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ORIGINAL ARTICLE

Design, Synthesis and Evaluation of Antifungal activity of Benzenamine Derivatives

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ABSTRACT

Pharmacophore based designed benzenamine derivatives were synthesized and evaluated for antifungal properties. All the synthesized fourty two benzenamine derivatives were found active against human pathogenic fungi. This may be due to the hydrophobic group, e.g. phenyl ring increasing the lipophilicity of molecules, as per the predictions of the developed pharmacophore model. The compound P3containing halogen substituent and 3-pyridyl ring has shown the broad-spectrum antifungal activity(MICs 0.5-2.0 µg/mL). Active structures were tested for fungal chitin synthase inhibitory activity. Amongst them compound P3showed highest chitin synthase inhibition (92 %).

Keywords: *Antifungal; Pharmacophore; Benzenamine; aldimine; Grignard.*

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INTRODUCTION

The treatment of opportunistic infections, caused by various pathogenic fungi has encountered a serious problem like toxicity of current antifungal drugs[1-3]. To obtain the more effective and safer drugs, an antifungal agent selectively acting on the fungi should be developed. The biosynthesis of chitin is essential for fungal growth and reproduction, which is catalyzed by the enzyme chitin synthase. Since chitin is absent in human cell, chitin synthase represents a selective antifungal target [4, 5].

The best inhibitors of chitin synthase are the naturally occurring polyoxin and nikkomycins[6-8]. Hydrolytic liability and decreased fungal permeability are the two major reasons why these compounds have not been effective in *vivo* to deal with human pathogenic fungi[7]. Similarly several naturally occurring compounds such as Tannins, Flavonoids, Triterpenoids and some antibiotics like Chaetoatrosin-A, Phellinsin A are known as chitin synthase inhibitors.[4, 8, 9]As of late, small organic molecules like homoallylamine and related compounds[10, 11], chalcones[12], Quinoline-2-one derivatives[13], maleimide derivatives[14], Quinazoline-2,4-dione derivatives[15], Coumarin derivatives [16], and UDP derivatives[17] have been reported as chitin synthase inhibitors. All these novel compounds are potential chitin synthase inhibitors. On the contrary, their modest antifungal activities imply that further investigation would be needed.So as to discover new and specific antifungal compound, we continued with pharmacophore-based 3D QSAR study of fungal chitin synthase inhibitors[18]The pharmacophore hypothesis yielded a statistically significant 3D-QSAR model. The compounds not aligning properly (fitness score < 1.5) with the associated pharmacophore hypothesis failed to occupy the favorable region in QSAR model. The aromatic and hydrophobic features were found to be important for the biological activity. In the present dataset molecules, the favorable regions were occupied by halogens,

aryl groups (phenyl, naphthyl, and phenanthrene), aliphatic side chain (saturated/unsaturated), and nonpolar hydrogens.

In this work, we represent design, synthesis and evaluation of fourty two benzenamine derivatives for antifungal activity. Compounds having better antifungal activity were tested for chitin synthase inhibitory activity.

MATERIAL AND METHODS

Chemistry

All reagents were procured from Rankem and Sigma-Aldrich, and are of laboratory grade. The melting points reported here-in are uncorrected and were determined in open capillaries using Thiele's melting point apparatus. Reactions were monitored by thin layerchromatography (TLC), which were performed on coated Silica gel G plates activated for 30 min.(120ºC) and spots were visualized by exposure to iodine vapors. FTIR spectrums were recorded on Shimadzu FTIR-8400S spectrometer. ^{1}H NMR spectra was determined on Mercury Plus 300MHz NMR Spectrometer in $CDCl_3$ with tetramethylsilane (TMS, δ 0 ppm) as an internal standard. ^{13}C NMR spectra were recorded with $CDCl_3$ as an internal standard at δ = 77.0 at 100MHz on a Mercury Plus NMR Spectrometer. An MS spectrum was obtained with a GCD - HP1800A gas chromatograph interfaced to a mass selective detector that used electron impact ionization (70 eV). Elemental analyses were performed on a Thermo Finnegan FLASH EA 1112 series analyzer.

Synthesis of Benzenamine Derivatives

The starting *N*-aryl aldimines were prepared from *p*-substituted anilines and *p*-substituted benzaldehydes[1-5], furan-2-carbaldehyde[6, 7], and pyridine-3-carbaldehyde[8-10], according to literature procedure.

General Procedure[11]

To a solution of benzyl magnesium chloride (**31)** was added $ZnCl_2$ (0.435gm, 3.2mmol) at room temperature under nitrogen atmosphere. This solution was stirred at that temperature for 1 h. Then, *N*-phenyl benzylidene amine (**1)** (1.6gm, 32.00 mmol) dissolved in 25mL of dry ether was added at room temperature. The mixture was stirred for 12 h, and the reaction was monitored by TLC. The resulting mixture was cooled to 0ºC and quenched by saturated aqueous NH_4Cl (50 mL), extracted with ether (50 mL×3), and washed with brine (50 mL). The combined extracts were dried over $MgSO_4$. The organic phase was concentrated under reduced pressure and the resultant residue was purified by column chromatography over silica (eluent: *n*-hexane: ethyl acetate), to give the desired homo benzylamine (**B1)**, which was obtained as a viscous oil. Similarly, all benzenamine (**B1-B30, F1-F6** and **P1-P6)** were obtained as oil (**Table S1**).

Table S1. Benzenamine derivatives (**Fig. 1**)

Compound	R_1	R_2	Mol. Formula	Mol. Wt (gm/mole)	% Yield
B1	H	H	$C_{20}H_{19}N$	273	72.00
B2	H	Cl	$C_{20}H_{18}NCl$	309	65.00
B3	H	F	$C_{20}H_{18}NF$	291	69.00
B4	H	Br	$C_{20}H_{18}NBr$	352	67.00
B5	H	CH_3	$C_{21}H_{21}N$	287	66.00
B6	H	OCH_3	$C_{21}H_{21}NO$	303	70.00
B7	Cl	H	$C_{20}H_{18}NCl$	309	67.00
B8	Cl	Cl	$C_{20}H_{17}NCl_2$	343	69.00
B9	Cl	F	$C_{20}H_{17}NClF$	290	61.00
B10	Cl	Br	$C_{20}H_{17}NClBr$	351	62.00
B11	Cl	CH_3	$C_{21}H_{20}NCl$	322	66.00
B12	Cl	OCH_3	$C_{21}H_{20}NClO$	338	68.00
B13	F	H	$C_{20}H_{18}NF$	291	62.00
B14	F	Cl	$C_{20}H_{17}NClF$	290	63.00
B15	F	F	$C_{20}H_{17}NF_2$	309	66.00
B16	F	Br	$C_{20}H_{17}NFBr$	370	68.00
B17	F	CH_3	$C_{21}H_{20}NF$	305	65.00
B18	F	OCH_3	$C_{21}H_{20}NFO$	321	65.00
B19	CH_3	H	$C_{21}H_{21}N$	287	66.00
B20	CH_3	Cl	$C_{21}H_{20}NCl$	323	67.00
B21	CH_3	F	$C_{21}H_{20}NF$	305	65.00
B22	CH_3	Br	$C_{21}H_{20}NBr$	366	69.00
B23	CH_3	CH_3	$C_{22}H_{23}N$	301	65.00

B24	CH_3	OCH_3	$C_{22}H_{23}NO$	317	62.00
B25	OCH_3	H	$C_{21}H_{21}NO$	303	65.00
B26	OCH_3	Cl	$C_{21}H_{20}NClO$	338	69.00
B27	OCH_3	F	$C_{21}H_{20}NFO$	321	70.00
B28	OCH_3	Br	$C_{21}H_{20}NBrO$	382	64.00
B29	OCH_3	CH_3	$C_{22}H_{23}NO$	317	68.00
B30	OCH_3	OCH_3	$C_{22}H_{23}NO_2$	333	62.00
F1	-	H	$C_{18}H_{17}NO$	263	61.00
F2	-	Cl	$C_{18}H_{16}NOCl$	298	65.00
F3	-	F	$C_{18}H_{16}NFO$	281	61.00
F4	-	Br	$C_{18}H_{16}NBrO$	342	64.00
F5	-	CH_3	$C_{19}H_{19}NO$	277	63.00
F6	-	OCH_3	$C_{19}H_{19}NO_2$	293	62.00
P1	-	H	$C_{19}H_{18}N_2$	274	66.00
P2	-	Cl	$C_{19}H_{17}N_2Cl$	309	65.00
P3	-	F	$C_{19}H_{17}N_2F$	292	67.00
P4	-	Br	$C_{19}H_{17}N_2Br$	353	65.00
P5	-	CH_3	$C_{20}H_{20}N_2$	288	68.00
P6	-	OCH_3	$C_{20}H_{20}N_2O$	304	66.00

***N*-(1, 2-diphenylethyl) aniline (B1)**:Oil, Yield 72 %. IR (KBr): ν 3404 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.98 (dd, *J* = 8.4 and 13.2 Hz, 1H), 3.11 (dd, *J* = 8.4 and 13.2 Hz, 1H), 4.10 (br s, 1H), 4.57 (t, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 8.8Hz, 2H), 6.61 (t, *J* = 8.2 Hz, 1H), 7.01-7.32 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 45.11,59.16, 113.59, 117.43, 126.41, 126.67, 128.51,129.17, 137.64, 143.39, 147.24; MS m/z (EI): 273, 274 (M+1), 182(M-C_7H_7, 100 %). Found: C, 87.83; H, 6.7; N, 5.0; calcd for $C_{20}H_{19}N$: C, 87.91; H, 6.95; N, 5.1.

