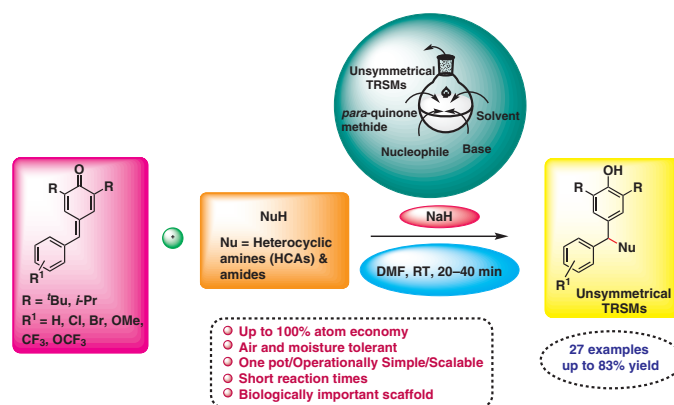


Base-Mediated 1,6-Aza-Michael Addition of Heterocyclic Amines and Amides to *para*-Quinone Methides Leading to Meclizine-, Hydroxyzine- and Cetirizine-like Architectures

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Abstract An expeditious, cost-effective synthetic methodology for a wide range of nitrogen-containing unsymmetrical trisubstituted methanes (TRSMs) is reported. The synthesis involves base-mediated 1,6-conjugate addition of heterocyclic amines and amides to substituted *para*-quinone methides, giving the unsymmetrical TRSMs in moderate to very good yields (up to 83%) in one pot. The low cost, mild temperature, high atom economy and yields, easy scale-up and broad substrate scope are some of the salient features of this protocol. Further, the methodology could be extended for the synthesis of meclizine-, hydroxyzine- and cetirizine-like molecules. The structure of one such compound, 2,6-di-*tert*-butyl-4-((4-chlorophenyl)(4-methylpiperazin-1-yl)methyl)phenol, was determined by single crystal X-ray analysis.

Key words trisubstituted methanes, aza-Michael addition, *para*-quinone methides, zine-like architectures, heterocyclic amines and amides

Trisubstituted methanes (TRSMs) are a select framework in organic chemistry possessing ubiquitous features of both biological and therapeutic pertinence.¹ Some examples have also revealed significant materials properties.² TRSM units are broadly found in various biologically active compounds.^{3,4} For example, letrozole, vorozole and compound **A** are potent nonsteroidal aromatase inhibitors whereas compound **B** is a potent antifungal agent (Figure 1). Another subgroup of the antihistamine class are the piperazine-containing tertiary amines like meclizine and cetirizine (Figure 1). All carry the same 1,1-diaryl motif with their structures differing at the other N-substituent of the piperazine ring. Our group has also reported the synthesis and bioactivity of diverse unsymmetrical triarylmethanes (TRAMs).⁵ In this paper, especially nitrogen-containing TRSMs are our concern.

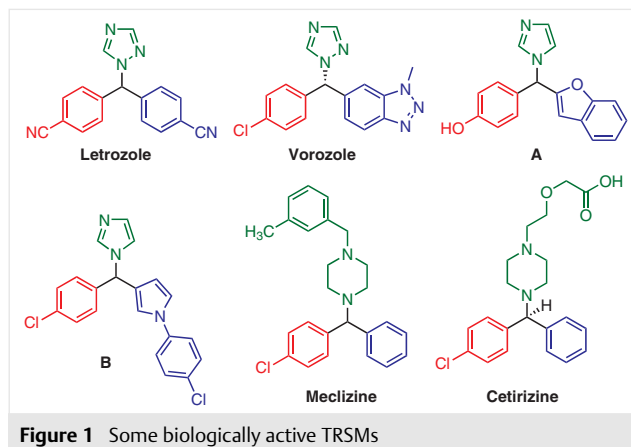
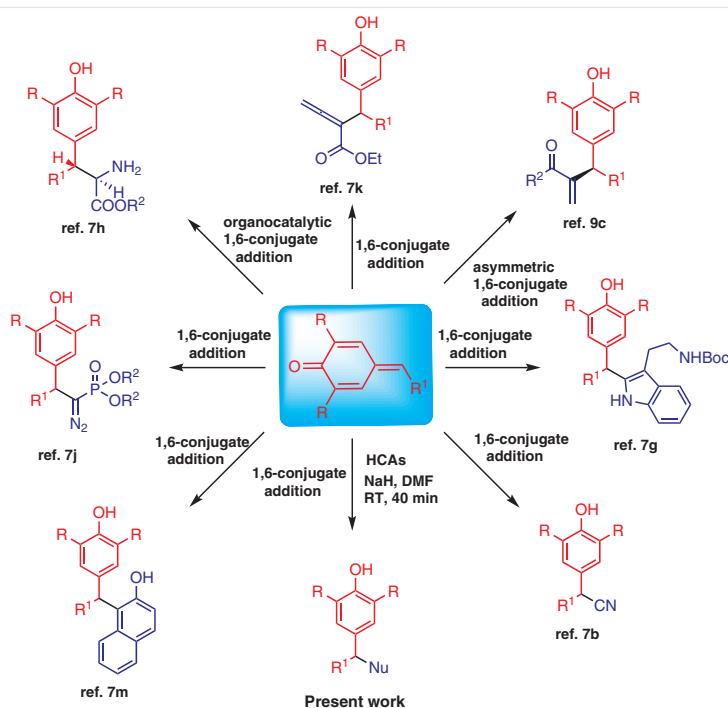


Figure 1 Some biologically active TRSMs

Quinone methides (QMs) are very common and highly reactive intermediates in organic chemistry. Two types of QMs are known, namely *o*-QMs and *p*-QMs. Aromatisation is the operating force for their distinctive reactivity towards various nucleophiles and therefore they have drawn a lot of attention from organic chemists.⁶ Recently, *p*-QMs have emanated as an interesting intermediate for 1,6-conjugate addition reactions to produce highly substituted diaryl- and triarylmethane derivatives. In the past few years, R. Vijaya Anand's group and others have reported that a diversity of nucleophiles, including cyanide, malonates, thiols, glycine Schiff bases, dicyanoolefins, the Seyferth–Gilbert reagent, allenic esters, styrenes and β -naphthols, can be used for 1,6-conjugate additions to *p*-QMs (Scheme 1).^{7,8} Eventually, enantioselective 1,6-conjugate additions to *p*-QMs have emerged as an attractive approach for the asymmetric synthesis of diarylmethane-containing molecules.^{6c,9} We have also reported the successful synthesis of triarylmethanes,



Scheme 1 Strategies for 1,6-conjugate addition to *p*-QMs

tetraarylmethanes and related molecules through the Friedel–Crafts alkylation of QMs.¹⁰ Motivated by these well-advanced approaches, we aimed to explore whether heterocyclic amines (HCAs) and amides could be used for the 1,6-conjugate addition reaction to produce nitrogen-containing unsymmetrical TRSMs. Herein, we report an efficient and atom economical, base-mediated strategy for the synthesis of nitrogen-containing unsymmetrical TRSMs through 1,6-addition of HCAs and amides to *p*-QMs (Scheme 1).

