



Synthesis of aminomethylphenol derivatives *via* magnetic nano Fe₃O₄ catalyzed one pot Petasis borono-Mannich reaction

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Abstract. A novel library of aminomethylphenol has been developed using magnetic Fe₃O₄ nanoparticles *via* Petasis borono-Mannich reaction of salicylaldehydes, secondary amines and phenyl boronic acids. This one-pot protocol features mild reaction conditions, excellent yields in short reaction times, readily available starting materials, good functional group tolerance and reusability of the catalyst for four consecutive cycles without significant loss in its activity.

Keywords. Aminomethylphenol; petasis borono-Mannich reaction; nano Fe₃O₄.

1. Introduction

Aminomethylphenol units are privileged structural motifs which have drawn much attention from the medicinal¹ and material science² communities owing to their biological and industrial significance. Enormous compounds belong to this family have entered preclinical and clinical trials over a longer period. Synthetic pharmaceuticals bearing this structural unit have been widely applied to clinical treatment as antibacterial,³ anti-inflammatory,⁴ antimicrobial⁵ and antimalarial⁶ agents. Some representative pharmacologically important drugs incorporating aminomethylphenol skeleton are WR-194,965, JPC-2997, MK-4815, JPC-3186 and JPC-3210 (Figure 1).^{7,8} Notably, a class of 2-aminomethylphenol displays saluretic profiles and can be used in the treatment of hypertension or edematous disorders.⁹ In addition, aminomethylphenol figure presents a key structural motif to prepare human hair dye coupler compounds,¹⁰ heat curable thermosetting surface coating,¹¹ corrosion inhibiting coating to a metal surface,¹² and as additives for lubricating oils.¹³

Considering the spectacular biological and chemo-physical properties of aminomethylphenol derivatives and their significant role in organic synthesis, the development of versatile, convenient, and effective

methods for the design of these scaffolds have been invited considerable attention from both the academic and industrial researchers. The known reactions for the aminomethylphenol motifs in synthetic chemistry are (i) three-component reaction among organoboronic acids, amines and salicylaldehydes,¹⁴ (ii) the reduction of iminomethylphenol derivatives,¹⁵ (iii) the reaction of 2-aminopyridine, benzaldehydes and phenols.¹⁶ Petasis borono-Mannich reaction had reported for pyridine and electron poor aromatic amines.¹⁷ Petasis reaction had reported at room temperature¹⁸ as well as 0 °C.¹⁹ The simplest and the most practical protocol, reported by Petasis borono-Mannich involves the three-component reaction of salicylaldehyde, secondary amine and boronic acid. However, these procedures were found to be sluggish, required a longer reaction time of more than 24 h, failed to proceed full conversion and microwave irradiation or heating was necessary. In the past two decades, several modifications to Petasis borono-Mannich reaction have been reported using catalysts such as CoFe₂O₄,²⁰ chitosan²¹ and [bmim]BF₄.²² The other interesting works describing this reaction were carried out using protonated trititanate (H₂Ti₃O₇) nanotubes²³ and tetranuclear Zn₂Ln₂ coordination clusters as catalysts.²⁴ Despite that, the development of an efficient and simple methodology for the synthesis of aminomethylphenol should take into consideration

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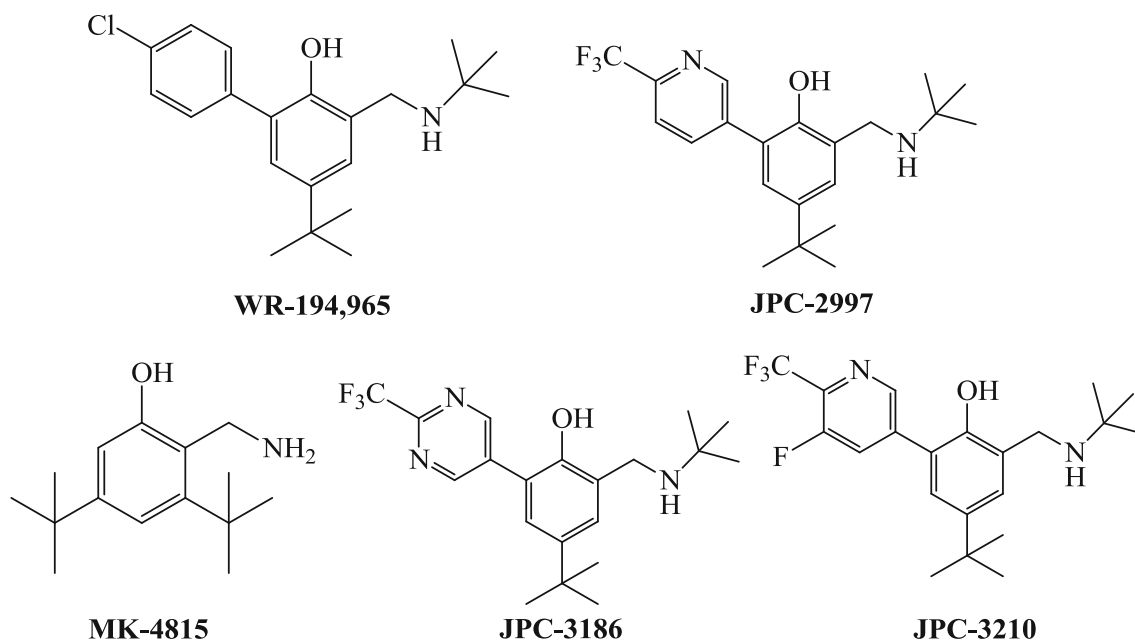


Figure 1. Representative examples of alkyl aminomethylphenol pharmaceuticals.

the reduction in the reaction time, simple reaction conditions, and reusability of the catalyst.

