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Novel 5-Dimethylamino-1- and 2-Indanyl Uracil Derivatives

Konstantin Ulanenko,[†] Eliezer Falb,[†] Hugo E. Gottlieb,[‡] and Yaacov Herzig*,[†]

Global Innovative R & D, Teva Pharmaceutical Industries Ltd., Netanya 42504, Israel, and Chemistry Department, Bar Ilan University, Ramat Gan 52900, Israel

yaacov.herzig@teva.co.il

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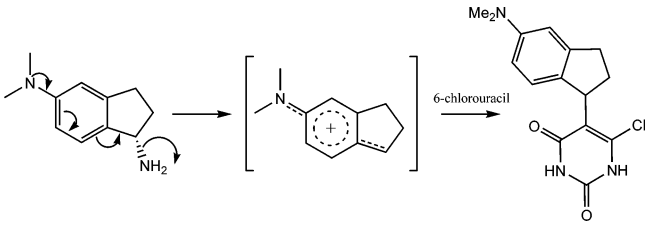
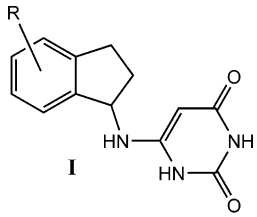


5-Dimethylamino-1-aminoindan undergoes thermal decomposition and reacts with 6-chlorouracil to give 5-indanyl-6-chlorouracil derivative **9**. The formation of **9** may be rationalized by a putative mechanism based on the intermediacy of the imminium methide species **8a**.

The connection between neurodegenerative diseases, such as Parkinson's (PD), Alzheimer's (AD), and multiple sclerosis (MS), and oxidative stress in the brain is well documented.[1]

In this context, it has been postulated that uric acid (UA) may act as an antioxidant and as one of the human defense damage repair mechanisms. An interesting observation on the reduced occurrence of idiopathic Parkinson's disease (IPD) in nearly 8000 patients suffering from gout (hyperuricaemia) provided clinical evidence to the remarkable neuroprotection conferred by UA.[2] In vitro, UA was found as a scavenger of active oxygen radicals (e.g., $OH^{\bullet}$, $O_2^{\bullet -}$)[3], and in vivo, it prevented the symptoms of experimental autoimmune encephalomyelitis (EAE), the mouse model of MS. Moreover, MS and gout are in fact mutually exclusive, strongly suggesting that hyperuricaemia may protect against MS.[4] Long alkyl chain derivatives of UA and aminouracils were shown by Fraisse et al.[5] to be effective free-radical scavengers and antioxidants. The neuroprotective effect of aminoindans and their *N*-propargyl derivatives such as *rasagiline*[6] has been reported. In this context, we synthesized a series of indanylaminouracils **I** (Figure 1) designed to combine the neuroprotective activity of 1-aminoindans with the antioxidant activity of uracils. These compounds were found to be moderately active in several MS and irritable bowel syndrome (IBD) models and were therefore deemed as potential treatments of autoimmune diseases, specifically MS.[7] Herein, we wish to report on a novel reaction between 5-(dimethylamino)-1-aminoindan **8** and 6-chlorouracil to yield 6-chloro-5-(5-(dimethylamino)-indan-1-yl)-1*H*-pyrimidine-2,4-dione **9** in which a C−C bond between the indan and the uracil systems was formed via a putative novel imminium methide intermediate **8a** (Scheme 1).



R= H, OMe, NMe_2

FIGURE 1. General structure of novel indanylaminouracils.

In the framework of our ongoing research on novel indanylaminouracils for the treatment of multiple sclerosis, we prepared 4- and 6-(dimethylamino)-indanylaminouracils **I** (R = Me_2N), whereas attempts to prepare the 5-analogue proved unsuccessful, affording **9** instead of the expected 5-dimethylamino isomer of **I**.

The key intermediates **6** and **8** were prepared from 2- and 1-aminoindan, respectively, by a four-step sequence comprising trifluoroacetylation, nitration, reductive alkylation, and hydrolysis. Nitration of **2** occurred exclusively at position 5[8] to give, after N-trifluoroacetylation, **3b** in an overall yield of 45%. Nitration of **1**, on the other hand, gave a mixture of regioisomers, from which we isolated by chromatography the 5-isomer in 5% yield. Reductive alkylation (hydrogenation over Pd/C in the presence of paraformaldehyde) gave the dimethylamino derivatives **4** and **5**, which were then hydrolyzed to afford **6** and **8**, respectively. Reacting **6** and **8** with 6-chlorouracil in DMSO at 130−140 °C in the presence of Et_3N gave **7** and **9**, respectively.

