



Calix[4]resorcinarene-Chitosan Hybrid *via* Amide Bond Formation

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Hybrid of calix[4]resorcinarene and chitosan has been prepared *via* amide bond formation as the key step between ester groups attached on calix[4]resorcinarene and amine group of chitosan. The synthesis was commenced by functionalizing hydroxyl group of vanillin with methyl-2-chloroacetate *via* Williamson synthesis. The acid catalyzed-tandem condensation-cyclization of vanillin derivative and resorcinol gave C-4-methoxycarbonylmethoxy-3-methoxyphenylcalix[4]resorcinarene. The calix[4]resorcinarene installed with the ester group was then coupled with amine group of chitosan to form hybrid of calix[4]resorcinarene and chitosan. The IR, XRD and SEM analyses of the hybrid revealed that physical properties of the hybrid were similar to chitosan.

Keywords: Hybrid, Calix[4]resorcinarene, Chitosan.

INTRODUCTION

Calixarenes are versatile macrocyclic compounds which possess unique and intriguing structure. Their versatilities and selective properties were obtained from their molecular cavities, their variety of conformations and various functionalization on their cyclic structure^{1,2}. Many examples of calix[4]arenes have been synthesized and applied in various fields as host molecule, adsorbent³, extractant⁴, catalyst⁵, etc. However, another member of calixarenes, *i.e.* calix[4]resorcinarenes derived from resorcinol and aldehyde, have been less studied compared to calix[4]arenes.

Several studies, such as on sorption of metal ions, reported that calix[4]resorcinarenes displayed high affinity toward either metal anions or cations. Several functionalized calix[4]-resorcinarenes were proved to effectively remove metal cations, such as Pb(II) and Cd(II)¹. Despite the facts that calix[4]-resorcinarenes displayed good performance on the cation removal, the application of those sorbents in the industrial scale seems to be quite difficult due to the loss of sorbent on the sorption process and also the low efficiency for the regeneration. To address the problems, one strategy proposed was to chemically couple the calix[4]resorcinarenes with polymeric material in order to give hybrid with better performances such as higher sorption capacity and mechanical strength.

Hybrids prepared from calix[4]arenes and other materials have been widely studied and applied as host molecules installed with efficient ligands as well as biologically active

compounds. Moreover, calix[4]arenes have been combined with simple organic molecules^{6,7}, MCM-41⁸, polymer^{9,10}, sugars, peptides and oligonucleotides¹¹. Various routes have been employed to develop the hybrids such as carbonyl group addition^{7,11}, nucleophilic substitution, ionic hydrogenation and transition-metal-mediated reactions¹².

Searching for the precursor to be coupled with calix[4]-resorcinarenes, we considered to use chitosan. It could be derived from chitin (which is abundantly available from the exoskeleton of crustaceans) *via* deacetylation reaction. Chitosan is a linear polysaccharide which is primarily composed of (1 → 4) linked 2-amino-2-deoxy-*D*-glucopyranose units and residual 2-acetamido-2-deoxy-*D*-glucopyranose units. The presence of hydroxyl (OH) and amino group (NH₂) along the chain enables chitosan to coordinate with heavy metal ions^{13,14}. The important property of this biopolymer is the amine (NH₂) group which could be coupled with calix[4]resorcinarenes *via* carbonyl group addition, *i.e.* amide bond formation. In this paper, we would functionalize calix[4]resorcinarene with carboxylic acid derivative (ester) and couple it with chitosan *via* amidation reaction to construct the hybrid of calix[4]resorcinarene-chitosan.

EXPERIMENTAL

All the chemicals were purchased in pro analysis (p.a.) grade and utilized without further purification. Vanillin, 2-chloroacetic acid, resorcinol, sodium metal, H₂SO₄, HCl,

NaCl, NaHCO₃, Na₂SO₄, methanol, ethanol, dichloromethane and DMF were obtained from E. Merck, while chitosan was purchased from CV. Chemix Pratama.

The products were characterized by using melting point apparatus (Electrothermal 9100, without any correction), infrared (FTIR, Shimadzu Prestige 21), ¹H- and ¹³C nuclear magnetic resonance (¹H- and ¹³C NMR, Agilent VNMR 400 MHz) as well as gas chromatography-mass spectrometers (GC-MS, Shimadzu QP-2010S). Further characterizations of the hybrid calix[4]resorcinarene-chitosan were carried out by means of X-ray diffractometer (XRD, Shimadzu 6000) and scanning electron microscope (SEM, Jeol JSM T300).

