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RESEARCH ARTICLE

Synthesis Characterization and Antibacterial Activity of Terazosin Hydrochloride Drug and Market Formulation

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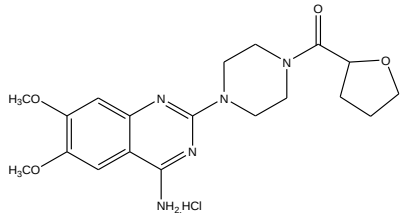
ABSTRACT:
Terazosin hydrochloride is an anti-hypertensive drug which is used to treat the diseases of hypertension. The literature survey shows the proposed synthesis of Terazosin hydrochloride derived from the starting material of 2-chloro-6, 7-dimethoxy–quinazoline-4-amine in the presence of 2-methoxy ethanol with n- benzyl piperazine to form the product. The Terazosin derivatives were prepared with the help of literature survey were 1, 4-bis-(furan-2-yl-carbonl) piperazine, 1, 4-bis-(tertrahydrofuran-2-yl) carbonyl piperazine, and 1-(4-amino-6, 7-dimethoxy- quinazoline-2-yl)- 4-formyl- piperazine were prepared by maintaining environmental condition. The characterization done for prepared derivative was done through ^{1}H-NMR, MASS and IR Spectroscopy. The antibacterial activity of prepared derivatives was performed on the various bacteria like *E. coli*, *Pseudomonas aeruginosa*, *Shigella sonneii*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Shigella flexneri*, *Vibrio cholera*, *Bacillus subtilis*, *Pseudomonas fluorescens*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*. The desired derivatives shown maximum zone of inhibition using concentration prepared 100µg and 200µg using standard drug. The derivatives that shows maximum inhibition 6, 7-dimethoxy-2-piperazine-1-yl-quinazoline -4-amine and minimum was shown by 1, 4-bis-(furan-2-yl-carbonl) piperazine, 1,4-bis-(tertrahydrofuran- 2-yl) carbonyl piperazine. The result should that prepared Terazosin derivatives shows potent actively when compared with standard ciprofloxacin.

KEYWORDS: Anti-hypertensive drugs, Antibacterial activity.

1. INTRODUCTION:

1.1 Terazosin hydrochloride:
Terazosin hydrochloride is an anti hypertensive drugs belonging to the alpha 1selective blocking drug. Other than the treatment of high blood pressure this drug is also used for the treatment of enlarged of prostate[1]. In 1975 Terazosin was patented and come to market in 1985[2]. The common side effects of Terazosin are headache, fatigue, sickness and priapism.

Drug Name: Terazosin Hydrochloride
Chemical name; 1-(4-amino-6, 7-dimethoxyquinazolin-2-yl)-4-[(tetrahydrofuranyl) carbonyl] piperazine.



Mol. Formula: $C_{19}H_{25}N_5O_4HCl$
Mol. Wt: 423.8
Colure: white, crystalline substance
Solubility: Dichloromethane and methanol.

1.2 Hypertension:
Hypertension is the very route heath complication and its increase the risk of stock, heart disease and death. Day by day the chance of hypertension increases. In 2009 the numbers of death due to hypertension were 348,102.

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According to the world health organization growing food industry, excess salt used in diet and modern life style are responsible for the hypertension. According to the American Heart Association (AHA) and hypertension is define as blood pressure over 130 (mmHg)[3].

1.2.1 Symptom:
It is very dangerous problem in hypertension is that you cannot understand that that you have this disease. In fact, approximately one-third of hypertension effected people in the world who have elevated blood pressure don't know it. The only way to detect this disease is regular checkups. If blood pressure is very high, then some symptom may be arising such as[4].

- Severe headache
- Problem in Vision
- Confusion or Fatigue
- Pain in Chest
- breathing problem
- Irregular heartbeat
- Blood in the urine
- Pounding in your neck, chest, or ears

1.2.2 Cause of hypertension:
Till now the exact cause of the high blood pressure in unworn, but it can be expected that there are some common factors play the important role like.

Age:
With the age the risk of high blood pressure increase. So the older person affected more in this disease.

Family history:
These people are more prone to hypertension disease who have family history of hypertension.

Ethnic background:
From the various surveys it was found that some places of people are more prone to hypertension such American and African people.

Obesity and being overweight:
Overweight people are more prone to heart disease

Some aspects of sex:
Numbers of survey give the evidence that men are more prone to hypertension than the female. But rich of hypertension increase in women after 55.

Physical inactivity:
Lack of exercise and having a sedentary lifestyle raise the risk of hypertension.

