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Synthesis of New Class of Functionalized Flavones/Isoxazole Derivatives-Nitrile oxide 1,3-Dipolar Cycloaddition

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A new series of functionalized flavone-isoxazole derivatives have been synthesized from alkyne tethered 3-hydroxy flavone by adopting facile synthetic method, intermolecular nitrile oxide 1,3-dipolar cycloaddition in the presence of eco-friendly sodium hypochloride oxidant under mild reaction conditions. Structures of all the synthesized compounds were established on the basis of ^{1}H NMR, ^{13}C NMR and ESI-mass.

Keywords: Propargyloxy flavone, Nitrile oxide, 1,3-Dipolar cycloaddition, Flavone, Isoxazole.

INTRODUCTION

Flavones are subclass of flavonoid secondary metabolites, widely found in natural plant seeds, nuts and some orange and yellow fruits, flowers and vagetables [1-5] and also play key role in biological processes [6,7]. Flavones usually occur in the plants as glycosides especially at C-7/C-5 positions. The flavones developed considerable interest due to their potential biological activities such as antioxidant [8,9], antimicrobial [10,11], anticancer [12-16], anti-HIV [17-19], anti-inflammatory [20], vasodilating [21] and several enzyme-inhibitory effects [22].

Isoxazole is a prominent heterocyclic scaffold considered as advantaged structural moiety due to its broad spectrum of pharmacological activities [23,24] like COX-2 inhibitory [25], antifungal [26], insecticidal [27,28], antibacterial [29] and herbicidal activities [30]. Isoxazole motiff also found in many drug molecules as a probable core group to improve their biological activities [31-35]. Additionally, isoxazoles used as versatile intermediates for the synthesis of polyfunctionalized organic small molecules and functional materials [36,37]. The classical 1,3-dipolar cycloaddition reactions of alkynes with nitrile oxides is the direct and efficient synthetic methodology for the preparation of substituted isoxazole derivatives [38-41]. Some bioactive flavones and isoxazoles (apigenin, luteolin, tangeritin, chrysin) are shown in Fig. 1.

Owing to the flavone and isoxazole unique chemical and biological properties, the development of expeditious and practical synthetic routes for the construction of these heterocyclic derivatives were continued to capture the interests of medicinal chemists [42,43]. In present study, the synthesis of series of functionalized alkoxy tethered isoxazole pendent flavone molecular hybrid derivatives and characterized. To the best of our knowledge on report in the literature on heterocycle pendent at C_2-phenyl ring of flavones, many synthetic pathways known to furnish flavones and other heterocycle hybrid linked at C_5/C_7 positions of flavone [44].

EXPERIMENTAL

Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers. All the solvents were purified as per the reported procedures [45]. All reactions were performed under N_2 atmosphere unless otherwise noted. Column chromatography was performed using Merck silica gel 60-120 mesh. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker spectrometer at 400 MHz and 101 MHz, respectively, tetramethylsilane as internal standard. Mass spectral analysis was accomplished using electrospray ionization (ESI) techniques.

General procedure for the synthesis of 3-hydroxy-2-(2-(prop-2-yn-1-yloxy)phenyl)-4*H*-chromen-4-one (4): KOH

