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Synthesis and SAR study of *N*-(4-hydroxy-3-(2-hydroxynaphthalene-1-yl)phenyl)-arylsulfonamides: Heat shock protein 90 (Hsp90) inhibitors with submicromolar activity in an in vitro assay

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ABSTRACT

Heat shock protein 90 is emerging as an important target in cancer chemotherapy. In a program directed toward identifying novel chemical probes for Hsp90, we found *N*-(4-hydroxy-3-(2-hydroxynaphthalene-1-yl)phenyl)benzene sulfonamide as an Hsp90 inhibitor with very weak activity. In this report, we present a new and general method for the synthesis of a variety of analogs around this scaffold, and discuss their structure–activity relationships.

Molecular chaperones are a class of proteins that are responsible for the correct folding and maturation of several cellular client proteins.[1] One among those chaperones is the heat shock protein 90 (Hsp90), which recently emerged as a very important and validated target in several diseases including cancer, neurodegeneration, viral, fungal, and microbial infection.[2,3] Hsp90 chaperone activity is found to be essential for the stability and function of a number of conditionally expressed signaling proteins, as well as for the mutated, chimeric, and/or overexpressed signaling proteins that promote cell growth and survival.[3] The client proteins found to interact with Hsp90 include Raf-1, mutant BRaf, IGF-IR, Akt, HER2, C-Met, C-Kit, mutant EGFR, and others.[4,5] These client members are found to play a crucial role in various types of cancers[2] and are found to undergo proteosome-mediated degradation when Hsp90 activity is inhibited.[6,7]

The natural product geldanamycin (GM) and its synthetic analog (17-AAG) were found to bind to the ATP binding site on the N-terminal domain of the Hsp90 and inhibit ATP-dependent chaperone activities.[8] Only the synthetic derivative 17-AAG is currently being evaluated for clinical use. Though Hsp90 is expressed abundantly in most tissues, studies employing GM, 17-AAG, and other compounds have concluded that cancer cells are more sensitive to Hsp90 inhibition compared to normal cells.[9] This conclusion is further supported by the studies of Kamal et al.,[10] who demonstrated that tumor cell Hsp90 is found to be in an activated complex with co-chaperones, whereas Hsp90 in normal tissue resides in a free and uncomplexed state. These observations gave the impetus to develop novel and effective small molecule Hsp90 inhibitors, and further affirm the notion that Hsp90 inhibition leads to selective killing of cancer cells over normal cells.

Structure-based design and high-throughput (HTS) screening efforts are underway to identify novel chemical scaffolds that can potentially generate lead structures for further development.[11] So far, this work has produced at least two clinical candidates (PU-H71,[12] CNF2024[13]) and several other preclinical candidates from the pyrazole/isoxazole class of compounds, demonstrating successful Hsp90 activity in both in vitro and in vivo tumor models.[14]

Under the MLSCN program,[15] we recently identified aminoquinolines by HTS[16] as a novel class of Hsp90 inhibitors. The work was complemented by ligand-based design and virtual screening exercises. Within this context, structures **1** and **2** (Fig. 1) were previously identified as Hsp90 blockers by means of virtual screening performed by Barril et al.[17] The compounds were found to show low micromolar activity in the malachite green assay[18] and subsequently in an FP assay.[19] However, these analogs showed a very poor activity in a cell growth inhibition assay (**2**: IC_{50} = 29 μM). Moreover, a very limited SAR study on the *N*-(4-hydroxy-3-(2-hydroxynaphthalene-1-yl)phenyl)benzene sulfonamide scaffold was reported.[17] This prompted us to perform a more expanded

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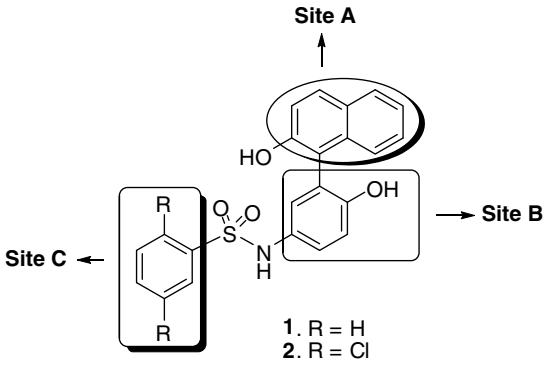


Figure 1. Potential sites for modification and SAR study.

SAR evaluation on this scaffold and to devise a synthetic method amenable to generating a variety of analogs. For instance, only derivatives on the terminal phenyl ring extending from the sulfone unit were reported; the naphthalene and middle rings remaining untouched.

