Arabian Journal of Chemistry (2015) 8, 474–479

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

# Synthesis, characterization and antimicrobial screening of substituted quiazolinones derivatives

**Priyanka G. Mandhane, Ratnadeep S. Joshi, Pravin S. Mahajan, Mukesh D. Nikam, Deepak R. Nagargoje, Charansingh H. Gill ***

*Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431 004, India*

Received 16 December 2010; accepted 21 January 2011
Available online 28 January 2011

**KEYWORDS**

Quinoline;
Quinazolinone;
Antimicrobial activity

**Abstract** A series of new quinazolinone derivatives have been synthesized. Elemental analysis, IR, $^1$H NMR and mass spectral data elucidated the structures of all newly synthesized compounds. In vitro antimicrobial activities of the synthesized compounds were investigated against Gram-positive *Bacillus subtilis* (ATCC No. 6633), *Staphylococcus aureus* (ATCC No. 25923), Gram-negative *Salmonella typhimurium* (ATCC No. 23564), *Pseudomonas aeruginosa* (ATCC No. 27853) and fungi *Candida albicans* and *Aspergillus niger*. Among all the tested compounds, some of the tested compounds showed equipotent activity with standard.



## 1. Introduction

Quinazolinone is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals and from microorganisms. Quinazolinone and its derivatives have also attracted a widespread interest due to the diverse biological activities associated with them. They are pharmaceutically important as antituberculars (Satsangi, 1979), thromboxane A2 synthetase inhibitors (Joshi and Chaudhari, 1987), antibacterial (Wright and Tomcufcik, 1987), antiparkinsons (Srivastava et al., 1987), antihelmintics (Gupta et al., 1988) and they also show blood platelet anti-aggregating activity (Sakai and Nahata, 1988). In the light of recent studies (Ma et al., 1997, 1999), it might be expected that a combination of quinolines moiety with such structures may increase their biological activities or create new medicinal properties. It is worthy to mention that the combination of this moiety, formulated a unique structure, which showed different biological activities, such as anti-tumor activity, cytotoxic toward the leukemia P388 cells, etc. Quinoline is frequently integrated into an organic compound in order to have enhanced or unexpected biological activities.

Literature survey reveals that quinolines are synthetic antibacterial drugs with potential activity against a wide spectrum of significant bacterial pathogens with resultant broad clinical activity. However, resistance to quinolines is a common phenomenon, so in order to meet this draw back synthesis of new quinoline derivatives is envisaged. Quinolines are present in a wide range of natural and unnatural compounds with remarkable medicinal activities (Balasubramanian et al.,

* Corresponding author. Tel.: +91 240 2403311; fax: +91 240 240049.
E-mail address: prof_gill@rediffmail.com (C.H. Gill).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2011.01.025

1996; Michael, 2007). In this regard, quinolines have occupied a unique position in the design and synthesis of novel biologically active compounds since they are often used as anti-inflammatory, antiasthmatic, antituberculosis, antibacterial, antihypertensive, antitumor and most notably, antimalarial agents (Maguire et al., 1994; Larsen et al., 1996; Kalluraya and Sreenivasa, 1998; Roma et al., 2000; Gabriele et al., 2007). Although quinolines are among the most extensively studied heterocyclic compounds, quinazolinone substituted quinolines are not often found in the literature. Therefore, the synthesis of quinazolinone derivatives directly linked to a quinoline unit is of considerable interest since their properly substituted analogues are biologically active and exist in the structures of various antitumor agents (Craig, 1972; Atwell et al., 1989).

General investigation also revealed that life threatening infections caused by pathogenic microbes are becoming increasingly common, especially in immuno-compromised individuals, such as persons undergoing cancer chemotherapy or AIDS patients. Antibacterial is a general term for drug, chemical or other substance that either kills or slows the growth of microbe. Bacteria is responsible for almost all of the common infectious diseases and the need for new antibacterial agents is greater than ever because of the emergence of multi drug resistance in common pathogens and the rapid emergence of new infections.

So, in the course of our research work to search a new potent and safe synthesis of biologically active heterocycles (Mandhane et al., 2010; Joshi et al., 2010; Jadhav et al., 2009; Diwakar et al., 2008), herein we report the ultrasound assisted synthesis of various derivatives of quinoline incorporated quinazolinones heterocycle and screen them for antimicrobial activities.

