Indian Journal of Chemistry
Vol. 45B, March 2006, pp. 752-757

Synthesis of 1,5-benzothiazepines: Part XXX-Synthesis and antimicrobial studies of 10-substituted-6a, 7-dihydro-6*H* -7-(4-fluorophenyl)-6-phenyl [1] benzopyrano [3,4-*c*] [1,5] benzothiazepines

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Received 15 October 2004; accepted (revised) 7 September 2005

Flavindogenide, 3-(4-fluorobenzylidene)-flavanone has been reacted with six 5-substituted-2-aminobenzenethiols, the substituents being halogens as fluoro, chloro bromo, alkyl as methyl and alkoxyl as methoxyl and ethoxyl, to obtain a series of six new compounds, 10-substituted-6a,7-dihydro-6*H*-7-(4-fluorophenyl)-6-phenyl[1] benzopyrano[3,4-*c*][1,5]benzothiazepines **3a-f**. The products are characterized on the basis of microanalytical data for elements and IR, ^{1}H NMR, ^{19}F NMR and mass spectral studies. All the synthesized compounds have been evaluated for their antimicrobial activity against the bacteria *Escherichia coli* and *GFC (Alteromonas tetraodonis* - a new *Gram-negative bacteria* family) and fungi*, Aspergillus niger, A. flavus* and *Curvularia lunata.* All the compounds showed equal/greater bactericidal activity but for **3d** showing lesser activity against *E. coli* and **3e** against *GFC*.

Keywords: 1,5-Benzothiazepines, bioactivity, fluorinated heterocycles

IPC: **Int.Cl.[7] C 07 D**

Earlier studies[1,2] reported the synthesis of 1,5-benzothiazepines having fluorine as a substituent at various positions, looking to the high degree of bioactivity shown by fluorinated heterocycles[3] and benzothiazepine compounds. It has been observed[1] that the incorporation of fluorine in the benzothiazepine nucleus enhances the antifungal activity besides imparting antitubercular activity to the compound. Most of the patented 1,5-benzodiazepine compounds are well known for their psychotropic activity but a structurally related 1,5-benzodiazepine compound, Zimet [(+)-*cis*-3, 4-dimethoxy-10,11-dimethyl-7*H*-6a,8,13,13a-tetrahydro-benzopyrano[4,3-*b*][1,5]-benzodiazepine] shows[4], interestingly, anti-neoplastic activity against leukemia, Lewis lung carcinoma and melanoma B_{16}. When analogous compounds containing fused benzothiazepine and benzopyran nucleus were prepared, they were found to show cardiovascular properties like anti-arrythmics[5], anti-ischemics[6], anti-hypertensives[7], coronary vasodilators[8] *etc*. In continuation of our studies on the syntheses of fluoro-1,5-benzothiazepines and looking to the importance of Zimet, having benzopyranobenzodiazepine nucleus, it was thought to be immensely interesting to synthesize analogous benzopyrano benzothiazepines having fluorine. Synthesis were, thus, planned to obtain compounds combining the features, namely, having a benzopyran moiety fused with the benzothiazepine ring[9] in addition to have a fluorophenyl group and to study their anti-microbial, anti-bacterial, anti-fungal activity. Reactions were carried out in parallel sets, one in acidic medium i.e. toluene containing trifluoroacetic acid and another in basic medium i.e. toluene containing piperidine with the aim to study the effect of medium on the percentage yield of the compounds. Thus, the synthesis of six new 10-substituted-6a,7-dihydro-6*H*-7-(4-fluorophenyl)-6-phenyl[1]benzopyrano[3,4-*c*][1,5] benzothiazepines **3a-f** are reported.

