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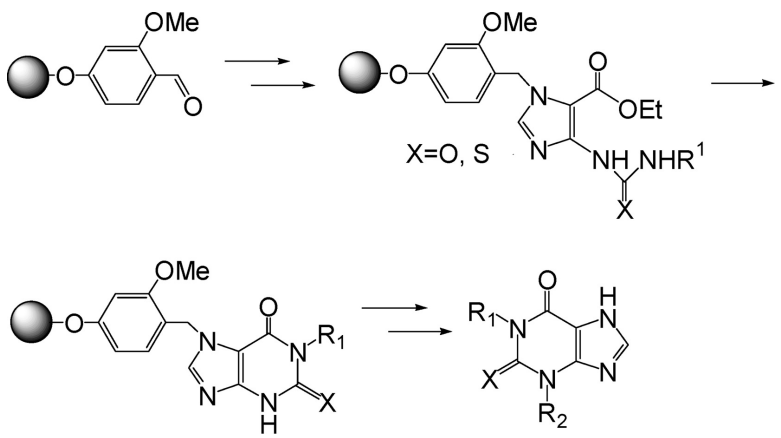

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A Highly Efficient Solid-Phase Synthesis of 1,3-Substituted Xanthines

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A first solid-phase route to 1,3-substituted xanthines has been developed using PS-MB-CHO resin. Cyclocondensation of the polymer-bound aminoimidazole with isocyanates followed by alkylation provided 1,3-substituted xanthines in high yields. Libraries of 12 xanthines and 4 thioxanthines were prepared.

Introduction

1,3-Substituted xanthines constitute an important class of pharmacologically active compounds with well-established activities as stimulants, phosphodiesterase inhibitors, CFTR chloride channel activators, and adenosine receptor antagonists.[1] In recent years, the spectrum of clinical applications of these xanthines has continued to widen and presently includes their use as anticonvulsants,[2] nootropics,[3] and therapeutics for the treatment of bronchial asthma and vascular diseases.[4] Accordingly, methodologies for the preparation of 1,3-substituted xanthines have attracted much attention, and various solution-phase syntheses of these compounds have been reported.[5] Generally, these syntheses involve multistep reactions and require tedious chromatographic separations which would limit the synthesis of a large number of compounds. A solid-phase approach to the synthesis of small organic molecule libraries[6] would offer a good pathway to a large number of these analogues; however, to our knowledge, only the derivatization of a xanthine scaffold has thus far been reported.[7] As part of a continuing effort toward solid-phase synthesis (SPS) protocols for generation of purine libraries, we present here the results of a new and efficient synthetic procedure for obtaining 1,3-substituted xanthines in good yields and high purity (Scheme 1). We reasoned that it would be more attractive to approach the synthesis via the cyclocondensation of 4-amino-5-alkoxycarbonylimidazole because this would allow the N1 and N3 substituents to be introduced later in the synthesis, thus avoiding the need to repeat almost the entire synthesis for each combination of N1 and N3 substituents. To facilitate the SPS of 4-amino-5-alkoxycarbonylimidazole, we required ready access to multigram quantities of CHO resin. Among the CHO functionalized resins available, the ArgoGel-MB-CHO or ArgoPore-MB-CHO resins are commonly used for solid-phase reactions due to their good swelling property in most organic solvents.[8] However, these resins are highly expensive, which limits their potential use on a large scale. The PS-MB-CHO resin **1** is a less expensive resin, but it has rarely been used in SPS due to its poor swelling in some solvents. We thought that by circumventing this problem, a wider applicability could be achieved for **1**.

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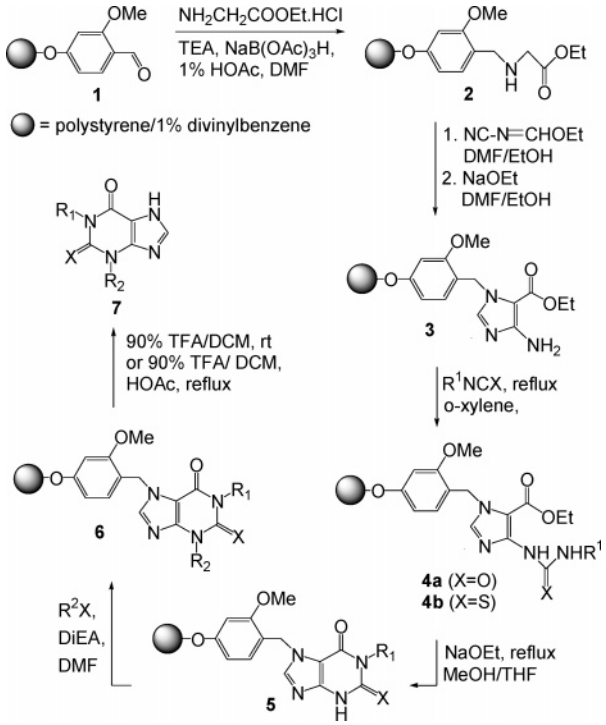
Scheme 1. SPS of 1,3-Substituted Xanthines



