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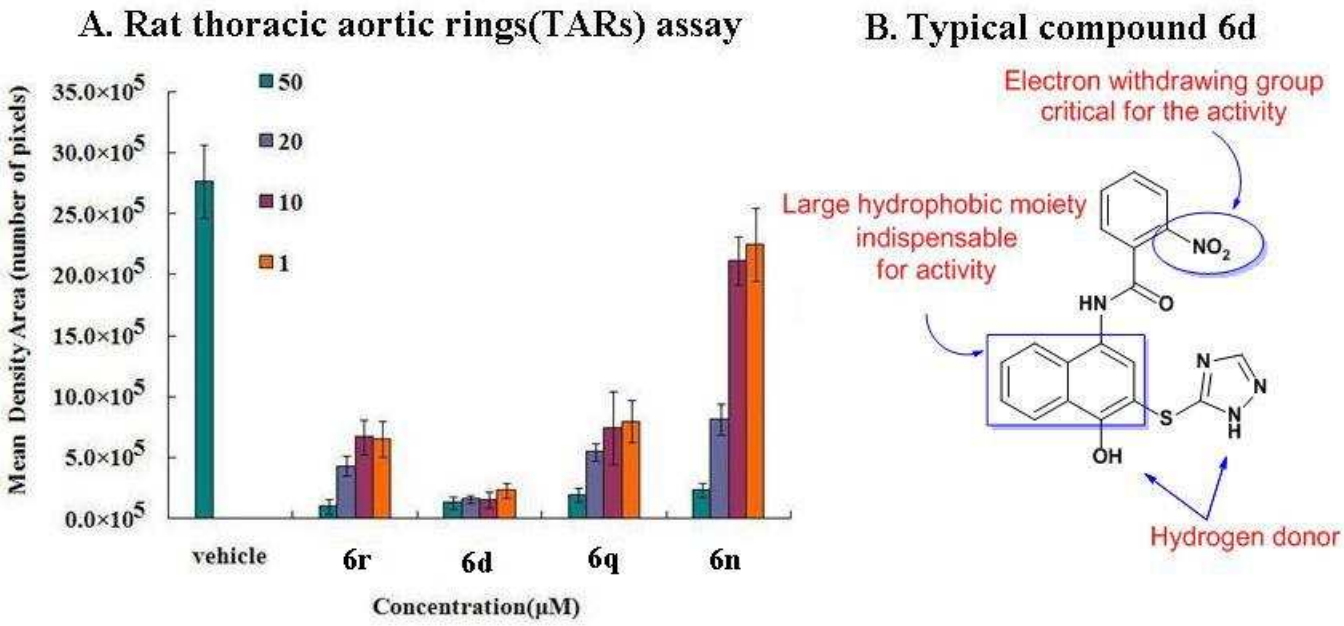
Graphical Abstract:



Synthesis and biological evaluation of N-(4-hydroxy-3-mercaptonaphthalen-1-yl)amides as inhibitors of angiogenesis and tumor growth

Fuming Xu[a], Yuping Jia[b], Qingli Wen[c], Xuejian Wang[a], Lei Zhang[a], Yingjie Zhang[a], Kanghui Yang[a], Wenfang Xu[a,*]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Shandong University, Ji'nan, Shandong 250012, PR China*

[b]*Shandong Institute of Pharmaceutical Industry, No. 989 High-tech Industrial Development Zone Xinluo road, Ji'nan, Shandong 250101, PR China*

[c]*Affiliated Hospital of Weifang Medical University, Weifang, Shandong 261031, PR China*

Abstract

A series of N-(4-hydroxy-3-mercaptonaphthalen-1-yl)amides were synthesized and investigated for their *in vitro* antiangiogenic activity. Among these compounds, **6d**, which possesses an ortho-nitro group at the benzene ring, exhibited potent inhibitory effect on the proliferation of HUVECs, A549, K562, PC-3, HCT116, MDA-MB-231 and MCF-7 cells (IC_{50} = 5.34, 40.53, 10.81, 52.52, 10.19, 21.37 and 2.81 μM, respectively). Meanwhile, compound **6d** inhibited *in vitro* angiogenesis markedly in both HUVECs tube formation assay and the rat thoracic aorta rings test. Further kinase assay study showed that compound **6d** had good VEGFR2, ALK, AKT1 and ABL inhibitory activities and moderate EGFR and PDGFR-β inhibitory activities. The data supports the further investigation of this class of compounds as potential antiangiogenic and anticancer agents.

Keywords: angiogenesis; HUVECs; tube formation; rat thoracic aorta rings; inhibitor; kinase

* Corresponding author. Tel./fax: +86 531 88382264. E-mail address: wfxu@yahoo.cn (W. Xu).

1. Introduction

Aberrant angiogenesis, the process that leads to the formation of newly abnormal vessels, is a prerequisite for tumor cell proliferation, invasion and metastasis [1-3]. Tumor-induced blood capillaries can help to create nutrient supply, to remove metabolic waste and to facilitate metastasis formation for several solid tumors and haematological malignancies [2, 4]. Protein kinases, especially protein tyrosine kinases (PTKs) such as vascular endothelial growth factor receptors (VEGFRs) [5, 6], epidermal growth factor receptor (EGFR) [7] and platelet-derived growth factor receptors (PDGFRs) [8] are closely associated with aberrant signaling leading to increased angiogenesis, tumor cell proliferation and metastasis [5, 9, 10].

It has been demonstrated that blockade of angiogenesis is one of the more attractive approaches for the treatment of cancer [11, 12], so design of small molecule inhibitors that target the adenosine triphosphate (ATP) binding site of protein kinases is currently of great interest [13-15]. In the past decade, there are several small-molecule angiogenesis inhibitors approved or in late stage clinical trials such as Sunitinib (SU11248) [16, 17], Sorafenib (BAY 43-9006) [18], Pazopanib [19], PTK787 (ZK222584, vatalanib) [20, 21], ZD6474 (vandetanib) [22, 23], Semaxanib (SU5416) [24], Imatinib (Gleevec®, STI571) [25], and so on. Recent preclinical studies show that inhibition of multiple PTKs by single-agents has the potential to increase antitumor activities [26-28].

Herein we report the antitumor and antiangiogenic activity for the newly synthesized 19 compounds. In the scaffold of our target compounds, naphthalene was selected as a hydrophobic domain because its distinctly plane geometrical conformation and structure could form special interaction with ATP binding site of protein kinases. In addition, naphthalene has been employed increasingly in anticancer drug design[29-32], which encourages us to search novel naphthalene-containing structures as inhibitors of angiogenesis and tumor growth. The possible mechanism for the antiangiogenic and antitumor activity was examined under *in vitro* condition. Among these compounds, **6d** exhibits potent inhibitory effects on both the proliferation of several tumor cell lines and *in vitro* angiogenesis by application of tube formation assay using HUVECs [33, 34], the rat thoracic aorta rings model [33, 35] and kinase inhibition assay.

2. Chemistry

The synthetic pathway for target compounds was illustrated in Scheme 1. We first introduced hydroxy into nitronaphthalene **1** in the presence of t-BuOOH and KOH [36, 37]. The nitro-group on compound **2** was then reduced to the amino group by Pd-C/H_2 in methanol solution [38] to give compound **3**, which was acylated using various substituted acyl chlorides [39] to form compounds **4a**-**4m**. Then, compounds **4a**-**4m** were oxidated using $NaIO_4/SiO_2$ [40] to obtain quinone type structures **5a**-**5m**. At last compounds **5a**-**5m** took Michael addition reaction [41] to gain the target compounds **6a**-**6s** with different arylthiol groups. The spectral characterization of all target

compounds is the chemical shift of three active hydrogens (1 × phenolic O<u>H</u> and 2 × aromatic N<u>H</u>) with (DMSO-d_6) δ 9.50-14.25. The chemical shift assignment mentioned above was illustrated in the appropriate part.

(**Scheme 1** should be listed here)

3. Results and discussion

3.1. In vitro antiproliferative activity

In vitro antiproliferative activity of the 19 novel N-(4-hydroxy-3-mercaptonaphthalen-1-yl)amides was initially evaluated against MDA-MB-231, PC-3 and HCT116 cell lines by MTT assay using Sorafenib as a positive control. From the data shown in Table 1, most compounds exhibited weak antiproliferative activity with high IC_{50} (>100 μM) values, while compounds **6c, 6d, 6q** and **6r** showed moderate activity. We can see that compounds that possess a para-chloro group or an ortho-nitro group on the benzene ring of the amide part displayed better antiproliferative activity than that of the other compounds. Comparing compounds **6n**-**6q** and **6c**, when the 1*H*-1,2,4-triazole ring was replaced by 5-methyl-1,3,4-thiadiazole ring or 1,3,4-thiadiazole ring or 1-methyl-1*H*-tetrazole ring, efficacy in inhibiting proliferation almost disappeared. Meanwhile, when the 7*H*-purine took place of 1*H*-1,2,4-triazole ring in the compounds, a slight decrease of the antiproliferative activity was perceived (for instance, the IC_{50} of the three cancer cell lines mentioned in this section of the compound **6c**/**6q** are 25.71/22.97, 5.52/66.43, and 43.27/>100 μM, respectively).

Taking the good *in vitro* activity of compounds **6c, 6d, 6q** and **6r** against MDA-MB-231, PC-3 and HCT116 cell lines into consideration, we further investigated the potential antiproliferative effect of these compounds against another four cell lines, HUVECs, MCF-7, A549 and K562 cells, which are all related to tumor-induced angiogenesis. The results were illustrated in Table 2, which showed that compounds **6d** and **6q** also exhibit low μM activities against the growth of these four cell lines.

(**Table 1** should be listed here)

(**Table 2** should be listed here)

3.2. In vitro antiangiogenesis assay

3.2.1. In vitro HUVECs tuber formation assay

In an effort to study the antiangiogenic effect of all the compounds reported above, we were interested in *in vitro* tube formation assay using HUVECs which were plated on Matrigel in order to mimic *in vivo* HUVEC associated angiogenesis. While the HUVECs were plated, elongated and robust tube-like structures were well established after incubation for 6 h in the negative control group; but treatment of HUVECs with each compound at the concentration of 50 μM inhibited the formation of tubular

structures in different ranks. As shown in Fig. 1A, significant inhibition (>80%) was observed with compounds **6d**, **6r**, **6b**, **6n**, **6o**, **6k** and **6l**. However, compound **6c** possessing good cytotoxic activity showed moderate inhibitory efficacy at 50 μM (65%). In order to determine whether compounds **6d**, **6r**, **6b**, **6n**, **6o**, **6**k, **6l** and **6c** could inhibit the HUVECs tuber formation in a concentration-dependent fashion, we employed another two concentrations (10 and 20 μM) for further tuber formation inhibition test. Surprisingly, almost all the tested compounds exhibited dose-dependent inhibition of tube formation (see Fig. 1B). Compound **6d** and **6n** were found to be the most potent and efficacious, inhibiting tube formation at 10 μM by 83% and 81% respectively, while compound **6c** showed faint tuber formation inhibitory activity at this concentration (data was not shown on Fig. 1B). Representative tube images are shown in Fig. 2.

(**Fig 1** should be listed here)

(**Fig 2** should be listed here)

3.2.2. Rat thoracic aorta rings (TARs) assay

TARs model is more close to *in vivo* condition compared with HUVECs tuber formation model in view of multi-steps involved in angiogenesis: sprouting, proliferation, migration and differentiation. Herein, TARs assay was employed to evaluate the antiangiogenic activity of all the synthesized compounds. The area of angiogenic sprouting, reported in number of pixels, was quantified using Adobe PhotoShop. The results are presented in Fig. 3. Compounds **6d**, **6r**, **6n** and **6q** showed outstanding angiogenesis inhibition ratio at the concentration of 50 μM (95%, 96%, 91% and 92%, respectively), while the rest compounds turned up to be moderate or weak ones (see Fig. 3A). Especially, compound **6c** having weak HUVECs tuber formation inhibitory efficacy still could not reduce microvessel outgrowth at 50 μM. Fig. 3B showed that Compounds **6d**, **6r**, **6n** and **6q** appeared to reduce microvessel outgrowth in a concentration-dependent manner. At 1 μM, compound **6d**, **6r** and **6q** demonstrated >70% inhibition of angiogenesis, comparable with Pazopanib. Among them, compound **6d** was more potent than compound **6r** and **6q**, with 91% reduction of angiogenesis at 1 μM. Interestingly, compound **6n** failed to inhibit microvessel outgrowth when the concentration was below 20 μM (23% and 18% at 10 μM and 1 μM, respectively). Representative images of aortic rings are illustrated in Fig. 4.

(**Fig 3** should be listed here)

(**Fig 4** should be listed here)

3.3. In vitro protein kinase assay

As many tyrosine and serine/threonine kinases are involved in oncogenic signaling, the in vitro kinase assay was carried out to test the kinase inhibition activity of all the

synthesized compounds at the concentration of 10 μM against EGFR, ABL, AKT1, and ALK kinases by measuring the levels of phosphorylation of the kinase-specific ligand peptides. The pan-kinase inhibitor Staurosporine was used as a positive reference compound. As shown in Table 3, most of the compounds showed moderate EGFR, ABL and AKT1 inhibitory activity but no obvious ALK inhibition effect. The only exception was compound **6d**, which still retained potency against ALK (56.83% at 10μM). Compounds **6d**, **6r** and **6q** were found to be more effective than the rest compounds against EGFR, ABL and AKT1. This result was consistent with cell cytotoxicity activity and antiangiogenic effect. Specifically, The most potent compound **6d** inhibited 36.79% , 87.18% and 85.77% of EGFR, ABL and AKT1 activity at 10 μM, respectively. It is interesting that compound **6n** which showed moderate antiangiogenic activity disclosed slight kinase inhibitory effect. A SAR study for all the synthesized compounds was undertaken. The phenyl group of R_1 contributed more to the activity rather than bigger substitutes (such as 2-naphthyl group) or longer substitutes (such as cinnamenyl group). For example, compounds **6a** and **6b** showed less kinase inhibition activity than compounds **6c** and **6d**. Compounds containing electron-withdrawing groups (for instance, -NO_2/-Cl group of **6d**/**6c**) attached to the phenyl ring of R_1 displayed much more inhibitory performances than compounds with electron-donating groups (for instance, -OMe/-Me group of **6e**/**6i**). Comparing compounds **6n**-**6p** and **6c**, when the 1H-1,2,4-triazole ring was replaced by 5-methyl-1,3,4-thiadiazole ring or 1,3,4-thiadiazole ring or 1-methyl-1H-tetrazole ring, efficacy in inhibiting EGFR, ABL and AKT1 kinases almost disappeared. Meanwhile, when the 7H-purine took place of 1H-1,2,4-triazole ring in the compounds (e.g. **6q** and **6c**, **6r** and **6d**), apparent decrease of kinase inhibitory activity was perceived (for instance, the inhibition rates(%) of the compound **6d**/**6r** against EGFR, ABL, AKT, and ALK are 36.79/24.73, 87.18/43.69, and 85.77/50.73, respectively). The inhibition values of compound **6d** against VEGFR2 and PDGFR-β which are both closely related to tumor-induced angiogenesis were further determined. Encouragingly, compound **6d** exhibited 65.23% and 37.93% of VEGFR2 and PDGFR-β inhibitory activity at 10 μM respectively, which indicated that **6d** was a promising lead compound against tumor angiogenesis for further study.

