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One Pot Synthesis of Some Novel Sulfonamide Derivatives Containing -NH2 Group: Spectral Characterization and Biological Evaluation

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Abstract

A series of sulfonamide derivatives HR1-HR5 were synthesized in one step reaction (nucleophilic substitution reaction SN^2). Structures of new products were confirmed by elemental and spectral analysis i.e., FTIR, UV, ^{1}H NMR, ^{13}C NMR, EIS-MS. *In-vitro*, antibacterial and anti-fungal activity of newly synthesized compounds was investigated against two bacterial strains: *Escherichia coli* and *Staphylococcus aureus* and two fungal strains: *Aspergillum flavous* and *Aspergillum niger*. It was found that among all tested compounds HR2 showed good antibacterial activity with MIC 1.13 × 10^{-3} and 1.54 × 10^{-3} for *S. aureus* and *E. coli* respectively. While HR4 showed good antifungal activity with inhibition zone 25.2 ± 0.12 mm (MIC: 71.2 × 10^{-3} mol/L) and 17.1 ± 55.5 mm (MIC: 98.9 × 10^{-3} mol/L) against *A. flavous* and *A. niger* respectively. Developed compounds were also screened for their *In-vitro* antioxidant activity by DPPH radical scavenging assay. All compounds showed moderate activity but potential activity with 15.75% at 6 mM was exhibited by compound HR2.

Keywords: Antibacterial activity; Antifungal activity; p-Toluene sulfonamides; Sulfonamide

Introduction

Sulfonamides have commercialized applications as antibacterial antibiotic agents as they inhibit activity of enzyme dihydropteroate synthase (DHPS) [1] and prevent synthesis of folic acid (Vitamin B9), which is an essential intermediate for life of bacteria. So sulfonamides and their derivatives are used as antibiotics medicines [2]. Apart from this application as an antibacterial agent, various sulfonamide derivatives are known to inhibit many enzymes such as Serine protease [3-5], cyclooxygenase [6], matrix metalloproteinase [7] and carbonic anhydrase [8-11]. Moreover their widespread potential values have led to discovery of various therapeutic applications in cancer chemotherapy, hypoglycemia, diuretics [12] and anti-impotence agent Viagra [13]. They have also received a considerable attention due to their diverse biological activities as HIV protease [14,15] and as an antitumor [16]. In recent year, novel sulfonamides were synthesized such as doriperiens with brand name doribax which is an injectable antibiotic [17]. Other developed sulfonamides drugs such as AZA (acetazolamide) and MZA (metahacetazoamides) are widely used mainly as anti-glucoma agents and also used for therapy of some other diseases [18-20]. Ester derivatives of sulfonamides are well known as cell proliferation inhibitor [21]. Newer sulfonamides and their derivatives have also got more attraction in the field of medicine [22,23]. On other hand disease causing organisms when treated with routine antibiotic become must resistance with appearance of some additional species as per mutation. So synthesis of novel sulfonamides and their derivatives have got much attention from researcher because of their widespread applications in the field of medical chemistry and medicine science [24,25]. Most practical and different method for the synthesis of sulfonamides (Scheme 1) involves sulfonation of amines and alcohols [26] in presence of some base such as Pyridine, triethylamine, or some metal hydroxides or carbonates.

In present study, we have synthesized five new sulfonamides **(HR1-HR5)** (Figure 1) derivatives by reaction of amine (-NH_2 group containing drug) and p-toluene sulfonyl chloride. These -NH_2 group containing drugs are cefotexime, ciprofloxacin, frusamide, amlodepine and indapamide respectively. These synthesized compounds not yet reported which is a strong evidence of their novelty. Synthesized compounds were biologically evaluated by using the bacterial and two fungal strains such as *Escherichia coli*, *Staphylococcus aureus*, *Aspergillum niger* and *Aspergillum flavous*.

Experimental

Chemistry

Chemicals used in present work were of analytical grade and used without further purification to synthesize desired compounds. Chemicals were obtained from E-Merck (Germany) and BDH (UK). Grade 1 quality water (0.01 μS/cm) was prepared in our own laboratory. ^{1}H NMR spectra were developed on Bruker spectrometer 400 MHz.

