: R_n = 5-Cl, 6-Cl, 5,6-Cl_2, 5-Cl-6-F, 6-Cl-5-F, 5-F, 6-F, 5,6-F_2, 6-OMe; Y = CH=CHZ, C≡CZ (Z = Et, Pr^i, cyclo-C_3H_5, Ph, 2-Py)

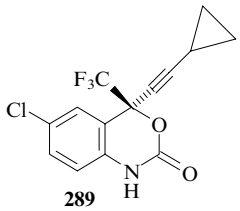
it was chosen as a drug candidate for the subsequent preclinical trials.[306]

It is not surprising that 4-alkenyl-4-trifluoromethyl- and 4-alkynyl-4-trifluoromethyl-substituted dihydroquinazolinones **288** with similar topology are also able to inhibit HIV-1 reverse transcriptase. As such, they are not inferior to known antiviral agents and, according to some *in vitro* tests, they are better than Nevirapine or Efavirenz (**289**).[308] Out of all these compounds, enhanced activity was noted for 5-halo derivatives, the highest activity being inherent in four single enantiomers with the *S*-configuration at the C(4) chiral atom, namely, compounds (*S*)-**288a – d**. In the antiviral profile and the protein binding ability tested on various HIV-1 strains, they are comparable with Efavirenz (**289**). The inhibitory activities (IC_{90}) of these products towards the HIV-1/RF strain are 2.0, 1.3, 2.1 and 2.0 nmol litre^{-1}, respectively, while for Efavirenz, it is 1.7 nmol litre^{-1}. However, they all proved to be inactive towards a different virus type — HIV-2.[308]

Structures (*S*)-288, 289



(*S*)-**288a – d**



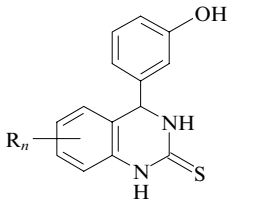
289

Compound	Y	R_n
(*S*)-**288a** (DPC 961)	C≡CC$_3$H$_5$-cyclo	6-Cl
(*S*)-**288b** (DPC 963)	C≡CC$_3$H$_5$-cyclo	5,6-F$_2$
(*S*)-**288c** (DPC 083)	CH=CHC$_3$H$_5$-cyclo	6-Cl
(*S*)-**288d** (DPC 082)	CH=CHC$_3$H$_5$-cyclo	5,6-F$_2$

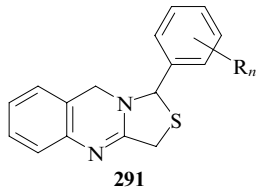
Structure modification of Monastrol (**74**), which inhibits mitotic kinesin Eg5 and exhibits antiproliferative properties towards tumour cells, furnished a number of analogues such as Enastron (**166**), Dimethylenastron (**167**) and Fluorastrol (**162**) containing an annulated cyclohexene moiety in the molecule. The above-listed agents possessed enhanced activity and improved pharmacological profile. The presence of dihydroquinazolinethione derivatives **290** in this series appears quite justified.[309, 310] A study of the antiproliferative effect of **290** on P-glycoprotein and human glioblastoma cells demonstrated that they are an order of magnitude more efficient than Monastrol, being at the level of upgraded Monastrol analogues; they are not deactivated either hydrolytically or upon binding to blood proteins and can penetrate through the blood – brain barrier. The benefits of 5-fluoro derivative **290a** (Vasostrol VS-83) among other compounds **290** were noted.[309]

The antiproliferative and cytotoxic properties were found in a number of 1-aryl-1*H*,3*H*-thiazolo[4,3-*b*]quinazolines **291** and **292** tested *in vitro* on several dozens tumour cell lines. Most compounds showed a 50% cell growth inhibition (GI_{50}) and a 50% cell lethal dose (LC_{50}) at concentrations of 10 – 100 μmol litre^{-1}. The 2,6-dichlorophenyl derivative (1*S*,3*S*)-**292** was most active, unlike the (1*S*,3*R*) diastereomer.[311]

