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Original article

Design of novel antimicrobial chloramphenicol chlornitrothienylcol and acetophenicol analogs via recombinant DNA technology

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ABSTRACT

Background: Bacterial resistance to antibiotics is an overwhelming serious problem worldwide. This necessitates searching for novel sources of antibiotics. Chloramphenicol resistance is mediated through the plasmid-encoded acetyltransferase gene. **The objective of the study**: Design of novel antimicrobial chloramphenicol analogs and screening of their in vitro antibacterial activity in Egypt to overcome the bacterial resistance against chloramphenicol. **Methodology:** Our study type was a screening experimental study. In our study, in vitro antimicrobial novel chloramphenicol analogs activity semi-synthetically produced from Streptomyces species in Egypt was evaluated by standard agar dilution technique determining their minimum inhibitory concentrations (MICs) of growth of different pathogenic bacteria in Egypt. Chloramphenicol was purified by column chromatography, then modified by chemo-informatics. Replacement of the phenyl group of chloramphenicol with the nitrothienyl group produced chloramphenicol analog A(chlornitrothienylcol). Also, the replacement of the p-nitro group with the acetyl group constituted chloramphenicol analog B (acetophenicol).**Results:**Both analogs were more active antibacterial agents than chloramphenicol but had less bacterial resistance than it. Both analogs had MICs of less than 10 micrograms/ml for bacterial growth.

Introduction

Micro-organism resistance against current antibiotics represents a serious irresistible juncture globally [1]. This obviates exploring new origins of antibiotics to get over this occasion [2].

The global difficulty of antibiotic resistance shuffle the demand for antimicrobial berth obvious [3].The revelation of antibiotic is extraordinary of the outstanding advances in medication and their utilization has considerably diminished mortality and morbidity globally [4]. Regrettably, with far-flung antibiotic usage we have uttered the egression of multi-drug resistant infectious agents and ablated efficacy of numerous of our most powerful antibacterials [5]. In step-up, we have as well acknowledged many adverse effects of antibiotics, to the highest degree notably the ascending rates of Clostridium difficile inflammatory bowel disease [6].

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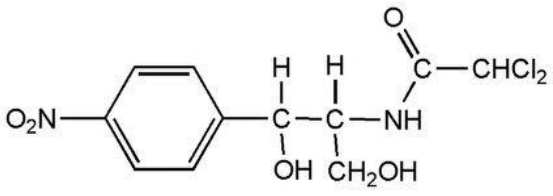
Mechanism of bacterial resistance:

Bacterial resistance to drugs is mediated by four major mechanisms. (i) The antibiotic is inactivated by enzymes produced by bacteria(cephalosporins and penicillins can be inactivated by beta-lactamases via clearing the beta-lactam ring of theantibiotic [7]. (ii) Modified targets are synthesized by bacteria against which the antibiotic possesses a decreased effect such as the resistance to streptomycin can result from a mutant protein in the 30S ribosomal subunit, as well as, the resistance to erythromycin can result from a methylated 23S ribosomal RNA [8]. (iii) The permeability to an antibiotic can be decreased by bacteria such that an effective drug intracellular concentration is not reached such as the amount of penicillin entering the bacterial cells is decreased by alterations in porins [9]. (iv) The antibiotics are actively exported by bacteria using a multi-drug resistance efflux pump.6 Protons are imported by a multidrug resistance pump (MDR) and a variety of diverse molecules including certain antibiotics such as tetracyclines are exported, in an exchange-type reaction [10]. A genetic change in bacteria either the acquisition of a plasmid or transposon or a chromosomal mutation causes most of the antibiotics resistance [11].

Mechanism of bacterial resistance against chloramphenicol antibiotic:

A plasmid-encoded acetyltransferase acetylating chloramphenicol, therefore inactivating it is the major cause of bacterial resistance to chloramphenicol antibiotic [12]. Overview of chloramphenicol: Bacterial protein synthesis is inhibited by chloramphenicol by blocking peptidyl transferase [13]. The new amino acid is added to the growing polypeptide by that enzyme [14]. Bone marrow depression and gray baby syndrome can be caused by chloramphenicol [15].