In recent years, magnetic nanoparticles have gained increased attention as a highly useful catalyst for organic synthesis. In particular, environmentally benign heterogeneous magnetic nano Fe_3O_4 (magnetite) have been achieved much interest owing to its ease of handling, lower cost, non-toxicity, the comfort of recovery with an external magnetic field, oxidative stability and biological compatibility.²⁵ In the last few years, nano Fe_3O_4 catalyst has been used for different organic transformation such as Sonogashira–Hagihara reaction,²⁶ Biginelli reactions,²⁷ synthesis of imidazoles,²⁸ Baeyer–Villiger oxidation²⁹ and as a support for homogeneous catalysts.³⁰

Despite these advances, to the best of our knowledge, the utilization of nano Fe_3O_4 catalyst in the three-component Petasis borono-Mannich reaction has not yet been documented. In continuation of our efforts to develop new synthetic methods for the important organic compounds,³¹ in this paper, we disclose the synthesis of aminomethylphenol library via one-pot three-component reaction of salicylaldehydes, secondary amines, and phenylboronic acids in the presence of catalytic amount of magnetic Fe_3O_4 nanoparticles.

2. Experimental

2.1 General information

Commercially available organic and inorganic compounds purchased from Sigma-Aldrich and Clearysynth Labs Limited

(Hyderabad) were used without further purification. Solvents were dried and stored over microwave-activated 4 Å molecular sieves. Melting points were determined on an electric melting point apparatus. Infrared spectra were taken with KBr pellets on an Agilent Cary 630 FT-IR spectrophotometer (only the structurally most important peaks are given). ^1H NMR (400 MHz) spectra were recorded on a Bruker WH-200 spectrometer and ^{13}C NMR (100 MHz) on Agilent VNRMS spectrometer using CDCl_3 as solvent and TMS as an internal standard. Chemical shifts were reported in parts per million (ppm) and coupling constant (J) in hertz (Hz). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Mass spectra were recorded on an Agilent LC-MS. High-resolution mass spectra (HMRS) were recorded using ion electrospray. Thin layer chromatography was performed on silica gel 60 F254 plates. Elemental analysis was performed on an Elemental Vario Micro Cube rapid analyzer.

2.2 Typical experimental procedure for the synthesis of (4a)

To a stirred solution of salicylaldehyde (0.5 g, 4.09 mmol) in 1,4-dioxane (5 mL) was added nano Fe_3O_4 (0.0189 g, 2 mol%) and the reaction mixture was stirred at room temperature for 5 min. 2-(Piperidin-4-yl)-1*H*-benzo[*d*]imidazole (0.82 g, 4.09 mmol) was added to this reaction mixture, stirred for another 10 min at the same temperature followed by the addition of 4-bromophenylboronic acid (0.82 g, 4.09 mmol) and stirring was continued until the completion of the reaction as indicated by TLC. The Fe_3O_4 nanoparticles were recovered by absorbing on to the magnetic stirring bar. The reaction mixture was extracted with ethyl

acetate (3 × 50 mL). The extract was washed with water, and finally with brine. The organic solution was dried with anhydrous Na₂SO₄ and concentrated by rotary evaporator. Finally, the residue was purified by recrystallization from ethanol.

2.2a 2-((4-(1*H*-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-bromophenyl)methyl)phenol (**4a**): Yield: 90% (1.697 g); Yellow solid; M.p.: 210–212 °C; IR (ATR, cm⁻¹): 3374 (NH), 3500 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 1.57 (m, 4H), 2.34 (t, 4H, *J* = 6.4 Hz), 2.74 (m, 1H), 4.75 (s, 1H, NH), 5.04 (s, 1H), 5.41 (s, 1H, OH), 6.96 (d, 1H, *J* = 9.6 Hz), 7.08 (t, 1H, *J* = 6.4 Hz), 7.39 (t, 1H, *J* = 6.8 Hz), 7.49 (d, 2H, *J* = 9.6 Hz), 7.73 (t, 2H, *J* = 7.2 Hz), 7.88 (d, 1H, *J* = 9.6 Hz), 8.02 (d, 2H, *J* = 9.6 Hz), 8.17 (d, 2H, *J* = 9.2 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 30.0 (2C), 35.4, 50.9 (2C), 76.0, 115.1 (2C), 116.4, 119.3, 120.5, 121.8, 123.1 (2C), 127.5, 130.0 (2C), 131.2, 132.4 (2C), 138.8 (2C), 141.5, 141.9, 157.9 ppm; LCMS: *m/z* Calcd. for C₂₅H₂₅BrN₃O 462.1, found 462.9 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₅H₂₄BrN₃O: C, 64.94; H, 5.23; N, 9.09; found (%): C, 64.90; H, 5.18; N, 9.00.

2.2b 2-((4-(1*H*-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-chlorophenyl)methyl)phenol (**4b**): Yield: 89% (1.521 g); Yellow solid; M.p.: 200–202 °C; IR (ATR, cm⁻¹): 3380 (NH), 3524 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 1.57 (m, 4H, *J* = 9.2 Hz), 2.18 (t, 4H, *J* = 6.4 Hz), 2.74 (m, 1H, *J* = 9.6 Hz), 4.61 (s, 1H, NH), 4.94 (s, 1H), 5.32 (s, 1H, OH), 6.97 (d, 1H, *J* = 9.6 Hz), 7.04 (t, 1H, *J* = 6.4 Hz), 7.39 (t, 1H, *J* = 6.8 Hz), 7.50 (d, 2H, *J* = 9.6 Hz), 7.73 (t, 2H, *J* = 7.2 Hz), 7.83 (d, 1H, *J* = 9.6 Hz), 7.97 (d, 2H, *J* = 8.8 Hz), 8.13 (d, 2H, *J* = 9.2 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 29.9 (2C), 35.5, 51.0 (2C), 76.2, 115.2 (2C), 116.3, 119.3, 121.6, 123.2 (2C), 127.6, 129.3 (2C), 130.0 (2C), 131.3, 131.8, 138.9 (2C), 140.8, 141.5, 157.9 ppm; LCMS: *m/z* Calcd. for C₂₅H₂₅ClN₃O 418.9, found 418.9 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₅H₂₄ClN₃O: C, 71.85; H, 5.79; N, 10.05; found (%): C, 71.79; H, 5.71; N, 10.01.

