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Synthesis and antimicrobial studies of benzimidazole[a]pyrrol-(3-phenoxy)-3-yl-4-ol

Arunkumar Manohar Shirahatti and Oblennavar Kotresh

Department of Chemistry, Karnatak Science College, Dharwad, India

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ABSTRACT

The novel Benzimidazole[a]pyrrol-(3-phenoxy)-3-yl-4-ol have been prepared by intramolecular cyclization intermediate 1-(1-H-benzo[d]imidazol-2-yl)-1-phenoxypropan-2-one and characterized by IR, ^{1}H NMR, ^{13}C NMR and GC-MS. Thus, the prepared compounds Benzimidazole[a]pyrrol-(3-phenoxy)-3-yl-4-ol has been screened antimicrobial activity, therefore all the compound shows very less active against standard.

Key words: Benzimidazole[a]pyrrol-(3-phenoxy)-3-yl-4-ol, *o*-phenylendiamine, 2-(phenoxymethyl)benzimidazoles and phenyl acetic acid.

INTRODUCTION

Benzimidazole derivatives are well known pharmacophore in drug discovery. The Pharmaceutical properties such as antiviral, antitumor[1], antihistaminic, antimicrobial [2], and antihelminthic [3] activities are quite characteristics known, since long ago and a privileged structure in medicinal chemistry. The most active benzimidazole derivative in nature is N-ribosyl-dimethylbenzimidazole, which serve as an axial legand for cobalt in vitamin B12 [4]. Since the benzimidazole derivatives are using as most bioactive molecule[5]. The various substituted benzimidazole derivatives are synthesized and studied the stability, bioavailability and showed significant biological activity [6, 7]. The better anti-ulcer activity was produced by dervatization at N-H of benzimidazole and electron donating group on substitution with long chain[8,9]. Thus, the various microbial are causing hazardeious health problems, due to the number of microbial agents are resistance towards microbial. Hence, the discovery of new drug is needed to overcome all the resistance drugs towards microbial. Therefore, in view of all above results, prompted us to synthesis new agents with higher microbial activity molecule.

MATERIALS AND METHODS

Melting points were determined by using Kofler hot-stage apparatus with microscope and are may uncorrected. IR spectra were recorded on a Nicolet-impact – 410 FT infrared spectrometer. The NMR was recorded on a Bruker 300 MHz FT NMR spectrometer. ^{1}H and ^{13}C Chemical shift were represented as δppm – values relative to the internal standard, tri-methylsilane. Substituted o-Phenylenediamines and phenols were commercially available and used after purification.

General Procedure for synthesis of 1-(1-*H*-benzo[d]imidazol-2-yl)-1-phenoxypropan-2-one (5a – 5j).
A mixture of anhydrous potassium carbonate (1.5 equiv.) and 2-(phenoxymethyl)benzimidazoles (**3**) (1.0 equiv.) was stirred for about half an hour in dry acetone (20 ml). To this acetyl chloride (1.5 equiv.) was added and the stirring was continued for 16-20 h at room temperature and reaction was monitored by TLC. The reaction mixture

was diluted with crushed ice. Separated solid was filtered and washed with water, then washed with dilute HCl (1:1) and then with water. The residual solid was purified by crystallization using ethanol, yield obtained around 65%. The representative data of compound **5a.** Colorless solid, yield 72%, MP. 126 ^{o}C; IR (KBr): 1727, 3431 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H, CH_3), 2.21 (s,3H,-$COCH_3$), 5.12 (s, 1H, CH), 6.62 (d, 2H, Ar-H, *J* = 5.8 Hz), 6.71 (d, 2H, Ar-H, *J* = 5.7 Hz), 6.88-7.01 (m, 4H, Ar-H and NH, D_2O exchanges), 7.04 (d, 1H, Ar-H, *J*= 6.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 24.11, 24.32, 88.23, 115.21, 116.14, 116.28, 121.31, 121.64, 128.32, 132.11, 136.34, 136.72, 141.23, 152.48, 192.01; GC-MS: m/z 280.

