Chapter 7

Diastereoselective Synthesis of 6,7-Dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-d][1,4]oxazepines via Sequential ArO–C Bond-Forming Intramolecular Epoxide Ring-Opening and Ar–O Bond-Forming Intramolecular S_NAr Reactions

Work of this Chapter has been *submitted* for publication.

Devi, R., Mukhopadhyay, S., Pathak, A., and Das, S. K. Diversity-oriented stereoselective synthesis of 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepines (*submitted*)

7.1. Introduction

Benzimidazole derivatives are associated with broad spectrum of bioactivities including antitumor, antidepressant, antimicrobial, antifungal, antidiabetic, analgesic, antitubercular, anti-inflammatory, and antiviral activities [1-8]. In fact, over a dozen of commercially available clinical drugs such as bendazol, bendamustine, rabeprazole, lansoprazole, telmisartan, esomeprazole etc. bear this core structure. Consequently, this ring system has been recognized as a privileged structural unit in medicinal chemistry. There has been widespread research in the design, synthesis and biological applications of diverse benzimidazole derivatives, benefitting from the versatile modification of this skeleton virtually on all positions [9-12]. Among different classes of benzimidazole derivatives, 2-arylbenzimidazoles (Figure 7.1) are a unique group of structural moieties that are regularly reported, certainly due to their easy accessibility from commercially available compounds and wide ranging applications [11].

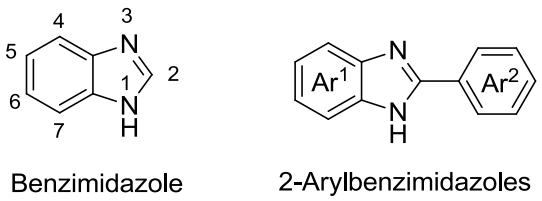


Figure 7.1. Benzimidazole and 2-arylbenzimidazoles

On the other hand, the heterocycle 1,4-benzoxazepine (Figure 7.2) belongs to the family of benzo-fused seven-membered ring systems containing two heteroatoms. The benzoxazepine core is also present in numerous pharmacological agents possessing antipsychotic, anticonvulsant, CNS depressant, antidepressant, neuroleptic, or antitumor activity among a long list of other effects [13,14]. The attractive biological profile of this core structure continues to safeguard that 1,4-benzoxazepine derivatives are noteworthy synthetic targets for organic and medicinal chemists [13,14].

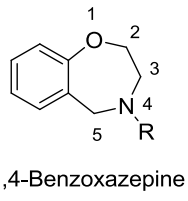


Figure 7.2. 1,4-Benzoxazepine scaffold

7.2. Background and Objectives

Synthesis of polycyclic molecules bearing two or three privileged scaffolds is an important research field in organic and medicinal chemistry. A variety of methods are available for the formation of such hybrid compounds ─ but the synthesis under complete regio-and stereocontrol with a high level of diversity points remains a challenging problem. In this context, straightforward and diversity-oriented synthetic approaches to structurally diverse benzimidazole-fused derivatives are highly anticipated to assist rapid development of polycyclic heteroaromatic compound-based drug leads.

Among the large numbers of benzimidazole-based small organic molecules, fused polycyclic benzimidazoles have attracted considerable interest due to their proficiency to display a wide range of biological and therapeutical activities. Commonly studied benzimidazole fused polycyclic heterocycles include pyrido[1,2-*a*]benzimidazoles, benzimidazo[1,2-*a*]quinolines, pyrimido[1,2-*a*]benzimidazoles, benzo[4,5]imidazo[2,1-*a*]isoquinolines, pyrrolo[1,2-*a*]benzimidazoles, benzo[4,5]imidazo[2,1-*b*]thiazoles, and imidazo[1,2-*a*]benzimidazoles [15].

The occurrence of fused polycyclic benzimidazoles in biologically relevant small molecules demands the synthesis of their structurally diverse analogues. In this perspective, 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepines **1** (Figure 7.3) ─ a particular type of fused polycyclic benzimidazoles have rarely been studied. To the best of our knowledge, the sole example of the synthesis of **1** has been reported by Chan et al [16]. These hybrid molecules, more specifically, can be regarded as a fusion of benzimidazole and 1,4-benzoxazepine skeletons, or rotationally restricted 2-arylbenzimidazoles.

This chapter of the thesis deals with the synthesis of 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepines **1** and chroman-linked 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepines **2** (Figure 7.3).

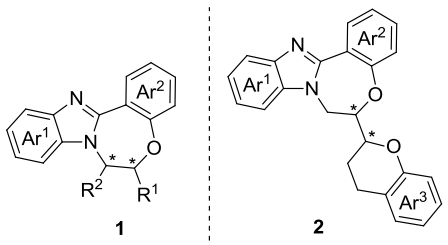
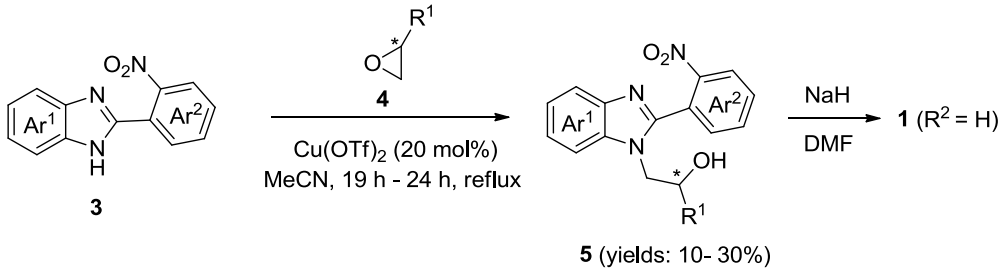


Figure 7.3. The chemical structures of the designed target compounds

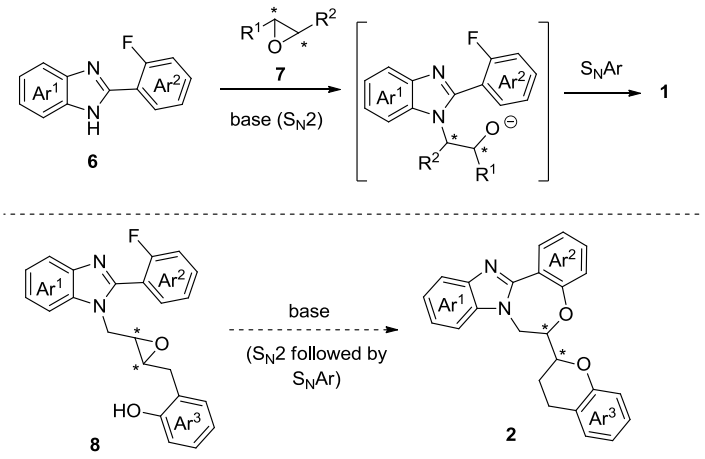
Synthesis of **1** has previously been achieved from 2-(2-nitrophenyl)-benzimidazoles **2** and terminal epoxides **3** in a two-step reaction sequence (Scheme 7.1) [16].



Scheme 7.1. Literature method for the preparation of 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo [1,2-*d*][1,4]oxazepines

The work mainly involved $Cu(OTf)_2$-catalyzed intermolecular ring-opening of terminal epoxides by 2-(2-nitrophenyl)-1*H*-benzimidazoles, followed by NaH-mediated intramolecular nucleophilic aromatic substitution (S_NAr) of the resulting epoxide- ring-opening products. Although effective at supplying **1**, the key issue with the route was the very low overall yield. More particularly, the epoxide ring-opening reactions (first step) were poor yielding (10-30%) ─ a major drawback of this work. Two factors were assumed to be responsible for this low yield. First, the free N-H group of 2-(2-nitrophenyl)-1*H*-benzimidazoles is poorly nucleophilic. Second, the catalytic cycle stopped relatively quickly due to the formation of unreactive Cu-complexes. Moreover, as far as epoxide substrates are concerned, only terminal epoxides were employed for this study.

To address these issues, first of all, the low yielding epoxide-ring opening step needed to be improved. We predicted that a base-mediated ring opening of epoxides by benzimidazoles could be more effective due to the higher nucleophilicity of N^- compared to N-H. Thus, we envisioned that 2-(2-fluorophenyl)-benzimidazoles **6** and epoxides **7** would provide **1** via a base-mediated one-pot, two-step reaction sequence that features an intermolecular epoxide ring-opening reaction, followed by an intramolecular S_NAr reaction (Scheme 7.2, upper panel). We also anticipated that intramolecular versions of both the steps are possible with substrates **8** which would serve as precursors for chroman-linked 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepines **2** (Scheme 7.2, lower panel). Overall, we believed that compare to the reported work, our design strategy would have additional advantageous features of much higher yield and more versatility with larger diversification positions.



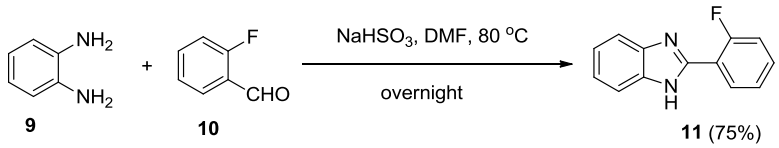
Scheme 7.2. Our envisioned strategy for the preparation of 6,7-dihydrobenzo[*f*]benzo[4,5] imidazo[1,2-*d*][1,4]oxazepines and their chroman-linked analogues

7.3. Results and Discussion

7.3.1. Synthesis of 6,7-Dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepines

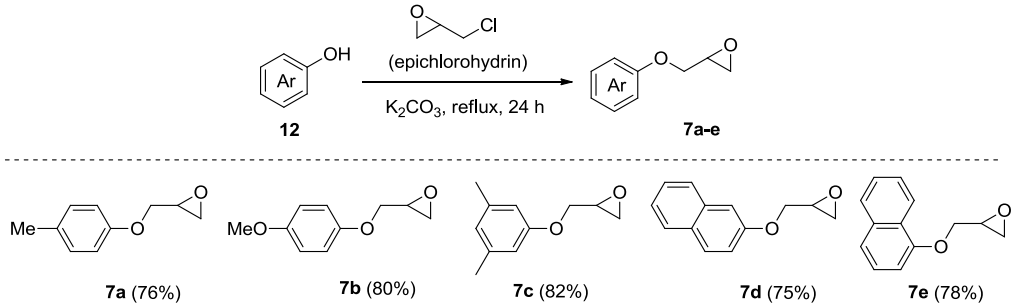
7.3.1.1. Preparation of Epoxide Substrates

Our study began with the synthesis of 2-(2-fluorophenyl)-benzimidazole **11**. Thus, a mixture of *o*-phenylenediamine **9**, 2-fluorobenzaldehyde **10** and $NaHSO_3$ in DMF was heated at 80 ^oC to obtain compound **11** in 75% yield (Scheme 7.3).



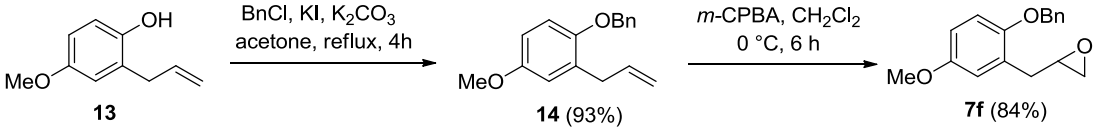
Scheme 7.3. Synthesis of 2-(2-fluorophenyl)-benzimidazole

Next, we synthesized a set of five aryl glycidyl ethers **7a-e** in good yields by treating phenols **12** with K_2CO_3 in epichlorohydrin under reflux conditions for 24 h (Scheme 7.4).



