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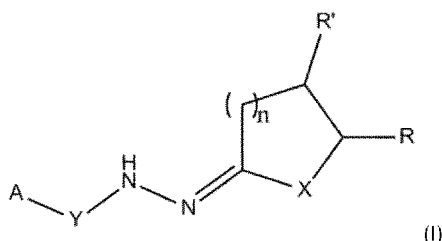
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(54) Title: HYDRAZONOPYRROLIDINE DERIVATIVES FOR USE IN PREVENTING AND/OR TREATING DISORDERS ASSOCIATED TO ACINETOBACTER BAUMANNII



(I)

(57) Abstract: The present invention relates to compounds of the following general formula (I): or a pharmaceutically acceptable salt and/or solvate thereof, for use for preventing and/or treating disorders associated to Acinetobacter baumannii. The present invention also relates to pharmaceutical compositions containing said compounds.



HYDRAZONOPYRROLIDINE DERIVATIVES FOR USE IN PREVENTING AND/OR
TREATING DISORDERS ASSOCIATED TO ACINETOBACTER BAUMANNII

FIELD OF THE INVENTION

5 The invention relates to hydrazonopyrrolidine derivatives compounds for use for preventing and/or treating disorders associated to *Acinetobacter baumannii*. The present invention also relates to pharmaceutical compositions containing said compounds and the process for preparing said compounds.

BACKGROUND OF THE INVENTION

10 Today, bacterial resistance to antibiotics is a serious global public health problem which is advancing very rapidly. Despite the mobilization of the World Health Organization (WHO), the number of victims (mortality, morbidity) continues to increase, with increasingly pessimistic forecasts. Faced with the emergency, it is possible to act at different levels, including the discovery of new therapies:
15 although antibiotic resistance is advancing at an alarming rate, it is a fact that no antibiotic with a new mechanism of action has been developed in the past 20 years. Given the situation, it is therefore essential to develop new classes of antibiotics. On 27 February 2017, WHO published the first catalogue listing the 12 families of bacteria that pose the greatest threat to humanity ever identified. These data show that the bacterium *Acinetobacter baumannii* is a genuine threat to populations and
20 that new compounds are urgently needed to fight this threat.

 Bacteria of the genus *Acinetobacter* are found in many natural environments (soil, water, plants, etc.) and are part of the normal skin flora of humans and animals. They are also isolated from oral, nasopharyngeal or faecal flora and may be present in food. *Acinetobacter baumannii* (AB) is a Gram-negative coccobacillus, a commensal of the skin, especially its moist regions, and of the
25 digestive tract. Like *Pseudomonas*, *Acinetobacter* is mainly responsible for nosocomial infections, especially in immune-depressed patients. The associated pathologies are sepsis, pneumopathy, meningitis, endocarditis, abscess, wound superinfection, urinary tract infection. The main species involved is *Acinetobacter baumannii*. *Acinetobacter* is strictly aerobic, oxidase negative and catalase positive. The use of glucose via the oxidative pathway is common but may be absent.

30 *Acinetobacter baumannii* has emerged as one of the most problematic pathogens in healthcare facilities. It is involved in 2% to 4% of nosocomial infections in the EU and the USA. Its capacity for long-term survival in hospitals, combined with the emergence of resistance, potentiates its ability for nosocomial spread. This pathogen generally targets the most vulnerable patients. Nosocomial pneumonia is the most common infection. Recently, however, bacteraemia and infections of the skin,
35 the soft tissue, the urinary tract or the central nervous system have emerged as highly problematic for certain institutions.

 The existence of strains resistant to all antibiotics used in human therapy places *A. baumannii* among the organisms that threaten the current therapeutic arsenal. Given the number and diversity of resistance determinants identified in this bacterium, the choice of molecules during empirical
40 treatment is a genuine challenge. Carbapenems have long been considered the treatment of choice

for *Acinetobacter* infections. Today, the clinical utility of this class is threatened by the emergence of resistance, fostered by its increasing use in connection with the emergence of multidrug-resistant Enterobacteriaceae. Currently, combinations of molecules and/or the use of older antibiotics such as colistin are often the only options. The main antibiotics used to treat it are carbapenems, ampicillin in combination with sulbactam, tigecycline, aminoglycosides and colistin. In the USA, 61% of *Acinetobacter baumannii* strains are resistant to carbapenems and 65% have combined resistance to at least 3 classes among carbapenems, ampicillin/sulbactam, aminoglycosides, cephalosporins, fluoroquinolones and piperacillin. The mortality rate for multidrug-resistant *A. baumannii* nosocomial infections is 25%, while the overall mortality rate for nosocomial infections is 0.9%.

With regard to *A. baumannii*, the diversity of resistance mechanisms developed is impressive: inactivation enzymes, efflux pumps, impermeability, target modifications. The same applies to genetic factors (mutations, acquisition of transposons, plasmids, integrons, promoter insertion sequence, etc.). At the origin of these processes is an ability to integrate genetic material from relatively genetically similar species. One of the most striking examples is the diversity of enzymes conferring resistance to carbapenems. These resistances are particularly worrying because, since the emergence of cephalosporinase-hyperproducing strains in the 1990s, carbapenems have been the reference antibiotics for *Acinetobacter* infections. The concomitant emergence of resistance to fluoroquinolones and to aminosides has given this bacterium the status of multidrug-resistant bacteria, or MDRB. It is therefore urgent to look for new alternatives in the fight against this bacterium.

Knowledge of the bacterium *A. baumannii* is relatively limited and impedes the discovery of new compounds with a specific mode of action. Therefore, compounds capable of specifically targeting *A. baumannii* to the detriment of other bacteria, fungi and yeasts have two significant advantages: 1) they limit the development of cross-resistance; 2) they have a particular mode of action that may lead to the discovery of a new biological target.

To date, the reference antibiotics are cephalosporinases as first-line treatment, with a high failure rate due to the resistances observed. The antibiogram of *A. baumannii* infection must be broad and complete in order to choose the best therapeutic approach. Colistin, a polypeptide antibiotic of the polymyxin family, often remains the drug used as a last resort against resistant strains. Unfortunately, certain multidrug-resistant strains with colistin resistance have recently been described.

One of the alternatives studied is the use of combinations of known antibiotics in the hope of a synergistic effect on resistant bacterial strains. However, this approach shows limitations in the choice of possible combinations and the long-term applicability of this strategy.

A second strategy aims to increase the sensitivity of bacterial strains to known antibiotics.

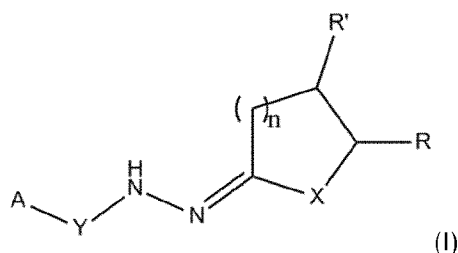
A third strategy is to discover new compounds capable of selectively controlling the bacterium *Acinetobacter baumannii*.

Thus, there is a need for new compounds capable of selectively controlling the bacterium *Acinetobacter baumannii*.

SUMMARY OF THE INVENTION

The inventors have discovered new compounds with antibacterial properties that are specific to the multidrug-resistant bacterium *Acinetobacter baumannii*. The compounds of the invention are therefore capable of selectively controlling the bacterium *Acinetobacter baumannii*.

A first object of the invention is a compound of the following general formula (I):



or a pharmaceutically acceptable salt and/or solvate thereof, wherein:

- A is a group selected from (C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl, aryl or heteroaryl; said (C₁-C₁₀)alkyl group being optionally substituted with one or several groups selected from halo, oxo, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; said (C₃-C₁₀)cycloalkyl group being optionally substituted with one or several groups selected from halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; and said aryl or heteroaryl group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇;
- X is -NR₁-, -S-, -O- or -CH₂-;
- n is 1, 2 or 3;
- Y is a single bond, -CO-, -SO₂- or -(CH₂)_m- with m = 1-10;
- R and R' are, independently of one another, hydrogen, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇;
- R₁ is a hydrogen atom or a (C₁-C₁₀)alkyl group being optionally substituted with one or several groups selected from halo, oxo, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; and
- Each R₇ to R₉ are, independently of one another, hydrogen atom, halo, (C₁-C₆)alkyl or halo(C₁-C₆)alkyl;

for use for preventing and/or treating disorders associated to *Acinetobacter baumannii*.

Another object of the invention is a pharmaceutical composition comprising at least one compound of formula (I) of the invention and at least one pharmaceutically acceptable excipient, for use for preventing and/or treating disorders associated to *Acinetobacter baumannii*.

- 5 Another object of the invention is a pharmaceutical composition comprising:
- (i) at least one compound of formula (I) as defined above, and
 - (ii) at least one other active ingredient, such as one other active ingredient that can be used for preventing and/or treating disorders associated to *Acinetobacter baumannii*,
for use for preventing and/or treating disorders associated to *Acinetobacter baumannii*.

10

DETAILED DESCRIPTION OF THE INVENTION

Definitions

15 For the purpose of the invention, the term “pharmaceutically acceptable” is intended to mean what is useful to the preparation of a pharmaceutical composition, and what is generally safe and non-toxic, for a pharmaceutical use.

The term “pharmaceutically acceptable salt or solvate” is intended to mean, in the framework of the present invention, a salt or solvate of a compound which is pharmaceutically acceptable, as defined above, and which possesses the pharmacological activity of the corresponding compound.

20 The pharmaceutically acceptable salts comprise:

(1) acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid and the like; or formed with organic acids such as acetic, benzenesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxynaphtoic, 2-hydroxyethanesulfonic, lactic, maleic, malic, mandelic, methanesulfonic, muconic, 2-naphtalenesulfonic, propionic, succinic, dibenzoyl-L-tartaric, tartaric, p-toluenesulfonic, trimethylacetic, and trifluoroacetic acid and the like, and

(2) base addition salts formed when an acid proton present in the compound is either replaced by a metal ion, such as an alkali metal ion, an alkaline-earth metal ion, or an aluminium ion; or coordinated with an organic or inorganic base. Acceptable organic bases comprise diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine and the like. Acceptable inorganic bases comprise aluminium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

35 Acceptable solvates for the therapeutic use of the compounds of the present invention include conventional solvates such as those formed during the last step of the preparation of the compounds of the invention due to the presence of solvents. As an example, mention may be made of solvates due to the presence of water (these solvates are also called hydrates) or ethanol.

The terms “(C₁-C₁₀)alkyl”, as used in the present invention, refers to a straight or branched saturated hydrocarbon chain containing from 1 to 10 carbon atoms including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *sec*-

pentyl, *tert*-pentyl, *n*-hexyl, *iso*-hexyl, *sec*-hexyl, *tert*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, and the like.

The terms “(C₁-C₆)alkyl”, as used in the present invention, refers to a straight or branched saturated hydrocarbon chain containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *iso*-pentyl, *sec*-pentyl, *tert*-pentyl, *n*-hexyl, *iso*-hexyl, *sec*-hexyl, *tert*-hexyl, and the like.

The term “(C₃-C₁₀)cycloalkyl”, as used in the present invention, refers to a hydrocarbon monocycle, bicycle or tricycle (i.e. comprising fused rings), each cycle having having 3 to 6 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, decahydronaphthyl, indenyl, indanyl, adamantyl and the like.

The term “aryl”, as used in the present invention, refers to an aromatic hydrocarbon group comprising preferably 6 to 10 carbon atoms and comprising one or more, notably 1 or 2, fused rings, such as, for example, a phenyl or naphthyl group. Advantageously, it will be a phenyl group.

The term “5- or 6-membered aryl” as used in the present invention, refers to an aryl as defined above having 5 or 6 carbon atoms in the ring(s).

The term “(C₁-C₆)alkylaryl”, as used in the present invention, refers to an aryl group as defined above, bound to the molecule via a (C₁-C₆)alkyl group as defined above.

The term “heteroaryl” as used in the present invention refers an aromatic hydrocarbon monocycle or bicycle (i.e. comprising fused rings), each cycle having advantageously 5 or 6 members, notably 6 members, and 1 to 4, notably 1 or 2, carbon atoms having each been replaced with a heteroatom such as a nitrogen, sulfur or oxygen atom, preferably nitrogen or oxygen atom.

A heteroaryl can be notably thiophene, furan, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, triazoles (1,2,3-triazole and 1,2,4-triazole), benzofuran, indole, benzothiophene, benzimidazole, indazole, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine, quinoline, isoquinoline, quinoxaline, quinazoline, etc.

The term “5- or 6-membered heteroaryl” as used in the present invention, refers to a heteroaryl as defined above having 5 or 6 atoms in the ring(s).

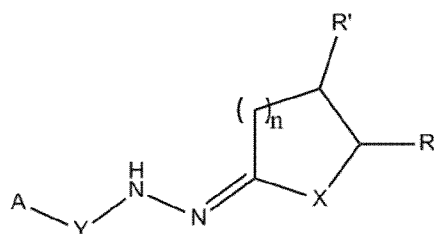
The term “halogen” or “halo”, as used in the present invention, refers to a fluorine, bromine, chlorine or iodine atom.

Within the meaning of this invention, “stereoisomers” is intended to designate diastereoisomers or enantiomers. These are therefore optical isomers. Stereoisomers which are not mirror images of one another are thus designated as “diastereoisomers,” and stereoisomers which are non-superimposable mirror images are designated as “enantiomers”.

Within the meaning of this invention, “conformers” is intended to designate a form of stereoisomers in which the isomers can be interconverted just by rotations about formally single bonds.

Compounds of the invention

A first object of the invention is a compound of formula (I):



or a pharmaceutically acceptable salt and/or solvate thereof, wherein A, X, Y, n, R and R' are as defined above.

- 5 In the compound of the invention, n is an integer between 1 to 3. Advantageously, n is 1 or 2, more advantageously, n is 1.

In the compound of the invention, A is a group selected from (C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl, aryl or heteroaryl; said (C₁-C₁₀)alkyl group being optionally substituted with one or several groups
 10 selected from halo, oxo, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; said (C₃-C₁₀)cycloalkyl group being optionally substituted with one or several groups selected from halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; and said aryl or heteroaryl group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; R₇ to R₉ being as defined above.

Advantageously, A is a group selected from (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl or heteroaryl;
 20 said (C₁-C₆)alkyl group being optionally substituted with one or several groups selected from halo, oxo, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; said (C₃-C₆)cycloalkyl group being optionally substituted with one or several groups selected from halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; and said aryl or heteroaryl group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; R₇ to R₉ being as defined above.

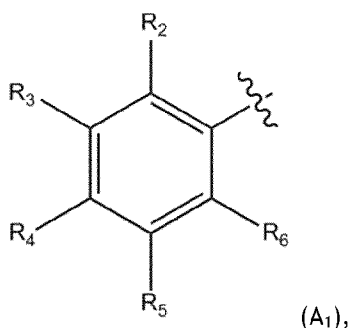
Advantageously, A is a group selected from aryl or heteroaryl, said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; R₇ to R₉ being as defined above.

Advantageously, A is a group selected from aryl or 5-6-membered heteroaryl, said group being
 35 optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -

NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; R₇ to R₉ being as defined above.

Advantageously, A is a group selected from phenyl, naphthyl, pyridyl, pyrrolyl, furyl, thienyl, benzotriazolyl said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; R₇ to R₉ being as defined above.

Advantageously, A is of the following formula (A₁):



wherein R₂ to R₆ are, independently of one another, hydrogen atom, halo, -CF₃, -CN, NO⁺, -NO₂, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, -OS(O)₂R₇, or (C₁-C₆)alkyl; R₇ to R₉ being as defined above.

Advantageously, in the compound of formula (A₁), one or two R₂ to R₆ are, independently of one another, halo, -CF₃, -CN, NO⁺, -NO₂, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, -OS(O)₂R₇, or (C₁-C₆)alkyl, preferably halo, -CF₃, -CN, -OR₇, -NR₇R₈, NO⁺, -NO₂, or (C₁-C₆)alkyl; the others R₂ to R₆ being hydrogen atoms; and wherein R₇ to R₉ are as defined above.

In the compound of the invention, X is -NR₁-, -S-, -O- or -CH₂-, and R₁ is a hydrogen atom or a (C₁-C₁₀)alkyl group being optionally substituted with one or several groups selected from halo, oxo, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇.

Advantageously, X is -NR₁-, -S-, -O- or -CH₂-, and R₁ is a hydrogen atom or a (C₁-C₁₀)alkyl group. Advantageously, X is -NR₁- or -CH₂-, and R₁ is a hydrogen atom or a (C₁-C₁₀)alkyl group. More advantageously, X is -NR₁-, R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl, preferably a hydrogen atom or a (C₁-C₆)alkyl, more preferably a hydrogen atom. In a preferred matter, X is -NH-.

In the compound of the invention, Y is a single bond, -CO-, -SO₂- or -(CH₂)_m- with m = 1-10. Advantageously, Y is a single bond, -CO- or -SO₂-. Advantageously, Y is a single bond or -SO₂-. More advantageously, Y is a single bond.

In the compound of the invention, R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇. Advantageously, R and R' are, independently of one another, H, -F, -NO₂, -CF₃ or -Cl.

5

Advantageously, in the compound of formula (I):

- n is 1, 2 or 3;
- A is as defined above;
- X is -NR₁-, -S-, -O- or -CH₂-, with R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl group;
- Y is a single bond, -CO- or -SO₂-; and
- R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

10

Advantageously, in the compound of formula (I):

- n is 1, 2 or 3;
- A is as defined above;
- X is -NR₁-, with R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl group;
- Y is a single bond, -CO- or -SO₂-; and
- R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

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20

Advantageously, in the compound of formula (I):

- n is 1, 2 or 3;
- A is as defined above;
- X is -NR₁-, -S-, -O- or -CH₂-, with R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl group;
- Y is a single bond; and
- R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

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30

Advantageously, in the compound of formula (I):

- n is 1, 2 or 3;
- A is a group selected from aryl or heteroaryl, said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇;
- X is -NR₁-, -S-, -O- or -CH₂-, with R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl group;
- Y is a single bond, -CO- or -SO₂-; and

35

- R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

Advantageously, in the compound of formula (I):

- 5
- n is 1 or 2;
 - A is a group selected from aryl or heteroaryl, said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇;
- 10
- X is -NR₁-, with R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl group;
 - Y is a single bond, -CO- or -SO₂-; and
 - R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

15 Advantageously, in the compound of formula (I):

- n is 1, 2 or 3;
 - A is a group selected from aryl or heteroaryl, said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇;
- 20
- X is -NR₁-, -S-, -O- or -CH₂-, with R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl group;
 - Y is a single bond; and
 - R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.
- 25

Advantageously, in the compound of formula (I):

- n is 1, 2 or 3;
 - A is of the general formula (A₁) as defined above;
 - X is -NR₁-, -S-, -O- or -CH₂-, with R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl group;
- 30
- Y is a single bond, -CO- or -SO₂-; and
 - R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

Advantageously, in the compound of formula (I):

- 35
- n is 1 or 2;
 - A is of the general formula (A₁) as defined above;
 - X is -NR₁-, with R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl group;
 - Y is a single bond, -CO- or -SO₂-; and

- R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

Advantageously, in the compound of formula (I):

- 5
- n is 1, 2 or 3;
 - A is of the general formula (A₁) as defined above;
 - X is -NR₁-, -S-, -O- or -CH₂-, with R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl group;
 - Y is a single bond; and
 - R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN,
- 10
- NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

Advantageously, in the compound of formula (I),

- n is 1 or 2;
 - A is as defined above;
- 15
- X is CH₂;
 - Y is a single bond; and
 - R and R' are as defined above.

