Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 124 (2014) 30–33

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

# Spectral studies of 2-pyrazoline derivatives: Structural elucidation through single crystal XRD and DFT calculations

D. Chinnaraja [a], R. Rajalakshmi [a,*], T. Srinivasan [b], D. Velmurugan [b], J. Jayabharathi [a]

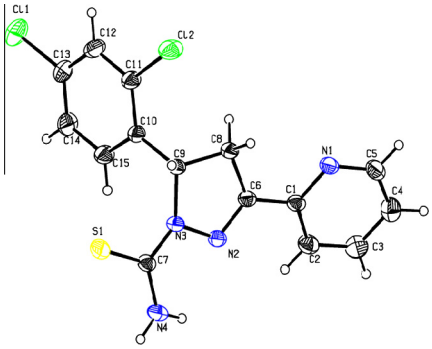
[a] Department of Chemistry, Annamalai University, Annamalainagar 608 002, Tamil Nadu, India
[b] CAS in Crystallography and Biophysics, University of Madras, Chennai 600 025, Tamil Nadu, India

## HIGHLIGHTS

- N-thiocarbamoyl pyrazoline derivatives have been synthesized.
- Spectral studies and single crystal XRD have been carried out.
- The XRD parameters and molecular modeling was carried out.

## GRAPHICAL ABSTRACT

Biologically active pyrazolines, synthesized and characterized by various spectroscopic techniques NMR, LCMS, CHN analysis, X-ray crystallographic and DFT calculations.




## ARTICLE INFO

*Article history:*
Received 24 August 2013
Received in revised form 21 November 2013
Accepted 5 December 2013
Available online 7 January 2014

*Keywords:*
2-Pyrazoline
Thiocarbamoyl
DFT
XRD
2-Acetyl pyridine

## ABSTRACT

A series of biologically active N-thiocarbamoyl pyrazoline derivatives have been synthesized using anhydrous potassium carbonate as the catalyst. All the synthesized compounds were characterized by FT-IR, $^{1}$H NMR, $^{13}$C NMR spectral studies, LCMS, CHN Analysis and X-ray diffraction analysis (compound **7**). In order to supplement the XRD parameters, molecular modelling was carried out by Gaussian 03W. From the optimized structure, the energy, dipolemoment and HOMO–LUMO energies of all the systems were calculated.



## Introduction

N-thiocarbamoyl pyrazolines are considered as important compounds in the organic chemistry because of their application in heterocyclic synthesis and medicinal applications [1–4]. Pyrazolines are compounds with noteworthy applications and have been reported to show a wide spectrum of biological activity, including antibacterial, antifungal, anti infalmmatery, antiamoebic, antidepressant and anticonvulsant activities [5–11]. They are used as fluorescent probes [12], in some elaborate chemosensors and as photosensitizers [13]. Moreover the 2-pyridinyl pyrazolines can themselves serve as N,N-bidentate ligands for metal ions [14]. Thus the characterization of 1-phenyl-3-(2-pyridyl) prop-2-en-1-one (**1**–**6**) are reported [15]. The pyrazoline function is a quite stable fragment in bioactive moieties to synthesize new compounds

* Corresponding author. Tel./fax: +91 4144 238282, mobile: +91 98943 85181.
*E-mail address:* chemrajalaksmi@gmail.com (R. Rajalakshmi).

1386-1425/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.saa.2013.12.032

possessing biological activities. This prompted us to synthesize various substituted N-thiocarbamoyl pyrazoline derivatives. In this article we focus the characterization of biologically active pyrazoline derivatives and to supplement the XRD parameters, theoretical calculations were made using Gaussian-03 package.

## Experimental section

### *Instruments*

The IR spectrum was recorded in AVATAR-330 FT-IR spectrophotometer and only noteworthy absorption levels (reciprocal centimeters) were listed. $^1$H NMR spectra were recorded at 300 and 400 MHz on Bruker AMX 300 and 400 MHz spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard. $^{13}$C NMR spectra were recorded at 75 and 100 MHz on Bruker AMX 300 and 400 MHz spectrophotometer using $CDCl_3$. The tubes used for recording NMR spectra were 5 mm diameter. The reactions and the purity of the products were assessed by performing TLC. All the reported melting points were taken in open capillaries and were uncorrected. Geometry optimization was carried out by Gaussion-03 ($AM_1$) package for all the compounds (**7–12**).