Scheme 7.4. Synthesis of aryl glycidyl ethers

Synthesis of another terminal epoxide substrate **7f** is shown in the Scheme 7.5. Benzylation of 2-allyl-4-methoxyphenol **13** furnished compound **14** in 93% yield. Next, epoxidation of **14** with *m*-CPBA provided epoxide **7f** in 84% yield.



Scheme 7.5. Synthesis of terminal epoxide 7f

For our study, we also used commercially available epoxide 2-phenyloxirane **7g** and literature known epoxide 2-(4-methoxyphenyl)oxirane **7h** (Figure 7.4) [17].

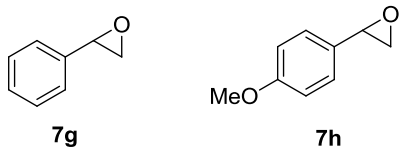
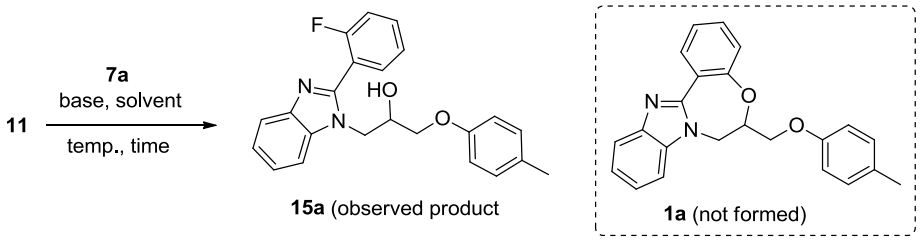


Figure 7.4. 2-Aryloxiranes 7g and 7h

7.3.1.2. Ring-Opening – Cyclization of Epoxides with 2-(2-Fluorophenyl)-benzimidazole

With 2-(2-fluorophenyl)-benzimidazole **11** and epoxides **7a-h** in hand, we turned our attention towards the two-step synthesis of 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepines. For the validation and optimization studies of the initial intermolecular epoxide ring-opening reaction, synthesis of **1a** from **11** and **7a** was selected as a model reaction (Table 7.1). Thus, treatment of **11** with **7a** in DMF in the presence of K_2CO_3 (1.5 equiv) at rt for 24 h did not provide any product – only unreacted starting materials were recovered (Table 7.1, entry 1). Next, we carried out this reaction at heating condition (80 ^oC) for 12 h (entry 2). The reaction furnished only the epoxide ring-opening product **15a** (yield: 87%) – **1a** was not observed. Nevertheless, this was an important improvement (with respect to the literature report; *vide supra*) in the *N*-alkylation of benzimidazoles using epoxides as alkylating agents. With increased amount of K_2CO_3 (2.5 equiv) (entry 3) or elevated reaction temperature (entry 4), **15a** was formed also as the sole product, albeit in slightly lower yield. The reaction did not proceed at all when NaH (1.15 equiv) was employed as a base in DMF at rt (entry 15). However, employing NaH (1.15 equiv) in DMF at 60 ^oC provided a complex product mixture (TLC) from which **15a** was isolated in very low yield (40%) (entry 6).

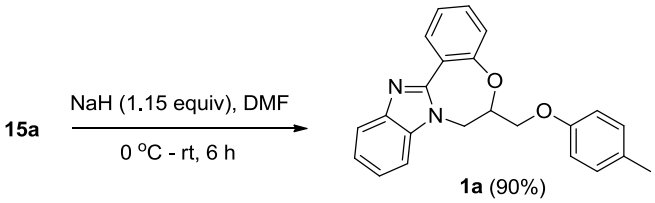
Table 7.1. Optimization of the reaction conditions for the epoxide ring-opening reaction[a]



entry	base (equiv)	solvent	temp (^{o}C)	time (h)	yield[b] (%)
1	K_2CO_3 (1.5)	DMF	rt	12	nr
2	**K_2CO_3 (1.5)**	**DMF**	**80**	**12**	**87**
3	K_2CO_3 (2.5)	DMF	80	12	84
4	K_2CO_3 (1.5)	DMF	120	12	80%
5	NaH (1.15)	DMF	rt	12	nr
6	NaH (1.15)	DMF	60	12	40%

[a]Reaction conditions: **11** (0.5 mmol, 1.0 equiv, **7a** (0.5 mmol, 1.0 equiv) and base in DMF (5 mL);
[b]Isolated yields

With the successful synthesis of epoxide ring-opening product **15a** with K_2CO_3 (1.5 equiv) in DMF at 60 ^{o}C, our next job was to convert it into the corresponding benzoxazepine-fused benzimidazole **1a**. Towards this objective, compound **15a** was treated with NaH (1.15 equiv) in DMF at rt for 6 h (Scheme 7.6). We were pleased to find that **15a** underwent smooth intramolecular S_NAr cyclization to provide **1a** in high yield (90%).



Scheme 7.6. Synthesis of 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1a

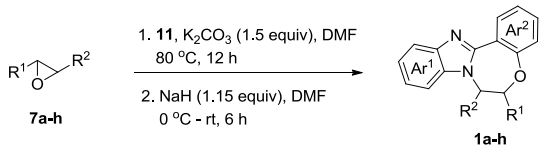
At this point, the practicability of our method to obtain a 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine such as **1a** in high overall yield had clearly been established; however we sensed that further simplification of this two-step synthetic protocol via process intensification would be more useful. Given the very clean nature of the epoxide ring-opening step, we anticipated that chromatographic isolation of the intermediate compound **15a** (epoxide ring-opening product) could be

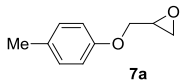
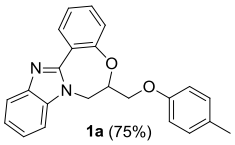
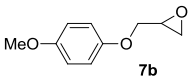
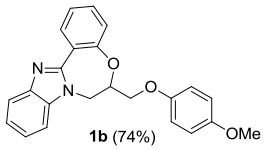
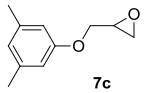
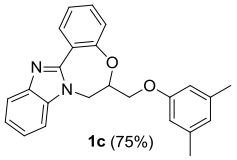
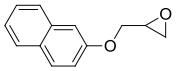
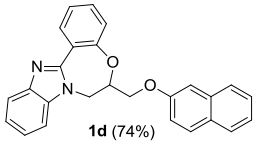
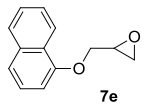
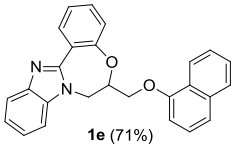
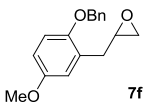
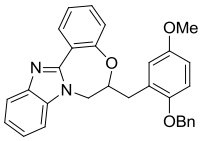
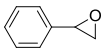
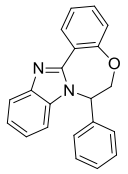
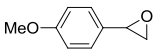
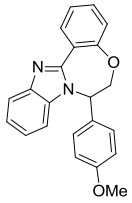
avoided, and so we began investigating a modified protocol that would need a sole chromatographic purification to isolate **1a**. In this context, unfortunately, performing the two-step synthesis in a one-pot fashion was problematic as no base (including NaH and K_2CO_3) was found to be suitable to deliver the final polycyclic product in high yield via this protocol. Having been unable to develop the one-pot protocol, we turned our focus to other options. Thus, a mixture of **11** (1 equiv), **7a** (1 equiv) and anh. K_2CO_3 (1.5 equiv) in anh. DMF was heated at 80 ^oC for 12 h, and then the reaction mixture was subjected to usual workup. Crude **15a** thus obtained was subsequently treated with NaH (1.15 equiv) in anh. DMF at rt for 6 h (Table 7.2, entry 1). This modified protocol delivered **1a** in 76% isolated yield over two steps (Table 7.2, entry 1). The overall yield was comparable with that of the stepwise protocol. With these findings, we then utilized **11** and the remaining epoxide substrates **7b-h** to synthesize polycyclic **1b-h** in good yields (Table 7.2, entries 2-8). While the initial nucleophilic attack of **11** (in the first step of intermolecular epoxide ring-opening) took place on the terminal side of the epoxide ring of **7a-f**, 2-aryloxiranes **7a** and **7h** experienced it at the benzylic position. These results did not come as a surprise since the benzylic position of 2-aryloxiranes is known to be the more electrophilic site whereas in case of non-benzylic terminal epoxides, this reactivity is almost completely restricted on the terminal carbon. It is also worth noting that the synthesis of **1f** is particularly appealing, since the benzyloxy substituent offers great prospects for further synthetic manipulations (entry 6).

7.3.2. Synthesis of a Chroman-Linked 6,7-Dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine

Inspired by the above-described successful synthesis of 6,7-dihydrobenzo [*f*]benzo[4,5] imidazo[1,2-*d*][1,4]oxazepines, we planned to apply this methodology for the synthesis of a chroman-linked 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine derivative. Thus, 2-allylphenol **16** was benzylated with benzyl bromide and anhd. K_2CO_3 to obtain compound **17** which was then converted into epoxy alcohol **21** following the steps described in the Scheme 6.4, **Chapter 6**. Tosylation of **21** with TsCl and Et_3N furnished epoxy tosylate **22** which was then used for the alkylation of 2-(2-fluorophenyl)-benzimidazole **11** in the presence of K_2CO_3 to obtain compound **23**.

