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Additive controlled, stereoselective benzylation of 2-thioxotetrahydropyrimidin-4(1*H*)-ones via chiral induction from a remote stereocenter

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ABSTRACT

Stereoselective alkylation reactions of 3-aryl-1-alkyl-2-thioxotetrahydropyrimidin-4(1*H*)-one derivatives were studied. The reaction conditions were optimized to obtain the monobenzylated adduct with improved diastereoselectivity by regulating the reaction kinetics using HMPA as the additive and chiral ethyl lactate as the quencher. The absolute configuration of the product was established by NMR experiments, computational calculations, and single crystal X-ray analysis.

1. Introduction

With the current surge in asymmetric synthesis, enolates have demonstrated high versatility for stereoselective carbon–carbon bond formation. This has facilitated the synthesis of various chiral building blocks, drug intermediates, and natural products.[1] The geometry and aggregation of enolates have been controlled by bases and additives, which influence the reactivity and selectivity of these reactions.[2] However, reactions of cyclic enolates are more complex due to rigid conformations and geometrical constraints. The stereoregulations are substrate specific with stereointegrity originating from ring conformation, aggregation state, *endo*- and *exo*-cyclic ring substituents, their position and relative orientation, and hence represent a vibrant area of research.[3] Our interests were on the alkylation reactions of conformationally restricted enolates of 3-aryl-1-alkyl-2-thioxotetrahydropyrimidin-4(1*H*)-ones, which are derivatives of dihydrothiouracil. Dihydrothiouracils have attracted considerable attention because of their vast therapeutic potential including anticancer, antibacterial, anticonvulsant, antiviral, antimicrobial, antidiabetic, and antiatherosclerotic properties.[4] Alkylation of these substrates suffer from serious drawbacks such as low yields, poor diastereoselectivity, quantitative formation of a dibenzylated adduct, and ambiguity in the determination of the absolute configuration, and hence negates its synthetic applicability.[5g] Therefore our efforts were focused on exploring the reaction kinetics by employing different bases and additives so as to modulate the reactivity of the enolates in favor of the monobenzylated adduct with improved diastereoselectivity, and to establish the absolute configuration at the newly generated stereocenter.

2. Results and discussion

With an ever increasing aim to identify new pharmacologically active heterocycles, our attention was mainly on synthesis and functionalization.[5] A one-pot synthesis of *N*-aryl-1-alkyl-2-thioxotetrahydropyrimidin-4-ones[5a] from aryl isothiocyanates and β-aminoesters afforded enantiomerically pure 3-aryl-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-ones **5**(**a**–**e**) and **5′**(**a**–**e**) (Scheme 1). The reaction afforded the desired products with excellent yields in short reaction time (Table 1) with ease of purification.

The alkylation reaction was studied on a model substrate, 3-cyano-4-chlorophenyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one **5c** by generating lithium enolates using different lithium bases (*n*-BuLi, LDA, and LHMDS) and then reacting them with 4-chlorobenzyl bromide (Table 2, entries 1–6). The reactions afforded low yields of the monobenzylated adduct with poor diastereoselectivity (Scheme 2). When the reaction was performed at an elevated temperature, the formation of dibenzylated adduct **7**(**c**)(**iii**) was favored. The poor selectivity indicates that the stereo- and electronic factors remain equivalent, and therefore have no π-facial selectivity to the incoming electrophile. This prompted us to employ chiral lithium bases, which are known to influence the stereochemical orientation of the product by steric influences,[6] however the starting material was recovered as such, although the dibenzylated adduct was observed in minute amounts at higher temperatures (Table 2, entries 7–10).

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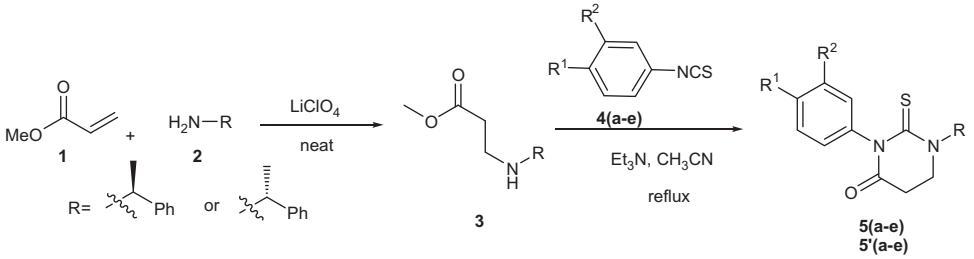
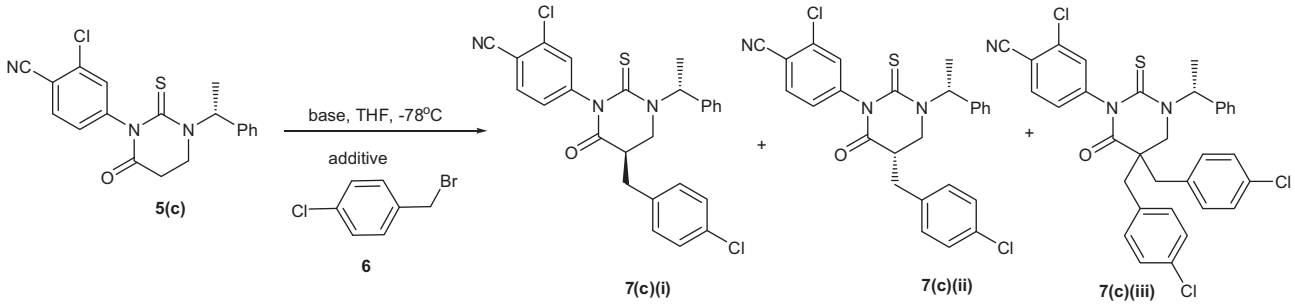


Scheme 1. One-pot synthesis of 3-aryl-1-alkyl-2-thioxotetrahydropyrimidin-4(1*H*)-ones.



Scheme 2. Reaction conditions employed for the selective formation of 5-(4-chlorobenzyl)-3-(3-cyano-4-chlorophenyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-ones.

