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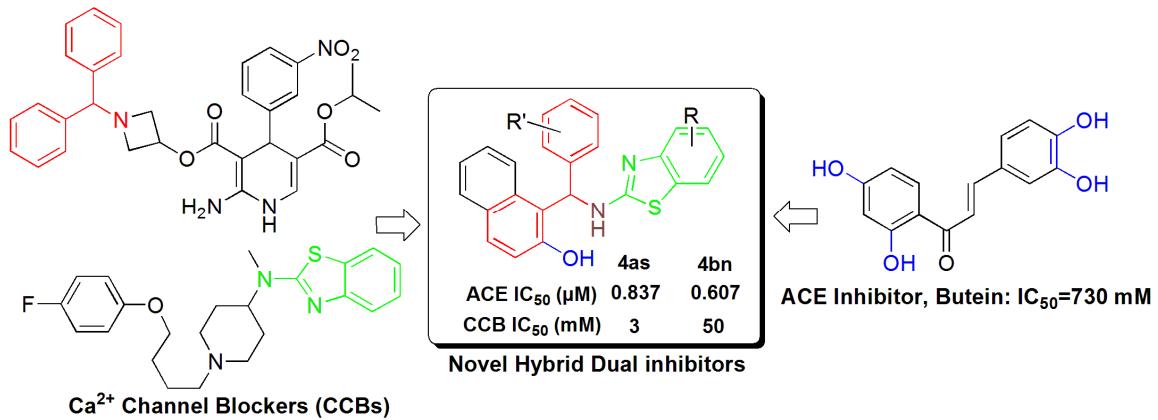
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Design and Green synthesis of 2-(diarylalkyl)aminobenzothiazole derivatives and their dual activities as Angiotensin Converting Enzyme Inhibitors and Calcium Channel Blockers.

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Abstract

A series of novel 2-(diarylalkyl)aminobenzothiazoles were designed based on commercial synthetic calcium channel blockers (CCBs) and angiotensin converting enzyme (ACE) inhibitors. Which are further modified based on the natural products which are angiotensin converting enzyme (ACE) inhibitors. Completely green protocol was developed for their synthesis. As they are initially designed based on CCBs, they were screened for their ACE inhibition property believing that almost all the compounds will be CCBs. Out of 42 compounds two lead molecules were identified as ACE inhibitors, which were further screened for CCB. As expected both were identified as CCBs with different selectivity over ACE inhibition. Their selectivity over ACE and CCB can be used to treat resistant hypertension.

Key words: ACE inhibitors, Calcium Channel Blockers, Green synthesis, 2-aminobenzothiazole, Diarylalkylamine, Resistant hypertension.

Abbreviations

- ACE- Angiotensin Converting Enzyme
BSC- Benzenesulfonyl Chloride
tACE- Testicular angiotensin converting enzyme
CCB- Calcium Channel Blocker
MVD- Molegro Virtual Docker
KHB- Krebs – Hensleit buffer
PDB- Protein Data Bank
RCSB- Research Collaboratory for Structural Bioinformatics
HHL- Hippuryl-histidyl-leucine
HA- Hippuric acid
PMA- Phosphomolybdic Acid

1. Introduction

Cardiovascular disease remains number one cause of death worldwide [1]. Although the causes of cardiovascular disease are diverse, hypertension remains the most common and crucial one. Elevated blood pressure is the most common disorder in developed as well as developing countries. Because of increasing prevalence of hypertension, efforts were made to find new drug molecules which may reduce blood pressure by inhibiting several important mediators of hypertension. Multiple etiologies and environmental factors contribute to the development of hypertension [2,3]. Despite extensive ongoing research in academia and industry, some forms of hypertension remain untreatable. Several drugs, available in the market as antihypertensives, are targeting different pathways or modulators of hypertension. But treating resistant hypertension is still in infancy. Combination of three or more classes of drugs like ACE inhibitors (or) angiotensin receptor blocker, CCBs and diuretics might be the right approach to reduce hypertension-related cardiovascular deaths [4]. Among all those classes of drugs, angiotensin converting enzyme (ACE) inhibitors got a wide acceptance and become first line of therapy. Several ACE inhibitors like Lisinopril, Enalapril (Fig 1) etc. are in clinical use for the treatment of hypertension [5,6]. All these compounds are arylalkylamines in which aryl and amine groups are separated by a three membered carbon chain. However, severe associated side effects (i.e., dry cough, hyperkalemia, rashes, loss of taste and first dose hypotension) limit their use justifying the development of new safe ACE inhibitors [7-9]. On the other hand there are several natural products such as chalcones (Butein, Fig 1) [10], Styrenes [11], flavanoids (Astragalin, Isoquercitrin etc.) [12], Xanthones [13] with multiple hydroxyl groups on aromatic rings. It is also evident that blocking the free hydroxyl groups on Xanthones with acetyl group decreases the ACE inhibition property of the compounds indicating that free hydroxyl groups playing a key role in inhibition of ACE [13].

Second most common antihypertensive drugs are calcium channel blockers (CCB) (Fig 1 and Fig 2). Most of these drug molecules are having the basic skeleton of arylalkylamine, with varying the length of alkyl chain from one to three and with different substituents on aryl, amine or on both the groups. There are very few reports on diarylalkylamines as antihypertensive agents such as Azelnidipine (Fig 1.) and Flunarizine (Fig 2) which act as CCB.

Similar to arylalkylamines, several 2-aminobenzothiazoles derivatives (Fig 1 and Fig 2) were also explored for their antihypertensive property. 2-aminobenzothiazoles act as antihypertensive by inhibiting acid induced Ca^{2+} uptake [14], altering intracellular Ca^{2+} concentration [15] and inhibiting veratridine-induced atrium contraction [16]. These derivatives are also effective inhibitor of histamine-induced angiogenesis [17] and veratridine-induced increase in oxygen consumption and uptake of Ca^{2+} ions [18], and showed protection in the veratridine-induced calcium (Ca^{2+}) overload model [19]. Commercially available drug Riluzole, a derivative of 2-aminobenzothiazole is known to act as glutamate uptake stimulator [20], membrane channel activity stimulator [21], intracellular Ca^{2+} level reducer [22], high voltage-activated calcium channel inhibitior [23].

It was observed that a diarylalkylamine i.e. Flunarizine and a 2-aminobenzothiazole i.e. R 56865 (Fig 2) suppress veratridine-induced increase in oxygen consumption and uptake of Ca^{2+} ions [18]. Based on all above data, we decided to replace the amino group in diarylalkylamine with 2-aminobenzothiazole and thus forming 2-(diarylalkyl)aminobenzothiazole derivatives to screen CCB properties. It is note worthy that all the CCBs are having phenyl group as aromatic group and they do not carry any hydroxyl group, whereas most of the natural products such as Xanthones, Flavones etc. which are ACE inhibitors, carry multiple hydroxyl groups on aromatic rings. Based upon earlier report that decrease in free hydroxyl groups on them decreases ACE inhibition [13]. We are interested to substitute 2-(diarylalkyl)aminobenzothiazole derivatives with at least one hydroxyl group on aryl groups. In over all we designed hybrid molecules in which two aryl groups and one 2-aminobenzothiazole group are attached to the same carbon with the properties based on CCB property and with atleast one hydroxyl group on aryl groups based on natural products which are ACE inhibitors. With the above hybrid structure we are expecting that the new analogues may also act as ACE inhibitors along with CCB, which is their inherent property.

2. Chemistry

In search for the existence of compounds with the above skeleton we found few methodologies in which the hydroxyl group is placed on the naphyl ring. [24-26]. However all these methodologies suffer from serious draw backs such as high temperatures, long reaction times, use of solvent and catalyst. As a result the reaction mixture needed to be purified by traditional

workup and column chromatography techniques. The low solubility of the product in several organic solvents makes the purification difficult and requires huge amounts of organic solvents for purification. Moreover, yield of the purified product after column chromatography is very low. Hence there is a need to develop a method for the synthesis of these compounds with better yield, good purity and least solvent consumption. Several attempts (**Table 1** and **Table 2**) were made to develop a methodology which gives higher yields with more purity. Finally we found the reaction proceeds smoothly on a preheated oilbath at a temperature of about 110-120 °C using no solvent and no catalyst with a relatively short span of time.

Initially we attempted a three component reaction using Benzaldehyde(1), β -Naphthol(2) and 2-Aminobenzothiazole (**3**) as substrates to stabilize the reaction. The methodology so developed is further applied to the synthesis of several of its derivatives (**4aa-4bp**). The reaction proceeds smoothly with a variety of substituents on both aldehyde and 2-aminobenzothiazole moieties and even with aryl substituted aliphatic aldehydes (compound **4aa**, entry1,**Table 3**). Schematically the reaction can be represented as in **Scheme1**.

From the above experiments it was observed that the rate of reaction is fast under solvent free conditions. But yield is very low without a catalyst. This is because during the traditional heating process β -Naphthol is reacting with aldehyde forming xanthenes leaving small amount of β -Naphthol available when it reaches 100 °C. This was further confirmed by carrying the reaction at lower temperature which forms xanthenes exclusively. To overcome the problem we kept the reaction over a preheated oil bath without any solvent and catalyst, good yields were obtained as shown in **Table 2**.

As observed above 110 °C was found to be the ideal temperature to carry out the reaction within a short span of time i.e. 40 min. Because of the low solubility of the product in many organic solvents the reaction mixture was cooled to room temperature and the so formed solid is powdered and washed with ethanol or methanol (3 X 8 mL) to obtain the pure product 1-((benzo[d]thiazol-2-ylamino)(phenyl)methyl) naphthalen-2-ol in 94% yield. It's analogues can be washed with 3 X 8 mL in case of halogenated compounds except fluorinated, 3 X 4 mL in case of fluoro and methoxy derivatives. It is noteworthy to handle fluoro and methoxy derivatives carefully which otherwise may easily washed off in methanol/ethanol. The scope and generality of the reaction is shown in **Table 3**.

Reactions with *ortho*-substituted aldehydes were relatively slow when compared to their *meta*- and *para*- counter parts. So such reactions were kept at a temperature of 120 °C and heated for few minutes excess. As expected the product **4aa** formed using 2-Phenylpropanal produced four isomers forming a pair of enantiomers as major leaving the other pair of enantiomers as minor products. The reaction mixture was washed repeatedly with methanol to remove the minor enantiomers. However it was observed that it is not always possible to purify these isomers by this method. Only major enantiomeric pair was screened for its ACE inhibitory activity.

3. Pharmacology

3.1. In vitro inhibition of ACE:

The ACE inhibition activity for new analogues **4aa-4bp** and the standard drug, Lisinopril were presented in Fig 3. The experiment was carried out at 1.0 µM concentration of test and standard compounds. Our data revealed that all compounds tested in the present study have 7-100% of ACE inhibition activity. Further analysis ACE inhibition activity indicated that two derivatives **4as** and **4bn** exhibited 61.75 % and 80.08 % ACE inhibition, respectively and are comparable to standard drug Lisinopril. Further, IC₅₀ value for test compounds and reference drug was calculated from dose-response curves obtained by plotting the percentage inhibition versus the concentration (Fig 4). IC₅₀ values of **4as** and **4bn** are 0.837 µM and 0.607 µM, respectively.

3.2. Effect of Nifedipine, **4as and **4bn** on dose-response curve induced by CaCl₂:**

Preincubation of rat aortic strips with Nifedipine or **4as** or **4bn** resulted in non-parallel shift to the right of calcium dose response curves. In addition, preincubation of aortic ring with Nifedipine caused a significant reduction of maximal contraction to CaCl₂. (Fig 5 and Fig 6). Vasorelaxants effects of newly synthesized derivatives **4aa-4bp** showed concentration dependent depressant effect on calcium-induced contractions. Our experimental data indicated that preincubation of both **4as** and **4bn**, antagonized the calcium-induced aortic contractions in concentration dependent manner. Among, both the compounds tested, **4as** showed better inhibition property of Ca²⁺ induced contraction in isolated aortic ring. As smooth muscle of blood vessel contracts in response to the activation of voltage-dependent and receptor-operated Ca²⁺ channels, our data suggest that both molecules cause vasorelaxation through inhibition of

voltage-operated Ca^{2+} channels in the isolated rat aortic rings. IC_{50} values of **4as** and **4bn** are 3 mM and 50 mM respectively.

4. Results and Discussion

4.1. Chemistry

We developed an efficient atom economic three component coupling reaction under completely green protocols. The reactions are fast, easy to handle and the products formed can be easily purified by simply washing the reaction mixture with methanol or ethanol which are considered as green solvents with low environmental factor.

4.2. Pharmacology

The compounds synthesized above were primarily screened for their ACE inhibition activity as they were designed based on CCBs and assuming all of they will be CCBs. Out of 42 compounds screened for their ACE inhibition activity two lead molecules **4as** and **4bn** were identified as strong ACE inhibitors and were further proved to be CCBs with varying activity against ACE and CCB. The extent of ACE inhibition is comparably best when compared with the natural product Butein ($\text{IC}_{50} = 730$ mM) based on which the molecules were designed. The structures and IC_{50} values of the compounds **4as** and **4bn** which are dual inhibitors were shown in Fig 7.

4.3. Molecular Docking

To gain insight into the interaction of the ACE enzyme with two potent analogues **4as** and **4bn**, they were docked on to surface of tACE (PDB code: 1O86) using Molegro Virtual Docker (MVD) software. The ligands were generated using Marvin sketch and saved in mol2 format. The typical poses obtained were presented in Fig 8. Results suggest that the docking position of **4aa-4bp** analogs showed a similar binding mode to that of A-ring of Lisinopril. The interactions were mainly seen with the His 353, Ala 354, Tyr 523, Tyr 520 and Glu 152 which are comparable to the standard drug, Lisinopril binding mode. We found that docking scores were matched with *in vitro* activity data.

5. Conclusion

In conclusion, we designed hybrid molecules which are effective against both ACE inhibition and CCB activity. Demonstrated an efficient three-component coupling for their synthesis. The synthesis and purification processes were completely green. The reaction procedure did not utilize any solvent or catalyst and did not use traditional workup and chromatography techniques for purification which generally requires huge amounts of solvents. Thus, we prepared a wide range of 2-(diarylalkyl)aminobenzothiazole derivatives in a single-step process through a multi-component reaction and were initially screened for their angiotensin-converting-enzyme (ACE) inhibition property. Two compounds **4as** and **4bn** which were found active against ACE inhibition, were further screened for their calcium channel blocker (CCB) property by using rat aortic contraction method. Both the compounds were found effective against calcium channel blocking property. From the present study, we developed two new lead molecules **4as** and **4bn** with dual inhibitory property, which may be useful in treating resistant hypertension. Treating resistant hypertension uses combination of drugs which usually contains an ACE inhibitor (or) angiotensin receptor blocker, CCBs and diuretics. The compounds **4as** and **4bn** being CCB along with ACE inhibition could be utilized as novel molecules to treat resistant hypertension.

6. Experimental protocols

6.1. Chemistry

Commercially available reagent grade chemicals and solvents were used in all the reaction and purification processes. All the reactions were monitored by TLC on E. Merck Kieselgel 60 F₂₅₄, with detection by UV light, charring with PMA charring solution or exposure to I₂ vapours. The ¹H (300 and 500 MHz) and ¹³C NMR (75, 100 and 125 MHz) were recorded on Avance-300, Inova-400, Avance-500 and Inova-500 in DMDO-d₆ and CDCl₃. Chemical shift values are reported in ppm relative to TMS (Tetramethylsilane) or DMSO as internal reference unless stated. Coupling constant value *J* is measured in hertz. s (singlet), d (doublet), t (triplet), brs (broad singlet), dd (double doublet), m (multiplet). Mass spectra were recorded on an Agilent LC/MSD trap SL 1100 series spectrometer with a 70 eV (ESI probe) and high-resolution mass spectra were obtained by using ESI-QTOF mass spectrometry. Infrared spectra recorded on a Thermo nicolet Nexus 670 FT-IR spectrometer.

6.1.1. Typical procedure for the synthesis of 2-(diarylalkyl)aminobenzothiazole derivatives (**4aa-4bp**).

To a 10 mL RB flask aldehyde (1.0mmol), 2-aminobenzothiazole (1.0 mmol) and β -naphthol (1.0 mmol) were added, mixed thoroughly and heated in preheated oil bath at 110-120°C for appropriate time (**Table 3**). After completion of reaction as indicated by TLC the reaction mixture was allowed to cool. The so formed solid is powdered and washed with methanol or ethanol (3 X 8 mL in case of halogenated compounds except fluorinated, 3 X 4 mL in case of fluoro and methoxy derivatives) to obtain the corresponding pure 2-(diarylalkyl)aminobenzothiazole derivative. It is noteworthy to handle fluoro and methoxy derivatives carefully which otherwise may easily washed off in methanol/ethanol.

6.1.1.1. 1-(1-(benzo[d]thiazol-2-ylamino)-2-phenylpropyl)naphthalen-2-ol (4aa). The reaction forms two enantiomeric pairs as expected. One of them being major, only that was obtained after several successful washings with methanol while the minor enantiomeric pair washed off with methanol. White solid; mp = 197-199 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.12-9.95 (brs, 1H), 8.41-8.08 (brs, 1H), 7.59 (d, 2H, J = 7.4 Hz), 7.51 (d, 1H, J = 8.7 Hz), 7.40-7.28 (m, 2H), 7.21-6.82 (m, 11H), 6.07-5.98 (brs, 1H), 4.00-3.88 (brs, 1H), 1.51 (d, 1H, J = 6.8 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.6, 153.2, 152.2, 143.9, 130.2, 128.6, 128.1, 127.9, 127.5, 127.2, 125.8, 125.6, 125.4, 121.9, 120.7, 120.6, 118.2, 117.7, 57.6, 42.7, 19.8; IR (KBr): ν_{max} 3450, 3371, 3062, 2964, 1602, 1551, 1448, 1331, 1266, 741, 701 cm⁻¹; ESI-MS: *m/z*: 411(M+H); HRMS calcd. for C₂₆H₂₃ON₂S: 411.15256, found: 411.15381.

6.1.1.2. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(2,4-dichlorophenyl)methyl)naphthalen-2-ol (4ab). Pink solid; mp = 212-214 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.04 (s, 1H), 9.22 (d, 1H, J = 7.2 Hz), 8.17 (d, 1H, J = 8.7 Hz), 7.79 (t, 2H, J = 7.2 Hz), 7.67-7.58 (m, 2H), 7.53 (d, 1H, 2.1 Hz), 7.48-7.38 (m, 2H), 7.32-7.11 (m, 4H), 6.98 (t, 1H, 7.9 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.0, 153.9, 148.8, 138.2, 133.3, 132.6, 132.1, 132.0, 131.2, 130.1, 128.7, 128.6, 128.3, 126.6, 125.6, 122.9, 122.5, 121.7, 121.7, 119.9, 118.4, 115.8, 52.5; IR (KBr): ν_{max} 3336, 2932, 1585, 1537, 1434, 1326, 1252, 882, 812, 735 cm⁻¹; ESI-MS: *m/z*: 485(M+H); HRMS calcd. for C₂₄H₁₆ON₂Cl₃S: 485.00434, found: 485.00457.

6.1.1.3. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(3-chlorophenyl)methyl)naphthalen-2-ol (4ac). White solid; mp = 221-223 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.33-10.13 (brs, 1H), 8.17 (d, 1H, J = 6.4 Hz), 8.02 (d, 1H, J = 6.8 Hz), 7.86-7.78 (m, 2H), 7.64 (d, 1H, J = 9.1 Hz), 7.46-7.16 (m, 9H), 6.99 (t, 1H, J = 7.9 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.8, 153.4, 148.6, 144.7, 132.9, 132.1, 130.1, 129.9, 128.6, 128.5, 126.6, 126.4, 125.7, 125.6, 124.8, 123.3, 122.6, 121.7, 119.9, 118.4, 118.0, 52.9; IR (KBr): ν_{max} 3376, 3064, 1590, 1546, 1413, 1307, 1264, 817,

770 cm⁻¹; ESI-MS: *m/z*: 451(M+H); HRMS calcd. for C₂₄H₁₇ON₂Cl₂S: 451.04332, found: 451.04224.

6.1.1.4. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-fluorophenyl)methyl)naphthalen-2-ol (4ad).* White solid; mp = 205-207 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.25-10.11 (brs, 1H), 9.16 (d, 1H, *J* = 7.6 Hz), 7.97 (d, 1H, 7.6 Hz), 7.84-7.76 (m, 2H), 7.63 (d, 1H, *J* = 7.7 Hz), 7.43-7.21 (m, 7H), 7.11 (t, 2H, *J* = 8.7 Hz), 6.99 (t, 1H, *J* = 7.9 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 162.4, 159.2, 153.3, 148.6, 137.8, 132.0, 129.7, 128.5, 128.0, 127.9, 126.3, 125.5, 123.4, 122.4, 121.6, 119.7, 118.3, 118.1, 114.9, 114.6, 52.9; IR (KBr): ν_{max} 3337, 2938, 1591, 1542, 1507, 1436, 1271, 1157, 812, 764 cm⁻¹; ESI-MS: *m/z*: 435(M+H); HRMS calcd. for C₂₄H₁₇ON₂ClFS: 435.07287, found: 435.07248.

6.1.1.5. *1-((6-chlorobenzo[d]thiazol-2-ylamino)(phenyl)methyl)naphthalen-2-ol (4ae).* White solid; mp = 202-204 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.16 (s, 1H), 8.92 (d, 1H, *J* = 7.6 Hz), 7.90-7.75 (m, 4H), 7.39-7.12 (m, 11H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 153.1, 151.0, 142.2, 132.4, 132.0, 129.5, 128.5, 128.5, 128.0, 126.2, 125.9, 125.5, 124.6, 123.6, 122.3, 120.4, 118.9, 118.4, 118.3, 53.1; IR (KBr): ν_{max} 3375, 3059, 3021, 1598, 1546, 1515, 1447, 1260, 806, 738 cm⁻¹; ESI-MS: *m/z*: 417(M+H); HRMS calcd. for C₂₄H₁₈ON₂ClS: 417.08229, found: 417.08234.

6.1.1.6. *1-((6-chlorobenzo[d]thiazol-2-ylamino)(*p*-tolyl)methyl)naphthalen-2-ol (4af).* White solid; mp = 191-193 °C; ¹H NMR (300 MHz, DMSO-d₆): 10.18-10.10 (brs, 1H), 8.91 (d, 1H, *J* = 7.6 Hz), 7.96-7.71 (m, 4H), 7.39-7.02 (m, 10H), 2.22 (s, 1H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 153.1, 151.0, 139.1, 137.1, 135.2, 132.4, 132.1, 129.4, 128.6, 128.5, 126.1, 125.9, 125.5, 124.6, 123.7, 122.3, 120.4, 118.9, 118.5, 118.3, 53.1, 20.5; IR (KBr): ν_{max} 3364, 3054, 2915, 1599, 1547, 1513, 1447, 1260, 806, 765 cm⁻¹; ESI-MS: *m/z*: 431 (M+H); HRMS calcd. for C₂₅H₂₀ON₂ClS: 431.09794, found: 431.09840.

6.1.1.7. *1-((6-chlorobenzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl)naphthalen-2-ol (4ag).* White solid; mp = 217-219 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.25-10.16 (brs, 1H), 8.92 (d, 1H, *J* = 7.3 Hz), 7.87-7.76 (m, 4H), 7.46 (d, 2H, *J* = 8.5 Hz), 7.41-7.33 (m, 2H), 7.30-7.14 (m, 6H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 153.2, 150.9, 141.9, 132.5, 132.0, 130.9, 129.8, 128.6, 128.3, 126.4, 125.5, 124.9, 123.4, 122.5, 120.5, 119.2, 119.0, 118.3, 118.0, 52.8; IR (KBr): ν_{max} 3560, 3366, 3054, 1598, 1545, 1447, 1258, 1070, 804, 767, 566 cm⁻¹; ESI-MS: *m/z*: 495(M+H); HRMS calcd. for C₂₄H₁₇N₂OSClBr: 494.9933, found: 494.9928.

6.1.1.8. *1-((benzo[d]thiazol-2-ylamino)(4-(dimethylamino)phenyl)naphthalen-2-ol (4ah).* White solid; mp = 156-158 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.22-10.04 (brs, 1H), 8.71 (d, 1H, *J* = 7.4 Hz), 7.93 (d, 1H, *J* = 7.5 Hz), 7.77 (t, 2H, *J* = 9.1 Hz), 7.64 (d, 1H, *J* = 7.4 Hz), 7.39-7.29 (m, 2H), 7.28-7.11 (m, 4H), 7.07 (d, 2H, *J* = 8.5 Hz), 6.99 (t, 1H, *J* = 7.9 Hz), 6.63 (d, 2H, *J* = 8.9 Hz), 2.80 (s, 6H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.2, 153.0, 152.1, 149.0, 132.1, 130.5, 129.5, 129.1, 128.6, 128.4, 126.8, 125.9, 125.3, 122.2, 120.7, 118.9, 118.4, 117.9, 112.2, 53.1,

40.1; IR (KBr): ν_{max} 3315, 2849, 1602, 1538, 1446, 1318, 1264, 1165, 810, 745 cm^{-1} ; ESI-MS: m/z : 426 (M+H); HRMS Calc. for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{OS}$: 426.1640, found: 426.1639.

6.1.1.9. *4-((benzo[d]thiazol-2-ylamino)(2-hydroxynaphthalen-1-yl)methyl)benzonitrile (**4ai**)*. White solid; mp = 213-215 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.31-10.20 (brs, 1H), 8.85 (d, 1H, J = 7.0 Hz), 7.89-7.78 (m, 3H), 7.76-7.65 (m, 3H), 7.46-7.33 (m, 5H), 7.31-7.17 (m, 3H), 7.03 (t, 1H, J = 7.4 Hz). ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.2, 151.9, 148.8, 132.0, 130.8, 130.0, 128.6, 128.5, 127.0, 126.5, 125.4, 123.2, 122.5, 121.2, 120.9, 118.8, 118.3, 117.8, 108.9, 53.0; IR (KBr): ν_{max} 3379, 3056, 2226, 1573, 1541, 1437, 1329, 1270, 1026, 751 cm^{-1} ; ESI-MS: m/z : 408 (M+H); HRMS Calc. for $\text{C}_{25}\text{H}_{18}\text{N}_3\text{OS}$: 408.1170, found: 408.1163.

6.1.1.10. *1-((benzo[d]thiazol-2-ylamino)(2-bromo-5-fluorophenyl)methyl)naphthalen-2-ol (**4aj**)*. white solid; mp = 198-200 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 9.92 (brs, 1H), 8.90 (d, 1H, J = 7.4 Hz), 8.05 (d, 1H, J = 8.7 Hz), 7.80 (t, 2H, J = 9.3 Hz), 7.66 (d, 1H, J = 7.7 Hz), 7.61-7.54 (m, 1H), 7.39-7.34 (m, 3H), 7.28 (t, 1H, J = 7.4 Hz), 7.20 (t, 1H, J = 7.6 Hz), 7.14-6.97 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d₆): δ 165.0, 162.6, 159.4, 153.7, 152.0, 144.2, 144.1, 134.1, 134.0, 132.8, 130.6, 129.9, 128.5, 128.1, 126.5, 125.3, 122.4, 122.3, 121.0, 120.8, 118.5, 118.2, 116.9, 116.7, 116.6, 115.6, 115.3, 54.7; IR (KBr): ν_{max} 3383, 1598, 1543, 1512, 1453, 1431, 1265, 812, 752 cm^{-1} ; ESI-MS: m/z : 479 (M+H); HRMS calcd. for $\text{C}_{24}\text{H}_{17}\text{BrFN}_2\text{OS}$: 479.0204, found: 479.0190.

6.1.1.11. *1-((benzo[d]thiazol-2-ylamino)(phenyl)methyl) naphthalen-2-ol (**4ak**)*. White solid: mp = 200-202 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.17 (brs, 1H), 8.78 (d, 1H, J = 7.6 Hz), 7.94-7.74 (m, 3H), 7.66 (d, 1H, J = 7.6 Hz), 7.40-7.13 (m, 10H), 7.0 (t, 1H, J = 7.4 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.3, 153.2, 152.1, 142.5, 132.1, 130.8, 129.6, 128.6, 128.6, 128.1, 126.2, 126.0, 125.4, 123.8, 122.4, 121.0, 120.9, 118.7, 118.4, 118.1, 53.1; IR (KBr): ν_{max} 3376, 3060, 1598, 1547, 1514, 1444, 1331, 1263, 744 cm^{-1} ; ESI-MS: m/z : 383 (M+H); HRMS calcd. for $\text{C}_{24}\text{H}_{19}\text{N}_2\text{OS}$: 383.1218, found: 383.1206.

6.1.1.12. *1-((benzo[d]thiazol-2-ylamino)(2,4-dichlorophenyl)methyl) naphthalen-2-ol (**4al**)*. White solid: mp = 190-192 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.02-9.91 (brs, 1H), 8.88 (d, 1H, J = 7.0 Hz), 8.02 (d, 1H, J = 8.5 Hz), 7.79 (t, 2H, J = 9.3 Hz), 7.70-7.63 (m, 2H), 7.49 (d, 1H, J = 2.1 Hz), 7.46-7.35 (m, 3H), 7.27 (t, 1H, J = 7.6 Hz), 7.23-7.12 (m, 3H), 7.01 (t, 1H, J = 7.6 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 165.2, 153.8, 152.1, 139.0, 133.0, 132.7, 131.8, 131.1, 130.7, 130.0, 128.7, 128.3, 126.6, 126.5, 125.5, 122.6, 122.4, 121.1, 120.9, 118.5, 118.3, 115.9, 52.3; IR (KBr): ν_{max} 3378, 3068, 1592, 1542, 1438, 1371, 1331, 1268, 751 cm^{-1} ; ESI-MS: m/z : 451 (M+H); HRMS calcd. for $\text{C}_{24}\text{H}_{17}\text{N}_2\text{OSCl}_2$: 451.0438, found: 451.0451.

6.1.1.13. *1-((benzo[d]thiazol-2-ylamino)(3-chlorophenyl)methyl) naphthalen-2-ol (**4am**)*. White solid: mp = 193-194 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.19 (brs, 1H), 8.4 (brs, 1H), 7.96 (brs, 1H), 7.77-7.64 (m, 2H), 7.52 (d, 1H, J = 7.7 Hz), 7.45-7.30 (m, 3H), 7.30-7.09 (m, 7H), 6.99 (t, 1H, J = 7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.1, 151.9, 145.3, 132.8,

131.9, 130.9, 130.7, 129.9, 129.8, 128.6, 128.5, 126.5, 126.1, 125.6, 125.4, 124.8, 122.5, 121.1, 120.9, 118.3, 118.2, 118.0, 52.6; IR (KBr): ν_{max} 3360, 3062, 1596, 1573, 1548, 1515, 1444, 1332, 1268, 749 cm⁻¹; ESI-MS: *m/z*: 417 (M+H); HRMS calcd. for C₂₄H₁₈N₂OSCl: 417.0828, found: 417.0809.

6.1.1.14. 1-((benzo[d]thiazol-2-ylamino)(*p*-tolyl)methyl) naphthalen-2-ol (4an**).** White solid: mp = 180-182 °C; (300 MHz, DMSO-d₆): δ 10.18-10.11 (brs, 1H), 8.78 (d, 1H, *J* = 7.6 Hz), 7.91-7.73 (m, 3H), 7.66 (d, 1H, *J* = 7.4 Hz), 7.39-6.96 (m, 11H), 2.22 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.2, 153.1, 152.1, 139.4, 135.1, 132.1, 130.7, 129.4, 128.6, 128.5, 126.1, 125.9, 125.4, 123.9, 122.4, 120.9, 120.8, 118.7, 118.3, 118.0, 52.9, 20.5; IR (KBr): ν_{max} 3307, 1535, 1441, 1317, 1261, 744 cm⁻¹; ESI-MS: *m/z*: 397 (M+H); HRMS calcd. for C₂₅H₂₁N₂OS: 397.1374, found: 397.1373.

6.1.1.15. 1-((benzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl) naphthalen-2-ol (4ao**).** White solid; mp = 202-204 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.24-10.16 (brs, 1H), 8.82 (d, 1H, *J* = 7.0 Hz), 7.89-7.75 (m, 3H), 7.67 (d, 1H, *J* = 7.6 Hz), 7.49-7.36 (m, 4H), 7.30-7.12 (m, 6H), 7.02 (t, 1H, *J* = 7.6 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.1, 151.9, 142.1, 131.9, 130.9, 130.8, 129.7, 128.5, 128.2, 126.3, 125.3, 123.5, 122.4, 121.0, 120.8, 119.1, 118.3, 118.1, 52.6; IR (KBr): ν_{max} 3373, 1627, 1541, 1442, 1332, 1267, 1206, 1070, 749, 571 cm⁻¹; ESI-MS: *m/z*: 461 (M+H); HRMS calcd. for C₂₄H₁₈N₂OSBr: 461.0323, found: 461.0320.

6.1.1.16. 1-((benzo[d]thiazol-2-ylamino)(4-fluorophenyl)methyl) naphthalen-2-ol (4ap**).** White solid; mp = 178-180 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 1.22-10.13 (brs, 1H), 8.81 (d, 1H, *j* = 7.4 Hz), 7.93-7.76 (m, 3H), 7.67 (d, 1H, *j* = 7.7 Hz), 7.42-7.32 (m, 2H), 7.31-7.15 (m, 6H), 7.93-6.95 (m, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.1, 162.2, 159.0, 153.1, 151.9, 138.4, 131.9, 130.7, 129.5, 128.5, 127.9, 127.8, 126.2, 125.3, 123.5, 122.3, 120.9, 120.8, 118.3, 118.0, 114.8, 114.5, 52.6; IR (KBr): ν_{max} 3308, 1537, 1436, 1319, 1286, 1060, 810, 746 cm⁻¹; ESI-MS: *m/z*: 401 (M+H).

6.1.1.17. 1-((benzo[d]thiazol-2-ylamino)(3-phenoxyphenyl)methyl) naphthalen-2-ol (4aq**).** White solid; mp = 171-173 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.16 (s, 1H), 8.78 (d, 1H, *j* = 7.4 Hz), 7.89-7.73 (m, 3H), 7.66 (d, 1H, *j* = 7.0 Hz), 7.43-7.16 (m, 9H), 7.06-6.93 (m, 4H), 6.87 (d, 2H, *j* = 7.6 Hz), 6.79 (dd, 1H, *j*₁ = 7.6 Hz, *j*₂ = 2.1 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.1, 156.5, 156.0, 153.1, 152.0, 145.0, 132.0, 130.7, 129.7, 128.6, 128.5, 126.2, 125.4, 123.0, 122.4, 121.3, 121.0, 120.8, 118.3, 118.1, 117.9, 116.6, 116.3, 52.7; IR (KBr): ν_{max} 3314, 3052, 1541, 1511, 1451, 1267, 814, 749 cm⁻¹; ESI-MS: *m/z*: 475 (M+H); HRMS calcd. for C₃₀H₂₃N₂O₂S: 475.1480, found: 475.1471.

6.1.1.18. 1-((benzo[d]thiazol-2-ylamino)(naphthalen-2-yl)methyl) naphthalen-2-ol (4ar**).** White solid; mp = 190-192 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.21-10.16 (brs, 1H), 8.91 (d, 1H, *j* = 7.4 Hz), 7.95 (d, 1H, *j* = 7.9 Hz), 7.89-7.74 (m, 6H), 7.68 (d, 1H, *j* = 7.9 Hz), 7.53-7.40 (m, 3H), 7.38-7.15 (m, 6H), 7.02 (m, 1H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.2, 153.1, 152.0,

140.1, 132.6, 132.1, 131.7, 130.7, 129.6, 128.5, 128.4, 127.5, 127.3, 126.1, 126.0, 125.4, 125.3, 124.9, 123.8, 123.6, 122.3, 120.9, 120.8, 118.5, 118.3, 118.0, 53.3; IR (KBr): ν_{max} 3313, 3052, 1541, 1442, 1264, 814, 749 cm^{-1} ; ESI-MS: m/z : 433 (M+H); HRMS Calc. for $\text{C}_{28}\text{H}_{21}\text{N}_2\text{OS}$: 433.1374, found: 433.1387.

6.1.1.19. 1-((benzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl) naphthalen-2-ol (4as). White solid; mp = 190-192 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.19-10.11 (brs, 1H), 8.79 (d, 1H, j = 7.4 Hz), 7.94-7.84 (brs, 1H), 7.79 (t, 2H, j = 8.7 Hz), 7.66 (d, 1H, j = 7.6 Hz), 7.42-7.12 (m, 9H), 7.0 (t, 1H, j = 7.9 Hz), 6.83 (d, 1H, j = 8.7 Hz), 3.68 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.2, 157.7, 153.0, 152.1, 134.1, 132.1, 130.6, 129.4, 128.6, 128.5, 127.2, 126.1, 125.3, 123.8, 122.3, 120.9, 120.8, 118.7, 118.4, 118.0, 113.5, 54.9, 52.8; IR (KBr): ν_{max} 3313, 3052, 1541, 1442, 1264, 814, 749 cm^{-1} ; ESI-MS: m/z : 413 (M+H); HRMS calcd. for $\text{C}_{25}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$: 413.1323, found: 413.1319.

6.1.1.20. 1-((benzo[d]thiazol-2-ylamino)(3,4,5-trimethoxyphenyl)methyl) naphthalen-2-ol (4at). White solid; mp = 170-172 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.42-10.30 (brs, 1H), 8.63-8.37 (brs, 1H), 7.98-7.87 (brs, 1H), 7.75-7.63 (m, 2H), 7.52-7.31 (m, 3H), 7.28-7.15 (m, 3H), 7.11-6.94 (m, 2H), 6.58 (s, 2H), 3.70 (s, 3H), 3.66 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.3, 153.3, 152.4, 137.0, 136.1, 132.0, 129.9, 129.1, 128.6, 128.1, 125.8, 125.1, 123.0, 122.2, 120.8, 120.1, 119.1, 118.8, 117.9, 103.6, 95.6, 59.8, 55.4, 54.3; IR (KBr): ν_{max} 3317, 2923, 2833, 1590, 1538, 1441, 1315, 1248, 1171, 1030, 813, 745 cm^{-1} ; ESI-MS: m/z : 473 (M+H).

6.1.1.21. 1-((benzo[d]thiazol-2-ylamino)(3-bromophenyl)naphthalen-2-ol (4au). White solid; mp = 201-203 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.27-10.20 (brs, 1H), 8.84 (d, 1H, j = 7.4 Hz), 7.92-7.77 (m, 3H), 7.68 (d, 1H, j = 7.6 Hz), 7.45-7.15 (m, 11H), 7.02 (t, 1H, j = 7.6 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.0, 153.1, 151.9, 145.5, 131.9, 130.7, 130.2, 129.8, 129.0, 128.5, 126.4, 125.4, 125.1, 123.3, 122.4, 121.4, 121.0, 120.8, 118.3, 118.1, 118.0, 52.6; IR (KBr): ν_{max} 3377, 3058, 1543, 1511, 1435, 1327, 1268, 747 cm^{-1} ; MS-ESI: m/z : 461 (M+H); HRMS calcd. for $\text{C}_{24}\text{H}_{18}\text{BrN}_2\text{OS}$: 461.0323, found: 461.0312.