(**Table 3** should be listed here)

3.4. Molecular docking

To further investigate the antiangiogenesis mechanism of compound **6d**, a molecular docking study of **6d** in the ATP-binding pocket of the ABL (PDB ID: 2HYY), EGFR (PDB ID: 2ITY), ALK (PDB ID: 3LCS) and VEGFR2 (PDB ID: 2QU5) kinase domains was performed using SYBYL 8.0 (Fig. 5). Compound **6d** interacted with the ATP binding pocket of the catalytic site of the four kinases mainly through hydrophobic interaction and hydrogen bonds. In this binding mode, the naphthalene ring structure of **6d** sitted in a lipophilic pocket and the two -NH groups interacted with Ile360 and Asp381 of ABL, which was proved to be an important binding site of

ABL inhibitor (see Fig. 5A). As shown in Fig. 5B, **6d** was nicely bound to the EGFR binding domain, of which the ortho-nitro group formd a hydrogen bond with the crucial amino acid MET97. It was consistent with the result that only compound **6d** showed more potent than any other ortho-nitro free compound as an EGFR kinase inhibitor. Comparing the molecular docking of compounds **6d** with ALK and VEGFR2 kinases displayed in Fig. 5C and 5D, the –OH and -S- groups of **6d** could also form hydrogen bonds with different amino acid side chains of the two kinases. The data supports the further investigation of this class of compounds as potential kinase inhibitors.

(**Fig 5** should be listed here)

4. Conclusions

In general, we presented for the first time the synthesis of 19 N-(4-hydroxy-3-mercaptonaphthalen-1-yl)amide derivatives. In light of the biological activity assay results, it is concluded that some of these compounds are selective against the proliferation of HUVECs and several cancer cell lines, microvessel tube formation using HUVECs and endothelial sprouting of TARs. The SAR indicated that electron-withdrawing substituent at the benzene ring of R_1 and 1H-1,2,4-triazole ring (R_2) contributed much to the cytotoxicity and kinase inhibition activity. The results of kinase assay and molecular docking studying exhibited that N-(4-hydroxy-3-mercaptonaphthalen-1-yl)amide derivatives were novel ABL, AKT1, and VEGFR2 kinases inhibitors. Among all the compounds, **6d** comprehensively showed strong inhibitory effect, which deserved further *in vitro* and *in vivo* studies on its mechanism of anti-angiogenesis activity.

5. Experimental part

5.1. Chemistry

Unless otherwise noted, all solvents and reagents were commercially available and used without further purification. All reactions were monitored by thin-layer chromatography on 0.25 mm silica gel plates (60 GF-254) and visualized with UV light, or iodine vapor. Proton NMR spectrums were determined on a Brucker DRX spectrometer (600/300 MHz), δ in parts per million and J in Hertz, using TMS as an internal standard. Measurements were made in DMSO-d_6 solutions. ESI-MS were determined on an API 4000 spectrometer. Melting points were determined on an electrothermal melting point apparatus and were uncorrected.

*5.1.1. 4-nitronaphthalen-1-ol (**2**)*

To a solution of compound **1** (0.86 g, 5 mmol) in 13 ml of DMSO, was added a solution of KOH (1.2 g, 20 mmol) in water (5 mL) at 0-5℃. The mixture was stirred for 5 min before t-BuOOH (1.8 g, 10 mmol) in DMSO (2 mL) was added [36, 37]. After stirring at room temperature for 2 h, the mixture was poured into 1N HCl (50mL) slowly, with yellow solid separation. Crude product compound **2** was obtained after

filtering to remove aqueous phase and then being allowed to dry in air. The crude product was at last recrystallized with ethyl acetate/petroleum ether to give 0.76 g of title compound **2** as a faint yellow powder. Yield: 90 %, mp: 166-168 ℃. ^{1}H NMR (DMSO-d_6) δ 7.00 (d, J = 9.00 Hz, 1H, aromatic H), 7.65 (t, J = 7.20 Hz, 1H, aromatic H), 7.82 (t, J = 7.20 Hz, 1H, aromatic H), 8.34 (d, J = 9.00 Hz, 1H, aromatic H), 8.42 (d, J = 9.00 Hz, 1H, aromatic H), 8.67 (d, J = 9.00 Hz, 1H, aromatic H), 11.95 (s, 1H, phenolic OH). ESI-MS *m/z* 190.4 $[M+H]^+$.

*5.1.2. 4-aminonaphthalen-1-ol (**3**)*

To a solution of compound **2** (1.89 g, 10 mmol) in 50 ml of CH_3OH, was added Pd/C catalyst (0.2 g) [38]. The mixture was stirred for 12h with hydrogen under 10 times standard atmospheric pressure, then the catalyst was filtered and washed with 20 mL of CH_3OH, and the filtrate was evaporated under vacuum. The black residues were purified by ethyl ether to obtain white solid 3. Yield: 85 %, mp: 198 ℃. ^{1}H NMR (DMSO-d_6) δ 6.93 (d, J = 8.04 Hz, 1H, aromatic H), 7.52 (d, J = 8.08 Hz, 1H, aromatic H), 7.58 (t, J = 7.80 Hz, 1H, aromatic H), 7.67 (t, J = 7.80 Hz, 1H, aromatic H), 7.95 (d, J = 8.40 Hz, 1H, aromatic H), 8.22 (d, J = 8.40 Hz, 1H, aromatic H), 10.56 (s, 2H, aromatic NH_2), 10.69 (s, 1H, phenolic OH). ESI-MS *m/z* 160.4 $[M+H]^+$.

*5.1.3. N-(4-hydroxynaphthalen-1-yl)-2-naphthamide (**4a**)*

Under the condition of ice bath, compound 3 (1.59 g, 10 mmol) was added to a solution of $NaHCO_3$ (2.52g, 30mmol) in THF/H_2O (50 mL/1mL). After 2-naphthoyl chloride (2.28 g, 12 mmol) was added drop by drop, the mixture was stirred at room temperature for 5 h (detected by TLC) [39]. Solvents were evaporated with the residues being taken up in EtOAc (50 mL). Then the organic layer was washed with saturated 1 N HCl (20 mL × 2), distilled water (20 mL × 2), brine (20 mL × 2), dried over $MgSO_4$ and evaporated under vacuum. The residues were purified by EtOH/H_2O to give 2.66 g of desired compound **4a** as white solid. Yield: 82 %, mp: 226-227 ℃. ^{1}H NMR (DMSO-d_6) δ 6.92 (d, J = 7.80 Hz, 1H, aromatic H), 7.38(d, J = 8.40 Hz, 1H, aromatic H), 7.48-7.54 (m, 2H), 7.62-7.67 (m, 2H), 7.90 (d, J = 8.40 Hz, 1H, aromatic H), 8.03 (d, J = 7.80 Hz, 1H, aromatic H), 8.06-8.13 (m, 3H), 8.20 (d, J = 7.80 Hz, 1H, aromatic H), 8.71 (s, 1H, aromatic H), 10.24 (s, 1H, phenolic OH),10.36 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d6) δ: 122.75, 123.68, 124.97, 125.11, 125.26, 125.36, 125.57, 126.65, 127.23, 128.11, 128.16, 128.42, 128.47, 129.41, 131.19, 132.39, 132.65, 134.72, 152.39, 166.43, 166.73. ESI-MS *m/z* 314.1 $[M+H]^+$.

Compounds 4b-4m were synthesized following the procedure described above.

5.1.3.1. *N-(4-hydroxynaphthalen-1-yl)cinnamamide (**4b**).* Yield: 68 %. ^{1}H NMR (DMSO-d_6) δ 6.87 (d, J = 8.40 Hz, 1H, aromatic H), 7.07 (d, J = 15.60 Hz, 1H, Ar-CH=CH-CO-), 7.40-7.43 (m, 1H), 7.45-7.48 (m, 2H), 7.49-7.55 (m, 2H), 7.59 (d, J = 15.60 Hz, 1H, Ar-CH=CH-CO-), 7.66 (d, J = 7.20 Hz, 2H, 2 × aromatic H), 7.95 (d, J = 9.00 Hz, 1H, aromatic H), 8.17 (d, J = 8.40 Hz, 1H, aromatic H), 9.90 (s, 1H, phenolic OH), 10.15 (s, 1H, aromatic NH). ESI-MS *m/z* 290.3 $[M+H]^+$.

*5.1.3.2. 4-chloro-N-(4-hydroxynaphthalen-1-yl)benzamide (**4c**).* Yield: 75 %. ^{1}H NMR (DMSO-d_6) δ 6.89 (d, J = 8.40 Hz, 1H, aromatic H), 7.32 (d, J = 7.80 Hz, 1H, aromatic H), 7.46-7.52 (m, 2H, 2 × aromatic H), 7.63 (d, J = 8.40 Hz, 2H, 2 × aromatic H), 7.82 (d, J = 8.40 Hz, 1H, aromatic H), 8.09 (d, J = 8.40 Hz, 1H, aromatic H), 8.18 (d, J = 7.80 Hz, 1H, aromatic H), 10.23 (s, 1H, phenolic O<u>H</u>), 10.26 (s, 1H, aromatic N<u>H</u>). ESI-MS *m/z* 298.4 $[M+H]^+$.

*5.1.3.3. N-(4-hydroxynaphthalen-1-yl)-2-nitrobenzamide (**4d**).* Yield: 81 %. ^{1}H NMR (DMSO-d_6) δ 6.77 (d, J = 7.80 Hz, 1H, aromatic H), 7.05 (d, J = 8.40 Hz, 1H, aromatic H), 7.34-7.40 (m, 2H, 2 × aromatic H), 7.62-7.65 (m, 2H, 2 × aromatic H), 7.78-7.80 (m, 1H, aromatic H), 7.88 (d, J = 7.80 Hz, 1H, aromatic H), 7.94 (d, J = 7.80 Hz, 1H, aromatic H), 8.08 (d, J = 7.80 Hz, 1H, aromatic H), 10.19 (s, 1H, phenolic O<u>H</u>), 10.37 (s, 1H, aromatic N<u>H</u>). ESI-MS *m/z* 309.4 $[M+H]^+$.

*5.1.3.4. N-(4-hydroxynaphthalen-1-yl)-4-methoxybenzamide (**4e**).* Yield: 77 %. ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H, OC<u>H</u>$_3$), 6.88 (d, J = 7.80 Hz, 1H, aromatic H), 7.07 (d, J = 7.80 Hz, 2H, 2 × aromatic H), 7.29 (d, J = 8.40 Hz, 1H, aromatic H), 7.45-7.51 (m, 2H, 2 × aromatic H), 7.81 (d, J = 7.80 Hz, 1H, aromatic H), 8.06 (d, J = 8.40 Hz, 1H, aromatic H), 8.17 (d, J = 7.80 Hz, 1H, aromatic H), 10.02 (s, 1H, phenolic O<u>H</u>), 10.18 (s, 1H, aromatic N<u>H</u>). ESI-MS *m/z* 294.3 $[M+H]^+$.

*5.1.3.5. 3-(3,4-dimethoxyphenyl)-N-(4-hydroxynaphthalen-1-yl)acrylamide (**4f**).* Yield: 82 %. ^{1}H NMR (DMSO-d_6) δ 3.81 (s, 3H, OC<u>H</u>$_3$), 3.84 (s, 3H, OC<u>H</u>$_3$), 6.87 (d, J = 8.40 Hz, 1H, aromatic H), 6.94 (d, J = 15.60 Hz, 1H, Ar-C<u>H</u>=CH-CO-), 7.03 (d, J = 8.40 Hz, 1H, aromatic H), 7.20 (d, J = 8.40 Hz, 1H, aromatic H), 7.25 (s, 1H, aromatic H), 7.46-7.54 (m, 4H), 7.95 (d, J = 8.40 Hz, 1H, aromatic H), 8.17 (d, J = 7.80 Hz, 1H, aromatic H), 9.79 (s, 1H, phenolic O<u>H</u>), 10.12 (s, 1H, aromatic N<u>H</u>). ESI-MS *m/z* 350.4 $[M+H]^+$.

*5.1.3.6. N-(4-hydroxynaphthalen-1-yl)-3-nitrobenzamide (**4g**).* Yield: 68 %. ^{1}H NMR (DMSO-d_6) δ 6.91 (d, J = 7.80 Hz, 1H, aromatic H), 7.36 (d, J = 7.80 Hz, 1H, aromatic H), 7.48-7.53 (m, 2H, 2 × aromatic H), 7.85-7.88 (m, 2H, 2 × aromatic H), 8.19 (d, J = 7.80 Hz, 1H, aromatic H), 8.47 (d, J = 8.40 Hz, 1H, aromatic H), 8.51 (d, J = 7.80 Hz, 1H, aromatic H), 8.90 (s, 1H, aromatic H), 10.27 (s, 1H, phenolic O<u>H</u>), 10.56 (s, 1H, aromatic N<u>H</u>). ESI-MS *m/z* 309.4 $[M+H]^+$.

*5.1.3.7. N-(4-hydroxynaphthalen-1-yl)-3-methoxybenzamide (**4h**).* Yield: 65 %. ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H, OC<u>H</u>$_3$), 8.90 (d, J = 7.80 Hz, 1H, aromatic H), 7.18 (d, J = 7.80 Hz, 1H, aromatic H), 7.32 (d, J = 7.80 Hz, 1H, aromatic H), 7.45-7.53 (m, 3H, 3 × aromatic H), 7.62 (s, 1H, aromatic H), 7.67 (d, J = 7.20 Hz, 1H, aromatic H), 7.82 (d, J = 8.40 Hz, 1H, aromatic H), 8.19 (d, J = 8.40 Hz, 1H, aromatic H), 10.17 (s, 1H, phenolic O<u>H</u>), 10.22 (s, 1H, aromatic N<u>H</u>). ESI-MS *m/z* 294.4 $[M+H]^+$.

*5.1.3.8. N-(4-hydroxynaphthalen-1-yl)-3-methylbenzamide (**4i**).* Yield: 60 %. ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H, C<u>H</u>$_3$), 6.89 (d, J = 8.00 Hz, 1H, aromatic H), 7.30 (d, J = 8.00 Hz, 1H, aromatic H), 7.41-7.52(m, 4H, 4 × aromatic H), 7.81 (d, J = 7.76 Hz, 1H, aromatic H), 7.85-7.88 (m, 2H, 2 × aromatic H), 8.17 (d, J = 7.60 Hz, 1H, aromatic H), 10.12 (s, 1H, phenolic O<u>H</u>), 10.21 (s, 1H, aromatic N<u>H</u>). ESI-MS *m/z* 278.4 $[M+H]^+$.

*5.1.3.9. N-(4-hydroxynaphthalen-1-yl)-3-(4-nitrophenyl)acrylamide (**4j**).* Yield: 65 %. ^{1}H NMR (DMSO-d_6) δ 6.89 (d, J = 7.80 Hz, 1H, aromatic H), 7.26 (d, J = 15.60 Hz, 1H, Ar-CH=CH-CO-), 7.50 (d, J = 7.80 Hz, 1H, aromatic H), 7.55 (d, J = 7.20 Hz, 2H, 2 × aromatic H), 7.71 (d, J = 15.60 Hz, 1H, Ar-CH=CH-CO-), 7.92 (d, J = 8.40 Hz, 1H, aromatic H), 7.96 (d, J = 9.00 Hz, 1H, aromatic H), 8.18 (d, J = 8.40 Hz, 1H, aromatic H), 8.32 (d, J = 7.80 Hz, 1H, aromatic H), 10.05 (s 1H, phenolic OH), 10.20 (s, 1H, aromatic NH). ESI-MS *m/z* 335.5 [M+H] $^+$.

