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Synthesis and antimicrobial activity of structurally flexible heterocycles with the 1,4-thiazine heterosystem

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Abstract In this work, 4H-1,4-benzothiazines were synthesized by an efficient synthetic method in a single step involving heterocyclization of substituted 2-aminobenzenethiols with β-ketoester. The structures of the synthesized compounds were confirmed by their analytical and spectral data. The synthesized compounds were evaluated for their antimicrobial activity against bacterial species; *E. coli* and *Bacillus cereus*. The synthesized compounds showed significant activity against microorganisms, which can be correlated with the privileged heterocyclic structural scaffolds.

Keywords 2-aminobenzenethiols · 4H-1,4-benzothiazines · Antimicrobial activities

Introduction

Nitrogen- and sulphur-containing heterocycles are undoubtedly the most important targets in the pharmaceutical chemistry because most of the natural products of pharmaceutical interest incorporate N- and S- heterocycles in their structures [1, 2]. The 1,4-thiazine ring system is an important heterosystem in heterocyclic chemistry because it constitutes the skeleton of natural products, such as the two cytotoxic terpene, quinones, conicaquinones A and B, xanthizone, and xnthiside. The 1,4-thiazine ring system is known to also play an important role in pigments and dyestuffs [3–7]. In addition, 4H-1,4-benzothiazine derivatives have been shown to exhibit wide-ranging biological activities, such as anticancer, antifungal, antagonistic, antioxidant, antihypertensive, analgesic, cardiovascular, antibacterial, antimalarial, and antimicrobial, etc. [8–21]. 1,4-Benzothiazines have also been reported

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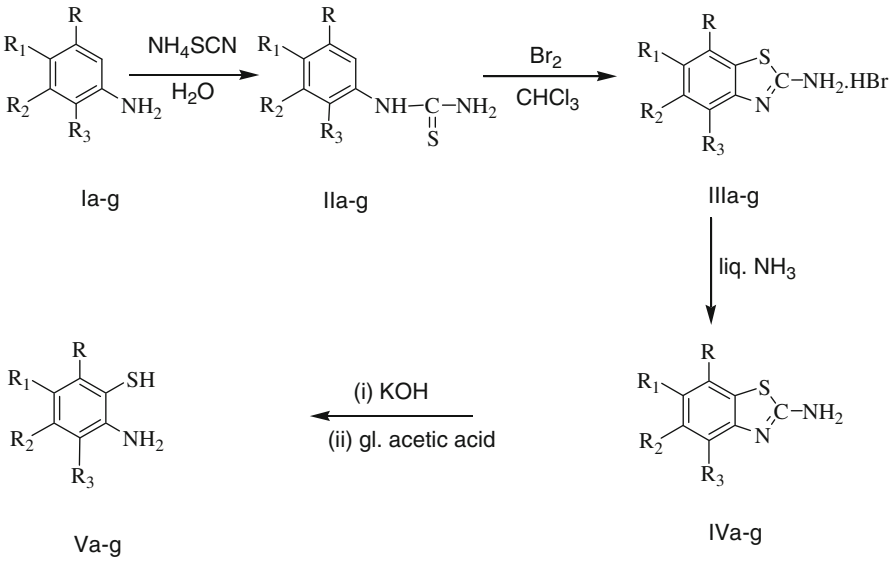
as new antiallergic and antirheumatic agents. 1,4-Benzothiazines annelated with benzopyrene have shown a very interesting cytoprotective effect against t-BHP-induced cytotoxicity. The diverse range of biological activities of 1,4- benzothiazines has been attributed to the structural specificity, i.e., structural flexibility due to folding along the N–S axis. The folding angle is affected to a larger extent by the nature and arrangement of the substituents which in turn influence the activity. The structural features present in the 1,4-benzothiazine heterosystem are also present in 10H-phenothiazine and are responsible for their wide-ranging activities, which makes them therapeutically as well as industrially interesting [22–24].

Encouraged by promising diverse biological activities of 1,4-benzothiazines, and as a part of our ongoing research program on the synthesis of nitrogen- and sulphur-containing novel heterocycles [25–29], we have designed and synthesized structurally diverse 1,4-benzothiazines and evaluated their activity against microorganisms.