To test the viability of the proposed protocol, we began our inspection by treating 2,6-di-*tert*-butyl-*p*-QM **1a** and *N*-methylpiperazine (**2a**) as model substrates. The various reaction conditions such as base, solvent, time and temperature were screened, and the results obtained are summarised in Table 1. Initially, a 60% yield of product **3a** was observed when the reaction was performed using 1.5 equivalents of *t*-BuOK in THF at RT (entry 1). Notably, there was no product formation using 2 equivalents of K₂CO₃ in THF at RT (entry 2). When the reaction was performed using 6 equivalents of K₂CO₃ in THF at RT for 24 hours, no improvement in the yield (only 5%) was observed (entry 3). When the solvent was changed from THF to toluene, there was no significant change in the yield (<10%) (entry 4). Similarly, KOH (2 equiv) in EtOAc at RT resulted in the formation of **3a** in 25% yield (entry 5). But, when the solvent was changed from EtOAc to EtOH, the yield of **3a** decreased (10%) (entry 6). Delightfully, the reaction using NaOEt (2 equiv) in EtOH proceeded smoothly to furnish **3a** in 40%

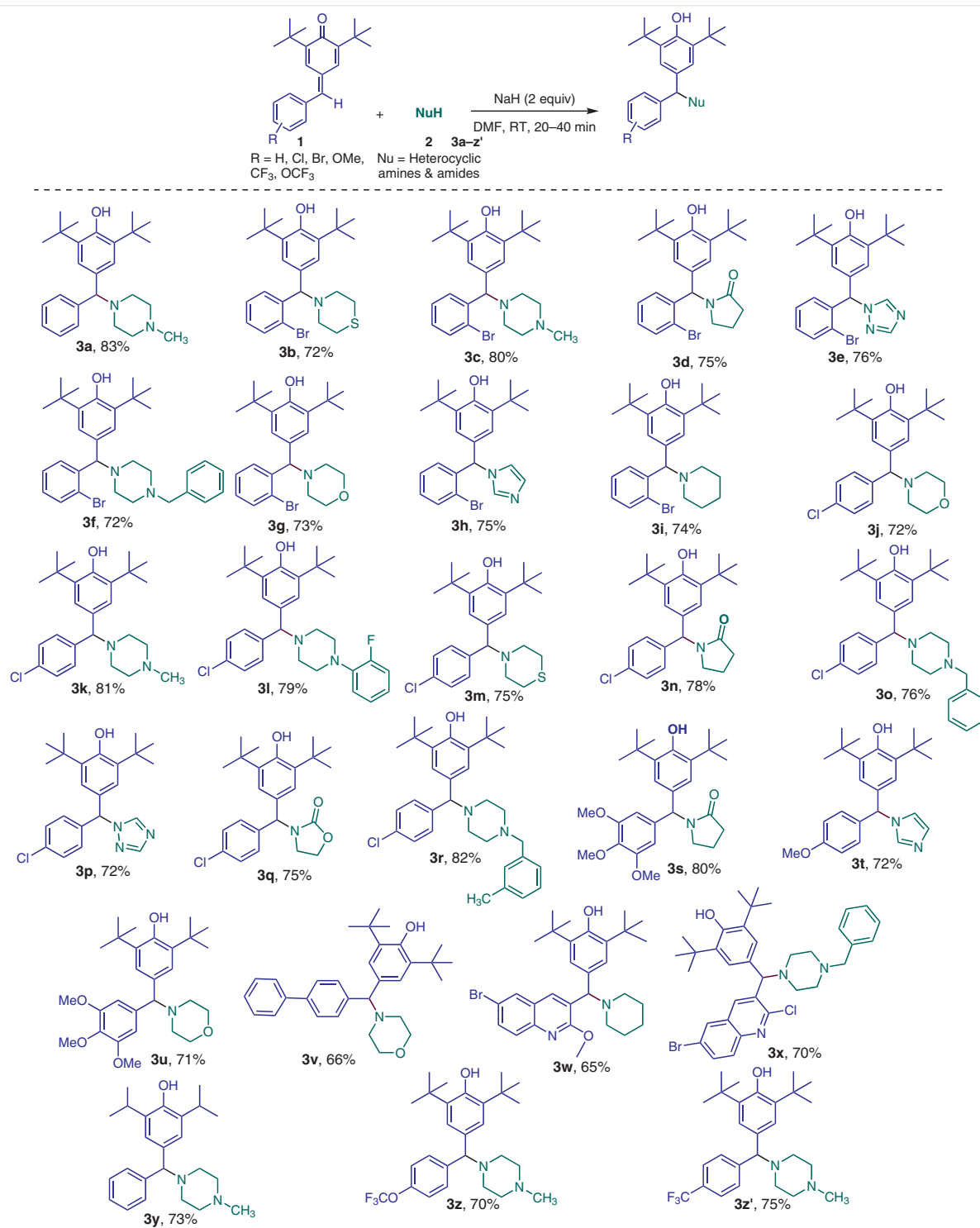
yield (entry 7). Unfortunately, our study with DBU (2 equiv) in MeCN was not successful (entry 8). Interestingly, in the presence of NaH (2 equiv) in DMF, the reaction furnished product **3a** in 82% yield (entry 9); furthermore, the reaction was very fast, only taking 20 minutes for completion at RT. Using the same substrates and NaH, further optimisation reactions were conducted using a series of solvents (entries 10–14). The best yield was obtained in DMF (entry 9) which indicated a polar aprotic solvent was needed for the proposed conversion. Heating the reaction mixture to a higher temperature did not improve the reaction yield, while application of lower or higher loadings of NaH resulted in decreased yields.

Further, to demonstrate the scope of this methodology, *p*-QMs **1** were reacted with a series of secondary HCAs and amides **2** under the optimised reaction conditions so as to obtain the corresponding products **3** (Scheme 2). Unfortunately, the reactions with acyclic amines and benzamides were not lucrative. A vast range of functional groups on the phenyl ring of the *p*-QMs and a huge set of nitrogen-containing nucleophiles were investigated. As is evident from Scheme 2, both electron-rich as well as electron-poor *p*-QMs were well suited for the conversion, giving a wide set of nitrogen-containing TRSMs in moderate to very good yields (65–83%).

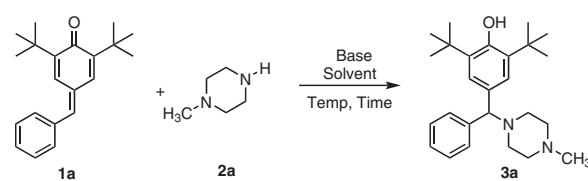
The *p*-QM containing halo substitution at the *ortho* position of the phenyl ring was effectively converted into the corresponding TRSM products **3b–i** in very good yields. Reactions of *p*-QMs with halo substitution at the *para*

position of the phenyl ring proceeded smoothly to give the corresponding products **3j–r**, **3z**, **3z'** in moderate to very good yields. Electron-rich *p*-QMs also worked well to pro-

duce the TRSM products **3s–u**. Notably, heteroaryl-derived *p*-QMs reacted nicely, furnishing the conjugate adducts **3w**, **3x** in fairly good yields. The *p*-QM generated from biphenyl-



Scheme 2 Substrate scope with different *p*-QMs. Reagents and conditions: **1** (0.1 mmol), **2** (0.1 mmol), NaH (0.2 mmol), DMF (2 mL), RT, 20–40 min. Isolated yields after silica gel column chromatography.