2.2c 2-((4-(1*H*-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-chlorophenyl)methyl)-4-bromophenol (**4c**): Yield: 85% (1.727 g); White solid; M.p.: 201–203 °C; IR (ATR, cm⁻¹): 3365 (NH), 3526 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 1.40 (m, 4H, *J* = 9.6 Hz), 2.16 (t, 4H, *J* = 7.6 Hz), 2.73 (m, 1H, *J* = 9.6 Hz), 4.73 (s, 1H, NH), 5.09 (s, 1H), 5.34 (s, 1H, OH), 6.86 (d, 1H, *J* = 9.6 Hz), 6.95 (d, 2H, *J* = 8.8 Hz), 7.09 (s, 1H), 7.39 (t, 2H, *J* = 6.8 Hz), 7.50 (d, 1H, *J* = 9.6 Hz), 7.71 (d, 2H, *J* = 9.2 Hz), 8.00 (d, 2H, *J* = 9.6 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 30.1 (2C), 35.6, 51.4 (2C), 75.5, 115.2 (2C), 116.2, 119.2, 121.7, 123.0 (2C), 123.3, 129.3 (2C), 129.6 (2C), 131.8, 134.4, 138.8 (2C), 140.8, 141.4, 156.8 ppm; LCMS: *m/z* Calcd. for C₂₅H₂₄BrClN₃O 497.0, found 497.4 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₅H₂₃BrClN₃O: C, 60.44; H, 4.67; N, 8.46; found (%): C, 60.38; H, 4.60; N, 8.39.

2.2d 2-((4-(1*H*-benzo[d]imidazol-2-yl)piperidin-1-yl)(phenylmethyl)-4-bromophenol (**4d**): Yield: 86% (1.626 g); White solid; M.p.: 199–201 °C; IR (ATR, cm⁻¹): 3361 (NH), 3530 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 1.56 (m, 4H, *J* = 9.6 Hz), 2.36 (t, 4H, *J* = 7.2 Hz), 2.75 (m, 1H, *J* = 7.6 Hz), 4.87 (s, 1H, NH), 5.04 (s, 1H), 5.32 (s, 1H, OH), 6.69 (d, 1H, *J* = 9.6 Hz), 7.09 (s, 1H), 7.36 (t, 2H, *J* = 6.8 Hz), 7.42 (d, 1H, *J* = 9.6 Hz), 7.67 (t, 1H, *J* = 6.4 Hz), 7.88 (t, 2H, *J* = 6.8 Hz), 8.02 (d, 2H, *J* = 9.6 Hz), 8.17 (d, 2H, *J* = 9.2 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 30.0 (2C), 35.5, 51.2 (2C), 75.5, 115.2 (2C), 116.4, 119.2, 121.7, 123.1 (2C), 123.3, 126.5, 128.3 (2C), 129.4 (2C), 134.3, 138.8 (2C), 141.5, 142.7, 156.8 ppm; LCMS: *m/z* Calcd. for C₂₅H₂₅BrN₃O 463.3, found 463.3 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₅H₂₄BrN₃O: C, 64.94; H, 5.23; N, 9.09; found (%): C, 64.88; H, 5.19; N, 9.01.

2.2e 2-((4-(1*H*-benzo[d]imidazol-2-yl)piperidin-1-yl)(phenylmethyl)-4-nitrophenol (**4e**): Yield: 80% (1.401 g); White solid; M.p.: 200–202 °C; IR (ATR, cm⁻¹): 3369 (NH), 3528 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 1.56 (m, 4H, *J* = 9.6 Hz), 2.37 (t, 4H, *J* = 6.8 Hz), 2.76 (m, 1H, *J* = 7.2 Hz), 4.87 (s, 1H, NH), 5.12 (s, 1H), 5.37 (s, 1H, OH), 7.07 (d, 1H, *J* = 9.2 Hz), 7.36 (t, 2H, *J* = 7.2 Hz), 7.43 (t, 1H, *J* = 6.8 Hz), 7.68 (t, 2H, *J* = 6.4 Hz), 7.87 (d, 2H, *J* = 9.6 Hz), 7.95 (d, 2H, *J* = 9.6 Hz), 8.07 (d, 1H, *J* = 9.2 Hz), 8.16 (s, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 29.7 (2C), 35.4, 51.8 (2C), 75.0, 115.1 (2C), 116.3, 120.5, 123.2 (2C), 126.1 (2C), 126.7, 128.4 (2C), 129.2 (2C), 138.9 (2C), 141.0, 141.5, 142.8, 164.2 ppm; LCMS: *m/z* Calcd. for C₂₅H₂₅N₄O₃ 429.9, found 429.4 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₅H₂₄N₄O₃: C, 70.08; H, 5.65; N, 13.08; found (%): C, 70.00; H, 5.59; N, 13.00.

