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One-Pot Synthesis of Pyrido[2,3-*d*]pyrimidines Catalyzed by Bismuth(III)Triflate

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Abstract

Synthesis of uracil derivatives, such as pyrido[2,3-*d*]pyrimidine, is very important for the pharmaceutical industry due to their many biological activities. In our continuing efforts into the development of new synthetic strategies for the preparation of heterocyclic compounds in this study, we performed reflux reactions with the catalyst $Bi(OTf)_3$ by using a one-pot, three-component method. The one-pot, three-component condensation of 6-amino-1,3-dimethyluracil, with arylaldehydes and malononitrile to generate a series of 7-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives has been carried out in the presence of bismuth triflate as a green and reusable catalyst.

Keywords

Bismuth Triflate, Pyrido[2,3-*d*]pyrimidine, One-Pot, Biological Activity

1. Introduction

Fused heterocyclic systems, incorporating a uracil ring in their structures, play important roles in biological and pharmaceutical processes [1] [2] [3]. Uracil and its derivatives, such as pyrido[2,3-*d*]pyrimidines, have received considerable attention over the past years because of their biological activities, such as dihydrofolate reductase inhibiting, antibacterial, antiallergic, antitumor, antimicrobial, tyrosine kinase inhibiting, anti-inflammatory, analgesic, calcium channel antagonists, antihypertensive, antitubercular, antileishmanial, potassium sparing, anti-aggressive and antifungal activities [4]-[13]. In addition, uracil fused compounds have also been found to display interesting luminescent properties [14].

Environmentally friendly methodologies for the preparation of heterocyclic compounds offer several important advantages. Multicomponent reactions (MCRs) have gained significant interest from modern medicinal and combina-

torial chemists due to the powerful bond forming efficiency, diversity-oriented synthesis, simple reaction design, atom-economy, and response to environmental concerns [15] [16]. In recent years, most of the procedures of the synthesis of pyrido[2,3-*d*]pyrimidine derivatives have been reported using different catalysts, such as DMAP [17] [18], L-proline [19], $BiCl_3$ [20], KF-alumina [21], ionic liquids [22] [23] [24] [25] [26], magnetic metal nanoparticles (γ-Fe_2O_3@HAp-SO_3H) [3] [27], Al-HSM-20 [28], DBA (dibutylamine) [29], organo catalyst (DABCO) [30], nano crystalline MgO [31] and ZrO_2 [32].

Bismuth derivatives are attracting the attention of an increasing number of organic chemists. As a result, bismuth (III) triflate was used as the Lewis-acidic catalyst due to its high catalytic activity, low toxicity and stability. Catalytic quantities of Bi(III) compounds are effective in promoting allylations and cyanations, etherification, Diels-Alder reactions, and protection/deprotection, Mannich reactions. The moisture-stable metal triflates, $Bi(OTf)_3$ (Tf = SO_2CF_3) have been reported as efficient catalysts for various types of organic reactions [33]-[39].

Pyrimidine and its derivatives have been synthesized using various approaches, including multi-component reactions (MCRs). However, most of the procedures which use organic solvents are better than other methods which are toxic and, expensive with non-recoverability of the catalyst.

According to the literature research, it was observed that pyrimidine and its derivatives were obtained by using different catalysts via one-pot method [40] [41]. We describe here an efficient and rapid method for the synthesis of novel pyrido[2,3-*d*]pyrimidines using triflate as the catalyst.

In this study, we have devised convenient one-pot, three-component reaction for the synthesis of the annulated derivatives of the pyrimidines (4a-h) **Scheme 1**. To study the effect of the amount of catalyst, the reactions were carried out using different amounts of $Bi(OTf)_3$ ranging from 10 to 30 mol%. The use of 10 mol% $Bi(OTf)_3$ in EtOH had optimum results. Using more triflate did not improve the reaction yields.

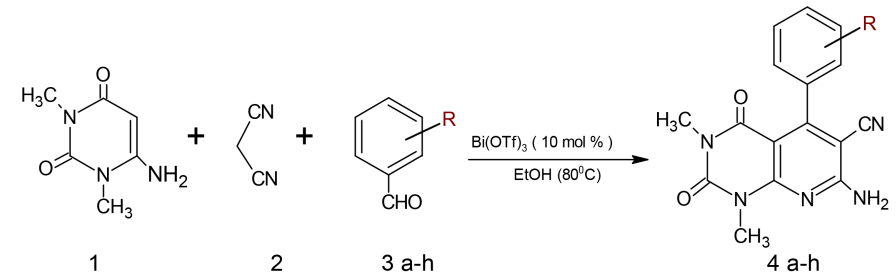
2. Results and Discussions

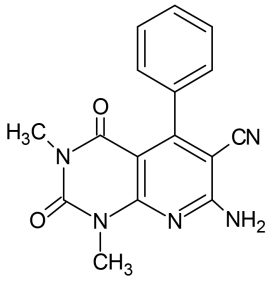
In our initial study, the preparation of pyrido[2,3-*d*]pyrimidines (4) was carried out by condensation of 6-amino-1,3-dimethyluracil (1), malononitrile (2) and various substituted aromatic aldehydes (3) in EtOH as the solvent (**Table 1**). $Bi(OTf)_3$ catalyst was used for the first time in this type of compound synthesis.

To optimize the loading of the catalyst, the reaction of benzaldehyde (1 mmol), malononitrile (1 mmol), and 6-amino-1,3-dimethyluracil (1 mmol) as a model was investigated. The results are presented in **Table 2**. According to the data, 20 mol% and 30 mol% of the catalyst was used and the most suitable amount of catalyst was 10 mol%.

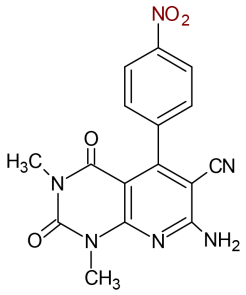
Based on with these results, 7-amino-5-(substitued-phenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-carbonitrile compounds (4a-h) were synthesized in the presence of mol 10% catalyst in ethanol at 80˚C (**Table 1**).

Table 1. Bismuth(III)triflate catalyzed three-component synthesis of pyrido[2,3-*d*]pyrimidine derivatives (**4 a-h**).

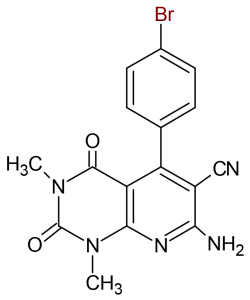




4a



4b



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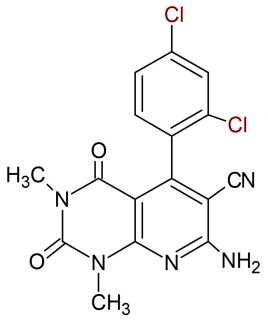
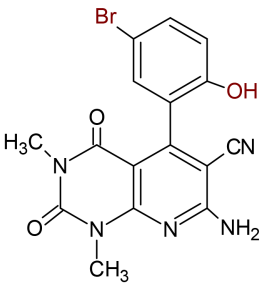
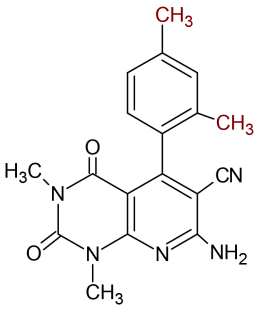


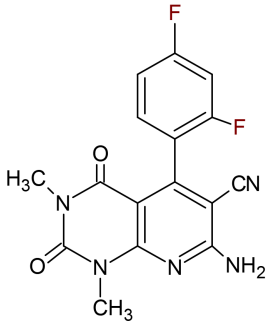
4d



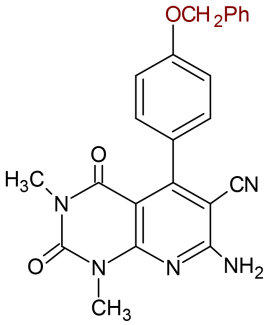
4e



4f



4g



4h

Conditions: aromatic aldehyde (1 mmol), malononitrile (1 mmol), 6-amino-1,3-dimethyluracil (1 mmol), $Bi(OTf)_3$ (10 mol %) in EtOH. a. Sample of a Table footnote (*Table footnote is dispensable*).

