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Efficient Synthesis of (*S*)-(+)-Clopidogrel Bisulfate-Capped Silver Nanoparticles

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In this manuscript primarily one-pot synthetic development in the preparation of clopidogrel bisulfate with a polymorphic crystalline form II in 90% yield was developed. This premade antiplatelet drug has been used to protect starch-stabilized silver nanoparticles (AgNPs).

Keywords

(*S*)-(+)-clopidogrel bisulfate, silver nanoparticles, functionalized silver nanoparticles

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Introduction

(*S*)-(+)-Clopidogrel bisulfate **1** (CLP) (Fig. 1), is a thienopyridine derivative as a potent oral antiplatelet agent often used in the treatment of coronary artery, peripheral vascular and cerebrovascular diseases.[1] This drug is one of the biggest selling drugs in the world. It can crystallize in various polymorphic crystalline forms and amorphous forms, but only forms I and II are used in pharmaceutical products.[2,3]

Nanoparticles (NPs) are promising as talented candidates for various biomedical applications such as enhanced resolution magnetic resonance imaging (MRI), drug delivery, tissue repair, cell and tissue targeting and transfection .[4-20] Silver nanoparticles (AgNPs) are a significant class of nanomaterial for a wide range of industrial and biomedical applications. The unique chemical properties of AgNPs make it a promising targeted delivery approach for drugs or gene specific cells. AgNPs also effectively inhibited integrin-mediated platelet functional responses like aggregation, secretion, adhesion to immobilized fibrinogen or collagen and retraction of fibrin clot in a dose-dependent manner, irrespective of the nature of agonists used.[21]

With increase use of AgNPs as drug carriers and their accepted antiplatelet property, it would be interesting to investigate its interaction with CLP. Here, synthetic improvement in the preparation of CLP also is described.

Experimental

Material and Measurements

$AgNO_3$ (99.9%), paraformaldehyde (PFA, 99%), *L*-camphorsulfonic acid (*L*-CSA), soluble starch and $NaBH_4$ (99%) were purchased from Merck. The FT-IR spectra for the samples were obtained using Shimadzu FT-IR-8900 spectrophotometer by using KBr pellets. All NMR data

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were recorded in DMSO-d_6 using Bruker Avance 500 MHz spectrometer. Chemical shifts are reported in ppm (δ) using deuterated solvents as internal references. Elemental analyses were made by a Carlo-Erba EA1110 CNNO-S analyzer and agreed with the calculated values. UV-Vis absorption spectra in the range 200-500 nm in EtOH were measured with a Shimadzu UV-2100 spectrophotometer. Melting points are uncorrected and determined by electrothermal 9100 melting point apparatus. The X-ray diffraction (XRD) patterns were recorded in a wide angle range (2θ = 10-70) by Phillips (pw-1840) X-ray diffractometer with Cu-Kα radiation. The morphology and particle sizes of synthesized powder were characterized by transmission electron microscope (TEM) images on a Phillips CM-10 instrument with an accelerating voltage of 100 kV.

One-pot procedure for the synthesis of racemic clopidogrel bisulfate (2)

To a vessel equipped with Dean-Stark assembly, 2-(thiophen-2-yl)ethanamine **5** (0.48 g, 4 mmol), PFA (0.13 g, 4.3 mmol) and toluene (6 mL) were added and the reaction mixture was refluxed for 2 h to obtain a yellow solution contain imine. After cooling to 20 °C, a solution of 6N HCl (0.7 mL) in DMF was added into the reaction mixture and continued to heat at 50 ^{o}C for 1 h to produce **4** as a white precipitate. The reaction was cooled to 25 °C and aqueous solution of 10 % Na_2CO_3 was added and stirred for 30 min. Then a solution of methyl-2-bromo-2-(2-chlorophenyl)acetate **3** (1.04 g, 4 mmol) in toluene (7 mL) was added to the reaction mixture. The reaction mixture stirred at r.t for 12 h. The aqueous layer is discarded and the organic layer was washed with water. The organic phase was evaporated, to afford viscose oil. To this oil, conc. H_2SO_4 (0.42 mL) and EtOAc (8 mL) was added. The mixture was stirred for 1 h. The precipitated crystals filtered off and washed with cool acetone. The pure racemic clopidogrel