## 2. Experimental

### 2.1. Instruments

The melting points were determined on a Veego apparatus and are uncorrected. The reactions were monitored by TLC. The mass spectra were taken on a Macro mass spectrometer (Waters). The IR spectra were recorded in Nujol on Schimatzu 8000 spectrophotometer. $^1$H NMR spectra were recorded on a Bruker 400 MHz instrument in DMSO and TMS as an internal standard. Elemental analysis was performed on Perkin–Elmer EAL-240 elemental analyzers.

### 2.2. Procedure

#### 2.2.1. 2-Chloroquinoline-3-carbaldehyde (**1a**)

The compound **1a** was prepared as per procedure reported in Meth-Cohn et al. (1981). Yield 79%, m.p. 148 °C; IR-(KBr): 2739, 1710, 1605 and 755 cm$^{-1}$; $^1$H NMR-(DMSO-*d*6): $\delta$ 10.36 (s, 1H), 8.57 (s, 1H), 8.06 (d, 1H), 7.92 (m, 2H), 7.75 (dd, 1H); MS: *m*/*z* 192.3 ($M^+$); Elemental analysis: $C_{10}H_6ClNO$ Calcd.: C, 62.68; H, 3.16; N, 7.31; O, 8.35; found C, 62.74; H, 3.21; N, 7.20; O, 8.31.

#### 2.2.2. Synthesis of 2-(p-tolyloxy)quinoline-3-carbaldehyde (**2a**)

To a mixture of *p*-cresol (0.031 mmol, 3.38 g) and $K_2CO_3$ (0.068 mmol, 9.51 g) in DMF, compound **1a** (0.031 mmol, 6 g) was added and the reaction mixture was stirred at 85–90 °C for 5 h. The completion of the reaction was monitored by TLC. After completion, water (50 ml) was poured in the reaction mixture and the solid thus obtained was filtered off and recrystallized from ethyl acetate. Yield 80%, m.p. 128 °C; IR-(KBr): 2945, 2750, 1720, 1600 and 1225 cm$^{-1}$; $^1$H NMR-(DMSO-*d*6): $\delta$ 10.65 (s, 1H), 8.71 (s, 1H), 7.88 (d, 1H), 7.74 (d, 1H), 7.71 (m, 1H), 7.45 (m, 1H), 7.39 (d, 2H), 7.19 (d, 2H), 2.41 (s, 3H); MS: *m*/*z* 264.1 ($M^+$); Elemental analysis: $C_{17}H_{13}NO_2$ Calcd.: C, 77.55; H, 4.98; N, 5.32; O, 12.15; found C, 77.63; H, 5.01; N, 5.21; O, 12.09.

#### 2.2.3. Synthesis of (2-chloroquinolin-3-yl)methanol (**3a**)

To a mixture of compound **2a** in methanol, sodium borohydride was added portion wise, and the mixture was stirred at room temperature for 15–20 min. The completion of the reaction was monitored by TLC and reaction mass was concentrated under vacuum. The reaction mass was poured into ice cold water and solid thus obtained was filtered and recrystallized from ethyl acetate.

*2.2.3.1. (2-Chloroquinolin-3-yl)methanol (**3a**).* Yield 94%, m.p. 168 °C; IR-(KBr): 2945, 2750, 1600 and 1125 cm$^{-1}$; $^1$H NMR-(DMSO-*d*6): $\delta$ 8.21 (s, 1H), 8.18 (dd, 1H), 7.91 (m, 1H), 7.82 (dd, 1H), 7.51 (dd, 1H), 4.96 (s, 2H), 3.75 (s, 1H); MS: *m*/*z* 193.9 ($M^+$); Elemental analysis: $C_{10}H_8ClNO$ Calcd.: C, 62.03; H, 4.16; N, 7.23; O, 8.26; found C, 62.21; H, 4.19; N, 7.18; O, 8.21.

#### 2.2.4. 2-(p-Tolyloxy)quinolin-3ylmethanol (**3f**)

Yield 77%, m.p. 120 °C; IR-(KBr): 3427, 2920, 1520 and 1225 cm$^{-1}$; $^1$H NMR-(DMSO-*d*6): $\delta$ 8.05 (s, 1H), 7.62 (d, 1H), 7.48 (d, 2H), 7.41 (d, 1H), 7.25 (dd, 2H), 7.23 (d, 2H), 4.74 (s, 2H), 4.01 (s, 1H), 3.51 (s, 1H), 2.46 (s, 3H); MS: *m*/*z* 266.1 ($M^+$); Elemental analysis: $C_{17}H_{15}NO_2$ Calcd.: C, 76.96; H, 5.70; N, 5.28; O, 12.06; found C, 77.13; H, 5.75; N, 5.17; O, 12.01.

