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Synthesis and characterization of new carbohydrate-based organic Schiff bases

Jhimli Sengupta* and Nandagopal Hudait

Department of Chemistry, West Bengal State University, Barasat, Kolkata-700 126, India

E-mail: jhimli.sengupta@gmail.com

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Carbohydrate-based organic Schiff bases having biological, catalytic and pharmaceutical activities have great demand. A series of new organic Schiff bases were synthesized starting from diacetone-D-glucose following the general protocol of condensation between amine and aldehyde, either both having sugar moiety (condensation of amino sugar with aldehyde sugar), and/or at least one component having sugar moiety. All the compounds that we synthesised were characterised by NMR, FT-IR, and mass spectral studies. One of the organic Schiff base **SSB-4** which was synthesized by condensation of amino sugar with aldehyde sugar, expected to be a good precursor for the synthesis of macrocycle and might also show some biological activity.

Keywords: D-Glucofuranose, carbohydrate, amino sugar, Schiff base, aldehyde sugar.

Introduction

Carbohydrates, known to be the most abundant biogenic class of compounds, play an important role in living organisms[1] as they are involved in a wide range of functions. Apart from storing energy[2], they are also used for performing other important functions, e.g. chiral pool for forming different chiral ligands, chiral building blocks, important tool for stereoselective synthesis, precursors for synthesis of drug and chiral catalysts in asymmetric synthesis[3]. Various strategies have been adopted to develop carbohydrate-based bioactive substances such as antibacterial[4], antiviral, antineoplastic[5], antiprotozoal[6–8], and antifungal[9]. Therefore, there is still need to develop carbohydrate-based therapeutics and bioactive substrates.

Schiff bases ("azomethine" group containing compounds) are synthesized by condensation of an amine with carbonyl (aldehyde and keto) compounds. Schiff bases have also been used as very important class of compounds having several biological applications such as antibacterial[10–13], antifungal[14–16], anticancer[17,18], anti-oxidant[19] in pharmaceutical/medicinal chemistry. Moreover, Schiff bases have immense industrial applications in the food industry, dye industry and agrochemical[20,21]. The nitrogen atom of the azomethine group in Schiff base can coordinate with metal ions, and used as ligands in catalysis[22,23]. A few imines have been reported, both by the reaction of sugar aldehydes with amines, and by the reaction of amino sugars with aldehydes[24]. Schiff bases and their sugar amino complexes have been applied to synthesise large member ring compounds[25,26], catalysts in oxygenations[27], and macrocyclic compound[28–30].

Prompted by this knowledge, herein we describe the design, synthesis of four organic Schiff base compounds derived from sugar (Fig. 1). Synthesis of carbohydrate-based compounds is very challenging due to its synthetic and analytical difficulty. After a lot of strenuous effort, we have been

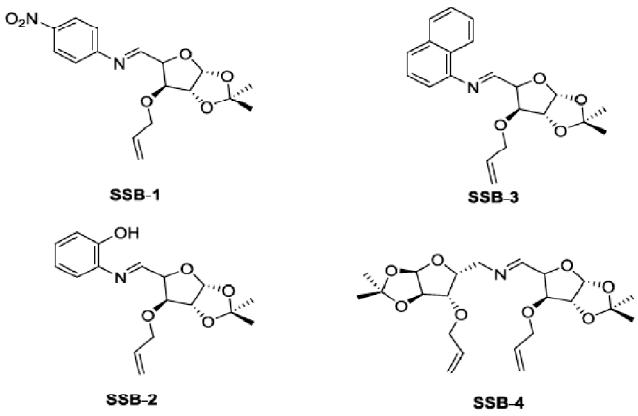


Fig. 1. Structures of the sugar-based Schiff bases (**SSB**) synthesized.

able to synthesize such sugar appended organic Schiff base compounds having sugar moiety in both carbonyl and amine part.

Experimental

Material and methods:

Commonly available chemicals, without any purification were used. Reagents and solvents of Sigma Aldrich and Mark India were used. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose was purchased from Acros Organic. Monitoring of reactions were carried out by thin-layer chromatography using E. Merck silica gel 60 F_{254} percolated plates (No. 1.05554). Organic extracts that we obtained were dried over anhydrous sodium sulfate. For column chromatography, 150–200 mesh silica gel was used. Solvents were distilled and dried prior to use. Petroleum ether refers to a fraction boiling between 60–80°C. ^{1}H NMR spectra were recorded on Bruker 400 MHz with TMS as the internal standard. ^{13}C NMR spectra were recorded on a Bruker 100 MHz. Infrared spectroscopic data were obtained using a Perkin-Elmer 250 FT-IR spectroscopy.