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bisulfate **2** was dried in oven at 50 °C (1.35 g, 90% yield). White powder; mp 220-222 ºC; IR: *v* (KBr, cm^{-1}) 3434 (OH stretch), 3100, 2989, 2953, 1755 (C=O stretch), 1239, 1222 (C-O stretch), 1063.

Preparation of (S)-(+)-clopidogrel camphorsulfonate salt

The racemic clopidogrel bisulfate **2** (1.5 g, 3.75 mmol) and *L*-CSA (0.88 g, 3.75 mmol) were dissolved in acetone and stirred at r.t for 12 h. The formed precipitate was filtered, washed and dried to give a white solid as a (*S*)-clopidogrel camphor sulfonate salt (0.96 g, 75% yield), $[\alpha]_D$ = +25 (*c* = 1.68 % in CH_3OH); IR: *v* (KBr, cm^{-1}) 3454 (N-H stretch), 2975, 1756 (C=O stretch), 1735, (C=O stretch), 1630, 1506, 1473, 1439, 1263, 1234, 1157, 1030, 753, 724, 701.

Preparation of (S)-(+)-clopidogrel bisulfate (1, CLP)

The (*S*)-(+)-clopidogrel camphorsulfonate salt obtained (0.96 g, 4.8 mmol) was suspended in EtOAc and stirred vigorously at 10 ^oC. Subsequently, H_2SO_4 (0.3 g, 3 mmol) was added dropwise into mixture and stirred for 4 h and (*S*)-(+)-clopidogrel bisulfate **1** was obtained by the usual filtering, washing and drying (0.78 g, 85% yield); mp 176-178 ºC; $[\alpha]_D$ = +55.10 (*c* = 1.68 % in CH_3OH); IR: *v* (KBr, cm^{-1}) 3435 (O-H stretch), 3121, 2956, 2550, 2552, 1753, 1591, 1439, 1188, 1154, 1029; ^1H NMR (500 MHz, DMSO-d_6): δ 3.10 (s, 2H), 3.49 (s, 2H), 3.76 (s, 3H), 4.24 (s, 2H), 5.67 (s, 1H), 6.89 (d, 1H, *J* = 4.7 Hz), 7.44 (d, 1H, *J* = 5.1 Hz), 7.52-7.58 (m, 2H), 7.66 (dd, 1H, *J* = 1.5, 7.8 Hz), 7.72 (dd, 1H, *J* = 1.5, 7.4 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.3, 54.5, 66.4, 125.9, 126.3, 129.4, 131.1, 131.5, 132.5, 133.1, 135.1, 168.3; *Anal*. Calcd for $C_{16}H_{18}ClNO_6S_2$: C, 45.77; H, 4.32; N, 3.34. Found: C, 45.61; H, 4.39; N, 3.48.

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Preparation of (S)-(+)-clopidogrel bisulfate-coated silver nanopaticles (Ag@CLP)

A solution of $AgNO_3$ (0.082 g, 0.48 mmol) in ultrapure H_2O (10 mL) was prepared. To this solution were added 0.03 g soluble starch in 5.0 mL ultrapure H_2O and then the mixture was stirred heavily for 30 min in an ice bath. A solution of $NaBH_4$ (0.018 g, 0.48 mmol) in ultrapure H_2O (6 mL) was added dropwise to the aqueous solution, the color of solution suddenly turned to bright yellow, attributed to the formation of AgNPs. Then, the color of solution turned to black. On complete addition of $NaBH_4$, the resulting mixture was further stirred for 30 min at r.t. Then, a solution of CLP (0.403 g, 0.96 mmol) in EtOH (10 mL) was added to the reaction vessel, and then the mixture was stirred for further 4 h at this stage the color of solution was turned to dark brown. The suspension obtained was then centrifuged at 10,000 rpm for 15 min and the precipitate washed three times with double distilled H_2O to remove any water soluble impurity. After that, the precipitate was washed 3 times by dispersion and centrifugation using EtOH to remove excess CLP and excess reducing agent. The precipitate was then dried in an oven at 60 °C for 10 h and the pale gray powder was obtained.

