Journal of the Korean Chemical Society
2011, *Vol. 55, No. 4*
Printed in the Republic of Korea
DOI 10.5012/jkcs.2011.55.4.656

Quinoline moiety를 가지고 있는 1,3,4-oxadiazol 유도체의 합성 및 항균활성

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(접수 2011. 2. 13; 수정 2011. 3. 31; 게재확정 2011. 4. 4)

Synthesis and Antibacterial Evaluation of Some Novel 1,3,4-oxadiazol Derivatives Incorporated with Quinoline Moiety

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(Received February 13, 2011; Revised March 31, 2011; Accepted April 4, 2011)

요 약. 5-(3,4,5-Triethoxyphenyl)-1,3,4-oxadiazole-2-thiol **6**을 3-(bromomethyl)-2-chloroquinoline or 2-(*p*-tolyloxy)-3-(bromomethyl) quinoline **4a-j** 화합물과 반응시켜서 3-((5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazol-2-ylthio)methyl)-2-chloroquinoline 또는 3-((5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazol-2-ylthio)methyl)-2-(*p*-tolyloxy)quinoline **7a-j**를 합성하였다. 합성한 화합물들에 대한 항균활성을 측정하였으며, 화합물 **7d**, **7i** 및 **7j** 은 우수한 활성을 나타내었다.

주제어: Gallic acid, 1,3,4-Oxadiazole, Quinoline-3-carbaldehyde, 항균활성

ABSTRACT. 5-(3,4,5-Triethoxyphenyl)-1,3,4-oxadiazole-2-thiol **6** on treatment with substituted 3-(bromomethyl)-2-chloroquinoline or 2-(*p*-tolyloxy)-3-(bromomethyl)quinoline **4a-j** afforded the corresponding 3-((5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazol-2-ylthio)methyl)-2-chloroquinoline or 3-((5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazol-2-ylthio)methyl)-2-(*p*-tolyloxy)quinoline **7a-j**, in the presence of K_2CO_3 and DMF under stirring at ambient temperature. All the synthesized compounds were further screened for their antibacterial activities. Some of our compounds showed excellent antibacterial activities against test organisms and reference standard.

Keywords: Gallic acid, 1,3,4-Oxadiazole, Quinoline-3-carbaldehyde, Antibacterial activity

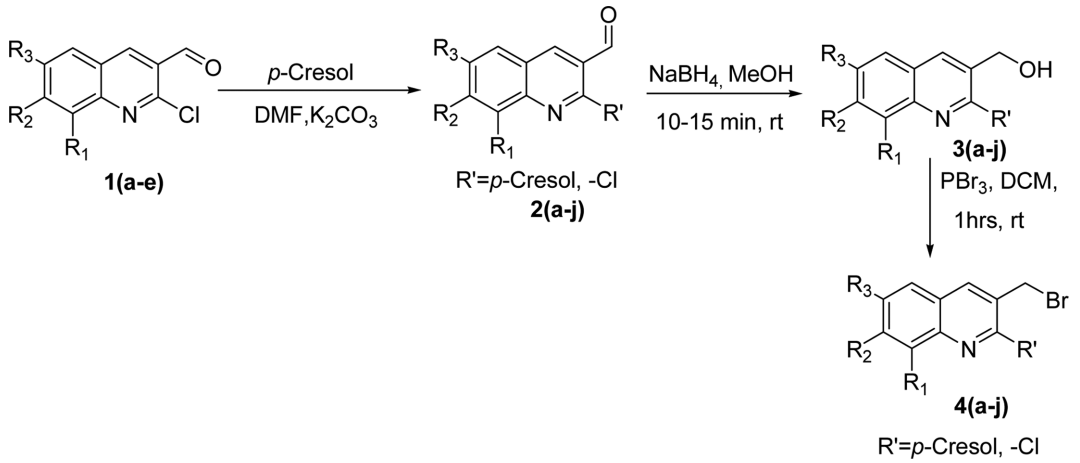
INTRODUCTION

Quinoline scaffold is prevalent in a variety of pharmacologically active compounds as well as in naturally occurring products.[1] Quinoline-containing drugs are widely used in the treatment of malaria,[2] HIV-1 replication inhibitors,[3] antimicrobial and anti-tuberculosis drugs[4] and antihelmintic properties.[5] Beside this quinolines have also occupied a unique position in the design and synthesis of novel biologically active compounds since they are often used as anti-inflammatory, antiasthmatic, antibacterial, antihypertensive, antitumor,[6,7] antiproliferative,[8] anticancer[9] and antiparasitic agents.[10]

