ISSN: 0974 - 7516 Volume 10 Issue 4

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 10(4), 2014 [134-139]

Microwave assisted synthesis and biological evaluation of 3-aryl-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazoles

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ABSTRACT

In this present work, microwave assisted synthesis of 3-aryl-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazoles were carried out.**(3a-i)** new compounds were synthesized by reactions of 2-(thiophen-3-yl) acetohydrazide and various aromatic nitriles. The synthesized derivatives were characterized by spectral studies and also by C, H, N analyses. Synthesized derivatives were screened for their anti-inflammatory activity by, the rat paw edema test method and analgesic activity by the tail flick method. The compounds **(3b, 3d, 3g)** and **(3i)** showed remarkable reduction in rat paw edema induced by carrageenan treatment. The compounds **(3b, 3d, 3g,)** and **(3i)** showed good analgesic activity.

KEYWORDS

Aromatic nitriles;
1, 2, 4-triazoles;
Anti-inflammatory activity;
Analgesic activity.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are usually used to treat the inflammation. NSAIDs exert their anti-inflammatory effect through inhibition of cyclooxygenases (COXs). COX-1 and COX-2 are two general COX isoforms[1,2]. 1, 2, 4-triazole derivatives are crucial heterocyclic scaffold that has been an interesting field of study for a long time.1, 2, 4-triazoles displayed admirable biological properties. In particular, they show antimalarials, anticonvulsant, anti-inflammatory[3,4], antibacterial[5], antifungal[6], antitubercular[7], antioxidant[8], anticancer[9], analgesic[10], and pesticidal properties. Looking to the immense biological significance of 1, 2, 4-triazole derivatives, we synthesized some novel derivatives by Microwave heating technology and screened them for anti-inflammatory activity and analgesic activity.

The aim of the present work was to synthesize some 3,5-disubstituted 1,2,4-triazoles derivatives by Microwave method because,conventional methods involving heating reaction mixtures with traditional equipments are not only slow, but it also creates a hot surface on the reaction vessel where products, substrates and reagents often decompose over time. Microwave energy, in contrast, passes through the walls of the reaction vessel, heating the reactants and solvents directly, where, temperature increase is uniform throughout the reaction mixture, leading to rapid reaction and fewer by-products and/or product decomposition[11].

EXPERIMENTAL

Materials and equipments

All chemicals used in this work were of laboratory

grade and were purchased from E

Merck Ltd., India, and Loba Chemical Ltd., India. Reactions involving microwave exposure were conducted in CATA-2R (Catalyst Systems) using microwave vials of capacity 10-20 ml. Progress of reaction was examined by TLC-reports, which was developed using pre-coated Silica gel G plates. Elemental analysis was carried out using FLASH EA 1112 CHN analyzer (Thermo Finnigan, Italy) and found within 0.4 of theoretical values. The ^{1}H-NMR and ^{13}C NMR spectra of synthesized compounds were obtained using Mercury Plus 300 MHz NMR spectrometer and JEOL-FT-NMR spectrometer, at IIT Powai and Indian Institute of Science, Banglore and mass spectra of the compounds were analyzed on VARIAN-500 mass spectrometer at IIT Powai, Mumbai, India.

General procedure for synthesis of aromatic nitriles

To a mixture of 1a-j (1 mmol) and aq NH_3 (3.0 mL, 45 mmol) was added I_2 (2.1 mmol) at rt under an empty balloon. The obtained mixture was stirred at 60^0 C. After 4h at the same temperature, the reaction mixture was quenched with H_2O (10 mL) and satd aq Na_2SO_3 (2 mL) at 0^0 C, and was extracted with Et_2O (3 X 15 mL). The organic layer was washed with brine and dried over Na_2SO_4 to provide aromatic nitriles with good yields in an almost pure state. If necessary, the product was purified by column chromatography (silica gel; hexane/EtOAc=4:1) to give pure aromatic nitriles. All synthesized compounds were confirmed by melting points, IR and ^{1}H NMR spectra of reported series.

General procedure for (*Conventional*) synthesis of 3-aryl-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole.

