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Spectral correlation of synthesized ethyl-4-(subs. phenyl)-6-methyl-2-oxo (or thio)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate

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Abstract

Urea or thiourea, ethyl acetoacetate, and substituted aromatic aldehydes were combined in a one-pot Biginelli coupling reaction to create a few 1, 2, 3, 4-tetrahydro pyrimidine-5-carboxylate derivatives without any unsafe organic solvent. The catalyst used for this reaction was nickel nitrate hexahydrate [$Ni(NO_3)_2.6(H_2O)$]. The elemental analyses, mass spectral data, ^{1}H-NMR, ^{13}C-NMR, UV, and IR were used to characterize the separated pure products.

Keywords: Biginelli reaction; Solvent free condition; Urea; Thiourea; Substituted aromatic aldehydes

Introduction

According to the report (Nascimento *et al.* 2020), multicomponent reactions (MCRs) are those in which the reaction of three or more reactants in a single reaction vessel produced a product that contained some of each reactant. The Biginelli reaction is the significant and promising in terms of multicomponent reactions (Tron *et al.* 2011), and the biological activities of its products are diverse that include anti-HIV (Puripat *et al.* 2015), anti-cancer (Raju *et al.* 2011), and antimalarial (Chiang *et al.* 2009). Pietro Biginelli published his groundbreaking work in 1893, which involved a three-component one-pot condensation between a β-keto ester, an aldehyde, and urea, yielding 4-aryl-3, 4-dihydropyrimidin-2(1H)-one (DHP) as the final product (Tron *et al.* 2011). Pyrimidine skeleton is present in several naturally occurring substances (vitamin B1, nucleic acids), pharmaceuticals used in chemotherapy (fluorouracil), and artificial medications (barbiturates). Pyrimidine skeleton is vital to numerous bodily processes in humans.

The synthesis of pyrimidine derivatives has garnered significant attention due to their biological significance (Akhter *et al.* 2019). Dihydropyrimidines (DHPMs) and their derivatives exhibit a wide range of pharmaceutical activities, including that of an a1A receptor antagonist agent (Nantermet *et al.* 2000), an antiviral, antibacterial, antitumour, antimalarial, anti-inflammatory, antitubercular, antileishmanial, antidiabetic, and antiproliferative agent (Singh *et al.* 2016; Rashid *et al.* 2016; Chikhale *et al.* 2015; Huseyenzada *et al.* 2021; Dhumaskar *et al.* 2014; Badolato *et al.* 2018; Lewis *et al.* 2010), an inhibitor of G protein-coupled receptor kinases (GRKs) (Feng *et al.* 2008), and an A_{2B} adenosine receptor antagonist (Crespo *et al.* 2013).

To increase the Biginelli reaction's efficiency, a number of Lewis acids have been added, including $LaCl_3$–$7H_2O$, $InCl_3$, $Mn(OAc)_3$, $ZrCl_4$, $SnCl_2.2H_2O$, $Cu(OTf)_2$, $CuCl_2 \cdot 2H_2O$, and $FeCl_3 \cdot 6H_2O$ (Saini *et al.* 2006; Sedova *et al.* 2007; Gohain *et al.* 2004; Paraskar *et al.* 2003).