#### 2.2.5. Synthesis of 3-(bromomethyl)-2-chloroquinoline (**4a**)

Compound **3a** was dissolved in DCM at 5 °C, after 10–15 min of stirring calculated amount of $PBr_3$ was added drop wise and the mixture was stirred at room temperature for 1 h. The completion of the reaction was monitored by TLC. The DCM was removed under vacuum and the reaction mass was poured on ice cold water and the solution was neutralized by adding saturated solution of $NaHCO_3$. The solid thus obtained was filtered and recrystallized from ethyl acetate.

*2.2.5.1. 3-(Bromomethyl)-2-chloroquinoline (**4a**).* Yield 77%, m.p. 129 °C; IR-(KBr): 1670, 1630, 750 and 665 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.25 (s, 1H), 8.16 (dd, 1H), 7.68 (dd, 1H), 7.40 (m, 1H), 7.52 (m, 1H), 4.47 (s, 2H); MS: *m*/*z* 257.4 ($M^+$); Elemental analysis: $C_{10}H_7BrClN$: C, 46.82; H, 2.75; N, 5.46; found C, 46.93; H, 2.81; N, 5.34.

*2.2.5.2. 2-(p-Tolyloxy)-3-(bromomethyl)-6-methylquinoline (**4i**).* Yield 76%, m.p. 151 °C; IR-(KBr): 2930, 1624, 1560, 1150 and 675 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.05 (s, 1H), 7.61 (dd, 1H), 7.48 (s, 1H), 7.40 (dd, 1H), 7.23 (m, 2H), 7.16 (d, 2H), 4.74 (s, 2H), 2.46 (s, 3H), 2.38 (s, 3H); MS: *m*/*z* 343.1 ($M^+$); Elemental analysis: $C_{18}H_{16}BrNO$ Calcd.: C, 63.17; H,

4.71; N, 4.09; O, 4.68; found C, 63.31; H, 4.83; N, 3.96; O, 4.52.

*2.2.5.3. Quinazolin-4(3H)-one (**7**).* Yield, 93%, m.p. 215–216 °C; (Li et al., 2007). $^1$H NMR (DMSO-*d*6) $\delta$ 7.53 (t, 1H, $J$ = 7.25 Hz), 7.67 (d, 1H, $J$ = 8.15 Hz), 7.82 (m, 1H), 8.09–8.13 (m, 2H), 12.24 (s, 1H, NH); GC–MS $m/z$ 146 ($M^+$).

*2.2.6. Synthesis of 3-((2-chloroquinolin-3-yl)methyl)quinazolin-4(3H)-ones (**8a**)*

To a mixture of 7 (1 eq.) and $K_2CO_3$ (1.2 eq.) in DMF, 4a (1.2 eq.) was added and the reaction mixture was irradiated under ultrasound irradiation for 5–10 min. The completion of the reaction was monitored by TLC. After completion ice cold water was added to the reaction mass and the solid thus obtained was filtered off and recrystallized from ethyl acetate.

*2.2.6.1. 3-((2-Chloroquinolin-3-yl)methyl)quinazolin-4(3H)-one (**8a**).* Yield 80%, m.p. 169 °C; IR-(KBr): 1690, 1580, 1227 and 750 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.23 (s, 1H, Ar–H), 8.11 (dd, 1H, Ar–H), 7.97 (dd, 1H, Ar–H), 7.93 (dd, 1H, Ar–H), 7.88 (ddd, 1H, Ar–H), 7.71 (s, 1H, N–C*H*–N), 7.62 (ddd, 1H, Ar–H), 7.53 (ddd, 1H, Ar–H), 7.41 (dd, 2H, Ar–H), 4.46 (s, 2H, $CH_2$); MS: $m/z$ 322.3 ($M^+$); Elemental analysis: $C_{18}H_{12}ClN_3O$ Calcd.: C, 67.19; H, 3.76; N, 13.06; found: C, 67.11; H, 3.71; N, 13.11.

*2.2.6.2. 3-((2-Chloro-5-methylquinolin-3-yl)methyl)quinazolin-4(3H)-one (**8b**).* Yield 77%, m.p. 178 °C; IR-(KBr): 1675, 1567, 1215 and 743 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.27 (s, 1H, Ar–H), 8.10 (dd, 1H, Ar–H), 7.91 (dd, 1H, Ar–H), 7.73 (s, 1H, N–C*H*–N), 7.60 (dd, 1H, Ar–H), 7.51 (dd, 2H, Ar–H), 7.45 (dd, 1H, Ar–H), 7.39 (t, 1H, Ar–H), 4.53 (s, 2H, $CH_2$), 2.51 (s, 3H, $CH_3$); MS: $m/z$ 336.1 ($M^+$); Elemental analysis: $C_{19}H_{14}ClN_3O$ Calcd.: C, 67.96; H, 4.20; N, 12.51; found C, 67.91; H, 4.25; N, 12.46.