Figure 1. shows the chloramphenicol chemical structure



In our study, we aimed to design and develop novel chloramphenicol analogs by chemoinformatics to overcome bacterial resistance to chloramphenicol.

Materials and Methods

Materials:

All chemicals and biochemicals were purchased from Algomhuria and Alnasr pharmaceutical and chemical companies in Egypt. This study was done in January 2022 in the faculty of pharmacy, Cairo University, Egypt.

Equipments:

Table 1. List of instruments

Instrument	**Model and manufacturer**
Autoclaves	Tomy, japan
Aerobic incubator	Sanyo, Japan
Digital balance	Mettler Toledo, Switzerland
Oven	Binder, Germany
Deep freezer -80	Artikel
Refrigerator 5	Whirpool
PH meter electrode	Mettler-toledo, UK
Deep freezer -20	whirlpool
Gyratory shaker	Corning gyratory shaker, Japan
190-1100nm Ultraviolet-visible spectrophotometer	UV1600PC, China
Light(optical) microscope	Amscope 120X-1200X,China

Source of animal models:

They were obtained from the faculty of pharmacy, Cairo University, Egypt.

Inclusion criteria for animal models:

I. Adult animals such as rabbit and mice models.

II. Can be infected by different bacterial infectious diseases such as lobar pneumonia and meningitis.III. Obese animals.

Exclusion criteria for animal models:

I. Young animal.

II. Pregnant female animals.

III. Can not be infected by bacterial infectious diseases such as pneumonia and meningitis.

IV. Thin animals.

Type of the study: Screening experimental study.

Methodology:

Isolation of Streptomyces on mineral Streptomyces agar(MSA) selective media:

A total of 50 grassland soil samples were collected from 1–10 cm depth in different locations in Egypt. We prepared these soil samples for the isolation of bacterial strains by the standard serial dilution method. We suspended one gram of each sample in 9 ml of distilled water and vortex-ed. Then, serial dilutions of each sample were carried out up to 10−3 dilutions. The 100 µL of each aliquot from final dilutions was spread over the surface of MSA containing humic acid dissolved in bacteriological agar 25 g, MgSO4 1 g, Na2HPO4 3 g, CaCO3 0.5 g, humic acid 7 g, KCL 15 g, cycloheximide 6 g, distilled water 1 L. The cultured plates were incubated at 25°C in darkness until sporulations of bacterial colonies for one week. Bacterial colonies were identified based on morphological characteristics by light microscopy. Pure and single colonies of Streptomyces were picked and preserved at 2–3°C for further evaluation of the antimicrobial activity.

Purification of chloramphenicol:

By Open Column chromatography on silica gel. The structure of chloramphenicol was determined by employing a mass spectrometer.

Preparation of chloramphenicol analogs by chemo-informatics:

Replacement of the phenyl group of chloramphenicol with nitrothienyl group produced chloramphenicol analog (A). This was done via reacting 5-Nitro-2-thienyl-malononitrile with chloramphenicol in neutral conditions at a temperature not exceeding 50 C. Also, replacement of p-nitro group with acetyl group via reacting chloramphenicol with concentrated acetic acid at neutral PH and temperature not exceeding 25 C constituted chloramphenicol analog (B).

Evaluation of antimicrobial activity:

Antimicrobial activity of chloramphenicol analogs (A and B) were tested by agar dilution technique against enteropathogenic Escherichia coli O157:H7, methicillin-resistant Staphylococcus aureus ATCC 43300, Enterococcus faecium, Pseudomonas aeruginosa, Haemophilus influenza type b, Neisseria meningitides, Streptococcus pneumonia, Bacteroids fragilis, Clostridium difficult, Clostridium perfringens, Clostridium tetani, Rickettsiae infectious bacteria (such as Rickettsia rickettsia, Rickettsia prowazekii, Coxiella burnetii, Analplasma phagocytophilum and Ehrlichia chaffeensis (all Rickettsia were grown in embryonated eggs), Salmonella typhi, Salmonella paratyphi, Chlamydiae trachomatis, and Chlamydiae pneumonae.

