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Synthesis and Antioxidant Activities of Novel 4,4'-Arylmethylene-bis(1*H*-pyrazole-5-ol)s from Lignin

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A series of novel bispyrazoles joined by arylmethylene at C-4 position were synthesized with aromatic aldehydes obtained from lignin and screened for their *in vitro* antioxidant activities by *N*,*N*-diphenyl-*N'*-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylenzothiazoline-sulphonic acid) diammonium salt ($ABTS^+$) radical scavenging assays. All of these compounds exhibited good DPPH and $ABST^+$ radical scavenging activities as compared to the standard, Trolox, which suggested their potential as promising agents for curing tumors or other free radical-related diseases.

Keywords pyrazole, microwave chemistry, aromatic aldehyde, 4,4'-arylmethylene-bis(1*H*-pyrazole-5-ol), lignin, antioxidants

Introduction

Pyrazoles and their related derivatives are an important class of pharmaceutical compounds with a broad spectrum of biological activities: analgesic, antipyretic, antioxidant and antihypertensive properties and potential antifungal, antibacterial,[1,2] anti-inflammatory[3-5] and anticancer activities.[6-8] In addition, some of the oxy pyrazole derivatives are used in the treatment for a variety of disorders caused by Human Immunodeficiency Virus (HIV) and other genetic ailments caused by retroviruses such as Acquired Immune Deficiency Syndrome (AIDS).[9] Pyrazole derivatives are also found applications as dyestuffs, analytical reagents and agrochemicals.[3,10]

It is well-known that lots of natural and synthesized antioxidants possessing phenolic hydroxyl groups can improve their antioxidant activities by reacting with free radicals.[11] Vanillin and syringaldehyde, two phenolic hydroxyl containing compounds obtained from lignin, are widely used as additives in food, pharmaceutical and cosmetic industries due to their antioxidant activity besides the fragrant odor and non-toxicity.[12-14] The synthesis of pyrazole derivatives with vanillin and syringaldehyde as starting materials is expected to afford better antioxidant properties. Starting from these considerations, we report herein the synthesis and *in vitro* antioxidant properties of novel 4,4'-arylmehtylene-bis(1*H*-pyrazole-5-ol)s using the aromatic aldehydes from lignin under microwave irradiation.

Experimental

General

Vanillin, *p*-hydroxybenzaldehyde and syringaldehyde were synthesized according to previously reported methods.[15-18] Other reagents were obtained from Sinopharm Chemical Reagent Co, Ltd. All reactions were conducted in CEM Discover. All synthesized compounds were characterized by infra-red (IR), ^{1}H NMR, ^{13}C NMR, mass spectrometry (MS) and elemental analysis (EA). IR spectra were recorded with a Nicolet Magna-IR 550 spectrometer. Mass spectra were recorded on WATERS Q-TOF Premier Mass Spectrometer using electrospray ionization (ESI). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DRX-300 Advance spectrometer at 300 MHz and 75 MHz, respectively. Elemental analyses (C, H, N, S) were conducted using a PE-2400 (II) Elemental Analyser, and results were found to be in good agreement (±0.2%) with the calculated values.

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Typical procedure to synthesize aromatic aldehydes from lignin

The aromatic aldehydes were synthesized according to the reported procedure.[15-18] Briefly, alkali lignin (100 g), 500 mL 2 mol•L^{-1} sodium hydroxide and 112 mL nitrobenzene were placed in a 2 L stainless steel autoclave. The mixture was heated at 170 ℃ at 1 MPa for 2 h. After the autoclave was cooled to room temperature, the mixture was then transferred to a liquid-liquid extractor for continuous extraction with chloroform (500 mL×3) to remove any nitrobenzene reduction product and excess of nitrobenzene. The oxidation mixture was acidified with concentrated HCl to pH 3 to 4 and further extracted with chloroform (500 mL×3). The solvent from the second chloroform solution was removed by using a rotary evaporator at 40 ℃ under reduced pressure to obtain the mixture of aromatic aldehydes. The residue was isolated by column chromatography to obtain syringaldehyde, vanillin and *p*-hydroxybenzaldehyde with total yield 12%—18%.

