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Synthesis and Characterization of Hexahydropyrimidines and Their New Derivatives

(Sintesis dan Pencirian Heksahidropirimidina serta Terbitan Baharunya)

Shukkur A. Hamed[1], Athraa Thaker[1], Bilal Majid Rudaini[2], Hasanain Salah Naeem[3], Muntaz Abu Bakar[4] & Siti Aishah Hasbullah[4,*]

[1]*Department of Chemistry, College of Education for Pure Science, University of Anbar, Al-Anbar, Iraq*
[2]*Department of Pharmacy, Al-Maarif University College, Al Anbar,31001, Iraq*
[3]*Faculty of Pharmacy, University of Al Muthanna, Samawah 66001, Iraq*
[4]*Department of Chemical Sciences, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, Selangor 43600, Malaysia*

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ABSTRACT

Three new hexahydropyrimidine derivatives **1a – 1c** were successfully synthesized using the Mannich-type reaction. Furthermore, the synthesis of three amino bases **2a** – **2c** was achieved through the reduction reaction of pyrimidine compounds using hydrazine, followed by the substitution reaction of nitro groups at diverse positions. Subsequently, one of the synthesized amino base derivatives **2c** underwent conversion into seven Schiff bases **3a** – **3g** via a condensation reaction involving the aforementioned amino base derivative and a selection of benzaldehyde derivatives. Four amide compounds **4a – 4d** have been synthesized by a reaction of the secondary amine group in the pyrimidine ring with benzoyl chloride. The products were subjected to comprehensive characterization employing rigorous analytical techniques, including FT-), ^{1}H-NMR (Proton Nuclear Magnetic Resonance Spectroscopy), and LC-MS (Liquid Chromatography–Mass Spectrometry). Additionally, the Molecular Electrostatic Potential (MEP) study was carried out to further investigate the properties of the synthesized compounds. The yields of the three methods used to synthesise new hexahydropyrimidine derivatives varied depending on the specific substituents added to the aromatic ring.

Keywords: Hexahydropyrimidine; Mannich-type reaction; Molecular Electrostatic Potential; Schiff-Bases

ABSTRAK

Sebanyak tiga terbitan heksahidropirimidin **1a** – **1c** telah berjaya disintesis menggunakan tindak balas jenis-Mannich. Selain itu, sintesis tiga bes amino **2a** – **2c** telah berjaya dijalankan melalui tindak balas penurunan sebatian pirimidina menggunakan sebatian hidrazina, diikuti oleh tindak balas penukargantian oleh kumpulan nitro pada posisi berlawanan. Sebatian **2c** telah ditukarkan kepada tujuh bes Shiff **3a** – **3g** melalui tindak balas kondensasi melibatkan terbitan bes amino dan terbitan benzaldehid terpilih. Empat sebatian amida **4a** – **4d** telah disintesis melalui tindak balas kumpulan amina sekunder pada gelang pirimidina dengan benzoil klorida. Hasil kemudian dicirikan secara komprehensif melibatkan kepelbagaian teknik termasuk FT-IR (Spektroskopi Inframerah Fourier Transform), ^{1}H-NMR (1H-Spektroskopi Nuklear Magnetik Resonan) dan LC-MS (Cecair Kromatografi–Spektrometri Jisim). Tambahan pula, kajian Potensi Elektrostatik Molekular (MEP) telah dijalankan untuk mengkaji dengan lebih mendalam ciri sebatian yang disintesis. Hasil yang diperoleh daripada tiga kaedah berbeza daripada sintesis sebatian baharu terbitan heksahidropirimidina menunjukkan variasi bergantung kepada penukarganti pada gelang aromatik.

Kata kunci: Bes-Schiff; heksahidropirimidina; Potensi Elektrostatik Molekul; tindak balas jenis Mannich

Introduction

Recent research in the synthetic molecular design of organic compounds has focused on obtaining extended molecular groups by assembling them from two or more small molecules used as building blocks. Pyrimidine and hydropyrimidine are compounds that have six-membered

heterocyclic rings, which contain two nitrogen atoms at 1,3-positions (Shukkur 2020). Heterocyclic compounds featuring the pyrimidine moiety have garnered substantial scholarly attention, primarily owing to their significance in the synthesis of natural and synthetic compounds. This class of compounds frequently showcases noteworthy biological activities and holds considerable relevance in clinical applications (Tolba et al. 2022). As a result, pyrimidine derivatives have been widely used as bioactive compounds in medicinal chemistry for their anticancer, anti-inflammatory, antibacterial, and antivirus properties (Xian et al. 2020).

Heterocyclic amines are important intermediates in the preparation of fine chemicals, biochemicals, and medicines (Feng et al. 2016). Although there are several synthetic pathways to produce such compounds, the hydrogenation of nitro compounds is one of the most widely used methods (Cantillo, Baghbanzadeh & Kappe 2012). Particularly, hydrazine hydrate ($N_2H_4.H_2O$) is a suitable reagent for the reduction of nitro groups since only N_2 and water are generated as by-products. Hydrazine hydrate is generally safe to handle (Cantillo, Moghaddam & Kappe 2013). Whereas, the catalytic reductions of nitro groups in the presence of metal complexes, metal sulfides, or metal powders have various practical drawbacks, such as toxic by-products and difficulty in reuse (Rai et al. 2014).

Several heterocyclic Schiff bases exhibit suitable chemical, physical, and biological properties (Orlova et al. 2021). Undoubtedly, interest in the discovery of heteroaromatic azomethines as attractive structures has increased due to their utility for the development of catalysts, intermediates in organic synthesis, pigments (Bolduc et al. 2012), corrosion inhibitors (Goyal et al. 2018), and polymer stabilizers. Until now, many synthesis methods have been reported, such as the oxidation, dimerization, or dehydrogenation of primary amines (Qin et al. 2013). Traditionally, the most common and effective way to produce heterocyclic Schiff bases was through the condensation of active aldehydes and heterocyclic amine compounds (Ahmed et al. 2019), wherein the carbonyl group (-C=O) is converted into imine or azomethine. (-HC=N-) activity when interacting with primary amine is termed an imine (Kasimala 2021). Some of the heterocyclic imines can function as chemosensors for the cations (Khan et al. 2021).

Heterocyclic amides have recently obtained considerable attention due to their varied pharmacological properties and their biological activity as anti-infectives, infections, diabetes, depression, as well as human and animal physiological diseases (Zarecki, Kolanowski & Markiewicz 2020). Where the formation of an amide bond is crucial, there are several known methods for the synthesis of carboxamides (Li, Wang & Wang 2008). In general, amides are formed from carboxylic acids and amines or via the reaction of acyl chlorides with amines in a solvent (Leggio et al. 2017). In addition, some reactions that involve amines and carboxylic acids are very inefficient, despite long reaction durations. Thus, there is still a high demand for methods that use acyl chlorides to synthesis amides (Shi et al. 2020). In this research endeavor, the synthesis of hexahydropyrimidines and their derivatives, encompassing amines, Schiff bases, and amides, was successfully accomplished. The molecular structures of these compounds were meticulously ascertained via rigorous analytical methods, including FT-IR, ^{1}H-NMR, and LC-MS. These characterization techniques were employed to authenticate the molecular framework of the synthesized compounds, thereby underscoring their potential suitability for future applications.