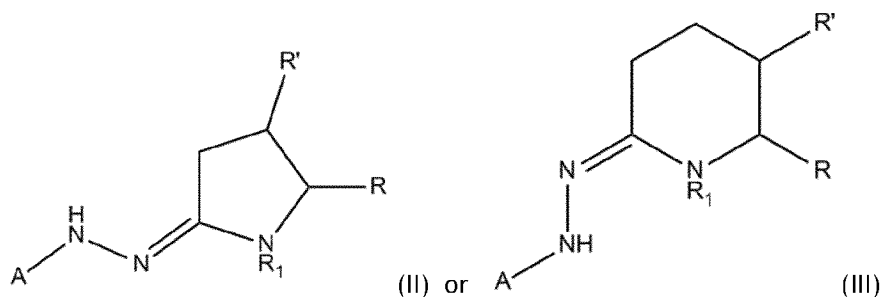
Advantageously, in the compound of formula (I),

- n is 1 or 2;
- 20
- A is a group selected from aryl or heteroaryl, said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇;
 - X is CH₂;
- 25
- Y is a single bond; and
 - R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

Advantageously, in the compound of formula (I),

- 30
- n is 1 or 2;
 - A is of the general formula (A₁) as defined above;
 - X is CH₂;
 - Y is a single bond; and
 - R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN,
- 35
- NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

Advantageously, the compound of the invention is of the following formula (II) or (III):



or a pharmaceutically acceptable salt and/or solvate thereof, wherein A, R₁, R and R' are as defined above.

5 Advantageously, in the compound of formula (II) or (III), R₁ is a hydrogen atom or a (C₁-C₁₀)alkyl, preferably a hydrogen atom or a (C₁-C₆)alkyl, more preferably a hydrogen atom; A, R and R' being as defined above.

Advantageously, in the compound of formula (II) or (III):

- 10 • A is a group selected from aryl or heteroaryl, said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇;
- R₁ is a hydrogen atom or a (C₁-C₁₀)alkyl; and
- 15 • R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

Advantageously, in the compound of formula (II) or (III):

- 20 • A is a group selected from aryl or heteroaryl, said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇;
- R₁ is a hydrogen atom; and
- 25 • R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

Advantageously, in the compound of formula (II) or (III):

- A is of the general formula (A₁) as defined above;
- R₁ is a hydrogen atom or a (C₁-C₁₀)alkyl; and
- 30 • R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

Advantageously, in the compound of formula (II) or (III):

- A is of the general formula (A₁) as defined above;
- R₁ is a hydrogen atom; and
- R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇.

In all the definitions recited above, each R₇, R₈, and R₉ are, independently of one another, hydrogen atom, halo, (C₁-C₆)alkyl or halo(C₁-C₆)alkyl.

- The compound of the invention can be advantageously in the form of a pharmaceutically acceptable salt, such as a salt selected from the group of hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid and the like; or formed with organic acids such as acetic, benzenesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxynaphtoic, 2-hydroxyethanesulfonic, lactic, maleic, malic, mandelic, methanesulfonic, muconic, 2-naphtalenesulfonic, propionic, succinic, dibenzoyl-L-tartaric, tartaric, *p*-toluenesulfonic, trimethylacetic, and trifluoroacetic acid and the like. Advantageously, the compound of the invention is in the form of hydrochloride salt.

- The compound according to the present invention can be in particular selected from the compounds 1 to 55, advantageously 1 to 22 and 23 to 53, in particular 1 to 22, preferably from compounds 1 to 12, 19 to 21, 23 to 29 and 32 to 53, in particular from compounds 1 to 12 and 19 to 21 of the examples below and the pharmaceutically acceptable salts and solvates thereof, in particular the hydrochloride salts thereof.

- The present invention also relates to the compounds of formula (I) as defined above, for use as antibacterial agent.

The present invention also relates to a method for preventing and/or for treating disorders associated to *Acinetobacter baumannii*, comprising the administration to a person in need thereof of an effective dose of a compound of formula (I) as defined above.

- The present invention also relates to the use of a compound of formula (I) as defined above, for the manufacture of a drug for preventing and/or treating disorders associated to *Acinetobacter baumannii*.

- The disorders associated to the human *Acinetobacter baumannii* may be in particular bacteremia, septic shock, ventilator-associated pneumonia, extensive soft tissue necrosis, and rapidly progressive systemic infections that ultimately lead to multi-organ failure and death are prone to occur in severely immunocompromised hosts. Said rapidly progressive systemic infections may be in particular pneumonia; bronchiolitis; tracheobronchitis; suppurative infection (eg abscesses) in any organ system, including the lungs, urinary tract, skin and soft tissues; bacteremia; septic shock; meningitis (primarily after neurosurgical procedures), cellulitis, or phlebitis in patients with an

indwelling venous catheter; ocular infections; native or prosthetic valve endocarditis; osteomyelitis; septic arthritis; or pancreatic and liver abscesses.

Pharmaceutical composition

5 The invention also relates to a pharmaceutical composition comprising a compound of formula (I) of the invention as disclosed above as active ingredient, in particular as antibacterial agent and/or antioxidant agent, and a pharmaceutically acceptable excipient, for use for preventing and/or treating disorders associated to *Acinetobacter baumannii*.

10 The pharmaceutical compositions according to the invention may be formulated notably for topical administration, oral administration or for injection, wherein said compositions are intended for mammals, including humans. The pharmaceutical composition can be administered orally by means of tablets and gelatin capsules.

15 When a solid composition is prepared in the form of tablets, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic and the like. The tablets may be coated with sucrose or with other suitable materials, or they may be treated in such a way that they have a prolonged or delayed activity and they continuously release a predetermined amount of active principle. A preparation in gelatin capsules may be obtained by mixing the active ingredient with a diluent and pouring the mixture obtained into soft or hard gelatin capsules.

20 For administration by injection, aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersing agents and/or wetting agents are used.

25 The pharmaceutical compositions according to the invention may also be administered topically by all the means and in particular cream, gel, stick or serum

 The active ingredient may be administered in unit dosage forms of administration, in mixture with standard pharmaceutical carriers, to animals or to humans.

30 The pharmaceutical compositions according to the invention may further comprise at least one other active ingredient, such as one other antibacterial agent, advantageously one other active ingredient that can be used for preventing and/or treating disorders associated to *Acinetobacter baumannii*. The other active ingredient is advantageously selected from any antibiotic compound currently used to prevent and/or treat disorders associated to *Acinetobacter baumannii* such as penicillins, cephalosporins, trimethoprim-sulfamethoxazole, fluoroquinolones, aminoglycosides, carbapenems, colistin, and polymyxins.

 The present invention relates also to a pharmaceutical composition comprising:
 (i) at least one compound of formula (I) as defined above, and
 (ii) at least one other active ingredient, such as one other active ingredient that
40 can be used for preventing and/or treating disorders associated to *Acinetobacter baumannii*,

for use for preventing and/or treating disorders associated to *Acinetobacter baumannii*.

The other active ingredient is advantageously selected from any antibiotic compound currently used to prevent and/or treat disorders associated to *Acinetobacter baumannii* such as penicillins, cephalosporins, trimethoprim-sulfamethoxazole, fluoroquinolones, aminoglycosides, carbapenems, colistin, and polymyxins.

The present invention also relates to a method for preventing and/or treating disorders associated to *Acinetobacter baumannii*, comprising the administration to a person in need thereof of an effective dose of a pharmaceutical composition as defined above.

The present invention also relates to the use of a pharmaceutical composition as defined above, for the manufacture of a drug for the prevention and/or the treatment of disorders associated to *Acinetobacter baumannii*.

The disorders associated to the human *Acinetobacter baumannii* may be in particular bacteremia, septic shock, ventilator-associated pneumonia, extensive soft tissue necrosis, and rapidly progressive systemic infections that ultimately lead to multi-organ failure and death are prone to occur in severely immunocompromised hosts. Said rapidly progressive systemic infections may be in particular pneumonia; bronchiolitis; tracheobronchitis; suppurative infection (eg abscesses) in any organ system, including the lungs, urinary tract, skin and soft tissues; bacteremia; septic shock; meningitis (primarily after neurosurgical procedures), cellulitis, or phlebitis in patients with an indwelling venous catheter; ocular infections; native or prosthetic valve endocarditis; osteomyelitis; septic arthritis; or pancreatic and liver abscesses.

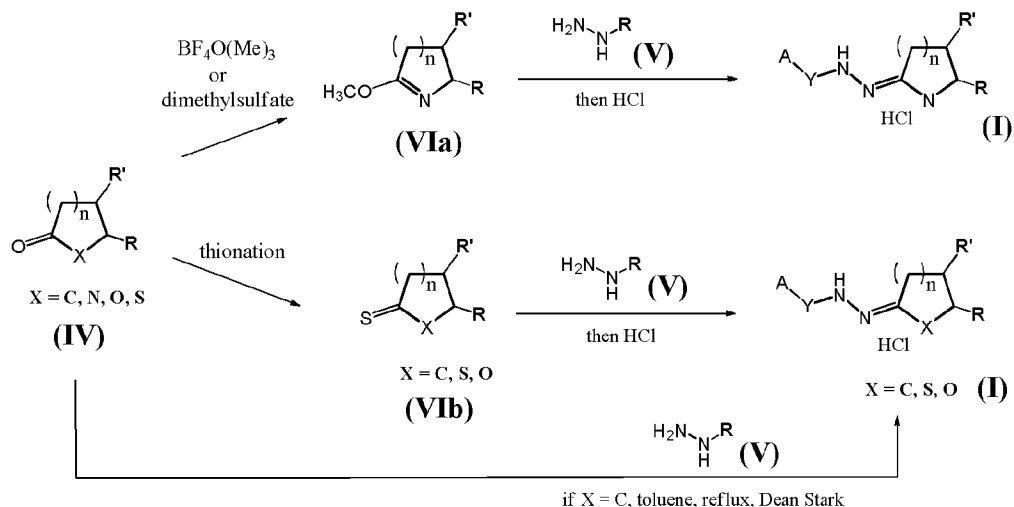
In a particular embodiment, the subject in need thereof is a mammal, in particular an animal or the human.

In a particular and preferred embodiment, the subject in need thereof is the human.

Method for preparing the compounds of the invention

The compounds of the invention (I) can be obtained by a one or two steps process as described in Scheme 1. In a first step, the derivative (IV) can be transformed to its activated form (VIa or VIb) by methyloxonium tetrafluoroborate (Me_3OBF_4) in dichloromethane as described by Mahatthananchai and Bode in *Chemical Science* 2012, 3(1), 192-197 or by Romanov-Michailidis et al in *Organic Letters* 2012, 14(18), 4906-4909. An alternative route to (VIa) may be the use of dimethylsulfate under heating as reported by Schann et al in the *Journal of Medicinal Chemistry* 2001, 44, 1588-1593 so as by Fasseur et al in *J. Heterocycl. Chem.* 1992, 29, 1285 Derivative (VIb) is obtained by thionation of compound IV with the Lawesson reagent as described by Matsumoto, Yohei et al in *Chemistry - A European Journal*, 2018, 24(23), 6062-6066 or using trimethyloxonium tetrafluoroborate (Me_3OBF_4) and NaSH as described by Kaloustian and Khouri in *Tetrahedron Letters*, 1981, 22(5), 413-16. Hydrazine derivatives of general formula (V) may then be added to a solution of the activated intermediate (VI)

in presence of a catalytic amount of acid. The reaction can be followed by NMR and is stopped as soon as compound (VI) has been totally converted. In a typical experiment, intermediate (VI) is dissolved in ethanol in presence of 1%mol equivalent of HCl and hydrazine derivatives of general formula (V) are added dropwise. The mixture can be then heated, for example at 60°C until completion of the reaction. If needed, the compound obtained may be then recovered as stable salts in particular stable hydrochloride salts after treatment, purification and salification. In the particular series where X = CH₂, derivatives IV could be used without activation and directly coupled with hydrazine in toluene at reflux using a Dean Stark device to eliminate water.



Scheme 1.

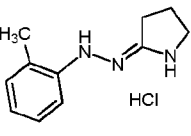
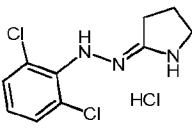
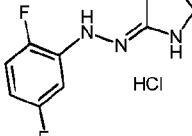
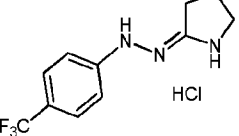
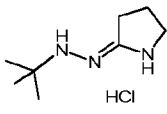
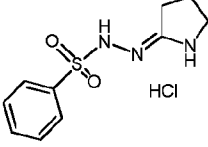
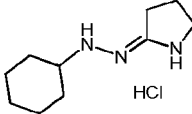
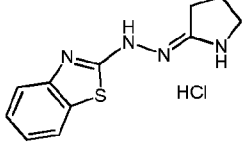
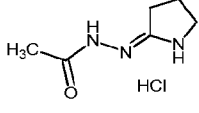
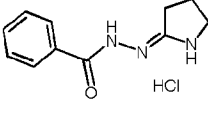
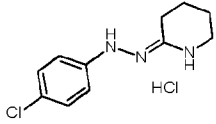
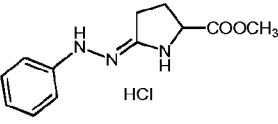
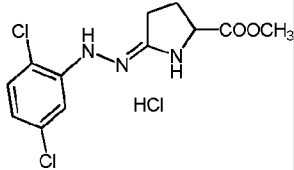
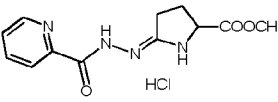
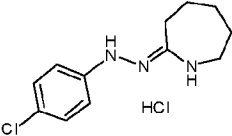
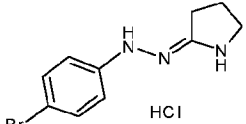
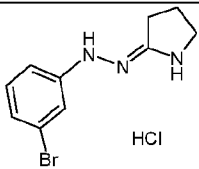
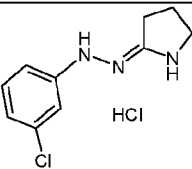
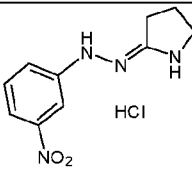
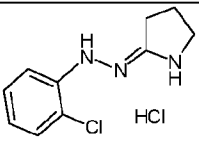
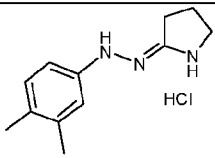
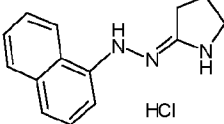
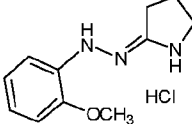
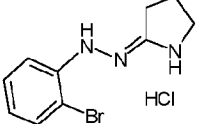
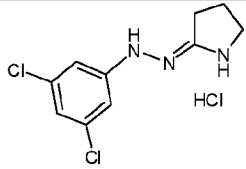
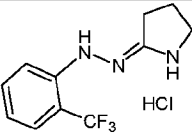
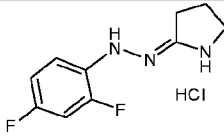
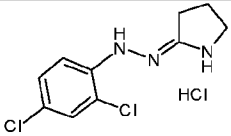
It will be appreciated that while some preferred conditions are herein disclosed for carrying out the processes, such as temperature, reagents, or solvents, for example, it will be matter of routine for the skilled in the art to adjust such conditions to each particular case to achieve optimized results and obtained the targeted products or intermediates.

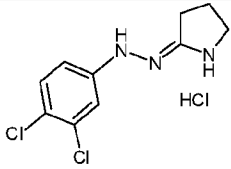
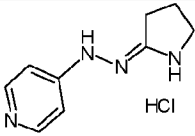
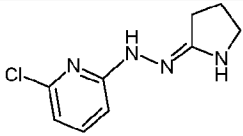
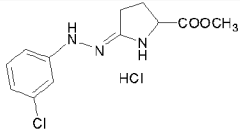
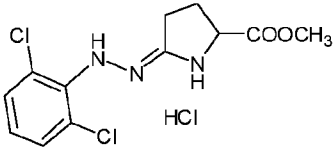
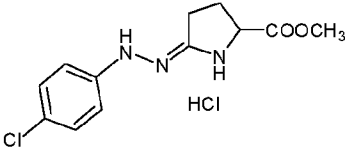
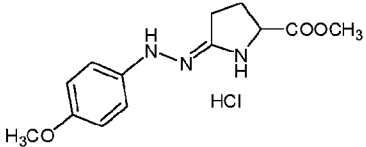
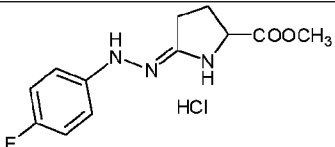
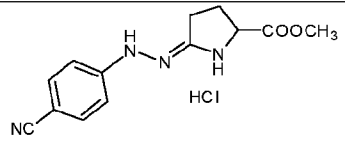
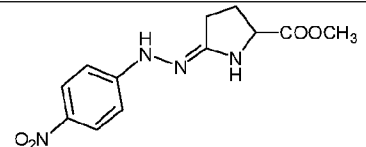
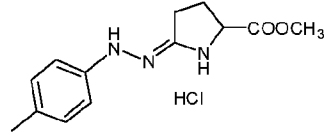
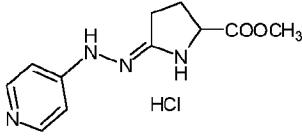
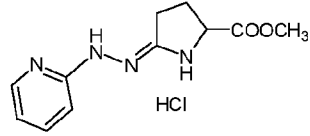
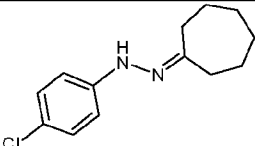
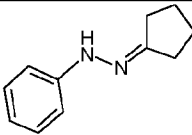
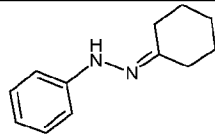
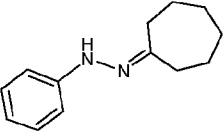
The invention is further illustrated by the following non-limitative examples.

