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TETRAHEDRON

Synthesis of Novel Fluorinated Derivatives of 1,3-Dimethylbarbituric Acid

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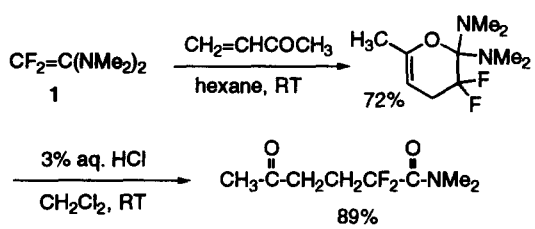
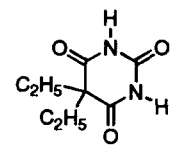
Abstract: Synthetic utility of the novel difluoro ketene aminal **1** was extended to the preparation of a number of potentially biologically-interesting difluoro barbituric acid derivatives via initial hetero-Diels-Alder reactions of **1** with *p*-substituted-5-benzylidene-1,3-dimethylbarbituric acids **3**. These cycloadducts **4** upon hydrolysis, provided the formal Michael addition product amides **5** which were readily converted to the respective carboxylic acids **6**. The acids were dehydratively cyclized to form novel bicyclic lactones **8**.

Recently we reported that novel difluoro ketene aminal **1** underwent cycloadditions with α,β-unsaturated carbonyl compounds, such as methyl vinyl ketone, as shown in Scheme 1, which, upon hydrolysis, resulted in excellent conversions to overall Michael addition products.[1]

Scheme 1



Barbiturates, such as barbital **2**, which are substituted derivatives of barbituric acid, were the first



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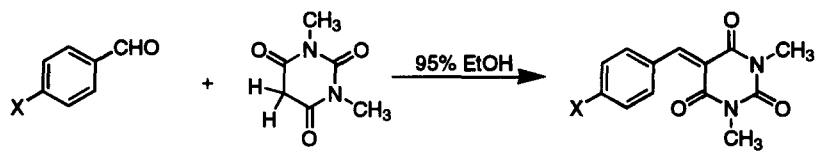
synthetic drugs found to exert significant action on the central nervous system.[2] They also show biological convulsant, anticonvulsant and analeptic effects. Such pharmacological properties of barbiturates have been reviewed.[3] Recently, it was found that derivatives of *5-benzyl*barbituric acid are potent chemotherapy agents, useful in the treatment of both cancer and AIDS.[4,5]

It is also well recognized that the selective introduction of fluorine substituents into a biologically active compound can enhance its pharmacological properties or increase its therapeutic effectiveness.[6-8] Thus, in order to synthesize some potentially biologically-interesting fluorinated derivatives of 5-benzylbarbituric acids, we decided to examine the chemistry of difluoro ketene aminal building block **1** with 5-benzylidene-1,3-dimethylbarbituric acid **3**. What resulted was not only the preparation of the expected initially-formed cycloaddition products and eventual Michael addition products (analogous to the chemistry in Scheme 1), but the observation of additional cyclization and tautomerization chemistry which is apparently unique to the barbituric acid system.

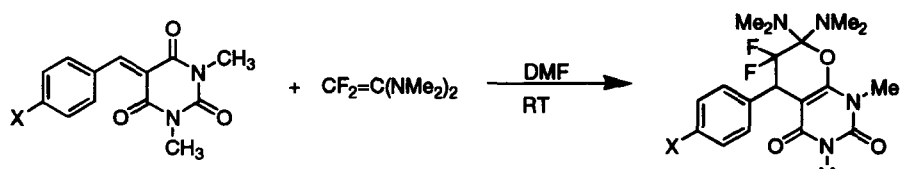
RESULTS AND DISCUSSION

5-Benzylidenene-1,3-dimethyl-barbituric acids **3a-d** were prepared in excellent yield by refluxing equimolar amounts of 1,3-dimethylbarbituric acid and the appropriate *p*-substituted benzaldehyde in 95% ethanol for 5-10 minutes.[9]



3a, X = H; **b**, X = OCH3
c, X = F; **d**, X = Br

The reaction of 3a-d, in DMF at room temperature, with a hexane solution of difluoroketene aminal **1** (generated by treatment of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane with a slight excess of *n*-BuLi), gave the expected hetero-Diels-Alder products **4a-d**.



3a, X = H; **b**, X = OCH3
c, X = F; **d**, X = Br

4a-d

The structures of **4a-d** were assigned on the basis of their NMR spectra, and confirmed by elemental analyses. In the ^{19}F NMR spectra of **4a-d** the two fluorine signals appear as a well-separated AB system (i.e., δ

-77.1 and -93.3 for **4a**). The signals for the single methine group in the ^1H spectra were typically observed as a doublet of doublets at about 5.30 ppm.