The previous crystallographic investigation of **2** by Barril et al. reveals that its naphthalene ring is buried deep within the ATP binding pocket in the N-terminal region of Hsp90.[17] Compound **2** follows the general pharmacophore established by other known Hsp90 inhibitors (Fig. 2): contact with the hydrophobic cluster by the naphthalene moiety and participation in a hydrogen bonding network with residues Thr184 and Asp93 (the numbering refers to Hsp90α). Analysis of the available steric space, and augmentation of the hydrophobic contacts and hydrogen bonds were considered during the optimization of the arylsulfonamide series.

The possible sites for modification are outlined in Figure 1. Site A: The 2-naphthol ring could be replaced with 2-phenol, 3,4-benzodioxane-2-phenol, and 2-hydroxy-carbazole. The latter was considered to be able to provide not only bulkiness to fill the cavity observed in the X-ray model, but also scaffold hydrophilicity which can promote increased compound solubility. Likewise, crystal structure analysis suggested modifications could be performed on site B by replacing the OH group with NH_2, F, etc. In addition, more than one functional group can be added to the middle ring, while the sulfonamide tail can be moved to other positions on the same ring. At site C with a limited SAR, there is a room for modification such as replacing the two chlorines with hydroxyl groups combined with the modification at sites A and B to explore potential activity enhancement.

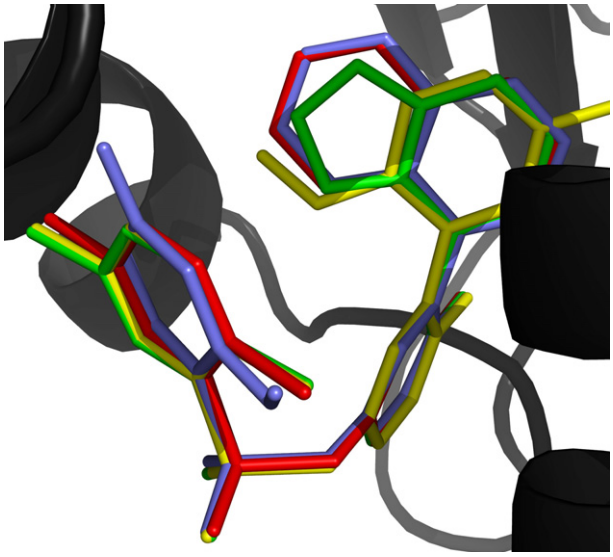


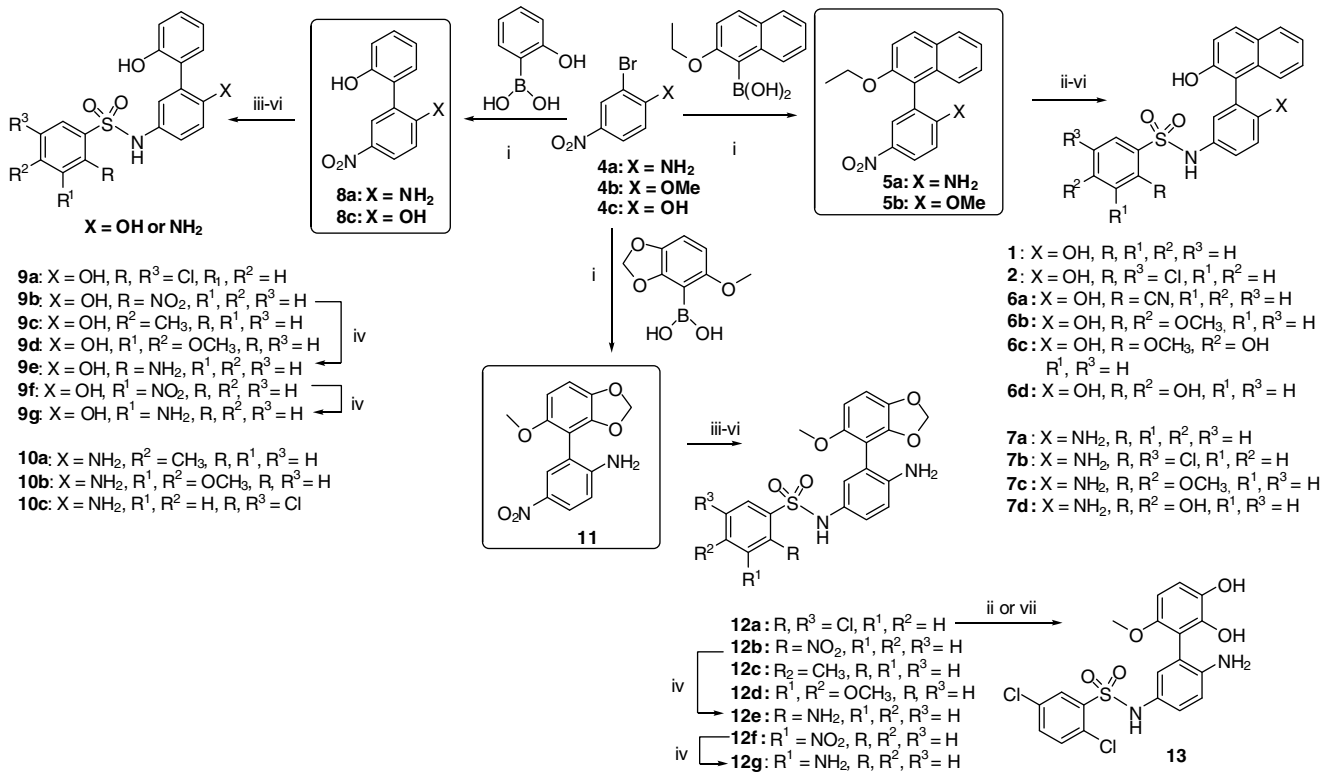
Figure 2. Docking of **6c** (blue), **13** (yellow), **17** (green) at N-terminal ATP binding site of Hsp90 (black, PDB: 2bz5). Docking poses are overlapped with co-crystallized pose of compound **2** (red). Figure shows that the docking poses were able to reproduce most heavy-atom positions of the crystal pose. Hydrogen, water, and residue atoms were not displayed. Coordinates for poses can be provided upon request.

