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Design, synthesis and antimicrobial activities of 1,2,3-triazole derivatives

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Abstract

Fifteen 1-(4-substituted phenyl)-4-(4-bromophenyl)-5-(halo-*o*-hydroxyphenyl)imino-1,2,3-triazoles were designed and synthesized based on rational combination of 1,2,3-triazoles and (halo)*o*-hydroxyphenyl group according to the superposition principle of reinforcement of biological activities. All the compounds were tested to an *in vitro* antimicrobial screening against *M.a.* and *E.c.*. Compounds **IIe–IIo** exhibited more potent antimicrobial activities against *M.a.* and *E.c.* than triclosan and fluconazole, which provided valuable information to further study of novel antimicrobial research.

Keywords: 1-(4-Substituted phenyl)-4-(4-bromophenyl)-5-(halo-*o*-hydroxyphenyl)imino-1,2,3-triazoles; 1-(4-Substituted phenyl)-4-(4-bromophenyl)-5-amino-1,2,3-triazoles; Synthesis; Antimicrobial activity

Some studies have showed that many triazoles had strong affinity and specificity to the targets of pathogen like lanosterol 14α-demethylase and HIV-RT and possessed brilliant application prospects in antibacterial [1–3], antifungal [4–6], anti-tumor [7] and anti-HIV [8] fields. Meanwhile, they also had many highlights like low cytotoxicity to human. As a result, triazoles in the design of novel biological and medical agents became more and more outstanding. Furthermore, the *o*-hydroxydiphenyl ethers were important compounds in broad-spectrum antibacterial fields. The key structures in these compounds like *o*-hydroxyphenyl or halo-*o*-hydroxyphenyl showed strong affinity and specificity to the targets of pathogen like FabI gene and NAD^+ coenzyme [9,10]. In addition, many Schiff base derivatives had good antibacterial, anticancer and antitumor activities [11,12].Based on the studies above, fifteen 1-(4-substituted phenyl)-4-(4-bromophenyl)-5-(halo-*o*-hydroxyphenyl)-imino-1,2,3-triazoles were designed and synthesized in this paper. The intermediates and all target compounds were screened for their *in vitro* antibacterial activities against *E.c.* and *M.a.* The results showed that the target compounds (**II**) possessed efficient antimicrobial activities at the concentration of 0.1 mg/mL. Under a lower concentration of 0.01 mg/mL, most of compounds still exhibited the antimicrobial activities against *M.a.* and *E.c.*, and higher than fluconazole and triclosan. Especially, the inhibitory ratio of **IIm** against *E.c.* came up to 79.9%, and **IIn** against *M.a.* reach up to 80.1%. These compounds were

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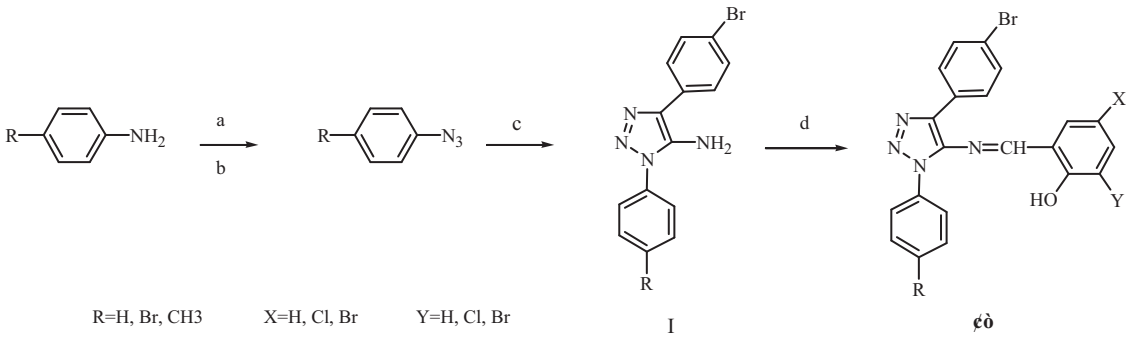

Scheme 1. The synthetic route of target compounds. Reagents and conditions: (a) $NaNO_2$, HCl, 0 to 5 °C; (b) NaN_3, −5 to 0 °C; (c) 4-bromophenylacetonitrile, MeOH, MeONa; (d) (halo)salicylaldehyde, toluene, reflux.

a series of excellent antimicrobial compounds. Further biological evaluation of all compounds is progressing. The structure–activity relationship and action mode of this class of compounds will be explored by molecular modeling.

1. Experimental

All the reagents were purchased from commercial sources and used without further purification. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds were carried out by thin chromatography (TLC), TLC analysis was performed on silica gel plate, which was obtained from Qingdao Ocean Chemicals. The melting point was taken in open capillary tubes and the thermometer was uncorrected. IR spectrum was recorded on Nicolet 370 DTGS spectrometer *via* KBr pellets. NMR spectrum was measured on a Bruker AVANCE III spectrometer operated at 400 MHz with $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal standard. Elemental analysis was carried out on a Perkin-Elmer 2400 elemental analyzer. Mass spectra were scanned on a shimadzu LCMS 2010 spectrometer (shimadzu, Tokyo, Japan).