Materials and Methods

All chemicals were of the highest purity and supplied by reputable companies. Acetone (99.5%, ROMIL), Ammonium acetate (99%, Sigma-Aldrich), Benzaldehyde (99%, Sigma-Aldrich), Benzoyl Chloride (99.7%, BDH), Ethanol Absolute (99.8%, ROMIL), Heptane (99%, ROMIL), Hydrazine hydrate (98%, Sigma-Aldrich), Hydrochloric acid (37%, BDH), Nitromethane (98%, Sigma-Aldrich), Pyridine (99.8%, ROMIL), Toluene (99.5%, ROMIL), 1-Butanol (99.5%, Sigma-Aldrich), 2-Chloro-4-fluorobenzaldehyde (97%, Sigma-Aldrich), 2-Nitrobenzaldehyde (98%, Sigma-Aldrich), 2,4-Dichlorobenzaldehyde (98.9%, Sigma-Aldrich), 3-Chlorobenzaldehyde (97%, Sigma-Aldrich), 3-Methoxy-4-hydroxybenzaldehyde (99%, EXIR), 3-Nitrobenzaldehyde (99%, Sigma-Aldrich), 3,4-Dimethoxybenzaldehyde (98%, Sigma-Aldrich), 4-Bromobenzaldehyde (98%, Sigma-Aldrich), 4-Chlorobenzaldehyde (97%, Sigma-Aldrich), 4-Ethoxybenzaldehyde (99.9%, Sigma-Aldrich), 4-Fluorobenzaldehyde (99%, Sigma-Aldrich), 4-Hydroxybenzaldehyde (97%, Sigma-Aldrich), 4-Methoxybenzaldehyde (98%, Sigma-Aldrich), 4-Methylbenzaldehyde (98%, EXIR),

4-Nitrobenzaldehyde (99%, Sigma-Aldrich), 4-Pyridine carboxaldehyde (99%, Sigma-Aldrich). Melting points were recorded in the laboratories of the Iraqi Anbar University using the Electro-Thermal Melting Point Apparatus. Thin layer chromatography (TLC) was performed on silica gel, and spots were visualized by iodine vapors. FT-IR spectra were recorded using Fourier transform infrared Shimazu (Bruker-Tensor27, ATR, Germany), ^{1}H-NMR spectra in ppm unit were recorded using DMSO-d_6 as a solvent and TMS (Tetramethylsilane $(CH_3)_4Si$) as an internal standard; and mass spectrometer using (MS 70 ev, 5973 Agilent Technology) apparatus; and the mass spectrometry of liquid chromatography was recorded using (LC-MS 90 ev, 6200 Agilent Technology) apparatus.

*General Synthesis of Hexahydropyrimidine Derivatives **(1a – 1c)**:*

0.03 mol of benzaldehyde derivatives, 0.02 mol of ammonium acetate and 0.01 mol of nitromethane were added in 35 mL of n-BuOH. The mixture was stirred under reflux for 40-70 min at a temperature of 125 °C until a suspended solution was formed. Thin layer chromatography (TLC) using mixture of benzene: acetone with ratio (9:1) was used to monitor the reaction until completion. Subsequently, the mixture was subjected to evaporation using a rotary evaporator, effectively separating the product from the solvent. The product was then dried in a fume chamber, and the precipitate was weighed and subjected to structural analysis.

5-Nitro-2,4,6-tris(4-ethoxyphenyl)hexahydropyrimidine **(1a)**

4-ethoxybenzaldehyde (4.5g; 0.03mol), ammonium acetate (1.54g; 0.02mol) and nitromethane (0.61g; 0.01mol) were mixed in n-BuOH and refluxed for 60 min at 125 °C to yield **1a** in 79% as a light green powder with a melting point of 118-120° C; $C_{28}H_{33}N_3O_5$. FT-IR (ATR) (ν, cm^{-1}): 3188 (N-H), 3054 (sp^2-C-H), 2957 (sp^3-C-H), 1597 (C=C), 1555 (-NO_2). ^{1}H-NMR (DMSO-d_6; 500MHz), δ, ppm: 2.9 (s, 2H, N-$H_{pyrimidine}$), 7.02-7.04(m, 4H, C-$H_{pyrimidine}$), 7.81-8.15 (m, 9H, Ar-H).

5-Nitro-2,4,6-tris(3,4-dimethoxyphenyl)hexahydropyrimidine **(1b)**

3,4-dimethoxybenzaldehyde (4.8g; 0.03mol), ammonium acetate (1.54g; 0.02mol) and nitromethane (0.61g; 0.01mol) were mixed in n-BuOH and refluxed for 75 min at 125 °C to yield **1b** in 81% as a yellow powder with a melting point of 144-146 °C; $C_{28}H_{33}N_3O_8$. FT-IR (ATR) (ν, cm^{-1}): 3121 (N-H), 2979 (sp^2-C-H), 2904 (sp^3-C-H), 1579 (C=C), 1557 (-NO_2). ^{1}H-NMR (DMSO-d_6; 500MHz), δ, ppm: 2.10 (s, 2H, N-$H_{pyrimidine}$), 7.06 ppm (2H, d, *J*=8.42; H4,$6_{pyrimidine}$), 7.43 ppm (m; H$5_{pyrimidine}$), 7.51 ppm (s; H$2_{pyrimidine}$), 7.05-8.24 (m, 9H, Ar-H) 3.82 ppm and 3.84 ppm (s, 18H; -O-CH_3). Mass spectrum m/z: $[M+H]^+$ at m/z 538.9 (for $C_{28}H_{33}N_3O_8$), $[M+2H]^{2+}$ at m/z 209.3 ($C_{10}H_{14}N_3O_2$), $[M+2H]^{2+}$ at m/z 162.2 ($C_9H_8NO_2$), $[M+2H]^{2+}$ at m/z 119.2 ($C_8H_7O_2$), $[M+H]^+$ at m/z 91.2 (C_7H_7), $[M+H]^{2+}$ at m/z 51.1 (C_4H_3).

5-Nitro-2,4,6-tris(3-hydroxyphenyl)hexahydropyrimidine **(1c)**

3-hydroxybenzaldehyde (3.6g; 0.03mol), ammonium acetate (1.54g; 0.02mol) and nitromethane (0.61g; 0.01mol) were mixed in n-BuOH and refluxed for 40 min 125 °C to yield **1c** in 77% as orange powder with a melting point of 124-126 °C; $C_{22}H_{21}N_3O_5$. FT-IR (ATR) (ν, cm^{-1}): 3327 (O-H) and (N-H), 3027 (sp^2-C-H), 2928 (sp^3-C-H), 1605 (C=C), 1550 (-NO_2). ^{1}H-NMR (DMSO-d_6; 500MHz), δ, ppm: 5.58ppm (s, 1H, C-H$2_{pyrimidine}$), 4.07ppm (t, *J*=6.49, 2H, C-H4,$6_{pyrimidine}$), 3.97ppm (d, *J*=2.29, 1H, C-H$5_{pyrimidine}$). 7.05-7.86 (m, 12H, Ar-H), 9.04 (s, 3H, OH).