General Procedure for synthesis of Benzimidazole[a]pyrrol-(3-phenoxy)-3-yl-4-ol (7a-7j).
Placed 1 gm (1.0 equiv.) of compound **5** in 30 mL of dry chloroform and add bromine in chloroform (1.1equiv.) drop wise at 10-15 ^{o}C under nitrogen atmosphere. The stirring was continued for overnight and reaction was monitored by TLC. The chloroform layer was removed under vacuum and solid obtained was washed with water and cooled ethanol, purified by crystallization using ethanol, yield obtained around 60%.

Synthesis of Benzimidazole[a]pyrrol-3-(phenoxy-4-methyl)-3-yl-4-ol (7a). Colorless solid, Yield 64 %, M. P. 142 ^{o}C, IR (KBr): 1617, 3414 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.26 (s, 3H, CH_3), 3.85 (br, s,1H,- OH and D_2O exchanges), 4.61 (s, 2H, CH_2), 6.68 (d, 2H, Ar-H, *J* = 4.2 Hz), 6.74 (d, 2H, Ar-H, *J* = 4.4 Hz), 6.80-7.00 (m, 3H, Ar-H), 7.02 (d, 1H, Ar-H, *J*= 5.1 Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 23.48, 49.22, 115.25, 116.16, 116.20, 120.92, 121.48, 129.22, 133.18, 138.14, 138.88, 142.22, 151.31, 152.18, 159.21; GC-MS: m/z 278.

Synthesis of Benzimidazole[a]pyrrol-3-(phenoxy-3-methyl)-3-yl-4-ol (7b). . Colorless solid, Yield 62 %, M P 148 ^{o}C, IR (KBr): 1611, 3421 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.82 (br, s,1H,- OH and D_2O exchanges), 4.59 (s, 2H, CH_2), 6.65 (d, 1H, Ar-H, *J* = 8.1 Hz), 6.70-6.83 (m,5H, Ar-H), 7.01 (d, 1H, Ar-H, *J* = 4.4 Hz), 7.22 (d, 1H, Ar-H, *J*= 2.2 Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 24.32, 48.51, 114.88, 116.12, 116.32, 116.56, 120.85, 121.48, 121.72, 129.11, 134.10, 138.31, 139.12, 143.16, 151.64, 152.31, 159.40; GC-MS: m/z 278.

Synthesis of Benzimidazole[a]pyrrol-3-(phenoxy-4-chloro)-3-yl-4-ol (7c). . Colorless solid, Yield 60 %, MP.162 ^{o}C, IR (KBr): 1620, 3392 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.86 (br, s,1H,- OH and D_2O exchanges), 4.61 (s, 2H, CH_2), 6.63 (d, 2H, Ar-H, *J* = 5.4 Hz), 6.68 (d, 1H, Ar-H, *J* = 4.8 Hz), 6.70-6.92 (m, 3H, Ar-H), 7.02 (d, 2H, Ar-H, *J*= 5.1 Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 48.63, 115.35, 116.21, 116.30, 121.12, 121.64, 129.52, 135.42, 138.31, 138.91, 142.13, 151.41, 152.23, 160.11; GC-MS: m/z 298.

Synthesis of Benzimidazole[a]pyrrol-3-(phenoxy-4-bromo)-3-yl-4-ol (7d). Colorless solid, Yield 60 %, MP. 156 ^{o}C, IR (KBr): 1612, 3388 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.81 (br, s,1H,- OH and D_2O exchanges), 4.66 (s, 2H, CH_2), 6.64 (d, 2H, Ar-H, *J* = 8.2 Hz), 6.66 (d, 1H, Ar-H, *J* = 5.6 Hz), 6.71-6.88 (m, 3H, Ar-H), 7.13 (d, 2H, Ar-H, *J*= 8.1 Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 48.72, 115.25, 116.11, 116.38, 121.18, 121.71, 129.57, 135.48, 138.41, 138.98, 142.19, 151.51, 152.28, 160.21; GC-MS: m/z 343.