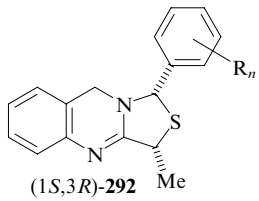
Structures 290 – 292



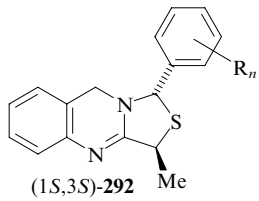
290



291



(1*S*,3*R*)-**292**



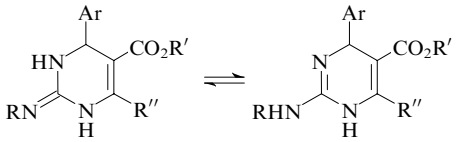
(1*S*,3*S*)-**292**

290: R_n = 5-F (**290a**); R_n = H, 6-Me, 7-Me, 6-Br, 6-Cl, 5-F, 6-F, 7-F, 6,7-F$_2$; **291**, **292**: R_n = H, 2-CF$_3$, 2-F, 3-F, 2,6-F$_2$, 2,6-Cl$_2$

IV. Tetrahydropyrimidine-2-imines as N-analogues of dihydropyrimidinones

Dihydropyrimidinone N-analogues containing a 2-imino group instead of oxygen (*e.g.*, compounds **293**) are also potentially biologically active; therefore, their synthesis is of interest.[68, 312 – 314] The presence of guanidine moiety increases the molecular basicity, providing additional stabilization of the molecules *via* salt formation, as well as possible existence of tautomers **IV** and **V** for these structures (Scheme 1). Tautomer **IV** is related to dihydropyrimidinone (thione) structure, while **V** resembles known pyridine calcium channel blockers, which suggests that both forms may be biologically active. For example, both enantiomers of Emmacin (**293b**) inhibit the growth of *S. aureus* resistant to many antibacterial drugs.[314]

Scheme 1



IV **V**

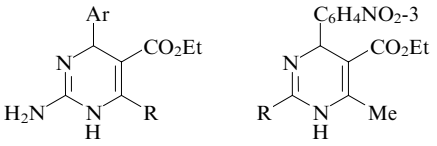
Some time ago, the vasodilator (relaxant) activities of ethyl 2-dimethylamino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyrimidine-5-carboxylate (**294**) and a number of corresponding 4-aryl derivatives of 2-methoxy- (**295**) and 2-methylthiodihydropyrimidines (**296**) were studied *in vitro*. The experiments carried out with K^+-depolarized rabbit thoracic aorta strips confirmed their blocking action on Ca-channels and allowed a comparative activity evalua-

Table 17. Vasodilator (relaxant) activities of 2-heterosubstituted 1,4-dihydropyrimidines **294 – 296**.[68]

Compound	IC_{50} /nmol litre^{-1}
294	6100
295	710
296	130
Nitrendipine (**11**)	1

tion. Table 17 presents the IC_{50} values for similarly substituted analogues **294** – **296** characterizing the inhibition of Nitrendipine[^{3}H] binding in K^+-depolarized rabbit thoracic aorta strips.[68] The results indicate a lower activity of these compounds compared with Nitrendipine (**11**) and a considerable increase in activity on going from N-dimethyl (**294**) to O-methyl (**295**) and S-methyl derivatives (**296**).

