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RESEARCH ARTICLE

Microwave induced synthesis of thieno[2,3-*b*]quinoline-2-carboxylic acids and alkyl esters and their antibacterial activity

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A series of thieno[2,3-*b*]quinoline-2-carboxylic acids and alkyl esters, (**3a–i**) have been synthesized by the condensation of 2-chloro-3-formyl quinolines (**1a–c**) with thioglycolic acid/alkyl esters under microwave irradiation using anhydrous potassium carbonate. These compounds were characterized by elemental analysis, IR, ^{1}H NMR, and mass spectral studies. Their antibacterial activity was also evaluated.

Keywords: Microwave irradiation; Thienoquinolines; Thioglycolic acid; Alkyl derivatives

1. Introduction

Five- and six-membered heterocyclic compounds containing one or two heteroatoms fused to quinoline ring in linear fashion are found in natural products as well as in the synthetic compounds of biological interest [1]. They are known to exhibit antiallergenic properties [2], antifungal activity [3], hypocholesterolemic, hypolemic [4], antibacterial [5] and antiviral activity [6]. On the other hand, thienoquinolines and benzothienoquinoline exhibit antitumor, antimicrobial, hypocholesterolemic, hypolemic antifungal and antiviral activities [7–10].

Development of microwave techniques have helped immensely in developing newer, synthetic protocols toward an eco-friendly mode. So a number of research papers have appeared proving the synthetic utility of Microwave-induced Organic Reaction Enhancement (MORE) chemistry in routine organic synthesis [11–14].

In continuation of our quest for the synthesis of hitherto undescribed quinoline derivatives [15, 16], herein we wish to report microwave assisted novel synthesis of thieno[2,3-*b*]quinoline-2-carboxylic acids and alkyl esters and their antibacterial activity were also evaluated.

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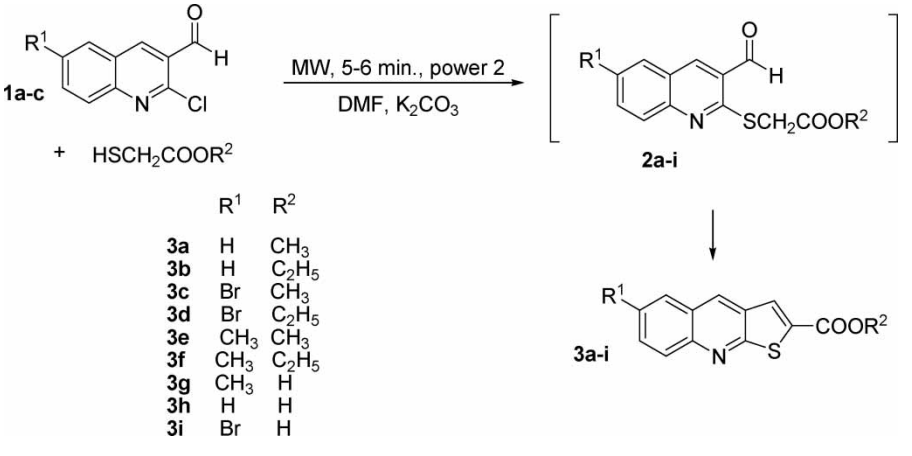
2. Results and discussion

The starting compounds 2-chloro-3-formyl quinolines, (**1a–c**), prepared according to literature method [17], were cyclised with thioglycolic acid/esters under microwave irradiation in one pot to furnish the title compounds (**3a–i**) in good yields (scheme 1). The structure of the compounds were confirmed on the basis of elemental analysis and spectral data (which are presented in the Experimental section). The IR (KBr) spectra of **3b–f** exhibit an absorption band in the region 1680–1700 cm^{-1} due to ester carbonyls and the ^1H NMR (DMSO-d6) spectrum of the compound (**3b**) displayed a triplet at δ 1.39 (3H) and a quartet at 4.38 (CH_2) characteristic of an ethyl group. Its mass spectrum showed the molecular ion peak at 257.

The reaction was known [18, 19] to proceed through the intermediate (**2a–i**), which was formed by the replacing chlorine at C-2 of (**1a–c**) by the alkyl thioglycolates. The carbanion results in the intermediate by base, adds on the aldehyde carbon with simultaneous elimination of water resulting in the formation of (**3a–i**) with good yields. We synthesized nine more title compounds, which exhibited similar spectral characteristics. The IR spectra of all the compounds exhibit C=O stretching frequency in the region 1680–1700 cm^{-1}. In the ^1H NMR thiophene C_3-H proton showed a signal at δ 8.20–8.35, may be due to hydrogen bonding and anisotropy effect of the adjacent carbonyl groups other aromatic protons resonated at δ 7.06–7.81 (4H).