Synthesis of Benzimidazole[a]pyrrol-3-(phenoxy-4-methoxy)-3-yl-4-ol (7e). Light yellow solid, Yield 63 %, MP. 132 ^{o}C, IR (KBr): 1620, 3422 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.51 (s,3H, OCH_3), 3.87 (br, s,1H,- OH and D_2O exchanges), 4.71 (s, 2H, CH_2), 6.67 (d, 2H, Ar-H, *J* = 6.0 Hz), 6.69 (d, 1H, Ar-H, *J* = 3.4 Hz), 6.70- 6.96 (m, 3H, Ar-H), 7.15 (d, 2H, Ar-H, *J*= 6.2 Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 48.68, 56.31, 114.88, 115.61, 115.92, 120.69, 120.75, 128.96, 134.82, 138.38, 138.81, 142.43, 151.65, 152.42, 159.78; GC-MS: m/z 294.

Synthesis of 5-Nitro-benzimidazole[a]pyrrol-3-(phenoxy-4-methyl)-3-yl-4-ol (7f). Yellow solid, Yield 61 %, MP. 145 ^{o}C, IR (KBr): 1622, 3415 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 4.01 (br, s,1H,- OH and D_2O exchanges), 4.75 (s, 2H, CH_2), 6.60 (d, 2H, Ar-H, *J* = 6.0 Hz), 6.73 (d, 2H, Ar-H, *J* = 6.1 Hz), 7.01 (d, 1H, Ar-H, J = 8.1 Hz), 7.7 (d, 1H, Ar-H, J = 8.0 Hz) 8.03 (s, 1H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 24.16, 48.75, 112.62, 115.56, 116.23 122.32, 124.11, 126.41, 127.20, 137.88, 138.88, 143.33, 151.61, 156.8, 159.68; GC-MS: m/z 323.

Synthesis of 5-Nitro-benzimidazole[a]pyrrol-3-(phenoxy-3-methyl)-3-yl-4-ol (7g). Yellow solid, Yield 60 %, MP. 133 ^{o}C, IR (KBr): 1612, 3431 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.40 (s, 3H, CH_3), 4.12 (br, s,1H,-OH and D_2O exchanges), 4.58 (s, 2H, CH_2), 6.69 (d, 1H, Ar-H, *J* = 3.8 Hz), 6.88 (t, 1H, Ar-H, *J* = 4.4 Hz), 6.91 (d, 1H, Ar-H, J = 5.1 Hz), 6.98 (d, 1H, Ar-H, J = 6.2 Hz), 7.13 (d, 1H, J = 2.1Hz) 7.22 (m, 2H, Ar-H) 8.04 (s, 1H, Ar-H);

^{13}C NMR (300 MHz, DMSO-d_6): δ 24.21, 49.15, 111.22, 115.16, 116.30, 119.11, 120.41, 123.41, 129.82, 132.52, 138.62, 139.33, 144.28, 152.72, 154.22, 157.81, 159.79; GC-MS: m/z 323.

Synthesis of 5-Nitro-benzimidazole[a]pyrrol-3-(phenoxy-4-chloro)-3-yl-4-ol (7h). Yellow solid, Yield 58 %, MP. 146 ^{o}C, IR (KBr): 1618, 3411 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.82 (br, s,1H,- OH and D_2O exchanges), 4.64 (s, 2H, CH_2), 6.74 (d, 2H, Ar-H, *J* = 4.4 Hz), 6.76 (d, 1H, Ar-H, *J* = 4.8 Hz), 6.78-6.82 (m, 2H, Ar-H), 6.97 (d, 2H, Ar-H, *J*= 4.2 Hz), 7.83(s, 1H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 49.71, 111.12, 116.41, 116.30, 118.32, 119.22, 122.78, 128.62, 132.61, 134.31, 141.81, 152.01, 154.11, 158.31; GC-MS: m/z 343.