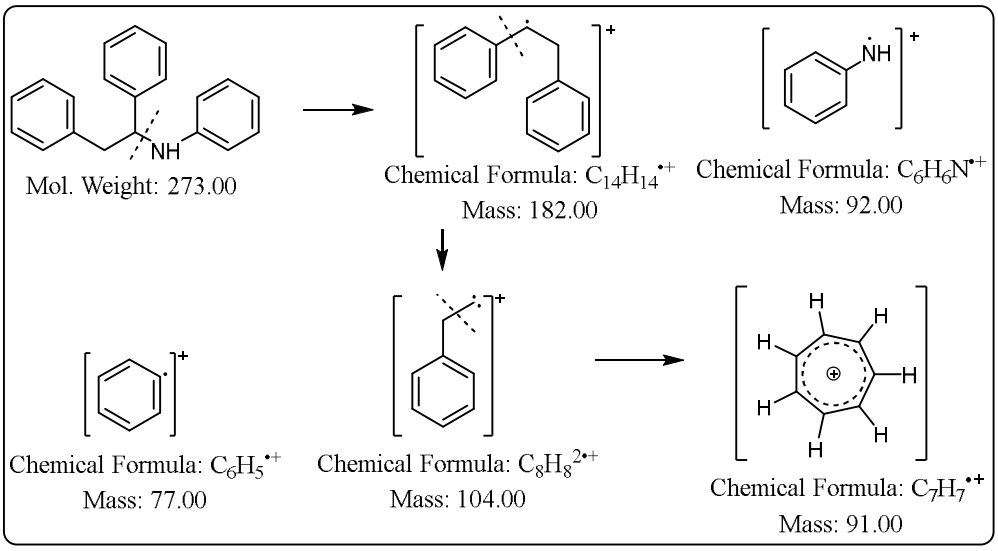


Figure S2. Mass fragmentation of *N*-(1, 2-diphenylethyl) aniline (**B1**)

***4-chloro-N-(1, 2-diphenylethyl) aniline* (B2).**

Oil, Yield 65 %. IR (KBr): ν 3411 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.03 (dd, *J* = 8.1 and 13.8 Hz, 1H), 3.12 (dd, *J* = 6.6 and 13.8 Hz, 1H), 4.12 (br s, 1H), 4.51-4.54 (m, 1H), 6.34-6.39 (m, 2H), 6.95-6.99 (m, 3H), 7.10 (t, J = 8.4 Hz, 2H), 7.12-7.34 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 45.13,59.46, 113.69, 126.43, 126.57, 128.51,129.37, 137.54, 141.24, 143.49; MS m/z (EI): 307 ,308 (M+1), 216 (M-C_7H_7, 100 %). Found: C, 78.03; H, 5.77; N, 4.45; calcd for $C_{20}H_{18}ClN$: C, 78.17; H, 5.86; N, 4.54.

***N-(1,2-diphenylethyl)-4-fluoroaniline* (B3).**

Oil, Yield 69 %. IR (KBr): ν 3415 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.01 (dd, *J* = 8.1 and 13.8 Hz, 1H), 3.13 (dd, *J* = 6.6 and 13.8 Hz, 1H), 4.11 (br s, 1H), 4.53 (t, *J* = 8.3 Hz, 1H), 7.03 (d, *J = 8.2 Hz*, 2H), 7.07 (d, *J = 8.2 Hz*, 2H), 7.19-7.26 (m, 6H), 7.34-7.37 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 43.23,60.56, 115.09, 125.13, 126.47, 128.58,129.77, 137.84, 141.14, 143.69, 154.97; MS m/z (EI): 291 ,292 (M+1), 200 (M-C_7H_7, 100 %). Found: C, 82.45; H, 6.23; N, 4.81; calcd for $C_{20}H_{18}FN$: C, 82.47; H, 6.18; N, 4.81

***4-bromo-N-(1,2-diphenylethyl)aniline*(B4).**

Oil, Yield 67 %. IR (KBr): ν 3412 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.97 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.04 (dd, *J* = 6.2 and 13.8 Hz, 1H), 4.08 (br s, 1H), 4.31 (t, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 7.13-7.21(m, 6H), 7.26-7.35(m,4H); ^{13}C NMR ($CDCl_3$): δ 42.27, 59.93, 114.68, 115.96, 116.24, 116.53, 126.81, 127.93, 128.01, 128.61, 129.46, 137.53, 139.29, 139.33, 144.31; MS m/z (EI): 352, 353(M+1), 261(M-C_7H_7, 100 %). Found: C, 68.29; H, 5.15; N, 3.98 calcd for $C_{20}H_{18}BrN$: C, 68.18; H, 5.11; N, 3.97

***N-(1,2-diphenylethyl)-4-methylaniline* (B5).**

Oil, Yield 66%. IR (KBr): ν 3403 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H), 3.02 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.07 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.87 (br s, 1H), 4.43 (t, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 8.1 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 7.09-7.21 (m, 6H), 7.26-7.39 (m, 4H) ; ^{13}C NMR ($CDCl_3$): δ 20.38, 45.27, 58.83, 113.82, 114.23, 126.65, 127.52, 128.51, 129.27, 129.55, 135.63, 137.97, 145.16; MS m/z (EI): 287, 288 (M+1), 196 (M-C_7H_7, 100 %). Found: C, 87.76; H, 7.36; N, 4.87; calcd for $C_{21}H_{21}N$: C, 87.80; H, 7.31; N, 4.87

***N-(1,2-diphenylethyl)-4-methoxylaniline* (B6).**

Oil, Yield 70%. IR (KBr): ν 3404 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.01 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.08 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.61 (s, 3H), 3.83 (br s, 1H), 4.45 (t, *J* = 7.8 Hz, 1H), 6.72-6.77 (m, 4H), 7.14-7.25 (m, 6H), 7.27-7.39 (m, 4H) ; ^{13}C NMR ($CDCl_3$): δ 45.24, 55.24, 58.81, 113.83, 114.22, 126.65, 127.54, 128.52, 129.25, 129.55, 135.67, 137.97, 145.16, 158.97; MS m/z (EI): 303, 304 (M+1), 212 (M-C_7H_7, 100 %). Found: C, 83.13; H, 6.98; N, 4.62; calcd for $C_{21}H_{21}NO$: C, 83.16; H, 6.93; N, 4.62

***N-[1-(4-chlorophenyl)-2-phenylethyl]aniline* (B7).**

Oil, Yield 67 %. IR (KBr): ν 3407 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.00 (dd, *J* = 8.1 and 13.2 Hz, 1H), 3.07 (dd, *J* = 6.2 and 13.6 Hz, 1H), 4.10 (br, 1H), 4.51 (t, *J* = 8.0 Hz, 1H), 6.45 (dd, *J* = 8.1 Hz, 2H), 6.65 (t, *J* = 7.8 Hz, 1H), 7.09-7.13 (m, 4H), 7.19-7.27 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 44.95,58.84, 113.49, 118.13, 126.17, 128.56,129.37, 132.47, 137.25, 142.10, 144.64; MS m/z (EI): 307 ,308 (M+1), 216 (M-C_7H_7, 100 %). Found: C, 78.00; H, 5.70; N, 4.45; calcd for $C_{20}H_{18}ClN$: C, 78.17; H, 5.86; N, 4.54.