*General Synthesis of Amine Derivatives in the Basic Procedure (**2a – 2c**):*

In a round-bottom flask, a specific quantity (0.002 mol, 1g) of previously synthesized hexahydropyrimidine derivatives, namely (5-Nitro-2,4,6-tris(4-nitrophenyl) hexahydropyrimidine, 5-Nitro-2,4,6-tris(2-nitrophenyl) hexahydropyrimidine (Athraa & Shukkur 2021), and (5-nitro-2,4,6-tris(3-nitrophenyl)hexahydropyrimidine) (Shukkur 2020), were combined with a mixture of hydrazine (98%) and absolute ethanol in a 10:10 mL ratio. The resulting mixture was refluxed at 120 °C for 4-9 h until a suspended solution formed. The progress of the reaction was monitored using thin layer chromatography (TLC) with a Benzene: Acetone mixture (8:2 ratio) until completion. Following the reaction, the solvent was evaporated using a rotary evaporator to isolate the product from the solvent. The obtained product was air-dried and subjected to further analysis for structural identification.

4,4'-(5-nitro-2-(4-nitrophenyl)hexahydropyrimidine-4,6-diyl) dianiline **(2a)**

5-Nitro-2,4,6-tris(4-nitrophenyl)hexahydropyrimidine (1.0g; 0.002mol) was added to a mixture of hydrazine (98%) and absolute ethanol (10:10 mL) and refluxed for 4 h at 120 °C to yield **2a** in 83% as a white powder with a melting point of 260-262 °C; $C_{22}H_{22}N_6O_4$. FT-IR (ATR) (ν, cm^{-1}): 3384 (N-H_2), 3325 (N-H), 3039 (sp^2-C-H), 2945 (sp^3-C-H), 1594 (-NO_2), 1589 (C=C). ^{1}H-NMR (DMSO-d_6; 500MHz), δ, ppm: 2.83 (s, 2H, N-$H_{pyrimidine}$), 5.04 (s, 4H, N-H_2), 3.93ppm (d, *J*=7.52, 2H, C-H4,$6_{pyrimidine}$), 4.41ppm (t, *J*=5.71, 1H, C-H$5_{pyrimidine}$), 4.90ppm (s, 1H, C-H$2_{pyrimidine}$), 6.61-8.15 (m, 12H, Ar-H). Mass spectrum m/z: $[M+2H]^{2+}$ at m/z 431.15 (for $C_{22}H_{19}N_6O_4$), $[M+2H]^{2+}$ at m/z 401.2 (for $C_{22}H_{17}N_4O_4$), $[M+2H]^{2+}$ at m/z 340.1 (for $C_{16}H_{14}N_5O_4$), $[M+H]^+$ at m/z 283.1 (for $C_{17}H_{21}N_4$), $[M+2]^{2+}$ at m/z 190.1 (for $C_{15}H_{10}$), $[M+2]^{2+}$ at m/z 89.0 (for C_7H_5).

2,2'-(5-nitro-2-(2-nitrophenyl)hexahydropyrimidine-4,6-diyl) dianiline **(2b)**

5-Nitro-2,4,6-tris(2-nitrophenyl)hexahydropyrimidine (4.5g; 0.03mol) was added to a mixture of hydrazine (98%) and absolute ethanol (10:10 mL) and refluxed for 9 h at 120 °C to yield **2b** in 78% as a white powder with a melting point of 212-214 °C; $C_{22}H_{22}N_6O_4$. FT-IR (ATR) (ν, cm^{-1}): 3333 (N-H_2), 3204 (N-H), 2921 (sp^2-C-H), 2852 (sp^3-C-H), 1596 (C=C), 1500 (-NO_2). ^{1}H-NMR (DMSO-d_6; 500MHz), δ, ppm: 2.17 (s, 2H, N-$H_{pyrimidine}$), 7.55 (s, 4H, N-H_2), 3.74ppm (d, *J*=5.96, 2H, C-H4,$6_{pyrimidine}$), 4.31ppm (t, *J*=8.30, 1H, C-H$5_{pyrimidine}$), 4.96ppm (s, 1H, C-H$2_{pyrimidine}$), 6.75-8.00 (m, 12H, Ar-H).

3,3'-(5-nitro-2-(3-nitrophenyl)hexahydropyrimidine-4,6-diyl) dianiline **(2c)**

5-nitro-2,4,6-tris(3-nitrophenyl)hexahydropyrimidine (4.5g; 0.03mol) was added to a mixture of hydrazine (98%) and absolute ethanol (10:10 mL) and refluxed for 5 h at 120 °C to yield **2c** in 40% as a white powder with a melting point of 98-100 °C; $C_{22}H_{22}N_6O_4$. FT-IR (ATR) (ν, cm^{-1}): 3457 (N-H_2), 3265 (N-H), 3028 (sp^2-C-H), 2982 (sp^3-C-H), 1600 (C=C), 1547 (-NO_2). ^{1}H-NMR (DMSO-d_6; 500MHz), δ, ppm: 2.77 (s, 2H, N-$H_{pyrimidine}$), 5.20 (s, 4H, N-H_2), 3.87ppm (d, *J*=8.30, 2H, C-H4,$6_{pyrimidine}$), 4.43ppm (t, *J*=8.30, 1H, C-H$5_{pyrimidine}$), 4.98ppm (s, 1H, C-H$2_{pyrimidine}$), 6.68-8.30 (m, 12H, Ar-H).

*General Synthesis of Schiff Bases (**3a – 3g**):*

In 25 mL of absolute ethanol, 0.002 mol of amine **2c** and 0.004 mol of benzaldehyde derivatives (benzaldehyde, 4-methoxybenzaldehyde, 3-chlorobenzaldehyde, 4-pyridinecarboxaldehyde, 4-ethoxybenzaldehyde, and 4-fluorobenzaldehyde, 4-methylbenzaldehyde) were mixed in a round flask, and then the mixture was refluxed for 5-9 h at 80 °C. TLC (using benzene: acetone mixture in an 8:2 ratio) was used to monitor the reaction until completion. Subsequently, the mixture was subjected to evaporation using a rotary evaporator to separate the product from the solvent. The produced product was dried in a fume chamber, and the obtained precipitate was weighed and subjected to structural analysis.

N,N'-((5-nitro-2-(3-nitrophenyl)hexahydropyrimidine-4,6-diyl)bis(3,1-phenylene))bis(1-phenylmethanimine) **(3a)**

Benzaldehyde (0.42g; 0.004mol) and **2c** (0.9g; 0.002mol) were mixed and refluxed for 6 h at 80 °C to yield **3a** in 92% as a white powder with a melting point of 122-124 °C; $C_{36}H_{30}N_6O_4$. FT-IR (ATR) (ν, cm^{-1}): 3331 (N-H), 3040 (sp^2-C-H), 2850 (sp^3-C-H), 1643.6 (C=N), 1595 (C=C), 1536 (-NO_2). ^{1}H-NMR (DMSO-d_6; 500MHz), δ, ppm: 2.74 (s, 2H, N-$H_{pyrimidine}$), 4.14 ppm (m, 3H, C-H4,5,$6_{pyrimidine}$), 5.62 ppm (s, 1H, C-H$2_{pyrimidine}$), 7.06-8.08 (m, 22H, Ar-H), 8.55 (s, 2H, CH=N). Mass spectrum m/z: $[M+2H]^{2+}$ at m/z 607.3 (for $C_{36}H_{28}N_6O_4$), $[M+2H]^{2+}$ at m/z 434.1 (for $C_{29}H_{30}N_4$), $[M+2H]^{2+}$ at m/z 476.9 (for $C_{29}H_{26}N_5O_2$), $[M+H]^+$ at m/z 315.41 (for $C_{22}H_{21}N_2$), $[M+H]^+$ at m/z 230.6 (for $C_{15}H_{21}N_2$), $[M+H]^+$ at m/z 156.8 (for $C_6H_{10}N_3O_2$).