Table 1
Reactions of chiral β-aminoesters with aryl isothiocyanates

Entry	R^1	R^2	R	Time (h)	Yield (%)	Product
1	Cl	H	(*R*)-α-MeBn	1.5	76	**5**(**a**)
2	F	Cl	(*R*)-α-MeBn	2.0	78	**5**(**b**)
3	CN	Cl	(*R*)-α-MeBn	1.5	75	**5**(**c**)
4	Cl	CF_3	(*R*)-α-MeBn	2.5	71	**5**(**d**)
5	CN	CF_3	(*R*)-α-MeBn	3.0	86	**5**(**e**)
6	Cl	H	(*S*)-α-MeBn	1.5	78	**5′**(**a**)
7	F	Cl	(*S*)-α-MeBn	2.0	77	**5′**(**b**)
8	CN	Cl	(*S*)-α-MeBn	1.5	74	**5′**(**c**)
9	Cl	CF_3	(*S*)-α-MeBn	2.5	73	**5′**(**d**)
10	CN	CF_3	(*S*)-α-MeBn	3.0	85	**5′**(**e**)

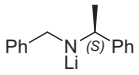
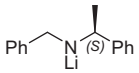
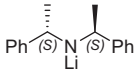
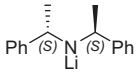
It could be assumed that at lower temperatures, lithium enolate is strongly aggregated and thus may not be reactive enough to undergo reaction with the electrophile. At a higher temperature, aggregation was disrupted causing the formation of the dibenzylated product. Therefore, it was necessary to modulate the reactivity of the enolates and consequently the reaction kinetics. Since the reactivity of enolates is governed by the counter cation, the reaction was next studied by generating different metal enolates. It was observed that titanium and zirconium enolates were unreactive, while the sodium and potassium enolates were highly reactive to form only dibenzylated adducts (Table 2, entries 11–14). Lithium enolates generated using LHMDS afforded better results among the various bases employed and hence were considered for further optimizations. Another attempt to improve the reactivity of lithium enolate was by changing the reaction medium. The reaction was thus tried in the polar aprotic solvent DMF but only the formation of the dibenzylated adduct was observed. The aggregation of the enolate in the solvent can be altered by the addition of chelating agents, such as tetramethyl ethylene diamine (TMEDA), lithium chloride (LiCl), and hexamethyl phosphoramide (HMPA), which can exert significant effects on the regio- and stereochemical outcomes of the reaction.[7] Therefore the reactions were evaluated by employing different chelating agents (Table 2, entries 15–20) and the best result was obtained with HMPA.

The addition of HMPA at low temperature (−78 °C) greatly improved the yields of monobenzylated product although the diastereoselectivity was moderate (65:35). However the use of an excess of base or alkylating agent under these conditions lowered the yield of the monobenzylated product. The increased reactivity of the enolate may be because of the coordination with HMPA. Since HMPA is highly polar and aprotic, it coordinates strongly with the lithium ion. This results in solvent metal dispersal allowing the enolate to react even at lower temperatures with reasonable diastereoselectivity. In order to improve the diastereoselectivity of the reaction, the role of quenchers were examined, either by adding them directly or by deprotonation followed by quenching. Various chiral and achiral reagents were screened (Table 3). Results were modest in most cases while a significant enhancement in diasteroselectivity (79:21) was observed with L-ethyl lactate. However, the diastereoselectivity was considerably reduced when deprotonation with an additional equivalent of LHMDS followed by quenching with chiral ethyl lactate, (Table 3, entry 8) was attempted.

Reacting 3-aryl-1-alkyl-2-thioxotetrahydropyrimidin-4(1*H*)-ones with LHMDS and HMPA at −78 °C followed by the addition of 4-chlorobenzylbromide and subsequent quenching with chiral ethyl lactate turned out to be the best conditions to obtain the monobenzylated product with good stereoselectivity (Scheme 3). The scope of the reaction was then examined on substrates **5**(**a**–**e**) bearing different substituents on the aryl ring at N3; in all the cases, the monobenzylated product was obtained in good yield and with high diastereoselectivity (Table 4) in favor of diastereomer 2. Similar reaction conditions were then employed for the monobenzylation of the corresponding enantiomers **5′**(**a**–**e**).

The relative configuration of the diastereomers **7**(**e**)(**i**) and **7**(**e**)(**ii**) at C5 can be predicted on the basis of energy calculations and NMR analysis [8]. NMR spectra of the diastereomers were compared and the structural assignments were made on the basis of chemical shifts and the inferences drawn from COSY, NOESY, DEPT,

Table 2
Reaction conditions employed for selective monobenzylation

Entry	Base	Additive	Temp (°C)	**5**(**c**)[a] (%)	**7**(**c**)(**i**)+**7**(**c**)(**ii**)[a] (%)	**7**(**c**)(**iii**)[a] (%)
1	*n*-BuLi	—	−78	—	15	34
2	*n*-BuLi	—	0	—	10	35
3	LDA	—	−78	—	25	30
4	LDA	—	0	—	18	32
5	LHMDS	—	−78	—	39	25
6	LHMDS	—	0	—	23	35
7		—	−78	80	—	—
8		—	0	70	—	10
9		—	−78	82	—	—
10		—	0	68	—	12
11	DIPEA	$TiCl_4$	−78	80	—	—
12	*n*-BuLi	$Zr(Cp)_2Cl_2$	−78	84	—	—
13	NHMDS	—	−78	40		45
14	KHMDS	—	−78	45	—	48
15	LHMDS	TMEDA	−78	70	—	10
16	LHMDS	TMEDA	0	30	—	40
17	LHMDS	LiCl	−78	75	—	8
18	LHMDS	LiCl	0	60	—	14
19	LHMDS	HMPA	−78	10	65	10
20	LHMDS	HMPA	0	10	20	30

[a] Isolated yields.

Table 3
Different quenching agents used for stereoselective monobenzylation

Entry	LHMDS equiv	Quenching agent	**7**(**c**)(**i**)+**7**(**c**)(**ii**)[a] (%)	**7**(**c**)(**iii**)[a] (%)	D2:D1[b]
1	0.99	NH_4Cl	65	10	65:35
2	0.99	1 N HCl	64	9	68:32
3	0.99	*N*-Boc proline	63	10	75:25
4	0.99	Ethyl-3(*R*)-hydroxybutyrate	60	12	70:30
5	0.99	Ethyl-3(*S*)-hydroxybutyrate	62	10	70:30
6	0.99	Prolinol	60	9	70:31
7	0.99	(*L*)-Ethyl lactate	67	8	79:21
8	2.1	(*L*)-Ethyl lactate	50	15	60:40

[a] Isolated yields.
[b] Ratio determined from ^1H NMR.

HMQC, and HMBC experiments. A comparison of the ^1H NMR spectra (Fig. 1) for the diastereomers **7**(**e**)(**i**) and **7**(**e**)(**ii**) indicated that the C5 proton appeared as a multiplet at δ values of 2.52 and 2.94, respectively. In order to determine the exact geometry of both diastereomers, energy optimizations were done by ab initio calculations performed using Gaussian B3LYP with basis set of 6–31G* (d,p) for the different possible conformations of diastereomers **7**(**e**)(**i**) and **7**(**e**)(**ii**). The most stable conformations were identified on the basis of the energy calculations (Fig. 2).[9]

A 3-dimensional structural representation of **7**(**e**)(**i**) (diastereomer 1), demonstrates that the proton at C5 is coplanar with respect to the carbonyl group, which in turn exhibits its anisotropy resulting in a net upfield shift of the signal to 2.52 ppm; hence an (*R*)-configuration can be assigned at C5 for diastereomer 1. However, the corresponding proton at C5 resonated at 2.94 ppm for **7**(**e**)(**ii**) (diastereomer 2), indicating that it is free from the shielding effect of the carbonyl group; hence an (*S*)-configuration can be assigned at C5 in accordance with the NMR spectra. The configuration was finally confirmed by single crystal X-ray analysis and an ORTEP diagram of **7**(**e**)(**ii**) is shown in Figure 3.

