Bioorganic & Medicinal Chemistry 24 (2016) 2423–2432

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and evaluation of 4-(2-hydroxypropyl)piperazin-1-yl) derivatives as Hsp90 inhibitors

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ARTICLE INFO

Article history:
Received 2 February 2016
Revised 21 March 2016
Accepted 29 March 2016
Available online 7 April 2016

Keywords:
Hsp90 inhibitors
Structure–activity relationships
Structure-based drug design

ABSTRACT

We previously reported 4-(3-((6-bromonaphthalen-2-yl)oxy)-2-hydroxypropyl)-*N*,*N*-dimethylpiperazine-1-sulfonamide (**1**) as a novel heat shock protein 90 inhibitor with moderate activity. In our ongoing efforts for the discovery of Hsp90 modulators we undertake structural investigations on **1**. Series of the titled compound were designed, synthesized and evaluated. We have found that compounds with a hydroxyl group at C-4 of the aryl ring on the piperazine moiety possess Hsp90 inhibition properties. Compound **6f** with improved activity could be further developed and optimized as Hsp90 inhibitor.

1. Introduction

The heat shock protein 90 (Hsp90), is an ATP-controlled machine that facilitates the correct folding and conformational maturation of both nascent polypeptides and denatured proteins.[1] Inhibition of Hsp90 ATP hydrolysis activity resulted in systemic degradation of client proteins, among which most are oncogenic.[2,3] Overexpressed Hsp90 has been implicated in variety of tumors, which is critical for the survival, adaptation, proliferation and metastasis as well as angiogenesis of cancer cells.[4] Inhibition of Hsp90 ATP hydrolysis activity resulted in systemic degradation of protein clients, and thus led to cancer cell growth inhibition and apoptosis. Therefore, small molecules targeting Hsp90 folding machinery have shown therapeutic success in solid and hematological malignancies, providing an opportunity for cancer therapy.[5] 17 small molecules as Hsp90 inhibitors have already reached clinical trials.[6] However, all of these inhibitors are targeting Hsp90 N-terminal domain (NTD). In fact, clinical studies have raised some crucial issues including the toxicity and the concomitant heat shock response induced upon use of N-terminal domain inhibitors, which compromised their efficacy and led to resistance and metastasis.[7,8] Recently more efforts focus on small molecules that bind the Hsp90 C-terminus or allosterically modulate Hsp90 function.[9]

We previously reported compound **1** was identified as an Hsp90 inhibitor with moderate activity, through ligand based virtual screening performed in our laboratory.[10] Compound **1** has showed potent in vitro activity with low micromolar IC_{50} values in both ATPase activity and anti-proliferation assays. Compound **1** could further promoted degradation of several Hsp90 client proteins and induced the apoptosis of MCF-7 cancer cell line. Therefore, further optimization and identification of novel privileged structures appears as an interesting challenge.

Our continuing efforts toward improving the activity of compound **1** began based on structural information about the binding of compound **1** into Hsp90. The availability of the 3D-structure of Hsp90 protein has enhanced opportunities for the rapid optimization of hit compounds. In order to obtain more potent compounds with improved druggability, the binding mode of **1** in the ATP-binding pocket of Hsp90 (Fig. 1A, PDB ID: 2XJX) was predicted using GOLD program using the procedure described previously.[10] Naphthalene ring was surrounded by hydrophobic residues Phe138, Tyr139, Val150 and Trp152. Although compound **1** bound well to Hsp90, it only inserted into part of the binding site. Indeed, sulfonamide group was missing the occupation of the hydrophobic sub-pocket formed by lys58. To solve this problem, we tried to change the *N*,*N*-dimethylsulfonyl amide with other substituents, including phenyl with electron-withdrawing and electron-donating groups (Fig. 1B), leading to the first series of compounds (ranging from **6a** to **6m**, the first series in Table 1).

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http://dx.doi.org/10.1016/j.bmc.2016.03.049
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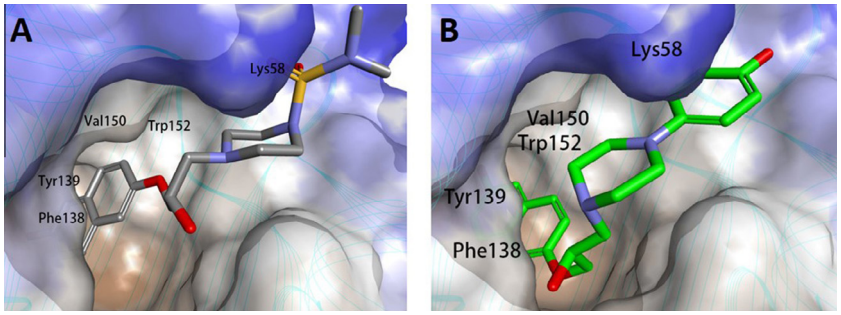


Figure 1. The binding patterns of compounds **1** (A) and **6f** (B) in the active site of Hsp90.

2. Methods

The preparation of compounds from first series was described in Scheme 1. Reaction of 6-bromonaphthalen-2-ol with epichlorohydrin in THF solvent in presence of sodium hydride base (NaH) afforded intermediate **3**. The intermediate **5** was prepared in two steps, first via reaction of commercially available dimethylsulfamoyl chloride with 1-Boc-piperazine in presence of base. Then N-Boc deprotection was achieved in DCM/TFA. Finally, compound **1** was synthesized by coupling the intermediates **3** and **5** in ethanol at reflux.[11]

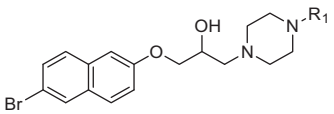
The inhibitory effects on Hsp90 ATPase activity were evaluated using Discover RX ADP Hunter™ Plus Assay kit (ADP assay) as described previously.[10] The anti-proliferative activity against MCF-7, A549, HTC-116, and MDA-MB-231 cancer cell lines was investigated using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Detailed synthetic and biologic procedures and the analytical data of all compounds were described in Section 5.

3. Results and discussion

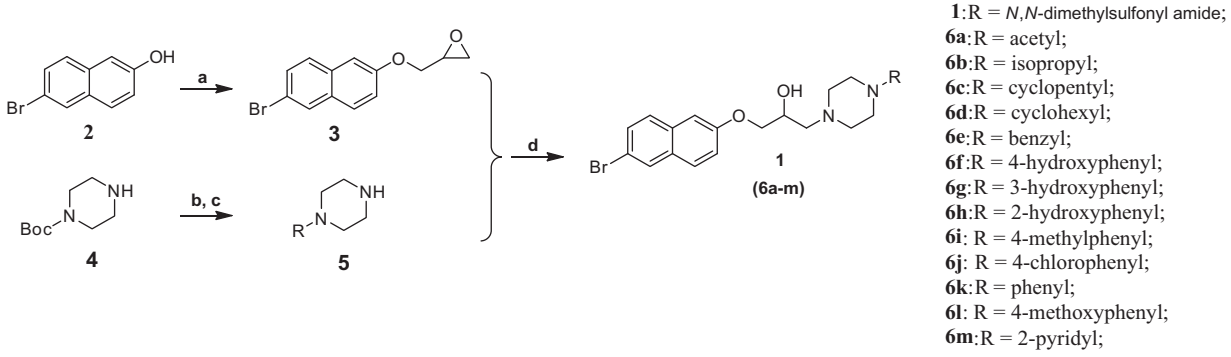
The compounds (**6a**–**m**) were derived by replacing the sulfonamide group in compound **1**. From results in Table 1, the methyl carbonyl, isopropyl and cyclopentyl groups were all detrimental (**6a**, **6b** and **6c**). Despite alterations on **6a**–**e** were suitable for cytotoxicity, this activity was apparently influenced by other factors than Hsp90 inhibition. Interestingly, substitution of *N*,*N*-dimethylsulfonyl amide with the 4-hydroxyphenyl moiety which directly attached to piperazine ring; significantly suppressed the Hsp90 ATPase activity with IC_{50} 0.91 ± 0.71 μM and simultaneously reduced the proliferative activity of all four types of cancer cells (compound **6f**; IC_{50} 1.101 ± 1.95 μM, 5.18 ± 1.26 μM, 8.51 ± 3.5 μM and 4.64 ± 1.16 μM against MCF-7, HCT-116, A549 and MDA-MB-231, respectively).