N,N'-((5-nitro-2-(3-nitrophenyl)hexahydropyrimidine-4,6-diyl)bis(3,1-phenylene))bis(1-(4-methoxyphenyl) methanimine) **(3b)**

4-methoxybenzaldehyde (0.54g; 0.004mol) and **2c** (0.9g; 0.002mol) were mixed and refluxed for 8 h at 80 °C to yield **3b** in 76% as a yellow powder with a melting point of 110-112 °C; $C_{38}H_{34}N_6O_6$. FT-IR (ATR) (ν, cm^{-1}): 3294 (N-H), 3074 (sp^2-C-H), 2866 (sp^3-C-H), 1636.2 (C=N), 1600 (C=C), 1525 (-NO_2), 1100 (C-O). ^{1}H-NMR (DMSO-d_6; 500MHz), δ, ppm: 2.78 (s, 2H, N-$H_{pyrimidine}$), 8.62 (s, 2H, CH=N), 3.77 ppm (d, 2H, *J*=8.30 C-H4,$6_{pyrimidine}$), 4.41 ppm (t, 1H, *J*=8.30 C-H$5_{pyrimidine}$), 5.14 ppm (s, 1H, C-H$2_{pyrimidine}$),7.03-8.31 (m, 20H, Ar-H), 3.75 (s, 6H, OCH_3).

N,N'-((5-nitro-2-(3-nitrophenyl)hexahydropyrimidine-4,6-diyl)bis(3,1-phenylene))bis(1-(3-chlorophenyl)methanimine) **(3c)**

3-chlorobenzaldehyde (0.56g; 0.004mol) and **2c** (0.9g; 0.002mol) were mixed and refluxed for 4 h at 80 °C to yield **3c** in 82% as a grey colour powder with a melting point of 144-146 °C; $C_{36}H_{28}Cl_2N_6O_4$. FT-IR (ATR) (ν, cm^{-1}): 3319 (N-H), 3050 (*sp²*-C-H), 2967 (*sp³*-C-H), 1629.7 (C=N), 1598 (C=C), 1530 (-NO_2), 745 (C-Cl). ^{1}H-NMR (DMSO-$d_{6;}$ 500MHz), δ, ppm: 2.64 (s, 2H, N-$H_{pyrimidine}$), 8.72 (s, 2H, CH=N), 3.54 ppm (d, 2H, *J*=7.32 C-H4,$6_{pyrimidine}$), 4.39 ppm (t, 1H, *J*=7.32 C-H$5_{pyrimidine}$), 5.07 ppm (s, 1H, C-H$2_{pyrimidine}$), 7.15-8.31 (m, 20H, Ar-H). Mass spectrum m/z: $[M+2H]^{2+}$ at m/z 675.6 (for $C_{36}H_{25}C_{l2}N_6O_4$), $[M+H]^+$ at m/z 157.0 (for $C_6H_{11}N_3O_2$), $[M+2H]^{2+}$ at m/z 564.3 (for $C_{34}H_{28}C_{l2}N_4$), $[M+2H]^{2+}$ at m/z 520.3 (for $C_{30}H_{23}Cl_1N_5O_2$), $[M+H]^+$ at m/z 432.2 (for $C_{29}H_{27}N_4$), $[M+H]^+$ at m/z 344.2 (for $C_{23}H_{25}N_3$).

N,N'-((5-nitro-2-(3-nitrophenyl)hexahydropyrimidine-4,6-diyl)bis(3,1-phenylene))bis(1-(pyridin-4-yl)methanimine) **(3d)**

4-pyridinecarboxaldehyde (0.42g; 0.004mol) and **2c** (0.9g; 0.002mol) were mixed and refluxed for 5 h at 80 °C to yield **3d** in 68% as a yellow powder with a melting point of 198-200 °C; $C_{34}H_{28}N_8O_4$. FT-IR (ATR) (ν, cm^{-1}): 3250 (N-H), 3059 (*sp²*-C-H), 2977 (*sp³*-C-H), 1643.4 (C=N), 1553 (C=C), 1530 (-NO_2), 1085 (C-N). ^{1}H-NMR (DMSO-$d_{6;}$ 500MHz), δ, ppm: 2.65 (s, 2H, N-$H_{pyrimidine}$), 9.69 (s, 2H, CH=N), 3.90 ppm (d, 2H, *J*=5.32 C-H4,$6_{pyrimidine}$), 5.17 ppm (t, 1H, *J*=5.32 C-H$5_{pyrimidine}$), 5.48 ppm (s, 1H, C-H$2_{pyrimidine}$), 7.15-8.63 (m, 20H, Ar-H).

N,N'-((5-nitro-2-(3-nitrophenyl)hexahydropyrimidine-4,6-diyl)bis(3,1-phenylene))bis(1-(4-ethoxyphenyl)methanimine) **(3e)**

4-ethoxybenzaldehyde (0.48g; 0.004mol) and **2c** (0.9g; 0.002mol) were mixed and refluxed for 9 h at 80 °C to yield **3e** in 81% as a yellow powder with a melting point of 170-172 °C; $C_{40}H_{38}N_6O_6$. FT-IR (ATR) (ν, cm^{-1}): 3260 (N-H), 3086 (*sp²*-C-H), 2958 (*sp³*-C-H), 1644.8 (C=N), 1590 (C=C), 1540 (-NO_2). ^{1}H-NMR (DMSO-$d_{6;}$ 500MHz), δ, ppm: 2.77 (s, 2H, N-$H_{pyrimidine}$), 8.63 (s, 2H, CH-N), 3.70 ppm (d, 2H, *J*=4.40 C-H4,$6_{pyrimidine}$), 4.49 ppm (t, 1H, *J*=4.40 C-H$5_{pyrimidine}$), 5.10 ppm (s 1H, C-H$2_{pyrimidine}$), 7.00-8.31 (m, 20H, Ar-H), 1.23-1.26 (t, 6H, CH_3), 3.99-4.03 (q, 4H, CH_2).

N,N'-((5-nitro-2-(3-nitrophenyl)hexahydropyrimidine-4,6-diyl)bis(3,1-phenylene))bis(1-(4-fluorophenyl)methanimine) **(3f)**

4-fluorobenzaldehyde (0.49g; 0.004mol) and **2c** (0.9g; 0.002mol) were mixed and refluxed for 4.5 h at 80 °C to yield **3f** in 84% as a grey colour powder with a melting point of 152-154 °C; $C_{36}H_{28}F_2N_6O_4$. FT-IR (ATR) (ν, cm^{-1}): 3294 (N-H), 3071 (*sp²*-C-H), 2987 (*sp³*-C-H), 1635.7 (C=N), 1579 (C=C), 1524 (-NO_2), 850 (C-Cl). ^{1}H-NMR (DMSO-$d_{6;}$ 500MHz), δ, ppm: 2.85 (s, 2H, N-$H_{pyrimidine}$), 8.63 (s, 2H, CH=N), 3.91 ppm (d, 2H, *J*=7.10 C-H4,$6_{pyrimidine}$), 4.48 ppm (t, 1H, *J*=7.10 C-H$5_{pyrimidine}$), 5.22 ppm (s, 1H, C-H$2_{pyrimidine}$), 7.17-8.32 (m, 20H, Ar-H).

