

Research Article

Microwave Assisted Synthesis of Novel Imidazolopyridinyl Indoles as Potent Antioxidant and Antimicrobial Agents

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We describe herein the design, synthesis, and pharmacological evaluation of novel series of imidazolopyridinyl indole analogues as potent antioxidants and antimicrobials. These novel compounds (**3a**-i) were synthesized by reacting 3,5-disubstituted-indole-2-carboxylic acid (**1a**-i) with 2,3-diamino pyridine (**2**) in excellent yield. The novel products were confirmed by their IR, ¹H NMR, ¹³C NMR, mass spectral, and analytical data. These compounds were screened for their antioxidant and antimicrobial activities. Among the compounds tested, **3a**-d showed the highest total antioxidant capacity, scavenging, and antimicrobial activities. Compounds **3c-d** and **3g-h** have shown excellent ferric reducing activity.

1. Introduction

The continuous search for novel agents which target pathological processes of human carcinogenesis has led to the synthesis of small molecules which may modulate cell cycle [1]. Free radicals are referred to as oxidizing agents because they tend to cause other molecules to donate their electrons [2]. Reactive oxygen species (ROS) are a product of normal cellular metabolism [3]. ROS plays a vital physiological role in several intracellular signaling and regulations [4]. Antioxidants have the ability to neutralize free radicals and prevent the damage caused by them [5]. Antioxidants, even at low concentration, significantly delay or prevent the oxidation of easy oxidizable substrates [6]; when in high concentrations, ROS can damage cell structures, nucleic acids, lipids, and proteins [7]. In the normal metabolism status, the level of free radicals and antioxidants in humans is maintained in balance, which is important for sustaining optimal physiological conditions [8]. The reactive oxygen species (ROS) are implicated in numerous pathological conditions such as diabetes, liver damage [9], inflammation, aging, atherosclerosis, carcinogenesis [10, 11], and neurodegenerative [12] disorders like

Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis (ALS) [13].

The treatment of infectious microbial disease remains a pressing problem worldwide [14, 15]. A major research emphasis to counter this growing problem is the development of antimicrobials structurally unrelated to the existing molecules. One possibility to achieve this goal is the combination of a molecule with structural elements possessing appropriate biological activities [16, 17]. Nitrogen-bridgehead fused heterocycles containing an imidazole ring is a common structural component in pharmacologically important molecules, with activities spanning an assorted range of targets [18], such as antiviral [19] and anticancer [20-22]. Imidazolopyridine analogues are an important class of biologically active compounds showing anticancer [1], antiviral [23], analgesic [24], and anti-HIV [25] activities. Diaminopyridine analogues possess a wide range of biological activities [26] such as treatment of multiple sclerosis and [27] antiviral, rodenticidal [28], antimicrobial, and cytotoxic [29, 30] activities

Besides, indoles are featured in a wide variety of biologically and pharmacologically active compounds [31]. One of

the natural antioxidants is melatonin possessing an indole ring, which is produced in the body and acts as a free radical scavenger [32]. The indole derivatives are known to possess anticancer DNA cleavage, antioxidant [33–37], antirheumatoidal, and anti-HIV [38] activities.

The search for an innovative key for the reduction of chemical steps, wastes, short reaction time, easy workup, and increased yield in organic processes has become a thoughtprovoking task. This can be overcome by carrying out the reaction in microwave condition. Microwave irradiation is an important method which is being increasingly used to accelerate organic reactions. Several methods have been reported for the synthesis of imidazoles in the presence of catalyst and solvents such as P₂O₅ and Methanesulfonic acid [39], Alumina-Methanesulfonic acid [40], HCl [41], polyphosphoric acid [42], and ethylene glycol [43]. However, it was noticed that all these methods involve an assortment of drawbacks such as difficult to workup, prolonged reaction time, low yields, and use of expensive and environmentally toxic organic reagents or catalyst or solvent. We have developed an ecofriendly, efficient, less energy, and catalyst free method for the synthesis of imidazolopyridinyl indoles. Therefore, considerable interest is focused on the microwave assisted synthesis of imidazolopyridinyl indole analogues as potent antioxidants (free radical scavenging, total antioxidant capacity, and ferric reducing antioxidant power) and antimicrobial activities of pharmacologically active compounds.

