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Research Article

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A study on synthesis, molecular properties and antimicrobial activity of some quinazoline derivatives

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ABSTRACT

The title compounds have been prepared by incorporating the anthranilic acid with substituted benzoylchloride which lead to the formation of oxazin-4-ones followed by subjecting it in the presence of pyridine, hydrazine hydrochloride, sodium cyano oxide lead to the formation of 1-(4-oxo-2-arylquinazolin-3(4H)-yl) semicarbazide. Various aromatic carbonyl compound with 1-(4-oxo-2-arylquinazolin-3(4H)-yl) semicarbazide in the presence of glacial acetic acid and ethanol gives (S1-S10) quinazoline derivatives. Structures of newly synthesized compound have been established on the basis of their IR and NMR spectral data. All the synthesized compounds have been screened for their antimicrobial activity.

Key words: Antibacterial activity, Antimicrobial activity, Quinazoline, Semicarbazide

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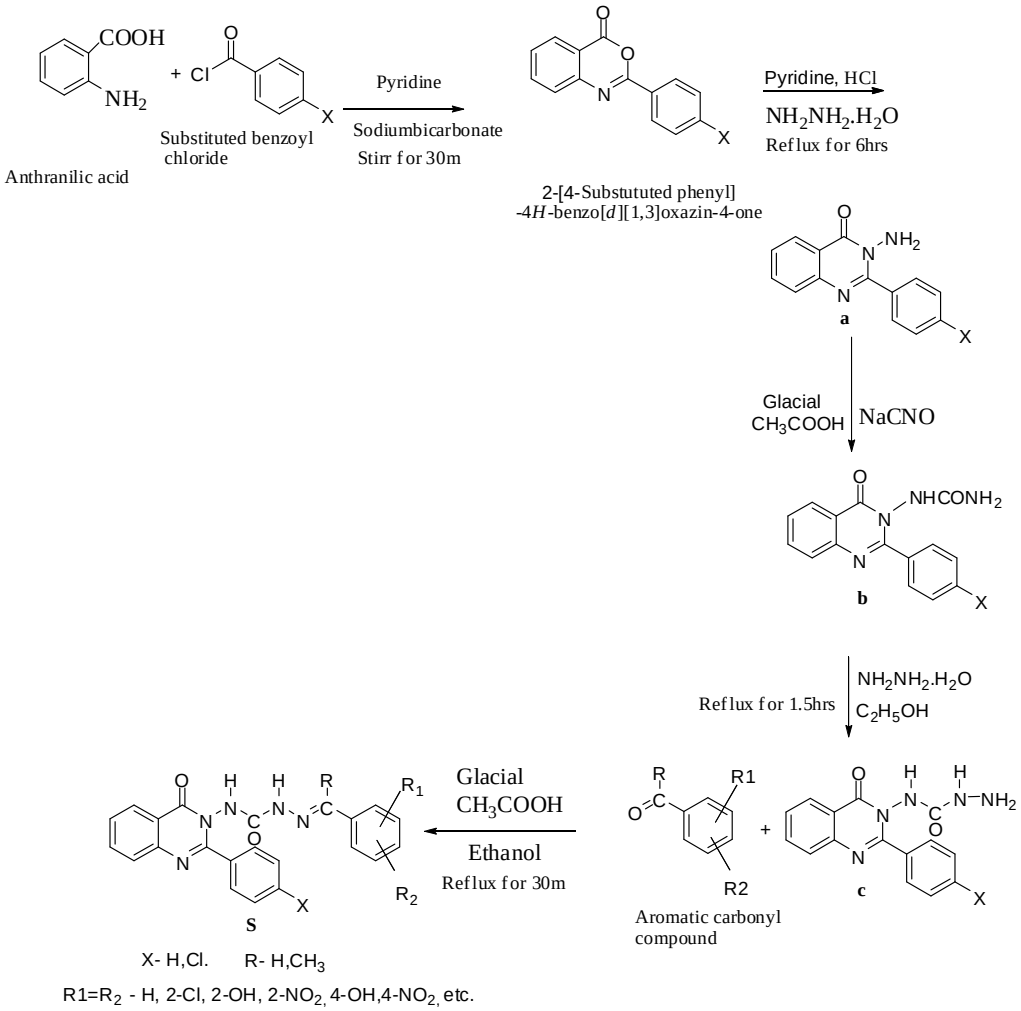
INTRODUCTION

