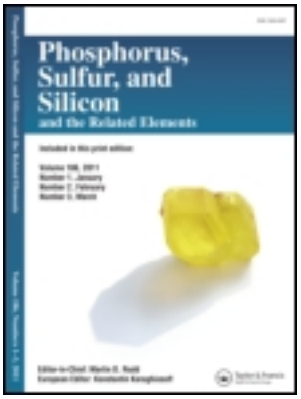

Phosphorus, Sulfur, and Silicon and the Related Elements

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Regioselective Synthesis of Diltiazem Analogue Pyrazolo[4,3-c][1,5]benzothiazepines and Antifungal Activity

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REGIOSELECTIVE SYNTHESIS OF DILTIAZEM ANALOGUE PYRAZOLO[4,3-c][1,5]BENZOTHIAZEPINES AND ANTIFUNGAL ACTIVITY

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A dry media procedure has been developed for the synthesis of a series of new class of pyrazolo [4,3-c][1,5]benzothiazepines 6 under microwave irradiation using montmorillonite K10 as solid support. The catalyst can be recovered and reused. Thus, the procedure provides a simple and green synthetic methodology under environmentally friendly conditions. Antifungal screening of synthesized compounds has shown promising activity.

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Keywords Microwaves; montmorillonite; pyrazolo-benzothiazepines

INTRODUCTION

The development of a privileged heterocyclic scaffold is a rapidly emerging subject in medicinal chemistry.[1] The pyrazole unit is one of the core structures in a number of natural products. Many pyrazole derivatives are known to exhibit a wide range of biological properties such as antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, antifungal, hypoglycemic, sedative-hypnotic, antitumor, and anticoagulant activities.[2–5] The 1,5-benzothiazepine class of compounds is important as calcium channel blockers of proven utility such as diltiazem and clentiazem, and those in which the fused benzene ring is substituted at various positions have been found to have enhanced pharmacological properties.[6,7] The incorporation of heterocyclic rings into prospective pharmaceutical candidates is a major tactic to gain activity and safety advantages. Although much work has been directed toward the design and synthesis of fused-pyrazole derivatives,[8–13] a search of the literature revealed very few reports concerning fused pyrazolo-benzothiazepines[14] having pyrazole fusion at various facets. Conventionally, the fusion of a pyrazole ring with

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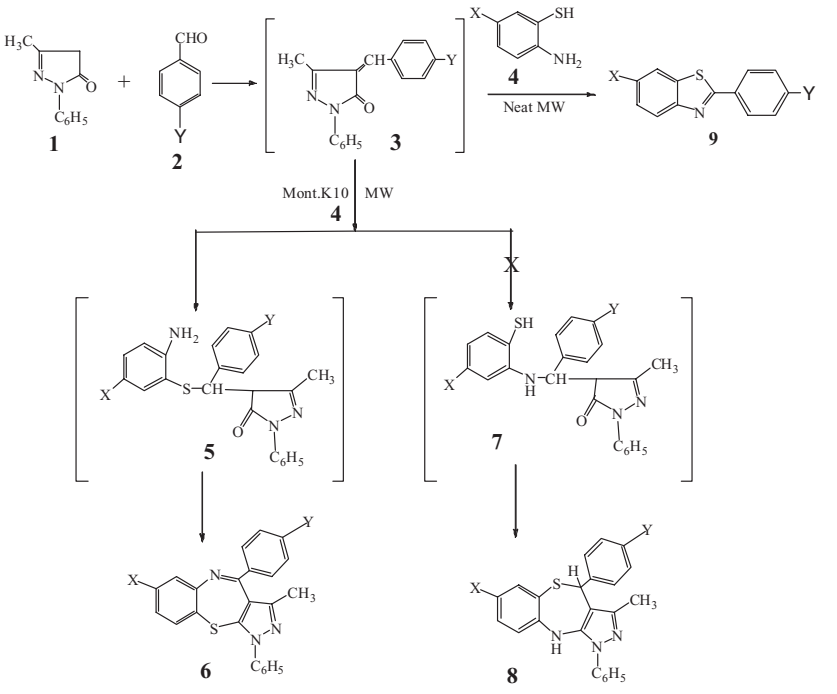


Scheme 1

a thiazepine nucleus requires a multistep procedure under harsh conditions with a tedious isolation process, due to the formation of a mixture of products.