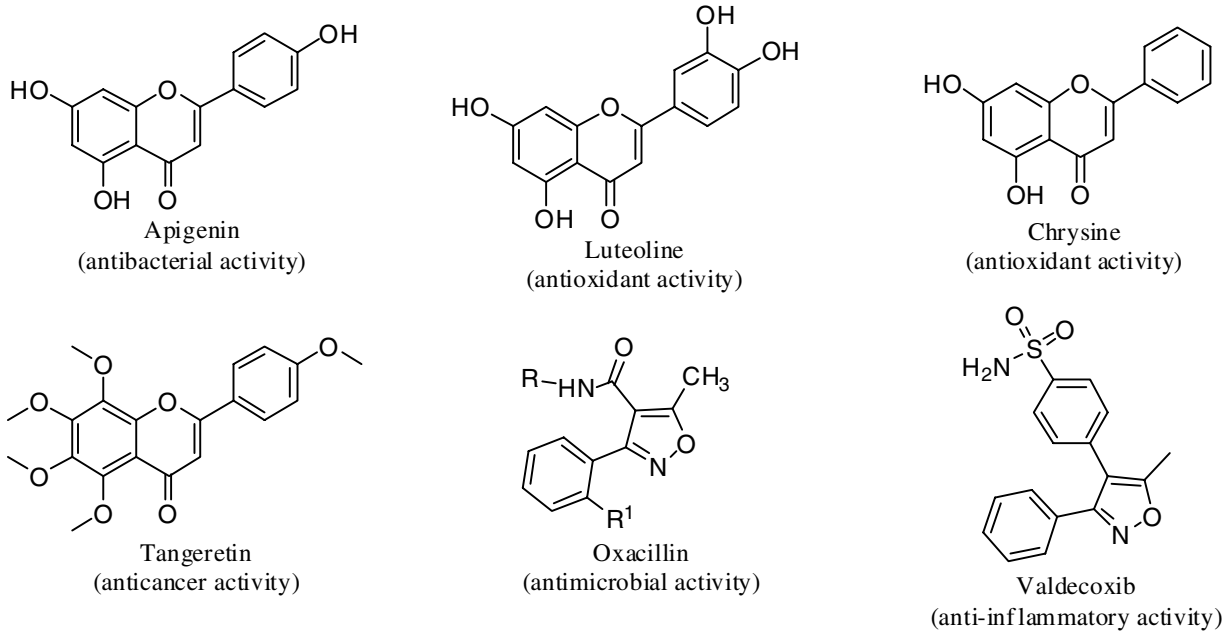


Fig. 1. Biologically active flavonoides/isoxazole derivatives

solution (5 M, 5 mL) was added to 2-hydroxy acetophenone (**1**) (3 g, 0.021 mmol) and 2-(prop-2-yn-1-yloxy)benzaldehyde (**2**) (5 g, 0.003 mmol) in ethanol solvent and the reaction mixture was stirred for 18 h at room temperature. After completion of reaction, indicated by TLC the reaction mixture was acidified with aq. HCl, yellow solid 2-hydroxy chalcone (5 g, **3**), filtered and dried. It was used for further reaction without column chromatography. To 2-hydroxychalcone (3 g, 0.010 mmol), $NaOH/H_2O_2$ (3 g/15 mL) was added and continued stirring for 4 h at room temperature, then acidified with 2 M HCl and transferred to ice cold water (200 mL) to get white colour crude product, it was filtered and purified with column chromatography (60-120) to yield of 3-hydroxy-2-(2-(prop-2-yn-1-yloxy)-phenyl)-4*H*-chromen-4-one (**4**, 4.5 g).

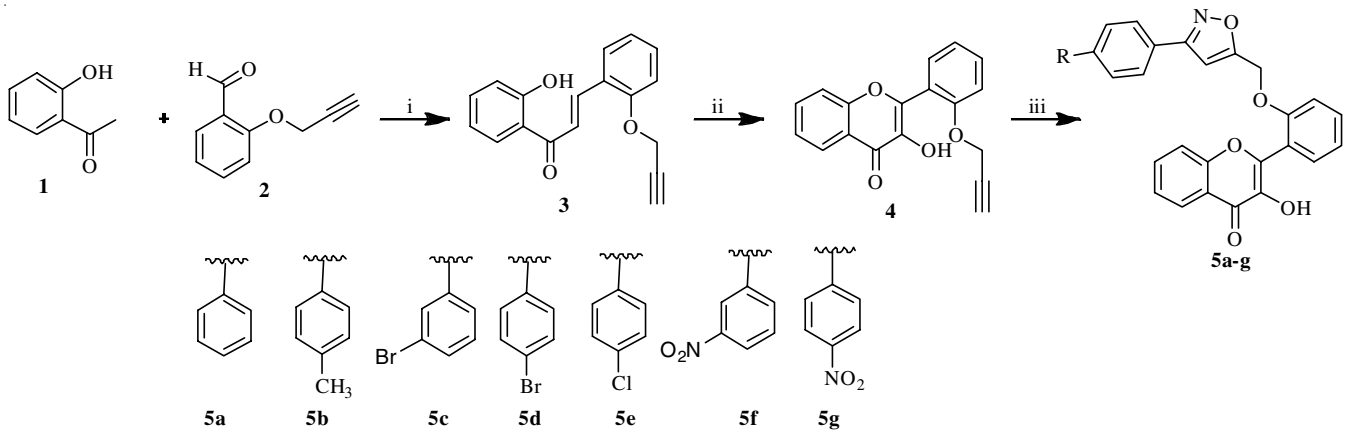
3-Hydroxy-2-(2-(prop-2-yn-1-yloxy)phenyl)-4*H*-chromen-4-one (4): White solid; yield 90%; m.p.: 80-82 ºC. IR (KBr, $\acute{\imath}_{max}$, cm^{-1}): 1710 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (s, 1H), 7.76 (s, 1H), 7.51 (s, 1H), 7.34 (d, *J* = 5.5 Hz, 2H), 7.05 (dd, *J* = 25.3, 20.5 Hz, 4H), 4.97-4.90 (m, 2H), 2.20 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.25, 158.80, 156.03, 150.93, 136.75, 133.03, 131.76, 131.18, 125.51, 124.83, 122.69, 120.41, 118.51, 117.32, 115.77, 80.00, 78.79, 59.70. MS (ESI): *m/z* 292 $[M+H]^+$. Anal. calcd. (found) % for $C_{18}H_{12}O_4$: C, 73.97 (73.83); H, 4.14 (4.08).

