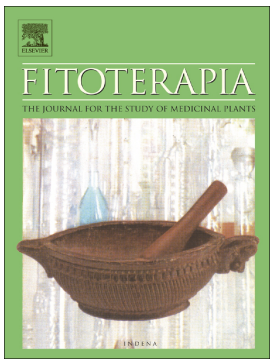

Microwave-assisted modified synthesis of C8-analogues of naturally occurring methylxanthines: Synthesis, biological evaluation and their practical applications

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PII: S0367-326X(20)30115-5

DOI: https://doi.org/10.1016/j.fitote.2020.104533

Reference: FITOTE 104533

To appear in: *Fitoterapia*

Received date: 9 January 2020

Revised date: 26 February 2020

Accepted date: 1 March 2020

Please cite this article as: B.R. Shyamlal, M. Mathur, D.K. Yadav, et al., Microwave-assisted modified synthesis of C8-analogues of naturally occurring methylxanthines: Synthesis, biological evaluation and their practical applications, *Fitoterapia* (2020), https://doi.org/10.1016/j.fitote.2020.104533

Microwave-Assisted Modified Synthesis of C_8-Analogues of Naturally Occurring Methylxanthines: Synthesis, Biological Evaluation and their Practical Applications

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Abstract – An efficient, microwave-assisted, oxidant-interceded, transition-metal-free, cross-dehydrogenative $C_{sp}{}^2$-$C_{sp}{}^3$ coupling of C_8-Caffeine **2**/Theobromine **3**/theophylline **4** with substituted aliphatic alcohols **11a-l** *via* C-H bond activation for the preparation of series of substituted C_8-(hydroxymethyl) Caffeine **12a-l** /theobromine **13a-c** /theophylline **14a-b** has been developed using microwave irradiation upto 98% yield. The reaction proceeds smoothly in the presence of *tert*-butyl hydroperoxide (TBHP) under solvolysis condition at 120 °C for 20 min to corresponding substituted C_8-(hydroxymethyl)-methylxanthine derivatives in good to excellent yields. The good substrate scope, control experiments, gram-scale synthesis and practical synthetic transformations further highlights the practicality of this methodology. These C_8-(hydroxymethyl) Caffeine **12a-l**, **13a-c** and **14a-b** have been found to show promising *in vitro* antioxidant as well as antiplatelet activities.

1. Introduction

Cross-Dehydrogenative Coupling (CDC) is a unique versatile strategy which have greatly enriched chemist's toolbox to construct most abundant, versatile, and important C-C bond in natural/synthetic motifs [1, 2, 3]. CDC methodology not only develop novel chemical reactions but also improves reaction conditions in order to make it cost-effective, maximize yield, less waste, step-/atom-economy, product selectivity, energy and resource competence, operational ease etc. Overall, it makes this reaction as environmentally benign reaction. Therefore, it had changed our perception to consider C–H bond as a functional group [4, 5, 6]. In this regard, several transition metal-catalyzed as well as metal-free or oxidant-promoted CDC reactions *via* double C-H bond activation has been reported in the literature. [1-6]

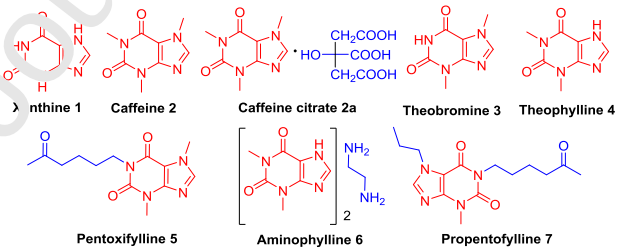

Figure 1: Structure of Xanthine and caffeine-based bioactive heterocycles **1-7**.

Xanthines, which includes caffeine, theophylline, theobromine and other related molecules **1-7**, are an important class of bioactive heterocycles which are generally present in tea, coffee, cocoa, chocolate etc. and exhibits diverse pharmaceutical activity such as anti-oxidant, adenosine receptor antagonist, anti-inflammatory, antimicrobial, anti-tumor, psycho-stimulant, cyclic nucleotide phosphodiesterase inhibition, histone deacetylase activity inducers, anti-asthmatic etc. [7] (Figure 1).

In our endeavor towards the development of novel methodologies for the synthesis of naturally occurring bioactive heterocycles *via* green approaches, Caffeine, being polar water-soluble molecule and having its versatile biological activity, was chosen as model substrate in the present study. Caffeine is a well-known central nervous system (CNS) stimulant, and used as psychoactive drug, liver protection, diabetes and Parkinson's risk reduction etc.[8] Several reports are available in the literature where caffeine has been utilized for metal-catalyzed C_8-H arylation (Pd, Ru, Cu) either with aryl halides or *via*

Keywords: Microwave, Cross-Dehydrogenative Coupling (CDC), Double C-H bond activation, TBHP, Antioxidant, Antiplatelet
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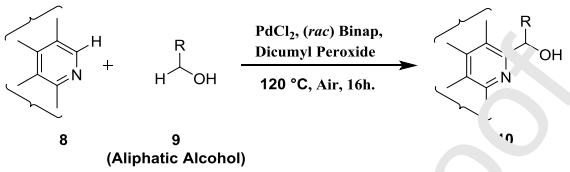
double C-H bond activation [9-15]. In addition, oxidant-promoted CDC reactions using DDQ [16], TBHP/TFA [17], TBHP [18], (DTBP) [19], molecular iodine [20] etc have also been reported.

It has been reported that the water-soluble molecules with biological origin could be potential candidates to be used as polar part (head) in the development of amphiphilic bioconjugates. These bioconjugates, then, gets self-assembled into different nanostructures in an aqueous media which can be used as delivery vehicles of the molecules of interest [21, 22]. Using this idea, we plan to synthesize caffeine-linked aliphatic alcohols for our anticancer drug delivery application *via* microwave irradiation. Thus, based on above facts, it is to be noted that no detailed study on metal-free C_8-H bond activation of caffeine with aliphatic alcohols has been carried out under microwave irradiations. Hence, the development of broad-spectrum, operationally simple, and environmentally benign rapid CDC protocol for the MW-assisted synthesis of caffeine-linked aliphatic alcohols *via* C_8-H bond activation of caffeine with aliphatic alcohols is highly desirable and is still an area of investigation.

Correia et al. reported Pd-catalyzed coupling of *N*-heterocycles with simple alcohols in the presence of (rac) binap and dicumyl peroxide as oxidant (scheme 1) [23].