Table 2. Effects of catalyst amount on the reaction yield.

entry	catalyst	solvent	Temp/time	React medium/yield[a]
1	$Bi(OTf)_3$, 10 mol%	EtOH	80˚C/6 h	One-pot, reflux/86%
2	$Bi(OTf)_3$, 20 mol %	EtOH	80˚C/6 h	One-pot, reflux/84%
3	$Bi(OTf)_3$, 30 mol %	EtOH	80˚C/6 h	One-pot, reflux/85%

Reaction conditions: Benzaldehyde (3a) (1 mmol), malononitrile (2) (1 mmol), 6-amino-1,3-dimethyluracil (1) (1 mmol), solvent (5 mL). [a]All yields refer to isolated products.

Reactions were carried out by stirring under reflux. Electron-donating and electron-withdrawning aromatic aldehydes were used following this one-pot, three-component procedure, to efficiently obtain the corresponding pyridopyrimidines.

7-amino-5-(5-bromo-2-hydroxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*] pyrimidine-6-carbonitrile, 4e, 7-amino-5-(2,4-dimethylphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*] pyrimidine-6-carbonitrile, 4f, 7-amino-5-(2,4-difluorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido-[2,3-*d*]pyrimidine-6-carbonitrile, 4g, and 7-amino-5-(4-benzyloxy-phenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile, 4h, were synthesized for the first time in this study. Compounds (4 a-d) can be found in the literature [15] [22] [28] [31].

7-amino-5-(substitue-phenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-carbonitrile compounds (4a-h) were isolated as solids by simple filtration, purified by column chromatography, and their structures were clarified by IR, NMR (^1H and ^{13}C) spectra, MS and elemental analysis.

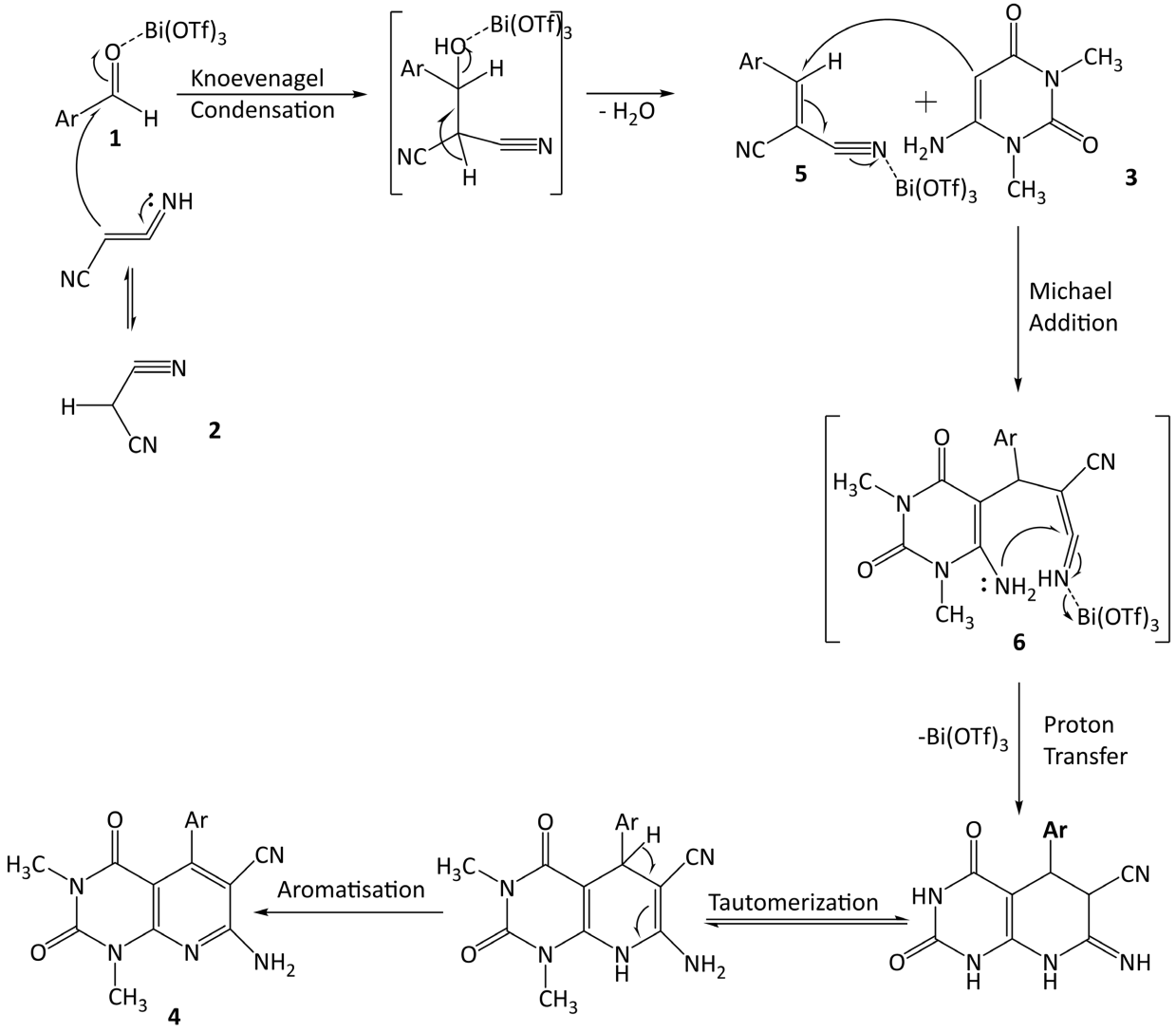
The FTIR spectra exhibited sharp absorption bands at 3300 - 3210 cm^{-1} (NH_2 amino), 2200 cm^{-1} (C≡N nitrile) and around 1716 and 1651 cm^{-1} (C=O carbonyls) stretching vibrations, respectively.

The ^1H nuclear magnetic resonance spectra of the compounds showed singlets of 3.04 and 3.91 ppm due to N-CH_3 protons, with peaks as a doublet or multiplet at 7.06 and 8.31 ppm indicating aromatic protons.

The singlet peaks observed between 6.80 and 7.40 ppm reveal the -NH_2 moiety in the structure of the compounds.

The formation of 7-amino-5-(substitue-phenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile through $Bi(OTf)_3$ catalyzed three component coupling involves Knoevenagel condensation, Michael addition, and then intra molecular cyclization. The possible reaction mechanism, obtained as a result of the literature research [31] [42], is shown in the general reaction equation in Scheme 1.

$Bi(OTf)_3$ (Bismuth Triflate) acts as a Lewis acid catalyst to form the aromatic aldehydes (**3a-h**) and malononitrile (**2**) as a result of the Knoevenagel condensation, resulting in benzylidene malononitrile **5**. 6-Amino-1,3-dimethyluracil; tautomerisation and aromatization result in product,**4**(**a-h**).



Scheme 1. Plausible mechanism course of the methodology for the synthesis of pyrido[2,3-*d*]pyrimidines.

3. Conclusion

We have synthesized a series of pyrido[2,3-*d*]pyrimidine derivatives 4a-h, in high yields, which may have pharmaceutical and biological applications, by one-pot, three-component reaction of 1,3-dimethyl-6-aminouracil(heteroamine), aromatic aldehyde and malononitrile (active methylene) using 10 mol% $Bi(OTf)_3$ as the catalyst in ethanol at 80˚C. The simplicity of the method, mild reaction conditions and reusable catalyst make this an ideal procedure for further investigation.

4. Experimental

The chemicals used were purchased from Merck and Aldrich without purification. Heidolph RV Laborata 4000 rotary evaporator was used to remove the compounds from the solvent. A TLC/3 Merck 5554 with silica gel layers with fluorescent indicator and a Camag (254/366 nm) "UV lamp were used. The

melting points of the pure materials were measured on Gallenkamp apparatus. Thermometer correction was not performed. Fourier Transform Infrared (FTIR) spectra of the starting materials and the obtained products were taken on a "Perkin Elmer Spectrum One" FTIR spectrometer by ATR technique. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were obtained from a "Bruker 500 MHz" spectrometer in DMSO-d6. LC-MS spectra were obtained by Agilient 6200 series TOF/6500 series TOF/Q-TOF Mass Spectrometer.

General Procedure for Synthesis of Pyrido[2,3-*d*]pyrimidines

A mixture of 6-amino-1,3-dimethyluracil (1 mmol), malononitrile (1 mmol), aromatic aldehyde (1 mmol) and a catalytic amount of $Bi(OTf)_3$ (10% mol) in ethanol (5 mL) was refluxed for the stipulated times at 80˚C. The progress of the reaction was monitored by TLC. After completion of the reaction, the precipitated solid was filtered, then washed with water and cold ethanol for separation of the catalyst. The crude product was purified by chromatographic methods.