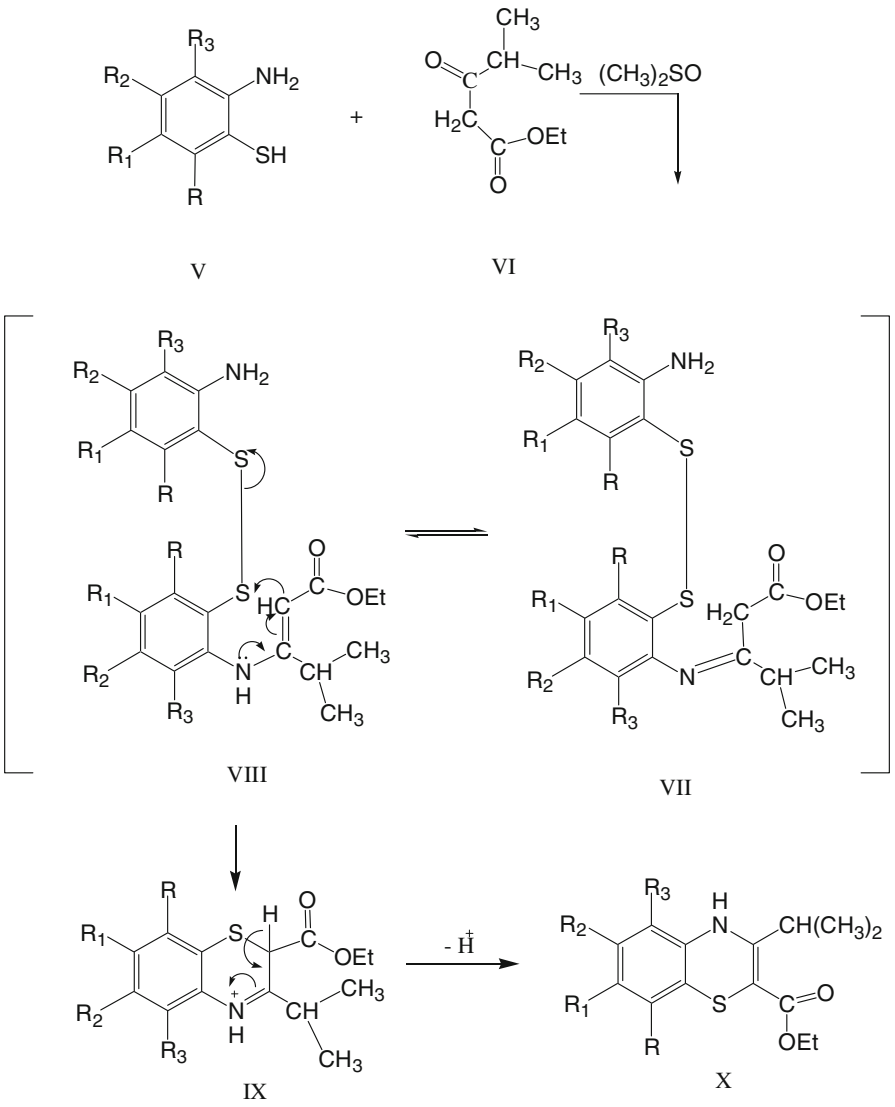
Results and discussion

2-Aminobenzenethiols **Va–g** were prepared by the heterolytic cleavage of substituted 2-aminobenzothiazoles **IVa–g**, which were prepared by brominative cyclization of the corresponding phenylthioureas **IIa–g** obtained by thiocyanogenation of substituted anilines **Ia–g** (Scheme 1) [30–34].

Substituted 4H-1,4-benzothiazines **Xa–g** have been synthesized by heterocyclization of 2-aminobenzenethiols with β-ketoester in the presence of dimethyl sulphoxide (Scheme 2).



