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Synthesis, Characterization and Evaluation of Thiourea Derivatives for Cytotoxicity of Breast Cancer

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Abstract. Background: Breast cancer is the leading cause of death in women worldwide and the second most common cause in the US. Rescovitine a clinical CDK2 inhibitor has been studied as a potential anticancer agent in breast cancer. has a short half-life (2–5 h), necessitating new analogs with improved pharmacokinetics. Objective: To design and synthesize five thiourea derivatives (VIa–VIe) that mimic rescovitine selectivity and low toxicity, while addressing its pharmacokinetic limitations. Evaluation the cytotoxicity in MCF-7 breast cancer cells. Materials & Methods: Derivatives were synthesized by reacting substituted benzoic acids with SOCl2, followed by the formation of isothiocyanates (IIa–e). Subsequent reflux with 5-amino-1H-pyrazole-4-carbonitrile yielded the thioureas VIa–VIe. Characterization: Melting points, NMR ($^{1}H/^{13}C$), FT-IR spectroscopy, and EI-MS. antiproliferative activity against MCF-7 cell (MTT assay, IC_{50}), compared to rescovitine. Results: VIa and VIe showed best MCF-7 inhibition (93.77%, IC_{50} = 123.64 µM; 94.55%, IC_{50} = 118.49µM) vs. rescovitine (97.33%, IC_{50} = 20.27µM). VIe (4-F substituent) and VIa (unsubstituted) exhibited strongest cytotoxicity against. All compounds complied with Lipinski's Rule of Five (0 violations) and showed excellent GI absorption but no BBB permeability. Electronic substituents (e.g., F in VIe) enhanced the activity, while steric groups (e.g., CH_3 in VIb) reduced the efficacy. Conclusion: VIa and VIe emerged as lead candidates with cytotoxicity comparable to that of rescovitine. Fluorine substitution (VIe) optimized the activity, highlighting structure-activity relationships for future to get more potent molecules.

Highlights:

1. Compounds Identified: VIa and VIe demonstrated strong antiproliferative activity in MCF-7 cells, approaching that of rescovitine, despite higher IC_{50} values.
2. Structure-Activity Relationship (SAR): Electron-withdrawing substituents like fluorine (VIe) enhanced cytotoxicity, while bulky groups reduced efficacy.
3. Pharmacokinetics Advantage: All synthesized compounds complied with Lipinski's Rule and exhibited excellent GI absorption—supporting their potential as orally available anticancer agents.

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Keywords: MCF-7 Inhibition, Thiourea Derivatives, Rescovitine, Anticancer Agents, Kinase Inhibitors.

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Introduction

Breast cancer is the second most common cause of cancer-related deaths among women in the United States and the leading cause of cancer-related deaths among women globally. Breast cancer risk can be determined by risk assessment tools, and high-risk patients may be eligible for risk-lowering drugs. With 2,261,419 new cases, the incidence rate of breast cancer (BC) is 11.7% worldwide, slightly higher than the prevalence of lung cancer (11.4%) [1], [2]. Less than 1% of all cancer cases in men are breast cancer, making it a rare disease. It is more prevalent in older adults with a family history of breast cancer, hormonal imbalances, and radiation exposure. The most prevalent risk factor for this illness in men is a mutation in the BRCA2 gene [3]. The incidence rate of breast cancer rises sharply with age and peaks during menopause, making age the most significant known risk factor for the disease [4]. Younger women, however, have more advanced stages, larger tumors, positive lymph nodes, and a lower chance of survival. Women with blood group AB and Rhesus negative have a lower risk of breast cancer than those with blood group A and Rhesus positive, Breast cancer is associated with reproductive factors, including ovarian hormones. The risk is doubled for younger menarche ages [5], [6]. A number of complicating factors, such as the side effects of traditional treatments like chemotherapy and radiation therapy, make managing patients with breast cancer more difficult [7]. As a result, a great deal of research is currently being conducted to develop alternative approaches to treating breast cancer. These tactics could be used as chemo preventive agents, adjuvant treatments in addition to current options, or therapies [8]. Certain urea derivatives have been shown to have strong cytotoxic effects on cancer cells. By preventing cell division, promoting apoptosis (programmed cell death), and changing the metabolism of cancer cells, these substances can cause cell death [9]. Derivatives of thiourea have also demonstrated strong anticancer properties. These compounds have been shown to be effective in preventing the growth of different cancer cell lines and have the potential to

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reverse drug resistance in cancer cells [10]. Derivatives of thiourea can target specific molecular pathways involved in the progression of cancer, such as the modulation of cancer cell signaling pathways and the inhibition of angiogenesis [11], [12]. This enables scientists to improve their structures and tailor them to specific drug delivery systems or cancer types. Furthermore, a variety of urea and thiourea derivatives have shown favorable pharmacokinetic properties, including efficient distribution, metabolism, excretion, and absorption profiles. They are therefore well-positioned to move forward with drug development [13]. The goal of this research is to create new thiourea derivatives that will alter the ratio of these compounds' hydrophilicity and lipophilicity and one of these derivatives shown in scheme (1), making it easier to examine how they inhibit human breast cancer cells. Rescovitine is a common drug used to assess cytotoxicity against the MCF-7 cell line [14].

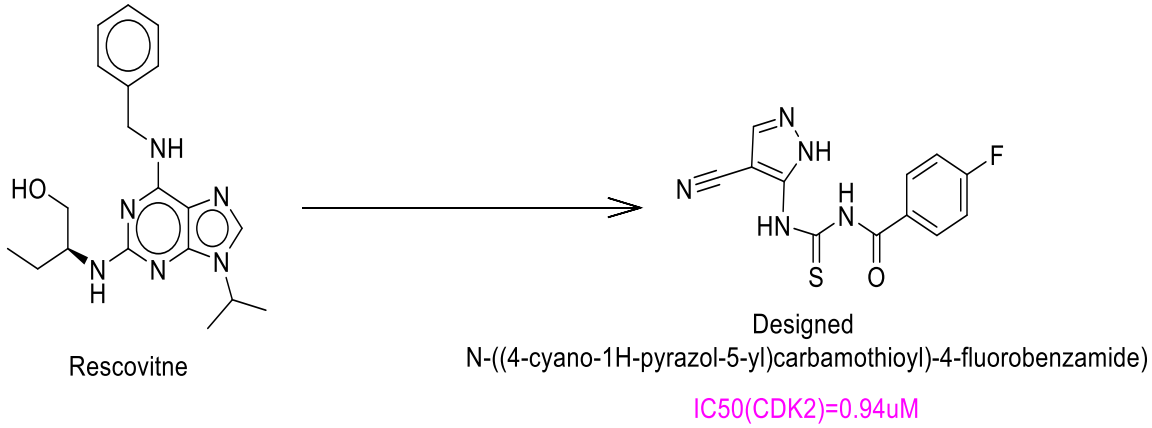

Figure 1. Potent Thiourea Derivative

1. Ethical Approval

This study was reviewed and approved by the Institutional Ethics Committee of the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Basrah in accordance with the ethical standards outlined in the Declaration of Helsinki for research involving human participants.

Approval Number: 669/5/3

Date of Approval: August .30. 2023

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Methodology

A. General

Starting materials which used in synthesis of compounds purchased from Sigma-Aldrich (Germany) or Baoji Guokang Bio/Technology Co., Ltd (China) Organics. were on Stuart Scientific apparatus which recorded the Melting points. The reaction is monitored by analytical TLC hexane-ethyl acetate 2-4ml, 13CNMR and 1HNMR spectra were recorded at University of Basrah/ College of Education for Pure Sciences/Department of Chemistry in δ scale given in ppm (on a Bruker 101 MHz for 13C and 400 MHz for 1H spectrophotometer) and internal reference were TMS. FT-IR spectra were recorded in University of Basrah by spectrometer of Therma Scientific Nicolet iS10. EI-MS spectra at the chemistry faculty at Tehran University and biological tests (CDK2I, MCF-7 and HTC-116) at the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo University .

