

Physicochemical and biological studies on 4-(*o,p*-dichlorophenyl)-2-aminothiazole

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ABSTRACT: 4-(*o,p*-dichlorophenyl)-2-aminothiazole (DCPAT) has been synthesised and characterized by elemental, spectral, thermal and X-ray diffraction analyses. The TG-DTA curve of the compound was critically analysed in order to calculate various kinetic parameters (*n*, *E*, *Z*, ΔS and *G*) using Coats – Redfern (C.R.), MacCallum-Tanner (M.T.) and Horowitz-Metzger (H.M.) method. X-ray diffraction studies suggested that the compound possesses a triclinic crystal system. The compound was tested for the evaluation of antibacterial activity against *S. aureus* and *K. pneumoniae* and antifungal activity against *A. niger* and *C. albicans*.

KEY WORDS: Aminothiazole, physicochemical studies, antibacterial and antifungal activities.

I. INTRODUCTION

Thiazoles and their derivatives belong to an important class of heterocyclic compounds having an important position in medicinal chemistry, because of their wide range of bioactivities. Many of them exhibit an excellent antibacterial and antifungal^{1, 2}, anti-HIV³, hypertension⁴, anti-inflammatory⁵, anticancer⁶, anti-convulsant⁷, analgesic⁸ and anti-tubercular activities⁹. Literature survey reveals that 2-aminothiazole could be used as a template for the development and designing of more potent therapeutic agents, and recent development in the chemistry of 2-aminothiazole has created interest among researchers owing to its role in treatment of neurological diseases and modulators of transcriptional repression for treatment of Huntington's disease¹⁰. In continuation of our earlier studies¹¹, we report herein synthesis, physicochemical and biological studies on 4-(*o,p*-dichlorophenyl)-2-aminothiazole (DCPAT) (fig. 1).

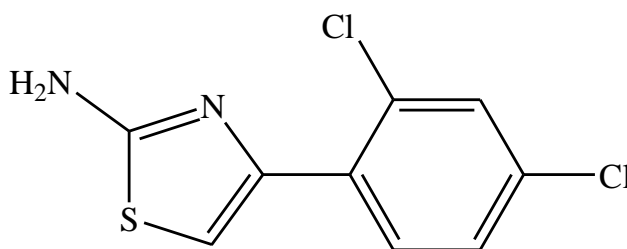


Fig.1: 4-(*o,p*-dichlorophenyl)-2-aminothiazole (DCPAT)

II. RESULTS AND DISCUSSION

4-(*o,p*-dichlorophenyl)-2-aminothiazole (DCPAT) is a colourless crystalline solid having sharp melting point 158°C. It is soluble in common organic solvents and gives satisfactory C, H and N analyses data. *Spectral analyses* Uv-visible spectrum of 2-aminothiazole¹² exhibits λ_{\max} at ~ 275 nm and compounds having comparable structures exhibit λ_{\max} at ~ 300 nm. Uv-visible spectrum of DCPAT exhibits λ_{\max} at ~ 300 nm, which is in accordance with the earlier reports¹². IR spectrum of DCPAT exhibits $\nu(\text{NH}_2)$, $\nu(\text{C}=\text{N})$ and $\nu(\text{C}-\text{S}-\text{C})$ modes at ~3440, ~1610 and ~ 556 cm^{-1} respectively and these values match well with the earlier reports¹³. ¹HNMR spectrum of DCPAT shows signals at (CDCl_3 , TMS, δ ppm) 5.05 (2H, s, NH_2), 7.05 (1H, s, H-thiazole), 7.4 (2H, d, Ar-H), 7.85 (1H, s, Ar-H). The assignments of these signals are in agreement with the earlier reported results¹⁴. Mass spectrum of DCPAT (fig. 2) exhibits M^+ peak at *m/z* ratio 244 (relative intensity 100 %) corresponding to the molecular weight of the compound and confirms the molecular formula as $\text{C}_9\text{H}_6\text{Cl}_2\text{N}_2\text{S}$. The $\text{M}^+ + 2$ (*m/z* 246* with relative intensity 66.67%) and $\text{M}^+ + 4$ (*m/z* 248* with relative intensity 15.15%) peaks are observed due to two isotopic chlorine. The peaks marked with (*) are due to isotopic chlorine. The