***4-chloro-N-[1-(4-chlorophenyl)-2-phenylethyl] aniline* (B8).**

Oil, Yield 69 %. IR (KBr): ν 3412 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.0 (dd, *J* = 8.1 and 13.8 Hz, 1H), 3.13 (dd, *J* = 6.0 and 13.8 Hz, 1H), 4.12 (br s, 1H), 4.54 (t, *J* = 7.2 Hz, 1H), 6.31-6.34 (m, 2H), 6.97-7.03 (m, 2H), 7.07 (t, J = 8.4 Hz, 2H), 7.1-7.34 (m, 7H) ; ^{13}C NMR ($CDCl_3$): δ 45.25,59.56, 113.67, 126.27, 128.55,129.37, 137.25, 141.24, 143.56; MS m/z (EI): 341 ,342 (M+1), 250 (M-C_7H_7, 100 %). Found: C, 70.18; H, 5.01; N, 4.09; calcd for $C_{20}H_{17}Cl_2N$: C, 70.38; H, 4.98; N, 4.10.

***N-[1-(4-chlorophenyl)-2-phenylethyl]-4-fluoroaniline* (B9).**

Oil, Yield 61 %. IR (KBr): ν 3413 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.03 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.09 (dd, *J* = 6.2 and 14.1 Hz, 1H), 4.14 (br s, 1H), 4.53 (t, *J* = 7.2 Hz, 1H), 6.30-6.33 (m, 2H), 6.97-7.02 (m, 2H), 7.04 (t, J = 8.4 Hz, 2H), 7.07-7.33 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 45.23,59.54, 113.65, 126.26, 128.53,129.34, 137.23, 141.22, 143.56; MS m/z (EI): 327 ,328 (M+1), 236 (M-C_7H_7, 100 %). Found: C, 70.28; H, 5.00; N, 4.07; calcd for $C_{20}H_{17}ClFN$: C, 70.38; H, 4.98; N, 4.10.

***4-bromo-N-(1-(4-chlorophenyl)-2-phenylethyl) aniline* (B10).**

Oil, Yield 62%. IR (KBr): ν 3412 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.97 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.05 (dd, *J* = 6.2 and 13.8 Hz, 1H), 4.07 (br s, 1H), 4.53 (t, *J* = 8.0 Hz, 1H), 6.39 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 7.03-7.16 (m, 3H), 7.19-7.39 (m, 6H) ; ^{13}C NMR ($CDCl_3$): δ 45.26, 59.55, 114.68, 114.97, 115.14, 115.53, 126.82, 127.87, 128.10, 128.61, 129.28, 137.54, 139.27, 139.31, 141.35; MS m/z (EI): 386, 387(M+1), 295 (M-C_7H_7, 100 %). Found: C, 62.12; H, 4.43; N, 3.62 calcd for $C_{20}H_{17}BrClN$: C, 62.17; H, 4.40; N, 3.62

***N-(1-(4-chlorophenyl)-2-phenylethyl)-4-methylaniline* (B11).**

Oil, Yield 66%. IR (KBr): ν 3407 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H), 2.99 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.06 (dd, *J* = 6.2 and 13.8 Hz, 1H), 3.95 (br s, 1H), 4.50 (t, *J* = 8.0 Hz, 1H), 6.34 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.19-7.28 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 20.29, 44.99, 58.84, 113.74, 126.77, 127.84, 128.55, 128.62, 129.16, 129.52,132.47, 137.25, 142.10, 144.64; MS m/z (EI): 322,323(M+1), 231 (M-C_7H_7, 100 %). Found: C, 78.18; H, 6.06; N, 4.16; calcd for $C_{21}H_{20}ClN$: C, 78.26; H, 6.21; N, 4.34.

***N-[1-(4-chlorophenyl)-2-phenylethyl]-4-methoxyaniline* (B12).**

Oil, Yield 68 %. IR (KBr): ν 3403 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.96 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.03 (dd, *J* = 6.2 and 13.8 Hz, 1H), 3.65 (s, 3H), 3.78 (br s, 1H), 4.49 (t, *J* = 7.2 Hz, 1H), 6.36 (d, *J* = 8.2 Hz, 2H), 6.62 (d, *J* = 8.2 Hz, 2H), 6.97 (t, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.19-7.28 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 45.39, 55.71, 59.54, 114.71, 115.01, 115.55, 126.84, 128.53,129.34, 137.57, 141.37, 160.24; MS m/z (EI): 338 ,339 (M+1), 247 (M-C_7H_7, 100 %). Found: C, 74.48; H, 5.86; N, 4.07; calcd for $C_{21}H_{20}ClNO$: C, 74.55; H, 5.91; N, 4.14.

***N-[1-(4-fluorophenyl)-2-phenylethyl] aniline* (B13).**

Oil, Yield 62 %. IR (KBr): ν 3405 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.02 (dd, *J* = 8.1 and 13.2 Hz, 1H), 3.08 (dd, *J* = 6.2 and 13.6 Hz, 1H), 4.11 (br, 1H), 4.53 (t, *J* = 8.0 Hz, 1H), 6.57-6.69 (m, 3H), 7.09-7.14 (m, 9H), 7.19-7.23 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 45.36, 55.73, 114.66, 114.96, 115.51, 126.81,127.99, 128.07, 129.25, 137.54, 141.32, 160.15; MS m/z (EI): 291 ,292 (M+1), 200 (M-C_7H_7, 100 %). Found: C, 82.45; H, 6.23; N, 4.81; calcd for $C_{20}H_{18}FN$: C, 82.47; H, 6.18; N, 4.81.

***4-fluoro-N-[1-(4-chlorophenyl)-2-phenylethyl]aniline*(B14).**Oil, Yield 63 %. IR (KBr): ν 3413 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.04 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.09 (dd, *J* = 6.2 and 14.1 Hz, 1H), 4.13 (br s, 1H), 4.52 (t, *J* = 7.2 Hz, 1H), 6.33 (d, *J* = 8.2 Hz, 2H), 7.02-7.14 (m, 9H), 7.27-7.33 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 45.27,59.51, 113.65, 126.27, 128.51,129.32, 137.21, 141.22, 143.56, 160.09; MS m/z (EI): 327 ,328 (M+1), 236 (M-C_7H_7, 100 %). Found: C, 70.28; H, 5.00; N, 4.07; calcd for $C_{20}H_{17}ClFN$: C, 70.38; H, 4.98; N, 4.10.

***4-fluoro-N-[1-(4-fluorophenyl)-2-phenylethyl] aniline* (B15).**Oil, Yield 66 %. IR (KBr): ν 3411 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.03 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.08 (dd, *J* = 6.2 and 14.1 Hz, 1H), 4.18 (br s, 1H), 4.50 (t, *J* = 7.2 Hz, 1H), 6.30-6.33 (m, 2H), 6.97-7.02 (m, 2H), 7.05 (t, J = 8.4 Hz, 2H), 7.10-7.33 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 45.25, 59.54, 113.55, 126.76, 128.55, 129.44, 137.23, 141.25, 143.65; MS m/z (EI): 310 ,311 (M+1), 220 (M-C_7H_7, 100 %). Found: C, 70.31; H, 4.91; N, 4.01; calcd for $C_{20}H_{17}F_2N$: C, 70.38; H, 4.98; N, 4.10

***4-bromo-N-(1-(4-fluorophenyl)-2-phenylethyl) aniline* (B16).**

Oil, Yield 68%. IR (KBr): ν 3413 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.99 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.06 (dd, *J* = 6.2 and 13.8 Hz, 1H), 4.06 (br s, 1H), 4.51 (t, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 8.2 Hz, 2H), 6.97-7.43 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 45.27, 59.53, 114.68, 114.96, 115.24, 115.53, 126.81, 127.97, 128.07, 128.61, 129.26, 137.53, 139.27, 139.31, 141.31; MS m/z (EI): 371(M+1), 280 (M-C_7H_7, 100 %). Found: C, 64.48; H, 4.33; N, 3.68 calcd for $C_{20}H_{17}BrFN$: C, 64.88; H, 4.63; N, 3.78

***N-(1-(4-fluorophenyl)-2-phenylethyl)-4-methylaniline* (B17).**

Oil, Yield 65%. IR (KBr): ν 3406 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H), 2.97 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.00 (dd, *J* = 6.2 and 13.8 Hz, 1H), 3.73 (br s, 1H), 4.45 (t, *J* = 7.8 Hz, 1H), 6.31 (d, *J* = 8.2 Hz, 2H), 6.65 (d, *J* = 8.2 Hz, 2H), 7.09 (t, *J* = 8.1 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.19-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.37, 45.31, 55.72, 114.64, 114.96, 115.57, 126.83, 127.97, 128.07, 129.26, 137.53, 141.33, 160.15.MS m/z (EI): 305, 306(M+1), 214 (M-C_7H_7, 100 %). Found: C, 82.59; H, 6.60; N, 4.59; calcd for $C_{21}H_{20}FN$: C, 82.62; H, 6.55; N, 4.59.