B. Synthesis

The process involves the reaction of 4-un/substituted benzoic acid (Ia-e) in anhydrous methylene chloride and thionyl chloride to form 4-un/substitutedbenzoic acid chloride, ammonium thiocyanate added to acid chloride, and heating under reflux for 5 h to form isothiocyanates (IIa-e) [15], [16]. The isothiocyanates were then filtered, and a solution of 2-(ethoxymethylene) malononitrile in anhydrous ethanol was added. The reaction mixture was refluxed for 5 h and the solvent was removed under vacuum[17] [18]. The isothiocyanates were then reacted with 5- amino-1H-pyrazole-4-carbonitrile in anhydrous acetone, resulting in thiourea derivatives (VIa–e) , which shown in scheme (2) [19] [20].

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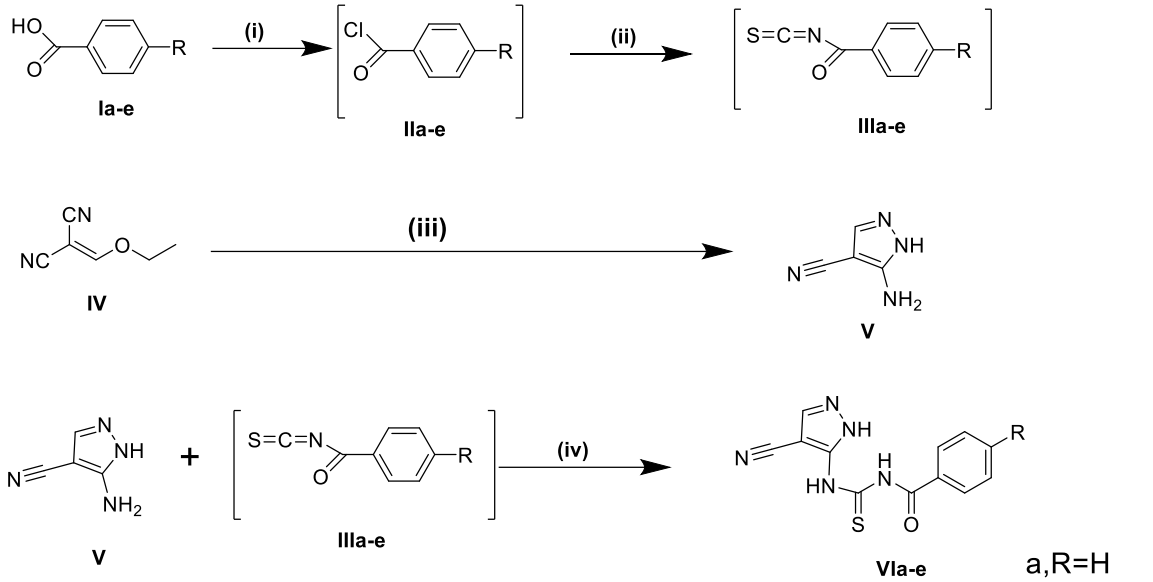

Reagents and reaction condition :
(i) SOCl2,methylene chloride,reflux 4-5 hrs
(ii) NH4SCN,acetone,reflux 0,5-1hrs
(iii)hydrazine hydrate,ethanol reflux3hrs
(iv) acetone,reflux2-3hrs

Figure 2. Synthesis of thiourea derivatives

Result and Discussion

A. The Swiss ADEM

The Swiss ADEM a free online tool that helps predict pharmacokinetics, drug-likeness, and medicinal chemistry properties of small molecules. It helps chemists and researchers evaluate a compound's suitability as a drug candidate, filter out toxic or poorly absorbed compounds, and speed up drug discovery. To be used as an oral medication, a drug must meet five requirements: a molecular weight (MWT) of over 500, more than five H-bond donors (NHD), ten H-bond acceptors (NHA), and a computed log P of more than five. The number of rotatable bonds (NRB) is a key factor in determining permeability properties. Lipinski's rule of five suggests that a drug's molecular weight must be less than 500 g/mol to increase permeability. The

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study found that five organic compounds have moderate lipophilicity, good for oral drugs. The Lipinski rule of five states that a drug's TPSA must be less than 140 Å for bioavailability [21]. All derivatives comply with Lipinski's Rule of Five (0 violations), exhibit excellent gastrointestinal absorption, lack blood-brain barrier permeability, and are water soluble. Molecular weights range from 271.3–350.19 g/mol, with consistent rotatable bonds (5) and hydrogen-bond acceptors/donors (3–4/3), according to Table (1).

Table 1. Properties for studied compounds according to Swiss ADME

Property	**VIa**	**VIb**	**VIc**	**VId**	**VIe**
Molecular Weight (g/mol)	271.3	285.32	350.19	305.74	289.29
Num. Rotatable Bonds	5	5	5	5	5
Num. H-bond Acceptors	3	3	3	3	4
Num. H-bond donr	3	3	3	3	3
Water Solubility Class	Soluble	Soluble	Soluble	Soluble	Soluble
Absorption in GI	Excellent	Excellent	Excellent	Excellent	Excellent
Permeant to BBB	Not pass	Not pass	Not pass	Not pass	Not pass
Lipinski Rule Violations	0	0	0	0	0

B. The Novel Derivatives of Thiourea Filtered as Solid Product With Different Melting Point and Different Characteristic as Below

1. N-((4-cyano-1H-pyrazol-5-yl) carbamothioyl) benzamide

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The product was filtrated as solid yellow color, (74%); m.p. 168°C 1H NMR δ ppm: 7.50 (Aromatic-H, 2H, triplet), 7.63 (Aromatic -H ,1H, triplet), 7,90 (Aromatic-H, 2H, doublet), 9.58 (D2O exchangeable, NH, singlet, 1H), 9.86(D2O exchangeable, NH, singlet ,1H), 8.08(cyclic ring, 1H, singlet), 11.26 (cyclic ring, NH, 1H, singlet). 13C NMR δ ppm: 92.66, 115.04, 128.88,129.06, 132.74, 133.46, 134.13, 138.55,168.28,182.28. FT.IR (KBr, v_{max} / cm^{-1}): 3309- 3155 cm^{-1} (br, NHs), nitrile (-CN) stretch at 2280 ,1681 (C=O), 1604 (C=N).

2. VIb(n-((4-eyno-1H-Pyrazol-5-yl))carbamothioyl)-4-methylbezamide)

The Product was filtrated as solid yellow color, (78.5%); m.p.168 °C 1H NMR δ ppm: 3.50(Aromatic.sub,1H, singlet),7.42 (Aromatic -H, 2H, doublet), 7.96 (Aromatic-H, 2H, doublet), 9.68 (D2O exchangeable, NH, 1H, singlet), 10.01(D2O exchangeable, NH,1H, singlet),8.22(cyclic ring, 1H, singlet), 11.29(cyclic ring, NH ,1H, singlet).

13C NMR δ ppm:21.60 ,98.93, 113.85, 128.48,129.15,129.60,129.80, 143.50,143.90, 167.78,182.59. FT.IR (KBr, v_{max} / cm^{-1}): 3307 (NHs), 1678 (C=Os), 1612 (C=N), at 2900 stretching of C-H of alkyl

3. VIc(4-bromo-N-((4-cyano-1H-pyrazol-5yl) carbamothioyl) benzamide)

The Product was filtrated as solid yellow color (yield: 68%), m.p. 244-245 °C ^{1}H NMR δ ppm: 7.62 (Aromatic-H, 2H, doublet), 7.97 (Aromatic-H, 2H, doublet), 9.81 (D_2O exchangeable, NH, 1H, singlet), 11.39(D_2O exchangeable, NH, 1H, singlet), 9.62 (cyclic ring,1H, singlet), 12.84(cyclic ring, NH, 1H, singlet). 13C NMR ppm:92.00, 116.80, 127.37,130.44, 131.77, 132.18, 148.74,155.64,167.09,181.46. FT-IR (KBr vmax / cm-1): 3309, 3221 and 3191 cm^{-1} (br, NHs), 1680 (C=Os), 1587 (C=N), 1425(C=S)

4. VId(4-chloro-N-((4-cyano-1H-pyrazol-5-yl) carbamothioyl) benzamide)

The Product was filtrated as solid yellow color, (yield:70%), m.p. 215°C ^{1}H NMR δ ppm: 7.53 (Aromatic-H, 2H, d), 7.91 (Aromatic-H, 2H, doublet), 9. 61 (D_2O exchangeable, NH, 1H, singlet), 9.80(D_2O exchangeable, NH, 1H, singlet), 8.72 (cyclic ring ,1H, singlet), 11.38(cyclic ring, NH,1H, singlet).

