New flavone and phenolic esters from *Callistemon lanceolatus* DC: Their molecular docking and antidiabetic activities

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**Keywords**

*Callistemon lanceolatus*; Flavone; Phenolic esters; PPAR-γ; Antidiabetic

**Abstract**

Phytochemical investigation of the antidiabetic chloroform fraction of the ethanolic extract obtained from the aerial parts of *Callistemon lanceolatus* DC led to the isolation of three new phytoconstituents, one flavone, 8-(1’00-hydroxyisopranyl)-5,6-dihydroxy-7,4’0-dimethoxy flavone (1) and two phenolic esters, 2,3,4-trihydroxyphenethyl tetracontanoate (2) and 2,3,4-trihydroxyphenethyl tetracontanoate-4-β-xylopyranoside (3). The isolated compound 1 exhibited significant *in vivo* blood glucose lowering effect comparable to the standard drugs Pioglitazone and Rosiglitazone in streptozotocin induced diabetic rats without causing any toxic effect on the pancreas and liver. Compound 1 showed a glide score of −7.89 against PPAR-γ target in molecular docking studies which is significantly higher than the glide score of reference molecule Rosiglitazone (glide score of −5.77). Compound 1 also exhibited moderate *in vitro* PPAR-γ transactivation activity of 48.52% in comparison with standard drugs rosiglitazone and pioglitazone, which showed a transactivation activity of 80.47% and 65.27%, respectively.

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**1. Introduction**

The genus *Callistemon* belongs to family Myrtaceae and comprises over 30 species. These are woody aromatic trees or shrubs and widely distributed all over the world (Anonymous, 1992). The plant is used for ornamental purposes, and has applications in folk medicine as antidiabetic...
(Nazreen et al., 2011), antimicrobial, antiinflammatory, anti-staphylococcal, and antithrombin (Kobayashi et al., 2006; Gomber and Saxena, 2007; Saxena and Gomber, 2006; Chistokhodova et al., 2002). It is also used for nematicidal, larvicidal and pupicidal effects (Sangwan et al., 1990). Previous phytochemical studies on different parts of Callistemon lanceolatus (commonly known as Red bottlebrush) have led to the isolation of C-methyl flavonoids, triterpenoids, tannins and phloroglucinol derivatives (Wrigley and Fagg, 1993; Huq and Misra, 1997; Wollenweber et al., 2000; Younes, 1975).

In our earlier studies we have reported the isolation of two new antidiabetic flavones from the chloroform fraction of the ethanolic extract of this plant (Nazreen et al., 2012). In continuation to our earlier studies, we report herein the presence of a new flavone and two new phenolic esters from the chloroform fraction of the ethanolic extract of this plant. These isolated compounds have been evaluated for in vivo antidiabetic potential, molecular docking study and in vitro Peroxisome Proliferator Activated Receptor (PPAR-γ) transactivation activity.

2. Experimental

2.1. General

Melting points were determined on Veego VMP-III and were uncorrected. UV spectra were measured on DV 20 Spectroscan spectrophotometer. IR spectra were recorded on Bruker spectrometer using KBr disc. $^1$H NMR, $^{13}$C NMR and 2D NMR were recorded on a Bruker AM-400 (400 MHz) spectrometer with TMS as the internal standard and chemical shifts are recorded on a Bruker AM-400 (400 MHz) spectrometer. IR spectra were recorded on Bruker spectrophotometer. Mass spectra were recorded on a Jeol JMS-D 300 instrument fitted with a JMS 2000 data system. Melting points were determined on Veego VMP-III and were uncorrected.

2.2. Plant material

The aerial parts of C. lanceolatus DC were collected from Saket Nursery, New Delhi in March 2010 and authenticated by Dr. H. B. Singh, Taxonomist, National Institute of Science Communication and Information resources, New Delhi. A voucher specimen (No. 1386/188) has been deposited in the author’s laboratory.

