

## Research Article

# Synthesis and Biological Evaluation of New (–)-Gossypol-Derived Schiff Bases and Hydrazones

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A series of 14 new (–)-gossypol Schiff bases and hydrazones have been synthesized via an in situ procedure in high yields. Structural data showed that all target compounds exist as the enamine tautomer. Bioassays showed that several compounds exhibited cytotoxic effects against three human cancer cell lines. Compound **8a** showed the greatest cytotoxic effect against hepatocellular carcinoma (HepG2), lung carcinoma (LU-1), and breast cancer (MCF-7) cell lines with IC<sub>50</sub> values of 20.93, 13.58, and 9.40 μM, respectively. However, in an antibacterial test, compounds **8a** and **8b** inhibited *Staphylococcus aureus* and *Bacillus cereus* and compound **8e** inhibited only *Staphylococcus aureus* at the same MIC values of 1024 μg/ml.

## 1. Introduction

Cancer is characterized by uncontrolled cell growth, metastasis, and invasion and is responsible for approximately 13% of all human deaths throughout the world [1]. The three most common and fatal types are lung, liver, and breast cancer. Currently, although there has been a lot of success in both cancer chemotherapy and anticancer drug development research, cancer remains a significant challenge in the future because of the drug resistance and adverse side effects of chemotherapy [2]. Novel antitumor agents based on natural products are becoming increasingly more popular in order to overcome these limitations and develop more effective anticancer agents [3].

Gossypol (**1**) (Figure 1), a polyphenolic dialdehyde found in high concentrations in the pigment glands of the cotton plant *Gossypium*, has recently received increased attention due to its wide range of biological activities, especially anticancer [4–7], contraceptive [8], antiviral [9–11], and antimicrobial [12] activities. However, the application of

gossypol as a therapeutic agent has been limited because of a number of serious side effects [13] that have been shown to be associated with the aldehyde groups. More recently, significant attention has been focused on the potential therapeutic value of gossypol as a promising starting point for the development of antitumor or antiviral derivatives for medicinal applications with enhanced bioactivity and reduced side effects [14–18], in which the aldehyde groups are altered to give gossypol derivatives (e.g., Schiff bases, esters, and ethers). Many of these derivatives exhibit a variety of unusual disease-inhibiting activities, especially anticancer activity [19]. Research regarding the biological effects of gossypol both *in vitro* and *in vivo* showed that the (–)-enantiomer is more potent than the (+)-enantiomer or the racemic mixture (**1**) [20]. It has also been hypothesized that while low doses of (–) gossypol are selective, higher doses of either enantiomer result in nonselective action [21, 22]. Also related to the mechanism of action, (–)-gossypol has been reported to target Bcl-2, Bcl-xL, and Mcl-1 proteins with high affinities and is now in clinical trials as an orally administered

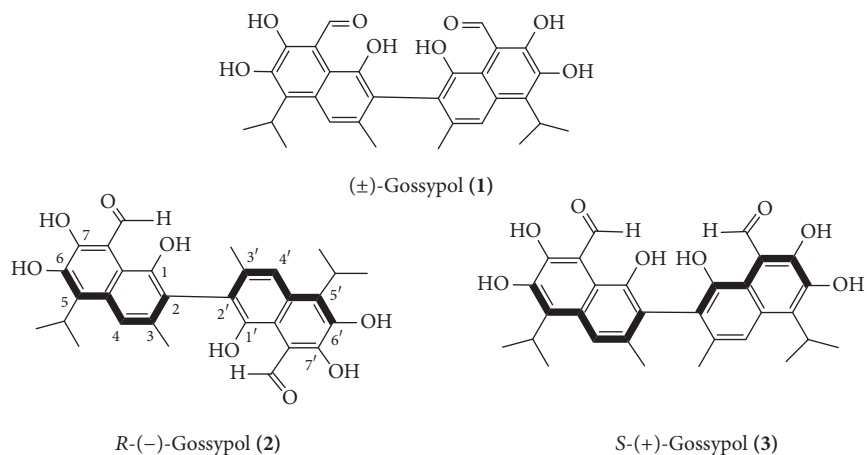
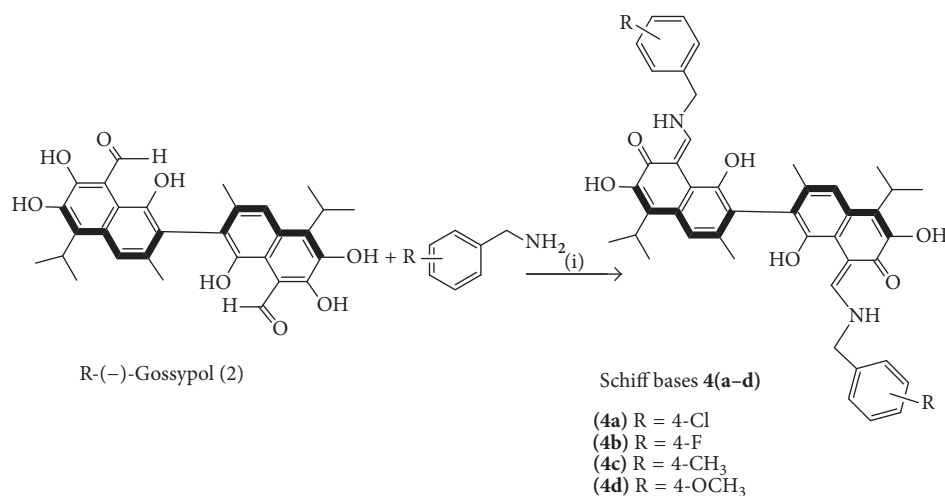


FIGURE 1: Racemic gossypol and its enantiomers.