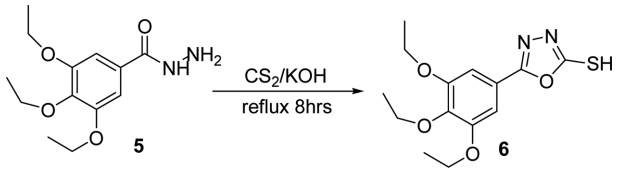
In addition, gallic acid and its related compounds are widely distributed in fruits & plants.[11,12] It has been reported to have anticarcinogenic, antioxidative, antimutagenic, antiallergic and anti-inflammatory activities.[13] Gallic acid has been a building block of choice for different pharmaceutical leads due to the presence of this moiety in several bioactive natural products.[14] Hence, numerous derivatisations have been done and are reported as anticancer,[15] HIV-1 Integrase[16] and HIV-1RT inhibitors,[17] antioxidants,[18] antimalarials agents,[19] etc.

Literature review also revealed that 1,3,4-Oxadiazoles are an important class of heterocyclic compounds with a wide range of pharmaceutical and biological activities. Their synthesis and transformations have been of interest from a long time. They have revealed anti-inflammatory, anticonvulsant and analgesic activities.[20,21] They have also shown antibacterial,[22] antifungal[23] and muscle relaxant[24] properties.

Prompted by the above-mentioned biological properties of quinoline and oxadiazole it was contemplated to synthesize a novel series of quinoline incorporated oxa-



***Scheme* 1.**



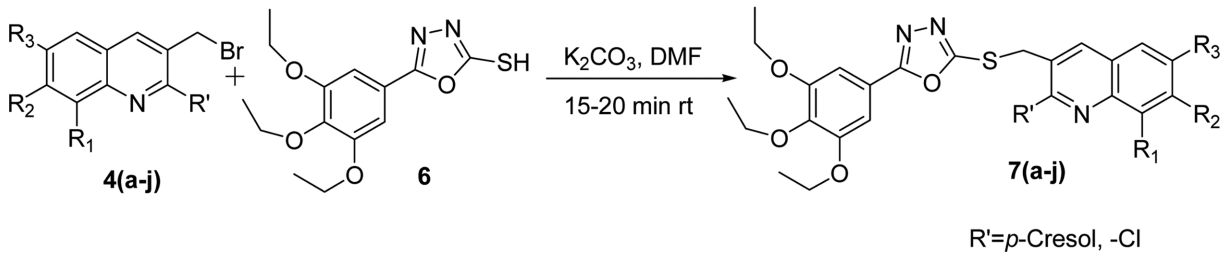
***Scheme* 2.**

diazole and its derivatives (*Scheme* 1, 2 & 3, *Table* 1). Antibacterial activities of the newly synthesized compounds are discussed in this paper.

RESULT AND DISCUSSION

Chemistry

In continuation on our research work to synthesize potent bioactive heterocycles.[25] Herein, we report the synthesis of a series of oxadiazole derivatives synthesized *via* 3-(bromomethyl)-2-chloroquinolines or 2-(*p*-tolyloxy)-(bromomethyl)quinolines **4a-j** which were synthesized by reduction of substituted 2-chloroquinoline-3-carbaldehyde or 2-(*p*-tolyloxy)quinoline-3-carbaldehyde **2a-j** in presence of catalytic amount of $NaBH_4$ and methanol giving (2-



