1-Proprargyloxy-forskolin (1) on reaction with different substituted azides (2a-e) gave 1,4-disubstituted triazol-forskolins (3a-e) and 1-propargyl-6-acetyl-7-deacetyl-forskolin (4) on reaction with different alkyl azides (2a-e) in presence of CuSO₄·5H₂O and sodium ascorbate in water gave 1,4-disubstituted triazol-forskolins (5a-e) in good yields.

**Keywords:** 1-Proprargyloxy-forskolin, 1-propargyl-6-acetyl-7-deacetyl-forskolin, CuSO₄·5H₂O

**INTRODUCTION**
Coleus forskohlii know as phashanabedi (telugu) a medicinal plant found in the Indian subcontinent is widely used in the Indian system of medicine. Forskolin a major diterpenoid isolated from the roots of Coleus forskohlii, directly activates the enzyme adenylyl cyclase thereby increasing the intracellular level of cAMP and leading to various physiological effects. It has hypertensive, positive inotropic, and intraocular pressure lowering activity, anti glaucoma cardiovascular and ant obesity activity.

With a view to synthesize novel triazole substituted forskolins, the click reaction strategy has been adopted. It was planned to introduce a propargyl moiety (CH=CH=H) at C-1 OH of forskolin, since it was earlier reported that the order of OH reactivity is OH-1>OH-6>OH-9. In view of the presence of several functional groups and three free hydroxyls, we expected problems of regioomers formation, elimination and rearrangements in the first step of the semi synthetic work on forskolin. The resulting 0-CH₃=C=CH moiety is proposed to be reacted with a wide range of alkyl azides(R-N₃) under the click reaction conditions to give regioselectively 1,4-disubstituted 1,2,3-triazol.

**RESULTS AND DISCUSSION**
Synthesis of 6-acetyl-7-deacetyl-1,4-disubstituted 1,2,3-triazolo-forskolins (6a-e)

1-Proprargyloxy-forskolin (1) on reaction with different alkyl azides (2a-e) in presence of CuSO₄·5H₂O and sodium acerate in water:t-butanol (1:1) medium gave 1,4-disubstituted triazolo-forskolins (6a-e). N-butyl-phthalimido-1,2,3-triazolo-7-deacetyl-6-acetyl-1,4-disubstituted forskolin (6a) its IR peaks at 3458 cm⁻¹ (OH), at 1735 cm⁻¹ (C=O ester), 1708 cm⁻¹ (C=O, ketone) and 1685 cm⁻¹ (C=O amide). In the ¹H NMR the triazol ring proton appeared at 8.74 as singlet, the phthalimide protons appeared as δ 8.14 N-ChH at δ 4.39. The protons of the 7-deacetyl-6-acetyl forskolin moiety are δ 6.79 (s, 9-0H) δ 6.12 (dd, H-14), δ 5.80 (d, H-7), δ 5.12 (dd, H-15 trans), δ 4.90 (dd, H-15 cis) δ 2.07 (6a-OOC); δ 1.54 (8-,CH₃), δ 1.40 (s, 10-ChH), δ 1.36 (s,13-ChH ), δ 1.08 (s, 4e-CH₃) and δ 1.08 (s, 4a-CH₃).

In ¹³C NMR the carbon signal assignments for the phthalimido triazole moiety as δ 147.1(C-7), δ 122.4(C5-7) δ 168.1(CO) and the carbon signal assignment for the 7-deacetyl-6-acetyl forskolin moiety δ 206.3 (CO), δ 170.3 (OCO) δ 143.7(C14), δ 109.7(C15) δ 32.6(4a-CH₃), δ 30.7 (13'-CH₃), δ 25.5(4e-CH₃) , δ 21.3 (COCH₃), δ 20.4 (8-CH₃) and δ 19.7 (10-ChH).

**MATERIAL AND METHODS**

**General:** Melting points were determined on a Polmon instrument (model no. MP-96). IR spectra were recorded on Perkin-Elmer 337 spectrometer, and ¹H NMR (400 MHz) and ¹³C NMR (100.6 MHz) were recorded on a Varian Gemini 200 spectrometer using TMS as internal standard (chemical shifts values were described in ppm 8). Mass spectra were recorded on a VG Micromass LCMS 2010 instrument.