SCHEME 1: Synthesis of (-)-gossypol Schiff bases **4a-d**; (i) EtOH, 8 h, r.t., 60.7–81.8%.

agent for the treatment of several types of human cancer [21, 22]. Intrigued by this observation, we synthesized and evaluated new (-)-gossypol hydrazones for their cytotoxic effects against three human cancer cell lines. This paper reports the results of this study.

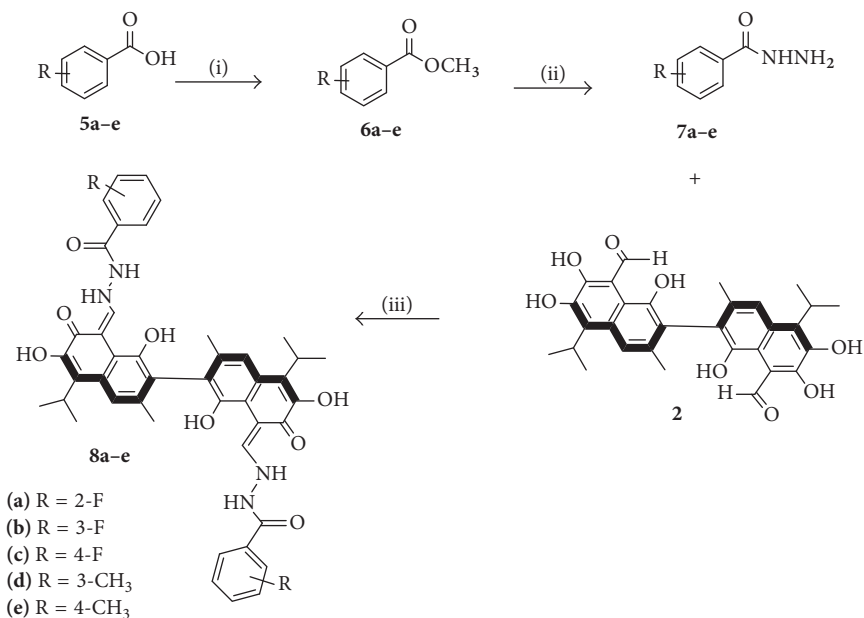
## 2. Results and Discussion

**2.1. Chemistry.** New Schiff bases and hydrazones of (-)-gossypol were synthesized as outlined (Schemes 1–3). The starting material (-)-gossypol was first prepared according to a known procedure with modification [23], using L-tryptophan methyl ester as an effective agent for the resolution of racemic gossypol. The yield of (-)-gossypol (**2**) obtained was comparable to that reported in the literature [23] (see Supplementary Material available online at <https://doi.org/10.1155/2017/3687182>).

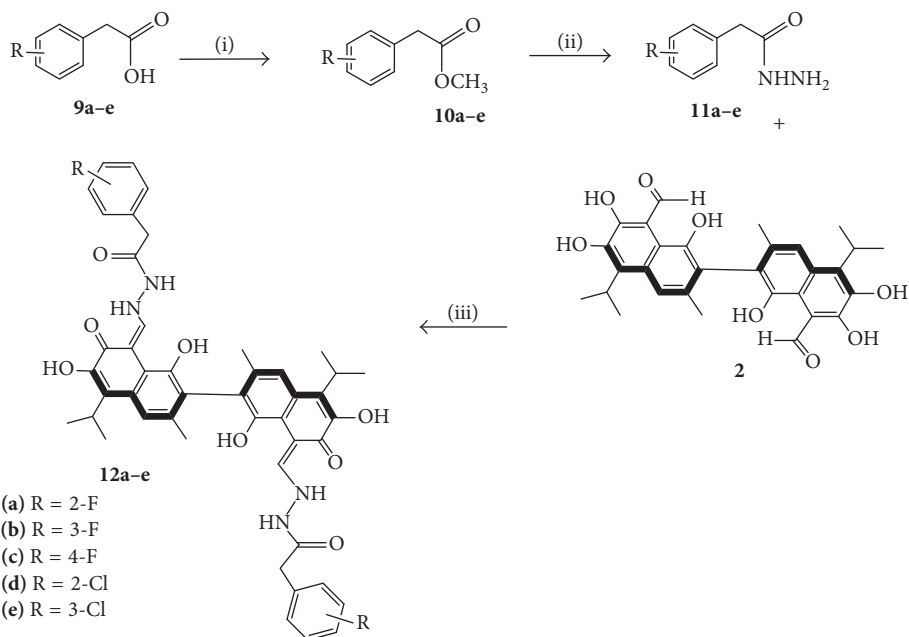
Schiff bases **4a-d** were synthesized (Scheme 1). The reactions of (-)-gossypol (**2**) with primary amines including 4-chlorobenzylamine, 4-fluorobenzylamine, 4-methylbenzylamine, and 4-methoxybenzylamine were conducted

in ethanol at room temperature for 8 h. The resulting Schiff bases **4a-d** were obtained by simple filtering and washing with methanol and dichloromethane. The NMR data showed the enamine-enamine tautomer of these Schiff bases via characteristic chemical shifts of NH protons resulting from hydrogen bonding formation ranging from 13.34 to 13.49 ppm in the <sup>1</sup>H NMR spectrum [24]. In the <sup>13</sup>C NMR spectrum, the chemical shifts of ketone C-7 were observed at the lowest field from 171.9 to 172.3 ppm, followed by the chemical shifts of C-6 around 162 ppm. The chemical shifts of C-1 were easily observed at around 149 ppm.