2.3. Extraction and Isolation

The air dried and powdered aerial parts of C. lanceolatus DC (5 kg) were extracted with 95% ethanol in a Soxhlet apparatus. The ethanolic extract was concentrated under reduced pressure to yield a brown viscous mass (550 g). The ethanolic extract was fractionated with petroleum ether (3 × 1.0 L), CHCl$_3$ (3 × 1.0 L), and MeOH (3 × 1.0 L) to furnish petroleum ether fraction (200 g), CHCl$_3$ fraction (150 g) and MeOH fraction (102 mg; R$_f$ 0.42; n-hexane-EtOAc, 3.5:1.5). Fraction 2b was further CC and recrystallized to yield 3 (90 mg; R$_f$ 0.42; n-hexane-EtOAc, 3.5:1.5).

2.3.1. Compound 1

Yellow crystals; m.p. 135–136°C; UV (MeOH) $\lambda_{max}$: 286, 323 nm; IR (KBr) $\nu_{max}$ (cm$^{-1}$): 3432 (OH), 1670 (C=O), 1075 (C–O); $^1$H and $^{13}$C NMR (CDCl$_3$); see Table 1; FAB MS (positive): $m/z$ 400 [M$^+$]$^+$ (calcd 400.42 for C$_{22}$H$_{24}$O$_7$), 313 [M-C$_6$H$_{11}$O]$^+$, 166 [181-Me]$^+$, 117 [132-Me]$^+$.

2.3.2. Compound 2

Silver colored crystals; m.p. 79–80°C; UV (MeOH) $\lambda_{max}$: 278 nm; IR (KBr) $\nu_{max}$ (cm$^{-1}$): 3460 (OH), 1729 (C=O), 1178 (C–O); $^1$H and $^{13}$C NMR (CDCl$_3$); see Table 2; FAB MS (positive): $m/z$ 744 [M$^+$]$^+$ (calcd 744.66 for C$_{46}$H$_{36}$O$_9$).

2.3.3. Compound 3

Orange flakes; m.p. 88–89°C; UV (MeOH) $\lambda_{max}$: 264 nm; IR (KBr) $\nu_{max}$ (cm$^{-1}$): 3437 (OH), 1722 (C=O), 1015 (C–O); $^1$H and $^{13}$C NMR (CDCl$_3$); see Table 2; FAB MS (positive): $m/z$ 876 [M$^+$]$^+$ (calcd 876.66 for C$_{53}$H$_{38}$O$_{15}$).

2.3.3.1. Acid hydrolysis of 3. Compound 3 was refluxed with 2 N HCl in 80% MeOH for one hour. After cooling, the reaction mixture was poured into crushed ice, and the hydrolysate was then extracted with EtOAc to give the aglycone, compound 2. The sugar in the concentrated water-soluble portion was compared with standard sugars on a TLC plate with the same solvent, followed by crystallization in CHCl$_3$–MeOH yielded compound 2 (102 mg; R$_f$ 0.83; n-hexane-EtOAc, 3.5:1.5). Fraction 2b was further CC and recrystallized to yield 3 (90 mg; R$_f$ 0.42; n-hexane-EtOAc, 3.5:1.5).

2.4. Antidiabetic activity

The antidiabetic activity was performed in streptozotocin (STZ) induced diabetic rats as per the previously reported method (Nazreen et al., 2011).

2.4.1. Experimental protocol

The rats were divided into seven groups comprising of five animals each.

Group I: Control rats receiving 0.1 M citrate buffer (pH 4.5).

Group II: Diabetic controls receiving STZ (60 mg/kg b.w.) intraperitoneally.

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New flavone and phenolic esters from Callistemon lanceolatus DC.

Group III: Diabetic rats given compound 1 (40 mg, equimolar to standard drug Pioglitazone) in aqueous solution orally.

Group IV: Diabetic rats given compound 2 (75.23 mg, equimolar to standard drug Pioglitazone) in aqueous solution orally.

