CHAPTER - 1.4

EXPERIMENTAL
1.4.1. CHEMISTRY

1.4.1.1. PYRIMIDINE

1.4.1.2. THIAZOLIDINONE
MATERIALS AND METHODS

Reagents & Solvents
Most of the solvents were of LR grade and purified prior to use in different reaction. Chemicals used were obtained from different manufacturers, Central Drug Pvt. Ltd., Merck, S. D. Fine Chemicals Ltd, SRL (P) Ltd, Thomas Bakers, Qualigens and Spectrochem (P) Ltd.

Equipment / Techniques
Melting point: The melting points were determined in one end open capillary tubes on a Labtronics melting point apparatus and are uncorrected.

IR Spectrometer: All the infra red (IR) spectra were recorded in KBr on the BIORED-WIN IR spectrophotometer.

NMR Spectrometer: Proton nuclear magnetic resonance ($^1$H-NMR) spectra were measured on Bruker Avance-400 instrument (400 MHz). Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were measured on Bruker Avance-400 Instrument (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) as internal standard.

Mass Spectrometer: MS spectral data were recorded on, Synapt mass spectrometer (UPLCMS/MS).

Elemental Analysis: Elemental analyses were undertaken with Perkin-Elmer model 240C analyzer.

Thin Layer Chromatography: The reactions were monitored by Silica gel-GF coated aluminum plate and visualized by iodine-vapors, UV light, DNP and ninhydrine as visualizing agents.

Purification of Organic Solvents
Commercially available grades of organic solvents are of adequate purity for use in such reaction provided that the presence of small quantities of water (the most widespread impurity in all organic solvents) is not harmful to reactions. The commercially available grade for general uses are often impurity containing, however, when the level of impurities including moisture, are not acceptable for particular reaction and when large volume of such solvents are likely to be required, it is more economical to purify the commercial grade.
Ethanol

Ethanol of high degree purity is frequently required in preparative organic chemistry. For some purpose ethanol of 99.5% purity is required. Rectified spirit is the constant boiling mixture, which ethanol forms with water and usually contains 95.6% of ethanol by weight.

Absolute alcohol (dehydration of rectified spirit by calcium oxide)

Rectified spirit (700mL) was poured in to 1L round bottom flask and added 200 gm of calcium oxide, freshly ignited over the Bunsen flame. Flask was fitted with a double surface condenser carrying a calcium chloride guard tube. The mixture was refluxed for 6 hrs and allowed to stand overnight. Then ethanol was distilled; the first 20ml of the distillate was discarded and the remaining was collected and stored in an air locked container.
1.4.1.1. Pyrimidine

Scheme 1
General procedure for Synthesis of 2-Mercapto-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (I)

Anisaldehyde (1mmol), ethyl cyanoacetate (1mmol) and thiourea (1mmol) were dissolved in absolute alcohol. Potassium carbonate (3mmol) was added to this reaction mixture and refluxed for 2hrs. The solvent was concentrated and poured into ice cold water with stirring. The solution was neutralized with glacial acetic acid, which caused the separation of compound I which was filtered, washed with water and recrystallized from methanol.
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Experimental

Yield: 90%; Rf value: 0.6; m.p.: 139-140°C.
Molecular Formula: C_{13}H_{10}N_{3}O_{3}S
% Carbon: Found: 55.59; Calcd.: 55.28
% Hydrogen: Found: 3.50; Calcd.: 3.48
% Nitrogen: Found: 16.21; Calcd.: 16.08
IR (KBr, cm⁻¹): 3245 (-NH of amide), 3215 (-NH), 2225 (C=N), 1674 (C=O), 1165 (C=S).

¹H NMR (400 MHz, DMSO-d₆): δ 3.81 (s, 3H, OCH₃), 7.07 (d, 2H, J=8.8Hz, H-3,5, Phenyl), 7.61 (d, 2H, J=8.8Hz, H-2,6, Phenyl), 13.07 (bs, 1H, NH-C=O), 13.16 (s, 1H, SH).

¹³C-NMR (100 MHz, DMSO-d₆): δ 56.05, 90.23, 114.34, 115.55, 131.34, 159.14, 160.95, 162.83, 176.69.
MS (EI): m/z 260 (M⁺+1).

General procedure of synthesis 2-Hydrazinyl-4-(4”methoxy-phenyl)-6-oxo-1,6-
dihydro-pyrimidine-5-carbonitrile (II)

Compound I (1mmol) was dissolved in absolute ethanol and to it hydrazine hydrate (99%; 4mmol) was added and refluxed for 1h. The reaction mixture was allowed to cool which caused the separation of solid. The precipitated product was filtered and washed with water. It was recrystallized with ethanol.

Yield: 82%; Rf 0.2; mp 180°C
Molecular Formula: C_{12}H_{11}N_{5}O_{2}
% Carbon: Found: 56.03; Calcd.: 56.18
% Hydrogen: Found: 4.31; Calcd.: 4.32
% Nitrogen: Found: 27.22; Calcd.: 27.16

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Experimental

IR (KBr, cm\(^{-1}\)): 3285-3218 (2NH\(\cdot\)NH\(_2\)), 2210 (C=N), 1680 (C=O), 1065 (C-O-C). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 3.82 (s, 3H, OCH\(_3\)), 3.35 (bs, 2H, NH\(\cdot\)NH\(_2\)), 7.02 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.83 (d, 2H, J=8.0Hz, H-2,6, phenyl), 10.26 (bs, 1H, NH). 13C-NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 55.77, 82.55, 113.82, 120.38, 130.36, 57, 161.26, 162.08, 169.22.

MS (EI): \(m/z\) 258(M\(^{+}\)+1).

General procedure of synthesis of 2-(2-arylidene-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrindine-5-carbonitrile [III\(_{Aa}\)]

Compound II (1mmol) was dissolved in a mixture of glacial acetic acid and alcohol (2:8). To this solution, alcoholic solution of aromatic aldehyde (1.1mmol) was added and refluxed for 2-3hrs. Solvent was concentrated to half of its volume, poured into ice water. The precipitate obtained was filtered, washed with water and recrystallized from methanol.

Synthesis of 2-(2-Benzylidene-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III\(_{Aa}\))

Yield: 65%; R\(_f\): 0.4; mp 205-06°C

Molecular Formula: C\(_{16}\)H\(_{13}\)N\(_3\)O\(_2\)
% Carbon: Found: 66.08; Calcd.: 66.84
% Hydrogen: Found: 4.38; Calcd.: 4.37
% Nitrogen: Found: 20.28; Calcd.: 20.26
IR (KBr, cm⁻¹): 3270 (-NH of amide), 3210 (-NH), 2215 (C=N), 1676 (C=O), 1609 (C=N), 1071 (C-O-C).

¹H NMR (400 MHz, DMSO-d⁶): δ 3.86 (s, 3H, OCH₃), 6.91 (d, 2H, J=8.8Hz, H-3,5, phenyl), 7.13-7.32 (m, 5H, ArH, arylidene ring), 7.83 (d, 2H, J=8.8Hz, H-2,6, phenyl), 8.01 (s, 1H, N=CH), 9.34 (bs, 1H, NH-N=), 12.03 (bs, 1H, NH-C=O)
Mass (EI): m/z 346(M⁺+1).

Synthesis of 2-(2-{2-Chloro-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIAₐ)

Yield: 84%; Rf; 0.4; mp 203-04°C
Molecular Formula: C₁₉H₁₄ClN₃O₂
% Carbon: Found: 60.09; Calcd.: 60.28
% Hydrogen: Found: 3.72; Calcd.: 3.71
% Nitrogen: Found: 9.33; Calcd.: 9.32
IR (KBr, cm⁻¹): 3296 (-NH of amide), 3218 (-NH), 2214 (C=N), 1670 (C=O), 1614 (C=N), 1102 (Ar-Cl).

¹H NMR (400 MHz, DMSO-d⁶): δ 3.85 (s, 3H, OCH₃), 6.97 (d, 2H, J=8.0Hz, H-3,5, phenyl), 7.32-7.56 (m, 4H, H-3',4',5',6', arylidene ring), 7.80 (d, 2H, J=8.0Hz, H-2,6, phenyl), 8.04 (s, 1H, N=CH), 11.65 (bs, 1H, NH-N=), 12.06 (bs, 1H, NH-C=O).
Mass (EI): m/z 381(M⁺+1), 382 (M+2).

Synthesis of 2-(2-{3-Chloro-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIAₜ)

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Yield: 73%; Rf: 0.43; mp 209-10°C
Molecular Formula: C_{10}H_{14}ClN_{5}O_{2}
% Carbon: Found: 60.09; Calcd.: 60.38
% Hydrogen: Found: 3.72; Calcd.: 3.71
% Nitrogen: Found: 9.33; Calcd.: 9.31
IR (KBr, cm^{-1}): 3295 (-NH of amide), 3222 (-NH), 2216 (C-N), 1677 (C=O), 1618 (C=N), 1089 (Ar-Cl).

\[ ^1H \text{ NMR (400 MHz, DMSO-d}_6\): s 3.90 (s, 3H, OCH}_3\), 6.94 (d, 2H, J=8.8Hz, H-3,5, phenyl), 7.35 (t, 1H, J=7.6Hz, H-5', arylidene ring), 7.50 (d, 1H, J=7.6Hz, H-6', arylidene ring), 7.58 (d, 1H, J=7.6Hz, H-4', arylidene ring), 7.78 (s, 1H, H-2', arylidene ring), 7.92 (d, 2H, J=8.8Hz, H-2,6, phenyl), 8.08 (s, 1H, N=CH), 11.83 (bs, 1H, NH-N=), 12.23 (bs, 1H, NH-C=O). \]

Mass (EI): m/z 381(M^{+}+1), 382 (M^{+}+2).

**Synthesis of 2-(2-{{4-Chloro-benzylidene}-hydrazinyl}-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III_A, )**

Yield: 78%; Rf: 0.50; mp 221-22°C
Molecular Formula: C_{19}H_{14}ClN_{5}O_{2}

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% Carbon: Found: 60.09; Calcd.: 60.34
% Hydrogen: Found: 3.72; Calcd.: 3.72
% Nitrogen: Found: 9.33; Calcd.: 9.32
IR (KBr, cm⁻¹): 3290 (-NH of amide), 3215 (-NH), 2218 (C=N), 1678 (C=O), 1617 (C=N), 1108 (Ar-Cl).

¹H NMR (400 MHz, DMSO-d₆): δ 3.85 (s, 3H, OCH₃), 6.96 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.46 (d, 2H, J=8.0Hz, H-2',6', arylidene ring), 7.72 (d, 2H, J=8.0Hz, H-3',5', arylidene ring), 7.81 (d, 2H, J=8.4Hz, H-2,6, phenyl), 8.06 (s, 1H, N=CH), 11.44 (bs, 1H, NH-N=), 12.04 (bs, 1H, NH-C=O).

Mass: m/z 380(M⁺+1), 382 (M⁺+2).

Synthesis of 2-(2-{3-Bromo-benzylidene-hydrazinyl}-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIA₄)

Yield: 64%; Rₛ: 0.50; mp 241-42°C
Molecular Formula: C₁₉H₁₄BrN₅O₂
% Carbon: Found: 53.79; Calcd.: 53.84
% Hydrogen: Found: 3.33; Calcd.: 3.34
% Nitrogen: Found: 16.51; Calcd.: 16.50
IR (KBr, cm⁻¹): 3368 (-NH of amide), 3313 (-NH), 2219 (C=N), 1676 (C=O), 1620 (C=N), 1078 (Ar-Br).

¹H NMR (400 MHz, DMSO-d₆): δ 3.91 (s, 3H, OCH₃), 6.93 (d, 2H, J=8.8Hz, H-3,5, phenyl), 7.33 (t, 1H, J=7.6Hz, H-5', arylidene ring), 7.48 (d, 1H, J=7.6Hz, H-6', arylidene ring), 7.52 (d, 1H, J=7.6Hz, H-4', arylidene ring), 7.81 (s, 1H, H-2', arylidene ring), 7.90 (d, 2H, J=8.8Hz, H-2,6, phenyl), 8.11 (s, 1H, N=CH), 11.85 (bs, 1H, NH-N=), 12.21 (bs, 1H, NH-C=O).