General procedure for the synthesis of 3-hydroxy-2-(2-((3-phenylisoxazol-5-yl)methoxy)phenyl)-4*H*-chromen-4-ones (5a-g): Bezaldehyde oximes (**6a-g**) and NaOCl (1 equiv., 0.03 mol%) were dissolved in dichloro methane (10 mL) then added 3-hydroxy-2-(2-(prop-2-yn-1-yloxy)phenyl)-4*H*-chromen-4-one (**4a**, 0.2 g), triethylamine (2 equiv., 0.05 mol%) and the reaction mixture was stirred for 5 h at room temperature. The reaction was monitored with TLC, after completion of the reaction, solvent was evaporated and the products **5a-g** purified by the column chromatogtaphy on silica gel (ethylacetate/hexane 2:8) (**Scheme-I**).

3-Hydroxy-2-(2-((3-phenylisoxazol-5-yl)methoxy)-phenyl)-4*H*-chromen-4-one (5a): White solid; yield 85%; m.p.: 80-82 ºC. IR (KBr, ν_{max}, cm^{-1}): 1712 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.69-7.66 (m, 3H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.41 (td, *J* = 5.3, 2.1 Hz, 3H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.53 (s, 1H), 5.35-5.27 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 195.72, 173.45, 168.25, 162.51, 156.00, 155.68, 145.79, 139.05, 133.62, 132.18, 131.35, 130.20, 130.14, 128.91, 128.47, 126.83, 125.64, 124.55, 121.99, 121.38, 120.59, 118.45, 113.41, 101.38, 62.45. MS (ESI): m/z 411 $[M+H]^+$. Anal. calcd. (found) % for $C_{25}H_{17}NO_5$: C, 72.99 (72.82); H, 4.17 (4.05).

3-Hydroxy-2-(2-((3-(*p*-tolyl)isoxazol-5-yl)methoxy)-phenyl)-4*H*-chromen-4-one (5b): White solid; yield 88%; m.p.: 91-92 ºC. IR (KBr, ν_{max}, cm^{-1}): 1695 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.70- 7.65 (m, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.54-7.48 (m, 2H), 7.43 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.20 (ddd, *J* = 8.4, 6.7, 2.9 Hz, 3H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.48 (s, 1H), 5.29 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.29, 168.03, 162.44, 156.03, 155.72, 145.18, 140.30, 138.91, 133.58, 132.16, 131.34, 129.59, 126.71, 125.77, 125.61, 124.48, 121.97, 121.26, 120.55, 118.47, 113.45, 101.23, 62.51, 21.45. MS (ESI): *m/z* 426 $[M+H]^+$. Anal. calcd. (found) % for $C_{26}H_{19}NO_5$: C, 73.40 (73.56); H, 4.50 (4.64).

2-(2-((3-(3-Bromophenyl)isoxazol-5-yl)methoxy)-phenyl)-3-hydroxy-4*H*-chromen-4-one (5c): Light yellow solid; yield 82%; m.p.: 90-92 ºC. IR (KBr, ν_{max}, cm^{-1}): 1706 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.68 (ddt, *J* = 7.1, 3.7, 1.8 Hz, 2H), 7.55-7.53 (m, 4H), 7.52-7.49 (m, 2H), 7.46 – 7.41 (m, 1H), 7.20 (td, *J* = 7.6, 0.9 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.48 (s, 1H), 5.30 (d, *J* = 0.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.30, 168.63, 161.59, 156.02, 155.63, 145.19, 138.94, 133.59, 132.14, 131.33, 128.31,



Scheme-I: Synthesis of compounds (**5a-g**), reagents and condition: i) KOH, EtOH, rt 12 h; ii) H_2O_2, NaOH, MeOH, 3 h rt; iii) oxime, NaOCl, triethylamine, DCM 4 h, rt

127.56, 125.64, 124.53, 124.47, 122.09, 121.28, 120.61, 118.44, 113.43, 101.11, 62.47. MS (ESI): *m/z* 489 $[M+H]^+$. Anal. calcd. (found) % for $C_{25}H_{16}BrNO_5$: C, 61.24 (61.32); H, 3.29 (3.38).