2.2f 2-((4-(1*H*-benzo[d]imidazol-2-yl)piperidin-1-yl)(phenylmethyl)-4-methoxyphenol (**4f**): Yield: 94% (1.589 g); White solid; M.p.: 205–207 °C; IR (ATR, cm⁻¹): 3374 (NH), 3527 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 1.57 (m, 4H, *J* = 9.2 Hz), 2.33 (t, 4H, *J* = 6.8 Hz), 2.75 (m, 1H, *J* = 7.2 Hz), 3.81 (s, 3H, OCH₃), 4.90 (s, 1H, NH), 5.06 (s, 1H), 5.36 (s, 1H, OH), 6.63 (d, 1H, *J* = 8.8 Hz), 6.74 (d, 1H, *J* = 9.6 Hz), 7.03 (s, 1H), 7.36 (t, 2H, *J* = 6.8 Hz), 7.43 (t, 1H, *J* = 6.4 Hz), 7.67 (t, 2H, *J* = 6.4 Hz), 7.87 (d, 2H, *J* = 9.6 Hz), 8.02 (d, 2H, *J* = 9.6 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 29.9 (2C), 35.4, 51.6 (2C), 55.8, 76.1, 113.1, 113.8, 115.2 (2C), 117.5, 120.5, 123.2 (2C), 126.0, 128.2 (2C), 129.3 (2C), 138.8 (2C), 141.5, 142.6, 150.2, 153.9 ppm; LCMS: *m/z* Calcd. for C₂₆H₂₈N₃O₂ 414.2, found 414.4 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₆H₂₇N₃O₂: C, 75.52; H, 6.58; N, 10.16; found (%): C, 75.48; H, 6.49; N, 10.09.

2.2g -((4-(1*H*-benzo[d]imidazol-2-yl)piperidin-1-yl)(phenylmethyl)-4-methylphenol (**4g**): Yield: 91% (1.479 g); White solid; M.p.: 204–206 °C; IR (ATR, cm⁻¹): 3371 (NH), 3525 (OH); ¹H NMR (CDCl₃, 400 MHz) δ:

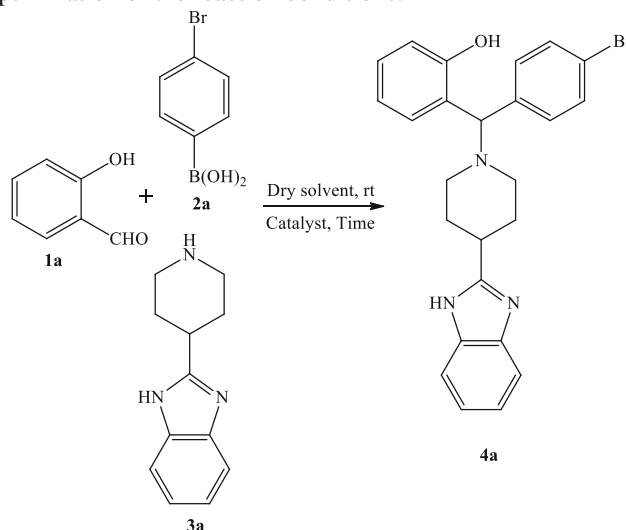
1.56 (m, 4H, $J = 9.6$ Hz), 2.20 (s, 3H, CH₃), 2.39 (t, 4H, $J = 6.4$ Hz), 2.75 (m, 1H, $J = 9.6$ Hz), 4.77 (s, 1H, NH), 5.07 (s, 1H), 5.32 (s, 1H, OH), 6.78 (d, 1H, $J = 9.2$ Hz), 6.88 (d, 1H, $J = 9.2$ Hz), 7.00 (s, 1H), 7.39 (t, 2H, $J = 6.8$ Hz), 7.50 (t, 1H, $J = 6.4$ Hz), 7.73 (t, 2H, $J = 7.2$ Hz), 7.84 (d, 2H, $J = 9.2$ Hz), 7.97 (d, 2H, $J = 8.8$ Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ : 21.6, 30.1 (2C), 35.6, 51.4 (2C), 76.1, 115.2 (2C), 116.1, 119.3, 123.0 (2C), 126.0, 127.8, 128.2 (2C), 129.3 (2C), 131.5 (2C), 138.8 (2C), 141.5, 142.6, 154.8 ppm; LCMS: m/z Calcd. for C₂₆H₂₆N₃O 396.2, found 396.4 [M – H][–]; Elem. anal. Calcd. (%) for C₂₆H₂₇N₃O: C, 78.56; H, 6.85; N, 10.57; found (%): C, 78.48; H, 6.78; N, 10.49.

$J = 9.2$ Hz), 6.69 (d, 1H, $J = 9.6$ Hz), 7.07 (t, 1H, $J = 6.4$ Hz), 7.34 (d, 1H, $J = 9.6$ Hz), 7.43 (t, 1H, $J = 6.8$ Hz), 7.52 (d, 2H, $J = 8.8$ Hz), 7.67 (t, 1H, $J = 6.4$ Hz), 7.88 (t, 2H, $J = 6.8$ Hz), 7.97 (d, 1H, $J = 9.6$ Hz), 8.08 (d, 1H, $J = 9.2$ Hz), 8.16 (d, 1H, $J = 9.2$ Hz), 8.22 (s, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ : 73.7, 100.9, 110.0, 113.3, 116.4, 121.0, 121.7, 124.7, 126.5, 127.5, 127.9, 128.1 (2C), 128.9, 129.4 (2C), 129.8, 130.7, 135.3, 137.8, 155.4 ppm; LCMS: m/z Calcd. for C₂₁H₁₅BrNO 377.2, found 377.4 [M – H][–]; Elem. anal. Calcd. (%) for C₂₁H₁₆BrNO: C, 66.68; H, 4.26; N, 3.70; found (%): C, 66.59; H, 4.19; N, 3.65.

