Synthesis and Pharmacological Evaluation of *N*-Substituted 4,6-Diaryl-3-pyridazinones as Analgesic, Antiinflammatory and Antipyretic Agents

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The synthesis and the pharmacological evaluation of 19 new 4,6-diaryl-3-pyridazinones are reported. All compounds were screened for analgesic, antiinflammatory and antipyretic activities. Introduction of an arylpiperazinomethyl moiety in the 2-position of the pyridazinone ring resulted in the most potent activities. Compounds 2a, 2b, 2h and 2i exhibited a higher analgesic activity than did aspirin or noramidopyrine in the hot plate test.

Keywords diaryl-pyridazinone; *N*-alkyl-pyridazinone; *N*-aminoalkylpyridazinone; analgesic activity; antiinflammatory activity; antipyretic activity

Various derivatives incorporating a 3-(2*H*)-pyridazinone ring have recently been described and their cardiotonic,[1,2] antisecretory and antiulcer,[3] as well as analgesic and antiinflammatory[4,5] activities have been investigated. With reference to the potential pharmacological interest of this class of compounds and in search of new types of analgesic-antiinflammatory agents, we synthesized a number of new pyridazinone derivatives bearing two aryl groups in the 4- and 6-positions and various substituents in the 2-position. The biological activity of these compounds was estimated in order to determine their pharmacological profile.

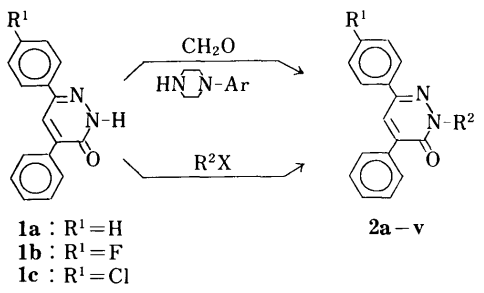
Chemistry 4,6-Diaryl-3-pyridazinones **1** were prepared by a previously published procedure.[6] The 4,6-diaryl-3-pyridazinones substituted by an aminoalkyl, a phenylethyl or a dihydroxyalkyl group were synthesized by the methods shown in Chart 1.

Compounds **2a**—**c**, **2h**—**j**, **2n**—**p**, were obtained through a Mannich reaction involving formaldehyde and *N*-aryl-piperazine. Compounds **2d**—**g**, **2k**—**m** and **2q**—**s** were prepared by reaction of alkyl halides.

Results and Discussion

Physical and spectral data are respectively reported in Tables I and II. Pharmacological data are summarized in Tables III and IV.

Oral acute toxicity was first investigated in mice. No significant behavioral effects were observed even at doses up to 800 mg/kg *p.o.* except with compounds **2d**, **2g**, **2k** and **2q**. In the case of derivative **2d**, from 600 mg/kg the animals presented a deep sedation that disappeared after 24 h. Compounds **2g**, **2k** and **2q** were particularly toxic with LD_{50} near 200 mg/kg; mice died with convulsions and increase of breathing amplitude. Therefore, no further investigation was performed with these 3 products. With other derivatives tested at the dose of 800 mg/kg, all animals were still alive after an observation period of one week.



1a : R^1=H
1b : R^1=F
1c : R^1=Cl

2a–**v**

Chart 1

A number of derivatives showed a good dose-dependent activity in the phenylquinone-induced writhing test in mice treated orally. Compounds **2a**, **2b**, **2h**, **2i**, **2n** and **2o** with a phenyl or a 3-trifluorophenyl piperazinomethyl substituent exhibited remarkable activity, as shown in Table III. Derivatives with a 2-methoxyphenyl piperazinomethyl group were less active. At 100 mg/kg, **2b** was more potent than aspirin; its activity was comparable with that of noramidopyrine (NAP) at the same dose level.

