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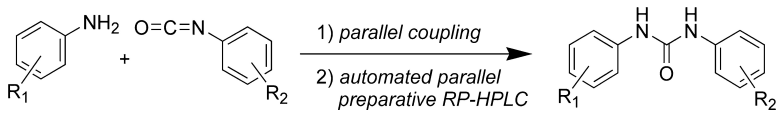

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Parallel Synthesis of Diarylureas and Their Evaluation as Inhibitors of Insulin-Like Growth Factor Receptor

Marc O. Anderson,[†] Hong Yu,[†] Cristina Penaranda,[‡] Betty A. Maddux,[‡] Ira D. Goldfine,[‡] Jack F. Youngren,[‡] and R. Kiplin Guy*[,†,§]

Department of Pharmaceutical Chemistry, University of California, Box 2280, San Francisco, California 94143-2280, Diabetes and Endocrine Research, University of California, Box 1616, San Francisco, California 94143-1616, and Department of Cellular and Molecular Pharmacology, University of California, San Francisco, Box 2280, California 94143-2280

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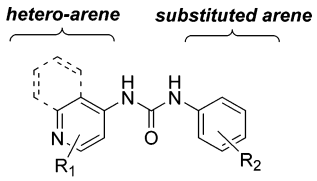
Diarylurea (DAU) compounds, particularly species composed of a heteroaryl ring system conjugated through a urea linkage to a substituted arene, were previously identified by the screening of a diverse chemical library to be active against the insulin growth factor receptor (IGF-1R). DAU compounds **4**{*a*,*b*} were synthesized in parallel by the coupling of aryl amines **2**{*a*} with aryl isocyanates **3**{*b*}. Preparative RP-HPLC purification was found necessary to remove an impurity **5**{*b*}, the symmetric urea resulting from the hydrolytic degradation of aryl isocyanates. Two libraries of DAU compounds were prepared to perform preliminary optimization of the two-ring systems for inhibitory activity against IGF-1R. In the first library, we explored a series of heteroaryl ring systems and found the 4-aminoquinaldine ring system to be optimal among those evaluated. The second library fixed the 4-aminoquinaldine ring system and we evaluated a series of substituted arenes conjugated to it. Overall, eight compounds based on the 4-aminoquinaldine heteroaryl system were found to have moderate activity against IGF-1R with IC_{50} values better than 40 μM.

Introduction

The insulin-like growth factor (IGF) system is an attractive target for the development of new anticancer drugs. The IGF system is composed of two ligands, IGF-1 and IGF-2, as well as the IGF receptor (IGF-1R), which is a member of the superfamily of transmembrane receptor tyrosine kinases and IGF binding proteins. The IGF system plays a critical role in essentially all stages of the development of breast and other cancers, including malignant transformation, mitogenic growth, and antiapoptotic mechanisms.[1−3] Several approaches have been studied to inhibit the IGF system, including suppression of IGF-1,[4−6] as well as the development of inhibitors of IGF-1R.[7−9] It is our goal to identify novel inhibitors of the IGF-1R. An initial screen of a diverse chemical library indicated that some diarylureas (DAUs) acted as dose-dependent inhibitors of IGF-1R in MCF-7 human breast cancer cells.[10] The general structure of DAU compounds active against IGF-1R appeared to consist of a heteroaryl ring system conjugated via a urea linkage to a substituted arene (**1**). Herein, we describe a parallel synthetic approach to generate libraries of DAUs along with preliminary results attempting to optimize DAU compounds for inhibitory activity against IGF-1R.

Results

DAUs **4**{*a*,*b*} can be prepared by the coupling of aryl amines **2**{*a*} with aryl isocyanates **3**{*b*}[11] (Figure 1). To increase throughput of this reaction and allow a feasible parallel approach, it was envisioned that the use of nucleophilic or electrophilic scavenger resins to consume excess reagents could be carried out to generate products sufficiently pure for screening without further purification[12−14] (eq 1). However, a potential barrier to implementation of this strategy was the well-known degradation of aryl isocyanates that leads to formation of an undesired symmetrical urea species (eq 2). Our initial studies revealed that this degradation pathway occurs readily for most aryl isocyanates, even during storage of the commercially obtained materials. Common scavenger resin strategies are unable to remove the resulting symmetrical urea from the desired asymmetrical urea. Thus, it was determined that chromatographic purification of the final products was unavoidable. Specifically, the products were purified by automated parallel RP-HPLC, done in an acceptable level of throughput to allow library synthesis of these compounds (eq 3). To solve the common problem of organic urea insolubility, the reactions were carried out in DMSO, which can be conveniently directly loaded into a preparative RP-HPLC instrument.



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An initial library of DAUs was designed to probe variation of the heteroaryl portion of the DAU structure for activity against IGF-1R (Figure 2). In examining the initial screening

* To whom correspondence should be addressed. E-mail: kip.guy@stjude.org.
[†] Department of Pharmaceutical Chemistry.
[‡] Diabetes and Endocrine Research.
[§] Department of Cellular and Molecular Pharmacology.