6.1.1.22. 1-((benzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)naphthalen-2-ol (4av). White solid; mp = 212-214 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.28-10.24 (brs, 1H), 8.87 (d, 1H, j = 7.2Hz), 7.93-7.79 (m, 3H), 7.69 (d, 1H, j = 7.6 Hz), 7.53 (d, 1H, j = 8.3 Hz), 7.47-7.37 (m, 3H), 7.32-7.15 (m, 5H), 7.03 (t, 1H j = 7.7 Hz). ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.0, 153.2, 151.8, 144.0, 131.9, 130.8, 130.6, 130.2, 130.0, 128.6, 128.4, 127.7, 126.6, 126.5, 125.4, 123.1, 122.5, 121.1, 120.9, 118.3, 118.2, 117.6, 52.3; IR (KBr): ν_{max} 3379, 1577, 1540, 11461, 1328, 1268, 1205, 1028, 816, 747 cm^{-1} ; ESI-MS: m/z : 451 (M+H); HRMS calcd. for $\text{C}_{24}\text{H}_{17}\text{Cl}_2\text{N}_2\text{OS}$: 451.0438, found: 451.0439.

6.1.1.23. 1-((benzo[d]thiazol-2-ylamino)(3-fluorophenyl)naphthalen-2-ol (4aw). White Solid; ^1H NMR (300 MHz, DMSO-d₆): δ 10.26-10.19 (brs, 1H), 8.84 (d, 1H, j = 7.4 Hz), 7.90-7.78 (m, 3H), 7.68 (d, 1H, j = 7.7 Hz), 7.43-7.17 (m, 7H), 7.07-6.96 (m, 4H). ^{13}C NMR (75 MHz, DMSO-

d_6): δ 166.1, 163.7, 160.5, 153.1, 151.9, 145.8, 145.8, 131.9, 130.7, 130.0, 129.9, 129.7, 128.5, 126.3, 125.4, 123.4, 122.4, 122.1, 121.0, 120.8, 118.3, 118.1, 113.0, 112.8, 112.5, 52.7; IR (KBr): ν_{max} 3387, 1587, 1536, 1482, 1439, 1329, 1244, 1053, 749 cm^{-1} ; ESI-MS: m/z : 401 (M+H); HRMS calcd. for $C_{24}H_{18}FN_2OS$: 401.1123, found: 401.1118.

6.1.1.24. 1-((benzo[d]thiazol-2-ylamino)(4-isopropylphenyl)naphthalen-2-ol (4ax**).** White solid; mp = 191-193 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.17-10.09 (brs, 1H), 8.78 (d, 1H, j = 7.6 Hz), 7.98-7.87 (brs, 1H), 7.79 (t, 2H, j = 7.8 Hz), 7.66 (d, 1H, j = 7.6 Hz), 7.4-7.32 (m, 2H), 7.30-7.10 (m, 8H), 7.00 (t, 1H, j = 8.1 Hz), 2.89-2.74 (m, 1H), 1.14 (dd, 6H, j_1 = 7.0 Hz, j_2 = 1.5 Hz). ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.2, 153.0, 152.1, 146.1, 139.6, 132.1, 130.6, 129.3, 128.5, 128.4, 126.1, 126.0, 125.9, 125.3, 123.7, 122.3, 120.8, 120.8, 118.7, 118.4, 118.0, 53.0, 32.9, 23.8, 23.7; IR (KBr): ν_{max} 3314, 3055, 2957, 1540, 1450, 1268, 1060, 746 cm^{-1} ; ESI-MS: m/z : 425 (M+H); HRMS calcd. for $C_{27}H_{25}N_2OS$: 425.1687, found: 425.1704.

6.1.1.25. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol (4ay**).** White solid; mp = 208-210 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.24 (s, 1H), 9.20 (d, 1H, j = 7.7 Hz), 8.07-7.97 (brs, 1H), 7.86-7.79 (m, 2H), 7.66 (d, 1H, j = 7.9 Hz), 7.55 (d, 1H, j = 8.3 Hz), 7.48-7.40 (m, 2H), 7.36-7.14 (m, 5H), 7.0 (t, 1H, 7.9 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.6, 153.4, 148.5, 143.4, 132.1, 132.0, 130.9, 130.3, 130.0, 128.8, 128.6, 128.4, 127.8, 126.7, 126.5, 125.6, 123.1, 122.6, 121.7, 119.8, 118.3, 117.6, 52.5; IR (KBr): ν_{max} 3352, 2935, 1590, 1544, 1254, 817, 738 cm^{-1} ; ESI-MS: m/z : 485 (M+H); HRMS calcd. for $C_{24}H_{16}N_2OSCl_3$: 485.0048, found: 485.0032.

6.1.1.26. 1-((6-chlorobenzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol (4az**).** White solid; mp = 215-217 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.28-10.23 (brs, 1H), 8.98 (d, 1H, j = 7.4 Hz), 7.9307.77 (m, 4H), 7.53 (d, 1H, j = 8.5 Hz), 7.47-7.14 (m, 8H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.6, 153.2, 150.8, 143.8, 132.6, 131.9, 130.7, 130.3, 130.0, 128.7, 128.6, 128.4, 127.7, 126.6, 126.5, 125.5, 124.9, 123.0, 122.6, 120.6, 119.1, 118.3, 117.5, 52.4; IR (KBr): ν_{max} 3360, 2865, 1598, 1545, 1446, 1254, 813, 740 cm^{-1} ; ESI-MS: m/z : 485 (M+H); HRMS calcd. for $C_{24}H_{16}N_2OSCl_3$: 485.0048, found: 485.0032.

6.1.1.27. 1-((4-methylbenzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol (4ba**).** White solid; mp = 222-224 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.26-10.16 (brs, 1H), 8.98 (d, 1H, j = 7.9 Hz), 8.17-8.02 (brs, 1H), 7.86-7.77 (m, 2H), 7.58-7.40 (m, 4H), 7.03 (d, 1H, j = 7.2 Hz), 6.91 (t, 1H, j = 7.7 Hz), 2.41 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 165.1, 153.3, 150.6, 143.7, 132.1, 130.6, 130.2, 130.1, 129.8, 128.7, 128.5, 128.3, 127.9, 127.3, 126.6, 126.5, 126.1, 123.1, 122.5, 121.0, 118.3, 118.3, 118.1, 52.4, 17.9; IR (KBr): ν_{max} 3340, 2923, 1585, 1545, 1516, 1252, 816, 739 cm^{-1} ; ESI-MS: m/z : 465 (M+H); HRMS calcd. for $C_{25}H_{19}Cl_2N_2OS$: 465.0595, found: 465.0575.

6.1.1.28. 1-((benzo[d]thiazol-2-ylamino)(2,4-dimethoxyphenyl)methyl)naphthalen-2-ol (4bb**).** White solid; mp = 174-176 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.22-10.08 (brs, 1H),

8.81 (d, 1H, $j = 7.2$ Hz), 7.95 (d, 1H, $j = 8.5$ Hz), 7.78 (t, 2H, $j = 8.9$ Hz), 7.65 (d, 1H, $j = 7.7$ Hz), 7.41-7.31 (m, 2H), 7.29-7.15 (m, 4H), 7.04-6.91 (m, 4H), 6.84 (d, 1H, $j = 8.5$ Hz), 6.73 (d, 1H, 8.7 Hz), 3.68 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.0, 152.0, 148.4, 147.4, 134.5, 132.1, 130.5, 129.3, 128.5, 128.4, 126.0, 125.3, 123.8, 122.3, 120.8, 118.6, 118.4, 117.9, 111.6, 110.6, 55.4, 53.1; IR (KBr): ν_{\max} 3368, 2930, 2834, 1573, 1542, 1509, 1271, 752 cm⁻¹; ESI-MS: *m/z*: 443 (M+H); HRMS calcd. for C₂₆H₂₃O₃N₂S: 443.14239, found: 443.14463.

6.1.1.29. 1-((benzo[d]thiazol-2-ylamino)(2-chlorophenyl)methyl)naphthalen-2-ol (4bc). White solid; mp = 197-199 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 9.99-9.93 (brs, 1H), 8.86 (d, 1H, $j = 7.4$ Hz), 8.05 (d, 1H, $j = 8.7$ Hz), 7.78 (t, 2H, $j = 9.3$ Hz), 7.64 (d, 2H, $j = 7.7$ Hz), 7.47-7.12 (m, 10H), 6.99 (t, 1H, $j = 7.9$ Hz); ^{13}C NMR (125 MHz, DMSO-d₆): δ 165.3, 153.7, 152.2, 139.4, 132.7, 132.4, 130.6, 129.7, 129.4, 128.6, 128.3, 126.4, 126.3, 125.4, 122.9, 122.3, 120.9, 120.8, 118.5, 118.2, 116.5, 52.7; IR (KBr): ν_{\max} 3456, 3381, 3066, 1571, 1528, 1438, 1319, 1270, 1040, 750 cm⁻¹; ESI-MS: *m/z*: 417(M+H); HRMS calcd. for C₂₄H₁₈ON₂ClS: 417.08229, found: 417.08426.

6.1.1.30. 1-((benzo[d]thiazol-2-ylamino)(4-(trifluoromethyl)phenyl)methyl)naphthalen-2-ol (4bd). White solid; mp = 203-205 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.20-10.13 (brs, 1H), 8.90 (d, 1H, $j = 7.6$ Hz), 7.91-7.72 (m, 4H), 7.44-7.16 (m, 7H), 7.15-7.02 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.2, 151.9, 147.7, 132.0, 130.8, 129.9, 128.6, 128.5, 127.4, 127.0, 126.7, 126.6, 126.5, 126.1, 125.4, 124.99, 124.96, 123.3, 122.5, 121.1, 120.9, 118.3, 118.2, 118.0, 52.9; IR (KBr): ν_{\max} 3380, 3059, 2867, 2599, 1574, 1541, 1326, 1267, 1158, 1125, 1068, 749 cm⁻¹; ESI-MS: *m/z*: 451 (M+H); HRMS calcd. for C₂₅H₁₈ON₂F₃S: 451.10865, found: 451.10976.

6.1.1.31. 1-((benzo[d]thiazol-2-ylamino)(3,4-dimethoxyphenyl)methyl)naphthalen-2-ol (4be). White solid; mp = 176-178 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.21-10.11 (brs, 1H), 8.78 (d, 1H, $j = 7.6$ Hz), 7.95 (d, 1H, $j = 7.4$ Hz), 7.77 (t, 2H, $j = 8.9$ Hz), 7.64 (d, 1H, $j = 7.4$ Hz), 7.41-7.31 (m, 2H), 7.28-7.14 (m, 4H), 7.03-6.92 (m, 2H), 6.83 (d, 1H, $j = 8.5$ Hz), 6.73 (d, 1H, $j = 7.6$ Hz), 3.68 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.3, 153.1, 152.1, 148.5, 147.5, 134.5, 132.2, 130.6, 129.4, 128.6, 128.5, 126.1, 125.5, 123.8, 122.4, 121.0, 120.9, 118.7, 118.5, 118.0, 111.7, 110.6, 55.5, 53.3; IR (KBr): ν_{\max} 3368, 2930, 2834, 1573, 1543, 1510, 1330, 1271, 752 cm⁻¹; ESI-MS: *m/z*: 443(M+H); HRMS calcd. for C₂₆H₂₃O₃N₂S: 443.14239, found: 443.14472.

6.1.1.32. 1-((benzo[d]thiazol-2-ylamino)(3,4-difluorophenyl)methyl)naphthalen-2-ol (4bf). White solid; mp = 177-179 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.38-10.13 (brs, 1H), 8.84 (d, 1H, $j = 7.0$ Hz), 7.94-7.78 (m, 3H), 6.8 (d, 1H, $j = 7.6$ Hz), 7.46-7.16 (m, 8H), 7.02 (t, 2H, $j = 7.2$ Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.0, 153.1, 151.8, 140.4, 131.9, 130.7, 129.8, 128.5, 128.5, 126.4, 125.3, 123.2, 122.6, 122.4, 121.0, 120.8, 118.3, 118.2, 117.8, 117.1, 116.9, 114.9, 114.7, 52.4; IR (KBr): ν_{\max} 3390, 3052, 1598, 1541, 1511, 1431, 1274, 754, 467

cm^{-1} ; ESI-MS: m/z : 419(M+H); HRMS calcd. for $\text{C}_{24}\text{H}_{17}\text{ON}_2\text{F}_2\text{S}$: 419.10242, found: 419.10338.

6.1.1.33. 1-((benzo[d]thiazol-2-ylamino)(4-chlorophenyl)methyl)naphthalen-2-ol (4bg). White solid; mp = 214-216 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.22-10.18 (brs, 1H), 8.82 (d, 1H, J = 7.4 Hz), 7.87-7.66 (m, 3H), 7.68 (d, 1H, J = 7.4 Hz), 7.42-7.16 (m, 10H), 7.02 (t, 3H, J = 7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.1, 152.0, 141.6, 132.0, 130.8, 130.6, 129.7, 128.5, 128.0, 127.9, 126.3, 125.4, 123.5, 122.4, 121.0, 120.8, 118.3, 118.2, 52.6; IR (KBr): ν_{max} 3375, 3056, 1574, 1541, 1514, 1436, 1330, 1269, 749 cm^{-1} ; ESI-MS: m/z : 417(M+H); HRMS calcd. for $\text{C}_{24}\text{H}_{18}\text{ON}_2\text{ClS}$: 417.08229, found: 417.08458.

6.1.1.34. 1-((benzo[d]thiazol-2-ylamino)(2,3-dichlorophenyl)methyl)naphthalen-2-ol (4bh). White solid; mp = 200-202 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.03-9.92 (brs, 1H), 8.93 (d, 1H, J = 6.6 Hz), 8.01 (d, 1H, J = 8.5 Hz), 7.80 (t, 2H, 8.9 Hz), 7.66 (d, 2H, J = 7.7 Hz), 7.53 (d, 1H, J = 7.7 Hz), 7.46-7.11 (m, 7H), 7.01 (t, 1H, J = 7.4 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 165.1, 153.8, 152.1, 142.6, 132.7, 131.7, 130.7, 130.0, 128.6, 128.6, 128.3, 127.2, 126.5, 125.4, 122.6, 122.4, 121.0, 120.8, 118.5, 118.3, 115.8, 53.3; IR (KBr): ν_{max} 3350, 3014, 1597, 1538, 1512, 1448, 1270, 1154, 810, 748, 586, 482 cm^{-1} ; ESI-MS: m/z : 451(M+H); HRMS calcd. for $\text{C}_{24}\text{H}_{17}\text{Cl}_2\text{N}_2\text{OS}$: 451.04332, found: 451.04577.

6.1.1.35. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(phenyl)methyl)naphthalen-2-ol (4bi). White solid; mp = 214-216 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.19-10.11 (brs, 1H), 9.18 (d, 1H, J = 7.4 Hz), 8.02-7.89 (brs, 1H), 7.84-7.76 (m, 2H), 7.64 (d, 1H, J = 7.7 Hz), 7.42-7.15 (m, 10H), 6.98 (t, 1H, J = 7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.9, 153.3, 148.7, 141.8, 132.1, 132.0, 129.6, 128.5, 128.4, 128.1, 126.3, 126.2, 126.0, 125.5, 123.7, 122.4, 121.5, 119.7, 118.3, 53.3; IR (KBr): ν_{max} 3350, 3314, 3059, 2937, 1587, 1537, 1416, 1325, 1253, 815, 747, 697 cm^{-1} ; ESI-MS: m/z : 417(M+H); HRMS calcd. for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{ClOS}$: 417.08229, found: 417.08168.

6.1.1.36. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(*p*-tolyl)methyl)naphthalen-2-ol (4bj). White solid; mp = 219-221 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.18-10.07 (brs, 1H), 9.23-9.11 (brs, 1H), 8.04-7.88 (brs, 1H), 7.83-7.74 (m, 2H), 7.63 (d, 1H, J = 7.0 Hz), 7.41-7.31 (m, H), 7.30-7.20 (m, 4H), 7.17-7.05 (m, 4H), 6.98 (t, 1H, J = 7.9 Hz), 2.24 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 167.1, 153.4, 148.8, 138.7, 135.5, 132.2, 132.0, 129.6, 128.8, 128.6, 128.5, 126.3, 126.0, 125.7, 123.8, 122.5, 121.6, 121.6, 119.8, 118.5, 118.4, 53.4, 20.6; IR (KBr): ν_{max} 3310, 2927, 1586, 1533, 1417, 1320, 1271, 1051, 883, 812, 679 cm^{-1} ; ESI-MS: m/z : 431(M+H); HRMS calcd. for $\text{C}_{25}\text{H}_{20}\text{ClN}_2\text{OS}$: 431.09794, found: 431.09731.

6.1.1.37. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl)naphthalen-2-ol (4bk). White solid; mp = 223-225 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO-d₆): δ 10.22-10.16 (brs, 1H), 9.18 (d, 1H, J = 7.6 Hz), 8.02-7.88 (brs, 1H), 7.84-7.77 (m, 2H), 7.65 (d, 1H, J = 7.7 Hz), 7.48 (d, 2H, J = 8.5 Hz), 7.39 (t, 1H, J = 7.7 Hz), 7.32-7.15 (m, 6H), 6.99 (t, 1H, J = 7.9 Hz); ^{13}C

NMR (75 MHz, DMSO-d₆): δ 166.8, 153.3, 148.7, 141.5, 132.0, 130.9, 129.8, 128.5, 128.3, 126.4, 125.5, 123.5, 122.5, 121.6, 119.7, 119.3, 118.3, 117.9, 52.9; IR (KBr): ν_{max} 3343, 3297, 1711, 1586, 1528, 1416, 881, 814, 744, 498 cm⁻¹; ESI-MS: *m/z*: (M+H); HRMS calcd. for C₂₄H₁₇BrClN₂OS: 494.9933, found: 494.9948.

6.1.1.38. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(3-phenoxyphenyl)methyl)naphthalen-2-ol (4bl). White solid; mp = 208-210 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.28-10.14 (brs, 1H), 9.23-9.12 (brs, 1H), 8.02-7.88 (brs, 1H), 7.84-7.78 (m, 2H), 7.64 (d, 1H, *J* = 7.2 Hz), 7.46-7.28 (m, 9H), 7.07-6.95 (m, 4H), 6.90 (d, 2H, *J* = 7.7 Hz), 6.82 (d, 1H, *J* = 7.7 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 156.6, 156.1, 153.4, 148.7, 144.4, 132.1, 129.7, 128.5, 126.3, 125.5, 123.7, 123.0, 122.4, 121.7, 121.6, 121.4, 119.7, 118.3, 118.1, 117.9, 116.8, 116.5, 53.1; IR (KBr): ν_{max} 3332, 2938, 1588, 1545, 1485, 1249, 1165, 884, 744, 491 cm⁻¹; ESI-MS: *m/z*: 509(M+H); HRMS calcd. for C₃₀H₂₂ClN₂O₂S: 509.10850, found: 509.10754.

6.1.1.39. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(naphthalen-2-yl)methyl)naphthalen-2-ol (4bm). White solid; mp = 236-238 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.25-10.14 (brs, 1H), 9.36-9.27 (brs, 1H), 8.13-7.96 (brs, 1H), 7.88-7.76 (m, 6H), 7.66 (d, 1H, *J* = 7.4 Hz), 7.55-7.21 (m, 8H), 6.99 (t, 1H, *J* = 7.7 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 167.0, 153.5, 148.8, 139.6, 132.7, 132.3, 132.1, 131.8, 129.7, 128.6, 128.5, 127.7, 127.6, 127.3, 126.3, 125.6, 125.5, 125.0, 124.0, 123.7, 122.4, 121.7, 121.6, 119.8, 118.5, 118.4, 53.7; IR (KBr): ν_{max} 3320, 3052, 2930, 1585, 1533, 1416, 1268, 816, 660, 478 cm⁻¹; ESI-MS: *m/z*: 467(M+H); HRMS calcd. for C₂₈H₁₉N₂ONaSCl: 489.0804, found: 489.0822.

6.1.1.40. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl)naphthalen-2-ol (4bn). White solid; mp = 211-213 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.22-10.08 (brs, 1H), 9.24-9.10 (brs, 1H), 8.05-7.93 (brs, 1H), 7.79 (m, 2H), 7.63 (d, 1H, *J* = 7.742 Hz), 7.42-7.13 (m, 7H), 6.98 (t, 1H, *J* = 7.9 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 3.69 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.9, 157.8, 153.3, 148.8, 133.4, 132.1, 131.9, 129.5, 128.6, 128.4, 127.3, 126.1, 125.5, 123.8, 122.4, 121.5, 121.5, 119.7, 118.4, 113.5, 54.9, 53.2; IR (KBr): ν_{max} 3315, 3066, 2925, 2830, 1583, 1510, 1433, 1319, 1250, 1173, 1032, 821, 668, 588 cm⁻¹; ESI-MS: *m/z*: 447(M+H); HRMS calcd. for C₂₅H₂₀O₂N₂ClS: 447.09285, found: 447.09345.

6.1.1.41. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(3,4,5-trimethoxyphenyl)methyl)naphthalen-2-ol (4bo). White solid; mp = 215-217 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.27-10.10 (brs, 1H), 9.32-9.17 (brs, 1H), 8.18-8.04 (brs, 1H), 7.79 (t, 2H, *J* = 8.3 Hz), 7.63 (d, 1H, *J* = 7.9 Hz), 7.42 (t, 1H, *J* = 7.5 Hz), 7.31-7.13 (m, 4H), 6.97 (t, 1H, *J* = 7.7 Hz), 6.66 (s, 2H), 3.62 (s, 6H), 3.61 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.9, 153.4, 152.6, 148.7, 137.2, 136.3, 132.2, 131.9, 129.6, 128.5, 126.3, 125.6, 123.6, 122.4, 121.5, 121.5, 119.7, 118.4, 118.3, 104.1, 59.9, 55.8, 54.0; IR (KBr): ν_{max} 3366, 2932, 1593, 1542, 1509, 1414, 1328, 1131, 818 cm⁻¹; ESI-MS: *m/z*: 507(M+H); HRMS calcd. for C₂₇H₂₄O₄N₂ClS: 507.11398, found: 507.11452.

6.1.1.42. *I-((4-chlorobenzo[d]thiazol-2-ylamino)(4-(dimethylamino)phenyl)methyl)naphthalen-2-ol (**4bp**)*. Pale yellow solid; mp = 205-207 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.20-10.03 (brs, 1H), 9.23-9.07 (brs, 1H), 8.07-7.93 (brs, 1H), 7.77 (t, 2H, J = 8.9 Hz), 7.62 (d, 1H, J = 7.9 Hz), 7.35 (t, 1H, J = 7.9 Hz), 7.25 (t, 3H, J = 7.6 Hz), 7.18-7.03 (m, 3H), 6.96 (t, 1H, J = 7.7 Hz), 6.64 (d, 2H, J = 8.9 Hz), 2.82 (S, 6H); ¹³C NMR (75 MHz, DMSO-d₆): δ 167.0, 153.3, 149.1, 148.9, 132.2, 131.8, 129.3, 128.7, 128.6, 128.4, 126.9, 126.0, 125.5, 124.0, 122.3, 121.4, 121.4, 119.7, 118.6, 118.4, 112.2, 53.5, 40.1; IR (KBr): ν_{max} 3353, 3321, 2851, 1587, 1533, 1433, 1269, 811 cm⁻¹; HRMS calcd. for C₂₆H₂₂N₃ONaSCl: 482.1069, found: 482.1089.

6.2. In vitro Angiotensin Converting Enzyme Inhibition assay:

ACE inhibition assay was performed using the method described by Jimsheena et al [27, 28]. Rabbit lung acetone powder (Sigma Aldrich, USA) was used as a source of ACE enzyme. 1 gm of rabbit lung acetone powder was suspended in 10 mL of 0.05 M sodium borate buffer pH 8.2 containing 0.3 M NaCl and 0.5% Triton X-100 at 4°C for 24hrs followed by centrifugation at 15,000 rpm for 60 min at 4 °C. Supernatant was used as a source of ACE enzyme for this assay. ACE inhibition activity was assayed by monitoring the release of hippuric acid (HA) from the hydrolysis of the substrate hippuryl-histidyl-leucine (HHL) (Sigma-Aldrich, USA). 7μl of ACE enzyme solution was preincubated with test and standard drug solution at 1μM concentration for 10min at 37°C. Final volume was adjusted using 0.05 M sodium borate buffer (pH 8.2) containing 0.3 M NaCl to get equal concentration. The enzyme reaction was then initiated by adding 50 μl of 5 mM substrate (HHL) followed by incubation at 37°C for 30 min. The reaction was then arrested by the addition of 0.1 mL of 1 M HCl. Hippuric acid produced in the reaction was then reacted with 0.2 mL of pyridine (SD Fine chemical, India) and 0.1 mL of Benzenesulfonyl chloride(BSC) (SD Fine chemical, India)to develop yellow color. The solution was mixed by inversion for 1 min and cooled on ice. The yellow color developed was measured at 410 nm. The decreased concentration of HA in the test reaction compared with the control. ACE inhibition was expressed as percentage inhibition and calculated from the equation: Inhibition% = 100 - [T/C] × 100, where T = absorbance of test reaction and C = absorbance of control reaction. The therapeutic drug Lisinopril was used as reference ACE inhibitor. The inhibitory concentration 50% (IC₅₀) was calculated by nonlinear regression. The dose-response curve was obtained by plotting the percentage inhibition versus the concentrations.

6.3. Ex-vivo model for measuring aortic contraction:

All the experiments were approved by the Institutional Animal Ethics Committee (IAEC, IICT, Hyderabad). Experiments were performed on male Sprague-Dawley rats that were 8-10 weeks old and weighed 180-200g. Aortic contraction was determined by measuring isometric tension from a rat aortic ring [29]. The rats were sacrificed by cervical dislocation and under xylazine and ketamine anesthesia. The thoracic aorta (from the arch of aorta to the diaphragm) was quickly excised and placed in 37° C oxygenated (95 % O₂ – 5 % CO₂) calcium free Krebs – Hensleit buffer (KHB). Aorta was cut into 5-mm segments and was cleared of adhering fat and adventitial tissues. Due care was taken to keep the endothelium intact. The composition of calcium free KHB (mM) was NaCl : 118, KCl : 4.7, MgSO₄ : 1.2, KH₂PO₄ : 1.2, NaHCO₃ : 25 and Glucose : 5.5 (pH 7.4). Each ring was suspended by stainless steel hooks in a water-jacketed organ bath, filled with 25 mL of oxygenated KHB maintained at 37° C. Response from isometric tension was measured using an isometric force transducer (AD Instruments, Australia). A resting tension of 1g was applied to aortic rings, which were then allowed to equilibrate for about 30 minutes. Once the tissue was stabilized, contraction was evoked by adding phenylephrine 1mM to the organ bath during which the buffer was changed every 15 minutes. After the initial contraction by epinephrine, concentration-response curve was measured with the cumulative concentration of calcium (10⁻³ to 10⁻¹ M). Similarly, the same cumulative concentration-response curve with calcium was prepared in presence of 100 mM test drugs (**4as** and **4bn**) and standard drug (Nifedipine).

6.4. Molecular Docking:

Molegro Virtual Docker (MVD, Ver: 2012.5.0.0) [30, 31] is a program for determining the most conformations of a ligand that bind to an enzyme site. The identification of ligand binding modes is done iteratively by evaluating a number of candidate solutions (ligand conformations) and estimating the energy of their interactions with the enzyme. The highest scoring solutions are returned for further analysis. MVD performs flexible ligand docking, so the optimal geometry of the ligand will be determined during the docking. In the present study, docking studies were performed with two active ligands **4as** and **4bn** using the software. Crystal structure of tACE (PDB ID: 1O86) along with the co-factor (Zinc) was downloaded from RCSB Protein Data Bank. Structure of tACE (residues 37-625) [32-34] adopts an overall ellipsoid shape with central

groove that extends for about 30 Å into molecules and divides the protein into two sub domains. Zinc is an important catalytic component of ACE, bound at the active site. The boundaries of the groove are provided by helices α and β strands. Structure of tACE-lisinopril complex used to locate the active site of the molecules. tACE contains 27 helices. Structure of tACE revealed the location of two buried chloride ions separated by 20.3 Å. Structures of both active compounds i.e., **4as** and **4bn** were prepared by using Chem Draw and saved to mol file format. These structures were further converted into mol2 file format by using Marvin Sketch. MVD was used to perform computational studies, cavity prediction, assigning bond orders, structure refinement, defining the active binding sites of the tACE and structure preparation. Residues from ACE enzyme involved in hydrogen bonding interaction with ligands are as follows: His 353, Ala 354, Tyr 523, Tyr 520 and Glu 152. As most of the ligands are surrounded by the above residues, it can be concluded that these residues are highly conserved and plays an important functional roles. Interaction of the ligands with these residues might be responsible for inhibition of ACE enzyme. Generally, low free energy is associated with high affinity binding with tACE.

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Table 1: Preliminary studies of three component coupling reaction.**Table 2:** Reactions on a preheated oilbath without solvent.

Table 3: Different derivatives of Aldehydes (R^1) and 2-Aminobenzothiazoles (R^2) reacting with β -Naphthol to produce 2-(diarylalkyl)aminobenzothiazoles.

Table 1: Preliminary studies of three component coupling reaction.

Entry	Solvent (mL)	Temp °C	Time (min)	Yield (%)
1	PEG-400 (3)	100	100	30
2	Toluene (3)	100	100	32
3	Toluene (3)	100	150	30
4	Toluene (1)	100	100	35
5	<i>m</i> -xylene (1)	100	100	35
6	-	100	100	20
7	-	100	150	25
8	-	50	100	0
9	-	75	150	23

Table 2: Reactions on a preheated oilbath without solvent.

Entry	Temp (°C)	Time (min)	Yield (%)
1	50	100	0
2	80	100	60
3	100	100	80
4	110	100	95
5	110	60	94
6	110	40	94
7	110	20	47
8	130	20	70

Table 3: Different derivatives of Aldehydes (R^1) and 2-Aminobenzothiazoles (R^2) reacting with β -Naphthol to produce 2-(diarylalkyl)aminobenzothiazoles.

Entry	Compound	R^1	R^2	Time (min)	Temp (°C)	Yield (%)
1	4aa	1-Phenylethyl	H	40	110	86
2	4ab	2,4-Dichlorophenyl	4-Chloro	55	120	92
3	4ac	3-Chlorophenyl	4-Chloro	45	110	89
4	4ad	4-Fluorophenyl	4-Chloro	45	110	88
5	4ae	Phenyl	6-Chloro	45	110	90
6	4af	4-Methylphenyl	6-Chloro	45	110	88
7	4ag	4-Bromophenyl	6-Chloro	50	110	91
8	4ah	4-(Dimethylamino)phenyl	H	40	110	93
9	4ai	4-Cyanophenyl	H	40	110	92
10	4aj	2-Bromo-5-fluorophenyl	H	50	120	92
11	4ak	Phenyl	H	40	110	94
12	4al	2,4-Dichlorophenyl	H	50	120	92
13	4am	3-Chlorophenyl	H	40	110	93
14	4an	4-Methylphenyl	H	45	110	91
15	4ao	4-Bromophenyl	H	50	110	94
16	4ap	4-Fluorophenyl	H	40	110	95
17	4aq	3-Phenoxyphenyl	H	45	110	92
18	4ar	2-Naphthyl	H	45	110	90
19	4as	4-Methoxyphenyl	H	45	110	91
20	4at	3,4,5-Trimethoxyphenyl	H	45	110	88
21	4au	3-Bromophenyl	H	40	110	94
22	4av	3,4-Dichlorophenyl	H	40	110	94
23	4aw	3-Fluorophenyl	H	40	110	93
24	4ax	4-Isopropylphenyl	H	45	110	90
25	4ay	3,4-Dichlorophenyl	4-Chloro	45	110	94
26	4az	3,4-Dichlorophenyl	6-Chloro	43	110	94
27	4ba	3,4-Dichlorophenyl	4-Methyl	40	110	94
28	4bb	2,4-Dimethoxyphenyl	H	50	110	90
29	4bc	2-Chlorophenyl	H	50	120	92
30	4bd	4-Trifluoromethoxyphenyl	H	40	110	88
31	4be	3,4-Dimethoxyphenyl	H	45	110	90
32	4bf	3,4-Difluorophenyl	H	40	110	87
33	4bg	4-Chlorophenyl	H	40	110	91
34	4bh	2,3-Dichlorophenyl	H	50	120	89
35	4bi	Phenyl	4-Chloro	40	110	90
36	4bj	4-Methylphenyl	4-Chloro	45	110	91
37	4bk	4-Bromophenyl	4-Chloro	45	110	90
38	4bl	3-Phenoxyphenyl	4-Chloro	45	110	88
39	4bm	2-Naphthyl	4-Chloro	45	110	89

40	4bn	4-Methoxyphenyl	4-Chloro	50	110	90
41	4bo	3,4,5-TrimethoxyPhenyl	4-Chloro	50	110	88
42	4bp	4-(Dimethylamino)phenyl	4-Chloro	45	115	90

Fig 1: Structures of ACE Inhibitors and Ca^{2+} Channel blockers

Fig 2. Structures of R 56865 and Flunarizine

Fig 3. *In vitro* Angiotensin Converting Enzyme (ACE) inhibition of new Diarylalkylamine analogues **4aa–4bp** and standard drug, Lisinopril.

Fig 4. Dose Response Curves of new Diarylalkylamine derivatives **4as** and **4bn** for ACE inhibition.

Fig 5. Dose-response curve of calcium-induced aortic ring contraction in presence and absence of standard (Nifedipine) and test compounds (**4as** and **4bn**).

Fig 6. Inhibitory effect of **4as** and **4bn** on aortic ring contraction induced by extracellular Ca^{2+} influxes at different cumulative concentration (10^{-1}M , 10^{-2}M , 10^{-3}M , 10^{-5}M and 10^{-6}M).

Fig 7. Structures and IC_{50} values of compounds **4as** and **4bn** which are showing dual activity as ACE inhibitors and CCBs.

Fig 8. a) Best predicted binding mode of **4as** at tACE binding site. b) Best predicted binding mode of lisinopril at tACE binding site. c) Best predicted binding mode of **4bn** at tACE binding site.

Scheme 1. Schematic representation of condensation of an Aldehyde, β -Naphthol and a 2-Aminobenzothiazole derivative producing 2-(diarylalkyl)aminobenzothiazole.

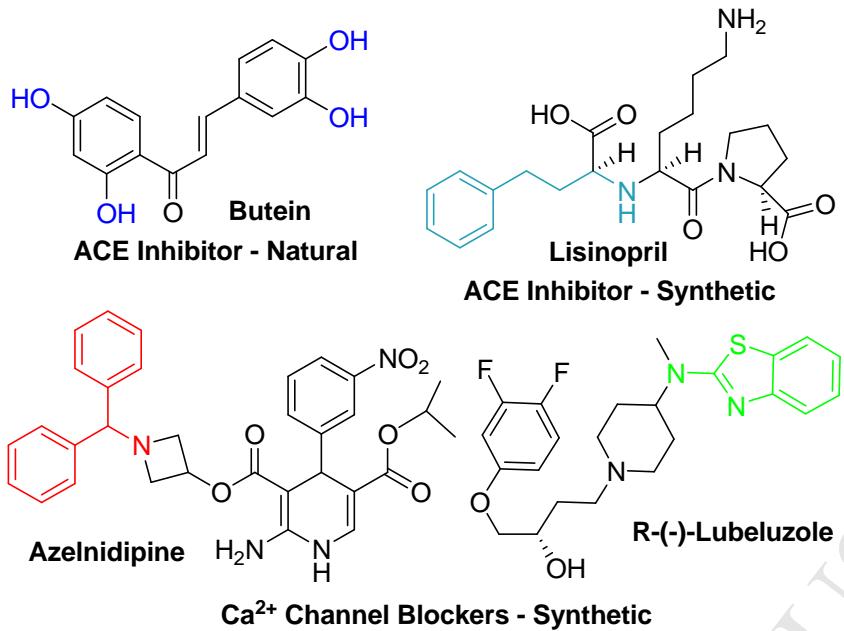


Fig 1: Structures of ACE Inhibitors and Ca²⁺ Channel blockers

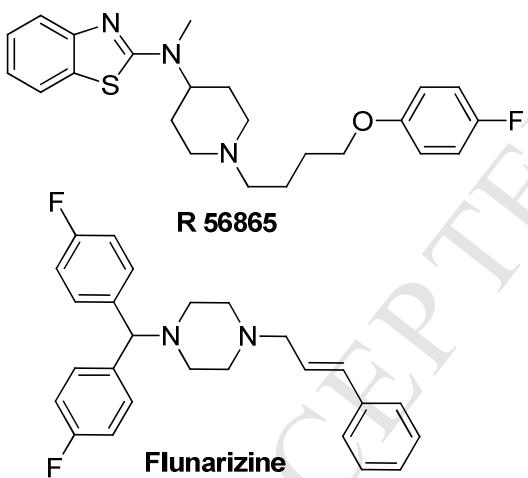


Fig 2. Structures of R 56865 and Flunarizine

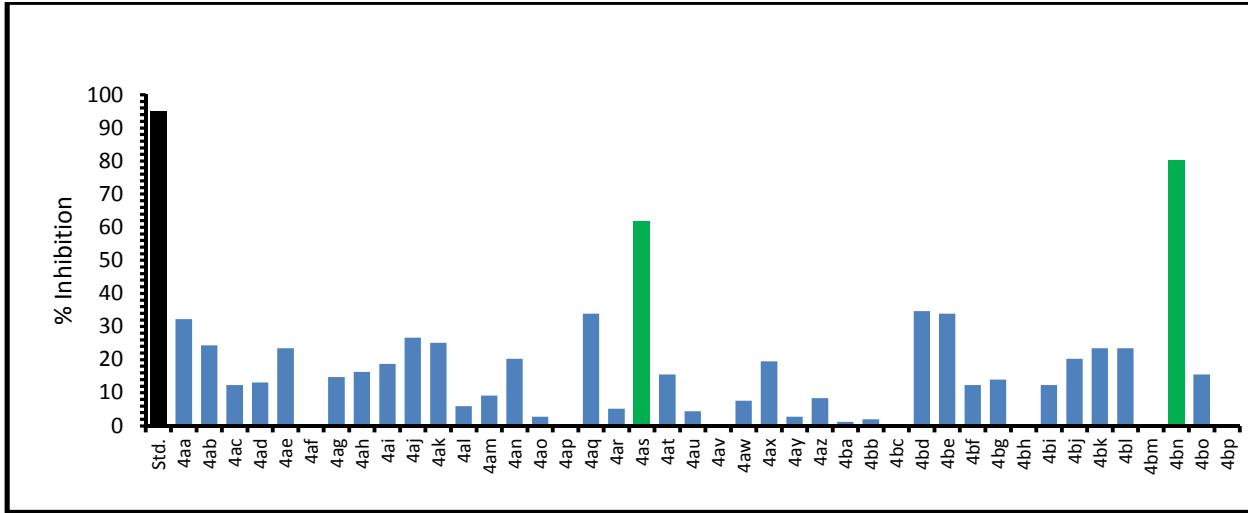


Fig 3. *In vitro* Angiotensin Converting Enzyme (ACE) inhibition of new Diarylalkylamine analogues **4aa–4bp** and standard drug, Lisinopril.