Results and Discussion

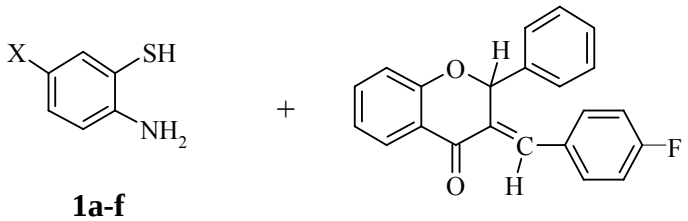
Acid catalysed condensation of 4-fluorobenzaldehyde with flavanone afforded 3-(4-fluorobenzylidene)-flavanone **2** (ref. 10), which was reacted with six 5-substituted-2-aminobenzenethiols **1a-f** (ref. 11), the substituents being F, Cl, Br, CH_3, OCH_3, OC_2H_5, to give the title compounds **3a-f** (**Scheme I**). On

refluxing the precursors **1** and **2** for 6-8 hr, the products were obtained in yields of 58-68% in acidic medium-toluene containing trifluoroacetic acid or basic medium-toluene containing piperidine. Looking to the percentage yield of the products (**Table I**) it may be inferred that there is not enough distinguishable difference in the yields of the products in either acidic or basic medium. This may be agreed upon as the reactions, which are catalyzed by an acid, can also be catalyzed by a base. The difference of the medium causes the different mode of initiation of the reaction resulting into the development of the polarity accordingly in the substrate or the reacting molecule as shown in the reaction carried out in the acidic and basic medium respectively (**Schemes II** and **III**).

Acid catalysed mechanism. In the presence of an acid, the proton gets attached with electronegative oxygen of carbonyl group of 3-(4-fluorobenzylidene)-flavanone **2** and this in turn causes drift of electrons from α,β-unsaturated carbon to carbonyl carbon. As a result vinyl carbon becomes poorer in electron density and is prone to nucleophilic attack by the sulphydryl electrons. This results in the formation of an intermediate, which further reacts immediately as the carbonyl carbon is still electron poor and is attacked by the lone pair of electrons of amino group. This leads finally to the removal of proton from nitrogen and its attachment with electronegative oxygen resulting in the formation of C=N bond by dehydrative cyclization[12-17] (**Scheme II**).

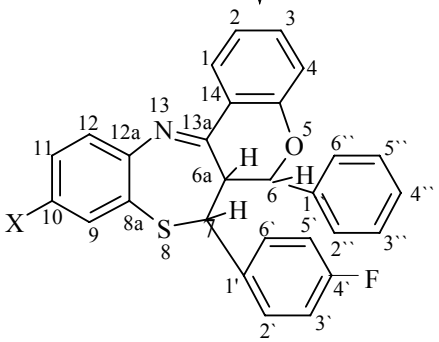
Base catalysed mechanism. Abstraction of a proton from sulphydryl group is facilitated by base to generate a strong nucleophile. The nucleophilic attack by this anion at electrophilic vinyl carbon results in the formation of new sulphur-carbon bond with the shift of sulphydryl proton. This results into the formation of intermediates (i, ii) which readily loses a water molecule by a concerted mechanism i.e. formation of carbon-sulphur bond accompanied by the elimination of a water molecule to form C=N bond (**Scheme III**).

The IR spectra of all the compounds showed strong absorption in the region 1615-1608 which may be assigned to C≡N, besides the absence of carbonyl



