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Research Article

Design Synthesis and Biological Evaluation of Novel *N*-Nitro Acid Amide Derivatives as Lead Compounds of Herbicide

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A series of *N*-nitro acid amide derivatives compounds were synthesized based on the active site of target acetohydroxyacid synthase (AHAS, EC: 2.2.1.6) enzyme. All the structures of newly prepared compounds were thoroughly characterized by satisfied IR and ^{1}H NMR spectra. The IC_{50} values against AHAS enzyme and EC_{50} values for herbicidal activity against *Amaranthus mangostanus L.* and *Sorghum sudanense* of all synthesized target compounds were determined. The compounds **II-10**, **II-21**, and **II-22** with IC_{50} values of 7.09 mg/L, 9.07 mg/L, and 9.11 mg/L and the compounds **II-8** and **II-22** with EC_{50} values of 9.87 mg/L and 19.88 mg/L against root of *Amaranthus mangostanus L.* and *Sorghum sudanense* were illustrated, respectively. Meanwhile, the possible reasons for the lower activity of compounds were analyzed by molecular docking prediction.

1. Introduction

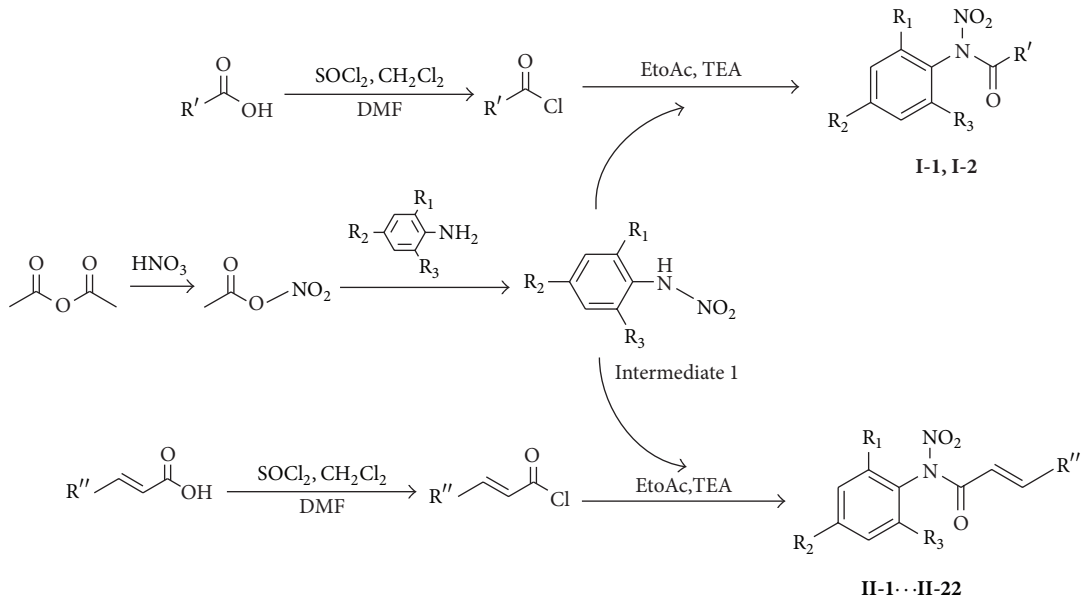
Weed management is a perennial challenge for growers, and continual innovation is essential to maintain the effectiveness of management technologies [1]. With the increasing numbers of herbicide-resistant weeds emergence [2, 3], there is an urgent need of new, more selective, and even more potent herbicides to control the unwanted vegetables.

N-nitro substituted anilines have been demonstrated to display diversely biological activities, including herbicidal properties [4], antifungal effects [5], and plant growth regulating activities [6]. Our laboratory has been engaged over the years to explore *N*-nitrourea compounds, and some of these compounds have acquired patents [7, 8]. Based on the similarity of structure between sulfonylureas and *N*-nitrourea compounds, we supposed they have the same targeted enzyme. Our hypothesis has been confirmed combining molecular docking and biological activity assay in our previous study [9]. Urea functionality is an attractive structural unit; it has displayed a broad range of biological activities, and it has been implicated in herbicidal [10], antifungal [11–17], antibacterial [18], plant growth regulator [19], and so on.