Scheme 1: Palladium-catalyzed dehydrogenative coupling of *N*-heterocycles with simple alcohols.

Few metal-free methods have also been reported in the literature; however, those were associated with limited substrate scope and requires more time [24a-f]. Herein, we report the first microwave assisted cross-dehydrogenative coupling of C_8-H of methylxanthines. The protocol is simple, efficient and works with several aliphatic/alicyclic alcohols as well as cyclic ethers in excellent yields.

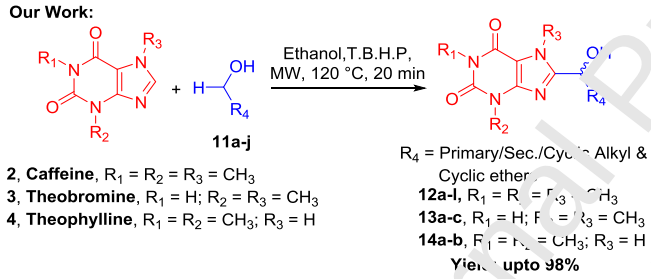


Figure 2. Schematic Representation of proposed work.

We also report the gram-scale synthesis, and practical synthetic transformation of caffeine-linked aliphatic alcohols to several moieties. For the first time, we also report the antioxidant as well as antiplatelet activities in comparison to ascorbic acid and acetyl salicylic acid taken as standard references, respectively.

2. Material and methods

2.1 Chemistry

All the glass apparatus were oven dried prior to use. Melting points were taken in open capillaries on Sisco melting point apparatus and are presented uncorrected. All the AR grade chemicals were used as supplied from commercial source (Sigma Aldrich, TCI, Alpha Aesar, Spectrochem etc.) and used without further purification. TBHP in decane (make: Sigma Aldrich) was used as an oxidant. Laboratory grade commercial reagents and solvents were purified by standard procedures prior to use. The silica gel (100-200 Mesh) used for column chromatography were supplied either from Qualigens TM (India) or Rankem (India), unless otherwise noted. UV fluorescence served as the visualizing agent for thin layer chromatography (Merck silica gel 60 F_{254} precoated plates (0.25 mm). ^{1}H NMR and ^{13}C NMR spectral data were recorded on a JEOL ECS-400 spectrometer working at 400 MHz for ^{1}H and 100 MHz for ^{13}C utilizing $CDCl_3$ and DMSO as a solvent. The ^{1}H-NMR (400 MHz) chemical shifts were measured relative to $CDCl_3$ as the internal reference ($CDCl_3$: δ = 7.246 ppm). Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), double doublet (dd), triplet (t), Quartet (q), triple doublet (td), multiplet (m), and broad (br). Infrared spectra were recorded on a FT-IR Spectrum 2 (Perkin-Elmer) spectrophotometer. Electron Impact Mass Spectroscopy (HR-EIMS) data were obtained from Xevo G2-S Q-Tof (Waters, USA) compatible with ACQUITY UPLC® and nano ACQUITY UPLC® systems. The BUCHI Rotavapor R-210 was used for drying and concentration of the solvents.

2.1 General procedures for the synthesis of 12a: Caffeine **2** (1 equiv. 50 mg) was dissolved in 2 mL of **11a** (ethanol) and TBHP (6 equiv. 375µL) was added. The reaction mixture was heated at 120 ˚C for 20 minute at 60 watt under microwave irradiation conditions. After completion of the reaction, the excess solvent was evaporated under reduced pressure. The usual work-up followed by column chromatography furnished the desired pure product **12a** (60 mg) in 98% yield.

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. Peroxy compounds should be added to the organic material, never the reverse. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Highly concentrated solutions of TBHP are potentially hazardous and can undergo violent decomposition upon exposure to certain metal salts. Strong acids must never be added to high-strength TBHP solutions. Highly concentrated solutions of TBHP are best stored in high-density polyethylene bottles rather than glass because of the potential for pressure buildup due to decomposition forming oxygen gas [25].

2.2 Characterization data:

2.2.1 ***8-(1-hydroxyethyl)-1, 3, 7-trimethyl-3, 7-dihydro-1H-purine-2, 6-dione (12a)***: This compound was prepared according to the GP. Yield 96%; White solid; m.p. 200-202 ˚C; R_f = 0.657 (4% MeOH/Chloroform), FT-IR (neat, cm^{-1}): 3392, 2987, 2934, 1704, 1644, 1218, 1093, 1036, 744, 511, 423; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.96-4.94 (m, 1H), 3.98 (s, 3H), 3.47 (s, 3H), 3.35 (s, 3H), 3.26 (br, 1H), 1.60 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.52, 155.02, 151.67, 147.29, 108.06, 63.08, 32.24, 29.80, 28.05, 21.95; HRMS (ESI) Calculated for $C_{10}H_{14}N_4O_3$ $[M+H]^+$: 239.1139, Found : 239.1137.

2.2.2 ***8-(hydroxymethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (12b)***: This compound was prepared according to the GP. Yield 91%; White solid; m.p. 244-246 ˚C; R_f = 0.32 (4% MeOH/Chloroform), FT-IR (neat, cm^{-1}): 3289, 2957, 1699, 1651, 1545, 1439, 1218, 1028, 961, 745, 498, 463, 409; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.75 (t, *J* = 6.0 Hz, 2H), 3.99 (s, 3H), 3.53 (s, 3H), 3.39 (s, 3H), 2.97-2.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.52, 151.67, 151.54, 147.45, 108.39, 56.75, 32.13, 29.83, 28.07; HRMS (ESI) Calculated for $C_9H_{12}N_4O_3$ $[M+H]^+$: 225.0982, Found : 225.0984.

2.2.3 ***8-(1-hydroxypropyl)-1, 3, 7-trimethyl - 3, 7-dihydro-1H-purine-2, 6-dione (12c)***: This compound was prepared according to the GP. Yield 91%; White solid; m.p. 168-170 ˚C; R_f = 0.55 (4% MeOH/Chloroform); FT-IR (Neat, cm^{-1}): 3411, 2971, 2933, 2883, 1702, 1641, 1544, 1220, 1036, 968, 745, 588, 465, 420; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.73 (m, 1H), 4.01 (s, 3H), 3.52 (s, 3H), 3.39 (s, 3H), 3.13 (d, *J* = 7.2 Hz, 1H), 1.99-1.90 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.51, 154.59, 151.69, 147.44, 108.00, 68.25, 32.25, 29.82, 29.28, 28.04, 9.86; HRMS (ESI) Calculated for $C_{11}H_{16}N_4O_3$ $[M+H]^+$: 253.1295, Found : 253.1297.