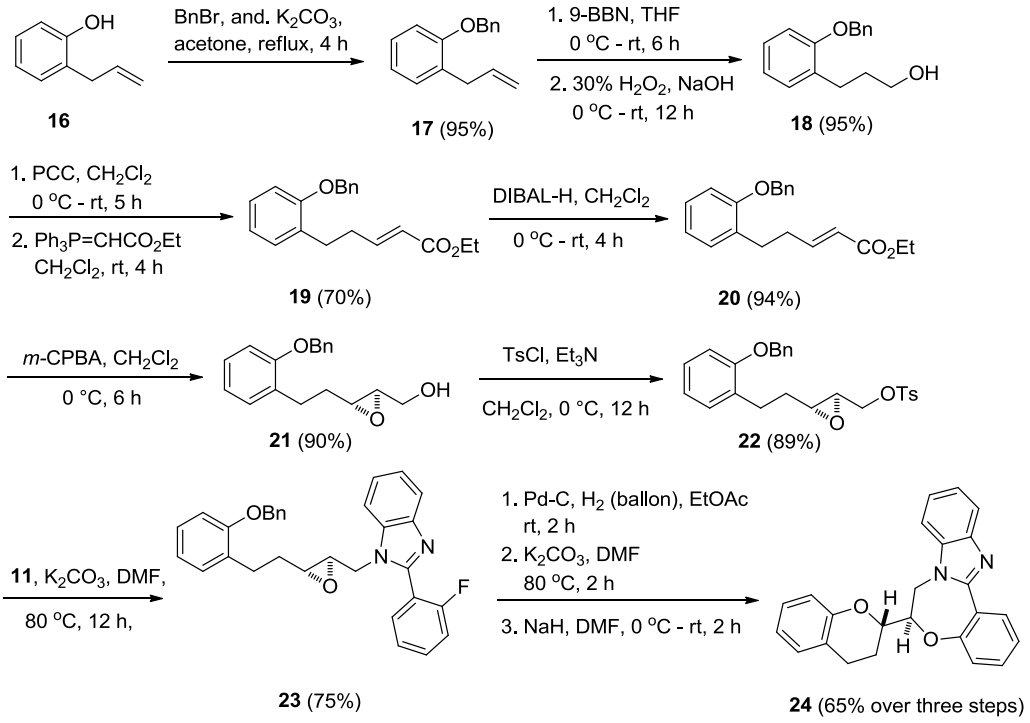
Table 7.2. Optimization of the reaction conditions for the epoxide ring-opening reaction[a]



entry	epoxide	benzimidazole-based polycycle
1	 **7a**	 **1a** (75%)
2	 **7b**	 **1b** (74%)
3	 **7c**	 **1c** (75%)
4	 **7d**	 **1d** (74%)
5	 **7e**	 **1e** (71%)
6	 **7f**	 **1f** (77%)
7	 **7g**	 **1g** (73%)
8	 **7h**	 **1h** (77%)

[a]Reaction conditions: **7** (0.5 mmol, 1.0 equiv), **11** (0.5 mmol, 1.0 equiv) and K_2CO_3 (0.75 mmol, 1.5 equiv) in DMF (5 mL) for the first step; NaH (0.575 mmol, 1.15 equiv), DMF (5 mL) for the second step. [b]The percentage values indicate overall isolated yields.

Compound **23** was then converted to **24** employing a three-step protocol. Thus, exposure of **23** to hydrogenation conditions (Pd-C, H_2) caused chemoselective removal of the benzyl group; treatment of the resulting crude phenolic derivative with K_2CO_3 resulted in the formation of the corresponding chroman derivative (via an intramolecular epoxide ring-opening cyclization), which was subjected to an intramolecular S_NAr reaction in the presence of NaH to furnish **24**.



Scheme 7.7. Synthesis of chroman-linked 6,7-dihydrobenzo[*f*]benzo[4,5] imidazo[1,2-*d*][1,4] oxazepine

7.4. Conclusion

In summary, we have demonstrated the efficiency of sequential epoxide ring-opening and intramolecular S_NAr reactions in the synthesis of benzoxazepine-fused benzimidazoles (6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepines). Compared with the literature method, the synthetic strategy reported herein has the advantages of readily available starting materials, structural diversity of products, and high overall yields. Moreover, we have also demonstrated that the protocol is also suitable to construct hitherto unreported chroman-linked 6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepines. The synthetic route appears to

be fairly general one, and should be subject to structural variation with respect to substituent diversity on all of the three aromatic subunits and the epoxide-bearing arm.

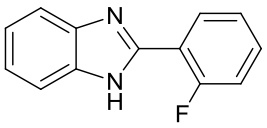
7.5. Experimental Section

7.5.1. General Remarks

Same as described in the **Chapter 2**, **Section 2.6.1** of this thesis.

7.5.2. Preparation of Compounds

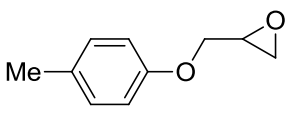
2-(2-Fluorophenyl)-1*H*-benzo[*d*]imidazole 11:



11

A mixture of *o*-phenylenediamine **9** (4.0 g, 29.36 mmol), *o*-fluorobenzaldehhyde **10** (2.87 g, 29.36 mmol) and $NaHSO_3$ (9.16 g, 88.08 mmol) in DMF (50 mL) was heated at 80 ^oC for overnight. The reaction mixture was cooled down to rt and then poured into ice-water. The solid compound that separated out was filtered off, washed with water several times, dried and then recrystallized from its solution in EtOAc and hexanes to afford the title compound **11** as a light yellow crystalline solid. mp: 270-277 °C; Yield: (4.67 g, 75%); ^1H NMR (400 MHz, DMSO-d6): δ 8.65 (s, 1H), 8.52 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 8.16-8.14 (m, 2H), 7.93 (t, *J* = 8.0 Hz, 1H), 7.71-7.64 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d6): δ 173.8, 168.4, 136.5, 132.3, 131.8, 131.4, 130.8, 129.3, 127.1, 125.8, 124.6, 117.6, 112.8. The spectral data were in complete agreement with the literature data [18].

2-((*p*-Tolyloxy)methyl)oxirane 7a:

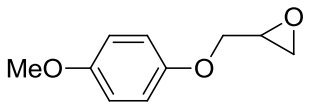


7a

A mixture of 4-methylphenol (1.5 g, 13.87 mmol) and anh. K_2CO_3 (2.29 g, 16.64 mmol) in epichlorohydrin (10 mL) was refluxed for 24 h. After allowing cooling to rt, the reaction mixture was poured into water (40 mL) and extracted with EtOAc (25 mL × 3). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4,

and filtered. The solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to afford **7a** as a colorless oil (1.73 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09–7.07 (m, 2H), 6.83-6.75 (m, 2H), 4.18 (dd, *J* = 11.0, 3.1 Hz, 1H), 3.93 (dd, *J* = 11.0, 5.6 Hz, 1H), 3.35–3.33 (m, 1H), 2.90–2.88 (m, 1H), 2.75–2.74 (m, 1H), 2.28 (s, 3H). The spectral data were in complete agreement with the literature data [19].

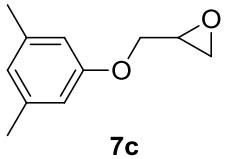
2-((4-Methoxyphenoxy)methyl)oxirane 7b:



7b

A mixture of 4-methoxyphenol (2.0 g, 16.11 mmol) and anh. K_2CO_3 (2.67 g, 19.33 mmol) was reacted in epichlorohydrin (10 mL) following the procedure described for **7a**. The crude residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to afford **7b** as a white semi-solid (2.32 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.94-6.81 (m, 4H), 4.19 (dd, *J* = 11.0, 3.2 Hz, 1H), 3.94 (dd, *J* = 11.1, 5.6 Hz, 1H), 3.79 (s, 3H), 3.40-3.32 (m, 1H), 2.92 (t, *J* = 4.5 Hz, 1H), 2.77 (dd, *J* = 5.0 Hz, 2.6 Hz, 1H). The spectral data were in complete agreement with the literature data [20].

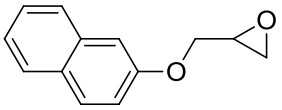
2-((4-Methoxyphenoxy)methyl)oxirane 7c:



7c

A mixture of 3,5-dimethylphenol (1.5 g, 12.27 mmol) and anh. K_2CO_3 (2.03 g, 14.72 mmol) was reacted in epichlorohydrin (10 mL) following the procedure described for **7a**. The crude residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to afford **7c** as a white solid (1.79 g, 82%). mp: 62–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (s, 3H), 4.18 (dd, *J* = 3.2, 11.0 Hz, 1H), 3.93-3.89 (m, 1H), 3.76 (s, 6H), 3.35–3.33 (m, 1H), 2.90 (t, *J* = 4.5 Hz, 1H), 2.75 (dd, *J* = 2.6, 4.9 Hz, 1H). The spectral data were in complete agreement with the literature data [21].

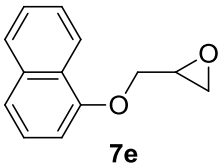
2-((Naphthalen-2-yloxy)methyl)oxirane 7d:



7d

A mixture of 2-naphthol (2.0 g, 13.87 mmol) and anh. K_2CO_3 (2.29 g, 16.64 mmol) was reacted in epichlorohydrin (10 mL) following the procedure described for **7a**. The crude residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to afford **7d** as a white foamy solid (2.08 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 -7.69 (m, 3H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.37-7.31 (m, 1H), 7.18 (dt, *J* = 8.7, 4.4 Hz, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 4.34 (dd, *J* = 11.0, 3.1 Hz, 1H), 4.07 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.48-3.37 (m, 1H), 2.99-2.89 (m, 1H), 2.81 (dd, *J* = 4.9, 2.7 Hz, 1H). The spectral data were in complete agreement with the literature data [22].

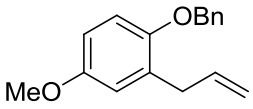
2-((Naphthalen-1-yloxy)methyl)oxirane 7e:



7e

A mixture of 1-naphthol (2.0 g, 13.87 mmol) and anh. K_2CO_3 (2.29 g, 16.64 mmol) was reacted in epichlorohydrin (10 mL) following the procedure described for **7a**. The crude residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to afford **7e** as a colorless gum (2.08 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35-8.27 (m, 1H), 7.85-7.76 (1H, m), 7.54-7.43 (3H, m), 7.37 (dd, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 7.0 Hz, 1H), 4.41 (dd, *J* = 11.0, 3.2 Hz, 1H), 4.16 (dd, *J* = 11.0, 5.6 Hz, 1H), 3.48-3.54 (1H, m), 2.98 (dd, *J* = 4.8, 4.2 Hz, 1H), 2.86 (dd, *J* = 4.9, 2.7 Hz, 1H). The spectral data were in complete agreement with the literature data [23].

2-Allyl-1-(benzyloxy)-4-methoxybenzene 14:

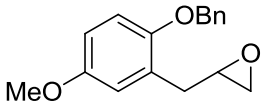


14

To a solution of 2-allyl-4-methoxyphenol **13** (200 mg, 1.22 mmol) in anh. acetone (150 mL) was added anh. K_2CO_3 (207 mg, 1.5 mmol) and benzyl bromide (0.15 mL, 1.26 mmol). The reaction mixture was refluxed for 4 h. Acetone was removed under

reduced pressure, and the resulting residue was redissolved in EtOAc (10 mL) and water (10 mL). The organic layer was separated, washed with brine (10 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% EtOAc in hexanes) to afford **14** as a colorless oil. Yield: (288 mg, 93%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.28 (m, 4H), 6.83 (d, *J* = 8.70 Hz, 1H), 6.75 (d, *J* = 3.21 Hz, 1H), 6.68 (dd, *J* = 3.21, 8.70 Hz, 1H), 6.04-5.94 (m, 1H), 5.10-5.03 (m, 2H), 5.01 (s, 2H), 3.74 (s, 3H), 3.42 (d, *J* = 6.41 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 150.5, 137.5, 136.7, 130.3, 128.4, 127.6, 127.1, 116.0, 115.7, 113.0, 111.2, 70.7, 55.5, 34.4. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13, found: C, 80.35; H, 7.06.

