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Design, synthesis and biological evaluation of novel triaryldimethylaminobutan-2-ol derivatives against *Mycobacterium tuberculosis*

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ABSTRACT

Bedaquiline (TMC207), a typical diarylquinoline anti-tuberculosis drug, has been approved by FDA to specifically treat *MDR-TB*. Herein we describe design, synthesis, and *in vitro* biological evaluation against *Mycobacterium tuberculosis* of a series of triaryldimethylaminobutan-2-ol derivatives obtaining from the structural modification of **TMC207**. Compounds **23**, **25**, **28**, **32**, **39** and **43** provided superior anti-mycobacterial activity than positive control **PC01** which shows the same configuration and contains **TMC207**. Compounds **16**, **20**, **29**, **34**, **37**, **45** and **47** exhibited the similar activity to positive control **PC01**. Most importantly, the series of compounds showed excellent activity against *XDR-Mtb*. The result of acute toxicity suggested that this class of triaryldimethylaminobutan-2-ol derivatives should be graded as low. Further SAR analysis indicates that a large steric bulk of triaryl and 7-Br, 3-OCH_3 on 1-naphthyl are critical.

1. Introduction

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). It is caused by the bacillus *Mycobacterium tuberculosis*, which is spread when people who are sick with TB expel bacteria into the air; for example, by coughing [1]. It is much more serious accompanying with the increasing of individuals that infect the human immunodeficiency virus (HIV). HIV can markedly enhance the rate of both new *Mtb* infection and activation of latent infection [2]. HIV-positive patients are more susceptible to *Mtb* with a 50-fold risk of incidence increase over HIV-negative patients [3]. Otherwise, the emergence of multidrug-resistant TB (*MDR-TB)* and recently developed extensive drug-resistant TB (*XDR-TB*) provide new challenges to current first-line TB drug regimens which were just developed more than 40 years ago [4–6]. All these alarming situations intensify the need to find novel, inexpensive, more efficient and lower toxicity anti-TB drugs.

Bedaquiline (TMC207), a diarylquinoline, improved cure rates when added to a multidrug-resistant tuberculosis (*MDR-TB*) treatment regimen in a previous placebo-controlled, phase 2 trial (NCT00449644) [7]. It exhibits a promising *in vitro* activity against both drug-sensitive and drug-resistive *Mtb* strains at a range of minimum inhibitory concentration (MIC) of 0.01–0.12 μg/mL [8]. Combinations of **TMC207** with current drugs [8–10] especially Pyrazinamide (PZA) [11] exerting a synergistic effect are more active and shorter regimens than those recommended by WHO. **TMC207** shows higher selectivity against mycobacteria than any other Organisms and almost innoxious in clinical study [8,12]. The fact **TMC207** retains activity against *MDR-TB* and *XDR-TB* [13] suggests that it exhibit marked effect through a different cellular target. The genomes of *Mtb* strains resist **TMC207** have been sequenced [14,15]. The point mutations identified as Asp^{28} → Val (D28V), Ala^{63} → Pro (A63P), Ile^{66} → Met (I66M), Asp^{28} → Pro (D28P) or Glu^{61} → Asp (E61D) in different **TMC207**-resistive strains are all located at adenosine triphosphate (ATP) synthase c subunit which is encoded by gene *atpE*. Accordingly, **TMC207** exerts its high anti-TB activity with a unique mechanism of action targeting the membrane-spanning domain c subunit acting as a proton pump of ATP synthase.

There already had been some structural modifications of **TMC207** due to its high activity and new target [16–20]. Studies on structure activity relationship (SAR) of the diarylquinoline compounds were reported. Docking research of **TMC207** and its another three stereoisomers suggested that the hydroxyl and N,N-dimethylamino moieties play a capital role in binding to the target protein [21]. It was also

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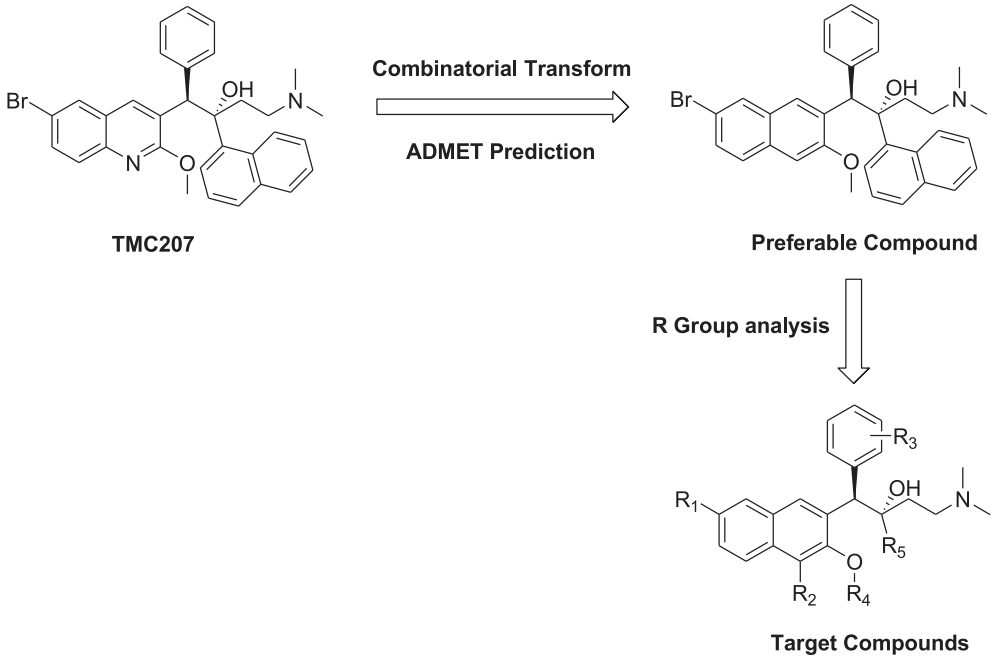


Fig. 1. Design of TMC207 derivatives. R_1: Br, H; R_2: Br, H; R_3: *para*, *meta*, *ortho*-CH_3, *para*, *meta*-Cl; R_4: CH_3, H; R_5: 1-naphthyl, phenyl, *para*, *meta*, *ortho*-bromophenyl, 2,4-difluorophenyl.

demonstrated by Ram et al. [16] the importance of the naphthalene moiety which presumably acts as a binding motif with its lipophilic nature. A large steric bulk of triaryl of **TMC207** is critical for its selectivity against *Mycobacterium tuberculosis* [21].

How can we get more hopeful anti-TB derivatives from the structure of **TMC207** keeping the demonstrated considerable moieties? We used computer aided drug design (CADD) software to design a series of novel anti-TB compounds (Fig. 1). 100 new compounds were generated through the functional module Combinatorial Transform of Med Chem Studio (Simulations Plus, Inc., USA, http://www.simulations-plus.com) [22] with setting up the parameter of one point derivatization (see Table S1 in the supplemental material). A preferable compound retains the active parts and changes quinoline ring into naphthalene. As there is no evidence to show effect on activity of quinoline's nitrogen nor binding between quinoline's nitrogen and the target protein in docking studies [21], the exchange may retain perfect properties **TMC207** has. Besides, the compound exhibits better predictive value in ADMET through another kind of software ADMET Predictor version 5.5 (Simulations Plus, Inc., USA, http://www.simulations-plus.com). The prediction of TMC207's ADMET risk is scored as 10 while the preferable compound is 8 ((see Table S2 in the supplemental material)).

After R-group and SAR analysis of **TMC207** and its analogs in patent using software Medchem Studio, we presented a series of triaryldimethylaminobutan-2-ol derivatives. At 1-position, we used phenyl substituted by electron withdrawing group (Cl) at *para*, *meta* position and electron donating group (CH_3) at *para*, *meta*, *ortho* position to investigate their influence of activity. At 2-position, we reasonably reduced the bulk of the molecule using halogen substituted phenyl in order to enhancing the membrane penetration which may lead to an improved fit into the binding site. We hope that these modifications of **TMC207** can provide satisfactory results for finding some new potential anti-TB drugs.

2. Results

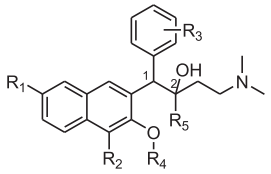
2.1. Synthetic studies

We have so far prepared a series of different triaryldimethylaminobutan-2-ol derivatives **11–48** (Table 1) and a Hydrochloride **49** using the synthetic sequence illustrated in Scheme 1 [23–25]. The synthesis was started with the reaction of 3-hydroxy-2-naphthoic acid (**1**) with bromine in AcOH to obtain **4**, 7-Dibromo-3-hydroxy-2-naphthoic Acid (**2**) in good yield (90%). Treatment of compound **2** with powdery tin in AcOH provided 7-Bromo-3-hydroxy-2-naphthoic Acid (**3**) in yield 96.5%. Methylation of compound **3** with $(CH_3)_2SO_4$ in acetone could afford Methyl 7-bromo-3-methoxy-2-naphthoate (**4a**) in yield 86%. In the same way, compounds Methyl 4,7-dibromo-3-methoxy-2-naphthoate (**4b**) and Methyl 3-methoxy-2-naphthoate (**4c**) were prepared respectively from compound **2** in 75% yield and compound **1** in 81% yield. Esters **4a-4b** were reduced to alcohols **5a-5b** with $LiAlH_4$ in ether in yields 85–98%. Compounds **5a-5b** were converted to aldehydes **6a-6b** respectively in the presence of active MnO_2 in acetone in yields 84–87%. Nucleophilic addition of aldehyde **6a** with different Grignard reagents prepared by substituted bromobenzene afforded compounds **7a-7f** in yields 90–95%. According to the same method, **7g** (94%) and **7h** (92%) were prepared from **6b**, and **7i** (89%) was from **6c**. The compounds **7a-7h** can be reduced to **8a-8h** (75–88%) in the presence of $NaBH_4$ and $AlCl_3$ in THF. Otherwise, **7i** was converted into two compounds **8i** (41%) and **8j** (36%) by the same method. Mannich bases (**10a-10f**) were prepared from the commercially available substituted-ethanones (**9a-9f**) with dimethylamine hydrochloride and paraformaldehyde in 95% ethanol in a range of 59–67% yields. Finally, **8a-8j** were allowed to react with **10a-10f** in the presence of LDA in THF to provide target compounds **11–48**. Hydrochloride **49** was prepared from compound **18** with HCl-Et_2O in acetone. All the synthesized compounds were fully characterized by ^1H NMR and MS. The configurations of Compounds **11** and **17** were confirmed by single crystal x-ray diffraction [26,27].

2.2. Antimycobacterial activity

All the compounds **11–49** were evaluated for their minimum inhibitory concentration (MIC) against the *Mtb* strain H37Rv in a microplate Alamar Blue assay (MABA) [28]. Several compounds were found to effectively inhibit the growth of replicating *Mtb* in with low MICs (Table 2). We synthesized two compounds **PC01** and **PC02** following the synthetic route in patent [25] as positive control. It was

Table 1
The structure of target compounds triaryldimethylaminobutan-2-ol derivatives.