(The pathogenic bacterial samples were purchased from the faculty of agriculture at Ain shams university in Egypt) . Their minimum inhibitory concentrations (MICs) of growth were determined.

Study of the pharmacokinetics of chloramphenicol analogs (A and B):

The pharmacokinetics of both analogs were studied on 50 mice and rabbit animal models in comparison with standard chloramphenicol. Also, both analogs were modified by the esterification at the 3-OH(hydroxyl group) position with palmitic and succinic acids.

Study of pharmacodynamics of chloramphenicol analogs (A and B):

The pharmacodynamics of both analogs were studied on 50 mice and rabbit animal models infected with different infectious bacterial diseases such as meningitis, pneumonia, and soft tissue infections.

Formulation of film coated oral chloramphenicol analogs Aand B drug delivery systems:

Tablets of micro-particles of analogs were prepared by the wet granulation method. Starch was added as a diluent,binder and disintegration agent. Magnesium stearate was added as a lubricant agent.All ingredients were passed through 80# mesh sieve.The film-coated tablets were prepared via the aqueous film coating method (film coating is a single process that involves the deposition of a thin film polymer such as 100-micrometer hydroxypropyl methylcellulose phthalate via spraying coating solution onto the tablet beds in a pan coater followed by immediate drying to form thin, film and enteric coat on the micronized tablets in presence of plasticizer such as polyethylene glycol(200-6000)).

Evaluation tests of oral nitrocycline tablets:

These tests were carried out as per British pharmacopeal specifications.

Compatibility study:

We characterized analogs and different excipients utilized in the preparation of oral tablet formulations by FT-IR spectroscopy and DSC to see the compatibility.

Hardness:

We performed a diametric compression test according to British pharmacopeal technique 2.9.8 utilizing Monsanto hardness tester.A hardness of 2kg/cm2 was acceptable in case of oral analog tablets according to standard literature.

Friability:

We dedusted, accurately weighed and placed a random sample of the whole tablets corresponding to 6.5 g in the drum of a Roche friability tester.we rotated the drum 100 times and tablets were accurately weighed ,dedusted and removed.1% was considered acceptable as a maximum weight loss.

Wetting time:

Two layers of a rectangular absorbent paper (10cm×7.5 cm)fitted into a petri dish and wetted thoroughly with distilled water were used for carrying out the test for wetting time. Then we placed the tablet at the centre of the plastic dish and recorded the time required for the water to diffuse from the absorbent paper using stop watch.

Determination of water absorption ratio:

We kept a piece of tissue paper folded twice in a petri dish (internal diameter 6 cm)incorporating 7 ml of purified water.Then we settled the tablets on the tissue paper and left to wet wholly. The wetted tablets were separated and reweighed.

Disintegration test:

The test was carried out according to British pharmacopoeia standards.we placed one tablet in each of the six tubes and utilizing distilled water maintained at 370 C;then tablets were observed for disintegration.The basket from the fluid was lifted up and observed for the tablets complete disintegration at the end of the time limit.

Weight variation:

From each batch 20 tablets were chosen randomly and their average weights were calculated utilizing digital weighing balance(Essae Teraoka ltd);then percentage weight difference was estimated and checked with British pharmacopoeia specifications.

Determination of uniformity of drug content:

From each formulation twenty tablets were weighed and powdered;then10mg of the powder was weighed and dissolved in 100 ml of distilled water.we sonicated the mixture for 170 seconds and filtered through Whatman filter paper No. 40.Then the filtrate was diluted with distilled water and the absorbance at 310 NM was estimated.

In vitro drug release profile :

Distilled water was used as the dissolution medium at 37 C and 50 rpm(paddle).We collected samples at 3,6,8,11,16,19,60,120,240 minutes intervals.The amount of analogs released was measured using UV spectrophotometer at 275 NM.

Stability study:

It was carried out for optimized formulation.The storage conditions utilized for stability studies were accelerated conditions 40 C and room temperature 30 C.Optimized formulation tablets were kept,striped and packed in humidity chamber for thirty days on above mention temperature.

Formulation of parenteral analogs drug delivery systems:

We processed IV and IM antibiotic standard solutions of analogs(1000 microgram/ml via solubility of 100 mg analogs standard powder in 100 ml deionized distilled water(DDW).