Results and Discussion

In continuation to our interest in the design and synthesis of chemically and biologically medicinal heterocycles,[22-27] in this paper, we attempts to functionalized AgNPs covalently with the CLP (Ag@CLP). There are many routes to synthesis of CLP.[28-32] Herein; first we report an efficient modified synthesis of CLP with excellent yield and in high optical purity resolution. The one-pot synthesis of CLP **1** is depicted in Scheme 1. In this effort 2-(thiophen-2-yl)ethanamine **5** upon reaction with paraformaldehyde (PFA) and HCl (6 *N*) in toluene followed by electrophilic cyclization afforded tetrahydrothieno pyridine **4**. Subsequently, this intermediate

undergoes reaction with methyl-2-bromo-2-(2-chlorophenyl)acetate **3** and acetone/conc. H_2SO_4 to obtain a pure racemic **2**, which was resolved using *L*-camphorsulfonic acid (*L*-CSA) in acetone to afford (*S*)-(+)-clopidogrel bisulfate **1**.

The mp, IR, ^{1}H NMR, ^{13}C NMR, XRD, $[\alpha]_D$ and elemental analysis confirm that a polymorphic crystalline form II of **1** was produced.[3]

The synthesis of tetrahydrothieno pyridine **4** was optimized and the results are shown in Table 1. When this reaction was carried out in the presence of DMF.HCl and toluene, the yield of **4** was increased up to 90% (Table 1, Entry 2).

In other efforts, we examined several other bases and solvents to optimize the reaction conditions for preparation of **1**. The results are listed in Table 2. It was found that using toluene along with Na_2CO_3 led to higher yields in shorter reaction times (Table 2, Entry 5).

The kinetic resolution of prepared racemic clopidogrel bisulfate **1** was completed by using *L*-CSA. An optimization of the reaction parameter such as utilized *L*-CSA (in mmol), solvent and yield with respect to the final product concentration were performed. It was found that using 0.012 mmol *L*-CSA in acetone led to higher yields (Table 3, Entry 3). Subsequently, the obtained (*S*)-clopidogrel camphor sulfonate salt, was converted to (*S*)-(+)-clopidogrel bisulfate **1** in H_2SO_4 / EtOAc condition (Table 4, Entry 5).

For preparation of Ag@CLP, solution of $AgNO_3$ in ultrapure H_2O and starch as a capping agent under vigorous stirring was added to the round bottom flask. Subsequently, a modified Brust reaction[33] was carried out by addition of excess amount of $NaBH_4$ as reducing agent. In order to reduce all of the Ag^+ ions to metallic silver, the molar ratio of metal to the reducing agent was selected as 1:2 respectively. Then, EtOH solution of CLP (molar ratio CLP/Ag = 2:1) was added

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to the reaction vessel. The sulfur of CLP bind strongly to AgNPs surface by self-assembly.[25,34-35] Formation of Ag@CLP was monitored by IR, X-ray diffraction, UV-Vis and TEM. To achieve a fine nanosized particle the amylose was used as a green capping agent.[36]

The interaction between CLP and AgNPs was recognized by IR spectra of CLP and Ag@CLP (Figure S3 and S4). In both spectra the C=O, O-H of the HSO_4^-, N^+-H and aromatic C-H stretching vibration bands at 1753, 3435, 2552 and 3121 cm^{-1} were observed respectively. The $C=C_{sym}$ and $C=C_{asym}$ bands of thiophene for CLP and Ag@CLP were observed at 1439, 1591 cm^{-1} and 1444, 1590 cm^{-1} respectively, indicating that sulfur is attached to the AgNPs surface.[34]