Smoking:
Smoking is one of the in forgetful reason for hypertension. Smoking narrowing the blood vessel.

Alcohol intake:
Concussion of alcohol is increase the risk of hypertension. Consumption of high amount alcohol dramatically rise the blood pressure and in the same time increase the risk of heart failure.

Poor diet:
Many healthcare professionals say that a diet high in fats and salt leads to a high risk of hypertension. However, most dietitians stress that the problem is the type of fat rather than the amount.

1.3 Antibacterial agents:
Antibacterial compounds play important role in prevention of infection or disease. They generally kill the bacteria by modifying the call structure internally. The word antibacterial is come from the Greek word "anti" which means against and "bacterial" which means bacteria[5]. Antibacterial drugs are used in prevention of the bacterial infection, either they kill the bacteria or they inhibit the growth of bacteria. Effectiveness of antibacterial drug and its easy access have lead to their misuse and it cause increasing of resistance in the human beings[6]. According to a survey in 2010, India was largest consumer of antibiotics about 13 billion followed by China about 10 billion and US with 7 billion units. The demand of antibiotics increased by 40% during 2005-2009 in India. Studies show that resistance for Salmonella Typhi is at high level in different region of India**.** The situation is vulnerable, and survey estimate says that more than 55,000 neonates die every year from sepsis attributed to bacterial resistance to first-line antibiotics in India[7].

1.3.1 Classification:
The Antibacterial agents are classified as:

- Spectrum activity
- Effect on bacteria
- Mode of action

1.3.2 Spectrum activity:
On the basis of their antibacterial activity, these agents are either with Broad spectrum and Narrow spectrum, the divided according to their range of susceptible. a). Broad spectrum antibacterial: These agents are potent to both types of the bacterial strains (gram-ve and gram +ve) like cephalosporins, penicillin etc. b). Narrow Spectrum antibacterial[8]: These antibacterial are against for the particular species of bacteria.

1.3.3 Effect on bacteria:
The all the antibacterial agents are work with the different mechanism as some kill the microbes by destroying of cell wall, they called bactericidal. Some antibacterial inhibit the protein synthesis and generally

known as bacteriostatic. For example penicillin as bactericidal and chloramphenicol as bacteriostatic.

1.3.4 According to Mode of action:
On the basis of their mode of action, the antibacterial agents are classified. These agents act by different mode in the bacterial cell as some inhibit the protein synthesis or some inhibit the metabolic process and it lead to the death of the bacterial cell.

1.4 The classify as follow:
1.4.1 Cell-wall inhibitors:
These antibacterial agents act by acting inhibition of cell wall synthesis. But the disadvantage of this mode is that some animals have do not call wall, and they are inactive in these type of organism. e.g. Penicillin.

1.4.2 Cell wall function inhibitors:
The bacterial cell wall is important barriers that segregate and regulate the intra and extracellular flow of cell materials. Thus these classes of agent inhibit the cell wall 3 function and they are generally active against both type of prokaryotic and eukaryotic cell. E.g Polymixin B

1.4.3 Inhibitors of Nucleic acid synthesis:
The antibacterial work by binding to component involved in the process of DNA and RNA synthesis. For e.g. quinolines. d). Inhibitors of metabolic process These agents kill the bacteria by inhibit of the metabolic process of bacterial cell. For e.g. sulfonamides bind to dihydropteroate synthase and kill the bacteria.

1.4.4 Resistance developed in the Bacterial cell:
The continued use of antibacterial drugs in the clinical practice caused development of resistance in bacterial organisms. It should be viewed as normal adaptive response followed by Darwin's principle of evaluation. The Antibacterial resistance has been evolved rapidly I last few decade and now it is a one of major threat for public health. Many diseases are untreatable due to development of the multidrug resistance. The mechanism by which the bacteria become resistant is the important strategies to developed resistance threat. Hence we need to developed antibacterial agents with the more potency and effectiveness[9].

1.5 The development of the resistance in the bacterial cell developed due to following reason:
1.5.1 Genetic basis of antibacterial resistance:
Bacterial cell have amazing genetic plasticity to respond a variety of environmental threats. The bacterial cell sharing the same ecological function with antibacterial producing organisms have to evolved antique mechanism to withstand the effect of antibiotic molecule. Generally, bacterial cell use two major strategies to developed resistance are:

- Mutation in gene
- Acquisition of the foreign DNA coding

1.5.2 Mechanistic basis Antibacterial resistance:
From the last two decade the cause of bacterial resistance increasing day by day, it cause untreatable infection occur in human beings and cause serious problem. The antibacterial resistance developed in the bacterial cell by change in drug molecule or by some other reason. The acquisition of the resistance occurs due to the evaluation factor in bacterial cell. Further classification of the antibacterial resistance mechanisms categorize them according to the route involved in the resistance[10].