molecular ion undergoes rupture of thiazole ring¹⁵ to give fragments at m/z 202/204*/206* (relative intensity 58/39.39/6.06 respectively). These fragment further loose two chlorine atoms one by one to give fragments having m/z 167 (23.8%) and 132 (11.3%). Fragmentation pattern is depicted in Scheme I. The fragment m/z 132 (11.3%) then undergoes decomposition to give smaller fragments, m/z (relative intensity %):123 (18.18), 104 (17.00), 87 (11.36), 73 (12.27), 45 (12.27).

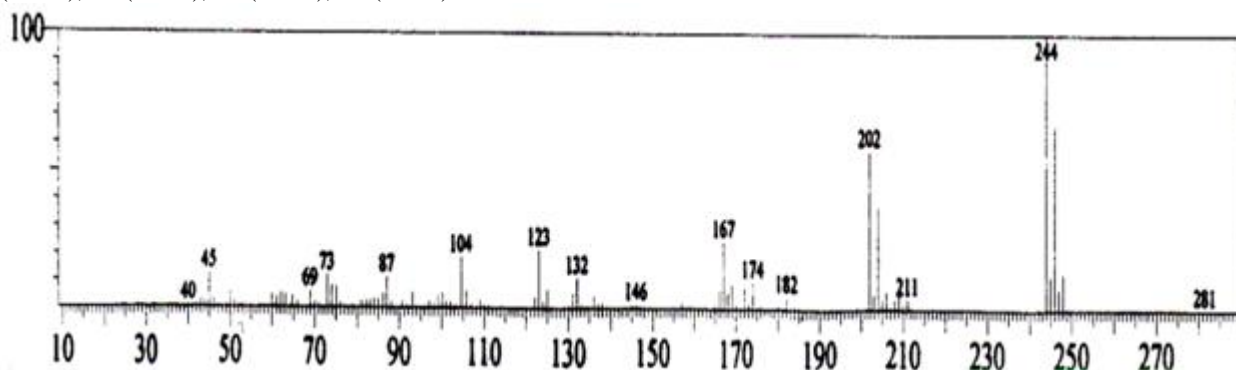
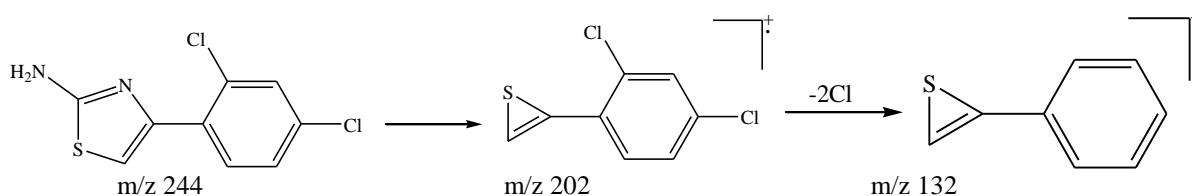


Fig. 2: Mass spectrum of DCPAT



Scheme I: Fragmentation pattern of DCPAT

Thermal analysis : Thermogravimetric analysis is one of the important techniques for the study of thermal properties of substances. From the TG-DTA curve, various kinetic parameters can be estimated using different methods which are broadly classified as differential methods and integral methods. The TG-DTA curve of DCPAT was critically analysed in view of evaluating various kinetic parameters such as **n** (order of reaction), **E** (energy of activation), **Z** (pre-exponential factor), ΔS (entropy change) and **G** (free energy change) using integral methods viz. Coats – Redfern (C.R.), MacCallum-Tanner (M.T.) and Horowitz-Metzger (H.M.) method as follows:

Coats-Redfern method¹⁶

$$\log \frac{1-(1-\alpha)^{1-n}}{(1-n)T^2} = \log \frac{ZR}{Eq} - \frac{E}{2.303R} \times \frac{1}{T} \quad \dots 1$$