Finnigan MAT 112 mass spectrometer was used for recording MS data. Elementary analysis of compound was conducted by using Elmer elemental analyzer. Gallen kamp MP70 was used to determine the m.p. For recording infrared spectra, Cary 630 Agilent FFIR was used. Absorption spectra were conducted on PGT90+UV-VIS spectrometer. Pre-coated TLC silica plates (Merck, Germany) were used for purification and to confirm progress of the synthesized compounds.

General procedure for synthesis of compounds

For the preparation of sulfonamide derivatives **(HR1-HR5)**, a proficient method based on Hinsberg Test was used i.e., sulfonylation of primary, secondary amine in presence of a base resulting in nucleophilic attack by amine. Tosylchloride was used for sulfonylation and Na_2CO_3

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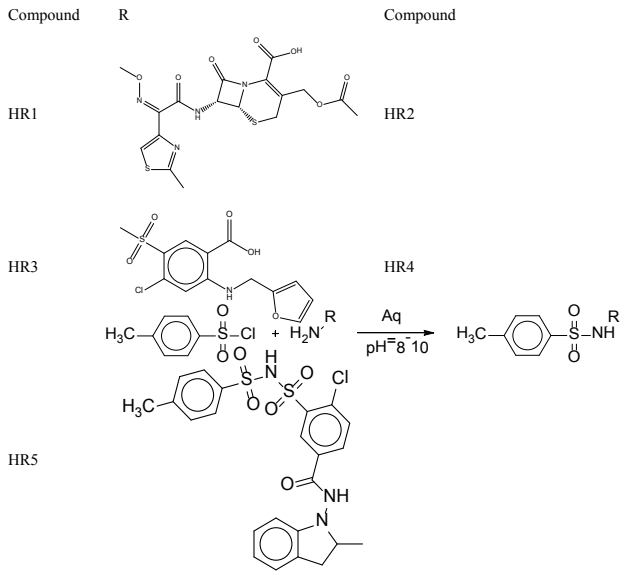
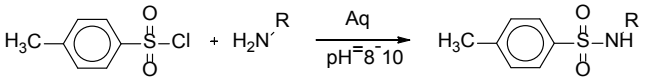


Figure 1: New sulphonamides (HR1-HR5).



Scheme 1: Synthesis of sulphonamides.

as base was used for neutralization of generated HCl. It is a one pot reaction. Drug containing -NH_2 group (0.001 M) was stirred in water while maintain the pH at 9, then sulfonyl chloride (0.001 M) was added and mixture was stirred 2 h. Precipitates were filtered and purified by using preparatory TLC.

Antimicrobial activity

Luria-Bertain broth was used as Growth media as it is highly supportive in bacterial growth [27]. In order to make media, 4.0 g of Tryptone, 2.0 g of yeast extract and 4.0 g of sodium chloride were added in 400 mL distilled water. The *p*H value of media was kept at 7. The media was then sterilized in autoclave at 125°C for 30 min. Sample solutions, in 5-50 µg concentration range, were prepared. For each bacterial strain, three test tubes were prepared i.e., *S. aureus* and *E. coli*. In above autoclaved tubes, 2 mL of LB Broth and 20 µL of bacterial strain were added, followed by the addition of stocks of 5 µL, 10 µL, 20 µL containing 5.0 µg, 12.5 µg and 50 µg. Then these tubes were incubated at 37°C for 72 h. At 600 nm, OD of each medium and control medium was measured. A comparative study for synthesized compounds was made with Graph plotted between concentration and OD of compounds.

Well diffusion test [28-32] was performed to evaluate Antifungal activity of compounds using PDA (potato dextrose agar). Inoculum was prepared by using a 24 h yeast culture of PDA. Suspension was made by using sterile saline solution (0.85%). Turbidity of above suspension was attuned by spectrophotometer at 600 nm for getting final concentration matching with 0.5 McFarland standard. Then Agar medium was autoclaved for 30 min at 120°C and cooled at 50°C and inoculated with 1.0 mL of above suspension having absorbance 0.5. Inoculated medium was then poured into all assay plates 9 cm in diameter and were allowed to cool down until solidified. Equidistance four wells 6 mm in diameter were cut out of agar upon solidification. 6 µL of medium, containing synthesized compounds, was added into these wells. Incubation of plates was done at 27°C for 48 h. For each compound, MIC values in µg/mL and zone of inhibition in mm were calculated, comparing it with standard antifungal isoconazol (ISC) in concentration 1.0 µg/mL in each plate as positive control. Results are mentioned in the Table 1.