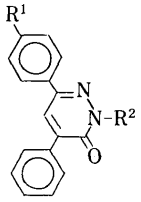
Introduction of a morpholinoethyl, phenylethyl or dihydroxy-propyl substituent in the 2-position of the pyridazinone ring reduced or abolished analgesic activity. The most active compounds in the phenyl-quinone-induced writhing test were run through a battery of screens and compared with aspirin, noramidopyrine, morphine and phenylbutazone (PBZ). In the hot plate test, derivatives **2a**, **2b** and **2h**, **2i** gave a better protection to animals than did NAP and were approximately equipotent at 100 mg/kg *p.o.* dose level to a 4 mg/kg s.c. dose of morphine (Table IV). Aspirin was inactive in this test. Compounds **2n** and **2o** with a 4-chlorophenyl group in the 6-position of the pyridazine ring were significantly less active than their fluorinated homologues in the two analgesic tests used.

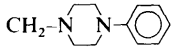
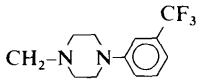
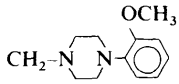
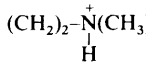
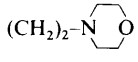
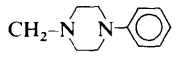
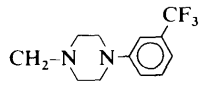
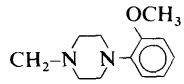
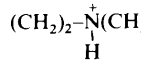
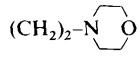
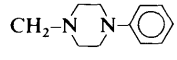
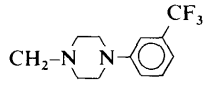
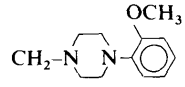
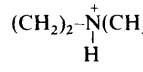
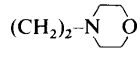
In the rat paw edema test, the tested derivatives were inactive except for **2h** and **2i**, which produced a good level of antiinflammatory activity at 200 mg/kg (Table IV). Furthermore compounds **2a**, **2b**, **2h**, **2i**, **2n**, **2o** were significantly effective against the yeast-induced fever in mice. At 200 mg/kg, **2h** with a phenylpiperazinomethyl group and a 4-fluorophenyl substituent in the 2- and 6-position of the pyridazine ring respectively, was more potent than PBZ at the same dose.

Spontaneous locomotor activity in mice was measured as a parameter of the sedative action of compounds in the central nervous system area. Most of the tested drugs provoked either a very slight increase or a decrease in spontaneous motor activity in the range of 50 to 100 mg/kg. The maximum decrease in motor activity was 65% at 100 mg/kg with **2h**.

In conclusion, the general pharmacological profile encountered in this series of compounds was predominated by

TABLE I. Physical Constants of 4,6-Diaryl-3-pyridazinone Derivatives



Compd. No.	R^1	R^2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)			
						C	H	F/Cl	N
2a	H		79	162	$C_{27}H_{26}N_4O$	76.78 (76.55	6.16 6.21		13.27 13.17)
2b	H		81	140	$C_{28}H_{25}F_3N_4O$	68.57 (68.85	5.10 5.23	11.63 11.49	11.43 11.10)
2c	H		67	132	$C_{28}H_{28}N_4O_2$	74.34 (74.30	6.19 6.31		12.39 12.31)
2d	H		68	155	$C_{20}H_{22}ClN_3O$	67.51 (67.34	6.19 6.20	9.99 10.06	11.81 11.54)
2e	H		88	144	$C_{22}H_{23}N_3O_2$	73.13 (73.09	6.37 6.37		11.64 11.68)
2f	H	$(CH_2)_2$–C_6H_5	80	104	$C_{24}H_{20}N_2O$	81.82 (81.67	5.68 5.62		7.95 7.88)
2g	H	CH_2–CHOH–CH_2OH	81	114	$C_{19}H_{18}N_2O_3$	70.81 (70.79	5.59 5.45		8.69 8.68)
2h	F		45	120	$C_{27}H_{25}FN_4O$	73.64 (75.75	5.68 5.50	4.32 4.29	12.73 12.48)
2i	F		83	126	$C_{28}H_{24}F_4N_4O$	66.14 (66.29	4.73 4.70	14.96 14.81	11.02 11.00)
2j	F		67	130	$C_{28}H_{27}FN_4O_2$	71.49 (71.40	5.75 5.80	4.04 4.04	11.91 11.64)
2k	F		72	208	$C_{20}H_{21}FClN_3O$	64.26 (64.24	5.62 5.58	5.09/9.51 4.96/9.32	11.24 11.12)
2l	F		92	113	$C_{22}H_{22}FN_3O_2$	69.26 (69.47	5.81 5.87	5.01 4.93	11.08 11.06)
2m	F	$(CH_2)_2$–C_6H_5	93	98	$C_{24}H_{19}FN_2O$	77.84 (77.87	5.14 5.15	5.13 5.06	7.57 7.66)
2n	Cl		81	156	$C_{27}H_{25}ClN_4O$	70.97 (70.78	5.48 5.43	7.78 7.64	12.27 12.19)
2o	Cl		95	153	$C_{28}H_{24}F_3ClN_4O$	64.06 (63.94	4.57 4.58	10.87/6.77 10.60/6.68	10.68 10.47)
2p	Cl		82	158	$C_{28}H_{27}ClN_4O_2$	69.06 (69.02	5.55 5.59	7.30 7.32	11.51 11.42)
2q	Cl		72	218	$C_{20}H_{21}Cl_2N_3O$	61.54 (61.30	5.38 5.38	18.21 18.36	10.77 10.39)
2r	Cl		89	128	$C_{22}H_{22}ClN_3O_2$	66.75 (66.98	5.56 5.54	8.98 9.13	10.62 10.36)
2s	Cl	$(CH_2)_2$–C_6H_5	32	87	$C_{24}H_{19}ClN_2O$	74.51 (74.53	4.92 5.02	9.19 9.37	7.24 7.09)