Unlike our expectations, the results showed most of these derivatives displayed decreased activity against Hsp90. Only compound **6f** exhibited slight improvement and its cytotoxicity was corroborated with inhibition of Hsp90 ATPase activity. Subsequently, on the basis of these findings, compound **6f** was selected for further optimization through in-depth structural modification. At first we planned to exploit the significance of the hydroxyl group on the phenyl of **6f**. Compounds **6h** and **6g** with the hydroxyl on *ortho*- and *meta*-positions respectively were prepared and evaluated. Data demonstrated the necessity of a hydrogen bonding group on the phenyl with preference to *para*-over *ortho*-position (**6a** > **6h**). Whereas, the hydroxyl on *meta*-position in analogue **6g** was not tolerated. From another hand, either alkylation or total removal of phenol's hydroxyl functional group (**6l** and **6k** respectively) resulted in complete loss of potency against Hsp90 in enzyme based assay. Also when we sought to replace the hydroxyl by other substituents, analogues (**6j** > **6i**) lost their potency against

Table 1
Anti-proliferative activity and Hsp90 ATPase activity inhibition of **6a**–**m**



Compd no.	R_1	Hsp90 IC_{50} (μM)	Antiproliferative activity on cancer cell lines (IC_{50}, μM)			
			MCF-7	HCT-116	A549	MDA-MB-231
1	*N*,*N*-Dimethylsulfonyl amide	1.61 ± 0.3	3.79 ± 0.8	4.66 ± 0.7	25.88 ± 2.3	2.27 ± 0.8
6a	Acetyl	>20	140.1 ± 1.2	140.1 ± 1.3	140.2 ± 2.8	15.99 ± 1.2
6b	Isopropyl	>20	1.4 ± 1.1	28.59 ± 3.5	1.8 ± 1.4	71.49 ± 1.2
6c	Cyclopentyl	>20	6.20 ± 1.4	31.4 ± 4.1	4.08 ± 1.2	31 ± 1.3
6d	Cyclohexyl	>20	174.01 ± 1.2	48.4 ± 1.3	141.9 ± 1.2	71.64 ± 1.22
6e	Benzyl	>20	17.33 ± 1.3	39.11 ± 1.3	48.81 ± 1.2	9.65 ± 1.2
6f	4-Hydroxyphenyl	0.91 ± 0.7	1.101 ± 1.9	5.18 ± 1.3	8.515 ± 3.5	4.642 ± 1.2
6g	3-Hydroxyphenyl	>20	165.9 ± 0.6	128.4 ± 2.2	189.5 ± 4.2	40.69 ± 0.3
6h	2-Hydroxyphenyl	4.09 ± 1.7	15.99 ± 0.5	21.29 ± 0.7	31.99 ± 3.2	18.75 ± 0.9
6i	4-Methylphenyl	>20	>200	151.3 ± 1.3	>200	35.92 ± 1.3
6j	4-Chlorophenyl	>20	63.35 ± 1.9	32.32 ± 1.2	55.83 ± 2.1	27.61 ± 1.2
6k	Phenyl	>20	>200	210	>200	33.31 ± 0.5
6l	4-Methoxyphenyl	>20	155.4 ± 1.2	230.1 ± 1.2	180.9 ± 1.3	254.3 ± 1.1
6m	2-Pyridyl	>20	22.73 ± 1.2	>200	20.18 ± 1.3	15.88 ± 1.4



Scheme 1. Reagents and conditions: (a) NaH, THF, epichlorohydrin, N_2; (b) dimethylsulfamoyl chloride, EDTA, DCM, rt; (c) TFA/DCM, rt; (d) EtOH, reflux.

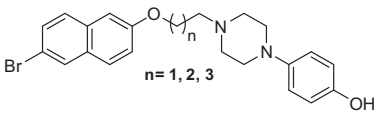
Hsp90. This loss of inhibitory effect on Hsp90 ATPase activity was accompanied with absence of anti-proliferative activity against cancer cell lines. From results described above, it was supposed that analogue **6f** unveiled on existence of key hydrogen-bonding interaction between the 4-hydroxyphenyl and protein target Hsp90, which was critical for anti-proliferative activity.

Basing the results on Hsp90 inhibitory effect of those analogues, we continued our study and selected **6f** for further modifications. In the next series, we were keen to explore the significance of the hydroxyl group on the carbon chain spacer between the 6-bromonaphthalene and the 1-(4-hydroxyphenyl)piperazine, since that this hydroxyl group might induce unstable metabolism. The length of this spacer was also investigated. Therefore, three compounds lacking the hydroxyl group on the linker were designed and synthesized as described in Scheme 2.

The synthesis of analogues (**8a**–**c**) began with the preparation of intermediate compounds (**7a**–**c**) through reaction of 6-bromonaphthelen-2-ol with the corresponding α,ω-dibromoaclane derivative (alkyl bromides) in DMF and presence of K_2CO_3 at room temperature. These intermediates were coupled with 4-(piperazin-1-yl)phenol in DMF at reflux with presence of K_2CO_3 (detailed synthetic procedures and analytical data of all compounds were described in Section 5). Unfortunately, we found that removal of the hydroxyl group from the spacer was detrimental for both cytotoxic and Hsp90 inhibition activities (Table 2).

In continuation of our work, we turned our attention to the 6-bromonaphthalene in compound **6f**. Several analogues with displace of 6-bromonaphthalenyl were prepared through the same synthetic sequence and evaluated as Hsp90 inhibitors (Table 3). As anticipated, most of analogues from this series showed similar inhibition activities against Hsp90 ATP hydrolysis function, compared to compound **6f**. Removing the bromine in compound **9a** resulted in gain of potency against Hsp90 (IC_{50} 0.4 ± 1.2 μM). Alteration of naphthalene ring to benzene ring was tolerated. The bromine, chlorine or electron donating substituents on the benzene ring, were all tolerated (**9b**, **9c** and **9h**) with more or less increase in potency compared to each other. Moreover, substitution on the forth position was more favorable than that on other positions (**9d** < **9c**, **9f** < **9e**), and analogue **9j** containing a 4-amino group showed slight increase in potency comparing to other analogues. Meanwhile, steric substitution (**9i**, **9k**) was unfavorable.

Table 2
Anti-proliferative activity of analogues **8a–c**



Compd no.	Antiproliferative activity on cancer cell lines (IC_{50}, μM)			
	MCF-7	HCT-116	A549	MDA-MB-231
8a (*n* = 1)	56.52 ± 0.8	16.83 ± 0.7	20.56 ± 0.7	5.26 ± 0.9
8b (*n* = 2)	>200	88.22 ± 1.3	>200	173.7 ± 2.3
8c (*n* = 3)	>250	112 ± 4.2	>250	49.86 ± 1.2

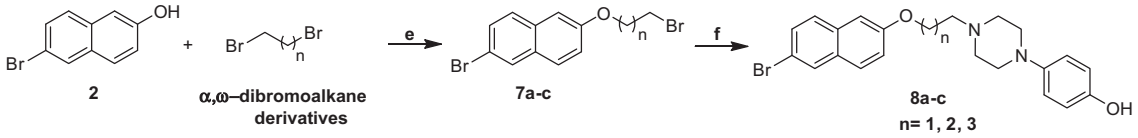
Finally, alteration of 6-bromonaphthalenyl to 1,3-benzodioxolyl (**9l**) was favorable over replacement with the indolyl (**9m**).

Results from structural alteration studies reported above, illustrated that the hydroxyl group on fourth position of the phenyl significantly modulated both cytotoxicity and potency against Hsp90. We concluded that compound **6f** was the optimal analogue among others, maintaining the best balance between Hsp90 inhibition and cytotoxicity.

To further investigate whether the antiproliferative activity was the functional consequence of Hsp90 inhibition, we determined the expression of Hsp90 client proteins which are crucial for tumor growth. MCF-7 cancer cells were exposed to a range of concentrations of **6f** for 24 h and various client proteins were explored by Western blot.

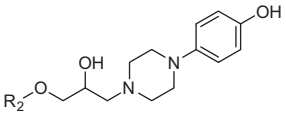
As shown in Figure 2, compound **6f** significantly down-regulated the level of client proteins including Akt, Erk1/2 and HER-2 in a dose-dependent manner. As expected, the expression level of Hsp90 was dose-dependently enhanced, which was considered as the feedback of Hsp90 inhibition. Together, these results indicated that **6f** inhibited proliferation of cancer cells through Hsp90 inhibition, thus degrading its client proteins.

We next explored whether **6f** could induce the apoptosis of MCF-7 cells and evaluated its influence on cell skeleton by a morphological observation. Treatment of MCF-7 cells with **6f** resulted in phenotypic changes including shrinkage, membrane blebbing and distortion and large proportion of cells turned round in shape and necrosis (Fig. 3D–F). In contrast, untreated cells (control) grew



Scheme 2. Reagents and conditions: (e) DMF, K_2CO_3, rt, N_2, 2 h; (f) 4-(piperazin-1-yl)phenol, DMF, K_2CO_3, reflux, 5 h.

Table 3
Anti-proliferative activity and inhibition of Hsp90 ATPase activity in ADP assay of compounds **9a–m**



Compd no.	R_2	Hsp90 IC_{50} (μM)	Antiproliferative activity on cancer cell lines (IC_{50}, μM)			
			MCF-7	HCT-116	A549	MDA-MB-231
6f	6-Bromonaphthyl	0.91 ± 1.7	1.101 ± 2.0	5.18 ± 1.3	8.52 ± 3.5	4.64 ± 1.2
9a	Naphthalenyl	0.4 ± 1.2	94.04 ± 2.9	50.8 ± 0.7	71.75 ± 0.7	49.25 ± 2.1
9b	4-Bromobenzyl	1.46 ± 1.5	19.43 ± 1.4	55.4 ± 1.4	18.18 ± 1.7	22.22 ± 1.1
9c	4-Chlorobenzyl	1.61 ± 1.5	19.45 ± 2.2	22.1 ± 1.4	14.23 ± 1.9	26.73 ± 1.3
9d	2-Chlorobenzyl	5.31 ± 1.2	28.8 ± 2.1	20.34 ± 2.0	30.32 ± 2.4	34.37 ± 1.7
9e	4-Methylbenzyl	2.25 ± 1.3	20.34 ± 1.5	24.51 ± 1.7	17.48 ± 2.4	27.56 ± 1.4
9f	3-Methylbenzyl	9.42 ± 1.6	32.45 ± 2.4	26.27 ± 2.4	28.48 ± 1.2	40.85 ± 2.9
9g	3-Methoxybenyl	6.19 ± 1.2	42.97 ± 2.7	28.26 ± 2.0	30.54 ± 2.1	41.86 ± 3.2
9h	4-Ethylbenzyl	1.29 ± 1.3	29.14 ± 2.3	28.52 ± 2.4	19.87 ± 2.1	32.81 ± 2.1
9i	4-*tert*-Butylbenzyl	19.8 ± 1.5	28.32 ± 1.6	55.91 ± 2.0	20.94 ± 1.3	26.02 ± 1.2
9j	4-Aminobenzyl	1.15 ± 1.3	30.98 ± 3.4	35.4 ± 1.1	24.95 ± 1.4	39.85 ± 4.1
9k	4-Phenylbenzyl	>20	1.90 ± 0.3	27.17 ± 0.9	1.013 ± 0.3	1.50 ± 0.3
9l	1,3-Benzodioxolyl	2.61 ± 1.2	48.98 ± 4.1	23.68 ± 1.5	30.21 ± 2.3	58.29 ± 3.5
9m	1*H*-Indolyl	5.91 ± 1.6	20.49 ± 1.4	1.83 ± 0.9	16.43 ± 0.9	25.47 ± 1.9

