Diastereoselective syntheses of 3-aryl-5-(arylalkyl)-6-methyl-1-(1-phenylethyl)thioxotetrahydropyrimidin-4(1*H*)-ones: A stereochemical perspective from *endo* and exocyclic chiral centres†

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Diastereoselective syntheses of 3-aryl-(*S*/*R*)-6-methyl-1-[(*S*/*R*)-1-phenylethyl)]-2-thioxotetrahydro pyrimidin-4(1*H*)-ones were achieved in good yields by the condensation of aryl isothiocyanates with ethyl 3-(1-phenylethylamino)butanoate in a one-pot reaction. Benzylation of these substrates illustrated that the orientations of the exocylic and endocylic groups determine the stereochemical outcome of the product formed.

Introduction

The importance of chirality in biological properties paved the path for continued interest and substantial efforts on asymmetric synthesis, particularly in the induction of organocatalysts, chiral auxiliaries, heterogenous catalysts as well as metal and bio catalysts, facilitating the syntheses of various chiral building blocks.[1] 3-Aryl-2-thioxotetrahydropyrimidin-4-ones are well known heterocyclic compounds which are extensively used in agrochemical and pharmaceutical research. They are found to be potent for treating atherosclerotic conditions such as dyslipoproteinemias and coronary heart disease.[2] These compounds also exhibit anticancer, antibacterial and insecticidal properties.[3,4] 3-aryl dihydrothiouracils are proven for their herbicidal and anticonvulsant activities.[5] Although various methods are known for the synthesis of 1-alkyl-3-aryl-2-thioxotetrahydropyrimidin-4(1*H*)-ones,[6] pharmaceutical effects of its derivatives have not been explored yet. Our interests were mainly focused to examine the influence of endocyclic and exocylic groups in the stereoselective benzylation of 3-aryl-2-thioxotetrahydropyrimidin-4-one derivatives.

Results and discussion

We herein report the diastereoselective benzylation of 3-aryl-(*S*/*R*)-6-methyl-1-[(*S*/*R*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-ones where the exocyclic chiral substituent at N1 and the endocyclic methyl group at C6 transmit a combined effect to impose the stereochemical orientation of the electrophile incorporated at position 5, adjacent to a carbonyl carbon. As a model reaction, 3-(3-chloro-4-cyanophenyl)-6-methyl-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one **6** was chosen for benzylation reaction. Ethylacetoacetate **1**, when reacted with (*S*)-α-methyl benzyl amine **2a** in presence of zirconium tetrachloride gave the corresponding enamines **3a** and **3b**, which were subsequently reduced with sodium triacetoxyborohydride to afford the diastereomers, (*S*/*R*)-ethyl 3-[(*S*)-1-phenylethylamino]butanoates[7] **4a** and **4b**, in quantitative yields (Scheme 1). The mixture of β-aminoesters obtained from the above step was treated with 2-chloro-4-isothiocyanatobenzonitrile **5a** in presence of triethyl amine and lithium perchlorate under reflux condition in acetonitrile[8] to afford 3-(3-chloro-4-cyanophenyl)-(*S*/*R*)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-ones **6a** and **6b** (Scheme 2) in a ratio of 2 : 1, with good yields (Table 1). Reaction with (*R*)-α-methyl benzylamine **2b**, also proceeded with the same diastereoselectivity affording the isomers **6c** and **6d**. Our efforts were then directed to determine the absolute configurations of the diastereomers. Molecules containing stereogenic centres with fixed configurations adjacent to a chiral centre with unknown stereochemistry facilitate the prediction of absolute configuration by NMR studies with ease and accuracy.[9] The chiral centre Cα attached to N1 would serve a similar purpose, assisting in the prediction of stereochemical configuration at the chiral centre C6, provided the anisotropy experienced by the methyl group and the proton at C6 from the phenyl ring at Cα is different for the diastereomers. The characterization of the diastereomers, **6a–6d** was made on the basis of chemical shifts and the inference drawn from COSY, DEPT-135, HSQC and HMBC experiments. The methyl groups at the chiral centre Cα and C6, distinguished on the basis of correlation spectra, were identified at 1.75 and 1.47 ppm respectively for **6a** and at 1.67 and 0.74 ppm respectively for **6b**. The proton at C6 resonated at δ values of 3.76 and 3.96 ppm respectively for the diastereomers **6a** and **6b**, which indicated that the proton at C6 is in the ring current of the phenyl group for the diastereomer **6a**.

Apparently, the methyl group at C6 for the diastereomer **6b** experienced an anisotropic effect from the phenyl ring with a consequent upfield shift to 0.74 ppm from 1.47 ppm observed for the diastereomer **6a** (Fig. 1). Based on the spatial orientations of groups at the chiral centre Cα, three different conformations are possible for each of the diastereomers. The total energy for each conformation of the diastereomer **6a** was calculated using PM3 Hamiltonian after optimization by MM2 method.[10] A

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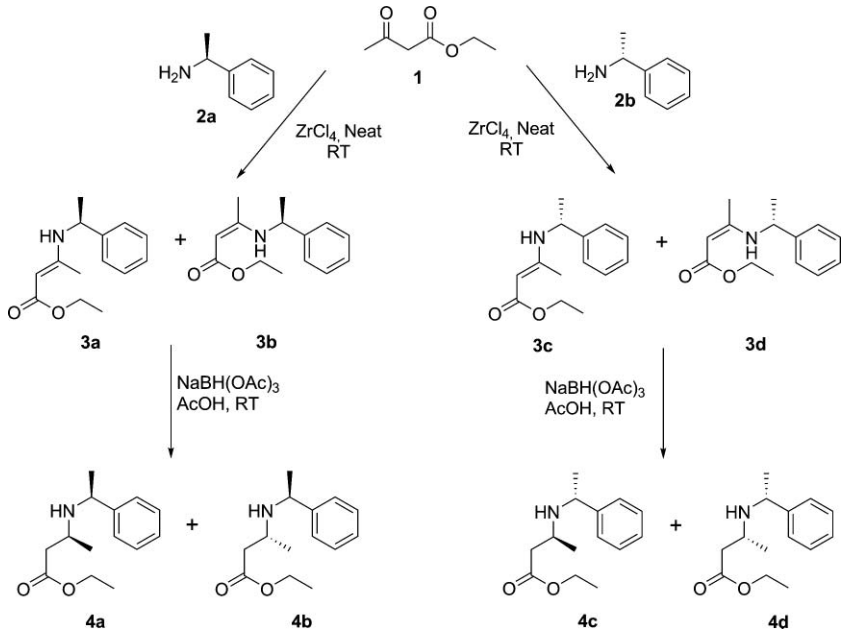
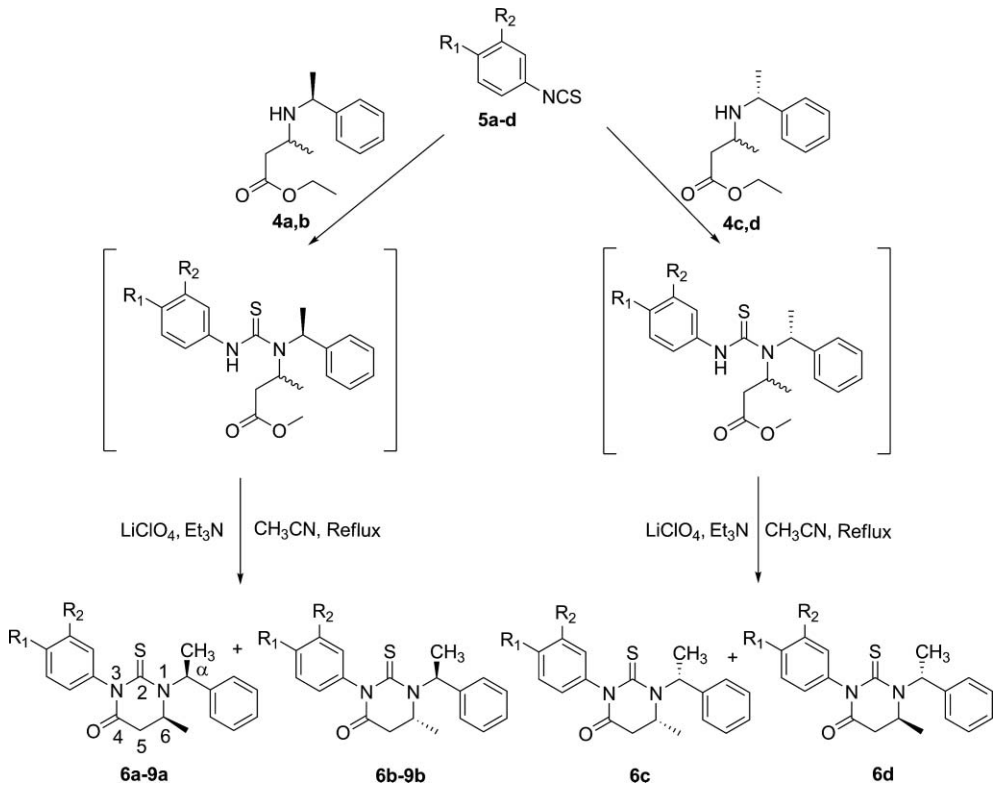


Scheme 1 Syntheses of (*S*/*R*)-ethyl 3-[(*S*/*R*)-1-phenylethylamino]butanoates.