2-(thiophen-3-yl) acetohydrazide (0.33 mmol) and appropriate aromatic nitriles (1.0 mmol),were mixed in MeOH (5 mL) as a solvent,then mixture was refluxed for 2-3 hrs in oil bath.Reactions were monitored by TLC.After completion of reaction the mixture was evaporated, diluted with MeOH, and then purified by reverse phase preparative HPLC (MeOH/H_2O).

General Procedure for (*MW assisted*) synthesis of 3-aryl-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole

2-(thiophen-3-yl) acetohydrazide (0.33 mmol) and appropriate aromatic nitriles (1.0 mmol), were mixed in ^{n}BuOH (2mL) as a solvent, then, K_2CO_3 (2 equi.) is added in a 10 ml microwave vial sealed by Teflon-lined rubber cap. This reaction mixture was irradiated with MW at, 420 Watt (60%) to 560 Watt (80%) for 8-20 min. After completion of reaction the mixture was evaporated, diluted with MeOH, and then purified by column chromatography (RP-MeOH/Water).

3-phenyl-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole

Yellow oil,^{1}H-NMR (DMSO-d_6): δ: 4.04 (2H, *s*,-CH_2), δ: 6.72-6.75 (2H, *d*, Thiopene C-H), δ: 7.38-7.49 (3H, *m*, ArH), δ: 7.63 (1H, *m*, Thiopene C-H), δ: 8.27 (2H, *d*, ArH) ; ^{13}C-NMR (DMSO-d_6) 172.15, 159.48, 137.55, 131.14,132.27, 129.16, 128.12,127.46,126.16,121.42,29.70; MS: *m/z:* 241.07 M+; Anal.Calcd. for $C_{13}H_{11}N_3S$: C, 64.70; H, 4.59; N, 17.41; S, 13.29.

3-(4-chlorophenyl)-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole

Brown oil,^{1}H-NMR (DMSO-d_6): δ: 4.02 (2H, *s*,-CH_2), δ: 6.74-6.75 (2H, *d*, Thiopene C-H), δ: 7.54-7.59 (3H, *m*, 2H of ArH + 1H of Thiopene C-H), δ: 8.17 (2H, *d*, ArH); ; ^{13}C-NMR (DMSO-d_6) 172.35, 159.73, 137.55, 134.36, 130.76, 129.38, 128.92, 128.16, 126.10, 121.32, 29.43; MS: m/z: 275.03 M+; Anal.Calcd. for $C_{13}H_{10}ClN_3S$ C, 56.62; H, 3.66; Cl, 12.86; N, 15.24; S, 11.63.

3-(4-bromophenyl)-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole

Brown oil,^{1}H-NMR (DMSO-d_6): δ: 4.02 (2H, *s*,-CH_2), δ: 6.74-6.75 (2H, *d*, Thiopene C-H), δ: 7.57 (1H, *m*, Thiopene C-H), δ: 7.66-7.68 (4H, *m*, ArH); ^{13}C-NMR (DMSO-d_6) 172.30, 159.77, 137.58, 132.36, 131.16, 128.16, 126.10, 123.15, 121.32, 29.40; MS; m/z: 318.98 M+; Anal.Calcd. for $C_{13}H_{10}BrN_3S$ C, 48.76; H, 3.15; Br, 24.95; N, 13.12; S, 10.01.

3-(4-nitrophenyl)-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole

Brown oil,^{1}H-NMR (DMSO-d_6): δ: 4.02 (2H, *s*,-CH_2), δ: 6.74-6.75 (2H, *d*, Thiopene C-H), δ: 7.59 (1H, *m*, Thiopene C-H), δ: 8.06 (2H, *d*, ArH), δ: 8.32

(2H, *d*, ArH); ^{13}C-NMR (DMSO-d_6) 172.30, 159.77, 147.90, 139.76, 138.65, 137.55, 128.30, 127.00, 126.18, 124.48, 121.32, 29.40; MS: m/z: 286.05 M+; Anal.Calcd. for $C_{13}H_{10}N_4O_2S$ C, 54.54; H, 3.52; N, 19.57; O, 11.18; S, 11.20.