Mass (EI): m/z 424(M⁺+1).
Synthesis of 2-(2-{4-Bromo-benzylidene}-hydrazyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIA$_{4}$)

![Chemical Structure](image)

Yield: 75%; $R_f$: 0.5; mp 235-36°C
Molecular Formula: C$_{19}$H$_{14}$BrN$_{5}$O$_{2}$
% Carbon: Found: 53.79; Caled.: 53.94
% Hydrogen: Found: 3.33; Caled.: 3.34
% Nitrogen: Found: 16.51; Caled.: 16.49

IR (KBr, cm$^{-1}$): 3348 (-NH of amide), 3272 (-NH), 2216 (C=N), 1668 (C=O), 1618 (C=N), 1084 (Ar-Br).

$^1$H NMR (400 MHz, DMSO-d$_6$): 8 3.87 (s, 3H, OCH$_3$), 6.92 (d, 2H, $J$=8.0Hz, H-3,5, phenyl), 7.41 (d, 2H, $J$=7.6Hz, H-2',6', arylidene ring), 7.64 (d, 2H, $J$=7.6Hz, H-3',5', arylidene ring), 7.87 (d, 2H, $J$=8.0Hz, H-2,6, phenyl), 8.10 (s, 1H, N-CH), 11.83 (bs, 1H, NH-N=), 12.25 (bs, 1H, NH-C=O).

Mass (EI): m/z 424(M$^+$+1).

Synthesis of 2-(2-{4-Floro-benzylidene}-hydrazyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIA$_{6}$)

![Chemical Structure](image)

Yield: 62%; $R_f$: 0.52; mp 273-74°C
Molecular Formula: C$_{19}$H$_{13}$FN$_{5}$O$_{2}$
% Carbon: Found: 62.18; Caled.: 62.29
% Hydrogen: Found: 3.88; Calcd.: 3.87
% Nitrogen: Found: 19.27; Calcd.: 19.24
IR (KBr, cm⁻¹): 3310 (-NH of amide), 3246 (-NH), 2219 (C=N), 1681 (C=O), 1615 (C=N), 1149 (Ar-F).
¹H NMR (400 MHz, DMSO-d₆): δ 3.87 (s, 3H, OCH₃), 7.01 (d, 2H, J=8.8Hz, H-3,5, phenyl), 7.13 (t, 2H, J=8.4Hz, H-3',5', arylidene ring), 7.92 (d, 2H, J=8.8Hz, H-2,6, phenyl), 8.03 (m, 2H, H-2',6', arylidene ring), 8.16 (s, 1H, N=CH), 12.22 (bs, 1H, NH-N=), 12.42 (bs, 1H, NH-C=O).
¹³C-NMR (100 MHz, DMSO-d₆): δ 55.60, 85.99, 113.76, 115.63, 115.84, 128.65, 130.38, 130.46, 130.55, 146.02, 153.55, 161.31, 162.05, 162.36, 170.11.
Mass (EI): m/z 364(M⁺+1).

Synthesis of 2-(2-[2-Hydroxy-benzylidene]-hydrazino)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIAₙ)

Yield: 76%; Rf: 0.61; mp 223-24°C
Molecular Formula: C₁₉H₁₅N₅O₃
% Carbon: Found: 63.15; Calcd.: 63.37
% Hydrogen: Found: 4.18; Calcd.: 4.19
% Nitrogen: Found: 19.38; Calcd.: 19.36
IR (KBr, cm⁻¹): 3420 (Ar-OH), 3306 (-NH of amide), 3239 (-NH), 2216 (C≡N), 1676 (C=O), 1614 (C=N).
¹H NMR (400 MHz, DMSO-d₆): δ 3.84 (s, 3H, OCH₃), 6.93 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.30-7.61 (m, 4H, H-3',4',5',6', arylidene ring), 7.87 (d, 2H, J=8.4Hz, H-2,6, phenyl), 8.11 (s, 1H, N=CH), 11.14 (bs, 1H, OH), 11.86 (bs, 1H, NH-N=), 12.07 (bs, 1H, NH-C=O).
Mass (EI): m/z 362(M⁺+1).
Synthesis of 2-(2-{4-Hydroxy-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III₄₄)

\[
\text{III}_4
\]

Yield: 80%; R₆ 0.5; mp 219-20°C
Molecular Formula: C₁₉H₁₅N₅O₃
% Carbon: Found: 63.15; Calcd.: 63.27
% Hydrogen: Found: 4.18; Calcd.: 4.19
% Nitrogen: Found: 19.38; Calcd.: 19.36
IR (KBr, cm⁻¹): 3467 (Ar-OH), 3315 (⁻NH of amide), 3242 (⁻NH), 2216 (C-N), 1661 (C=O), 1620 (C=N).

¹H NMR (400 MHz, DMSO-d₆): δ 3.84 (s, 3H, OCH₃), 6.81 (d, 2H, J=8.8Hz, H-3',5', arylidene ring), 6.95 (d, 2H, J=8.0Hz, H-3,5, phenyl), 7.52 (d, 2H, J=8.8Hz, H-2',6', aryldiene ring), 7.84 (d, 2H, J=8.0Hz, H-2,6, phenyl), 8.08 (s, 1H, N=CH), 10.38 (s, 1H, OH), 11.36 (s, 1H, NH-N=), 12.01 (s, 1H, NH-C=O).
Mass (EI): m/z 362(M⁺+1).

Synthesis of 2-(2-{4-Methoxy-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III₄₄)

\[
\text{III}_4
\]

Yield: 75%; R₆ 0.55; mp 229-30°C
Molecular Formula: C₂₀H₁₇N₅O₃
% Carbon: Found: 63.99; Calcd.: 63.37
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% Hydrogen: Found: 4.56; Calcd.: 4.55
% Nitrogen: Found: 18.66; Calcd.: 18.62
IR (KBr, cm\(^{-1}\)): 3275 (\(-\text{NH of amide}\)), 3206 (\(-\text{NH}\)), 2213 (\(\text{C=\text{N}}\)), 1673 (\(\text{C=O}\)), 1615 (\(\text{C=\text{N}}\)).

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)): \(\delta\) 3.75 (s, 3H, OCH\(_3\)), 3.77 (s, 3H, OCH\(_3\)), 6.81 (d, 2H, J = 8.4Hz, H-3,5, phenyl), 6.88 (d, 2H, J = 8.4Hz, H-3',5', aryldiene ring), 7.76 (d, 2H, J = 8.4Hz, H-2,6, phenyl), 7.82 (d, 2H, J = 8.4Hz, H-2',6', aryldiene ring), 8.02 (s, 1H, N=\(\text{CH}\)), 11.61 (bs, 1H, NH-N=), 12.11 (bs, 1H, NH-C=O).

\(^1\text{C-NMR}\) (100 MHz, DMSO-\(d_6\)): \(\delta\) 55.80, 55.90, 85.35, 114.15, 114.51, 118.12, 126.78, 128.71, 130.28, 130.71, 147.29, 153.60, 161.59, 162.11, 162.43, 170.11.
Mass (EI): \(m/z 376\) (\(M^+1\)).

Synthesis of 2-(2-{3,4-Di-methoxy-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III\(_\text{A}_{4}\))

Yield: 65%; \(R_f\) 0.6; mp 264-65°C
Molecular Formula: \(C_{21}H_{19}N_5O_4\)
% Carbon: Found: 62.22; Calcd.: 62.38
% Hydrogen: Found: 4.72; Calcd.: 4.71
% Nitrogen: Found: 17.27; Calcd.: 17.26
IR (KBr, cm\(^{-1}\)): 3365 (\(-\text{NH of amide}\)), 3318 (\(-\text{NH}\)), 2219 (\(\text{C-N}\)), 1678 (\(\text{C=O}\)), 1611 (\(\text{C-N}\)), 1090 (\(\text{C-O-C}\)).

\(^1\text{H NMR}\) (400 MHz, DMSO-\(d_6\)): \(\delta\) 3.86 (s, 3H, OCH\(_3\)), 3.88 (s, 3H, OCH\(_3\)), 6.91 (d, 2H, J = 8.4Hz, H-3,5, phenyl), 7.04 (d, 1H, J = 8.8Hz, H-5', aryldiene ring), 7.48 (d, 1H, J = 8.8Hz, H-6', aryldiene ring), 7.63 (s, 1H, H-2', aryldiene ring), 7.93 (d, 2H, J = 8.4Hz, H-2,6, phenyl), 8.14 (s, 1H, N=\(\text{CH}\)), 11.74 (bs, 1H, NH-N=), 12.06 (bs, 1H, NH-C=O).

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Mass (EI): \textit{m/z} 405(M^+1).

Synthesis of \textit{2-(2-{3,4,5-Tri-methoxy-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile} (IIA_i)

![Chemical structure](image)

Yield: 70\%; Rf: 0.6; mp 244-45°C
Molecular Formula: C_{22}H_{21}N_{5}O_{5}
% Carbon: Found: 60.68; Calcd.: 60.58
% Hydrogen: Found: 4.86; Calcd.: 4.85
% Nitrogen: Found: 16.08; Calcd.: 16.09

IR (KBr, cm\(^{-1}\)): 3324 (-NH of amide), 3242 (~NH), 2214 (C=N), 1668 (C=O), 1615 (C=N), 1068 (C-O-C).

\(^1\)H NMR (400 MHz, DMSO-d_6): \(\delta\ 3.83\) (s, 3H, OCH\(_3\)), \(3.88\) (s, 9H, 3xOCH\(_3\)), \(6.83\) (s, 2H, H-2',6', arylidene ring), \(6.92\) (d, 2H, J=8.4Hz, H-3,5, phenyl), \(7.93\) (d, 2H, J=8.4Hz, H-2,6, phenyl), \(8.03\) (s, 1H, N=CH), \(11.92\) (bs, 1H, NH-N=), \(12.11\) (bs, 1H, NH-C=O).
Mass (EI): \textit{m/z} 435(M^+1).

Synthesis of \textit{2-(2-{2-Nitro-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile} (IIA_m)

![Chemical structure](image)

Yield: 63\%; Rf: 0.62; mp 207-08°C
Molecular Formula: C_{19}H_{14}N_{6}O_{4}
% Carbon: Found: 58.46; Calcd.: 58.72

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% Hydrogen: Found: 3.61; Calcd.: 3.60
% Nitrogen: Found: 21.53; Calcd.: 21.55
IR (KBr, cm\textsuperscript{-1}): 3346 (-NH of amide), 3282 (-NH), 2218 (C≡N), 1675 (C=O), 1614 (C=N), 1524, 1342 (NO\textsubscript{2}).
\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): δ 3.90 (s, 3H, OCH\textsubscript{3}), 7.01 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.29-8.03 (m, 6H, H-2,6, phenyl & H-3',4',5',6', arylidene ring), 8.11 (s, 1H, N=CH), 11.89 (bs, 1H, NH-N=), 12.21 (bs, 1H, NH-C=O).
Mass (EI): m/z 391(M\textsuperscript{+}+1).

**Synthesis of 2-(2-([3-Nitro-benzylidene]-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III\textsubscript{Aa})**

![Chemical structure of IIIA\textsubscript{A}](image)

Yield: 80%; R\textsubscript{f}: 0.6; mp 191-92°C
Molecular Formula: C\textsubscript{19}H\textsubscript{14}N\textsubscript{6}O\textsubscript{4}
% Carbon: Found: 58.46; Calcd.: 58.74
% Hydrogen: Found: 3.61; Calcd.: 3.60
% Nitrogen: Found: 21.53; Calcd.: 21.57
IR (KBr, cm\textsuperscript{-1}): 3354 (-NH of amide), 3292 (-NH), 2226 (C=N), 1669 (C=O), 1612 (C=N), 1524, 1346 (NO\textsubscript{2}).
\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): δ 3.90 (s, 3H, OCH\textsubscript{3}), 7.02 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.67 (dd, 1H, J=8.7,6Hz, H-5', arylidene ring), 7.85 (d, 2H, J=8.4Hz, H-2,6, phenyl), 8.04 (d, 1H, J=7.6Hz, H-6', arylidene ring), 8.13 (s, 1H, N=CH), 8.27 (d, 1H, J=8.0Hz, H-4', arylidene ring), 8.46 (s, 1H, H-2', arylidene ring), 11.91 (bs, 1H, NH-N=), 12.34 (bs, 1H, NH-C=O).
Mass (EI): m/z 391(M\textsuperscript{+}+1).