Scheme 2 Syntheses of 3-aryl-(*S*/*R*)-6-methyl-1-[(*S*/*R*)-1-phenylethyl)]-2-thioxotetrahydropyrimidin-4(1*H*)-ones.

3-dimensional structural representation corresponding to the most stable conformation of the diastereomer **6a** indicated that the proton at C6 is in anisotropy with the phenyl ring at the chiral centre Cα while the methyl group did not experience any such effect (Fig. 2), which is in accordance with the NMR spectra, and hence an *SS* configuration can be fairly assigned. A similar computational study for the three possible conformations of the diastereomer **6b** revealed the most stable conformation and the corresponding 3-dimensional structural representation showed that the methyl group at C6 is in anisotropy with the phenyl group at Cα, as concluded from the NMR studies, and hence an *SR* configuration could be assigned for the diastereomer **6b**. Thus the chiral centre at Cα assisted not only in the separation of the diastereomers but also in predicting the stereochemistry in an

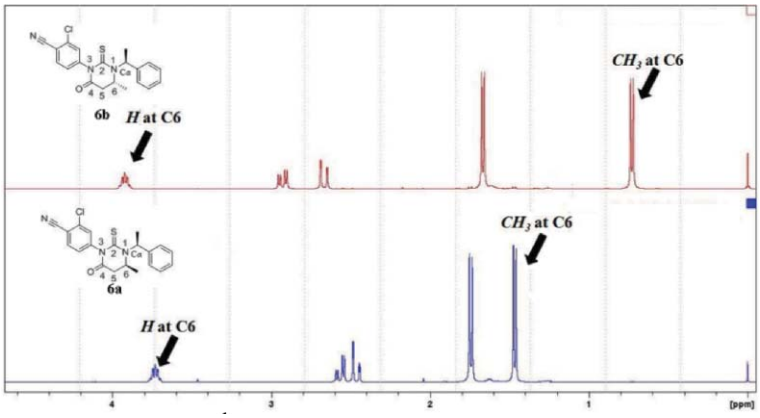


Fig. 1 Expanded ^{1}H NMR spectra of the diastereomers **6a** and **6b**.

Table 1 Syntheses of 3-aryl-(*S*/*R*)-6-methyl-1-[(*S*)-1-phenylethyl)]-2-thioxotetrahydropyrimidin-4(1*H*)-ones

Entry	R_1	R_2	Time/h	Product	Yield (%)	Ratio (a:b)[a]
1	CN	Cl	3	**6a**,**6b**	73	2 : 1
2	F	Cl	3	**7a**,**7b**	78	2 : 1
3	Cl	H	3	**8a**,**8b**	80	2 : 1
4	H	NO_2	3	**9a**,**9b**	77	2 : 1

[a] Ratio calculated from isolated yields.

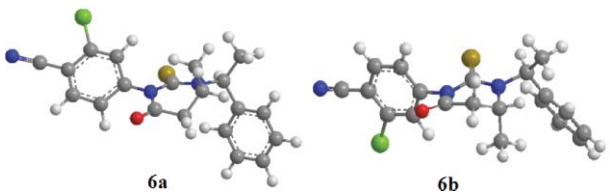


Fig. 2 Most stable conformation of the diastereomers **6a** and **6b**.

unambiguous manner; the energy calculations and NMR analyses corroborated the conclusions drawn.

Finally, the structural confirmation was made from the single crystal X-ray structure of **6a** (Fig. 3) which proved an *SS* configuration with a conformation identical to that proposed. Similar analyses set forth for the isomers **6c** and **6d** led to the assignment of *RR* and *RS* configurations respectively and a structural affirmation from single crystal X-ray analysis for the isomer **6d** (Fig. 4) substantiated our conclusion.

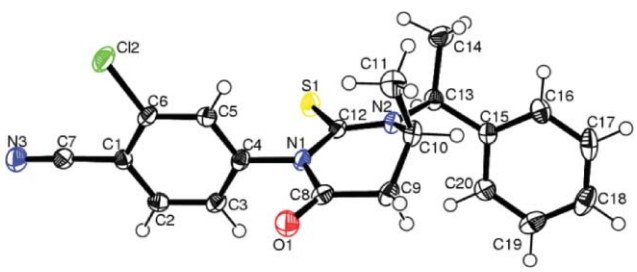


Fig. 3 ORTEP diagram of the diastereomer **6a**.

To comprehend the influences collectively exerted by the exocyclic chiral substituent and the endocyclic methyl group in determining the π-facial selectivity during the approach

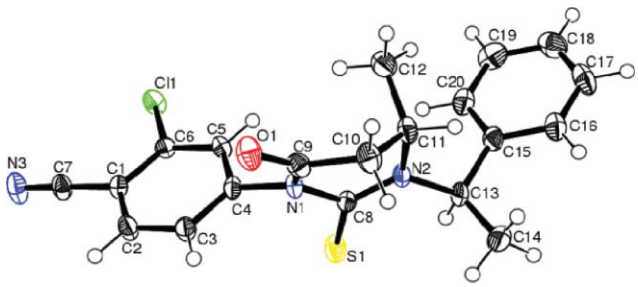
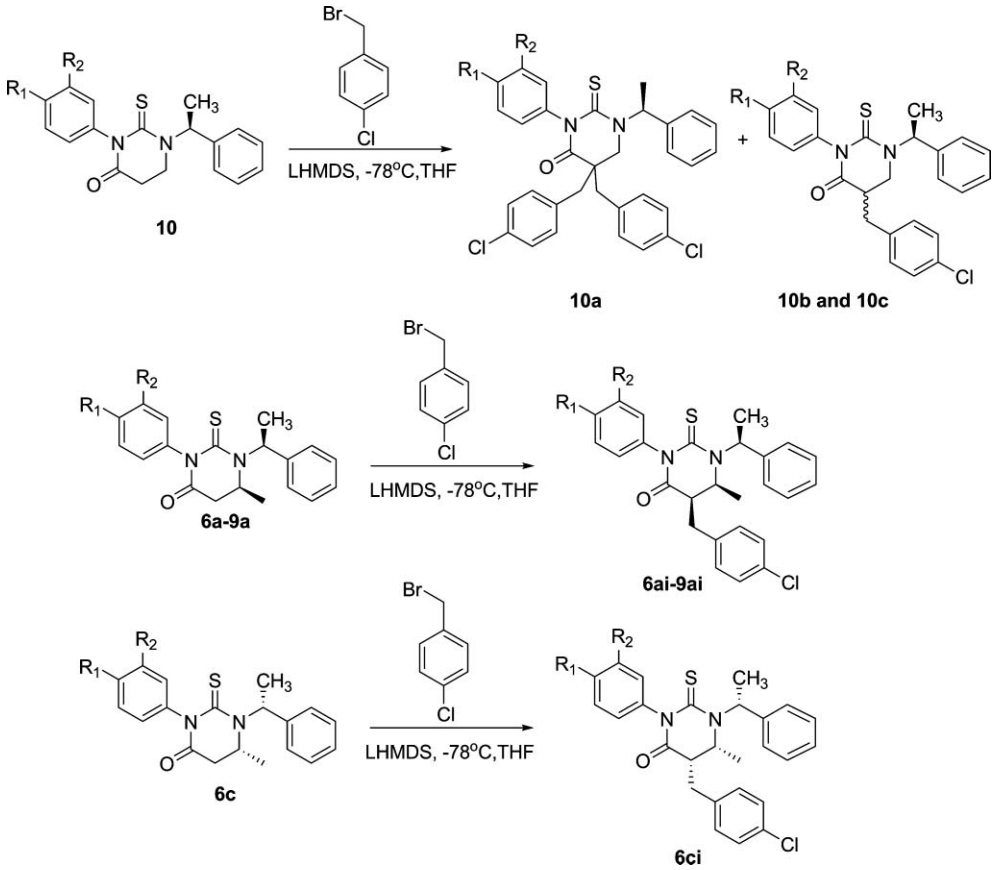


Fig. 4 ORTEP diagram of the diastereomer **6d**.

of an electrophile and the ensuing diastereoselectivity, 3-(3-chloro-4-cyanophenyl)-6(*S*)-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one **6a** was enolized using the lithium base LHMDS at −78 °C and subsequently treated with 4-chlorobenzylbromide to afford the corresponding benzylated product (Scheme 3). The incorporation of the methyl group led to diastereospecificity in the reaction; the chiral centre Cα remaining fixed, the methyl group at C6 influenced the stereoselectivity of the substitution at C5, forming the product **6ai** exclusively, whereas the substrate 3-(3-chloro-4-cyanophenyl)-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one **10** which lacked the methyl group at C6 afforded the mixture of monobenzylated diastereomers **10b** and **10c**, along with the dibenzylated product **10a**. The DEPT-135 experiment for the diastereomer **6ai** displayed a signal at 30.37 ppm corresponding to the benzylic carbon with the chemical shifts of the attached protons at 2.60 and 3.24 ppm, as revealed by the correlation obtained from HMQC and COSY spectra.