At this juncture, we recognized the lack of a general synthetic strategy for preparing the contemplated compounds. Only one synthetic method making use of the preformed *N*-arenesulfonyl-*p*-benzoquinonimines as starting materials had been reported in a Russian journal.[20] Unfortunately, the procedure is unsuitable to a wide range of quinones. Thus, we envisioned an alternative and versatile synthetic method for *N*-(4-hydroxy-3-(2-hydroxynaphthalene-1-yl)phenyl)benzene sulfonamide. Below, we show that this method is applicable to a variety of analogs by means of a split pool synthetic approach as shown in Schemes 1 and 2. A preliminary SAR for these analogs is also described.

The synthesis of **1**–**2** and their analogs is depicted in Scheme 1. Thus, 2-bromo-4-nitroanisole or 2-bromo-4-nitroanilines (**4a** or **4b**) were subjected to the Suzuki–Miyaura cross-coupling reaction[21] with 2-ethoxynaphthalen-1-ylboronic acid in a microwave initiator for 15 min to produce product **5** in 95–98% yield. To our surprise, such a cross-coupling strategy does not seem to have been reported previously for unsymmetrical 2,2′-binaphthols and/or 1,1′-biphenols, though palladium-mediated procedures have been employed to generate self-coupled symmetrical 1,1′-binaphthols or 2,2′-biphenols.[22] The methyl- and ethyl-ethers were deprotected by treating **5a** and **5b** with borontribromide in dichloromethane solution, then the resulting hydroxyl and amino groups (from **5a**) or two hydroxyls (from **5b**) were protected with Boc-groups before reducing the nitro group by hydrogenation with 10%–palladium on carbon. The resulting amine was subsequently treated with substituted arylsulfonylchlorides in pyridine to provide Boc-protected sulfonamides. The latter were subjected to 2%-trifluoroacetic acid in dichloromethane to provide final products **1**–**2**, **6**–**7**.[23]

The palladium cross-coupling strategy appeared promising for generating a variety of building blocks such as biphenol (**8**) and aminophenol ether (**11**). Indeed both these intermediates were synthesized analogous to **5** and were carried forward by similar synthetic steps for **1** to provide **9a**–**g**, **10a**–**c**, and **12a**–**g**. Selective demethylation of **12a** with either borontribromide or aqueous hydrogen bromide yielded only methylenedioxy ring opened product **13**. As part of our study, we decided to prepare **17**, a benzodioxane moiety as a replacement for the naphthalene core of **2**. To this end, 5-hydroxybenzo-1,3-dioxo-4-yl-boronic acid (**14**) was synthesized albeit in a very low yield and in a poor quality as shown in Scheme 2. Coupling **14** with 2-bromo-4-nitrophenol by the same Suzuki procedure provided intermediate **16** in a very low yield**.** Nevertheless, this was smoothly carried through to the final product **17** as shown in Scheme 2.

Docking calculations were performed to determine if the proposed synthesized analogs (**6c**, **13**, and **17**) could attain a binding pose similar to that of the X-ray pose of **2** (Fig. 2). Schrödinger's GLIDE[24] program was utilized for the docking calculation and the receptor was downloaded from the Protein Data Bank (PDB ID: 2BZ5).[25] The receptor geometry was optimized using Schrödinger's protein preparation protocol. Receptor optimization was constrained to 0.3 Å for all atoms. All waters were deleted except 150 and 286. Examination of other Hsp90 crystals showed water 150 to be an important interaction for a variety of Hsp90 inhibitors.[8,11a,12,17] Water 286 was retained since GLIDE varied the poses tremendously for sulfonamide compounds when it was removed, suggesting 286 was important exclusively for the sulfonamide