*5.1.3.10. 3-chloro-N-(4-hydroxynaphthalen-1-yl)benzamide (**4k**).* Yield: 63 %. ^{1}H NMR (DMSO-d_6) δ 6.89 (d, J = 7.80 Hz, 1H, aromatic H), 7.32 (d, J = 7.80 Hz, 1H, aromatic H), 7.47-7.52 (m, 2H, 2 × aromatic H), 7.59 (t, J = 7.80 Hz, 1H, aromatic H), 7.69 (d, J = 8.40 Hz, 1H, aromatic H), 7.83 (d, J = 8.40 Hz, 1H, aromatic H), 8.03 (d, J = 7.20 Hz, 1H, aromatic H), 8.11 (s, 1H, aromatic H), 8.18 (d, J = 7.80 Hz, 1H, aromatic H), 10.24 (s, 1H, phenolic OH), 10.30 (s, 1H, aromatic NH). ESI-MS *m/z* 298.4 [M+H] $^+$.

*5.1.3.11. N-(4-hydroxynaphthalen-1-yl)-4-nitrobenzamide (**4l**).* Yield: 78 %. ^{1}H NMR (DMSO-d_6) δ 6.92 (d, J = 8.00 Hz, 1H, aromatic H), 7.37 (d, J = 8.00 Hz, 1H, aromatic H), 7.47-7.54 (m, 2H, 2 × aromatic H), 7.86 (d, J = 8.00 Hz, 1H, aromatic H), 8.20 (d, J = 7.68 Hz, 1H, aromatic H), 8.30 (d, J = 8.68 Hz, 2H, 2 × aromatic H), 8.40 (d, J = 8.72 Hz, 2H, 2 × aromatic H), 10.30 (s, 1H, phenolic OH), 10.52 (s, 1H, aromatic NH). ESI-MS *m/z* 309.4 [M+H] $^+$.

*5.1.3.12. 3-(4-chlorophenyl)-N-(4-hydroxynaphthalen-1-yl)acrylamide (**4m**).* Yield: 83 %. ^{1}H NMR (DMSO-d_6) δ 6.87 (d, J = 8.40 Hz, 1H, aromatic H), 7.07 (d, J = 15.60 Hz, 1H, Ar-CH=CH-CO-), 7.47-7.51 (m, 2H, aromatic H), 7.53 (d, J = 8.40 Hz, 3H, aromatic H), 7.58 (d, J = 15.60 Hz, 1H, Ar-CH=CH-CO-), 7.68 (d, J = 7.80 Hz, 2H, aromatic H), 7.94 (d, J = 8.40 Hz, 1H, aromatic H), 8.17 (d, J = 7.20 Hz, 1H, aromatic H). 9.92 (s, 1H, phenolic OH), 10.17 (s, 1H, aromatic NH). ESI-MS *m/z* 324.4 [M+H] $^+$.

*5.1.4. (E)-N-(4-oxonaphthalen-1(4H)-ylidene)-2-naphthamide (**5a**)*

To a solution of compound **4a** (3.13 g, 10.0 mmol) in 200 mL of CH_2Cl_2, was added 22 g (15 mmol) of $NaIO_4/SiO_2$(0.68mmol of NaIO4/1g of SiO_2) [40]. After stirring at room temperature for 2 h, the solid particles were filtered from the solution and washed with 20 mL of CH_2Cl_2, and the filtrates were evaporated in vacuum to obtain reddish-brown crude compound **5a** which was then purified by recrystallization using EtOAc. Yield: 88 %, mp: 148-149 ℃. ^{1}H NMR (DMSO-d_6) δ 6.85 (d, J = 10.20 Hz, 1H, aromatic H), 7.22 (d, J = 10.20 Hz, 1H, aromatic H), 7.62 (t, J = 7.80 Hz, 1H, aromatic H), 7.70 (t, J = 7.80 Hz, 1H, aromatic H), 7.89 (t, J = 7.80 Hz, 1H, aromatic H), 7.94 (t, J = 7.80 Hz, 1H, aromatic H), 8.01-8.05 (m, 2H), 8.10 (d, J = 7.80 Hz, 2H, 2 × aromatic H), 8.15 (d, J = 7.80 Hz, 2H, aromatic H), 8.42 (d, J = 7.80 Hz, 1H, aromatic H), 8.57 (s, 1H, aromatic H). ^{13}C NMR (150 MHz, DMSO-d6) δ: 124.86, 126.31, 127.08, 128.00, 128.04, 128.21, 128.26, 128.47, 129.31, 132.00, 132.12, 132.62, 134.62, 134.66, 135.05, 139.16, 168.42, 185.28. ESI-MS *m/z* 312.1 [M+H] $^+$.

Compounds **5b**-**5m** were synthesized following the procedure described above.

*5.1.4.1. (E)-N-(4-oxonaphthalen-1(4H)-ylidene)cinnamamide (**5b**).* Yield: 90 %. ^{1}H NMR ($CDCl_3$) δ 6.70-6.74 (m, 2H, 2 × aromatic H), 7.11 (d, J = 10.28 Hz, 1H, Ar-C<u>H</u>=CH-CO-), 7.38-7.39 (m, 3H), 7.52-7.56 (m, 3H), 7.71-7.77 (m, 2H), 8.11 (dd, J = 7.40 Hz, 1.72 Hz, 1H, aromatic H), 8.32 (dd, J = 7.56 Hz, 1.44 Hz, 1H, aromatic H). ESI-MS *m/z* 288.1 $[M+H]^+$.

*5.1.4.2. (E)-4-chloro-N-(4-oxonaphthalen-1(4H)-ylidene)benzamide (**5c**).* Yield: 89 %. ^{1}H NMR (DMSO-d_6) δ 6.74 (d, J = 10.28 Hz, 1H, aromatic H), 7.09 (d, J = 10.32 Hz, 1H, aromatic H), 7.46 (d, J = 8.64 Hz, 1H, aromatic H), 7.73-7.80 (m, 2H , 2 × aromatic H), 7.91 (d, J = 8.56 Hz, 2H, 2 × aromatic H), 8.17 (d, J = 7.16 Hz, 1H, aromatic H), 8.37 (d, J = 7.24 Hz, 1H, aromatic H). ESI-MS *m/z* 296.3 $[M+H]^+$.

*5.1.4.3. (E)-2-nitro-N-(4-oxonaphthalen-1(4H)-ylidene)benzamide (**5d**).* Yield: 72 %. ^{1}H NMR ($CDCl_3$) δ 6.80 (d, J = 10.44 Hz, 1H, aromatic H), 7.53 (d, J = 10.32 Hz, 1H, aromatic H), 7.66-7.73 (m, 4H), 7.84 (d, J = 7.20 Hz, 1H, aromatic H), 7.95 (d, J = 9.60 Hz, 1H, aromatic H), 8.10 (d, J = 8.40 Hz, 1H, aromatic H). ESI-MS m/z 393.3 $[M+H]^+$.

*5.1.4.4. (E)-4-methoxy-N-(4-oxonaphthalen-1(4H)-ylidene)benzamide (**5e**).* Yield: 85 %. ^{1}H NMR (DMSO-d_6) δ 3.84 (s, 3H, OC<u>H</u>$_3$), 6.83 (d, J = 10.20 Hz, 1H, aromatic H), 7.08 (d, J = 9.60 Hz, 2H, 2 × aromatic H), 7.13 (d, J = 9.60 Hz, 1H, aromatic H), 7.85-7.91 (m, 4H), 8.07 (d, J = 7.20 Hz, 1H, aromatic H), 8.33 (d, J = 7.80 Hz, 1H, aromatic H). ESI-MS *m/z* 292.3 $[M+H]^+$.

5.1.4.5.
*(2E,NE)-3-(3,4-dimethoxyphenyl)-N-(4-oxonaphthalen-1(4H)-ylidene)acrylamide (**5f**).* Yield: 80 %. ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H, OC<u>H</u>$_3$), 3.88 (s, 3H, OC<u>H</u>$_3$), 6.60 (d, J = 15.96 Hz, 1H, Ar-C<u>H</u>=CH-CO-), 6.73 (d, J = 10.44 Hz, 1H, aromatic H), 6.87 (d, J = 8.28 Hz, 1H, aromatic H), 7.07-7.6 (m, 3H), 7.49-7.52 (m, 1H), 7.72-7.77 (m, 3H), 8.14 (d, J = 7.40 Hz, 1H, aromatic H), 8.35 (d, J = 7.56 Hz, 1H, aromatic H). ESI-MS *m/z* 348.4 $[M+H]^+$.

*5.1.4.6. (E)-3-nitro-N-(4-oxonaphthalen-1(4H)-ylidene)benzamide (**5g**).* Yield: 88 %. ^{1}H NMR (DMSO-d_6) δ 6.78 (d, J = 10.28 Hz, 1H, aromatic H), 7.15 (d, J = 10.32 Hz, 1H, aromatic H), 7.72 (t, J = 8.00 Hz, 1H, aromatic H), 7.78-7.82 (m, 2H, 2 × aromatic H), 7.20 (dd, J = 7.08 Hz, 2.00 Hz, 1H, aromatic H), 8.35 (d, J = 6.48 Hz, 1H, aromatic H), 8.40 (dd, J = 7.12 Hz, 4.76 Hz, 1H, aromatic H), 8.48 (d, J = 8.24 Hz, 1H, aromatic H), 8.80 (s, 1 H, aromatic H). ESI-MS *m/z* 393.3 $[M+H]^+$.

*5.1.4.7. (E)-3-methoxy-N-(4-oxonaphthalen-1(4H)-ylidene)benzamide (**5h**).* Yield: 91 %. ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H, OC<u>H</u>$_3$), 6.75 (d, J = 10.32 Hz, 1H, aromatic H), 7.12 (d, J = 10.28 Hz, 1H, aromatic H), 7.16-7.19 (m, 1H, aromatic H), 7.39 (t, J = 10.28 Hz, 1H, aromatic H), 7.50 (dd, J = 6.52 Hz, 1.16 Hz, 1H, aromatic H), 7.57 (s,1H, aromatic H), 7.74-7.82 (m, 2H, 2 × aromatic H), 8.20 (d, J = 7.28 Hz, 1H, aromatic H), 8.41 (d, J = 7.36 Hz, 1H, aromatic H). ESI-MS *m/z* 292.3 $[M+H]^+$.

*5.1.4.8. (E)-3-methyl-N-(4-oxonaphthalen-1(4H)-ylidene)benzamide (**5i**).* Yield: 88 %. ^{1}H NMR (DMSO-d_6) δ 2.41 (s, 3H, C<u>H</u>$_3$), 6.72 (d, J = 10.32 Hz, 1H, aromatic H), 7.09 (d, J = 10.60 Hz, 1H, aromatic H), 7.26-7.38 (m, 1H, aromatic H), 7.57 (t, J = 12.80 Hz, 1H, aromatic H), 7.64 (s, 1H, aromatic H), 7.73-7.77 (m, 2H, 2 × aromatic

H), 8.09 (dd, *J* = 6.82 Hz, 2.82 Hz, 1H, aromatic H), 8.7 (d, *J* = 7.32 Hz, 1H, aromatic H), 8.39 (d, *J* = 7.24 Hz, 1H, aromatic H). ESI-MS *m/z* 276.4 $[M+H]^+$.

*5.1.4.9. (2E,NE)-3-(4-nitrophenyl)-N-(4-oxonaphthalen-1(4H)-ylidene)acrylamide (**5j**).* Yield: 83 %. ^{1}H NMR ($CDCl_3$) δ 6.75 (d, *J* = 10.28 Hz, 1H, aromatic H), 6.84 (d, *J* = 16.12 Hz, 1H, Ar-C<u>H</u>=CH-CO-), 7.13 (d, *J* = 10.28 Hz, 1H, aromatic H), 7.62 (d, *J* = 16.12 Hz, 1H, Ar-CH=C<u>H</u>-CO-), 7.75-7.77 (m, 2H, 2 × aromatic H), 8.14 (d, *J* = 7.24 Hz, 1H, aromatic H), 8.23 (d, *J* = 8.80 Hz, 1H, 2 × aromatic H), 8.33 (d, *J* = 7.24 Hz, 1H, aromatic H). ESI-MS *m/z* 333.4 $[M+H]^+$.

*5.1.4.10. (E)-3-chloro-N-(4-oxonaphthalen-1(4H)-ylidene)benzamide (**5k**).* Yield: 90 %. ^{1}H NMR (DMSO-d_6) δ 6.74 (d, *J* = 10.28 Hz, 1H, aromatic H), 7.09 (d, *J* = 10.28 Hz, 1H, aromatic H), 7.43 (t, *J* = 10.28 Hz, 1H, aromatic H), 7.58 (dd, *J* = 8.00 Hz, 0.96 Hz, 1H, aromatic H), 7.77-7.81 (m, 2H, 2 × aromatic H), 7.85 (d, *J* = 7.72 Hz, 1H, aromatic H), 7.95 (s, 1H, aromatic H), 8.17 (d, *J* = 7.12 Hz, 1H, aromatic H), 8.39 (d, *J* = 8.00 Hz, 1H, aromatic H). ESI-MS *m/z* 296.4 $[M+H]^+$.

*5.1.4.11. (E)-4-nitro-N-(4-oxonaphthalen-1(4H)-ylidene)benzamide (**5l**).* Yield: 81 %. ^{1}H NMR ($CDCl_3$) δ 6.79 (d, *J* = 10.28 Hz, 1H, aromatic H), 7.12 (d, *J* = 10.40 Hz, 1H, aromatic H), 7.77-7.83 (m, 2H, 2 × aromatic H), 8.16-8.20 (m, 3H, 3 × aromatic H), 8.35 (d, *J* = 8.88 Hz, 2H, 2 × aromatic H), 8.40 (d, *J* = 9.00 Hz, 1H, aromatic H). ESI-MS *m/z* 307.4 $[M+H]^+$.

*5.1.4.12. (2E,NE)-3-(4-chlorophenyl)-N-(4-oxonaphthalen-1(4H)-ylidene)acrylamide (**5m**).* Yield: 92 %. ^{1}H NMR ($CDCl_3$) δ 6.70 (d, *J* = 16.12 Hz, 1H, Ar-C<u>H</u>=CH-CO-), 6.74 (d, *J* = 10.36 Hz, 1H, aromatic H), 7.12 (d, *J* = 10.28 Hz, 1H, aromatic H), 7.37 (d, *J* = 8.56 Hz, 2H, 2 × aromatic H), 7.48-7.54 (m, 3H), 7.72-7.76 (m, 2H), 8.13 (d, *J* = 7.28 Hz, 1H, aromatic H), 8.32 (d, *J* = 7.40 Hz, 1H, aromatic H). ESI-MS *m/z* 322.1 $[M+H]^+$.

*5.1.5. N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-2-naphthamide (**6a**)*

To a solution of 1*H*-1,2,4-triazole-5-thiol (2.53 g, 25 mmol) in 10 mL of DMF, was added 3.11 g (10 mmol) of compound **5a**, slowly [41]. After stirring at room temperature for 4 h, the solution was poured into 100 mL of distilled water with slight yellow solid precipitation. After standing for 20 minutes the slight yellow solid was filtered with suction, pressed to remove excess water, and allowed to dry in air. The dry residues were recrystallized with MeOH to give 2.84 g of title compound 6a as white powder. Yield: 69 %, mp: 229-230 □. ^{1}H NMR (DMSO-d_6) δ 7.43 (s, 1H, aromatic H), 7.50-7.68 (m, 5H), 7.89-8.12 (m, 6H), 8.29 (q, *J* = 3.20 Hz, 1H, aromatic H), 8.54 (s, 1H, aromatic H), 8.70 (s, 1H, aromatic H), 10.43 (s, 1H, aromatic N<u>H</u>). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 110.4, 122.7, 123.5, 124.4, 125.1, 125.6, 125.7, 126.4, 126.7, 126.9, 127.6, 127.7, 127.9, 128.1, 128.9, 130.6, 131.6, 132.1, 134.3, 146.3, 151.4, 155.2, 166.3. ESI-MS *m/z* 413.6 $[M+H]^+$.