The absolute configuration at the newly generated chiral centre C5 was deduced from the coupling constant. A mutiplet was observed for the proton at C6, while the methyl group appeared as a doublet for the diastereomer **6ai**. Irradiation of the methyl protons at C6 to decouple, displayed a coupling constant of 4.56 Hz; demonstrating a *syn* relation between the two vicinal protons at C5 and C6 (Fig. 5). The absolute configuration at C5 can thus be fairly concluded as *R*, since the configurations at Cα and C6 were already known from the established structure of **6a**. Based on these assumptions, the overall configuration of the molecule is expected to be *SRS* at the chiral centres Cα, C5 and C6 respectively. The absolute configuration was finally confirmed



Scheme 3 Syntheses of **10a–10c**, **6ai–9ai** and **6ci**.

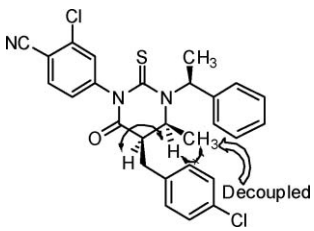


Fig. 5 Vicinal coupling of the protons at C5 and C6 for the diastereomer **6ai**.

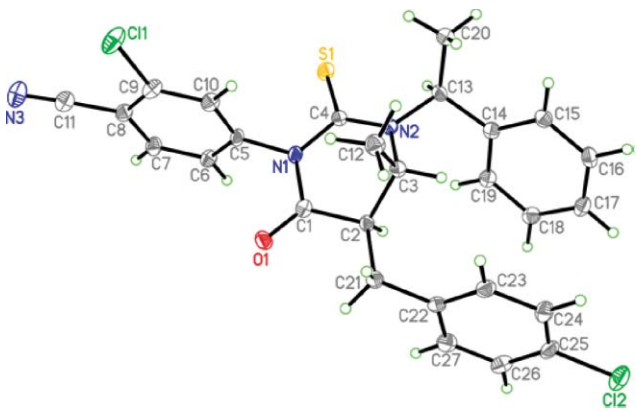


Fig. 6 ORTEP diagram of the diastereomer **6ai**.

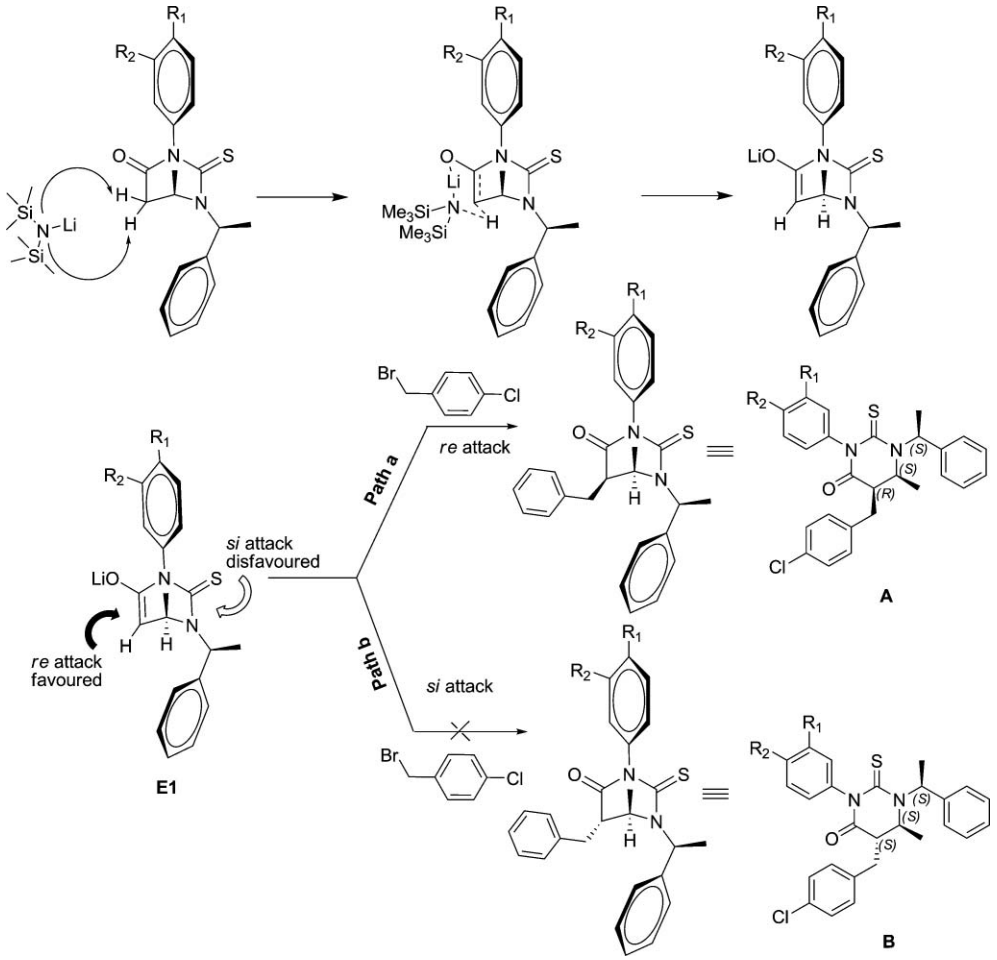
by single crystal X-ray analysis and the ORTEP diagram of the product **6ai** is shown in Fig. 6. The results of benzylation with various 2-thioxotetrahydropyrimidin-4-one analogues (**6a–9a**) with *SS* configuration are listed in Table 2.

The diastereospecificity of the reaction can be explained on the basis of a model proposed in Scheme 4. The lithium enolate **E1** has an *E* geometry due to the rigid skeleton and in this conformationally locked position benzylation can occur either from the *re* face (Path a) or from the *si* face (Path b) which can afford the product **A** or **B**. The steric effects due to the methyl group at C6 and the chiral substituent at N1 favoured the *re* approach of the electrophile leading to the exclusive formation of the product **A**. The proposed model justifies discrimination between the two faces and the consequent perturbation in the approach of the electrophile resulting in a diastereospecific reaction.

Benzylation of **6c**, the enantiomer of **6a**, at C5 using LHMDS provided the corresponding enantiomeric product **6ci**, as confirmed from the NMR studies and optical rotation. However

Table 2 Reactions of 3-aryl-(*S*)-6-methyl-1-[(*S*)-1-phenylethyl)]-2-thioxotetrahydropyrimidin-4(1*H*)-ones (**6a–9a**) with 4-chlorobenzyl bromide

Entry	R_1	R_2	Base	Product/Yield(%)	de
1	CN	Cl	LHMDS	**6ai**/68	>99
2	F	Cl	LHMDS	**7ai**/65	>99
3	Cl	H	LHMDS	**8ai**/60	>99
4	H	NO_2	LHMDS	**9ai**/64	>99



Scheme 4 Proposed model for the diastereospecific formation of (5*R*,6*S*)-3-aryl-5-(4-chlorobenzyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-ones.

benzylation of the isomer **6b** with *SR* configuration exhibited poor selectivity and a mixture of diastereomeric products **6bi** and **6bii** was obtained in approximately equal amounts which is indicative of the fact that the orientation of the methyl group at C6 with respect to the chiral centre Cα plays a decisive role in the product geometry (Scheme 5). For the diastereomers **6bi** and **6bii**, the signals for the benzylic carbon were observed at 30.99 and 34.68 ppm respectively. To determine the absolute configuration of the diastereomers **6bi** and **6bii**, methyl protons at C6 were irradiated to decouple, and the relation between the protons at C5 and C6 was deduced from the coupling constant; the configurations at Cα and C6 were already known from the structure of **6b**. For the diastereomer **6bi** decoupling of the methyl protons showed a vicinal coupling constant of 4.56 Hz indicative of the *syn* relation between the protons at C5 and C6 and hence the configuration at C5 can be fairly assigned as *S* leading to an overall *SSR* configuration at the chiral centres Cα, C5 and C6 respectively. For the diastereomer **6bii**, the decoupling of the methyl protons revealed lack of interaction between the protons at C5 and C6, demonstrating an orthogonal relation and hence an *R* configuration at the stereocentre C5 and an *SRR* configuration for the molecule. The results of benzylation on various 2-thioxotetrahydropyrimidin-4-one analogues (**6b–9b**) with *SR* configuration are listed in Table 3.