7-Amino-1,3-dimethyl-5-phenyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (4a). Yield 0.27 g 86%, ligth yellow crystals, mp > 300˚C. IR spectrum, *ν*, cm^{-1}: 1710, 1662 (C=O), 2211 (C≡N), 3310, 3221 (NH_2). ^{1}H NMR (500 MHz, DMSO-d_6,) spectrum, *δ*, ppm (*J*, Hz): 3.09 (3H, s, CH_3), 3.52 s (3H, s, CH_3), 7. 23 (2H, d, *J* = 8.11 H Ar), 7.43 (2H, s, NH_2), 7.85 m (3H, m, H Ar). ^{13}C NMR (DMSO-d_6) spectrum *δ*C ppm: 27.65, 29.60, 88.51, 98.65, 115.30, 127.21, 127.71, 128.08, 128.62, 129.32, 137.22, 150.88, 153.61, 158.41, 159.34, 160.24. Found, %: C 62.23; H 4.12; N 22.31. $C_{16}H_{13}N_5O_2$. Calculated, %: C, 62.53; H, 4.26; N, 22.79. *M* 307.

7-Amino-1,3-dimethyl-5-(4-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido [2,3-*d*] pyrimidine-6-carbonitrile (4b). Yield 0.32 g 90%, yellow crystals, mp > 300˚C. IR spectrum, *ν*, cm^{-1}: 1706, 1651 (C=O), 2230 (C≡N), 3321, 3229 (NH_2) (Figure 1). ^{1}H NMR (DMSO-d_6,) spectrum, *δ*, ppm: 3.07 s (3H, CH_3), 3.51 s (3H, CH_3), 7.98 s (broad, 2H, NH_2), 7.56 d (*j* = 8.0 Hz, 2H, Ar-H), 8.31 d (*j* = 8.8 Hz, 2H, Ar-H) (Figure 2). ^{13}C NMR (DMSO-d_6) *δ*C, ppm: 27.69, 29.59, 87.71, 98.45, 113.76, 123.66, 123.77, 128.90, 130.83, 142.43, 144.40, 147.26, 153.55, 157.02, 158.58, 160.02 (Figure 3). LCMS (ESI-QTOF) m/z: $C_{16}H_{12}N_6O_4$, calculated, 352.09, found, 375.08234 [M + Na].

7-Amino-1,3-dimethyl-5-(4-bromophenyl)-2,4-dioxo-1,2,3,4-tetrahydrop yrido-[2,3-*d*] pyrimidine-6-carbonitrile (4c). Yield 0.33 g 86%, white crystals mp > 300˚C. IR spectrum, v, cm^{-1}: 1712, 1660 (C=O), 2224 (C≡N), 3307, 3218 (NH_2). ^{1}HNMR (DMSO-d_6, *δ* ppm: 3.08 s (3H, CH_3), 3.50 s (3H, CH_3), 7.20 s (2H, NH_2), 7.39 d (*j* = 8.11, 2H, ArH), 7.64 d (*j* = 8.89 Hz, 2H, ArH). ^{13}CNMR (DMSO-d_6) *δ*C, ppm: 24.25, 27.67, 88.21, 98.57, 115.47, 121.63, 129.51, 130.78, 136.52, 150.83, 153.59, 158.04, 158.52, 160.19. Found, %: C, 49.93; H, 3.19; N, 18.32. $C_{16}H_{12}Br\ N_5O_2$. Calculated. %: C, 49.76; H, 3.13; N, 18.18. *M* 386.

7-Amino-1,3-dimethyl-5-(2,4-dichlorophenyl)-2,4-dioxo-1,2,3,4-tetrahyd ropyrido[2,3-*d*] pyrimidine-6-carbonitrile (4d). Yield 0.33 g 88%, white crystals mp > 300˚C. IR spectrum, v, cm^{-1}: 1670 (C=O), 2228 (C≡N), 3353,

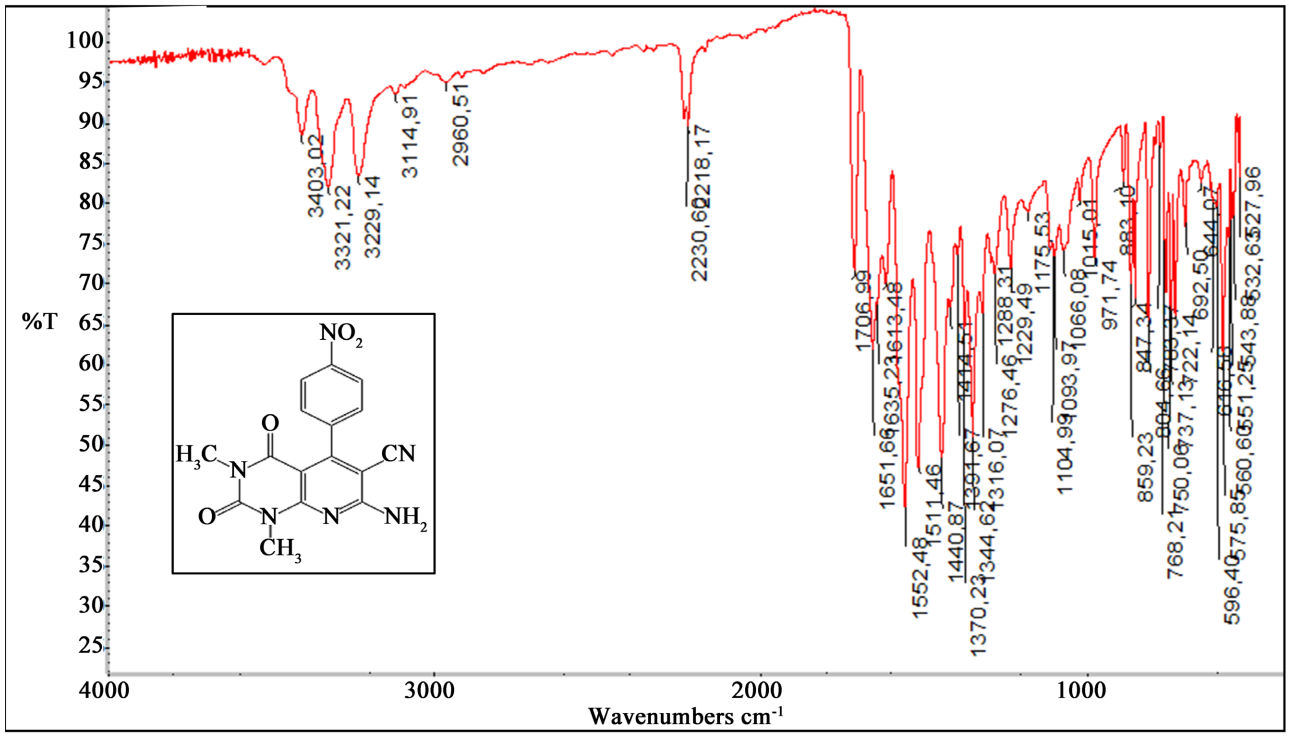


Figure 1. FTIR Spectrum of 4b.