The structure of **9** was unequivocally determined by elemental analysis, HRMS, and NMR. Unexpectedly, the chlorine remained, and the only methine of the 6-chlorouracil moiety was replaced by a carbon. Because of the lack of hydrogens in the uracil unit, few long-range CH correlations were observed in the HMBC spectrum (see Figure 2). In the IR spectrum, absorptions in the 3000 and 1600 cm^{-1} region, characteristic of hydroxy-pyrimidines,[9] were found.

Hydrogenation of **9** to give 5-(5-(dimethylamino)-indan-1-yl)-1*H*-pyrimidine-2,4-dione **10** further substantiates the as-

[†] Teva Pharmaceutical Industries Ltd.

[‡] Bar Ilan University.

(1) (a) Benzi, G.; Moretti, A. *Neurobiol. Aging* **1995**, *16*, 661−674. (b) Jesberger, J. A.; Richardson, J. S. *Int. J. Neurosci.* **1991**, *57*, 1−17.

(2) Davis, J. W.; Grandinetti, A.; Waslien, C. I.; Ross, G. W.; White, L. R.; Morens, D. M. *Am. J. Epidemiol.* **1996**, *144*, 480−484.

(3) Simic, M. G.; Jovanovic, S. V. *J. Am. Chem. Soc.* **1989**, *111*, 5778−5782. And refs cited in ref 5.

(4) (a) Hooper, D. C.; Spitsin, S.; Kean, R. B.; Champion, J. M.; Dickson, G. M.; Chaudhry, I.; Koprowski, H. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 675−680. (b) Hooper, D. C.; Bagasra, O.; Marini, J. C.; Zborek, A.; Ohnishi, S. T.; Kean, R.; Champion, J. M.; Sarker, A. B.; Bobroski, L.; Farber, J. L.; Akaike, T.; Maeda, H.; Koprowski, H. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 2528−2533.

(5) Fraisse, L.; Verlhac, J.-B.; Roche, B.; Rascle, M.-C.; Rabion, A.; Seris, J.-L. *J. Med. Chem.* **1993**, *36*, 1465−1473.

(6) (a) Abu-Raya, S.; Blaugrund, E.; Trembovler, V.; Shilderman-Bloch, E.; Shohami, E.; Lazarovici, P. *J. Neurosci. Res.* **1999**, *58*, 456−463. (b) Youdim, M. B.; Wadia, A.; Tatton, W.; Weinstock, M. *Ann. N.Y. Acad. Sci.* **2001**, *939*, 450−458.

(7) Teva Pharmaceutical Industries Ltd. WO 2006/020070 A2, February 23, 2006.

(8) Warner-Lambert Co. WO 01/83425, November 8, 2001.

(9) Bellamy, L. J. *The Infra-red Spectra of Complex Molecules*; John Wiley & Sons: New York, 1958.