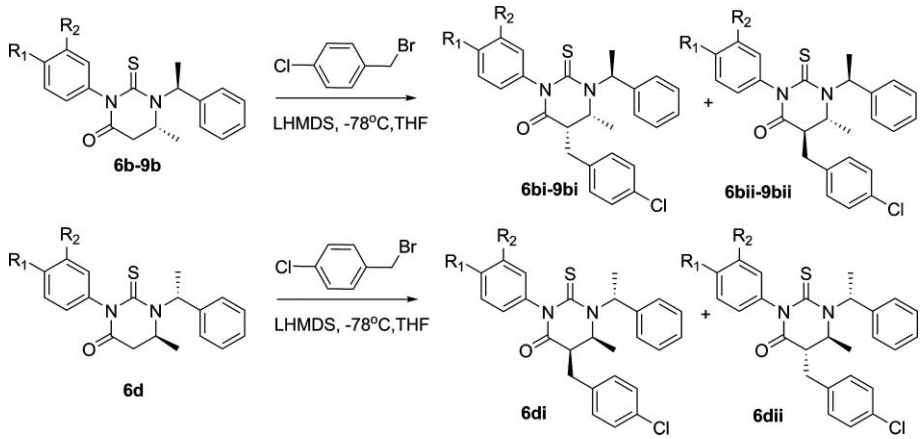
Table 3 Reactions of 3-aryl-(*R*)-6-methyl-1-[(*S*)-1-phenylethyl)]-2-thioxotetrahydropyrimidin-4(1*H*)-ones (**6b–9b**) with 4-chlorobenzyl bromide

Entry	R_1	R_2	Base	Product(bi+bii)/Yield (%)	Ratio (bi:bii)[a]
1	CN	Cl	LHMDS	**6bi**,**6bii**/66	40 : 60
2	F	Cl	LHMDS	**7bi**,**7bii**/68	40 : 60
3	Cl	H	LHMDS	**8bi**,**8bii**/70	40 : 60
4	H	NO_2	LHMDS	**9bi**,**9bii**/65	40 : 60

[a] Ratio calculated from isolated yields.

The reaction of the diasteroemer **6d** with LHMDS followed by the treatment with 4-chlorobenzylbromide afforded two diastereomers **6di** and **6dii** which were found to be the enantiomers of **6bi** and **6bii**, as identified from the NMR spectra and specific rotations. The absolute configuration of the diastereomer **6di** was convincingly proved by the crystal structure, and the ORTEP diagram is shown in Fig. 7.

A model similar to that proposed in Scheme 3, illustrates that the enolate **E2** can afford the products **C** (Path a) and **D** (Path b) depending on the approach of electrophile from the *re* and *si* faces respectively (Scheme 6). The orientation of the substituents at the chiral centre Cα and the methyl group at C6 would demonstrate that the enolate **E2** experiences almost the same kind of steric



Scheme 5 Syntheses of **6bi–9bi**, **6bii–9bii**, **6di** and **6dii**.

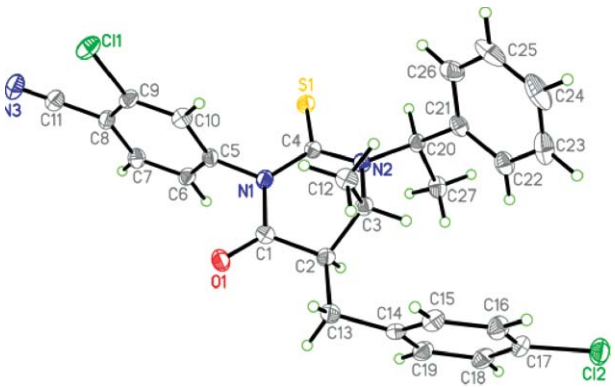


Fig. 7 ORTEP diagram of the diastereomer **6di**.

effects on both the faces, making it impossible for the approaching electrophile to distinguish between the two faces; thus resulting in a poor diasteroselectivity.

Conclusions

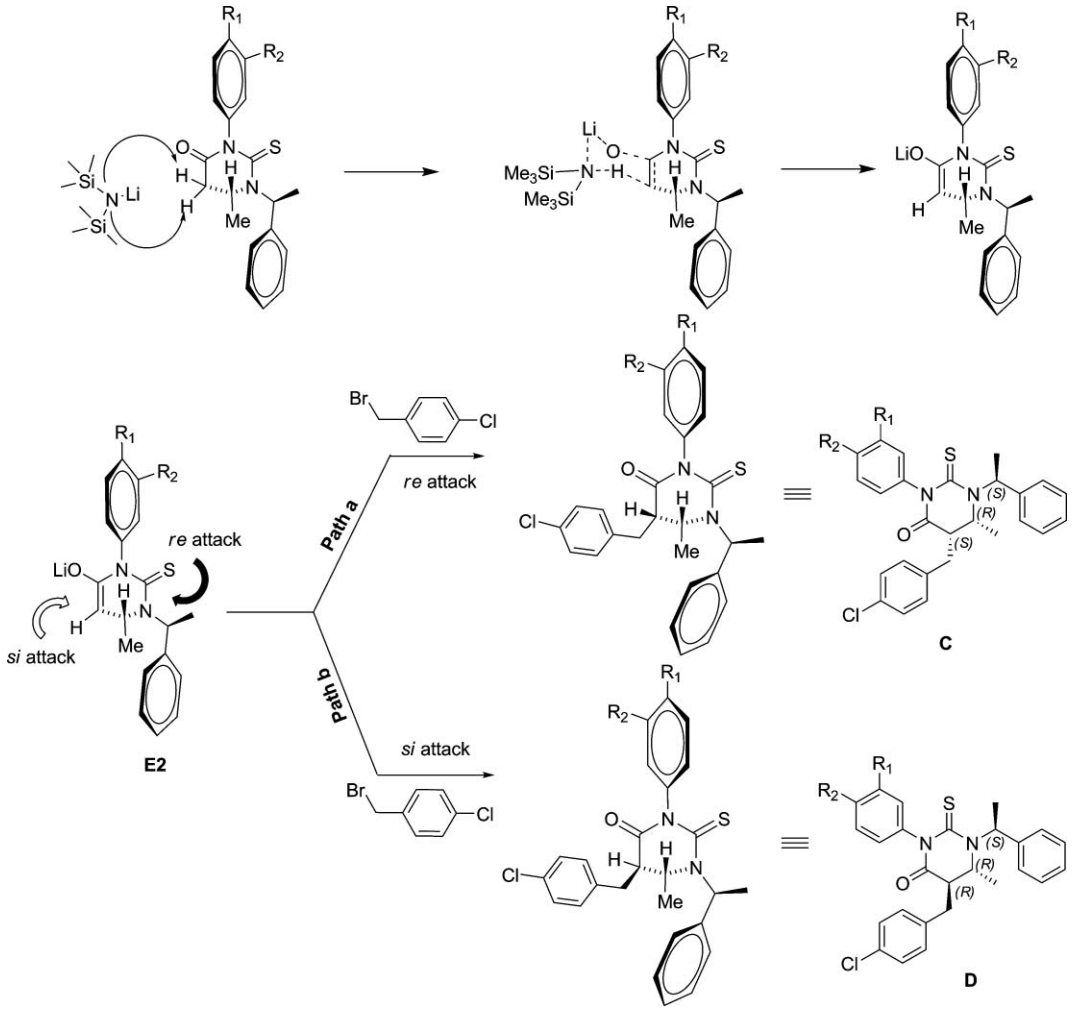
Benzylation reactions of the diastereomers of 3-aryl-6-methyl-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-ones with *SS* and *RR* configurations afforded diastereospecificity but the diastereomers with *SR* and *RS* configurations gave poor selectivity. The absence of the methyl substituent at C6 resulted in the formation of a mixture of diastereomers, while its presence dictated the selectivity of the substitution at C5. A *trans* relation between the substituents at C6 and N1 gave no stereochemical control over the substitution, whereas the *syn* orientation afforded the specificity; which provides a convincing evidence for the combined effect exerted by the *endo* and exocyclic groups.

Experimental section

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively on a Bruker Avance 400 (400 MHz) spectrometer in $CDCl_3$ using TMS as an internal standard. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvent. Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded on Finnigan Mat LCQ LCMS spectrometer and HRMS were recorded on Bruker Maxis spectrometer. The reactions were monitored by TLC (Merck). Evaporation of solvents was performed under reduced pressure using a Buchi rotary evaporator. Commercial grade reagents and solvents were used without further purification.

General procedure for the syntheses of ethyl 3-(1-phenylethylamino)butanoates (4a–4d). To ethyl acetoacetate (8.0 g, 61.47 mmol) taken in a RB flask was added $ZrCl_4$ (0.2 g, 0.95 mmol) followed by (*S*)-α-methyl benzylamine (6.0 mL, 61.47 mmol) in a dropwise manner. Reaction mixture was stirred at room temperature for 2 h and monitored by TLC. After completion of the reaction, the reaction mixture was diluted with DCM, washed with water (2 × 25 mL), then with brine (1 × 25 mL), dried over anhydrous Na_2SO_4 and concentrated to give a mixture of *E* and *Z* ethyl 3-[(*S*)-1-phenylethylamino]but-2-enoates **3a** and **3b** as a colourless liquid (12.1 g, 84%). A solution of $NaBH(OAc)_3$ was prepared by adding $NaBH_4$ (4.3 g, 113.20 mmol) to 30 mL of glacial acetic acid maintained between 15 to 20 °C. After the evolution of H_2 had ceased the above mixture of ethyl 3-(1-phenylethylamino)but-2-enoates (8.8 g, 37.74 mmol) was added to it and the reaction mixture was stirred for 4 h at RT. Evaporation of acetic acid in vacuum followed by dissolution of the residue in DCM and subsequent washing with sodium carbonate provided (*S*/*R*)-ethyl 3-[(*S*)-1-phenylethylamino] butanoates **4a** and **4b**, as mixture of diastereomers (2 : 1) (7.2 g, 82%) which was used in the next step without separation. Reaction with (*R*)-α-methyl benzylamine afforded (*S*/*R*)-ethyl 3-[(*R*)-1-phenylethylamino]butanoates **4c** and **4d**, as a diastereomeric mixture in the ratio 2 : 1.

