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HETEROCYCLIC DIURETICS

I. V. Ukrainets[1]* and N. L. Bereznyakova[1]

Information about the preparation, properties, structure-biological relationships, and the prospects of further development of synthetic heterocyclic diuretics is generalized and systematized.

Keywords: benzothiadiazine, furan, imidazole, indoline, pyrazine, pyridine, pyrimidine, tetrazole, 1,3,4-thiadiazole, thiophene, 4-quinazolone, quinoline, diuretic activity.

Diuretics are substances causing an increased production of urine in an organism thus decreasing the fluid volume in its tissues and serous cavities. This biological property common for all diuretics is of first importance for determining the medical area of their use, i.e. in the treatment of kidney, cardiac, hepatic, and other kinds of edema. Different groups of diuretic medications differ markedly in their mechanism of effect on the organism, their ability to affect the electrolyte balance, indications (or conversely contraindications) for use, side effects, etc. [1-3].

The history of the systematic study and practical use of diuretics amounts to a little more than 50 years. The basis of the current arsenal of the most effective of these medications is a variety of heterocyclic derivatives. In this review we have attempted to follow the steps of creating heterocyclic diuretics, to correlate their structure-biological relationships, and also to determine current trends in the further development of medicines in this pharmacological group.

THIAZIDE DIURETICS

The starting moment for the creation of the first diuretic medications based on heterocyclic compounds was the noticed in 1949 development of acidosis in patients receiving antibacterial sulfanilamides [4]. As it turned out, the effect was due to a concurrent inhibition of carbonic anhydrase in the kidneys while the increased diuresis in the presence of such compounds was explained with the ability to block the same enzyme. Almost at the same time Krebs discovered another characteristic important for subsequent studies, namely, the efficient inhibition of carbonic anhydrase by aromatic and heterocyclic compounds with an unsubstituted sulfamide group [5]. The final result was not long in coming and already in 1951 the novel diuretic 2-acetylamino-1,3,4-thiadiazole-5-sulfamide (acetazolamide) was introduced into medicinal practice after experimental study of some tens of heterocyclic sulfamides. Less known although similar in properties are methazolamide which is acetazolamide derivative with the fixed by the 3-(*N*-methyl) group imino form, and ethoxzolamide (6-ethoxy-2-benzothiazolesulfonamide) [2].

*To whom correspondence should be addressed, e-mail: uiv@kharkov.ua.

[1]National University of Pharmacy, 53 Pushkinska St., Kharkiv 61002, Ukraine.

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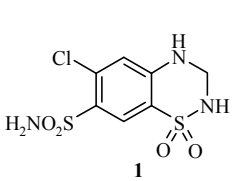
A following advanced study of substances chemically close to acetazolamide led to the preparation of benzothiadiazine diuretics, the progenitor of which was chlorothiazide. However, greater value in medicinal practice was achieved by 3,4-dihydro benzothiadiazine derivatives as the most numerous group approved to medicinal use and brought to industrial production of diuretic agents [2]. The best known of these is hydrochlorothiazide (**1**) which is much more active than its non-hydrogenated precursor and is widely used at the current time.



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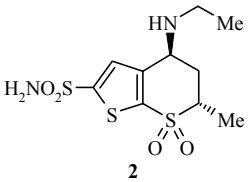

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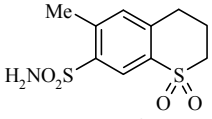

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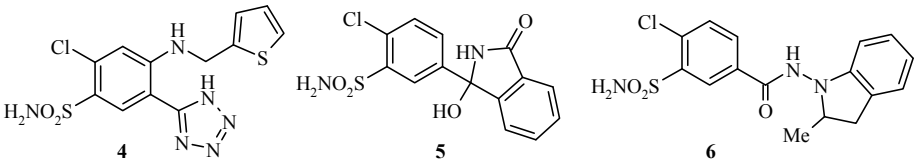
Despite some structural similarity to acetazolamide, benzothiadiazines are much more efficient as diuretics while they are much less able to inhibit carbonic anhydrase. It is interesting that dorzolamide (**2**), although structurally close to benzothiadiazines, has a mechanism of diuretic activity identical to acetazolamide. Its distinguishing feature is the pronounced ability to block carbonic anhydrase in the ciliary body of the eye, thanks to which this medication has been successfully used in ophthalmology for lowering intraocular pressure in glaucoma patients [1]. At the same time another thiopyran diuretic meticrane [3] belongs to the typical thiazide medications [6].