Synthesis of methyl-2-chloroacetate (2): 2-Chloroacetic acid (**1**) (9.45 g, 0.1 mol) and methanol (9.60 g, 0.3 mol) were mixed together in the presence of concentrated sulfuric acid (0.1 mL). The mixture was then refluxed for 5 h. The reaction was quenched by the addition of saturated solution of NaCl (50 mL). The mixture was extracted with dichloromethane. The combined organic layer was, respectively washed with 10 % NaHCO₃ solution, water, dried and evaporated to give methyl-2-chloroacetate (**2**) as yellowish oil (70 % yield). ¹H NMR (400 MHz, CDCl₃): δ_H = 4.00 (s, 2H) and 3.70 (s, 3H) ppm. IR (neat, cm⁻¹): 1751 (C=O ester) and 1172 (C-O ester). MS (EI): *m/z*: 108 (M⁺).

Synthesis of 4-methoxycarbonylmethoxy-3-methoxybenzaldehyde (4): Sodium metal (0.38 g, 16.5 mmol) was added into 10 mL of methanol and the mixture was stirred until the metal was dissolved. The methanolate solution was then stirred with vanillin (**3**) (1.25 g, 8.2 mmol) for 15 min at 40 °C. The produced mixture was added dropwise into methyl 2-chloro acetate (**2**) (2.67 g, 24.6 mmol). The mixture was refluxed for 20 h. The reaction mixture was then evaporated to give the residue, which was then dissolved in water and was treated with 2M NaOH. The mixture was extracted with dichloromethane. The combined organic layer was washed with water, dried and evaporated to yield 4-methoxy-carbonylmethoxy-3-methoxybenzaldehyde (**4**) as dark yellow solid (97 % yield). ¹H NMR (400 MHz, CDCl₃): δ_H = 9.90 (s, 1H), 7.50 (m, 2H), 6.80 (s, 1H), 4.80 (s, 2H), 4.00 (s, 3H) and 3.7 (s, 3H). IR (KBr, ν_{max}, cm⁻¹): 2746 and 2854 (C-H aldehyde), 1751 (C=O ester), 1689 (C=O aldehyde) and 1172 (C-O ester). MS (EI): *m/z*: 224 (M⁺).

Synthesis of C-4-methoxycarbonylmethoxy-3-methoxyphenylcalix[4]resorcinarene (6): The mixture of produced benzaldehyde (**4**) (1.02 g, 4.54 mmol), resorcinol (**5**) (0.50 g, 4.54 mmol), conc. HCl (0.5 mL) in ethanol (10 mL) was refluxed for 20 h. The formed solid was filtered, washed with ethanol and dried to afford C-4-methoxycarbonylmethoxy-3-methoxyphenylcalix[4]resorcinarene (**6**) as white solid (88 % yield). ¹H NMR (400 MHz, DMSO-*d*₆): δ_H = 8.40 (s, 4H), 6.30 (m, 4H), 6.20 (s, 4H), 6.10 (s, 12H), 5.40 (s, 4H), 4.50 (s, 8H), 4.20 (q, 7, 1 Hz, 8H), 3.4 (s, 12H) and 1.2 (t, 7, 1 Hz, 12H). ¹³C NMR (400 MHz, DMSO-*D*₆): δ_C = 169.70, 152.50, 153.30, 148.20, 144.50, 138.10, 122.00 and 120.50 ppm. IR (KBr, ν_{max}, cm⁻¹): 1612 (C=C aromatic). MS (EI): *m/z*: 224 (M⁺).

Synthesis of calix[4]resorcinarene-chitosan hybrid (8): Calix[4]resorcinarene (**6**) (0.53 g, 0.40 mmol) and chitosan (**7**) (0.71 g, 4 mmol) were mixed in DMF (25 mL) and were

refluxed for 24 h. Then, water was added into the cooled reaction mixture to give the solid. The solid was filtered and dried to produce the calix[4]resorcinarene-chitosan hybrid as dark orange solid (28 % yield). IR (KBr, ν_{max}, cm⁻¹): 3448 (NH) and 1658 (C=O amide).