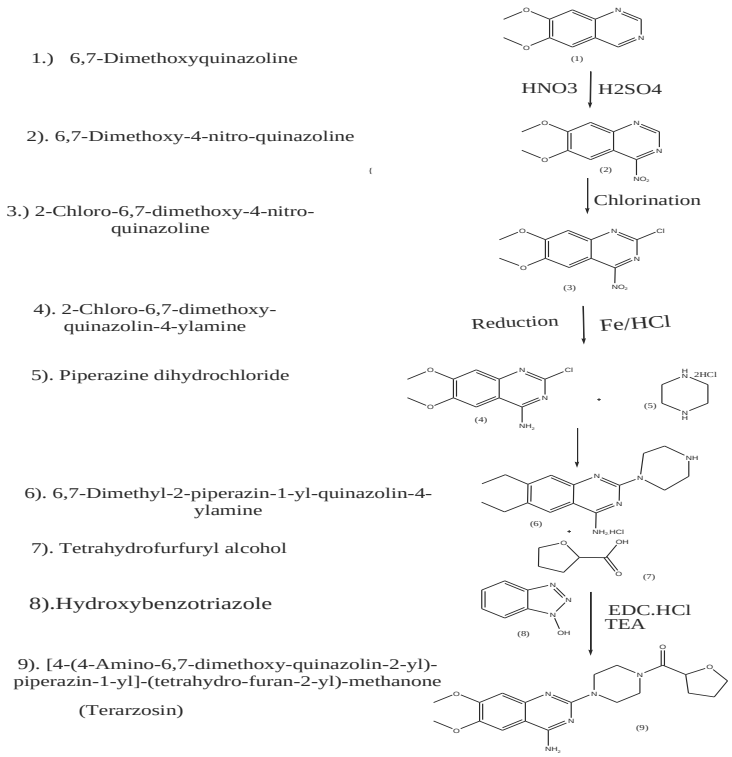
The antibacterial resistance developed by following ways:

- Modification or change in the biochemical molecule
- Avoidance to make antibiotic target by decreasing the penetration of the
- Antibacterial compounds. Resistance developed due to global cell adaptive process

1.5.3 Development in antibacterial resistance:
Most of the bacteria developed resistance against the antibacterials agents, which are commonly used by patient. According to a survey report in East Africa conducted for E.coli in urinary tract infection, around 80% of people shown resistant to the drug ampicillin, clotrimoxazole and tetracycline. In 1967 report shown that penicillin G shown resistant against strains of pneumococci and it increased by 20% in 1991. Penicillin G are still effective to all natural strains of Streptococci (group A) while for resistance to tetracycline has reached at peak level. A survey in Tanzania shown that spectinommycin, cephalosporins (2nd and 3rd generation) and ciprofloxacin are effective against the variety of strains of N. gonorrhoeae, however, 65% of N. gonorrhoeae are beta-lactamase producers. Vibrio cholerae shown resistant to multiple antibacterial drugs and id widely spread globally, however recent report show that withdrawal of these drugs can be reason to loss of antibiotics resistance factors. The N. meningitides strains show susceptibility worldwide, it isolate in Tanzania are still susceptible to commonly drugs like penicillin G and chloramphenicol[11].

Experiment:
To study synthesized of Terazosin hydrochloride (2-[4-(2-tetrahydrofuranyl) carbonyl]-1-piperazinyl-6,7-di-methoxy- 4-quinazolinamine monohydro-chloride dehydrate)

Scheme:



Biological Activity:

The following bacterial strains are used to evaluation on Antibacterial activity:

Preparation of stock solution:

To prepare the 120ml Nutrient Broth solution and transfer 10ml nutrient broth transfer solution in 12 test tube and plug with cotton. Place in beaker and top with brown paper and sterilize in Autoclave for 1hr. after test tube remove in autoclave and incubate all the test tube in BOD for 18 hr. 37°C temperature.

To prepare 600ml molten agar solution and transfer with help of measuring cylinder 29ml in each 21 nos. conical flask, plug with cotton and put in autoclave for sterilize. Then Petri dishes scale with help of marker divided in 12 parts and sterilize solution and synthesized compound different concentration (in µg/ml) is added solution transfer in Petri dishes and one by one all organism add in Petri dishes 12 organism carefully complete process under laminar flow. Incubate in BOD for 18 hr. at 37°C temperature.