Structures 293 – 296

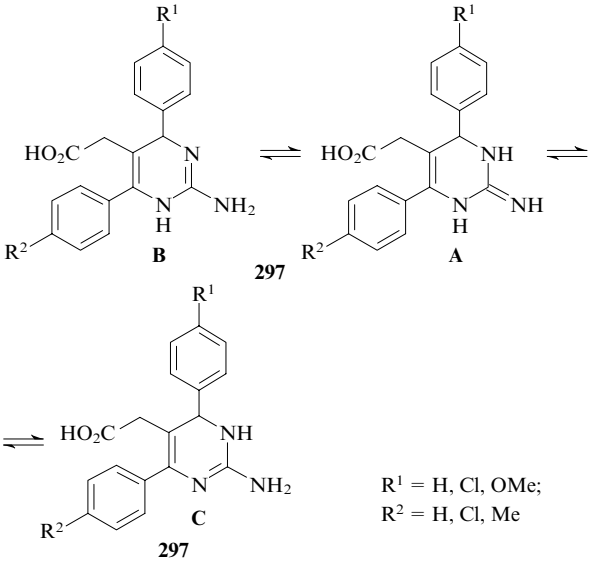


293 **294 – 296**

293: R = Ph: Ar = C_6H_4X-4 (X = H, Me, OMe, Cl, NO_2) (**a**); R = Et: Ar = C_6H_2OH-2-Cl_2-3,5 (**b**); R = Me: Ar = Ph, $C_6H_4NO_2$-3, $C_6H_4NO_2$-4, 2-Th;
294 – 296: R = NMe_2 (**294**), OMe (**295**), SMe (**296**)

2-Amino-4,6-diaryl-1,6-dihydropyrimidin-5-ylacetic acids (**297**), which contain a guanidine moiety capable of prototropic tautomerism **B** ⇌ **A** ⇌ **C** (Scheme 2), possess a clear-cut anti-inflammatory activity;[315, 316] 4-methoxyphenyl derivatives (R^1 = OMe; R^2 = H, Cl, Me) were only slightly inferior to Diclofenac in experiments on rats (10 mg kg^{-1} dose).[316] Polycyclic 2-hydrazino derivative **298** also showed anti-inflammatory activity comparable with that of Prednisolone.[276]

Scheme 2

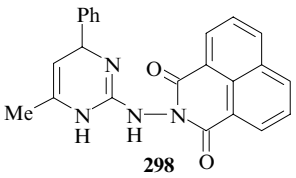


B **297** **A**

C
297

R^1 = H, Cl, OMe;
R^2 = H, Cl, Me

Structure 298



298

The search for antitumour agents among aminodihydropyrimidines resulted in the synthesis of 5-carbamoyl derivatives incorporating aryl and hetaryl moieties. Testing of various substituted structures similar to compound **299** as cycline-dependent kinase (CDK2) inhibitors revealed some 2-arylamino and 2-hydrazino derivatives with a noticeable selective antiproliferative activity towards human carcinoma cells.[317] Among these products, furfurylmethylidene and thienylmethylidene derivatives **299** (R = 2-Fu and 2-Th) were more active than the reference compound (Roscovitine) and had IC_{50} of 0.4 and 0.3 μmol $litre^{-1}$ (Ref. 317).

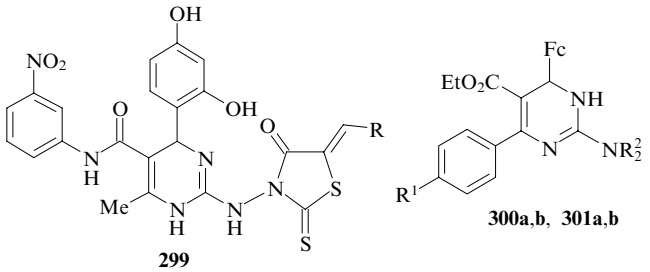
The existing view on the enhancement of biological activity of an organic compound upon introduction of a ferrocenyl group in its molecule was lately demonstrated in relation to a small series of ethyl 2-amino-4-ferrocenyl-3,4-dihydropyrimidine-5-carboxylates **300** and **301**.[318] Testing *in vitro* on six human tumour cell lines revealed an antitumour activity. The highest inhibitory activity, exceeding the activity of Cisplatin, was found for two agents, **300a**,**b** (Table 18). Note that 2-(*N*-dimethylamino) analogues **301**, which are not subject to tautomerism of the guanidine moiety, are less active.