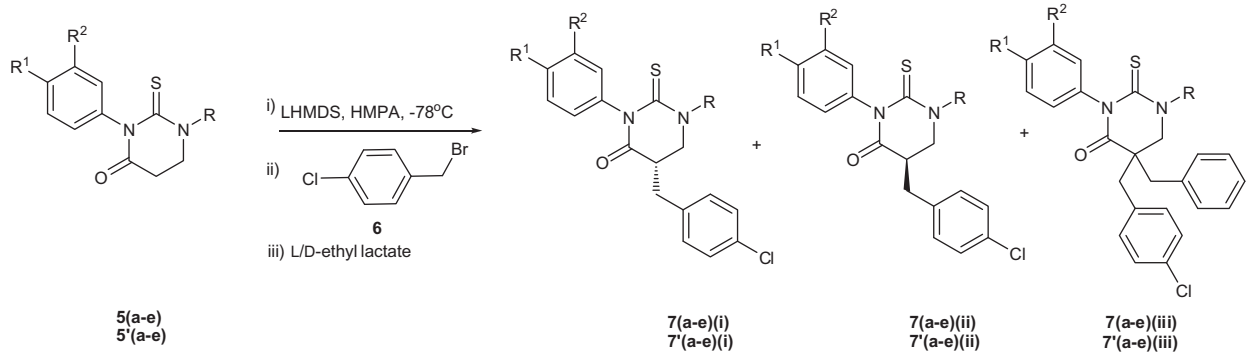
3. Conclusion

Benzylation reactions of enantiomerically pure 3-aryl-1-alkyl-2-thioxotetrahydropyrimidin-4(1*H*)-ones were studied from the perspective of the stereocontrol originating from the chiral substituent at N1, the additive, and the quenching agent. The absolute configuration of the product was assigned by NMR experiments based on the anisotropic effect exerted by the carbonyl group on the adjacent proton at C5, and confirmed by single crystal XRD analysis.

4. Experimental

4.1. General

The ^1H 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 ^1H and ^{13}C are given in ppm relative to residual signals of the solvent. Coupling constants are given in Hz. The following



Scheme 3. Syntheses of 5-(4-chlorobenzyl)-3-aryl-1-((*R*/*S*)-1-phenyl ethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-ones.

Table 4
Alkylation reactions of 3-aryl-1-((*R*/*S*)-1-phenyl ethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-ones

Entry	R^1	R^2	R	Diastereomer 1 D1	Diastereomer 2 D2	Dibenzylated adduct	D2:D1[c]
1	Cl	H	(*R*)-α-MeBn	**7**(**a**)(**i**), 13%	**7**(**a**)(**ii**), 55%	**7**(**a**)(**iii**), 8%	81:19
2	F	Cl	(*R*)-α-MeBn	**7**(**b**)(**i**), 14%	**7**(**b**)(**ii**), 52%	**7**(**b**)(**iii**), 9%	79:21
3	CN	Cl	(*R*)-α-MeBn	**7**(**c**)(**i**), 14%	**7**(**c**)(**ii**), 53%	**7**(**c**)(**iii**), 8%	79:21
4	Cl	CF_3	(*R*)-α-MeBn	**7**(**d**)(**i**), 13%	**7**(**d**)(**ii**), 54%	**7**(**d**)(**iii**), 9%	80:20
5	CN	CF_3	(*R*)-α-MeBn	**7**(**e**)(**i**), 14%	**7**(**e**)(**ii**), 55%	**7**(**e**)(**iii**), 9%	79:21
6	Cl	H	(*S*)-α-MeBn	**7′**(**a**)(**i**), 12%	**7′**(**a**)(**ii**), 54%	**7′**(**a**)(**iii**), 10%	82:18
7	F	Cl	(*S*)-α-MeBn	**7′**(**b**)(**i**), 14%	**7′**(**b**)(**ii**), 53%	**7′**(**b**)(**iii**), 8%	79:21
8	CN	Cl	(*S*)-α-MeBn	**7′**(**c**)(**i**), 15%	**7′**(**c**)(**ii**), 52%	**7′**(**c**)(**iii**), 9%	78:12
9	Cl	CF_3	(*S*)-α-MeBn	**7′**(**d**)(**i**), 13%	**7′**(**d**)(**ii**), 53%	**7′**(**d**)(**iii**), 8%	81:19
10	CN	CF_3	(*S*)-α-MeBn	**7′**(**e**)(**i**), 14%	**7′**(**e**)(**ii**), 55%	**7′**(**e**)(**iii**), 9%	79:21

[c] Isolated yield.

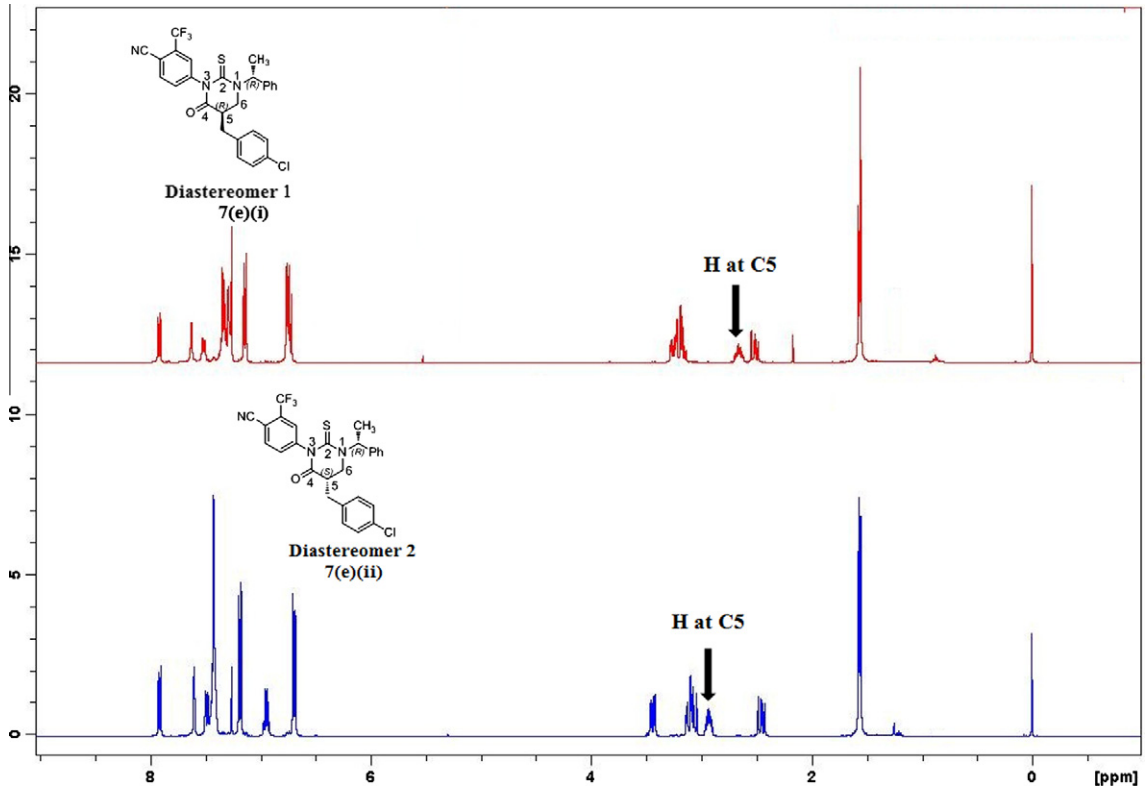


Figure 1. Comparison of ^{1}H NMR spectra for the diastereomers **7**(**e**)(**i**) and **7**(**e**)(**ii**).

abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; m, multiplet. Mass spectra were recorded on Finnigan Mat LCQ LCMS and HRMS were recorded on a Bruker Maxis spectrometer. The reactions were monitored by TLC (Merck). Evapora-

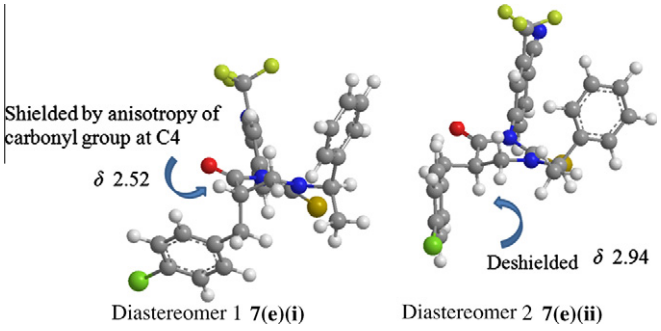


Figure 2. Most stable conformations for diastereomers **7**(**e**)(**i**) and **7**(**e**)(**ii**).

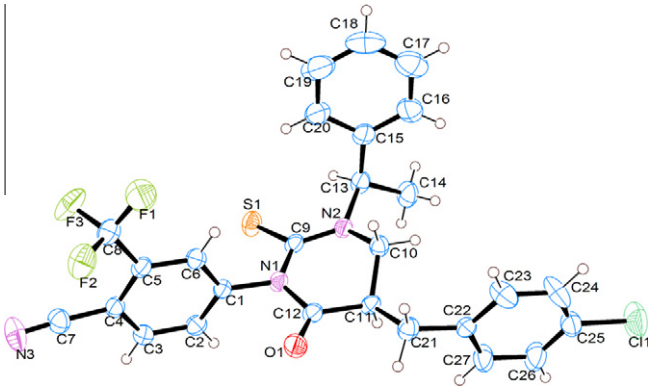


Figure 3. ORTEP diagram for **7** (**e**)(**ii**).

tion of solvents was performed under reduced pressure using a Buchi rotary evaporator. Commercial grade reagents and solvents were used without further purification.

4.2. Single crystal X-ray analysis

A suitable crystal of **7**(**e**)(**ii**) was subjected to X-ray diffraction analysis. The intensity data were collected; and the lattice parameters and standard deviations were obtained. The data were corrected for Lorentz and polarization factors. The structure was solved by direct methods program SHELX–97 (Sheldrick, 1997) package and also refined using the same. The final model was plotted using the program ORTEP. Crystallographic data for the compound have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 857508. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.3. General procedure for the synthesis of 3-(1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-ones

To a solution of aryl isothiocyanate (2.57 mmol) in 30 mL of acetonitrile taken in a round-bottomed flask was added β-amino ester (0.53 g, 2.57 mmol) followed by triethylamine (0.43 mL, 3.08 mmol) and $LiClO_4$ (0.03 g, 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 Na_2SO_4. It was then concentrated and purified by column chromatography on silica gel (60–120) using hexane–ethyl acetate mixture (85:15) as the eluent and recrystallized from MeOH.

4.3.1. (*R*)-3-(4-Chlorophenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5(a) (Table 1, entry 1)

White solid; yield = 76%; mp = 202–204 °C; $[\alpha]_D^{20} = +240.60$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66–1.69 (d, *J* = 7.0 Hz, 3H), 2.61–2.78 (m, 2H), 3.26–3.32 (m, 1H), 3.47–3.54 (m, 1H), 6.92–6.97 (q, *J* = 7.0 Hz, 1H), 7.13–7.16 (d, *J* = 8.4 Hz, 2H), 7.34–7.45 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.56, 31.99, 39.19, 59.36, 127.11, 128.31, 128.95, 129.22, 130.78, 134.20, 138.21, 138.62, 166.36, 181.49; MS (APCI): $[M+1]^+$ = 344.93.

4.3.2. (*R*)-3-(3-Chloro-4-fluorophenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5(b) (Table 1, entry 2)

White solid: yield = 75%; mp =190–191 °C; $[\alpha]_D^{20} = +232.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.69 (d, *J* = 7.2 Hz, 3H), 2.61–2.78 (m, 2H), 3.26–3.33 (m, 1H), 3.47–3.54 (m, 1H), 6.90–6.95 (q, *J* = 7.2 Hz, 1H), 7.07–7.11 (m, 1H), 7.22–7.28 (m, 2H), 7.33–7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.55, 31.93, 39.17, 59.45, 116.56, 116.78, 121.22, 127.12, 128.38, 128.99, 129.49, 131.87, 135.88, 135.92, 138.5, 156.53, 159.02, 166.39, 181.27; MS (APCI): $[M+1]^+$ = 362.93.

4.3.3. (*R*)-3-(3-Chloro-4-cyanophenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5(c) (Table 1, entry 3)

White solid; yield = 78%; mp = 230–231 °C; $[\alpha]_D^{20} = +259.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.69 (d, *J* = 6.8 Hz, 3H), 2.62–2.79 (m, 2H), 3.28–3.35 (m, 1H), 3.52–3.57 (m, 1H), 6.84–6.89 (q, *J* = 6.8 Hz, 1H), 7.23–7.27 (m, 1H), 7.35–7.45 (m, 6H), 7.73–7.75 (d, *J* = 8.0 Hz, 1H); ^{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.

4.3.4. (*R*)-3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5(d) (Table 1, entry 4)

White solid: yield = 71%; mp = 123–125 °C; $[\alpha]_D^{20} = +234.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.69 (d, *J* = 6.8 Hz, 3H), 2.62–2.79 (m, 2H), 3.29–3.35 (m, 1H), 3.50–3.56 (m, 1H), 6.87–6.93 (q, *J* = 6.8 Hz, 1H), 7.31–7.44 (m, 6H), 7.51–7.52 (d, *J* = 2.4 Hz, 1H), 7.58–7.60 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.55, 31.91, 39.27, 59.44, 121.09, 123.81, 127.12, 128.43, 128.86, 129.00, 129.18, 131.93, 132.18, 134.15, 138.26, 138.42, 166.34, 180.92; MS (APCI): $[M+1]^+$ = 413.00.

