Journal of Asian Natural Products Research
Vol. 12, No. 11, November 2010, 978–984

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Synthesis and biological evaluation of novel benzyl-substituted flavones as free radical (DPPH) scavengers and α-glucosidase inhibitors

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(*Received 4 June 2010; final version received 23 July 2010*)

Pharmacologically motivated natural product investigations have yielded a large variety of structurally unique lead compounds with interesting biomedical properties, but the natural roles of these molecules often remain unknown. In the present investigation, a series of benzyl substituted-flavone derivatives have been synthesized from the lead compounds and were screened against 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and α-glucosidase inhibitory properties. The resulting activity profiles of these flavone derivatives were compared for degree of similarity to the profile of **1**–**3**. Most of the synthesized derivatives displayed potent activities when compared to the parent compounds. Maximum potencies for DPPH free radical scavenging activity were observed only in compounds containing the 4-hydroxyl substitution and 3-methoxyl group on the phenyl ring. While the 2- and 4-hydroxyl group substitutions on the phenyl ring seem to be crucial for the intestinal α-glucosidase inhibitory activity.

Keywords: flavones; cinnamic acids; benzyl-substituted flavones; DPPH free radical scavenging activity; α-glucosidase inhibitory activity

1. Introduction

The search for novel therapeutic agents and approaches for diabetes mellitus and cardiovascular diseases is still an active research field stimulated by the discovery of new biological targets and by the possibility of obtaining new bioactive compounds with multiple biological activities. The past decade has witnessed an increasing interest in search of plant-based lead compounds for the development of new pharmaceuticals [1]. In this regard, flavonoids/flavonoid derivatives, which are the most common families of green plant secondary metabolites [2], have attracted the scientific interest because of their wide range of biological activities such as antioxidant, antidiabetic, anti-cancer, antibacterial, antiviral, anti-inflammatory, antiallergic, and vasodilatory actions [3]. In addition, flavonoids inhibit lipid peroxidation platelet aggregation, capillary permeability, and fragility, and the activity of enzyme systems including cyclooxygenase and lipoxygenase [4]. Recent interest in these substances has been stimulated by potential health benefits arising from the antioxidant activity and their high propensity to transfer electrons, to chelate ferrous ions, and to scavenge reactive oxygen species [5]. Because of these properties, flavonoids

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ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020.2010.511190
http://www.informaworld.com

have been considered as potential therapeutics of interest in combating multiple disorders.

2. Results and discussion

In the course of our continuing efforts in discovery and identification of potential bioactive constituents from traditional Indian flora, we have explored the use of *in vitro* screening, in conjunction with a pattern-matching algorithm, as a means of identifying natural product extracts potentially containing new free radical scavenging and intestinal α-glucosidase inhibitory leads [6]. Stemming from that effort, we had reported the identification of baicalein (**1**), oroxylin A (**2**), and chrysin (**3**) (Figure 1) as bioactive principles from the plant *Oroxylum indicum* [7] and further demonstrated antibacterial effects of oroxylin A (**2**) derivatives. We have also reported antibacterial and α-glucosidase inhibitory properties for the derivatives of compounds **2** and **3** [7,8].

Prompted by the above-mentioned biological properties of flavone derivatives and in continuation of our previous work on related analogs, the present study was devised to synthesize new derivatives using the above-mentioned lead compounds and investigated their free radical scavenging and α-glucosidase inhibitory properties. We have also extended our efforts to establish structure–activity relationships within this biologically interesting class of compounds, both to ascertain potential directions for synthetic lead optimization studies, and to identify an optimal candidate among currently available compounds for *in vitro* studies. Herein, we report simple and new synthetic methodology for the one-pot synthesis of benzyl-substituted flavone derivatives and their results of *in vitro* free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) and α-glucosidase inhibitory potentials. This is the first report of the synthesis of benzyl-substituted flavones.

For the synthesis of the target compounds, we have developed new synthetic strategy as depicted in Scheme 1. In our initial experimentation for the synthesis of compound **7**, we used $La(NO_3)_3{\cdot}6H_2O$ as the catalyst with baicalein **1** and caffeic acid **2**; however, compound **7** was afforded in 40% yield. In order to improve the yields and synthesize flavone derivatives expeditiously in the one-pot procedure, we examined various Lewis acid catalysts (Table 1). Among these, the best result was obtained with $CeCl_3{\cdot}7H_2O$–NaI (10 mol%) (Table 1, entry 2). We also tested the effect of solvents on the formation of **7** and found that among MeOH, EtOH, 1,4-dioxane, acetonitrile, dichloromethane, dichloroethane, and THF, acetonitrile was the best solvent in terms of the yield and the reaction time (Table 2). Considering the amount of the catalyst, the reaction time, the nature of the solvent, and the yield, $CeCl_3{\cdot}7H_2O$–NaI (10 mol%) [9] in the acetonitrile system was found to be effective, and subsequently this was utilized for the preparation of a series of derivatives. The reactions were completed within 9–12 h. The products were formed at reflux temperature and in high yields.