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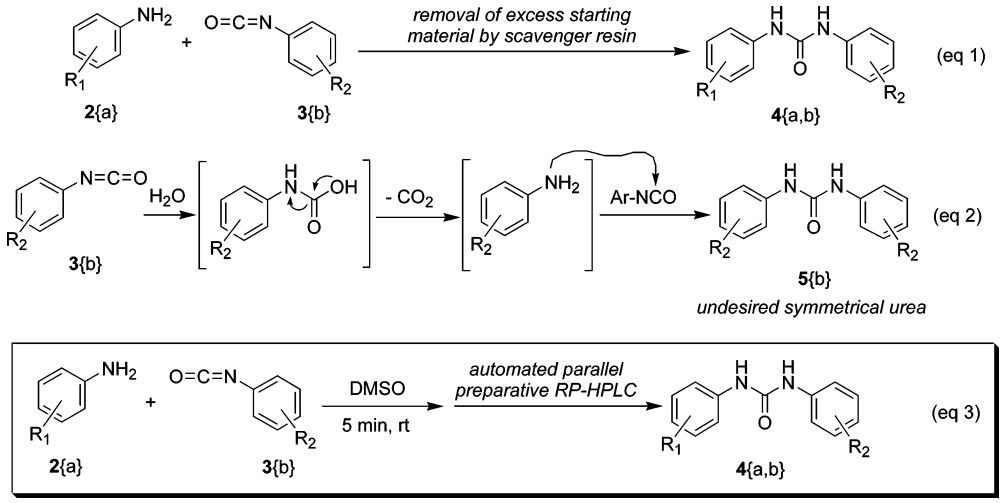

Figure 1. Parallel synthesis of diarylureas.

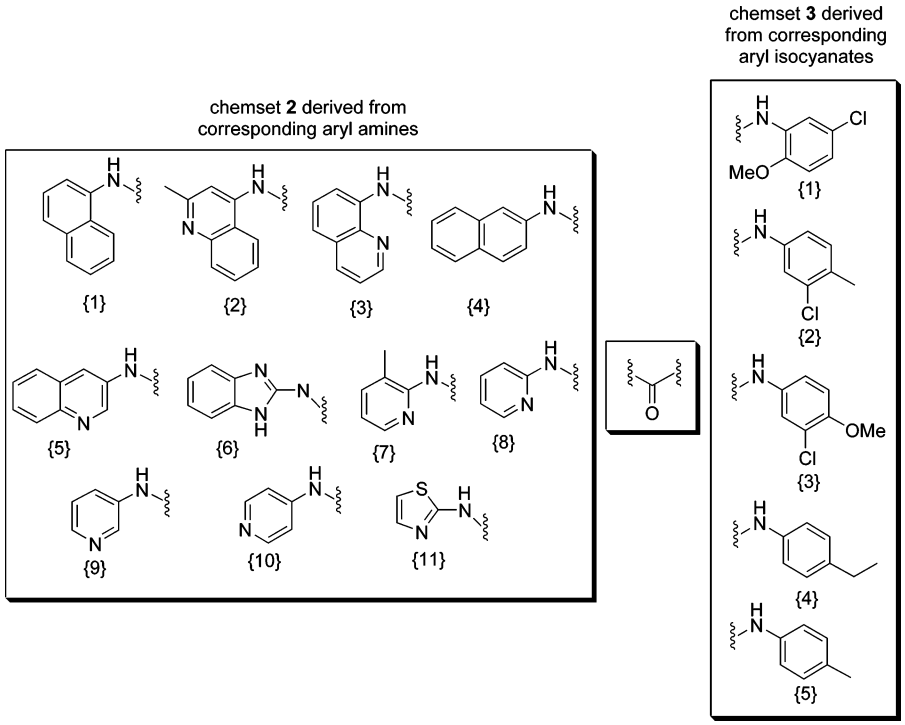

Figure 2. Initial DAU library design.

data against IGF-1R, we assumed that the two aryl systems of the molecule could be optimized independently. Thus, a variety of monocyclic and bicyclic ring systems **2**{*1*−*11*} were conjugated to a simple set of commercially available aryl isocyanates **3**{*1*−*5*} to generate a library of the corresponding DAU species **4**{*1*−*11*,*1*−*5*}.

The results of the synthesis of initial library are outlined in Table 1. The final product yields varied greatly from very low to excellent, yet overall the yields at this scale (10-mg) generated quantities acceptable for preliminary screening. The purity of the post-HPLC products was fairly high (>85%), with the only impurity being symmetrical diaryl urea **5**{*b*} (0−10% in most cases) generated from decomposition of the aryl isocyanate (Figure 1, eq 2). Both the often toxic aryl amine starting and reactive electophilic materials were always removed by the purification strategy. RP-HPLC/MS analysis confirmed the identity of all products (Table S1, Supporting Information), and ^{1}H NMR analysis was also performed on a subset of the library. The library was screened for inhibitory activity against IGF-1R in CHO cells transfected with and overexpressing the human IGF-1R (CHOIGF-1R). The results shown in Table 1 are represented as the percent of IGF-1R autophosphorylation in the presence of compound (at 30 μM), as compared to the vehicle-treated control. Of these library members, only **4**{*2,1*} and **4**{*2,3*}, both containing the 4-aminoquinaldine ring system **2**{*2*}, appeared to have promising inhibitory activity of IGF-1R at this concentration. Interestingly, several entries containing 2- and 3-pyridyl rings (among entries 31−45) appeared to have an agonistic effect on the receptor, with a notable increase in observed IGF-1R autophosphorylation. Although agonists of tyrosine kinase receptors are uncommon, we have previously reported on a small molecule sensitizer of the highly homologous insulin receptor.[15]

Of the heterocyclic scaffolds evaluated in the initial library, the 4-aminoquinaldine-derived DAUs, based on aryl amine

