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A Fast and Parallel Route to Cyclic Isothioureas and Guanidines with Use of Microwave-Assisted Chemistry

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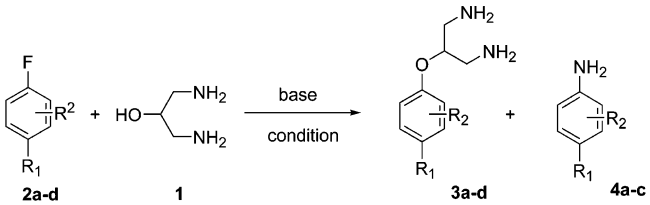
A fast and simple approach to novel cyclic isothioureas and related guanidine derivatives is presented in this study. The construction of the central basic scaffolds is achieved solely by the application of microwave-assisted chemistry, without any need of activating agents or protecting group manipulations. The product formation of various substituted guanidines from the corresponding isothiouronium salts was controlled by the nucleophilicity of the counterion and influenced by the reaction temperature. Further, a new fast-track access to tetrahydropyrimidin-2-ylamines was developed.

Introduction

Isothioureas as well as cyclic guanidines are frequently used in bioactive compounds, mainly to modulate solubility or to pick up electrostatic interactions.[1] However, their use as central scaffolds in drug design is very limited due to the lack of general applicable and mild synthetic methods or straightforward protocols. Although the construction of isothioureas and guanidines is known from the dawn of organic chemistry,[2] publications from the last years demonstrate a continuous interest in the development of synthetic methodologies for cyclic guanidines and their chemical precursors.[3]

In 2000 Marmillon et al.[4] reported the reaction of protected 1,3-diaminopropane-2-ol (**1**) with 1-chloro-4-trifluoromethylbenzene. The resulting diamino ether **3** was cyclized to the corresponding thiourea with carbon disulfide and a carbodiimide.[5] The thiourea was finally transformed in two thermal reactions to the guanidine. Given the high temperatures employed in this protocol, we were confident to shorten reaction times by applying microwave-assisted procedures.[6] Further, ab initio calculations suggested chemoselectivity for the generation of diaminoaryl ethers eradicating the need for protecting group manipulations in the first step of the reaction. Here we report a fast and efficient general strategy for the parallel synthesis of compounds carrying isothioureas and guanidines as a central motif.

TABLE 1. Effects of Different Reaction Conditions on the Formation of Aryl Ethers



entry	substrate	R_1	R_2	base	conditions	yield (**3**:**4**)
1	**2a**	Cl	*o*-Cl	KHMDS[a]	180 °C, 500 s	30% (5:2)
2	**2a**	Cl	*o*-Cl	NaH[b]	170 °C, 250 s	54% (100:0)
3	**2b**	Cl	H	KHMDS[a]	180 °C, 500 s	51% (5:1)
4	**2b**	Cl	H	NaH[b]	170 °C, 250 s	63% (100:0)
5	**2c**	Cl	*m*-Cl	KHMDS[a]	180 °C, 500 s	52% (5:1)
6	**2c**	Cl	*m*-Cl	NaH[b]	170 °C, 250 s	62%(100:0)
7	**2d**	CF_3	H	NaH[b]	170 °C, 250 s	67% (100:0)

[a] In DMF. [b] In DMA.

Results and Discussion

To find a more straightforward method to synthesize diaminoaryl ether **3**, we reacted 1,3-diaminopropane-2-ol (**1**) directly with fluorobenzenes **2** (Table 1). The reaction was first carried out in DMF with NaH or KHMDS as base and the reaction mixture was heated in the microwave at 170−180 °C for 250−500 s, respectively. Many byproducts were formed in the reaction probably due to the cleavage of DMF.[7] Surprisingly, when

(1) (a) Kienzle, F.; Kaiser, A.; Madhukar, S. C. *Eur. Med. Chem.* **1982**, *17*, 547. (b) Weinhardt, K.; Wallach, M. B.; Marx, M. *J. Med. Chem.* **1985**, *28*, 694. (c) Laufer, S. A.; Striegel, H.-G.; Wagner, G. K. *J. Med. Chem.* **2002**, *45*, 4695. (d) Rockway, T. W. *Expert Opin. Ther. Pat.* **2003**, *13*, 773. (e) Chiron Corp. *Expert Opin. Ther. Pat.* **2003**, *13*, 551. (f) Donnelly, L. E.; Rogers, D. F. *Expert Opin. Ther. Pat.* **2003**, *13*, 1345. (g) Lehmann, J.; Rob, B. *Liebigs Ann. Chem.* **1994**, 805.

(2) (a) Unger *Liebigs Ann. Chem.* **1846**, *59*, 69. (b) Heintz *Ann. Phys.* **1848**, *74*, 133. (c) Hofmann, A. W. *Liebigs Ann. Chem.* **1948**, *67*, 131. (d) Beilstein; Geuther *Liebigs Ann. Chem.* **1858**, *108*, 94. (e) Maly *Z. Chem.* **1869**, 259. (f) Rathke, B. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1774.

(3) (a) Katritzky, A. R.; Cai, X.; Rogovoy, B. V. *J. Comb. Chem.* **2003**, *5*, 392. (b) Woo, J. C. S.; MacKay, D. B. *Tetrahedron Lett.* **2003**, *44*, 2881. (c) Summary of guanylation and guanidinylation methods: Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2003**, *68*, 2300. (d) Luthin, D. R.; Anderson, M. B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3467. (e) Moroni, M.; Koksch, B.; Osipov, S. N.; Crucianelli, M.; Frigerio, M.; Bravo, P.; Burger, K. *J. Org. Chem.* **2001**, *66*, 130.

(4) Marmillon, C.; Bompart, J.; Calas, M.; Escale, R.; Bonnet, P.-A. *Heterocycles* **2000**, *53*, 1317.

(5) Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron* **1981**, *37*, 233.

(6) Lindström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tedrahedron* **2001**, *57*, 9225.

(7) *Bretherick's Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth-Heinemann: Boston, MA, 1995; Compound No. 4294.

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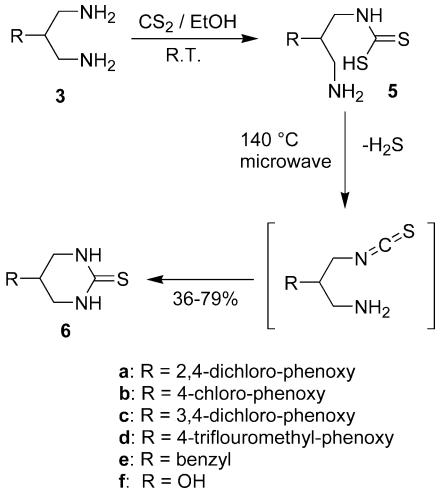
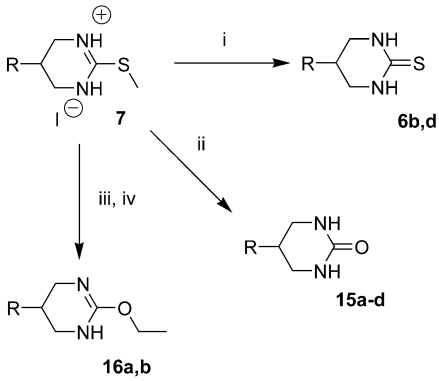
SCHEME 1



KHMDS was used the major side reaction was the formation of the aniline, despite the steric bulk of KHMDS (Table 1, entries 1, 3, and 5).[8] Keeping NaH as a nonnucleophilic base, another approach was to replace DMF with a solvent of similar properties. DMA seemed to be a good alternative since it has the polar aprotic properties needed to dissolve the alkoxides formed in the reaction, and it is less prone toward decomposition in the presence of NaH. When the reaction was carried out under the conditions stated in Table 1, the pure products **3** could be isolated in moderate to good yields. Hence, we found this reaction a facile and immediate method for preparing diaminoaryl ethers without any need of additional protecting and deprotecting steps.

After successfully obtaining the building blocks **3**, we set about preparing the thiourea substrates **6** (Scheme 1). According to the literature,[9] a dithiocarbamate is formed spontaneously when primary or secondary amines are treated with CS_2. Cyclization can then be achieved by two different methods, either by addition of carbodiimide to facilitate the formation of isocyanate or by thermolytic cleavage.[5,9,10] We found the latter alternative more straightforward. Since this method often requires higher temperatures than the boiling point of the solvent, we assumed that the reaction was suitable for microwave-assisted chemistry. Addtion of CS_2 to a solution of **3** in EtOH resulted in immediate precipitation of the dithiocarbamates **5**. The thermal extrusion of H_2S was then carried out in the microwave, giving the cyclized products **6** within 200 s. The thioureas **6a**−**f** crystallized spontaneously and the products could be filtered off without any need for further purification. No intermolecular oligo- or polymerization could be observed.[11]

SCHEME 2 [a]



R	2,4-Cl_2PhO	4-ClPhO	3,4-Cl_2PhO	4-CF_3PhO
	a	**b**	**c**	**d**

[a] Reagents and conditions: (i) primary alkylamine, acetonitrile, microwave or ≥70 °C; (ii) NH_3/H_2O, or water, microwave, 50−87%; (iii) deprotonation of **7**; (iv) NH_3/EtOH, microwave, 88%.

We next examined the reactivity of the thioureas **6** toward different alkylating agents.[14] When **6d** was allowed to react with MeI at 130 °C for 500 s in the microwave, the product **7d** was formed quantitatively (Table 2, entry 1). To test the scope of this reaction, the thioureas **6** were reacted with alkyl halides possessing various functionalities. All isothioureas **7**−**14** were successfully isolated in good to high yields. The obtained results conspicuously demonstrate the feasibility of this protocol. Reaction times and yields correlate with the reactivity of the alkylhalides. In the case of the alkyl chlorides, a catalytic amount of potassium iodide accelerated the reaction.[15]

Turning to the synthesis of unsubstituted guanidines, isothiouronium salts **7** were treated with aqueous ammonia at 150 °C in the microwave. Mass spectrometry showed molpeaks, which lay one mass unit above the anticipated signal, indicating the formation of the corresponding ureas **15**[16] (Scheme 2). To prove this, **7a**−**d** were dissolved in pure water and heated in the microwave. NMR spectroscopy and MS analysis confirmed that in both cases only the ureas **15a**−**d** were formed. In the next attempt, we followed a procedure similar to that used by Rathke,[2f] using NH_3/EtOH and thereby increasing the nucleophilicity of ammonia. Surprisingly, when the mixtures were heated in the microwave the only products obtained were the ethanol adducts **16a**,**b** (Scheme 2).[17] 6-31G* Hartree−Fock calculations revealed a high LUMO-HOMO gap between the isothiourea **7b** and NH_3 (14.88 eV) or EtOH (15.30 eV), respectively, giving no

(8) Sampson, D. F. J.; Simmonds, R. G.; Bradley, M. *Tetrahedron Lett.* **2001**, *42*, 5517.