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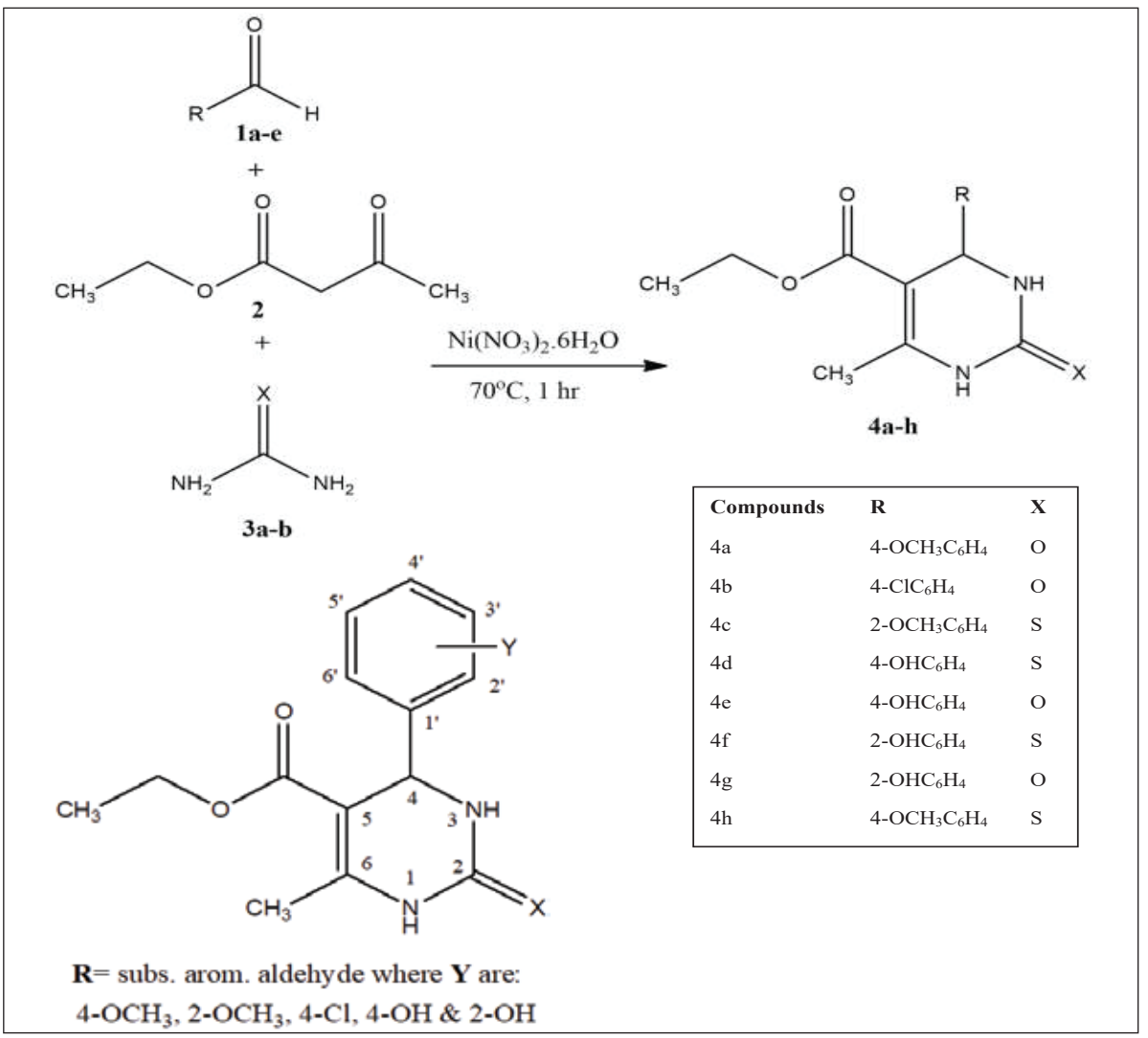
The Lewis acid catalyst (Paraskar *et al.* 2003) was used for most of the reactions, allowing for greater yields and softer conditions than those described in Biginelli's original protocol. Furthermore, the Biginelli reaction has also been carried out in basic conditions using t-BuOK at 70°C (Shen *et al.* 2010), ammonium carbonate in water (Tamaddon *et al.* 2010), and PPh_3 (Debache *et al.* 2008). It has also been discovered that microwave irradiation is beneficial (Pasunooti *et al.* 2011).

Several one-pot DHPM derivative synthesis techniques have recently been developed. While some of the current technologies have advantages over these issues, many of them have disadvantages, including environmental pollution caused using catalysts in stoichiometric quantities, unusual reaction conditions, insufficient yields, and complex processes. The many benefits of inorganic nickel nitrate hexahydrate, including its solubility in water, low cost, and environmental friendliness, make it a useful and often used catalyst for a variety of synthetic reactions.

Here, we present a straightforward, effective method for the one-pot synthesis of derivatives 4a–h of 3, 4-dihydropyrimidin-2(1H)-thiones, employing Biginelli reactions with $Ni(NO_3)_2.6H_2O$ as a catalyst in a solvent-free environment.