The use of microwave (MW) heating can dramatically cut down on reaction time, increase product purity and yields, and allow precise control of reaction conditions, all of which make it suited to meet the increased demands of high throughput chemistry.[1516] The reports concerning microwave-assisted rapid synthesis of fused pyrazolo-benzothiazepines is not available. Hence, in continuation of our interest in the synthesis of 1,5-benzothiazepines and annulated 1,5 benzothiazepines[17] in a search for better and improved cardiovascular drugs and to establish a structure–activity relationship, we have investigated the reaction of benzylidene-pyrazolinones **3** with aminothiophenol **4** under microwave irradiation. The results obtained showed the exclusive formation of pyrazolo[4,3-c][1,5]benzothiazepine **6** instead of the other possible isomer pyrazolo[3,4-b][1,5]benzothiazepine **8** (Scheme 1).

RESULTS AND DISCUSSION

Various inorganic solid supports, i.e., montmorillonite K10/montmorillonite KSF/ basic alumina, have been used to find the best medium (Table I). However, montmorillonite K10 is the most adaptable support for synthesizing **6**, since a comparatively higher yield was achieved in a shorter time. The reaction has also been performed under neat conditions

Table I Comparative results obtained for the synthesis of pyrazolo[4,3-c][1,5]benzothiazepines **6a** by reacting **3c** and **4a**

Experiment	Support/solvent	Method	Time (min)	Temp[a] (°C)	Product	Isolated Yield (%)
1	Ethanol + gl AcOH	Δ	420	Reflux	6	15
2	Montmorillonite KSF	MW	15	138	6	82
3	**Montmorillonite K10**	**MW**	**7**	**142**	**6**	**90**
4	Basic alumina	MW	16	132	6	80
5	Montmorillonite K10 (MCR)	MW	8	144	6	76
6	Neat (MCR)	MW	8	145	**9c**	89
7	Montmorillonite K10 (MCR)[b]	Δ	7	142	Unchanged reactant	Nil
8	Montmorillonite K10 (MCR)[b]	Δ	480	142	Traces of mixture	12

[a]Final temperature is measured at the end of microwave irradiation by introducing a glass thermometer into the reaction mixture in the beaker.

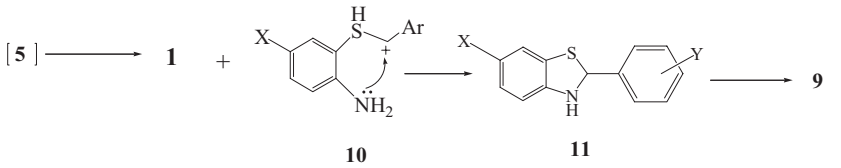
[b]The reaction mixture was placed in a preheated oil bath.

under microwave irradiation, where 2-phenyl-benzothiazole **9** was formed exclusively instead of the expected product pyrazolo[4,3-c][1,5]benzothiazepines **6**. During the literature survey, we came across one report[18] in which pyrazolo[3,4-b][1,5]benzothiazepine **8** was synthesized conventionally by the reaction of **3** with **4** using ethanol and glacial acetic acid in lower yield. To check this possibility we have also carried out the same reaction under identical conditions where an intractable mixture of product was formed. By tedious isolation and chromatographic separation, the product was obtained in very low yield (15%) and identified as **6**, not **8** as reported earlier.[18]