***Scheme* 3.**

***Table* 1.** Characterization data for compounds **7(a-j)**

Compounds	R_1	R_2	R_3	R'	M.P. (°C)	Yield (%)
7a	H	H	H	-Cl	100-103	69
7b	CH_3	H	H	-Cl	79-81	65
7c	H	CH_3	H	-Cl	105-107	75
7d	H	H	CH_3	-Cl	120-123	81
7e	H	H	OCH_3	-Cl	116-118	78
7f	H	H	H	4-$CH_3C_6H_4O$-	80-82	73
7g	CH_3	H	H	4-$CH_3C_6H_4O$-	107-109	68
7h	H	CH_3	H	4-$CH_3C_6H_4O$-	82-84	74
7i	H	H	CH_3	4-$CH_3C_6H_4O$-	92-95	79
7j	H	H	OCH_3	4-$CH_3C_6H_4O$-	119-121	82

chloroquinolin-3yl)methanol or (2-(*p*-tolyloxy)quinolin-3yl)methanol **3a-j**, which was further brominated with PBr_3 in presence of DCM under ice cold condition to afford **4a-j** (*Scheme* 1).

On the other hand, 3,4,5-triethoxybenzohydrazide **5** was further reacted with carbon disulfide in presence of potassium hydroxide under reflux condition to afford 5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazole-2-thiol **6** (*Scheme* 2). Finally 5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazole-2-thiol **6** was alkylated with substituted 3-(bromomethyl)-2-chloroquinoline or 2-(*p*-tolyloxy)-(bromomethyl)quinoline **4a-j** to afford 3-((5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazol-2-ylthio)methyl)-2-chloroquinoline or 3-((5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazol-2-ylthio)methyl)-2-(*p*-tolyloxy)quinoline **7a-j** in presence of K_2CO_3 and DMF at ambient temperature stirring for 15-20 min.

Spectral analysis

The structures of the synthesized compounds were confirmed by spectral analysis (IR, ^{1}H NMR and Mass). The IR spectrum of compound **2a** showed a peak at 1722 cm^{-1} due to C=O stretch. In ^{1}H NMR spectrum it exhibited two singlets, one at δ 2.41 due to CH_3 proton, second at δ 10.65 due to CHO proton. Mass spectrum was consisted with assigned structure.

As estimated the ^{1}H NMR spectrum of compound **3a** showed singlet at δ 3.71 due to the presence of OH proton, while another singlet at δ 10.65 due to CHO proton get disappeared due to reduction of aldehyde. Similarly, in the ^{1}H NMR spectrum of compound **4a** the broad peak of OH disappeared due to bromination.

^{1}H NMR spectrum of compound **6** showed a highly deshielded singlet at δ 11.23 attributed to SH proton, which get disappeared in compound **7a** due to the alkylation of compound **6** with compound **4a-j**. The IR and mass spectral data of compound **4**, **6** and **7a** were consisted with the assigned structure.

The antibacterial screening results revealed that most of the newly synthesized compounds exhibited promising antibacterial activities. Generally, the test compounds showed better activity against the Gram Negative bacteria (*Table* 2). Out of the compounds tested, compounds **7d**, **7i** and **7j** exhibited excellent antibacterial activity against the Gram Negative bacteria i.e. *Salmonella typhi* and *Pseudomonus aeroginosa* and moderate activity against gram positive bacteria i.e. *Bacillus subtilis* and *Staphylococcus aureus* as compared with the broad spectrum antibiotic Streptomycine and Ampicilline.

***Table* 2.** Minimal inhibitory concentrations (MIC μg/mL) of tested compounds **7(a-j)**

Tested Compounds	*B. subtilis*	*S. aureus*	*S. typhi*	*P. aeroginosa*
7a	>300	>300	>200	>200
7b	>250	>250	200	200
7c	300	300	>200	>200
7d	>150	>150	>100	>100
7e	200	200	>150	>150
7f	>200	>200	>150	>150
7g	>300	>300	200	200
7h	300	300	200	200
7i	150	150	100	100
7j	>200	>200	100	100
Streptomycin	100	100	50	50
Ampicilline	50	50	25	25

Conclusion

In conclusion, we have synthesized some novel 1,3,4-oxadiazol derivatives incorporated with quinoline moiety and evaluate their *in-vitro* antibacterial activity. Out of the compounds tested, compounds **7d**, **7i** and **7j** exhibited excellent antibacterial activity against the Gram Negative bacteria i.e. *Salmonella typhi* and *Pseudomonas aeroginosa* and moderate activity against gram positive bacteria i.e. *Bacillus subtilis* and *Staphylococcus* as compared with commercially available drug.