Table 1. Initial Library Results

entry	aryl amine	aryl isocyanate	product	purified yield, % (UV_{254} purity),	IGF-1R Tyr-autophosphorylation relative to control, % (30 μM compound)
1	**2**{*1*}	**3**{*1*}	**4**{*1,1*}	86 (90)	104
2	**2**{*1*}	**3**{*2*}	**4**{*1,2*}	41 (85)	119
3	**2**{*1*}	**3**{*3*}	**4**{*1,3*}	65 (100)	100
4	**2**{*1*}	**3**{*4*}	**4**{*1,4*}	100 (88)	97
5	**2**{*1*}	**3**{*5*}	**4**{*1,5*}	61 (95)	112
6	**2**{*2*}	**3**{*1*}	**4**{*2,1*}	31 (100)	33
7	**2**{*2*}	**3**{*2*}	**4**{*2,2*}	20 (98)	106
8	**2**{*2*}	**3**{*3*}	**4**{*2,3*}	98 (100)	61
9	**2**{*2*}	**3**{*4*}	**4**{*2,4*}	100 (100)	74
10	**2**{*2*}	**3**{*5*}	**4**{*2,5*}	100 (100)	96
11	**2**{*3*}	**3**{*1*}	**4**{*3,1*}	100 (100)	108
12	**2**{*3*}	**3**{*2*}	**4**{*3,2*}	96 (92)	98
13	**2**{*3*}	**3**{*3*}	**4**{*3,3*}	56 (100)	92
14	**2**{*3*}	**3**{*4*}	**4**{*3,4*}	78 (100)	95
15	**2**{*3*}	**3**{*5*}	**4**{*3,5*}	91 (94)	95
16	**2**{*4*}	**3**{*1*}	**4**{*4,1*}	15 (90)	80
17	**2**{*4*}	**3**{*2*}	**4**{*4,2*}	16 (100)	96
18	**2**{*4*}	**3**{*3*}	**4**{*4,3*}	46 (88)	110
19	**2**{*4*}	**3**{*4*}	**4**{*4,4*}	25 (100)	101
20	**2**{*4*}	**3**{*5*}	**4**{*4,5*}	46 (93)	104
21	**2**{*5*}	**3**{*1*}	**4**{*5,1*}	40 (100)	103
22	**2**{*5*}	**3**{*2*}	**4**{*5,2*}	24 (100)	96
23	**2**{*5*}	**3**{*3*}	**4**{*5,3*}	28 (100)	116
24	**2**{*5*}	**3**{*4*}	**4**{*5,4*}	19 (100)	108
25	**2**{*5*}	**3**{*5*}	**4**{*5,5*}	26 (100)	109
26	**2**{*6*}	**3**{*1*}	**4**{*6,1*}	75 (100)	111
27	**2**{*6*}	**3**{*2*}	**4**{*6,2*}	42 (100)	103
28	**2**{*6*}	**3**{*3*}	**4**{*6,3*}	58 (100)	108
29	**2**{*6*}	**3**{*4*}	**4**{*6,4*}	51 (100)	110
30	**2**{*6*}	**3**{*5*}	**4**{*6,5*}	60 (100)	101
31	**2**{*7*}	**3**{*1*}	**4**{*7,1*}	12 (100)	120
32	**2**{*7*}	**3**{*2*}	**4**{*7,2*}	6 (100)	121
33	**2**{*7*}	**3**{*3*}	**4**{*7,3*}	6 (100)	129
34	**2**{*7*}	**3**{*4*}	**4**{*7,4*}	7 (100)	100
35	**2**{*7*}	**3**{*5*}	**4**{*7,5*}	7 (95)	129
36	**2**{*8*}	**3**{*1*}	**4**{*8,1*}	6 (100)	101
37	**2**{*8*}	**3**{*2*}	**4**{*8,2*}	7 (100)	134
38	**2**{*8*}	**3**{*3*}	**4**{*8,3*}	6 (100)	136
39	**2**{*8*}	**3**{*4*}	**4**{*8,4*}	7 (100)	129
40	**2**{*8*}	**3**{*5*}	**4**{*8,5*}	7 (100)	138
41	**2**{*9*}	**3**{*1*}	**4**{*9,1*}	64 (100)	115
42	**2**{*9*}	**3**{*2*}	**4**{*9,2*}	53 (100)	140
43	**2**{*9*}	**3**{*3*}	**4**{*9,3*}	38 (100)	97
44	**2**{*9*}	**3**{*4*}	**4**{*9,4*}	56 (100)	139
45	**2**{*9*}	**3**{*5*}	**4**{*9,5*}	37 (100)	97
46	**2**{*10*}	**3**{*1*}	**4**{*10,1*}	19 (100)	98
47	**2**{*10*}	**3**{*2*}	**4**{*10,2*}	27 (98)	100
48	**2**{*10*}	**3**{*3*}	**4**{*10,3*}	19 (100)	94
49	**2**{*10*}	**3**{*4*}	**4**{*10,4*}	14 (100)	118
50	**2**{*10*}	**3**{*5*}	**4**{*10,5*}	15 (100)	105
51	**2**{*11*}	**3**{*1*}	**4**{*11,1*}	31 (100)	105
52	**2**{*11*}	**3**{*2*}	**4**{*11,2*}	13 (100)	87
53	**2**{*11*}	**3**{*3*}	**4**{*11,3*}	19 (100)	114
54	**2**{*11*}	**3**{*4*}	**4**{*11,4*}	14 (100)	109
55	**2**{*11*}	**3**{*5*}	**4**{*11,5*}	22 (57)	96

species **2**{*2*}, appeared to have the most promising inhibitory activity against IGF-1R. Thus, a follow-up library was designed utilizing only the 4-aminoquinaldine heterocycle, but with greater diversity in the substituted arene portion of the molecule (Figure 3). Although a variety of substituted aryl amines are commercially available, a smaller selection of substituted aryl isocyanates can be purchased. Because of this, it was convenient to couple the components of the follow-up library in a manner opposite to the initial library. Namely, a series of substituted aryl amines **2**{*12*−*48*} was coupled to 4-aminoquinaldine isocyanate **3**{*6*} to generate the follow-up library of DAUs **4**{*12*−*48,6*}. Aryl isocyanate **3**{*6*} was readily generated by treatment of 4-aminoquinaldine with 1,1′-carbonyldiimidazole.