Materials and methods

Each product was characterized using mass spectra, elemental analysis, ^{1}H-NMR, ^{13}C-NMR, MP, UV, and IR. Every chemical was purchased from E. Merck. Spots were



Compounds	R	X
4a	4-$OCH_3C_6H_4$	O
4b	4-ClC_6H_4	O
4c	2-$OCH_3C_6H_4$	S
4d	4-OHC_6H_4	S
4e	4-OHC_6H_4	O
4f	2-OHC_6H_4	S
4g	2-OHC_6H_4	O
4h	4-$OCH_3C_6H_4$	S

Scheme 1: Synthesis of compounds 4a-h using $Ni(NO_3)_2.6H_2O$ as a catalyst

identified by thin layer chromatography (TLC) on plates that had been percolated with silica gel 60 F_{254} by utilizing iodine vapour. An electro thermal micro melting point apparatus was used to determine the uncorrected melting points. A Shimadzu IR 470A spectrophotometer was used to record the samples' infrared spectra, which ranged from 4000 to 400 cm^{-1}. With a scanning range of 800-200 nm, the Shimadzu UV-160A spectrometer was used to record the samples' ultraviolet spectra. The spectra of solid samples were recorded using a chloroform solution. Using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as the solvent, the samples' ^{1}H- and ^{13}C-NMR spectra were obtained using a Bruker 400 MHz spectrophotometer.

General procedure

Hexahydrated nickel nitrate, urea or thiourea (6 mmol), ethylacetoacetate (6 mmol), and substituted aromatic aldehyde (3 mmol) were heated for a duration of one to two hours while being constantly stirred (Scheme 1). The stirring process was done at a temperature of roughly 70°C. TLC was used to track the reaction's conclusion. After that, ice water was added to the reaction mixture. After creating a gummy substance, it was filtered through a bückner funnel and dissolved in absolute alcohol. After a while, a solid product was produced and cleaned with cold pure alcohol. Finally, the dried product was recrystallized from absolute alcohol.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4–tetrahydropyrimidine-5-carboxylate, 4a:

Yield 48%; white crystalline solid; mp 209-211°C; R_f value in TLC: 0.62 (ethyl acetate: chloroform, 1:1); UV (λ_{max} in nm): 277 ($\pi\rightarrow\pi^*/n\rightarrow\pi^*$ of C=O); IR (KBr) (υ_{max} in cm^{-1}): 3250 (N-H stretching), 1724 (-C=O stretching for ester group), 1614 (C=C stretching in conj. with C=O), 1368 (CH_3), 1222, 1176 (C-O stretching), 953, 840, 791 (=C-H of aromatic ring); ^{1}H-NMR (δ in ppm): 8.74 (s, N-H, H-1), 6.82-7.28 (m, $4H_{arom}$), 6.30 (s, N-H, H-3), 4.07-4.08 (broad peak for -OC$H_2$$CH_3$), 5.34 (s, 1H, H-4), 3.72 (s, -OCH_3), 2.3 (-CH_3), 1.17 (t, 3H, *J*=7.2, CH_3-CH_2-O); ^{13}C-NMR (δ in ppm): 165.74 (-O-CO-), 159.22 (C-4'), 153.93 (C-2), 146.18 (C-6), 136.21 (C-1') , 127.78 (C-2', 6'), 113.98 (C-3', 5'), 101.55 (C-5), 59.93 (O-CH_2), 55.23 (C-OCH_3), 55.00 (C-4), 18.47 (CH_3-), 14.16 (C$H_3$$CH_2$-); MS: m/z 290.13 (100.0%), 291.13 (16.2%), 292.13 (1.2%); Anal. Found: C, 61.86; H, 6.21; N, 9.45; Calc. for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65%.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, 4b:

Yield 45%; white crystalline solid; mp 213-216°C; R_f value in TLC: 0.46 (ethyl acetate: chloroform, 1:1); UV (λ_{max} in nm): 279 ($\pi\rightarrow\pi^*/n\rightarrow\pi^*$ of C=O); IR (KBr) (υ_{max} in cm^{-1}): 3243 (N-H stretching), 1711 (-C =O stretching for ester group), 1647 (C=C stretching in conj. with C=O), 1423 (CH_3 group), 1220, 1170 (C-O stretching), 1040 (C-Cl stretching), 865, 853, 781 (=C-H of aromatic ring); ^{1}H-NMR (δ in ppm): 8.41 (1-H, N-H, H-1), 7.24-7.30 (m, $4H_{arom}$), 6.15 (1H, N-H, H-3), 4.10 (q, *J*=5.6, CH_3CH_2-O), 5.39 (s, 1H, H-4), 2.34 (s, CH_3), 1.19 (t, 3H, *J*=7.2, CH_3-CH_2-O); ^{13}C-NMR (δ in ppm): 165.44 (CH_3CH_2O-CO-), 133.76 (C-4'), 146.45 (C-2), 142.21 (C-1', C-6), 128.87 (C-2', C-6'), 128.01 (C-3', C-5'), 101.15 (C-5), 60.14 (O-CH_2), 55.13 (C-4), 18.67 (-CH_3) , 14.15 (CH_3CH_2-); MS: m/z 294.08 (100.0%), 296.07 (32.0%), 295.08 (15.1%), 297.08 (4.8%), 296.08 (1.1%); Anal. Found: C, 56.95; H, 5.05; N, 9.45%; Calc. for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.50%.