*2.2.6.3. 3-((2-Chloro-6-methylquinolin-3-yl)methyl)quinazolin-4(3H)-one (**8c**).* Yield 71%, m.p. 129 °C; IR-(KBr): 1683, 1561, 1231 and 731 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.29 (s, 1H, Ar–H), 8.11 (dd, 1H, Ar–H), 7.93 (s, 1H, Ar–H), 7.86 (d, 1H, Ar–H), 7.81(s, 1H, N–CH–N), 7.58 (dd, 2H, Ar–H), 7.31 (d, 1H, Ar–H), 4.57 (s, 2H, CH2), 2.46 (s, 3H, $CH_3$); MS: $m/z$ 336.3 ($M^+$); Elemental analysis: $C_{19}H_{14}ClN_3O$ Calcd.: C, 67.96; H, 4.20; N, 12.51; found C, 67.87; H, 4.29; N, 12.44.

*2.2.6.4. 3-((2-Chloro-7-methylquinolin-3-yl)methyl)quinazolin-4(3H)-one (**8d**).* Yield 80%, m.p. 182 °C; IR-(KBr): 1687, 1575, 1225 and 741 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.25 (s, 1H, Ar–H), 8.13 (d, 1H, Ar–H), 8.05 (dd, 1H, Ar–H), 7.92 (s, 1H, N–CH–N), 7.72 (ddd, 1H, Ar–H), 7.63 (s, 1H, Ar–H), 7.59 (d, 1H, Ar–H), 7.42 (dd, 2H, Ar–H), 4.51 (s, 2H, $CH_2$), 2.49 (s, 3H, $CH_3$); MS: $m/z$ 336.4 ($M^+$); Elemental analysis: $C_{19}H_{14}ClN_3O$ Calcd.: C, 67.96; H, 4.20; N, 12.51; found C, 67.90; H, 4.26; N, 12.53.

*2.2.6.5. 3-((2-Chloro-7-methoxyquinolin-3-yl)methyl)quinazolin-4(3H)-one (**8e**).* Yield 84%, m.p. 127 °C; IR-(KBr): 1696, 1577, 1231 and 731 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.13 (s, 1H, Ar–H), 8.07 (d, 1H, Ar–H), 7.94 (dd, 1H, Ar–H), 7.82 (s, 1H, N–CH–N), 7.71 (ddd, 1H, Ar–H), 7.53 (dd, 2H, Ar–H), 7.25 (d, 1H, Ar–H), 7.16 (s, 1H, Ar–H), 4.51 (s, 2H, $CH_2$), 4.03 (s, 3H, $OCH_3$); MS: $m/z$ 352.2 ($M^+$); Elemental analysis: $C_{19}H_{14}ClN_3O_2$ Calcd.: C, 64.87; H, 4.01; N, 11.94; found C, 64.81; H, 4.09; N, 11.90.

*2.2.6.6. 3-((2-(p-Tolyloxy)-quinolin-3-yl)methyl)quinazolin-4(3H)-one (**8f**).* Yield 79%, m.p. 171 °C; IR-(KBr): 1676, 1583, 1232 and 745 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.13 (dd, 1H, Ar–H), 8.07 (dd, 1H, Ar–H), 7.93 (s, 1H, Ar–H), 7.86 (dd, 1H, Ar–H), 7.81 (ddd, 1H, Ar–H), 7.72 (s, 1H, N-CH-N), 7.61 (ddd, 1H, Ar–H), 7.54 (dd, 2H, Ar–H), 7.43 (ddd, 1H, Ar–H), 7.21 (d, 2H, Ar–H), 7.01 (d, 2H, Ar–H), 4.50 (s, 2H, $CH_2$), 2.39 (s, 3H, $CH_3$); MS: $m/z$ 393.9 ($M^+$); Elemental analysis: $C_{25}H_{19}N_3O_2$ Calcd.: C, 76.32; H, 4.87; N, 10.68; found C, 76.21; H, 4.93; N, 10.71.