To further explore a series of novel structural potential compounds as excellent herbicides, an idea that joined the different trisubstituted *N*-nitro aniline and benzamides, cinnamic amides together were performed in this study. Twenty-four *N*-nitro acid amide derivatives compounds were synthesized, and all the target compounds were subject to biological activity tests against AHAS enzyme and herbicidal activity tests against *Amaranthus mangostanus L.* and *Sorghum sudanense*. Meanwhile, the possible reasons for the lower activity of target compounds were analyzed by molecular docking prediction.

2. Materials and Methods

2.1. Instrumentation and Chemicals. All chemical reagents were purchased from Shenshi Chemical Instrumentation Network Ltd. (Wuhan, China) at AR grade. ^{1}H NMR spectra were recorded on an AM-600 MHz spectrometer (Bruker, Bremen, Germany) with tetramethylsilane as interior reference and $CDCl_3$ as the solvent. Infrared (IR) spectra were acquired on an AVATAR330 infrared spectrometer (Nicolet, Waltham, MA, USA) with KBr compression method. Melting



R_1, R_2, R_3 = F, Cl, Br

R' = phenyl, -CH_3

R'' = phenyl, 4-OCH_3Ph, 4-ClPh, 2,4-di-ClPh, 3-NO_3Ph, 3-ClPh, 2-FPh, 4-CH_3Ph, thienyl

Scheme 1: The synthetic routes of target compounds.

points (m.p.) were determined on an X-4 digital display microscope melting point apparatus (Tech Instrument Co. Ltd., Beijing, China). The progress of the reactions was monitored by thin layer chromatography (TLC) on silica gel plates visualized with UV light.

2.2. General Procedure for Intermediate 1. The AC_2O (30 mmol) was added into a 50 mL round-bottomed flask and the temperature was controlled to 10°C, and HNO_3 (30 mmol) was slowly added over a period of 0.5 h, and then the reaction was stirred for about 0.5 h. Subsequently, the mixture was added into another 100 mL round-bottomed which contained 2,4,6-trisubstituted aniline (20 mmol) and acetic acid (25 mL) solvent over a period of 0.5 h, and the temperature was controlled to 15°C. The reactions were kept and stirred for about 1 h under the controlled temperature whilst monitoring its progress by TLC.

Then the mixtures were poured into ice water (200 mL), and a large amount of orange precipitate appeared. The orange precipitate was filtered under reduced pressure, dissolved into $NaHCO_3$ (5%, 30 mL) solution, and then HCl (2 mol/L) was added until the PH value of the solution reached 5-6 with a large amount of white precipitate that appeared again. Finally, the crude product was recrystallized from ethanol to get the intermediate 1. The spectra data of intermediate are included in the Supporting Information (see Supplementary Material available online at http://dx.doi.org/10.1155/2016/8583765).

*2.3. General Procedure for the Synthesis Target Compounds **II-2** and **III–22**.* Different substituted carboxylic acid (5 mmol) and $SOCl_2$ (7.5 mmol) were dissolved into CH_2Cl_2 (10 mL) solvent, two drops of *N*, *N*-dimethylformamide (DMF) as catalyst and triethylamine (TEA) (5 mmol) as acid-binding agent were added into the above solution. The reaction was executed for 12 h at room temperature under continuous stirring, which was detected by TLC. Then, the redundant CH_2Cl_2 solvent has been removed by reduced pressure distillation at 40°C. Finally, the crude product of different substituted acryloyl chlorides was obtained.

The intermediate 1 (3.5 mmol) was dissolved into 10 mL ethyl acetate solvent in the 100 mL round-bottomed flask, and the solution was kept into ice water bath. Then the obtained different substituted acryloyl chlorides in the previous step were dropped into the mixture solution over a period of 0.5 h; the reaction was kept and stirred for about 2 h under the controlled temperature whilst monitoring its progress by TLC. At the end of reaction, target compounds were got from silica gel column with eluent which consisted of petroleum ether and ethyl acetate, respectively. The synthetic route for target compounds **II-2** and **II1–22** is outlined in Scheme 1. The physicochemical properties of the target compounds were summarized in Table 1, and the spectra data, the ^1H NMR, and IR spectra of target compounds (as shown in Figure S1–Figure S48) are included in the Supporting Information.