The powder XRD patterns of the CLP and Ag@CLP are shown in Fig. 2. The peaks position of the CLP were observed at 2θ = 8.87°, 13.04°, 17.76°, 18.59°, 20.24°, 21.69°, 23.04°, 23.86°, 24.79°, 26.61°, 27.72°, 29.44°, 34.30°, 35.76°, 41.15° and 48.68° (Figure 2a). This pattern correlated well with the crystalline structure of form II.[3] In Figure 2b, the characteristic peaks of AgNPs were at 2θ = 38.24°, 44.43° and 64.56° respectively, assigned as (111), (200) and (220) reflection lines of the face centered cubic (fcc) structure of metallic silver. The average crystallite size, D, was calculated from Scherrer's equation to be 29 nm while $D = K\lambda/(\beta cos\theta)$ and λ is the wavelength of Cu-Kα radiation used (λ = 1.54 ˚A), β is the full width at half-maximum (FWHM) intensity (0.31) of the diffraction line, θ is the Bragg angle for the measured *hkl* peak, and K is a constant equal to 0.94. This value is in good agreement with the TEM image. The intensity of peaks reflected the high degree of crystallinity of the AgNPs.

UV-Vis Absorption Spectra

Fig. 3, illustrates the UV-Vis absorption spectra of CLP and Ag@CLP in EtOH solution. The pure CLP, shows a λ_{max} at 243 nm corresponds to the π-π* transition of the chlorobenzene and

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thiophene moiety while, solution of Ag@CLP shows absorption peaks at 243 and 412 nm corresponds to CLP and surface plasmon resonance absorption band (SPRAB) of AgNPs, respectively. The weaker absorption band of Ag@CLP, compared to absorption band of free CLP at 243 nm, confirms a lower concentration of CLP on AgNPs. The appearance of two new peaks at 297 and 346 nm probably are related to the formation of Ag-CLP complex.

TEM Imaging

The TEM of Ag@CLP image reveals that particles are spherical shape with approximate size of < 40 nm; Scherrer's calc. = 29 nm (Fig. 4).

Conclusions

We have developed one-pot process for the synthesis of polymorphic crystalline form II CLP and utilizing a novel method for adsorption of premade CLP molecule on AgNPs surface. The sulfur of CLP bind strongly to AgNPs surface by self-assembly as confirmed by IR and UV-Vis. This Ag@CLP system may provide an advantage model system for the development of new effective antiplatelet drug.

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References

1. Jarvis, B.; Simpson, K. Clopidogrel: A review of its use in the prevention of atherothrombosis. *Drugs* **2000**, 60, 347-377.

2. Javeed, M. S. M.; Merwade, A. Y.; Khan, A. R. A novel process for the manufacture of (+)-(S)-clopidogrel bisulfate form-i. W.O. Patent 2005/012300 A1. 2005.

3. Koradia, V.; Chawla, G.; Bansal, A. K. Qualitative and quantitative analysis of clopidogrel bisulphate polymorphs. *Acta. Pharm.* **2004**, 54, 193-204.

4. Torchilin, V. P. Multifunctional nanocarriers. *Adv. Drug. Deliv. Rev*. **2006**, 58, 1532-1555.

5. Sun, C.; Lee, J. S. H.; Zhang, M. Magnetic nanoparticles in MR imaging and drug delivery. *Adv. Drug. Deliv. Rev*. **2008**, 60, 1252-1265.

6. Gao, X. H.; Cui, Y. Y.; Levenson, R. M.; Chung, L. W. K.; Nie, S. M. In vivo cancer targeting and imaging with semiconductor quantum dots. *Nat. Biotechnol*. **2004**, 22, 969-976.

7. Sanvicens, N.; Marco, M. P. Multifunctional nanoparticles-properties and prospects for their use in human medicine. *Trends. Biotechnol*. **2008**, 26, 425-433.