(9) (a) Ahlbrecht, H.; Kornetzki, D. *Synthesis* **1988**, 775. (b) Ahlbrecht, H.; Schmitt, C.; Kornetzki, D. *Synthesis* **1991**, 637. (c) Matsumura, N.; Konishi, T.; Hayashi, H.; Yasui, M.; Iwasaki, F.; Mizuno, K. *J. Heterocycl. Chem.* **2002**, *39*, 189.

(10) (a) Ferris, A. F.; Schutz, B. A. *J. Org. Chem.* **1963**, *28*, 71. (b) Blonty, G. *Liebigs Ann. Chem.* **1982**, 1927.

(11) Interestingly, when **3f** was cyclized with CS_2, out of two possible products only the thiourea **6f** was formed. The alternative oxazolidinethione[12] could not be detected in the crude. When 3-aminopropane-1,2-diol was treated with CS_2 under the same conditions, only the oxazolidinethione[13] was isolated. This indicates that the six-membered-ring system is less favored. The formation of **6f** can be explained by the higher nucleophilicity of nitrogen compared to oxygen.

(12) Eichel, H. J.; Meyer, R. J.; Buzzi, P. F. *J. Med. Chem.* **1967**, *10*, 942.

(13) Li, G.; Ohtani, T. *J. Heterocycl. Chem.* **1997**, *45*, 2471.

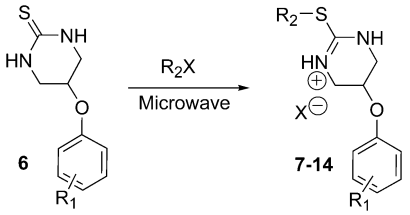
(14) (a) Wilson, B. *J. Chem. Soc.* **1955**, 1389. (b) Van Allan *J. Org. Chem.* **1956**, *21*, 24. (c) Lantos, L.; Gombatz, K.; McGuire, M.; Pridgen, L.; Remich, J.; Shilcrat, S. *J. Org. Chem.* **1988**, *53*, 4223 (d) Wei, J.; Liu, H.; Dick, A. R.; Yamamoto, H.; He, Y.; Waldeck, D. *J. Am. Chem. Soc.* **2002**, *124*, 9591.

(15) Norman, R. O. C.; Coxon, J. M. *Principles of Organic Synthesis*, 3rd ed.; Nelson Thornes: Cheltenham, UK, 2001; p 107.

(16) (a) Augustin, M.; Richter, M.; Salas, S. *J. Prakt. Chem* **1980**, *322*, 55. (b) Effenberger, F.; Beisswenger, T.; Dannenhauer, F. *Chem. Ber.* **1988**, *121*, 2209.

(17) Birtwell, S.; Curd, F. H. S.; Hendry, J. A.; Rose, F. L. *J. Chem. Soc.* **1948**, *30*, 1645.

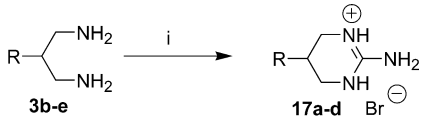
TABLE 2. Synthesis of Isothioureas with Use of a Microwave-Assisted Protocol



		yield of product (%) for R_1 =				
entry	R_2X	2,4-Cl_2	4-Cl	3,4-Cl_2	4-CF_3	time [s]/*T* [°C]
1	MeI	**7a** (86)	**7b** (91)	**7c** (95)	**7d** (99)	500/130
2	4-$FPhCH_2Br$	**8a** (69)	**8b** (83)	**8c** (71)	**8d** (69)	600/150
3	$NC(CH_2)_2Br$	**9a** (92)	**9b** (71)	**9c** (75)	**9d** (58)	600/150
4	$HO(CH_2)_2Br$	**10a** (79)	**10b** (71)	**10c** (52)	**10d** (71)	600/150
5[a]	2-H_2NCO-4-$ClPhO(CH_2)_2Cl$		**11** (94)			1000/160
6[a]	2-CH_3CO-$PhO(CH_2)_2Cl$	**12** (91)				1000/160
7[a]	4-$ClPhO(CH_2)_2Cl$	**13** (93)				1000/160
8[a]	3-Me-4-$NO_2PhO(CH_2)_2Cl$	**14** (90)				1000/160

[a] Potassium iodide was added as a catalyst

SCHEME 3 [a]



3b, **17a** R = 4-chloro-phenoxy
3c, **17b** R = 3,4-dichlorophenoxy
3d, **17c** R = 4-CF_3-phenoxy
3e, **17d** R = benzyl

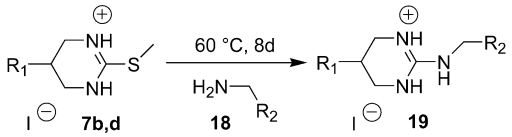
[a] Reagents and conditions: (i) cyanogen bromide, 2-propanol, 120 °C, 600 s, microwave, 53−61%.

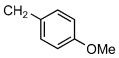
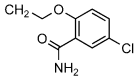
hint to a plainly preferred interaction. The total energy of 2-ethoxytetrahydropyrimidine **16b** and NH_3 is, however, 4.40 kcal/mol below the total energy of the free guanidine **17a** and EtOH, making the ethanol adduct **16b** the *product development controlled* product.[18] When using an inert solvent such as THF instead, no reaction was observed. Other known synthetic equivalents to ammonia are NaN_3 and $NaNH_2$ but these reactions were also unsuccessful.

An alternative approach to the desired cyclic guanidine is the reaction of a diamine with cyanogen bromide.[19] However, the fusion of six-membered-ring systems often requires long reaction times.[20] Heating the reaction mixture for only 600 s in the microwave afforded the guanidines **17a**−**d** in up to 60% yield and NMR spectroscopy verified complete ring closure (Scheme 3).

In an initial effort to prepare substituted guanidines, we applied the procedure described in the literature.[4,21] The isothiouronium iodides **7** were treated with the primary amines **18** in acetonitrile (Table 3). In our hands, this reaction proceeded very slowly; however, after 8 days

TABLE 3. Synthesis of Guanidines from Isothiouronium Iodides Following a Standard Protocol



entry	substrate	R_1	R_2	product (yield)
1	**7b**	4-ClPhO	$PhCH_2$	**19a** (69%)
2	**7b**	4-ClPhO		**19b** (67%)
3	**7b**	4-ClPhO	Ph_2CHCH_2	**19c** (61%)
4	**7d**	4-CF_3PhO	Ph_2CHCH_2	**19d** (73%)
5	**7d**	4-CF_3PhO		**19e** (84%)
6	**7d**	4-CF_3PhO	$PhNHMe(CH_2)_2$	**19f** (86%)
7	**7d**	4-CF_3PhO	$PhCHMeCH_2$	**19g** (46%)
8	**7b**	4-ClPhO		**19h** (76%)

the products **19a**−**h** could be isolated in good yields (Table 3).

Since this type of reaction is known to require high temperature and high pressure, we were confident to shorten the reaction time significantly by microwave heating. When the same reactions as above (Table 3, entries 1 and 4) were carried out at 160 °C for 1000 s, only one compound was obtained in each reaction. Astonishingly, it was not the expected guanidine but the thiourea **6** (Scheme 2). A possible explanation for this unexpected outcome of the reaction is a re-attack of the iodide ion on the methyl group of the isothiourea **7**. The formed methyl iodide then reacts immediately with the primary amine shifting the equilibrium toward the thiourea **6**. A similar profile of reactivity was observed when heating the reaction mixture in a sealed pressure

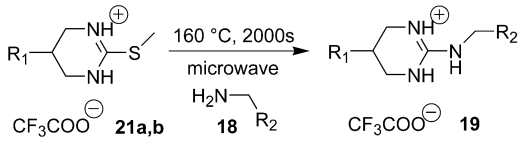
(18) The same calculations in water gave a somewhat less pronounced difference of 2.40 kcal/mol.

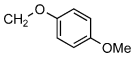
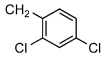
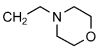
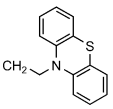
(19) Ishikawa, F.; Kosayana, A.; Nakamura, S.; Kono, T. *Chem. Pharm. Bull.* **1978**, *26*, 3657.

(20) Weinhardt, K.; Wallach M. B.; Marx, M. *J. Med. Chem.* **1985**, *28*, 694.

(21) (a) McKay, A. F.; Hatton, W. G. *J. Am. Chem. Soc.* **1956**, *78*, 1618. (b) Esser, F.; Pook, K. H.; Carpy, A.; Leger, J. M. *Synthesis* **1994**, *1*, 77.

TABLE 4. Synthesis of Guanidines from Isothiouronium Trifluoroacetates Following a Microwave-Assisted Protocol



entry	substrate	R_1	R_2	product (yield)
1	**21a**	4-ClPhO	^{i}Pr	**19i** (71%)
2	**21a**	4-ClPhO	$Me_2N(CH_2)_2$	**19j** (77%)
3	**21a**	4-ClPhO	$AcNHCH_2$	**19k** (81%)
4	**21a**	4-ClPhO	2-Py	**19l** (53%)
5	**21b**	3,4-Cl_2PhO	Ph_2CHCH_2	**19m** (32%)
6	**21a**	4-ClPhO	$PhOCH_2$	**19n**[a] (84%)
7	**21b**	3,4-Cl_2PhO	$Ph(CH_2)_2$	**19o** (78%)
8	**21b**	3,4-Cl_2PhO	$MeOCH_2$	**19p** (70%)
9	**21a**	4-ClPhO		**19q** (76%)
10	**21b**	3,4-Cl_2PhO		**19r** (35%)
11	**21a**	4-ClPhO		**19s** (93%)
12	**21a**	4-ClPhO		**19t**(80%)

[a] The compound was isolated as the hydrochloride.

tube above 70 °C. To eliminate the attack of the counterion, the isothiouronium salt was neutralized to give the unprotonated isothiourea. Unfortunately no reaction occurred when the electrophilicity of **7** was decreased by deprotonation. This is also in accordance with 6-31G* Hartree−Fock calculations, which predict a more accessible LUMO-lobe of C2 at the van der Waals surface in the thiouronium salt. At the same time, the LUMO energy of the cation (−0.59 eV for **7b**) is lower than the LUMO energy of the free base (3.43 eV). We therefore surmised that the isothiourea must exist as a salt to react. Hence, a less nucleophilic counterion than iodide would be preferred. According to our hypothesis yields gradually improved by exchanging the anion from iodide to chloride and finally to trifluoroacetate. Treating the TFA salts **21a**,**b** with the amines **18** in the microwave at 160 °C for 2000 s afforded the guanidines **19i**−**t** with no thiourea formation (Table 4).