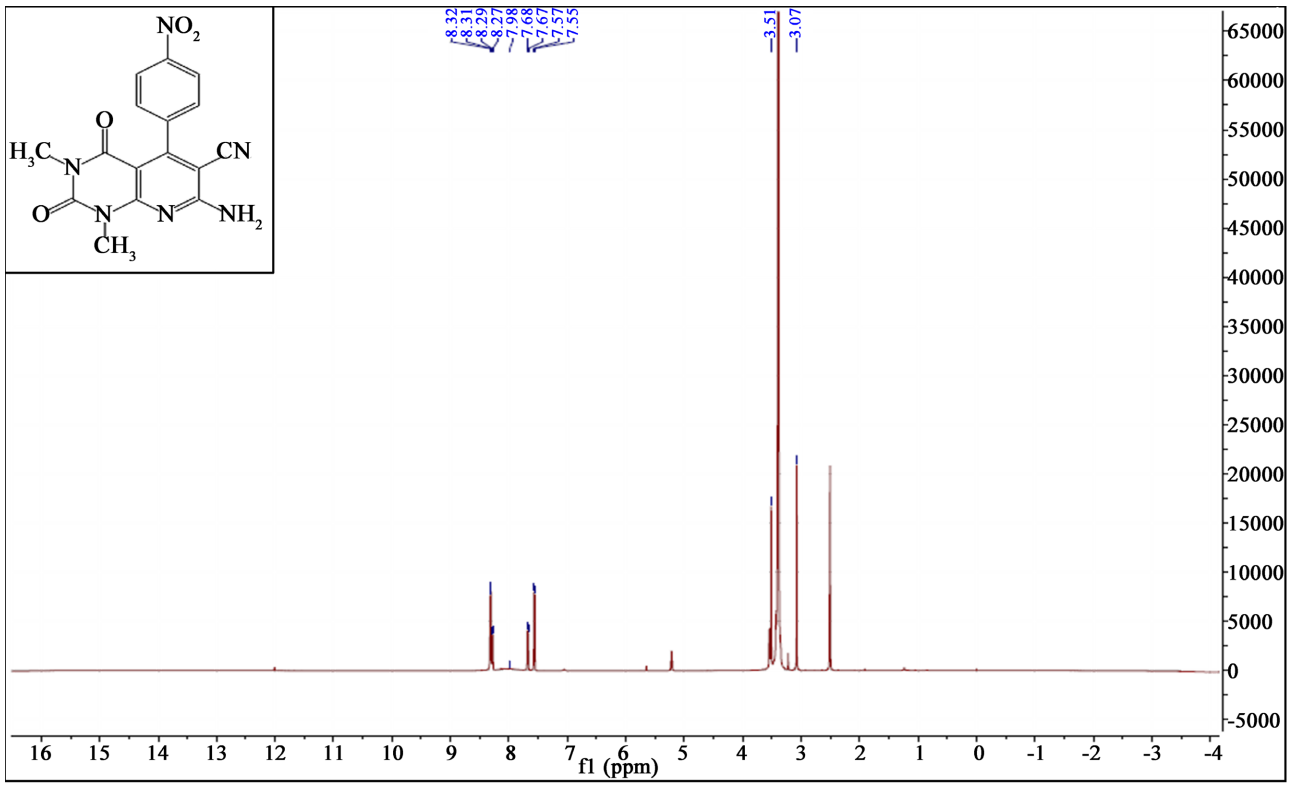


Figure 2. [1]H NMR Spectrum of 4b.

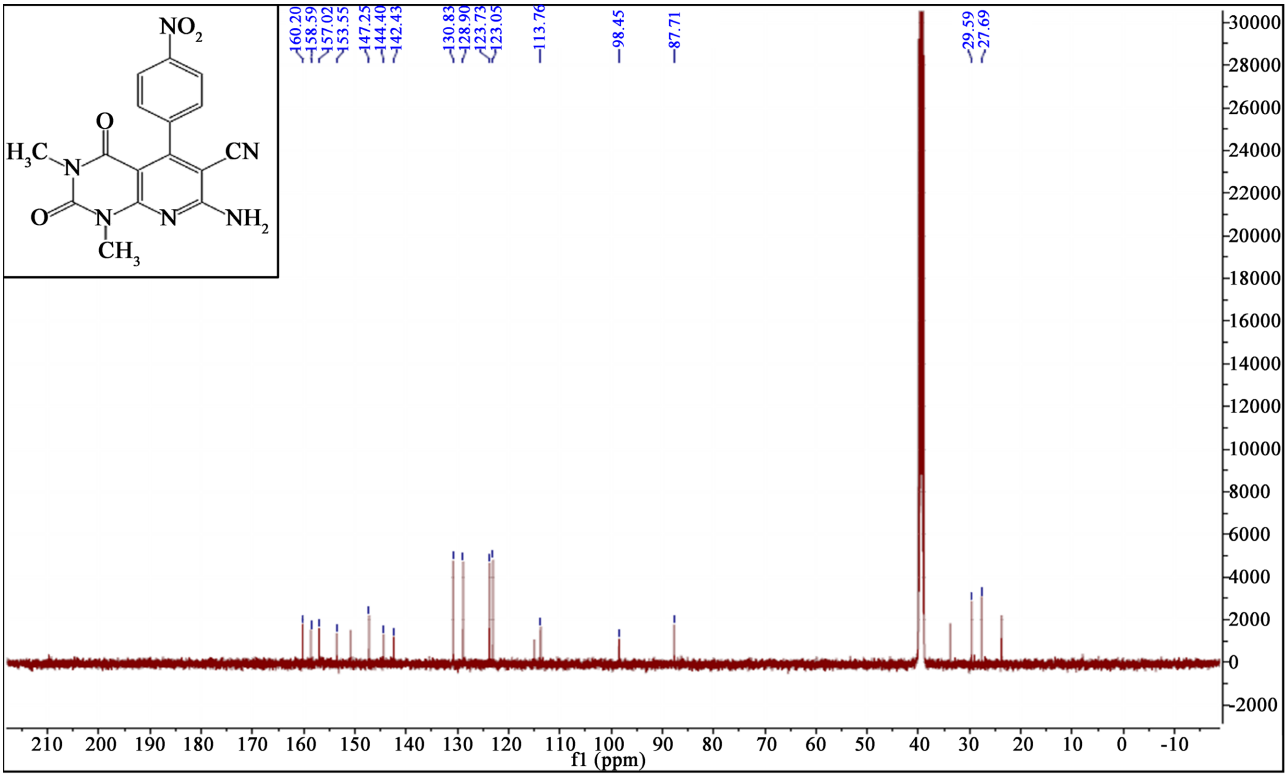


Figure 3. ^{13}C NMR spectrum of 4b.

3210 (NH_2). ^{1}H NMR (DMSO-d_6) spectrum, δ, cm^{-1}: 3.04 s (3H, CH_3), 3.20 s (3H, CH_3), 7.28 d (j = 8.11 Hz, 2H, ArH), 6.98 s (2H, NH_2), 7.36 d (j = 8.89 Hz, 2H, ArH). ^{13}C NMR (DMSO-d_6) spectrum, δC, ppm: 30.07, 34.37, 87.09, 112.22, 113.31, 128.29, 128.59, 130.02, 130.44, 130.96, 133.19, 135.55, 137.61, 150.31, 156.79. Found, %: C,50.98; H, 2.87; N, 18.57. $C_{16}H_{11}Cl_2N_5O_2$. Calculated, %: C, 51.08; H, 2.95; N, 18.62. M 376.

7-Amino-5-(5-bromo-2-hydroxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido [2,3-*d*]pyrimidine-6-carbonitrile (4e). Yield 0.33 g 83%, yellow crystals, mp > 300˚C. IR spectrum, ν, cm^{-1}: 1653, 1625 (C=O), 2209 (C≡N), 3343, 3249 (NH_2) (Figure 4). ^{1}H NMR (DMSO-d_6) spectrum, δ, ppm: 3.32 s (1H, CH_3), 3.40 s (1H, CH_3), 6.76 s (1H, OH), 7.13 s (2H, NH_2), 7.23 d (j = 7.22 Hz, 1H, Ar-H), 7.52 d (j = 7.52 Hz, 1H, Ar-H), 7.64 d (j = 7.64 Hz, 1H, Ar-H) (Figure 5). ^{13}C NMR (DMSO-d_6) spectrum, δC, ppm: 30.43, 34.40, 70.61, 83.10, 112.68, 113.23, 115.22, 116.12, 119.14, 120.15, 131.29, 132.93, 150.90, 156.96, 159.94, 160.43 (Figure 6). Found, %: C, 47.52; H, 2.98; N, 17.29. $C_{16}H_{12}BrN_5O_3$. Calculated, %: C, 47.78; H, 3.01; N, 17.41. M 402.

7-Amino-5-(2,4-dimethylphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*] pyrimidine-6-carbonitrile (4f). Yield 0.29g 85%, white crystals, mp > 300˚C. IR spectrum, ν, cm^{-1}: 1659 (C=O), 2221 (C≡N), 3455, 3354 (NH_2) (Figure 7). ^{1}HNMR (DMSO-d_6) spectrum, δ, ppm: 2.35 s (3H, CH_3), 2.40 s (3H, CH_3), 3.07 s (3H, CH_3), 3.22 s (3H, CH_3), 6.80 s (2H, NH_2), 7.22 d (j = 7.,23 Hz, 1H, ArH), 7.87 d (j = 7.87 Hz, 1H, ArH), 8.64 s (1H, ArH) (Figure 8).