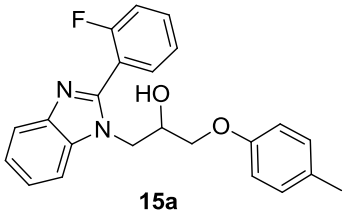
2-(2-(Benzyloxy)-5-methoxybenzyl)oxirane 7f:



7f

To a stirred solution of **14** (150 mg, 0.59 mmol) in CH_2Cl_2 (5 mL) was added *m*CPBA (77% purity, 195 mg, 0.88 mmol) at 0 °C. The reaction mixture was vigorously stirred at rt for 6 h. The mixture was diluted with CH_2Cl_2 (10 mL) and then washed successively with aq. solutions of Na_2SO_3 (5 mL), $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (5-10% EtOAc in hexanes) to afford **7f** as a colorless oil. Yield: (134 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.31 (m, 5H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.82 (d, *J* = 2.75 Hz, 1H), 6.73 (dd, *J* = 2.75, 8.70 Hz, 1H), 5.03 (s, 2H), 3.77 (s, 3H), 3.23-3.18 (m, 1H), 3.28 (dd, *J* = 5.50, 14.2 Hz, 1H), 2.82 (dd, *J* = 5.50, 14.2 Hz, 1H), 2.75 (t, *J* = 4.58 Hz, 1H), 2.55-2.53(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 150.8, 137.3, 128.5, 127.8, 127.2, 116.8, 112.7, 111.9, 70.6, 55.6, 51.6, 47.2, 33.6; Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71, found: C, 75.48; H, 6.65.

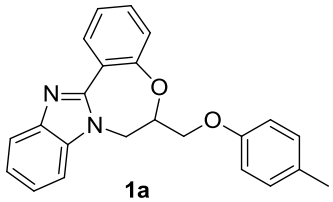
1-(2-(2-Fluorophenyl)-1*H*-benzo[*d*]imidazol-1-yl)-3-(*p*-tolyloxy)propan-2-ol 15a:



15a

A mixture of **11** (106 mg, 0.5 mmol), epoxide **7a** (82 mg, 0.5 mmol) and anh. K_2CO_3 (103 mg, 0.75 mmol) in anh. DMF (5 mL) was heated at 80 °C under N_2 atmosphere for 12 h. The reaction was terminated by adding water (10 mL), and then diluted with diethyl ether (20 mL). The organic layer was separated, washed by brine (20 mL) and dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (50% EtOAc in hexane) to afford **15a** as a colorless solid. Yield: (164 mg, 87%); R_f: 0.36 (60% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.71 (m, 1H), 7.54-7.47 (m, 2H), 7.43-7.39 (q, *J* = 5.9 Hz, 1H), 7.31-7.27 (m, 2H), 7.14-7.09 (m, 2H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.7 Hz, 2H), 4.46-4.26 (m, 2H), 4.21 (q, *J* = 4.5 Hz, 1H), 3.74-3.63 (m, 2H), 3.24 (br s, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (d, *J* = 249.2 Hz), 155.9, 149.1, 142.8, 135.5, 132.5, 132.2 (d, *J* = 7.6 Hz), 130.7, 129.9, 124.7 (d, *J* = 2.8 Hz), 123.4, 122.8, 119.9, 118.4 (d, *J* = 15.3 Hz), 116.0 (d, *J* = 21.0 Hz), 114.2, 110.8, 68.8, 68.6, 47.3, 20.5; Anal. calcd for $C_{23}H_{21}FN_2O_2$: C, 73.39; H, 5.62; N, 7.44, found: C, 73.41; H, 5.59; N, 7.40.

6-((4-Methoxyphenoxy)methyl)-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1a:



1a

To a stirred solution of **15a** (150 mg, 0.39 mmol) in freshly dried DMF (5 mL) was added powdered NaH (11 mg, 0.46 mmol) at 0 °C under an argon atmosphere. After stirring for 6 h at rt, the reaction mixture was quenched with saturated aq. NH_4Cl solution (10 mL), and diluted with EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (5-15% EtOAc/hexanes) afforded **1a** as a white solid. m.p.: 90-93 ^{o}C; Yield: (125 mg,

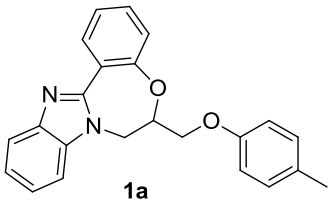
90%); R_f: 0.66 (silica gel, 30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (dd, *J* =7.8, 1.4 Hz, 1H),7.87 (dd, *J* = 6.4, 1.8 Hz, 1H), 7.43-7.23 (m, 5H), 7.13 (t, *J* = 9.1 Hz, 3H), 6.86 (d, *J* = 8.2 Hz, 2H), 4.78-4.71 (m, 2H), 4.53-4.39 (m, 2H), 4.23 (q, *J* = 7.3 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 155.4, 131.3, 131.2, 131.0, 130.1, 123.8, 123.7, 123.1, 123.0, 122.9, 121.3, 119.6, 118.5, 114.4, 109.24, 109.22, 78.3, 67.7, 47.3, 20.4; Anal. calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86, found: C, 77.57; H, 5.63; N, 7.88.

General procedure for the synthesis of polycyclic benzimidazoles 1a-h by the two-step protocol (without chromatographic purification of the intermediates; Table 7.2):

First step: A mixture of **11** (106 mg, 0.5 mmol), epoxide **7** (0.5 mmol) and anh. K_2CO_3 (103 mg, 0.75 mmol) in anh. DMF (5 mL) was heated at 80 °C under N_2 atmosphere for 12 h. The reaction was terminated by the addition of water (10 mL), and then diethyl ether (20 mL) was added. The organic layer was separated, washed by brine (20 mL) and dried over anh. Na_2SO_4. After filtration, the solution was evaporated to dryness under reduced pressure. The resulting crude product was further dried by a high vacuum pump, and then used it for the next step without further purification.

Second step: To a stirred solution of the above crude product in freshly dried DMF (5 mL) was added powdered NaH (14 mg, 0.575 mmol) at 0 °C under an argon atmosphere. After stirring for 2 h at rt, the reaction mixture was quenched with saturated aq. NH_4Cl solution (10 mL), and diluted with EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (5-15% EtOAc/hexanes) afforded the desired product **1**.

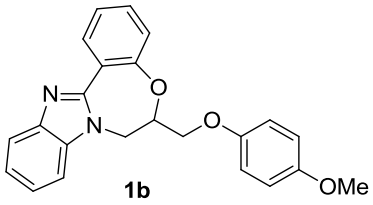
6-((4-Methoxyphenoxy)methyl)-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1a:



1a

According to the **General Procedure**, compound **11** (106 mg, 0.5 mmol) and epoxide **7a** (82 mg, 0.5 mmol) were subjected to the sequential intermolecular epoxide ring-opening ─ intramolecular S_NAr reaction to obtain the title compound **1a**.Yield: (133 mg, 75%). Physical and spectral data are already described.

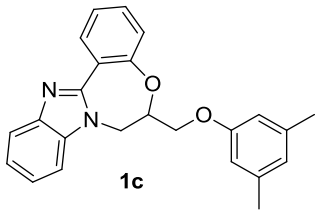
6-((4-Methoxyphenoxy)methyl)-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1b:



1b

According to the **General Procedure**, compound **11** (106 mg, 0.5 mmol) and epoxide **7b** (90 mg, 0.5 mmol) were subjected to the sequential intermolecular epoxide ring-opening ─ intramolecular S_NAr reaction to obtain the title compound **1b** as a white solid. m.p.: 85-87 ^oC; Yield: (138 mg, 74%); R_f: 0.62 (silica gel, 30% EtOAc in hexanes); ^1H NMR (400MHz, $CDCl_3$): δ 8.59 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.84 (dd, *J* = 6.4, 1.8 Hz, 1H), 7.40-7.20 (m, 5H), 7.12 (d, *J* = 8.2 Hz, 1H), 6.90-6.83 (m, 4H), 4.74-4.64 (m, 2H), 4.47-4.32 (m, 2H), 4.17 (q, *J* = 6.8 Hz, 1H), 3.762 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 154.4, 152.1, 150.2, 142.7, 136.1, 131.4, 131.1, 123.6, 122.8, 122.7, 121.2, 119.73, 119.71, 115.6, 114.7, 109.1, 78.3, 68.3, 55.6, 47.3; Anal. calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52, found: C, 74.23; H, 5.46; N, 7.56.

6-((3,5-Dimethylphenoxy)methyl)-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1c:

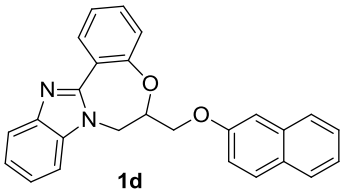


1c

According to the **General Procedure**, compound **11** (106 mg, 0.5 mmol) and epoxide **7c** (89 mg, 0.5 mmol) were subjected to the sequential intermolecular epoxide ring-opening ─ intramolecular S_NAr reaction to obtain the title compound **1c** as a white solid. m.p.: 92-94 ^oC; Yield: (139 mg, 75%); R_f: 0.65 (silica gel, 30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 8.61 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.85 (dd, *J* =

6.4, 1.8 Hz, 1H), 7.42-7.22 (m, 5H), 7.14 (d, *J* = 8.2 Hz, 1H), 6.66 (s, 1H), 6.59 (s, 1H), 4.78-4.69 (m, 2H), 4.50-4.38 (m, 2H), 4.22 (q, *J* = 7.3 Hz, 1H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 155.4, 150.2, 142.6, 139.5, 136.1, 131.6, 131.2, 123.7, 123.4, 122.9, 122.8, 121.2, 119.7, 119.6, 112.3, 109.1, 99.8, 78.3, 67.5, 47. 4, 21.4; Anal. calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56, found: C, 77.75; H, 5.93; N, 7.52.

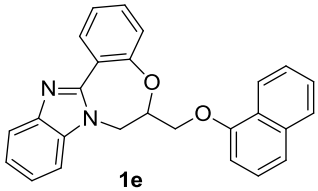
6-((Naphthalen-2-yloxy)methyl)-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1d:



1d

According to the **General Procedure**, compound **11** (106 mg, 0.5 mmol) and epoxide **7d** (100 mg, 0.5 mmol) were subjected to the sequential intermolecular epoxide ring-opening ─ intramolecular S_NAr reaction to obtain the title compound **1d** as a white solid. m.p.: 81-83 ^oC; Yield: (145 mg, 74%); R_f: 0.46 (silica gel, 20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.85 (d, *J* = 6.87 Hz, 1H), 7.78-7.71 (m, 3H), 7.44 (t, *J* = 7.33 Hz, 1H), 7.40-7.13 (m, 9H), 4.79-4.64 (m, 2H), 4.48-4.43 (m, 2H), 4.32-4.28 (q, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 155.3, 150.2, 142.7, 136.1, 134.2, 131.5, 131.2, 129.6, 129.2, 127.6, 126.77, 126.5, 124.0, 123.7, 122.8, 122.7, 121.2, 119.74, 119.71, 118.3, 109.1, 106.9, 78.2, 67.5, 47.2; Anal. calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14, found: C, 79.72; H, 5.19; N, 7.18.

