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REGULAR ARTICLE

Synthesis of aminomethylphenol derivatives *via* magnetic nano Fe_3O_4 catalyzed one pot Petasis borono-Mannich reaction

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Abstract. A novel library of aminomethylphenol has been developed using magnetic Fe_3O_4 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 Fe_3O_4.

1. Introduction

Aminomethylphenol units are privileged structural motifs which have drawn much attention from the medicinal[1] and material science[2] 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] antimicrobial[5] and antimalarial[6] 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 temperature[18] 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 $CoFe_2O_4$,[20] chitosan[21] and [bmim]BF_4.[22] The other interesting works describing this reaction were carried out using protonated trititanate ($H_2Ti_3O_7$) nanotubes[23] and tetranuclear Zn_2Ln_2 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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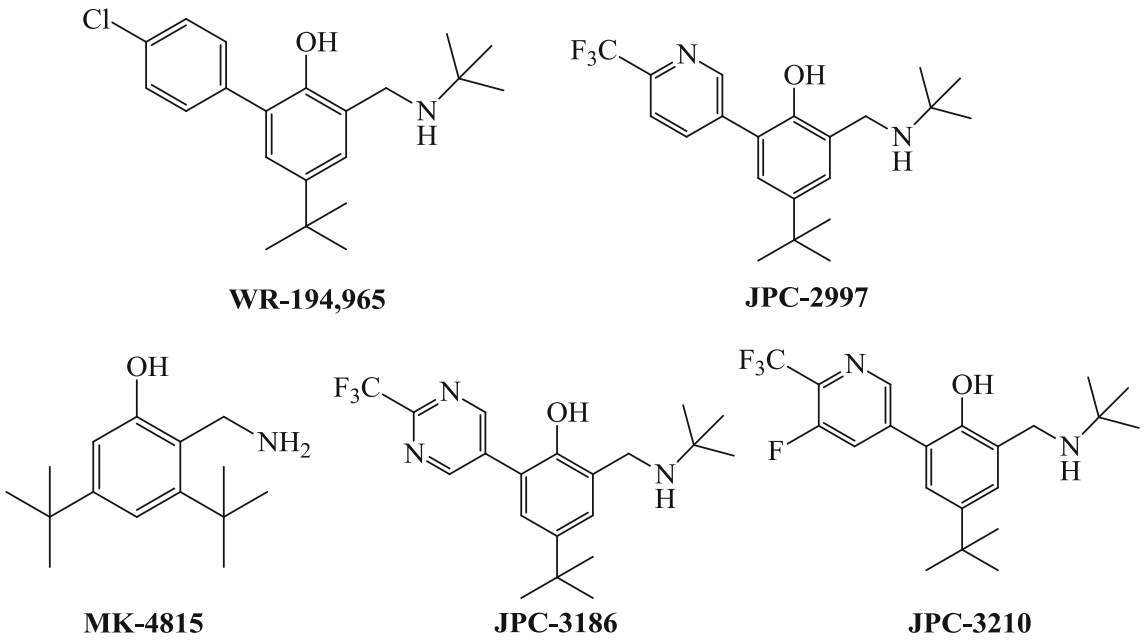


Figure 1. Representative examples of alkyl aminomethylphenol pharmaceuticals.

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 oxidation[29] 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 Clearsynth 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). ^{1}H 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 Na_2SO_4 and concentrated by rotary evaporator. Finally, the residue was purified by recrystallization from ethanol.

2.2a *2-((4-(1H-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); ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{25}H_{25}BrN_3O$ 462.1, found 462.9 $[M + H]^+$; Elem. anal. Calcd. (%) for $C_{25}H_{24}BrN_3O$: C, 64.94; H, 5.23; N, 9.09; found (%): C, 64.90; H, 5.18; N, 9.00.

2.2b *2-((4-(1H-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); ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{25}H_{25}ClN_3O$ 418.9, found 418.9 $[M + H]^+$; Elem. anal. Calcd. (%) for $C_{25}H_{24}ClN_3O$: C, 71.85; H, 5.79; N, 10.05; found (%): C, 71.79; H, 5.71; N, 10.01.