8. Ogino, C.; Shibata, N.; Sasai, R.; Takaki, K.; Miyachi, Y.; Kuroda, S.; Ninomiya, K.; Shimizu, N. Construction of protein-modified TiO_2 nanoparticles for use with ultrasound irradiation in a novel cell injuring method. *Bioorg. Med. Chem. Lett*. **2010**, 20, 5320-5325.

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9. Tom, R. T.; Suryanarayanan, V.; Reddy, P. G.; Baskaran, S.; Pradeep, T. Ciprofloxacin-protected gold nanoparticles. *Langmuir* **2004**, 20, 1909-1914.

10. QingShan, W.; Jian, J.; JinHong, F.; JiaCong, S. Norvancomycin-capped silver nanoparticles. *Sci. China. Ser. B-Chem*. **2007**, 50, 418-424.

11. Cinta, S.; Iliescu, T.; Astilean, S.; David, L.; Cozar, O.; Kiefer, W. 1,4-Benzodiazepine drugs adsorption on the Ag colloidal surface. *J. Mol. Struct*. **1999**, 482/483, 685-688.

12. Mirza, A. Z.; Shamshad, H. *Eur. J. Med. Chem.* Preparation and characterization of doxorubicin functionalized gold nanoparticles. **2011**, 46, 1857-1860.

13. Gibson, J. D.; Khanal, B. P.; Zubarev, E. R. Paclitaxel-functionalized gold nanoparticles. *J. Am. Chem. Soc*. **2007**, 129, 11653-11661.

14. Whaley, S. R.; English, D. S.; Hu, E. L.; Barbara, P. F.; Belcher, A. M. Selection of peptides with semiconductor binding specificity for directed nanocrystal assembly. *Nature* **2000**, 405, 665-668.

15. Goldman, E. R.; Balighian, E. D.; Mattoussi, H.; Kuno, M. K.; Mauro, J. M.; Tran, P. T.; Anderson, G. P. Avidin: a natural bridge for quantum dot-antibody conjugates. *J. Am. Chem. Soc*. **2002**, 124, 6378-6382.

16. Bhattacharya, S.; Srivastava, A. Synthesis and characterization of novel cationic lipid and cholesterol-coated gold nanoparticles and their interactions with dipalmitoylphosphatidylcholine membranes. *Langmuir* **2003**, 19, 4439-4447.

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17. Ni, J.; Lipert, R. J.; Dawson, G. B.; Porter, M. D. Immunoassay readout method using extrinsic raman labels adsorbed on immunogold colloids. *Anal. Chem*. **1999**, 71, 4903-4908.

18. Goldman, E. R.; Anderson, G. P.; Tran, P. T.; Mattoussi, H.; Charles, P. T.; Mauro, J. M. Conjugation of luminescent quantum dots with antibodies using an engineered adaptor protein to provide new reagents for fluoroimmunoassays. *Anal. Chem.* **2002**, 74, 841-847.

19. Joshi, H. M.; Bhumkar, D. R.; Joshi, K.; Pokharkar, V.; Sastry, M. Gold nanoparticles as carriers for efficient transmucosal insulin delivery. *Langmuir* **2006**, 22, 300-305.

20. Gu, H. W.; Ho, P. L.; Tong, E.; Wang, L.; Xu, B. Presenting vancomycin on nanoparticles to enhance antimicrobial activities. *Nano. Lett*. **2003**, 3, 1261-1263.

21. Shrivastava, S.; Bera, T.; Singh, S. K.; Singh, G.; Ramachandrarao, P.; Dash, D. Characterization of antiplatelet properties of silver nanoparticles. *ACS. Nano*. **2009**, 3, 1357-1364.

22. Sharifzadeh, B.; Mahmoodi, N. O.; Mamaghani, M.; Tabatabaeian, K.; Salimi Chirani, A.; Nikokar, I. Facile regioselective synthesis of novel bioactive thiazolyl-pyrazoline derivatives via a three-component reaction and their antimicrobial activity. *Bioorg. Med. Chem. Lett*. **2013**, 23, 548-551.

