SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL EVALUATION OF FEW 2, 3-SUBSTITUTED QUINOXALINES

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ABSTRACT

The quinoxaline derivatives (**i-v**) were synthesized through cyclization-oxidation of α - bromo carbonyl compounds with o-phenyl diamines (**7a** and **10a**) and further coupling at 6-position via Suzuki reaction using PdCl_2 (dppf).DCM, ter. BuNH_2 , Na_2CO_3 in IPA, H_2O refluxed for 16 h. As the results of antibacterial screening tests done by paper disc method, quinoxaline derivatives (**i**) and (**v**) revealed significant inhibition zone on *Bacillus spericus* and quinoxaline derivatives (**iii**) and (**v**) on *Escherichia coli* cultures.

Key words: Quinoxaline, Suzuki Coupling, microwave, *Bacillus spericus*, *Escherichia coli*

INTRODUCTION

Quinoxaline derivatives are an important class of nitrogen containing heterocyclic in medicinal chemistry, have been reported to show biological, including antibacterial activity¹. For example, quinoxaline is a part of various antibiotics such as echinomycin, levomycin, and actinoleutin that are known to inhibit growth of gram positive bacteria², and are reactive against various transplantable tumors³. These have high activity and a broad spectrum of antibacterial activity.

In addition, the frequency of serious nosocomial bacterial and fungal infections is rising due to the use of newer and more powerful antimicrobial agents. As additional new antimicrobial agents are being found, microorganisms become more resistant to existing chemotherapies. Thus, there is continuous need to develop novel antimicrobial compounds that would be effective against these and other pathogens¹⁶.

In recent times, microwave^{4, 5} syntheses in organic chemistry is quickly growing. Many organic reactions proceed much faster with higher yields under microwave irradiation compared to conventional heating. It has long been known that molecules undergo excitation with electromagnetic radiation is a technique for microwave synthesis^{6,7}. In present synthesis, AlCl_3 catalyzes the Friedel-Crafts acylation on *H*-imidazo[1,2-*a*]pyridine (**1a**) efficiently under microwave irradiation in solvent free conditions. We synthesized and studied antibacterial activity of few 2, 3- substituted quinoxaline derivatives, including those with substituted phenyl ring by replacing halide at 6- position.

EXPERIMENTAL

All reagents and solvents were purchased from Srinivasa traders, Hyderabad, India. Microwave reactions were carried out using monomode and multi-power biotage sixty microwave instrument. TLC (Pre-coated silica gel 60 F₂₅₄, Merck) was performed with visualization by UV-light. Melting points were taken in open capillary tubes and corrected with reference to benzoic acid. IR spectra in KBr pellets were recorded. ¹H NMR recorded in CDCl_3 and DMSO-d_6 with 200 MHz instrument as TMS was used as an internal standard. MS spectra were recorded on Agilent 6310 Ion Trap and Shimadzu LCMS (e/z and relative intensity).

1-(H-imidazo[1,2-*a*]pyridin-3-yl)propan-1-one (3a): The mixture of *H*-imidazo[1,2-*a*]pyridine (**1a**) (500 mg, 4.23 mmol), propanoic anhydride (**2a**) (2.75 g, 21.18 mmol) and AlCl_3 (1.12 g, 8.46 mmol) were irradiated in microwave for 20 min at 100°C. The reaction mixture was neutralized by using sat. Na_2CO_3 and extracted product into ethyl acetate (25 mL), dried (anhy. Na_2SO_4) and concentrated by using rotavapour. The crude material was purified through silica gel column chromatography, eluted product by using 2% MeOH/DCM to afford 1-(H-imidazo[1,2-*a*]pyridin-3-yl)propan-1-one (**3a**) (352 mg, 47.7% yield) as a solid. **MS** (e/z): 175 (M+1); IR cm^{-1} 1632 (C=O); ¹H NMR (200 MHz, CDCl_3): δ 8.56 (d, *J*=6.6 Hz, 1H), 8.63 (s, 1H), 7.84 (d, *J*=9.2 Hz, 1H), 7.63 (t, *J*=6.8 Hz, 1H), 7.26 (t, *J*=6.6 Hz, 1H), 3.04-2.93 (q, 2H), 1.15 (t, *J*=7.4 Hz, 3H).