Cycloadducts **4a-d** underwent hydrolysis within 10 minutes at room temperature upon treatment with minimal amounts of 36% HCl in methylene chloride to give the formal Michael addition products, amides **5a-d**. Longer stirring led to hydrolysis of the amides to the acids. Indeed, refluxing the amides for 2 hours under the same 36% HCl/CH_2Cl_2 conditions led to formation of the respective carboxylic acids **6a-d** in excellent yield. Most notable in the ^1H NMR spectra of the amides were their two methine signals (i.e., at 4.38 and 4.61 ppm, for **5a**), the latter signal being strongly (18 Hz) coupled to the CF_2 group. The fluorine signals appear in the ^{19}F NMR as a much less separated AB system (i.e., at δ -96.6 and -98.2 ppm, for **5a**). The fluorine AB systems of the carboxylic acids were shifted to considerably lower fields (i.e., δ - 102.8 and -105.3 ppm for **6a**). As revealed by elemental analysis, three of the carboxylic acids **6a-c** incorporated a molecule of water upon recrystallization.

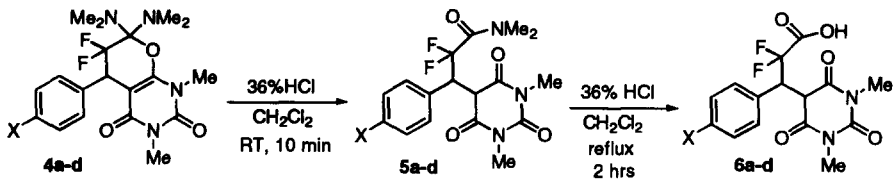
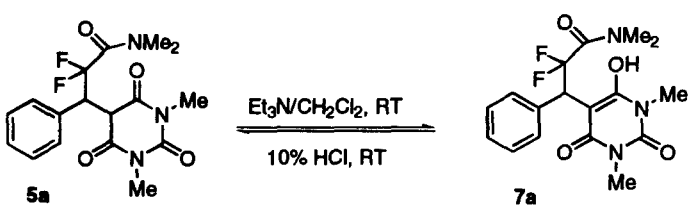


Table. Yields of Substrates and Products (%)

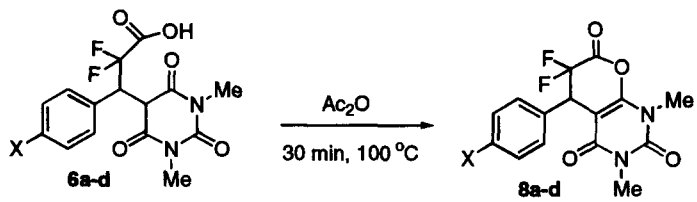
X	Substrate		Cycloadduct		Amide		Acid		Enol-Amide		Lactone	
H	**3a**	92	**4a**	87	**5a**	84	**6a**	89	**7a**	93	**8a**	89
OCH_3	**3b**	93	**4b**	93	**5b**	87	**6b**	81	-	-	**8b**	93
F	**3c**	95	**4c**	90	**5c**	86	**6c**	86	-	-	**8c**	90
Br	**3d**	90	**4d**	88	**5d**	82	**6d**	80	-	-	**8d**	91

Unlike N,N-dimethylbarbituric acid itself, the enol forms of 5-substituted barbituric acids are of comparable stability to their keto forms.[10] In the case of amide **5a**, either tautomer could be obtained by control of the conditions. It could be converted completely to its enol form **7a** by treatment with



triethylamine. The proton NMR spectrum of the enol-amide was notable for its single, relatively low field methine signal at 5.42 ppm. Although the other amides were not attempted, presumably they also would have been similarly converted. Upon treatment of this enol with 10% HCl, it was transformed back to its keto form.

In a reaction which, to our knowledge, has little precedent,[11-13] the carboxylic acids **6a-d** underwent cyclization to the fused lactones **8a-d** in excellent yields upon treatment with acetic anhydride. Since the enol form of **6** is readily accessible, the observed lactonization process should not be surprising. The proton NMR spectra of these novel barbiturate derivatives were also notable for their single methine signals at ~ 4.7 ppm. Again, as was the case for the other cyclized system **4**, the fluorine AB signals observed for the lactones were also much more significantly separated (i.e., -100.8 and -116.8 ppm, for **8a**) than were the AB signals for the non-cyclized products **5**, **6**, and **7**. The lactones were observed to be very sensitive to moisture.