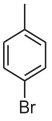
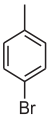
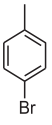
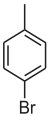
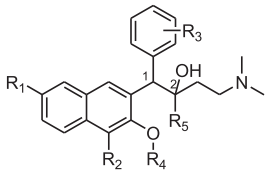
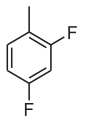
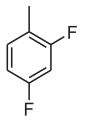
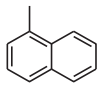
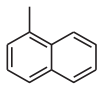
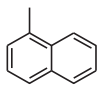
Compd. No.	R_1	R_2	R_3	R_4	R_5	Config.
11	Br	H	H	CH_3		1R,2R/1S,2S
12	Br	H	H	CH_3		1R,2S/1S,2R
13	H	H	H	CH_3		1R,2S/1S,2R
14	H	H	H	CH_3		1R,2R/1S,2S
15	Br	H	*p*-Cl	CH_3		1R,2R/1S,2S
16	Br	H	*p*-Cl	CH_3		1R,2S/1S,2R
17	H	H	*p*-Cl	CH_3		1R,2R/1S,2S
18	H	H	*p*-Cl	CH_3		1R,2S/1S,2R
19	Br	H	*p*-Cl	CH_3		1R,2R/1S,2S
20	Br	H	*p*-Cl	CH_3		1R,2S/1S,2R
21	Br	H	*p*-Cl	CH_3		1R,2R/1S,2S
22	Br	H	*p*-Cl	CH_3		1R,2S/1S,2R
23	Br	H	H	CH_3		1R,2S/1S,2R
24	Br	H	H	CH_3		1R,2R/1S,2S

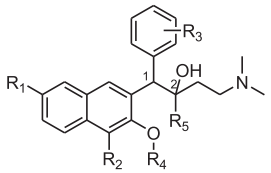
Table 1 (*continued*)



Compd. No.	R_1	R_2	R_3	R_4	R_5	Config.
25	Br	H	H	CH_3		1R,2S/1S,2R
26	Br	H	H	CH_3		1R,2R/1S,2S
27	Br	H	*p*-Cl	CH_3		1R,2R/1S,2S
28	Br	H	*p*-Cl	CH_3		1R,2S/1S,2R
29	Br	H	H	CH_3		1R,2S/1S,2R
30	Br	H	H	CH_3		1R,2R/1S,2S
31	Br	H	*p*-Cl	CH_3		1R,2R/1S,2S
32	Br	H	*p*-Cl	CH_3		1R,2S/1S,2R
33	Br	H	H	CH_3		1R,2R/1S,2S
34	Br	H	H	CH_3		1R,2S/1S,2R
35	H	H	*p*-Cl	CH_3		1R,2R/1S,2S
36	H	H	*p*-Cl	CH_3		1R,2S/1S,2R
37	Br	H	*p*-CH_3	CH_3		1R,2S/1S,2R
38	Br	H	*p*-CH_3	CH_3		1R,2R/1S,2S
39	Br	Br	H	CH_3		1R,2S/1S,2R

(*continued on next page*)

Table 1 (*continued*)



Compd. No.	R_1	R_2	R_3	R_4	R_5	Config.
40	Br	Br	H	CH_3		1R,2R/1S,2S
41	Br	Br	H	OH		1R,2S/1S,2R
42	Br	Br	H	OH		1R,2R/1S,2S
43	Br	H	*m*-Cl	CH_3		1R,2S/1S,2R
44	Br	H	*m*-Cl	CH_3		1R,2R/1S,2S
45	Br	H	*m*-CH_3	CH_3		1R,2S/1S,2R
46	Br	H	*m*-CH_3	CH_3		1R,2R/1S,2S
47	Br	H	*o*-CH_3	CH_3		1R,2S/1S,2R
48	Br	H	*o*-CH_3	CH_3		1R,2R/1S,2S

found that racemate whose configuration was 1R,2S/1S,2R possess superior antituberculosis activity than racemate whose configuration was 1R,2R/1S,2S. Compounds **23**, **25**, **28**, **32**, **39** and **43** provided superior anti-mycobacterial activity than positive control **PC01** which shows the same configuration and contains **TMC207**. Compounds **16**, **20**, **29**, **34**, **37**, **45** and **47** exhibited the similar activity to positive control **PC01**.

In addition, compounds **23, 25, 28, 32, 39, 43** and **45** who showed high activity against drug-sensitive strains H37Rv were evaluated especially their MICs against two clinical-isolated *Mtb* strains 040 and 004 in MABA (Table 3). 040 is a kind of strains resistant to Isoniazid (INH), Rifampin (RMP), Protionamid (Pto), Rifapeatine (RPT), Ofloxacin (OFX), Levofloxcin (LVFX) and 004 is resistant to Streptomycin (SM), RMP, RPT, Kanamycin KM, OFX. They are all sort of *XDR-Mtb* strains. The results showed that the compounds **28** and **39** exhibited exciting activity against *XDR-Mtb* strains and illustrated the promise of this series of compounds.

2.3. Acute toxicity

Preliminary assessment of acute toxicity of compounds **12**, **16**, **20, 23, 25, 28, 32, 39 and 43** in mice is shown in Table 4. During the 7 days there was no mice dead after the intragastric administration in a single dose of 500 mg/kg in test groups. And no obvious pathological changes were observed in tissues of mice dissected at the 7th day.

3. Discussion

Based on our strategy of modifying **TMC207**, we have presented a new class of anti-TB compounds. Table 2 reveals that triaryl-based compounds show good anti-TB activity. Comparing target compounds with the positive control compounds, we can find out that some target compounds replacing the quinoline rings of **TMC207** and its derivates with naphthalene rings show satisfactory anti-TB activity. Thereby it can confirm that quinoline's nitrogen atom of **TMC207** is not the binding site attaching to ATP synthase and not contributed to its high activity.

The MICs against *M. tuberculosis* H37Rv of **TMC207**, **PC01** and **PC02** are 0.025, 0.189 and > 32 μg/mL respectively. **TMC207** shows the strongest anti-TB activity due to its most stable connection to amino acid residues of ATP synthase. Like **TMC207** and its stereoisomers, racemate of target compounds which contain (1R, 2S) compounds summarized in Table 2 display superior anti-TB activity than those racemate which contain another configuration.

From the structures we can observe that compound **12** has a Br atom at 7-position of 1-naphthyl but compound **13** has not. This small difference has led to various activities. MIC of compound **12** is 0.594 μg/mL while **13** is 2.047 μg/mL. The same phenomenon can be observed between compounds **16** and **18**. It implicates that 7-Br attaching to 1-naphthyl plays an important role in keeping compound's anti-TB activity.

Compounds **39** bearing a hydrogen bond acceptor (OCH_3) at 3-position of 1-naphthyl has shown very high activity (MIC is 0.124 μg/mL). Replacement of hydrogen bond receptor (OCH_3) with hydrogen bond donor (OH) in compound **41** resulted in poor activity profile (MIC is 1.000 μg/mL). It might suggest that the docking site of ATP synthase with 1-naphthyl's 3-position of target compound provide a hydrogen bond donor.

Compounds **16**, **37**, **43**, **45** and **47** whose 1-phenyl were linked with an electron-withdrawing group (Cl) or an electron-donating group (CH_3) at *ortho*, *meta* or *para* positions exhibited comparable activity profile to positive control **PC01**. In addition, compounds **20**, **23**, **25**, **28**, **29**, **32** and **34** whose 2-naphthyl were replaced with *ortho*, *meta* or *para* bromo-substituted phenyl also showed comparable activity profile to positive control **PC01**. From the information mentioned above we consider that substituent type and its position attaching to 1-phenyl and 2-phenyl of target compounds are unimportant.

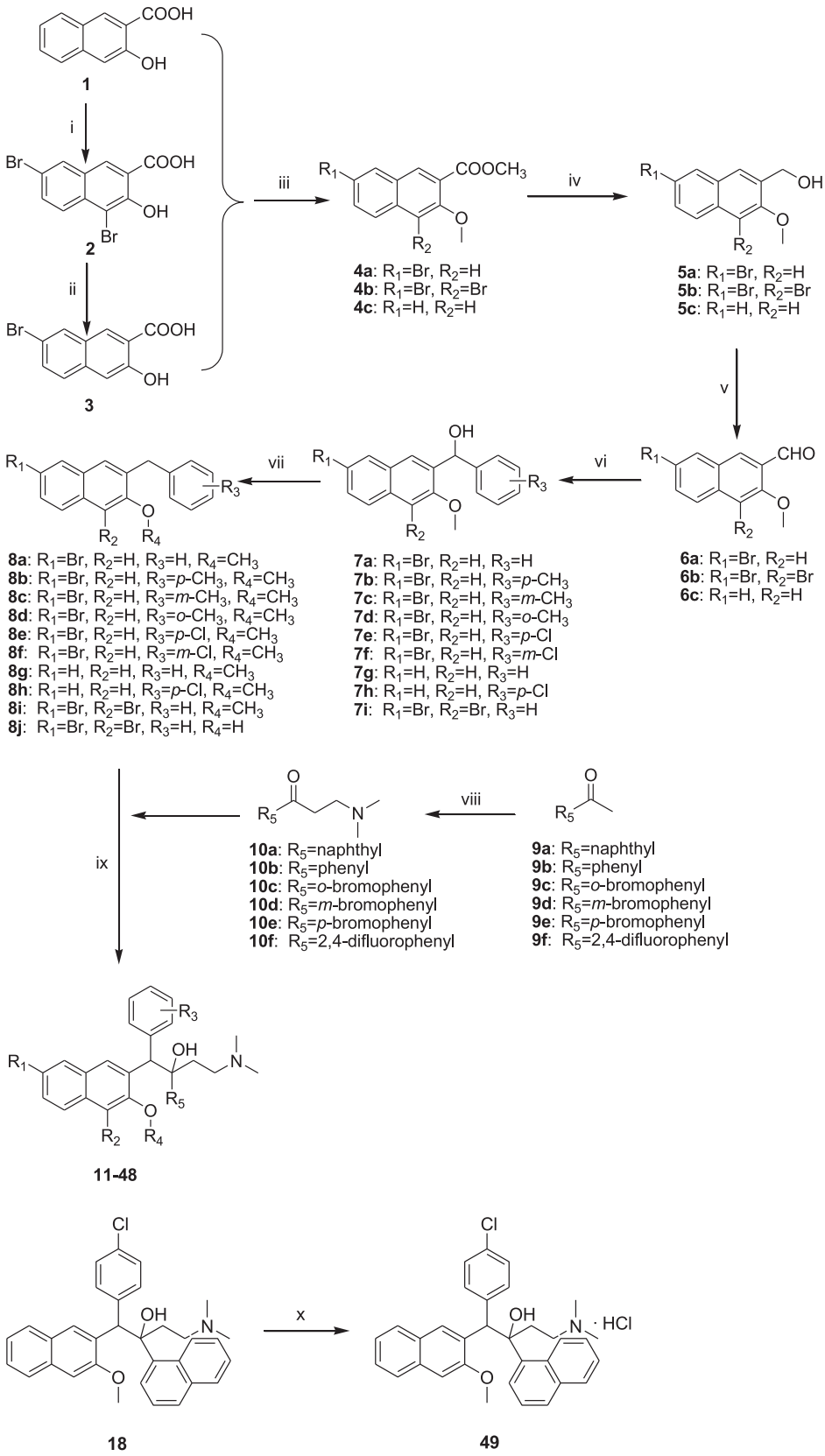
Comparing compound **18** and its hydrochloride **49**, we saw that the MIC of **18** is 1.454 μg/mL while **49** is 0.962 μg/mL. It might indicate that salification can enhance the compound's activity profile.