Table 1 Optimisation of the Reaction Conditions^a


Entry	Solvent	Base (equiv)	Time	Temp	Yield ^b (%)
1	THF	<i>t</i> -BuOK (1.5)	1 h	RT	60
2	THF	K ₂ CO ₃ (2)	24 h	RT	nr ^c
3	THF	K ₂ CO ₃ (6)	24 h	RT	5
4	toluene	K ₂ CO ₃ (6)	24 h	RT	<10
5	EtOAc	KOH (2)	24 h	RT	25
6	EtOH	KOH (2)	24 h	RT	10
7	EtOH	NaOEt (2)	1.30 h	RT	40
8	MeCN	DBU (2)	24 h	RT	<5
9	DMF	NaH (2)	20 min	RT	82
10	THF	NaH (1.5)	1.15 h	RT	65
11	MeCN	NaH (2)	24 h	RT	30
12	acetone	NaH (2)	20 h	RT	42
13	DMF/MeCN/DCM	<i>t</i> -BuOK (1.5)	3–4 h	RT	<30
14	DMSO	NaH (2)	1.5 h	RT	40

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), base (0.2 mmol), solvent (2 mL).

^b Isolated yield after column chromatography.

^c nr = no reaction.

4-carboxaldehyde could also be successfully utilised in the reaction, providing **3v**. Similarly, *p*-QMs without any substitution in the phenyl ring also worked very well to give the corresponding products **3a**, **3y** in very good yields within a short period of time. Particularly, cyclic amides reacted with the *p*-QMs faster than HCAs. The structure of **3k** was confirmed by X-ray analysis (Figure 2).¹¹

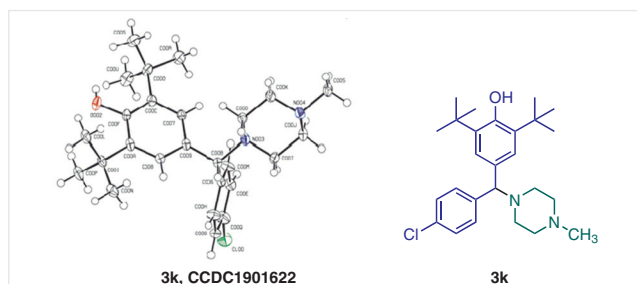
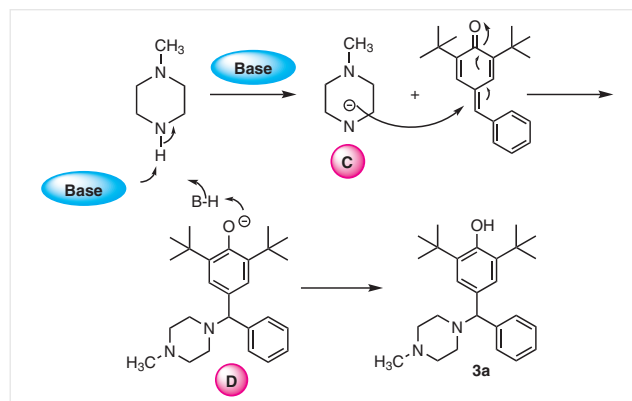


Figure 2 X-ray crystal structure of **3k**; ellipsoids are drawn at the 30% probability level

Based on our observations and the literature, a plausible mechanism for the 1,6-conjugate addition of heterocyclic amines and amides to *p*-QMs has been depicted in Scheme

3,7j,8c,12 The beginning step involves abstraction of a proton from HCAs and amides by the base to form a nitrogenous anion **C**. Afterwards, anion **C** readily reacts with the electrophilic *p*-QM in a 1,6-conjugate addition manner to furnish intermediate **D**. Ultimately, intermediate **D** through protonation gives the required product, for example **3a** (Scheme 3).

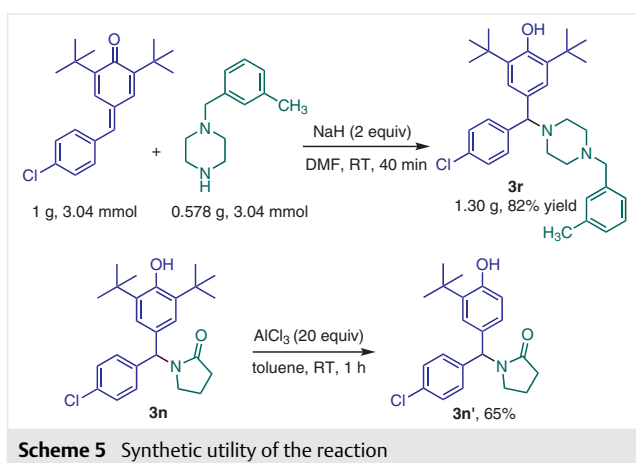
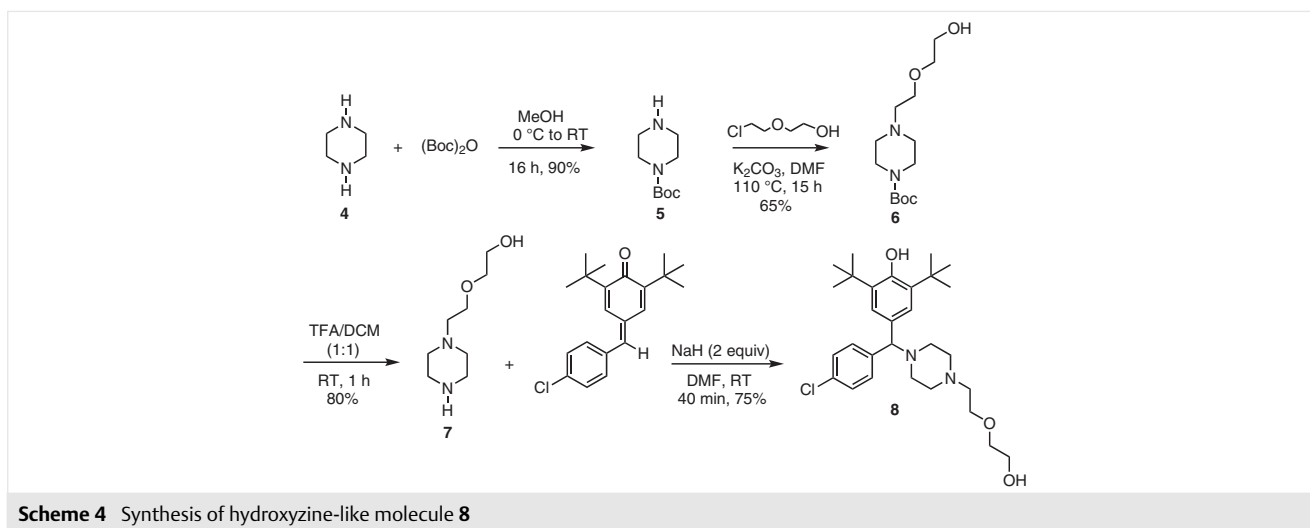


Scheme 3 Proposed mechanistic pathway

To further illustrate the applicability of the protocol towards development of new bioactive molecules, we made a new class of histamine H1 antagonist, hydroxyzine-like molecule **8**, through this methodology (Scheme 4). Thus, piperazine (**4**) was reacted with (Boc)₂O in MeOH to give **5** in excellent yield (90%). The Boc-protected compound **5** was then reacted with 2-(2-chloroethoxy)ethanol using K₂CO₃ as a base in DMF to give compound **6** in 65% yield. After Boc deprotection, compound **7** was reacted with NaH and 2,6-di-*tert*-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one in DMF to give hydroxyzine-like molecule **8**.