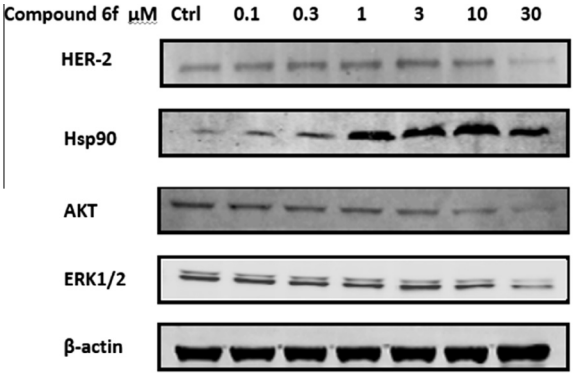


Figure 2. Western blot analyses of Hsp90-dependent client proteins from MCF-7 breast cancer cell lysate upon treatment with derivative **6f**. Concentrations (in μM) were indicated above each lane. Ctrl represents dimethylsulfoxide (D, 100%) employed as negative control.

well with normal shapes and clear cytoskeletons (Fig. 3A–C). Taken together, these results confirmed that **6f** as Hsp90 inhibitor could induce apoptosis in tumor cells.

4. Conclusion

Three series of derivatives were prepared and evaluated as Hsp90 inhibitors. Replacement of the *N*,*N*-dimethyl sulfonyl amide group with 4-hydroxyphenyl was the most effective with better binding with Hsp90. Attempts to replace the 6-bromonaphthalenyl with other substituents demonstrated no advantage as compared to the initial fragment. Finally, the hydroxyl group on the linker was necessary for activity (Fig. 4). Through the observed structure–activity trends, compound **6f** was the most potent. The compound showed balance between inhibition of Hsp90 ATP hydrolysis activity and cytotoxicity.

5. Experimental section

5.1. Materials and measurements

The melting points were taken in Mel-TEMP II melting point apparatus and were not corrected. ^{1}H NMR spectra were recorded with a Bruker Avance 300 MHz spectrometer at 300 K, using TMS as an internal standard and chemical shifts were expressed in ppm and peaks were listed as singlet (s), doublet (d), triplet (t), quintet (q), and multiplet (m), with coupling constants (*J*) expressed in Hertz. MS spectra were recorded on a Shimadzu GC–MS 2010 (EI) or a Mariner Mass Spectrum (ESI), or an LC/MSD TOF HR-MS Spectrum. All compounds were routinely checked by TLC, ^{1}H NMR and ^{13}C NMR. TLCs and preparative thin-layer chromatography were performed on silica gel GF/UV 254 supported by glass plate, and the chromatograms run on silica gel (200–300 mesh) visualized in UV light at 254 and 365 nm. Purity of the final compounds was measured by HPLC with Agilent Technologies 1260 infinity C18 4.60 mm × 150 mm column using a mixture of solvent methanol/water at the flow rate of 0.5 ml/min and peak detection at 245 nm under UV which was greater than 90%. All solvents were reagent grade and, when necessary, were purified and dried by standard methods. Processes of concentration and extraction for different Solutions after reactions involved the use of a rotary evaporator operating at a reduced pressure of ca. 20 Torr. Organic solutions were dried over anhydrous sodium sulfate. Analytical results are within (0.40% of the theoretical values).

5.2. Synthesis

5.2.1. General procedure for the synthesis of intermediates 3 and 3a–m

Compound **2** (1 equiv) and NaH (3 equiv) were solved in anhydrous THF (25 ml) then put in round bottom flask. After 1 h of stirring under nitrogen atmosphere at room temperature, epichlorohydrin (5 equiv) in THF was dropwise added into the reaction mixture. The mixture was hold at reflux for 8 h. After cooling to room temperature, the solution mixture was poured into water (100 ml) and extracted with Et_2O (3 × 50 ml). The organic layers were combined and dried over anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:10) to afford intermediates **3** and **3a–m**.

5.2.1.1. 12-(((6-Bromonaphthalen-2-yl)oxy)methyl)oxirane (3). The intermediate **3** was obtained according to general procedure using 6-bromonaphthalen-2-ol **2**. Yield 60%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.9 (1H, s), 7.68 (1H, d,

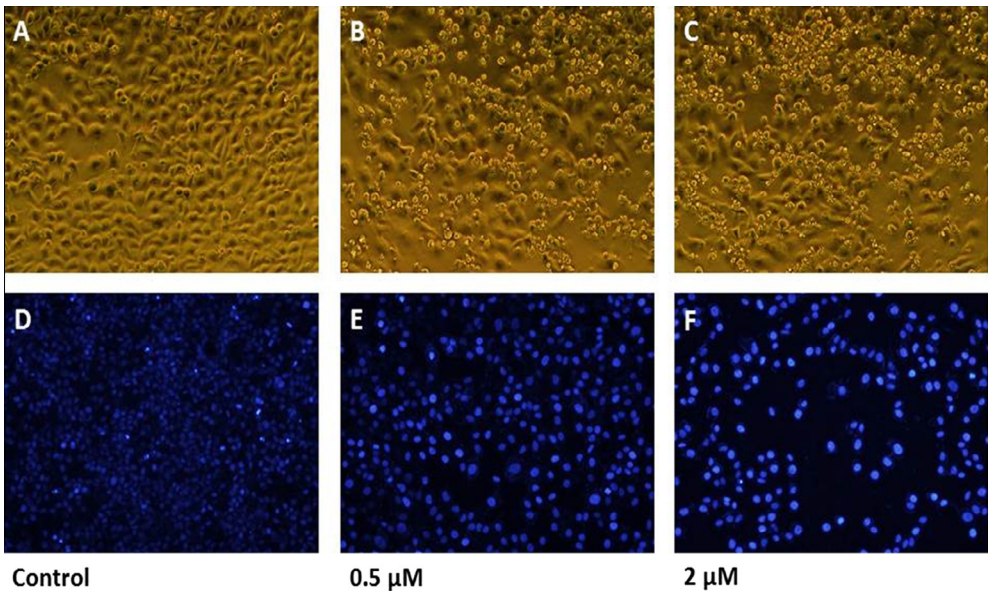


Figure 3. Morphologic changes of MCF-7 whole cancer cell (A–C) and the nucleus (D–F) induced by compound **6f**. Cultured MCF-7 cells were treated with compound **6f** at the indicated concentrations. The cell nucleus was visualized by fluorescence microscopy following DNA staining with the fluorescent dye DAPI, as described in Section 5. A; control, B; 0.5 μM of **6f**, C; 2 μM of **6f**, D; control, E; 0.5 μM of **6f**, F; 2 μM of **6f**.

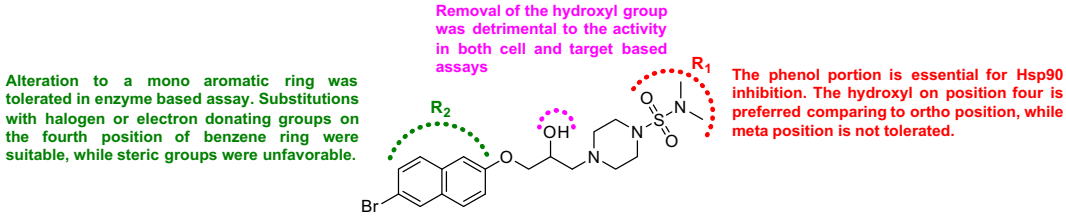


Figure 4. Summary of results from SAR study.

J = 8.9 Hz), 7.61 (1H, d, *J* = 8.7 Hz), 7.51 (1H, m). 7.21 (1H, d, *J* = 8.9 Hz), 7.12 (1H, d, *J* = 7.0 Hz), 4.35 (1H, d, *J* = 10.9 Hz), 4.08 (1H, d, 10.9 Hz), 3.44 (1H, m), 2.96 (1H, t, *J* = 4.5 Hz), 2.82 (1H, d, 4.8 Hz). MS (Mwt.: 277.99).

5.2.1.2. 2-((Naphthalen-2-yloxy)methyl)oxirane (3a). The intermediate **3a** was obtained according to general procedure using naphthalen-2-ol **2a**. Yield 54%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (3H, m), 7.32 (4H, m), 4.36 (1H, d, *J* = 10.9 Hz), 4.09 (1H, d, *J* = 10.9 Hz), 3.45 (1H, m), 2.96 (1H, t, *J* = 4.5 Hz), 2.83 (1H, d, *J* = 4.8 Hz). MS (Mwt.: 200.08).

5.2.1.3. 2-((4-Bromophenoxy)methyl)oxirane (3b). The intermediate **3b** was obtained according to general procedure using 4-bromophenol **2b**. Yield 26.44%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 (2H, d, *J* = 5.2 Hz), 6.81 (2H, d, *J* = 5.2 Hz), 4.22 (1H, d, *J* = 11.0 Hz), 3.9 (1H, d, *J* = 11.0 Hz), 3.35 (1H, m), 2.92 (1H, t, *J* = 4.5 Hz), 2.75 (1H, d, *J* = 4.8 Hz). MS (Mwt.: 227.98).