The results of the synthesis of the follow-up library are outlined in Table 2. The yields obtained in the follow-up library were overall satisfactory and consistent with those obtained in the initial library. Inhibitory activity of these compounds (fixed at 30 uM) relative to the vehicle-treated control, was also measured against IGF-1R using the same method employed in the initial library. Notably, several compounds with promising activity at this concentration were discovered: **4**{*25,6*}, **4**{*27,6*}, **4**{*28,6*}, **4**{*35,6*}, **4**{*39,6*}, and **4**{*45,6*}.

IC_{50}'s (50% inhibitory concentrations) were determined for the most promising compounds of the initial and follow-up libraries (Figure 4). The DAU concentrations used in the initial 30 μM fixed-concentration screening results (Tables 1 and 2) were estimated from the isolated mass of the RP-HPLC purified compounds. To derive meaningful dose−response curves, we considered alternative techniques in quantifying these compounds. The reasons for this are the relatively small masses of the library components (<10 mg) coupled with the physically isomorphic species commonly produced in library synthesis, which often hinders quantitative solvent removal (particularly water).[16,17] Thus, the technique of chemiluminescent nitrogen detection (CLND) was employed,[18] which has been shown to be useful for quantifying compounds in library synthesis.[16,17] In our own experience, as well as other published reports,[16−18] CLND gives a degree of error (±10%) that we think is generally acceptable for preliminary characterization of biological responses, including IC_{50}'s.

The compounds in Figure 4 are grouped according to similar substituent patterns found in the substituted aromatic rings. From these results, some preliminary structure−activity information was derived for 4-aminoquinaldine-derived DAUs that are active against IGF-1R. Entries **4**{*2,1*} and **4**{*2,3*} show activity in ortho/meta- and para/meta-disubstituted arenes. These compounds have a meta-chloro group in the presence of either ortho- or para-methoxy groups. The remaining promising compounds were all ortho- or para-monosubstituted arenes. Compounds **4**{*27,6*}, **4**{*28,6*}, and **4**{*25,6*} contain O- and S- linked electron-withdrawing trifluoromethyl groups, whereas the electronically distinct compounds **4**{*2,4*}, **4**{*39,6*}, and **4**{*45,6*} also displayed promising activity. Two ortho-substituted compounds were evaluated: **4**{*25,6*} and **4**{*35,6*}. In both cases, the para-monosubstituted compounds were more potent than the analogous ortho-monosubstituted compounds. Overall, the electronic diversity of the phenyl substituents in the series of compounds is notable, suggesting that steric interactions in the active site of IGF-1R may be more important than electronics in regulating the inhibitory activity of these compounds.

Conclusion

A parallel synthetic scheme to generate libraries of diarylureas (DAUs) was described. Preparative RP-HPLC purification was required to generate compounds of high