We report herein the new and unreported yet the synthesis of quinazoline derivatives. The chemistry and pharmacology of quinazoline derivatives have been of great interest because, of its various biological activities. In search for new bioactive potent molecule, it was thought worthwhile to incorporate some additional semicarbazone moieties in the quinazoline nucleus and study their biological activity, the review of literature reveal prompted us to synthesis substituted quinazoline derivatives with semicarbazone side chain and those will be screened for anticancer and antimicrobial activity [1-3].

EXPERIMENTAL SECTION

The entire chemicals were procured from S.D Fine chem. (Mumbai), Final Chem. Ltd. (Ahemadabad) and Loba Chemie. Pvt. Ltd. (Mumbai). Melting points were determined by open tube Capillary method and were uncorrected. Purity of compounds was checked by thin layer chromatography (TLC) on Silica gel-G (E- merck) in solvent system ethyl acetate-butanol: water (6:3:1) and the spots were located under iodine vapours and UV light. The infrared spectral study was done on JASCO 4100 FTIR by KBr disc method. NMR spectral study was done on JEOL, FX90Q Fourier Transform-NMR Spectrometer [4-6].

SYNTHETIC PATHWAY



a) 2-aryl-3-amino-4(3H) quinazolinone
b) 1-(4-oxo-2-arylquinazolin-3(4H)-yl) urea
c) 1-(4-oxo-2-arylquinazolin-3(4H)-yl) semicarbazide

GENERAL PROCEDURES [7-15]

Synthesis of 2-aryl-3-amino-4(3H) quinazolinone from anthranilic acid

Anthranilic acid (0.1mol, 13.71gm) was dissolved in 30ml of dry pyridine by stirring slowly at room temperature. The solution was cooled to 0°C and a solution of an aromatic acid chloride (4-Chlorobenzoyl chloride) (0.02mole) in 30ml of dry pyridine was added slowly with constant stirring. After this addition the reaction mixture was further stirred for half an hour at room temperature and set aside for 1h. The pasty mass obtained was diluted with 50 ml of water and treated with aqueous sodium bicarbonate solution. When the effervescence ceased, the precipitate obtained was filtered and washed with water. The crude benzoxazine obtained was dried and recrystallized from diluted ethanol.

To a cold solution of 2-[4-Chloro phenyl]-4H-benzo[d] [1, 3] oxazin-4-one(0.05mol) in anhydrous pyridine, (20ml) added a solution of hydrazine hydrate (0.1mol) in anhydrous pyridine (25ml) drop wise with constant stirring. When the addition was complete, the reaction mixture was stirred vigorously for 30min at room temperature and subsequently heated under reflux for 6 h under anhydrous reaction conditions. The reaction mixture was allowed to cool at room temperature and poured into ice cold water containing dilute hydrochloric acid. On standing for 1h solidification occurred which was allowed to settle down. It was filtered off, washed repeatedly with water and dried, recrystallized from dilute ethanol.

Synthesis of 1-(4-oxo-2-arylquinazolin-3(4H)-yl) urea from 2-aryl-3-amino-4(3H) quinazolinone

3-Amino-2-(4-chlorophenyl)-4(3H) quinazolinone (0.1mole) was dissolved in 10-30ml of glacial acetic acid and diluted to 100ml with water. To this equimolar quantity of sodium cyanate (0.1mol, 6.5gm) in 50ml of warm water was added with constant stirring. The solution was allowed to stand for 30min. and then cooled in ice for further 30min.The precipitate obtained was filtered with suction, washed with water and dried. The precipitate was recrystallized from boiling water and ethanol mixture.

