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Original Article

SYNTHESIS, SCREENING OF NOVEL 1-SUBSTITUTED-3-(4-OXO-2-PHENYLQUINAZOLIN-3(4H)-YL) UREA AND THIOUREA ANALOGUES AS POTENT ANTIBACTERIALS

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ABSTRACT

Objective: The proposed study is an attempt to determine antibacterial activity of synthesized novel 1-substituted-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) urea and thiourea analogues as potent antibacterials against *S. aureus* and *E. coli* bacteria.

Methods: The present study reports new series of 1-substituted-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) urea and thiourea derivatives as potent antibacterial agents. Reagents used in the present study were of synthetic grade and solvents were used after distillation. Novel quinazolinone analogues were synthesized by considering substitution pattern, characterization of the synthesized analogues was performed using various techniques like Thin layer chromatography, Melting point, Infrared spectroscopy, Proton NMR spectrometry and Mass spectrometry. TLC of the synthesized analogues was carried out by using (toluene: methanol in the ratio 2:1), melting point was found by open capillary method, IR spectrum was recorded on JASCO V-530, 1H NMR was recorded on Bruker Avance Spectrometer and Mass spectra were obtained from G6460A, triple quadrupole/MS/MS system. *In vitro* antibacterial activity was performed against *S. aureus and E. coli.*

Results: Six derivatives of quinazolinone analogues were synthesized. The structures of 1-substituted-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) urea and thiourea derivatives were confirmed by physical and spectral analysis. Synthesized molecules showed *Rf* of 0.45-0.80 in toluene: methanol mobile phase, melting point was carried out by open capillary method and were in range of 90-210 ° C, IR spectrum was recorded in range of 14000-400 $cm^{-1}$and showed characteristic peaks of NH and of C-O-NH, 1H NMR of the compounds was distinct to confirm structures with delta values in the range of 7.53-11.960, Mass spectra proved parent peaks of synthesized compounds confirming molecular weight. The compounds were assayed for antibacterial activity against *S. aureus* and *E. coli* using ciprofloxacin as standard. The synthesized analogues have shown good yield and comparable antibacterial.

Conclusion: The present study delivers a convenient and efficient protocol for the quinazolinone analogues synthesis.

Keywords: Antibacterial, Ciprofloxacin, *E. coli*, Quinazolinone analogues, *S. aureus*

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INTRODUCTION

Heterocyclic compounds in particularly nitro-heterocyclic compounds contribute staggeringly diverse and equally important class of molecules. The importance of heterocyclic compound in medicinal chemistry is well established, most of the drugs available today contain heterocyclic scaffolds. Quinazolinone scaffold is one of the most important and privileged pharmacophore. Quinazolinones have wide spectrum of their antibacterial, anticonvulsant, antifungal, anticancer, anti-HIV, anti-inflammatory, antitubercular and analgesic activities. Its structure represents capable binding at multiple sites with high affinity and facilitate more rapid discovery of useful medicinally active compounds [1]. There are several approved drugs with quinazoline structure in the market namely alfuzosine, prazosin, terazosine hydrochloride and doxazosine mesylate [2]. In 1860's, the first quinazolinone was synthesized from anthranilic acid and cyanogen to give 2-cynoquinazolinone [3]. In the present research work we have mainly focused on antibacterial activity; because nowadays, worldwide bacterial resistance to available drugs is a growing problem. Antimicrobial agents can benefit in cancer treatment by killing oncogenic-related microorganisms by protecting from recurring immune-suppression-induced infection and by their direct antiproliferative/cytotoxic effects [4]. Quinazoline possess antibacterial activity against the gram positive strains and fungi through their interaction with cell wall and DNA structure. Early reports for fluorinated compounds conjugated quinazolines conjugated with lysine, 1-[2-(6 nitro-4-oxo-2-phenyl-4H-quinazoline) 3yl) ethyl] 3 phenyl urea's, quinazoline imidazoles substituted with amino acids and salicylic acids have shown potent antibacterial activity against *E. coli* [5-10].