Antioxidant activity

In-vitro antioxidant activity of synthesized compounds, using DDPH, was evaluated by a reported method [33]. In order to produce precise results, all compounds were run in triplicate. Trolox was used for standard curve. Relative concentrations of compounds were determined using R^2 value, and scavenging percentage that directly represents the antioxidant activity was calculated using formula i.e.,

$$\text{Inhibition\%} = (1\text{-sample}_{530}/\text{blank}_{530}) \times 100$$

Results are given in Table 2.

Results

Spectral characterization of sulfonamides

(6R,7R)-3-(acetoxymethyl)-7-((Z)-2-(methoxyimino)-2-(2-(4-methylphenylsulfonamido)thiazol-4-yl)acetamido)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (HR1): Yield: 82%, Colour: off white, m.p. (decomp.): 185°C. FTIR (cm^{-1}): 1159.48 (S=O str), 1086.0 (C-N str), 1652.8 (C=O), 819.62 (C-S str), 958.9 (S-N str), 3368.2 (-OH). ^{1}HNMR (DMSO-d6, ppm): 11.08 (1H, s, -COOH), 8.09-8.12 (1H, d, J=6.0, -NHCO), 7.82-7.84 (2H, d, J=8.2, -ArH), 7.62 (1H, s, -C=CHS-), 7.40-7.44 (2H, d, J=8.3, -ArH), 5.52-5.54 (1H, d, J=6.1, -NHCHCO-), 5.11-5.16 (1H, d, J=6.9, -SCHN-), 4.79 (2H, s, -OCH_2-), 4.02 (1H, s, -$NHSO_2$-), 3.92 (3H, s, -OCH3), 3.19-3.23 (1H, d, J=7.1, -CHHS-), 3.08-3.10 (1H, d, J=7.0, -CHHS-), 2.35 (3H, s, -$ArCH_3$), 2.27 (3H, s, -$OCOCH_3$).^{13}C NMR (δ, ppm): (170.27), (167.47), (164.52), (163.78), (161.73), (151.39), (144.97), (137.41), (136.82), (130.32), (129.38), (129.38), (129.38), (128.79), (128.79), (113.21), (63.27), (62.31), (60.69), (56.85), (24.23), (21.84), (20.92). MS (m/z, ESI): Calcd. for $C_{23}H_{23}N_5O_9S_3^+$ $[M+H]^+$ 609.07; Found 609.05. Anal. Calcd. for $C_{23}H_{23}N_5O_9S_3$ (609.05): C: 45.31; H: 3.80; N: 14.49; Found: C: 45.13; H: 3.81; N: 14.45.

1-cyclopropyl-6-fluoro-4-oxo-7-(4-tosylpiperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (HR2): Yield: 75%, Colour: Yellow, M.p. (decomp.): 240°C. FTIR (cm^{-1}): 1155.2 (S=O str), 1055.2 (C-N str), 1642.1 (C=O), 814.0 (C-S str), 932.5 (S-N str), 3388.3 (-OH). ^{1}HNMR (DMSO-d6, ppm): 11.08 (1H, s, -COOH), 8.68 (1H, s, -CH=CCOOH), 8.15 (1H, s, -ArH), 7.78-7.81 (2H, d, J=8.1, -ArH), 7.40-7.46 (2H, d, J=8.3, -ArH), 6.06 (1H, s, -ArH), 4.11-4.28 (1H, q, J=7.2, -NCH), 3.19-3.30 (8H, d, J=6.2, -NCH_2CH_2N-), 2.36 (3H, s, -$ArCH_3$), 1.83-2.05 (2H, dq, J=7.2,8.3 -CHCHHCH$_2$-), 1.11-1.37 (2H, dq, J=7.2,8.2 -CHCHHCH$_2$-).^{13}C NMR (δ, ppm): (176.67), (166.27), (152.87), (147.92), (146.38), (143.92), (137.48), (134.57), (129.42), (129.42), (128.26), (128.26), (115.87), (112.81), (109.79), (102.59), (53.37), (53.37), (48.51), (48.51), (35.85), (21.53), (7.59), (7.59). MS (m/z, ESI): Calcd. for $C_{24}H_{24}FN_3O_5S^+$ $[M+H]^+$ 485.14; Found 485.04. Anal. Calcd. for $C_{24}H_{24}FN_3O_5S$ (485.04): C: 59.37; H: 4.98; N: 8.65; Found: C: 59.35; H: 4.94; N: 8.60.