Target compounds **6b**-**6s** were synthesized following the procedure described above.

*5.1.5.1. N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)cinnamamide (**6b**).* Yield: 85 %, mp: 307-309 □. ^{1}H NMR (DMSO-d_6) δ 7.13 (d, *J* = 15.76 Hz, 1H,

Ar-CH=CH-CO-), 7.39-7.48 (m, 4H), 7.57-7.66 (m, 6H), 7.77 (s, 1H, aromatic H), 8.07 (d, *J* = 7.32 Hz, 1H, aromatic H), 8.37 (d, *J* = 7.28 Hz, 1H, aromatic H), 9.42 (s, 1H, phenolic OH), 10.04 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 119.6, 122.4, 122.6, 122.9, 125.1, 125.3, 126.1, 127.6, 128.4, 128.9, 129.6, 134.9, 139.8, 147.1, 164.3. ESI-MS *m/z* 389.4 $[M+H]^+$.

5.1.5.2.

*N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-4-chlorobenzamide (**6c**).* Yield: 70 %., mp: 146-148 ℃. ^{1}H NMR (DMSO-d_6) δ 7.38 (s, 1H, aromatic H), 7.51-7.67 (m, 4H), 7.81-7.85 (m, 1H, aromatic H), 8.06 (d, *J* = 8.40 Hz, 2H, aromatic H), 8.26-8.31 (m, 1H, aromatic H), 8.53 (s, 1H, aromatic H), 8.89 (s, 1H, aromatic NH), 10.33 (s, 1H, phenolic OH), 10.60 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 110.3, 122.7, 123.4, 125.6, 125.7, 126.0, 126.9, 128.0, 128.4, 129.6, 130.5, 133.0, 136.4, 146.3, 151.5, 155.2, 165.1. ESI-MS *m/z* 397.4 $[M+H]^+$.

5.1.5.3.

*N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-2-nitrobenzamide (**6d**).* Yield: 91 %, mp: 265-266 ℃. ^{1}H NMR (DMSO-d_6) δ 7.55 (s,1H, aromatic H), 7.57-7.64 (m, 2H, 2 × aromatic H), 7.74-7.78 (m, 1H, aromatic H), 7.87-7.94 (m,1H, aromatic H), 8.05 (d, *J* = 7.84 Hz,1H, aromatic H), 8.16 (d, *J* = 8.04 Hz,1H, aromatic H), 8.29 (d, *J* = 7.64 Hz,1H, aromatic H), 8.64 (s, 1H, aromatic H), 10.21 (s, 1H, aromatic NH), 10.51 (s, 1H, phenolic OH), 14.25 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 123.2, 123.6, 124.7, 125.7, 125.09, 126.3, 127.5, 128.1, 129.9, 130.0, 130.6, 131.3, 133.2, 134.5, 145.6, 147.1, 165.7. ESI-MS *m/z* 408.4 $[M+H]^+$.

5.1.5.4.

*N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-4-methoxybenzamide (**6e**).* Yield: 92 %, mp: 142-143 ℃. ^{1}H NMR (DMSO-d_6) δ 3.84 (s, 3H, CH_3), 7.06 (d, *J*=8.70 Hz, 2H, 2 × aromatic H), 7.34 (s, 1H, aromatic H), 7.53~7.57 (m, 2H, aromatic H), 8.02 (d, *J*=8.70 Hz, 2H, 2 × aromatic H), 8.24~8.27 (m, 1H, aromatic H), 8.61 (s, 1H, aromatic H), 10.08 (s, 1H, aromatic NH), 10.13 (s, 1H, phenolic OH), 14.23 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 55.3, 110.6, 113.6, 122.6, 123.5, 125.6, 125.7, 126.3, 126.5, 126.7, 128.0, 129.5, 130.6, 146.5, 151.2, 161.8, 165.6. ESI-MS *m/z* 393.3 $[M+H]^+$.

5.1.5.5.

*(E)-N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-3-(3,4-dimethoxyphenyl)acrylamide (**6f**).* Yield: 93 %, mp: 252-253 ℃. ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.92 (d, *J* = 15.60 Hz, 1H, Ar-CH=CH-CO-), 7.03 (d, *J* = 8.40 Hz, 1H, aromatic H), 7.20 (d, *J* = 8.40 Hz, 1H, aromatic H), 7.24 (s, 1H, aromatic H), 7.49-7.63 (m, 4H), 8.00 (d, *J* = 7.80 Hz, 1H, aromatic H), 8.26 (d, *J* = 6.90 Hz, 1H, aromatic H), 8.63 (s, 1H, aromatic H), 9.85 (s, 1H, aromatic NH), 10.03 (s, 1H, phenolic OH), 14.23 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 55.4, 55.5, 110.1, 111.0, 111.7, 119.7, 121.6, 122.7, 122.8, 125.5, 125.7, 126.3, 126.7, 127.6, 128.9, 140.1, 145.1, 148.9, 150.3, 157.4, 164.5. ESI-MS *m/z* 449.5 $[M+H]^+$

5.1.5.6.

N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-3-nitrobenzamide ***(6g)***. Yield: 57 %, mp: 155-157 ℃. ^{1}H NMR (DMSO-d_6) δ 7.42 (s, 1H, aromatic H), 7.55-7.61 (m, 2H), 7.83-7.89 (m, 2H), 8.28-8.33 (m, 1H, aromatic H), 8.44-8.51 (m, 1H, aromatic H), 8.57 (s, 1H, aromatic H), 8.88 (s, 1H, aromatic H), 10.66 (s, 1H, phenolic O<u>H</u>). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 110.2, 122.5, 122.7, 123.4, 125.6, 125.8, 126.1, 127.0, 128.1, 130.1, 130.4, 134.1, 135.7, 146.2, 147.7, 151.7, 155.1, 164.1. ESI-MS *m/z* 408.5 [M+H] $^{+}$.

5.1.5.7.

N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-3-methoxybenzamide ***(6h)***. Yield: 81 %, mp: 202-204 ℃. ^{1}H NMR (DMSO-d_6) δ 3.84 (s, 3H, OC<u>H</u>$_3$), 7.16 (dd, *J* = 8.10 Hz, 2.10Hz, 1H, aromatic H), 7.36 (s, 1H, aromatic H), 7.45 (t, *J* = 8.10 Hz, 1H, aromatic H), 7.55-7.64 (m, 4H), 7.81-7.84 (m, 1H, aromatic H), 8.25-8.28 (m, 1H, aromatic H), 8.62 (s, 1H, aromatic H), 10.14 (s, 1H, aromatic N<u>H</u>), 10.22 (s, 1H, phenolic O<u>H</u>), 14.23 (s, 1H, aromatic N<u>H</u>). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 55.3, 110.7, 112.7, 117.5, 119.9, 122.6, 123.5, 125.6, 125.7, 126.2, 126.8, 128.0, 129.5, 130.5, 135.6, 145.1, 151.3, 159.2, 165.8. ESI-MS *m/z* 393.3 [M+H] $^{+}$.

5.1.5.8.

N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-3-methylbenzamide ***(6i)***. Yield: 97 %, mp: 195-196 ℃. ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H, C<u>H</u>$_3$), 7.36 (s, 1H, aromatic H), 7.42 (d, *J*=4.50 Hz, 1H, aromatic H), 7.54~7.58 (m, 2H), 7.82~7.86 (m, 3H), 8.25~8.28 (m, 1H, aromatic H), 8.62 (s, 1H, aromatic H), 10.11 (s, 1H, aromatic N<u>H</u>), 10.19 (s, 1H, phenolic O<u>H</u>), 14.25 (s, 1H, aromatic N<u>H</u>). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 20.9, 110.9, 122.6, 123.5, 124.8, 125.6, 125.7, 126.3, 126.8, 128.2, 130.5, 132.1, 134.2, 137.6, 145.0, 151.2, 166.3. ESI-MS *m/z* 377.5 [M+H] $^{+}$.

5.1.5.9.

(E)-N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-3-(4-nitrophenyl)acrylamide ***(6j)***. Yield: 79 %, mp: 202-204 ℃. ^{1}H NMR (DMSO-d_6) δ 7.25 (d, *J* = 15.60 Hz, 1H, Ar-C<u>H</u>=CH-CO-), 7.57-7.70 (m, 4H), 7.91 (d, *J* = 8.40 Hz, 2H, 2 × aromatic H), 8.01 (d, *J* = 7.80 Hz, 1H, aromatic H), 8.27 (d, *J* = 7.80 Hz, 1H, aromatic H), 8.31 (d, *J* = 8.40 Hz, 2H, aromatic H), 8.54 (s, 1H, aromatic H), 10.09 (s, 1H, aromatic N<u>H</u>), 10.20 (s, 1H, phenolic O<u>H</u>), 14.31 (s, 1H, aromatic N<u>H</u>). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 111.3, 123.2, 124.6, 125.9, 126.0, 126.3, 126.4, 126.9, 127.3, 129.1, 129.3, 138.0, 141.9, 148.0, 151.0, 164.0. ESI-MS *m/z* 434.4 [M+H] $^{+}$.

5.1.5.10.

N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-2-naphthamide ***(6k)***. Yield: 88 %, mp: 209-212 ℃. ^{1}H NMR (DMSO-d_6) δ 7.38 (s, 1H, aromatic H), 7.51-7.67 (m, 3H), 7.68 (d, *J* = 8.40 Hz, 1H, aromatic H), 7.92-7.98 (m, 1H, aromatic H), 7.99 (d, *J* = 7.50 Hz, 1H, aromatic H), 8.16 (s, 1H, aromatic H), 8.26-8.28 (m, 1H, aromatic H), 8.62 (s, 1H, aromatic H), 10.15 (s, 1H, aromatic N<u>H</u>), 10.35 (s, 1H, phenolic O<u>H</u>), 14.23 (s, 1H, aromatic N<u>H</u>). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 110.7, 122.6, 123.4, 125.5, 125.8, 125.9, 126.4, 126.9, 127.5, 128.1, 130.3, 130.4, 131.3, 133.2, 136.2, 145.3, 151.5, 157.2, 164.8. ESI-MS *m/z* 397.4 [M+H] $^{+}$.

5.1.5.11.

N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-4-nitrobenzamide ***(6l)***. Yield: 87 %, mp: 243-244 ℃. ^{1}H NMR (DMSO-d_6) δ 7.43 (s, 1H, aromatic H), 7.57-7.59 (m, 2H), 7.87 (s, 1H, aromatic H), 8.25 (s, 1H, aromatic H), 8.28 (d, J = 9.00 Hz, 2H, 2 × aromatic H), 8.39 (d, J=9.00 Hz, 2H, 2 × aromatic H), 8.63 (s, 1H, aromatic H), 10.21 (s, 1H, aromatic NH), 10.58 (s, 1H, phenolic OH), 14.24 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 123.2, 123.8, 124.0, 126.0, 126.1, 126.3, 127.5, 128.6, 129.7, 130.8, 140.5, 149.6, 152.1, 162.7, 165.1. ESI-MS *m/z* 408.4 [M+H] $^{+}$.

5.1.5.12.

(E)-N-(3-((1H-1,2,4-triazol-5-yl)thio)-4-hydroxynaphthalen-1-yl)-3-(4-chlorophenyl)acrylamide ***(6m)***. Yield: 83 %. ^{1}H NMR (DMSO-d_6) δ 7.18 (d, J = 15.60 Hz, 1H, Ar-CH=CH-CO-), 7.58-7.65 (m, 4H), 7.84 (d, J = 7.80 Hz, 2H, 2 × aromatic H), 7.93 (d, J = 7.80 Hz, 2H, 2 × aromatic H), 7.99 (d, J = 7.80 Hz, 1H, aromatic H), 8.26 (d, J = 7.80 Hz, 1H, aromatic H), 8.64 (s, 1H, aromatic H), 10.09 (s, 1H, aromatic NH), 10.19 (s, 1H, phenolic OH),14.25 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 111.7, 112.0, 119.1, 123.2, 126.0, 126.1, 126.3, 126.6, 127.2, 128.8, 129.3, 133.3, 138.5, 139.9, 145.6, 150.9, 157.8, 164.1. ESI-MS *m/z* 423.4 [M+H] $^{+}$.

5.1.5.13.

4-chloro-N-(4-hydroxy-3-((5-methyl-1,3,4-thiadiazol-2-yl)thio)naphthalen-1-yl)benzamide ***(6n)***. Yield: 86 %, mp: 229-230℃. ^{1}H NMR (DMSO-d_6) δ 2.58 (s, 3H, CH_3), 7.61-7.68 (m, 5H), 7.93 (d, J = 8.40 Hz, 1H, aromatic H), 8.09 (d, J = 8.40 Hz, 2H, 2 × aromatic H), 8.35 (d, J = 8.40 Hz, 1H, aromatic H), 10.41 (s, 1H, phenolic OH), 10.69 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 15.6, 109.1, 123.8, 124.0, 126.1, 126.6, 127.1, 128.6, 128.9, 129.8, 130.1, 132.3, 133.5, 136.9, 154.4, 165.7, 166.3, 168.4. ESI-MS *m/z* 428.5 [M+H] $^{+}$.

5.1.5.14.

N-(3-((1,3,4-thiadiazol-2-yl)thio)-4-hydroxynaphthalen-1-yl)-4-chlorobenzamide ***(6o)***. Yield: 70 %, mp: 254℃. ^{1}H NMR (DMSO-d_6) δ 7.61-7.70 (m,5H), 7.95 (d, J = 8.00 Hz, 1H, aromatic H), 8.09 (d, J = 8.28 Hz, 2H, 2 × aromatic H), 8.36 (d, J = 7.80 Hz, 1H, aromatic H), 9.42 (s, 1H, aromatic H), 10.40 (s, 1H, phenolic OH), 10.69 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 108.8, 123.8, 124.1, 126.1, 126.7, 127.1, 128.7, 128.9, 129.9, 130.1, 132.4, 133.5, 136.9, 154.5, 154.7, 165.7, 169.2. ESI-MS *m/z* 414.4 [M+H] $^{+}$.

5.1.5.15.

4-chloro-N-(4-hydroxy-3-((1-methyl-1H-tetrazol-5-yl)thio)naphthalen-1-yl)benzamide ***(6p)***. Yield: 91 %, mp: 255-257℃. ^{1}H NMR (DMSO-d_6) δ 4.05 (s, 3H, CH_3), 7.50 (s, 1H), 7.60-7.65 (m, 4H), 7.91 (d, J = 8.40 Hz, 1H, aromatic H), 8.08 (d, J = 8.40 Hz, 1H, aromatic H), 8.31 (d, J = 9.60 Hz, 1H, aromatic H), 10.40 (s, 1H, phenolic OH), 10.47 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 34.5, 107.1, 123.4, 124.1, 126.0, 126.6, 126.6, 126.9, 128.1, 128.9, 129.0, 130.1, 131.7, 133.4, 136.9, 153.0, 153.3, 165.7. ESI-MS *m/z* 412.5 [M+H] $^{+}$.