Study of the pharmacokinetics of analogs A and B:

The pharmacokinetics of analogs A and B were studied on 50 mice and rabbit animal models in a comparison with standard chloramphenicol.

Study of pharmacodynamics of analog A and B:

The pharmacodynamics of analogs were studied on 50 mice and rabbit animal models infected with different infectious bacterial diseases such as meningitis, pneumonia, and soft tissue infections.

Human evaluation of oral and par-enteral drug delivery systems of analogs via human clinical trials phases 1/2:

3 groups of adult patients with different bacterial infections were included in our study. Each group consisted of 100 subjects:

Group(1)(negative control group) were administrated graded amounts of the placebo by IV,IM and oral routes of administration.Group(2)(positive control group) were administrated graded amounts of the standard chloramphenicol antibiotic intravenous, intramuscular and oral routes of administration. Group(3)(test group) were administrated graded amounts of the test antibiotic. The activity of each analog was estimated by the reduction in bacterimia, septicemia and observation of the clinical signs of infectious disease.

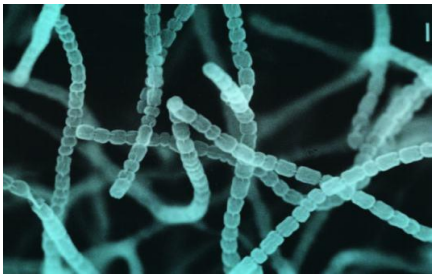
In vivo bio-availability study:

Before dosing IV, IM or oral tablets 0.7-0.9ml of blood samples were withdrawn ,and immediately after dosing at 30,60,120,240 minutes.Blood samples were further refrigerated and centrifuged at 4 C within one hour of sampling. Analogs concentrations were determined using HPLC.HPLC analysis was through a reversed phase column utilizing phosphate buffer(PH 4.4) and acetonitrile(660/340, v/v) as mobile phase with a flow rate 0.9ml/min. The limit of UV estimation of tetracycline concentration in blood was at 275 NM. **Area under the curve(AUC) and the % of relative bio-availability were measured. % of relative bio-availability was determined by the following equation:**

% Relative oral bio-availability=(AUC Oral/AUC Intravenous)×(Dose Intravenous/Dose oral)×100%.

% Relative intramuscular bio-availability=(AUC Intramuscular/AUC Intravenous)×(Dose Intravenous/Dose Intramuscular)×100%.

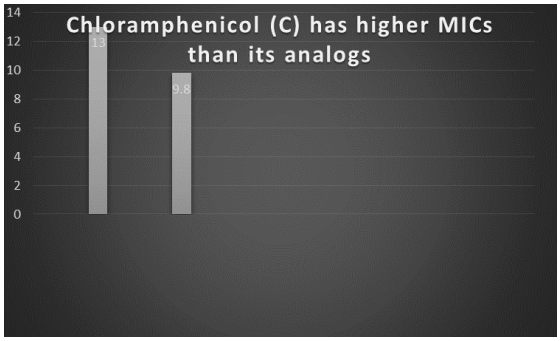
Figure 2. shows soil Streptomyces producing chloramphenicol in Egypt.



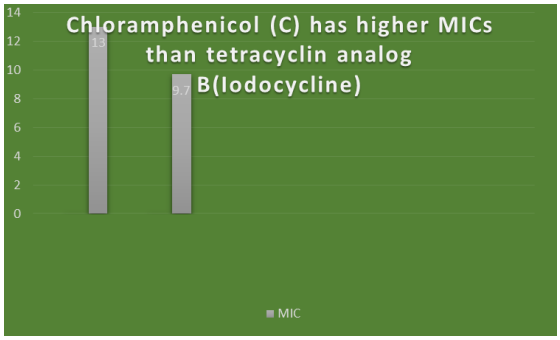
Statistical analysis

All cultures were conducted in triplets. Their presentation was by means and standard deviation. One-way analysis of variance (p value≤.05) was used as means for performing statistical analysis and also, statistical analysis based on excel-spreadsheet-software.