Novel hydrazones **8a-e** were synthesized in a three-step procedure as outlined (Scheme 2). First, benzoic acid derivatives **5a-e** were converted to the corresponding esters **6a-e** in quantitative yields by Fisher esterification. These esters were then refluxed with hydrazine hydrate (80%) in ethanol to give the corresponding hydrazides (**7a-e**) in high yields, which were then used for the next step without further purification. Unlike the case of Schiff bases **4a-d**, hydrazides (**7a-e**) were less active than the primary amines. Initially, hydrazides (**7a-e**) were reacted with (-)-gossypol (**2**) in ethanol at room



SCHEME 2: Synthesis of (-)-gossypol hydrazone **8a-e**; (i) MeOH, H<sub>2</sub>SO<sub>4</sub>, MeOH, reflux, 12 h; (ii) EtOH, NH<sub>2</sub>NH<sub>2</sub> (80%), r.t, 10 h; (iii) EtOH, ZnCl<sub>2</sub>, r.t, 16 h, 50.4–63.0%.



SCHEME 3: Synthesis of hydrazones **12a-e**; (i) MeOH, H<sub>2</sub>SO<sub>4</sub>, MeOH, reflux, 12 h; (ii) EtOH, NH<sub>2</sub>NH<sub>2</sub> (80%), r.t, 10 h; (iii) EtOH, ZnCl<sub>2</sub>, r.t, 12 h, 48.7–53.0%.

temperature for 16 h with very poor yields. The reaction was next carried out at reflux but failed to give the desired products owing to the decomposition of gossypol. Hydrazones are easily prepared in the presence of acetic acid as a catalyst. However, the reaction of **7a-e** with (-)-gossypol did not proceed as expected in the presence of acetic acid. In this study, ZnCl<sub>2</sub> was examined and found to be an excellent catalyst for the hydrazone formation. The reaction of hydrazides (**7a-e**) with (-)-gossypol (**2**) in the presence of a small amount of

ZnCl<sub>2</sub> led to the formation of a series of hydrazones (**8a-e**) in high yields. To the best of our knowledge, this is the first time that ZnCl<sub>2</sub> has been used as an effective catalyst for the synthesis of new gossypol hydrazones (**8a-e**). An analysis of <sup>1</sup>H and <sup>13</sup>C NMR spectra data showed that hydrazones **8a-e** exist as the enamine-enamine tautomer [24].

Compound **8c** was used as an example for the structural elucidation of hydrazones. The <sup>1</sup>H NMR spectrum of compound **8c** showed the characteristic resonance signal of

NH at the lowest field  $\delta$  14.76 ppm due to hydrogen bonding with the adjacent ketone group. The chemical shift at  $\delta$  12.39 ppm is attributed to the other NH group. Additionally, the resonance signal at  $\delta$  10.19 ppm as a sharp singlet is also attributed to 6-OH. The vinylic proton in the enamine is easily observed as a single peak at 8.81 ppm; signals at higher field belonging to the protons H-4 and 1-OH at  $\delta$  8.16 and 7.63 ppm, respectively, are coupled. Besides, the presence of the aromatic ring protons can be observed as doublets ( $J = 8.0$  Hz) at  $\delta$  8.02 and 7.37 ppm. The  $^{13}\text{C}$  NMR showed all the signals of the gossypol skeleton and aromatic rings in which the signals at 165.2 and 163.3 ppm are attributed to C-7 and C-6, respectively. The carbon connected to Fluorine in the aromatic ring resonates at  $\delta$  161.7 ppm, based on the characteristic splitting of Fluorine and the hydrazide carbonyl at  $\delta$  153.2 ppm.

Novel hydrazones **12a–e** were synthesized in the same way as mentioned above, starting from different phenylacetic acid derivatives (**9a–e**) (Scheme 3). The structure of synthesized hydrazones was confirmed similarly, based on NMR and mass spectroscopy data.

### 3. Biological Activity

The *in vitro* cytotoxic evaluation of the synthesized compounds was carried out according to the described protocol [25]. Briefly, a stock solution of the target compound was prepared in dimethylsulfoxide (DMSO) at a concentration of 1 mg/mL, followed by dilution to obtain a solution at a concentration of 100  $\mu\text{g/mL}$ , which was serially diluted further for bioassays in 96-well plates. The determination of  $\text{IC}_{50}$  was carried out using three cancer cell lines, HepG2, LU-1, and MCF-7, with ellipticine and (–)-gossypol as positive controls. The  $\text{IC}_{50}$  values were determined from a dose-dependent curve plotted from five different concentration regimens (0–100  $\mu\text{M}$ ). At each regimen, mean of triplicate experiment was used for a point in the curve. The bioassay results are described in Table 1.