RESULTS AND DISCUSSION

In this study, calix[4]resorcinarene was employed as the main framework as it is rapid and easy to prepare comparing to calix[4]arene and calix[6]arene^{15,16}. Design of calix[4]resorcinarene as an adsorbent for heavy metal cation was conducted by introducing functional groups which have affinity towards the metal ion. Previous studies showed that incorporation of carboxylic acid or its derivatives on calixarenes could give high either adsorption or extraction performances for metal ion, such as Pb(II) ion^{2,4,17}. In addition, such groups offer various conversions into other groups and also enable calix[4]resorcinarene to be combined with polymeric material of chitosan to form calix[4]resorcinarene-chitosan hybrid.

Functionalization of calix[4]resorcinarene was performed on the benzaldehyde residues. On the other hand, the resorcinol residues were remained unfunctionalized as it could serve as coordinating site for metal ion. The benzaldehyde (**4**) was prepared from methyl ester (**2**) (derived from the corresponding acid *via* esterification) and vanillin (**3**) based on Williamson ether synthesis and was afforded in quantitative yield. Next, acid-catalyzed-condensation followed with cyclization reactions between aldehyde (**4**) and resorcinol (**5**) gave C-4-methoxycarbonylmethoxy-3-methoxyphenylcalix[4]resorcinarene (**6**) in 88 % yield. As predicted before, the ester group on the benzaldehyde residues was transesterified from methyl ester to ethyl ester as the reaction was carried out in ethanol in the presence of acid catalyst. This transformation was confirmed by NMR analysis. With the cyclic tetramer **6** in hand, we then prepared the calix[4]resorcinarene-chitosan hybrid (**8**). The key step of the hybrid formation was the amide bond formation between ethyl ester groups of calix[4]resorcinarene (**6**) and amine groups of chitosan **7** (Fig. 1).

Based on IR analysis (Fig. 2), the formation of the hybrid could be indicated from the peaks at 3448, 1658 and 1080 which represented secondary amine (-NH-), carbonyl amide (C=O) and C-N groups, respectively. Further analysis using XRD (Fig. 3) showed that **6** had higher crystallinity comparing to **7** and **8**. The crystal lattice of the hybrid **8** was similar to that of chitosan **7**. Both of them displayed the diffraction pattern at 2θ 10.1 and 20.1 representing the monoclinic system which was the main diffraction of chitosan^{14,18}. The SEM analysis (Figs. 4 and 5) for the three materials gave similar results as the XRD analysis. It was observed that both chitosan **7** and hybrid **8** had similar shape and morphology. The measured particle sizes of **6**, **7** and **8** were 23.85, 69.50, 179.25 μm. Furthermore, the pore diameters of **6**, **7** and **8** were 0.80, 1.56 and 5.7 μm. Among the three materials, the hybrid possessed the highest either particle size or pore diameter, indicating that calix[4]resorcinarene inserted to the lattice of chitosan and interacted with the amine group of chitosan (**7**), hence increased the pore diameter.