For a parallel synthesis methodology, an easy workup procedure was required. Using our experience that isothiourea reacts with ethanol, Wang resin was added to the reaction mixture removing unreacted starting material. The excess of the amine was then scavenged by addition of methylisocyanate resin.[22] Both resins were simply filtered off to give the products in high yields.

(22) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882.

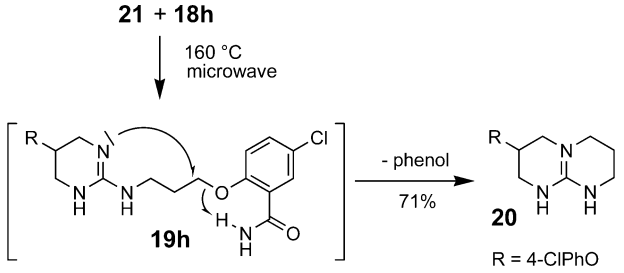


FIGURE 1. Intramolecular proton transfer leading to the formation of **20**.

One particular exception in the synthesis of guanidines **19** was observed when the amino-alkoxy-benzamide **18h** (Figure 1) was submitted to our previously elaborated pathway with use of microwave radiation. The reaction completely failed to provide the expected guanidine **19h**. Instead, ^{1}H NMR and ^{13}C NMR spectroscopy confirmed the loss of the phenoxy group and cyclization, resulting in compound **20**. The different results from this experiment (Figure 1) and entry 8 (Table 3) suggest that high temperatures and the presence of an intramolecular proton source are crucial for the phenol to leave.

It is noteworthy that this peculiar reactivity profile of the guanidine **19h** is not shared by the isothiourea analouge **11** (Table 2, entry 5).

In summary, we have developed a simple and efficient approach to cyclic thioureas and guanidines. Most important, by using microwave-assisted chemistry it was possible to assemble all intermediates and target molecules without any need of activation or protecting groups. Applying our protocol, reaction- and workup times could be cut to a minimum. Further, we discovered a counterion-depending effect in the fusion of isothiouronium salts and primary amines. The best results were achieved with trifluoroacetate giving all guanidines in high yields. We expect that the methodology described herein should offer a general access to the preparation of the biologically important building blocks.

Experimental Section

2-(3-Aminopropoxy)-5-chlorobenzamide (18h). To a solution of 5-chloro-2-hydroxybenzamide (1.0 mmol, 171 mg) and 1,3-diiodopropane (2.0 mmol, 592 mg) in MeCN (4 mL) was added potassium carbonate (1.5 mmol, 207 mg). The mixture was heated at 150 °C for 1000 s in the microwave. The solvent was removed in vacuo and aqueous 1 M NaOH added. The aqueous layer was extracted with CH_2Cl_2 and the organic phase was dried (Na_2SO_4) and concentrated to give the crude arylpropoxyiodide (300 mg). The iodide (0.9 mmol, 300 mg) was redissolved in DMA (4 mL) and potassium phthalimide (0.9 mmol, 163 mg) was added. The mixture was heated at 170 °C for 500 s in the microwave. DMA was removed in vacuo and the residue was taken up in CH_2Cl_2, washed with water, dried (Na_2SO_4), and concentrated. Methylamine (4 mL, 8 M in EtOH) was added and the solution was heated at 100 °C for 300 s in the microwave. The precipitate was filtered off, the solution concentrated in vacuo, and EtOAc added. The benzamide was precipitated from the solution as hydrochloride with HCl/EtOAc (2.5 M) and washed with EtOAc. The free base was extracted with CH_2Cl_2 from aqueous 5 M NaOH to give **18h** in 70% overall yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 2.8 Hz, 1H), 7.89 (br s, 1H), 7.36 (dd, J = 8.8, 2.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.48 (br s, 1H), 4.19 (t, J = 6.1 Hz, 2H), 2.92 (t, J = 6.6 Hz, 2H), 1.98 (m_c, 2H), 1.30 (br s, 2H).

Representative Experimental Procedures for Preparation of Phenoxypropane-1,3-diamines: Preparation of 2,4-Dichlorophenoxypropane-1,3-diamine (3a). Method A: 1,3-Diamino-2-hydroxypropane (**1**) (1.0 mmol, 91 mg) was dissolved in dry DMF (1 mL). A solution of potassium hexamethyldisilazane (1.0 mmol, 200 mg) in dry DMF (1.5 mL) was added and the mixture was stirred for 20 min at room temperature. 1,3-Dichloro-4-fluorobenzene (**2a**) (4.3 mmol, 709 mg) was added and the reaction mixture was heated in the microwave at 180 °C for 500 s. The solvent was removed in vacuo to give a brown residue. HCl (1 N, 5 mL) was added and the excess of fluorobenzene was extracted with diethyl ether (3 × 3 mL). The aqueous layer was adjusted with aqueous 5 M NaOH to pH >12 and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give **3a** as a brown oil. Crude yield: 113 mg.

Method B: To a solution of 1,3-diamino-2-hydroxypropane (**1**) (2.0 mmol, 180 mg) in dry DMA (3 mL) was added sodium hydride (2.4 mmol, 58 mg). The mixture was stirred until the sodium hydride was fully reacted. 1,3-Dichloro-4-fluorobenzene (**2a**) (2.2 mmol, 363 mg) was added and the reaction mixture was heated in the microwave at 170 °C for 250 s. The solvent was removed in vacuo to give a brown residue. HCl (1 N, 7 mL) was added and the solution was extracted with diethyl ether (3 × 5 mL). The aqueous layer was adjusted with aqueous 5 M NaOH to pH >12 and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give **3a** as a yellow oil. Yield 253 mg (54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 2.6 Hz, 1H), 7.17 (dd, J = 8.8, 2.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 4.23 (m_c, 1H), 3.05−3.00 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 130.1, 127.8, 126.5, 125.0, 117.3, 84.4, 43.2. ESI-MS: m/z (%) 235 (100) [M + H$^+$]. Anal. Calcd for $C_9H_{12}Cl_2N_2O$: C, 45.98; H, 5.14; N, 11.91. Found: C, 46.3; H, 5.48; N, 11.7.

2-(4-Chlorophenoxy)propane-1,3-diamine (3b). Following method A described for **3a** gave **3b** as a brown oil. Crude yield: 78 mg. Following method B described for **3a** gave **3b** as a yellow oil. Yield 63%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (m, J = 9.0 Hz, 2H), 6.91 (m, J = 9.0 Hz, 2H), 4.19 (m_c, 1H), 2.98−2.97 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 129.5, 126.0, 117.4, 81.8, 43.2. ESI-MS: m/z (%) 201 (100) [M + H$^+$]. Anal. Calcd for $C_9H_{13}ClN_2O$: C, 53.87; H, 6.53; N, 13.96. Found: C, 53.3; H, 6.69; N, 13.32.

2-(3,4-Dichlorophenoxy)propane-1,3-diamine (3c). Following method A described for **3a** gave **3c** as a brown oil. Crude yield: 52%. Following method B described for **3a** gave **3c** as a yellow oil. Yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.9 Hz, 1H), 7.10 (d, J = 2.9 Hz, 1H), 6.84 (dd, J = 8.9, 2.9 Hz, 1H), 4.19 (quint, J = 5.3 Hz, 1H), 2.99 (m_c, J = 5.3 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 133.0, 130.8, 124.4, 118.1, 115.8, 82.2, 43.0. ESI-MS: m/z (%) 235 (100) [M + H$^+$].

2-(4-Trifluoromethylphenoxy)propane-1,3-diamine (3d). Following method B described for **3a** gave **3d** as a yellow oil. Yield 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 4.33 (m_c, 1H), 3.02 (d, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 127.1, 124.4, 123.2, 115.7, 81.4, 43.1. ESI-MS: m/z (%) 235 (100) [M + H$^+$]. Anal. Calcd for $C_{10}H_{13}F_3N_2O$: C, 51.28; H, 5.59; N, 11.96. Found: C, 50.2; H, 5.86; N, 11.4.

Representative Experimental Procedures for Preparation of 5-Phenoxytetrahydropyrimidine-2-thione: Preparation of 5-(2,4-Dichlorophenoxy)tetrahydropyrimidine-2-thione (6a). To a solution of **3a** (1.0 mmol, 240 mg) in dry EtOH (2 mL) was added carbon disulfide (2.1 mmol, 160 mg) and the reaction mixture was heated in the microwave at 140 °C for 200 s. The reaction mixture was allowed to attain room temperature and diethyl ether (2 mL) was added. The precipitate was filtered off, washed with ether, and dried in vacuo to give **6a** as a yellow solid. Yield 199 mg (70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (br s, 2H), 7.59 (d, J = 2.5 Hz, 1H), 7.38 (dd, J = 8.9, 2.5 Hz, 1H), 7.30 (d, J = 8.9 Hz, 1H), 4.89 (br s, 1H), 3.41−3.25 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.1, 151.6, 130.1, 128.6, 126.0, 124.5, 118.2, 66.6, 43.4. ESI-MS: m/z (%) 235 [M − CS + H$^+$], 277 (100) [M + H$^+$]. Anal. Calcd for $C_{10}H_{10}Cl_2N_2OS$: C, 43.34; H, 3.64; N, 10.11; S, 11.57. Found: C, 43.3; H, 3.87; N, 10.0; S, 11.4.