EXAMPLES

1) Table of compounds

1	2	3	4
5	6	7	8

			
9	10	11	12
			
13	14	15	16
			
17	18	19	20
			
21	22	23	24
			
25	26	27	28
			
29	30	31	32
			

33	34	35	36
			
37	38	39	40
			
41	42	43	
			
44	45	46	
			
47	48	49	
			
50	51	52	
			
53			

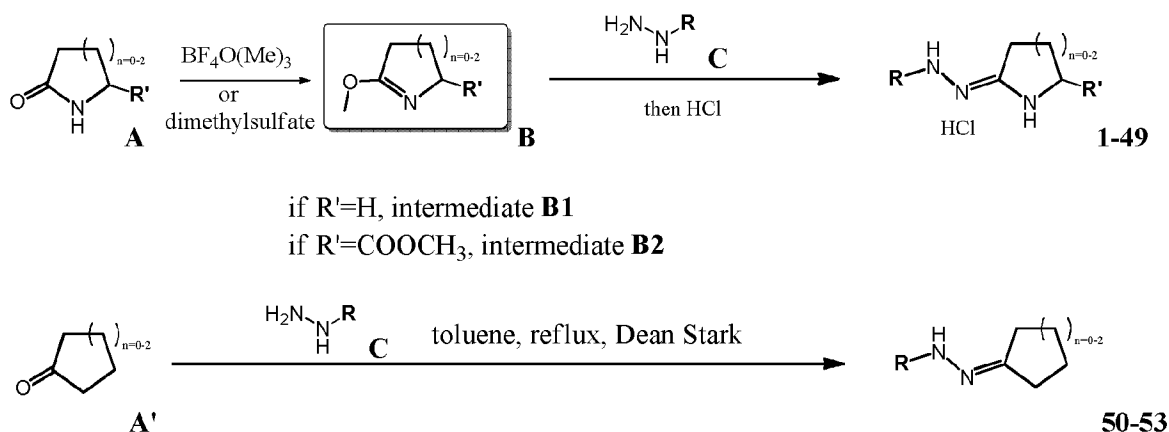
2) Synthesis of the compounds according to the invention:

General methods

In the following examples, the products 1-53 can be obtained by a one or two steps process as described in Scheme 1. In a first step, the lactam derivative **A** is transformed to its iminoether **B**. The iminoether **B** could be obtained by treatment of lactam **A** by use of trimethyloxonium tetrafluoroborate (Me_3OBF_4) in dichloromethane as described by *Mahatthananchai and Bode in Chemical Science 2012, 3(1), 192-197* or by *Romanov-Michailidis et al in Organic Letters 2012, 14(18), 4906-4909*. An alternative route to iminoether **B** may be the use of dimethylsulfate under heating as reported by *Schann et al in the Journal of Medicinal Chemistry 2001, 44, 1588-1593* so as by *Fasseur et al in J. Heterocycl. Chem. 1992, 29, 1285*. Hydrazine derivatives **C** may then be added to a solution of iminoether **B** in presence of a catalytic amount of acid. The reaction can be followed by NMR and is stopped as soon as the iminoether **B** has been totally converted. In a typical experiment, intermediate **B** is dissolved in ethanol in presence of 1%mol equivalent of HCl and phenylhydrazine derivatives **C** are added dropwise. The mixture is then heated to 60°C until completion of the reaction. In the following examples, the products 1-49 are then recovered as stable hydrochloride salts after treatment, purification and salification.

It is to be noted that qualified chemists can use other activation form of the lactam, as thio iminoether, lactam thione, iminochloride and so on.

In the particular series where $\text{X} = \text{CH}_2$, derivatives IV (compounds 50-53) can be obtained in one step from the lactam **A** without activation and directly coupled with hydrazine in toluene at reflux using a Dean Stark device to eliminate water.



Scheme 1.

Abbreviations

TEA: triethylamine

THF: tetrahydrofuran

DCM: dichloromethane

EtOH: ethanol

TLC: thin layer chromatography

5 Et₂O: diethylether

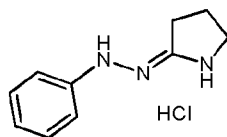
DMSO: dimethylsulfoxide

D₂O: deuterium oxide

Starting materials are commercially available and were used without further purification. Melting
10 points were measured on a MPA 100 OptiMelt® apparatus. Nuclear magnetic resonance (NMR) spectra
were acquired at 400 MHz for ¹H NMR, 100 MHz for ¹³C NMR and 376 MHz for ¹⁹F NMR on a Varian 400-
MR spectrometer, at 25 °C. Chemical shifts (δ) are quoted in parts per million (ppm) and are
referenced to TMS as an internal standard. Coupling constants (J) are quoted in hertz. Comparisons
15 with known or reported compounds and 2D methods (HMBC and HSQC experiments) have been used
to confirm the NMR peak assignments. Organic solutions have been concentrated under reduced
pressure using a Büchi rotary evaporator. Column chromatography was performed with a CombiFlash
Rf Companion (Teledyne-Isco System) using RediSep packed columns. IR spectra were recorded on a
Varian 640-IR FT-IR Spectrometer. Elemental analyses (C, H, N, S) of new compounds were determined
20 on a Thermo Electron apparatus by 'Pôle Chimie Moléculaire-Welience', Faculté de Sciences Mirande,
Université de Bourgogne, Dijon, France. Yield refers to the isolated analytically pure material.

3) Description of the compounds 1-53

Example 1. 2-(2-phenylhydrazono) pyrrolidine hydrochloride - 1



25

Following the general procedure, 2-(2-phenylhydrazono)pyrrolidine hydrochloride was obtained
through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and phenylhydrazine (2.2
g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at
50 °C for 3 h. The crude product was obtained by the evaporation of residual solvent and after
30 transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was
washed with ethanol, affording **1** as a white solid (1.3 g, 30 % yield).

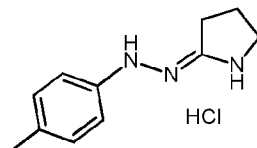
m.p. 230-231 °C

¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (s, 1H, NH), 10.43 (s, 1H, NH), 8.75 (s, 1H, NH), 7.27 (q, J =
7.2 Hz, 2H, CHAr), 6.88 (m, 3H, CHAr), 3.56 (t, J = 7.2 Hz, 2H, CH₂), 2.9 (t, J = 8.0 Hz, 2H, CH₂), 1.81
35 (bs, J = 7.2 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 170.9 (C_{IV}), 146.8 (C_{IV}), 129.4 (2 CHAr), 121.1 (CHAr), 113.8 (2
CHAr), 47.3 (CH₂), 29.0 (CH₂), 21.1 (CH₂).

IR ν (cm^{-1}): 3097, 2994, 1696, 1494, 1313, 1247, 1064.

Example 2. 2-(2-(*p*-tolyl)hydrazono) pyrrolidine hydrochloride - 2



- 5 Following the general procedure, 2-(2-(*p*-tolyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and *p*-tolylhydrazine hydrochloride (3.2 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50°C for 3 h. The crude product was obtained by the evaporation of residual solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **2** as a white solid (2.5 g, 55 % yield).

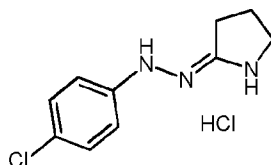
m.p. 249-250°C

^1H NMR (400 MHz, DMSO- d_6): δ 11.58 (s, 1H, NH), 9.99 (s, 1H, NH), 8.59 (s, 1H, NH), 7.05 (d, J = 8.4 Hz, 2H, CHAr), 6.77 (d, J = 8.4 Hz, 2H, CHAr), 3.56 (t, J = 7.2 Hz, 2H, CH₂), 2.96 (t, J = 8.0 Hz, 2H, CH₂), 2.21 (s, 3H, CH₃), 2.14 (m, 2H, CH₂).

- 15 $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): 170.7 (C_{IV}), 144.4 (C_{IV}), 129.9 (C_{IV}), 129.8 (2CHAr), 114.1 (2CHAr), 49.5 (CH₂), 28.9 (CH₂), 21.1 (CH₂), 20.6 (CH₃).

IR ν (cm^{-1}): 3149, 2968, 1704, 1513, 1311, 1253, 1066.

Example 3. 2-(2-(4-chlorophenyl) hydrazono)pyrrolidine hydrochloride - 3



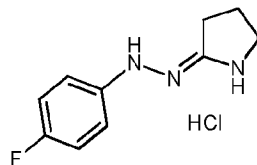
- 20 Following the general procedure, 2-(2-(4-chlorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and (4-chlorophenyl)hydrazine hydrochloride (3.5 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50°C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **3** as a white solid (3.2 g, 65 % yield).

m.p. 244-245°C

- 30 ^1H NMR (400 MHz, DMSO- d_6): δ 11.68 (bs, 1H, NH), 10.08 (s, 1H, NH), 8.94 (bs, 1H, NH), 7.30 (t, J = 8.8 Hz, 2H, CHAr), 6.90 (dd, J = 8.4 Hz, 2H, CHAr), 3.56 (t, J = 6.8 Hz, 2H, CH₂), 2.98 (t, J = 6.8 Hz, 2H, CH₂), 2.16 (t, J = 6.8 Hz, 2H, CH₂).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): 170.9 (C_{IV}), 145.9 (C_{IV}), 129.1 (2CHAr), 124.5 (C_{IV}), 115.5 (2CHAr), 47.4 (CH₂), 29.0 (CH₂), 21.1 (CH₂).

IR ν (cm^{-1}): 3120, 3079, 2968, 1698, 1488, 1314, 1253.

Example 4. 2-(2-(4-fluorophenyl) hydrazono)pyrrolidine hydrochloride - 4

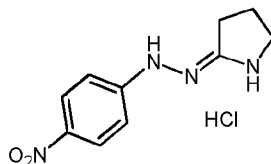
Following the general procedure, 2-(2-(4-fluorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and (4-fluorophenyl)hydrazine hydrochloride (3.3 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50°C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **4** as a white solid (4.0 g, 87 % yield).

m.p. 251-252°C

¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H, NH), 10.05 (s, 1H, NH), 8.81 (s, 1H, NH), 7.10 (t, J = 9.2 Hz, 2H, CHAr), 6.91 (dd, J = 9.2 Hz, J = 2.4 Hz, 2H, CHAr), 3.56 (t, J = 7.2 Hz, 2H, CH₂), 2.96 (t, J = 8.0 Hz, 2H, CH₂), 2.16 (t, J = 7.2 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 170.8 (C_{IV}), 157.4 (C_{IV}, J_{C-F} = 233.3 Hz), 143.3 (d, C_{IV}, J = 2.2 Hz), 115.9 (2CHAr, J_{C-F} = 22.8 Hz), 115.9 (2CHAr, J_{C-F} = 7.6 Hz), 47.3 (CH₂), 29.0 (CH₂), 21.1 (CH₂).

IR ν (cm⁻¹): 3162, 3089, 2971, 1694, 1505, 1313, 1212, 1155.

Example 5. 2-(2-(4-nitrophenyl) hydrazono)pyrrolidine hydrochloride - 5

Following the general procedure, 2-(2-(4-nitrophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and (4-nitrophenyl)hydrazine (3.0 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50°C for 3 h. The crude product was obtained by the evaporation of residual solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **5** as a red solid (1.5 g, 30 % yield).

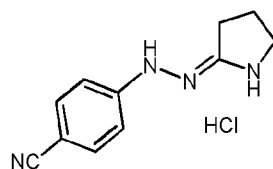
m.p. 237-238°C

¹H NMR (400 MHz, DMSO-d₆): δ 9.17 (s, 1H, NH), 7.98 (dd, J = 8.0 Hz, J = 1.2 Hz, 2H, CHAr), 6.78 (d, J = 9.2 Hz, 2H, CHAr), 6.72 (s, 1H, NH), 3.37 (m, 2H, CH₂), 2.49 (m, 2H, CH₂), 2.06 (m, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 156.4 (C_{IV}), 152.3 (C_{IV}), 135.8 (C_{IV}), 126.7 (2CHAr), 110.1 (2CHAr), 45.3 (CH₂), 29.4 (CH₂), 22.4 (CH₂).

IR ν (cm⁻¹): 3250, 1633, 1583, 1461, 1283, 1252, 1110.

Example 6. 2-(2-(4-cyanophenyl) hydrazono)pyrrolidine hydrochloride - 6



Following the general procedure, 4-(2-(pyrrolidin-2-ylidene)hydrazinyl)benzonitrile hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (1 g, 10.0 mmol) and 4-hydrazinylbenzonitrile hydrochloride (1.7 g, 10.0 mmol), in the presence of 37% HCl (0.1 mmol), in 15 mL EtOH. The mixture was stirred at 50°C for 3 h. The crude product was obtained by the evaporation of residual solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **6** as a white solid (0.7 g, 30 % yield).

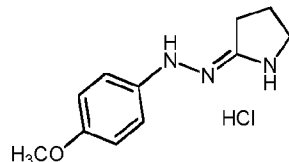
m.p. 231-232 °C

¹H NMR (400 MHz, DMSO-d₆): δ 11.72 (s, 1H, NH), 10.18 (s, 1H, NH), 9.51 (s, 1H, NH), 7.68 (d, J = 6.8 Hz, 2H, CHAr), 6.97 (d, J = 6.8 Hz, 2H, CHAr), 3.58 (t, J = 6.8 Hz, 2H, CH₂), 3.00 (t, J = 8 Hz, 2H, CH₂), 2.19 (t, J = 8.4 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 171.1 (C_{IV}), 150.7 (C_{IV}), 134.0 (2CHAr), 120.0 (C_{IV}), 113.6 (2CHAr), 102.0 (C_{IV}), 47.6 (CH₂), 29.2 (CH₂), 21.0 (CH₂).

IR ν (cm⁻¹): 3048, 2964, 2854, 2212, 1694, 1605, 1518, 1312, 1264, 1169.

Example 7. 2-(2-(4-methoxyphenyl)hydrazono)pyrrolidine hydrochloride - 7



Following the general procedure, 2-(2-(4-methoxyphenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and (4-methoxyphenyl)hydrazine hydrochloride (3.5 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50°C for 3 h. The crude product was obtained by the evaporation of residual solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **7** as a white solid (2.2 g, 45 % yield).

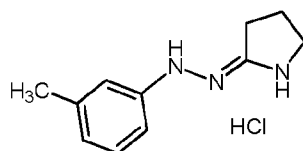
m.p. 237-238 °C

¹H NMR (400 MHz, DMSO-d₆): δ 11.53 (s, 1H, NH), 10.00 (s, 1H, NH), 8.44 (s, 1H, NH), 6.84 (s, 4H, CHAr), 3.69 (s, 3H, OCH₃), 3.56 (t, J = 7.2 Hz, 2H, CH₂), 2.95 (t, J = 7.6 Hz, 2H, CH₂), 2.14 (t, J = 7.2 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 170.6 (C_{IV}), 154.5 (C_{IV}), 140.3 (C_{IV}), 115.6 (2CHAr), 114.8 (2CHAr), 55.8 (OCH₃), 47.2 (CH₂), 28.9 (CH₂), 21.1 (CH₂).

IR ν (cm⁻¹): 3149, 3092, 2983, 1704, 1506, 1235, 1172, 1031.

Example 8. 2-(2-(*m*-tolyl)hydrazono)pyrrolidine hydrochloride - 8



Following the general procedure, 2-(2-(m-tolyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and m-tolylhydrazine hydrochloride (3.2 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of residual solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **8** as a white solid (1.8 g, 40 % yield).

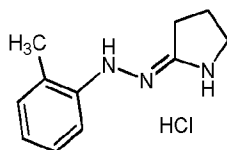
m.p. 234-235 °C

¹H NMR (400 MHz, DMSO-d₆): δ 11.60 (s, 1H, NH), 10.00 (s, 1H, NH), 8.69 (s, 1H, NH), 7.12 (t, J = 7.2 Hz, 1H, CHAr), 6.80 (d, J = 9.2 Hz, 3H, CHAr), 3.54 (t, J = 6.8 Hz, 2H, CH₂), 2.98 (t, J = 8.0 Hz, 2H, CH₂), 2.25 (s, 3H, CH₃), 2.08 (m, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 170.8 (C_{IV}), 146.8 (C_{IV}), 138.7 (C_{IV}), 129.3 (CHAr), 121.9 (CHAr), 114.3 (CHAr), 111.1 (CHAr), 47.3 (CH₂), 28.9 (CH₂), 21.6 (CH₃), 21.1 (CH₂).

IR ν (cm⁻¹): 3099, 2876, 1704, 1592, 1488, 1310, 1170, 1063.

Example 9. 2-(2-(o-tolyl)hydrazono) pyrrolidine hydrochloride - **9**



Following the general procedure, 2-(2-(o-tolyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and o-tolylhydrazine hydrochloride (3.2 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of residual solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **9** as a white solid (2.3 g, 50 % yield).

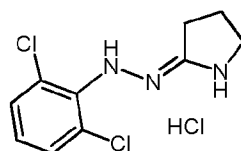
m.p. 256-257 °C

¹H NMR (400 MHz, DMSO-d₆): δ 11.70 (s, 1H, NH), 9.95 (s, 1H, NH), 8.13 (s, 1H, NH), 7.08 (d, J = 7.2 Hz, 2H, CHAr), 6.80 (m, 2H, CHAr), 3.56 (t, J = 7.2 Hz, 2H, CH₂), 3.01 (t, J = 8.0 Hz, 2H, CH₂), 2.24 (s, 3H, CH₃), 2.18 (m, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 170.5 (C_{IV}), 144.3 (C_{IV}), 130.8 (CHAr), 126.9 (CHAr), 123.9 (CHAr), 120.9 (CHAr), 112.05 (C_{IV}), 47.2 (CH₂), 29.0 (CH₂), 21.1 (CH₂), 17.7 (CH₃).

IR ν (cm⁻¹): 3173, 1687, 1591, 1311, 1252, 1049.

Example 10. 2-(2-(2,6-dichlorophenyl) hydrazono)pyrrolidine hydrochloride - **10**



Following the general procedure, 2-(2-(2,6-dichlorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and (2,6-dichlorophenyl)hydrazine hydrochloride (4.6 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **10** as a white solid (3.0 g, 55 % yield).

