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

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

Synthesis, characterization and antimicrobial screening of substituted quiazolinones derivatives

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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.,

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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): δ 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): δ 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): δ 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): δ 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-($CDCl_3$): δ 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-($CDCl_3$): δ 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,