Graph 1.represents a comparison between MICs of chloramphenicol and its analog A.MICs of chloramphenicol were greater than 10µg/ml, while MICs of its analog A were less than 10 µg/ml, thus chloramphenicol analog A had higher antimicrobial activities than standard chloramphenicol.



Graph 2. represents MICs of chloramphenicol(C) and analog B.MICs of chloramphenicol were greater than 10µg/ml, while MICs of its analog B were less than 10 µg/ml, thus chloramphenicol analog B had higher antimicrobial activities than standard chloramphenicol.



Results

In our study, we prepared different batches of chloramphenicol analogs A and B Oral tablets utilizing various ingredients as starch, sucrose DC , talc, etc(Table 2).

Table 2. Batch formulation of Oral tablets of chloramphenicol analog A F1-F5 by wet granulation technique.

Ingredients(mg/tablet)	F1	F2	F3	F4	F5
chloramphenicol analog A	250	250	250	250	250
Starch	15	17	16	12	14
Sucrose DC	11	10	11	13	10
Talc	1	3	1	3	2
Mg stearate	3	1	2	2	4
Total weight(mg)	280	280	280	280	280

Table 3. Batch formulation of Oral tablets of chloramphenicol analog B F1-F5 by wet granulation technique.

Ingredients(mg/tablet)	F1	F2	F3	F4	F5
chloramphenicol analog B	250	250	250	250	250
Starch	15	17	16	12	14
Sucrose DC	11	10	11	13	10
Talc	1	3	1	3	2
Mg stearate	3	1	2	2	4
Total weight(mg)	280	280	280	280	280

Table 4. represents MIC of chloramphenicol(C) and analog(A).

	C	A
MIC	13	9.8

Table 5. represents MIC of chloramphenicol(C) and analog(B).

	C	B
MIC	13	9.7

Isolation of streptomyces sp producing chloramphenicol on MSA:

We picked and preserved 28 pure and single colonies of streptomyces at 3°C for further evaluation of an antibacterial activity.

Evaluation of antimicrobial activity by standard agar dilution technique:

(i)For analog A, 8.7µg/ml,5.3µg/ml,9.4µg/ml,5.8µg/ml,7.2µg/ml,4.1 µg/ml,4.7µg/ml,8.4µg/ml,6.2µg/ml,7.7µg/ml,5.8µg/ml,9.3µg/ml,6.5µg/ml,4.7µg/ml,5.9µg/ml,6.1µg/ml, 7.8µg/ml MIC values were observed against Escherichia coli 0157:H7, Enterococcus faecium, Staphylococcus aureus , Pseudomonas aeruginosa,Haemophilus influenza type b,Neisseria meningitides,Streptococcus pneumonae,Bacteroids fragilis,Clostridium difficile,Clostridium perfringens,Clostridium tetani, Rickettsia rickettsia,Rickettsia prowazekii, Coxiella burnetii,Analplasma phagocytophilum , Ehrlichia chaffeensis ,Salmonella typhi and Salmonella paratyphi respectively.(ii) For analog B, 5.4 µg/ml, 8.1 µg/ml,7.0µg/ml,4.7µg/ml,5.2µg/ml,9.2µg/ml,5.0µg/ml,8.9µg/ml,5.8µg/ml,4.4µg/ml,5.3µg/ml,7.3µg/ml, 9.4µg/ml,4.1µg/ml,6.1µg/ml,4.5µg/ml,7.2µg/ml MIC values were observed against Escherichia coli 0157:H7, Enterococcus faecium, Staphylococcus aureus ,Pseudomonas aeruginosa,Haemophilus influenza type b,Neisseria meningitides,Streptococcus pneumonae,Bacteroids fragilis,Clostridium difficile,Clostridium perfringens,Clostridium tetani, Rickettsia rickettsia,Rickettsia prowazekii, Coxiella burnetii,Analplasma phagocytophilum , Ehrlichia chaffeensis ,Salmonella typhi and Salmonella paratyphi respectively.Both analogs showed more antimicrobial activity than standard chloramphenicol but showed less bacterial resistance.