4-chloro-2-((furan-2-ylmethyl)amino)-5-(N-tosylsulfamoyl) benzoicacid (HR3): Yield: 62%, Colour: White, M.p. (decomp.): 212°C. FTIR (cm^{-1}): 1155.3 (S=O str), 1050 (C-N str), 1640 (C=O), 814 (C-S

Compounds	Bacterial Strains				Fungal Strains			
	Staphylococcus aureus, Gram (+)		*Escherichia coli*, Gram (-)		*Aspergillum flavous*		*Aspergillum niger*	
	MIC[b]	Zone of inhibition[a]	MIC[b]	Zone of inhibition[a]	MIC[b]	Zone of inhibition[a]	MIC[b]	Zone of inhibition[a]
HR1	4.5×10^{-3}	2.8	4.9×10^{-3}	3	8.4×10^{-3}	10.4 ± 0.22	18.8×10^{-3}	9.6 ± 0.10
HR2	1.13×10^{-3}	7.5	1.54×10^{-3}	13	1.54×10^{-3}	24.5 ± 0.32	2.57×10^{-3}	14.3 ± 0.23
HR3	6.1×10^{-3}	3	9.2×10^{-3}	4.5	23.7×10^{-3}	14.9 ± 0.11	64.0×10^{-3}	13.9 ± 0.22
HR4	2.6×10^{-3}	1.5	4.9×10^{-3}	2.8	71.2×10^{-3}	25.2 ± 0.12	98.9×10^{-3}	17.1 ± 0.12
HR5	3.0×10^{-3}	1.6	4.2×10^{-3}	2.2	12.5×10^{-3}	23.5 ± 0.10	23.1×10^{-3}	17.1 ± 0.11
Standard*	0.78×10^{-3}	0.2	0.15×10^{-3}	0.04	1.20×10^{-3}	30	1.82×10^{-3}	29.5

[a]Zone of inhibition was measured in mm; [b]MIC (minimum inhibitory concentrations) were measured in mol/L; *Sulfmethoxazole is used as standard for bacterial strains and Isoconazole for fungal strains.

Table 1: Zone of inhibition[a] and MIC[b] of Sulfonamides against pathogenic bacterial and fungal strains.

Compounds	% Antioxidant Activity	
	4 mM	6 mM
HR1	1.22	13.60
HR2	1.76	15.72
HR3	1.21	13.06
HR4	1.19	12.17
HR5	1.18	12.07
Trolox	1.53	12.87

Table 2: Antioxidant Activity of Sulfonamide Derivatives HR1-HR5.

Compounds	Molecular Formula	Molecular Weight	m.p. (°C)	Time (h)	Yield (%)	R_f[a]	λ_{max}[b] (nm)
HR1	$C_{23}H_{23}N_5O_9S_3$	609.07	185	3	82	0.72	275
HR2	$C_{24}H_{24}FN_3O_5S$	485.04	240	3	75	0.57	270
HR3	$C_{19}H_{17}ClN_2O_7S_2$	484.05	212	3	62	0.53	280
HR4	$C_{27}H_{31}ClN_2O_7S$	562.05	200	3	72	0.64	285
HR5	$C_{23}H_{22}ClN_3O_5S_2$	519.09	187	3	75	0.68	280

Table 3: Physiochemical and Analytical Data of Sulfonamides, (HR1-HR5).