General procedure for the syntheses of N-aryl-2-thioxotetrahydropyrimidin-4-one derivatives (6a–6d, 7a–9a, 7b–9b). To a solution of aryl isothiocyanate (2.57 mmol) in 30 mL acetonitrile taken in a RB flask was added (*S*/*R*)-ethyl 3-[(*S*)-1-phenylethylamino]butanoate (0.6 g, 2.57 mmol) followed by triethylamine (0.4 mL, 3.08 mmol) and $LiClO_4$ (10 mol%, 30 mg, 0.26 mmol). The reaction mixture was refluxed for 1.2 h and then concentrated at reduced pressure. The residue was diluted with DCM, washed with water (2 × 25 mL), then with brine (1 × 25 mL) and dried over anhydrous



Scheme 6 Proposed model for the formation of (5*S*,6*R*)/(5*R*,6*R*)-3-aryl-5-(4-chlorobenzyl)-6-methyl-1-[(*S*)-1-phenylethylthioxotetrahydropyrimidin-4(1*H*)-ones.

Na_2SO_4. Reaction mixture was concentrated and the diastereomers were separated by column chromatography on silica gel (230–400) using hexane–ethyl acetate mixture (85 : 15) as the eluent to obtain 3-aryl-(*S*/*R*)-6-methyl-1-[(*S*)-1-phenylethyl)]-2-thioxotetrahydropyrimidin-4(1*H*)-ones which were recrystalized from MeOH.

3-(3-Chloro-4-cyanophenyl)-6(*S*)-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6a). White solid; Yield 48%; mp 218–220 °C; R_f 0.50 (7 : 3 hexane–EtOAc); $[\alpha]_D$ −195.87 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, 3H, *J* = 6.80 Hz), 1.75 (d, 3H, *J* = 7.20 Hz), 2.44–2.59 (m, 2H), 3.76 (m, 1H), 6.91 (q, 1H, *J* = 7.20 Hz), 7.22–7.46 (m, 7H), 7.75 (d, 1H, *J* = 8.00 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.35, 19.50, 38.62, 46.42, 59.72, 113.07, 115.64, 127.04, 128.61, 128.90, 129.06, 131.50, 134.02, 137.13, 138.91, 144.28, 165.53, 179.53; MS (APCI): $[M+1]^+$ = 384.20; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{20}H_{18}ClN_3OS$: 406.0757, Found: 406.0757.

3-(3-Chloro-4-cyanophenyl)-6(*R*)-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6b). White solid; Yield 25%; mp 179–181 °C; R_f 0.39 (7 : 3 hexane–EtOAc); $[\alpha]_D$ −510.18 (*c* 1.000, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (d, 3H, *J* = 6.68 Hz), 1.67 (d, 3H, *J* = 7.00 Hz), 2.69 (dd, 1H), 2.95 (dd, 1H), 3.95 (m, 1H), 7.03 (q, 1H, *J* = 7.00 Hz), 7.22 (d, 1H, *J* = 8.08 Hz), 7.35–7.54 (m, 6H), 7.75 (d, 1H, *J* = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.33, 18.26, 39.08, 45.97, 59.26, 113.10, 115.62, 128.30, 128.89, 128.92, 131.43, 134.01, 137.17, 137.28, 144.18, 165.55, 178.87; MS (APCI): $[M+1]^+$ = 384.20; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{20}H_{18}ClN_3OS$: 406.0757, Found: 406.0762.

3-(3-Chloro-4-cyanophenyl)-6(*R*)-methyl-1-[(*R*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6c). White solid; Yield 50%; mp 218–220 °C; R_f 0.50 (7 : 3 hexane–EtOAc); $[\alpha]_D$ +195.57 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (d, 3H, *J* = 6.80 Hz), 1.76 (d, 3H, *J* = 7.20 Hz), 2.45–2.60 (m, 2H), 3.77 (m, 1H), 6.92 (q, 1H, *J* = 7.20 Hz), 7.23–7.47 (m, 7H), 7.75 (d, 1H, *J* = 8.00 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.32, 19.46, 38.62, 46.38, 59.73, 113.10, 115.53, 127.03, 128.28, 128.86, 129.03, 131.52, 133.92, 137.08, 138.99, 144.29, 165.40, 179.64; MS (APCI): $[M+1]^+$ = 384.20; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{20}H_{18}ClN_3OS$: 406.0757, Found: 406.0766.

3-(3-Chloro-4-cyanophenyl)-6(*S*)-methyl-1-[(*R*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6d). White solid; Yield 24%; mp 179–181 °C; R_f 0.39 (7 : 3 hexane–EtOAc); $[\alpha]_D$ +510.97

(*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (d, 3H, J = 6.68 Hz), 1.67 (d, 3H, J = 7.00 Hz), 2.69 (dd, 1H), 2.95 (dd, 1H), 3.96 (m, 1H), 7.00–7.05 (q, 1H, J = 7.00 Hz), 7.22 (d, 1H, J = 8.08 Hz), 7.33–7.55 (m, 6H), 7.75 (d, 1H, J = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.26, 18.21, 39.13, 45.96, 59.25, 113.12, 115.51, 128.27, 128.85, 131.44, 133.90, 137.10, 137.39, 144.21, 165.41, 179.01; MS (APCI): $[M+1]^+$ = 384.20; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{20}H_{18}ClN_3OS$: 406.0757, Found: 406.0759.

3-(3-Chloro-4-fluorophenyl)-6(*S*)-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (7a). White solid; Yield 54%; mp 170–171 °C; R_f 0.66 (7 : 3 hexane–EtOAc); $[\alpha]_D$ −168.20 (*c* 1.000, $CHCl_3$); ^{1}H NMR; (400 MHz, $CDCl_3$): δ 1.46 (d, 3H, J = 6.80 Hz), 1.76 (d, 3H, J = 7.20 Hz), 2.42–2.57 (m, 2H), 3.75 (m, 1H), 6.98 (q, 1H, J = 7.20 Hz), 7.07 (m, 1H), 7.21–7.27 (m, 1H), 7.35–7.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.33, 19.41, 38.70, 46.27, 59.80, 116.55, 121.25, 127.04, 128.46, 128.98, 131.64, 135.89, 139.20, 156.53, 165.80, 180.49; MS (APCI): $[M+1]^+$ = 377.13; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{19}H_{18}ClFN_2OS$: 399.0710, Found: 399.0714.

3-(3-Chloro-4-fluorophenyl)-6(*R*)-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (7b). White solid; Yield 24%; mp 140–142 °C, R_f 0.45 (7 : 3 hexane–EtOAc); $[\alpha]_D$ −459.59 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (d, 3H, J = 6.68 Hz), 1.67 (d, 3H, J = 7.04 Hz), 2.67 (dd, 1H), 2.93 (dd, 1H), 3.92 (m, 1H), 7.03–7.08 (q, 2H, J = 6.92 Hz), 7.19–7.25 (m, 2H), 7.35–7.43 (m, 3H), 7.54 (d, 2H, J = 7.80 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.32, 18.16, 39.13, 45.83, 59.34, 116.61, 116.83, 121.26, 121.45, 128.32, 128.81, 135.75, 137.52, 156.52, 159.01, 165.89, 179.76; MS (APCI): $[M+1]^+$ = 377.13; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{19}H_{18}ClFN_2OS$: 399.0710, Found: 399.0714.

3-(4-Chlorophenyl)-6(*S*)-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (8a). White solid; Yield 53%; mp 177–179 °C; R_f 0.66 (7 : 3 hexane–EtOAc); $[\alpha]_D$ −173.62 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (d, 3H, J = 6.80 Hz), 1.74 (d, 3H, J = 7.20 Hz), 2.41–2.58 (m, 2H), 3.72 (m, 1H), 6.99 (q, 1H, J = 7.20 Hz), 7.13 (s, 1H), 7.25–7.46 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.34, 19.36, 38.72, 46.28, 59.71, 127.06, 128.42, 128.97, 129.26, 129.73, 134.19, 138.14, 139.28, 165.85, 180.65; MS (APCI): $[M+1]^+$ = 359.07; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{19}H_{19}ClN_2OS$: 381.0805, Found: 381.0808.

3-(4-Chlorophenyl)-6(*R*)-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (8b). White solid; Yield 27%; mp 76–78 °C; R_f 0.55 (7 : 3 hexane–EtOAc); $[\alpha]_D$ −472.85 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (d, 3H, J = 6.64 Hz), 1.69 (d, 3H, J = 7.04 Hz), 2.66 (dd, 1H), 2.94 (dd, 1H), 3.93 (m, 1H), 7.08–7.16 (m, 3H), 7.36–7.43 (m, 5H), 7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.25, 18.06, 39.24, 45.80, 59.20, 128.28, 128.66, 128.73, 129.17, 130.15, 134.16, 137.77, 138.09, 165.71, 180.12; MS (APCI): $[M+1]^+$ = 359.13; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{19}H_{19}ClN_2OS$: 381.0805, Found: 381.0804.