Other than with respect to the ease of hydrolysis of the amides **5** which certainly hydrolyze much more readily because of the proximate fluorine substituents, the presence of the fluorine substituents should not have been mechanistically-instrumental for any of the other reported reactions, including the cycloadditions and the lactone-forming processes.

BIOLOGICAL ACTIVITY

All of the cycloadducts **4a-d** and the amides **5a-d** were, upon request, submitted for screening as potential anticancer agents by the National Cancer Institute. Unfortunately, in a recent report provided to us, none of these compounds exhibited sufficient anti-cancer activity to warrant further action by the NCI. The other derivatives have not yet been tested.

CONCLUSIONS

In summary, it has been possible to utilize our newly discovered and readily available difluoro ketene aminal (**1**) to prepare a number of difluoro barbituric acid derivatives through hetero-Diels-Alder cycloadditions

which lead, upon hydrolysis, to Michael-type products. Additional chemistry was described, including formation of novel lactone derivatives.

EXPERIMENTAL SECTION

General procedure for the synthesis of 1,3-dimethyl-barbiturylbenzylidenes **3a-d.**

Compounds **3a-d** were obtained according to a described method[9] by condensing the appropriate substituted benzaldehyde (20mmol) with 1,3-dimethylbarbituric acid (20mmol) dissolved in hot 95% ethanol (20mL). The precipitate was filtered off, washed with cooled ethanol and dried, to yield compounds **3a-d** (90-95%).

5-Benzylidene-1,3-dimethylbarbituric acid **3a**

Yield: 92%; ^{1}H NMR (DMSO-d^6) δ 3.18 (s, 3H), 3.23 (s, 3H), 7.43-7.58 (m, 3H), 8.02 (d, 2H, J=6.8 Hz), 8.35 ppm (s,1H).

5-(4-methoxyphenyl)-1,3-dimethylbarbituric acid **3b**

Yield: 93%; ^{1}H NMR (DMSO-d^6) δ 3.19 (s, 3H), 3.21 (s, 3H), 3.87 (s, 3H), 7.05 (d, 2H, J=9.0 Hz), 8.32 (d, 2H, J=9.0 Hz), 8.30 ppm (s, 1H).

5-(4-fluorophenyl)-1,3-dimethylbarbituric acid **3c**

Yield: 95%; ^{1}H NMR (DMSO-d^6) δ 3.38 (s, 3H), 3.41 (s, 3H), 7.15 (t, 2H, J=8.79 Hz), 8.19 (dd, 2H, J=8.79, 5.8 Hz), 8.51 ppm (s, 1H); 19F NMR (DMSO-d^6) δ -103.81 ppm (m, 1F).

5-(4-bromophenyl)-1,3-dimethylbarbituric acid **3d**

Yield: 90%; ^{1}H NMR (DMSO-d^6) δ 3.37 (s, 3H), 3.42 (s, 3H), 7.60 (d, 2H, J=8.5 Hz), 7.93 (d,2H, J=8.5 Hz), 8.47 ppm (s, 1H).

General procedure for the synthesis of compounds **4a-d**

To a solution of 1,1-bis(dimethylamino)-2,2,2-trifluoroethane (1.7g, 10mmol) in hexane (10mL) at 0 °C under nitrogen was added *n*-BuLi (2.5 M in hexanes, 4.5 mL), after which the reaction mixture was allowed to warm to room temperature and stirred 10 hours. Then the reaction mixture was distilled at reduced pressure into a dry ice/acetone-cooled receiving flask (100mL round bottom) equipped with rubber septum, magnetic stir bar, and a water-cooled condenser. Before and after distillation, the apparatus was maintained under a dry nitrogen atmosphere. 5-Benzylidene-1,3-dimethylbarbituric acid (8mmol) in 3mL of DMF was added. The reaction mixture was stirred for 10 minutes at room temperature under dried nitrogen. The viscous solid was filtered and washed with hexane till the solid became powder.

The powder was recrystallized from methylene chloride. The yields are reported with respect to the 5-benzylidene-1,3-dimethylbarbituric acids.