Meena *et al.* synthesized series of quinazolinone semicarbazone derivatives with 2-isopropyl-5-methylcyclohexan-1-one substitution and nitrophenol which exhibited good anticonvulsant activity. Divyesh *et al.* synthesized series of β-aryloxyquinolines, which were investigated against representative panel of pathogenic strains specifically *Bacillus subtilis, Clostridium tetani, Streptococcus pneumoniae, Escherichia coli, Salmonella typhi, Vibrio cholera, Aspergillus fumigates, Candida albicans and mycobacterium tuberculosis*. Compound bearing chloro, methyl and methoxy substitution exhibited comparable potent antifungal, antimicrobial and antitubercular activity. Bhupinder *et al.* synthesized series of amino acid and peptide derivatives of 5-(2-(2-chlorophenyl)-4-oxoquinazolin-3*(4H)*-yl)-2-hydroxy benzoic acid. The compounds screened for their antimicrobial potential against *S. pyogenes, S. aureus, P. aeruginosa,* and *E. coli*. All the derivatives have shown promising antimicrobial activity, but the compounds with isopropyl and indole derivatives were having more promising and reproducible effect [11-13].

Priya *et al.* synthesized series of mannich bases which were screened for anti-oxidant and anti-microbial activity. The compounds with naphthalene derivatives exhibited good anti-oxidant and antibacterial activity. Niraj *et al.* synthesized pyrazoline bearing 4(3H)-quinazolinone derivatives, which exhibits analgesic and anti-inflammatory activity. The compounds bearing halo and hydroxyl substitution gave comparatively potent analgesic and anti-inflammatory activitiy. Megha *et al.* synthesized quinazolinone derivatives with various substitutions on nitrogen and oxygen derivatives. The compounds exhibited potent activity against DHFR for various human cancer cell lines. Compounds with bromo-

substitution, tri flouro-methyl group substitution on nitrogen containing ring exhibited comparatively high potency as anticancer agents [14-16].

Prompted by these findings and medicinal importance of quinazolinone we report here the synthesis of novel analogues of 1-substituted-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) urea and thiourea derivatives as potential bioactive molecules.

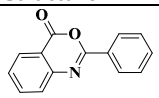
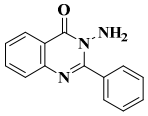
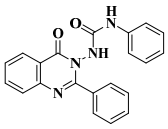
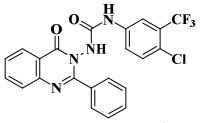
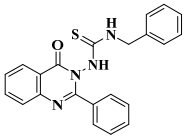
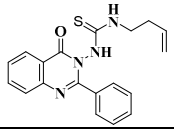
MATERIALS AND METHODS

Solvents and materials were purchased from Sigma Aldrich Merck and were of synthetic grade. Reaction procedures were optimized on Radley's six station parallel combinatorial synthesizers and monitored on pre-coated aluminum plates (Merck silica gel 60F-254) using UV visualization technique and iodine vapors. Melting points (uncorrected) were determined on programmable melting point and boiling point apparatus (VEEGO, India). IR spectra were recorded on JASCO V-530 FTIR 4100.^{1}H NMR was recorded on "Bruker Avance" Spectrometer at 100, 300, 400 MHz frequency in $CDCl_3$ and DMSO in presence of TMS as internal standard (Chemical shift in ppm). Mass spectra were obtained from G6460A triple quadrupole/MS/MS system (Agilent technologies) equipped with electrospray ionization technique. The *In silico* drug properties calculation was performed using OSIRIS Data warrior (version 5.0.0.) which is based on Lipinski rule of five. *In vitro* antibacterial evaluation was carried out against *Staphylococcus aureus* (NCIM 2079) and *Escherichia coli* (NCIM 2065) as a microbial strain. (Microbial Strains were obtained from National Centre for Cell Science (NCCS), Pune).

Synthesis of analogues

On the basis of literature survey and structural activity relationship, six quinazolinone analogues were synthesized [17, 18] i.e. SS-A, SS-B, SS-01, SS-02, SS-03, SS-04 as depicted in (table 1).