### *Synthesis*

#### *Synthesis of 1-thiocarbamoyl-3-pyridyl-5-phenyl-2-pyrazolines (**7–12**)*

Synthesis of pyrazoline derivative was performed in a manner as outlined in Scheme S1. The cyclization of chalcones with thiosemicarbazide under basic condition (anhydrous potassium carbonate) in 50 mL of ethanol led to the formation of pyrazoline compound and it is stable in solid state. The structures of pyrazoline derivatives (**7–12**), are given in Scheme S1.

#### *Synthesis of 1-thiocarbamoyl-3-pyridyl-5-(2,4-dichlorophenyl)-2-pyrazoline (**7**)*

Yield 70%; mp 115 °C; white crystal; molecular formula $C_{15}H_{12}N_4SCl_2$; $\upsilon_{max}$ cm$^{-1}$ 1595 (C=N), 3061 (HC=Ar), 3442–3369 ($NH_2$); $^1$H NMR (300 $MH_Z$ $CDCl_3$) δ(ppm): 3.3 (dd, 1H, $J_1$ = 4.2$H_Z$, $J_2$ = 18.9$H_Z$, $H_A$), 4.0 (dd, 1H, $J_1$ = 11.7 3$H_Z$, $J_2$ = 18.9$H_Z$ $H_B$), 6.2 (dd, 1H, $J_1$ = 4.2$H_Z$, $J_2$ = 11.7$H_Z$ $H_c$), 6.5 and 6.4 (2H, $NH_2$), 6.9–8.6 (m, 7H, Ar—H); $^{13}$C NMR (75 $MH_Z$ $CDCl_3$) δ(ppm): 157.38 (C=N), 177.25 (C=S), 41.74(C-4), 61.23(C-5), 121.48–149.69 (aromatic carbons). Anal. Calcd. (%) for: C, 51.29; H, 3.42; N, 15.93. Found (%): C, 51.31; H, 3.40; N, 15.82; LC–MS (*m*/*z*): 350.

#### *Synthesis of 1-thiocarbamoyl-3-pyridyl-5-(4-chlorophenyl)-2-pyrazoline (**8**)*

Yield: 70%; mp: 159 °C; white solid; molecular formula $C_{15}H_{13}N_4SCl$; IR $\upsilon_{max}$(cm$^{-1}$): 1604 (C=N); 1366 (C—N); 3043(Ar—H); 3442–3369 ($NH_2$); $^1$H NMR ($CDCl_3$) δ(ppm): 3.3 (dd, 1H, $H_A$, $J_1$: 7.5, $J_2$: 16.18), 3.9 (dd, 1H, $H_B$, $J_1$: 12.5, $J_2$: 18), 6.3 (dd, 1H, $H_C$, $J_1$: 7.6 $J_2$: 12.57), 6.5 and 6.4 (2H, $NH_2$), 6.8–8.7(Ar—H), 2$^{13}$C NMR ($CDCl_3$) δ(ppm): 152.37 C=N, 177.67 (C=S), 43.08 $CH_2$, 63.94 CH, 113.63–149.93(Ar—C). Anal. Calcd. (%) for: C, 56.87; H, 4.17; N, 17.82. Found (%): C, 56.81; H, 4.11; N, 17.72; LC–MS (*m*/*z*): 316.