*General procedure for the synthesis of Schiff bases **SSB-1** – **SSB-3**:*

To a solution of aldehyde **4** (5 mmol) in methanol (5 mL) was added dropwise, a methanolic (10 ml) solution of the appropriate amino derivatives (9 mmol). After refluxing for 2 h at 40°C, the reaction mixture was then cooled to room temperature. Methanol was evaporated under reduced pressure and further purification was done by column chromatography yielding **SSB-1** – **SSB-3** respectively.

*(E)-N-(((3aR,6S,6aR)-6-(allyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methylene)-4-nitroaniline (**SSB-1**):*

FT-IR (KBr, ν_{max}, cm^{-1}): 1631 (medium, C=N stretching. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.03 (m, 2H), 6.68–6.57 (m, 2H), 6.11–5.98 (dd, *J* 6.8, 3.7 Hz, 1H), 5.29–5.22 (m, 2H), 4.66–4.55 (m, 1H), 4.40–4.38 (m, 1H), 4.17–4.13 (d, *J* 12.7 Hz, 1H), 4.06–4.02 (m, 1H), 3.85–3.97 (dd, *J* 12.7, 6.0 Hz, 1H), 1.47 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.19 (CH), 151.29 (q), 144.23 (q), 131.25 (q), 126.43 (CH), 126.36 (CH), 126.27 (CH), 118.26 (CH_2), 106.20 (CH), 84.61 (CH), 82.34 (CH), 80.47 (CH), 71.39 (CH_2), 26.99 (CH_3), 26.35 (CH_3). Mass (ESI) $C_{17}H_{20}N_2O_6$: *m/z* 349.1223 $[M+H]^+$.

*2-((E)-(((3aR,6S,6aR)-6-(allyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methylene)amino)phenol (**SSB-2**):* To a solution of aldehyde **4** (1 g, 4.4 mmol) in methanol (10 mL) was added dropwise, methanolic (5 ml) solution of the 2-aminophenol (1 g, 9.1 mmol). After refluxing for 2 h, the reaction mixture was then cooled to room temperature. Solvent was evaporated first under reduced pressure and further purification was done by column chromatography yielding **SSB-2** (1.9 g, 74%) as black sticky liquid.

FT-IR (KBr, ν_{max}, cm^{-1}): 3449 (broad, O-H stretching), 1665 (medium, C=N stretching). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* 7.1 Hz, 2H), 7.64 (t, *J* 8.0 Hz, 1H), 7.50 (t, *J* 7.7 Hz, 1H), 5.97 (t, *J* 3.0 Hz, 1H), 4.82 (t, *J* 4.2 Hz, 1H), 4.66 (d, *J* 3.4 Hz, 1H), 4.54 (d, *J* 3.8 Hz, 2H), 432 (dd, *J* 11.9, 6.7 Hz, 1H), 4.14 (q, *J* 7.1 Hz, 2H), 3.97 (dd, *J* 8.9, 6.6 Hz, 1H), 3.62–3.42 (m, 2H), 1.53 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.59 (CH), 151.11 (q), 133.67 (q), 130.17 (CH), 128.49 (CH), 122.11 (CH): 121.18 (q), 118.38 (CH_2), 115.04 (CH_2), 113.02 (CH), 106.85 (CH), 85.44 (CH), 85.05 (CH), 82.43 (CH), 72.47 (CH_2), 27.47 (CH_3), 26.80 (CH_3). Mass (ESI) $C_{17}H_{21}NO_5$: *mlz* 320.1268 $[M+H]^+$.

*(E)-N-(((3aR,6S,6aR)-6-(allyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methylene)naphthalen-1-amine (**SSB-3**):*

FT-IR (KBr, ν_{max}, cm^{-1}): 1626 (medium, C=N stretching). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* 7.1 Hz, 1H), 7.64 (t, *J* 8.0 Hz, 1H), 7.50 (t, *J* 7.7 Hz, 1H), 7.42–7.30 (m, 2H), 5.88 (d, *J* 3.5 Hz, 1H), 4.73 (t, *J* 4.2 Hz, 1H), 4.57 (d, *J* 3.5 Hz, 1H), 4.45 (d, *J* 3.8 Hz, 1H), 4.23 (dd, *J* 11.7, 6.8 Hz, 1H), 3.88 (dd, *J* 8.9, 6.5 Hz, 1H), 3.44 (dd, *J* 8.8, 7.5 Hz, 1H), 1.44 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.59 (CH), 147.00 (q), 135.07 (CH), 133.67 (CH), 128.49 (CH), 126.15 (CH), 121.16 (q), 117.09 (CH_2), 113.02 (CH), 106.85 (CH), 85.44 (CH), 85.05 (CH), 82.43 (CH), 72.42 (CH_2), 27.47 (CH_3), 26.80 (CH_3). Mass (ESI) $C_{21}H_{23}NO_4$: *m/z* 354.1766 $[M+H]^+$.