7,7-bis(dimethylamino)-6,6-difluoro-1,3-dimethyl-5-phenyl-1,3,4,5,6,7-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-2,4-dione **4a**

Yield: 87%; mp 198-200 °C; ^{1}H NMR ($CDCl_3$) δ 3.06-3.32 (b, 18H), 5.28 (dd, 1H, J=32.7, 10.4 Hz), 7.25 (m, 3H), 7.65 ppm (d, 2H, J=6.8 Hz); ^{19}F NMR δ -77.06 (d, J=268.6 Hz), -93.30 ppm (dd, J=268.6, 31.7 Hz); ^{13}C NMR δ 27.15, 44.25, 46.49 (t, J=22.9 Hz), 80.05 (d, J=9.2 Hz), 121.23 (dd, J=268.0 Hz, 255.4 Hz), 126.55, 127.52, 130.36, 137.45, 152.48, 162.71, 164.43 ppm (t, J=28.6 Hz); HRMS (EI) Calcd for $C_{19}H_{24}F_2N_4O_3$: 394.1816, Found: 394.1869; Anal. Calcd for $C_{19}H_{24}F_2N_4O_3$: C, 57.87; H, 6.09; N, 14.21. Found: C, 57.97; H, 6.37; N, 14.30.

7,7-bis(dimethylamino)-6,6-difluoro-1,3-dimethyl-5-(4'-methoxyphenyl)-1,3,4,5,6,7-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-2,4-dione **4b**

Yield: 93%; mp 204-207 °C; ^{1}H NMR ($CDCl_3$) δ 3.04-3.40 (m, 18H), 3.74 (s, 3H), 5.30 (dd, 1H, J=29.9, 11.0 Hz), 6.80 (d, 2H, J=6.8 Hz), 7.62 ppm (d, 2H, J=8.5 Hz); ^{19}F NMR δ -79.84 (d, J=273.5 Hz), -92.37 ppm (dd, J=273.5, 29.3 Hz); ^{13}C NMR δ 27.51, 44.87, 47.03 (t, J=24.1 Hz), 55.07, 81.84, 113.24, 121.08 (dd, J=264.3, 255.6 Hz), 128.67, 131.63, 153.37, 158.60, 163.70, 167.02 ppm (t, J=34.0 Hz); HRMS (CI) Calcd for $C_{20}H_{27}F_2N_4O_4$+H: 425.2000, Found: 425.1971; Anal. Calcd for $C_{20}H_{27}F_2N_4O_4$: C, 56.60; H, 6.13; N, 13.21. Found: C, 56.31; H, 6.29; N, 13.20.

7,7-di(dimethylamino)-6,6-difluoro-1,3-dimethyl-5-(4'-fluorophenyl)-1,3,4,5,6,7-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-2,4-dione **4c**

Yield: 90%; mp 193-195 °C; ^{1}H NMR ($CDCl_3$) δ 3.02-3.40 (b, 18H), 5.35 (dd, 1H, J=30.8, 10.4 Hz), 6.95 (t, 2H, J=8.79 Hz), 7.67 ppm (dd, 2H, J=8.51, 5.76 Hz); ^{19}F NMR δ -79.24 (dd, 1F, J=273.5, 5.3 Hz), -93.22 (dd, 1F, J=273.5, 31.7 Hz), -116.35 ppm (m, 1F); ^{13}C NMR δ 27.53, 44.95, 46.83 (t, J=22.9 Hz), 81.42 (d, J=8.0 Hz), 114.62 (d, J=20.6 Hz), 121.10 (dd, J=266.8, 256.5 Hz), 131.99 (d, J=8.0 Hz), 132.28 (d, J=3.5 Hz), 153.37, 161.91(d, J=245.1 Hz), 163.71, 166.95 ppm (t, J=29.8 Hz); HRMS (EI) Calcd for $C_{19}H_{23}F_3N_4O_3$: 412.1722, Found: 412.1758; Anal. Calcd for $C_{19}H_{23}F_3N_4O_3$: C, 55.34; H, 5.58; N, 13.59. Found: C, 55.07; H, 5.65; N, 13.48.

7,7-di(dimethylamino)-6,6-difluoro-1,3-dimethyl-5-(4'-bromophenyl)-1,3,4,5,6,7-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-2,4-dione **4d**

Yield: 88%; mp 185-187 °C; ^{1}H NMR ($CDCl_3$) δ 3.1-3.40 (b, 18H), 5.29 (dd, 1H, J=31.3, 9.8 Hz), 7.37 (d, 2H, J=8.3 Hz), 7.54 ppm (d, 2H, J=8.3 Hz); ^{19}F NMR δ -79.08 (dd, J=273.4, 4.9 Hz), -93.79 ppm (dd, J=273.4, 31.7 Hz); ^{13}C NMR δ 27.52 (q, J=5.5 Hz), 44.97, 46.77 (td, J=20.2, 4.0 Hz), 81.08 (d, J=9.1 Hz), 120.99, 121.01 (dd, J=263.9, 257.3 Hz), 130.89, 131.89, 135.57, 153.31, 163.65, 166.73 ppm (t, J=28.4 Hz); HRMS (EI) Calcd for $C_{19}H_{23}BrF_2N_4O_3$:

472.0922. Found: 472.0925; Anal. Calcd for $C_{19}H_{23}BrF_2N_4O_3$: C, 48.20; H, 4.86; N, 11.84. Found: C, 48.09; H, 4.91; N, 11.90.

