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Biginelli reaction for synthesis of novel trifluoromethyl derivatives of bis(tetrahydropyrimidinone)benzenes

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ABSTRACT

A facile one-pot three-component condensation of terephthalic aldehyde with urea and fluorinated 1,3-dicarbonyl derivatives is developed using catalytic quantities of chlorotrimethylsilane at ambient temperature. As a consequence, efficient synthesis of novel trifluoromethyl derivatives of bis(tetrahydropyrimidinone)benzenes is observed within short time periods. The procedure is shown to be equally efficient when urea is replaced with thiourea or guanidine.

1. Introduction

Multicomponent reactions (MCRs) [1,2] are nowadays of particular importance in synthetic organic chemistry [3,4] since they offer one-pot combination of more than two components in one step allowing direct access to complex target molecules. In this context, the one-pot cyclocondensation of acetoacetic esters with aromatic aldehydes and (thio)urea, known as Biginelli reaction [5], has been one of the most well studied MCRs in recent years. The reaction affords formation of dihydropyrimidine derivatives as an important substructure of many synthetic [6–9] and natural compounds [10–13] that exhibit diverse pharmacological and therapeutic properties [14–17] such as antiviral, antibacterial, anti-inflammatory, and antitumor activities. In addition, several dihydropyrimidine containing alkaloids are isolated from marine sources which possess bilological and anti-HIV properties [18,19]. To extend the scopes of the Biginelli reaction, many alterations are made to the original high temperature HCl catalyzed condensation of ethylacetoacetate, benzaldehyde, and urea in ethanol [5] by variation of the three components [20–25] and the conditions [26–30].

Due to their unique physical, chemical, and biological properties, fluorinated organic compounds [31–33] have attracted much attention. Particularly, some of the fluorine-containing heterocycles have been known with potential interesting medicinal and agricultural applications [34–36]. In the frame work of our program to develop the chemistry of heterocyclic compounds [37–42] and in connection with our ongoing interests in MCRs [43–48], we would like to introduce a facile procedure for the synthesis of trifluoromethyl derivatives of bis(tetrahydropyrimidinone)benzenes via one-pot condensation of terephthalic aldehyde with (thio)urea or guanidine and fluorinated 1,3-dicarbonyl derivatives (Scheme 1). The reaction proceeds at ambient temperature using catalytic amount of TMSCl to afford high yields of the title compounds in short time periods.

2. Results and discussion

Table 1 summarizes the results for reactions of terephthalic aldehyde with various derivatives of **1** and **2**. We initially examined the reaction of urea (**2a**) with terephthalic aldehyde and 1,1,1-trifluoropentane-2,4-dione (**1a**) in the presence of TMSCl (Scheme 1). When the reaction was conducted in acetonitrile, TLC experiments showed complete consumption of the starting materials to form **3aa**. Control experiments were conducted to study the role of TMSCl. Experiments showed that 10 mol% quantities of the catalyst are enough for the reaction to complete in

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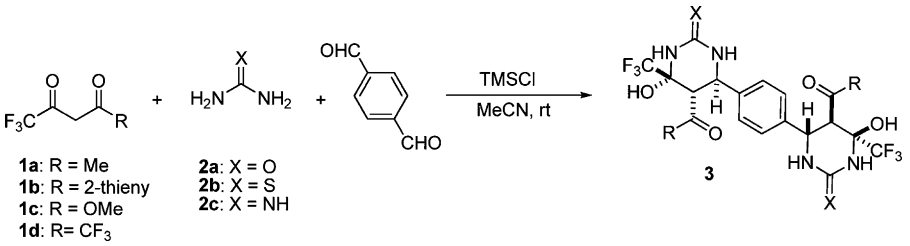


Scheme 1.

less than 1 h. Alternatively, in the absence of TMSCl, formation of only 10% of **3aa** was observed after 24 h to illustrate the crucial role of TMSCl for the reaction to proceed. The structure of **3aa** was elucidated by spectroscopic methods and its purity was confirmed by elemental analysis. A diagnostic coupling constant value ($^3J_{H,H}$ = 11.4 Hz) for the two peaks at δ = 3.13 and 4.77 ppm in the ^{1}H NMR spectrum was indicative for the *trans* stereochemistry of the vicinal hydrogens in both tetrahydropyrimidine rings. This stereochemistry is also confirmed by NOE and X-ray crystallography experiments [24]. In addition, it can be concluded from both ^{1}H NMR and ^{13}C NMR spectra of the product that the reaction is stereospecific leading to exclusive formation of one of the *meso* or *dl* diastereoproducts from which the *meso* product is shown here for the simplicity.