N,N'-((5-nitro-2-(3-nitrophenyl)hexahydropyrimidine-4,6-diyl)bis(3,1-phenylene))bis(1-4-tolylmethanimine) **(3g)**

4-methylbenzaldehyde (0.48g; 0.004mol) and **2c** (0.9g; 0.002mol) were mixed and refluxed for 7 h at 80 °C to yield **3g** in 71% as a white powder with a melting point of 142-144 °C; $C_{38}H_{34}N_6O_4$. FT-IR (ATR) (ν, cm^{-1}): 3288 (N-H), 3025 (*sp²*-C-H), 2965 (*sp³*-C-H), 1641.1 (C=N), 1545 (C=C), 1337 (-NO_2). ^{1}H-NMR (DMSO-$d_{6;}$ 500MHz), δ, ppm: 2.77 (s, 2H, N-$H_{pyrimidine}$), 8.62 (s, 2H, CH=N), 3.87 ppm (d, 2H, *J*=5.46 C-H4,$6_{pyrimidine}$), 4.57 ppm (t, 1H, *J*=5.46 C-H$5_{pyrimidine}$), 5.18ppm (s, 1H, C-H$2_{pyrimidine}$), 7.16-8.31 (m, 20H, Ar-H), 2.22 (s. 9H, CH_3).

*General Synthesis of Amides (**4a – 4d**):*

5-Nitro-2,4,6-tris(4-nitrophenyl)hexahydropyrimidine, 5-Nitro-2,4,6-tris(4-methoxyphenyl)hexahydropyrimidine (Athraa & Shukkur 2021), 5-nitro-2,4,6-triphenylhexahydropyrimidine (Shukkur 2020), and 5-Nitro-2,4,6-tris(3,4-dimethoxyphenyl) hexahydropyrimidine **1b** were employed in this study. The derivative was added to 15 mL of pyridine, followed by the gradual dropwise addition of benzoyl chloride to the mixture under continuous stirring until the addition was completed. The mixture was stirred at room temperature for 5-8 h. The progress of the reaction was monitored using thin layer chromatography (TLC) with a benzene: acetone mixture (8:2 ratio) until the reaction reached completion. Following the reaction, the solvent was evaporated using a rotary evaporator to isolate the product from the solvent. The obtained product was dried in a fume chamber and subjected to further analysis for structural identification.

5-(Nitro-2,4,6-tris(4-nitrophenyl)hexahydropyrimidine-1,3-diyl)bis(phenylmethanone)

(4a)

5-Nitro-2,4,6-tris(4-nitrophenyl)hexahydropyrimidine (0.96g; 0.002mol), pyridine (15 mL), and benzoyl chloride (0.56 mL; 0.004 mol) were mixed and stirred at room temperature for 5 h at a melting point of 300-302 °C to yield **4a** in 83% as a white powder; $C_{36}H_{26}N_6O_{10}$. FT-IR (ATR) (ν, cm^{-1}): 3024 (sp^2-C-H), 2885 (sp^3-C-H), 1604 (C=C), 1657 (N C=O), 1529 (-NO_2). ^{1}H-NMR (DMSO-$d_{6;}$ 500MHz), δ, ppm: 4.78 ppm (d, 2H, *J*=9.33 C-H4,6$_{pyrimidine}$), 5.78 ppm (t, 1H, *J*=9.33 C-H5$_{pyrimidine}$), 6.79 ppm (s, 1H, C-H2$_{pyrimidine}$), 7.43-8.16 ppm (m, 22H, Ar-H).

5-(Nitro-2,4,6-tris(4-nitrophenyl)hexahydropyrimidine-1,3-diyl)bis(phenylmethanone)

(4b)

5-Nitro-2,4,6-tris(4-methoxyphenyl)hexahydropyrimidine (0.88g; 0.002mol), pyridine (15 mL) and benzoyl chloride (0.56 mL; 0.004 mol) were mixed and stirred for 7 h at a melting point of 114-116 °C to yield **4b** in 69% as a white powder; $C_{39}H_{35}N_3O_7$. FT-IR (ATR) (ν, cm^{-1}): 3050 (sp^2-C-H), 2975 (sp^3-C-H), 1646 (C=O), 1592 (C=C), 1535 (-NO_2), 1125 (C-O). ^{1}H-NMR (DMSO-$d_{6;}$ 500MHz), δ, ppm: 4.88 ppm (d, 2H, *J*=9.59 C-H4,6$_{pyrimidine}$), 5.92 ppm (t, 1H, *J*=9.59 C-H5$_{pyrimidine}$), 6.98 ppm (s, 1H, C-H2$_{pyrimidine}$), 6.91-7.61 ppm (m, 22H, Ar-H), 3.79 (s, 9H, OCH_3).

5-(Nitro-2,4,6-tris(3,4-dimethoxyphenyl) hexahydropyrimidine-1,3-iyl)bis(phenylmethanone) **(4c)**

Compound **1b** (1.0g; 0.002mol), pyridine (15 mL), and benzoyl chloride (0.56 mL; 0.004 mol) were mixed and stirred for 8 h at a melting point of 118-120 °C to yield **4c** in 40% as a white colour powder; $C_{42}H_{41}N_3O_{10}$. FT-IR (ATR) (ν, cm^{-1}): 3068 (sp^2-C-H), 2954 (sp^3-C-H), 1680 (C=O), 1590 (C=C), 1509 (-NO_2), 1128 (C-O). ^{1}H-NMR (DMSO-$d_{6;}$ 500MHz), δ, ppm: 4.88 ppm (d, 2H, *J*=6.44 C-H4,6$_{pyrimidine}$), 5.92 ppm (d, 2H, *J*=7.98 C-H2,5$_{pyrimidine}$), 7.55-8.55 (m, 20H, Ar-H), 3.67 ppm (s, 9H, 4-OCH_3), 4.12 ppm (s, 9H, 3-OCH_3). Mass spectrum m/z: $[M+2H]^2$ at m/z 749.2 (for $C_{42}H_{41}N_3O_{10}$), $[M+2H]^{2+}$ at m/z 557.1 (for $C_{34}H_{25}N_2O_6$), $[M+2H]^{2+}$ at m/z 643.2 (for $C_{40}H_{37}N_2O_6$), $[M+3H]^{3+}$ at m/z 432.2 (for $C_{29}H_{24}N_2O_2$), $[M+H]^+$ at m/z 375.1 (for $C_{23}H_{22}N_2O_3$), $[M+2H]^{2+}$ at m/z 242.0 (for $C_{15}H_{17}N_2O$), $[M+2H]^{2+}$ at m/z 157.0 (for $C_6H_{11}N_3O_2$).

