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Synthesis, Characterization and Antimicrobial Evaluation of Some Arylidenehydrazonofuropyrimidines and Thienopyrimidines

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Abstract. Cyclization of heteroaromatic *o*-aminoester with formamide afforded furo[2,3-d]pyrimidin-4(3*H*)-one which was then chlorinated with thionyl chloride followed by displacement by hydrazine hydrate to furnish hydrazinofuro [2,3-d]pyrimidine. Reaction of hydrazino derivative with formic acid gave furo[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine. Treatment of hydrazino derivative with aromatic aldehydes afforded arylidenehydrazonofuro[2,3-d]pyrimidine derivatives. Reaction of *o*-aminonitrile with carbon disulphide, followed by methylation with methyl iodide and subsequent reaction with hydrazine hydrate afforded hydrazinothieno[2,3-d]pyrimidine. 14 derivatives were synthesized. Some of these derivatives exhibited pronounced antimicrobial activities against *S. typhi, S. aureus, S. dysenteriae, V. cholerae, C. lunata, A. alternata, C. corchori, F. equeseti* and *M. phaseolina*.

Keywords: aminoester, aminonitrile, furo-pyrimidine, thieno-pyrimidine, antimicrobial activity, pyrimidines

Introduction

Among the wide range of heterocycles explored to develop pharmaceutically important molecules, pyrimidine has played an important role in medicinal chemistry. Compounds having a pyrimidine nucleus possess a broad range of biological activities such as antibacterial (Bekhit *et al*., 2003), antiviral (Kumar *et al*., 2002), anticancerous (Haggarty *et al*., 2000), antimalarial (Agarwal *et al*., 2005), antihypertensive (Ismail *et al*., 2006) and anti-inflammatory activities (Sondhi *et al*., 2005; Ferri *et al*., 2003). Some furans are useful for the inhibition of thrombin formation. Furano derivatives are also associated with various biological activities such as antihypertensive, antiallergic, anticonvulsive, anxiolytic, antiamnestic and antidepressant activities (Nalbandyan *et al*., 1999; Sauter *et al*., 1996; Patil *et al*., 1984). In continuation of our search for antimicrobial molecules (Bhuiyan *et al*., 2006; 2005a,b,c; 2004), furano- and thienopyrimidine derivatives were synthesized and evaluated for their anti-microbial activities.

Materials and Methods

Melting points were recorded with electrothermal melting point apparatus and are uncorrected. Evaporation of solvents was performed under reduced pressure on a Buchi rotary evaporator. Thin layer chromatography was performed on Kieselgel GF_{254} and visualization was accomplished by iodine flask or UV Flame. ^{1}H-NMR (500 MHz and 300 MHz) spectrum was recorded for solutions in deuterio chloroform $CDCl_3$ as solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and *J* values are given in Hz.

Ethyl 2-amino-4,5-diphenylfuran-3-carboxylate (1). A suspension of ethyl cyanoacetate (2.125 g, 33.3 mmol) and benzoin (5.24 g, 25 mmol) in DMF (7.5 ml) was treated with diethylamine (4 ml). After 12 h standing and 12 h stirring, the mixture was poured onto ice-water (60 ml). The conversion was checked by TLC (*n*-hexane:ethyl acetate; 4:1, v/v) on silica gel which showed complete conversion into the product. The separated solid was collected by filtration and recrystallized from ethanol to give ethyl 2-amino-4,5-diphenylfuran-3-carboxylate **(1)** (75%) as yellow crystals, m.p. 208-210 °C. ^{1}H-NMR(500 MHz, $CDCl_3$): δ_H 9.24 (s, 2H, NH_2), 7.96-7.38 (m, 10H, 2×Ph), 2.66 (q, 2H, CH_2), 1.03 (t, 3H, CH_3).

5,6-Diphenylfuro[2,3-d]pyrimidin-4(3H)-one (2). A solution of **1** (3.85 mmol) in formamide (5 ml) was refluxed for 2 h. The precipitate that formed on cooling was filtered and recrystallized from ethanol to give **2** (70%) as yellow crystals, m.p. 210-212 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.84 (s, 1H, CH), 7.6-7.4 (m, 10H, 2×Ph), 1.70 (s, 1H, NH).