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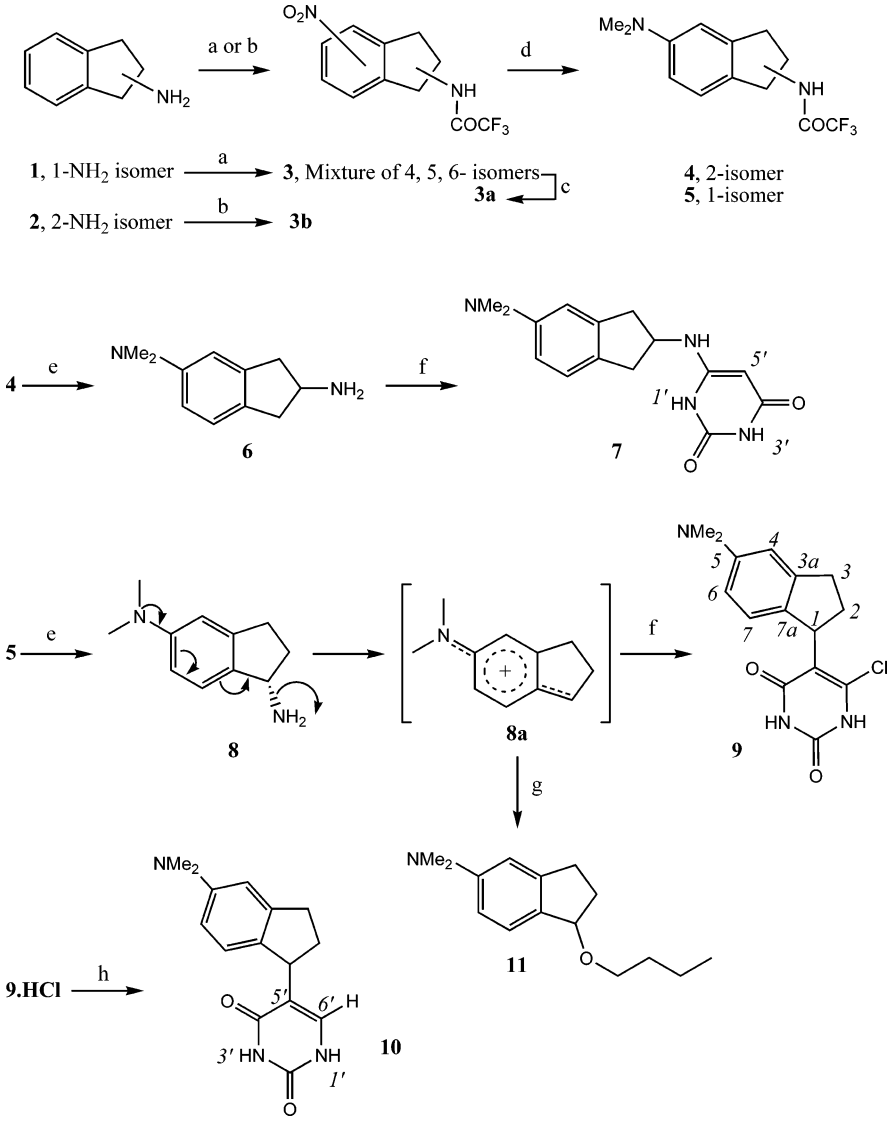
SCHEME 1. Preparation of 6-(5-(Dimethylamino)-2-indanylamino) Uracil 7 and 5-(5-Dimethylaminoindanyl)-6-chlorouracil 9[a]



[a] (a) 1. $(CF_3CO)_2O$. 2. H_2SO_4/HNO_3. (b) 1. H_2SO_4/HNO_3. 2. $(CF_3CO)_2O$. (c) Chromatography. (d)10% Pd/C, $(CH_2O)_n$. (e) K_2CO_3/MeOH/water. (f) 6-chlorouracil/DMSO/Et_3N, 130−140 °C. (g) *n*-BuOH, 110 °C, 1.5 h. (h) 10% Pd/C, H_2 40 psi, 5 h, Et_3N, MeOH/water.

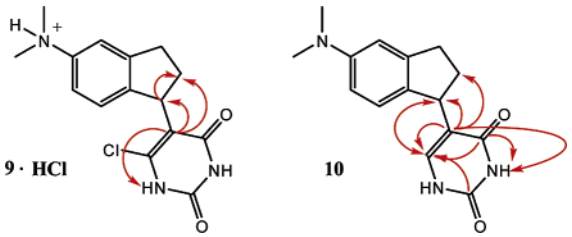


FIGURE 2. HMBC correlations for 5-indanyl-6-chlorouracil **9**·HCl and its reductive displacement product **10**.

signed structure by providing several more CH correlations in the HMBC (Figure 2).

The formation of **9** may be attributed to the intermediacy of the reactive imminium methide **8a**. The para orientation of the dimethylamine and the benzylic amine moieties in **8** facilitates elimination of ammonia to yield the reactive electrophile **8a**, which may then electrophilically attack the uracil ring at the 5-position. Indeed, refluxing **8** (as a free base) in *n*-butanol for 1.5 h afforded (1-butoxy-indan-5-yl)-dimethyl-amine **11**, in good accord with the putative mechanism suggested above. In contrast, **8**·HCl as well as 6-(dimethylamino)-1-aminoindan were all inert under these conditions. Both 4- and 6-regioisomers and compound **6** act as nucleophiles, attacking the uracil ring at the 6-position. Formation of both **9** and **11** is accompanied by full racemization of the chiral center at the indan C1 carbon (as indicated by the loss of optical activity), which supports the planar structure of **8a**.

The *N*,*N*-dimethyliminoquinoindene moiety seems to have been reported only when incorporated in either triarylmethane dyes[10] or fused polycyclic ring systems.[11]

The reaction of 6-chlorouracil with *p*-aminobenzylamine (the ring-opened analogue of **8**) was reported[12] to result in a mixture

(10) Guinot, S. G. R.; Hepworth, J. D.; Wainwright, M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 297−303.
(11) Guinot, S. G. R.; Hepworth, J. D.; Wainwright, M. *Dyes Pigm.* **1999**, *40*, 151−156.
(12) Brown, N. C.; Gambino, J.; Wright, G. E. *J. Med. Chem.* **1977**, *20*, 1186−1189.

