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One-pot acid-catalysed synthesis of bis(1-imidazo[1,5-*a*]pyridyl)arylmethanes and evaluation of cytotoxic activities†

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A practical and efficient approach for the acid-catalysed synthesis of bis(1-imidazo[1,5-*a*]pyridyl) arylmethane (BimPy) derivatives has been described. Interestingly, these BimPys showed potential cytotoxicity against various cancer cell lines (SK-LU-1, MCF-7, HepG2).

Imidazo[1,5-*a*]pyridines (ImPys) are extremely essential molecules that are receiving a lot of attention because of their unique features.[1] Most of them are water soluble and biocompatible, making them easily absorbed by living cells.[1] As a result, the ImPy moiety has been exploited as a fundamental component in the development of novel bioactive compounds for a variety of medical purposes.[1] ImPy derivatives have been shown in recent pharmaceutical chemistry research to have a variety of important biological activities, including anticancer[2] and cardiotonic agents,[3] aromatase,[4] kinase,[5] HIV-protease,[6] phosphodiesterase 10A,[7] thromboxane A2 synthetase[8] and tubulin polymerization inhibitors,[9] neurokinin antagonists,[10] and agonists[11] in several Alzheimer's and inflammatory disease studies (Fig. 1).[12]

Furthermore, ImPy derivatives have found numerous applications in other fields, including optoelectronic materials,[13] confocal microscopy sensors,[14] bioimaging,[15] and chemotherapeutic drugs for DNA breakage.[16] Notably, the ImPy core has been introduced into the structure of carbene ligands, leading to potential applications in the catalysis field.[17]

Because ImPy derivatives are important in medicinal chemistry,[17] organometallics,[18] and materials research, several methods for synthesizing them have emerged.[1] ImPys could be conventionally synthesized using cyclization processes.[1] To date, a number of noncatalytic and catalytic approaches for accessing ImPys have been reported using cyclocondensation.[19] A second method to ImPy derivatives *via* [3 + 2] cycloaddition processes is well known.[20] Recently, modern synthetic approaches based on oxidative cyclization and transannulation processes in the presence of transition metal catalysts have provided more effective strategies for preparing ImPys that can tolerate functional groups.[21,22]

In 2009, Murai *et al.* published an interesting research on the synthesis of bis(1-imidazo[1,5-*a*]pyridyl)arylmethanes (BimPy) *via* iodine-mediated annulation of *N*-thioacyl-1-(2-pyridyl)-1,2-aminoalcohols.[23] These interesting molecules could have applications in pharmaceutical chemistry, catalysis, and materials science. However, *N*-thioacyl-1-(2-pyridyl)-1,2-aminoalcohols are complicated starting materials that require numerous steps to prepare. In 2023, we presented a facile and efficient iodine-promoted synthesis of BimPy derivatives by tandem cyclization

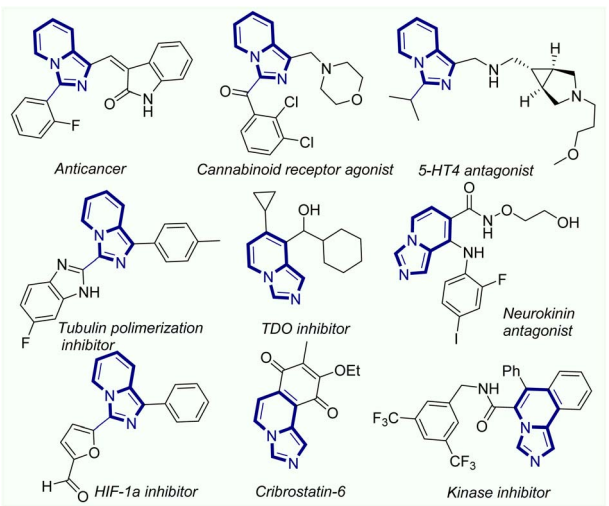

Fig. 1 Biologically active ImPy derivatives.