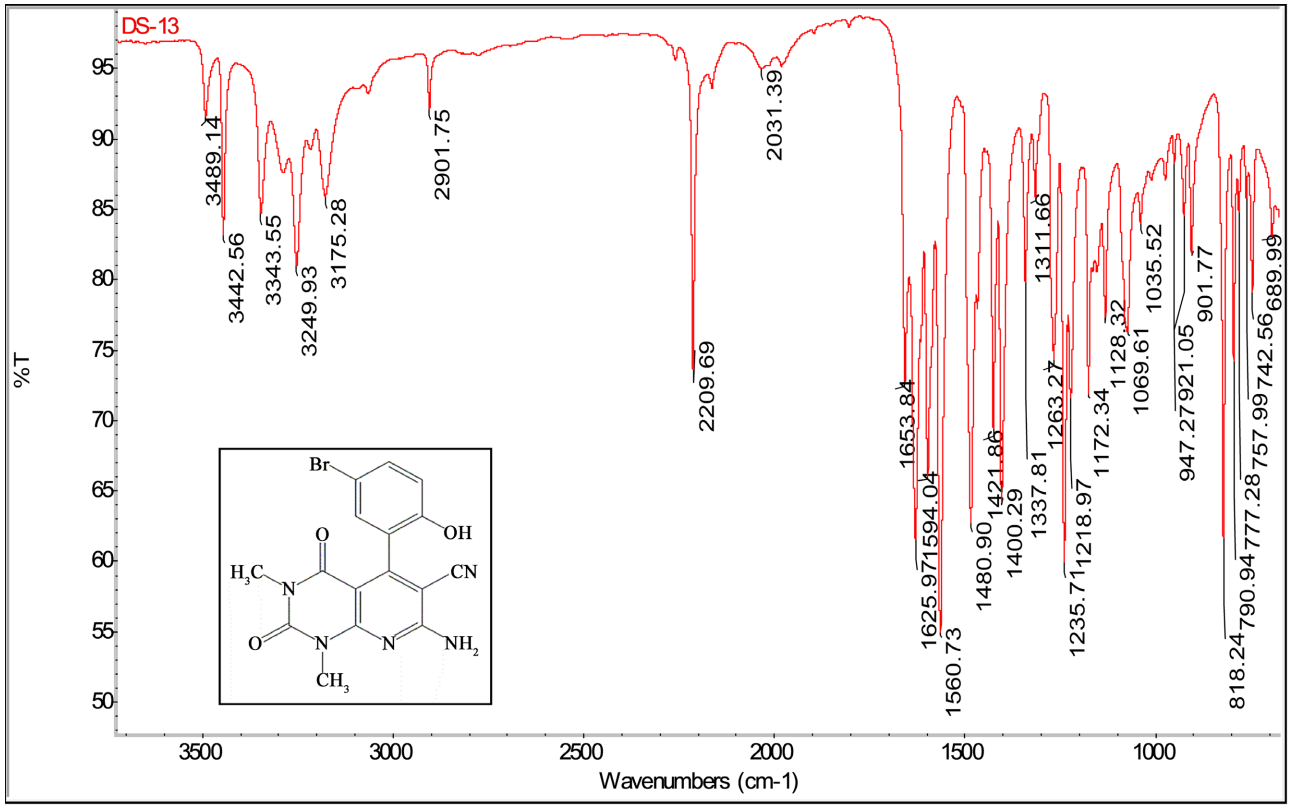


Figure 4. FTIR spectrum of 4e.

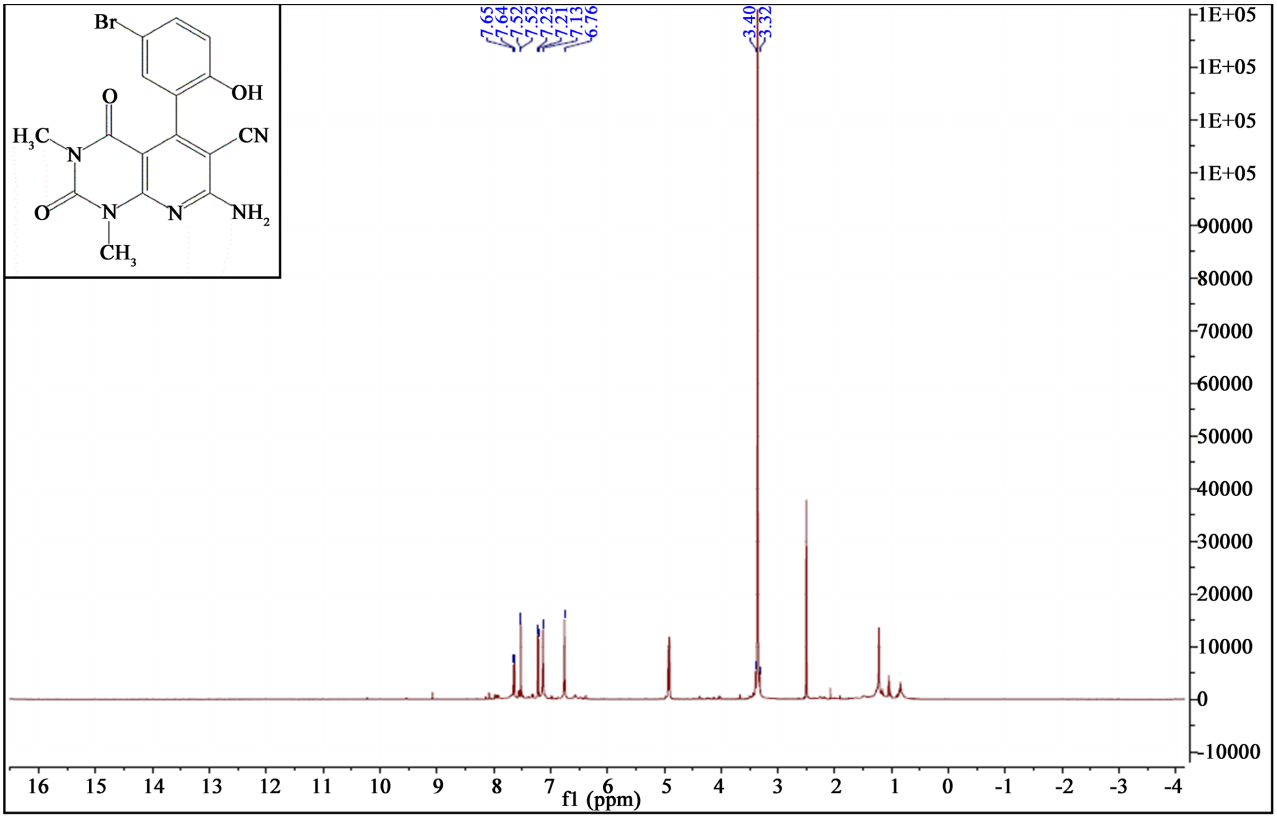


Figure 5. ^{1}H NMR spectrum of 4e.