Group V: Diabetic rats given compound 3 (88.58 mg, equimolar to standard drug Pioglitazone) in aqueous solution orally.

Group VI: Diabetic rats given standard drug pioglitazone (36 mg/kg b.w.) in aqueous solution orally.

Group VII: Diabetic rats given standard drug rosiglitazone (36 mg/kg b.w.) in aqueous solution orally.

The compounds (1-3) were administered a single dose on the 1st day and the blood glucose level was measured on the 1st, 7th and 15th day of the experiment as per standard protocols by glucose oxidase method (Dahlqvist, 1961).

At the end of the experimental period, the rats were anesthetized and sacrificed by cervical dislocation. Organs (pancreas and liver) were removed for histopathological evaluation.

2.5. Molecular docking study

Molecular docking studies involve mainly protein selection & preparation, grid generation, ligand preparation, docking & further analysis of docking studies. Schrodinger Software was mainly used for all the above steps. Protein with Accession number 3CS8 was selected and downloaded from Protein Data Bank, and is reported to bind with the drug Rosiglitazone. The protein was imported, optimized, minimized while removing unwanted molecules and other defects reported by the software. Molecules drawn in 3D form were refined by LigPrep module. The molecules were subjected to OPLS-2005 force field to generate single low energy 3-D structure. Docking study was done using Extra precision and Write XP descriptor information. This generates favourable ligand poses which are further screened through filters to examine spatial fit of the ligand in the active site. Ligand poses which pass through initial screening are subjected to evaluation and minimization of grid approximation. Scoring is then done on energy minimized poses to generate glide score.

2.6. PPARγ transactivation assay

Human embryonic kidney (HEK) 293 cells were cultured in DMEM with 10% heat inactivated foetal bovine serum in a humidified 5% CO₂ atmosphere at 37 °C. Cells were seeded in 6-well plates the day before transfection to give a confluency of 70–80% at transfection. Cells grown in Dulbecco’s Modified Eagle’s Medium (DMEM) were inoculated in 96-well plate containing 60,000 cells/well. Cells were transfected with 2.5 μL of Peroxisome Proliferator Response Element-Luciferase (PPRE-Luc), 6.67 μL of PPAR-γ 1.0 μL of Renilla and 20 μL of Lipofectamine. Following 5 h after transfection, cells were treated with compound (10 μM) for 24 h and then collected with Cell Culture Lysis buffer. Luciferase activity was monitored on luminometer (Perkinelmer, USA) using the luciferase kit (Promega) according to the manufacturer’s instructions. Rosiglitazone and Pioglitazone were used as standards.

2.7. Statistical analysis

Data was analysed by GraphPad Instat 3.1 software by one way ANOVA followed by Dunnett’s ‘t’ test (n = 5), *p < 0.05, **p < 0.01 significant from diabetic control.

