Revisión bibliográfica

La química medicinal (química-farmacéutica) en la salud pública: nuestra experiencia en el diseño de moléculas con potencial terapéutico

Medicinal chemistry in public health: our experience in the design of potential therapeutic molecules

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Resumen

En este artículo se describe de manera breve el trabajo que ha desarrollo nuestro grupo de investigación en el diseño, síntesis y evaluación biológica de moléculas con potencial terapéutico para problemas de salud pública tales como la obesidad, cáncer, tuberculosis y la tripanosomiasis americana o enfermedad de Chagas. Se realizó una revisión concisa de la relevancia de cada una de las enfermedades, los fármacos que se han usado para su tratamiento y aquellos que se han desarrollado recientemente. Además, se describen las estrategias de diseño racional y síntesis conducidas por nuestro grupo de investigación, las cuales se han enfocado en el desarrollo de nuevos compuestos con actividad biológica como potenciales agentes anti-obesidad, anti-cáncer, anti-tuberculosis y anti-tripanosomiasis.

Abstract

This paper briefly describes the progress that our research group has achieved in the design, synthesis and biological evaluation of new potential therapeutic molecules for public health problems such as obesity, cancer, tuberculosis, and American trypanosomiasis or Chagas disease. We briefly reviewed the relevance of each of these diseases, the drugs that have been used for treatment and those that are in development. Furthermore, we describe the rational design and synthesis strategies conducted by our research group, which have been focused on the development of new compounds with biological activity as potential anti-obesity, anti-cancer, anti-tuberculosis, and anti-trypanosomiasis agents.

Palabras clave: Química medicinal y/o farmacéutica, obesidad, cáncer, tuberculosis, tripanosomiasis.

Key words: Medicinal chemistry, obesity, cancer, tuberculosis, trypanosomiasis.

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Introducción

Medicinal chemistry (MC) is a chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. The term MC is equivalent to and sometimes adsorbed by the term "Química-Farmacéutica", which is commonly used in Spanish speaking countries and others like France, Italy or Germany due to their long-established traditions. MC is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships (SAR).[1] One of the main aims of the MC is the rational design or search of new "lead compounds", and their modifications that can provide more effective compounds with low side effects. Currently, the development of new synthetic methods, instrumental techniques, bioinformatics, molecular biology, among others, allow the search based on the knowledge of a biological target, which is known as "Rational Drug Discovery".[2] Additionally, other important techniques employed in drug discovery are, analogue-based drug discovery (strategy for drug discovery and/or optimization in which structural modification of an existing drug provides a new drug with improved chemical and/or biological properties), high-throughput screening (method for the rapid assessment of the activity of samples from large compound collections), and *in silico* screening (evaluation of compounds using computational methods).[3]

MC has been strongly developed in developed countries, especially in the United States. However, in recent years, countries with emerging economies, such as the People's Republic of China and India have had considerable progresses in the field. According to a bibliometric analysis conducted in 2009, countries such as Brazil, Mexico, and Argentina have developed the highest scientific production related to MC in Latin America.[4] In Mexico several, developing and consolidated research groups are conducting studies on aspects of MC, such as molecular modeling, chemical synthesis, biological evaluation with *in vitro* and *in vivo* models, and natural products. The most relevant institutions on this matter are: Instituto Politécnico Nacional (IPN), Universidad Nacional Autónoma de México (UNAM), Universidad Autónoma Metropolitana (UAM), Universidad Autónoma de Nuevo León (UANL), Universidad Autónoma del Estado de Morelos (UAEM), Benemérita Universidad Autónoma de Puebla (BUAP), and Universidad Autónoma de Tamaulipas (UAT), among others. Despite the importance of this field of research, the "Consejo Nacional de Ciencia y Tecnología" (National Council of Science and Technology) (CONACYT) from Mexico does not contemplate any postgraduate program focused on MC exclusively. Howeve, some postgraduate programs with a different name (chemistry, pharmacy, health, among others) include research lines and training in MC related subjects. Since 2005, our research group has been working on various projects focused on the discovery of new therapeutic options for obesity, cancer, tuberculosis, and Chagas disease.

Development of anti-obesity agents

In the past two decades, obesity has become a public health problem that has occurred in both developing and developed countries. Traditionally obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. The Body Mass Index (BMI), which is calculated by dividing the individuals weight expressed in kilograms by their height in square meters, has been established as the most important obesity measure. The World Health Organization (WHO) has issued the following classification for obesity (Table 1).[5]

Table 1. Classification by body weight according to the world health organization

Classification according to weight	Body Mass Index (kg/m^2)	Health risk
Underweight	Below 18.5	Moderate to high
Normal weight	18.5 to 25	Normal to low
Overweight	25 to 30	Moderate
Class I Obesity	30 to 35	High
Class II Obesity	35 to 40	High to very high
Class III Obesity	40 and more	Extremely high