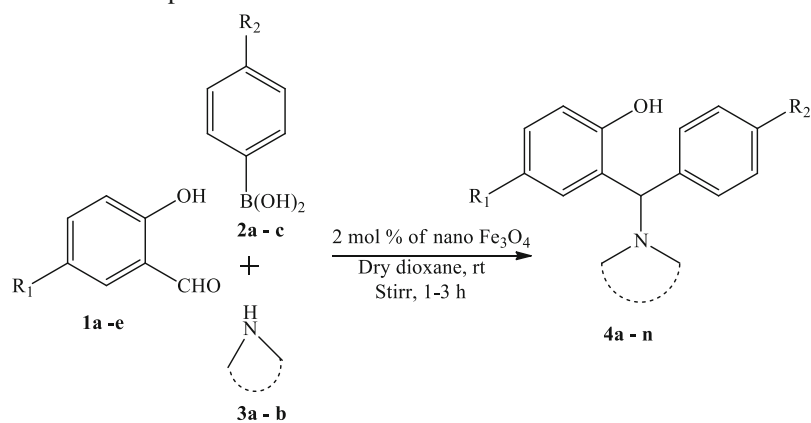
2.2h 2-((5-Bromo-1H-indol-1-yl)(phenyl) methyl) phenol (4h): Yield: 88% (1.361 g); White solid; M.p.: 189–191 °C; IR (ATR, cm^{–1}): 3521 (OH). ¹H NMR (CDCl₃, 400 MHz) δ : 5.33 (s, 1H, OH), 6.24 (s, 1H), 6.42 (d, 1H,

2.2i 2-((5-Bromo-1H-indol-1-yl)(4-chlorophenyl) methyl)phenol (4i): Yield: 86% (1.451 g); White solid; M.p.: 189–191 °C; IR (ATR, cm^{–1}): 3524 (OH); ¹H NMR (CDCl₃, 400 MHz) δ : 5.35 (s, 1H, OH), 6.10 (s, 1H), 6.23 (d, 1H, $J = 9.2$ Hz), 6.69 (d, 1H, $J = 9.6$ Hz), 6.85 (t, 1H,

Table 1. Optimization of the reaction conditions.



Entry	Catalyst	Amount of catalyst (mol %)	Solvent (Dry)	Time (h)	Yield (%)
1	No catalyst	–	DMF	24	–
2	BDMS	5	DMF	10	28
3	T ₃ P	5	DMF	10	5
4	HIO ₃	5	DMF	10	10
5	Iodine	5	DMF	10	29
6	Co ₃ O ₄	5	DMF	10	35
7	TiO ₂	5	DMF	10	32
8	CuCl	5	DMF	10	28
9	Nano Fe ₃ O ₄	5	DMF	10	47
10	Nano Fe ₃ O ₄	5	CH ₃ CN	10	50
11	Nano Fe ₃ O ₄	5	DMSO	10	59
12	Nano Fe ₃ O ₄	5	Toluene	10	75
13	Nano Fe ₃ O ₄	5	1,4-Dioxane	10	81
14	Nano Fe ₃ O ₄	4	1,4-Dioxane	5	86
15	Nano Fe ₃ O ₄	3	1,4-Dioxane	2	90
16	Nano Fe ₃ O ₄	2	1,4-Dioxane	2	90
17	Nano Fe ₃ O ₄	1	1,4-Dioxane	2	84

Table 2. Scope of substrates in the Petasis borono-Mannich reaction.


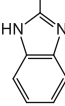

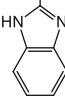

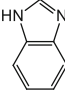

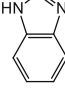

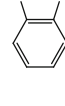
Entry	R_1	R_2	Amine	Product	Time (h)	Yield (%)
1	H	Br		4a	2	90
						
2	H	Cl		4b	2	89
						
3	Br	Cl		4c	3	85
						
4	Br	H		4d	2	86
						
5	NO_2	H		4e	3	80
						

Table 2. (contd.)

Entry	R ₁	R ₂	Amine	Product	Time (h)	Yield (%)
6	OMe	H		4f	1	94
7	Me	H		4g	1	91
8	H	H		4h	2	88
9	H	Cl		4i	2	86
10	OMe	Cl		4j	1	93
11	NO ₂	Cl		4k	3	82
12	Me	H		4l	1	90
13	Br	H		4m	2	87
14	Br	Cl		4n	2	84

$J = 6.8$ Hz), 7.06 (d, 1H, $J = 9.6$ Hz), 7.30 (t, 1H, $J = 6.4$ Hz), 7.42 (d, 2H, $J = 9.6$ Hz), 7.47 (d, 2H, $J = 9.2$ Hz), 7.66 (d, 1H, $J = 8.8$ Hz), 7.87 (d, 1H, $J = 9.2$ Hz), 8.02 (d, 1H, $J = 9.6$ Hz), 8.17 (s, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ : 73.8, 100.9, 110.2, 113.2, 116.3, 121.0, 121.7, 124.8, 127.4, 127.9, 128.4 (2C), 128.8, 129.5 (2C), 129.8, 130.7, 132.0, 135.4, 135.9, 154.5 ppm; LCMS: m/z Calcd. for C₂₁H₁₆BrClNO 413.7, found 413.4 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₁H₁₅BrClNO: C, 61.11; H, 3.66; N, 3.39; found (%): C, 61.04; H, 3.59; N, 3.31.

