A facile L-serine catalysed asymmetric synthesis of pharmacologically important heterocycles derivatives-pyrimidin-one/pyrimidine-thione
3.1 Introduction

Multi-component reactions (MCRs) in recent era are the methods of choice in synthetic organic chemistry, as they possess all the features that contributes to an ideal synthesis with high atom efficiency, time and energy reduction, environment friendly and at the same time offering a targeted and diversity oriented synthesis.\(^1\) Biginelli reaction is one of the classical efficient multi-component reactions involving aldehyde, urea/thiourea with C-H activated compounds.\(^{1a}\) Biginelli reaction prompted the synthesis of a number of biologically active scaffolds like octahydroquinazolinone/thione, pyrimido [4,5-\(d\)] pyrimidines, chromeno pyrimidine-2, 5-dione and thioxo chromeno pyrimidin-5-one derivatives which possesses pyrimidin-one/pyrimidine-thione as the main skeleton.

Pyrimido pyrimidines are basically annulated uracils which are of great interest, especially derivatives of pyrimido pyrimidine are known to exhibit a wide spectrum of pharmacological activities as they possess potent inhibitory properties regarding the tyrosine kinase domain of epidermal growth factor receptor,\(^2\) in 5-phosphoribo-syl-1-pyrophosphate synthetase\(^3\) and dihydrofolate reductase.\(^4\) These compounds are well known for their antitumour,\(^5\) antiviral,\(^6\) antioxidant,\(^7\) antibacterial\(^8\) and hepatoprotective properties.\(^9\) Pyrido pyrimidines are also known as analgetics,\(^10\) CNS depressent activities,\(^11\) while pyrano pyrimidines has antifungal and antibacterial property.\(^12\) Considering coumarins which also exhibit various physiological activities,\(^13\) the fusion of it with the pyrimidine fragment thus, gives rise to compounds with enhanced biological property.\(^14\) Octahydroquinazolinone derivatives are also an important class of compounds and have attracted attention in recent years owing to their potential antibacterial activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa,\(^15\) and also as a calcium antagonist.\(^16\)

Owing to the importance of these structurally diverse molecules, a number of synthetic protocols\(^{15,17}\) have been reported. Most of the methods in past are in acidic medium,\(^18\) under microwave irradiation,\(^19\) in refluxing solvent like benzene, xylene with azeotropic water removal,\(^20\) refluxing in ethanol/acetic acid mixtures etc.\(^{21}\)

Yarım et al. employed strong acidic condition to synthesise octahydro quinazoline-2,5-diones (136) by condensing 134 or 135 with 5,5-dimethyl-1,3-cyclohexanedione (56) and appropriate aromatic aldehydes (55) in compliance with
Biginelli reaction (Scheme 3.1). The group tested the calcium antagonist activity of the compounds \textit{in vitro} on isolated rat ileum and lamb carotid artery.\(^{16}\)

\[ \text{Scheme 3.1 Synthesis of octahydroquinazoline-2,5-diones.} \]

Gupta and co-workers achieved a set of reaction under various reaction conditions to synthesise diverse heterocyles. They performed the condensation of 137, urea/thiourea (138/139) and aldehyde (7) in the mole ratio of 1:1:3 in solvent-free condition in presence of NiCl$_2$/KI to afford 1,5-diaryl-3-thioxo-2,4-diazaspiro [5.5] undecane-7,11-dione/1,5-diaryl-2,4-diazaspiro[5.5]undecane-3,7,11-trione analogues and 7,11-diaryl-9-thioxo-2, 4, 8, 10-tetraazaspiro [5.5] undecane-1, 3, 5,-trione /7, 11-diaryl-2, 4, 8, 10-tetraazaspiro [5.5] undecane-1, 3, 5, 9-tetraone analogues (140) respectively (Scheme 3.2). The group also performed the condensation of 137, 138/139 and substituted aldehyde (7) in the mole ratio of 1:1:1 in refluxing methanol to afford 4-aryl / heteroaryl-2-thioxo-1, 2, 3, 4, 5, 6, 7, 8- octahydroquinazolin -5-one, 4-aryl / heteroaryl -1,2, 3, 4, 5, 6, 7, 8-octahydroquinazoline -2, 5-dione analogues (141) and 5-aryl-7-thioxo-1, 2, 3, 4, 5, 6, 7, 8-octahydropyrimido[4,5-\textit{d}]pyrimidine-2,4-dione / 5-aryl-1, 2, 3, 4, 5, 6, 7, 8-octahydropyrimido[4,5-\textit{d}]pyrimidine-2, 4, 7-trione analogues (142) respectively\(^{22}\) (Scheme 3.3).

\[ \text{Scheme 3.2 Synthesis of Spiro Pyrimidinethiones/SpiroPyrimidinones.} \]
Scheme 3.3 Synthesis of Quinazolinethiones/Quinazolinones and Pyrimidopyrimidines.

An attractive method for the synthesis of 3-isopropyl-4-aryl-1,4,5,7-tetrahydropyrazolo[3,4-d]pyrimidine-6-thiones and 7-aryl-5-thioxo-4,5,6,7-tetrahydro-3H-thiazolo[4,5-d]pyrimidin-2-ones were reported by Akbari et al.\textsuperscript{23} The Condensation of 5-isopropyl-2,4-dihydro-3-pyrazolone (143) or 2,4-thiazolidine (144) with various aromatic aldehydes (55) by Knoevenagel condensation in the presence of piperidine under reflux condition resulted in the intermediate 4-benzylidene-5-isopropyl-2,4-dihydro-3-pyrazolone (145) or benzylidene-thiazolidine-2,4-dione (146) respectively. After refluxing the intermediate with thiourea (139) in ethanolic HCl it resulted in the formation of 3-isopropyl-4-aryl-1,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidine-6-thiones (147) and 7-aryl-5-thioxo-4,5,6,7-tetrahydro-3H-thiazolo[4,5-d]pyrimidin-2-ones (148) respectively (Scheme 3.4). The group also tested the antibacterial and antifungal activity of the newly synthesised compounds.

