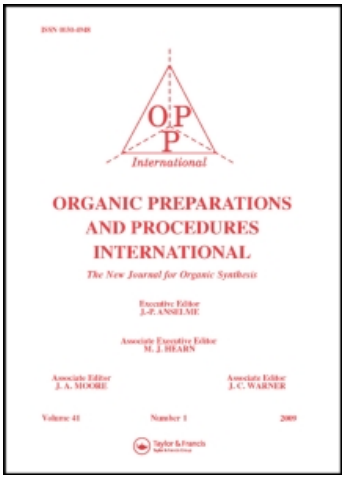

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SYNTHESIS OF 1-[4-(1,5-DIALKYL-1*H*-1,2,4-TRIAZOL-3-YL)]BENZYL-1*H*-INDOLES AND 5,6-DIHALOQUINOLONES

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

Submitted by (03/05/02)

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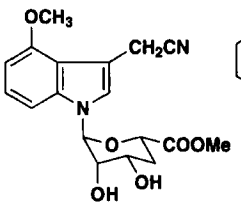
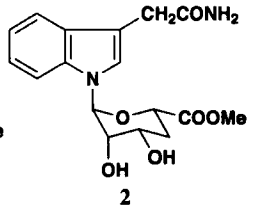
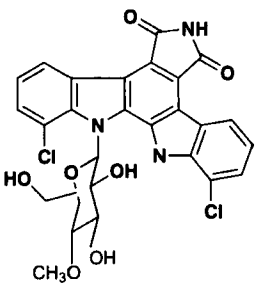
During the last decade, several synthetic nucleosides and non-nucleosides analogues have been synthesized as useful anticancer, antiviral and antibacterial chemotherapeutic agents, and some of them are anti-HIV drugs. Among these compounds are the indole and quinolone analogues, such as the naturally occuring 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*]indoles[6] proved to be effective cerebral vasodilators.