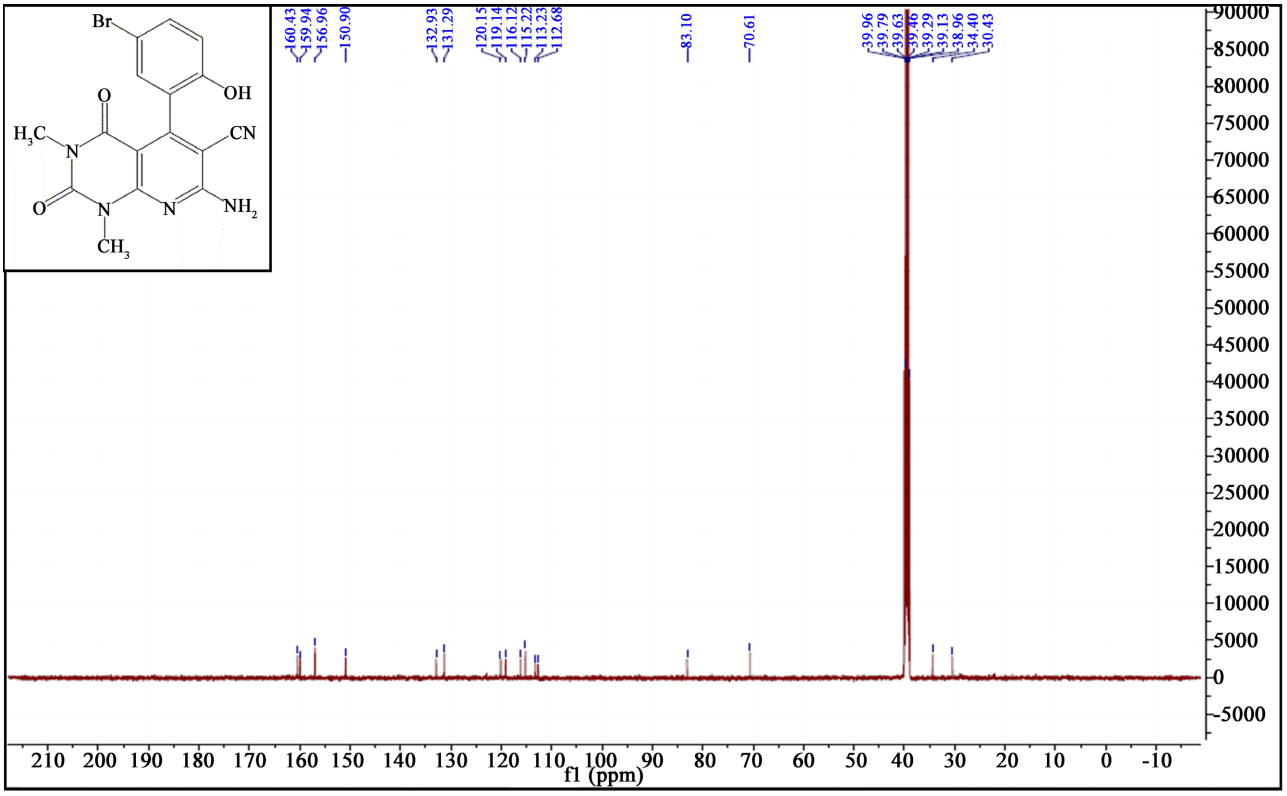


Figure 6. ^{13}C NMR spectrum of 4e.

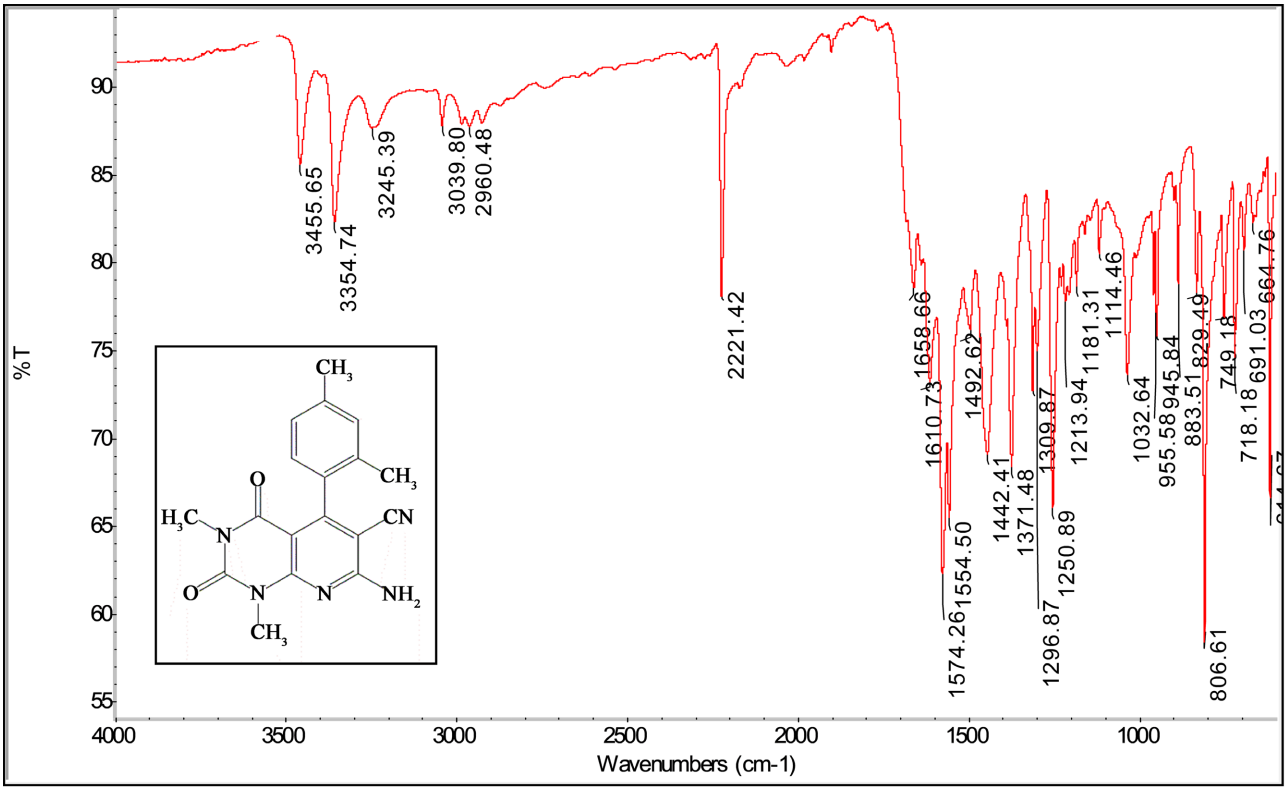


Figure 7. FTIR spectrum of 4f.

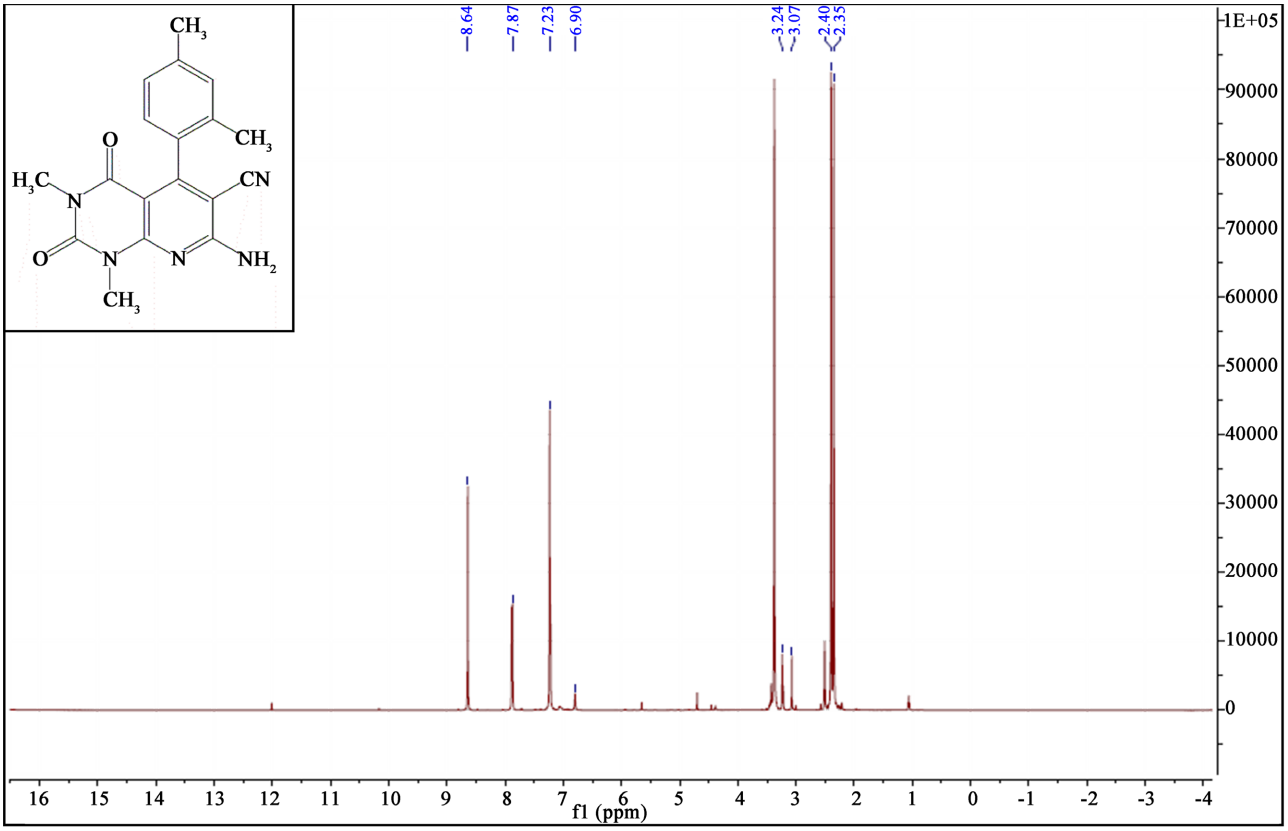


Figure 8. ^{1}H NMR spectrum of 4f.