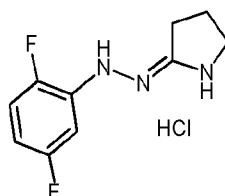
m.p. 249-250 °C

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.9 (s, 1H, NH), 10.25 (s, 1H, NH), 8.00 (s, 1H, NH), 7.48 (t, *J* = 7.6 Hz, 2H, CHAr), 7.12 (t, *J* = 8.0 Hz, 1H, CHAr), 3.65 (t, *J* = 7.2 Hz, 2H, CH₂), 2.86 (t, *J* = 7.6 Hz, 2H, CH₂), 2.17 (t, *J* = 7.6 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-*d*₆): 169.5 (C_{IV}), 138.7 (C_{IV}), 129.9 (2CHAr), 126.3 (CHAr), 125.8 (C_{IV}), 47.5 (CH₂), 29.1 (CH₂), 21.3 (CH₂).

IR ν (cm⁻¹): 3214, 2978, 2814, 1698, 1446, 1303, 1265.

Example 11. 2-(2-(2,5-difluorophenyl) hydrazono)pyrrolidine hydrochloride - **11**



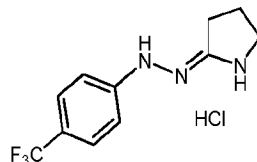
Following the general procedure, 2-(2-(2,5-difluorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and (2,5-difluorophenyl)hydrazine (2.9 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **11** as a white solid (1.0 g, 20 % yield).

m.p. 247-248 °C

¹H NMR (400 MHz, DMSO-*d*₆): δ 11.75 (s, 1H, NH), 10.14 (s, 1H, NH), 8.92 (s, 1H, NH), 7.20 (m, 1H, CHAr), 6.91 (dd, *J* = 7.2 Hz, *J* = 3.2 Hz, 1H, CHAr), 6.70 (d, *J* = 5.2 Hz, 1H, CHAr), 3.58 (t, *J* = 6.8 Hz, 2H, CH₂), 3.01 (t, *J* = 7.6 Hz, 2H, CH₂), 2.19 (t, *J* = 7.6 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-*d*₆): 171.2 (C_{IV}), 159.3 (dd, C_{IV}, *J* = 237 Hz, *J* = 1.5 Hz), 147.0 (dd, C_{IV}, *J* = 237 Hz), 136.1 (dd, C_{IV}, *J* = 13 Hz, *J* = 10.7 Hz), 116.1 (dd, CHAr, *J* = 20.0 Hz, *J* = 10.0 Hz), 106.7 (dd, CHAr, *J* = 33 Hz, *J* = 7.6 Hz), 102.2 (dd, CHAr, *J* = 28.5 Hz, *J* = 3.0 Hz), 47.5 (CH₂), 29.2 (CH₂), 21.0 (CH₂).

IR ν (cm⁻¹): 3144, 2957, 1696, 1504, 1434, 1312, 1157, 1052.

Example 12. 2-(2-(4-trifluoromethylphenyl)hydrazono)pyrrolidine hydrochloride - 12

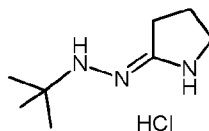
Following the general procedure, 2-(2-(4-(trifluoromethyl)phenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.55 g, 20.1 mmol) and 4-(trifluoromethyl)phenylhydrazine (1 g, 5.6 mmol), in the presence of 37% HCl (0.05 mmol), in 15 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of residual solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **12** as a white solid (1.5 g, 95 % yield).

m.p. 243-244 °C

¹H NMR (400 MHz, DMSO-d₆): δ 11.81 (s, 1H, NH), 10.13 (s, 1H, NH), 9.35 (s, 1H, NH), 7.59 (d, J = 8.4 Hz, 2H, CHAr), 7.00 (d, J = 8.4 Hz, 2H, CHAr), 3.57 (td, J = 6.8 Hz, J = 4.0 Hz, 2H, CH₂), 3.08 (t, J = 7.6 Hz, 2H, CH₂), 2.18 (t, J = 7.2 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 171.0 (C_{IV}), 150.2 (C_{IV}), 126.8 (C_{IV}, J_{C-F} = 3.2 Hz), 123.8 (C_{IV}, J_{C-F} = 269.6 Hz), 113.4 (4CHAr), 47.5 (CH₂), 29.1 (CH₂), 21.1 (CH₂).

IR ν (cm⁻¹): 3088, 2980, 1698, 1615, 1315, 1100.

Example 13. 2-(2-(tert-butyl)hydrazono)pyrrolidine hydrochloride - 13

Following the general procedure, 2-(2-(tert-butyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and tert-butylhydrazine hydrochloride (2.6 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 6 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **13** as a white solid (2.7 g, 70 % yield).

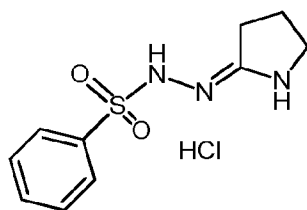
m.p. 244-245 °C

¹H NMR (400 MHz, DMSO-d₆): δ 10.75 (s, 1H, NH), 9.50 (s, 1H, NH), 5.50 (s, 1H, NH), 3.51 (t, J = 7.2 Hz, 2H, CH₂), 2.85 (t, J = 8.0 Hz, 2H, CH₂), 2.10 (t, J = 7.6 Hz, 2H, CH₂), 1.06 (s, 9H, CH₃).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 170.5 (C_{IV}), 54.7 (C_{IV}), 46.7 (CH₂), 28.8 (CH₂), 27.2 (3CH₃), 21.1 (CH₂).

IR ν (cm⁻¹): 3154, 2947, 1680, 1356, 1306, 1220, 1052.

Example 14. N'-(pyrrolidin-2-ylidene) benzenesulfonylhydrazide hydrochloride - 14



Following the general procedure, N'-(pyrrolidin-2-ylidene)benzenesulfonohydrazide was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and benzenesulfonohydrazide (3.4 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **14** as a white solid (2.9 g, 60 % yield).

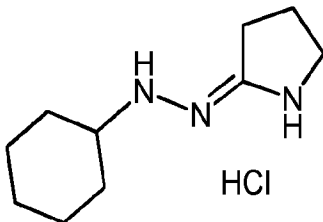
m.p. 191-192 °C

¹H NMR (400 MHz, DMSO-d₆): δ 8.81 (bs, 1H, NH), 7.80 (d, J = 8.4 Hz, 2H, CHAr), 7.54 (d, J = 8.4 Hz, 3H, CHAr), 6.81 (bs, 1H, NH), 3.25 (t, J = 6.4 Hz, 2H, CH₂), 2.17 (bs, 2H, CH₂), 1.83 (t, J = 8.4 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 163.4 (C_{IV}), 140.2 (C_{IV}), 132.4 (CHAr), 129.0 (2CHAr), 127.8 (2CHAr), 45.3 (CH₂), 29.0 (CH₂), 22.1 (CH₂).

IR ν (cm⁻¹): 3247, 1688, 1549, 1262, 1132, 1108, 1067.

Example 15. 2-(2-cyclohexylhydrazono)pyrrolidine hydrochloride - 15



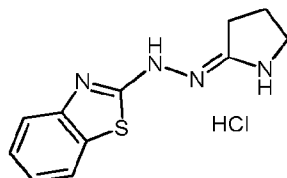
Following the general procedure, 2-(2-cyclohexylhydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and cyclohexylhydrazine hydrochloride (3.0 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **15** as a white solid (2.4 g, 55 % yield).

m.p. 170-171 °C

¹H NMR (400 MHz, DMSO-d₆): δ 11.05 (s, 1H, NH), 9.47 (s, 1H, NH), 5.71 (s, 1H, NH), 3.49 (bs, 2H, CH₂), 2.80 (bs, 2H, CH₂), 2.79 (bs, 1H, CH), 1.81 (bs, 2H, CH₂), 1.81-1.68 (m, 6H, CH₂) 1.20-1.08 (m, 4H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 169.2 (C_{IV}), 58.08 (CH), 46.8 (CH₂), 30.7 (2CH₂), 28.7 (CH₂), 26.0 (CH₂), 24.4 (2CH₂), 21.1 (CH₂).

IR ν (cm⁻¹): 3171, 2923, 2852, 1688, 1454, 1305, 1057.

Example 16. 2-(2-(pyrrolidin-2-ylidene)hydrazinyl)benzo[d]thiazole hydrochloride - 16

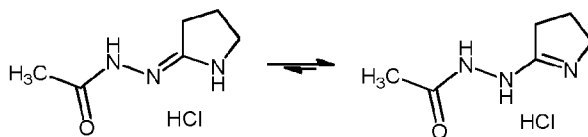
Following the general procedure, 2-(2-(pyrrolidin-2-ylidene)hydrazinyl)benzo[d]thiazole hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (2 g, 20.1 mmol) and 2-hydrazinylbenzo[d]thiazole (3.3 g, 20.1 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **16** as a yellowish solid (1.33 g, 25 % yield).

m.p. 237-238 °C

¹H NMR (400 MHz, DMSO-d₆): δ 12.2 (s, 1H, NH), 9.86 (s, 1H, NH), 7.70 (d, J = 8.0 Hz, 1H, CHAr), 7.30 (d, J = 4.8 Hz, 2H, CHAr), 7.12 (d, J = 8.0 Hz, 1H, CHAr), 3.59 (t, J = 6.8 Hz, 2H, CH₂), 2.95 (t, J = 8.0 Hz, 2H, CH₂), 2.20 (t, J = 7.6 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 165.9 (C_{IV}), 164.9 (C_{IV}), 142.3 (C_{IV}), 126.6 (2CHAr), 122.1 (2CHAr), 114.5 (C_{IV}), 47.0 (CH₂), 28.6 (CH₂), 20.6 (CH₂).

IR ν (cm⁻¹): 2931, 1679, 1607, 1463, 1393, 1305, 1248.

Example 17. (E)-N'-(pyrrolidin-2-ylidene)acetohydrazide hydrochloride - 17

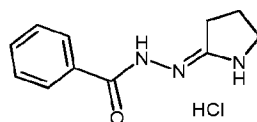
Following the general procedure, (E)-N'-(pyrrolidin-2-ylidene)acetohydrazide hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (1.24 g, 12.8 mmol) and acetohydrazide (0.95 g, 12.8 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **17** as a white solid (1.60 g, 70 % yield).

m.p. 194-195 °C

¹H NMR (400 MHz, DMSO-d₆): δ 9.0 (bs, 1H, NH, isomer 1), 9.1 (s, 1H, NH, isomer 2), 6.70 (bs, 1H, NH, isomers 1 + 2), 3.30-3.26 (m, 2H, CH₂, isomers 1 + 2), 2.34-2.29 (m, 2H, CH₂, isomers 1 + 2), 1.94-1.77 (m, 5H, CH₂ + CH₃ isomers 1 + 2).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 170.8 (C_{IV}), 164.4 (C_{IV}), 158.8 (C_{IV}), 153.3 (C_{IV}), 45.2 (CH₂), 45.1 (CH₂), 29.3 (CH₂), 29.2 (CH₂), 22.4 (CH₂), 22.2 (CH₂), 21.8 (CH₃), 20.6 (CH₃).

Example 18. N'-(pyrrolidin-2-ylidene)benzohydrazide hydrochloride - 18



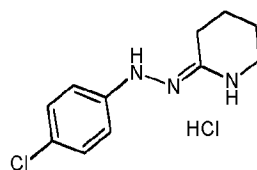
Following the general procedure, N'-(pyrrolidin-2-ylidene)benzohydrazide hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (1.24 g, 12.8 mmol) and benzohydrazide (1.74 g, 12.8 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50°C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **18** as a white solid (2.15 g, 70 % yield).

m.p. 243-244°C

¹H NMR (400 MHz, DMSO-d₆): δ 9.90 (bs, 1H, NH), 7.86 (t, *J* = 6.4 Hz, 2H, CHAr), 7.45-7.38 (m, 3H, CHAr), 7.20-7.10 (bs, 1H, NH), 3.33 (t, *J* = 6.4 Hz, 2H, CH₂), 2.50-2.45 (m, 2H, CH₂), 1.96-1.90 (m, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 162.9 (C_{IV}), 160.5 (C_{IV}), 138.6 (C_{IV}), 130.6 (CHAr), 128.3 (2CHAr), 127.7 (2CHAr), 45.2 (CH₂), 29.3 (CH₂), 22.1 (CH₂).

Example 19. 2-(2-(4-chlorophenyl)hydrazono)piperidine hydrochloride - 19



Following the general procedure, 2-(2-(4-chlorophenyl)hydrazono)piperidine hydrochloride was obtained through the reaction of 6-methoxy-2,3,4,5-tetrahydropyridine (2 g, 17.6 mmol) and (4-chlorophenyl)hydrazine hydrochloride (3.1 g, 17.6 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50°C for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **19** as a white solid (4.5 g, 100 % yield).

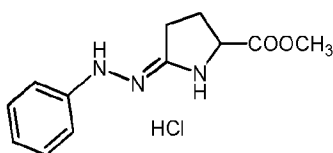
m.p. 267-268°C

¹H NMR (400 MHz, DMSO-d₆): δ 11.35 (s, 1H, NH), 9.68 (s, 1H, NH), 8.72 (s, 1H, NH), 7.28 (d, *J* = 8.8 Hz, 2H, CHAr), 6.89 (d, *J* = 8.4 Hz, 2H, CHAr), 3.26 (s, 2H, CH₂), 2.71 (s, 2H, CH₂), 1.77 (s, 4H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 165.3 (C_{IV}), 145.9 (C_{IV}), 129.1 (2CHAr), 124.5 (C_{IV}), 115.6 (2CHAr), 41.3 (CH₂), 24.0 (CH₂), 21.1 (CH₂), 17.7 (CH₂).

IR ν (cm⁻¹): 3081, 2976, 1658, 1593, 1488, 1412, 1250.

Example 20. Methyl 5-(2-hydrazono)pyrrolidine-2-carboxylate hydrochloride - 20

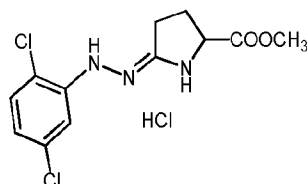


Following the general procedure, methyl 5-(2-hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (2 g, 12.8 mmol) and phenylhydrazine (1.4 g, 12.8 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of residual solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **20** as a yellowish solid (2.0 g, 60 % yield).

m.p. 175-178 °C

¹H NMR (400 MHz, DMSO-d₆): δ 7.23 (t, *J* = 7.6 Hz, 2H, CHAr), 6.92 (t, *J* = 7.6 Hz, 1H, CHAr), 6.80 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 2H, CHAr), 4.60-4.55 (m, 1H, CH), 3.64 (s, 3H, CH₃), 2.98-2.93 (m, 2H, CH₂), 2.70-2.50 (m, 1H, CH₂), 2.40-2.20 (m, 1H, CH₂).

Example 21. Methyl 5-(2-(2,5-dichlorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 21



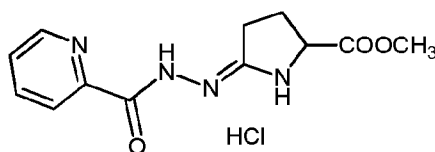
Following the general procedure, methyl 5-(2-(2,5-dichlorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (2 g, 12.8 mmol) and 2,5-dichlorohydrazine (2.26 g, 12.8 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by the evaporation of residual solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **21** as a white solid (2.38 g, 55 % yield).

m.p. 197-198 °C

¹H NMR (400 MHz, DMSO-d₆): δ 12.6 (bs, 1H, NH), 10.44 (bs, 1H, NH), 8.80 (s, 1H, NH), 7.41 (d, *J* = 8.0 Hz, 1H, CHAr), 7.06 (s, 1H, CHAr), 6.96 (m, 1H, CHAr), 4.60 (dd, *J* = 12.4 Hz, *J* = 3.6 Hz, 1H, CH), 3.16-2.97 (m, 2H, CH₂), 2.51 (s, 3H, CH₃), 2.58-2.05 (m, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 172.3 (C_{IV}), 171.4 (C_{IV}), 143.9 (C_{IV}), 133.1 (C_{IV}), 131.4 (CHAr), 121.3 (CHAr), 117.2 (C_{IV}), 113.7 (CHAr), 60.4 (CH), 53.0 (CH₃), 28.5 (CH₂), 25.7 (CH₂).

Example 22. Methyl 5-(2-picolinoylhydrazono)pyrrolidine-2-carboxylate hydrochloride - 22



Following the general procedure, methyl 5-(2-picolinoylhydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (2 g, 12.8 mmol) and picolinohydrazide (1.75 g, 12.8 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained

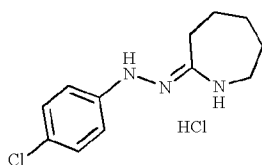
by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording **22** as a yellowish solid (2.1 g, 55 % yield).

m.p. 199-200 °C

- 5 ¹H NMR (400 MHz, DMSO-d₆): δ 10.5-10.0 (bs, 1H, NH), 9.01 (s, 1H, CHAr), 8.64 (dd, *J* = 4.8 Hz, *J* = 1.2 Hz, 1H, CHAr), 8.17 (d, *J* = 8.0 Hz, 1H, CHAr), 7.46 (dd, *J* = 8.0 Hz, *J* = 4.4 Hz, 1H, ArH), 4.34 (m, 1H, CH), 3.68 (s, 3H, CH₃), 2.56-2.50 (m, 2H, CH₂), 2.35-2.29 (m, 1H, CH₂), 2.07-2.00 (m, 1H, CH₂).
- ¹³C{¹H}NMR (100 MHz, DMSO-d₆): 173.3 (C_{IV}), 171.8 (C_{IV}), 161.5 (C_{IV}), 159.6 (C_{IV}), 151.4 (CHAr), 149.0 (CHAr), 135.4 (CHAr), 123.6 (CHAr), 58.6 (CH), 52.5 (CH₃), 28.3 (CH₂), 26.1 (CH₂).