The generality of the process was demonstrated by variation of the starting materials. Same results were observed when urea was

Table 1
One-pot synthesis of products **3**

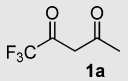
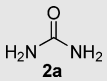
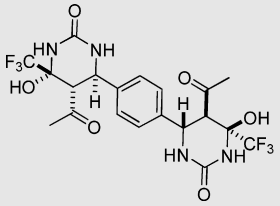
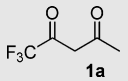
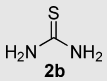
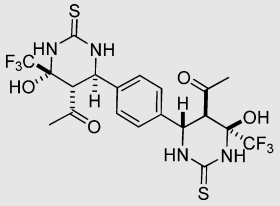
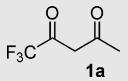
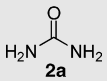
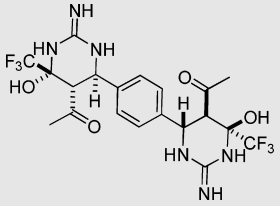
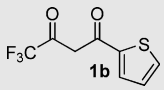
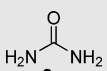
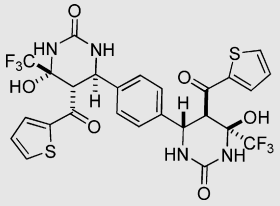
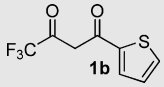
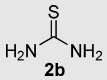
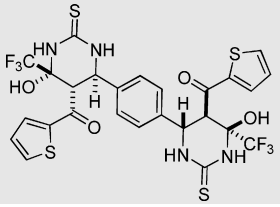
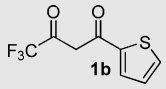
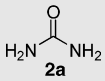
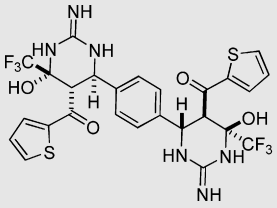
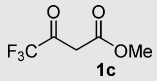
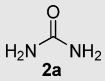
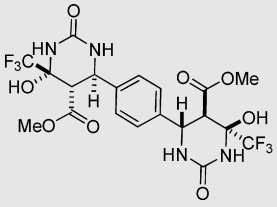
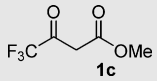
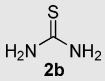
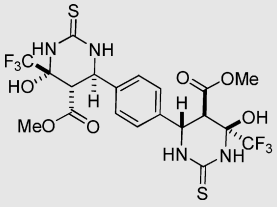
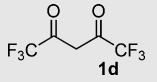
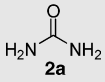
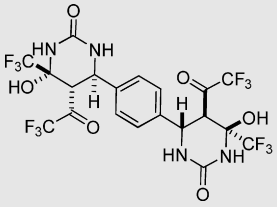
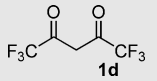
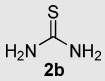
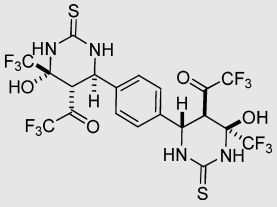
Entry	Substrates		Product	Time (min)	Yield[a] (%)
1	 **1a**	 **2a**	 **3aa**	45	87
2	 **1a**	 **2b**	 **3ab**	55	85
3	 **1a**	 **2a**	 **3ac**	60	82
4	 **1b**	 **2a**	 **3ba**	50	87
5	 **1b**	 **2b**	 **3bb**	55	83

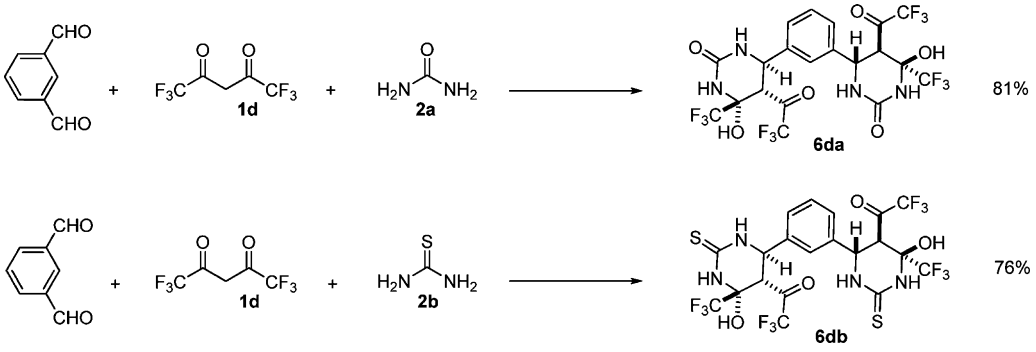
Table 1 (*Continued*)