Oral dosage:

For quickly ejected chloramphenicol analogs A and B,The oral dosage was 25–50 mg/kg/d for children older than two years and 50–100 mg/kg/d three times daily for adults. The higher dosage is indicated, at least for the first few days for severe systemic infections. chloramphenicol analogs A and B might be the oral analog of selection as their absorption was not importantly subjected by food. chloramphenicol analogs A and B .No possibility of interaction between chloramphenicol analogs A and B and excipients was shown by FT-IR and DSC study.The determination of the hardness of the tablets was done and was observed between 3.79 to 3.98 kg/cm2.The variation of wight of all formulations was estimated which were within the standard limit as per British pharmacopoeia.We found percentage friability in the range of 0.71 to 0.89% which was in the limit of extent. The ratio of water absorption for all formulations was observed between 38.23 to 39.67.The wetting time for all formulations was estimated between 19 to 24 seconds. We subjected the oral tablets for evaluation of in vitro disintegration time.For formulations F1 to F5,in vitro disintegration time was found to be in the range of 7 to 9 minutes.Rapid disintegration time of 7 minutes was observed by the formulation F2.This is because of burst effect and the rapid water uptake from the medium .All formulations percentage drug content was observed between 98.83 to 99.67 of chloramphenicol analogs A and B which was in the unexceptionable extent. The release time for the immediate release insulin tablets ranged from 98.71% to 99.34% at 2 hours at 37 C and 50 rpm but 98.19% to 99.13 at 4-6 hours at 37 C and 50 rpm for the controlled release tablets. Batch F2 displayed quicker drug release than all the other batches.98.45 % cumulative drug release in 240 minutes was demonstrated by batch F2 at 37 C and 50 rpm. Batch F2 t50 % was observed to be 180 minutes.Owing to the rapid disintegration time and dissolution profile Batch F2 was well-advised as an optimized formulation.Batch F2 was formulated with 10 mg sucrose DC and 17 mg starch. The optimum storage temperature of chloramphenicol analogs A and B oral tablets(batch F1 to F5) was noticed between 2-8 C.

Par-enteral dosage:

In doses of 0.3–0.7 g every 12 hours, chloramphenicol analogs A and B were available for intravenous injection.

Pharmacokinetics:

Fifty to 100 mg/kg/d were the usual dosage of chloramphenicol analogs. Crystalline chloramphenicol analogs were completely and rapidly absorbed, After oral administration. Blood levels between 10 and 15 mcg/mL for both analogs were produced by 1gram oral dose. Hydrolysis of Chloramphenicol analogs palmitate prodrugs in the intestine yield free chloramphenicol analogs. The

parenteral formulation was a prodrug, chloramphenicol succinate, which hydrolyzed to yield a free chloramphenicol analog, giving blood levels somewhat lower than those achieved with an orally administered drug. Chloramphenicol analogs were widely distributed to virtually all body fluids and tissues, including cerebrospinal fluid and the central nervous system, such that the concentration of chloramphenicol in brain tissue was equal to that in serum. Cell membranes were readily penetrated by both analogs. Both analogs were inactivated either by reduction to inactive aryl amines or by conjugation with glucuronic acid (principally in the liver). A small % of active drugs were excreted into bile and feces. Active chloramphenicol analogs (about 10-15% of the total dose administered) and their inactive degradation products (about 85- 90% of the total) were eliminated in the urine. The systemic dosage of chloramphenicol analogs was necessary to be reduced markedly in hepatic cirrhosis, but it did not need to be altered in renal insufficiency. Premature infants and also newborns less than a week old clear chloramphenicol less well, and the dosage should be decreased to 15 mg/kg/d. Esterification of the 3-OH group of both chloramphenicol analogs with palmitic acid resulted in prodrugs that masked the bitter taste and prolonged the duration of action of the drugs. This is recommended in oral suspension for pediatrics. Esterification of 3-OH group with succinic acid produced water-soluble prodrugs. This is recommended for parenteral administration. Both analogs were administered as oral, intravenous, or topical eye drops and ointments.