#### *Synthesis of 1-thiocarbamoyl-3-pyridyl-5-(4-methoxyphenyl)-2-pyrazoline (**9**)*

Yield: 70%; mp: 177 °C; pale yellow powder; molecular formula $C_{16}H_{16}N_4SO$; IR $\upsilon_{max}$(cm$^{-1}$): 1621 (C=N); 1378 (C—N); 3043 (Ar—H); 3442–3369 ($NH_2$); $^1$H NMR ($CDCl_3$) δ(ppm): 3.3 (dd, 1H, $H_A$, $J_1$: 7.5, $J_2$: 16.74), 4.0 (dd, 1H, $H_B$, $J_1$: 12, $J_2$: 18), 6.1 (dd, 1H, $H_C$, $J_1$: 7.6 $J_2$: 12.45), 6.5 and 6.4 (2H, $NH_2$), 3.9 (S,3H, $OCH_3$), 6.8–8.5(Ar—H), $^{13}$C NMR ($CDCl_3$) δ(ppm): 161.88 C=N, 177.92 (C=S), 50.00 $CH_2$, 94.98 CH, 55.43 ($OCH_3$), 114.22–149.21(Ar—C). Anal. Calcd. (%) for: C, 61.49; H, 5.03; N, 17.63. Found (%): C, 61.51; H, 5.12; N, 17.42; LC–MS (*m*/*z*): 312.

#### *Synthesis of 1-thiocarbamoyl-3-pyridyl-5-(3,4-dimethoxyphenyl)-2-pyrazoline (**10**)*

Yield: 60%; mp: 147 °C; yellow solid; molecular formula $C_{17}H_{18}N_4O_2S$; IR $\upsilon_{max}$(cm$^{-1}$): 1594 (C=N); 1387 (C—N); 3052(Ar—H); 3442–3369 ($NH_2$); $^1$H NMR ($CDCl_3$) δ(ppm): 3.4 (dd, 1H, $H_A$, $J_1$: 7.6, $J_2$: 16.82), 4.1 (dd, 1H, $H_B$, $J_1$: 12, $J_2$: 18), 6.3 (dd, 1H, $H_C$, $J_1$: 7.6 $J_2$: 12.33), 6.5 and 6.4 (2H, $NH_2$), 3.8 (S,6H, $(OCH_3)_2$), 6.7–8.4(Ar—H), $^{13}$C NMR ($CDCl_3$) δ(ppm): 161.61 C=N, 177.38 (C=S), 50.13 $CH_2$, 95.22 CH, 56.16 ($OCH_3$), 109.02–149.37(Ar—C).). Anal. Calcd. (%) for: C, 59.67; H, 5.47; N, 16.33. Found (%): C, 59.71; H, 5.41; N, 16.37; LC–MS (*m*/*z*): 342.

#### *Synthesis of 1-thiocarbamoyl-3-pyridyl-5-(3,4,5-trimethoxyphenyl)-2-pyrazoline (**11**)*

Yield: 65%; mp: 183 °C; pale yellow powder; molecular formula $C_{18}H_{20}N_4SO_3S$; IR $\upsilon_{max}$(cm$^{-1}$): 1600 (C=N); 1385 (C—N); 3051 (Ar—H); 3442–3369 ($NH_2$); $^1$H NMR ($CDCl_3$) δ(ppm): 3.3 (dd, 1H, $H_A$, $J_1$: 7.6, $J_2$: 16.65), 4.1 (dd, 1H, $H_B$, $J_1$: 12, $J_2$: 18), 6.2 (dd, 1H, $H_C$, $J_1$: 7.6 $J_2$: 18.41), 6.5 and 6.4 (2H, $NH_2$), 3.9 (S, 9H, $(OCH_3)_3$), 6.8–8.5(Ar—H), $^{13}$C NMR ($CDCl_3$) δ(ppm): 161.61 C=N, 177.74 (C=S), 50.63 $CH_2$, 95.25 CH, 56.77 ($OCH_3$), 110.05–149.65(Ar—C). Anal. Calcd. (%) for: C, 58.07; H, 5.31; N, 15.27. Found (%): C, 58.11; H, 5.22; N, 15.25; LC–MS (*m*/*z*): 372.