Results and Discussion

Solution-Phase Synthesis of 1,3-Substituted Xanthines. Prior to SPS, preliminary solution-phase studies (Scheme 2) were carried out to survey the requisite reaction conditions and establish the optimizations required for SPS. To begin our investigation, we had to prepare *N*-(2,4-dimethoxybenzyl)glycine ethyl ester **8** by reductively alkylating 2,4-dimethoxybenzaldehyde (a mimic of the PS-MB-CHO resin) with glycine ethyl ester. Attempts to carry out the reaction with $NaBH_4$/EtOH,[9a] $NaB(OAc)_3H$/NaOAc/MeOH,[9b] or $NaB(OAc)_3H$/DMF gave yields of 20−68%, which were not optimal for SPS. Further experimentation eventually provided $NaB(OAc)_3H$/1% HOAc/DMF, which gave **8** in 95% yield. Subsequently, **8** was treated with ethoxymethyl cyanamide using a slightly modified form of the procedure described by Asberom et al.,[10] to give the intermediate **9**, which was cyclized with NaOEt in a one-pot reaction to give ethyl-4-amino-1-(2,4-dimethoxybenzyl)imidazole-5-carboxylate **10** in 70% overall yield. Treatment of **10** with phenyl isocyanate

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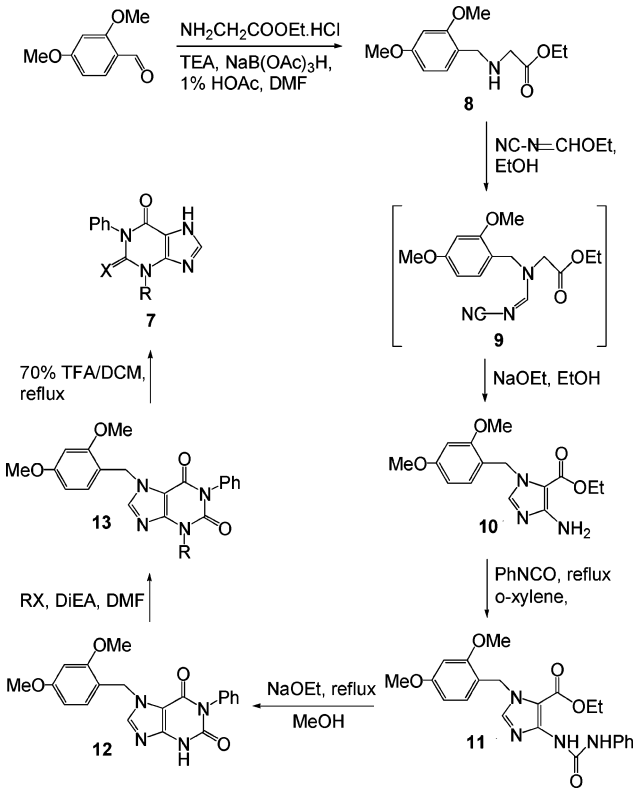
Scheme 2. Solution-Phase Study



in *o*-xylene (120 °C, 8 h) provided **11** in 90% yield and traces of unreacted **10**. Prolonged heating or the addition of a base as a catalyst[11] did not further improve the yield. Subsequent ring closure of **11** with NaOEt/MeOH afforded 1-substituted xanthine **12** in quantitative yield.

To obtain 1,3-substituted xanthines, **12** was treated with various alkyl halides in DMF under basic conditions. The reaction proceeded readily at room temperature to provide **13** in good yields (92−96%). Removal of the 2,4-dimethoxybenzyl moiety was achieved by refluxing **13** in 70% TFA/DCM.

Solid-Phase Synthesis of 1,3-Substituted Xanthines. With the solution-phase pathway established, we proceeded to prove the versatility of this methodology for SPS. Resin **1** was converted to **2** by reductive amination in DMF. The formation of **2** was amenable to KBr FTIR monitoring (i.e., disappearance of the CH stretch of aldehyde at 2763 cm^{-1} and the shift of the C═O stretch at 1681 cm^{-1} to 1737 cm^{-1}, indicating the presence of an ester). Due to the poor swelling ability of polystyrene/1% divinylbenzene in EtOH, treatment of **2** with ethoxymethyl cyanamide was carried out in a DMF/EtOH (v/v 1:2) mixture. This was followed by the addition of NaOEt/EtOH to afford the polymer-supported 4-amino-5-ethoxycarbonylimidazole **3**. Treatment of **3** with various isocyanates in *o*-xylene (120 °C, 24 h) provided **4a**, which was cyclized using NaOEt in MeOH/THF (v/v 1:4) to give **5**. The N1-substituted xanthines could be released from the solid support with 90% TFA/CH_2Cl_2 at room temperature, or it could be treated with alkyl halides in DIEA/DMF to afford **6**. To illustrate the versatility of this chemistry, a library of 12 compounds (**7a**−**7l**) was prepared (Figure 1). The overall yields obtained were 35−64% (purities of >95%

