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Synthesis, Characterization and Thermal Analysis for New Amoxil Ligands

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In the present study, new heterocyclic organic ligands were synthesized using amoxil drug as a starting material through multi steps. The ligands were prepared through condensation reaction to form thiazole and imidazole derivatives containing azo or anil groups in their structures *via* azotization reaction and imination reaction. The new ligands of amoxil have been characterized by means of spectral (IR and ^{1}H NMR) and thermal analyses.

Keywords: Amoxicillin, Heterocyclic ligands, Imidazole, Thiazole.

INTRODUCTION

Amoxil (Fig.1) is a well known antibiotic used to prevent bacterial infection and also used in the treatment for wide types of infections like (*Staphylococcus*, *Streptococcus*, *H. influenza* and *H. pylori*) and preventing the ulcers of returning. According to amoxil chemical structure, it can be used in medicine as well as in chemistry as a starting material in synthetic reactions [1]. One of the important reactions is cyclization [2-6] and already used in the synthesis of several industrial compounds [6-10], relaxant drugs like diazepam and oxazepam [11-17], different types of heterocyclic compounds [18-24] and other compounds in different applications [25-31].

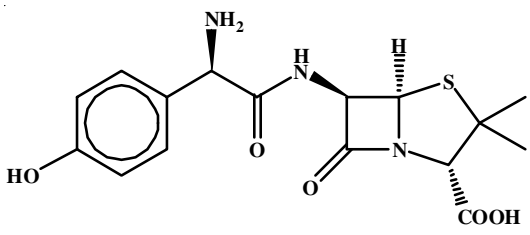


Fig. 1. Amoxicillin

The heterocyclic compounds containing imidazoles and thiazoles plays an important role in the field of medicinal chemistry [32,33]. Furthermore, due to the presence of (-NH_2) group in the amoxil structure, this could be exploited to synthesize useful azo dyes and Schiff bases [1]. Thus, in this article, the authors reported the synthesis and characterization of few new amoxil ligands containing imidazole, thiazole, azo and imine groups.

EXPERIMENTAL

All the chemicals used were purchased from Sigma-Aldrich without any further purification. FT-IR spectra were recorded on Perkin Elmer-spectrum with KBr disc. ^{1}H NMR were recorded at (400 MHz) by using (DMSO-d_6) as a solvent and the thermal analyses were recorded on differential scanning calorimetry 601, (DSC)-Thermal analysis instrument. All the chemical shifts (δ) were reported in ppm relative to tetramethyl silane (TMS) as reference.

Synthesis of ligands containing imidazole unit: Amoxil (0.1 mol, 0.86 g) was refluxed with *o*-phenylendiamine (0.2 mol, 1.68 g) in the presence of HCl (4 N) for 3 h to yield imidazole amoxil ligand (**1**). Yield: 68 %; R_f: 0.52 TLC solvent (ethanol: dioxane).^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.29 (1H, OH), 5.34 (2H, NH_2), 10.30 (1H, N-H-CO), 0.90 (6H, $2CH_3$); (7.54-7.83), (8H, 2Ph); 8.57 (1H, NH imidazole ring). IR (KBr, ν_{max}, cm^{-1}): 3350 (O-H), 3200 and 3280 (NH_2), 3120 (N-H-CO), 1690 (C=O-N-), 1640 (C=N).

Now, imidazole amoxil ligand (**1**) (0.01 mol, 0.55 g) was refluxed for 2 h with benzaldehyde (0.01 mol, 0.38 g) in the

presence of few drops of glacial acetic acid. The resulted compound was filtered, dried and recrystallized to yield imidazole anilamoxil ligand (**2**). Yield: 66 %; R_f: 0.66 TLC solvent (ethanol: dioxane). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.20 (1H, OH phenol), 8.19 (1H, CH=N), 10.12 (1H, NH-CO), 0.98 (6H, $2CH_3$), (7.22-7.95) (13H, 3Ph), 8.71 (1H, NH imidazole ring). IR (KBr, ν_{max}, cm^{-1}): 3410 (O-H), 1610 (CH=N), 3200 (N-H-CO), 1685 (C=O-N), 3110 (N-H imidazole).