10

Example 23. (E)-2-(2-(4-chlorophenyl)hydrazono)azepane hydrochloride - 23

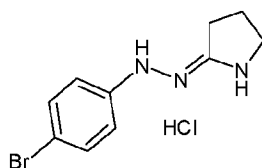


- 15 (E)-2-(2-(4-chlorophenyl)hydrazono)azepane hydrochloride was obtained through the reaction of 7-methoxy-3,4,5,6-tetrahydro-2H-azepine (2.23 g, 17.6 mmol) and (4-chlorophenyl)hydrazine hydrochloride (3.1 g, 17.6 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent and after transformed into the corresponding salt, employing acetyl chloride in MeOH. The obtained salt was washed with ethanol, affording the compound as a white solid (0.5 g, 11 % yield).

m.p. 236-238 °C

- 20 ¹H NMR (400 MHz, DMSO-d₆): δ 11.50 (s, 1H, HCl), 9.69 (br s, 1H, NH), 8.72 (s, 1H, NH), 7.32 (d, *J* = 8.8 Hz, 2H, CHAr), 6.84 (d, *J* = 8.0 Hz, 2H, CHAr), 3.42 (m, 2H, CH₂), 2.81 (m, 2H, CH₂), 1.73 (m, 4H, 2CH₂), 1.54 (m, 2H, CH₂).
- ¹³C NMR (100 MHz, DMSO-d₆): δ 170.8 (C=N), 145.0 (C_{IV}), 128.9 (2CHAr), 124.3 (C_{IV}), 115.1 (2CHAr), 43.1 (CH₂), 29.0 (CH₂), 28.5 (CH₂), 27.4 (CH₂), 23.4 (CH₂).
- 25 IR ν (cm⁻¹): 3144, 3082, 2932, 2876, 2843, 1665, 1593, 1489, 1449, 1248, 1121.

Example 24. (E)-2-(2-(4-bromophenyl)hydrazono)pyrrolidine hydrochloride - 24



- 30 Following the general procedure, 2-(2-(4-bromophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.5 g, 5 mmol) and (4-bromophenyl)hydrazine hydrochloride (1.1 g, 5 mmol) in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was washed with ethanol, affording the wanted as a white solid (1.0 g, 68 % yield).

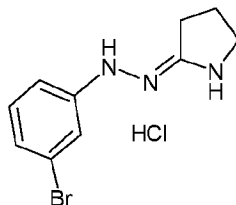
m.p. 246-247 °C

¹H NMR (400 MHz, DMSO-d₆): δ 11.54 (br s, 1H, HCl), 10.09 (br s, 1H, NH), 8.86 (br s, 1H, NH), 7.38 (d, *J* = 8.7 Hz, 2H, CHAr), 6.84 (d, *J* = 8.7 Hz, 2H, CHAr), 3.55 (t, *J* = 7.4 Hz, 2H, CH₂), 2.97 (t, *J* = 7.7 Hz, 2H, CH₂), 2.17 (quint, *J* = 7.7 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): δ 170.5 (C=N), 145.8 (C_{IV}), 131.6 (2CHAr), 115.5 (2CHAr), 111.8 (C_{IV}), 47.0 (CH₂), 28.6 (CH₂), 20.6 (CH₂).

IR ν (cm⁻¹): 3124, 2966, 1703, 1588, 1487, 1314, 1282, 1254, 1071.

Example 25. (E)-2-(2-(3-bromophenyl)hydrazono)pyrrolidine hydrochloride - 25



Following the general procedure, 2-(2-(3-bromophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2*H*-pyrrole (0.5 g, 5 mmol) and (3-bromophenyl)hydrazine hydrochloride (1.1 g, 5 mmol) in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was washed with ethanol, affording the wanted as a white solid (0.8 g, 54 % yield).

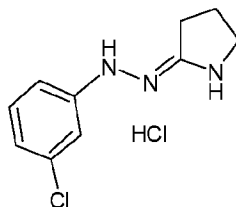
m.p. 247-248 °C

¹H NMR (400 MHz, DMSO-d₆): δ 11.66 (br s, 1H, HCl), 10.02 (br s, 1H, NH), 9.03 (br s, 1H, NH), 7.16 (t, *J* = 7.9 Hz, 1H, CHAr), 7.05-7.01 (m, 2H, CHAr), 6.85 (d, *J* = 7.9 Hz, 1H, CHAr), 3.54 (t, *J* = 7.9 Hz, 2H, CH₂), 2.97 (t, *J* = 7.9 Hz, 2H, CH₂), 2.17 (quint, *J* = 7.9 Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): δ 170.3 (C=N), 148.2 (C_{IV}), 130.9 (CHAr), 123.0 (CHAr), 122.2 (C_{IV}), 115.5 (CHAr), 112.4 (CHAr), 46.9 (CH₂), 28.6 (CH₂), 20.6 (CH₂).

IR ν (cm⁻¹): 3145, 2971, 1693, 1596, 1478, 1312, 1242.

Example 26. (E)-2-(2-(3-chlorophenyl)hydrazono)pyrrolidine hydrochloride - 26



Following the general procedure, 2-(2-(3-chlorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2*H*-pyrrole (1.0 g, 10 mmol) and (3-chlorophenyl)hydrazine hydrochloride (1.7 g, 10.1 mmol), in 20 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was washed with ethanol, affording the wanted compound as a white solid (0.73 g, 30 % yield).

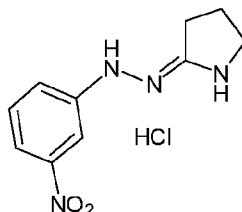
m.p. 242-243 °C

^1H NMR (400 MHz, DMSO- d_6): δ 11.79 (br s, 1H, HCl), 10.09 (br s, 1H, NH), 9.12 (br s, 1H, NH), 7.25 (t, J = 7.9 Hz, 1H, CHAr), 6.89-6.93 (m, 2H, CHAr), 6.84 (d, J = 7.9 Hz, 1H, CHAr), 3.55 (t, J = 7.9 Hz, 2H, CH₂), 2.99 (t, J = 7.9 Hz, 2H, CH₂), 2.16 (quint, J = 7.9 Hz, 2H, CH₂).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 170.6 (C=N), 148.1 (C_{IV}), 133.7 (C_{IV}), 130.6 (CHAr), 120.1 (CHAr), 112.8 (CHAr), 112.1 (CHAr), 47.0 (CH₂), 28.6 (CH₂), 20.6 (CH₂).

IR ν (cm⁻¹): 3166, 3084, 2969, 1690, 1587, 1471, 1307, 1248.

Example 27. (E)-2-(2-(3-nitrophenyl)hydrazono)pyrrolidine hydrochloride - 27



Following the general procedure, (E)-2-(2-(3-nitrophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (1.24 g, 12.8 mmol) and (3-nitrophenyl)hydrazine (1.96 g, 12.8 mmol), in the presence of 37% HCl (0.2 mmol), in 30 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was obtained by filtration. The obtained salt was washed with ethanol, affording **27** as a white solid (1.02 g, 31 % yield).

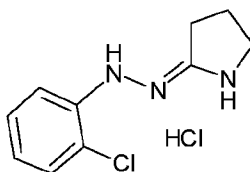
m.p. 242-243 °C

^1H NMR (400 MHz, DMSO- d_6): δ 11.79 (br s, 1H, HCl), 10.09 (br s, 1H, NH), 9.12 (br s, 1H, NH), 7.25 (t, J = 7.9 Hz, 1H, CHAr), 6.89-6.93 (m, 2H, CHAr), 6.84 (d, J = 7.9 Hz, 1H, CHAr), 3.55 (t, J = 7.9 Hz, 2H, CH₂), 2.99 (t, J = 7.9 Hz, 2H, CH₂), 2.16 (quint, J = 7.9 Hz, 2H, CH₂).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 170.6 (C=N), 148.1 (C_{IV}), 133.7 (C_{IV}), 130.6 (CHAr), 120.1 (CHAr), 112.8 (CHAr), 112.1 (CHAr), 47.0 (CH₂), 28.6 (CH₂), 20.6 (CH₂).

IR ν (cm⁻¹): 3153, 3078, 2988, 1692, 1523, 1349, 1311.

Example 28. (E)-2-(2-(2-chlorophenyl)hydrazono)pyrrolidine hydrochloride - 28



Following the general procedure, 2-(2-(2-chlorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (1.0 g, 10 mmol) and (2-chlorophenyl)hydrazine hydrochloride (1.7 g, 10.1 mmol), in 20 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was washed with ethanol, affording the wanted compound as a white solid (1.4 g, 56% yield).

m.p. 246-247 °C

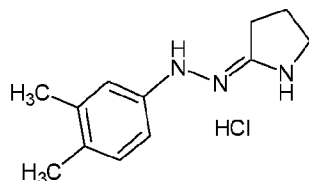
^1H NMR (400 MHz, DMSO- d_6): δ 11.77 (br s, 1H, HCl), 10.06 (br s, 1H, NH), 8.44 (br s, 1H, NH), 7.35 (dd, J = 7.8, 1.2 Hz, 1H, CHAr), 7.22 (td, J = 7.8, 1.3 Hz, 1H, CHAr), 6.95 (dd, J = 8.2, 1.5 Hz, 1H,

CHAr), 6.88 (td, $J = 7.8, 1.7$ Hz, 1H, CHAr), 3.56 (t, $J = 7.8$ Hz, 2H, CH₂), 3.01 (t, $J = 7.8$ Hz, 2H, CH₂), 2.18 (quint, $J = 7.8$ Hz, 2H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): δ 170.4 (C=N), 142.1 (C_{IV}), 129.6 (CHAr), 128.0 (CHAr), 121.6 (CHAr), 118.3 (C_{IV}), 114.0 (CHAr), 47.1 (CH₂), 28.8 (CH₂), 20.6 (CH₂).

5 IR ν (cm⁻¹): 3169, 2963, 1690, 1595, 1493, 1302, 1159.

Example 29. (E)-2-(2-(3,4-dimethylphenyl)hydrazono)pyrrolidine hydrochloride - 29



10 Following the general procedure, 2-(2-(3,4-dimethylphenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.86 g, 8.7 mmol) and 3,4-dimethylphenylhydrazine (1.19 g, 8.7 mmol) in 30 mL EtOH. The mixture was stirred at 50 °C for 24 h. The crude product was obtained by filtration. The obtained salt was washed with ethanol, affording 29 as a white solid (0.50 g, 25 % yield).

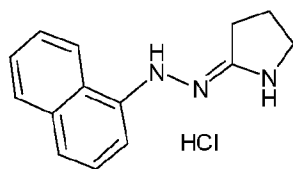
m.p. 212-213 °C

15 ¹H NMR (400 MHz, DMSO-d₆): δ 11.61 (s, 1H, HCl), 9.97 (s, 1H, NH), 8.55 (s, 1H, NH), 6.99 (d, $J = 8.0$ Hz, 1H, CHAr), 6.66 (s, 1H, CHAr), 6.60 (d, $J = 8.0$ Hz, 1H, CHAr), 3.54 (t, $J = 7.6$ Hz, 2H, CH₂), 2.97 (t, $J = 8.0$ Hz, 2H, CH₂), 2.17 (quint, $J = 7.6$ Hz, 2H, CH₂), 2.17 (s, 3H, CH₃), 2.13 (s, 3H, CH₃).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): δ 170.1 (C=N), 144.3 (CHAr), 136.6 (C_{IV}), 129.8 (CHAr), 128.2 (C_{IV}), 114.9 (CHAr), 111.1 (C_{IV}), 46.8 (CH₂), 28.5 (CH₂), 20.7 (CH₂), 19.6 (CH₃), 18.6 (CH₃).

20 IR ν (cm⁻¹): 3157, 2878, 1697, 1614, 1504, 1310, 1300.

Example 30. (E)-2-(2-(naphthalen-1-yl)hydrazono)pyrrolidine hydrochloride - 30



25 Following the general procedure, 2-(2-(naphthalen-1-yl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.5 g, 5 mmol) and naphthalen-1-ylhydrazine hydrochloride (1.0 g, 5 mmol) in 20 mL EtOH. The mixture was stirred at 50 °C for 3 h. The crude product was washed with ethanol, affording a white solid (1.0 g, 76 % yield).

m.p. 256-257 °C

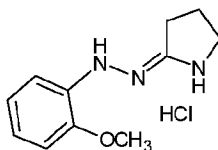
30 ¹H NMR (400 MHz, DMSO-d₆): δ 11.74 (br s, 1H, HCl), 10.04 (br s, 1H, NH), 9.16 (br s, 1H, NH), 8.18-8.16 (m, 1H, CHAr), 7.90-7.88 (m, 1H, CHAr), 7.54-7.52 (m, 2H, CHAr), 7.46 (d, $J = 7.6$ Hz, 1H, CHAr), 7.39 (t, $J = 7.6$ Hz, 1H, CHAr), 6.88 (d, $J = 7.6$ Hz, 1H, CHAr), 3.57 (t, $J = 7.9$ Hz, 2H, CH₂), 3.08 (t, $J = 7.9$ Hz, 2H, CH₂), 2.21 (quint, $J = 7.9$ Hz, 2H, CH₂).

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 170.2 (C=N), 141.2 (C_{IV}), 133.8 (C_{IV}), 128.0 (CHAr), 126.2 (CHAr), 126.0 (CHAr), 125.0 (CHAr), 122.4 (C_{IV}), 122.0 (CHAr), 120.5 (CHAr), 106.2 (CHAr), 47.0 (CH_2), 28.7 (CH_2), 20.7 (CH_2).

IR ν (cm^{-1}): 3234, 2956, 1686, 1583, 1526, 1403, 1310.

5

Example 31. (E)-2-(2-(2-methoxyphenyl)hydrazono)pyrrolidine hydrochloride - 31



Following the general procedure, 2-(2-(2-methoxyphenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.5 g, 5 mmol) and (2-methoxyphenyl)hydrazine hydrochloride (1.1 g, 5 mmol) in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was washed with ethanol, affording the wanted as a white solid (0.75 g, 60 % yield).

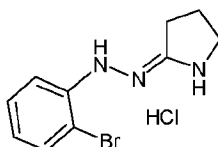
m.p. 262-263 °C

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.35 (br s, 1H, HCl), 9.97 (br s, 1H, NH), 8.06 (br s, 1H, NH), 6.98 (dd, J = 7.3, 2.2 Hz, 1H, CHAr), 6.89-6.85 (m, 2H, CHAr), 6.81 (dd, J = 7.3, 2.2 Hz, 1H, CHAr), 3.82 (s, 3H, OCH_3), 3.55 (t, J = 7.8 Hz, 2H, CH_2), 2.97 (t, J = 7.8 Hz, 2H, CH_2), 2.17 (quint, J = 7.8 Hz, 2H, CH_2).

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 170.3 (C=N), 146.9 (C_{IV}), 134.9 (C_{IV}), 121.1 (CHAr), 120.7 (CHAr), 112.7 (CHAr), 110.9 (CHAr), 55.5 (CH_3), 46.9 (CH_2), 28.6 (CH_2), 20.7 (CH_2).

IR ν (cm^{-1}): 3185, 1698, 1596, 1506, 1456, 1306, 1253, 1229, 1033.

Example 32. (E)-2-(2-(2-bromophenyl)hydrazono)pyrrolidine hydrochloride - 32



Following the general procedure, 2-(2-(2-bromophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.5 g, 5 mmol) and (2-bromophenyl)hydrazine hydrochloride (1.1 g, 5 mmol) in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was washed with ethanol, affording the wanted as a white solid (0.75 g, 60 % yield).

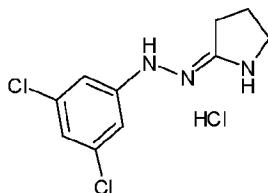
m.p. 227-228 °C

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.75 (br s, 1H, HCl), 10.02 (br s, 1H, NH), 8.23 (br s, 1H, NH), 7.54 (dd, J = 7.9, 1.3 Hz, 1H, CHAr), 7.29 (t, J = 7.6 Hz, 1H, CHAr), 6.96 (dd, J = 8.3, 1.3 Hz, 1H, CHAr), 6.85 (td, J = 7.5, 1.4 Hz, 1H, CHAr), 3.56 (t, J = 7.2 Hz, 2H, CH_2), 3.00 (t, J = 7.2 Hz, 2H, CH_2), 2.18 (quint, J = 7.2 Hz, 2H, CH_2).

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 170.3 (C=N), 143.1 (C_{IV}), 132.9 (CHAr), 128.5 (CHAr), 122.1 (CHAr), 114.2 (CHAr), 107.9 (C_{IV}), 47.1 (CH_2), 28.8 (CH_2), 20.7 (CH_2).

IR ν (cm^{-1}): 3168, 2962, 1690, 1593, 1489, 1301, 1020.

Example 33. (E)-2-(2-(3,5-dichlorophenyl)hydrazono)pyrrolidine hydrochloride - 33



Following the general procedure, (E)-2-(2-(3,5-dichlorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (1.24 g, 12.8 mmol) and (3,5-dichlorophenyl)hydrazine (2.26 g, 12.8 mmol) in 30 mL EtOH. The mixture was stirred at 50°C for 24 h. The crude product was obtained by filtration. The obtained salt was washed with ethanol, affording **33** as a white solid (1.32 g, 37 % yield).

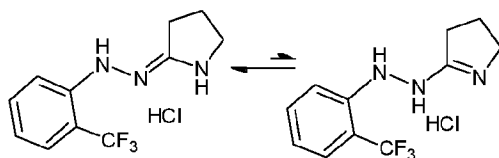
m.p. 216-218 °C

^1H NMR (400 MHz, DMSO- d_6): δ 11.81 (s, 1H, HCl), 10.14 (s, 1H, NH), 9.46 (s, 1H, NH), 7.01 (s, 1H, CHAr), 6.93 (s, 2H, CHAr), 3.55 (t, J = 7.2 Hz, 2H, CH₂), 2.99 (t, J = 7.2 Hz, 2H, CH₂), 2.16 (quint, J = 7.2 Hz, 2H, CH₂).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6): δ 170.8 (C=N), 149.2 (C_{IV}), 134.5 (CHAr), 119.3 (2C_{IV}), 111.6 (2CHAr), 47.1 (CH₂), 28.8 (CH₂), 20.6 (CH₂).

IR ν (cm^{-1}): 2970, 2899, 1682, 1584, 1514, 1449, 1414, 1306.

Example 34. (E)-2-(2-(2-(trifluoromethyl)phenyl)hydrazono)pyrrolidine hydrochloride - 34



Ratio isomer 1/isomer 2 : 91/09

Following the general procedure, 2-(2-(2-(trifluoromethyl)phenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.7 g, 7.1 mmol) and 2-(trifluoromethyl)phenylhydrazine (1.25 g, 7.1 mmol) in 30 mL EtOH. The mixture was stirred at 50°C for 24 h. The crude product was obtained by filtration. The obtained salt was washed with ethanol, affording **34** as a white solid (0.48 g, 30 % yield).