The bioassay results (Table 1) showed that only half of the target compounds exhibited cytotoxic effects against cancer cell lines tested, ranging from 9.40 to 99.55  $\mu\text{M}$ . Unexpectedly, Schiff bases **4a–c**, bearing both electron withdrawing groups (Cl and F) and an electron donating group ( $\text{CH}_3$ ) at the *para* position of the aromatic ring, showed no cytotoxicity against all three cell lines except compound **4d**, which contains an electron donating group ( $\text{OCH}_3$ ). **4d** revealed a weak inhibitory effect against only the LU-1 cell line. For hydrazones **12a–e**, compounds **12c–e** containing electron withdrawing groups at *ortho*, *meta*, and *para* positions were inactive against all cell lines. However, compounds **12a** and **12b** containing electron withdrawing groups at *ortho* and *para* positions exhibited weak-to-moderate cytotoxic effects. The observation also shows that cytotoxic effects of hydrazones **8a–e** derived from benzoic acid derivatives were better than those of phenyl acetic acid derivatives, excluding compound **8e**, and that series **8a–d** were more cytotoxic towards MCF-7 and LU-1 than towards HepG2 cell line. It seems that the electron withdrawing group (F) at *ortho* position contributes towards greater toxicity compared to the *meta* position. In

terms of  $\text{IC}_{50}$  values, all synthesized hydrazones exhibited less potency than that of the control, ellipticine, or the parent (–)-gossypol and some other gossypol derivatives reported [16, 17]. Regarding mechanism of action, most of gossypol derivatives were reported to target Bcl-2 family proteins [20]. In this study, it is early and hard to come up with a mechanism of action at this stage without predicted binding models of designed hydrazones to such target protein as Bcl-2 or Mcl-1 [20–22]. However, it can be predicted that such possible target proteins as Bcl-2 or Mcl-1 participate in the mechanism of action.

Among synthesized hydrazones, compound **8a** showed the best cytotoxic effect against HepG2, LU-1, and MCF-7 with  $\text{IC}_{50}$  values of 20.93, 13.58, and 9.40  $\mu\text{M}$ , respectively. Accordingly, this compound could be considered as a lead for future design of gossypol hydrazones in which bioisosteric replacements in *ortho* position of the phenyl ring could be performed to improve the cytotoxic activity.

In order to expand the biological spectrum of gossypol derivatives, synthesized hydrazones were also evaluated for antibacterial activity against human pathogenic bacteria, including *Staphylococcus aureus* (ATCC 6538), *Bacillus cereus* (ATCC 21768), *Bacillus subtilis* (ATCC 6633), *Escherichia coli* (ATCC 25931), and *Pseudomonas aeruginosa* (ATCC 9027), according to described protocol [26]. Briefly, five bacterial species including two Gram-negative strains (*Escherichia coli* ATCC 25931 and *Pseudomonas aeruginosa* ATCC 9027) and three Gram-positive strains (*Bacillus subtilis* ATCC 6633, *Bacillus subtilis* ATCC 6633, and *Staphylococcus aureus* ATCC 6538) were obtained from the ATCC (Manassas, VA, USA). The bacterial strains were cultured aerobically on nutrient agar (NA) plates at 37°C for 24 h. For the antibacterial activity test, the bacteria were aerobically cultured in nutrient broth (NB) at 37°C for 24 h and then suspended in sterile saline at a density equivalent to that of the 0.5 McFarland standards. Bacterial suspensions with a concentration of 10<sup>5</sup> cfu/ml were used for *in vitro* antibacterial activity test.

The results (Table 2) showed that most of the synthesized hydrazones were inactive against the bacteria tested. Compounds **8a** and **8b** inhibited *Staphylococcus aureus* and *Bacillus cereus* and **8e** inhibited only *Staphylococcus aureus* at the same MIC values of 1024  $\mu\text{g/mL}$  and showed less bacterial activity than that of the parent compound, (–)-gossypol and some aza-derivatives of gossypol [24]. From the structure activity relationship, inactivity or weak activity of new hydrazones can be a result of the presence in its structure of the moieties attached to gossypol, which probably do not enable better interaction of these derivatives with the lipid bilayer of bacteria.

### 4. Conclusions

We have presented the synthesis of new Schiff bases and hydrazones of (–)-gossypol and screened for *in vitro* cytotoxic activity against several human cancer cell lines and antibacterial activity against human pathogenic bacteria. In this research, for the first time,  $\text{ZnCl}_2$  has been effectively used for the synthesis of gossypol hydrazones. Although no compounds were as effective as positive controls or gossypol

TABLE 1: Cytotoxic activity of target compounds.

Number	Compounds	IC <sub>50</sub> (μM)		
		HepG2	LU-1	MCF-7
(1)	<b>4a</b>	>100	>100	>100
(2)	<b>4b</b>	>100	>100	>100
(3)	<b>4c</b>	>100	>100	>100
(4)	<b>4d</b>	>100	66.83	>100
(5)	<b>8a</b>	20.93	13.58	9.40
(6)	<b>8b</b>	55.82	56.82	48.48
(7)	<b>8c</b>	89.72	79.83	86.40
(8)	<b>8d</b>	86.46	64.56	65.72
(9)	<b>8e</b>	>100	>100	>100
(10)	<b>12a</b>	55.68	54.70	63.33
(11)	<b>12b</b>	95.30	99.55	>100
(12)	<b>12c</b>	>100	>100	>100
(13)	<b>12d</b>	>100	>100	>100
(14)	<b>12e</b>	>100	>100	>100
(15)	Ellipticine	1.71	1.87	1.91
(16)	(-)-Gossypol	4.5	4.3	4.0

Note. The reference substance, ellipticine, exhibited cytotoxic activity against HepG2 (ATCC-HB 8065), LU-1 (ATCC-HTB-57), and MCF-7 (ATCC-HTB22) with IC<sub>50</sub> values of 1.71, 1.87, and 1.91 μM, respectively. The values shown for these compounds are the average of three determinations.