EXPERIMENTAL SECTION

All chemicals and solvents were purchased from Merck, Spectrochem and S.D. Fine-chem. (India). Melting points were determined in open capillaries on Kumar's melting point apparatus (India) and are uncorrected. IR spectra were recorded on JASCO FT-IR 4100, Japan using KBr discs. ^{1}H-NMR spectra were recorded on a Varian as 400 MHz spectrometer in $CDCl_3$/DMSO-*d*6, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (*J*) are expressed in hertz (Hz). Mass spectra were recorded on Single-Quadrupole Mass Detector 3100, Waters. Elemental analyses were performed on CHNS analyzer Flash 1112, Thermo Finnigan. The progress of the reactions was monitored by TLC on Merck silica plates. Multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), m (multiplet). Solvents were commercially available materials of reagent grade.

Synthesis of 2-chloroquinoline-3-carbaldehyde (1a): The compound **1a** was prepared as per procedure reported in the literature.[2] m.p: 148 ºC IR-(KBr): 2739, 1710, 1605 and 755 (cm^{-1}); ^{1}H NMR-(DMSO-*d6*): δ 10.36 (s, 1H), 8.57

(s, 1H), 8.06 (d, 1H), 7.92 (m, 2H), 7.75 (dd, 1H); MS: m/z 192.3 (M+); Anal. Calcd for $C_{10}H_6ClNO$: C, 62.68; H, 3.16; N, 7.31; O, 8.35; found C, 62.74; H, 3.21; N, 7.20; O, 8.31.

Synthesis of 2-(p-tolyloxy)quinoline-3-carbaldehyde (2a): To a mixture of *p*-cresol (0.031 mmol, 3.38 gms) and K_2CO_3 (0.068 mmol, 9.51 gms) in DMF, compound **1a** (0.031 mmol, 6 gms) was added and the reaction mixture was stirred at 85-90 ºC for 5 hrs. The completion of the reaction was monitored by TLC. After completion, water (50 ml) was poured in the reaction mixture & the solid thus obtained was filtered off & recrystallized from ethyl acetate. **2a** m.p: 129 ºC, IR-(KBr): 2945, 2750, 1720, 1600 and 1225 (cm^{-1}); ^1H NMR-(DMSO-*d6*): δ 10.65 (s, 1H), 8.71 (s, 1H), 7.88 (d, 1H), 7.74 (d, 1H), 7.71 (m, 1H), 7.45 (m, 1H), 7.39 (d, 2H), 7.19 (d, 2H), 2.41 (s, 3H); MS: m/z 264.1 (M+); Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32; O, 12.15; found C, 77.63; H, 5.01; N, 5.21; O, 12.09.

Synthesis of (2-chloroquinolin-3-yl)methanol (3a): To the mixture of compound **2a** in methanol, sodium borohydride was added portion wise, & the mixture was stirred at room temperature for 15-20 min. The completion of the reaction was monitored by TLC & reaction mass was concentrated under vacuum. The reaction mass was poured into ice cold water and the solid thus obtained was filtered & recrystallized from ethyl acetate.

Compounds 3a: m.p: 134 ºC IR-(KBr): 2945, 2750, 1722, 1600 and 1125 (cm^{-1}); ^1H NMR-(DMSO-d_6): δ 8.21 (s, 1H), 8.18 (dd, 1H), 7.91 (m, 1H), 7.82 (dd, 1H), 7.51 (dd, 1H), 4.96 (s, 2H), 3.75 (s, 1H); MS: m/z 193.9 (M+); Anal. Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.23; O, 8.26; found C, 62.21; H, 4.19; N, 7.18; O, 8.21.