Scheme 1 Mechanistic presentation of synthesis of substituted 2-aminobenzenethiols



(Xa) R = H, $R_1 = CH_3$, $R_2 = H$, $R_3 = H$
(Xb) R = Cl, R_1 = H, $R_2 = H$, $R_3 = CH_3$
(Xc) R = H, $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$
(Xd) R = H, R_1 = H, $R_2 = H$, $R_3 = Cl$
(Xe) R = H, R_1 = H, $R_2 = H$, $R_3 = H$
(Xf) R = H, $R_1 = OC_6H_5$, $R_2 = H$, $R_3 = H$
(Xg) R = H, R_1 = Cl, $R_2 = H$, $R_3 = H$

Scheme 2 Mechanistic presentation of synthesis of substituted 4H-1,4-benzothiazines

The reaction is considered to proceed via in situ formation of an enaminoketone intermediate **VIII**, which is simultaneously cyclized to 4H-1,4-benzothiazine with the cleavage of S–S bond involving intramolecular nucleophilic attack. Thus, the reaction is regioselective and occurs through the predominately keto form of β-ketoester (Scheme 2). Although different methods have been reported in the literature [35–50], the present method has been considered as one of the best methods as far as its operational simplicity and the yields of the products are concerned.

The structures of the newly synthesized 4H-1,4-benzothiazines have been assigned by their elemental analyses and IR, ^{1}H NMR, ^{13}C NMR, and mass spectral studies. The absence of the absorption bands corresponding to $-NH_2$ and –SH groups and the appearance of the absorption bands corresponding to the N–H and C=O stretching vibrations in the regions, 3,325–3,450 and 1,625–1,740 cm^{-1}, respectively, in IR spectra revealed that heterocyclization has occurred under the reaction conditions and provided substituted 4H-1,4-benzothiazines (**Xa**–**g**) involving the proposed reaction mechanism (Scheme 2). An absorption band in the region 790–820 cm^{-1} is observed due to C–Cl stretching vibrations in the compounds **Xb**, **Xd**, and **Xg**.

^{1}H NMR spectra of all the synthesized 4H-1,4-benzothiazines exhibit a singlet in the region δ 8.10–8.24 ppm due to N–H proton. All 4H-1,4-benzothiazines show multiplet in the region δ 7.00–7.75 ppm due to aromatic protons. In compound (**Xf**) a multiplet is observed in the region δ 6.87–6.98 ppm due to aromatic protons of $-OC_6H_5$. In compound (**Xc**) a singlet is observed at δ 3.93 ppm due to CH_3 protons of OCH_3. All 4H-1,4-benzothiazines show a triplet in the region δ 1.21–1.33 ppm due to CH_3 protons of OC_2H_5 and a quartet in the region δ 3.72–4.79 ppm due to CH_2 protons of OC_2H_5. All 4H-1,4-benzothiazines show a heptate (appears as multiplet) in the region δ 2.33–2.92 ppm due to CH of isopropyl group and a doublet in the region δ 1.29–1.13 ppm due to $(CH_3)_2$ protons of isopropyl group. ^{13}C NMR spectrum of the synthesized 1,4-benzothiazine **Xg** showed distinct resonance signals including for aromatic carbons and other carbons in agreement with the assigned structure. ^{13}C NMR spectra of the synthesized compounds (**Xa**–**f**) are similar to that of Xg except for the substituents CH_3, OCH_3, and OC_6H_5, which exhibit characteristics resonance signals with appropriate chemical shifts. In the mass spectrum of compound **Xg**, the molecular ion peak observed at 297 (M^+) is in accordance with the molecular weight of the synthesized compound. The base peak at *m/z* 136 (100%) and other peaks (*m/z*, I > 5%) 91, 109, 124, 147, 176, 190, 218, 234, 235, 269 are according to the structural fragments of the compound **Xg**.

Pharmacological activity

All the synthesized compounds were screened for their antibacterial activity against *Bacillus cereus* (Gram-positive bacteria) and *E. coli* (Gram-negative bacteria) at a concentration of 30 μg/mL using ethanol as a solvent by well-diffusion method [51–54]. After 24 h of incubation at 37°C, the zone of inhibition was measured in millimeters (Table 1).