Entry	Substrates		Product	Time (min)	Yield[a] (%)
6	 **1b**	 **2a**	 **3bc**	60	80
7	 **1c**	 **2a**	 **3ca**	45	84
8	 **1c**	 **2b**	 **3cb**	50	81
9	 **1d**	 **2a**	 **3da**	45	87
10	 **1d**	 **2b**	 **3db**	50	85

[a] Isolated yields.

replaced with thiourea (**2b**) or guanidine (**2c**). Consequently, efficient formation of **3ab** and **3ac** was observed in 85% and 82% yields, respectively. Similarly, use of other 1,3-dicarbonyl derivatives (**1b–d**) led to the synthesis of products **3ba–3db** in high yields. All products precipitated during the course of the reactions, were separated from the reaction mixtures via simple filtration, and were characterized based on their spectroscopic and physical data.

To further expand the scope of this procedure, reactions of other regioderivatives of phthalaldehyde were next investigated under



Scheme 2.

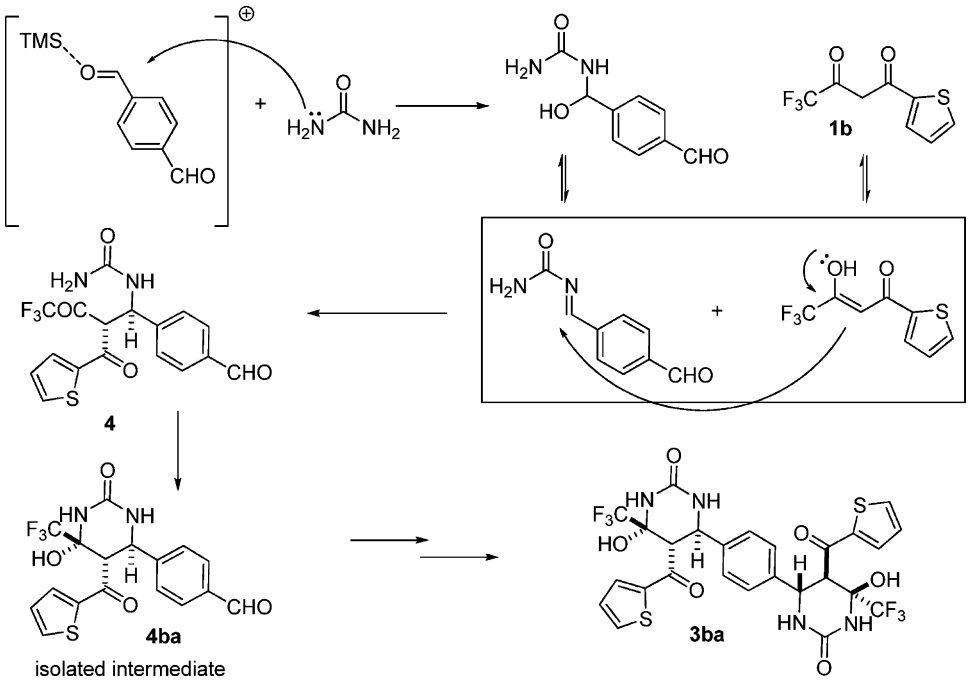
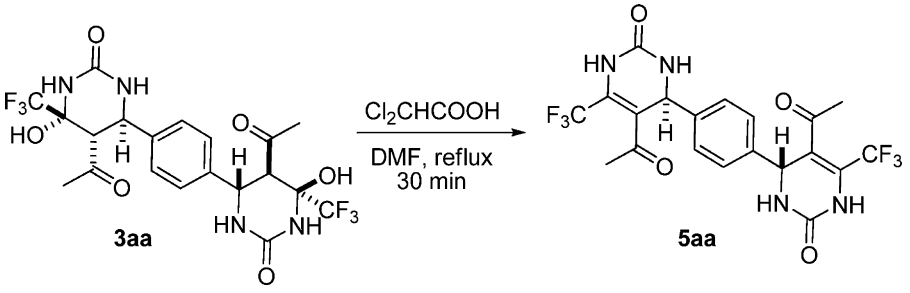


Fig. 1. Suggested mechanism.