Table 18. Human tumour cell growth inhibition (%) at the agent concentration of 50 μmol $litre^{-1}$ in DMSO.[318]

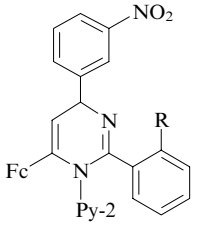
Compound	Cell lines					
	U-251	PC-3	K-562	HCT-15	MCF-7	SKLU-1
300a	100	100	100	100	100	100
300b	100	100	100	100	100	100
301a	42.1	71.9	53.8	35.4	42.9	44.8
301b	57.8	71.8	69.3	62.0	63.4	36.6
Cisplatin	89.9	86.7	74.4	81.8	77.9	95.8

Although ferrocenyl-substituted dihydropyrimidines lack a guanidine moiety, they still possess antitumour activity. Most efficient agents were compounds **302**, which fully suppressed the breast cancer cell growth when present in concentration of < 100 μmol $litre^{-1}$, which is only slightly inferior to Doxorubicin.[319]

Structures 299 – 302



299 **300a**,**b**, **301a**,**b**



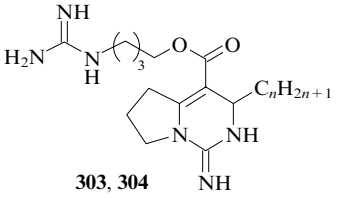
302

299: R = Ph, 2-Fu, 2-Th;
300: R^2 = H: R^1 = H (**a**), NO_2 (**b**);
301: R^2 = Me: R^1 = H (**a**), NO_2 (**b**);
302: R = Me, Cl; Fc is ferrocenyl

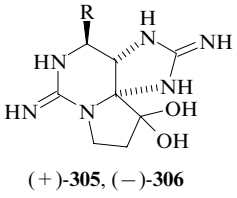
Guanidine moieties incorporated in the compounds mentioned above are also found in complex structures of some natural molecules such as Dehydrocrambine A (**303**)

and its analogue Sch575948 (**304**),[63] Saxitoxin (**305**), Decarbamoyloxysaxitoxins [(+)-**306** and (−)-**306**],[320] Batzelladine A, B, C, D, E, F, K, L, M and N line[321, 322] (Batzelladine A, **307**), Ptilomycalin A (**308**), Crambescidines 816, 830, 844 and 800 (Crambescidine 800, **309**), Merobatzelladines A and B (Merobatzelladine A, **310**), Isocrambescidines and other alkaloids of this type.[3, 322 – 324]

Structures 303 – 306



303, **304**

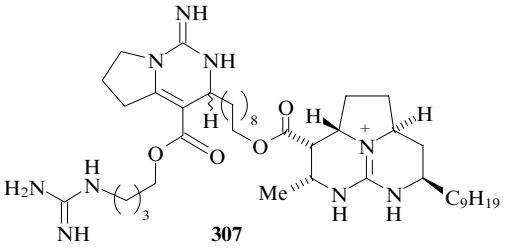


(+)-**305**, (−)-**306**

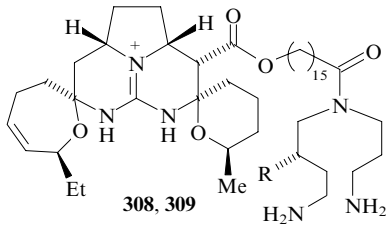
n = 5 (**303**), 11 (**304**); R = $CH_2OC(O)NH_2$ (**305**), Me (**306**)

Toxic alkaloids were first isolated from some marine organisms back in the mid-20th century and their chemical structure was determined in the late-20th century by several research teams.[322, 323, 325 – 329] Various types of biological activity have been identified in these compounds. (+)-Saxitoxin (**305**), isolated from a toxic shellfish, is a neurotoxin that blocks ion passage through voltage-dependent sodium channel. Many natural Saxitoxin analogues also show a characteristic biological activity towards the Na-channel.[320]

Structures 307 – 310

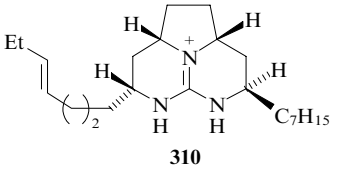


307



308, **309**

R = H (**308**), OH (**309**)