*Procedure for the synthesis of compound **8**:*

Sodium azide (0.4 g, 6.4 mmol) was added to the solution of compound **6** (0.5 g 1.6 mmol) in DMF (10 mL) and the reaction mixture was stirred at 80°C for 5 h. It was then cooled to room temperature, extracted with ethyl acetate (40 mL). Organic layer was subsequently washed with water and then dried over Na_2SO_4 to give the desired azide intermediate **7** (0.31 g, 75%) as a sticky liquid. Next, to a stirred solution of

azide **7** (0.31 g, 1.2 mmol) in THF (15 mL), $LiAlH_4$ (0.19 g, 5 mmol) at 0°C was added. Stirring was continued for 10 h at room temperature. After full conversion confirmed by thin layer chromatography (TLC), quenching was done by adding water (7 ml). The residue part which we got after removal of solvent was extracted with ether, washed with brine. It was then dried and concentrated to obtain a yellow solid which was further chromatographed (pet ether:ethyl acetate, 9:1) to give **8** (0.2 g, 72%) as a yellow solid.

*((3aR,6S,6aR)-6-(allyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methanamine (**8**):*

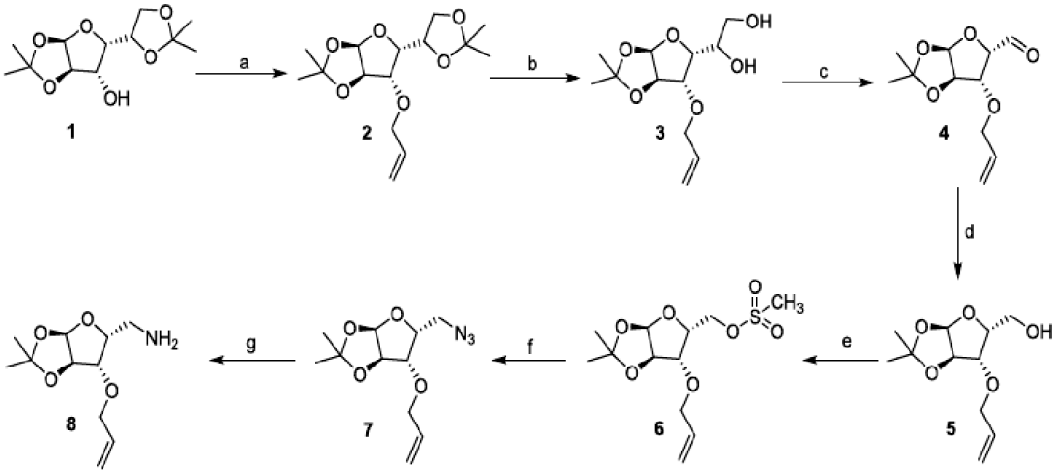
FT-IR (KBr, ν_{max}, cm^{-1}): 3437 (broad, N-H stretching), 2994 (C-H stretching), 1356 (C-N stretching). ^1H NMR (400 MHz, $CDCl_3$) δ 6.25–629 (dd, *J* 8.9, 6.5 Hz, 1H), 5.85–5.92 (m, 1H), 5.20–5.31 (d, *J* 4.5 Hz, 2H), 5.00 (s, 1H), 4.75–4.85 (m, 2H), 4.51–4.00 (dd, *J* 9.2, 3.8 Hz, 1H), 4.01–4.10 (dd, *J* 9.9, 7.5 Hz, 2H), 3.47–3.60 (t, *J* 7.4 Hz, 1H), 2.80–2.90 (dd, *J* 8.7, 3.4 Hz, 1H), 2.48–2.59 (dd, *J* 7.6, 4.0 Hz, 1H), 1.3 (s, 6H). ^{13}C NMR (100 MHz, CD_3OD) δ 139.06 (CH), 124.39 (q), 117.54 (CH_2), 116.88 (CH), 94.12 (CH), 84.02 (CH), 79.61 (CH), 73.03 (CH_2), 42.01 (CH_2), 26.00 (CH_3). Mass (ESI) $C_{11}H_{19}NO_4$: *m/z* 230.0955 $[M+H]^+$.