TABLE 2: Antibacterial activity of compounds against human pathogenic bacteria.

Number	Compounds	MIC (μg/ml)				
		<i>Staphylococcus aureus</i> (ATCC 6538)	<i>Bacillus cereus</i> (ATCC 21768)	<i>Bacillus subtilis</i> (ATCC 6633)	<i>Escherichia coli</i> (ATCC 25931)	<i>Pseudomonas aeruginosa</i> (ATCC 9027)
(1)	<b>4a</b>	—	—	—	—	—
(2)	<b>4b</b>	—	—	—	—	—
(3)	<b>4c</b>	—	—	—	—	—
(4)	<b>4d</b>	—	—	—	—	—
(5)	<b>8a</b>	1024	1024	—	—	—
(6)	<b>8b</b>	1024	—	1024	—	—
(7)	<b>8c</b>	—	—	—	—	—
(8)	<b>8d</b>	—	—	—	—	—
(9)	<b>8e</b>	1024	—	—	—	—
(10)	<b>12a</b>	—	—	—	—	—
(11)	<b>12b</b>	—	—	—	—	—
(12)	<b>12c</b>	—	—	—	—	—
(13)	<b>12d</b>	—	—	—	—	—
(14)	<b>12e</b>	—	—	—	—	—
(15)	Streptomycin sulfate	20	20	5	20	20
(16)	(-)-Gossypol	15	15	16	Nd*	Nd*

\* Not determined.

in terms of biological effects, the research could make contribution to the discovery of new gossypol derivatives based on research published herein.

## 5. Experimental

All chemicals and reaction solvents were purchased from Merck and Sigma-Aldrich. Melting points were determined

in open capillaries on a Shimadzu Electrothermal IA 9200 apparatus and uncorrected. IR spectra were recorded on a Impact 410 FTIR using KBr discs. 1D-NMR and 2D-NMR Spectra were recorded on a Bruker AVANCE 500 MHz spectrometer in CDCl<sub>3</sub> and DMSO-d<sub>6</sub>. Chemical shifts (δ) are in ppm relative to TMS; multiplicities are shown as follows: s (singlet), d (doublet), t (triplet), and m (multiplet); and coupling constants (*J*) are expressed in hertz (Hz). HRMS

was recorded by using a FT-ICR MS and ESI-TOF-MS Agilent 6230 spectrophotometer (Varian). Progress of the reaction was monitored by thin-layer chromatography (TLC) using precoated TLC sheets with ultraviolet (UV) fluorescent silica gel (Merck 60F254) and spots were visualized by UV lamp at 254 nm. Column chromatography was carried out using silica gel (40–230 mesh).

**5.1. Separation of (–)-Gossypol from (±)-Gossypol.** A solution of L-tryptophan methyl ester hydrochloride (9.824 g, 0.038 mol) and NaOH (1.52 g, 0.038 mol) in ethanol (60 mL) was stirred at 45°C, and the racemic gossypol (9.85 g, 0.019 mol) was added. The mixture was stirred for 2 h. The reaction was monitored by TLC and then allowed to warm to room temperature. The resulting precipitate from the reaction was then filtered, washed with cold ethanol, and dried under reduced pressure to obtain Schiff base intermediate (8.28 g, 95%). Schiff base intermediate (8.808 g, 9.59 mmol) was dissolved in a mixture of acetic acid and ether (4 : 1) (50 mL). The reaction mixture was kept at –5–0°C under nitrogen atmosphere, and concentrated hydrochloric acid (1.5 mL) was slowly added for 10 minutes. The reaction was then stirred at room temperature for 72 and monitored by TLC. After the completion of reaction, the resulting D-tryptophan methyl ester was filtered and washed by an amount of dichloromethane. The filtrate was concentrated to dryness and was dissolved in 30 mL of mixture of dichloromethane and *n*-hexane (2 : 1) and was kept at 4°C for crystallization. (–)-Gossypol was obtained by filtering and washing with cold acetone in 85.2% yield (4.23 g), 94.4% ee by HPLC.

**5.2. General Procedure for the Synthesis of Schiff Bases (4a–d).** A mixture of (–)-gossypol (100 mg, 1 eq, and 0.193 mmol) and corresponding amines (2.2 eq, 0.42 mmol) in EtOH (10 mL) was stirred at room temperature for 8 h. The resulting precipitate was then filtered and washed with cold methanol and dichloromethane to afford desired Schiff bases **4a–d**.

(*R*,8*Z*,8'*Z*)-8,8'-Bis(((4-chlorobenzyl)amino)methylene)-1,1',6,6'-tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-[2,2'-binaphthalene]-7,7'(8*H*,8'*H*)-dione (**4a**). Yield 77.8%; mp: 227–229°C; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): 13.45 (t, *J* = 5.5 Hz, 2H, NH), 9.85 (d, *J* = 12.5 Hz, 2H), 8.37 (s, 2H), 7.83 (s, 2H), 7.44 (m, 3H), 7.39 (d, *J* = 8.5 Hz, 4H), 4.75 (m, 4H, ArCH<sub>2</sub>), 3.69 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.94 (s, 6H, 2CH<sub>3</sub>), 1.43 (t, *J* = 7.0 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): 172.2, 162.4, 149.6, 146.2, 136.7, 132.4, 131.4, 129.4, 128.7, 126.9, 126.7, 120.3, 116.6, 115.8, 103.5, 52.3, 26.5, 20.3, 20.14. HR-ESIMS [M + H]<sup>+</sup> found 765.24945; calculated C<sub>44</sub>H<sub>43</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>6</sub> : 765.24982.