Synthesis of 5-Nitro-benzimidazole[a]pyrrol-3-(phenoxy-4-bromo)-3-yl-4-ol (7i). Light yellow solid, Yield 58 %, MP. 150 ^{o}C , IR (KBr): 1624, 3423 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.42 (br, s,1H,- OH and D_2O exchanges), 4.73 (s, 2H, CH_2), 6.69 (d, 2H, Ar-H, *J* = 7.2 Hz), 6.74 (d, 1H, Ar-H, *J* = 5.4 Hz), 6.76-6.84 (m, 2H, Ar-H), 6.92 (d, 2H, Ar-H, *J*= 7.1 Hz), 7.81(s, 1H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 49.64, 111.22, 116.51, 116.40, 118.41, 119.31, 122.80, 128.71, 132.68, 134.38, 141.89, 152.21, 154.23, 158.38; GC-MS: m/z 388.

Synthesis of 5-Nitro-benzimidazole[a]pyrrol-3-(phenoxy-4-methoxy)-3-yl-4-ol (7j). Colorless solid, Yield 61%, MP.144 ^{o}C, IR (KBr): 1614, 3386 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.42 (br, s,1H,- OH and D_2O exchanges), 3.51 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2), 6.62 (d, 2H, Ar-H, *J* = 6.1 Hz), 6.69 (d, 1H, Ar-H, *J* = 4.6 Hz), 6.72-6.81 (m, 2H, Ar-H), 6.85 (d, 2H, Ar-H, *J*= 6.3 Hz), 7.88(s, 1H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ 49.79, 54.66, 111.32, 116.48, 116.46, 118.44, 119.35, 122.72, 128.73, 132.72, 134.42, 142.65, 152.12, 154.25, 158.68; GC-MS: m/z 339.

RESULTS AND DISCUSSION

The continuation of our efforts on studies towards the benzimidazole and its derivatives, we have initiated to develop a new and general strategy for the biologically interested molecule. The synthetic pathway for the preparation of compound **7** was presented in scheme 1. The 2-(phenoxymethyl)benzimidazoles (**3**) were prepared by condensing substituted phenyl acetic acid (**1**) and *o*-phenylendiamine (**2**) in presence of 4N hydrochloric acid at refluxing temperature. On acetylating compound **3** in presence of anhydrous potassium carbonate we expected N-acetylated product **4** instead of **5**, but IR spectral value revels that presence of NH stretching band around 3431 cm^{-1}, carbonyl strong stretching band around 1727 cm^{-1} and not observed amide band, further ^{1}H NMR spectrum supported the compound **5** showed singlet at 5.23 δppm for one proton with excellent yield. The desired product **7a to 7j** obtained around 60 % yield when treated with bromine (1.0 equiv.) in chloroform at 0-5 ^{o} C (Table 2), the expected product **6** (scheme 1) was not fond due to bromination followed by intramolcular cyclization via nucleophilic substation. Whereas, the products **7** were supported by IR, ^{1}H NMR, ^{13}C NMR and mass spectra. In IR spectrum absence of carbonyl stretching band and presences of OH stretching band around 3414 cm^{-1}, then in ^{1}H NMR spectrum singlet at 4.61 δppm for two protons and ^{13}C NMR gives one aliphatic carbons at 46.12 δppm due to *sp3* carbons attached to nitrogen.