5-(Nitro-2,4,6-trisphenyl)hexahydropyrimidine-1,3-diyl) bis(phenylmethanone)

(4d)

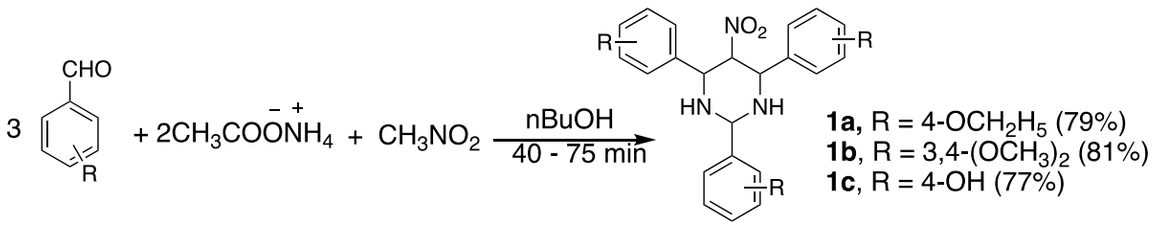
5-nitro-2,4,6-triphenylhexahydropyrimidine (0.71g; 0.002mol), pyridine (15 mL), and benzoyl chloride (0.56 mL; 0.004 mol) were mixed and stirred for 6 h at a melting point of 124-126 °C to yield **4d** in 71% as a white powder; $C_{36}H_{29}N_3O_4$. FT-IR (ATR) (ν, cm^{-1}): 3068 (sp^2-C-H), 2873 (sp^3-C-H), 1678 (C=O), 1601 (C=C), 1579 (-NO_2). ^{1}H-NMR (DMSO-$d_{6;}$ 500MHz), δ, ppm: 4.07 ppm (d, 2H, *J*=6.51 C-H4,6$_{pyrimidine}$), 5.59 ppm (t, 1H, *J*=6.51 C-H5$_{pyrimidine}$), 6.77 ppm (s, 1H, C-H2$_{pyrimidine}$), 6.93-7.76 ppm (m, 25H, Ar-H). Mass spectrum m/z: $[M+2H]^2$ at m/z 569.3 (for $C_{36}H_{29}N_3O_4$), $[M+2H]^{2+}$ at m/z 157.0 (for $C_6H_{11}N_3O_2$), $[M+2H]^{2+}$ at m/z 525.2 (for $C_{36}H_{29}N_2O_2$), $[M+4H]^{4+}$ at m/z 481.2 (for $C_{33}H_{25}N_2O_2$), $[M+2H]^{2+}$ at m/z 393.2 (for $C_{26}H_{21}N_2O_2$), $[M+H]^+$ at m/z 349.1 (for $C_{21}H_{22}N_3O_2$), $[M+H]^+$ at m/z 296.1 (for $C_{17}H_{17}N_3O_2$).

Results and Discussion

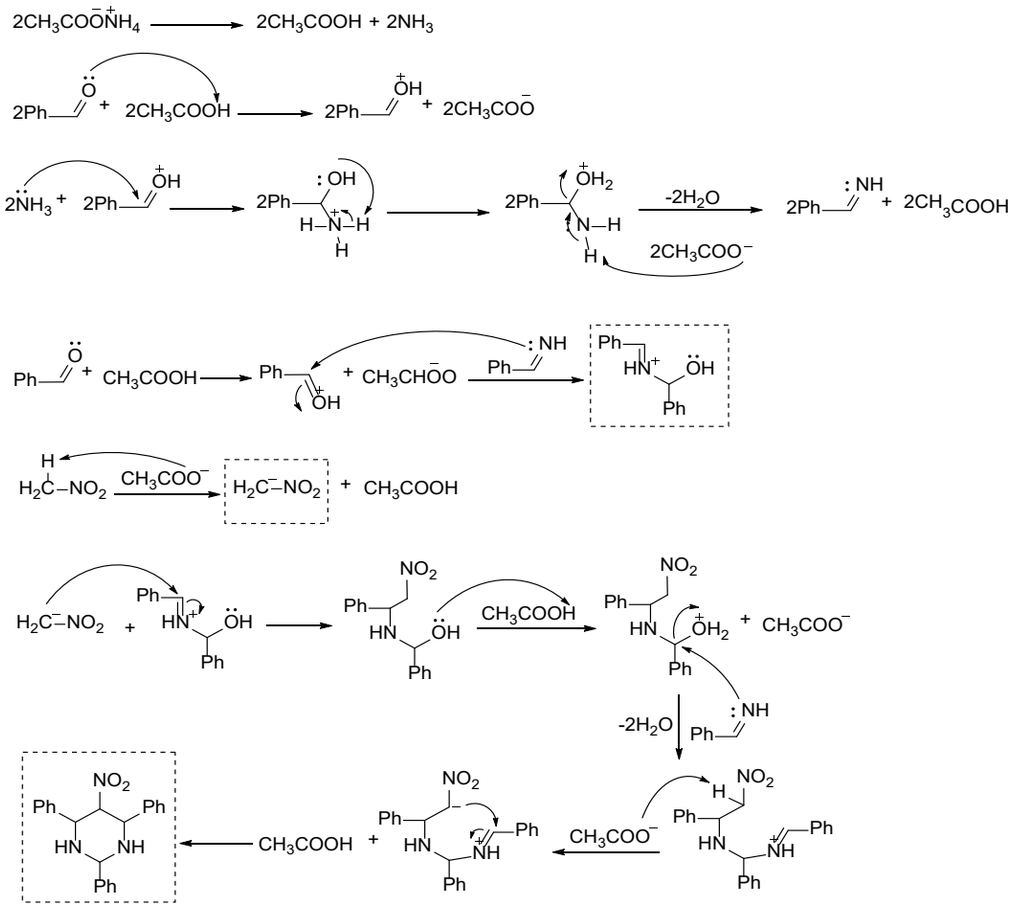
The present work involves four stages. The first pathway included the synthesis of three new hexahydropyrimidine derivatives **1a – 1c** that were successfully synthesized in high yield (77% - 81%) using the Mannich type reaction between benzaldehyde, ammonium acetate, and nitromethane in the presence of *n*-butanol as a solvent. The synthesis reaction of these compounds is shown in Scheme 1. These compounds were recorded by FT-IR, ^{1}H-NMR and, mass spectroscopy.

Understanding how this transition occurs is especially crucial; therefore, the plausible mechanism can be suggested as follows as shown in Scheme 2.

The overall mechanism of the reaction showed that the oxygen atom of the carbonyl group in benzaldehyde derivatives depends on the substitution group on the benzene ring for deprotonation to acid. Furthermore, the substitution groups on the benzene ring affect the percentage yield of the new derivatives. In the first reaction, **1a – 1c** has the major method of producing three hexahydropyrimidine derivatives via substituent group dislocation. 4-ethoxy, 3,4-dimethoxy, and 4-hydroxy were the substituted groups. Hamed (2020) achieved an 86% yield when synthesising the triphenyl hexahydropyrimidine compound. In the presence of substitution groups, the percentage of yield decreased. Every replacement is a group that donates electrons. The attack of oxygen on the acid to remove the proton was the initial step of the reaction mechanism. The



SCHEME 1. The synthesis of derivatives **1a – 1c**



SCHEME 2. The general mechanism of hexahydropyrimidine derivatives synthesis **1a – 1c**