1a-f **2**

Dry toluene +
TFA or Piperidine



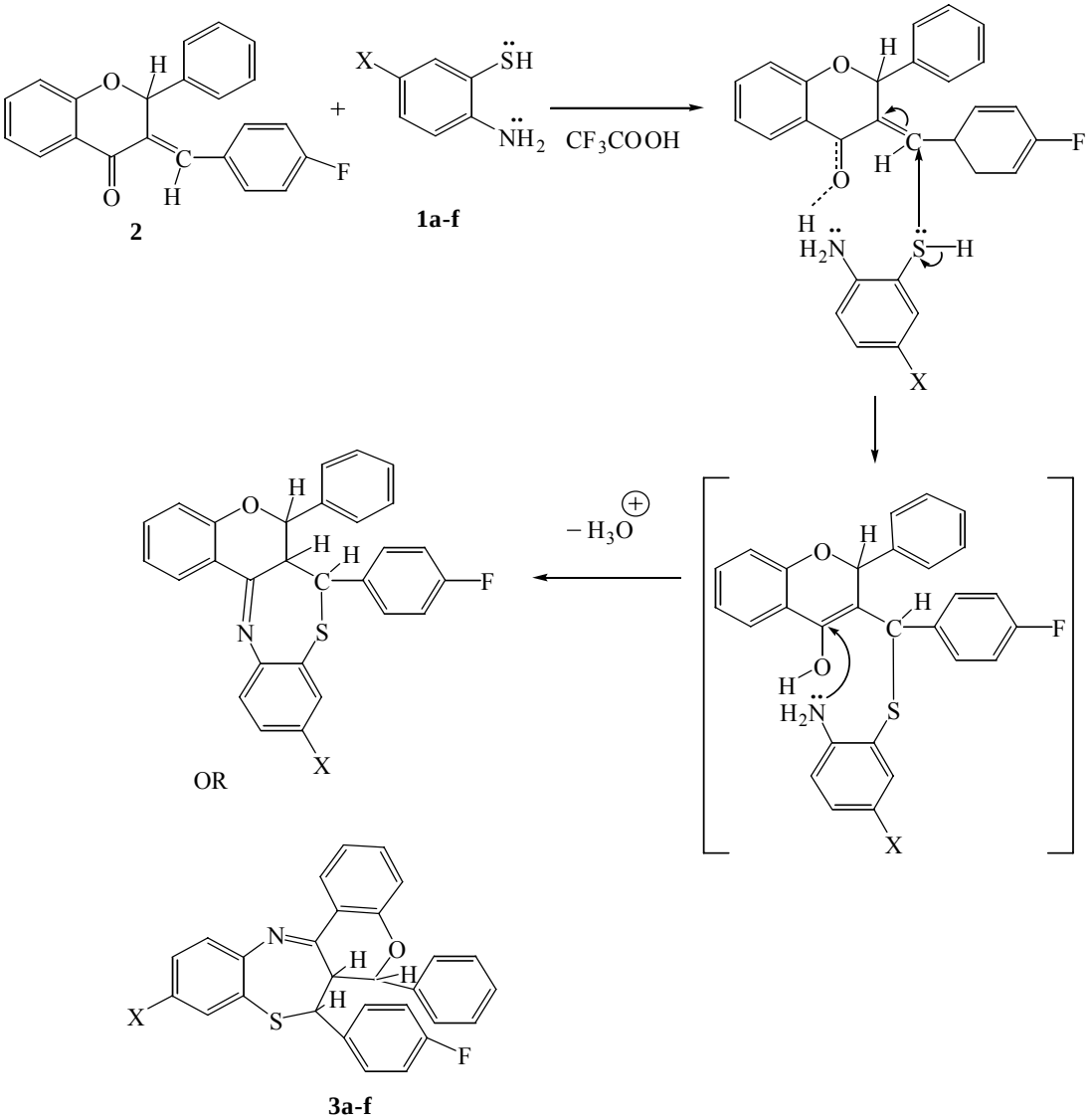
3a-f

Compd	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**
X	F	Cl	Br	CH_3	OCH_3	OC_2H_5