With the aim of improving the biological properties, a chemical modification of both chlorothiazide and hydrochlorothiazide was carried out in many directions by introduction of different substituents and change of specific elements [7, 8]. As a result it was found that the presence of a sulfamide group in position 7 is a totally necessary condition for the appearance of a diuretic effect. An atom of chlorine at position 6 can be exchanged for a bromine or trifluoromethyl group, but not by fluorine. Substituents on the nitrogen atom in position 4 almost completely deactivate the molecule whereas 2-benzyl derivatives prove to be several times more active than non-alkylated analogs. The most pronounced diuretic effects are seen in substances with substituents in position 3 of the benzothiadiazine ring while an increase in the hydrophobicity of this substituent promotes strengthening of the diuretic effect [8].

DERIVATIVES OF SULFAMOYLBENZOIC AND PHENOXYACETIC ACIDS

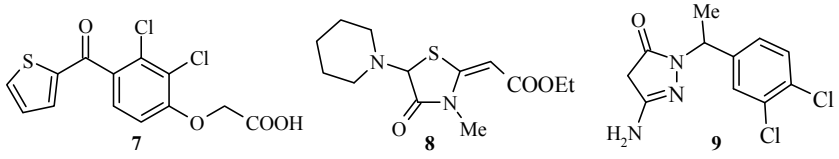
In the mid 1950's Sturm [9] has studied the reaction of 2,4-dihalo-5-sulfamoylbenzoic acids with primary and secondary amines. Pharmacological testing of the *N*-substituted anthranilic acids synthesized in this way showed that one of the compounds, namely 4-chloro-*N*-(2-furylmethyl)-5-sulfamoyl anthranilic acid, had both powerful diuretic activity and also hypotensive action. This substance entered very rapidly into medicinal practice under the name furosemide and is currently used in many countries of the world.

The discovery of such an efficient diuretic as furosemide proved to be the beginning of a large series of works associated with derivatives of aromatic carboxylic and sulfo acids. Hence azosemide (**4**), chlortalidone (**5**), mefruside (containing a tetrahydrofuran ring), chlorexolone (an isoindole diuretic), and piretanide (a pyrrolidinebenzoic acid derivative) were developed [2]. However, these medications have not found a widespread use. There is much more demand in the pharmaceutical market for clopamide, tripamide, and especially indapamide (**6**) [2], differing only in the structure of the heterocyclic fragment. The latter is considered as an optimum diuretic for prolonged treatment of arterial hypertonia [10].



The next stage in the history of diuretics has started with the appearance of medications having novel pharmacological properties. After the thiazide era there followed diuretic agents able to cause both saluretic and uricosuric effects which are very important for treatment of patients with high blood uric acid levels. A requirement for this type of investigation was the study of nephron function and mechanisms of ion transport [11]. As a result, etacrynic acid with clearly pronounced diuretic activity was prepared [2]. This powerful diuretic does not contain any kind of heterocyclic fragments in its structure. None the less we consider it as a striking example of a lead structure serving as a prototype for numerous studies. Attempts to modify etacrynic acid by the introduction of various substituents were not specially successful. In particular, only one compound (the 2,3-dichloro-4-(2-nitrophenyl)phenoxy derivative) out of a large series of aryloxyacetic acids showed activity at the level of the starting molecule [12]. Indazole, benzisothiazole, benzisothiazole-1,1-dioxide, and benzisoxazole derivatives proved more interesting analogs of etacrynic acid. An important role for the heteroatom at position 1 of the heterocyclic ring was noted, the diuretic activity of the corresponding derivatives changing in the following order: O > S > N = SO_2 [13, 14]. Overall, the experimental data in numerous studies carried out until now in the series of aryloxyacetic acids (also including heterocyclic derivatives) has failed to reveal substances which would markedly exceed the standard (i.e. etacrynic acid) in the level of diuretic action [15-17]. Attention should be paid only to tienilic acid (**7**) as the single heteroanalog of etacrynic acid that has found use in medicine [2].

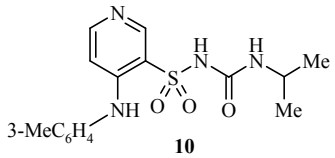
We should also note here etozoline (**8**) and muzolimine (**9**). The structure of these preparations does not have anything in common with etacrynic acid, but the mechanism of the diuretic activity is the same [18, 19].