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^{13}C NMR δ ppm: 72.69, 109.82, 128.92,131.07, 131.58, 137.54, 138.30,147.77, 167.30,182.43. IR FT-IR (KBr vmax / cm-1): 319-3223 (br, NHs), 1685 (C=Os), 1595 (C=N),1535 (C=S),

5. VIe(N-((4-cyano-1H-pyrazol-5-yl) carbamothioyl)-4-fluorobenzamide)

The Product was filtrated as solid yellow color (yield: 62%), m.p. 169-171°C ^{1}H NMR δ ppm: 7. 74 (Aromatic-H,2H, doublet), 7.81 (Aromatic-H,2H, doublet), 9.82 (D_2O exchangeable, NH, 1H, singlet), 11.40(D_2O exchangeable, NH, 1H, singlet), 9.63(cyclic ring, 1H, singlet), 13.22(cyclic ring, NH, 1H, singlet).

^{13}C NMR δ ppm: 81.41, 106.42, 115.92,116.21,127.82,129.25, 132.53, 132.62, 139.02,164.13, 166,85.30,180.26. FT-IR (KBr vmax / cm-1): 3309, 3290 and 3082 (br, NHs), 1687 (C=Os), 1604 (C=N), 1510(C=S)

The mass spectra are characterized by the presence of molecular ion peak M·+, which is found to be equal to the molecular weight of the studied compounds[22] [23].

The 1H-NMR are similar and characterized by the presence Aromatic protons(7.4–8.0) Present in all compounds (multiplets/doublets for aromatic Hs), NH protons(9.5–10.1) and (11.2–13.2) Two singlets D_2O exchangeable NHs in each compound[24] [25], consistent for thioamide and amide, Pyrazole H -cyclic (8.0–9.6), (11–13),One or two singlets for heterocyclic (pyrazole) NH, consistent in all in addition Alkyl proton 3.50ppm (VIbonly) Seen due to methyl substitution in VIb. The 13C-NMR spectra show three groups of signals: Aromatic carbons (127–139) Observed all compounds C=S(180–182)Common for thioamide, C=O(164–168) All show clear carbonyl signals in addition CN (nitrile) (92–116) Present in all (CN or pyrazole) , according to Table (2) . The FT-IR spectra revealed the presence of important bands associated with the functional groups of the studied compounds. Broad peaks around 3300 cm^{-1} seen in all compounds for (N-H), Strong absorption around 1680–1687 cm^{-1} in all compounds for Carbonyl (C=O), Present in all, usually ~1587–1612 $cm^{-1}$for C=N stretch [26] [27] [28], according to Table (3). All chart of FT-IR and NMR were below.

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Table 2. NMR of thiourea dervitives

Compound	^{1}H NMR (Aromatic Hs)	^{1}H NMR (NHs)	^{13}C NMR (C≡N/Pyrazole)	^{13}C NMR (C=O)	^{13}C NMR (C=S)
VIa	7.50–7.90	9.58, 9.86, 11.26	92.66, 115.04	168.28	182.28
VIb	7.42, 7.96	9.68, 10.01, 11.29	98.93,113.85	167.78	182.59
VIc	7.62, 7.97	9.81, 11.39, 12.84	92.00, 116.80	167.09	181.46
VId	7.53, 7.91	9.61, 9.80, 11.38	72.69, 109.82	167.30	182.43
VIe	7.74, 7.81	9.82, 11.40, 13.22	81.41, 106.42	166	180.26

Table 3. FT-IR of thiourea dervitives

Compound	IR v(NH)	IR v(C=O)	IR v(C=N)	IR v(C=S)	IR v(C–O)
VIa	3309–3155	1681	1604	1238	1109
VIb	3307	1678	1612	1286	1182
VIc	3309–3191	1680	1587	1425	1012
VId	3319–3223	1685	1595	1535	1014
VIe	3309	1687	1604	1510	1016

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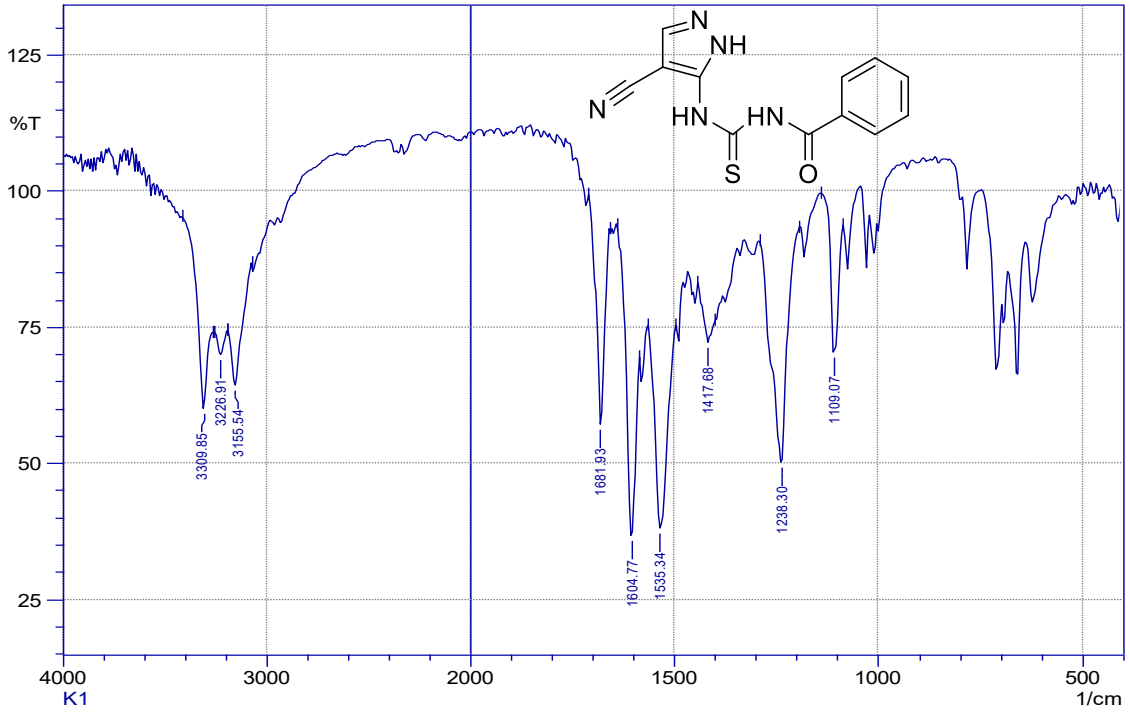