(*R*,8*Z*,8'*Z*)-8,8'-Bis(((4-fluorobenzyl)amino)methylene)-1,1',6,6'-tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-[2,2'-binaphthalene]-7,7'(8*H*,8'*H*)-dione (**4b**). Yield 81.8%; mp: 223–225°C; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): 13.47 (t, *J* = 5.0 Hz, 2H, NH), 9.87 (d, *J* = 12.5 Hz, 2H), 8.37 (s, 2H), 7.84 (s, 2H), 7.45–7.37 (m, 6H), 7.21 (m, 4H), 4.74 (brs, 4H, ArCH<sub>2</sub>), 3.70 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.94 (s, 6H, 2CH<sub>3</sub>), 1.43 (t, *J* = 6.5 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): 172.1, 162.6,

162.3, 160.7, 149.6, 146.2, 133.8, 131.3, 129.6, 126.9, 126.7, 120.3, 116.6, 115.6, 103.4, 52.3, 26.5, 20.3, 20.1. HR-ESIMS [M + H]<sup>+</sup> found 733.30890; calculated C<sub>44</sub>H<sub>43</sub>F<sub>2</sub>N<sub>2</sub>O<sub>6</sub> : 733.30892.

(*R*,8*Z*,8'*Z*)-8,8'-Bis(((4-methylbenzyl)amino)methylene)-1,1',6,6'-tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-[2,2'-binaphthalene]-7,7'(8*H*,8'*H*)-dione (**4c**). Yield 60.7%; mp: 211–213°C; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): 13.49 (t, *J* = 6.0 Hz, 2H, NH), 9.88 (d, *J* = 12.5 Hz, 2H), 8.36 (s, 2H), 7.86 (s, 2H), 7.45 (s, 2H), 7.26 (d, *J* = 8.0 Hz, 4H, Ar), 7.19 (d, *J* = 8.0 Hz, 4H, Ar), 4.70 (m, 4H, ArCH<sub>2</sub>), 3.69 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.28 (s, CH<sub>3</sub>), 1.93 (s, 6H, 2CH<sub>3</sub>), 1.43 (t, *J* = 7.0 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): 171.9, 162.4, 149.7, 146.2, 136.9, 134.5, 131.3, 129.3, 128.7, 127.5, 126.6, 126.6, 120.2, 115.8, 103.4, 52.9, 26.5, 20.6, 20.2, 20.1. HR-ESIMS [M + H]<sup>+</sup> found 725.35891; calculated C<sub>46</sub>H<sub>49</sub>N<sub>2</sub>O<sub>6</sub> : 725.35906.

(*R*,8*Z*,8'*Z*)-8,8'-Bis(((4-methoxybenzyl)amino)methylene)-1,1',6,6'-tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-[2,2'-binaphthalene]-7,7'(8*H*,8'*H*)-dione (**4d**). Yield 65.0%; mp: 230–232°C; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): 13.34 (s, 2H, NH), 9.89 (d, *J* = 7.0 Hz, 2H), 7.42 (s, 2H), 7.36–7.29 (m, 6H), 6.95–6.92 (m, 6H), 4.68 (br, 4H, 2CH<sub>2</sub>-Ph), 3.75 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.72 (s, 6H, OCH<sub>3</sub>), 1.98 (s, 6H, 2CH<sub>3</sub>), 1.45 (t, *J* = 7.0 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): 172.3, 162.5, 159.2, 158.9, 149.7, 131.2, 130.2, 129.3, 129.1, 126.6, 116.3, 114.2, 113.9, 103.4, 55.2, 52.7, 52.9, 26.5, 20.6, 20.2. HR-ESIMS [M + H]<sup>+</sup> found 757.34880; calculated C<sub>46</sub>H<sub>49</sub>N<sub>2</sub>O<sub>8</sub> : 757.34889.

**5.3. Representative Procedure for the Synthesis of Hydrazones (8a–e and 12a–e).** A mixture of 2-fluorobenzoic acid (**5a**) (1 g, 7.13 mmol) in MeOH (20 mL) was stirred for a few minutes. Concentrated H<sub>2</sub>SO<sub>4</sub> (1 mL) was added, and the mixture was refluxed for 12 h. The reaction was monitored by TLC using *n*-hexane, with ethyl acetate as a developing system. CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was then added, and the mixture was extracted with distilled H<sub>2</sub>O (3 × 20 mL). The organic phase was separated, dried on anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum to afford corresponding ester **6a** in almost quantitative yield in oil form (1.09 g). The oil was then dissolved in EtOH, and NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (3 eq) was added. The mixture was refluxed for 10 h. CH<sub>2</sub>Cl<sub>2</sub> (30 mL) was then added and extracted with distilled H<sub>2</sub>O (3 × 20 mL). The organic phase was separated, dried on anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated under vacuum to afford corresponding hydrazide **7a** in very good yield (white solid, 1.02 g, 93%) and used for next step. (–)-Gossypol (200 mg, 0.38 mmol) and ZnCl<sub>2</sub> (5 mg) were added to the solution of hydrazide **7a** (122 g, 0.80 mmol, and 2.1 eq) in ethanol (10 mL). The reaction was stirred at room temperature for 16 h. The resulting precipitate was then filtered and washed with cold methanol and dichloromethane to give hydrazone **8a**.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1',6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(2-fluorobenzohydrazide) (**8a**). Yield 50.4%; mp: 236–238°C; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): 14.53 (s, 2H, NH), 12.32 (s, 2H, NH), 10.09 (s,

