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Research Article

# SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF NEW ISATIN DERIVATIVES

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**ABSTRACT**

In search of novel antimicrobial agents, a new isatin derivatives(5a-b)have been synthesized by heterocyclization of 5-substituted ethyl-((2-oxo-1-piperedin-1-ylmethyl)indolin-3-ylidene) hydrazinyl)acetohydrazide**(4a-b)** on treatment with CS2 in ethanolic KOH. Compounds synthesized have been characterized by IR spectroscopy and elemental analysis. In addition, the in vitro antimicrobial activity have been tested against *E. coli, P. aeruginosa, Bacillus cereus, S. aureus and C.albicans* by employing the well diffusion technique. The synthesized compounds were showing good antimicrobial activity and from comparisons of the compounds, compound 5b were found to be the most active compound.

**KEY WORDS:** Isatin, Br-Isatin, Isatin-3- hydrazine, N-Mannich base, 1,3,4-Oxadiazole , antibacterial , antifungal activity

## INTRODUCTION

Isatins (Indoline-2,3-diones or indole-1H-2,3-diones), have an interesting due to their diverse pharmacological activities and synthetic versatility. Isatins act as endogenous biological regulators, found in different tissues, and body fluids of humans [1]. The synthetic importance in the chemistry of isatin and its derivatives derived from its easy synthetic accessibility and exhibition of broad spectrum biological effects, including antibacterial, antifungal, anticonvulsant, antiviral, anticancer, antioxidant, anti-inflammatory and antiproliferative activities[2-4].

1,3,4 oxadiazole molecules and their derivatives have exhibited very prominent antimicrobial activity against a wide range of microbes especially 2,5-disubsistuted 1,3,4 oxadiazole has gained the attention of the medical chemists [5]. 1,3,4 oxadiazole were seen to possess many activities such as antibacterial [6], antifungal7 [7], anti-cancer[8] and anti-inflammatory [9,10]. The synthesis of a newer class of antimicrobial agents is in need of time. The synthetic versatility of isatin and oxadiazole derivatives has led to the wide utilize of these compounds in organic synthesis. In view of biological importance of these newly synthesized isatin oxadiazole derivatives, it was planned to evaluate these new compounds for antimicrobial activities.

## MATERIAL AND METHOD

All solvents used were of laboratory grade, all chemicals used were reagent grade and were used as received without further purification, all chemicals (Isatin and Piperidine, hydrazine hydrate, $CS_2$, ethylchloroacetate) were obtained from Sigma Aldrich/Germany. Melting points (uncorrected) were detected using electrical melting point apparatus, Electro-thermal 9300, USA. The IR spectra were recorded in specac ® Quest ATR (diamond)-IK on FT-IR spectrophotometer /Shimadzu-japan. Compounds were routinely checked for their purity on Silica gel G (Merck) Thin layer chromatography (TLC) plates. Iodine chamber and UV lamp were used for visualization of TLC spots. Elemental data for C, H, and N were performed by Euro-vector EA 3000A, Italy. All the compound have exhibited satisfactory chemical analysis.

**Synthesis of 1-(piperidin-1-ylmethyl)indoline-2,3-dione, (compound-1a)[11].**

The compound 1a has been synthesized as follows, as shown in scheme 1: Isatin(2,3-indolineendione) (2gr,0.0136 mole) was dissolved in (20ml) methanol and then formaldehyde 37%, 4ml was added to the mixture. The reaction mixture was cooled to 0 $^0$C and then piperidine (hexahydropyridine) (0.0136 mole,1.14 gr) was added with stirring. The stirring was continues for 1 h at room temperature. the precipitate collected and recrystallized from methanol and the required compound was obtained as orang solid, yield 69%, M.WT=244, M.F=$C_{14}H_{16}N_2O_2$, m.p=142-144°C , Rf :0.56 (ethanol :chloroform, UV active). The elemental Analysis: found C, 68.91 Cal. C, 68.83 ; found H, 6.60, Cal. H, 6.60; found N, 11.48, Cal. N, 11.47 , IR (cm-1) [11] : 2941(C-H str. CH2 Asy.) , 2852 C-H str. CH2 sy.), 1348 (C-N aliphatic), 1469-1412 (C=C Ar.), 3043 (C-H str. Ar.), 1732 (C=O indole), 1612(CO-NH) , 860-762 (HC= Ar. bending).