*(E)-1-((3aR,6S,6aR)-6-(allyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-N-(((3aR,6S,6aR)-6-(allyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methylene)-methanamine (**SSB-4**):* Amino sugar **8** (0.51 g, 2.2 mmol) and compound **4** (0.50 g, 2.1 mmol) were mixed in a 50 mL of round bottom flask and then methanol (20 mL) was added and the whole mixture was stirred at 40°C for 2 h. It was then cooled to room temperature. First under reduced pressure, the solvent was evaporated and further purification was done by column chromatography yielding **SSB-4** (0.7 g, 76%) as a yellowish sticky liquid.

FT-IR (KBr, ν_{max}, cm^{-1}): 3452 (broad), 1644 (m). ^1H NMR (400 MHz, $CDCl_3$) δ 6.01–6.00 (d, *J* 3.8 Hz, 1H), 5.89–5.80 (m, 2H), 5.30 (s, 1H), 5.24–5.18 (t, *J* 3.0 Hz, 1H), 4.59 (s, 1H), 4.54–4.50 (m, 2H), 4.33–4.24 (d, *J* 3.4 Hz, 1H), 4.19 (s, 1H), 4.16–4.10 (dd, *J* 11.9, 6.1 Hz, 1H), 3.99–3.93 (dd, *J* 11.9, 6.6 Hz, 1H), 3.87–3.80 (m, 2H), 3.66–3.60 (m, 1H), 1.46–1.43 (s, 6H), 1.35 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.80 (CH), 130.30 (CH), 121.35 (CH_2), 112.23 (q), 105.17 (CH), 82.28 (CH), 79.80 (CH), 78.90 (CH_2), 68.25 (CH_2), 64.35 (CH), 26.76 (CH_3), 26.33 (CH_3). Mass (ESI) $C_{22}H_{33}NO_8$: *m/z* 440.1784 $[M+H]^+$.

Results and discussion

To synthesize the new Schiff bases, we followed the synthetic procedure as shown in Scheme 1 and Scheme 2. Compound **6** was already reported by us before[31]. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**1**) was dissolved in dichloromethane and subsequent treatment with allyl bromide under the basic condition in presence of TBAB gave



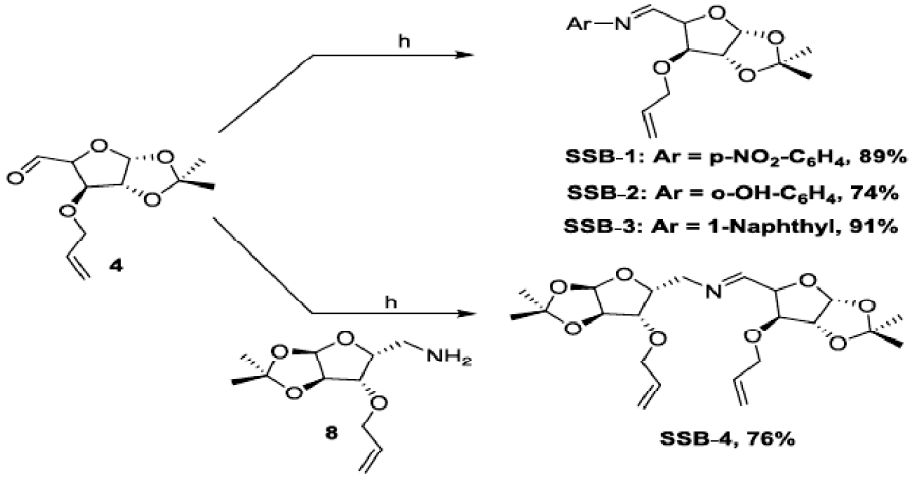
Scheme 1. Synthesis of the amino sugar intermediate **8**.