5.2.1.4. 2-((4-Chlorophenoxy)methyl)oxirane (3c). The intermediate **3c** was obtained according to general procedure using 4-chlorophenol **2c**. Yield 24%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22 (2H, d, *J* = 6.8 Hz), 6.83 (2H, d, *J* = 9 Hz), 4.2 (1H, d, *J* = 11.0 Hz), 3.86 (1H, d, *J* = 11.0 Hz), 3.32 (1H, m), 2.88 (1H, t, *J* = 4.3 Hz), 2.73 (1H, d, *J* = 4.8 Hz). MS (Mwt.: 184.03).

5.2.1.5. 2-((2-Chlorophenoxy)methyl)oxirane (3d). The intermediate **3d** was obtained according to general procedure using 2-chlorophenol **2d**. Yield 31.46%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (1H, d, *J* = 10.8 Hz), 7.25 (1H, m), 6.96 (2H, m), 4.31 (1H, d, *J* = 3.0 Hz), 4.08 (1H, d, *J* = 11.2 Hz), 3.60 (1H, m), 2.86 (1H, t, *J* = 2.4 Hz), 2.72 (1H, d, *J* = 4.7 Hz). MS (Mwt.: 184.03).

5.2.1.6. 2-((*p*-Tolyloxy)methyl)oxirane (3e). The intermediate **3e** was obtained according to general procedure using *p*-cresol **2e**. Yield 61.53%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.11 (2H, d, *J* = 8.2 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 4.21 (1H, d, *J* = 11.0 Hz), 3.95 (1H, d, *J* = 11.0 Hz), 3.35 (1H, m), 2.92 (1H, t, *J* = 4.5 Hz), 2.76 (1H, d, *J* = 4.9 Hz), 2.31 (3H, s). MS (Mwt.: 164.08).

5.2.1.7. 2-((*m*-Tolyloxy)methyl)oxirane (3f). The intermediate **3f** was obtained according to general procedure using *m*-cresol **2f**. Yield 26.49%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 (2H, d, *J* = 5.3 Hz), 6.82 (2H, d, *J* = 5.2 Hz), 4.21 (1H, d, *J* = 2.9 Hz), 3.91 (1H, m), 3.35 (1H, m), 2.91 (1H, t, *J* = 4.5 Hz), 2.78 (1H, d, *J* = 4.8 Hz), 2.32 (3H, s). MS (Mwt.: 164.08).

5.2.1.8. 2-((3-Methoxyphenoxy)methyl)oxirane (3g). The intermediate **3g** was obtained according to general procedure using 3-methoxyphenol **2g**. Yield 41.37%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18 (1H, t, *J* = 7.9 Hz), 6.54 (3H, m), 4.21 (1H, d, *J* = 11.0 Hz), 3.95 (1H, d, *J* = 11.0 Hz), 3.79 (3H, s), 3.35 (1H, m), 2.9 (1H, t, *J* = 4.5 Hz), 2.75 (1H, d, *J* = 4.9 Hz). MS (Mwt.: 180.08).

5.2.1.9. 2-((4-Ethylphenoxy)methyl)oxirane (3h). The intermediate **3h** was obtained according to general procedure using 4-ethylphenol **2h**. Yield 96.21%; oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.14 (2H, d, J = 8.6 Hz), 6.89 (2H, d, J = 8.6 Hz), 4.21 (1H, d, J = 11.0 Hz), 3.96 (1H, d, J = 11.0 Hz), 3.36 (1H, m), 2.92 (1H, t, J = 4.5 Hz), 2.76 (1H, d, J = 4.8 Hz), 2.62 (2H, q, J = 7.5 Hz), 1.24 (3H, t, J = 7.6 Hz). MS (Mwt.: 178.10).

5.2.1.10. 2-((4-(*tert*-Butyl)phenoxy)methyl)oxirane (3i). The intermediate **3i** was obtained according to general procedure using 4-(*tert*-butyl)phenol **2i**. Yield 43.79%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22 (2H, d, J = 8.8 Hz), 6.79 (2H, d, J = 8.8 Hz), 4.1 (1H, d, J = 11.1 Hz), 3.85 (1H, m), 2.79 (1H, t, J = 4.5 Hz), 2.64 (1H, d, J = 4.9 Hz), 1.23 (9H, s). MS (Mwt.: 206.13).

5.2.1.11. *tert*-Butyl(4-(oxiran-2-ylmethoxy)phenyl)carbamate (3j). The intermediate **3j** was obtained according to general procedure using *tert*-butyl (4-hydroxyphenyl)carbamate **2j**. Yield 44.92%; Pink solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28 (2H, t, J = 8.6 Hz), 6.87 (2H, d, J = 10.2 Hz), 6.36 (1H, s), 4.19 (1H, d, J = 11.0 Hz), 3.95 (1H, d, J = 10.9 Hz), 3.35 (1H, m), 2.8 (1H, t, J = 4.5 Hz), 2.76 (1H, d, J = 4.8 Hz), 1.52 (9H, s). MS (Mwt.: 265.13).

5.2.1.12. 2-(([1,1′-Biphenyl]-4-yloxy)methyl)oxirane (3k). The intermediate **3k** was obtained according to general procedure using [1,1′-biphenyl]-4-ol **2k**. Yield 57.29%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (4H, m), 7.44 (2H, m), 7.33 (1H, m), 7.02 (2H, d, J = 8.5 Hz), 4.28 (1H, d, J = 11.0 Hz), 4.01 (1H, d, J = 10.9 Hz), 3.40 (1H, m), 2.93 (1H, t, J = 4.4 Hz), 2.8 (1H, d, J = 4.4 Hz), MS (Mwt.: 226.10).

5.2.1.13. 5-(Oxiran-2-ylmethoxy)benzo[*d*][1,3]dioxole (3l). The intermediate **3l** was obtained according to general procedure using benzo[*d*][1,3]dioxol-5-ol **2l**. Yield 58.66%; Oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.67 (1H, d, J = 8.4 Hz), 6.5 (1H, d, J = 6.2 Hz), 6.31 (1H, d, J = 8.4 Hz), 5.89 (2H, s), 4.12 (1H, d, J = 11.0 Hz), 3.83 (1H, d, J = 11.0 Hz), 3.3 (1H, m), 2.81 (1H, t, J = 4.5 Hz), 2.71 (1H, d, J = 4.8 Hz). MS (Mwt.: 194.06).

5.2.1.14. 6-(Oxiran-2-ylmethoxy)-1*H*-indole (3m). The intermediate **3m** was obtained according to general procedure using 1*H*-indol-6-ol **2m**. Yield 89.43%; oily liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.2 (1H, s), 7.27 (1H, d, J = 9.5 Hz), 7.15 (2H, m), 6.9 (1H, d, J = 8.7 Hz), 6.48 (1H, s), 4.26 (1H, d, J = 11.0 Hz), 4.01 (1H, d, J = 11.0 Hz), 3.42 (1H, m), 2.92 (1H, t, J = 4.2 Hz), 2.79 (1H, d, J = 4.9 Hz). MS (Mwt.: 189.08).

5.2.2. General procedure for the synthesis of intermediates 4 and 5

Under an inert atmosphere (N_2), a mixture of Boc-piperazine1-1carboxylate (1 equiv), Dimethyl-sulfamoyl chloride (1 equiv), and *N*-ethyl-*N*-isopropylpropan-2-amine (1 equiv) in DCM was stirred at room temperature for 24 h. The reaction mixture was diluted into 100 ml of water, and then extracted with DCM (10 ml × 6). The organic layers were combined then dried over Na_2SO_4. Concentration under vacuum provided the intermediate **4** which was further reacted in DCM/TFA (7:3) at room temperature. After the reaction was completed, the solution was diluted in water and 1 N KOH was used to make the solution slightly basic. The wanted compound **5** was obtained after extraction by DCM and drying under reduced pressure; to be used directly in the next step without further purification.

5.2.2.1. *tert*-Butyl 4-(*N*,*N*-dimethylsulfamoyl)piperazine-1-carboxylate (4). Yield 100%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.48 (6H, s), 3.19 (4H, s), 2.84 (4H, s), 1.47 (9H, s). MS (Mwt.: 293.14).

5.2.2.2. *N*,*N*-Dimethylpiperazine-1-sulfonamide (5). Yield 87.33%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.24 (4H, t, J = 4.9 Hz), 2.93 (4H, t, J = 4.9 Hz), 2.83 (6, s). MS (Mwt.: 193.09).

5.2.3. General procedure for the synthesis of compound 1 and derivatives 6a–m

A mixture of intermediate **3** (1 equiv) with the appropriate piperazine derivative (1.2 equiv) in EtOH (10 ml) was heated at reflux for 5–8 h. The reaction mixture was cooled to room temperature then concentrated. The mixture was purified by column chromatography using PE/EA or recrystallization in EtOAc to afford compounds **1** and **6a**–**m**.

5.2.3.1. 4-(3-((6-Bromonaphthalen-2-yl)oxy)-2-hydroxypropyl)-*N*,*N*-dimethylpiperazine-1-sulfonamide (1). The compound **1** was obtained according to general procedure using *N*,*N*-dimethylpiperazine-1-sulfonamide. Yield 37%; white solid; mp 148 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.93 (1H, s), 7.64 (2H, m), 7.53 (1H, m), 7.19 (1H, d, J = 8.9 Hz), 7.13 (1H, s), 4.12 (2H, t, J = 4.6 Hz), 3.45 (2H, m), 2.81 (14H, m). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 156.33, 132.43, 129.69, 129.23, 129.17, 128.10, 127.91, 128.10, 127.91, 119.25, 116.81, 106.36, 69.62, 65.17, 59.93, 52.35, 45.71, 37.73, 29.18. HRMS (ESI): calculated for $C_{19}H_{26}BrN_3O_4S$ $[M+H]^+$ 474.08, found 474.0882. Purity: 99.57% by HPLC (MeOH/H_2O = 80:20).