Table 1: Synthesized 1-substituted-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) urea and thiourea analogues

Compound code	Structure	IUPAC name
SS-A		2-phenyl-4H benzo[d][1,3]oxazin-4-one
SS-B		3-amino-2-phenyl quinazoline-4(3h)-one-4-one
SS-01		1-(4-oxo-2-phenylquinazolin-3(4H)-yl)-3-phenylurea
SS-02		1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)urea
SS-03		1-benzyl-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiourea
SS-04		1-(but-3-en-1-yl)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiourea

Step I

Scheme for synthesis of 2-phenyl-4H benzo[d][1,3]oxazin-4-one (SS-A)

Anthranilic acid solution was prepared by adding 6.85 g (0.05 mol) of anthranilic acid to 60 ml of pyridine. To this mixture 5.67 ml (0.05 mol) of benzoyl chloride was added drop wise at 0-2 ° C for 2 h. Reaction mixture was stirred for 2 h. The reaction mixture was neutralized with saturated sodium bicarbonate solution and solid product was filtered and re-crystallized from ethanol. The reaction step is depicted in (fig. 1).

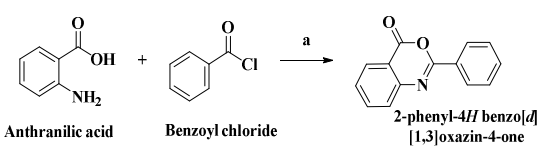


Fig. 1: Scheme for synthesis of 2-phenyl-4H benzo[d][1,3]oxazin-4-one (SS-A)

Step II

Scheme for synthesis of 3-amino-2-phenyl quinazoline-4(3h)-one-4-one (SS-B)

2.2 g (0.01 mol) of 4H-benzo[d] [1, 3] Oxazin-4-one was dissolved in ethanol and 0.5 ml (0.01 mol) of hydrazine hydrate was added to it with catalytic amount of pyridine. Reaction mixture was refluxed for 1 h and after cooling a crystalline product was filtered and re-crystallized from ethanol. The reaction step is depicted in (fig. 2)

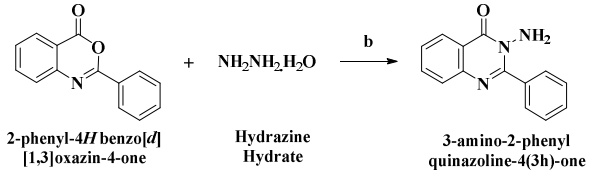


Fig. 2: Synthesis of 3-amino-2-phenyl quinazoline-4(3h)-one-4-one

Step III

Scheme for synthesis of 1-substituted-3-(4-oxo-2-phenyl-quinazolin-3(4H)-yl) urea and thiourea analogues

2 g (0.0090 mol) of 3-amino-4H-quinazolinone was dissolved in 10 ml di-chloro methane (DCM). After stirring the reaction mixture for 5 min at room temperature 1.99 g (0.00900 mol) of respective isocynates were added in it and was stirred. After completion of reaction, product was filtered and re-crystallized from ethanol. The reaction step is depicted in (fig. 3).

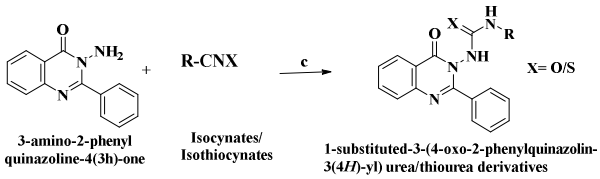


Fig. 3: Scheme for synthesis of 1-substituted-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) urea and thiourea analogues

***In silico* drug properties**

The correlation of absorption, distribution, metabolism, excretion, toxicity and the prediction of physicochemical properties is necessary. For the prediction of physicochemical properties, OSIRIS Data warrior (version 5.0.0.) software was used which is based on Lipinski rule of five [19].