According to the prevalence of obesity in recent years, the United States and Mexico are the two main countries with this public health problem.[6] In Mexico, according to the National Health and Nutrition Survey, adult men and women (> 20 years) have a prevalence of obesity (BMI >30) of 26.8 and 37.5%, respectively. [7]

Currently, measures for the treatment of obesity focus on a reduction in calorie intake and increased energy expenditure, which at first instance can be provided in a simple manner through diet (balanced nutrition) and exercise. Subsequently, and only under medical supervision, anorectic drugs (those that reduce appetite or increase satiety), drugs that interfere with the absorption or metabolism of nutrients, and drugs that increase energy expenditure could be administered. For example, sibutramine is a neurotransmitter reuptake inhibitor that reduces the reuptake of serotonin, norepinephrine, and dopamine to help enhance satiety. Ephedrine is a sympathomimetic amine commonly used as an appetite suppressant (Fig. 1).[8] Unfortunately, the use of these products have been associated with increased cardiovascular events and strokes, reasons whereby these products have been withdrawn from the market in the United States and European Union.

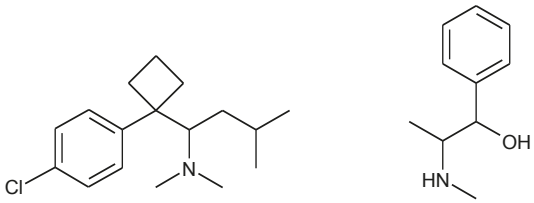

Figure 1. Drugs with anti-obesity activity

In recent years, new compounds with antagonistic activity on neuropeptide Y (NPY), cannabinoid receptors (CB) and melanin concentrating hormone (MCH) receptors for obesity treatment have been discovered.[9-11] Particularly, MCH offered great relevance during the first decade of the twenty-first century, since MCH receptor was reported as a treating obesity drug target. This fact triggered the search for new specific antagonists compounds of the MCH-R1 receptor by multinational pharmaceutical companies such as Takeda, Synaptic, GlaxoSmithKline, and Schering-Plough, among others.[12-14] Compounds that highlighted due to their inhibition and selectivity values for MCH-R1 are shown in Fig. 2.

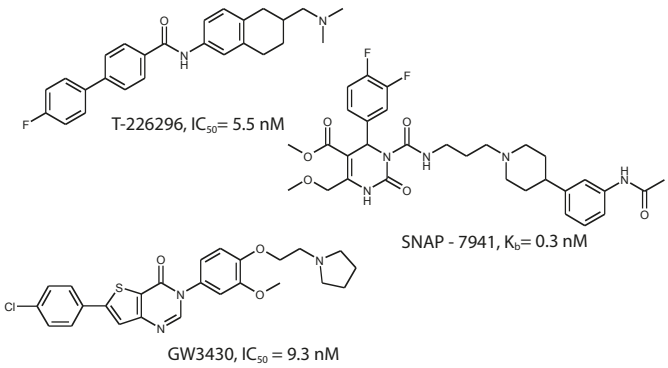

Figure 2. Compounds MCH-R1 antagonists

Under the supervision of Antonio Monge Ph.D. from the Drug Development and Research Unit of the University of Navarra, Spain, our research group addressed the development of new MCH-R1 receptor antagonists. Thus, in 2007, we reported the design and synthesis of two new series derived from biphenylmethylurea as MCH-R1 receptor antagonists (Fig. 3). Design strategy (pharmacophore based drug design) to generate structures with potential antagonistic activity against the MCH-R1 receptor, included biphenyl as a lipophilic moiety, urea as a donor/acceptor group, and the presence of a basic amine via a linker (substituted piperidine ring). It was interesting to observe that the biphenylmethylurea derivatives showed better biological activity if biphenyl moiety and the linker on the same nitrogen atom of the urea group are replaced. Then the resulting compound 2t (Fig. 4), exhibited the best inhibitory activity of the MCH-R1 receptor with a Ki value of 43 nM.[15] Later, in 2008, research group reported two new series of amide derivatives (Fig. 5), which worked also as MCH-R1 receptor antagonists. These series were considered analogous to those reported by Takeda and GlaxoSmithKline due to the presence of the lipophilic biphenyl moiety, the presence of a hydrogen donor-acceptor group such as the amide, the inclusion of both aromatic and aliphatic linkers, and the presence of a second nitrogen atom. Interestingly new agents with the classic biphenylamide building block from the series of amide derivatives did not exhibit good inhibitory activity on the MCH-R1 receptor ($IC_{50} \geq 100\ \mu M$). Surprisingly it was found that these compounds with a building block derived from diphenylamide improved inhibitory activity ($IC_{50} \leq 100\ \mu M$) (Fig. 6).[16] Finally, after a review of prospects for MCH-R1 receptor antagonists as viable options for the pharmacologic treatment of obesity, it was noticed that the development and interest in these agents had decreased due to the fact that various MCH-R1 receptor antagonists caused cardiovascular complications *in vivo* models.[17]