MacCallum- Tanner Method¹⁷

$$\log \left(\frac{1-(1-\alpha)^{1-n}}{(1-n)} \right) = \log \frac{ZE}{Rq} - 0.485E^{0.435} - \frac{0.449 + 0.217E}{T} \cdot 10^3 \quad \dots 2$$

Horowitz – Metzger Method¹⁸

$$\log \left(\frac{1-(1-\alpha)^{1-n}}{(1-n)} \right) = \log \frac{ZRT_s^2}{Eq} - \frac{E}{2.303 RT_s} + \frac{E \theta}{2.303 RT_s^2} \quad \dots 3$$

In all three equations: α is the fraction of weight loss at the particular temperature, T_s is the temperature at half weight loss, q is the rate of heating, θ is difference of particular temperature and temperature at half weight loss ($T-T_s$). From the calculated values of E and Z , the values of ΔS and G were determined by using the equations as follows:

$$\Delta S = 2.303 \times \log [(Z \times h) / (T_s \times k)]$$

$$G = E - (\Delta S \times T_s)$$

DCPAT undergoes decomposition in two stages, Stage-I: 158^oC to 262^oC (83.59% weight loss) and Stage-II: 262^oC to 600^oC (8.25% weight loss). Two DTA peaks (endothermic) are located at 158.74^oC and 262.58^oC. The residue (5.414%) remaining at the end may be due to formation of thermally stable compound at high temperature. Major weight loss occurs in Stage I only and hence the kinetic parameters (n, E, Z, ΔS and G) have been calculated for this stage. The values of kinetic parameters calculated by Coats – Redfern (C.R.), MacCallum-Tanner (M.T.) and Horowitz-Metzger (H.M.) method are given in Table1. The values of E (occurring in the range 21-27 Kcal mol⁻¹) and G (22 – 28 Kcal mol⁻¹) are sufficiently high and suggest that DCPAT is a thermally stable compound. The TG-DTA curve is depicted in figure 3.

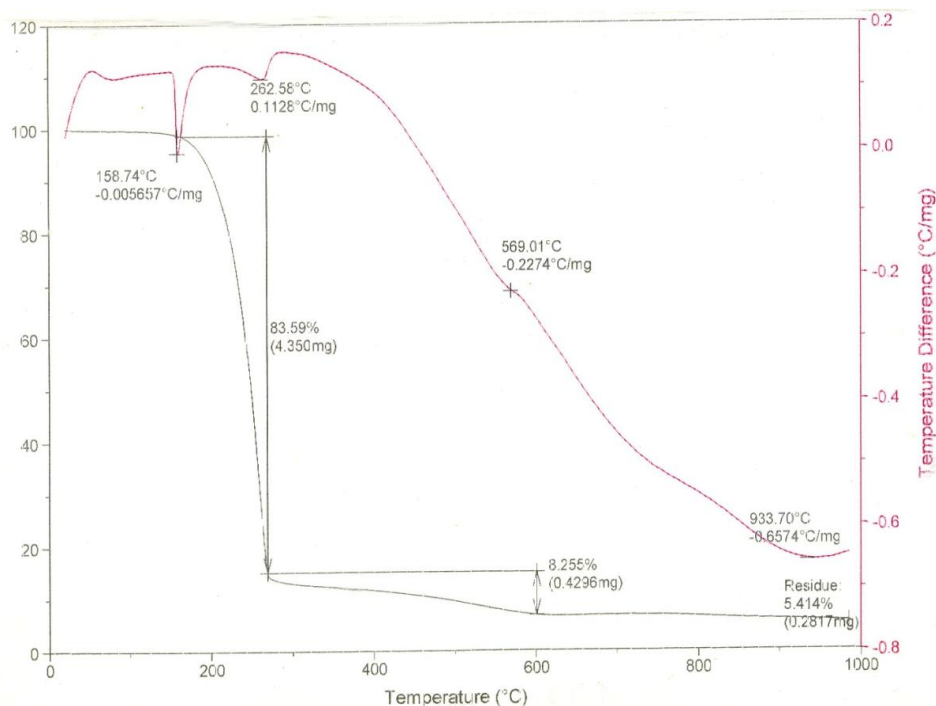


Fig. 3: TG-DTA curve of DCPAT

Table 1: Kinetic parameters estimated by Coats – Redfern (C.R.), MacCallum-Tanner (M.T.) and Horowitz-Metzger (H.M.) method.