I. General procedure for the synthesis of 1,4-disubstituted-1,2,3-triazole-forskolins (3a-e)

1-Proprargyloxy-forskolin (1) (0.29, 0.45 mmol) and N-butylation-phthalimido (2a) (0.10g, 0.45 mmol) were suspended in a 1:1 mixture of water and tert-butanol (5 mL). Sodium ascorbate (0.3mmol) was added, followed by copper (II) sulfate pentahydrate (7.5 mg, 0.03 mmol). The heterogeneous mixture was stirred vigorously overnight, at which point it cleared and TLC analysis indicated complete consumption of the reactants. The reaction mixture was diluted with water (50 mL), cooled in ice, and the white precipitate was collected by filtration. After washing the precipitate with cold water (2 x 25 mL), it was dried under vacuum to afford (0.27 g, 87%) of pure product 3a as white powder, mp 170 °C.
i) [1-{4- phthalimidobutyloyl}-1H-1,2,3-triazol-4-yl] methoxy-1-forskolin (3a)

IR (KBr): 3458 cm⁻¹(ΟΗ), 1735 cm⁻¹(ΟCO), 1708 cm⁻¹(ΟCO), 1685 cm⁻¹(NCO).

1H NMR (400 MHz): δ 7.83 (dd, J=5.8 Hz, 5.8 Hz, 4.4 Hz, 3.4 Hz), 7.77 (t, J=5.8 Hz, 1.2 Hz, 1.0 Hz, 0.9 Hz, 0.9 Hz, 0.8 Hz, 0.8 Hz)

Employing the similar procedure as mentioned for 3a, compounds 3b-e were obtained from 1 and 5b-e obtained from 4 as solids.

ii) 1-Benzyl-1H-1,2,3-triazol-4-yl] methoxy-1-forskolin (3b):

White solid, mp 73°C, 90% yield.

IR (KBr): 3326 cm⁻¹(ΟΗ), 1734 cm⁻¹(ΟCO), 1712 cm⁻¹(ΟCO).

1H NMR (400 MHz): δ 7.18 (s, J=5.8 Hz, 5.8 Hz, 4.4 Hz, 3.4 Hz), 7.77 (t, J=5.8 Hz, 1.2 Hz, 1.0 Hz, 0.9 Hz, 0.8 Hz, 0.8 Hz)

iii) [1-{4-{3-allyloxy-2-propyl]-1H,1,2,3-triazol-4-yl}] methoxy-1-forskolin (3c):

White solid, mp 173°C, 82% yield.

IR (KBr): 3329 cm⁻¹(ΟΗ), 1735 cm⁻¹(ΟCO), 1712 cm⁻¹(ΟCO).

1H NMR (400 MHz): δ 7.40 (s, J=5.8 Hz, 5.8 Hz, 4.4 Hz, 3.4 Hz), 7.77 (t, J=5.8 Hz, 1.2 Hz, 1.0 Hz, 0.9 Hz, 0.8 Hz, 0.8 Hz)

DIPS MS: m/z 582 [M]+.

iv) [1-{4-{4-allyloxy-2-propyl]-1H,1,2,3-triazol-4-yl}] methoxy-1-forskolin (3d):

White solid, mp 59°C, 86% yield.

IR (KBr): 3337 cm⁻¹(ΟΗ), 1734 cm⁻¹(ΟCO), 1713 cm⁻¹(ΟCO).

1H NMR (400 MHz): δ 7.40 (s, J=5.8 Hz, 5.8 Hz, 4.4 Hz, 3.4 Hz), 7.77 (t, J=5.8 Hz, 1.2 Hz, 1.0 Hz, 0.9 Hz, 0.8 Hz, 0.8 Hz)

DIPS MS: m/z 582 [M]+.

v) [1-{4-{4-allyloxy-2-propyl]-1H,1,2,3-triazol-4-yl}] methoxy-1-forskolin (3e):

Light yellow solid, mp 125°C, 80% yield.

IR (KBr): 3356 cm⁻¹(ΟΗ), 1748 cm⁻¹(ΟCO), 1715 cm⁻¹(ΟCO).
**vi.** [1-j-4-phthalimidobutyl]-1H-2,3-triazolo-4-yl methoxy-1-(6-acetyl-7-deacetyl-forskolin (Sa)

White solid, mp 177 °C. 84 % yield.

IR (KBr): 3432 cm⁻¹ (OH), 1732 cm⁻¹ (CO). 1711 cm⁻¹ (CO).