Antibacterial activity

Antibacterial activity was performed by agar well diffusion method by measuring zone of inhibition. All the test compounds were screened for antibacterial activity against bacterial strains of *Staphylococcus aureus* (NCIM 2079) and *Escherichia coli* (NCIM 2065) at concentrations of 1000, 500, 250, 125, 62.5 µg/ml respectively. Ciprofloxacin was used as standard drug at a concentration of 100 µg/ml. Nutrient agar was used as culture medium and DMSO was used as solvent control. Laminar airflow bench was swapped with 70 % alcohol and UV lamp was switched on. After 30 min, the UV lamp was switched off. All the reagents, media, inoculums and glass wares were placed in laminar air flow bench observing all aseptic conditions. The plates were inoculated within minutes of the preparation of suspension, so that the density does not change. A sterile cotton swab over was dipped into the suspension and the medium was inoculated by even streaking of the swab over the entire surface of the plate in three directions. After the inoculums had dried, wells of diameter 6 mm were made in the agar plate with a sterile cork borer. The drug solutions were added to these wells with a micropipette and the plates were than incubated at 37 ° C for 24 h. The zone of inhibition was measured using mm scale [20, 21].

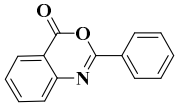
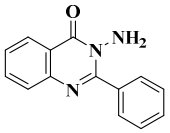
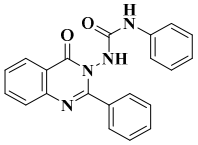
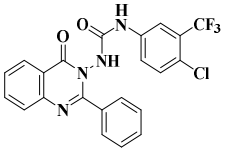
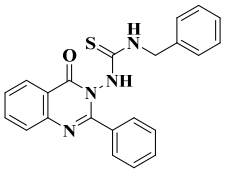
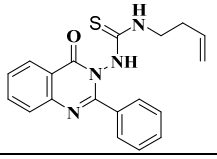
RESULTS AND DISCUSSION

Characterization study

Six quinazolinone derivatives SS-A to SS-04 were synthesized. The yields of final products were obtained in the range of 90-95 %. Recrystallisation was performed using ethanol; TLC was carried out by using toluene: methanol in the ratio 2:1.

The IR spectrum showed characteristic peaks of N-H in range of (3300-3285 cm^{-1}) and of C-O-NH of amide in range of (1640-1687 cm^{-1}). Mass spectra proved parent peaks of the synthesized compounds confirming molecular weight. ^1H NMR of the compounds was distinct to confirm structures [22]. Summary of physical constants of synthesized derivatives is depicted in (table 2).

Table 2: Physical constants of synthesized compounds

Code	Structure	Physical constants			
		Melting point (°C)	Yield (%)	Mol. Formula	R_f
SS-A		118.0-120.8	95	$C_{14}H_9NO_2$	0.85
SS-B		90.0-93.5	92	$C_{14}H_{11}N_3O$	0.60
SS-01		108.5-109.8	90	$C_{21}H_{16}N_4O_2$	0.65
SS-02		108.5-109.8	95	$C_{22}H_{17}N_4O_2$	0.65
SS-03		208.5-210.7	91	$C_{22}H_{18}N_4OS$	0.58
SS-04		101.5-103.8	95	$C_{22}H_{18}N_4OS$	0.47

2-phenyl-4H benzo[d][1,3]oxazin-4-one (SS-A)

IR *vmax* (cm^{-1}) (KBr): 3034.44, 1764.55, 1617.02, 1256.4, 1518.67; ^1H NMR (δ, DMSO): 7.53-8.15 (m,-Ar, 9H); ESI-MS (*m/z*) for $C_{14}H_9NO_2$ calculated 223.13, found 223.19

3-amino-2-phenylquinazolin-4(3H)-one (SS-B)

IR *vmax* (cm^{-1}) (KBr): 3355.53, 3306.36, 1672.95, 1590.02; ^1H NMR (δ, DMSO): 7.53-8.15 (m,-Ar, 9H, s,-NH, 2H); ESI-MS (*m/z)* for $C_{14}H_{11}N_3O$ calculated 237.13, found 237.19