2.2.4 ***8-(1-hydroxybutyl)-1, 3, 7-trimethyl-3, 7-dihydro-1H-purine-2, 6-dione (12d)***: This compound was prepared according to the GP. yield 83%; white solid; m.p.178-180 ˚C; R_f = 0.548 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3405, 2954, 2926, 2871, 1703, 1639, 1438, 1220, 1026, 964, 744, 586; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.79-4.76 (m, 1H), 3.97 (s, 3H), 3.50 (s, 3H), 3.36 (s, 3H), 3.00 (br, 1H), 1.89-1.81 (m, 2H), 1.50-1.39 (m, 2H), 0.97-0.93 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.52, 154.77, 151.69, 147.44, 107.99, 66.72, 38.26, 32.24, 29.85, 28.04, 18.68, 13.85; HRMS (ESI) Calculated for $C_{12}H_{18}N_4O_3$ $[M+H]^+$: 267.1452, Found : 267.1457.

2.2.5 ***8-(2-hydroxypropan-2-yl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (12e)***: This compound was prepared according to the GP. yield 76%; white solid; m.p. 208-210˚C; R_f = 0.6 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3400, 2997, 2945, 1738, 1697, 1636, 1544, 1367, 1222, 1172, 752, 598, 525, 425; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.17 (s, 3H), 3.53 (s, 3H), 3.38 (s, 3H), 2.99 (br, 1H), 1.70 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.01, 155.59, 151.75, 146.66, 108.54, 70.82, 34.04, 29.75, 29.38, 28.05; HRMS (ESI) Calculated for $C_{11}H_{15}N_4O_3$ $[M+H]^+$: 253.1295, Found : 253.1293.

2.2.6 ***8-(2-hydroxybutan-2-yl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (12f)***: This compound was prepared according to the GP. yield 83%; white solid; m.p.136-138 ˚C; R_f = 0.5 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3461, 2957, 1698, 1646, 1538, 1440, 1367, 1285, 1218, 1050, 743, 561, 524, 463; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (s, 3H), 3.52 (s, 3H), 3.37 (s, 3H), 3.09 (br, 1H), 2.01-1.88 (m, 2H), 1.63 (s, 3H), 0.85 (t, *J* = 7.4 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.64, 155.64, 151.73, 146.66, 108.60, 73.63, 34.31, 33.96, 29.78, 28.02, 27.39, 8.21; HRMS (ESI) Calculated for $C_{12}H_{17}N_4O_3$ $[M+H]^+$: 267.1452, Found : 267.1455.

2.2.7 ***1,3,7-trimethyl-8-(tetrahydrofuran-2-yl)-3,7-dihydro-1H-purine-2,6-dione (12g)***: This compound was prepared according to the GP. yield 92%; white solid; m.p. 142-144 ˚C; R_f = 0.775 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 2952, 2878, 1704, 1658, 1548, 1436, 1342, 1220, 1042, 744, 502, 468, 413; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.02-4.99 (m, 1H), 4.01 (s, 3H), 3.97-3.87 (m, 2H), 3.54 (s, 3H), 3.38 (s, 3H), 2.60-2.51 (m, 1H), 2.31-2.22 (m, 1H), 2.19- 2.11 (m, 1H), 2.06- 1.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.62, 152.46, 151.82, 147.45, 108.46, 72.70, 69.02, 32.34, 29.83, 29.71, 28.00, 26.04; HRMS (ESI) Calculated for $C_{12}H_{15}N_4O_3$ $[M+H]^+$: 265.1295, Found : 265.1293.

2.2.8 ***8-(1-hydroxypentyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (12h)***: This compound was prepared according to the GP. yield 88%; white solid; m.p. 138-140 ˚C; R_f = 0.563 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3419, 2951, 2934, 2870, 1700, 1641, 1542, 1436, 1218, 1035, 971, 744, 423; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.76-4.74 (m, 1H), 3.97 (s, 3H), 3.48 (s, 3H), 3.35 (s, 3H), 3.13 (br, 1H), 1.90-1.83 (m, 2H), 1.37 (m, 4H), 0.90-0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.50, 154.82, 151.68, 147.43, 107.96, 67.00, 35.82, 32.26, 29.84, 28.04, 27.55, 22.48, 14.04; HRMS (ESI) Calculated for $C_{13}H_{20}N_4O_3$ $[M+H]^+$: 281.1608, Found : 281.1607.

2.2.9 ***8-(1-hydroxy-3-methylbutyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (12i)***: This compound was prepared according to the GP. yield 85%; white solid; m.p. 106-108˚C; R_f = 0.50 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3389, 2959, 2933, 2872, 1699, 1649, 1544, 1439, 1218, 1037, 975, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.83 (m, 1H), 3.97 (s, 3H), 3.49 (s, 3H), 3.35 (s, 3H), 3.24 (br, 1H), 1.87-1.78 (m, 2H), 1.64-1.56 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.51, 155.07, 151.69, 147.44, 107.95, 65.21, 44.93, 32.22, 29.64, 28.04, 24.56, 23.27, 21.89; HRMS (ESI) Calculated for $C_{13}H_{20}N_4O_3$ $[M+H]^+$: 281.1608, Found : 281.1609.

2.2.10 ***8-(1-hydroxy-2-methylpropyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (12j)***: This compound was prepared according to the GP. Yield 90%; white solid; m.p. 194-196 ˚C; R_f = 0.40 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3431, 2956, 2924, 2871, 1694, 1641, 1544, 1433, 1217, 1033, 971, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.45 (t, *J* = 6.5 Hz, 1H), 3.97 (s, 3H), 3.51 (s, 3H), 3.36 (s, 3H), 3.05 (br, 1H), 2.14 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.51, 154.55, 151.68, 147.52, 107.84, 72.11, 34.14, 32.35, 29.86, 28.04, 18.91, 17.96; HRMS (ESI) Calculated for $C_{12}H_{18}N_4O_3$ $[M+H]^+$: 267.1452, Found : 267.1455.