**Synthesis of 2-(2-[4-Nitro-benzylidene]-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III\textsubscript{An})**
Yield: 65%; Rf: 0.62; mp 233-34°C
Molecular Formula: C_{10}H_{14}N_{6}O_{4}
% Carbon: Found: 58.46; Calcd.: 58.62
% Hydrogen: Found: 3.61; Calcd.: 3.59
% Nitrogen: Found: 21.53; Calcd.: 21.47
IR (KBr, cm⁻¹): 3362 (-NH of amide), 3290 (--NH), 2221 (C≡N), 1676 (C=O), 1613 (C=N), 1529, 1349 (NO₂).

^1H NMR (400 MHz, DMSO-d₆): δ 3.92 (s, 3H, OCH₃), 7.04 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.83 (d, 2H, J=8.4Hz, H-2,6, phenyl), 8.02 (d, 2H, J=8.8Hz, H-2',6', arylidene ring), 8.16 (s, 1H, N=CH), 8.33 (d, 2H, J=8.8Hz, H-3',5', arylidene ring), 11.96 (bs, 1H, NH-N=), 12.38 (bs, 1H, NH-C=O).

^{13}C-NMR (100 MHz, DMSO-d₆): δ 55.65, 86.05, 115.76, 115.98, 126.71, 128.78, 130.63, 130.79, 144.36, 147.13, 153.67, 161.73, 162.14, 162.48, 170.19. Mass (EI): m/z 391(M⁺+1).

Synthesis of 2-(2-{4-Hydroxy-3-methoxy-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III_A₉)

Yield: 78%; Rf: 0.5; mp 227-28°C
Molecular Formula: C_{20}H_{17}N_{5}O_{4}
% Carbon: Found: 61.38; Calcd.: 61.17

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% Hydrogen: Found: 4.38; Calcd.: 4.39
% Nitrogen: Found: 17.89; Calcd.: 17.91
IR (KBr, cm⁻¹): 3445 (Ar-OH), 3306 (-NH of amide), 3215 (-NH), 2218 (C-N), 1672 (C=O), 1624 (C=N), 1072 (C-O-C).

¹H NMR (400 MHz, DMSO-d₆): δ 3.88 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃), 6.82 (d, 1H, J=8.4Hz, H-5', arylidene ring), 7.00 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.14 (d, 1H, J=8.4Hz, H-6', arylidene ring), 7.92 (d, 2H, J=8.4Hz, H-2,6, phenyl), 7.95 (s, 1H, H-2', arylidene ring), 8.07 (s, 1H, N=CH), 9.37 (s, 1H, OH), 11.73 (bs, 1H, NH-N=), 12.24 (bs, 1H, NH-C=O).

¹³C-NMR (100 MHz, DMSO-d₆): δ 54.33, 54.81, 83.35, 108.88, 112.62, 112.68, 114.03, 116.59, 122.14, 124.00, 126.80, 126.93, 129.26, 146.89, 147.04, 148.02, 151.56, 160.68, 161.02, 169.01.
Mass (El): m/z 391(M⁺+1).

Synthesis of 2-(2-{2-Methyl-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIₐ₉)

Yield: 69%; R_f: 0.45; mp 239-40°C
Molecular Formula: C₂₀H₁₇N₅O₂
% Carbon: Found: 66.84; Calcd.: 66.54
% Hydrogen: Found: 4.77; Calcd.: 4.76
% Nitrogen: Found: 19.49; Calcd.: 19.47
IR (KBr, cm⁻¹): 3288 (-NH of amide), 3236 (-NH), 2213 (C=O), 1678 (C=N), 1613 (C=N).

¹H NMR (400 MHz, DMSO-d₆): δ 2.38 (s, 3H, CH₃), 3.87 (s, 3H, OCH₃), 6.92 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.28-7.51 (m, 4H, H-3',4',5',6', arylidene ring), 7.84 (d,
2H, J=8.4Hz, H-2,6, phenyl), 8.09 (s, 1H, N=CH), 11.80 (bs, 1H, NH-N=), 12.06 (bs, 1H, NH-C=O).

Mass (EI): m/z 360(M⁺+1).

Synthesis of 2-(2-{4-Methyl-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIA₄)

Yield: 72%; Rₚ: 0.44; mp 235-36°C

Molecular Formula: C₂₀H₁₇N₅O₂

% Carbon: Found: 66.84; Calcd.: 66.59
% Hydrogen: Found: 4.77; Calcd.: 4.76
% Nitrogen: Found: 19.49; Calcd.: 19.45

IR (KBr, cm⁻¹): 3282 (-NH of amide), 3219 (-NH), 2215 (C≡N), 1679 (C=O), 1617 (C=N).

¹H NMR (400 MHz, DMSO-d₄): δ 2.36 (s, 3H, CH₃), 3.89 (s, 3H, OCH₃), 6.96 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.30 (d, 2H, J=7.6Hz, H-3',5', arylidene ring), 7.54 (d, 2H, J=7.6Hz, H-2',6', arylidene ring), 7.85 (d, 2H, J=8.4Hz, H-2,6, phenyl), 8.04 (s, 1H, N=CH), 11.87 (bs, 1H, NH-N=), 12.09 (bs, 1H, NH-C=O).

Mass (EI): m/z 360(M⁺+1).

Synthesis of 2-(2-{2,4,6-Trimethyl-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIA₅)

Yield: 65%; Rₚ: 0.4; mp 225-26°C

Molecular Formula: C₂₂H₂₁N₅O₂
% Carbon: Found: 68.20; Calcd.: 68.33
% Hydrogen: Found: 5.46; Calcd.: 5.45
% Nitrogen: Found: 18.08; Calcd.: 18.09
IR (KBr, cm\(^{-1}\)): 3336 (-NH of amide), 3281 (-NH), 2228 (C=N), 1676 (C=O), 1624 (C=N).

\[^1^H \text{NMR}\) (400 MHz, DMSO-d\(_6\)): \(\delta\) 2.28 (s, 3H, CH\(_3\)), 2.54 (s, 6H, 2xCH\(_3\)), 3.86 (s, 3H, OCH\(_3\)), 6.81 (s, 2H, H-3',5', aryldene ring), 6.93 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.88 (d, 2H, J=8.4Hz, H-2,6, phenyl), 8.04 (s, 1H, N=CH), 11.69 (bs, 1H, NH-N=), 12.04 (bs, 1H, NH-C=O).

Mass (EI): m/z 397(M^+1).

Synthesis of **2-(2'-{4-Dimetniyl-amino-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIA)**

Yield: 75%; R\(_f\): 0.5; mp 215-16°C
Molecular Formula: C\(_{21}\)H\(_{20}\)N\(_6\)O\(_2\)
% Carbon: Found: 64.94; Calcd.: 65.12
% Hydrogen: Found: 5.19; Calcd.: 5.18
% Nitrogen: Found: 21.64; Calcd.: 21.62
IR (KBr, cm\(^{-1}\)): 3318 (-NH of amide), 3258 (-NH), 2211 (C=N), 1672 (C=O), 1618 (C=N).

\[^1^H \text{NMR}\) (400 MHz, DMSO-d\(_6\)): \(\delta\) 2.32 (s, 6H, 2xCH\(_3\)), 3.88 (s, 3H, OCH\(_3\)), 6.86 (d, 2H, J=8.8Hz, H-3',5', aryldene ring), 6.96 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.84 (d, 2H, J=8.4Hz, H-2,6, phenyl), 7.92 (d, 2H, J=8.8Hz, H-2',6', aryldene ring), 8.01 (s, 1H, N=CH), 11.86 (bs, 1H, NH-N=), 12.08 (bs, 1H, NH-C=O).

Mass (EI): m/z 388(M^+1).

Synthesis of **2-(2'-{2,4-Dichloro-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIA)**

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Yield: 80%; Rf 0.5; mp 217-18°C
Molecular Formula: C_{19}H_{13}Cl_{2}N_{5}O_{2}
% Carbon: Found: 55.09; Calcd.: 54.79
% Hydrogen: Found: 3.16; Calcd.: 3.17
% Nitrogen: Found: 16.91; Calcd.: 16.92

IR (KBr, cm\(^{-1}\)): 3314 (-NH of amide), 3230 (-NH), 2220 (C=N), 1665 (C=O), 1614 (C=N), 1112 (Ar-Cl).

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \delta 3.87 (s, 3H, OCH\(_3\)), 7.01 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.34 (d, 1H, J=8.8Hz, H-5', arylidene ring), 7.48 (d, 1H, J=8.8Hz, H-6', arylidene ring), 7.75 (s, 1H, H-3', arylidene ring), 7.86 (d, 2H, J=8.4Hz, H-2,6, phenyl), 8.06 (s, 1H, N=CH), 11.54 (bs, 1H, NH-N=), 12.12 (bs, 1H, NH-C=O).

Mass: m/z 414(M\(^+\)+1), 415(M\(^+\)+2).

Synthesis of 2-(2-{2,6-Dichloro-benzylidene}-hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIA\(_a\))

Yield: 80%; Rf 0.4; mp 211-12°C
Molecular Formula: C_{19}H_{13}Cl_{2}N_{5}O_{2}
% Carbon: Found: 55.09; Calcd.: 54.82
% Hydrogen: Found: 3.16; Calcd.: 3.17
% Nitrogen: Found: 16.91; Calcd.: 16.9
IR (KBr, cm⁻¹): 3311 (-NH of amide), 3265 (-NH), 2209 (C=O), 1672 (C=O), 1613 (C=N), 1096 (Ar-Cl).
¹H NMR (400 MHz, DMSO-d₆): δ 3.80 (s, 3H, OCH₃), 6.98 (d, 2H, J=8.4Hz, H-3,5, phenyl), 7.43 (t, 1H, J=8.8Hz, H-4', aryldiene ring), 7.67 (d, 2H, J=8.8Hz, H-3',5', aryldiene ring), 7.88 (d, 2H, J=8.4Hz, H-2,6, phenyl), 8.09 (s, 1H, N=CH), 11.83 (bs, 1H, NH-N=), 12.17 (bs, 1H, NH-C=O).
Mass (El): m/z 414(M⁺+1), 415(M⁺+2).
1.4.1.1. Pyrimidine

Scheme 2
Scheme 2

Reagents and conditions: (i) Absolute alcohol, K₂CO₃, reflux; (ii) Absolute alcohol, Hydrazine hydrate, reflux; (iii) Aromatic ketone, Glacial acetic acid & Alcohol (2:8), reflux.
General procedure for Synthesis of 2-Mercapto-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (I)
The compound (I) was synthesized by the method reported on page number .58-59

\[
\begin{array}{c}
\text{MeO} \\
\text{SH} \\
\text{N} \\
\text{C} \\
\text{O}
\end{array}
\]

General procedure of synthesis 2-Hydrazinyl-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (II)
The compound (II) was synthesized by the method reported on page number .59-60

\[
\begin{array}{c}
\text{MeO} \\
\text{NC} \\
\text{NH} \\
\text{N} - \text{NH}_2
\end{array}
\]

General procedure of synthesis of 2-(2-{1-[substituted-phenyl]-ethylidene}hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile [IIIB(a-n)]
Compound II (1mmol) was dissolved in a mixture of glacial acetic acid and alcohol (8:2). To this solution, alcoholic solution of different substituted acetophenones (1.1mmol) was added and refluxed for 2-3hrs. Solvent was concentrated to half of its volume and poured into ice water. The precipitate obtained was filtered, washed with water and recrystallized from methanol to get title compounds [IIIBa-n].