PYRIDINE DIURETICS

Transition from benzenesulfonic acid derivatives to their pyridine analogs proved very productive. The most successful example of such a change is the currently very popular loop diuretic torasemide (**10**) [2]. The compound is similar to furosemide in its diuretic activity and, although discovered at virtually the same time, the active use of torasemide in the clinic has only started recently. Despite the differences in chemical structure the pharmacodynamics of these medicines in chronic heart failure is approximately the same. At the same time the therapy of torasemide has a series of advantages when compared to treatment with the standard loop diuretic furosemide. It is characterized by improved bioavailability and a prolonged effect which rarely causes the phenomenon of "bounce back", not affecting the function of the proximal renal tubules thus causing a much decreased kaliuretic effect [20].

It is apparent that work to modify benzenesulfonic acids to pyridine analogs has not been limited with that. With time, it has become clear that the presence of a sulfamide group in the pyridine nucleus is not necessary for diuretic activity [21]. Many condensed heterocycles like 3-(2-cyclohexenyl-3-oxo-2,3-dihydro-pyridazin-6-yl)-2-phenylpyrazolo[1,5-*a*]pyridines [22] or 6-methylfuro[3,4-*c*]pyridin-7-ones **11** [2, 23] exhibit diuretic activity.



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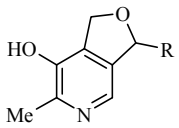

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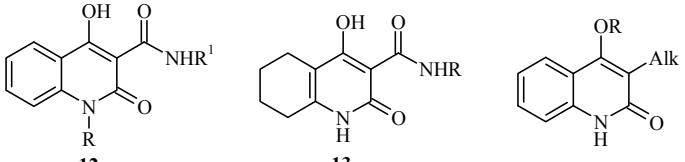
Until recent times, benzannelated pyridines or quinolines and their hydrogenated analogs have been considered as unpromising class of compounds for preparing diuretics. Certainly studies have been carried out [24], but unfortunately without any particular success.

The first positive results were achieved accidentally during biological screening of a small series of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid benzylamides **12** [25]. Following this, targeted studies revealed a number of important features of structure-diuretic activity relationship, characteristic for quinoline-3-carboxamides. Thus, for example, the role of the substituent in the benzene fragment and on the quinoline nitrogen atom has been clearly traced [26]. Broadening the range of the studied objects showed that the diuretic activity is markedly decreased with lengthening of the hydrocarbon chain separating the aromatic ring and the amide nitrogen atom [27]. This dependence is also preserved in 4-methyl-2-oxo-1,2-dihydroquinoline analogs [28].

Replacement of the phenyl ring in the arylalkylamide residue with halogen or a hydroxyl group generally causes a decrease in diuretic activity although in a series of examples it still remains quite high. However, the change to the alkylamides **12** has an unambiguously negative effect on the biological properties [29]. Exchange of the phenyl ring for a furan, tetrahydrofuran, or 1,2,4-benzothiadiazine-1,1-dioxide-3-yl fragment also showed little promise despite the fact that the said heterocycles are contained in the known diuretics. From the whole group of the corresponding hetarylalkylamides **12** that have been studied only few approach the activity level of hydrochlorothiazide [29].

It was interesting that, at first glance, such a small structural rebuild of the molecule as the introduction of a methylene bridge between the heterocyclic ring and carbamide group is accompanied by a diametrically opposite pharmacological effect – 4-hydroxy-2-oxo-1,2-dihydroquinolin-3-ylacetic acid arylalkylamides proved to be quite active antidiuretics [30].

Reduction of the benzene part of the molecule of amides **12** is not so clearly reflected in diuretic properties. In the overwhelming majority of cases a suppression of urine release was observed, and this can be extremely strong (amides **13**, R = 4-fluoro- or 4-methoxybenzyl, 2-picolyl, or piperonyl). At the same time, there are also revealed substances (**13**, R = tetrahydofurfuryl) which are not inferior to hydrochlorothiazide in specific activity at a significantly lower dose.