Synthesis of ligands containing thiazole moiety: Amoxil (0.1 mol, 0.86 g) was mixed with *o*-aminomercaptane (0.2 mol, 1.96 g) and HCl (4 N). The reaction mixture was refluxed for 3 h to give thiazoleamoxil ligand (**3**). Yield: 70 %; R_f: 0.60 TLC solvent (ethanol:dioxane). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.27 (1H, OH), 5.14 (2H, NH_2), 10.20 (1H, NH-CO), 1.10 (6H, $2CH_3$), (7.54-7.88) (8H, 2Ph). IR (KBr, ν_{max}, cm^{-1}): 3372(O-H), 3225 and 3265 (NH_2), 3134 (N-H-CO), 1693 (C=O-N-), 1632 (C=N) and 786 (C-S).

Thiazoleamoxil ligand (**3**) (0.01 mol, 0.82 g) was refluxed with benzaldehyde (0.01 mol, 0.38 g) in the presence of few drops of glacial acetic acid. The product was filtered, dried and recrystallized to give thiazole anilamoxil ligand (**4**). Yield: 72 %; R_f: 0.68 TLC solvent (ethanol:dioxane). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.14 (1H, OH), 8.24 (1H, CH=N), 10.07 (1H, NH-CO), 1.09 (6H, $2CH_3$), (7.11- 7.78) (13H, 3Ph). IR (KBr, ν_{max}, cm^{-1}): 3418 (O-H); 1616 (CH=N); 3228 (N-H-CO); 1692 (C=O-N); 782 (C-S).

Diazotization of ligand 3: Thiazoleamoxil ligand (**3**) (0.01 mol, 0.82 g) was dissolved in HCl (3 mL, 4 N) and this solution was placed in an ice bath to maintain the reaction temperature at 0-5 ºC. Then sodium nitrite solution was added to an ethanolic solution of resorcinol followed by the addition of ligand (**3**). The resulting compound (thiazole-azoamoxil) was filtered, dried and recrystallized to obtain azo ligand (**5**). Yield: 78 %; R_f: 0.60 TLC solvent (ethanol:dioxane). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.11, 11.12 (3H, OH), 9.08 (1H, NH-CO), 1.30 (6H, $2CH_3$), 7.42-8.06 (11H, 3Ph). IR (KBr, ν_{max}, cm^{-1}): 3483 (O-H); 3300 (N-H-CO); 1466, 1505 (N=N); 1686 (C=O-N); 776 (C-S).

Diazotization of ligand 1: Imidazole containing amoxil ligand (**1**) (0.01 mol, 0.55 g) was dissolved in HCl (3 mL, 4 N) and this solution was placed in an ice bath to maintain the reaction temperature at 0-5 ºC. A solution of sodium nitrite was added to a solution of 5-methyl-1-hydroxy phenol in ethanol and the diazonium solution was added to imidazole amoxil ligand (**1**) solution. The resulting compound (imidazole-azo amoxil) was filtered, dried and recrystallized to obtain ligand (**6**). Yield: 76 %; R_f: 0.56 TLC solvent (ethanol:dioxane). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.21, 11.26 (3H, 3OH), 9.17 (1H, NH-CO), 1.14 and 1.17 (9H, $3CH_3$), (7.20-7.99) (10H, 3Ph). IR (KBr, ν_{max}, cm^{-1}): 3413 (O-H); 3274 (N-H-CO); 3215 (NH for imidazole ring); 2944 (CH) aliphatic of methyl group; 1687 (C=O-N), 1445 and 1514 (N=N).

RESULTS AND DISCUSSION

In this work, six new organic ligands linked with anil or azo group were synthesized as shown in **Schemes I and II**. In **Scheme-I**, carboxylic acid of amoxicillin was cyclized to thiazole and imidazole by the reaction of amoxicillin with aromatic amines in the presence of HCl to give the ligands **1** and **3**. Then these ligands (**1** and **3**) were reacted with benzaldehyde to form Schiff base (**2** and **4**).

On the other hand, in **Scheme-II** the conversion of the ligands **1** and **3** to azo compounds was achieved by their reactions with 5-methyl-1-hydroxyphenol and resorcinol, respectively to give **5** and **6**.