Kinetic parameters	Stage - I		
	C.R.	M.T.	H.M.
n	0.47	0.45	0.75
E	21.507	21.329	26.826
Z	3.83x10 ⁶	6.20x10 ¹²	9.36x10 ¹¹
ΔS	-15.15	-0.8514	-2.44
G	24.032	22.4715	27.128
Units: E (kcal mol ⁻¹), Z (S ⁻¹), ΔS (JK ⁻¹ mol ⁻¹), G (kcal mol ⁻¹)			

X-ray diffraction study

DCPAT has been characterized by powder x-ray diffraction studies to predict the crystal system. The diffractogram is depicted in fig. 4 which shows 47reflection (2θ) between 10.67^o to 93.03^o with maximum at 2θ = 34.83^o and d = 2.57Å. The cell parameters calculated are mentioned in parenthesis (a = 8.1851Å, b = 8.7875 Å, c = 7.0573 Å and α = 90.3050°, β = 97.7880°, γ = 109.4140°) and these values are found to be in agreement with those required for a triclinic crystal system¹⁹ where a ≠ b ≠ c and α ≠ β ≠ γ. Therefore it may be concluded that the crystal system of the DCPAT is triclinic. The volume of unit cell is 473.90 Å³.

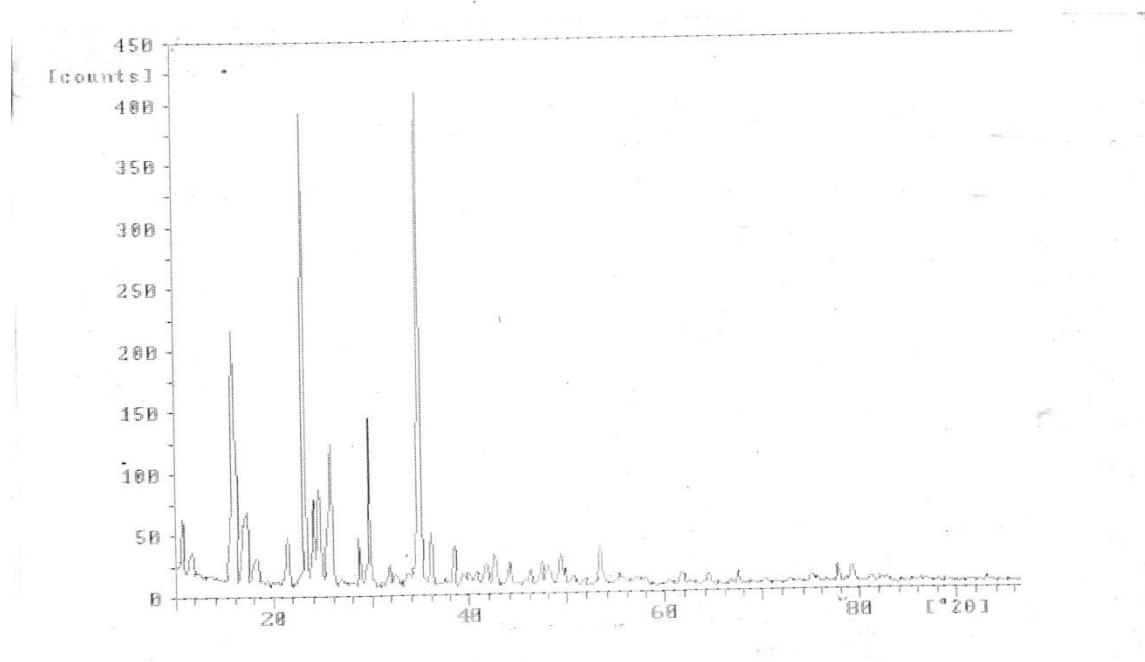


Fig. 4: X-ray diffractogram of DCPAT

Biological activity : We have tested DCPAT for the evaluation of antibacterial activity against *S. aureus* and *K. pneumoniae* and antifungal activity against *A. niger* and *C. albicans* in DMF as solvent using serial dilution technique²⁰. Eight test tubes containing 5 ml of sterile nutrient / sabouraud broth were inoculated with 0.02ml of 24 h old culture of bacteria *S. aureus* and *K. pneumoniae* and fungi *A. niger* and *C. albicans* respectively. Different amounts of DCPAT were added with the help of sterile pipette from the stock solution 200 µg/ml to 5 ml quantities of respective media so as to reach the concentration from 1µg/ml to 20µg/ml. All test tubes were inoculated at 37°C and at room temperature for bacteria and fungi respectively. Test tubes inoculated with organisms were observed for presence of turbidity after 24h and 48h respectively. The lowest concentration of DCPAT inhibiting the growth of test organism was determined as MIC value. The minimum inhibition concentration (MIC) values for DCPAT lie in the range 8-12 µg/ml for antibacterial activity and 4-8 µg/ml antifungal activity (Table 2 and 3). DCPAT was found to exhibit pronounced antifungal activity compared to antibacterial activity