**Synthesis of 5-bromo-1-(piperidin-1-ylmethyl)indoline-2,3-dione, (compound-1b).**

The compound 1b has been synthesized as follows, as shown in scheme 1:Br- Isatin(5- bromo2,3-indolineendione) (2gr,0.0088 mole) was dissolved in (20ml) methanol and then formaldehyde 37%, 4ml was added to the mixture. The reaction mixture was cooled to 0 $^0$C and then piperidine (hexahydropyridine) (0.0088 mole,0.75 gr) was added with stirring. The stirring was continues for 1 h at room temperature. the precipitate collected and recrystallized from methanol and the required compound was obtained as gray solid, yield 61%,M.WT=: 323.19, M.F=$C_{14}H_{15}BrN_2O_2$, m.p=154-156°C , Rf :0.51 (ethanol :chloroform, UV active). The elemental Analysis: found C,51.89 , Cal. C,52.03; found H, 4.60, Cal. H,4.68; found N, 8.49, Cal. N,8.67 , IR (cm-1)6: 2931(C-H str. CH2 Asy.) , 2850 C-H str. CH2 sy.), 1346 (C-N aliphatic), 3062 (C-H str. Ar.), 1712 (C=O indole), 1604(CO-NH) , 864-758 (HC= Ar. bending), 532(C-Br).

**Synthesis of (Z)-3-hydrazono-1-(piperidin-1-ylmethyl)indolin-2-one,(compound-2a)**[11]

The compound 2a has been synthesized as follows, as shown in scheme 1: compound-1a (0.01 mole 1.4 gr) was dissolved in methanol ( 20 ml) and added hydrazine hydrate (80% ) while shaking. the reaction mixture was refluxed for 30 min. then the solution was allowed to cool to RT and left at refrigerator overnight and the product obtained was recrystallized from petroleum ether as yellow ppt., yield 70%, m.p.=165-170°C, M.WT=258, M.F=$C_{14}H_{18}N_4O$, Rf:0.54 (ethanol :chloroform , UV active). The elemental Analysis: found C, 65.17, Cal. C,65.09 ; found H, 7.03, Cal. H, 7.02 ; found N, 21.71, Cal. N, 21.69 , IR (cm-1) [11]: 1660 (C=N); 1550-1464 (C=C Aromatic); 3357, 3155 (N-H str. ), 3064 (C-H Ar.); 1685 (C=O amide isatin), 931-677(HC= Ar. bending), 2931-2850(C-H aliphatic).

**Synthesis of 5-bromo-3-hydrazono-1-(piperidin-1-ylmethyl)indolin-2-one,(compound-2b)**.

The compound 2b has been synthesized as follows, as shown in scheme 1: compound-1b(0.001 mole,3.2 gr) was dissolved in methanol (20 ml) and added hydrazine hydrate (80% ) while shaking. the reaction mixture was refluxed for 30 min. then the solution was allowed to cool to RT and left at refrigerator. overnight and the product obtained was recrystallized from petroleum ether as green ppt., yield 71%, m.p.=182-184°C, M.WT=337.22, M.F=$C_{14}H_{17}BrN_4O$, Rf:0.52 (ethanol :chloroform, UV active). The elemental Analysis: found C, 49.54, Cal. C,49.86; found H, 5.03, Cal. H, 5.08; found N, 16.49, Cal. N,16.61, IR ($cm^{-1}$)7: 1666 (C=N); 1508-1435 (C=C Aromatic); 3394, 3232 (N-H str. ), 3032 (C-H Ar.); 1739(C=O amide isatin), 937-698(HC= Ar. bending), 2954-2843(C-H aliphatic), 536 (C-Br).