2.2j 2-((5-Bromo-1H-indol-1-yl)(4-chlorophenyl)methyl)-4-methoxyphenol (**4j**): Yield: 93% (1.683 g); White solid; M.p.: 179–181 °C; IR (ATR, cm⁻¹): 3531 (OH); ¹H NMR (CDCl₃, 400 MHz) δ : 3.80 (s, 3H, -OCH₃), 5.37 (s, 1H, OH), 6.29 (s, 1H), 6.36 (d, 1H, $J = 9.2$ Hz), 6.63 (d, 1H, $J = 8.8$ Hz), 6.74 (d, 1H, $J = 9.6$ Hz), 7.00 (s, 1H), 7.13 (d, 2H, $J = 9.6$ Hz), 7.35 (d, 2H, $J = 8.8$ Hz), 7.44 (d, 1H, $J = 9.6$ Hz), 7.66 (d, 1H, $J = 9.2$ Hz), 7.87 (d, 1H, $J = 8.8$ Hz), 8.12 (s, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ : 55.7, 74.0, 100.9, 110.2, 113.2 (2C), 113.7,

117.5, 121.0, 124.7, 128.3 (2C), 128.9 (2C), 129.4 (2C), 130.7, 131.8, 135.4 (2C), 147.5, 153.5 ppm; LCMS: *m/z* Calcd. for C₂₂H₁₈BrClNO₂443.0, found 443.2 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₂H₁₇BrClNO₂: C, 59.68; H, 3.87; N, 3.16; found (%): C, 59.61; H, 3.79; N, 3.09.

2.2k 2-((5-Bromo-1H-indol-1-yl)(4-chlorophenyl)methyl)-4-nitrophenol (4k): Yield: 82% (1.535 g); White solid; M.p.: 170–172 °C; IR (ATR, cm⁻¹): 3528 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 5.39 (s, 1H, OH), 6.20 (s, 1H), 6.30 (d, 1H, *J* = 9.2 Hz), 7.00 (d, 1H, *J* = 9.6 Hz), 7.12 (d, 2H, *J* = 8.8 Hz), 7.29 (d, 2H, *J* = 9.2 Hz), 7.40 (d, 1H, *J* = 9.6 Hz), 7.64 (d, 1H, *J* = 8.8 Hz), 7.75 (d, 1H, *J* = 9.2 Hz), 7.87 (d, 1H, *J* = 9.2 Hz), 8.03 (s, 1H), 8.18 (s, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 72.8, 100.8, 110.1, 113.2, 116.1, 121.0, 124.8, 126.0, 126.5, 128.5 (2C), 128.8 (2C), 129.4 (2C), 130.7, 131.9, 135.5 (2C), 141.0, 161.3 ppm; LCMS: *m/z* Calcd. for C₂₁H₁₅BrClN₂O₃457.0, found 457.2 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₁H₁₄BrClN₂O₃: C, 55.11; H, 3.08; N, 6.12; found (%): C, 55.06; H, 3.00; N, 6.03.

2.2l 2-((5-Bromo-1H-indol-1-yl)(phenyl)methyl)-4-methylphenol (4l): Yield: 90% (1.444 g); White solid; M.p.: 175–177 °C; IR (ATR, cm⁻¹): 3526 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 2.22 (s, 3H, CH₃), 5.33 (s, 1H, OH), 6.10 (s, 1H), 6.27 (d, 1H, *J* = 9.6 Hz), 6.56 (d, 1H, *J* = 9.2 Hz), 6.78 (d, 1H, *J* = 8.8 Hz), 7.03 (s, 1H), 7.12 (d, 2H, *J* = 8.8 Hz), 7.30 (t, 1H, *J* = 6.4 Hz), 7.41 (t, 2H, *J* = 7.2 Hz), 7.64 (d, 1H, *J* = 8.8 Hz), 7.76 (d, 1H, *J* = 8.8 Hz), 7.87 (d, 1H, *J* = 9.6 Hz), 8.02 (s, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 21.5, 74.0, 100.9, 110.1, 113.2, 116.3, 121.0, 124.7, 126.2, 127.9 (2C), 128.3 (2C), 128.9, 129.5 (2C), 130.8, 131.5 (2C), 135.6, 137.4, 152.4 ppm; LCMS: *m/z* Calcd. for C₂₂H₁₉BrNO 393.3, found 393.4 [M + H]⁺; Elem. anal. Calcd. (%) for C₂₂H₁₈BrNO: C, 67.36; H, 4.62; N, 3.57; found (%): C, 67.29; H, 4.58; N, 3.49.

2.2m 4-Bromo-2-((5-bromo-1H-indol-1-yl)(phenyl)methyl)phenol (4m): Yield: 87% (1.626 g); White solid; M.p.: 173–175 °C; IR (ATR, cm⁻¹): 3523 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 5.35 (s, 1H, OH), 6.14 (s, 1H), 6.31 (d, 1H, *J* = 9.6 Hz), 6.61 (d, 1H, *J* = 9.2 Hz), 6.80 (s, 1H), 7.00 (d, 2H, *J* = 8.8 Hz), 7.13 (d, 1H, *J* = 9.6 Hz), 7.31 (t, 1H, *J* = 6.8 Hz), 7.41 (t, 2H, *J* = 7.6 Hz), 7.48 (d, 1H, *J* = 10 Hz), 7.76 (d, 1H, *J* = 8.8 Hz), 7.87 (d, 1H, *J* = 8.8 Hz), 8.02 (s, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 73.0, 100.9, 110.2, 113.1, 116.1, 119.2, 121.0, 123.2, 124.6, 126.1, 128.2 (2C), 128.9, 129.3 (2C), 130.1, 130.6, 134.4, 135.7, 137.6, 154.3 ppm; HRMS: *m/z* Calcd. for C₂₁H₁₅Br₂NONa 480.1600, found 480.1170 [M + Na]⁺; Elem. anal. Calcd. (%) for C₂₁H₁₅Br₂NO: C, 55.17; H, 3.31; N, 3.06; found (%): C, 55.11; H, 3.25; N, 2.99.