4.3.5. (*R*)-3-(4-Cyano-3-(trifluoromethyl)phenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5(e) (Table 1, entry 5)

White solid; yield = 86%; mp = 180–182 °C; $[\alpha]_D^{20} = +240.05$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68–1.70 (d, *J* = 7.2 Hz, 3H), 2.64–2.82 (m, 2H), 3.32–3.38 (m, 1H), 3.53–3.60 (m, 1H), 6.83–6.88 (q, *J* = 7.0 Hz, 1H), 7.36–7.48 (m, 5H), 7.52–7.54 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 1H), 7.91–7.93 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.56, 31.83, 39.20, 59.40, 109.67, 115.13, 123.40, 126.12, 127.12, 128.55, 128.72, 129.07, 135.23, 138.18, 143.78, 166.14, 180.25; MS (APCI): $[M+1]^+$ = 404.00.

4.3.6. (*S*)-3-(4-Chlorophenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5′(a) (Table 1, entry 6)

White solid; yield = 78%; mp = 202–204°C; $[\alpha]_D^{20} = -240.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65–1.67 (d, *J* = 7.0 Hz, 3H), 2.60–2.77 (m, 2H), 3.25–3.31 (m, 1H), 3.46–3.53 (m, 1H), 6.90–6.95 (q, *J* = 7.0 Hz, 1H), 7.11–7.14 (d, *J* = 8.5 Hz, 2H), 7.32–7.43 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.56, 31.99, 39.19, 59.36, 127.11, 128.31, 128.95, 129.22, 130.78, 134.20, 138.21, 138.62, 166.36, 181.49; MS (APCI): $[M+1]^+$ = 344.93

4.3.7. (*S*)-3-(3-Chloro-4-fluorophenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5′(b) (Table 1, entry 7)

White solid: yield = 74%; mp =190–191 °C; $[\alpha]_D^{20} = -232.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.69 (d, *J* = 7.2 Hz, 3H), 2.61–2.78 (m, 2H), 3.27–3.32 (m, 1H), 3.46–3.54 (m, 1H), 6.90–6.95 (q, *J* = 7.2 Hz, 1H), 7.07–7.11 (m, 1H), 7.21–7.28 (m, 2H), 7.33–7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.55, 31.93, 39.17, 59.45, 116.78, 121.22, 127.12, 128.99, 129.49, 131.87, 135.88, 138.5, 156.53, 159.02, 166.39, 181.27; MS (APCI): $[M+1]^+$ = 362.93.

4.3.8. (*S*)-3-(3-Chloro-4-cyanophenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5′(c) (Table 1, entry 8)

White solid; yield = 77%; mp = 230–231 °C; $[\alpha]_D^{20} = -259.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.69 (d, *J* = 6.8 Hz, 3H), 2.62–2.79 (m, 2H), 3.29–3.35 (m, 1H), 3.50–3.57 (m, 1H), 6.84–6.89 (q, *J* = 6.8 Hz, 1H), 7.23–7.27 (m, 1H), 7.35–7.45 (m, 6H), 7.73–7.75 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.57, 31.85, 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.

4.3.9. (*S*)-3-(4-Chloro-3-(trifluoromethyl)phenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5′(d) (Table 1, entry 9)

White solid; yield = 73%; mp = 123–125 °C; $[\alpha]_D^{20} = -234.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66–1.68 (d, *J* = 7.2 Hz, 3H), 2.61–2.77 (m, 2H), 3.27–3.34 (m, 1H), 3.48–3.56 (m, 1H), 6.84–6.89 (q, *J* = 7.0 Hz, 1H), 7.29–7.43 (m, 6H), 7.49–7.50 (d, *J* = 2.3 Hz, 1H), 7.56–7.58 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.54, 31.93, 39.17, 59.40, 127.12, 128.41, 128.64, 128.86, 129.00, 129.18, 131.91, 132.18, 134.14, 138.28, 138.45, 166.30, 180.97; MS (APCI): $[M+1]^+$ = 413.00.

4.3.10. (*S*)-3-(4-Cyano-3-(trifluoromethyl)phenyl)-1-(1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 5′(e) (Table 1, entry 10)

White solid; yield = 85%; mp = 180–182 °C; $[\alpha]_D^{20} = -239.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66–1.68 (d, *J* = 7.2 Hz, 3H), 2.63–2.80 (m, 2H), 3.30–3.37 (m, 1H), 3.52–3.58 (m, 1H), 6.81–6.87 (q, *J* = 7.0 Hz, 1H), 7.35–7.47 (m, 5H), 7.50–7.53 (d, *J* = 8.2 Hz, 1H), 7.63 (s, 1H), 7.89–7.91 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.55, 31.84, 39.21, 59.40, 109.68, 115.09, 123.39, 127.12, 128.54, 128.72, 129.06, 133.70, 135.19, 138.21, 143.77, 166.09, 180.29; MS (APCI): $[M+1]^+$ = 404.00.

4.4. General procedure for the syntheses of 5-(4-chlorobenzyl)-3-aryl-1-((*R*)/(*S*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-ones

In a typical experiment, 3-aryl-1-((*R*)/(*S*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one (0.25 g, 0.70 mmol) dissolved in anhydrous THF (5 mL) and cooled to −78 °C, was treated with LHMDS (0.70 mL, 0.70 mmol, 1.0 M solution in THF) under nitrogen atmosphere and stirred for 30 min followed by the addition of HMPA (0.13 g, 0.77 mmol). The reaction mixture was stirred for 1 h, and then 4-chlorobenzylbromide (0.15 g, 0.70 mmol) was added, and stirred for another 2 h. It was then quenched with chiral ethyl lactate 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 the desired compound as a mixture of diastereomers. The diastereomers were further 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 spectroscopic methods.

4.4.1. (*R*)-3-(4-Chlorophenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7(a)(i) (Table 4, entry 1)

White solid; yield = 13%; mp = 130–132 °C; $[\alpha]_D^{20} = +266.75$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54–1.56 (d, *J* = 7.0 Hz, 3H), 2.48–2.54 (m, 1H), 2.62–2.67 (m, 1H), 3.09–3.26 (m, 3H), 6.73–6.75 (d, *J* = 8.3 Hz, 2H), 6.79–6.84 (q, *J* = 7.0 Hz, 1H), 7.03–7.17 (m, 3H), 7.25–7.35 (m, 6H), 7.42–7.44 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.11, 31.99, 41.79, 42.72, 59.28, 127.07, 128.31, 128.52, 128.85, 129.26, 129.50, 130.68, 132.56, 134.25, 135.29, 138.27, 138.69, 168.66, 181.07; MS (APCI): $[M+1]^+$ = 468.94; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{25}H_{22}Cl_2N_2OS$: 491.0728. Found: 491.0738.