Synthesis of 1-(4-oxo-2-arylquinazolin-3(4H)-yl) semicarbazide from 1-(4-oxo-2-arylquinazolin-3(4H)-yl) urea

To a solution of 1-(4-oxo-2-(4-chloro phenyl) -quinazolin-3(4h)-yl) urea (0.1mole) in 200ml of water, an equimolar quantity of hydrazine hydrate (0.1mol, 5gm) was added. The reaction mixture was made alkaline by adding 4gm of sodium hydroxide and added 30ml of ethanol to get a clear solution. The reaction mixture was refluxed for 3h with stirring. Excess of ethanol was distilled off under vacuum and then poured in to ice. The obtained precipitate was filtered and recrystallized from 95% ethanol.

Synthesis of 1-(4-oxo-2-arylquinazolin-3(4H)-yl) aryl semicarbazones from 1-(4-oxo-2-arylquinazolin-3(4H)-yl) semicarbazide

1-(4-oxo-2-arylquinazolin-3(4H)-yl) semicarbazide (0.01mol) was dissolved in ethanol (20ml) and added slowly to an ethanolic solution of aromatic carbonyl compound (0.01mole). The reaction mixture was acidified with 5ml of glacial acetic acid and refluxed for half an hour. The precipitate obtained was filtered and washed with the mixture of ether and water and dried. The product obtained was recrystallized from 95% ethanol.

Physical Data of the Synthesized Compounds

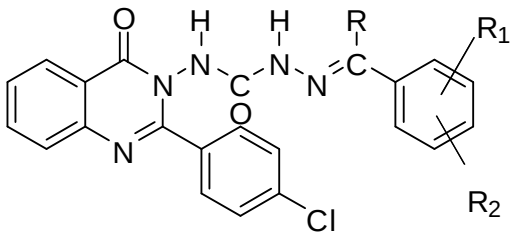


Table 1. Physical Data of the Synthesized Compounds

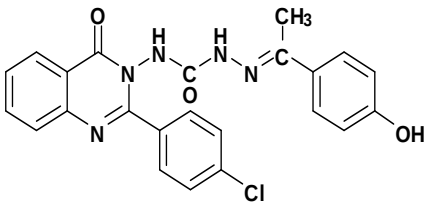
Compd.	Substituent's		Yield (%)	Melting Point (°C)	Molecular Formula	Mol. Wt.	R_f	logP^*
	R	R1, R2						
S1	CH_3	4-OH	90	188°C	C23H18ClN5O3	447	0.62	1.88
S2	CH_3	4-Cl	93	204°C	C23H17Cl2N5O2	465	0.69	2.08
S3	H	4-OH	89	210°C	$C22H16ClN5O_3$	433	0.68	2.14
S4	H	H	86	198°C	C22H16ClN5O2	417	0.52	2.18
S5	H	4-NO_2	91	196°C	C22H15ClN6O4	462	0.58	1.89
S6	---	Isatin	88	203°C	C23H17ClN6O2	444	0.66	2.18
S7	----	5-Bromo isatin	92	214°C	$C_{23}H_{14}BrClN_6O_3$	537	0.56	3.87
S8	H	Furfural	96	232°C	C21H15ClN4O3	406	0.52	3.64
S9	H	2-OCH_3	92	212°C	C24H19ClN4O3	446	0.42	4.24
S10	C_6H_5	H	86	216°C	C29H21ClN4O2	492	0.54	4.56

**Log P was calculated by partition coefficient determination using Octanol and buffer system*

R_f. Solvent system- ethyl acetate-butanol:water (6:3:1)

IR DATA

Compound S1

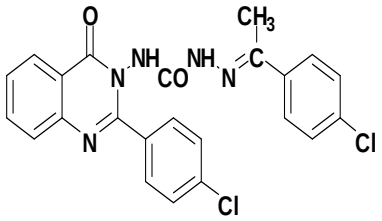


(*E*)-*N*-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl)-2-(1-(4-hydroxyphenyl)ethylidene)hydrazinecarboxamide