6-((Naphthalen-1-yloxy)methyl)-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1e:

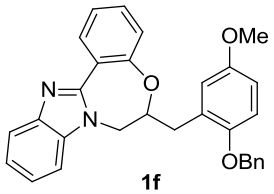


1e

According to the **General Procedure**, compound **11** (106 mg, 0.5 mmol) and epoxide **7e** (100 mg, 0.5 mmol) were subjected to the sequential intermolecular epoxide ring-opening ─ intramolecular S_NAr reaction to obtain the title compound **1e** as a white solid. m.p.: 85-86 ^oC; Yield: (139 mg, 71%); R_f: 0.46 (silica gel, 20% EtOAc in hexanes); ^{1}H

NMR (400 MHz, $CDCl_3$): δ 8.64 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.21 (d, *J* = 7.79 Hz, 1H), 7.88-7.82 (m, 2H), 7.53-7.46 (m, 3H), 7.43-7.24 (m, 6H), 7.18-7.16 (d, *J* = 8.24 Hz, 1H), 6.88-6.86 (d, *J* = 7.33 Hz, 1H), 4.92-4.77 (m, 2H), 4.62-4.56 (m, 2H), 4.44 (q, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 153.7, 150.2, 147.9, 142.5, 136.0, 134.5, 131.7, 131.3, 127.6, 126.6, 125.7, 125.6, 125.3, 123.8, 123.0, 122.9, 121.5, 121.33, 121.31, 119.7, 109.0, 104.9, 78.3, 67.9, 47.5; Anal. calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14, found: C, 79.66; H, 5.23; N, 7.08.

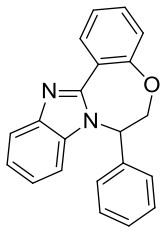
6-(2-(Benzyloxy)-5-methoxybenzyl)-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1f:



1f

According to the **General Procedure**, compound **11** (106 mg, 0.5 mmol) and epoxide **7f** (135 mg, 0.5 mmol) were subjected to the sequential intermolecular epoxide ring-opening ─ intramolecular S_NAr reaction to obtain the title compound **1f** as a white solid. m.p.: 131-133 ^{o}C; Yield: (178 mg, 77%); R_f: 0.59 (silica gel, 30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (dd, *J* = 1.83, 8.24 Hz, 1H), 7.81 (d, *J* = 7.79 Hz, 1H), 7.36-7.16 (m, 9H), 7.10 (d, *J* = 7.79 Hz, 1H), 6.99 (dd, *J* = 1.37, 8.24 Hz, 1H), 6.88 (d, *J* = 8.70 Hz, 1H), 6.85 (d, *J* = 2.75 Hz, 1H), 6.77 (dd, *J* = 2.75, 8.70 Hz, 1H), 5.01(s, 2H), 4.73-4.67 (m, 1H), 4.45 (dd, *J* = 1.83, 13.74 Hz, 1H), 4.25 (dd, *J* = 8.70, 13.74 Hz, 1H), 3.76(s, 3H), 3.29-3.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 153.6, 150.7, 142.6, 136.9, 136.2, 131.3, 131.1, 128.5, 127.9, 127.1, 126.3, 123.1, 122.64, 122.60, 121.1, 119.5, 117.6, 112.9, 112.6, 109.1, 79.1, 70.6, 55.6, 50.0, 34.8; Anal. Calcd. for $C_{30}H_{26}N_2O_3$: C, 77.90; H, 5.67; N, 6.06, found: C, 77.96; H, 5.74; N, 6.13.

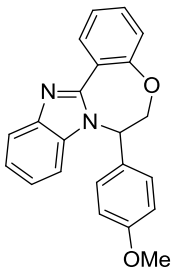
7-Phenyl-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1g:



1g

According to the **General Procedure**, compound **11** (106 mg, 0.5 mmol) and epoxide **7g** (60 mg, 0.5 mmol) were subjected to the sequential intermolecular epoxide ring-opening ─ intramolecular S_NAr reaction to obtain the title compound **1g** as a white solid. m.p.: 135-138 ^oC; Yield: (114 mg, 73%); R_f: 0.56 (silica gel, 20% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (dd, *J* = 1.37, 7.79 Hz, 1H), 7.85 (d, *J* = 7.79 Hz, 1H), 7.53-7.21 (m, 10H), 7.13 (d, *J* = 8.24 Hz, 1H), 5.39 (d, *J* = 8.70 Hz, 1H), 4.62-4.49 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$): δ 156.2, 14.9, 142.6, 138.1, 136.2, 131.4, 131.2, 128.9, 128.8, 126.1, 123.5, 122.8, 121.3, 119.7, 119.6, 109.1; Anal. calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97, found: C, 80.69; H, 5.21; N, 8.83.

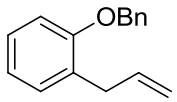
7-(4-Methoxyphenyl)-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazepine 1h:



1h

According to the **General Procedure**, compound **11** (106 mg, 0.5 mmol) and epoxide **7h** (75 mg, 0.5 mmol) were subjected to the sequential intermolecular epoxide ring-opening ─ intramolecular S_NAr reaction to obtain the title compound **1f** as a white solid. m.p.: 148-150 ^oC; Yield: (114 mg, 77%); R_f: 0.52 (silica gel, 20% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.38-7.20 (m, 5H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 5.35 (dd, *J* = 2.7, 7.79 Hz, 1H), 4.59-4.50 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 156.2, 150.0, 142.6, 136.2, 131.3, 131.2, 130.2, 127.4, 123.4, 122.7, 121.3, 119.7, 119.6, 114.2, 109.1, 81.1, 55.3, 52.5; Anal. calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18, found: C, 77.11; H, 5.37; N, 8.22.

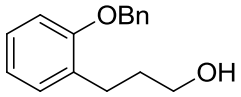
1-Allyl-2-(benzyloxy)benzene 17:



17

To a solution of 2-allyl phenol **16** (11.36 g, 84.66 mmol) in anh. acetone (150 mL) was added anh. K_2CO_3 (14.01 g, 101.59 mmol) and benzyl bromide (10.0 mL, 84.66 mmol). The reaction mixture was refluxed for 4 h. Acetone was removed under reduced pressure, and the resulting residue was redissolved in EtOAc (200 mL) and water (200 mL). The organic layer was separated, washed with brine (100 mL), dried over anh. Na_2SO_4 and filtered. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (2% EtOAc in hexanes) to afford **17** as a colorless oil. Yield: (18.0 g, 95%); R_f: 0.46 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.28 (m, 5H), 7.20–7.14 (m, 2H), 6.93–6.89 (m, 2H), 6.08–5.95 (m, 1H), 5.08 (s, 2H), 5.05–5.02 (m, 2H), 3.45 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 137.4, 137.0, 129.9, 129.0, 128.5, 127.7, 127.3, 127.1, 120.8, 115.4, 111.7, 69.9, 34.4. The spectral data were in complete agreement with the literature data [24].

3-(2-(Benzyloxy)phenyl)propan-1-ol 18:

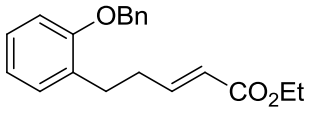


18

To stirred solution of **17** (7.0 g, 31.20 mmol) in anh. THF (80 mL) was added 9-BBN (0.5 M solution in THF, 46.8 mL, 46.8 mmol) dropwise under a nitrogen atmosphere at 0 °C. The mixture was then stirred at rt for 6 h. The reaction was carefully terminated by the addition of H_2O (5 mL) at 0 °C. Next, 3 N NaOH solution (50 mL) and 30% H_2O_2 (40 mL) were added to it sequentially. The reaction mixture was then stirred for an additional 2 h at 60 °C. After cooling to rt, the reaction mixture was then partitioned between brine (80 mL) and EtOAc (80 mL). The layers were separated and the aqueous phase was extracted with EtOAc (50 mL). The combined organic extracts were washed with brine (100 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (8% EtOAc in hexane) afforded **18** as a colorless gum. Yield: (7.18 g, 95%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41–7.25 (m, 5H), 7.16–7.10 (m, 2H), 6.91–6.86 (m, 2H), 5.03 (s, 2H),

3.54 (t, *J* = 6.3 Hz, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.01 (s, 1H), 1.87–1.78 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 156.5, 137.1, 130.4, 130.1, 128.5, 127.8, 127.1, 127.0, 120.9, 111.7, 70.0, 61.8, 32.8, 26.1. The spectral data were in complete agreement with the literature data [24].

(*E*)-Ethyl 5-(2-(benzyloxy)phenyl)pent-2-enoate 19:

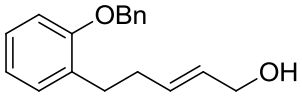


19

To a stirred solution of compound **18** (6.9 g, 28.47 mmol) in anh. dichloromethane (100 mL) was added PCC (9.18 g, 42.69 mmol) at 0 °C and the mixture was stirred at rt for 5 h. After evaporating dichloromethane under reduced pressure, the reaction mixture was suspended indiethyl ether (150 mL) and filtered through a small pad of silica gel. The filter cake was washed by diethyl ether (50 x 3mL). Concentration of the whole filtrate gave the corresponding crude aldehyde which was used for the next step without further purifiaction.

To a stirred solution of the above crude aldehyde in dichloromethane (150 mL), was added (carbethoxymethylene)triphenylphosphorane afforded (9.90 g, 28.47 mmol) and the reaction was further stirred for an additional 4 h. Removal of the solvent under reduced pressure gave the crude product which was purified by silica gel column (5% EtOAc in hexane) to afford compound **19** as a colorless oil. Yield: (6.18 g, 70% over two steps); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41–7.21 (m, 5H), 7.16–6.98 (m, 2H), 6.92–6.88 (m, 3H), 5.81 (d, *J* = 15.6 Hz, 1H), 5.07 (s, 2H), 4.16 (m, 2H), 2.82 (t, *J* = 7.9 Hz, 2H), 2.57–2.46 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.2, 157.0, 149.3, 137.7, 130.4, 130.0, 129.0, 128.2, 127.9, 127.5, 121.9, 121.2, 112.0, 70.2, 60.6, 32.9, 29.6, 14.7; Anal. calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14, found: C, 77.35; H, 7.06. The spectral data were in complete agreement with the literature data [24].

(*E*)-5-(2-(Benzyloxy)phenyl)pent-2-en-1-ol 20:

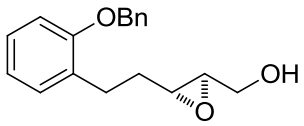


20

To a stirred solution of compound **19** (5.5 g, 17.71 mmol) in anh. toluene (75 mL) was added DIBAL-H (44 mL, 1 M solution in heptane) dropwise at -78 ^{o}C under a

nitrogen atmosphere. The resulting mixture was allowed to warm to rt over 4 h. The reaction mixture was then poured in a saturated aq. solution of potassium sodium tartarate (200 mL) and stirred vigorously. The organic layer was separated, and the aqueous phase was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (100 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (20% EtOAc in hexanes) afforded **20** as a colorless gum. Yield: (5.3 g, 95%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.35 (m, 5H), 7.29–7.13 (m, 2H), 6.91(d, *J* = 6.0 Hz, 2H), 5.75–5.58 (m, 2H), 5.08 (s, 2H), 4.05 (d, *J* = 5.0 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.43–2.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 137.9, 133.3, 130.9, 129.7, 128.9, 128.2, 127.5, 127.4, 121.1, 112.0, 70.2, 64.1, 32.8, 30.6. The spectral data were in complete agreement with the literature data [25].