The formation of **6** can be explained by involving the intermediacy of **5** instead of **7** as assumed by Fawi et al.[18] The mechanistic pathway of the reaction of benzylidene-pyrazolinones **3** with aminothiophenol **4** first involves the formation of intermediate Michael adduct **5** via nucleophilic attack[19] of the sulphydryl group on the β-carbon atom of the double bond of **3**, which is rendered electrophilic due to vinyl–carbonyl conjugation, which is in agreement with the observations of several other workers, where they have mentioned that when substituents are present in an α,β-unsaturated ketone, only the nucleophilic addition of the mercapto group to the β-carbon atom takes place, followed by condensation of the carbonyl group with the aromatic primary amine to give a seven-membered[20–22] ring system leading to the formation of a new class of tricyclic ring system **6**. Formation of intermediate **5** is confirmed by its isolation during the course of the reaction. It is also synthesized separately[22] using isopropanol and their further conversion to final product, which is found to be identical with compound **6** synthesized using montmorillonite KSF. Formation of intermediate **5** rules out the possibility of the formation of product **8.**

In view of the immense utility of a green synthetic approach, and in order to develop a facile procedure for the synthesis of **6**, we have also carried out the improved synthesis of key intermediates **3a–c** in solvent-free conditions (neat) under microwave irradiation by irradiating a mixture of p-substituted benzaldehyde **2a–c** and 3-methyl-1-phenyl-2-pyrazolin-5-one **1** for 1–2 min to give **3a–c**. TLC studies indicated ∼100% conversion of reactants and formation of a single product; therefore it was used as such for further reaction with aminothiophenol **4**. Hence, we extended this condition for one-pot synthesis of **6** but surprisingly, the product isolated was identified as 2-phenyl-benzothiazole **9** instead of the expected product **6**, The formation of which can be explained by the mechanism given in Scheme 2, which involved losses of pyrazolone moiety **1** from the intermediate **5**.

Intramolecular nucleophilic attack by a lone pair of nitrogens on the electrophilic carbon leads to the dihydro intramediate **11**, which is readily oxidized to the corresponding 2-aryl-benzothiazoles.



Scheme 2

Further, an increasing number of organic compounds are formed by multicomponent reactions that convert more than two adducts directly into their products by a one-pot reaction.[23] Hence, promoted by these observations and in continuation of our earlier interest in multicomponent reactions under microwaves,[24] we have also investigated this reaction via the MCR of **1**, **2**, and **4** under microwave irradiation using montmorillonite K10 and through a neat reaction. The results showed the formation of the pyrazolo[4,3-c][1,5]benzothiazepines **6** under microwave irradiation coupled with inorganic supports and the synthesis of 2-phenyl-benzothiazole **9** in neat conditions. However, the yield of isolated product was comparatively low because it requires chromatographic separation.

Finally, in order to check the possible intervention of specific (non-thermal) microwave effects,[25] the results obtained under microwave irradiation were compared to conventional heating. The reaction in the case of compounds **6a** has been carried out using a preheated oil bath under the same conditions as under microwaves (time, temperature, vessel, solid support). It has been found that reactants remained unchanged up to 7 min, while traces of mixture of product were obtained when the reaction time was extended to 7–8 h (Table I).

Evaluation of the Antifungal Activity

The synthesized compounds were screened for antifungal activity against three pathogenic fungi, namely *Rhizoctonia Solani*, which causes root rot of okra; *Fusarium oxysporum*, which causes wilt of mustard; and *Colletotrichum capsici*, which causes leaf spot and fruit rot of chilli using (i) the poison plate technique[26] and (ii) the pot trial method.[27] The results are summarized in Tables S1 and S2 (Supplemental Materials, available online).