In Table 3, we can see that MICs of compound **39** against *XDR-Mtb* strains 040 and 004 are 0.085 μg/mL and 0.182 μg/mL separately while their MICs against H37Rv are0.074 μg/mL. The comparable activity tells us the series of compounds can perfectly inhibit drug-resistant *Mtb* even *XDR-Mtb* and illustrate their promising future.

From the results of acute toxicity listed in Table 4, we can find out that IC_{50}s of compounds **12, 16, 20, 23, 25, 28, 32, 39 and 43** are all greater than 500 mg/kg. Also, no obvious pathological changes were observed in tissues of mice. Therefore, the toxicity of this series of compounds we synthesized could be graded as low.

4. Conclusion

In summary, we synthesized a series of compounds modified from **TMC207**. All target compounds were evaluated for their MICs against *M. tuberculosis* strain H37Rv in MABA. Compounds **16**, **20**, **23**, **25**, **28**, **29**, **32**, **34**, **37**, **39**, **43**, **45** and **47** showed comparable activity profile to positive control **PC01**. Especially importantly, they also showed excellent activity against *XDR-Mtb*. From SAR analysis of this series of compounds, it was demonstrated that quinoline's nitrogen atom of



Scheme 1. Reagents and conditions: (i) bromine (2.5 equiv), AcOH, reflux, 10 h, 90%; (ii) powdery tin (1.2 equiv), 12 N HCl (1.5 equiv), AcOH, reflux, 12 h, 96%; (iii) $(CH_3)_2SO_4$ (2.5 equiv), K_2CO_3 (5 equiv), acetone, reflux, 10 h, 75–86%; (iv) $LiAlH_4$ (1.1 equiv), diethyl ether, reflux, 5 h, 85–98%; (v) MnO_2 (15 equiv), acetone, r.t., 48 h, 84–87%; (vi) substituted bromobenzene (1.2 equiv), Mg turnings (1.2 equiv), I_2 (catalytic amount), THF, reflux, 3 h, 89–95%; (vii) $NaBH_4$ (5 equiv), $AlCl_3$ (3 equiv), THF, reflux, 20 h, 81–86%; (viii) (a) dimethylamine hydrochloride (1.3 equiv), paraformaldehyde (1.3 equiv), 12 N HCl (0.02 equiv), 95% ethanol, reflux, 2 h, 69–85%; (b) $NaHCO_3$, alkalization, 90–95%; (ix) **8a-8j** (1 equiv), **10a-10f** (1.5 equiv), 2.5 M *n*-BuLi (1.1 equiv), Diisopropyl amine (1.1 equiv), THF, −78 °C, 10 h; (x) HCl-Et_2O, acetone, r.t., 88%.

TMC207 is not necessary for its activity. We also found out that 7-Br and 3-position hydrogen bond acceptor (OCH_3) play a key role in anti-TB activity. In addition, a large steric bulk of triaryl is necessary for high selectivity against mycobacterium. The experiment of acute toxicity in mice provided the point that the toxicity of triaryldimethylaminobutan-2-ol derivatives we synthesized could be graded as low. Accordingly, this class of triaryldimethylaminobutan-2-ol derivatives has shown a great potential to develop novel, high effective and hypotoxic anti-TB agents.

Table 2
MICs of compounds against *M. tuberculosis* H37Rv.

Compd. No.	Config.	MIC (μg/mL)	Compd. No.	Config.	MIC (μg/mL)
PC01[a]	**1R,2S/1S,2R**	0.189	**PC02**[b]	**1R,2R/1S,2S**	> 32
12		0.594	**11**		1.977
13		2.047	**14**		3.178
16		0.244	**15**		2.883
18		1.454	**17**		3.052
20		0.184	**19**		2.166
22		0.956	**21**		1.000
23		0.118	**24**		2.000
25		0.103	**26**		1.000
28		0.109	**27**		2.000
29		0.206	**30**		2.000
32		0.111	**31**		2.000
34		0.224	**33**		> 32
36		0.754	**35**		1.000
37		0.222	**38**		1.000
39		0.124	**40**		1.000
41		1.000	**42**		4.000
43		0.114	**44**		3.773
45		0.180	**46**		8.000
47		0.258	**48**		1.999
49		0.962			
TMC207		0.025			
INH		0.047			
RFP		0.040			

[a] **PC01** means one compound which was consist of TMC207 and its enantiomer for positive control.

[b] **PC02** means one compound which was consist of another two diastereomer of TMC207 for positive control.

Table 3
MICs of compounds against clinical-isolated *M. tuberculosis* strains 040 and 004.

Compd. No.	MICs against *Mtb* strains (μg/mL)	
	040	**004**
43	0.125	0.5
45	0.125	0.5
23	0.152	0.331
25	0.084	0.298
28	0.091	0.307
32	0.096	0.348
39	0.085	0.182
TMC207	0.019	0.118

040 is the clinical ***M. tuberculosis*** resistant to INH RMP Pto RPT OFX LVFX
004 is the clinical ***M. tuberculosis*** resistant to SM RMP RPT KM OFX
(INH = isoniazid, RMP = rifampin, SM = streptomycin RPT = rifapeatine OFX = ofloxacin , Pto = protionamid LVFX = levofloxcin, KM = kanamycin)

5. Experimental section

5.1. Chemistry-general methods

All chemicals and reagents used were of analytical reagent. Purification and drying of reagents and solvents was carried out according to literature procedure. Melting points were determined using a RY-1 apparatus. Thin-layer chromatography (TLC) was carried out on silica gel (Yantai dexin Bio-Technology Co., Ltd., Yantai, China) GF/UV 254 and the column chromatography were performed on silica gel (10–40 μm) (200–300 mesh; Yantai Chemical Industry Research Institute, Yantai, China) visualized under UV light at 254 and 365 nm. ^{1}H NMR spectra was recorded at 400 MHz on JNM-ECA-400 instrument (JEOL Ltd., Tokyo, Japan) in the solvent indicated below. The values of chemical shifts (δ) are expressed in ppm and the coupling constants (J) in hertz (Hz). Mass spectra were recorded on Micromass ZabSpec high-resolution magnetic-sector mass spectrometer (FAB MS) (Waters, Milford, MA, USA) and the Agilent G6230A mass spectrometer for accurate mass detection (Agilent, Santa Clara, CA, USA).

Table 4
Acute toxicity of compounds in mice (IC_{50}).

Compd. No.	**IC_{50} (mg/kg)**
12	> 500
16	> 500
20	> 500
23	> 500
25	> 500
28	> 500
32	> 500
39	> 500
43	> 500

4,7-Dibromo-3-hydroxy-2-naphthoic Acid (2). In 1 L three-necked bottle, 3-hydroxy-2-naphthoic acid (**1**, 50 g, 0.27 mol) was suspended in glacial acetic acid (600 mL). To this mechanically stirred mixture was added dropwise a solution of bromine (34 mL, 0.67 mol) in glacial acetic acid (100 mL) maintaining the reaction temperature in the range of 20–30 °C, Following the addition, the reaction mixture was refluxed for 10 h, then cooled to room temperature and filtered. Washed the filter cake with water (3 × 100 mL), ether (100 mL) and dried to obtain yellow product (82.8 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (dd, J = 2.0, 9.2 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 8.40 (d, J = 2.0 Hz, 1H), 8.63 (s, 1H). FAB MS (m/z): $[M]^+$ = 344.8.

7-Bromo-3-hydroxy-2- naphthoic Acid (3). In 1 L three-necked bottle, 4,7-dibromo-3-hydroxy-2-naphthoic acid (**2**, 40 g, 0.116 mol) was suspended in glacial acetic acid (500 mL) then 12 N HCl (130 mL) and powdery tin (18 g, 0.153 mol) was added. The reaction mixture was refluxed for 12 h, then cooled to room temperature and filtered. Washed the filter cake with water (3 × 100 mL) and dried to obtain yellow product (29.9 g, 96.5%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.36 (s, 1H), 7.64 (dd, J = 2.0, 8.8 Hz, 1H), 7.75 (d, J = 9.2 Hz, 1H), 8.28 (d, J = 1.6 Hz, 1H), 8.54 (s, 1H), 11.21 (br s, 1H).

Methyl 7-bromo-3-methoxy-2-naphthoate (4a). In 2 L three-necked bottle, 7-bromo-3-hydroxy-2- naphthoic acid (**3**, 112 g, 0.42 mol) was suspended in acetone (1 L). To this mechanically stirred mixture was added anhydrous potassium carbonate (288 g, 2.08 mol) and dimethyl sulfate (99 mL, 1.05 mol). The reaction was refluxed for about 10 h, then cooled to room temperature and water (50 mL) was added stirred for 2 h to destroy any remaining dimethyl sulfate. The inorganic material was filtered and the acetone was removed under reduced pressure. The residue was taken up in methylene chloride, washed several times with water, dried over anhydrous magnesium sulfate, filtered, concentrated and recrystallized in ethyl acetate and petroleum ether to afford white product (105.6 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 3H), 4.00 (s, 3H), 7.18 (s, 1H), 7.58 (dd, J = 2.0, 8.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 8.19 (s, 1H). GC MS (m/z): $[M]^+$ = 294.0.

Methyl 4,7-dibromo-3-methoxy-2-naphthoate (4b). 4b was prepared from compound **2** according to the method of compound **4a** in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3H), 4.03 (s, 3H), 7.80 (s, 1H), 8.07 (dd, J = 1.6, 9.2 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.49 (s, 1H). GC MS (m/z): $[M]^+$ = 371.9.

Methyl 3-methoxy-2-naphthoate (4c). 4c was prepared from compound **1** according to the method of compound **4a** in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.89 (s, 3H), 7.42 (s, 1H), 7.53–7.57 (m, 1H), 7.61–7.65 (m, 1H), 7.89–7.95 (m, 3H). GC MS (m/z): $[M]^+$ = 216.1.

(7-Bromo-3-methoxynaphthalen-2-yl)methanol (5a). In 2 L three-necked bottle, lithium aluminum hydride (16 g, 0.42 mol) was suspended in dry ether (200 mL) under the nitrogen. To the stirred mixture was added dropwise a solution of Methyl 7-bromo-3-methoxy-2-naphthoate (4a, 116.2 g, 0.39 mol) dissolved in dry ether (1 L) keeping the solution boiling. Then the reaction was refluxed for about

5 h and cooled to room temperature. Water (100 mL) was added dropwise carefully. The inorganic material was filtered, and the ether was removed under reduced pressure. The residue was taken up in ethyl acetate, washed several times with water, dried over anhydrous magnesium sulfate, filtered and concentrated to get white crude product which was pure enough for next step (102.5 g, 98%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3H), 4.83 (s, 2H), 7.10 (s, 1H), 7.51 (dd, J = 1.6, 8.8 Hz, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.66 (s, 1H), 7.92 (s, 1H). GC MS (m/z): $[M]^+$ = 266.0.

(4,7-Dibromo-3-methoxynaphthalen-2-yl) methanol (5b). 5b was prepared from compound **4b** according to the method of compound **5a** in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02 (s, 3H), 4.85 (s, 2H), 7.43 (s, 1H), 7.61 (dd, J = 1.6, 8.8 Hz, 1H), 7.78 (d, J = 9.2 Hz, 1H), 8.03 (d, J = 9.2 Hz, 1H). GC MS (m/z): $[M]^+$ = 343.9.