Scheme 3.

similar conditions (Scheme 2). As a result, when isophthalaldehyde was subjected to react with **1d** and urea or thiourea, formation of 81% and 76% of **6da** and **6db** was observed, respectively. In contrast, when ortho-phthalaldehyde was subjected to react with the same reactants, complex mixtures containing several unidentified products formed.

As exemplified in Fig. 1 for the reaction between urea, terephthalic aldehyde, and **1b**, a mechanistic pathway can be suggested for the formation of the products [49]. The fact that 1,3-dicarbonyls such as **1b** primarily exist in their tautomeric enol form [50], and the separation of **4ba** as the intermediate of the reaction support the suggested mechanism. Finally, the structure of the products was verified by conversion of **3aa** to **5aa** at elevated temperature using dichloroacetic acid (Scheme 3).

3. Conclusion

We have presented the first synthesis of novel fluorinated derivatives of bis(tetrahydropyrimidinone)benzenes using mild reaction conditions. High yield products are directly obtained from the reaction mixtures using a simple filtration and easily purified by washing with ethanol. The procedure is applicable to a variety of starting substrates, reactions complete in short time periods, and low quantities of an inexpensive catalyst are used for reactions to proceed. It is noteworthy that this work presents one of a few available procedures for Biginelli reaction of guanidine. Moreover, the final usual dehydration step in Biginelli reaction can be avoided due to mild conditions of the procedure. Development of the method to one-pot synthesis of products containing two different tetrahydropyrimidinone units and determination of the stereochemistry of the products by X-ray crystallography are currently under investigation in our laboratories.

4. Experimental

4.1. General

Reactions were monitored by TLC using silica gel coated plates and ethyl acetate/$CHCl_3$ solutions as the mobile phase. Melting points are uncorrected and were measured using Electrothermal 9100 apparatus. FT-IR spectra were recorded using KBr disks on a Bomem-MB 100 infrared spectrometer and absorptions are reported as wave numbers (cm^{-1}). NMR spectra were obtained on a FT-NMR Bruker Spectro Spin DRX-300 MHz instrument as DMSO-d_6 or acetone-d_6 solutions and the chemical shifts are expressed as δ units with Me_4Si as the

internal standard. Mass spectra were obtained on a MS Model 5973 Network apparatus at ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. All other reagents were purchased from commercial sources and were freshly used after being purified by standard procedures.

4.2. Typical procedure for the preparation of 3aa–3db

A solution of terephthalic aldehyde (1 mmol), (thio)urea or guanidine (3 mmol), **1** (2 mmol), and TMSCl (0.2 mmol) in MeCN (3 mL) was stirred at room temperature for the time specified in Table 1 until TLC showed complete disappearance of terephthalic aldehyde. Reaction mixture was poured into cold water (25 mL) and stirred for 10 min. The precipitates were filtered and washed with cold water (2 × 10 mL) and then with 90% ethanol (10 mL) to give pure products. Products were characterized by analyzing their ^{1}H NMR, ^{13}C NMR, IR, and mass spectra and their purity was confirmed by elemental analysis.

4.3. Procedure for dehydration of 3aa

A solution of **3aa** (1 mmol) in DMF (5 mL) was refluxed in the presence of $Cl_2CHCOOH$ (2.2 mmol) for 30 min. After cooling the mixture, it was poured into 10 mL of cold water and washed with saturated sodium bicarbonate and brine solutions to obtain precipitates of **5aa**. The product was filtered, washed with cold water, and recrystallized from water and ethanol. The yield of the product was 81% (397 mg).