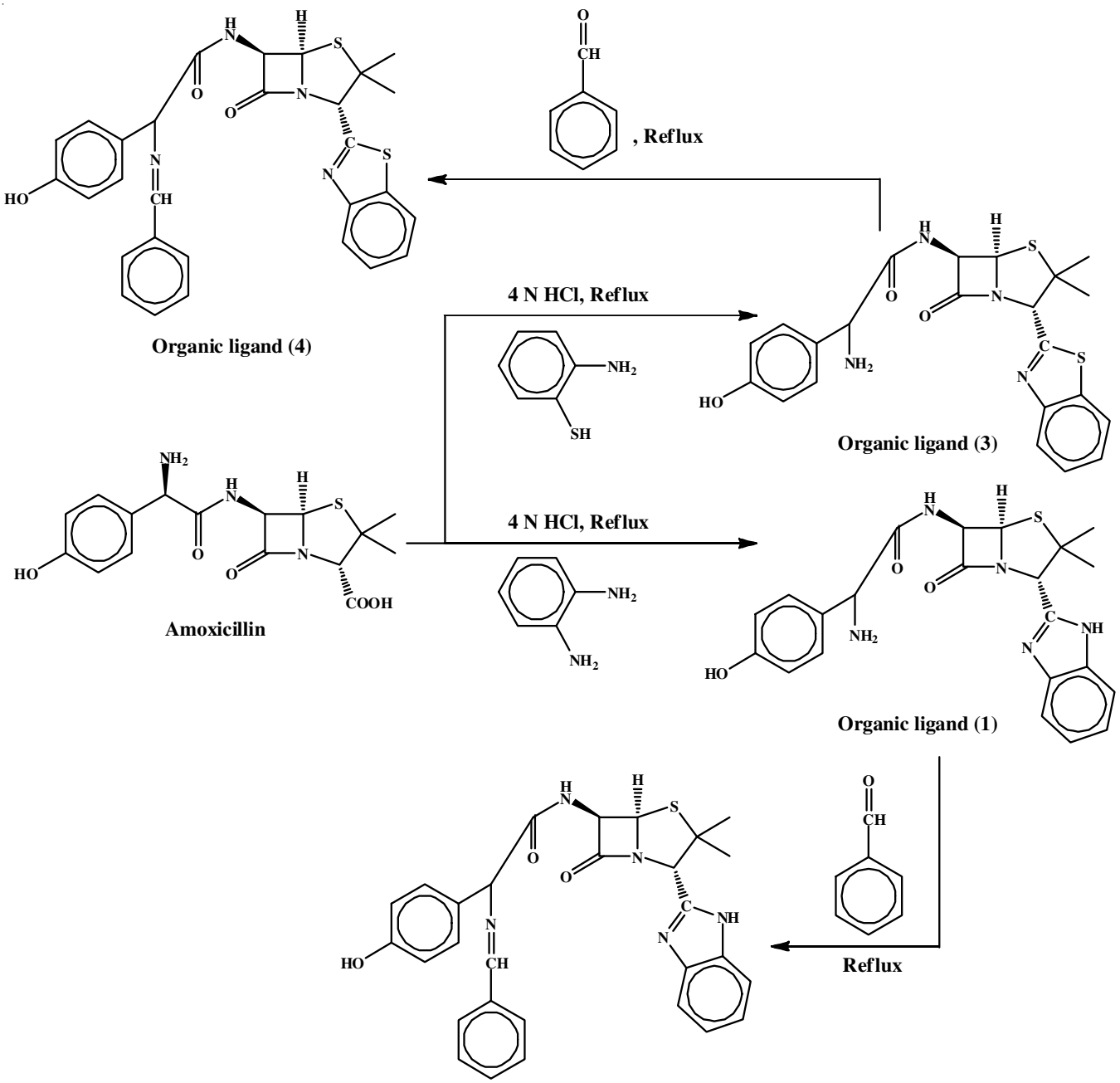
Solubility: The solubility of all the synthesized ligands were studied in various solvents. The solubility differs according to the functional groups present in the structure and polarity of the organic ligands. Table-1 shows the solubility results of these ligands.

