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THE SYNTHESIS OF NOVEL, RIGID AND WATER SOLUBLE ANALOGUES OF COLEONOL (FORSKOLIN)*

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Abstract : The synthesis of new, rigid and water soluble analogues (**3-6**) of coleonol (forskolin) were carried out and evaluated for their antihypertensive activity. Among all the tested compounds, only **4** exhibited hypotensive activity.

Coleonol (forskolin) (**1**), a major labdane diterpenoid isolated from the roots of Coleus forskohlii[1,2], exhibited hypotensive, nonspecific spasmolytic[3], positive inotropic, intraocular pressure lowering, bronchospasmolytic and adenylate cyclase stimulant activity[4]. In view of its unique adenylate cyclase action, forskolin has been an attractive target for the structure-activity relationship studies[5].

There has been a controversy regarding the identities of coleonol and forskolin. But recently it has been found that both possess identical physical and chemical properties[6,7] and are represented by the common structure **1**[8].

Coleonol (forskolin), though a very potent biochemical tool to study the regulations of the enzymes, its poor solubility in pharmaceutically suitable solvents limits it to undergo detailed biological studies. It was, therefore, decided to have piperazines at position C-15, after converting four hydroxyls

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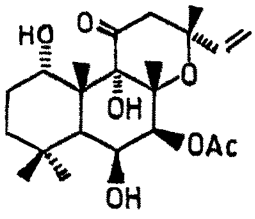
into isopropylidene groups (Scheme - 1). The piperazine pharmacophore was chosen because of its established use in CVS chemotherapy as well as the hydrochloride of piperazines becomes water soluble. For this reason, the water soluble analogue of coleonol (**6**) was prepared and its activity is reported in this paper.

Forskolin (**1**) was isolated from Coleus forskohlii as described earlier[1,2]. It was hydrolysed with 1N methanolic NaOH to afford 7-deacetyl coleonol (tetraol) (**2**). Tetraol (**2**) was then treated with acetone in the presence of conc. H_2SO_4, which gave 1,9,6,7-diisopropylidene coleonol (**3**) and 6,7-mono-isopropylidene coleonol (**4**) in 55% and 24% yield respectively. The reaction of **3** with meta-perchlorobenzoic acid in methanol yielded 1,9,6,7-diisopropylidene coleonol-14,15-epoxide (**5**) (75%) which was then allowed to react with phenyl piperazine to yield 1,9,6,7-diisopropylidene-14-hydroxy-15-(1-phenylpiperzine-4-yl) coleonol (**6**) in 65% yield. Treatment of **6** with methanolic HCl gave its hydrochloride.

^1H NMR and mass spectra confirmed the structures of all the synthesized compounds[9].

The antihypertensive activity of new analogues of coleonol was also tested according to standard pharmacological procedures[10]. Only **4** demonstrated 64 mm Hg fall for 5 and 14 minutes at 0.5 and 2.5 mg/kg, i.v. while **6** showed 14 mm Hg fall for 10 minutes at 0.5 mg/kg, i.v.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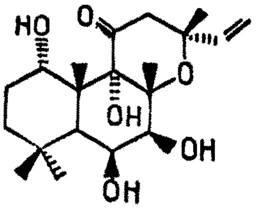
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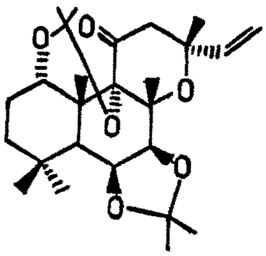
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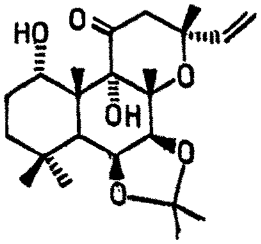
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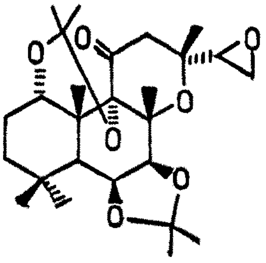
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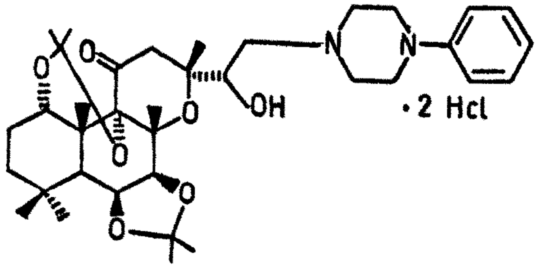

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(9) ^{1}H NMR and mass spectral data are the following : 3, (400 MHz, CDCl$_3$) : 1.02 (s, 3H, CH$_3$), 1.20 (s, 3H, CH$_3$), 1.30 (s, 3H, CH$_3$), 1.36-1.42 (m, 15H, 5 x CH$_3$), 1.51 (s, 3H, CH$_3$), 4.36 (d, 1H, J = 4 Hz, H-7), 4.40 (d, 1H, J = 6 Hz, H-1), 4.58 (dd, 1H, J = 4 & 2 Hz, H-6), 4.95 (dd, 1H, J = 1.5 & 10 Hz, H-15), 5.23 (dd, 1H, J = 1.5 & 17 Hz, H-15), 6.02 (dd, 1H, J = 17 & 10 Hz, H-14). Mass (m/z) : 448 (M$^+$), **4**, (400 MHz, CDCl$_3$) : 1.06 (s, 3H, CH$_3$), 1.30 (s, 6H, 2 x CH$_3$), 1.38 (s, 6H, 2 x CH$_3$), 1.46 (s, 3H, CH$_3$), 1.58 (s, 3H, CH$_3$), 4.01 (d, 1H, J = 4 Hz, H-7), 4.30 (br, 1H, H-1), 4.48 (br, 1H, H-6), Mass (m/z) : 408 (M$^+$). **5**, (90 MHz, CDCl$_3$ + DMSO-d$_6$) : 0.96 (s, 3H, CH$_3$), 1.08 (s, 3H, CH$_3$), 1.14 (s, 3H, CH$_3$), 1.26 (s, 12H, 4 x CH$_3$), 1.34 (s, 3H, CH$_3$), 1.42 (s, 3H, CH$_3$), 2.90-3.30 (m, 4H, H-12ax & oxiran), 4.55 (dd, 1H, J = 4 & 2 Hz, H-6). Mass (m/z) : 464 (M$^+$). **6**, (400 MHz, CDCl$_3$) : 1.08 (s, 3H, CH$_3$), 1.20 (s, 3H, CH$_3$), 1.27 (s, 3H, CH$_3$), 1.35 (s, 3H, CH$_3$), 1.40 (s, 3H, CH$_3$), 1.43 (s, 3H, CH$_3$), 1.48 (s, 6H, 2 x CH$_3$), 1.55 (s, 3H, CH$_3$), 2.40-2.85 (m, 5H, N-(CH$_2$) & H-5), 3.25 (m, 2H, CH$_2$-15), 3.53-3.94 (m, 5H, Ph-N-(CH$_2$)$_2$ & CHOH-14), 6.82-7.00 (m, 3H, Ar-H), 7.20-7.35 (m, 2H, Ar-H). Mass (m/z) : 626 (M$^+$).

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