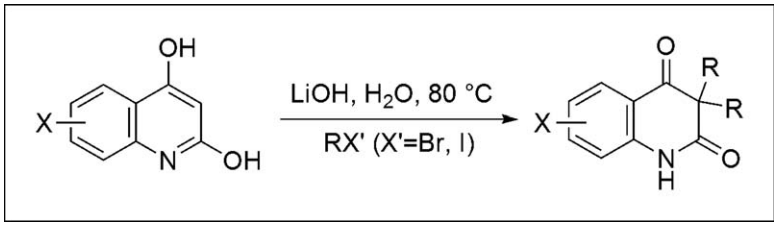
Efficient Chemoselective Alkylation of Quinoline 2,4-diol Derivatives in Water

Nafees Ahmed, Keyur G. Brahmbhatt, Inder P. Singh, and Kamlesh K. Bhutani*

Department of Natural Products, National Institute of Pharmaceutical Education and Research (NIPER), Mohali, Punjab 160062, India
*E-mail: kkbhutani@niper.ac.in

Received August 4, 2009
DOI 10.1002/jhet.364
Published online 7 October 2010 in Wiley Online Library (wileyonlinelibrary.com).



Synthesis of various C-3-dialkyl derivatives of quinoline 2,4-diol was achieved by condensation of aniline or substituted anilines with diethyl malonate, followed by chemoselective alkylation at C-3 in water. The higher yields, easy work up and environmental compatible conditions are the main aspects of our method.

J. Heterocyclic Chem., **48**, 237 (2011).

INTRODUCTION

''Quinoline 2,4-diol'' moiety is present in large number of natural products and synthetic molecules. These compounds have shown variety of biological activities [1]. The C-3-dialkyl derivative of quinoline 2,4-diol, buchapine **1**, was isolated from methanolic extract of the epigeal part of *Haplophyllum bucharicum* [2], *H. tuberculatum* [3,4], *Euodia roxburghiana*. Compound **2** was isolated from CH_2Cl_2-MeOH (1:1) extract of *E. roxburghiana* along with **1**. The natural products **1** and **2** (Fig. 1) exhibit anti-HIV activity against HIV-1 in cultured human lymphoblastoid CEM-SS cells (EC_{50} 0.94 μM and EC_{50} 1.64 μM respectively) [5]. However, these molecules are not extensively explored to obtain potent anti-HIV agents. As a part of our ongoing work [6,7] to identify newer anti-HIV agents, we designed several C-3-dialkyl quinoline 2,4-dione derivatives based on compound **1** to study their anti-HIV potential. Here, we report the synthesis of C-3-dialkyl derivatives of quinoline 2,4-diol by using water—a green solvent.

RESULTS AND DISCUSSION

Two strategies are possible for synthesis of C-3-dialkyl quinoline 2,4-dione derivatives. First strategy is cyclization of 2,2-dialkyl diethyl malonate with aniline or substituted anilines. We attempted the synthesis of dialkyl derivatives **6** by using methods reported for similar types of compounds, i.e., cyclization by microwave irradiation [8] or heating with polyphosphoric acid [9]. As shown in Scheme 1, diethyl malonate **3** was alkylated using NaH in THF to form **4a–b** in about 80% yield. Compounds **4a–b** were re-alkylated under similar reaction condition to form **5a–c** by reported method [10]. However, cyclization of aniline with **5a–c** did not take place when they were irradiated in microwave. The desired products **6a–c** were also not obtained when aniline was heated with **5a–c** in polyphosphoric acid.

Second strategy for synthesis of C-3-dialkyl quinoline 2,4-dione derivatives is to cyclize diethyl malonate with aniline or substituted anilines followed by chemoselective C-3 alkylation. As depicted in Scheme 2, quinoline 2,4-diol derivatives **7a–d** were synthesized in quantitative yields by condensation of aniline or substituted anilines with **3** under microwave irradiation using few drops of DMF [8]. The direct alkylation of **7a** is reported in the literature by using Mitsunobu reaction employing prenyl alcohol [11]. Further, alkylation of C-

