

## GENESIS OF PHARMACEUTICALS: FROM PRONTOSIL RUBRUM TO ANTIPSYCHOTICS – A HISTORY OF SULFA DRUGS FROM THE PERSPECTIVE OF MEDICINAL CHEMISTRY

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### ABSTRACT

Based on research conducted on dye Prontosil Rubrum, it was possible to obtain the first synthetic bacteriostatic, the sulfas, which present sulfanilamide as its pharmacophore. This prototype made possible to obtain pharmaceuticals of different pharmacological classes, such as diuretics, hypoglycemics, anti-inflammatories, antipsychotics, anti-leprosy drugs and antiadrenergics. This paper intends to report, through a bibliographic review, the structural alterations that characterize the different therapeutic classes of sulfanilamide derivatives, through chemical structure versus pharmacological activity relationship analysis. As a result, it was observed that some chemical groups are essential to define the pharmacological action. Diuretic drugs derived from sulfanilamide present groups of benzothiazide, thiaziazole and associated to sulfamoylbenzoic acid in their chemical structure. As for hypoglycemics, they present the group sulfonylurea in their chemical structure. In the chemical structure of oxicams, there is cyclization of the pharmacophore, 4-hydroxy-2-methyl-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The coxibs present in their chemical structures two aromatic rings linked by a furan or trifluoromethyl pyrazole ring, the antipsychotics show the group N-(pyrrolidin-2-yl)-sulfonylbenzamide. Thus, it is clear that through knowledge of Medicinal Chemistry, and only one prototype, it was possible to obtain several important drugs for therapeutic throughout history.

**Keywords:** SAR; sulfas; sulfa derivatives; genesis of pharmaceuticals.

### INTRODUCTION

According to the International Union of Pure and Applied Chemistry (IUPAC), medicinal chemistry is responsible for discovering, identifying, developing and preparing prototypes. In addition, it covers pharmacokinetic knowledge (absorption, distribution, metabolism and excretion) on a new drug and establishes its structure-activity relationship (SAR). For this purpose, in order to obtain more efficient drugs, biology, pharmacy and medicine knowledge must be used.<sup>1</sup>

When it comes to sulfas, history starts on the late 20s from last century. German chemical industry I.G. Farbenindustrie produced several types of synthetic dye. Due to the necessity of antibacterial substances, the industry started a research program, searching for the possibility of modifying some of their products which owned medicinal potential.<sup>2,3</sup>

In 1932, Gerhard Domagk showed that Prontosil Rubrum (red dye) protected rabbits and mice infected with hemolytic Staphylococci and Streptococci. Some time after the discovery, Domagk's daughter had a septicemia. Prontosil was administered and worked. Based on the success, I.G. Farbenindustrie patented the substance and Domagk received a Nobel Prize in Medicine in 1939.<sup>3</sup>

Later, it was observed that Prontosil is a pro-drug, as it did not show antibacterial activity *in vitro*, and it needs to be bio activated on hepatic level to show its pharmacological effect. This way, the active metabolite is sulfanilamide.<sup>4</sup> Prontosil Rubrum metabolization is shown in Figure 1.

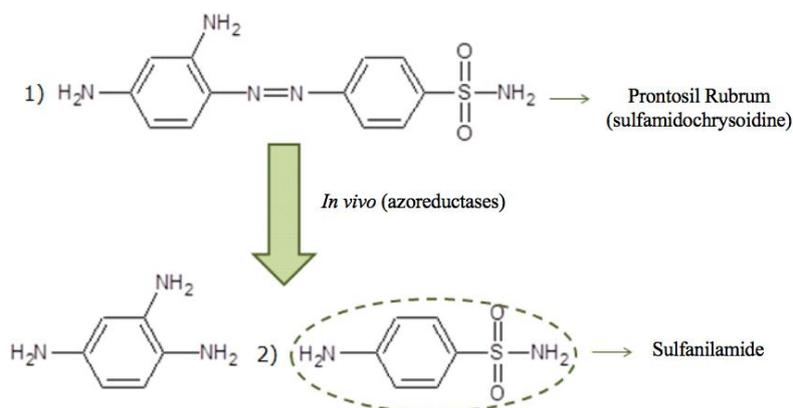


Fig. 1: Prontosil Rubrum metabolization

Sulfanilamide is the pharmacophore of sulfas.<sup>5</sup> The “para” position of the sulfanilamide ( $N_1$ ) will have substituents responsible for defining the hydrophilic characteristics of each drug and a  $N_2$  connected directly to the sulfoxide, which substituents will provide the lipophilic properties of each molecule (Figure 2).

From the sulfonamides' pharmacophore it was possible to obtain topic and systemic action sulfas and drugs with different pharmacological activities, such as hydrochlorothiazide, sulfonyleureas, amisulpride and others. This way, the present paper proposes to analyze the chemical structures of the main sulfa derived drugs, making a relationship between chemical structure and pharmacological activity, under the perspective of medicinal chemistry.

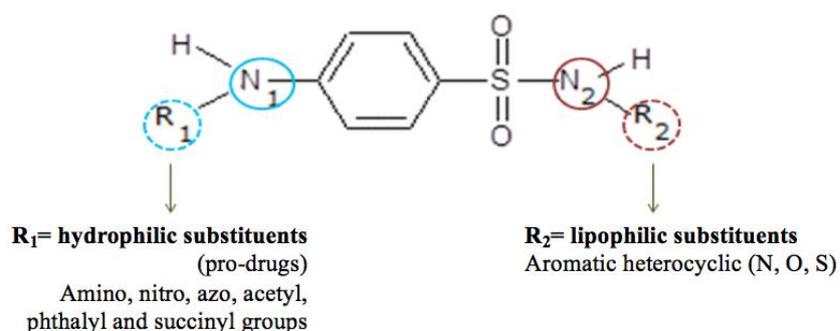


Fig. 2: Sulfanilamides' pharmacophore

## CHEMICAL STRUCTURE *versus* PHARMACOLOGICAL ACTIVITY RELATIONSHIP OF SULFAS AND DERIVATIVES

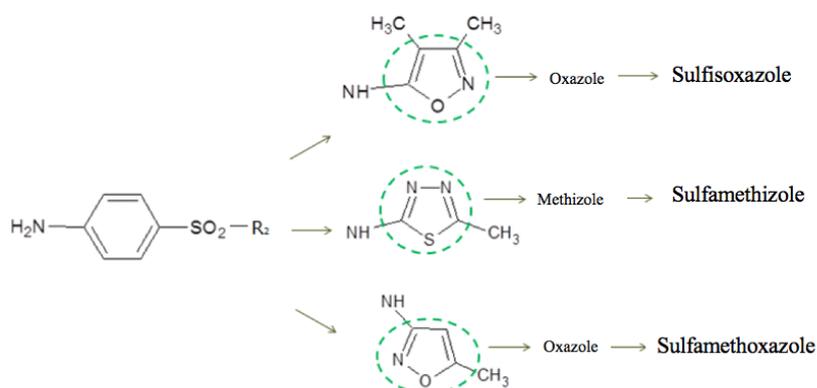
### SAR analysis of antibacterial sulfonamides

