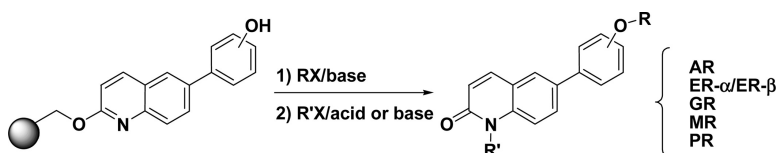


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Solid-Phase Synthesis of a 6-Phenylquinolin-2(1H)-one Library Directed toward Nuclear Hormone Receptors

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A library of 6-phenylquinolin-2(1H)-ones with diversity at position 1 and the ortho, meta, and para positions of the pendant phenyl ring has been synthesized using solid-phase parallel synthetic techniques. A key step in the synthesis of the library is a tandem alkylation cleavage in which diversity can be introduced at position 1 simultaneously to the cleavage from the resin. The yields of this step were significantly improved over what has previously been reported by addition of cesium carbonate to scavenge the acid that is formed during the reaction. Furthermore, we have shown that the solid support linkage is tolerant to Suzuki coupling and etherification reaction conditions and that selective cleavage of the linkage can take place in the presence of esters. The resulting 6-phenylquinolin-2(1H)-one library was screened against a panel of nuclear hormone receptors (androgen, estrogen α and β isoforms, glucocorticoid, mineralocorticoid, and progesterone). Certain members of this library display moderate affinity for several of these receptors, and consequently, the 6-phenylquinolin-2(1H)-one core of the library may be considered a privileged structure for nuclear hormone receptors. In contrast, other members of the library display high selectivity for a particular receptor. The highest affinity ligand (**9**{2,1,1}) possesses an affinity of 330 nM for the androgen receptor, whereas the most selective ligand (**9**{2,4,1}) displays an affinity of 900 nM for the androgen receptor and a selectivity of 140-fold over the next highest affinity receptor.

Introduction

Nuclear receptors are ligand-activated transcription factors which regulate the expression of genes in a cell- and promoter-specific manner.¹ Many of the proteins coded by these regulated genes are situated at key developmental, immunological, and metabolic intervention points. Hence, drugs which bind to and modulate the activity of nuclear receptors have wide therapeutic applications ranging from treatment of age-related diseases (e.g., cachexia and osteoporosis), cancer, inflammatory conditions, and metabolic syndromes (e.g., diabetes, dyslipidemia, and obesity).²

There are 48 nuclear receptors in humans, and at least 25 of these are known to bind endogenous hormones or metabolic intermediates.³ The tertiary structure of the ligand binding domain of these nuclear receptors is highly conserved and adopts an α -helical sandwich fold.⁴ The ligand binding pocket of these receptors is buried within the interior of the protein and in general contains a hydrophobic center with hydrogen bond accepting or donating groups situated at the ends of the binding cavity. On the basis of the gross similarity

of the binding cavity of these receptors, it should be possible to develop a “privileged” core⁵ with the potential to bind to many of these receptors, whereas specificity of binding to a particular receptor can be achieved by introduction of appropriate substituents to the privileged core using parallel synthetic methods.

Given the therapeutic importance of nuclear receptor ligands, we desired to develop a library of compounds based on a privileged core which have the potential for selective high affinity binding to this class of receptors. One core which has this potential is 6-phenylquinolin-2(1H)-one. Similar core structures have been synthesized before, targeting 5- α -reductase (an enzyme that reduces testosterone to 5 α -dihydrotestosterone) for treatment of prostatic hyperplasia.^{6,7} 2-Pyridone exists as an equilibrium between the lactam and 2-hydroxypyridine tautomers (Figure 1), and therefore, this ring in principle can act as either a hydrogen bond acceptor or donor to mimic the A-ring hydrogen bonding groups of classical steroidal nuclear receptor ligands, such as hydrocortisone and 17- β -estradiol, respectively. In addition, the 6-phenylquinolin-2(1H)-one ring system sterically mimics the A-, B-, and D-rings of these steroidal nuclear receptor ligands. Substituents added to the pendant phenyl ring would provide hydrogen-bonding groups to interact with complementary hydrogen bonding centers at the opposite end of the nuclear receptor-binding cavity. Furthermore, pyri-

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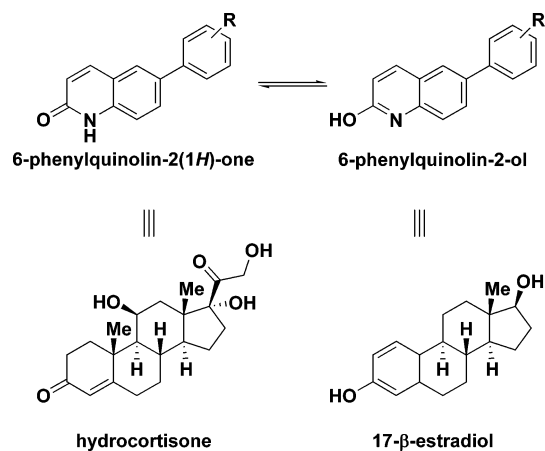


Figure 1. Tautomeric equilibrium between lactam and 2-hydroxypyridine forms of 6-phenylquinolin-2(1*H*)-one which mimic the 3-keto group of hydrocortisone and the 3-hydroxyl group of 17- β -estradiol, respectively.

ones which bind to at least one member of the nuclear receptor family the androgen receptor have been previously described.^{8–11}

We have previously described the preparation of *N*-alkylated pyridones via selective *N*-alkylation of 2-alkoxy-pyridines on solid phase.¹² In addition to providing flexibility for the selective preparation of either free or *N*-alkylated pyridones, this solid-phase method can be extended to provide additional diversity at other sites of this ring system. We now wish to describe the application of this method to the synthesis of a library of 6-phenylquinolin-2(1*H*)-ones and the screening of this library against a panel of nuclear hormone receptors.