1H NMR (400 MHz, CDCl₃): 7.37 (s, H-5), 7.37-7.34 (m, 3,4,5'-H). 7.27-7.24 (m, 2', 6'-H). 6.67 (s, 9-OH). 6.06 (d, J=17.2Hz, 10-H). 5.75 (m, 4-H). 5.49 (s, N-C'H). 5.07 (dd, J=17.3Hz, 12-H, 15-H). 4.85 (dd, J=12.0Hz, 109.7(C-14), 133.9(C-14), 133.5(C-14), 131.9(C-14), 129.0(C-3), 72.8(C-7), 12.8(C-2), 122.3(C-4), 109.7(C-15), 85.6(C-9), 82.2(C-13), 81.8(C-14), 75.4(C-7), 4.12(C-8), 1.31(C-9), 0.99 (s, 4e-CH3). 1.35 (s, 13-CH3). 0.68 (s, 4e-CH3).

C NMR (100 MHz, CDCl₃): 170.6(CO), 173.0(CO). 170.3(C-14). 134.5 (C-11) 139.2(C-14). 141.4(C-14). 131.5(C-15). 129.0(C-3). 72.8(C-7). 12.8(C-2). 122.3(C-4). 109.7(C-15). 85.6(C-9). 82.2(C-13). 81.8(C-14). 75.4(C-7). 4.12(C-8). 1.31(C-9). 0.99 (s, 4e-CH3). 1.35 (s, 13-CH3). 0.68 (s, 4e-CH3).

Dip MS: m/z 582 [M+H].

**vii.** (1-Benzy1-1H-2,3-triazolo-4-yl) methoxy-1-(6-acetyl-7-deacetyl-forskolin (5b):

White solid, mp 177 °C. 84 % yield.

IR (KBr): 3342 cm⁻¹ (OH), 1732 cm⁻¹ (CO). 1711 cm⁻¹ (CO).

1H NMR (400 MHz, CDCl₃): 7.37 (s, H-5), 7.37-7.34 (m, 3,4,5'-H). 7.27-7.24 (m, 2', 6'-H). 6.67 (s, 9-OH). 6.06 (d, J=17.2Hz, 10-H). 5.75 (m, 4-H). 5.49 (s, N-C'H). 5.07 (dd, J=17.3Hz, 12-H, 15-H). 4.85 (dd, J=12.0Hz, 109.7(C-14), 133.9(C-14), 133.5(C-14), 131.9(C-14), 129.0(C-3), 72.8(C-7), 12.8(C-2), 122.3(C-4), 109.7(C-15), 85.6(C-9), 82.2(C-13), 81.8(C-14), 75.4(C-7), 4.12(C-8), 1.31(C-9), 0.99 (s, 4e-CH3). 1.35 (s, 13-CH3). 0.68 (s, 4e-CH3). 0.98 (s, 4e-CH3).

C NMR (100 MHz, CDCl₃): 170.6(CO), 173.0(CO). 170.3(C-14). 134.5 (C-11) 139.2(C-14). 141.4(C-14). 131.5(C-15). 129.0(C-3). 72.8(C-7). 12.8(C-2). 122.3(C-4). 109.7(C-15). 85.6(C-9). 82.2(C-13). 81.8(C-14). 75.4(C-7). 4.12(C-8). 1.31(C-9). 0.99 (s, 4e-CH3). 1.35 (s, 13-CH3). 0.68 (s, 4e-CH3).

Dip MS: m/z 582 [M+H].

**ix.** 1-Allyl-1H-2,3-triazolo-4-yl methoxy-1-(6-acetyl-7-deacetyl-forskolin (5c):

Yellow solid, mp, 89 °C 83 % yield.

IR (KBr): 3470 cm⁻¹ (OH), 1735 cm⁻¹ (CO), 1715 cm⁻¹ (CO).

1H NMR (400 MHz): 7.54 (s, H-5), 6.65 (s, 9-OH). 6.10 (m, H-14, 17-CH3). 5.80 (br, H-17, 5.36 (m, CH-1), 5.11 (d, J=17.6Hz, 15-H). 4.95 (d, J= 5.2 Hz, N-C'H). 4.71 (d, J=10.8Hz, 15-H). 4.49 (d, J=12.0Hz, 1OH-C). 4,42 (m, H-6), 4.36 (m, H-13). 3.17 (d, J=16.8Hz, 12-H). 2.43 (d, J=16.8Hz, 12-H). 2.28 (d, J=2.2Hz, 5-H). 2.16 (s, COCH3). 1.55 (s, 8-CH3). 1.48 (s, 10-CH3). 1.38 (d, J=13.0Hz, 3-H). 1.02 (s, 4e-CH3). 0.97 (4e-CH3).

C NMR (100 MHz): 135.6(CO), 170.0(C-14), 134.7(C-14), 131.3 (C-10). 122.3(C-4), 120.3(C-7). 37.5(C-10), 37.7(C-13). 31.8(C-12). 30.1(C-8). 29.3(C-11).