4.4.2. (*S*)-3-(4-Chlorophenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7(a)(ii) (Table 4, entry 1)

White solid; yield = 55%; mp = 178–180 °C; $[\alpha]_D^{20} = +266.55$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54–1.56 (d, *J* = 6.9 Hz, 3H), 2.40–2.46 (m, 1H), 2.81–2.92 (m, 1H), 2.99–3.04 (m, 1H), 3.09–3.13 (m, 1H), 3.36–3.40 (m, 1H), 6.67–6.69 (d, *J* = 7.4 Hz, 2H), 7.01–7.05 (q, *J* = 6.7 Hz, 1H), 7.09–7.11 (d, *J* = 7.6 Hz, 2H), 7.16–7.18 (d, *J* = 7.4 Hz, 2H), 7.35–7.44 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.67, 33.01, 42.28, 42.72, 59.10, 127.70, 128.53, 128.85, 129.03, 129.31, 130.08, 130.65, 132.81, 134.25, 135.66, 138.25, 138.39, 168.22, 181.09; MS (APCI): $[M+1]^+$ = 468.94; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{25}H_{22}Cl_2N_2OS$: 491.0728. Found: 491.0745.

4.4.3. (*R*)-3-(3-Chloro-4-fluorophenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7(b)(i) (Table 4, entry 2)

White solid; yield = 14%; mp = 142–144 °C; $[\alpha]_D^{20} = +424.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54–1.56 (d, *J* = 7.0 Hz, 3H), 2.47–2.53 (m, 1H), 2.58–2.64 (m, 1H), 3.10–3.26 (m, 3H), 6.73–6.75 (d, *J* = 8.4 Hz, 2H), 6.77–6.82 (q, *J* = 7.0 Hz, 1H), 7.11–7.14 (m, 3H), 7.19–7.34 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.10, 31.97, 41.82, 42.70, 59.37, 116.80, 121.26, 121.45, 127.06, 128.36, 128.88, 129.49, 132.61, 135.19, 135.98, 136.02, 138.59, 156.55, 159.04, 168.69, 180.88; MS (APCI): $[M+1]^+$ = 486.94; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{25}H_{21}Cl_2FN_2OS$: 509.0634. Found: 509.0626.

4.4.4. (*S*)-3-(3-Chloro-4-fluorophenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7(b)(ii) (Table 4, entry 2)

White solid; yield = 52%; mp = 155–158 °C; $[\alpha]_D^{20} = +224.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54–1.56 (d, *J* = 6.8 Hz, 3H), 2.40–2.45 (m, 1H), 2.82–2.91 (m, 1H), 2.98–3.04 (m, 1H), 3.07–3.16 (m, 1H), 3.34–3.41 (m, 1H), 6.67–6.69 (d, *J* = 7.5 Hz, 2H), 6.99–7.05 (m, 2H), 7.12–7.25 (m, 4H), 7.36–7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.66, 32.99, 41.28, 42.72, 59.20, 116.63, 116.85, 121.32, 121.51, 127.70, 128.58, 128.88, 129.06, 129.35, 130.06, 131.76, 132.86, 136.11, 138.14, 168.23, 180.91; MS (APCI): $[M+1]^+$ = 486.89; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{25}H_{21}Cl_2FN_2OS$: 509.0633. Found: 509.0636.

4.4.5. (*R*)-3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7(c)(i) (Table 4, entry 3)

White solid; yield 14%; mp 130–132 °C; $[\alpha]_D^{20} = +130.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56–1.58 (d, *J* = 7.0 Hz, 3H), 2.49–2.56 (m, 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, *J* = 8.3 Hz, 1H); ^{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 $[M+Na]^+$ Calcd for $C_{26}H_{21}Cl_2N_3OS$: 516.0680. Found: 516.0674.

4.4.6. (*S*)-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7(c)(ii) (Table 4, entry 3)

White solid; yield 52%; mp 135–137 °C; $[\alpha]_D^{20} = +139.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.56–1.58 (d, *J* = 7.0 Hz, 3H), 2.40–2.46 (m, 1H), 2.89–2.94 (m, 1H), 3.01–3.12 (m, 2H), 3.38–3.43 (m, 1H), 6.67–6.69 (d, *J* = 8.0 Hz, 2H), 6.92–6.97 (q, *J* = 7.0 Hz, 1H), 7.12–7.21 (m, 3H), 7.33–7.45 (m, 6H), 7.73–7.75 (d, *J* = 8.2 Hz, 1H); ^{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 $[M+Na]^+$ Calcd for $C_{26}H_{21}Cl_2N_3OS$: 516.0680. Found: 516.0672.

4.4.7. (*R*)-3-(4-Chloro-3-(trifluoromethyl)phenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydro pyrimidin-4(1*H*)-one 7(d)(i) (Table 4, entry 4)

White solid; yield 13%; mp 160–163 °C; $[\alpha]_D^{20} = +228.6$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.57 (d, *J* = 7.0 Hz, 3H), 2.47–2.53 (m, 1H), 2.61–2.67 (m, 1H), 3.10–3.27 (m, 3H), 6.72–6.80 (m, 3H), 7.11–7.13 (d, *J* = 8.0 Hz, 2H), 7.27–7.36 (m, 6H), 7.50 (s, 1H), 7.57–7.59 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.10, 31.92, 41.85, 42.71, 59.37, 121.08, 123.80, 127.06, 128.40, 128.68, 128.91, 129.22, 129.47, 131.95, 132.23, 132.65, 135.11, 138.36, 138.51, 168.68, 180.53; MS (APCI): $[M+1]^+ = 536.91$; HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{26}H_{21}Cl_2F_3N_2OS$: 559.0602. Found: 559.0635.

4.4.8. (*S*)-3-(4-Chloro-3-(trifluoromethyl)phenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydro pyrimidin-4(1*H*)-one 7(d)(ii) (Table 4, entry 4)

White solid; yield 13%; mp 152–154 °C; $[\alpha]_D^{20} = +439.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.54–1.56 (d, *J* = 7.0 Hz, 3H), 2.41–2.49 (m, 1H), 2.86–2.93 (m, 1H), 3.01–3.13 (m, 2H), 3.38–3.43 (m, 1H), 6.67–6.69 (d, *J* = 8.2 Hz, 2H), 6.95–7.00 (q, *J* = 7.0 Hz, 1H), 7.11–7.19 (m, 2H), 7.25–7.36 (m, 1H), 7.37–7.45 (m, 5H), 7.47 (s, 1H), 7.57–7.59 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.66, 32.99, 42.29, 42.73, 59.20, 121.06, 123.78, 127.72, 128.63, 128.90, 129.08, 129.26, 130.05, 131.99, 132.23, 132.91, 134.01, 135.46, 138.06, 138.45, 168.20, 180.56; MS (APCI): $[M+1]^+ = 536.99$; HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{26}H_{21}Cl_2F_3N_2OS$: 559.0602. Found: 559.0635.