PABA (p-aminobenzoic acid) is essential for folic acid synthesis, needed for bacterial growth. Sulfonamides, PABA analogues, by inhibiting dihydropteroate synthase do not allow folic acid, purine and nucleic acids production, showing bacteriostatic action.<sup>6,7</sup> Sulfonamides can be divided in three big groups: oral systemic action, oral local action and topic use sulfas. Oral systemic action sulfas are classified according to their half lives ( $T_{1/2}$ ) in: short, intermediate and long-acting.<sup>6</sup>

### SAR of oral sulfonamides of systemic action

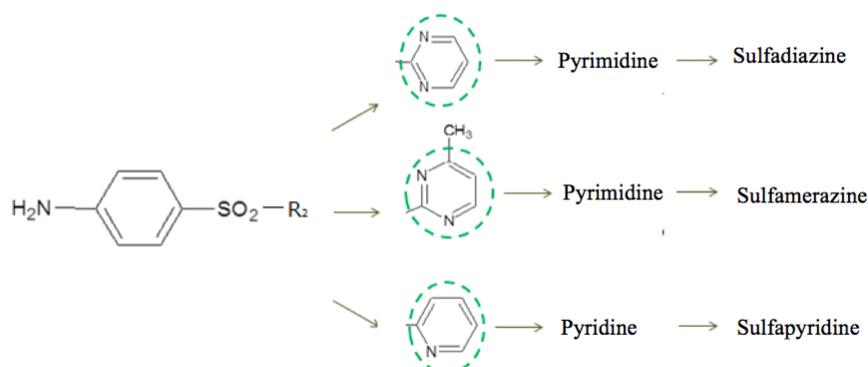
Sulfisoxazole, sulfamethizole and sulfamethoxazole (Figure 3) are short-acting oral drugs used on urinary infection treatment.<sup>6</sup> By observing their chemical structures we can notice that these drugs hold low lipophilicity radicals on  $R_2$ , five members heterocyclic, such as oxazole and methizole, justifying their short and systemic action. Besides the oxazole ring, sulfisoxazole owns two methyl

groups that enable extensive binding to plasmatic proteins.<sup>8</sup> Sulfamethizole shows a methizole ring and a methyl as radicals. Sulfamethoxazole, as sulfisoxazole, shows an oxazole ring, but only one methyl group bonded to it. Their half life is 6, 9 and between 10 and 12 hours, respectively.<sup>9</sup>



**Fig. 3: Short-acting sulfas**

Differently from short-acting sulfas, intermediate-acting sulfas (Figure 4) present in  $R_2$  more lipophilic groups, such as six members heterocyclic constituted of carbons and electron accepting elements present on drugs from this group. Sulfadiazine presents a pyrimidine ring as radical, with intermediate lipophilicity, resulting in a 10 to 17 hours half life. When used with pyrimethamine it is very effective to treat acute toxoplasmosis thanks to their synergic action.<sup>10</sup> The same way, sulfamerazine with intermediate-acting effect and  $T_{1/2}$  between 4 and 7 hours, shows as radical in  $R_2$  a pyrimidine ring, like sulfadiazine, differing only by being substituted with a methyl group, ensuring its binding to plasmatic proteins.<sup>8</sup> Sulfapyridine has a  $T_{1/2}$  of 17 hours and a pyridine ring as radical that, the same as the pyrimidine ring, justifies its systemic action.<sup>10</sup>



**Fig. 4: Intermediate-acting sulfas**

Sulfadoxine is the only long-acting sulfa available in the USA and is used together with pyrimethamine as second line treatment for malaria.<sup>11</sup> As substituent in  $R_2$ , it shows a pyrimidine ring bonded to two methoxyl groups. These groups provide a high liposolubility to the structure, leading to a high  $T_{1/2}$ , of 7 to 9 days, and extensive binding to plasmatic proteins.<sup>10</sup> Sulfalene, also used in combination with pyrimethamine on the treatment of malaria, shows a very similar structure to sulfadoxine, with a pyrazine ring bounded to only one methoxyl group. This substituent provides a  $T_{1/2}$  of about 62 hours for the drug.<sup>12</sup> The chemical structures of sulfadoxine and sulfalene are observed in Figure 5.

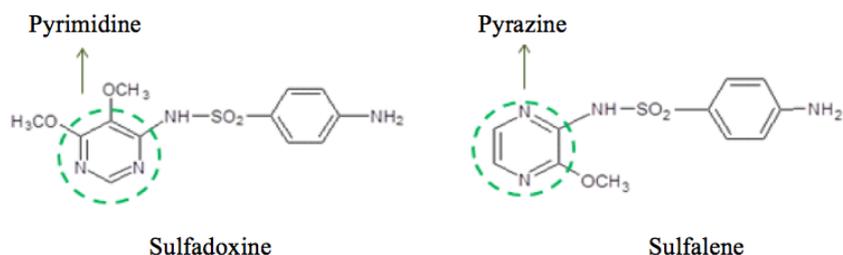


Fig. 5: Long-acting sulfas

### SAR of oral sulfonamides of local action

Drugs from this class are pro-drugs and show in  $R_1$  substituents that provide hydrosolubility, such as phthalyl and succinyl groups, having local action. On the other hand, they also show substituents that allow increase in half life.

Sulfasalazine (Figure 6) shows in  $R_1$  a hydrosoluble group phthalyl substituted with a hydroxyl group. Its half life is 3 to 7 hours, provided by the presence of a pyridine ring.<sup>6</sup> Phthalylsulfathiazole shows in  $R_1$  a phthalyl ring and a carbonyl group, both groups providing hydrosolubility. It also shows in  $R_2$ , a thiazole ring, with intermediate lipophilicity.<sup>9</sup> It is suggested that its half life is inferior to sulfasalazine, since it shows a lower lipophilicity. Succinylsulfathiazole shows in  $R_1$  a succinyl group. By comparing the importance of substituents in  $R_1$ , succinyl versus phthalyl groups, found in the same position of sulfasalazine and phthalylsulfathiazole, we can see that it allows the drug succinylsulfathiazole to be more hydrosoluble and to have a lower  $T_{1/2}$ . The same as the phthalylsulfathiazole shows a thiazole in  $R_2$ , that provides an intermediate-acting to the molecule, not eliminated so quickly.

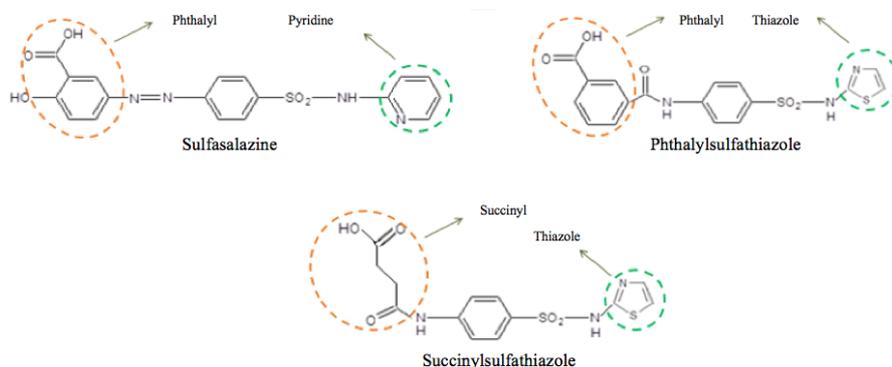


Fig. 6: Local action sulfas

### SAR of topical use sulfonamides

Topical use sulfas (Figure 7) show alkyl substitutions and only sulfadiazine presents a heterocycle in  $R_2$  for the fact that it is also used orally.

