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SYNTHESIS OF 1-[4-(1,5-DIALKYL-1H-1,2,4-TRIAZOL-3-YL)]BENZYL-1H-INDOLES AND 5,6-DIHALOQUINOLONES

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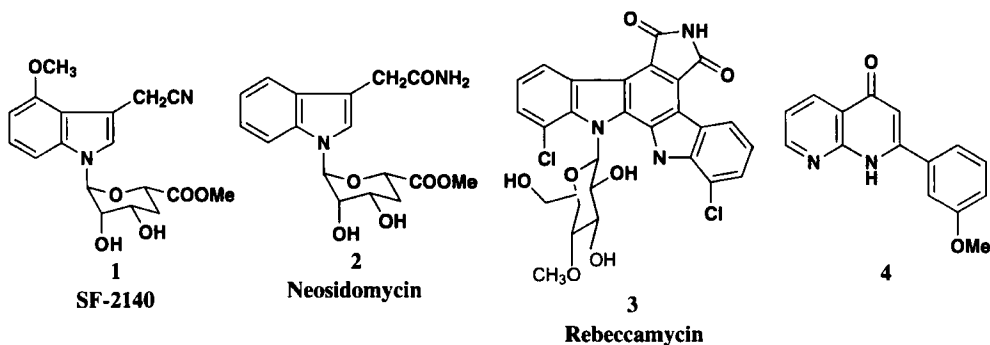
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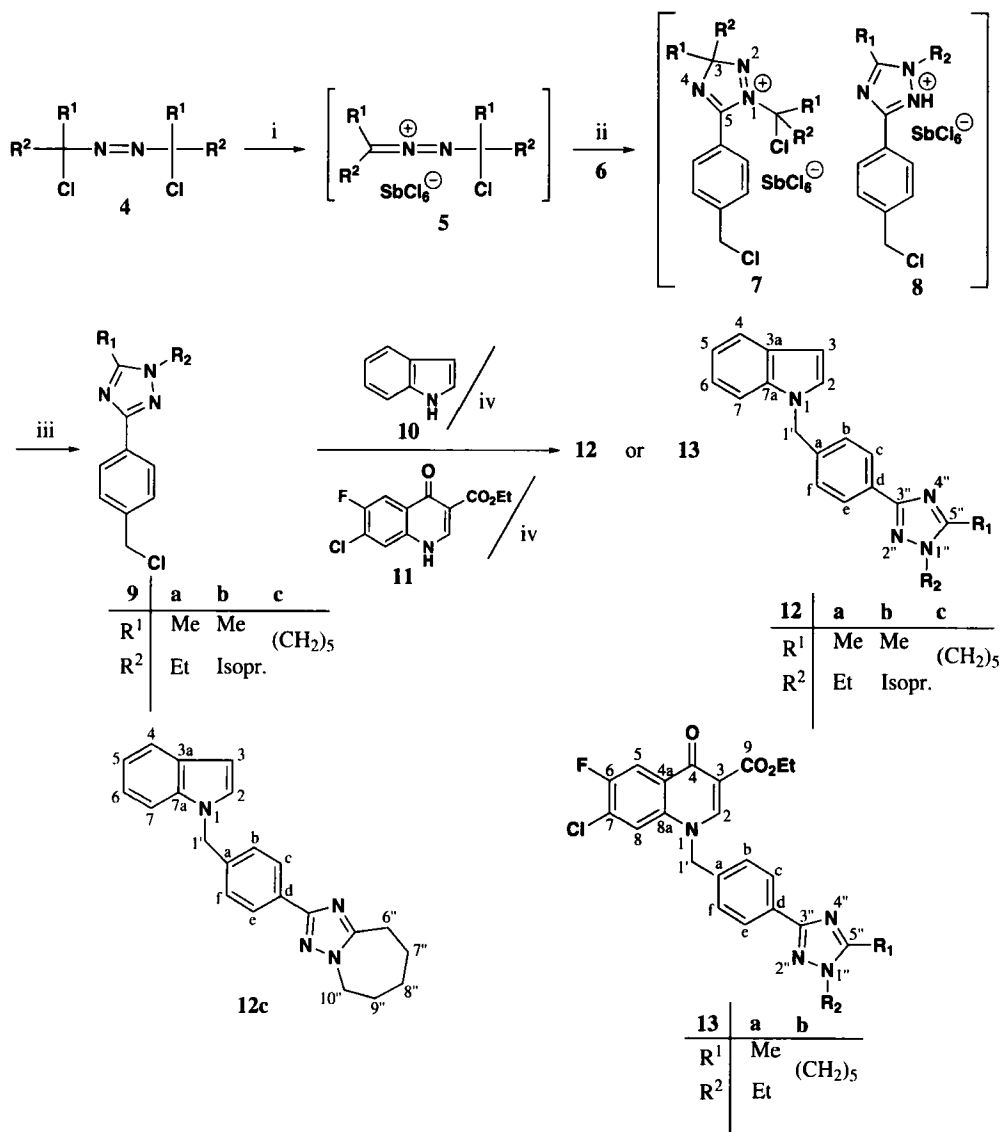
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During the last decade, several synthetic nucleosides and non-nucleosides analogues have been synthesized as useful anticancer, antiviral and antibacterial chemotherapeutic agents, and some of them are anti-HIV drugs. Among these compounds are the indole and quinolone analogues, such as the naturally occurring antibiotics SF-2140 (**1**)¹ and neosidomycin (**2**)², which are antiviral agents against several strains of influenza virus *in vitro* and *in vivo*. These antibiotics are the only examples of simple indole-*N*-glycosides of biological origin so far reported. The antibiotic rebeccamycin (**3**) which contains a fused indole (indolocarbazole) moiety, exhibited *in vivo* antitumor activity against P388 and L1210 leukemias and B16 melanoma in mice.³ More indole nucleosides related to the antibiotics SF-2140 and neosidomycin have been reported.⁴ In addition, substituted indoles such as vincamine and Cavinton® (vinpocetine),⁵ as well as some azepino[3,6-*b*]indoles⁶ proved to be effective cerebral vasodilators.