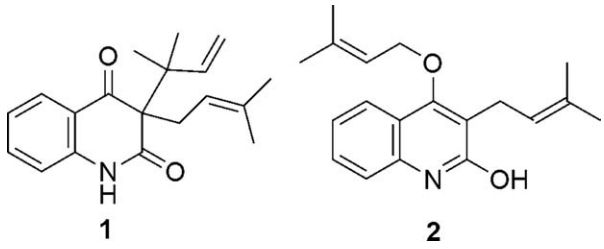
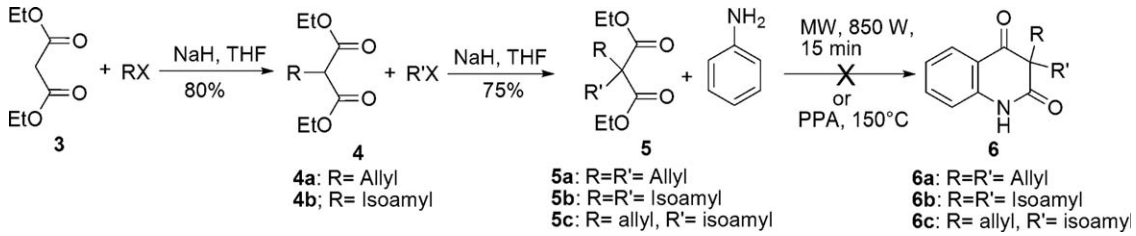


Figure 1. Anti-HIV natural products.

Scheme 1



3-alkyl quinoline 2,4-diol is carried out by employing K_2CO_3 as base and acetone as solvent [12]. However, yields are low by these methods as the mixture of products is formed. The chemoselectivity of C versus O-alkylation depends on nature of solvents. Polar aprotic solvents like DMF, DMSO, HMPA, and acetone enhance the O-alkylation by generating solvent separated ion-pairs [13,14]. Polar protic solvents like water protonate hydroxyl anion by forming hydrogen bond and promote C-alkylation [15]. Therefore, we postulated that yields of C-3-dialkylated derivatives can be improved by using water as solvent. To achieve chemoselective dialkylation of **7** at C-3, reaction conditions, which favor C-alkylation, were optimized by varying the base, solvent, and temperature as shown in Table 1. Allyl bromide was used as alkylating agent to optimize the reaction. The desired C-3-diallyl quinoline 2,4-dione **8a** was obtained in 70% yield with use of lithium hydroxide as base and water as solvent at 80°C (Table 1, entry 2). Although the product **8a** was formed using NaOH or KOH as base and methanol or water as solvent, yields were unsatisfactory (Table 1, Entries 6–9). C-alkylation was preferred when counter-ion of base was Li^+ as ion compared to Na^+ and K^+ ions. As the size of Li^+ ion is less than that of Na^+ and K^+ ions, Li^+ ion strongly binds to oxygen nucleophile and prevents O-alkylation [14]. The compounds **8a–m** were synthesized in 60–80% yields by using optimized method (Scheme 2).

In conclusion, a simple and efficient method for chemoselective alkylation of quinoline 2,4-diol derivatives at C-3 was achieved by employing water as solvent. The yields of reactions were good. The reaction required easy work up as the products were precipitated out in water. This method can be utilized for alkylation of other types of heterocyclic compounds having similar functionality. The synthesized compounds may be developed as good anti-HIV agents; the activity data will be published elsewhere.

EXPERIMENTAL

The known compounds **4a–b**, **5a–c**, **7a–d** [8] and **8b** [11] were identified by their Mass and NMR spectroscopic data. The FTIR spectra were recorded as KBr pellets on Perkin-Elmer spectrophotometer and values are expressed as υ_{max} cm^{-1}. ^1H and ^{13}C NMR spectra were recorded either on Bruker Avance 300 MHz spectrometer (DPX) or Bruker Avance III 400 MHz spectrometer using TMS as internal standard (chemical shifts in ppm (δ) & coupling constants in Hz). Mass spectra were recorded on LCMS Waters (Micromass ZQ). The combustion analyses were carried out using Vario EL Elementar elemental analyzer.