Note minimum inhibitory concentration (MIC) of synthesized compound.

Determination of Minimum Inhibitory:

Concentration:

To prepare 600ml molten agar solution and transfer with help of measuring cylinder 29ml in each 21 nos. conical flask, plug with cotton and put in autoclave for sterilize. Then Petri dishes scale with help of marker divided in 12 parts and sterilize solution and synthesized compound different concentration (in µg/ml) is added solution transfer in Petri dishes and one by one all organism add in Petri dishes 12 organism carefully complete process under laminar flow. Incubate in BOD for 18 hr. at 37°C temperature[12].

Note minimum inhibitory concentration (MIC) of synthesized compound.

Determination of Zone of inhibition:

A solution of concentration 5µg, 10µg and 25µg of synthesized analogs and the standard drug (ciprofloxacin) were prepared in presterilized McCartney bottles. The Sterile molten agar media plates were arranged and kept for incubated at 25-26°C for 24 hours. On next day each prepared agar plate was poured with the liquid culture of bacterial suspension, dried the Petri plate for about 30-40 minutes at 25-26°C. The prepared sterile Whatman filter paper disc (4mm diameter) were soaked in desired compounds and kept in the flooded plate with each quadrant marked by the permanent marker with different concentration of derivatives and standard drug. Kept these prepared Petri plates in BOD incubator for 24 hours at 35-37°C and checked out the zone of inhibition on next day and measured the diameter accordingly. The similar procedure was followed for ciprofloxacin, and respective zone diameter was measured and compared.

Table 1: Minimum Inhibitory Concentration of Synthesized compounds (MIC µg/ml)

Compound -1								
S. No.	**Name of organism**	**Minimum Inhibitory Concentration of Synthesized Compound. (µG/ML)**						
		0	**10**	**25**	**50**	**100**	**200**	**400**
1	*Escherichia coli*	+	+	+	-	-	-	-
2	*Pseudomonas aeruginosa*	+	+	+	+	+	+	+
3	*Shigella sonneii*	+	+	+	+	+	+	+
4	*Klebsiella pneumonia*	+	+	+	+	+	+	+
5	*Staphylococcus aureus*	+	+	+	+	+	+	+
6	*Shigella flexnerI*	+	+	+	+	+	+	+
7	*Vibrio cholera*	+	+	+	+	+	+	+
8	*Bacillus subtilis*	+	+	+	+	+	+	+
9	*Pseudomonas fluorescens*	+	+	+	+	-	-	-
10	*E. Coli*	+	+	+	+	+	+	+
11	*Pseudomonas aeruginosa*	+	+	+	+	+	+	+
12	*Staphyloccus aureus*	+	+	+	+	-	-	-

Table 2: Zone of Inhibition (mm) of Prepared compounds by disc diffusion method.

Zone of Inhibition (in mm) Produced by Sample (compound 1) and Standard drug (Ciprofloxacin)					
S. No.	**Name of organs**	**Sample (µg/ml)**		**Standard (µg/ml)**	
		100	**200**	**100**	**200**
1	*Escherichia coli*	6	8	8	9
2	*Pseudomonas fluorescens*	12	16	18	20
3	*Staphylococcus aureus*	6	7	8	10

Table 3: Minimum Inhibitory Concentration of Synthesized compounds (MIC µg/ml)

Compound -2								
S. No.	**Name of Organism**	**Minimum Inhibitory Concentration of Synthesized Compound (µg/ml)**						
		0	10	25	50	100	200	400
1	*Escherichia coli*	+	+	-	-	-	-	-
2	*Pseudomonas aeruginosa*	+	+	+	+	+	+	+
3	*Shigella sonneii*	+	+	+	+	+	+	+
4	*Klebsiella pneumonia*	+	+	+	+	+	+	+
5	*Staphylococcus aureus*	+	+	+	+	-	-	-
6	*Shigella flexnerty*	+	+	+	+	+	+	+
7	*Vibrio cholera*	+	+	+	+	+	+	+
8	*Bacillus subtilis*	+	+	+	+	+	-	-
9	*Pseudomonas fluorescens*	+	+	-	-	-	-	-
10	*E. Coli*	+	+	+	+	+	+	+
11	*Pseudomonas aeruginosa*	+	+	+	+	+	+	+
12	*Staphyloccus aureus*	+	+	+	+	+	+	+

Table 4: Zone of Inhibition (mm) of Prepared compounds by disc diffusion method.