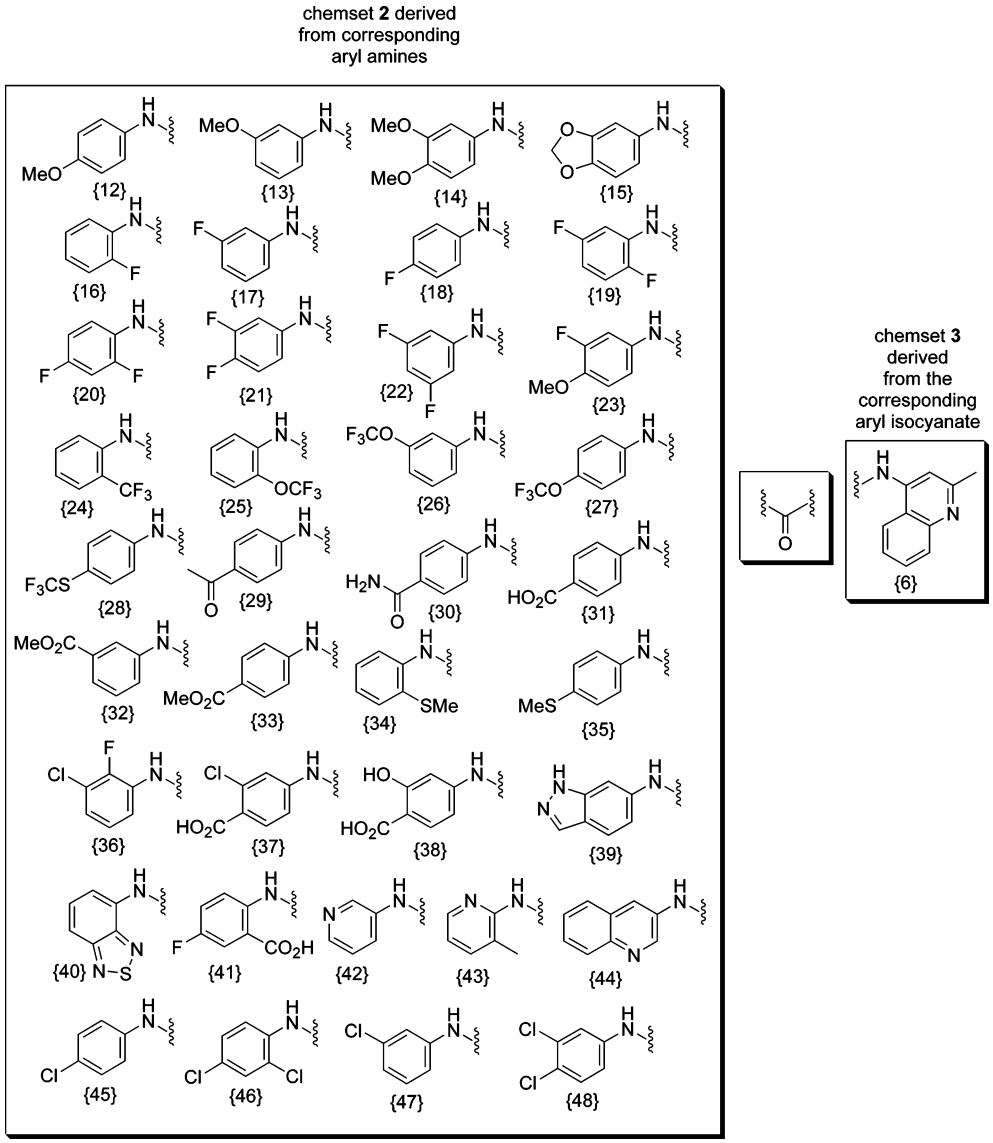

Figure 3. Follow-up DAU library design.

purity, and yields were acceptable in all cases for biological screening purposes. Two libraries of DAU compounds were prepared in an attempt to optimize the two aryl ring systems of DAU compounds for inhibitory activity against a model of human IGF-1R. The first library was designed to examine a series of heteroaryl ring systems, which found the 4-aminoquinaldine ring system to be optimal among those evaluated. The second library was designed to hold the 4-aminoquinaldine system constant while varying a series of substituted arenes. Overall, nine compounds were shown to be moderately active against IGF-1R, with IC_{50} values <40 μM.

Experimental Section

General. Crude and final product analytical RP-HPLC/ESI-MS was carried out on a Waters 2695 Separations Module coupled to a Waters Micromass ZQ system, with UV/PDA detection, using the gradient H_2O/CH_3CN (0.05% CF_3CO_2H) 100:0 to 50:50 (over 1 min), and then 50:50 to 0:100 (over 6 min). Preparative RP-HPLC was carried out on an four-channel Biotage Parallel Flex system with dual-wavelength UV detection (219, 254 nm) using the gradient H_2O/CH_3CN (0.05% CF_3CO_2H) 100:0 to 70:30 (over 5 min), 70:30 to 50:50 (over 5 min), and then 50:50 to 0:100 (over 1 min). NMR spectra were recorded on a Varian model AS 400-MHz machine. The following abbreviations are used to describe peak splitting when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, bs =broad singlet, mult = multiplet. Reagents were of commercial quality unless otherwise indicated.

Measurement of in Vitro Activity against IGF-1R. Assays were conducted with CHO cells transfected with and overexpressing the human IGF-1R.[15] For the screening, CHOIGF-1R cells were plated in 96-well plates at a density of 20 000 cells/well in Ham's F-12 medium supplemented with glutamine (2 mM), fungizone (2.5 ug/mL), penicillin (100 U/mL), streptomycin (100 mcg/mL), and 10% fetal bovine serum. After 24 h, cells were serum-starved for 2 h. DAU compounds were dissolved in DMSO and diluted with serum-free culture medium before being added to cells for 1 h at 37 °C. The final concentration of DMSO during the incubation was 1%. Cells were then stimulated with 3 nM IGF-I diluted in serum-free culture medium containing 0.35% BSA for 10 min at 37 °C. Reactions were terminated by washing cells two times with ice-cold PBS. Cells were

Table 2. Follow-up DAU Library Results

entry	aryl amine	aryl isocyanate	product	purified yield, % (UV_{254} purity)	IGF-1R Tyr-autophosphorylation relative to control, % (30 μM compound)
1	**2**{*12*}	**3**{*6*}	**4**{*12,6*}	48 (100)	95
2	**2**{*13*}	**3**{*6*}	**4**{*13,6*}	36 (100)	100
3	**2**{*14*}	**3**{*6*}	**4**{*14,6*}	39 (100)	102
4	**2**{*15*}	**3**{*6*}	**4**{*15,6*}	23 (100)	102
5	**2**{*16*}	**3**{*6*}	**4**{*16,6*}	31 (100)	101
6	**2**{*17*}	**3**{*6*}	**4**{*17,6*}	31 (100)	93
7	**2**{*18*}	**3**{*6*}	**4**{*18,6*}	37 (100)	106
8	**2**{*19*}	**3**{*6*}	**4**{*19,6*}	35 (100)	101
9	**2**{*20*}	**3**{*6*}	**4**{*20,6*}	18 (100)	103
10	**2**{*21*}	**3**{*6*}	**4**{*21,6*}	29 (98)	118
11	**2**{*22*}	**3**{*6*}	**4**{*22,6*}	23 (100)	98
12	**2**{*23*}	**3**{*6*}	**4**{*23,6*}	17 (100)	96
13	**2**{*24*}	**3**{*6*}	**4**{*24,6*}	33 (100)	99
14	**2**{*25*}	**3**{*6*}	**4**{*25,6*}	16 (91)	7
15	**2**{*26*}	**3**{*6*}	**4**{*26,6*}	32 (100)	96
16	**2**{*27*}	**3**{*6*}	**4**{*27,6*}	32 (100)	11
17	**2**{*28*}	**3**{*6*}	**4**{*28,6*}	25 (100)	4
18	**2**{*29*}	**3**{*6*}	**4**{*29,6*}	29 (100)	99
19	**2**{*30*}	**3**{*6*}	**4**{*30,6*}	52 (100)	102
20	**2**{*31*}	**3**{*6*}	**4**{*31,6*}	29 (100)	110
21	**2**{*32*}	**3**{*6*}	**4**{*32,6*}	33 (100)	101
22	**2**{*33*}	**3**{*6*}	**4**{*33,6*}	22 (100)	60
23	**2**{*34*}	**3**{*6*}	**4**{*34,6*}	29 (99)	73
24	**2**{*35*}	**3**{*6*}	**4**{*35,6*}	29 (93)	8
25	**2**{*36*}	**3**{*6*}	**4**{*36,6*}	22 (100)	110
26	**2**{*37*}	**3**{*6*}	**4**{*37,6*}	11 (100)	103
27	**2**{*38*}	**3**{*6*}	**4**{*38,6*}	22 (100)	102
28	**2**{*39*}	**3**{*6*}	**4**{*39,6*}	23 (100)	12
29	**2**{*40*}	**3**{*6*}	**4**{*40,6*}	11 (100)	109
30	**2**{*41*}	**3**{*6*}	**4**{*41,6*}	50 (100)	100
31	**2**{*42*}	**3**{*6*}	**4**{*42,6*}	45 (100)	91
32	**2**{*43*}	**3**{*6*}	**4**{*43,6*}	25 (100)	111
33	**2**{*44*}	**3**{*6*}	**4**{*44,6*}	34 (100)	101
34	**2**{*45*}	**3**{*6*}	**4**{*45,6*}	21 (92)	34
35	**2**{*46*}	**3**{*6*}	**4**{*46,6*}	27 (95)	84
36	**2**{*47*}	**3**{*6*}	**4**{*47,6*}	34 (90)	99
37	**2**{*48*}	**3**{*6*}	**4**{*48,6*}	16 (95)	99