str), 932 (S-N str), 3388 (-OH). ^{1}HNMR (DMSO-d6, ppm): 10.48 (1H, s, -COOH), 8.31 (1H, s, -ArH), 7.76-7.78 (1H, d, J=7.2, -CH=CH-O-), 7.66-7.68 (2H, d, J=8.1, -ArH), 7.39-7.42 (2H, d, J=8.3, -ArH), 7.25 (1H, s, -ArH), 6.46-6.50 (1H, t, J=6.9, -CH=CH-O-), 6.25-6.27 (1H, d, J=7.1, -CH-CH=CH-O-), 4.72-4.74 (2H, d, J=6.3, -CH_2NH-), 4.01-4.04 (1H, t, J=6.1, -CH_2NH-), 2.37 (3H, s, -ArCH_3), 2.11 (1H, s, -$NHSO_2$-). ^{13}CNMR (δ, ppm): (169.92), (154.47), (142.17), (141.35), (137.74), (137.72), (136.21), (128.79), (128.79), (129.38), (128.71), (128.71), (125.57), (114.35), (110.79), (106.55), (105.26), (40.17), (21.42). MS (m/z, ESI): Calcd. for $C_{19}H_{17}ClN_2O_7S_2^+$ $[M+H]^+$ 484.02; Found 484.05. Anal. Calcd. for $C_{19}H_{17}ClN_2O_7S_2$ (484.05): C: 47.09; H: 3.41; Cl: 7.31; N: 5.78; S:13.22; Found: C: 47.01; H: 3.47; N: 5.76; Cl: 7.27; S:13.20.

3-ethyl-5-methyl-4-(2-chlorophenyl)-6-methyl-2-((2-(4-methylphenylsulfonamido)ethoxy)methyl)-1,4-dihydropyridine-3,5-dicarboxylate (HR4): Yield: 72%, Colour: White, M.p. (decomp.): 200°C. FTIR (cm^{-1}): 1150 (S=O str), 1048 (C-N str), 1645 (C=O), 813 (C-S str), 930 (S-N str), 3380 (-OH). ^{1}H NMR (400 MHz, DMS-d6, δ) 7.94-7.98 (2H, m, -ArH), 7.76-7.79 (1H, t, J=5.2, -$NHSO_2$), 7.59-7.61 (1H, d, J=8.0, -ArH), 7.40-7.43 (2H, d, J=7.9, -ArH), 7.14-7.20 (3H, m, -ArH), 4.78 (1H, s, -CHArCl), 4.20-4.29 (2H, q, J=6.2, -OCH_2CH_3), 4.07 (2H, s, -$CH_2OCH_2CH_2$-), 3.87 (3H, s, -$OCOCH_3$), 3.76-3.78 (2H, t, J=6.5, -OCH_2CH_2NH-), 3.42-3.47 (2H, q, J=6.2, -OCH_2CH_2NH-), 2.36 (3H, s, -ArCH_3), 2.24 (3H, s, -CH_3), 1.56 (1H, s, -NH-), 1.31-1.37 (3H, t, J=6.9, -OCH_2CH_3). ^{13}CNMR (δ, ppm): (167.37), (167.37), (149.47), (145.67), (143.59),(143.31), (137.59), (137.59), (131.58), (129.74), (129.74), (128.32), (128.32), (128.31), (126.63), (126.63), (126.21), (104.71), (100.73), (100.73), (70.89), (69.72), (61.97), (52.41), (21.53), (19.54), (14.32). MS (m/z, ESI): Calcd. for $C_{27}H_{31}ClN_2O_7S^+$ $[M+H]^+$ 562.1; Found 562.05. Anal. Calcd. for $C_{27}H_{31}ClN_2O_7S$ (562.15): C: 57.59; H: 5.55; N: 4.98; O: 19.89; Cl: 6.30; S: 5.96; Found: C: 57.54; H: 5.53; N: 4.94; O: 19.87; Cl: 6.27; S: 5.67.