*5.1.5.16. N-(3-((7H-purin-6-yl)thio)-4-hydroxynaphthalen-1-yl)-4-chlorobenzamide (**6q**).* Yield: 69 %, mp: 275-276℃. ^{1}H NMR (DMSO-d_6) δ 7.59-7.68 (m, 3H), 7.94 (d, J = 8.12 Hz, 1H, aromatic H), 8.11 (d, J = 8.08 Hz, 1H, aromatic H), 8.21 (s, 1H, aromatic H), 8.35 (d, J = 8.08 Hz, 1H, aromatic H), 8.41 (s, 1H, aromatic H), 8.54 (d, J = 9.20 Hz, 1H, aromatic H), 10.17 (s, 1H, aromatic H), 10.33 (s, 1H, aromatic H), 10.40 (s, 1H, aromatic NH), 10.54 (s, 1H, phenolic OH), 13.76 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 105.6, 105.7, 123.6, 123.9, 126.0, 126.1, 128.0, 128.9, 129.6, 130.1, 130.2, 131.6, 132.1, 133.6, 136.8, 144.1, 144.9, 145.1, 151.0, 152.0, 155.3, 165.7, 171.3. ESI-MS *m/z* 448.4 $[M+H]^+$.

*5.1.5.17. N-(3-((7H-purin-6-yl)thio)-4-hydroxynaphthalen-1-yl)-2-nitrobenzamide (**6r**).* Yield: 78 %, mp: 209-212℃. ^{1}H NMR (DMSO-d_6) δ 7.59-7.67 (m, 3H), 7.95 (d, J = 7.80 Hz, 1H, aromatic H), 8.29 (d, J = 9.00 Hz, 2H, 2 × aromatic H), 8.33 (d, J = 7.80 Hz, 1H, aromatic H), 8.39 (d, J = 9.00 Hz, 2H, 2 × aromatic H), 8.49 (s, 1H, aromatic H), 8.51 (s, 1H, aromatic H), 10.18 (s, 1H, aromatic NH), 10.63 (s, 1H, phenolic OH), 13.58 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 105.6, 123.7, 123.8, 124.0, 125.8, 126.0, 126.2, 128.1, 129.7, 131.6, 131.9, 140.6, 144.1, 149.6, 152.0, 155.5, 165.2. ESI-MS *m/z* 459.3 $[M+H]^+$.

*5.1.5.18. N-(3-((7H-purin-6-yl)thio)-4-hydroxynaphthalen-1-yl)-4-nitrobenzamide (**6s**).* Yield: 74 %, mp: 262-263℃. ^{1}H NMR (DMSO-d_6) δ 7.59 (s, 1H, aromatic H), 7.62 (t, J = 7.80 Hz, 1H, aromatic H), 7.67 (t, J = 7.80 Hz, 1H, aromatic H), 7.95 (d, J = 7.80 Hz, 1H, aromatic H), 8.30 (d, J = 8.40 Hz, 2H, 2 × aromatic H), 8.34 (d, J = 7.80 Hz, 1H, aromatic H), 8.40 (d, J = 7.80 Hz, 1H, aromatic H), 8.49 (s, 1H, aromatic H), 8.52 (s, 1H, aromatic H), 10.19 (s, 1H, aromatic NH), 10.63 (s, 1H, phenolic OH), 13.58 (s, 1H, aromatic NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 105.7, 123.7, 123.8, 123.9, 124.0, 125.8, 126.0, 126.2, 128.1, 129.7, 129.9, 131.5, 131.9, 140.6, 144.1, 149.7, 152.0, 155.5, 165.2. ESI-MS *m/z* 459.3 $[M+H]^+$.

5.2. Biological assay

5.2.1. MTT assay

HUVECs, A549, K562, PC-3,HCT116, MDA-MB-231 and MCF-7 cells were respectively grown in RPMI 1640 medium containing 10 % FBS at 37 °C in 5 % CO_2 humidified incubator. Cell proliferation was determined by the MTT (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl-2*H*-tetrazolium bromide) assay. Briefly, cells were plated in a 96-well plate at 5,000 cells per well, cultured for 4 h in complete growth medium, then treated with serial dilutions of the compounds for 48 h. During the last 4 h, 10 μL of 0.5 % MTT solution was added to each well. After further incubation for 4 h, formazan formed from MTT was extracted by adding 200 μL of DMSO and mixed for 15 min. Optical density was read with an ELISA reader at 570 nm.

5.2.2. In vitro HUVECs tuber formation assay

Forty eight-well slide chambers were coated with 100 μL of Matrigel (BD Biosciences, NJ) and allowed to gel at 37 °C and 5 % CO_2 for 30 min. HUVECs were

then seeded at 40,000 cells/well in M199 (5 % FBS) containing either the vehicle (0.5 % DMSO), Pazopanib or synthesized compounds and incubated at 37 °C and 5 % CO_2 for 6 h. The morphological changes of the cells and HUVEC tubes formation were observed under a phase-contrast microscope and photographed at ×200 magnification. The corresponding area was measured as the number of pixels using Adobe PhotoShop [33, 34]. Experiments were repeated three times.

5.2.3. Rat thoracic aorta rings (TARs) assay

Forty eight-well tissue culture plates were coated with 100 μL of Matrigel (BD Biosciences, NJ) and allowed to gel for 30 min at 37 °C and 5 % CO_2. Thoracic aortas were excised from 8- to 10-week-old male Sprague Dawley rats. After careful removal of fibroadipose tissues, the aortas were cut into 1-mm-long cross-sections, placed on Matrigel-coated wells, and covered with an additional 100 μL of Matrigel. After the second layer of Matrigel set, the rings were incubated for 30 min at 37 °C and 5 % CO_2. Aorta rings were treated every other day with either the vehicle (0.5 % DMSO), Pazopanib, or synthesized compounds for 6 days and photographed on the 7^{th} day at ×200 magnification. The area of angiogenic sprouting, reported in the number of pixels, was quantified using Adobe PhotoShop [33, 35]. Experiments were repeated three times.

5.2.4. In vitro kinase activity

The kinase selectivity of compounds (at 10 μM) was profiled by screening as follows: The test compounds, reference compound or water (control) were mixed with the appropriate enzyme in a buffer containing Hepes/Tris (pH 7.4), EGTA/Tris, $MgCl_2$, DTT and 0.008 % Tween 20. Thereafter, the reaction was initiated by adding the substrate and ATP, and the mixture was incubated for 30 min at room temperature. For control basal measurements, the enzyme was omitted from the reaction mixture. Following incubation, the reaction was stopped by adding EDTA. After 5 min, the anti-phopho-PT66 antibody labeled with europium chelate was added. After 60 more min, the fluorescence transfer was measured using a microplate reader (Envision, Perkin Elmer). The results were expressed as a percent inhibition of the control enzyme activity. The standard inhibitory reference compound was Staurosporine. The experiment was performed in duplicate.

5.2.5. Docking study

Compound **6d** was docked to the active site of the modeled ABL, EGFR, ALK and VEGFR2, respectively. Surflex dock program[42, 43] in Sybyl 8.0 software was used, ten poses was generated for each ligand. The protomol was generated based on the ligand in the crystal structure. Other parameter was set referring the default values.

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Figure captions

Fig. 1. The tuber formation inhibitory effects of all the synthesized compounds using bar graphs of the total tube area in the microscopic field measured as number of pixels compared to the vehicle control (0.5% DMSO): (A) Tube formation assay of all the synthesized compounds at 50 μM; (B) The tuber formation inhibitory effects of compounds **6d**, **6r**, **6b**, **6n**, **6o**, **6k** , **6l** and **6c** at concentrations of 50, 20 and 10 μM, respectively. Bar graph represents the mean ± SD of three independent experiments.

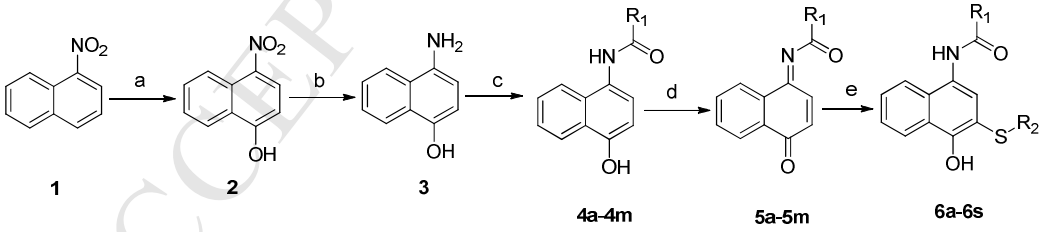
Fig. 2. Representative images of the tube formation assay depicting the formation of a HUVEC capillary-like tubular network by treatment with synthesized compounds, pazopanib (positive control) and 0.5% DMSO (vehicle control).

Fig. 3. The thoracic aorta rings (TARs) inhibitory effects of all the synthesized compounds using bar graphs of the total microvessel area in the microscopic field measured as number of pixels compared to the vehicle control (0.5% DMSO): (A) TARs assay of all the synthesized compounds at 50 μM; (B) The TARs inhibitory effects of compounds **6r**, **6d**, **6b**, 6**q** and **6n** at concentrations of 50, 20, 10 and 1 μM, respectively. Bar graph represents the mean ± SD of three independent experiments.

Fig. 4. Representative images of rat aortic rings treated with synthesized compounds, pazopanib (positive control) and 0.5% DMSO (vehicle control).

Fig. 5. Calculated binding modes of compound **6d** in the ATP-binding pocket of the ABL (A), EGFR (B), ALK (C) and VEGFR2 (D) kinase domains. The structural framework of compound **6d** was colored according to the atomic coloring scheme (S in yellow, C in green, O in red and N in blue). Hydrogen bonds were indicated by dash lines.

Scheme 1

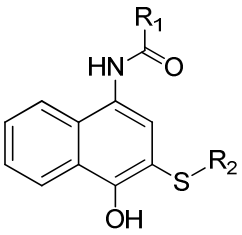


Scheme 1. Reagents and conditions：(a) t-BuOOH, KOH, DMSO/H_2O(3/1); (b) Pd-C, H_2, MeOH; (c) THF/H_2O (50/1), $NaHSO_3$; (d) $NaIO_4/SiO_2$, DCM; (e) DMF, R_2SH.

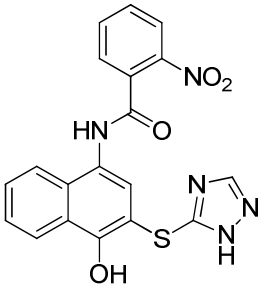
> A series of N-(4-hydroxy-3-mercaptonaphthalen-1-yl)amides were synthesized.
> The compounds were evaluated as inhibitors of angiogenesis and tumor growth.
> Some of them exhibited remarkably *in vitro* antiangiogenic activity.
> Inhibitory activity of **6d** was similar to clinically used drug pazopanib.

Table 1

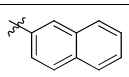
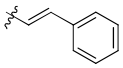
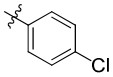
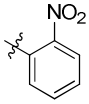
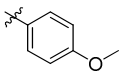
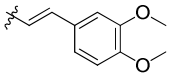
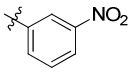
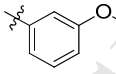
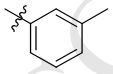
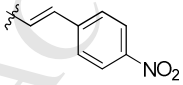
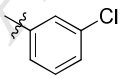
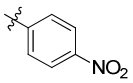
The structures and *in vitro* antiproliferative activity of the target compounds and Sorafenib



General structure



Typical compound **6d**

Cmpd	R_1	R_2	IC_{50} (μM)		
			MDA-MB-231	PC-3	HCT116
6a			45.08±0.97	>100	>100
6b			>100	>100	>100
6c			25.71±0.84	5.52±0.36	43.27±1.35
6d			21.37±0.72	52.52±1.15	10.19±0.65
6e			>100	>100	>100
6f			52.45±1.17	>100	>100
6g			48.00±1.02	26.91±0.46	70.22±2.96
6h			>100	42.13±1.87	>100
6i			>100	59.54±2.77	>100
6j			>100	>100	>100
6k			>100	85.61±1.26	>100
6l			>100	53.51±0.95	>100

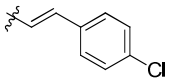
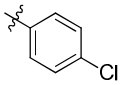
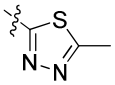
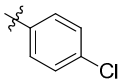
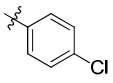
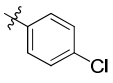
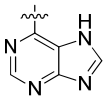
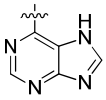
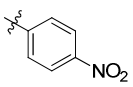
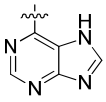
6m			>100	>100	>100
6o			>100	49.53±1.01	>100
6p			>100	>100	>100
6q			>100	>100	>100
6r			22.97±0.74	66.43±3.14	>100
6s			54.18±1.46	>100	31.73±0.87
6t			>100	>100	>100
Sorafenib			14.62±0.96	24.20±1.03	8.08±0.86

Table 2.
Antiproliferative activity of compounds against HUVECs, MCF-7, A549 and K562 cells

Cmpd	IC_{50} (μM)			
	HUVEC	MCF-7	A549	K562
6c	>100	>100	41.85±1.82	18.76±2.43
6d	5.34±0.76	2.81±0.55	40.53±1.92	10.81±0.19
6q	7.53±0.69	14.43±1.26	38.39±1.88	16.94±1.53
6r	ND [a]	>100	>100	37.18±1.75
Sorafenib	6.42±1.13	7.33±0.65	12.54±0.95	13.85±0.89

[a] Not determined.

Table 3
Enzyme inhibitory activity assay results

Cmpd	Kinase inhibition (%) at 10 μM			
	EGFR	ABL	AKT1	ALK
6a	14.96	28.40	41.64	NA[a]
6b	10.66	18.51	26.15	NA[a]
6c	21.94	36.97	50.13	NA[a]
6d	36.79	87.18	85.77	56.83
6e	14.40	27.83	30.84	NA[a]

6f	26.41	1.77	31.65	14.87
6g	20.64	31.30	29.26	NA[a]
6h	11.76	12.82	19.38	NA[a]
6i	11.15	24.08	20.20	NA[a]
6j	20.86	41.21	40.59	NA[a]
6k	17.94	52.37	45.96	NA[a]
6l	14.60	30.08	37.34	3.37
6m	21.32	30.92	31.84	0.70
6n	1.20	13.93	8.48	9.25
6o	7.93	8.07	7.50	4.20
6p	4.34	16.72	13.10	NA[a]
6q	37.77	32.80	21.72	NA[a]
6r	24.73	43.69	50.73	NA[a]
Staurosporine	97.60	94.87	96.52	97.89

[a] Not active.