harvested and solubilized in 200 μL of solubilization buffer (50 mM HEPES pH 7.4, 150 mM NaCl, 1% Triton X-100, 1 mM PMSF, and 2 mM vanadate) by freezing the plate for 30 min at −80 °C and thawing for 1 h at 4 °C.

IGF-1R autophosphorylation was determined by ELISA. Briefly, 100 μL of lysate was added to triplicate wells in a 96-well plate coated with 2 μg/mL of αIR3, a monoclonal antibody to the IGF-IR,[19] and incubated 18 h at 4 °C. Plates were washed five times with TBST (20 mM Tris, pH 7.6, 150 mM NaCl, 0.05% Tween-20) and then incubated with HRP-conjugated anti-phosphotyrosine antibody (0.1 μg/mL, Santa Cruz Biotechnology) diluted in solution B (50 mM HEPES pH 7.6, 150 mM NaCl, 0.05% Tween-20, 1% BSA, 1 mM PMSF, 2 mM vanadate, and 1 mg/mL bacitracin) for 2 h at 22 °C. Plates were washed five times with TBST prior to color development with TMB substrate, which was terminated with 1.0 M H_3PO_4. Values for receptor autophosphorylation were determined by measuring absorbance at 450 nm.

General Procedure for the Synthesis of the Diarylurea Chemset 4{*a,b*}. DMSO stock solutions (0.2 M) of all aryl amines **2**{*a*} and aryl isocyanates **3**{*b*} were freshly prepared, stored over 3-Å molecular sieves, and used quickly after preparation. The coupling reaction was carried out in 96-well, polypropylene, deep-well (1.8 mL) plates, which also served as the loading vessels for preparative RP-HPLC purification. To the wells of a 96-well plate were added each of the aryl amines (0.26 mL, 0.2 M in DMSO, 0.052 mmol), followed by each of the aryl isocyanates (0.2 mL, 0.2 M in DMSO, 0.04 mmol). The plate was covered with covered with Parafilm, and carefully agitated on a laboratory vortex

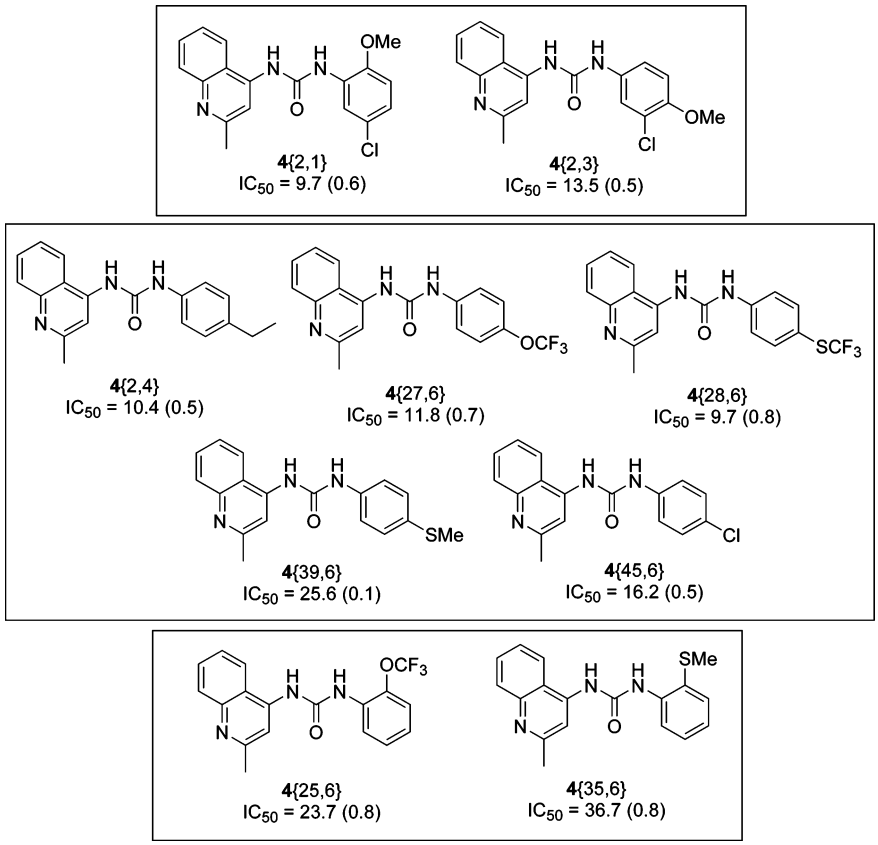

Figure 4. IC_{50} values for initial and follow-up library hits against IGF-1R (standard deviations in paranthesis).

