RESEARCH ARTICLE JPAR 2020

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

Antibacterial Screening of Novel Quinazoline Derivatives

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Received: 10.10.2020 Revised: 18.11.2020 Accepted: 24.11.2020 Published: 30.11.2020

ABSTRACT: Background: The background of the present work is to synthesise 11 different derivatives of quinazoline compounds and to analyse the anti-bacterial activity of these compounds using paper disc diffusion model and agar dilution method. **Aim**: The aim of the present study is to investigate the antibacterial activity of quinazoline derivatives. **Method**: From the 11 derivatives of quinazoline compounds, 6 compounds were analysed for antibacterial activity. The activity of the derivatives were made by preliminary screening methods such as paper disc diffusion method and minimum inhibitory concentration (MIC) was performed using agar plate dilution method against *S. aureus*a nd *E. coli* using ciprofloxacin as standard drug. **Result**: From the data view, most of the synthesized compounds exhibited moderate to good anti-microbial activity in opposition to the tested microorganisms. The synthesized compounds were (50, 100 and 150 µg/ml) screened for antibacterial activity by paper disc diffusion method and agar streak dilution method. From the synthesized compounds, compound D3, D4 and D6 (100 µg/ml) were found to show evidence of good antimicrobial activity due to 2-fluoro, 4-fluoro, and methyl substituents. Compound D1 has higher MIC value compared to other compounds. The MIC values were 13 and 20 µg/ml against *S. aureus* and *E. coli.* **Conclusion**: From the findings it reveals that synthesized quinazoline derivatives have antimicrobial activity against *S. aureus* and *E. coli.* In outlook it would be a large part of a hopeful molecule to perform against various micro-organisms and also signifying strong potential for their development as antibacterial agents.

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Keywords: Quinazolines, Antibacterial, Fluorosubstituent's, Minimum inhibitory concentration, Agar plate dilution method.

INTRODUCTION:

Heterocycles have a central position in medicinal as well as in organic chemistry and their synthesis is focused considerably. Nitrogen heterocyclic in particular exhibits diverse biological and pharmacological activities [1]. Quinazoline is one of the most important and prosperous structures in medicinal chemistry. They are building blocks for about 150 naturally occurring alkaloids with a broad range of biological activity. Moreover quinazolines are one of the most extensively studied classes of heterocyclic compounds. In general, quinazoline compounds have been well-recognized for their pharmacological properties, such as anti-

inflammatory, antihypertensive, anti-HIV, bronco-dilatory, antiallergic, anticancer, anticonvulsant, anthelmintic, analgesic, antimalarial and antimicrobial activities [2-4].

Emergence of drug resistance has created a critical and unmet medical requirement for the innovation and development of novel classes of antibacterial agents. Due to the appearance of drug resistance bacterial strains, there is an escalating need for the development of novel antibiotics to treat the resistant bacteria stain [5-7]. Several research groups have successfully investigated and reported the promising antimicrobial properties and structure-activity relationships (SAR) of various quinazolinone derivatives [8,9].

However, search is continuously on to identify a more potent lead molecule as these molecules are developing resistance over a period. Based on the importance of these molecules, our attention was attracted towards synthesis of novel quinazoline derivatives in order to find more potent biologically active molecules [10-12]. Hence, we report here the synthesis and characterization of novel quinazoline derivatives. In addition, the antibacterial activities of all synthesized quinazolines against different bacteria were evaluated. Among the compounds tested some quinazolines were found to be superior in inhibiting all the bacteria and strains [13,14].

MATERIAL AND METHODS:

The thiourea, acetonitrile, ethyl acetate, n-hexane were purchased from HiMedia Laboratory Pvt Ltd, Mumbai, India. The dimethyl sulfate, HCl, NaOH, dimethylformamide and Silica Gel-G were purchased from Merck Pvt Ltd, India. The standard drug Ciprofloxacin was procured as a gift sample from Micro Labs Ltd, India. All other chemicals and reagents used in this study were of analytical grade and procured from authorised dealers. All glassware used were of Borosil Grade.