**Synthesis of ethyl-(Z)-((2-oxo-1-piperedin-1-ylmethyl) indolin-3-ylidene) amino)glycinate, (compound-3a)**[12] .

Compound 3a have been synthesized by A mixture of 3-hydrazono-1-(piperidin-1-ylmethyl)indolin-2-one (2a) (1.29g, 0.005 mole) ethylchloroacetate (0.69ml, 0.005 mole) and potassium carbonate(1.04 gr, 0.0075 mole) in dry acetone was refluxed for 20 h. The reaction mixture was poured onto crushed ice, and the solid was then filtered, washed with water and recrystallized from methanol to give compound 3a as yellow compound with yield: 63% ;M.F= $C_{18}H_{24}N_4O_3$, M.WT= 344.42, Elemental Analysis :cal. C, 62.77, found C 61.51 ; cal. H, 7.02 , found H 6.95 ; cal. N, 16.27 , found N 16.21 ; m. p. =102-105°C , IR($cm^{-1}$):3028(C-H Ar.),1319(C-N),2970-2866(C-H aliphatic), 1095(C-O), 1685(C=N),1739(C=O isatin), 1793(C=O) .

**Synthesis of ethyl (Z)-((5-bromo-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)amino)glycinate, (compound-3b).**

Compound 3b have been synthesized by A mixture of (Z)-5-bromo-3-hydrazono-1-(piperidin-1-ylmethyl)indolin-2-one (2b) (1.69 gr,0.005mole), ethylchloroacetate (0.69ml, 0.005 mole) and potassium carbonate(1.04 gr, 0.0075 mole) in dry acetone was refluxed for 20 h. The reaction mixture was poured onto crushed ice, and the solid was then filtered, washed with water and recrystallized from methanol to give 1.01 gr of compound 3b as yellowish green powder with yield: 60% M.F= $C_{18}H_{23}BrN_4O_3$ , M.WT=423.31, Elemental Analysis :calc. C,51.07, found C,51.01;calc. H,5.48, found H,5.29;calc. N, 13.24, foundN,13.15;m.p.=126-128°C;IR($cm^{-1}$):3028(C-HAr.),1342(C-N),2931-2850(C-H aliphatic), 1165(C-O), 1651(C=N),1716(C=O isatin), 1793(C=O), 532(C-Br) .

**Synthesis of (Z)-2--((2-oxo-1-piperedin-1-ylmethyl)indolin-3-ylidene) hydrazinyl)acetohydrazide , (compound -4a )** [13] **.**

A mixture of ethyl-(Z)-((2-oxo-1-piperedin-1-ylmethyl)indolin-3-ylidene)amino)glycinate (3a) (1.72 gr, 0.005 mole) and hydrazine hydrate 80% (0.25ml, 0.005 mole) in methanol (10 ml) was refluxed for about 5 h on steam bath. After completion of reaction (monitored by TLC), the mixture was cooled and the resulting solid was filtered, dried and recrystallized from ethanol to give 1.03 gr of compound 4a pale yellow colored compound with yield 60%, M.F.= $C_{16}H_{22}N_6O_2$, M.WT.= 330.39 Elemental Analysis : calc. C, 58.17, found C 57.59 ; calc. H, 6.71, found H 6.57 ; calc. N, 25.44, found N 25.19 ; m. p.=205-209°C ; IR ($cm^{-1}$): 1350(C-N), 3348, 3228(N-H hydrazide),1654(C=N), 1739(C=O isatin),1681(C=O hydrazide), 3039(C-H Ar.), 2989-2854(C-H aliphatic).

**Synthesis of (Z)-2-(2-(5-bromo-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)acetohydrazide , (compound- 4b)**.

A mixture of ethyl (Z)-((5-bromo-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)amino)glycinate. (3b) (2.1gr, 0.005 mole) and hydrazine hydrate 80% (0.25ml, 0.005 mole) in methanol (10 ml) was refluxed for about 5 h on steam bath. After completion of reaction (monitored by TLC), the mixture was cooled and the resulting solid was filtered, dried and recrystallized from ethanol to give 1.24 gr of compound 4a as yellow compound with yield 59%, M.F.= $C_{16}H_{21}BrN_6O_2$ , M.WT.= 409.29 Elemental Analysis : calc.C,46.95, foundC,46.69 ; calc. H, 5.17, found H,5.05; calc.N,20.53 , found N,20.43; m.p.=223-225°C;IR($cm^{-1}$): 1365(C-N), 3378, 3240(N-H hydrazide),1624(C=N), 1743(C=O isatin),1693(C-O hydrazide), 3039(C-H Ar.), 2989-2873(C-H aliphatic), 590(C-Br).