for 5 min. Samples for RP-HPLC/ESI-MS analysis were prepared by extracting aliquots from the crude reaction mixture plate (5 μL each) and diluting each with DMSO (100 μL). Crude RP-HPLC/ESI-MS generally showed the presence of product **4**{*a*,*b*} as well as varying amounts of the undesired symmetrical diarylurea **5**{*b*}. The crude reaction mixtures were purified by parallel preparative RP-HPLC. The purified fractions were concentrated in vacuo on a GeneVac HT4-1200 system, redissolved in THF, combined, and concentrated in vacuo using a GeneVac HT-4 parallel evaporation system. A final round of analysis was performed by HPLC/ESI-MS before samples were prepared for biological screening (30 mM in DMSO).

Generation of 4-Aminoquinaldine Isocyanate 3{*6*}. A solution of 4-aminoquinaldine (0.405 g, 2.2 mmol) in DMSO (11.0 mL) was treated with 1,1′-carbonyldiimidazole (0.463 g, 2.86 mmol). The solution was stirred under argon for 2 h and then used directly as a stock solution (0.2 M in DMSO) for DAU library synthesis using the procedure described above.

1-(5-Chloro-2-methoxyphenyl)-3-naphthalen-1-ylurea 4{*1,1*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.92 (s, 3H), 6.98 (dd, 1H, J = 2, 8 Hz), 7.05 (d, 1H, J = 8 Hz), 7.43−7.67 (mult, 4H), 7.93 (d, 1H, J = 8 Hz), 8.01 (d, 1H, J = 8 Hz), 8.19 (d, 1H, J = 8 Hz), 8.25−8.30 (mult, 1H), 8.93 (bs, 1H), 9.39 (bs, 1H).

1-(3-Chloro-4-methylphenyl)-3-naphthalen-1-ylurea 4-{*1,2*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 7.24 (dd, 2H, J = 3, 9 Hz), 7.46−7.66 (mult, 4H), 7.73−7.77 (mult, 1H), 7.95 (dd, 2H, J = 2,8 Hz), 8.10 (d, 1H, J = 8 Hz), 8.79 (bs, 1H), 9.13 (bs, 1H).

1-(3-Chloro-4-methoxyphenyl)-3-naphthalen-1-ylurea 4{*1,3*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.77 (s, 3H), 7.06 (d, 1H, J = 9 Hz), 7.24 (dd, 1H, J = 3, 9 Hz), 7.41−7.61 (mult, 4H), 7.68 (d, 1H, J = 2 Hz), 7.89 (d, 1H, J = 8 Hz), 7.92 (d, 1H, J = 7 Hz), 8.06 (d, 1H, J = 8 Hz), 8.70 (bs, 1H), 8.97 (bs, 1H).

1-(4-Ethylphenyl)-3-naphthalen-1-ylurea 4{*1,4*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, 3H, J = 8 Hz), 2.56 (q, 2H, J = 7 Hz), 7.14 (d, 2H, J = 8 Hz), 7.40−7.64 (mult, 6H), 7.93 (d, 1H, J = 8 Hz), 8.02 (d, 1H, J = 8 Hz), 8.12 (d, 1H, J = 8 Hz), 8.71 (bs, 1H), 8.96 (bs, 1H).

1-(5-Chloro-2-methoxyphenyl)-3-(2-methylquinolin-4-yl)-urea 4{*2,1*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.44 (s, 3H), 3.89 (s, 3H), 6.87−7.05 (mult, 2H), 7.51−7.54 (mult, 1H), 7.64−7.67 (mult, 1H), 7.82−7.83 (mult, 1H), 8.08−8.14 (mult, 1H), 8.18−8.25 (mult, 2H), 8.20 (s, 1H), 9.66 (s, 1H).

1-(3-Chloro-4-methylphenyl)-3-(2-methyquinolin-4-yl)-urea 4{*2,2*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H), 7.15 (d, 1H, J = 9 Hz), 7.26 (d, 1H, J = 9 Hz), 7.36−7.39 (mult, 1H), 7.61−7.62 (mult, 1H), 7.70 (s, 1H), 8.07−8,18 (mult, 2H), 8.39 (s, 1H), 9.14 (bs, 1H), 9.50 (bs, 1H).

1-(4-Ethylphenyl)-3-(2-methylquinolin-4-yl)-urea 4{*2,4*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.17 (t, 3H, J = 8 Hz), 2.58 (q, 2H, J = 8 Hz), 2.81 (s, 3H), 7.21 (d, 2H, J = 8 Hz), 7.47 (d, 2H, J = 8 Hz), 7.84−7.88 (mult, 1H), 8.04−8.07 (mult, 2H), 8.48 (bs, 1H), 8.49−8.52 (mult, 2H), 9.82 (bs, 1H).

1-(3-Chloro-4-methylphenyl)-3-quinolin-8-ylurea 4{*3,2*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 7.21−7.30 (mult, 2H), 7.56 (d, 2H, J = 4 Hz), 7.64 (dd, 1H, J = 4, 8 Hz), 7.77 (s, 1H), 8.40 (d, 1H, J = 5 Hz), 8.54 (t, 1H, J = 4 Hz), 8.90−8.94 (mult, 1H), 9.69 (bs, 1H), 9.95 (bs, 1H).