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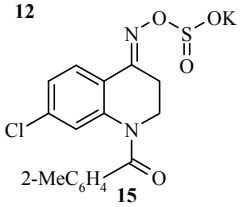

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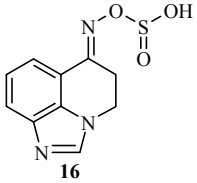

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An unusual tendency was also noted in the study of the effect of the 3-alkyl-substituted 4-hydroxyquinol-2-ones **14** (R = H) on the diuretic function of the kidney. Hence substances with an even number of carbon atoms in the 3-alkyl chain exibit clear diuretic activity and only slightly inferior to hydrochlorothiazide. At the same time, compounds with an odd number of carbon atoms generally do not affect

urine release or, conversely, even lower it. Such a dependence is not evident in the 4-*O*-acyl derivatives **14** (R = AlkCO), although they produce diuretic effect, but quite small [31].

Japanese scientists have studied a series of quinolinone oximes as potential diuretic agents [32]. The highest activity of all the substances studied with a clear saluretic effect was seen in the potassium salt **15**. The efficiency of this compound as regards diuretic, natriuretic, and chloruretic action was significantly greater than hydrochlorothiazide and almost the same as furosemide [33]. The results obtained allow to classify the potassium salt **15** as a "powerful diuretic" [34].

Use of the accumulated data about the dependence of biological activity for this group of chemicals on their chemical structure gradually led to tri- and tetracyclic analogs. The pharmacological studies showed that derivatives of imidazoquinolineoxime-*O*-sulfonic acid **16** deserved attention and they showed diuretic activity comparable with those of the prototype **15** or even higher [35].

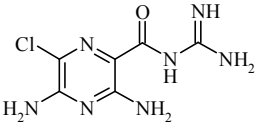
The performed studies allowed to clearly state that the quinolinoneoxime-*O*-sulfonic acids and their derivatives are a novel and promising class of biologically active substances with high diuretic action.

PYRAZINE AND PYRIMIDINE DERIVATIVES

The search for novel diuretics linked with the introduction into the pyridine ring of a further nitrogen atom was interesting from both the theoretical and the practical viewpoint. Numerous pyrazine derivatives [36, 37] were synthesized and studied following this scheme. One of these compounds has showed high diuretic activity and is currently used in medicine under the name amiloride (**17**) [2]. It should be noted that pyrazine derivatives are generally assigned as potassium-sparing diuretics and, particularly importantly, cause a stable hypotensive effect [38].

Attempts to modify the structure of amiloride by exchange of the acylguanidine residue with a bioisosteric 1,2,4-oxadiazol-3-amine fragment have been unsuccessful and the desired increase in diuretic effect has not been achieved [39].

It has been quite interesting to expand the six-membered 1,4-diazabenzene (pyrazine) ring to a seven-membered 1,4-diazepine. Works of this type have been rarely reported, only 1-(2-amino-1-phenylethyl)-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines having been tested as potential diuretics. However, specific dependencies of the interaction between chemical structure and biological activity have been established. In particular, it has been shown that an aminoethyl side chain in position 1 is an absolute prerequisite for the appearance of diuretic activity. The presence of a substituent in position 8, e.g. methylsulfanyl group or halogen, is desirable. Structures with phenyl or 2-pyridyl in position 8 preserve the activity. However, introduction of a phenyl fragment in position 6 proves necessary only in those cases where there is simultaneously a chlorine (but not a bromine) atom present in position 8 [40].



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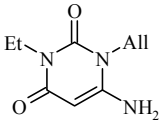

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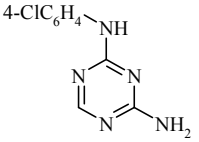

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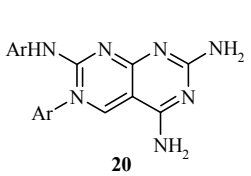
In contrast to pyrazines, their isomeric 1,3-diazabenzenes or pyrimidines do not themselves show diuretic activity. A single representative of this group (aminometradine (**18**) [41]) has little effect and is not being used for a long time. The introduction of a further nitrogen atom into the heterocycle is positively reflected in diuretic properties, the triazine diuretic chlorazanil (**19**) [2] is more active than aminometradine, but is used usually in veterinary practice.

The absence of a pronounced diuretic effect for pyrimidines is more than compensated by numerous related condensed heterocycles, created on their basis. Striking examples of such compounds are the 2-aryl-substituted 1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-4-ones which demonstrate stable properties depending little on the substituents in positions 1, 3, or 6, but mainly determined by the structure of the 2-aryl fragment [42]. A similar picture is seen in the case of 3-*R*-pyrido[3,2-*e*]thiazolo[3,2-*a*]pyrimidines, the diuretic activity of which is directly determined by the chemical structure of the substituent in position 3 [43].