Zone of Inhibition (in mm) Produced by Sample (Compound 2) and Standard (Ciprofloxacin) drug (mm)					
S. No.	**Name of Organism**	**Sample (µg/ml)**		**Standard (µg/ml)**	
		100	**200**	**100**	**200**
1	*Escherichia coli*	7	9	9	12
2	*Staphylococcus aureus*	10	12	13	15
3	*Bacillus subtilis*	10	14	13	17
4	*Pseudomonas fluorescens*	12	18	15	19

Table 5: Minimum Inhibitory Concentration of Synthesized compounds (MIC µg/ml)

Compound -3								
S. No.	**Name of Organism**	**Minimum Inhibitory Concentration of Synthesized Compound (µG/ML)**						
		0	**10**	**25**	**50**	**100**	**200**	**400**
1	*Escherichia coli*	+	+	+	+	+	+	+
2	*Pseudomonas aeruginosa*	+	+	-	-	-	-	-
3	*Shigella sonneii*	+	+	+	+	+	+	+
4	*Klebsiella pneumonia*	+	+	+	+	+	+	+
5	*Staphylococcus aureus*	+	+	+	+	+	+	+
6	*Shigella flexneri*	+	+	+	+	+	+	+
7	*Vibrio cholera*	+	+	+	+	+	+	-
8	*Bacillus subtilis*	+	+	+	+	+	-	-
9	*Pseudomonas fluorescens*	+	+	+	+	+	-	-
10	*E. Coli*	+	+	+	+	+	+	+
11	*Pseudomonas aeruginosa*	+	+	+	+	+	+	+
12	*Staphylococcus aureus*	+	+	+	-	-	-	-

RESULT:

Table 6: Minimum Inhibitory Concentration of Synthesized compounds (MIC µg/ml)

Compound	*E. coli*	*P. aeruginosa*	*S. sonneii*	*K. pneumonia*	*S. aureus*	*S. flexneri*
Compound 1	50	-	-	-	-	-
Compound 2	25	-	-	-	100	-
Compound 3	-	25	-	-	-	-

Table 6: Continue

Compound	*V. cholera*	*B. subtilis*	*P. fluorescens*	*E. Coli*	*P. aeruginosa*	*S. aureus*
Compound 1	-	-	100	-	-	100
Compound 2	-	-	25	-	-	-
Compound 3	-	200	200	-	-	50

Table 7: Zone of Inhibition (mm) of Prepared compounds by disc diffusion method

Compound		*Escherichia coli*	*Pseudomonas fluorescens*	*Staphylococcus aureus*	*Bacillus subtilis*	*Vibrio cholera*	*Pseudomonas aeruginosa*
Compound 1	100	6	12	6	-	-	-
	200	8	16	7	-	-	-
Compound 2	100	7	12	10	10	-	-
	200	9	18	12	14	-	-
Compound 3	100	-	12	11	7	11	10
	200	-	13	14	9	11	12
Ciprofloxacin	100	9	18	15	13	12	12
	200	12	20	17	17	15	16

CONCLUSION:

The Terazosin Hydrochloride derivatives Containing quinazoline moiety that increase the potency of the drug. The work entitled synthesis of Terazosin derivatives and its anti bacterial activity work characterized through ^{1}H-NMR, Mass and IR Spectroscopy. Thus the Study Shos that Terazosin hydrochloride gives valuable insight to the researcher across the globe to develop moderate anti bacterial activity. A total number of 5 derivatives were synthesized and all these analogs prepared were 1,4-Bis(furan-2-ylcarbonyl) piperazine, 1,4-bis[tetrahydrofuran-2-yl] piperazine, 1-(4-Amino-6,7-dimethoxyquinazolin-2yl)-4-formylpiprazine, 1-(4-hydroxy-6,7-dimethoxyquinazolin-2yl)-4[{(2RS)-tetrahydrofuran-2-yl} carbonyl] piperazine show potent activity with MIC 100µg/ml and 200µg/ml were evaluated when compared with standard Ciprofloxacin drug. The derivatives that shows maximum inhibition 6,7-dimethoxy-2-piperazine – 1-yl-quinazoline -4-amine and minimum was shown by 1,4-bis-(furan-2-yl-carbonl) piperazine, 1,4-bis-(tertrahydrofuran- 2-yl) carbonyl piperazine. The prepared derivatives characterized by melting point, 1H-NMR and IR spectroscopy. The evaluation of prepared compounds for the antibacterial activity was done by agar discs diffusion technique. Thus our study on prepare derivatives showed a valuable insight to the researcher across the globe to developing new antibacterial agents with more potent activity with resistance free against gram-ve and gram+ve bacterial strains.

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