Scheme 1. Synthesis of *N*-(4-hydroxy-3-(2-hydroxynaphthalene-1-yl)phenyl)arylsulfonamides and analogs. Reagents and conditions: (i) **4a** or **4b** (1 equiv), boronic acids (1.8–2 equiv), $Pd(PPh_3)_4$ (5–10 mol%), K_2CO_3 (3–3.3 equiv), DME/EtOH/H_2O (3:2:1 ml), microwave initiator, 15 min, 160 °C, 95–98%; (ii) BBr_3, CH_2Cl_2, −78 °C–rt, 1 h, 85–90%; (iii) Boc_2O, DMAP, THF, reflux, 3–4 h, 95%, (iv) H_2, 10% Pd–C, MeOH/EtOAc (6:2 ml), 12 psi, 1 h, 80–85%; (v) $ArSO_2Cl$, Py, 100%; (vi) 2% TFA in CH_2Cl_2, rt, 90%; (vii) aq HBr, 80 °C, 65%.

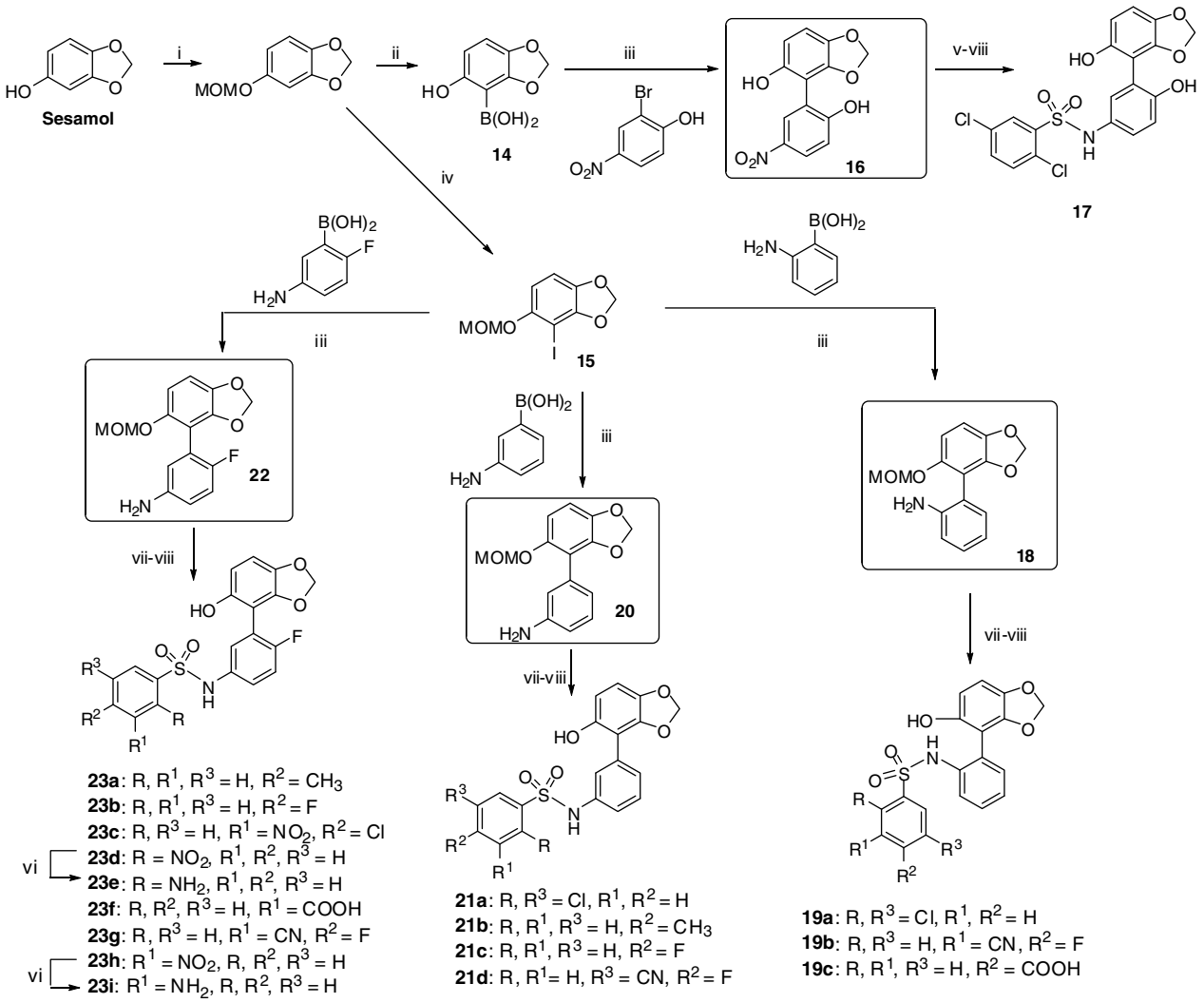
Hsp90 inhibitors. Standard docking precision was performed in which non-planar amide bond conformations were penalized and van der Waals radii were scaled to a factor of 0.8. No constraints were used for the docking calculation. Each compound structure was allowed to generate up to 5 poses. The Glide docking poses for **2** and its analogs were energy-rescored using MMGBSA.[26] The top scoring MMGBSA pose of each analog was overlaid with the crystallographic pose as shown in Figure 2. Although the Glide score and the MMGBSA rescore favor different compounds as shown in Table 1, the overall overlap shows that the different sulfonamide analogs take advantage of the same protein-ligand interactions with the Hsp90 receptor as **2**.