Table 1. The antibacterial and MIC value of title compounds (7a-7j)

	Staphylococcus aureus,						
Sample	**0.0625 mg**	**0.125 mg**	**0.25 mg**	**0.5 mg**	**1.0 mg**	**2.0 mg**	**MIC mg**
7a	0	0	0	12	14	15	0.5
7b	0	0	0	0	0	15	2
7c	0	0	0	0	14	16	1
7d	0	0	0	14	15	16	0.5
7e	0	0	0	0	11	16	1
7f	0	0	0	0	15	23	1
7g	0	0	0	0	0	20	2
7h	0	0	0	17	18	19	0.5
7i	0	0	0	0	14	16	1
7j	0	0	0	0	17	19	1
Gentamycin	**25 µg**	**50µg**	**100µg**	**200µg**	**400µg**	**800µg**	**MIC µg**
	13	18	21	25	27	34	25

Antimicrobial Activity

All the synthesized compounds **7a-j** were screened the antimicrobial activity against Gram positive and Gram negative species with *Staphylococcus aureus*, *Escherichia coli* and *Aspergillus niger*, *Candida albicans* respectively

were employed as bacterial and fungal strains, DMSO was used as a solvent control. The reference drugs used were Gentamycin and Amphotericin. Tests were carried out by the Agar diffusion method at a 6 concentration mL^{-1}. After 48 h of incubation at 37◦C, the zone of inhibition was measured in mm. The percent inhibition of test compounds was related to the standard whose zone of inhibition was taken as 100%. The obtained results, of antibacterial and antifungal activity has been found less than the standard used, hence all the compounds found to be moderate activity against Gram positive and Gram negative species. The results are summarized in the **tables 1** to **4.**

Table 2. The antibacterial and MIC value of title compounds (7a-7j)

	Escherichia coli						
Sample	**0.0625 mg**	**0.125 mg**	**0.25 mg**	**0.5 mg**	**1.0 mg**	**2.0 mg**	**MIC mg**
7a	0	0	0	0	18	20	1
7b	0	0	0	19	21	23	0.5
7c	0	0	0	0	16	20	1
7d	0	0	0	0	17	19	1
7e	0	0	0	0	0	16	2
7f	0	0	0	0	14	17	1
7g	0	0	0	13	20	25	0.5
7h	0	0	0	0	0	20	2
7i	0	0	0	0	16	17	1
7j	0	0	0	0	0	19	2
	25 µg	**50µg**	**100µg**	**200µg**	**400µg**	**800µg**	**MIC µg**
Gentamycin	18	20	23	26	28	31	25

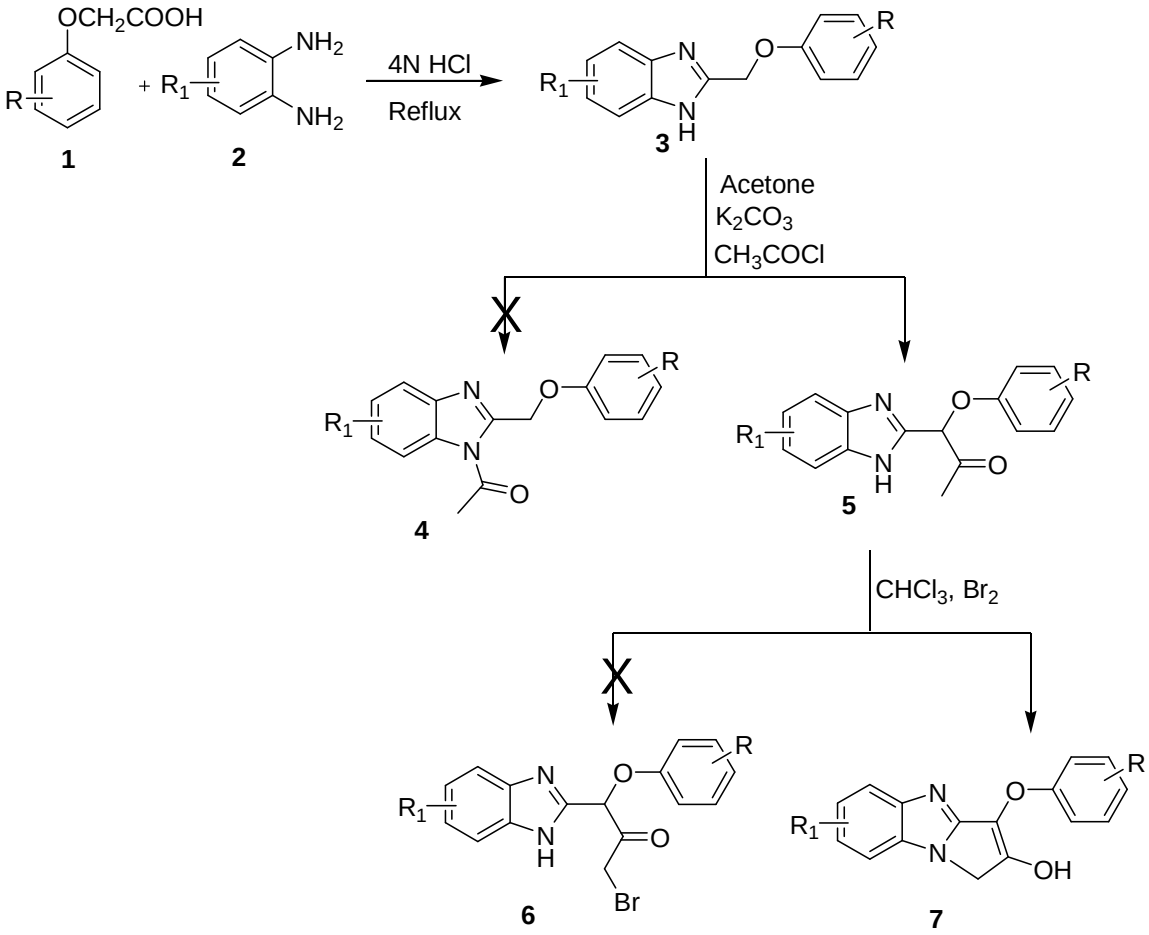
Table 3. The antifungal and MIC value of title compounds (7a-7j)