4.4.9. (*R*)-3-(4-Cyano-3-(trifluoromethyl)phenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydro pyrimidin-4(1*H*)-one 7(e)(i) (Table 4, entry 5)

White solid; yield 13%; mp 82–85 °C; $[\alpha]_D^{20} = +140.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.56–1.58 (d, *J* = 7.0 Hz, 3H), 2.48–2.54 (m, 1H), 2.62–2.70 (m, 1H), 3.13–3.26 (m, 3H), 6.69–6.75 (m, 3H), 7.12–7.14 (d, *J* = 8.2 Hz, 2H), 7.23–7.34 (m, 5H), 7.50–7.52 (d, *J* = 7.9 Hz, 1H), 7.66 (s, 1H), 7.90–7.92 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.13, 31.83, 41.86, 42.73, 59.35, 109.74, 115.07, 116.14, 120.64, 127.06, 128.52, 129.44, 130.28, 132.75, 133.43, 133.77, 134.48, 135.24, 138.27, 143.81; 168.50, 179.88; MS (APCI): $[M+1]^+ = 528.06$; HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{27}H_{21}ClF_3N_3OS$: 550.0944. Found: 550.0961.

4.4.10. (*S*)-3-(4-Cyano-3-(trifluoromethyl)phenyl)-5-(4-chlorobenzyl)-1-((*R*)-1-phenylethyl)-2-thioxotetrahydro pyrimidin-4(1*H*)-one 7(e)(ii) (Table 4, entry 5)

White solid; yield 13%; mp 166–168 °C; $[\alpha]_D^{20} = +107.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.57 (d, *J* = 7.0 Hz, 3H), 2.42–2.48 (m, 1H), 2.89–2.96 (m, 1H), 3.04–3.13 (m, 2H), 3.41–3.46 (m, 1H), 6.67–6.69 (d, *J* = 8.3 Hz, 2H), 6.91–6.96 (q, *J* = 7.0 Hz, 1H), 7.16–7.20 (d, *J* = 8.3 Hz, 2H), 7.36–7.49 (m, 6H), 7.59 (s, 1H), 7.90–7.92 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.68, 32.95, 42.34, 42.69, 59.14, 109.78, 115.05, 120.62, 127.72, 128.75, 128.96, 129.14, 130.03, 133.03, 133.48, 133.71, 133.81, 135.23, 135.28, 137.83, 143.89, 168.02, 179.89; MS (APCI): $[M+1]^+ = 527.97$; HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{27}H_{21}ClF_3N_3OS$: 550.0944. Found: 550.0945.

4.4.11. (*S*)-3-(4-Chlorophenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7′(a)(i) (Table 4, entry 6)

White solid; yield = 12%; mp = 130–132 °C; $[\alpha]_D^{20} = -266.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.54–1.56 (d, *J* = 7.0 Hz, 3H), 2.48–2.54 (m, 1H), 2.62–2.67 (m, 1H), 3.09–3.26 (m, 3H), 6.73–6.75 (d, *J* = 8.3 Hz, 2H), 6.79–6.84 (q, *J* = 7.0 Hz, 1H), 7.03–7.17 (m, 3H), 7.25–7.35 (m, 6H), 7.42–7.44 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.11, 31.99, 41.79, 42.72, 59.28, 127.07, 128.31, 128.52, 128.85, 129.26, 129.50, 130.68, 132.56, 134.25, 135.29, 138.27, 138.69, 168.66, 181.07; MS (APCI): $[M+1]^+ = 468.93$; HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{25}H_{22}Cl_2N_2OS$: 491.0728. Found: 491.0719.

4.4.12. (*R*)-3-(4-Chlorophenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7′(a)(ii) (Table 4, entry 6)

White solid; yield = 54%; mp = 178–180 °C; $[\alpha]_D^{20} = -266.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.57 (d, *J* = 6.8 Hz, 3H), 2.41–2.47 (m, 1H), 2.86–2.93 (m, 1H), 3.00–3.06 (m, 1H), 3.10–3.15 (m, 1H), 3.37–3.42 (m, 1H), 6.69–6.71 (d, *J* = 8.4 Hz, 2H), 7.01–7.05 (q, *J* = 6.8 Hz, 1H), 7.10–7.12 (d, *J* = 8.0 Hz, 2H), 7.17–7.19 (d, *J* = 8.0 Hz, 2H), 7.31–7.45 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.66, 33.01, 42.31, 42.73, 59.09, 127.68, 128.51, 128.85, 129.01, 129.28, 130.06, 130.64, 132.82, 134.25, 135.67, 138.26, 138.39, 168.19, 181.12; MS (APCI): $[M+1]^+ = 469.00$; HRMS (ESI): m/z $[M+Na]^+$ Calcd for for $C_{25}H_{22}Cl_2N_2OS$: 491.0728. Found: 491.0713.

4.4.13. (*S*)-3-(3-Chloro-4-fluorophenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7′(b)(i) (Table 4, entry 7)

White solid; yield = 14%; mp = 142–144 °C; $[\alpha]_D^{20} = -424.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.57 (d, *J* = 7.0 Hz, 3H), 2.49–2.55 (m, 1H), 2.60–2.65 (m, 1H), 3.14–3.28 (m, 3H), 6.74–6.76 (d, *J* = 8.4 Hz, 2H), 6.79–6.85 (q, *J* = 7.0 Hz, 1H), 7.12–7.16 (m, 3H), 7.21–7.36 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.10, 31.96, 41.80, 42.69, 59.37, 116.80, 121.26, 121.45, 127.06, 128.36, 128.88, 129.49, 132.61, 135.19, 135.98, 136.02, 138.59, 156.55, 159.04, 168.69, 180.88; MS (APCI): $[M+1]^+ = 486.93$. HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{25}H_{21}Cl_2FN_2OS$: 509.0633. Found: 509.0623.

4.4.14. (*R*)-3-(3-Chloro-4-fluorophenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7′(b)(ii) (Table 4, entry 7)

White solid; yield = 53%; mp = 155–158 °C; $[\alpha]_D^{20} = -224.3$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.54–1.56 (d, *J* = 6.8 Hz, 3H), 2.40–2.45 (m, 1H), 2.82–2.91 (m, 1H), 2.98–3.04 (m, 1H), 3.07–3.16 (m, 1H), 3.34–3.41 (m, 1H), 6.67–6.69 (d, *J* = 7.5 Hz, 2H), 6.99–7.05 (m, 2H), 7.12–7.25 (m, 4H), 7.36–7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.66, 33.00, 42.28, 42.71, 59.20, 116.63, 116.85, 121.32, 121.51, 127.70, 128.59, 128.88, 129.06, 129.42, 130.06, 131.76, 132.86, 136.08, 138.14, 168.24, 180.91; MS (APCI): $[M+1]^+ = 486.92$; HRMS (ESI): m/z $[M+Na]^+$ Calcd for for $C_{25}H_{21}Cl_2FN_2OS$: 509.0633. Found: 509.0626.