Based on the published X-ray crystal data of Barril et al. and our computational docking results, we decided to retain the 3,4-dioxane moiety and prepare derivatives by altering other parts of the molecule. Difficulties in the preparation of good quality boronic acid **14** and the low yields in coupling reactions with it prompted us to revise the synthetic strategy as shown in Scheme 2. A known iodide building block **15**[27] was prepared in large quantity, starting from sesamol, and this was coupled to various commercially available boronic acids by Suzuki-coupling to generate intermediates **18**, **20**, and **22** in excellent yields. All of the compounds were subjected to synthetic steps similar to those used in Scheme 1 to generate final products **19**, **21**, and **23** as shown in Scheme 2.

All synthesized compounds were tested in a fluorescent polarization (FP) assay,[28] which measures the interaction of small molecule ligands with fluorescently labeled GM and displaces the latter from the ATP binding site of Hsp90. To our surprise, we have not identified compounds more active than **2**. Apart from the analogs tabulated in Table 2, the other analogs have shown no inhibitory activity at the maximum concentration tested (50 μM). Only structural modifications at the terminal phenyl ring (**6a**–**6d**) appear to be tolerated and thereby retain activity. Replacing the OH on the middle ring with amine decreased the activity (**7b**–**d**). Substituting the 2-naphthol unit with the less bulky 2-phenol moiety completely eliminated activity (**9b**–**g** and **10a**–**b**), except for **9a** which showed about 20-fold less activity than **2**. However, replacing it with the 3,4-methylenedioxy-2-phenol moiety was well tolerated and decreased the activity by approximately 1.5- to 2-fold (**17**). This observation reinforces the suggestion made by the docking model that substituents equal in size or bulkier than the 2-naphthol ring might be better in this region to fill the hydrophobic cavity. Surprisingly, however, **13** exhibits a submicromolar IC_{50} approximately equal to the IC_{50} of **2**.

The compounds presented in Table 2 were also tested in the Western blot assay by examining client protein (HER2, Raf-1, PRAS40) degradation. Disappointingly, none of the analogs showed any promising effect, except **2** and **13**, both of which possess IC_{50} values of approximately 20 μM in HER2 degradation. However, neither had any effect on Raf-1 and PRAS40. Though, it is difficult to hypothesize that these analogs bind to Hsp90 protein with high affinity, but do not enforce disruption of client member association, it could be speculated to their poor permeability properties which might cause them to be less potent in cell-based WB assay. To support this hypothesis, we predicted ADME properties for the best active compounds by QikProp software.[29] As shown in Table 3, the compounds **2**, **6c**, **13**, and **17** are outside of the projected range.

The best active sulfonamides (**2**, **6c**, **6d**, **13**, and **17**) in FP assay were also tested in cell growth inhibition assay against HER2 overexpressing SKBr3 breast cancer cells.[30] As shown in Table 2, these derivatives exhibited only low micromolar IC_{50} values in this cell line, however, these values were only about 1.4- to 3.1-fold (except



Scheme 2. *N*-(4-Hydroxy-3-(5-hydroxybenzo-(1,3)-dioxol-4-yl)phenyl)benzene sulfonamides. Reagents and conditions: (i) NaH, MOMCl, DMF, 0 °C–rt, 98%; (ii) *n*-BuLi, THF, $B(OMe)_3$, −78 °C, then 10% HCl, rt tech-grade (50%); (iii) **15** (1 equiv, 2 mmol), boronic acids (1.8–2 equiv), $Pd(PPh_3)_4$ (5–10 mol%), K_2CO_3 (3–3.3 equiv), DME/EtOH/H_2O (3:2:1 ml), microwave initiator, 15 min, 160 °C, 90–95% (except for the **16** which only obtained in 20% yield based on recovered SM); (iv) *n*-BuLi, THF, I_2, 0 °C–rt; (v) Boc_2O, DMAP, THF, reflux, 3–4 h, 95%; (vi) H_2, 10% Pd–C, MeOH/EtOAc (6:2 ml), 12 psi, 1 h, 80–85%; (vii) $ArSO_2Cl$, Py, 100%; (viii) 2 M HCl, THF/MeOH, 90%.