Scheme 3.4 Synthesis of substituted pyrazolo[3,4-d]pyrimidine and thiazolo[4,5-d] pyrimidine derivatives.
Recently, Abdolmohammadi and co-workers synthesised quinazolinones (150) and chromeno[4,5-d]pyrimidinones (151) from the reaction of aryl aldehydes (55), urea/thiourea (138/139) and active methylene compounds (dimedone (56)/4-hydroxycoumarin(149)) using nano-sized CuI particles under solvent-free conditions (Scheme 3.5). The protocol used a recyclable catalyst, affording good yields of the products.

**Scheme 3.5** Synthesis of quinazolinone and chromeno[4,5-d]pyrimidinone derivatives.

A number of effective methods are available in the literature, but although they have some merits of their own, they are hampered by use of toxic reagents, higher boiling point organic solvents, longer reaction time, elevated reaction temperature and poor yield. Thus, a better strategy to synthesise these bio-active compounds is essential. The importance of the new method will be enhanced many fold if an asymmetric centre can be induced in these pyrimidinone/pyrimidine-thione derivatives. As chirality is a vital factor in molecular recognition it finds key applications in the fields of chemistry, biology and medicine. Although L-proline a chiral organo-catalyst was employed in the synthesis of pyrimido [4,5-d] pyrimidine-2-(1H)-one, there was no report of enantioselective induction.

L-serine a chiral organo-catalyst and its derivatives have been employed in a number of synthesis including chiral synthesis. L-serine is a readily available, cost
efficient amino-acid which can be used as a catalyst. Thus, this homogenous catalyst can be exploited for the synthesis of diverse heterocycles.

In this chapter we have screened the catalytic efficiency of this most neglected amino acid for the synthesis of pyrimidin-one/pyrimidine-thione derivatives which was accomplished by the condensation of substituted aryl aldehydes, urea/thiourea with C-H activated compounds. To our delight, we found that L-serine was an effective catalyst for the synthesis of a library of compound with great enantioselectivity.

3.2 Results and Discussion

In the previous chapters, we have discussed on the efficiency of L-proline, an amino acid in enantioselective synthesis. In this chapter the focus is on the efficiency of another amino acid L-serine as catalyst in the enantioselective synthesis of varied heterocycles. The three-component Biginelli condensation of aldehyde (7), urea/thiourea (138/139) and various C-H activated compounds like dimedone (56) /cyclohexan-1,3-dione (93) / barbituric acid (130) / 4-hydroxy coumarin (149) /5-methyl-1H-pyrazol-3(2H)-one (152) at 40°C in presence of 15 mol% of L-serine in ethanol:water (1:1) solvent system was found to efficiently afford the quinazolinones (153/154), pyrimido[4,5-d]pyrimidine-trione/thiones (155), chromeno[d]pyrimidinones/thiones (156), pyrazolo[3,4-d]pyrimidinone/thione (157) respectively within 4 hrs time (Scheme 3.6).

In our endeavour to develop L-serine catalysed MCRs that can impart stereoselectivity, we performed a model reaction involving 4-Chloro bezaldehyde (7a) (2.0 mmol), urea (138) (2.5 mmol) and 5, 5-dimethylcyclohexane-1, 3-dione (56) (2.0 mmol) in presence of catalytic amount of L-serine. Stirring at room temperature in EtOH for 12 hrs resulted in the formation of the desired product, 4-(4-chlorophenyl)-7,7-dimethyl-3,4,7,8-tetrahydro quinazoline-2,5(1H,6H)-dione (153a) with 55% yield. In order to increase the efficiency of the reaction the catalyst loading was increased to 10 mol%, which resulted in enhance yield of 65%. Water is regarded as a green solvent thus we performed the reaction in aqueous medium with the same reaction condition which resulted in only a little increase in efficiency of the reaction resulting in reduced time of reaction to 8 hrs and yield to 69%. In quest of more efficient protocols we performed the model reaction in 1:1 ratio of water:ethanol mixture as solvent system
which resulted in 83% yield with shorter reaction time of 6 hrs. To raise the percentage yield, we then examined the reaction in 15 mol% catalyst loading and stirred the reaction mixture to a temperature of 40°C, which gave a drastic increase in the product formation with yield of 93% only in 4 hrs (Table 3.1). In course of further optimisation it was found that increase in the reaction temperature resulted in undesired product formation, even further increase in catalyst loading did not give any better results. It was also observed that in absence of any catalyst upon prolonged heating upto 18 hrs resulted only in trace amount of product. Encouraged by this result, we performed the condensation of 4-Nitro benzaldehyde (7c) (2.0 mmol), thiourea (139) (2.5 mmol) and 5, 5-dimethylcyclohexane-1, 3-dione (56) (2.0 mmol) under identical conditions which also resulted excellent yield (92%) of the product (153c). The structures of the compounds formed were confirmed by $^1$H & $^{13}$C NMR, Mass and IR analyses.