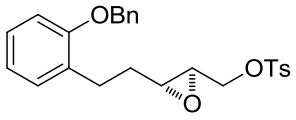
((2*R,3*R**)-3-(2-(benzyloxy)phenethyl)oxiran-2-yl)methanol 21:**



21

To a stirred solution of compound **20** (5.0 g, 18.6 mmol) in CH_2Cl_2 (150 mL) was added *m*-CPBA (77%, 6.26 g, 27.94 mmol) at 0 ^{o}C. The reaction mixture was then vigorously stirred at 0 ^{o}C for 6 h. A saturated aq. solution of $NaHSO_3$ (50 mL) was added to quench excess *m*-CPBA. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ solution (100 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (30% EtOAc in hexanes) afforded **21** as a colorless gum. Yield: (4.8 g, 90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.29 (m, 5H), 7.20-7.15 (m, 2H), 6.92–6.87 (m, 2H), 5.07 (s, 2H), 3.79-3.75 (m, 1H), 3.55-3.47 (m, 1H), 2.98-2.74 (m, 4H), 2.00-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 137.2, 130.0, 129.8, 128.5, 127.8, 127.4, 127.1, 120.8, 111.7, 69.9, 61.7, 58.6, 55.7, 31.7, 26.9. The spectral data were in complete agreement with the literature data [25].

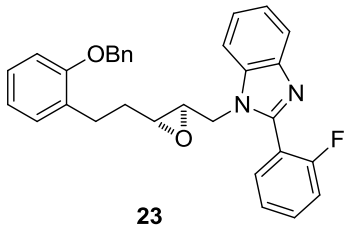
((2*R,3*R**)-3-(2-(Benzyloxy)phenethyl)oxiran-2-yl)methyl 4-methylbenzene sulfonate 22:**



22

To a stirred solution of epoxyalcohol **21** (4.0 g, 26.63 mmol) in anh. CH_2Cl_2 (80 mL) at 0 ^oC was seqentially added triethyl amine (5.6 mL, 40.12 mmol) and tosyl chloride (6.35 g, 33.30 mmol). The reaction mixture was kept in a refrigerator for 12 h. The reaction mixture was diluted with H_2O (100 mL), and extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were washed with brine (50 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (10-30% EtOAc in hexanes) afforded epoxy tosylate **22** as light yellow gummy liquid; Yield: 7.25 g, 89%; R_f: 0.5 (30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 7.84-7.74 (m, 2H), 7.44-7.11 (m, 9H), 6.93-6.87 (m, 2H), 5.07 (s, 2H), 4.15-4.08 (m, 1H), 3.86-3.81 (m, 1H), 2.87-2.74 (m, 3H), 2.44 (s, 3H), 1.93-1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 144.9, 137.0, 132.5, 129.9, 129.7, 129.2, 128.4, 127.7, 127.4, 127.0, 125.5, 120.6, 111.5, 70.1, 69.6, 56.0, 54.6, 31.3, 26.6, 21.5; Anal. calcd for $C_{25}H_{26}O_5S$: C, 68.47; H, 5.98, found: C, 68.55; H, 5.86.

1-(((2*R,3*R**)-3-(2-(Benzyloxy)phenethyl)oxiran-2-yl)methyl)-2-(2-fluorophenyl)-1*H*-benzo[*d*]imidazole 23:**

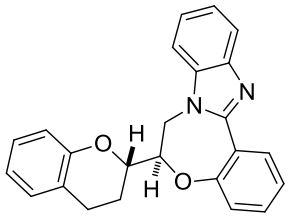


23

A mixture of **22** (200 mg, 0.47 mmol), **11** (99 mg, 0.47 mmol) and K_2CO_3 (70 mg, 0.56 mmol) in DMF (8 mL) was heated at 80 ^oC for overnight. The mixture was cooled down to rt and then poured into a mixture of water (20 mL) and diethyl ether (40 mL). The organic layer was separated, washed with brine (20 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc in hexanes) to afford **23** as a light yellow gum. Yield: (0.225 g, 75%); R_f: 0.52 (30% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.84-7.82 (m,1H), 7.67-7.63 (m, 1H), 7.56-7.49 (m, 2H), 7.39-7.12 (m, 10H),

7.06-7.05 (d, *J* = 7.3 Hz, 1H), 6.87-6.82 (m, 2H), 5.02 (s, 2H), 4.25 (dd, *J* = 2.7, 15.5 Hz, 1H), 3.99 (dd, *J* = 5.5, 15.1 Hz, 1H), 2.84-2.67 (m, 4H), 1.90-1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8 (d, *J* = 244.4 Hz), 156.4, 148.7, 143.1, 137.1, 135.5, 132.7 (d, *J* = 1.9 Hz), 132.1 (d, *J* = 8.6 Hz), 129.9, 129.4, 128.5, 127.8, 127.4, 127.1, 124.8 (d, *J* = 2.8 Hz), 123.3, 122.6, 120.7, 119.9, 118.5, 115.9 (d, *J* = 22.0 Hz), 111.5, 110.8, 69.7, 56.8, 56.5 (d, *J* = 2.8 Hz), 46.7(d, *J* = 2.8 Hz), 31.5, 26.7; Anal. calcd for $C_{31}H_{27}FN_2O_2$: C, 77.80; H, 5.69; N, 5.85, found: C, 77.88; H, 5.75; N, 5.89.

(*R)-6-((*S**)-Chroman-2-yl)-6,7-dihydrobenzo[*f*]benzo[4,5]imidazo[1,2-*d*][1,4] oxazepine 24:**



24

To a stirred solution of **23** (0.225 g, 0.47 mmol) in EtOAc (10 mL) was added 10% Pd-C (25 mg). After stirring for 4 h at rt under pressure of a hydrogen balloon, the reaction mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure to get the corresponding phenolic derivative as a colorless semi-solid that was used for the next step without further purification.

To a stirring solution of the above debenzylated product in anh. DMF (5 mL), was added anh. K_2CO_3 (97 mg, 0.7 mmol) and the mixture was stirred for 2 h at 80 ^{o}C. The mixture was cooled down to rt and then poured into a mixture of water (20 mL) and diethyl ether (40 mL). The organic layer was separated, washed by brine (20 mL) and dried over anh. Na_2SO_4.The crude product thus obtained was dissolved in anh. DMF (5 mL). NaH (10 mg, 0.42 mmol) was added to it under a nitrogen atmosphere at 0 ^{o}C. After stirring for 2 h at rt, the reaction mixture was quenched with saturated aq. NH_4Cl solution (10 mL), and diluted with EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc in hexanes) to afford **24** as a light yellow semi-solid. Yield: (122 mg, 65% over three steps); R_f: 0.5 (30% EtOAc in hexane).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.85 (dd, *J* = 5.9, 2.2 Hz, 1H), 7.47-7.23 (m, 5H), 7.16-7.06

(m, 3H), 6.90-6.87 (m, 2H), 4.83 (dd, *J* = 14.2, 1.8 Hz, 1H), 4.57-4.51 (m, 1H), 4.43 (td, *J* = 8.2, 1.8 Hz, 1H), 4.27-4.22 (m, 1H), 2.90-2.84 (m, 2H), 2.54-2.47 (m, 1H), 2.04-1.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 153.5, 150.1, 142.4, 136.1, 131.6, 131.2, 129.6, 127.4, 123.8, 123.0, 122.8, 121.8, 121.0, 120.9, 120.0, 119.6, 116.6, 109.3, 81.6, 74.6, 36.6, 23.9, 23.7; Anal. calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60, found: C, 78.36; H, 5.49; N, 7.68.

7.6. References

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7.7. NMR Spectra of Selected Compounds