The instruments used in this study were autoclave (Meditech Portable Sterilizer, Meditech System, India) and Incubator (Tecsonic Platelet Incubator, TPI-01, A V Exports, Poonamallee, Chennai).

Synthesis of 4-(2-methoxyphenyl)-3, 4, 5, 6-tetrahydrobenzo[*h*]quinazoline-2(1*H*)-thione:

A mixture of alpha-tetralone (0.01 mole, 1.46 g), 4-methoxy benzaldehyde (0.01 mole, 1.36 ml), thiourea (0.01 mole, 0.76 g) and concentrated HCl (3 to 4 drops) was dissolved in acetonitrile (5 ml) which was taken in borosil beaker (100 ml) and was irradiated in unmodified domestic microwave at 30 % microwave power for 5.00 min [15,16]. The reaction was monitored by thin layer chromatography (TLC) using silica gel-G plates. Ethyl acetate and n-hexane mixture was used as eluting solvent (1:1). After drying the plates, spots were exposed to the iodine chamber. The reaction mixture on standing for a few hours afforded product which was filtered under reduced pressure and recrystallized out of alcohol for 2 to 3 times to give pure product (Fig 1) [17,18].

Synthesis of 4-(2-methoxyphenyl)-2-(methylthio)-1,4,5,6-tetrahydrobenzo[*h*]quinazoline:

The compound 4-(4-methoxyphenyl)-3, 4, 5, 6-tetrahydrobenzo[*h*]quinazoline-2(1*H*)-thione Ia (0.004 mole, 1.288 g) was dissolved in 25 ml ethanol. To it, NaOH solution was added, which was prepared by dissolving NaOH (0.004 moles, 0.160 g) in water (2 ml). The mixture was cooled. To this mixture, dimethyl sulphate (0.5 ml, 0.004 mole) was added dropwise while stirring the mixture continuously. The reaction mixture was refluxed for 3 h. The reaction was monitored by thin layer chromatography (TLC) using silica gel-G plates. Ethyl acetate and n-hexane mixture was used as eluting solvents (1:1) and after drying, the retention factor value was noted (Fig 2) [19,20].

Preliminary Screening of Anti-bacterial activity:

***Paper disc diffusion method*:**

The sterilized (autoclaved at 120 °C for 30 min) medium was inoculated (1 ml/100 ml of medium) with the suspension [10^5 cfu m/l (colony forming unit per ml)] of the microorganism (matched to McFarland barium sulphate standard) and poured in Petridish to give a depth of 3 to 4 mm. The paper impregnated with the test compounds (50, 100 and 150 µg/ml in dimethyl formamide) was placed on the solidified medium. The plates were pre-incubated for 1 h at room temperature and incubated at 37 °C for 24 h for antibacterial activity. Ciprofloxacin (100 µg/disc) was used as a standard. The observed zone of inhibition was compared with standard drug which observed zones of inhibition [21-26].

Determination of MIC:

***Agar streak dilution method*:**

MIC of the synthesized compounds was determined by agar streak dilution method. A stock solution of the synthesized compounds (100 µg/ml) in Dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantities of molten nutrient agar medium.