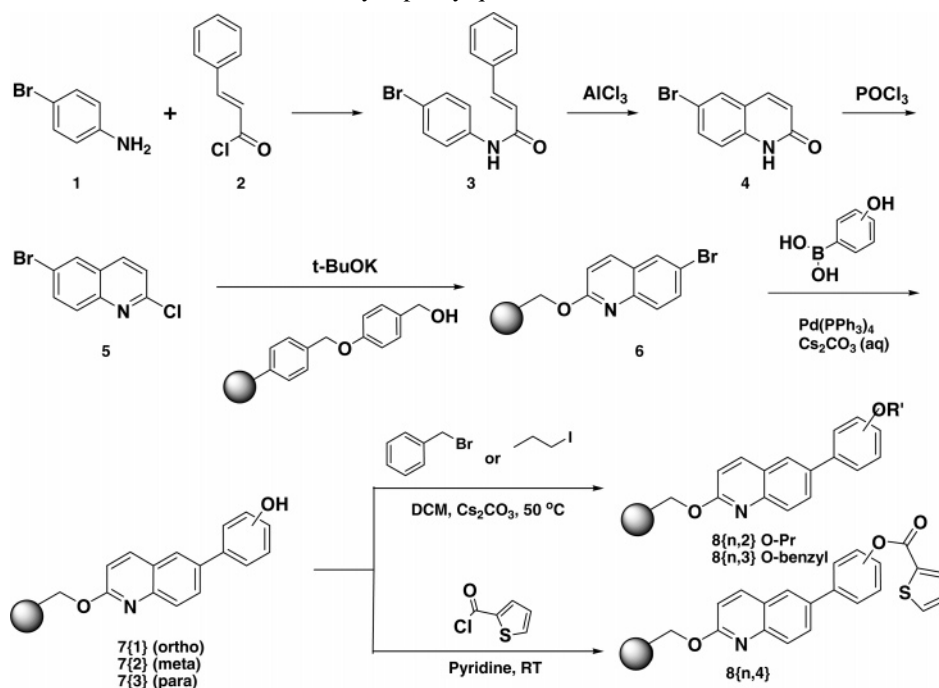
Results and Discussion

The synthesis of the solid-phase linked 2-alkoxy-6-phenylquinolines **7** is outlined in Scheme 1. The production of compounds **3–5** was made in the same fashion as

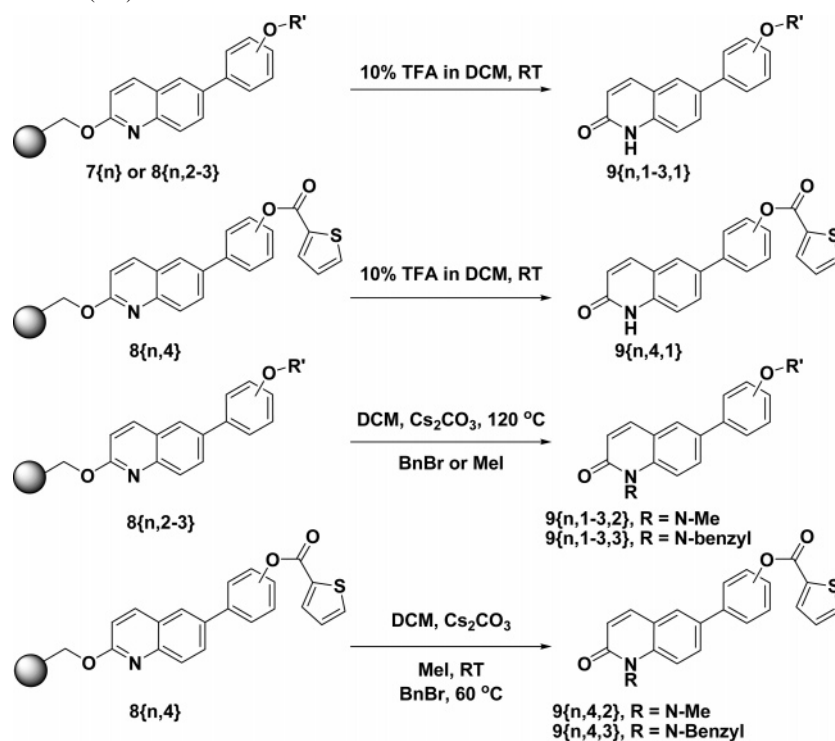
described by Becker et al.¹³ The 2-chloroquinoline **5** was linked to a Wang resin in the presence of potassium *tert*-butoxide in dimethylformamide at 80 °C using the procedure we previously developed¹² to afford the 6-bromo-2-alkoxyquinoline **6**. This bromide, in turn, was coupled with either ortho, meta, or para hydroxyphenylboronic acid via a Suzuki coupling reaction in refluxing 1,2-dimethoxyethane in the presence of palladium tetrakis(triphenylphosphine) catalyst and aqueous cesium carbonate as base to afford the solid-phase bound 2-alkoxy-6-phenylquinoline chemset **7**{*1–3*}. The reaction times of the different boronic acids in the Suzuki coupling ranged from 1 to 3 h; the ortho hydroxyphenylboronic acid required the shortest reaction time, followed by meta and then para. The 2', 3', or 4'-hydroxyl groups of the 6-phenylquinoline chemset **7** were optionally alkylated with benzyl bromide or propyl iodide in the presence of cesium carbonate in DCM to yield the ether chemset **8**{*n,2–3*}. The optimal temperature for the reaction was 50 °C \pm 5 °C, since higher temperatures cleaved the product from the resin via an alternative alkylation cleavage reaction (see below). During the phenol alkylation step, the reaction was monitored by LC/MS to ensure that no cleavage occurred. The meta-substituted phenol reacted faster than either ortho or para-. Propyl iodide had a shorter reaction time (24 h) than benzyl bromide (3–4 days). Alternatively, the hydroxyphenylquinoline chemset **7** was esterified with thiophene-2-carbonyl chloride in pyridine overnight at room temperature to afford the ester chemset **8**{*n,4*}.