1-(4-oxo-2-phenylquinazolin-3(4H)-yl)-3-phenyl urea (SS-01)

IR *vmax* (cm^{-1}) (KBr): 3286.11, 3032.51, 1674.88, 1572.66, 1504.2; ^1H NMR (δ, DMSO): 8.5380 (s, 1H, NH), 8.559 (s, 1H, NH), 6.9543-7.9363 (m 14H,-Ar); ESI-MS (*m/z*) for $C_{21}H_{16}N_4O_2$ calculated 356.13, found 356.29

1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-oxo-2-phenyl-quinazolin-3(4H)-yl) urea (SS-02)

IR *vmax* (cm^{-1}) (KBr): 3340, 1654, 1605, 1526; ^1H NMR (δ, DMSO):11.86 (s, 1H), 9.39 (s, 1H), 7.522-8.670 (m, 12H); ESI-MS (*m/z*) for $C_{22}H_{17}N_4O_2$ calculated 458.08, found 458.49

1-benzyl-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) thiourea (SS-03)

IR *vmax* (cm^{-1}) (KBr): 3204.15, 2933.2 1660.14, 1602.56, 1520.16; 1H NMR (δ, DMSO):11.960 (s, 1H,-NH), 10.738 (s, 1H,-NH), 4.721(t, 2H,-CH_2-), 7.185-8.772 (m, 14H,-Ar); ESI-MS (*m/z)* for $C_{22}H_{18}N_4OS$ calculated 386.12, found 386.14

1-(but-3-en-1-yl)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) thiourea (SS-04)

IR *vmax* (cm^{-1}) (KBr): 3274.54, 3023, 2950.55, 2845.45, 1684.52, 1602, 1534.11, 1447.31; 1H NMR (δ, DMSO):11.960 (s, 1H,-NH), 10.738 (s, 1H,-NH), 3.95 (t, 2H,-CH_2-), 7.185-8.772 (m, 9H,-Ar); ESI-MS (*m/z*) for $C_{22}H_{18}N_4OS$ calculated 350.12, found 350.44

***In silico* drug likeness**

The compounds were screened physicochemical properties and drug toxicity. All compounds have shown less toxicity risks, with no violation for Lipinski rule of five. Less solubility of the synthesized compound was predicted and was observed practically. The compounds were screened for antibacterial activity on the basis of drug likeness score as shown in the (table 3).

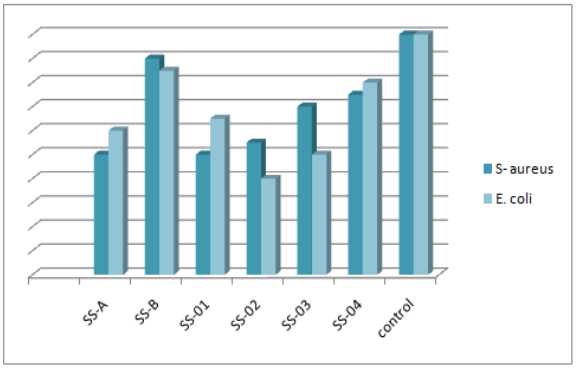
Table 3: OSIRIS calculation for lipinski rule of five

Code	Mol. weight	cLogP	cLogS	H-acceptors	H-donors	Drug likeness	Drug score
SS-A	223.13	0.351	-3.341	3	0	4.81418	0.571266
SS-B	237.13	0.8997	-3.061	4	1	5.77379	0.598914
SS-01	356.13	2.5345	-4.389	5	1	0.2575	0.321117
SS-02	458.08	3.9888	-5.903	5	1	2.8979	0.716608
SS-03	386.13	2.5326	-4.354	5	1	0.35094	0.316608
SS-04	350.12	2.1636	-3.716	4	1	2.8868	0.716708

Table 4: Antibacterial activity of synthesized compounds against *S. aureous* and *E. coli* in terms of zone of inhibition in mm