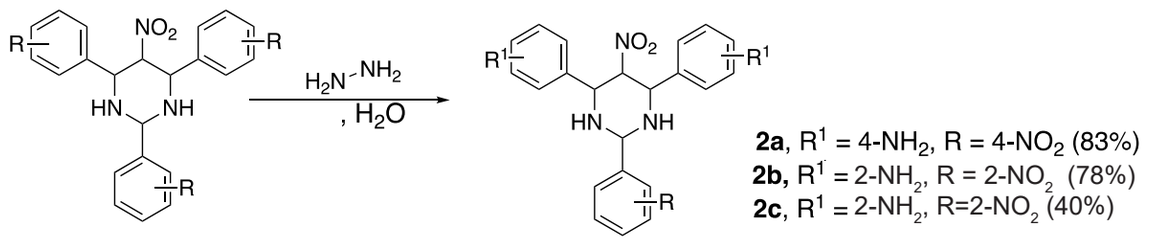
electron density of the benzene ring plays a crucial role in determining the rate of this reaction. The high electron density within the benzene ring, attributed to the presence of hydrogen and oxygen atoms, facilitates resonance and enhances the availability of the aldehyde group. Consequently, the deprotonation reaction proceeds at an accelerated pace, especially in the presence of the hydroxyl group. The electrical density in the ethoxy and methoxy groups transitions to the benzene ring from hydrogen to carbon (electronegativity = 2.5) and subsequently to oxygen. Although derivative **1b** has the maximum yield of 81% in this first phase of synthesis, the methoxy group has a larger inductive impact than the ethoxy. This is owing to the presence of two methoxy groups at the *para* and *meta*-sites (Press et al., 2014), with the *meta*-methoxy group leading to a reduction in electronic density on the carbonyl group.

The FT-IR spectra of all compounds **1a – 1c** indicated the disappearance of carbonyl aldehyde group (ν C=O) peaks and the appearance of the (ν N-H) vibration group in the range of 3121-3327 cm^{-1}. Another significant peak of (ν O-H) stretching is observed at 3327 cm^{-1} and belongs to the **1c** compound. The ^{1}H-NMR spectra of the DMSO-d_6 solution of compounds **1a – 1c** showed well-resolved signals, which provide further evidence of the successful formation of the products. Moreover, the chemical shift of the proton peak of the OH group was shown at 9.04 ppm, which belongs to the **1c** compound. In addition, the presence of a peak at a chemical shift around 2.09-2.73 ppm indicates the protons of N-$H_{pyrimidine}$.

The second reaction involved the synthesis of amine derivatives **2a – 2c** by reduction of nitro groups by hydrazine for three derivatives of hexahydropyrimidines synthesized [$\mathbf{R_1, R_2, S_7}$]. Hydrazine was tested in various quantities (10 mL, 20 mL, and 30 mL), and it was determined that just two of the nitro groups were reduced, so there was no reduction in the other nitro groups due to the symmetry between two reduced nitro groups. The synthesis reaction of these compounds is shown in Scheme 3. The compounds were subjected to analysis using FT-IR, ^{1}H-NMR, and mass spectroscopy techniques.

The electron-drawing nature of the nitro groups in the substituted compounds arises from their significant induction and resonance effects. This electron attraction is responsible for their substantial influence on the electron density. The reduction of two out of the three nitro groups to amine groups represents an alternative pathway in the synthesis processes of compounds **2a – 2c**. The new compound's yield of 83%, 78%, and 40% was limited by the position of the nitro-substituted groups on the benzene rings. Nitro groups were substituted on the *ortho*, *meta*, and *para* positions for the reacting hexahydropyrimidine derivatives. Jezuita et al. (2021) demonstrated that when a nitro group is substituted for the *para* site in the benzene ring, the electronic density distribution is equal, and all carbon atoms have double bonds during the induction action of nitro groups. The nitro group in the *meta* position, on the other hand, causes a deformation in the electrical density on the benzene ring, where carbon atoms have double bonds and others carry charges (positive and negative). The decrease in the yield of the ortho position, on the other hand, is attributable to the steric hindrance of the nitro-substituted group.

The FT-IR spectra of compounds **2a–2c** exhibited two weakly sharp peaks at bands around 3204–3457 cm^{-1} representing the stretching frequencies of the primary amine N-H_2 for all compounds. Accordingly, the appearance of the primary amine peaks was evidence of the respective compounds' formation. The ^{1}H-NMR spectra of compounds **2a** – **2c** possessing a primary amine (-NH_2) showed a singlet peak at chemical shifts of 5.04, 7.55, and 5.20 ppm, respectively. However, the chemical



SCHEME 3. The synthesis of derivatives **2a** – **2c**

shift value of **2b** is more shifted than **2a** and **2c** due to the presence of a hydrogen bond between the hydrogen atoms in the two amine groups in position (2) with the nitro group of the pyrimidine ring, which causes it to be more shifted. Mass spectrometry analysis was carried out to determine the molecular weight of the synthesized compound **2a**. The spectrum of this compound showed two peaks: one at m/z: 431.15, which corresponds to the molecular ion $C_{22}H_{19}N_6O_4^{2+}$, and another peak at m/z: 89.0, which is also known as the base peak $C_7H_5^{2+}$. Conclusive evidence of the successful synthesis of the prepared compounds is obtained by integrating the infrared spectrum, nuclear resonance spectrum, and mass spectrometry results, along with the presence of fragment peaks resulting from the molecule's ionization.

MOLECULAR ELECTROSTATIC POTENTIAL (MEP)

Molecular electrostatic potential (MEP) studies provide information on the molecular charge distribution. It is based on electro-negativity of the molecules, as well as their partial charges, dipole moment, and chemical reactivity (Hakiri et al. 2018). According to the results, reduction was observed in only two of the nitro groups, while the remaining groups did not undergo any reduction. In addition, as seen in Figure 1, there are several colours shown: red, orange, yellow, green, and blue, which are associated with the electronic density distribution. Red and yellow represented the maximum negative potential, the positive regions of nucleophilic reactivity, and green represented regions of zero potential.

The MEP map indicated the most negative regions (red) surrounding the oxygen atoms of the NO^{2-} groups, whereas the most positive regions (blue) were located around the hydrogen atoms of the NH^{2+} groups. The red regions are the most suitable sites for the electrophilic attack. In contrast, the blue spaces represented the sites of the highest reactivity towards the nucleophilic attack (Scrocco & Tomasi 1978).

In the third reaction, a series of Schiff bases **3a – 3g** was obtained by reacting the amine group of the derivative **2c** that was synthesized in the first pathway. **2c** was reacted with benzaldehyde, which had different substitutions, while ethanol was used as the solvent. The synthesis reaction of **3a – 3g** compounds is shown in Scheme 4. The compounds were subjected to analysis using FT-IR, ^{1}H-NMR, and mass spectroscopy techniques.

Although the fluorine and chlorine groups replaced on the benzaldehyde rings had strong electronegativity, they gave electronegativity to the benzaldehyde ring's carbonyl group, allowing the reaction to occur. When the yield of compound **3a** was compared to the yields of compounds **3c** and **3f**, it was discovered that the yield of **3a** was 92%, while the yields of **3c** and **3f** declined. This is owing to an increase in the high electronic density on the carbon atom of the carbonyl group during the amine group's nucleophilic attack.