***N-(1-(4-fluorophenyl)-2-phenylethyl)-4-methoxyaniline*(B18).**

Oil, Yield 65%. IR (KBr): ν 3403 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.00 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.03 (dd, *J* = 6.2 and 13.8 Hz, 1H), 3.65 (s, 3H), 3.72 (br s, 1H), 4.47 (t, *J* = 7.8 Hz, 1H), 6.37 (d, *J* = 8.2 Hz, 2H), 6.63 (d, *J* = 8.2 Hz, 2H), 6.97 (t, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 7.19-7.28 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 45.37, 55.71, 59.48,114.68, 114.96, 115.53, 126.81,127.97, 128.07, 129.26, 137.53, 141.31, 160.25. MS m/z (EI): 321, 322(M+1), 230 (M-C_7H_7, 100 %).Found: C, 74.51; H, 5.89; N, 4.12; calcd for $C_{21}H_{20}FNO$: C, 74.55; H, 5.91; N, 4.14.

4.2.19. *N-(2-phenyl-1-(p-tolyl) ethyl) aniline* (B19).

Oil, Yield 66%. IR (KBr): ν 3403 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.13(s, 3H), 2.99 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.10 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.86 (br s, 1H), 4.45 (t, *J* = 7.8 Hz, 1H), 6.46 (t, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 2H), 7.10-7.21 (m, 6H), 7.27-7.40 (m, 5H) ; ^{13}C NMR ($CDCl_3$): δ 20.32, 45.27, 58.85, 113.86, 114.25, 126.65, 127.52, 128.51, 129.27, 129.55, 135.53, 137.92, 145.16; MS m/z (EI): 287, 288 (M+1), 196 (M-C_7H_7, 100 %). Found: C, 87.76; H, 7.36; N, 4.87; calcd for $C_{21}H_{21}N$: C, 87.80; H, 7.31; N, 4.87

***4-chloro-N-(2-phenyl-1-(p-tolyl)ethyl)aniline* (B20).**

Oil, Yield 67 %. IR (KBr): ν 3411 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.14(s, 3H), 3.02 (dd, *J* = 8.1 and 13.8 Hz, 1H), 3.11 (dd, *J* = 6.6 and 13.8 Hz, 1H), 4.11 (br s, 1H), 4.49(t, *J* = 7.8 Hz, 1H), 6.34 (d, *J* = 8.1 Hz, 2H), 6.95-6.97 (m, 4H), 7.10-7.12 (m, 3H), 7.21-7.31 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 20.31, 45.13, 59.66, 113.69, 126.43, 126.59, 128.57, 129.37, 137.56, 141.25, 143.57; MS m/z (EI): 321 ,322 (M+1), 230 (M-C_7H_7, 100 %). Found: C, 78.37; H, 6.26; N, 4.35; calcd for $C_{21}H_{20}ClN$: C, 78.50; H, 6.23; N, 4.36

***4-fluoro-N-(2-phenyl-1-(p-tolyl)ethyl)aniline* (B21).**

Oil, Yield 65 %. IR (KBr): ν 3415 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.14(s, 3H), 3.01 (dd, *J* = 8.1 and 13.8 Hz, 1H), 3.13 (dd, *J* = 6.6 and 13.8 Hz, 1H), 4.11 (br s, 1H), 4.53 (t, *J* = 8.3 Hz, 1H), 7.03 (d, *J = 8.2 Hz*, 2H), 7.05 (d, *J = 8.2 Hz*, 2H), 7.16-7.19 (m, 4H), 7.24-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.31, 43.23, 60.56, 115.29, 125.13, 126.47, 128.88,129.77, 137.74, 141.14, 143.79, 154.99; MS m/z (EI): 305 ,306 (M+1), 214 (M-C_7H_7, 100 %). Found: C, 82.59; H, 6.60; N, 4.59; calcd for $C_{21}H_{20}FN$: C, 82.62; H, 6.55; N, 4.59

***4-bromo-N-(2-phenyl-1-(p-tolyl)ethyl)aniline* (B22).**

Oil, Yield 69 %. IR (KBr): ν 3414 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.14(s, 3H), 3.01 (dd, *J* = 8.1 and 13.8 Hz, 1H), 3.11 (dd, *J* = 6.6 and 13.8 Hz, 1H), 4.11 (br s, 1H), 4.53 (t, *J* = 8.3 Hz, 1H), 6.39 (d, *J = 8.2 Hz*, 2H), 7.07

(d, *J = 8.2 Hz*, 2H), 7.16-7.24 (m, 5H), 7.26-7.37 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 20.31, 43.24, 59.56, 115.09, 125.14, 126.46, 128.58,129.87, 137.84, 141.17, 143.71; MS m/z (EI): 365 ,366 (M+1), 274 (M-C_7H_7, 100 %). Found: C, 68.86; H, 5.50; N, 3.82; calcd for $C_{21}H_{20}BrN$: C, 69.04; H, 5.47; N, 3.83

***4-methyl-N-(2-phenyl-1-(p-tolyl)ethyl)aniline*(B23).**

Oil, Yield 65%. IR (KBr): ν 3403 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 6H), 3.02 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.07 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.87 (br s, 1H), 4.43 (t, *J* = 7.8 Hz, 1H), 6.30 (d, *J* = 8.1 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 7.09-7.11 (m, 4H), 7.23-7.37 (m, 5H) ; ^{13}C NMR ($CDCl_3$): δ 20.38, 45.27, 58.83, 113.82, 114.23, 126.65, 127.52, 128.51, 129.27, 129.55, 135.63, 137.97, 145.16; MS m/z (EI): 301, 301 (M+1), 210 (M-C_7H_7, 100 %). Found: C, 87.66; H, 7.69; N, 4.65; calcd for $C_{22}H_{23}N$: C, 87.70; H, 7.64; N, 4.65

***4-methoxy-N-(2-phenyl-1-(p-tolyl)ethyl)aniline* (B24).**

Oil, Yield 62%. IR (KBr): ν 3404 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H), 3.01 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.06 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.76 (s, 3H), 3.85 (br s, 1H), 4.49 (t, *J* = 7.8 Hz, 1H), 6.57 (s, 4H), 6.89-6.91 (m, 4H), 7.09-7.35 (m, 5H) ; ^{13}C NMR ($CDCl_3$): δ 20.36, 45.27, 55.26, 58.89, 113.81, 114.21, 126.63, 127.51, 128.54, 129.28, 129.56, 135.64, 137.97, 145.13, 151.23; MS m/z (EI): 317, 318 (M+1), 226 (M-C_7H_7, 100 %). Found: C, 83.24; H, 7.30; N, 4.41; calcd for $C_{22}H_{23}NO$: C, 83.28; H, 7.25; N, 4.41

***N-[1-(4-methoxyphenyl)-2-phenylethyl] aniline* (B25).**

Oil, Yield 65 %. IR (KBr): ν 3404 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 3.01 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.06 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.76 (s, 3H), 3.85 (br s, 1H), 4.49 (t, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.09-7.25 (m, 7H), 7.29-7.31(m. 2H); ^{13}C NMR ($CDCl_3$): δ 45.27, 55.26, 58.89, 113.67, 114.21, 126.77,127.97, 128.07, 129.26, 129.55, 137.95, 142.1,144.64, 159.05; MS m/z (EI): 303 ,304 (M+1), 212 (M-C_7H_7, 100 %). Found: C, 83.13; H, 6.98; N, 4.62; calcd for $C_{21}H_{21}NO$: C, 83.16; H, 6.93; N, 4.62.

***4-chloro-N-[1-(4-methoxyphenyl)-2-phenylethyl] aniline* (B26).**

Oil, Yield 69 %. IR (KBr): ν 3412 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 3.03 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.09 (dd, *J* = 14.0, 6.1 Hz, 1H), 3.77 (s, 3H), 4.11 (br s, 1H), 4.53 (t, *J* = 7.8 Hz, 1H), 6.34(d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 7.05(d, *J* = 8.2 Hz, 2H), 7.16-7.19 (m, 5H), 7.21-7.25(m, 2H); ^{13}C NMR ($CDCl_3$): δ 45.17, 55.24, 59.39,113.68, 126.44,126.67, 128.47, 129.26, 137.59, 142.11,144.54, 159.25; MS m/z (EI): 338, 339(M+1), 247(M-C_7H_7, 100 %). Found: C, 74.66; H, 5.97; N, 4.15; calcd for $C_{21}H_{20}ClNO$: C, 74.55; H, 5.91; N, 4.14.