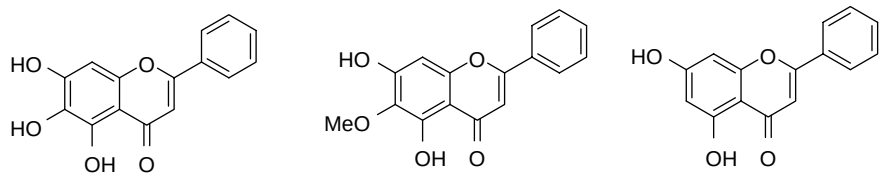
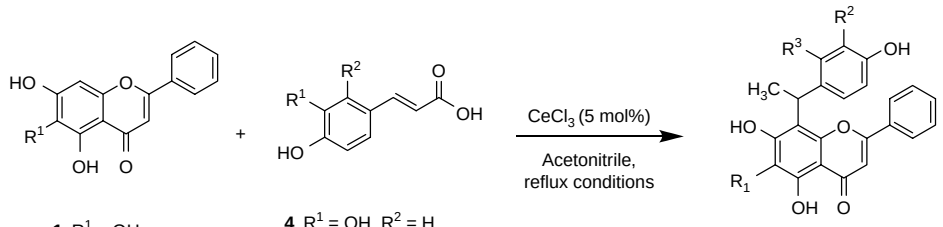


Figure 1. Structures of the lead compounds isolated from *O. indicum*.



1. R^1 = OH
2. R^1 = OMe
3. R^1 = H

4. R^1 = OH, R^2 = H
5. R^1 = OMe, R^2 = H
6. R^1 = H, R^2 = OH

7.R^1 = R^2 = OH, R^3 = H
8. R^1 = OH, R^2 = OMe, R^3 = H
9. R^1 = OH, R^2 = H,R^3 = OH
10. R^1 = OMe, R^2 = OH, R^3 = H
11. R^1 = OMe, R^2 = OMe,R^3 = H
12. R^1 = OMe, R^2 = H, R^3 = OH
13.R^1 = H, R^2 = OH, R^3 = H
14. R^1 = H, R^2 = OMe, R^3 = H
15. R^1 = R^2 = H, R^3 = OH

Scheme 1. Synthesis of benzyl-substituted flavone derivatives.

Table 1. Studies on the catalyst optimization.

S. no.	Catalyst	Time (min)	Yield (%)
1	La $(NO_3)_3{\cdot}6H_2O$ (5 mol%)	15	40
2	$CeCl_3{\cdot}7H_2O$ NaI (10 mol%)	12	80
3	$BF_3.OEt_2$ (catalytic amount)	20	Trace
4	Bi $(NO_3)_3{\cdot}5H_2O$ (5 mol%)	20	Trace
5	La $(OTf)_3$ (5 mol%)	15	40
6	Cu $(OTf)_2$ (5 mol%)	18	30
7	I_2 (10 mol%)	18	50
8	$InCl_3$ (10 mol%)	20	20
9	$KHSO_4{\cdot}SiO_2$	24	None
10	Amberlyst-15 (10 mg)	15	75

The resulting crude compounds were purified by column chromatography to yield title compounds as racemic mixtures.

The biological significance of the synthesized compounds was evaluated *in vitro* for their potential for DPPH free radical scavenging and rat intestinal α-glucosidase inhibitory activity by methods reported earlier [7]. Interestingly, DPPH free radical scavenging activity was dramatically improved by the presence of the benzyl ring on the flavone skeleton. The activities were expressed in IC_{50} (concentration required for 50% inhibition) values (Table 3). As shown in Table 3, compounds **8**, **10**, and **14** showed potent DPPH free radical scavenging activity and compounds **12** and **15** showed moderate α-glucosidase inhibitory activity. Regarding the general structure–activity relationship of compounds, the following points were noteworthy: (a) 3-hydroxy and 4-methoxy substitution pattern in the phenyl ring, as

Table 2. Optimization of solvents.

S. no.	Solvent	Yield (%)[a]
1	Dichloroethane	Trace
2	THF	Trace
3	Ethanol	60
4	Acetonitrile	80
5	1,4-Dioxane	45
6	DMSO	None
7	ACOH	None
8	Acetonitrile + water	20
9	Dichloromethane	Trace

Note: [a]Isolated yields.