N,N-dimethyl-3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidiryl)-2,2-difluoro-3-phenylpropanamide **5a**

Compound **4a** (1.71g, 4.3 mmol) was dissolved in 10 mL of methylene chloride and stirred at room temperature with 36% of HCl (0.2 mL) for 30 min.. ^{19}F NMR spectra showed that the reaction was finished. Methylene chloride (20mL) was added, and the reaction mixture was washed with water (2x10mL), and then dried by MgSO4. The solvent was evaporated to give solid which was recrystallized in methylene chloride to give a white solid 1.3g (84%).

Yield: 84%; mp 109-110 °C; ^1H NMR δ 2.95 (s,3H), 3.07 (s,3H), 3.18 (s, 3H), 3.21 (s, 3H), 4.38 (d, J=3.7 Hz, 1H), 4.61 (td, J=18.3, 3.7 Hz, 1H), 7.30 ppm (m, 5H); ^{19}F NMR δ -96.59 (dd, J=288.1, 19.5 Hz), -98.16 ppm (dd, J=288.1, 19.5 Hz); ^{13}C NMR δ 28.35, 28.43, 37.03 (t, J=7.6 Hz), 37.20, 50.57 (t, J=2.3Hz), 51.88 (t, J=24.4 Hz), 117.51 (dd, J=264.8, 259.4 Hz), 128.46, 128.65, 129.71, 132.58 , 150.86, 162.31 (t, J=27.5 Hz), 166.67, 166.96 ppm; HRMS (CI) Calcd for $C_{17}H_{20}F_2N_3O_4$: 368.1422. Found: 368.1417; Anal. Calcd for $C_{17}H_{19}F_2N_3O_4$: C, 55.58; H, 5.21; N, 11.44. Found: C, 55.76; H, 5.26; N, 11.33.

N,N-dimethyl-3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidiryl)-2,2-difluoro-3-(4-methoxyphenyl) propanamide **5b**

Yield: 87%; mp 131-132 °C; ^1H NMR δ2.95 (s,3H), 3.09 (s,3H), 3.18 (s, 3H), 3.22 (s, 3H), 3.78 (3, 3H), 4.36 (d, J=3.0 Hz, 1H), 4.57 (dt, J=35.5, 3.0 Hz, 1H), 6.82 (d, J=8.0 Hz, 2H), 7.21 ppm (d, J=8.0 Hz, 2H); ^{19}F NMR δ -97.01 (dd, J=285.7, 17.2 Hz, 1F), -98.22 ppm (dd, J=285.7, 17.2 Hz, 1F); ^{13}C NMR δ 28.42, 28.42, 37.07 (t, J=7.6 Hz), 37.24, 50.62, 51.25 (t, J=24.1 Hz), 55.09, 113.86, 117.50 (t, J=262.3 Hz), 124.24, 130.97, 150.92, 159.68, 162.78 (t, J=28.6 Hz), 166.78, 167.13 ppm; HRMS (CI) Calcd for $C_{18}H_{22}F_2N_3O_5$: 398.1528. Found: 398.1513; Anal. Calcd for $C_{18}H_{21}F_2N_3O_5$: C, 54.41; H, 5.33; N, 10.57. Found: C, 54.04; H, 5.33; N, 10.42.

N,N-dimethyl-3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidiryl)-2,2-difluoro-3-(4-fluorophenyl) propanamide **5c**

Yield: 86%; mp 98-99 °C; ^1H NMR δ 2.95 (s,3H), 3.14 (s, 3H), 3.18 (s, 3H), 3.24 (s, 3H), 4.32 (d, J=3.3 Hz, 1H), 4.68 (td, J=18.4, 3.3 Hz, 1H), 7.01 (t, J=8.5 Hz, 2H), 7.33 ppm (dd, J=7.7, 5.2 Hz, 2H); ^{19}F NMR δ -96.69 (dd, J=285.6, 16.9Hz, 1F), -98.07 (dd, J=285.6, 16.9Hz, 1F), -133.25 ppm (m, 1F); ^{13}C NMR δ 28.57, 28.64, 37.12 (t, J=8.1 Hz), 37.29, 50.76, 50.86 (t, J=16.0 Hz), 115.57 (d, J=21.8 Hz), 117.41 (t, J=260.0 Hz), 128.87, 131.81 (d, J=6.9 Hz), 150.94, 162.77 (d, J=248.5 Hz), 162.32 (t, J=28.6 Hz), 166.67, 166.82 ppm; HRMS (EI) Calcd for $C_{17}H_{19}F_3N_3O_4$: 386.1327. Found: 386.1379;

Anal. Calcd for $C_{17}H_{18}F_3N_3O_4$: C, 52.99; H, 4.71; N, 10.88. Found: C, 52.99; H, 4.82; N, 10.89.