3. Biological screening

The antimicrobial activity of the newly synthesized compounds was screened *in vitro* for Euro strains of bacteria *Staphylococcus aureus* and *Escherichia coli* using Cup plate method [20]. The antimicrobial activity was carried out against 24 hr old cultures of two bacteria. The compounds were tested at a concentration (0.001 mol/ml) in dimethylformamide against both organisms. Ciprofloxacine (0.001 mol/ml) was used as standard for comparison of antimicrobial activities. The plates were inoculated with a 24 hr old culture of bacteria. The zone of inhibition was compared with the standard drug after 24 hrs of inoculation at 37 °C for antimicrobial activity. The results are presented in table 1. The results reveal that the compounds



SCHEME 1 General synthetic procedure of thieno[2,3-*b*]quinoline-2-carboxylic acids alkyl esters **3a–i**.

Table 1. Biological screening of thieno[2,3-*b*] quinoline-2-carboxylic acids alkyl esters (**3a–i**).

Compound	Amount in grams (0.001 mol/ml)	*Staphylococcus aureus*	*Escherichia coli*
3a	0.243	+	+
3b	0.257	++	++
3c	0.322	+++	+++
3d	0.336	+++	+++
3e	0.257	++	++
3f	0.257	++	++
3g	0.243	++	+
3h	0.229	+	+
3i	0.308	+++	+++

+: (0.2–0.5 cm) less active, ++: (0.6–1.4 cm) moderately active +++: (1.5–3 cm) highly active. Standard: Ciprofloxacin (250 gml^{-1})

3c, 3d and **3i** show more activity with respect to *Staphylococcus aureus* and *Escherichia coli* compared to the other compounds. This may be due to the presence of halogens in their structure [21]. While compound **3c** and **3h** exhibited less bacterial activities with respect to *Escherichia coli* and *Staphylococcus aureus*. Most of the synthesized compounds showed moderate antimicrobial activity against the tested organisms.

4. Experimental

The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using petroleum ether:ethyl acetate solvent. Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer 157 IR Spectrophometer. ^{1}H NMR spectra were recorded in DMSO-d6 on EM-390 (300 MHz) NMR spectrometer and mass spectra were recorded on MASPEC low resolution instrument operating at 70 eV.

4.1 *General procedure for the synthesis of substituted thieno[2,3-*b*]quinolines (3a–f)*

To a mixture of suitable substituted quinolines **3a** 0.764 g (0.004 mol) and anhydrous (thioglycolic ester) 0.530 g (0.005 mol), anhydrous potassium carbonate 1.756 g (0.012 mol) and anhydrous dimethylformamide (10 ml) were added and the contents were irradiated in a microwave oven for about 6 mins at an interval of 1 min at 160 Watt. The completion of reaction was monitored by TLC, the product **3a** was poured into ice-cold water, stirred well, filtered, dried and recrystallised from ethanol:dioxane (6:4) mixture. The physicochemical data for the synthesized compounds are as shown below. The same procedure was used for the synthesis of other compounds (**3b–f**).

4.2 *Methyl thieno[2,3-*b*]quinoline-2-carboxylate (3a)*

Solid, mp. 240–243 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 3.91 (s, 3H, $-O-CH_3$), 7.05–8.07 (m, 5, Ar−H), 8.22 (s, 1H, H-3); IR (KBr) ν (cm^{-1}): 1690 (C=O). MS, m/z (relative intensity) 243 (65), 212 (100), 184 (70). Calcd (%) for $C_{13}H_9NSO_2$: C; 64.19, H; 3.70, N; 5.76, S; 13.16. Found: C; 64.18, H; 3.72, N; 5.79, S; 13.20.

4.3 *Ethyl thieno[2,3-*b*]quinoline-2-carboxylate (3b)*

Solid, mp. 203–205 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.38 (t, 3H, J = 7.0 Hz, $-CH_3$), 4.37 (q, 2H, J = 7.0 Hz, $-OCH_2$), 7.06–8.07 (m, 5H, Ar−H), 8.24 (s, 1H, H-3); IR (KBr) ν (cm^{-1}): 1685 (C=O). MS, m/z (relative intensity) 257 (60), 212 (100), 184 (69). Calcd (%) for $C_{14}H_{11}NSO_2$: C; 65.36, H; 4.28, N; 5.44, S; 12.45. Found: C; 65.28, H; 4.24, N; 5.42, S; 12.43.