Typical procedure to synthesize 4,4'-arylmehtylene-bis(1*H*-pyrazole-5-ol)s

A stirred aqueous mixture of phenylhydrazine (10 mmol) and *β*-ketoesters (10 mmol) was placed into a sealed microwave oven (300 W) at 100 ℃ for 5 min. After the mixture was cooled, aromatic aldehydes (5 mmol) were added successively at 100 ℃ for another 5 min. The reaction mixture was cooled to room temperature to afford the product as a precipitate. The solid residue was filtered, washed with water and 5 mL of 50% ethanol, and then recrystallized from ethyl acetate/ethanol (80∶20, *V*/*V*) to give products.

4,4'-[(4-Hydroxy-3,5-dimethoxyphenyl)methylene]-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**4a**): 2.18 g, yield 85%; ^{1}H NMR (DMSO-d_6, 300 MHz) *δ*: 7.69 (d, *J*=8.1 Hz, 4H, Ar-H), 7.44 (t, *J*=8.1 Hz, 4H, Ar-H), 7.21—7.27 (m, 2H, Ar-H), 6.60 (s, 2H, Ar-H), 4.82 (s, 1H, CH), 3.67 (s, 6H, 2×OCH_3), 1.99 (s, 6H, 2×CH_3); ^{13}C NMR (DMSO-d_6, 75.5 MHz) *δ*: 147.6, 146.1, 134.0, 132.6, 128.8, 125.5, 120.5, 105.3, 56.0, 33.3, 11.6; IR (KBr) *v*: 3220, 3072, 2939, 2842, 1608, 1581, 1506, 1455, 1113, 763 cm^{-1}; MS (ESI) *m*/*z*: 513.2 $[M+H]^+$, 535.2 $[M+Na]^+$. Anal. calcd for $C_{29}H_{28}N_4O_5$: C 67.96, H 5.51, N 10.93; found C 68.07, H 5.62, N 10.81.

4,4'-[(4-Hydroxy-3-methoxyphenyl)methylene]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**4b**): 2.01 g, yield 83%; ^{1}H NMR (DMSO-d_6, 300 MHz) *δ*: 7.89 (d, *J*=8.4 Hz, 4H, Ar-H), 7.30 (t, *J*=8.4 Hz, 4H, Ar-H), 7.01—7.06 (m, 3H, Ar-H), 6.76 (d, *J*=8.1 Hz, 1H, Ar-H), 6.58 (d, *J*=8.1 Hz, 1H, Ar-H), 4.50 (s, 1H, CH), 3.67 (s, 3H, OCH_3), 2.14 (s, 6H, 2×CH_3); ^{13}C NMR (DMSO-d_6, 75.5 MHz) *δ*: 157.0, 146.7, 145.7, 143.8, 140.8, 138.2, 128.1, 122.7, 119.5, 118.9, 114.5, 112.2, 55.5, 34.5, 13.0; IR (KBr) *v*: 3354, 3527, 3070, 2950, 2841, 1596, 1512, 1502, 1377, 1363, 1273, 1036, 750 cm^{-1}; MS (ESI) *m*/*z*: 483.1 $[M+H]^+$, 500.2 $[M+NH_4]^+$, 505.1 $[M+Na]^+$. Anal. calcd for $C_{28}H_{26}N_4O_4$: C 69.70, H 5.43, N 11.61; found C 69.79, H 5.33, N 11.50.

4,4'-[(4-Hydroxyphenyl)methylene]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**4c**): 2.00 g, yield 88%; ^{1}H NMR (DMSO-d_6, 300 MHz) *δ*: 7.92 (d, *J*=8.1 Hz, 4H, Ar-H), 7.29 (t, *J*=8.1 Hz, 4H, Ar-H), 7.13 (d, *J*=8.4 Hz, 2H, Ar-H), 7.02 (t, *J*=7.5 Hz, 2H, Ar-H), 6.56 (d, *J*=8.4 Hz, 2H, Ar-H), 4.50 (s, 1H, CH), 2.12 (s, 6H, 2×CH_3); ^{13}C NMR (DMSO-d_6, 75.5 MHz) *δ*: 157.0, 154.6, 145.8, 140.1, 128.4, 128.2, 128.0, 123.2, 119.1, 118.8, 114.2, 33.5, 12.7; IR (KBr) *v*: 3646, 3435, 3045, 2966, 2859, 1597, 1501, 1424, 1270, 769 cm^{-1}; MS (ESI) *m*/*z*: 453.2 $[M+H]^+$, 475.2 $[M+Na]^+$. Anal. calcd for $C_{27}H_{24}N_4O_3$: C 71.67, H 5.35, N 12.38; found C 71.76, H 5.27, N 12.31.