Table 2: Antibacterial activity of DCPAT

Conc. of thiazole in µg/ml	Growth (+) /inhibition (-) of (<i>S. aureus</i>)	Growth (+) /inhibition (-) of (<i>K. pneumoniae</i>)
4	+	+
6	+	+
8	-	+
10	-	+
12	-	-
14	-	-

Table 3: Antifungal activity of DCPAT

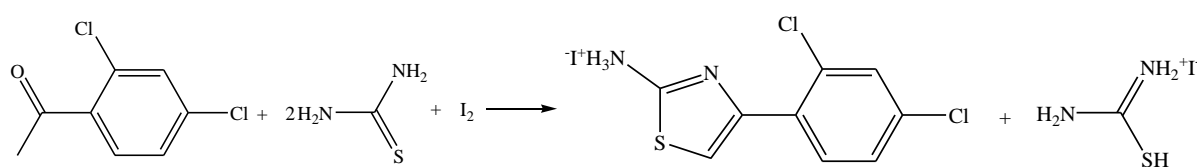
Conc. of thiazole in µg/ml	Growth (+) /inhibition (-) of (<i>A. Niger</i>)	Growth (+) /inhibition (-) of (<i>C. albicans</i>)
2	+	+
4	-	+
6	-	+
8	-	-
10	-	-
12	-	-

III. CONCLUSION

DCPAT is a thermally stable compound having sharp melting point and possesses a triclinic crystal system. It is biologically active and exhibits pronounced *antifungal activity* compared to *antibacterial activity*.

Experimental : All the chemicals used were of A. R. Grade. The solvents were dried according to standard procedures and distilled before use. Elemental analyses (C, H and N) were performed using micro analytical technique. Physical measurements were performed as reported in our earlier communication¹¹.
*Synthesis of 4-(o, p-dichlorophenyl)-2-aminothiazole (DCPAT)*²¹

A mixture of 2,4-dichloroacetophenone (0.05mol), thiourea (0.1mol) and iodine (0.1mol) was refluxed on water bath for eight hours and again 12 to 16 hours after removal of the condenser. The crude reaction product was kept in contact with diethyl ether with occasional shaking for 48 hours. The ether layer was then removed and reaction product was treated with sodium thiosulphate solution to remove traces of iodine. The product was boiled with water and filtered in hot condition. The filtrate was treated with concentrated ammonia to obtain DCPAT, which was recrystallized from 50% ethanol and dried under reduced pressure and its purity was tested by TLC. Scheme II represents synthesis of DCPAT.



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