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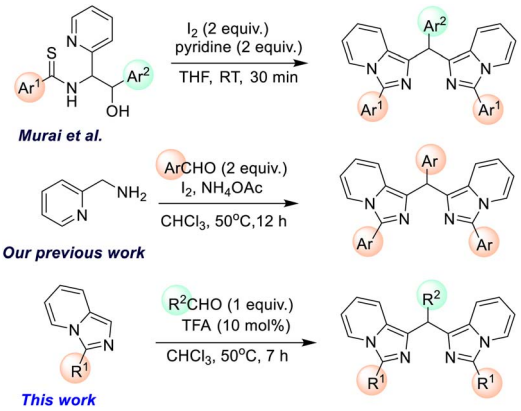


Scheme 1 Synthetic pathways for preparation of BimPys.

of pyridin-2-ylmethanamines and aldehydes.[24] Recently, several studies on the synthesis and exploration of anticancer activities of imidazoheterocycles and other indole-fused N-heterocycles have been developed in our group.[25] In continuous progress of our research, herein, we wish to disclose a new approach for the convenient acid-catalysed synthesis of BimPys and evaluation of their cytotoxic activities (Scheme 1).

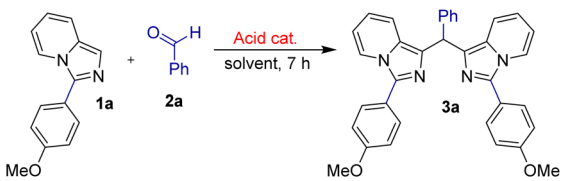
Initial screening investigations utilizing ImPy **1a** and benzaldehyde **2a** in the employment of several acid catalysts (10 mol%) were carried out at 50 °C. To confirm the real role of acid catalyst, the reaction was performed in the absence of any acid catalysts, in fact, **3a** product was not formed under our condition (entry 1, Table 1). Interestingly, BimPy (**3a**) was prepared in 98% isolated yield the presence of trifluoroacetic acid (TFA) catalyst (entry 4, Table 1). Then, several organic solvents were examined in order to understand the effect of solvents on the formation of product **3a** (entries 3–9, Table 1). However, $CHCl_3$ was determined to be the best solvent for this transformation, producing **3a** in highest isolated yield. Further screenings under different temperatures were also investigated (entries 11 and 12). Notably, we did not achieve the target product **3a** in better yield.

With the optimal condition in hand, we wanted to investigate the substrates scope of this transformation. In general, the alkylation reaction of ImPy **1a** with a series of aldehydes **2a–o** under optimal conditions resulted in the desired BimPy products **3a–o** in good to excellent yields (Table 2). The coupling reactions of ImPy **1a** with halogenated benzaldehydes **2d–j** afforded corresponding products **3d–j** with excellent yields ranging from 95 to 98%. Interestingly, the reaction of **1a** with thiophene-3-carbaldehyde (**2l**) indole-3-carbaldehyde (**2m**) resulted in a novel BimPys (**3l**, **3m**) in 98% and 88% yields, respectively. Notably, the reaction of ImPy **1a** with challenging aliphatic aldehydes **2n**, **2o** gave desired BimPys **3n**, **3o** in lower yields (55% and 60% yields).

To prepare other highly functionalized BimPy derivatives with a variety of substituents, we employed ImPy derivatives **1b–g** and benzaldehyde derivatives **2a**, **2p**, **2q** as the starting materials in this synthetic approach. Notably, under optimized condition, eight novel BimPy compounds **3p–x** with various substituents were successfully synthesized in excellent yields (82–98%) (Tables 3 and 4).

Relying on previous research on acid-catalysed condensation reactions, we would like to propose a possible mechanism for the formation of BimPys in the presence of TFA (Scheme 2). Firstly, the condensation of ImPy with an aldehyde to form

Table 1 Optimization for the synthesis of BimPy **3a**[a]



Entry	Catalyst (equiv.)	Solvent	Time (h)	Temp. (°C)	Yield[b] (%)
1	—	$CHCl_3$	7	50	Trace
2	CH_3COOH	$CHCl_3$	7	50	20
3	*p*-TsOH.H_2O	1,4-Dioxane	7	50	30
4	**TFA**	**$CHCl_3$**	**7**	**50**	**98**
5	H_2SO_4	$CHCl_3$	7	50	96
6	TFA	EtOH	7	50	69
7	TFA	Toluene	7	50	90
8	TFA	DMSO	7	50	72
9	TFA	THF	7	50	81
10	TFA	$CHCl_3$	7	50	75
11	TFA	$CHCl_3$	7	60	85
12	TFA	$CHCl_3$	7	40	66

[a] Condition: **1** (0.67 mmol), **2a** (0.67 mmol), acid catalyst (10 mol%), solvent (0.3 mL). [b] Isolated yields.