FT-IR analysis: The absorption band at 3350 cm^{-1} is assigned to -OH of phenol, 3280-3200 cm^{-1} due to amine group, 3120 cm^{-1} for amide (NH-CO), 1690 cm^{-1} for carbonyl of amide (CO-NH-) and 1640 cm^{-1} for (C=N) endocycle of imidazole ring due to cyclization of diamine with carbonyl of carboxylic acid in ligand (**1**). The bands appeared at 3410 cm^{-1} was due to OH of phenol, 3200 cm^{-1} for amide (NH-CO), 3110 cm^{-1} for amine of imidazole ring (NH), 1685 cm^{-1} for carbonyl of amide (CO-NH-) and 1610 cm^{-1} for imine group (CH=N)imine in ligand (**2**). While, the absorption band at 3372 cm^{-1} is assigned for OH of phenol, 3265-3265 cm^{-1} due to amine group, 3134 cm^{-1} for amine of amide (NH-CO), 1693 cm^{-1} for carbonyl of amide (CO-NH-), 1632 cm^{-1} for (C=N) endocycle of thiazole ring and (C-S) at 786 cm^{-1} for thiazole ring in ligand (3).

Similarly, the bands appeared at 3418 cm^{-1} for OH of phenol, 3228 cm^{-1} for amide (NH-CO), 1692 cm^{-1} for carbonyl of amide (CO-NH), 1616 cm^{-1} for imine group (CH=N)imine, 782 cm^{-1} for thiazole ring (C-S) in ligand (**4**), while similar bands appeared at 3483 cm^{-1} for OH of phenol, 3300 cm^{-1} for amine of amide (NH-CO), 1686 cm^{-1} for carbonyl of amide (CO-NH-), 1505-1466 cm^{-1} for azo group (N=N) and 776 cm^{-1} for thiazole ring (C-S) in ligand (**5**), In case of ligand **6**, the bands appeared at 3413 cm^{-1} for OH of phenol, 3274 cm^{-1} for amide (NH-CO-), 3215 cm^{-1} for (NH) for imidazole ring, 2944 cm^{-1} for aliphatic methyl group (CH_3), 1687 cm^{-1} for carbonyl of amide (CO-NH-) and 1514-1445 cm^{-1} for azo group (N=N).

TABLE-1
SOLUBILITY TEST OF ORGANIC LIGANDS IN DIFFERENT SOLVENTS

Organic ligands	Solvents					
	C_2H_5OH	Methanol	Dioxane	CCl_4	DMSO	Toluene
1	+	+	–	–	+	–
2	+	+	–	–	+	–
3	+	+	–	–	+	–
4	+	+	–	–	+	–
5	+	+	–	–	+	–
6	+	+	–	–	+	–