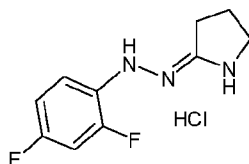
m.p. 204-205 °C

^1H NMR (400 MHz, DMSO- d_6): δ 12.06 (s, 1H, HCl, conformer 1), 11.97 (br s, 1H, HCl, conformer 2), 10.19 (s, 1H, NH, conformer 2), 9.95 (s, 1H, NH, conformer 1), 8.46 (s, 1H, NH, conformer 2), 8.40 (s, 1H, NH, conformer 1), 7.58 (m, 2H, CHAr, conformers 1+2), 7.12 (d, J = 8.4 Hz, 1H, CHAr, conformers 1+2), 7.04 (t, J = 7.7 Hz, 1H, CHAr, conformers 1+2), 3.69 (t, J = 7.6 Hz, 2H, CH₂, conformer 2), 3.57 (t, J = 6.8 Hz, 2H, CH₂, conformer 1), 3.02 (t, J = 8.0 Hz, 2H, CH₂, conformer 1), 2.87 (t, J = 8.0 Hz, 2H, CH₂, conformer 2), 2.18 (t, J = 7.2 Hz, 2H, CH₂, conformer 1), 2.04 (t, J = 8.0 Hz, 2H, CH₂, conformer 2).

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 170.3 (C=N), 143.3 (d, CHAr, $J = 1.1$ Hz), 133.7 (CHAr), 126.6 (q, C_{IV} , $J = 6.1$ Hz), 124.2 (q, CF_3 , $J = 271.8$ Hz), 120.6 (CHAr), 114.1 (CHAr), 113.5 (q, C_{IV} , $J = 12.1$ Hz), 47.2 (CH_2), 28.9 (CH_2), 20.6 (CH_2).

IR ν (cm^{-1}): 3200, 2899, 1694, 1612, 1591, 1454, 1317, 1269, 1163, 1109.

5 **Example 35. (E)-2-(2-(2,4-difluorophenyl)hydrazono)pyrrolidine hydrochloride - 35**



Following the general procedure, 2-(2-(2,4-difluorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.82 g, 8.3 mmol) and 2,4-difluorophenylhydrazine (1.2 g, 8.3 mmol) in 30 mL EtOH. The mixture was stirred at 50 °C for 6 h.

10 The crude product was obtained by filtration. The obtained salt was washed with ethanol, affording **35** as a white solid (0.92 g, 45 % yield).

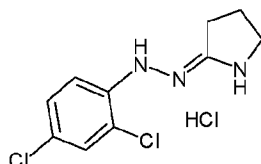
m.p. 162-163 °C

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.80 (s, 1H, HCl), 10.11 (s, 1H, NH), 8.67 (s, 1H, NH), 7.27 (ddd, $J = 12.4, 9.4, 3.4$ Hz, 1H, CHAr), 7.00-7.08 (m, 2H, CHAr), 3.56 (t, $J = 6.8$ Hz, 2H, CH_2), 2.98 (t, $J = 7.2$ Hz, 2H, CH_2), 2.17 (t, $J = 7.6$ Hz, 2H, CH_2).

15 $^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 170.4 (C=N), 156.6 (dd, C_{IV} , $J = 239.0$ Hz, $J = 11.1$ Hz), 150.8 (dd, C_{IV} , $J = 244.4$ Hz, $J = 12.1$ Hz), 131.3 (dd, CHAr, $J = 10.7$ Hz, $J = 2.9$ Hz), 116.3 (dd, CHAr, $J = 9.2$ Hz, $J = 3.4$ Hz), 111.5 (dd, C_{IV} , $J = 21.8$ Hz, $J = 3.4$ Hz), 104.2 (dd, CHAr, $J = 27.6$ Hz, $J = 23.2$ Hz), 46.9 (CH_2), 28.7 (CH_2), 20.7 (CH_2).

20 IR ν (cm^{-1}): 2978, 2880, 1694, 1612, 1508, 1310, 1267, 1202, 1144.

Example 36. (E)-2-(2-(2,4-dichlorophenyl)hydrazono)pyrrolidine hydrochloride - 36



Following the general procedure, 2-(2-(2,4-dichlorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.47 g, 4.7 mmol) and 2,4-dichlorophenylhydrazine (0.76 g, 4.7 mmol) in 30 mL EtOH. The mixture was stirred at 50 °C for 24 h. The crude product was obtained by filtration. The obtained salt was washed with ethanol, affording **36** as a white solid (0.78 g, 60 % yield).

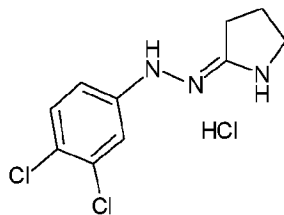
m.p. 210-212 °C

30 ^1H NMR (400 MHz, D_2O): δ 7.51 (d, $J = 2.4$ Hz, 1H, CHAr), 7.31 (dd, $J = 8.8, 2.4$ Hz, 1H, CHAr), 6.94 (d, $J = 8.4$ Hz, 1H, CHAr), 3.73 (t, $J = 7.2$ Hz, 2H, CH_2), 3.07 (t, $J = 8.0$ Hz, 2H, CH_2), 2.34 (t, $J = 8.0$ Hz, 2H, CH_2).

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 170.7 (C=N), 146.8 (C_{IV}), 131.5 (C_{IV}), 130.8 (CHAR), 121.6 (C_{IV}), 114.5 (CHAR), 113.9 (CHAR), 47.0 (CH_2), 28.7 (CH_2), 20.6 (CH_2).

IR ν (cm^{-1}): 3186, 2880, 1697, 1568, 1485, 1450, 1387, 1306, 1290.

Example 37. (E)-2-(2-(3,4-dichlorophenyl)hydrazono)pyrrolidine hydrochloride - 37



Following the general procedure, 2-(2-(3,4-dichlorophenyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (0.7 g, 7.1 mmol) and 3,4-dichlorophenylhydrazine (1.25 g, 7.1 mmol) in 30 mL EtOH. The mixture was stirred at 50°C for 24 h. The crude product was obtained by filtration. The obtained salt was washed with ethanol, affording **37** as a white solid (1.03 g, 52 % yield).

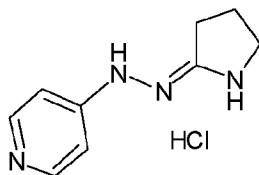
m.p. 208-210 °C

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.60 (s, 1H, HCl), 10.12 (s, 1H, NH), 9.11 (s, 1H, NH), 7.48 (d, J = 8.8 Hz, 1H, CHAR), 7.13 (d, J = 2.0 Hz, 1H, CHAR), 6.88 (dd, J = 7.2, 2.0 Hz, 1H, CHAR), 3.56 (t, J = 7.6 Hz, 2H, CH_2), 2.98 (t, J = 7.6 Hz, 2H, CH_2), 2.17 (t, J = 7.6 Hz, 2H, CH_2).

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 170.7 (C=N), 146.8 (C_{IV}), 131.5 (C_{IV}), 130.8 (CHAR), 121.6 (C_{IV}), 114.5 (CHAR), 113.9 (CHAR), 47.0 (CH_2), 28.7 (CH_2), 20.6 (CH_2).

IR ν (cm^{-1}): 3138, 2965, 2866, 2758, 1694, 1601, 1584, 1466, 1310; 1290.

Example 38. (E)-4-(2-(pyrrolidin-2-ylidene)hydrazinyl)pyridine hydrochloride - 38



Following the general procedure, 2-(2-(4-pyridinyl)hydrazono)pyrrolidine hydrochloride was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (1 g, 10.0 mmol) and 4-hydrazonopyridine (1.47 g, 10.0 mmol) in 30 mL EtOH. The mixture was stirred at 50°C for 24 h. The crude product was obtained by filtration. The obtained salt was washed with heptane (3x 20 mL) and ethanol (15 mL), affording **38** as a white solid (675.1 mg, 32 % yield).

m.p. 195-196 °C

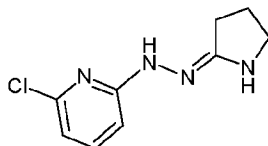
^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.50 (s, 1H, HCl), 10.04 (s, 1H, NH), 8.91 (s, 1H, NH), 7.16 (d, J = 8.0 Hz, 1H, CHAR), 7.00-7.03 (m, 2H, CHAR), 6.82-6.84 (m, 1H, 1CHAR), 3.52 (t, J = 7.2 Hz, 2H, CH_2), 2.95 (t, J = 8.0 Hz, 2H, CH_2), 2.14 (quint, J = 7.6 Hz, 2H, CH_2).

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 170.8 (C=N), 149.2 (C_{IV}), 134.5 (CHAR), 119.3 (CHAR), 111.6 (2CHAR), 47.1 (CH_2), 28.8 (CH_2), 20.6 (CH_2).

IR ν (cm^{-1}): 3144, 2978, 2889, 1694, 1595, 1

481, 1312.

Example 39. (E)-2-chloro-6-(2-(pyrrolidin-2-ylidene)hydrazinyl)pyridine - 39



5 Following the general procedure, (E)-2-chloro-6-(2-(pyrrolidin-2-ylidene)hydrazinyl)pyridine was obtained through the reaction of 5-methoxy-3,4-dihydro-2H-pyrrole (1.04 g, 10.0 mmol) and 2-chloro-6-hydrazinylpyridine (1.43 g, 10.0 mmol) in 30 mL EtOH. The mixture was stirred at 50°C for 24 h. The crude product was obtained by filtration. The obtained salt was washed with ethanol, affording **39** as a white solid (0.25 g, 11 % yield).

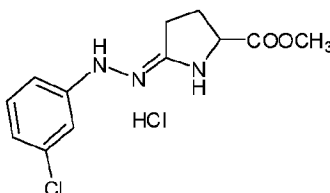
10 **m.p.** 165-166 °C

^1H NMR (400 MHz, DMSO-d_6): δ 8.74 (br s, 1H, NH), 7.42 (t, J = 8.0 Hz, 1H, CHAr), 6.69 (d, J = 8.0 Hz, 1H, CHAr), 6.12 (br s, 1H, NH), 6.48 (d, J = 7.6 Hz, 1H, CHAr), 3.27 (t, J = 7.2 Hz, 2H, CH_2), 2.35 (t, J = 8.0 Hz, 2H, CH_2), 1.86 (quint, J = 7.2 Hz, 2H, CH_2).

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO-d_6): δ 158.4 (C=N), 153.1 (C_{IV}), 147.9 (C_{IV}), 140.3 (CHAr), 110.6 (CHAr), 103.7 (CHAr), 44.8 (CH_2), 28.9 (CH_2), 22.1 (CH_2).

15 IR ν (cm^{-1}): 3242, 2860, 1638, 1589, 1431, 1285, 1269, 1153.

Example 40. (E)-Methyl 5-(2-(3-chlorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 40



20 Following the general procedure methyl 5-(2-(3-chlorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (1.0 g, 6.4 mmol) and (3-chlorophenyl)hydrazine hydrochloride (1.2 g, 6.4 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent. The obtained mixture was washed with ethanol, affording an off-white solid (1.5 g, 77 % yield).

25 **m.p.** 217-218 °C.

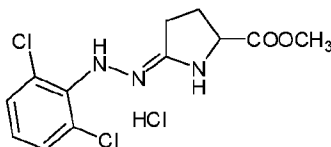
^1H NMR (400 MHz, DMSO-d_6): δ 12.15 (br s, 1H, HCl), 10.51 (br s, 1H, NH), 9.18 (s, 1H, NH), 7.28 (t, J = 8.4 Hz, 1H, CHAr), 6.92-6.95 (m, 2H, CHAr), 6.84 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H, CHAr), 4.64 (dd, J = 9.2, 3.6 Hz, 1H, CH), 3.71 (s, 3H, OCH_3), 3.05-3.09 (m, 2H, CH_2), 2.53-2.63 (m, 1H, CH_2), 2.22-2.28 (m, 1H, CH_2).

30

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 171.6 (C=O), 170.9 (C=N), 147.8 (C_{IV}), 133.7 (CHAr), 130.7 (CHAr), 120.4 (C_{IV}), 112.9 (CHAr), 112.3 (CHAr), 59.8 (CH), 52.6 (CH_3), 27.8 (CH_2), 25.2 (CH_2).

IR ν (cm^{-1}): 3163, 2952, 1750, 1692, 1597, 1477, 1272, 1214.

5 **Example 41. (E)-Methyl 5-(2-(2,6-dichlorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 41**



Following the general procedure methyl 5-(2-(2,6-dichlorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (1.0 g, 6.4 mmol) and (2,6-dichlorophenyl)hydrazine hydrochloride (1.35 g, 6.4 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent. The obtained mixture was washed with ethanol, affording an off-white solid (1.3 g, 60 % yield).

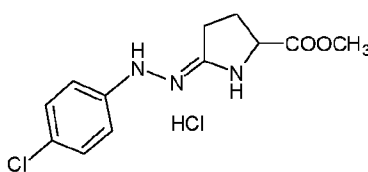
m.p. 189-190° C.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.12 (bs, 1H, NH), 10.60 (s, 1H, NH), 8.13 (s, 1H, NH), 7.49 (m, 2H, CHAr), 7.17 (m, 1H, CHAr), 4.72 (bs, 1H, CH), 3.73 (s, 3H, CH_3), 2.94 (t, J = 6.75 Hz, 2H, CH_2), 2.57 (m, 1H, CH_2), 2.25 (bs, 1H, CH_2).

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (100 MHz, $\text{DMSO}-d_6$): 171.3 (C_{IV}), 170.4 (C_{IV}), 138.6 (C_{IV}), 129.9 (2CHAr), 126.8 (CHAr), 126.2 (2 C_{IV}), 60.3 (CH), 53.0 (CH_3), 28.2 (CH_2), 25.8 (CH_2).

IR ν (cm^{-1}): 3202, 2950, 1748, 1695, 1567, 1449, 1204, 1096.

Example 42. (E)-Methyl 5-(2-(4-chlorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 42



Following the general procedure methyl 5-(2-(3-chlorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (1 g, 6.4 mmol) and (4-chlorophenyl)hydrazine hydrochloride (1.2 g, 6.4 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent. The obtained mixture was washed with ethanol, affording an off-white solid (1.36 g, 70% yield).

m.p. 227-228° C.

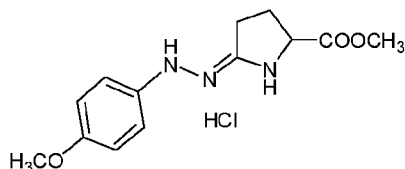
^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.95 (bs, 1H, NH), 10.51 (s, 1H, NH), 8.97 (s, 1H, NH), 7.32 (dd, J = 8.65 Hz, J = 1.92 Hz, 2H, CHAr), 6.91 (dd, J = 8.65 Hz, J = 1.92 Hz, 2H, CHAr), 4.64 (q, J = 4.3 Hz,

1H, CH), 3.74 (s, 3H, CH₃), 3.07 (t, *J* = 8.74 Hz, 2H, CH₂), 2.61-2.51 (m, 1H, CH₂), 2.32-2.25 (m, 1H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 171.4 (C_{IV}), 170.8 (C_{IV}), 145.0 (C_{IV}), 128.7 (2 CHAr), 124.4 (C_{IV}), 115.1 (2CHAr), 59.6 (CH), 52.5 (CH₃), 27.6 (CH₂), 25.1 (CH₂).

5 IR ν (cm⁻¹): 3159, 2953, 1755, 1693, 1489, 1270, 1253, 1093.

Example 43. (E)-Methyl 5-(2-(4-methoxyphenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 43



10 Following the general procedure methyl 5-(2-(4-methoxyphenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2*H*-pyrrole-2-carboxylate (0.5 g, 3.2 mmol) and (4-methoxyphenyl)hydrazine hydrochloride (0.55 g, 3.2 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent. The obtained mixture was washed with ethanol, affording an off-white solid (0.74 g, 78 % yield).

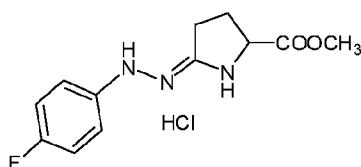
15 m.p. 197-198° C.

¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (bs, 1H, NH), 10.35 (s, 1H, NH), 8.53 (s, 1H, NH), 6.85 (d, *J* = 1.6 Hz, 4H, CHAr), 4.61 (q, *J* = 4.4 Hz, 1H, CH), 3.71 (s, 3H, CH₃), 3.73 (s, 3H, CH₃), 3.06 (t, *J* = 8.2 Hz, 2H, CH₂), 2.66-2.49 (m, 1H, CH₂), 2.32-2.18 (m, 1H, CH₂).

20 ¹³C{¹H}NMR (100 MHz, DMSO-d₆): 171.0 (C=O), 170.9 (C_{IV}), 154.1 (C_{IV}), 139.5 (C_{IV}), 115.3 (2CHAr), 114.4 (2CHAr), 59.4 (CH), 55.2 (CH₃), 52.5 (CH₃), 27.5 (CH₂), 25.2 (CH₂).

IR ν (cm⁻¹): 3173, 2950, 2861, 1749, 1689, 1510, 1238, 1177, 1031.

Example 44. (E)-Methyl 5-(2-(4-fluorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 44



25 Following the general procedure methyl 5-(2-(4-fluorophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2*H*-pyrrole-2-carboxylate (1.0 g, 6.4 mmol) and (4-fluorophenyl)hydrazine hydrochloride (1.0 g, 6.4 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent. The obtained mixture was washed with ethanol, affording an off-white solid (1.5 g, 80 % yield).

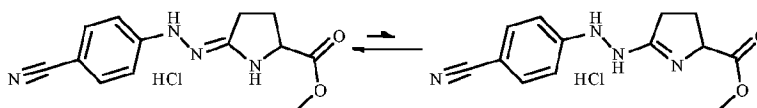
30 m.p. 217-218° C.

¹H NMR (400 MHz, DMSO-d₆): δ 12.12 (s, 1H, NH), 10.45 (s, 1H, NH), 8.90 (s, 1H, NH), 7.12 (t, J = 8.4 Hz, 2H, CHAr), 6.92 (d, J = 2.4 Hz, 2H, CHAr), 4.63 (t, J = 2.4 Hz, 1H, CH), 3.71 (s, 3H, CH₃), 3.05 (d, J = 6.4 Hz, 2H, CH₂), 2.64 (m, 1H, CH₂), 2.24 (d, J = 6.8 Hz, 1H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 171.8 (C_{IV}), 170.7 (C_{IV}), 157.6 (d, C_{IV}, J_{C-F} = 235.4 Hz), 143.0 (C_{IV}), 116.0 (d, CHAr, J_{C-F} = 22.0 Hz), 115.6 (d, CHAr, J_{C-F} = 8.3 Hz), 60.0 (CH), 53.0 (CH₃), 28.1 (CH₂), 25.7 (CH₂).