3. Results and discussion

3.1. Structure elucidation

Compound 1 was isolated as yellow crystals and gave positive Thinodora test for flavonoids. Its UV absorption maxima at 286 and 323 nm were typical of substituted flavonones (Boue et al., 2003). The +ve FAB mass spectrum exhibited a molecular ion peak at m/z 400 consistent with the molecular formula of a flavone, C_{22}H_{20}O_{7}. The other prominent ion peaks appeared at m/z 313 [M-C_{6}H_{11}O] -, 181 [C_{6}H_{11}O] -, 166 [C_{6}H_{5}O-3,5-Me] -, 132 [C_{6}H_{9}O] -, 117 [C_{6}H_{9}O-Me] supporting the existence of two methoxy moieties in the molecule. The IR spectrum revealed absorption bands at 3432 cm⁻¹ (OH), 1670 cm⁻¹ (C=O) and 1075 cm⁻¹ (C–O) functionalities. The ¹H NMR spectrum showed the presence of four aromatic protons (ring B) at δH 7.83 (d, J = 8.2 Hz, H-2', H-6'), and δH 7.02 (d, J = 8.8 Hz, H-3', H-5') and two methoxy groups at δH 3.92 (6H, s) forming an AA’XX’ system. The presence of two aromatic OH groups at δH 12.91 (s, 5-OH) and δH 9.92 (s, 6-OH) and a olefinic proton at δH 6.57 (s, H-3) indicated 5,6-dihydroxy pattern for ring A of flavone skeleton. The presence of α-hydroxy-γ,γ-dimethylpropyl group was supported by proton signals at δH 3.85 (1H, t, J = 7.2 Hz, H-1'), δH 2.21 (1H, m, H-3'), δH 1.25 (2H, brs, H-2'), δH 6.48 (1H, s, 1H-1'), δH 0.88 (3H, d, J = 8.8 Hz, H-4') and δH 0.81 (3H, d, J = 8.4 Hz, H-5') and carbon signals at δC 89.33, 31.94, 29.71, 8.57, 7.29 respectively in the 13C NMR spectrum. The ¹H-¹H COSY spectrum of I showed correlations of H-1' (δH 3.85) with H-2' (δH 1.25) and H-3' (δH 2.21), H-4' (δH 0.88) with H-3' (δH 2.11), H-1' (δH 0.81) and H-2' (δH 1.25) and H-2' (δH 7.83) with H-3' (δH 7.02) and H-6' (δH 7.83); δH 0.8 (3H, d, J = 8.4 Hz, H-5') with H-2' (δH 7.83) and H-5' (δH 7.02). The long-range 1H-13C correlations (HMBC) of H-3 (δH 6.57) with C-2 (δH 163.60), C-1' (δH 123.75), C-4 (δH 182.40), C-10 (δH 105.32) indicated that there is a proton at C-3. The presence of two hydroxyl groups at C-5 and C-6 is based on the long range 1H-13C correlations which showed correlations of 5-OH (δH 12.91) with C-5 (δH 162.38), C-6 (δH 155.93), C-10 (δH 105.32) while 6-OH (δH 9.92) revealed correlations with C-6 (δH 155.93), C-5 (δH 162.38), C-7 (δH 163.86). The attachment of two methoxy groups at C-7 and C-4 is evident from the long range correlations observed between δH 3.92 (7-OMe) with C-7 (δH 163.86), C-6 (δH 155.93), C-8 (δH 123.87) and δH 3.92 (4'-OMe) with C-4' (δH 162.60). By analogy, the side chain at C-8 could be deduced from the long-range 1H-13C correlations between H-1" (δH 3.85) with C-8 (δH 123.87), C-9 (δH 158.76), C-7 (δH 163.86); H-2" (δH 1.25) with C-8 (δH 123.87), C-4" (δH 8.57), C-7" (δH 7.29) (Fig. 1). Thus, the compound 1 was identified as 8-(1"'-hydroxyisopropy)-5,6-dihydroxy-7,4'-dimethoxy flavone.