2.2.11 ***8-(1-hydroxycyclohexyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (12k)***: This compound was prepared according to the GP. Yield 71%; white solid; m.p. 216-218 ˚C; R_f = 0.55 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3439, 2933, 2851, 1688, 1642, 1536, 1427, 1217, 972, 743, 523; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (s, 3H), 3.45 (s, 3H), 3.31 (s, 3H), 3.03 (br, 1H), 2.01-1.89 (m, 4H), 1.72-1.62 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.44, 155.48, 151.73, 146.78, 108.24, 72.06, 36.39, 34.16, 29.73, 28.04, 25.20, 21.44; HRMS (ESI) Calculated for $C_{14}H_{20}N_4O_3$ $[M+H]^+$: 293.1608, Found : 293.1607.

2.2.12 ***8-(1-hydroxycyclopentyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (12l)***: This compound was prepared according to the GP. Yield 73%; white solid; m.p. 182-184 ˚C; R_f = 0.5 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3440, 2938, 2859, 1680, 1641, 1533, 1425, 1215, 972, 743, 523; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.06 (s, 3H), 3.41 (s, 3H), 3.33 (s, 3H), 2.26 (m, 2H), 2.11-2.05 (m, 2H), 1.92-1.89 (m, 2H), 1.79-1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.95, 155.45, 151.60, 146.57, 108.36, 79.97, 39.54, 33.60, 29.68, 28.10, 23.89; HRMS (ESI) Calculated for $C_{13}H_{18}N_4O_3$ $[M+H]^+$: 279.1452, Found : 279.1455.

2.2.13 ***8-(hydroxymethyl)-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione (13a)***: This compound was prepared according to the GP. Yield 65%; white solid; decompose at 280 ˚C; R_f = 0.40 (10% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3237, 3154, 3018, 2960, 2831, 1681, 1546, 1420, 1217, 1027, 869, 814, 670, 537; ^{1}H NMR (400 MHz, DMSO) δ = 11.05 (s, 1H) 5.58 (t, *J* = 5.8 Hz, 1H), 4.52 (d, *J* = 5.8 Hz, 2H), 3.83 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (100 MHz,) δ = 155.53, 153.14, 151.39, 149.03, 108.04, 55.79, 32.28, 28.91; HRMS (ESI) Calculated for $C_8H_{10}N_4O_3$ $[M+H]^+$: 211.0826, Found : 211.0827.

2.2.14 ***8-(1-hydroxyethyl)-3,7-dimethyl-3,7-dihydro-1H-purine-2,6-dione (13b)***: This compound was prepared according to the GP. Yield 68%; white solid; m.p. 250-254 ˚C; R_f = 0.525 (10% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3527, 3332, 3149, 3021, 2828, 1678, 1547, 1421, 1297, 1218, 1156, 1105, 1025, 870, 752, 672, 546, 454; ^{1}H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 5.59 (d, *J* = 5.8 Hz, 1H), 4.86 (p, *J* = 6.4 Hz, 1H), 3.37 (s, 3H), 3.29 (s, 3H), 1.44 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ 155.70, 155.59, 151.40, 148.90, 107.83, 61.59, 32.33, 28.92, 21.70; HRMS (ESI) Calculated for $C_9H_{12}N_4O_3$ $[M+H]^+$: 225.2273, Found : 225.2275.

2.2.15 ***3,7-dimethyl-8-(tetrahydrofuran-2-yl)-3,7-dihydro-1H-purine-2,6-dione (13c)***: This compound was prepared according to the GP. Yield 54%; white solid; m.p. 236-238 ˚C; R_f = 0.70 (10% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3154, 3029, 2828, 1680, 1545, 1414, 1340, 1217, 1043, 861, 752, 544, 465; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 5.02 (t, *J* = 6.9 Hz, 1H), 4.02 (s, 3H), 3.94 (dt, *J* = 15.6, 7.8 Hz, 2H), 3.52 (s, 3H), 2.62 – 2.52 (m, 1H), 2.33 – 2.25 (m, 1H), 2.21 – 2.12 (m, 1H), 2.09 – 2.00 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.81, 153.11, 151.06, 149.39, 108.67, 72.69, 69.06, 32.45, 29.72, 29.07, 26.03; HRMS (ESI) Calculated for $C_{11}H_{14}N_4O_3$ $[M+H]^+$: 251.1139, Found : 251.1141.

2.2.16 ***8-(1-hydroxyethyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (14a)***: This compound was prepared according to the GP. Yield 41%; white solid; m.p. 190-192 ˚C; R_f = 0.375 (10% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3413, 3252, 2980, 1700, 1638, 1554, 1504, 1366, 1218, 1163, 1106, 1057, 988, 748, 500; ^{1}H NMR (400 MHz, DMSO) δ 5.59 (d, *J* = 4.9 Hz, 1H), 4.73 (dt, *J* = 11.8, 5.9 Hz, 1H), 3.38 (s, 3H), 3.18 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 157.71, 154.65, 151.73, 148.28, 106.61, 63.53, 30.21, 28.23, 22.91; HRMS (ESI) Calculated for $C_9H_{12}N_4O_3$ $[M+H]^+$: 225.0982, Found : 2250983.

2.2.17 ***1,3-dimethyl-8-(tetrahydrofuran-2-yl)-3,7-dihydro-1H-purine-2,6-dione (14b)***: This compound was prepared according to the GP. Yield 45%; white solid; m.p. 228-230 ˚C; R_f = 0.714 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 3206, 2944, 2882, 1707, 1635, 1549, 1489, 1405, 1351, 1219, 1062, 986, 739, 504; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.79 (s, 1H), 5.14 (dd, *J* = 7.6, 5.8 Hz, 1H), 4.12 (dd, *J* = 13.7, 7.6 Hz, 1H), 3.97 (dd, *J* = 15.0, 7.2 Hz, 1H), 3.61 (s, 3H), 3.47 (s, 3H), 2.45 (tt, *J* = 15.0, 7.6 Hz, 1H), 2.30 – 2.19 (m, 1H), 2.12 – 1.94 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.67, 155.44, 151.77, 149.26, 106.65, 74.93, 69.41, 32.21, 30.23, 28.38, 25.75; HRMS (ESI) Calculated for $C_{11}H_{14}N_4O_3$ $[M+H]^+$: 251.1139, Found : 251.1137.

2.2.18 ***8-acetyl-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (16)***: Dissolved the 8-(1-hydroxyethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (50 mg) in TBHP (1mL) and heated the reaction mixture at 100 ˚C for overnight. The usual work-up procedure followed by column chromatography furnished the desired pure product. Yield 96%; solid; m.p. 182-184 ˚C; R_f = 0.857 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 2957, 1766, 1685, 1653, 1594, 1542, 1460, 1414, 1369, 1231, 1185, 1033, 968, 742, 656, 530, 412; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.33 (s, 1H), 3.61 (s, 1H), 3.43 (s, 1H), 2.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ = 191.48, 156.01, 151.58, 146.54, 143.76, 110.72, 34.86, 29.85, 28.31, 28.16; HRMS (ESI) Calculated for $C_{10}H_{12}N_4O_3$ $[M+H]^+$: 237.0982, Found : 237.0981.