Table 2 TFA-catalysed synthesis of BimPy derivatives **3a–o**

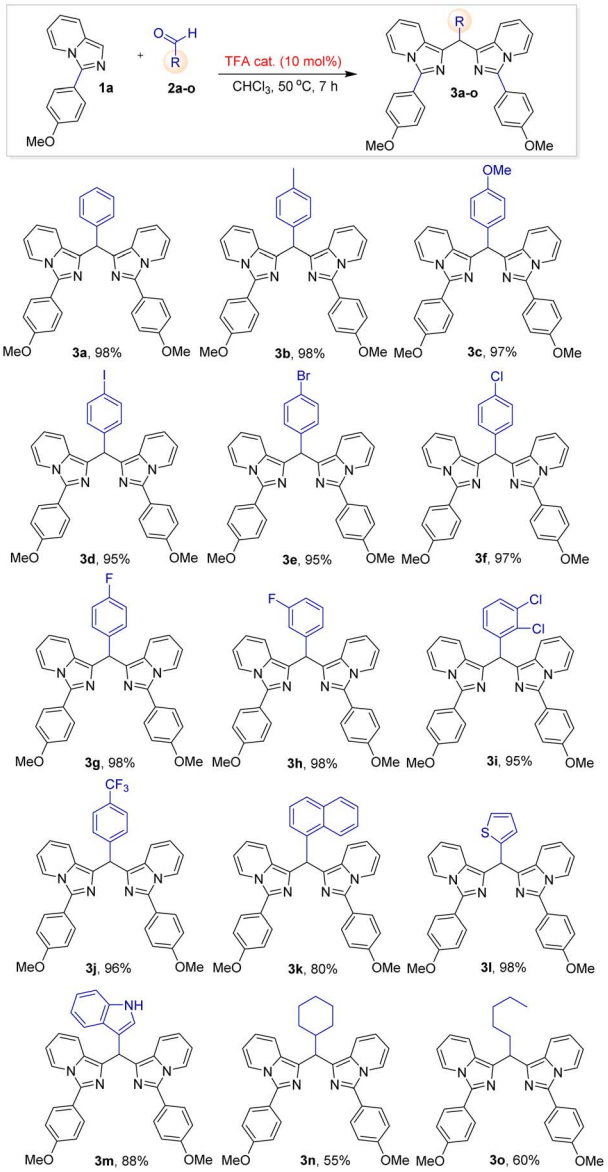


Table 3 TFA-catalysed synthesis of BimPy derivatives **3p–t** from ImPys **1b–f** and benzaldehyde **2a**

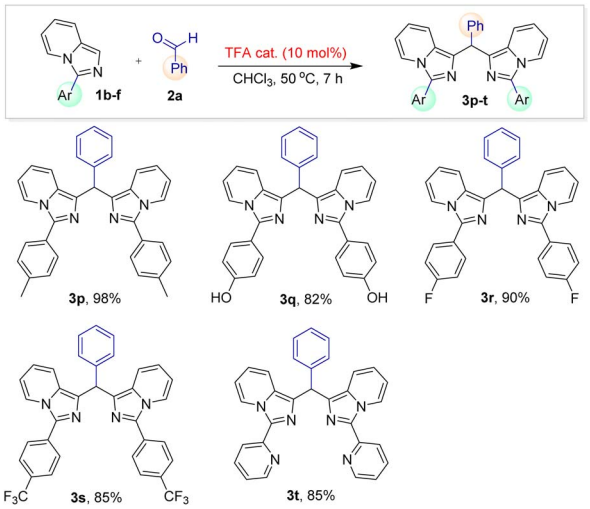
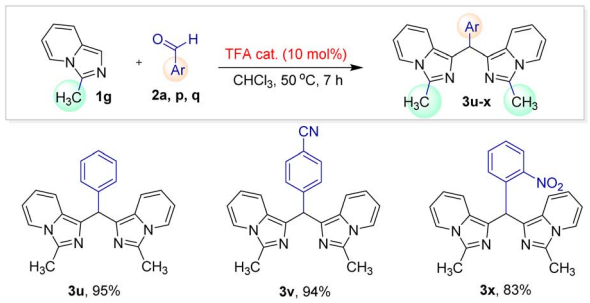