![Scheme 3.6 Synthesis of pyrimidin-one/pyrimidine-thione derivatives.](image)

As our aim is to induce seteroselectivity in the synthesised compounds they were therefore subjected to HPLC analyses using a chiral column. To our delight, the reaction proceeded with excellent enantioselectivity. The HPLC analysis of 153a obtained from the model reaction was performed using chiral ADV column with 10%
isopropanol: hexane with a flow rate of 0.5 mL/min displayed two peaks at retention time: $t_R$ (major) 5.064 min, $t_R$ (minor) 5.909 min, area 97% and 03% respectively. Similarly, when the derivative 153c was screened for the enantioselectivity it also showed enantiomeric excess (ee) of 96% with major and minor peaks with retention time $t_R$ (minor) 3.355 min, $t_R$ (major) 4.041 min, area 98% and 02% respectively with eluent $i$-propanol : $n$-hexane = 07:43, at 25 °C, 254 nm, 0.5 mL/min flow rate.

**Table 3.1** Optimisation of the reaction condition for product 153a

<table>
<thead>
<tr>
<th>Product</th>
<th>Reaction Condition</th>
<th>Catalyst</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>153a</td>
<td>EtOH, 12 hrs, RT</td>
<td>No catalyst</td>
<td>0</td>
</tr>
<tr>
<td>153a</td>
<td>EtOH: H$_2$O, 18 hrs, 40°C</td>
<td>No Catalyst</td>
<td>Trace</td>
</tr>
<tr>
<td>153a</td>
<td>EtOH, 12 hrs, RT</td>
<td>L-serine (catalytic amount)</td>
<td>55</td>
</tr>
<tr>
<td>153a</td>
<td>EtOH, 12 hrs, RT</td>
<td>L-serine (10 mol %)</td>
<td>65</td>
</tr>
<tr>
<td>153a</td>
<td>H$_2$O, 8 hrs, RT</td>
<td>L-serine (10 mol %)</td>
<td>69</td>
</tr>
<tr>
<td>153a</td>
<td>EtOH: H$_2$O (1:1), 6 hrs, RT</td>
<td>L-serine (10 mol %)</td>
<td>83</td>
</tr>
<tr>
<td>153a</td>
<td>EtOH: H$_2$O (1:1), 4 hrs, 40°C</td>
<td>L-serine (15 mol %)</td>
<td>93</td>
</tr>
</tbody>
</table>

$^a$ Amount of materials in the reaction: 4-Chloro benzaldehyde (2.0 mmol), dimeredone (2.0 mmol), urea (2.5 mmol).

$^b$ Isolated yield.
To establish the scope of the method, a number of substituted aromatic aldehydes were used in the reaction. It was noted that substituent effect did not play much role as the same reaction condition afforded the desired product in percentage yields ranging from good to excellent. In presence of electron withdrawing or releasing substituent in the ortho-, meta- and para-positions reactions proceeded smoothly imparting great enantioselectivity. After successful asymmetric synthesis of quinazoline-2, 5(1H, 3H)-dione/thione derivatives (153 (a-d), 154 (a-b)), we extended our protocol to the synthesis of pyrimido [4, 5-d] pyrimidine, chromeno pyrimidine-2, 5-dione/thione and pyrazolo [3,4-d]pyrimidine derivatives. The same optimum reaction condition was employed for the synthesis of various derivatives which involved condensation of C-H active compounds viz. barbituric acid (130), 4-hydroxy coumarin (149), 5-methyl-1H-pyrazol-3(2H)-one (152) with urea/thiourea (138/139) and varying substituted aromatic aldehydes (7) for the Biginelli type reaction. All the synthesised compounds (155(a-d), 156(a-f), 157(a-d)) are summarised in Table 3.2, were obtained by simple filtration, washing with water and recrystallisation from EtOH, then was characterised by $^1$H & $^{13}$C NMR, Mass and IR analyses.

To check the enantioselectivity imparted in the synthesised compounds HPLC analyses were performed using Chiral ADV column with isopropanol and hexane as mobile phase with a flow rate of 0.5 mL/min which provided excellent result as listed in Table 3.2 showing the enantioselectivity upto 99% ee (compounds 153d, 155c). For the rest of the compounds enantiomeric excess (ee) was found to be in the range of to 81% ee to 98% ee. Compound 154b and 155a the 4-F and 3-F substituted compounds displayed a little less enantioselectivity as compared to other derivatives showing 66% ee and 74% ee, respectively.
Table 3.2 L-serine catalyzed synthesis of pyrimidin-one/pyrimidine-thione derivatives

![Chemical structures and reactions]

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
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<th>Product</th>
<th>Time(hrs)</th>
<th>Yield</th>
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<td>O</td>
<td></td>
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<tr>
<td>3</td>
<td>S</td>
<td></td>
<td></td>
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<td>92</td>
<td>96</td>
</tr>
<tr>
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<td>66</td>
</tr>
<tr>
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<td>O</td>
<td></td>
<td></td>
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<td>4</td>
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<td>74</td>
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<tr>
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<td>O</td>
<td></td>
<td></td>
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<td>4</td>
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<tr>
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<td></td>
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<tr>
<td>12</td>
<td>O</td>
<td></td>
<td></td>
<td>156b</td>
<td>4</td>
<td>83</td>
<td>90</td>
</tr>
</tbody>
</table>
Isolated yields

Products were characterized by $^1$H & $^{13}$C NMR, Mass and IR analyses, absolute configuration is not determined.

Enantiomeric excess (ee) was determined by chiral HPLC analysis.