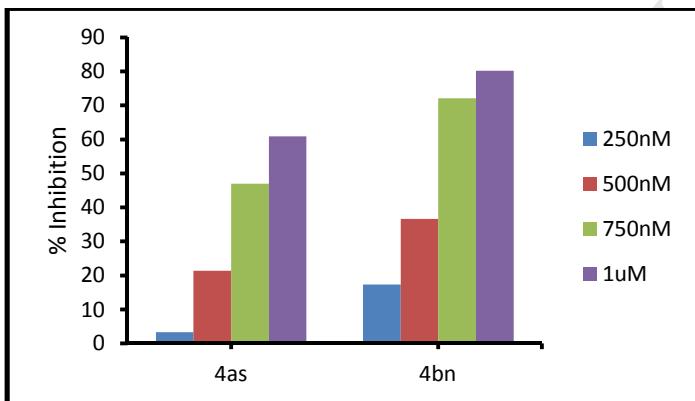


Fig 4. Dose Response Curves of new Diarylalkylamine derivatives **4as** and **4bn** for ACE inhibition.

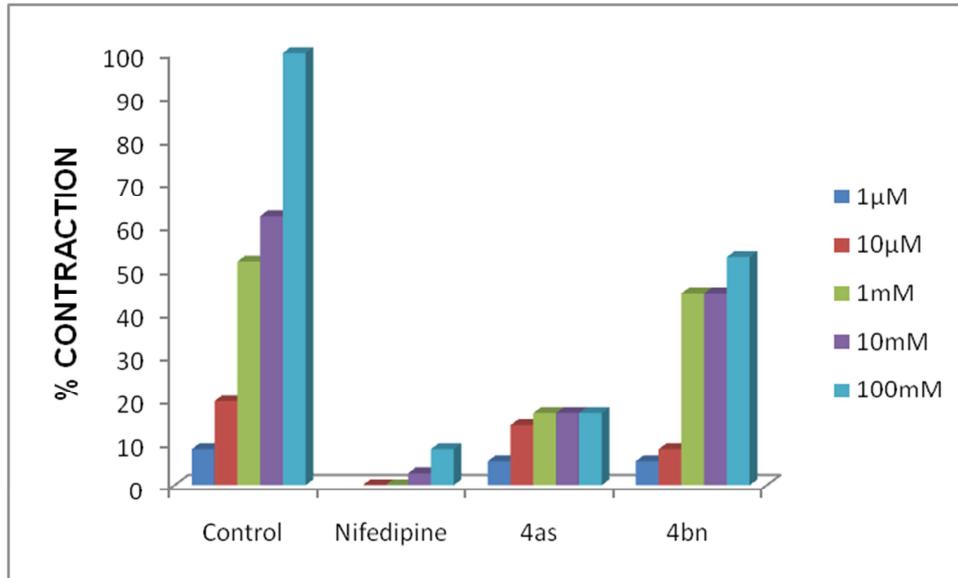


Fig 5. Dose-response curve of calcium-induced aortic ring contraction in presence and absence of standard (Nifedipine) and test compounds (**4as** and **4bn**).

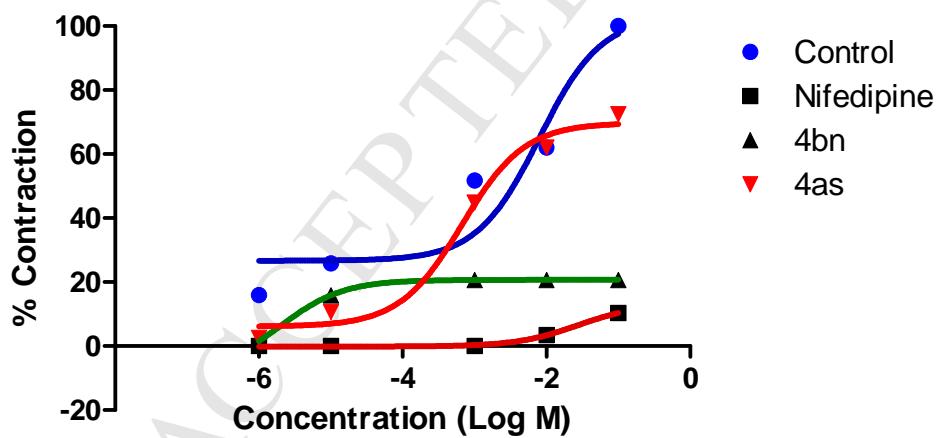


Fig 6. Inhibitory effect of **4as** and **4bn** on aortic ring contraction induced by extracellular Ca^{2+} influxes at different cumulative concentration (10^{-1}M , 10^{-2}M , 10^{-3}M , 10^{-5}M and 10^{-6}M).

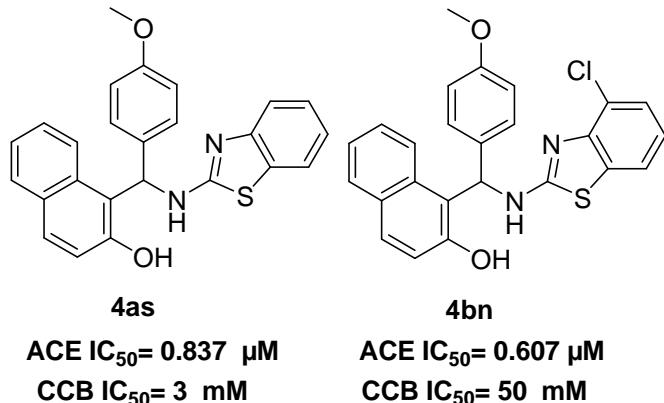
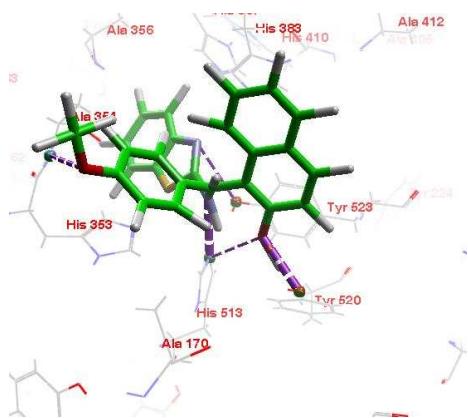
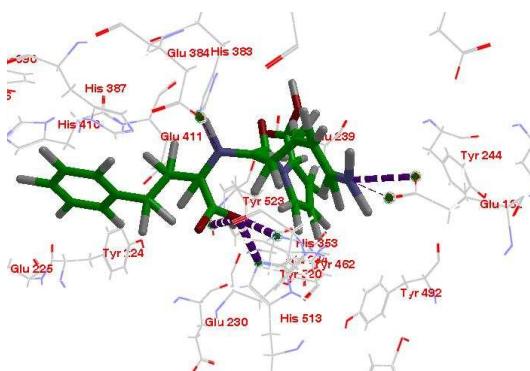


Fig 7. Structures and IC₅₀ values of compounds **4as** and **4bn** which are showing dual activity as ACE inhibitors and CCBs.

[a]



[b]



[c]

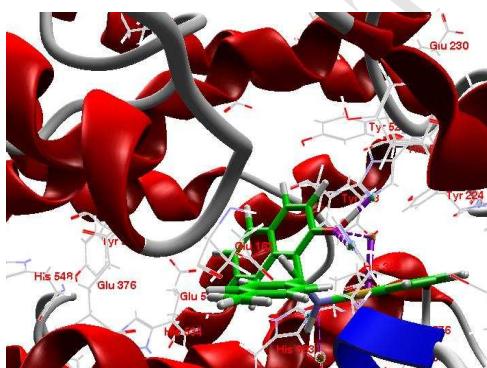
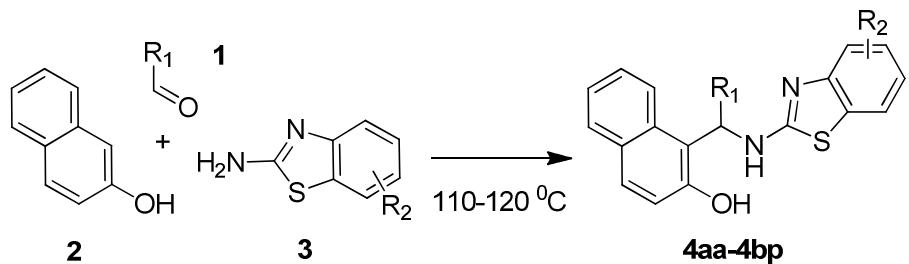


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Scheme 1. Schematic representation of condensation of an Aldehyde, β -Naphthol and a 2-Aminobenzothiazole derivative producing 2-(diarylalkyl)aminobenzothiazole.

HIGHLIGHTS

- Novel hybrids were designed based on Calcium Channel Blockers and ACE inhibitors.
- A green protocol was developed for their synthesis.
- Two lead molecules **4as** and **4bn** were identified as dual inhibitors.
- These new hybrids may be useful in treating resistant hypertension.

Supporting Information**Design and Green synthesis of 2-(diarylalkyl)aminobenzothiazole derivatives and their dual activities as Angiotensin Converting Enzyme Inhibitors and Calcium Channel Blockers.**

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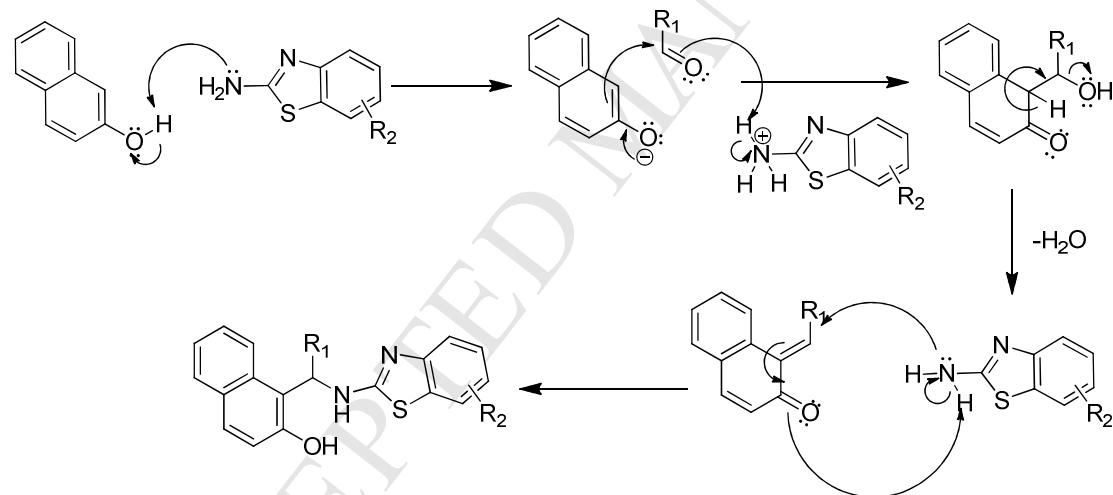
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S1. General procedure for the synthesis of 2-(diarylalkyl)aminobenzothiazole derivatives (4aa-4bp).

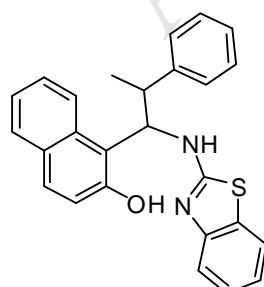
To a 10 mL RB flask aldehyde (1.0 mmol), 2-aminobenzothiazole (1.0 mmol) and β -naphthol (1.0 mmol) were added, mixed thoroughly and heated in preheated oil bath at 110-120°C for appropriate time (40 – 55 min). After completion of reaction as indicated by TLC the reaction mixture was allowed to cool. The so formed solid is powdered and washed with methanol or ethanol (3 X 8 mL in case of halogenated compounds except fluorinated, 3 X 4 mL in case of fluoro and methoxy derivatives) to obtain the corresponding pure 2-(diarylalkyl)aminobenzothiazole derivative. It is noteworthy to handle fluoro and methoxy derivatives carefully which otherwise may easily washed off in methanol/ethanol.

S2. Plausible mechanistic pathway for the formation of 2-(diarylalkyl)aminobenzothiazoles through Ortho Quinone Methide (OQM) intermediate.



S3. ¹H NMR and ¹³C NMR Spectral data for compounds 4aa-4bp.

4aa. 1-(1-(benzo[d]thiazol-2-ylamino)-2-phenylpropyl)naphthalen-2-ol. Starting materials used 2-phenylpropanal (1 mmol, 134.2 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). The reaction forms two enantiomeric pairs as expected. One of them being major, only that was obtained after several successful washings with methanol while the minor enantiomeric pair washed off with methanol. White solid; Mol. Wt. = 410.5, Yield = 353 mg. Percentage of yield = 86 % mp = 197-199 °C; ¹H NMR (300



MHz, DMSO-d₆): δ 10.12-9.95 (brs, 1H), 8.41-8.08 (brs, 1H), 7.59 (d, 2H, *J* = 7.4 Hz), 7.51 (d, 1H, *J* = 8.7 Hz), 7.40-7.28 (m, 2H), 7.21-6.82 (m, 11H), 6.07-5.98 (brs, 1H), 4.00-3.88 (brs, 1H), 1.51 (d, 1H, *J* = 6.8 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.6, 153.2, 152.2, 143.9, 130.2, 128.6, 128.1, 127.9, 127.5, 127.2, 125.8, 125.6, 125.4, 121.9, 120.7, 120.6, 118.2, 117.7, 57.6, 42.7, 19.8; IR (KBr): ν_{max} 3450, 3371, 3062, 2964, 1602, 1551, 1448, 1331, 1266, 741, 701 cm⁻¹; ESI-MS: *m/z*: 411(M+H); HRMS calcd. for C₂₆H₂₃ON₂S: 411.15256, found: 411.15381.

4ab. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(2,4-dichlorophenyl)methyl)naphthalen-2-ol.*

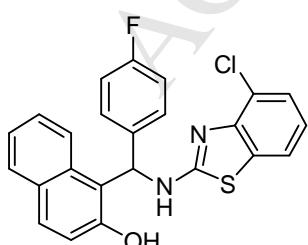
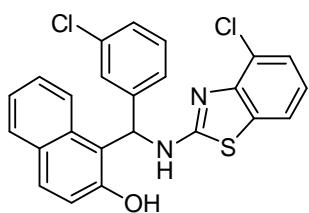
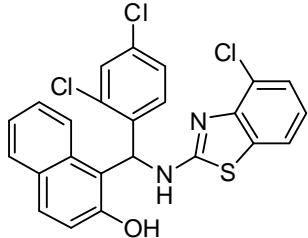
Starting materials used 2,4-dichlorobenzaldehyde (1 mmol, 175.0 mg), β-naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). Pink solid; Mol. Wt. = 485.8, Yield = 446 mg. Percentage of yield = 92 %. mp = 212-214 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.04 (s, 1H), 9.22 (d, 1H, *J* = 7.2 Hz), 8.17 (d, 1H, *J* = 8.7 Hz), 7.79 (t, 2H, *J* = 7.2 Hz), 7.67-7.58 (m, 2H), 7.53 (d, 1H, 2.1 Hz), 7.48-7.38 (m, 2H), 7.32-7.11 (m, 4H), 6.98 (t, 1H, 7.9 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.0, 153.9, 148.8, 138.2, 133.3, 132.6, 132.1, 132.0, 131.2, 130.1, 128.7, 128.6, 128.3, 126.6, 125.6, 122.9, 122.5, 121.7, 121.7, 119.9, 118.4, 115.8, 52.5; IR (KBr): ν_{max} 3336, 2932, 1585, 1537, 1434, 1326, 1252, 882, 812, 735 cm⁻¹; ESI-MS: *m/z*: 485(M+H); HRMS calcd. for C₂₄H₁₆ON₂Cl₃S: 485.00434, found: 485.00457.

4ac. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(3-chlorophenyl)methyl)naphthalen-2-ol.*

Starting materials used 3-chlorobenzaldehyde (1 mmol, 140.6 mg), β-naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 451.4, Yield = 401 mg. Percentage of yield = 89 %. mp = 221-223 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.33-10.13 (brs, 1H), 8.17 (d, 1H, *J* = 6.4 Hz), 8.02 (d, 1H, *J* = 6.8 Hz), 7.86-7.78 (m, 2H), 7.64 (d, 1H, *J* = 9.1 Hz), 7.46-7.16 (m, 9H), 6.99 (t, 1H, *J* = 7.9 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 153.4, 148.6, 144.7, 132.9, 132.1, 130.1, 129.9, 128.6, 128.5, 126.6, 126.4, 125.7, 125.6, 124.8, 123.3, 122.6, 121.7, 119.9, 118.4, 118.0, 52.9; IR (KBr): ν_{max} 3376, 3064, 1590, 1546, 1413, 1307, 1264, 817, 770 cm⁻¹; ESI-MS: *m/z*: 451(M+H); HRMS calcd. for C₂₄H₁₇ON₂Cl₂S: 451.04332, found: 451.04224.

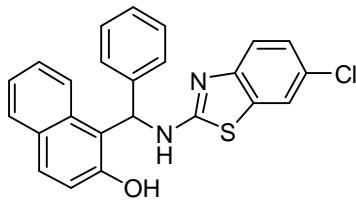
4ad. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-fluorophenyl)methyl)naphthalen-2-ol.*

Starting materials used 4-fluorobenzaldehyde (1 mmol, 124.1 mg), β-naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 434.9, Yield = 382 mg. Percentage of yield = 88 %. mp = 205-207 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.25-10.11 (brs, 1H), 9.16 (d, 1H, *J* = 7.6 Hz), 7.97 (d, 1H, 7.6 Hz), 7.84-7.76 (m, 2H), 7.63 (d, 1H, *J* = 7.7 Hz), 7.43-7.21 (m, 7H), 7.11 (t, 2H, *J* = 8.7 Hz), 6.99 (t, 1H, *J* = 7.9 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 162.4, 159.2,



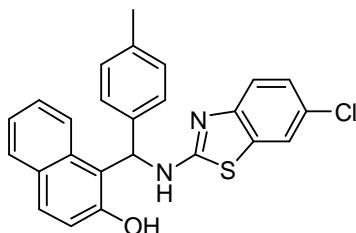
153.3, 148.6, 137.8, 132.0, 129.7, 128.5, 128.0, 127.9, 126.3, 125.5, 123.4, 122.4, 121.6, 119.7, 118.3, 118.1, 114.9, 114.6, 52.9; IR (KBr): ν_{max} 3337, 2938, 1591, 1542, 1507, 1436, 1271, 1157, 812, 764 cm^{-1} ; ESI-MS: m/z : 435(M+H); HRMS calcd. for C₂₄H₁₇ON₂ClFS: 435.07287, found: 435.07248.

4ae. *1-((6-chlorobenzo[d]thiazol-2-ylamino)(phenyl)methyl)naphthalen-2-ol.* Starting



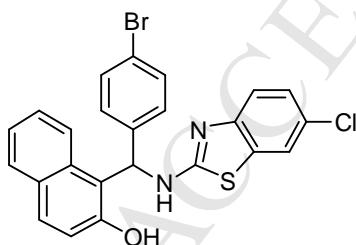
materials used benzaldehyde (1 mmol, 106.1 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-6-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 416.9, Yield = 375 mg. Percentage of yield = 90 %. mp = 202-204 $^{\circ}\text{C}$; ¹H NMR (300 MHz, DMSO-d₆): δ 10.16 (s, 1H), 8.92 (d, 1H, J = 7.6 Hz), 7.90-7.75 (m, 4H), 7.39-7.12 (m, 11H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 153.1, 151.0, 142.2, 132.4, 132.0, 129.5, 128.5, 128.0, 126.2, 125.9, 125.5, 124.6, 123.6, 122.3, 120.4, 118.9, 118.4, 118.3, 53.1; IR (KBr): ν_{max} 3375, 3059, 3021, 1598, 1546, 1515, 1447, 1260, 806, 738 cm^{-1} ; ESI-MS: m/z : 417(M+H); HRMS calcd. for C₂₄H₁₈ON₂ClS: 417.08229, found: 417.08234.

4af. *1-((6-chlorobenzo[d]thiazol-2-ylamino)(p-tolyl)methyl)naphthalen-2-ol.* Starting materials used

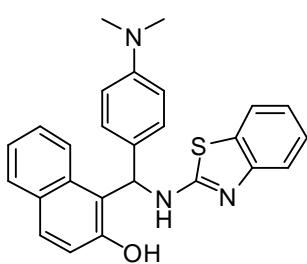


4-methylbenzaldehyde (1 mmol, 120.1 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-6-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 430.9, Yield = 379 mg. Percentage of yield = 88 %. mp = 191-193 $^{\circ}\text{C}$; ¹H NMR (300 MHz, DMSO-d₆): 10.18-10.10 (brs, 1H), 8.91 (d, 1H, J = 7.6 Hz), 7.96-7.71 (m, 4H), 7.39-7.02 (m, 10H), 2.22 (s, 1H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 153.1, 151.0, 139.1, 137.1, 135.2, 132.4, 132.1, 129.4, 128.6, 128.5, 126.1, 125.9, 125.5, 124.6, 123.7, 122.3, 120.4, 118.9, 118.5, 118.3, 53.1, 20.5; IR (KBr): ν_{max} 3364, 3054, 2915, 1599, 1547, 1513, 1447, 1260, 806, 765 cm^{-1} ; ESI-MS: m/z : 431 (M+H); HRMS calcd. for C₂₅H₂₀ON₂ClS: 431.09794, found: 431.09840.

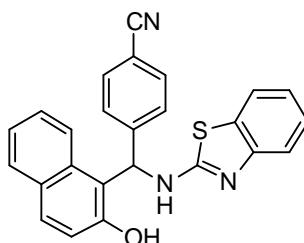
4ag. *1-((6-chlorobenzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl)naphthalen-2-ol.*



Starting materials used 4-bromobenzaldehyde (1 mmol, 185.0 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-6-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 495.8, Yield = 451 mg. Percentage of yield = 91 %. mp = 217-219 $^{\circ}\text{C}$; ¹H NMR (300 MHz, DMSO-d₆): δ 10.25-10.16 (brs, 1H), 8.92 (d, 1H, J = 7.3 Hz), 7.87-7.76 (m, 4H), 7.46 (d, 2H, J = 8.5 Hz), 7.41-7.33 (m, 2H), 7.30-7.14 (m, 6H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 153.2, 150.9, 141.9, 132.5, 132.0, 130.9, 129.8, 128.6, 128.3, 126.4, 125.5, 124.9, 123.4, 122.5, 120.5, 119.2, 119.0, 118.3, 118.0, 52.8; IR (KBr): ν_{max} 3560, 3366, 3054, 1598, 1545, 1447, 1258, 1070, 804, 767, 566 cm^{-1} ; ESI-MS: m/z : 495(M+H); HRMS calcd. for C₂₄H₁₇N₂OSClBr: 494.9933, found: 494.9928.

4ah. *1-((benzo[d]thiazol-2-ylamino)(4-(dimethylamino)phenyl)naphthalen-2-ol.*

Starting materials used 4-(dimethylamino)benzaldehyde (1 mmol, 149.2 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 425.5, Yield = 396 mg. Percentage of yield = 93 %. mp = 156-158 $^{\circ}$ C; 1 H NMR (1 H NMR (300 MHz, DMSO-d₆): δ 10.22-10.04 (brs, 1H), 8.71 (d, 1H, J = 7.4 Hz), 7.93 (d, 1H, J = 7.5 Hz), 7.77 (t, 2H, J = 9.1 Hz), 7.64 (d, 1H, J = 7.4 Hz), 7.39-7.29 (m, 2H), 7.28-7.11 (m, 4H), 7.07 (d, 2H, J = 8.5 Hz), 6.99 (t, 1H, J = 7.9 Hz), 6.63 (d, 2H, J = 8.9 Hz), 2.80 (s, 6H); 13 C NMR (75 MHz, DMSO-d₆): δ 166.2, 153.0, 152.1, 149.0, 132.1, 130.5, 129.5, 129.1, 128.6, 128.4, 126.8, 125.9, 125.3, 122.2, 120.7, 118.9, 118.4, 117.9, 112.2, 53.1, 40.1; IR (KBr): ν_{max} 3315, 2849, 1602, 1538, 1446, 1318, 1264, 1165, 810, 745 cm⁻¹; ESI-MS: *m/z*: 426 (M+H); HRMS Calc. for C₂₆H₂₄N₃OS: 426.1640, found: 426.1639.

4ai. *4-((benzo[d]thiazol-2-ylamino)(2-hydroxynaphthalen-1-yl)methyl)benzonitrile.*

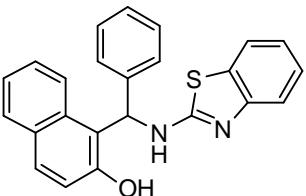
Starting materials used 4-cyanobenzaldehyde (1 mmol, 131.1 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 407.5, Yield = 375 mg. Percentage of yield = 92 %. mp = 213-215 $^{\circ}$ C; 1 H NMR (300 MHz, DMSO-d₆): δ 10.31-10.20 (brs, 1H), 8.85 (d, 1H, J = 7.0 Hz), 7.89-7.78 (m, 3H), 7.76-7.65 (m, 3H), 7.46-7.33 (m, 5H), 7.31-7.17 (m, 3H), 7.03 (t, 1H, J = 7.4 Hz). 13 C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.2, 151.9, 148.8, 132.0, 130.8, 130.0, 128.6, 128.5, 127.0, 126.5, 125.4, 123.2, 122.5, 121.2, 120.9, 118.8, 118.3, 117.8, 108.9, 53.0; IR (KBr): ν_{max} 3379, 3056, 2226, 1573, 1541, 1437, 1329, 1270, 1026, 751 cm⁻¹; ESI-MS: *m/z*: 408 (M+H); HRMS Calc. for C₂₅H₁₈N₃OS: 408.1170, found: 408.1163.

4aj. *1-((benzo[d]thiazol-2-ylamino)(2-bromo-5-fluorophenyl)methyl)naphthalen-2-ol.*

Starting materials used 2-bromo-5-fluorobenzaldehyde (1 mmol, 203.0 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). white solid; Mol. Wt. = 479.4, Yield = 441 mg. Percentage of yield = 92 %. mp = 198-200 $^{\circ}$ C; 1 H NMR (300 MHz, DMSO-d₆): δ 9.92 (brs, 1H), 8.90 (d, 1H, J = 7.4 Hz), 8.05 (d, 1H, J = 8.7 Hz), 7.80 (t, 2H, J = 9.3 Hz), 7.66 (d, 1H, J = 7.7 Hz), 7.61-7.54 (m, 1H), 7.39-7.34 (m, 3H), 7.28 (t, 1H, J = 7.4 Hz), 7.20 (t, 1H, J = 7.6 Hz), 7.14-6.97 (m, 4H). 13 C NMR (75 MHz, DMSO-d₆): δ 165.0, 162.6, 159.4, 153.7, 152.0, 144.2, 144.1, 134.1, 134.0, 132.8, 130.6, 129.9, 128.5, 128.1, 126.5, 125.3, 122.4, 122.3, 121.0, 120.8, 118.5, 118.2, 116.9, 116.7, 116.6, 115.6, 115.3, 54.7; IR (KBr): ν_{max} 3383, 1598, 1543, 1512, 1453, 1431, 1265, 812, 752 cm⁻¹; ESI-MS: *m/z*: 479 (M+H); HRMS calcd. for C₂₄H₁₇BrFN₂OS: 479.0204, found: 479.0190.

4ak. *1-((benzo[d]thiazol-2-ylamino)(phenyl)methyl) naphthalen-2-ol.* Starting materials used benzaldehyde (1 mmol, 106.1 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole

(1 mmol, 150.2 mg). White solid; Mol. Wt. = 382.5, Yield = 359 mg. Percentage of yield = 94 %. mp = 200-202 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.17 (brs, 1H), 8.78 (d, 1H, *J* = 7.6 Hz), 7.94-7.74 (m, 3H), 7.66 (d, 1H, *J* = 7.6 Hz), 7.40-7.13 (m, 10H), 7.0 (t, 1H, *J* = 7.4 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.3, 153.2, 152.1, 142.5, 132.1, 130.8, 129.6, 128.6, 128.6, 128.1, 126.2, 126.0, 125.4, 123.8, 122.4, 121.0, 120.9, 118.7, 118.4, 118.1, 53.1; IR (KBr): ν_{max} 3376, 3060, 1598, 1547, 1514, 1444, 1331, 1263, 744 cm⁻¹; ESI-MS: *m/z*: 383 (M+H); HRMS calcd. for C₂₄H₁₉N₂OS: 383.1218, found: 383.1206.

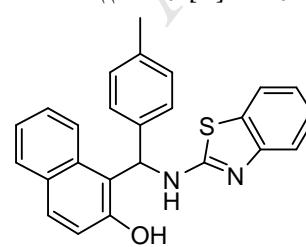


1-((benzo[d]thiazol-2-ylamino)(2,4-dichlorophenyl)methyl) naphthalen-2-ol. Starting materials used 2,4-dichlorobenzaldehyde (1 mmol, 175.0 mg), β-naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 451.4, Yield = 415 mg. Percentage of yield = 92 %. mp = 190-192 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.02-9.91 (brs, 1H), 8.88 (d, 1H, *J* = 7.0 Hz), 8.02 (d, 1H, *J* = 8.5 Hz), 7.79 (t, 2H, *J* = 9.3 Hz), 7.70-7.63 (m, 2H), 7.49 (d, 1H, *J* = 2.1 Hz), 7.46-7.35 (m, 3H), 7.27 (t, 1H, *J* = 7.6 Hz), 7.23-7.12 (m, 3H), 7.01 (t, 1H, *J* = 7.6 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 165.2, 153.8, 152.1, 139.0, 133.0, 132.7, 131.8, 131.1, 130.7, 130.0, 128.7, 128.3, 126.6, 126.5, 125.5, 122.6, 122.4, 121.1, 120.9, 118.5, 118.3, 115.9, 52.3; IR (KBr): ν_{max} 3378, 3068, 1592, 1542, 1438, 1371, 1331, 1268, 751 cm⁻¹; ESI-MS: *m/z*: 451 (M+H); HRMS calcd. for C₂₄H₁₇N₂OSCl₂: 451.0438, found: 451.0451.

4al. *1-((benzo[d]thiazol-2-ylamino)(2,4-dichlorophenyl)methyl) naphthalen-2-ol.* Starting materials used 2,4-dichlorobenzaldehyde (1 mmol, 175.0 mg), β-naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 451.4, Yield = 415 mg. Percentage of yield = 92 %. mp = 190-192 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.02-9.91 (brs, 1H), 8.88 (d, 1H, *J* = 7.0 Hz), 8.02 (d, 1H, *J* = 8.5 Hz), 7.79 (t, 2H, *J* = 9.3 Hz), 7.70-7.63 (m, 2H), 7.49 (d, 1H, *J* = 2.1 Hz), 7.46-7.35 (m, 3H), 7.27 (t, 1H, *J* = 7.6 Hz), 7.23-7.12 (m, 3H), 7.01 (t, 1H, *J* = 7.6 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 165.2, 153.8, 152.1, 139.0, 133.0, 132.7, 131.8, 131.1, 130.7, 130.0, 128.7, 128.3, 126.6, 126.5, 125.5, 122.6, 122.4, 121.1, 120.9, 118.5, 118.3, 115.9, 52.3; IR (KBr): ν_{max} 3378, 3068, 1592, 1542, 1438, 1371, 1331, 1268, 751 cm⁻¹; ESI-MS: *m/z*: 451 (M+H); HRMS calcd. for C₂₄H₁₇N₂OSCl₂: 451.0438, found: 451.0451.

4am. *1-((benzo[d]thiazol-2-ylamino)(3-chlorophenyl)methyl) naphthalen-2-ol.* Starting materials used 3-chlorobenzaldehyde (1 mmol, 140.6 mg), β-naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 416.9, Yield = 388 mg. Percentage of yield = 93 %. mp = 193-194 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.23 (s, 1H), 8.81 (d, 1H, *J* = 7.6 Hz), 7.94-7.77 (m, 3H), 7.67 (d, 1H, *J* = 7.6 Hz), 7.45-7.15 (m, 10H), 7.02 (t, 1H, *J* = 7.4 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.1, 151.9, 145.3, 132.8, 131.9, 130.8, 130.0, 129.8, 128.6, 128.5, 126.5, 126.1, 125.6, 125.4, 124.8, 123.3, 122.5, 121.1, 120.9, 118.3, 118.2, 118.0, 52.6; IR (KBr): ν_{max} 3360, 3062, 1596, 1573, 1548, 1515, 1444, 1332, 1268, 749 cm⁻¹; ESI-MS: *m/z*: 417 (M+H); HRMS calcd. for C₂₄H₁₈N₂OSCl: 417.0828, found: 417.0809.

4an. *1-((benzo[d]thiazol-2-ylamino)(*p*-tolyl)methyl) naphthalen-2-ol.* Starting materials used 4-methylbenzaldehyde (1 mmol, 120.1 mg), β-naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 396.5, Yield = 361 mg. Percentage of yield = 91 %. mp = 180-182 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.18-10.11 (brs, 1H), 8.78 (d, 1H, *J* = 7.6 Hz), 7.91-7.73 (m, 3H), 7.66 (d, 1H, *J* = 7.4 Hz), 7.39-6.96 (m, 11H), 2.22 (s, 3H); ¹³C NMR



(75 MHz, DMSO-d₆): δ 166.2, 153.1, 152.1, 139.4, 135.1, 132.1, 130.7, 129.4, 128.6, 128.5, 126.1, 125.9, 125.4, 123.9, 122.4, 120.9, 120.8, 118.7, 118.3, 118.0, 52.9, 20.5; IR (KBr): ν_{max} 3307, 1535, 1441, 1317, 1261, 744 cm⁻¹; ESI-MS: *m/z*: 397 (M+H); HRMS calcd. for C₂₅H₂₁N₂OS: 397.1374, found: 397.1373.

4ao. *1-((benzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl) naphthalen-2-ol.*

Starting materials used 4-bromobenzaldehyde (1 mmol, 185.0 mg), β-naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 461.4, Yield = 434 mg. Percentage of yield = 94 %. mp = 202-204 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.24-10.16 (brs, 1H), 8.82 (d, 1H, *J* = 7.0 Hz), 7.89-7.75 (m, 3H), 7.67 (d, 1H, *J* = 7.6 Hz), 7.49-7.36 (m, 4H), 7.30-7.12 (m, 6H), 7.02 (t, 1H, *J* = 7.6 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.1, 151.9, 142.1, 131.9, 130.9, 130.8, 129.7, 128.5, 128.2, 126.3, 125.3, 123.5, 122.4, 121.0, 120.8, 119.1, 118.3, 118.1, 52.6; IR (KBr): ν_{max} 3373, 1627, 1541, 1442, 1332, 1267, 1206, 1070, 749, 571 cm⁻¹; ESI-MS: *m/z*: 461 (M+H); HRMS calcd. for C₂₄H₁₈N₂OSBr: 461.0323, found: 461.0320.

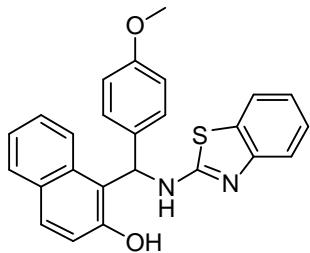
4ap. *1-((benzo[d]thiazol-2-ylamino)(4-fluorophenyl)methyl) naphthalen-2-ol.*

Starting materials used 4-fluorobenzaldehyde (1 mmol, 124.1 mg), β-naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 400.5, Yield = 380 mg. Percentage of yield = 95 %. mp = 178-180 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 1.22-10.13 (brs, 1H), 8.81 (d, 1H, *j* = 7.4 Hz), 7.93-7.76 (m, 3H), 7.67 (d, 1H, *j* = 7.7 Hz), 7.42-7.32 (m, 2H), 7.31-7.15 (m, 6H), 7.93-6.95 (m, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.1, 162.2, 159.0, 153.1, 151.9, 138.4, 131.9, 130.7, 129.5, 128.5, 127.9, 127.8, 126.2, 125.3, 123.5, 122.3, 120.9, 120.8, 118.3, 118.0, 114.8, 114.5, 52.6; IR (KBr): ν_{max} 3308, 1537, 1436, 1319, 1286, 1060, 810, 746 cm⁻¹; ESI-MS: *m/z*: 401 (M+H).

4aq. *1-((benzo[d]thiazol-2-ylamino)(3-phenoxyphenyl)methyl) naphthalen-2-ol.*

Starting materials used 3-phenoxybenzaldehyde (1 mmol, 198.2 mg), β-naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 474.6, Yield = 436 mg. Percentage of yield = 92 %. mp = 171-173 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.16 (s, 1H), 8.78 (d, 1H, *j* = 7.4 Hz), 7.89-7.73 (m, 3H), 7.66 (d, 1H, *j* = 7.0 Hz), 7.43-7.16 (m, 9H), 7.06-6.93 (m, 4H), 6.87 (d, 2H, *j* = 7.6 Hz), 6.79 (dd, 1H, *j*₁ = 7.6 Hz, *j*₂ = 2.1 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.1, 156.5, 156.0, 153.1, 152.0, 145.0, 132.0, 130.7, 129.7, 128.6, 128.5, 126.2, 125.4, 123.0, 122.4, 121.3, 121.0, 120.8, 118.3, 118.1, 117.9, 116.6, 116.3, 52.7; IR (KBr): ν_{max} 3314, 3052, 1541, 1511, 1451, 1267, 814, 749 cm⁻¹; ESI-MS: *m/z*: 475 (M+H); HRMS calcd. for C₃₀H₂₃N₂O₂S: 475.1480, found: 475.1471.

4ar. *1-((benzo[d]thiazol-2-ylamino)(naphthalen-2-yl)methyl) naphthalen-2-ol.* Starting materials used 2-naphthaldehyde (1 mmol, 156.2 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 432.5, Yield = 389 mg. Percentage of yield = 90 %. mp = 190-192 $^{\circ}$ C; 1 H NMR (300 MHz, DMSO-d₆): δ 10.21-10.16 (brs, 1H), 8.91 (d, 1H, *j* = 7.4 Hz), 7.95 (d, 1H, *j* = 7.9 Hz), 7.89-7.74 (m, 6H), 7.68 (d, 1H, *j* = 7.9 Hz), 7.53-7.40 (m, 3H), 7.38-7.15 (m, 6H), 7.02 (m, 1H); 13 C NMR (75 MHz, DMSO-d₆): δ 166.2, 153.1, 152.0, 140.1, 132.6, 132.1, 131.7, 130.7, 129.6, 128.5, 128.4, 127.5, 127.3, 126.1, 126.0, 125.4, 125.3, 124.9, 123.8, 123.6, 122.3, 120.9, 120.8, 118.5, 118.3, 118.0, 53.3; IR (KBr): ν_{max} 3313, 3052, 1541, 1442, 1264, 814, 749 cm⁻¹; ESI-MS: *m/z*: 433 (M+H); HRMS Calc. for C₂₈H₂₁N₂OS: 433.1374, found: 433.1387.