2. Experimental

2.1. Chemistry. All chemicals used in this investigation were analytical grade and were purified whenever necessary. Melting points of the synthesized compounds are measured in open capillaries and are uncorrected. Reactions are monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} aluminium sheets (MERCK). Iodine vapour was used as detecting agent. IR spectra are recorded in KBr on Perkin Elmer and FTIR spectrophotometer (ν_{max} in cm⁻¹). ¹H NMR and ¹³C NMR spectra are recorded on BRUKER AVENE II 400-MHz NMR spectrometer (chemical shift in δ ppm down field from TMS as internal reference). The mass spectra are recorded on LC-MSD-Trap-SL instruments. The elemental analysis was determined on FLASH EA 1112 SERIES instrument.

2.1.1. General Procedure for the Synthesis of Compound **1a-i**. The precursors 3,5-disubstituted indol-2-carboxylic acid (**1a-i**) were obtained from 3,5-disubstituted indol-2-carboxylates by reported method [44].

2.1.2. General Procedure for the Synthesis of Compound 3a-i

Conventional Method. A mixture of 3,5-disubstituted indol-2-carboxylic acid (1a-i) (0.01 mol) and 2,3-diaminopyridine 2 (0.01 mol) were refluxed 5-6 h in 15–20 mL of ethanol. The completion of reaction was monitored by TLC. After completion of the reaction, excess of solvent was removed under reduced pressure and kept at room temperature for a few hours for the formation of crystals. The product obtained was filtered and purified with ethanol. All the newly synthesized compounds were characterized by elemental analysis and IR, ¹H NMR, ¹³C NMR, and mass spectroscopic data; yield was 65–75%.

Microwave Assisted Synthesis. A mixture of 3,5-disubstituted indol-2-carboxylic acid (1a-i) (0.01 mol) and 2,3-diaminopyridine (2) (0.01 mol) were powdered, mixed, and introduced in an open borosil glass vessel containing a few drops of ethanol. This was subjected to microwave irradiation for 10 minutes with 70% microwave power. After completion (TLC), the reaction mixture was brought to room temperature, washed with aqueous ethanol, and recrystallized to get the title compound 3a-i, which was found to be in high purity (TLC) and in excellent yield (80-98%).

(1) 2-(5-Chloro-3-phenyl-1H-indol-2-yl)-3H-imidazolo[4,5b]pyridine (**3a**). m.p. 251-252°C; IR (KBr) ν_{max} (cm⁻¹): 3449, 3416; ¹H NMR (DMSO-d₆ + CDCl₃) δ (ppm): 12.02 (s, 1H, Indole NH), 11.50 (s, 1H, Imidazolopyridine NH), 7.28–7.52 (m, 11H, Ar-H); ¹³CNMR (DMSO-d₆) δ (ppm): 115, 120, 122, 125, 125, 127, 128, 131, 133, 134, 153; MS: m/z = 344 [M]⁺, 346 [M+2]. Anal. calcd. For C₂₀H₁₃ClN₄ (344): C, 69.67; H, 3.80; N, 16.25. Found: C, 69.52; H, 3.74; N, 16.16.

(2) 2-(5-Bromo-3-phenyl-1H-indol-2-yl)-3H-imidazolo[4,5b]pyridine (**3b**). m.p. 267-268°C; IR (KBr) ν_{max} (cm⁻¹): 3435, 3412; ¹H NMR (DMSO-d₆ + CDCl₃) δ (ppm): 11.52 (s, 1H, Indole NH), 10.95 (s, 1H, Imidazolopyridine NH), 7.21–7.69 (m, 11H, Ar-H); MS: $m/z = 390 \text{ [M]}^{+}$, 392 [M+2]. Anal. calcd. For C₂₀H₁₃BrN₄ (390): C, 61.71; H, 3.37; N, 14.39. Found: C, 61.59; H, 3.29; N, 14.31.