To demonstrate the potential utility of our method, we performed a gram-scale reaction of 2,6-di-*tert*-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one with 1-(3-methylbenzyl)piperazine (Scheme 5). The desired meclizine-like antihistamine product 2,6-di-*tert*-butyl-4-((4-chlorophenyl)(4-(3-methylbenzyl)piperazin-1-yl)methyl)phenol (**3r**) was obtained in 82% yield (1.30 g), demonstrating that the reaction is scalable. Moreover, one *tert*-butyl group in product **3n** could be efficiently removed to generate product **3n'** (Scheme 5).

The current work describes an efficient protocol for the one-pot synthesis of nitrogen-containing unsymmetrical trisubstituted methanes in high yields and atom economy. The methodology could further be extended for the synthesis of biologically important first-generation antihistamines, namely meclizine-, hydroxyzine- and cetirizine-like molecules, highlighting the utility of the work. Importantly, the presence of a halo substituent in most of the molecules



allows for further late-stage functionalisation which paves the way for the generation of chemical libraries for drug discovery.

Unless otherwise noted, all commercial reagents were used without further purification. All reactions were performed in a round-bottom flask, stirred with a magnetic bar under nitrogen atmosphere and monitored by TLC (0.2 mm silica gel coated GF₂₅₄ plates) with visualisation under UV light or by staining with Dragendorff solution. The starting *para*-quinone methides were prepared through literature procedures.^{7a} Flash column chromatography was carried out on silica gel 60–120 and 100–200 mesh basified by triethylamine. NMR spectra were recorded using a Bruker Avance 400 spectrometer. ¹H and ¹³C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to the residual solvent peak (CHCl₃, δ_H = 7.26 and δ_C = 77.00). Standard abbreviations are used for peak multiplicities. High-resolution mass spectra were taken using a Waters Agilent 6520 Q-

TOF MS/MS system or a JEOL AccuTOF JMS-T100LC system. Melting points are uncorrected and were determined in capillary tubes on an SMP10 melting point apparatus.

Unsymmetrical Trisubstituted Methanes **3**; General Procedure

To a solution of **1** (0.1 mmol) in DMF (2 mL) in a 10-mL round-bottom flask, **2** (0.1 mmol) was added. Then, the reaction mixture was cooled to 0 °C, NaH (2 equiv) was added, and the mixture was stirred for 20–40 min at RT. The solvent was evaporated and the crude mixture was extracted several times with chilled Et₂O. The combined organic extracts were washed with water and brine, dried (anhydrous Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography to give pure product **3**.

2,6-Di-*tert*-butyl-4-((4-methylpiperazin-1-yl)(phenyl)methyl)phenol (**3a**)

Off-white solid; mp 133 °C; yield: 33 mg (83%).

¹H NMR (400 MHz, CDCl₃): δ = 7.42–7.40 (m, 2 H), 7.26–7.22 (m, 2 H), 7.17–7.12 (m, 3 H), 5.05 (s, 1 H), 4.14 (s, 1 H), 2.43 (br s, 8 H), 2.26 (s, 3 H), 1.40 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 152.55, 143.62, 135.61, 132.93, 128.33, 127.95, 126.58, 124.52, 76.13, 55.55, 51.71, 45.99, 34.34, 30.45.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₆H₃₉N₂O: 395.3057; found: 395.3032.

4-((2-Bromophenyl)(thiomorpholino)methyl)-2,6-di-*tert*-butylphenol (**3b**)

Off-white solid; mp 191 °C; yield: 35 mg (72%).

¹H NMR (400 MHz, CDCl₃): δ = 7.72–7.70 (m, 1 H), 7.48–7.45 (m, 1 H), 7.29–7.27 (m, 1 H), 7.24 (s, 2 H), 7.03–6.99 (m, 1 H), 5.07 (s, 1 H), 4.83 (s, 1 H), 2.71–2.62 (m, 8 H), 1.40 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 152.73, 142.28, 135.67, 133.00, 131.29, 129.04, 127.90, 127.64, 124.90, 124.67, 72.59, 53.44, 34.35, 30.39, 28.04.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₅H₃₅BrNOS: 476.1617; found: 476.1633.

4-((2-Bromophenyl)(4-methylpiperazin-1-yl)methyl)-2,6-di-tert-butylphenol (3c)

White solid; mp 190 °C; yield: 38 mg (80%).

¹H NMR (400 MHz, CDCl₃): δ = 8.00 (s, 1 H), 7.78–7.76 (m, 1 H), 7.47–7.44 (m, 1 H), 7.28–7.26 (m, 2 H), 7.02–6.97 (m, 1 H), 5.07 (s, 1 H), 4.68 (s, 1 H), 2.94 (s, 4 H), 2.88 (s, 4 H), 2.27 (s, 3 H), 1.39 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 162.54, 152.64, 142.53, 135.55, 132.89, 131.67, 129.12, 127.77, 127.57, 124.85, 124.43, 72.84, 55.42, 51.60, 45.90, 34.32, 30.38.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₆H₃₈BrN₂O: 473.2162; found: 473.2158.

1-((2-Bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyrrolidin-2-one (3d)

White solid; mp 173 °C; yield: 34 mg (75%).

¹H NMR (400 MHz, CDCl₃): δ = 7.53–7.51 (m, 1 H), 7.17–7.13 (m, 1 H), 7.09–7.04 (m, 1 H), 6.91–6.88 (m, 1 H), 6.80 (s, 2 H), 6.49 (s, 1 H), 5.10 (s, 1 H), 3.18–3.12 (m, 1 H), 2.89–2.83 (m, 1 H), 2.44–2.40 (m, 2 H), 1.98–1.94 (m, 2 H), 1.31 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 174.66, 152.98, 139.50, 135.94, 133.23, 130.62, 129.11, 128.49, 127.12, 125.23, 124.07, 58.90, 45.92, 34.34, 31.14, 30.28, 18.75.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₅H₃₃BrN₂O: 458.1689; found: 458.1694.

4-((2-Bromophenyl)(1H-1,2,4-triazol-1-yl)methyl)-2,6-di-tert-butylphenol (3e)

White solid; mp 164 °C; yield: 34 mg (76%).