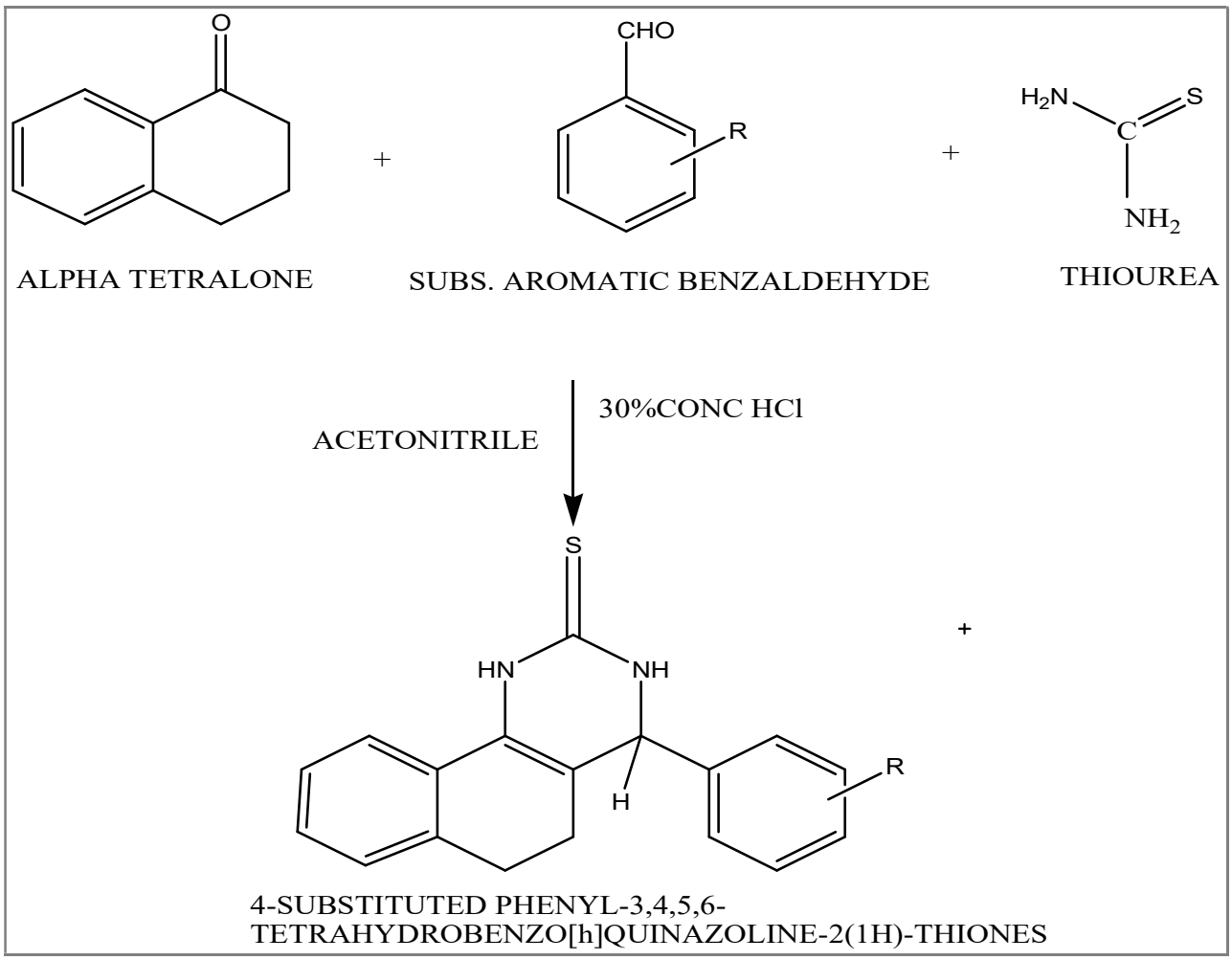


Fig 1. Step 1 - Synthesis of 4-substituted phenyl-3,4,5,6 tetrahydrobenzo[h] quinazoline-2(1H)-thiones.