(3-Methoxynaphthalen-2-yl) methanol (5c). 5c was prepared from compound **4c** according to the method of compound **5a** in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.82 (s, 2H), 7.13 (s, 1H), 7.33–7.37 (m, 1H), 7.42–7.46 (m, 1H), 7.72–7.77 (m, 3H). GC MS (m/z): $[M]^+$ = 188.1.

7-Bromo-3-methoxy-2-naphthaldehyde (6a). In 500 mL three-necked bottle, (7-bromo-3-methoxynaphthalen-2-yl) methanol (**5a**, 34.1 g, 0.128 mol) was dissolved in acetone (350 mL), then manganese dioxide (167 g, 1.92 mol) was added. The mixture was stirred mechanically at room temperature for 48 h. Filtered and the filter cake was washed with acetone (4 × 200 mL). The filtrate was concentrated then recrystallized in methanol to get yellow solid (29.3 g, 87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.01 (s, 3H), 7.59 (s, 1H), 7.72 (dd, J = 2.0, 8.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 8.35 (s, 1H), 10.47 (s, 1H). GC MS (m/z): $[M]^+$ = 264.0.

4,7-Dibromo-3-methoxy-2-naphthaldehyde (6b). 6b was prepared from compound **5b** according to the method of compound **6a** in 84% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.04 (s, 3H), 7.80 (dd, J = 2.0, 9.2 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 8.39 (d, J = 8.8 Hz, 1H), 8.64 (s, 1H), 10.47 (s, 1H). GC MS (m/z): $[M]^+$ = 341.9.

3-Methoxy-2-naphthaldehyde (6c). 6c was prepared from compound **5c** according to the method of compound **6a** in 87% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.02 (s, 3H), 7.41–7.45 (m, 1H), 7.53 (s, 1H), 7.59–7.63 (m, 1H), 7.90 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 8.36 (s, 1H), 10.48 (s, 1H). GC MS (m/z): $[M]^+$ = 186.1.

(7-Bromo-3-methoxynaphthalen-2-yl) (phenyl)methanol (7a). In 500 mL three-necked bottle, a mixture of magnesium turnings (6 g, 0.25 mol), anhydrous tetrahydrofuran (50 mL) and a grain of iodine (catalytic amount) was unstirred. A solution of bromobenzene (26.3 mL, 0.25 mol) in anhydrous tetrahydrofuran (40 mL) was mixed in dropping funnel and 10 mL of the mixture was added into the three-necked bottle without stirring. About 10 min later, the color of iodine was disappeared accompanying the generation of gas bubble. The reaction mixture was stirred and the rest of solution of bromobenzene was added dropwise into it. The reaction was refluxed for 3 h and then cooled to room temperature. A solution of 7-Bromo-3-methoxy-2-naphthaldehyde (**6a**, 26.4 g, 0.1 mol) in anhydrous tetrahydrofuran (150 mL) was added dropwise into the reaction and it was refluxed for another 1.5 h then cooled. Hydrochloric acid (50 mL, 5%) was added slowly and the reaction solution was concentrated to remove tetrahydrofuran. The mixture was extracted with ethyl acetate and washed several times with water, dried over anhydrous magnesium sulfate, filtered and concentrated to get white crude product (36 g) which could be used for the next step without further purification. The crude product could be also purified by column chromatography over silica gel (10–40 μm), eluent: methylene chloride/petroleum ether (1/2, v/v) to afford **7a** (30.4 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 6.15 (s, 1H), 7.09 (s, 1H), 7.30–7.28 (m, 1H), 7.36–7.32 (m, 2H), 7.42–7.40 (m, 2H), 7.49 (dd, J = 2.0, 8.8 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.90 (d, J = 1.6 Hz, 1H). GC MS (m/z): $[M]^+$ = 342.1. Compounds **7b-7i** were prepared without further purification from **6a-6c** reacted with different commercially available substituted bromobenzenes in a range of 89–95% yields.

3-Benzyl-6-bromo-2-methoxynaphthalene (8a). In 500 mL three-necked bottle, (7-bromo-3-methoxynaphthalen-2-yl) (phenyl)methanol (**7a**, 30.4 g, 0.09 mol) was dissolved in anhydrous tetrahydrofuran (200 mL) and sodium borohydride (17 g, 0.45 mol) was suspended in it under nitrogen gas. The mixture was stirred and cooled in ice water about 30 min and then anhydrous aluminum trichloride (35.6 g, 0.27 mol) was added in batch maintaining the reactive temperature under 20 °C. The mixture was refluxed for about 20 h and cooled to room temperature. Water (100 mL) was added slowly and the mixture was extracted with ethyl acetate (3 × 100 mL) and dried over anhydrous magnesium sulfate, then filtered and concentrated to get white crude product. The crude product was purified by column chromatography over silica gel (10–40 μm), eluent: petroleum ether to afford **8a** (25.5 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.09 (s, 2H), 7.05 (s, 1H), 7.31–7.21 (m, 5H), 7.34 (s, 1H), 7.44 (dd, J = 2.0, 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H). GC MS (m/z): $[M]^+$ = 326.0.

6-Bromo-2-methoxy-3-(4-methylbenzyl) naphthalene (8b). 8b was prepared from compound **7b** according to the method of compound **8a** in75 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H), 3.91 (s, 3H), 4.05 (s, 2H), 7.05 (s, 1H), 7.11 (dd, J = 8.4, 12.0 Hz, 4H), 7.34 (s, 1H), 7.43 (dd, J = 2.0, 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H). GC MS (m/z): $[M]^+$ = 340.1.

6-Bromo-2-methoxy-3-(3-methylbenzyl) naphthalene (8c). 8c was prepared from compound **7c** according to the method of compound **8a** in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.92 (s, 3H), 4.05 (s, 2H), 7.06–7.02 (m, 4H), 7.19 (t, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.44 (dd, J = 2.0, 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H). GC MS (m/z): $[M]^+$ = 340.1.

6-Bromo-2-methoxy-3-(2-methylbenzyl) naphthalene (8d). 8d was prepared from compound **7d** according to the method of compound **8a** in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.95 (s, 3H), 4.06 (s, 2H), 7.08–7.06 (m, 3H), 7.21–7.14 (m, 3H), 7.44 (dd, J = 2.0, 8.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H). GC MS (m/z): $[M]^+$ = 340.1.

3-(4-Chlorobenzyl)-6-bromo-2-methoxynaphthalene (8e). 8e was prepared from compound **7e** according to the method of compound **8a** in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.06 (s, 2H), 7.07 (s, 1H), 7.11 (d, J = 6.8 Hz, 1H), 7.26–7.23 (m, 3H), 7.35 (s, 1H), 7.45 (dd, J = 2.0, 8.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H). GC MS (m/z): $[M]^+$ = 360.0.

3-(3-Chlorobenzyl)-6-bromo-2-methoxynaphthalene (8f). 8f was prepared from compound **7f** according to the method of compound **8a** in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.05 (s, 2H), 7.06 (s, 1H), 7.17–7.14 (m, 2H), 7.23–7.16 (m, 2H), 7.38 (s, 1H), 7.46 (dd, J = 1.6, 8.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 1.2 Hz, 1H). GC MS (m/z): $[M]^+$ = 360.0.

2-Benzyl-3-methoxynaphthalene (8g). 8g was prepared from compound **7g** according to the method of compound **8a** in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.11 (s, 2H), 7.10 (s, 1H), 7.31–7.19 (m, 6H), 7.40–7.36 (m, 1H), 7.47 (s, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H). GC MS (m/z): $[M]^+$ = 248.0.

2-(4-Chlorobenzyl)-3-methoxynaphthalene (8h). 8h was prepared from compound **7h** according to the method of compound **8a** in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 4.06 (s, 2H), 7.10 (s, 1H), 7.17–7.15 (m, 2H), 7.24–7.22 (m, 2H), 7.30 (dt, J = 0.8, 7.6 Hz, 1H), 7.39 (dt, J = 1.6, 7.6 Hz, 1H), 7.46 (s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H). GC MS (m/z): $[M]^+$ = 282.1.

3-Benzyl-1,6-dibromo-2-methoxynaphthalene (8i) and 3-Benzyl-1,6-dibromonaphthalen-2-ol (8j). 8i and 8j were prepared from compound **7i** according to the method of compound **8a** in 41% and 36% yield respectively. **8i** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 4.19 (s, 2H), 7.25–7.22 (m, 3H), 7.33–7.30 (m, 2H), 7.41 (s, 1H),

7.58 (dd, J = 2.0, 9.2 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 9.6 Hz, 1H), GC MS (m/z): $[M]^+$ = 404.0. **8j** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17 (s, 2H), 6.05 (s,1H), 7.34–7.24 (m, 5H), 7.38 (s, 1H), 7.56 (dd, J = 2.0, 9.2 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.84 (s, 1H). ESI MS (m/z): $[M\text{-}H]^+$ = 388.9.

3-(Dimethylamino)-1-(naphthalen-1-yl) propan-1-one (10a). In 500 mL three-necked bottle, 1-(naphthalen-1-yl) ethanone (**9a**, 25 g, 0.15 mol), dimethylamine hydrochloride (15.6 g, 0.19 mol) and paraformaldehyde (7.2 g, 0.08 mol) were placed in the bottle. After the addition of 0.3 mL of concentrated hydrochloric acid in 40 mL of 95% ethanol, the mixture was refluxed for 2 h. Then the acetone (100 mL) was added while the solution was still hot. Cooled slowly to room temperature and chilled overnight in the refrigerator. Filtered and washed with acetone (2 × 20 mL) to afford white solid 3-(dimethylamino)-1-(naphthalen-1-yl)propan-1-one Hydrochloride (26.8 g, 69%). The solid was dissolved in water, alkalinized with saturated Sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, then filtered and concentrated to get colorless oleosus product (**10a**, 20.5 g, 89%) which was easily decomposed but suitable for next step without further purification. Compounds **10b-10f** were prepared without further purification from different commercially available substituted-ethanones in a range of 59–67% yields.

1-(7-Bromo-3-ethylnaphthalen-2-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (11 and 12). In 100 mL three-necked bottle, *n*-Butyl Lithium (2.5 M in hexane, 4 mL, 10 mmol) was added slowly using an injector at −40 °C under nitrogen gas to a solution of diisopropylamine (1.4 mL, 10 mmol) in anhydrous tetrahydrofuran (15 mL). The mixture was stirred at −40 °C for 30 min and cooled to −78 °C. A solution of 3-benzyl-6-bromo-2-methoxynaphthalene (**8a**, 3.0 g, 9.2 mmol) in anhydrous tetrahydrofuran (15 mL) was dropped into the reaction. The mixture was stirred at −78 °C for 40 min. A solution of 3-(dimethylamino)-1-(naphthalen-1-yl) propan-1-one (**10a**, 2.9 g, 12.8 mmol) in anhydrous tetrahydrofuran (15 mL) was added dropwise. The mixture was stirred at −78 °C for 10 h and hydrolyzed with saturated ammonium chloride aqueous solution at −40 °C. The mixture was extracted with ethyl acetate and the organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (10–40 μm), eluent: ethyl acetate/petroleum ether/methanol/ammonia water (1/50/0.05/0.01, v/v) to afford two fractions. The first fraction was crystallized in isopropyl ether to obtain compound **11** and the second fraction was crystallized in isopropyl ether to obtain compound **12**.