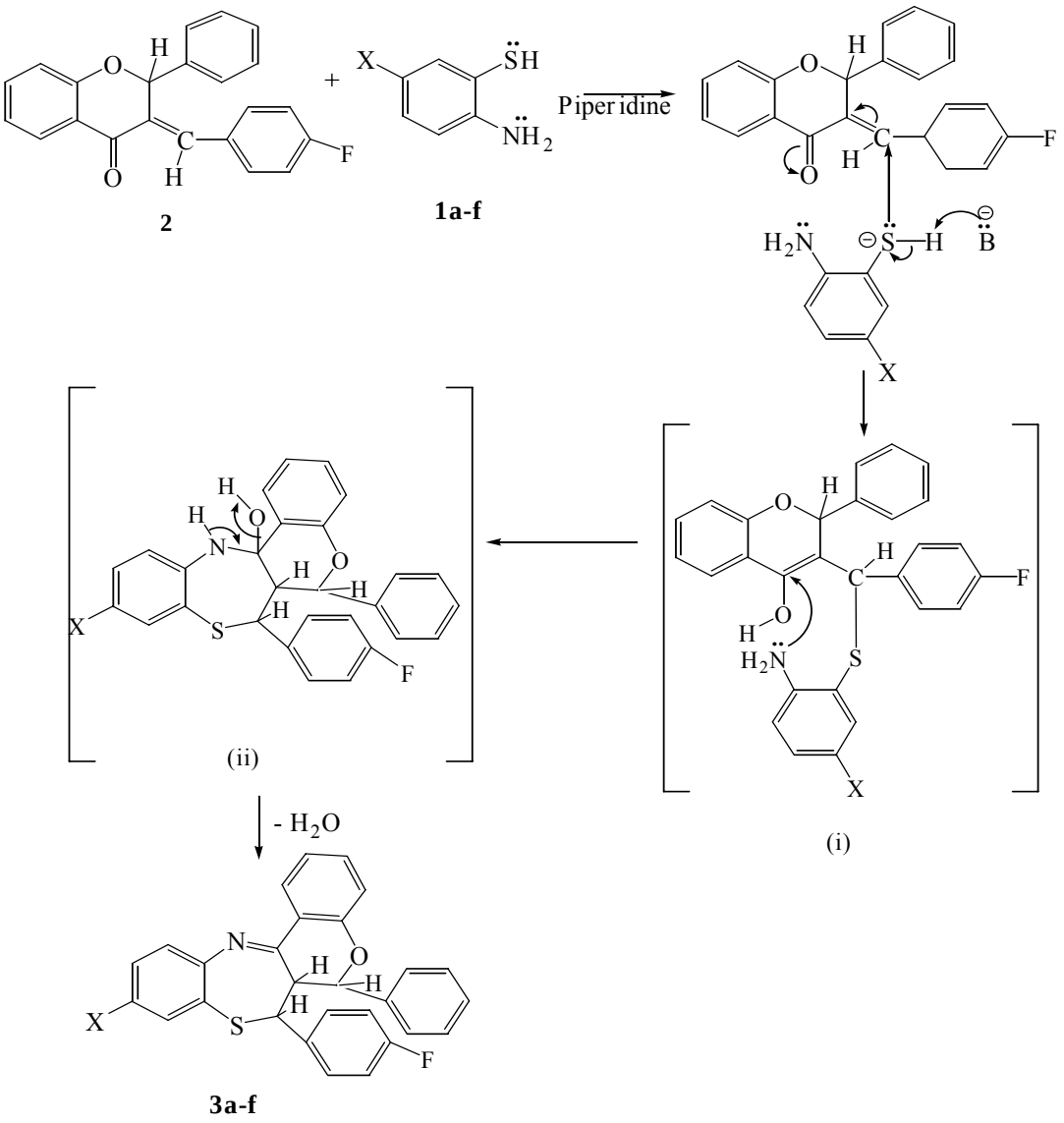
Scheme I

Table I — Characterization data of compounds **3a-e**

Compd	m.p. °C	R_f	Acidic medium Yield (%)	Basic medium Yield (%)	Mol. Formula (Mol. Wt.)	N Found (Calcd) %
3a	104-06	0.86	66	62	$C_{28}H_{19}OF_2SN$ (455)	3.16 (3.07)
3b	101-02	0.72	64	60	$C_{28}H_{19}OFClSN$ (471.5)	2.90 (2.96)
3c	110-12	0.78	68	64	$C_{28}H_{19}OFBrSN$ (516)	2.65 (2.71)
3d	105-06	0.74	62	55	$C_{29}H_{22}OFSN$ (451)	3.26 (3.10)
3e	104-05	0.72	59	58	$C_{29}H_{22}O_2FSN$ (467)	3.12 (2.99)



Scheme II — Mechanism of the acid catalysed reaction



Scheme III — Mechanism of the base catalysed reaction

absorptions around 1680 and primary amino absorptions in the range 3400-3100 cm^{-1}, indicating that the precursors have reacted to give the title compounds in a single step.