IR Values
3127 cm^{-1}: NH bending vibration, 1688 cm^{-1}: C=N imine stretching, 1545 cm^{-1}: C=O amide keto stretching, 1400cm^{-1}: C-O bending vibration, 1092 cm^{-1}: C-C stretching, 754cm^{-1}: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm): 2.08-2.50 (s, 1H, ArCH), 3.43(s, 1H, ArNH), 6.7 (s, 2H, Ar-OH),7.6-7.65 (m, 3H, Ar-H), 8.3-8.49 (m, 9H, Ar-H), 9.24(s, 1H, CONH)

Compound S2

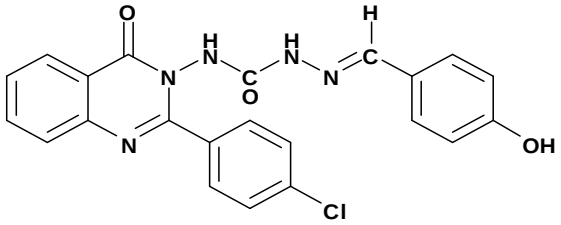


(*E*)-*N*-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl)-2-(1-(4-chlorophenyl)ethylidene)hydrazinecarboxamide

IR Values
3127 cm^{-1}: NH bending vibration, 1681 cm^{-1}: C=N imine stretching, 1532 cm^{-1}: C=O amide keto stretching, 1170 cm^{-1}: C-C stretching, 757cm^{-1}: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm):2.49-2.51(s, 1H, ArCH), 3.32(s, 1H, ArNH), 3.40 (m, 6H, Ar-OCH_3), 7.23-7.62 (s, 3H, ArH), 7.7-8.2(m, 9H, ArH), 9.2(s, 1H, CONH)

Compound S3

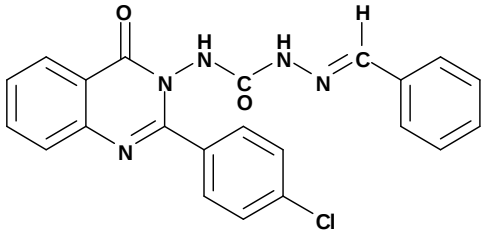


(E)-N-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-(4-hydroxybenzylidene) hydrazinecarboxamide

IR Values
3136 cm^{-1}: NH bending vibration, 1680 cm^{-1}: C=N imine stretching, 1525 cm^{-1}: C=O amide keto stretching, 1400 cm^{-1}: C-O bending vibration, 1159 cm^{-1}: C-C stretching, 756cm^{-1}: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm): 3.7(s,1H, ArNH), 6.8-7.78 (m, 10H, Ar-H), 8.1-8.6 (m, 9H, Ar-H), 9.5(s, 1H, CONH)

Compound S4

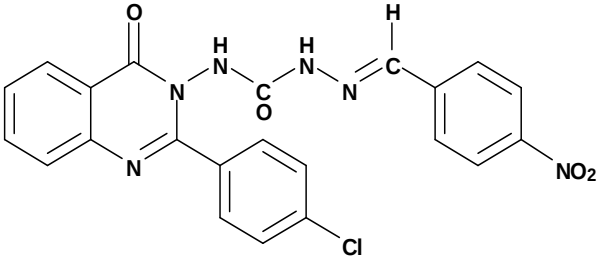


(*E*)-2-benzylidene-*N*-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl)hydrazinecarboxamide

IR Values
3126 cm^{-1}: NH bending vibration, 1680 cm^{-1}: C=N imine stretching, 1551 cm^{-1}: C=O amide keto stretching, 1092 cm^{-1}: C-C stretching, 754cm^{-1}: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm): 2.49 (s, 1H, ArCH), 3.29(s, 1H, ArNH), 7.1-7.73 (m, 4H, ArH), 8.0-8.6 (m, 9H, ArH), 10.01(s, 1H, CONH)