Ethyl 4-(2-methoxyphenyl)–6–methyl-2-thio-1,2,3,4–tetrahydropyrimidin-5-carboxylate, 4c

Yield 51%; white crystalline solid; mp 188-191°C; R_f value in TLC: 0.58 (ethyl acetate: chloroform, 1:1); UV (λ_{max} in nm): 309 ($\pi\rightarrow\pi^*/n\rightarrow\pi^*$ of C=O); IR (KBr) (υ_{max} in cm^{-1}): 3132 (N-H stretching), 1699 (-C=O) stretching for ester group, 1637 (C=C stretching for -C=O in conj. with C=C group), 1433 (-CH_3 group), 1321(C=S stretching), 1179, 1130 (C-O stretching), 845, 809, 716 (=C-H of aromatic ring); ^{1}H-NMR (δ in ppm): 8.71 (1-H, N-H, H-1), 6.87-7.29 (m, $4H_{arom}$), 7.41 (1H, N-H, H-3), 4.05 (q, *J*=7.2, CH_3-CH_2-O), 5.75 (s, 1H, H-4), 3.66 (s, -OCH_3), 2.40 (s, CH_3), 1.08 (t, 2H, *J*=7.2, CH_3-CH_2-O); ^{13}C-NMR (δ in ppm): 165.44 (CH_3CH_2O-CO-), 174.43 (C-2), 144.72 (C-6), 128.76 (C-1'), 110.76 (C-3'), 156.75 (C-2'),129.49 (C-6', C-4'), 120.66 (C-5'), 100.08 (C-5), 60.18 (O-CH_2), 56.11 (C-4), 55.18 (-OCH_3), 17.97 (-CH_3), 14.03 (C$H_3$$CH_2$-); MS: m/z 306.10 (100%), 307.11 (16.2%), 308.10 (4.5%), 308.11 (1.2%); Anal. Found: C, 58.80; H, 5.92; N, 9.14; Calc. for $C_{15}H_{18}N_2O_3S$: C, 58.72; H, 5.80; N, 9.04%.

Ethyl 4-(4-hydroxyphenyl)–6–methyl-2-thio-1,2,3,4–tetrahydropyrimidin-5-carboxylate, 4d:

Yield 56%; pale brown crystalline solid; mp 206-208°C; R_f value in tlc: 0.34 (chlorform: pet. ether, 4:1); UV (λ_{max} in nm): 309 ($\pi\rightarrow\pi^*/n\rightarrow\pi^*$ of C=O); IR (KBr) (υ_{max} in

cm^{-1}): 3498 (stretching for phenolic -OH), 3182 (N-H stretching), 1687 (-C=O stretching for ester group), 1643, 1577 (C=C stretching in conj. with C=O), 1465, 1373 (CH_3 group), 1311 (C=S stretching), 1251, 1199 (C-O stretching), 852, 810, 765 (=C-H of aromatic ring); ^{1}H-NMR (δ in ppm): 8.47 (s, 1-H, N-H, H-1), 7.84 (s, 1H, N-H, H-3), 7.21 (d, 2H, *J*=8.0, H-2'& 6'), 6.84 (d, 2H, *J*=8.0, H-3'& 5') 5.37 (s, 1H, H-4), 4.02 (q, 2H, *J*=7.2, -OC$\underline{H}_2$CH$_3$), 3.68 (s, 1H, -O$\underline{H}$), 2.36 (s, 3H, -C$\underline{H}_3$-C=C), 1.17 (t, 3H, *J*=7.2, C$\underline{H}_3$-CH$_2$-O); ^{13}C-NMR (δ in ppm): 165.64 (C-2, $\underline{C}$=S), 153.13 (-O-$\underline{C}$O-), 146.82 (C-6, CH$_3$-$\underline{C}$=C), 141.40 (C-4', $\underline{C}$-OH) 134.60 (C-1'), 130.65, 127.86 (C-2', 6'), 127.17, 126.84 (C-3', 5'), 100.64 (C-5), 59.88 (O-$\underline{C}$H$_2$), 52.18 (C-4), 18.45 ($\underline{C}$H$_3$-), 14.04 ($\underline{C}$H$_3$CH$_2$-); MS: m/z 292.09 (100.0%), 293.09 (17.0%), 294.08 (4.5%), 294.09 (1.9%); Anal. Found: C, 58.06; H, 5.41; N, 9.45; Calc. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58%.