The plausible mechanism is depicted in Scheme 3.7. The reaction presumably proceeds through the initial activation of the aldehyde A (7) by L-serine presumably leads to the formation of two enantiomeric intermediates B and B' of which one is formed in excess over the other. There by nucleophilic attack of the C-H activated group D (56 / 93 / 130 / 149 / 152 ) activated by L-serine takes place at the electrophilic carbon centre of the aldehyde of the intermediate C followed by subsequent addition of urea (138) / thiourea(139) (F) and intermolecular cyclisation afforded the final product H (153/154/155/156/157).
In conclusion, L-serine which is readily available, inexpensive amino-acid proved to be an efficient catalyst for the synthesis of a library of pyrimidin-one/thione derivatives. The advantages offered by this protocol are high yields of the product which is obtained by simple procedures like recrystallisation, short reaction time and induction of high enantioselectivity in the synthesised products. Thus, a new efficient asymmetric inductive synthetic protocol was developed.
3.3 Experimental Section

All chemicals and reagents commercially available were purchased from Merck, Sigma Aldrich and were used without further purification. Infrared (IR), $^1$H NMR, $^{13}$C NMR and mass analyses were performed to analyse the purity of the compound. IR spectra were recorded in KBr pellets on a Perkin Elmer Spectrum 400 FTIR instrument and the frequencies are expressed in cm$^{-1}$. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker Avance II-400 spectrometer in CDCl$_3$/DMSO-$d_6$ (Chemical shifts in δ with TMS as internal standard). Mass spectral data were obtained with a JEOL D-300 (ESI) mass spectrometer. Melting points were determined in open capillary tubes and are uncorrected. All reactions were monitored by thin layer chromatography (TLC) using precoated aluminum sheets (silica gel 60 F$_{254}$ 0.2-mm thickness). HPLC analyses were performed on Waters M515 series equipped with a Agela chiral ADV analytical column (5 μm, 1000 Å, 4.6x250 mm.). UV-detection at 254 nm was used to analyse the data. The analytical separation was carried out at 25°C using a mobile phase (A) of isopropanol and (B) of n-Hexane as eluent with flow rate 0.5 mL/min. All the solvents were HPLC-grade.

**General procedure for the synthesis pyrimidin-one/pyrimidine-thione derivatives (153(a-d), 154(a-b), 155(a-d), 156(a-f), 157(a-d))**

A mixture of aldehyde (7) (2.0 mmol), urea/thiourea (138/139) (2.5 mmol), 5,5-dimethylcyclohexane-1,3-dione (56) / cyclohexane-1,3-dione (93) / barbituric acid (130) / 4-hydroxy coumarin (149) / pyrazolone (152) (2.0 mmol) in EtOH:H$_2$O (1:1) 5 mL mixture was stirred at 40°C for appropriate time in the presence of L-serine (15 mol %). The completion of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was filtered and washed with water. The residue was then recrystallised from ethanol to obtain the pure product.
3.4 Physical, Spectral and Analytical data

4-(4-chlorophenyl)-7,7-dimethyl-3,4,7,8-tetrahydro quinazoline-2,5(1H,6H)-dione,(153a)

Appearance: Yellow solid.

Yield: 93%.

Mp: 303-305 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: t_R (major) 5.064 min, t_R (minor) 5.909 min, ee = 94%; IR ν_max (KBr): 3324, 3250, 2957, 1710, 1685, 1451, 1254 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ_H (ppm) 1.03 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 2.22-2.41(m, 4H, CH₂), 5.40 (s, 1H, 4H), 6.94 (d, 2H, J = 8Hz, Ar-H) , 7.15 (d, 2H, J=8Hz, Ar-H), 9.91 (s, 1H, NH), 11.81 (s, 1H, NH);¹³C NMR (100 MHz, CDCl₃): δ_C (ppm) 26.37, 28.56, 30.35, 31.36, 45.36, 45.98, 114.27, 127.14, 127.71, 128.28, 128.43, 133.66, 139.91, 167.98, 188.44; MS (ES⁺) calcd. for C_{16}H_{17}ClN₂O₂: 304.10 found m/z 305.40 (M + H)⁺.

4-(4-ethoxyphenyl)-7,7-dimethyl-3,4,7,8-tetrahydro quinazoline-2,5(1H,6H)-dione,(153b)

Appearance: White solid.

Yield: 86%.

Mp: 289-291 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: t_R (minor) 5.463 min, t_R (major) 6.043 min, ee = 81%; IR ν_max (KBr): 3328, 3245, 2954, 1701, 1687, 1458, 1251 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ_H (ppm) 1.02 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 2.22-2.41(m, 4H, CH₂), 5.40 (s, 1H, 4H), 6.94 (d, 2H, J = 8Hz, Ar-H) , 7.15 (d, 2H, J=8Hz, Ar-H), 9.91 (s, 1H, NH), 11.81 (s, 1H, NH);¹³C NMR (100 MHz, CDCl₃): δ_C (ppm) 26.37, 28.56, 30.35, 31.36, 45.36, 45.98, 114.27, 127.14, 127.71, 128.28, 128.43, 133.66, 139.91, 167.98, 188.44; MS (ES⁺) calcd. for C_{16}H_{17}ClN₂O₂: 304.10 found m/z 305.40 (M + H)⁺.
1.29 (t, 3H, J = 8 Hz, CH₃), 2.08-2.38 (m, 4H, CH₂), 3.88 (q, 2H, J = 8Hz, CH₂), 5.41 (s, 1H, 4H), 6.72 (d, 2H, J=8Hz, Ar-H) , 6.90 (d, 2H, J = 8Hz, Ar-H), 9.80 (s, 1H, NH), 11.88 (s, 1H, NH); ¹³C NMR(100 MHz, DMSO-d₆): δc (ppm) 14.93, 27.39, 29.69, 31.38, 46.41, 47.05, 63.92, 114.17, 115.77, 127.76, 132.02, 146.81, 156.94, 190.88 ;
MS (ES⁺) calcd. for C₁₈H₂₂N₂O₃: 314.16 found m/z 315.40 (M + H)⁺.