(3) 2-(5-Methyl-3-phenyl-1H-indol-2-yl)-3H-imidazolo[4,5b]pyridine (**3c**). m.p. 245-246°C; IR (KBr) v_{max} (cm⁻¹): 3470, 3418; ¹H NMR (DMSO-d₆ + CDCl₃) δ (ppm): 11.66 (s, 1H, Indole NH), 11.10 (s, 1H, Imidazolopyridine NH), 7.10–7.48 (m, 11H, Ar-H), 2.41 (s, 3H, CH₃); MS: m/z = 324 [M]^{+.} Anal. calcd. for C₂₁H₁₆N₄ (324): C, 77.76; H, 4.97; N, 17.27. Found: C, 77.65; H, 4.91; N, 17.35.

(4) 2-(5-Methoxy-3-phenyl-1H-indol-2-yl)-3H-imidazolo[4,5b]pyridine (3d). m.p. 225-226°C; IR (KBr) ν_{max} (cm⁻¹): 3341, 2845; ¹H NMR (DMSO-d₆ + CDCl₃) δ (ppm): 12.77 (s, 1H, Indole NH), 11.67 (s, 1H, Imidazolopyridine NH), 6.85–7.51 (m, 11H, Ar-H), 3.89 (s, 3H, CH₃); MS: m/z = 340 [M]⁺. Anal. calcd. For C₂₁H₁₆N₄O (340): C, 74.10; H, 4.74; N, 16.46. Found: C, 74.25; H, 4.68; N, 16.58.

(5) 2-(5-Chloro-3-methyl-1H-indol-2-yl)-3H-imidazolo[4,5b]pyridine (**3e**). m.p. 236-237°C; IR (KBr) ν_{max} (cm⁻¹): 3422, 2849; ¹H NMR (DMSO-d₆ + CDCl₃) δ (ppm): 11.54 (s, 1H, Indole NH), 10.85 (s, 1H, Imidazolopyridine NH), 7.21–7.69 (m, 6H, Ar-H), 2.50 (s, 3H, CH₃); MS: $m/z = 282 \text{ [M]}^+$, 284 [M+2]. Anal. calcd. For C₁₅H₁₁ClN₄ (282): C, 63.72; H, 3.92; N, 19.82. Found: C, 63.67; H, 3.85; N, 19.71.

(6) 2-(5-Bromo-3-methyl-1H-indol-2-yl)-3H-imidazolo[4,5b]pyridine (**3***f*). m.p. 256-257°C; IR (KBr) ν_{max} (cm⁻¹): 3439, 2849; ¹H NMR (DMSO-d₆ + CDCl₃) δ (ppm): 11.53 (s, 1H, Indole NH), 11.00 (s, 1H, Imidazolopyridine NH), 7.44–8.04 (m, 11H, Ar-H), 2.44 (s, 3H, CH₃); MS: $m/z = 328 \text{ [M]}^+$, 330 [M+2]. Anal. calcd. For C₁₅H₁₁BrN₄ (328): C, 55.06; H, 3.39; N, 17.12. Found: C, 55.12; H, 3.31; N, 17.07.

(7) 2-(3,5-Dimethyl-1H-indol-2-yl)-3H-imidazolo[4,5-b]pyridine (**3g**). m.p. 240-241°C; IR (KBr) ν_{max} (cm⁻¹): 3422, 2852; ¹H NMR (DMSO-d₆ + CDCl₃) δ (ppm): 11.17 (s, 1H, Indole NH), 9.83 (s, 1H, Imidazolopyridine NH), 7.22–7.78 (m, Ar-H, 6H), 2.07 (d, 6H, CH₃); ¹³CNMR (DMSO-d₆) δ (ppm): 21, 10, 112, 118, 120, 124, 127, 128, 128, 135, 164; MS: m/z = 262 [M]^{+.}. Anal. calcd. For C₁₆H₁₄N₄ (262): C, 73.26; H, 5.38; N, 21.36. Found: C, 73.19; H, 5.29; N, 21.28.

(8) 2-(5-Methoxy-3-methyl-1H-indol-2-yl)-3H-imidazolo[4,5b]pyridine (**3h**). m.p. 275-276°C; IR (KBr) ν_{max} (cm⁻¹): 3422, 2852; ¹H NMR (DMSO-d₆ + CDCl₃) δ (ppm): 12.77 (s, 1H, Indole NH), 11.20 (s, 1H, Imidazolopyridine NH), 7.05–7.38 (m, Ar-H, 6H), 2.50 (S, 3H, CH₃), 3.34 (S, 3H, OCH₃); MS: $m/z = 278 \text{ [M]}^+$. Anal. calcd. For C₁₆H₁₄N₄O (278): C, 69.05; H, 5.07; N, 20.13. Found: C, 68.45; H, 5.01; N, 20.01.