Sulfacetamide is used topically for the treatment of bacterial conjunctivitis as well as adjuvant on the treatment of trachoma. Its  $T_{1/2}$  is of 7 to 12 hours due to the presence of a methyl group belonging to acetamide in  $R_2$ , a hydrosoluble radical.<sup>13</sup> The presence of non-heterocyclic groups in  $R_2$  of the molecule allows the drug not to be absorbed systematically and remain in the conjunctive for local action. Mafenide shows a carbon between the aromatic ring of the pharmacophore and  $N_1$  and it is used topically for the treatment of burns. However, because it is applied in lesions it is almost always absorbed, bringing some limitations for its use, once its primary metabolite can cause metabolic acidosis by inhibiting carbonic anhydrase.<sup>6</sup> Sulfadiazine, oralof intermediate-acting, when used topically to avoid infections in burns is preferred over mafenide because of its lower toxicity when absorbed.<sup>10</sup> Its absorption happens due to the presence of a pyrimidine ring in  $R_2$ , that provides lipophilicity to the molecule. Sulfabenzamide shows a benzamide radical in  $R_2$ , providing with lipophilicity.

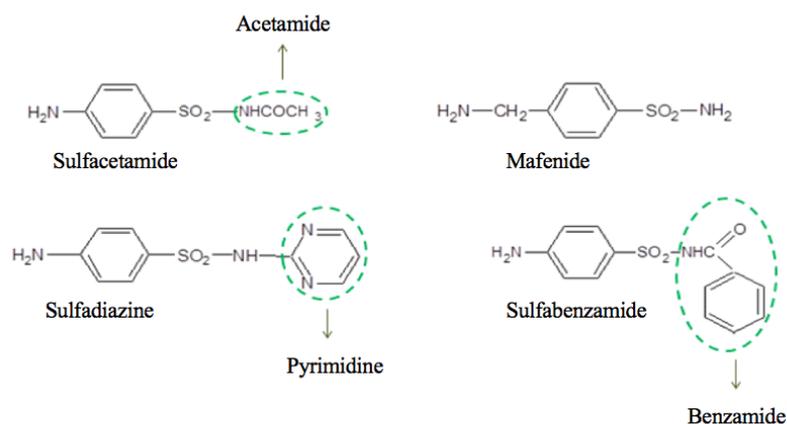


Fig. 7: Topical use sulfas

## SAR ANALYSIS OF DIURETIC ACTION SULFONAMIDES

### SAR of carbonic anhydrase inhibitor diuretics

Carbonic anhydrase inhibitor diuretics were synthesized after the knowledge on metabolic acidosis as an adverse effect when sulfanilamide was used on chemotherapy. Based on this, their activity as carbonic anhydrase inhibitor was verified and acetazolamide, dichlorphenamide and methazolamide were synthesized.<sup>6</sup> The main characteristics on drugs belonging to this class is that they are non-substituted sulfonamidic derivatives, resulting in a less lipophilic molecule and contributing for a lower half life. The pharmacophore of carbonic anhydrase inhibitor diuretics (Figure 8), differently from sulfanilamide prototype, shows a five members heterocyclic, 1,2,3-thiadiazole, favoring the diuretic activity.

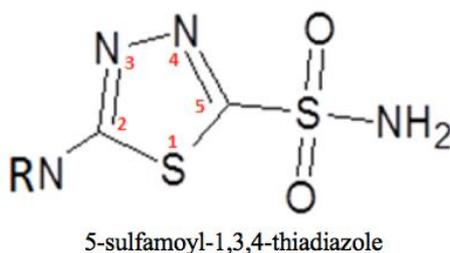


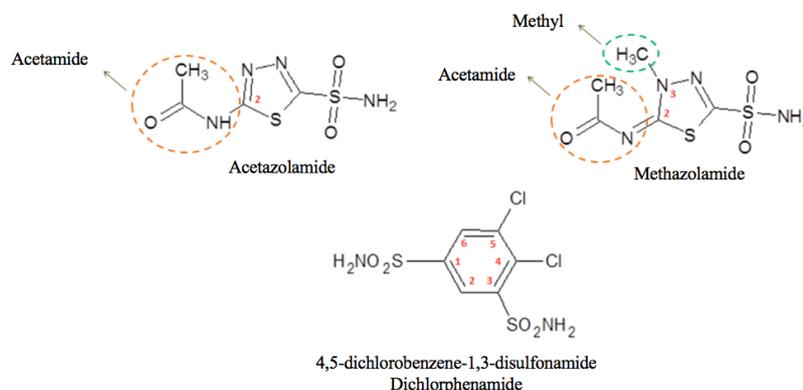
Fig. 8: Carbonic anhydrase inhibitor diuretics' pharmacophore

In this class of diuretics, we can observe that acetazolamide and methazolamide share similar chemical structures, with 1,3,4-thiadiazole ring in their structures, differently from dichlorphenamide, that presents a different pharmacophore, a benzene instead of 1,3,4-thiadiazole.

Acetazolamide (Figure 9), class prototype, shows in position 2 an acetamide group that provides hydrosolubility to the drug and facilitates its renal elimination. The presence of a methyl group from acetamide makes acetazolamide have an increase in  $T_{1/2}$  and bind to plasmatic proteins, remaining bioavailable for a longer time. Based on this, acetazolamide's half life varies between 10 and 15 hours and 90% of the drug binds to plasmatic proteins.<sup>14</sup>

Methazolamide is used topically on the treatment of open angle glaucoma or ocular hypertension with insufficient response for beta-blockers, through reduction of intra-ocular pressure.<sup>10</sup> It has a half life of about 14 hours, justifiable by its chemical structure.<sup>14</sup> In position 2, the structure is substituted with an acetamide group, explaining its topical use. This radical provides the drugs with hydrosolubility, however, this hydrosolubility is not meaningful due to double bond resonance. Besides, the presence of a methyl group in position 3 results in binding to plasmatic proteins, contributing to high half life and bioavailability of the drug. It differs from acetazolamide by the presence of a 1,2,3-thiadiazole ring substituted with a methyl group in position 3.

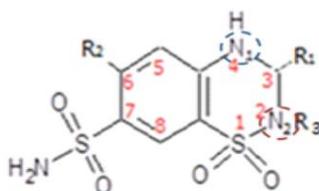
Dichlorphenamide, instead of the 5-sulfamoyl-1,3,4-thiadiazole ring, has as pharmacophore 4,5-dichlorobenzene-1,3-disulfonamide. The presence of chlorine, electronegative element in positions 4 and 5, provides with liposolubility to the molecule and maximum diuretic activity for the drug. Oxygen atoms in positions 1 and 3 favor renal elimination. With these molecular characteristics it is suggested that dichlorphenamide's bioavailability and half life are intermediate. In addition, the presence of two sulfonamidic groups results in an increased diuretic activity for the molecule, however, it is observed a decrease in carbonic anhydrase inhibition.