2.2.19 ***8-(1-chloroethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (17)*****:** Dissolved the 8-(1-hydroxyethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (1 Eq.), 4-methylbenzenesulfonyl chloride (1.2 Eq.), DIPEA (1.5 Eq.) and DMAP in catalytic amount in dry DCM (20 mL). The reaction mixture was stirred at r.t for 24h. The usual work-up procedure followed by column chromatography furnished the desired pure product. Yield 48%; white solid; m.p. 170-172 °C; R_f = 0.625 (40% Ethyl acetate/Hexane); FT-IR (neat, cm^{-1}): 2924, 1703, 1646, 1540, 1447, 1217, 1035, 978, 744, 644, 596, 504; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.11 (q, *J* = 6.8 Hz, 1H), 4.03 (s, 3H), 3.56 (s, 3H), 3.39 (s, 3H), 2.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.64, 151.69, 150.99, 147.36, 108.52, 47.36, 32.07, 29.89, 28.06, 22.19; HRMS (ESI) Calculated for $C_{10}H_{13}ClN_4O_2$ $[M+H]^+$: 257.0800, Found : 257.0802.

2.2.20 ***(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl(1-(1,3,7 trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)ethyl) succinate (18)*****:** To a solution of 8-(1-hydroxyethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione (1 Eq.) in dichloromethane (10 mL), 4-oxo-4-(((R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)butanoic acid (1 Eq.), DCC (2.1 Eq.) and DMAP in catalytic amount were added at RT. The reaction mixture was stirred at room temperature for 3 h. The usual work-up procedure followed by filtration/column chromatography furnished the desired pure product as viscous oil. Yield 96%; viscous; R_f = 0.575 (4% MeOH/Chloroform); FT-IR (neat, cm^{-1}): 2928, 2856, 2117, 1743, 1705, 1661, 1601, 1449, 1144, 1074, 1222, 1144, 752 ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.00 (q, *J* = 6.7 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 1H), 3.98 (s, 3H), 3.54 (s, 3H), 14.38 – 1.86 (m, 38H), 3.38 (s, 3H), 2.92 (td, *J* = 6.1, 3.2 Hz, 2H), 2.77 (td, *J* = 6.3, 2.2 Hz, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.46 – 2.08 (m, 1H), 1.83 – 1.67 (m, 5H), 1.67 – 1.56 (m, 1H), 1.67 – 1.16 (m, 24H), 1.16 – 0.85 (m, 11H), 0.83 (dd, *J* = 5.6, 3.4 Hz, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.93, 170.82, 155.58, 151.70, 150.72, 149.57, 147.58, 140.36, 126.61, 124.87, 123.16, 117.48, 108.04, 75.18, 75.18, 63.76, 63.75, 60.50, 39.45, 37.61, 37.53, 37.49, 37.47, 37.36, 32.87, 32.86, 32.80, 32.78, 32.12, 29.89, 29.05, 28.71, 28.07, 28.04, 24.91, 24.89, 24.54, 22.82, 22.72, 21.17, 21.13, 21.11, 20.66, 19.84, 19.77, 19.74, 19.71, 19.68, 18.67, 14.29, 12.99, 12.14, 11.90; HRMS (ESI) Calculated for $C_{43}H_{66}N_4O_7$ $[M+H]^+$: 751.5005, Found : 751.5007.

2.3 Biological assays

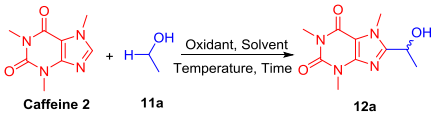
In vitro **antioxidant DPPH radical scavenging activity: [**26] See SI

Platelet aggregation inhibitory activity evaluation: [27, 28, 29] See SI

3. Results and discussion

Our initial investigation for the development of metal-free cross-dehydrogenative $C_{sp}{}^2$-$C_{sp}{}^3$ coupling *via* C-H bond activation takes place by reacting C_8-Caffeine **2** with ethanol **11a** (2 ml) in presence of H_2O_2 (2 equiv.) as oxidant at 110 °C for 20 min which furnished the target 8-(1-hydroxyethyl)-1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione i.e., 8-(1-hydroxyethyl)-caffeine **12a** in 25% yield under microwave irradiation conditions and 20% yield under thermal conditions, respectively (Table 1, entry 1). The structure of the coupled product was confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR and HR-MS spectroscopic analysis.

Table 1: Optimization study: Development of oxidant promoted, metal-free cross-dehydrogenative $C_{sp}{}^2$-$C_{sp}{}^3$ coupling on C_8-Caffeine **2** via C-H bond activation.



Caffeine 2 11a 12a

Entry No.	Oxidant (equiv.)	Solvent (2 mL)	Temp. (°C)	Time (in min)	Yield of 12a (%)
1	H_2O_2 (2)	Ethanol	110	20	25 (20)[b]
2	DCP (2)	Ethanol	110	20	15
3	Oxone (2)	Ethanol	110	20	Nil
4	$K_2S_2O_8$ (2)	Ethanol	110	20	Nil
5	TEMPO (2)	Ethanol	110	20	Nil
6	DTBP (2)	Ethanol	110	20	10
7	TBHP (2)	Ethanol	110	20	69 (62)[b]
8	TBHP (4)	Ethanol	110	20	80
9	TBHP (6)	Ethanol	110	20	92
10	TBHP (8)	Ethanol	110	20	89
11[c]	TBHP (6)	Water	110	20	39
12[c]	TBHP (6)	DMSO	110	20	Nil
13[c]	TBHP (6)	ACN	110	20	9
14[c]	TBHP (6)	DCE	110	20	3
15[c]	TBHP (6)	Mesitylene	110	20	3
16	**TBHP (6)**	**Ethanol**	**120**	**20**	**98**