Table 1
Docking scores for compound **2** and higher affinity compounds

Compound	MMGBSA (kcal/mol)	G_{score} (kcal/mol)
2	−44.6	−8.1
6c	−42.1	−8.6
13	−41.3	−7.1
17	−40.4	−7.9

Table 2
Inhibitory activities of sulfonamides against FP assay and SKBr3 breast cancer cells[a,b]

Compound	IC_{50} (μM)		Compound	IC_{50} (μM)	
	FP	SKBr3		FP	SKBr3
1	4.5	na	**9a**	19.4	na
2	0.70	6.5	**13**	0.55	6.0
6a	4.5	na	**17**	1.7	4.4
6b	2.5	na	**21a**	14.5	na
6c	1.3	9.7	**21b**	31.3	na
6d	1.8	>50	**21c**	19.6	na
7b	9.4	na	**23a**	28.0	na
7c	25.0	na	**23c**	26.0	na
7d	9.5	na	**23g**	27.0	na

na, not tested in SKBr3 cells.
[a] Mean of two independent determinations.
[b] The other compounds which did not show any inhibitory effect up to 50 μM concentration are not shown in this table.

for **6d**) less to IC_{50} values observed for a known pyrazole inhibitor.[31] Nonetheless, the potencies of **2**, **6c**, **13**, and **17** are at least 2.6- to 11-fold less in antiproliferative assay compared to the in vitro binding (FP) assay. Further studies are necessary to explain the activity differences in the two assays, but partly could be attributed to their poor cell permeability properties as predicted by QikProp.

In conclusion, a ligand-based design strategy centered on the sulfonamide scaffold was conceived to develop effective Hsp90 inhibitors. Although the anticipated nanomolar activity was not observed by examining synthetic representatives of this scaffold, a new and versatile synthesis was developed. The procedure should not only enable us to prepare a number of analogs for SAR, but also may be generally applicable for the synthesis of unsymmetrical biphenols and binaphthols, for example **5**, **8**, **11**, **16**, **18**, **20**, and **22**. The SAR study suggests that still more work needs to be done to manipulate the naphthalene moiety and also the middle phenyl ring of the scaffold, an effort that will be exerted in due course.

Table 3
Predicted cell membrane permeability[a]

	2	6c	13	17	Ranges (nm/s)
Caco2	242	84.9	81.8	249.7	<25 poor, >500 great
MDCK	439.3	35.1	128.8	491.9	<25 poor, >500 great

[a] Schrodinger's QikProp employed for these calculations.