**Table 1**
The selected bond distance, bond angles and dihedral angle for compound **7**.

| Connectivity | Bond distance* | Connectivity | Bond angle* | Connectivity | Dihedral angle* |
|---|---|---|---|---|---|
| S1—C7 | 1.6838(1.6205) | C7—N3—N2 | 118.37(121.71) | N3—N2—C6—C1 | 175.03(−176.40) |
| C1—N1 | 1.3467(1.3612) | N2—N3—C9 | 112.50(110.34) | N2—C6—C1—C2 | 16.4(−169.02) |
| C5—N1 | 1.331(1.3421) | C6—N2—N3 | 107.91(111.91) | N2—C6—C1—N1 | −160.89(10.97) |
| C5—C4 | 1.369(1.4088) | C5—N1—C1 | 117.29(117.48) | N2—N3—C7—S1 | 172.20(157.89) |
| C7—N4 | 1.329(1.3685) | N2—C6—C8 | 114.92(102.98) | N2—N3—C7—N4 | −7.4(−24.80) |
| C6—N2 | 1.2817(1.5042) | N1—C1—C2 | 122.72(122.34) | C9—N3—C7—S1 | 9.7(11.36) |
| N2—N3 | 1.3976(1.3608) | N4—C7—N3 | 116.11(118.72) | C7—N3—N2—C6 | −159.05(−149.93) |
| N3—C9 | 1.4839(1.3228) | N4—C7—S1 | 122.43(120.76) | C9—N3—N2—C6 | 5.93(−1.43) |
| C6—C8 | 1.492(1.5592) | N3—C7—S1 | 121.46(120.44) | C7—N3—C9—C8 | 154.80(149.57) |
| C8—C9 | 1.542(1.5221) | C15—C10—C11 | 116.62(118.45) | N2—N3—C9—C10 | 112.45(119.86) |
| N3—C7 | 1.354(1.425) | C6—C8—C9 | 102.63(101.58) | C9—C10—C15—C14 | 179.32(−179.77) |
| | | N1—C5—C4 | 123.81(123.99) | C9—C10—C11—C12 | 0.8(179.88) |
| | | C13—C12—C11 | 118.76(119.42) | C6—C1—C2—C3 | −176.26(179.84) |
| | | C4—C3—C2 | 119.41(119.12) | N1—C1—C2—C3 | 0.8(−0.15) |
| | | C3—C2—C1 | 118.32(118.93) | C1—N1—C5—C4 | 1.9(0.06) |
| | | N3—C9—C8 | 101.30(113.11) | C6—C8—C9—N3 | 7.59(1.26) |
| | | C12—C11—C10 | 122.35(120.93) | C6—C8—C9—C10 | −113.36(−120.97) |

* The values in the parenthesis are theoretically calculated.

**Table 2**
Dipole moment, optimized energy level, HOMO LUMO energies of **7–12**.

| Compounds | Dipole moment | Optimized energy level kcal/mol | HOMO | LUMO |
|---|---|---|---|---|
| **7**. $(D—Cl)_2$ | 5.92 | 143.85 | −0.28 | −0.19 |
| **8**. $—OCH_3$ | 4.18 | 113.07 | −0.31 | −0.02 |
| **9**. $(—OCH_3)_2$ | 3.78 | 72.99 | −0.31 | 0.03 |
| **10**. P—Cl | 5.67 | 148.85 | −0.31 | 0.03 |
| **11**. $N—(CH_3)_2$ | 5.19 | 166.74 | 0.30 | −0.02 |
| **12**. $(—OCH_3)_3$ | 4.85 | 67.11 | −0.31 | 0.03 |