5-(4-Chlorophenoxy)tetrahydropyrimidine-2-thione (6b). Following the method described for **6a** gave **6b** as a yellow solid. Yield 36%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (br s, 2H), 7.34 (d, J = 8.9 Hz, 2H), 7.02 (d, J = 8.9 Hz, 2H), 4.82 (br s, 1H), 3.39−3.22 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.0, 155.7, 129.9, 125.4, 118.2, 65.0, 43.5. ESI-MS: m/z (%) 243 (100) [M + H$^+$]. Anal. Calcd for $C_{10}H_{11}ClN_2OS$: C, 49.48; H, 4.57; N, 11.54; S, 13.21. Found: C, 49.2; H, 4.64; N, 11.1; S, 12.6.

5-(3,4-Dichlorophenoxy)tetrahydropyrimidine-2-thione (6c). Following the method described for **6a** gave **6c** as a yellow solid. Yield 53%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (br s, 2H), 7.53 (d, J = 8.9 Hz, 1H), 7.33 (d, J = 2.9 Hz, 1H), 7.02 (dd, J = 8.9, 2.9 Hz, 1H), 4.9 (br s, 1H), 3.40−3.22 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.0, 156.4, 132.2, 131.6, 123.6, 118.3, 114.3, 65.5, 43.4. ESI-MS: m/z (%) 235 [M − CS + H$^+$], 277 (100) [M + H$^+$]. Anal. Calcd for $C_{10}H_{10}Cl_2N_2OS$: C, 43.34; H, 3.64; N, 10.11; S, 11.57. Found: C, 43.3; H, 3.94; N, 9.85; S, 11.7.

5-(4-Trifluoromethylphenoxy)tetrahydropyrimidine-2-thione (6d). Following the method described for **6a** gave **6d** as a yellow solid. Yield 79%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (br s, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 4.97 (br s, 1H), 3.43−3.27 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.0, 159.9, 127.5, 124.9, 122.1, 116.6, 64.9, 43.4. ESI-MS: m/z (%) 277 (100) [M + H$^+$]. Anal. Calcd for $C_{11}H_{11}F_3N_2OS$: C, 47.82; H, 4.01; N, 10.14; S, 11.60. Found: C, 47.9; H, 4.12; N, 9.94; S, 11.1.

5-Benzyltetrahydropyrimidine-2-thione (6e). Following the method described for **6a** gave **6e** as a white solid. Yield 56%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, 2H), 7.32−7.29 (m, 2H), 7.23−7.20 (m, 3H), 3.06−3.02 (m, 2H), 2.85−2.80 (m, 2H), 2.55 (d, J = 7.5 Hz, 2H), 2.03 (m_c, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 139.0, 128.7, 128.3, 126.1, 44.4, 36.1, 30.9. ESI-MS: m/z (%) 207 (100) [M + H$^+$].

5-Hydroxytetrahydropyrimidine-2-thione (6f). Following the method described for **6a** gave **6f** as a yellow solid. Yield 64%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (br s, 2H), 5.10 (br s, 1H), 3.88 (br s, 1H), 3.17−3.14 (m, 2H), 2.94−2.90 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.9, 58.6, 46.7. ESI-MS: m/z (%) 133 (100) [M + H$^+$]. Anal. Calcd for $C_4H_8N_2OS$: C, 36.35; H, 6.10; N, 21.19. Found: C, 36.2; H, 6.04; N, 19.7.

Representative Experimental Procedures for Preparation of 5-Phenoxy-2-methylsulfanyl-3,4,5,6-tetrahydropyrimidin-1-ium Iodide: Prepararion of 5-(2,4-Dichlorophenoxy)-2-methylsulfanyl-3,4,5,6-tetrahydropyrimidin-1-ium Iodide (7a). To a solution of **6a** (0.5 mmol, 139 mg) in MeCN (4 mL) was added methyl iodide (1.0 mmol, 142 mg) and the reaction mixture was heated in the microwave at 130 °C for 500 s. The solvent was removed in vacuo and diethyl ether (4 mL) was added to the residue. The precipitate was filtered off, washed with ether, and dried in vacuo to give **7a** as a yellow solid. Yield 181 mg (86%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.50 (d, J = 2.5 Hz, 1H), 7.35 (dd, J = 8.8, 2.5 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 5.19 (t, J = 2.4 Hz, 1H), 3.71 (m_c, J = 2.4 Hz, 4H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 164.8, 150.3, 129.9, 128.0, 127.7, 125.5, 118.3, 65.6, 43.5, 12.3. ESI-MS: m/z (%) 291 (100) [M + H$^+$].

Extraction from aqueous 1 M NaOH with CH_2Cl_2 gave the free base as a white solid. Anal. Calcd for $C_{11}H_{12}Cl_2N_2OS$: C, 45.37; H, 4.15; N, 9.62; S, 11.01. Found: C, 45.1; H, 4.24; N, 9.58; S, 10.9.

5-(4-Chlorophenoxy)-2-methylsulfanyl-3,4,5,6-tetrahydropyrimidin-1-ium Iodide (7b). Following the method described for **7a** gave **7b** as a yellow solid. Yield 91%. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.33 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 5.09 (br s, 1H), 3.75−3.68 (m, 4H), 2.66 (s, 3H);

^{13}C NMR (100 MHz, MeOH-d_4) δ 164.7, 154.6, 129.4, 127.0, 117.7, 64.0, 43.5, 12.3. ESI-MS: *m/z* (%) 257 (100) [M + H$^+$].

5-(3,4-Dichlorophenoxy)-2-methylsulfanyl-3,4,5,6-tetrahydropyrimidin-1-ium Iodide (7c). Following the method described for **7a** gave **7c** as a yellow solid. Yield 95%. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.47 (d, J = 8.9 Hz, 1H), 7.26 (d, J = 2.9 Hz, 1H), 7.00 (dd, J = 8.9, 2.9 Hz, 1H), 5.12 (m_c, 1H), 3.73−3.66 (m, 4H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 166.6, 157.0, 134.6, 132.8, 127.0, 120.0, 118.1, 66.1, 45.2, 14.0. ESI-MS: *m/z* (%) 291 (100) [M + H$^+$].

Extraction from aqueous 1 M NaOH with CH_2Cl_2 gave the free base as a white solid. Anal. Calcd for $C_{11}H_{12}Cl_2N_2OS$: C, 45.37; H, 4.15; N, 9.62; S, 11.01. Found: C, 45.6; H, 4.40; N, 9.88; S, 10.2.

2-Methylsulfanyl-5-(4-trifluoromethylphenoxy)-3,4,5,6-tetrahydropyrimidin-1-ium Iodide (7d). Following the method described for **7a** gave **7d** as a yellow solid. Yield 96%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.68 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 5.26 (t, J = 2.5 Hz, 1H), 3.80−3.73 (m, 4H), 2.68 (s, 3H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 166.6, 160.5, 128.8, 117.8, 65.5, 45.3, 13.9. ESI-MS: *m/z* (%) 291 (100) [M + H$^+$].

Extraction from aqueous 1 M NaOH with CH_2Cl_2 gave the free base as a white solid. Anal. Calcd for $C_{12}H_{13}F_3N_2OS$: C, 49.65; H, 4.51; N, 9.65; S, 11.04. Found: C, 50.0; H, 4.61; N, 9.90; S, 10.9.

Representative Experimental Procedures for Preparation of 5-Phenoxy-2-alkylsulfanyl-3,4,5,6-tetrahydropyrimidin-1-ium Bromide: Preparation of 5-(2,4-Dichlorophenoxy)-2-(4-fluorobenzylsulfanyl)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (8a). To a solution of **6a** (0.1 mmol, 27 mg) in MeCN (1 mL) was added 4-fluorobenzyl bromide (0.4 mmol, 50 μL) and the reaction mixture was heated in the microwave at 150 °C for 600 s. The solvent was removed in vacuo, diethyl ether was added, and the precipitate was triturated overnight. The solid was filtered off, washed with ether, and dried in vacuo to give **8a** as a yellow solid. Yield: 29 mg (69%). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.50 (d, J = 2.4 Hz, 1H), 7.44 (dd, J = 8.5 Hz, $J_{H,F}$ = 5.4 Hz, 2H), 7.34 (dd, J = 8.8, 2.4 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.11 (dd, J = 8.5 Hz, $J_{H,F}$ = 8.5 Hz, 2H), 5.13 (br s, 1H), 4.44 (s, 2H), 3.69 (br s, 4H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 162.7, 162.5, 150.3, 130.7, 130.4, 129.9, 127.9, 127.8, 125.4, 118.2, 115.5, 65.7, 43.6, 34.7. ESI-MS: *m/z* (%) 385 (100) [M + H$^+$]. Anal. Calcd for $C_{17}H_{16}Cl_2FN_2OSBr$: C, 43.80; H, 3.46; N, 6.01; S, 6.88. Found: C, 44.0; H, 3.54; N, 5.99; S, 6.66.

5-(4-Chlorophenoxy)-2-(4-fluorobenzylsulfanyl)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (8b). Following the method described for **8a** gave **8b** as a yellow solid. Yield 83%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.31−7.28 (m, J = 8.8 Hz, $J_{H,F}$ = 5.2 Hz, 2H), 7.16−7.14 (m, J = 9.1 Hz, 2H), 6.97−6.94 (m, J = 8.8 Hz, 2H), 6.76−6.74 (m, J = 9.1 Hz, 2H), 4.88 (t, J = 2,5 Hz, 1H), 4.28 (s, 2H), 3.51 (m_c, 4H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 164.5, 164.0, 156.3, 132.5, 131.2, 128.8, 119.5, 117.3, 65.7, 45.4, 36.6. ESI-MS: *m/z* (%) 351 (100) [M + H$^+$]. Anal. Calcd for $C_{17}H_{17}ClFN_2OSBr$: C, 47.29; H, 3.97; N, 6.49; S, 7.43. Found: C, 47.3; H, 3.96; N, 6.40; S, 7.08.