4as. *1-((benzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl) naphthalen-2-ol.* Starting materials used 4-methoxybenzaldehyde (1 mmol, 136.1mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 412.5, Yield = 375 mg. Percentage of yield = 91 %. mp = 190-192 $^{\circ}$ C; 1 H NMR (300 MHz, DMSO-d₆): δ 10.19-10.11 (brs, 1H), 8.79 (d, 1H, *j* = 7.4 Hz), 7.94-7.84 (brs, 1H), 7.79 (t, 2H, *j* = 8.7 Hz), 7.66 (d, 1H, *j* = 7.6 Hz), 7.42-7.12 (m, 9H), 7.0 (t, 1H, *j* = 7.9 Hz), 6.83 (d, 1H, *j* = 8.7 Hz), 3.68 (s, 3H); 13 C NMR (75 MHz, DMSO-d₆): δ 166.2, 157.7, 153.0, 152.1, 134.1, 132.1, 130.6, 129.4, 128.6, 128.5, 127.2, 126.1, 125.3, 123.8, 122.3, 120.9, 120.8, 118.7, 118.4, 118.0, 113.5, 54.9, 52.8; IR (KBr): ν_{max} 3313, 3052, 1541, 1442, 1264, 814, 749 cm⁻¹; ESI-MS: *m/z*: 413 (M+H); HRMS calcd. for C₂₅H₂₁N₂O₂S: 413.1323, found: 413.1319.

4at. *1-((benzo[d]thiazol-2-ylamino)(3,4,5-trimethoxyphenyl)methyl) naphthalen-2-ol.* Starting materials used 3,4,5-trimethoxybenzaldehyde (1 mmol, 196.2mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 472.6, Yield = 415 mg. Percentage of yield = 88 %. mp = 170-172 $^{\circ}$ C; 1 H NMR (300 MHz, DMSO-d₆): δ 10.42-10.30 (brs, 1H), 8.63-8.37 (brs, 1H), 7.98-7.87 (brs, 1H), 7.75-7.63 (m, 2H), 7.52-7.31 (m, 3H), 7.28-7.15 (m, 3H), 7.11-6.94 (m, 2H), 6.58 (s, 2H), 3.70 (s, 3H), 3.66 (s, 6H); 13 C NMR (75 MHz, DMSO-d₆): δ 166.3, 153.3, 152.4, 137.0, 136.1, 132.0, 129.9, 129.1, 128.6, 128.1, 125.8, 125.1, 123.0, 122.2, 120.8, 120.1, 119.1, 118.8, 117.9, 103.6, 95.6, 59.8, 55.4, 54.3; IR (KBr): ν_{max} 3317, 2923, 2833, 1590, 1538, 1441, 1315, 1248, 1171, 1030, 813, 745 cm⁻¹; ESI-MS: *m/z*: 473 (M+H).

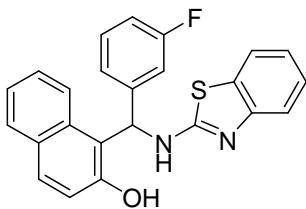
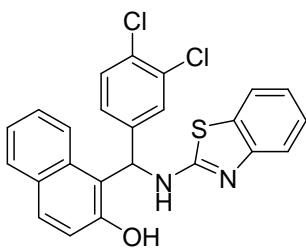
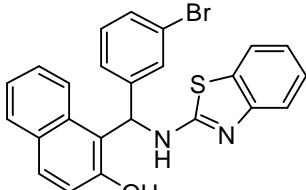
4au. *1-((benzo[d]thiazol-2-ylamino)(3-bromophenyl)naphthalen-2-ol.* Starting materials used 3-bromobenzaldehyde (1 mmol, 185.0mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 461.4, Yield = 433 mg. Percentage of yield = 94 %. mp = 201-203 $^{\circ}$ C; 1 H NMR (300 MHz, DMSO-d₆): δ 10.27-

10.20 (brs, 1H), 8.84 (d, 1H, j = 7.4 Hz), 7.92-7.77 (m, 3H), 7.68 (d, 1H, j = 7.6 Hz), 7.45-7.15 (m, 11H), 7.02 (t, 1H, j = 7.6 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.0, 153.1, 151.9, 145.5, 131.9, 130.7, 130.2, 129.8, 129.0, 128.5, 126.4, 125.4, 125.1, 123.3, 122.4, 121.4, 121.0, 120.8, 118.3, 118.1, 118.0, 52.6; IR (KBr): ν_{max} 3377, 3058, 1543, 1511, 1435, 1327, 1268, 747 cm⁻¹; MS-ESI: m/z : 461 (M+H); HRMS calcd. for C₂₄H₁₈BrN₂OS: 461.0323, found: 461.0312.

4av. *1-((benzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)naphthalen-2-ol.* Starting materials used 3,4-dichlorobenzaldehyde (1 mmol, 175.0 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 451.4, Yield = 424 mg. Percentage of yield = 94 %. mp = 212-214 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.28-10.24 (brs, 1H), 8.87 (d, 1H, j = 7.2 Hz), 7.93-7.79 (m, 3H), 7.69 (d, 1H, j = 7.6 Hz), 7.53 (d, 1H, j = 8.3 Hz), 7.47-7.37 (m, 3H), 7.32-7.15 (m, 5H), 7.03 (t, 1H, j = 7.7 Hz). ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.0, 153.2, 151.8, 144.0, 131.9, 130.8, 130.6, 130.2, 130.0, 128.6, 128.4, 127.7, 126.6, 126.5, 125.4, 123.1, 122.5, 121.1, 120.9, 118.3, 118.2, 117.6, 52.3; IR (KBr): ν_{max} 3379, 1577, 1540, 11461, 1328, 1268, 1205, 1028, 816, 747 cm⁻¹; ESI-MS: m/z : 451 (M+H); HRMS calcd. for C₂₄H₁₇Cl₂N₂OS: 451.0438, found: 451.0439.

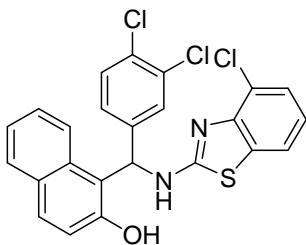
4aw. *1-((benzo[d]thiazol-2-ylamino)(3-fluorophenyl)naphthalen-2-ol.* Starting materials used 3-fluorobenzaldehyde (1 mmol, 124.1 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White Solid; Mol. Wt. = 400.5, Yield = 372 mg. Percentage of yield = 93 %. ^1H NMR (300 MHz, DMSO-d₆): δ 10.26-10.19 (brs, 1H), 8.84 (d, 1H, j = 7.4 Hz), 7.90-7.78 (m, 3H), 7.68 (d, 1H, j = 7.7 Hz), 7.43-7.17 (m, 7H), 7.07-6.96 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.1, 163.7, 160.5, 153.1, 151.9, 145.8, 145.8, 131.9, 130.7, 130.0, 129.9, 129.7, 128.5, 126.3, 125.4, 123.4, 122.4, 122.1, 121.0, 120.8, 118.3, 118.1, 113.0, 112.8, 112.5, 52.7; IR (KBr): ν_{max} 3387, 1587, 1536, 1482, 1439, 1329, 1244, 1053, 749 cm⁻¹; ESI-MS: m/z : 401 (M+H); HRMS calcd. for C₂₄H₁₈FN₂OS: 401.1123, found: 401.1118.

4ax. *1-((benzo[d]thiazol-2-ylamino)(4-isopropylphenyl)naphthalen-2-ol.* Starting materials used 4-isopropylbenzaldehyde (1 mmol, 148.2 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 424.6, Yield = 382 mg. Percentage of yield = 90 %. mp = 191-193 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.17-10.09 (brs, 1H), 8.78 (d, 1H, j = 7.6 Hz), 7.98-7.87 (brs, 1H), 7.79 (t, 2H, j = 7.8 Hz), 7.66 (d, 1H, j = 7.6 Hz), 7.4-7.32 (m, 2H), 7.30-7.10 (m, 8H), 7.00 (t, 1H, j = 8.1 Hz), 2.89-2.74 (m, 1H), 1.14 (dd, 6H, j_1 = 7.0 Hz, j_2 = 1.5 Hz). ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.2, 153.0, 152.1, 146.1, 139.6, 132.1, 130.6, 129.3, 128.5, 128.4, 126.1, 126.0, 125.9, 125.3, 123.7,



122.3, 120.8, 120.8, 118.7, 118.4, 118.0, 53.0, 32.9, 23.8, 23.7; IR (KBr): ν_{max} 3314, 3055, 2957, 1540, 1450, 1268, 1060, 746 cm^{-1} ; ESI-MS: m/z : 425 (M+H); HRMS calcd. for C₂₇H₂₅N₂OS: 425.1687, found: 425.1704.

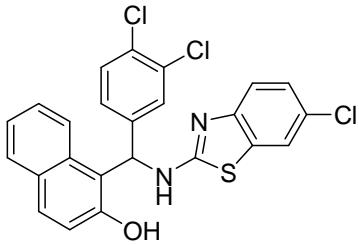
4ay. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol.*



Starting materials used 3,4-dichlorobenzaldehyde (1 mmol, 175.0 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 485.8, Yield = 456 mg. Percentage of yield = 94 %. mp = 208-210 $^{\circ}\text{C}$; ¹H NMR (300 MHz, DMSO-d₆): δ 10.24 (s, 1H), 9.20 (d, 1H, j = 7.7 Hz), 8.07-7.97 (brs, 1H), 7.86-7.79 (m, 2H), 7.66 (d, 1H, j = 7.9 Hz), 7.55 (d, 1H, j = 8.3 Hz), 7.48-7.40 (m, 2H), 7.36-

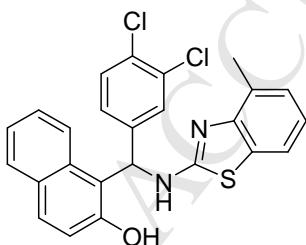
7.14 (m, 5H), 7.0 (t, 1H, 7.9 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.6, 153.4, 148.5, 143.4, 132.1, 132.0, 130.9, 130.3, 130.0, 128.8, 128.6, 128.4, 127.8, 126.7, 126.5, 125.6, 123.1, 122.6, 121.7, 119.8, 118.3, 117.6, 52.5; IR (KBr): ν_{max} 3352, 2935, 1590, 1544, 1254, 817, 738 cm^{-1} ; ESI-MS: m/z : 485 (M+H); HRMS calcd. for C₂₄H₁₆N₂OSCl₃: 485.0048, found: 485.0032.

4az. *1-((6-chlorobenzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol.*

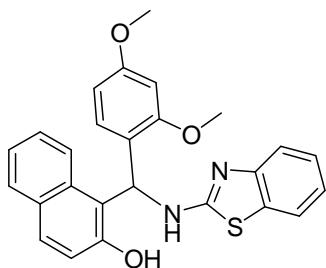


Starting materials used 3,4-dichlorobenzaldehyde (1 mmol, 175.0 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-6-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 485.8, Yield = 456 mg. Percentage of yield = 94 %. mp = 215-217 $^{\circ}\text{C}$; ¹H NMR (300 MHz, DMSO-d₆): δ 10.28-10.23 (brs, 1H), 8.98 (d, 1H, j = 7.4 Hz), 7.9307.77 (m, 4H), 7.53 (d, 1H, j = 8.5 Hz), 7.47-7.14 (m, 8H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.6, 153.2, 150.8, 143.8, 132.6, 131.9, 130.7, 130.3, 130.0, 128.7, 128.6, 128.4, 127.7, 126.6, 126.5, 125.5, 124.9, 123.0, 122.6, 120.6, 119.1, 118.3, 117.5, 52.4; IR (KBr): ν_{max} 3360, 2865, 1598, 1545, 1446, 1254, 813, 740 cm^{-1} ; ESI-MS: m/z : 485 (M+H); HRMS calcd. for C₂₄H₁₆N₂OSCl₃: 485.0048, found: 485.0032.

4ba. *1-((4-methylbenzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol.*



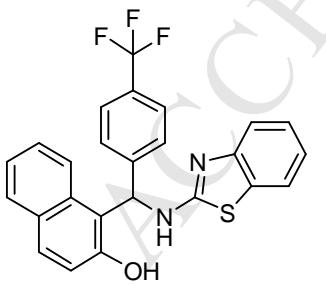
Starting materials used 3,4-dichlorobenzaldehyde (1 mmol, 175.0 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-4-methylbenzothiazole (1 mmol, 164.2 mg). White solid; Mol. Wt. = 465.4, Yield = 437 mg. Percentage of yield = 94 %. mp = 222-224 $^{\circ}\text{C}$; ¹H NMR (300 MHz, DMSO-d₆): δ 10.26-10.16 (brs, 1H), 8.98 (d, 1H, j = 7.9 Hz), 8.17-8.02 (brs, 1H), 7.86-7.77 (m, 2H), 7.58-7.40 (m, 4H), 7.03 (d, 1H, j = 7.2 Hz), 6.91 (t, 1H, j = 7.7 Hz), 2.41 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 165.1, 153.3, 150.6, 143.7, 132.1, 130.6, 130.2, 130.1, 129.8, 128.7, 128.5, 128.3, 127.9, 127.3, 126.6, 126.5, 126.1, 123.1, 122.5, 121.0, 118.3, 118.3, 118.1, 52.4, 17.9; IR (KBr): ν_{max} 3340, 2923, 1585, 1545, 1516, 1252, 816, 739 cm^{-1} ; ESI-MS: m/z : 465 (M+H); HRMS calcd. for C₂₅H₁₉Cl₂N₂OS: 465.0595, found: 465.0575.

4bb. *1-((benzo[d]thiazol-2-ylamino)(2,4-dimethoxyphenyl)methyl)naphthalen-2-ol.*

Starting materials used 2,4-dimethoxybenzaldehyde (1 mmol, 166.2 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 442.5, Yield = 398 mg. Percentage of yield = 90 %. mp = 174-176 $^{\circ}$ C; 1 H NMR (300 MHz, DMSO-d₆): δ 10.22-10.08 (brs, 1H), 8.81 (d, 1H, *j* = 7.2 Hz), 7.95 (d, 1H, *j* = 8.5 Hz), 7.78 (t, 2H, *j* = 8.9 Hz), 7.65 (d, 1H, *j* = 7.7 Hz), 7.41-7.31 (m, 2H), 7.29-7.15 (m, 4H), 7.04-6.91 (m, 4H), 6.84 (d, 1H, *j* = 8.5 Hz), 6.73 (d, 1H, 8.7 Hz), 3.68 (s, 3H), 3.60 (s, 3H); 13 C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.0, 152.0, 148.4, 147.4, 134.5, 132.1, 130.5, 129.3, 128.5, 128.4, 126.0, 125.3, 123.8, 122.3, 120.8, 118.6, 118.4, 117.9, 111.6, 110.6, 55.4, 53.1; IR (KBr): ν_{max} 3368, 2930, 2834, 1573, 1542, 1509, 1271, 752 cm⁻¹; ESI-MS: *m/z*: 443 (M+H); HRMS calcd. for C₂₆H₂₃O₃N₂S: 443.14239, found: 443.14463.

4bc. *1-((benzo[d]thiazol-2-ylamino)(2-chlorophenyl)methyl)naphthalen-2-ol.* Starting materials used 2-chlorobenzaldehyde (1 mmol, 140.6 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 416.9, Yield = 383 mg. Percentage of yield = 92 %. mp = 197-199 $^{\circ}$ C; 1 H NMR (300 MHz, DMSO-d₆): δ 9.99-9.93 (brs, 1H), 8.86 (d, 1H, *j* = 7.4 Hz), 8.05 (d, 1H, *j* = 8.7 Hz), 7.78 (t, 2H, *j* = 9.3 Hz), 7.64 (d, 2H, *j* = 7.7 Hz), 7.47-7.12 (m, 10H), 6.99 (t, 1H, *j* = 7.9 Hz); 13 C NMR (125 MHz, DMSO-d₆): δ 165.3, 153.7, 152.2, 139.4, 132.7, 132.4, 130.6, 129.7, 129.4, 128.6, 128.3, 126.4, 126.3, 125.4, 122.9, 122.3, 120.9, 120.8, 118.5, 118.2, 116.5, 52.7; IR (KBr): ν_{max} 3456, 3381, 3066, 1571, 1528, 1438, 1319, 1270, 1040, 750 cm⁻¹; ESI-MS: *m/z*: 417(M+H); HRMS calcd. for C₂₄H₁₈ON₂ClS: 417.08229, found: 417.08426.
4bd. *1-((benzo[d]thiazol-2-ylamino)(4-(trifluoromethyl)phenyl)methyl)naphthalen-2-ol.*

Starting materials used 4-(trifluoromethyl)benzaldehyde (1 mmol, 174.1 mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 450.5, Yield = 396 mg. Percentage of yield = 88 %. mp = 203-205 $^{\circ}$ C; 1 H NMR (300 MHz, DMSO-d₆): δ 10.20-10.13 (brs, 1H), 8.90 (d, 1H, *j* = 7.6 Hz), 7.91-7.72 (m, 4H), 7.44-7.16 (m, 7H), 7.15-7.02 (m, 4H); 13 C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.2, 151.9, 147.7, 132.0, 130.8, 129.9, 128.6, 128.5, 127.4, 127.0, 126.7, 126.6, 126.5, 126.1, 125.4, 124.99, 124.96, 123.3, 122.5, 121.1, 120.9, 118.3, 118.2, 118.0, 52.9; IR (KBr): ν_{max} 3380, 3059, 2867, 2599, 1574, 1541, 1326, 1267, 1158, 1125, 1068, 749 cm⁻¹; ESI-MS: *m/z*: 451 (M+H); HRMS calcd. for C₂₅H₁₈ON₂F₃S: 451.10865, found: 451.10976.



4be. *1-((benzo[d]thiazol-2-ylamino)(3,4-dimethoxyphenyl)methyl)naphthalen-2-ol.* Starting materials used 3,4-dimethoxybenzaldehyde (1 mmol, 166.2mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 442.5, Yield = 398 mg. Percentage of yield = 90 %. mp = 176-178 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.21-10.11 (brs, 1H), 8.78 (d, 1H, j = 7.6 Hz), 7.95 (d, 1H, j = 7.4 Hz), 7.77 (t, 2H, j = 8.9 Hz), 7.64 (d, 1H, j = 7.4 Hz), 7.41-7.31 (m, 2H), 7.28-7.14 (m, 4H), 7.03-6.92 (m, 2H), 6.83 (d, 1H, j = 8.5 Hz), 6.73 (d, 1H, j = 7.6 Hz), 3.68 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.3, 153.1, 152.1, 148.5, 147.5, 134.5, 132.2, 130.6, 129.4, 128.6, 128.5, 126.1, 125.5, 123.8, 122.4, 121.0, 120.9, 118.7, 118.5, 118.0, 111.7, 110.6, 55.5, 53.3; IR (KBr): ν_{max} 3368, 2930, 2834, 1573, 1543, 1510, 1330, 1271, 752 cm⁻¹; ESI-MS: *m/z*: 443(M+H); HRMS calcd. for C₂₆H₂₃O₃N₂S: 443.14239, found: 443.14472.

4bf. *1-((benzo[d]thiazol-2-ylamino)(3,4-difluorophenyl)methyl)naphthalen-2-ol.* Starting materials used 3,4-difluorobenzaldehyde (1 mmol, 142.1mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 418.5, Yield = 364 mg. Percentage of yield = 87 %. mp = 177-179 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.38-10.13 (brs, 1H), 8.84 (d, 1H, j = 7.0 Hz), 7.94-7.78 (m, 3H), 6.8 (d, 1H, j = 7.6 Hz), 7.46-7.16 (m, 8H), 7.02 (t, 2H, j = 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.0, 153.1, 151.8, 140.4, 131.9, 130.7, 129.8, 128.5, 128.5, 126.4, 125.3, 123.2, 122.6, 122.4, 121.0, 120.8, 118.3, 118.2, 117.8, 117.1, 116.9, 114.9, 114.7, 52.4; IR (KBr): ν_{max} 3390, 3052, 1598, 1541, 1511, 1431, 1274, 754, 467 cm⁻¹; ESI-MS: *m/z*: 419(M+H); HRMS calcd. for C₂₄H₁₇ON₂F₂S: 419.10242, found: 419.10338.

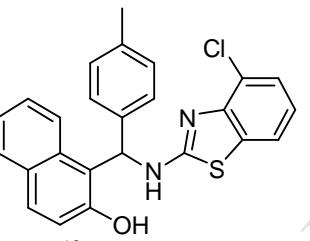
4bg. *1-((benzo[d]thiazol-2-ylamino)(4-chlorophenyl)methyl)naphthalen-2-ol.* Starting materials used 4-chlorobenzaldehyde (1 mmol, 140.6mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 416.9, Yield = 379 mg. Percentage of yield = 91 %. mp = 214-216 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.22-10.18 (brs, 1H), 8.82 (d, 1H, j = 7.4 Hz), 7.87-7.66 (m, 3H), 7.68 (d, 1H, j = 7.4 Hz), 7.42-7.16 (m, 10H), 7.02 (t, 3H, j = 7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.1, 153.1, 152.0, 141.6, 132.0, 130.8, 130.6, 129.7, 128.5, 128.0, 127.9, 126.3, 125.4, 123.5, 122.4, 121.0, 120.8, 118.3, 118.2, 52.6; IR (KBr): ν_{max} 3375, 3056, 1574, 1541, 1514, 1436, 1330, 1269, 749 cm⁻¹; ESI-MS: *m/z*: 417(M+H); HRMS calcd. for C₂₄H₁₈ON₂ClS: 417.08229, found: 417.08458.

4bh. *1-((benzo[d]thiazol-2-ylamino)(2,3-dichlorophenyl)methyl)naphthalen-2-ol.* Starting materials used 2,3-dichlorobenzaldehyde (1 mmol, 175.0mg), β -naphthol (1 mmol, 144.2 mg) and 2-aminobenzothiazole (1 mmol, 150.2 mg). White solid; Mol. Wt. = 451.4, Yield = 401 mg. Percentage of yield = 89 %. mp = 200-202 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.03-9.92 (brs, 1H), 8.93 (d, 1H, j = 6.6 Hz), 8.01 (d, 1H, j = 8.5 Hz), 7.80 (t, 2H, 8.9 Hz), 7.66 (d,

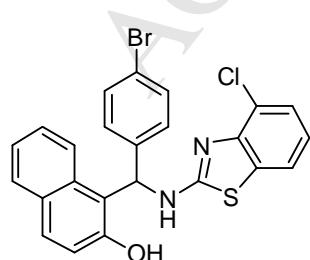
2H, $j = 7.7$ Hz), 7.53 (d, 1H, $j = 7.7$ Hz), 7.46-7.11 (m, 7H), 7.01 (t, 1H, $j = 7.4$ Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 165.1, 153.8, 152.1, 142.6, 132.7, 131.7, 130.7, 130.0, 128.6, 128.6, 128.3, 127.2, 126.5, 125.4, 122.6, 122.4, 121.0, 120.8, 118.5, 118.3, 115.8, 53.3; IR (KBr): ν_{max} 3350, 3014, 1597, 1538, 1512, 1448, 1270, 1154, 810, 748, 586, 482 cm⁻¹; ESI-MS: m/z : 451(M+H); HRMS calcd. for C₂₄H₁₇Cl₂N₂OS: 451.04332, found: 451.04577.

4bi. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(phenyl)methyl)naphthalen-2-ol.* Starting materials used benzaldehyde (1 mmol, 106.1 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 416.9, Yield = 375 mg. Percentage of yield = 90 %. mp = 214-216 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.19-10.11 (brs, 1H), 9.18 (d, 1H, $j = 7.4$ Hz), 8.02-7.89 (brs, 1H), 7.84-7.76 (m, 2H), 7.64 (d, 1H, $j = 7.7$ Hz), 7.42-7.15 (m, 10H), 6.98 (t, 1H, $j = 7.7$ Hz); ^{13}C NMR (75 MHz, DMSO-d₆): δ 166.9, 153.3, 148.7, 141.8, 132.1, 132.0, 129.6, 128.5, 128.4, 128.1, 126.3, 126.2, 126.0, 125.5, 123.7, 122.4, 121.5, 119.7, 118.3, 53.3; IR (KBr): ν_{max} 3350, 3314, 3059, 2937, 1587, 1537, 1416, 1325, 1253, 815, 747, 697 cm⁻¹; ESI-MS: m/z : 417(M+H); HRMS calcd. for C₂₄H₁₈N₂ClOS: 417.08229, found: 417.08168.

4bj. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(p-tolyl)methyl)naphthalen-2-ol.* Starting materials used 4-methylbenzaldehyde (1 mmol, 120.1 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 430.9, Yield = 392 mg. Percentage of yield = 91 %. mp = 219-221 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.18-10.07 (brs, 1H), 9.23-9.11 (brs, 1H), 8.04-7.88 (brs, 1H), 7.83-7.74 (m, 2H), 7.63 (d, 1H, $j = 7.0$ Hz), 7.41-7.31 (m, H), 7.30-7.20 (m, 4H), 7.17-7.05 (m, 4H), 6.98 (t, 1H, $j = 7.9$ Hz), 2.24 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d₆): δ 167.1, 153.4, 148.8, 138.7, 135.5, 132.2, 132.0, 129.6, 128.8, 128.6, 128.5, 126.3, 126.0, 125.7, 123.8, 122.5, 121.6, 121.6, 119.8, 118.5, 118.4, 53.4, 20.6; IR (KBr): ν_{max} 3310, 2927, 1586, 1533, 1417, 1320, 1271, 1051, 883, 812, 679 cm⁻¹; ESI-MS: m/z : 431(M+H); HRMS calcd. for C₂₅H₂₀ClN₂OS: 431.09794, found: 431.09731.

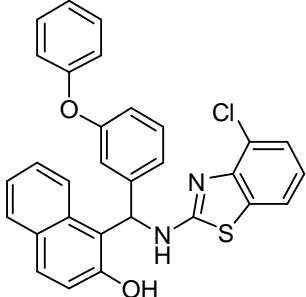


4bk. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl)naphthalen-2-ol.* Starting materials used 4-bromobenzaldehyde (1 mmol, 185.0 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 495.8, Yield = 446 mg. Percentage of yield = 90 %. mp = 223-225 °C; ^1H NMR (300 MHz, DMSO-d₆): δ 10.22-10.16 (brs, 1H), 9.18 (d, 1H, $J = 7.6$ Hz), 8.02-7.88 (brs, 1H), 7.84-7.77 (m, 2H), 7.65 (d, 1H, $J = 7.7$ Hz), 7.48 (d, 2H, $J = 8.5$ Hz), 7.39 (t, 1H, J



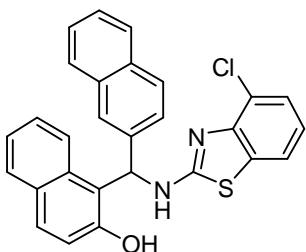
= 7.7 Hz), 7.32-7.15 (m, 6H), 6.99 (t, 1H, *J* = 7.9 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 153.3, 148.7, 141.5, 132.0, 130.9, 129.8, 128.5, 128.3, 126.4, 125.5, 123.5, 122.5, 121.6, 119.7, 119.3, 118.3, 117.9, 52.9; IR (KBr): ν_{max} 3343, 3297, 1711, 1586, 1528, 1416, 881, 814, 744, 498 cm⁻¹; ESI-MS: *m/z*: (M+H); HRMS calcd. for C₂₄H₁₇BrClN₂OS: 494.9933, found: 494.9948.

4bl. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(3-phenoxyphenyl)methyl)naphthalen-2-ol.*



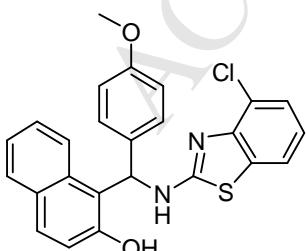
Starting materials used 3-phenoxybenzaldehyde (1 mmol, 198.2 mg), β-naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 509.0, Yield = 448 mg. Percentage of yield = 88 %. mp = 208-210 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.28-10.14 (brs, 1H), 9.23-9.12 (brs, 1H), 8.02-7.88 (brs, 1H), 7.84-7.78 (m, 2H), 7.64 (d, 1H, *J* = 7.2 Hz), 7.46-7.28 (m, 9H), 7.07-6.95 (m, 4H), 6.90 (d, 2H, *J* = 7.7 Hz), 6.82 (d, 1H, *J* = 7.7 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.8, 156.6, 156.1, 153.4, 148.7, 144.4, 132.1, 129.7, 128.5, 126.3, 125.5, 123.7, 123.0, 122.4, 121.7, 121.6, 121.4, 119.7, 118.3, 118.1, 117.9, 116.8, 116.5, 53.1; IR (KBr): ν_{max} 3332, 2938, 1588, 1545, 1485, 1249, 1165, 884, 744, 491 cm⁻¹; ESI-MS: *m/z*: 509(M+H); HRMS calcd. for C₃₀H₂₂ClN₂O₂S: 509.10850, found: 509.10754.

4bm. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(naphthalen-2-yl)methyl)naphthalen-2-ol.*



Starting materials used 2-naphthaldehyde (1 mmol, 156.2 mg), β-naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 467.0, Yield = 415 mg. Percentage of yield = 89 %. mp = 236-238 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.25-10.14 (brs, 1H), 9.36-9.27 (brs, 1H), 8.13-7.96 (brs, 1H), 7.88-7.76 (m, 6H), 7.66 (d, 1H, *J* = 7.4 Hz), 7.55-7.21 (m, 8H), 6.99 (t, 1H, *J* = 7.7 Hz); ¹³C NMR (75 MHz, DMSO-d₆): δ 167.0, 153.5, 148.8, 139.6, 132.7, 132.3, 132.1, 131.8, 129.7, 128.6, 128.5, 127.7, 127.6, 127.3, 126.3, 125.6, 125.5, 125.0, 124.0, 123.7, 122.4, 121.7, 121.6, 119.8, 118.5, 118.4, 53.7; IR (KBr): ν_{max} 3320, 3052, 2930, 1585, 1533, 1416, 1268, 816, 660, 478 cm⁻¹; ESI-MS: *m/z*: 467(M+H); HRMS calcd. for C₂₈H₁₉N₂ONaSCl: 489.0804, found: 489.0822.

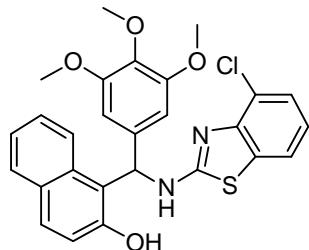
4bn. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl)naphthalen-2-ol.*



Starting materials used 4-methoxybenzaldehyde (1 mmol, 136.1 mg), β-naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 446.5, Yield = 401 mg. Percentage of yield = 90 %. mp = 211-213 °C; ¹H NMR (300 MHz, DMSO-d₆): δ 10.22-10.08 (brs, 1H), 9.24-9.10 (brs, 1H), 8.05-7.93 (brs, 1H), 7.79 (m, 2H), 7.63 (d, 1H, *J* = 7.742 Hz), 7.42-7.13 (m, 7H), 6.98 (t, 1H, *J* = 7.9 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 3.69 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 166.9, 157.8, 153.3, 148.8, 133.4, 132.1, 131.9, 129.5, 128.6, 128.4, 127.3, 126.1, 125.5, 123.8, 122.4, 121.5,

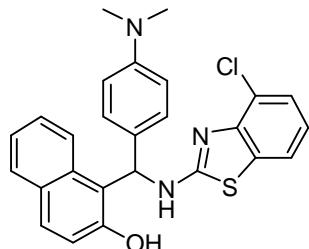
121.5, 119.7, 118.4, 113.5, 54.9, 53.2; IR (KBr): ν_{max} 3315, 3066, 2925, 2830, 1583, 1510, 1433, 1319, 1250, 1173, 1032, 821, 668, 588 cm^{-1} ; ESI-MS: m/z : 447(M+H); HRMS calcd. for $\text{C}_{25}\text{H}_{20}\text{O}_2\text{N}_2\text{ClS}$: 447.09285, found: 447.09345.

4bo. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(3,4,5-trimethoxyphenyl)methyl)naphthalene-2-ol.*



Starting materials used 3,4,5-trimethoxybenzaldehyde (1 mmol, 196.2 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). White solid; Mol. Wt. = 507.0, Yield = 446 mg. Percentage of yield = 88 %. mp = 215-217 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO- d_6): δ 10.27-10.10 (brs, 1H), 9.32-9.17 (brs, 1H), 8.18-8.04 (brs, 1H), 7.79 (t, 2H, J = 8.3 Hz), 7.63 (d, 1H, J = 7.9 Hz), 7.42 (t, 1H, J = 7.5 Hz), 7.31-7.13 (m, 4H), 6.97 (t, 1H, J = 7.7 Hz), 6.66 (s, 2H), 3.62 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 166.9, 153.4, 152.6, 148.7, 137.2, 136.3, 132.2, 131.9, 129.6, 128.5, 126.3, 125.6, 123.6, 122.4, 121.5, 121.5, 119.7, 118.4, 118.3, 104.1, 59.9, 55.8, 54.0; IR (KBr): ν_{max} 3366, 2932, 1593, 1542, 1509, 1414, 1328, 1131, 818 cm^{-1} ; ESI-MS: m/z : 507(M+H); HRMS calcd. for $\text{C}_{27}\text{H}_{24}\text{O}_4\text{N}_2\text{ClS}$: 507.11398, found: 507.11452.

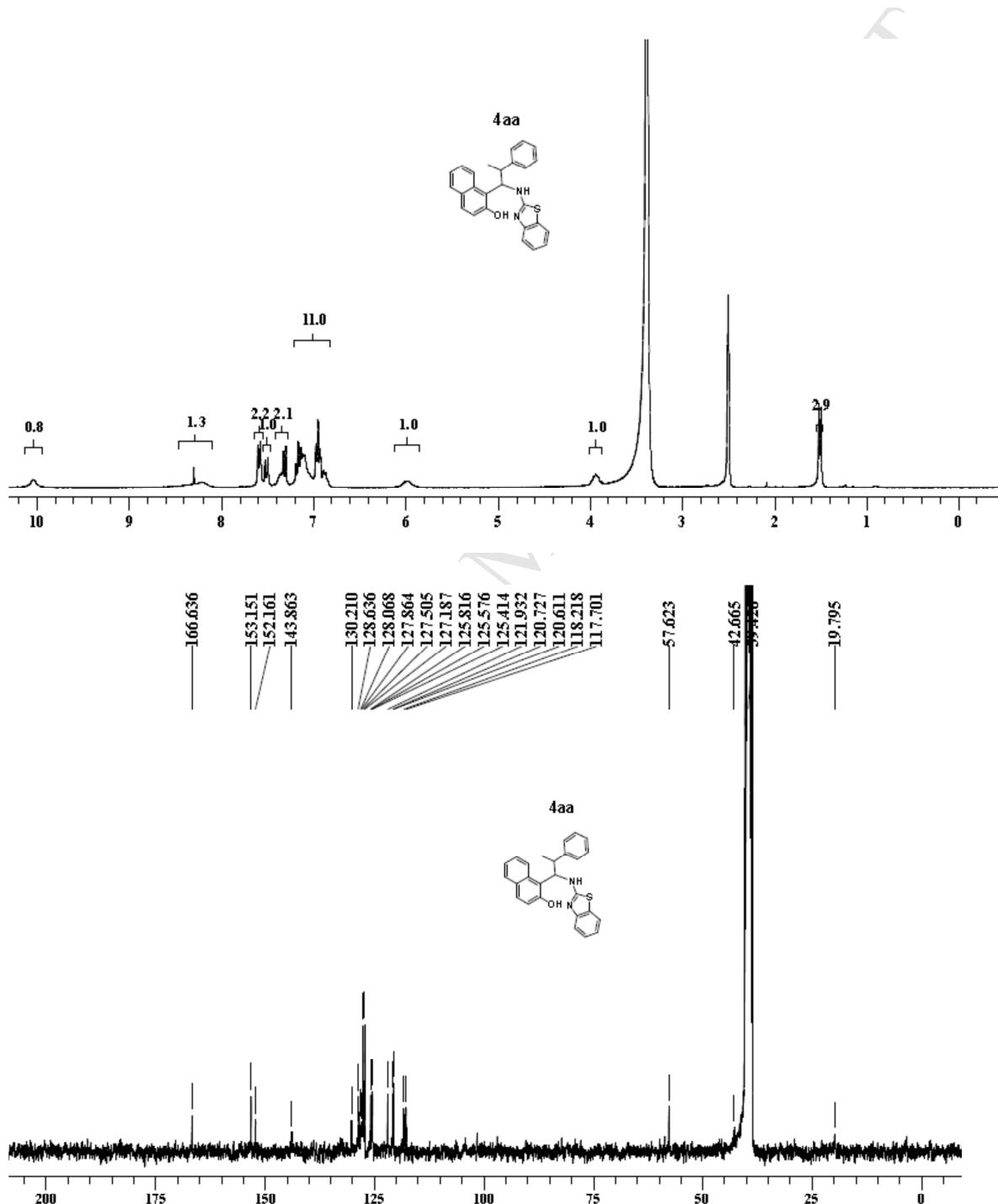
4bp. *1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-(dimethylamino)phenyl)methyl)naphthalen-2-ol.*



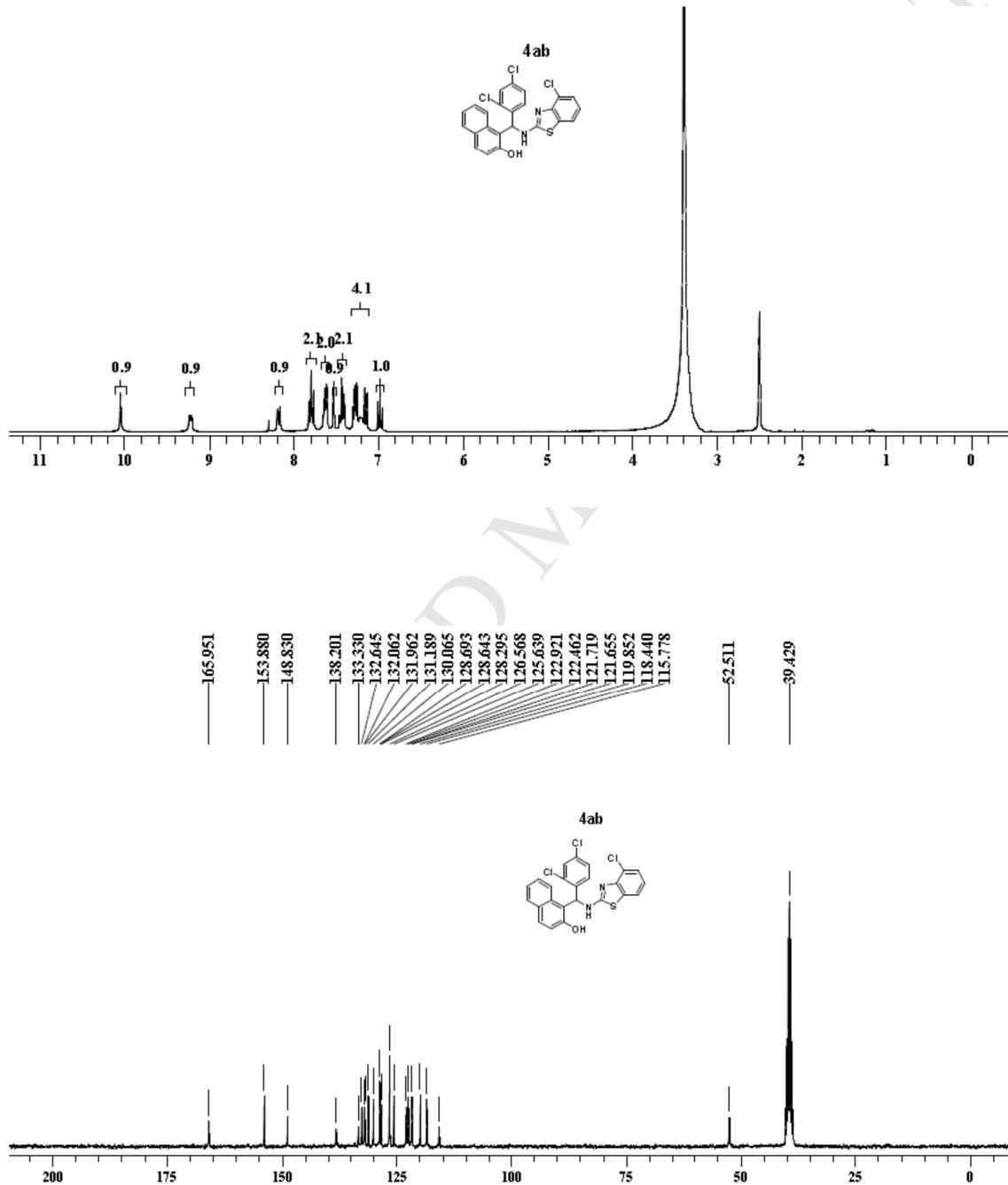
Starting materials used 4-(dimethylamino)benzaldehyde (1 mmol, 149.2 mg), β -naphthol (1 mmol, 144.2 mg) and 2-amino-4-chlorobenzothiazole (1 mmol, 184.6 mg). Pale yellow solid; Mol. Wt. = 460.0, Yield = 414 mg. Percentage of yield = 90 %. mp = 205-207 $^{\circ}\text{C}$; ^1H NMR (300 MHz, DMSO- d_6): δ 10.20-10.03 (brs, 1H), 9.23-9.07 (brs, 1H), 8.07-7.93 (brs, 1H), 7.77 (t, 2H, J = 8.9 Hz), 7.62 (d, 1H, J = 7.9 Hz), 7.35 (t, 1H, J = 7.9 Hz), 7.25 (t, 3H, J = 7.6 Hz), 7.18-7.03 (m, 3H), 6.96 (t, 1H, J = 7.7 Hz), 6.64 (d, 2H, J = 8.9 Hz), 2.82 (s, 6H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 167.0, 153.3, 149.1, 148.9, 132.2, 131.8, 129.3, 128.7, 128.6, 128.4, 126.9, 126.0, 125.5, 124.0, 122.3, 121.4, 121.4, 119.7, 118.6, 118.4, 112.2, 53.5, 40.1; IR (KBr): ν_{max} 3353, 3321, 2851, 1587, 1533, 1433, 1269, 811 cm^{-1} ; HRMS calcd. for $\text{C}_{26}\text{H}_{22}\text{N}_3\text{ONaSCl}$: 482.1069, found: 482.1089.

