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Antimicrobial Study of Novel Triazoles Synthesized from Chalcones

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ABSTRACT

Heterocyclic compound such as quinazoline derivatives shows wide range of medicinal application in the area such as anticonvulsant, antitumor, antifungal, antimalaria, anti-hyperlipidemic and anti-inflammatory etc. activity because of these it shows great interest to study. In the presence study, we have synthesized triazole based quinazolinones by condensation reaction between α-methyl ketone and aromatic aldehydes under ethanol as the solvent to produced chalcones derivatives. This chalcone derivative have α,β-unsaturated part which is enhanced the reactivity of compound. Chalcone further reacted with 2-aminotriazole under alkali media in the presence of ethanol as the solvent to produced quinazolinone. This prepared compound has further possibility to modified at N atom upon reaction with halogen containing compound. Prepared quinazolinone were further treated with cyanuric chloride to increase heterocyclic part in the compound. Characterization of all synthesized product were done using spectroscopic techniques. All prepared compounds were screen for their biological evaluation against *gram+ve* and *gram-ve* bacteria.

Keywords: 2-Aminotriazole, Quinazolinone, Antimicrobial activity, Cyanuric chloride.

INTRODUCTION

Chalcone is the one of the well-known heterocyclic motif in the field of heterocyclic chemistry. Chalcone word originally came from the Greek latter “chalcones” which is called “bronze” is the term for the chalcone origination. Chalcones containing wide variety of compounds shows various medicinal application[1]. Chalcones is the example of the molecule with two types of double bond called α,β-unsaturated compounds with carbon oxygen and carbon carbon double bond are present. Here in the chalcones two double bond are in conjugation with respect to each other and in the reaction carbon carbon double bond gets easily break and provide reactivity at this site in the chalcones so number of heterocyclic compounds will be synthesized by this rout.

Chalcones are frequently found in many plants as the naturally occurring compounds and its provide separate class of the compounds. Various precursor for the synthesis of flavanones and Isoflavones are the chalcones which are very useful in the biosynthesis.

Two aromatic rings with carbonyl group containing compound 1,3-diphenyl-2propen-1-ones are crucial precursor in the flavonoid and isoflavanoid synthesis. Claisen Schmidt reaction of alpha methyl ketone and aldehyde under basic condition produces chalcones. Other methods are also available for the synthesis of chalcones. Chloroquine resistance and chloroquine sensitive compounds are exhibited antimalarial activity in the *in vitro* against various plasmodium[2]. Synthesis of chalcones using acetic acid and perchloric acid as the acidic condition has been reported by M. A. Shalaby *et al.,*[3]. Various chalcones were identified as the tyrosinases and new depigmenting agent which shows antioxidant and ant inhibitor activity[4].

Quinazoline and quinazolinone chemicals are also included in many pharmacological molecules and are utilized to prepare a variety of functional materials for synthetic chemistry. Quinazoline and quinazolinones shows divers antimicrobial activity provide study in the field as a good promising[5]. Based on the ring system's substitution patterns, quinozolinones will be categorized into five groups[6]. 2,3,2,4- disubstituted 4 (3H) quinazolinones, It consists of 2,4-disubstituted-4(3H)-quinazolinones, 4-substituted quiinazolines, 2,3-disubstituted-4(3H)-quinazolinones and 5-disubstituted-4(3H)-quinazolinones. These compounds can be categorized into three different groups[7] based on where the keto or oxo group is located. Out of the three quinazolinone structures 2-(1H)-quinazolinones, 4-(3H)-quinazolinones and 2,4 (1H, 3H)-diquinazolinones are very common as the intermediates in number of biosynthesis or as in the several natural products. Due to its numerous pharmacological actions, the quinazolinone nucleus has drawn considerable attention[8]. Many of them have therapeutic properties, including anticancer[9–11], anti-inflammatory[12–13], antimicrobial[14], antihypertensive[15], and antifungal effects. According to reports, different substituents at the quinazolinone nucleus' 2/3 position have a significant impact on pharmacological action[16].