2-bromo-1-(H-imidazo[1,2-*a*]pyridin-3-yl)propan-1-one (4a): To a solution of 1-(H-imidazo[1,2-*a*]pyridin-3-yl)propan-1-one (**3a**) (300 mg, 1.72 mmol) in diethyl ether (10 mL) and dichloromethane (2 mL) was added bromine (325 mg, 2.06 mmol) drop wise at 0°C. The reaction mixture was warmed to RT, and further stirred for 30 min. The reaction mixture was diluted with diethyl ether (20 mL). The precipitated solids were filtered and dried by using vacuum to afford 2-bromo-1-(H-imidazo[1,2-*a*]pyridin-3-yl)propan-1-one (**4a**) (200 mg, 46% yield) as a pale brown solid. **MS** (e/z): 254 (M+1); IR cm^{-1} 1665 (C=O); ¹H NMR (200 MHz, CDCl_3): δ 9.82 (d, *J*=6.6 Hz, 1H), 9.24 (s, 1H), 8.60 (d, *J*=9.2 Hz, 1H), 8.15 (t, *J*=6.8 Hz, 1H), 7.62 (t, *J*=6.6 Hz, 1H), 5.51-5.59 (q, 1H), 2.01 (d, *J*=7.4 Hz, 3H).

6-bromo-3-(H-imidazo[1,2-*a*]pyridin-3-yl-methylquinoxaline (5a): To a solution of tert-butyl 2-amino-4-bromophenylcarbamate (**10a**) (150 mg, 0.522 mmol) in acetonitrile (5 mL) were added triethylamine (132 mg, 1.305 mmol) and 2-bromo-1-(H-imidazo[1,2-*a*]pyridin-3-yl)propan-1-one (**4a**) (132 mg, 0.522 mmol) slowly at RT. The reaction mixture was further stirred for 12 h. Trifluoro acetic acid (0.5 mL) was added to the above reaction mixture drop wise at RT and stirred for 5 h at 85°C. The reaction mixture was concentrated by using rotavapour. The residue was diluted with water and adjusted pH ~ 8 by using Sat. NaHCO_3 solution. The precipitated solids were filtered, washed with water and dried under vacuum to afford 6-bromo-3-(H-imidazo[1,2-*a*]pyridin-3-yl-methylquinoxaline (**5a**) (101 mg, 56% yield) as a solid. **MS** (e/z): 340 (M+1). ¹H NMR (200 MHz, DMSO-d_6): δ 9.87 (d, *J*=4.2 Hz, 1H), 8.73-8.71 (m, 2H), 7.99-7.81 (m, 2H), 7.21 (m, 1H), 7.01 (t, *J*=6 Hz, 1H), 6.70 (d, *J*=7.8 Hz, 1H), 2.99 (s, 3H).

6-(4-fluorophenyl)-3-(H-imidazo[1,2-*a*]pyridin-3-yl)-2-methylquinoxaline (i): 6-bromo-3-(H-imidazo[1,2-*a*]pyridin-3-yl-methylquinoxaline (**5a**) (75 mg, 0.221 mmol) was dissolved in *i*PrOH- H_2O (mL, 1:1) and de-oxygenated by bubbling with N_2 for 5 min. Then PdCl_2 (dppf).DCM (cat), tert- BuNH_2 (1.8 mL), Na_2CO_3 (47 mg, 0.442) were added to the reaction mixture at RT. After being stirred for 15 min, 4-fluoro phenylboronic acid (**6a**) (31 mg, 0.221 mmol) was added to the reaction mixture and heated at 100°C for 16 h. After the completion, the volatiles were concentrated by using rotavapour. The residue was diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over anhy. Na_2SO_4 and concentrated by using rotavapour. The obtained crude material was purified by column chromatography, eluted product by using 1% MeOH/DCM to afford 6-(4-fluorophenyl)-3-(H-imidazo[1,2-*a*]pyridin-3-yl)-2-methylquinoxaline (**i**) (32 mg, 40% yield) as a solid. **MS** (e/z): 355 (M+1). ¹H NMR (200 MHz, DMSO-d_6): δ 9.64 (d, *J*=7 Hz, 1H), 8.86 (s, 1H), 8.36 (s, 1H), 8.24 (s, 2H), 8.09-7.95 (m, 4H), 7.53 (t, *J*=6.6 Hz, 1H), 7.40 (t, *J*=8.8 Hz, 2H), 2.98 (s, 3H).