Table 1 Pharmacological activity substituted 4H-1,4-benzothiazines (**Xa–g**)

	Compounds (30 μg/mL)				Antimicrobial (zone of inhibition in mm)	
	R	R_1	R_2	R_3	*E. Coli* (A)	*Bacillus cereus* (B)
I	**II**	**III**	**IV**	**V**	**VI**	**VII**
Xa	H	CH_3	H	H	11	10
Xb	Cl	H	H	CH_3	12	13
Xc	H	OCH_3	H	H	12	12
Xd	H	H	H	Cl	11	10
Xe	H	H	H	H	12	9
Xf	H	OC_6H_5	H	H	13	12
Xg	H	Cl	H	H	9	12
Chloramphenicol					10	11

Conclusions

It has been observed that all the synthesized benzothiazines **Xa–g** show activity against microbes. Compounds **Xb**, **Xc**, and **Xf** show excellent activity against both bacteria, whereas compounds **Xa** and **Xd** show moderate activity against *E. coli*. However, weak activity was shown by the compounds **Xa** and **Xd** against *B. cereus*. Compound **Xe** shows moderate activity against *E. coli* while weak activity is shown against *B. cereus*. Compound **Xg** shows weak activity against *E. coli*, whereas moderate activity was shown against *B. cereus*. Chloramphenicol (30 μg/mL) was used as reference drug for the activity (Fig. 1) .

Experimental

Melting points of the synthesized compounds were determined on an electric melting apparatus and the values are uncorrected. The IR spectra were recorded on a Shimadzu 470 spectrometer in KBr discs. The ^{1}H NMR and ^{13}C NMR spectra were

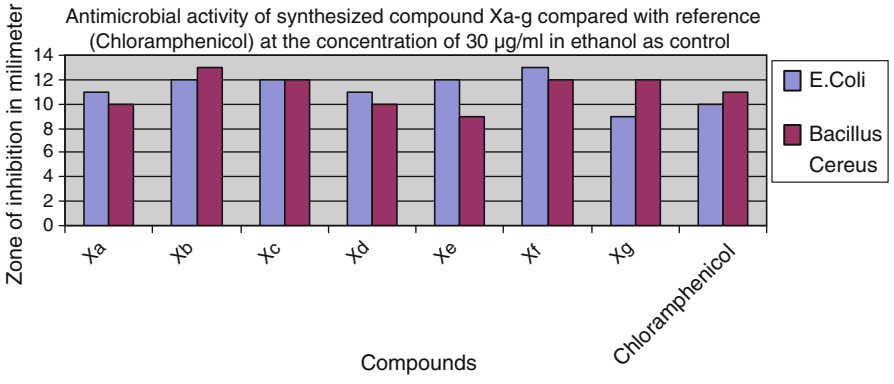


Fig. 1 Graphical representation of in vitro antibacterial activity of the synthesized compounds (**Xa–g**)

recorded on a JEOL 300-MHz spectrophotometer using TMS as an internal standard in $CDCl_3$/DMSO as solvent. The chemical shifts are expressed as δ ppm. Mass spectrum data was recorded on a JEOL SX-102/Da-600 using Argon/Xenon (6 kV, 10 mA0 as the FAB gas) mass spectrometer.

General method of preparation

Preparation of substituted 2-aminobenzenethiols (**Va–g**)

Substituted 2-aminobenzenthiols have been prepared from substituted anilines in the three steps shown below:

1. Preparation of substituted phenylthioureas

A mixture of substituted aniline (0.1 mol) conc. HCl (9 mL) and water (25 mL) was formed in an R.B. flask and refluxed for 30 min. The solution of aniline hydrochloride obtained was then allowed to cool to room temperature and then ammonium thiocyanate (0.1 mol) was added. The reaction mixture was then refluxed for 4 h until two layers were separated out. The solution was poured into crushed ice and was then filtered, dried, and crystallized from ethanol.

2. Preparation of substituted 2-aminobenzothiazoles

Substituted phenylthiourea (0.1 mol) and chloroform (100 mL) were taken in two-necked R.B. flask (500 mL) equipped with a mechanical stirrer. A solution of bromine (0.1 mol) in chloroform (100 mL) was added dropwise with stirring to the reaction mixture by maintaining the temperature below 5°C. After the complete addition of bromine, the stirring was continued for a period of 4 h and the contents of the flask were refluxed on water bath until the evolution of HBr ceased. Chloroform was removed by filtration and the resulting solid material was treated with aqueous sulphur dioxide solution and then filtered. The filtrate was neutralized by aqueous ammonia solution and the precipitate obtained was filtered, washed with water, and crystallized from ethanol.