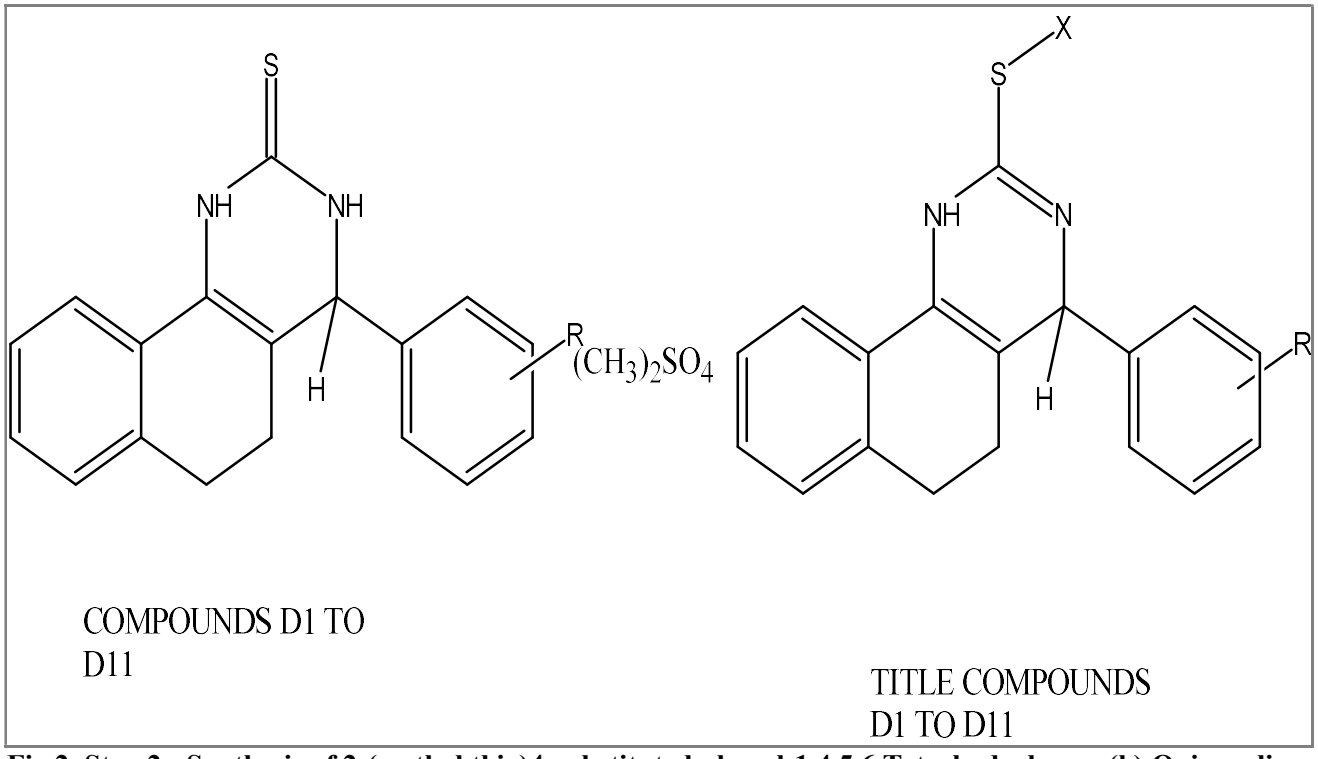
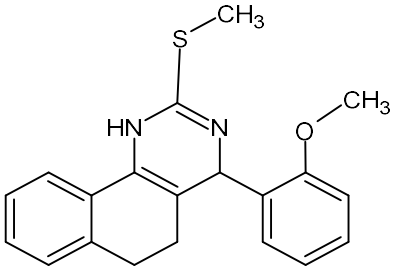
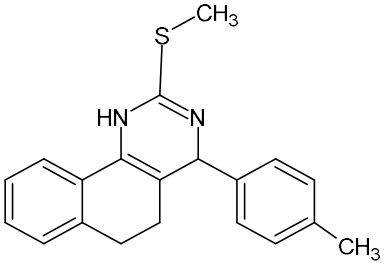


Fig 2. Step 2 - Synthesis of 2-(methyl thio)4-substituted phenyl-1,4,5,6 Tetrahydrobenzo (h) Quinazolines.