Scheme 2

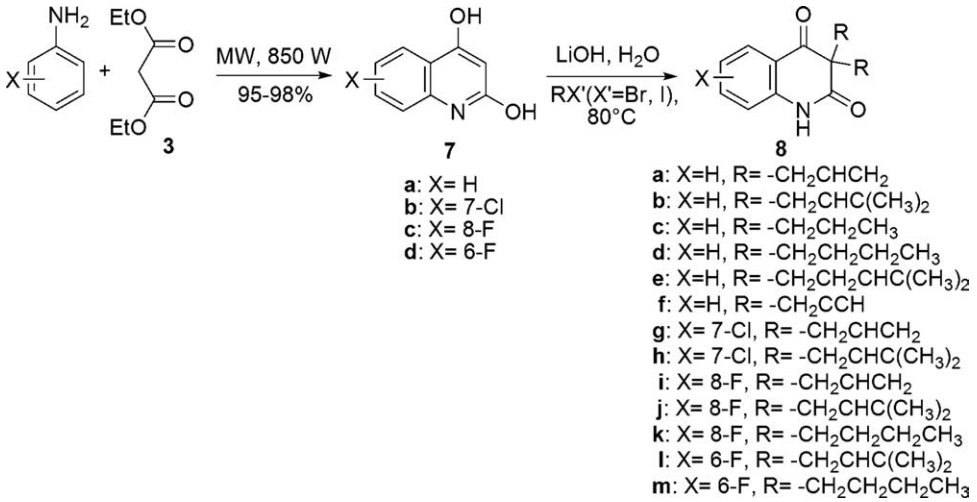


Table 1

Reaction conditions for C-3 allylation of quinoline 2,4-diol **7a**.

S. No.	Reagents	Conditions	Ratio of mono:diallyl[a]	Yields[b] (%)
1	LiOH, water	30°C, 24 h	60:40	20
2	LiOH, water	80°C, 24 h	10:90	70
3	LiOH, MeOH	Reflux, 24 h	60:40	20
4	LiOH, dioxane	Reflux, 24 h	–	No product
5	LiOH, THF	Reflux, 24 h	–	No product
6	NaOH, water	80°C, 24 h	50:50	35
7	NaOH, MeOH	Reflux, 24 h	50:50	35
8	KOH, water	80°C, 24 h	50:50	35
9	KOH, MeOH	Reflux, 24 h	50:50	35
10	NaH, THF	Reflux, 24 h	–	No product
11	NaH, DMF	80°C, 24 h	80:20	20

[a] Calculated after chromatographic isolation.
[b] Yield of C-3-diallyl quinoline 2,4-dione **8a**.

General procedure for C-3 dialkylation of quinoline 2,4-diol.

3,3-diallylquinoline-2,4(1H,3H)-dione (8a). To a suspension of quinoline 2,4-diol (200 mg, 1.25 mmol) in water (30 mL), lithium hydroxide (130 mg, 3.1 mmol) was added and stirred at 30°C to give homogeneous solution. Allyl bromide (0.32 mL, 2.7 mmol) was added drop wise and reaction mixture was heated at 80°C for 24 h. Reaction mixture was cooled to 30°C and crude product was filtered out. The remaining product in water layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water (2 × 20 mL) and brine solution (1 × 10 mL), evaporated on vacuo rotavapor and dried over $MgSO_4$ to give crude product. The combined crude product was subjected to column chromatography (silica gel #60–120, Hexane:EtOAc-gradient) to afford the 3,3-diallyl quinoline-2,4-dione **(8a)** (210 mg, 70% yield). FTIR (KBr, υ cm^{-1}): 3247 (NH stretching), 1697 (C=O stretching), 1660. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81 (t, J = 7.5, 5.6 Hz, 2H), 2.74 (t, J = 7.5, 5.7 Hz, 2H), 5.0 (dd, J = 10.1, 17 Hz, 4H), 5.56 (m, 1H), 5.62 (m, 1H), 6.95 (d, J = 8 Hz, 1H), 7.13 (t, J = 7.5, 15 Hz, 1H), 7.5 (t, J = 6.2, 13.9 Hz, 1H), 7.95 (d, J = 7.7 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 43.2, 62.0, 116.9, 119.9, 120.2, 124.1, 127.9, 132.3, 136.7, 141.5, 175.1, 197.1. MS APCI: m/z 242 $[M+1]^+$. Analysis calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81; Found: C, 74.70; H, 6.35; N, 5.67.