N,N-dimethyl-3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidiryl)-2,2-difluoro-3-(4-bromophenyl) propanamide **5d**

Yield: 82%; mp 135-137 °C; ^{1}H NMR δ 2.94 (s, 3H), 3.16 (s, 3H), 3,17 (s, 3H), 3.25 (s, 3H), 4.29 (d, J=3.6 Hz, 1H), 4.67 (td, J=18.4, 3.6 Hz, 1H), 7.24 (d, J=7.7Hz, 2H), 7.45 ppm (d, J=7.7Hz, 2H); ^{19}F NMR δ -96.39 (dd, J=285.7, 17.1 Hz), -97.76 ppm (dd, J=285.7, 17.1 Hz); ^{13}C NMR δ 28.60, 28.65, 37.07 (t, J=8.0 Hz), 37.24, 50.58, 50.79 (t, J=22.9 Hz),117.29 (t, J=260.0 Hz), 122.95, 131.69, 132.30, 134.73, 150.88, 162.21 (t, J=28.6 Hz), 166.55, 166,61ppm; HRMS (CI) Calcd for $C_{17}H_{19}BrF_2N_3O_4$: 446.0527. Found: 446.0466; Anal. Calcd for $C_{17}H_{18}BrF_2N_3O_4$: C, 45.76; H, 4.07; N, 9.42. Found: C, 45.84; H, 4.00; N, 9.36.

3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2,2-difluoro-3-phenylpropanic acid **6a**

Compound **5a** was dissolved in methylene chloride (20mL), and stirred at reflux with 36% HCl (0.2 mL) for 2 hours. ^{19}F NMR showed that the reaction was finished. Methylene chloride (20mL) was added and the mixture washed with water (2x10mL), then dried using $MgSO_4$. The solvent was removed to give a solid which was dissolved in saturated aqueous $NaHCO_3$ solution (30mL) and washed with methylene chloride (2x10mL). The aqueous solution was acidified (pH<ca. 3.0) with 6N HCl and was extracted with CH_2Cl_2 (3x10mL). The extracts were washed with water, dried with (MgSO4), and the solvent removed to give a solid product.

Yield: 89%; mp 163-165 °C; ^{1}H NMR δ 3.08 (s, 3H), 3.21 (s, 3H), 4.15 (d, J=3.3 Hz, 1H), 4.36 (ddd, J=17.3, 14.9, 3.3, 1H), 6.37 (br., 1 H), 7.18-7.40 ppm (m, 5H); ^{19}F NMR δ -102.78 (dd, J=266.1, 14.7 Hz), -105.32 ppm (dd, J=266.1, 14.7 Hz); ^{13}C NMR δ 28.66, 28.76, 51.32, 53.53 (t, J=18.6Hz), 116.87(t, J=258.3 Hz), 129.69, 130.13, 130.87, 132.80, 152.48, 165.43 (t, J=25.0 Hz), 168.16, 169.06 ppm; HRMS (CI) Calcd for $C_{15}H_{15}F_2N_2O_5$: 341.0949. Found: 341.0977; Anal. Calcd for $C_{15}H_{14}F_2N_2O_5 \bullet H_2O$: C, 50.14; H, 4.45; N, 7.79. Found: 50.26, H; 4.46, N; 7.78.

3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2,2-difluoro-3-(4-methoxyphenyl)propanic acid **6b**

Yield: 81%; mp 116-118 °C; ^{1}H NMR δ 3.10 (s, 3H), 3.22 (s, 3H), 3.79 (s, 3H), 4.11 (d, J=3.3 Hz, 1H), 4.33 (ddd, J=22.2, 12.6, 3.3 Hz, 1H), 6.83 (d, J=8.5 Hz, 2H), 7.15 ppm (d, J=8.5 Hz, 2H); ^{19}F NMR δ -102.61 (dd, J=263.8, 13.5 Hz), -106.43 ppm (dd, J=263.8, 13.5 Hz); ^{13}C NMR δ 28.51, 28.60, 50.76, 52.06 (t, J=22.9 Hz), 55.52, 114.74, 116.47 (t, J=252.8 Hz), 123.84, 132.01, 151.90, 161.04, 164.27 (t, J=32.1 Hz), 167.14, 168.23 ppm; HRMS (CI) Calcd. for $C_{16}H_{17}N_2F_2O_6$: 371.1054. Found: 371.1040; Anal. Calcd for $C_{16}H_{16}F_2N_2O_6 \bullet H_2O$: C, 49.36; H, 4.63; N, 7.20. Found: C, 49.50; H, 4.55; N, 7.18.