Table 3. DPPH scavenging and α-glucosidase inhibitory activities of benzyl-substituted flavone derivatives.

Compound	DPPH scavenging activity (SC_{50}; μM)	α-Glucosidase inhibitory activity (IC_{50}; μM)
Baicalein	34.48	25.78
Oroxylin A	NA	43.45
Chrysin	NA	67.74
7	13.47	NA
8	8.05	NA
9	47.85	NA
10	7.54	NA
11	12.13	NA
12	46.19	39.21
13	17.88	NA
14	6.93	512.58
15	58.05	44.11
Trolox	5.96	–
Acarbose	–	18.63

Notes: NA = not active (compounds were considered not active at a concentration of 50 mg/ml giving activity less than 15%); IC_{50} or SC_{50} values were determined by linear regression analysis using at least five different concentrations in triplicate and represent the mean of the experiment; SDM were within 10% in any case.

in compound **14**, presents a better situation to achieve a high degree of DPPH free-radical scavenging activity. (b) With intact of substitutions of 3-hydroxy and 4-methoxy on the phenyl ring, introduction of 6-hydroxyl or 6-methoxyl substitutions of the flavone ring (**8** and **11**) led to the decrease in the activity. However, neither **14** nor **8**, **11** displayed α-glucosidase inhibitory activity. (c) Comparing the compounds **8**, **11**, and **14** with **7**, **10**, and **13**, it was observed that 3- and 4-hydroxyl group substitutions had less activity except in **10**, as showing more potent activity than compound **11**, respectively. However, we were unable to obtain improvement in α-glucosidase inhibitory activity. (d) Comparison of DPPH free radical scavenging activity of **9**, **12**, and **15** with **7**, **10**, and **13** showed that the *ortho* positions of the hydroxyl groups on the phenyl ring are favorable for the activity compared to the *meta* positions (as in compounds **9**, **12**, and **15**). It is important to mention that all the synthesized derivatives exhibited more potent activity than the flavones (**1**–**3**), from which the derivatives have been synthesized. This is the first report identifying the DPPH free radical scavenging and rat intestinal α-glucosidase inhibitory activity for the benzyl-substituted flavones. All the new compounds were characterized by detailed spectroscopic analysis [10].

In conclusion, we have developed the synthetic methodology for the preparation of flavonoid derivatives, and their DPPH free radical scavenging and intestinal α-glucosidase inhibitory properties were investigated. The results of our study indicated that **14**, **10**, and **8** showed potent DPPH free radical scavenging activity, while compound **15** displayed moderate α-glucosidase inhibitory activity.

3. Experimental

3.1 General experimental procedures

Melting points were recorded on a Fisher Johns apparatus and are uncorrected. FAB-MS was recorded on a VG Auto spec-M instrument. IR spectra were recorded on a Nicolet spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on Varian 200, 400 MHz, and Bruker 300 MHz spectrometers using TMS as the internal

standard. HMBC, HSQC, and NOESY experiments were obtained using an Oxford 500 MHz spectrometer. The solvents used were all of AR grade and were distilled under the positive pressure of dry nitrogen atmosphere where necessary. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates. Visualization was performed using 5% H_2SO_4 solution followed by heating. Column chromatography was performed on silica gel (60–120 mesh) purchased from Merck Specialities Private Ltd, Navi Mumbai, India.

3.2 Extraction and isolation

Fresh *O. indicum* roots were collected from the Manuguru forest, Andhra Pradesh and processed as per the literature method to obtain oroxylin A, baicalein, and chrysin [10].

3.3 Typical experimental procedure for the synthesis of benzyl flavones

A mixture of flavone (1 mmol), cinnamic acid (2 mmol), and $CeCl_3{\cdot}7H_2O$–NaI (75 mg, 10 mol%) in acetonitrile/ethanol was stirred at reflux temperature overnight. After completion of the reaction (monitored by TLC), the solvent was evaporated to dryness and 50 ml ice water was added. The mixture was extracted with ethyl acetate (3 × 20 ml), and the extracts were washed with water (3 × 20 ml), dried over Na_2SO_4, and the solvent was removed using a rotary evaporator. The crude mixture was chromatographed on silica gel (100–200 mesh) to yield the target compounds as racemic mixtures.