23. Mahmoodi, N. O.; Safari, N.; Sharifzadeh, B. One-Pot synthesis of novel 2-(thiazol-2-yl)-4,5-dihydropyridazin-3(2h)-one derivatives catalyzed by activated KSF. *Synth. Commun.* **2014**, 44, 245-250.

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24. Mahmoodi, N. O.; Rineh, A.; Abdollahi, M.; Foroumadi, A.; Sorkhi, M.; Shafiee, A. Synthesis, analgesic and anti-inflammatory activity of 4-(2-phenoxyphenyl)semicarbazones. *Archiv. Der. Pharmazie*. **2007**, 340, 409-415.

25. Ghavidast, A.; Mahmoodi, N. O.; Zanjanchi, M. A. Synthesis and photochromic properties of a novel thiol-terminated 1,3-diazabicyclo[3.1.0]hex-3-ene on silver nanoparticles. *J. Mol. Struct*. **2013**, 1048, 166-171.

26. Ghavidast, A.; Mahmoodi, N. O.; Zanjanchi, M. A. Synthesis and photochromic properties of disulfide-1,3-diazabicyclo[3.1.0]hex-3-ene functionalized silver nanoparticles. *J. Mol. Liq*. **2014**, 198, 128-133.

27. Zare, L.; Mahmoodi, N. O.; Yahyazadeh,, A.; Mamaghani, M.; Tabatabaeian, K. An efficient one-pot synthesis of pyridazinones and phthalazinones using HY-zeolite. *J. Heterocyclic. Chem.* **2011**, 48, 864-867.

28. Madivada, L. R.; Anumala, R. R.; Gilla, G.; Kagga, M.; Bandichhor, R. An efficient and large scale synthesis of Clopidogrel: Antiplatelet drug. *Der. Pharma. Chemica*. **2012**, 4, 479-488.

29. Kim, J. S.; Kim, N. H.; Lee, N. K.; Lee, J. Y. Process for the preparation of S-(+)-clopidogrel by optical resolution. U.S. Patent 2009/0275755 A1, 2009.

30. Reddy, A. V.; Rao, V. K.; Kumari, S. A.; Reddy, B. S.; Reddy, B. R.; Reddy, G. S.; Raghumitra, A. Process for preparation of clopidogrel bisulfate form 1. W.O. Patent 2007/094006 A1. 2007.

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31. Lixin, W.; Jianfen, S.; Yi, T.; Yi, C.; Wen, W.; Zegui, C.; Zhenjun, D. Synthetic improvements in the preparation of clopidogrel. *Org. Process. Res. Dev.* **2007**, 11, 487-489.

32. Li, J. J.; Johnson, D. S.; Sliscovic, D. R.; Roth, B. D. Contemporary Drug Synthesis; John Wiley & Sons, Inc., 2004; pp 4-9.

33. Brust, M.; Walker, M.; Bethell, D.; Schiffrin, D. J.; Whyman, R. Synthesis of thiol-derivatised gold nanoparticles in a two-phase Liquid-Liquid system. *J. Chem. Soc. Chem. Commun*. **1994**, 7, 801-802.

34. Lee, C. J.; Karim, M. R.; Lee, M. S. Synthesis and characterization of silver/thiophene nanocomposites by UV-irradiation method. *Mater. Lett*. **2007**, 61, 2675-2678.

35. Love, J. C.; Estroff, L. A.; Kriebel, J. K.; Nuzzo, R. G.; Whitesides, G. M. Self-assembled monolayers of thiolates on metals as a form of nanotechnology. *Chem. Rev*. **2005**, 105, 1103-1169.

36. Raveendran, P.; Fu, J.; Wallen, S. L. Completely "green" synthesis and stabilization of metal nanoparticles. *J. Am. Chem. Soc*. **2003**, 125, 13940-13941.

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Table 1. Reaction conditions for the synthesis of tetrahydrothieno pyridine **4**.