S4. ^1H NMR and ^{13}C NMR Spectrum for compounds 4aa-4bp.

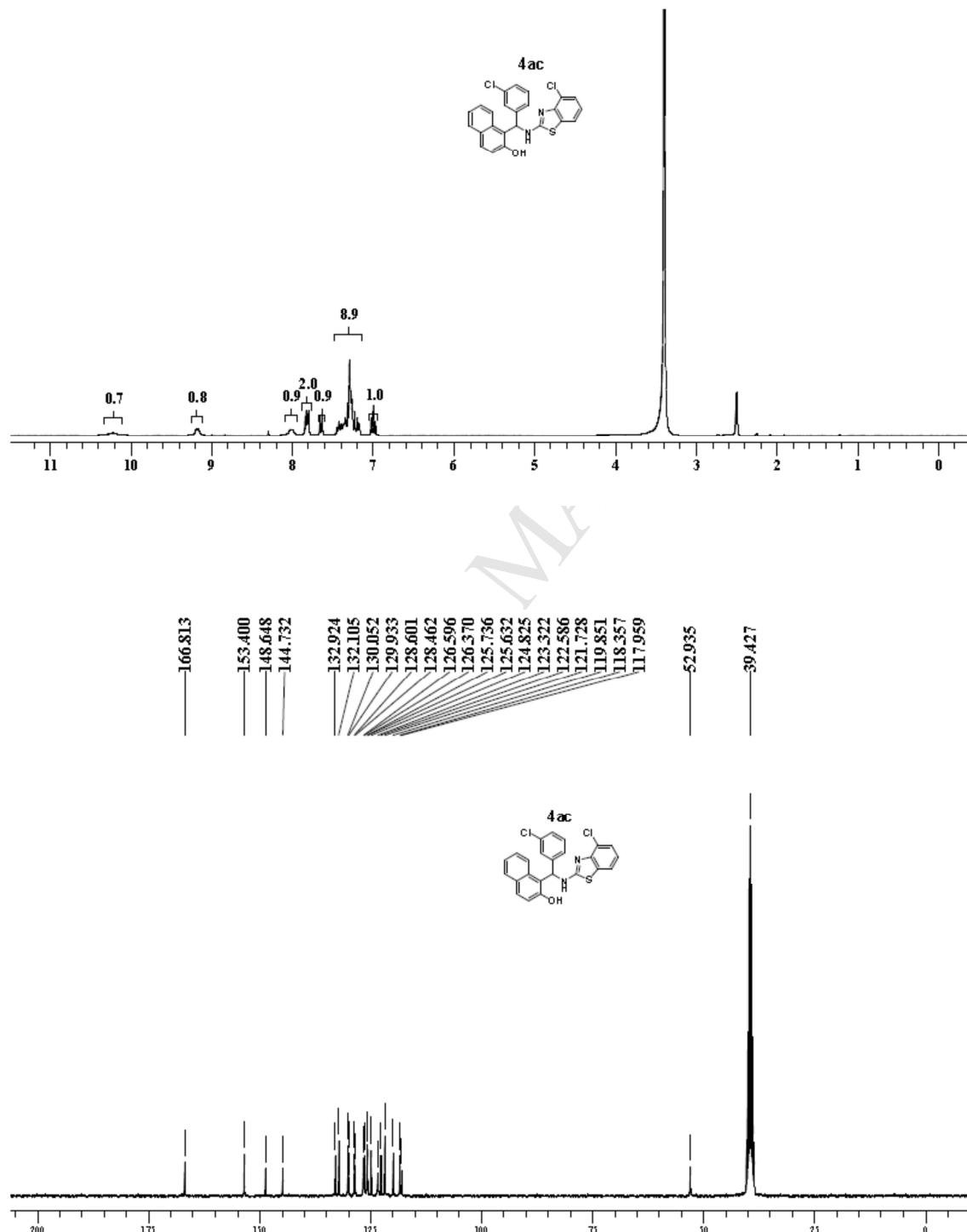
S4-4aa. ^1H and ^{13}C NMR of compound **4aa**. 1-(1-(benzo[d]thiazol-2-ylamino)-2-phenylpropyl)naphthalen-2-ol.



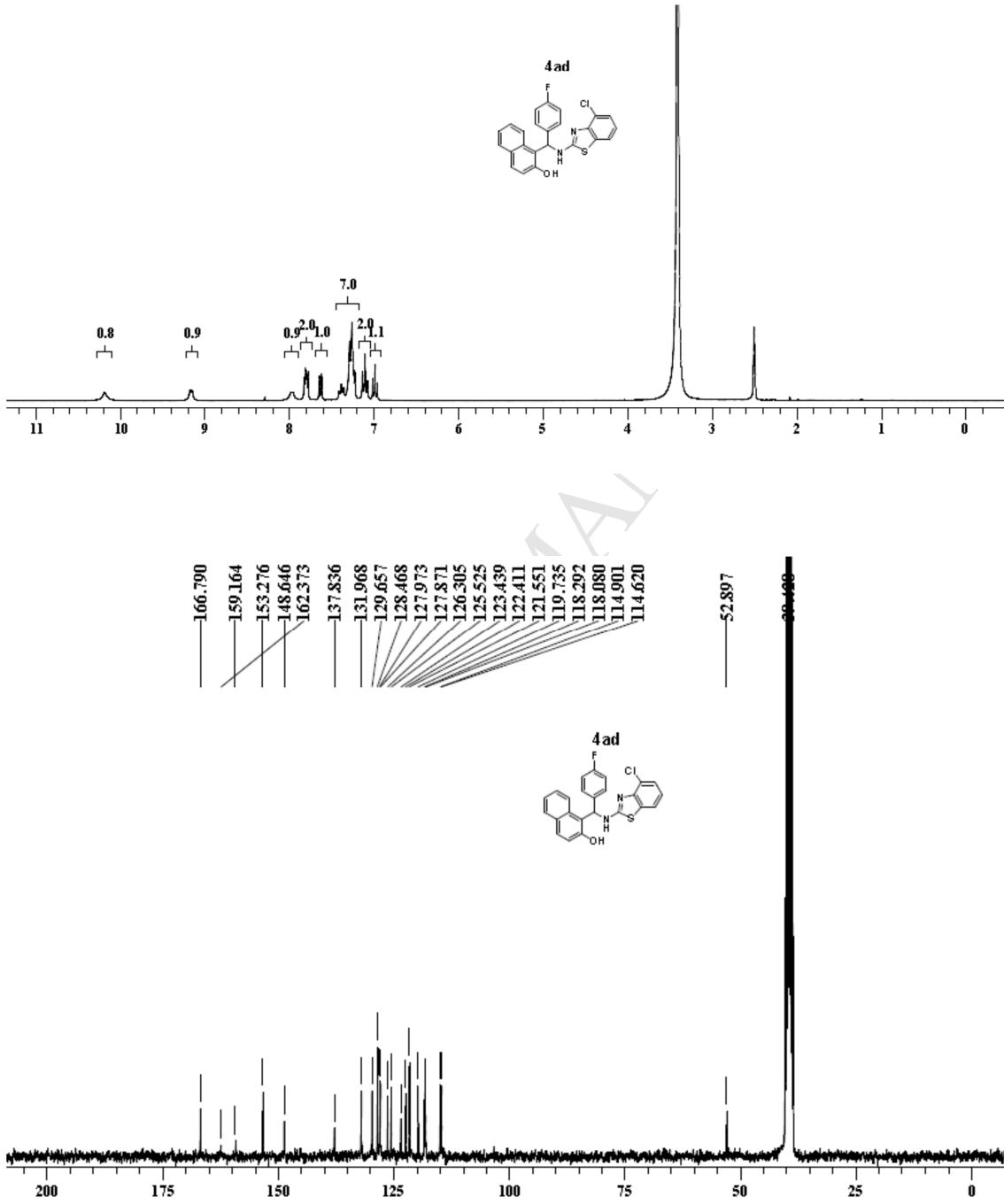
S4-4ab. ^1H NMR and ^{13}C NMR of compound **4ab**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(2,4-dichlorophenyl)methyl)naphthalen-2-ol.



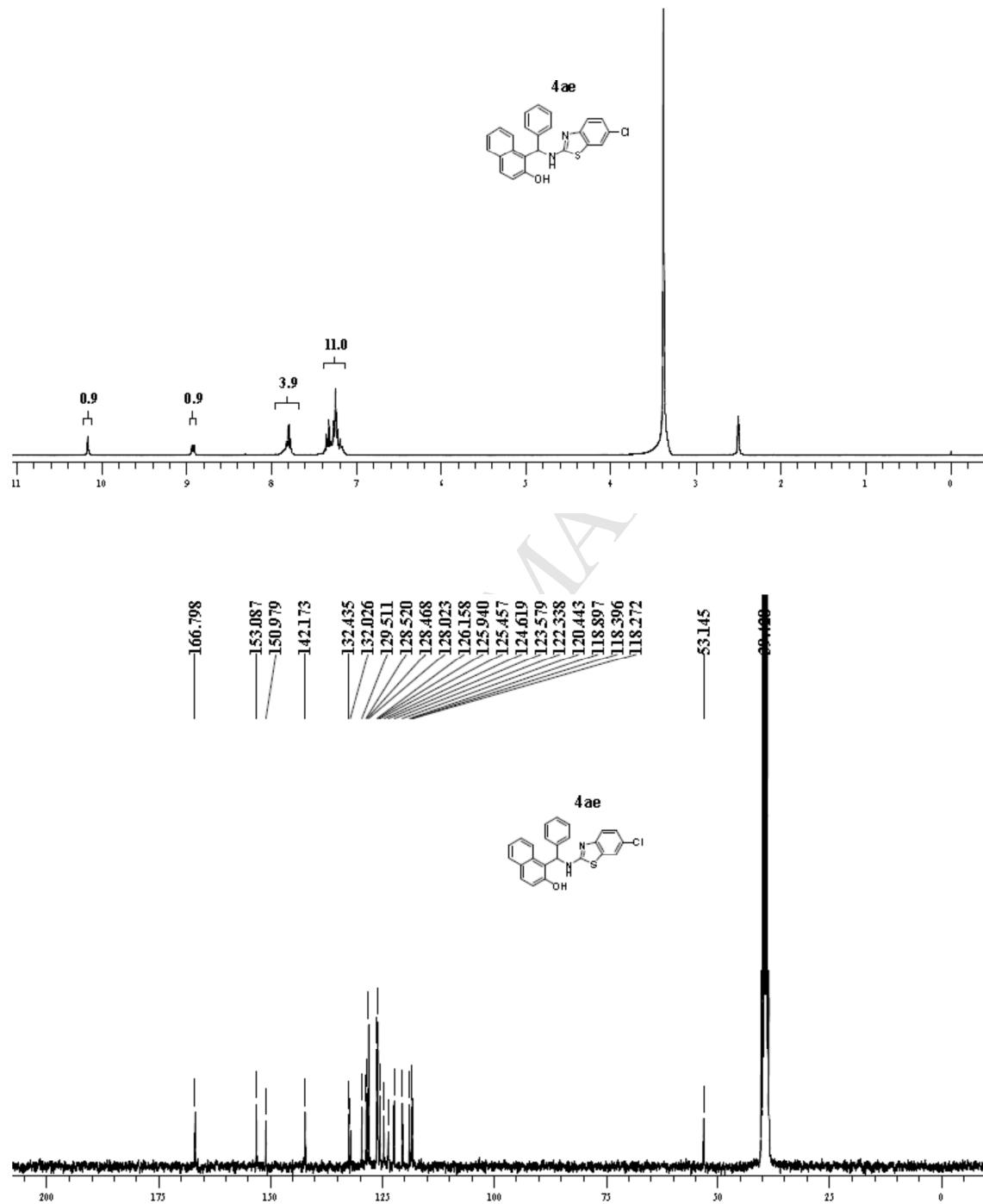
S4-4ac. ^1H NMR and ^{13}C NMR of compound **4ac**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(3-chlorophenyl)methyl)naphthalen-2-ol.



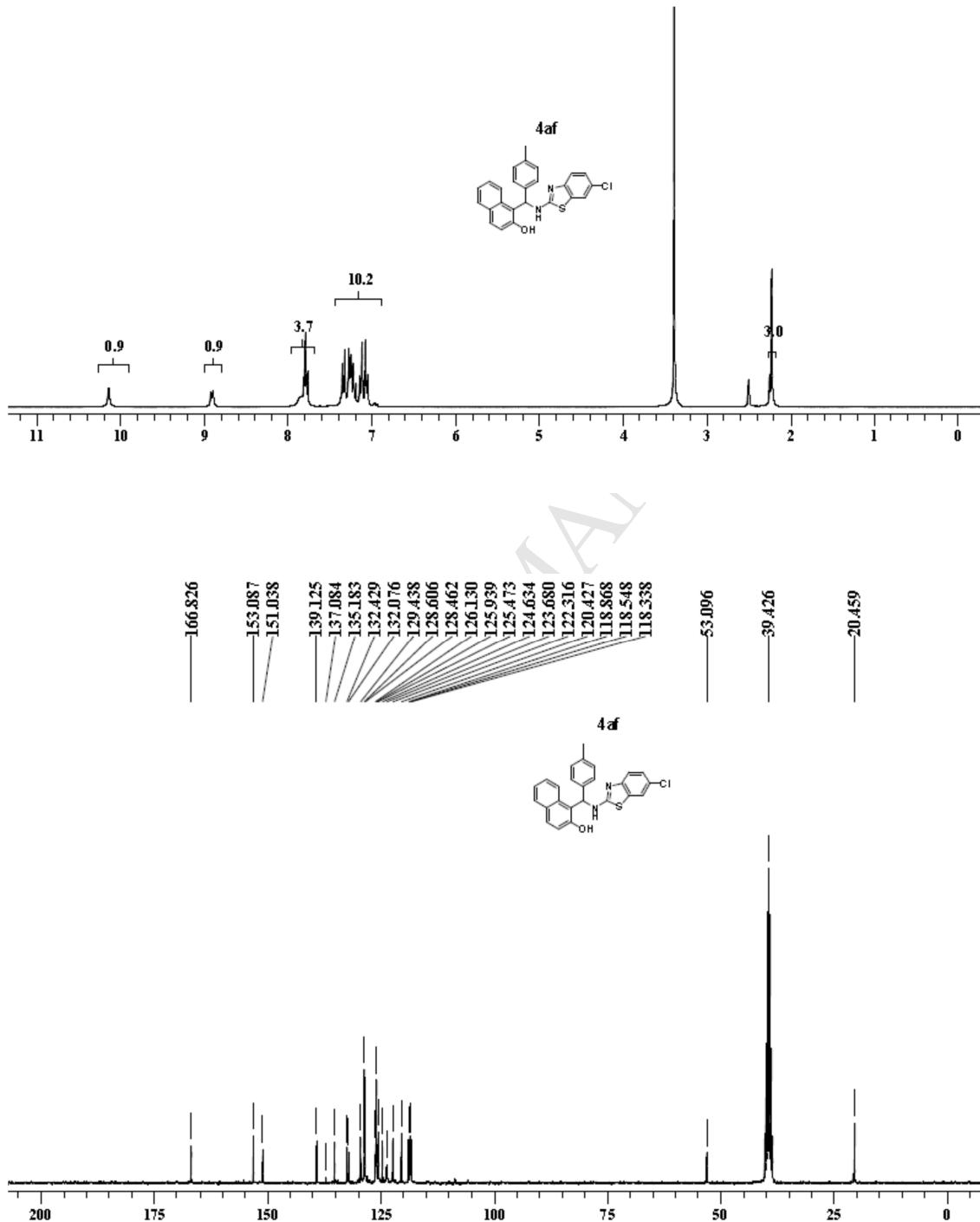
S4-4ad. ^1H NMR and ^{13}C NMR of compound **4ad**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-fluorophenyl)methyl)naphthalen-2-ol.



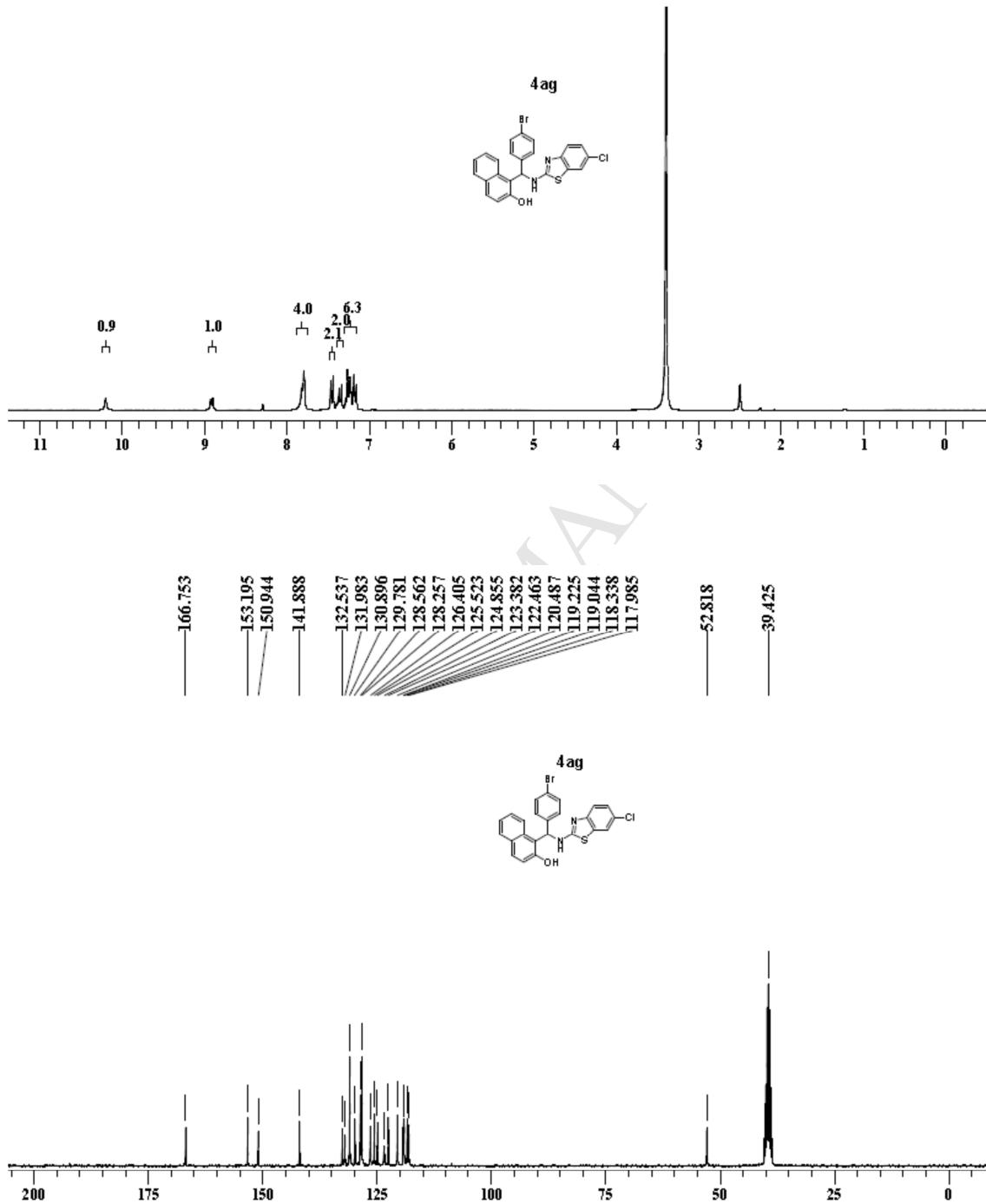
S4-4ae. ^1H NMR and ^{13}C NMR of compound **4ae**. 1-((6-chlorobenzo[d]thiazol-2-ylamino)(phenyl)methyl)naphthalen-2-ol.



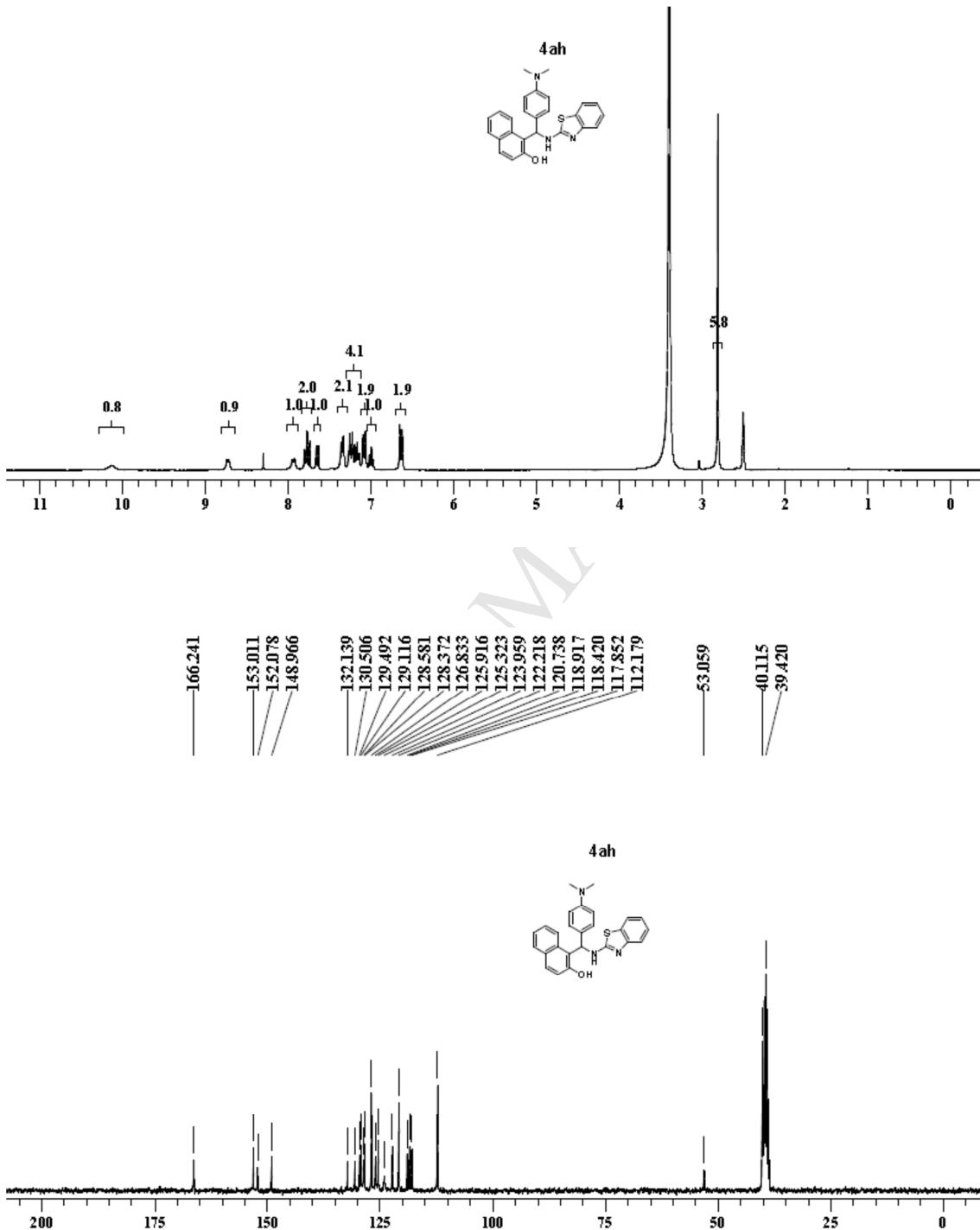
S4-4af. ^1H NMR and ^{13}C NMR of compound **4af**. 1-((6-chlorobenzo[d]thiazol-2-ylamino)(p-tolyl)methyl)naphthalen-2-ol.



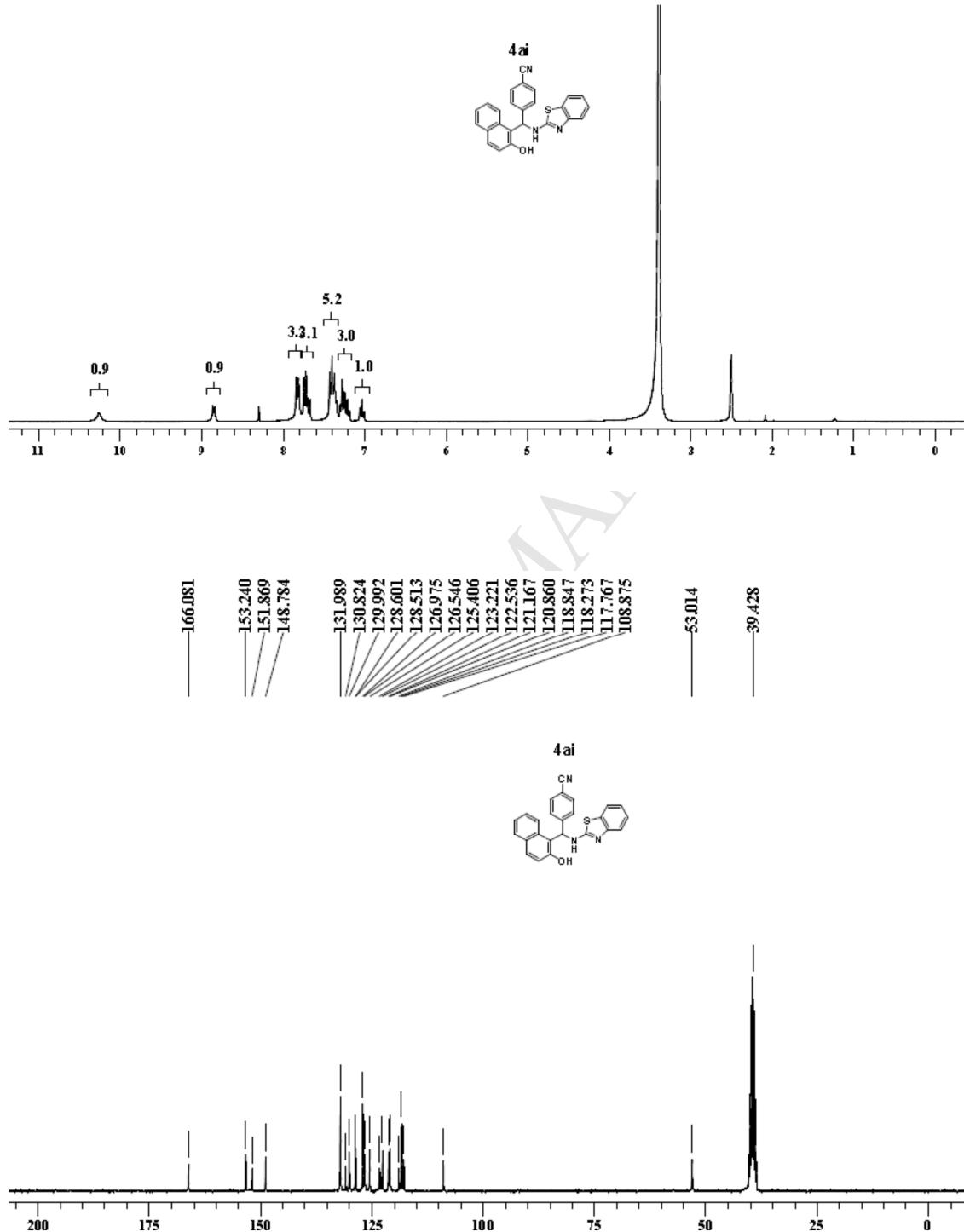
S4-4ag. ^1H NMR and ^{13}C NMR of compound **4ag**. 1-((6-chlorobenzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl)naphthalen-2-ol.



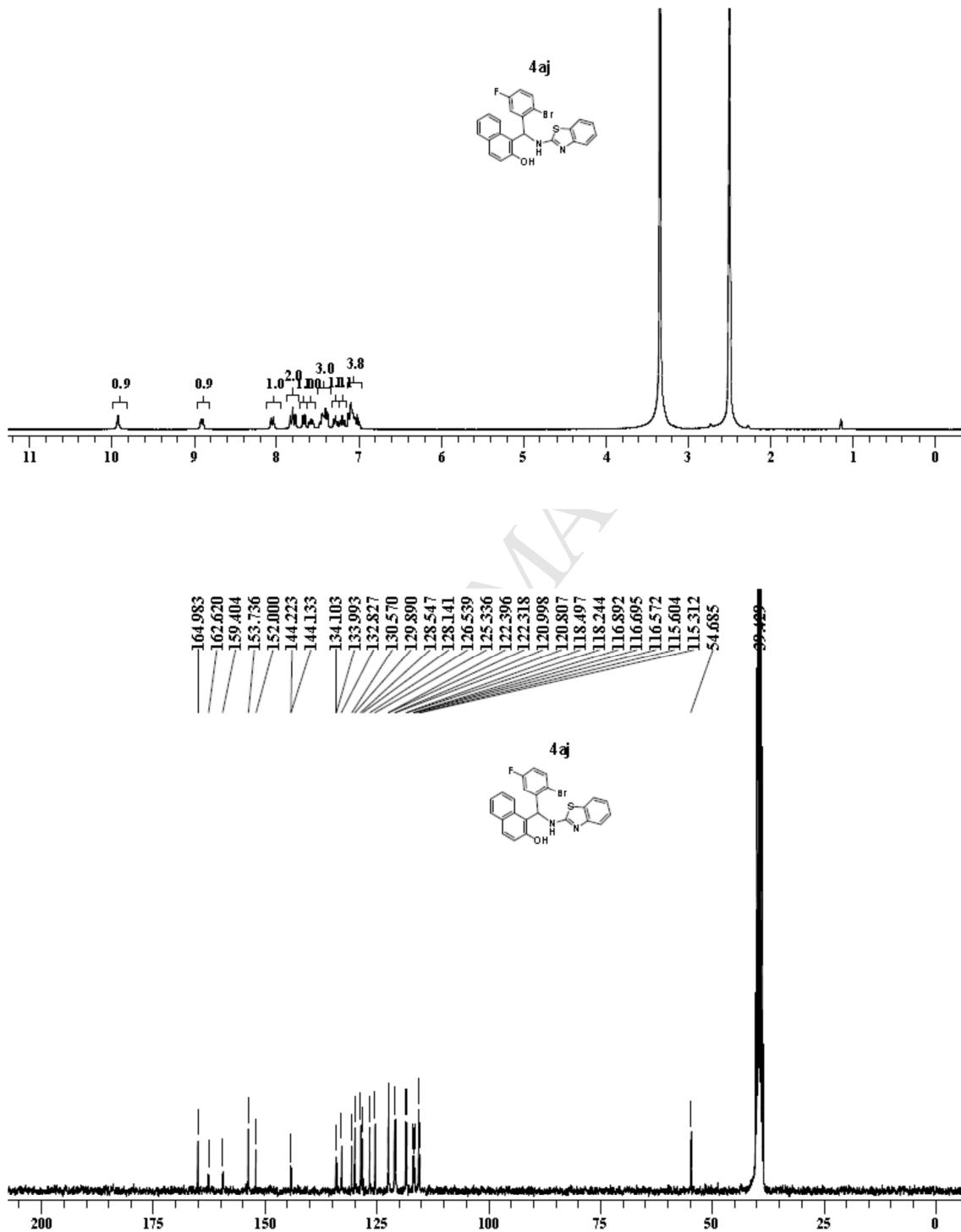
S4-4ah. ^1H NMR and ^{13}C NMR of compound **4ah**. 1-((benzo[d]thiazol-2-ylamino)(4-(dimethylamino)phenyl)methyl)naphthalen-2-ol.



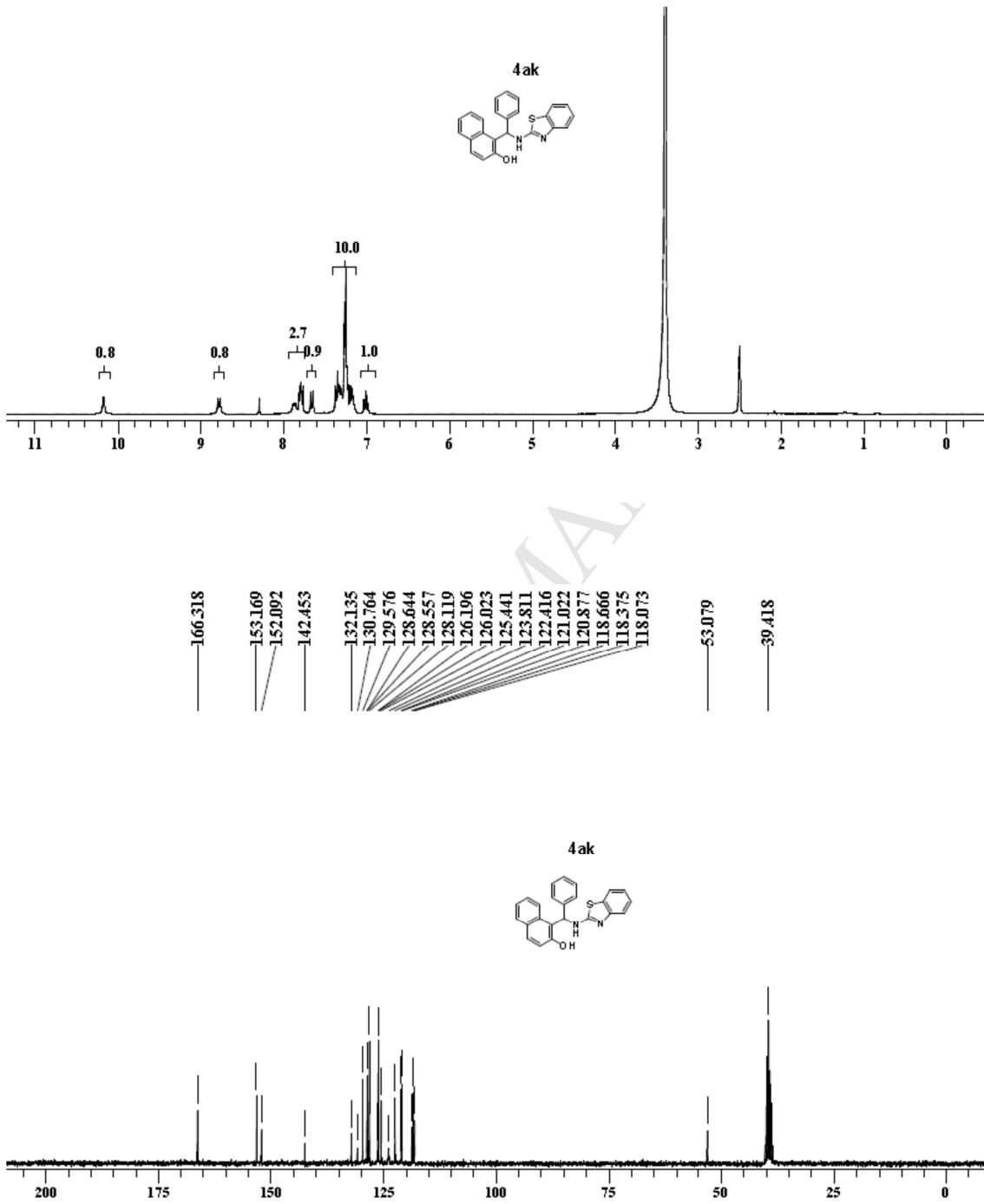
S4-4ai. ^1H NMR and ^{13}C NMR of compound **4ai**. 4-((benzo[d]thiazol-2-ylamino)(2-hydroxynaphthalen-1-yl)methyl)benzonitrile.