4-Chloro-5,6-diphenylfuro[2,3-d]pyrimidine (3). A mixture of pyrimidinone **2** (2.28 g, 10 mmol) and thionyl chloride (40 ml) was refluxed at 85 °C for 4 h with continuous stirring. The reaction mixture was then cooled and poured into ice-water. The obtained precipitate was collected and recrystallized from ethanol to give **3** (64%) as yellow needle crystals, m.p. 156-158 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 7.84 (s, 1H, CH), 7.6-7.4 (m, 10H, 2×Ph).

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4-Hydrazino-5,6-diphenylfuro[2,3-d]pyrimidine (4). A solution of the chloro compound **3** (1.56 g, 74.32 mmol) and hydrazine hydrate (5.5 ml, 76.74 mmol) in dioxane (25 ml) was refluxed for 4 h at 90 ^{0}C with stirring. The separated solid was filtered and recrystallized from dioxane to give **4** (68%) as brown crystals, m.p. 170-172 °C. ^{1}H-NMR(500 MHz, $CDCl_3$): δ_H 8.14 (s, 1H, CH), 7.80-7.45 (m, 10H, 2×Ph), 5.55 (bs, 1H, NH), 4.84 (bs, 2H, NH_2).

8,9-Diphenylfuro[3,2-e][1,2,4]triazolo[4,3-c]pyrimidine (5). A suspension of hydrazino compound **4** (0.74 g, 57.98 mmol) in formic acid (15 ml) was refluxed for 6 h. The solid that precipitated was collected and recrystallized from ethanol to give **5** (65%) as pink crystals, m.p. 120-121 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 9.92 (s, 1H, 5-CH), 8.37 (s, 1H, 3-CH), 7.38 (m, 10H, 2×Ph); ^{13}C-NMR ($CDCl_3$): δ_C 158.0, 149.2, 147.1, 140.8, 135.6, 131.2, 129.0, 128.6, 127.3, 103.1.

Arylidene-hydrazono-5, 6-diphenylfuro[2,3-d]pyrimidines. ***General procedure:*** A mixture of hydrazino compound **4** (0.74 g, 57.98 mmol) and aromatic aldehyde (7 ml) in ethanol (25 ml) was refluxed for 8 h. The reaction mixture was then cooled and poured into ice-water. The separated solid was filtered and recrystallized from ethanol to give arylidenehydrazono-5, 6-diphenylfuro[2,3-d] pyrimidine.

4-(Benzylidenehydrazono)-5,6-diphenylfuro[2,3-d] pyrimidine (6). The title compound was prepared from hydrazino compound **4** and benzaldehyde in 70% yield as brown crystals, m.p. 90-92 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.68 (s, 1H, 2-CH), 7.85 (s, 1H, = CH), 7.59-7.61 (m, 5H, Ph), 7.47-7.34 (m, 10H, 2×Ph), 4.93 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ_C 167.4, 156.8, 154.3, 148.9, 141.0, 136.2, 132.1, 130.4, 129.4, 128.5, 103.5.

4-(4-Hydroxybenzylidenehydrazono)-5,6-diphenylfuro[2,3-d] pyrimidine (7). This compound was prepared from compound **4** and 4-hydroxybenzaldehyde in 68 % yield as pink crystals, m.p. 122-124 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 8.61 (s, 1H, 2-CH), 7.98 (s, 1H, =CH), 7.77 (d, 2H, *J*= 8.4 Hz), 7.42 (d, 2H, J= 8.4 Hz), 7.4-7.3 (m, 10H, 2×Ph), 6.21 (s, 1H, OH), 4.93 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ_C 168.0, 159.3, 157.0, 153.7, 149.5, 141.3, 136.0, 131.0, 130.5, 129.0, 128.6, 127.2, 123.8, 115.2, 103.7.