¹H NMR (400 MHz, CDCl₃): δ = 7.76–7.74 (m, 1 H), 7.40–7.37 (m, 1 H), 7.23–7.16 (m, 5 H), 6.95–6.91 (m, 1 H), 4.98 (s, 1 H), 4.43 (s, 1 H), 1.33 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 152.67, 143.12, 135.49, 132.86, 132.47, 128.98, 127.77, 127.66, 126.30, 124.79, 124.13, 75.05, 34.34, 30.40.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₃H₂₉BrN₃O: 442.1489; found: 442.1480.

4-((4-Benzylpiperazin-1-yl)(2-bromophenyl)methyl)-2,6-di-tert-butylphenol (3f)

Colourless oil; yield: 40 mg (72%).

¹H NMR (400 MHz, CDCl₃): δ = 7.71–7.68 (m, 1 H), 7.37–7.35 (m, 1 H), 7.21–7.15 (m, 8 H), 6.92–6.88 (m, 1 H), 4.95 (s, 1 H), 4.61 (s, 1 H), 3.43–3.42 (m, 2 H), 2.36 (br s, 8 H), 1.31 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 152.64, 142.60, 138.26, 135.49, 132.89, 131.74, 129.23, 129.21, 128.15, 127.76, 127.53, 126.95, 124.96, 73.05, 63.09, 53.44, 51.77, 34.33, 30.41.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₃₂H₄₂BrN₂O: 549.2475; found: 549.2479.

4-((2-Bromophenyl)(morpholino)methyl)-2,6-di-tert-butylphenol (3g)

Off-white solid; mp 195 °C; yield: 34 mg (73%).

¹H NMR (400 MHz, CDCl₃): δ = 7.74–7.71 (m, 1 H), 7.39–7.37 (m, 1 H), 7.21–7.16 (m, 3 H), 6.94–6.90 (m, 1 H), 4.99 (s, 1 H), 4.59 (s, 1 H), 3.63–3.60 (m, 4 H), 2.30–2.29 (m, 4 H), 1.32 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 152.79, 142.06, 135.65, 133.00, 131.04, 129.11, 127.93, 127.65, 124.99, 124.60, 73.40, 67.26, 52.52, 34.35, 30.40.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₅H₃₅BrNO₂: 460.1846; found: 460.1855.

4-((2-Bromophenyl)(1H-imidazol-1-yl)methyl)-2,6-di-tert-butylphenol (3h)

Off-white solid; mp 160 °C; yield: 33 mg (75%).

¹H NMR (400 MHz, CDCl₃): δ = 7.61–7.59 (m, 1 H), 7.36 (br s, 1 H), 7.31–7.27 (m, 1 H), 7.21–7.17 (m, 1 H), 7.10 (br s, 1 H), 6.88–6.82 (m, 4 H), 6.75 (s, 1 H), 1.36 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 153.86, 139.35, 136.50, 133.32, 129.69, 129.21, 127.73, 125.06, 124.09, 64.63, 34.38, 30.20.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₄H₃₀BrN₂O: 441.1536; found: 441.1533.

4-((2-Bromophenyl)(piperidin-1-yl)methyl)-2,6-di-tert-butylphenol (3i)

Colourless solid; mp 182 °C; yield: 34 mg (74%).

¹H NMR (400 MHz, CDCl₃): δ = 7.80–7.77 (m, 1 H), 7.45–7.43 (m, 1 H), 7.27 (s, 2 H), 7.25–7.23 (m, 1 H), 6.99–6.95 (m, 1 H), 5.02 (s, 1 H), 4.65 (s, 1 H), 2.31–2.30 (m, 5 H), 1.55–1.51 (m, 5 H), 1.40 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 152.48, 143.25, 135.40, 132.77, 132.38, 129.33, 127.56, 127.49, 124.91, 124.50, 73.52, 53.01, 34.34, 30.44, 26.27, 24.06.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₆H₃₇BrNO: 458.2053; found: 458.2051.

2,6-Di-tert-butyl-4-((4-chlorophenyl)(morpholino)methyl)phenol (3j)

Colourless oil; yield: 30 mg (72%).

¹H NMR (400 MHz, CDCl₃): δ = 7.30–7.28 (m, 2 H), 7.18–7.15 (m, 2 H), 7.05 (m, 2 H), 5.00 (s, 1 H), 4.00 (s, 1 H), 3.63–3.60 (m, 4 H), 2.28–2.24 (m, 4 H), 1.32 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 152.80, 141.77, 135.88, 132.31, 131.96, 129.20, 128.59, 124.40, 75.96, 67.24, 52.52, 34.34, 30.37.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₅H₃₅ClNO₂: 416.2351; found: 416.2341.

2,6-Di-tert-butyl-4-((4-chlorophenyl)(4-methylpiperazin-1-yl)methyl)phenol (3k)

White solid; mp 142 °C; yield: 35 mg (81%).

¹H NMR (400 MHz, CDCl₃): δ = 7.36–7.34 (m, 2 H), 7.23–7.21 (m, 2 H), 7.11 (m, 2 H), 5.06 (s, 1 H), 4.12 (s, 1 H), 2.43–2.42 (br s, 8 H), 2.27 (s, 3 H), 1.40 (s, 18 H).

¹³C NMR (100 MHz, CDCl₃): δ = 152.68, 142.19, 135.75, 132.28, 129.21, 128.47, 124.44, 75.29, 55.50, 51.61, 45.98, 34.33, 30.40.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₆H₃₈ClN₂O: 429.2667; found: 429.2660.

2,6-Di-tert-butyl-4-((4-chlorophenyl)(4-(2-fluorophenyl)piperazin-1-yl)methyl)phenol (3l)

Off-white solid; mp 139 °C; yield: 39 mg (79%).

^1H NMR (400 MHz, CDCl_3): δ = 7.40–7.37 (m, 2 H), 7.26–7.23 (m, 1H), 7.16 (s, 2 H), 7.05–6.86 (m, 5 H), 5.07 (s, 1 H), 4.19 (s, 1 H), 3.14–3.08 (m, 4 H), 2.57–2.51 (m, 4 H), 1.40 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 156.99, 152.80, 142.02, 135.85, 132.29, 132.24, 129.28, 128.59, 124.48, 122.32, 122.24, 118.87, 116.21, 116.00, 75.42, 51.82, 50.85, 34.38, 30.43.

HRMS (ESI): m/z $[\text{M} + \text{H}]^-$ calcd for $\text{C}_{31}\text{H}_{39}\text{ClFN}_2\text{O}$: 509.2729; found: 509.2712.

2,6-Di-*tert*-butyl-4-((4-chlorophenyl)(thiomorpholino)methyl)phenol (3m)

Light yellow solid; mp 135 °C; yield: 34 mg (75%).

^1H NMR (400 MHz, CDCl_3): δ = 7.24–7.22 (m, 2 H), 7.17–7.15 (m, 2 H), 7.00 (s, 2 H), 5.01 (s, 1 H), 4.23 (s, 1 H), 2.59–2.55 (m, 8 H), 1.32 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 152.77, 141.46, 135.81, 132.30, 131.62, 129.35, 128.52, 124.56, 75.12, 53.37, 34.36, 30.39, 28.21.