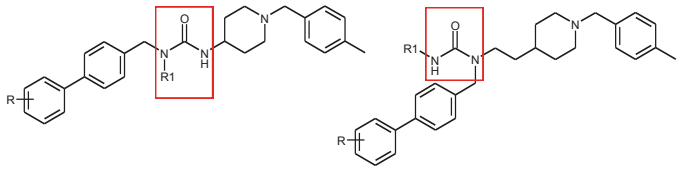

Figure 3. General structure of biphenylmethylurea derivatives designed as MCH-R1 antagonists

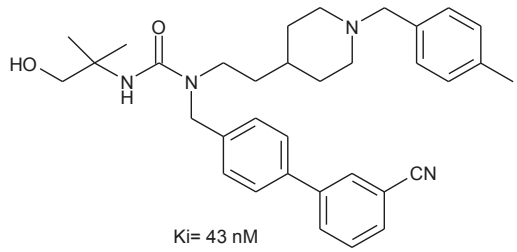

Figure 4. Compound 2t, a biphenylmethylurea derivative as MCH-R1 antagonist

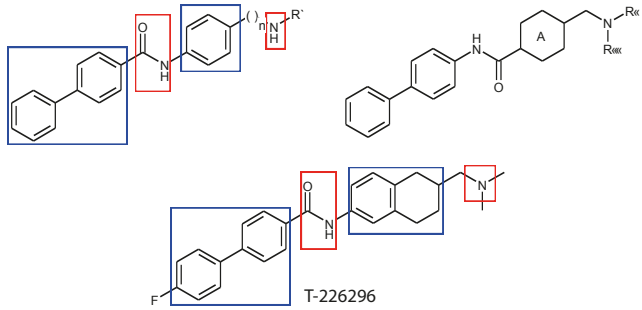

Figure 5. General structure of amide derivatives as potential MCH-R1 antagonists and structure of T-226296

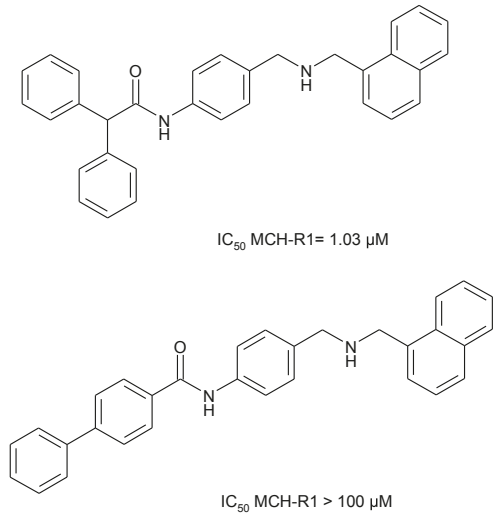

Figure 6. Diphenylamide and biphenylamide derivatives as MCH-R1 antagonists

Development of anti-cancer agents

According to the WHO, cancer is defined as the proliferation and uncontrolled growth of cells, which can affect any part of the body. This can cause the invasion of surrounding tissue and it can spread to different locations through metastases. Various types of cancer can now be cured by surgery, radiotherapy, or chemotherapy (Table 2), if detected early.[18]

Table 2. Chemistry entity and mechanism of action of drugs used in cancer chemotherapy

Agents	Drug	Mechanism of action
Alkylating agents	Melphalan	Interfere with the DNA molecule, altering its structure or function so it cannot replication, prevent the cell from multiplying.
Antimetabolites	Methotrexate	Interfere in the steps of DNA or RNA synthesis, inhibiting cell division.
Plant Alkaloids	Vinca	Arrest cell division, preventing the formation of new cells.
Antibiotics	Anthracycline	Cause DNA damage, inhibiting cell replication.
Hormone therapy	Tamoxifen	Increases or decreases the amount of certain hormones, limiting the growth of cancers that depend on these or are inhibited by them.

In the search for new anti-cancer agents, compounds that inhibit carbonic anhydrase (CA), topoisomerases I and II, and kinases have been developed.[19-21] Our group has approached the development of new CA inhibitors. CA is a metallo-enzyme that regulates the physiological pH of cells, and it has been observed that isoforms II, IX, and XII are over-expressed in certain types of tumors, therefore its inhibition may be a viable option for controlling tumor growth.[22] The main compounds with CA inhibitory activity that have been developed present one or two sulfonamide groups (Compound E70770, Fig. 7). The free sulfonamide group is primarily responsible for interaction with the drug target.[23]

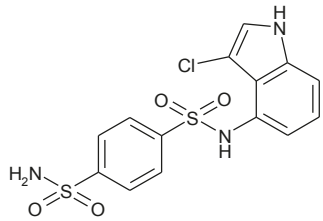

Figure 7. Compound E70770, a sulfonamide derivative as carbonic anhydrase inhibitor

Sulfonamides are considered to have a "privileged structure"[3] because they are present in compounds with diverse biological activities as shown in Fig. 8. It is noteworthy that they can lead us to find new chemical entities not only with potential anti-cancer activity but also with a second potential activity as a hypoglycemic, diuretic, and anti-bacterial drug, among others.