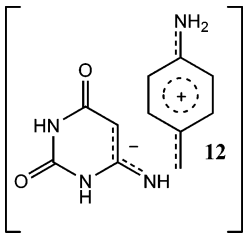


FIGURE 3. Reactive species proposed by Wright.[13]

of "unidentifiable products" instead of the expected 6-(*p*-aminobenzylamino)uracil, whereas 6-aminouracil gave 6-amino-5-(*p*-aminobenzyl)uracil. Formation of the latter was rationalized in a later report[13] by the same author via a thermal [1,3]-rearrangement of the former to the latter, facilitated by the oxo groups in the pyrimidine ring and by electron-releasing moieties in the aromatic ring (stabilizing the reactive benzyl carbocation species **12**) (Figure 3). Although this mechanism is not applicable in our case (chloro, not amino, at position 6), the putative **12** supports our proposed imminium methide **8a** as the reactive species.

The *N*,*N*-dimethylamino analogue of **12** was proposed to result from the irradiation of a solution of *N*,*N*-dimethylaniline in CH_2Cl_2.[14]

Although substitutions at position 5 by various electrophiles, such as phenylselenyl chloride[15] and benzenesulfenyl chloride,[16] as well as acylation with acid chlorides such as cinnamoyl chloride[17] or hydroximoyl chloride[18] are known, electrophilic *alkylations* have, to the best of our knowledge, not been reported. 5-Alkyl-6-chlorouracils[19] were reportedly synthesized via 5-alkyl-barbituric acid.[20,21] Alternatively, hydroxymethyl at position 5 of 4-chloro-2,6-dimethoxypyrimidine was introduced by metalation of the latter followed by addition of ethyl formate and further reduction.[22] Similarly, nucleoside derivatives containing a 5-allyl/propyl uracil moiety were prepared via the 5-chloromercury intermediate. Also, the electrophilic substitution of arylmethyl cations on the C-5 of 2-amino-4,6-dichloropyrimidine and further nitration resulted in 5-diphenylmethyl-6-chlorouracil.[23]

The relative orientation of the dimethylamino and amino groups in 5-dimethylamino aminoindans was found to strongly affect the course of their reaction with 6-chlorouracil. Thus, compound **6** afforded the expected **7**, and **9** was obtained from **8**. Formation of **9** may be rationalized by the conversion of **8** to a reactive *p*-imminium methide intermediate **8a** and represents a novel entry for electrophilic alkylation at the uracil 5-position. This proposed mechanism resembles that reported by us for 5- and 7-hydroxy aminoindans,[24] as well as the documented self-immolative connector concept in prodrugs, which undergo spontaneous fragmentation to afford quinine methides and enamine methides.[25]

Experimental Section

2,2,2-Trifluoro-*N*-(5-nitro-indan-1-*S*-yl)-acetamide, 3a. A solution of 1-*S*-aminoindan (33.9 g, 0.255 mol) in toluene (50 mL) was added dropwise to a mixture of trifluoroacetic anhydride (58.5 g, 39.4 mL, 0.278 mol) and toluene (250 mL) at 0−5 °C. The reaction mixture was stirred at this temperature for 3.5 h. Potassium hydroxide (17.1 g, 0.306 mol, 1.2 equiv) in water (150 mL) was added gradually to the reaction mixture under cooling. The mixture was stirred at room temperature for 1 h, and the precipitated white solid was collected by filtration and washed with water. The crude product (37.3 g, 64%) was used for the next step without purification. Crude 2,2,2-trifluoro-*N*-(5-indan-1-*S*-yl)-acetamide (37.0 g, 0.16 mol) was added slowly to 65−67% nitric acid (370 mL), and the suspension was stirred for 20 h. The reaction mixture was poured onto a water-ice mixture (2000 mL), and the resulting yellow solid was collected by filtration, washed with water to pH 6−7, and dried, to give 39.3 g (89%) of a ∼ 30:5:70 (by TLC) mixture of 2,2,2-trifluoro-*N*-(4-, 5-, and 6-indan-1-*S*-yl)-acetamides **3**. This crude product was crystallized twice from toluene (15 mL/g) to give 17 g of a 95:5 mixture of 6- and 5-isomers, from which the latter was isolated by flash column chromatography to give 1.5 g (2%) of **3a**: mp 199−200 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (m, 2H), 7.45 (d, 1H, J = 9 Hz), 6.62 (br d, 1H), 5.61 (q, 1H, J = 8 Hz), 3.19 (ddd, 1H, J = 17, 9, 4 Hz), 3.07 (dt, 1H, J = 17, 8 Hz), 2.8 (dddd, 1H, J = 17, 9, 8, 4 Hz), 2.07 (dq, 1H, J = 17, 8 Hz); ^{13}C NMR ($CDCl_3$ + CD_3OD) δ 156.0, 149.1, 148.3, 145.0, 124.7, 122.6, 120.0, 114.1, 54.5, and 54.4 (for two rotamers of C-1), 32.7, 30.0; HRMS calcd for $C_{11}H_9F_3N_2O_3$ 274.0565, found 274.0605.