Figure 1. FT-IR spectrum of VIa

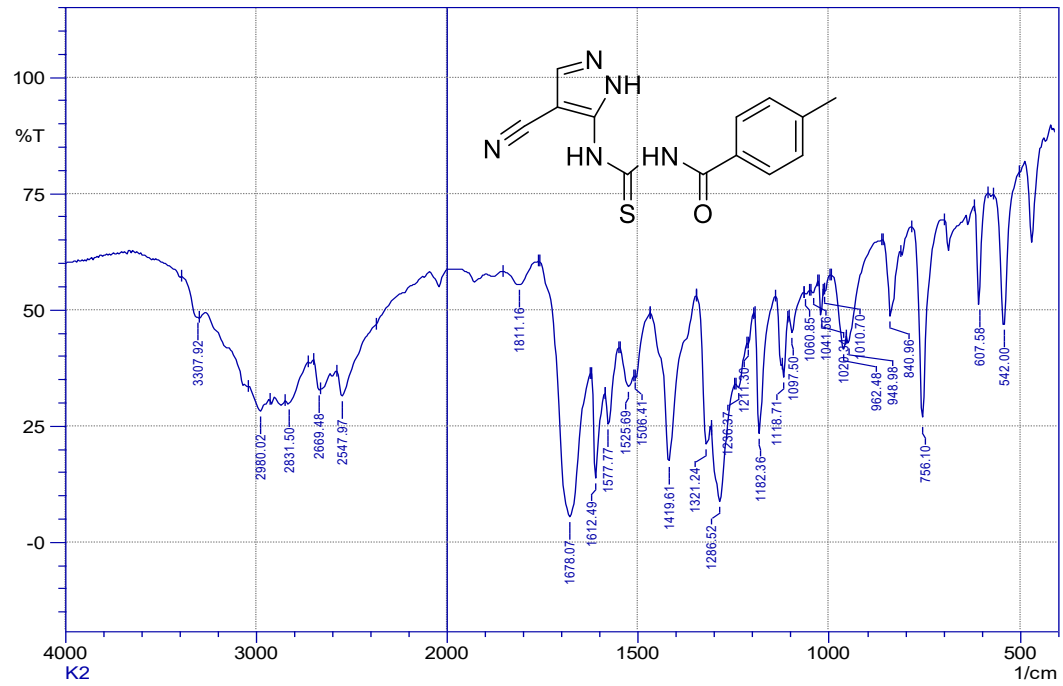

Figure 2. FT-IR spectrum of VIb

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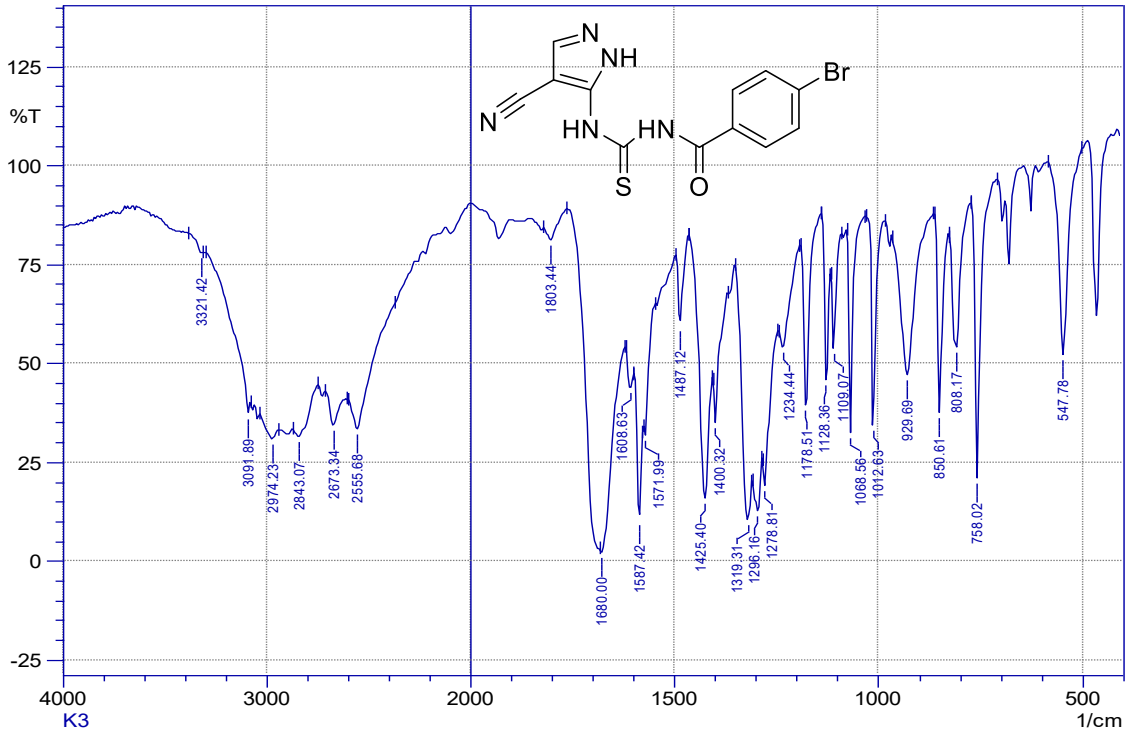

Figure 3. FT-IR spectrum of VIc

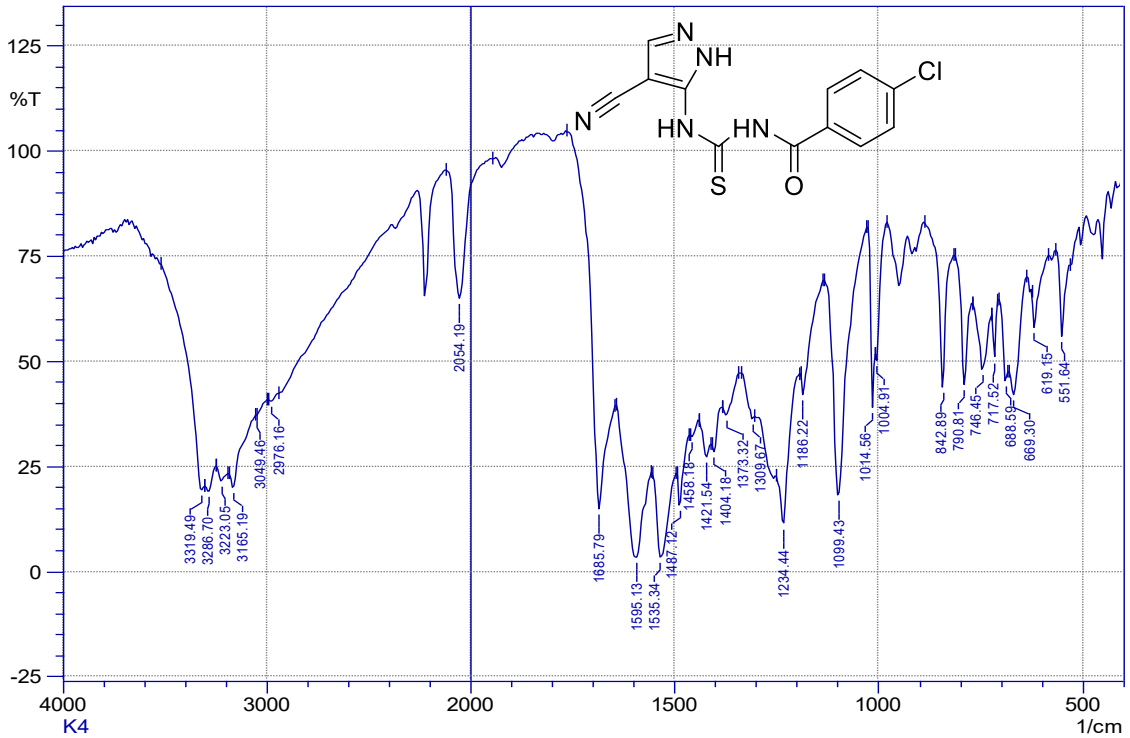

Figure 4. FT-IR spectrum of VId

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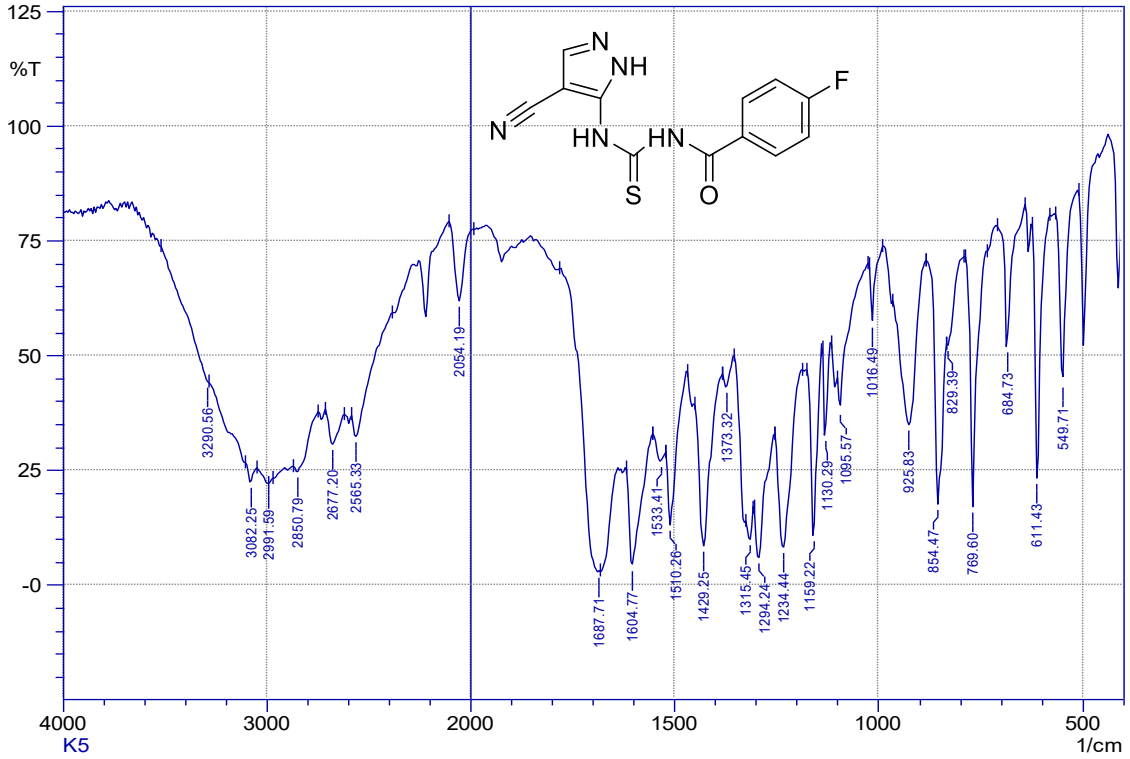