7,7-dimethyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one,(153c)

Appearance: White solid.

Yield: 92%.

Mp: 284-286 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column ), i-propanol : n-hexane = 07:43, 25 °C, 254 nm, 0.5 mL/min, retention times: t_R (major) 3.355 min, t_R (minor) 4.041 min, ee = 96 %; IR νmax (KBr): 3370, 3271, 2958, 1726, 1661, 1488, 1240 cm⁻¹; ¹H NMR (400 MHz ,CDCl₃): δH (ppm)  1.05 (s, 3H, CH₃), 1.17 (s, 3H, CH₃), 2.24-2.45 (m, 4H, CH₂), 5.48 (s, 1H, 4H), 7.18 (d, 2H, J=8Hz, Ar-H) , 8.07 (d, 2H, J=8Hz, Ar-H), 10.09 (s,1H,NH), 11.76 (s, 1H, NH); ¹³C NMR(100 MHz, CDCl₃): δC (ppm) 27.43, 29.54, 31.46, 33.23, 46.36, 46.95, 114.88, 123.52, 124.31,127.65, 130.51, 140.03, 146.06, 151.08, 163.16, 190.98 ; MS (ES⁺) calcd. for C₁₆H₁₇N₂O₅S: 331.10 found m/z 332.15 (M + H)⁺.

4-(3,4-dimethoxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one,(153d)

Appearance: White solid.

Yield: 94%.

Mp: 289-291 °C.
Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), *i*-propanol : *n*-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: *t_R* (major) 5.515 min, *t_R* (minor) 6.283 min, ee = 99 %; IR *ν*<sub>max</sub> (KBr): 3356, 3189, 2956, 1723, 1660, 1485, 1278 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-<sub>d6</sub>): *δ*<sub>H</sub> (ppm) 0.91 (s, 3H, CH<sub>3</sub>), 1.04 (s, 3H, CH<sub>3</sub>), 2.04-2.29 (m, 4H, CH<sub>2</sub>), 3.68 (s, 6H, CH<sub>3</sub>), 4.45 (s, 1H, 4H), 6.65-6.71 (m, 3H, Ar-H), 8.09 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> + DMSO-<sub>d6</sub>): *δ*<sub>C</sub> (ppm) 26.56, 28.79, 31.64, 39.15, 50.18, 55.04, 55.22, 55.26, 110.60, 111.73, 114.91, 119.77, 136.68, 147.70, 147.95, 162.00, 188.70, 195.87; MS (ES<sup>+</sup>) calcd. for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S: 346.14 found m/z 347.20 (M + H)<sup>+</sup>.

4-(4-chlorophenyl)-3,4,7,8-tetrahydroquinazoline 2,5(1H,6H)-dione,(154a)

Appearance: Off white solid.

Yield: 89%.

Mp: 260-262 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), *i*-propanol : *n*-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: *t_R* (major) 6.026 min, *t_R* (minor) 6.950 min, ee = 98 %; IR *ν*<sub>max</sub> (KBr): 3224, 3093, 2951, 1698, 1615, 1486, 1242 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> + DMSO-<sub>d6</sub>): *δ*<sub>H</sub> (ppm) 1.85-1.95 (m, 2H, CH<sub>2</sub>), 2.21-2.26 (m, 2H, CH<sub>2</sub>), 2.40-2.43 (m, 2H, CH<sub>2</sub>), 5.47 (s, 1H, 4H), 7.06 (d, 2H, *J*=8 Hz, Ar-H), 7.17 (d, 2H, *J*=8 Hz, Ar-H), 7.95 (s, 2H, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> + DMSO-<sub>d6</sub>): *δ*<sub>C</sub> (ppm) 24.72, 31.74, 37.15, 64.23, 104.93, 132.24, 132.80, 134.51, 134.81, 135.20, 142.96, 148.83, 150.44, 195.50; MS (ES<sup>+</sup>) calcd. for C<sub>14</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>: 276.07 found m/z 277.15 (M + H)<sup>+</sup>.
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**4-(3-fluorophenyl)-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione, (154b)**

![Chemical Structure](image)

Appearance: Yellow solid.

Yield: 84%.

Mp: 281-283°C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: $t_R$ (major) 6.733 min, $t_R$ (minor) 8.823 min, ee = 66%; IR $\nu_{\text{max}}$ (KBr): 3330, 3068, 2958, 1691, 1601, 1484, 1242 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ (ppm) 1.87-1.96 (m, 2H, CH$_2$), 2.15-2.20 (m, 2H, CH$_2$), 2.38-2.48 (m, 2H, CH$_2$), 5.84 (s, 1H, 4H), 6.72-7.18 (m, 4H, Ar-H), 8.24 (s, 2H, NH); $^{13}$C NMR (100 MHz, CDCl$_3$ + DMSO-$d_6$): $\delta_C$ (ppm) 20.35, 28.57, 36.50, 59.47, 100.82, 114.60, 115.23, 123.65, 128.78, 147.42, 148.03, 160.34, 162.92, 195.90; MS (ES$^+$) calcd. for C$_{14}$H$_{13}$FN$_2$O$_2$: 261.21 found m/z 261.21 (M + H)$^+$.  

**5-(4-fluorophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione, (155a)**

![Chemical Structure](image)

Appearance: Yellow solid.

Yield: 90%.