2H), 8.82 (s, 2H), 8.17 (s, 2H), 7.69 (m, 2H), 7.61–7.56 (m, 4H), 7.36–7.32 (m, 4H), 3.91 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.99 (s, 6H, 2CH<sub>3</sub>), 1.48 (t, *J* = 7.0 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 160.2, 160.0, 158.3, 153.5, 150.8, 149.9, 133.1, 133.0, 132.8, 130.3, 128.7, 127.9, 124.7, 122.5, 122.4, 118.8, 116.3, 116.1, 115.9, 107.3, 56.0, 20.9, 20.5. HR-ESIMS [M + H]<sup>+</sup> found 791.28920; calculated C<sub>44</sub>H<sub>41</sub>F<sub>2</sub>N<sub>4</sub>O<sub>8</sub>: 791.28925.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1'*I*6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(3-fluorobenzohydrazide) (**8b**). Yield 63.0%; mp: 230–233°C; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): 14.69 (s, 2H, NH), 12.43 (s, 2H, NH), 10.20 (s, 2H), 8.83 (s, 2H), 8.19 (s, 2H), 7.79 (dd, *J* = 7.5 Hz, 4H), 7.63 (s, 2H), 7.58 (m, 2H), 7.46–7.42 (m, 2H), 7.69 (m, 2H), 7.61–7.56 (m, 4H), 7.36–7.32 (m, 4H), 3.91 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.99 (s, 6H, 2CH<sub>3</sub>), 1.48 (t, *J* = 7.0 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 162.9, 161.4, 160.9, 153.6, 150.7, 150.1, 143.9, 134.9, 132.7, 130.7, 128.7, 127.9, 123.9, 118.9, 118.7, 116.2, 114.6, 114.4, 107.3, 56.0, 26.0, 20.4.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1'*I*6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(4-fluorobenzohydrazide) (**8c**). Yield 57.9%; mp: 235–237°C; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): 14.76 (s, 2H, NH), 12.39 (s, 2H, NH), 10.19 (s, 2H), 8.81 (s, 2H), 8.16 (s, 2H), 8.02 (d, *J* = 8.0 Hz, 4H), 7.63 (s, 2H), 7.37 (d, *J* = 8.0 Hz, 4H), 3.92 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.03 (s, 6H, 2CH<sub>3</sub>), 1.50 (t, *J* = 6.0 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 165.2, 163.3, 161.7, 153.2, 150.8, 150.1, 143.9, 132.7, 130.4, 129.1, 128.64, 127.73, 118.87, 116.15, 115.90, 115.59, 115.42, 107.37, 56.0, 26.0, 20.4.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1'*I*6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(3-methylbenzohydrazide) (**8d**). Yield 57.8%; mp: 204–206°C; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): 14.77 (s, 2H, NH), 12.29 (s, 2H, NH), 10.16 (s, 2H), 8.81 (s, 2H), 8.80 (s, 2H), 8.12 (s, 2H), 7.75–7.72 (m, 4H), 7.62 (s, 2H), 7.40 (m, 4H), 3.91 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.37 (s, 6H, 2CH<sub>3</sub>), 2.02 (s, 6H, 2CH<sub>3</sub>), 1.47 (t, *J* = 5.5 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 165.79, 153.07, 150.72, 150.08, 137.83, 132.59, 132.51, 128.63, 128.39, 128.14, 127.65, 124.80, 118.84, 116.18, 107.39, 26.60, 20.91, 20.56.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1'*I*6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(4-methylbenzohydrazide) (**8e**). Yield 60.4%; mp: 213–215°C; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): 14.81 (s, 2H, NH), 12.28 (s, 2H, NH), 10.18 (s, 2H), 8.81 (s, 2H), 8.80 (s, 2H), 8.13 (s, 2H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.63 (s, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 2H), 3.92 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.37 (d, *J* = 10.5 Hz, 6H, 2CH<sub>3</sub>), 2.02 (s, 6H, 2CH<sub>3</sub>), 1.47 (t, *J* = 5.5 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 162.56, 152.91, 150.72, 150.09, 142.06, 141.68, 132.61, 129.73, 129.41, 129.02, 128.97, 127.66, 127.16, 118.81, 116.16, 107.41, 21.01, 20.96, 20.58. HR-ESIMS [M + H]<sup>+</sup> found 783.33931; calculated C<sub>46</sub>H<sub>47</sub>N<sub>4</sub>O<sub>8</sub>: 783.33939.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1'*I*6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(2-(2-fluorophenyl)acetohydrazide) (**12a**). Yield 51.7%; mp: 202–204°C; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): 15.26 (s, 2H, NH), 12.89 (s, 2H, NH), 10.83 (s, 2H), 9.61 (s, 2H), 9.03 (s, 2H), 8.44 (s, 2H), 8.23 (m, 2H), 8.16 (m, 2H), 8.01 (m, 4H), 4.73 (brs, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 4.48 (s, 4H, CH<sub>2</sub>-Ph), 2.83 (s, 6H, 2CH<sub>3</sub>), 2.31 (t, *J* = 5.0 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 165.21, 161.55, 159.61, 152.13, 150.81, 149.72, 143.83, 132.85, 131.95, 128.98, 127.65, 124.29, 122.53, 118.63, 116.02, 115.15, 114.98, 107.25, 33.84, 20.56, 20.51. HR-ESIMS [M + H]<sup>+</sup> found 819.32005; calculated C<sub>46</sub>H<sub>45</sub>F<sub>2</sub>N<sub>4</sub>O<sub>8</sub>: 819.32055.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1'*I*6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(2-(3-fluorophenyl)acetohydrazide) (**12b**). Yield 48.7%; mp: 188–190°C; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): 14.41 (s, 2H, NH), 12.04 (s, 2H, NH), 9.96 (s, 2H), 8.76 (s, 2H), 8.17 (s, 2H), 7.59 (s, 2H), 7.37 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 4H), 7.08 (m, 2H), 3.90 (brs, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.62 (s, 4H, CH<sub>2</sub>-Ph), 1.99 (s, 6H, 2CH<sub>3</sub>), 1.48 (t, *J* = 7.0 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 165.60, 163.01, 161.07, 152.21, 150.77, 149.73, 143.84, 138.21, 132.65, 130.21, 128.66, 127.68, 125.26, 118.62, 115.99, 115.81, 113.55, 107.21, 40.20, 26.55, 20.55.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1'*I*6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(2-(4-fluorophenyl)acetohydrazide) (**12c**). Yield 54.8%; mp: 195–197°C; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): 14.42 (s, 2H, NH), 12.00 (s, 2H, NH), 9.98 (s, 2H), 8.76 (s, 2H), 8.15 (s, 2H), 7.60 (s, 2H), 7.36–7.30 (m, 4H), 7.17–7.10 (m, 4H), 3.89 (brs, 2H, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.56 (s, 4H, CH<sub>2</sub>-Ph), 1.98 (s, 6H, 2CH<sub>3</sub>), 1.47 (t, *J* = 5.0 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 168.83, 166.03, 162.12, 160.19, 152.11, 150.78, 149.73, 143.83, 132.63, 128.85, 127.63, 118.62, 116.00, 115.11, 114.97, 107.22, 40.20, 26.50, 20.51.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1'*I*6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(2-(2-chlorophenyl)acetohydrazide) (**12d**). Yield 52.7%; mp: 206–208°C; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): 14.43 (s, 2H, NH), 12.07 (s, 2H, NH), 9.99 (s, 2H), 8.78 (s, 2H), 8.19 (s, 2H), 7.61 (s, 2H), 7.44 (m, 4H), 7.31 (m, 4H), 3.91 (brs, 2H, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.76 (s, 4H, CH<sub>2</sub>-Ph), 2.00 (s, 6H, 2CH<sub>3</sub>), 1.48 (t, *J* = 5.5 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 165.07, 152.03, 150.79, 149.71, 143.85, 133.55, 133.41, 132.64, 132.43, 132.15, 129.04, 128.91, 128.68, 127.63, 127.10, 118.62, 116.02, 107.25, 38.31, 20.55, 20.5.