In the ^{1}H NMR spectrum of **3d**, the C_{10} -CH_3 protons absorbed as a singlet at δ 2.20. The doublet at δ 4.93 (J=1.1 Hz) may be assigned to C_6; a double doublet at 3.69 (J_1=12.3 Hz, J_2=1.1 Hz) may be assigned to C_{6a}. A doublet at δ 4.98 (J=12.3 Hz) may be assigned to C_7-H. The multiplet at δ 6.04-8.26 may be assigned to 16-aromatic protons. In the ^{13}C NMR, the signal at δ 21.4 may be assigned to the methyl carbon at C-10.^{19}F NMR showed the presence of fluorine, by showing the absorption at δ -111.05. ^{19}F NMR spectra confirm the presence of fluorine in compounds **3a-f.** Single fluorine at position-7 in phenyl ring **3a-f** and two at position-10 and position-7 in phenyl ring **3a** appeared in the range δ -108.20 to -113.00. In ^{19}F NMR of compound **3a**, two peaks at δ -108.20 and -110.00 correspond to fluorine at position -10 and position -7 respectively in phenyl ring, and in compound **3c**, peak at δ -113.00 may be assigned to phenyl ring at position-7 (**Table II**).

The mass spectra of **3b** showed M^+ and $[M+2]^+$ peaks at 471 and 473. The $[M+2]^+$ peak was found to be nearly one third of M^+ peak which may be assigned to chlorine.

The micro analytical data of C, H and N were found to be satisfactory within the permissible limits of error. The analytical data (**Table I**) and ^{1}H NMR

Table II — Characteristic data of compounds **3a-e**

Compd	^{1}H NMR (δ, ppm)					^{19}F NMR (δ, ppm)
	C_{10}-XH	C_6-H	C_{6a}-H	C_7-H	Aromatic protons (16H, m)	
3a	-	4.91 (d, *J*=1.2)	3.68 (dd, J_1=12.3, J_2=1.2)	4.97	6.02-8.30	-108.00 -110.00
3b	-	4.92 (d, *J*=1.2)	3.68 (dd, J_1=12.2, J_2=1.2)	4.98	6.25-8.24	-112.08
3c	-	4.90 (d, *J*=1.1)	3.66 (dd, J_1=12.2, J_2=1.1)	4.97	6.14-8.22	-113.00
3d	2.32 (s, 3H)	4.92 (d, *J*=1.1)	3.67 (dd, J_1=12.2, J_2=1.2)	4.98	6.16-8.21	-111.05
3e	3.82 (s, 3H)	4.91 (d, *J*=1.3)	3.70 (dd, J_1=12.3, J_2=1.3)	4.98	6.12-8.24	-110.00

Table III — Antimicrobial activity of compounds **3a-f**

Compd	Bacteria		Fungi								
	E. coli	*GFC*	*A. niger*			*A. flavus*			*C. lunata*		
			40 hr	72 hr	90 hr	40 hr	72 hr	90 hr	40 hr	72 hr	90 hr
3a	0.80 (1.14)	0.70 (1.00)	14 (0.93)	11 (0.73)	7 (0.46)	14 (0.93)	10 (0.66)	8 (0.53)	15 (1.00)	10 (0.66)	8 (0.53)
3b	0.90 (1.28)	0.80 (1.14)	16 (1.06)	14 (0.93)	8 (0.53)	12 (0.80)	8 (0.60)	6 (0.40)	14 (0.93)	11 (0.73)	8 (0.53)
3c	0.70 (1.00)	0.80 (1.14)	15 (1.00)	11 (0.73)	7 (0.46)	19 (1.26)	15 (1.00)	10 (0.66)	14 (0.93)	10 (0.66)	7 (0.46)
3d	0.60 (0.85)	0.70 (1.00)	13 (0.86)	10 (0.66)	6 (0.40)	13 (0.86)	9 (0.60)	-	14 (0.93)	10 (0.66)	7 (0.46)
3e	0.70 (1.00)	0.60 (0.85)	12 (0.80)	9 (0.60)	6 (0.40)	15 (1.00)	11 (0.73)	8 (0.53)	17 (1.13)	12 (0.80)	8 (0.53)
3f	0.80 (1.14)	0.90 (1.28)	16 (1.06)	14 (0.93)	10 (0.66)	16 (1.06)	12 (0.80)	8 (0.53)	16 (1.06)	11 (0.73)	9 (0.60)

Values in parentheses represent activity index

and ^{19}F NMR (**Table II**) of the final products enabled the assignment of the proposed structures (**3a-f, Schemes II** and **III**).