**Fig. 9: Chemical structures of acetazolamide, methazolamide and dichlorphenamide**

#### SAR of thiazide diuretics

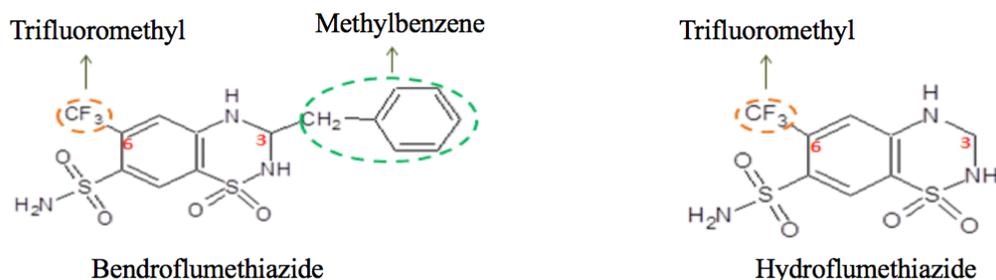
Thiazide diuretics are commonly prescribed drugs that emerged as a consequence of research for more potent carbonic anhydrase inhibitor drugs.<sup>10,15</sup> However, it was noticed that these increase the excretion of NaCl, independent of carbonic anhydrase inhibition. These diuretics share very similar chemical structures.<sup>6,16,17</sup> The binding to plasmatic proteins in this class, provided by the presence of a methyl group in the molecule, is variable and is determinant for tubular release of thiazides. On Figure 10 we notice the pharmacophore of thiazide diuretics. Substitutions that will alter its pharmacokinetics characteristics are in positions 3 and 6. Drugs belonging to this class have big structural similarity, differing only in positions 3 and 6 substituents. The main difference between these diuretics is the change of the electronegative element in position 6, that will imply directly on half life of the drugs.



3,4-dihydro-2H-1,2,4-benzothiazide-7-sulfonamide-1,1-dioxide

**Fig. 10: Thiazide diuretic's pharmacophore**

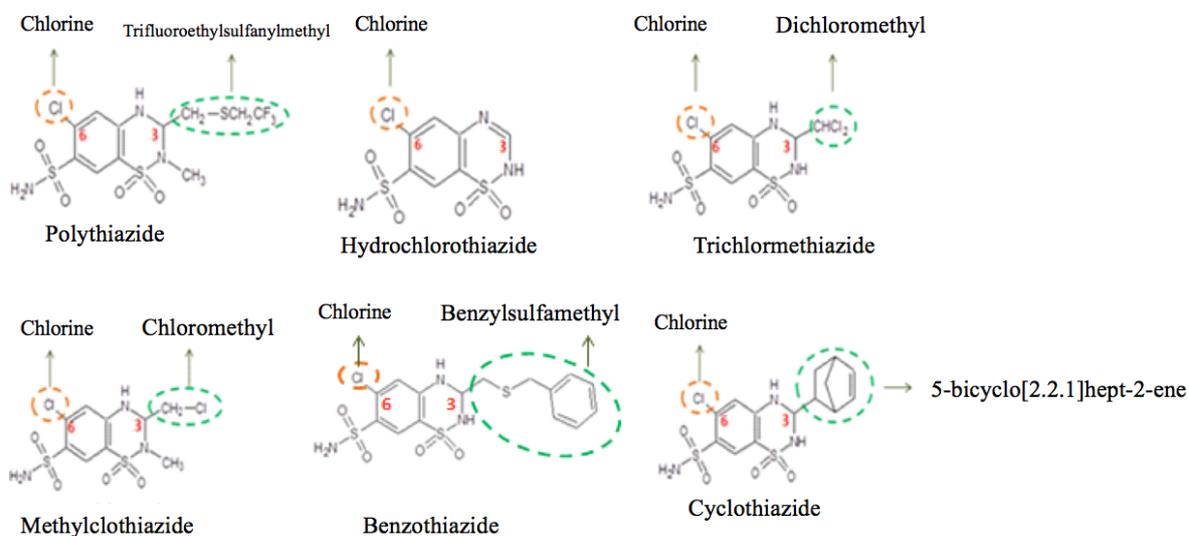
The presence of electronegative element of position 6 of the molecule is essential for diuretic activity on drugs from this class. Bendroflumethiazide and hydroflumethiazide (Figure 11) have half lives of 8,5 hours and between 12 and 27 hours respectively. This is due to the fact that they show in this position a trifluoromethyl group, and fluorine is an electronegative element that contributes directly to an increase in liposolubility and, consequently, on half life.<sup>14,18</sup> Additionally, bendroflumethiazide has in position 3 a methylbenzene group, making it more liposoluble.



**Fig. 11: Chemical structures of bendroflumethiazide and hydroflumethiazide**

Polythiazide, hydrochlorothiazide, trichlormethiazide, methylclothiazide, benzothiazide and cyclothiazide (Figure 12) have a shorter half life compared to drugs on Figure 11. This difference can be explained by their chemical structures, once these drugs are less liposoluble for having in position 6 a chlorine atom, instead of fluorine, and electronegativity provides lipophilicity to the molecule.

From these drugs, polythiazide has the highest  $T_{1/2}$ , of 25 hours, followed by hydrochlorothiazide that has  $T_{1/2}$  between 5,6 and 14,8 hours and trichlormethiazide with  $T_{1/2}$  between 2,3 and 7,3 hours.<sup>19,20</sup> In addition, polythiazide shows in position 3 a radical trifluoroethylsulfanylmethyl that increases its lipophilicity and allows the drug to remain for longer in the organism. Trichlormethiazide has in position 3 a dichloromethyl group, and methylclothiazide has, in the same radical, a chloromethyl group. These increase the lipophilicity of the molecules, contributing for a longer acting time, but inferior to polythiazide's. Benzothiazide has in position 3 a benzylsulfamethyl group and, the same as cyclothiazide that has in this position a 5-bicyclo[2.2.1]hept-2-ene, shows an inferior lipophilicity compared to drugs with electronegative elements in this position, chlorine and fluorine.