3,3-dipropylquinoline-2,4(1H,3H)-dione (8c). 60% yield. IR (KBr, υ cm^{-1}): 3435 (NH stretching), 1642 (C=O stretching), 1611. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, J = 9, 16.3 Hz, 3H), 0.87 (t, J = 6.3, 13.2 Hz, 3H), 1.24 (m, 4H), 1.99 (m, 4H), 6.93 (d, J = 8.4 Hz, 1H), 7.11 (t, J = 7.5, 15.3 Hz, 1H), 7.52 (t, J = 6.9, 11.7 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7, 16.1, 32.1, 61.8, 123.6, 125.9, 129.5, 133.3, 138.8, 177.9, 198.1. MS APCI: m/z 246 $[M+1]^+$. Analysis calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71; Found: C, 73.65; H, 7.58; N, 5.43.

3,3-dibutylquinoline-2,4(1H,3H)-dione (8d). 60% yield. IR (KBr, υ cm^{-1}): 3445 (NH stretching), 1759, 1638 (C=O stretching). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (t, J = 6.7, 13.1 Hz, 6H), 1.06 (m, 4H), 1.22 (m, 4H), 2.01 (t, J = 10.8, 19.8 Hz, 4H), 6.93 (d, J = 7.8 Hz, 1H), 7.12 (t, J = 7.3, 14.8 Hz, 1H), 7.55 (t, J = 7.2, 14.2 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.2, 23.4, 27.6, 30.2, 40.2, 62.3, 116.6, 120.3, 124.0, 127.9, 136.6, 141.4, 175.8, 198.7. MS APCI: m/z 274 $[M+1]^+$. Analysis calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12; Found: C, 74.45; H, 8.77; N, 5.01.

3,3-bis(4-methylpent-3-enyl)quinoline-2,4(1H,3H)-dione (8e). 65% yield. IR (KBr, υ cm^{-1}): 3257 (NH stretching), 1679 (C=O stretching), 1635. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (s, 6H), 1.76 (s, 6H), 2.33 (q, J = 7.2, 14.7 Hz, 2H), 2.57 (t, J = 6.8, 13.3 Hz, 4H), 2.73 (q, J = 7.8, 15.7 Hz, 2H), 5.23 (t, J = 8.7, 15 Hz, 2H), 7.2 (t, J = 7.1, 17.1 Hz, 1H), 7.37 (d, J = 8 Hz, 1H), 7.4 (t, J = 6.9, 15 Hz, 1H), 7.78 (d, J = 8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.4, 22.5, 24.1, 24.8, 32.5, 66.3, 123.8, 124.1, 124.6, 128.7, 130, 131.3, 132.1, 133, 138.2, 177.2, 198.4. MS APCI: m/z 326 $[M+1]^+$. Analysis calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30; Found: C, 77.23; H, 8.48; N, 4.31.

3,3-di(prop-2-ynyl)quinoline-2,4(1H,3H)-dione (8f). 70% yield. IR (KBr, υ cm^{-1}): 3294 (NH stretching), 1700, 1662 (C=O stretching). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (s, 1H), 1.87 9s, 1H), 2.81 (s, 4H), 6.99 (d, J = 6.0 Hz, 1H), 7.17 (t, J = 7.5, 15.1 Hz, 1H), 7.58 (t, J = 7.3, 15.3 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): 24.6, 57, 69.5, 114.5, 117.5, 121.6, 125.5, 134.4, 138.9, 170.5, 192.3. MS APCI: m/z 238 $[M+1]^+$. Analysis calcd. for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90; Found: C, 75.99; H, 4.52; N, 5.86.