HRMS (ESI): m/z $[\text{M} + \text{H}]^-$ calcd for $\text{C}_{25}\text{H}_{35}\text{ClNO}_2$: 432.2122; found: 432.2068.

1-((4-Chlorophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)pyrrolidin-2-one (3n)

Yellow solid; mp 220 °C; yield: 33 mg (78%).

^1H NMR (400 MHz, CDCl_3): δ = 7.31–7.29 (m, 2 H), 7.13–7.10 (m, 2 H), 6.92 (s, 2 H), 6.48 (s, 1 H), 5.25 (s, 1 H), 3.20–3.16 (m, 2 H), 2.50–2.46 (m, 2 H), 2.06–1.99 (m, 2 H), 1.39 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 174.91, 153.24, 138.06, 136.01, 133.06, 129.65, 128.50, 128.35, 125.29, 58.10, 44.20, 34.36, 31.24, 30.29, 18.31.

HRMS (ESI): m/z $[\text{M} + \text{H}]^-$ calcd for $\text{C}_{25}\text{H}_{33}\text{ClNO}_2$: 414.2194; found: 414.2196.

4-((4-Benzylpiperazin-1-yl)(4-chlorophenyl)methyl)-2,6-di-*tert*-butylphenol (3o)

Off-white solid; mp 154 °C; yield: 39 mg (76%).

^1H NMR (400 MHz, CDCl_3): δ = 7.35–7.33 (m, 2 H), 7.29–7.28 (m, 4 H), 7.24–7.21 (m, 3 H), 7.09 (s, 2 H), 5.04 (s, 1 H), 4.13 (s, 1 H), 3.50–3.49 (m, 2 H), 2.45–2.36 (m, 8 H), 1.38 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 152.67, 142.16, 138.19, 135.71, 132.29, 132.11, 129.26, 128.43, 128.16, 126.98, 124.54, 75.33, 63.15, 53.48, 51.63, 34.33, 30.40.

HRMS (ESI): m/z $[\text{M} + \text{H}]^-$ calcd for $\text{C}_{32}\text{H}_{42}\text{ClN}_2\text{O}$: 505.2980; found: 505.2981.

2,6-Di-*tert*-butyl-4-((4-chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl)phenol (3p)

Yellow solid; mp 140 °C; yield: 29 mg (72%).

^1H NMR (400 MHz, CDCl_3): δ = 7.44–7.41 (m, 1 H), 7.39–7.36 (m, 3 H), 7.25–7.23 (m, 2 H), 7.12–7.11 (m, 2 H), 5.06 (s, 1 H), 3.92 (s, 1 H), 1.40 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 152.68, 142.90, 140.61, 135.72, 133.20, 131.47, 129.08, 128.95, 128.49, 124.26, 77.48, 34.33, 30.39.

HRMS (ESI): m/z $[\text{M} + \text{H}]^-$ calcd for $\text{C}_{23}\text{H}_{29}\text{ClN}_3\text{O}$: 398.1994; found: 398.1930.

3-((4-Chlorophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-oxazolidin-2-one (3q)

Off-white solid; mp 205 °C; yield: 31 mg (75%).

^1H NMR (400 MHz, CDCl_3): δ = 7.34–7.32 (m, 2 H), 7.18–7.16 (m, 2 H), 6.96 (m, 2 H), 6.23 (s, 1 H), 4.39–4.30 (m, 2 H), 3.41–3.30 (m, 2 H), 1.40 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 171.12, 158.25, 153.56, 137.40, 136.19, 133.40, 129.40, 128.65, 127.75, 125.34, 67.95, 62.08, 60.37, 41.56, 34.37, 30.25, 25.61, 21.03, 14.19.

HRMS (ESI): m/z $[\text{M} + \text{H}]^-$ calcd for $\text{C}_{24}\text{H}_{31}\text{ClNO}_3$: 416.1987; found: 416.1968.

2,6-Di-*tert*-butyl-4-((4-chlorophenyl)(4-(3-methylbenzyl)piperazin-1-yl)methyl)phenol (3r)

Yellow solid; mp 108 °C; yield: 43 mg (82%).

^1H NMR (400 MHz, CDCl_3): δ = 7.26–7.24 (m, 2 H), 7.13–7.11 (m, 2 H), 7.08–7.05 (m, 2 H), 7.01–6.98 (m, 4 H), 4.95 (s, 1 H), 4.05 (s, 1 H), 3.37–3.36 (m, 2 H), 2.38–2.27 (m, 8 H), 2.22 (s, 3 H), 1.30 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 152.72, 142.17, 138.08, 137.71, 135.70, 132.30, 132.18, 129.99, 129.27, 128.46, 128.06, 127.76, 126.40, 124.59, 75.38, 63.25, 53.59, 51.63, 34.34, 30.43, 22.77.

HRMS (ESI): m/z $[\text{M} + \text{H}]^-$ calcd for $\text{C}_{33}\text{H}_{44}\text{ClN}_2\text{O}$: 519.3137; found: 519.3136.

1-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(3,4,5-trimethoxyphenyl)methyl)pyrrolidin-2-one (3s)

White solid; mp 168 °C; yield: 38 mg (80%).

^1H NMR (400 MHz, CDCl_3): δ = 6.90 (s, 2 H), 6.37 (s, 1 H), 6.34 (s, 2 H), 5.15 (s, 1 H), 3.78 (s, 3 H), 3.71 (s, 6 H), 3.18–3.11 (m, 2 H), 2.44–2.40 (m, 2 H), 1.98–1.91 (m, 2 H), 1.33 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 174.91, 153.09, 137.27, 135.81, 134.93, 128.27, 125.11, 105.92, 60.85, 58.59, 56.19, 44.27, 34.37, 31.36, 30.33, 18.45.

HRMS (ESI): m/z $[\text{M} + \text{H}]^-$ calcd for $\text{C}_{28}\text{H}_{40}\text{NO}_5$: 470.2901; found: 470.2893.

2,6-Di-*tert*-butyl-4-((1*H*-imidazol-1-yl)(4-methoxyphenyl)methyl)phenol (3t)

White solid; mp 142 °C; yield: 28 mg (72%).

^1H NMR (400 MHz, CDCl_3): δ = 7.93 (s, 1 H), 6.98 (m, 3 H), 6.81–6.75 (m, 5 H), 6.29 (s, 1 H), 3.73 (s, 3 H), 1.29 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 162.51, 159.28, 153.67, 137.37, 136.43, 132.10, 129.79, 129.05, 128.96, 124.77, 119.33, 114.00, 64.86, 55.28, 34.36, 30.19.

HRMS (ESI): m/z $[\text{M} + \text{H}]^-$ calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_2$: 393.2537; found: 393.2523.

2,6-Di-*tert*-butyl-4-(morpholino(3,4,5-trimethoxyphenyl)methyl)phenol (3u)

White solid; mp 158 °C; yield: 34 mg (71%).