their analgesic and antipyretic effects. In view of the remarkable properties noted for **2a**, **2b**, **2h**, **2n** and **2o**, it seemed that the analgesic and antipyretic activity of these target compounds was due to a large extent to the presence of the 4-fluorophenyl and arylpiperazinomethyl substituents on the pyridazine ring.

TABLE II. Spectral Data for 4,6-Diaryl-3-pyridazinone Derivatives

Compd. No.	R^1	R^2	IR ν (cm^{-1}) KBr	^{1}H-NMR Chemical shift (δ) (in DMSO-d_6)
2a	H	CH_2(a)–N(b,c)–N–Ar	1640, 1600, 1500	3.00 (m, 4H, b), 3.20 (m, 4H, c), 5.30 (s, 2H, a), 7.50 (m, 16H, Ar)
2b	H	CH_2(a)–N(b,c)–N–Ar(CF_3)	1635, 1610, 1490	3.00 (m, 4H, b), 3.25 (m, 4H, c), 5.20 (s, 2H, a), 7.60 (m, 15H, Ar)
2c	H	CH_2(a)–N(b,c)–N–Ar(OCH_3)	1650, 1600, 1500	2.90 (m, 8H, b et c), 3.70 (s, 3H, OCH_3), 5.15 (s, 2H, a), 7.50 (m, 15H, Ar)
2d	H	CH_2(a)–CH_2(b)–$\overset{+}{N}H(CH_3)_2$, Cl^-	3440, 1630, 1590, 1490	2.80 (d, 6H, $2CH_3$), 3.60 (t, 2H, b), 4.60 (t, 2H, a), 7.80 (m, 11H, Ar), 11.20 (br s, 1H, NH^+)
2e	H	CH_2(a)–CH_2(b)–N(c,d)–O	1640, 1595, 1490	2.45 (m, 4H, c), 2.80 (t, 2H, b), 3.50 (m, 4H, d), 4.30 (t, 2H, a), 7.70 (m, 11H, Ar)
2f	H	CH_2(a)–CH_2(b)–C_6H_5	1650, 1600, 1500	3.30 (m, 2H, b), 4.60 (m, 2H, a), 7.90 (m, 16H, Ar)
2g	H	CH_2(a)–CHOH(b,c)–CH_2OH(d,e)	3350, 1640, 1595, 1490	3.45 (m, 2H, d), 4.00 (br s, 1H, e), 4.20 (m, 2H, a), 4.50 (m, 1H, b), 4.90 (br s, 1H, c), 7.60 (m, 11H, Ar)
2h	F	CH_2(a)–N(b,c)–N–Ar	1645, 1610, 1510	2.90 (m, 4H, b), 3.10 (m, 4H, c), 5.15 (s, 2H, a), 7.40 (m, 15H, Ar)
2i	F	CH_2(a)–N(b,c)–N–Ar(CF_3)	1635, 1600, 1510	2.90 (m, 4H, b), 3.25 (m, 4H, c), 5.20 (s, 2H, a), 7.60 (m, 14H, Ar)
2j	F	CH_2(a)–N(b,c)–N–Ar(OCH_3)	1640, 1600, 1510	2.95 (m, 8H, b et c), 3.75 (s, 3H, OCH_3), 5.20 (s, 2H, a), 7.40 (m, 14H, Ar)
2k	F	CH_2(a)–CH_2(b)–$\overset{+}{N}H(CH_3)_2$, Cl^-	3450, 1650, 1605, 1510	2.90 (br s, 6H, $2CH_3$), 3.65 (m, 2H, b), 4.70 (t, 2H, a), 7.80 (m, 10H, Ar), 11.10 (br s, 1H, NH^+)