2.2c *2-((4-(1H-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); ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{25}H_{24}BrClN_3O$ 497.0, found 497.4 $[M + H]^+$; Elem. anal. Calcd. (%) for $C_{25}H_{23}BrClN_3O$: C, 60.44; H, 4.67; N, 8.46; found (%): C, 60.38; H, 4.60; N, 8.39.

2.2d *2-((4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl)(phenyl)methyl)-4-bromophenol* (**4d**): Yield: 86% (1.626 g); White solid; M.p.: 199–201 °C; IR (ATR, cm^{-1}): 3361 (NH), 3530 (OH); ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{25}H_{25}BrN_3O$ 463.3, found 463.3 $[M + H]^+$; Elem. anal. Calcd. (%) for $C_{25}H_{24}BrN_3O$: C, 64.94; H, 5.23; N, 9.09; found (%): C, 64.88; H, 5.19; N, 9.01.

2.2e *2-((4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) (phenyl)methyl)-4-nitrophenol* (**4e**): Yield: 80% (1.401 g); White solid; M.p.: 200–202 °C; IR (ATR, cm^{-1}): 3369 (NH), 3528 (OH); ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{25}H_{25}N_4O_3$ 429.9, found 429.4 $[M + H]^+$; Elem. anal. Calcd. (%) for $C_{25}H_{24}N_4O_3$: C, 70.08; H, 5.65; N, 13.08; found (%): C, 70.00; H, 5.59; N, 13.00.

2.2f *2-((4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) (phenyl)methyl)-4-methoxyphenol* (**4f**): Yield: 94% (1.589 g); White solid; M.p.: 205–207 °C; IR (ATR, cm^{-1}): 3374 (NH), 3527 (OH); ^{1}H NMR ($CDCl_3$, 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, OCH_3), 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; ^{13}C NMR ($CDCl_3$, 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 $C_{26}H_{28}N_3O_2$ 414.2, found 414.4 $[M + H]^+$; Elem. anal. Calcd. (%) for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16; found (%): C, 75.48; H, 6.49; N, 10.09.

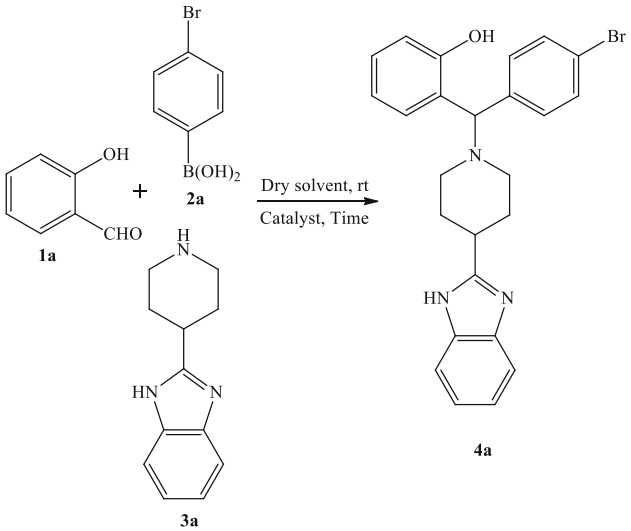
2.2g *-((4-(1H-benzo[d]imidazol-2-yl) piperidin-1-yl) (phenyl)methyl)-4-methylphenol* (**4g**): Yield: 91% (1.479 g); White solid; M.p.: 204–206 °C; IR (ATR, cm^{-1}): 3371 (NH), 3525 (OH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ:

1.56 (m, 4H, J = 9.6 Hz), 2.20 (s, 3H, CH_3), 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; ^{13}C NMR ($CDCl_3$, 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 $C_{26}H_{26}N_3O$ 396.2, found 396.4 $[M-H]^-$; Elem. anal. Calcd. (%) for $C_{26}H_{27}N_3O$: C, 78.56; H, 6.85; N, 10.57; found (%): C, 78.48; H, 6.78; N, 10.49.

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). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.33 (s, 1H, OH), 6.24 (s, 1H), 6.42 (d, 1H, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{15}BrNO$ 377.2, found 377.4 $[M-H]^-$; Elem. anal. Calcd. (%) for $C_{21}H_{16}BrNO$: C, 66.68; H, 4.26; N, 3.70; found (%): C, 66.59; H, 4.19; N, 3.65.