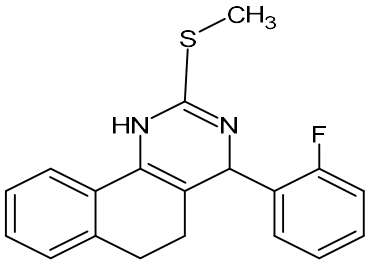
D1-2-(methyl thio)-4-(2-methoxyphenyl) 1,4,5,6 Tetrahydrobenzo (h) Quinazolines



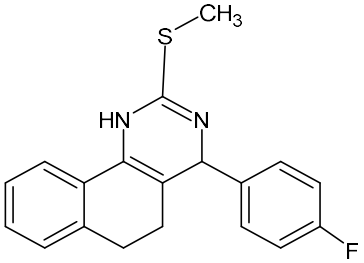
D2-2-(methyl thio)4-(4-methylphenyl)1,4,5,6 Tetrahydrobenzo (h)Quinazolines



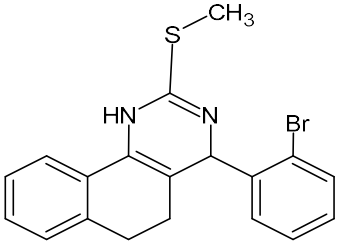
D3-2-(methyl thio)4-(2fluoro phenyl) 1,4,5,6 Tetrahydrobenzo (h)Quinazolines



D4-2-(methyl thio)4-(4fluoro phenyl) 1,4,5,6 Tetrahydrobenzo (h)Quinazolines



D5-2-(methyl thio)4-(2-bromophenyl)1,4,5,6 Tetrahydrobenzo (h)Quinazolines



D6-2-(methyl thio)4-(2methyl thio phenyl) 1,4,5,6 Tetrahydrobenzo (h)Quinazolines

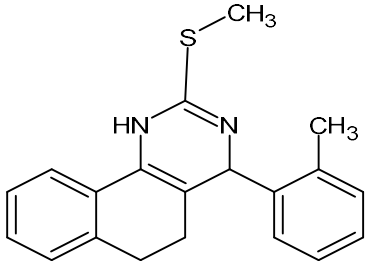


Fig 3. The selected Compounds D1 to D6 for Anti-bacterial activity.

A specified quantity of the medium containing the compounds was poured into a Petridish to give a depth of 3 to 4 mm and allowed to solidify. Suspension of the microorganism were prepared to contain approximately10^5 cfu m/l and applied to plates with serially diluted compounds in Dimethyl formamide to be tested and incubated at 37 °C for 24 h for bacteria and fungi. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria on the plate [27-33].

RESULTS AND DISCUSSION:

From the data (MIC data given in Table 1), the observation was made as follows that all synthesized compounds exhibited moderate to good antibacterial activity with a MIC ranges from 13 to 47 µg/ml. The compound D1 was found to exhibit the highest antimicrobial activity against *S. aureus* (MIC: 13 µg/ml), *E. coli* (MIC: 20 µg/ml). The compounds were active against all the tested microorganisms with a range of MIC values of *S. aureus* (MIC: 24 to 47 µg/ml), *E. coli* (MIC: 20 to 42 µg/ml).

Table 1. Minimum Inhibitory Concentration (MIC) of synthesized compounds.