2-(2-((3-(4-Bromophenyl)isoxazol-5-yl)methoxy)-phenyl)-3-hydroxy-4*H*-chromen-4-one (5d): Light yellow; yield 81%; m.p.: 112-114 ºC. IR (KBr, ν_{max}, cm^{-1}): 1711 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (dt, *J* = 5.2, 2.6 Hz, 1H), 7.68 (ddt, *J* = 7.1, 3.7, 1.8 Hz, 2H), 7.55-7.54 (m, 4H), 7.53-7.49 (m, 2H), 7.46-7.41 (m, 1H), 7.20 (td, *J* = 7.6, 0.9 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.48 (s, 1H), 5.30 (d, *J* = 0.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.30, 168.63, 161.59, 156.02, 155.63, 145.19, 138.94, 133.59, 132.14, 131.33, 128.31, 125.64, 124.53, 124.47, 122.09, 121.28, 120.61, 118.44, 113.43, 101.11, 62.47. MS (ESI): *m/z* 489 $[M+H]^+$. Anal. Calcd. (found) % for $C_{25}H_{16}NO_5Br$: C, 61.24 (61.36); H, 3.29 (3.34).

2-(2-((3-(4-Chlorophenyl)isoxazol-5-yl)methoxy)-phenyl)-3-hydroxy-4*H*-chromen-4-one (5e): White solid; yield 81%; m.p.: 110-112 ºC. IR (KBr, ν_{max}, cm^{-1}): 1714 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.33-8.26 (m, 1H), 7.70-7.66 (m, 2H), 7.63-7.60 (m, 2H), 7.54-7.50 (m, 2H), 7.43 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H), 7.40-7.37 (m, 2H), 7.20 (td, *J* = 7.6, 0.9 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 6.48 (s, 1H), 5.30 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.29, 168.60, 161.53, 156.02, 155.63, 145.16, 138.93, 136.18, 133.59, 132.18, 131.33, 129.19, 128.08, 127.11, 125.64, 124.52, 122.08, 121.27, 120.61, 118.44, 113.43, 101.14, 62.48. MS (ESI): *m/z* 445 $[M+H]^+$. Anal. calcd. (found) % for $C_{25}H_{16}NO_5Cl$: C, 67.35 (67.44); H, 3.62 (3.74).

3-Hydroxy-2-(2-((3-(3-nitrophenyl)isoxazol-5-yl)-methoxy)phenyl)-4*H*-chromen-4-one (5f): White solid; yield 81%; m.p.: 88-90 ºC. IR (KBr, ν_{max}, cm^{-1}): 1721 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (t, *J* = 1.9 Hz, 1H), 8.35-8.26 (m, 2H), 8.12-8.02 (m, 1H), 7.73-7.67 (m, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.56-7.51 (m, 2H), 7.44 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.22 (td, *J* = 7.6, 0.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.60 (s, 1H), 5.32 (d, *J* = 17.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 175.92, 165.41, 163.49, 160.38, 159.85, 159.01, 155.80, 153.38, 152.90, 152.50, 152.25, 144.84, 142.88, 138.68, 138.05, 137.06, 136.60, 136.19, 135.96, 132.73, 132.46, 132.04, 130.27, 130.16, 129.79, 129.25, 129.06, 128.95, 128.78, 128.11, 127.71, 126.55, 126.14, 124.82, 123.60, 123.29, 123.14, 118.45, 118.23, 107.00, 104.07, 61.35. MS (ESI): *m/z* 456 $[M+H]^+$. Anal. calcd. (found) % for $C_{25}H_{16}N_2O_7$: C, 65.79 (65.52); H, 3.53 (3.48).