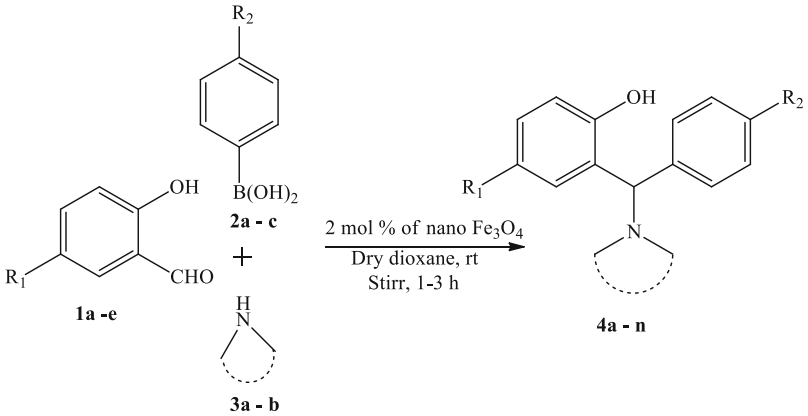
2.2i *2-((5-Bromo-1H-indol-1-yl)(4-chlorophenyl) methyl)phenol* (**4i**): Yield: 86% (1.451 g); White solid; M.p.: 189–191 °C; IR (ATR, cm^{-1}): 3524 (OH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.35 (s, 1H, OH), 6.10 (s, 1H), 6.23 (d, 1H, J = 9.2 Hz), 6.69 (d, 1H, J = 9.6 Hz), 6.85 (t, 1H,

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_3P	5	DMF	10	5
4	HIO_3	5	DMF	10	10
5	Iodine	5	DMF	10	29
6	Co_3O_4	5	DMF	10	35
7	TiO_2	5	DMF	10	32
8	CuCl	5	DMF	10	28
9	Nano Fe_3O_4	5	DMF	10	47
10	Nano Fe_3O_4	5	CH_3CN	10	50
11	Nano Fe_3O_4	5	DMSO	10	59
12	Nano Fe_3O_4	5	Toluene	10	75
13	Nano Fe_3O_4	5	1,4-Dioxane	10	81
14	Nano Fe_3O_4	4	1,4-Dioxane	5	86
15	Nano Fe_3O_4	3	1,4-Dioxane	2	90
16	Nano Fe_3O_4	2	1,4-Dioxane	2	90
17	Nano Fe_3O_4	1	1,4-Dioxane	2	84

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



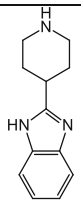
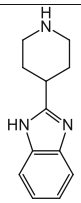
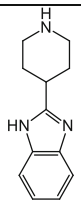
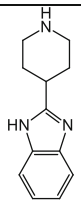
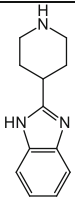
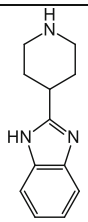
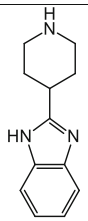
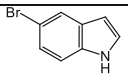
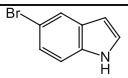
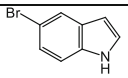
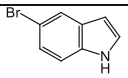
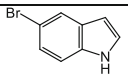
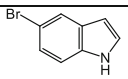
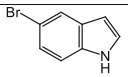
Entry	R_1	R_2	Amine	Product	Time (h)	Yield (%)
1	H	Br		**4a**	2	90
2	H	Cl		**4b**	2	89
3	Br	Cl		**4c**	3	85
4	Br	H		**4d**	2	86
5	NO_2	H		**4e**	3	80

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; ^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{16}BrClNO$ 413.7, found 413.4 $[M + H]^+$; Elem. anal. Calcd. (%) for $C_{21}H_{15}BrClNO$: 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); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.80, (s, 3H, -OCH_3), 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; ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{18}BrClNO_2$443.0, found 443.2 $[M + H]^+$; Elem. anal. Calcd. (%) for $C_{22}H_{17}BrClNO_2$: 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); ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{15}BrClN_2O_3$457.0, found 457.2 $[M + H]^+$; Elem. anal. Calcd. (%) for $C_{21}H_{14}BrClN_2O_3$: 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); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.22 (s, 3H, CH_3), 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; ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{19}BrNO$ 393.3, found 393.4 $[M + H]^+$; Elem. anal. Calcd (%) for $C_{22}H_{18}BrNO$: 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); ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{15}Br_2NONa$ 480.1600, found 480.1170 $[M + Na]^+$; Elem. anal. Calcd. (%) for $C_{21}H_{15}Br_2NO$: 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); ^{1}H NMR ($CDCl_3$, 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; ^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{14}Br_2ClNONa$ 514.6000, found 514.0392 $[M + Na]^+$; Elem. anal. Calcd. (%) for $C_{21}H_{14}Br_2ClNO$: C, 51.31; H, 2.87; N, 2.85; found (%): C, 51.25; H, 2.80; N, 2.79.