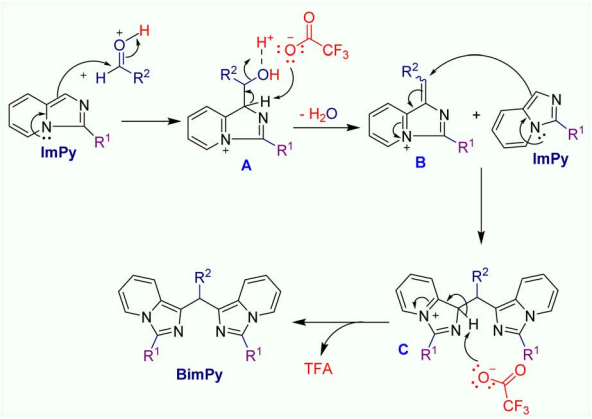
Table 4 TFA-catalysed synthesis of BimPy derivatives **3u–x** from ImPys **1g** and benzaldehyde derivatives



a secondary alcohol (intermediate A) which subsequently attend in an acid-activated dehydration to result in the formation of iminium intermediate B. Then the intermediate B reacts with a second ImPy molecule to give an intermediate C *via* 1,4-addition reaction. Finally, the BimPy product could be formed by deprotonation process and regenerate TFA catalyst for the next catalytic cycle.

The novel BimPy derivatives were tested for cytotoxicity against three human cancer cell lines SK-LU-1 (non-small cell lung cancer), HepG2 (liver cancer), and MCF-7 (breast cancer). Ellipticine served as a standard sample for the comparison. As shown in Table 5, compounds **3b** and **3c** (entries 1 and 2) were discovered to be effective cytotoxic agents against human cancer cell lines. Interestingly, compound **3b** showed significant toxicity against lung, breast, and liver cell lines. In fact, the high toxicity of compound **3c** against the three cell lines (entry 2) was reported in our recent paper.[24a] As a result, the most promising molecules **3b**, **3c** will be studied further to determine their ability to impact cell cycle progression and apoptosis in various cells.

The cytotoxic results in Table 5 revealed that **3b** and **3c** were the most effective compounds in comparison with other compounds. Indeed, compound **3b** (entry 1, Table 5), featuring a 4-methyl group substituent at phenyl ring, exhibited potent cytotoxic activity with IC_{50} values of 5.36, 2.58, and 1.72 μM against lung, breast, and liver cancer cell lines, respectively. Similarly, compound **3c** (entry 2), with a 4-methoxy group substituent at phenyl ring, displayed IC_{50} values of 2.49, 3.41, and 4.34 μM against the same cell lines, though slightly less effective than compound **3b**. However, the halogenated derivatives **3j**, **3m** (entries 3 and 4) demonstrated low toxicity across all cell lines, suggesting limited activity for these groups. In order to understand the role of functional groups in BimPy structures (**3b** and **3c**), several molecular docking studies have been performed to investigate the interaction between the functional groups and the epidermal growth factor receptor (EGFR),



Scheme 2 A plausible mechanism for the TFA-catalysed synthesis of BimPys.

Table 5 Cytotoxicity of BimPy derivatives to several SK-LU-1, MCF-7, and HepG2 cell lines (IC_{50}: μM)

Entry	Compound	SK-LU-1	MCF-7	HepG2
1	**3b**	5.36 ± 0.30	2.58 ± 0.27	1.72 ± 0.05
2	**3c**	2.49 ± 0.19	3.41 ± 0.48	4.34 ± 0.67
3	**3d**	27.12 ± 2.20	23.34 ± 1.40	9.19 ± 0.33
4	**3j**	50.46 ± 4.20	67.91 ± 1.30	25.47 ± 0.89
5	**3m**	57.37 ± 3.52	66.09 ± 4.04	47.23 ± 1.71
6	**3n**	80.84 ± 4.62	87.64 ± 6.44	39.33 ± 2.67
7	**3q**	>100	>100	59.17 ± 4.67
8	**3s**	>100	>100	>100
9	Ellipticine	1.88 ± 0.35	1.89 ± 0.29	1.46 ± 0.56