IR ν (cm⁻¹): 3178, 2957, 2864, 1737, 1687, 1507, 1278, 1214.

Example 45. Methyl 5-(2-(4-cyanophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 45



Ratio conformer 1 / conformer 2: 90/10

Following the general procedure methyl 5-(2-(4-cyanophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (0.5 g, 3.2 mmol) and 4-hydrazinylbenzonitrile hydrochloride (0.5 g, 3.2 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent. The obtained mixture was washed with ethanol, affording an off-white solid (0.56 g, 60 % yield).

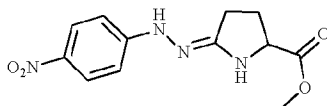
m.p. 221-222 °C.

¹H NMR (400 MHz, DMSO-d₆): δ 12.10 (s, 1H, HCl, conformers 1 + 2), 10.63 (s, 1H, NH, conformer 1), 9.72 (s, 1H, NH, conformer 2), 9.70 (s, 1H, NH, conformer 1), 9.15 (s, 1H, NH, conformer 2), 7.70 (d, J = 8.0 Hz, 2H, CHAr, conformers 1 + 2), 7.06 (d, J = 8.0 Hz, 2H, CHAr, conformer 2), 6.99 (d, J = 8.0 Hz, 2H, CHAr, conformer 1), 6.99 (dd, J = 9.6, 4.4 Hz, 1H, CH, conformer 2), 4.65 (dd, J = 9.6, 4.4 Hz, 1H, CH, conformer 1), 3.74 (s, 3H, CH₃, conformer 2), 3.71 (s, 3H, CH₃, conformer 1), 3.08 (t, J = 8.0 Hz, 2H, CH₂, conformers 1 + 2), 2.55-2.63 (m, 1H, CH₂, conformers 1 + 2), 2.21-2.29 (m, 1H, CH₂, conformers 1 + 2).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): δ 171.7 (C=O), 170.8 (C=N), 150.1 (C_{IV}), 133.6 (2CHAr), 119.5 (C_{IV}), 113.2 (2CHAr), 101.8 (C_{IV}), 59.9 (CH₃), 52.6 (CH), 27.9 (CH₂), 25.1 (CH₂).

IR ν (cm⁻¹): 2996, 2963, 2218, 1751, 1681, 1609, 1519, 1217, 1175.

Example 46. Methyl 5-(2-(4-nitrophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 46



Following the general procedure, methyl 5-(2-(4-nitrophenyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (0.5 g, 3.2 mmol) and (4-nitrophenyl)hydrazine (0.49 g, 3.2 mmol), in 30 mL EtOH. The

mixture was stirred at 50° for 3 h and the precipitate was filtered off. The obtained solid was washed with ethanol, affording the wanted compound as a red solid (0.5 g, 57 % yield).

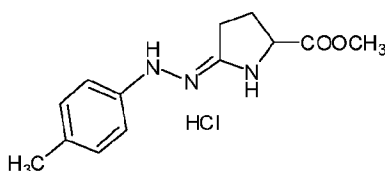
m.p. 204-205° C.

¹H NMR (400 MHz, DMSO-d₆): δ 10.64 (bs, 1H, NH), 9.59 (s, 1H, CHAr), 8.64 (dd, J = 4.8 Hz, J = 1.2 Hz, 1H, CHAr), 8.17 (d, J = 8.0 Hz, 1H, CHAr), 7.46 (dd, J = 8.0 Hz, J = 4.4 Hz, 1H, CHAr), 4.34 (m, 1H, CH), 3.68 (s, 3H, CH₃), 2.56-2.50 (m, 2H, CH₂), 2.35-2.29 (m, 1H, CH₂), 2.07-2.00 (m, 1H, CH₂).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 173.3 (C_{IV}), 171.8 (C_{IV}), 161.5 (C_{IV}), 159.6 (C_{IV}), 151.4 (CHAr), 149.0 (CHAr), 135.4 (CHAr), 123.6 (CHAr), 58.6 (CH), 52.5 (CH₃), 28.3 (CH₂), 26.1 (CH₂).

IR ν (cm⁻¹): 3507, 3253, 1740, 1667, 1591, 1460, 1310, 1228.

Example 47. (E)-Methyl 5-(2-(p-tolyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 47



Following the general procedure methyl 5-(2-(p-tolyl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (1 g, 6.4 mmol) and p-tolylhydrazine hydrochloride (1 g, 6.4 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent. The obtained mixture was washed with ethanol, affording an off-white solid (1.54 g, 85 % yield).

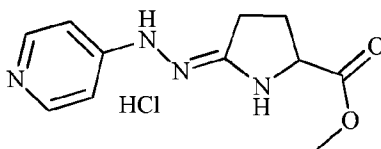
m.p. 204-205° C.

¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (bs, 1H, NH), 10.36 (s, 1H, NH), 8.69 (s, 1H, NH), 7.03 (d, J = 8.4 Hz, 2 H, CHAr), 6.79 (d, J = 8.4 Hz, 2 H, CHAr), 4.61 (q, J = 4.4 Hz, 1H, CH), 3.73 (s, 3H, CH₃), 3.03 (t, J = 7.0 Hz, 2H, CH₂), 2.66-2.49 (m, 1H, CH₂), 2.32-2.25 (m, 1H, CH₂), 2.25 (s, 3H, CH₃).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): 171.0 (C_{IV}), 170.9 (C_{IV}), 143.6 (C_{IV}), 129.6 (C_{IV}), 129.3 (2CHAr), 113.7 (2CHAr), 59.4 (CH), 52.5 (CH₃), 27.5 (CH₂), 25.2 (CH₂), 20.1 (CH₃).

IR ν (cm⁻¹): 3168, 2947, 1745, 1692, 1513, 1276, 1211.

Example 48. Methyl 5-(2-(pyridin-4-yl)hydrazono)pyrrolidine-2-carboxylate hydrochloride - 48

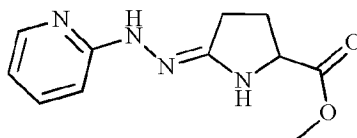


Following the general procedure methyl 5-(2-(4-(pyridin-4-yl)hydrazono)pyrrolidine-2-carboxylate hydrochloride was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (1.0 g, 6.4 mmol) and 4-hydrazinylpyridine hydrochloride (0.92 g, 6.4 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent. The obtained mixture was washed with ethanol, affording an off-white solid (1.05 g, 60 % yield).

m.p. 185-186° C.

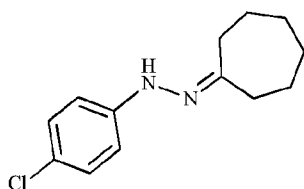
¹H NMR (400 MHz, DMSO-d₆): δ 12.05 (br s, 1H, HCl), 10.42 (br s, 1H, NH), 9.10 (s, 1H, NH), 7.18 (t, *J* = 8.6 Hz, 1H, CHAr), 7.07 (s, 2H, CHAr), 6.88 (d, *J* = 8.0 Hz, 1H, CHAr), 4.64 (dd, *J* = 8.8, 6.8 Hz, 1H, CH), 3.72 (s, 3H, OCH₃), 3.01-3.07 (m, 2H, CH₂), 2.52-2.62 (m, 1H, CH₂), 2.22-2.25 (m, 1H, CH₂).
¹³C{¹H}NMR (100 MHz, DMSO-d₆): δ 171.0 (C=O), 148.0 (C=N), 131.0 (CHAr), 123.2 (C_{IV}), 122.2 (CHAr), 115.6 (CHAr), 112.5 (CHAr), 59.7 (CH), 52.6 (CH₃), 27.7 (CH₂), 25.2 (CH₂).
 IR ν (cm⁻¹): 3162, 2951, 2858, 1749, 1689, 1594, 1475, 1271, 1212.

Example 49. Methyl 5-(2-(pyridin-2-yl)hydrazono)pyrrolidine-2-carboxylate - 49



- Following the general procedure methyl 5-(2-(pyridin-2-yl)hydrazono)pyrrolidine-2-carboxylate was obtained through the reaction of methyl 5-methoxy-3,4-dihydro-2H-pyrrole-2-carboxylate (1 g, 6.4 mmol) and 2-hydrazinylpyridine (0.92 g, 6.4 mmol), in 30 mL EtOH. The mixture was stirred at 50° for 3 h. The crude product was obtained by the evaporation of left solvent. The obtained mixture was washed with ethanol, affording an off-white solid (0.64 g, 37 % yield).
- m.p.** 185-186 °C.
- ¹H NMR (400 MHz, DMSO-d₆): δ 12.06 (bs, 1H, NH), 10.41 (s, 1H, NH), 9.10 (s, 1H, NH), 7.23 (t, *J* = 6.75 Hz, 1H, CHAr), 7.07 (m, 2H, CHAr), 6.89 (d, *J* = 6.75 Hz, 1H, CHAr), 4.64 (d, *J* = 5.05 Hz, 1H, CH), 3.71 (s, 3H, CH₃), 3.05 (t, *J* = 7.0 Hz, 2H, CH₂), 2.62-2.49 (m, 1H, CH₂), 2.24 (m, 1H, CH₂).
¹³C{¹H}NMR (100 MHz, DMSO-d₆): 171.4 (C_{IV}), 148.4 (C_{IV}), 131.4 (CHAr), 123.6 (C_{IV}), 122.7 (CHAr), 116.0 (CHAr), 113.0 (CHAr), 60.1 (CH), 53.0 (CH₃), 28.2 (CH₂), 25.7 (CH₂).
 IR ν (cm⁻¹): 3162, 2951, 2858, 1749, 1689, 1594, 1475, 1271, 1212.

Example 50. 1-(4-Chlorophenyl)-2-cycloheptylidenehydrazine - 50



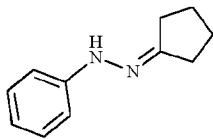
Ratio conformer 1/conformer 2: 94/06

- 1-(4-Chlorophenyl)-2-cycloheptylidenehydrazine was obtained from reaction of cycloheptanone (0.31 g, 2.8 mmol) and 4-chlorophenylhydrazine hydrochloride (0.5, 2.8 mmol) in presence of sodium methoxide 30% (0.5 mL, 2.8 mmol), which were dissolved in toluene. The reaction was stirred at reflux during 3h, in a Dean-Stark apparatus. The mixture was then filtered. The toluene was then evaporated under vacuum and the crude was left to crystallize at room temperature. Crystals was then washed with cold heptane (2x 15mL) and filtered, affording the compound as red oil (210.5 mg, 32%).
- ¹H NMR (400 MHz, DMSO-d₆): δ 11.50 (s, 1H, NH, conformer 2) 8.69 (s, 1H, NH, conformer 1), 7.73 (d, *J* = 8.5 Hz, 2H, CHAr, conformer 2), 7.60 (d, *J* = 8.4 Hz, 2H, CHAr, conformer 2), 7.15 (d, *J* = 8.8 Hz, 2H, CHAr, conformer 1), 7.06 (d, *J* = 8.4 Hz, 2H, CHAr, conformer 1), 2.40 (m, 4H, CH₂ x2,

conformer 1), 1.86 (m, 6H, 3CH₂, conformer 2), 1.69 (m, 2H, CH₂, conformer 1), 1.54 (m, 6H, 3CH₂, conformer 1).

IR ν (cm⁻¹): 3341, 2928, 2857, 1688, 1599, 1493, 1456, 1246.

Example 51. 1-Cyclopentylidene-2-phenylhydrazine - 51



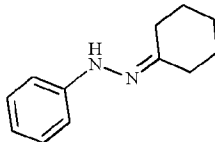
Ratio conformer1/conformer 2: 91/09

1-Cyclopentylidene-2-phenylhydrazine was obtained from reaction of cyclopentanone (0.39 g, 4.6 mmol) and phenylhydrazine (0.5, 4.6 mmol) which were dissolved in toluene. The reaction was stirred at reflux during 3h, in a Dean-Stark apparatus. The toluene was then evaporated under vacuum and the crude was left to crystalize at room temperature. Crystals was then washed with cold heptane (2x 15mL) and filtered, affording the compound as brown oil (142.4 mg, 18%).

¹H NMR (400 MHz, DMSO-d₆): δ 11.8 (s, 1H, NH, conformer 2), 8.45 (s, 1H, NH, conformer 1), 7.72 (m, 2H, CHAr, conformer 2), 7.54 (m, 3H, CHAr, conformer 2), 7.13 (t, *J* = 7.4 Hz, 2H, CHAr, conformer 1), 7.02 (d, *J* = 7.4 Hz, 2H, CHAr, conformer 1), 6.65 (t, *J* = 7.4 Hz, 1H, CHAr, conformer 1), 2.34 (t, *J* = 7.3 Hz, 2H, CH₂, conformer 1), 2.29 (t, *J* = 7.3 Hz, 2H, 2CH₂, conformer 1), 1.99-2.09 (m, 4H, 2CH₂, conformer 2), 1.83-1.93 (m, 4H, 2CH₂, conformer 2), 1.78 (quint, *J* = 6.7 Hz, 2H, CH₂, conformer 1), 1.67 (quint, *J* = 6.7 Hz, 2H, CH₂, conformer1).

IR ν (cm⁻¹): 3323, 2961, 2870, 1724, 1601, 1499, 1258, 1206.

Example 52. 1-Cyclohexylidene-2-phenylhydrazine - 52



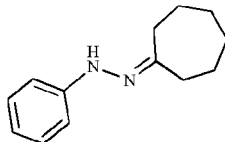
1-Cyclohexylidene-2-phenylhydrazine was obtained from reaction of cyclohexanone (0.45 g, 4.6 mmol) and phenylhydrazine (0.5, 4.6 mmol) which were dissolved in toluene. The reaction was stirred at reflux during 3h, in a Dean-Stark apparatus. The toluene was then evaporated under vacuum and the crude was left to crystalize at room temperature. Crystals was then washed with cold heptane (2x 15mL) and filtered, affording the compound as brown solid (326.7 mg, 38%).

m.p. 53-54 °C

¹H NMR (400 MHz, DMSO-d₆): δ 8.78 (br s, 1H, NH) 7.12 (t, *J* = 7.8 Hz, 2H, ArH), 7.01 (d, *J* = 7.6 Hz, 2H, ArH), 6.64 (t, *J* = 7.2 Hz, 1H, ArH), 2.39 (s, 2H, CH₂), 2.25 (t, *J* = 5.2 Hz, 2H, CH₂), 1.59 (s, 6H, CH₂ x3).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): δ 149.0 (C_{IV}), 146.8 (C_{IV}), 128.6 (2CHAr), 117.7 (CHAr), 112.1 (2CHAr), 35.0 (CH₂), 27.0 (CH₂), 25.9 (CH₂), 25.5 (CH₂), 25.4 (CH₂).

IR ν (cm⁻¹): 3281, 2932, 2860, 1701, 1599, 1495, 1433, 1238, 1225, 1111.

Example 53. 1-Cycloheptylidene-2-phenylhydrazine - 53

1-Cycloheptylidene-2-phenylhydrazine was obtained from reaction of cycloheptanone (0.5 g, 4.6 mmol) and phenylhydrazine (0.52, 4.6 mmol) which were dissolved in toluene. The reaction was stirred at reflux during 3h, in a Dean-Stark apparatus. The toluene was then evaporated under vacuum and the crude was left to crystalize at room temperature. Crystals was then washed with cold heptane (2x 15mL) and filtered, affording the compound as brown solid (835.3 mg, 89%).

m.p. 71-72 °C

¹H NMR (400 MHz, DMSO-d₆): δ 8.49 (br s, 1H, NH), 7.12 (t, *J* = 7.2 Hz, 2H, ArH), 7.05 (d, *J* = 7.2 Hz, 2H, ArH), 6.65 (t, *J* = 7.2 Hz, 1H, ArH), 2.41 (t, *J* = 6.0 Hz, 4H, CH₂x2), 1.70 (s, 2H, CH₂), 1.55 (s, 6H, CH₂ x3).

¹³C{¹H}NMR (100 MHz, DMSO-d₆): δ 151.6 (C_{IV}), 146.7 (C_{IV}), 128.6 (2CHAr), 117.9 (CHAr), 112.4 (2CHAr), 36.6(CH₂), 30.2 (CH₂), 30.1 (CH₂), 30.1 (CH₂), 27.9 (CH₂), 24.2 (CH₂).

IR ν (cm⁻¹): 3331, 2913, 2853, 1599, 1499, 1418, 1310, 1240.

4) Antimicrobial activity**Activity assay**

A sampling of the products of the present invention were tested for their activity against *Acinetobacter baumannii* (*A. baumannii*) as well as against the following bacteria: *Staphylococcus aureus* (*S. aureus*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa* (*P. aeruginosa*). The title compound 1 was also tested against the following fungi/yeasts: *Candida albicans* (*C. albicans*) and *Cryptococcus neoformans* (*C. neoformans*).

Determination of MIC and MBC

The minimum inhibitory concentration (MIC) for *Acinetobacter baumannii* (LMG 1025, ATCC 17978), was determined using the colorimetric resazurine microtitre assay (REMA). Briefly, ampules of frozen bacterial stocks were thawed, and bacteria diluted into Cation Adjusted Mueller Hinton Broth (CAMHB, Difco), to a final working concentration (OD₆₀₀, optical density at 600 nm, of 0.0003 for *A. baumannii*). Working bacterial cultures were then added to the wells of a 96-well plate using a repeater pipette (100 µL in all wells, except first column with 200 µL). To the wells of the first column of the plate (containing the 200 µL of culture), 2 µL of test compound was added at a concentration of 10 mg/mL in DMSO, giving a final concentration of 100 µg/mL (lower concentrations were used for more potent compounds). Eleven serial 1-in-2 dilutions were then made down the plate by transferring 100 µL between wells. The last column of the plate remained without compound as control. Plates were then incubated at 37°C for 5 hrs. To evaluate bacterial viability, 10 µL of 0.025% resazurin was added to the wells and let to incubate for up to 2 hours. Bacterial resazurin turnover to fluorescent resorufin was measured by fluorescence (Ex, 530 nm, Em: 590 nm). The MIC was defined as the

concentration of compound that prevented the turnover of resazurin (less than 10 % resazurin turnover compared to the non-treated control).