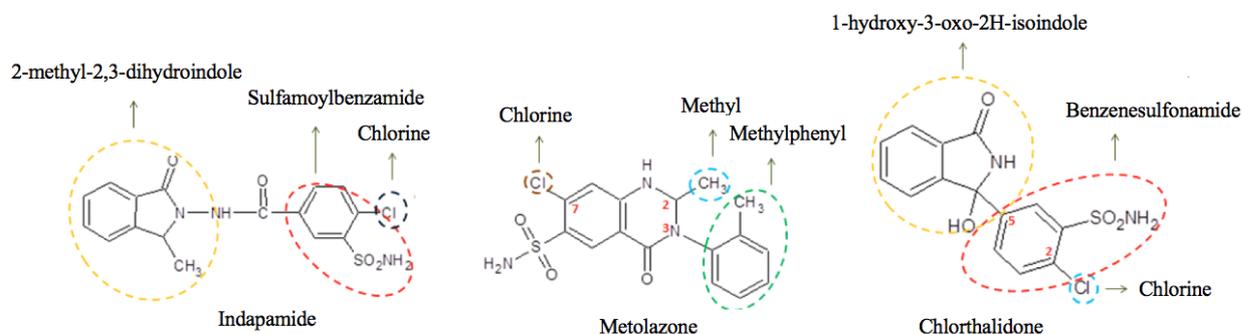


**Fig. 12: Chemical structures of polythiazide, hydrochlorothiazide, trichlormethiazide, methylclothiazide, benzothiazide and cyclothiazide**

The differences between  $T_{1/2}$  come from the fact that when the drug is administered orally it suffers first-pass metabolism on the liver, where part of the drug will be degraded decreasing its bioavailability and consequently  $T_{1/2}$ . When the drug is administered intravenously, it does not suffer this metabolism and, therefore, will not be degraded and will have a longer half life.<sup>21</sup>

Metolazone and indapamide (Figure 13) are used to treat congestive heart failure, where the anti-hypertensive action is extra renal causing a decrease of the vascular hyperactivity and a reduction in total arteriolar and peripheral resistance. Indapamide presents structural similarities compared to thiazide diuretics for having a sulfamoylbenzamide group. However, what differs its structure is the absence of the double ring system, characteristic of the class. The presence of sulfamoylbenzamide group and chlorine provides with lipophilicity to the molecule, that has a half life of approximately 14 hours. The 2-methyl-2,3-dihydroindole group provides with hidrosolubility to the drug and facilitates its

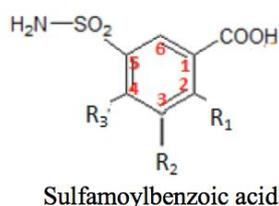
metabolism.<sup>22</sup> Metolazone shows a double ring system characteristic of thiazide diuretics on the pharmacophore and, the same as indapamide, it has a half life of approximately 14 hours.<sup>23</sup> It shows in position 2 a methyl group, in position 3 a methylphenyl group and a chlorine in position 7, that provide with high lipophilicity to the drug. Chlorthalidone, used to treat hypertension and edema, has a  $T_{1/2}$  of 40 hours<sup>24</sup> that can be explained by the presence of a chlorine in position 2 and a 1-hydroxy-3-oxo-2H-isoindole group in position 5, providing with high lipophilicity. 1-hydroxy-3-oxo-2H-isoindole group allows its metabolism.



**Fig. 13: Chemical structures of indapamide, metolazone and chlorthalidone**

### SAR of loop diuretics

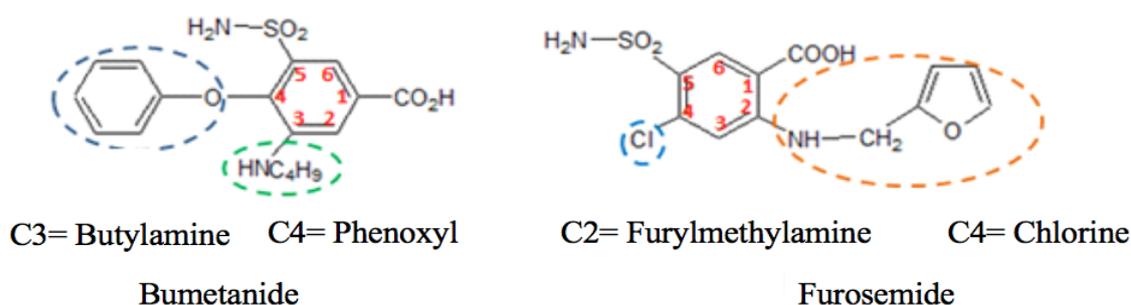
These drugs inhibit the transport of NaCl to the interior of the tissue by a co-transport membrane system, acting on the rising portion of Henle's loop.<sup>24</sup> These diuretics have the highest therapeutic efficacy due to high capacity of NaCl reabsorption and the fact that their diuretic action is not limited by development of acidosis, differently from what happens with carbonic anhydrase inhibitors.<sup>10</sup> The pharmacophore of this class is represented on Figure 14.



Sulfamoylbenzoic acid

**Fig. 14: Pharmacophore of loop diuretics**

Bumetanide and furosemide (Figure 15), both belonging to this class, bind extensively to plasmatic proteins, around 95 and 98% and, for that reason, their release for the tubules through filtration is limited.<sup>6</sup> The presence of sulfamoylbenzoic acid observed in both molecules is essential for diuretic activity. This action is due to substitution with phenoxy on bumetanide and furylmethylamine and chlorine on furosemide in position 4 of the pharmacophore, providing increase on pharmacological potency.<sup>24</sup>

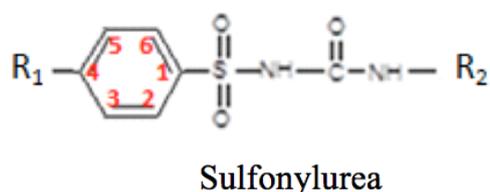


**Fig. 15: Chemical structures of loop diuretics**

Due to the presence of carboxylic acid, a highly hydrosoluble radical,  $T_{1/2}$  is approximately 1 hour for bumetanide and 2 hours for furosemide.<sup>14</sup> By observing the chemical structure of these drugs we can notice this difference, once furosemide shows in position 4 a chlorine that provides more liposolubility and a furylmethylamine group in position 2. On the other hand, bumetanide shows in position 3 a butylamine group and in position 4 a phenoxy group, both with lower lipophilicity, justifying the shorter  $T_{1/2}$ .

### SAR analysis of sulfonamides of hypoglycemic action

Sulfonylureas had their hypoglycemic action proved in 1954, facilitating diabetes treatment previously done only with insulin.<sup>25</sup> They are divided in first and second generation drugs. The second generation (glyburide, glipizide) is more potent than the first generation (tolbutamide, tolazemide, chlorpropamide and acetohexamide). These drugs increase insulin secretion by binding of the pharmacophore to the sulfonylurea receptor of  $K_{ATP}$  channel of beta pancreatic cells, that will be inhibited. This results in depolarization of the membrane that will open the voltage-dependent calcium channels, resulting in influx of calcium and consequent release of insulin.<sup>6,10,26</sup> Drugs that constitute this class differentiate in their chemical structures through substitutions in  $R_1$  and  $R_2$  of the sulfonylurea (Figure 16).<sup>6</sup>