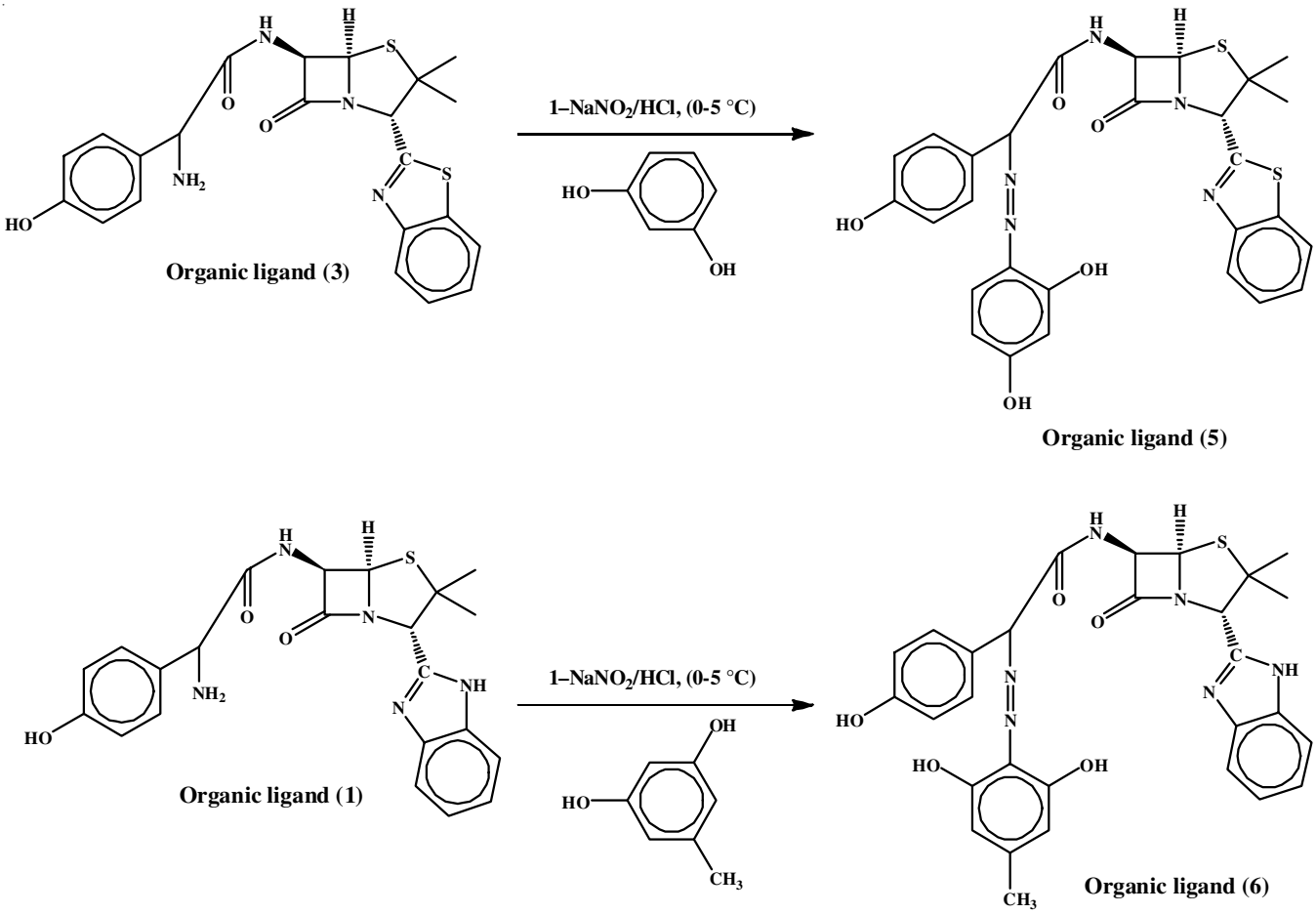
Scheme-I: Preparation of the organic ligands (**1-4**)

^{1}H NMR analysis: ^{1}H NMR spectra was recorded in DMSO-d_6 as a solvent with its signal at 2.5 ppm. The proton of OH of phenol was showed at 11.29 ppm, signals at 5.34 ppm for NH_2, protons of amide group (NH-CO) at 10.30 ppm, methyl groups at 0.90 ppm, phenyl groups at 7.54-7.83 ppm, amine in imidazole ring at 8. 57 ppm in ligand (**1**). Similar signals were also noted in ligand **2** for example, 11.20 ppm was for proton of OH phenol, 8.19 ppm for (CH=N)imine group, amide group (NH-CO) at 10.12 ppm, methyl groups at 0.98 ppm, phenyl groups at 7.22-7.95 ppm, amine in imidazole ring at 8.71 ppm.

For ligand **3**, the protons of OH of phenol at 11.27 ppm, 5.14 ppm for NH_2, amide group (NH-CO) at 10.20 ppm, methyl groups at 1.10 ppm, phenyl groups at 7.54-7.88 ppm were observed. For ligand **4**, the signals at 11.14 ppm for OH phenol, at 8.24 ppm for CH=N) imine group, amide group (NH-CO) at 10.07 ppm, methyl groups at 1.09 ppm, phenyl groups at 7.11-7.78 ppm were observed.

The NMR spectra of ligands **5** and **6** are almost similar. The peaks appeared at 11.11-11.12 and 11.21-11.26 ppm were protons of OH phenol, amide group (NH-CO) at 9.08 and 9.17 ppm, methyl groups at 1.30 and 1.14-1.17 ppm, phenyl groups at 7.42-8.06 and 7.20-7.99 ppm were assigned to ligands **5** and **6**, respectively.

Thermal analysis: All the ligands were characterized using thermal analysis which showed their stability against different temperatures. The thermograms of all the ligands are shown in Figs. 2-7.