To explore if the binding pocket A would tolerate substituents other than hydrogen, the 2-alkoxy-6-phenylquinolines **8**{*n,m*} were cleaved either with TFA to afford nonalkylated chemset **9**{*n,m,l*}, or via a tandem alkylation cleavage (TAC) method with a small nonpolar electrophile (methyl iodide) or a large electrophile (benzyl bromide), also of nonpolar nature, to provide the *N*-alkylated chemset

Scheme 1. Synthesis of Solid-Phase Linked 2-Alkoxy-6-phenylquinolines



Scheme 2. Conditions for the Cleavage of 2-Alkoxy-6-phenylquinolines to Produce either 6-Phenylquinolin-2(1H)-ones or N-Alkylated 6-Phenylquinolin-2(1H)-ones



$9\{n,m,2-3\}$. The TAC method was performed as described earlier by us¹² with chemset $8\{n,2-3\}$. Unfortunately, in all of the reactions, the unwanted unalkylated product was formed. This unwanted product was trapped on an anion-exchange column, and the product could then be filtered off the column. With the rest of the TAC-method reactions, cesium carbonate was added to scavenge generated acid, that is, HBr and HI formed via reaction of the alkylating agent with moisture. The addition of cesium carbonate improved the purity, and none of the undesired unalkylated byproduct could be seen. Yields for the nonalkylated products $9\{n,m,1\}$ were quantitative, whereas lower yields were obtained for the products from the TAC cleavage, in which methyl iodide gave a somewhat higher yield than benzyl bromide. Earlier investigations of the resin after the TAC cleavage by MAS NMR¹² have indicated the formation of an undesired byproduct formed via site-site reaction of $8\{n,2-4\}$ with polymer-bound benzyl halide resin formed during the reaction. This effect is probably more pronounced in the procedure using benzyl bromide, in which the desired alkylation reaction is slower, than for the reactions with methyl iodide, which proceed more rapidly, and is indicated by the higher yields obtained in the latter case. When these conditions were applied to chemset $8\{n,4\}$, the thiophene-2-carboxylic acid moiety was replaced with the electrophile that was used in the reaction, and the product **10** or **11** was formed (Figure 2). Different temperatures were tried for the TAC method, in which the high reactivity of methyl iodide allowed the alkylation to proceed at room temperature, whereas for benzyl bromide, a reaction temperature of 60 °C was optimal. Even though the temperature had been lowered to 60 °C in the reaction with benzyl bromide, the outcome of the reaction was a mixture of **11** and the desired product.

Chemset **9** was screened using a competitive binding assay against a panel of nuclear receptors (AR, androgen; ER- α and - β , estrogen α and β isoforms; GR, glucocorticoid; MR, mineralocorticoid; and PR, progesterone receptors). Several members of the library display significant affinity for multiple receptors (see Table 1). For example, ligand $9\{1,2,1\}$ displays measurable binding for all 6 receptors included in the panel, although the affinity of this ligand for both ER isoforms was weak. In contrast, several of the ligands display high selectivity for one receptor vs the other five included in the screen. The most selective ligand was $9\{2,4,1\}$, which had a measured binding affinity of 900 nM for AR and 140-fold selectivity over the next highest affinity receptor (ER- β). The highest affinity ligand was $9\{2,1,1\}$ which displays a 330 nM affinity for the androgen receptor. Moderate affinity ligands were detected for all of the receptors except ER. The low affinity observed for ER is not surprising, since the preferred tautomer of pyridones is the keto form, whereas ER generally prefers groups such as hydroxyl that can act as both a hydrogen bond acceptor and donor.

Generally, ortho substituents on the pendant phenyl ring ($9\{1,m,o\}$) are favored over meta ($9\{2,m,o\}$), which in turn

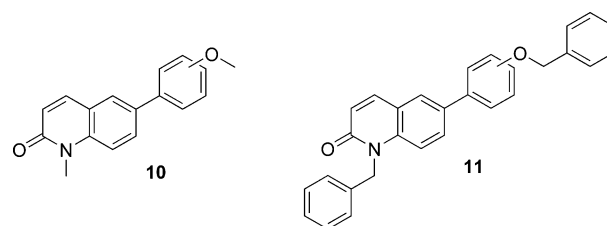
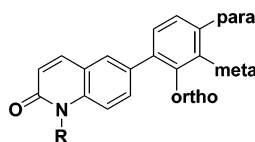


Figure 2. Byproducts when performing the tandem N-alkylation cleavage step on ester derivatives.

Table 1. Affinities^a for the 6-Phenylquinolin-2(1*H*)-one Library of Nuclear Hormone Receptors^b

compound	NR	ortho	meta	para	purity (%)	yield (%)	receptor pIC ₅₀ ^c					
							ER-α	ER-β	AR	GR	MR	PR
control ^d							8.3	8.2	8.94	8.15	7.76	8.59
9{1,1,1}	H	OH	H	H	89	100			5.55			
9{2,1,1}	H	H	OH	H	90	100			6.48		4.55	5.26
9{3,1,1}	H	H	H	OH	95	100						
9{1,2,1}	H	O- <i>n</i> -Pr	H	H	>98	100	3.6	3.8	5.12	4.55	4.74	4.94
9{2,2,1}	H	H	O- <i>n</i> -Pr	H	92	100			4.89		4.58	
9{3,2,1}	H	H	H	O- <i>n</i> -Pr	94	100						
9{1,3,1}	H	OCH ₂ Ph	H	H	95	100				4.85	4.01	4.98
9{2,3,1}	H	H	OCH ₂ Ph	H	>98	100						
9{3,3,1}	H	H	H	OCH ₂ Ph	87	100						
9{1,4,1}	H	T2C ^e	H	H	94	100	3.9	3.9	5.80			
9{2,4,1}	H	H	T2C ^e	H	94	100	3.9	3.9	6.05			
9{3,4,1}	H	H	H	T2C ³	88	100	3.8	4.2				
9{1,2,2} ^f	methyl	O- <i>n</i> -Pr	H	H	98	51			5.52	4.57	5.01	5.46
9{2,2,2}	methyl	H	O- <i>n</i> -Pr	H	85	77						
9{3,2,2} ^f	methyl	H	H	O- <i>n</i> -Pr	97	46						
9{1,3,2}	methyl	OCH ₂ Ph	H	H	>98	92			5.57		4.91	4.92
9{2,3,2} ^f	methyl	H	OCH ₂ Ph	H	98	31					4.75	5.56
9{3,3,2}	methyl	H	H	OCH ₂ Ph	85	100						
9{1,4,2}	methyl	T2C ³	H	H	>98	37						
9{2,4,2}	methyl	H	T2C ^e	H	83	29						
9{3,4,2}	methyl	H	H	T2C ^e	>98	66						
9{1,2,3} ^f	benzyl	O- <i>n</i> -Pr	H	H	96	29					5.04	
9{2,2,3} ^f	benzyl	H	O- <i>n</i> -Pr	H	94	8			5.05	4.72	4.77	
9{3,2,3} ^f	benzyl	H	H	O- <i>n</i> -Pr	94	13				4.32	4.54	
9{1,3,3}	benzyl	OCH ₂ Ph	H	H	>98	14					4.48	
9{2,3,3} ^f	benzyl	H	OCH ₂ Ph	H	98	16						
9{3,3,3}	benzyl	H	H	OCH ₂ Ph	>98	33						
9{1,4,3} ^g	benzyl	T2C ^e	H	H	69	15				4.46	4.65	
9{2,4,3} ^g	benzyl	H	T2C ³	H	54	15					4.55	
9{3,4,3} ^g	benzyl	H	H	T2C ^e	47	15					4.57	