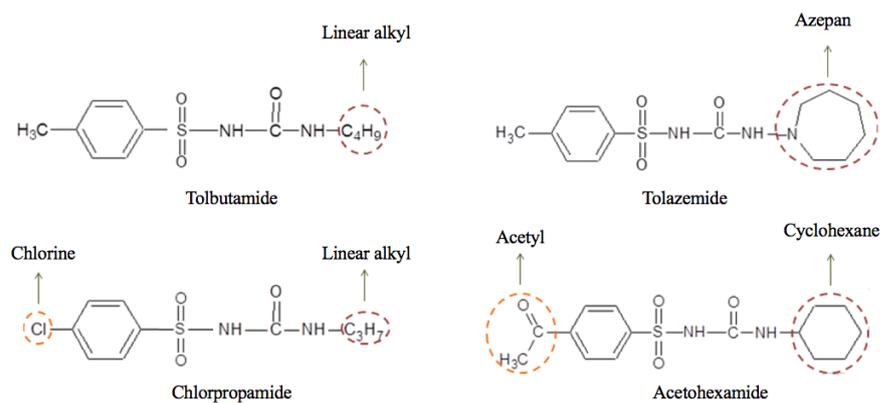


**Fig. 16: Pharmacophore of sulfonylureas**

Tolbutamide (Figure 17) shows in  $R_2$  linear alkyl substitutions. These facilitate its metabolism, excretion and, consequently, decrease its  $T_{1/2}$ . In addition, results in a less potent drug, safe for treatment of diabetes on elderly in fractionate doses.<sup>10</sup>

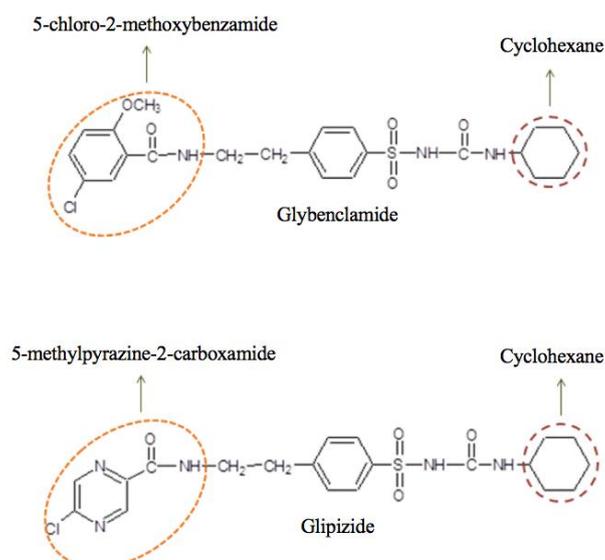
Due to the presence of linear alkyl substitutions in  $R_2$ , tolbutamide is metabolized quickly while tolazemide shows in this same radical an azepan group that by being cyclic results in slower metabolism. This can be observed on chemical structures of these molecules with  $T_{1/2}$  of approximately 5 and 7 hours, respectively.<sup>10</sup>

Chlorpropamide is poorly metabolized and shows a  $T_{1/2}$  of 32 hours, being a drug of high pharmacological potency.<sup>27</sup> This characteristic can be observed on its chemical structure, with a chlorine as radical in position 4, making the molecule liposoluble. Tolazemide shows pharmacological potency comparable to chlorpropamide, however, shows a  $T_{1/2}$  of 7 hours and shorter duration of action.<sup>10</sup> This is due to the fact that it shows a methyl group in position 4 instead of chlorine, as in chlorpropamide. Acetohexamide shows about one third of the pharmacological potency of chlorpropamide, and is twice more potent than tolbutamide. Its  $T_{1/2}$  is between 3,5 and 11 hours.<sup>28</sup> These characteristics can be explained by its chemical structure, once acetohexamide shows an acetyl group in position 4. It is less liposoluble than chlorine observed in chlorpropamide, however, it is more liposoluble than the methyl group in the same position in tolbutamide.



**Fig. 17: Chemical structures of first generation sulfonylureas**

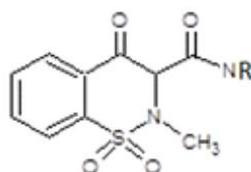
Glibenclamide (Figure 18), most potent drug of the class, shows in position 4 a 5-chloro-2-methoxybenzamide group that provides with an increase in liposolubility and  $T_{1/2}$  of about 2 hours for unaltered drug and 10 hours with metabolites included. In contrast, glipizide presents the shortest  $T_{1/2}$  between the most potent drugs. It shows in position 4 a 5-methylpyrazine-2-carboxamide that provides a half life of 2 to 4 hours, being 99% bonded to albumin.<sup>6,10</sup> Additionally, glyburide is twice as potent as glipizide, once it does not show in its structure an electronegative element such as chlorine, main responsible for the increase in pharmacological potency.<sup>28</sup> Both drugs share a similar metabolism, once both show a cyclohexane in  $R_2$ .



**Fig. 18: Chemical structures of second generation sulfonylureas**

### SAR ANALYSIS OF ANTI-INFLAMMATORY SULFONAMIDES – OXICAMS AND COXIBS

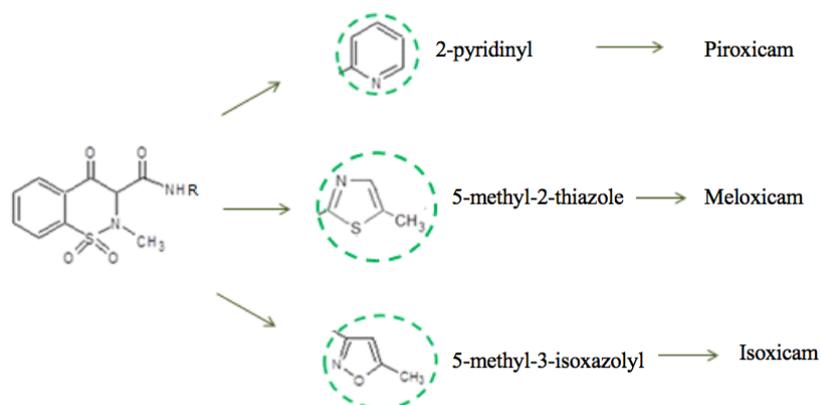
Selective cyclooxygenase-2 inhibitor anti-inflammatories were synthesized to inhibit the synthesis of prostaglandins in locals of inflammation without causing inhibition of COX-1.<sup>10</sup> Oxicams are inhibitors of cyclooxygenase enzyme and show antipyretic, anti-inflammatory and analgesic activity. Differently from other nonsteroidal anti-inflammatories, these show higher selectivity for COX-2, inhibiting it and stopping the formation of chemical mediators of the inflammation process.<sup>6</sup> They are specially used to treat rheumatoid arthritis and osteoarthritis.<sup>10,14</sup> Oxicams' pharmacophore is represented in Figure 19 and drugs' structures in Figure 20.