13C NMR (DMSO-d_6), δC, ppm: 19.16, 21.18, 27.00, 29.24, 74.87, 81.80, 113.41, 114.31127.23, 127.73, 127.89, 131.81, 140.38, 144.63, 151.56, 154.84, 160.13, 161.38 (Figure 9). Found, %: C, 64.21; H, 5.01; N, 20.72. $C_{18}H_{17}N_5O_2$. Calculeted, %: C, 64.47; H, 5.11; N, 20.88. M 335.

7-Amino-5-(2,4-difluorophenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*] pyrimidine-6-carbonitrile (4 g). Yield 0.31g 90%, white crystals mp. > 300˚C. IR spectrum, ν, cm^{-1}: 1675 (C=O), 2161 (C≡N), 3347, 3206 (NH_2). ^{1}HNMR (DMSO-d_6) spectrum, δ, ppm: 3.14 s (3H, CH_3), 3.23 s (3H, CH_3), 6.90 s (2H, NH_2), 6.92 m (1H, Ar-H), 7.04 m (1H, ArH), 7.22 m (1H, ArH). ^{13}CNMR (DMSO-d_6) spectrum, δC, ppm: 29.96, 30.93, 103.07, 103.49, 109.96, 110.12, 123.47, 123.57, 129.64, 150.29, 153.66, 159.38, 159.50, 159.60, 161.45, 164.54 ppm. Found: C, 56.01; H, 3.31; N, 20.47. $C_{16}H_{11}F_2N_5O_2$: Calculated, %: C, 55.98; H, 3.23; N, 20.40. *M* 343.

7-amino-5-(4-benzyloxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*] pyrimidin-6-carbonitrile (4h). Yield 0.34g 82%, white crystals, mp > 300 ˚C. IR spectrum, ν, cm^{-1}: 1716, 1662 (C=O), 2220 (C≡N), 3313, 3217 (NH_2) (Figure 10). ^{1}HNMR (DMSO-d_6) spectrum, δ, ppm: 3.07 s (3H, CH_3), 3.50 s (3H, CH_3), 5.15 s (2H, CH_2), 7.06 s (2H, NH_2), 7.19 d (2H, j = 8.75 Hz, Ar-H), 7.37 m (1H, Ar-H), 7.42 - 7.45 m (4H, Ar-H), 7.52 d, (2H, j = 7.23 Hz, Ar-H). (Figure 11). ^{13}CNMR (DMSO-d_6), δ, ppm: 32.96, 34.89, 74.57, 93.98, 104.04, 119.10, 120.88, 120.98, 133.20, 133.77, 134.31, 134.58, 142.25, 156.16,

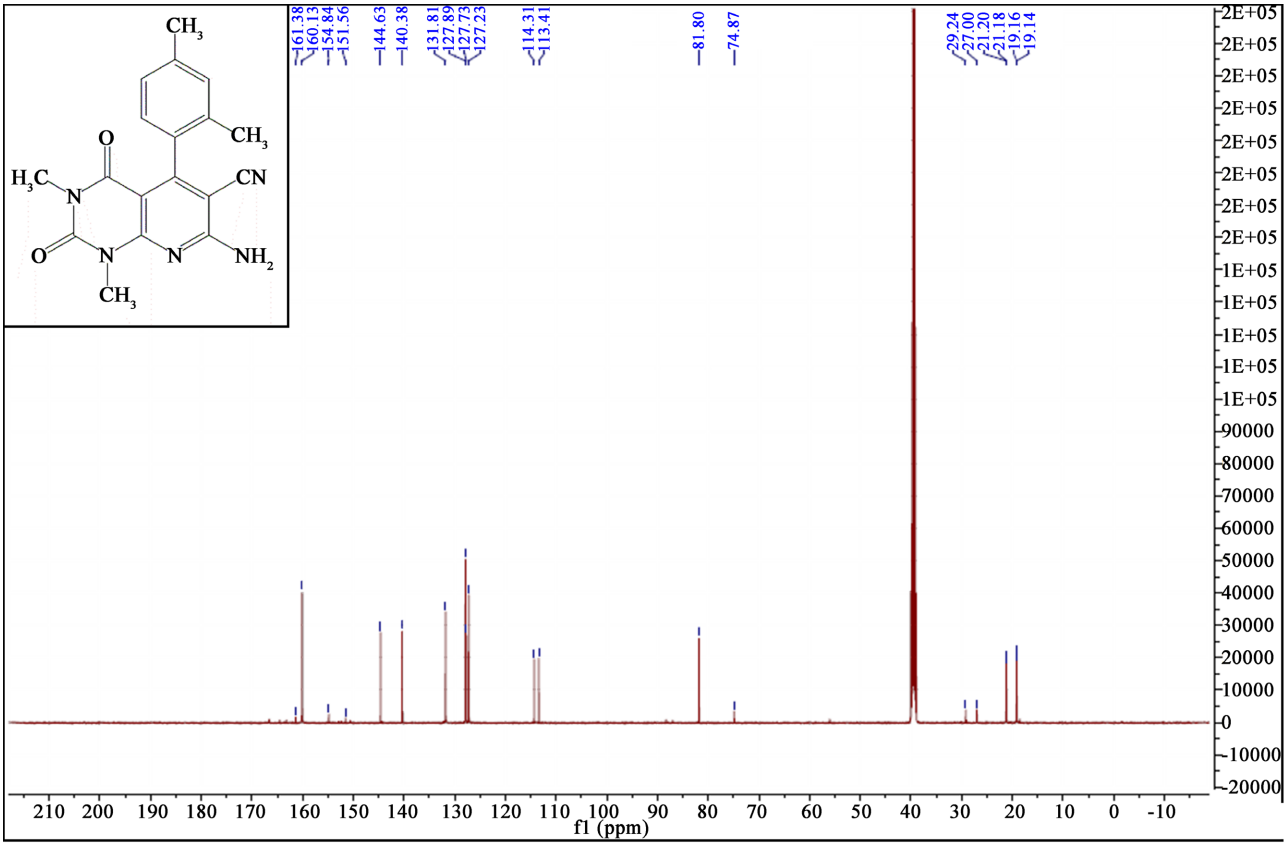


Figure 9. ^{13}C NMR spectrum of 4f.