4,4'-((4-Hydroxy-3,5-dimethoxyphenyl)methylene)-bis(1,3-diphenyl-1*H*-pyrazol-5-ol) (**4d**): 2.52 g, yield 79%; ^{1}H NMR (DMSO-d_6, 300 MHz) *δ*: 7.70 (d, *J*=8.1 Hz, 4H, Ar-H), 7.12—7.47 (m, 16H, Ar-H), 6.60 (s, 2H, Ar-H), 5.11 (s, 1H, CH), 3.68 (s, 6H, 2×OCH_3); ^{13}C NMR (DMSO-d_6, 75.5 MHz) *δ*: 147.8, 146.0, 140.2, 134.0, 132.5, 128.8, 128.5, 128.2, 127.7, 127.5, 126.8, 119.7, 119.6, 105.2, 55.3, 33.4; IR (KBr) *v*: 3066, 1596, 1500, 1455, 1408, 1313, 754, 690 cm^{-1}; MS (ESI) *m*/*z*: 637.2 $[M+H]^+$. Anal. calcd for $C_{39}H_{32}N_4O_5$: C 73.57, H 5.07, N 8.80; found C 73.64, H 5.01, N 8.93.

4,4'-[(4-Hydroxy-3-methoxyphenyl)methylene]bis-(1,3-diphenyl-1*H*-pyrazol-5-ol) (**4e**): 2.56 g, yield 84%; ^{1}H NMR (DMSO-d_6, 300 MHz) *δ*: 8.00 (d, *J*=8.1 Hz, 4H, Ar-H), 7.10—7.39 (m, 16H, Ar-H), 6.83 (s, 1H, Ar-H), 6.61 (s, 1H, Ar-H), 5.09 (s, 1H, CH), 3.58 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6, 75.5 MHz) *δ*: 157.9, 149.4, 146.8, 144.1, 140.4, 135.0, 134.9, 128.6, 128.3, 127.9, 127.8, 126.9, 123.6, 119.8, 119.7, 114.8, 112.3, 55.5, 33.6; IR (KBr) *v*: 3067, 3032, 1597, 1499, 1454, 1406, 1311, 754, 688 cm^{-1}; MS (ESI) *m*/*z*: 607.1 $[M+H]^+$. Anal. calcd for $C_{38}H_{30}N_4O_4$: C 75.23, H 4.98, N 9.24; found C 75.30, H 4.91, N 9.29.

4,4'-[(4-Hydroxyphenyl)methylene]bis(1,3-diphenyl-1*H*-pyrazol-5-ol) (**4f**): 2.34 g, yield 81%; ^{1}H NMR (DMSO-d_6, 300 MHz) *δ*: 7.59 (d, *J*=7.8 Hz, 4H, Ar-H), 7.14—7.48 (m, 16H, Ar-H), 7.00 (d, *J*=8.1 Hz, 2H, Ar-H), 6.63 (d, *J*=8.1 Hz, 2H, Ar-H), 5.12 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, 75.5 MHz) *δ*: 157.8, 154.9, 149.2, 139.2, 133.4, 128.8, 128.5, 128.1, 128.0, 127.8, 127.6, 126.1, 124.5, 120.6, 120.1, 114.6, 33.0; IR (KBr) *v*: 3609, 3063, 1596, 1567, 1501, 1454, 754, 695 cm^{-1}; MS (ESI) *m*/*z*: 577.3 $[M+H]^+$. Anal. calcd for $C_{37}H_{28}N_4O_3$: C 77.07, H 4.89, N 9.72; found C 77.01, H 4.97, N 9.78.