11, yield 2.95%, mp 168.1–169.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00–2.05 (m, 8H), 2.35 (br s, 1H), 2.51 (br s, 1H), 3.01 (s, 3H), 5.87 (s, 1H), 6.48 (s, 1H), 7.21–7.27 (m, 4H), 7.35–7.44 (m, 3H), 7.52–7.57 (m, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.91–7.95 (m, 3H), 8.21 (br s, 1H), 8.33 (s, 1H), 8.51 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.15, 143.17, 133.52, 131.25, 130.98, 129.38, 128.52, 127.47, 126.91, 126.13, 125.98, 125.40, 124.87, 124.27, 123.85, 123.49, 104.62, 88.55, 78.34, 77.52, 77.37, 76.31, 76.08, 56.54, 54.93, 51.32, 43.89, 35.01. ESI MS (m/z): $[M + H]^+$ = 556.5. HRMS (ESI) m/z calcd for $C_{33}H_{32}BrNO_2$ $[M + H]^+$: 556.1674, found 556.1670.

12, yield 2.36%, mp 200.9–201.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (m, 2H), 1.98 (s, 6H), 2.18 (t, J = 9.6 Hz, 1H), 2.45 (m, 1H), 4.07 (s, 3H), 6.05 (s, 1H), 6.88 (t, J = 3.2 Hz, 3H), 7.11 (s, 2H), 7.16 (s, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.47–7.51 (m, 2H), 7.60 (t, J = 8.8 Hz, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 8.03 (s, 1H), 8.34 (br s, 1H), 8.64 (d, J = 8.4 Hz, 1H), 8.75 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.98, 142.41, 133.18, 130.36, 130.01, 129.90, 128.44, 127.95, 127.84, 127.55, 127.36, 126.39, 125.88, 125.01, 124.66, 124.29, 104.08, 81.95, 77.44, 77.33, 77.12, 76.81, 76.73, 56.44, 54.64, 50.56, 44.81, 34.39. ESI MS (m/z): $[M + H]^+$ = 556.5. HRMS (ESI) m/z calcd for $C_{33}H_{32}BrNO_2$ $[M + H]^+$: 556.1674, found 556.1670.

4-(Dimethylamino)-1-(3-methoxynaphthalen-2-yl)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (13 and 14). 13 and 14 was prepared from **8g** and **10a** according to the method of compound **11** and **12**. But the purification was changed by column chromatography over silica gel (10–40 μm) using a different eluent: methylene chloride/methanol/ammonia water (400/1/0.1, v/v) to afford two fractions. The first fraction was crystallized in isopropyl ether to obtain compound **13** and the second fraction was crystallized in isopropyl ether to obtain compound **14**.

13, yield 2.14%, mp 154.0–154.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (br s, 8H), 2.25–2.28 (m, 1H), 2.45–2.47 (m, 1H), 4.07 (s, 3H), 6.07 (s, 1H), 6.88–6.89 (m, 3H), 7.10 (s, 2H), 7.20 (s, 1H), 7.31–7.38 (m, 2H), 7.43 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.59–7.63 (m, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.88–7.90 (m, 3H), 8.37 (br s, 1H), 8.67 (d, J = 8.0 Hz, 1H), 8.85 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.21, 143.31, 141.26, 135.42, 133.35, 131.42, 130.51, 130.02, 129.14, 128.10, 127.85, 127.44, 127.23, 126.35, 125.63, 125.33, 125.28, 125.18, 124.63, 123.64, 105.15, 82.53, 76.87, 56.48, 56.17, 48.43, 44.67, 32.67. ESI MS (m/z): $[M + H]^+$ = 476.4. HRMS (ESI) m/z calcd for $C_{33}H_{33}NO_2$ $[M + H]^+$: 476.2589, found 476.2590.

14, yield 2.86%, mp 185.7–187.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (br s, 8H), 2.34–2.37 (m, 1H), 2.48–2.51 (m, 1H), 3.02 (s, 3H), 5.89 (s, 1H), 6.53 (s, 1H), 7.18–7.24 (m, 5H), 7.35–7.43 (m, 4H), 7.54 (t, J = 7.2 Hz, 2H), 7.71 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 7.6 Hz, 2H), 7.98 (d, J = 6.4 Hz, 1H), 8.19 (br s, 1H), 8.39 (s, 1H), 8.54 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.68, 142.73, 141.46, 134.85, 133.27, 131.49, 130.31, 129.88, 129.00, 128.23, 128.07, 127.48, 127.02, 126.30, 125.84, 125.70, 125.48, 125.18, 124.52, 123.53, 104.93, 82.74, 77.45, 56.52, 56.00, 48.97, 44.78, 33.57. ESI MS (m/z): $[M + H]^+$ = 476.3. HRMS (ESI) m/z calcd for $C_{33}H_{33}NO_2$ $[M + H]^+$: 476.2589, found 476.2590.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-1-(4-chlorophenyl)-4-(dimethylamino)-2-(naphthalen-1-yl) butan-2-ol (15 and 16). 15 and 16 was prepared from **8e** and **10a** according to the method of compound **11** and **12**.

15, yield 31.6%, mp 185.1–185.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86–1.91 (m, 8H), 2.01–2.08 (m, 2H), 3.28 (s, 3H), 5.82 (s, 1H), 6.79 (s, 1H), 7.29–7.45 (m, 6H), 7.56–7.60 (m, 2H), 7.79–7.84 (m, 4H), 7.92 (d, J = 1.6 Hz, 1H), 8.10 (d, J = 7.6 Hz, 1H), 8.48 (s, 1H), 8.57 (d, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-D6) δ 142.22, 140.81, 134.63, 133.90, 133.62, 129.87, 129.72, 129.47, 129.35, 128.83, 128.69, 128.34, 127.91, 127.43, 126.02, 125.67, 125.11, 116.34, 105.12, 81.45, 56.08, 55.72, 50.01, 44.89, 34.87. ESI MS (m/z): $[M + H]^+$ = 590.3. HRMS (ESI) m/z calcd for $C_{33}H_{31}BrClNO_2$ $[M + H]^+$: 590.1284 found 590.1279.

16, yield 25.3%, mp 149.0–149.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94–1.99 (m, 8H), 2.17 (br s, 1H), 2.45 (br s, 1H), 4.07 (s, 3H), 6.01 (s, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 7.16 (s, 1H), 7.35 (t, J = 8.0 Hz, 2H), 7.47–7.51 (m, 2H), 7.58–7.63 (m, 2H), 7.69 (d, J = 7.6 Hz, 2H), 7.90 (t, J = 8.0 Hz 2H), 8.02 (s, 1H), 8.39 (br s, 1H), 8.59 (d, J = 8.4 Hz, 1H), 8.67 (s, 1H). ^{13}C NMR (100 MHz, DMSO-D6) δ 143.12, 141.35, 134.81, 133.93 133.68, 129.98, 129.72, 129.35, 129.10, 127.90, 127.14, 127.04, 126.83, 125.84, 125.02, 124.82, 124.31, 116.29, 103.79, 80.86, 57.23, 54.31, 50.42, 43.93, 35.15. ESI MS (m/z): $[M + H]^+$ = 590.3. HRMS (ESI) m/z calcd for $C_{33}H_{31}BrClNO_2$ $[M + H]^+$: 590.1284 found 590.1280.

1-(4-Chlorophenyl)-4-(dimethylamino)-1-(3-methoxynaphthalen-2-yl)-2-(naphthalen-1-yl) butan-2-ol (17 and 18). 17 and 18 was prepared from **8h** and **10a** according to the method of compound **11** and **12**.

17, yield 30.1%, mp 215.4–215.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00 (br s, 8H), 2.27 (t, J = 12.4 Hz, 1H), 2.48 (d, J = 12.8 Hz, 1H), 3.09 (s, 3H), 5.85 (s, 1H), 6.54 (s, 1H), 7.17–7.24 (m, 3H), 7.32 (d, J = 8.0 Hz, 2H), 7.38–7.42 (m, 2H), 7.51–7.55 (m, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 6.8 Hz, 1H), 8.24 (br s, 1H), 8.37 (s, 1H), 8.48 (d,

J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):δ 155.37, 141.15, 134.47, 133.90, 130.98, 130.53, 130.27, 130.05, 129.84, 129.16, 128.81, 128.15, 127.62, 127.41, 126.63, 125.35, 124.72, 124.38, 124.27, 123.81, 123.14, 104.31, 57.31, 56.43, 47.15, 43.26, 35.72. ESI MS (m/z): $[M + H]^+$ = 510.4. HRMS (ESI) m/z calcd for $C_{33}H_{32}ClNO_2$ $[M + H]^+$: 510.2200 found 510.2194.

18, yield 24.8%, mp 180.5–181.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (br s, 8H), 2.24 (br s, 1H), 2.43 (br s, 1H), 4.07 (s, 3H), 6.03 (s, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 7.6 Hz, 2H), 7.20 (s, 1H), 7.33–7.38 (m, 2H), 7.43 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.86–7.91 (m, 3H), 8.41 (br s, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.76 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):δ 156.48, 140.16, 134.87, 133.30, 131.91, 131.60, 131.34, 131.21, 130.07, 129.96, 128.94, 128.24, 128.19, 127.51, 127.16, 126.33, 125.99, 125.48, 125.27, 124.60, 123.67, 105.01, 56.48, 56.00, 48.37, 44.76, 33.41. ESI MS (m/z): $[M + H]^+$ = 510.4. HRMS (ESI) m/z calcd for $C_{33}H_{32}ClNO_2$ $[M + H]^+$: 510.2200 found 510.2194.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-2-(3-bromophenyl)-1-(4-chlorophenyl)-4-(dimethylamino) butan-2-ol (19 and 20). 19 and 20 was prepared from **8e** and **10d** according to the method of compound **11** and **12**.

19, yield 35.3%, mp 177.1–177.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (br s, 1H), 2.06 (br s, 8H), 2.22–2.24 (m, 1H), 3.73 (s, 3H), 4.93 (s, 1H), 6.75 (s, 1H), 6.98 (t, J = 8.0 Hz, 1H), 7.14 (dd, J = 0.8 Hz, 8.0 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.32–7.39 (m, 3H), 7.63 (s, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 1.6 Hz, 2H), 8.23 (br s, 1H), 8.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.59, 149.93, 140.30, 132.96, 132.38, 132.18, 130.00, 129.23, 129.12, 129.06, 128.80, 127.95, 124.97, 122.03, 104.50, 81.01, 77.45, 55.91, 55.59, 51.26, 44.85, 36.03. ESI MS (m/z): $[M + H]^+$ = 618.1. HRMS (ESI) m/z calcd for $C_{29}H_{28}Br_2ClNO_2$ $[M + H]^+$: 618.0233 found 618.0229.

20, yield 27.2%, mp 183.9–184.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (d, J = 11.2 Hz, 1H), 2.05–2.23 (m, 9H), 3.96 (s, 3H), 4.95 (s, 1H), 6.97 (d, J = 8.4 Hz, 2H), 7.08 (s, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.46 (dd, J = 2.0, 8.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.60 (s, 1H), 7.96 (d, J = 1.6 Hz, 1H), 8.27 (s, 1H), 8.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.39, 150.12, 139.64, 133.33, 131.68, 131.52, 130.02, 129.95, 129.52, 129.35, 129.23, 128.00, 127.54, 125.10, 122.40, 117.08, 104.91, 81.56, 77.46, 56.08, 55.85, 51.10, 44.88, 34.64. ESI MS (m/z): $[M + H]^+$ = 618.2. HRMS (ESI) m/z calcd for $C_{29}H_{28}Br_2ClNO_2$ $[M + H]^+$: 618.0233 found 618.0228.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-2-(4-bromophenyl)-1-(4-chlorophenyl)-4-(dimethylamino)butan-2-ol (21 and 22). 21 and 22 was prepared from **8e** and **10e** according to the method of compound **11** and **12**.