2.4. Determination of IC_{50} Values for AHAS Enzyme. The AHAS enzyme assay of the target compounds was performed with the same method as our previously reported work [20]. All the IC_{50} values of each target compound for AHAS enzyme were calculated as described in the reference.

Table 1: The structure and physical data summary of all target compounds.

Number	$R_{1,2,3}$	R'	Yield/%
I-1	2,4,6-tri-Cl	Phenyl	45
I-2	2,4,6-tri-Br	$-CH_3$	42
Number	$R_{1,2,3}$	R''	Yield/%
II-1	2,4,6-tri-F	Phenyl	59
II-2	2,4,6-tri-F	4-OCH_3Ph	63
II-3	2,4,6-tri-F	4-ClPh	51
II-4	2,4,6-tri-F	2,4-di-ClPh	49
II-5	2,4,6-tri-F	3-NO_3Ph	45
II-6	2,4,6-tri-F	3-ClPh	43
II-7	2,4,6-tri-F	2-FPh	53
II-8	2,4,6-tri-F	4-CH_3Ph	49
II-9	2,4,6-tri-F	Thienyl	55
II-10	2,4,6-tri-Cl	Phenyl	57
II-11	2,4,6-tri-Cl	2,4-di-ClPh	62
II-12	2,4,6-tri-Cl	3-NO_3Ph	70
II-13	2,4,6-tri-Cl	3-ClPh	67
II-14	2,4,6-tri-Cl	2-FPh	44
II-15	2,4,6-tri-Cl	4-CH_3Ph	73
II-16	2,4,6-tri-Cl	Thienyl	56
II-17	2,4,6-tri-Br	Phenyl	53
II-18	2,4,6-tri-Br	4-OCH_3Ph	71
II-19	2,4,6-tri-Br	3-NO_2Ph	65
II-20	2,4,6-tri-Br	3-ClPh	41
II-21	2,4,6-tri-Br	2-FPh	57
II-22	2,4,6-tri-Br	Thienyl	50

2.5. Determination of the Herbicidal Activity. With reference to the "Agricultural Industry Standard of the People's Republic of China Pesticide Indoor Bioassay Test Criteria (herbicides) AGAR Method," the *Amaranthus mangostanus L.* and *Sorghum sudanense* as the target plant, the herbicidal activity of all target compounds were tested.

Each of the target compounds was dissolved in dimethyl sulfoxide (DMSO) solution to the concentration of 10000 mg/L, and then the solution was diluted with distilled water containing 0.1% Tween-80 to the concentration of 10, 50, 100, and 200 mg/L. The concentration of DMSO in all assays was maintained <1.5%. Twenty seeds of each plant including *Amaranthus mangostanus L.* and *Sorghum sudanense* were placed into a 9 cm diameter plate containing two pieces of filter paper and 9 mL solution of tested compound (0, 10, 50, 100, and 200 mg/L). The plate was placed in a greenhouse and allowed to germinate for 5 days at a temperature of 25 ± 1°C. The mixture of the same amount of water, DMSO, and Tween-80 was used as the control. Water was a blank control. Each treatment was repeated thrice and the lengths of roots and hypocotyl in each plate were measured and the means were calculated. DPS2000 standard statistical software for data processing system was utilized to perform the regression analysis for the EC_{50} values of each target compound.

3. Results and Discussion

3.1. Synthesis. The synthetic route for target compounds **I1-2** and **II1–22** is outlined in Scheme 1. Traditionally, the key trisubstituted phenyl-nitramines intermediate 1 was synthesized using nitric acid in the presence of acetic anhydride with low yield according to the reference method [21, 22]. In this study, the acetyl nitric acid ester was prepared first, and then trisubstituted phenyl-amine was added to obtain the intermediates 1 with high yield.

Then different substituted acryloyl chlorides were prepared with $SOCl_2$ (7.5 mmol), using DMF as catalyst and TEA as acid-binding agent in the presence of CH_2Cl_2 solvent. The different substituted acryloyl chlorides could not be achieved for their water and air sensitivity. Hence, different trisubstituted phenyl-nitramines intermediates 1 were directly added into the above reaction mixture in the presence of TEA to afford target compounds in 41–73% yields (as shown in Table 1).