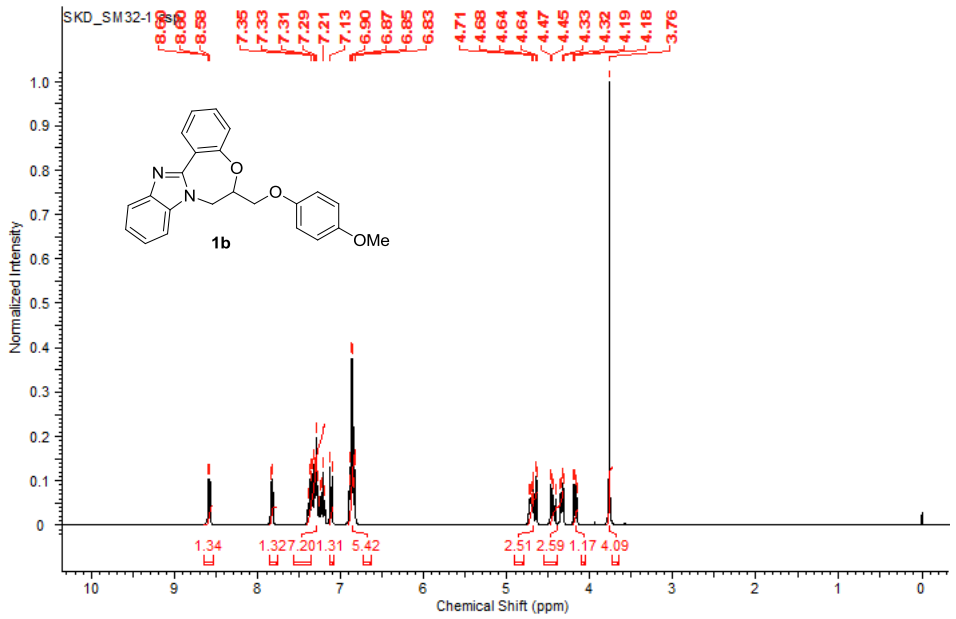

Figure 7.5. ^{1}H NMR (400 MHz, $CDCl_3$) of 1b

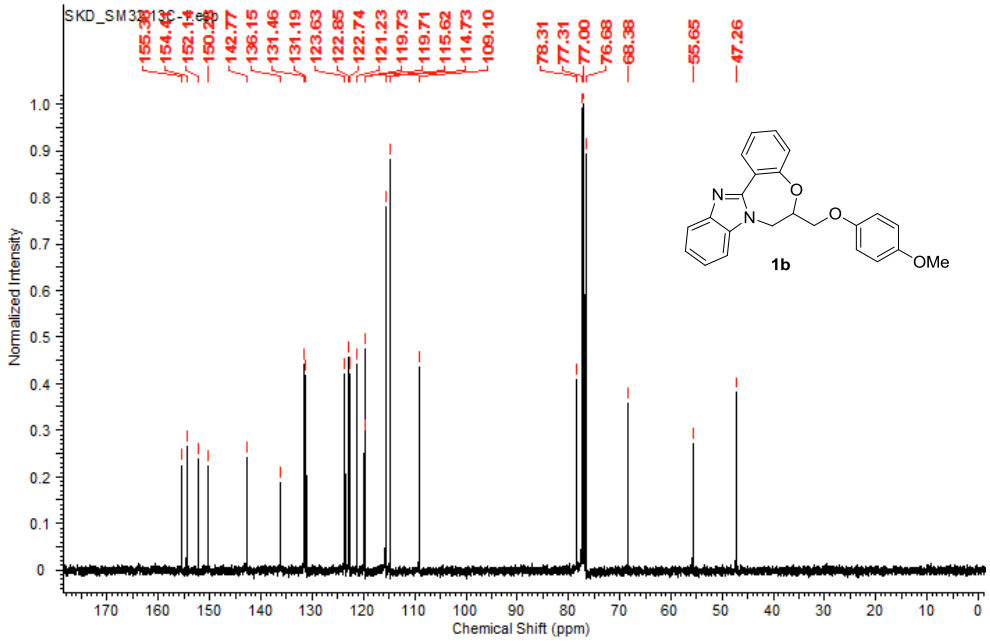

Figure 7.6. ^{13}C NMR (100 MHz, $CDCl_3$) of 1b

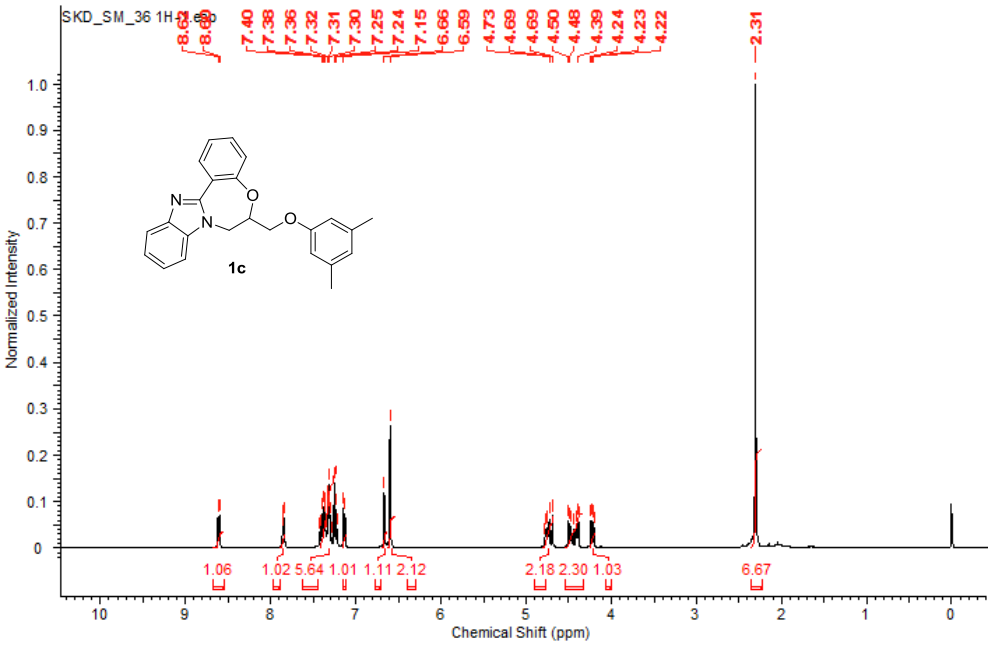

Figure 7.7. ^{1}H NMR (400 MHz, $CDCl_3$) of 1c

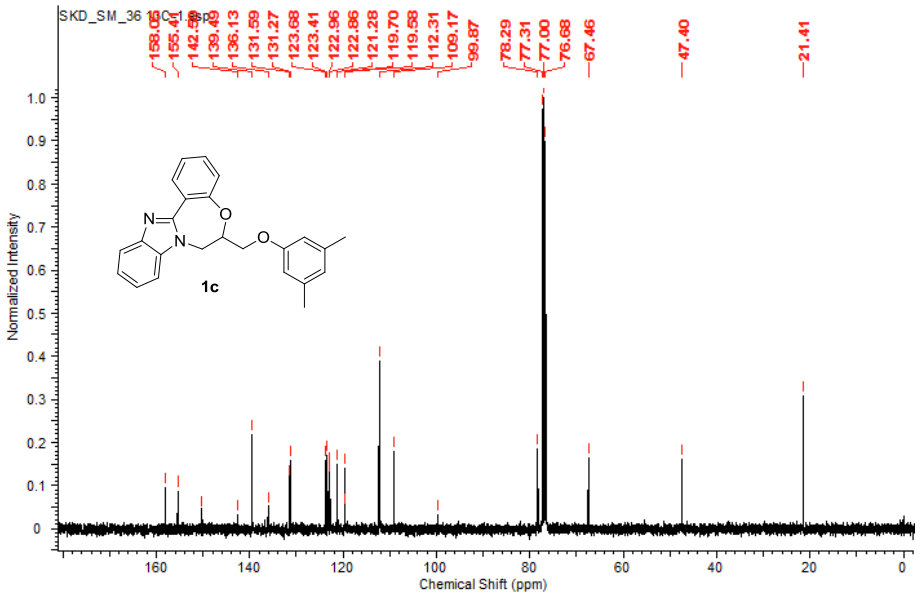

Figure 7.8. ^{13}C NMR (100 MHz, $CDCl_3$) of 1c

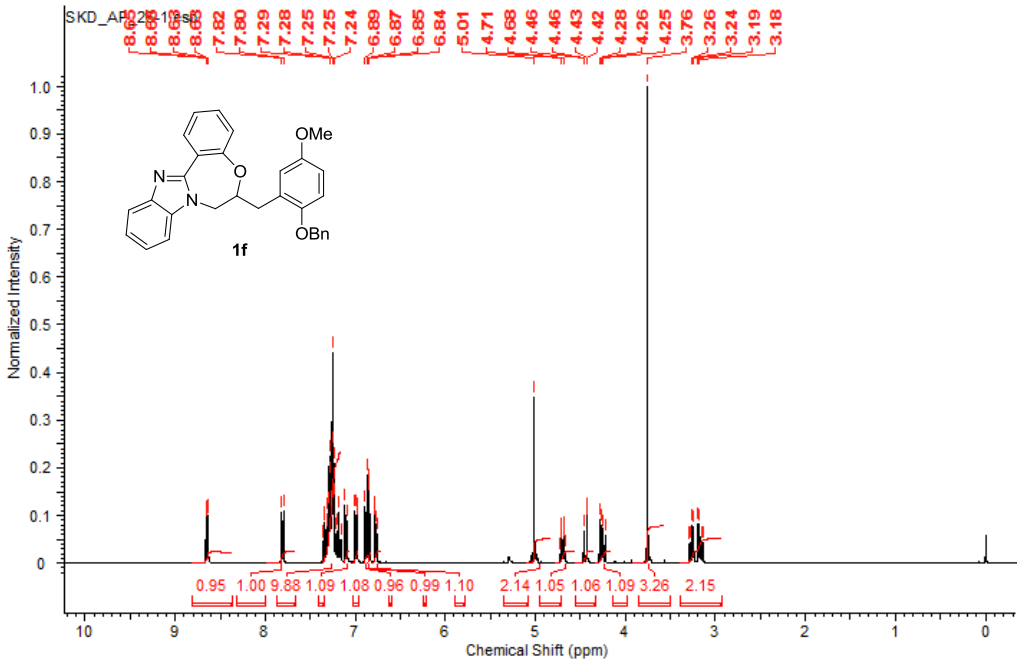

Figure 7.9. ^{1}H NMR (400 MHz, $CDCl_3$) of 1f

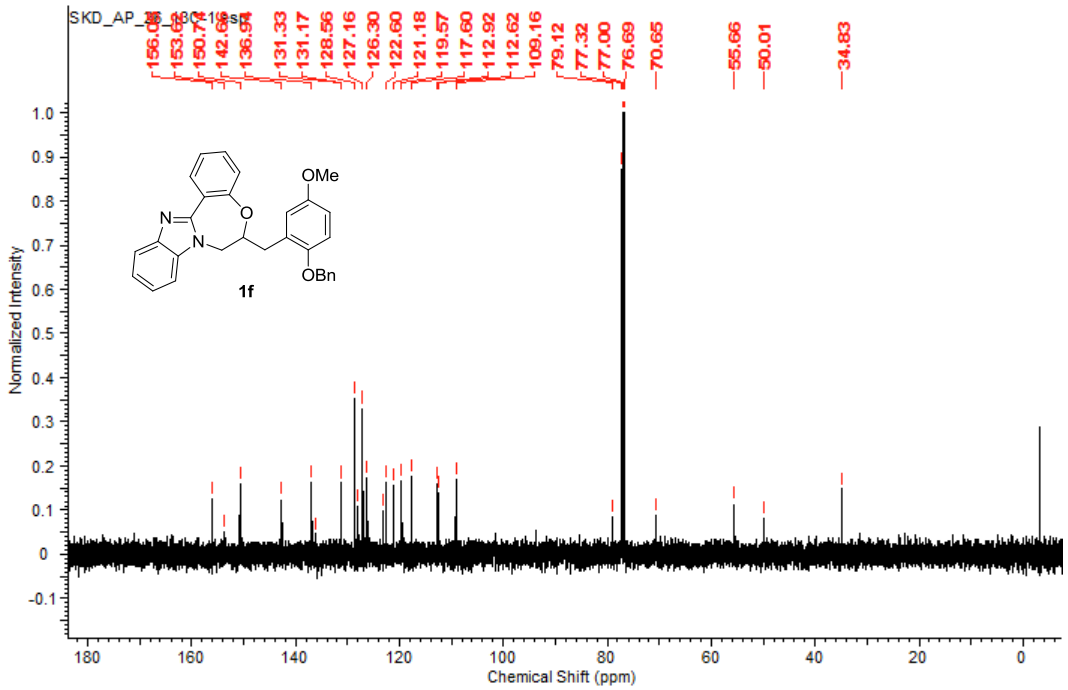

Figure 7.10. ^{13}C NMR (100 MHz, $CDCl_3$) of 1f