The theoretical rationale for the synthesis of pyrimido[4,5-*d*]pyrimidines **20** was subsequently fully justified structural similarity between the bicyclic nucleus that lies at their basis and pteridine – the compounds studied have been proved to be more powerful diuretic agents than triamterene (**21**) [44].



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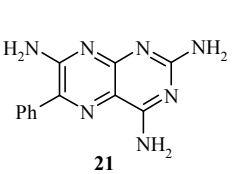

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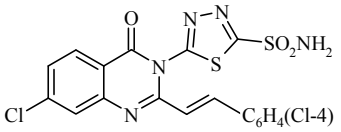

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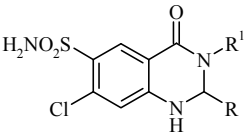

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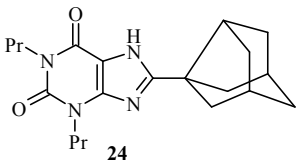
4-Quinazolones or benzopyrimidin-4-ones are a pharmaceutically very important class of heterocyclic compounds. They are characterized by an extremely broad spectrum of biological activities including diuretic [45]. This is not surprising since their 4-quinazolone structures are very similar to benzothiadiazines and are, in principle, their carbo analogs. According to data in a large number of German, United States, Japanese, and British patents a quite diverse chemical modification of the quinazolones mostly preserves the diuretic action at the level of chlorothiazide or even higher.

The relatively simple methods of preparing quinazolones and the availability and variety of starting reagents allow a virtually unlimited change in the base structure to achieve optimum results. For example, combining in a single molecule quinazolin-4(3*H*)-one and thiazole or 1,3,4-thiadiazole heterocycles was carried out with the specific aim of examining how such a combination is reflected in the overall properties of the molecule, knowing about the potentially high diuretic activity of their components. Pharmacological evaluation showed that several of the compounds obtained have a marked diuretic action, in particular the thiadiazolyl quinazoline **22** [46].

At the same time 3-amino-2-methylquinazolin-4(3*H*)-one derivatives did not at all affect the renal excretory function [47].

It should be noted that the diuretic activity of quinazolones after hydrogenation of the N(1)–C(2) bond in their nucleus is markedly increased. Position wise this corresponds to the C(3)–N(4) bond of benzothiadiazines, and their reduction is accompanied by the same effect (see the above reported change from chlorothiazide to hydrochlorothiazide). Likely the best known diuretic agents in group of hydrogenated quinazolones are fenquizone (**23**, R = Ph, R^1 = H) and metolazone (**23**, R = Me, R^1 = *ortho*-tolyl) [2].

Xanthines deserve special attention as another type of bicyclic pyrimidine derivative. Being an important class of adenosine receptor antagonists [48], these compounds sometimes exhibit extremely high diuretic activity. For example, noradamantyl xanthine **24** has been proposed as a promising medication for acute renal insufficiency [49]. By the mechanism of action, this compound proved to be a selective and powerful adenosine A1 receptor antagonist causing a marked increase in the volume of urinary output with predominant excretion of sodium, but little loss of potassium [50].



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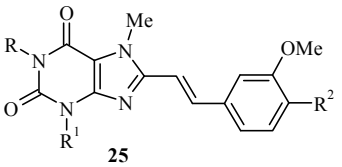

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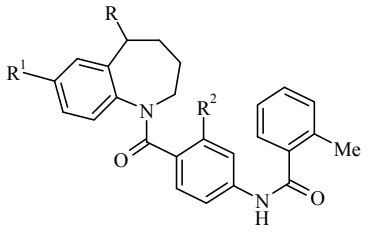
It was found that the selectivity of action of xanthines on one or another adenosine receptor is determined by the nature of the substituent in position 8 of the purine ring. Hence a change of the noradamantane fragment for a styryl also changes the receptor target. In particular istradefylline (**25**, R = R^1 = Et, R^2 = OMe), MSX-2 (**25**, R = CH_2CN, R^1 = $(CH_2)_3OH$, R^2 = H), or MSX-3 (**25**, R = CH_2CN, R^1 = $(CH_2)_3OPO(ONa)_2$, R^2 = H) [51] are not selective antagonists of A1, but exclusively of adenosine A(2A) receptors. These compounds successfully combine in their properties a positive inotropic action and a clear diuretic effect, thanks to which they are recommended for clinical studies as promising agents for treating heart failure.