3. Results and Discussion

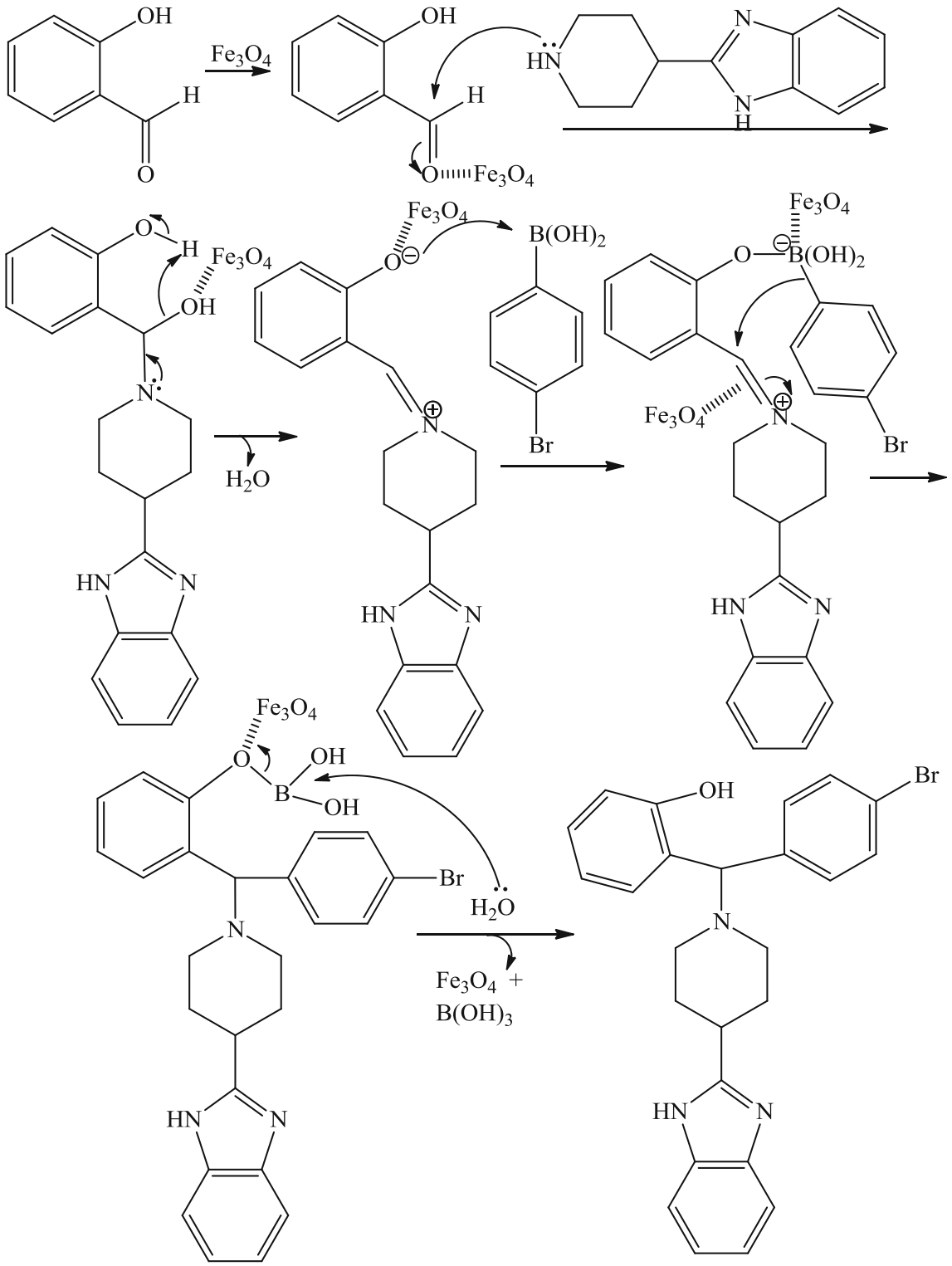
We initiated our investigation with the reaction of salicylaldehyde (**1a**), 4-bromophenylboronic acid (**2a**) and 2-(piperidin-4-yl)-1*H*-benzo[*d*]imidazole (**3a**) to optimize various reaction conditions in DMF solvent at room temperature. Product formation did not happen when the reaction was 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 Fe_3O_4 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, CH_3CN, DMSO and toluene. Subsequently, the investigation of the effect of catalyst loading found that the best yield was obtained when 2 mol% nano Fe_3O_4 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 Fe_3O_4 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)-1*H*-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-(1*H*-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 Fe_3O_4 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 Fe_3O_4 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 H_3BO_3. 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 Fe_3O_4 magnetic nano catalyst, which is easily recoverable and reusable for four cycles.