(*S*)-6-Methyl-3-(3-nitrophenyl)-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (9a). Light yellow solid; Yield 51%; mp 156–158 °C; R_f 0.44 (7 : 3 hexane–EtOAc); $[\alpha]_D$ −175.33 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (d, 3H, J = 6.40 Hz), 1.75 (d, 3H, J = 7.20 Hz), 2.45–2.62 (m, 2H), 3.77 (m, 1H), 6.95 (q, 1H, J = 7.20 Hz), 7.25–7.64 (m, 7H), 8.06 (s, 1H), 8.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.35, 19.50, 38.68, 46.41, 59.83, 123.23, 125.13, 127.06, 128.52, 129.03, 129.50, 136.09, 139.08, 140.63, 148.56, 165.82, 180.11; MS (APCI): $[M+1]^+$ = 370.13; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{19}H_{19}N_3O_3S$: 392.1045, Found: 392.1049.

(*R*)-6-Methyl-3-(3-nitrophenyl)-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (9b). Light yellow solid; Yield 26%; mp 95–97 °C; R_f 0.35 (7 : 3 hexane–EtOAc); $[\alpha]_D$ −439.55 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, 3H, J = 6.68 Hz), 1.70 (d, 3H, J = 7.04 Hz), 2.72 (dd, 1H), 2.40–3.00 (dd, 1H), 3.98 (m, 1H), 7.08 (q, 1H, J = 6.96 Hz), 7.34–7.59 (m, 3H), 7.54–7.66 (m, 3H), 7.62–7.66 (t, 1H, J = 8.00 Hz), 8.06 (s, 1H), 8.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.33, 18.27, 39.14, 45.95, 59.31, 123.29, 128.33, 128.86, 129.50, 137.42, 140.50, 148.57, 165.85, 179.42; MS (APCI): $[M+1]^+$ = 370.20; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{19}H_{19}N_3O_3S$: 392.1045, Found: 392.1045.

General procedure for the syntheses of 3-aryl-5-(4-chlorobenzyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-ones (6ai–6dii, 7ai–9ai, 7bi–9bi, 7bii–9bii). In a typical experiment, 3-aryl-(*S*)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (0.70 mmol) dissolved in anhydrous THF (5 mL) and cooled to −78 °C, was treated with LHMDS (0.76 mL, 0.77 mmol, 1.0 M solution in THF) under nitrogen atmosphere and stirred for 30 min. 4-chlorobenzyl-bromide (0.16 g, 0.77 mmol) was added to the reaction mixture, stirred for another 2 h, then quenched with saturated aq. NH_4Cl and extracted into ethyl acetate. The organic layer was dried and concentrated to provide a gummy compound, which upon purification by column chromatography on silica gel (60–120 mesh) using hexane–ethyl acetate mixture (85 : 15) as the eluent afforded 3-aryl-(*R*)-5-(4-chlorobenzyl)-(*S*)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one. Reactions of 3-aryl-(*R*)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one afforded diastereomers of the desired product which were separated by column chromatography on silica gel (230–400 mesh) using hexane–ethyl acetate mixture (90 : 10) as the eluent. The products were characterized by analytical and spectral methods.

(5*R*,6*S*)-3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6ai). White solid; Yield 68%; mp 193–195 °C; R_f 0.35 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −325.33 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (d, 3H, J = 6.68 Hz), 1.62 (d, 3H, J = 7.12 Hz), 2.36 (dd, 1H), 2.76 (m, 1H), 3.24 (dd, 1H), 3.35 (m, 1H), 6.55 (d, 2H, J = 8.16 Hz), 6.87 (q, 1H, J = 7.12 Hz), 7.08 (d, 2H, J = 8.20 Hz), 7.22–7.43 (m, 7H), 7.76 (d, J = 8.28 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.30, 14.86, 30.38, 46.59, 47.79, 59.58, 113.15, 115.56, 127.11, 128.53, 128.95, 129.01, 129.17, 131.41, 134.76, 137.20, 138.72, 144.28, 167.90, 179.33; MS (APCI): $[M+1]^+$ = 508.40; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{27}H_{23}Cl_2N_3OS$: 530.0837, Found: 530.0843.

(5*S*,6*R*)-3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6bi). White solid; Yield 26%; mp 179–181 °C; R_f 0.45 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −105.37 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65 (d, 3H, *J* = 6.64 Hz), 1.46 (d, 3H, *J* = 7.00 Hz), 2.48 (dd, 1H), 3.08 (m, 1H), 3.38 (dd, 1H), 3.55 (m, 1H), 6.92 (q, 1H, *J* = 6.88 Hz), 7.13 (d, 2H, *J* = 8.28 Hz), 7.28 (d, 1H, *J* = 7.88 Hz), 7.37 (m, 8H), 7.75 (d, 1H, *J* = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.14, 15.22, 30.99, 47.97, 48.12, 59.22, 113.12, 115.57, 116.15, 128.10, 128.76, 128.86, 129.18, 131.36, 133.05, 134.04, 135.87, 137.08, 137.20, 144.24, 167.84, 178.74; MS (APCI): $[M+1]^+$ = 508.40; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{27}H_{23}Cl_2N_3OS$: 530.0837, Found: 530.0832.

(5*R*,6*R*)-3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6bii). White solid; Yield 32%; mp 132–134 °C; R_f 0.30 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −251.23 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65 (d, 3H, *J* = 6.68 Hz), 1.63 (d, 3H, *J* = 7.08 Hz), 2.89–3.04 (m, 3H), 3.69 (q, 1H, *J* = 6.72 Hz), 7.05–7.13 (m, 2H), 7.17–7.19 (d, 2H, *J* = 8.40 Hz), 7.25–7.27 (s, 1H), 7.33–7.46 (m, 7H), 7.71–7.74 (d, 1H, *J* = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.68, 19.38, 34.69, 48.82, 50.16, 58.94, 113.15, 115.54, 128.42, 128.96, 129.07, 129.24, 129.86, 131.38, 133.42, 134.08, 134.46, 137.24, 137.56, 144.29, 167.19, 178.12; MS (APCI): $[M+1]^+$ = 508.40; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{27}H_{23}Cl_2N_3OS$: 530.0837, Found: 530.0841.

(5*S*,6*R*)-3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-6-methyl-1-[(*R*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6ci). White solid; Yield 65%; mp 193–195 °C; R_f 0.35 (8 : 2 hexane–EtOAc); $[\alpha]_D$ +326.64 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, 3H, *J* = 6.68 Hz), 1.64 (d, 3H, *J* = 7.12 Hz), 2.37 (dd, 1H), 2.77 (m, 1H), 3.25 (dd, 1H), 3.37 (m, 1H), 6.57 (d, 2H, *J* = 8.28 Hz), 6.83–6.88 (q, 1H, *J* = 7.08 Hz), 7.10 (d, 2H, *J* = 9.04 Hz), 7.23–7.42 (m, 7H), 7.77 (d, 1H, *J* = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.30, 14.86, 30.38, 46.59, 47.78, 59.58, 113.15, 115.57, 127.11, 128.53, 128.95, 129.01, 129.17, 131.43, 134.01, 134.76, 137.20, 138.72, 144.28, 167.90, 179.33; MS (APCI): $[M+1]^+$ = 508.40; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{27}H_{23}Cl_2N_3OS$: 530.0837, Found: 530.0830.

(5*R*,6*S*)-3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-6-methyl-1-[(*R*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6di). White solid; Yield 27%; mp 179–181 °C; R_f 0.45 (8 : 2 hexane–EtOAc); $[\alpha]_D$ +105.63 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.66 (d, 3H, *J* = 6.68 Hz), 1.47 (d, 3H, *J* = 7.00 Hz), 2.49 (dd, 1H), 3.10 (m, 1H), 3.39 (dd, 1H), 3.56 (m, 1H), 6.93 (q, 1H, *J* = 6.96 Hz), 7.15 (d, 2H, *J* = 8.36 Hz), 7.22 (d, 1H, *J* = 8.24 Hz), 7.33-7.41 (m, 8H), 7.76 (d, 1H, *J* = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.13, 15.22, 30.99, 47.97, 48.13, 59.20, 113.13, 115.57, 116.15, 128.10, 128.76, 128.86, 129.18, 129.83, 131.36, 133.05, 134.03, 135.87, 137.08, 137.21, 144.23, 167.84, 178.74; MS (APCI): $[M+1]^+$ = 508.40; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{27}H_{23}Cl_2N_3OS$: 530.0837, Found: 530.0834.