Ethyl 4-(4-hydroxyphenyl)–6–methyl-2-oxo-1,2,3,4–tetrahydropyrimidin-5-carboxylate, 4e:

Yield 44%; white crystalline solid; mp 210-212°C; R_f value in TLC: 0.30 (chlorform: pet. ether, 4:1); UV (λ_{max} in nm): 305 (π→π*/n→π* of C=O); IR (KBr) (υ_{max} in cm^{-1}): 3496 (stretching for phenolic -OH), 3250 (N-H stretching), 1683 (-C=O stretching for ester group), 1649, 1579 (C=C stretching in conj. with C=O), 1463 (-CH_3 group), 1309 (C=S stretching), 1221, 1192, 1093 (C-O stretching), 846, 765 (=C-H of aromatic ring); ^{1}H-NMR (δ in ppm): 8.94 (s, 1-H, N-H, H-1), 7.25 (s, 1H, N-H, H-3), 7.03 (d, 2H, *J*=8.4, H-2'& 6'), 6.67 (d, 2H, *J*=8.4, H-3'& 5') 5.20 (s, 1H, H-4), 4.02 (q, 2H, *J*=7.2, -OC$\underline{H}_2$CH$_3$), 3.76 (s, 1H, -O$\underline{H}$), 2.26 (s, 3H, -C$\underline{H}_3$-C=C), 1.09 (t, 3H, *J*=7.2, C$\underline{H}_3$-CH$_2$-O); ^{13}C-NMR (δ in ppm): 165.78 (-O-$\underline{C}$O-), 156.71(C-4', $\underline{C}$-OH), 142.89 (C-2, $\underline{C}$=O), 134.60 (C-1'), 133.98 (C-6, CH3-$\underline{C}$=C) 127.96 (C-2', 6'), 115.36 (C-3', 5'), 102.81 (C-5), 60.27 (O-$\underline{C}$H$_2$), 55.14 (C-4), 17.66 ($\underline{C}$H$_3$-), 13.84 ($\underline{C}$H$_3$CH$_2$-); MS: m/z 276.11 (100.0%), 277.11 (15.9%), 278.12 (1.9%); Anal. Found: C, 61.06; H, 5.61; N, 10.21; Calc. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14%.

Ethyl 4-(2-hyrdroxyphenyl)–6–methyl-2-thio-1,2,3,4–tetrahydropyrimidin-5-carboxylate, 4f:

Yield 57%; white crystalline solid; mp 112-114°C; R_f value in TLC: 0.52 (ethyl acetate: chloroform, 1:1); UV (λ_{max} in nm): 307 (π→π*/n→π* of C=O); IR (KBr) (υ_{max} in cm^{-1}): 3435 (stretching for phenolic -OH), 3365 (N-H stretching), 1726 (-C=O stretching for ester group), 1568 (C=C stretching in conj. with C=O), 1485, 1379 (-CH_3 group), 1325 (C=S stretching), 1230, 1180, 1151, 1087 (C-O stretching), 900, 844, 759 (=C-H of aromatic ring); ^{1}H-NMR (δ in ppm): 7.25 (s, 1-H, N-H, H-1), 6.84 (s, 1H, N-H, H-3), 6.86-7.23 (m, 4H, aromatic), 4.83 (s, 1H, H-4), 4.22 (q, 2H, *J*=7.2, -OC$\underline{H}_2$CH$_3$), 3.14 (s, 1H, -O$\underline{H}$), 2.09 (s, 3H, -C$\underline{H}_3$-C=C), 1.28 (t, 3H, *J*=7.2, C$\underline{H}_3$-CH$_2$-O); ^{13}C-NMR (δ in ppm): 167.31(C-2, $\underline{C}$=S), 150.35 (-O-$\underline{C}$O-), 130.50 (C-6, CH3-$\underline{C}$=C), 128.62 (C-2', $\underline{C}$-OH), 121.64 (C-1'), 121.86 (C-4', 5', 6'), 117.18 (C-3'), 81.55 (C-5), 61.91 (O-$\underline{C}$H$_2$), 49.47 (C-4), 24.19 ($\underline{C}$H$_3$-), 14.09 ($\underline{C}$H$_3$CH$_2$-);MS: m/ 292.09 (100.0%), 293.09 (17.0%), 294.08 (4.5%), 294.09 (1.9%); Anal. Found: C, 61.86; H, 6.21; N, 9.45; Calc. for $C_{14}H_{16}N_2O_3S$: C, 61.52; H, 6.22; N, 9.58%.