Compound No.	*S. aureus*	*E. coli*
D1	13	20
D2	17	15
D3	32	30
D4	47	24
D5	38	35
D6	35	28
Ciprofloxacin	0.22	0.17

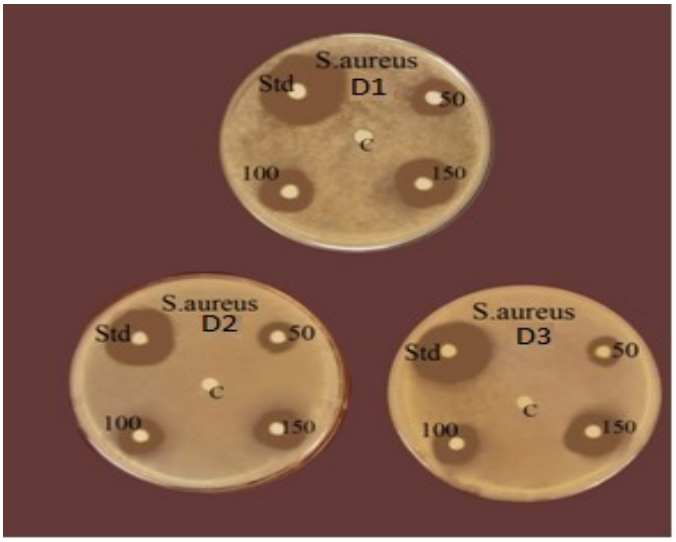


Fig 4. The MIC values of compounds D1 to D3 against *S. aureus*.
Control if DMF (Dimethyl Formamide), Standard is Ciprofloxacin at dose of 100 µg/ml.

From the data shown in Table 2, the observation was made as follows that most of the synthesized compounds exhibited moderate to good antimicrobial activity against the tested microorganisms. When compared to the standard drug (ciprofloxacin for antibacterial respectively) compounds D3, D4 and D6 (At dose of 100 mg/ml) were found to exhibit good antimicrobial activity due to 2 fluoro, 4 fluoro, and 2 methyl substituents.

The MIC of the synthesized compounds was screened by the agar streak dilution method. The synthesized compounds were (50, 100, and 150 µg/ml) screened for antibacterial activity by paper disc diffusion method and agar streak dilution method.

Table 2. Zone of inhibition of the synthesized compounds.

Compound	Zone of Inhibition (mm)					
	S. aureus			*E. Coli*		
	50 µg/ml	100 µg/ml	150 µg/ml	50 µg/ml	100 µg/ml	150 µg/ml
D1	23	28	30	25	28	31
D2	16	18	25	20	27	32
D3	11	14	18	24	32	29
D4	13	18	23	22	29	27
D5	12	15	19	14	19	23
D6	20	23	30	21	31	30
CFC	---	41	---	----	41	----

CFC – Ciprofloxacin as standard at 100 µg/ml.

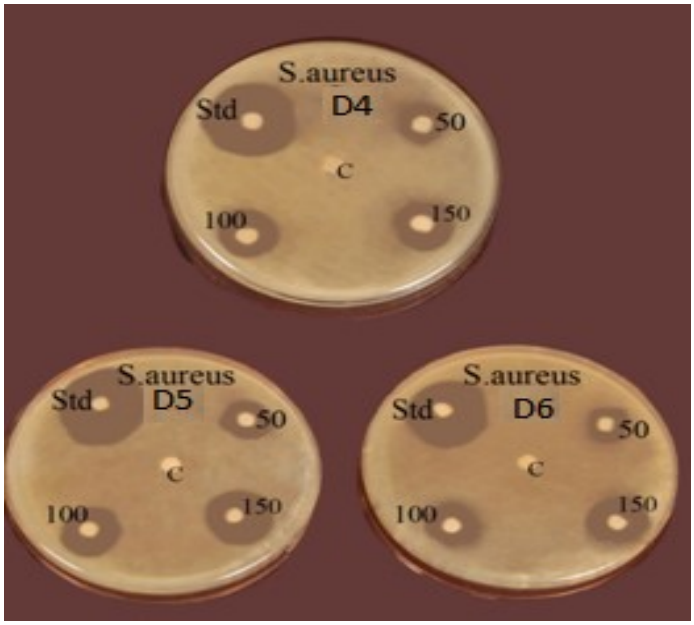


Fig 5. The MIC values of compounds D4 to D6 against *S. aureus*.
Control if DMF (Dimethyl Formamide), Standard is Ciprofloxacin at dose of 100 µg/ml.