Generally it should be noted that adenosine receptor antagonists prove extremely useful for preventing and treating numerous human illnesses including disorders of the cardiovascular and central nervous systems as well as many other pathological states in which diuretic activity is very important. It is quite evident that the medico-biological potential of xanthines in this context is still a long way from exhausted and that scientific studies in this area will continue.

DIURETICS OF DIFFERENT CHEMICAL GROUPS HAVING EFFECTS ON THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Discovery of the antidiuretic hormone vasopressin became a stimulus in the search for novel medications which are angiotensin II receptor antagonists (AT-1 receptor blockers). Angiotensin II is a basic peptide of the renin-angiotensin-aldosterone system. Under its influence, blood vessels are strongly narrowed and hence arterial pressure rises quickly. It also stimulates the aldosterone secretion and, at high concentrations, increases the secretion of an antidiuretic hormone. Long term studies have shown that prolonged activation of the renin-angiotensin-aldosterone system is one of the main pathogenic mechanisms for the progression of cardiovascular diseases. Therefore, compounds targeted to act on individual members of this system, in principle, can be used for treating ischemic heart disease, arterial hypertension, and heart failure.

Apart from common diuretics one group of such medications are the angiotensin II inhibitors. Experiments have shown that a variety of different compounds can block angiotensin II formation or its action, thus lowering the renin-angiotensin-aldosterone system activity. The first member of this group of medicines introduced therapeutically in 1971 was saralasin which is a peptide compound close in structure to angiotensin II. However, for many reasons including the presence of agonist activity, too difficult synthesis, and the need for parenteral administration it has never received widespread practical use. Only very recently, it became possible to prepare a nonpeptide selective AT-1 receptor antagonist which preserved the efficiency by the oral route, namely OPC-31260 (**26**, R = NMe_2. R^1 = R^2 = H). This compound blocks antidiuretic hormones, i.e. the mechanism of its diuretic activity is markedly different from other diuretics [52]. In addition, if, for example, furosemide causes an increased excretion of Na^+ and K^+ then following use of OPC-31260 the organism loses only insignificant amounts of Na^+ [53]. It is interesting that OPC-41061 or tolvaptan (**26**, R = OH, R^1 = Cl, R^2 = Me) prepared by the same principle has a possibility of also blocking arginine-vasopressin V2 receptors [54]. This preparation exceeds furosemide in increasing diuresis [55] and has been well recommended for renal [56] and heart [57] failure treatment.



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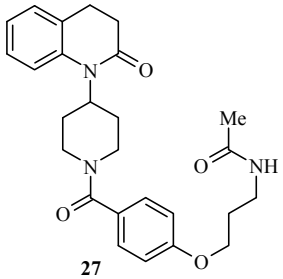

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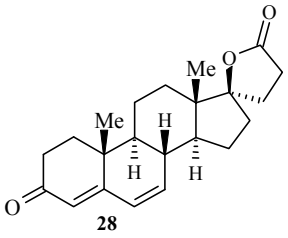
Similar properties have also been demonstrated by quinolinone **27** or OPC-21268 [58]. At the present time the list of synthetic nonpeptide selective AT-1 blockers has been markedly increased and the use of several preparations of this type have been approved worldwide which are based on tetrazole (valsartan, irbesartan, candesartan, losartan, tasosartan), imidazole (eprosartan), or benzimidazole (telmisartan).

A separate group of clinically important medications influencing the activity of another member of the renin-angiotensin-aldosterone system comprises aldosterone antagonists. The first medicine of this type was spironolactone. For a long time this has been considered the only diuretic enabling efficient removal of excess fluid from the abdominal cavity [1, 2]. Although prepared at the same time as spironolactone the similar in structure and activity canrenone (**28**, lactone form) which is often used as the potassium salt of the free acid (potassium canrenoate) has only received very limited usage [41].