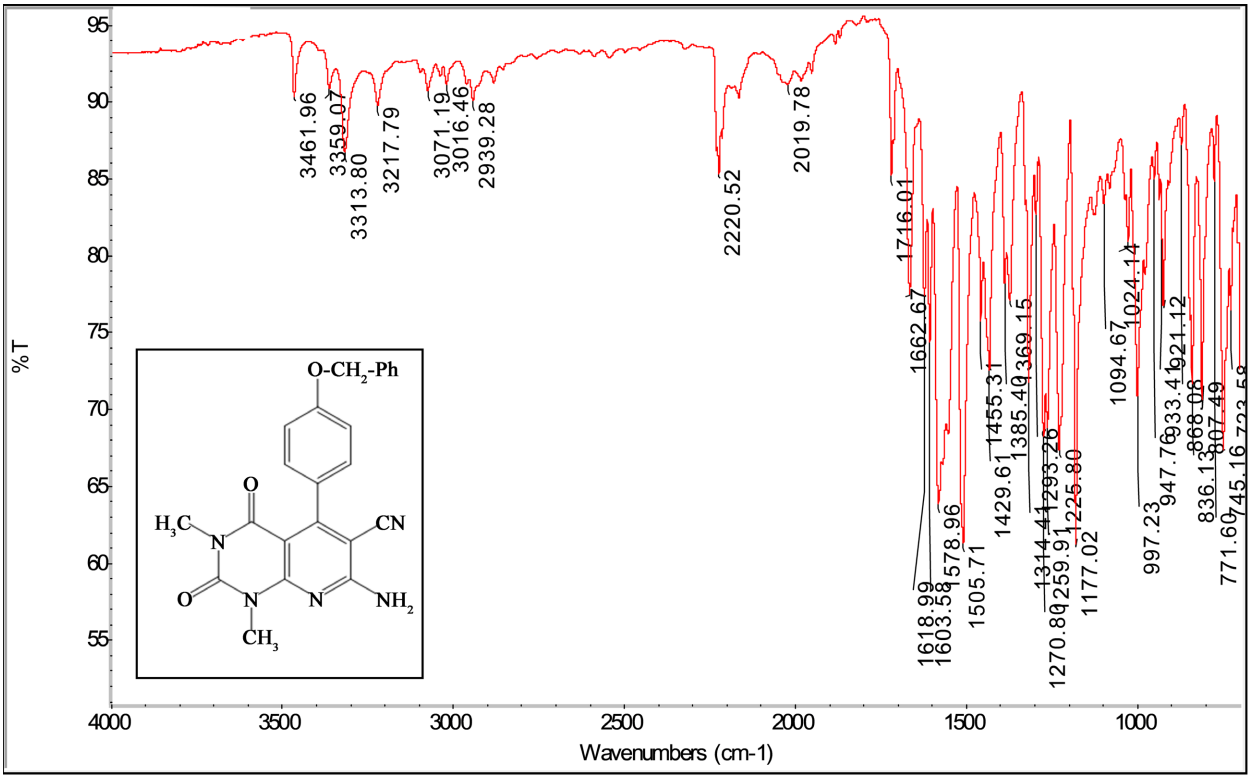


Figure 10. FTIR Spectrum of 4h.

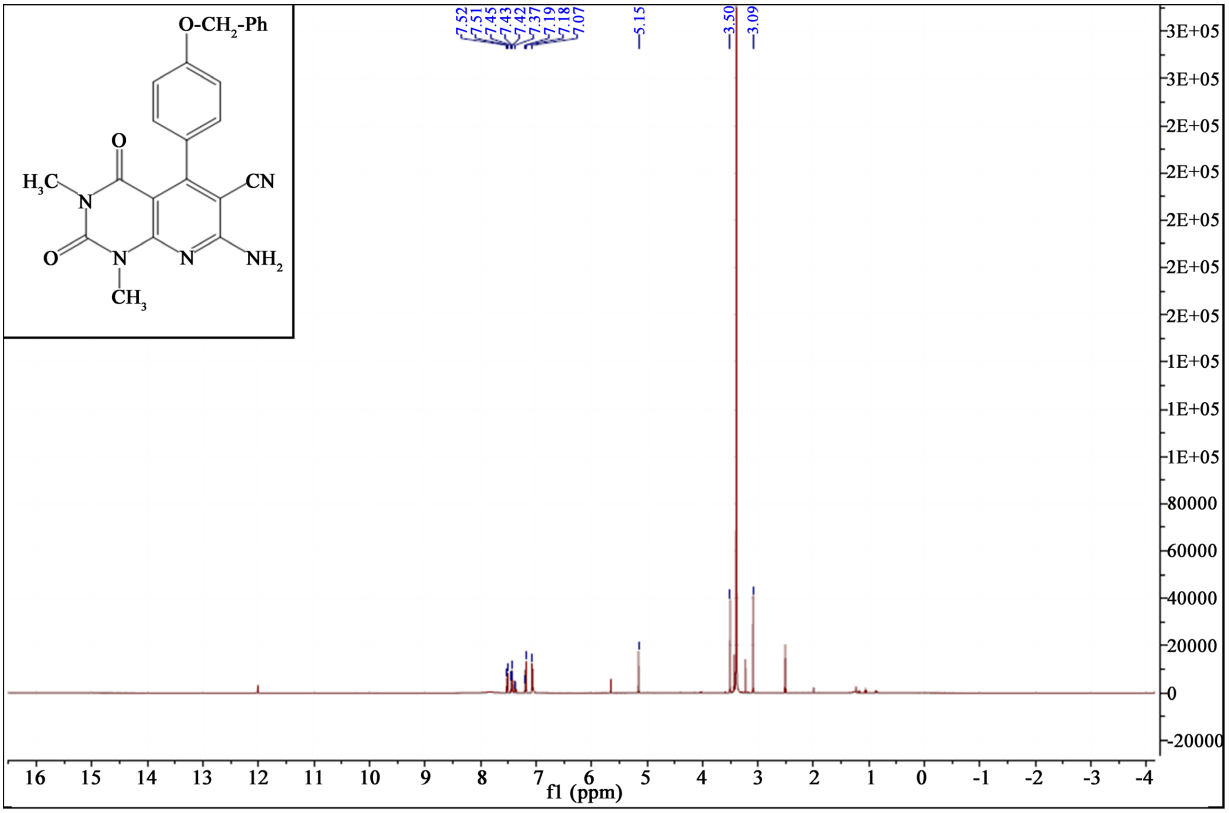


Figure 11. [1]H NMR Spectrum of 4h.

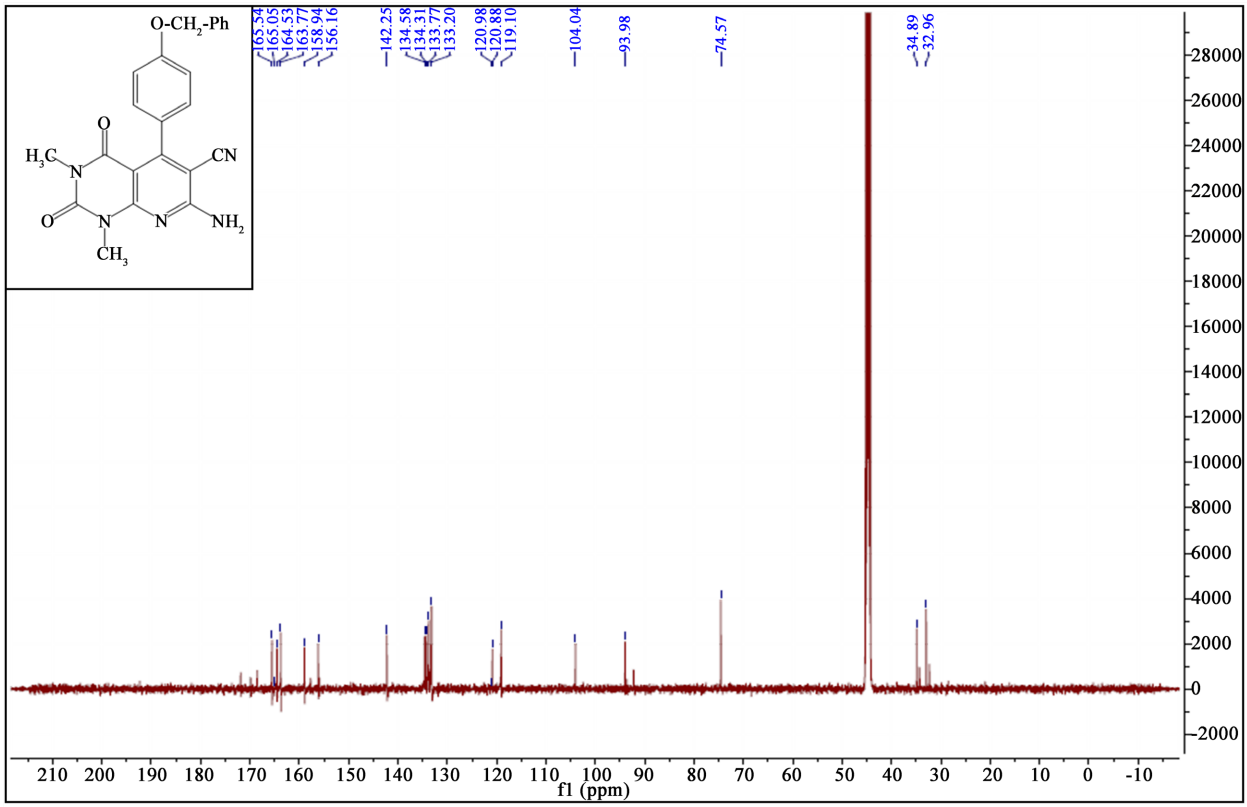


Figure 12. [13]C NMR Spectrum of 4h.

158.94, 163.77, 164.53, 165.06, 165.54 (Figure 12). LCMS (ESI-QTOF) m/z: $C_{23}H_{19}N_5O_3$ için calculated: 413.43, found: 436.13762 $[M + Na]^+$.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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