Figure 5. FT-IR spectrum of VIe

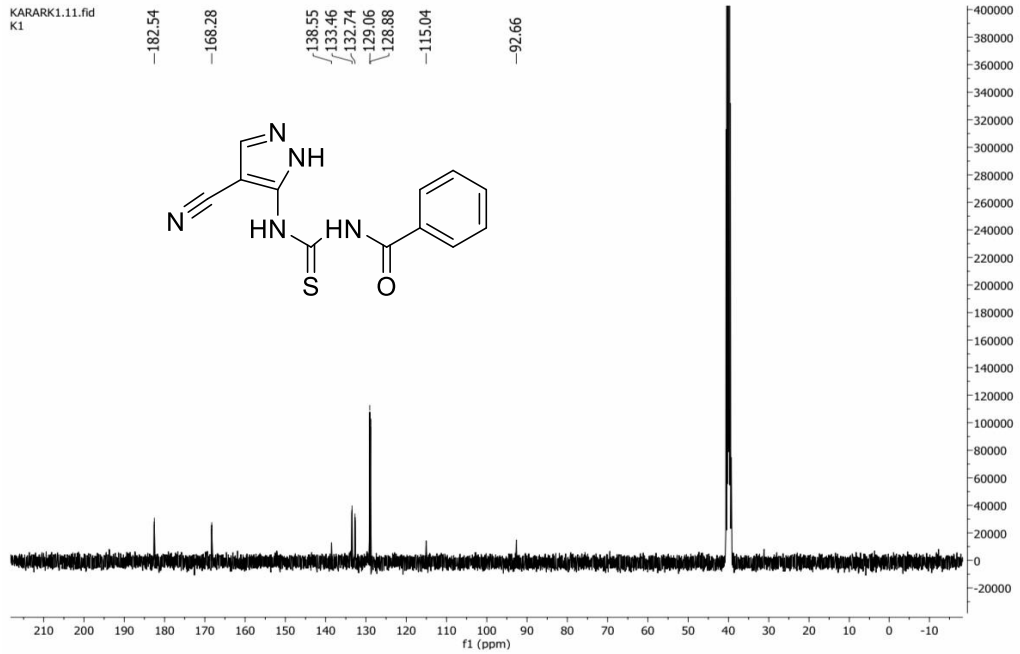

Figure 6. The ^{13}C- NMR spectrum of VIa

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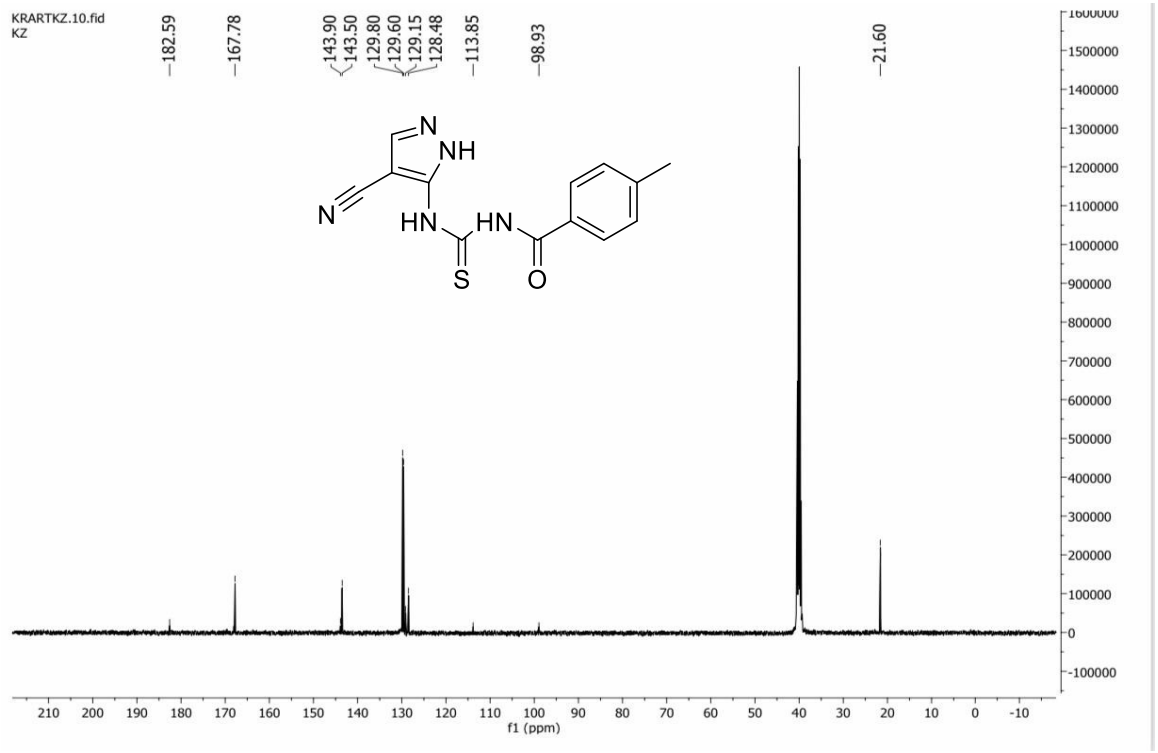