21, yield 34.7%, mp 219.5–220.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (br s, 1H), 2.05–2.24 (m, 9H), 3.70 (s, 3H), 4.90 (s, 1H), 6.75 (s, 1H), 724–7.28 (m, 4H), 7.33–7.40 (m, 4H), 7.65 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 1.6 Hz, 1H), 8.16 (br s, 1H), 8.35 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.65, 146.47, 140.19, 133.07, 132.12, 131.40, 130.71, 130.00, 129.75, 129.03, 128.81, 127.95, 127.92, 127.02, 120.15, 116.42, 104.12, 81.73, 77.05, 55.92, 55.76, 50.97, 45.29, 33.57. ESI MS (m/z): $[M + H]^+$ = 618.3. HRMS (ESI) m/z calcd for $C_{29}H_{28}Br_2ClNO_2$ $[M + H]^+$: 618.0233 found 618.0228.

22, yield 25.3%, mp 213.5–214.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (d, J = 11.2 Hz, 1H), 2.04–2.20 (m, 9H), 3.94 (s, 3H), 4.95 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.08 (s, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 9.2 Hz, 2H), 7.46 (dd, J = 2.0, 8.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 8.20 (br s, 1H), 8.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.17, 146.81, 141.02, 133.41, 132.80, 130.74, 130.02, 129.74, 129.55, 128.97, 128.65, 128.31, 127.90, 127.78, 119.91, 116.66, 104.52, 80.97, 77.07, 55.85, 55.47, 51.49, 44.83, 36.08. ESI MS (m/z): $[M + H]^+$ = 618.3. HRMS (ESI) m/z calcd for $C_{29}H_{28}Br_2ClNO_2$ $[M + H]^+$: 618.0233 found 618.0227.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-2-(4-bromophenyl)-4-(dimethylamino)-1-phenylbutan-2-ol (23 and 24). 23 and 24 was prepared from **8a** and **10e** according to the method of compound **13** and **14**.

23, yield 3.17%, mp 189.8–190.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70 (br s, 1H), 2.04–2.21 (m, 9H), 3.95 (s, 3H), 5.00 (s, 1H), 6.96–7.02 (m, 3H), 7.08 (s, 1H), 7.23 (d, J = 7.2 Hz, 2H), 7.34 (dd, J = 8.8, 12.0 Hz, 4H), 7.45 (dd, J = 2.0, 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H), 8.15 (br s, 1H), 8.67 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ155.17, 134.02, 131.73, 131.38, 130.97, 130.27, 129.31, 128.92, 128.28, 128.05, 127.51, 120.05, 117.38, 105.18, 80.29, 78.02, 77.21, 77.15, 76.21, 54.93, 55.21, 52.72, 45.17, 35.29. ESI MS (m/z): $[M + H]^+$ = 584.2. HRMS (ESI) m/z calcd for $C_{29}H_{29}Br_2NO_2$ $[M + H]^+$: 584.0623 found 584.0619.

24, yield 4.34%, mp 228.2–229.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (br s, 1H), 2.03–2.17 (m, 9H), 3.69 (s, 3H), 4.94 (s, 1H), 6.74 (s, 1H), 7.19–7.40 (m, 9H), 7.71 (d, J = 6.8 Hz, 2H), 7.86 (d, J = 1.6 Hz, 1H), 8.08 (br s, 1H), 8.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ155.80, 133.42, 131.34, 131.10, 130.58, 130.01, 129.21, 128.64, 128.03, 127.78, 126.32, 119.77, 116.50, 104.41, 81.03, 77.40, 77.31, 77.07, 76.77, 55.87, 55.46, 52.08, 44.79, 36.07. ESI MS (m/z): $[M + H]^+$ = 584.2. HRMS (ESI) m/z calcd for $C_{29}H_{29}Br_2NO_2$ $[M + H]^+$: 584.0623 found 584.0617.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-2-(3-bromophenyl)-4-(dimethylamino)-1-phenylbutan-2-ol (25 and 26). 25 and 26was prepared from **8a** and **10d** according to the method of compound **13** and **14**.

25, yield 2.96%, mp 212.3–212.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70 (d, J = 10.8 Hz, 1H), 2.04–2.25 (m, 9H), 3.96 (s, 3H), 4.99 (s, 1H), 6.94–7.12 (m, 5H), 7.24 (d, J = 7.6 Hz, 3H), 7.39 (d, J = 7.6 Hz, 1H), 7.45 (dd, J = 1.6, 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.600 (s, 1H), 7.97 (d, J = 1.6 Hz, 1H), 8.20 (br s, 1H), 8.67 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ156.58, 140.86, 133.74, 131.63, 130.36, 130.04, 129.62, 129.45, 129.34, 129.16, 129.05, 127.94, 127.37, 125.74, 125.14, 122.26, 116.93, 104.81, 81.68, 77.40, 77.08, 56.10, 55.83, 51.76, 44.87, 34.73. ESI MS (m/z): $[M + H]^+$ = 584.3. HRMS (ESI) m/z calcd for $C_{29}H_{29}Br_2NO_2$ $[M + H]^+$: 584.0623 found 584.0618.

26, yield 4.17%, mp 200.2–200.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (br s, 1H), 2.05–2.24 (m, 9H), 3.73 (s, 3H), 4.98 (s, 1H), 6.74 (s, 1H), 6.98 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 7.19–7.42 (m, 6H), 7.64 (s, 1H), 7.75 (s, 2H), 7.86 (d, J = 1.6 Hz, 1H), 8.15 (br s, 1H), 8.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ155.72, 141.07, 134.05, 131.21, 130.72, 130.40, 129.93, 129.55, 129.01, 128.87, 128.52, 127.31, 127.01, 125.25, 125.11, 123.06, 117.13, 103.92, 82.02, 77.41, 77.04, 55.83, 55.65, 51.26, 44.72, 35.73. ESI MS (m/z): $[M + H]^+$ = 584.2. HRMS (ESI) m/z calcd for $C_{29}H_{29}Br_2NO_2$ $[M + H]^+$: 584.0623 found 584.0616.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-1-(4-chlorophenyl)-4-(dimethylamino)-2-phenylbutan-2-ol (27 and 28). 27 and 28 was prepared from **8e** and **10b** according to the method of compound **11** and **12**.

27, yield 30.2%, mp 196.8–197.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (br s, 1H), 2.05–2.26 (m, 9H), 3.69 (s, 3H), 4.96 (s, 1H), 6.73 (s, 1H), 7.01 (t, J = 7.2 Hz, 1H), 7.15 (t, J = 7.6 Hz, 2H), 7.24 (s, 1H), 7.26 (s, 1H), 7.32 (dd, J = 2.0, 8.8 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.49 (d, J = 6.8 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 1.6 Hz, 1H), 8.06 (br s, 1H), 8.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.85, 147.13, 140.47, 132.58, 131.96, 128.62, 127.75, 127.64, 125.98, 125.90, 116.50, 81.09, 55.94, 51.74, 44.85, 36.41. ESI MS (m/z): $[M + H]^+$ = 540.2. HRMS (ESI) m/z calcd for $C_{29}H_{29}BrClNO_2$ $[M + H]^+$: 540.1128 found 540.1119.

28, yield 25.7%, mp 182.2–182.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (d, J = 10.0 Hz, 1H), 2.04–2.22 (m, 9H), 3.95 (s, 3H), 5.02 (s, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.08 (s, 1H), 7.13–7.17 (m, 3H), 7.24–7.27 (m, 2H), 7.43–7.47 (m, 3H), 7.58 (d, J = 8.4 Hz, 1H), 7.97 (d,

J = 1.6 Hz, 1H), 8.14 (br s, 1H), 8.68 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.35, 147.63, 141.02, 133.18, 132.64, 129.12, 127.25, 126.92, 125.08, 124.91, 116.02, 82.39, 54.03, 51.47, 44.21, 35.41. ESI MS (m/z): $[M + H]^+$ = 540.2. HRMS (ESI) m/z calcd for $C_{29}H_{29}BrClNO_2$ $[M + H]^+$: 540.1128 found 540.1120.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-4-(dimethylamino)-1,2-diphenylbutan-2-ol (29 and 30). 29 and 30 was prepared from **8a** and **10b** according to the method of compound **13** and **14**.

29, yield 2.73%, mp 170.9–171.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (d, J = 10.8 Hz, 1H), 1.98–2.25 (m, 9H), 3.95 (s, 3H), 5.06 (s, 1H), 6.93–7.00 (m, 3H), 7.05 (s, H), 7.11 (t, J = 7.2 Hz, 1H), 7.21–7.24 (m, 3H), 7.44–7.46 (m, 3H), 7.57 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 8.08 (s, 1H), 8.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.65, 148.52, 142.74, 133.53, 131.56, 130.52, 129.17, 128.78, 128.00, 127.02, 126.54, 125.32, 104.78, 80.73, 77.43, 75.93, 55.21, 51.34, 44.72, 35.87. ESI MS (m/z): $[M + H]^+$ = 506.4. HRMS (ESI) m/z calcd for $C_{29}H_{30}BrNO_2$ $[M + H]^+$: 506.1517 found 506.1515.

30, yield 3.51%, mp 201.9–203.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (br s, 1H), 2.02–2.29 (m, 9H), 3.68 (s, 3H), 5.00 (s, 1H), 6.72 (s, 1H), 7.00 (t, J = 7.2 Hz, 1H), 7.12–7.21 (m, 3H), 7.26–7.37 (m, 4H), 7.50 (d, J = 8 Hz, 2H), 7.73 (d, J = 7.2 Hz, 2H), 7.86 (d, J = 1.6 Hz, 1H), 8.00 (br s, 1H), 8.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.02, 147.45, 141.91, 133.88, 131.23, 130.04, 129.26, 128.46, 127.66, 126.17, 126.06, 125.76, 104.32, 81.16, 77.39, 76.75, 55.97, 52.31, 44.82, 36.40. ESI MS (m/z): $[M + H]^+$ = 506.4. HRMS (ESI) m/z calcd for $C_{29}H_{30}BrNO_2$ $[M + H]^+$: 506.1517 found 506.1517.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-2-(2-bromophenyl)-1-(4-chlorophenyl)-4-(dimethylamino)butan-2-ol (31 and 32). 31 and 32 was prepared from **8e** and **10c** according to the method of compound **11** and **12**.

31, yield 29.3%, mp 219.1–219.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–2.18 (m, 9H), 2.77 (br s, 1H), 3.66 (s, 3H), 5.89 (s, 1H), 6.73 (s, 1H), 6.89 (dt, J = 1.6, 6.8 Hz, 1H), 7.10 (dt, J = 1.2, 8.0 Hz, 1H), 7.25–7.28 (m, 2H), 7.39–7.41 (m, 3H), 7.68 (d, J = 8.4 Hz, 2H), 7.84 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 8.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.57, 144.88, 140.54, 135.26, 131.92, 130.94, 130.03, 129.98, 129.01, 128.82, 128.24, 127.21, 127.01, 126.53, 119.25, 117.31, 104.72, 82.16, 77.39, 77.05, 76.82, 55.31, 54.73, 45.57, 44.83, 32.17. ESI MS (m/z): $[M + H]^+$ = 618.3. HRMS (ESI) m/z calcd for $C_{29}H_{28}Br_2ClNO_2$ $[M + H]^+$: 618.0233 found 618.0226.