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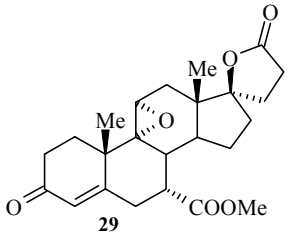

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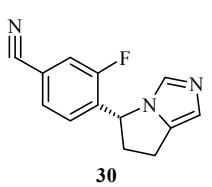
Only quite recently there has been registered and released to the world pharmaceutical market a novel competitive aldosterone receptors blocker eplerenone (**29**) which possess simultaneously the diuretic activity and effect on the vascular wall. Its main difference from spironolactone is a higher selectivity towards the mineralocorticoid receptors. In addition eplerenone is characterized by a much greater tolerance and lower frequency of side reactions, and the presence of the 9α,11α-epoxy group removes the unwanted antiandrogenic effects typical for spironolactone. At present, this preparation is included in the protocols of treating postinfarction heart failure and arterial hypertension [59] by recommendations of the leading world cardiology communities.

An alternative for use of competitive aldosterone antagonists in overcoming the unwanted action of this hormone may become a quite different route to resolving the problem in the near future. It is proposed not to block access of the aldosterone to the corresponding receptors, but generally to stop its production at the right moment by neutralization of the aldosterone synthetase. The enzyme catalyzes the three final stages of the biosynthesis of aldosterone while in patients with cardiovascular pathology it is always observed in increased concentration. For this reason the development of efficient and safe aldosterone synthetase inhibitors is currently one of the most promising routes to the medicinal therapy of heart failure and arterial hypertension [60].

So far there are unfortunately no medications of this type officially approved for the medical use. However, the potential aldosterone synthetase inhibitor 4-[(5*R*)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-5-yl]-3-fluorobenzonitrile (**30**) (LCI699) [61] is undergoing the final stage of clinical trials. It is interesting that in the homologous compound 4-[(5*R*)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridin-5-yl]benzonitrile (or FAD286) only one enantiomer with the same (*R*)- configuration at the chiral center possesses similar biological properties. The racemic product inhibits a totally different (aromatase) enzyme and is used under the name fadrozole for treating estrogen dependent breast cancer [62].



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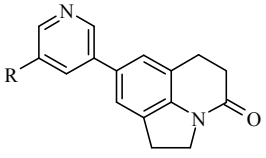

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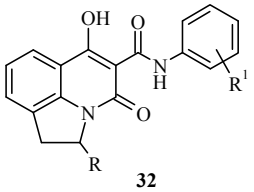

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The search for novel aldosterone synthetase inhibitors has been quite successful among the series of imidazole [63], pyridine [64] and quinoline [65] derivatives. The last successful and promising discovery was the tricyclic pyrroloquinolines **31** with high selectivity and possibility for oral administration [66].

Attention is drawn to the structural similarity of these compounds with the pyrroloquinoline-5-carboxylic acid anilides **32**. On its own this fact, of course, has little importance. However, considering the high diuretic activity of the anilides **32** [67, 68], their modest kaliuretic action, low toxicity, pronounced dehydration activity, and ability to lower arterial pressure in hypertensive animals, the interest in such objects is markedly increased. It is not to be discounted that part of the biological effects caused by them is, in fact, realized through the mechanism of lowering the aldosterone production.

In recent times, novel pharmacological properties are often discovered in well known diuretics, which open up the possibility of using these far from new medicines in quite unexpected areas of application. It was found that several diuretics have reasonable chances of success in the control of bronchial asthma [69], epilepsy [70], diabetes insipidus [71], glaucoma [72], and even oncologic [73] and neuropsychiatric disorders, which clearly deviates from areas of their traditional usage.

There is also a significant medical interest in diuretics which exhibit also anti-inflammatory [74], cholagogue [75], antimicrobial [76], and other useful properties. Even a brief look at the specialist scientific literature allows one to note a progressive broadening of the list of indications of the usage of diuretics in the clinical practice. However, in the last 30 years there has not appeared on the world pharmaceutical market a single new medication to be claimed principally as a diuretic. Latest technological advancements have found use in this area only as improving of certain properties of already known substances and creation of novel medical forms based on them. The prolonged action diuretic Indapamide retard [77] is an example. But even in this case the aim of the study was to attempt an approximation to an "ideal" antihypertensive and not a diuretic medication. In other words, under current conditions there are hardly any serious prospects for "pure" diuretics. Nowadays there are demands for complex activity products permitting both increased excretion of fluid from the organism and effectively resisting such global human problems like cardiovascular and other widespread diseases. It is most likely that this tendency will continue in the nearest future.

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