Figure 7. The ^{13}C- NMR spectrum of VIb

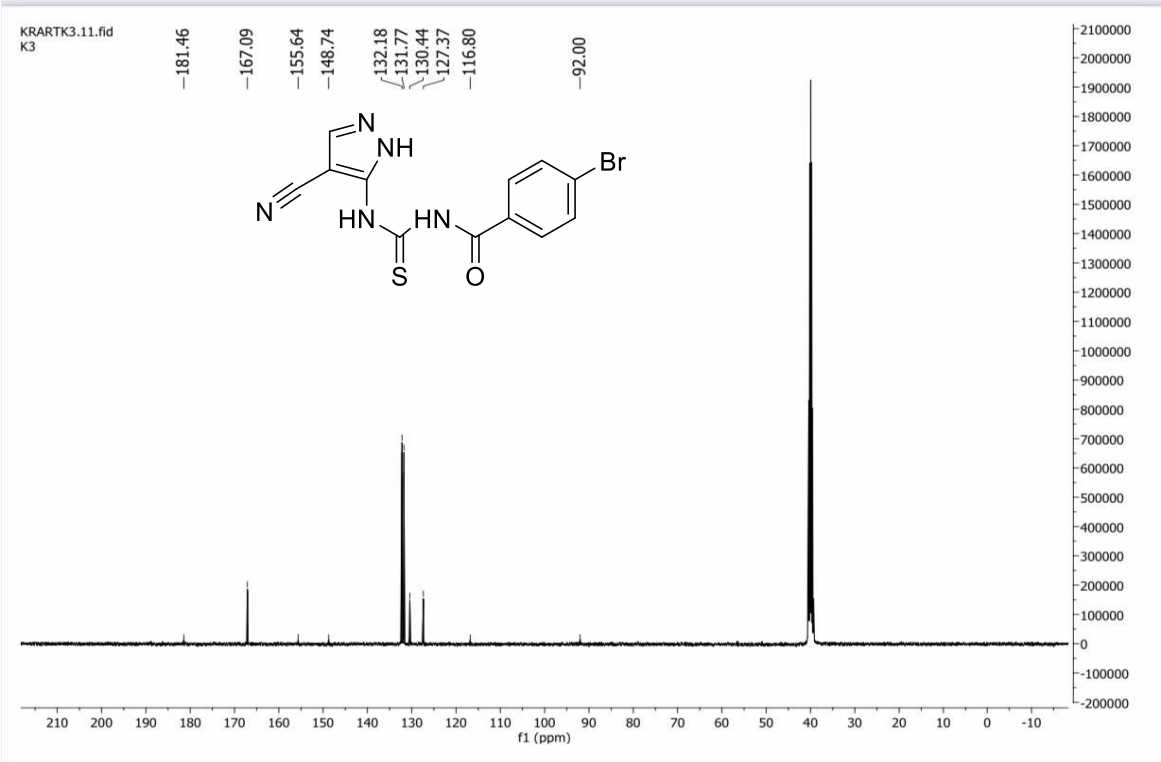

Figure 8. The ^{13}C- NMR spectrum of VIc

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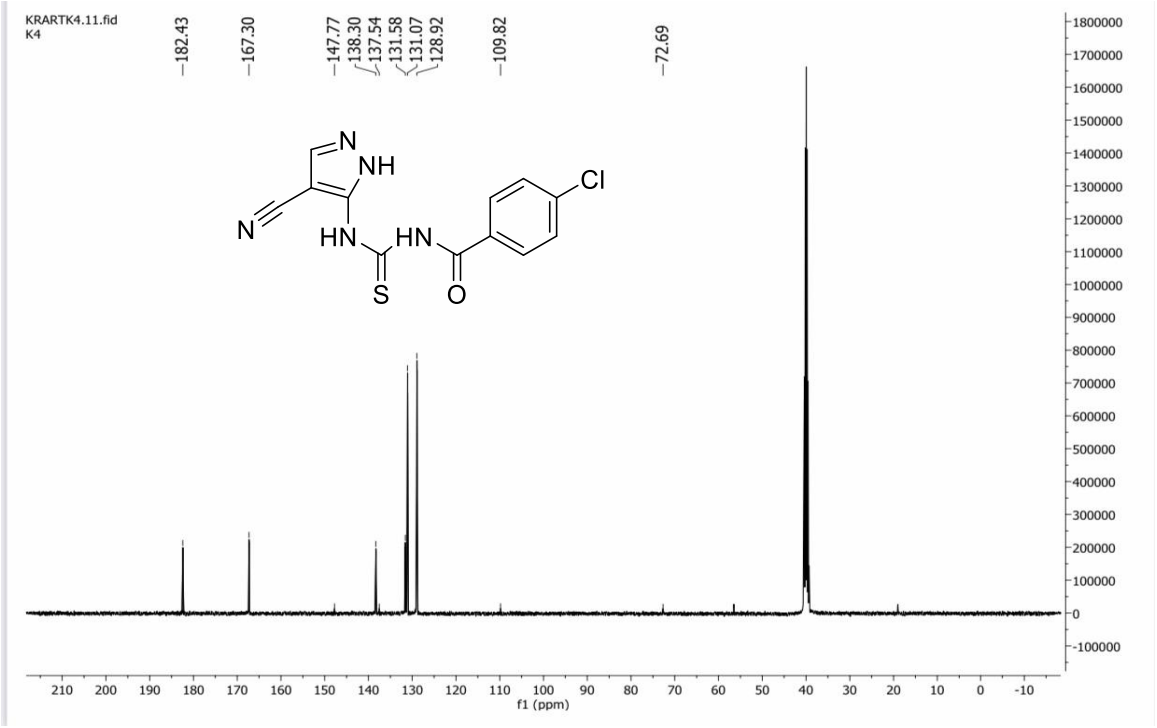

Figure 9. The ^{13}C- NMR spectrum of VId

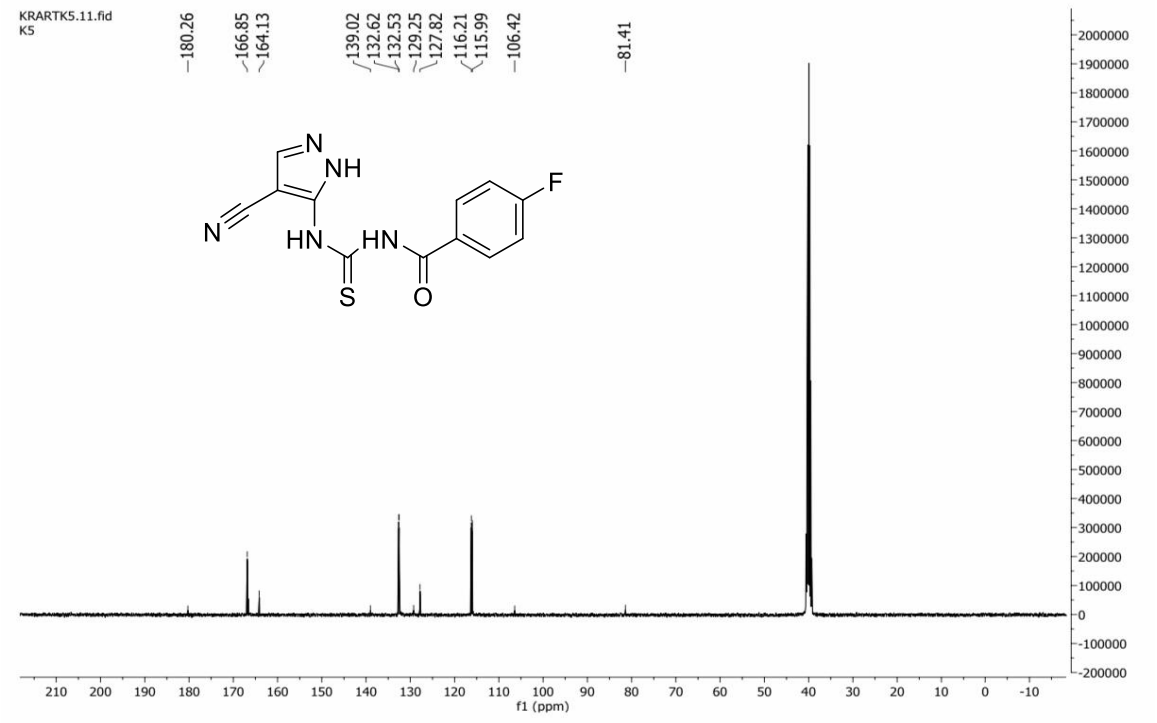

Figure 10. The ^{13}C- NMR spectrum of VIe

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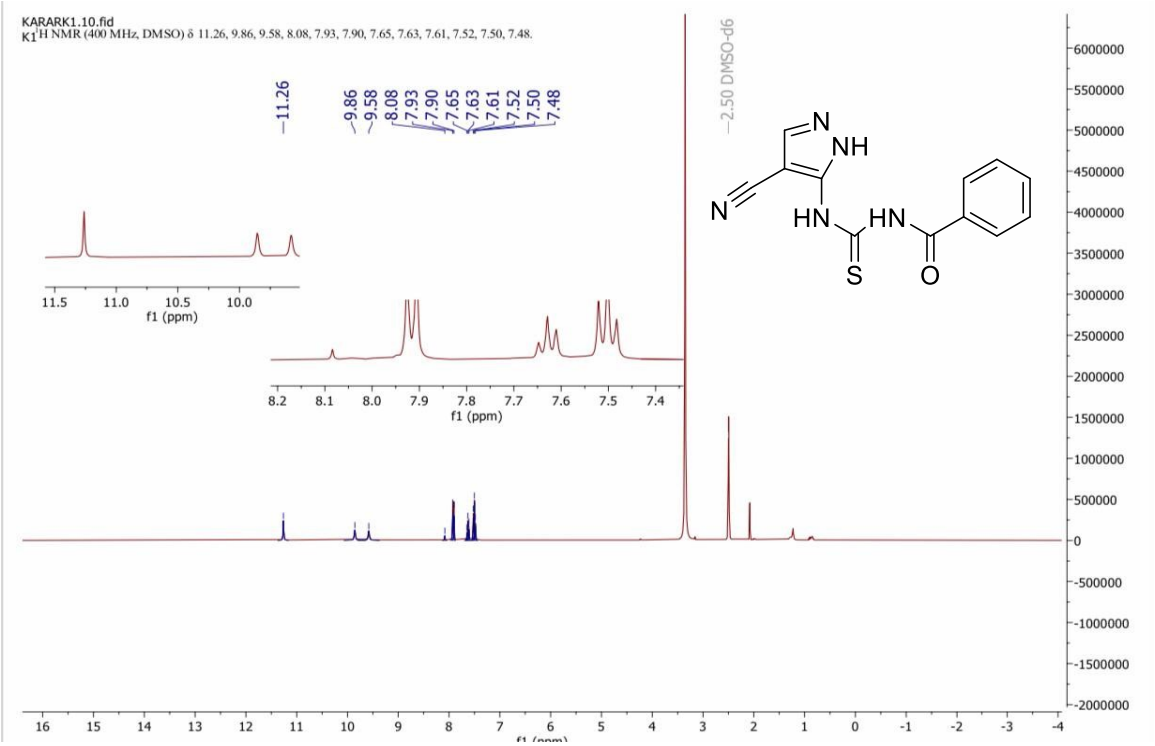