Mp: 279-281°C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: $t_R$ (minor) 4.877 min, $t_R$ (major) 5.284 min, ee = 74%; IR $\nu_{\text{max}}$ (KBr): 3366, 3260, 2851, 1742, 1679, 1400, 1236 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 5.22 (s, 1H, 4H), 7.30 (d, 2H, J = 8.0 Hz, Ar-H), 8.22 (d, 2H, J = 8.0 Hz), 11.16 (s, 1H, NH), 11.27 (s, 1H, NH), 11.41 (s, 1H, NH), 11.51 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta_C$ (ppm) 56.96, 60.22, 113.97, 115.27, 129.15, 129.48, 136.36, 148.59, 150.18, 160.05, 162.87, 163.37; MS (ES$^+$) calcd. for C$_{12}$H$_9$FN$_4$O$_3$: 276.07 found m/z 277.16 (M + H)$^+$. 

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5-(3,4,5-trimethoxyphenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione, (155b)

Appearance: Yellow solid.
Yield: 92%.
Mp: 287-289 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 03:47, 25 °C, 254 nm, 0.5 mL/min, retention times: t_R (major) 6.456 min, t_R (minor) 7.080 min, ee = 85%; IR ν_max (KBr): 3395, 3265, 2865, 1698, 1623, 1490, 1256 cm^{-1}; \textsuperscript{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 5.72 (s, 1H, 4H), 7.79 (s, 2H, Ar-H), 8.21 (s, 2H, NH), 11.21 (s, 1H, NH), 11.34 (s, 1H, NH); \textsuperscript{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 51.82, 55.83, 60.14, 112.48, 117.03, 127.39, 141.78, 150.02, 151.82, 155.12, 161.98, 163.62; MS (ES\textsuperscript{+}) calcd. for C\textsubscript{15}H\textsubscript{16}N\textsubscript{4}O\textsubscript{6}: 348.11 found m/z 349.16 (M + H\textsuperscript{+}).

5-(3-fluorophenyl)-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione, (155c)

Appearance: Off white solid.
Yield: 93%.
Mp: 276-278 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 08:42, 25 °C, 254 nm, 0.5 mL/min, retention times: t_R (major) 4.321 min, t_R (minor) 4.662 min, ee = 99 %; IR ν_max (KBr): 3310, 3251, 2899, 1735, 1656, 1486, 1277 cm^{-1}; \textsuperscript{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 5.31 (s, 1H, 4H), 7.44-8.08 (m, 4H, Ar-H), 9.07 (s, 1H, NH), 11.40 (s, 1H, NH), 11.52 (s, 1H, NH), 11.75(s, 1H, NH); \textsuperscript{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 55.14, 60.31, 114.45, 116.18, 123.70, 130.59, 148.31, 160.46, 161.48, 163.10, 165.23, 177.14; MS (ES\textsuperscript{+}) calcd. for C\textsubscript{12}H\textsubscript{9}FN\textsubscript{4}O\textsubscript{2}S: 292.04 found m/z 293.08(M + H\textsuperscript{+}).
7-thioxo-5-(p-tolyl)-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione,(155d)

Appearance: Yellow solid.

Yield: 91%.

Mp: 266-268 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column ), \( i\)-propanol : \( n\)-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: \( t_R \) (minor) 4.734 min, \( t_R \) (major) 5.297 min, ee = 96%; IR \( \nu_{\text{max}} \) (KBr): 3375, 3199, 2938, 1712, 1658, 1433, 1298 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)+DMSO-\( d_6 \)): \( \delta_H \) (ppm) 2.43(s, m, 3H), 5.22 (s, 1H, \( 4H \)), 7.28 (d, 2H, \( J = 8.0 \) Hz, Ar-H), 8.13 (d, 2H, \( J = 8.0 \) Hz), 8.30 (s, 2H, NH), 11.28 (s, 1H, NH), 11.41 (s, 1H, NH); \(^{13}\)C NMR(100 MHz, CDCl\(_3\)+DMSO-\( d_6 \)): \( \delta_C \) (ppm) 21.36, 50.52, 61.37, 117.29, 128.68, 129.65, 133.81, 143.43, 161.59, 163.43, 167.41, 169.60 ; MS (ES\(^+\)) calcd. for C\(_{13}\)H\(_{12}\)N\(_4\)O\(_2\)S: 288.07 found \( m/z \) 289.16 (M + H)\(^+\).

4-(4-chlorophenyl)-3,4-dihydro-1H-chromeno[4,3-d] pyrimidine-2,5-dione,(156a)

Appearance: White solid.

Yield: 86%.

Mp: 244-246 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column ), \( i\)-propanol : \( n\)-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: \( t_R \) (major) 5.424 min, \( t_R \) (minor) 5.997 min, ee = 87 %; IR \( \nu_{\text{max}} \) (KBr): 3051, 2931, 1660, 1621, 1532, 1432, 1278 cm\(^{-1}\); \(^1\)H NMR (400 MHz,CDCl\(_3\)+DMSO-\( d_6 \)): \( \delta_H \) (ppm) 2.09 (s, 2H, NH), 6.23 (s, 1H, \( 4H \)), 7.05-7.88 (m, 8H, Ar-H); \(^{13}\)C NMR(100 MHz, CDCl\(_3\)+DMSO-\( d_6 \)): \( \delta_C \) (ppm) 35.73, 108.34, 115.4, 120.49, 122.90, 124.84, 127.94, 129.42, 132.60, 133.31, 135.85, 145.11, 157.53, 171.35, 174.17; MS (ES\(^+\)) calcd. for C\(_{17}\)H\(_{11}\)ClN\(_2\)O\(_3\): 326.05 found \( m/z \) 327.01 (M + H)\(^+\).
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4-(4-fluorophenyl)-3,4-dihydro-1H-chromeno[4,3-d]pyrimidine-2,5-dione, (156b)

Appearance: Off white solid.

Yield: 83%.