(9) 2-(1H-Indol-2-yl)-3H-imidazolo[4,5-b]pyridine (**3i**). m.p. 238-239°C; IR (KBr) ν_{max} (cm⁻¹): 3207, 2952; ¹H NMR (DMSO-d₆ + CDCl₃) δ (ppm): 12.304 (s, 1H, Indole NH), 10.98 (s, 1H, Imidazolopyridine NH), 6.54–7.53 (m, Ar-H, 6H); MS: $m/z = 234 \text{ [M]}^+$. Anal. calcd. For C₁₄H₁₀N₄ (234): C, 71.78; H, 4.30; N, 23.92. Found: C, 71.65; H, 4.25; N, 23.85.

2.2. Biological Activities

2.2.1. Antioxidant Activities

(1) Free Radical Scavenging Activity. Free radical scavenging activity was done by DPPH method [45]. Different concentrations (10, 50, and 100 μ g) of samples and butylated hydroxy anisole (BHA) were taken in different test tubes. The volume was adjusted to 100 μ L by adding MeOH. Five milliliters of 0.1 mM methanolic solution of DPPH was added to these tubes and shaken vigorously. The tubes were allowed to stand at 27°C for 20 min. The control was prepared as above without any extract. The absorbance of samples was measured at 517 nm. Radical scavenging activity was calculated using the following formula:

% Radical scavenging activity

$$= \left[\frac{\text{Control OD} - \text{Sample OD}}{\text{Control OD}}\right] \times 100.$$
⁽¹⁾

(2) Total Antioxidant Capacity. Various concentrations of extracts (10, 50, and 100 μ g) were taken in a series of test tubes. To this, 1.9 mL of reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate) was added. The tubes were incubated at 95°C for 90 min and allowed to cool. The absorbance of each aqueous solution was measured at 695 nm against a blank. Antioxidant capacities are expressed as equivalents of ascorbic acid. Ascorbic acid equivalents are calculated using standard graph of ascorbic acid. The values are expressed as ascorbic acid equivalents in μ g per mg of extract.

(3) Ferric Reducing Antioxidant Power. Various concentrations of extracts (10, 50, and 100 μ g) were mixed with 2.5 mL of 200 mmol/L sodium phosphate buffer (pH 6.6) and 2.5 mL of 1% potassium ferricyanide. The mixture was incubated at 50°C for 20 min. Next, 2.5 mL of 10% trichloroacetic acid (w/v) was added. From this solution, 5 mL was mixed with 5 mL of distilled water and 1 mL of 0.1% ferric chloride and absorbance was measured spectrophotometrically at 700 nm. BHA was used as standard.

2.2.2. Antimicrobial Activity. A series of novel imidazolopyridinyl indole analogues are tested for *in vitro* antimicrobial activity against gram-negative bacteria *Escherichia coli* ATCC 25922 and *Klebsiella Pneumoniae* ATCC 33499 and grampositive bacteria *Staphylococcus aureus* ATCC 6538 and antifungal activity against *Candida tropicalis* ATCC 8302 and *Candida albicans* ATCC 60193 by applying the agar plate diffusion technique [46]. Dilution process was adopted at 25, 50, and 100 μ g/mL concentrations. The activity is compared with reference drugs Gentamycin for antibacterial and Fluconazole for antifungal activity. The zone of inhibition after 24 hr of incubation at 37°C, in case of antibacterial activity and 48 hr in case of antifungal activity, was compared with that of standards.