Supplementary Information (SI)

Full characterization data, NMR spectra (^{1}H and ^{13}C 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.

References

1. Kragler A, Hofner G and Wanner K T 2008 Synthesis and Biological Evaluation of Aminomethylphenol Derivatives as Inhibitors of the Murine GABA Transporters mGAT1–mGAT4 *Eur. J. Med. Chem.* **43** 2404
2. Zettlemoyer A C and Nace D M 1950 Use of Amine Additives to Prevent Drying Loss on Aging *Ind. Eng. Chem.* **42** 491
3. Halve A K, Dubey P K, Kankoriya A and Tiwari K 2009 4-Phenyldiazenyl 2-(Phenylimino methyl) Phenols; Synthesis and In-Vitro Biological Evaluation as Potential Antibacterial Agents *J. Enzyme Inhib. Med. Chem.* **24** 176

4. a) Zhang Y S, Cao G K, Peng S X, Dni D Z and Jin L 1986 Studies on Nonsteroidal Anti-inflammatory Drugs: Synthesis and Biological Activity of 4-Hydroxy-3-Aminomethyl-Diphenyl and 4(2)-Cyclohexyl-2(4)-Aminomethyl-Phenol Derivatives *Acta Pharm. Sin.* **21** 345; (b) Itoh H, Konno M, Tokuhiro T, Iguchi S and Hayashi M 1981 *2-Acyl-6-Aminomethylphenol Derivatives* U.S. Patent 4245099 A; (c) Xia Z N, Cao G K and Peng S X 1988 Synthesis and Quantum Chemical Calculation of 4-Heteroaryl-Mono/Di-Aminomethylphenol Derivatives *Acta Pharm Sin.* **23** 574
5. Ade S B, Kolhatkar D G and Deshpande M N 2012 Synthesis, Characterization and Biological Studies of 2-[(2-Hydroxy-5-Nitro Benzylidene)-Amino]-4-Methyl-Phenol with Ti(IV) and Zr(IV) Complexes *Int. J. Pharma Bio Sci.* **3** 6
6. Birrell G W, Chavchich M, Ager A L, Shieh H M, Heffernan G D, Zhao W, Krasucki P E, Saionz K W, Terpinski J, Schiehser G A, Jacobus L R, Shanks G D, Jacobus D P and Edstein M D 2015 JPC-2997, a New Aminomethylphenol with High In Vitro and In Vivo Antimalarial Activities against Blood Stages of Plasmodium *Antimicrob. Agents Chemother.* **59** 170
7. McCallum F, Harris I, Breda K V, De S L, Stanisic D I, Good M F, Jacobus D P and Edstein M D 2016 Evaluation of the 2-Aminomethylphenol JPC-2997 in Aotus Monkeys Infected with Plasmodium falciparum *Antimicrob. Agents Chemother.* **60** 1948
8. Chavchich M, Birrell G W, Ager A L, MacKenzie D O, Heffernan G D, Schiehser G A, Jacobus L R, Shanks G D, Jacobus D P and Edstein M D 2016 Lead Selection of a New Aminomethylphenol, JPC-3210, for Malaria Treatment and Prevention *Antimicrob. Agents Chemother.* **60** 3115
9. Englert H C, Lang H J, Hropot M and Kaiser J 1988 *2-Aminomethylphenol Derivatives, a Process for Their Preparation, Their Use, and Pharmaceutical Formulations Based on These Compounds* CA 1238908 A
10. (a) Pan Y G, Chan A and Hochman L 1993 *Hair Dye Coupler Compounds* U. S. Patent 5183941 A; (b) Umbricht G Dr, Rosato F J and Braun H J Dr 2006 *3-Amino-2-Aminomethylphenol Derivatives and Colorants Comprising These Compounds* WO 2006086374 A2
11. Evans J M and Woo J T K 1983 *Aminomethyl-Phenol Cross-Linking Compounds* U.S. Patent 4369290 A
12. Lawson J R 1992 *Composition and Method* CA 2066307 A1
13. (a) Babaev E R 2006 Aminomethyl Derivatives of 2,4-Di-α-Methylbenzylphenol as Multifunctional Additives for Lubricating Oils *Pet. Chem.* **46** 206; (b) Parlman R M and Burns L D 1982 *Bis(Disubstituted Aminomethyl)Phenols as Ashless Hydrocarbon Additives* U. S. Patent 4322304 A
14. Petasis N A and Boral S 2001 One-Step Three-Component Reaction Among Organoboronic Acids, Amines *Tetrahedron Lett.* **42** 539