^1H NMR (400 MHz, CDCl_3): δ = 7.20 (s, 2 H), 6.70 (s, 2 H), 5.10 (s, 1 H), 3.85 (s, 6 H), 3.80 (s, 3 H), 3.71–3.69 (m, 4 H), 2.35–2.34 (m, 4 H), 1.42 (s, 18 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 153.13, 152.77, 138.93, 136.66, 135.73, 132.36, 124.48, 104.64, 76.96, 67.23, 60.77, 56.05, 52.61, 34.35, 30.41.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{42}NO_5$: 472.3057; found: 472.3054.

4-([1,1'-Biphenyl]-4-yl(morpholino)methyl)-2,6-di-*tert*-butylphenol (3v)

Yellow solid; mp 165 °C; yield: 30 mg (66%).

1H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.54 (m, 2 H), 7.50 (s, 4 H), 7.42–7.38 (m, 2 H), 7.25 (s, 1 H), 7.22 (s, 2 H), 5.06 (s, 1 H), 4.14 (s, 1 H), 3.73–3.70 (m, 4 H), 2.39–2.37 (m, 4 H), 1.41 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.72, 142.31, 140.95, 139.61, 135.77, 132.49, 128.70, 128.30, 127.19, 127.07, 126.98, 124.51, 67.32, 52.66, 34.35, 30.41, 29.72.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{31}H_{40}NO_2$: 458.3034; found: 458.3023.

4-((6-Bromo-2-methoxyquinolin-3-yl)(piperidin-1-yl)methyl)-2,6-di-*tert*-butylphenol (3w)

Yellow solid; mp 232 °C; yield: 36 mg (65%).

1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 7.82–7.81 (s, 1 H), 7.58–7.55 (m, 1 H), 7.52–7.50 (m, 1 H), 7.12 (s, 2 H), 4.95 (s, 1 H), 4.52 (s, 1 H), 3.96 (s, 3 H), 2.26 (s, 4 H), 1.54–1.47 (m, 6 H), 1.31 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.94, 152.47, 143.83, 135.41, 133.88, 131.71, 130.06, 129.48, 128.42, 127.16, 124.95, 116.87, 68.06, 53.42, 53.14, 34.30, 30.43, 26.30, 24.86.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{30}H_{40}BrN_2O_2$: 539.2268; found: 539.2271.

4-((4-Benzylpiperazin-1-yl)(6-bromo-2-chloroquinolin-3-yl)methyl)-2,6-di-*tert*-butylphenol (3x)

Yellow solid; mp 149 °C; yield: 45 mg (70%).

1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 7.87–7.86 (m, 1 H), 7.69–7.67 (m, 1 H), 7.60–7.57 (m, 1 H), 7.29–7.28 (m, 5 H), 7.24 (s, 2 H), 5.04 (s, 1 H), 4.74 (s, 1 H), 3.51–3.50 (m, 2 H), 2.45 (br s, 8 H), 1.37 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.08, 152.70, 144.77, 135.47, 134.91, 133.41, 131.76, 131.71, 129.31, 129.25, 128.18, 127.53, 127.02, 124.86, 117.58, 68.92, 63.17, 53.56, 52.33, 34.32, 30.38.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{35}H_{42}BrClN_3O$: 634.2194; found: 634.2156.

2,6-Diisopropyl-4-((4-methylpiperazin-1-yl)(phenyl)methyl)phenol (3y)

Colourless oil; yield: 27 mg (73%).

1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.73 (m, 1 H), 7.29–7.26 (m, 2 H), 7.16 (s, 2 H), 7.06–7.04 (m, 2 H), 5.02 (s, 1 H), 4.30 (s, 1 H), 2.41–2.36 (m, 10 H), 2.28 (s, 3 H), 1.38 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.45, 141.86, 135.67, 135.45, 134.86, 132.23, 130.84, 130.42, 127.04, 126.11, 126.00, 124.98, 71.18, 55.51, 51.92, 45.92, 34.28, 30.39.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{35}N_2O$: 367.2744; found: 367.2723.

2,6-Di-*tert*-butyl-4-((4-methylpiperazin-1-yl)(4-(trifluoromethoxy)phenyl)methyl)phenol (3z)

Colourless oil; yield: 34 mg (70%).

1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.42 (m, 2 H), 7.12–7.09 (m, 4 H), 5.08 (s, 1 H), 4.17 (s, 1 H), 2.43 (br s, 8 H), 2.27 (s, 3 H), 1.40 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.74, 147.87, 142.26, 135.78, 132.19, 129.11, 124.53, 120.75, 75.21, 55.49, 51.60, 45.95, 34.34, 30.88.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{38}F_3N_2O_2$: 479.2880; found: 479.2875.

2,6-Di-*tert*-butyl-4-((4-methylpiperazin-1-yl)(4-(trifluoromethyl)phenyl)methyl)phenol (3z')

Colourless oil; yield: 35 mg (75%).

1H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.50 (m, 4 H), 7.13 (s, 2 H), 5.08 (s, 1 H), 4.20 (s, 1 H), 2.43 (br s, 8 H), 2.28 (s, 3 H), 1.40 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.84, 147.83, 135.89, 131.85, 130.34, 128.07, 125.34, 124.50, 75.68, 55.44, 51.66, 45.96, 34.34, 30.37.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{38}F_3N_2O$: 463.2931; found: 463.2929.

2-(2-(Piperazin-1-yl)ethoxy)ethan-1-ol (7)

Colourless oil; yield: 140 mg (80%).

1H NMR (400 MHz, $CDCl_3$): δ = 3.69–3.66 (m, 2 H), 3.64–3.62 (m, 2 H), 3.58–3.55 (m, 2 H), 2.90–2.88 (m, 4 H), 2.58–2.55 (m, 2 H), 2.49 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.53, 67.63, 61.27, 58.32, 54.35, 45.51.

2,6-Di-*tert*-butyl-4-((4-chlorophenyl)(4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)methyl)phenol (8)

Yellow crystalline solid; mp 106 °C; yield: 38 mg (75%).

1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.33 (m, 2 H), 7.23–7.21 (m, 2 H), 7.10 (s, 2 H), 5.06 (s, 1 H), 4.09 (s, 1 H), 3.68–3.64 (m, 4 H), 3.60–3.58 (s, 2 H), 2.61–2.59 (s, 2 H), 2.40 (s, 8 H), 1.39 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.72, 140.60, 135.80, 134.85, 134.37, 131.46, 129.08, 128.54, 124.33, 75.52, 67.48, 62.09, 57.98, 53.61, 51.42, 34.32, 30.37.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{29}H_{44}ClN_2O_3$: 503.3035; found: 503.3032.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0039-1690677>.