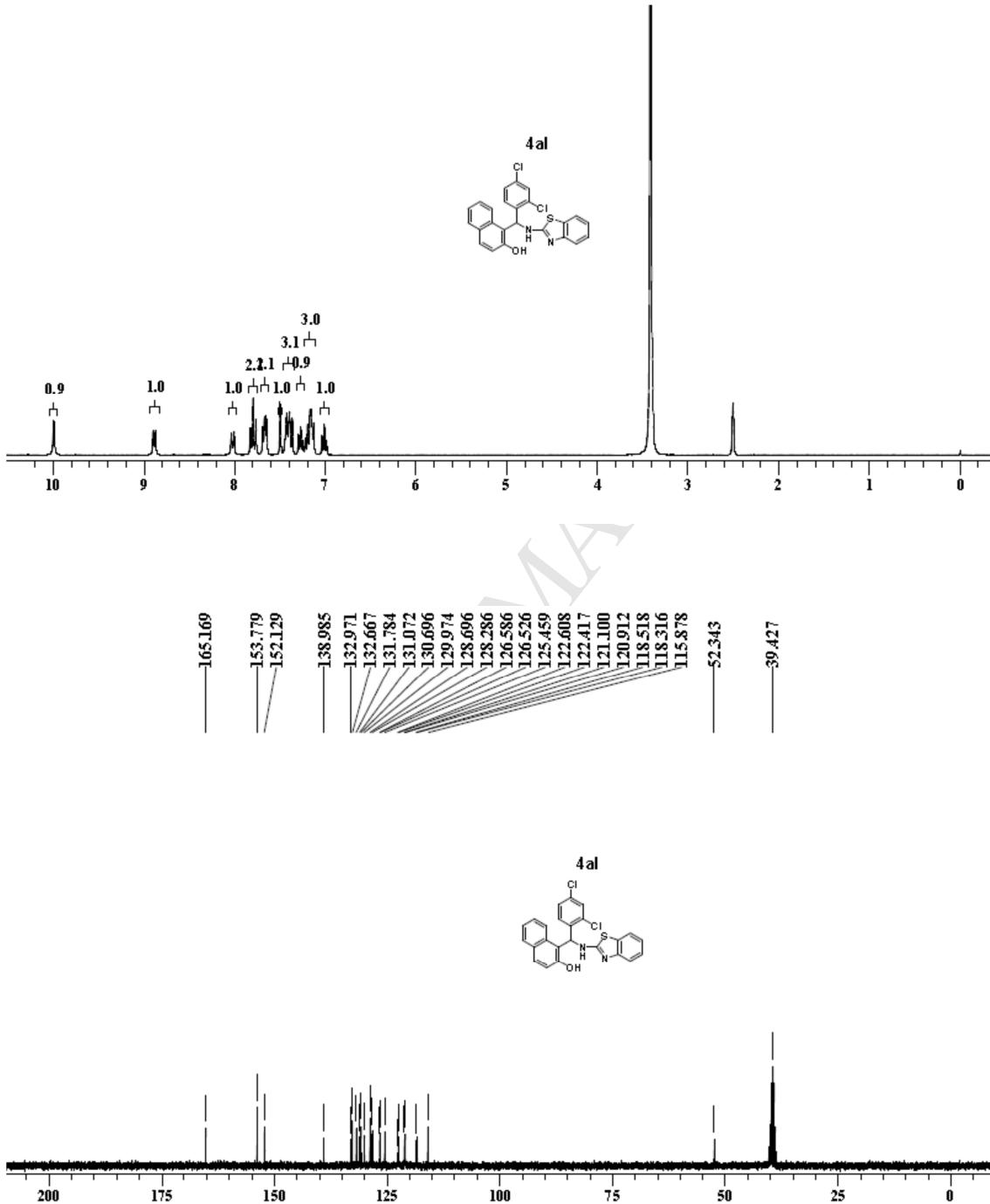
S4-4aj. ^1H NMR of compound **4aj**. 1-((benzo[d]thiazol-2-ylamino)(2-bromo-5-fluorophenyl)methyl)naphthalen-2-ol.



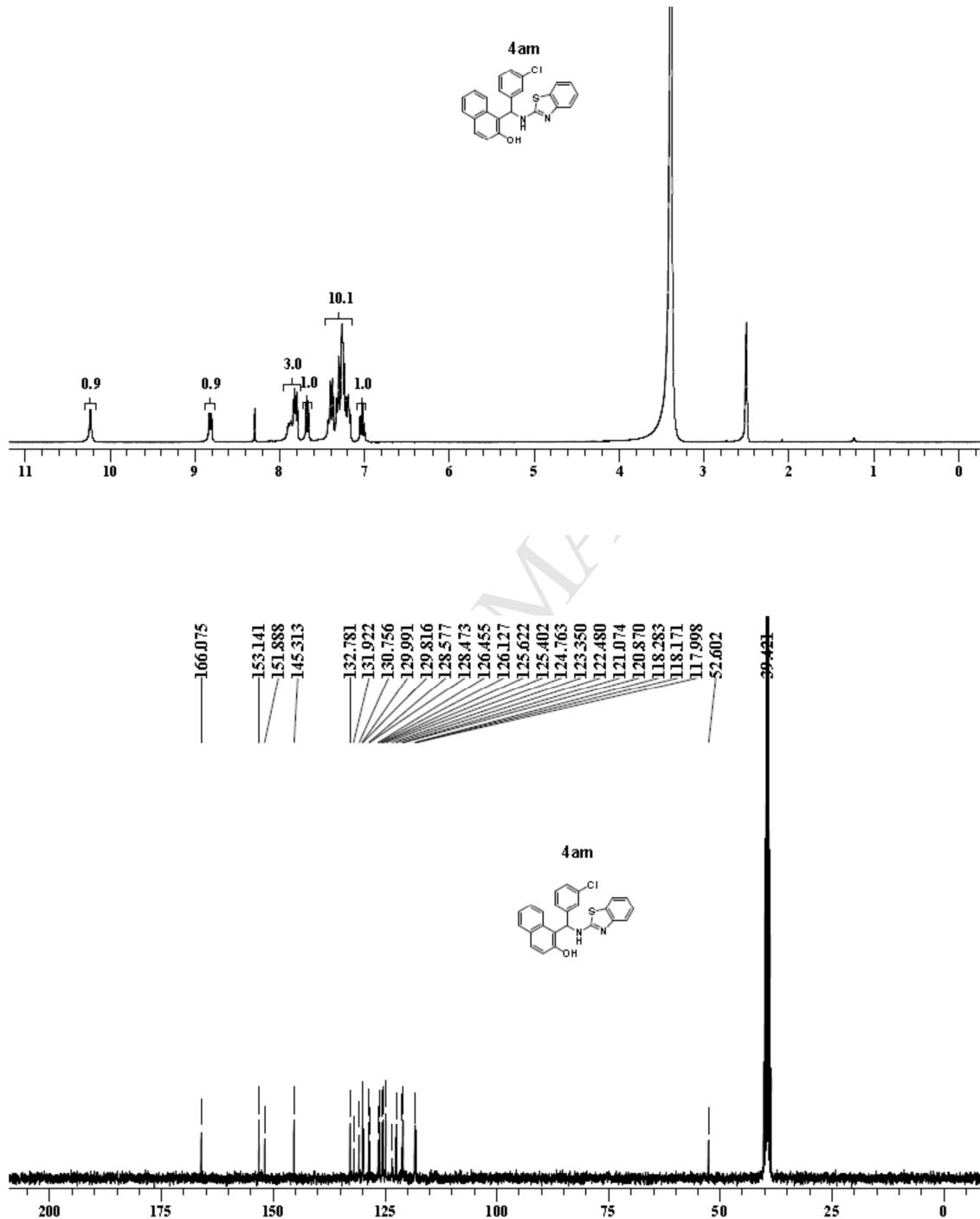
S4-4ak. ^1H NMR and ^{13}C NMR of compound **4ak**. 1-((benzo[d]thiazol-2-ylamino)(phenyl)methyl)naphthalen-2-ol.



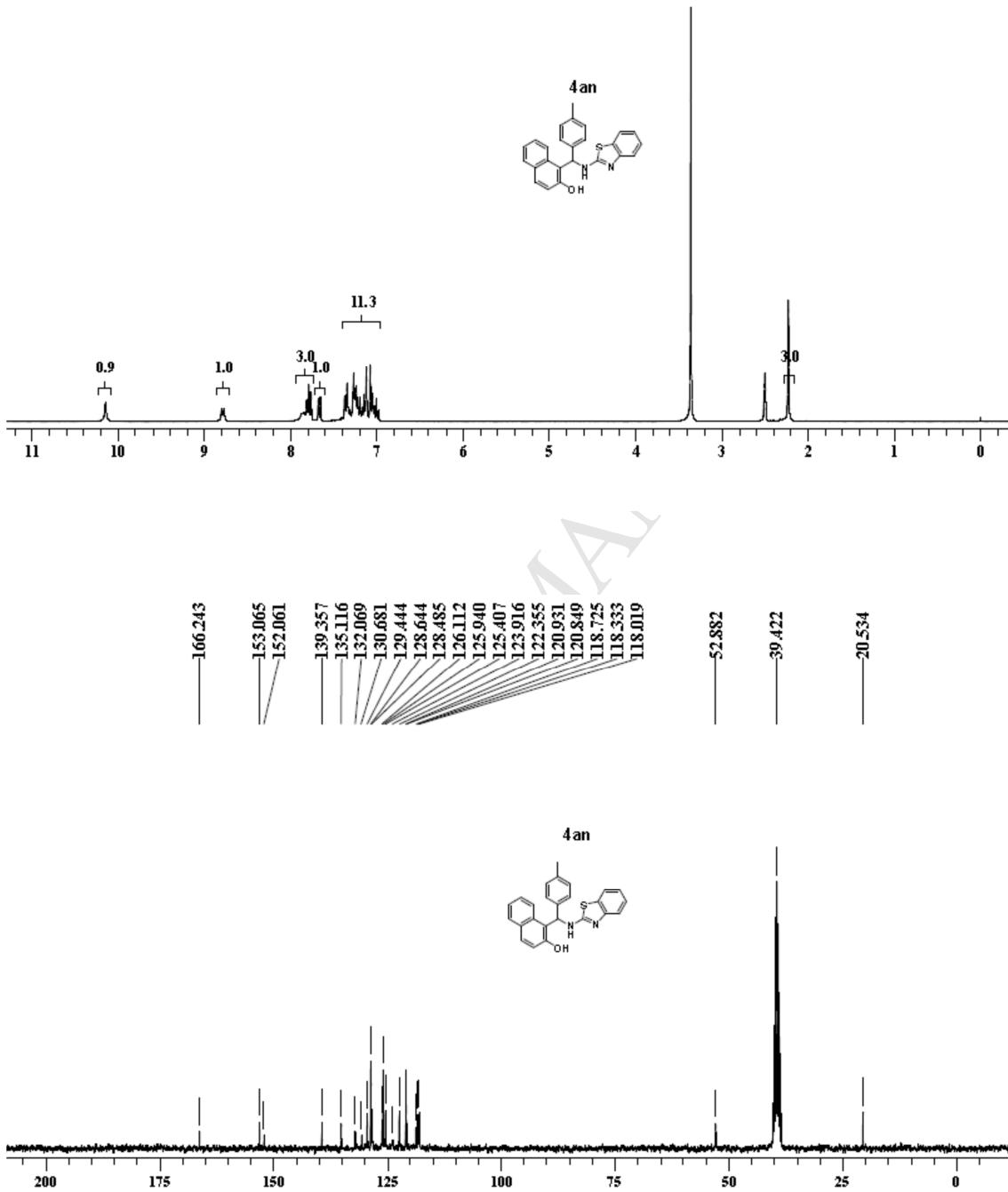
S4-4al. ^1H NMR and ^{13}C NMR of compound **4al**. 1-((benzo[d]thiazol-2-ylamino)(2,4-dichlorophenyl)methyl)naphthalen-2-ol.



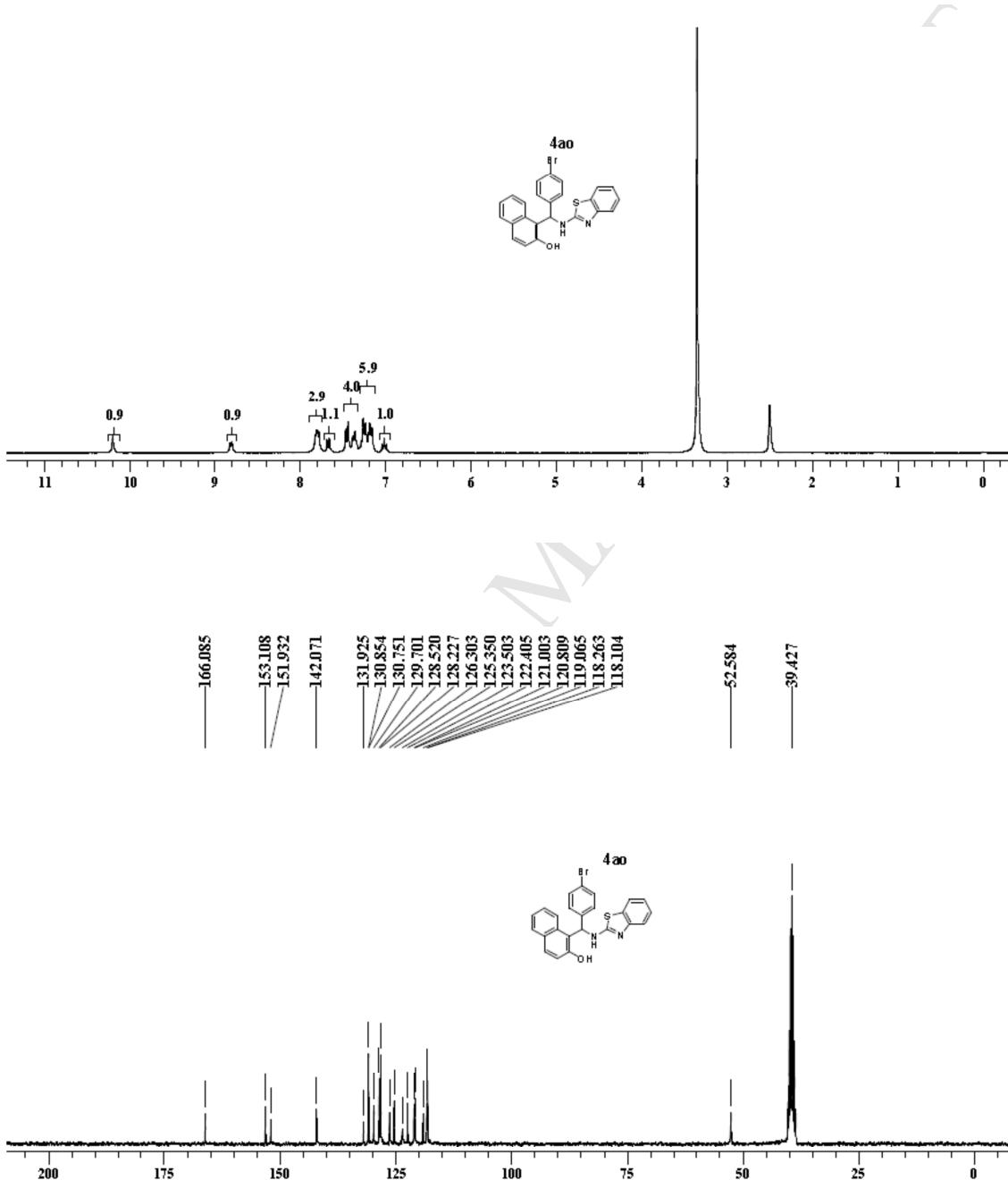
S4-4am. ^1H NMR and ^{13}C NMR of compound **4am**. 1-((benzo[d]thiazol-2-ylamino)(3-chlorophenyl)methyl)naphthalen-2-ol.



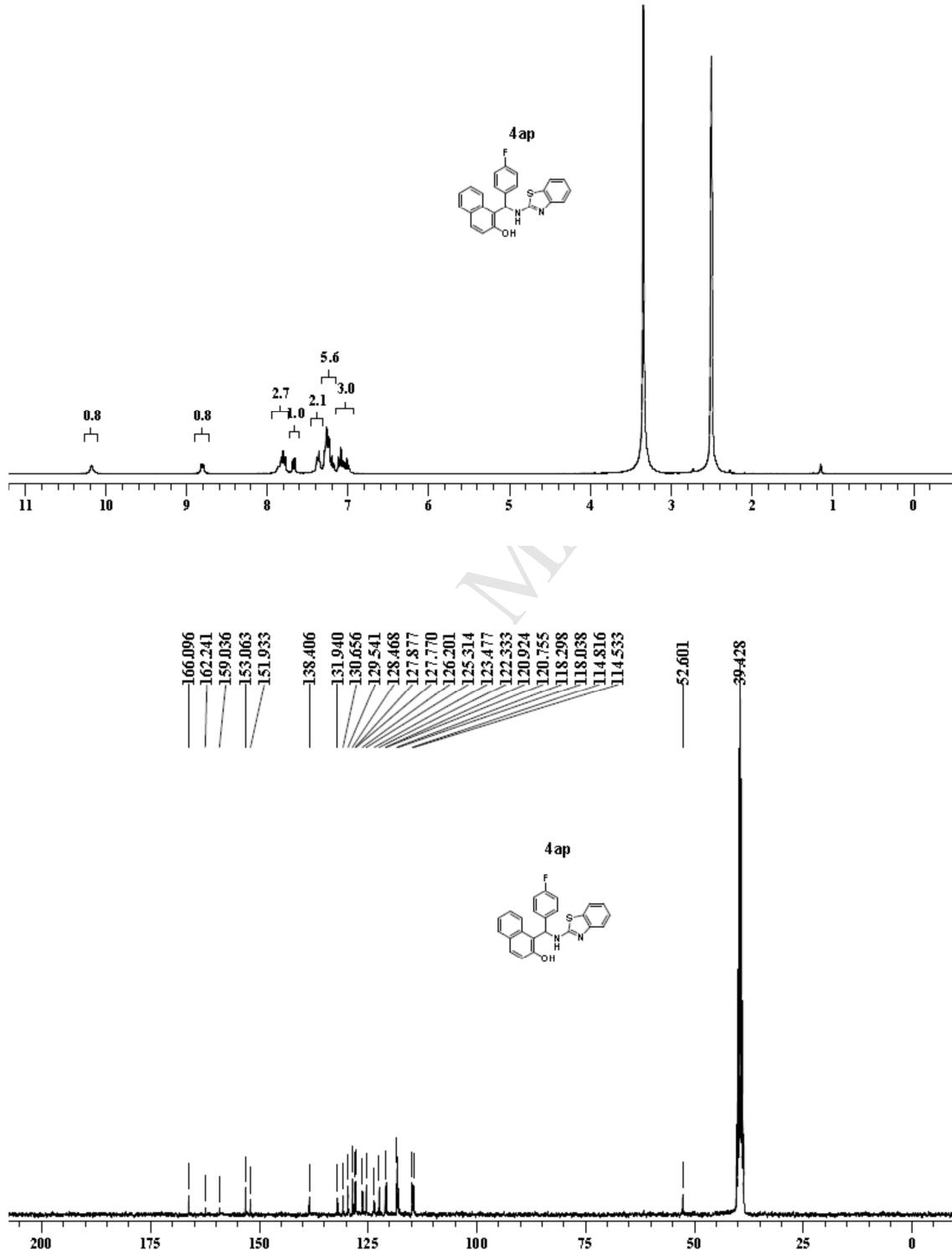
S4-4an. ^1H NMR and ^{13}C NMR of compound **4an**. 1-((benzo[d]thiazol-2-ylamino)(p-tolyl)methyl)naphthalen-2-ol.



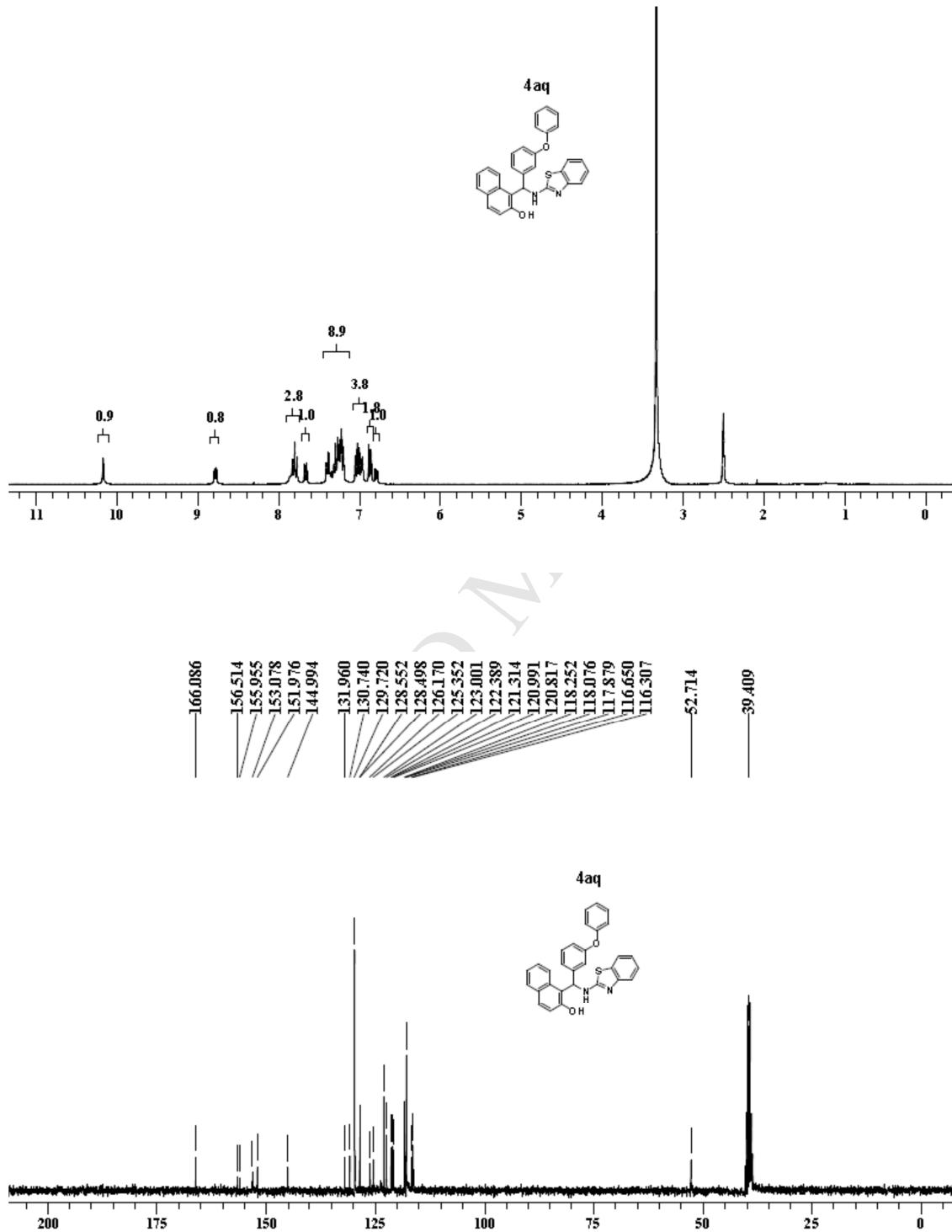
S4-4ao. ^1H NMR and ^{13}C NMR of compound **4ao**. 1-((benzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl)naphthalen-2-ol.



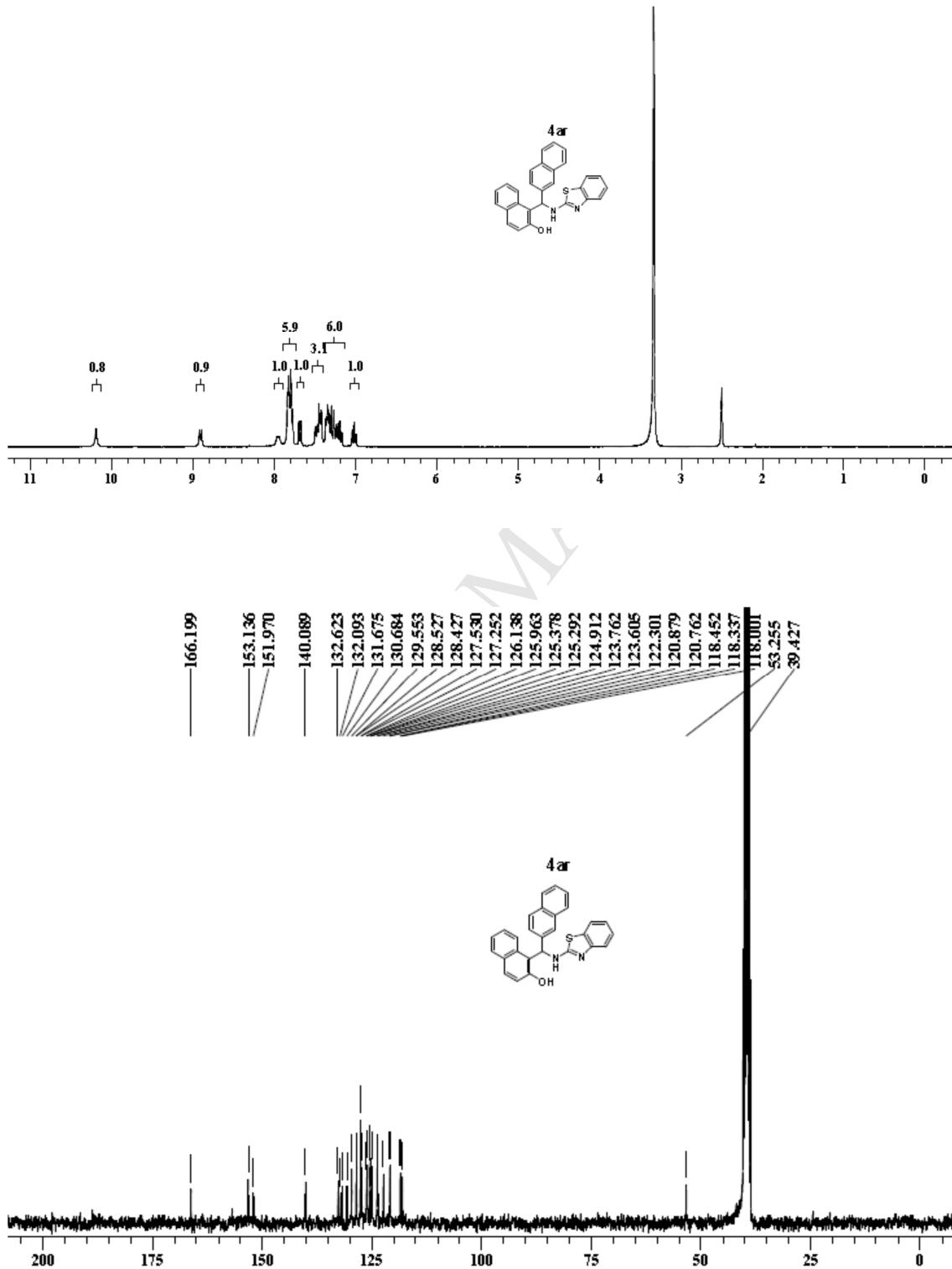
S4-4ap. ^1H NMR and ^{13}C NMR of compound **4ap**. 1-((benzo[d]thiazol-2-ylamino)(4-fluorophenyl)methyl)naphthalen-2-ol.



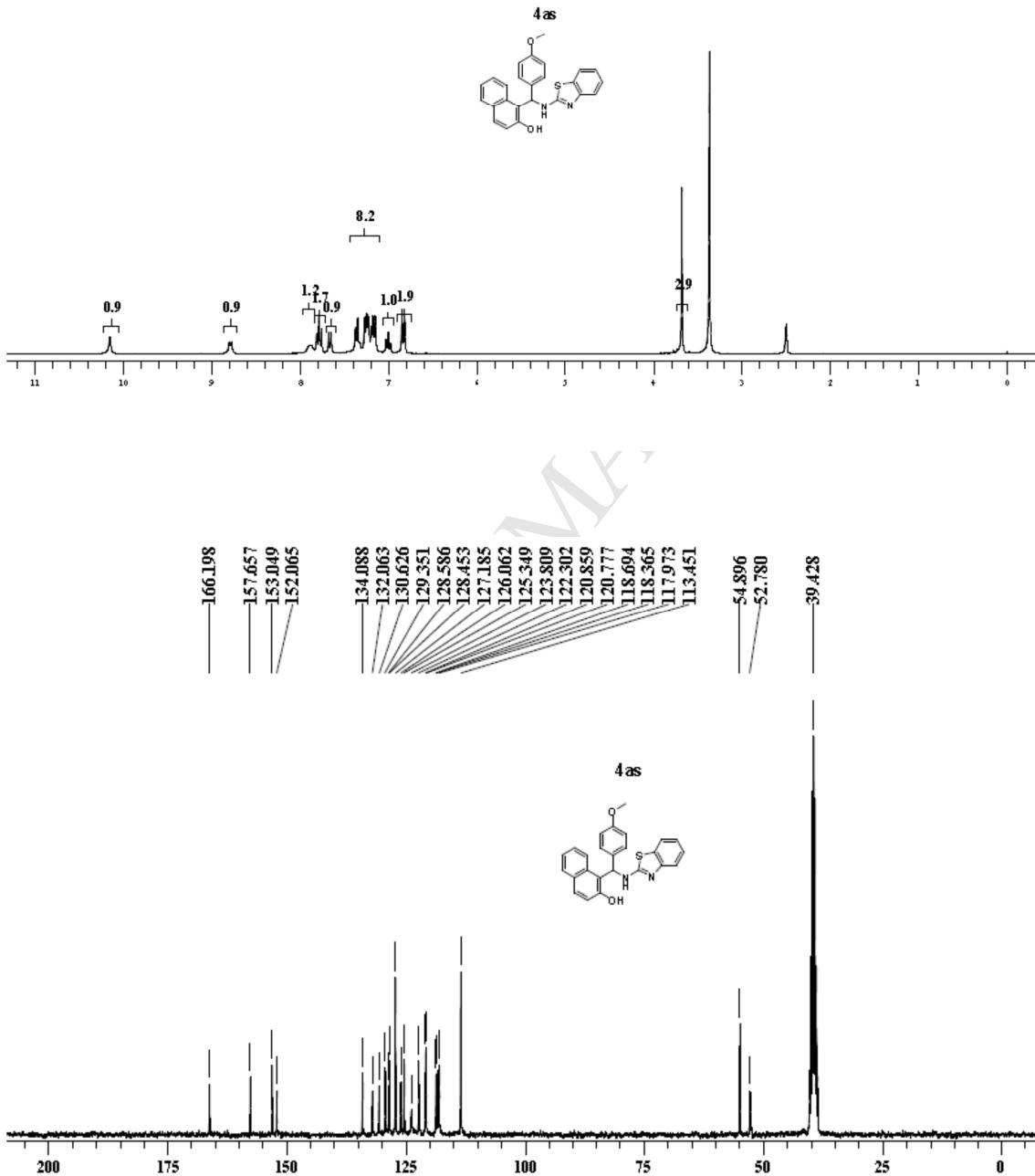
S4-aq. ^1H NMR and ^{13}C NMR of compound **4aq**. 1-((benzo[d]thiazol-2-ylamino)(3-phenoxyphenyl)methyl)naphthalen-2-ol.



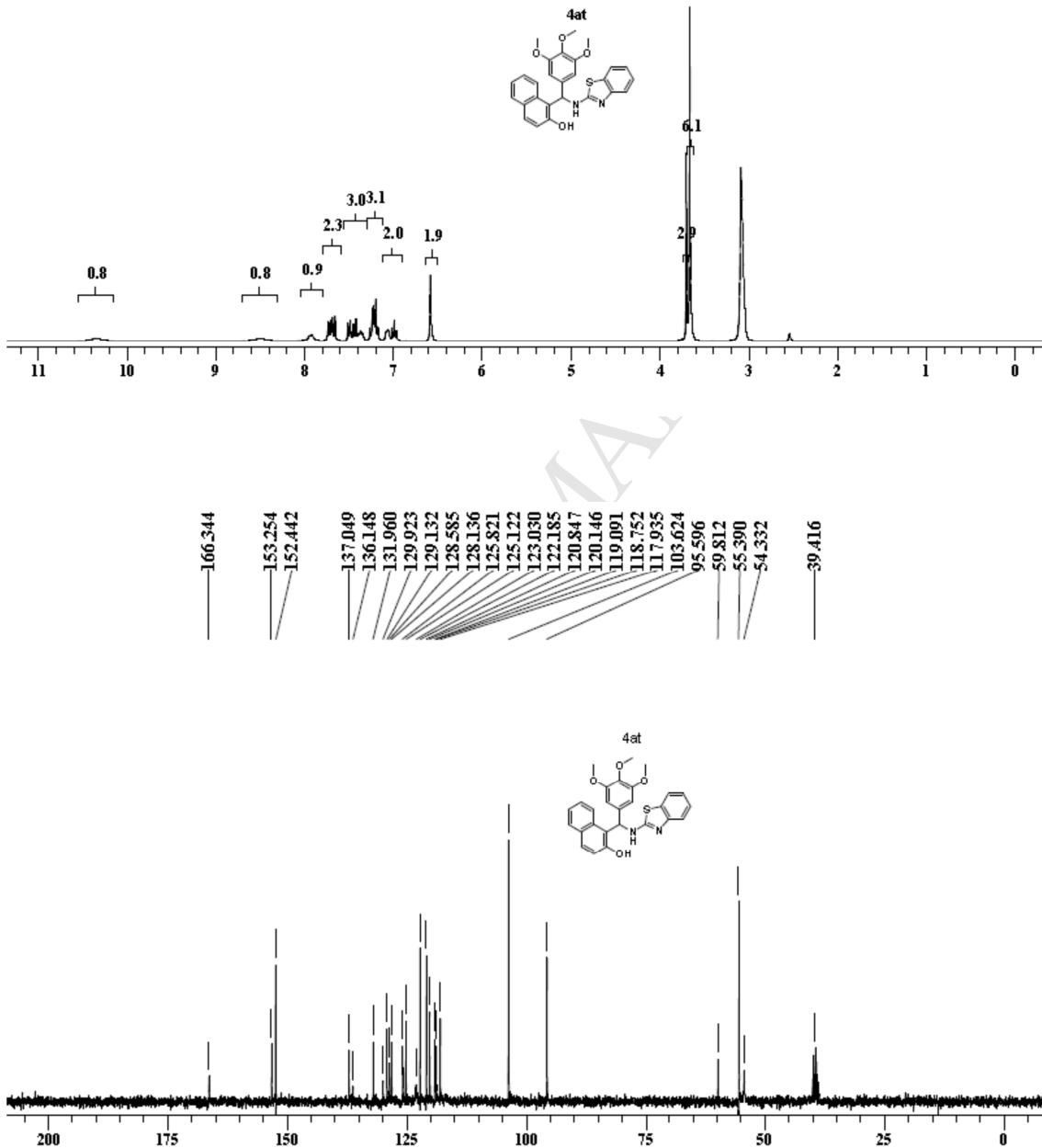
S4-4ar. ^1H NMR and ^{13}C NMR of compound **4ar**. 1-((benzo[d]thiazol-2-ylamino)(naphthalen-2-yl)methyl)naphthalen-2-ol.



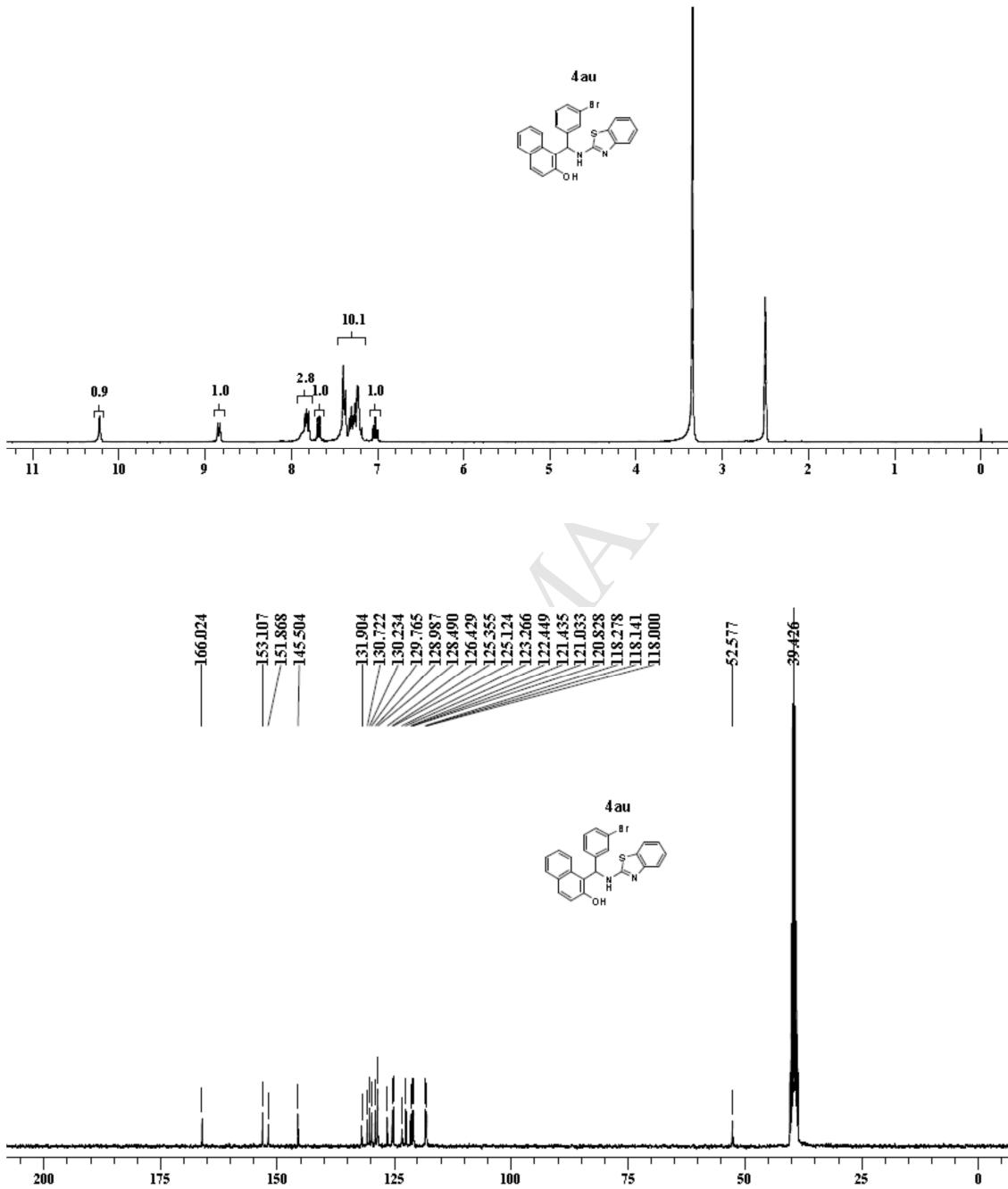
S4-4as. ^1H NMR and ^{13}C NMR of compound **4as**. 1-((benzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl)naphthalen-2-ol.