^a Measured as pIC₅₀. ^b ER-α and ER-β, estrogen receptor α and β isoforms respectively; AR, androgen receptor; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; and PR, progesterone receptor. ^c Receptor pIC₅₀ = -log (IC₅₀/10⁹). - = no binding detected (pIC₅₀ < 4.0). ^d Control ligands, ER-α and -β = 17-β-estradiol, AR = mibolerone, GR = dexamethasone, MR = aldosterone, PR = progesterone. ^e T2C = thiophene-2-carboxylate. ^f Were synthesized with the same method as reported before and then purified through an ion exchange column. ^g Compounds 9{1,4,3}–9{3,4,3} were obtained as mixture with 9{1,3,3}–9{3,3,3}, respectively.

is favored over para (9{3,*m*,*o*}) for most of the receptors, included in the screen. However, there are some notable exceptions, especially for AR, for which the meta substituted derivatives 9{2,1,1} and 9{2,4,1} display the highest affinity.

Conclusions

We have developed a versatile method for the solid-phase synthesis of a library of 6-phenylquinolin-2(1*H*)-ones in which diversity can be introduced at both position 1 and the pendant phenyl ring. The TAC method to introduce diversity on position 1 was improved by adding cesium carbonate to scavenge acid that is formed in the reaction. In addition, we have developed methods under which Suzuki coupling and etherification reactions can take place without cleavage from the linker. Furthermore, optimized conditions were found which allow selective cleavage of the linker in the presence of esters. On the basis of this chemistry, we have synthesized a 30-membered library of compounds, which was subsequently screened against a panel of six nuclear hormone receptors. Several members of the library display moderate

affinity for multiple receptors in the panel, and therefore, the 6-phenylquinolin-2(1*H*)-one core of this library can be considered a privileged structure for nuclear hormone receptors. In contrast, several members of the library show selective binding against one particular receptor included in the panel, which demonstrates that it is possible to develop selective high affinity nuclear receptor ligands based on the 6-phenylquinolin-2(1*H*)-one core structure.

Experimental Section

Proton NMR spectra were measured on a Bruker 500 MHz instrument. The LC/MS analysis were performed on a Shimadzu LC-10AD HPLC with a Zorbax 5-μm 2.1 × 50 mm column and Shimadzu SPD-10A UV-vis detector at 254 nm that was connected to a Perkin-Elmer SCIEX API 1500EX mass spectrometer.

Chemicals and solvents were purchased from Aldrich, Lancaster, VWR, and Acros and were used without further purification. Wang resin (100–200 mesh, 1% cross-linked, 0.91 mmol/g) was purchased from NovaBiochem.

Procedure for Screening 6-Phenylquinolin-2(1H)-one Library. 1. Scintillation Proximity Assay (SPA) for Human ER- α and - β Ligand Binding Domains (LBD). The SPA method can be briefly described as follows: Fluoromicrosphere beads containing scintillant are coated with either ER- α or - β (coupled to the beads by a streptavidin-biotin linkage). When the radioligand (tritiated 17- β -estradiol) is bound to the receptor, it is sufficiently close that an emitted β particle will produce light (as a result of energy transfer to the scintillant). Radioligand displaced from the receptor by a competing ligand will not generate light due to loss of proximity to the scintillating material.

2. Filtration Radioligand Binding Assay for AR, GR, MR and PR (All Full-Length Human Receptors). Filtration radioligand binding requires that the receptor (AR, GR, MR, or PR) be incubated with the radioligand and competing ligand for a period of time (usually for equilibrium to be reached). After equilibrium, the radioligand is either bound to the receptor or "free". The bound radioligand is then separated from the free radioligand and is quantified by liquid-scintillation counting. The separation method used is to rapidly filter the assay solution "through" a glass-fiber filter (which retains the receptor-bound radioligand but allows the free ligand to pass through). This filter is then coated with a scintillating material and measured on a microplate liquid-scintillation counter (Wallac Microbeta).

General Procedure for Suzuki Coupling. To 0.455 mmol of **6** preswollen in 10 mL of DME was added 6 equiv of phenylboronic acid and a solution of 6 equiv of cesium carbonate dissolved in 1.5 mL of water. The reaction vessel was then flushed three times by first applying a vacuum and then filling with nitrogen. A slurry of 0.05 equiv Pd(PPh₃)₄ in 0.5 mL DME was added to the reaction mixture, which was refluxed and stirred for 3 h. The resin was washed with 2 \times dimethoxyethane, 3 \times 20% saturated aqueous ammonium chloride in THF, 2 \times 20% water in THF, 3 \times THF, and 3 \times DCM. A small sample of the product was treated with 10% TFA in DCM for 1 h and then analyzed with LC/MS.