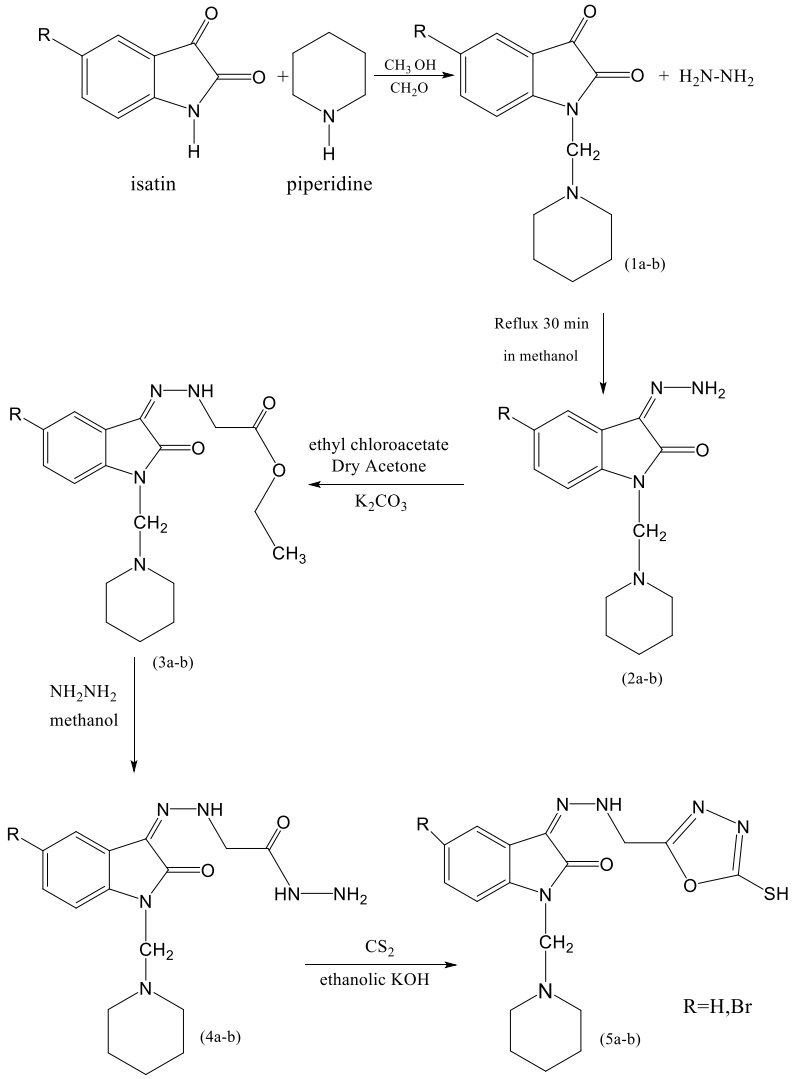
**Synthesis of (Z)-3-(2-((5-mercapto-1,3,4oxdiazole-2yl)methyl)hydrozono)-1-piperedin-1-ylmethyl)indoiln-2-one, (compound5a)** [14] **.**

To a cooled solution of (Z)-2-(2-oxo-1-piperedin-1-ylmethyl)indolin-3-ylidene) hydrazinyl) acetohydrazide (2.06 gr, 0.005 mole ) in ethanolic KOH (7.5ml) to 0 °C added $CS_2$ (0.48 ml , 0.005 mole). The mixture was refluxed for 8 h and allowed to stand at room temperature overnight. The mixture was then concentrated to a small volume, water was added to it and neutralized with 1*N* HCl and the organics were extracted with ethyl acetate. The organic layer was then dried over sodium sulfate, filtered and concentrated under reduced pressure to 1.34 gr of compound 5a as pale yellow colored compound with yield: 81%; M.F.= $C_{17}H_{20}N_6O_2S$,M.WT.= 372.45, Elemental Analysis : calc. C, 54.82,found C54.26 ; calc. H, 5.41, found H 5.36 ; calc. N, 22.56; found N 22.49 , m. p.=105-107°C ,IR ($cm^{-1}$): 1365 g (C-N), 1527,1481,1446(for oxadiazole),1018(C-O-C) (C=N), 648 (C-S), 1739 (C = O isatin), 1693, 2605 (SH)