5.2.3.2. 1-(4-(3-((6-Bromonaphthalen-2-yl)oxy)-2-hydroxypropyl)piperazin-1-yl)ethanone (6a). The compound **6a** was obtained according to general procedure using 1-(piperazin-1-yl)ethanone. Yield 30%; white solid; mp 148 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.91 (1H, s), 7.61 (2H, m), 7.49 (1H, d, 8.7 Hz), 7.15 (1H, d, J = 8.9 Hz), 7.09 (1H, s), 4.12 (3H, m), 3.61 (2H, m), 3.5 (2H, t, J = 4.8 Hz), 2.55 (6H, m), 2.10 (3H, s). HRMS (ESI): calculated for $C_{19}H_{23}BrN_2O_3$ $[M+H]^+$ 407.09, found 407.0981. Purity: 99.87% by HPLC (MeOH/H_2O = 90:10).

5.2.3.3. 1-((6-Bromonaphthalen-2-yl)oxy)-3-(4-isopropylpiperazin-1-yl)propan-2-ol (6b). The compound **6b** was obtained according to general procedure using 1-isopropylpiperazine. Yield 45%; white solid; mp 138.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.91 (1H, s), 7.61 (2H, m), 7.49 (1H, d, J = 8.4 Hz), 7.21 (1H, d, J = 10.7 Hz), 7.11 (1H, s), 4.15 (3H, m), 2.71 (2H, m), 2.61 (9H, m), 1.06 (6H, d, J = 6.3 Hz). HRMS (ESI): calculated for $C_{20}H_{27}BrN_2O_2$ $[M+H]^+$ 409.12, found 409.1297. Purity: 99.69% by HPLC (MeOH/H_2O = 95:05).

5.2.3.4. 1-((6-Bromonaphthalen-2-yl)oxy)-3-(4-cyclopentylpiperazin-1-yl)propan-2-ol (6c). The compound **6c** was obtained according to general procedure using 1-cyclopentylpiperazine. Yield 57%; white solid; mp 154 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.91 (1H, s), 7.6 (2H, m), 7.49 (1H, d, J = 8.7 Hz), 7.21 (1H, d, J = 8.9 Hz), 7.11 (1H, s), 4.09 (3H, m), 2.77 (2H, m), 2.53 (9H, m), 1.87 (2H, m), 1.69 (2H, m), 1.56 (2H, m), 1.33 (2H, m). HRMS (ESI): calculated for $C_{22}H_{29}BrN_2O_2$ $[M+H]^+$ 433.14, found 433.1474. Purity: 99.76% by HPLC (MeOH/H_2O = 95:05).

5.2.3.5. 1-((6-Bromonaphthalen-2-yl)oxy)-3-(4-cyclohexylpiperazin-1-yl)propan-2-ol (6d). The compound **6d** was obtained according to general procedure using 1-cyclohexylpiperazine. Yield 73%; white solid; mp 162 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.90 (1H, s), 7.61 (2H, m), 7.48 (1H, d, J = 8.7 Hz), 7.19 (1H, d, J = 8.9 Hz), 7.17 (1H, s), 4.11 (3H, m), 2.68 (2H, m), 2.55 (8H, m), 2.22 (1H, m), 1.72 (4H, m), 1.26 (6H, m). HRMS (ESI): calculated for $C_{23}H_{31}BrN_2O_2$ $[M+H]^+$ 447.16, found 447.1646. Purity: 99.82% by HPLC (MeOH/H_2O = 90:20).

5.2.3.6. 1-(4-Benzylpiperazin-1-yl)-3-((6-bromonaphthalen-2-yl)oxy)propan-2-ol (6e). The compound **6e** was obtained according to general procedure using 1-benzylpiperazine. Yield 82%; white solid; mp 108.8. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.92 (1H, s), 7.61 (2H, m), 7.52 (1H, d, J = 10.5 Hz), 7.25 (6H, m), 7.12 (1H, d, J = 9.2 Hz), 4.09 (3H, m), 3.52 (2H, d, J = 3.7 Hz), 2.61 (2H, m), 2.55 (8H, m). HRMS (ESI): calculated for $C_{24}H_{27}BrN_2O_2$ $[M+H]^+$ 455.13, found 455.1329. Purity: 97.84% by HPLC (MeOH/H_2O = 95:10).

5.2.3.7. 4-(4-(3-((6-Bromonaphthalen-2-yl)oxy)-2-hydroxypropyl)piperazin-1-yl)phenol (6f). The compound **6f** was obtained according to general procedure using 4-(piperazin-1-yl) phenol. Yield 67%; white solid; mp 257 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.77 (1H, s), 8.1 (1H, s), 7.79 (2H, m), 7.55 (1H, d, J = 8.4 Hz), 7.23 (1H, d, J = 8.6 Hz), 6.75 (2H, d, J = 8.7 Hz), 6.62 (2H, d, J = 8.5 Hz), 4.95 (1H, s), 4.06 (3H, m), 2.95 (4H, m), 2.46 (6H, m). ^{13}C NMR (75 MHz, DMSO, δ ppm): 157.33, 150.05, 144.18, 132.87, 129.58, 129.29, 129.14, 128.83, 128.52, 119.94, 117.61, 116.16, 115.38, 106.75, 71.19, 66.47, 61.05, 53.66, 50.01. HRMS (ESI): calculated for $C_{23}H_{25}BrN_2O_3$ $[M+H]^+$ 459.10, found 459.1113. Purity: 98.61% by HPLC (MeOH/H_2O = 95:10).

5.2.3.8. 3-(4-(3-((6-Bromonaphthalen-2-yl)oxy)-2-hydroxypropyl)piperazin-1-yl)phenol (6g). The compound **6g** was obtained according to general procedure using 3-(piperazin-1-yl) phenol. Yield 75%; white solid; mp 236 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 9.11 (1H, s), 8.12 (1H, s), 7.81 (2H, m), 7.56 (1H, d, J = 8.7 Hz), 7.38 (1H, s), 7.25 (1H, d, J = 9.0 Hz), 6.97 (1H, t, J = 6.8 Hz), 6.36 (1H, d, J = 8.3 Hz), 6.30 (1H, s), 6.21 (1H, d, J = 3.9 Hz), 4.98 (1H, d, J = 4.3 Hz), 4.09 (3H, m), 3.08 (4H, m), 2.55 (6H, m). ^{13}C NMR (75 MHz, DMSO, δ ppm): 158.54, 157.53, 152.88, 133.36, 130.08, 129.96, 129.80, 129.65, 129.35, 129.04, 120.45, 116.68, 118.91, 107.22, 106.53, 102.81, 71.66, 66.96, 61.55, 53.96, 48.69. HRMS (ESI): calculated for $C_{23}H_{25}BrN_2O_3$ $[M+H]^+$ 457.10, found 457.1122. Purity: 92.84% by HPLC (MeOH/H_2O = 90:10).

5.2.3.9. 2-(4-(3-((6-Bromonaphthalen-2-yl)oxy)-2-hydroxypropyl)piperazin-1-yl)phenol (6h). The compound **6h** was obtained according to general procedure using 2-(piperazin-1-yl) phenol. Yield 67%; white solid; mp 153 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.92 (1H, s), 7.62 (2H, m), 7.51 (1H, d, J = 6.9 Hz), 7.21 (2H, m), 7.1 (2H, m), 6.95 (1H, d, J = 9.2 Hz), 6.89 (1H, t, J = 8.9 Hz), 4.22 (1H, m), 4.13 (2H, d, J = 3.9 Hz), 2.91 (6H, m), 2.68 (4H, m). ^{13}C NMR (75 MHz, DMSO, δ ppm): 157.56, 150.50, 140.34, 133.38, 130.08, 129.80, 129.66, 129.36, 129.04, 123.12, 120.47, 119.83, 118.91, 116.66, 115.95, 107.22, 71.73, 66.91, 61.68, 54.22, 50.60. HRMS (ESI): calculated for $C_{23}H_{25}BrN_2O_3$ $[M+H]^+$ 457.10, found 457.1122. Purity: 95.60% by HPLC (MeOH/H_2O = 90:10).

5.2.3.10. 1-((6-Bromonaphthalen-2-yl)oxy)-3-(4-(*p*-tolyl)piperazin-1-yl)propan-2-ol (6i). The compound **6i** was obtained according to general procedure using 1-(*p*-tolyl)piperazine. Yield 88%; white solid; mp 194.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.92 (1H, s), 7.78 (2H, m), 7.5 (1H, d, J = 8.7 Hz), 7.21 (1H, m), 7.12 (3H, m), 6.86 (2H, d, J = 8.5 Hz), 4.21 (1H, m), 4.12 (2H, d, J = 4.8 Hz), 3.17 (4H, m), 2.87 (2H, m), 2.67 (4H, m), 2.28 (3H, s). HRMS (ESI): calculated for $C_{24}H_{27}BrN_2O_2$ $[M+H]^+$ 455.13, found 455.1328. Purity: 94.85% by HPLC (MeOH/H_2O = 90:10).