1,2-dihydro-3-(H-imidazo[1,2-*a*]pyridine-3-yl)-2-methylquinoxaline (ii): To a solution of 2-bromo-1-(H-imidazo[1,2-*a*]pyridin-3-yl)propan-1-one (**4a**) (100 mg, 0.395 mmol) in acetonitrile (10 mL) was added benzene-1,2-diamine (**7a**) (43 mg, 0.395 mmol) at RT, and further stirred for 4 h. The reaction mixture was concentrated by using rotavapour. The residue was diluted with water and pH of the solution was adjusted to ~8 by using sat. NaHCO_3 . The precipitated solids were filtered, washed with water and dried

under vacuum to afford 1,2-dihydro-3-(H-imidazo[1,2-a]pyridine-3-yl)-2-methylquinoxaline (**ii**) (40 mg, 39% yield) as a solid. **MS** (*m/z*): 263 (*M*+1); **IR** cm^{-1} 3375 (-NH); **¹H NMR** (200 MHz, DMSO-*d*₆): δ 10.26 (d, *J*=7.2 Hz, 1H), 8.71 (s, 1H), 7.96-7.81 (m, 3H), 7.46-7.43 (m, 1H), 7.32 (d, *J*=6.8 Hz, 1H), 7.01 (t, *J*=7.8 Hz, 1H), 6.70 (d, *J*=7.8 Hz, 2H), 6.58 (brs, 1H), 4.78-4.73 (q, 1H), 1.17 (d, *J*=6.6 Hz, 3H).

tert-butyl 4-bromo-2-nitrophenylcarbamate (9a): To a solution of 4-bromo-2-nitrobenzenamine (**8a**) (2.5 g, 11.5 mmol) in DMF (20 mL) was added NaH (60%) (690 mg, 17.25 mmol) portion wise at 0°C. Then added ditertiary butyl dicarbonate (3 g, 13.8 mmol) drop wise at 0°C. The reaction mixture was warmed to RT, and further stirred for 4 h. The reaction mixture was slowly poured into ice-cold water (50 mL), and further stirred for 1 h. The precipitated solids were filtered, washed with water and dried under vacuum. The crude material was purified through silica gel column chromatography, eluted product by using 1% ethyl acetate/hexanes to afford tert-butyl 4-bromo-2-nitrophenylcarbamate (**9a**) (2.1 g, 57% yield) as yellow solid. **MS** (*m/z*): 318 (*M*+1); **IR** cm^{-1} 3349 (-NH), 1636 (C=O), 1499 (N=O); **¹H NMR** (200 MHz, DMSO-*d*₆): δ 9.60 (brs, 1H), 8.51 (d, *J*=8.4 Hz, 1H), 8.32 (d, *J*=2.2 Hz, 1H), 7.64 (dd, *J*=8.6, 2.4 Hz, 1H), 1.59 (s, 9H).

tert-butyl 2-amino 4-bromophenylcarbamate (10a): To a suspended solution of tert-butyl 4-bromo-2-nitrophenylcarbamate (**9a**) (2 g, 6.3 mmol) in methanol (20 mL) was added hydrazine hydrate (6 mL) and ferric chloride (cat) at RT. The reaction mixture was heated to reflux, and further stirred for 3 h. The reaction mixture was filtered through celite bed, washed with ethyl acetate. The filtrate was concentrated by using rotavapour. The crude material was diluted with water and then stirred for 30 min. The precipitated solids were filtered, washed with water and dried under vacuum to afford tert-butyl 2-amino 4-bromophenylcarbamate (**10a**) (1.4 g, 77% yield) as a solid. **MS** (*m/z*): 288 (*M*+1); **IR** cm^{-1} 3410 (-NH), 3345 (-NH), 1686 (C=O); **¹H NMR** (200 MHz, DMSO-*d*₆): δ 8.31 (brs, 1H), 7.15 (d, *J*=8.4 Hz, 1H), 6.85 (d, *J*=2.2 Hz, 1H), 6.64 (dd, *J*=6.2, 2.4 Hz, 1H), 5.18 (brs, 2H), 1.44 (s, 9H).