2,2,2-Trifluoro-*N*-(5-nitro-indan-2-yl)-acetamide, 3b. 2-Aminoindan·HCl (5.04 g, 0.0294 mol) was dissolved in trifluoroacetic acid (30 mL), and H_2SO_4 (3 mL) and HNO_3 (2 mL, 0.03 mol) were added at 0 °C. After ∼3/4 h, the red solution was allowed to warm to room temperature and stirred for 6 h. Et_2O was added over 30 min, and the resultant suspension was stirred overnight and filtered to give 5-nitro-2-aminoindan·H_2SO_4 as a white solid (7.37 g, 90%). This solid was dissolved in water (50 mL), and the solution was made basic with 25% NH_4OH (∼15 mL) to pH 10 and then extracted with EtOAc (130 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated to give 4.2 g. A toluene solution of this free base (5.5 mL) was added slowly (over 40 min) into a stirred and ice-cooled mixture of trifluoroacetic anhydride (3.6 mL, 0.025 mol) in toluene (20 mL). After stirring for 1/2 h at 0 °C, the mixture was allowed to warm to room temperature and further stirred for 1/2 h. KOH solution (1.5 g in 10 mL of water) was added to the mixture at room temperature, and the precipitated gray solid was collected by filtration, washed with toluene and water, and thoroughly dried to give **3b** (3.05 g, 47%) as a grayish solid: mp 102−104 °C; ^{1}H NMR (DMSO-d_6) δ 9.75 (br d, 1H, J = 6.5 Hz), 8.11 (br s, 1H), 8.07 (dd, 1H, J = 8, 2 Hz), 7.50 (d, 1H, J = 8 Hz), 4.67 (sextet, 1H, J = 6.5 Hz), 3.37 (dd, 2H, J = 16, 8 Hz), 3.05 (dd, 2H, J = 16, 6 Hz); ^{13}C NMR (DMSO-d_6) δ 156.1, 149.4, 146.8, 143.1, 125.5, 122.2, 119.5, 115.8, 50.8, 38.9, 38.7; MS TOF ES+ m/z (275, MH^+), 257 ($MH^+ - H_2O$); HRMS calcd for $C_{11}H_9F_3N_2O_3$ + H 275.0644, found 275.0674.

***N*-(5-(Dimethylamino)-indan-2-yl)-2,2,2,-trifluoro-acetamide, 4.** A mixture of **3b** (7.0 g, 0.0255 mol) and paraformaldehyde (5.67 g, 0.189 mol, ∼7.5 equiv) in MeOH (136 mL)

(13) Wright, G. E. *J. Org. Chem.* **1980**, *45*, 3128−3131.
(14) Latowski, T.; Zelent, B. *Rocz. Chem.* **1977**, *51*, 1405−1420.
(15) Kim, Y. H.; Lee, C. H.; Lee, D. H. *Heteroat. Chem.* **1993**, *4*, 463−470.
(16) Peach, M. E.; Scott, C.; Woo, J. *Sulfur Lett.* **1986**, *5*, 23−28.
(17) Bernier, J.-L.; Hénichart, J.-P.; Warin, V.; Trentesaux, C.; Jardillier, J.-C. *J. Med. Chem.* **1985**, *28*, 497−502.
(18) Kim, J. N.; Ryu, E. K. *J. Org. Chem.* **1992**, *57*, 1088−1092.
(19) Koroniak, H.; Jankowski, A.; Krasnowski, M. *Org. Prep. Proced. Int.* **1993**, *25*, 563−568.
(20) Volwiler, E. H. *J. Am. Chem. Soc.* **1925**, *47*, 2236−2240.
(21) Su, T.-L.; Watanabe, K. A.; Schinazi, R. F.; Fox, J. J. *J. Med. Chem.* **1986**, *29*, 151−154.
(22) Plé, N.; Bardin, T. F.; Queguiner, G. *J. Heterocycl. Chem.* **1992**, *29*, 467−470.
(23) Whitehead, C. W.; Whitesitt, C. A. *J. Org. Chem.* **1974**, *39*, 591−595.
(24) Herzig, Y.; Lerman, L.; Goldenberg, W.; Lerner, D.; Gottlieb, H. E.; Nudelman, A. *J. Org. Chem*. **2006**, *71*, 4130−4140.
(25) Leenders, R. G. G.; Damen, E. W. P.; Bijsterveld, E. J. A.; Scheeren, H. W.; Houba, P. H. J.; van der Meulen-Muileman, I. H.; Boven, E.; Haisma, H. J. *Bioorg. Med. Chem.* **1999**, *7*, 1597−1610.