3.3.1 Compound **7**

IR ν_{max} (KBr): 3417, 2923, 2854, 1656, 1029 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 12.84 (1H, s, OH), 8.72 (1H, s, OH), 8.24 (1H, s, OH), 7.82 (1H, s, OH), 7.57 (2H, m), 7.43 (3H, m), 7.31 (1H, s, OH), 6.77 (1H, br s), 6.72 (2H, br s), 6.54 (1H, s, H-3), 4.85 (1H, q, $J = 7.2$ Hz), 1.71 (3H, d, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 182.3, 163.2, 150.8, 147.9, 144.6, 143.8, 142.2, 136.0, 131.3, 130.7, 128.3 (2C), 127.8, 125.8 (2C), 117.4, 114.3, 113.9, 111.1, 104.5, 104.1, 32.0, 17.6. ESI-MS: *m/z* 407.1 $[M + H]^+$.

3.3.2 Compound **8**

IR ν_{max} (KBr): 3450, 2924, 2853, 1651, 1030 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 12.81 (1H, s, OH), 8.80 (1H, s, OH), 8.28 (1H, s, OH), 7.56 (2H, m), 7.42 (3H, m), 6.97 (1H, s, OH), 6.83 (1H, s), 6.80 (1H, d, $J = 8.1$ Hz), 6.73 (1H, d, $J = 8.1$ Hz), 6.55 (1H, s, H-3), 4.90 (1H, q, $J = 7.1$ Hz), 3.72 (3H, s, OMe), 1.75 (3H, d, $J = 7.1$ Hz).^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 182.3, 163.2, 150.8, 147.9, 146.3, 144.7, 143.6, 135.9, 131.4, 130.7, 128.3 (2C), 127.9, 125.8 (2C), 119.0, 114.0, 110.7, 110.0, 104.5, 104.4, 55.2, 30.2, 17.9. ESI-MS: *m/z* 421.1 $[M + H]^+$.

3.3.3 Compound **9**

^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 12.83 (1H, s, OH), 9.12 (1H, s, OH), 8.96 (1H, s, OH), 8.88 (1H, s, OH), 8.69 (1H, s, OH), 7.93 (2H, m), 7.52 (3H, m), 7.08 (1H, d, $J = 8.4$ Hz), 6.66 (1H, s, H-3), 6.31 (1H, br s), 6.13 (1H, dd, $J = 8.4$ and 1.7 Hz), 5.03 (1H, q, $J = 7.1$ Hz), 1.67 (3H, d, $J = 7.1$ Hz). ^{13}C NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 182.5, 163.2, 157.2, 155.8, 155.2, 150.0, 131.0, 128.6 (2C), 128.2, 126.9, 126.2 (2C), 121.1, 110.9, 107.7, 106.1, 105.3, 104.1, 102.6, 102.2, 29.2, 18.0. ESI-MS: *m/z* 407.3 $[M + H]^+$.

3.3.4 Compound **10**

IR ν_{max} (KBr): 3444, 2931, 2858, 1655, 1073 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$

+ DMSO-d_6): δ (in ppm) 12.99 (1H, s, OH), 8.44 (1H, s, OH), 7.62 (1H, s, OH), 7.56 (2H, d, $J = 7.7$ Hz), 7.43 (3H, m), 7.26 (1H, s, OH), 6.79 (1H, br s), 6.71 (2H, m), 6.54 (1H, s, H-3), 4.83 (1H, q, $J = 7.2$ Hz), 3.98 (3H, s, OMe), 1.71 (3H, d, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 182.4, 163.3, 153.8, 150.2, 150.0, 143.8, 142.1, 135.9, 131.0, 130.8, 130.2, 128.3 (2C), 125.8 (2C), 117.5, 114.3, 113.7, 110.9, 104.7, 104.4, 59.9, 31.9, 17.5. ESI-MS: *m/z* 421 $[M + H]^+$.

3.3.5 Compound **11**

IR ν_{max} (KBr): 3438, 2936, 2851, 1656, 1072 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 12.98 (1H, s, OH), 9.35 (1H, s, OH), 7.56 (2H, m), 7.51 (1H, s, OH), 7.43 (3H, m), 6.84 (1H, d, $J = 1.3$ Hz), 6.75 (1H, dd, $J = 8.1$,1.3 Hz), 6.70 (1H, d, $J = 8.1$ Hz), 6.55 (1H, s, H-3), 4.85 (1H, q, $J = 7.3$ Hz), 4.09 (3H, s, OMe), 3.75 (3H, s, OMe), 1.76 (3H, d, $J = 7.3$ Hz).^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 182.3, 163.1, 154.3, 150.4, 150.2, 146.5, 143.9, 135.5, 131.2, 130.8, 130.5, 128.3 (2C), 125.8 (2C), 119.0, 114.3, 110.8, 110.3, 104.5 (2C), 59.8, 55.2, 32.3, 17.9. ESI-MS: *m/z* 435 $[M + H]^+$.