3. Preparation of substituted 2-aminobenzenethiols

In a round-bottomed flask, substituted 2-aminobenzothiazole, KOH (five times by weight of thiazole) and water (ten times by weight of thiazole) were placed and refluxed until evolution of ammonia ceased. The contents were filtered and diluted by ice-cold water. Adding 5 N acetic acid with vigorous stirring neutralized the filtrate. The temperature of the solution was not allowed to rise above room temperature (controlled by adding ice) otherwise a decomposed greenish mass is obtained. The semisolid yellowish precipitate was extracted 2–3 times with ether. Ether was evaporated and the product was crystallized from ethanol.

β-ketoester(active methylene compound) (**VI**)

β–ketoester used for the synthesis of 4H-1,4-benzothiaines was purchased from Sigma-Aldrich.

Preparation of substituted 4H-1,4-benzothiazines (**Xa–g**)

2-aminobenzenethiol (**Va–g**; 0.01 mol) was added to the stirred suspension of β-ketoester (VI; 0.01 mol) in DMSO (5 mL) and then the reaction mixture was refluxed for 25 min. The reaction mixture was cooled to room temperature and the solid obtained was filtered and washed with petroleum ether. The synthesized 4H-1,4-benzothiazines were crystallized from methanol.

Xa. Ethyl 3-isopropyl-7-methyl-4H-1,4-benzothiazine-2-carboxylate

Yield 81% M.P. °C 192; IR (KBr, cm^{-1}): 3,325(–NH), 1,625(C=O); ^1H NMR ($CDCl_3$, δ ppm); 2.92 (s, 3H, CH_3 proton at C_7), 8.14 (s, 1H,–NH proton), 2.39–2.54 (m, 1H, Isopropyl CH proton at C_3), 1.18 (d, $J = 6.9$ Hz, 6H, Isopropyl $(CH_3)_2$ proton at C_3), 3.86 (q, 2H, Ester CH_2 protons), 1.25 (t, $J = 7.1$ Hz, 3H, Ester CH_3 proton), 7.20–7.75 (m, 3H, Aromatic protons); Anal. Calcd. for $C_{15}H_{19}NO_2S$: C, 64.95, H, 6.90, N, 5.05. Found: C, 64.88, H, 6.83, N, 5.01.

Xb. Ethyl 8-chloro-3-isopropyl-5-methyl-4H-1,4-benzothiazine-2-carboxylate

Yield 72% M.P. °C 206; IR (KBr, cm^{-1}): 3,450(–NH), 1,730(C=O); ^1H NMR ($CDCl_3$, δ ppm); 2.71(s, 3H, CH_3 proton at C_5), 8.18 (s, 1H,-NH proton), 2.33–2.50 (m, 1H, Isopropyl CH proton at C_3), 1.14–1.16 (d, $J = 6.9$ Hz, 6H, Isopropyl $(CH_3)_2$ proton at C_3), 3.92 (q, 2H, Ester CH_2 protons), 1.25 (t, $J = 7.1$ Hz, 3H, Ester CH_3 proton), 7.00–7.42 (dd, $J = 8.1$ Hz, 2H, Aromatic protons); Anal. Calcd. for $C_{15}H_{18}ClNO_2S$: C, 57.78, H, 5.82, N, 4.49. Found: C, 57.71, H, 5.77, N, 4.41.

Xc. Ethyl 3-isopropyl-7-methoxy-4H-1,4-benzothiazine-2-carboxylate

Yield 65% M.P. °C 202; IR (KBr, cm^{-1}): 3,360(–NH), 1,680(C=O); ^1H NMR ($CDCl_3$, δ ppm); 3.93(s, 3H, OCH_3 proton at C_7), 8.22 (s, 1H,–NH proton), 2.59(m, 1H, Isopropyl CH proton at C_3), 1.17–1.19 (d, $J = 6.9$ Hz, 6H, Isopropyl $(CH_3)_2$ proton at C_3), 3.78–3.84 (q, 2H, Ester CH_2 protons), 1.21–1.29 (t, $J = 7.1$ Hz, 3H, Ester CH_3 proton), 7.46–7.50 (m, 3H, Aromatic protons); Anal. Calcd. for $C_{15}H_{19}NO_3S$: C, 61.41, H, 6.53, N, 4.77. Found: C, 61.39, H, 6.49, N, 4.71.