2l	F	CH_2(a)–CH_2(b)–N(c,d)–O	1640, 1600, 1510	2.50 (m, 4H, c), 2.80 (t, 2H, b), 3.60 (m, 4H, d), 4.50 (t, 2H, a), 7.75 (m, 10H, Ar)
2m	F	CH_2(a)–CH_2(b)–C_6H_5	1650, 1610, 1510	3.20 (t, 2H, b), 4.50 (t, 2H, a), 7.60 (m, 15H, Ar)
2n	Cl	CH_2(a)–N(b,c)–N–Ar	1645, 1600, 1500	2.90 (m, 4H, b), 3.10 (m, 4H, c), 5.15 (s, 2H, a), 7.40 (m, 15H, Ar)
2o	Cl	CH_2(a)–N(b,c)–N–Ar(CF_3)	1655, 1610, 1490	2.90 (m, 4H, b), 3.30 (m, 4H, c), 5.25 (s, 2H, a), 7.65 (m, 14H, Ar)
2p	Cl	CH_2(a)–N(b,c)–N–Ar(OCH_3)	1640, 1600, 1500	2.95 (m, 8H, b et c), 3.75 (s, 3H, OCH_3), 5.20 (s, 2H, a), 7.50 (m, 14H, Ar)
2q	Cl	CH_2(a)–CH_2(b)–$\overset{+}{N}H(CH_3)_2$, Cl^-	3400, 1640, 1590, 1490	2.70 (s, 6H, $2CH_3$), 3.60 (t, 2H, b), 4.65 (t, 2H, a), 7.90 (m, 10H, Ar), 11.00 (br s, 1H, NH^+)
2r	Cl	CH_2(a)–CH_2(b)–N(c,d)–O	1640, 1600, 1500	2.50 (m, 4H, c), 2.80 (t, 2H, b), 3.60 (m, 4H, d), 4.50 (t, 2H, a), 7.90 (m, 10H, Ar)
2s	Cl	CH_2(a)–CH_2(b)–C_6H_5	1650, 1600, 1490	3.10 (t, 2H, b), 4.40 (t, 2H, a), 7.60 (m, 15H, Ar)

TABLE III. Phenylquinone Writhing Test in Mice

Compd. No.	Analgesic activity % at 100 mg/kg	Compd. No.	Analgesic activity % at 100 mg/kg
2a	$61 \pm 2^{a)}$	**2l**	$10 \pm 4^{c)}$
	($57 \pm 3^{a)}$ at 50 mg/kg)	**2m**	5 ± 2 (NS)
	($45 \pm 3^{a)}$ at 25 mg/kg)	**2n**	$60 \pm 4^{a)}$
2b	$87 \pm 3^{a)}$		($17 \pm 4^{a)}$ at 50 mg/kg)
	($68 \pm 2^{a)}$ at 50 mg/kg)		(3 ± 2 (NS) at 25 mg/kg)
	($15 \pm 5^{b)}$ at 25 mg/kg)	**2o**	$52 \pm 3^{a)}$
2c	$45 \pm 4^{a)}$		($26 \pm 5^{a)}$ at 50 mg/kg)
2e	$35 \pm 6^{a)}$		(6 ± 5 (NS) at 25 mg/kg)
2f	$10 \pm 5^{c)}$	**2p**	$48 \pm 3^{a)}$
2g	$32 \pm 3^{a)}$	**2r**	$9 \pm 3^{c)}$
2h	$83 \pm 2^{a)}$	**2s**	2 ± 1 (NS)
	($66 \pm 2^{a)}$ at 50 mg/kg)	Aspirin	$70 + 3^{a)}$
	($51 \pm 3^{a)}$ at 25 mg/kg)		($30 \pm 5^{a)}$ at 50 mg/kg)
2i	$81 \pm 3^{a)}$		($10 \pm 4^{c)}$ at 25 mg/kg)
	($71 \pm 2^{a)}$ at 50 mg/kg)	NAP	$91 \pm 2^{a)}$
	($64 \pm 4^{a)}$ at 25 mg/kg)		($55 \pm 3^{a)}$ at 50 mg/kg)
2j	$42 \pm 5^{a)}$		($25 \pm 3^{a)}$ at 25 mg/kg)