Scheme-II: Preparation of organic ligands (**5,6**)

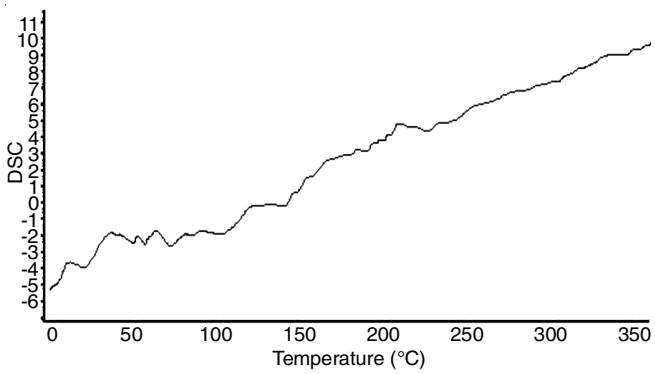


Fig. 2. Thermal curve of ligand **1**

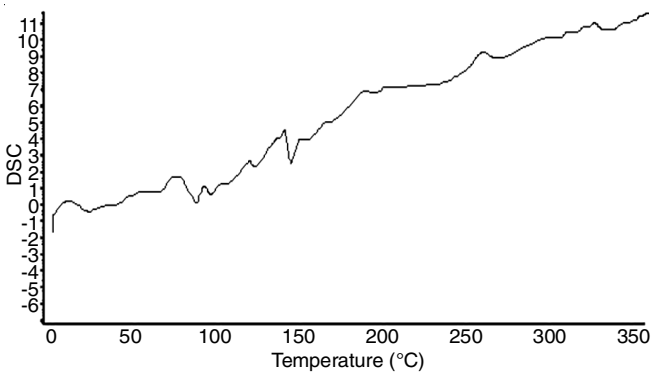


Fig. 4. Thermal curve of ligand **3**

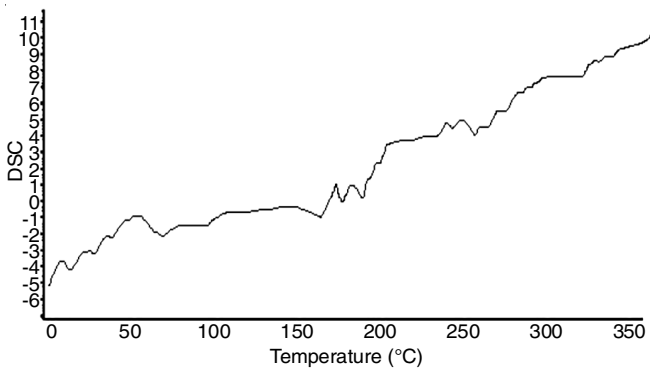


Fig. 3. Thermal curve of ligand **2**

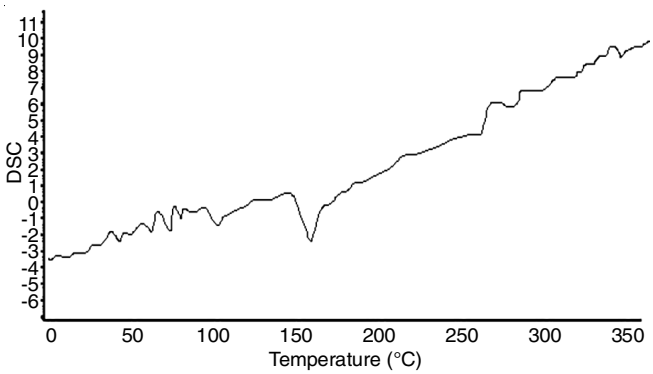


Fig. 5. Thermal curve of ligand **4**

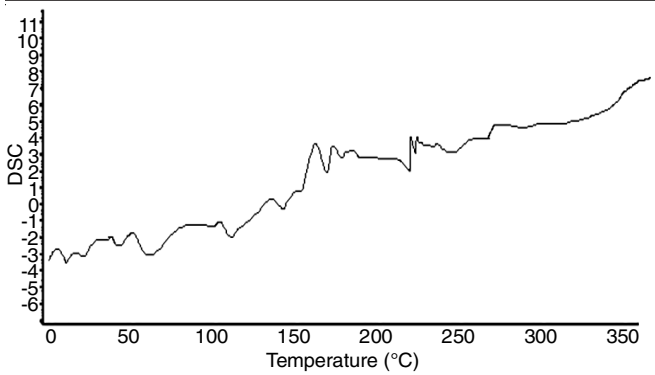


Fig. 6. Thermal curve of ligand **5**

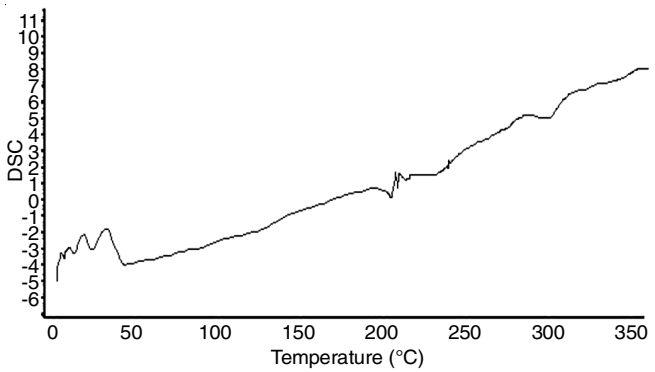


Fig. 7. Thermal curve of ligand **6**

Conclusion

In this study, six new heterocyclic Schiff base and azo compounds containing thiazole and imidazole moeity were synthesized from amoxil. All the synthesized compounds were characterized using spectral and thermal techniques.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. W.A. Al Masoudi, H.T. Mohammad and A.A. Hama, *Int. Res. J. Pharm.*, **6**, 386 (2015); https://doi.org/10.7897/2230-8407.06680.
2. D.A. Kummer, D. Li, A. Dion and A.G. Myers, *Chem. Sci.*, **2**, 1710 (2011); https://doi.org/10.1039/c1sc00303h.
3. M.G. Charest, C.D. Lerner, J.D. Brubaker, D. Siegel and A.G. Myers, *Science*, **308**, 395 (2005); https://doi.org/10.1126/science.1109755.
4. C. Sun, Q. Wang, J.D. Brubaker, P. Wright, C.D. Lerner, K. Noson, M. Charest, D.R. Siegel, Y.-M. Wang and A.G. Myers, *J. Am. Chem. Soc.*, **130**, 17913 (2008); https://doi.org/10.1021/ja806629e.
5. K.C. Nicolaou, C. Nilewski, C.R.H. Hale, H.A. Ioannidou, A. ElMarrouni and L.G. Koch, *Angew. Chem. Int. Ed.*, **52**, 8736 (2013); https://doi.org/10.1002/anie.201304691.
6. Y.F. Baba, H. Elmsellem, Y.K. Rodi, H. Steli, C. Ad, Y. Ouzidan, F.O. Chahdi, N.K. Sebbar, E.M. Essassi and B. Hammouti, *Der Pharma Chemica*, **8**, 159 (2016).