Compound S5

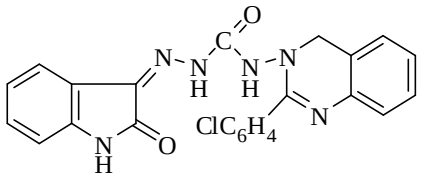


(E)-N-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl)-2-(4-nitrobenzylidene) hydrazinecarboxamide

IR Values
3124 cm-1: NH bending vibration, 1681 cm-1: C=N imine stretching, 1545 cm-1: C=O amide keto stretching, 1322 cm^{-1}: NO_2 stretching, 1093 cm-1: C-C stretching, 753cm-1: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm):2.49 (s,1H, ArNH),3.29 (s, 3H, Ar-C-CH_3), 7.5-7.9(m, 4H,Ar-H), 8.0-8.6 (m, 9H, Ar-H), 10.1(s,1H, CONH)

Compound S6

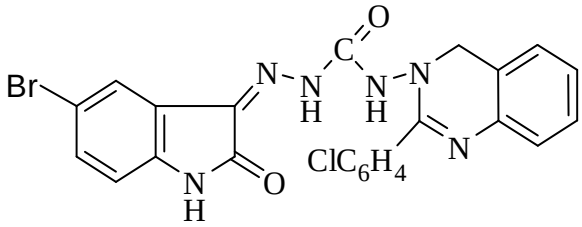


(Z)-N-(2-(chlorohexa-1,3,5-triynyl)quinazolin-3(4H)-yl)-2-(2-oxoindolin-3-ylidene) hydrazinecarboxamide

IR Values
3127 cm^{-1}: NH bending vibration, 1679 cm^{-1}: C=N imine stretching, 1590 cm^{-1}: C=O amide keto stretching, 1091 cm^{-1}: C-C stretching, 760 cm^{-1}: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm): 2.50-3.40(s, 1H, ArNH), 7.10-7.60 (m, 4H, ArH), 7.61-8.22(m, 9H, ArH), 11.1(s, 1H, CONH), 11.3-12 (s, 1H, NH isatinyl)

Compound S7

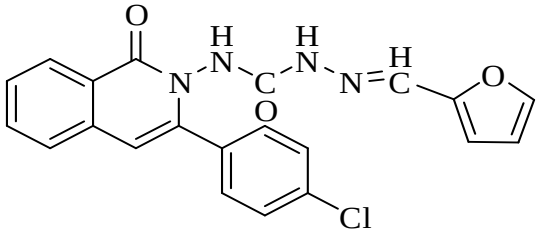


(Z)-2-(5-bromo-2-oxoindolin-3-ylidene)-N-(2-(chlorohexa-1,3,5-triynyl)quinazolin-3(4H)-yl)hydrazinecarboxamide

IR Values
3127 cm^{-1}: NH bending vibration, 1689 cm^{-1}: C=N imine stretching, 1590 cm^{-1}: C=O amide keto stretching, 1092 cm^{-1}: C-C stretching, 754cm^{-1}: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm): 3.4(s, 1H, ArNH), 7.3-7.48 (m, 3H, ArH), 7.5-8.25 (m, 9H, ArH), 9.19(s, 1H, CONH), 10.43(s, 1H, NH isatinyl)

Compound S8

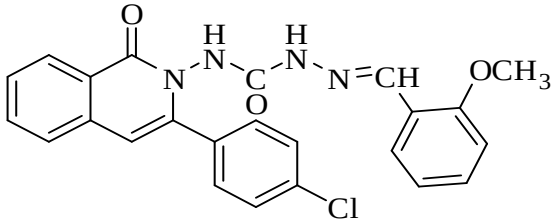


(E)-N-(3-(4-chlorophenyl)-1-oxoisoquinolin-2(1H)-yl)-2-(furan-2-ylmethylene) hydrazinecarboxamide