	Aspergillus niger						
Sample	**0.0625 mg**	**0.125 mg**	**0.25 mg**	**0.5 mg**	**1.0 mg**	**2.0 mg**	**MIC mg**
7a	0	0	0	0	0	3	2
7b	0	0	0	0	0	0	NF
7c	0	0	0	0	0	3	2
7d	0	0	0	0	0	5	2
7e	0	0	0	0	0	6	2
7f	0	0	0	0	0	4	2
7g	0	0	0	0	0	5	2
7h	0	0	0	0	0	0	NF
7i	0	0	0	0	0	4	2
7j	0	0	0	0	0	8	2
	25 µg	**50µg**	**100µg**	**200µg**	**400µg**	**800µg**	**MIC µg**
Amphotericin	0	0	2	3	5	7	100

Table 4. The antifungal and MIC value of title compounds (7a-7j)

	Candida albicans						
Sample	**0.0625 mg**	**0.125 mg**	**0.25 mg**	**0.5 mg**	**1.0 mg**	**2.0 mg**	**MIC mg**
7a	0	0	0	0	0	8	2
7b	0	0	0	0	0	6	2
7c	0	0	0	0	0	9	2
7d	0	0	0	0	0	5	2
7e	0	0	0	0	0	0	NF
7f	0	0	0	0	0	6	2
7g	0	0	0	0	0	7	2
7h	0	0	0	0	0	9	2
7i	0	0	0	0	0	5	2
7j	0	0	0	0	0	7	2
	25 µg	**50µg**	**100µg**	**200µg**	**400µg**	**800µg**	**MIC µg**
Amphotericin	0	2	7	9	13	15	50

Note: *NF- MIC not found among the concentrations screened*



Scheme 1: R = *p*- CH_3, *m*-CH_3, *p*- Cl, *p*- Br, *p*-OCH_3,
R_1 = H and NO_2

CONCLUSION

The benzimidazole ring system is important pharmacophore in modern drug discovery. Therefore, the attention has been given in the synthesis of benzimidazole derivatives for new antimicrobial agents. Hence, we have synthesized the benzimidazole fused pyrrole unite successfully and characterized by analytical data and screened microbiological activity, the compound showed very less activity against standard.

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