The use of synthetic quinolones as antibacterial⁷, antiviral,⁸ or anticancer agents,^{9a} such as naphthyridinone isostere **4**^{9b} and dehydrogenase inhibitors¹⁰ has stimulated extensive research in the synthesis of this class of compounds, owing to their potent activity against various infectious diseases.^{11,12} 7-Chloro-[(*E*)-4-chloro-2-butene-1-yl]-1,4-dihydro-6-fluoro-4-oxoquinoline-3-carboxylic acid exhibited potent activity against HIV-1 ($EC_{50} > 2.0 \mu\text{g/mL}$) and HIV-2 ($EC_{50} > 1.0 \mu\text{g/mL}$),¹³ although these values are lower than the CC_{50} , but other quinolone nucleosides^{14,15} showed no activity against this virus. This paper presents the synthesis of some new *N*-substituted indoles and quinolones, where the substituents are 1H-1,2,4-triazole precursors carrying different alkyl groups, as promising anticancer or antiviral candidates.

Recently, the 4,5-dihydro-3*H*-pyrazolium salts have been synthesized from the cycloaddition of the short-lived 1-(chloroalkyl)-1-aza-2-azoniaallenes **5**¹⁶⁻¹⁸ to various electron-rich alkenes in the presence of Lewis acids like SbCl₅; similarly some 1,2,4-triazolo C-nucleosides¹⁹ were prepared recently *via* the cycloaddition of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide to intermediates **5**. Meanwhile our recent work dealt with the synthesis of various 1,2,4-triazole C-nucleosides,²⁰ acyclic C-nucleosides,²¹ pyrimidines,²² and *N*-alkyl-substituted phthalimides²³ from cycloaddition of the intermediates **5** with glycosyl cyanide, acyclic (2-hydroxyethoxy)alkyl cyanides, 1-(cyanomethyl)thymine,