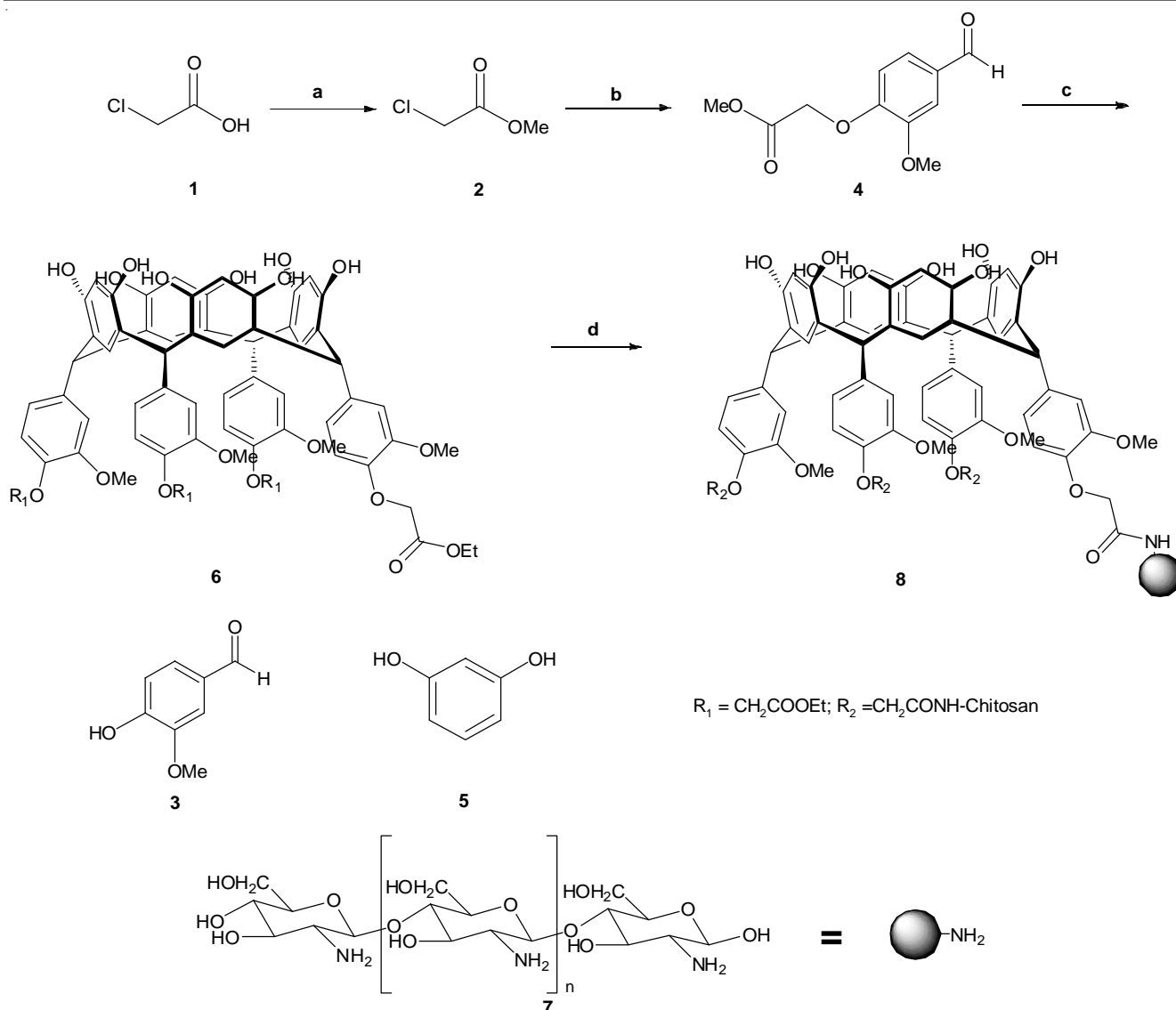


Fig. 1. Preparation of calix[4]resorcinarene-chitosan hybrid. Reaction condition: (a). MeOH, H_2SO_4 , reflux, 5 h; (b). 3, Na, MeOH, reflux, 20 h; (c). 5, HCl, EtOH, reflux, 20 h; (d). 7, DMF, reflux, 24 h

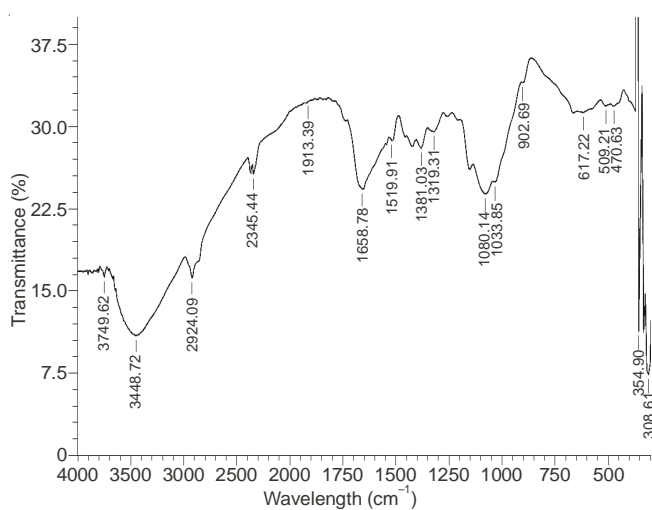


Fig. 2. IR spectrum of calix[4]resorcinarene-chitosan hybrid

For the future works, the synthesized hybrid calix[4]-resorcinarene-chitosan will be employed in the adsorption of heavy metal ions such as Pb(II) , Cd(II) and Cr(III) .