Entry	Utilized Acid	Solvent	Yield (%)
1	DMF.HCl	$C_2H_4Cl_2$	80
2	DMF.HCl	Toluene	90
3	*i*-Pr.HCl	$C_2H_4Cl_2$	75
4	*i*-Pr.HCl	Toluene	80
5	*p*-TSA	Toluene	65

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Table 2. Reaction conditions for the synthesis of racemic-CLP.

Entry	Solvent	Base	Time (h)	Yield (%)
1	$C_2H_4Cl_2$	NEt_3	6	80
2	$C_2H_4Cl_2$	Na_2CO_3	10	85
3	DMF	K_2CO_3	5	80
4	Toluene	NEt_3	5	85
5	Toluene	Na_2CO_3	2	90
6	CH_3OH	Na_2CO_3	4	88

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Table 3. Reaction conditions for the kinetic resolution.

Entry	*L*-CSA (mmol)	Solvent	Time (h)	Optical rotation	Yield (%)
1	0.015	acetone	4	+23	72
2	0.012	acetone	4	+24	66
3	0.012	acetone	12	+25	75
4	0.015	Toluene	4	+22	70
5	0.012	Toluene	4	+23	75
6	0.009	Toluene	12	+24.5	74

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Table 4. Variation of solvent for resolution of (*S*)-(+)-clopidogrel bisulfate.

Entry	Solvent	Time (h)	Yield (%)
1	MIPK*	8	80
2	THF	8	75
3	*i*-PrOH	12	80
4	acetone	5	80
5	EtOAc	4	85

*Methyl isopropyl ketone

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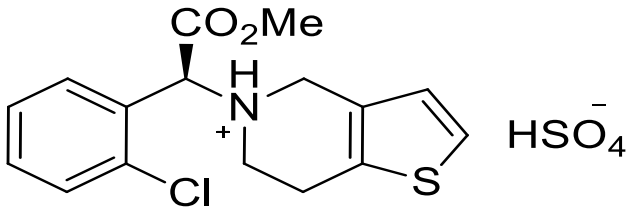

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Fig.1. Chemical structure of (*S*)-(+)-clopidogrel bisulfate (CLP).

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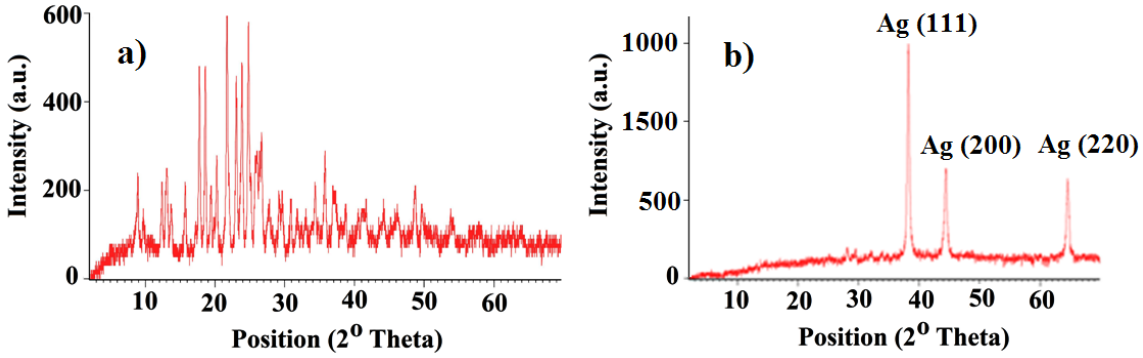

Fig. 2. X-ray diffraction patterns of the (a) CLP and (b) Ag@CLP.