4-(4-Chlorobenzylidenehydrazono)-5,6-diphenylfuro[2,3-d] pyrimidine (8). The title compound was prepared from hydrazino compound **4** and 4-chlorobenzaldehyde in 70% yield as brown crystals, m.p. 130-132 °C. ^{1}H-NMR(500 MHz, $CDCl_3$): δ_H 8.61(s, 1H, 2-CH), 7.98 (s, 1H, =CH), 7.77 (d, 2H, J= 8.4 Hz), 7.42 (d, 2H, J= 8.4 Hz), 7.41-7.38 (m, 10H, 2×Ph), 4.93 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ_C 166.5, 156.8, 154.3, 148.7, 141.5, 136.4, 131.0, 130.1, 120.0, 128.2, 127.2, 103.6.

4-(2-Chloroybenzylidenehydrazono)-5,6-diphenylfuro[2,3-d] pyrimidine (9). The title compound was prepared from hydrazino compound **4** and 2-chlorobenzaldehyde in 65% yield as pink crystals, m.p. 135-138 °C. ^{1}H-NMR(500 MHz, $CDCl_3$): δ_H 9.08(s, 1H, 2-CH), 7.92 (s, 1H, =CH), 7.60-7.49 (m, 4H, Ph), 7.41(m, 10H, 2×Ph), 4.91 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ_C 168.0, 156.8, 153.9, 148.9, 141.5, 135.3, 134.0, 132.1, 131.4, 130.0, 129.0, 128.2, 127.0, 103.1.

2-Amino-4-ethyl-5-methylthiophene-3-carbonitrile (10). Diethyl amine (4 ml) was added dropwise to a mixture of diethylketone (3.2 g, 20 mmol), malononitrile (10.09 ml, 20 mmol) and elemental sulphur (0.64 g, 20 mmol) in 95% ethanol (20 ml). The temperature was maintained below 60 °C by means of ice bath. The mixture was stirred continuously for 8 h and then poured into ice water. The precipitate was filtered, washed with water and recrystallized from ethanol to *o*-aminonitrile **10** as brown crystals, m.p. 80-82 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 4.1 (bs, 2H, -NH_2), 2.4 (q, 2H, CH_2), 2.14 (s, 3H, CH_3), 1.36 (t, 3H, CH_3).

5-Ethyl-6-methylthieno[2,3-d]pyrimidine-2,4(1H,3H)-dithione (11). *o*-Aminonitrile **10** (0.4 g, 2.4 mmol) and carbon disulphide (2 ml) in pyridine (5 ml) was refluxed for 8 h. After cooling the reaction mixture was poured into ice-water and the separated solid was filtered and recrystallized from ethanol to give **11** (75%) as pink crystals, m.p. 85-87 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H 8.67 (s, 1H, 3-NH), 7.93 (s, 1H, 1-NH), 2.83 (q, 2H, CH_2), 1.17 (s, 3H, CH_3), 0.9 (t, 3H, CH_3).

2,4-Dimethylthio-5-ethyl-6-methylthieno[2,3-d]pyrimidine (12). Methyl iodide (2.46 mmol) was added dropwise to a suspension of **11** (0.3 g, 1.23 mmol) in aqueous NaOH (10 ml) and stirred at room temperature for 12 h. The formed yellowish solid was collected and recrystallized from ethanol to give compound **12** (83%) as yellow crystals, m.p. 105-107 °C. ^{1}H-NMR(300 MHz, $CDCl_3$): δ_H 2.85 (q, 2H, CH_2), 2.61 (s, 3H, 4-SCH_3), 2.56 (s, 3H, CH_3), 2.50 (s, 3H, 2-SCH_3), 1.12 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ_C 167.4, 165.4, 135.7, 135.0, 129.0, 123.8, 18.6, 17.0, 14.3, 8.0.