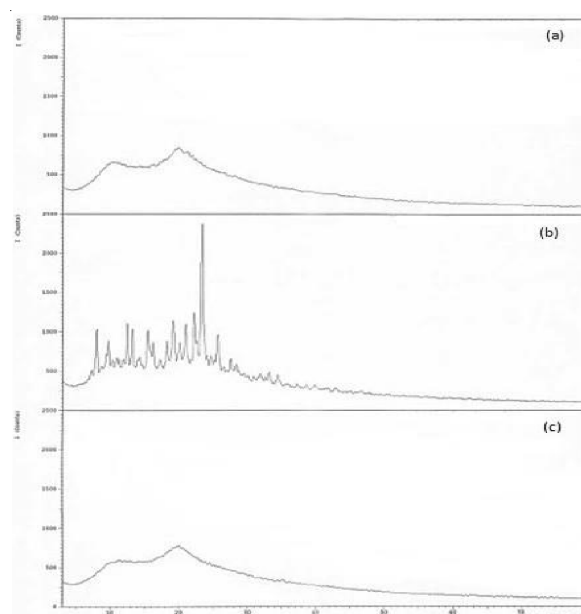


Fig. 3. Diffractogram XRD of: (a) calix[4]resorcinarene-chitosan hybrid; (b) calix[4]resorcinarene; and (c) chitosan

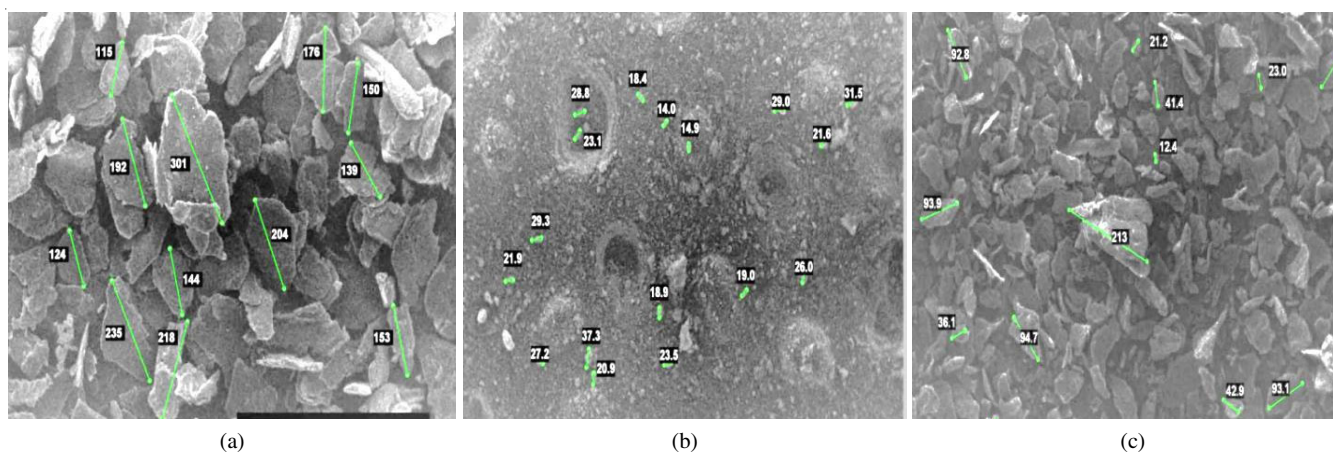


Fig. 4. SEM image 100x scale of: (a) calix[4]resorcinarene-chitosan hybrid; (b) calix[4]resorcinarene; and (c) chitosan