General Procedure for Alkylation of Phenols 7{1}-7{3}. To 0.182 mmol of resin 7{1}-7{3} preswollen in 3 mL DCM was added 10 equiv of cesium carbonate and 20 equiv of benzyl bromide. The mixture was slowly stirred at 50 °C, followed by cleavage of small aliquots every 12 h, which were analyzed by LC/MS until the reaction was complete. The resin was washed 3 \times 20% water in THF, 3 \times THF, and 3 \times DCM.

General Procedure for Acylation of Phenols 7{1}-7{3}. To 0.218 mmol of resin 7{1}-7{3} preswollen in 3 mL pyridine was added 10 equiv of thiophene-2-carbonyl chloride. The mixture was slowly stirred at room temperature overnight. The resin was washed 3 \times pyridine, and 3 \times DCM.

General Procedure for Tandem Alkylation Cleavage of 8{n,I}-8{n,3}. To 0.046 mmol of chemset 8{n,I}-8{n,3}, preswollen in 3 mL of DCM, was added 10 equiv of cesium carbonate and 37 equiv of alkyl halide in a Supelco 18-mm screw cap with a PTFE liner. The mixture was stirred under nitrogen atmosphere at 120 °C for 48 h, except for

ester-substituted starting materials, for which the temperature was lower. For alkylation of the esters with methyl iodide, the reaction temperature was 25 °C, and for benzyl bromide, 60 °C. The reaction mixture was filtered, the resin was washed two times with DCM, and then the filtrate was evaporated to remove the excess of methyl iodide.

The reaction mixture containing benzyl bromide had to be purified from the excess of benzyl bromide. The DCM solution from the reaction was added to a dry-packed silica gel column (2 g). The column was first eluted with 15 mL of DCM to remove excess benzyl bromide, whereupon the product was eluted with 6 mL of 10% MeOH in DCM. The MeOH/DCM solvent mixture was evaporated, and the residue was analyzed with NMR and ES-MS.

1-Methyl-6-(3-propoxyphenyl)-1H-quinolin-2-one (9{2,2,2}). ¹H NMR (500 MHz, CDCl₃) δ 1.07 (t, 3H, J = 7.3 Hz), 1.85 (m, 2H), 3.76 (s, 3H), 4.00 (t, 2H, J = 6.6 Hz), 6.75 (d, 1H, J = 9.5 Hz), 6.92 (m, 1H), 7.16 (m, 1H), 7.19 (m, 1H), 7.38 (t, 1H, J = 7.9 Hz), 7.43 (d, 1H, J = 8.8 Hz), 7.73 (d, 1H, J = 9.5 Hz), 7.76 (m, 1H) and 7.81 (dd, 1H, J = 8.8 and 2.2 Hz); ES-MS m/z 294 ((M + H)⁺).

6-(2-Benzyloxyphenyl)-1-methyl-1H-quinolin-2-one (9{1,3,2}). ¹H NMR (500 MHz, CDCl₃) δ 3.76 (s, 3H), 5.12 (s, 2H), 6.73 (d, 1H, J = 9.5 Hz), 7.06-7.10 (m, 2H), 7.27-7.35 (m, 6H), 7.38-7.41 (m, 2H), 7.67 (d, 1H, J = 9.5 Hz), 7.78 (m, 1H) and 7.83 (dd, 1H, J = 8.8 and 2.2 Hz); ES-MS m/z 342 ((M + H)⁺).

6-(4-Benzyloxyphenyl)-1-methyl-1H-quinolin-2-one (9{3,3,2}). ¹H NMR (500 MHz, CDCl₃) δ 3.76 (s, 3H), 5.13 (s, 2H), 6.75 (d, 1H, J = 9.5 Hz), 7.08 (m, 2H), 7.33-7.48 (m, 6H), 7.56 (m, 2H), 7.71-7.73 (m, 2H) and 7.77 (dd, 1H, J = 8.5 and 2.2 Hz); ES-MS m/z 342 ((M + H)⁺).

Thiophene-2-carboxylic Acid 2-(1-Methyl-2-oxo-1,2-dihydroquinolin-6-yl)-phenyl Ester (9{1,4,2}). ¹H NMR (500 MHz, CDCl₃) δ 3.71 (s, 3H), 6.69 (d, 1H, J = 9.5 Hz), 7.10 (dd, 1H, J = 5.0 and 3.8 Hz), 7.33-7.36 (m, 2H), 7.40 (dd, 1H, J = 7.6 and 1.6 Hz), 7.44 (dd, 1H, J = 7.9 and 1.9 Hz), 7.60 (dd, 1H, J = 5.0 and 1.3 Hz), 7.63 (d, 1H, J = 9.5 Hz), 7.70-7.73 (m, 3H) and 7.82 (dd, 1H, J = 3.8 and 1.3 Hz); ES-MS m/z 362 ((M + H)⁺).

Thiophene-2-carboxylic Acid 3-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)-phenyl Ester (9{2,4,2}). ¹H NMR (500 MHz, CDCl₃) δ 3.77 (s, 3H), 6.76 (d, 1H, J = 9.5 Hz), 7.21 (dd, 1H, J = 5.0 and 3.8 Hz), 7.24 (m, 1H), 7.45 (d, 1H, J = 8.5 Hz), 7.50 (m, 1H), 7.52-7.54 (m, 2H), 7.70 (dd, 1H, J = 5.0 and 1.3 Hz), 7.73 (d, 1H, J = 9.5 Hz), 7.79 (m, 1H), 7.83 (dd, 1H, J = 8.5 and 2.2 Hz) and 8.02 (dd, 1H, J = 3.8 and 1.3 Hz); ES-MS m/z 362 ((M + H)⁺).

Thiophene-2-carboxylic Acid 4-(1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)-phenyl Ester (9{3,4,2}). ¹H NMR (500 MHz, CDCl₃) δ 3.77 (s, 3H), 6.77 (d, 1H, J = 9.5 Hz), 7.21 (dd, 1H, J = 5.0 and 3.8 Hz), 7.34 (m, 2H), 7.53 (d, 1H, J = 8.5 Hz), 7.67 (m, 2H), 7.70 (dd, 1H, J = 5.0 and 1.3 Hz), 7.72 (d, 1H, J = 9.5 Hz), 7.76-7.78 (m, 2H) and 8.02 (dd, 1H, J = 3.8 and 1.3 Hz); ES-MS m/z 362 ((M + H)⁺).