Figure 11. The ^{1}H - NMR spectrum of VIa

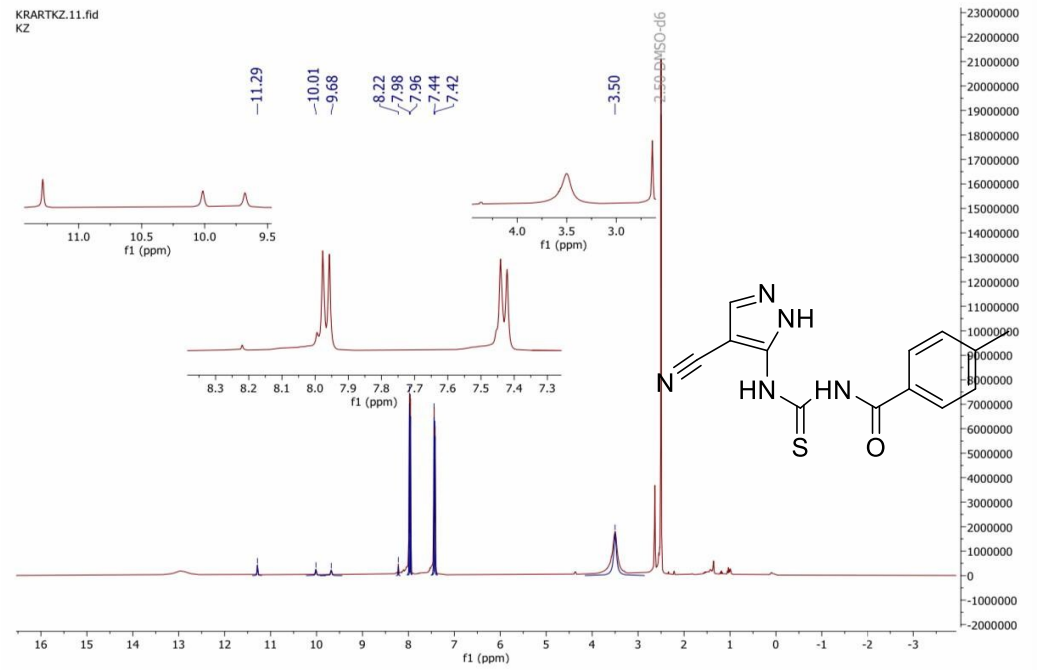

Figure 12. The ^{1}H - NMR spectrum of VIb

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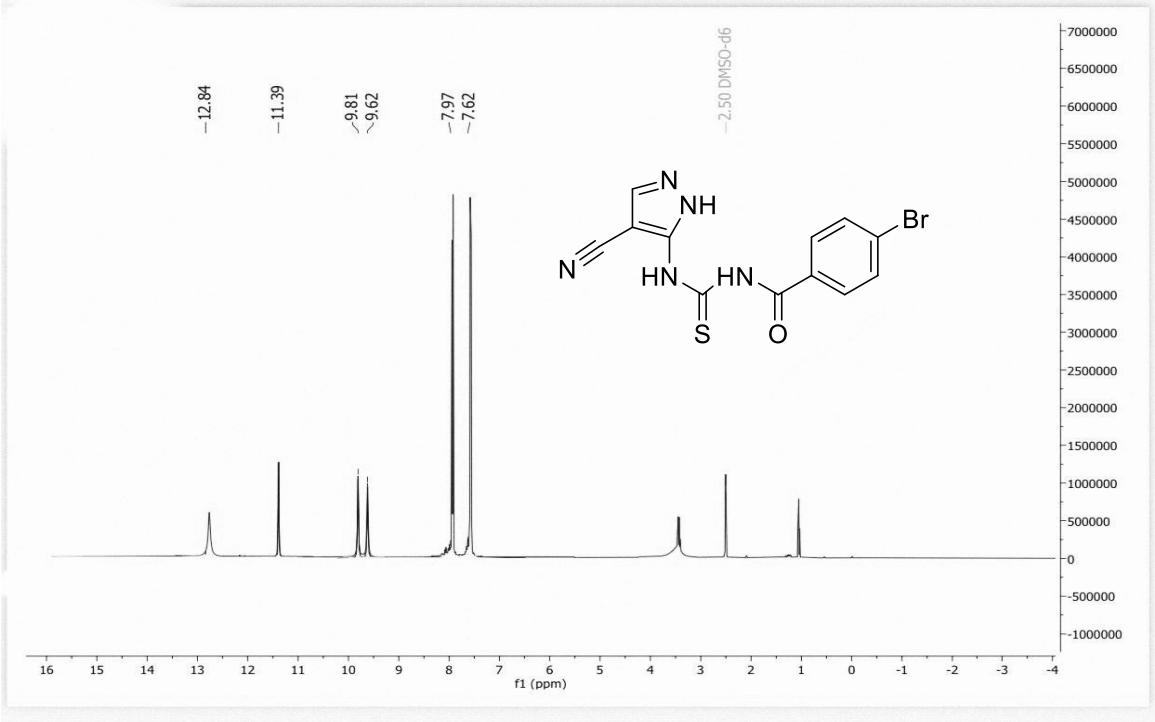