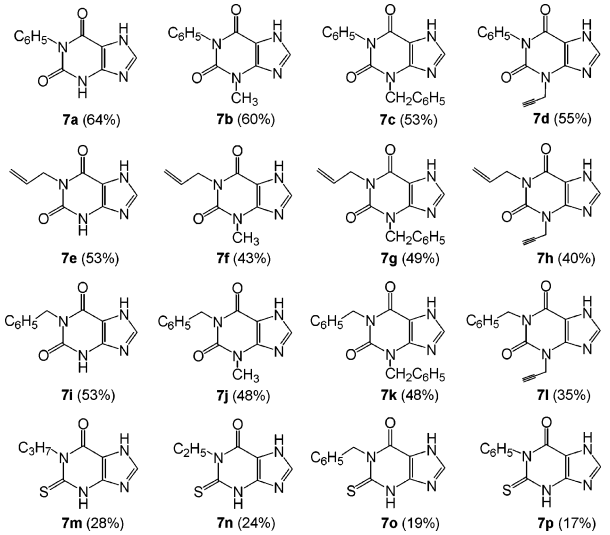


Figure 1. Library of **7**.

by NMR), indicating an average yield of 86−93% for each step of the SPS.

We have also examined the application of this methodology for the synthesis of thioxanthines. Due to the lower reactivity of isothiocyanates, formation of **4b** was carried out at 140 °C, and by iterating this procedure 3 times, the yield was increased more than 4-fold. Cleavage of **5** from the support with 90% TFA/CH_2Cl_2 at room temperature liberated products which did not correspond to the desired substituted thioxanthines **7m**−**7p**, and treatment with refluxing glacial acetic acid gave a mixture of **7** and byproducts. Hence, to simplify the purification of **7**, a two-step cleavage procedure was used: the resin was first treated with 90% TFA/CH_2Cl_2 at room temperature to detach the byproducts before liberating the thioxanthines with refluxing glacial acetic acid.

In summary, an efficient and scaleable synthetic procedure affording 1,3-substituted xanthines in good overall yields has been developed. Further studies are currently in progress to extend this methodology to other purine systems.

Experimental Section

General Procedures. All chemical reagents were obtained from either Aldrich, Merck, Lancaster, or Fluka and used without further purification. The solid-phase room reactions were agitated on a flask shaker SF1 (Stuart Scientific). Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. Flash column chromatography was performed with silica (Merck, 70−230 mesh). CC refers to flash column chromatography.

^{1}H NMR and ^{13}CNMR spectra were measured at 298K on a Bruker DPX 300 Fourier transform spectrometer. Chemical shifts were reported in δ (parts per million), relative to the internal standard of tetramethylsilane (TMS). The signals observed are described as: s (singlet), d (doublet), t (triplet), m (multiplet). The number of protons (*n*) for a given resonance is indicated as *n*H. All infrared (IR) spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra

were performed on VG Micromass 7035 spectrometer under electron impact (EI).

Synthesis of *N*-(2,4-Dimethoxybenzyl)glycine Ethyl Ester (8). To 4-dimethoxylbenzaldehyde (0.166 g, 1 mmol) in DMF (5 mL) was added glycine ethyl ester hydrochloride (0.2790 g, 2 mmol) and triethylamine (0.2780 mL, 2 mmol). The mixture was stirred for 5 min, and sodium triacetoxyborohydride (0.4240 g, 2 mmol) and HOAc (0.10 mL) were added. After that, the reaction mixture was stirred at room temperature for another 24 h. The reaction was quenched with saturated $NaHCO_3$ and concentrated. The residue obtained was diluted with water (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layer was dried with $MgSO_4$, filtered, concentrated, and purified by CC (EtOAc/hexane = 4:1, then MeOH/CH_2Cl_2 = 1:7) to give **8** as a colorless liquid (0.2400 g, 95%). ^{1}H NMR ($CDCl_3$): δ 7.12−7.09 (d, J = 7.7 Hz, *ArH*, 1H), 6.44−6.39 (m, *ArH*, 2H), 4.18−4.10 (q, J = 7.1 Hz, CH_3*CH_2*, 2H), 3.80 (s, ArO*CH_3*, 3H), 3.78 (s, ArO*CH_3*, 3H), 3.73 (s, Ar*CH_2*, 2H), 3.35 (s, NH*CH_2*CO, 2H), 2.10 (s, *NH*, 1H), 1.27−1.22 (t, J = 7.1 Hz, *CH_3*CH_2, 3H). ^{13}C NMR ($CDCl_3$): δ 172.2, 160.0, 158.4, 130.3, 119.8, 103.5, 98.2, 60.3, 55.0, 49.8, 47.8, 13.9. Exact mass calcd for $C_{13}H_{19}NO_4$: *m/z* 253.1314; found 253.1304.