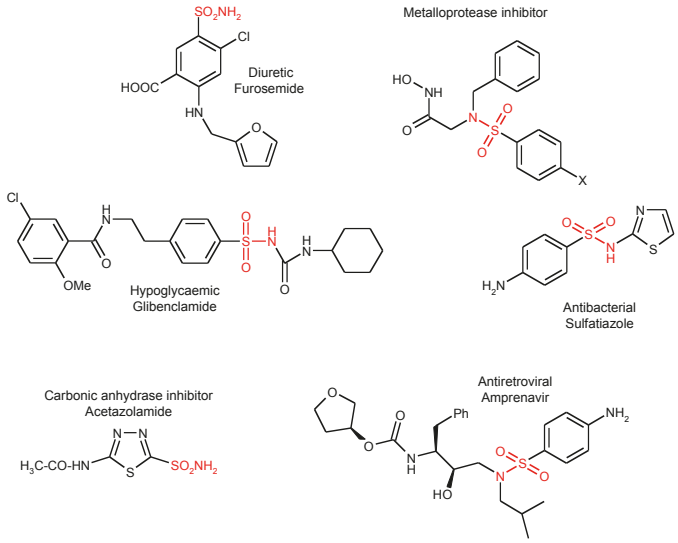

Figure 8. Drugs with sulfonamide group

Based on the above, our group has developed a series of compounds derived from sulfonamides that have been evaluated by the National Cancer Institute (NCI) of the United States in a panel of 60 tumor cell lines at a single test concen-

tration of 1.00E-5 M (Fig. 9 and Table 3, 4, and 5). However, none of them have shown effective inhibitory activity of cell growth (> 68%) so far.[24] Despite the low anti-cancer activity found in sulfonamide derivatives that have been synthesized and evaluated, it is important to mention that we continue with the design and synthesis of more sulfonamide-derived compounds to determine potential anti-cancer activity, implementing different design strategies such as analogue based drug design, hybridization, bioisosteres, among others.

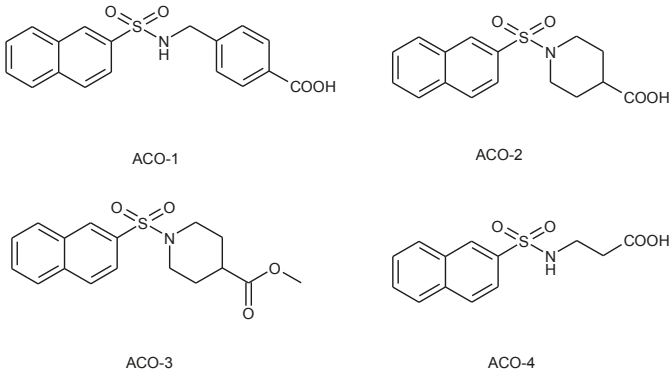

Figure 9. Screening of compounds ACO-1, ACO-2, ACO-3 and ACO-4 on 60 tumor cell lines

Table 3. Screening of compounds ACO-1, ACO-2, ACO-3 and ACO-4 on leukemia, non-small cell lung cancer and colon cancer cell lines

Panel/ Cell Line		Growth % 1.00E-5 M			
		ACO-1	ACO-2	ACO-3	ACO-4
Leukemia	CCRF-CEM	117.12	90.08	138.12	110.86
	HL-60 (TB)	68.06	45.63	-	188.20
	K-562	94.52	108.56	103.37	113.64
	MOLT-4	84.09	106.84	160.92	118.47
	RPMI-8226	112.00	58.74	144.12	69.00
	SR	33.39	-	75.71	88.95
Non-Small Cell Lung Cancer	EKVX	111.28	103.34	107.74	91.62
	HOP-62	122.02	111.64	113.38	102.62
	HOP-92	131.91	90.77	86.84	83.87
	NCI-H226	100.30	90.60	93.31	92.02
	NCI-H23	118.88	98.32	97.70	98.42
	NCI-H322M	113.52	123.96	116.09	128.88
	NCI-H460	120.31	111.60	110.27	114.21
	NCI-H522	104.06	92.94	99.78	98.41
Colon Cancer	COLO 205	104.81	111.16	108.47	110.73
	HCC-2998	271.33	93.56	103.13	110.56
	HCT-116	109.00	112.15	114.67	107.76
	HCT-15	104.19	106.86	110.20	99.20
	HT29	102.02	111.38	108.50	110.46
	KM12	100.89	111.47	102.14	116.73
	SW-620	99.85	98.23	102.43	95.43

Table 4. Screening of compounds ACO-1, ACO-2, ACO-3 and ACO-4 on CNC, cancer, melanoma and ovarian cancer cell lines