***In vitro* biological evaluation**

The compounds were evaluated for their *in vitro* free radical scavenging activity by the 2,2'-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-sulphonic acid) diammonium salt ($ABTS^+$) radical scavenging method.[19-21]

DPPH radical scavenging assay

This assay is based on the measurement of the scavenging ability of compounds towards the stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical and performed according to the reported method.[19,21] Briefly, an ethanol solution (200 μL) of 100 μmol•L^{-1} DPPH (Aldrich, USA) was incubated at 30 ℃ with 1 μL of compound or Trolox solutions in deionized H_2O. The final concentration of compounds was 100 μmol•L^{-1}. A decrease in absorbance was measured at 517 nm (Perkin Elmer Lambda 2 Spectrophotometer). The rate constant was calculated as the average value of 5 to 6 time-points (intervals) until the absorbance diminished by 50%. The radical scavenging activity was expressed as the reduction rate constant (k) of DPPH and calculated according to the Eq. (1), where $[DPPH]_0$ is the starting concentration and $[DPPH]_t$ is the concentration at the time 't'.

$$k\ (\mathrm{mol^{-1}\cdot L\cdot s^{-1}}) = \frac{[\mathrm{DPPH}]_0[\mathrm{DPPH}]_t}{t[\mathrm{DPPH}]_0[\mathrm{DPPH}]_t} \quad (1)$$

The percentage of scavenged DPPH was plotted versus the concentration of antioxidants and the concentration of antioxidant required obtaining 50% inhibition (50% inhibition concentration, *i.e.*, IC_{50}) was obtained from the graph.

$ABST^+$ radical cation scavenging assay

The concentration of $ABST^+$ remaining after reaction with the antioxidants was determined according to previously published procedure.[20,21] The procedure to prepare the $ABST^+$ stock solution was modified slightly. Sufficient amounts of the diammonium salts of $ABTS^+$ (Sigma, USA) and $K_2S_2O_8$ (Sigma, USA) were dissolved in 2.0 mL water to achieve concentrations of 4.00 and 1.41 mmol•L^{-1}, respectively. This solution was kept in the dark for at least 16 h to form $ABST^+$, then diluted to 100 mL with 80% ethanol so that the solution had an absorbance value (Abs_{ref}) of 0.70±0.05 at 734 nm (Perkin Elmer Lambda 2 Spectrophotometer). Various concentrations of compounds (10 μL) were added to $ABST^+$ solution (200 μL) at ambient temperature to reach a stable absorbance (Abs_{detect}). The percentage of $ABST^+$ scavenged was calculated using Eq. (2).

$$\mathrm{ABST^+_{scavenged}}(\%) = \left(1 - \frac{\mathrm{Abs_{detect}}}{\mathrm{Abs_{ref}}}\right) \times 100 \quad (2)$$

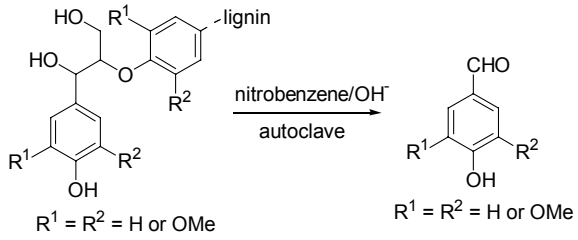
The percentage of scavenged $ABST^+$ was plotted versus the concentration of antioxidants and the concentration of antioxidant required obtaining 50% inhibition (50% inhibition concentration, *i.e.*, IC_{50}) was obtained from the graph.