In the presence research paper, we have synthesized novel Triazole based Quinazolinones C1–C12 from chalcones and 2-aminotriazole. Chalcones were synthesized from alpha methyl ketone and a variety of aromatic aldehydes. Characterization of all synthesized compounds were done using various spectroscopic techniques and all synthesized compounds were screened for their biological activity.

MATERIALS AND METHODS

Chemicals (Reagents)

Aldehydes, cyanuric chloride, 2-amino-triazole, sodium hydroxide and ethanol were purchased from the Merck, Mumbai, India and all are of reagent grade and used as obtained without doing further purification.

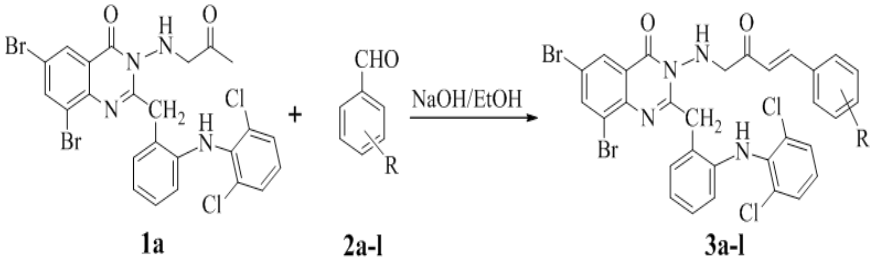
EXPERIMENTAL

^{1}HNMR spectra were recorded using instrument BRUKER AVANCE with 400MHz frequency and 100MHz frequency were used for ^{13}CNMR spectra. Parts per million (ppm) unit is used for the chemical shift value. FTIR-3000 Spectrophotometer of ABB Bomem Inc. was used for IR spectra. Shimadzu LCMS-2010 instrument is used for MASS spectrum analysis.

Synthesis of Quinazolinones

Synthesis of Compounds 3a-l

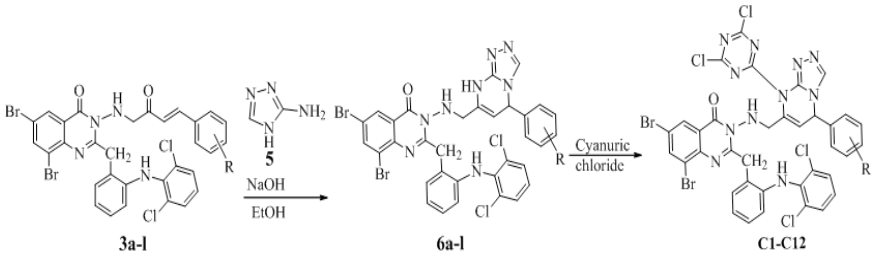
Take 5.79 g (0.01mol) of compound 1a having alpha methyl group in 500 mL round bottom flask, add 40 mL ethyl alcohol to it and stir it. Add 0.01mol aromatic aldehyde to it followed by addition of 0.01mol amount of 2% sodium hydroxide solution and reflux the entire mixture for 10-12 hours. After completion of reaction, cool the mixture and pour it in to ice water. Filter the product obtained and recrystallized it using ethanol (Scheme 1).



Scheme 1. Synthesis of chalcones from Aromatic aldehydes

Substituted triazole based Quinazolinones C1-C12 Synthesis

Take this prepared chalcone (6.67 g 0.02 mol) and 2-aminotriazole (1.0 g 0.02 mol) in ethanolic sodium hydroxide solution (25 mL), stirred the mixture. Reflux the entire mixture for 8-10 hours. The reaction mixture was refluxed for 8-10 hours. After completion of reaction, cool the mixture and pour it in to ice water. Filter the product obtained and recrystallized it using ethanol. The product obtained is substituted Triazole based quinazoline 4-one derivative. Further modification of this prepared compound is possible by react it with 0.01 mol of cyanuric chloride using 40 mL of 40% sodium hydroxide in 40 mL of ethanol for 30- to 40-minutes. TLC is used to confirm the reaction's completion. After the reaction was completed, the solution was cooled and put into crushed ice (Scheme 2).