The FT-IR spectra of the synthesized compounds **3a – 3g** indicated the disappearance of absorption bands of ν -NH_2 at regions 3204–3457 cm^{-1} and the appearance of a strong and distinct band at 1635–1648 cm^{-1} for the azomethine group νC=N, which indicates the formation of the respective compounds. The ^{1}H-NMR spectra of compounds **3a – 3g** showed signals in the range of 2.64-2.85 ppm for the secondary amine (-NH) groups; all compounds demonstrated signals in the range of chemical

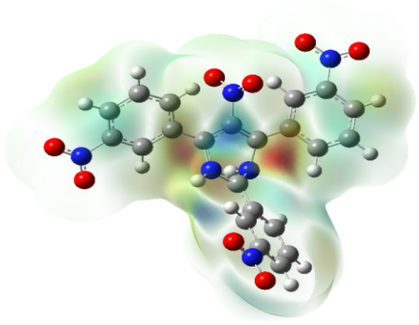
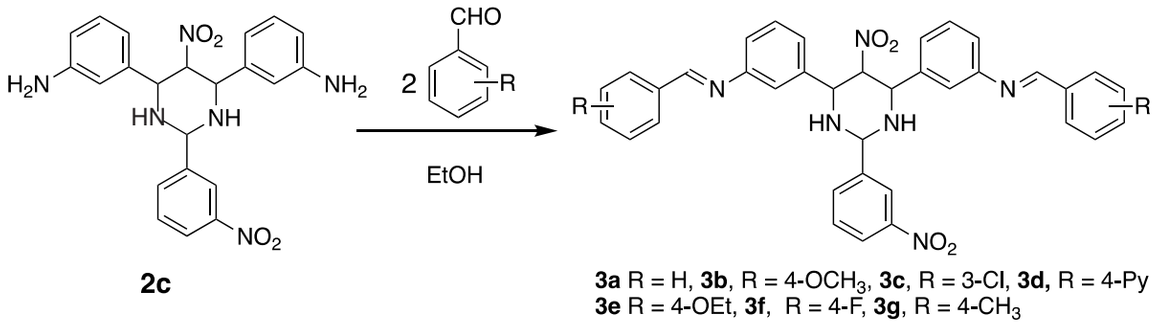


FIGURE 1. Molecular electrostatic potential mapped of **2a – 2c** compounds



SCHEME 4. The synthesis of derivatives **3a – 3g**

shift. 3.54-5.62 ppm indicated $CH_{ring\ pyrimidine}$, various signals appeared at different positions in the range of 7.00-8.63 ppm, representing the aromatic ring protons; at a chemical shift of 8.55-9.69 ppm, there is a singlet peak that refers to the protons of the imine (CH=N) group. The mass spectrometry analysis was used to figure out the molecular weight of the prepared compounds. This was done by determining the molecular ion peak and the base peak of the synthesized compounds, in addition to some of the peaks of the fragments generated by the molecule after ionization. The integration of the results of the FT-IR, ^{1}H-NMR spectrum, and mass spectrometry gives clear evidence for the validity of the molecular structures of the synthesized compounds.

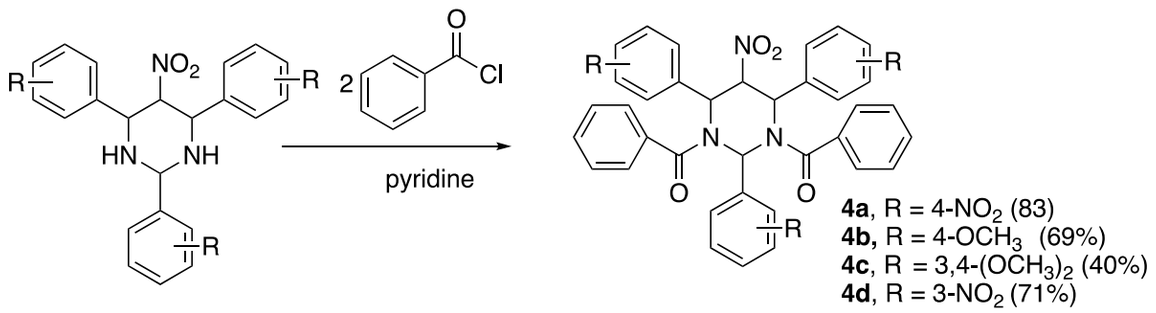
In the fourth reaction, the amide compounds **4a – 4d** were synthesized by reacting the amine group of the pyrimidine derivatives, three of which were synthesized in our previous work and one of them synthesized in this work **1b** with benzoyl chloride in pyridine as a solvent to produce the amide compounds. The general reaction of **4a – 4d** compounds is shown in Scheme 5.

The yield-time estimates for the most recent series of **4a – 4d** synthesis produced surprising results. The reaction time reduced as the substituent groups changed (with an increase in yield). The yield of the **4a** derivative was 83%, whereas the **4d** derivative yielded 71%. The nitro collector (electron withdrawing group) works to reduce the electrical density on the nitrogen atom in the hexahydropyrimidine ring, which reduces the time required to lose the proton N-H in the form of HCl (as a by-product). The resonance effect boosts the electron density on the hexahydropyrimidine ring in the **4d** molecule, which has no substituents. Due to the induction effect (the ethoxy group is an electron donor) and the steric hindrance effect, the yield of the **4c** derivative is 40% lower. The presence of the ethoxy group at the para and meta locations causes steric hindrance. The inductive action, on the other hand, raises the alkalinity of the hexahydropyrimidine ring, making it more difficult to lose N-H protons.

The FT-IR spectra of all synthesized compounds **4a – 4d** showed all the basic functional group peaks and the disappearance of the secondary amine peak in the range 3121-3418 cm^{-1} from the spectra, as well as the presence of absorption bands in the range 1646-1680 cm^{-1} of $\nu C{=}O_{amide}$. Accordingly, the presence of $\nu C{=}O_{amide}$ and the disappearance of secondary amine confirmed the formation of the synthesized compounds. In the ^{1}H-NMR spectra, all compounds **4a** – **4c** showed proton peaks of the methylene group in the pyrimidine ring C–H around 4.07–6.79 ppm, and protons of the aromatic rings showed peaks in the chemical shift around 6.91–8.55 ppm. In addition, the appearance of peaks in different positions with a chemical shift of 3.67–4.12 ppm indicated the presence of the O-CH_3 group for compounds **4b** and **4c**. Mass spectrometry analysis was performed to determine the molecular mass of the synthesized compounds **4c** and **4d.** By determining the molecular ion peak of the synthesized compounds and the base peak, in addition to some of the tops of the fragments produced by ionization of the molecule's fragments.

Conclusion

In conclusion, this study underscores a significant contribution to the field by presenting the synthesis of three new pyrimidine derivatives employing Mannich's reaction. An insightful aspect of this study lies in the exploration of how substituted groups on aromatic rings play a pivotal role as determining factors in influencing the outcome of this reaction. Furthermore, the paper



SCHEME 5. The synthesis of derivatives **4a – 4d**

provides a comprehensive examination of the process involved in generating amine derivatives. This includes the reduction of pyrimidine compounds using hydrazine, along with the strategic substitution of nitro groups at various positions. The synthesis is further enriched by delving into the intricate process of creating Schiff base compounds derived from one of the initial amine compounds, specifically compound **2c**. Finally, the culmination of this study involves a detailed exploration of the reaction between the amine group within previously synthesized pyrimidine derivatives and benzoyl chloride, resulting in the production of amide compounds. This multifaceted approach enhances our understanding of the synthesis and reactivity of pyrimidine derivatives, opening avenues for further research and applications in diverse scientific domains.

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*Corresponding author; email: aishah80@ukm.edu.my