7. K.M. Kulkarni, S.A. Jadhav, P.B. Patil, V.R. Dhole and S.S. Patil, *Der Pharma Chemica*, **8**, 38 (2016).
8. S.-J. Chao, X.-P. Hui, S. Li, Z.-Z. Qiu, P.-F. Xu, Z.-Y. Zhang, Q. Wang and Z.-W. Guan, *J. Chin. Chem. Soc.*, **52**, 539 (2005); https://doi.org/10.1002/jccs.200500079.
9. Ö. Ates, A. Kocabalkanli, N. Cesur and G. Ötük, *Farmaco*, **53**, 541 (1998); https://doi.org/10.1016/S0014-827X(98)00063-9.
10. C.A.G.N. Montalbetti and V. Falque, *Tetrahedron*, **61**, 10827 (2005); https://doi.org/10.1016/j.tet.2005.08.031.
11. N.M. Aljamali, *Pak. J. Biotechnol.*, **15**, 219 (2018).
12. S.N. Swamy, Basappa, B.S. Priya, B. Prabhuswamy, B.H. Doreswamy, J.S. Prasad and K.S. Rangappa, *Eur. J. Med. Chem.*, **41**, 531 (2006); https://doi.org/10.1016/j.ejmech.2005.12.009.
13. L. Jin, J. Chen, B. Song, Z. Chen, S. Yang, Q. Li, D. Hu and R. Xu, *Bioorg. Med. Chem. Lett.*, **16**, 5036 (2006); https://doi.org/10.1016/j.bmcl.2006.07.048.
14. M. Mohammed, N.M. Aljamali and N.A. Abbas, *J. Global Pharm. Technol.*, **10**, 20 (2018).
15. F.J. Uribe-Romo, J.R. Hunt, H. Furukawa, C. Klock, M. O'Keeffe and O.M. Yaghi, *J. Am. Chem. Soc.*, **131**, 4570 (2009); https://doi.org/10.1021/ja8096256.
16. N.M. Aljamali and I.O. Alfatlawi, *Res. J. Pharm. Technol.*, **8**, 1225 (2015); https://doi.org/10.5958/0974-360X.2015.00224.3.
17. M. Mohammed, N.M. Aljamali, S.A. Abdalrahman and W.A. Shubber, *Biochem. Cell. Arch.*, **18**, 847 (2018).
18. J.C. Hindson, B. Ulgut, R.H. Friend, N.C. Greenham, B. Norder, A. Kotlewski and T.J. Dingemans, *J. Mater. Chem.*, **20**, 937 (2010); https://doi.org/10.1039/B919159C.
19. R.J. Cremlyn, An Introduction to Organosulfur Chemistry, John Wiley & Sons: Chichester (1996).
20. N.M. Aljamali, S.M. Jawd, Z.M. Jawad and I.O. Alfatlawi, *Res. J. Pharm. Technol.*, **10**, 1683 (2017); https://doi.org/10.5958/0974-360X.2017.00297.9.