Synthesis of 2-(2-{1-phenyl-ethylidene}hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIBa)
Yield: 68%; Rf: 0.66; mp 203-04°C
Molecular Formula: C_{20}H_{17}N_{5}O_{2}
% Carbon: Found: 66.84; Calcd.: 67.02
% Hydrogen: Found: 4.77; Calcd.: 4.78
% Nitrogen: Found: 19.49; Calcd.: 19.51
IR (KBr, cm\(^{-1}\)): 3310 (CONH), 3240 (NH), 2218 (C=N), 1679 (C=O), 1604 (C=N).
\(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 2.44 (s, 3H, CH\(_3\)), 3.89 (s, 3H, OCH\(_3\)), 7.03 (d, 2H, J=8.8Hz, H\(_{3,5}\)), 7.41-7.43 (m, 3H, H\(_{4,4',5'}\)), 7.92 (d, 1H, J=8.4Hz, H\(_6\)), 7.96 (d, 2H, J=8.8Hz, H\(_{2,6}\)), 8.06 (d, 1H, J=8.0Hz, H\(_7\)), 11.42 (bs, 1H, NH), 11.71 (bs, 1H, CONH).
\(^{13}\)C-NMR (100 MHz, DMSO-d\(_6\)): \(\delta\) 15.13, 55.61, 86.19, 113.73, 117.73, 127.30, 128.34, 128.61, 129.88, 130.59, 130.68, 137.50, 153.51, 154.17, 161.98, 162.05, 169.83
Mass (EI): m/z 360(M\(^+\)+1).

Synthesis of 2-[[2-[1-[4-Chloro-phenyl(ethylidene)hydrazinyl]-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carboxitrile (IIIB\(_b\))

![IIIB\(_b\)](image)

Yield: 75%; Rf: 0.64; mp: 235-36°C
Molecular Formula: C\(_{20}\)H\(_{16}\)ClN\(_5\)O\(_2\)
% Carbon: Found: 61.00; Calcd.: 61.13
% Hydrogen: Found: 4.09; Calcd.: 4.08
% Nitrogen: Found: 17.78; Calcd.: 17.77
IR (KBr, cm\(^{-1}\)): 3316 (CONH), 3281 (NH), 2219 (C=N), 1678 (C=O), 1607 (C=N).
\(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 2.42 (s, 3H, CH\(_3\)), 3.79 (s, 3H, OCH\(_3\)), 6.95 (d, 2H, J=8.4Hz, H\(_{3,5}\)), 7.38 (d, 2H, J=8.0Hz, H\(_{2,6}\')), 7.69 (d, 2H, J=8.0Hz, H\(_{3,5}'\)), 7.83 (d, 2H, J=8.4Hz, H\(_{2,6}'\)), 10.52 (bs, 1H, NH), 11.46 (bs, 1H, CONH).
Mass: m/z 395(M\(^+\)+1), 396(M\(^+\)+2).

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Synthesis of 2-(2-{1-[4-Bromo-phenyl]ethylidene}hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III B_2)

![Chemical Structure of III B_2](image)

Yield: 72%; Rf: 0.65; mp: 265-66°C
Molecular Formula: C_{20}H_{16}BrN_{5}O_{2}
% Carbon: Found: 54.81; Calcd.: 54.62
% Hydrogen: Found: 3.68; Calcd.: 3.67
% Nitrogen: Found: 15.98; Calcd.: 15.98
IR (KBr, cm^{-1}): 3308 (CONH), 3234 (NH), 2225 (C=N), 1676 (C=O), 1604 (C=N).

^1H NMR (400 MHz, DMSO-d_{6}): δ 2.42 (s, 3H, CH$_3$), 3.84 (s, 3H, OCH$_3$), 6.99 (d, 2H, J=8.4Hz, H$_3$), 7.37 (dd, 1H, J=8.0, 7.6Hz, H$_5$), 7.51 (d, 1H, J=8.0Hz, H$_6$), 7.57 (d, 1H, J=7.6Hz, H$_4$), 7.79 (s, 1H, H$_2$), 7.95 (d, 2H, J=8.4Hz, H$_5$), 11.26 (bs, 1H, NH), 11.96 (bs, 1H, CONH).

Mass (EI): m/z 438 (M^+ + 1).

Synthesis of 2-(2-{1-[3-Bromo-phenyl]ethylidene}hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III B_4)

![Chemical Structure of III B_4](image)

Yield: 66%; Rf: 0.65; mp: 255-56°C
Molecular Formula: C_{20}H_{16}BrN_{5}O_{2}

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% Carbon: Found: 54.81; Calcd.: 54.96
% Hydrogen: Found: 3.68; Calcd.: 3.68
% Nitrogen: Found: 15.98; Calcd.: 15.93
IR (KBr, cm\(^{-1}\)): 3346 (CONH), 3311 (NH), 2213 (C-N), 1675 (C=O), 1608 (C-N).
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 2.40 (s, 3H, CH\(_3\)), 3.80 (s, 3H, OCH\(_3\)), 6.94 (d, 2H, J=8.8Hz, H\(_{3,5}\)), 7.39 (d, 2H, J=8.0Hz, H\(_{1,3}\)), 7.62 (d, 2H, J=8.0Hz, H\(_{2,6}\)), 7.91 (d, 2H, J=8.8Hz, H\(_{2,6}\)), 11.08 (bs, 1H, NH), 11.68 (bs, 1H, CONH).
\(^1^3\)C-NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 14.87, 55.56, 86.55, 113.66, 117.51, 123.88, 128.66, 129.08, 130.66, 131.28, 136.54, 154.09, 162.04, 162.07, 170.13.
Mass (EI): \(m/z\) 438(M\(^+\)+1).

Synthesis of 2-(2-{1-[4-Floro-phenyl]ethylidene}hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIB\(_6\))

Yield: 60%; R\(_f\): 0.64; mp: 271-72°C
Molecular Formula: C\(_{26}\)H\(_{16}\)FN\(_5\)O\(_2\)
% Carbon: Found: 63.66; Calcd.: 63.75
% Hydrogen: Found: 4.27; Calcd.: 4.28
% Nitrogen: Found: 18.56; Calcd.: 18.57
IR (KBr, cm\(^{-1}\)): 3319 (CONH), 3284 (NH), 2220 (C=N), 1672 (C=O), 1605 (C=N).
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 2.43 (s, 3H, CH\(_3\)), 3.90 (s, 3H, OCH\(_3\)), 7.03 (d, 2H, J=8.4Hz, H\(_{3,5}\)), 7.16 (t, 2H, J=8.4Hz, H\(_{1,3}\)), 7.93 (d, 2H, J=8.4Hz, H\(_{2,6}\)), 8.07 (m, 2H, J=8.4Hz, H\(_{2,6}\)), 10.49 (bs, 1H, NH), 11.78 (bs, 1H, CONH).
Mass (EI): \(m/z\) 378(M\(^+\)+1).
Synthesis of 2-(2-{1-[2-Hydroxy-phenyl]ethylidene}hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIB_{f})

Yield: 70%; R_{f}: 0.67; mp: 213-14°C
Molecular Formula: C_{20}H_{17}N_{5}O_{3}
% Carbon: Found: 63.99; Calcd.: 63.74
% Hydrogen: Found: 4.56; Calcd.: 4.55
% Nitrogen: Found: 18.66; Calcd.: 18.67
IR (KBr, cm^{-1}): 3426 (OH), 3334 (CONH), 3264 (NH), 2215 (C-N), 1683 (C=O), 1606 (C=N).
^{1}H NMR (400 MHz, DMSO-d_{6}): δ 2.38 (s, 3H, CH_{3}), 3.85 (s, 3H, OCH_{3}), 6.95-7.02 (m, 4H, H_{3,5,3',5'}), 7.42 (t, 1H, J=7.6Hz, H_{4}), 7.73 (d, 1H, J=8.0Hz, H_{6}), 7.87 (d, 2H, J=8.4Hz, H_{2,6}), 10.34 (s, 1H, OH), 11.13 (bs, 1H, NH), 12.01 (bs, 1H, CONH).
Mass (EI): m/z 378(M^{+}+1).

Synthesis of 2-(2-{1-[4-Hydroxy-phenyl]ethylidene}hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIB_{g})

Yield: 76%; R_{f}: 0.66; mp: 251-52°C
Molecular Formula: C_{20}H_{17}N_{5}O_{3}
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% Carbon: Found: 63.99; Calcd.: 63.79  
% Hydrogen: Found: 4.56; Calcd.: 4.57  
% Nitrogen: Found: 18.66; Calcd.: 18.67  

IR (KBr, cm\(^{-1}\)): 3418 (OH), 3345 (CONH), 3246 (NH), 2215 (C=\(\text{=N}\)), 1674 (C=O), 1606 (C=\(\text{=N}\)).  

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 2.26 (s, 3H, CH\(_3\)), 3.78 (s, 3H, OCH\(_3\)), 6.71 (d, 2H, J=8.4Hz, H\(_{1,5}\)), 7.00 (d, 2H, J=8.4Hz, H\(_{3,5}\)), 7.80 (d, 2H, J=8.4Hz, H\(_{2,6}\)), 7.85 (d, 2H, J=8.4Hz, H\(_{2,6}\)), 9.96 (s, 1H, OH), 11.25 (bs, 1H, NH), 11.73 (bs, 1H, CONH).  
Mass (EI): m/z 376(M\(^{+}\)+1).

Synthesis of 2-(2-{1-[4-Methoxy-phenyl]ethyliene}hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIB\(_b\))

![IIIB\(_b\)](image)

Yield: 68%; \(R_f\): 0.67; mp: 223-24°C  
Molecular Formula: C\(_{21}\)H\(_{19}\)N\(_5\)O\(_3\)  
% Carbon: Found: 64.77; Calcd.: 64.93  
% Hydrogen: Found: 4.92; Calcd.: 4.91  
% Nitrogen: Found: 17.98; Calcd.: 17.97  
IR (KBr, cm\(^{-1}\)): 3287 (CONH), 3229 (NH), 2216 (C=\(\text{=N}\)), 1671 (C=O), 1603 (C=\(\text{=N}\)).  
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 2.39 (s, 3H, CH\(_3\)), 3.81 (s, 3H, OCH\(_3\)), 3.83 (s, 3H, OCH\(_3\)), 6.90 (d, 2H, J=7.6Hz, H\(_{1,5}\)), 6.97 (d, 2H, J=8.4Hz, H\(_{3,5}\)), 7.76 (d, 2H, J=7.6Hz, H\(_{2,6}\)), 7.84 (d, 2H, J=8.4Hz, H\(_{2,6}\)), 11.13 (bs, 1H, NH), 11.84 (bs, 1H, CONH).  
Mass (EI): m/z 390(M\(^{+}\)+1).
Synthesis of 2-(2-[[3,4-Dimethoxy-phenyl]ethylidene]hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIB₄)

Yield: 78%; Rf: 0.67; mp: 167-68°C
Molecular Formula: C₂₂H₂₁N₅O₄
% Carbon: Found: 63.00; Calcd.: 63.17
% Hydrogen: Found: 5.05; Calcd.: 5.04
% Nitrogen: Found: 16.70; Calcd.: 16.71
IR (KBr, cm⁻¹): 3318 (CONH), 3265 (NH), 2221 (C=N), 1677 (C=O), 1610 (C=N).
¹H NMR (400 MHz, DMSO-d₆): δ 2.41 (s, 3H, CH₃), 3.88 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 6.93 (d, 1H, J=8.4Hz, H₅), 6.99 (d, 2H, J=8.8Hz, H₆, H₇), 7.47 (s, 1H, H₂), 7.58 (d, 1H, J=8.4Hz, H₆), 7.93 (d, 2H, J=8.8Hz, H₂, H₆), 11.29 (bs, 1H, NH), 12.13 (bs, 1H, CONH).
Mass (EI): m/z 420(M⁺+1).