*2.2.6.7. 3-((2-(p-Tolyloxy)-5-methylquinolin-3-yl)methyl)quinazolin-4(3H)-one (**8g**).* Yield 76%, m.p. 175 °C; IR-(KBr): 1677, 1556, 1221 and 716 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.03 (dd, 1H, Ar–H), 7.89 (s, 1H, Ar–H), 7.70 (s, 1H, N-CH-N), 7.63 (ddd, 1H, Ar–H), 7.61 (dd, 1H, Ar–H), 7.53 (dd, 2H, Ar–H), 7.41 (dd, 1H, Ar–H), 7.25 (dd, 1H, Ar–H), 7.05 (d, 2H, Ar–H), 7.89 (d, 2H, Ar–H), 4.51 (s, 2H, CH2), 2.37 (s, 6H, $CH_3$); MS: $m/z$ 407.6 ($M^+$); Elemental analysis: $C_{26}H_{21}N_3O_2$ Calcd.: C, 76.64; H, 5.19; N, 10.31; found C, 76.51; H, 5.23; N, 10.39.

*2.2.6.8. 3-((2-(p-Tolyloxy)-6-methylquinolin-3-yl)methyl)quinazolin-4(3H)-one (**8h**).* Yield 75%, m.p. 125 °C; IR-(KBr): 1669, 1545, 1216 and 746 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.04 (dd, 1H, Ar–H), 7.94 (s, 1H, Ar–H), 7.89 (s, 1H, Ar–H), 7.81 (dd, 1H, Ar–H), 7.79 (s, 1H, N-CH-N), 7.57 (ddd, 1H, Ar–H), 7.61, 7.45 (dd, 2H, Ar–H), 7.23 (d, 1H, Ar–H), 6.98 (d, 2H, Ar–H), 6.71 (d, 2H, Ar–H), 4.49 (s, 2H, $CH_2$), 2.43 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$); MS: $m/z$ 407.9 ($M^+$); Elemental analysis: $C_{26}H_{21}N_3O_2$ Calcd.: C, 76.64; H, 5.19; N, 10.31; found C, 76.53; H, 5.21; N, 10.43.

*2.2.6.9. 3-((2-(p-Tolyloxy)-7-methylquinolin-3-yl)methyl)quinazolin-4(3H)-one (**8i**).* Yield 82%, m.p. 188 °C;IR-(KBr): 1688, 1584, 1234 and 746 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.16 (dd, 1H, Ar–H), 8.04 (d, 1H, Ar–H), 7.93 (s, 1H, Ar–H), 7.84 (s, 1H, N–CH–N), 7.71 (ddd, 1H, Ar–H), 7.62 (d, 1H, Ar–H), 7.51 (s, 1H, Ar–H), 7.46 (dd, 2H, Ar–H), 6.91 (d, 2H, Ar–H), 6.75 (d, 2H, Ar–H), 4.51 (s, 2H, $CH_2$), 2.41 (s, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$); MS: $m/z$ 408.1 ($M^+$); Elemental analysis: $C_{26}H_{21}N_3O_2$ Calcd.: C, 76.64; H, 5.19; N, 10.31; found C, 76.50; H, 5.27; N, 10.33.

*2.2.6.10. 3-((2-(p-Tolyloxy)-7-methoxyquinolin-3-yl)methyl)-quinazolin-4(3H)-one (**8j**).* Yield 84%, m.p. 185 °C; IR-(KBr): 1691, 1583, 1231 and 746 cm$^{-1}$; $^1$H NMR-($CDCl_3$): $\delta$ 8.06 (dd, 1H, Ar–H), 7.94 (d, 1H, Ar–H), 7.76 (s, 1H, Ar–H), 7.74 (s, 1H, N–CH–N), 7.61 (ddd, 1H, Ar–H), 7.54 (dd, 2H, Ar–H), 7.35 (d, 1H, Ar–H), 7.23 (d, 2H, Ar–H), 7.03 (s, 1H, Ar–H), 6.75 (d, 2H, Ar–H), 4.52 (s, 2H, $CH_2$), 3.91 (s, 3H, $OCH_3$), 2.37 (s, 3H, $CH_3$); MS: $m/z$ 423.8 ($M^+$); Elemental analysis: $C_{26}H_{21}N_3O_3$ Calcd.: C, 73.74; H, 5.00; N, 9.92; found C, 73.61; H, 5.07; N, 10.01.