310

Other alkaloids mentioned above exhibit antitumour, antiviral and antimicrobial activities. Indeed, Ptilomycalin A (**308**) is cytotoxic against the cell cultures P388 (IC_{50} = 0.1 μg ml^{-1}), L1210 (IC_{50} = 0.4 μg ml^{-1}) and KB (IC_{50} = 1.3 μg ml^{-1}) and has an antiviral activity against HSV-1 in concentration of 0.2 μg ml^{-1}.[321, 326] According to other data, Ptilomycalin A (**308**) and Crambescidine 800 (**309**) have high cytotoxicity against Vero cells (TC_{50} < 0.53 μg ml^{-1}) and activity against HIV-1 [EC_{50} (EC_{90}) are 0.011 (0.046) and 0.04 (0.12) μmol litre^{-1}, respectively] and many cancer cell lines but are inactive towards tuberculosis mycobacterium.[321] Meanwhile, Ptilomycalin A, Crambescidine 800 and Batzelladines C, L, M showed themselves as fairly good antiprotozoal (in particular, antimalarial) agents.[321] Crambescidines 800, 844 and 816 demonstrated high cytotoxicity against L1210 cells (98% at 0.1 μg ml^{-1}, IC_{50} = 0.04 μg ml^{-1}) and the latter fully inhibited the herpes simplex virus HSV-1 at a concentration of 1.25 μg ml^{-1} and was a potent Ca-channel blocker.[330, 331]

V. Conclusion

The examples of biological activity covered in the review were mainly concerned with compounds belonging to the class of 3,4-dihydropyrimidin-2-ones and their S- and N-analogues, which hold promise for the design of drugs for preventing and treating human diseases. We considered compounds that modulate ion channels, various receptors and enzymes, functioning in the body at the cellular and molecular levels, and compounds that exhibit antitumour, antiviral, antimicrobial, antibacterial, insecticidal, fungicidal and other activities. Splitting of the review into sections helps to elucidate common and peculiar features in the biological activity of various 5-functional DHPMs and evaluate the advantages of each of them. For convenience of the readers, Table 19 summarizes the activity data, which are arranged according to the functional types.

To date, pharmacologists have most comprehensively studied DHPMs with an ester group that show diverse biological activities. Some series and single compounds demonstrate combined activities: compounds of series **20** possess antibacterial,[131] antihypertensive,[50] anti-inflammatory [50] and antituberculosis activities;[131] compounds **29** and **30** have anti-arrhythmic, antihypertensive and antidiabetic activities;[58, 59] some representatives of series **91** and **92** have antitumour and antituberculosis activities;[129, 130] and compounds of series **94** and **114** show antimalarial and antituberculosis [132, 134] properties.

Other functional DHPMs appear moderate compared with the above examples; this may be due to their lower synthetic accessibility and an insufficiently broad range of available pharmacological investigations. Nevertheless, carbonyl and carbamoyl derivatives of dihydropyrimidinethiones demonstrated the best results on antitumour activity; nitro-substituted dihydropyrimidinones behaved as anti-arrhythmic and inotropic agents; and dihydroquinazolinones **284 – 288** showed themselves as anti-HIV agents.[306 – 308]

Lead compounds for further modification and more in-depth pharmacological investigations were identified for many DHPM series. At the current stage of development, combinations of *in silico* and *in vitro* methods are used for chemical structure modification. A relevant task is to study single enantiomers in order to increase the selectivity of agents.[13] The task of development of dual-acting agents is not overlooked either.

Combined use of two targeted chemical agents of different chemical nature but with similar mechanism of action incorporated in a common formulation has started in the therapeutic practice. This principle can be implemented at the molecular level using hybrid molecules in which two pharmacophores are chemically bonded in a single mole-

Table 19. Dihydropyrimidine derivatives that showed noticeable biological activities.