3. Results and Discussion

3.1. Chemistry. The compounds were designed with the aim of exploring their antioxidant and antimicrobial activities. The target compounds were synthesized as outlined in Scheme 1. 3,5-Disubstituted indol-2-carboxylic acids (1ai) were reacted with 2,3-diaminopyridine (2) in ethanol affords imidazolopyridinyl indoles. Completion of the reaction was monitored by TLC. All the novel compounds were characterized by elemental analysis and IR, ¹H NMR, ¹³C NMR, and mass spectroscopic data. The IR spectrum of 2-(5-chloro-3-phenyl-1H-indol-2-yl)-3H-imidazo[4, 5-b]pyridine **3a** showed strong absorption at 3449 cm^{-1} corresponding to indole NH and absorption at 3416 cm^{-1} corresponding to imidazolopyridine NH. The ¹HNMR spectrum of **3a** has exhibited a singlet at δ 12.02 due to indole NH; singlet at δ 11.50 corresponds to imidazolopyridine NH which are D_2O exchangeable. A multiplet between δ 7.28–7.52 is assigned to the eleven aromatic protons present in the molecule. The ¹³CNMR spectrum of **3a** has shown peaks at δ 115, 120, 122, 125, 125, 127, 128, 131, 133, 134, and 153. The mass spectrum of compound 3a has shown isotopic peaks at m/z 344 [M]^{+,} 346 [M+2]. The above spectral data supports the formation of compound 3a. The various new indole derivatives synthesized during the present investigation are listed in Table 1.

3.2. Biological Activities. The target compounds **3a-i** have been synthesized as illustrated in Scheme 1 and screened for antioxidant (free radical scavenging, total antioxidant capacity and ferric reducing antioxidant power) and antimicrobial activities.

Product	Substituent's		Convention	al method	Microwave method		
	R	R′	Time (Min)	Yield (%) ^a	Time (Min)	Power	Yield (%) ^a
3a	Cl	Ph	300-360	75	10	70	98
3b	Br	Ph	300-360	70	10	70	97
3c	Me	Ph	300-360	60	10	70	95
3d	OMe	Ph	300-360	60	10	70	95
3e	Cl	Me	300-360	75	10	70	98
3f	Br	Me	300-360	75	10	70	98
3g	Me	Me	300-360	60	10	70	94
3h	OMe	Me	300-360	60	10	70	94
3i	Н	Н	300-360	60	10	70	80

TABLE 1: Comparative data of conventional and microwave method for the imidazolopyridinyl indole analogues 3a-i.

^aIsolated yields.



SCHEME 1: Schematic representation of the synthesized novel imidazolopyridinyl indoles **3a–i**.

3.2.1. Antioxidant Activities

(1) Free Radical Scavenging Activity. The target compounds were screened for free radical scavenging activity by DPPH method [45]. The samples were prepared at concentrations of 10, 50, and 100 μ g/100 μ L and butylated hydroxy anisole (BHA) is taken as standard. DPPH is a stable free radical in a methanolic solution. Because of the unpaired electron of DPPH, it gives a strong absorption maximum at 517 nm by visible spectroscopy (purple color). In addition, the unpaired electron of a hydrogen donor (a free radical scavenging antioxidant), decreasing the absorption. Therefore, DPPH loses color in



FIGURE 1: Free radical scavenging activity of 3a-i.

proportion to the number of electrons captured [47]. This reaction has been widely used as a simple, rapid, and convenient method independent of sample polarity for screening many samples for radical scavenging activity [48, 49]. These advantages have made the DPPH method interesting for testing our analogs. Among the tested compounds, 3a-d has shown very potent scavenging activity. The increased scavenging activity is due to the presence of halogen, methyl, and methoxy substitution at the five positions and a phenyl ring at the third position of indole ring. The hydrogen of indole NH/imidazolopyridine NH could be donated to the DPPH to form DPPH free radical; by the presence of phenyl ring at third position of indole, the DPPH free radical will be stabilized by the resonance. Compounds 3e-h have shown equipotent activities. The decreased activity is due to the presence of "H" at five positions of indole ring. The bar graph representation of percentage of free radical scavenging activity is shown in Figure 1.

(2) Total Antioxidant Capacity. Total antioxidant activity was performed on all the newly synthesized compounds [50]. Antioxidant capacities are expressed as equivalents of ascorbic acid. Among the tested compounds, **3a-d** have shown excellent activity. The results of total antioxidant activity are shown in Figure 2.