References

- (1) (a) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289. (b) Al-Qawasmeh, R. A.; Lee, Y.; Cao, M.-Y.; Gu, X.; Vassilakos, A.; Wright, J. A.; Young, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 347. (c) Shagufta, G.; Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P. S. R.; Panda, G. *Bioorg. Med. Chem.* **2006**, *14*, 1497. (d) Palchaudhuri, R.; Nesterenko, V.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 10274.
- (2) (a) Gindre, C. A.; Screttas, C. G.; Fiorini, C.; Schmidt, C.; Nunzi, J. M. *Tetrahedron Lett.* **1999**, *40*, 7413. (b) Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev.* **2003**, *32*, 170. (c) Beija, M.; Afonso, C. A. M.; Martinho, J. M. G. *Chem. Soc. Rev.* **2009**, *38*, 2410.
- (3) Conn, M. M.; Rebek, J. Jr. *Chem. Rev.* **1997**, *97*, 1647.
- (4) Mondal, S.; Panda, G. *RSC Adv.* **2014**, *4*, 28317.
- (5) (a) Panda, G.; Shagufta; Mishra, J. K.; Chaturvedi, V.; Srivastava, A. K.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem.* **2004**, *12*, 5269. (b) Kumar, S.; Das, S. K.; Dey, S.; Maity, P.; Guha, M.; Choubey, V.; Panda, G.; Bandyopadhyay, U. *Antimicrob. Agents Chemother.* **2008**, *52*, 705. (c) Goyal, M.; Singh, P.; Alam, A.; Das, S. K.; Iqbal, M. S.; Dey, S.; Bindu, S.; Pal, C.; Das, S. K.; Panda, G.; Bandyopadhyay, U. *Free Radical Biol. Med.* **2012**, *53*, 129. (d) Panda, G.; Parai, M. K.; Srivastava, A. K.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2009**, *48*, 1121.
- (6) For selected relevant examples, see: (a) Ma, C.; Huang, Y.; Zhao, Y. *ACS Catal.* **2016**, *6*, 6408. (b) Yuan, Z.; Wei, W.; Lin, A.; Yao, H. *Org. Lett.* **2016**, *18*, 3370. (c) Chen, M.; Sun, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 4583. (d) Saha, S.; Alamsetti, S. K.; Schneider, C. *Chem. Commun.* **2015**, *51*, 1461. (e) Mondal, S.; Roy, D.; Jaiswal, M. K.; Panda, G. *Tetrahedron Lett.* **2018**, *59*, 89.
- (7) (a) Goswami, P.; Sharma, S.; Singh, G.; Anand, R. V. *J. Org. Chem.* **2018**, *83*, 4213. (b) Goswami, P.; Singh, G.; Anand, R. V. *Org. Lett.* **2017**, *19*, 1982. (c) Jadhav, A. S.; Anand, R. V. *Eur. J. Org. Chem.* **2017**, 3716. (d) Jadhav, A. S.; Anand, R. V. *Org. Biomol. Chem.* **2017**, *15*, 56. (e) Arde, P.; Anand, R. V. *Org. Biomol. Chem.* **2016**, *14*, 5550. (f) Arde, P.; Anand, R. V. *RSC Adv.* **2016**, *6*, 77111. (g) Goswami, P.; Anand, R. V. *ChemistrySelect* **2016**, *1*, 2556. (h) Reddy, V.; Anand, R. V. *Org. Lett.* **2015**, *17*, 3390. (i) Zhang, X. Z.; Deng, Y. H.; Yan, X.; Yu, K. Y.; Wang, F. X.; Ma, X. Y.; Fan, C. A. *J. Org. Chem.* **2016**, *81*, 5655. (j) Gupta, A. K.; Ahamad, S.; Vaishanv, N. K.; Kant, R.; Mohanan, K. *Org. Biomol. Chem.* **2018**, *16*, 4623. (k) Vaishanv, N. K.; Gupta, A. K.; Kant, R.; Mohanan, K. *J. Org. Chem.* **2018**, *83*, 8759. (l) Jadhav, A. S.; Pankhade, Y. A.; Hazra, R.; Anand, R. V. *J. Org. Chem.* **2018**, *83*, 10107. (m) Zhou, T.; Li, S.; Huang, S.; Li, C.; Zhao, Y.; Chen, J.; Chen, A.; Xiao, Y.; Liu, L.; Zhang, J. *Org. Biomol. Chem.* **2017**, *15*, 4941.
- (8) (a) Santra, S.; Porey, A.; Guin, J. *Asian J. Org. Chem.* **2018**, *7*, 477. (b) Molleti, N.; Kang, J. Y. *Org. Lett.* **2017**, *19*, 958. (c) Yang, C.; Gao, S.; Yao, H.; Lin, A. *J. Org. Chem.* **2016**, *81*, 11956. (d) Pan, R.; Hu, L.; Han, C.; Lin, A.; Yao, H. *Org. Lett.* **2018**, *20*, 1974. (e) Yuan, Z.; Liu, L.; Pan, R.; Yao, H.; Lin, A. *J. Org. Chem.* **2017**, *82*, 8743.
- (9) (a) Zhang, Z. P.; Chen, L.; Li, X.; Cheng, J. P. *J. Org. Chem.* **2018**, *83*, 2714. (b) Zhang, Z. P.; Xie, K. X.; Yang, C.; Li, M.; Li, X. *J. Org. Chem.* **2018**, *83*, 364. (c) Wang, H.; Wang, K.; Man, Y.; Gao, X.; Yang, L.; Ren, Y.; Li, N.; Tang, B.; Zhao, G. *Adv. Synth. Catal.* **2017**, *359*, 3934. (d) Chu, W. D.; Zhang, L. F.; Bao, X.; Zhao, X. H.; Zeng, C.; Du, J. Y.; Zhang, G. B.; Wang, F. X.; Ma, X. Y.; Fan, C. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9229. (e) Zhang, X. Z.; Gan, K. J.; Liu, X. X.; Deng, Y. H.; Wang, F. X.; Yu, K. Y.; Zhang, J.; Fan, C. A. *Org. Lett.* **2017**, *19*, 3207. (f) Caruana, L.; Kniep, F.; Johansen, T. K.; Poulsen, P. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2014**, *136*, 15929. (g) Zhao, K.; Zhi, Y.; Wang, A.; Enders, D. *ACS Catal.* **2016**, *6*, 657. (h) Zhao, K.; Zhi, Y.; Shu, T.; Valkonen, A.; Rissanen, K.; Enders, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 12104. (i) Liu, Q.; Li, S.; Chen, X. Y.; Rissanen, K.; Enders, D. *Org. Lett.* **2018**, *20*, 3622. (j) Wang, Z.; Wong, Y. F.; Sun, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 13711. (k) Li, S.; Liu, S.; Huang, B.; Zhou, T.; Tao, H.; Xiao, Y.; Liu, L.; Zhang, J. *ACS Catal.* **2017**, *7*, 2805. (l) Deng, Y. H.; Zhang, X. Z.; Yu, K. Y.; Yan, X.; Du, J. Y.; Huanga, H.; Fan, C. A. *Chem. Commun.* **2016**, *52*, 4183.
- (10) Roy, D.; Panda, G. *Tetrahedron* **2018**, *74*, 6270.
- (11) CCDC 1901622 (**3k**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
- (12) (a) Mahesh, S.; Anand, R. V. *Org. Biomol. Chem.* **2017**, *15*, 8393. (b) Ge, L.; Lu, X.; Cheng, C.; Chen, J.; Cao, W.; Wu, X.; Zhao, G. *J. Org. Chem.* **2016**, *81*, 9315.