Synthesis of 2-(2-[[1,3-Dimethoxy-phenyl]ethylidene]hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIB₄)

Yield: 82%; Rf: 0.66; mp: 161-62°C
Molecular Formula: C₂₂H₂₁N₅O₄

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% Carbon: Found: 63.00; Calcd.: 63.12
% Hydrogen: Found: 5.05; Calcd.: 5.04
% Nitrogen: Found: 16.70; Calcd.: 16.69

IR (KBr, cm\(^{-1}\)): 3319 (CONH), 3236 (NH), 2218 (C=N), 1674 (C=O), 1609 (C=N).

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 2.40 (s, 3H, CH\(_3\)), 3.88 (s, 3H, OCH\(_3\)), 3.90 (s, 3H, OCH\(_3\)), 3.92 (s, 3H, OCH\(_3\)), 6.81 (s, 1H, H\(_3\)), 6.91 (d, 1H, J=7.6Hz, H\(_5\)), 6.99 (d, 2H, J=8.4Hz, H\(_3\)), 7.32 (d, 1H, J=7.6Hz, H\(_6\)), 7.91 (d, 2H, J=8.4Hz, H\(_2\)), 11.11 (bs, 1H, NH), 11.72 (bs, 1H, CONH).

Mass (EI): \(m/z\) 420(M\(^{+}\)+1).

Synthesis of 2-(2-[[2-Nitro-phenyl]ethyldene]hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIb\(_k\))

Yield: 80%; R\(_f\): 0.64; mp: 241-42°C

Molecular Formula: C\(_{26}\)H\(_{16}\)N\(_6\)O\(_4\)
% Carbon: Found: 59.40; Calcd.: 59.31
% Hydrogen: Found: 3.99; Calcd.: 4.00
% Nitrogen: Found: 20.78; Calcd.: 20.77

IR (KBr, cm\(^{-1}\)): 3342 (CONH), 3251 (NH), 2222 (C=N), 1689 (C=O), 1602 (C=N).

\(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 2.41 (s, 3H, CH\(_3\)), 3.90 (s, 3H, OCH\(_3\)), 6.97 (d, 2H, J=8.4Hz, H\(_3\)), 7.58 (t, 1H, J=7.6Hz, H\(_4\)), 7.73 (t, 1H, J=8.0Hz, H\(_5\)), 7.82 (d, 1H, J=8.4Hz, H\(_6\)), 7.89 (d, 2H, J=8.4Hz, H\(_2\)), 8.13 (d, 1H, J=8.0Hz, H\(_3\)), 11.21 (bs, 1H, NH), 11.64 (bs, 1H, CONH).

Mass (EI): \(m/z\) 405(M\(^{+}\)+1).
Synthesis of 2-(2-[[3-Nitro-phenyl]ethylidene]hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIB₃)

Yield: 75%; Rf: 0.64; mp: 245-46°C
Molecular Formula: C₂₀H₁₆N₆O₄
% Carbon: Found: 59.40; Calcd.: 59.25
% Hydrogen: Found: 3.99; Calcd.: 3.98
% Nitrogen: Found: 20.78; Calcd.: 20.79
IR (KBr, cm⁻¹): 3326 (CONH), 3276 (NH), 2227 (C-N), 1683 (C-O), 1607 (C=N),
¹H NMR (400 MHz, DMSO-d₆); δ 2.39 (s, 3H, CH₃), 3.86 (s, 3H, OCH₃), 7.04 (d, 2H, J=8.8Hz, H₃,5), 7.62 (dd, 1H, J=8.4Hz, H₅), 7.93 (d, 2H, J=8.8Hz, H₂,₆), 8.09 (d, 1H, J=8.8Hz, H₆), 8.24 (d, 1H, J=8.4Hz, H₄), 8.37 (s, 1H, H₂), 10.36 (bs, 1H, NH), 12.21 (bs, 1H, CONH).
Mass (EI): m/z 404(M⁺+1).

Synthesis of 2-(2-[[4-Nitro-phenyl]ethylidene]hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (IIIB₄)

Yield: 65%; Rf: 0.65; mp: 241-42°C
Molecular Formula: C₂₀H₁₆N₆O₄
Chapter - 1.4

Part - I

Experimental

% Carbon: Found: 59.40; Calcd.: 59.27
% Hydrogen: Found: 3.99; Calcd.: 3.98
% Nitrogen: Found: 20.78; Calcd.: 20.77

IR (KBr, cm\(^{-1}\)): 3353 (CONH), 3273 (NH), 2224 (C=N), 1668 (C=O), 1613 (C=N).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 2.36 (s, 3H, CH\(_3\)), 3.85 (s, 3H, OCH\(_3\)), 6.96 (d, 2H, J=8.4Hz, H\(_{3,5}\)), 7.68 (d, 2H, J=8.8Hz, H\(_{2,6}\)), 7.94 (d, 2H, J=8.4Hz, H\(_{2,6}\)), 8.26 (d, 2H, J=8.8Hz, H\(_{3,5}\)), 11.39 (bs, 1H, NH), 11.92 (bs, 1H, CONH).

Mass (EI): \(m/z\) 405(M\(^+\)+1).

Synthesis of 2-(2-[1-[4-Methyl-phenyl]ethyldene]hydrazinyl)-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (III\(B_a\))

Yield: 74%; R\(_f\) 0.64; mp: 215-16°C
Molecular Formula: C\(_{21}\)H\(_{19}\)N\(_5\)O\(_2\)
% Carbon: Found: 67.55; Calcd.: 67.45
% Hydrogen: Found: 5.13; Calcd.: 5.14
% Nitrogen: Found: 18.75; Calcd.: 18.76

IR (KBr, cm\(^{-1}\)): 3320 (CONH), 3274 (NH), 2223 (C=N), 1681 (C=O), 1601 (C=N).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 2.31 (s, 3H, CH\(_3\)), 2.39 (s, 3H, CH\(_3\)), 3.81 (s, 3H, OCH\(_3\)), 6.98 (d, 2H, J=8.4Hz, H\(_{3,5}\)), 7.21 (d, 2H, J=7.6Hz, H\(_{3,5}\)), 7.47 (d, 2H, J=7.6Hz, H\(_{2,6}\)), 7.89 (d, 2H, J=8.4Hz, H\(_{2,6}\)), 11.27 (bs, 1H, NH), 11.81 (bs, 1H, CONH).

Mass (EI): \(m/z\) 374(M\(^+\)+1).

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1.4.1.2. Thiazolidinone

Scheme 3
Scheme 3

Reagents and conditions: (i) Absolute alcohol, K$_2$CO$_3$, reflux; (ii) Absolute alcohol, Hydrazine hydrate, reflux; (iii) Aromatic aldehyde, Glacial acetic acid & Alcohol (2:8), reflux; (iv) Anhydrous ZnCl$_2$, Thioglycollic acid, DMF, reflux.
General procedure for Synthesis of 2-Mercapto-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (I)

The compound (I) was synthesized by the method reported on page number-.58-59

\[
\text{I}
\]

General procedure of synthesis 2-Hydrazinyl-4-(4-methoxy-phenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile (II)

The compound (II) was synthesized by the method reported on page number-.59-60

\[
\text{II}
\]

General procedure of synthesis of 2-(2-[substituted benzylidene] hydrazinyl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile [IIIA(a-n)]

The compounds [IIIA(a-n)] were synthesized by the method reported on page number-.58-75

\[
\text{IIIA(a-n)}
\]
General procedure of synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-(substituted-phenyl)-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVA-n)

To the mixture of compound [IIIA_n] (1mmol) and thioglycollic acid (1.1mmol) in dry 1,4-dioxane, a pinch of anhydrous zinc chloride was added and the mixture was refluxed for 16-20 hrs. After completion of reaction, the mixture was cooled to room temperature and poured into crushed ice water. The solid obtained was filtered and recrystallized from ethanol to get pure compounds IVa-n.

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-phenyl-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVA)

![Diagram of IVa]

Yield: 68%; R_f: 0.62; mp 225-26°C
Molecular Formula: C_{21}H_{17}N_{5}O_{3}S
% Carbon: Found: 60.13; Calcd.: 60.57
% Hydrogen: Found: 4.08; Calcd.: 4.07
% Nitrogen: Found: 16.70; Calcd.: 16.54
IR (KBr, cm\(^{-1}\)): 3315 (NHCO), 3286 (NH), 2218 (CN), 1712 (CO, Thialactam), 1678 (CONH).

\(^1\)H NMR (400 MHz, DMSO-d_6): \(\delta\) 3.75 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 6.16 (Ar-CH), 7.02 (d, 2H, J=8.4Hz, H_2,5, Phenyl ring), 7.31-7.44 (m, 5H, H_2,3',4',5',6'), 7.84 (d, 2H, J=8.4Hz, H_2,6, Phenyl ring), 11.43 (bs, 1H, NH), 11.94 (bs, 1H, NHCO).
Mass (EI): m/z 420(M^+1).
Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{2-chloro-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVb)

Yield: 67%; Rf: 0.55; mp 249-50°C
Molecular Formula: C_{21}H_{16}ClN_{5}O_{3}S
% Carbon: Found: 55.57; Calcd.: 55.25
% Hydrogen: Found: 3.55; Calcd.: 3.54
% Nitrogen: Found: 15.43; Calcd.: 15.44
IR (KBr, cm^{-1}): 3298 (NHCO), 3265 (NH), 2223 (CN), 1714 (CO, Thialactam), 1679 (CONH).
^1H NMR (400 MHz, DMSO-d_6): δ 3.75 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 6.13 (Ar-CH), 6.92 (d, J=8.0Hz, H_{3,5}, Phenyl ring), 7.38-7.60 (m, 4H, H_{4',5',5',6'}), 7.85 (d, 2H, J=8.0Hz, H_{2,6}, Phenyl ring), 11.70 (bs, 1H, NH), 12.01 (bs, 1H, NHCO).
Mass (EI): m/z 455(M^+1).

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{4-chloro-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVc)

Yield: 60%; Rf: 0.56; mp 243-44°C
Molecular Formula: C_{21}H_{16}ClN_{5}O_{3}S

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% Carbon: Found: 55.57; Calcd.: 55.32  
% Hydrogen: Found: 3.55; Calcd.: 3.54  
% Nitrogen: Found: 15.43; Calcd.: 15.46  
IR (KBr, cm\(^{-1}\)): 3310 (NHCO), 3281 (NH), 2225 (CN), 1713 (CO, Thialactam), 1675 (CONH), 1118 (Ar-Cl).  
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 3.77 (s, 2H, CH\(_2\)), 3.81 (s, 3H, OCH\(_3\)), 6.18 (Ar-CH), 6.93 (d, 2H, J=8.4Hz, H\(_{3,5}\), Phenyl ring), 7.40 (d, 2H, J=8.0Hz, H\(_{2,6}\)), 7.67 (d, 2H, J=8.0Hz, H\(_{3,5}'\)), 7.86 (d, 2H, J=8.4Hz, H\(_{2,6}'\), Phenyl ring), 11.25 (bs, 1H, NH), 11.93 (bs, 1H, NHCO).  
Mass (EI): \(m/z\) 455(M\(^+\)+1).  