Synthesis of 5-Amino-3-(2,4-dimethoxybenzyl)-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (10). Compound **8** (0.1226 g, 0.484 mmol) was dissolved in EtOH (5 mL), and the solution was cooled in a dry ice−acetone bath. Ethoxymethyl cyanamide (0.0520 g, 0.532 mmol) in EtOH (5 mL) was added dropwise, after which the dry ice−acetone bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was subsequently cooled in a dry ice−acetone bath, and NaOEt (21% (w/w) in denatured EtOH, 0.18 mL, 0.484 mmol) was then added. The reaction mixture was stirred at room temperature for another 20 h, after which the mixture was concentrated and purified by CC (EtOAc/CH_2Cl_2 = 2:1) to give **10** as a colorless solid (0.1030 g, 70%). ^{1}H NMR ($CDCl_3$): δ 7.18 (s, *CH*, 1H), 7.09−7.06 (d, J = 8.0 Hz, *ArH*, 1H), 6.45−6.40 (m, *ArH*, 2H), 5.25 (s, Ar*CH_2*, 2H), 4.83 (s, *NH_2*, 2H), 4.32−4.25 (q, J = 7.2 Hz, CH_3*CH_2*, 2H), 3.81 (s, ArO*CH_3*, 3H), 3.79 (s, ArO*CH_3*, 3H), 1.34−1.29 (t, J = 7.1 Hz, *CH_3*-CH_2, 3H). ^{13}C NMR ($CDCl_3$): δ 161.1, 161.0, 158.2, 155.4, 139.5, 130.3, 117.1, 104.2, 102.0, 98.4, 59.5, 55.3, 55.3, 45.5, 14.4. Exact mass calcd for $C_{15}H_{19}N_3O_4$: *m/z* 305.1376; found 305.1377.

Synthesis of 3-(2,4-Dimethoxybenzyl)-5-(3-phenylureido)-3*H*-imidazole-4-carboxylic Acid Ethyl Ester (11). To **10** (0.1000 g, 0.328 mmol) was added *o*-xylene (6 mL) and phenyl isocyanate (0.12 mL, 0.984 mmol), and the mixture was heated at 120 °C for 8 h, after which the mixture was concentrated and purified by CC (EtOAc/hexane = 1:3) to give **11** as a colorless oil (0.1253 g, 90%). ^{1}H NMR ($CDCl_3$): δ 11.06 (s, Ar*NH*CO, 1H), 8.08 (s, *NH*, 1H), 7.58−7.55 (*CH* and *ArH*, 2H), 7.33−7.26 (m, *ArH*, 3H), 7.14−7.12 (d, J = 8.0 Hz, *ArH*, 1H), 7.05−7.00 (t, J = 7.0 Hz, *ArH*, 1H), 6.46−6.42 (m, *ArH*, 2H), 5.32 (s, Ar*CH_2*, 2H), 4.40−4.33 (q, J = 7.1 Hz, CH_3*CH_2*, 2H), 3.80 (s, ArO*CH_3*, 3H), 3.78 (s, ArO*CH_3*, 3H), 1.39−1.34 (t, J = 7.0 Hz, *CH_3*-CH_2, 3H). ^{13}C NMR ($CDCl_3$): δ 161.3, 159.9, 158.3, 151.8, 147.2, 138.6, 137.7, 130.8, 128.7, 122.9, 119.7, 115.7, 104.3, 103.8, 98.5, 60.5, 55.2, 45.9, 14.3. Exact mass calcd for $C_{22}H_{24}N_4O_5$: *m/z* 424.1747; found 424.1739.