32, yield 25.2%, mp 180.8–181.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–2.17 (m, 9H), 2.74 (br s, 1H), 3.97 (s, 3H), 6.08 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 7.00 (t, J = 7.6 Hz, 1H), 7.09 (s, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 7.2 Hz, 2H), 7.45 (d, J = 8.4 Hz, 1H), 7.53–7.59 (m, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.97 (s, 1H), 8.36 (br s, 1H), 8.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.00, 145.08, 140.23, 134.96, 133.22, 131.44, 130.13, 130.04, 129.91, 129.10, 128.44, 127.95, 127.41, 127.13, 119.61, 116.91, 104.89, 82.76, 77.44, 77.12, 76.80, 56.51, 55.90, 45.77, 44.77, 30.81. ESI MS (m/z): $[M + H]^+$ = 618.5. HRMS (ESI) m/z calcd for $C_{29}H_{28}Br_2ClNO_2$ $[M + H]^+$: 618.0233 found 618.0227.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-2-(2-bromophenyl)-4-(dimethylamino)-1-phenylbutan-2-ol (33 and 34). 33 and 34 was prepared from **8a** and **10c** according to the method of compound **13** and **14**.

33, yield 2.95%, mp 210.8–212.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–2.18 (m, 9H), 2.82 (br s, 1H), 3.64 (s, 3H), 5.90 (s, 1H), 6,71 (s, 1H), 6.88 (dt, J = 1.6, 7.6 Hz, 1H), 7.07 (dt, J = 1.2, 8.0 Hz, 1H), 7.21 (d, J = 7.2 Hz, 1H), 7.28–7.38 (m, 5H), 7.43 (dd, J = 1.6, 8.0 Hz, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 1.2 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H), 8.15 (br s, 1H), 8.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.85, 145.21, 141.31, 135.32, 133.51, 131.72, 130.57, 129.82, 129.71, 129.27, 128.76, 127.47, 127.32, 126.84, 119.15, 116.03, 103.98, 81.83, 55.97, 55.15, 46.32, 45.07, 31.27. ESI MS (m/z): $[M + H]^+$ = 584.3. HRMS (ESI) m/z calcd for $C_{29}H_{29}Br_2NO_2$ $[M + H]^+$: 584.0623 found 584.0616.

34, yield 3.46%, mp 200.2–200.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03–2.17 (m, 9H), 2.75 (br s, 1H), 3.97 (s, 3H), 6.09 (s, 1H), 6.92–7.01 (m, 4H), 7.08 (s, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.33–7.35 (m, 2H), 7.45 (dd, J = 2.0, 8.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H), 8.29 (br s, 1H), 8.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.00, 145.08, 140.23, 134.96, 133.22, 131.44, 130.13, 130.04, 129.91, 129.10, 128.44, 127.95, 127.41, 127.13, 119.61, 116.91, 104.89, 82.76, 56.51, 55.90, 45.77, 44.77, 30.81. ESI MS (m/z): $[M + H]^+$ = 584.0. HRMS (ESI) m/z calcd for $C_{29}H_{29}Br_2NO_2$ $[M + H]^+$:$^+$: 584.0623 found 584.0617.

1-(4-Chlorophenyl)-2-(2,4-difluorophenyl)-4-(dimethylamino)-1-(3-methoxynaphthalen-2-yl)butan-2-ol (35 and 36). 35 and 36 was prepared from **8g**and **10f** according to the method of compound **11** and **12**.

35, yield 9.57%, oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04–2.34 (m, 10*H*), 3.68 (s, 3H), 5.24 (s, 1H), 6.58–6.64 (m, 2H), 6.78 (s, 1H), 7.21–7.30 (m, 4H), 7.52 (d, J = 8.0 Hz, 2H), 7.61–7.72 (m, 4H), 8.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ141.21, 132.25, 131.27, 131.28, 128.53, 128.02, 126.86, 126.35, 123.92, 111.03, 105.39, 104.17, 103.82, 81.38, 77.35, 58.64, 56.17, 47.23, 45.21, 33.62. ESI MS (m/z): $[M + H]^+$ = 496.0. HRMS (ESI) m/z calcd for $C_{29}H_{28}ClF_2NO_2$ $[M + H]^+$: 496.1855 found 496.1849.

36, yield 5.31%, mp 190.6–192.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05–2.23 (m, 10*H*), 3.94 (s, 3H), 5.29 (s, 1H), 6.70–6.77 (m, 2H), 6.96 (d, J = 8.4 Hz, 2H), 7.12 (s, 1H), 7.23–7.28 (m, 2H), 7.33 (dt, J = 1.2, 6.8 Hz, 1H), 7.40 (dt, J = 1.2, 6.8 Hz, 1H), 7.48–7.54 (m, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.6 Hz, 2H), 8.43 (br s, 1H), 8.76 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ140.27, 131.95, 131.42, 130.41, 128.12, 127.42, 126.26, 125.94, 123.55, 110.81, 104.99, 103.85, 103.60, 80.99, 77.34, 56.61, 55.81, 48.37, 44.71, 32.44. ESI MS (m/z): $[M + H]^+$ = 496.3. HRMS (ESI) m/z calcd for $C_{29}H_{28}ClF_2NO_2$ $[M + H]^+$: 496.1855 found 496.1848.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-*p*-tolylbutan-2-ol (37 and 38). 37 and 38 was prepared from **8b** and **10a** according to the method of compound **13** and **14**.

37, yield 1.75%, oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90–2.19 (m, 12H), 2.55 (d, J = 12.4 Hz, 1H), 4.06 (s, 3H), 6.02 (s, 1H), 6.69 (d, J = 7.6 Hz, 2H), 7.01 (d, J = 6.8 Hz, 2H), 7.14 (s, 1H), 7.32–7.37 (m, 1H), 7.45–7.50 (m, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 6.8 Hz, 1H), 8.01 (s, 1H), 7.63 (s, 1H), 8.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.79, 135.04, 134.82, 131.71, 130.55, 130.08, 130.01, 129.92, 129.06, 128.17, 127.99, 127.46, 125.29, 125.21, 124.60, 116.99, 104.97, 56.22, 56.05, 48.67, 44.57, 33.67, 20.94. ESI MS (m/z): $[M + H]^+$ = 569.9. HRMS (ESI) m/z calcd for $C_{34}H_{34}BrNO_2$ $[M + H]^+$: 570.1830 found 570.1831.

38, yield 3.03%, mp 189.5–190.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86–1.91 (m, 8H), 2.09–2.11 (m, 2H), 2.28 (s, 3H), 3.20 (s, 3H), 5.77 (s, 1H), 6.75 (s, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.27–7.36 (m, 2H), 7.42–7.46 (m, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 7.6 Hz, 2H), 7.80 (d, J = 7.6 Hz, 1H), 7.92 (s, 1H), 8.04 (d, J = 7.2 Hz, 1H), 8.48 (s, 1H), 8.57 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.36, 135.57, 134.68, 132.41, 131.58, 130.37, 130.29, 129.29, 128.83, 128.07, 127.21, 128.79, 125.37, 125.02, 124.17, 117.03, 104.21, 57.17, 56.72, 47.1, 45.37, 35.67, 22.31. ESI MS (m/z): $[M + H]^+$ = 570.1. HRMS (ESI) m/z calcd for $C_{34}H_{34}BrNO_2$ $[M + H]^+$: 570.1830 found 570.1830.

1-(4,7-Dibromo-3-methoxynaphthalen-2-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (39 and 40). 39 and 40 was prepared from **8i** and **10a** according to the method of compound **13** and **14**.

39, yield 20.5%, mp 181.2–181.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94–2.08 (m, 9H), 2.48 (br s, 1H), 3.85 (s, 3H), 5.91 (s, 1H), 6.89–6.91 (m, 3H), 7.02–7.04 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.61–7.71 (m, 3H), 7.81 (d, J = 7.2 Hz, 1H), 7.92 (d,

J = 8.4 Hz, 1H), 8.11 (d, J = 9.2 Hz, 2H), 8.45 (br s, 1H), 8.64 (d, J = 8.8 Hz, 1H), 8.96 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.33, 137.63, 134.83, 132.65, 130.57, 130.44, 130.19, 128.51, 127.50, 127.26, 126.00, 125.56, 125.22, 124.70, 82.69, 61.66, 56.41, 50.90, 44.77, 33.61. ESI MS (m/z): $[M + H]^+$ = 634.6. HRMS (ESI) m/z calcd for $C_{33}H_{31}Br_2NO_2$ $[M + H]^+$: 634.0779 found 634.0773.

40, yield 24.4%, mp 189.9–190.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97–2.03 (m, 8H), 2.22 (t, J = 13.2 Hz, 1H), 2.49 (t, J = 14.4 Hz, 1H), 3.23 (s, 3H), 5.71 (s, 1H), 7.22–7.25 (m, 1H), 7.32–7.43 (m, 5H), 7.53–7.57 (m, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.73–7.80 (m, 4H), 7.93 (d, J = 1.6 Hz, 1H), 8.31 (d, J = 7.2 Hz, 1H), 8.37 (br s, 1H), 8.51 (d, J = 8.8 Hz, 1H), 8.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.52, 138.07, 134.23, 133.54, 130.57, 130.57, 130.02, 128.37, 127.16, 126.76, 126.25, 125.81, 124.87, 123.81, 81.62, 60.57, 56.58, 51.26, 44.38, 34.15. ESI MS (m/z): $[M + H]^+$ = 634.5. HRMS (ESI) m/z calcd for $C_{33}H_{31}Br_2NO_2$ $[M + H]^+$: 634.0779 found 634.0774.

1,6-Dibromo-3-(4-(dimethylamino)-2-hydroxy-2-(naphthalen-1-yl)-1-phenylbutyl)naphthalen-2-ol (41 and 42). 41 and 42 was prepared from **8j** and **10a** according to the method of compound **13** and **14**.

41, yield 23.3%, mp 186.7–187.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (br s, 8H), 2.30–2.38 (m, 1H), 2.60 (d, J = 12.8 Hz, 1H), 5.45 (s, 1H), 6.81–6.97 (m, 5H), 7.38 (t, J = 8.0 Hz, 1H), 7.55–7.59 (m, 2H), 7.68 (t, J = 7.6 Hz, 2H), 7.77–7.82 (m, 2H), 7.93 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 9.2 Hz, 1H), 8.36 (d, J = 7.2 Hz, 1H), 12.11 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ151.53, 141.07, 139.26, 134.39, 132.18, 131.16, 131.01, 129.71, 129.51, 129.00, 128.92, 128.48, 127.50, 127.37, 126.01, 125.72, 125.56, 125.15, 124.72, 116.19, 56.82, 45.10, 33.07. ESI MS (m/z): $[M + H]^+$ = 620.3. HRMS (ESI) m/z calcd for $C_{32}H_{29}Br_2NO_2$ $[M + H]^+$: 620.0623 found 620.0617.