Figure 1

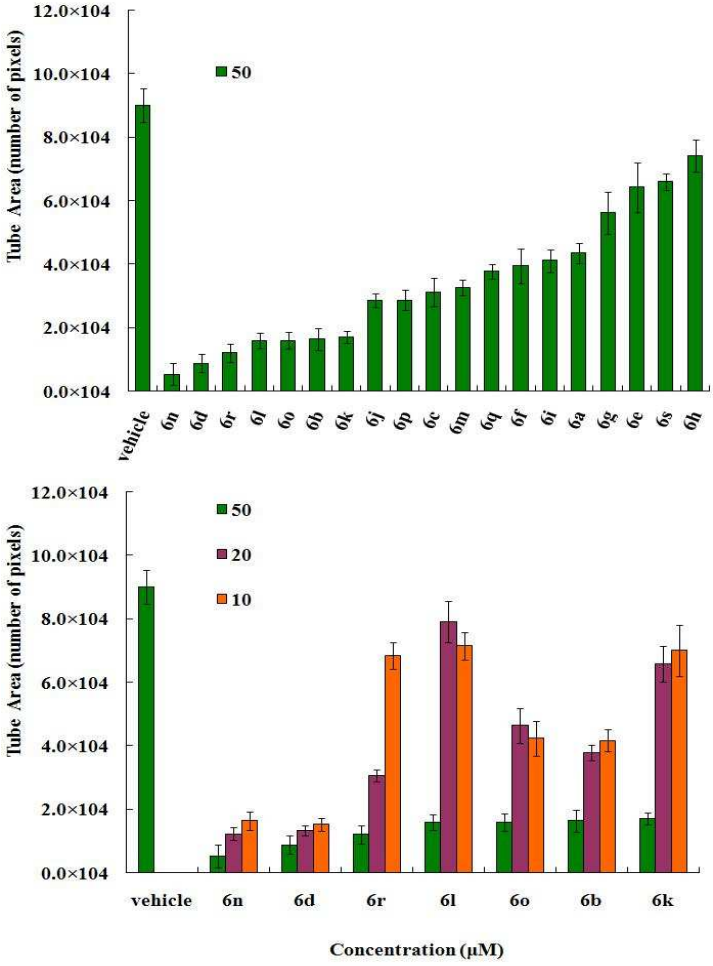


Figure 2

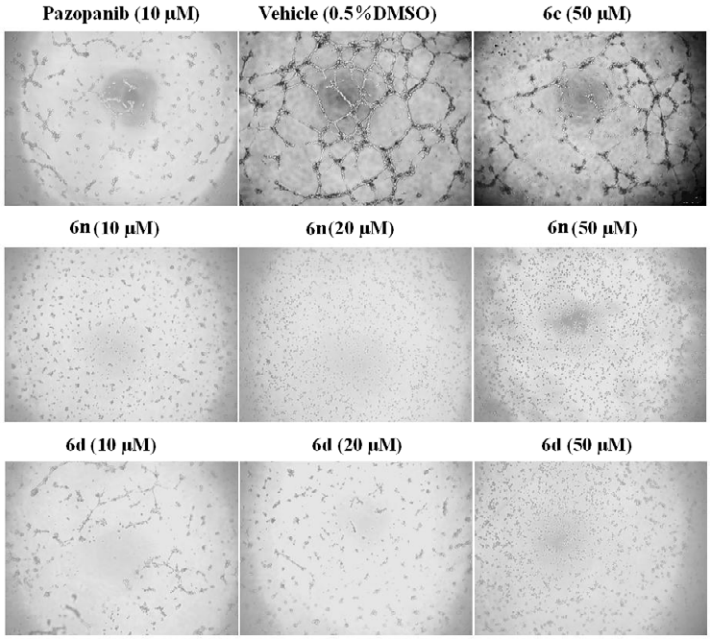


Figure 3

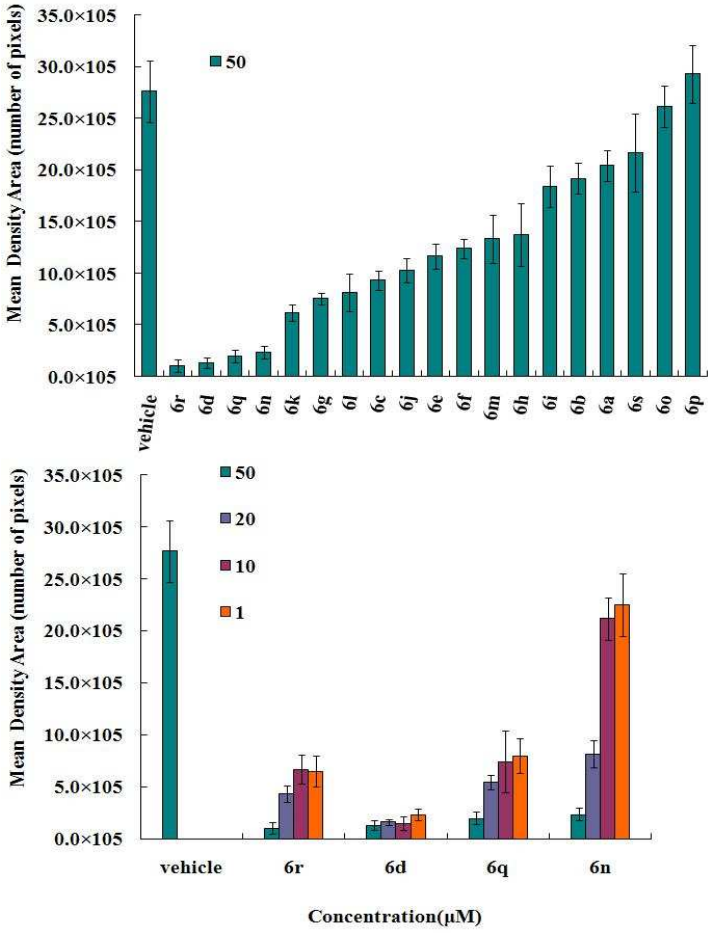


Figure 4

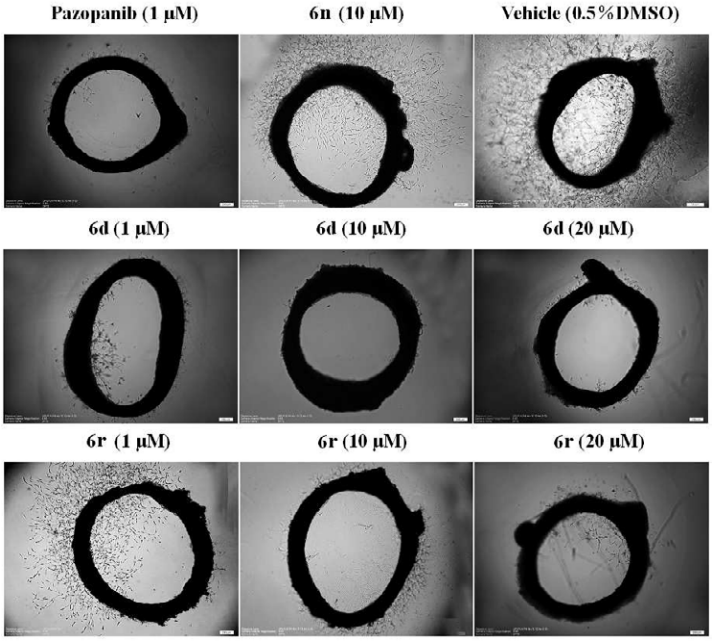
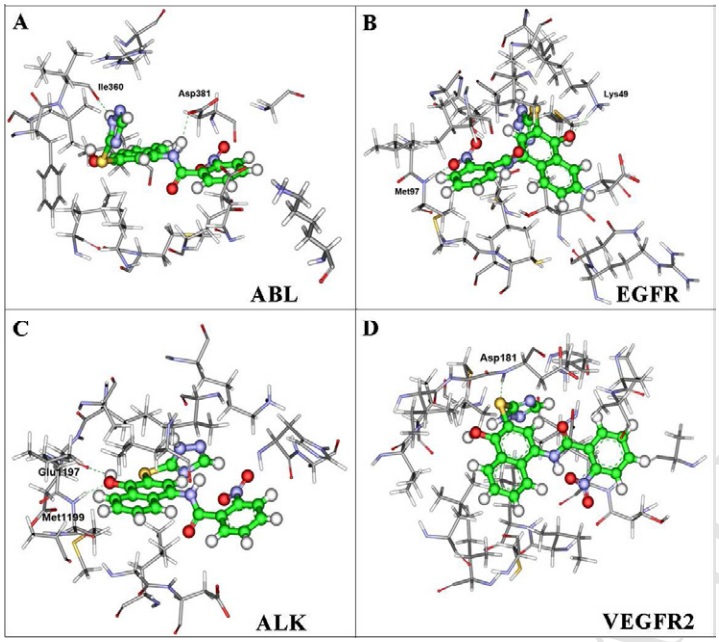
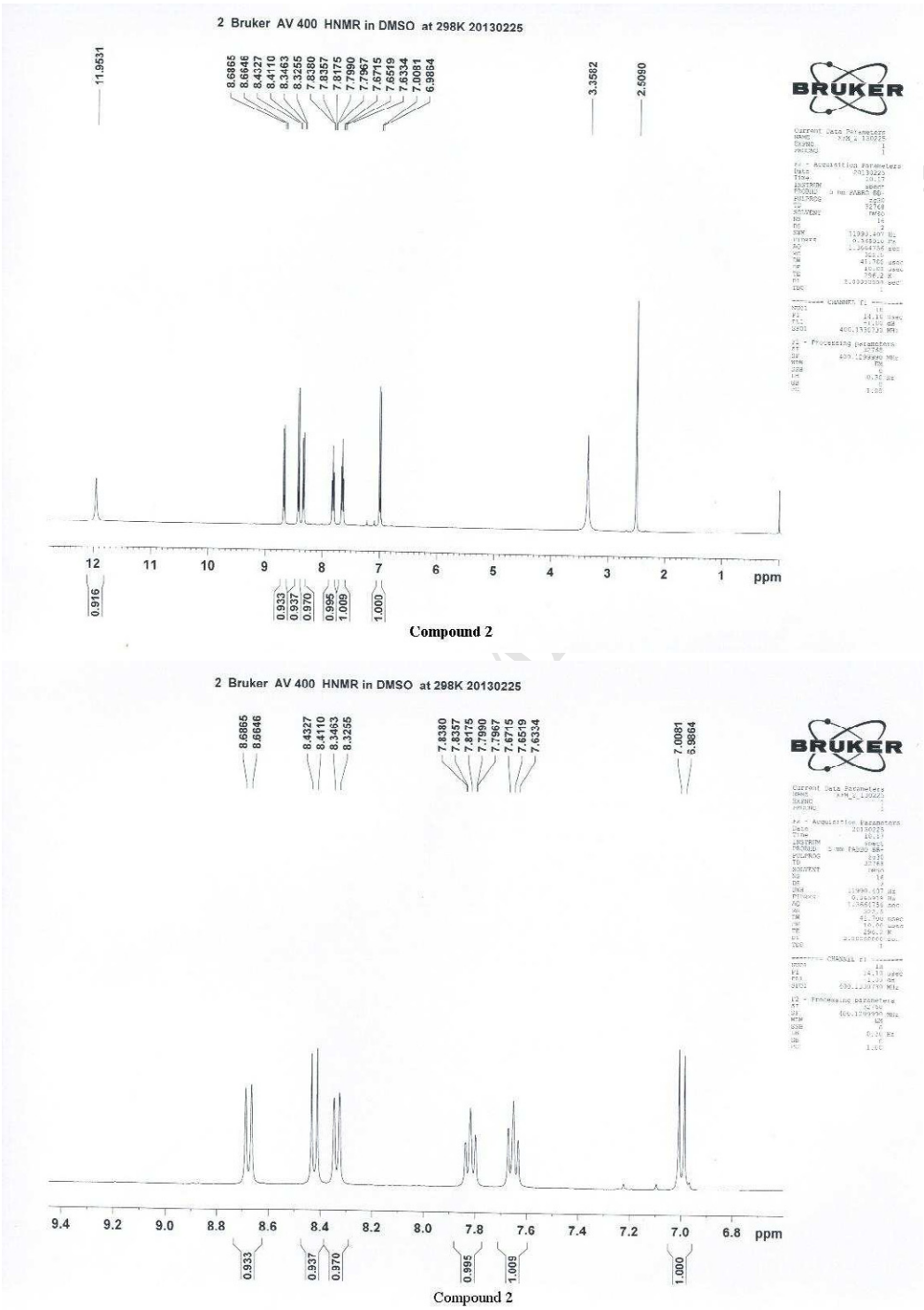


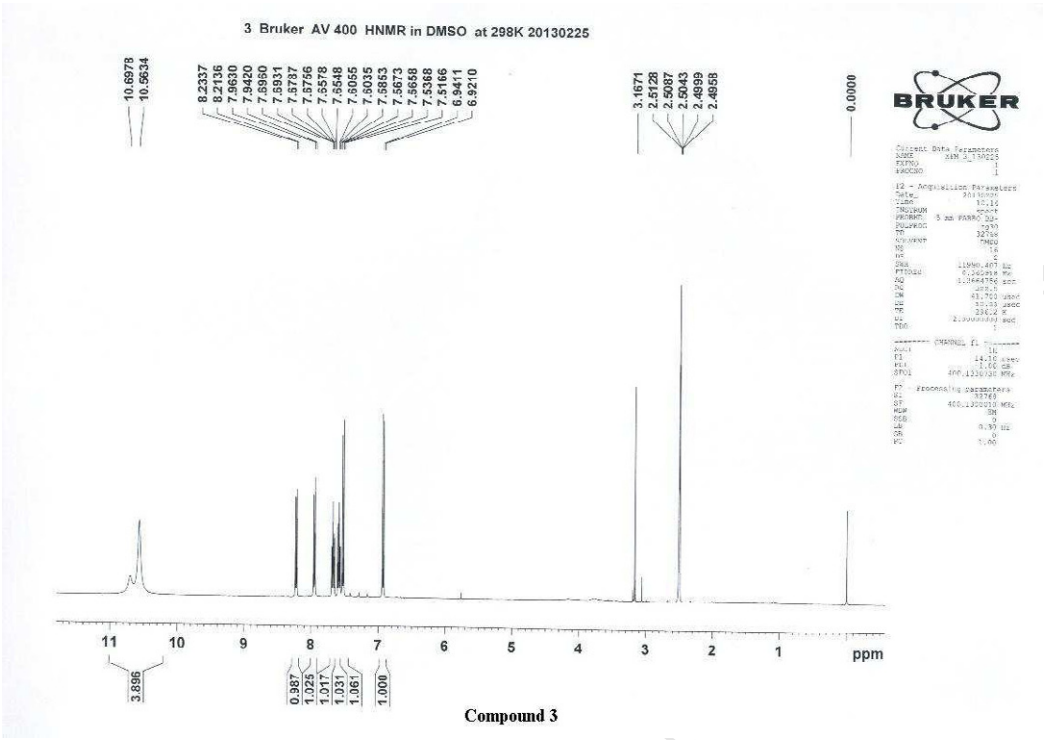
Figure 5



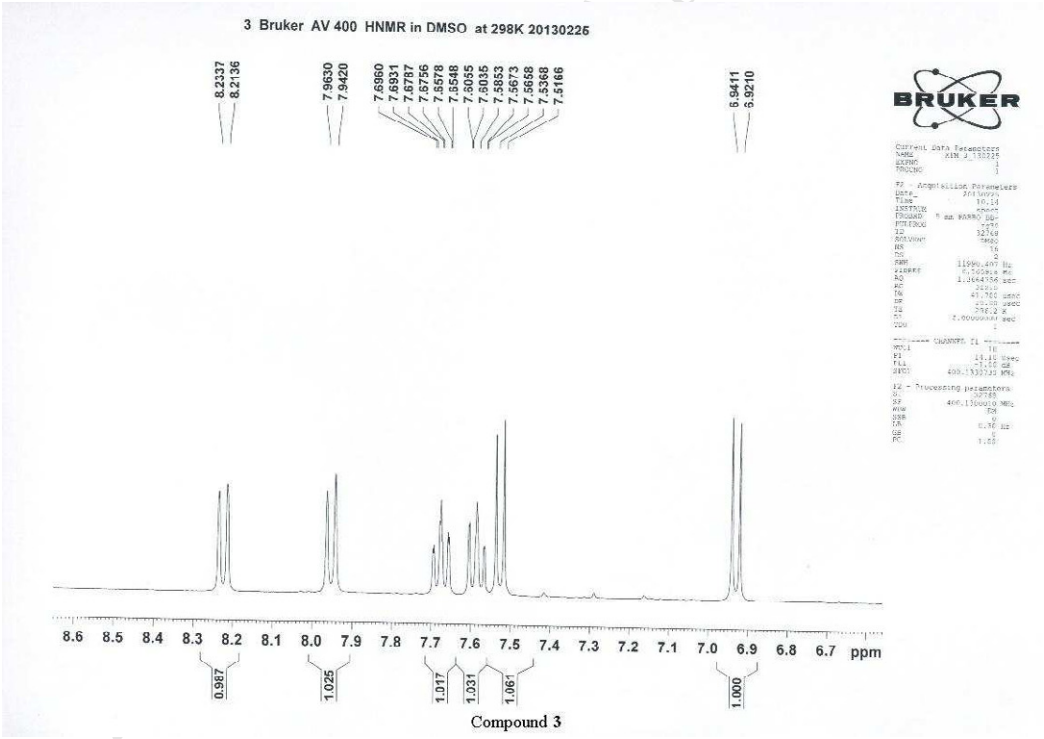
Supplementary material for publication online with representative ^{1}H and ^{1}13C NMR spectra