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23. *Synthesis of* ***2*** *(typical procedures):* 2-Bromo-4-nitroanisole (**4b**) (425 mg, 1.8 mmol), 2-ethoxynaphthalen-1-ylboronic acid (800 mg, 2 equiv), $Pd(PPh_3)_4$ (100 mg, 5 mol%), and K_2CO_3 (735 mg, 3 equiv) were charged into a microwave reaction vessel. To this vessel, a three-solvent mixture (5 ml) (DME/EtOH/H_2O, 3:2:1) was added, and then the reaction mixture was irradiated in Biotage-microwave initiator for 15 min. Reaction mixture was partitioned between ethyl acetate and water. The organics were separated and washed with water, brine, dried over Na_2SO_4, and concentrated (usual work up). The crude mass obtained was purified by chromatography over silica gel, eluting with 5–8% ethyl acetate in hexanes to provide 2-ethoxy-1-(2-methoxy-5-nitrophenyl) naphthalene (**5b**) (580 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, 1H), 8.21 (d, 1H), 7.91 (d, 1H), 7.84 (m, 1H), 7.36 (m, 4H), 7.08 (d, 1H), 4.12 (q, 2H), 3.77 (s, 3H), 1.24 (t, 3H). ^{13}C NMR (100 MHz): δ 163.2, 153.9, 141.5, 133.3, 130.2, 129.2, 128.7, 128.4, 126.9, 126.7, 125.5, 124.6, 123.9, 119.9, 115.1, 110.7, 65.3, 56.4, 15.2. HRMS Calcd for $C_{19}H_{18}N_4O$, 324.12263; observed 324.12303 (M+H). To a solution of **5b** (525 mg, 1.62 mmol) in dichloromethane (15 ml), BBr_3 (3 equiv) was added at −78 °C and the reaction mixture was brought to room temperature overnight. Reaction mixture was quenched by addition to ice-cold water, and the product was extracted with ethyl acetate. The organic layer was on usual work up gave black residue, which was purified by silica gel chromatography by eluting with 20–30% ethyl acetate in hexanes to provide diol, 1-(2-hydroxy-5-nitrophenyl)naph-thalen-2-ol (400 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, 1H), 8.18 (d, 1H), 7.83 (d, 1H), 7.80 (dd, 1H), 7.37 (m, 2H), 7.26 (m, 1H), 7.21 (d, 1H), 7.14 (d, 1H). ^{13}C NMR (100 MHz): δ 160.3, 151.9, 141.8, 133.1, 131.9, 129.4, 128.9, 128.7, 128.0, 126.5, 124.4, 123.8, 121.7, 118.1, 117.0, 112.5. HRMS Calcd for $C_{16}H_{12}N_4O$, 282.07583; observed 282.07608 (M+H). To the above diol-compound (400 mg, 1.43 mmol) in tetrahydrofuran (10 ml) were added $(Boc)_2O$ (4.3 mmol, 3 equiv), DMAP (cat), and Et_3N (3.6 mmol, 2.5 equiv), and the reaction mixture was refluxed for 4 h. Reaction mixture was cooled and filtered through a short silica gel column, eluting with 10% ethyl acetate in hexanes. The filtrate was concentrated to give the Boc-protected product (700 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, 1H), 8.28 (d, 1H), 7.94 (d, 1H), 7.88 (d, 1H), 7.52–7.38 (m, 5H), 1.36 (s, 9H), 1.14 (s, 9H). The above compound (650 mg, 1.35 mmol) was dissolved in EtOAc/MeOH (6:2, 6 ml) and Pd–C was added (10% on charcoal) and hydrogenated at 12 psi for 45 min. The catalyst was filtered off through a short silica gel column by eluting with dichloromethane. The filtrate was concentrated to give amino-product (490 mg, 80%), which was used for the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, 1H), 7.80 (dd, 1H), 7.61 (d, 1H), 7.39 (m, 3H), 7.06 (d, 1H), 6.72 (dd, 1H), 6.61 (d, 1H), 1.39 (s, 9H), 1.07 (s, 9H). HRMS Calcd for $C_{26}H_{30}NO_6$, 452.20576; observed 452.20676 (M+H). To the above solution of amine (40 mg, 0.088 mmol) in pyridine (1 ml) was added 2,5-dichlorobenzenesulfonyl chloride (36 mg, 1.4 equiv) and stirred for 8 h. The pyridine was removed and the residue was dissolved in dichloromethane (2 ml) and TFA (0.3 ml) was added, and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with ethyl acetate and worked up as usual. The crude mass obtained was purified by silica gel preparative-TLC eluting with 0.8% methanol in dichloromethane to provide **2** (35 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, 1H), 7.82 (d, 1H), 7.78 (d, 1H), 7.42 (m, 2H), 7.34 (m, 2H), 7.21 (m, 2H), 6.98 (d, 2H), 6.95 (d, 1H). ^{13}C NMR (100 MHz): δ 153.4, 151.7, 137.5, 134.3, 133.8, 133.0, 132.8, 131.9, 131.4, 129.7, 129.3, 128.6, 128.4, 127.7, 127.6, 127.0, 124.2, 123.7, 120.7, 118.0, 117.7, 113.1. HRMS Calcd for $C_{22}H_{15}Cl_2NO_4S$, 459.00934; observed 459.009343. Similar procedures were employed to make other compounds. ^{1}H NMR data (recorded on Unity-400 MHz in $CDCl_3$) for selected compounds are given below. *Compound* ***5a****:* 8.15 (dd, 1H), 8.0 (d, 1H), 7.92 (d, 1H), 7.83 (dd, 1H), 7.36 (m, 4H), 6.76 (d, 1H), 4.10 (q, 2H), 1.24 (t, 3H). *Compound* ***6b****:* 7.69 (dd, 1H), 7.64 (d, 1H), 7.30–7.12 (m, 5H), 7.0 (s, 1H), 6.94 (d, 1H), 6.88 (d, 1H), 6.85 (d, 1H), 6.42 (dd, 2H), 3.84 (s, 3H), 3.78 (s, 3H). *Compound* ***6c****:* 7.80 (m, 2H), 7.40 (d, 1H), 7.33 (m, 2H), 7.24–7.15 (m, 2H), 7.10 (m, 1H), 7.0 (d, 1H), 6.80 (d, 1H), 6.54 (br s, 1H), 6.43 (dd, 1H), 6.34 (d, 1H), 3.71 (s, 3H). *Compound* ***6d****:* 7.69 (m, 2H), 7.38 (d, 1H), 7.21 (m, 2H), 7.13 (m, 2H), 6.88 (m, 1H), 6.83 (dd, 2H), 6.30 (dd, 1H), 6.26 (d, 1H). *Compound* ***7b****:* 7.91 (d, 1H), 7.77 (d, 2H), 7.42 (dd, 1H), 7.36–7.27 (m, 3H), 7.20 (d, 1H), 7.12 (dd, 1H), 6.97 (dd, 2H), 6.81 (d, 1H), 6.75 (d, 1H). *Compound* ***8a****:* 7.94 (m, 2H), 7.15 (t × d, 1H), 7.08 (d, 1H), 6.87 (t, 2H), 6.64 (d, 1H). *Compound* ***8c****:* 8.18 (d, 1H), 8.06 (dd, 1H), 7.24 (m, 2H), 6.94 (m, 3H). *Compound* ***9a****:* 7.89 (s, 1H), 7.40 (s, 2H), 7.22 (t, 2H), 6.95 (m, 6H), 6.80 (dd, 1H). *Compound* ***10a****:* 7.58 (d, 2H), 7.24 (m, 2H), 7.20 (d, 1H), 7.03 (dd, 1H), 6.96 (m, 3H), 6.77 (d, 1H), 6.68 (d, 1H). *Compound* ***10c****:* 7.92 (m, 1H), 7.43 (m, 2H), 7.28 (m, 1H), 7.0–6.96 (m, 6H), 6.90 (d, 1H), 6.72 (d, 1H). *Compound* ***11***. 8.0 (m, 2H), 6.80 (d, 1H), 6.72 (d, 1H), 6.42 (d, 1H), 5.93 (d, 2H), 3. 72 (s, 3H). *Compound* ***12a****:* 7.97 (dd, 1H), 7.53 (t, 2H), 7.21 (m, 3H), 6.84 (d, 1H), 6.52 (d, 1H), 5.90 (dd, 2H), 3.68 (s, 3H). *Compound* ***13****:* 7.92 (s, 1H), 7.41 (s, 2H), 6.98 (m, 3H), 6.86 (d, 1H), 6.72 (d, 1H), 6.44 (d, 1H), 3.59 (s, 3H). *Compound* ***16****:* 8.32 (d, 1H), 8.08 (d, 1H), 7.00 (d, 1H), 6.68 (d, 1H), 6.40 (d, 1H), 5.89 (s, 2H). *Compound* ***17****:* 7.89 (dd, 1H), 7.36 (m, 2H), 7.16 (d, 1H), 7.0 (dd, 1H), 6.82 (d, 1H), 6.63 (d, 1H), 6.38 (d, 1H), 5.82 (s, 2H). *Compound* ***19a****:* 7.49 (dd, 2H), 7.28 (m, 1H), 7.19 (m, 3H), 6.98 (d, 1H), 6.48 (d, 1H), 6.22 (d, 1H), 5.62 (dd, 2H). *Compound* ***21a****:* 7.86 (t, 1H), 7.25 (m, 3H), 7.18 (d × t, 1H), 7.12 (t, 1H), 6.93 (d × q, 1H), 6.45 (d, 1H), 6.19 (d, 1H), 5.70 (s, 2H). *Compound* ***22****:* 6.93 (t, 1H), 6.73 (d, 1H), 6.66 (m, 2H), 5.90 (d, 1H), 4.98 (s, 2H), 3.30 (s, 3H). *Compound* ***23a****:* 7.62 (d, 2H), 7.16 (d, 2H), 7.12 (m, 2H), 7.0 (m, 2H), 6.66 (d, 1H), 6.36 (d, 1H), 5.85 (s, 2H). *Compound* ***23c***: 8.21 (d, 1H), 7.80 (dd, 1H), 7.61 (d, 1H), 7.10 (m, 3H), 6.67 (d, 1H), 6.34 (d, 1H), 5.88 (s, 2H). All the synthetic products showed satisfactory analytical (^{13}C NMR, MS) data, consistent with the assigned structure.
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30. The SKBr3 breast cancer cells were grown in RPMI-1640 medium supplemented with 10% FBS. 1250 cells in 50 μl of culture medium were plated in 384-well microtiter plates (Costar) and allowed to attach for overnight. After treated with either compounds or vehicle (DMSO) for 72 h, the viability of the cells was measured by CellTiter-Blue (Promega). Briefly,

10 μl of CellTiter-Blue was added and incubated at 37 °C for 4 h. The fluorescence intensity (FI) was measured using the Analyst HT plate reader (Molecular Devices) with an excitation at 545 nm and an emission at 595 nm. The IC_{50} was calculated as the compound concentration that inhibits cell viability by 50% compared to vehicle control wells. The data reported are average values from four replicates. IC_{50} values were determined using a nonlinear regression analysis as implemented in Prism 4.0 (Graphpad Software). O'Brien, J. et al. *Eur. J. Biochem.* **2000**, *267*, 5421.

31. A known pyrazole derivative was resynthesized as reported in Ref. 11a (compound **16a** from Ref. 11a) and used as a positive control in the biological testing. This analog has shown IC_{50} value 1.6, 3.1 μM in FP and cell growth inhibition (against SKBr3 cells) assays, respectively.