3.2. Evaluation IC_{50} Values of Target Compounds against AHAS Enzyme. To estimate the IC_{50} values of target compounds against AHAS enzyme, the method of previous reported bioactive assay of AHAS in vitro was utilized by detecting the change in absorbance of acetoin at 525 nm using UV-Vis absorption spectrophotometry. All of the candidate compounds were dissolved in DMSO and its concentration was controlled at 1.5% in final reaction volume. The commercialized herbicide nicosulfuron was taken as a reference. The detailed experimental data were summarized in Table 2.

The result showed that the range of IC_{50} values of all the compounds was 7 mg/L–510 mg/L, and about three-quarters of IC_{50} values were <40 mg/L. Different trisubstituted phenyl target compounds showed some difference in activity against AHAS enzyme; the activity of 2,4,6-tri-Br and 2,4,6-tri-Cl substituted phenyl were similar and generally better than 2,4,6-tri-F substituted phenyl target compound. The compounds **II-10**, **II-21**, and **II-22** had the best biological activity in the all candidate compounds with IC_{50} values of 7.09 mg/L, 9.07 mg/L, and 9.11 mg/L, respectively. Although the inhibition rate of lead compound was lower than the commercial herbicides, we considered it would be able to act as a lead compound for the further study of structural optimization so as to improve the inhibitory activity to AHAS.

3.3. Determination EC_{50} Values of Target Compounds for Herbicidal Activity. The herbicidal activity of all the candidate compounds against *Amaranthus mangostanus L.* and *Sorghum sudanense* has been investigated at the dosages of 0, 10, 50, 100, and 200 mg/L according to the method described in the experimental section. The inhibition rate was increased with the concentration of the compound dose; most of the compounds EC_{50} did not exceed 100 mg/L. All of the results of bioassay testing were summarized in Table 3. According to the determination EC_{50} values for herbicidal activity, the target compounds exhibited higher herbicidal activity against both roots and hypocotyls of dicotyledonous plant *Amaranthus mangostanus L.* than monocotyledonous plant *Sorghum sudanense*. Most of target compounds showed

Table 2: The IC_{50} values results summary of candidate compounds against AHAS.

Number	IC_{50} (mg/L)
Nicosulfuron	0.068
I-1	21.06
I-2	29.75
II-1	23.52
II-2	37.6
II-3	28.66
II-4	28.25
II-5	36.2
II-6	10.43
II-7*	394.41
II-8	24.35
II-9*	273.38
II-10	7.09
II-11*	252.81
II-12	14.28
II-13	12.53
II-14	19.93
II-15*	301.96
II-16*	509.66
II-17c	14.64
II-18*	393.12
II-19	17.01
II-20	18.15
II-21	9.07
II-22	9.11

The concentrations of the "∗" target compounds were 100 mg/L, 200 mg/L, 300 mg/L, 400 mg/L, and 500 mg/L. The concentrations of the nicosulfuron were 0.01 mg/L, 0.025 mg/L, 0.05 mg/L, 0.075 mg/L, and 0.1 mg/L. The concentrations of the rest of the target compounds were 1 mg/L, 5 mg/L, 10 mg/L, 25 mg/L, and 50 mg/L.

Table 3: Herbicidal activity summary of target compounds.

Number	*Sorghum sudanense*		*Amaranthus mangostanus L.*	
	Root EC_{50} (mg/L)	Hypocotyl EC_{50} (mg/L)	Root EC_{50} (mg/L)	Hypocotyl EC_{50} (mg/L)
I-1	110.25	102.61	48.85	148.20
I-2	36.92	96.34	27.97	99.98
II-1	89.48	70.87	129.06	91.16
II-2	46.76	187.57	18.90	80.82
II-3	62.11	108.38	87.53	129.29
II-4	70.96	113.90	102.56	50.33
II-5	87.88	113.62	25.64	98.45
II-6	63.51	52.78	35.06	81.78
II-7	21.22	152.11	42.37	92.66
II-8	37.12	56.53	9.87	147.68
II-9	85.70	88.28	44.83	108.84
II-10	44.19	106.26	74.19	58.54
II-11	97.25	139.01	35.91	102.58
II-12	58.14	61.84	61.89	108.30
II-13	77.33	80.23	17.46	92.12
II-14	58.56	109.33	53.83	124.35
II-15	84.02	105.05	22.97	126.53
II-16	75.31	61.97	91.90	102.88
II-17	59.59	134.57	64.50	68.14
II-18	80.45	69.28	20.54	253.95
II-19	35.09	104.52	53.44	193.37
II-20	77.62	165.19	20.51	103.68
II-21	82.60	111.93	75.74	156.46
II-22	19.88	111.08	114.64	55.52

better inhibition activity against root than that of hypocotyl of the two testing plants.