4-Hydrazino-2-methylthio-5-ethyl-6-methylthieno[2,3-d]-pyrimidine (13). A mixture of compound **12** (0.3 g, 1.10 mmol) and hydrazine hydrate (1.10 mmol) in dioxane (10 ml) was refluxed for 4 h. The mixture was concentrated in vacuum. The solid was collected and recrystallized from ethanol to give compound **13** (80%) as pink crystals, m.p. 137-139 °C. ^{1}H-NMR(300 MHz, $CDCl_3$): δ_H 4.3 (s, 1H, NH), 3.45 (s, 2H, NH_2), 2.85 (q, 2H, CH_2), 2.15 (s, 3H, 2-SCH_3), 1.14 (s, 3H, CH_3), 0.9 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ_C 168.0, 165.2, 135.6, 135.0, 129.1, 123.5, 18.5, 17.0, 14.5, 8.0.

3-Benzoyl-5-ethyl-6-methylthieno[2,3-d]pyrimidin-2,4(1H,3H)-dithione (14). A mixture of compound **11** (0.3 g, 1.23 mmol) and benzoyl chloride (1.8 mmol) in pyridine (4 ml) was stirred at room temperature for 2 h. The mixture was poured into ice-water, neutralized with 10% HCl, washed with saturated sodium bicarbonate and water and extracted with chloroform. The solvent was removed under reduced pressure and the separated solid was recrystallized from ethanol to give compound **14** (80%) as white crystals, m.p. 140-142 °C. ^{1}H-NMR(300 MHz, $CDCl_3$): δ_H 7.54 (m, 5H, Ph), 4.93 (s, 1H, NH), 2.80 (q, 2H, CH_2), 1.20 (s, 3H, CH_3), 0.88 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ_C 165.5, 152.3, 147.4, 133.7, 132.0, 131.5, 129.5, 128.6, 127.0, 125.1, 16.9, 10.2, 7.3.

Antibacterial and antifungal screening. Some of the synthesized compounds (**5-9, 11-14**) were screened for antibacterial activity against pathogenic organisms; *Bacillus cereus* (BTCC 19), *Salmonella typhi* (AE 14612), *Staphylococcus aureus* (ATCC 6538), *Shigella dysenteriae* (AE 14396) and *Vibrio cholerae* (Table 1) and antifungal activity against C*urvularia lunata*, *Alternaria alternata* (Fr.) Kedissler, *Colletotrichum corchori* Ikata (Yoshida), *Fusarium equiseti* (Corda) Sacc and *Macrophomina phaseolina* (Tassi) Goid (Table 2). The disc diffusion method (Bauer *et al*., 1966) and poisoned-food technique (Grover and Moore, 1962) were used for antibacterial and antifungal activities, respectively.

The tested compounds were dissolved in *N*,*N*-dimethyl formamide (DMF) to get a solution of 1 mg/ml. The inhibition zones were measured in mm at the end of an incubation period of 48 h at 28 °C. DMF alone showed no inhibition zone.

Table 1. Antibacterial activity of the synthesized compounds

Comp. No.	Diameter of zone of inhibition in mm (100 µg(dw)/disc)				
	Bacillus cereus	*Salmonella typhi*	*Staphylococcus aureus*	*Shigella dysenteriae*	*Vibrio cholerae*
5	6	7	8	-	-
6	-	6	-	-	6
7	-	6	8	-	-
8	6	8	6	-	-
9	6	-	7	-	-
11	10	7	-	6	-
12	-	10	10	7	6
13	10	8	-	6	10
14	-	10	-	13	12
Ampicillin 25µg(dw)/disc	21	24	13	30	17

Table2. Antifungal activity of the synthesized compounds

Comp. No.	Percentage inhibition of mycelial growth (100 µg(dw)/ml PDA)				
	Curvularia lunata	*Alternaria alternata*	*Colletotrichum corchori*	*Fusarium equiseti*	*Macrophomina phaseolina*
5	20.70	31.04	2.00	21.20	-
6	20.70	27.00	20.00	22.11	17.60
7	30.00	6.89	20.40	21.40	-
8	32.00	34.00	26.53	28.00	25.50
9	15.00	12.00	26.60	13.00	33.30
11	31.00	100.00	20.00	26.00	27.77
12	29.00	27.00	28.57	19.50	-
13	23.00	7.00	32.65	36.00	11.11
14	50.00	44.82	36.70	11.00	22.20
Nystatin 25µg(dw)/ ml PDA	75.00	51.55	40.51	44.70	71.78

Nutrient agar (NA) and potato dextrose agar (PDA) were used as basal media, respectively, to test the bacteria and fungi. Commercial antibacterial Ampicillin and antifungal Nystatin were also tested under similar conditions for comparison.