Synthesis of 1-Phenyl-7-(2,4-dimethoxybenzyl)xanthine (12). To **11** (0.1920 g, 0.450 mmol) in MeOH (6 mL) was added NaOEt (21% (w/w) in denatured EtOH, 0.5 mL, 1.360 mmol). The mixture was refluxed for 2 h, after which the mixture was concentrated, and the resulting residue was diluted with water (10 mL) and acidified with 1.5 M HCl. The white precipitate which formed was filtered, washed with water, and dried to give **12** as a white power (0.1702 g, 100%). ^{1}H NMR (DMSO-d_6): δ 11.96 (s, *NH*, 1H), 7.95 (s, *CH*, 1H), 7.48−7.36 (m, *ArH*, 3H), 7.24−7.22 (d, J = 7.0 Hz, *ArH*, 2H), 7.14−7.12 (d, J = 8.3 Hz, *ArH*, 1H), 6.57−6.45 (m, *ArH*, 2H), 5.28 (s, Ar*CH_2*, 2H), 3.81 (s, ArO*CH_3*, 3H), 3.73 (s, ArO*CH_3*, 3H). ^{13}C NMR (DMSO-d_6): δ 160.7, 158.1, 155.0, 150.9, 148.0, 143.1, 135.8, 130.3, 129.3, 128.6, 127.8, 116.4, 106.1, 104.6, 98.4, 55.4, 55.2, 44.3, 40.3. Exact mass calcd for $C_{20}H_{18}N_4O_4$: *m/z* 378.1328; found 378.1339.

Synthesis of 1-Phenyl-3-methyl-7-(2,4-dimethoxybenzyl)xanthine (13, R=CH_3). To a mixture of **12** (0.0200 g, 0.0529 mmol) in DMF (3 mL) and DIEA (0.19 mL, 1.060 mmol) was added iodomethane (0.033 mL, 0.529 mmol) dropwise. The reaction mixture was stirred for 1 h at room temperature and then concentrated. The resulting residue was purified by CC (MeOH/CH_2Cl_2 = 1:7) to give **13** as a white solid (0.0199 g, 96%). ^{1}H NMR ($CDCl_3$): δ 7.71 (s, *CH*, 1H), 7.54−7.41 (m, *ArH*, 4H), 7.27−7.24 (m, *ArH*, 2H), 6.45−6.41 (m, *ArH*, 2H), 5.40 (s, Ar*CH_2*, 2H), 3.85 (s, ArO*CH_3*, 3H), 3.79 (s, ArO*CH_3*, 3H), 3.58 (s, *CH_3*, 3H). ^{13}C NMR ($CDCl_3$): δ 161.7, 158.6, 155.2, 151.7, 149.3, 142.1, 135.7, 132.3, 129.3, 128.8, 128.6, 116.0, 107.1, 104.4, 98.6, 55.4, 45.2, 29.7. Exact mass calcd for $C_{21}H_{20}N_4O_4$: *m/z* 392.1485; found 392.1482.

Synthesis of 1-Phenyl-3-methylxanthine (7b). A mixture of **13** (0.1000 g, 0.255 mmol), TFA (7 mL), and CH_2Cl_2 (3 mL) was refluxed for 6 h. The mixture was concentrated and purified by CC (MeOH/CH_2Cl_2 = 1:10) to give **7b** as a white solid (0.0555 g, 90%). ^{1}H NMR ($CDCl_3$): δ 12.41 (s, *N7H*, 1H), 7.52−7.42 (m, *ArH* and *CH*, 4H), 7.26−7.24 (d, J = 7.3 Hz, *ArH*, 2H), 3.64 (s, *CH_3*, 3H). ^{13}C NMR ($CDCl_3$): δ 155.8, 151.6, 149.4, 140.6, 135.5, 129.4, 128.8, 128.7, 107.1, 30.3. Exact mass calcd for $C_{12}H_{10}N_4O_2$: *m/z* 242.0804; found 242.0802.

Preparation of *N*-(2-methoxy-4-phenoxybenzyl) Glycine Ethyl Ester Resin (2). PS-MB-CHO resin **1** (3.000 g, 4.02 mmol) was placed in a dry 100-mL round-bottom flask, Glycine ethyl ester hydrochlodride (1.6830 g, 12.06 mmol), DMF (30 mL), and Et_3N (1.68 mL, 12.06 mmol) were added, and the mixture was shaken at room temperature for 30 min, after which sodium triacetoxyborohydride (2.5560 g, 12.06 mmol) and HOAc (0.3 mL) were added, and the reaction mixture was shaken at room temperature for another 24 h. The reaction was quenched with saturated $NaHCO_3$; filtered; and washed with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and Et_2O (20 mL × 2). The resin was then dried overnight in a vacuum oven at 50 °C.