1-(2-methylimidazo[1,2-b]pyridazin-3-yl)ethanone (13a): A mixture of pyridazine-3-amine (**11a**) (10 g, 105.15 mmol) and 3-chloropentane-2,4-dione (**12a**) (21.2 g, 157.7 mmol) in ethanol (100 mL) was refluxed at 80°C for 24 h. The volatiles were concentrated under reduced pressure. The crude material was purified through silica gel column chromatography, eluted product with 80% ethylacetate/hexanes to afford 1-(2-methylimidazo[1,2-b]pyridazin-3-yl)ethanone (**13a**) (7.1 g, 39% yield) as a solid. **MS** (*m/z*): 176 (*M*+1); **IR** cm^{-1} 1621 (C=O); **¹H NMR** (200 MHz, CDCl₃): δ 8.49-8.46 (dd, *J*=2.6, 1.8 Hz, 1H), 8.00-7.95 (dd, *J*=7.6, 1.6 Hz, 1H), 7.25-7.18 (m, 1H), 2.83 (s, 3H), 2.77 (s, 3H).

2-bromo-1-(2-methylimidazo[1,2-b]pyridazin-3-yl)ethanone (14a): Synthesis procedure followed similar analogue (**4a**) (cal. 62% yield), as a light white solid. **MS** (*m/z*): 255 (*M*+1); **IR** cm^{-1} 1674 (C=O); **¹H NMR** (200 MHz, DMSO-*d*₆): δ 8.79 (d, *J*=3 Hz, 1H), 8.28-8.23 (dd, *J*=9.2, 1.4 Hz, 1H), 7.56-7.49 (m, 1H), 4.95 (s, 2H), 2.64 (s, 3H).

7-bromo-2-(2-methylimidazo[1,2-b]pyridazin-3-yl)quinoxaline (15a): Synthesis procedure followed similar analogue (**5a**) (cal. 60% yield), as a pale yellow solid. **MS** (*m/z*): 341 (*M*+1). **¹H NMR** (200 MHz, DMSO-*d*₆): δ 9.89 (d, *J*=6 Hz, 1H), 8.72 (d, *J*=4.4 Hz, 1H), 8.40 (s, 1H), 8.24 (d, *J*=9.6 Hz, 1H), 8.08 (t, *J*=8.11, 1H), 7.43 (m, 1H), 6.61-6.65 (m, 1H), 2.81 (s, 3H).

7-(4-fluorophenyl)-2-(2-methylimidazo[1,2-b]pyridizin-3-yl)quinoxaline (iii): Synthesis procedure followed similar analogue (**i**) (cal. 42% yield), as a pale yellow solid. **MS** (*m/z*): 356 (*M*+1). **¹H NMR** (200 MHz, DMSO-*d*₆): δ 9.84 (s, 1H), 8.78 (d, *J*=4.2 Hz, 1H), 8.39-8.23 (m, 4H), 8.04-7.97 (m, 2H), 7.52 (m, *J*=9.2, 4.6 Hz, 1H), 7.39 (t, *J*=9 Hz, 2H), 2.85 (s, 3H).

2-(2-methylimidazo[1,2-b]pyridazin-3-yl)quinoxaline (iv): Synthesis procedure followed similar analogue (**ii**) (cal. 41% yield), as a solid. **MS** (*m/z*): 262 (*M*+1). **¹H NMR** (200 MHz, DMSO-*d*₆): δ 9.82 (s, 1H), 8.69 (d, *J*=4.4 Hz, 1H), 8.25-8.11 (m, 3H), 7.90-7.86 (m, 2H), 7.41 (m, 1H), 2.81 (s, 3H).

1-(2-methylH-imidazo [1, 2-a] pyridin-3-yl) ethanone (17a): Synthesis procedure followed similar analogue (**13a**) (cal. 42% yield), as a solid. **MS** (*m/z*): 175 (*M*+1). **¹H NMR** (200 MHz, CDCl₃): δ 9.75 (d, *J*=8.2 Hz, 1H), 7.66 (d, *J*=8.8 Hz, 1H), 7.50 (t, *J*=7 Hz, 1H), 7.03 (t, *J*=7 Hz, 1H), 2.80 (s, 3H), 2.63 (s, 3H).