15. Palaska E, Erdogan H, Safak C, Sarac S and Yulug N 1993 *Turk J. Med. Sci.* **18** 209
16. Shushizadeh M R and Azizyan S 2014 Solvent-Free Preparation of Novel 2-[Phenyl (Pyridine-2-Ylamino) Methyl] Phenols as Pseudo-Betti Processor for Natural Products *Jundishapur J. Nat. Pharm. Prod.* **9** e17808
17. (a) Morin M S T, Lu Y, Black D A and Arndtsen B A 2012 Copper-Catalyzed Petasis-Type Reaction: A General Route to α-Substituted Amides From Imines, Acid Chlorides, and Organoboron Reagents *J. Org. Chem.* **77** 2013; (b) Wang J, Li P, Shenm Q and Song G 2014 Concise Synthesis of Aromatic Tertiary Amines via a Double Petasis–Borono Mannich Reaction Of Aromatic Amines, Formaldehyde, and Organoboronic Acids *Tetrahedron Lett.* **55** 3888
18. Nanda K K and Trotter B W 2005 Diastereoselective Petasis Mannich Reactions Accelerated by Hexafluoroisopropanol: A Pyrrolidine-Derived Arylglycine Synthesis *Tetrahedron Lett.* **46** 2025
19. Han W Y, Zuo J, Zhang X M and Yuan W C 2013 Enantioselective Petasis Reaction Among Salicylaldehydes, Amines, and Organoboronic Acids Catalyzed by BINOL *Tetrahedron* **69** 537
20. Kulkarni A M, Pandit K S, Chavan P V, Desai U V and Wadgaonkar P P 2015 Cobalt Ferrite Nanoparticles: A Magnetically Separable and Reusable Catalyst for Petasis-Borono–Mannich Reaction *RSC Adv.* **5** 70586
21. Reddy S R S, Reddy B R P and Reddy P V G 2015 Chitosan: Highly Efficient, Green, and Reusable Biopolymer Catalyst for the Synthesis of Alkylaminophenols via Petasis Borono Mannich-Reaction *Tetrahedron Lett.* **56** 4984
22. Yadav J S, Reddy B V S and Lakshmi P N 2007 Ionic Liquid Accelerated Petasis Reaction: A Green Protocol for the Synthesis of Alkylaminophenols *J. Mol. Catal. A: Chem.* **274** 101
23. Reddy B R P, Reddy P V G, Kumar D P, Reddy B N and Shankar M V 2016 Rapid Synthesis of Alkylaminophenols via the Petasis Borono–Mannich Reaction Using Protonated Trititanate Nanotubes as Robust Solid–Acid Catalysts *RSC Adv.* **6** 14682
24. Kumar P, Griffiths K, Lymperopoulou S and Kostakis G E 2016 Tetranuclear Zn_2Ln_2 Coordination Clusters as Catalysts in the Petasis Borono-Mannich Multicomponent Reaction *RSC Adv.* **6** 79180
25. (a) Zeng T, Chen W W, Cirtiu C M, Moores A, Song G H and Li C J 2010 Fe_3O_4 Nanoparticles: A Robust and Magnetically Recoverable Catalyst for Three-Component Coupling of Aldehyde, Alkyne and Amine *Green Chem.* **12** 570; (b) Muller R H, Maa Ben S, Weyhers H, Specht F and Lucks J S 1996 Cytotoxicity of Magnetite-Loaded Polylactide, Polylactide/Glycolide Particles and Solid Lipid Nanoparticles *Int. J. Pharm.* **138** 85; (c) Zhang Z H, Lu H Y, Yang S H and Gao J W 2010 Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-Ones by Three-Component Coupling of Isatoic Anhydride, Amines, and Aldehydes Catalyzed by Magnetic Fe_3O_4 Nanoparticles in Water *J. Comb. Chem.* **12** 643; (d) Sreedhar B, Kumar A S and Reddy P S 2010 Magnetically Separable Fe_3O_4 Nanoparticles: An Efficient Catalyst for the Synthesis of Propargylamines *Tetrahedron Lett.* **51** 1891; (e) Kassaee M Z, Motamedi E, Movassagh B and Poursadeghi S 2013 Iron-Catalyzed Formation of C–Se and C–Te Bonds Through Cross Coupling of Aryl Halides with Se(0) and Te(0)/Nano-Fe_3O_4@GO *Synthesis* **45** 2337
26. Firouzabadi H, Iranpoor N, Gholinejad M and Hoseini J 2011 Magnetite (Fe_3O_4) Nanoparticles-Catalyzed