4.4. Spectral data

4.4.1. (4S,5R,6S)-5-acetyl-6-(4-((4R,5S,6R)-5-acetyl-6-hydroxy-2-oxo-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-4-hydroxy-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (3aa)

Yield: 87%; m.p. 300 °C (dec). IR (KBr, cm^{-1}) ν 3428 (OH), 3195 (NH), 2965 (NH), 1719 (C=O), 1705 (C=O); ^{1}H NMR (DMSO-d_6): δ 7.70 (2H, s, OH), 7.61 (2H, s, NH), 7.31 (4H, s, Ar), 7.20 (2H, s, NH), 4.77 (2H, d, J = 11.4 Hz, CH), 3.13 (2H, d, J = 11.4 Hz, CH), 1.78 (6H, s, Me); ^{13}C NMR (DMSO-d_6): δ 193.9, 153.5, 144.3, 132.5, 125.6, 80.5, 54.6, 52.3, 33.1; MS (70 eV) m/z (%) 526 (M$^+$, 9), 269 (30), 268 (100), 85 (53), 69 (50). Anal. Calcd for $C_{20}H_{20}F_6N_4O_6$: C, 45.63; H, 3.83. Found: C, 45.78; H, 3.41.

4.4.2. 1-((4R,5S,6R)-6-(4-((4S,5R,6S)-5-acetyl-6-hydroxy-2-thioxo-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-4-hydroxy-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl)ethanone(3ab)

Yield: 85%; m.p. 300 °C (dec). IR (KBr, cm^{-1}) ν 3423 (OH), 3197 (NH), 3102 (NH) 1720 (C=O), 1190 (CF) ^{1}H NMR (DMSO-d_6): δ 9.07 (2H, s, OH), 8.95 (2H, s, NH), 8.15 (2H, s, NH), 7.30 (4H, s, Ar), 4.76 (2H, d, J = 11.7 Hz, CH), 3.20 (2H, d, J = 11.7 Hz, CH), 1.81 (6H, s, Me); ^{13}C NMR (DMSO-d_6): δ 203.5, 177.6, 138.1, 129.3, 125.6, 80.5, 55.8, 54.8, 31.5; MS (70 eV) m/z (%) 558 (M$^+$, 10), 481 (45), 422 (64), 284 (100), 69 (51). Anal. Calcd for $C_{20}H_{20}F_6N_4O_4S_2$: C, 43.01; H, 3.61. Found: C, 43.09; H, 3.55.

4.4.3. 1-((4R,5S,6R)-6-(4-((4S,5R,6S)-5-acetyl-6-hydroxy-2-imino-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-4-hydroxy-2-imino-4-(trifluoromethyl)hexahydropyrimidin-5-yl)ethanone(3ac)

Yield: 82%; m.p. 300 °C (dec). IR (KBr) ν 3392 (OH), 3216 (NH), 2922 (NH), 1698 (C=O), 2235 (C=N), 1189 (CF) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.75 (2H, s, NH), 8.03 (2H, s, OH), 7.89 (2H, s, NH), 7.50 (4H, s, Ar), 6.95 (2H, br s, NH), 4.52 (2H, d, J = 11.2 Hz, CH), 3.35 (2H, d, J = 11.2 Hz, CH), 1.90 (6H, s, Me); ^{13}C NMR (DMSO-d_6): δ 201.5, 156.9, 139.6, 128.3, 125.4, 80.7, 56.0, 52.1, 31.5; MS (70 eV) m/z (%) 524 (M$^+$, 11), 368 (20), 313 (18), 236 (21), 57 (100). Anal. Calcd for $C_{20}H_{22}F_6N_6O_4$: C, 45.81; H, 4.23. Found: C, 45.74; H, 4.26.

4.4.4. (4S,5R,6S)-4-hydroxy-6-(4-((4R,5S,6R)-6-hydroxy-2-oxo-5-(thiophene-2-carbonyl)-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-5-(thiophene-2-carbonyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (3ba)

Yield: 87%; m.p. 265 °C (dec). IR (KBr) ν 3385 (OH), 3180 (NH), 2970 (NH), 1758 (C=O), 1704 (C=O), 1203 (CF) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.91 (2H, d, J = 4.8 Hz, thienyl), 7.78 (2H, d, J = 4 Hz, thienyl), 7.39 (4H, s, Ar), 7.06 (2H, dd, J = 4, 4.8 Hz, thienyl), 7.03 (2H, s, OH), 6.14 (2H, bs, NH), 6.02 (2H, s, NH), 4.97 (2H, d, J = 11.2 Hz, CH), 4.30 (2H, d, J = 11.2 Hz, CH); ^{13}C NMR (DMSO-d_6): δ 191.5, 156.3, 143.0, 137.7, 135.6, 133.4, 129.1, 128.7, 124.3, 81.6, 55.6, 49.5; MS (70 eV) m/z (%) 662 (M$^+$, 6), 626 (10), 438 (40), 266 (51), 69 (100). Anal. Calcd for $C_{26}H_{20}F_6N_4O_6S_2$: C, 47.13; H, 3.04. Found: C, 47.16; H, 3.06.