3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2,2-difluoro-3-(4-fluorophenyl)propanic acid **6c**

Yield: 86%; mp 102-104 °C; ^{1}H NMR δ 3.21(s, 3H), 3.23 (s, 3H), 4.05 (d, J=3.3 Hz, 1H), 4.46 (ddd, J=25.2, 9.6, 3.3 Hz, 1H), 7.02 (t, J=8.4 Hz, 2H), 7.30 ppm (t, J=5.1 Hz, 2H);

^{19}F NMR δ -100.98 (dd, J=261.2, 7.3 Hz, 1F), -108.65 (dd, J=261.2, 7.3 Hz, 1F), -112.04 ppm (m, 1F); ^{13}C NMR δ 28.67, 49.67, 51.29 (t, J=21.8 Hz), 115.80 (d, J=20.6 Hz), 115.08 (t, J=255.4 Hz), 127.04, 131.7 (d, J=8.0 Hz), 150.74,

163.05 (d, J=248.1 Hz), 162.33 (t, J=31.4 Hz), 166.01, 166.45 ppm; HRMS (CI) Calcd for $C_{15}H_{14}O_5N_2F_3$: 359.0855. Found: 359.1765; Anal. Calcd for $C_{15}H_{13}F_3N_2O_5 \bullet H_2O$: C, 47.87; H, 3.98; N, 7.45. Found: C, 48.05; h, 4.03; N, 7.45.

3-(1,3-dimethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)-2,2-difluoro-3-(4-bromophenyl)propanic acid **6d**

Yield: 80%; mp 188-190 °C; ^{1}H NMR δ 2.94 (s, 3H), 2.95 (s, 3H), 4.19 (dd, J=23.6,11.3 Hz, 1H), 7.03 (d, J=8.0 Hz, 2H), 7.30 ppm (d, J=8.0 Hz, 2H); ^{19}F NMR δ -99.86 (dd, J=263.7, 9.8 Hz), -104.67 ppm (dd, J=263.7, 9.8 Hz); ^{13}C NMR δ 28.85, 50.70, 52.40 (t, J=21.8 Hz), 116.52 (dd, J=264.6, 251.9 Hz), 124.17, 132.45, 132.76, 132.89, 152.48, 165.19 (t, J=32.0 Hz), 168.02, 168.57 ppm; HRMS (CI) Calcd for $C_{15}H_{13}F_2N_2BrO_5$: 399.9870. Found: 399.9864; Anal. Calcd for $C_{15}H_{13}BrF_2N_2O_5$: C, 42.98; H, 3.13; N, 6.68. Found: C, 42.94; H, 3.06; N, 6.64.

N,N-dimethyl-3-(1,3-dimethyl-6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)-2,2-difluoro-3-phenylpropanamide **7a**

Yield: 93%; ^{1}H NMR δ 2.21(s,3H), 2.87 (s, 3H), 3.23 (s, 3H), 3.29 (s, 3H), 5.42 (dd, J=29.1, 13.5 Hz,1H), 7.24 (m, 3H), 7.55 ppm (d, J=7.0 Hz); ^{19}F NMR δ -90.07 (dd, J=248.9, 14.7 Hz), -97.1 ppm (dd, J=248.9, 14.7 Hz); ^{13}C NMR δ 27.76, 37.41, 38.33, 45. 12 (t, J=22.9 Hz), 83.56 (d, J=9.2 Hz),121.18 (dd, J=258.81, 254.3 Hz), 126.70, 128.10, 129.21, 137.10, 153.05, 164.16, 165.05 ppm (t, J=28.6 Hz); IR 3436.4 (-OH), 1660.5 (C=O), 1574.1 (C=O); HRMS (CI) Calcd for $C_{17}H_{20}F_2N_3O_4$: 368.1422. Found: 368.1418; Anal. Calcd for $C_{17}H_{19}F_2N_3O_4$: C, 55.58; H, 5.21; N, 11.44. Found: C, 55.27; H, 5.08; N, 11.32.