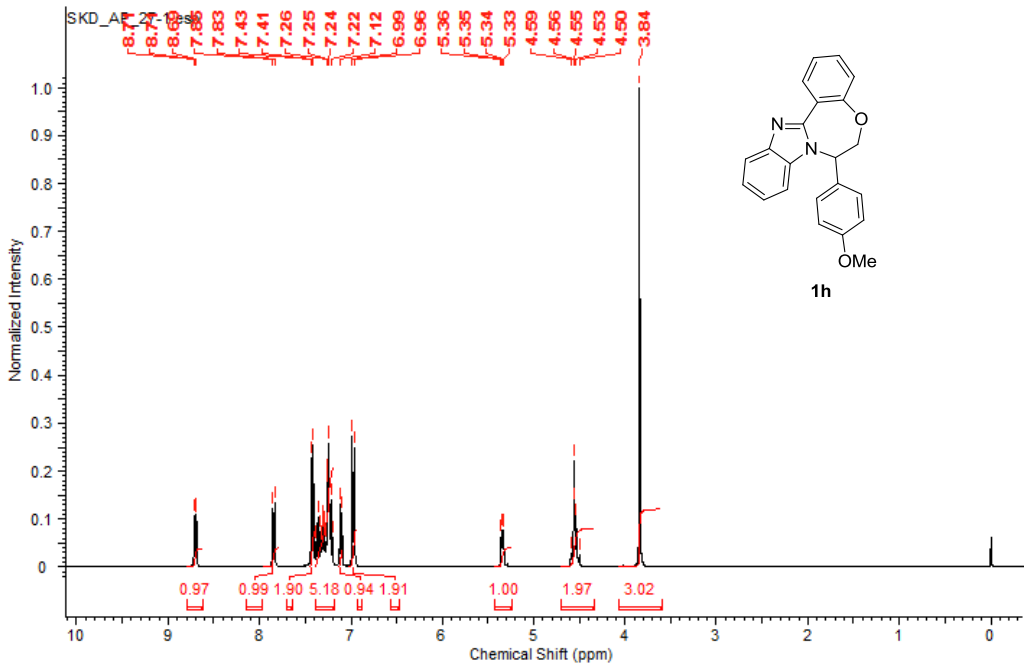

Figure 7.11. ^{1}H NMR (400 MHz, $CDCl_3$) of 1h

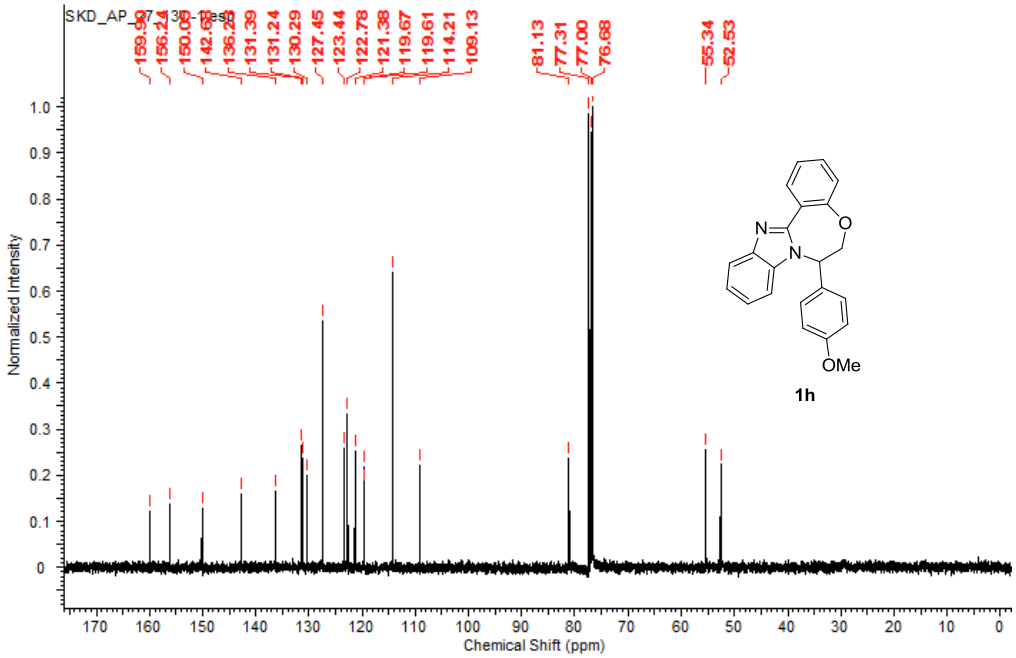

Figure 7.12. ^{13}C NMR (100 MHz, $CDCl_3$) of compound 1h

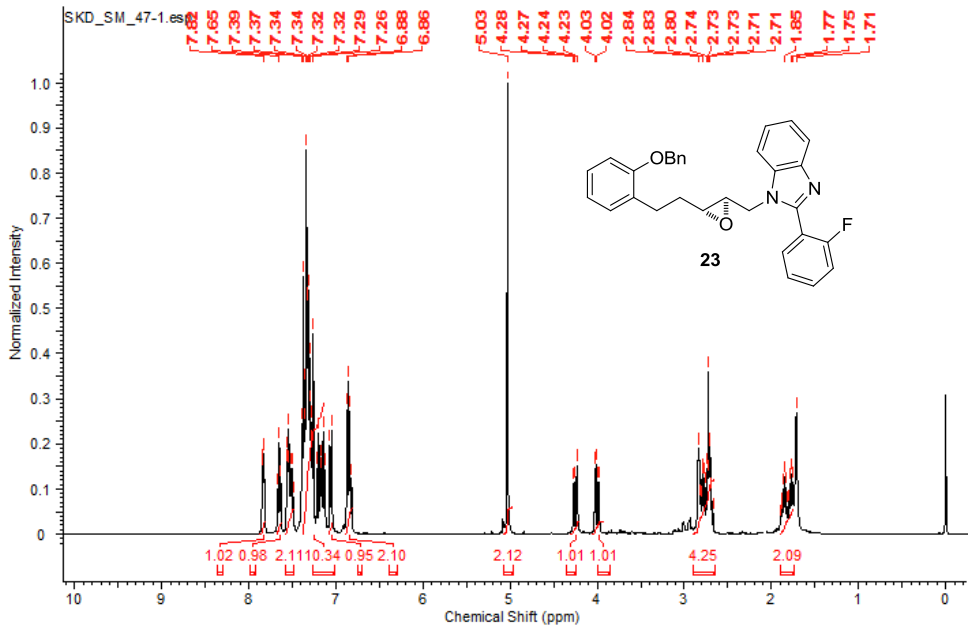

Figure 7.13. ^{1}H NMR (400 MHz, $CDCl_3$) of 23

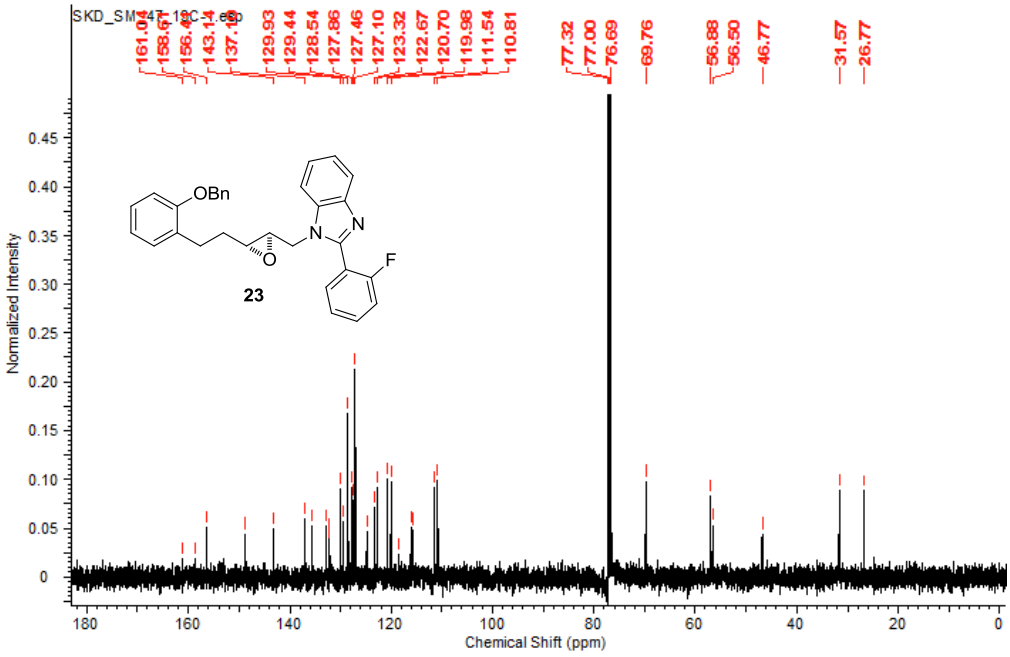

Figure 7.14. ^{13}C NMR (100 MHz, $CDCl_3$) of compound 23

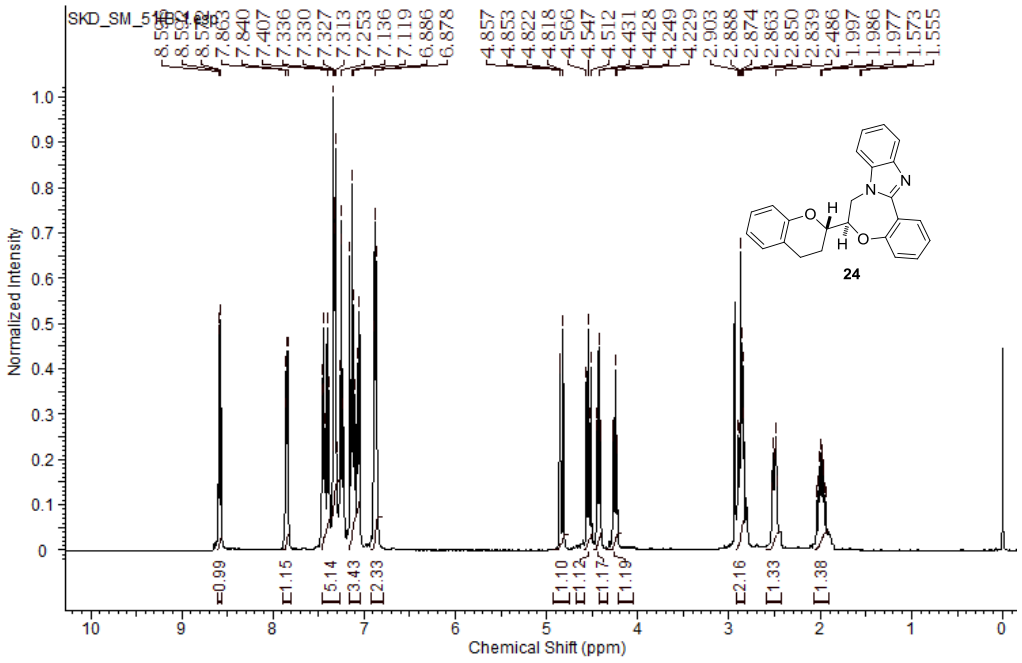

Figure 7.15. ^{1}H NMR (400 MHz, $CDCl_3$) of 24

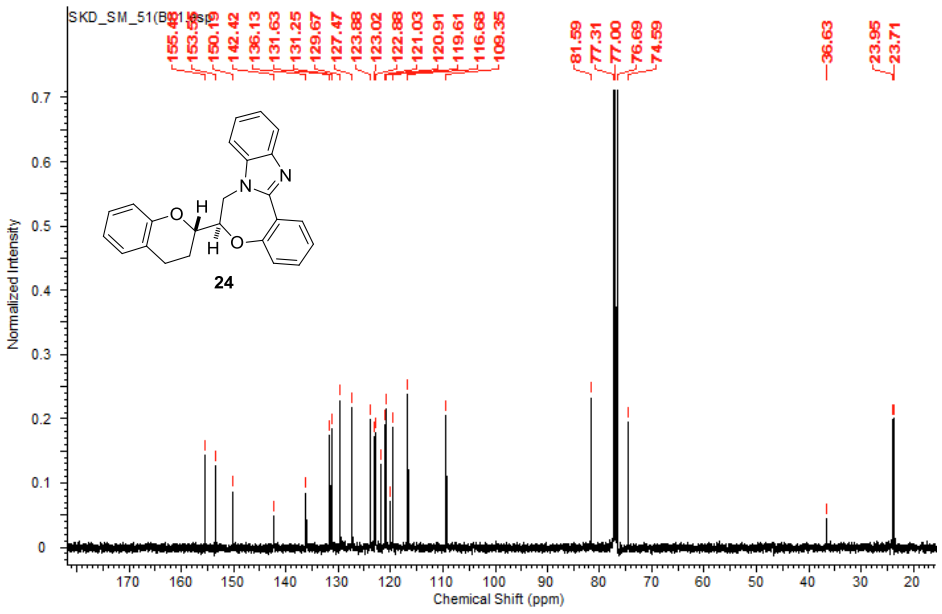

Figure 7.16. ^{13}C NMR (100 MHz, $CDCl_3$) of compound 24