was hydrogenated, initially at 2 atm, at 30−35 °C for 0.5 h, then at 4 atm at 50 °C for 1.5 h, over 10% Pd/C (1.4 g, 20 wt % per nitro compound). The reaction mixture was filtered through Celite, and the solvent evaporated to leave a white solid (7.5 g), which was purified by Combi-Flash (hexane/EtOAc, 0−20% EtOAc gradient over 35 min) to give **4** as a white solid (4.5 g, 65%): mp 156−157 °C; ^{1}H NMR (DMSO-d_6) δ 9.68 (br s, 1H), 7.02 (d, 1H, J = 8 Hz), 6.62 (br d, 1H, J = 1.5 Hz), 6.57 (dd, 1H, J = 8, 1.5 Hz), 4.52 (quintet, 1H, J = 7 Hz), 3.13 (two dd, 2H, J = 14, 8 Hz), 2.85 (s and two dd, 8H, J = 14, 8 Hz); ^{13}C NMR (DMSO-d_6) δ 156.1, 150.1, 141.4, 128.1, 124.6, 115.9, 111.6, 108.8, 51.0, 38.9, 38.6, 37.3; MS TOF ES+ m/z (273, MH$^+$); HRMS calcd for $C_{13}H_{15}F_3N_2O$ 272.1136, found 272.1120.

2,2,2-Trifluoro-*N*-(5-(dimethylamino)-indan-1-*S*-yl)-acetamide, 5. A mixture of **3a** (1.5 g, 0.0058 mol), paraformaldehyde (1.75 g, 0.044 mol), and 10% Pd/C (0.3 g, 20%) in MeOH (40 mL) was hydrogenated (4 atm) at 50 °C for 2.5 h. The reaction mixture was filtered (Celite), and the filtrate was evaporated to dryness, to give **5** as a white solid (1.5 g, 98%), which was used without further purification: mp 188−189 °C (dec); $[\alpha]^{25}_D$ −180 (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 9.67 (br s, 1H), 7.00 (d, 1H, J = 8 Hz), 6.58 (s and dd, 2H, J = 8, 2 Hz), 5.27 (br t, 1H, J = 7 Hz), 2.93 (ddd, 1H, J = 15, 9, 5 Hz), 2.86 (s, 6H), 2.76 (dt, 1H, J = 15, 7.5 Hz), 2.39 (dddd, 1H, J = 12.5, 8, 7, 5 Hz), 1.93 (dtd, 1H, J = 12.5, 8, 7 Hz); ^{13}C NMR (DMSO-d_6) δ 155.8, 151.0, 144.3, 129.9, 124.2, 116.1, 111.4, 108.3, 54.0, 40.5, 31.9, 30.2; MS TOF ES+ m/z (273, MH$^+$); HRMS calcd for $C_{13}H_{15}F_3N_2O$ 272.1136, found 272.1130.

5-*N*,*N*-(Dimethylamino)-indan-2,5-diamine, 6. Compound **4** (1.5 g, 5.5 mmol) was suspended in a mixture of MeOH/water (20:12 mL), and K_2CO_3 (1.5 g, 9.48 mmol) was added. The mixture was heated to 85−90 °C with stirring. The reaction mixture was cooled to room temperature and evaporated to dryness. The solid residue was partitioned between EtOAc (5 × 30 mL) and water (10 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated to dryness to give **6** as an oily liquid (0.95 g, 98%): ^{1}H NMR (DMSO-d_6) δ 7.00 (d, 1H, J = 8 Hz), 6.60 (br d, 1H, J = 1.5 Hz), 6.53 (dd, 1H, J = 8, 2 Hz), 3.75 (quintet, 1H, J = 7 Hz), 3.03 (two dd, 2H, J = 15, 7 Hz), 2.83 (s, 6H), 2.62 (two dd, 2H, J = 15, 6 Hz); ^{13}C NMR (DMSO-d_6) δ 150.0, 141.9, 128.7, 124.6, 111.46, 109.0, 52.2, 40.8, 40.7; MS TOF ES+ m/z (177, MH$^+$).