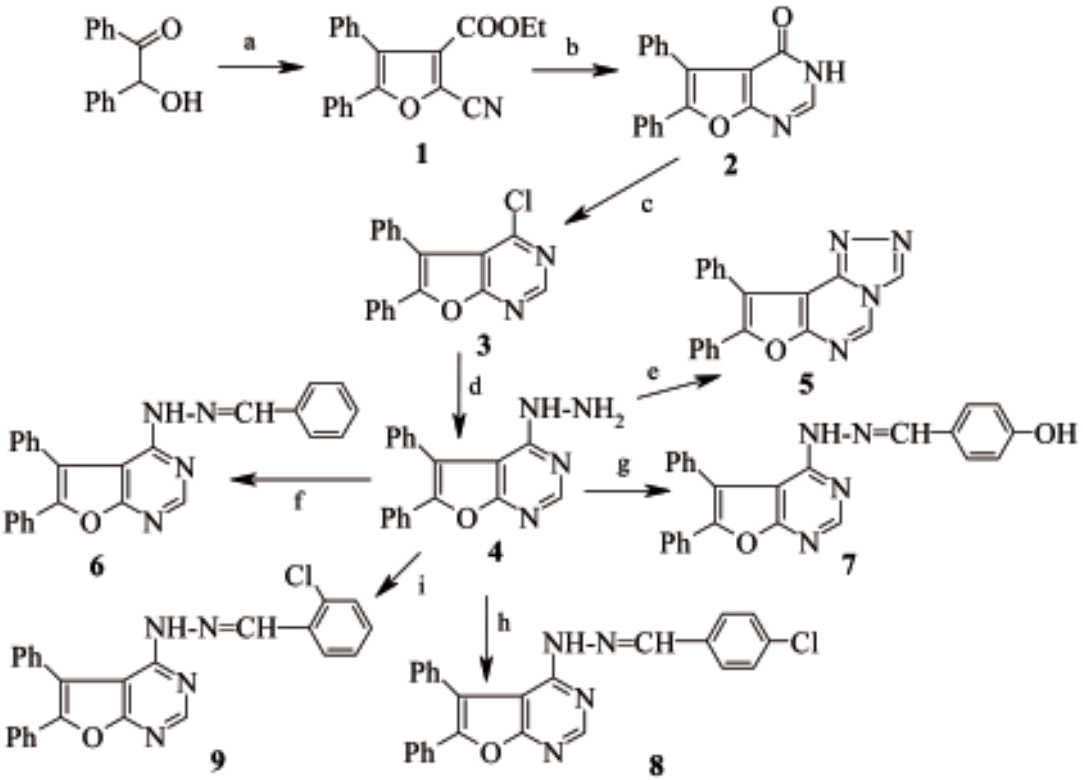
Results and Discussion

The starting material, ethyl 2-amino-4,5-diphenylfuran-3-carboxylate (**1**) was prepared from benzoin and ethyl cyanoacetate according to the procedure of Gewald *et al*. (1966). Refluxing of *o*-aminoester **1** with formamide afforded 5,6-diphenylfuro [2,3-d]pyrimidin-4(*3H*)-one (**2**) (Scheme-1). The structural assignment of compound **2** was confirmed by spectroscopic analysis. Its ^{1}H-NMR spectrum exhibited signal a one-proton singlet at δ 7.84 for CH proton at 2-position. Other peaks were in accordance with the structure. Chlorination of compound **2** with thionyl chloride gave 4-chloro-5,6-diphenylfuro [2,3-d] pyrimidine (**3**).