5-(thiophen-3-ylmethyl)-3-(p-tolyl)-1H-1, 2, 4-triazole

Brown oil,^{1}H-NMR (DMSO-d_6): δ: 2.34 (3H, *s*,-CH_3), δ: 4.02 (2H, *s*,-CH_2), δ: 6.74-6.75 (2H, *d*, Thiopene C-H), δ: 7.59 (1H, *m*, Thiopene C-H), δ: 7.30 (2H, *d*, ArH), δ: 8.54 (2H, *d*, ArH); ^{13}C-NMR (DMSO-d_6) 172.30, 159.77, 137.55, 131.76, 129.30, 128.10, 126.00, 125.72, 121.32, 29.40, 21.32; MS: m/z: 255.08 M+; Anal.Calcd. for $C_{14}H_{13}N_3S$ C, 65.85; H, 5.13; N, 16.46; S, 12.56.

3-(4-methoxyphenyl)-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole

Yellow oil,^{1}H-NMR (DMSO-d_6): δ: 3.84 (3H, *s*,-CH_3), δ: 4.02 (2H, *s*,-CH_2), δ: 6.74-6.76 (2H, *d*, Thiopene C-H), δ: 7.60 (1H, *m*, Thiopene C-H), δ: 7.05 (2H, *d*, ArH), δ: 7.96 (2H, *d*, ArH); ^{13}C-NMR (DMSO-d_6) 172.30, 160.62, 159.77, 130.35, 128.82, 126.12, 124.86, 121.32, 55.84, 29.40 ; MS: m/z: 271.08M+; Anal.Calcd. for $C_{14}H_{13}N_3OS$ C, 61.97; H, 4.83; N, 15.49; O, 5.90; S, 11.82.

3-(thiophen-2-yl)-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole

Brown oil,^{1}H-NMR (DMSO-d_6): δ: 4.02 (2H, *s*,-CH_2), δ: 6.74-6.76 (2H, *d*, Thiopene C-H), δ: 7.60 (1H, *m*, Thiopene C-H), δ: 7.18 (1H, *m*, Thiopene C-H), δ: 7.58 (1H, *m*, Thiopene C-H), δ: 7.70 (1H, *d*, Thiopene C-H), δ: 7.86 (1H, *d*, Thiopene C-H); ^{13}C-NMR (DMSO-d_6) 172.30, 157.11, 142.70, 137.30, 129.00, 128.00, 128.12, 128.63, 126.16, 121.32, 29.40 ; MS: m/z: 247.02 M+; Anal.Calcd. for $C_{11}H_9N_3S_2$ C, 53.42; H, 3.67; N, 16.99; S, 25.93.

3-(naphthalen-2-yl)-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole

Yellow oil,^{1}H-NMR (DMSO-d_6): δ: 4.00 (2H, *s*,-CH_2), δ: 6.74-6.76 (2H, *d*, Thiopene C-H), 7.60 (3H, *m*, Thiopene C-H & ArH), δ: 7.90 (1H, *d*, ArH), δ: 8.00 (2H, *m*, ArH), δ: 8.48 (1H, *d*, ArH), δ: 9.10 (1H, *s*, ArH); ^{13}C-NMR (DMSO-d_6) 172.30, 159.72, 137.49, 133.91, 133.83, 133.12, 128.16, 126.24, 125.70, 124.55, 121.31, 29.40 ; MS: m/z: 291.08 M+; Anal.Calcd. for $C_{17}H_{13}N_3S$ C, 70.08; H, 4.50; N, 14.42; S, 11.00.