1-(3-Chloro-4-methoxyphenyl)-3-quinolin-8-ylurea 4-{*3,3*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H), 7.11 (d, 1H, J = 8 Hz), 7.32 (dd, 1H, J = 2, 8 Hz), 7.55 (d, 2H, J = 4 Hz), 7.63 (dd, 1H, J = 4, 8 Hz), 7.74 (d, 1H, J = 2 Hz), 8.35−8.42 (mult, 1H), 8.54 (t, 1H, J = 4 Hz), 8.79−8.95 (mult, 1H), 9.63 (bs, 1H), 9.84 (bs, 1H).

1-(4-Ethylphenyl)-3-quinolin-8-ylurea 4{*3,4*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, 3H, J = 8 Hz), 2.59 (q, 2H, J = 8 Hz), 7.09 (d, 2H, J = 8 Hz), 7.37 (d, 2H, J = 8 Hz), 7.47−7.50 (mult, 2H), 7.56−7.59 (mult, 1H), 8.37−8.33 (mult, 1H), 8.46−8.49 (mult, 1H), 7.84−7.87 (mult, 1H), 9.59 (bs, 1H), 9.68 (bs, 1H).

1-Quinolin-8-yl-3-*p*-tolylurea 4{*3,5*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55 (s, 3H), 7.11 (d, 2H, J = 8 Hz), 7.42 (d, 2H, J = 8 Hz), 7.51−7.56 (mult, 2H), 7.61−7.64 (mult, 1H), 8.37−7.39 (mult, 1H), 8.54−8.57 (mult, 1H), 8.80−8.92 (mult, 1H), 9.64 (bs, 1H), 9.74 (bs, 1H).

1-(3-Chloro-4-methoxyphenyl)-3-naphthalen-2-ylurea 4{*4,3*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H), 7.09 (d, 1H, J = 8 Hz), 7.29−7.37 (mult, 2H), 7.43−7.50 (mult, 2H), 7.71 (s, 1H), 7.79−7.84 (mult, 3H), 8.09 (s, 1H), 8.82 (s, 1H), 8.96 (s, 1H).

1-(5-Chloro-2-methoxyphenyl)-3-quinolin-3-ylurea 4-{*5,1*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 3H), 7.00−7.07 (mult, 2H), 7.54−7.67 (mult, 2H), 7.94 (t, 2H, J = 8 Hz), 8.25 (s, 1H), 8.60 (s, 2H), 8.83 (bs, 1H), 9.90 (bs, 1H).

1-(1*H*-Benzoimidazol-2-yl)-3-(5-chloro-2-methoxyphenyl)-urea 4{*6,1*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H), 7.06 (bs, 2H), 7.22−7.25 (mult, 2H), 7.49−7.51 (mult, 2H), 8.19 (bs, 1H).

1-(1*H*-Benzoimidazol-2-yl)-3-(3-chloro-4-methylphenyl)-urea 4{*6,2*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 7.19−7.21 (mult, 2H), 7.25 (s, 2H), 7.44−7.47 (mult, 2H), 7.75 (s, 1H), 9.89 (bs, 1H).

1-(1*H*-Benzoimidazol-2-yl)-3-(3-chloro-4-methoxyphenyl)-urea 4{*6,3*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.79 (s, 3H), 7.11 (d, 1H, J = 8 Hz), 7.23−7.25 (mult, 2H), 7.36 (dd, 1H, J = 2, 8 Hz), 7.48−7.51 (mult, 2H), 7.73 (d, 1H, J = 2 Hz), 10.06 (bs, 1H).

1-(1*H*-Benzoimidazol-2-yl)-3-(4-ethylphenyl)-urea 4{*6,4*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.65 (t, 3H, J = 8 Hz), 2.57 (q, 2H, J = 8 Hz) 7.19 (d, 2H, J = 8 Hz), 7.25−7.28 (mult, 2H), 7.45 (d, 2H, J = 8 Hz), 7.52−7.55 (mult, 2H), 9.84 (bs, 1H).

1-(5-Chloro-2-methoxyphenyl)-3-pyridin-3-ylurea 4{*9,1*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H), 6.95−6.99 (mult, 2H), 7.60−7.63 (mult, 1H), 8.05−8.16 (mult, 2H), 8.33 (s, 1H), 8.56 (bs, 1H), 8.88 (s, 1H), 9.91 (bs, 1H).

1-(3-Chloro-4-methylphenyl)-3-pyridin-3-ylurea 4{*9,2*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H), 7.21−7.27 (mult, 2H), 7.66−7.71 (mult, 2H), 8.17 (d, 2H, J = 9 Hz), 8.37 (s, 1H), 8.91 (s, 1H), 9.37 (bs, 1H), 9.64 (bs, 1H).

1-(4-Ethylphenyl)-3-pyridin-3-ylurea 4{*9,4*}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (t, 3H, $J = 8$ Hz), 2.54 (q, 2H, $J = 8$ Hz), 7.14 (d, 2H, $J = 8$ Hz), 7.37 (d, 2H, $J = 8$ Hz), 7.70−7.75 (mult, 1H), 8.20 (d, 1H, $J = 8$ Hz), 8.28−8.52 (mult, 1H), 8.84−9.08 (mult, 1H), 9.15 (bs, 1H), 9.58 (bs, 1H).

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Supporting Information Available. Supporting Information as noted in text. This material is available free of charge via the Internet at http://pubs.acs.org.

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