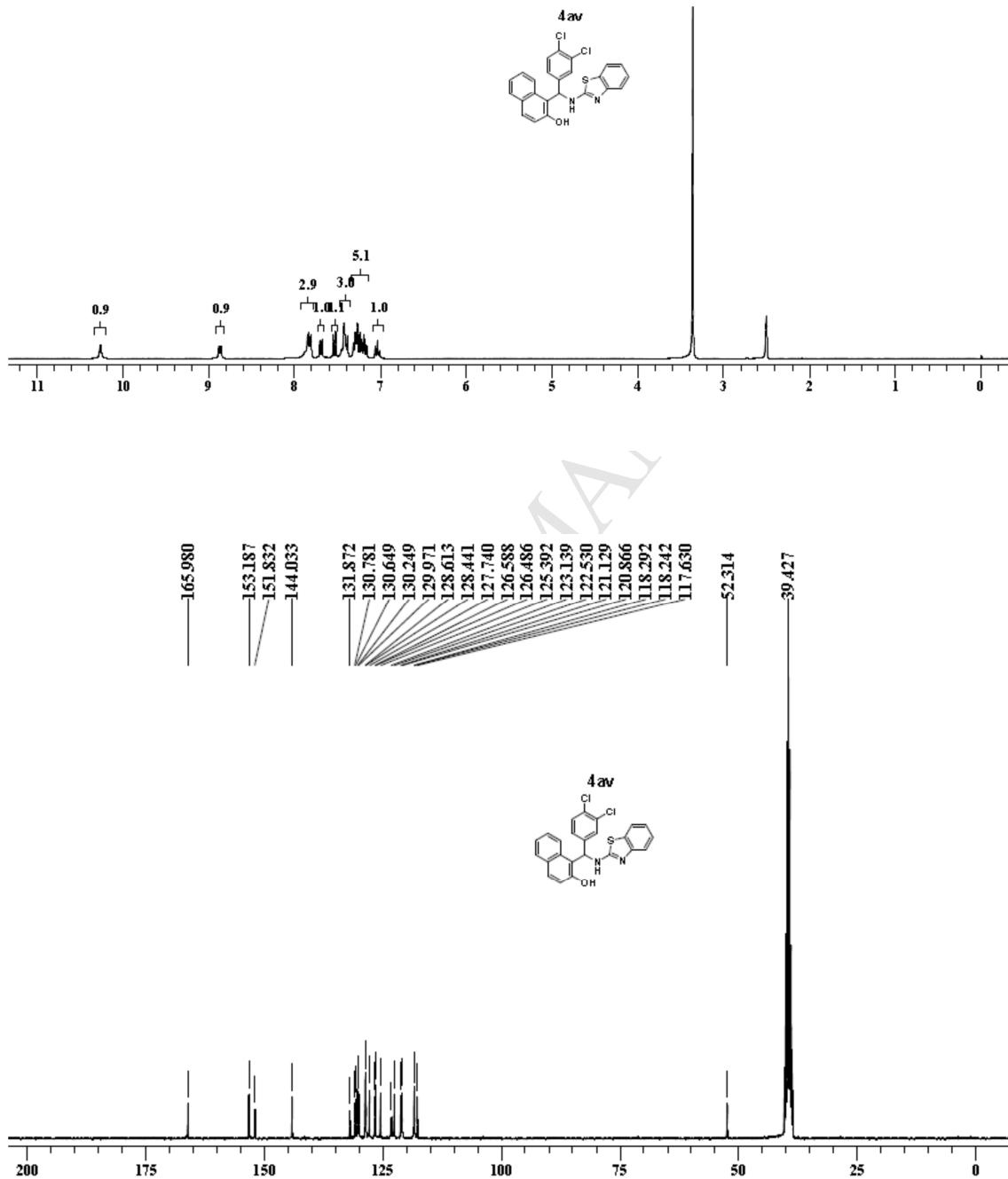
S4-4at. ^1H NMR and ^{13}C NMR of compound **4at**. 1-((benzo[d]thiazol-2-ylamino)(3,4,5-trimethoxyphenyl)methyl)naphthalen-2-ol.



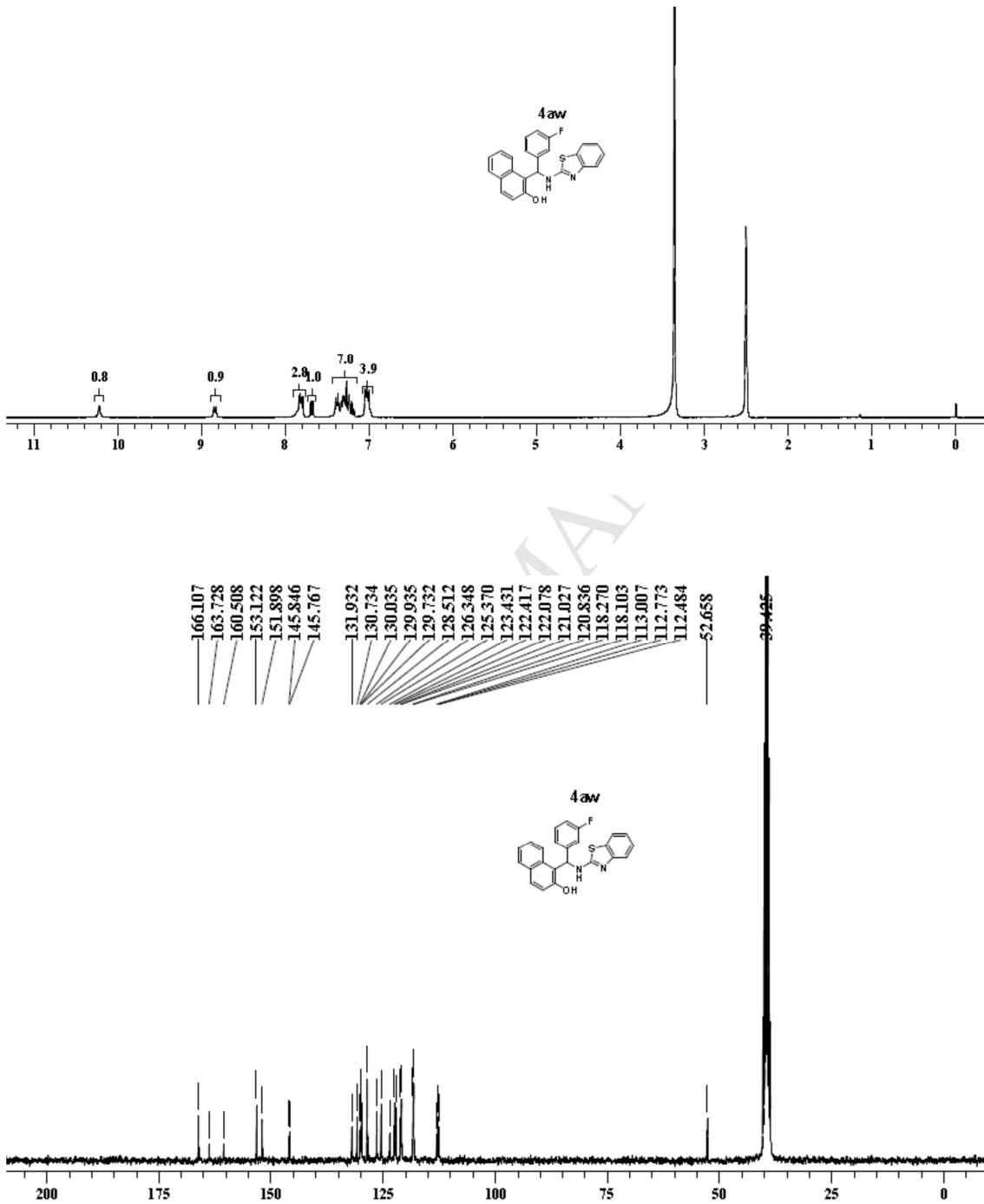
S4-4au. ^1H NMR and ^{13}C NMR of compound **4au**. 1-((benzo[d]thiazol-2-ylamino)(3-bromophenyl)methyl)naphthalen-2-ol.



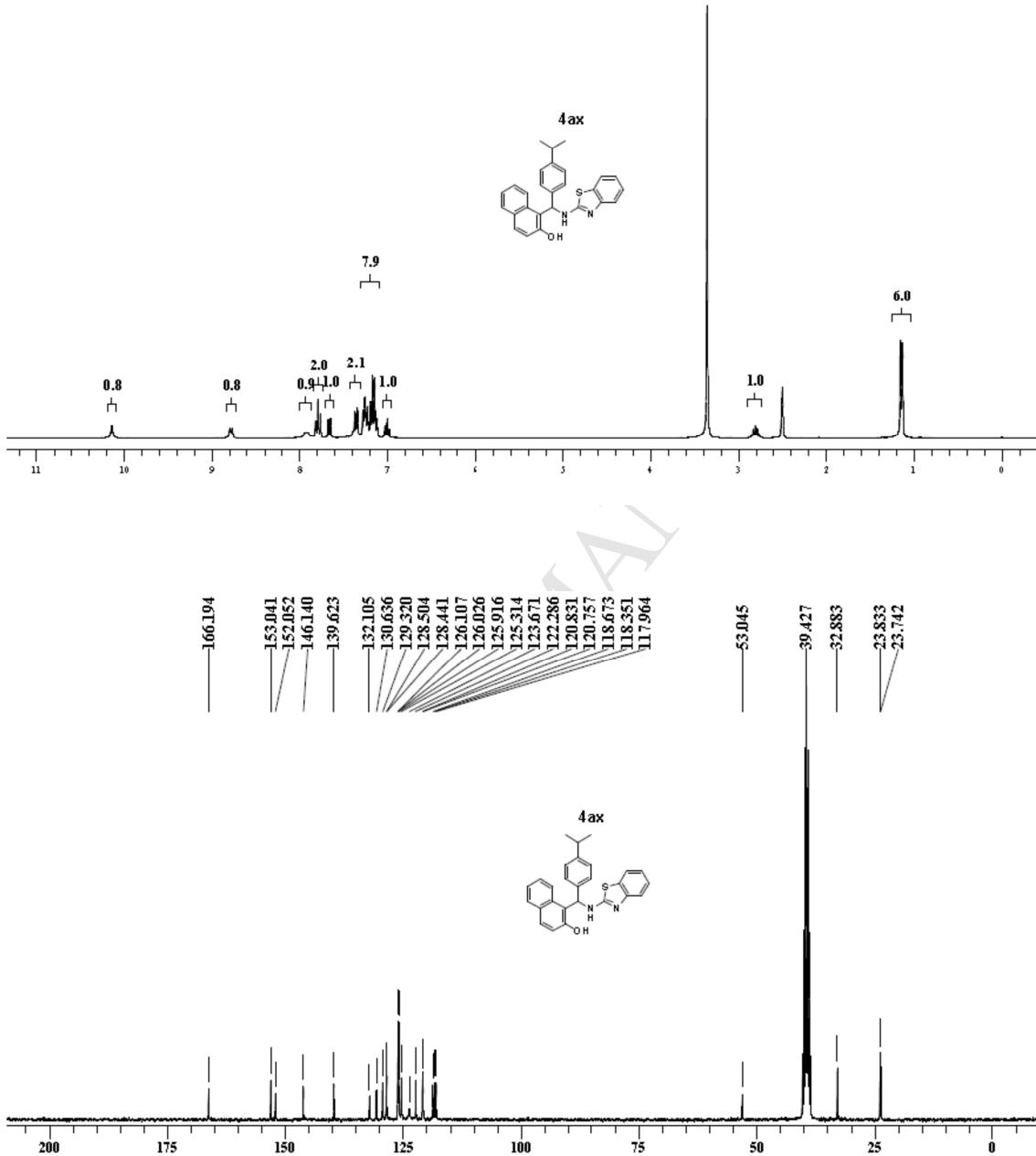
S4-4av. ^1H NMR and ^{13}C NMR of compound **4av**. 1-((benzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol.



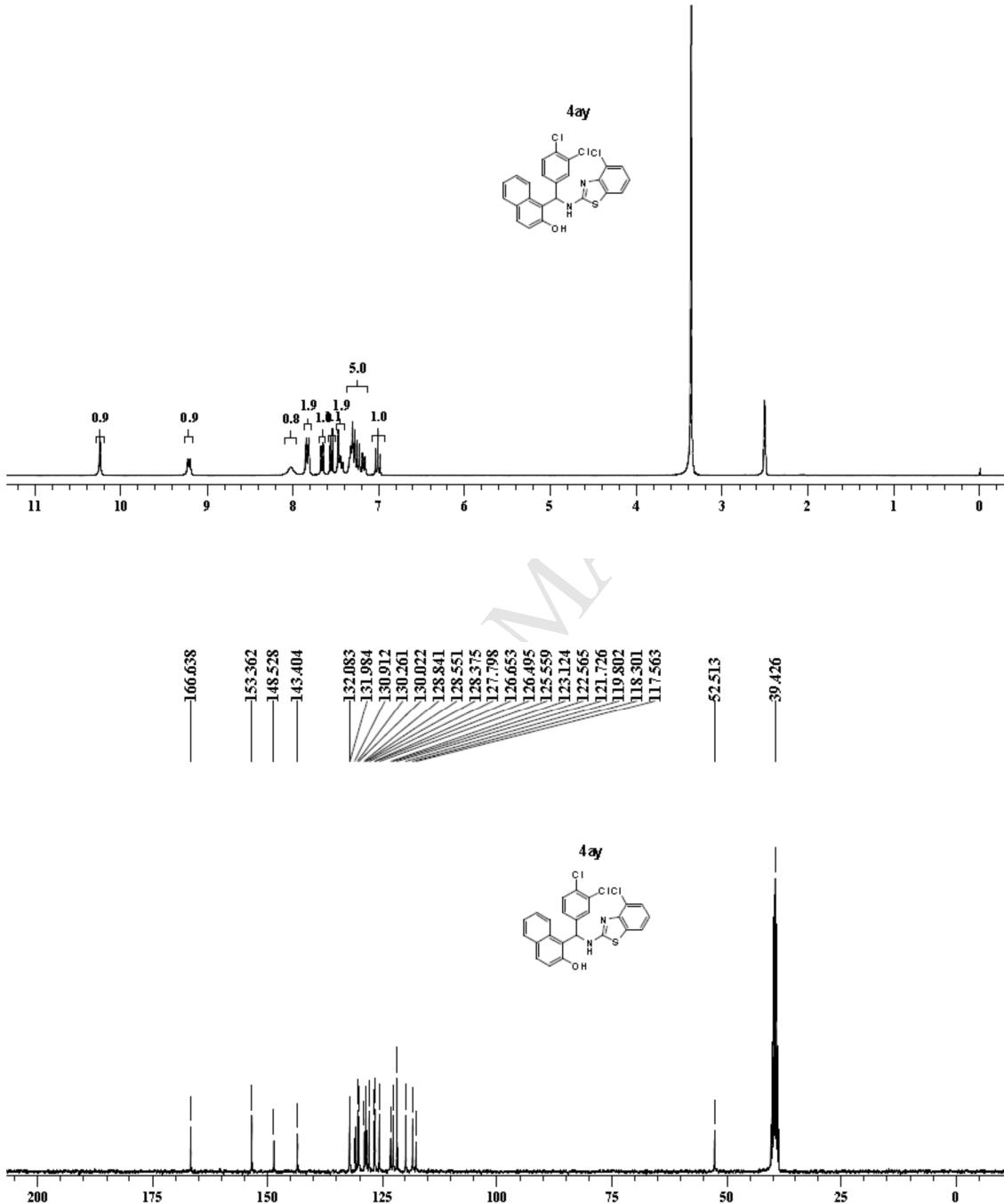
S4-4aw. ^1H NMR and ^{13}C NMR of compound **4aw**. 1-((benzo[d]thiazol-2-ylamino)(3-fluorophenyl)methyl)naphthalen-2-ol.



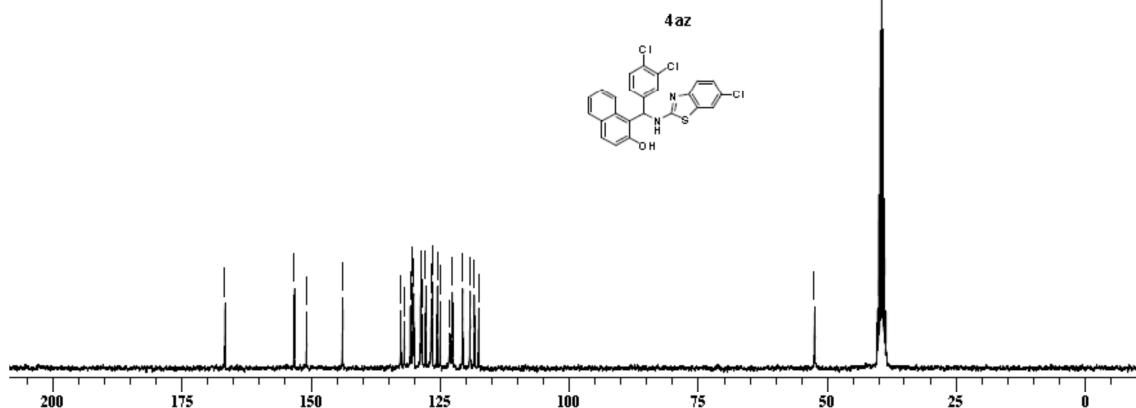
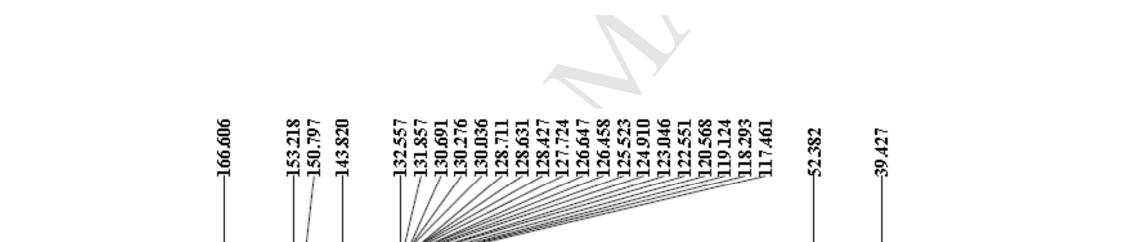
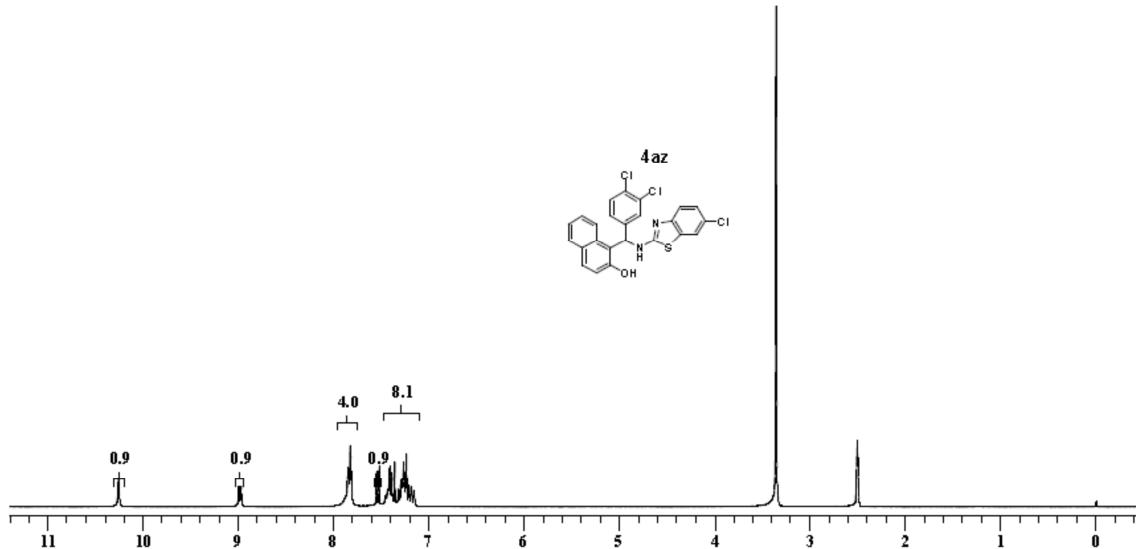
S4-4ax. ^1H NMR and ^{13}C NMR of compound **4ax**. 1-((benzo[d]thiazol-2-ylamino)(4-isopropylphenyl)methyl)naphthalen-2-ol.



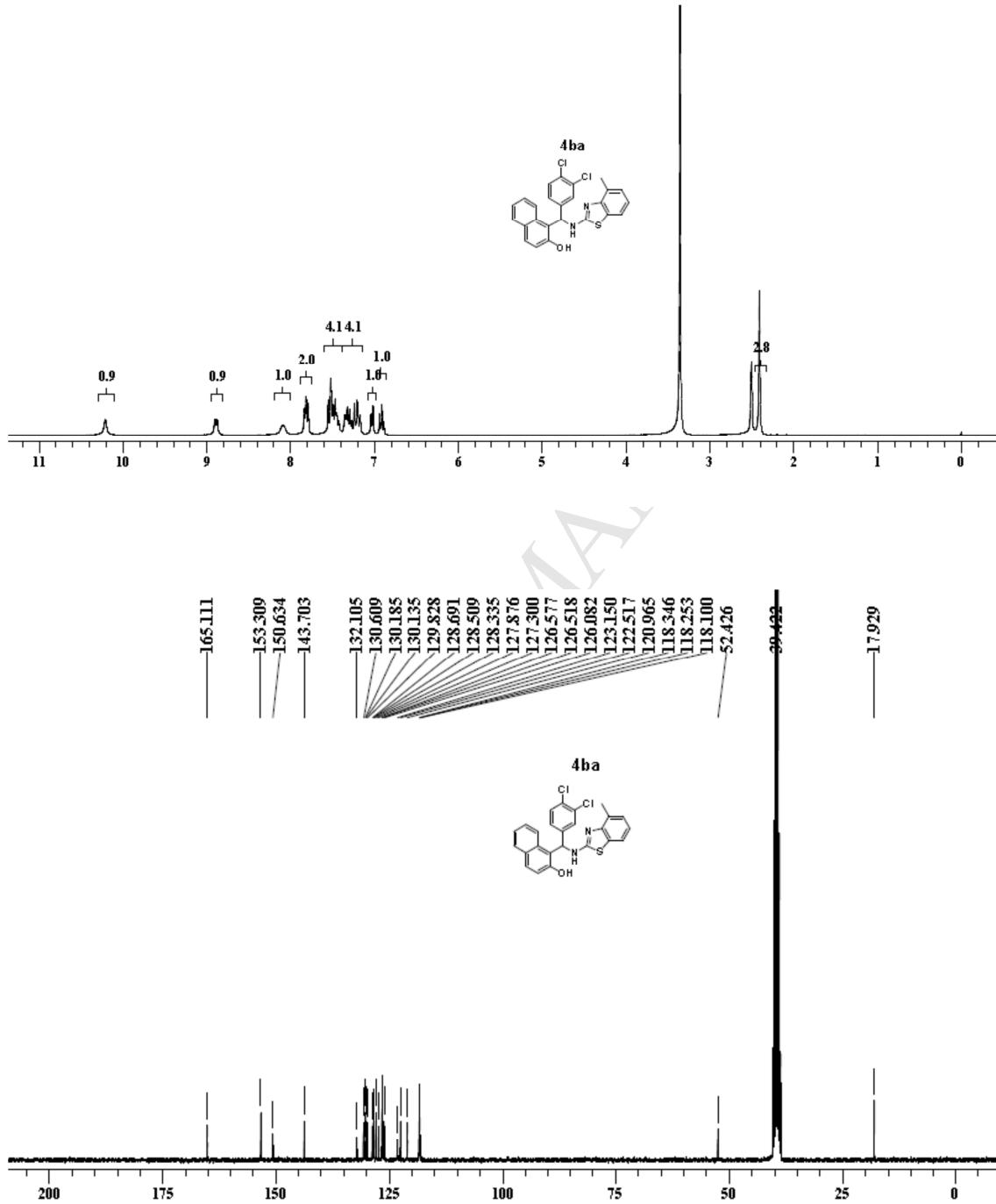
S4-4ay. ^1H NMR and ^{13}C NMR of compound **4ay**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol.



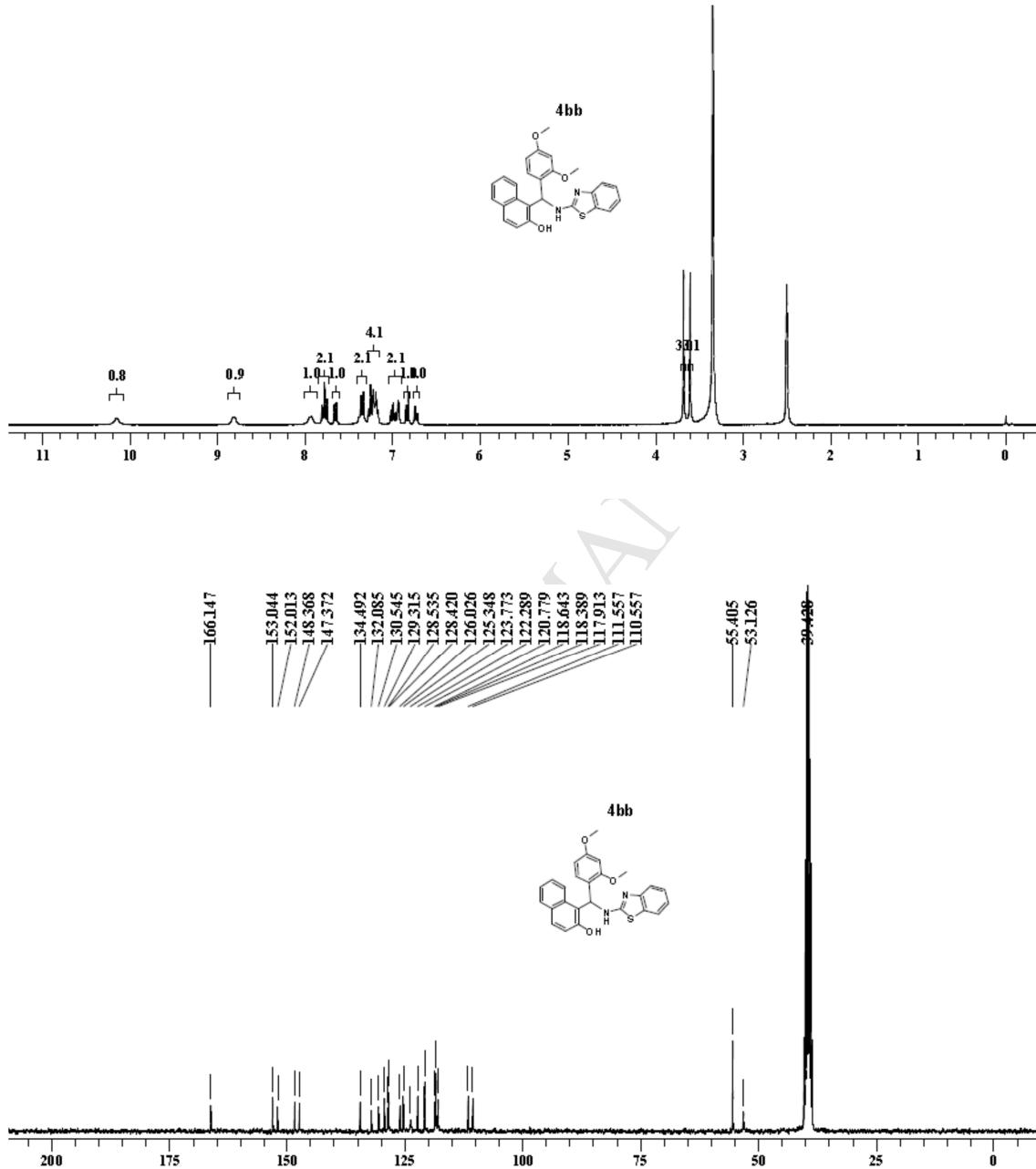
S4-4az. ^1H NMR of compound **4az**. 1-((6-chlorobenzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol.



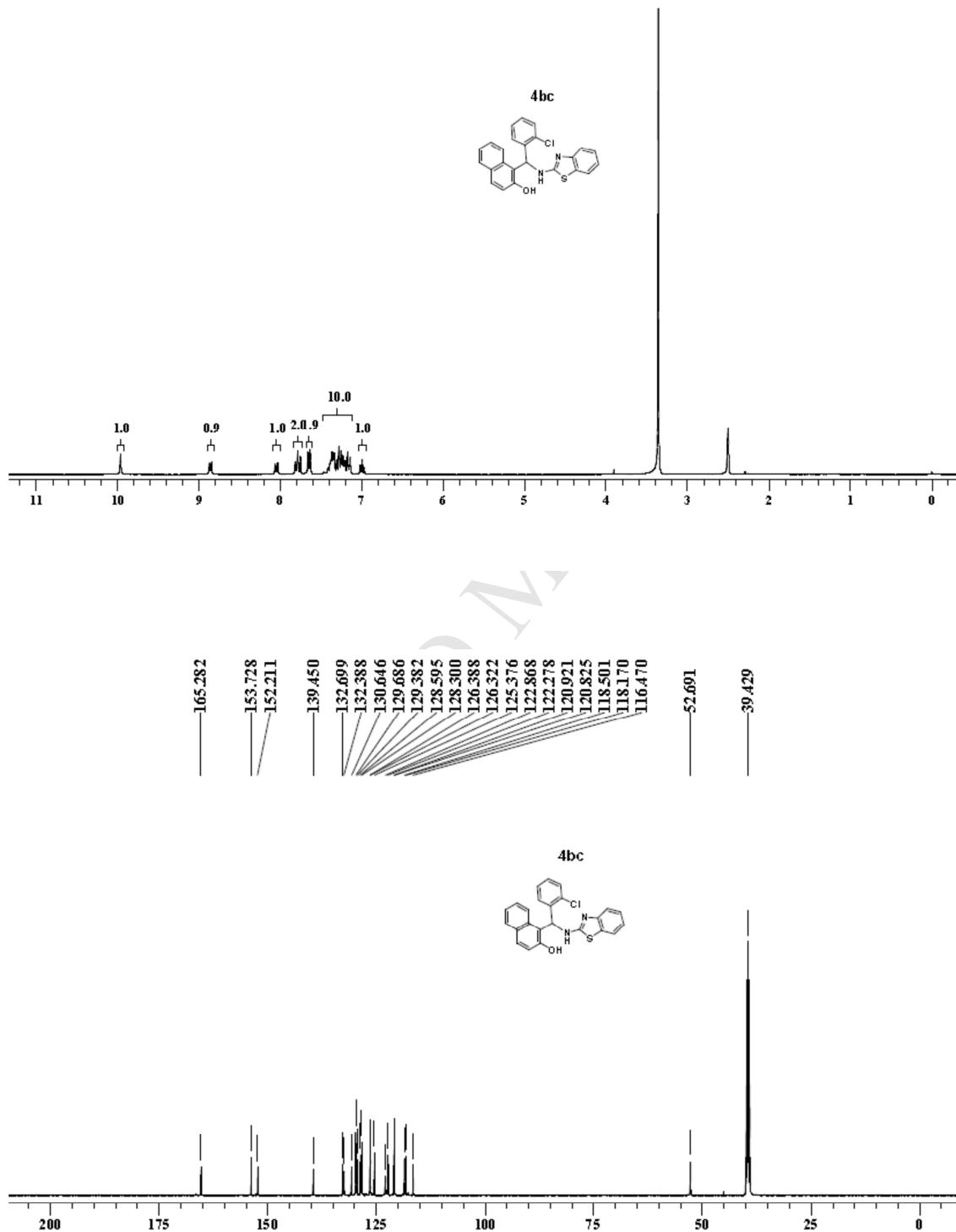
S4-4ba. ^1H NMR and ^{13}C NMR of compound **4ba**. 1-((4-methylbenzo[d]thiazol-2-ylamino)(3,4-dichlorophenyl)methyl)naphthalen-2-ol.



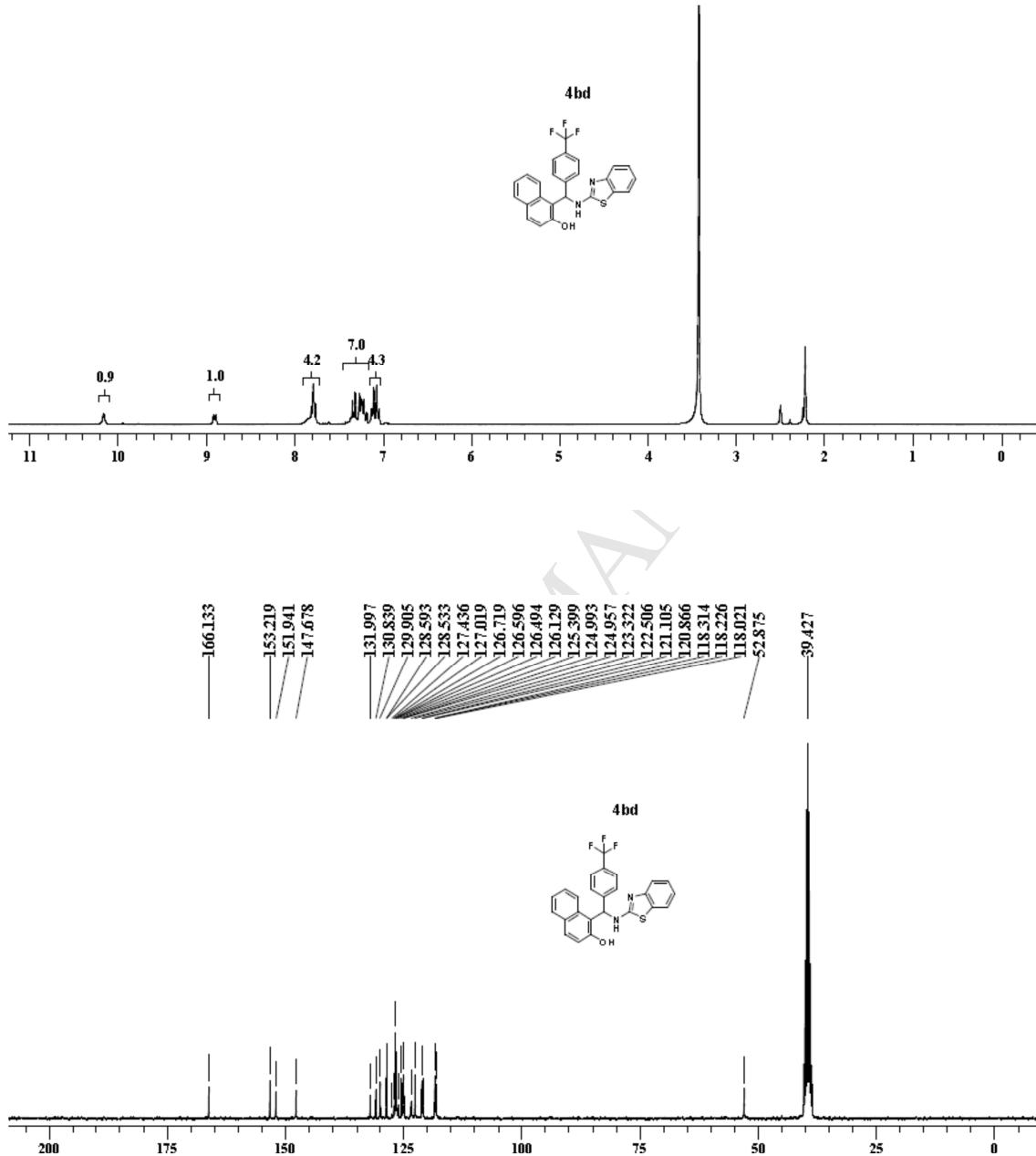
S4-4bb. ^1H NMR and ^{13}C NMR of compound **4bb**. 1-((benzo[d]thiazol-2-ylamino)(2,4-dimethoxyphenyl)methyl)naphthalen-2-ol.



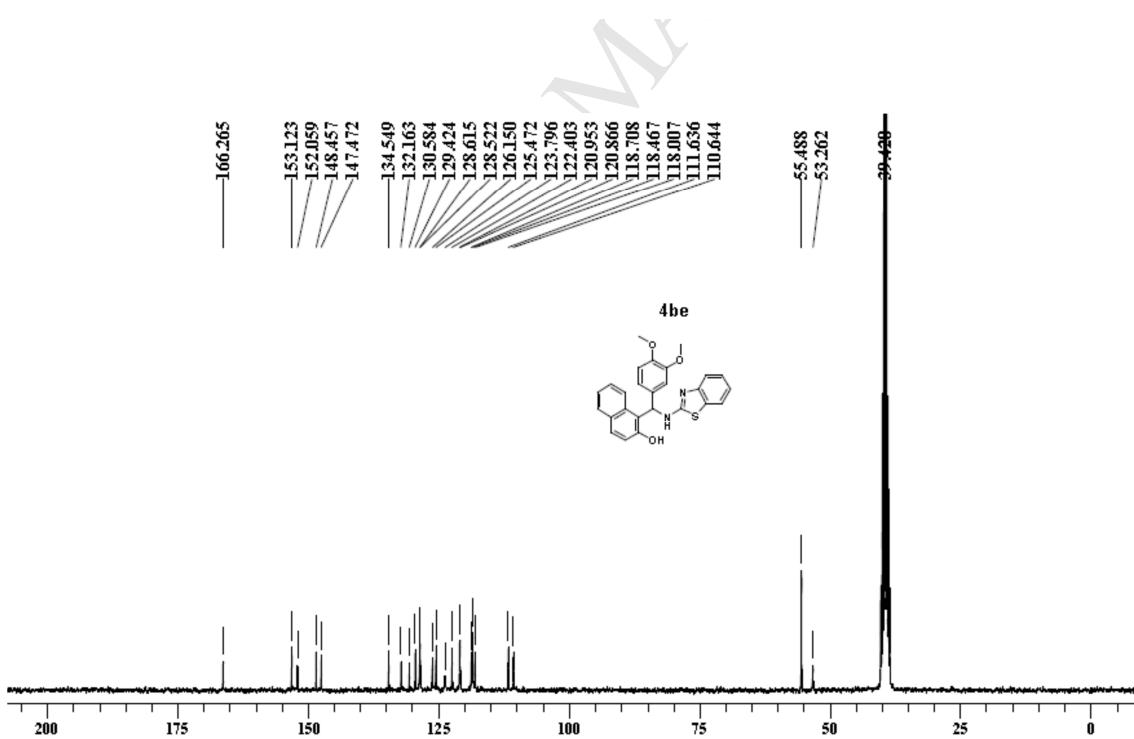
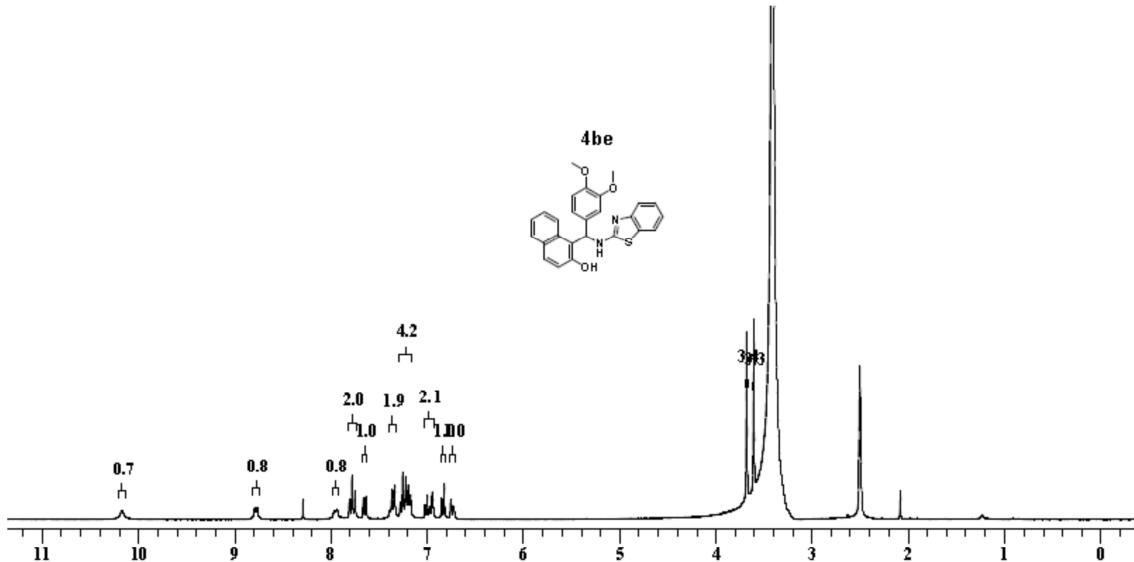
S4-4bc. ^1H NMR and ^{13}C NMR of compound **4bc**. 1-((benzo[d]thiazol-2-ylamino)(2-chlorophenyl)methyl)naphthalen-2-ol.