4.4.5. ((4S,5R,6S)-4-hydroxy-6-(4-((4R,5S,6R)-6-hydroxy-5-(thiophene-2-carbonyl)-2-thioxo-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl)(thiophen-2-yl)methanone (3bb)

Yield: 83%; m.p. 278 °C (dec). IR (KBr) ν 3392 (OH), 3175 (NH), 2973 (NH), 1663 (C=O), 1205 (CF) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.99 (2H, s, OH), 8.72 (2H, s, NH), 7.85 (2H, d, J = 4.5 Hz, thienyl), 7.80 (2H, d, J = 4 Hz, thienyl), 7.69 (2H, s, NH), 7.24 (4H, s, Ar), 6.99 (2H, dd, J = 4, 4.5 Hz, thienyl), 4.86 (2H, d, J = 11.2 Hz, CH), 4.30 (2H, d, J = 11.2 Hz, CH); ^{13}C NMR (DMSO-d_6): δ 187.8, 177.5, 145.5, 137.8, 135.8, 130.1, 129.3, 128.3, 125.5, 81.2, 62.8, 55.7; MS (70 eV) m/z (%) 694 (M$^+$, 5), 523 (7), 438 (40), 380 (39), 172 (55), 111 (50), 69 (100). Anal. Calcd for $C_{26}H_{20}F_6N_4O_4S_4$: C, 44.95; H, 2.90. Found: C, 44.89; H, 3.03.

4.4.6. ((4S,5R,6S)-4-hydroxy-6-(4-((4R,5S,6R)-6-hydroxy-2-imino-5-(thiophene-2-carbonyl)-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-2-imino-4-(trifluoromethyl)hexahydropyrimidin-5-yl)(thiophen-2-yl)methanone (3bc)

Yield: 80%; m.p. 258 °C (dec). IR (KBr) ν 3456 (OH), 3288 (NH), 2857 (NH), 1690 (C=O), 1210 (CF) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.75 (2H, s, OH), 8.08 (2H, s, NH), 7.98 (2H, d, J = 3 Hz, thienyl), 7.95 (2H, s, NH), 7.81 (2H, d, J = 4.5 Hz, thienyl), 7.56 (4H, s, Ar), 7.13 (2H, dd, J = 3, 4.5 Hz, thienyl), 7.04 (2H, br s, NH), 4.96 (2H, d, J = 12 Hz, CH), 4.61 (2H, d, J = 12 Hz, CH); ^{13}C NMR (DMSO-d_6): δ 196.0, 156.5, 143.2, 140.1, 138.5, 134.5, 129.2, 128.3, 125.3, 80.7, 54.5, 46.1; MS (70 eV) m/z (%) 660 (M$^+$, 5), 522 (11), 378 (37), 269 (71), 111 (74), 69 (85), 57 (100). Anal. Calcd for $C_{26}H_{22}F_6N_6O_4S_2$: C, 47.27; H, 3.36. Found: C, 47.44; H, 3.53.

4.4.7. (4S,5R,6S)-methyl 4-hydroxy-6-(4-((4R,5S,6R)-6-hydroxy-5-(methoxycarbonyl)-2-oxo-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-2-oxo-4-(trifluoromethyl)hexahydropyrimidine-5-carboxylate (3ca)

Yield: 84%; m.p. 290 °C (dec). IR (KBr) ν 3452 (OH), 3227 (NH), 2912 (NH), 1738 (C=O), 1662 (C=O), 1201 (CF) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.63 (2H, s, OH), 7.41 (2H, s, NH), 7.28 (4H, s, Ar), 7.19 (2H, s, NH), 4.77 (2H, d, J = 11.5 Hz, CH), 3.81 (2H, d, J = 11.5 Hz, CH), 3.69 (6H, s, OMe); ^{13}C NMR (DMSO-d_6): δ 166.7, 153.6, 138.5, 127.7, 124.1, 80.2, 60.2, 52.7, 50.6; ^{19}F NMR (DMSO-d_6): δ −81.53 (q, J = 275 Hz); MS (70 eV) m/z (%) 558 (M$^+$, 8), 477 (34), 435 (80), 268 (100), 87 (45). Anal. Calcd for $C_{20}H_{20}F_6N_4O_8$: C, 43.02; H, 3.61. Found: C, 43.14; H, 3.66.