Cytotoxicity assay

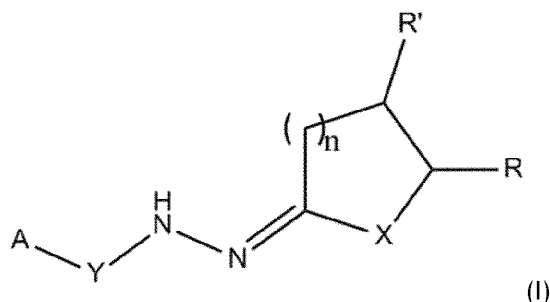
- 5 HepG2 cells (human hepatocellular cell line, ATCC HB-8065) were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA) and maintained in Dulbecco's modified Eagle's Medium (DMEM, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% heat-inactivated fetal bovine serum (FBS, Thermo Fisher Scientific) in a humidified atmosphere of 5% CO₂, 95% air at 37 °C. HepG2 cells were seeded at a density of 2500 cells/well on a 96-well plate in 100 µl of DMEM without red phenol supplemented with 10% FBS. Cells were allowed to attach overnight. Thereafter, 1 mL of
- 10 two-fold serial dilutions of 100x compound in DMSO were added to the cell culture (final concentration 100 µg/mL to 0.4 µg/mL). As a positive control, 1 mM staurosporine was used (final concentration, Biaffin, Kassel, Germany).
- Plates were incubated for 3 days (37 °C 5% CO₂) before the addition of 10 µl of 0.04% resazurin
- 15 (Thermo Fisher Scientific). After 4h of culture, the fluorescence of the resazurin metabolite resorufin was determined (excitation, 530 nm; emission, 590 nm; gain, 850) using FLUOstar OPTIMA microplate reader (BMG Labtech, Ortenberg, Germany). Cytotoxicity was evaluated as a concentration of compound that prevented 50% of resazurin turnover (Cytotoxic IC₅₀) compared to staurosporine.
- 20 As shown in Table of results 1, compounds according to the present invention are highly effective antibacterial against *A. baumannii*. Particularly the MIC values obtained in the assays were lower than 5 µg/mL for most of the tested compounds. The majority of compounds indeed exhibited MIC values lower than 1 µg/mL.

25 Table of results 1

Compounds	1	2	3	4	5
MIC ₁₀₀ (µg/mL)	0.391-1.25	0.391-1.25	0.156-0.313	0.195-0.625	0.078-0.156
Cytotoxicity (µg/mL)	47.4	1.9	56.3	>100	>100
Compounds	6	7	8	9	10
MIC ₁₀₀ (µg/mL)	0.078-0.313	0.391	0.195-0.625	0.391-1.25	0.195
Cytotoxicity (µg/mL)	>100	10.4	>100	>100	>100
Compounds	11	12	19	20	21
MIC ₁₀₀ (µg/mL)	0.156-0.313	0.625	0.078	1	6.25
Cytotoxicity (µg/mL)	>100	>100	nd	>100	>100

CLAIMS

1. A compound of following general formula (I):



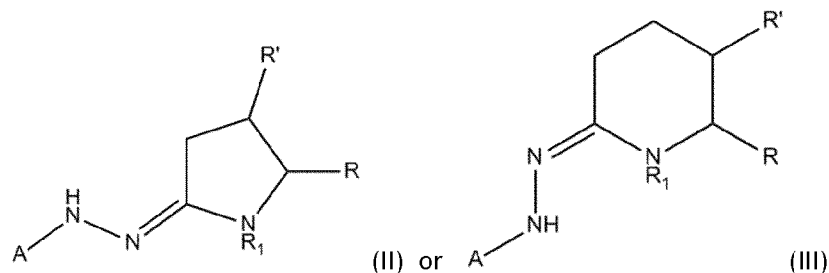
or a pharmaceutically acceptable salt and/or solvate thereof, wherein:

- A is a group selected from (C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl, aryl or heteroaryl; said (C₁-C₁₀)alkyl group being optionally substituted with one or several groups selected from halo, oxo, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; said (C₃-C₁₀)cycloalkyl group being optionally substituted with one or several groups selected from halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; and said aryl or heteroaryl group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇;
 - X is -NR₁-, -S-, -O- or -CH₂-;
 - n is 1, 2 or 3;
 - Y is a single bond, -CO-, -SO₂- or -(CH₂)_m- with m = 1-10;
 - R and R' are, independently of one another, hydrogen atom, halo, oxo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, or -OS(O)₂R₇;
 - R₁ is a hydrogen atom or a (C₁-C₁₀)alkyl group being optionally substituted with one or several groups selected from halo, oxo, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇NR₈R₉, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -CONR₇NR₈R₉, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; and
 - each R₇ to R₉ are, independently of one another, hydrogen atom, halo, (C₁-C₆)alkyl or halo(C₁-C₆)alkyl;
- for use for preventing and/or treating disorders associated to *Acinetobacter baumannii*.

2. The compound for use according to claim 1, wherein Y is a single bond.

3. The compound for use according to claim 1 or 2, wherein X is -NR₁-, R₁ being a hydrogen atom or a (C₁-C₁₀)alkyl, preferably a hydrogen atom or a (C₁-C₆)alkyl, more preferably a hydrogen atom.

4. The compound for use according to any one of claims 1 to 3, being of the following general formula (II) or (III):



or a pharmaceutically acceptable salt and/or solvate thereof, wherein:

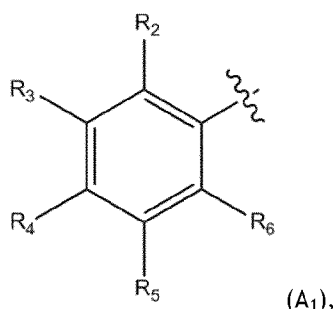
- R₁ is a hydrogen atom or a (C₁-C₁₀)alkyl, preferably a hydrogen atom or a (C₁-C₆)alkyl, more preferably a hydrogen atom; and

- A, R and R' are as defined in claim 1.

5. The compound for use according to any one of claims 1 to 4, wherein A is a group selected from aryl or heteroaryl, said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; R₇ to R₉ being as defined in claim 1.

6. The compound for use according to any one of claims 1 to 5, wherein A is a group selected from aryl or 5-6-membered heteroaryl, said group being optionally substituted with one or several groups selected from halo, (C₁-C₆)alkyl, -CF₃, -CN, -NO₂, -NO⁺, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -CO(NR₇R₈)₂, -SR₇, -S(O)₂R₇, -OCOR₇, -OCONR₇R₈, and -OS(O)₂R₇; R₇ to R₉ being as defined in claim 1.

7. The compound for use according to any one of claims 1 to 6, wherein A is of the following formula (A₁):



wherein R₂ to R₆ are, independently of one another, hydrogen atom, halo, -CF₃, -CN, NO⁺, -NO₂, -OR₇, -NR₇R₈, -NR₇COR₈, -NR₇CO₂R₈, -NR₇S(O)₂R₈, -NR₇NR₈R₉, -CONR₇NR₈R₉, -CO₂R₇, -COR₈, -CONR₇R₈, -

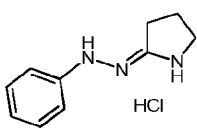
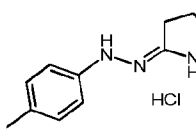
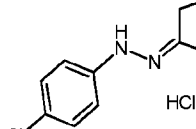
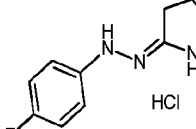
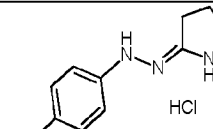
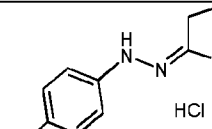
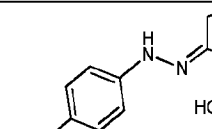
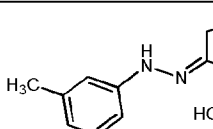
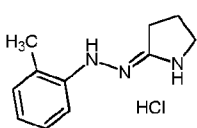
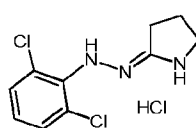
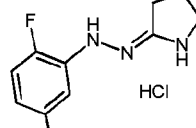
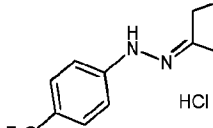
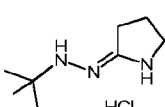
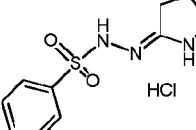
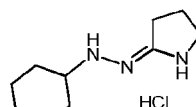
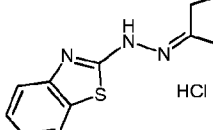
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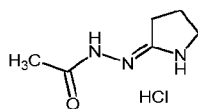
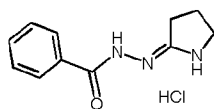
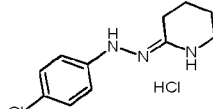
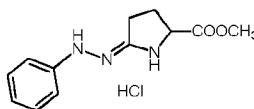
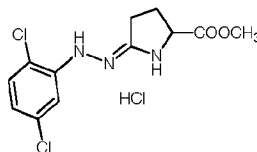
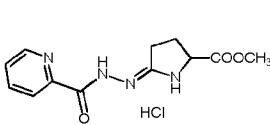
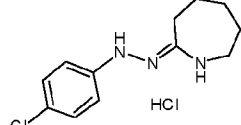
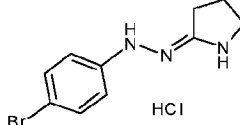
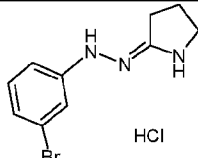
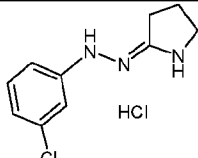
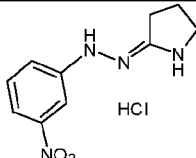
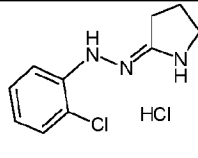
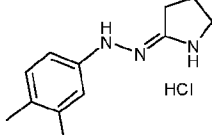
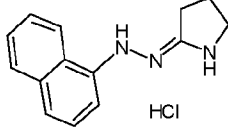
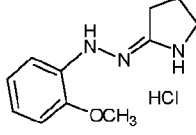
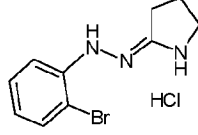
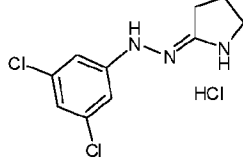
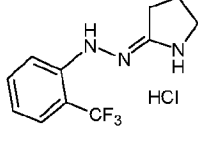
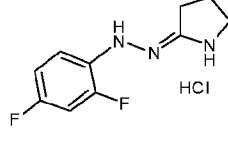
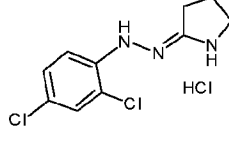
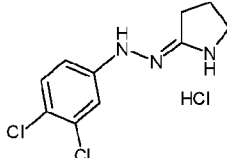
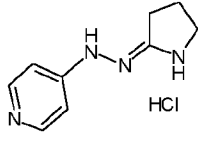
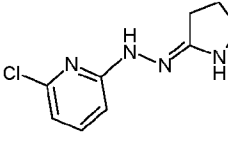
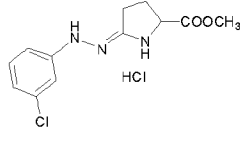
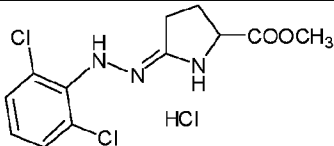
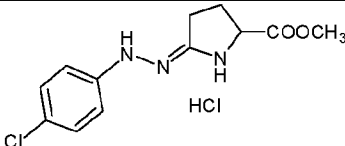
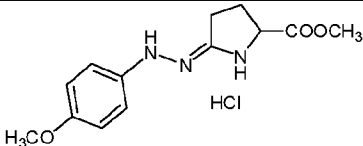
8. The compound for use according to claim 7, wherein one or two R_2 to R_6 are, independently of one another, halo, $-\text{CF}_3$, $-\text{CN}$, NO^+ , $-\text{NO}_2$, $-\text{OR}_7$, $-\text{NR}_7\text{R}_8$, $-\text{NR}_7\text{COR}_8$, $-\text{NR}_7\text{CO}_2\text{R}_8$, $-\text{NR}_7\text{S}(\text{O})_2\text{R}_8$, $-\text{NR}_7\text{NR}_8\text{R}_9$, $-\text{CONR}_7\text{NR}_8\text{R}_9$, $-\text{CO}_2\text{R}_7$, $-\text{COR}_8$, $-\text{CONR}_7\text{R}_8$, $-\text{CO}(\text{NR}_7\text{R}_8)_2$, $-\text{SR}_7$, $-\text{S}(\text{O})_2\text{R}_7$, $-\text{OCOR}_7$, $-\text{OCONR}_7\text{R}_8$, $-\text{OS}(\text{O})_2\text{R}_7$, or $(\text{C}_1\text{-C}_6)\text{alkyl}$, preferably halo, $-\text{CF}_3$, $-\text{CN}$, $-\text{OR}_7$, $-\text{NR}_7\text{R}_8$, NO^+ , $-\text{NO}_2$, or $(\text{C}_1\text{-C}_6)\text{alkyl}$; the others R_2 to R_6 being hydrogen atoms; and wherein R_7 to R_9 are as defined in claim 1.

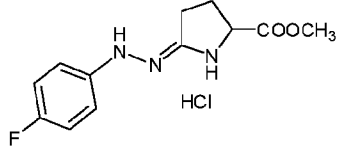
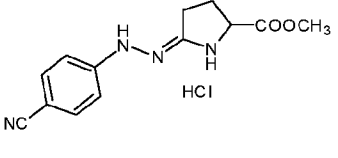
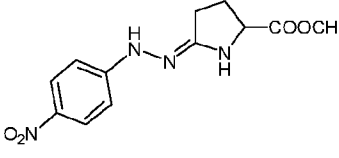
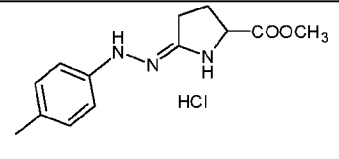
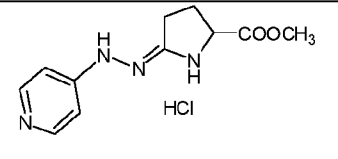
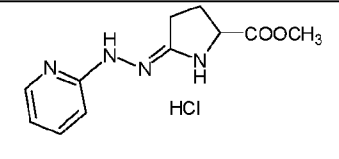
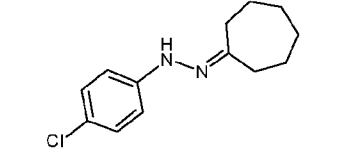
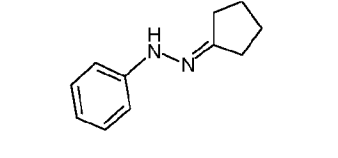
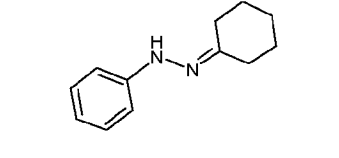
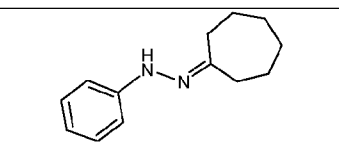
9. The compound for use according to any one of claims 1 to 8, wherein R and R' are, independently of one another, hydrogen atom, $-\text{F}$, $-\text{NO}_2$, $-\text{CF}_3$ or $-\text{Cl}$.

10. The compound for use according to any one of claims 1 to 8, wherein R and R' are hydrogen atom.

11. The compound for use according to claim 1, wherein it is selected from the group:

			
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53		

12. The compound for use according to claim 1, wherein the disorders associated to *Acinetobacter baumannii* are in particular bacteremia, septic shock, ventilator-associated pneumonia, extensive soft tissue necrosis, and rapidly progressive systemic infections.

5

13. A pharmaceutical composition comprising at least one compound according to any one of claims 1 to 11 and at least one pharmaceutically acceptable excipient, for use for preventing and/or the treating disorders associated to *Acinetobacter baumannii*.

10 14. The pharmaceutical composition for use according to claim 13, wherein the disorders associated to *Acinetobacter baumannii* are bacteremia, septic shock, ventilator-associated pneumonia, extensive soft tissue necrosis, and rapidly progressive systemic infections.

15. A pharmaceutical composition comprising:

- 15 (i) at least one compound of formula (I) according to any one of claims 1 to 11, and
(ii) at least one other active ingredient, that can be used for preventing and/or treating disorders associated to *Acinetobacter baumannii*,
for use for preventing and/or treating disorders associated to *Acinetobacter baumannii*.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/054393

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/40 A61K31/427 A61K31/4439 A61K31/4458 A61K31/15 A61K45/06 A61P31/04 A61P11/00 ADD. According to International Patent Classification (IPC) or to both national classification and IPC														
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, SCISEARCH, WPI Data														
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>WO 2018/020004 A1 (ABAC THERAPEUTICS S L [ES]) 1 February 2018 (2018-02-01) pages 85-86; example 31 claims 13, 15</td> <td>1-15</td> </tr> <tr> <td>A</td> <td>WO 2016/016291 A1 (FERRER INT [ES]) 4 February 2016 (2016-02-04) pages 64-66; example 22 claim 24</td> <td>1-15</td> </tr> <tr> <td></td> <td style="text-align: center;">----- -/-</td> <td></td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	WO 2018/020004 A1 (ABAC THERAPEUTICS S L [ES]) 1 February 2018 (2018-02-01) pages 85-86; example 31 claims 13, 15	1-15	A	WO 2016/016291 A1 (FERRER INT [ES]) 4 February 2016 (2016-02-04) pages 64-66; example 22 claim 24	1-15		----- -/-	
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
A	WO 2018/020004 A1 (ABAC THERAPEUTICS S L [ES]) 1 February 2018 (2018-02-01) pages 85-86; example 31 claims 13, 15	1-15												
A	WO 2016/016291 A1 (FERRER INT [ES]) 4 February 2016 (2016-02-04) pages 64-66; example 22 claim 24	1-15												
	----- -/-													
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.														
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Date of the actual completion of the international search 17 April 2020		Date of mailing of the international search report 30/04/2020												
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Cielen, Elsie												

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	PEREIRA DE SÁ NÍVEA ET AL: "Thiazole compounds with activity againstCryptococcus gattiiandCryptococcus neoformans in vitro", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, ELSEVIER, AMSTERDAM, NL, vol. 102, 17 July 2015 (2015-07-17), pages 233-242, XP029267389, ISSN: 0223-5234, DOI: 10.1016/J.EJMECH.2015.07.032 abstract figure 2; compound 1b page 239, column 2, paragraph 2 -----	1,2,5,6, 9-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2020/054393

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