CONCLUSION:

From the above results the following observations were noted. Compound D1 exhibits elevated antibacterial action compared to compounds D2 to D6 and in relevance to the literature survey, it was concluded that compared to other Quinazoline derivatives, fluoro substituted compounds exhibited superior antibacterial activity (D2, D3). Even though these recently synthesized molecules represents a fruitful matrix for the development of a new class of biological molecules that would deserve further investigation and derivatization. In future it would be most promising and leading derivatives can act in opposition to micro-organism.

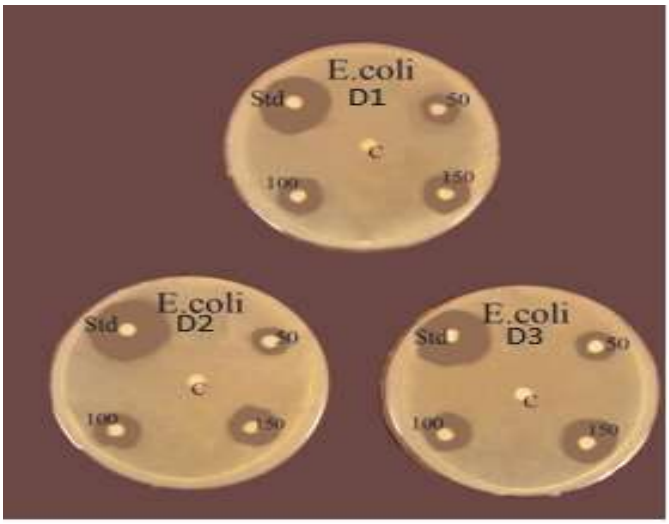


Fig 6. The zone of inhibition of compounds D1 to D3 against *E. coli*.
Control if DMF (Dimethyl Formamide), Standard is Ciprofloxacin at dose of 100 µg/ml.

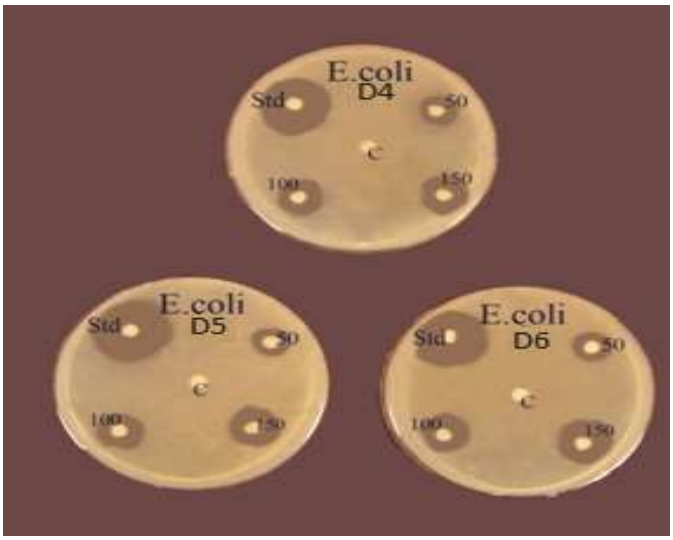


Fig 7. The zone of inhibition of compounds D4 to D6 against *E. coli*.
Control if DMF (Dimethyl Formamide), Standard is Ciprofloxacin at dose of 100 µg/ml.

ACKNOWLEDGEMENT:

The authors are very grateful to thank the institution and co-workers for their eminent support to complete the research work in successful mode.

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Conflict of Interest: None
Source of Funding: Nil
Paper Citation: Dhunmati K*, Sandhiya V, Remya RS, Sankari E, Kousalya M, Kavitha C. Antibacterial Screening of Novelquinazoline Derivatives. J Pharm Adv Res, 2020; 3(11): 1054-1061.