The target compounds possessed higher herbicidal activity against root than that of hypocotyl. In particular, compounds **II-8** and **II-22** exhibited considerable herbicidal activity to root of *Amaranthus mangostanus L.* and *Sorghum sudanense* with EC_{50} values of 9.87 mg/L and 19.89 mg/L, respectively. The activity of 2,4,6-tri-F substituted phenyl target compounds was better than 2,4,6-tri-Br and 2,4,6-tri-Cl substituted phenyl type compounds, such as compounds **II-2**, **II-5**, **II-6**, **II-7**, **II-8**, and **II-9** with EC_{50} values of 18.90 mg/L, 25.64 mg/L, 35.06 mg/L, 42.37 mg/L, 9.87 mg/L, and 44.83 mg/L against the root of *Amaranthus mangostanus L.*

3.4. Analysis for the Lower Activity of the Target Compounds. Most of the synthesized target compounds showed lower activity than the commercial herbicides and the inconsistence between IC_{50} values and EC_{50} values in the biological testing. For the discrepancy reason we performed some analysis based on the compound structure and binding conformation in the active site of AHAS target.

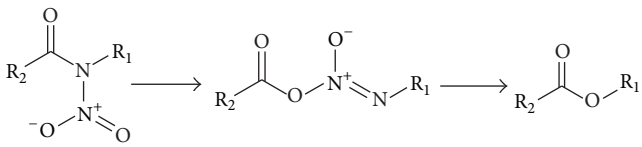
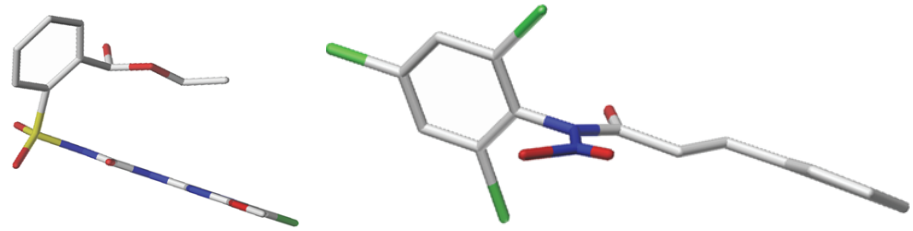


Figure 1: The rearrangement in the *N*-nitro amides part of the target compound.

First of all, all the target compounds possess *N*-nitro amides part which is unstable and usually occur rearrangement as reported in [23]. The part of target compound may rearrange during activity testing as shown in Figure 1, and the rearrangement may result in the reduced inhibition activity.

The interactions between candidate compounds and AHAS enzyme were predicted by molecular docking analysis. The structures of all compounds were sketched by Sybyl [24]. The Surflex docking module was performed in this study; the docking procedure and parameters were set the same as in our previous reported work [20]. Compared to the binding model of the known commercialized herbicide sulfonylureas and the characteristics of amino acids in the active site of AHAS, it was found that most of synthesized compounds form similar



(a) (b)

Figure 2: The comparison between the docking conformation of the known commercialized herbicide sulfonylureas (a) and the target compound **II-10** (b) in the active site of AHAS.

binding conformation in the active site of AHAS, as shown in Figure 2. However, further careful analysis found that the synthesized compounds cannot form fully orthogonal bend at the *N*-nitro amides group for strong conjugation formed between adjacent the phenyl and carbonyl. Although the *N*-nitro amides group and the adjacent aromatic ring are located in the entrance of channel leading to the active site, they could not very effectively prevent the substrate entrance. Thus the candidate compounds showed lower inhibition activity compared to sulfonylureas. Next, we would synthesize novel target compounds with canceled strong conjugation formed between adjacent phenyl and carbonyl.