5-(3,4-Dichlorophenoxy)-2-(4-fluorobenzylsulfanyl)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (8c). Following the method described for **8a** gave **8c** as a yellow solid. Yield 71%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.49−7.46 (m, 2H), 7.48 (d, J = 8.9 Hz, 1H), 7.16−7.13 (m, 2H), 7.14 (d, J = 2.9 Hz, 1H), 6.92 (dd, J = 8.9, 2.9 Hz, 1H), 5.10 (t, J = 2.5 Hz, 1H), 4.45 (s, 2H), 3.69 (m_c, 4H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 165.0, 164.0, 156.9, 134.6, 132.7, 132.5, 127.0, 120.1, 117.9, 117.3, 66.0, 45.3, 36.5. ESI-MS: *m/z* (%) 385 (100) [M + H$^+$]. Anal. Calcd for $C_{17}H_{16}Cl_2FN_2OSBr$: C, 43.80; H, 3.46; N, 6.01; S, 6.88. Found: C, 43.9; H, 3.51; N, 6.37; S, 6.40.

2-(4-Fluorobenzylsulfanyl)-5-(4-trifluoromethylphenoxy)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (8d). Following the method described for **8a** gave **8d** as a yellow solid. Yield 69%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.68−7.65 (m, 2H), 7.49−7.46 (m, 2H), 7.15−7.10 (m, 4H), 5.21 (t, J = 2.5 Hz, 1H), 4.45 (br s, 2H), 3.73 (m_c, 4H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 164.5, 163.9, 160.4, 132.5, 128.7, 125.3, 117.8, 117.3, 65.5, 45.4, 36.5. ESI-MS: *m/z* (%) 385 (100) [M + H$^+$]. Anal. Calcd for $C_{18}H_{17}F_4N_2OSBr$: C, 46.46; H, 3.68; N, 6.02; S, 6.89. Found: C, 46.9; H, 3.88; N, 6.17; S, 6.67.

2-(2-Cyanoethylsulfanyl)-5-(2,4-dichlorophenoxy)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (9a). Following the method described for **8a** gave **9a** as a yellow solid. Yield 92%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.49 (d, J = 2.5 Hz, 1H), 7.34 (dd, J = 8.8, 2.5 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 5.20 (m_c, 1H), 3.73−3.67 (m, 4H), 3.48 (t, J = 6.7 Hz, 2H), 2.98 (t, J = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 163.5, 152.1, 131.7, 129.8, 129.5, 127.0, 119.7, 119.1, 67.2, 45.5, 28.9, 19.8. ESI-MS: *m/z* (%) 330 (100) [M + H$^+$]. Anal. Calcd for $C_{13}H_{14}Cl_2N_3OSBr$: C, 37.98; H, 3.43; N, 10.22. Found: C, 37.2; H, 3.52; N, 9.83.

5-(4-Chlorophenoxy)-2-(2-cyanoethylsulfanyl)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (9b). Following the method described for **8a** gave **9b** as a yellow solid. Yield 71%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.33−7.30 (m, J = 9.0 Hz, 2H), 7.04−7.01 (m, J = 9.0 Hz, 2H), 5.11 (t, J = 2.5 Hz, 1H), 3.72−3.68 (m, 4H), 3.48 (t, J = 6.6 Hz, 2H), 2.98 (t, J = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 163.5, 156.4, 131.2, 128.9, 119.5, 119.1, 65.7, 45.5, 28.9, 19.8. ESI-MS: *m/z* (%) 296 (100) [M + H$^+$]. Anal. Calcd for $C_{13}H_{15}ClN_3OSBr$: C, 41.45; H, 4.01; N, 11.15; S, 8.51. Found: C, 41.2; H, 4.00; N, 11.1; S, 7.48.

2-(2-Cyanoethylsulfanyl)-5-(3,4-dichlorophenoxy)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (9c). Following the method described for **8a** gave **9c** as a yellow solid. Yield 75%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.44 (d, J = 8.9 Hz, 1H), 7.25 (d, J = 2.9 Hz, 1H), 6.99 (dd, J = 8.9, 2.9 Hz, 1H), 5.12 (t, J = 2.5 Hz, 1H), 3.71−3.66 (m, 4H), 3.46 (t, J = 6.6 Hz, 2H), 2.96 (t, J = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 163.6, 157.0, 134.6, 132.8, 127.0, 120.0, 119.1, 118.0, 66.0, 45.4, 28.9, 19.8. ESI-MS: *m/z* (%) 330 (100) [M + H$^+$]. Anal. Calcd for $C_{13}H_{14}Cl_2N_3OSBr$: C, 37.98; H, 3.43; N, 10.22; S, 7.80. Found: C, 37.9; H, 3.61; N, 10.3; S, 7.36.

2-(2-Cyanoethylsulfanyl)-5-(4-trifluoromethylphenoy)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (9d). Following the method described for **8a** gave **9d** as a yellow solid. Yield 58%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.64 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 5.26 (t, J = 2.5 Hz, 1H), 3.80−3.71 (m, 4H), 3.49 (t, 2H), 2.99 (t, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 163.6, 160.4, 128.8, 126.1, 125.6, 119.1, 117.8, 65.4, 45.5, 28.9, 19.8. ESI-MS: *m/z* (%) 330 (100) [M + H$^+$]. Anal. Calcd for $C_{14}H_{15}F_3N_3OSBr$: C, 40.99; H, 3.68; N, 10.24; S, 7.82. Found: C, 41.0; H, 3.87; N, 10.2; S, 7.31.

5-(2,4-Dichlorophenoxy)-2-(2-hydroxyethylsulfanyl)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (10a). Following the method described for **8a** gave **10a** as a yellow solid. Yield 79%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.49 (d, J = 2.1 Hz, 1H), 7.34 (dd, J = 8.8, 2.1 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 5.16 (br s, 1H), 3.90 (t, J = 5.2 Hz, 2H), 3.72 (m_c, 4H), 3.33 (t, J = 5.2 Hz, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 164.4, 150.3, 129.9, 127.9, 127.7, 125.5, 118.3, 65.7, 60.8, 43.5, 34.4. ESI-MS: *m/z* (%) 321 (100) [M + H$^+$]. Anal. Calcd for $C_{12}H_{15}Cl_2N_2O_2SBr$: C, 35.84; H, 3.76; N, 6.97; S, 7.97. Found: C, 35.7; H, 3.78; N, 6.79; S, 7.20.

5-(4-Chlorophenoxy)-2-(2-hydroxyethylsulfanyl)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (10b). Following the method described for **8a** gave **10b** as a yellow solid. Yield 71%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.33−7.31 (m, J = 9.0 Hz, 2H), 7.03−7.01 (m, J = 9.0 Hz, 2H), 5.07 (t, J = 2.6 Hz, 1H), 3.88 (m_c, 2H), 3.70−3.69 (m, 4H), 3.33−3.31 (m, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 166.1, 156.4, 131.2, 128.8, 119.6, 65.9, 62.6, 45.3, 36.2. ESI-MS: *m/z* (%) 287 (100) [M + H$^+$]. Anal. Calcd for $C_{12}H_{16}ClN_2O_2SBr$: C, 39.20; H, 4.39; N, 7.62; S, 8.72. Found: C, 39.6; H, 4.31; N, 7.77; S, 7.58.

5-(3,4-Dichlorophenoxy)-2-(2-hydroxyethylsulfanyl)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (10c). Fol-

lowing the method described for **8a** gave **10c** as a yellow solid. Yield 52%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.46 (d, J = 8.9 Hz, 1H), 7.26 (d, J = 2.9 Hz, 1H), 7.00 (dd, J = 8.9, 2.9 Hz, 1H), 5.11 (t, J = 2.5 Hz, 1H), 3.88 (t, J = 5.3 Hz, 2H), 3.70 (m, 4H), 3.32 (t, J = 5.3 Hz, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 166.1, 157.0, 134.6, 132.8, 127.0, 120.1, 118.1, 66.2, 62.6, 45.3, 36.2. ESI-MS: *m*/*z* (%) 321 (100) [M + H$^+$]. Anal. Calcd for $C_{12}H_{15}Cl_2N_2O_2SBr$: C, 35.84; H, 3.76; N, 6.97; S, 7.97. Found: C, 35.6; H, 4.04; N, 7.22; S, 7.03.

2-(2-Hydroxyethylsulfanyl)-5-(4-trifluoromethylphenoxy)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (10d). Following the method described for **8a** gave **10d** as a yellow solid. Yield 71%. ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.64 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 5.22 (t, J = 2.5 Hz, 1H), 3.88 (t, J = 5.3 Hz, 2H), 3.77−3.71 (m, 4H), 3.32 (t, J = 5.3 Hz, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 166.1, 160.5, 128.8, 117.9, 65.5, 62.7, 45.3, 36.2. ESI-MS: *m*/*z* (%) 321 (100) [M + H$^+$]. Anal. Calcd for $C_{13}H_{16}F_3N_2O_2SBr$: C, 38.92; H, 4.02; N, 6.98; S, 7.99. Found: C, 39.2; H, 4.20; N, 7.25; S, 7.44.

General Procedure for the Synthesis of (2-Chloroethoxy)benzenes. A mixture of the appropriate phenol (3 equiv), 1-bromo-2-chloroethane (1 equiv), potassium carbonate (8 equiv), and acetonitrile were heated at 150 °C for 100 s in the microwave. The solvent was removed and aqueous 1 M NaOH was added to the residue. The aqueous layer was extracted with $CHCl_3$, and the organic layer was concentrated under reduced pressure to afford the crude, which was used without further purification.

Representative Experimental Procedures for Preparation of 5-Phenoxy-2-alkylsulfanyl-3,4,5,6-tetrahydropyrimidinium Chloride: Preparation of 2-[2-(2-Carbamoyl-4-chlorophenoxy)ethylsulfanyl]-5-(4-chlorophenoxy)-3,4,5,6-tetrahydropyrimidinium Chloride (11). To a solution of **6b** (0.10 mmol, 24 mg) and 5-chloro-2-(2-chloroethoxy)-benzamide (0.15 mmol, 35 mg) in acetonitrile (0.6 mL) was added a catalytic amount of potassium iodide and the mixture was heated for 1000 s at 160 °C. The solvent was removed in vacuo and the residue was extracted under vigorous agitation with CH_2Cl_2 (2 mL) from aqueous 1 M NaOH (2 mL). The organic layer was concentrated and submitted to flash column chromatography EtOAc:MeOH:NEt$_3$ (15:1:0 → 30:2:1) to give **11** as a white solid. Yield 94%. ^{1}H NMR (400 MHz, DMSO) δ 10.12 (s, 2H), 7.75 (s, 1H), 7.69 (d, J = 2.8 Hz, 1H), 7.65 (s, 1H), 7.53 (dd, J = 8.9, 2.8 Hz, 1H), 7.36 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 9.0 Hz, 2H), 5.10 (t, J = 2.3 Hz, 1H), 4.35 (t, J = 5.7 Hz, 2H), 3.74 (t, J = 5.7 Hz, 2H), 3.66 (dd, J = 14.8, 2.3 Hz, 2H), 3.55 (d, J = 14.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO) δ 165.1, 161.0, 154.5, 154.2, 131.5, 129.7, 129.4, 125.5, 124.8, 117.9, 115.1, 67.1, 63.5, 43.3, 30.1. ESI-MS: *m*/*z* (%) 440 (100) [M + H$^+$].