5.2.3.11. 1-((6-Bromonaphthalen-2-yl)oxy)-3-(4-(4-chlorophenyl)piperazin-1-yl)propan-2-ol (6j). The compound **6j** was obtained according to general procedure using 1-(4-chlorophenyl)piperazine. Yield 61%; white solid; mp 193.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.95 (1H, s), 7.70–7.54 (2H, m), 7.51 (1H, d, J = 7.5 Hz), 7.26 (3H, m), 7.16 (1H, s), 6.88 (2H, d, J = 8.9 Hz), 4.23 (1H, m), 4.16 (2H, d, J = 4.7 Hz), 3.22 (4H, m), 2.88 (2H, m), 2.71 (4H, m). HRMS (ESI): calculated for $C_{23}H_{24}BrClN_2O_2$ $[M+H]^+$ 475.07, found 475.0787. Purity: 96.52% by HPLC (MeOH/H_2O = 90:10).

5.2.3.12. 1-((6-Bromonaphthalen-2-yl)oxy)-3-(4-phenylpiperazin-1-yl)propan-2-ol (6k). The compound **6k** was obtained according to general procedure using 1-phenylpiperazine. Yield 82%; white solid; mp 192 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.92 (1H, s), 7.9 (2H, m), 7.5 (1H, d, J = 8.7 Hz), 7.26 (3H, m), 7.13 (1H, s), 6.91 (3H, m), 4.2 (1H, m), 4.13 (2H, d, J = 4.7 Hz), 3.24 (4H, m), 2.91 (2H, m), 2.67 (4H, m). HRMS (ESI): calculated for $C_{23}H_{25}BrN_2O_2$ $[M+H]^+$ 441.11, found 441.1166. Purity: 95.45% by HPLC (MeOH/H_2O = 90:10).

5.2.3.13. 1-((6-Bromonaphthalen-2-yl)oxy)-3-(4-(4-methoxyphenyl)piperazin-1-yl)propan-2-ol (6l). The compound **6l** was obtained according to general procedure using 1-(4-methoxyphenyl)piperazine. Yield 30%; white solid; mp 182.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.92 (1H, s), 7.63 (2H, m), 7.5 (1H, d, J = 8.7 Hz), 7.21 (H, d, J = 8.9 Hz), 7.12 (1H, s), 6.88 (4H, m), 4.21 (1H, m), 4.1 (2H, d, J = 4.4 Hz), 3.77 (3H, s), 3.13 (4H, m), 2.90–2.86 (2H, m), 2.70 (4H, m). HRMS (ESI): calculated for $C_{24}H_{27}BrN_2O_3$ $[M+H]^+$ 471.12, found 471.1292. Purity: 95.73% by HPLC (MeOH/H_2O = 90:10).

5.2.3.14. 1-((6-Bromonaphthalen-2-yl)oxy)-3-(4-(pyridin-2-yl) piperazin-1-yl)propan-2-ol (6m). The compound **6m** was obtained according to general procedure using 1-(pyridin-2-yl) piperazine. Yield 13.29%; white solid; mp 165 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.21 (1H, d, J = 4.7 Hz), 7.93 (1H, s), 7.63 (2H, m), 7.51 (2H, m), 7.22 (1H, d, J = 9 Hz), 7.14 (1H, s), 6.66 (2H, m), 4.21 (1H, m), 4.14 (2H, d, J = 4.2 Hz), 3.6 (4H, m), 2.84 (2H, m), 2.66 (4H, m). HRMS (ESI): calculated for $C_{22}H_{24}BrN_3O_2$ $[M+H]^+$ 442.11, found 442.1132. Purity: 99.37% by HPLC (MeOH/H_2O = 80:20).

5.2.4. General procedure for the synthesis of intermediates 7a–c

6-Bromonaphtalen-2-ol (1 equiv) and K_2CO_3 (1.5 equiv) were introduced into a round bottom flask then stirred in DMF under an inert atmosphere. Corresponding α,ω-dibromoalkane derivative (2 equiv) was dropwise added. The reaction was stirred at room temperature; overnight. After the reactions was completed, water (200 ml) was dropped into the reaction solution to allow the precipitation of the desired compound (**7a**–**c**) as a white solid, to be collected through filtration under vacuum.

5.2.4.1. 2-Bromo-6-(2-bromoethoxy)naphthalene (7a). The intermediate **7a** was obtained according to general procedure using 1,2-dibromoethane. Yield 37.54%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.94 (1H, s), 7.6 (3H, m), 7.2 (1H, d, J = 8.9 Hz), 7.09 (1H, s), 4.41 (2H, t, J = 6.2 Hz), 3.72 (2H, t, J = 6.2 Hz), MS (Mwt.: 327.91).

5.2.4.2. 2-Bromo-6-(3-bromopropoxy)naphthalene (7b). The intermediate **7b** was obtained according to general procedure using 1,3-dibromopropane. Yield 35.44%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (1H, s), 7.62 (2H, m), 7.51 (1H, d, J = 8.7 Hz), 7.13 (2H, m), 4.1 (2H, t, J = 5.8 Hz), 3.52 (2H, t, J = 6.4 Hz), 2.13 (4H, m), MS (Mwt.: 341.93).

5.2.4.3. 2-Bromo-6-(4-bromobutoxy)naphthalene (7c). The intermediate **7c** was obtained according to general procedure using 1,4-dibromobutane. Yield 35.46%; white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (1H, s), 7.64 (2H, m), 7.51 (1H, d,

J = 10.2 Hz), 7.13 (2H, m), 4.1 (2H, t, *J* = 5.9 Hz), 3.52 (2H, t, *J* = 6.4 Hz), 2.12 (4H, m), MS (Mwt.: 355.94).

5.2.5. General procedure for the synthesis of compounds 8a–c

4-(Piperazin-1-yl)phenol (1.1 equiv) and K_2CO_3 (1.5 equiv) were introduced into a round bottom flask in DMF under N_2. 1 equiv of the corresponding intermediate (**7a**–**c**) was added. The mixture was stirred at 60 °C under reflux during 5 h. After the reaction was completed, it was allowed to cool to room temperature. 100 ml of water was added which allowed the precipitation of our target compound (**8a**–**c**).

5.2.5.1. 4-(4-(2-((6-Bromonaphthalen-2-yl)oxy)ethyl)piperazin-1-yl)phenol (8a). Compound **8a** was obtained according to general procedure using the intermediate **7a**. Yield 20%; white solid; mp 153 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.78 (1H, s), 8.09 (1H, s), 7.78 (2H, m), 7.55 (1H, d, *J* = 8.5 Hz), 7.39 (1H, s), 7.21 (1H, d, *J* = 8.5 Hz), 6.76 (2H, d, *J* = 8.6 Hz), 6.62 (2H, d, *J* = 8.6 Hz), 4.21 (2H, t, *J* = 5.3 Hz), 2.96 (4H, m), 2.8 (2H, t, *J* = 5.3 Hz), 2.63 (4H, m). HRMS (ESI): calculated for $C_{22}H_{23}BrN_2O_2$ $[M+H]^+$ 427.09, found 427.1019. Purity: 92.47% by HPLC (MeOH/H_2O = 90:10).

5.2.5.2. 4-(4-(3-((6-Bromonaphthalen-2-yl)oxy)propyl)piperazin-1-yl)phenol (8b). Compound **8b** was obtained according to general procedure using the intermediate **7b**. Yield 58.37%; white solid; mp 194.1 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.78 (1H, s), 8.08 (1H, s), 7.78 (2H, t, *J* = 10.2 Hz), 7.54 (1H, d, *J* = 8.7 Hz), 7.34 (1H, s), 7.2 (1H, d, *J* = 8.9 Hz), 6.75 (2H, d, *J* = 8.6 Hz), 6.62 (2H, d, *J* = 8.6 Hz), 4.12 (2H, t, *J* = 6.0 Hz), 2.94 (4H, m), 2.49 (4H, m), 1.93 (2H, t, *J* = 6.9 Hz), 1.32 (2H, m). HRMS (ESI): calculated for $C_{23}H_{25}BrN_2O_2$ $[M+H]^+$ 442.11, found 442.1172. Purity: 94.51% by HPLC (MeOH/H_2O = 90:10).

5.2.5.3. 4-(4-(4-((6-Bromonaphthalen-2-yl)oxy)butyl)piperazin-1-yl)phenol (8c). Compound **8c** was obtained according to general procedure using the intermediate **7c**. Yield 24.73%; white solid; mp 162.1 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.78 (1H, s), 8.08 (1H, s), 7.77 (2H, m), 7.53 (1H, d, *J* = 8.7 Hz), 7.34 (1H, s), 7.21 (1H, d, *J* = 8.8 Hz), 6.73 (2H, d, *J* = 8.4 Hz), 6.62 (2H, d, *J* = 8.3 Hz), 4.1 (2H, t, *J* = 6.04 Hz), 2.91 (4H, m), 2.48 (4H, m), 2.36 (2H, t, *J* = 6.8 Hz), 1.79 (2H, m), 1.63 (2H, m). HRMS (ESI): calculated for $C_{24}H_{27}BrN_2O_2$ $[M+H]^+$ 455.13, found 455.1325. Purity: 93.59% by HPLC (MeOH/H_2O = 90:10).

5.2.6. General procedure for the synthesis of derivatives 9a–m

A mixture of the appropriate intermediate compound **3a**–**m** (1 equiv) and 4-(piperazin-1-yl)phenol (1.1 equiv) in ethanol (10 ml), was heated at reflux for 5–8 h. After concentration under reduced pressure of the reaction mixture, the crude compounds were purified through column chromatography or recrystallization in EtOAc or EtOH.