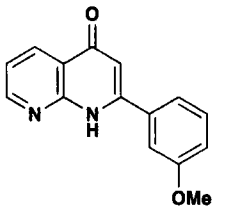
1
SF-2140



2
Neosidomycin



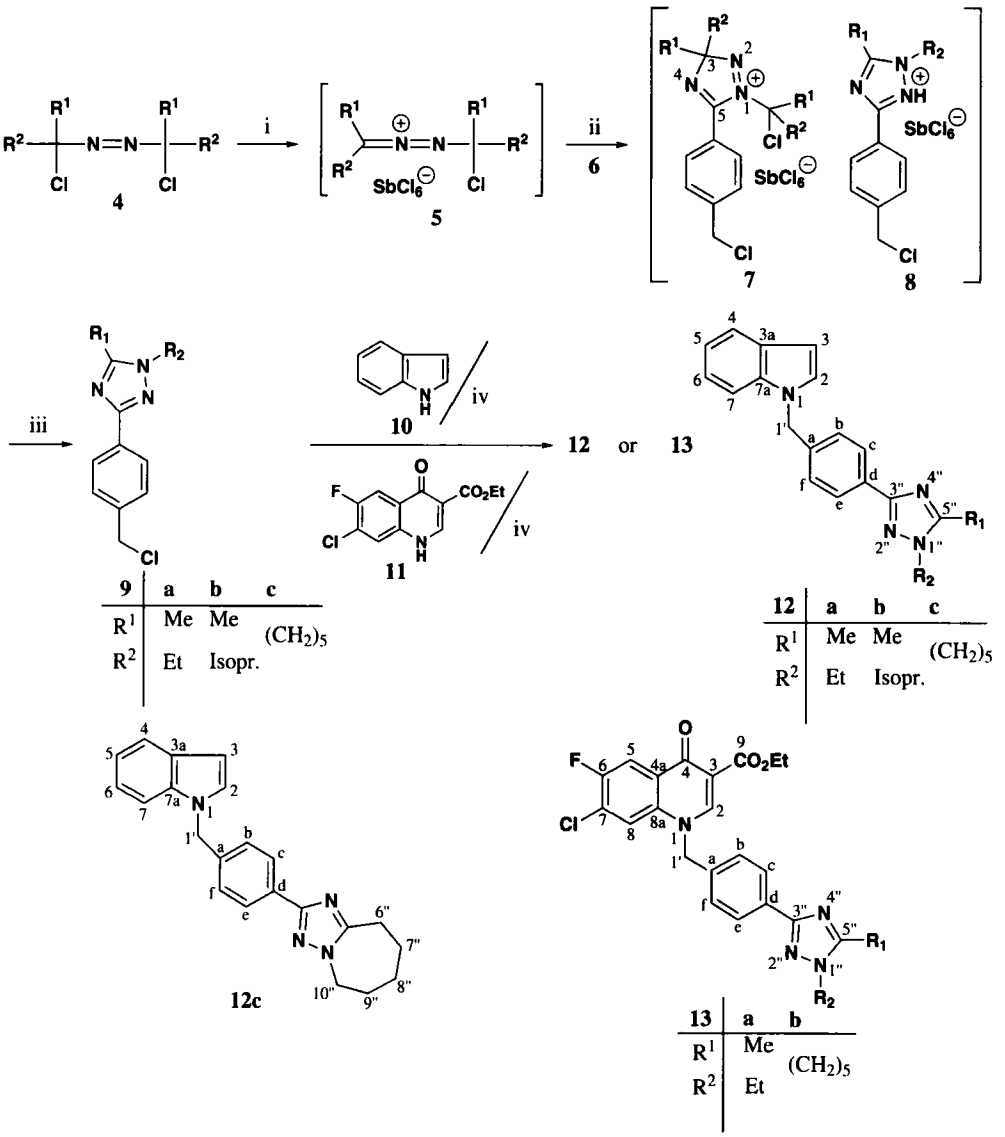
3
Rebeccamycin



4

The use of synthetic quinolones as antibacterial[7], antiviral,[8] or anticancer agents,[9a] such as naphthyridinone isostere **4**[9b] and dehydrogenase inhibitors[10] 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 μg/mL) and HIV-2 (EC_{50} > 1.0 μg/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 1*H*-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 $SbCl_5$; similarly some 1,2,4-triazolo C-nucleosides[19] 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 phthalimides[23] from cycloaddition of the intermediates **5** with glycosyl cyanide, acyclic (2-hydroxyethoxy)alkyl cyanides, 1-(cyanomethyl)thymine,



Reagents and conditions: i) $SbCl_5$, CH_2Cl_2, -60°; ii) *p*-cyanobenzyl chloride (6), CH_2Cl_2, -60° to 23°; iii) $NaHCO_3$, NH_3, 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] migration[16] 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 spectrum[25] and mass spectra (see Table 1 and 2). The ^1H NMR spectra of **12a-c** showed similar patterns. The CH_2-1' 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 ~ 3.0 Hz) were attributed to H-2 (indole ring), whereas the doublets at δ 6.44, 6.46 and 6.48 (J ~ 3.0 Hz) were indentified 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 Sectral Data of Compounds (**9-13**)[a]

Cmpd	Yield (%)	mp (°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, C_5-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, $CH(Me)_2$]; 2.63 (s, 3H, C_5-Me); 1.61 [d, 6H, J = 6.8 Hz, $CH(Me)_2$]
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, $ArH_{b,f}$); 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, $ArH_{c,e}$); 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, CH_2-1'); 4.11 (q, 2H, J = 7.3 Hz, $N^{1"}CH_2CH_3$); 2.41 (s, 3H, $C_{5"}$-Me); 1.33 (t, 3H, $N^{1"}$-CH_2CH_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 = 3.3Hz, 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, $CO_2CH_2CH_3$, H-10"a, H-10"b); 4.17 (q, 2H, J = 7.5 Hz, $N^{1''}$-CH_2CH_3); 2.41 8s, 3H, $C_{5''}$-Me); 1.32 (t, 3H, $N^{1''}$-CH_2CH_3); 1.28 8t, 3H, $CO_2CH_2CH_3$)
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, $CO_2CH_2CH_3$, H-10"a,, 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, $CO_2CH_2CH_3$)

a) Solvent: $CDCl_3$ for **9**; DMSO-d_6 at 600 MHz for **12** and **13**.

EXPERIMENTAL SECTION

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

Preparation of 1,5-Dialkyl-3-[(4-chloromethyl)phenyl]-1*H*-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 mml) in 20 mL of CH_2Cl_2 was added dropwise a solution of $SbCl_5$ (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 ($R^1 = CH_3$, $R^2 = C_2H_5$): From **4a** (0.66 g, 3.0 mmol). Yield: 0.56 g.

Anal. Calcd for $C_{12}H_{14}ClN_3$: C, 61.15; H, 5.99; N, 17.83. Found: C, 60.93; H, 5.89; N, 17.72

9b [$R^1 = CH_3$, $R^2 = CH(CH_3)_2$]: From **4b** (0.72 g, 3.0 mmol). Yield: 0.57 g.

Anal. Calcd for $C_{13}H_{16}ClN_3$: C, 62.52; H, 6.46; N, 16.83. Found: C, 62.31; H, 6.38; 16.72

9c ($R^1 = R^2 = (CH_2)_5$]: From **4c** (0.79 g, 3.0 mmol). Yield: 0.55 g.

Anal. Calcd for $C_{14}H_{16}ClN_3$: 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-1*H*-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 SiO_2 column using $CHCl_3$-MeOH (9:1) as eluent to give a colorless solid, which was recrystallized from CH_2Cl_2-ether to afford **12** or **13**.

12a ($R^1 = CH_3$, $R^2 = C_2H_5$): From **9a** (0.56 g, 2.40 mmol). Yield: 0.57 g.

Anal. Calcd for $C_{20}H_{20}N_4$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.81; H, 6.29; N, 17.58.

12b [$R^1 = CH_3$, $R^2 = CH(CH_3)_2$]: From **9b** (0.69 g, 2.40 mmol). Yield: 0.43 g.

Anal. Calcd for $C_{21}H_{22}N_4$: C, 76.35; H, 6.71; N, 16.96. Found: C, 76.21; H, 6.62; N, 16.76.

12c [$R^1 = R^2 = (CH_2)_5$]: From **9c** (0.63 g, 2.40 mmol). Yield: 0.57 g.

Anal. Calcd for $C_{22}H_{22}N_4$: 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-1*H*-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 $C_{24}H_{22}ClFN_4O_3$: 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-5*H*-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 $C_{26}H_{24}ClFlN_4O_3$: C, 63.09; H, 4.89; N, 11.32. Found: C, 62.88; H, 4.75; N, 11.21.

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