1-(2-{2-[5-(2,4-Dichlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-ylsulfanyl]ethoxy}phenyl)ethanone (12). Following the method described for **11** gave **12** as a white solid. Yield 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.9, 1.8 Hz, 1H), 7.42 (ddd, J = 9.1, 7.9, 1.5 Hz, 1H), 7.36 (d, J = 2.6 Hz, 1H), 7.17 (dd, J = 8.8, 2.6 Hz, 1H), 7.00 (m, 2H), 6.93 (d, J = 8.8 Hz, 1H), 4.60 (m$_c$, 1H), 4.29 (t, J = 6.2 Hz, 2H), 3.60 (br s, 4H), 3.41 (t, J = 6.2 Hz, 2H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9, 157.9, 152.6, 151.4, 133.7, 130.5, 130.4, 127.7, 127.4, 126.0, 120.8, 118.3, 112.5, 69.7, 67.6, 32.2, 29.4. ESI-MS: *m*/*z* (%) 439 (100) [M + H$^+$].

2-[2-(4-Chlorophenoxy)ethylsulfanyl]-5-(2,4-dichlorophenoxy)-1,4,5,6-tetrahydropyrimidine (13). Following the method described for **11** gave **13** as a white solid. Yield 93%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 2.5 Hz, 1H), 7.20 (d, J = 9.1 Hz, 2H), 7.17 (dd, J = 8.8, 2.5 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 9.1 Hz, 2H), 4.59 (mc, 1H), 4.15 (t, J = 6.6 Hz, 2H), 3.60−3.56 (m, 4H), 3.32 (t, J = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 152.8, 151.4, 130.4, 129.3, 127.6, 127.5, 126.1, 125.8, 118.4, 116.0, 69.7, 67.5, 46.2, 29.3. ESI-MS: *m*/*z* (%) 431 (100) [M + H$^+$].

5-(2,4-Dichlorophenoxy)-2-[2-(3-methyl-4-nitrophenoxy)-ethylsulfanyl]-1,4,5,6-tetrahydropyrimidine (14). Following the method described for **11** gave **14** as a yellow solid. Yield 90%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 10.0 Hz, 1H), 7.37 (d, J = 2.5 Hz, 1H), 7.18 (dd, J = 8.8, 2.5 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.87−6.85 (m, 2H), 4.61 (m$_c$, 1H), 4.25 (t, J = 6.8 Hz, 2H), 3.70−3.54 (m, 4H), 3.32 (m$_c$, 2H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.5, 151.3, 142.2, 137.1, 130.4, 127.7, 127.5, 126.0, 118.2, 118.0, 112.6, 69.6, 67.5, 28.8, 21.7. ESI-MS: *m*/*z* (%) 456 (100) [M + H$^+$].

Representative Experimental Procedures for Preparation of 5-Phenoxytetrahydropyrimidin-2-one: Preparation of 5-(2,4-Dichlorophenoxy)tetrahydropyrimidin-2-one (15a). Method A: Ammonium hydroxide (1 mL) was added to **7a** (0.10 mmol, 29 mg) and the mixture was heated in the microwave at 150 °C for 500 s. All volatiles were removed in vacuo giving **15a** as a white solid. Yield: 23 mg (87%).

Method B: Water (1 mL) was added to **7a** (0.10 mmol, 29 mg) and the mixture was heated in the microwave at 150 °C for 1000 s. Water was removed in vacuo to give **15a** as a white solid. Yield: 13 mg (50%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.58 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 8.8, 2.4 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 6.10 (br s, 2H), 4.79 (br s, 1H), 3.44−3−24 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.5, 151.8, 130.1, 128.5, 125.7, 124.4, 118.0, 68.3, 43.2. ESI-MS: *m*/*z* (%) 261 (100) [M + H$^+$], 302 [M + ACN]. Anal. Calcd for $C_{10}H_{10}Cl_2N_2O_2$: C, 46.00; H, 3.86; N, 10.73. Found: C, 45.4; H, 4.19; N, 10.6.

5-(4-Chlorophenoxy)tetrahydropyrimidin-2-one (15b). Following method A described for **15a** gave **15b** as a white solid. Yield 95%. Following method B described for **15a** gave **15b** as a white solid. Yield 35%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 9.0 Hz, 2H), 7.01 (d, J = 9.0 Hz, 2H), 6.08 (br s, 1H), 4.71 (br s, 1H), 3.38−3.22 (m, 4H). ESI-MS: *m*/*z* (%) 227 (100) [M + H$^+$].

5-(3,4-Dichlorophenoxy)tetrahydropyrimidin-2-one (15c). Following method A described for **15a** gave **15c** as a white solid. Yield quantitative. Following method B described for **15a** gave **15c** as a white solid. Yield 19%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54 (d, J = 8.9 Hz, 1H), 7.33 (d, J = 2.9 Hz, 1H), 7.03 (dd, J = 8.9, 2.9 Hz, 1H), 6.12 (br s, 1H), 4.80 (m$_c$, 1H), 3.38−3.23 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.5, 155.4, 132.3, 131.5, 123.3, 118.2, 117.2, 67.0, 43.0. ESI-MS: *m*/*z* (%) 261 [M + H$^+$], 302 (100) [M + ACN]. Anal. Calcd for $C_{10}H_{10}Cl_2N_2O_2$: C, 46.00; H, 3.86; N, 10.73. Found: C, 45.2; H, 4.08; N, 10.4.

5-(4-Trifluoromethylphenoxy)tetrahydropyrimidin-2-one (15d). Following method A described for **15a** gave **15d** as a white solid. Yield quantitative. Following method B described for **15a** gave **15d** as a white solid. Yield: 17 mg (65%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.66 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 6.16 (br s, 1H), 4.88 (m$_c$, 1H), 3.43−3.40 (m, 2H), 3.32−3.27 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.0, 155.4, 127.4, 124.9, 121.6, 116.4, 66.5, 43.0. ESI-MS: *m*/*z* (%) 261 [M + H$^+$], 302 (100) [M + ACN]. Anal. Calcd for $C_{11}H_{11}F_3N_2O_2$: C, 50.77; H, 4.26; N, 10.76. Found: C, 50.6; H, 4.59; N, 10.6.

5-(2,4-Dichlorophenoxy)-2-ethoxy-1,4,5,6-tetrahydropyrimidine (16a). 7a (0.10 mmol, 29 mg) was washed with 1 M aqueous NaOH and extracted with $CHCl_3$. The solvent was removed in vacuo, the residue was added to ammonia in ethanol (1 mL), and the solution was heated in the microwave at 150 °C for 1000 s. Ammonia and ethanol were removed in vacuo giving **16a** as a white solid. Yield: 28 mg (99%). ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.45 (d, J = 2.6 Hz, 1H), 7.30 (dd, J = 8.8, 2.6 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 4.74 (m$_c$, 1H), 3.64 (q, J = 7.0 Hz, 2H), 3.52 (m$_c$, 4H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 157.9, 153.5, 131.4, 129.3, 128.2, 127.1, 119.5, 70.4, 58.7, 45.9, 18.8. ESI-MS: *m*/*z* (%) 289 (100) [M + H$^+$]. Anal. Calcd for $C_{12}H_{14}Cl_2N_2O_2$: C, 49.84; H, 4.88; N, 9.69. Found: C, 49.2; H, 5.14; N, 9.75.

5-(4-Chlorophenoxy)-2-ethoxy-1,4,5,6-tetrahydropyri-

midine (16b). Following the method described for **16a** gave **16b** as a white solid. Yield 99%. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.27 (d, J = 4.0 Hz, 2H), 7.26 (d, J = 4.0 Hz, 2H), 4.63 (m_c, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.47 (m_c, 4H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 155.9, 155.3, 129.0, 125.7, 117.3, 67.0, 61.1, 44.2, 13.4.

Representative Experimental Procedures for Preparation of 2-Amino-5-phenoxy-3,4,5,6-tetrahydropyrimidin-1-ium Bromide: 2-Amino-5-(4-chlorophenoxy)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (17a). To a solution of cyanogen bromide (1.2 mmol, 127 mg) in 2-propanol (2.5 mL) was added **3b** (1.0 mmol, 200 mg) and the reaction mixture was heated in the microwave at 120 °C for 600 s. Isopropyl ether (2.5 mL) was added and the precipitate was filtered off, washed with isopropyl ether, and dried in vacuo over P_4O_{10} to give **17a** as a white solid. Yield 61%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (br s, NH, 2H), 7.36 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 6.95 (br s, NH, 1H), 4.93 (m_c, 1H), 3.44 (m_c, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.4, 153.7, 129.9, 125.7, 118.3, 65.9, 41.6. ESI-MS: m/z (%) 226 (100) [M + H$^+$]. Anal. Calcd for $C_{10}H_{13}BrClN_3O$: C, 39.18; H, 4.27; N, 13.71. Found: C, 39.6; H, 4.25; N, 13.5.

2-Amino-5-(3,4-dichlorophenoxy)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (17b). Following the method described for **17a** gave **17b** as a white solid. Yield 53%. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.46 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 2.9 Hz, 1H), 6.99 (dd, J = 8.9, 2.9 Hz, 1H), 4.97 (m_c, 1H), 3.56−3.52 (m, 4H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 155.5, 154.0, 132.7, 130.9, 124.9, 118.1, 116.2, 65.3, 41.3. ESI-MS: m/z (%) 260 (100) [M + H$^+$], 301 [M + ACN]. Anal. Calcd for $C_{10}H_{12}Cl_2N_3OBr$: C, 35.22; H, 3.55; N, 12.32. Found: C, 35.3; H, 3.81; N, 11.6.