6-(5-(Dimethylamino)-indan-2-ylamino)-1*H*-pyrimidine-2,4-dione, 7·HCl Salt. Compound **6** (∼3 g, 0.016 mol) was dissolved in DMSO (5 mL), and 6-chlorouracil (1.24 g, 8.46 mmol) was added portionwise over a few min at 70−80 °C. The homogeneous dark mixture was heated to 135−140 °C. After 3 h, the reaction mixture was cooled to 100 °C. Ethylene glycol dimethyl ether (40 mL) was added, and the dark solution was refluxed for ∼1 h, cooled to room temperature, and filtered. The filtrate was evaporated to dryness, and the dark residue was boiled in water (∼50 mL) for 0.5 h; the suspension was filtered, and the collected solid was washed with Et_2O to give a brown solid, which after drying under vacuum (2 g) was suspended in MeOH. Ethanolic HCl (∼3 N, 2−3 mL) was added, and the resulting solution was evaporated to dryness. The residue was treated with dichloromethane (DCM) to give a brown solid which was purified by Combi-Flash (DCM/MeOH) to give **7**·HCl as a grayish solid (1.1 g, 20%): mp 232−233 °C (dec); ^{1}H NMR (DMSO-d_6) δ 10.36 (bs, 1H), 10.14 (bs, 1H), 7.70 (bs, 1H), 7.60 (bd, 1H, J = 8 Hz), 7.42 (d, 1H, J = 8 Hz), 7.32 (bd, 1H, J = 5.5 Hz), 4.61 (s, 1H), 4.26 (tq, 1H, 7, 5 Hz), 3.33 (bdt, 2H, J = 16.5, 7 Hz), 3.10 (s, 6H), 2.87 (dd, 1H, J = 16.5, 4.5 Hz), 2.85 (dd, 1H, J = 16.5, 4.5); ^{13}C NMR (DMSO-d_6) δ 164.3, 154.0, 150.5, 142.9, 142.8, 141.7, 125.9, 119.1, 116.9, 73.1, 52.4, 45.5, 40.0, 39.5; MS TOF ES+ m/z (287, MH$^+$); HRMS calcd for $C_{15}H_{19}N_4O_2$ + H 287.1508, found 287.1472.

***N*$_5$,*N*$_5$-Dimethyl-indan-1-*S*, 5-diamine, 8.** A mixture of **5** (1.5 g, 0.0055 mol) and potassium carbonate (1.14 g, 0.082 mol) in a 2:1 MeOH/water mixture (30 mL) was heated at reflux for 2.5 h. The clear solution was evaporated to dryness. The residue was dissolved in water (20 mL), and the product was extracted with ethyl acetate (6 × 80 mL). The organic layers were combined, dried, and evaporated to dryness to give **8** as slightly brown oil (1 g, 99%): ^{1}H NMR ($CDCl_3$) δ 7.22 (d, 1H, J = 8 Hz), 6.67 (dd, 1H, J = 8, 2 Hz), 6.65 (br s, 1H), 4.33 (t, 1H, J = 7 Hz), 2.95 (m and s, 7H), 2.79 (dt, 1H, J = 16, 8 Hz), 2.49 (dddd, 1H, J = 12.5, 8.5, 7.5, 4 Hz), 2.28 (br s, 2H), 1.70 (dtd, 1H, J = 12.5, 8.5, 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 150.8, 144.4, 135.4, 123.9, 111.7, 109.0, 56.6, 41.2, 37.3, 30.5; HRMS calcd for $C_{11}H_{16}N_2$ 176.1313, found 176.1316.