2.2n 4-Bromo-2-((5-bromo-1H-indol-1-yl)(4-chlorophenyl)methyl)phenol (4n): Yield: 84% (1.688 g); White solid; M.p.: 163–165 °C; IR (ATR, cm⁻¹): 3527 (OH); ¹H NMR (CDCl₃, 400 MHz) δ: 5.35 (s, 1H, OH), 6.19 (s, 1H),

6.32 (d, 1H, *J* = 9.6 Hz), 6.89 (d, 1H, *J* = 9.2 Hz), 7.03 (s, 1H), 7.12 (d, 2H, *J* = 8.8 Hz), 7.29 (d, 1H, *J* = 9.2 Hz), 7.39 (d, 2H, *J* = 9.6 Hz), 7.47 (d, 1H, *J* = 8.8 Hz), 7.76 (d, 1H, *J* = 8.8 Hz), 7.87 (d, 1H, *J* = 9.6 Hz), 8.17 (s, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ: 73.2, 100.9, 110.1, 113.2, 116.0, 119.2, 121.0, 123.2, 124.7, 128.3 (2C), 128.9, 129.5 (2C), 130.1, 130.7, 131.8, 134.4, 135.5 (2C), 154.4 ppm; HRMS: *m/z* Calcd. for C₂₁H₁₄Br₂CINONa 514.6000, found 514.0392 [M + Na]⁺; Elem. anal. Calcd. (%) for C₂₁H₁₄Br₂CINO: C, 51.31; H, 2.87; N, 2.85; found (%): C, 51.25; H, 2.80; N, 2.79.

3. Results and Discussion

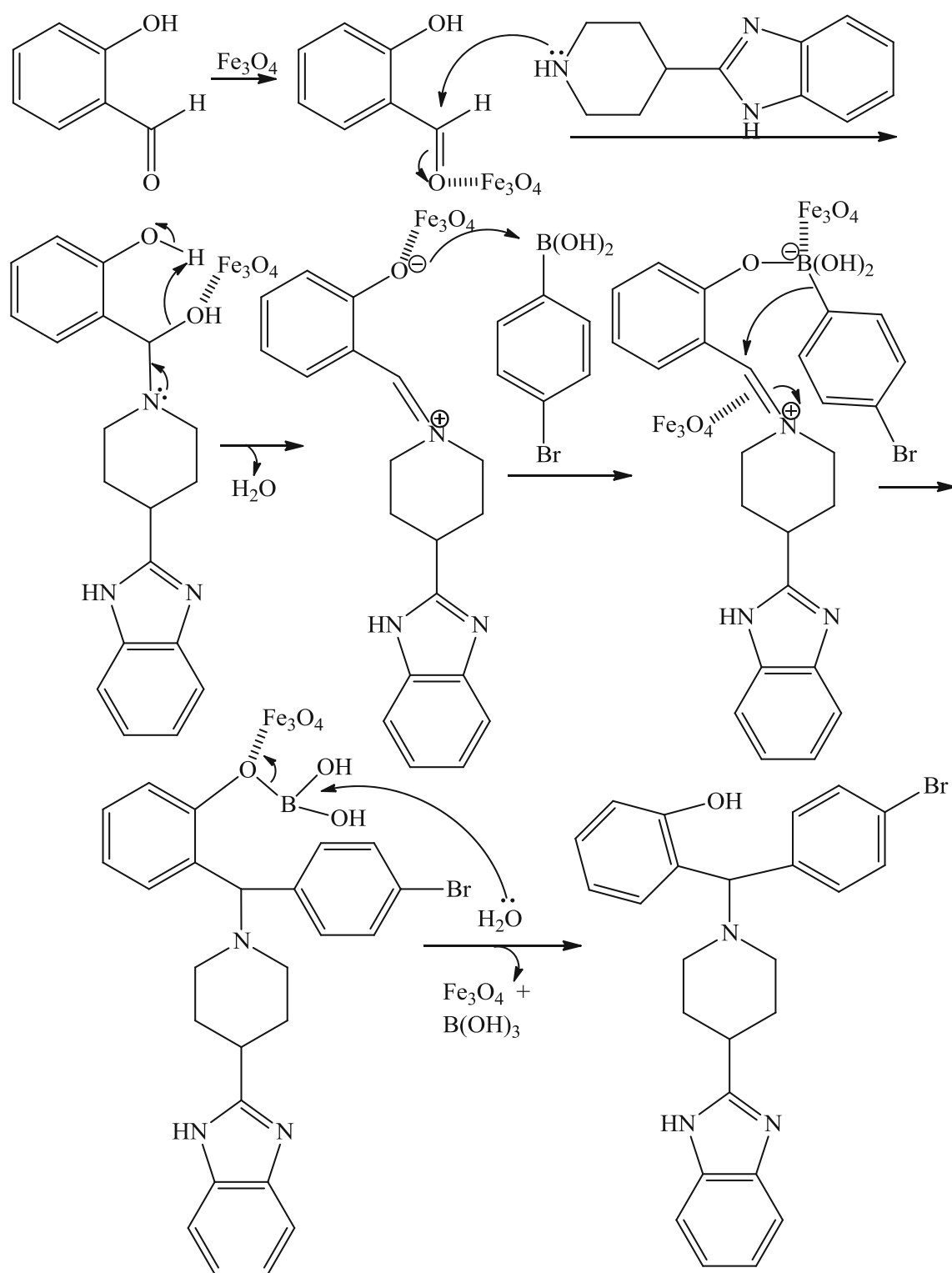
We initiated our investigation with the reaction of salicylaldehyde (**1a**), 4-bromophenylboronic acid (**2a**) and 2-(piperidin-4-yl)-1H-benzo[d]imidazole (**3a**) to optimize various reaction conditions in DMF solvent at room temperature. Product formation did not happen when the reaction was performed in the absence of a catalyst. When the reaction was performed in the presence of bromodimethylsulfonium bromide (BDMS), and iodine, under the same reaction conditions, 28% and 29% of the desired adduct (**4a**) was obtained respectively. However, in all catalysts evaluated, the reaction was slow and stalled at low conversions. Eventually, we focussed on metal catalysts and its screen revealed a 5 mol% nano Fe₃O₄ provided superior to all catalysts with the benefit of an improved isolated yield (47%) of (**4a**) (Table 1, entry 9).