Compounds 3f: IR-(KBr): 3427, 2920, 1720, 1520 and 1225 (cm^{-1}); ^1H NMR-(DMSO-*d6*): δ 8.05 (s, 1H), 7.62 (d, 1H), 7.48 (d, 2H), 7.41 (d, 1H), 7.25 (dd, 2H), 7.23 (d, 2H), 4.74 (s, 2H), 4.01 (s, 1H), 3.51 (s, 1H), 2.46 (s, 3H); MS: m/z 266.1 (M+); Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28; O, 12.06; found C, 77.13; H, 5.75; N, 5.17; O, 12.01.

Synthesis of 3-(bromomethyl)-2-chloroquinoline (4a): Compound **3a** was dissolved in DCM at 5 ºC, after 10-15 min. of stirring calculated amount of PBr_3 was added drop wise and the mixture was stirred at room temperature for 1 hr. The completion of the reaction was monitored by TLC. The DCM was removed under vacuum and the reaction mass was poured on ice cold water & the solution was neutralized by adding saturated solution of $NaHCO_3$. The solid thus obtained was filtered and recrystallized from ethyl acetate.

Compound 4a: m.p: 179 ºC IR-(KBr): 1670, 1630, 750 and 710 (cm^{-1}); ^1H NMR-($CDCl_3$): δ 8.25 (s, 1H), 8.16 (dd, 1H), 7.68 (dd, 1H), 7.40 (m, 1H), 7.52 (m, 1H), 4.47 (s, 2H); MS: m/z 257.4 (M+); Anal. Calcd for $C_{10}H_7BrClN$: C, 46.82; H, 2.75; N, 5.46; found C, 46.93; H, 2.81; N, 5.34.

Compound 4i: IR-(KBr): 2930, 1624, 1560, 1150 and 735 (cm^{-1}); ^1H NMR-($CDCl_3$): δ 8.05 (s, 1H), 7.61 (dd, 1H), 7.48 (s, 1H), 7.40 (dd, 1H), 7.23 (m, 2H), 7.16 (d, 2H), 4.74 (s, 2H), 2.46 (s, 3H), 2.38 (s, 3H); MS: m/z 343.1 (M+); Anal. Calcd for $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71; N, 4.09; O, 4.68; found C, 63.31; H, 4.83; N, 3.96; O, 4.52.

Synthesis of 5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazole-2-thiol (6): To the compound **5** (0.01 mole) in ethanol 50 ml was added a solution of KOH (0.015 mole) in ethanol 20 ml, followed by the addition of CS_2 (20 ml). The reaction mixture was heated under reflux for 8hrs. Then it was concentrated, acidified with dilute hydrochloric acid & the resulting solid was collected, washed with water & recrystallized with ethyl acetate to afford the desired product. m.p: 203 ºC, IR-(KBr): 2870, 2580 and 1570 (cm^{-1}); ^1H NMR-(CDCl3): δ 11.23 (s, 1H), 7.13 (s, 2H), 4.02 (m, 6H), 1.54 (t, 9H); MS: m/z 310.9 (M+); Anal. Calcd for $C_{14}H_{18}N_2O_4S$: C, 54.18; H, 5.85; N, 9.03; O, 20.62; found C, 54.31; H, 5.92; N, 8.91; O, 20.51.

Synthesis of 3-((5-(3,4,5-triethoxyphenyl)-1,3,4-oxadiazol-2-ylthio)methyl)-2-(p-tolyloxy) quinoline) (7a): To the mixture of **6** (1 eq.) and K_2CO_3 (1.2 eq.) in DMF, **4a** (1.2 eq.) was added and the reaction mixture was stirred at room temperature for 15-20 min. The completion of the reaction was monitored by TLC. After completion ice cold water was added to the reaction mass and the solid thus obtained was filtered off and recrystallized from ethyl acetate.