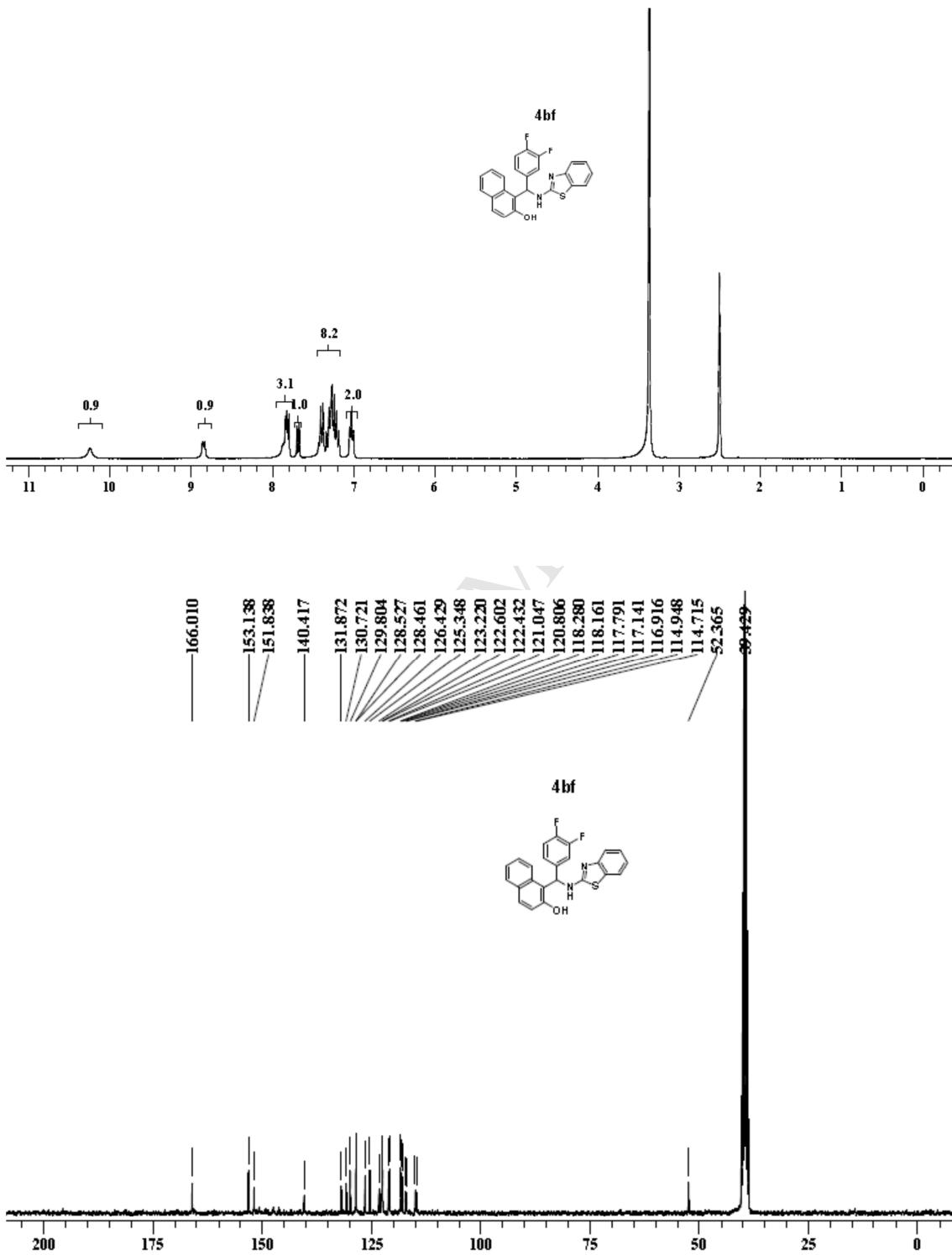
S4-4bd. ^1H NMR and ^{13}C NMR of compound **4bd**. 1-((benzo[d]thiazol-2-ylamino)(4-(trifluoromethyl)phenyl)methyl)naphthalen-2-ol.



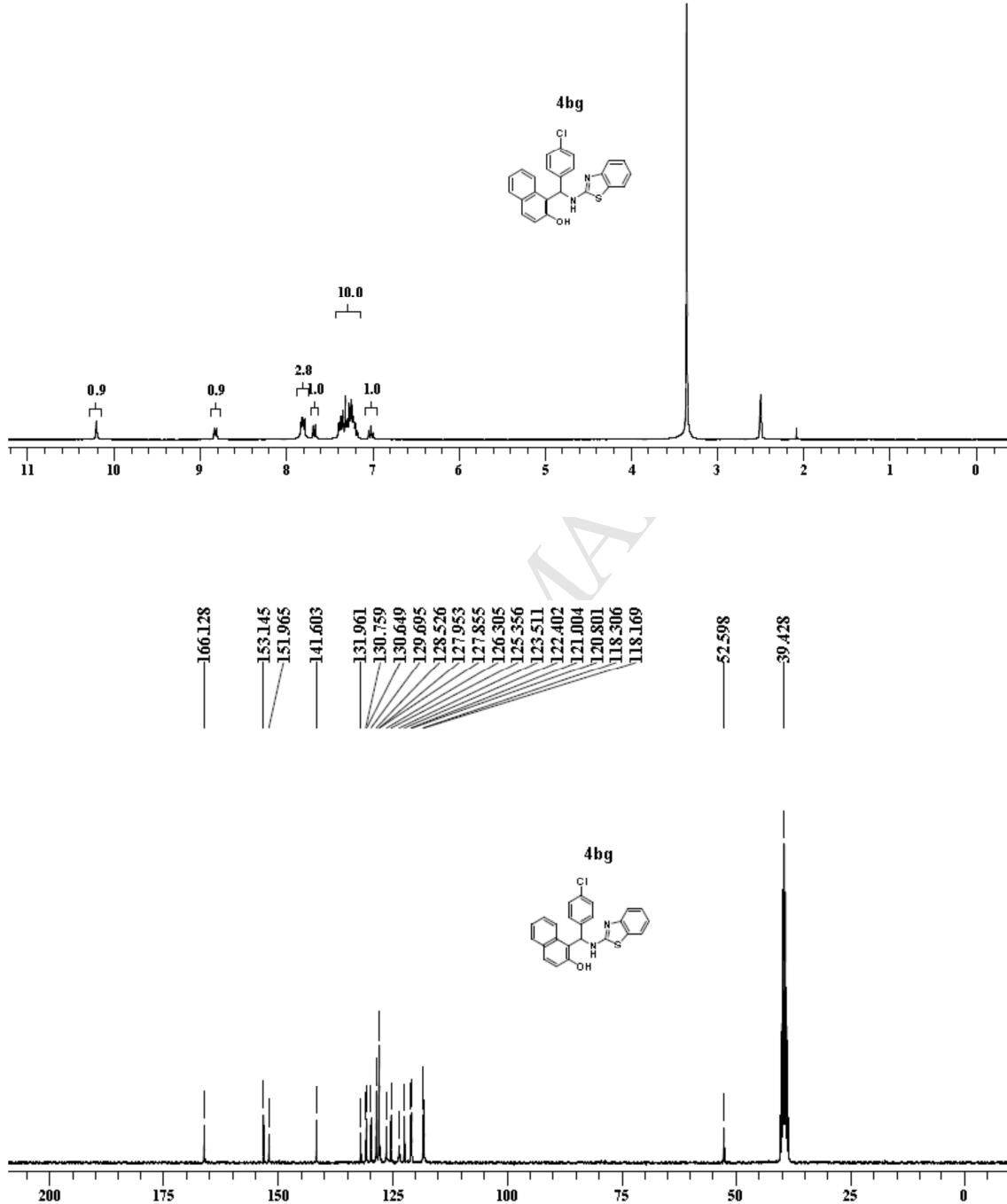
S4-4be. ^1H NMR and ^{13}C NMR of compound **4be**. 1-((benzo[d]thiazol-2-ylamino)(3,4-dimethoxyphenyl)methyl)naphthalen-2-ol.



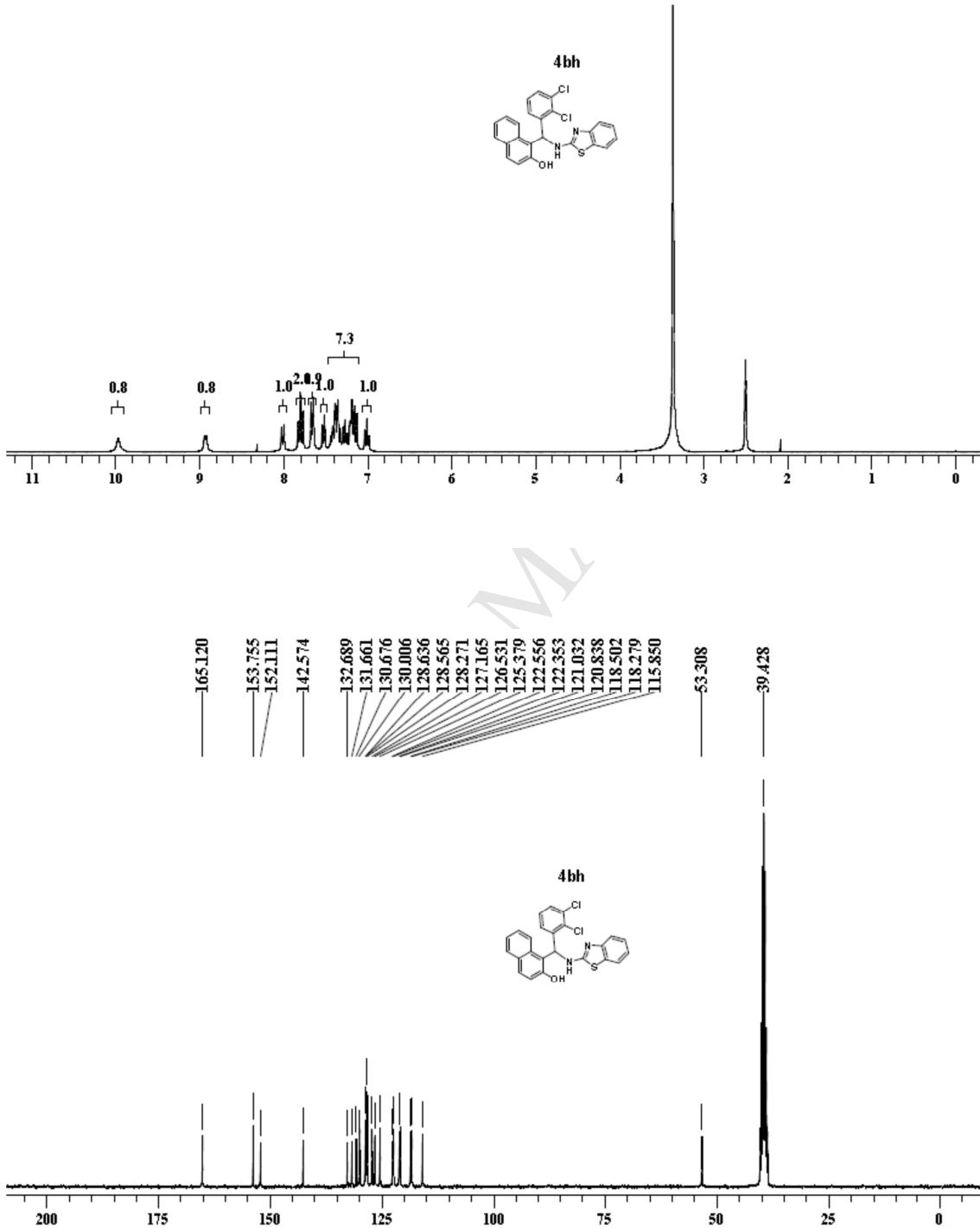
S4-4bf. ^1H NMR and ^{13}C NMR of compound **4bf**. 1-((benzo[d]thiazol-2-ylamino)(3,4-difluorophenyl)methyl)naphthalen-2-ol.



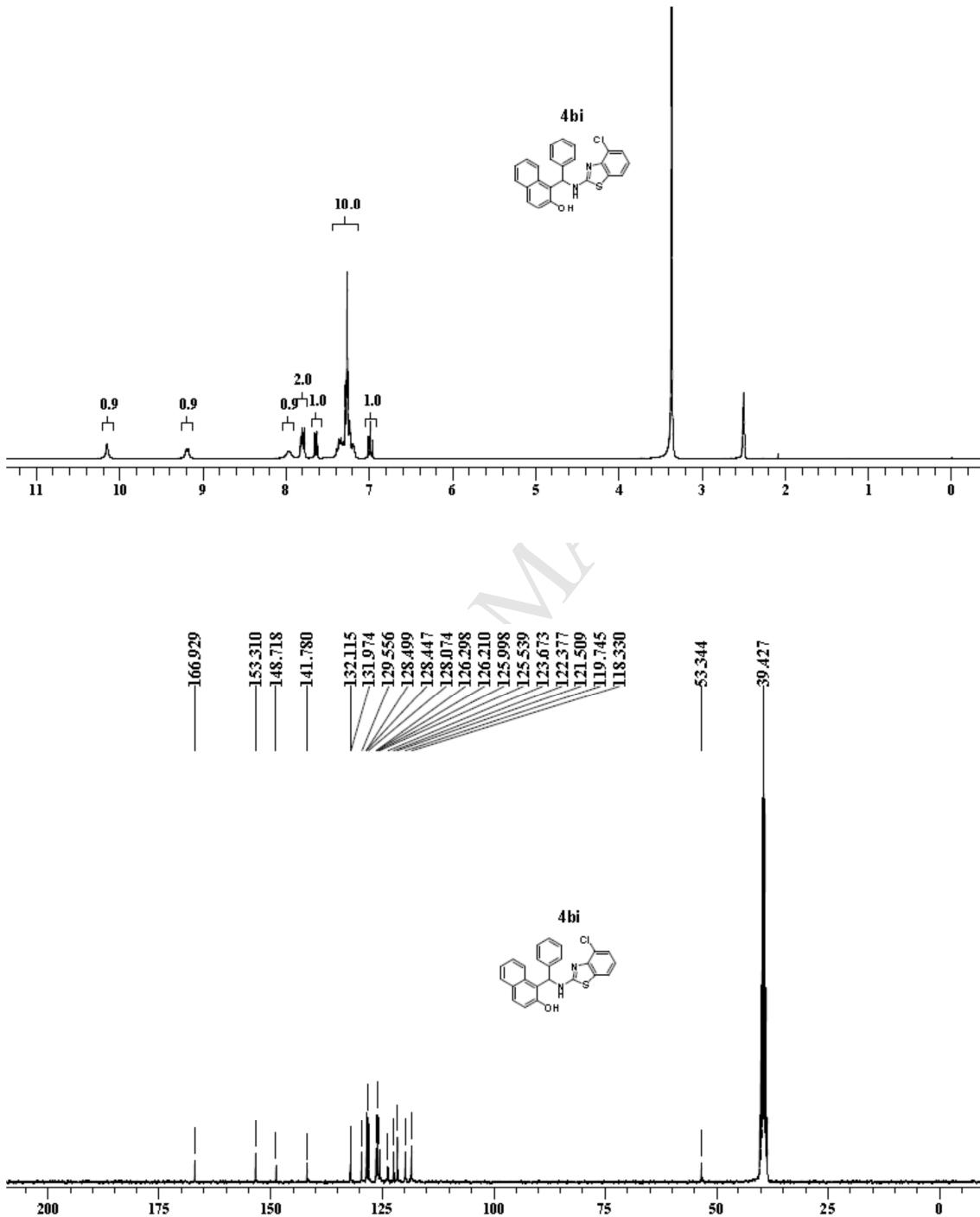
S4-4bg. ^1H NMR and ^{13}C NMR of compound **4bg**. 1-((benzo[d]thiazol-2-ylamino)(4-chlorophenyl)methyl)naphthalen-2-ol.



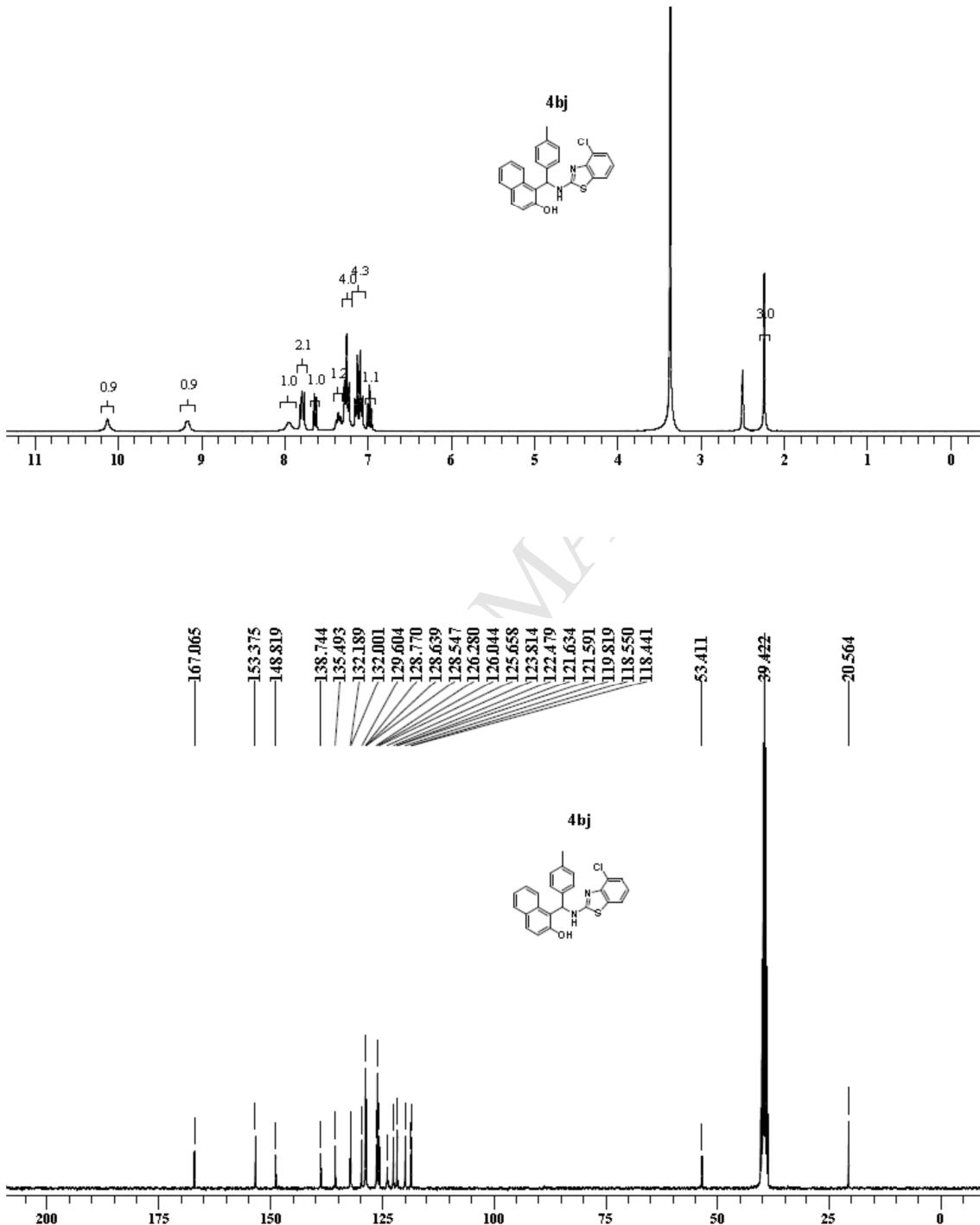
S4-4bh. ^1H NMR and ^{13}C NMR of compound **4bh**. 1-((benzo[d]thiazol-2-ylamino)(2,3-dichlorophenyl)methyl)naphthalen-2-ol.



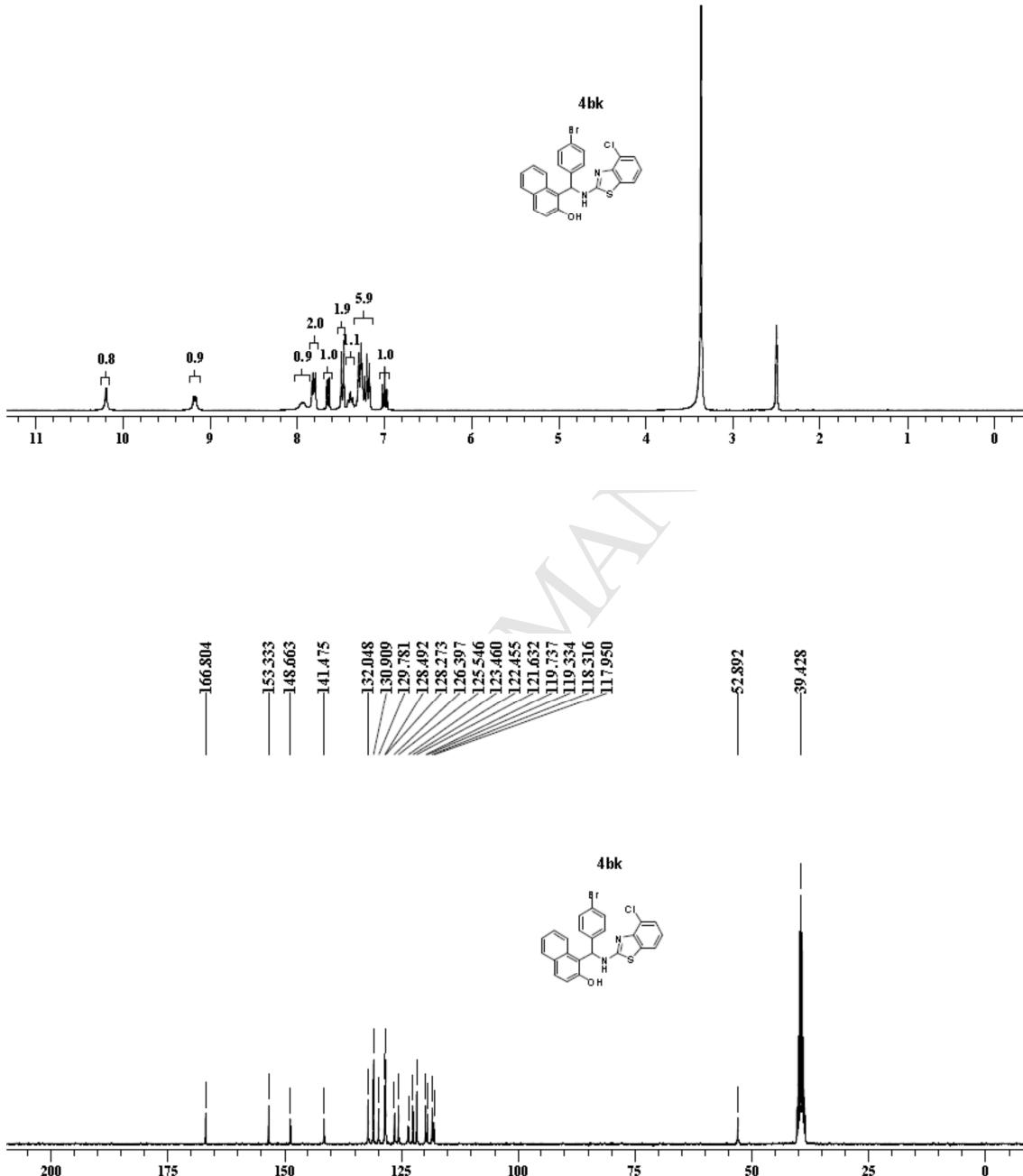
S4-4bi. ^1H NMR and ^{13}C NMR of compound **4bi**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(phenyl)methyl)naphthalen-2-ol.



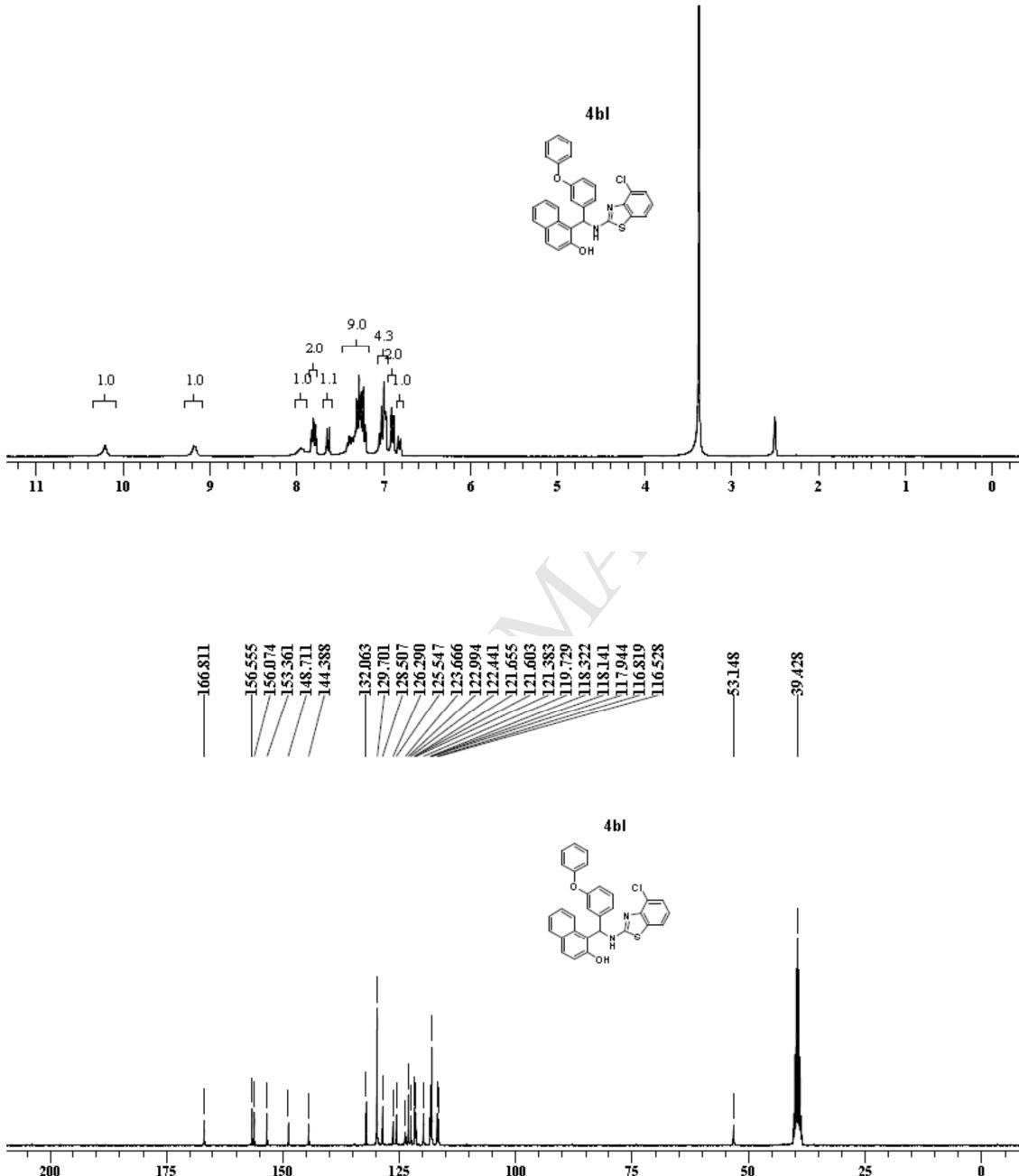
S4-4bj. ^1H NMR and ^{13}C NMR of compound **4bj**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(p-tolyl)methyl)naphthalen-2-ol.



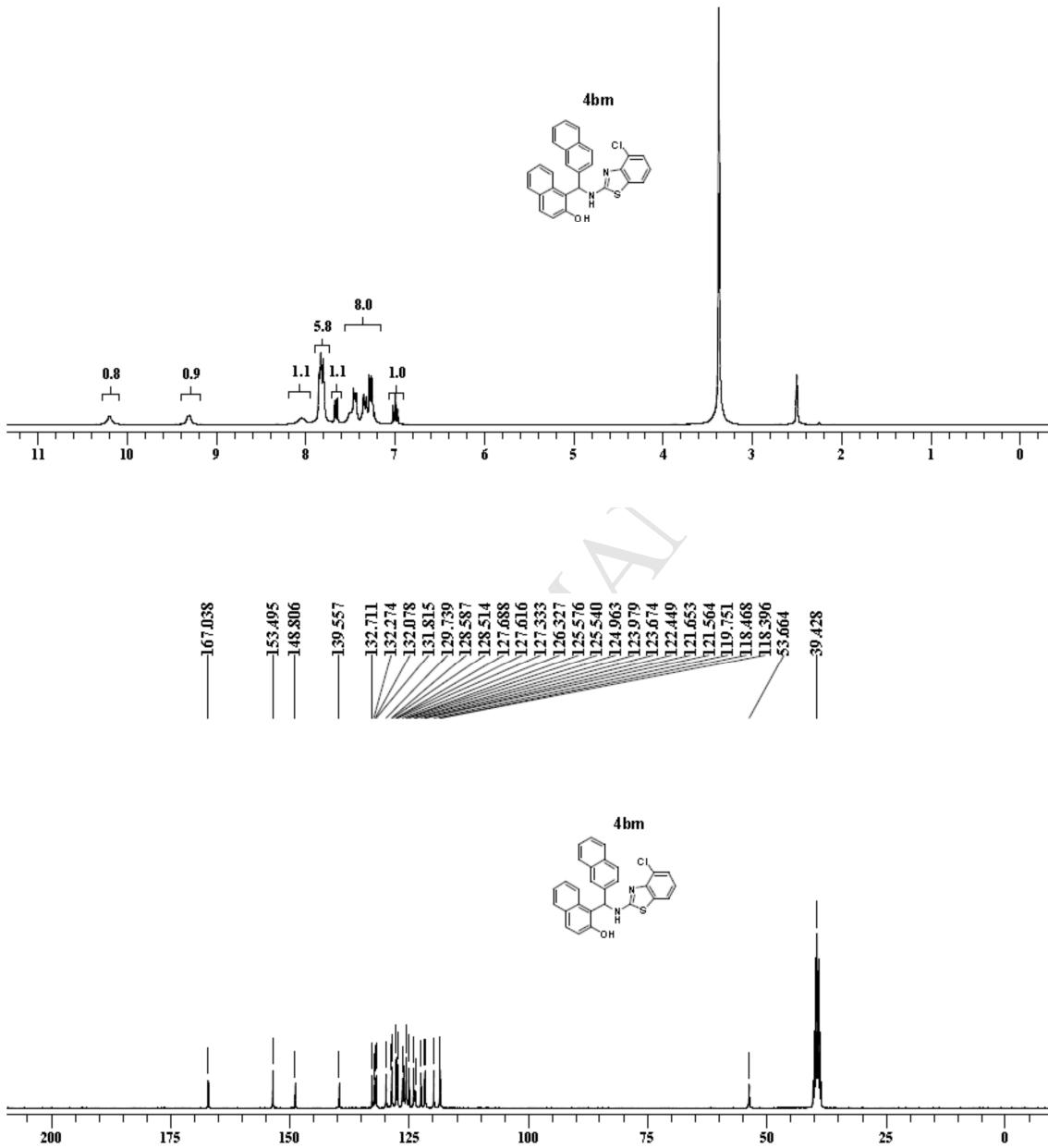
S4-4bk. ^1H NMR and ^{13}C NMR of compound **4bk**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-bromophenyl)methyl)naphthalen-2-ol.



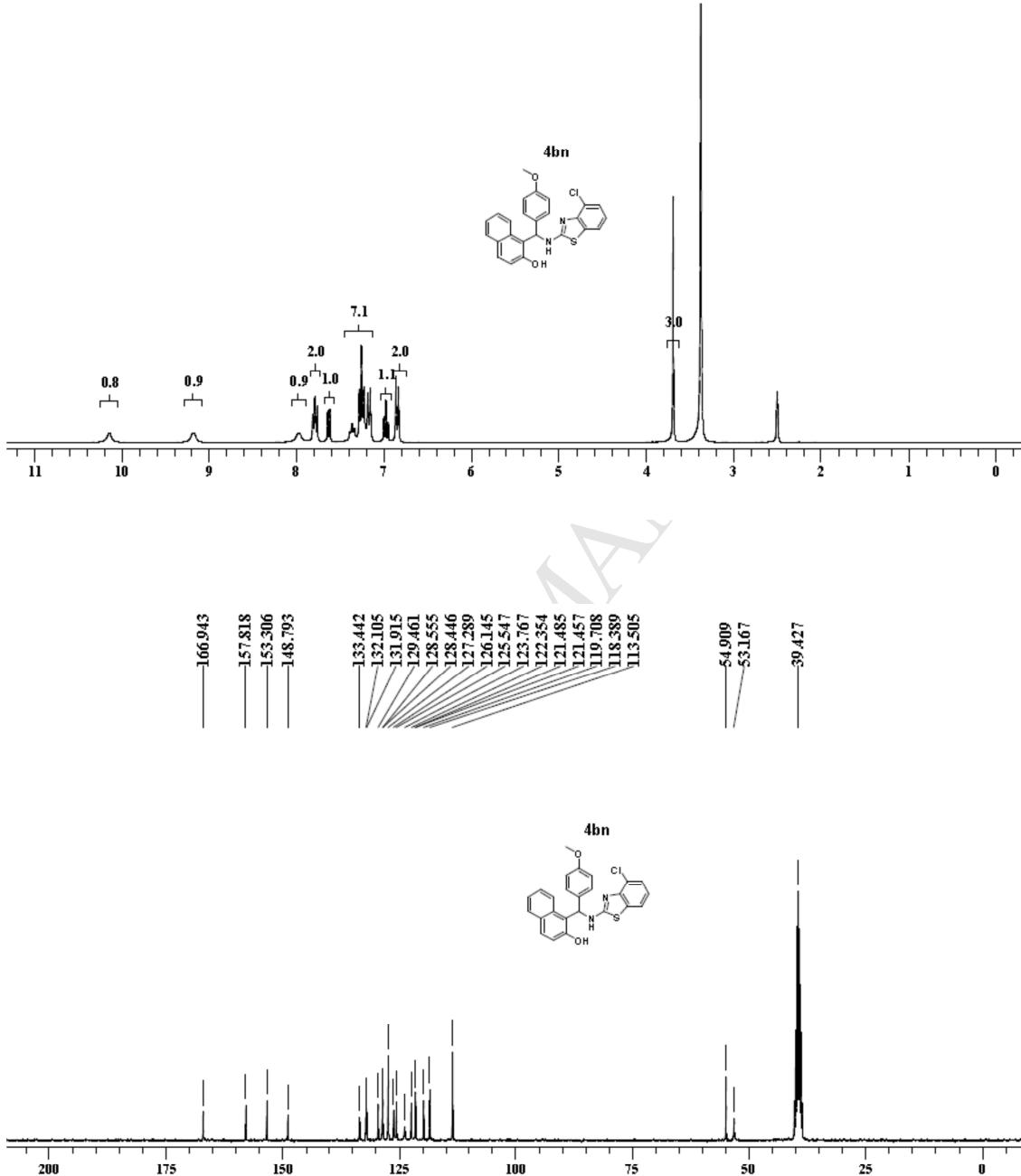
S4-4bl. ^1H NMR and ^{13}C NMR of compound **4bl**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(3-phenoxyphenyl)methyl)naphthalen-2-ol.



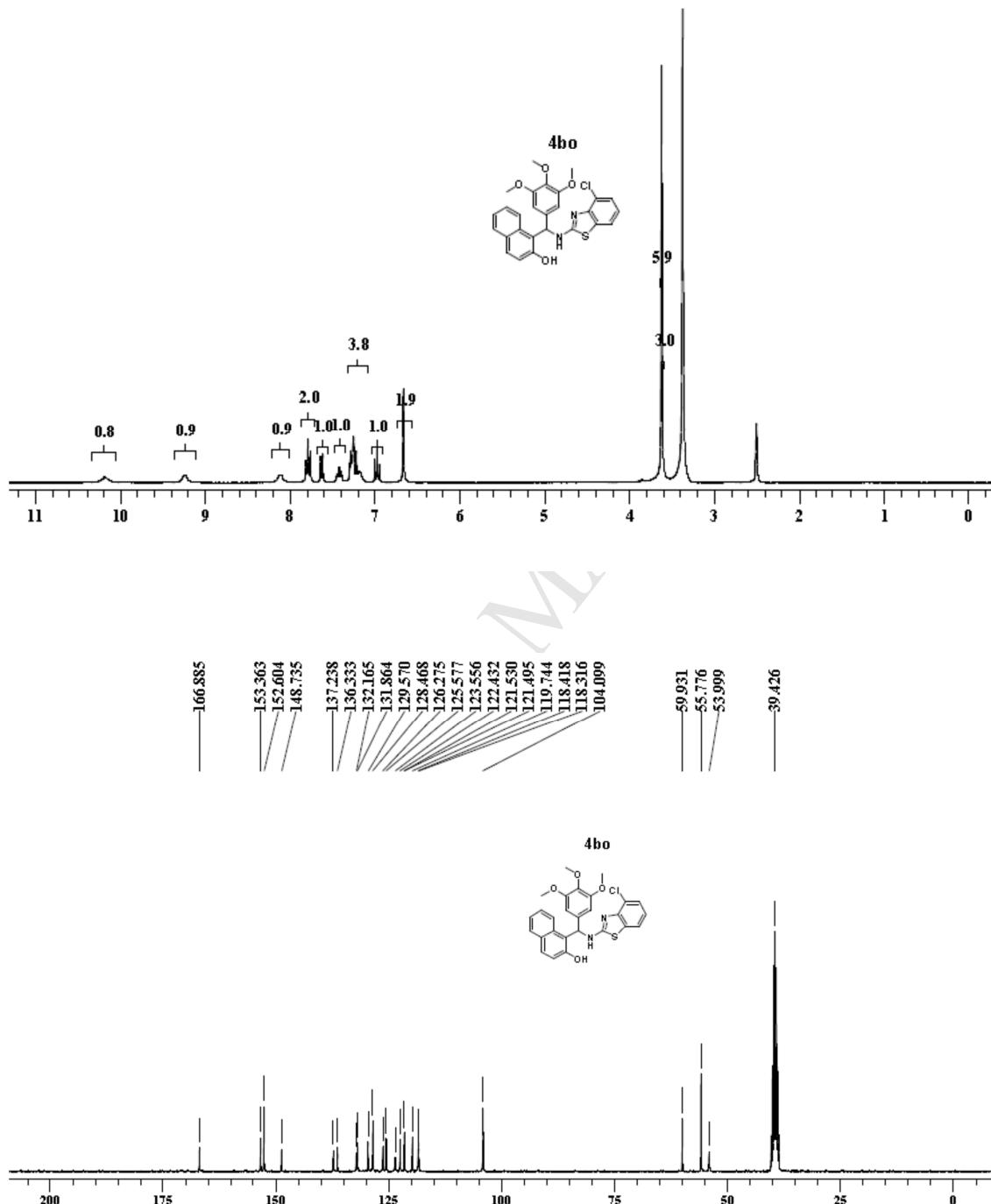
S4-4bm. ^1H NMR and ^{13}C NMR of compound **4bm**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(naphthalen-2-yl)methyl)naphthalen-2-ol.



S4-4bn. ^1H NMR and ^{13}C NMR of compound **4bn**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-methoxyphenyl)methyl)naphthalen-2-ol.



S4-4bo. ^1H NMR and ^{13}C NMR of compound **4bo**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(3,4,5-trimethoxyphenyl)methyl)naphthalene-2-ol.



S4-4bp. ^1H NMR and ^{13}C NMR of compound **4bp**. 1-((4-chlorobenzo[d]thiazol-2-ylamino)(4-(dimethylamino)phenyl)methyl)naphthalen-2-ol.