***4-fluoro-N-(1-(4-methoxyphenyl)-2-phenylethyl)aniline*(B27).**

Oil, Yield 70 %. IR (KBr): ν 3414 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 3.01 (dd, *J* = 8.1 and 13.8 Hz, 1H), 3.13 (dd, *J* = 6.6 and 13.8 Hz, 1H), 3.77 (s, 3H),4.11 (br s, 1H), 4.53 (t, *J* = 8.3 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 2H), 6.99-7.01 (m, 4H), 7.05 (d, *J = 8.2 Hz*, 2H), 7.16-7.19 (m, 3H), 7.24-7.27 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 43.23, 55.37, 60.56, 115.29, 125.13, 126.49, 128.89,129.76, 137.74, 141.15, 143.79, 154.99, 158.99; MS m/z (EI): 321 ,322 (M+1), 230 (M-C_7H_7, 100 %). Found: C, 78.48; H, 6.27; N, 4.36; calcd for $C_{21}H_{20}FNO$: C, 78.50; H, 6.23; N, 4.36

***4-bromo-N-(1-(4-methoxyphenyl)-2-phenylethyl)aniline*(B28).**

Oil, Yield 64 %. IR (KBr): ν 3414 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 3.02 (dd, *J* = 8.1 and 13.8 Hz, 1H), 3.12 (dd, *J* = 6.6 and 13.8 Hz, 1H), 3.77 (s, 3H), 4.11 (br s, 1H), 4.52 (t, *J* = 8.3 Hz, 1H), 6.36(d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 7.01-7.06 (m, 4H), 7.16-7.21 (m, 3H), 7.24-7.26 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 43.23, 55.37, 60.56, 115.29, 125.13, 126.49, 128.89,129.76, 137.74, 141.15, 143.79, 158.67; MS m/z (EI): 381 ,382 (M+1), 290 (M-C_7H_7, 100 %). Found: C, 65.98; H, 5.27; N, 3.66; calcd for $C_{21}H_{20}BrNO$: C, 66.14; H, 5.24; N, 3.67

***N-(1-(4-methoxyphenyl)-2-phenylethyl)-4-methylaniline* (B29).**

Oil, Yield 68%. IR (KBr): ν 3404 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H), 3.01 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.06 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.76 (s, 3H), 3.85 (br s, 1H), 4.49 (t, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 8.1 Hz, 2H), 6.61 (t, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.09-7.35 (m, 8H) ; ^{13}C NMR ($CDCl_3$): δ 20.39, 45.29, 55.26, 58.89, 113.81, 114.21, 126.65, 127.54, 128.54, 129.28, 129.55, 135.64, 137.95, 145.13, 159.03; MS m/z (EI): 317, 318(M+1), 226 (M-C_7H_7, 100 %). Found: C, 83.24; H, 7.30; N, 4.41; calcd for $C_{22}H_{23}NO$: C, 83.28; H, 7.25; N, 4.41

4-*methoxy-N-(1-(4-methoxyphenyl)-2-phenylethyl)aniline*(B30).

Oil, Yield 62%. IR (KBr): ν 3405 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 3.01 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.06 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.76 (s, 6H), 3.84 (br s, 1H), 4.50 (t, *J* = 7.8 Hz, 1H), 6.61-6.62 (m, 4H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.07-7.33 (m, 7H) ; ^{13}C NMR ($CDCl_3$): δ 45.26, 55.26, 58.91, 113.81, 114.20, 126.65, 127.52, 128.51, 129.28, 129.55, 135.64, 137.95, 145.13, 151.11, 158.03; MS m/z (EI): 333, 334(M+1), 242 (M-C_7H_7, 100 %). Found: 79.25; H, 6.95; N, 4.20; calcd for $C_{22}H_{23}NO_2$: C, 79.27; H, 6.90; N, 4.20

***N-(1-(furan-2-yl)-2-phenylethyl) aniline* (F1).**

Oil, Yield 61%. IR (KBr): ν3413 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.23 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.30 (dd, *J* = 14.1, 7.8 Hz, 1H), 4.04 (br, 1H), 4.81 (t, *J* = 6.4 Hz, 1H), 6.13 (*d, J* = 3.2 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.8Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 7.09-7.42 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 40.72, 52.95, 106.45, 110.81, 113.94, 120.84, 126.65, 128.54, 129.28, 129.55, 137.95, 145.13, 155.13; MS m/z (EI): 263, 264 (M+1), 172 (M-C_7H_7, 100 %). Found: C, 82.10; H, 6.50; N, 5.42; calcd for $C_{18}H_{17}NO$: C, 82.12; H, 6.46; N, 5.32

***4-chloro-N-(1-(furan-2-yl)-2-phenylethyl)aniline*(F2).**

Oil, Yield 65%. IR (KBr): ν3413 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.13 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.24 (dd, *J* = 14.1, 7.8 Hz, 1H), 4.08 (br, 1H), 4.67 (t, *J* = 6.6 Hz, 1H), 6.01-6.27 (m, *2*H), 6.45-6.50 (m, 2H), 6.99-7.04 (m, 5H), 7.16-7.33 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 40.59, 53.35, 106.45, 110.21, 113.94, 120.84, 126.65, 128.54, 129.28, 129.55, 137.95, 141.36, 144.99, 154.13; MS m/z (EI): 298, 299(M+1), 207(M-C_7H_7, 100 %). Found: C, 72.60; H, 5.42; N, 4.70; calcd for $C_{18}H_{16}ClNO$: C, 72.48; H, 5.36; N, 4.69

***4-fluoro-N-(1-(furan-2-yl)-2-phenylethyl)aniline*(F3).**

Oil, Yield 61%. IR (KBr): ν3413 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.13 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.23 (dd, *J* = 14.1, 7.8 Hz, 1H), 4.09 (br, 1H), 4.67 (t, *J* = 6.6 Hz, 1H), 6.01-6.24 (*m, 2*H), 6.99-7.02 (m, 4H), 7.11-7.15 (m, 3H), 7.19-7. 30 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 40.54, 53.41, 106.42, 110.12, 115.91, 120.84, 126.65, 128.54, 129.18, 129.55, 137.32, 141.31, 145.01, 151.13, 154.96; MS m/z (EI): 281, 282(M+1), 190 (M-C_7H_7, 100 %). Found: C, 76.85; H, 5.73; N, 4.98; calcd for $C_{18}H_{16}FNO$: C, 76.86; H, 5.69; N, 4.98

***4-bromo-N-(1-(furan-2-yl)-2-phenylethyl)aniline*(F4).**

Oil,Yield 64%. IR (KBr): ν3413 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.12 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.23 (dd, *J* = 14.1, 7.8 Hz, 1H), 4.08 (br, 1H), 4.67 (t, *J* = 6.6 Hz, 1H), 6.02-6.26 (m, *2*H), 6.45 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 7.12-7.16 (m, 3H), 7.21- 7. 33 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 40.57, 53.39, 106.47, 110.19, 115.94, 120.84, 126.65, 128.54, 129.28, 129.55, 137.95, 141.36, 144.99, 151.13; MS m/z (EI): 342, 343(M+1), 251 (M-C_7H_7, 100 %). Found: C, 63.17; H, 4.71; N, 4.09; calcd for $C_{18}H_{16}BrNO$: C, 63.15; H, 4.67; N, 4.09

***N-(1-(furan-2-yl)-2-phenylethyl)-4-methylaniline* (F5).**

Oil, Yield 63%. IR (KBr): ν 3416 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 2.21 (s, 3H), 3.12 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.22 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.90 (br, 1H), 4.70 (t, *J* = 6.5 Hz, 1H), 6.02 (d, *J* = 3.2 Hz, 1H), 6.22 (t, *J* = 1.7 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 2H), 6.93-7.33 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 20.33, 40.57, 53.39, 106.47, 110.19, 115.94, 120.84, 126.65, 128.54, 129.28, 129.55, 137.35, 141.36, 144.41, 154.13; MS m/z (EI): 277, 278(M+1), 186 (M-C_7H_7, 100 %). Found: C, 82.28; H, 6.90; N, 5.05; calcd for $C_{19}H_{19}NO$: C, 82.31; H, 6.85; N, 5.05