Reagents and conditions: i) SbCl₅, CH₂Cl₂, -60°; ii) *p*-cyanobenzyl chloride (**6**), CH₂Cl₂, -60° to 23°; iii) NaHCO₃, NH₃, MeCN, 0°, 2 h; iv) NaH, DMF, 23°, 6 h

and *N*-alkylphthalimide cyanides. In the present study, the reactive intermediates **5** and 4-cyanobenzyl chloride **6** were selected for the synthesis of new 1,2,4-triazole precursors. The dichlorides **4** were

converted, at approximately -60° , to the salts **5** in the presence of SbCl_5 . At -30° , the color reaction was changed indicating that **5** underwent cycloaddition with the nitrile **6** to give the unseparable 5-[4-(chloromethyl)-benzo-1-yl]-3*H*-1,2,4-triazolium hexachloroantimonates **7**. As the temperature was raised above -30° , **7** rearranged to the protonated triazole **8** by [1,2] migration¹⁶ of the alkyl group (R^2) at C-3 to N-2, accompanied by elimination of the CClR^1R^2 group. *In situ* hydrolysis of **8** with aqueous NaHCO_3 afforded the triazoles **9** in 80, 76, and 70% yield, respectively. Indole **10** and the quinolone derivative **11** were treated with sodium hydride in dry DMF at 23° to afford the N-anions,²⁴ which reacted readily with compounds **9**, giving the title products **12a,b** (75 and 55% yield, respectively) and **13a-c** (70, 72 and 68% yield). These compounds were identified by heteronuclear NMR spectroscopic methods, HMBC spectrum²⁵ and mass spectra (see Table 1 and 2). The ^1H NMR spectra of **12a-c** showed similar patterns. The $\text{CH}_2\text{-1'}$ appeared as singlets at δ 5.44, 5.38 and 5.44, respectively. The doublets at δ 7.50, 7.47 and 7.50 ($J \sim 3.0$ Hz) were attributed to H-2 (indole ring), whereas the doublets at δ 6.44, 6.46 and 6.48 ($J \sim 3.0$ Hz) were identified as H-3 (indole ring), respectively. The alkyl groups at N-1" and C-5" were assigned. The ^{13}C NMR spectra of **12a-c** contained the resonance signals of the triazole ring (C-3" and C-5") at higher field between δ 157.9 – 158.9 and δ 151.1 – 157.7, respectively. The indole carbon atoms (C-2, C-3) appeared in the regions δ 129.0 – 129.1 and δ 100.7 – 101.0, respectively, meanwhile C-1' appeared at δ 48.8, 50.0 and 50.1, respectively. The structures of **13a,b** were identified from their NMR spectra and in comparison with the known structures of quinolone nucleosides.^{13,14,26} The anticancer activity of compounds **12a-c** and **13a,b** is currently under investigation.

Table 1. Physical and ^1H -NMR Spectral Data of Compounds (**9-13**)^a

Cmpd	Yield (%)	mp ($^\circ\text{C}$)	MS (M^+)	^1H -NMR (d)
9a	80	109-111	235/237	8.15 (d, 2H, ArH); 7.46 (d, 2H, Ar); 4.60 (s, 2H, CH_2Ph); 4.21 (q, 2H, $J = 7.0$ Hz, CH_2CH_3); 2.51 (s, 3H, $\text{C}_5\text{-Me}$); 1.52 (t, 3H, CH_2CH_3)
9b	76	148-151	249/251	8.16 (d, 2H, ArH); 7.47 (d, 2H, ArH); 4.71 (s, 2H, CH_2Ph); 4.50 [m, 1H, $\text{CH}(\text{Me})_2$]; 2.63 (s, 3H, $\text{C}_5\text{-Me}$); 1.61 [d, 6H, $J = 6.8$ Hz, $\text{CH}(\text{Me})_2$]
9c	70	123-125	261/263	8.11 (d, 2H, ArH); 7.43 (d, 2H, ArH); 4.73 (s, 2H, CH_2Ph); 4.40 (dt, 2H, H-10a, H-10b); 3.08 (dt, 2H, H-6a, H-6b); 1.91 (m, 2H, H-9a, H-9b); 1.80 (m, 2H, H-8a, H-8b); 1.72 (m, 2H, H-7a, H-7b)
12a	75	230-235	316	7.87 (d, 2H, $J = 8.2$ Hz, $\text{ArH}_{b,f}$); 7.55 (d, 1H, $J = 7.0$ Hz, H-4); 7.50 (d, 1H, $J = 3.2$ Hz, H-2); 7.43 (d, 1H, $J = 7.0$ Hz, H-7); 7.23 (d, 2H, $J = 8.2$ Hz, $\text{ArH}_{c,e}$); 7.08 (t, 1H, $J = 7.0$ Hz, H-6); 7.00 (t, 1H, $J = 7.0$ Hz, H-5); 6.44 (d, 2H, $J = 3.2$ Hz, H-3); 6.44 (d, 2H, $J = 3.2$ Hz, H-3); 5.44 (s, 2H, $\text{CH}_2\text{-1'}$); 4.11 (q, 2H, $J = 7.3$ Hz, $\text{N}^{1''}\text{CH}_2\text{CH}_3$); 2.41 (s, 3H, $\text{C}_5\text{-Me}$); 1.33 (t, 3H, $\text{N}^{1''}\text{-CH}_2\text{CH}_3$)