Compound 2 isolated as white shiny crystals exhibited a molecular ion peak at m/z 744 (caled 744.66) in its +ve FAB MS, calculated for the molecular formula C_{30}H_{82}O_{8}. It showed UV absorption maxima (MeOH) at 278 nm, and characteristic IR absorption bands at 3460, 1729 and 1178 cm⁻¹ for.
hydroxy, carbonyl and ether functionalities, respectively. The
$^1$H NMR spectrum of 2 showed the presence of only two aromatic protons at $\delta$ 7.07 (1H, d, $J = 8.4$ Hz, H-6) and $\delta$ 6.76 (1H, d, $J = 8.4$ Hz, H-5) indicating the aromatic ring is tetr substi tuted. The signals of a long alkyl side chain appeared at $\delta$
2.85 (2H, t, $J = 7.2$ Hz, H$_2$-7), 4.23 (2H, t, $J = 7.2$ Hz, H$_2$-8),
2.27 (2H, t, $J = 7.6$ Hz, H$_2$-20), 1.60 (74 H, brs, 37 $\times$ CH$_2$) for
methylene protons. A three proton signal appeared at $\delta$
0.88 (3H, t, $J = 6.3$ Hz, Me-40) for terminal methyl protons. This
data was supported by $^{13}$C NMR spectrum which exhibited
signals at $\delta$ 34.38 (C-7), $\delta$ 64.97 (C-8), 34.29 (C-20), $\delta$
31.94–22.71 (37 $\times$ CH$_2$) and $\delta$ 14.41 (Me-40). The $^{13}$C NMR spec-
trum also revealed downfield signals at $\delta$
173.97 for carbonyl
carbon (C-10), $\delta$ 156.21, 156.05 & 154.26 for three oxygenated
aromatic carbons (C-4, C-3, C-2) and $\delta$
129.99 (C-6) & 115.33
(C-5) for unsubstituted aromatic carbons. Assignment of each
substituent in the aromatic ring was determined by HSQC and
HMBC correlations (Fig. 1). From the HSQC spectrum, the
aromatic protons H-6 ($\delta$ 7.07) showed correlation with C-6
($\delta$ 129.99), H-5 ($\delta$ 6.76) with C-5 (115.33), benzylic protons
H$_2$-7 ($\delta$ 2.85) with C-7 ($\delta$ 34.38), oxygenated methane
protons H$_2$-8 ($\delta$ 4.23) with C-8 ($\delta$ 64.97), methylene protons
H$_2$-20 ($\delta$ 2.27) with C-20 ($\delta$ 34.29), remaining seventy four meth-
ylene protons ($\delta$ 1.60) with C-3$'$ to C-37$'$ ($\delta$ 31.94–22.71) and
terminal methyl protons H$_3$-40 ($\delta$ 0.88) with C-40 ($\delta$
14.41). The presence of three hydroxy groups at C-2, C-3 and C-4
was determined from the long-range $^1$H–$^{13}$C correlations
(HMBC) which showed interactions of 2-OH ($\delta$
9.42) with
C-2 ($\delta$
154.26), C-3 ($\delta$
156.05), C-1 ($\delta$
130.05); 3-OH ($\delta$
10.82) with C-3 ($\delta$
156.05), C-2 ($\delta$
154.26), C-4 ($\delta$
156.21); 4-
OH ($\delta$
11.58) with C-4 ($\delta$
156.21), C-3 ($\delta$
156.05), C-5 ($\delta$
115.33). The protons H$_2$-7 ($\delta$
2.85) exhibited HMBC correla-
tions with C-1 ($\delta$
130.05), C-2 ($\delta$
154.26), C-6 ($\delta$
129.99), C-8 ($\delta$
64.97); H$_2$-8 ($\delta$
4.23) with C-7 ($\delta$
34.38), C-1 ($\delta$
130.05), C-1$'$ ($\delta$
173.97); H$_2$-20 ($\delta$
2.27) with C-1$'$ ($\delta$
173.97), C-3$'$ to C-37$'$ ($\delta$
31.94–22.71). Thus, the compound was characterized
as 2,3,4-trihydroxyphenethyl tetracontanoate.

Compound 3 was isolated as orange flakes and gave the
molecular formula C$_{53}$H$_{96}$O$_9$ by +ve FAB MS [M]$^+$ at
$m/z$
876 (calc 877.32), which was supported by its IR and NMR
data. It showed UV absorption maxima (MeOH) at 264 nm,
and IR absorption bands at 3437, 1722 and 1015 cm$^{-1}$ for

![Figure 1](https://example.com/f1.png)