5.2.6.1. 4-(4-(2-Hydroxy-3-(naphthalen-2-yloxy)propyl)piperazin-1-yl)phenol (9a). Compound **9a** was obtained according to general procedure using the intermediate **3a**. Yield 34.80%; white solid; mp 207.4 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.79 (1H, s), 7.79 (2H, t, *J* = 7.0 Hz), 7.43 (1H, t, *J* = 7.5 Hz), 7.32 (2H, d, *J* = 6.0 Hz), 7.17 (1H, d, *J* = 8.9 Hz), 6.76 (2H, d, *J* = 8.9 Hz), 6.62 (2H, d, *J* = 8.9 Hz), 4.96 (1H, s), 3.98 (3H, m), 2.94 (4H, m), 2.52 (6H, m). HRMS (ESI): calculated for $C_{23}H_{26}N_2O_3$ $[M+H]^+$ 379.19, found 379.2015. Purity: 98.61% by HPLC (MeOH/H_2O = 95:10).

5.2.6.2. 4-(4-(3-(4-Bromophenoxy)-2-hydroxypropyl)piperazin-1-yl)phenol (9b). Compound **9b** was obtained according to general procedure using the intermediate **3b**. Yield 84.50%; white solid; mp 184.6 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.81 (1H, s), 7.43 (2H, d, *J* = 8.9 Hz), 6.91 (2H, d, *J* = 8.9 Hz), 6.74 (2H, d, *J* = 8.9 Hz), 6.62 (2H, d, *J* = 8.8 Hz), 4.92 (1H, s), 3.97 (2H, d, *J* = 7.4 Hz), 3.85 (1H, m), 2.92 (4H, m), 2.46 (6H, m). HRMS (ESI): calculated for $C_{19}H_{23}BrN_2O_3$ $[M+H]^+$ 407.09, found 407.0955. Purity: 96.83% by HPLC (MeOH/H_2O = 95:10).

5.2.6.3. 4-(4-(3-(4-Chlorophenoxy)-2-hydroxypropyl)piperazin-1-yl)phenol (9c). Compound **9c** was obtained according to general procedure using the intermediate **3c**. Yield 22.25%; white solid; mp 181.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.27 (2H, d, *J* = 12.6 Hz), 6.87 (6H, m), 4.16 (1H, m), 4.0 (2H, d, *J* = 3.3 Hz), 3.13 (4H, m), 2.87 (2H, m), 2.62 (4H, m). HRMS (ESI): calculated for $C_{19}H_{23}ClN_2O_3$ $[M+H]^+$ 363.14, found 363.1464. Purity: 97.67% by HPLC (MeOH/H_2O = 95:10).

5.2.6.4. 4-(4-(3-(2-Chlorophenoxy)-2-hydroxypropyl)piperazin-1-yl)phenol (9d). Compound **9d** was obtained according to general procedure using the intermediate **3d**. Yield 31.38%; white solid; mp 100.7 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.84 (1H, s), 7.42 (1H, d, *J* = 7.8 Hz), 7.29 (1H, t, *J* = 7.7 Hz), 7.18 (1H, d, *J* = 7.5 Hz), 6.95 (1H, t, *J* = 7.5 Hz), 6.71 (4H, m), 4.96 (1H, s), 4.05 (3H, m), 2.95 (4H, m), 2.52 (6H, m). HRMS (ESI): calculated for $C_{19}H_{23}N_2O_3$ $[M+H]^+$ 363.14, found 363.1453. Purity: 94.23% by HPLC (MeOH/H_2O = 95:10).

5.2.6.5. 4-(4-(2-Hydroxy-3-(*p*-tolyloxy)propyl)piperazin-1-yl)phenol (9e). Compound **9e** was obtained according to general procedure using the intermediate **3e**. Yield 6.64%; white solid; mp 172.5 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.81 (1H, s), 7.08 (2H, d, *J* = 8.2 Hz), 6.81 (4H, m), 6.63 (2H, d, *J* = 8.8 Hz), 4.88 (1H, s), 3.94 (2H, m), 3.83 (1H, m), 2.94 (4H, m), 2.47 (6H, m), 2.23 (3H, s). HRMS (ESI): calculated for $C_{20}H_{26}N_2O_3$ $[M+H]^+$ 343.19, found 343.2011. Purity: 95.98% by HPLC (MeOH/H_2O = 95:10).

5.2.6.6. 4-(4-(2-Hydroxy-3-(*m*-tolyloxy)propyl)piperazin-1-yl)phenol (9f). Compound **9f** was obtained according to general procedure using the intermediate **3f**. Yield 46.30%; white solid; mp 146.2 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.85 (1H, s), 7.35 (8H, m), 4.86 (1H, s), 3.97 (2H, d, *J* = 7.2 Hz), 3.91 (1H, m), 2.95 (4H, m), 2.55 (6H, m), 2.28 (3H, s). HRMS (ESI): calculated for $C_{20}H_{26}N_2O_3$ $[M+H]^+$ 343.19, found 343.2000. Purity: 98.61% by HPLC (MeOH/H_2O = 95:10).

5.2.6.7. 4-(4-(2-Hydroxy-3-(3-methoxyphenoxy)propyl)piperazin-1-yl)phenol (9g). Compound **9g** was obtained according to general procedure using the intermediate **3g**. Yield 7.41%; white solid; mp 127 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.21 (1H, t, *J* = 7.9 Hz), 6.89 (2H, d, *J* = 8.9 Hz), 6.79 (2H, d, *J* = 8.9 Hz), 6.56 (3H, m), 4.18 (1H, m), 4.03 (2H, d, *J* = 4.8 Hz), 3.82 (3H, s), 3.14 (4H, m), 2.89 (2H, m), 2.66 (4H, m). HRMS (ESI): calculated for $C_{20}H_{26}N_2O_4$ $[M+H]^+$ 359.19, found 359.1951. Purity: 99.47% by HPLC (MeOH/H_2O = 95:10).

5.2.6.8. 4-(4-(3-(4-Ethylphenoxy)-2-hydroxypropyl)piperazin-1-yl)phenol (9h). Compound **9h** was obtained according to general procedure using the intermediate **3h**. Yield 28.54%; white solid; mp 151.4 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.83 (1H, s), 7.12 (2H, d, *J* = 8.4 Hz), 6.86 (2H, d, *J* = 8.5 Hz), 6.77 (2H, d, *J* = 8.8 Hz), 6.65 (2H, d, *J* = 8.8 Hz), 4.9 (1H, s), 3.95 (2H, d, *J* = 6.1 Hz), 3.85 (1H, m), 2.95 (4H, m), 2.53 (6H, m), 2.4 (2H, m), 1.14 (3H, t, *J* = 7.5 Hz). HRMS (ESI): calculated for $C_{21}H_{28}N_2O_3$ $[M+H]^+$ 357.21, found 357.2170. Purity: 98.61% by HPLC (MeOH/H_2O = 95:10).

5.2.6.9. 4-(4-(3-(4-(*tert*-Butyl)phenoxy)-2-hydroxypropyl)piperazin-1-yl)phenol (9i). Compound **9i** was obtained according to general procedure using the intermediate **3i**. Yield 40.06%; white

solid; mp 166 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.31 (2H, t, J = 8.8 Hz), 6.86 (4H, m), 6.8 (2H, d, J = 7.2 Hz), 4.14 (2H, m), 4.0 (1H, d, J = 4.8 Hz), 3.1 (4H, m), 2.62 (2H, m), 2.06 (4H, m), 1.30 (9H, s). HRMS (ESI): calculated for $C_{23}H_{32}N_2O_3$ $[M+H]^+$ 385.24, found 385.2477. Purity: 99.76% by HPLC ($MeOH/H_2O$ = 95:10).

5.2.6.10. 4-(4-(3-(4-Aminophenoxy)-2-hydroxypropyl)piperazin-1-yl)phenol (9j). Compound **9j** was obtained according to general procedure using the intermediate **3j**. Yield 60%; Brown solid; mp 182.6 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 8.82 (1H, s), 6.63 (8H, m), 4.73 (2H, s), 3.81 (3H, m), 2.95 (4H, m), 2.4 (6H, m). HRMS (ESI): calculated for $C_{19}H_{25}N_3O_3$ $[M+H]^+$ 344.19 found 344.1984. Purity: 96.58% by HPLC ($MeOH/H_2O$ = 95:10).

5.2.6.11. 4-(4-(3-([1,1′-Biphenyl]-4-yloxy)-2-hydroxypropyl) piperazin-1-yl)phenol (9k). Compound **9k** was obtained according to general procedure using the intermediate **3k**. Yield 41.78%; white solid; mp 226.7 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 7.59 (4H, m), 7.41 (2H, t, J = 7.4 Hz), 7.3 (1H, t, J = 7.2 Hz), 7.03 (2H, d, J = 8.5 Hz), 6.75 (2H, d, J = 9 Hz), 6.62 (2H, d, J = 8.7 Hz), 4.98 (1H, s), 4.01 (3H, m), 2.94 (4H, m), 2.53 (6H, m). HRMS (ESI): calculated for $C_{25}H_{28}N_2O_3$ $[M+H]^+$ 405.21, found 405.2172. Purity: 96.99% by HPLC ($MeOH/H_2O$ = 95:10).

5.2.6.12. 4-(4-(3-(Benzo[*d*][1,3]dioxol-5-yloxy)-2-hydroxypropyl)piperazin-1-yl)phenol (9l). Compound **9l** was obtained according to general procedure using the intermediate **3l**. Yield 64.63%; white solid; mp 143.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.8 (5H, m), 6.56 (1H, s), 6.37 (1H, d, J = 9.5 Hz), 5.95 (2H, s), 4.12 (1H, m), 3.96 (2H, d, J = 4.6 Hz), 3.12 (4H, m), 2.88 (2H, m), 2.62 (4H, m). HRMS (ESI): calculated for $C_{20}H_{24}N_2O_5$ $[M+H]^+$ 373.17, found 373.1735. Purity 95.19% by HPLC ($MeOH/H_2O$ = 95:10).