Panel/ Cell Line		Growth % 1.00E-5 M			
		ACO-1	ACO-2	ACO-3	ACO-4
CNC Cancer	SF-268	96.24	108.35	101.66	115.16
	SF-295	104.97	192.33	195.47	130.56
	SF-539	105.92	109.01	101.45	108.01
	SNB-19	104.46	102.69	98.48	101.79
	SNB-75	90.80	102.50	87.76	90.59
	U251	106.14	104.06	111.04	94.52
Melanoma	LOX IMVI	100.21	102.68	106.57	92.13
	MALME-3M	93.67	127.06	121.84	112.31
	M14	103.32	109.12	107.03	103.97
	MDA-MB-435	110.22	119.93	111.42	101.90
	SK-MEL-2	0.43	5.44	8.48	0.62
	SK-MEL-28	106.41	91.36	105.14	94.33
	SK-MEL-5	104.97	107.64	107.26	97.85
	UACC-257	99.07	56.24	62.72	87.48
	UACC-62	101.82	94.54	98.19	96.70
Ovarian Cancer	OVCAR-3	94.89	111.81	113.95	113.95
	OVCAR-4	98.29	105.73	102.82	100.64
	OVCAR-5	114.90	124.86	106.28	106.98
	OVCAR-8	67.70	81.44	81.63	97.66
	NCI/ADR-RES	128.09	116.75	116.05	107.74
	SK-OV-3	108.57	110.91	98.36	107.46

Table 5. Screening of compounds ACO-1, ACO-2, ACO-3 and ACO-4 on renal cancer, prostate cancer and breast cancer cell lines

Panel/ Cell Line		Growth % 1.00E-5 M			
		ACO-1	ACO-2	ACO-3	ACO-4
Renal Cancer	786-0	106.23	103.31	112.60	105.50
	A498	102.13	103.57	125.12	115.36
	ACHN	101.02	109.30	110.43	97.92
	CAKI-1	112.34	103.74	99.78	103.97
	SN12C	100.17	100.60	105.05	94.98
	TK-10	109.26	133.06	122.03	135.54
	UO-31	94.72	100.95	97.09	92.77
Prostate Cancer	PC-3	103.58	80.87	90.32	89.63
	DU-145	93.70	113.65	110.19	126.79
Breast Cancer	MCF-7	106.62	100.89	99.68	106.18
	MDA-MB-231/ATCC	105.01	98.74	114.54	123.44
	HS 578T	80.97	113.03	117.37	9.34
	BT-549	104.35	109.34	128.77	126.94
	T-47D	100.20	107.03	101.77	107.62

The most common process in the formation of a sulfonamide group involves the reaction of a sulfonyl chloride with a primary or secondary amine derivative using triethylamine (TEA) as a catalyst. It is noteworthy that our group has developed

a sulfonamide derivatives synthesis process using solid supports, such as silica gel, alumine, fluorosil, montmorillonite KSF and K10 as catalysts. The advantage of using these supports is that they are easily separated and recovered from the reaction. In addition they are an economically and environmentally friendly option for the development of synthetic processes.[25] Moreover, our sulfonamide derivatives exhibit trypanocide activity against *Trypanosoma cruzi*. Compound P-012 (Fig. 10) showed better lytic activity than the reference drugs, nifurtimox and beznidazole on two (NINOA and INC-5) strains endemic from Mexico, suggested the importance of the sulfonamide group as a scaffold for designing new anti-trypanosomiasis agents.[26]

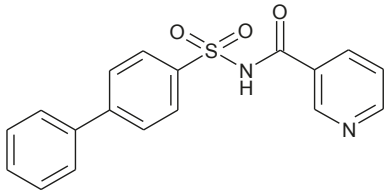

Figure 10. Compound P-012, a sulfonamide derivative with anti-trypanosomiasis activity

On the other hand, according to multiple reports of new azetidin-2-one derivatives (better known as β-lactams) with anti-cancer activity (Fig. 11)[27] we followed a second strategy to synthesize a new series of β-lactams derivatives as potential anti-cancer agents.[28,29] Nowadays these derivatives are under biological evaluation in tumor cell lines to determine their potential anti-cancer activity, together with Dr. Banik and his research group from the University of Texas-Pan American in the United States. The formation of azetidin-2-one derivatives was carried out by reaction of an imine derivative and the corresponding acyl chloride, via the Staudinger reaction (Fig. 12).