2-bromo-1-(2-methylH-imidazo[1,2-a]pyridin-3-yl)ethanone (18a): Synthesis procedure followed similar analogue (**4a**) (cal. 61% yield), as a pale brown solid. **MS** (*m/z*): 255 (*M*+1). **¹H NMR** (200 MHz, CDCl₃+DMSO-*d*₆): δ 9.85 (d, *J*=8.2 Hz, 1H), 8.21 (d, *J*=8.8 Hz, 1H), 8.02 (t, *J*=7 Hz, 1H), 7.61 (t, *J*=7 Hz, 1H), 4.45 (s, 2H), 3.05 (s, 3H).

1,2-dihydro-3-(2-methylH-imidazo[1,2-a]pyridin-3-yl)quinoxaline (v): Synthesis procedure followed similar analogue (**ii**) (cal. 45% yield), as a solid. **MS** (*m/z*): 263 (*M*+1); **IR** cm^{-1} 3389 (-NH); **¹H NMR** (200 MHz, DMSO-*d*₆): δ 10.03 (d, *J*=7.0 Hz, 1H), 7.79-7.66 (m, 2H), 7.28 (t, *J*=7.2 Hz,

1H), 7.19 (d, *J*=7 Hz, 1H), 6.96 (t, *J*=6.2 Hz, 1H), 6.68 (t, *J*=6 Hz, 2H), 6.23 (brs, 1H), 4.37 (s, 2H), 2.68 (s, 3H).

RESULTS AND DISCUSSION

All the Quinoxaline derivatives (**i-v**) in this report were synthesized through cyclization-oxidation with *o*-phenyl diamine analogs, then further synthesized quinoxaline-phenyl substituted compounds (**i** and **iii**) were prepared by coupling with 4-fluoro phenyl boronic acid via Suzuki Coupling using PdCl₂ (dppf).DCM, tert-BuNH₂, Na₂CO₃ in *i*-PrOH-H₂O refluxed for 16 h.

A microwave synthesis^{4,5} of Friedel-Crafts acylation^{4,8} on *H*-imidazo[1,2-a]pyridine (**1a**) by using AlCl₃, propanoic anhydride (**2a**) irradiating in microwave at 100°C for 20 min to afford acylated product (**3a**) (cal. 48% yield). The bromination^{9,10} at α -carbon of acylated product (**3a**) using Br₂ in diethyl ether and dichloromethane at 0°C - RT for 2 h to afford bromo compound (**4a**) (cal. 46% yield). The alkylation of bromo compound (**4a**) with *N*-boc-phenyl diamine (**10a**) using triethyl amine in acetonitrile at 80°C for 12 h, and *in situ* further cyclization-oxidation carried *in situ* using trifluoro acetic acid under refluxed condition for 4 h to afford bromo quinoxaline (**5a**) (cal. 56% yield). This compound (**5a**) further coupled with 4-fluoro phenyl boronic acid (**6a**) via Suzuki Coupling^{11,12} using PdCl₂ (dppf).DCM, tert. BuNH₂, Na₂CO₃ in *i*-PrOH-H₂O under reflux condition for 16 h to afford quinoxaline derivative (**i**) compound (cal. 40% yield) according to the Scheme-I.

The 1,2-dihydro quinoxaline derivative (**ii**) was prepared by cyclization¹², of bromo compound (**4a**) with *o*-phenyl diamine (**7a**) in acetonitrile at RT for 4 h according to scheme-I.

Reagents & Conditions: (a) AlCl₃, microwave, 100°C, 20min (b) Br₂, Et₂O, DCM, 0°C-rt, 2h (c) ACN, rfx, 12h (d) trifluoro acetic acid, 3h (e) PdCl₂ (dppf).DCM, tert-BuNH₂, Na₂CO₃, *i*-PrOH-H₂O, rfx, 16h (f) ACN, RT, 4h

Tert-butyl-2-amino-4-bromophenyl carbamate (**10a**) was prepared by boc protection of 4-bromo-2-nitrobenzenamine (**9a**) (cal. 57% yield), further reduced with hydrazine hydrate, ferric chloride (cat) in methanol refluxed for 3 h (cal. 77% yield) according to the Scheme-II.