Compound 7a: IR-(KBr): 2890, 1680, 1180 and 1090 (cm^{-1}); ^1H NMR-($CDCl_3$): δ 8.27 (dd, 1H), 8.13 (s, 1H), 7.92 (dd,1H), 7.86 (dd, 1H), 7.61 (m, 1H), 6.69 (s, 2H), 4.35 (s, 2H), 3.95 (m, 6H), 1.54 (t, 9H); MS: m/z 486.8 (M+); Anal. Calcd for $C_{24}H_{24}ClN_3O_4S$: C, 59.31; H, 4.98; N, 8.65; S, 6.60; found C, 59.52; H, 5.03; N, 8.38; S, 6.54.

Compound 7c: IR-(KBr): 2922, 1660, 1310 and 1210 (cm^{-1}); ^1H NMR-($CDCl_3$): δ 8.21 (d, 1H), 8.10 (s, 1H), 7.87 (d, 1H), 7.45 (s, 1H), 6.71 (s, 2H), 4.32 (s, 2H) 4.01 (m, 6H), 3.95 (s, 3H), 1.57 (t, 9H); MS: m/z 515.9 (M+); Anal. Calcd for $C_{25}H_{26}ClN_3O_5S$: C, 58.19; H, 5.08; N, 8.14; S, 6.21; found C, 58.34; H, 5.16; N, 8.01; S, 6.13.

Compound 7f: IR-(KBr): 2910, 1670, 1315 and 1275 (cm^{-1}); ^1H NMR-($CDCl_3$): δ 8.02 (dd, 1H), 7.92 (s, 1H),

7.81 (dd, 2H), 7.56 (m, 1H), 7.32 (d, 2H), 7.21 (d, 2H), 7.05 (s, 2H), 4.45 (s, 2H), 3.94 (m, 6H), 2.81 (s, 3H), 1.55 (t, 9H); MS: m/z 558.2 (M+); Anal. Calcd for $C_{31}H_{31}N_3O_5S$: C, 66.77; H, 5.60; N, 7.54; S, 5.75; found C, 66.86; H, 5.67; N, 7.43; S, 5.69.

Compound 7i: IR-(KBr): 2950, 1645, 1290 and 1150 (cm^{-1}); ^1H NMR-($CDCl_3$): δ 8.05 (d, 1H), 7.89 (s, 1H), 7.68 (d, 2H), 7.27 (d, 2H), 7.02 (d, 2H), 6.63 (s, 2H), 4.37 (s, 2H), 3.94 (m, 6H), 2.86 (s, 3H), 1.57 (t, 9H); MS: m/z 572.1 (M+); Anal. Calcd for $C_{32}H_{33}N_3O_5S$: C, 67.23; H, 5.82; N, 7.35; S, 5.61; found C, 67.41; H, 5.91; N, 7.25; S, 5.53.

Antibacterial activity

The MICs of the chemical compounds assays were carried out as described by well-diffusion method.[26] Two Gram-positive (Staphylococcus aureus ATCC 25923 and Bacillus subtilis ATCC 6633) and two Gram-negative (Salmonella typhimurium (ATCC No, 23564) and Pseudomonas aeruginosa ATCC 27853) bacteria were used as quality control strains. Streptomycin and Ampicilline were used as standard antibacterial agent. The bacterial liquid cultures were prepared in fusion broth for their activity tests. The compounds were dissolved in DMSO at concentration of 1 mg/ml. Antibacterial activity of DMSO against the test organisms was investigated, and was found to be nil. Molten nutrient agar (15 cm^3), kept at 45 °C, was then poured into the Petri dishes and allowed to solidify. Ten millimeter diameter holes were then punched carefully using a sterile cork borer and completely filled with the test solutions. The plates were incubated for 24 h at 37 °C. After 24 h, the inhibition zone that appeared around the holes in each plate was measured. Antibacterial activity was determined by examining the minimal inhibitory concentration (MICs, μg/mL) of the tested compounds, which are recorded in (*Table* 2).

Acknowledgements. The authors are thankful to to The Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, for his valuable support and laboratory facilities. And RSJ is thankful to University Grants Commission, New Delhi, for awarding the fellowship.

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