6-Chloro-5-(5-(dimethylamino)-indan-1-yl)-1*H*-pyrimidine-2,4-dione, 9·HCl Salt. A mixture of **8** (1 g, 0.0055 mol), 6-chlorouracil (0.83 g, 0.0055 mol), and Et_3N (0.55 g, 0.0055 mol) in DMSO (1 mL) was heated at 130−140 °C for 4 h under nitrogen. The reaction mixture was cooled to 45−50 °C, and water (50 mL) was added. The suspension was heated at reflux for 0.5 h and filtered. The collected solid (free base, 1.3 g, 77%) was dissolved in Et_2O (50 mL), and 4 N ethanolic HCl (1.1 equiv) was added. The suspension was then further stirred for 0.5 h at room temperature, and the solid was collected by filtration to give 1.1 g (75%): mp 236−238°C (dec). Free base: ^{1}H NMR (DMSO-d_6) δ 11.24 (br s, 1H), 6.75 (d, 1H, J = 9 Hz), 6.60 (d, 1 H, J = 2 Hz), 6.47 (dd, 1H, J = 9, 2 Hz), 4.42 (br m, 1H), 2.95 (m, 1H), 2.84 (s, 6H), 2.82 (m, 1H), 2.20 (br m, 2H); ^{13}C NMR (DMSO-d_6) δ 162.0, 149.6, 145.6, 145.2, 142.4, 142.2, 124.1, 118.6, 116.7, 110.3, 45.6, 42.2, 31.4, 29.9. HCl salt: ^{1}H NMR (DMSO-d_6) δ 11.89 (bs, 1H), 11.20 (bs, 1H), 7.69 (bs, 1H), 7.53 (bd, 1H, J = 8 Hz), 7.15 (bd, 1H, J = 8 Hz), 4.50 (bt, 1H, J = 8 Hz), 3.08 (s, 6H), 3.07 (bddd, 1H, 16, 7, 5 Hz), 2.94 (bdt, 1H, J = 16, 9 Hz), 2.30 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 161.2, 149.4, 145.1, 145.06, 142.22, 142.18, 123.9, 118.3, 116.4, 110.4, 45.4, 42.0, 31.3, 29.7. Microanal. calcd for $C_{30}H_{36}Cl_4N_6O_5$ (two molecules of free base + 2 × HCl + H_2O): C, 51.29; H, 5.17; Cl, 20.19; N, 11.96; O, 11.39. Found: C, 50.96; H, 5.13; Cl, 20.13; N, 11.82.

5-(5-(Dimethylamino)-indan-1-yl)-1*H*-pyrimidine-2,4-dione, 10. Triethylamine (0.1 mL) and 10% Pd/C (20 mg) were added to a solution of **9**·HCl (100 mg, 0.3 mmol) in a 2:1 MeOH/water solution (3 mL). The mixture was reduced under hydrogen (40−45 psi) for 5 h and filtered. The catalyst was washed with hot MeOH. The filtrates were combined and evaporated to dryness, and the residue was washed with water and filtered to give a white solid (50 mg, 60%): mp 261−262 °C; ^{1}H NMR (DMSO-d_6) δ 11.07 (bs, 1H), 10.54 (bs, 1H), 6.89 (d, 1H, J = 8.5 Hz), 6.65 (s, 1H), 6.64 (d, 1H, J = 2.5 Hz), 6.55 (dd, 1H, J = 8.5, 2.5 Hz), 4.06 (dd, 1H, J = 8, 6.5 Hz), 2.86 (s, 6H), 2.83 (bddd, 1H, J = 15.5, 7.5, 6 Hz), 2.74 (bddd, 1H, J = 15.5, 8, 6.5 Hz), 2.28 (ddd, 1H, J = 12.5, 8, 6 Hz), 1.84 (ddd, 1H, 12.5, 8, 6 Hz); ^{13}C NMR (DMSO-d_6) δ 164.3, 151.2, 150.0, 144.9, 136.9, 131.9, 124.4, 116.0, 111.3, 108.7, 40.8, 40.6, 32.8, 31.1; HRMS calcd for $C_{15}H_{17}N_3O_2$ 271.1321, found 271.1303.

(1-Butoxy-indan-5-yl)-dimethylamine, 11. A solution of compound **8** (0.3 g, 1.7 mmol) in *n*-butanol (3 mL) was heated at 110°C for 1.5 h under nitrogen. The solvent was evaporated to dryness, and the residue was purified by column chromatography (hexane/EtOAc 95:5) to give 0.15 g (38%) of a clear oil: ^{1}H NMR (DMSO-d_6) δ 7.30 (m, 1H), 6.67 (m, 2H), 4.89 (dd, 1H, J = 7.5, 6.5 Hz), 3.11 (bdt, 1H, J = 16, 8 Hz), 2.98 (s, 6H), 2.80 (ddd, 1H, J = 16, 8.5, 4.5 Hz), 2.34 (ddt, 1H, J = 13, 8.5, 6.5 Hz), 2.13 (dddd, 1H, 13, 8.5, 4.5, 3.5 Hz); ^{13}C NMR (DMSO-d_6) δ 151.4, 145.6, 131.6, 125.7, 111.4, 108.8, 82.8, 41.1, 32.8, 32.3; HRMS calcd for $C_{15}H_{23}NO$ 233.1780, found 233.1730.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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