Preparation of Ethyl 4-amino-1-(2-methoxy-4-phenoxybenzyl)-imidazole-5-carboxylate Resin (3). A stirring suspension of **2** (3.325 g, 4.02 mmol) in DMF (52.8 mL) and EtOH (80 mL) was cooled in a dry ice- actone bath. A solution of ethoxymethyl cyanamide (0.7880 g, 8.04 mmol) in anhydrous EtOH (25 mL) was added dropwise, and the mixture was shaken at room temperature for 24 h, after which the reaction mixture was cooled in a dry ice−acetone bath again, and NaOEt (21% (w/w) in denatured EtOH, 3 mL, 8.04 mmol) was added dropwise. The mixture was shaken at room temperature for another 24 h. The resin was filtered; washed with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and Et_2O (20 mL × 2); and dried overnight at 50 °C in a vacuum oven.

General Procedure for the Preparation of Ethyl 4-(3-Substituted) Ureido-1-(2-methoxy-4-phenoxybenzyl)imidazole-5-carboxylate Resin (4). Resin **3** (0.3000 g, 0.3386 mmol), alkyl isocyanates (5 equiv), and *o*-xylene (6 mL) were heated at 120 °C for 24 h. The resin was then filtered; washed with EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and Et_2O (20 mL × 2); and dried overnight at 50 °C in a vacuum oven.

General Procedure for the Preparation of 1-Substituted 7-(2-Methoxy-4-phenoxybenzyl)xanthine Resin (5). Resin **4** (0.3300 g, 0.3386 mmol), NaOEt (21% (w/w) in denatured EtOH, 0.8 mL, 5 equiv), anhydrous THF (5 mL), and anhydrous MeOH (15 mL) were heated under refluxing for 12 h. The resin was then filtered; acidified with 1.5 M HCl; washed with H_2O (20 mL × 2), EtOH (20 mL × 2), and CH_2Cl_2 (20 mL × 2); and dried overnight at 50 °C in a vacuum oven.

General Procedure for the Preparation of 1,3-Substituted 7-(2-Methoxy-4-phenoxybenzyl)xanthine Resin (6). Resin **5** (0.3300 g, 0.3386 mmol) was swelled in DMF (6 mL). DIEA (1.2 mL, 20 equiv) and the respective halide (10 equiv) were added, and the mixture was shaken at room temperature for 24 h, after which the resin was filtered; washed with DMF (20 mL × 2), H_2O (20 mL × 2), EtOH (20 mL × 2), CH_2Cl_2 (20 mL × 2), and Et_2O (20 mL × 2); and dried overnight in a vacuum oven at 50 °C.

General Procedure for the Preparation of 1,3-Substituted Xanthine (7a−7l). A mixture of resin **6** (0.3400 g, 0.3386 mmol), TFA (9 mL), and CH_2Cl_2 (1 mL) was shaken at room temperature for 12 h. The resin was then filtered and washed with MeOH (20 mL × 2) and CH_2Cl_2 (20 mL × 2). The combined filtrate was concentrated, and the residue was purified by CC (EtOAc/CH_2Cl_2 = 1.5:1) to give xanthine **7**.

General Procedure for the Preparation of 1-Substituted Thioxanthine (7m−7p). A mixture of resin **6** (0.3600 g, 0.3386 mmol), TFA (9 mL), and CH_2Cl_2 (1 mL) was shaken at room temperature for 12 h, after which the resin was filtered and washed with MeOH (20 mL × 2) and CH_2Cl_2 (20 mL × 2). The resulting resin was then refluxed with HOAc (8 mL 140 mmol) for 24 h, after which the resin was filtered and washed with MeOH (20 mL × 2) and CH_2Cl_2 (20 mL × 2). The combined filtrate was concentrated, dried, and washed with cold EtOAc to give thioxanthine **7**.

1-Phenylxanthine (7a). ^{1}H NMR (DMSO-d_6): δ 13.48 (s, *N3H*, 1H), 11.95 (s, *N7H*, 1H), 8.01 (s, *CH*, 1H), 7.48−7.37 (m, *ArH*, 3H), 7.27−7.24 (d, J = 7.3 Hz, *ArH*, 2H). ^{13}C NMR (DMSO-d_6): δ 155.1, 151.1, 147.7, 140.9, 136.2, 129.3, 128.7, 127.8, 106.5. Exact mass calcd for $C_{11}H_8N_4O_2$: *m/z* 228.0647; found 228.0644.

1-Phenyl-3-benzylxanthine (7c). ^{1}H NMR ($CDCl_3$): δ 12.29 (s, *N7H*, 1H), 7.57−7.39 (m, *CH* and *ArH*, 6H), 7.33−7.22 (m, *ArH*, 5H), 5.31 (s, ArCH_2, 2H). ^{13}C NMR ($CDCl_3$): δ 155.9, 151.3, 149.2, 140.5, 136.1, 135.4, 129.4, 129.0, 128.8, 128.7, 128.5, 128.0, 107.2, 47.2. Exact mass calcd for $C_{18}H_{14}N_4O_2$: *m/z* 318.1117; found 318.1111.