Ethyl 4-(2-hydroxyphenyl)–6–methyl-2-oxo-1,2,3,4–tetrahydropyrimidin-5-carboxylate, 4g:

Yield 47%; pale yellow crystalline solid; mp 150-152°C; R_f value in TLC: 0.50 (ethyl acetate: chloroform, 1:1); UV (λ_{max} in nm): 311 (π→π*/n→π* of C=O); IR (KBr) (υ_{max} in cm^{-1}): 3429 (stretching for phenolic -OH), 3228 (N-H stretching), 1741 (-C=O stretching for ester group), 1681, 1602 (C=C stretching in conj. with C=O), 1458, 1332 (-CH_3 group), 1251, 1182, 1069, 1029 (C-O stretching), 906, 858, 758 (=C-H of aromatic ring); ^{1}H-NMR (δ in ppm): 7.24 (s, 1-H, N-H, H-1), 6.19 (s, 1H, N-H, H-3), 6.82-7.22 (m, 4H, aromatic), 4.64 (s, 1H, H-4), 4.25 (q, 2H, *J*=7.2, -OC$\underline{H}_2$CH$_3$), 4.61 (s, 1H, -O$\underline{H}$), 2.34 (s, 3H, -C$\underline{H}_3$-C=C), 1.12 (t, 3H, *J*=7.2, C$\underline{H}_3$-CH$_2$-O); ^{13}C-NMR (δ in ppm): 168.05 (-O-$\underline{C}$O-), 150.76 (C-2', $\underline{C}$-OH), 130.04 (C-2, $\underline{C}$=O), 128.16 (C-6, CH3-$\underline{C}$=C), 121.52 (C-4', 5', 6'), 117.25 (C-3'), 82.59 (C-5), 61.50 (O-$\underline{C}$H$_2$), 48.68 (C-4), 24.86 ($\underline{C}$H$_3$-), 14.06 ($\underline{C}$H$_3$CH$_2$-); MS: m/z 276.11 (100.0%), 277.11 (15.9%), 278.12 (1.9%); Anal. Found: C, 60.66; H, 6.01; N, 10.09; Calc. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14%.

Ethyl 4-(4-methoxyphenyl)–6–methyl-2-thio-1,2,3,4–tetrahydropyrimidin-5-carboxylate, 4h:

Yield 52%; white crystalline solid; mp 190-192°C; R_f value in TLC: 0.65 (ethyl acetate: chloroform, 1:1); UV (λ_{max} in nm): 308 (π→π*/n→π* of C=O); IR (KBr) (υ_{max} in cm^{-1}): 3309, 3169 (N-H stretching), 1666 (C=O in conj. with C=C), 1570 (C=C in conj. with C=O), 1460, 1382 (CH_3 group), 1325 (C=S stretching), 1267, 1184, 1111, 1020 (C-O stretching), 831, 769 (=C-H of aromatic ring); ^{1}H-NMR (δ in ppm): 8.43 (s, 1-H, N-H, H-1), 6.81 (s, 1H, N-H, H-3), 7.14 (d, 2H, *J*=8.0, H-2'& 6'), 7.12 (d, 2H, *J*=8.0, H-3'& 5') 5.64 (s, 1H, H-4), 3.97 (q, 2H, *J*=7.2,

-OC<u>H</u>$_2$CH$_3$), 2.35 (s, 3H, -C<u>H</u>$_3$-C=C), 3.70 (s, 3H, -OC<u>H</u>$_3$), 1.04 (t, 3H, *J*=7.2, C<u>H</u>$_3$-CH$_2$-O); ^{13}C-NMR (δ in ppm): 165.29 (C-2, <u>C</u>=S), 159.54 (-O-<u>C</u>O-), 142.73 (C-6, CH3-<u>C</u>=C), 134.75 (C-4', <u>C</u>-OCH$_3$) 134.60 (C-1'), 128.10 (C-2', 6'), 114.23 (C-3', 5'), 103.23 (C-5), 60.38 (O-<u>C</u>H$_2$), 55.78 (C-4), 55.26 (C-O<u>C</u>H$_3$), 18.19 (<u>C</u>H$_3$-), 14.09 (<u>C</u>H$_3$CH$_2$-); MS: m/z 306.10 (100.0%), 307.11 (16.5%), 308.10 (4.6%), 308.11 (2.0%), 307.10 (1.5%); Anal. Found: C, 61.86; H, 6.21; N, 9.45; Calc. for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14%.