^{1}H NMR spectra of compound **2**

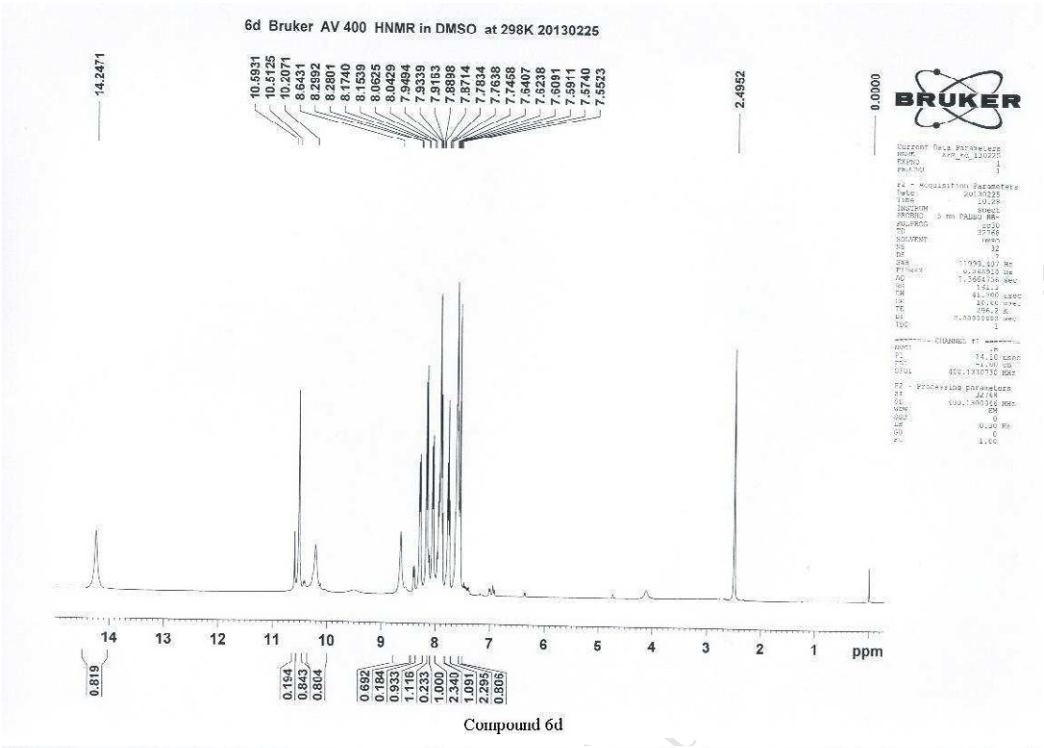


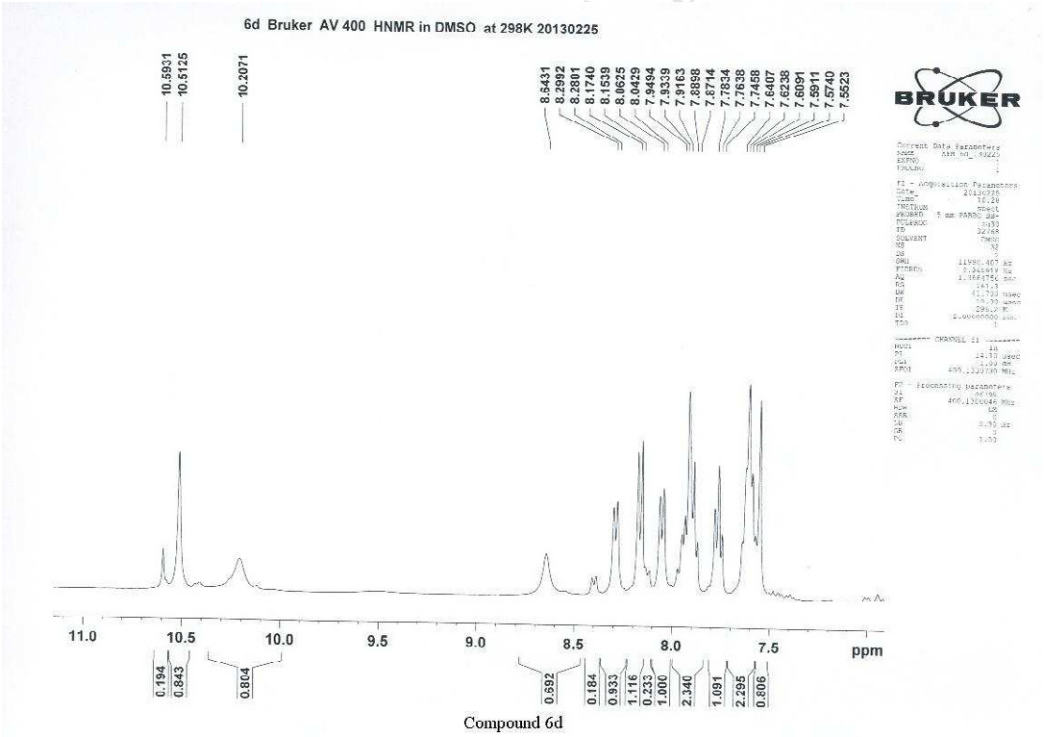
Compound 3



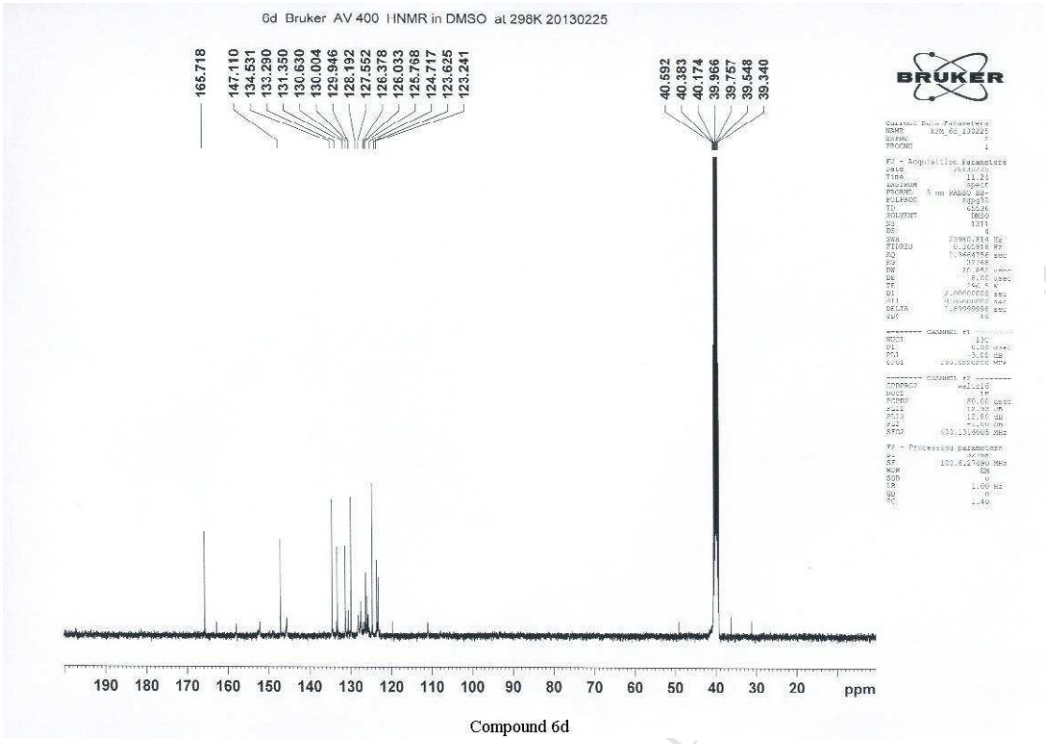
Compound 3

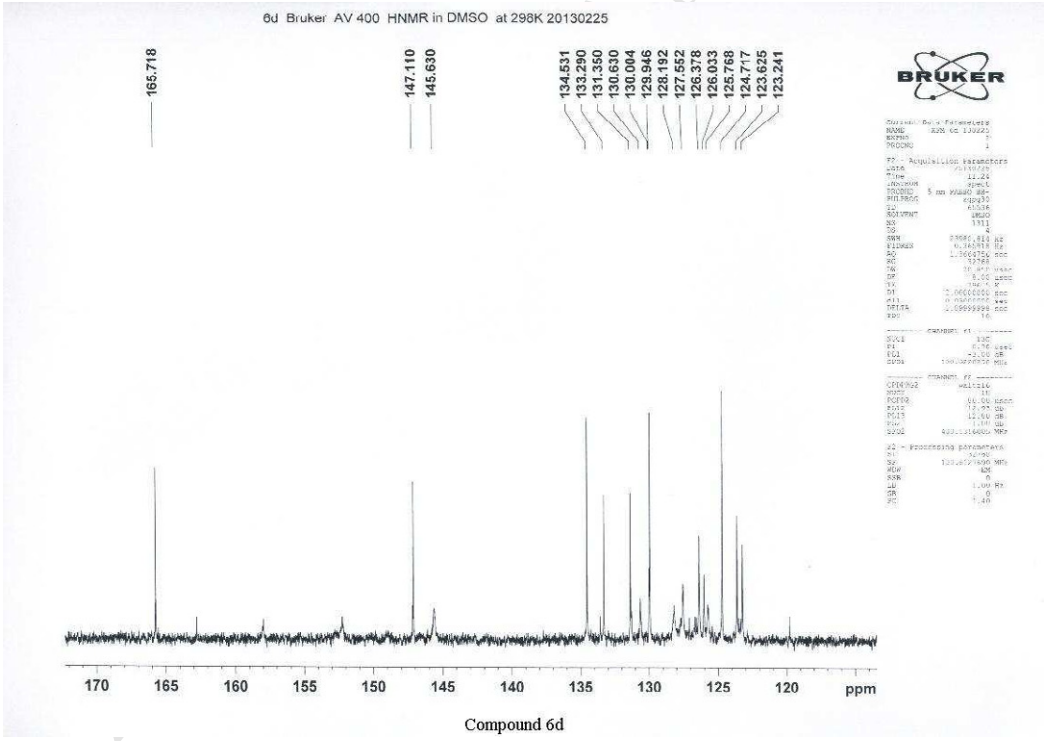
^{1}H NMR spectra of compound **3**



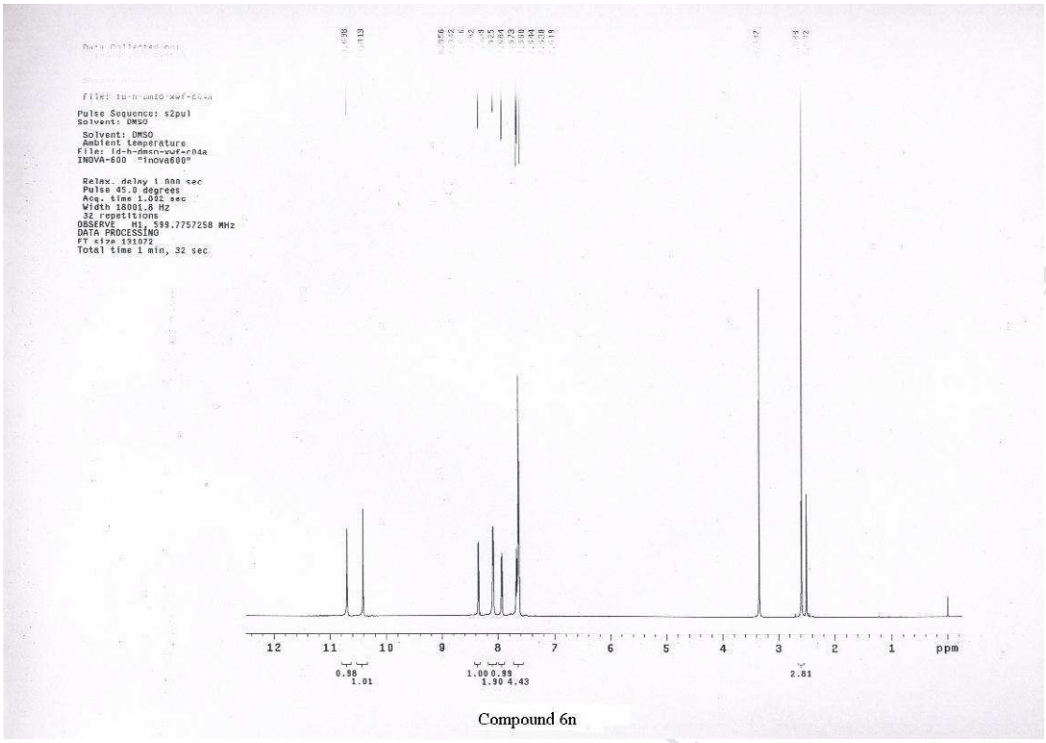


^{1}H NMR spectra of compound **6d**

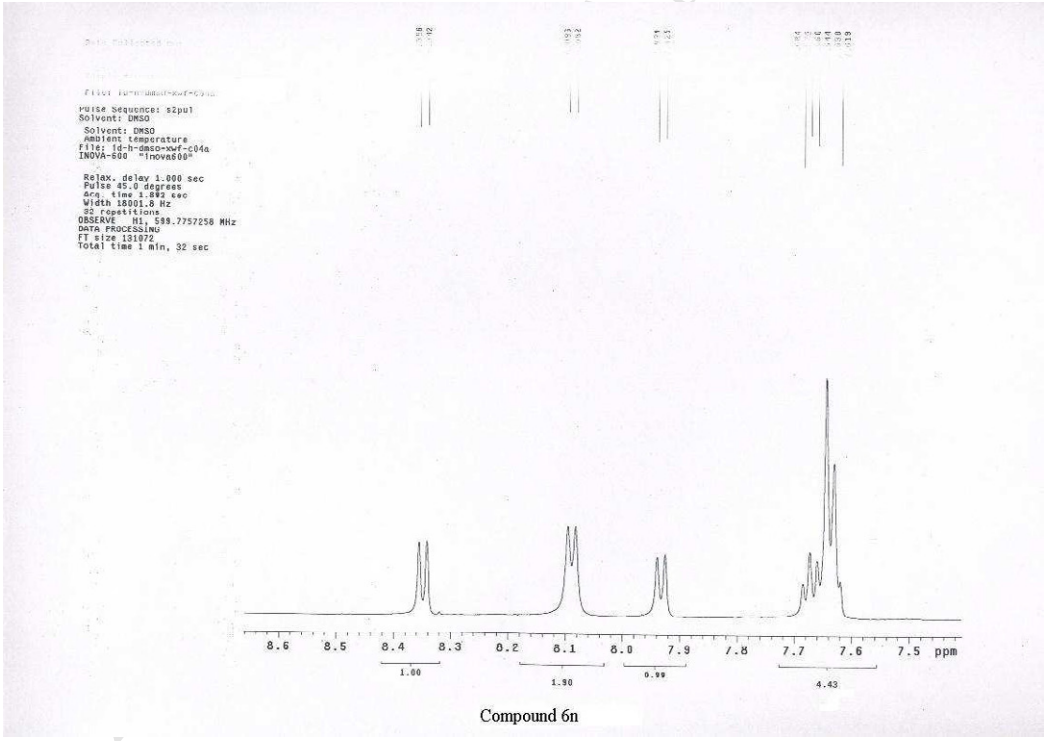




^{13}C NMR spectra of compound **6d**