Scheme 2. Synthesis of substituted Triazole based Quinazolinones C1-C2

Table 1.1: Data of synthesis of triazole based quinazolinones C1-C12

S. No	Code	R	% Yield[a]	Melting Point (°C)
1	C1	-H	82	212
2	C2	2-OH	77	242
3	C3	3-OH	78	255
4	C4	4- OH	79	232
5	C5	2-CL	76	228
6	C6	3-Cl	82	225
7	C7	4-Cl	84	240
8	C8	2-NO_2	84	221
9	C9	3-NO_2	84	247
10	C10	4-NO_2	83	214
11	C11	2-OCH_3	75	205
12	C12	4-OCH_3	74	226

[a]Isolated yield

RESULT AND DISCUSSION

Optimization of Reaction

A reaction between alpha methyl ketone **1a** and benzaldehyde **2a** in 40 mL ethanol using different concentration of sodium hydroxide to produced compound **3a** was taken as the model reaction. Data obtained are shown in the Table 1.2.

Table 1.2: Effect of different amount of NaOH on synthesis of chalcones

Entry	% of NaOH Sol	Moles of NaOH mL	Timea (Hours)	Yieldsb(%)
1	1	0.01	10	65
2	2	0.01	10	82
3	3	0.01	10	75
4	4	0.01	11	78
5	5	0.01	11	79

[a]Reaction was monitored by TLC, b Isolated yields.

It was found that best result was obtained by taking 2% 0.01 mol NaOH solutionamount with 82% yield of product in 10 hours. So, this amount was taken as optimum amount and a library of triazole based Quinazolinones C1-C12 were synthesized according Scheme 2.

Biological activity

Preparation of Media

Nutrient agar is used for measure of bacterial activity. These steps are used to create nutrient agar: 15 g Agar-Agar, 5 g Peptone, 3 g Metal Extract, 5 g NaCl To dissolve all the components, one liter of distilled water was mixed with peptone before being boiled. The medium was stabilized in an autoclave for 20 min at 125°C and 15 pound pressure. A sterilized Petri plate was filled with 20 cc of the medium after it had been cooled to 45°C. The medium's pH was changed to be in the range of 7.0 and 7.5. The aforesaid organism's culture was created in nutrient broth that had been dissolved in purified water. Nutritional broth contains the following:

(1) 10 g Beef extract, (2) 10 g Peptone and (3) 5 g Sodium chloride

Experimental results of biological activity

Table 1.3: Data of biological activity of synthesized compounds C1-C12

Compound code	*S. aureus gram+ve*	*B. megaterium gram+ve*	*E. coli gram-ve*	*P. vulgaris gram-ve*
C1	8	12	7	8
C2	6	8	9	6
C3	8	8	6	9
C4	10	7	10	5
C5	9	8	8	7
C6	6	4	7	6
C7	5	6	5	9
C8	8	10	9	11
C9	7	9	10	12
C10	9	5	8	9
C11	5	8	11	10
C12	11	9	6	10
Ampicillin	15	14	17	16
Gentamycin	16	15	14	16