The level of significance was *a*) $p<0.001$, *b*) $p<0.01$, *c*) $p<0.05$, or NS, not significant.

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. The infrared spectra were recorded on a Beckman 4240 spectrophotometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian EM 360A spectrometer. Resonance positions are given on the δ scale (parts per million) relative to internal tetramethylsilane. The NMR signals were designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; m, multiplet.

4,6-Diaryl-2-arylpiperazinomethyl-3-pyridazinones (2a—c, 2h—j, 2n—p) A solution of 35% aqueous formaldehyde (1.7 ml, 0.02 mol), pyridazinone **1** (0.02 mol) and arylpiperazine (0.02 mol) in ethanol (75 ml) was refluxed for 12 h with continuous stirring and evaporated *in vacuo*. The oily residue was triturated with diisopropyl ether and the resulting solid was collected by filtration and dried.

4,6-Diaryl-2-(2-dimethylaminoethyl)-3-pyridazinones Hydrochlorides (2d, 2k, 2q) The appropriate pyridazinone **1** (0.02 mol) was added to an ethanolic solution (50 ml) of sodium (0.46 g, 0.02 gatom). On the other hand, a solution of 2-dimethylaminoethyl chloride hydrochloride (0.02 mol) in absolute ethanol (40 ml) was added to an ethanolic solution (50 ml) of sodium (0.46 g, 0.02 gatom). The two solutions were mixed and refluxed for 8 h. The sodium chloride was filtered off and the solution was evaporated to dryness *in vacuo*. The residue was dissolved in absolute ethanol (20 ml) and the solution was saturated with gaseous hydrochloric acid. Compounds **2d**, **2k**, **2q** were precipitated by addition of diethyl ether and recrystallized from ethanol.

TABLE IV. Hot Plate Test, Carrageenin-Induced Paw Edema Test, Yeast-Induced Pyrexia Test, Spontaneous Motor Activity Test

Compd. No.	Analgesic activity (%)		Antiinflammatory activity (%)	Antipyretic activity at 200 mg/kg			Effect on motor activity (%) (−) decrease (+) increase	
				Rectal temperature at the following times after treatment		Δ		
	50	100 (mg/kg)	200 (mg/kg)	0	3 (h)		50	100 (mg/kg)
2a	2±1 (NS)	76±11[a]	3±1 (NS)	38.90±0.06	36.10±0.15[a]	−2.80	5±1 (NS)	19±6[c]
2b	38±9[a]	>100[a]	2±1 (NS)	38.50±0.09	37.10±0.15[a]	−1.40	−3±1 (NS)	11±6 (NS)
2h	62±12[a]	89±12[a]	61±4[a]	38.60±0.10	34.20±0.15[a]	−4.40	−58±3[a]	−65±4[a]
2i	94±13[a]	>100[a]	44±3[a]	38.50±0.05	35.70±0.14[a]	−2.80	−2±1 (NS)	−20±3[a]
2n	11±10 (NS)	42±8[a]	2±1 (NS)	38.70±0.07	36.50±0.18[a]	−2.20	10±5 (NS)	−7±6 (NS)
2o	2±1 (NS)	27±7[b]	8±6 (NS)	38.50±0.17	36.60±0.24[a]	−1.90	−3±2 (NS)	−29±4[a]
Aspirin	Inactive		51±10[a]	38.60±0.14	36.90±0.09[a]	−1.70	−4±2 (NS)	−9±3 (NS)
NAP	25±10[a]	51±11[a]	62±3[a]	38.80±0.04	35.90±0.33[a]	−2.90	−15±4[c]	−23±2[a]
PBZ	No tested		77±2[a] at 100 mg/kg	38.50±0.07	35.50±0.22[a]	−3.00	No tested	
Morphin	96±10[a] at 4 mg/kg s.c.		No tested	No tested			−21±3[a] at 4 mg/kg s.c.	