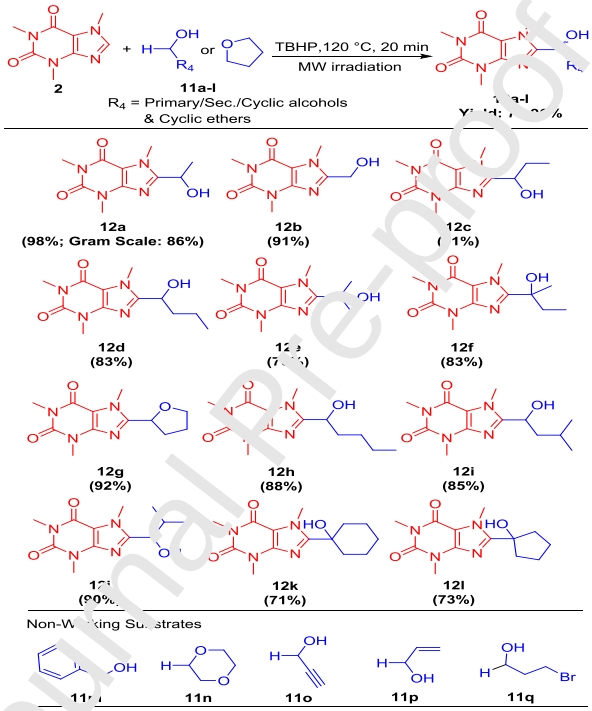
17	TBHP (6)	Ethanol	100	20	74
18	TBHP (6)	Ethanol	120	10	50
19	TBHP (6)	Ethanol	120	30	95
20[b]	TBHP (6)	Ethanol	150	1440	96

[a]*Reaction Parameters*: **2** (1 equiv.), oxidant (2-8 equiv.), solvent **(**2 mL**)**. [b]Reaction carried out under thermal conditions. [c]ethanol = 0.5 mL.

Then, we carried out the screening of several well-known oxidants such as dicumyl peroxide (DCP), oxone, $K_2S_2O_8$, TEMPO, DTBP, TBHP etc. while keeping other reaction condition constant (Table1, entries 2-7). Among all, TBHP afforded **12a** in promising yield of 69% under microwave irradiation conditions and 62% yield under thermal conditions, respectively (Table 1, entry 7). Further, the screening of mole equivalents of TBHP was carried out (Table 1, entries 8-10). It was noticed that increasing the mole equivalents of TBHP from two to four furnished **12a** in 80% yield while keeping same all the other reaction parameters (Table 1, entry 8). Further, increase in equivalents of TBHP to six and eight furnished **12a** in 92% and 89% yields, respectively (Table 1, entries 9-10).

Substrate scope and versatility

Scheme 2: Substrate Scope.[a]



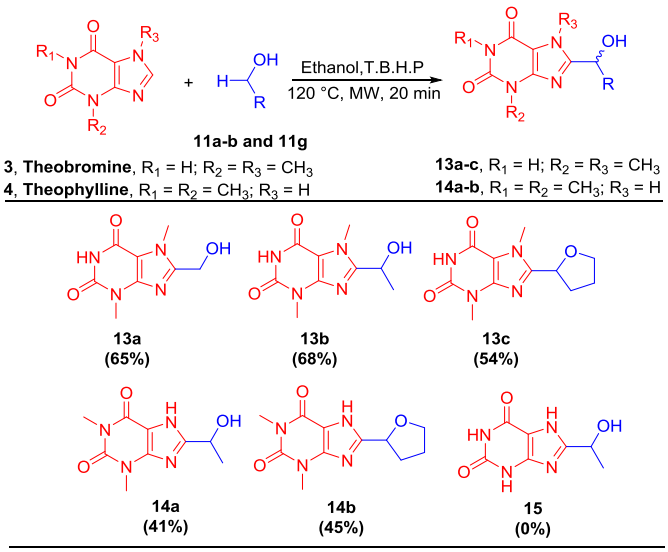
[a]*Optimized reaction condition*: **2** (1.equiv.), **11a-l** (2 mL), TBHP (6 equiv.), 120 °C, 20 min in a sealed tube.

Subsequently, we also carried out the screening of several solvents (water, DMSO, ACN, DCE, mesitylene) taking 6 equiv. of TBHP along with ethanol **11a** (0.5 mL) at 110 °C for 20 min (Table 1, entries 11-15). It was observed that changing the solvents other than ethanol drastically decreases the yield of the reaction. Then, we studied the effect of variation in temperature and time taking 6 equivalents of TBHP (Table 1, entries 16-19). Interestingly, 98% yield of **12a** was observed when **2** was reacted with 6 equivalents of TBHP with ethanol **11a** (2 mL) at 120 °C for 20 min (Table 1, entry 16). As expected, decreasing the temperature or time do not have incremental effect on the yield of **12a** (Table 1, entries 17-18). Moreover, prolonging the reaction upto 30 min also do not show influential effect on the yield of **12a** (Table 1, entry 19). Under thermal conditions, caffeine **2** on reaction with ethanol **11a** at 150 °C furnished **12a** in 96% yield *albeit* in more reaction time i.e., 24 h (Table 1, entry 20). Thus, the microwave-assisted reaction is advantageous with respect to time. *Overall, 6 equiv. of TBHP with neat ethanol as solvent (2 mL) at 120 °C temperature for 20 min. is the best-optimized reaction conditions for this metal-free CDC reaction*.

The generality and versatile nature of our optimized reaction conditions was then investigated. Different primary/secondary/alicyclic alcohols **11a-l** were reacted with Caffeine **2** under optimized reaction conditions which furnished the desired 8-(1-hydroxyethyl)-caffeine **12a-l** in 71-98% yield range (Scheme 2). It was observed that C_8-H of caffeine always links to the adjacent carbon of the hydroxy group of the alcohol. Similarly, different other xanthines such as theobromine **3** and theophylline **4**, were also reacted with different alcohols under the optimized reaction conditions which furnished the corresponding 8-(1-hydroxyethyl)-theobromine **13a-c** and 8-(1-hydroxyethyl)-theophylline **14a-b** in 41-68% yield range (Scheme 3). The basic moiety i.e., xanthine **1** was also reacted with ethanol as well as with cyclic ethers under

optimized reaction conditions; however, no formation of **15** was observed. This could be anticipated that all the three free -NH groups deactivates the ring in this C-C coupling.

Scheme 3: Further Substrate scope.[a]



It has been also observed that the Caffeine **2** having all the three *N*-protected group showed excellent behaviour with several primary/secondary/alicyclic alcohols and are also well tolerable under our optimized reaction conditions as the desired products were obtained in high isolated yields. This indicates the versatile nature of this methodology. However, in the case of theobromine **3** and theophylline **4** having one free –NH group, the yields were found relatively lesser.