2-Amino-5-(4-trifluoromethylphenoxy)-3,4,5,6-tetrahydropyrimidin-1-ium Bromide (17c). Following the method described for **17a** gave **17c** as a white solid. Yield 57%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 6.98 (br s, 2H), 5.08 (br s, 1H), 3.48 (m_c, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.5, 153.7, 127.6, 124.9, 122.4, 116.7, 64.9, 41.6.

5-Benzyl-3,4,5,6-tetrahydropyrimidin-2-ylammonium Bromide (17d). Following the method described for **17a**, using **3e**[23,24] as starting material, gave **17d** as a white solid. Yield 56%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (br s, 2H), 7.33−7.23 (m, 3H), 7.13 (d, J = 7.0 Hz, 2H), 6.88 (br s, 2H), 3.35 (d, J = 12.0 Hz, 2H), 3.01 (dd, J = 11.0, 9.5 Hz, 2H), 2.64 (d, J = 7.5 Hz, 2H), 2.25 (m_c, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.7, 137.4, 128.8, 128.7, 127.0, 43.0, 36.9, 32.1. ESI-MS: m/z (%) 190 (100) [M + H$^+$]. Anal. Calcd for $C_{11}H_{16}BrN_3$: C, 48.90; H, 5.97; N, 15.55. Found: C, 49.2; H, 6.54; N, 15.6.

Representative Experimental Procedures for Preparation of [5-Phenoxy-1,4,5,6-tetrahydropyrimidin-2-yl]-alkylammonium Iodide: Preparation of [5-(4-Chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl]phenethylammonium Iodide (19a). To a solution of the isothiouronium iodide **7b** (39 mg, 0.10 mmol) in acetonitrile (2 mL) was added phenethylamine **18a** (13 mg, 0.11 mmol) and the mixture was heated at 90 °C for 6 d. The mixture was diluted with THF (4 mL) and the excess of the amine was scavenged with use of methyl isocyanate on polystyrene (0.20 mmol). After 3 h of agitation at room temperature, the resin was filtered off and washed with CH_2Cl_2 (2 mL) and MeOH (2 mL), and the organic layer was concentrated in vacuo. Flash column chromatography (EtOAc:MeOH; 15:1 → 10:1) of the residue afforded **19a** as a yellow solid. Yield: 20 mg (69%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 (t, J = 6.8 Hz, 1H), 7.31−7.21 (m, 5H), 7.26 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 4.58 (m_c, 1H), 3.54 (dt, J = 6.8, 6.6 Hz, 2H), 3.45−3.39 (m, 4H), 2.95 (t, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.3, 153.2, 137.8, 129.9, 129.1, 129.0, 127.8, 127.0, 117.9, 65.3, 43.8, 47.0, 35.4. ESI-MS: m/z (%) 330 (100) [M + H$^+$].

[5-(4-Chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl][2-(4-methoxyphenyl)ethyl]ammonium Iodide (19b). Following the method described for **19a** gave **19b** as a yellow oil. Yield 67%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.61 (t, J = 5.8 Hz, 1H), 7.26 (d, J = 9.0 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 4.58 (m_c, 1H), 3.72 (s, 3H), 3.47 (dt, J = 6.8, 5.8 Hz, 2H), 3.46−3.40 (m, 4H), 2.89 (t, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.6, 154.3, 153.3, 130.2, 129.9, 129.7, 127.8, 117.8, 114.4, 65.3, 55.3, 44.1, 42.0, 34.6. ESI-MS: m/z (%) 360 (100) [M + H$^+$]. Anal. Calcd for $C_{19}H_{23}ClIN_3O_2$: C, 46.79; H, 4.75; N, 8.61. Found: C, 46.2; H, 5.33; N, 8.13.

(3,3-Diphenylpropyl)[5-(4-chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl]ammonium Iodide (19c). Following the method described for **19a** gave **19c** as a yellow solid. Yield 61%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.64 (t, J = 5.6 Hz, 1H), 7.30−7.15 (m, 10H), 7.24 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 4.59 (m_c, 1H), 4.23 (t, J = 8.1 Hz, 1H), 3.50−3.40 (m, 4H), 3.20 (dt, J = 6.9, 5.6 Hz, 2H), 2.38 (dt, J = 8.1, 6.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.2, 153.0, 143.2, 129.9, 128.7, 127.9, 127.8, 117.9, 65.3, 47.6, 41.9, 40.1, 34.3. ESI-MS: m/z (%) 420 (100) [M + H$^+$]. Anal. Calcd for $C_{25}H_{27}ClIN_3O$: C, 54.81; H, 4,97; N, 7.67. Found: C, 54.4; H, 5.40; N, 7.45.

(3,3-Diphenylpropyl)[5-(4-trifluoromethylphenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl]ammonium Iodide (19d). Following the method described for **19a** gave **19d** as a yellow solid. Yield 73%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 (t, J = 5.4 Hz, 1H), 7.55 (d, J = 8.6 Hz, 2H), 7.30−7.15 (m, 10H), 6.94 (d, J = 8.6 Hz, 2H), 4.74 (m_c, 1H), 4.23 (t, J = 8.0 Hz, 1H), 3.50 (br s, 4H), 3.20 (dt, J = 6.9, 5.4 Hz, 2H), 2.39 (dt, J = 8.0, 6.9 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.1, 152.9, 143.2, 128.7, 127.9, 127.4, 126.7, 116.0, 64.7, 47.7, 41.9, 40.1, 34.3. ESI-MS: m/z (%) 454 (100) [M + H$^+$].

[3-(2-oxopyrrolidin-1-yl)propyl][5-(4-trifluoromethylphenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl]ammonium Iodide (19e). Following the method described for **19a** gave **19e** as a yellow oil. Yield 84%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.36 (br s, 1H), 7.88−7.81 (m, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 8.2 Hz, 2H), 4.84 (m_c, 1H), 3.57 (m_c, 4H), 3.50 (t, J = 7.2 Hz, 2H), 3.33−3.29 (m, 4H), 2.46−2.42 (m, 2H), 2.14−2.07 (m, 2H), 1.86 (m_c, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 177.2, 158.4, 154.9, 127.4, 116.1, 65.2, 48.6, 41.9, 40.7, 39.7, 31.3, 29.5, 17.8. ESI-MS: m/z (%) 385 (100) [M + H$^+$].

[3-(Methylphenylamino)propyl][5-(4-trifluoromethylphenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl]ammonium Iodide (19f). Following the method described for **19a** gave **19f** as a yellow oil. Yield 86%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80−7.71 (m, 3H), 7.56 (d, J = 8.8 Hz, 2H), 7.21 (dd, J = 8.7, 7.4 Hz, 1H), 6.92−6.88 (m, 4H), 6.83 (t, J = 7.4 Hz, 1H), 4.68 (m_c, 1H), 3.42 (br s, 4H), 3.31 (dd, J = 6.1, 6.0 Hz, 2H), 3.25 (t, J = 6.3 Hz, 2H), 2.84 (s, 3H), 1.93 (tt, J = 6.3, 6.1 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.2, 154.0, 149.9, 129.5, 127.4, 125.0, 120.6, 116.6, 115.7, 64.7, 48.5, 42.0, 40.7, 38.5, 26.8. ESI-MS: m/z (%) 224 (100), 245 (80), 407 (55) [M + H$^+$].

(2-Phenylpropyl)[5-(4-trifluoromethylphenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl]ammonium Iodide (19g). Following the method described for **19a** gave **19g** as a yellow oil. Yield 46%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.65 (t, J = 6.1 Hz, 1H), 7.57 (d, 2H, J = 8.8 Hz, 2H), 7.35−7.31 (m, 4H), 7.20 (m_c, 1H), 6.93 (d, J = 8.8 Hz, 2H), 4.69 (m_c, 1H), 3.50−3.33 (m, 6H), 3.12−3.09 (m, 1H), 1.39 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.2, 143.1, 129.1, 127.5, 127.4, 115.9, 64.7, 49.6, 41.9, 39.9, 18.7. ESI-MS: m/z (%) 378 (100) [M + H$^+$].

[3-(2-Carbamoyl-4-chlorophenoxy)propyl]-[5-(4-chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl]ammonium Iodide (19h). Following the method described for **19a** gave **19h** as a pale yellow oil. Yield 33%. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 (t, J = 5.8 Hz, 1H), 7.61 (s, 1H), 7.54 (d, J = 2.7

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Hz, 1H), 7.34 (dd, J = 8.9, 2.7 Hz, 1H), 7.23 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 8.9 Hz, 1H), 6.77 (d, J = 9.0 Hz, 2H), 6.55 (s, 1H), 6.12 (s, 1H), 4.60 (m_c, 1H), 4.18 (t, J = 5.3 Hz, 2H), 3.61 (dt, J = 5.8, 5.7 Hz, 2H), 3.51 (m_c, 4H), 2.15 (m_c, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 154.8, 154.5, 153.0, 132.9, 129.9, 128.9, 127.6, 126.1, 123.4, 117.8, 114.0, 66.4, 65.6, 42.1, 39.6, 28.2. ESI-MS: *m/z* (%) 438 (100) [M + H$^+$].

General Procedure for the Transformation of 2-Methylsulfanyl-5-phenoxy-3,4,5,6-tetrahydropyrimidin-1-ium Iodide into Its Trifluoroacetate Form 21. The appropriate iodide salt **7** was deprotonated in aqueous 1 M NaOH and extracted with $CHCl_3$. The organic layer was concentrated in vacuo and CH_2Cl_2 was added. Trifluoroacetic acid (5 equiv) was carefully added and all volatiles were removed in vacuo. The residue was recrystallized from MeOH/Et_2O to give **21** as a pale yellow solid.