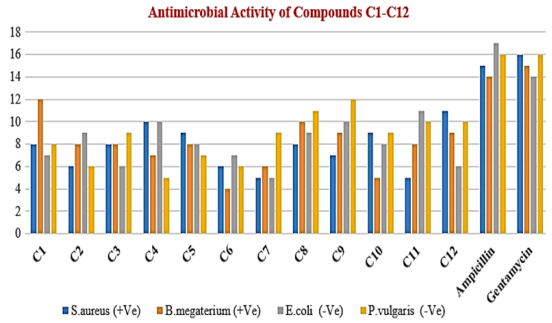


Fig. 1. Biological activity of synthesized compounds C1-C12

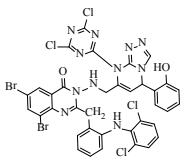
- Compound C12 shows maximum activities against gram positive *Staphylococcus aures* with 11.0mm zone of inhibition is very near to that of standard drugs while compounds C7 and C11 shows minimum activities against *Staphylococcus* as 5.0mm zone of inhibition.
- Compound C1 shows maximum activities against *Gram-positive Bacillus megaterium* with 12.0mm zone of inhibition while compound C6 shows minimum activities against same Bacterial Strains 4.0mm zone of inhibition.
- Compound C11 shows maximum activities against *Gram-negative Escherichia coli* with 11.0mm zone of inhibition while compound C7 shows minimum activities against same Bacterial Strains 4.0mm zone of inhibition.
- Compound C9 shows maximum activities against *Gram-negative* Proteus vulgaris with 12.0mm zone of inhibition while compound C4 shows minimum activities against same Bacterial Strains 5.0mm zone of inhibition.

Characterization

All the synthesized compounds were confirm using spectroscopic techniques such as ^{1}HNMR, ^{13}CNMR, IR and MASS. Here we have given the data of the two selected model compounds called C2 and C11 as below as the representative compounds of the series.

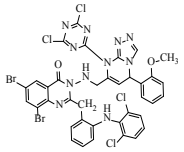
Compound-C2

Mol. Formula: $C_{36}H_{23}Br_2Cl_4N_{11}O_2$



Melting Point:	242°C
^{1}HNMR (400 MHz, $CDCl_3$) δ ppm:	
^{13}CNMR (100 MHz, $CDCl_3$)δ ppm:	33.0, 40.1, 45.0, 28.9, 129.2, 145.1, 142.3, 143.2, 145.0, 145.4, 146.1, 147.2, 147.3, 147.5, 147.9, 148.2, 148.4, 148.6, 160.2, 160.5, 175.2, 180.2.
IR cm^{-1} (KBr):	3402, 3332, 3310, 3010, 2950, 2850, 1680, 1675, 1610, 1615, 1534, 1530, 1410, 1218, 1032, 615.
Mass (M+1):	938.1
Elemental analysis:	Calculated (%) : C-45.84, H-2.46 and N-16.33 Found (%) : C-45.81, H-2.42 and N-16.24

Compound-C11

Mol. Formula: $C_{37}H_{25}Br_2Cl_4N_{11}O_2$	
Melting Point:	205°C
^{1}HNMR (400 MHz, $CDCl_3$) δ ppm:	2.4 (1H, s, NH), 3.2 (1H, s, NH), 3.5 (3H, -OCH3 group), 4.1 (2H, s), 4.2 (2H, s), 5.0 (1H, s), 6.0 – 8.4 (15 aromatic proton, complex).
^{13}CNMR (100 MHz, $CDCl_3$) δ ppm:	33.1, 40.2, 45.0, 46.2, 28.9, 129.3, 145.3, 142.3, 143.2, 145.0, 145.4, 146.1, 147.2, 147.2, 147.5, 147.9, 148.2, 148.4, 148.6, 160.2, 160.5, 174.2, 179.2.
IR cm^{-1} (KBr):	3331, 3315, 3005, 2952, 2850, 1675, 1675, 1610, 1615, 1534, 1530, 1410, 1218, 1210, 1032, 615.
Mass (M+1):	947.1
Elemental analysis:	Calculated (%): C-46.42, H-2.63 and N-16.09 Found (%) : C-46.45, H-2.68 and N-16.15

CONCLUSION

In conclusion the highly functionalized substituted triazole based quinazoline 4-one derivative C1-C12 were synthesized from substituted chalcone and 2-Aminotriazole followed by further reaction with Cyanuric Chloride using ethanol as the solvent. All synthesized compounds were screened for their biological activities against *Gram-positive* and *Gram-negative* bacterial strands. Most of compounds shows the satisfactory results in the biological activity.

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Conflict of interest

The authors declare no conflict of interest.

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