4-hydroxy-2-methyl-1,2-benzothiazine-3-carboxamide-1,1-dioxide

**Fig. 19: Oxicams' pharmacophore**

Piroxicam shows in R a 2-pyridinyl group where nitrogen, electron acceptor element, provides  $T_{1/2}$  of approximately 57 hours and a long duration of action.<sup>10</sup> Meloxicam shows higher COX-2 inhibitory activity than piroxicam. It presents in R a 5-methyl-2-thiazole group and elimination  $T_{1/2}$  of 15 to 20 hours, additionally, binds 99% to albumin.<sup>24</sup> Isoxicam shows in the same position a 5-methyl-3-isoxazolyl, that despite showing electron accepting elements, has  $T_{1/2}$  of approximately 40 hours, shorter when compared to piroxicam and explained by the fact that the ring is made of five members.<sup>10</sup>



**Fig. 20: Chemical structure of oxicams**

Coxibs were obtained after the discovery of compounds with COX-2 selective inhibitory activity. The same as oxicams, they are commonly used to treat rheumatoid arthritis and osteoarthritis and show higher selectivity to COX-2, because they do not have a ketone group in their structures, observed in other nonsteroidal anti-inflammatory drugs (NSAID).<sup>6,29</sup>

Celecoxib (Figure 21) causes less gastrointestinal effects, however, it can cause skin rashes due to the presence of sulfonamide group. Its  $T_{1/2}$  is 11 hours, being excreted totally via urinary system.<sup>10</sup> It shows a trifluoromethylpyrazole group that provides with lipophilicity and guarantees its long  $T_{1/2}$ . Rofecoxib shows a furan ring that results in  $T_{1/2}$  of approximately 17 hours. Its excretion is renal and its metabolites can go through biliary excretion.<sup>24</sup>

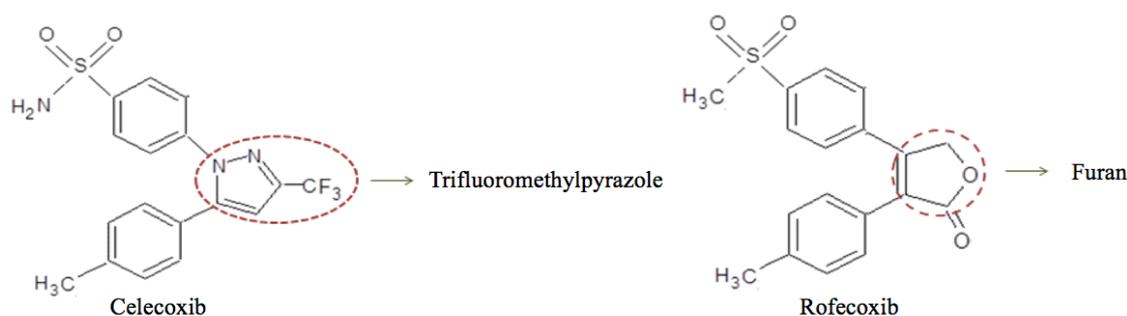
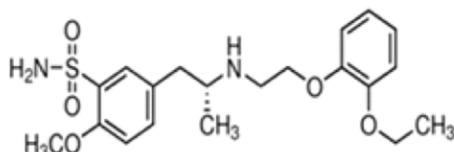


Fig. 21: Chemical structure of coxibs

### SAR OF OTHER DRUGS ORIGINATED AFTER SULFAS

#### Tamsulosin

Tamsulosin (Figure 22) is a competitive alpha-1 adrenergic antagonist frequently used to treat benign prostatic hyperplasia and its binding on alpha-1 receptor is due to structural similarity with adrenaline. It was developed to obtain more selective alpha-adrenergic antagonist drugs.<sup>30,31</sup> This way, shows higher affinity for prostate receptors (alpha-1A) than the ones in aorta (alpha-1B), which may result in decrease in the incidence of adverse cardiovascular effects.<sup>6</sup> It shows a very different chemical structure compared to other alpha-1 antagonists, having a  $T_{1/2}$  that varies from 9 to 15 hours and a high oral bioavailability.<sup>10</sup> Its pharmacokinetic data can be explained according to its structure, that shows methoxyl groups and allows binding to plasmatic proteins, as well as phenoxy and benzene groups that increase its oral bioavailability and  $T_{1/2}$ .



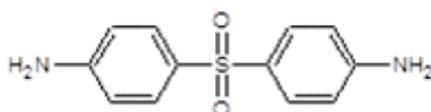
5-[2-[2-(2-ethoxyphenoxy)ethylamino]propyl]-methoxybenzenesulfonamide

Fig. 22: Chemical structure of tamsulosin

#### Dapsone

Dapsone (Figure 23) is a p-aminobenzoic acid (PABA) analogue and competitor inhibitor of dihydropteroate synthase. It was synthesized in 1908 by Wittman and From and in 1937 Buttle et al. and Forneau et al. discovered its structural similarity with sulfonamides.<sup>6</sup> This drug is extensively used in the long term treatment of leprosy and is absorbed in the intestine and distributed through all body liquid. This way it is present in every tissue and stays retained in skin, muscles, liver and kidneys. Its urinary excretion is variable and a big part of the drug goes through acetylation. Because it has a long  $T_{1/2}$ , of 1 to 2 days, traces of the drug can be found in organs until three weeks after the end of the therapy.<sup>10</sup>

Its chemical structure is very liposoluble, once it shows basically a sulfoxide group and two aminobenzene groups. It is suggested that the hepatotoxicity related to this drug can be due to release of aniline during its hepatic metabolism.<sup>6</sup>

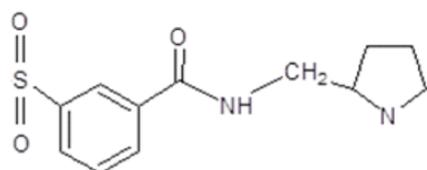


4-(4-aminobenzene)sulfonylaniline

Fig. 23: Chemical structure of dapsone

## ANTIPSYCHOTICS

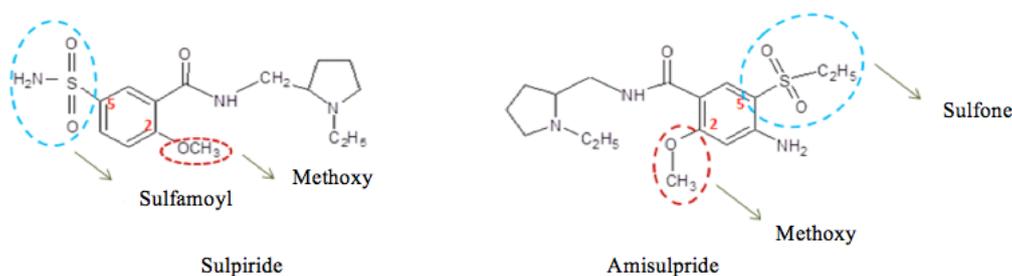
Sulpiride was first discovered in the late 60s in Europe and in Brazil had its first use as antidepressant and in anxiety disorders.<sup>32</sup> Amisulpride was introduced in therapeutics as antipsychotic only during the 80s, belonging to a second generation of benzamides.<sup>33</sup> The pharmacophore of antipsychotics, N-(pyrrolidin-2-yl)-sulfonylbenzamide, is represented in Figure 24.



N-(pyrrolidin-2-yl)-sulfonylbenzamide

**Fig. 24: Antipsychotics' pharmacophore**

Sulpiride and amisulpride (Figure 25) are atypical antipsychotics classified as substituted benzamides. These have antagonist action over dopaminergic receptors, being selective to D2.<sup>34</sup> Both drugs share very similar structures, differing by the fact that sulpiride shows a sulfamoyl group in position 5, while amisulpride shows a sulfone in the same position. Sulpiride has  $T_{1/2}$  between 6 and 8 hours and amisulpride of approximately 12 hours.<sup>34,35</sup> This can be observed in the chemical structures with intermediate lipophilicity, once they show an ethylpyrrolidine group and a methoxy group in position 2, contributing to said lipophilicity.