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{3-bromo-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVd)

Yield: 58%; \(R_f\): 0.46; mp 257-58°C  
Molecular Formula: C\(_{21}\)H\(_{16}\)BrN\(_5\)O\(_3\)S  
% Carbon: Found: 50.61; Calcd.: 50.74  
% Hydrogen: Found: 3.24; Calcd.: 3.24  
% Nitrogen: Found: 14.05; Calcd.: 14.08  
IR (KBr, cm\(^{-1}\)): 3294 (NHCO), 3253 (NH), 2225 (CN), 1702 (CO, Thialactam), 1674 (CONH).  
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 3.80 (s, 2H, CH\(_2\)), 3.89 (s, 3H, OCH\(_3\)), 6.14 (Ar-CH), 6.91 (d, 2H, J=8.8Hz, H\(_{3,5}\), Phenyl ring), 7.29 (t, 1H, J=7.6Hz, H\(_5\)), 7.45 (d, 1H, J=7.6Hz, H\(_6\)), 7.50 (d, 1H, J=7.6Hz, H\(_6'\)), 7.74 (s, 1H, H\(_2\)), 7.82 (d, 2H, J=8.8Hz, H\(_{2,6}\), Phenyl ring), 11.92 (bs, 1H, NH), 12.27 (bs, 1H, NHCO).  
Mass (EI): \(m/z\) 499(M\(^+\)+1).
Chapter - 1.4

Part-I

Experimental

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{4-bromo-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVe)

Yield: 53%; R f: 0.50; mp 259-60°C
Molecular Formula: C₂₅H₁₆BrN₅O₃S
% Carbon: Found: 50.61; Calcd.: 50.81
% Hydrogen: Found: 3.24; Calcd.: 3.25
% Nitrogen: Found: 14.05; Calcd.: 14.07
IR (KBr, cm⁻¹): 3296 (NHCO), 3250 (NH), 2221 (CN), 1710 (CO, Thialactam), 1665 (CONH).
¹H NMR (400 MHz, DMSO-d₆): δ 3.73 (s, 2H, CH₂), 3.83 (s, 3H, OCH₃), 6.10 (Ar-CH), 6.98 (d, 2H, J=8.0Hz, H₃,₅, Phenyl ring), 7.35 (d, 2H, J=8.4Hz, H₂,₆'), 7.59 (d, 2H, J=8.4Hz, H₂,₆'), 7.82 (d, 2H, J=8.0Hz, H₂,₆', Phenyl ring), 11.47 (bs, 1H, NH), 11.82 (bs, 1H, NHCO).
Mass (El): m/z 499(M⁺+1).

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{4-floro-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVf)

Yield: 53%; R f: 0.50; mp 259-60°C
Molecular Formula: C₂₅H₁₆BrN₅O₃S
% Carbon: Found: 50.61; Calcd.: 50.81
% Hydrogen: Found: 3.24; Calcd.: 3.25
% Nitrogen: Found: 14.05; Calcd.: 14.07
IR (KBr, cm⁻¹): 3296 (NHCO), 3250 (NH), 2221 (CN), 1710 (CO, Thialactam), 1665 (CONH).
¹H NMR (400 MHz, DMSO-d₆): δ 3.73 (s, 2H, CH₂), 3.83 (s, 3H, OCH₃), 6.10 (Ar-CH), 6.98 (d, 2H, J=8.0Hz, H₃,₅, Phenyl ring), 7.35 (d, 2H, J=8.4Hz, H₂,₆'), 7.59 (d, 2H, J=8.4Hz, H₂,₆'), 7.82 (d, 2H, J=8.0Hz, H₂,₆', Phenyl ring), 11.47 (bs, 1H, NH), 11.82 (bs, 1H, NHCO).
Mass (El): m/z 499(M⁺+1).
Yield: 50%; \( R_f: 0.55 \); mp 241-42°C

**Molecular Formula:** \( C_{21}H_{16}FN_5O_3S \)

% Carbon: Found: 57.66; Calcd.: 57.91
% Hydrogen: Found: 3.69; Calcd.: 3.70
% Nitrogen: Found: 16.01; Calcd.: 16.04

**IR (KBr, cm\(^{-1}\)):** 3302 (NHCO), 3262 (NH), 2217 (CN), 1718 (CO, Thialactam), 1674 (CONH).

\(^1\text{H NMR (400 MHz, DMSO-d}_6\):} \delta 3.67 (s, 2H, CH\(_2\)), 3.80 (s, 3H, OCH\(_3\)), 6.14 (Ar-CH), 6.95 (d, 2H, J=8.0Hz, H\(_{3.5}\), Phenyl ring), 7.21 (m, 2H, H\(_{2.6}\)), 7.90 (d, 2H, J=8.0Hz, H\(_{2.6}\), Phenyl ring), 7.98 (t, 2H, J=8.4Hz, H\(_{1.3}\)), 12.03 (bs, 1H, NH), 12.26 (bs, 1H, NHCO).

**Mass (EI):** \( m/z 438(M^+1) \).

### Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{4-hydroxy-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVg)

![IVg](image)

Yield: 55%; \( R_f: 0.65 \); mp 255-56°C

**Molecular Formula:** \( C_{21}H_{17}N_5O_4S \)

% Carbon: Found: 57.92; Calcd.: 57.63
% Hydrogen: Found: 3.93; Calcd.: 3.92
% Nitrogen: Found: 16.08; Calcd.: 16.04

**IR (KBr, cm\(^{-1}\)):** 3483 (OH), 3318 (NHCO), 3291 (NH), 2219 (CN), 1709 (CO, Thialactam), 1672 (CONH).

\(^1\text{H NMR (400 MHz, DMSO-d}_6\):} \delta 3.70 (s, 2H, CH\(_2\)), 3.85 (s, 3H, OCH\(_3\)), 6.06 (Ar-CH), 7.05 (d, 2H, J=8.4Hz, H\(_{3.5}\), Phenyl ring), 6.84 (d, 2H, J=8.8Hz, H\(_{3.5}\)), 7.57 (d,
2H, J=8.8Hz, H_{2,6}), 7.89 (d, 2H, J=8.4Hz, H_{2,6}, Phenyl ring), 10.13 (bs, 1H, OH), 11.55 (bs, 1H, NH), 12.03 (bs, 1H, NHCO).

Mass (El): m/z 436(M^+1).

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{4-methoxy-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVh)

![Chemical Structure IVh]

Yield: 70%; Rf: 0.57; mp 275-76°C

Molecular Formula: C_{22}H_{19}N_{5}O_{4}S

% Carbon: Found: 58.79; Calcd.: 58.61

% Hydrogen: Found: 4.26; Calcd.: 4.25

% Nitrogen: Found: 15.58; Calcd.: 15.52

IR (KBr, cm^{-1}): 3325 (NHCO), 3303 (NH), 2210 (CN), 1706 (CO, Thialactam), 1679 (CONH).

^1H NMR (400 MHz, DMSO-d6): δ 3.76 (s, 2H, CH₂), 3.81 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 6.11 (Ar-CH), 6.98 (d, 2H, J=8.0Hz, H_{5,6}, Phenyl ring), 6.93 (d, 2H, J=8.4Hz, H_{3,4}, Phenyl ring), 7.78 (d, 2H, J=8.4Hz, H_{2,6}), 7.85 (d, 2H, J=8.0Hz, H_{2,6}, Phenyl ring), 11.72 (bs, 1H, NH), 12.08 (bs, 1H, NHCO).

Mass: m/z 450(M^+1).

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{3,4-dimethoxy-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVi)

![Chemical Structure IVi]
Yield: 63%; R_f: 0.58; mp 267-68°C
Molecular Formula: C_{23}H_{21}N_{5}O_{5}S
% Carbon: Found: 57.61; Calcd.: 57.36
% Hydrogen: Found: 4.41; Calcd.: 4.42
% Nitrogen: Found: 14.61; Calcd.: 14.59
IR (KBr, cm^{-1}): 3320 (NHCO), 3283 (NH), 2221 (CN), 1710 (CO, Thialactam), 1678 (CONH).

\[^1\text{H} \text{NMR (400 MHz, DMSO-d}_6\text{): }\delta 3.75 (s, 2H, CH}_2, 3.84 (s, 3H, OCH}_3, 3.87 (s, 6H, 2\times\text{OCH}_3), 6.05 (\text{Ar-CH}), 6.87 (d, 2H, J=8.4Hz, H_{3,5}, \text{Phenyl ring}), 7.01 (d, 1H, J=8.8Hz, H_5), 7.43 (d, 2H, J=8.8Hz, H_6), 7.67 (s, 1H, H_2), 7.86 (d, 2H, J=8.4Hz, H_2,\text{Phenyl ring}), 11.49 (bs, 1H, NH), 11.83 (bs, 1H, NHCO).

Mass (EI): m/z 480(M^+1).

**Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-[3-nitro-phenyl]-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVj)**

![IVj](image)

Yield: 55%; R_f: 0.46; mp 245-46°C
Molecular Formula: C_{21}H_{16}N_{6}O_{5}S
% Carbon: Found: 54.31; Calcd.: 54.62
% Hydrogen: Found: 3.47; Calcd.: 3.48
% Nitrogen: Found: 18.09; Calcd.: 18.11
IR (KBr, cm^{-1}): 3327 (NHCO), 3303 (NH), 2218 (CN), 1709 (CO, Thialactam), 1668 (CONH).

\[^1\text{H} \text{NMR (400 MHz, DMSO-d}_6\text{): }\delta 3.79 (s, 2H, CH}_2, 3.86 (s, 3H, OCH}_3, 6.09 (\text{Ar-CH}), 7.08 (d, 2H, J=8.4Hz, H_{3,5}, \text{Phenyl ring}), 7.62 (dd, 1H, J=7.6 & 8.0 Hz, H_5),
7.89 (d, 2H, J=8.4Hz, H\textsubscript{2,6}, Phenyl ring), 8.00 (d, 1H, J=7.6Hz, H\textsubscript{4}), 8.15 (d, 1H, J=8.0Hz, H\textsubscript{3}), 8.23 (s, 1H, H\textsubscript{2}), 11.96 (bs, 1H, NH), 12.21 (bs, 1H, NHCO).

Mass (EI): m/z 465(M\textsuperscript{+}+1).

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{4-nitro-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IV\textsubscript{k})

Yield: 60%; R\textsubscript{f}: 0.44; mp 237-38°C
Molecular Formula: C\textsubscript{21}H\textsubscript{16}N\textsubscript{6}O\textsubscript{5}S
% Carbon: Found: 54.31; Calcd.: 54.56
% Hydrogen: Found: 3.47; Calcd.: 3.48
% Nitrogen: Found: 18.09; Calcd.: 18.10
IR (KBr, cm\textsuperscript{-1}): 3352 (NHCO), 3318 (NH), 2229 (CN), 1721 (CO, Thialactam), 1686 (CONH).

\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): δ 3.72 (s, 2H, CH\textsubscript{2}), 3.86 (s, 3H, OCH\textsubscript{3}), 6.17 (Ar-CH), 7.02 (d, 2H, J=8.4Hz, H\textsubscript{3,5}, Phenyl ring), 7.87 (d, 2H, J=8.4Hz, H\textsubscript{2,6}, Phenyl ring), 8.09 (d, 2H, J=7.6Hz, H\textsubscript{2,6}), 8.28 (d, 2H, J=7.6Hz, H\textsubscript{3,5}), 11.79 (bs, 1H, NH), 12.11 (bs, 1H, NHCO).

Mass (EI): m/z 465(M\textsuperscript{+}+1).

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{4-hydroxy-3-methoxy-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IV\textsubscript{l})
Yield: 61%; Rf: 0.62; mp 265-66°C
Molecular Formula: C_{22}H_{19}N_{5}O_{3}S
% Carbon: Found: 56.77; Calc.: 56.48
% Hydrogen: Found: 4.11; Calc.: 4.12
% Nitrogen: Found: 15.05; Calc.: 15.03
IR (KBr, cm\(^{-1}\)): 3451 (OH), 3318 (NHCO), 3290 (NH), 2219 (CN), 1712 (CO, Thialactam), 1673 (CONH).
\(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 3.74 (s, 2H, CH\(_2\)), 3.78 (s, 3H, OCH\(_3\)), 3.85 (s, 3H, OCH\(_3\)), 6.15 (Ar-CH), 6.72 (d, 1H, J=8.0Hz, H), 6.89 (d, 2H, J=8.4Hz, H\(_{3,5}\), Phenyl ring), 7.03 (d, 1H, J=8.0Hz, H\(_6\)), 7.56 (s, 1H, H\(_2\)), 7.82 (d, 2H, J=8.4Hz, H\(_{2,6}\), Phenyl ring), 9.24 (bs, 1H, OH), 11.61 (bs, 1H, NH), 12.14 (bs, 1H, NHCO).
\(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta\) 37.23, 55.90, 56.49, 62.55, 85.09, 110.87, 113.84, 114.15, 115.66, 118.17, 123.73, 130.51, 130.70, 148.11, 148.52, 149.93, 153.46, 162.10, 162.42, 169.19, 170.09.
Mass (El): m/z 466(M\(^{+}\)+1).