42, yield 26.1%, mp 185.8–186.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08–2.19 (m, 8H), 2.38 (br s, 1H), 2.55 (br s, 1H), 5.40 (s, 1H), 7.27–7.38 (m, 6H), 7.48 (t, J = 7.6 Hz, 1H), 7.60–7.66 (m, 2H), 7.74 (d, J = 8.8 Hz, 1H), 7.80–7.85 (m, 3H), 8.16 (d, J = 7.2 Hz, 1H), 8.45 (d, J = 8.8 Hz, 1H), 12.29 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ150.97, 140.28, 139.74, 134.93, 131.93, 130.67, 130.34, 129.88, 129.66, 129.32, 129.15, 128.58, 127.30, 127.17, 126.14, 125.88, 125.36, 125.01, 124.20, 116.63, 56.20, 44.21, 32.54. ESI MS (m/z): $[M + H]^+$ = 620.3. HRMS (ESI) m/z calcd for $C_{32}H_{29}Br_2NO_2$ $[M + H]^+$: 620.0623 found 620.0619.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-1-(3-chlorophenyl)-4-(dimethylamino)-2-(naphthalen-1-yl)butan-2-ol (43 and 44). 43 and 44 was prepared from **8f** and **10a** according to the method of compound **13** and **14**.

43, yield 26.3%, mp 176.8–177.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88–2.16 (m, 9H), 2.46 (d, J = 14.4 Hz, 1H), 4.08 (s, 3H), 6.00 (s, 1H), 6.78 (t, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 7.17 (s, 1H), 7.24 (s, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.47–7.5 (m, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 8.03 (d, J = 1.2 Hz, 1H), 8.33 (br s, 1H), 8.60 (d, J = 8.8 Hz, 1H), 8.63 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.22, 135.20, 133.07, 131.02, 130.23, 129.53, 129.01, 128.17, 127.83, 127.05, 125.18, 124.19, 124.00, 123.01, 115.13, 105.14, 83.57, 57.52, 56.18, 49.62, 41.21, 33.91. ESI MS (m/z): $[M + H]^+$ = 590.6. HRMS (ESI) m/z calcd for $C_{33}H_{31}BrClNO_2$ $[M + H]^+$: 590.1284 found 590.1281.

44, yield 29.7%, mp 194.7–195.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (br s, 8H), 2.25–2.31 (m, 1H), 2.49 (d, J = 14.0 Hz, 1H), 3.03 (s, 3H), 5.826 (s, 1H), 6.49 (s, 1H), 7.25–7.31 (m, 6H), 7.41 (d, J = 7.6 Hz, 1H), 7.52–7.56 (m, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.87 (s, 1H), 7.95 (d, J = 7.6 Hz, 2H), 8.31 (s, 2H), 8.46 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.68, 134.89, 132.82, 130.68, 130.00, 129.24, 128.44, 128.31, 128.03, 127.65, 125.81, 125.33, 125.20, 124.62, 117.12, 104.91, 82.44, 56.43, 56.07, 48.75, 44.81, 33.41. ESI MS (m/z): $[M + H]^+$ = 590.5. HRMS (ESI) m/z calcd for $C_{33}H_{31}BrClNO_2$ $[M + H]^+$: 590.1284 found 590.1281.

1-(7-Bromo-3-methoxynaphthalen-2-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-*m*-tolylbutan-2-ol (45 and 46). 45 and 46 was prepared from **8c** and **10a** according to the method of compound **13** and **14**.

45, yield 2.35%, mp 190.7–192.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87–1.99 (m, 8H), 2.01 (s, 3H), 2.09–2.16 (m, 1H), 2.46 (d, J = 14.4 Hz, 1H), 4.07 (s, 3H), 6.00 (s, 1H), 6.68 (d, J = 7.2 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 6.89 (s, 1H), 6.96 (d, J = 7.6 Hz, 1H), 7.15 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.46–7.49 (m, 2H), 7.57–7.62 (m, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 7.2 Hz, 1H), 8.02 (s, 1H), 8.24 (br s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 8.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ156.92, 142.58, 141.24, 136.36, 134.86, 133.76, 131.70, 131.04, 130.79, 130.13, 129.88, 129.01, 128.09, 127.60, 127.32, 126.95, 126.40, 125.60, 125.18, 124.51, 116.93, 104.82, 82.69, 56.51, 56.04, 48.93, 44.84, 33.66, 21.49. ESI MS (m/z): $[M + H]^+$ = 570.7. HRMS (ESI) m/z calcd for $C_{34}H_{34}BrNO_2$ $[M + H]^+$: 570.1830, found 570.1829.

46, yield 3.14%, mp 185.6–186.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95–2.00 (m, 8H), 2.36–2.51 (m, 5H), 2.92 (s, 3H), 5.82 (s, 1H), 6.46 (s, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.26–7.29 (m, 3H), 7.42 (t, J = 7.2 Hz, 1H), 7.53–7.56 (m, 2H), 7.70 (s, 1H), 7.78–7.83 (m, 2H), 7.88–7.89 (m, 2H), 8.17 (br s, 1H), 8.30 (s, 1H), 8.52 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ155.81, 143.97, 141.72, 137.16, 135.36, 133.80, 131.20, 130.81 130.61, 130.23, 129.61, 129.51, 128.59, 127.16, 127.22, 126.71, 126.10, 125.81, 125.23, 123.96, 116.42, 103.97, 83.01, 55.21, 56.81, 49.17, 45.04, 31.82, 22.62. ESI MS (m/z): $[M + H]^+$ = 570.5. HRMS (ESI) m/z calcd for $C_{34}H_{34}BrNO_2$ $[M + H]^+$: 570.1830, found 570.1830.

1-(7-bromo-3-methoxynaphthalen-2-yl)-4-(dimethylamino)-2-(naphthalen-1-yl)-1-*o*-tolylbutan-2-ol (47 and 48). 47 and 48 was prepared from **8d** and **10a** according to the method of compound **13** and **14**.

47, yield 2.16%, mp 198.6–199.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79 (s, 3H), 1.89–2.00 (m, 9H), 2.62 (d, J = 9.6 Hz, 1H), 4.20 (s, 3H), 6.18 (s, 1H), 6.61 (d, J = 7.2 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 6.99 (t, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.37–7.45 (m, 3H), 7.54 (dt, J = 1.6, 7.2 Hz, 1H), 7.61 (t, J = 8.0 Hz, 2H), 7.81 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 1.6 Hz, 1H), 8.12 (s, 1H), 8.20 (br s, 1H), 8.22 (d, J = 6.4 Hz, 1H), 8.47 (d, J = 7.6 Hz, 1H), 8.74 (d, J = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.02, 141.98, 141.03, 137.82, 134.51, 133.03, 131.53, 131.07, 130.92, 130.19, 130.08, 129.69, 129.12, 128.18, 128.00, 127.91, 127.05, 126.02, 125.00, 124.83, 124.10, 124.00, 116.08, 102.77, 81.45, 55.05, 53.02, 47.01, 44.29, 31.92, 22.10. ESI MS (m/z): $[M + H]^+$ = 570.7. HRMS (ESI) m/z calcd for $C_{34}H_{34}BrNO_2$ $[M + H]^+$: 570.1830, found 570.1829.

48, yield 2.85%, mp 207.8–208.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01–2.05 (m, 8H), 2.40–2.59 (m, 5H), 2.88 (s, 3H), 6.10 (s, 1H), 6.46 (s, 1H), 7.13–7.23 (m, 3H), 7.28–7.29 (m, 3H), 7.43 (t, J = 7.6 Hz, 1H), 7.52–7.59 (m, 2H), 7.82 (d, J = 7.2 Hz, 1H), 7.86–7.89 (m, 2H), 8.20 (br s, 1H), 8.24 (s, 1H), 8.49–8.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.25, 142.58, 140.82, 137.51, 134.63, 132.80, 131.69, 131.20, 130.78, 130.16, 130.03, 129.57, 129.49, 128.46, 127.85, 127.51, 127.39, 126.12, 125.59, 125.01, 124.64, 124.28, 116.20, 103.74, 82.22, 56.43, 54.32, 45.06, 44.79, 33.74, 21.10. ESI MS (m/z): $[M + H]^+$ = 570.6. HRMS (ESI) m/z calcd for $C_{34}H_{34}BrNO_2$ $[M + H]^+$: 570.1830, found 570.1831.

1-(4-Chlorophenyl)-4-(dimethylamino)-1-(3-methoxynaphthalen-2-yl)-2-(naphthalen-1-yl)butan-2-ol hydrochloride (49). In 50 mL three-necked bottle, compound (**18**, 100 mg, 0.196 mmol) was dissolved in acetone (5 mL). To the mixture was added dropwise saturated Hydrogen Chloride-ether solution (20 mL). The reaction solution was stirred for 12 h at room temperature, then filtered and washed with ether to obtain off-white solid **49** (68 mg, yield 63.6%): mp > 255 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.04 (br s, 2H), 2.39 (s, 3H), 2.44 (s, 3H), 2.97–3.10 (m, 2H), 4.16 (s, 3H), 5.87

(s, 1H), 5.94 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 7.6 Hz, 2H), 7.33–7.39 (m, 2H), 7.44–7.47 (m, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.83–7.87 (m, 3H), 7.95 (d, J = 8.4 Hz, 1H), 8.25 (s, 1H), 8.66 (d, J = 8.0 Hz, 1H), 9.53 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6):δ 156.27, 140.35, 134.92, 133.39, 130.72, 130.04, 129.74, 129.29, 129.01, 128.75, 128.21, 128.00, 127.93, 127.01, 126.07, 125.71, 125.09, 124.78, 124.17, 123.79, 123.27, 104.83, 56.92, 56.03, 48.38, 44.19, 33.01.

5.2. Biological analysis

The test compound MICs against *Mtb* strains were assessed by the MABA using **TMC207, RMP, INH, PC01 and PC02** as positive controls. Compound stock solutions were prepared in DMSO at a concentration of 5 mg/mL. Two-fold dilutions of compounds were prepared in Middlebrook 7H9 broth medium in a volume of 100 μL in 96-well plastic microtiter plates (Falcon3072, Becton Dickinson, Lincoln Park, N. J.) and the final test concentrations ranged from 12.5 to 0.0125 μg/ml. *Mtb* (100 μL inoculum of 2 × 10^6 CFU/mL) was added, yielding a final testing volume of 200 μL. The plates were incubated at 37 °C. On the 7th day of incubation 50 μL of 5% Tween 80 and 20 μL of Alamar Blue (Setotec, England) were added to the test plate. After incubation at 37 °C for 24 h, the fluorescence was read in a computer-controlled fluorometer (spectramax Gemini EM, Molecular Devices) at an excitation wavelength of 530 nm and an emission wavelength of 590 nm. The MICs were defined as the lowest concentration effecting a reduction in fluorescence of ≥90% relative to the mean of replicate bacteria-only controls. Reported MICs are an average of three individual measurements.

5.3. Acute toxicity

Suspensions of test compounds were prepared in 0.5% carboxymethyl cellulose (CMC) at a concentration of 50 mg/mL. The test groups of mice (BALB/C, male, 18–20 g) were treated with intragastric administration in a single dose of 0.2 mL suspensions (drug dose greater than or equal to 500 mg/kg). The blank group was treated with water. Mental status, behavior and the amount of death of mice were observed during the next 7 days. Finally the survivors were dissected to investigate changes of their tissues. The results were expressed as median lethal doses (IC_{50}) which were defined as the concentration while half maximal amount of mice were killed during the defined period.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Combinatorial Transform from **TMC207** and ADMET prediction of **TMC207** and preferable compound could be found in supplementary data. Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2020.104054.

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