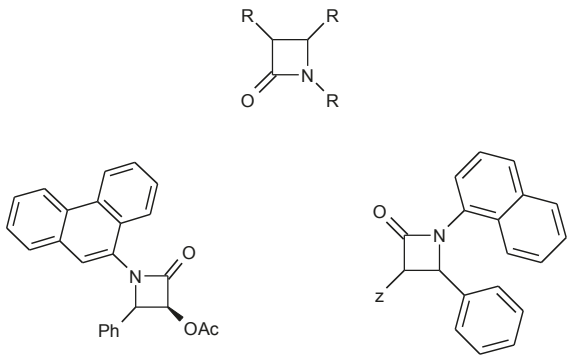

Figure 11. Azetidin-2-one (β-lactam) ring and derivatives with anti-cancer activity

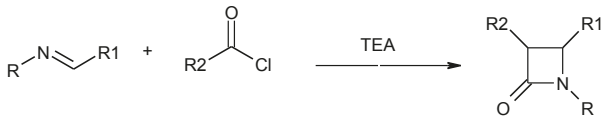

Figure 12. Azetidin-2-one formation via Staudinger reaction

Development of anti-tuberculosis agents

Tuberculosis is an acute or chronic infectious disease caused by the *Mycobacterium tuberculosis* complex.[30,31] This complex currently includes five species: *M. tuberculosis, M. bovis, M. africanum, M. microti*, and *M. canetti*. Tuberculosis caused by *M. tuberculosis* is the most important disease from a point of view of health.[32] According to the WHO, tuberculosis causes greater mortality in more people than any other individual curable infectious disease in the world. Approximately four people die every minute from tuberculosis, and every second, emerges a new infection. About one third of mankind is considered to be infected and at risk of developing the disease. It is estimated that the incidence is around 9 million new cases per year.[33]

Mexican states with a high incidence of tuberculosis are found in the west, along with the Gulf of Mexico. Tamaulipas and Baja California states show double the national rate (13.5); Along with Veracruz, Chiapas, Nuevo León, Jalisco, Sinaloa, Nayarit, Guerrero, Sonora, Oaxaca, and Chihuahua concentrate 70% of the tuberculosis cases identified throughout the country (Fig. 13).[34]

Figure 13. Incidence of tuberculosis by states in Mexico (2008)

For the treatment of tuberculosis, anti-tuberculosis drugs have been classified as first- and second-line drugs depending on their risk-benefit ratio.

First-line drugs: these are the drugs of choice (Fig. 14), which have a different therapeutic target.

Second-line, secondary or minor drugs: these can be used when toxicity of the former impedes their use or when treatments fail because of resistance.[35] Some of the secondary drugs used in tuberculosis treatment are shown in Fig. 15.

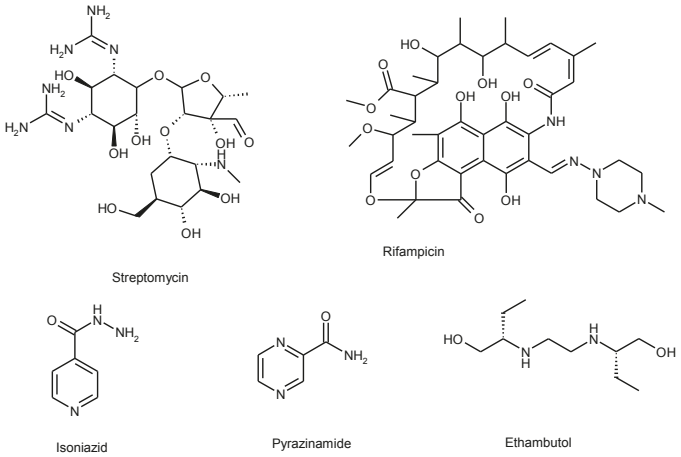

Figure 14. First-line drugs for the treatment of tuberculosis

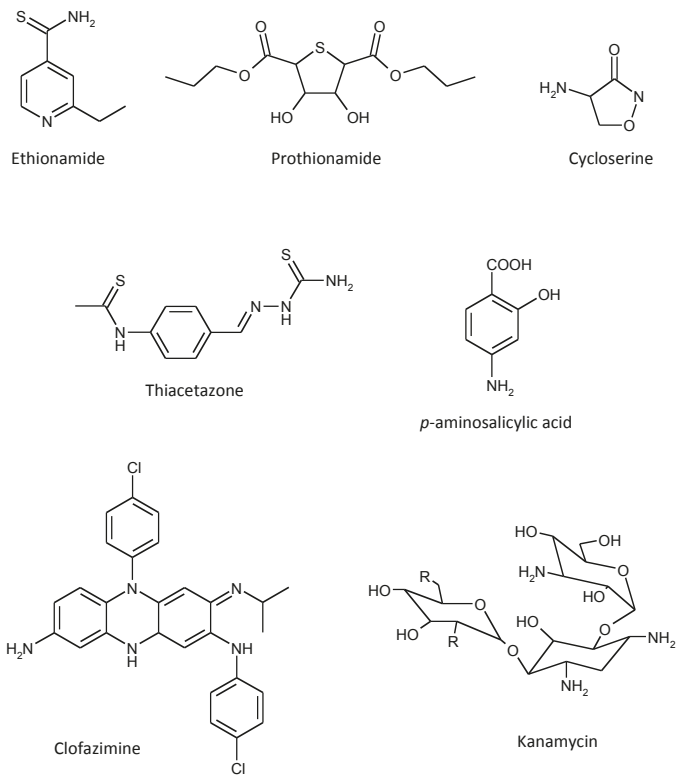

Figure 15. Second-line drugs for the treatment of tuberculosis

In the development of anti-tuberculosis drugs, several studies have highlighted compounds containing a nitrogen atom in their structure. A good example is quinoxaline derivatives. They show numerous biological activities, and their ring is described as a bioisoster of the quinoline rings, naphthalene, benzothiophene and other aromatic rings, such as pyridine and pyrazine. Some of them are the basis of known anti-malarial and anti-tuberculosis agents for clinical use (Fig. 16).[36]