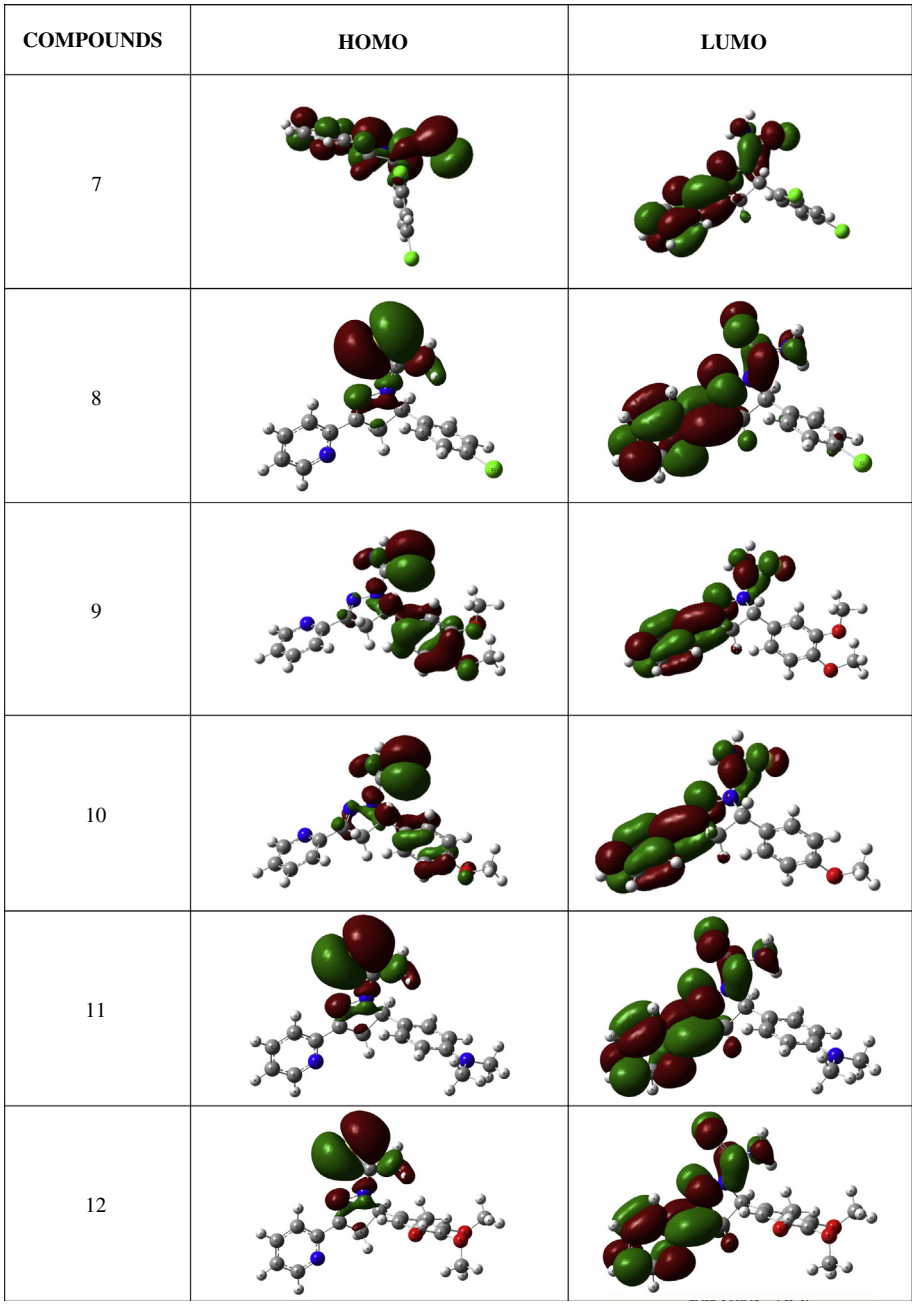



**Fig. 1.** The 3D plot of –HOMO–LUMO orbital picture of **7–12**.

*Synthesis of 1-thiocarbamoyl-3-pyridyl-5-(4-N,N-dimethylaminophenyl)-2-pyrazoline (12)*

Yield: 75%; mp: 133 °C; Orange powder; molecular formula $C_{17}H_{19}N_5S$; IR $\upsilon_{max}(cm^{-1})$: 1599 (C=N); 1355 (C—N); 3065(Ar—H); 3442–3369 ($NH_2$); $^1H$ NMR ($CDCl_3$) δ(ppm): 3.3 (dd, 1H, $H_A$, $J_1$: 7.0, $J_2$: 18.15), 4.0 (dd, 1H, $H_B$, $J_1$: 12.5, $J_2$: 18), 6.3 (dd, 1H, $H_C$, $J_1$: 7.0 $J_2$: 12.59), 6.5 and 6.4 (2H, $NH_2$), 2.9 (S, 6H, $(CH_3)_2$), 6.7–8.6 (Ar—H), $^{13}C$ NMR ($CDCl_3$) δ(ppm): 152.37 C=N, 177.45 (C=S), 64.33 $CH_2$,

113.63 CH, 43.13 ($CH_3$), 119.33–149.93(Ar—C). Anal. Calcd. (%) for: C, 62.70; H, 5.66; N, 21.63. Found (%): C, 62.71; H, 5.71; N, 21.42; LC–MS (*m*/*z*): 325.