Results and discussion

To synthesize di-(or tetra)-hydropyrimidines, 4a-h, in an analogous manner as previously reported (Akhter *et al.* 2019), a three component solvent free condensation reaction of substituted benzaldehydes, 1a-e, with corresponding β-dicarbonyl compounds, 2a-b, and urea or thiourea, 3a-b, was carried out in the presence of Nickel Nitrate hexahydrate [Ni(NO$_3$)$_2$.6H$_2$O] (Scheme 1). The compounds' 4a–h structures were clarified using elemental analyses, mass spectral data, ^{1}H–NMR, ^{13}C–NMR, UV, and FT-IR investigations.

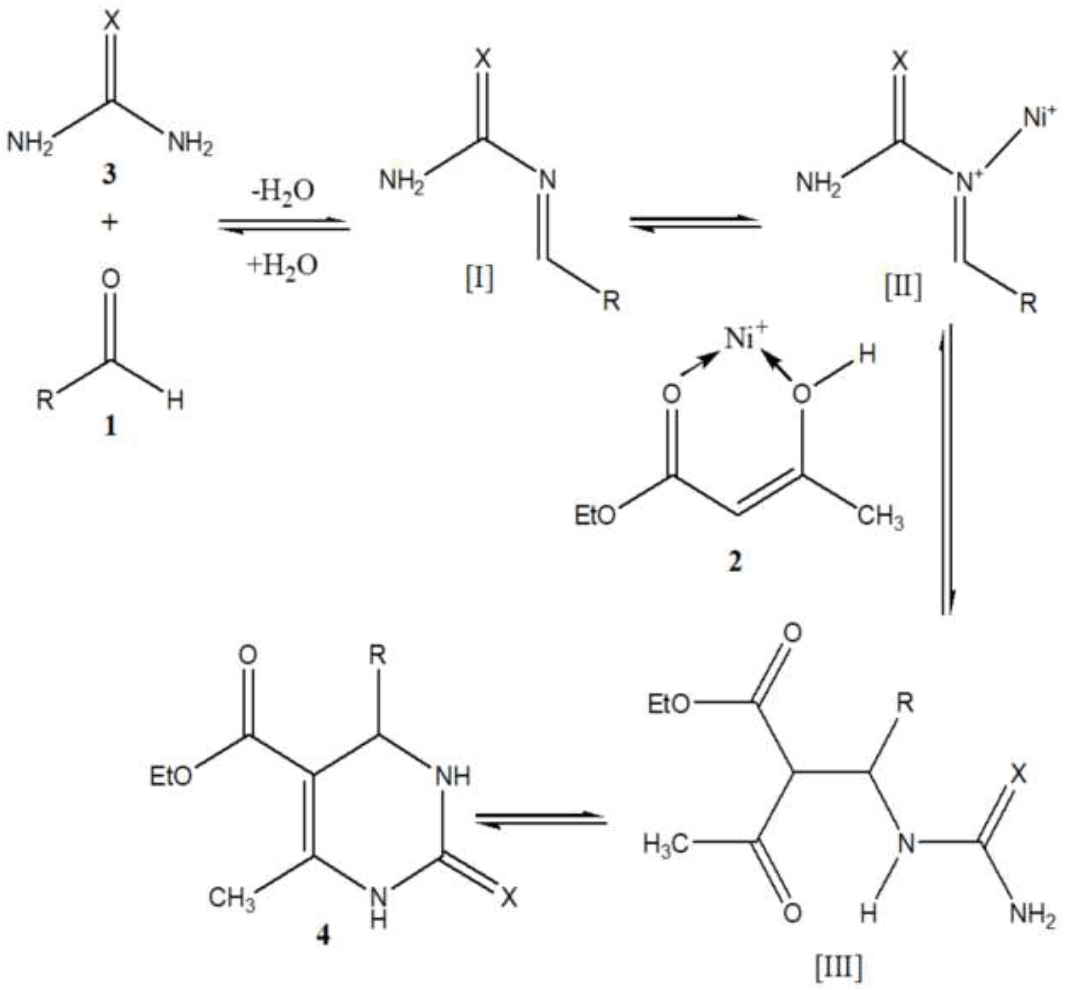
The UV spectra of compounds 4a–h show good agreement with the predicted λ_{max} values. The π→π* of C=O in these compounds is ascribed to the absorption bands in the region of 311-279 nm. These compounds' weak n→π* absorption bands result from C=O being veiled within the π→π* absorption bands.