**Fig. 25: Sulpiride and amisulpride**

## FINAL CONSIDERATIONS

Sulfas' origin was a result of Gerhard Domagk's research, in 1932, on a compound present on Prontosil Rubrum dye, p-amino-sulfamido-chrysoidine, a pro-drug that needs to be bioactivated to sulfanilamide to show its antibacterial effect. From this chemical group, it was possible to obtain other analogues with different therapeutical purposes.

In the present paper, it was observed that the presence of the electronegative element in position 6 of 3,4-dihydro-2H-1,2,4-benzothiazide-7-sulfonamide-1,1-dioxide group is essential for diuretic activity on thiazide diuretics. As for carbonic anhydrase inhibitors it is the 1,3,4-thiadiazole ring, and for loop diuretics, the sulfamoylbenzoic acid group. In relation to oral hypoglycemics the sulfonylurea group must remain in all drugs of this class. On oximams, differently from other sulfa derivatives, it is observed the cyclization of the pharmacophore 4-hydroxy-2-methyl-1,2-benzothiazine-3-carboxamide-1,1-dioxide that, in addition to being fundamental for action maintenance, allows a high  $T_{1/2}$  for these drugs. Coxibs show in their chemical structure two aromatic rings connected by a five members ring, trifluoromethylpyrazole or furan. As for antipsychotics, the group N-(pyrrolidin-2-yl)-sulfonylbenzamide is essential for dopaminergic antagonist activity. Tamsulosin shares structural similarities with adrenaline and dapson with PABA. Additionally, it was observed that drugs with local action have as substituents groups of lower lipophilicity such as thiazole or hydrophilic groups (e.g. succinyl, phthalyl) to ensure that the drug will not be absorbed systemically. Systemic action drugs show substitutions of higher lipophilicity such as aromatic rings and heteroatoms.

In conclusion, Medicinal Chemistry provides with important information about pharmacokinetic and pharmacodynamic aspects, facilitating the evaluation and understanding on possible drug interactions, specially those sharing the same prototype compound. Knowledge on SAR is an important tool for pharmaceutical care, once it adds chemical and pharmaceutical knowledge that can result in a more effective, safe and rational drug therapy.

## REFERENCES

1. Lima LM. *Quim. Nova*. 2007;30:1456.
2. Sneider W. *Drug discovery: a history*, Hoboken: Wiley. 2005.
3. Wermuth CG. *The Practice of Medicinal Chemistry*, 3<sup>rd</sup> ed., Londres: Elsevier/Academic Press. 2008
4. Singh G and Sharma PD. *Indian Journal of Pharmaceutical Science*. 1994;56:69.
5. Carvalho I, Federman Neto A, Ponte GD, Borges ADL and Quim Nova. 2005;28:727.
6. Brunton LL, Chabner BA and Knollmann BC. *As Bases farmacológicas da terapêutica de Goodman & Gilman*. 12th ed., Porto Alegre: AMGH. 2012.
7. Obasi LN. Synthesis, Characterization and Antibacterial Studies of N-(Benzothiazol-2-yl)-4-chlorobenzenesulphonamide and Its Neodymium(III) and Thallium(III) Complexes. *Molecules*. 2017;22(2):1-11.
8. Suyenaga ES, Konrath EL, Dresch RR, Apel MA, Zuanazzi JA, Chaves CG and Henriques A T. *Planta Med*. 2011;77:698.
9. Lemke TL, Williams DA, Roche VF and Zito SL. *Foye's principles of medicinal chemistry*, 6th ed., Baltimore: Lippincott Williams e Wilkins, 2008.
10. Katzung BG, Masters SB and Anthony J. *Farmacologia básica e clínica*, 12th ed., Porto Alegre: AMGH, 2010.
11. Raman J, Little F, Roper C, Kleinschmidt I, Cassam Y, Maharaj R and Barnes KI. *Am J Trop Med Hyg*. 2010;82:788.
12. Olliaro PL and Trigg PI. *Bul World Health Organ*. 1995;73:565.
13. Del Rosso JQ. *Cutis*. 2004;73:29.
14. Hardman JG, Limbird LE, Molinoff PB, Goodman A, Goodman G and Gilman's. *The pharmacological basis of therapeutics*, 9th ed., Nova York: McGraw-Hill, 1996.
15. Shahin MH and Johnson JA. Mechanisms and pharmacogenetic signals underlying thiazide diuretics blood pressure response. *Current Opinion in Pharmacology*. 2016;27:31-37.
16. Overington JP, Al-Lazikani B and Hopkins AL. *Nat Rev Drug Discov*. 2006;5:993.
17. Imming P, Sinning C and Meyer A. *Nat Rev Drug Discov*. 2006;5:821.
18. Lysaa RA, Giverhaug T, Wold HL and Aarbakke J. *Eur J Clin Pharmacol*. 1996;49:393.
19. Race JE, Grassl SM, Williams WJ and Holtzman EJ. *Biochem Biophys Res Commun*. 1999; 16:508.
20. Uwai Y, Saito H, Hashimoto Y and Inui KI. *J Pharmacol Exp Ther*. 2000;295:261.
21. Pereira DG, Unit GR, Coelho RL and Quim Nova. 2007;30:171.
22. Vinereanu D, Dulgheru R, Magda S, Dragoi Galrinho R, Florescu M, Cinteza M, Granger C and Ciobanu AO. *Am Heart J*. 2014;4:446.
23. Rosenberg J, Gustafsson F, Galatius S and Hildebrandt PR. *Cardiovasc Drugs Ther*. 2005;19:301.
24. Larini L. *Fármacos e medicamentos*. Porto Alegre: Artmed. 2008.
25. Rendell M. *Diabetes Mellitus. Drugs*. 2004;24:1339.
26. Monami M, Luzzi C, Lamanna C, Chiasserini V, Addante F, Desideri CM, Masotti G, Marchionni N and Mannucci E. *Diabetes Metab Res Rev*. 2006;22:477.
27. Mizuno CS, Chittiboyina AG, Kurtz TW, Pershadsingh HA and Avery MA. *Curr Med Chem*. 2008;15:61.
28. Imamura Y and Shimada H. *Biol Pharm Bull*. 2005;28:185.
29. Silva PC, Perassolo MS and Suyenaga ES. *REF*. 2010;7:14.
30. Wilt TJ, Ishani A, MacDonald R and Rutks I. *Public Health Nutr*. 2000;3:459.
31. Pourmand A. Tamsulosin for urolithiasis: a review of the recent literature and current controversies. *American Journal of Emergency Medicine*. 2016;11(31):2217-2221.
32. Mann K, Bartels M, Bauer H and Gaertner HJ. *Pharmacopsychiatry*. 1984;17:111.
33. Rosenzweig P, Canal M, Patat A, Bergoignan L, Zieleniuk I and Bianchetti G. *Hum Psychopharmacol*. 2002;17:1.
34. Oliveira IR. *Rev Bras Psiquiatr*. 2000;22:38.
35. Wiesel FA, Alfredsson G, Ehrnebo M and Sedvall G. *Eur J Clin Pharmacol*. 1980;17:385.