Sonogashira-Hagihara Reactions in Ethylene Glycol under Ligand-Free Conditions *Adv. Synth. Catal.* **353** 125
27. Esfahani M N, Hoseini S J and Mohammadi F 2011 Fe_3O_4 Nanoparticles as an Efficient and Magnetically Recoverable Catalyst for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-Ones Under Solvent-Free Conditions *Chin. J. Catal.* **32** 1484
28. Safari J and Zarnegar Z 2012 Magnetic Fe_3O_4 Nanoparticles as a Highly Efficient Catalyst for the Synthesis of Imidazoles Under Ultrasound Irradiation *Iran. J. Catal.* **2** 121
29. Saikia P K, Sarmah P P, Borah B J, Saikia L, Saikia K and Dutta D K 2016 Stabilized Fe_3O_4 Magnetic Nanoparticles Into Nanopores of Modified Montmorillonite Clay: A Highly Efficient Catalyst for the Baeyer–Villiger Oxidation Under Solvent Free Conditions *Green Chem.* **18** 2843
30. Govan J and Gunko Y K 2014 Recent Advances in the Application of Magnetic Nanoparticles as a Support for Homogeneous Catalysts *Nanomaterials* **4** 222
31. (a) Chacko P and Shivashankar K 2017 Nano Structured Spinel Co_3O_4-Catalyzed Four Component Reaction: A Novel Synthesis of Ugi Adducts from Aryl Alcohols as a Key Reagent *Chin. Chem. Lett.* **28** 1619; (b) Chacko P and Shivashankar K 2018 I_2-Catalyzed One-Pot Synthesis of Benzofuro/Thieno[2,3-*b*]Pyrrole Motifs *Tetrahedron* **74** 1520; (c) Chacko P and Shivashankar K 2018 Montmorillonite K10-Catalyzed Synthesis of N-Fused Imino-1,2,4-Thiadiazolo Isoquinoline Derivatives *Synth. Commun.* **48** 1363
32. Shekouhy M, Moaddeli A and Nezhad A K 2016 Magnetic Fe_3O_4–BF_3: Highly Efficient Lewis Acid Catalyst for the Synthesis of α-Aminonitriles *Res. Chem. Intermed.* **42** 3805
33. Follmann M, Gaul F, Schafer T, Kopec S and Hamley P 2005 Petasis Boronic Mannich Reactions of Electron-Poor Aromatic Amines under Microwave Conditions *Synlett* 1009