Representative Experimental Procedures for Preparation of 5-Phenoxy-1,4,5,6-tetrahydropyrimidin-2-yl]-alkylammonium: Preparation of [5-(4-Chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl]isobutylammonium Trifluoroacetate (19i). To a solution of the isothiouronium trifluoroacetate **21a** (37 mg, 0.10 mmol) in acetonitrile (0.6 mL) was added isobutylamine **18i** (8 mg, 0.11 mmol) and the mixture was heated for 800 s at 160 °C in the microwave. The mixture was diluted with acetonitrile (0.3 mL) and THF (0.9 mL) and the excess of **21a** was scavenged with Wang resin (0.25 mmol). After the mixture was heated for an additional 1000 s at 150 °C in the microwave, methyl isocyanate on resin (0.30 mmol) was added to remove the unreacted amine. The resins were filtered off and washed with CH_2Cl_2 (2 mL) and MeOH (2 × 2 mL), and the organic layer was concentrated in vacuo to give **19i** as a yellow oil. Yield 20 mg (71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (t, J = 5.4 Hz, 1H), 7.26 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.65 (m_c, 1H), 4.60−4.49 (m, 4H), 2.93 (dd, J = 6.8, 5.4 Hz, 2H), 1.89 (m_c, 1H), 0.94 (d, J = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 153.2, 129.9, 127.7, 117.8, 65.8, 48.7, 42.1, 28.2, 20.0. ESI-MS: *m/z* (%) 282 (100) [M + H$^+$]. Anal. Calcd for $C_{16}H_{21}ClF_3N_3O_3$: C, 48.55; H, 5.35; N, 10.62. Found: C, 48.4; H, 5.62; N, 10.4.

[5-(4-Chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl](3-(dimethylamino)propyl)ammonium Trifluoroacetate (19j). Following the method described for **19i** gave **19j** as a yellow oil. Yield 77%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.67 (m_c, 1H), 3.58−3.43 (m, 4H), 3.29−3.19 (m, 2H), 2.50−2.18 (m, 2H), 2.19 (s, 6H), 1.74 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 129.9, 127.4, 117.2, 65.5, 53.3, 44.1, 42.9, 37.4, 27.2. ESI-MS: *m/z* (%) 311 (100) [M + H$^+$].

(2-Acetylaminoethyl)-[5-(4-chlorophenoxy)-3,4,5,6-tetrahydropyrimidin-2-yl]ammonium Trifluoroacetate (19k). Following the method described for **19i** gave **19k** as a yellow solid. Yield 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (br s, 1H), 7.24 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.67 (m_c, 1H), 3.64−3.53 (m, 4H), 3.33 (m_c, 2H), 3.28 (m_c, 2H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 154.5, 153.6, 129.9, 127.7, 117.8, 65.7, 42.0, 39.7, 39.4, 22.8. ESI-MS: *m/z* (%) 311 (100) [M + H$^+$].

[5-(4-Chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl]pyridin-2-ylmethylammonium Trifluoroacetate (19*l*). Following the method described for **19i** gave **19*l*** as a yellow oil. Yield 53%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (t, J = 5.8 Hz, 1H), 8.44 (ddd, J = 5.0, 1.6, 0.8 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.32 (ddd, J = 7.7, 5.0, 1.1 Hz, 1H), 7.26 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 4.70 (m_c, 1H), 4.38 (d, J = 5.8 Hz, 2H), 3.64−3.53 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 155.9, 154.4, 148.3, 138.5, 129.8, 127.7, 123.9, 123.5, 118.0, 65.4, 47.5, 42.0. ESI-MS: *m/z* (%) 317 (100) [M + H$^+$].

[5-(3,4-Dichlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl](3,3-diphenylpropyl)ammonium Trifluoroacetate (19m). Following the method described for **19i** gave **19m** as a yellow oil. Yield 32%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, J = 5.3 Hz, 1H), 7.36 (d, J = 8.9 Hz, 1H), 7.30−7.18 (m, 10H), 6.98 (d, J = 2.9 Hz, 1H), 6.74 (dd, J = 8.9, 2.9 Hz, 1H), 4.61 (m_c, 1H), 4.05 (t, J = 8.0 Hz, 1H), 3.50−3.40 (m, 4H), 3.07 (dt, J = 6.5, 5.3 Hz, 2H), 2.39 (dt, J = 8.0, 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 153.0, 143.3, 133.5, 131.3, 128.8, 127.8, 126.8, 126.2, 118.1, 115.9, 65.6, 48.0, 41.9, 39.4, 34.5. ESI-MS: *m/z* (%) 454 (100) [M + H$^+$].

[5-(4-Chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl](2-phenoxyethyl)ammonium Chloride (19n). Following the method described for **19i** gave the trifluoroacetate salt. After extraction from 1 M NaOH with EtOAc, the guanidine was precipitated from 2.5 M HCl/EtOAc, washed (EtOAc, Et_2O), and dried in vacuo to give **19n** as a yellow oil. Yield 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (t, J = 5.6 Hz, 1H), 7.29−7.26 (m, 2H), 7.21 (d, J = 8.9 Hz, 2H), 7.03 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 7.8 Hz, 2H), 6.76 (d, J = 8.9 Hz, 2H), 4.68 (br s, 1H), 4.16 (t, J = 4.4 Hz, 2H), 3.67 (m_c, 2H), 3.67−3.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.2, 155.0, 154.2, 129.9, 129.9, 127.6, 122.4, 117.7, 114.7, 69.0, 65.3, 42.1, 41.8. ESI-MS: *m/z* (%) 346 (100) [M + H$^+$].

[5-(3,4-Dichlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl](3-phenylpropyl)ammonium Trifluoroacetate (19o). Following the method described for **19i** gave **19o** as a pale yellow solid. Yield 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (t, J = 5.2 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.27−7.23 (m, 2H), 7.18−7.15 (m, 3H), 6.96 (d, J = 2.9 Hz, 1H), 6.72 (dd, 1H, J = 8.9, 2.9 Hz, 1H), 4.56 (m_c, 1H), 3.52−3.42 (m, 4H), 3.18 (dt, J = 7.1, 5.2 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), 2.83 (tt, J = 7.6, 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 153.0, 140.7, 133.4, 131.2, 128.6, 128.5, 126.2, 126.0, 118.2, 116.0, 65.8, 41.9, 40.6, 32.6, 30.3. ESI-MS: *m/z* (%) 378 (100) [M + H$^+$]. Anal. Calcd for $C_{21}H_{22}Cl_2F_3N_3O_3$: C, 51.23; H, 4.50; N, 8.53. Found: C, 51.7; H, 5.10; N, 8.70.

5-(3,4-Dichlorophenoxy)-2-(2-methoxyethylamino)-3,4,5,6-tetrahydropyrimidin-1-ium Chloride (19p). Following the method described for **19i** gave **19p** as a yellow solid. Yield 70%. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.46 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 2.7 Hz, 1H), 7.00 (dd, J = 8.8, 2.7 Hz, 1H), 4.98 (br s, 1H), 3.58 (m_c, 4H), 3.54 (t, 2H), 3.41−3.31 (m, 5H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 155.5, 153.4, 132.7, 130.9, 124.9, 118.2, 116.2, 70.5, 65.6, 57.8, 41.5, 40.9.

[5-(4-Chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl][2-(4-methoxyphenoxy)ethyl]ammonium Trifluoroacetate (19q). Following the method described for **19i** gave **19q** as a yellow oil. Yield 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.22 (m_c, 1H), 7.22 (d, J = 9.0 Hz, 2H), 6.83−6.77 (m, 4H), 6.74 (d, J = 9.1 Hz, 2H), 4.71 (m_c, 1H), 4.08 (m_c, 2H), 3.78 (s, 3H), 3.67−3.53 (m, 4H), 3.61−3.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 155.1, 154.2, 151.1, 129.9, 127.6, 117.7, 116.0, 114.9, 71.1, 65.5, 55.7, 42.1, 41.7. ESI-MS: *m/z* (%) 376 (100) [M + H$^+$].

[5-(3,4-Dichlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl][2-(2,4-dichlorophenyl)ethyl]ammonium Trifluoroacetate (19r). Following the method described for **19i** gave **19r** as a colorless oil. Yield 35%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (br s, 1H), 7.36−7.34 (m, 2H), 7.28 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 2.9 Hz, 1H), 6.73 (dd, J = 8.9, 2.9 Hz, 1H), 4.63 (m_c, 1H), 3.57−3.45 (m, 4H), 3.39 (m_c, 2H), 3.00 (t, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 153.2, 134.3, 133.8, 133.5, 132.5, 131.3, 129.3, 127.7, 126.3, 118.3, 116.0, 65.7, 42.0, 40.6, 32.8. ESI-MS: *m/z* (%) 434 (100) [M + H$^+$].

[5-(4-Chlorophenoxy)-1,4,5,6-tetrahydropyrimidin-2-yl](morpholin-4-ylpropyl)ammonium Trifluoroacetate (19s). Following the method described for **19i** gave **19s** as a yellow oil. Yield 93%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 9.0 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 4.67 (m_c, 1H), 3.72 (br s, 1H), 3.59 (br s, 4H), 3.57−3.46 (m, 4H), 3.22 (t, J = 6.8 Hz, 2H), 2.43 (t, J = 6.0 Hz, 2H), 2.38 (br s, 4H), 1.74 (m_c, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 154.5, 129.9, 127.2, 117.1, 66.7, 65.8, 53.0, 52.6, 42.1, 37.6, 25.7. ESI-MS: *m/z* (%) 353 (100) [M + H$^+$].

[5-(4-Chlorophenoxy)-3,4,5,6-tetrahydropyrimidin-2-yl](3-phenothiazin-10-ylpropyl)ammonium Trifluoroacetate (19t). Following the method described for **19i** gave **19t** as a yellow oil. Yield 80%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (t, J = 6.3 Hz), 7.28−7.21 (m, 6H), 7.02−6.87 (m, 4H), 6.69 (d, J = 9.0 Hz, 2H), 4.29 (m_c, 1H), 3.99 (t, J = 5.7 Hz, 2H), 3.19 (dt, J = 6.3, 5.5 Hz, 2H), 2.14 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 153.1, 145.2, 129.8, 128.2, 128.0, 127.5, 125.9, 123.7, 117.6, 116.6, 65.5, 42.2, 41.8, 36.7, 26.0. ESI-MS: *m*/*z* (%) 465 (100) [M + H$^+$].

7-(4-Chlorophenoxy)-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidinium Trifluoroacetate (20). Following the method described for **19i** gave **20** as a yellow oil. Yield 71%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (br s, 2H), 7.28 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 4.69 (m_c, 1H), 3.63−3.25 (m, 10H), 2.10−2.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 151.2, 129.9, 127.8, 117.8, 66.4, 50.3, 47.2, 41.2, 37.9, 20.7. ESI-MS: *m*/*z* (%) 266 (100) [M + H$^+$].

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **19a**−**t** and **20** and a listing of the binding energies of **7b**, **16b**, and unprotonated **17a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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