(5*S*,6*S*)-3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-6-methyl-1-[(*R*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (6dii). White solid; Yield 32%; mp 132–134 °C; R_f 0.30 (8 : 2 hexane–EtOAc); $[\alpha]_D$ +250.78 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65 (d, 3H, *J* = 6.68 Hz), 1.63 (d, 3H, *J* = 7.08 Hz), 2.89–3.04 (m, 3H), 3.69 (q, 1H, *J* = 6.72 Hz), 7.05–7.15 (m, 2H), 7.17–7.19 (d, 2H, *J* = 8.40 Hz), 7.25–7.27 (s, 1H), 7.33–7.46 (m, 7H), 7.71–7.74 (d, 1H, *J* = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.68, 19.38, 34.69, 48.82, 50.16, 58.94, 113.15, 115.54, 128.42, 128.96, 129.07, 129.24, 129.86, 131.38, 133.42, 134.08, 134.46, 137.24, 137.56, 144.29, 167.20, 178.12; MS (APCI): $[M+1]^+$ = 508.40; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{27}H_{23}Cl_2N_3OS$: 530.0837, Found: 530.0846.

(5*R*,6*S*)-3-(3-Chloro-4-fluorophenyl)-5-(4-chlorobenzyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (7ai). White solid; Yield 65%; mp 108–110 °C; R_f 0.54 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −303.96 (*c* 1.000, $CHCl_3$).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, 3H, *J* = 6.72 Hz), 1.63 (d, 3H, *J* = 7.12 Hz), 2.37 (dd, 1H), 2.76 (m, 1H), 3.26 (dd, 1H), 3.35 (m, 1H), 6.54–6.58 (d, 2H, *J* = 8.32 Hz), 6.94 (q, 1H, *J* = 7.08 Hz), 7.07–7.09 (d, 2H, *J* = 9.04 Hz), 7.21–7.26 (m, 2H), 7.29–7.41 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.21, 14.84, 30.49, 46.49, 47.64, 59.64, 116.60, 116.83, 121.31, 121.50, 127.12, 128.41, 128.89, 128.95, 129.20, 130.37, 132.32, 134.99, 135.89, 135.93, 138.96, 156.54, 168.22, 180.19; MS (APCI): $[M+1]^+$ = 500.93; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{26}H_{23}Cl_2FN_2OS$: 523.0790, Found: 523.0792.

(5*S*,6*R*)-3-(3-Chloro-4-fluorophenyl)-5-(4-chlorobenzyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (7bi). White solid; Yield 30%; mp 138–140 °C; R_f 0.60 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −243.50 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65 (d, 3H, *J* = 6.64 Hz), 1.47 (d, 3H, *J* = 7.00 Hz), 2.49 (dd, 1H), 3.07 (m, 1H), 3.40 (dd, 1H), 3.54 (m, 1H), 6.99 (q, 1H, *J* = 6.96 Hz), 7.15 (d, 2H, *J* = 8.36 Hz), 7.20–7.24 (t, 2H, *J* = 8.64 Hz), 7.25–7.40 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.02, 15.19, 31.11, 47.81, 48.10, 59.24, 116.58, 116.80, 121.28, 121.47, 128.10, 128.71, 128.77, 129.11, 129.84, 132.94, 135.84, 135.88, 136.14, 137.36, 156.53, 159.02, 168.09, 179.64; MS (APCI): $[M+1]^+$ = 500.93; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{26}H_{23}Cl_2FN_2OS$: 523.0790, Found: 523.0790.

(5*R*,6*R*)-3-(3-Chloro-4-fluorophenyl)-5-(4-chlorobenzyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (7bii). White solid; Yield 36%; mp 172–174 °C; R_f 0.40 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −258.22 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.66 (d, 3H, *J* = 6.68 Hz), 1.62–1.64 (d, 3H, *J* = 7.08 Hz), 2.91–3.05 (m, 3H), 3.64–3.68 (m, 1H), 7.00 (m, 1H), 7.13–7.24 (m, 5H), 7.35–7.42 (m, 5H), 7.44–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.67, 19.30, 34.68, 48.85, 49.99, 59.04, 116.65, 116.87, 121.34, 121.52, 128.44, 128.88, 129.16, 129.88, 132.28, 134.72, 135.91, 135.95, 137.82, 156.52, 159.01, 167.49, 179.05; MS (APCI): $[M+1]^+$ = 500.93; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{26}H_{23}Cl_2FN_2OS$: 523.0790, Found: 523.0790.

(5*R*,6*S*)-5-(4-Chlorobenzyl)-3-(4-chlorophenyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (8ai). 60%; White solid; Yield 60%; mp 193–195 °C; R_f 0.53 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −116.98 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, 3H, *J* = 6.76 Hz), 1.63 (d, 3H, *J* = 7.12 Hz), 2.37 (dd, 1H), 2.77 (m, 1H), 3.26 (dd, 1H), 3.33 (m, 1H), 6.57 (d, 2H, *J* = 8.28 Hz), 6.96 (q, 1H, *J* = 7.12 Hz), 7.06–7.15 (m, 4H), 7.28–7.41 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.15, 14.86, 30.51, 46.48, 47.63, 59.54, 127.14, 128.36, 128.86,

128.92, 129.22, 129.26, 132.28, 134.21, 135.12, 138.20, 139.07, 168.16, 180.40; MS (APCI): $[M+1]^+$ = 483.10; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{26}H_{24}Cl_2N_2OS$: 505.0884, Found: 505.0884.

(5*S*,6*R*)-5-(4-Chlorobenzyl)-3-(4-chlorophenyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (8bi). White solid; Yield 30%; mp 112–115 °C; R_f 0.59 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −343.32 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.66 (d, 3H, *J* = 6.64 Hz), 1.47 (d, 3H, *J* = 7.04 Hz), 2.48 (dd, 1H), 3.09 (m, 1H), 3.41 (dd, 1H), 3.54 (m, 1H), 7.02 (q, 1H, *J* = 6.96 Hz), 7.13–7.15 (m, 4H), 7.31–7.37 (m, 7H), 7.41–7.45 (d, 2H, *J* = 7.64 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.97, 15.21, 31.12, 47.78, 48.05, 59.12, 128.10, 128.33, 128.67, 128.75, 129.08, 129.29, 130.47, 132.87, 134.21, 136.22, 137.44, 138.12, 168.06, 179.81; MS (APCI): $[M+1]^+$ = 483.17; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{26}H_{24}Cl_2N_2OS$: 505.0884, Found: 505.0884.

(5*R*,6*R*)-5-(4-Chlorobenzyl)-3-(4-chlorophenyl)-6-methyl-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (8bii). White solid; Yield 35%; mp 186–188 °C; R_f 0.47 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −308.64 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.66 (d, 3H, *J* = 6.64 Hz), 1.63 (d, 3H, *J* = 7.04 Hz), 2.89–3.08 (m, 3H), 3.67 (q, *J* = 6.60 Hz, 1H), 7.06 (d, 2H, *J* = 7.52 Hz), 7.14–7.19 (m, 3H), 7.35–7.48 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.69, 19.25, 34.70, 48.86, 49.97, 58.92, 128.43, 128.86, 128.89, 129.14, 129.36, 133.20, 134.22, 134.81, 137.91, 138.19, 167.49, 179.20; MS (APCI): $[M+1]^+$ = 483.20; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{26}H_{24}Cl_2N_2OS$: 505.0884, Found: 505.0884.

(5*R*,6*S*)-5-(4-Chlorobenzyl)-6-methyl-3-(3-nitrophenyl)-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (9ai). Light yellow solid; Yield 64%; mp 110–112 °C; R_f 0.36 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −115.96 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (d, 3H, *J* = 6.76 Hz), 1.65 (d, 3H, *J* = 7.16 Hz), 2.39 (dd, 1H), 2.81 (m, 1H), 3.27 (dd, 1H), 3.39 (m, 1H), 6.58 (d, 2H, *J* = 8.28 Hz), 6.92 (q, 1H, *J* = 7.1 Hz), 7.08–7.12 (m, 2H), 7.31–7.42 (m, 5H), 7.51–7.67 (m, 2H), 8.10 (s, 1H), 8.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.32, 14.87, 30.43, 46.55, 47.75, 59.67, 123.31, 127.14, 128.48, 128.93, 128.99, 129.20, 129.54, 132.38, 134.87, 138.86, 140.62, 148.57, 168.22, 179.83; MS (APCI): $[M+1]^+$ = 494.47; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{26}H_{24}ClN_3O_3S$: 516.1125, Found: 516.1128.

(5*S*,6*R*)-5-(4-Chlorobenzyl)-6-methyl-3-(3-nitrophenyl)-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (9bi). Light yellow solid; Yield 28%; mp 88–90 °C; R_f 0.45 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −281.94 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (d, 3H, *J* = 6.68 Hz), 1.49 (d, 3H, *J* = 7.00 Hz), 2.51 (dd, 1H), 3.14 (m, 1H), 3.42 (dd, 1H), 3.58 (m, 1H), 6.97 (q, 1H, *J* = 6.96 Hz), 7.12–7.18 (d, 2H, *J* = 9.12 Hz), 7.35–7.66 (m, 9H), 8.05 (s, 1H), 8.27–8.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.14, 15.24, 31.05, 47.93, 48.12, 59.27, 123.32, 128.13, 128.33, 128.81, 128.84, 129.16, 129.56, 129.85, 132.99, 136.00, 137.20, 140.56, 148.58, 168.14, 179.25; MS (APCI): $[M+1]^+$ = 494.40; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{26}H_{24}ClN_3O_3S$: 516.1125, Found: 516.1133.