EXPERIMENTAL

Melting points were determined on a Toshniwal apparatus. Thin layer chromatography on silica gel "G" coated plates using benzene:ethyl acetate (8:2) as eluent was used for monitoring the progress of the reactions. IR spectra (KBr) were recorded on a Magna FT IR-550 spectrophotometer, and ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 using $CDCl_3$ at 300.15 and 75.47, respectively. TMS was used as the internal reference. Mass spectra of representative compounds were recorded on a Kratos 50 mass spectrometer at 70 eV. The microwave-assisted reactions were carried out in a commercial multimode MW oven equipped with inverter technology and also attached with a magnetic stirrer and reflux condenser, operating at 1000W generating 2450 MHz

frequency. 5-Substituted-2-aminobenzenethiols (**4a–e**) were prepared by the method in the literature.[28]

Synthesis of 4-Benzylidene-5-methyl-2-phenyl-2,4-dihydro-pyrazol-3-one 3a

Classical thermal method. An equimolar mixture (0.01 mol) of 3-methyl-1-phenyl-2-pyrazolin-5-one **1** and p-methoxybenzaldehyde **2a** in absolute ethanol (20 mL) was taken in a conical flask. Aqueous 4% KOH solution was added dropwise at room temperature with continuous stirring. The color of the solution changed to blue within 10 min, and the solution became blurred with suspension of particles, then ice cold HCl was added. This was kept for 3–4 h. The solid thus obtained was filtered, dried, and crystallized from methanol to give cream-colored crystals of **3a**, mp 119°C, yield 80%.

Neat reaction. A neat equimolar mixture (0.01 mol) of **1** and **2a** was irradiated inside a microwave oven until the completion of reaction for 1–2 min (monitored by TLC). The resulting solid mass was dissolved in methanol, and cream-colored crystals separated out, which were found to be pure as indicated by TLC. For analytical purposes, the product was further recrystallized from ethanol.

3a: Mp 119°C, yield ~93%. IR (cm^{-1}): 1600 (C=C), 1680 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, CH_3), 3.93 (s, 3H, $-OCH_3$), 4.93 (s, 1H, methine proton), 6.92–7.11 (m, 9H, Ar-H).

Investigation of the Reaction of 3 with 4 Under Different Reaction Conditions

Reaction in isopropanol. 2-Aminothiophenol **4a** (2 mmol) was added dropwise to a solution of 4-benzylidene-5-methyl-2-phenylpyrazolin-3-one **3c** (2 mmol) in isopropanol (20 mL) with stirring. After being stirred for 2–4 h, the reaction mixture was cooled in an ice bath. The resulting crystals were collected and recrystallized from isopropanol to afford colorless crystals identified as 3-(2-amino-phenylthio)-3-pyrazoliones **5**, mp 134–135°C, yield 62%.

IR (cm^{-1}): 3500–3350 (NH_2 asym. and sym), 1685 (C=O), 1595 (C=N). ^1H NMR ($CDCl_3$) Diastereomeric ratio (3:1) δ 2.06/2.01 (s, 3H, CH_3), 4.08/3.88 (d, 1H, J = 11.7 Hz), 4.69/4.48 (d, 1H, J = 11.7 Hz), 5.03–5.08 (bs, 2H, NH_2 exchangeable with D_2O), 7.77–7.30 (Ar-CH, m). ^{13}C NMR 17.7 (CH_3), 39.9 (S-CH), 51.21(CH), 115.4, 118.6, 120.6, 122.9, 124.9, 125.8, 126.2, 126.9, 128.2, 130.1, 140.3, 142.2, 144.8, 155.8 (C=N), 174.6 (C=O); Anal. Calcd. for $C_{23}H_{21}N_3OS$: C, 71.29; H,5.46; N,10.84; Found: C, 71.08; H, 5.42; N, 10.79.

Neat condition. Equimolar quantities of **3c** and **4a** were gently mixed and irradiated inside the microwave oven for an appropriate time (TLC). Upon completion of the reaction, the mixture was cooled, and the product was extracted from methanol to give **9a**. The compounds **9b** and **9c** were prepared in same manner as described above.