The chlorine group of **3** underwent nucleophilic displacement by reflux with hydrazine hydrate in dioxane to produce 4-hydrazino-5,6-diphenylfuro[2,3-d]pyrimidine (**4**). Upon boiling with formic acid, hydrazino compound **4** cyclized to produce 8,9-diphenylfuro[3,2-e][1,2,4]triazolo[4,3-c] pyrimidine (**5**). Its ^{1}H-NMR spectrum exhibited signals a one-proton singlet at δ 9.92 for CH proton at 5-position and another one-proton singlet at δ 8.37 for CH proton at 3-position.

The hydrazino compound **4** was condensed with aromatic aldehydes, benzaldehyde, 4-hydroxybenzaldehyde, 4-chlorobenzaldehyde and 2-chlorobenzaldehyde to give 4-(benzylidenehydrazono)-5,6-diphenylfuro[2,3-d]pyrimidine (**6**), 4-(4-hydroxybenzylidenehydrazono)-5,6-diphenylfuro[2,3-d] pyrimidine (**7**), 4-(4-chlorobenzylidenehydrazono)-5, 6-diphenylfuro[2,3-d]pyrimidine (**8**) and 4-(2-chlorobenzylidene-hydrazono)-5,6-diphenylfuro[2,3-d]pyrimidine (**9**), respectively. Assignments of the structures **6-9** to the proposed reaction products are based on spectral data.

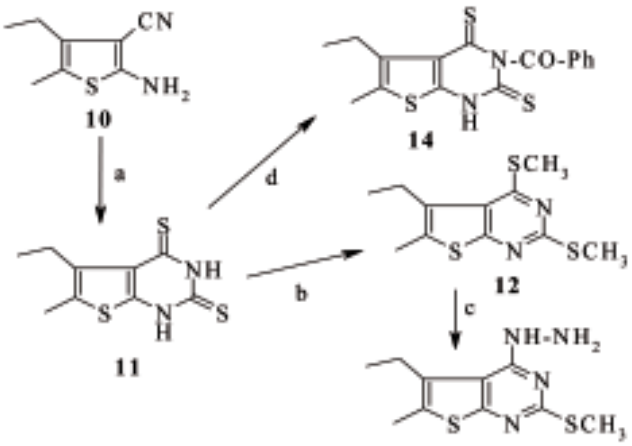
o-Aminonitrile **10** was readily cyclized to the corresponding 5-ethyl-6-methylthieno[2,3-d]pyrimidin-2,4(*1H,3H*)-dithione (**11**) upon treatment with carbon disulphide in refluxing pyridine (Scheme-2). Methylation of dithione **11** with methyl iodide in aqueous NaOH afforded compound 2,4-dimethylthio-



Scheme-1

Reagents: a) $NCCH_2COOEt$, Et_2NH, DMF; b) $HCONH_2$, reflux; c) $SOCl_2$; d) $NH_2NH_2.H_2O$; e) HCOOH; f) benzaldehyde, EtOH, reflux; g) 4-hydroxybenzaldehyde, EtOH, reflux; h) 4-chlorobenzaldehyde, EtOH, reflux; i) 2-chlorobenzaldehyde, EtOH, reflux.

5-ethyl-6-methylthieno[2,3-d]pyrimidine (**12**). Treatment of compound **12** with hydrazine hydrate furnished 4-hydrazino-2-methylthio-5-ethyl-6-methylthieno[2,3-d]pyrimidine (**13**) in good yield. Acylation of **11** with benzoyl chloride afforded 3-benzoyl-5-ethyl-6-methylthieno[2,3-d]pyrimidin-2,4(1*H*,3*H*)-dithione (**14**). The structures of **11-14** were established from their spectral data.



Scheme-2

Reagents: (a) CS_2, pyridine; (b) CH_3I, aq. NaOH; (c) $NH_2NH_2.H_2O$; (d) benzoyl chloride.

Most of the synthesized compounds showed moderate antibacterial activity whereas some did not show inhibition (Table 1). Most of the tested compounds exhibited good to excellent results against all the fungi (Table 2).

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