Xd. Ethyl 5-chloro-3-isopropyl-4H-1,4-benzothiazine-2-carboxylate

Yield 60% M.P. °C 198; IR (KBr, cm^{-1}): 3,340(–NH), 1,740(C=O); ^1H NMR ($CDCl_3$, δ ppm); 8.21 (s, 1H, –NH proton), 2.58 (m, 1H, Isopropyl CH proton at C_3), 1.26–1.29 (d, $J = 6.9$ Hz, 6H, Isopropyl $(CH_3)_2$ proton at C_3), 3.72–3.80 (q, 2H, Ester CH_2 protons), 1.33 (t, $J = 7.1$ Hz, 3H, Ester CH_3 proton), 7.19–7.31 (m, 3H, Aromatic protons); Anal. Calcd. for $C_{14}H_{16}ClNO_2S$: C, 56.46, H, 5.42, N, 4.70. Found: C, 56.41, H, 5.39, N, 4.65.

Xe. Ethyl 3-isopropyl-4H-1,4-benzothiazine-2-carboxylate.

Yield 85% M.P. °C 190; IR (KBr, cm^{-1}): 3,425(–NH), 1,680(C=O); ^1H NMR ($CDCl_3$, δ ppm); 8.24 (s, 1H, –NH proton), 2.61 (m, 1H, Isopropyl CH proton at C_3),

1.13–1.15 (d, $J = 6.9$ Hz, 6H, Isopropyl $(CH_3)_2$ proton at C_3), 4.79 (q, 2H, Ester CH_2 protons), 1.24–1.27 (t, $J = 7.1$ Hz, 3H, Ester CH_3 proton), 7.09–7.56 (m, 4H, Aromatic protons); Anal. Calcd. for $C_{14}H_{17}NO_2S$: C, 63.85, H, 6.51, N, 5.32 Found: C, 63.80, H, 6.49, N, 5.29.

Xf. Ethyl 3-isopropyl-7-phenoxy-4H-1,4-benzothiazine-2-carboxylate

Yield 78% M.P. °C 210; IR (KBr, cm^{-1}): 3,400(–NH), 1,740 (C=O); ^1H NMR ($CDCl_3$, δ ppm); 6.87–6.98 (m, 5H, OC_6H_5 at C_7) 8.10 (s, 1H, –NH proton), 2.92 (m, 1H, Isopropyl CH proton at C_3), 1.27–1.28 (d, $J = 6.9$ Hz, 6H, Isopropyl $(CH_3)_2$ proton at C_3), 4.08 (q, 2H, Ester CH_2 protons), 1.25 (t, $J = 7.1$ Hz, 3H, Ester CH_3 proton), 7.28–7.46 (m, 3H, Aromatic protons); Anal. Calcd. for $C_{20}H_{21}NO_3S$: C, 67.58, H, 5.95, N, 3.94 Found: C, 67.51, H, 5.91, N, 3.90.

Xg. Ethyl 7-chloro-3-isopropyl-4H-1,4-benzothiazine-2-carboxylate

Yield 64% M.P. °C 195; IR (KBr, cm^{-1}): 3,390(–NH), 1,690(C=O); ^1H NMR ($CDCl_3$, δ ppm); 8.24 (s, 1H, –NH proton), 2.55(m, 1H, Isopropyl CH proton at C_3), 1.17–1.18 (d, $J = 6.9$ Hz, 6H, Isopropyl $(CH_3)_2$ proton at C_3), 4.30–4.37 (q, 2H, Ester CH_2 protons), 1.25–1.30 (t, $J = 7.1$ Hz, 3H, Ester CH_3 proton), 7.12–7.54 (m, 4H, Aromatic protons); ^{13}C NMR ($CDCl_3$, δ ppm); 158.24, 147.92, 146.51, 129.65, 128.15, 127.05, 124.75, 118.47, 117.63, 64.44, 35.45, 18.24,19.52 MS: *m/z*: 297 (M^+), BP: *m/z*: 136; Anal. Calcd. for $C_{14}H_{16}ClNO_2S$: C, 63.85, H, 6.51, N, 5.32 Found: C, 63.80, H, 6.49, N, 5.29.

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