The level of significance was *a*) $p<0.001$, *b*) $p<0.01$, *c*) $p<0.05$, or NS, not significant.

4,6-Diaryl-2-(2-morpholinoethyl)-3-pyridazinones (2c, 2l, 2r) A suspension of pyridazinone **1** (0.01 mol), 2-morpholinoethyl chloride (5.98 g, 0.04 mol) and potassium carbonate (5.52 g, 0.04 mol) in acetone (100 ml) was stirred and refluxed for 24 h. The reaction mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The oily residue was triturated with water and the resulting solid was collected by filtration and recrystallized from ethanol/water.

4,6-Diphenyl-2-(2,3-dihydroxypropyl)-3-pyridazinones (2g) These compounds were prepared according to the same procedure as described for **2e**, **2l** and **2r**.

4,6-Diaryl-2-(2-phenylethyl)-3-pyridazinones (2f, 2m, 2s) Potassium hydroxide (1.12 g, 0.02 mol) and *N*-tetrabutylammonium bromide (0.76 g, 0.002 mol) were added to a solution of pyridazinone **1** (0.02 mol) and phenylethyl bromide (3.70 g, 0.02 mol) in benzene (100 ml). The mixture was stirred and refluxed for 24 h. After evaporation, the residue was triturated with diisopropyl ether. The crude product was recrystallized from ethanol.

Pharmacological Studies In the studies described below, all compounds were administered orally in a 0.5% hydroxypropylmethyl cellulose aqueous suspension. Iffa Credo OF1 male mice (20 g) and OFA Sprague Dawley male rats were used.

Behavioral Effects and Acute Toxicity in Mice The compounds were administered at various doses. The animals were observed over 24 h and the symptomatology was noted. In addition, they were kept under observation for 8 d to detect any sign of toxicity.

Analgesic Activity For the phenylquinone writhing test,[7,8] groups of 10 mice were given i.p. a 0.02% solution (ethanol–water, 5:95) of phenylquinone (P.B.Q) 30 min after oral administration of test drugs. The writhing response frequency of each animal was counted between the 5th and the 15th min after the injection of the irritant agent.

For the hot plate test,[9,10] groups of 10 mice were used. Animals were placed on a copper plate maintained at a constant temperature of 56 °C. The time necessary to induce the licking reflex of the fore paws was then recorded. Two basal measurements of the pain threshold were made before administration. Measurements were carried out 30 min later.

Antiinflammatory Activity[11,12] This activity was studied by the method of Winter using groups of 6 rats weighing 100—120 g and employing carrageenin as the phlogogenic agent. Edema was induced in the right hind paw by intradermal injection (0.05 ml) of 1% carrageenin solution. The drugs were administered orally 60 min before edema induction. The volume of the inflamed paw was measured before and 3 h after carrageenin infection with a Ugo Basile apparatus.

Antipyretic Activity[13] Groups of 6 rats weighing 220 g were injected s.c. with a 20% aqueous yeast suspension in a volume of 10 ml/kg. Sixteen hours later, rectal temperature was measured by a Carrieri thermorapid apparatus. Temperature was measured 3 h after administration of test drugs, recording the difference from the initial values.

Sedative Activity[14] This activity was evaluated by a study of the spontaneous motor activity. Groups of 10 mice were used. This test was done by using the method of Boissier and Simon, in photoelectric activity cages (Apelex). Test drugs were administered 30 min before evaluation of spontaneous motor activity and the number of passages was scored during 10 min.

Data Analysis Statistical analysis of the results was performed by using the method of Schwartz.[15] Pharmacological data were expressed as mean ±S.E. and the significance of differences was analyzed by using Student's *t* test.

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