Mp: 258-260 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 04:46, 25 °C, 254 nm, 0.5 mL/min, retention times: t_R (major) 6.491 min, t_R (minor) 8.732 min, ee = 95%; IR ν_max (KBr): 3066, 2892, 1667, 1620, 1567, 1453, 1281 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ_H (ppm) 5.98 (s, 1H, 4H), 6.94-7.99 (m, 8H, Ar-H), 11.25 (s, 1H, NH), 11.47 (s, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): δ_C (ppm) 35.64, 103.91, 115.40, 115.62, 116.67, 116.84, 124.39, 124.98, 128.12, 130.84, 133.01, 144.54, 152.26, 152.51, 160.47, 162.91; MS (ES⁺) calcd. for C₁₇H₁₁FN₂O₃: 310.08 found m/z 311.00 (M + H)⁺.

4-(4-methoxyphenyl)-3,4-dihydro-1H-chromeno[4,3-d]pyrimidine-2,5-dione, (156c)

Appearance: Yellow solid.

Yield: 93%.

Mp: 264-266 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 04:46, 25 °C, 254 nm, 0.5 mL/min, retention times: t_R (minor) 5.198 min, t_R (major) 6.499 min, ee = 92%; IR ν_max (KBr): 3057, 2988, 1652, 1610, 1570, 1484, 1273 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ_H (ppm) 3.89 (s, 3H, CH₃), 6.35 (s, 1H, 4H), 6.80-8.19 (m, 8H, Ar-H), 9.87 (s, 2H, NH); ¹³C NMR (100 MHz, DMSO- d₆): δ_C (ppm) 35.09, 55.49, 104.19, 113.31, 114.28, 115.77, 118.01, 123.54, 123.85, 127.60, 129.49, 131.68, 152.13, 157.21, 164.12, 165.50; MS (ES⁺) calcd. for C₁₉H₁₄N₂O₄: 322.10 found m/z 321.20 (M + H)⁺.
4-(p-tolyl)-3,4-dihydro-1H-chromeno[4,3-d]pyrimidin-2,5-dione, (156d)

Appearance: White solid.

Yield: 86%.

Mp: 263-265 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: \( t_R \) (major) 4.502 min, \( t_R \) (minor) 5.181 min, ee = 83 %; IR \( \nu_{\text{max}} \) (KBr): 3051, 2998, 1662, 1620, 1567, 1493, 1281 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta_H \) (ppm) 2.26 (s, 3H, CH\(_3\)), 5.99 (s, 1H, 4\( H \)), 7.01-7.98 (m, 8H, Ar-\( H \)), 11.23 (s, 1H, NH), 11.45 (s, 1H, NH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta_C \) (ppm) 21.01, 35.85, 104.07, 116.64, 116.93, 124.38, 126.37, 129.22, 129.34, 130.24, 132.03, 132.83, 136.47, 152.27, 152.51, 165.73; MS (ES\(^+\)) calcd. for C\(_{18}\)H\(_{14}\)N\(_2\)O\(_3\): 306.10 found m/z 307.15 (M + H)\(^+\).

4-(4-chlorophenyl)-2-thioxo-3,4-dihydro-1H-chromeno[4,3-d]pyrimidin-5(2H)-one, (156e)

Appearance: Yellow solid.

Yield: 94%.

Mp: 240-241 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: \( t_R \) (minor) 4.847 min, \( t_R \) (major) 5.437 min, ee = 99 %; IR \( \nu_{\text{max}} \) (KBr): 3061, 2953, 1663, 1600, 1419, 1266 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)+DMSO-d\(_6\)): \( \delta_H \) (ppm) 6.30 (s, 1H, 4\( H \)), 7.11-7.54 (m, 4H, Ar-\( H \)), 7.78 (d, 2H, \( J=8 \) Hz, Ar-\( H \)), 7.92 (d, 2H, \( J=8 \) Hz, Ar-\( H \)), 9.92 (s, 2H, NH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)+DMSO-d\(_6\)): \( \delta_C \) (ppm) 35.31, 103.77, 115.86, 117.14, 123.92, 127.90, 128.00, 129.01, 130.78, 131.97, 136.69, 140.06, 152.04, 165.52, 166.80; MS (ES\(^+\)) calcd. for C\(_{17}\)H\(_{14}\)ClN\(_2\)O\(_2\)S: 342.02 found m/z 343.05 (M + H)\(^+\).
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4-(3-bromophenyl)-2-thioxo-3,4-dihydro-1H-chromeno[4,3-d]pyrimidin-5(2H)-one, (156f)

Appearance: White solid.

Yield: 89%.

Mp: 223-225 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: $t_R$ (minor) 4.504 min, $t_R$ (major) 5.190 min, ee = 94%; IR $\nu_{max}$ (KBr): 3068, 2970, 1671, 1604, 1562, 1264 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ (ppm) 5.99 (s, 1H, 4H), 7.11-8.02 (m, 8H, Ar-H), 11.23 (s, 1H, NH), 11.50 (s, 1H, NH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta_C$ (ppm) 34.88, 102.33, 115.24, 115.69, 121.87, 123.39, 123.97, 124.20, 128.44, 129.05, 132.04, 136.78, 151.20, 151.46, 163.64, 168.10; MS (ES$^+$) calcd. for C$_{17}$H$_{11}$BrN$_2$O$_2$: 385.97 found m/z 386.86 (M + H)$^+$. 

4-(4-chlorophenyl)-3-methyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one, (157a)

Appearance: Orange solid.

Yield: 91%.