Antimicrobial activity. All the compounds were screened for their antimicrobial activity against the fungi *Aspergillus niger, A. flavus* and *Curvularia lunata* and the bacteria *E. coli* and *GFC* (the bacterial strain *GFC* was described originally as *Alteromonas tetraodonis* which has all the features characteristic for the genus *Pseudoalteromonas*, a new Gram-negative bacteria family) at the concentration 100 μg/disc, using the filter paper disc method[18], with mycostatin and bacitracin as the reference compounds, respectively. The test fungi/bacteria were grown in the petri dishes in the culture media comprising agar-agar, sucrose and starch for fungi and agar-agar, NaCl, glucose and peptone for bacteria, with the *p*H maintained between 6.8-7.0. The filter paper discs, saturated with the test compounds were incubated for 40, 72 and 90 hr for fungi and 40 hr for bacteria.

The compounds **3a**, **3b** and **3f** showed higher relative activity (activity index = 1.14-1.28) against *E. coli* whereas against *GFC*, the compound **3f** was found to be of higher relative activity (activity index=1.28, **Table III**). All the compounds showed equal/greater bactericidal activity, with **3d** showing lesser activity against *E. coli* and **3e** against *GFC*. This indicates that the fluoro substituent may play an important role in imparting bioactivity to the 1,5-benzothiazepine compounds.

Experimental Section

All the melting points are uncorrected. Purity of the compounds was checked by TLC on silica gel G coated glass plates using benzene-methanol-ammonia (aq., 7:2:1) as solvent system. The IR spectra were taken in KBr pellets on a Perkin-Elmer RXI (FT IR) spectrometer, ^{1}H and ^{13}C NMR spectra were recorded on Jeol 90 MHz FT NMR and Bruker DRX300 spectrometer using $CDCl_3$ and TMS as internal standard and the FAB mass spectra were recorded on

a JEOL SX 102/DA-6000 mass spectrometer/data system using Argon/Xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and the spectra were recorded at room temperature. *m*-Nitrobenzyl alcohol (NBA) was used as the matrix. The spectral analysis and microestimations for carbon, hydrogen and nitrogen were carried out in Elemental Analyzer-Carlo Erba 1108 Heraceus at the Sophisticated Analytical Instrument Facility, CDRI, Lucknow.

6a,7-Dihydro-10-ethoxy-7-(4-fluorophenyl)-6*H*-6-phenyl[1]benzopyrano[3,4-*c*][1,5] benzothiazepine 3f. 2-Amino-5-ethoxy benzenethiol **1f** (0.001 mole) dissolved in dry toluene (5 mL) and 3-(4-fluoro-benzylidene)-flavanone **2** (0.001 mole) dissolved in dry toluene (10 mL) were mixed and trifluoroacetic acid (5 drops) was added to one set and piperidine (10 drops) was added to another similar set of reaction mixture. Refluxing was carried out for 8 hr and solvent was removed under reduced pressure. The crude solid thus obtained was crystallized from dry methanol to give 6a,7-dihydro-10-ethoxy-7-(4-fluoro-phenyl)-6*H*-6-phenyl[1]benzopyrano[3,4-*c*][1,5]benzo-thiazepine **3f**, m.p.110-12°C; yield 0.31 g (65%, acidic medium); yield, 0.29 g (62%, basic medium); R_f 0.76; ^{1}H NMR: δ 1.42 (t, 3H, *J*=6 Hz), 4.10 (q, 2H, *J*=6 Hz), 4.92 (d, 1H, *J*=1.2 Hz,); 3.68 (dd, 1H, J_1=12.2 Hz, J_2=1.2 Hz); 4.99 (d, 1H, *J*=12.2 Hz); 6.60-8.20 (m, 16H, aromatic protons); ^{19}F NMR -110.00; Anal. Found: N, 3.04. Calcd for $C_{30}H_{24}O_2FSN$: N, 2.91%.

On similar lines, **3a-e** were prepared. Their physical constants and spectral data are given in **Tables I** and **II** respectively.

Acknowledgement

The authors gratefully acknowledge the financial assistance granted by the UGC, New Delhi and the Head, Department of Chemistry, University of Rajasthan, Jaipur for providing the facility to work. Thanks are also due to SAIF, Central Drug Research Institute, Lucknow for providing analysis data for N and IR, PMR, ^{19}F NMR and mass spectra.

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