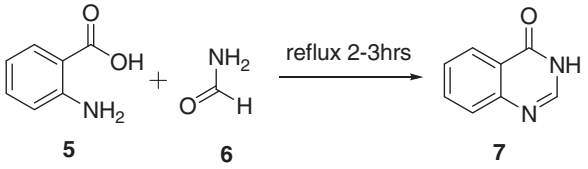
## 3. Results and discussion

In the present work, a series of quinazolinone derivatives were synthesized via 3-(bromomethyl)-2-chloroquinoline or 2-(*p*-tolyloxy)-(bromomethyl)quinoline **4a–j** which has been synthesized by reduction of 2-chloroquinoline-3-carbaldehyde or 2-(*p*-tolyloxy)quinoline-3-carbaldehyde **2a–j** in the presence of the catalytic amount of $NaBH_4$ and methanol yielding (2-chloroquinolin-3yl)methanol or (2-(*p*-tolyloxy)quinolin-3yl)methanol **3a–j**. In the IR spectrum of compound **3a**, a band in the range of 2945 was obtained due to –OH stretching, as expected for the formation of **3a–j**. In the $^1$H NMR spectrum, the signal was found at $\delta$ 3.71 (singlet), which showed the presence of –OH group. Compound **3a–j**, on treatment with $PBr_3$ in the presence of DCM under ice cold condition, afforded **4a–j**. In the IR spectrum of **4a**, a band in the range of 665 was obtained due to C–Br stretching, as expected for the formation of **4a**. In the $^1$H NMR spectrum, the signal was found at $\delta$ 4.47 (singlet), which showed the presence of $CH_2$–Br group (Scheme 1).

Secondly quinazolin-4(3*H*)-one 7 has been synthesized by Nimentowiski reaction of Anthranilic 5 acid and Formamide 6 under the reflux temperature for 1 h. The structure of the product was elucidated further on the basis of CONH group in the compound, which caused a peak at 1620 $cm^{-1}$. In the $^1$H NMR spectrum, the characteristic proton of the CONH group was observed at $\delta$ 8.21 as a singlet (Scheme 2).

Finally 3-((2-chloroquinolin-3-yl)methyl)quinazolin-4(3*H*)-one and 3-((2-(*p*-tolyloxy)quinolin-3-yl)methyl)quinazolin-4(3*H*)-one **8a–j** were synthesized by reacting quinazolin-4(3*H*)-one 7 with various substituted 3-(bromomethyl)-2-chloroquinoline or 2-(*p*-tolyloxy)-(bromomethyl)quinoline **4a–j** in the presence of $K_2CO_3$ in DMF under ultrasound irradiation for 10–15 min. Formation of the compound was confirmed by $^1$H NMR spectrum, the characteristic proton of the N–Ch2 group was observed at $\delta$ 4.46 as a singlet (Scheme 3).

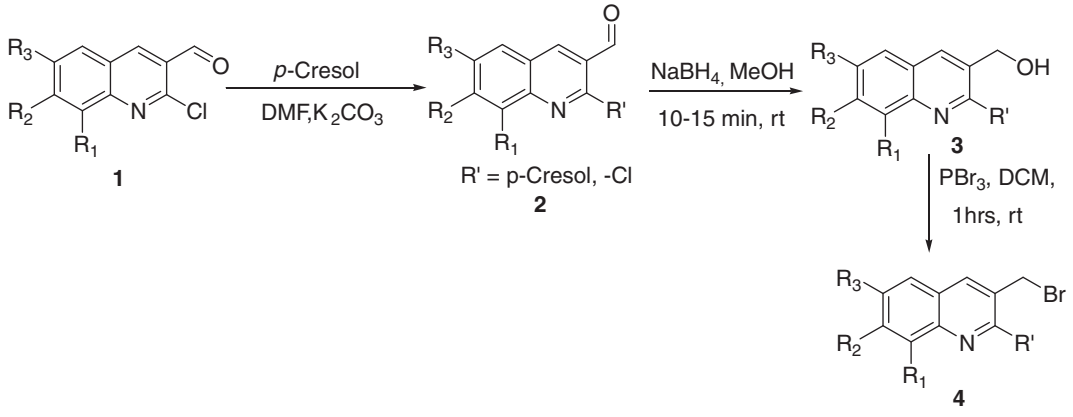
The synthesized compounds **8a–j** was screened "*in vitro*" for antimicrobial activity. From the data presented in Tables 1 and 2, it is clear that compound **8b** and **8g** are highly active against *Bacillus subtilis* (ATCC No. 6633), *Staphylococcus aureus* (ATCC No. 25923), *Salmonella typhimurium* (ATCC No, 23564), *Pseudomonas aeruginosa* (ATCC No. 27853) as compared to the standard (streptomycin and amphiciline). Other compounds exhibit moderate to good antibacterial activity against all organisms. Similarly, **8b** and **8g** exhibit good antifungal activity against *Candida albicans* and *Aspergillus fumigatus* as compared to the standard drug used (fluconazole). The remaining compounds are moderately active against these two micro-organisms (*C. albicans* and *A. fumigatus*). It can be concluded that the antimicrobial activity of such compounds may change by the introduction or elimination of a specific group.