Figure 13. The ^{1}H - NMR spectrum of VIc

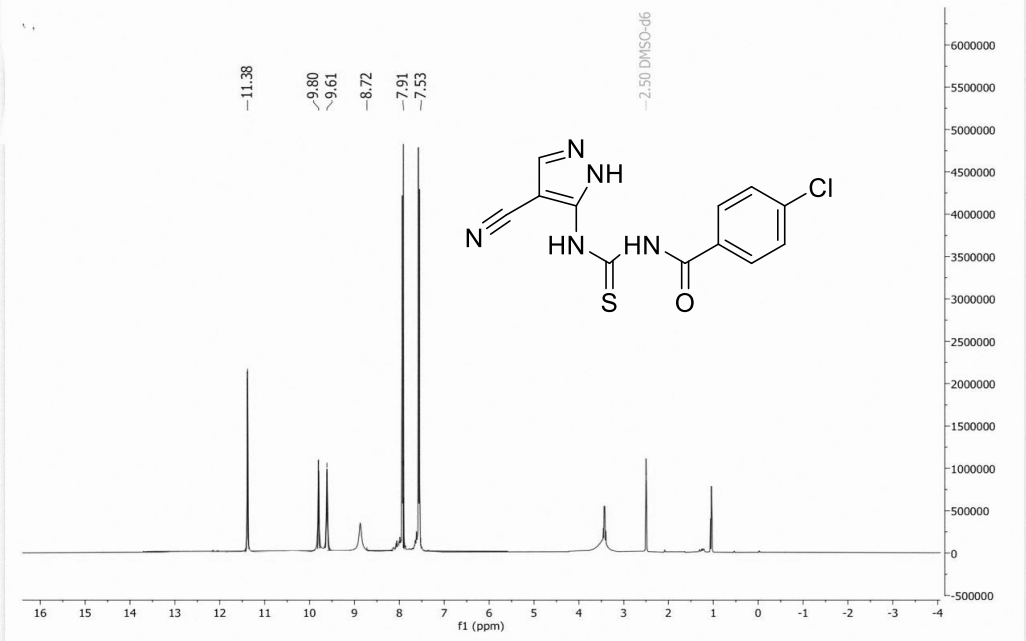

Figure 14. The ^{1}H - NMR spectrum of VId

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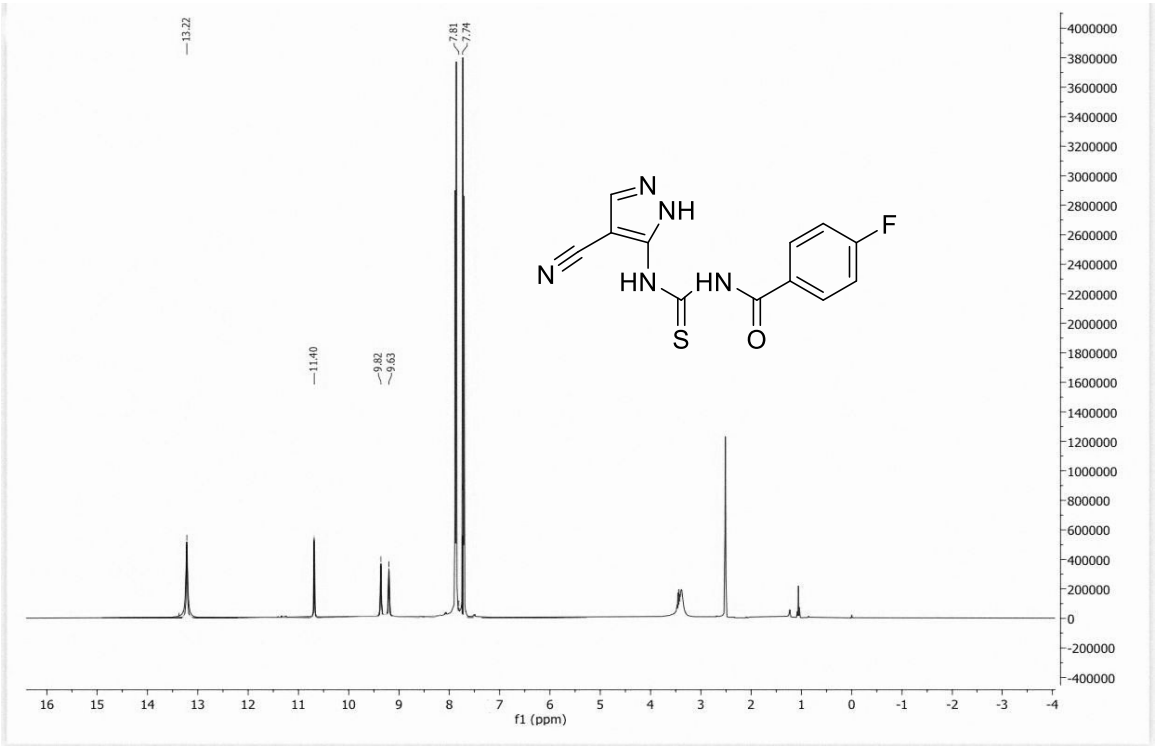

Figure 15. The ^{1}H - NMR spectrum of VIe

C. Biological evaluation Cytotoxicity against MCF-7

The cytotoxicity of VIa- VIe was evaluated MCF-7 (breast cancer) cell lines. The results indicated that several of the compounds were highly cytotoxic, particularly against cell line. VIa and VIe exhibited low IC_{50} values, suggesting strong anticancer activity and potential for further development. Conversely, VIc and VId exhibited moderate toxicity, while VIb with a methyl group showed activity but with higher IC_{50} values. The structural modifications, including the nature of substituents on the benzamide ring, are crucial in influencing both enzyme inhibition and cell killing activity. The results indicated that several of the compounds were highly cytotoxic, particularly against the MCF-7 cell line. VIa and VIe exhibited low IC_{50} values, suggesting strong anticancer activity and potential for further development. Conversely, VIc and VId exhibited moderate toxicity against both cell lines, while VIb with a methyl group showed activity but with higher IC_{50} values, according to Table (4) and Figure (16). Overall, the pyrazole–thiourea derivatives

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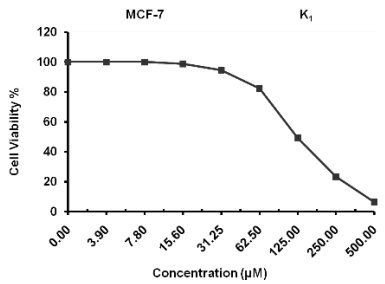
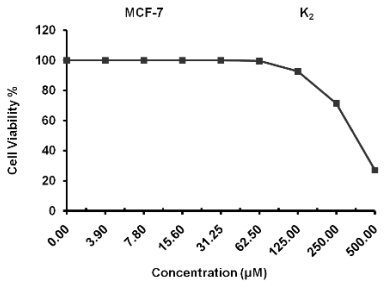
(VIa- VIe) exhibit promising anticancer properties through cytotoxicity in cancer cell lines [29] [30]

Table 4. Cytotoxicity against MCF-7

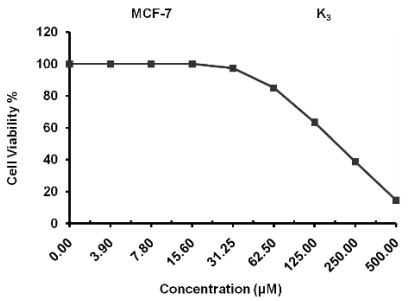
I.D	(IC50)	MCF-7 inhibition (%)
VIa	**123.64**	**93.77**
VIb	**370.27**	**73.02**
VIc	**192.96**	**85.41**
VId	**137.94**	**90.13**
VIe	**118.49**	**94.55**
Rescovitine	**20.27**	**97.33**



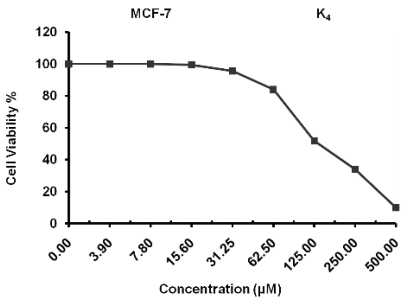
VIa



VIb



VIc



VId

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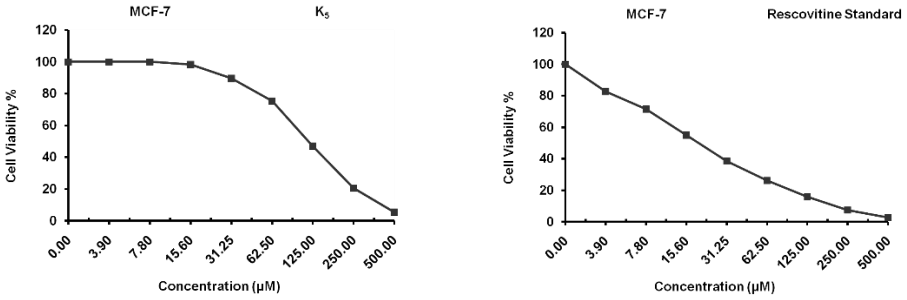

VIe **Rescovitine**

Figure 16. Cytotoxicity of thiourea against MCF-7

Conclusion

The study found that compounds VIa and VIe showed the most potent Cytotoxicity against MCF-7, comparable to Rescovitine. The variation in activity suggests that different substituents on the benzamide ring significantly influence inhibition. VIa and VIe showed strong anticancer activity, while VIc and VId showed moderate activity. VIb with a methyl group showed activity but higher IC_{50} values. Overall, pyrazole–thiourea derivatives VIa-VIe showed promising anticancer properties. Structure-activity analysis revealed that electron-withdrawing substituents (e.g., fluorine in VIe) enhanced binding affinity, whereas steric groups (e.g., methyl in VIb) diminished activity. All compounds exhibited favorable ADMET properties, including solubility, GI absorption, and drug-likeness, according to Lipinski's rule. These findings identify VIa and VIe as promising scaffolds for further development of targeted CDK2 inhibitors with improved pharmacokinetic profiles.

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