3-Hydroxy-2-(2-((3-(4-nitrophenyl)isoxazol-5-yl)-methoxy)phenyl)-4H-chromen-4-one (5g): White solid; yield 83%; m.p.: 85-87 ºC. IR (KBr, ν_{max}, cm^{-1}): 1732 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (t, *J* = 1.9 Hz, 1H), 8.33-8.25 (m, 2H), 8.11-8.03 (m, 1H), 7.73-7.67 (m, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.56-7.51 (m, 2H), 7.44 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.22 (td, *J* = 7.6, 0.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.60 (s, 1H), 5.32 (d, *J* = 18.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.28, 169.38, 160.68, 156.03, 155.54, 148.62, 145.02, 139.26, 138.92, 138.48, 133.69, 132.54, 132.20, 131.39, 130.44, 130.07, 125.66, 124.74, 124.62, 122.23, 121.80, 121.25, 120.68, 118.36, 113.44, 101.18, 62.43. MS (ESI): m/z 456 $[M+H]^+$. Anal. calcd. (found) for $C_{25}H_{16}N_2O_7$: C, 65.79 (65.63); H, 3.53 (3.42).

RESULTS AND DISCUSSION

Chemistry: 2-Hydroxyacetophenone (**1**) condensed with 2-proporgyloxy benzaldehyde (**2**) in presence of KOH/ethanol at room temperature for 18 h to give corresponding 2-hydroxy chalcone (**3**). Intermediate **3** was treated with H_2O_2/NaOH in methanol to involve in Algar-Flynn-Oyamada (AFO) cyclization to yield 3-hydroxyflavones (**4**). The hydroxyl intermediate **4** was reacted with functionalized benzoldoximes using oxidant NaOCl to afford flavone/isoxazole derivatives (**5a-g**) (**Scheme-I**) in good yields (80-85%). A variety of oxidants NaOCl/Et_3N, I_2, BF_3·Et_2O, CAN, $Sc(OTf)_3$ were studied using appropriate solvents for the *in situ* nitrile oxides formation from corresponding benzaldoximes by regioselective intermolecular 1,3-dipolar cycloaddition at terminal alkyne of compound **4** to give flavone/isoxazole hybrids (**5a-g**) in high yields. From the employed various oxidants /catalysts we found that higher yields of products **5a-g** with NaOCl/Et_3N oxidant. All the final desired products **5a-g** structures were established with spectral analysis.

In the ^{1}H NMR spectra of compound **5a**, the newly formed isoxazole protons appeared at δ 6.53 (s, 1H), 5.35-5.27 (s, 2H, OCH_2). In ^{13}C NMR of compound **5a**, isoxazole carbons resonated at δ 62.45 (OCH_2), 101.38 (=CH). A plausible mechanism (Fig. 2) involve the formation of chloro benzaldoxime

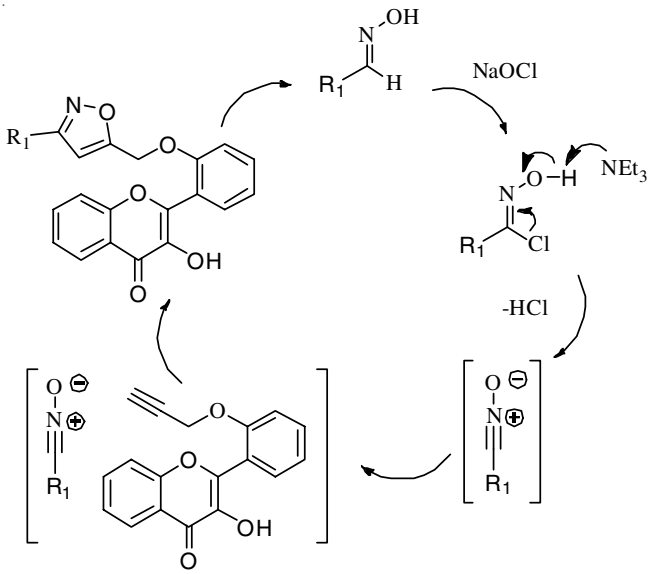


Fig. 2. Plausible mechanism for the formation of compound **5a**

with NaOCl followed by *in situ* generation of nitrile oxide and regioselective 1,3-dipolar cycloaddition at terminal alkyne to transform it into five membered isoxazole ring.

Conclusion

A developed simple and practical one-pot methodology for the synthesis of isoxazole embedded flavone derivatives (**5a-g**) by coupling of generated nitrile oxides to the terminal alkyne (**4**) in presence of environmentally benign sodium hypochloride in good yields under mild reaction conditions.

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CONFLICT OF INTEREST

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

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