IR Values
3126 cm^{-1}: NH bending vibration, 1685 cm^{-1}: C=N imine stretching, 1590 cm^{-1}: C=O amide keto stretching, 1159 cm^{-1}: C-C stretching, 805cm^{-1}: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm):2.48 (s,1H, ArCH), 3.03(s, 1H, ArNH), 5.6-6.7(m, 6H, Ar-OCH_3), 7.5-7.7 (s, 3H, ArH), 7.82-8.1(m, 9H, ArH), 9.6(s, 1H, CONH)

Compound S9



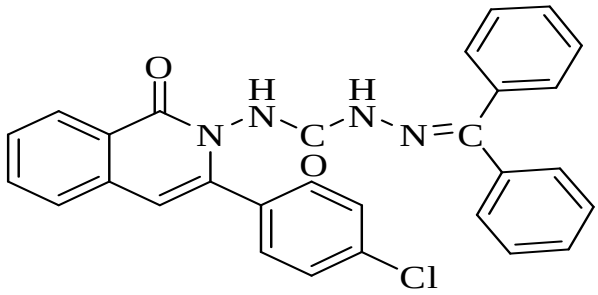
(E)-N-(3-(4-chlorophenyl)-1-oxoisoquinolin-2(1H)-yl)-2-(2-methoxybenzylidene) hydrazinecarboxamide

IR Values

3127 cm-1: NH bending vibration, 1685 cm-1 : C=N imine stretching, 1591 cm-1 : C=O amide keto stretching, 1093 cm-1: C-C stretching, 753cm-1: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm): 2.49 (s, 1H, ArCH), 3.31(s, 1H, ArNH), 7.2 (s, 3H, Ar-OCH_3), 7.41-7.77 (m, 4H, ArH), 7.81-8.26(m, 9H, ArH), 9.49(s, 1H, CONH)

Compound S10



N-(3-(4-chlorophenyl)-1-oxoisoquinolin-2(1H)-yl)-2-(diphenylmethylene) hydrazinecarboxamide

IR Values
3425 cm^{-1} : NH bending vibration, 1677 cm^{-1} : C=N imine stretching, 1592 cm^{-1}: C=O amide keto stretching, 1096 cm^{-1} : C-C stretching, 755cm^{-1}: C-H aromatic out of plane bending vibration.

NMR VALUES
δ (ppm): 2.49 (s, 1H, ArCH), 3.28 (s, 1H, ArNH), 7.2-7.50 (s, 3H, Ar-H), 7.57-8.65 (m, 9H, Ar-H), 9.20(s, 1H, CONH)

Table 2. Antibacterial activity of the synthesized compounds

Compound	Conc. (µg)	Zone of inhibition(in millimeter)			
		Staphylococcus aureus	***Escherichia coli***	***Bacilus lintus***	***Salmonella typhi***
S1	100	11	23	8	7
S2	100	12	16	13	7
S3	100	10	14	12	9
S4	100	13	18	15	10
S5	100	9	10	8	14
S6	100	12	10	16	8
S7	100	20	26	20	16
S8	100	22	27	23	15
S9	100	13	13	10	15
S10	100	15	14	16	16
Ciprofloxacin	100	26	30	26	19

Table 3. Minimum Inhibitory Concentration (MIC) of the synthesized compounds

Escherichia coli								
Test tube No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Concentration(µg)	**100**	**50**	**25**	**12.5**	**6.25**	**3.125**	**1.5625**	**Controlled**
S1	-	-	-	-	+	+	+	+
S2	-	-	-	-	+	+	+	+
S3	-	-	-	-	+	+	+	+
S4	-	-	_	-	+	+	+	+
S5	-	-	-	-	+	+	+	+
S6	-	-	-	-	+	+	+	+
S7	-	-	-	-	-	-	+	+
S8	-	-	-	-	-	-	+	+
S9	-	-	-	-	-	+	+	+
S10	-	-	-	-	-	+	+	+

(-) Inhibition, (+) Growth

ANTIBACTERIAL ACTIVITY
The newly synthesized compound were screened for their *In-Vitro* antimicrobial activity against bacteria's such as *Staphylococcus aureus, Escherichia coli, Vibrio cholera, Klebsilla pneumonia, Pseudomonas aureginosa, Bacillus*

subtilis, Carynebacterium, St. albus, B. lintus, Salmonella typhi etc. whereas Antifungal activity was screened for fungus *Streptomyces griseus, Monoscus rubrum, Candida albicans* etc [16-18].