Table 1. Continued...

Cmpd	Yield (%)	mp (°C)	MS (M ⁺)	¹ H-NMR (d)
12b	55	215-218	330	7.85 (d, 2H, J = 8.0 Hz, ArH _{b,f}); 7.52 (d, 1H, J = 7.0 Hz, H-4); 7.47 (d, 1H, J = 3.0 Hz, H-2); 7.45 (d, 1H, J = 7.0 Hz, H-7); 7.19 (d, 2H, J = 8.1 Hz, ArH _{c,e}); 7.05 (dd, 1H, J = 8.0 Hz, H-6); 7.00 (t, 1H, J = 7.0 Hz, H-5); 6.46 (d, 2H, J = 3.3 Hz, H-3); 5.38 (s, 2H, CH ₂ -1'); 4.75 [m, 1H, CH(Me) ₂]; 2.65 (s, 3H, C ₅ -Me); 1.57, 1.54 [d, 6H, CH(Me) ₂]
12c	70	220-224	342	7.86 (d, 2H, J = 8.1 Hz, ArH _{b,f}); 7.55 (d, 2H, J = 7.0 Hz, H-4); 7.50 (d, 1H, J = 3.1 Hz, H-2); 7.43 (d, 1H, J = 8.0 Hz, H-7); 7.24 (d, 2H, J = 7.2 Hz, ArH _{c,e}); 7.08 (dd, 1H, J = 8.0 Hz, H-6); 7.00 (t, 1H, J = 7.3 Hz, H-5); 6.48 (d, 1H, J = 3.1 Hz, H-3); 5.44 (s, 2H, CH ₂ -1'); 4.25 (m, 2H, H-10'a, H-10'b); 2.91 (m, 2H, H-6'a, H-6'b); 1.82 (m, 2H, H-9'a, H-9'b); 1.71 (m, 2H, H-8'a, H-8'b); 1.62 (m, 2H, H-7'a, H-7'b)
13a	72	247-249	468/470	8.92 (s, 1H, H-2); 8.05 (d, 1H, J _{5,F} = 9.2 Hz, H-5); 7.95-7.91 (m, 3H, H-8, ArH _{b,f}); 7.25 (d, 1H, J = 8.2 Hz, ArH _{c,e}); 5.75 (s, 1H, CH ₂ -1'); 4.27-4.15 (m, 4H, CO ₂ CH ₂ CH ₃ , H-10'a, H-10'b); 4.17 (q, 2H, J = 7.5 Hz, N ^{1'} -CH ₂ CH ₃); 2.41 (s, 3H, C ₅ -Me); 1.32 (t, 3H, N ^{1'} -CH ₂ CH ₃); 1.28 (t, 3H, CO ₂ CH ₂ CH ₃)
13b	68	230-234	494/496	8.93 (s, 1H, H-2); 8.05 (d, 1H, J _{5,F} = 9.4 Hz, H-5); 7.95 (d, 1H, J _{5,8} = 7.9 Hz, H-8); 7.90 (d, 1H, J = 8.0 Hz, ArH _{b,f}); 7.29 (d, 1H, J = 8.0 Hz, ArH _{c,e}); 5.78 (s, 1H, CH ₂ -1'); 4.27-4.15 (m, 4H, CO ₂ CH ₂ CH ₃ , H-10'a, H-10'b); 2.93 (m, 2H, H-6'a, H-6'b); 1.82 (m, 2H, H-9'a, H-9'b); 1.73 (m, 2H, H-8'a, H-8'b); 1.61 (m, 2H, H-7'a, H-7'b); 1.28 (t, 3H, J = 7.5 Hz, CO ₂ CH ₂ CH ₃)