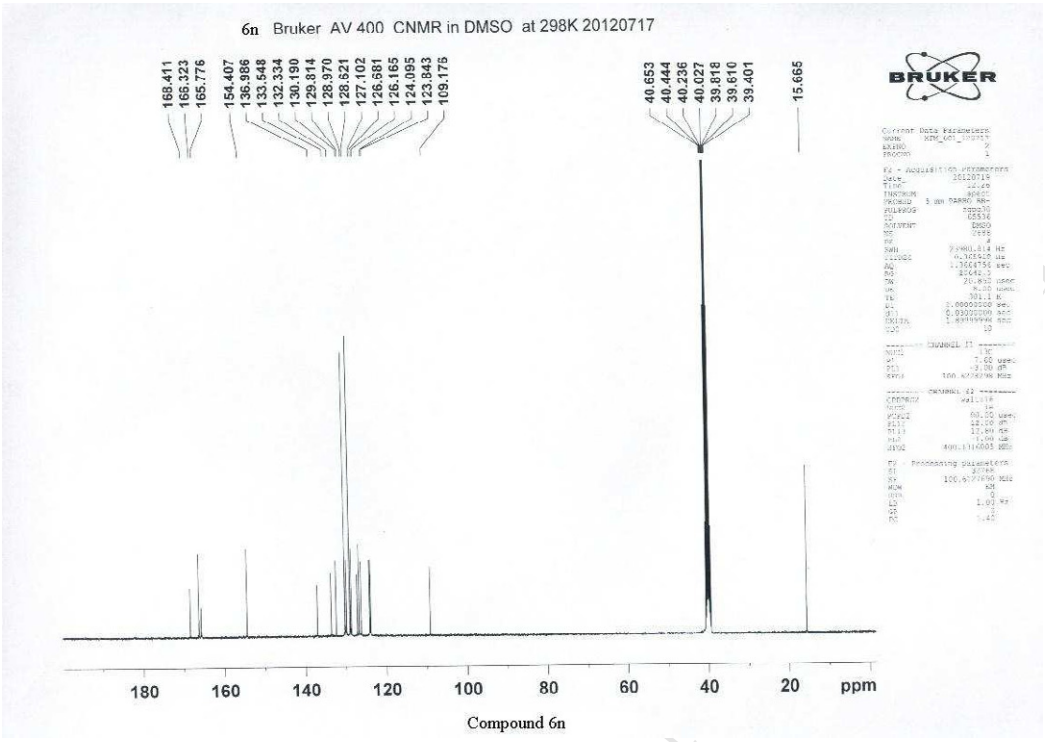


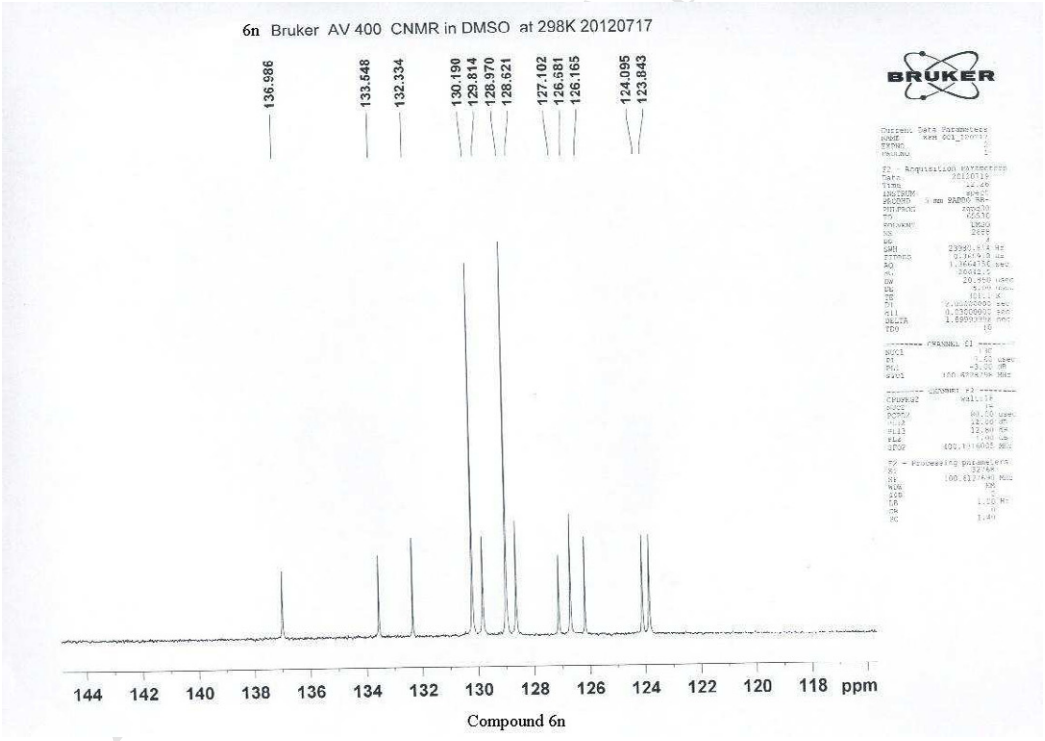
Compound 6n



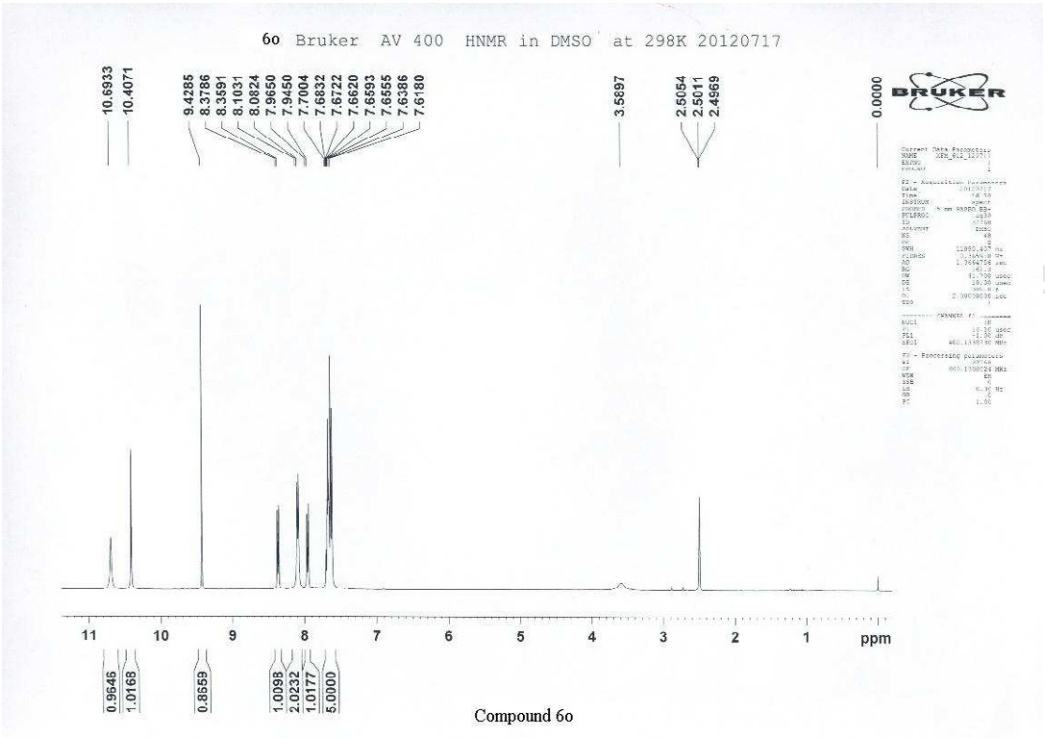
Compound 6n

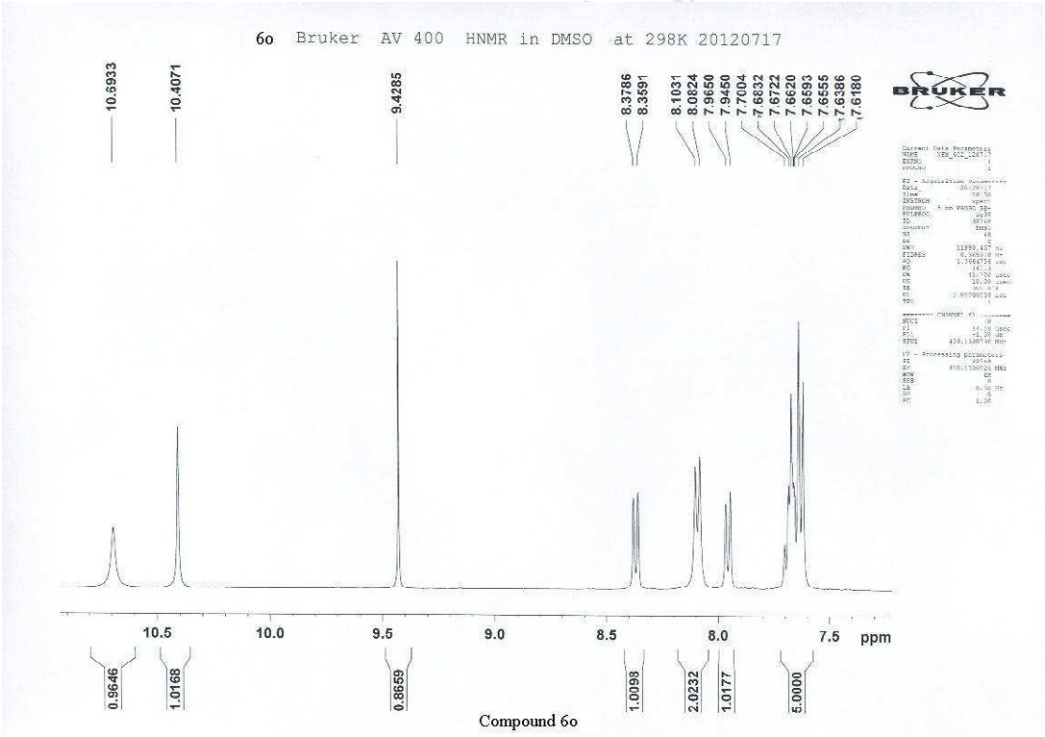
^{1}H NMR spectra of compound **6n**



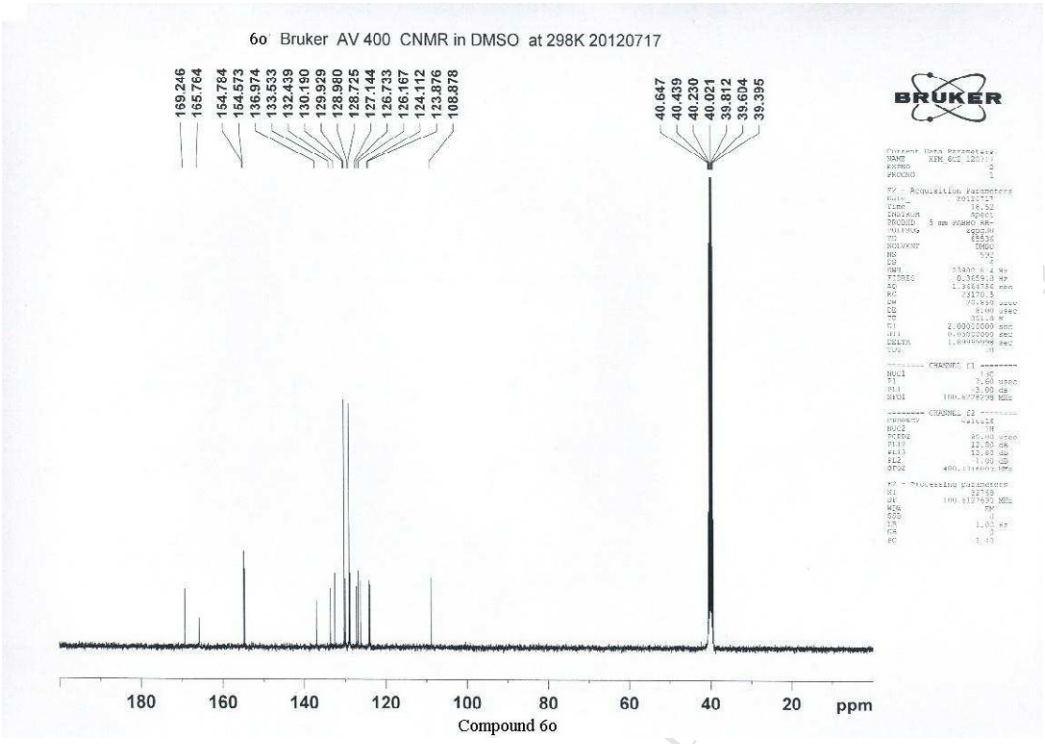


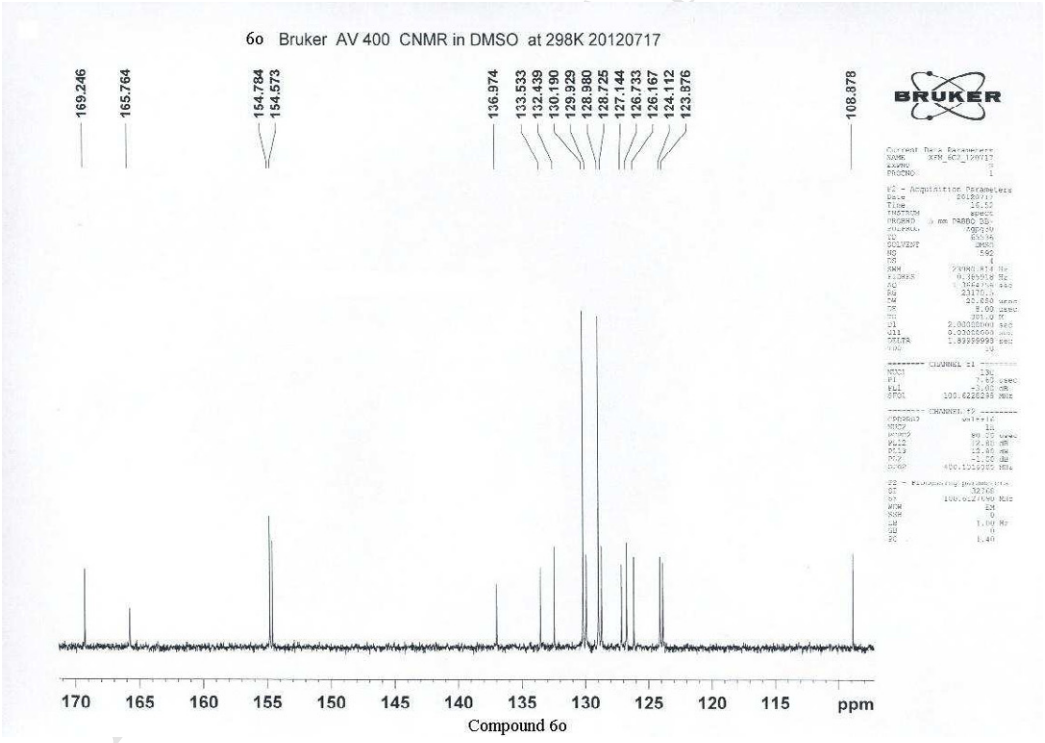
^{13}C NMR spectra of compound **6n**





^{1}H NMR spectra of compound **6o**





^{13}C NMR spectra of compound **6o**