Reagents & Conditions: (a) (BOC)₂O, NaH(60%), DMF, 0°C-RT, 5 h (b) NH₂NH₂·H₂O, ferric chloride (cat), MeOH, rfx, 4 h

The quinoxaline -phenyl derivative (**iii**) was prepared according to the method describes for preparation of analogue of (**i**). The intermediate compounds (**13a**, **14a**, **15a**) also prepared according to the method describes for preparation of analogue of (**3a**, **4a** and **5a**) according to the Scheme-III.

The quinoxaline derivative (**iv**) prepared by cyclization-oxidation of bromo compound (**14a**) with *o*-phenyl diamine (**7a**) in acetonitrile at RT for 4 h according to the Scheme-III.

Reagents & Conditions: (a) EtOH, rfx, 24 h (b) Br₂, Et₂O, DCM, 0°C-RT, 2 h (c) ACN, rfx, 12 h (d) trifluoro acetic acid, 3 h (e) PdCl₂ (dppf).DCM, tert-BuNH₂, Na₂CO₃, iPrOH-H₂O, rfx, 16h (f) ACN, RT, 4 h

The 1,2-dihydro quinoxaline derivative (v) prepared by cyclization¹², of bromo compound (18a) with o-phenyl diamine (7a) in acetonitrile at RT for 4 h. The intermediate compounds (17a and 18a) also prepared according to the method describes for preparation of analogue of (3a and 4a) according to the Scheme-IV.

Reagents & Conditions: (a) EtOH, rfx, 24 h (b) Br₂, Et₂O, DCM, 0°C-RT, 2 h (c) ACN, RT, 4 h

The antibacterial testing was done by the paper disc method¹³. After solidification of media, petriplates inoculated with actively growing culture of Gram positive (*Staphylococcus aureus* and *Bacillus sphericus*) and Gram negative (*Escherichia coli* and *Enterobacter aerogens*) separately. The organisms were maintained on agar slopes at 4°C and sub cultured for 24 h before use. The bacterial susceptibility was with the agar plate. A standardized inoculums 1-2 × 10⁷ cfu/ml 0.5 MC Farland standards was introduced onto the surface of sterile agar plate and evenly distributed the inoculums by using a sterile glass spreader. Simultaneously 8 mm wells were cut from the plate using a sterile cork borer. 100 µl of extract at a concentration of 10 mg/ml was introduced into each well. The agar plates were incubated aerobically at 37°C. After 24 h the inhibition zones were measured with a ruler and compared with the control well containing only solvent and 100 µl of extract at a concentration of 10 mg/ml of streptomycin served as control. All the tests were conducted in triplicates. The data of all the parameters were statistically analyzed and expressed as mean ± S.D.

After 24 hours the petridishes were checked for growth inhibition zone. The presence of clear zone of growth inhibition around the paper disc indicated the inhibition of growth of organism. The antibacterial activity observed by the length of the zone of inhibition area in mm.

As the results of antibacterial screening tests *in vitro* incorporated in the Table-A.

Table-A: Antibacterial activity of quinoxaline derivatives (Zone of inhibition in mm).

Titled compounds	Organisms			
	<i>S. aureus</i>	<i>B. sphericus</i>	<i>E. coli</i>	<i>E. aerogens</i>
(i)	4	12	-ve	2
(ii)	4	-ve	-ve	2
(iii)	-ve	-ve	20	-ve
(iv)	2	-ve	-ve	-ve
(v)	-ve	12	10	2
Solvent control	-ve	-ve	-ve	-ve
Streptomycin	19	20	-ve	7

Solvent control – 10% DMSO; (-ve) -indicates no inhibition zone.

CONCLUSIONS

Synthesis of some 2,3-substituted quinoxaline derivatives (i-v) were prepared by cyclization-oxidation with o-phenyl diamines and further extended coupling at 6,7-postions by Suzuki coupling successfully. Surprisingly, isolated cyclized products (ii & v) and cyclization-oxidized product (iv) under similar conditions. All the synthesized compounds were screened for their antibacterial activities. Compounds (i) and (v) revealed better activity on *Bacillus sphericus* and (iii) and (v) on *Escherichia coli* cultures. The compound (v) showing better activity against both *Escherichia coli* and *Bacillus sphericus*.

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