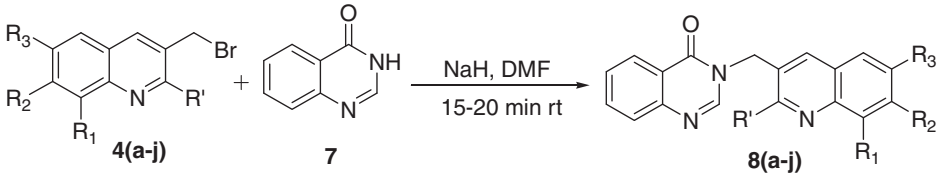

**Scheme 2**

### 3.1. In vitro antimicrobial screening

The antibacterial activities of the synthesized compounds **8a–j** were determined by the well-diffusion method (Ansari et al., 2005). In this work, two Gram positive bacterial isolates, *B. subtilis* (ATCC No. 6633), *S. aureus* (ATCC No. 25923), and two Gram negative bacteria, *S. typhimurium* (ATCC No. 23564), *P. aeruginosa* (ATCC No. 27853) were used to investigate the antibacterial activities. The antifungal activity was screened against Candida albicans and Aspergillus fumigates using Sabouraded dextrose agar medium. The bacterial liquid cultures were prepared in infusion broth for their activity tests. The compounds were dissolved in DMSO at concentration of 1 mg/ml. Antibacterial and antifungal activities of DMSO against the test organisms were investigated, and were found to be nil. Molten nutrient agar and Sabouraded dextrose agar (15 $cm^3$), kept at 45 °C, were then poured into the Petri dishes and allowed to solidify. Ten millimeter diameter holes were then punched carefully using a sterile cork borer and completely filled with the test solutions. The plates were incubated at 37 °C for 24 and 48 h for antibacterial and antifungal activities, respectively. The inhibition zone that appeared around the holes in each plate was measured. Activity was determined by measuring the diameter of the inhibition zone and also the minimal inhibitory concentration. Antibacterial activity of each compound was compared with streptomycin and amphiciline (300 mg/ml) as standards, whereas fluconazole (300 mg/ml) was used in antifungal activity study. The observed zone of inhibition for antibacterial and antifungal activities is presented in Tables 1 and 2, respectively.




**Scheme 1**




**Scheme 3**

**Table 1** Antibacterial activity of tested compounds **8a–j**.

| Tested compounds | *B. subtilis* ZI[a] (MIC)[b] | *S. aureus* ZI[a] (MIC)[b] | *S. typhi* ZI[a] (MIC)[b] | *P. aeroginosa* ZI[a] (MIC)[b] |
|---|---|---|---|---|
| **8a** | 13.2 (15) | 13.5 (15) | 14.8 (10) | 14.5 (10) |
| **8b** | 14.8 (10) | 13.4 (10) | 16.7 (05) | 16.4 (05) |
| **8c** | 14.3 (10) | 14.1 (10) | 12.8 (15) | 12.7 (15) |
| **8d** | 15.1 (10) | 14.7 (10) | 13.5 (15) | 13.4 (15) |
| **8e** | 14.8 (10) | 14.6 (10) | 12.9 (15) | 12.8 (15) |
| **8f** | 13.1 (15) | 13.6 (15) | 14.2 (10) | 14.0 (10) |
| **8g** | 15.4 (10) | 15.7 (10) | 16.5 (05) | 16.3 (05) |
| **8h** | 13.1 (15) | 13.2 (15) | 11.1 (20) | 10.4 (20) |
| **8i** | 14.1 (10) | 14.6 (10) | 12.2 (15) | 12.5 (15) |
| **8j** | 15.6 (10) | 15.3 (10) | 11.7 (15) | 11.2 (15) |
| Streptomycin | 15.1 (10) | 14.9 (10) | 16.4 (05) | 16.1 (05) |
| Ampicilline | 14.3 (10) | 14.7 (10) | 16.3 (05) | 15.9 (05) |

[a] Zone of inhibition.
[b] Minimum inhibitory concentration.