1-Benzyl-6-(2-benzyloxyphenyl)-1H-quinolin-2-one (9{1,3,3}). ¹H NMR (500 MHz, CDCl₃) δ 5.09 (s, 2H), 5.59 (br s, 2H), 6.82 (d, 1H, J = 9.5 Hz), 7.05-7.08 (m, 2H), 7.25-

7.36 (m, 13H), 7.67 (dd, 1H, $J = 8.8$ and 2.2 Hz), 7.73 (d, 1H, $J = 9.5$ Hz) and 7.79 (m, 1H); ES-MS m/z 418 ((M + H)⁺).

1-Benzyl-6-(4-benzyloxyphenyl)-1H-quinolin-2-one (9{3,3,3}). ¹H NMR (500 MHz, CDCl₃) δ 5.11 (s, 2H), 5.59 (br s, 2H), 6.84 (d, 1H, $J = 9.5$ Hz), 7.05 (m, 2H), 7.22–7.26 (m, 2H), 7.29–7.42 (m, 7H), 7.44–7.47 (m, 2H), 7.50 (m, 2H), 7.62 (dd, 1H, $J = 8.5$ and 2.2 Hz), 7.71 (m, 1H) and 7.79 (d, 1H, $J = 9.5$); ES-MS m/z 418 ((M + H)⁺).

General Procedure for Tandem Alkylation Cleavage of 8{1–3,2} and 8{2,3}. The resin was first dried by placing 50 mg in a 15-mL Supelco screw-top reaction vial with 10 mL of anhydrous toluene followed by azeotropic evaporation of the solvent at 40 °C with a Speedvac (model no. AES2010). This drying cycle was repeated an additional two times. The reaction vessel containing the dried resin was then charged with 3 mL of DCM followed by 200 μ L of alkyl halide, flushed with argon, and sealed with a Supelco 18-mm screw cap with a PTFE liner. The reaction mixture was heated to 120 °C for 24 h. The mixture was transferred to a filter column and was washed sequentially with DCM (2 \times 1 mL), 10% MeOH in DCM (1 mL), MeOH (1 mL), and DCM (2 \times 1 mL). The solvent was evaporated to remove the excess of methyl iodide, and the residue was directly analyzed by NMR.

The reaction mixture containing benzyl bromide had to be purified from the excess of benzyl bromide. The DCM solution from the reaction was added to a dry-packed silica gel column (2 g). The column was first eluted with 15 mL of DCM to remove excess benzyl bromide, whereupon the product was eluted with 6 mL of 10% MeOH in DCM. The MeOH/DCM solvent mixture was evaporated, and the residue was analyzed with NMR and ES-MS.

General Procedure To Purify N-Alkylated 2-Quinolones from Parent 2-Quinolone. The product mixture from a tandem alkylation cleavage reaction, in which a mixture of N-alkylated 2-quinolone and the parent 2-quinolone had been formed, was dissolved in 1 mL of 1:1 DCM/MeCN. This solution was applied to a 1-g SAX (quaternary amine with chloride as counterion) ion exchange column that had been pretreated with 2 \times 4 mL of NaOH, 1 M; 1 \times 4 mL of MeCN; and 1 \times 4 mL of 1:1 DCM/MeCN. The N-alkylated 2-quinolone was washed from the column with 8 mL of 1:1 DCM/MeCN.

1-Methyl-6-(2-propoxyphenyl)-1H-quinolin-2-one (9{1,2,2}). ¹H NMR (500 MHz, CDCl₃) δ 0.98 (t, 3H, $J = 7.6$ Hz), 1.75 (m, 2H), 3.77 (s, 3H), 3.96 (t, 2H, $J = 6.3$ Hz), 6.73 (d, 1H, $J = 9.5$ Hz), 7.00 (dd, 1H, $J = 8.2$ and 1.0 Hz), 7.05 (m, 1H), 7.33 (m, 1H), 7.37 (dd, 1H, $J = 7.6$ and 1.9 Hz), 7.40 (d, 1H, $J = 8.8$ Hz), 7.70 (d, 1H, $J = 9.5$ Hz), 7.76 (m, 1H) and 7.81 (dd, 1H, $J = 8.5$ and 1.9 Hz); ES-MS m/z 294 ((M + H)⁺).

1-Methyl-6-(4-propoxyphenyl)-1H-quinolin-2-one (9{3,2,2}). ¹H NMR (500 MHz, CDCl₃) δ 1.06 (t, 3H, $J = 7.6$ Hz), 1.84 (m, 2H), 3.78 (s, 3H), 3.98 (t, 2H, $J = 6.6$ Hz), 6.74 (d, 1H, $J = 9.5$ Hz), 7.00 (m, 2H), 7.42 (d, 1H, $J = 8.5$ Hz), 7.54 (m, 2H), 7.70–7.73 (m, 2H) and 7.77 (dd, 1H, $J = 8.5$ and 2.2 Hz); ES-MS m/z 294 ((M + H)⁺).

6-(3-Benzyloxyphenyl)-1-methyl-1H-quinolin-2-one (9{2,3,2}). ¹H NMR (500 MHz, CDCl₃) δ 3.76 (s, 3H), 5.14 (s, 2H), 6.75 (d, 1H, $J = 9.5$ Hz), 7.00 (dd, 1H, $J = 8.5$ and 2.2 Hz), 7.22–7.25 (m, 2H), 7.33–7.45 (m, 5H), 7.46–7.49 (m, 2H), 7.73 (d, 1H, $J = 9.5$ Hz), 7.75 (m, 1H) and 7.80 (dd, 1H, $J = 8.5$ and 1.9 Hz); ES-MS m/z 342 ((M + H)⁺).