1-Phenyl-3-propargylxanthine (7d). ^{1}H NMR (CD_3-OD): δ 8.00 (s, *CH*, 1H), 7.53−7.42 (m, *ArH*, 3H), 7.29−7.26 (d, J = 7.0 Hz, *ArH*, 2H), 4.89−4.88 (d, J = 2.4 Hz, N3CH_2, 2H), 2.71−2.69 (t, J = 2.3 Hz, CH_2C*CH*, 1H). ^{13}C NMR (CD_3OD): δ 156.3, 152.6, 149.0, 142.0, 137.1, 130.3, 130.1, 129.7, 108.9, 78.6, 73.3, 33.9. Exact mass calcd for $C_{14}H_{10}N_4O_2$: *m/z* 266.0804; found 266.0805.

1-Allylxanthine (7e). ^{1}H NMR (CD_3OD): δ 7.88 (s, *CH*, 1H), 5.98−5.85 (m, CH_2*CH*CH_2, 1H), 5.20−5.11 (m, CH_2-CHCH_2, 2H), 4.58−4.55 (m, N1CH_2, 2H); ^{13}C NMR (CD_3-OD): δ 156.97, 153.2, 148.4, 141.7, 133.7, 117.2, 108.6, 43.6. Exact mass calcd for $C_8H_8N_4O_2$: *m/z* 192.0647; found 192.0648.

1-Allyl-3-methylxanthine (7f). ^{1}H NMR ($CDCl_3$): δ 13.02 (s, *NH*, 1H), 7.82 (s, *CH*, 1H), 6.00−5.87 (m, CH_2*CH*CH_2, 1H), 5.29−5.18 (m, CH_2CHCH_2, 2H), 4.71−4.69 (d, J = 5.6 Hz, N1CH_2, 2H), 3.65 (s, CH_3, 3H). ^{13}C NMR ($CDCl_3$): δ 155.9, 151.0, 149.2, 140.4, 132.0, 117.7, 106.9, 43.8, 30.2. Exact mass calcd for $C_9H_{10}N_4O_2$: *m/z* 206.0804; found 206.0808.

1-Allyl-3-benzylxanthine (7g). ^{1}H NMR ($CDCl_3$): δ 7.93 (s, *CH*, 1H), 7.40−7.24 (m, *ArH*, 5H), 5.97−5.84 (m, CH_2*CH*CH_2, 1H), 5.29 (s, ArCH_2, 2H), ∼5.17 to 5.11 (m, CH_2, 2H), 4.61−4.59 (d, J = 5.2 Hz, N1CH_2, 2H). ^{13}C NMR ($CDCl_3$): δ 155.7, 150.9, 148.8, 140.1, 136.3, 132.1, 128.7, 128.6, 127.9, 117.9, 107.0, 47.1, 43.8. Exact mass calcd for $C_{15}H_{14}N_4O_2$: *m/z* 282.1117; found 282.1118.

1-Allyl-3-propargylxanthine (7h). ^{1}H NMR ($CDCl_3$): δ 12.75 (s, *NH*, 1H), 7.87 (s, *CH*, 1H), 6.01−5.88 (m, CH_2*CH*CH_2, 1H), 5.32−5.20 (m, CH_2CHCH_2, 2H), 4.95−4.95 (d, J = 2.5 Hz, N3CH_2, 2H), 4.72−4.70 (d, J = 5.9 Hz, N1CH_2, 2H), 2.29−2.27 (t, J = 2.5 Hz, CH_2C*CH*, 1H). ^{13}C NMR ($CDCl_3$): δ 155.7, 150.2, 147.9, 140.5, 131.8, 118.0, 116.2, 107.1, 72.1, 43.9, 33.0. Exact mass calcd for $C_{11}H_{10}N_4O_2$: *m/z* 230.0804; found 230.0802.

1-Benzylxanthine (7i). ^{1}H NMR (DMSO-d_6): δ 13.43 (s, *N3H*, 1H), 11.93 (s, *N7H*, 1H), 7.99 (s, *CH*, 1H), 7.29−7.22 (m, *ArH*, 5H), 5.03 (s, ArCH_2, 2H). ^{13}C NMR (DMSO-d_6): δ 154.9, 151.0, 147.3, 141.0, 137.8, 128.2, 127.2, 126.8, 106.1, 42.9. Exact mass calcd for $C_{12}H_{10}N_4O_2$: *m/z* 242.0804; found 242.0795.

1-Benzyl-3-methylxanthine (7j). ^{1}H NMR ($CDCl_3$): δ 7.70 (s, *CH*, 1H), 7.47−7.45 (d, J = 6.6 Hz, *ArH*, 2H), 7.32−7.25 (m, *ArH*, 3H), 5.27 (s, ArCH_2, 2H), 3.64 (s, CH_3, 3H). ^{13}C NMR ($CDCl_3$): δ 156.1, 151.3, 149.1, 140.4, 137.0, 128.5, 128.4, 127.6, 106.9, 45.0, 30.3. Exact mass calcd for $C_{13}H_{12}N_4O_2$: *m/z* 256.0960; found 256.0961.

1-Benzyl-3-benzylxanthine (7k). ^{1}H NMR ($CDCl_3$): δ 12.78 (s, *NH*, 1H), 7.65 (s, *CH*, 1H), 7.49−7.43 (m, *ArH*, 4H), 7.31−7.25 (m, *ArH*, 6 H), 5.32 (s, N1CH_2, 2H), 5.27 (s, N3CH_2, 2H). ^{13}C NMR ($CDCl_3$): δ 156.2, 151.2, 148.9, 140.4, 137.0, 136.2, 128.5, 128.5, 128.4, 127.9, 127.6, 107.0, 47.1, 45.1. Exact mass calcd for $C_{19}H_{16}N_4O_2$: *m*/*z* 332.1273; found 332.1276.

1-Benzyl-3-propargylxanthine (7l). ^{1}H NMR ($CDCl_3$): δ 12.71 (s, *NH*, 1H), 7.75 (s, *CH*, 1H), 7.48−7.46 (d, J = 6.6 Hz, *ArH*, 2H), 7.34−7.24 (m, *ArH*, 3H), 5.28 (s, Ar*CH2*, 2H), 4.94−4.93 (d, J = 2.4 Hz, N3*CH2*, 2H), 2.28−2.27 (t, J = 2.4 Hz, CH2C*CH*, 1H). ^{13}C NMR ($CDCl_3$): δ 156.1, 150.6, 148.0, 140.5, 136.8, 128.7, 128.5, 127.8, 107.1, 77.4, 72.1, 45.2, 33.1. Exact mass calcd for $C_{15}H_{12}N_4O_2$: *m*/*z* 280.0960; found 280.0958.

1-Propyl-2-thioxanthine (7m). ^{1}H NMR (DMSO-d_6): δ 13.65 (s, *N3H*, 1H), 13.49 (s, *N7H*, 1H), 8.09 (s, *CH*, 1H), 4.36−4.31 (t, J = 7.7 Hz, N1CH_2, 2H), 1.71−1.63 (m, $CH_3CH_2CH_2$, 2H), 0.91−0.87 (t, J = 7.3 Hz, CH_3, 3H). ^{13}C NMR (DMSO-d_6): δ 173.9, 153.4, 147.2, 142.0, 109.8, 47.1, 19.7, 11.1; Exact mass calcd for $C_8H_{10}N_4OS$: *m*/*z* 210.0575; found 210.0570.

1-Ethyl-3-hydro-2-thioxanthine (7n). ^{1}H NMR (DMSO-d_6): δ 13.67 (s, *N3H*, 1H), 13.51 (s, *N7H*, 1H), 8.11 (s, *CH*, 1H), 4.48−4.42 (q, J = 6.9 Hz, CH_3CH_2, 2H), 1.22−1.18 (t, J = 6.9 Hz, CH_3CH_2, 3H). ^{13}C NMR (DMSO-d_6): δ 173.6, 153.1, 147.2, 142.0, 109.0, 41.0, 12.0. Exact mass calcd for $C_7H_8N_4OS$: *m*/*z* 196.0419; found 196.0412.

1-Benzyl-3-hydro-2-thioxanthine (7o). ^{1}H NMR (DMSO-d_6): δ 13.66 (s, *N3H*, 2H), 8.14 (s, *CH*, 1H), 7.31−7.21 (m, *ArH*, 5H), 5.66 (s, ArCH_2, 2H). ^{13}C NMR (DMSO-d_6): δ 174.5, 153.4, 147.3, 142.2, 136.8, 128.1, 126.9, 126.7, 109.9, 48.6.. Exact mass calcd for $C_{12}H_{10}N_4OS$: *m*/*z* 258.0575; found 258.0576.

1-Phenyl-2-thioxanthine (7p). ^{1}H NMR (DMSO-d_6): δ 14.15 (s, *N3H*, 1H), 8.66 (s, *CH*, 1H), 8.00−7.89 (m, *ArH*, 3H), 7.73−7.71 (d, J = 7.3 Hz, *ArH*, 2H). ^{13}C NMR (DMSO-d_6): δ 174.8, 153.3, 147.2, 141.4, 139.2, 128.7, 128.3, 127.3, 110.3. Exact mass calcd for $C_{11}H_8N_4OS$: *m*/*z* 244.0419; found 244.0409.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra of all compounds and IR spectra of resin **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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