a) Solvent: CDCl₃ for **9**; DMSO-d₆ at 600 MHz for **12** and **13**.

EXPERIMENTAL SECTION

Melting points are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded at Bruker AC-250, WM-250, and DRX 600 spectrometers. The signal assignments for protons were verified by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by ¹H-¹³C COSY or HMQC experiments. The cycloadditions were performed under nitrogen with exclusion of moisture.

Preparation of 1,5-Dialkyl-3-[(4-chloromethyl)phenyl]-1H-1,2,4-triazoles (**9**). General Procedure.-

To a stirred, cooled (−60°) solution of the required 1-(chloroalkyl)azo compound **4** and 4-cyanobenzyl chloride **6** (2.0 mmol) in 20 mL of CH₂Cl₂ was added dropwise a solution of SbCl₅ (3.0 mmol) in 30

Table 2 ^{13}C -NMR Spectral Data of Compounds **12** and **13**^a

Cmpd	C-2 C-3	C-3a/ C-4a ($J_{4a,F}$)	C-4 C-5	C-6 ($J_{6,F}$) C-7 ($J_{7,F}$)	C-8	C-7a/ C-8a	C-1' C-3'' C-5''	R ₁	R ₂	Ar
12a	129.1 101.0	138.7	120.4 119.0	121.1	----	135.7	48.8 158.8 152.4	11.3	42.7(CH ₂) 14.8(CH ₃)	130.1(d) 128.2(a) 127.2(c,e) 125.6(b,f)
12b	129.0 100.7	138.2	120.1 118.7	120.9 109.8	----	135.6	50.0 158.9 151.1	11.2	48.7(CH) 29.2(CH ₃) 22.8(CH ₃)	130.5(d) 130.2(a) 128.0(c,e) 125.4(b,f)
12c	129.1 100.7	138.2	120.2 118.8	120.8 109.8	----	135.7	50.1 157.9 157.7	11.2	50.1(10'') 29.1(8'') 26.2(6'') 26.7(9'') 24.3(7'')	132.4(d) 128.2(a) 127.0(c,e) 125.4(b,f)
13a	143.4 109.5	126.5d (6.5)	165.2 113.3d (23.3)	156.0d (253.5) 129.0d (20.6)	118.7	135.4	48.6 158.6 152.1	11.2	42.5(CH ₂) 14.5(CH ₃)	130.0(d) 128.0(a) 127.1(c,e) 125.2(b,f)
13b	142.9 109.0	126.1d (6.2)	165.2 113.1d (22.5)	156.1d (252.2) 128.9d (20.2)	118.0	135.1	48.2 158.0 157.2	11.2	49.8(10'') 29.0(8'') 26.5(6'') 26.0(9'') 24.1(7'')	130.2(d) 128.1(a) 127.0(c,e) 125.2(b,f)

a) Solvent: DMSO- d_6 for **12** and **13**. b) C=O at 177.2 c) C=O at 177.5

mL of CH_2Cl_2 . Stirring was continued at -60° for 1 h, then at 0° for 1 h and finally at 23° for 10 min., followed by addition of pentane (50 mL). The precipitated solid was dissolved in 40 mL of CH_3CN , cooled to 0° followed by addition of an aqueous solution of NaHCO_3 (2.52 g, 30 mmol in 30 mL of H_2O) and ammonia solution (2 mL) and the mixture was stirred at room temperature for 2 h. The organic solvent was evaporated and the residue was extracted with 3 x 20 mL of CHCl_3 . The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness. The residue was recrystallized from CH_2Cl_2 -ether.