Using inorganic solid supports. An equimolar mixture of **3b** (0.01 mol) and **4a** (0.01 mol) was adsorbed on inorganic solid supports (4 g) (montmorillonite K10/montmorillonite KSF/basic alumina) via a methanolic solution (5 mL). The dry, free-flowing powder was kept in the microwave oven and irradiated at a power output of 90% (640 watts) for the time indicated in Table I. After completion of the reaction (monitored by TLC), the recyclable inorganic solid support was separated by filtration after eluting the

Table II Physical and analytical data of compounds **6a–i** and **9a–c**

Compound	X	Y	Time (min)	Mp (°C)	Yield[a] (%)	Rf[b]
6a	H	H	6	122	90	.81
6b	H	Cl	7	112	80	.72
6c	OCH_3	OCH_3	8	102	85	.76
6d	OC_2H_5	OCH_3	9	109	80	.82
6e	Cl	OCH_3	8	92	82	.79
6f	Br	OCH_3	7	98	88	.81
6g	CH_3	Cl	6	124	80	.88
6h	Cl	Cl	7	128	76	.75
6i	CH_3	OCH_3	7	105	89	.71
9a	H	Cl	6	220	89	.83
9b	OCH_3	OCH_3	7	210	87	.82
9c	H	H	7	112	90	.79

[a]Yield of the isolated products.
[b]Using solvent system benzene:ethylacetate (8:2).

product with methanol. The solvent was evaporated to give crystals, which are identified as pyrazolo[4,3-c][1,5]benzothiazepine **6a**, and which were crystallized from methanol.

All other compounds **6b–i** were similarly prepared using montmorillonite K10 as the solid support under microwave irradiation (Table II).

Multicomponent reaction (MCR).

MCR in neat condition. An equimolar mixture (0.01mol) of **1,** benzaldehyde **2b**, and 2-aminothiophenol **4a** was irradiated at 640 watts until the completion of the reaction (TLC). The light brown, sticky solid mass that was obtained was triturated with pet ether and crystallized with methanol to give pale yellow, shiny crystals of compounds 2-arylbenzenthiazole **9a**.

MCR using solid supports. An equimolar mixture of (0.001 mol) **1**, **2c**, and **4a** was adsorbed on an inorganic solid support (2 g) such as montmorillonite K10 via a methanolic solution and swirled for a while, followed by removal of the solvent under gentle vacuum. The dry powder thus obtained was placed on an alumina bath and irradiated in microwave oven at power output of 90% (640 watt) for 8 min (TLC) listed in Table I. The product was extracted with methanol and identified as pyrazolo[4,3-c][1,5]benzothiazepine **6a** after using column chromatography.

Compound 6a. ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, CH_3), 4.91(s, 1H, methine proton), 6.92–7.51 (m, 14H, Ar-H), 8.26 (bs, 1H, NH). IR (KBr)/cm^{-1} 3350(NH), 1601 (C=N); Analysis calcd for $C_{23}H_{19}N_3S$; C, 74.77; H, 5.18; N, 11.37; S, 8.68. Found C, 74.52; H, 5.16; N, 11.33; S, 8.64. Mass (m/z) 369 (M^+, 3.47%), 331 (3.9%), 300 (43.4%), 275 (4.1%), 210 (100%), 114 (18.95), 72(6.4%).

Compound 6b. ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H, CH_3), 4.91 (s, 1H, methine proton), 6.99–7.59, (m, 13H, Ar-H), 8.16 (bs, 1H, NH). IR (KBr)/cm^{-1} 3352 (NH), 1600 (C=N); Analysis calcd for $C_{23}H_{17}Cl_2N_3S$; C, 68.39; H, 4.49; N, 10.40; S, 7.94. Found C, 68.15; H, 4.47; N, 10.43, S, 7.91. Mass (m/z) 403 (M^+, 25%), 326 (100%), 270 (29%) etc. ^{13}C NMR ($CDCl_3$) δ7.1 (CH_3), 34.2 (methine carbon), 106.8, 119.1, 118.2, 122.8. 124.9, 126.8. 128.2, 129.8, 130.3, 131.2, 138.8, 139.5, 141.8, 145.8, 148.3 (aromatic and other ring carbons) 154.3 (C=N).