Adverse Reactions:

Diarrhea, Nausea, and vomiting were caused by Both analogs. Oral or vaginal candidiasis occurs as a result of an alteration of normal microbial flora. Chloramphenicol analogs caused a dose-related reversible suppression of red cell production at dosages exceeding 60 mg/kg/d after 1–2 weeks. They showed less tendency to cause aplastic anemia or gray bay syndrome than chloramphenicol.

Interaction with other drugs:

Bactericidal drugs such as quinolones and cephalosporins were antagonized by chloramphenicol analogs, Like other bacteriostatic inhibitors of microbial protein synthesis. They showed less inhibition of hepatic microsomal enzymes than chloramphenicol.

Discussion

Estimation of biological activity of chloramphenicol analogs:

In the present study, we prepared different batches of chloramphenicol analogs A and B Oral tablets utilizing various ingredients as starch, sucrose DC , talc, etc. Both analogs showed MICs of less than 10 µg/ml for the bacterial growth of pathogenic bacteria ; while chloramphenicol showed MICs greater than 10 µg/ml. Chloramphenicol analogs were potent inhibitors of bacterial protein synthesis. They bind reversibly to the 50S bacterial ribosome subunit and suppress the peptidyl transferase step of protein synthesis. Chloramphenicol analogs were bacteriostatic broad-spectrum antibiotics that were active against both aerobic and anaerobic gram-positive and gram-negative organisms. They were active also against Rickettsia but not Chlamydiae. Most gram-positive bacteria were inhibited at concentrations of 4–10 mcg/mL, and many gram-negative bacteria are inhibited by concentrations of 4–9.5 mcg/mL.

H. influenzae, N. meningitidis, and some strains of Bacteroides were highly susceptible, and for them, chloramphenicol analogs might be bactericidal. Neither chloramphenicol nor its analogs showed bacterial activity against Chlamydiae infections.Chloramphenicol analogs possess a characteristic and uncomplicated composition. They are efficacious parenterally and also orally and are broadly dispersed, Promptly crossing the blood-brain and placental barriers. Enterohepatic cycling is undergone by Chloramphenicol analogs, and a little portion of the dosage is ejected in the urine unaltered. To the highest degree of the drugs are set off via a hepatic glucuronosyltransferase.

Chloramphenicol analogs are commonly bacteriostatic and have a comprehensive spectrum of germicide activity . Some strains of Neisseria meningitidis, Bacteroides,and Haemophilus influenzae are extremely amenable and for these bacteria chloramphenicol analogs might be bactericidal. Chlamydia species is resistant against chloramphenicol. Resistance to chloramphenicol analogs, which is plasmid-mediated, takes place via the acetyltransferases formation that deactivate the analogs.

Clinical Uses:

Due to its toxicity, chloramphenicol has precise some uses as a systemic medicine; while analogs showed few toxicity. They are backup agents for the management of meningococcal and pneumococcal meningitis in beta lactam sensitive individuals and for intense pathological process reasoned by Salmonella species .

Chloramphenicol analogs may be utilized for infections caused by anaerobes such as Bacteroides fragilis and for rickettsial diseases. The analogs are remarkably utilized as topical germicide factors.

Toxicity of analogs:

Bone marrow:

A decrement in circulating erythrocytes results from Prohibition of red cell maturation. This state is reversible and dose-dependent. Aplastic anemia is an infrequent idiosyncratic reaction which was not reported.

Gray baby syndrome:

This syndrome takes place in infants and is defined by cyanosis, cardio vascular collapse and reduced red blood cells . Neonates Lacking hepatic glucuronosyltransferase are amenable to doses of chloramphenicol that would be tolerated in older infants. This was less reported for analogs.

Gastrointestinal disturbances:

These circumstances may fall out from superinfections, particularly candidiasis and from direct irritation .

Drug interactions:

Chloramphenicol analogs stamp down hepatic medicate metabolizing enzymes, hence exploding the excretion half-lives of medicines considering tolbutamide, warfarin and phenytoin .

Conclusion

Our study was a promising approach because we could develop novel chloramphenicol analogs by chemo-informatics. Both analogs have considerable in vitro antibacterial activity against a broad spectrum of chloramphenicol-resistant pathogenic bacteria in Egypt.

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