## Results and discussion

### *Spectral analysis*

Several N-thiocarbamoyl pyrazoline derivatives were synthesized according to Scheme 1. Allthe synthesized compounds were characterized by IR, $^1$H and $^{13}$C NMR, Mass spectral techniques (LC–MS) and CHN analysis. In the IR spectrum of compound 7, the stretching frequency at 1595 $cm^{-1}$ is due to (C═N), the doublet at 3442 and 3369 $cm^{-1}$ is due to ($NH_2$) and the aromatic (C—H) stretching frequencies are observed at 3061 $cm^{-1}$. High resolution $^1$H NMR, $^{13}$C NMR have been recorded in $CDCl_3$ and analyzed. In the $^1$H NMR spectrum of compound **7**, the double doublet centered at 3.3 ppm with coupling constants $J_1$ = 4.2 $H_Z$ and $J_2$ = 18.9 $H_Z$ are due to $H_a$ proton at (C-4) and another double doublet centered at 4.0 ppm with coupling constants $J_1$ = 11.7 $H_Z$ and $J_2$ = 18.9 $H_z$ are due to $H_b$ proton at C-4. The double doublet observed at 6.2 ppm with $J_1$ = 4.2 $H_Z$ and $J_2$ = 11.7 $H_Z$ is due to $H_c$ proton at C-5. The two amino protons are appearing at 2.03 ppm. The signals appearing at 6.9 and 8.6 ppm are obviously due to aromatic protons.

In the $^{13}$C NMR spectrum of compound **7** the signal at 41.74 ppm is assigned to methylene carbon (C-4). The signal observed at 157.38 ppm, is due to (C═N) C-3 carbon. The signal at 61.23 ppm is assigned to C-5 carbon. The down field signal at 177.25 ppm is obviously due to the thiocarbamoyl ($H_2N$—C═S) carbon. The aromatic carbons could be readily distinguished by their characteristic absorption between 121.48 and 149.69 ppm. Similar results were obtained for all other synthesized compounds (**8–12**). The LC–MS compound **7** shows molecular ion peak at (*m*/*z*): 350.

### *ORTEP diagram*

The structure as well as the stereochemistry of compound **7** was confirmed by X-ray crystallographic analysis. Compound **7** shows an extended system involving pyridyl-C═N2—N3-thiocarbamoyl system with atoms N2 and N1 present in an anticonformation. The C1—C6 bond distance (1.46 Å) is lightly shorter than C—C single bond length but longer than C═C bond length. But the C9—C10 bond distance (1.515 Å) is almost equal to C—C single bond distance and hence the rotation of the molecule is possible and the molecule belongs to triclinic (p1) crystal lattice. The ORTEP diagram Fig. S1 and close packing structures are given in Fig. S2.

Though the five membered rings cannot be planar due to the presence of two $SP^3$ carbon atoms, from the ORTEP diagram it seems that the thiocarbamoyl group and pyrazoline ring are lying in a plane but the aryl ring is perpendicular to the plane of the molecule. The XRD parameters for compound (**7**) are given below.

### *Computational studies*

#### *Molecular modelling*

Molecular modelling was carried out by Gaussian-03 package using B3LYP/6-31G*(d, p) method. In order to supplement the XRD data the theoretical parameters were compared with the XRD data and are displayed in Table 1. The bond length, bond angle and dihedral angle were extracted from the optimized structure of (**7**). The theoretical parameters are higher than that of XRD parameters because the theoretical calculations were made for molecules which are in gaseous state. The representative molecular modelling of compound **7** is shown in Fig. S1. The non-co-planar geometry of the molecule was confirmed by XRD data which is further evidenced from the molecular modelling studies. Only selected bond distances, bond angles and dihedral angles are given in Table 1.