Results and Discussion

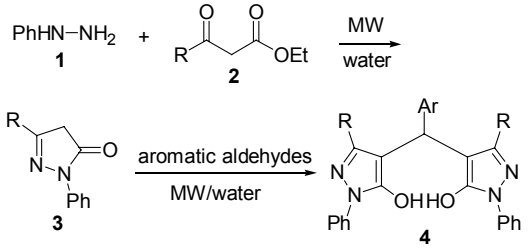
Chemistry

Aromatic aldehydes were prepared from lignin according to the reported methods (Scheme 1).[15-18] Due to the high macromolecular complexity of lignin, it must be liberated to monomers via oxidative degradation. Nitrobenzene oxidation, cupric oxidation and permanganate oxidation are the common delignification methods. Cupric oxidation often leads to the production of acetoguaiacone and acetosyringone as major compounds in lignin, while permanganate oxidation produces significant amount of carboxylic acid methyl esters. Therefore, nitrobenzene oxidation was used to break down the lignin into monomers in our study since vanillin and syringaldehyde are the major compounds by this delignification method. The total yield of aromatic aldehydes using this method, up to 12%—18%; seems low but also satisfactory considering the recycle of the by-products, macromolecular polymers, and their utilization in the synthesis of polymeric materials such as polyurethane, phenolic resin, adhesive and so on.

Scheme 1 Preparation of aromatic aldehydes from lignin



Scheme 2 Microwave-assisted synthesis of 4,4'-arylmehtylene-bis(1*H*-pyrazole-5-ol)s



It is well-known that the formation of 4,4'-arylmehtylene-bis(1*H*-pyrazole-5-ol) is proposed to involve the following tandem reactions: pyrazolone formation by reaction between phenylhydrazine and *β*-ketoesters, followed by aldol condensation of pyrazolone with aromatic aldehydes, and tautomerization (Scheme 2).[22,23] Recently, the progress in the field of reactions in aqua media is gaining significance because of their operational simplicity and environmentally benign processes.[24] Herein, we wished to develop a new eco-friendly procedure with our continuation to the use of the microwave technology for efficient and catalyst-free synthesis of pyrazole derivatives in water because microwave irradiation can accelerate reaction rate, shorten reaction time, and improve product yields by transferring energy directly to the reactive species.[25,26] The workup procedure is very simple without separation

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of the intermediates, pyrazolones, which were consumed in the next condensation reaction directly. So this protocol is very simple just like "one-pot reaction", economical and environmentally benign.

As indicated in Table 1, the reactions were performed in water at 80 ℃ within 5 min under microwave irradiation without catalysts with good yielded (≥79%). All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.

Table 1 Microwave-assisted synthesis of 4,4'-arylmehtylene-bis(1*H*-pyrazole-5-ol)s **4a**—**4f** in water

Entry	Product	Ar	R	yield[a]/%
1	**4a**	syringyl	Me	85
2	**4b**	guaiacyl	Me	83
3	**4c**	*p*-hydroxyphenyl	Me	88
4	**4d**	syringyl	Ph	79
5	**4e**	guaiacyl	Ph	84
6	**4f**	*p*-hydroxyphenyl	Ph	81

[a] Isolated yield.

In vitro biological evaluation

All the synthesized compounds were evaluated for antioxidant activity by *N*,*N*-diphenyl-*N*′-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) diammonium salt ($ABTS^+$) assays.

DPPH is a well-known method for determining antioxidant activity of plant flavonoids. DPPH radical scavenging activities of compounds **4b**, **4c**, **4e** and **4f** were found to be good to moderate, while those of **4a** and **4d** were found to be good to excellent as compared to the standard Trolox (Figure 1). Especially, the radical scavenging activity of compound **4a** was almost two times as high as that of Trolox, while compound **4d** showed nearly the same radical scavenging activity as Trolox.

In view of their good antioxidant activity, their 50% inhibitory concentrations (IC_{50}) against DPPH and $ABST^+$ were tested (Table 2). The values of IC_{50} for all the compounds were lower than that of Trolox in reaction with DPPH, while the compounds **4a**, **4b**, **4d** and **4e** showed almost the same IC_{50} as Trolox in the $ABST^+$ radical cation scavenging assays. As showed in Figures 1 and 2, the antioxidant activities of **4a** and **4d** are the best, those of **4b** and **4e** are middle, and those of **4c** and **4f** are relatively poor. It is easy to find that the structure of 4,4'-arylmehtylene-bis(1*H*-pyrazole-5-ol)s has a major influence on their antioxidant activities. The presence of methoxy groups in aromatic groups increased their antioxidant properties. Especially, antioxidant activity of compounds **4a** and **4d** containing two methoxy groups increased more sharply. On the other hand, the substituted groups at C-4 position of pyrazoles also produced an effect on their antioxidant activities, for example, methyl substituted pyrazole **4a** had much better antioxidant property than phenyl substituted