9a ($\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{C}_2\text{H}_5$): From **4a** (0.66 g, 3.0 mmol). Yield: 0.56 g.

Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{ClN}_3$: C, 61.15; H, 5.99; N, 17.83. Found: C, 60.93; H, 5.89; N, 17.72

9b [$\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{CH}(\text{CH}_3)_2$]: From **4b** (0.72 g, 3.0 mmol). Yield: 0.57 g.

Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{ClN}_3$: C, 62.52; H, 6.46; N, 16.83. Found: C, 62.31; H, 6.38; N, 16.72

9c ($\text{R}^1 = \text{R}^2 = (\text{CH}_2)_5$): From **4c** (0.79 g, 3.0 mmol). Yield: 0.55 g.

Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{ClN}_3$: C, 64.24; H, 6.16; N, 16.05. Found: C, 64.03; H, 6.08; N, 15.94

Preparation of 1-[(1,5-dialkyl-1H-1,2,4-triazol-3-yl)benzyl]indoles (12) and Quinolones (13).

General Procedure.- To a stirred suspension of **10** (230 mg, 2.0 mmol) or **11** (540 mg, 2.0 mmol) in dry DMF (20 mL) was added sodium hydride (58 mg, 2.4 mmol, 60% in oil) and the reaction mixture was stirred at 23° for 30 min. The chloro compound **9** (2.4 mmol) was added and the reaction mixture was stirred overnight at 23°, filtered and evaporated to dryness. The crude product was purified by flash SiO₂ column using CHCl₃-MeOH (9:1) as eluent to give a colorless solid, which was recrystallized from CH₂Cl₂-ether to afford **12** or **13**.

12a (R¹ = CH₃, R² = C₂H₅): From **9a** (0.56 g, 2.40 mmol). Yield: 0.57 g.

Anal. Calcd for C₂₀H₂₀N₄: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.81; H, 6.29; N, 17.58.

12b [R¹ = CH₃, R² = CH(CH₃)₂]: From **9b** (0.69 g, 2.40 mmol). Yield: 0.43 g.

Anal. Calcd for C₂₁H₂₂N₄: C, 76.35; H, 6.71; N, 16.96. Found: C, 76.21; H, 6.62; N, 16.76.

12c [R¹ = R² = (CH₂)₃]: From **9c** (0.63 g, 2.40 mmol). Yield: 0.57 g.

Anal. Calcd for C₂₂H₂₂N₄: C, 77.16; H, 6.48; N, 16.36. Found: C, 77.01; H, 6.39; N, 16.06.

Ethyl 7-chloro-[(1-ethyl-5-methyl-1H-1,2,4-triazol-3-yl)benzyl]-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (13a).- From **9a** (0.56 g, 2.40 mmol). Yield: 0.81 g.

Anal. Calcd for C₂₄H₂₂ClFN₄O₃: C, 61.47; H, 4.73; N, 11.95. Found: C, 61.20; H, 4.63; N, 11.78.

Ethyl 7-chloro-6-fluoro-1-[4-(6,7,8,9-tetrahydro-5H-1,2,4-triazol[1,5-*a*]azepin-2-yl)benzyl]-1,4-dihydro-4-oxoquinoline-3-carboxylate (13b).- From **9b** (0.56 g, 2.40 mmol). Yield: 0.80 g.

Anal. Calcd for C₂₆H₂₄ClFIN₄O₃: C, 63.09; H, 4.89; N, 11.32. Found: C, 62.88; H, 4.75; N, 11.21.