*4.4.8. (4S,5R,6S)-methyl 4-hydroxy-6-(4-((4R,5S,6R)-6-hydroxy-5-(methoxycarbonyl)-2-thioxo-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidine-5-carboxylate (**3cb**)*

Yield: 81%; m.p. 295 °C (dec). IR (KBr) ν, 3437 (OH), 3194 (NH), 2986 (NH), 1738 (C=O), 1569 1212 (CF) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.10 (2H, s, OH), 8.86 (2H, s, NH), 7.88 (2H, s, NH), 7.32 (4H, s, Ar), 4.78 (2H, d, J = 11.8 Hz, CH), 3.83 (2H, d, J = 11.5 Hz, CH), 3.74 (6H, s, OMe); ^{13}C NMR (DMSO-d_6): δ 177.2, 166.3, 137.3, 128.3, 123.8, 79.5, 60.4, 53.8, 49.2; MS (70 eV) m/z (%) 590 (M^+, 7), 473 (35), 356 (41), 284 (100), 74 (41). Anal. Calcd for $C_{20}H_{20}F_6N_4O_6S_2$: C, 40.68; H, 3.41. Found: C, 40.54; H, 3.56.

*4.4.9. (4S,5R,6S)-4-hydroxy-6-(4-((4R,5S,6R)-6-hydroxy-2-oxo-5-(2,2,2-trifluoroacetyl)-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-5-(2,2,2-trifluoroacetyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (**3da**)*

Yield: 87%; m.p. 258–260 °C. IR (KBr) ν 3442 (OH), 3345 (NH), 2920 (NH), 1758 (C=O), 1687 (C=O), 1206 (CF) cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.51 (4H, s, Ar), 7.15 (2H, br s, NH), 7.00 (2H, s, OH), 6.48 (2H, s, NH), 5.12 (2H, d, J = 11.1 Hz, CH), 4.06 (2H, d, J = 11.1 Hz, CH); ^{13}C NMR (DMSO-d_6): δ 158.2, 151.1, 138.5, 129.4, 124.5, 117.1, 81.5, 54.8, 50.7; MS (70 eV) m/z (%) 634 (M^+, 10), 548 (30), 268 (100), 68 (65), 57 (40). Anal. Calcd for $C_{20}H_{14}F_{12}N_4O_6$: C, 37.87; H, 2.22. Found: C, 37.79; H, 2.29.

*4.4.10. 2,2,2-Trifluoro-1-((4S,5R,6S)-4-hydroxy-6-(4-((4R,5S,6R)-6-hydroxy-2-thioxo-5-(2,2,2-trifluoroacetyl)-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl)ethanone (**3db**).*

Yield: 85%; m.p. 265–267 °C. IR (KBr) ν 3565 (OH), 3184 (NH), 2976 (NH), 1756 (CO), 1209 (CF) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.64 (2H, s, OH), 9.73 (2H, s, NH), 8.49 (2H, s, NH), 7.65 (4H, s, Ar), 4.98 (2H, d, J = 11.1 Hz, CH), 4.16 (2H, d, J = 11.1 Hz, CH); ^{13}C NMR (DMSO-d_6): δ 177.8, 166.5, 143.1, 137.3, 130.5, 124.5, 81.5, 55.9, 49.3; MS (70 eV) m/z (%) 666 (M^+, 8), 523 (30), 284 (100), 69 (45), 43 (55). Anal. Calcd for $C_{20}H_{14}F_{12}N_4O_4S_2$: C, 36.04; H, 2.12. Found: C, 36.14; H, 2.21.