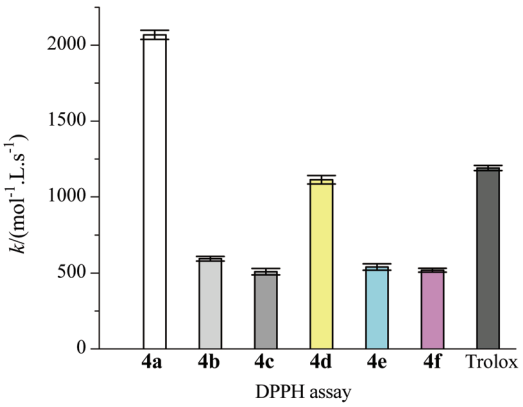

Figure 1 Radical scavenging activity of compounds **4a**—**4f** and Trolox in *N*,*N*-diphenyl-*N*′-picrylhydrazyl (DPPH) assay. Results were expressed as reduction rate costant (k) of DPPH±S.D. Significance was calculated according to the Student's t-test, $p<0.05$.

Table 2 Radical scavenging activity of compounds **4a**—**4f** and Trolox in DPPH and $ABST^+$ assays

Sample	IC_{50}/(μmol•L^{-1})	
	DPPH	$ABST^+$
4a	4.37±0.17	2.00±0.08
4b	14.97±0.96	2.26±0.15
4c	15.00±1.21	2.82±0.12
4d	5.51±0.21	2.18±0.13
4e	5.91±0.15	2.41±0.11
4f	7.28±0.28	4.48±0.25
Trolox	37.35±2.89	2.29±0.18

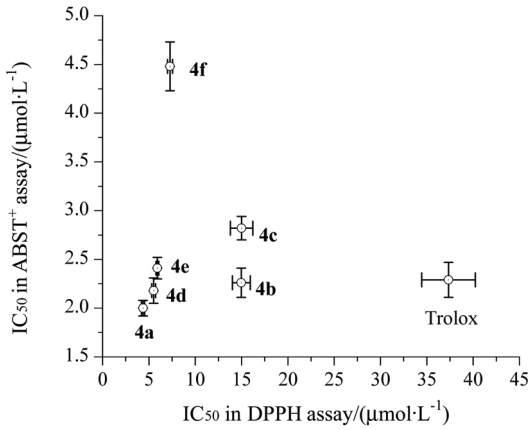

Figure 2 The 50% inhibitory concentrations (IC_{50}) against DPPH and $ABST^+$ for compouds **4a**—**4f** and Trolox.

pyrazole **4d**. In general, the activity order of them is as follows: syringyl (4-hydroxy-3,5-dimethoxyphenyl) modified bis(1*H*-pyrazol-5-ol)s>>guaiacyl (4-hydroxy-3-methoxyphenyl) modified bis(1*H*-pyrazol-5-ol)s > *p*-hydroxyphenyl modified bis(1*H*-pyrazol-5-ol)s.

The strong antioxidant abilities of these compounds indicated their potential usefulness in the drug devel-

opment, thus providing an effective approach for value-added application of lignin.

Conclusions

A series of novel bispyrazoles having arylmethylene substituent at the C-4 position were obtained from lignin and screened for their *in vitro* biological activities. Almost all compounds showed good DPPH and $ABST^+$ radical scavenging activities. The procedure is very environmentally benign, which were performed in water without catalysts in good to excellent yields. Compounds **4a** and **4d** showed the best antioxidant activities against DPPH and $ABST^+$. In addition, antioxidant activities of those compounds increased markedly with the introduce of the methoxy groups. What's more, these compounds were nontoxic,[3] which favored further studies to explore them as potential chemotherapeutic agents for tumors or other free radical induced deseases. Synthesis of heterocyclic compounds from lignin for pharmaceutical industry could obtain high value-added products from lignin.

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