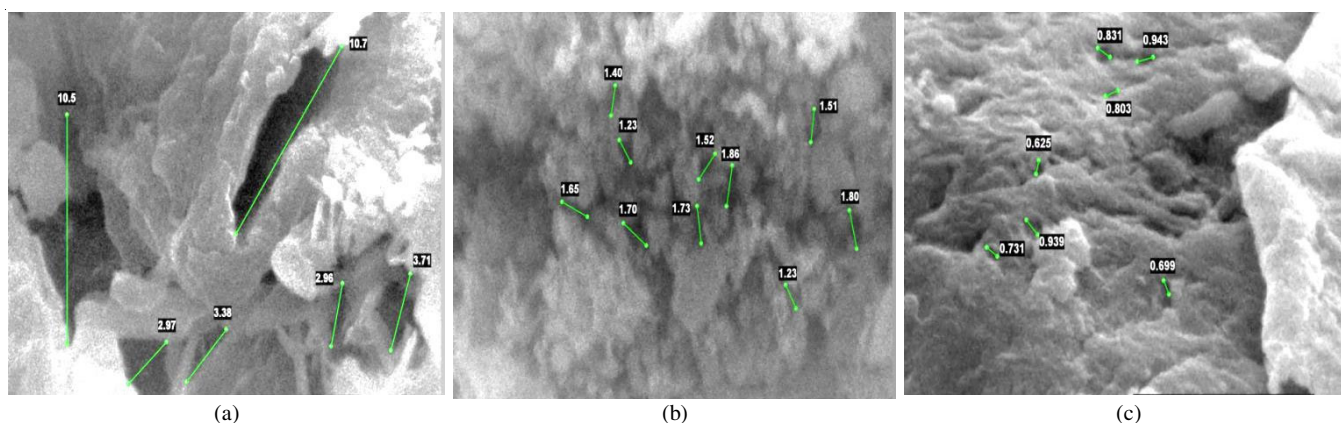


Fig. 5. SEM image 5,000x scale of: (a) calix[4]resorcinarene-chitosan hybrid; (b) calix[4]resorcinarene; and (c) chitosan

Conclusion

Another example of calix[4]resorcinarene **6** has been simply prepared from ester group-functionalized-vanillin **4** and resorcinol **5** via acid-catalyzed-condensation and cyclization reactions. The ester group installed on the benzaldehyde residue of calix[4]resorcinarene (**6**) could be coupled with the amino group of chitosan (**7**) to give the hybrid of calix[4]-resorcinarene-chitosan (**8**). The IR, XRD and SEM analyses of the hybrid revealed that the physical properties of the hybrid were similar to chitosan.

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REFERENCES

- S.B. Utomo, Jumina, D. Siswanta and Mustofa, *Indo. J. Chem.*, **12**, 49 (2012).
- B.B. Adhikari, M. Gurung, A.B. Chetry, H. Kawakita and K. Ohto, *RSC. Adv.*, **3**, 25950 (2013).
- D.S. Handayani, Jumina, D. Siswanta, Mustofa, K. Ohto and H. Kawakita, *Indo. J. Chem.*, **11**, 191 (2011).
- B.B. Adhikari, M. Gurung, H. Kawakita and K. Ohto, *Chem. Eng. Sci.*, **78**, 144 (2012).
- P. Nandi, A. Solovyov, A. Okrut and A. Katz, *ACS Catal.*, **4**, 2492 (2014).
- G.M. Consoli, E. Galante, C. Daquino, G. Granata, F. Consolo and C. Geraci, *Tetrahedron Lett.*, **47**, 6611 (2006).
- C. Sgarlata, V. Zito, G. Arena, G.M.T. Consoli, E. Galante and C. Geraci, *Polyhedron*, **28**, 343 (2009).
- Y.J. Li, B. Yan and L. Wang, *J. Solid State Chem.*, **184**, 2571 (2011).
- H.Y. Zhang, X.F. Qiao and B. Yan, *Inorg. Chem. Commun.*, **13**, 1231 (2010).
- X.F. Qiao, H.Y. Zhang and B. Yan, *Dalton Trans.*, **39**, 8882 (2010).
- S.J. Kim and B.H. Kim, *Nucleic Acids Res.*, **31**, 2725 (2003).
- S.P. Bew, R.A. Brimage, G. Hiatt-Gipson, S.V. Sharma and S. Thurston, *Org. Lett.*, **11**, 2483 (2009).
- N.V. Suc and H.T.Y. Ly, *J. Chem. Technol. Biotechnol.*, **88**, 1641 (2013).
- V.P. Raut and P.S. Jassal, *Energ. Environ. Eng. J.*, **1**, 68 (2012).
- Jumina, R.E. Sarjono, B.W. Paramita, D. Siswanta, S.J. Santosa, C. Anwar, H. Sastrohamidjojo, K. Ohto and T. Oshima, *J. Chin. Chem. Soc.*, **54**, 1167 (2007).
- Jumina, R.E. Sarjono, D. Siswanta, S.J. Santosa and K. Ohto, *J. Korean Chem. Soc.*, **55**, 454 (2011).
- B.B. Adhikari, K. Ohto and M.P. Schramm, *Chem. Commun.*, **50**, 1903 (2014).
- L.E. Abugoch, C. Tapia, M.C. Villamán, M. Yazdani-Pedram and M. Díaz-Dosque, *J. Food Hyd.*, **25**, 879 (2011).