4.4 *Methyl 6-bromothieno[2,3-*b*]quinoline-2-carboxylate (3c)*

Solid, mp. 230–233 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 3.90 (s, 3H, OCH_3), 7.03–8.02 (m, 4H, Ar−H), 8.23 (s, 1H, H-3); IR (KBr) ν (cm^{-1}): 1694 (C=O). MS, m/z (relative intensity) 322 (64), 291 (100), 263 (70). Calcd (%) for $C_{13}H_8NSO_2Br$: C; 45.34, H; 2.48, N; 4.34, S; 9.93. Found: C; 45.31, H; 2.44, N; 4.30, S; 9.92.

4.5 *Ethyl 6-bromothieno[2,3-*b*]quinoline-2-carboxylate (3d)*

Solid, mp. 247–250 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.37 (t, 3H, J = 7.0 Hz, $-CH_3$), 4.38 (q, 2H, J = 7.0 Hz, $-OCH_2$), 7.06–8.07 (m, 4H, Ar−H), 8.23 (s, 1H, H-3); IR (KBr) ν (cm^{-1}): 1680 (C=O). MS, m/z (relative intensity) 336 (61), 291 (100), 263 (70). Calcd (%) for $C_{14}H_{10}NSO_2Br$: C; 50.00, H; 2.97, N; 4.16, S; 9.52. Found: C; 50.04, H; 2.95, N; 4.13, S; 9.56.

4.6 *Methyl 6-methylthieno[2,3-*b*]quinoline-2-carboxylate (3e)*

Solid, mp. 246–249 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 2.09 (s, 3H, $-OCH_3$), 7.08–8.09 (m, 4H, Ar-H), 8.23 (s, 1H, H-3),; IR (KBr) ν (cm^{-1}): 1695 (C=O). MS, m/z (relative intensity) 257 (64), 226 (100), 198(71). Calcd (%) for $C_{14}H_{11}NSO_2$: C; 61.80, H; 4.72, N; 6.08, S; 13.73. Found: C; 61.84, H; 4.70, N; 6.10, S; 13.77.

4.7 *Ethyl 6-methylthieno[2,3-*b*]quinoline-2-carboxylate (3f)*

Solid, mp. 232–235 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 1.38 (t, 3H, J = 7.0 Hz, $-CH_3$), 2.11 (s, 3H, $-CH_3$), 4.37 (q, 2H, J = 7.0 Hz, $-OCH_2$), 7.16–8.14 (m, 4H, Ar−H), 8.23 (s, 3H, H-3); IR (KBr) ν (cm^{-1}): 1695 (C=O). MS, m/z (relative intensity) 257 (62), 212 (100), 184 (69). Calcd (%) for $C_{15}H_{13}NSO_2$: C; 72.87, H; 5.26, N; 5.66, S; 12.95. Found: C; 72.85, H; 5.24, N; 5.63, S; 12.93.

4.8 *General procedure for the synthesis of substituted thieno[2,3-*b*]quinoline (3g–i)*

To a mixture of suitable substituted quinoline **3a** 0.764 g (0.004 mol), anhydrous thioglycolic acid 0.552 g (0.006 mol), anhydrous potassium carbonate 1.756 g (0.012 mol) and anhydrous dimethylformamide (10 ml) were added and the contents were irradiated in a microwave oven for about 6 mins at an interval of 1 min at 160 Watt. The completion of reaction was monitored by TLC, the product was poured onto ice-cold water, stirred well, with dilute HCl, the resultant suspension was filtered, the solid that separated out was filtered, washed with water and dried. The compound was purified by dissolving in aqueous K_2CO_3 and reprecipitating with dilute HCl solution.

4.9 *6-methylthieno[2,3-*b*]quinoline-2-carboxylic acid (3g)*

Solid, mp. 225–228 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 7.17–8.09 (m, 4H, Ar−H), 8.23 (s, 3H, H-3) 10.21 (s, H, −COOH); IR (KBr) ν (cm^{-1}): 1690 (C=O). MS, m/z (relative intensity) 243 (85), 226 (100), 198 (70). Calcd (%) for $C_{13}H_9NSO_2$: C; 64.19, H; 3.70, N; 5.76, S; 13.16. Found: C; 64.15, H; 3.67, N; 5.72, S; 13.20.