**Synthesis of (Z)-5-bromo-3-(2-((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)hydrazono)-1-(piperidin-1-ylmethyl)indolin-2-one,(compound-5b) .**

To a cooled solution of (Z)-2-(2-(5-bromo-2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)hydrazinyl)acetohydrazide (1.65 gr, 0.005 mole ) in ethanolic KOH (7.5ml) to 0 °C added $CS_2$ (0.48 ml , 0.005 mole). The mixture was refluxed for 8 h and allowed to stand at room temperature overnight. The mixture was then concentrated to a small volume, water was added to it and neutralized with 1*N* HCl and the organics were extracted with ethyl acetate. The organic layer was then dried over sodium sulfate, filtered and concentrated under reduced pressure to 1.24 gr of compound 5b as yellow powder with yield: 75%; M.F.=

$C_{17}H_{19}BrN_6O_2S$,M.WT.=451.34, Elemental Analysis : calc. C,45.24 , found C,45.09; calc.H,4.24 ,found H, 4.19 ; calc. N, 18.62, found N,18.38, m. p.=121-123 °C; IR ($cm^{-1}$): 594 (C-Br), 1338 (C-N), 1527,1481,1446(for oxadiazole), 1743 (C= O isatin), 1693 (C=N isatin), 2549 (S-H), 594 (C-Br),1006 (C-O-C) .

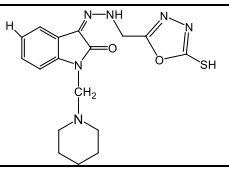
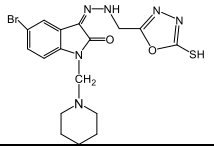



**Scheme1. Synthesis of 5-subsitituuted -3-(2-((5-mercapto-1,3,4 oxdiazole-2yl)methyl)hydrozono)-1-piperedin-1-ylmethyl)indoiln-2-one**

## RESULTS AND DISCUSSION

The physical data of the synthesized compounds **(5a,5b)** and the elemental analysis, the percentage of C, H and N atoms are present Table 1.

**Table 1: Physicochemical data of the synthesized test compounds (5a-b)**

| Compound | structure | Physical Appearance | % Yield | M.P. (C°) | Molecular formula | Elemental Analysis found(Calc.): |
|---|---|---|---|---|---|---|
| 5a |  | yellow | 81 | 105-107 | $C_{17}H_{20}N_6O_2S$ | ( 54.82),54.26 (5.41), 5.36 , ( 22.56), 22.49 |
| 5b |  | yellow | 75 | 121-123 | $C_{17}H_{19}BrN_6O_2S$ | (45.24) 45.09, (4.24) 4.19, (18.62) 18.38 |

**Spectral data of synthesized compounds (3a–b)**

The IR characteristic bands of compound **5a**,1365(C-N),1527,1481,1446(for oxadiazole),1018(C-O-C), 648 (C-S), 1739 (C = O isatin), 1693 (C= N), 2605 (S-H). The IR spectrum of final compound **(5a)** exhibited the isatin carbonyl at 1739 cm-1 and S-H of 5-mercapto oxadiazole at 2605 $cm^{-1}$, which confirms the formation of the final compound, Elemental Analysis : calc. C, 54.82,found C54.26 ; calc. H, 5.41, found H 5.36 ; calc. N, 22.56; found N 22.49 , the percentage of C, H and N atoms are present in the range of ± 0.03.