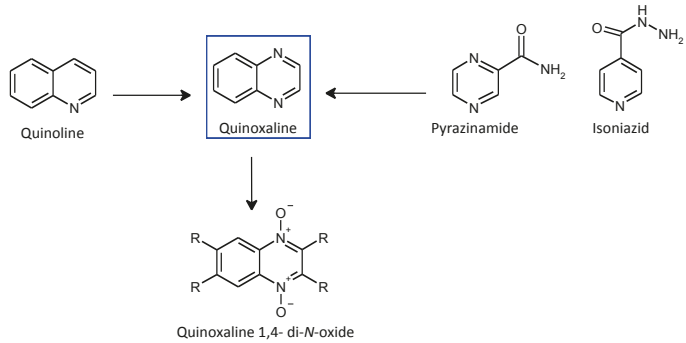

Figure 16. Quinoxaline ring, a quinoline bioisoster, and drugs-tuberculosis relationship.

Interestingly, in recent decades several studies have indicated that quinoxaline mono and di-*N*-oxides derivatives exhibit diverse biological activities.[37,38] Particularly quinoxaline 1,4-di-*N*-oxide derivatives stand out in preclinical studies as anti-tuberculosis agents.[39] In this sense, our research group in collaboration with Dr. Monge´s group has focused on the design and synthesis of new quinoxaline 1,4-di-*N*-oxide derivatives with the aim of improving the bioavailability of these derivatives. Although the formation of the quinoxaline ring commonly proceeds through the condensation reaction of an ortho-diamine derivative and the corresponding diketone derivative (Fig. 17)[40] we conduct a cycloaddition reaction of a benzofuroxan derivative and the respective α,β-unsaturated diene ketone, 1,3-diketone, enamine or enolate derivative, to form new quinoxaline 1,4-di-*N*-oxide derivatives (Fig. 17).[41]

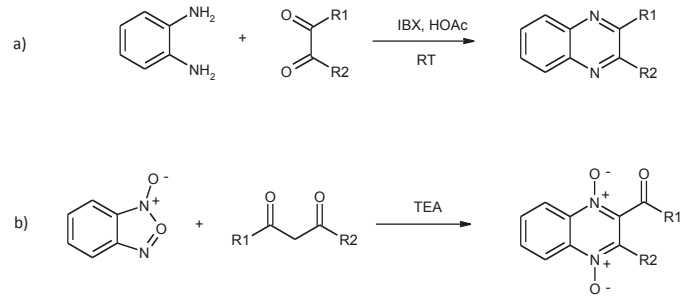

Figure 17. a) Quinoxaline ring formed by condensing ortho-diamines with 1,2-diketones. b) Quinoxaline 1,4-di-*N*-oxide formed by benzofuroxane condensing with 1,3-diketones.

Development of anti-trypanosomiasis agents

American trypanosomiasis, also called Chagas disease, was first described by Carlos Chagas in Minas Gerais, Brazil by 1909. The discovery was made through observation of flagellate parasites in peripheral blood from a 2-year-old girl who suffered from a disease whose signs and symptoms did not correlate with any of the conditions reported so far. Months later, this same scientist described and named three important parasites:

Trypanosoma cruzi (*T. cruzi*), a pathogenic flagellate from the order Kinetoplastida as the causative agent of Chagas disease. *Trypanosoma brucei*, the causative agent of sleeping sickness, and *Leishmania* spp, which causes visceral and tegumentary leishmaniasis and belongs to the Trypanosomatidae family.[42]

Chagas disease is transmitted primarily through the feces at the moment of the bite by insects belonging to the Reduviidae family, subfamily Triatominae: *Triatoma infestans* (commonly known as "kissing bug-Chinche besucona, Vinchuca or Chipo"). According to data collected by the WHO, Chagas disease causes the heaviest burden of morbidity and mortality produced by parasites distributed in Central and South America with 16-18 million people affected by this condition and more than 100 million at risk of being infected.[43]