1-Benzyl-6-(2-propoxyphenyl)-1H-quinolin-2-one (9{1,2,3}). ¹H NMR (500 MHz, CDCl₃) δ 0.95 (t, 3H, $J = 7.3$ Hz), 1.73 (m, 2H), 3.94 (t, 2H, $J = 6.6$ Hz), 5.60 (br s, 2H), 6.82 (d, 1H, $J = 9.5$ Hz), 6.98 (d, 1H, $J = 7.9$ Hz), 7.02 (m, 1H), 7.22–7.33 (m, 8H), 7.65 (dd, 1H, $J = 8.8$ and 2.2 Hz), 7.76 (d, 1H, $J = 9.5$ Hz) and 7.78 (m, 1H); ES-MS m/z 370 ((M + H)⁺).

1-Benzyl-6-(3-propoxyphenyl)-1H-quinolin-2-one (9{2,2,3}). ¹H NMR (500 MHz, CDCl₃) δ 1.05 (t, 3H, $J = 7.6$ Hz), 1.83 (m, 2H), 3.97 (t, 2H, $J = 6.6$ Hz), 5.59 (br s, 2H), 6.84 (d, 1H, $J = 9.5$ Hz), 6.89 (dd, 1H, $J = 8.2$ and 2.2 Hz), 7.10 (m, 1H), 7.14 (m, 1H), 7.23–7.27 (m, 3H), 7.30–7.36 (m, 4H), 7.66 (dd, 1H, $J = 8.8$ and 2.2 Hz), 7.76 (m, 1H) and 7.80 (d, 1H, $J = 9.5$ Hz); ES-MS m/z 370 ((M + H)⁺).

1-Benzyl-6-(4-propoxyphenyl)-1H-quinolin-2-one (9{3,2,3}). ¹H NMR (500 MHz, CDCl₃) δ 1.05 (t, 3H, $J = 7.6$ Hz), 1.83 (m, 2H), 3.96 (t, 2H, $J = 6.6$ Hz), 5.59 (br s, 2H), 6.83 (d, 1H, $J = 9.5$ Hz), 6.97 (m, 2H), 7.22–7.26 (m, 3H), 7.29–7.33 (m, 3H), 7.49 (m, 2H), 7.62 (dd, 1H, $J = 8.8$ and 2.2 Hz), 7.71 (m, 1H) and 7.79 (d, 1H, $J = 9.5$ Hz); ES-MS m/z 370 ((M + H)⁺).

1-Benzyl-6-(3-benzyloxyphenyl)-1H-quinolin-2-one (9{2,3,3}). ¹H NMR (500 MHz, CDCl₃) δ 5.12 (s, 2H), 5.59 (br s, 2H), 6.84 (d, 1H, $J = 9.5$ Hz), 6.97 (m, 2H), 7.16–7.20 (m, 2H), 7.22–7.26 (m, 2H), 7.29–7.42 (m, 7H), 7.43–7.47 (m, 2H), 7.64 (dd, 1H, $J = 8.8$ and 2.2 Hz), 7.75 (m, 1H) and 7.79 (d, 1H, $J = 9.5$ Hz); ES-MS m/z 418 ((M + H)⁺).

General Procedure for TFA Cleavage. To 50 mg of resin, preswollen in DCM, was added 3 mL of 10% TFA in DCM. The reaction was shaken for 1 h. The resin was filtered off and washed twice with 1 mL of DCM, followed by 1 mL of toluene, and dried under vacuum.

6-(2-Hydroxyphenyl)-1H-quinolin-2-one (9{1,1,1}). ¹H NMR (500 MHz, DMSO) δ 6.50 (d, 1H, $J = 9.5$ Hz), 6.88 (m, 1H), 6.95 (dd, 1H, $J = 8.2$ and 1.3 Hz), 7.16 (m, 1H), 7.28 (dd, 1H, $J = 7.6$ and 1.6 Hz), 7.32 (d, 1H, $J = 8.5$ Hz), 7.70 (dd, 1H, $J = 8.5$ and 1.9 Hz), 7.81 (m, 1H), 7.94 (d, 1H, $J = 9.5$ Hz) and 9.57 (s, 1H); ES-MS m/z 238 ((M + H)⁺), 236 ((M – H)[–]).

6-(3-Hydroxyphenyl)-1H-quinolin-2-one (9{2,1,1}). ¹H NMR (500 MHz, DMSO) δ 6.53 (d, 1H, $J = 9.5$ Hz), 6.76 (m, 1H), 7.05 (m, 1H), 7.10 (m, 1H), 7.26 (t, 1H, $J = 7.9$ Hz), 7.36 (d, 1H, $J = 8.5$ Hz), 7.76 (dd, 1H, $J = 8.5$ and 2.2 Hz), 7.92 (m, 1H), 7.97 (d, 1H, $J = 9.5$ Hz) and 9.55 (s, 1H); ES-MS m/z 238 ((M + H)⁺), 236 ((M – H)[–]).

6-(4-Hydroxyphenyl)-1H-quinolin-2-one (9{3,1,1}). ¹H NMR (500 MHz, DMSO) δ 6.51 (d, 1H, $J = 9.5$ Hz), 6.85 (m, 2H), 7.33 (d, 1H, $J = 8.5$ Hz), 7.51 (m, 2H), 7.74 (dd, 1H, $J = 8.5$ and 1.9 Hz), 7.87 (m, 1H), 7.94 (d, 1H, $J = 9.5$ Hz) and 9.56 (s, 1H); ES-MS m/z 238 ((M + H)⁺), 236 ((M – H)[–]).

6-(2-Propoxyphenyl)-1H-quinolin-2-one (9{1,2,I}). ¹H NMR (500 MHz, CDCl₃) δ 0.96 (t, 3H, *J* = 7.6 Hz), 1.74 (m, 2H), 3.96 (t, 2H, *J* = 6.3 Hz), 6.90 (d, 1H, *J* = 9.1 Hz), 7.01 (dd, 1H, *J* = 8.8 and 1.0 Hz), 7.06 (m, 1H), 7.36 (m, 1H), 7.37 (d, 1H, *J* = 7.6 Hz), 7.60 (d, 1H, *J* = 8.5 Hz), 7.88 (d, 1H, *J* = 1.9 Hz), 7.94 (dd, 1H, *J* = 8.5 and 1.9 Hz) and 8.13 (d, 1H, *J* = 9.5 Hz); ES-MS *m/z* 280 ((M + H)⁺), 278 ((M - H)⁻).