The IR characteristic bands of compound **5b**, 594 (C-Br), 1338 (C-N), 1527,1481,1446(for oxadiazole), 1743 (C= O isatin), 1693 (C=N isatin), 2549 (S-H), 594 (C-Br),1006 (C-O-C) . The IR spectrum of final compound **(5b)** exhibited the isatin carbonyl at 1743 cm-1 and S-H of 5-mercapto oxadiazole at 2549 $cm^{-1}$, which confirms the formation of the final compound, Elemental Analysis : calc. C,45.24 , found C,45.09; calc.H,4.24 ,found H, 4.19 ; calc. N, 18.62, found N,18.38, the percentage of C, H and N atoms are present in the range of ± 0.03.

**BIOLOGICAL EVALUATION**

**In vitro Antibacterial & Antifungal Activity.**

The synthesized compounds have evaluated for their antimicrobial activity by well-diffusion method[15] as shown in table 2 and 3. The zone of inhibition (mm) was measured in comparison with amoxicillin for antibacterial activity and with fluconazole for antifungal activity. These compounds were subjected against four types of bacteria *(Bacillus cereus, S. aureus E. coli, P. aeruginosa,)* and against one type of fungus *(C.albicans)*. The antimicrobial activity was performed in nutrient agar medium at concentrations (250,500 µg/well). The activity was determined after incubation for 24 h at 37°C by the comparison of inhibition of growth of bacteria by (amoxicillin) and inhibition of growth of fungus by fluconazole using dimethylsulfoxide (DMSO) as the solvent and the result shown in table 2 and 3.

**Table 2: Antimicrobial activities of the compounds 5a-b at 200 µg/ml**

| compound | R | Zone of inhibition (mm) | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial activity (250 µg/ml) | | | | Antifungal activity (250µg/ml) |
| | | ***S.aureus*** | ***B.cereus*** | ***P.aeruginosa*** | ***E.coli*** | ***C. albicans*** |
| 5a | H | 17 | 15 | 10 | 15 | 9 |
| 5b | Br | 19 | 17 | 16 | 14 | 11 |
| fluconazole | | - | - | - | - | 10 |
| amoxicillin | | 12 | - | - | 13 | - |
| DMSO | | - | - | - | - | - |

Key to symbols: (-) = no inhibition

**Table 3: Antimicrobial activities of the compounds 5a-b at 500 µg/ml**

| compound | R | Zone of inhibition (mm) | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial activity (500µg/ml) | | | | Antifungal activity (500µg/ml) |
| | | ***S.aureus*** | ***B.cereus*** | ***P.aeruginosa*** | ***E.coli*** | ***C. albicans*** |
| 5a | H | 33 | 25 | 22 | 28 | 25 |
| 5b | Br | 37 | 29 | 29 | 30 | 34 |
| fluconazole | | - | - | - | - | 23 |
| amoxicillin | | 28 | - | - | 22 | - |
| DMSO | | - | - | - | - | - |

Key to symbols: (-) = no inhibition

According to the data shown in **Table 2, 3** Compound5a and 5b had broad spectrum and more antibacterial activity when compare with standard antibiotic (amoxicillin) and more antifungal activity than fluconazole at two different concentration .

When compare between compound 5a and 5b it was observed that in case of compound 5b bearing bromo group at C-5 and 1,3,4 oxadiazole group at C-3, there was increase in the antimicrobial activity as compared to compound 5a bearing hydrogen at C-5 position of isatin and 1,3,4 oxadiazole group at C-3. Introduction of bromine at the C-5 position of the isatin derivatives increases the antimicrobial activity, this is mostly due to increase cell permeability and hydrophobicity of bromo substituted derivatives. Our results agreed with the earlier findings that electron withdrawing groups at C-5 position of isatin increases inhibitory activity simultaneous presence of electron-attracting groups in the isatin scaffold as well as 1,3,4 oxadiazole group at C-3 position result in significant antimicrobial activity of compound 5b . 1,3,4 oxadiazole ring is heterocyclic which has been incorporated in the isatin scaffold at positions 3 to enhance its pharmacological property by synergetic effect agreed with incorporating two or more biologically active moieties in a single structure are comparatively more active than the individual components.

**CONCLUSION**

A new derivatives of isatin have been synthesized successfully in appreciable yields and screened for their antimicrobial activities using well-diffusion method. It is concluded that the new derivatives of isatin possess good antimicrobial activities. Furthermore, that remarkable inhibition is observed in the new derivative (compound 5b) .

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