Compound 6c. ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.85 (s, 1H, methine proton), 7.16–7.97, (m, 12H, Ar-H), 8.25 (bs, 1H, NH). IR (KBr)/cm^{-1} 3353 (NH), 1604 (C=N); Analysis calcd for $C_{25}H_{23}N_3O_2S$; C, 69.91; H, 5.40; N, 9.78. Found C, 70.11; H, 5.42; N, 9.75. Mass (m/z) 429 (M^+ 82.2%), 411 (100%), 377 (66.5%), 308 (2.1%), 211 (12.4%).^{13}C NMR ($CDCl_3$) δ7.3 (CH_3), 36.7 (methine carbon), 55.3 (OCH_3), 56.2 (OCH_3), 104.98, 118.1, 119.2, 123.8. 125.9, 126.8. 127.2, 128.6, 130.9, 131.9, 137.3, 138.9, 142.8, 147.1, 149.20 (aromatic and other ring carbons) 155.3 (C=N).

Compound 6d. ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7Hz,) 2.07 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.02 (q, 2H, J = 7Hz), 4.85 (s, 1H, methine proton), 7.26–7.97, (m, 12H, Ar-H), 8.26 (bs, 1H, NH). IR (KBr)/cm^{-1} 3352 (NH), 1602 (C=N); Analysis calcd for $C_{26}H_{25}N_3O_2S$; C, 70.40; H, 5.68; N, 9.47. Found C, 70.19; H, 5.70; N, 9.45. ^{13}C NMR ($CDCl_3$) δ7.4 (CH_3), 15.2 (CH_3), 35.2 (methine carbon), 55.6 (OCH_3), 59.7 (OCH_2), 105.2, 114.8, 115.3, 117.6. 118.6. 119.2, 123.1. 126.9, 128.2, 130.8 134.2, 138.2, 138.8, 140.5, 146.8, 150.7, 152.4, 159.2 (aromatic and other ring carbons).

Compound 6e. ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.89 (s, 1H, methine proton), 7.23–7.70, (m, 12H, Ar-H), 8.19 (bs, 1H, NH). IR (KBr)/cm^{-1} 3350 (NH), 1600 (C=N); Analysis calcd for $C_{24}H_{20}ClN_3OS$; C, 66.43; H, 4.65; N, 9.68.Found C, 66.64; H, 4.67; N, 9.71.

Compound 6f. ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.83 (s, 1H, methine proton), 7.20–7.69 (m, 12H, Ar-H), 8.17 (bs, 1H, NH). IR (KBr)/cm^{-1} 3352 (NH), 1601 (C=N); Analysis calcd for $C_{24}H_{20}BrN_3OS$; C, 60.25; H, 4.21; N, 8.78. Found C, 60.03; H, 4.23; N, 8.75.

Compound 6g. ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 4.82 (s, 1H, methine proton), 7.22–7.81, (m, 12H, Ar-H), 8.20 (bs, 1H, NH). IR (KBr)/cm^{-1} 3350 (NH), 1603 (C=N); Analysis calcd for $C_{24}H_{20}ClN_3S$; C, 68.97; H, 4.82; N, 10.53. Found C, 68.75; H, 4.84; N, 10.50.

Compound 6h. ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H,CH_3), 4.91 (s, 1H, methine proton), 7.19–7.59, (m, 12H, Ar-H), 8.16 (bs, 1H, NH). IR (KBr)/cm^{-1} 3355 (NH), 1605 (C=N); Analysis calcd for $C_{23}H_{17}Cl_2N_3S$; C, 63.02; H, 3.91; N, 9.59. Found, C, 63.25; H, 3.93; N, 9.56.

Compound 6i. ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H,CH_3), 2.12 (s, 3H,CH_3), 3.72 (s, 3H, OCH_3), 4.89 (s, 1H, methine proton), 7.23–7.70, (m, 12H, Ar-H), 8.19 (bs, 1H, NH). IR (KBr)/cm^{-1} 3350 (NH), 1601 (C=N); Analysis calcd for $C_{25}H_{23}N_3OS$; C, 72.61; H, 5.61; N, 10.16. Found, C, 72.84; H, 5.63; N, 10.12.

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