4. Conclusions

Through this study, twenty-four *N*-nitro acid amide derivatives compounds were synthesized based on the active site of target AHAS enzyme, and all of the target compounds were performed biological testing against AHAS enzyme and herbicidal activity against *Amaranthus mangostanus L.* and *Sorghum sudanense*. Compounds **II-10**, **II-21**, and **II-22** with IC_{50} values of 7.09 mg/L, 9.07 mg/L, and 9.11 mg/L were confirmed, respectively. Compounds **II-8** and **II-22** exhibited considerable herbicidal activity to root of *Amaranthus mangostanus L.* and *Sorghum sudanense* with EC_{50} values of 9.87 mg/L and 19.88 mg/L, respectively. Further analysis was carried out based on the structure and interaction conformation in the active site of AHAS predicted by molecular docking to argue possible reason for the lower activity of target compounds. Based on the interaction mechanism analysis, further optimization for the lead compound would be performed to improve inhibition activity in our research group.

Disclosure

Xiaojuan Qi and Wenjie Tang both are co-first authors.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

Authors' Contributions

Xiaojuan Qi and Wenjie Tang contributed equally to this paper.

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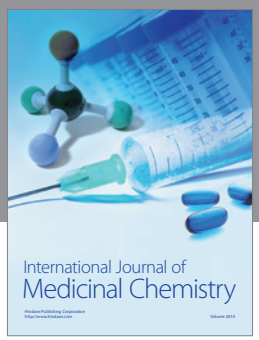

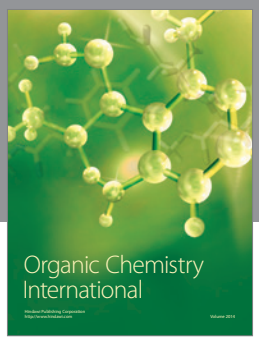

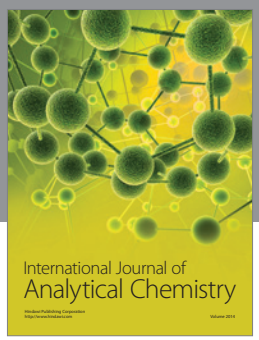

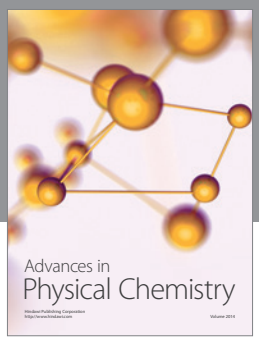

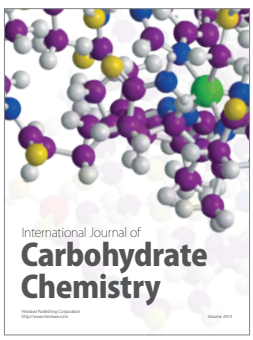

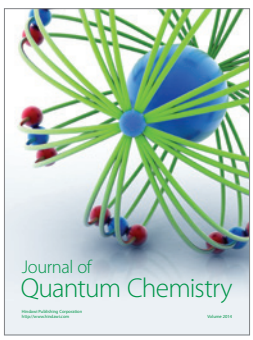

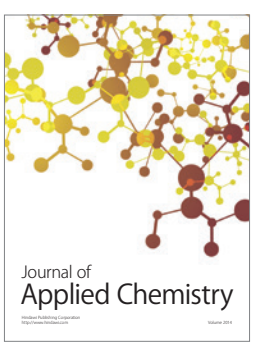

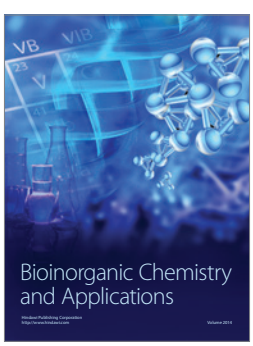

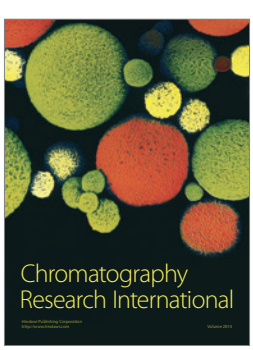

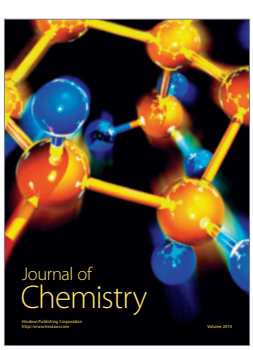

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