Compound code conc.	Zone of inhibition (mm)±Std deviation[a]									
	S. aureus					*E. coli*				
	1000 µg/ml	500 µg/ml	250 µg/ml	125 µg/ml	62.5 µg/ml	1000 µg/ml	500 µg/ml	250 µg/ml	125 µg/ml	62.5 µg/ml
Std (Ciprofloxacin)	--	36.00±1.00	34.00±2.00	39.33±1.15	27.67±2.08	--	26.00±1.00	34.00±2.00	25.33±1.15	21.00±1.00
Control	--	--	--	--	--	--	--	--	--	--
SS-A	11.00±1.25	10.00±2.00	8.33±1.15	6.67±2.08	0.00±0.00	11.33±2.00	9.33±1.15	7.67±2.08	6.00±1.00	0.00±0.00
SS-B	10.00±1.25	8.00±2.00	6.33±1.15	5.67±2.08	0.00±0.00	10.25±2.00	8.33±1.15	6.67±2.08	4.00±1.00	0.00±0.00
SS-01	5.00±1.25	4.52±1.15	4.12±2.08	0.00±0.00	0.00±0.00	4.52±1.15	4.12±2.08	3.00±1.15	2.00±2.08	0.00±0.00
SS-02	16.00±1.25	15.67±1.00	11.33±1.15	10.67±2.08	0.00±0.00	13.00±1.25	12.00±1.00	11.00±1.15	9.00±2.08	0.00±0.00
SS-03	9.01±1.25	7.01±2.00	4.52±1.15	4.12±2.08	0.00±0.00	4.52±1.15	4.12±2.08	0.00±0.00	0.00±0.00	0.00±0.00
SS-04	17.57±1.25	16.57±2.00	14.67±1.15	12.00±2.08	0.00±0.00	11.00±1.25	11.00±2.00	12.00±1.15	10.00±2.08	0.00±0.00

A: each value is the mean of three values.



X axis : Concentration 500 µg/ml Y-axis : Microbial inhibition in mm

Fig. 4: Comparative zone of inhibition of synthesized compounds

Antibacterial evaluation

All six synthesized analogues bearing various substitutions were screened for antibacterial activity. All the compounds have shown significant activity at 500 µg/ml for *S. aureus* and *E. coli*. The summary of antibacterial activity is shown in the (fig. 4 and table 4).

CONCLUSION

In the proposed research work an attempt was made to synthesize novel quinazolinone analogues by considering the substitution pattern on quinazolinone moiety as microbial inhibitors. The study performed includes various aliphatic and aromatic substitutions on the nitrogen of quinazolinone. All the synthesized compounds were confirmed by IR, NMR and Mass Spectrometry. These synthesized compounds were evaluated for preliminary antibacterial activity. Amongst the six analogues SS-02 and SS-04 have shown comparable against *S. aureus and E. coli* using Ciprofloxacin as standard. Thus the result reveals that the synthesized analogues may be used for designing of novel antibacterial agents.

DISCUSSION

In the present study we have synthesized quinazolinone derivatives with 1-substituted-3-(4-oxo-2-phenylquinazolin-3(4H)-yl) urea and thiourea. The compounds exhibited comparable antibacterial activity. The reported literature of quinazolinone with substitutions of chloro, methyl, methoxy, hydroxyl, ethers, thioethers,1-chloro-2-(trifluoromethyl) benzene and N-but-3-ene thiourea derivatives exhibited good antibacterial and anticancer activity [23-28]. When we compared our synthesized derivatives with them we could find a new target wherein we can structurally modify our derivatives to develop new series of quinazolines with antibacterial as well as anticancer activity.

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AUTHORS CONTRIBUTIONS

Deepali A Bansode conceived the idea, supervised the experiments, analyzed the results and drafted the manuscript. Sandhya R Dhokale and Snehal R Thakar have contributed as research associate in performing experiments. Kakasaheb R Mahadik contributed in carrying out research work by providing the essential infrastructure.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this research article.

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