*4.4.11. 4-((4R,5S,6R)-6-hydroxy-2-oxo-5-(thiophene-2-carbonyl)-6-(trifluoromethyl)hexahydropyrimidin-4-yl)benzaldehyde (**4ba**)*

M.p. 234–236 °C. IR (KBr) ν 3410 (OH), 3216 (NH), 2925 (NH), 1681 (C=O), 1606 (C=O), 1204 (CF) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.93 (1H, s, CH=O), 7.92 (1H, d, J = 3.9 Hz, thienyl), 7.88 (1H, d, J = 3.3 Hz, thienyl), 7.78 (2H, d, J = 8.3 Hz, Ar), 7.72 (2H, d, J = 8.3 Hz, Ar), 7.21 (1H, s, OH), 7.07 (1H, dd, J = 3.3, 3.9 Hz, thienyl), 6.78 (1H, s, NH), 6.24 (1H, s, NH), 5.19 (1H, d, J = 11.1 Hz, CH), 4.42 (1H, d, J = 11.1 Hz, CH); ^{13}C NMR (DMSO-d_6): δ 192.6, 187.9, 153.6, 144.8, 136.2, 135.8, 133.9, 129.2, 129.1, 128.6, 123.8, 122.5, 81.9, 54.3, 49.4; MS (70 eV) m/z (%) 398 (M^+, 7), 360 (6), 287 (14), 269 (100), 111 (90). Anal. Calcd for $C_{17}H_{13}F_3N_2O_4S$: C, 51.26; H, 3.29. Found: C, 51.24; H, 3.25.

*4.4.12. (4R,4′S)-4,4′-(1,4-phenylene)bis(5-acetyl-6-(trifluoromethyl)-3,4-dihydropyrimidin-2(1H)-one) (**5aa**)*

Yield: 81%; m.p. 330 °C (dec). IR (KBr) ν 3324 (NH), 2962 (NH), 1710 (C=O), 1645 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.48 (2H, s, NH), 7.76 (2H, s, NH), 7.31 (4H, s, Ar), 5.14 (2H, s, CH), 2.25 (6H, s, Me); ^{13}C NMR (DMSO-d_6): δ 193.9, 152.6, 144.4, 132.5, 129.1, 125.9, 107.8, 50.5, 27.6; MS (70 eV) m/z (%) 490 (M^+, 11), 256 (100), 69 (85), 43 (63).

*4.4.13. (4S,5R,6S)-4-hydroxy-6-(3-((4R,5S,6R)-6-hydroxy-2-oxo-5-(2,2,2-trifluoroacetyl)-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-5-(2,2,2-trifluoroacetyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1H)-one (**6da**).*

Yield: 81%; m.p. 174–175 °C. IR (KBr) ν 3417 (OH), 3252 (NH), 1763 (C=O), 1697 (C=O), 1275 (CF) cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.33 (2H, s, OH), 7.85 (2H, br s, NH), 7.44 (1H, s, Ar), 7.32 (1H, t, J = 7.8 Hz, Ar), 7.23 (2H, s, NH), 7.13 (2H, d, J = 7.8 Hz, Ar), 5.08 (2H, d, J = 11.2 Hz, CH), 4.09 (2H, d, J = 11.2 Hz, CH); ^{13}C NMR (DMSO-d_6): δ 169.5, 154.9, 138.1, 130.6, 128.8, 127.9, 124.2, 117.9, 81.8, 55.1, 50.2; MS (70 eV) m/z (%) 634 (M^+, 8), 531 (12), 463 (21), 268 (100), 167 (55).

*4.4.14. 2,2,2-Trifluoro-1-((4S,5R,6S)-4-hydroxy-6-(3-((4R,5S,6R)-6-hydroxy-2-thioxo-5-(2,2,2-trifluoroacetyl)-6-(trifluoromethyl)hexahydropyrimidin-4-yl)phenyl)-2-thioxo-4-(trifluoromethyl)hexahydropyrimidin-5-yl)ethanone (**6db**).*

Yield: 76%; m.p. 189–190 °C. IR (KBr) ν 3424 (OH), 3260 (NH), 1760 (C=O), 1220 (CF) cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.04 (2H, s, OH), 7.96 (2H, s, NH), 7.90 (2H, s, NH), 7.23 (1H, t, J = 7.5 Hz, Ar), 7.16 (1H, s, Ar), 7.08 (2H, d, J = 7.5 Hz, Ar), 5.06 (2H, d, J = 11.5 Hz, CH), 3.96 (2H, d, J = 11.5 Hz, CH); ^{13}C NMR (DMSO-d_6): δ 192.1, 177.5, 141.0, 129.1, 128.7, 127.1, 124.3, 115.7, 82.4, 56.3, 48.9; MS (70 eV) m/z (%) 666 (M^+, 7), 630 (10), 523 (21), 298 (76), 69 (100).

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