Reagents and conditions: (a) 50% aq. NaOH, DCM, TBAB, allyl bromide, 12 h, rt, 95%; (b) 75% aq. CH_3COOH, 20 h, rt, 82%; (c) $NaIO_4$-H_2O, CH_3OH, 2 h, 0°C, 80%; (d) $NaBH_4$, MeOH, 6 h, rt, 75%; (e) Et_3N, MsCl, DCM (anhydrous), 2 h, 0°C, 80%; (f) NaN_3, DMF, 5 h, 80°C, 75%; (g) $LiAlH_4$, THF, 10 h, 0°C, 72%.

the corresponding allylated product **2**. Then subsequent deprotection, oxidation, and finally reduction furnished the alcohol **5**, which on mesylation with $MeSO_2Cl$ gave mesyl derivatives **6**. The conversion of mesyl compound to azide, and then reduction of the corresponding azide gave amine compound containing sugar moiety (**8**). Next a solution of aldehyde **4** in MeOH was mixed with appropriate amine (*p*-nitroaniline, 2-aminophenol, 1-naphthylamine), and the whole reaction was refluxed for 2-3 h to afford the desired Schiff bases **SSB-1** – **SSB-3**. Schiff base **SSB-4** was synthesized similarly by mixing aldehyde **4** and amino sugar **8**.

In FT-IR spectra, the peak at 1720 cm^{-1} indicates the formation of sugar aldehyde **4**. The broad peak at 3437 cm^{-1} in the IR spectrum of amino sugar (**8**) is due to N-H stretching. The compound **8** was also confirmed by NMR and mass spectra. In the proton NMR spectrum, the multiplet peak at δ 6.25 ppm indicates the presence of allyl group; and peak at δ 2.5–2.7 ppm indicates the presence of $-CH_2$ adjacent to $-NH_2$. In ^{13}C spectrum, the peak at δ 42 ppm indicates the presence of the methylene group attached to the amine functionality. On the other hand, the peak at *m/z* peak at 230.0955 in the mass spectra due to $[M+H]^+$ strongly indicates the formation of the desired compound **8**. The formation of imine bond in Schiff base **SSB-4** containing sugar moiety both in aldehyde and amine part was confirmed by the presence of the broad peak at 1644 cm^{-1} in the IR spectrum. The peak is due to -C=N bond stretching. ^1H NMR spectrum again confirmed the presence of the imine group by showing the peak at δ 2.15 ppm for the proton attached to the imine bond. In ^{13}C NMR spectra, the peak at 160 ppm is for imine carbon. In HRMS, peak at *m/z* 440.1784 due to $[M+H]^+$ was also in accordance with results obtained from other spectral studies. IR spectrum of compound **SSB-1** reveals the formation of imine as it gives a peek at 1631 cm^{-1}. The peaks at 839 cm^{-1}, 1304 cm^{-1}, 1505 cm^{-1} indicate the presence of $-NO_2$ group. In ^1H NMR spectra, it shows peak at δ 8.00–8.10 region which corresponds to protons of the aromatic ring. In the ^{13}C NMR, the peak at δ 162 ppm is due to C=N and δ 151 ppm is due to the carbon atom of benzene ring having $-NO_2$ group; in HRMS spectra *m/z* 349.1223 is due to $[M+H]^+$.

In compound **SSB-2**, the peaks at 1665 cm^{-1} and 3449 cm^{-1} in the IR spectrum are due to C=N bond stretching and hydroxyl group respectively. The peak at δ 7.33–7.66 in ^1H NMR spectra corresponds to protons for aromatic rings. The *m/z* peak at 320.1268 in HRMS spectra due to $[M+H]^+$, strongly indicates the formation of the desired compound. Similarly, in compound **SSB-3**, the peak at 1686 cm^{-1} in FT-IR spectrum is due to C=N bond stretching, and 3056 cm^{-1} is due to aromatic C-H bond stretching. In ^1H NMR spectra, it shows some peaks at δ 7.33–7.66 range indicating the presence of naphthalene moiety. In HRMS spectra, *m/z* peak at 354.1766 is due to $[M+H]^+$. In all cases, the absence of NH_2 and C=O absorption bands and the apparence of a



Scheme 2. Synthesis of sugar-based Schiff bases **SSB-1** – **SSB-4**.

Reagents and conditions: (h) MeOH, reflux, 2–3 h, showing the overall synthetic yields.

strong to moderate band at 1650–1670 cm^{-1} (due to C=N stretching) in the IR spectrum confirm the formation of desired Schiff base compounds.

Conclusions

In summary, new series of carbohydrate-based organic Schiff base were synthesized and characterized by NMR, FT-IR and HRMS analysis. One of the Schiff base **SSB-4** has unique structural feature as it is derived from the condensation between an amino sugar (**8**) and an aldehyde sugar (**4**), expected to be a good precursor for the synthesis of macrocycle. The newly synthesized Schiff bases might have some biological activity which needs further research.

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Supporting information

All the characterization by ^{1}H, FT-IR, ^{13}C NMR, and mass spectra of newly synthesized compounds have been shown in supporting information.