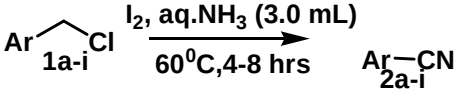
3-mesityl-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole

Yellow oil,^{1}H-NMR (DMSO-d_6): δ: 2.35 (3H, *s*,-CH_3), δ: 2.60 (6H, s,-CH_3), δ: 6.74-6.76 (2H, *d*, Thiopene C-H), δ: 6.98 (1H, *m*, *ArH*), δ: 7.60 (1H, *m*, Thiopene C-H); ^{13}C-NMR (DMSO-d_6) 172.30, 159.72, 138.22, 136.73, 128.42, 128.16, 126.10, 122.71, 121.34, 29.40, 21.92, 19.28; MS: m/z: 283.11 M+; Anal.Calcd. for $C_{16}H_{17}N_3S$ C, 67.81; H, 6.05; N, 14.83; S, 11.31.

RESULTS AND DISCUSSION

Chemistry

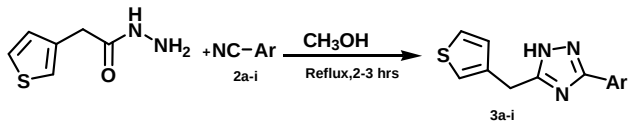
Conversion of various benzylic halides into aromatic nitriles with I_2 in aq NH_3 (Scheme 1).These aromatic nitriles were synthesized by reported procedure[12], In one pot synthesis, primary alkyl halides of benzylic halides reacts with ammonia via the SN^2 nucleophilic substitution mechanism to form corresponding primary amines, then after oxidation thereof by molecular iodine. All synthesized aromatic nitriles were characterized by IR, MS, ^{1}H-NMR and ^{13}C NMR spectra, and matched with reported nitriles.



Scheme 1

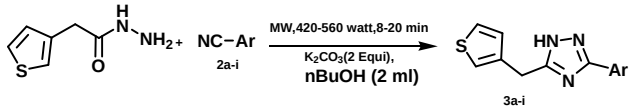
To afford 3-aryl substituted 5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazoles, 2-(thiophen-3-yl) acetohydrazide is mixed with aromatic nitriles (2a-i) using MeOH as solvent (Scheme 2), being conventional heating method, few reactions got failed and rest reaction gave less yields of target compounds. Compounds **(3a-e)** got yields between 20-25%, 2-3 hrs. Compounds **(3f, 3h, 3i)** were not obtained (TABLE 1). This Scheme was carried out on the ground of reported reaction of refluxing benzonitrile and benzoic hydrazide in MeOH[13].Durring the course of our study we have observed that reaction between 2-

(thiophen-3-yl) acetohydrazide with aromatic nitriles by conventional reflux heating method, mixture of products obtained and yield of pure compounds was also very less.



Scheme 2

So, plan was shifted to change the solvent (nBuOH) and 2 equivalents of K_2CO_3 (Scheme 3).Same reactions were performed by microwave heating (420-560 watt for 8-20 min). All reaction went successfully, progress of reaction was examined by TLC-reports (ethyl acetate/hexane), which were developed using precoated Silica gel G plates.



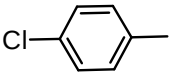
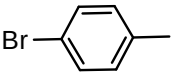
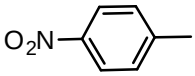
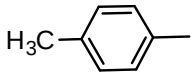
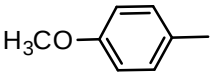
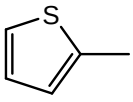
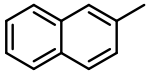
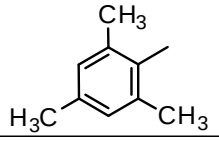
Scheme 3

Due to strong nucleophilicity of 2-(thiophen-3-yl) acetohydrazide, condensation of it with nitriles was possible by microwave irradiation rather conventional high temperature heating (Pinner reaction). The condensation is possible by without prior treatment of acid to hydrazide, which is needed in Pinner reaction. The yields obtained are depicted in (TABLE 1). The reaction of *p*-nitro substituted benzyl nitrile gave higher yield compared to other nitriles,this fact gives the conclusion of condensation of 2-(thiophen-3-yl) acetohydrazide with nitriles not goes like pinner reaction which requires high temperature and more time. By performing reactions under microwave irradiation the 1, 2, 4-triazoles depend on nucleophilic nature of hydrazide and electrophilic nature of nitriles. For stability concerns of hydrazides under alkaline reaction condition, in every reaction 3 equivalents of nitriles are used.