**Table 2** Antifungal activity of compounds **8a–j**.

| Tested compounds | *C. albicans* ZI[a] (MIC)[b] | *S. fumigatus* ZI [a](MIC)[b] |
|---|---|---|
| **8a** | 13.6 (10) | 12.1 (15) |
| **8b** | 16.2 (05) | 16.6 (05) |
| **8c** | 13.8 (10) | 13.2 (15) |
| **8d** | 13.0 (10) | 13.1 (15) |
| **8e** | 14.1 (10) | 12.2 (15) |
| **8f** | 13.4 (10) | 14.4 (10) |
| **8g** | 16.8 (05) | 16.5 (05) |
| **8h** | 13.8 (10) | 12.8 (15) |
| **8i** | 13.4 (10) | 14.2 (10) |
| **8j** | 14.2 (10) | 13.4 (20) |
| Fluconazole | 16.4 (05) | 16.5 (05) |

[a] Zone of inhibition,
[b] Minimum inhibitory concentration.

## Acknowledgments

The authors are thankful to Dr. Babasaheb Ambedkar Marathwada University, Aurangabad for financial support and The Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431004 (MS), India for his valuable guidance and laboratory facility.

## References

Ansari, F.L., Nazir, S., Noureen, H., Mirza, B., 2005. Chem. Biodiv. 2, 1656.
Atwell, G.J., Baguley, B.C., Denny, W.A., 1989. J. Med. Chem. 32, 396.
Balasubramanian, M., Keay, J.G., Katritzky, A.R., Rees, C.W., Scriven, E.F.V. (Eds.), 1996. Comprehensive Heterocyclic Chemistry II, vol. 5. Pergamon Press, Oxford, New York, p. 245.
Craig, P.N., 1972. J. Med. Chem. 15, 144.
Diwakar, S.D., Bhagwat, S.S., Shingare, M.S., Gill, C.H., 2008. Bioorg. Med. Chem. Lett. 18, 4678.
Gabriele, B., Mancuso, R., Salerno, G., Ruffolo, G., Plastina, P., 2007. J. Org. Chem. 72, 6873.
Gupta, D.P., Ahmad, S., Kumar, A., Shanker, K., 1988. Indian J. Chem. 27 (B), 1060.
Jadhav, G.R., Shaikh, M.U., Kale, R.P., Shiradkar, M., Gill, C.H., 2009. Eur. J. Med. Chem. 44 (9), 2930.
Joshi, R.S., Mandhane, P.G., Diwakar, S.D., Gill, C.H., 2010. Ultrason. Sonochem. 17, 298.
Joshi, V., Chaudhari, R.P., 1987. Indian J. Chem. 26 (B), 602.
Kalluraya, B., Sreenivasa, S., 1998. Farmaco 53, 399.
Larsen, R.D., Corley, E.G., King, A.O., Carroll, J.D., Davis, P., Verhoeven, T.R., Reider, P.J., Labelle, M., Gauthier, J.Y., Xiang, Y.B., Zamboni, R.J., 1996. J.Org.Chem. 61, 3398.
Li, F., Feng, Y., Meng, Q., Li, W., Li, Z., Wang, Q., Tao, F., 2007, Arkivoc (i) 40.
Ma, Z.Z., Hano, Y., Nomura, T., Chen, Y.J., 1997. Heterocycles 46, 541.
Ma, Z.Z., Hano, Y., Nomura, T., Chen, Y.J., 1999. Heterocycles 51, 1883.
Maguire, M.P., Sheets, K.R., McVety, K., Spada, A.P., Zilberstein, A., 1994. J. Med. Chem. 37, 2129.
Mandhane, P.G., Joshi, R.S., Nagargoje, D.R., Gill, C.H., 2010. Tet. Lett. 51, 1490.
Meth-Cohn, O., Narine, B., Tarnowski, B., 1981. J. Chem. Soc. Perkin Trans. I 67, 1537.
Michael, J.P., 2007. Nat. Prod. Rep. 24, 223.

Roma, G., Braccio, M.D., Grossi, G., Mattioli, F., Ghia, M., 2000. Eur. J. Med. Chem. 35, 1021.
Sakai, K., Nahata, H., 1988. Jpn. Kokai Tokkyo Koho JP 63,51,329, Chem. Abstr. 109, 86338.
Satsangi, R.K., 1979. Indian Drugs 17, 79.
Srivastava, V.K., Gulati, S.S., Shanker, K., 1987. Indian J. Chem. 26B, 652.
Wright Jr., W.B., Tomcufcik, A.S., 1987. US 4,684,654, Chem. Abstr. 107, 198354.