The wave number (ν_{max}) in the infrared spectral data of compounds 4a–h is where the compounds' functional groups are verified by their distinctive peaks. The presence of N-H and O-H (4d, 4e, 4f, and 4g) groups is indicated by the wide bands in the range (ν_{max}) 3132-3365 cm^{-1} and 3429-3498 cm^{-1}, respectively. Esters with non-conjugated C=O stretching, including pyrimidine moieties, were discovered to be in the range of 1666–1741 cm^{-1}. The range of C=C in conjugation with C=O was found to be 1568–1681 cm^{-1}; the range of C=S stretching was found to be 1311–1325 cm^{-1} (4c, 4d, 4f, and 4h); and the range of C–Cl for the halogenated aromatic compound (4b) was found to be 1040 cm^{-1}.

Due to anisotropy and their link to an electron-withdrawing carbonyl group, the two N-H protons at positions 1 and 3 in compounds 4a–h were significantly deshielded in their ^{1}H-NMR spectra, resulting in two broad singlets at 7.24–8.94 ppm and 6.15-7.84 ppm, respectively. Compound 4b exhibited a peak at δ 8.41 ppm for one amide proton (NH-1) and δ 6.15 ppm for another proton (NH-3). Interestingly, compound 4c showed a small fluctuation in the N-H proton at position 3 (δ7.41 ppm), which could be caused by the ortho instead of para position shift of the substituent on the benzene ring, while the proton at position 1 signaled at δ 8.71 ppm. Within the compounds 4a-h, a singlet was produced by methyl protons attached to a sp^2 carbon at δ 2.09-2.40 ppm, a triplet was produced by another methyl group linked to an ester group in a shielded region δ 1.04-1.28, and a quartet signal was produced by a methylene group directly attached to an electronegative oxygen atom in an ester in a deshielded region δ 3.97-4.25. Because of the bonded electronegative oxygen atom, the protons of the methoxy group in compounds 4a, 4c, and 4h displayed peak in slightly deshielded area (δ 3.60-3.72). Because of the vicinal interaction with the proton at position 3, the proton at sp^3 carbon (position 4) in compounds 4a-h displayed a broad singlet, and the chemical shift values were found at δ 4.64-5.75 ppm. In these compounds, every aromatic proton produced a peak in the predicted area.

The ^{13}C-NMR spectra of the compounds, 4a-h, provided additional structural confirmation. The thiocarbonyl carbon (C-2) in compounds 4c, 4d, 4f, and 4h gave peak in a higher deshielded region of δ 165.29-174.43 ppm because the sulfur atom in those compounds is more polar than the oxygen atom in those compounds. Because of the nearby electronegative oxygen atom, the ester group's carbonyl carbon displayed a signal in a deshielded area of δ 150.35-165.78. A substantial deshielding of the methylene carbon in an ester group connected to an oxygen atom was discovered, with a peak observed at δ 59.88-61.91 ppm. Additionally, the ester-attached methyl carbon showed a peak at δ 13.84–14.16 ppm. The benzene ring's methoxy substituent exhibited the anticipated peak at δ 55.18-55.26 ppm. The olefinic carbons C-5 and C-6 produced peaks at δ 81.55-103.23 ppm and δ 128.16-146.83 ppm, respectively, because the electronic behavior of their substituents causes a push and pull effect in sp^2 carbons. The C-4 location of the methyne carbon displayed a signal at δ 48.68-56.11 ppm.

Even though other mechanistic paths have been suggested in the past (Tamaddon *et al.* 2010), we think that the reaction might move forward via an imine intermediate [I] that was first created via the interaction between aldehyde, 1 and thiourea, 3 (Scheme 2). The lone pair of the Ni$^+$ ion in the Lewis acid may coordinate to produce the iminum ion [II] in situ. This ion is sufficiently electrophilic to react with the ethyl acetoacetate enol form, 2 resulting in the creation of the open chain intermediate [III]. Ultimately, the pyrimidine-5-carboxylate derivatives, 4a-h, are the product of intramolecular cyclization with the loss of an H$_2$O molecule.



Scheme 2: Plausible mechanism for the reaction of 4a-h

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