*N*<sup>1</sup>,*N*<sup>'''</sup>-((1*Z*,1'*Z*)-((*R*)-1,1'*I*6,6'-Tetrahydroxy-5,5'-diisopropyl-3,3'-dimethyl-7,7'-dioxo-[2,2'-binaphthalene]-8,8'(7*H*,7'*H*)-diylidene)bis(methanylylidene))bis(2-(3-chlorophenyl)acetohydrazide) (**12e**). Yield 53.0%; mp: 194–196°C; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): 14.39 (s, 2H, NH), 12.04 (s, 2H, NH), 9.97 (s, 2H), 8.77 (s, 2H), 8.19 (s, 2H), 7.60 (s, 2H), 7.39–7.28 (m, 8H), 3.89 (brs, 2H, 2H, CH(CH<sub>3</sub>)<sub>2</sub>), 3.60 (s, 4H, CH<sub>2</sub>-Ph),

1.99 (s, 6H, 2CH<sub>3</sub>), 1.47 (t, *J* = 5.5 Hz, 12H, 4CH<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): 165.58, 152.24, 150.77, 149.72, 143.82, 137.89, 132.86, 130.15, 128.98, 128.65, 127.87, 127.69, 126.65, 118.63, 116.00, 107.21, 40.1, 20.55, 20.50. HR-ESIMS [*M* + *H*]<sup>+</sup> found 851.26141; calculated C<sub>46</sub>H<sub>45</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>8</sub> : 851.26144.

## Conflicts of Interest

The authors confirm that there are no conflicts of interest related to the contents of this article.

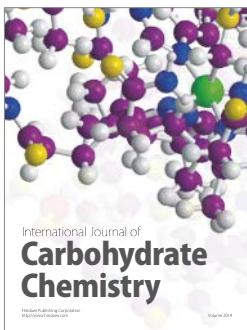
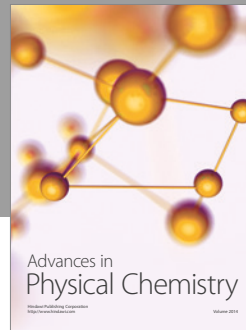
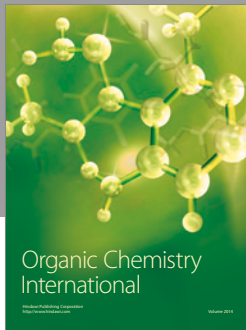
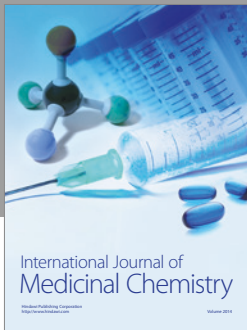
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