4.10 *Thieno[2,3-*b*]quinoline-2-carboxylic acid (3h)*

Solid, mp. 236–238 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 7.17–8.13 (m, 5H, Ar−H), 8.23 (s, 3H, H-3) 10.21 (s, H, −COOH); IR (KBr) ν (cm^{-1}): 1695 (C=O). MS, m/z (relative intensity) 229 (84), 212 (100), 184 (70). Calcd (%) for $C_{12}H_7NSO_2$: C; 62.88, H; 3.05, N; 6.11, S; 13.97. Found: C; 62.90, H; 3.09, N; 6.13, S; 14.07.

4.11 *6-bromothieno[2,3-*b*]quinoline-2-carboxylic acid (3i)*

Solid, mp. 225–228 °C; ^{1}H NMR (300 MHz, DMSO-d6) δ (ppm): 7.18–8.12 (m, 4H, Ar−H), 8.23 (s, 3H, H-3) 10.21 (s, H, −COOH); IR (KBr) ν (cm^{-1}): 1700 (C=O). MS, m/z (relative intensity) 308 (84), 291(100), 263 (70). Calcd (%) for $C_{12}H_6NSO_2Br$: C; 46.75, H; 1.94, N; 4.54, S; 10.38. Found: C; 46.77, H; 1.92, N; 4.58, S; 10.42.

References

[1] H. Thomys. *Ber. Deut. Pharm. Ges.*, **33**, 68 (1923).
[2] T.H. Althuis, S.B. Khadin, L.J. Czuba, P.F. Moore, H.J. Hess. *J. Med. Chem.*, **23**, 262 (1980).
[3] J.B. Jiang, D. Isaacson. US Patent 4656274 (1987); *Chem. Abstr.*, **107**, 39643 (1987).
[4] R.E. Graeve, J.R. Pociask, R.G. Stein. US Patent 3600393 (1971).
[5] A.M. Farghaly, N.S. Habib, M.A. Khalil, O.A. El-Sayed, A. Alaxandria. *J. Pharm. Sci.*, **3**, 90 (1989); *Chem. Abstr.*, **112**, 7420 (1990).
[6] V. Zikan, S. Radl, F. Smejkal, D. Zelena. Czech. Patent 233445 (1986); *Chem. Abstr.*, **106**, 138447 (1987).
[7] P. Siminoff, A.M. Bernard, V.S. Hursky, K.E. Price. *Antimicrob. Agents. Chemothev.*, **3**, 742 (1973).
[8] S.V. Nielsen, E.B. Pedersen. *Chem. Sci.*, **26**, 331 (1986); *Chem. Abstr.*, **106**, 102151 (1987).
[9] S. Radi, V. Zikan. *Collect. Czech. Chem. Commun.*, **51,** 1692 (1986); *Chem. Abstr.*, **107**, 77686 (1987).
[10] Y. Mastoshi, T. Yasuo, H. Kuniko, I. Yuji, C.M. Rang, T. Kyoko, M. Mayumi, T. Takashi, T.T. Tazyko, T. Shigeru, Y. Yoshinori. *J. Med. Chem.*, **32**, 1295 (1989).
[11] S. Caddick. *Tetrahedron*., **51**, 10403 (1995).
[12] S.A. Galema. *Chem. Soc. Rev.*, **26**, 233 (1997).
[13] R.S. Varma. *J. Heterocycl. Chem.*, **35**, 1565 (1999).
[14] A.R. Katritzky, K.S. Sandeep. *Arkivoc*., **XIII**, 68 (2003).
[15] B.P. Nandeshwarappa, D.B. Arun Kumar, H.S. Bhojya Naik, V.P. Vaidya, K.M. Mahadevan. *J. Sulfur Chem*., **26**, 373 (2005).
[16] B.P. Nandeshwarappa, D.B. Arun Kumar, H.S. Bhojya Naik, V.P. Vaidya, K.M. Mahadevan. *Indian J. Chem*., **44B**, 2155 (2005).
[17] O. Meth-Cohn, B. Narine, B. Tarnowski. *J. Chem. Soc, Perkin Trans*, **1**, 1520 (1981).
[18] J.R. Meck. *J. Org. Chem.*, **27**, 3224 (1972).
[19] J.A. Valderrama, C. Valderrama. *Synth. Commun.*, **27**, 2143 (1997).
[20] E. Gradwol. *Clinical Laboratory methods and diagnosis*. Vol II, 7th edition, p. 1407, Mosby, C.V. Company, Berlin (1970).
[21] Z. Xilin, E. William, P.R. Nathan. *Antimicrobial and Chemotherapy*, **47**, 1023 (2003).