References

1. V. Ferreira, D. Da Rocha and F. De Carvalho Da Silva, *Quimica Nova,* 2009, **32**, 623.
2. R. Stick, "Carbohydrates: Te Sweet Molecules of Life", Academic Press, 2001.
3. N. Asim, K. Sopian, S. Ahmadi, K. Saeedfar, K. Alghoul, O. Saadatian and S. Zaidi, *Renewable and Sustainable Energy Reviews,* 2012, **16**, 5834.
4. M. Dieguez, O. Pamies and C. Claver, *Chem. Rev.,* 2004, **104**, 3189.
5. M. Dieguez, O. Pamies and C. Claver, *Eur. J.Org. Chem.,* 2007, **2007**, 4621.
6. S. Kumar, D. Dhar and P. Saxena, *J. Sci. Indust. Res.,* 2009, **68**, 181.
7. S. Woodward, M. Dieguez and O. Pamies, *Coord. Chem. Rev.,* 2010, **254**, 2007.
8. M. Boysen, *Chemistry,* 2007, **13**, 8648.
9. J. Costamagna, L. Lillo, B. Matsuhiro, M. Noseda and M. Villagran, *Carbohyd. Res.,* 2003, **338**, 1535.
10. A. Hussen, *J. Coord. Chem.,* 2006, **59**, 157.
11. S. Karthikeyan, M. Prasad, D. Poojary and B. Bhat, *Bioorg. Med. Chem.*, 2006, **14**, 7482.
12. K. Singh, M. Barwa and P. Tyagi, *Eur. J. Med. Chem.,* 2006, **41**, 147.
13. P. Pannerselvam, R. Nair, G. Vijayalakshmi, E. Subramanian and S. Sridhar, *Eur. J. Med. Chem.,* 2005, **40**, 225.
14. S. Sridhar, M. Saravan and A. Ramesh, *Eur. J. Med. Chem.,* 2006, **36**, 615.
15. S. Pandeya, D. Sriram, G. Nath and E. Declercq, *Eur. J. Pharmacol.,* 1999, **9**, 25.
16. R. Mladenova, M. Ignatova, N. Manolova, T. Petrova and I. Rashkov, *Eur. Polym. J.,* 2002, **38**, 989.
17. O. Walsh, M. Meegan, R. Prendergast and T. Nakib, *Eur. J. Med. Chem.,* 1996, **31**, 989.
18. M. Cacic, M. Molnar, B. Sarkanj, E. Has-Schon and V. Rajkovic, *Molecules,* 2010, **15**, 6795.
19. S. Dave and N. Bansal, *International Journal of Current Pharmaceutical Research,* 2013, **5**, 6.
20. S. Kumar, M. Niranjan, K. Chaluvaraju, C. Jamakhandi and D. Kadadevar, *Journal of Current Pharmaceutical Research,* 2010, **01**, 39.
21. P. Vigato and S. Tamburini, *Coord. Chem. Rev.,* 2004, **248**, 1717.
22. T. Katsuki, *Coord. Chem. Rev.,* 1995, **140**, 189.
23. A. Sharma and M. Shah, *OSR Journal of Applied Chemistry,* 2013, **03**, 45.
24. J. Sengupta, R. Mukhopadhyay and A. Bhattacharjya, *J. Org. Chem.,* 2007, **72**, 4621.
25. J. Segura, M. Mancheno and F. Zamora, *Chem. Soc. Rev.,* 2016, **45**, 5635.
26. M. Said, D. Hughes, M. Al-Mamary, N. Al-Kaff and S. Al-Harbi, *J. Mole. Struct.,* 2018, **1165**, 305.
27. Y. Wu, H. Xu, X. Chen, J. Gao and D. Jiang, *Chem. Commun.,* 2015, **51**, 10096.
28. F. Uribe-Romo, J. Hunt, H. Furukawa, C. Klöck, M. O'Keeffe and O. Yaghi, *J. Am. Chem. Soc.,* 2009, **131**, 4570.
29. P. Cozzi, *Chem. Soc. Rev.,* 2004, **33**, 410.
30. S. Casolari, G. Cozzi and P. Orioli, *Chem. Commun.,* 1997, **21**, 2123.
31. (a) J. Sengupta, R. Mukhopadhyay and A. Bhattacharjya, *J. Org. Chem.*, 2007, **72**, 4621; (b) J. Sengupta and A. Bhattacharjya, *J. Org. Chem.*, 2008, **73**, 6860.