3,3-diallyl-7-chloroquinoline-2,4(1H,3H)-dione (8g). 78% yield. IR (KBr, υ cm^{-1}): 3272 (NH stretching), 1692, 1661 (C=O stretching). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (d, J = 8 Hz, 2H), 2.76 (d, J = 7.4 Hz, 2H), 5.06 (dd, J = 2.5, 10.4 Hz, 2H), 5.15 (dd, J = 2.5, 11 Hz, 2H), 5.88 (m, 2H), 7.1 (d, J = 8.8 Hz, 1H), 7.4 (d, J = 8 Hz, 1H), 7.80 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.3, 54.9, 116.9, 119.6, 123.8, 130.1, 133.9, 134.7, 139.9, 168.1, 198.1. MS APCI: m/z 276 $[M+1]^+$. Analysis calcd. for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08; Found: C, 65.41; H, 5.16; N, 5.06.

7-chloro-3,3-bis(3-methylbut-2-enyl)quinoline-2,4(1H,3H)-dione (8h). 80% yield. IR (KBr, υ cm^{-1}): 3281(NH stretching), 1664 (C=O stretching), 1596. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (s, 6H), 1.68 (s, 6H), 2.76 (t, J = 7.3, 14 Hz, 4H), 5.18 (t, J = 7.6, 14.8 Hz, 2H), 7.11 (d, J = 8.3 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 24.5, 29.9, 55.4, 118, 119.4, 123.8, 129.7, 134, 135, 139.4, 169, 201.5. MS APCI: m/z 332 $[M+1]^+$.

Analysis calcd. for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; N, 4.22; Found: C, 68.71; H, 6.72; N, 4.33.

3,3-diallyl-8-fluoroquinoline-2,4(1H,3H)-dione (8i). 68% yield. IR (KBr, υ cm^{-1}): 3288 (NH stretching), 1687 (C=O stretching), 1650, 1616. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (t, J = 7.2, 14.4 Hz, 4H), 5.16 (dd, J = 1.6, 10.4 Hz, 2H), 5.18 (dd, J = 1.3, 10.2 Hz, 2H), 5.85 (m, 2H), 7.09–7.17 (m, 2H, aromatic), 8.28 (t, J = 8, 15.6 Hz, 1H), 8.69 (s, 1NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37, 56.3, 114.9, 115.1, 119.1, 122.1, 133.1, 151.6, 154.1, 168, 199.5. ^{9}F NMR (376 MHz, $CDCl_3$): δ 128.8. MS APCI: m/z 260.1 $[M+1]^+$. Analysis calcd. for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.44; N, 5.40; Found: C, 69.45; H, 5.42; N, 5.51.

8-fluoro-3,3-bis(3-methylbut-2-enyl)quinoline-2,4(1H,3H)-dione (8j). 75% yield. IR (KBr, υ cm^{-1}): 3269 (NH stretching), 1674 (C=O stretching), 1619. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 6H), 1.71 (s, 6H), 2.82 (d, J = 7.2 Hz, 4H), 5.24 (t, J = 7.1, 13.8 Hz, 2H), 7.07–7.16 (m, 2H, aromatic), 8.32 (t, J = 7.3, 15.1 Hz, 1H), 9.30 (s, 1NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18, 26, 35, 58.9, 114.8, 115, 118.4, 124.77, 126.2, 137.1, 154, 170.9, 199.2. MS APCI: m/z 316 $[M+1]^+$. Analysis calcd. for $C_{19}H_{22}FNO_2$: C, 72.36; H, 7.03; N, 4.44; Found: C, 72.43; H, 6.98; N, 4.51.

3,3-dibutyl-8-fluoroquinoline-2,4(1H,3H)-dione (8k). 70% yield. IR (KBr, υ cm^{-1}): 3263 (NH stretching), 1680 (C=O stretching), 1615, 1533. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.2, 16.4 Hz, 6H), 1.35–1.49 (m, 8H), 2.14 (t, J = 7.3, 13.6 Hz, 4H), 7.06–7.17 (m, 2H, aromatic), 8.28 (t, J = 7.6, 16.1 Hz, 1H), 8.63 (s, 1NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 22.3, 29.5, 33.1, 57, 114.9, 115.1, 122.1, 124.5, 125.1, 125.7, 154.6, 169.8, 198.1. ^{9}F NMR (376 MHz, $CDCl_3$): δ 129.7. MS APCI: m/z 292 $[M+1]^+$. Analysis calcd. for $C_{17}H_{22}FNO_2$: C, 70.08; H, 7.61; N, 4.81; Found: C, 70.32; H, 7.65; N, 4.90.