Proposed mechanism

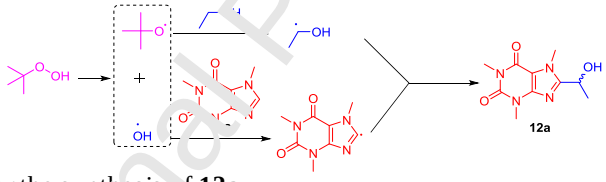
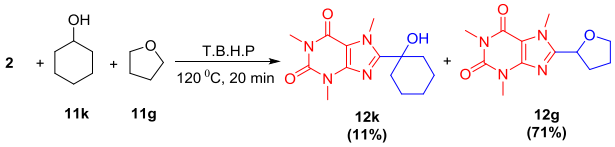


Figure 3. Proposed mechanism for the synthesis of **12a**.

In order to illustrate the plausible mechanism, reaction of **2** with ethanol **11a** under our optimized reaction conditions was carried out in the presence of free-radical scavangers such as TEMPO, BHT etc. The desired coupled product was not obtained which indicates the free-radical mechanism of this reaction [30]. It has been speculated that, for the product formation, there must be at least one hydrogen present at the adjacent carbon of the hydroxy group of alcohol and the radical developed at this position must be only stabilized by lone pair of hydroxy group. [23] This was confirmed by carrying out reaction of Caffeine with *tert*-butyl alcohol under optimized reaction conditions which did not furnished the expected coupled product. This concept was also further supported by the formation of **12g**. Based on these facts, the plausible mechanism has been depicted in figure 3.

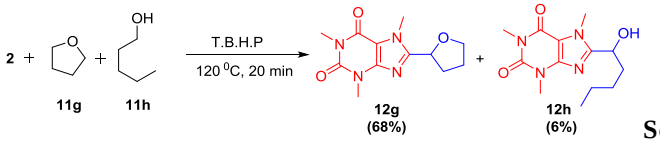
We further demonstrated the practicality of our novel methodology by performing the model reaction in gram-scale in which **12a** was obtained in 86% yield. Similarly, in order to illustrate the reactivity order of the various alcohols, control experiments were carried out. Caffeine **2** (100 mg, 1 equiv.) and TBHP (0.75 mL, 6 equiv.) were dissolved in a mixture of alicyclic alcohol i.e., cyclohexanol (1 mL) and cyclic ether i.e., tetrahydrofuran (1 mL) and subjected to MW-irradiations at 120 °C for 20 min which afforded caffeinated-cyclic alcohol and caffeinated-ether in 11% and 71% yields, respectively. This confirms that the reaction proceeds faster with cyclic ether as compared to cyclic alcohols with caffeine under optimized reaction conditions (Scheme 4).



Scheme 4. Control experiment of **2** with cyclic alcohol **11k** and ether **11g**.

Likewise, in another control experiment with cyclic ether **11g** and primary alcohol **11h**; caffeine **2** (100 mg, 1 equiv.) and TBHP (0.75 mL, 6 equiv.) were dissolved in a mixture of cyclic ether i.e., tetrahydrofuran **11g** (1 mL) and pentanoyl **11h** (1

mL) and subjected to MW-irradiations at 120 °C for 20 min which afforded caffeinated-cyclic ether **12g** and caffeinated-alcohol **12h** in 68% and 6% yields, respectively (Scheme 5).

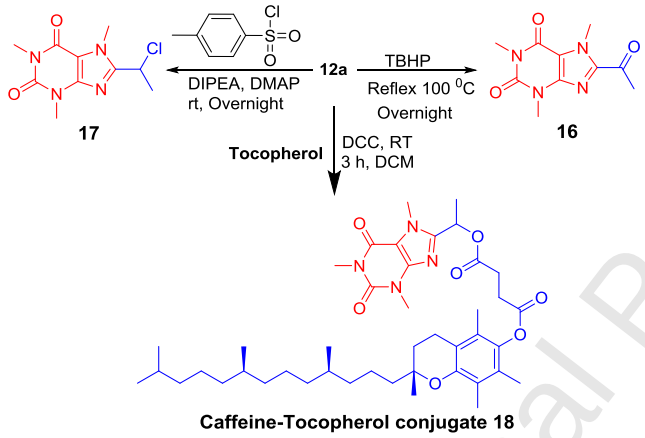


Scheme 5. Control experiment of **2** with cyclic ethers **11g** and primary alcohol **11h**.

This observation also confirms that the reactivity order of caffeinated ether is more than that of alcohols. Therefore, the overall reaction order between Caffienated primary/cyclic/ether is given below:

Ether>cyclic alcohols>primary/secondary alcohols

Finally, the various functional group transformation of the caffeinated coupled product has been demonstrated. Caffienated alcohol **12a** was subjected to excess of TBHP and refluxed overnight at 100 °C which furnished the corresponding ketone **16** in 98% yield. Sequentially, **12a** was then reacted with 4-methylbenzenesulphonyl chloride at r.t overnight which afforded the corresponding caffeinated chloride **17** in 48% yield. In another application to the development of amphiphilic bioconjugates for drug delivery application, caffeine-tocopherol conjugates **18** have also been prepared in excellent (98%) yield *via* DCC coupling (Scheme 6).



Scheme 6. Functional-group transformation.

Since caffeine is a well-known antioxidant and several naturally occurring aliphatic alcohols such as geraniol, linalool, citronellal, gingerol etc. have also been recognized as antioxidants as well as antiplatelet agents; [31a-f] all the caffeinated alcohols **12a-l**, **13a-c** and **14a-b** were assessed for their *in vitro* antioxidant activities (DPPH free radical scavenging assay) [26] and arachidonic acid (AA)-induced antiplatelet activities [27] taking ascorbic acid (IC_{50} = 4.56 µg/mL) and aspirin (IC_{50} = 21.39 µg/mL), as standard references, respectively. The result are shown in Table 2.

Table 2. *In vitro* antioxidant and antiplatelet activity of synthesized compounds.