5.2.6.13. 4-(4-(3-((1*H*-Indol-6-yl)oxy)-2-hydroxypropyl)piperazin-1-yl)phenol (9m). Compound **9m** was obtained according to general procedure using the intermediate **3m**. Yield 32.10%; white solid; mp 172.2 °C. ^{1}H NMR (300 MHz, DMSO, δ ppm): 7.25 (2H, d, J = 8.4 Hz), 7.03 (1H, s), 6.74 (3H, m), 6.62 (2H, d, J = 8.6 Hz), 6.30 (1H, s), 4.85 (1H, s), 3.95 (3H, m), 2.94 (4H, m), 2.54 (6H, m). HRMS (ESI): calculated for $C_{21}H_{25}N_3O_3$ $[M+H]^+$ 368.19, found 368.1961. Purity: 95.70% by HPLC ($MeOH/H_2O$ = 95:10).

5.3. Docking studies

Docking studies were carried out using GOLD docking software 5.0. It is one of the best docking programs which use a powerful genetic algorithm (GA) method for conformation search and docking. We selected the Hsp90-ligand complex (PDB id: 2xjx) to perform our docking studies. The active site was consisted of residues around the original ligand (radius 8.0 Å), which completely covered the Hsp90 ATP binding pocket. Various possible stereoisomers, ionized forms and conformations of ligands were generated by Prepare Ligands protocol in DS at pH 7.0 ± 0.2. Docking studies were performed using the standard default settings with 10 GA runs on each molecule. For each of the GA runs, a maximum of 125,000 operations were performed. All options including; flipping of ring corners, secondary and tertiary amines, amides, pyramidal nitrogens, and rotation of carboxylate groups, as well as torsion angle distribution and post process rotatable bonds were used as default, with respect to the ligand flexibility. The annealing parameters were used as default cutoff values of 3.0 Å for hydrogen bonds and 4.0 Å for van der Waals interactions. To facilitate the correct starting orientation of the compound for docking; the hydrophobic fitting points were calculated. When the top three solutions attained root-mean-square deviation (rmsd) values within 1.5 Å, docking was terminated. The scoring function parameter of the software uses the intra- and intermolecular hydrogen bonding interaction energy, van der Waals energy, and ligand torsion energy, to evaluate the dimensionless fitness of the ligands into the binding site.

5.4. Protein preparation

Escherichia coli cultures were grown in LB media (yeast extract, TRYPTONE, NaCl), the region encoding full-length of Hsp90 was sub-cloned into Kana. Expression of Protein in *E. coli* cells was induced with 0.5 mM IPTG. Cells were harvested after 20 h of growth at 16 °C and then disrupted by sonication. After clarification of the soluble lysate by centrifugation, it was applied to a Ni2+ -nitrilotriacetic acid (NTA) agarose column in buffer (50 mM Tris-Cl, 300 mM NaCl, 10 mM Imidazole, 10% [v/v] Glycerol, 10 mM PMSF, 10 mM DTT). Hsp90 Protein was eluted with a linear gradient of 20–1000 mM imidazole. Hsp90 was identified by SDS–PAGE, and the high concentrated fraction was dialyzed against ATPase buffer (20 mM Tris-Cl, pH 7.5; 6 mM MgCl2; 20 mM KCl) and then aliquoted, frozen in liquid nitrogen, stored at −80 °C.

5.5. The measurement of ATP hydrolysis inhibition

The ATPase activity assay was based on the conversion of ATP to ADP. ATP hydrolysis inhibitory effects of the compounds against HSP90 full length were evaluated using the Discover RX ADP HunterTM Plus Assay kit (Discoverx, Fremont, CA). The tested compounds were diluted to 100 μM in 2.0% (v/v) DMSO, 20 μL of test compounds solution of different concentrations was added to each well of the 384-well black flat-bottomed polystyrene plate. The first and last rows of assay plates contained the appropriate concentration of DMSO as blank control. ATP was dissolved in the assay buffer (15 mM HEPES (pH 7.4), 20 mM NaCl, 1 mM EDTA, 10 mM $MgCl_2$, and 0.02% Tween) to give a stock concentration of 100 mM and stored at room temperature. 20 μL aliquot of prepared ATP solution was added to each well. Hsp90 protein was thawed on ice before usage and then suspended in chilled assay buffer to a stock concentration of 3 μM. The incubation was started by adding 20 μL of the stock Hsp90 to each well (except for the background wells which received 20 μL of assay buffer), leading to a final assay volume of 60 μL. The assay was carried out and The Discover RX ADP HunterTM plus Assay kit reagents were added after 3 h of incubation at 37 °C for detection of ATP hydrolysis following the manufacturer's instructions. The concentration of ADP was measured using Varioskan spectrophotometer (Thermo, 540 nm excitation and 620 nm emission). Fluorescence intensity values measured for Hsp90 without any testing compound was assumed as 100% of enzyme activity. The background reaction rate was measured in a reaction lacking enzyme or substrate and subtracted from the experimental rates.

5.6. Anti-proliferation activity

Cell viabilities were measured by a colorimetric assay using 3-(4, 5-dimethylthiaz-ol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT, *Sigma, Ltd*). Cells were supplemented with medium culture (PH 7.4) containing NaHCO3 (2.2 g), penicillin-G-sodium salt (0.1 g), streptomycin sulfate (0.1 g), and L-glutamine then grown in a humidified atmosphere (37 °C, 5% CO_2), seeded in 96-well plates (5000/well, 100 μL) and allowed to attach overnight. The experiments were carried out in triplicate in a parallel manner for each concentration of target compounds with the appropriate volumes of medium culture which were added to cells. After incubation for 72 h, absorbance was measured at 570 nm. IC_{50} was taken as the concentration that caused 50% inhibition of cell viabilities and calculated by the GraphPad Prism 6.

5.7. Western blotting analysis

MCF-7 cells were cultured then treated with various concentrations of **6f** dissolved in the medium culture. After stimulation and treatment with lysis buffer (50 mM Tris-Cl, pH 7.6, 150 Mm NaCl, 1 mM EDTA, 1% (m/v) Nonidet P-40 (NP-40), 0.2 mM Phenylmethanesulfonyl fluoride (PMSF), 0.1 mM NaF and 1.0 mM dithiothreitol (DTT)), the protein concentration was determined through BCA protein assay kit and equal amounts of proteins were uploaded (50 μg). The Protein lysates were separated on (5–12%) gradient gels, transferred onto a PVDF membrane and then immunoblotting with the corresponding specific antibodies (Actin, ERK1/2, Akt, HER-2 and Hsp90) overnight at 4 °C. After repeated washes of the membranes using TBS (5 min for each wash), the membranes were incubated with appropriate secondary antibodies in 5% milk for 1 h. Signals were detected using Odyssey Infrared Imaging System (LI-COR; Lincoln, NE).

5.8. Cell morphological assessment

Detection of morphological evidence of apoptosis in MCF-7 cancer cell nucleus was visualized following DNA staining with the fluorescent dye DAPI. Briefly, 1×10^5 cells (by well) were incubated with or without the selected compound **6f** at concentrations of 0.5 μM and 2 μM in 6-well tissue culture plates. At the end of incubation, the morphology of cells was monitored under an inverted light microscope. Cells were then fixed with 4% paraform for 20 min and washed with PBS, and then incubated with DAPI (1 μg/ml) for 10 min. the medium was discarded and cells were washed with PBS. Morphological changes of apoptotic cells were observed using fluorescent microscopy (Olympus, Japan) with a peak excitation wave length of 340 nm.

Acknowledgments

This work is supported by the project 81502990 (Youth Foundation), BK20150691 (Foundation Research Project of Jiangsu Province), 1501033C (Postdoctoral Fund in Jiangsu Province), and the Priority Academic Program Development of Jiangsu Higher Education Institutions. The authors declare no other conflicts of Interest.

Supplementary data

Supplementary data (experimental procedures and characterization for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2016.03.049.

References and notes

1. Li, J.; Buchner, J. *Biomed. J.* **2013**, *36*, 106.
2. Sreedhar, A. S.; So, C.; Csermely, P. *Biochim. Biophys. Acta, Proteins Proteom.* **2004**, *1697*, 233.
3. Workman, P.; Burrows, F.; Neckers, L.; Rosen, N. *Ann. N.Y. Acad. Sci.* **2007**, *1113*, 202.
4. Zuehlke, A.; Johnson, J. L. *Biopolymers* **2010**, *93*, 211.
5. Solit, D. B.; Chiosis, G. *Drug Discovery Today* **2008**, *13*, 38.
6. Jhaveri, K.; Taldone, T.; Modi, S.; Chiosis, G. *Biochim. Biophys. Acta, Mol. Cell Res.* **2012**, *1823*, 742.
7. Wang, Y.; McAlpine, S. R. *Future Med. Chem.* **2015**, *7*, 87.
8. Kanamaru, C.; Yamada, Y.; Hayashi, S.; Matsushita, T.; Suda, A.; Nagayasu, M.; Kimura, K.; Chiba, S. *J. Toxicol. Sci.* **2014**, *39*, 59.
9. Hall, J. A.; Forsberg, L. K.; Blagg, B. S. *Future Med. Chem.* **2014**, *6*, 1587.
10. Jia, J.; Xu, X.; Liu, F.; Guo, X.; Zhang, M.; Lu, M.; Xu, L.; Wei, J.; Zhu, J.; Zhang, S. *PLoS One* **2013**, e59315.
11. Jia, J.-M.; Liu, F.; Xu, X.-L.; Guo, X.-K.; Jiang, F.; Cherfaoui, B.; Sun, H.-P.; You, Q.-D. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1557.