The chemotherapy of Chagas disease includes only two trypanocide drugs, nifurtimox (Lampit®) and benznidazole (Radanil®), which are of limited access. Nifurtimox (Nfx) is a nitro derivative (Fig. 18), which mechanism of action is the generation of a partial reduction of oxygen to hydrogen peroxide, hydroxyl radicals, and superoxide anions at different cell levels to nitro-anion radicals and the transfer of electrons from the activated drug. The reactions of free radicals with cellular macromolecules include lipid peroxidation and membrane damage, inactivation of enzymes, and DNA damage. Nfx can also damage host tissue, by redox radical formation, causing severe side effects in mammals, such as anorexia, gastrointestinal intolerance, nervous irritability, insomnia, weight loss, and less commonly seizures.[44] The mechanism of action of benznidazole (Bnz) (Fig. 19) also requires electron transfer, which occurs in the cell. After this, nitro radicals form covalent bonds with macromolecules, which culminate in the damage that destroys parasites. In spite of its high efficiency, Bnz administration causes some side effects such as anorexia, arthralgia, headache, and neuropathy.[45,46] In addition, Nfx and Bnz have shown trypanocidal action on trypomastigote and amastigote forms of *T. cruzi*.[47,48]

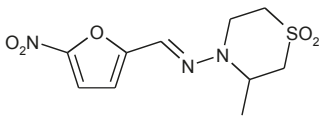

Figure 18. Nifurtimox

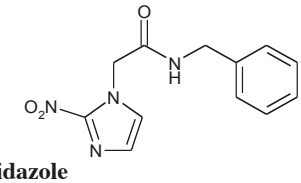

Figure 19. Benznidazole

In the design of new therapeutic anti-trypanosomiasis drugs, the most recently used therapeutic targets are farnesyl pyrophosphate synthase (FPPS), *trans*-sialidase (TS), the cysteine protease cruzain, trypanothione reductase (TR), glucose-6-phosphate dehydrogenase (GPDH), glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and α-hydroxyacid dehydrogenase (α-HADH), among others.[49] Considering this, our research group is designing (ligand based drug design) and synthesizing new compounds that inhibit *trans*-sialidase and cruzain as new therapeutic options for Chagas disease and working in the development of a recombinant model of the trypanothione reductase from T. *cruzi* for *in vitro* assays in search of inhibitory compounds.

***Trans*-sialidase (TS)**

Trans-sialidase (TS) has 632 amino acid residues and a molecular mass of 110,109 kDa. It is a protein located on the surface of the parasite, attached to the cell membrane by a glycosylphosphatidylinositol anchor.[50] The TS of *T. cruzi* presents a novel biochemical pathway that is the only way to capture sialic acid residues in the parasite, the presence of these sugars becomes necessary for the recognition and/or infection of mammalian cells. Sialic acid is an important component of the *T. cruzi* membrane. Experimental evidence shows that the presence of sialic acid on the surface of the parasite plays an important role in the establishment of infection; however, the parasite is unable to synthesize it de *novo* or from its natural precursors. Therefore, expression of TS is essential for obtaining competent infective and invasive parasites.[51-54] Considering the above and the comments recently made by Buchini *et al*. TS becomes a potential target for the design of inhibitors with potential therapeutic activity against *T. cruzi*.[55] Buschiazzo *et al*. have presented the possible interaction between TS and the ligand 2,3-dehydro-3-deoxy-*N*-acetylneuraminic acid (DANA) through hydrogen bonds, although they mention that the protein presents conformational changes introduced by the DANA substrate.[56] Recently, Neres *et al*. reported pyridine derivatives and benzoic acid as TS inhibitors of *T. cruzi*. These compounds are important because they occur in the sialic acid structure.[57] In this sense, our research group has focused on the development of new TS inhibitors.

Cysteine protease Cruzain

Cruzain, is the largest *T. cruzi* cysteine protease. It has a molecular mass of 22,704 kDa and a polypeptide chain of 215 amino acid residues, consisting of two domains. The protease is expressed in all stages of the parasite life cycle and it is essential for replication of its intracellular form.[58] Selective inhibitors of this enzyme block the proliferation of extra-cellular epimastigotes and intracellular amastigotes *in vitro*.[59]

In recent years there have been two main types of cruzain inhibitors: thiosemicarbazones and acylhydrazides derivatives.[60] Du *et al*. reported thiosemicarbazone derivatives as effective trypanocide cruzain inhibitors showing activity at concentrations that do not exhibit toxicity in mammalian cells.[61] Moreover, Rodriguez *et al* reported new inhibitors from alkylhydrazide cruzain derivatives (Fig. 20).[62] Thus, our research group has also considered cruzain inhibition as one of its strategies in the design of new drugs to treat Chagas disease.

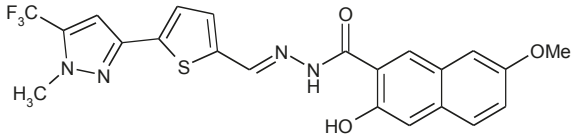

Figure 20. Acylhydrazone derivative as cruzain inhibitor

Conclusions

Currently, there are health problems that have a high impact on our society such as obesity and cancer, and the "neglected diseases", such as tuberculosis and Chagas, for which the development of new drugs for treatment is a current urgent need. However, it is a process that will take many years and involve constant work of a multidisciplinary team, and large economic resources. In our laboratory, we have started with the formation of human resources trained in Medicinal Chemistry with promising progress. However, further measures are needed, both locally and nationally, to enable the country to have better development in drug design.

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