#### *HOMO–LUMO analysis*

The optimized energy, dipole moment and HOMO–LUMO energies of the compound (**7–12**) were calculated theoretically and are given in Table 2. From the HOMO and LUMO analysis it is clear that the intra molecular charge transfer must occur within the molecule. The 3D plot of HOMO and LUMO orbital picture is displayed in Fig. 1 (**7–12**). From the dipole moment values given in Table 2, it is evident that all the pyrazoline derivatives are highly polar and expected to possess Non–Linear Optical properties. Analyses of NLO behavior of the synthesized compounds are currently in progress.

## Conclusion

Biologically active pyrazoline derivatives have been synthesized and characterized by various spectroscopic techniques. ORTEP diagram of 1-thiocarbamoyl-3-pyridyl-5-(2,4-dichlorophenyl)-2-pyrazoline shows that pyrazoline derivatives exist as non-coplanar rings. DFT calculations also support the same and are expected to be highly polar. From the HOMO–LUMO electron density analysis it is evident that the intermolecular charge transfer takes place within the molecule.

## Acknowledgements

We are grateful to the UGC Networking Resource Centre, University of Hyderabad for providing characterization facilities and to Dr. R. Nagarajan, School of Chemistry, University of Hyderabad for providing laboratory facilities.

## Appendix A. Supplementary material

The crystallographic data of compound **7** (Figs. S1 and S2) have been deposited at Cambridge Crystallographic Data Centre (CCDC number: 893125). Copies of the data can be obtained free of charge on application to CCDC, 12 Union road, Cambridge CB2 1EZ UK. UK (fax: +44(01)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2013.12.032.

## References

[1] D.N. Dhar, The Chemistry of Chalcones and Related Compounds, JohnWiley, New York, 1981.
[2] K.B. Raut, Wender, J. Org. Chem. 25 (1960) 50–52.
[3] Z.S. Ariyan, H.J. Suschitzky, J. Chem. Soc. (1961). pp. 2242.
[4] A. Jurasek, V. Knoppava, M. Danderova, J. Kovar, Reinprecht, Tetrahedron 34 (1978) 1833–1836.
[5] M.A. Berghot, E.B. Moawad, Eur. J. Pharm. Sci. 20 (2003) 173–179.
[6] D. Nauduri, G.B. Reddy, Chem. Pharm. Bull. 46 (1998) 1254–1260.
[7] S.S. Korgaokar, P.H. Patil, M.T. Shah, H.H. Parekh, Indian J. Pharm. Sci. 58 (1996) 222–225.
[8] R.H. Udupi, A.R. Kushnoor, A.R. Bhat, Indian J. Heterocycl. Chem. 8 (1998) 63–66.
[9] M. Abid, A. Azam, Bioorg. Med. Chem. 15 (2005) 2213–2220.
[10] A. Bilgin, E. Palaska, R. Sunal, Arzneim.-Forsch. 43 (1993) 1041–1044.
[11] K.S. Guniz, S. Rollas, H. Erdeniz, M. Kiraz, E.A. Cevdet, A. Vidin, Eur. J. Med. Chem. 35 (2000) 761–777.
[12] Y. Fushizaki, K. Sakikawa, Jpn. Patent. JP. (1971) 4600357.
[13] R.A. Bissell, A.P. de Silva, H.Q.N. Gunaratne, P.L.M. Lynch, G.E.M. Maguire, C.P. McCoy, K.R.A.S. Sandanayake, Top. Curr. Chem. 168 (1993) 223–264.
[14] P. Wang, N. Onozawa-Komatsuzaki, Y. Himeda, H. Sugihara, H. Arakawa, K. Kasuga, Tetrahedron. Lett. 42 (2001) 9199–9201.
[15] Y.R. Prasad, P. Praveen kumar, P. Ravikumar, A. Srinivasan rao, E-J. Chem. 5 (2008) 144–148.