	Antibacterial activity									
Compound	S. aureus			E. coli			K. Pneumoniae			
	25	50	100	25	50	100	25	50	100	
3a	11	13	15	10	11	13	11	12	14	
3b	12	14	14	11	12	12	10	12	15	
3c	10	13	14	09	11	12	10	12	13	
3d	12	15	13	10	10	12	09	12	13	
3e	08	09	10	04	06	06	05	06	07	
3f	05	07	09	05	07	08	04	06	06	
3g	07	06	08	06	07	08	06	08	09	
3h	08	08	09	06	06	09	07	06	08	
3i	05	05	05	03	04	03	05	04	05	
Std. 1	12	14	15	10	12	13	11	13	15	

TABLE 2: Antibacterial activity of synthesized compounds 3a-i (zone of inhibition in mm).

Std. 1: Gentamycin.



FIGURE 2: Total antioxidant activity of 3a-i.

(3) Ferric Reducing Antioxidant Power Activity. All the novel compounds were screened for ferric reducing antioxidant activity [51]. Butylated hydroxy anisole (BHA) was used as standard. All the tested compounds have shown a positive tendency towards the ferric reducing activity. The presence of reducer (i.e., antioxidant) causes the reduction of the Fe⁺³/ferricyanide complex to the ferrous form after the addition of trichloroacetic acid and ferric chloride. The reducing power of test compounds **3c-d** and **3g-h** have shown excellent ferric reducing activity and **3a-b** and **3e-f** have shown moderate to high activity. The presence of methyl and methoxy groups at five positions of indole ring has enhanced the ferric reducing power activity of the compounds. The results are presented in Figure 3.

3.2.2. Antimicrobial Activity. Results of antimicrobial activity are summarized in Tables 2 and 3. Applying the agar plate diffusion technique [46], a series of novel imidazolopy-ridinyl indole analogues were screened for *in vitro* antibacterial activity against gram-negative bacteria *Escherichia coli* (*E. coli*) and *Klebsiella Pneumoniae* (*K. Pneumoniae*) and

TABLE 3: Antifungal activity of synthesized compounds **3a-i** (zone of inhibition in mm).

	Antifungal activity							
Compound	C. tropicalis			C. albicans				
	25	50	100	25	50	100		
3a	15	18	21	14	16	19		
3b	16	18	20	15	17	20		
3c	14	17	19	13	16	18		
3d	15	16	18	14	15	17		
3e	10	11	13	11	13	14		
3f	09	10	12	10	11	13		
3g	10	10	12	09	11	12		
3h	11	11	12	08	10	11		
3i	03	04	06	05	09	10		
Std. 2	18	20	23	16	17	21		

Std. 2: Fluconazole.



FIGURE 3: Ferric reducing antioxidant power activity of 3a-i.

gram-positive bacteria *Staphylococcus aureus* (*S. aureus*) at 25 μ g/mL, 50 μ g/mL, and 100 μ g/mL concentrations, respectively. Gentamycin was used as standard. The zones of inhibitions were measured in mm for each concentration. Most

of the screened compounds were found to have significant antibacterial activity. Compounds **3a–d** have shown very good activity against all three bacterial strains. Antifungal screening of the compounds was carried out *in vitro* against two fungi *Candida tropicalis* and *Candida albicans* at 25 μ g/mL, 50 μ g/mL, and 100 μ g/mL concentrations using Fluconazole as standard. Among the tested imidazolopyridinyl indole systems, the majority of the compounds exhibited moderate to significant antifungal activity.

4. Conclusion

In conclusion, we have synthesized title compound 3a-i by a safer method. The title compound 3a-i was subjected to screening for its antioxidant and antimicrobial activities. Compounds 3a-d have shown profound scavenging and antioxidant activities. Compounds 3c-d and 3g-h have shown excellent ferric reducing activity and compounds 3a-d have shown very promising antimicrobial activity. Very promising scavenging, antioxidant, and antimicrobial activities are observed with compounds containing halogens, methyl, and methoxy groups at five positions and a phenyl ring at the third position of indole ring. Excellent ferric reducing activity is observed with compounds containing CH₃ and OCH₃ at five positions of indole. Development of new methodologies for the synthesis of indole derivatives will be very important to the chemists, which will yield subsets of heterocycles having potentiality to serve as templates for new biologically active molecules. Hence, investigation by rapid means to make novel imidazolopyridinyl indoles would be highly beneficial.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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