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REFERENCES

1. T. Ito, K. Ohba, M. Koyama, M. Sezaki, H. Tohyama, T. Shomura, H. Fukuyasu, Kazuno, T. Niwa and T. Niida, *J. Antibiotics*, **37**, 931 (1984).
2. R. Furuta, S. Naruto, A. Tamura and K. Yokogawa, *Tetrahedron Lett.*, **37**, 701 (1979).
3. J. A. Bush, B. H. Long, J. J. Catino, W. T. Bradner and K. Tomita, *J. Antibiotics*, **40**, 668 (1987), and references cited therein.
4. N. S. Girgis, H. B. Cottam and R. K. Robins, *J. Heterocyclic Chem.*, **25**, 361 (1988).
5. Cs. Szantay, L. Szabo and Gy. Kalaus, *Tetrahedron*, **33**, 1803 (1977).
6. A. Dancso, M. Kajtar-Peredy and C. Szantay, *J. Heterocyclic Chem.*, **34**, 1267 (1997).
7. J. T. Smith and C. S. Lewis, "The Quinolones", ed by V. T. Andriole, Academic Press, London (1988), CH 2.
8. M. Nasr, J. C. Drach, S. H. Smith, C. Shipman and J. H. Burckhalter, *J. Med. Chem.*, **31**, 1347 (1988).

9. a) H. I. El-Subbagh, A. H. Abadi, I. E. Al-Khawad and K. A. Al-Rashood, *Arch. Pharm. Pharm. Med. Chem.*, **332**, 19 (1999) and references cited therein. b) G. Shi, K. Chen, L. Li, J. Chang, C. Autry, M. Kozuka, T. Konoshima, J. Estes, C. Lin, E. Hamle, A. McPhail and K. Lee, *J. Nat. Prod.*, **58**, 475 (1995), and references cited therein.
10. B. R. Baker and R. R. Bramhall, *J. Med. Chem.*, **15**, 230 (1972).
11. D. C. Hooper and J. C. Wolfson, *N. Eng. J. Med.*, 384 (1991).
12. T.-C. Ko, M.-J. Hour, J.-C. Lien, C.-M. Teng, K.-H. Lee, S.-C. Kuo and L.-J. Haung, *Bioorg. Med. Chem. Lett.*, **11**, 279 (2001).
13. N. A. Al-Masoudi, Y. A. Al-Soud, M. Eherman and E. De Clercq, *Bioorg. Med. Chem.*, **8**, 1407 (2000).
14. N. A. Al-Masoudi, Y. A. Al-Soud, M. Eherman and E. De Clercq, *Nucleosides & Nucleotides*, **17**, 255 (1998).
15. N. A. Al-Masoudi, Y. A. Al-Soud and I. Al-Masoudi, *Sulfur Lett.*, **24**, 13 (2000).
16. Y. A. Al-Soud, W. Wirschum, N. A. M. Hassan, G. M. Maier and J. C. Jochims, *Synthesis*, 721 (1998), and references cited therein.
17. E. Benzig, *Liebigs Ann. Chem.*, **631**, 1 (1960).
18. E. Benzig, *Liebigs Ann. Chem.*, **631**, 10 (1960).
19. N. A. Al-Masoudi, N. A. Hassan, Y. A. Al-Soud, P. Schmidt, AE.-DM. Gaafar, S. Marino, A. Schoch, A. Amer and J. C. Jochims, *J. Chem. Soc. Perkins Trans. 1*, 947 (1998)
20. Y. A. Al-Soud, W. A. Al-Masoudi, R. A. EL-Halawa and N. A. Al-Masoudi, *Nucleosides & Nucleotides*, **18**, 1985 (1999).
21. N. A. Al-Masoudi, Y. A. Al-Soud and A. Geyer, *Tetrahedron*, **55**, 751 (1999).
22. Y. A. Al-Soud and N. A. Al-Masoudi, *Arch. Pharm. Pharm. Med. Chem.*, **332**, 143 (1999).
23. Y. A. Al-Soud and N. A. Al-Masoudi, *Pharmazie*, **5**, 372 (2001).
24. P. T. Izzo and V. Lee, *J. Heterocyclic Chem.*, **25**, 289 (1988).
25. W. Willker, D. Leibfritz, W. Kerssebaum and W. Bermel, *Magn. Reson. Chem.*, **31**, 287 (1993).