21. J. Drabowicz, J. Lewkowski, W. Kudelska and T. Girek, ed.: N. Kamble, S,S-Dialkylsulfoximides, In: Science of Synthesis, Thieme, vol. 39, pp. 154-173 (2008).
22. J. Drabowicz, J. Lewkowski, W. Kudelska and T. Girek, ed.: N. Kamble, S,S-Dialkylsulfonediimines, In: Science of Synthesis, Thieme, vol. 39, pp. 173–180 (2008).
23. Y. Zhang and N. Hogg, *Free Radic. Biol. Med.*, **38**, 831 (2005); https://doi.org/10.1016/j.freeradbiomed.2004.12.016.
24. S. Braverman, M. Cherkinsky and S. Levinger, ed.: N. Kamble, Alkyl-sulfur Trihalides, In: Science of Synthesis, Thieme, vol. 39, pp. 187-188 (2008).
25. J. Drabowicz, J. Lewkowski, W. Kudelska and T. Girek, ed.: N. Kamble, Dialkylsulfur Tetrahalides, In: Science of Synthesis, Thieme, vol. 39, pp. 123-124 (2008).
26. P. Arora, V. Arora, H.S. Lamba and D. Wadhwa, *Int. J. Pharm. Res. Sci.*, **3**, 2947 (2012).
27. N.M. Aljamali and D. Rahi, *J. Chem. Pharm. Sci.*, **10**, 1461 (2017).
28. H.S. Eman and N.M. Aljamali, *J. Global Pharma Technol.*, **11**, 165 (2017).
29. N.M. Aljamali, Reactions and Mechanisms, IJMRA Publication: Germany, edn 1 (2018).
30. I. Schneider, E. Keuleyan, R. Rasshofer, R. Markovska, A.M. Queenan and A. Bauernfeind, *Antimicrob. Agents Chemother.*, **52**, 2977 (2008); https://doi.org/10.1128/AAC.00175-08.
31. P. Bogaerts, C. Bauraing, A. Deplano and Y. Glupczynski, *Antimicrob. Agents Chemother.*, **51**, 1584 (2007); https://doi.org/10.1128/AAC.01603-06.
32. D. Mijin, B. Bozic-Nedeljkovic, B. Bozic, I. Kovrlija, J. Ladarevic and G. Uscumlic, *Turk. J. Chem.*, **42**, 896 (2018); https://doi.org/10.3906/kim-1711-97.
33. K.J. Al-Adilee, K.A. Abedalrazaq and Z.M. Al-Hamdiny, *Asian J. Chem.*, **25**, 10475 (2013); https://doi.org/10.14233/ajchem.2013.15735.