4-chloro-N-(2-methylindolin-1-yl)-3-(N-tosylsulfamoyl) benzamide (HR5): Yield: 75%, Colour: Yellow, M.p. (decomp.): 187°C. FTIR (cm^{-1}): 1148 (S=O str), 1055 (C-N str), 1640 (C=O), 814 (C-S str), 932 (S-N str), 3388 (-OH). ^{1}H NMR (DMSO-d6, ppm): 2.35 (s, 6H, CH_3), 6.9 (s, 1H, pyrimidine), 7.2-7.5 (m, 3H, Cl-Ph), 7.7-8.2 (m, 4H, N-Ph), 8.91 (s, 1H, azomethine), 8.9 (s, 1H, SO_2NH-), 12.42 (s, 1H, OH). ^{13}CNMR (δ, ppm): (166.37), (160.15), (151.67), (139.68), (137.78), (136.41), (134.27), (133.37), (132.45), (129.71), (129.71), (129.42), (128.38), (128.38), (126.99), (126.09), (125.41), (122.53), (121.81), (108.23), (36.71), (21.84), (18.32). MS (m/z, ESI): Calcd. for $C_{23}H_{22}ClN_3O_5S_2^+$ $[M+H]^+$ 519.07; Found 519.09. Anal. Calcd. for $C_{23}H_{22}ClN_3O_5S_2$(519.09): C: 53.12; H: 4.26; N: 8.08; O: 15.38 Cl: 6.82; S: 12.33; Found: C: 53.02; H: 4.12; N: 8.06; O: 15.37 Cl: 6.80; S: 12.31.

Discussion

A series of five sulfonamides were synthesized using efficient method based on Hinsberg Test and details of reaction conditions are explained in experimental section. The compounds **HR1, HR2** and **HR5** were obtained in excellent yield (above 75%) while the **HR3** and **HR4** gave the good yield (above 62%). Conformation of compounds was done by elemental analysis and measurement of absorption maximum (λ_{max}) provided the justification. The physiochemical and analytical data of synthesized sulfonamides are presented in Table 3. The synthesized compounds were characterized by FT-IR; the characteristics band at 1148-1155.5 cm^{-1} of S=O stretching and 1048-1055 cm^{-1} for (C-N) and 813-814 cm^{-1} (C-S) and 930-958.9 cm^{-1} (S-N) for all compounds reveals the formation of sulfonamides. In **HR1** and **HR2**, peaks of Ar-CH_3 were

found in their concerned region i.e., 2.34-2.36 ppm. In **HR1** there is a stereo-centre i.e., -CH_aH_bS-, both protons attached to carbon atom are in different environment. That's why they couple with each other to give their own doublets. A broad triplet was found in **HR2** due to a six member ring containing two nitrogen atoms i.e., -$N_2(CH_2)_4$- at 3.19-3.30 ppm. In **HR3** and **HR4,** -$ArCH_3$ peaks were recorded at 2.37 and 2.36 ppm respectively. In both compounds chemical shift values of -ArH which are in the vicinity of chlorine containing carbon were shifted to the downfield side due to electron withdrawing inductive effect of -Cl atom than other -ArH. In case of **HR4** there is an ethyl group which is directly attached to the ester group. Methyl group (-CH_3) showed its triplet at 1.31-1.37 ppm and methylene group (-CH_2-) showed its quartet at 4.20-4.29 ppm. In **HR5** there are two -CH_3 groups, one group is aromatic methyl and second group is attached to a five member ring. Their peaks were found at 2.35 ppm and 1.25-1.27 ppm respectively. Similarly, chemical shift values of -ArH in -Cl containing ring has been shifted to down field side than other aromatic protons. This shifting is due to the high electronegativity of chlorine atom and its electron withdrawing effect. Developed compounds were also screened for their antioxidant and antimicrobial activities. All exhibited moderate activity but potential activity with 15.75% at 6 mM was shown by compound **HR2**. Compounds **HR4** and **HR2** exhibited good activities against fungal strain *A. flavous* almost comparable with the reference Isoconazole. MIC values and zone of inhibition are presented in Table 1.

Conclusion

In conclusion, sulfonamides derivatives of five novel compounds, **HR1**-**HR5**, were synthesized and their antioxidant, antimicrobial and cytotoxicity test were also done. Remarkable antioxidant activity of concerned compounds guided and motivated us about their possible clinical significance. Antimicrobial activity was not so pronounced. Compound **HR4** showed remarkable antifungal results, but compound **HR2** was found to have potential antioxidant activity. However they did not give so pronounced cytotoxic effects.

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Conflict of Interest

Authors declare that there is no conflict of interest regarding the publication of this paper.

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