3.3.6 Compound **12**

IR ν_{max} (KBr): 3376, 2922, 2850, 1656, 1046 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 13.0 (1H, s, OH), 9.50 (1H, s, OH), 9.04 (1H, s, OH), 7.94 (2H, m), 7.51 (3H, m), 7.08 (1H, d, $J = 8.1$ Hz), 6.65 (1H, s, H-3), 6.34 (1H, s, OH), 6.30 (1H, d, $J = 2.2$ Hz), 6.25 (1H, dd, $J = 8.1$, 2.2 Hz), 5.03 (1H, q, $J = 7.2$ Hz), 3.85 (3H, s, OMe), 1.67 (3H, d, $J = 7.2$ Hz).^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 182.5, 163.2, 157.3, 156.1, 155.1, 154.7, 150.0, 131.1, 129.0, 128.6 (2C), 126.9, 126.2 (2C), 121.11, 118.44, 117.57, 107.75, 106.09, 102.64, 102.16, 59.81, 30.31, 18.15. ESI-MS: *m/z* 421 $[M + H]^+$.

3.3.7 Compound **13**

IR ν_{max} (KBr): 3357, 2923, 2853, 1653, 1028 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 12.73 (1H, s, OH), 9.95 (1H, s, OH), 7.88 (2H, m), 7.73 (1H, s, OH), 7.53 (2H, m), 7.43 (1H, m), 7.25 (1H, s, OH), 6.78 (1H, br s), 6.72 (2H, m), 6.53 (1H, s, H-3), 6.36 (1H, s), 4.81 (1H, q, $J = 7.2$ Hz), 1.68 (3H, d, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 181.8, 161.6, 143.7, 142.0, 136.1 131.1, 130.8, 130.6, 128.2 (2C), 125.7 (2C), 125.5, 117.7, 117.4, 114.1, 113.7, 104.9, 104.6, 98.9, 93.5, 29.0, 17.3. ESI-MS: *m/z* 391 $[M + H]^+$.

3.3.8 Compound **14**

IR ν_{max} (KBr): 3312, 2922, 2852, 1647, 1032 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 13.27 (1H, s, OH), 7.86 (2H, m), 7.62 (1H, s, OH), 7.50 (3H, m), 7.47 (1H, s, OH), 6.99 (1H, d, $J = 8.1$ Hz), 6.90 (1H, d, $J = 8.1$, 1.7 Hz), 6.80 (1H, d, $J = 1.7$ Hz), 6.66 (1H, s, H-3), 6.38 (1H, s), 4.86 (1H, q, $J = 7.3$ Hz), 3.84 (3H, s, OMe), 1.64 (3H, d, $J = 7.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 182.5, 163.7, 161.5, 159.2, 156.2, 145.0, 134.4, 131.7, 129.1 (2C), 126.4, 126.3 (2C), 118.9, 116.0, 114.7, 114.2, 110.3, 109.7, 105.6, 95.3, 55.8, 31.8, 17.2. ESI-MS: *m/z* 405 $[M + H]^+$.

3.3.9 Compound **15**

IR ν_{max} (KBr): 3440, 2923, 2853, 1653, 1037 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 12.85 (1H, s, OH), 9.02 (1H, s, OH), 8.86 (1H, s, OH), 8.76 (1H, s, OH), 7.93 (2H, m), 7.50 (3H, m), 6.84 (1H, d, $J = 8.4$ Hz), 6.61 (1H, s, H-3), 6.30 (1H, d, $J = 2.2$ Hz), 6.25 (1H, s), 6.22 (1H, dd, $J = 8.4$, 2.2 Hz), 4.98

(1H, q, $J = 7.2$ Hz), 1.66 (3H, d, $J = 7.2$ Hz).^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): δ (in ppm) 182.0, 163.1, 159.0, 157.2, 155.7, 155.1, 154.5, 128.4 (2C), 126.9, 126.2 (2C), 118.4, 117.5, 107.7, 106.0, 105.2, 104.5, 102.6, 102.1, 99.2, 29.1, 17.7. ESI-MS: *m/z* 390 $[M + H]^+$.

3.4 Assay of α-glucosidase inhibitory activity and DPPH free radical scavenging activity

Determination of α-glucosidase inhibitory activity and DPPH free radical scavenging activity was done according to the procedure described in the literature [7].

Acknowledgements

The authors thank Dr J.S. Yadav, Director, IICT, for his encouragement and support during the course of this work. G.S.K. and R.S.R. thank CSIR, New Delhi for the financial support.

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