Biological activity

All the compounds prepared, were screened for their potential anti-inflammatory activity by the carrag-

TABLE 1 : Data for synthesis of 3-aryl-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazole.

Entry	Ar	Irradiation (Watt)	Yield (%) MW[a]	T(min)	Yield (%) Conventional[b]	T(hrs)
3a		420	70	20	28	3
3b		560	72	15	20	2
3c		560	72	08	20	2
3d		560	74	08	25	2
3e		490	66	15	25	3
3f		420	52	20	No Reaction Observed	2.5
3g		560	64	20	25	2.5
3h		490	58	08	No Reaction Observed	2.5
3i		490	48	15	No Reaction Observed	2.5

[a]All MW-assisted reactions were conducted in CATA-2R ; [b]Conventional yields were obtained after refluxing reactants in MeOH for 2-3 h.

eenan induced rat paw edema test method[14]. The compounds **(3b, 3d, 3g)** and **(3i)** showed good anti-inflammatory activity (TABLE 2). The anti-inflammatory activity is observed to be good compared to standard drug used in compounds containing electron withdrawing substituent on 3-substituted aryl moiety. Also almost equal activity exhibited by 3i molecule which contains bulky aryl group on 1, 2, 4-triazole.

Protocol for anti-inflammatory activity

The animals were divided into groups of six each and were kept on fast for 24 h before the experiment with free water for feed. Control group was administered only 0.5% carboxymethyl cellulose solution. Standard drug flurbiprofen (dose of 10 mg/kg) was administered orally. The test compounds were administered orally at an equimolar oral dose of standard drug, into the sub plantar region of the right hind paw of each rat, carrageenan solution (0.1 ml of 1%) in saline was injected subcutaneously, 1 h after the administration of the test compounds and standard drug. The right hind paw volume was measured before and after 3 and 4 h of carrageenan treatment by means of a plethysmometer. The percent edema inhibition was calculated.

TABLE 2 : Anti-inflammatory activity of the synthesized compounds

Compounds	Paw Volume			% Inhibition SEM[a]		Potency
	0 hrs (Basal)	After 3 hrs	After 4 hrs	After 3 hrs	After 4 hrs	
3a	0.36 ±0.016	0.73 ±0.017	0.72 ±0.019	15.90 ±2.73	18.18±2.25**	0.24
3b	0.36±0.017	0.46±0.016	0.45 ±0.015	77.27 ±1.92	79.54±1.91	1.00
3c	0.36±0.013	0.66±0.019	0.66 ± 0.017	31.81 ±3.45	31.81± 3.71**	0.39
3d	0.37±0.011	0.48±0.015	0.46 ±0.016	75.00±2.79	79.54± 3.19	1.00
3e	0.37±0.010	0.53 ±0.014	0.53±0.014	63.63 ± 1.92	63.63±1.92**	0.80
3f	0.34 ±0.015	0.55 ± 0.016	0.54 ± 0.017	52.27 ±2.17	54.54±2.62**	0.67
3g	0.32 ±0.009	0.43 ±0.017	0.40 ±0.016	75.00 ± 2.73	75.00±2.73	1.02
3h	0.36 ±0.014	0.55 ±0.015	0.54 ±0.014	56.81 ±1.94	59.09±2.73**	0.74
3i	0.39 ±0.012	0.50 ± 0.014	0.49 ±0.015	75.00 ±2.53	77.27±1.91	0.97
Flurbiprofen	0.33 ±0.011	0.44 ±0.016	0.42 ± 0.019	75.00±2.53	79.54± 2.25	1.00
Control	0.33 ±0.011	0.77 ±0.013	0.77 ±0.016	--	--	--

[a]**Relative to standard and data were analyzed by ANOVA followed by Dunnett's multiple comparison test for n = 6; **p < 0.01.**

The percent edema inhibition was calculated.

Percent edema inhibition = (*Vc*-*Vt*/*Vc*) X 100

Where, *Vt* = the mean increase in paw volume in rats treated with test compounds, and *Vc* = the mean increase in paw volume in control group of rats.