**Figure 1** COSY, HSQC and HMBC correlations of compounds 1–3.
hydroxy, carbonyl and ether functionalities, respectively. The signals in $^1$H NMR and $^{13}$C NMR spectra were similar to compound 2 except that it showed additional signals for a sugar moiety. The $^1$H NMR revealed the characteristic anomeric signal (H-1") as a doublet at $\delta_H$ 5.37 ($J = 8.7$ Hz). The H-2" appeared as doublet at $\delta$ 3.80 ($J = 5.3$, 6.1 Hz). The H-3", H-4" and H-5" were observed as multiplets at $\delta$ 3.62, 3.35 and 3.92, respectively. The $^{13}$C NMR of 3 were similar to compound 2 except that it exhibited five additional signals of the sugar unit at $\delta_C$ 108.11, 73.90, 79.94, 71.69 and 67.67 which were assigned to C-1", C-2", C-3", C-4" and C-5", respectively (Aydogmus et al., 2006). Acid hydrolysis of 3 yielded an aglycone compound 2 and xylose sugar. The aglycone moiety was confirmed from mass spectrum showing fragment ion peak at $m/z$ 744 for the molecular formula C$_{48}$H$_{87}$O$_5$. The position of glycosidation was confirmed by HMBC spectrum which showed a long range correlation of anomeric proton H-1" ($\delta$ 5.37, $J =$ 8.7 Hz) with C-4 (156.61) (Fig. 1).

Based on these evidences, compound 3 was characterized as 2,3,4-trihydroxyphenethyl tetracontanoate-4-β-xylopyranoside.

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The isolated compounds 1-3 were tested for in vivo antidiabetic activity in streptozotocin-induced diabetic rats. Compound 1 significantly lowered blood glucose level to 149.92 mg/dl ± 8.63 (p < 0.01) in comparison with standard drugs pioglitazone (132 ± 5.02) and rosiglitazone (144 ± 6.3) after 15 days of study (Fig. 2). Compound 2 and 3 lowered blood glucose level to 202 mg/dl ± 9.72 and 203 mg/dl ± 9.92, respectively. The histopathological examination of the pancreas and liver of STZ-induced diabetic rats revealed extensive alterations. STZ caused significant damage to islets of Langerhans of the pancreas showing markedly reduced islet cells, which were restored to near normal upon treatment with compound 1 and pioglitazone (Fig. 3). The liver of diabetic rats showed perivenular inflammatory infiltration filling over the sinusoidal vacuolation of the hepatocyte nuclei. The pathological changes observed in STZ-induced diabetes appeared closer to the normal after treatment with compound 1 and pioglitazone. It was observed that the compound 1 has the protective effect on the liver as well as the pancreas of the diabetic rats.

In order to validate the results of in vivo antidiabetic activity, the active compound 1 was docked for in silico studies against PPAR-γ target. PPAR-γ receptor has been found to be an important drug target for regulating fatty acid storage and glucose metabolism. On activation by ligands, this receptor leads to an increased insulin sensitivity and further glucose uptake. Molecular docking studies were done to provide insights of binding modes of molecules inside the large pocket of PPAR-γ receptors. It was observed that compound 1 showed glide core of -7.89 which is significantly higher than the glide score of standard drug Rosiglitazone (glide score of -5.77). Compound 1 was found to show π-π interaction with LYS 261 residue of the protein and is deeply buried into hydrophobic pocket of PPAR-γ receptor. The in silico ADME

### Table 1

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### Table 3

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Absorption, Distribution, Metabolism and Excretion) prediction of compound \(1\) was found to be within the acceptable range. The calculated glide score, binding energies and predicted ADME of compound \(1\) are presented in Table 3 and Fig. 4. In order to confirm the mechanism of action the compound \(1\) was evaluated for in vitro PPAR-\(\gamma\) transactivation activity. It was found to exhibit moderate in vitro PPAR-\(\gamma\) transactivation activity of 48.52% in comparison with the standard drugs Rosiglitazone and Pioglitazone, which showed a transactivation activity of 80.47% and 65.27% respectively. Compound \(1\) may have exerted the antidiabetic effect by activating PPAR-\(\gamma\) receptors.

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2014.11.029.

**References**