***N-(1-(furan-2-yl)-2-phenylethyl)-4-methoxyaniline* (F6).**

Oil, Yield 62%. IR (KBr): ν3415 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.13 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.22 (dd, *J* = 14.1, 7.8 Hz, 1H), 3.78 (s, 3H), 3.93 (br s, 1H), 4.71 (t, *J* = 6.5 Hz, 1H), 6.01 (d, *J* = 3.2 Hz, 1H), 6.23 (t, *J* = 1.7 Hz, 1H), 6.67-6.69 (m, 4H), 6.93-7.27 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 40.56, 53.39, 55.67, 106.44, 110.21, 115.94, 120.84, 126.65, 128.54, 129.38, 129.55, 137.35, 141.36, 150.13; MS m/z (EI): 293, 294 (M+1), 202 (M-C_7H_7, 100 %). Found: C, 77.79; H, 6.53; N, 4.77; calcd for $C_{19}H_{19}NO_2$: C, 77.81; H, 6.48; N, 4.77

***N-[2-phenyl-1-(pyridin-3-yl) ethyl] aniline* (P1).**

Oil, Yield 66 %. IR (KBr): ν 3257 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.03 (dd, *J* = 8.4 and 13.2 Hz, 1H), 3.09 (dd, *J* = 7.2 and 13.2 Hz, 1H), 4.16 (br s, 1H), 4.57 (t, *J* = 8.4 Hz, 1H), 6.47 (d, *J* =5.8 Hz, 2H), 6.67 (t, *J* =5.3 Hz, 1H), 7.09 (t, *J* =5.3 Hz, 2H), 6.98-7.23 (m, 6H), 7.67 (d, *J*=5.8 Hz, 1H), 8.50 (d, *J*=3.0 Hz, 1H), 8.65 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 43.17, 55.04, 113.68, 118.1, 119.24, 124.1, 129.26, 133.59, 134.1, 139.0, 146.77, 148.54, 149.0; MS m/z (EI): 274, 275 (M+1), 183 (M-C_7H_7, 100 %). Found: C, 83.19; H, 6.6; N, 10.19; calcd for $C_{19}H_{18}N_2$: C, 83.21; H, 6.56; N, 10.29.

***4-chloro-N-[2-phenyl-1-(pyridin-3-yl)ethyl]aniline* (P2).**

Oil, Yield 65 %. IR (KBr): ν 3307 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.02 (dd, *J* = 8.1 and 13.8 Hz, 1H), 3.10 (dd, *J* = 6.6 and 13.8 Hz, 1H), 4.14 (br s, 1H), 4.45-4.49 (m, 1H), 6.31-6.35 (m, 2H), 6.91-6.96 (m, 2H), 7.17-7.29 (m, 6H), 7.56-7.59 (m, 1H), 8.45 (dd, *J* = 1.5 and 4.8 Hz, 1H), 8.56 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 43.07, 55.01, 114.38, 119.24, 122.39, 123.1, 129.0, 133.69, 134.0, 138.0, 145.27, 148.44, 148.7; MS m/z (EI): 309, 310 (M+1), 218 (M-C_7H_7, 100 %). Found: C, 73.69; H, 5.6; N, 9.0; calcd for $C_{19}H_{17}ClN_2$: C, 73.78; H, 5.50; N, 9.06.

***4-fluoro-N-(2-phenyl-1-(pyridin-3-yl) ethyl) aniline*(P3).**

Oil, Yield 67%. IR (KBr): ν 3294 cm^{-1} (s, NH); ^1H NMR ($CDCl_3$): δ 3.03 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.10 (dd, *J* = 6.2 and 14.1 Hz, 1H), 4.20 (br s, 1H), 4.65 (t, *J* = 7.2 Hz, 1H), 6.43 (d, *J* = 6.8 Hz, 2H), 6.68 (t, *J* = 6.8 Hz, 2H), 7.15-7.31 (m, 6H), 7.64 (d, *J* = 5.8 Hz, 1H), 8.49 (dd, *J*=1.1 and 3.6 Hz, 1H), 8.61 (d, *J*=1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 43.25, 55.26, 114.21, 115.30, 120.84, 126.65, 130.45, 135.64, 137.95, 145.13, 148.58,

155.58; MS m/z (EI): 292, 202(M-C_7H_7, 100 %).Found: C, 78.09; H, 5.8; N, 9.5; calcd for $C_{19}H_{17}FN_2$: C, 78.08; H, 5.82; N, 9.58.

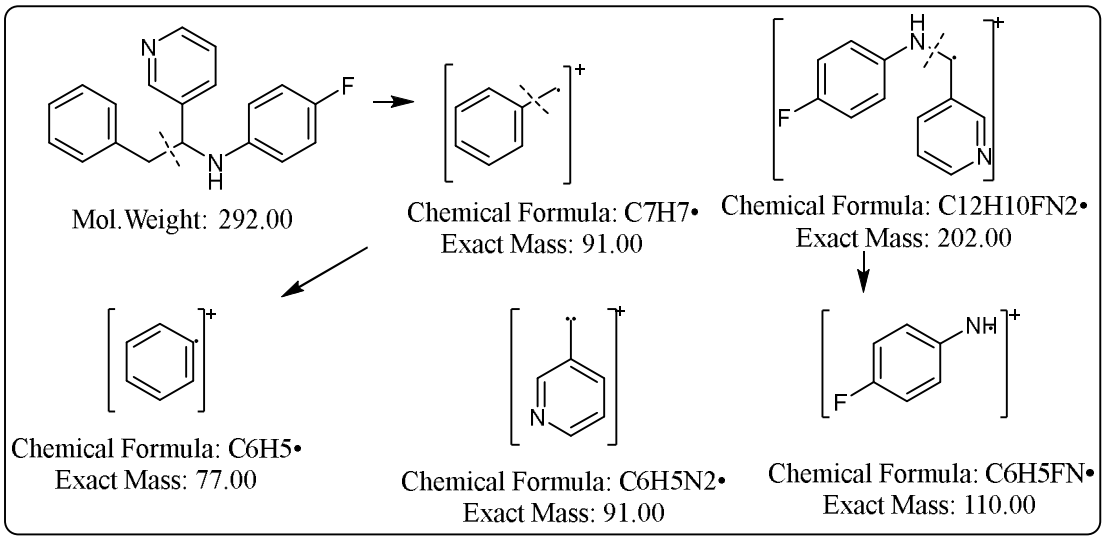


Figure S3. Mass fragmentation of 4-fluoro-*N*-(2-phenyl-1-(pyridin-3-yl) ethyl) aniline (**P3)**

4-bromo-N-(2-phenyl-1-(pyridin-3-yl)ethyl)aniline **(P4).**

Oil, Yield 65%. IR (KBr): ν 3304 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 3.03 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.11 (dd, *J* = 6.2 and 14.1 Hz, 1H), 4.20 (br s, 1H), 4.66 (t, *J* = 7.2 Hz, 1H), 6.37 (d, *J* = 6.8 Hz, 2H), 6.89 (d, *J* = 6.8 Hz, 2H), 7.16-7.30 (m, 6H), 7.63 (d, *J* = 5.8 Hz, 1H), 8.47 (dd, *J*=1.1 and 3.6 Hz, 1H), 8.57 (d, *J*=1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 43.24, 55.27, 114.21, 115.30, 120.84, 126.65, 130.35, 135.64, 137.85, 145.13, 145.58, 145.98; MS m/z (EI): 352, 353 (M+1), 261 (M-C_7H_7, 100 %).Found: C, 64.60; H, 4.85; N, 7.93; calcd for $C_{19}H_{17}BrN_2$: C, 64.77; H, 4.82; N, 7.95.

4-methyl-N-(2-phenyl-1-(pyridin-3-yl)ethyl)aniline **(P5).**

Oil, Yield 68%. IR (KBr): ν 3302 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 2.19(s, 3H), 3.02 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.10 (dd, *J* = 6.2 and 14.1 Hz, 1H), 4.17 (br s, 1H), 4.56 (t, *J* = 7.2 Hz, 1H), 6.36 (d, *J* = 6.8 Hz, 2H), 6.71 (d, *J* = 6.8 Hz, 2H), 7.18-7.33 (m, 6H), 7.67 (d, *J* = 5.8 Hz, 1H), 8.24 (dd, *J*=1.1 and 3.6 Hz, 1H), 8.51 (d, *J*=1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.56, 43.24, 53.44, 114.22, 120.81, 126.65, 130.35, 135.64, 137.85, 140.13, 143.58, 145.98, 148.31; MS m/z (EI): 288, 289(M+1), 197 (M-C_7H_7, 100 %).Found: C, 83.30; H, 6.99; N, 9.71; calcd for $C_{20}H_{20}N_2$: C, 83.33; H, 6.94; N, 9.72.