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-[4-methyl-phenyl]-thiazolidin-3-yl-amino)-1,6-dihydropyrimidine-5-carbonitrile (IVm)

Yield: 53%; Rf: 0.55; mp 231-32°C
Molecular Formula: C_{22}H_{19}N_{5}O_{3}S
% Carbon: Found: 60.96; Calc.: 60.64
% Hydrogen: Found: 4.42; Calc.: 4.41
% Nitrogen: Found: 16.16; Calc.: 16.13
IR (KBr, cm\(^{-1}\)): 3360 (NHCO), 3294 (NH), 2220 (CN), 1715 (CO, Thialactam), 1676 (CONH).
\(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 2.41 (s, 3H, CH\(_3\)), 3.79 (s, 2H, CH\(_2\)), 3.87 (s, 3H, OCH\(_3\)), 6.14 (Ar-CH), 6.96 (d, 2H, J=8.4Hz, H\(_{3,5}\), Phenyl ring), 7.06-7.23 (m, 4H,
H$_{2,3',5',6'}$, 7.81 (d, 2H, J=8.4Hz, H$_{2,6}$, Phenyl ring), 11.52 (bs, 1H, NH), 11.86 (bs, 1H, NHCO).
Mass (EI): m/z 434(M$^+$+1).

Synthesis of 4-(4-methoxy-phenyl)-6-oxo-2-(2-oxo-4-{4-dimethylamino-phenyl}-thiazolidin-3-yl-amino)-1,6-dihydropyrimidin-5-carbonitrile (IVn)

Yield: 58%; Rf: 0.53; mp 279-80°C
Molecular Formula: C$_{23}$H$_{22}$N$_6$O$_3$S
% Carbon: Found: 59.73; Calcd.: 59.64
% Hydrogen: Found: 4.79; Calcd.: 4.80
% Nitrogen: Found: 18.17; Calcd.: 18.19
IR (KBr, cm$^{-1}$): 3287 (NHCO), 3246 (NH), 2216 (CN), 1707 (CO, Thialactam), 1677 (CONH).
$^1$H NMR (400 MHz, DMSO-d$_6$): δ 2.36 (s, 6H, CH$_3$), 3.76 (s, 2H, CH$_2$), 3.82 (s, 3H, OCH$_3$), 6.08 (Ar-CH), 6.87 (d, 2H, J=8.8Hz, H$_{2,5}$), 6.93 (d, 2H, J=8.4Hz, H$_{3,6}$, Phenyl ring), 7.76 (d, 2H, J=8.8Hz, H$_{2,6}$), 7.88 (d, 2H, J=8.4Hz, H$_{2,6}$, Phenyl ring), 11.74 (bs, 1H, NH), 12.05 (bs, 1H, NHCO).
Mass (EI): m/z 463(M$^+$+1).
1.4.2. BIOLOGY
1.4.2.1. Anticonvulsant Activity
Introduction

The word "epilepsy" is derived from the Greek word "epilambanein" which means "to seize or attack". An epileptic seizure is a transient occurrence of signs/and or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and social consequences of this condition.

Etiology

All the factors that can affect the brain, i.e. head, traumas, neoplasms, degenerative diseases, infections, metabolic diseases, ischemia and hemorrhages, can predispose a person to epilepsy. At present, more and more genetic factors underlying different types of epileptic syndromes are revealed. It is also known that certain brain areas, i.e. temporal and frontal lobes are more susceptible to produce epileptic seizure activity than the others.

The proportion of incidence cases of epilepsy by etiology is shown in the table below.

<table>
<thead>
<tr>
<th>ETIOLOGY OF EPILEPSY</th>
<th>PROPORTION OF INCIDENCE CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic/cryptogenic</td>
<td>65.5%</td>
</tr>
<tr>
<td>Vascular</td>
<td>10.9%</td>
</tr>
<tr>
<td>Congenital</td>
<td>8.0%</td>
</tr>
<tr>
<td>Trauma</td>
<td>5.5%</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>4.1%</td>
</tr>
<tr>
<td>Degenerative</td>
<td>3.5%</td>
</tr>
<tr>
<td>Infection</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Animal Models of Epilepsy

In order to enhance the understanding about the mechanisms of pharmaco-resistance in epilepsy, studies on brain tissue from drug-resistant patients and suitable experimental models of intractable epilepsy are mandatory. Common
pathological features between the human condition and the animal models may indicate a fundamental involvement of the given pathology in the process of epileptogenesis. New or improved animal models of epilepsy play an important role in understanding the basic mechanism of epilepsy.

An ideal model of epilepsy should meet the following requirements:

- Development of spontaneously occurring recurrent seizures
- Seizure type similar in clinical phenomenology to those occurring in human epilepsy
- An aged-dependent onset of epilepsy as in GTCS in man
- The clinical seizures should be accompanied by epileptic form activity in the electroencephalogram
- Pharmacokinetics of antiepileptic drugs similar to those in human thus, allowing the maintenance of effective drug levels during chronic treatment
- Effective plasma concentrations of antiepileptic drugs similar to those required for controlling the particular seizure type in humans.

Though no present model is ideal, genetic models of epilepsy resembles idiopathic epilepsy in humans more closely than any other experimental model.

The models available for the screening the antiepileptic activity may be classified as:

(i) Genetic animal models
(ii) Electrically-induced seizure models
(iii) Chemically-induced seizure models

**Genetic Models**

Though rarely used in preclinical testing, these models have a good potential for AEDs development. The reason for this limitation could be non availability of sufficient number of homozygotes; long lengths of time involved, and barring few exceptions, their unsuitability for acute studies. They are classified as (Table): Spontaneously occurring seizures and reflex seizures.
### Table: Genetic models of epilepsy

<table>
<thead>
<tr>
<th>EPILEPSY</th>
<th>SPONTANEOUSLY OCCURRING SEIZURES</th>
<th>REFLEX SEIZURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTCS</td>
<td>Beagle dogs; Quaking mice; BIO86.93 mutant hamsters; C57BL/10 Bg mice</td>
<td>Baboons(^a), Domestic fowl(^d), DBA/2 mice(^b), Genetically epilepsy prone rat (GEPR)(^b), Mongolian gerbil(^a,b,c), Papio papio(^a), SJL/J(^b)</td>
</tr>
<tr>
<td>Absence</td>
<td>Sprague-Dawley, Wistar rats; Totterer mice; Lethargic mice</td>
<td>Baboons(^a), Mongolian gerbil(^a,b,c)</td>
</tr>
<tr>
<td>Focal</td>
<td>Beagle dogs; Sprague-Dawley, Wistar rats</td>
<td>El mouse</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Quaking mice; BIO86.93 mutant hamsters</td>
<td></td>
</tr>
<tr>
<td>Complex partial with secondary generalization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stimuli: \(^a\) Photic; \(^b\) Audiogenic; \(^c\) air blast (average pressure 5-10 bars); \(^d\) Vestibular

### Chemically-induced seizure models

Innumerable chemicals and drugs at toxic doses are capable of inducing seizures in animals. These chemoconvulsants may be administered either chemically or tropically.

A. Systemically administered chemoconvulsants:

- GABA antagonists: Pentylenetetrazole (PTZ); Benzylpenicillin; Bicuculline; Picrotoxin
- GABA synthesis inhibitors: D-penicillamine; Isoniazid; Thiosemicarbazide
- Glutamic acid decarboxylase antagonist: 3-mercaptopropionic acid
- GABAergic neurotransmission inhibitor: Gamma-hydroxybutyric acid; Gamma-butyrolactone
- Inverse benzodiazepine receptor agonist: β-carbolines (methyl-β-carboline-3-carboxylate); DMCM; FG 7142
- Glycine antagonist: Strychnine
Excitatory amino acid agonist: Kainic acid
Cholinomimetic drugs: Pilocarpine

B. Tropical convulsants:
- Alumina cream
- Cobalt
- Tungstic acid
- Premarin

C. Others (focal application):
- Penicillin
- Kainic acid
- Quinolinic acid

scPTZ (Sub-cutaneous Pentylenetetrazol [Metrazol]) Test:

scPTZ was conducted by administering PTZ dissolved in 0.9% sodium chloride solution in the posterior midline of the animals. A minimal time of 30min subsequent to s.c. administration of PTZ was used for seizure detection. Protection was referred to as the failure to observe an episode of clonic spasms of at least 5s duration during this time period.

Subcutaneous injection of the convulsant pentylenetetrazol produces clonic seizures in laboratory animals. The scPTZ test detects the ability of a test compound to raise the seizure threshold of an animal and thus protect it from exhibiting a clonic seizure.

A scPTZ dose of 85mgkg⁻¹ administered subcutaneously to mice causes seizures in more than 97% of the animals. This is called Convulsive dose-97 (CD₉₇: 85mgkg⁻¹). The animals were pretreated with various doses of the test compounds. The PTZ is injected into the loose fold of the skin in the midline of the neck and observed for the next 30minutes for the presence or absence of seizure. An episode of clonic spasms, approximately 3-5seconds, of the fore and/or hind limbs, jaw, or vibrissae was taken as the end point. Animals which did not meet this criterion were considered protected[6,7].
Electrically-induced seizure models

Maximal Electroshock Seizure (MES) test\textsuperscript{4,5}:

It is used to evaluate the inhibitory activities of the drugs on supramaximal electroshock on rats and mice. A current, generally 50mA in mice, 150mA in rats for 0.2sec is applied by means often electro-convulsimeter via ear or corneal electrodes. The end point is tonic hind limb extension. A disadvantage is that it cannot be used to screen the drugs that are not potent enough to raise the seizure threshold above 50mA (in mice) or 150mA (in rats).

Different types of epilepsies i.e. grandmal, petitmal or psychomotor type have been studied in laboratory animals. For screening of anticonvulsant activity of the compounds the MES method was used to induce convulsions in animal and represents grandmal type of epilepsy.

In MES convulsions electroshock applied through the corneal electrodes and through optic stimulation cortical excitation is produced. The MES convulsions are divided into five phases as

1. tonic flexion
2. tonic extensor
3. clonic convulsions
4. stupor and
5. recovery or death

A substance is known to possess anticonvulsant property if it reduces or abolishes the extensor phase of MES convulsions.
Experimental studies

Animals: Swiss male albino mice of both sexes weighing 25-30 g, procured from the Central Animal House Facility of Jamia Hamdard, New Delhi were used. The animals were housed in polypropylene cages and kept under controlled environmental conditions (temperature: 22-29°C, natural light dark cycle). The mice were maintained on standard pellet feed (Amrut Laboratory rat and mice feed, Navmahrashtra Chakan Oil Mills Ltd., Pune) and water ad libitum. All experiments were performed during the daytime on healthy animals.

Equipments: Electro-convulsimeter

Standard drug: Phenytoin, 30 mg kg\(^{-1}\) body weight

Test Compound: 30, 100 and 300 mg kg\(^{-1}\) body weight

Route of administration and dosage form: All the test compounds and standard drug were administered i.p.

Method Used:

A. Electrically induced model:

(i) Maximum electroshock seizure test (MES)\(^{4,8}\):

Maximal electroshock seizure was elicited with a 60 cycle altering current of 50 mA intensity delivered for 0.25 s via ear clip electrodes. Animals were previously given the test drug i.p. Abolition of the hind limb tonic extension spasm was recorded as the anticonvulsant activity. In preliminary screening, each compound was administered through an i.p. injection at three dose levels (30, 100 and 300 mg kg\(^{-1}\) body mass) and the anticonvulsant activity was assessed after 0.5 h and 4 h intervals of administration.
B. Chemically induced model:

(i)  *scPTZ (Sub-cutaneous Pentylene tetrazol {Metrazol}) Test*[^9]:

*scPTZ* was conducted by administering PTZ dissolved in 0.9% sodium chloride solution in the posterior midline of the animals. A minimal time of 30min subsequent to *s.c.* administration of PTZ was used for seizure detection. Protection was referred to as the failure to observe an episode of clonic spasms of at least 5s duration during this time period. During study each compound was administered through an *i.p.* injection at three dose levels (30, 100 and 300mgkg^{-1} body mass) and the anticonvulsant activity was assessed after 0.5h and 4h intervals of administration.
1.4.2.2. Motor Impairment Study
To assess a compound’s undesirable side effect (toxicity), animals are monitored for overt signs of impairment neurological or muscular function. Minimal motor impairment is measured in mice by the rotarod test.