6-fluoro-3,3-bis(3-methylbut-2-enyl)quinoline-2,4(1H,3H)-dione (8l). 80% yield. IR (KBr, υ cm^{-1}): 3272 (NH stretching), 1662 (C=O stretching), 1620. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 6H), 1.70 (s, 6H), 2.75 (d, J = 7.3 Hz, 4H), 5.17 (t, J = 7.7, 14.2 Hz, 2H), 7.05 (m, 1H), 7.53 (m, 1H), 9.121 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8, 25.7, 32.1, 56.1, 115.6, 118.8, 122.2, 133.3 134.2, 136.3, 160.8, 169.1, 198.3. ^{9}F NMR (376 MHz, $CDCl_3$): δ 116.8. MS APCI: m/z 316.4 $[M+1]^+$. Analysis calcd. for $C_{19}H_{22}FNO_2$: C, 72.36; H, 7.03; N, 4.44; Found: C, 72.47; H, 7.10; N, 4.49.

3,3-dibutyl-6-fluoroquinoline-2,4(1H,3H)-dione (8m). 73% yield. IR (KBr, υ cm^{-1}): 3283 (NH stretching), 3058, 1679 (C=O stretching), 1613, 1509. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.4, 16.1 Hz, 6H), 1.33–1.46 (m, 8H), 2.10 (t, J = 7.6, 14.3 Hz, 4H), 7.03 (m, 1H), 7.55 (m, 1H), 9.10 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 22.2, 29.6, 33.3, 56.4, 115.5, 115.8, 122, 122.1, 133.3, 133.4, 158.4, 169.4, 197.5. MS ESI: m/z 291.2 $[M]^+$. Analysis calcd. for $C_{17}H_{22}FNO_2$: C, 70.08; H, 7.61; N, 4.81; Found: C, 69.97; H, 7.59; N, 4.86.

REFERENCES AND NOTES

[1] Ukrainets, I. V.; Bereznyakova, N. L.; Mospanova, E. V. Chem Heterocycl Compd 2007, 43, 856.

[2] Nesmelova, E. F.; Bessonova, I. A.; Yunusov, S. Y. Khim Prir Soedin 1982, 4, 532.

[3] Giuma, M. S.; karima, A.; Bahlul, Z. E.; Aziza, S. A.; Fatma, A. A.; Hala, H. A. Phytochemistry 1987, 26, 3339.

[4] Al-Rehaily, A. J.; Al-Howiriny, T. A.; Ahmad, M. S.; Al-Yahya, M. A.; El-Feraly, F. S.; Hufford, C. D.; McPhail, A. T. Phytochemistry 2001, 57, 597.

[5] McCormick, J. L.; McKee, T. C.; Cardellina, J. H.; Boyd, M. R. J Nat Prod 1996, 59, 469.

[6] Brahmbhatt, K. G.; Nafees, A.; Singh, I. P.; Bhutani, K. K. Tetrahedron Lett 2009, 50, 5501.

[7] This work was supported by grant entitled ''Identification of anti-viral compounds for development of microbicides to prevent HIV infection and transmission'' (GP-284) from the Department of Biotechnology (DBT), India.

[8] Kapil, A.; Agarwal, M. Bioorg Med Chem Lett 2007, 17, 86.

[9] Naoshi, I. A.; Yuki, T. M.; Mary, O. Y. US Patent 4,904,787, 1990.

[10] Takanori, Y.; Alaksandr, K.; Yasufumi, K.; Fumie, S. J Org Chem 1996, 61, 2266.

[11] Giancarlo, C.; Gian, M. N.; Giovanni, P.; Silvia, T. Heterocycles 2003, 60, 351.

[12] Michael, F. G.; Ramachandran, V. N. Tetrahedron Lett 1985, 26, 4253.

[13] Kornblum, N.; Berrigan, P. J.; Le Noble, W. J. J Am Chem Soc 1963, 85, 1141.

[14] Kornblum, N.; Berrigan, P. J.; Le Noble, W. J. J Am Chem Soc 1960, 82, 1257.

[15] Le Noble, W. J. Synthesis 1970, 1, 1.