4-methoxy-N-(2-phenyl-1-(pyridin-3-yl)ethyl)aniline **(P6).**

Oil, Yield 66%. IR (KBr): ν3302 cm^{-1} (s, NH); ^{1}H NMR ($CDCl_3$): δ 3.03 (dd, *J* = 8.1 and 14.1 Hz, 1H), 3.11 (dd, *J* = 6.2 and 14.1 Hz, 1H), 3.78 (s, 3H), 4.16 (br s, 1H), 4.57 (t, *J* = 7.2 Hz, 1H), 6.65-6.67 (m, 4H), 7.17-7.34 (m, 6H), 7.67 (d, *J* = 5.8 Hz, 1H), 8.24 (dd, *J*=1.1 and 3.6 Hz, 1H), 8.51 (d, *J*=1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 43.24, 53.24, 55.89, 115.22, 120.81, 126.65, 130.35, 135.64, 137.85, 140.13, 145.98, 148.31, 151.01; MS m/z (EI): 304, 305(M+1), 213 (M-C_7H_7, 100 %).Found: C, 78.92; H, 6.62; N, 9.20; calcd for $C_{20}H_{20}N_2O$: C, 78.94; H, 6.57; N, 9.21.

Antifungal Screening (*in vitro*)

Microorganisms and media

The microorganisms used for the antifungal evaluation were obtained from National Collection of Industrial Microorganism (Pune): *Candida albicans 3471, Saccharomyces cerevisiae 3046, Aspergillus niger 545* and *Aspergillus flavus 524.* Yeast and Fungi strains were grown on the Malt extract glucose yeast extract peptone and Potato dextrose agar slants for 48 h at 30°C, respectively. Cell suspensions in sterile distilled water were adjusted to give a final concentration of 10^8 viable yeast cells and 10^6 viable fungi spores per mL.

Agar diffusion assay (Zone of inhibition)

All the synthesized compounds were screened for their *in vitro* antifungal activities. For preliminary screening, the antifungal tests were carried out by disc-diffusion method.[12] The preweighed benzenamine and maleimide derivatives were dissolved in DMSO to get final concentrations 100µg/mL. The test microorganisms were seeded into the respective medium by gently mixing 0.5 mL (containing 10^8 viable yeast cells and 10^6 viable fungi spores per mL) of the 48 hrs fresh cultures with 20 mL sterile melted agar cooled to about 45°C in sterile Petri plates. After hardening, the (6 mm diameter) disc containing compounds (100 µg/disc)and solvent blanks were considered. The plates were kept at 4°C in

the refrigerator for diffusion of the respective liquid in the plate. The Petri plates containing antifungal assay assembly were incubated at 30°C for 48 h. The standard discs of Nystatin(100U/mL) served as a positive antifungal control. DMSO (50% v/v) was used as a control. The diameter of the zone of inhibition around each of the disc was taken as a measure of the antifungal activity. Each experiment was carried out in triplicate and mean diameter of inhibition zone was recorded.

Broth dilution assay (Minimum inhibitory concentration)

The antifungal activity of benzenamine and maleimide derivatives was determined by the broth dilution method according to reported procedures.[12] The minimum inhibitory concentration (MIC) values were determined for microorganisms, which were sensitive to the compounds in the agar disc diffusion assay. The compounds were prepared at the highest concentration (1.5 mg/mL). The two rows of 12 sterile 7.5 x1.3 cm capped tubes were arranged in the rack. Various dilutions of compounds were achieved by serial double dilution method. Compounds were diluted in sequential range- 1025, 512, 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5, and 0.125µg/mL. In a capped tube 5mL of each solution was taken and to it was added 5mL double strength media. Tubes were inoculated with 0.2mL (containing 10^8 viable yeast cells and 10^6 viable fungi spores per mL) suspension of yeast and fungi spores. A blank 2mL of compound free broth was added to the last tube in each row. The tubes were incubated for 48 h at 37°C. A tube containing 2mL broth was inoculated with the organism and kept at +4°C in a refrigerator overnight to be used as a standard for the determination of complete inhibition. MIC was defined as the lowest compound concentration, showing no visible fungal growth after incubation time.

Chitin synthase assay

The chitin synthase inhibition assays were performed using yeast cell extracts, which was performed according to a modified procedure described by *Lucero* and *Bulik*.[13]The yeast *Saccharomyces cerevisiae* was cultured overnight by shaking in YPD (1% yeast extract, 2% peptone, and 2% glucose) at 30°C, and then the cells were harvested by centrifugation at 1500 x g for 10 min at 4°C. Cells were disrupted by grinding method with glass beads under liquid nitrogen condition.

The WGA-coated 96-well microtiter plates stored at -20°C in blocking buffer were thawed at room temperature and discharged by shaking. Then the pretreated whole cell extracts, tested samples and reaction mixtures were added to the appropriate wells, respectively, to a final volume of 100 µL. For each complete assay mixture, the corresponding incomplete reaction mixture (without UDP-GlcNAc) was used to assess the assay background. Immediately after the addition of reaction mixtures, plates were shaken slowly on a vortex shaker for 60 s and then incubated on the shaking table at room temperature for about 90 min. Then 20 µL of 50 mM EDTA was added and plates were gently shaken for the 30s on a vortex shaker. After this, plates were emptied and washed eight times with the amount of double distilled water, followed by the addition of 100 µL WGA-HP (1 µg/mL, 20 mg/mL BSA, 50 mM Tris-HCl, pH 7.5), and incubated for 15 min at room temperature. Plates were then emptied by vigorous shaking of their content and washed six times with double distilled water. Then 100 µL TMB reaction reagent was added and plates were immediately placed on the enzyme-linked analyzer for detection of the optical density (OD) at 600 nm by enzyme kinetic method. Each reaction was carried out in triplicate [14].

Cytotoxicity test

The cytotoxic activity in vitro was measured against mammalian cells, human 293T using the MTT assay. The cell was grown in DMEM medium supplemented with 10% PBS and 1x antimycotic and antibacterial solution (sigma USA) at 37°C, in (5%) CO_2incubator. 100 μL of the confluent fibroblast stock suspension was dispensed in 96-well plate. The original medium from the wells was replaced with 100 μL serum free DMEM when the cells reached 90% confluence after 5 h incubation in a CO_2 incubator. Various concentrations of the compounds were added to the growing cells and incubated for 24 h. The absorbance was measured at a wavelength of 490 nm (OD 490 nm) on an ELISA microplate reader. Three replicate wells were used for each concentration and each assay was measured three times, after which the average of IC_{50} was calculated. The cytotoxicity of each compound was expressed as the concentration of compound that inhibited cell viability to 50% (IC_{50}) [15]. The results were summarized in **Table S2.**

Table S2. Cytotoxicity of compounds.

Compound	IC_{50}µg/ml (mean±SD)
P2	24.12±0.19
P3	21.65±0.23
Nikkomycin Z	16.09±0.67

RESULT AND DISCUSSION

Rational designing of benzenamines

New compounds were designed with the help of the developed pharmacophore based 3D- QSAR model[18]. The model demonstrated that the activity may be increased by substituting the hydrophobic groups. Also, it was apparent that substitution of a hydrophobic group (a benzyl instead of an allyl group) in homoallylamine (FigureS3) would yield compounds with improved chitin synthase inhibitory activity. Based on the whole pharmacophore model inference a library of benzenamines (Table S2) was prepared and screened through the developed pharmacophore model.