All Compounds are also evaluated for their analgesic activity. Compounds which showed good results for anti-inflammatory activity observed to be containing good analgesic property also. Out of the newly synthesized compounds, **(3g)** showed significant activity at 30 min and highly significant activity at 60 and 90min.

Protocol for analgesic activity: the tail flick method[15].

Young male Wistar strain albino rats of 160-200 gm body weight were selected for the activity. Six animals in each group like wise fourteen groups were taken. 0.5% CMC was administered to group one, which was kept as vehicle control and Pentazocin (2 mg/kg) is administered to group two by i.p. route. Remaining groups administered test drug by i.p route (200 mg/kg). Fluid intake is kept same in all groups.They were placed into individual restraining cages leaving the tail hanging out freely. Before testing, the animals were allowed to become accustomed to the cages for 30 min. The lower 5 cm portion of the tail was noticed. This part of the tail was immersed in a cup of freshly filled water at 54 ± 2 °C. Within a few seconds, the rat reacts by withdrawing the tail. The reaction time was recorded. After each determination, the tail was carefully dried. The reaction time was recorded before and periodically after oral administration of the test substance (after 0, 30, 60 and 90 min). 10 sec was the cut off time of the immersion. Percent analgesic activity shown by the test compounds is depicted in TABLE 3.

Statistical analysis was done by one way analysis of variance (ANOVA) followed by

TABLE 3 : Analgesic activity (tail flick method) of synthesized compounds

Compounds	% Inhibition ±SEM (n = 6)			
	0 min	30 min	60 min	90 min
3a	2.43 ± 0.24	2.65 ±0.26[a]	2.77 ±0.26	2.95 ±0.28[a]
3b	2.53 ± 0.31	2.64 ±0.38[b]	2.33 ±0.27[c]	2.36 ±0.23[c]
3c	2.62 ±0.28	2.77±0.21[a]	2.83 ±0.22[a]	2.90±0.22
3d	2.64 ± 0.37	2.83 ±0.23[b]	2.57 ±0.26[c]	2.59 ±0.28[c]
3e	2.85 ±0.33	2.93±0.32	2.25 ±0.11	3.08 ±0.33
3f	2.38 ±0.29	2.84±0.26	2.39 ±0.31	3.14 ±0.33
3g	2.67 ± 0.41	2.52 ±0.31[b]	2.28 ±0.20[c]	2.20 ±0.13[c]
3h	3.13±0.3	3.27 ±0.39	3.43 ±0.41	3.63 ±0.39
3i	2.63 ± 0.25	2.55 ±0.29[a]	2.37 ±0.27	2.62 ±0.31[a]
Control	1.9 ±0.12	4.20 ±0.12	4.18 ±0.13	4.20±0.10
Pentazocin	1.9 ± 0.12	2.17 ±0.06[c]	2.18±0.06[c]	2.22 ±0.07[c]

Dunnet's test, n = 6. Values were compared with respect to standard drug pentazocin.

a $P < 0.05$ (Significant from the control).

b $P < 0.01$ (Significant from the control).

c $P < 0.001$ (Significant from the control).

CONCLUSION

By choosing proper experimental conditions under microwave irradiation technology we have been able to synthesize novel 3-aryl-5-(thiophen-3-ylmethyl)-1H-1, 2, 4-triazoles derivatives from aromatic nitriles and investigate for anti-inflammatory and analgesic activity. The anti-inflammatory activity is observed to be good compared to standard drug used, in compounds containing electron withdrawing substituent on 3-substituted aryl moiety. Also almost equal activity exhibited by 3i molecule which contains bulky aryl group on 1, 2, 4-triazole.Same compounds are being observed to have significant analgesic activity compared to control group and standard drug used.

ACKNOWLEDGEMENTS

The authors are grateful to The Principal, Prof. S. J. Surana, R.C.Patel Institute of Pharmaceutical Education and Research, Shirpur, India, for providing necessary laboratory facilities. Words of gratitude are also expressed for IIT Powai and Indian Institute of Science, Banglore for providing NMR and Mass spectra of the compounds.

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