The next parameter explored was solvents and the result obtained in dry 1,4-dioxane was significantly better than those conducted in dry DMF, CH₃CN, DMSO and toluene. Subsequently, the investigation of the effect of catalyst loading found that the best yield was obtained when 2 mol% nano Fe₃O₄ was used (Table 1, entry 16) in the present reaction system. On increasing the load of catalyst, the yield of (**4a**) decreases. This is due to dissociation of the product.

Further optimization of various reactants showed that optimum reaction condition was set at a molar

Table 3. Reusability of Fe₃O₄ nanoparticles.

Run	Time (h)	Yield (%)
1	2	90
2	2	88
3	2	87
4	2	85



Scheme 1. A plausible mechanism for the magnetic nano Fe_3O_4 catalyzed Petasis borono-Mannich reaction.

ratio of 1a/2a/3a = 1:1:1. When a mixture of salicylaldehyde (**1a**), 4-bromophenylboronic acid (**2a**) and 2-(piperidin-4-yl)-1H-benzo[d]imidazole (**3a**) in 1,4-dioxane was stirred in the presence of 2 mol% of nano Fe_3O_4 at room temperature for 2 h, the

product 2-((4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)(4-bromophenyl)methyl)phenol (**4a**) was obtained in excellent yield (90%).

Under the established reaction conditions, the scope of the nano Fe_3O_4 mediated Petasis borono-Mannich

reaction was explored, with the results summarized in Table 2. Various boronic acids bearing halogen substituents, such as bromo and chloro were well tolerated leading to the expected products (**4a–c**), (**4i–k**) and (**4n**) in excellent yields. The study was further extended to a variety of salicylaldehydes. Salicylaldehydes with electron donating substituents were well-tolerated under the standard reaction conditions, generating the corresponding products (**4f** and **4g**) in 94% and 91% yields respectively. On the other hand, electron withdrawing groups such as bromo was compatible and gave the corresponding product (**4c**) and (**4d**) in 85 and 86% yields, respectively. Moreover, when a strong electron withdrawing nitro group was used, the desired product (**4e**) was obtained in 80% yield. The electron donating salicylaldehydes exhibited relatively higher reactivities than electron withdrawing salicylaldehydes.

In the light of a successful process for the synthesis of 2-((4-(1*H*-benzo[*d*]imidazol-2-yl)piperidin-1-yl)(phenyl)methyl)phenol, we sought to further extend the scope of this practical approach by replacing 2-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole with 5-bromo-1*H*-indole under the optimal reaction conditions. Following the above protocol, gratifyingly, the reaction worked equally well and gave the corresponding products (**4h–n**) in excellent yields.

One of the added advantages of this catalyst is that it can readily be separated from the reaction mixture by simply applying an external magnetic field and then reused without any significant loss of catalytic activity. The recovery and reuse of the nano Fe₃O₄ catalyst were studied for salicylaldehyde (**1a**), 4-bromophenylboronic acid (**2a**) and 2-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole (**3a**) in 1,4-dioxane under the established optimal reaction conditions at room temperature. The reaction time was maintained constant in each cycle (2 h), and the results are collected in Table 3. The catalyst was recovered after each cycle by magnetic separation, washed with 1,4-dioxane, dried, weighed and reused in the next cycle. The results showed that the catalyst can be reused four successive cycles without a noticeable drop in its activity.

On the basis of the present results, a plausible mechanism for this magnetite catalyzed Petasis borono-Mannich reaction is illustrated in Scheme 1. Salicylaldehyde is activated by the Fe₃O₄ catalyst because of its Lewis acid property.³² The nucleophilic addition of the secondary amine to activated salicylaldehyde produces carbinolamine intermediate, followed by its dehydration to produce iminium ion intermediate. This iminium intermediate would coordinate to the organoboronic acid. The carbon–carbon bond formation would occur by migration of the boronic acid substituent to the

electropositive carbon. The final product would be obtained by the liberation of H₃BO₃. Further, when 5-bromo-1*H*-indole is used as amine, resonance donating effect is facilitated by bromo group in the aromatic ring. Since bromo group is present in position 5 of the indole ring, it reduces the chance of electron withdrawing effect. So nitrogen in the indole ring facilitates nucleophilic addition.³³

4. Conclusion

In summary, we have accomplished a novel and convenient one-pot protocol for the synthesis of aminomethylphenol libraries *via* three component Petasis borono-Mannich reaction. This versatile, environmentally benign and straightforward procedure features a broad substrate scope with inexpensive, non-hygroscopic and non-toxic Fe₃O₄ magnetic nano catalyst, which is easily recoverable and reusable for four cycles.

Supplementary Information (SI)

Full characterization data, NMR spectra (¹H and ¹³C NMR) of all the compounds **4a–n**, LCMS spectra of **4a–l**, and HRMS of **4m**, as well as **4n**, were reported in the supplementary information. Supplementary information is available at www.ias.ac.in/chemsci.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare.

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