The Rotarod test is a performance test based on a rotating rod with forced motor activity being applied, usually by a rodent. This measures parameters such as riding time (seconds) or endurance. This is used to measure the effect of experimental drugs by evaluating balance and coordination of the animals under study.

The test involves a rodent being placed on a horizontally oriented, rotating cylinder (rod) suspended above a cage floor, (not high enough to injure the animal, but high enough to induce avoidance of fall). Rodents naturally try to stay on the rotating cylinder, or rotarod, and avoid falling to the ground. The length of time that a given animal stays on this rotating rod is a measure of their balance, coordination, physical condition, and motor-planning. The speed of the rotarod is mechanically driven, and may either be held constant, or accelerated.

The advantage of this test is that it creates a discretely measurable, continuous variable (length of time) that can be used for statistical purposes to quantify the effects of different drugs, conditions, and procedures.

Because of concern for impairment in human motor behavior from the use of prescription medications, the rotarod test is frequently used in early stages of drug development to screen-out drugs that might later cause impairment in human driving, etc., that might not be detected epidemiologically in the human population for a very long time. The test may be useful as a sensitive indicator of trauma induced by brain injury to laboratory rats.
Experimental studies

Animals: Swiss male albino mice of both sexes weighing 25-30 g, procured from the Central Animal House Facility of Jamia Hamdard, New Delhi were used. The animals were housed in polypropylene cages and kept under controlled environmental conditions (temperature: 22-29°C, natural light dark cycle). The mice were maintained on standard pellet feed (Amrut Laboratory rat and mice feed, Navmahrashtra Chakan Oil Mills Ltd., Pune) and water ad libitum. All experiments were performed during the daytime on healthy animals.

Equipments: Knurled plastic rod

Standard drug: Phenytoin, 30mgkg⁻¹ body weight

Test Compound: 30, 100 and 300mgkg⁻¹ body weight

Route of administration and dosage form: All the test compounds and standard drug were administered i.p.

Method Used: Rotarod test

In that test mice were trained to stay on the knurled plastic rod having diameter of 3.2cm. Normal mice could maintain equilibrium on the rotating rod for longer period of time. The neurotoxicity was indicated by inability of mice to maintain equilibrium on the rod for at least one minute in each of the three trials. The dose which impairs the ability of 50% of the animals to remain on the revolving rod was considered the end point. Each compound was administered through an i.p. injection at three dose levels (30, 100 and 300 mgkg⁻¹ body mass) and the neurotoxicity was assessed after 0.5h and 4h intervals of administration.
1.4.2.3. CNS depressant Activity
Animal models of depression are research tools used to find out the effect of antidepressants under study. They are also used to find out depressive illness, if any.

Introduction

Depression, a common psychiatric disorder, indicated by symptoms like deficits of cognitive, psychomotor, and emotional processes. The illness can be referred to a wide variety of abnormal variations in an individual's mood, which is characterized by periods of depressed mood, profound sadness, or loss of interest in activities (Anhedonia). The negative moods caused by depression significantly interfere with the normal functional ability of affected people, and the symptoms include a persistent sad or empty mood, feeling of hopelessness and worthlessness; changes in sleep and appetite, difficulty of concentrating and making decisions, and recurring thoughts of death or suicide.

Modeling depression in animals

It is difficult to develop an animal model that perfectly reproduces the symptoms of depression in patients. Animals lack self-consciousness, self-reflection, and consideration; moreover, hallmarks of the disorder such as depressed mood, low self-esteem or suicidality are hardly accessible in non-humans. However, depression, as other mental disorders, constitutes of endophenotypes that can be reproduced independently and evaluated in animals. An ideal animal model offers an opportunity to understand molecular, genetic, and epigenetic factors that may lead to depression. By using animal models, the underlying molecular alterations and the causal relationship between genetic or environmental alterations and depression can be examined, which would afford a better insight into pathology of depression. In addition, animal models of depression are indispensable for identifying novel therapies for depression.

Endopheno types in animal model of depression

The following endopheno types have been described:
- **Anhedonia**: The loss of interest is a core symptom of depression. Anhedonia in rodents can be assessed by sucrose preference or by intracranial self-stimulation.

- **Behavioral despair**: Behavioral despair might be assessed with tests such as the forced-swimming test or the tail suspension test.

- **Changes in appetite or weight gain**: Depression is often associated with changes in appetite or weight gain, which is easily measured in rodents.

- **Neuroanatomy**: Depressed subjects display decreased hippocampal volume and rodents exposed to chronic stress or excess glucocorticoids exhibit similar signs of hippocampal loss of neurons and dendritic atrophy.

- **Neuroendocrine disturbances**: Disturbances of the hypothalamic–pituitary–adrenal axis (HPA) are one of the most consistent symptoms in major depression. The functionality of the HPA can be assessed by dexamethasone suppression test.

- **Alterations in sleep architecture**: Disturbances in the circadian rhythm and especially in the sleep architecture are often observed in depressed. In rodents, it is accessible via electroencephalography (EEG).

- **Anxiety-related behavior**: Anxiety is a symptom with high prevalence in depression. Therefore, animal models of depression often display altered anxiety-related behavior.

### CNS depressant screening tests:

They are classified as:

1. Despair based: Example Forced Swimming test
2. Reward-based: Example Sucrose preference test
3. Anxiety Based: Example Elevated plus maze test

#### Forced-swimming test

The forced-swimming test (FST) is based on the observation that animals develop an immobile posture in an inescapable cylinder filled with water. In this test, immobility is interpreted as a passive stress-coping strategy or depression-like behavior (behavioral despair). After antidepressant administration, the animals will actively perform escape-directed behaviors with longer duration than animals with control
saline treatment. FST is the most widely used tool in depression research, more specifically as a screen for acute antidepressants.

The advantages of FST are that it is low-costing and is a fast and reliable tool, easy to handle and has proven its reliability across laboratories, for testing potential antidepressants activities with a strong predictive validity. Besides, it allows rapid screening of large numbers of drugs. The major disadvantages of FST are that it has poor face and construct validities. The test is sensitive to acute treatment only, and its validity for non-monoamine antidepressants is uncertain.
Experimental studies

Animals: Swiss male albino mice of both sexes weighing 25-30g, procured from the Central Animal House Facility of Jamia Hamdard, New Delhi were used. The animals were housed in polypropylene cages and kept under controlled environmental conditions (temperature: 22-29°C, natural light dark cycle). The mice were maintained on standard pellet feed (Amrut Laboratory rat and mice feed, Navmahrashtra Chakan Oil Mills Ltd., Pune) and water ad libitum. All experiments were performed during the daytime on healthy animals.

Equipments: Glass chamber

Standard drug: Carbamzaepine, 100mgkg⁻¹ body weight

Test Compound: 100mgkg⁻¹ body weight

Route of administration and dosage form: All the test compounds and standard drug were administered i.p.

Method Used: Porsolt's swim pool test¹⁴

Male albino mice are placed in a chamber (diameter 45cm, height: 20cm) containing water up to a height of 15cm at 25±2°C. Two swim sessions are conducted, an initial 15min pre-test, followed by a 5min test session 24h later. The animals are administered an i.p. injection (100 mgkg⁻¹) of the test compounds 30min before the test session. The period of immobility (passive floating without struggling, making only those movements which are necessary to keep its head above the surface of water) during the 5min test period are measured.
4.2.4. Table
Table 1: Anticonvulsant, neurotoxicity screening and CNS depression study of compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Anticonvulsant activity</th>
<th>Neurotoxicity screening</th>
<th>CNS depression study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MES</td>
<td>scPTZ</td>
<td>NT</td>
</tr>
<tr>
<td></td>
<td>After 0.5h</td>
<td>After 4h</td>
<td>After 0.5h</td>
</tr>
<tr>
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<td>300</td>
<td>300</td>
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<tr>
<td>Phenytoin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30</td>
<td>30</td>
<td>(-)</td>
</tr>
<tr>
<td>Carbamazepine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Control</td>
<td>58.17±1.01***</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Doses of 30, 100, 300 mg/kg were administered i.p. Test compounds were suspended in 0.5% methylcellulose/water mixture or in polyethylene glycol (PEG). Figures in the table indicate the minimum dose with bioactivity demonstrated in half or more of the mice. The dash (-) indicates the absence of activity at maximum dose administered (300 mg/kg). X denotes not tested.

<sup>b</sup>Data from references.<ref>

<sup>c</sup>Dose= 300 mg/kg; n=6; ***p<0.001, Data were analysed by unpaired students "t" test
Table 2: Anticonvulsant, neurotoxicity screening and CNS depression study of compounds HIBa-a.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Anticonvulsant activity</th>
<th>Neurotoxicity screening</th>
<th>CNS depression study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MES After 0.5h</td>
<td>scPTZ After 4h</td>
<td>NT After 0.5h</td>
</tr>
<tr>
<td>HIBa</td>
<td>100</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>HIBb</td>
<td>100</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>HIBc</td>
<td>30</td>
<td>100</td>
<td>100</td>
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<td>HIBd</td>
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<td>HIBe</td>
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<td>-</td>
</tr>
<tr>
<td>HIBf</td>
<td>(-)</td>
<td>(-)</td>
<td>-</td>
</tr>
<tr>
<td>HIBg</td>
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<td>100</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Doses of 30, 100, 300mgkg⁻¹ were administered i.p. Test compounds were suspended in 0.5% methylcellulose/water mixture or in polyethylene glycol (PEG). Figures in the table indicate the minimum dose with bioactivity demonstrated in half or more of the mice. The dash (-) indicates the absence of activity at maximum dose administered (300mgkg⁻¹). X denotes not tested.
*Data from references
**Dose= 300mgkg⁻¹; n=6; ***p<0.001. Data were analysed by unpaired students “t” test
Table-3: Anticonvulsant, neurotoxicity screening and CNS depression study of compounds IVa-n.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Anticonvulsant activity</th>
<th>Neurotoxicity screening</th>
<th>CNS depression study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MES</td>
<td>scPTZ</td>
<td>NT</td>
</tr>
<tr>
<td></td>
<td>After 0.5h</td>
<td>After 4h</td>
<td>After 0.5h</td>
</tr>
<tr>
<td>IVa</td>
<td>100</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>IVb</td>
<td>100</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>IVc</td>
<td>30</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IVd</td>
<td>100</td>
<td>100</td>
<td>X</td>
</tr>
<tr>
<td>IVe</td>
<td>30</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>IVf</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>IVg</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IVh</td>
<td>100</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>IVi</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IVj</td>
<td>300</td>
<td>300</td>
<td>X</td>
</tr>
<tr>
<td>IVk</td>
<td>30</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IVl</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IVm</td>
<td>300</td>
<td>(-)</td>
<td>X</td>
</tr>
<tr>
<td>IVn</td>
<td>300</td>
<td>300</td>
<td>X</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>30</td>
<td>30</td>
<td>(-)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>30</td>
<td>100</td>
<td>(-)</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Doses of 30, 100, 300mgkg weren administered i.p. Test compounds were suspended in 0.5% methylcellulose/water mixture or in polyethylene glycol (PEG). Figures in the table indicate the minimum dose with bioactivity demonstrated in half or more of the mice. The dash (-) indicates the absence of activity at maximum dose administered (300mgkg). X denotes not tested.

Data from references. Data were analysed by unpaired students "t" test.
1.4.2.5. References