Compound No.	Antioxidant Activity IC_{50} (µg/mL)	Antiplatelet activity IC_{50} (µg/mL)
12a	62.52±1.18	**18.00± 0.24**
12b	**11±0.06**	23.33± 0.23
12c	**10.62±0.05**	36.67± 1.01
12d	38.27±0.30	**6.67± 0.05**
12e	42.62±0.46	22.67± 0.19
12f	78.93±1.36	**11.33± 0.11**
12g	59.09±1.18	33.33± 0.95
12h	39.82±0.31	**12.00± 0.11**
12i	92.66±1.54	32.67± 0.92
12j	**8.33±0.08**	**8.00± 0.09**
12k	21.9±0.40	23.33± 0.23
12l	18.21±0.33	26.67± 0.36
13a	39.18±4.12	**6.99±0.34**
13b	83.09±5.76	**7.08±0.36**
13c	65.92±4.38	**7.15±0.38**
14a	81.37±5.84	**6.32±0.27**
14b	91.21±5.91	**7.23±0.41**
Ascorbic acid	4.56	---
Aspirin	---	21.39

As can be seen from Table 2, Compound **12j** (IC_{50} = 8.33±0.08 µg/mL) was found to show promising antioxidant activity as compared to standard reference ascorbic acid (IC_{50} = 4.56 µg/mL). Then, the next best compounds, **12b-c** showed an IC_{50} values of 11±0.06 µg/mL and 10.62±0.05 µg/mL, respectively as compared to ascorbic acid. Rest of the compounds have shown moderate or poor antioxidant activity. Similarly, compounds **12d**, **13a** and **14a**, the three most active compounds of the series, have shown IC_{50} values of 6.67± 0.05 µg/mL, 6.99±0.34 µg/mL and 6.32±0.27 µg/mL, respectively and were 3-folds more active than standard reference drug aspirin (IC_{50} = 21.39 µg/mL). Similarly, the next best compounds of the series, 13b-c and 14b, have shown IC_{50} values of 7.08±0.36 µg/mL, 7.15±0.38 µg/mL and 7.23±0.41 µg/mL, respectively in comparison to aspirin. Compounds **12j** was found approximately ~2.5 folds more active than aspirin. Two compounds, **12f** and **12h** have shown ~2-folds more activity than aspirin. The antiplatelet activity of **12a** was comparable to that of aspirin. Rest of the compounds were found moderately active. To the best of our knowledge, this is the first report of caffeinated alcohols having dual antioxidant as well as antiplatelet activities.

4. Conclusions

We disclose an efficient, microwave-assisted, oxidant-interceded, transition-metal-free, cross-dehydrogenative $C_{sp}{}^2$-$C_{sp}{}^3$ coupling of Caffeine and other naturally occurring methylxanthines (C_8-position) with substituted aliphatic primary/secondary/alicyclic/cyclic alcohols/cyclic ethers *via* C-H bond activation upto 98% yield. The reaction proceeds smoothly in the presence of *tert*-butyl hydroperoxide (TBHP) under solvolysis condition at 120 °C for 20 min in good to excellent yields. The reaction was also found feasible under thermal conditions. The large substrate scope, gram-scale synthesis, control experiments, and practical synthetic transformations further highlights the practicality of this methodology. For the first time, *in vitro* antioxidant as well as AA-induced platelet aggregation inhibitory activities of C_8-(hydroxymethyl) caffeine's **12a-l**, **13a-c** and **14a-b** has been evaluated and showed promising antioxidant and antiplatelet activities. The amphiphilic bioconjugate i.e., caffeine-tocopherol conjugate have also been prepared for the first time and will be utilized it for self-assembly into nanostructures for anticancer drug delivery application.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

S. C. acknowledges DST, New Delhi for DST-NRF India South Africa Joint Research Project (**DST/INT/South Africa/P-19/2016**). B.R.K.S acknowledges UGC, New Delhi for providing financial assistance in the form of Senior Research fellowships (SRF). D.K.Y. is thankful to National Research Foundation of Korea (NRF), the Ministry of Education, Science, and Technology (No: **2017R1C1B2003380**) for providing financial assistance at the Gachon University, Incheon city, South Korea. Materials Research Centre (MRC), MNIT, Jaipur is acknowledged for providing analytical facilities.

Appendix A. Supplementary data

The supporting information related to this article includes, general experimental procedure, characterization data of all synthesized compounds (**12a-l, 13a-c** and **14a-b**) and copies of ^{1}H and ^{13}C spectral data of some representative compounds (**12a-l, 13a-c, 14a-b, 16, 17** and **18**).

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Graphical Abstract

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Microwave-Assisted Modified Synthesis of C_8-Analogues of Naturally Occurring Methylxanthines: Synthesis, Biological Evaluation and their Practical Applications

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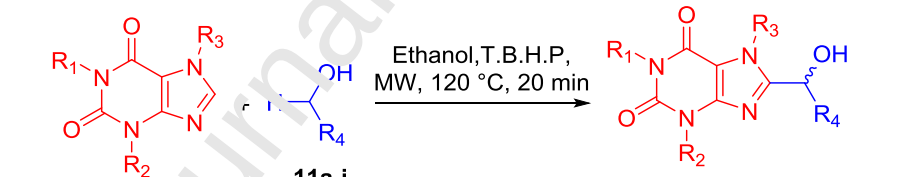
Bharti Rajesh Kumar Shyamlal, Manas Mathur, Dharmendra K. Yadav, and Sandeep Chaudhary,*



2, **Caffeine**, $R_1 = R_2 = R_3 = CH_3$
3, **Theobromine**, $R_1 = H$; $R_2 = R_3 = CH_3$
4, **Theophylline**, $R_1 = R_2 = CH_3$; $R_3 = H$

R_4 = Primary/Sec./Cyclic Alkyl & Cyclic ethers
12a-l, $R_1 = R_2 = R_3 = CH_3$
13a-c, $R_1 = H$; $R_2 = R_3 = CH_3$
14a-b, $R_1 = R_2 = CH_3$; $R_3 = H$
Yield: upto 98%

- *Microwave-assisted*
- *Oxidant-promoted*
- *Transition-metal-free CDC*
- *Gram-scale synthesis*
- *Antioxidant and Antiplatelet agents*

HIGHLIGHTS

Title: **Microwave-Assisted Modified Synthesis of C_8-Analogues of Naturally Occurring Methylxanthines: Synthesis, Biological Evaluation and their Practical Applications**

- An efficient, microwave-assisted, oxidant-interceded, transition-metal-free, cross-dehydrogenative coupling is reported.

- Several substituted C_8-(hydroxymethyl) methylxanthines were synthesized using this new methodology.
- Good substrate scope, control experiments, gram-scale synthesis, and practical synthetic transformations further highlights the practicality of this methodology
- C_8-(hydroxymethyl)Caffeine **12a-l**, **13a-c** and **14a-b** showed promising *in vitro* antioxidant and antiplatelet activities.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: