2-Substituted-4,5-Dihydroxypyrimidine-6-Carboxamide Antiviral Targeted Libraries

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To identify novel *potentially* broad spectrum antiviral compounds against RNA viruses, we have developed the parallel synthesis of a structurally interesting class of 2-substituted-4,5-dihydroxypyrimidine-6-carboxamides. Variously 2-substituted-4,5-dihydroxypyrimidine-6-carboxylate methyl esters were initially prepared and were then diversified via a facile amidation reaction. This strategy affords libraries of thousands of diverse drug-like compounds for screening. Biological evaluation of a set of these compounds, via a small initial screen, identified antiviral compounds against a representative RNA virus (Sendai virus, a paramyxovirus). We provide details on the synthetic protocols and the in vitro antiviral activity studies, as part of our initial investigation of the resulting targeted libraries.

Introduction

There is an ongoing need to identify and characterize new molecular targets for antiviral therapy. This interest has led to an upsurge in interest in developing new treatments for pathogenic viruses including negative-strand RNA viruses (such as paramyxoviruses, orthomyxoviruses, and other virus families).[1−3] These viral families all require a viral RNA dependent RNA polymerase (RdRp) protein for replication.[2,4] To target the RdRp proteins of diverse RNA viruses, we aimed to prepare RdRp-targeted libraries as part of our program to discover new lead compounds for several members of these pathogenic viral families. In our initial studies, we chose to investigate the potential for such libraries to demonstrate in vitro activity against Sendai virus, the murine counterpart of human parainfluenza virus 1 (a respiratory paramyxovirus). The human parainfluenza viruses (HPIV1−4) are collectively the second leading viral cause of acute respiratory infection (ARI) in young children, with an estimated hospitalization rate of 7% in the United States.[5] HPIV infection is also a significant cause of morbidity with up to 35% mortality in cancer patients whom are immunocompromised as a result of their underlying disease or anticancer treatment.[6] Because there are currently no licensed HPIV-specific vaccines or drugs, there is an urgent need to develop antiviral drugs against these ubiquitous pathogens.

Some other important human pathogens from the paramyxovirus family include the human respiratory syncytial virus (HRSV), measles virus, mumps virus, and the newly emerging, highly pathogenic Nipah and Hendra viruses. The paramyxoviruses also include numerous animal pathogens that have proven useful in studying mechanisms of infectious disease and its prevention in animal models, including Newcastle disease virus (NDV), canine distemper virus (CDV), and Sendai virus (SeV), which is the murine counterpart of HPIV1. During paramyxovirus infection, both viral-gene transcription and viral-RNA replication are catalyzed in the cytoplasm by a viral RdRp complex formed by the L and P proteins.[7] The domain responsible for polymerase activity resides within the highly conserved L protein.[8] The parainfluenza virus RdRp constitutes an attractive target for the development of virus-specific small molecule inhibitors since it is essential for viral protein expression and viral genome replication. It is also highly conserved, and has no known human homologue. Moreover, the recent discovery of a non-nucleoside inhibitor of the measles virus RdRp by high-throughput screening in a cell-based assay helps validate RdRp as an attractive drug target.[9]

Our interest in the identification of drug-like inhibitor templates that might exhibit broad spectrum RdRp antiviral activity led us to investigate 2-substituted-4,5-dihydroxypyrimidine derivatives, which have been proposed as a class of compounds that interact with several proteins involved in the modification of nucleic acids.[10,11] Members of this interesting class of compounds have been shown to be versatile inhibitor agents for both HIV integrase and HCV RdRp targets. Summa and co-workers investigated the structure−activity profile of some of these compounds, particularly with a free 6-carboxylic moiety, and found that HCV NS5b RdRp was significantly inhibited by several compounds in this class.[10] It was proposed that the keto-acid moiety coordinates to an active-site metal and thereby inhibits the enzymatic activity of HCV RdRp, or when properly substituted, HIV integrase.[11,12] Though HCV polymerase inhibitors containing this substructure have not reached advanced stages of drug development, the same group of researchers eventually developed this class of

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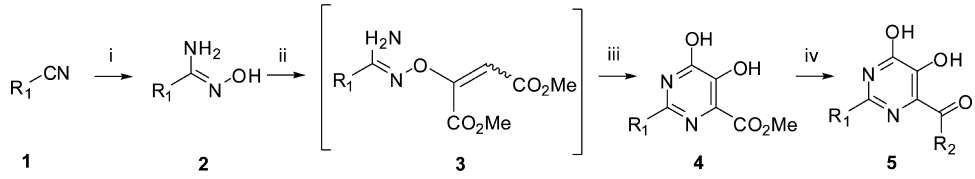
Scheme 1. Library Preparation of 2-Substituted 4,5-Pyrimidine-6-carboxyamide[a]



[a] Initial synthesis of the 2-substituted 4,5-dihydroxypyrimidine-6-carboxy methyl ester (**4**), followed by amidation is depicted. Reaction conditions: (i) hydroxyamine, methanol, reflux; (ii) dimethyl acetylenedicarboxate, methanol or chloroform, 60 °C; (iii) xylenes, 140 °C; (iv) R_3R_4NH, 90 °C, DMF or NMP.

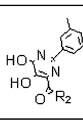
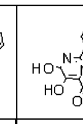
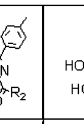
compounds into highly selective HIV integrase inhibitors by "dialing out" the inhibition of the HCV RdRp activity.[11] This work ultimately resulted in the first-in-class HIV integrase drug Raltegravir, which was approved in 2007.[11] The above observations led us to believe that 2-substituted-4,5-dihydroxypyrimidines represent an excellent starting point in the discovery of other drug-like RdRp inhibitors. For these reasons, we sought to create libraries of 2-substituted-4,5-dihydroxypyrimidine-6-carboxamide derivatives for the purpose of discovering small molecule RdRp inhibitors with an initial focus on the inhibition of Sendai virus RdRp.

Results and Discussion

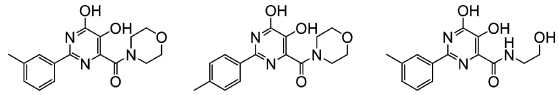
The general approach that was used for the synthesis of our targeted library is shown in Scheme 1. Preparation of hydroxyamidines **1** from nitrile derivatives has been described by Summa and others.[10,13−16] We found that the addition of one equivalent of a stock solution of hydroxyamine to a solution of diverse nitriles in methanol, followed by heating to 60 °C for 4 h, directly provides a solution of the substituted hydroxyamidine derivatives (**2**). Thus, the isolation and crystallization of the hydroxylamidine as described by Summa et al. was circumvented, for production simplicity, with no adverse effects on the yields of the desired products. As has been reported by the Summa and Culbertson groups[10,11,17] various hydroxyamidine derivatives (**2**) were found to undergo a Michael addition with dimethyl acetylenedicarboxylate to form an initial adduct **3**. Removal of the solvent and dissolution of this crude adduct in xylenes (followed by heating) directly affords the desired intermediate ester derivatives (**4**) as precipitates. Isolation by simple filtration gave reasonable amounts of the esters **4** with purities of >85%, in most cases. The typical overall yields were similar to those published (in the range of 15−50%). This synthetic approach allowed us to prepare a large and diverse set of 2-substituted pyrimidine ester intermediates (**4**) that were suitable for parallel amidation reactions (see Table 1 for examples).

For the subsequent amide coupling step, the use of coupling reagents (i.e., BOP, HBTU) is unnecessary because the 5-hydroxy of the pyrimidine appears to serve as a neighboring group activator of the methyl ester. This allows for the direct amidation simply by heating the ester with a diversifying amine in dimethylformamide or *N*-methyl-2-pyrrolidone in MiniBlock XT synthesizers to provide amides of the general structure **5** (see Scheme 1). After completion of the reaction, the reactions are filtered through a filter plate into a collection plate and purified by supercritical fluid chromatography (SFC) or reverse-phase high performance liquid chromatography (RPLC). A collection of primary, secondary, aryl, and hindered amines were used (see Table 1) and were able to define the scope and limitations of this process; for example the *N*,*N*-diisopropyl secondary amine failed to undergo amide coupling under these conditions, while hindered primary *t*-butylamine and less-hindered secondary amines coupled with reasonable success. In addition, reactions with anilines proceeded with lower yields of the final products in general, suggesting that the nucleophilicity of these building blocks may be a contributing factor

Table 1. Examples of the R1 Substitution of Scheme *1* and the Various Amines (R2) Utilized to Produce the Amidation Products (Reaction IV) with Isolated Percent Yields Displayed[a]

R2			
	**6** (27%)	**7** (33%)	**8** (39%)
	9 (37%)	**10** (59%)	**11** (47%)
	**12** (3%)	**13** (4%)	**14** (82%)
	**15** (51%)	**16** (47%)	**17** (17%)
	**18** (44%)	**19** (42%)	**20** (40%)
	**21** (3%)	**22** (4%)	**23** (23%)
	**24** (6%)	**25** (11%)	**26** (32%)
	**27** (NP)	**28** (NP)	**29** (NP)
	**30** (38%)	**31** (7%)	**32** (46%)
	**33** (46%)	**34** (49%)	**35** (47%)
	**36** (15%)	**37** (3%)	**38** (5%)
	**39** (3%)	**40** (4%)	**41** (3%)
	**42** (33%)	**43** (10%)	**44** (11%)
	**45** (49%)	**46** (44%)	**47** (NP)
	**48** (22%)	**49** (5%)	**50** (6%)
	**51** (33%)		
	**52** (18%)		

[a] NP equals no product isolated.



6 **7** **51**

Compound	EC_{50} μM ± SEM*	CC_{50} μM	Selectivity Index
6	21 ± 6	> 130	≥ 6
7	32 ± 6	> 130	≥ 4
51	14 ± 3	> 130	≥ 9

Figure 1. Structure of hit compounds **6**, **7**, and **51**, along with associated activity against recombinant Sendai virus luciferase expression in LLC-MK2 cell cultures, cytotoxicity, and selectivity. EC_{50} = effective concentration of compound needed to inhibit the expression of luciferase to 50% of control value. CC_{50} = cytotoxic concentration of the compound that reduced cell viability to 50%. Asterisk (*) indicates the mean (SEM) of 4 assays.

to the production. We found that temperature elevation increases the conversion in these cases; however under these conditions, it was observed side-products became more prevalent.

This general methodology worked effectively with most amines that we investigated and provided sufficient material for purification of the amides (**5**) in the production runs. These procedures were ultimately applied to the production of nearly 3600 well-characterized diverse compounds with >85% purity (measured by an average of the purities from the PDA and ELSD). Product amounts yielded between 1−25 mg of each compound, which were suitable for assay evaluation against a modified recombinant Sendai virus that expresses the firefly luciferase reporter protein when infected in LLC-MK2 cells. Approximately forty initial compounds were selected from early production for a Sendai virus reporter based screen (see Supporting Information) and screened for their inhibition of enzyme activity using the luciferase assay system (Promega). Using this screen, we identified six compounds that gave >50% inhibition of luciferase activity, which were then tested for cell viability. Of these, three compounds had no observed toxicity up to 75 μM in LLC-MK2 cells (**6**, **7**, and **51**) and were progressed to dose response studies for IC_{50} determination. Compounds **6**, **7**, and **51** exhibited IC_{50} values of 21, 32, and 14 μM respectively (see Figure 1).

These hits were further evaluated to determine whether compound **6**, **7**, and **51** specifically inhibit infectious SeV-Luc production. Thus infected LLC-MK2 cells were treated with 60, 20, or 6 μM concentrations of compound (see Supporting Information). Compounds **6** and **51** showed fluorescent foci inhibition of greater than 90% at the lowest concentration examined (6 μM), while **7** displayed approximately 80% inhibition at 6 μM, confirming the antiviral activity of these hit compounds.

Conclusion

Our interest in the identification of drug-like inhibitors with the potential for broad spectrum antiviral activity against RNA viruses led us to investigate 2-substituted-4,5-dihydroxypyrimidine as a core group for library synthesis. This compact, highly amendable scaffold is easily prepared with diverse 2-substitutions on a reasonable large scale and is adaptable to amidation with a variety of amines without the need for a coupling reagent. A small set of compounds from this library were screened and the initial hits were evaluated in cell based assays, which identified three compounds as inhibitors of Sendai virus. We believe that libraries based on this core group have the potential to be highly valuable in the identification of compounds that are active against numerous other pathogenic single-stranded negative strand RNA viruses, which will be the subject of future reports.

Experimental Section

General. All chemicals (reagents and solvents) were used as purchased from commercial suppliers. Parallel synthesis was accomplished with MiniBlock XT synthesizers obtained from Mettler Toledo AutoChem, accompanied by a stirring hot plate. Intermediate preparation was carried out with dried glassware or in parallel using a 6-position MiniBlock XT synthesizer. A Thomson 2 mL 96-well filter plate (25 μm) used in plate filtrations was packed with approximately 50 mg of Celite 545 filter aid in each well. All automated weighing was done on a Bohdan Balance Automator (Mettler Toledo AutoChem), and parallel evaporations were performed on a GeneVac HT-24 system.

^{1}H NMR spectra were recorded on a Bruker-400 (400 MHz) spectrometer. Chemical shifts are reported as parts per million (ppm) and are referenced by the corresponding solvent peak. Data is reported as: chemical shift, multiplicity, coupling constants, and integration. Pre-purification and QC analysis was done on a Waters Acquity UPLC/PDA/ELSD/MS system carried out with a BEH C18 2.1 × 50 mm column using gradient elution. Each analysis includes the ^{1}H NMR spectrum followed in order by the expected mass ion scan (Scan ES+), the evaporative light scattering detector (ELSD) chromatogram, the UV diode array chromatogram, and finally the total ion current (TIC) chromatogram (see Supporting Information). Water/acetonitrile/0.1% formic acid or 10 mM ammonium bicarbonate/acetonitrile was used for mobile phase depending on compound resolution and polarity. Methanol with 4% tetrahydrofuran was substituted for the acetonitrile when needed. Library purification was performed either on a Berger supercritical fluid chromatography (SFC) prep system utilizing a cyano 21 × 150 mm column and a gradient elution of 5−25% methanol at a rate of 2%/min at 50 mL/min or a Dionex mass directed HPLC purification system using a Phenomenex Gemini Aixia packed C18 30 × 50 mm, 5 μm column. Gradient methods and mobile phases were adjusted based on the prepurification results.

General Intermediate Preparation of 4,5-Dihydroxypyrimidines. Dimethyl acetyenedicarboxylate (DMAD, 1 mL, 1 equiv) was added to a stirred solution of 2-substituted amidoxime (8.16 mmol) in chloroform (0.335M) and maintained at 60 °C for 75 min to 4 h as determined by TLC or UPLC. Upon cooling and evaporation of the solvent, the crude mixture was charged with xylenes (0.335M) and heated to 140 °C for 8 h more before cooling slowly to rt. The resulting heavy precipitate is collected, washed with ethyl ether, and then dried under vacuum to afford desired 4,5-dihydroxypyrimidine methyl esters in yields ranging from

15−50%. Spectral comparison to referenced compounds confirmed desired starting intermediates.[10,11,17]

General Protocol for the Amidation of 4,5-Dihydroxypyrimidines-6-carboxyester. To a 48-position MiniBlock XT containing 11.5 × 110 mm reaction tubes with stir bars was charged with a solution of starting 5,6-dihydroxypyrimidine methyl esters (0.15 mmol) in dimethylformamide or *N*-methyl-2-pyrrolidone (300 μL) to each vessel. Three equivalents of the appropriate amine (0.45 mmol) from a 1 M stock solution (DMF) were added accordingly to plate mapping. An inert atmosphere manifold is installed on the MiniBlock XT, and the reactions are placed under a nitrogen atmosphere then gently heated to 90 °C and maintained for at least 8 h with medium stirring. Once completed, the reaction mixtures were allowed to cool to room temperature, then were diluted with 500 μL of DMSO, and were transferred to a Thomson filter plate (prepacked with Celite connected to a Waters 2 mL 96-deep well plate). Following filtration and an additional washing of the filter plate with 200 μL more of DMSO, the crude products were analyzed by UPLC and purified by either supercritical fluid chromatography (SFC) or reverse-phase liquid chromatography (RPLC). Final purity was measured by the total wavelength current (TWC) from λ = 210−400 nm on a UPLC.

Compound 6. Purity (TWC): 100%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.94 (s, 1H), 10.11 (br s, 1H), 7.83 (s, 1H), 7.79 (d, *J* = 7.5, 1H), 7.36 (m, 2H), 3.60 (m, 4H), 3.36 (m, 4H), 2.37 (s, 3H).

Compound 7. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.34 (br s, 2H), 7.83 (d, *J* = 8.0, 2H), 7.35 (d, *J* = 8.0, 2H), 4.30 (s, 1H), 3.84 (m, 4H), 3.52 (s, 1H), 3.31−3.08 (m, 1H), 2.45 (s, 3H).

Compound 11. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.51 (s, 2H), 8.32 (s, 1H), 8.26 (d, *J* = 7.6, 1H), 7.99 (d, *J* = 8.1, 1H), 7.83 (d, *J* = 7.7, 1H), 7.74 (t, *J* = 7.8, 1H), 7.43 (d, *J* = 4.5, 3H), 7.35 (dq, *J* = 8.6, 4.3, 1H), 5.35−5.24 (m, 1H), 1.70 (d, *J* = 6.9, 3H).

Compound 14. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$ and DMSO-d_6): δ 8.23 (s, 1H), 8.14 (s, 1H), 7.79 (s, 1H), 7.66 (d, *J* = 7.5, 3H), 7.43−7.36 (m, 2H), 7.21 (d, *J* = 7.5, 1H).

Compound 15. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.50 (s, 1H), 11.85−11.55 (m, 1H), 7.86−7.77 (m, 2H), 7.46 (t, *J* = 7.7, 1H), 7.38 (d, *J* = 7.6, 1H), 3.52 (dd, *J* = 15.0, 6.2, 2H), 2.50 (s, 3H), 1.73 (td, *J* = 13.3, 6.7, 1H), 1.59 (dd, *J* = 14.8, 7.1, 2H), 1.01 (d, *J* = 6.6, 6H).

Compound 16. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.48 (s, 1H), 11.71 (br s, 1H), 7.90 (d, *J* = 8.3, 2H), 7.80 (t, *J* = 5.9, 1H), 7.37 (d, *J* = 8.0, 2H), 3.55−3.46 (m, 2H), 2.46 (s, 3H), 1.72 (td, *J* = 13.3, 6.6, 1H), 1.63−1.53 (m, 2H), 1.01 (d, *J* = 6.6, 6H).

Compound 18. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.38 (s, 1H), 11.42 (br s, 1H), 8.13 (s, 1H), 7.83 (s, 1H), 7.79 (d, *J* = 7.8, 1H), 7.46 (t, *J* = 7.7, 1H), 7.38 (d, *J* = 7.6, 1H), 3.69 (m, 2H), 3.63 (m, 2H), 3.45 (s, 3H), 2.50 (s, 3H).

Compound 19. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.37 (s, 1H), 11.73−11.29 (br s, 1H), 8.12 (s, 1H), 7.90 (d, *J* = 8.1, 2H), 7.37 (d, *J* = 7.9, 2H), 3.69 (dd, *J* = 10.4, 5.6, 2H), 3.62 (t, *J* = 4.8, 2H), 3.45 (s, 3H), 2.46 (s, 3H).

Compound 25. Purity (TWC): 91.2%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.1, 2H), 7.34 (d, *J* = 7.9, 2H), 4.24 (s, 2H), 3.87 (s, 2H), 2.62−2.51 (m, 4H), 2.44 (s, 3H), 2.38 (s, 3H).

Compound 30. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.43−12.13 (s, 1H), 11.64−11.10 (br s, 1H), 8.06 (s, 1H), 7.73−7.62 (m, 2H), 7.38−7.22 (m, 7H), 4.61 (d, *J* = 6.3, 2H), 2.38 (s, 3H).

Compound 32. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$ and DMSO-d_6): δ 8.17 (s, 1H), 8.09 (d, *J* = 8.0, 1H), 7.75 (d, *J* = 7.8, 1H), 7.61 (t, *J* = 7.9, 1H), 7.39−7.29 (m, 5H), 4.64 (s, 2H).

Compound 33. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.50 (s, 1H), 11.74 (s, 1H), 7.83 (m, 3H), 7.46 (t, *J* = 7.6, 1H), 7.38 (d, *J* = 7.6, 1H), 3.47 (dd, *J* = 14.1, 6.5, 2H), 2.50 (s, 3H), 1.79−1.66 (m, 2H), 1.05 (t, *J* = 7.4, 3H).

Compound 34. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.48 (s, 1H), 11.73 (s, 1H), 7.91 (d, *J* = 8.2, 2H), 7.86 (s, 1H), 7.37 (d, *J* = 8.0, 2H), 3.46 (dd, *J* = 14.1, 6.5, 2H), 2.46 (s, 3H), 1.78−1.67 (m, 2H), 1.04 (t, *J* = 7.4, 3H).

Compound 42. Purity (TWC): 97.0%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 2H), 7.62 (d, *J* = 10.2, 2H), 7.28 (m, 5H), 4.59 (s, 2H), 2.35 (s, 3H).

Compound 44. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$ and DMSO-d_6): δ 8.40 (dd, *J* = 4.6, 1.6, 2H), 8.16 (s, 1H), 8.06 (d, *J* = 8.0, 1H), 7.68 (d, *J* = 7.8, 1H), 7.55 (t, *J* = 7.9, 1H), 7.23 (d, *J* = 6.1, 2H), 4.57 (s, 2H).

Compound 45. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.50 (s, 1H), 11.58 (s, 1H), 7.92 (s, 1H), 7.86−7.78 (m, 2H), 7.47 (t, *J* = 7.7, 1H), 7.39 (d, *J* = 7.6, 1H), 3.41−3.31 (m, 2H), 2.51 (s, 3H), 1.14 (m, 1H), 0.68−0.58 (m, 2H), 0.36 (m, 2H).

Compound 46. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.34 (s, 1H), 11.53 (s, 1H), 7.77 (d, *J* = 8.2, 3H), 7.23 (d, *J* = 8.0, 2H), 3.24−3.16 (m, 2H), 2.31 (s, 3H), 1.04−0.91 (m, 1H), 0.53−0.44 (m, 2H), 0.21 (q, *J* = 4.7, 2H).

Compound 48. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.6, 2H), 7.39−7.29 (m, 3H), 6.32 (dt, *J* = 8.0, 2.5, 2H), 4.61 (s, 2H), 3.35 (dt, *J* = 3.3, 1.6, 1H), 2.42 (s, 3H).

Compound 50. Purity (TWC): 100%. ^{1}H NMR (400 MHz, $CDCl_3$ and DMSO-d_6): δ 8.18 (s, 1H), 8.10 (d, *J* = 8.1, 1H), 7.76 (d, *J* = 8.0, 1H), 7.63 (t, *J* = 7.7, 1H), 7.38 (d, *J* = 1.0, 1H), 6.36−6.28 (m, 2H), 4.62 (s, 2H).

Compound 52. Purity (TWC): 90.3%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.13 (s, 1H), 11.68−11.18 (br s, 1H), 8.52 (s, 1H), 7.77 (d, *J* = 9.7, 2H), 7.47 (t, *J* = 7.6, 1H), 7.40 (d, *J* = 7.5, 1H), 3.97−3.87 (m, 4H), 3.11−3.00 (m, 4H), 2.57−2.46 (m, 3H).

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Supporting Information Available. Final product characterization data, including ^{1}H NMR spectra, LC traces, and MS spectra of library compounds, an assay description, and other related material. This material is available free of charge via the Internet at http://pubs.acs.org.

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