(5*R*,6*R*)-5-(4-Chlorobenzyl)-6-methyl-3-(3-nitrophenyl)-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (9bii). Light yellow solid; Yield 35%; mp 102–104 °C; R_f 0.33 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −242.59 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 (d, 3H, *J* = 6.68 Hz), 1.66 (d, 3H, *J* = 7.08 Hz), 2.92–3.05 (m, 3H), 3.72 (q, 1H, *J* = 6.76 Hz), 7.16 (q, 1H, *J* = 7.08 Hz), 7.22 (d, 2H, *J* = 8.36 Hz), 7.29–7.54 (m, 8H), 7.61–7.65 (t, 1H, *J* = 8.80 Hz), 7.99 (s, 1H), 8.26–8.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.69, 19.39, 34.76, 48.88, 50.15, 59.06, 123.30, 128.34, 128.46, 128.95, 129.03, 129.23, 129.62, 129.91, 133.35, 134.60, 137.67, 140.64, 148.59, 167.51, 178.63; MS (APCI): $[M+1]^+$ = 494.33; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{26}H_{24}ClN_3O_3S$: 516.1125, Found: 516.1129.

3-(3-Chloro-4-cyanophenyl)-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(*1H*)-one (10). White solid; Yield 75%; mp 230–231 °C; R_f 0.21 (7 : 3 hexane–EtOAc); $[\alpha]_D$ −259.30 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69 (d, 3H, *J* = 6.80 Hz), 2.62–2.79 (m, 2H), 3.28–3.35 (m, 1H), 3.52–3.57 (m, 1H), 6.84–6.89 (q, 1H, *J* = 6.80 Hz), 7.23–7.27 (m, 1H), 7.35–7.45 (m, 6H), 7.75 (d, 1H, *J* = 8.00 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.57, 31.90, 39.21, 59.33, 113.12, 115.63, 127.11, 128.51, 129.05, 131.65, 133.99, 137.13, 138.24, 144.31, 166.03, 180.32; MS (APCI): $[M+1]^+$ = 370.00; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{19}H_{16}ClN_3OS$: 392.0601, Found: 392.0600.

3-(3-Chloro-4-cyanophenyl)-5,5-bis(4-chlorobenzyl)-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (10a). White solid; Yield 30%; mp 130–132 °C; R_f 0.56 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −167.22 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (d, 3H, *J* = 7.20 Hz), 2.38–2.42 (d, 2H, *J* = 13.98 Hz), 2.64–2.68 (d, 1H, *J* = 13.98 Hz), 3.08–3.15 (dd, 2H), 3.26–3.30 (d, 1H, *J* = 13.68 Hz), 6.57–6.59 (d, 2H, *J* = 8.36 Hz), 6.98–7.03 (m, 4H), 7.14–7.16 (d, 3H, *J* = 8.36 Hz), 7.25–7.27 (d, 2H, *J* = 8.16 Hz), 7.41–7.51 (m, 5H), 7.70–7.72 (d, 1H, *J* = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.32, 39.06, 39.55, 46.10, 46.77, 59.23, 113.60, 115.53, 128.10, 128.64, 128.82, 129.01, 129.15, 131.46, 131.58, 131.72, 132.74, 133.48, 133.52, 133.63, 134.02, 137.19, 137.89, 144.56, 168.42, 179.25; MS (APCI): $[M+1]^+$ = 619.93; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{33}H_{26}Cl_3N_3OS$: 640.0760, Found: 640.0760.

3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (10b). White solid; Yield 17%; mp 130–132 °C; R_f 0.29 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −130.36 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56–1.58 (d, 3H, *J* = 7.04 Hz), 2.49–2.56 (dd, 1H), 2.64–2.67 (m, 1H), 3.14–3.27 (m, 3H), 6.74–6.79 (m, 3H), 7.13–7.17 (m, 2H), 7.22–7.40 (m, 7H), 7.74–7.76 (d, 1H, *J* = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.13, 31.87, 41.84, 42.75, 59.29, 113.15, 115.60, 127.06, 128.48, 128.94, 129.48, 131.62, 132.72, 134.00, 134.97, 137.16, 138.35, 144.40, 168.36, 179.97; MS (APCI): $[M+1]^+$ = 494.20; HRMS (ESI): *m/z* $[M+Na]^+$ Calculated for $C_{26}H_{21}Cl_2N_3OS$: 516.0680, Found: 516.0680.

3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-1-[(*S*)-1-phenylethyl]-2-thioxotetrahydropyrimidin-4(1*H*)-one (10c). White solid; Yield 21%; mp 135–137 °C; R_f 0.22 (8 : 2 hexane–EtOAc); $[\alpha]_D$ −139.48 (*c* 1.000, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (d, 3H, *J* = 7.04 Hz), 2.40–2.46 (dd, 1H), 2.89–2.94 (m, 1H), 3.01–3.12 (m, 2H), 3.38–3.43 (dd, 1H), 6.67–6.69 (d, 2H,

Crystal data

Crystal	6a	6d	6ai	6di
Empirical formula	$C_{20}H_{18}ClN_3OS$	$C_{20}H_{18}ClN_3OS$	$C_{27}H_{23}Cl_2N_3OS$	$C_{27}H_{23}Cl_2N_3OS$
Formula mass	383.88	383.88	508.44	508.44
Color	Colorless	Colorless	Colorless	Colorless
Description	Block	Block	Plate	Block
Symmetry	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_1$
Z	4	4	2	2
Length (Å)	*a* 7.2935(2) *b* 12.3730(3) *c* 20.6291(5)	*a* 7.5879(2) *b* 10.1912(2) *c* 24.2981(4)	*a* 9.7540(9) *b* 9.3273(8) *c* 13.3001(12)	*a* 10.8114(11) *b* 10.9871(11) *c* 11.0108(11)
Angle (°)	α 90.00 β 90.00 γ 90.00	α 90.00 β 90.00 γ 90.00	α 90.00 β 89.90 γ 90.00	α 90.00 β 107.048(2) γ 90.00
Collection ranges	$-8 \le h \le 7$; $-10 \le k \le 14$; $-24 \le l \le 24$	$-9 \le h \le 8$; $-12 \le k \le 11$; $-28 \le l \le 28$	$-9 \le h \le 12$; $-11 \le k \le 11$; $-16 \le l \le 15$	$-12 \le h \le 13$; $-13 \le k \le 13$; $-13 \le l \le 13$
Temperature (K)	150(2)	150(2)	100(2)	100(2)
Volume (Å^3)	1861.62(8)	1878.97(7)	1210.02(19)	1250.5(2)
Radiation	Mo-Kα ($\lambda = 0.71073$)	Mo-Kα ($\lambda = 0.71073$)	Mo-Kα ($\lambda = 0.71073$)	Mo-Kα ($\lambda = 0.71073$)
Absorption coefficient (mm^{-1})	0.331	0.328	0.381	0.369
***F*(000)**	800	800	528	528
θ range (°)	3.39–25.00	3.35–25.00	1.53–25.94	1.93–25.96
Reflections Collected	8067	13418	6817	9363
Independent Reflections	3272 ($R_{int} = 0.0208$)	3299 ($R_{int} = 0.0210$)	4421 ($R_{int} = 0.0356$)	4769 ($R_{int} = 0.0244$)
Data/Restraints	3272/0	3299/0	4421/1	4769/1
Parameters	237	237	313	309
Maximum Shift	0.00	0.00	0.00	0.00
Goodness-of-fit on F^2	1.040	1.073	1.025	1.033
Final *R* Indices $I > 2\sigma(I)$	$R_1 = 0.0254$ w$R_2 = 0.0643$	$R_1 = 0.0211$ w$R_2 = 0.0567$	$R_1 = 0.0435$ w$R_2 = 0.1125$	$R_1 = 0.0282$ w$R_2 = 0.0689$
***R* indices (all data)**	$R_1 = 0.0283$ w$R_2 = 0.0652$	$R_1 = 0.0226$ w$R_2 = 0.0571$	$R_1 = 0.0443$ w$R_2 = 0.1133$	$R_1 = 0.0289$ w$R_2 = 0.0694$
CCDC Number	772207	772208	772209	772210

J = 8.00 Hz), 6.92–6.97 (q, 1H, *J* = 7.00 Hz), 7.12–7.21 (m, 3H), 7.33–7.45 (m, 6H), 7.33–7.75 (d, 1H, *J* = 8.24 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.68, 32.95, 42.37, 42.67, 59.09, 113.17, 115.59, 127.69, 128.71, 128.94, 129.12, 130.05, 131.48, 131.56, 132.98, 134.05, 135.32, 137.20, 137.91, 144.48, 167.92, 179.96; MS (APCI): $[M+1]^+$ = 494.27; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calculated for $C_{26}H_{21}Cl_2N_3OS$: 516.0680, Found: 516.0676.

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