Type of agent	5-Functional group in DHPM					Other DHPMs	Quinazolinones	2-Imines
	ester	carbonyl	carbamoyl	carbonitrile	nitro group			
Analgesics	**32**		**203**, **204**			**250**, **255**, **256**		
Adrenergic blockers	**26**, **50a**, **52 – 59**		**189 – 198**				**283**	
Anti-arrhythmic	**27 – 31**				**219**, **238**, **240 – 242**			
Anti-asthmatic	**29**, **30**							
Antibacterial	**20**, **96**, **123**, **126**, **127**			**212**		**265**, **267**, **269**		**293**
Anti-HIV	**141 – 143**					**142**	**284 – 288**	
Anti-hepatitis	**144 – 147**	**169 – 172**						
Antihypertensive	**20**, **29 – 31**	**176 – 180**	**184**, **184b**, **185 – 188**		**229 – 234**			
Antidepressants	**65**					**249**		
Antidiabetic	**1**, **29**, **30**, **60**, **61**							
Antimicrobial	**90**, **91**, **119 – 122**, **127**, **129**, **130**		**203**, **204**			**251**, **268**, **270**		
Antiproliferative	**74 – 76**, **86**, **89**, **95**, **98**, **99**, **102**, **103**, **108 – 111**	**155**		**208 – 211**		**264**	**290 – 292**	**299**
Antifilarial	**117**, **118**							
Vasodilators	**7**, **8**, **15**, **16**, **21 – 24**, **39**, **40**		**186**		**231 – 234**			**294 – 296**
NO-synthase inhibitors	**42**, **43**							
Bone resorption inhibitors	**72**, **73**							
Inotropic	**25**, **26**				**226**, **229**, **230**			
Ion channel modulators	**14**, **15**, **17 – 20**, **25 – 33**, **35** **45 – 47**	**151**, **152**, **154**	**184**, **184a**		**226**, **229**		**271 – 282**	**294 – 296**, **305**
Antiviral	**2**, **3**, **136 – 138**				**237**			
Anti-inflammatory	**17**, **20**, **34**, **69 – 71**, **112**, **113** **131 – 135**	**69**, **71** **181 – 183**	**203**, **204**	**217**, **218**		**250**, **253 – 256**, **258**, **259**, **267**		**297**, **298**
Antiherpetic	**139**, **140**		**203**, **204**					
Antimalarial	**94**, **104**, **105** **112**, **114**, **116**					**268**		
Antitumour	**74 – 76**, **85 – 95**, **98 – 114**		**201**, **203 – 206**			**261**, **263**		**300 – 302**
Antituberculosis	**20**, **91**, **92b**, **94**, **112**, **114**, **115**		**201**, **202**			**250**, **252**, **260** **266**, **270**		
Spasmolytics	**27**, **28**							
Fungicides, insecticides	**1**, **124 – 128**	**173 – 175**	**207**		**243 – 246**	**252**		
Cytoprotectors	**106 – 108**							
Cytostatics	**84**	**155**, **161 – 168**					**292**, **293**	**308**, **309**

cule.[332, 333] It was shown that doubling of identical chemical moieties in the same molecule is of low value for enhancing the activity.

Primary attention is given to the search for efficient agents for treatment and prevention of socially significant diseases, in particular, cardiovascular and neurodegenerative diseases, all types of cancer, hepatitis B, AIDS, diabetes, tuberculosis and malaria.

A new trend is the design of labelled metal complex compounds to study the pharmacokinetics of compound accumulation, metabolism and excretion from the body.[334]

The extensive range of chemical structures demonstrating various types of biological activity covered in the review provides a reliable basis for further research and improvement of molecules. In recent years, chemists have become interested in the synthesis of 5-functionally substituted dihydropyrimidinones (-thiones) such as thio, sulfinyl, sulfonyl and phosphoryl derivatives, which are functional analogues of the biologically active agents covered in the review. It can be expected that the presence of such groups in a heterocycle would not only change the agent activity and pharmacological profile but also enhance the target-direction and selectivity of their action.

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