4.4.15. (*S*)-3-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7′(c)(i) (Table 4, entry 8)

White solid; yield 14%; mp 130–132 °C; $[\alpha]_D^{20} = -130.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.56–1.58 (d, *J* = 7.0 Hz, 3H), 2.49–2.55 (m, 1H), 2.61–2.67 (m, 1H), 3.12–3.27 (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, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.12, 31.85, 41.82, 42.72, 59.28, 113.19, 115.60, 127.06, 128.49, 128.94, 129.46, 131.60, 132.72, 134.02, 134.93, 137.20, 138.34, 144.35, 168.37, 179.96; MS (APCI): $[M+1]^+$ = 493.95; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{26}H_{21}Cl_2N_3OS$: 516.0680. Found: 516.0672.

4.4.16. (*R*)-(3-Chloro-4-cyanophenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydropyrimidin-4(1*H*)-one 7′(c)(ii) (Table 4, entry 8)

White solid; yield 52%; mp 135–137 °C; $[\alpha]_D^{20} = -139.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.54–1.56 (d, *J* = 7.0 Hz, 3H), 2.40–2.46 (m, 1H), 2.87–2.94 (m, 1H), 3.01–3.12 (m, 2H), 3.38–3.43 (m, 1H), 6.67–6.69 (d, *J* = 8.3 Hz, 2H), 6.92–6.97 (q, *J* = 7.0 Hz, 1H), 7.12–7.21 (m, 3H), 7.33–7.45 (m, 6H), 7.73–7.75 (d, *J* = 8.2 Hz, 1H); ^{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): $[M+1]^+$= 493.96; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{26}H_{21}Cl_2N_3OS$: 516.0680. Found: 516.0674.

4.4.17. (*S*)-3-(4-Chloro-3-(trifluoromethyl)phenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydro pyrimidin-4(1*H*)-one 7′(d)(i) (Table 4, entry 9)

White solid; yield 13%; mp 160–163 °C; $[\alpha]_D^{20} = -228.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.57 (d, *J* = 7.0 Hz, 3H), 2.47–2.53 (m, 1H), 2.61–2.67 (m, 1H), 3.11–3.27 (m, 3H), 6.73–6.80 (m, 3H), 7.11–7.13 (d, *J* = 8.0 Hz, 2H), 7.27–7.36 (m, 6H), 7.49 (s, 1H), 7.57–7.59 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.11, 31.91, 41.84, 42.70, 59.37, 121.06, 123.80, 127.06, 128.41, 128.68, 128.91, 129.22, 129.46, 131.95, 132.23, 132.65, 135.09, 138.33, 138.50, 168.69, 180.53; MS (APCI): $[M+1]^+$ = 536.87; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{26}H_{21}Cl_2F_3N_2OS$: 559.0602. Found: 559.0593.

4.4.18. (*R*)-3-(4-Chloro-3-(trifluoromethyl)phenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydro pyrimidin-4(1*H*)-one 7′(d)(ii) (Table 4, entry 9)

White solid; yield 13%; mp 152–154 °C; $[\alpha]_D^{20} = -439.65$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.54–1.56 (d, *J* = 7.0 Hz, 3H), 2.41–2.47 (m, 1H), 2.86–2.93 (m, 1H), 3.01–3.13 (m, 2H), 3.38–3.43 (m, 1H), 6.67–6.69 (d, *J* = 8.2 Hz, 2H), 6.95–7.00 (q, *J* = 7.0 Hz, 1H), 7.11–7.19 (m, 2H), 7.25–7.36 (m, 1H), 7.37–7.45 (m, 5H), 7.47 (s, 1H), 7.57–7.59 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.67, 33.00, 42.29, 42.73, 59.21, 121.08, 123.80, 127.72, 128.64, 128.91, 129.09, 129.25, 130.06, 132.00, 132.24, 132.91, 134.02, 135.47, 138.06, 138.47, 168.21, 180.56; MS (APCI): $[M+1]^+$ = 536.87; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{26}H_{21}Cl_2F_3N_2OS$: 559.0602. Found: 559.0597.

4.4.19. (*S*)-3-(4-Cyano-3-(trifluoromethyl)phenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydro pyrimidin-4(1*H*)-one 7′(e)(i) (Table 4, entry 10)

White solid; yield 13%; mp 82–85 °C; $[\alpha]_D^{20} = -140.3$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.56–1.58 (d, *J* = 7.0 Hz, 3H), 2.48–2.54 (m, 1H), 2.62–2.70 (m, 1H), 3.13–3.26 (m, 3H), 6.70–6.75 (m, 3H), 7.12–7.14 (d, *J* = 8.2 Hz, 2H), 7.26–7.36 (m, 5H), 7.50–7.52 (d, *J* = 7.9 Hz, 1H), 7.62 (s, 1H), 7.90–7.92 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.13, 31.83, 41.86, 42.73, 59.35, 109.74, 115.07, 116.14, 120.64, 127.06, 128.52, 129.44, 130.28, 132.75, 133.43, 133.77, 134.48, 135.24, 138.27, 143.81; 168.50, 179.88; MS (APCI): $[M+1]^+$ = 528.06; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{27}H_{21}ClF_3N_3OS$: 550.0944. Found: 550.0912.

4.4.20. (*R*)-3-(4-Cyano-3-(trifluoromethyl)phenyl)-5-(4-chlorobenzyl)-1-((*S*)-1-phenylethyl)-2-thioxotetrahydro pyrimidin-4(1*H*)-one 7′(e)(ii) (Table 4, entry 10)

White solid; yield 13%; mp 166–168 °C; $[\alpha]_D^{20} = -107.6$ (*c* 1.0, CHC_{l3}); ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.57 (d, *J* = 7.0 Hz, 3H), 2.42–2.48 (m, 1H), 2.89–2.96 (m, 1H), 3.04–3.13 (m, 2H), 3.41–3.47 (m, 1H), 6.67–6.69 (d, *J* = 8.3 Hz, 2H), 6.90–6.96 (q, *J* = 7.0 Hz, 1H), 7.17–7.19 (d, *J* = 8.3 Hz, 2H), 7.35–7.50 (m, 6H), 7.59 (s, 1H), 7.90–7.92 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.68, 32.95, 42.36, 42.69, 59.16, 109.72, 115.08, 120.64, 127.72, 128.76, 128.96, 129.14, 130.04, 133.02, 133.46, 133.74, 133.79, 135.24, 135.29, 137.83, 143.93, 168.04, 179.88; MS (APCI): $[M+1]^+$ = 527.95; HRMS (ESI): *m*/*z* $[M+Na]^+$ Calcd for $C_{27}H_{21}ClF_3N_3OS$: 550.0944. Found: 550.0927.

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