From the screening results in Gram positive bacterial strains compounds S4, S10showed good activity against *Staphylococcus aureus* and *Bacilus lintus,* whereas compounds S7, S8 showed very good activity in gram negative strains, the compounds S7, S8 showed very good activity against *Escherichia coli and Salmonella typhi.*

RESULTS AND DISCUSSION

The compounds were synthesized by various reaction intermediate such as:
1. Synthesis of 2-(4-chloro phenyl)– 4H-3, 1- Benzoxazin-4 one through
N-Benzoylation followed by dehydrative cyclisation mechanism.
2. Synthesis of 2-(4-chloro phenyl)-3-amino-4(3H)-Quinazoline.
3. Synthesis of 2-(4-chloro phenyl)-3-amino-4(3H)-Quinazoline urea.
4. Synthesis of 2-(4-chloro phenyl)-3-amino-4(3H)-Quinazoline semicarbazide.
5. Semicarbazones reactions of 2-(4-chloro phenyl)-3-amino-4(3H)-Quinazoline semicarbazide and aromatic aldehydes and ketones.

Newly synthesized compounds purity and its structural elucidation were done by various analytical techniques such as Melting point, Thin Layer Chromatography (TLC), Ultra Violet Spectroscopy (UV), Infrared Spectra (IR) and H^1 Nuclear magnetic resonance (H^1NMR).

Melting Point
A synthesized compounds melting point and its reactants melting point were recorded by open capillary tube method, which are uncorrected. A reactant and products melting point were differing from each other. It clearly indicates that the formation of a new chemical entities. The melting point values are given **in table 1.**

Thin Layer Chromatography
Thin layer chromatography techniques were performed for all synthesized compound as well as the parent compounds, all synthesized compounds gave a single spot whose R_f values are different from their reactants. It ultimately shows that the compound's purity and completion of the reaction. The R_f value are given in **table 3.**

Infra Red spectra
Infra Red spectroscopy was taken for all the synthesized compounds. The characteristic absorption peaks were observed for all relevant groups. Aromatic acid chlorides strongly absorb at 1800-1770cm^{-1} which was not observed in spectrum, it clearly gives a chemical entity in step I. The absorption peaks around 1600-1500cm^{-1} indicates that the formation of C=N Schiff bases. C=O stretching vibration around 1870 $cm^{-1}$was not appeared in spectrum. It shows that there was no impurities like aldehyde/ketone.,C-C, C=C & C=N ring stretching vibration at 1050-1200,754 cm^{-1} also appeared and aromatic amide N-H was observer at 3100-3500cm^{-1} and all other relevant groups absorption were observed for all the synthesized compounds.

H^1 Nuclear Magnetic Resonance
^{1}H nuclear magnetic spectra were taken for all the synthesized compounds. Aromatic protons were observed 6.68-8.13δ ppm, Amide N-H proton was observed at 6.05-6.40δ ppm, for all the synthesized compounds. It further established the structure of compounds.

Biological Evaluation:Antibacterial activity
The synthesized compounds were screened against various strains of micro organism by using Zone of inhibition technique and minimum inhibitory concentration [19-21]. Ciprofloxacin was used as a standard. Among the compounds tested all compounds were moderately active against tested micro organism. S7 and S8 were found to be most active against every organism. However none of them was superior than the standard. These results need to be refined in terms of active concentration and toxicity. Further studies needed to acquire more information about designing of structural activity relationship and their pharmacological activities.

CONCLUSION

From the results of antibacterial and antifungal activity, it can be concluded that the compounds bearing isatin, and furan rings are more potent than the remaining compounds. They showed comparatively good antibacterial as well as antifungal activity.

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