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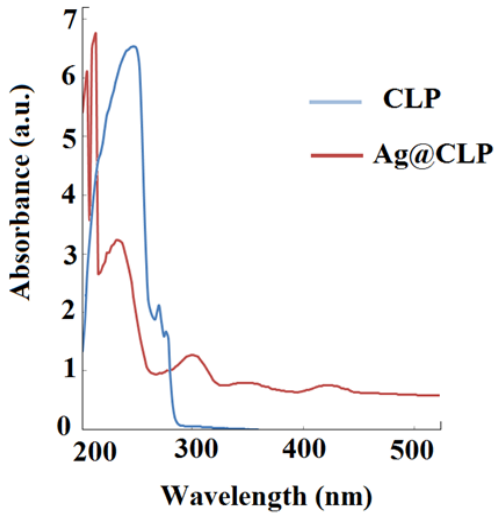

Fig. 3 UV-Vis absorption spectra of CLP and Ag@CLP (EtOH, c = 1.0 × 10^{-4} M, 293 K).

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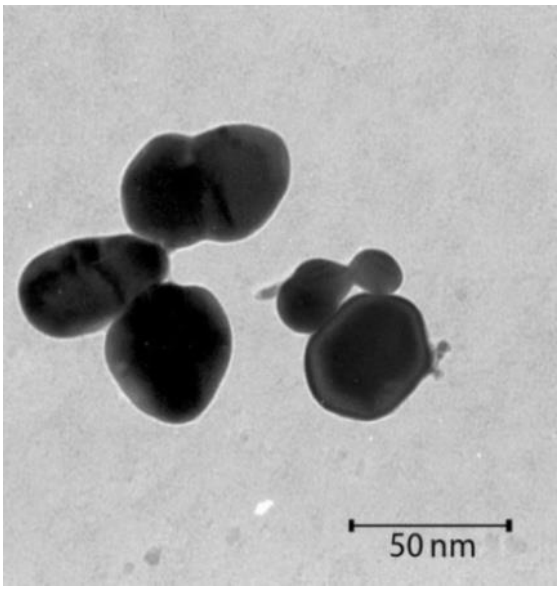

Fig. 4. TEM image of the Ag@CLP.

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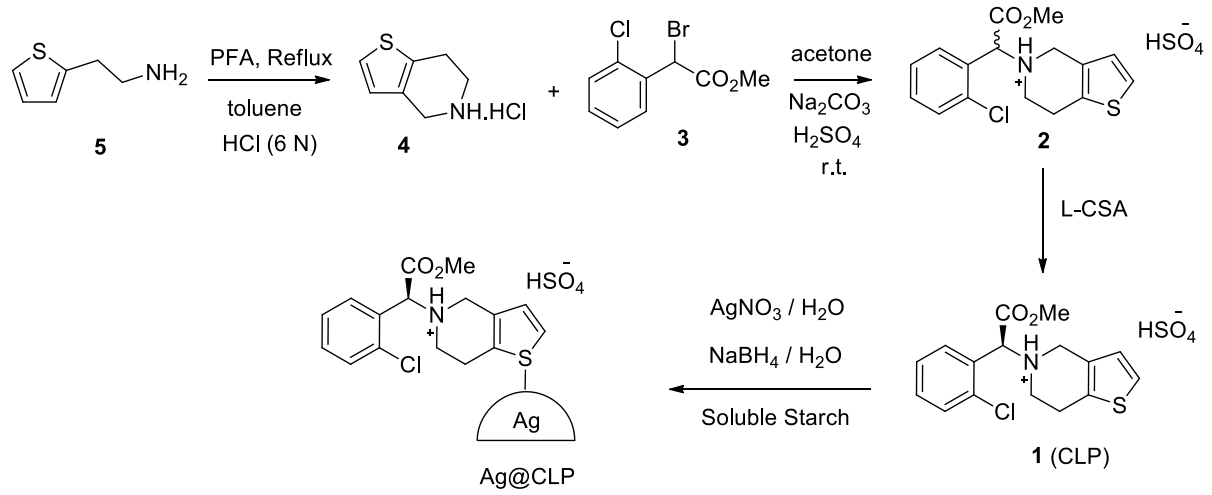

Scheme 1. Preparation of Ag@CLP.

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