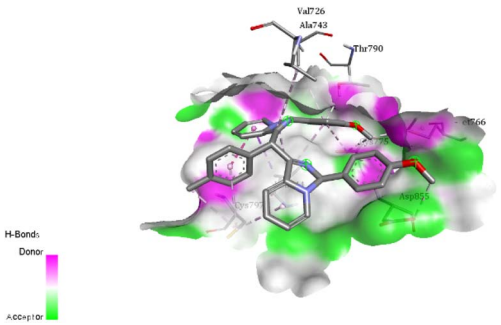


Fig. 2 Molecular docking 3D diagram of **3b** with EGFR kinase.

a target kinase previously identified in our group's molecular dynamics (MD) studies.[24b] Previous studies demonstrated that similar BimPy derivatives exhibited free energy profiles during transitions from bound to unbound states, comparable to those of Erlotinib anticancer drug (PDB: 1M17).[24b] Encouraged by these findings, docking analyses for **3b** and **3c** were performed to elucidate their interaction with the EGFR kinase domain. The docking results demonstrated strong binding interactions for both compounds within EGFR's active sites, particularly with residues C797, T790, and L844 (Fig. 2 and 3). Notably, compound **3b** showed a notable π–alkyl interaction between its

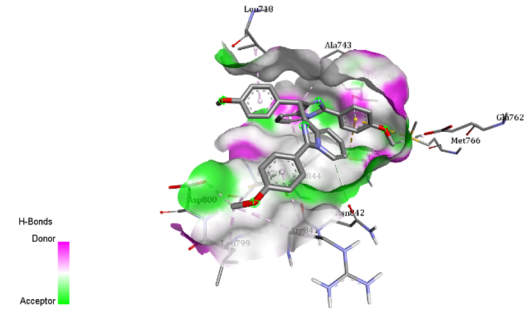


Fig. 3 Molecular docking 3D diagram of **3c** with EGFR kinase.

4-methyl group and residue C797, highlighting the role of the methyl substituent in enhancing binding affinity (Fig. 2). On the other hand, compound **3c** formed two π–sulfur interactions with residues M766 and C775, suggesting that sulfur-containing substituents may promote S–S bridge formation, further stabilizing the binding interaction (Fig. 3).

Conclusions

In summary, we present a one-pot convenient method for the TFA-catalysed synthesis of bis(1-imidazo[1,5-*a*]pyridyl)arylmethane (BimPy) derivatives from simple starting materials such as ImPys and aldehydes. Notably, BimPy derivatives with the tolerance of various substituents can be produced in high yield from imidazo[1,5-*a*]pyridines (ImPys) and aldehydes in the presence of 10 mol% of TFA catalyst under mild conditions. Interestingly, these BimPy compounds showed some potential applications as anticancer agents against various cancer cell lines (SK-LU-1, MCF-7, HepG2). Notably, compound **3b** showed very promising cytotoxic activities with IC_{50} values of 5.36, 2.58, and 1.72 μM against lung, breast, and liver cancer cell lines, respectively. A molecular docking study was conducted to visualize more information about the interactions between the promising compounds **3b**, **3c** and the kinase domain of the EGFR. As a result, this discovery has the potential to significantly advance pharmaceutical chemistry and metal-free catalysis into organic synthesis.

Experimental

General procedure for preparation of 1,1′-(phenylmethylene) bis(3-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine) 3a and derivatives