Mp: 209-211 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: $t_R$ (minor) 5.078 min, $t_R$ (major) 5.062 min, ee = 98%; IR $\nu_{max}$ (KBr): 3415, 3235, 2948, 1754, 1656, 1415, 1249 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta_H$ (ppm) 2.06 (s, 3H, CH$_3$), 4.74 (s, 1H, 4H), 6.76 (d, 2H, J=8 Hz, Ar-H), 7.01 (d, 2H, J=8 Hz, Ar-H), 10.01 (s, 1H, NH), 11.25 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta_C$ (ppm) 10.27, 54.89, 104.49, 113.07, 113.62, 128.31, 135.06, 139.79, 157.14, 161.01; MS (ES$^+$) calcd. for C$_{12}$H$_{11}$ClN$_3$O: 262.06 found m/z 263.08 (M + H)$^+$. 

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3-methyl-4-(p-tolyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-one, (157b)

Appearance: Orange solid.
Yield: 93%.
Mp: 216-218 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 05:45, 25 °C, 254 nm, 0.5 mL/min, retention times: \( t_R \) (major) 5.048 min, \( t_R \) (minor) 5.538 min, ee = 97 %; IR \( \nu_{\text{max}} \) (KBr): 3412, 3225, 2951, 1712, 1660, 1421, 1218 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) : \( \delta_H \) (ppm) 2.11 (s, 3H, CH\(_3\)), 2.27 (s, 3H, CH\(_3\)), 4.81 (s, 1H, NH), 5.46 (s, 1H, 4H), 7.03-7.09 (m, 4H, Ar-H), 7.86 (s, 1H, NH), 10.00 (s, 1H, NH); \(^{13}\)C NMR(100 MHz, DMSO-\(d_6\)) : \( \delta_C \) (ppm) 10.27, 21.31, 54.86, 104.36, 127.24, 128.26, 129.56, 134.24, 140.07, 159.75, 161.04; MS (ES\(^+\)) calcd. for C\(_{13}\)H\(_{14}\)N\(_4\)O: 242.12 found \( m/z \) 243.09 (M + H\(^+\)).

4-(4-fluorophenyl)-3-methyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine-6(7H)-thione, (157c)

Appearance: Orange solid.
Yield: 92%.
Mp: 221-223 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 04:46, 25 °C, 254 nm, 0.5 mL/min, retention times: \( t_R \) (minor) 4.495 min, \( t_R \) (major) 5.062 min, ee = 97 %; IR \( \nu_{\text{max}} \) (KBr): 3405, 3198, 2926, 1701, 1589, 1490, 1286 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) : \( \delta_H \) (ppm) 2.24 (s, 3H, CH\(_3\)), 4.07(s, 1H, NH), 6.36 (s, 1H, 4H), 6.95-7.04 (m, 4H, Ar-H), 7.97 (s, 1H, NH), 9.98 (s, 1H, NH); \(^{13}\)C NMR(100 MHz, DMSO-\(d_6\)) : \( \delta_C \) (ppm) 11.98, 59.64, 104.28, 115.82, 116.04, 128.60,
128.68, 138.29, 140.56, 159.28, 160.91, 167.0; MS (ES⁺) calcd. for C₁₂H₁₁FN₄S: 262.07 found m/z 263.13 (M + H)⁺.

**4-(4-ethoxyphenyl)-3-methyl-4,5-dihydro-1H-pyrazolo [3,4-d]pyrimidine-6(7H)-thione,(157d)**

Appearance: Yellow solid.

Yield: 88%.

Mp: 236-238 °C.

Enantiomeric excess (ee) was determined by HPLC (Chiral ADV column), i-propanol : n-hexane = 04:46, 25 °C, 254 nm, 0.5 mL/min, retention times: tᵣ (major) 6.018 min, tᵣ (minor) 6.901 min, ee = 94%; IR νmax (KBr): 3468, 3222, 2994, 1720, 1619, 1391, 1243 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δH (ppm) 1.21 (m, 3H, CH₃), 2.63 (s, 3H, CH₃), 2.80 (m, 2H, CH₂), 4.97 (s, 1H, NH), 6.08 (s, 1H, 4H), 6.81 (d, 2H, J=8 Hz, Ar-H), 7.28 (d, 2H, J=8 Hz, Ar-H), 8.52 (s, 1H, NH), 9.71 (s, 1H, NH); ¹³C NMR(100 MHz, DMSO-d₆): δC (ppm) 14.74, 15.43, 56.94, 68.02, 104.96, 118.70, 119.10, 132.51, 138.19, 161.77, 162.69, 168.68; MS (ES⁺) calcd. for C₁₄H₁₆N₄O₅S: 288.10 found m/z 289.15 (M + H)⁺.
3.5 Representative $^1$HNMR, $^{13}$CNMR, IR, Mass and HPLC Spectra

$^1$H NMR Spectrum of 4-(4-fluorophenyl)-3,4-dihydro-1H-chromeno[4,3-d]pyrimidine-2,5-dione, (156b)
$^{13}$C NMR Spectrum of 4-(4-fluorophenyl)-3,4-dihydro-1$H$-chromeno[4,3-$d$]pyrimidine-2,5-dione, (156b)
IR Spectrum of 4-(4-fluorophenyl)-3,4-dihydro-1H-chromeno[4,3-d]pyrimidine-2,5-dione, (156b)
Mass Spectrum of 4-(4-fluorophenyl)-3,4-dihydro-1H-chromeno[4,3-d]pyrimidine-2,5-dione, 156b

![Mass Spectrum Diagram](image-url)
HPLC Spectrum of 4-(4-fluorophenyl)-3,4-dihydro-1\(H\)-chromeno[4,3-\(d\)]pyrimidine-2,5-dione, (156b)
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