6,6-difluoro-1,3-dimethyl-5-phenyl-1,3,4,5,6,7-hexahydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-trione **8a**

The mixture of the acid **6a** and acetic anhydride (1mL) was heated at 100 °C under dry nitrogen for 30 minutes, and the excess anhydride was then evaporated in vacuo. The solid residue was shown to be the lactone.

Yield: 89%; ^{1}H NMR δ 3.30 (s, 3H), 3.53 (s,3H), 4.75 (dd, J=15.7, 2.7 Hz, 1H), 7.13, 7.42 ppm (m, 5H); ^{19}F NMR δ -100.82 (dd, J=265.4, 15.7 Hz), -116.79 ppm (dd, J=265.4, 3.4 Hz); ^{13}C NMR δ 28.51, 29.76, 44.57 (t, J=24.1 Hz), 89.69 (d, J=6.9 Hz), 111.81 (dd, J=261.1, 246.2 Hz), 127.99, 128.77, 129.36, 130.68, 150.15, 151.92, 154.38 ppm (t, J= 35.5 Hz); HRMS (CI) Calcd for $C_{15}H_{12}N_2F_2O_4$: 322.0765. Found: 322.0762.

6,6-difluoro-1,3-dimethyl-5-(4-methoxy-phenyl)-1,3,4,5,6,7-hexahydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-trione **8b**

Yield: 93%; ^{1}H NMR δ 3.33 (s, 3H), 3.55 (s, 3H), 3.78 (s,3H), 4.70 (dd, J=15.1, 3.3 Hz, 1H), 6.87(d, J=8.52Hz, 2H), 7.09 ppm (d, J=8.52 Hz, 2H); ^{19}F NMR δ -101.16 (dd, J=264.2, 15.2 Hz), -117.24 ppm (dd, J=264.2, 3.4 Hz); ^{13}C NMR δ 28.56, 29.79, 43.86 (t, J= 22.9 Hz), 55.28, 89.87, 111.18 (dd, J=261.2, 246.2 Hz), 114.83, 122.39, 129.21, 150.19, 151.77, 154.58 (t, J=32.1 Hz), 160.39 ppm; HRMS (CI) Calcd for $C_{16}H_{14}N_2F_2O_5$: 352.0871. Found: 352.0853.

6,6-difluoro-1,3-dimethyl-5-(4-fluoro-phenyl)-1,3,4,5,6,7-hexahydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-trione **8c**

Yield: 90%; ^{1}H NMR δ 3.32(s, 3H), 3.54 (s,3H), 4.76 (dd, J=15.4, 3.1 Hz, 1H), 7.05 (t, J=8.6 Hz, 2H), 7.16 ppm (dd, J=8.6, 5.5 Hz, 2H); ^{19}F NMR δ -101.19 (dd, J=266.1, 14.7 Hz, 1F), 112.72 (m, 1F), -116.92 ppm (d, J=263.7 Hz); ^{13}C NMR δ 28.46, 29.71, 43.87 (t, J=24.2 Hz), 89.32 (d, J=6.6 Hz), 110.98 (dd, J=260.4, 246.2 Hz), 116.40 (d, J=21.7 Hz), 129.86 (d, J=8.5 Hz), 126.54, 150.05, 151.90, 160.27, 154.29 (t, J=35.8 Hz), 163.08 ppm (d, J=249.3 Hz); HRMS (EI) Calcd for $C_{15}H_{11}O_4N_2F_3$: 340.0671. Found: 340.0673.

6,6-difluoro-1,3-dimethyl-5-(4-bromo-phenyl)-1,3,4,5,6,7-hexahydro-2H-pyrano[2,3-d]pyrimidine-2,4,7-trione **8d**

Yield: 91%; ^{1}H NMR δ 3.32 (s, 3H), 3.54 (s, 3H), 4.71 (dd, J=15.9, 3.0 Hz, 1H), 7.05 (d, J=8.1 Hz, 2H), 7.48 ppm, (J=8.1 Hz, 2H); ^{19}F NMR δ -100.95 (dd, J=266.5,15.7 Hz), -116.66 ppm (dd, J=266.5, 15.7 Hz); ^{13}C NMR δ 28.57, 29.83, 44.18 (t, J=24.0 Hz), 89.14, 110.80 (dd, J=261.1, 247.4 Hz), 123.64, 129.69, 131.98, 132.59, 150.04, 151.98, 154.18 (t, J=33.2 Hz), 160.25 ppm; HRMS (CI) Calcd for $C_{15}H_{11}N_2BrF_2O_4$: 399.9870. Found: 399.9864.

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