6-(3-Propoxyphenyl)-1H-quinolin-2-one (9{2,2,I}). ¹H NMR (500 MHz, CDCl₃) δ 1.07 (t, 3H, *J* = 7.3 Hz), 1.86 (m, 2H), 4.01 (t, 2H, *J* = 6.6 Hz), 6.91 (d, 1H, *J* = 9.5 Hz), 6.94 (dd, 1H, *J* = 8.5 and 2.8 Hz), 7.15 (m, 1H), 7.19 (m, 1H), 7.39 (t, 1H, *J* = 7.9 Hz), 7.61 (d, 1H, *J* = 9.1 Hz), 7.89–7.91 (m, 2H) and 8.13 (d, 1H, *J* = 9.5 Hz); ES-MS *m/z* 280 ((M + H)⁺), 278 ((M - H)⁻).

6-(4-Propoxyphenyl)-1H-quinolin-2-one (9{3,2,I}). ¹H NMR (500 MHz, CDCl₃) δ 1.07 (t, 3H, *J* = 7.3 Hz), 1.85 (m, 2H), 3.98 (t, 2H, *J* = 6.6 Hz), 6.80 (d, 1H, *J* = 9.5 Hz), 7.00 (m, 2H), 7.50 (d, 1H, *J* = 8.2 Hz), 7.54 (m, 2H), 7.75–7.78 (m, 2H) and 7.95 (d, 1H, *J* = 9.5 Hz); ES-MS *m/z* 280 ((M + H)⁺), 278 ((M - H)⁻).

6-(2-Benzyloxyphenyl)-1H-quinolin-2-one (9{1,3,I}). ¹H NMR (500 MHz, CDCl₃) δ 5.11 (s, 2H), 6.83 (d, 1H, *J* = 9.5 Hz), 7.07–7.11 (m, 2H), 7.27–7.40 (m, 7H), 7.52 (d, 1H, *J* = 8.5 Hz), 7.85 (m, 1H), 7.88 (dd, 1H, *J* = 8.5 and 1.9 Hz) and 7.98 (d, 1H, *J* = 9.5 Hz); ES-MS *m/z* 328 ((M + H)⁺), 326 ((M - H)⁻).

6-(3-Benzyloxyphenyl)-1H-quinolin-2-one (9{2,3,I}). ¹H NMR (500 MHz, CDCl₃) δ 5.15 (s, 2H), 6.79 (d, 1H, *J* = 9.5 Hz), 7.00 (dd, 1H, *J* = 8.5 and 2.8 Hz), 7.21–7.24 (m, 2H), 7.33–7.43 (m, 3H), 7.45–7.49 (m, 4H), 7.76–7.79 (m, 2H) and 7.92 (d, 1H, *J* = 9.5 Hz); ES-MS *m/z* 328 ((M + H)⁺), 326 ((M - H)⁻).

6-(4-Benzyloxyphenyl)-1H-quinolin-2-one (9{3,3,I}). ¹H NMR (500 MHz, CDCl₃) δ 5.13 (s, 2H), 6.84 (d, 1H, *J* = 9.5 Hz), 7.09 (m, 2H), 7.35 (m, 1H), 7.39–7.43 (m, 2H), 7.45–7.48 (m, 2H), 7.52–7.57 (m, 3H), 7.78–7.82 (m, 2H) and 7.98 (d, 1H, *J* = 9.5 Hz); ES-MS *m/z* 328 ((M + H)⁺), 326 ((M - H)⁻).

Thiophene-2-carboxylic Acid 2-(2-oxo-1,2-dihydroquinolin-6-yl)-phenyl Ester (9{1,4,I}). ¹H NMR (500 MHz, CDCl₃) δ 6.82 (d, 1H, *J* = 9.5 Hz), 7.10 (dd, 1H, *J* = 5.0 and 3.8 Hz), 7.34 (dd, 1H, *J* = 7.9 and 1.0 Hz), 7.40 (m, 1H), 7.46 (dd, 1H, *J* = 7.9 and 1.9 Hz), 7.48–7.51 (m, 2H), 7.60 (dd, 1H, *J* = 5.0 and 1.3 Hz), 7.78–7.82 (m, 3H) and 7.98 (d, 1H, *J* = 9.5 Hz); ES-MS *m/z* 348 ((M + H)⁺), 346 ((M - H)⁻).

Thiophene-2-carboxylic Acid 3-(2-oxo-1,2-dihydroquinolin-6-yl)-phenyl Ester (9{2,4,I}). ¹H NMR (500 MHz, CDCl₃) δ 6.91 (d, 1H, *J* = 9.5 Hz), 7.21 (dd, 1H, *J* = 5.0 and 3.8 Hz), 7.27 (m, 1H), 7.50 (m, 1H), 7.52–7.56 (m, 2H), 7.60 (d, 1H, *J* = 8.5 Hz), 7.70 (dd, 1H, *J* = 5.0 and 1.3 Hz), 7.87–7.90 (m, 2H), 8.02 (dd, 1H, *J* = 3.8 and 1.3 Hz) and 8.10 (d, 1H, *J* = 9.5 Hz); ES-MS *m/z* 348 ((M + H)⁺), 346 ((M - H)⁻).

Thiophene-2-carboxylic Acid 4-(2-oxo-1,2-dihydroquinolin-6-yl)-phenyl Ester (9{3,4,I}). ¹H NMR (500 MHz, CDCl₃) δ 6.92 (d, 1H, *J* = 9.5 Hz), 7.21 (dd, 1H, *J* = 5.0 and 3.8 Hz), 7.35 (m, 2H), 7.62 (d, 1H, *J* = 9.1 Hz), 7.67 (m, 2H), 7.70 (dd, 1H, *J* = 5.0 and 1.0 Hz), 7.88–7.91 (m, 2H), 8.02 (dd, 1H, *J* = 3.8 and 1.3 Hz) and 8.14 (d, 1H, *J* = 9.5 Hz); ES-MS *m/z* 348 ((M + H)⁺), 346 ((M - H)⁻).

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