ImPy **1a** (150 mg; 0.67 mmol) and benzaldehyde **2a** (71 mg; 0.67 mmol) were introduced to a flask fitted with a magnetic stir bar. The flask was added with a 6 μL solution of trifluoroacetic acid (TFA) and 0.3 mL of chloroform. After that, the reaction temperature gradually increased to 50 °C using an oil bath and stirred for 7 hours. After completion, the reaction mixture was cooled to room temperature and quenched with aqueous sodium bicarbonate ($NaHCO_3$, 3 M) solution until the pH reached neutral. The mixture was then extracted using ethyl acetate and water. The organic layer was separated, dried over

anhydrous sodium sulfate (Na_2SO_4), filtered, and the solvent evaporated under low pressure with a rotary evaporator. The resulting brown residue was purified by column chromatography (silica gel, hexane/DCM/ethyl acetate (9/4/2)) to yield **3a** (352 mg, 98%) as a bright green solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.1 (dt, $J = 7.3$, 1.1 Hz, 2H), 7.7–7.6 (m, 4H), 7.5–7.5 (m, 2H), 7.4 (dt, $J = 9.3$, 1.2 Hz, 2H), 7.3 (t, $J = 7.7$ Hz, 2H), 7.2–7.2 (m, 1H), 7.0–7.0 (m, 4H), 6.5 (ddd, $J = 9.3$, 6.3, 1.0 Hz, 2H), 6.4 (ddd, $J = 7.4$, 6.3, 1.3 Hz, 2H), 6.3 (s, 1H), 3.8 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.7, 143.2, 136.7, 133.6, 129.6, 128.9, 128.2, 128.2, 126.2, 123.1, 121.1, 119.7, 117.4, 114.3, 112.7, 55.4, 45.0.

Protein and ligand preparation

The X-ray crystal structure coordinates EGFR tyrosine kinase domain (PDB 4ZAU) was retrieved from the RCSB Protein Data Bank[26] and prepared with the UCSF ChimeraX.[27] During the protein preparation, the AZD9291 was removed, the bond orders were assigned, and hydrogen atoms and formal charges were added to hetero groups. The water molecules in the ligand-binding area were preserved for docking, and all other water molecules 5 Å beyond hetero groups were deleted. The hydrogen bonding network of binding site residues was optimized by selecting the histidine tautomer and by predicting the ionization states. The optimized protein structure was then subjected to all-atom constrained energy minimization using the Optimize Geometry module of Open Babel GUI with MMFF94 force field.[28] The prepared domain structure of EGFR tyrosine kinase was used for molecular docking simulations. All chemical structures of the ligands were constructed using MarvinSketch,[29] and energy-minimized using the minimization protocol of Avogadro2. Ligand volume was evaluated using the analytical tools included in Avogadro2.

Docking protocol

Molecular docking studies were conducted using AutoDock4 software to evaluate the binding affinities of the ligands.[30] The default settings in AutoDock4 were applied for grid generation and flexible docking, utilizing the Lamarckian Genetic Algorithm and an empirical free energy scoring function. A binding site radius of 15 Å from the center of the binding cavity was defined, and docking results were clustered with a root mean square deviation (RMSD) of 2.0 Å. For the docking calculations, AutoDock version 4.2 (Scripps Research Institute, San Diego, CA, USA) was used on a Dell personal computer. Grid maps representing the receptor molecule were generated using AutoGrid (Scripps Research Institute), with the grid centered at the ligand-binding pocket (LBP). The grid box was defined with dimensions of $x = 80$ Å, $y = 80$ Å, $z = 80$ Å, and the centroid coordinates were $x = -56.673$, $y = -1.725$, $z = -23.122$. Docking simulations were performed 100 times using the Lamarckian Genetic Algorithm (GA). The run parameters included 100 GA runs, a maximum of 2.5×10^7 energy evaluations, and a maximum of 1.0×10^6 generations. All input structures for proteins and ligands were prepared in the PDBQT format.

The free energy change associated with each conformation was calculated as the sum of van der Waals forces, electrostatic interactions, hydrogen bonding events, de-solvation effects, and torsional energetics, as defined by the AutoDock scoring function.[31]

Data availability

The data supporting this research are available in the ESI.†

Author contributions

T. Q. Hung, T. T. Dang wrote this manuscript and conceived this project; B. V. Phuc, T. H. Tran, H. Y. Nguyen, N. T. Phuoc, T. M. Chi performed the experiments and analyzed the data; H. N. Do, H. Nguyen carried out all molecular docking studies; D. V. Do, T. T. T. Nga conducted NMR analysis; V. T. Nguyen edited the manuscript and gave discussions about the mechanism.

Conflicts of interest

There are no conflicts to declare.

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