Substituted aminobenzene was used as raw material, azidobenzene was synthesized through diazotization and azidation, then 1-(4-substituted phenyl)-4-(4-bromophenyl)-5-amino-1,2,3-triazoles (**I**) was obtained by the reaction of azidobenzene and 4-bromophenylacetonitrile in the MeOH in the presence of MeONa. The target compounds were prepared by the reaction of (**I**) and (halo) salicylaldehyde in toluene, the solution was adjusted to pH 4–5 with acetic acid. The synthetic route of target compounds was outline in Scheme 1.

According to the national standard GB15979-2002, the antimicrobial activity was evaluated against different bacterial strains such as *Monilia albicans* (*M.a.*) (ATCC10231) and *Escherichia coli* (*E.c.*) (8099) at the concentration of 0.1 mg/mL and 0.01 mg/mL. Fluconazole and triclosan were used as a standard for the comparison of antimicrobial activity.

2. Results and discussions

All the target compounds are first reported and their structure were confirmed by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. The spectra of **IIa** exhibited absorptions at 3513 cm^{-1} for (str. of –OH), 3130 cm^{-1} for (str. of Ar–H), 1618 cm^{-1} for (str. of C=C), 1556 cm^{-1} for (str. of N=N), 1267 cm^{-1} for (str. of C–OH), 1141 cm^{-1} for (str. of C–N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.74 (s, 1H, OH), 8.687 (s, 1H, N=CH), 7.78–7.77 (d, 2H, J = 7.2 Hz, Ar–H), 7.74–7.71 (d, 2H, J = 8.8 Hz, Ar–H), 7.58–7.56 (d, 2H, J = 8.8 Hz, Ar–H), 7.50–7.40 (m, 4H, Ar–H), 7.15–7.13 (dd, 1H, J_1 = 8.0 Hz, J_2 = 2.4 Hz, Ar–H), 7.04–7.02 (d, 1H, J = 8.4 Hz, Ar–H), 6.96–6.92 (t, 1H, J = 7.2 Hz, Ar–H). The ^{13}C NMR (100 MHz, DMSO-d_6) of compound **IIa** showed singlet at δ 168.92 for (N=CH), 139.31 and 136.00 for (triazole), 161.29, 135.33, 134.63, 133.35, 132.81, 130.13, 129.19, 128.55, 127.38, 125.95, 123.54, 119.85, 118.22, 117.70 for aromatic carbon. Anal. calcd. for $C_{21}H_{15}BrN_4O$: C 60.16, H 3.61, N 13.36%; found: C 60.23, H 3.76, N 13.41%. MS *m/z*: 419.04 $[M+1]^+$. Similarly, all these compounds were characterized on the basis of spectral studies.

The structures and the results of antimicrobial activities (inhibitory ratios = (No. of Colony in control group − No. of Colony in experimental group)/No. of Colony in control group × 100%) *in vitro* of target compounds were listed in Table 1.

Table 1
The structures and antibacterial activity of the compounds (inhibitory ratio %).

Compounds	Substituents			Yield (%)	Melting point (°C)	Inhibitory (0.1 mg/mL)		Inhibitory (0.01 mg/mL)	
	R	X	Y			*E.c.*	*M.a.*	*E.c.*	*M.a.*
IIa	H	H	H	87.0	164–166	96.9	99.6	<50	<50
IIb	Br	H	H	89.4	191–193	97.1	100	<50	50.1
IIc	CH_3	H	H	87.9	184–186	96.0	99.0	<50	<50
IId	H	Br	H	91.3	187–189	97.8	100	50.9	60.2
IIe	Br	Br	H	90.5	187–188	98.0	100	60.2	65.7
IIf	CH_3	Br	H	89.3	207–208	98.1	100	66.2	60.3
IIg	H	Br	Br	91.5	229–231	98.1	100	64.2	70.8
IIh	Br	Br	Br	92.3	256–257	99.2	100	70.0	76.5
IIi	CH_3	Br	Br	90.7	194–196	98.6	100	65.4	69.7
IIj	H	Cl	H	90.7	172–174	98.3	100	70.0	63.4
IIk	Br	Cl	H	90.1	194–195	98.9	100	70.6	65.6
IIl	CH_3	Cl	H	89.7	200–202	98.3	100	62.3	63.1
IIm	H	Cl	Cl	93.6	215–216	100	100	79.9	71.9
IIn	Br	Cl	Cl	93.7	254–256	99.1	100	72.8	80.1
IIo	CH_3	Cl	Cl	94.0	255–257	99.0	100	70.3	71.9
Triclosan						90.7	86.7	51.9	43.8
Fluconazole						95.5	99.2	41.0	42.6

The results showed that all target compounds possessed efficient antimicrobial activities at the concentration of 0.1 mg/mL. They had above 96.0% inhibitory ratio against *E.c.*, especially, **IIm** reached up to 100%; except **IIa** and **IIc**, other compounds had 100% inhibitory ratio against *M.a.* Moreover, under a lower concentration of 0.01 mg/mL, except **IIa** and **IIc**, other compounds still exhibited the antifungal activity against *M.a.*, which were much better than that of fluconazole (42.6%) and triclosan (43.8%), the inhibitory ratio of **IIn** reached up to 80.1%; compounds **IIe**–**IIo** still had antibacterical activity against *E.c.* and higher than triclosan (51.9%) and fluconazole (41.0%), especially, the inhibitory ratio of **IIm** reached up to 79.9%. These results may provide some guidance for novel antimicrobial research.

Further biological evaluation of all compounds is in progress. The structure–activity relationship and action mode of this class of compounds will be explored by molecular modeling.

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