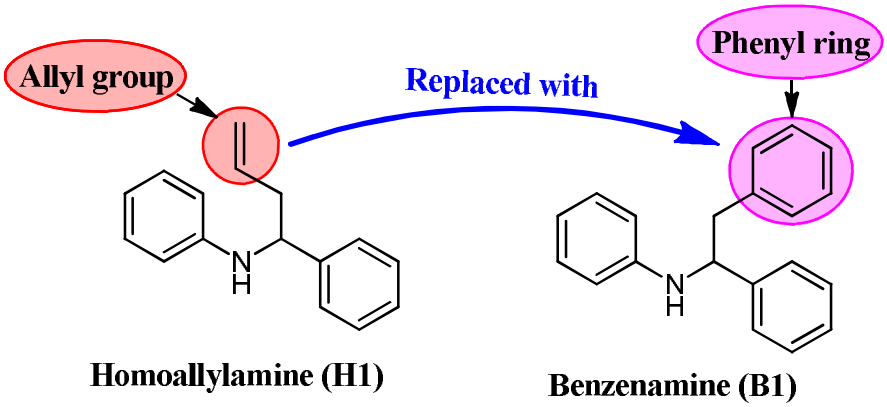
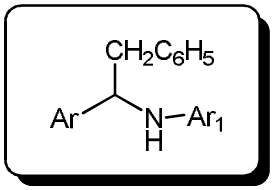


Figure S3. Homoallylamine (**H1)** and benzenamine (B**1)**

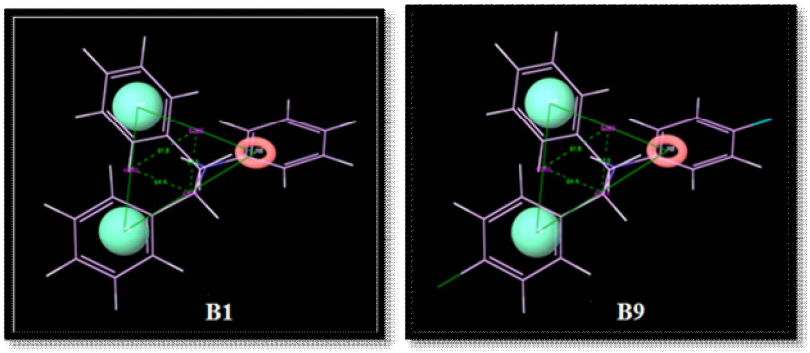
Table S3. Library of benzenamines



Sr.No	Ar	Ar_1	Sr.No	Ar	Ar_1
1	C_6H_5	C_6H_5	**57**	*p*-$CH_3C_6H_4$	*o*-BrC_6H_4
2	C_6H_5	*p*-ClC_6H_4	**58**	*p*-$CH_3C_6H_4$	*m*-BrC_6H_4
3	C_6H_5	*o*-ClC_6H_4	**59**	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$
4	C_6H_5	*m*-ClC_6H_4	**60**	*p*-$CH_3C_6H_4$	*o*- $CH_3C_6H_4$
5	C_6H_5	*p*-FC_6H_4	**61**	*p*-$CH_3C_6H_4$	*m*- $CH_3C_6H_4$
6	C_6H_5	*o*-FC_6H_4	**62**	*p*-$CH_3C_6H_4$	*p*- $OCH_3C_6H_4$
7	C_6H_5	*m*-FC_6H_4	**63**	*p*-$CH_3C_6H_4$	*o*- $OCH_3C_6H_4$
8	C_6H_5	*p*-BrC_6H_4	**64**	*p*-$CH_3C_6H_4$	*m*- $OCH_3C_6H_4$
9	C_6H_5	*o*-BrC_6H_4	**65**	*p*- $OCH_3C_6H_4$	C_6H_5
10	C_6H_5	*m*-BrC_6H_4	**66**	*p*- $OCH_3C_6H_4$	*p*-ClC_6H_4
11	C_6H_5	*p*-$CH_3C_6H_4$	**67**	*p*- $OCH_3C_6H_4$	*o*-ClC_6H_4
12	C_6H_5	*o*- $CH_3C_6H_4$	**68**	*p*- $OCH_3C_6H_4$	*m*-ClC_6H_4
13	C_6H_5	*m*- $CH_3C_6H_4$	**69**	*p*- $OCH_3C_6H_4$	*p*-FC_6H_4
14	C_6H_5	*p*- $OCH_3C_6H_4$	**70**	*p*- $OCH_3C_6H_4$	*o*-FC_6H_4
15	C_6H_5	*o*- $OCH_3C_6H_4$	**71**	*p*- $OCH_3C_6H_4$	*m*-FC_6H_4
16	C_6H_5	*m*- $OCH_3C_6H_4$	**72**	*p*- $OCH_3C_6H_4$	*p*-BrC_6H_4
17	*p*-ClC_6H_4	C_6H_5	**73**	*p*- $OCH_3C_6H_4$	*o*-BrC_6H_4
18	*p*-ClC_6H_4	*p*-ClC_6H_4	**74**	*p*- $OCH_3C_6H_4$	*m*-BrC_6H_4
19	*p*-ClC_6H_4	*o*-ClC_6H_4	**75**	*p*- $OCH_3C_6H_4$	*p*-$CH_3C_6H_4$
20	*p*-ClC_6H_4	*m*-ClC_6H_4	**76**	*p*- $OCH_3C_6H_4$	*o*- $CH_3C_6H_4$
21	*p*-ClC_6H_4	*p*-FC_6H_4	**77**	*p*- $OCH_3C_6H_4$	*m*- $CH_3C_6H_4$
22	*p*-ClC_6H_4	*o*-FC_6H_4	**78**	*p*- $OCH_3C_6H_4$	*p*- $OCH_3C_6H_4$
23	*p*-ClC_6H_4	*m*-FC_6H_4	**79**	*p*- $OCH_3C_6H_4$	*o*- $OCH_3C_6H_4$
24	*p*-ClC_6H_4	*p*-BrC_6H_4	**80**	*p*- $OCH_3C_6H_4$	*m*- $OCH_3C_6H_4$
25	*p*-ClC_6H_4	*o*-BrC_6H_4	**81**	2-Furyl	C_6H_5
26	*p*-ClC_6H_4	*m*-BrC_6H_4	**82**	2-Furyl	*p*-ClC_6H_4
27	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	**83**	2-Furyl	*o*-ClC_6H_4

28	*p*-ClC_6H_4	*o*- $CH_3C_6H_4$	**84**	2-Furyl	*m*-ClC_6H_4
29	*p*-ClC_6H_4	*m*- $CH_3C_6H_4$	**85**	2-Furyl	*p*-FC_6H_4
30	*p*-ClC_6H_4	*p*- $OCH_3C_6H_4$	**86**	2-Furyl	*o*-FC_6H_4
31	*p*-ClC_6H_4	*o*- $OCH_3C_6H_4$	**87**	2-Furyl	*m*-FC_6H_4
32	*p*-ClC_6H_4	*m*- $OCH_3C_6H_4$	**88**	2-Furyl	*p*-BrC_6H_4
33	*p*-FC_6H_4	C_6H_5	**89**	2-Furyl	*o*-BrC_6H_4
34	*p*-FC_6H_4	*p*-ClC_6H_4	**90**	2-Furyl	*m*-BrC_6H_4
35	*p*-FC_6H_4	*o*-ClC_6H_4	**91**	2-Furyl	*p*-$CH_3C_6H_4$
36	*p*-FC_6H_4	*m*-ClC_6H_4	**92**	2-Furyl	*o*- $CH_3C_6H_4$
37	*p*-FC_6H_4	*p*-FC_6H_4	**93**	2-Furyl	*m*- $CH_3C_6H_4$
38	*p*-FC_6H_4	*o*-FC_6H_4	**94**	2-Furyl	*p*- $OCH_3C_6H_4$
39	*p*-FC_6H_4	*m*-FC_6H_4	**95**	2-Furyl	*o*- $OCH_3C_6H_4$
40	*p*-FC_6H_4	*p*-BrC_6H_4	**96**	2-Furyl	*m*- $OCH_3C_6H_4$
41	*p*-FC_6H_4	*o*-BrC_6H_4	**97**	3-Pyridyl	C_6H_5
42	*p*-FC_6H_4	*m*-BrC_6H_4	**98**	3-Pyridyl	*p*-ClC_6H_4
43	*p*-FC_6H_4	*p*-$CH_3C_6H_4$	**99**	3-Pyridyl	*o*-ClC_6H_4
44	*p*-FC_6H_4	*o*- $CH_3C_6H_4$	**100**	3-Pyridyl	*m*-ClC_6H_4
45	*p*-FC_6H_4	*m*- $CH_3C_6H_4$	**101**	3-Pyridyl	*p*-FC_6H_4
46	*p*-FC_6H_4	*p*- $OCH_3C_6H_4$	**102**	3-Pyridyl	*o*-FC_6H_4
47	*p*-FC_6H_4	*o*- $OCH_3C_6H_4$	**103**	3-Pyridyl	*m*-FC_6H_4
48	*p*-FC_6H_4	*m*- $OCH_3C_6H_4$	**104**	3-Pyridyl	*p*-BrC_6H_4
49	*p*-$CH_3C_6H_4$	C_6H_5	**105**	3-Pyridyl	*o*-BrC_6H_4
50	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	**106**	3-Pyridyl	*m*-BrC_6H_4
51	*p*-$CH_3C_6H_4$	*o*-ClC_6H_4	**107**	3-Pyridyl	*p*-$CH_3C_6H_4$
52	*p*-$CH_3C_6H_4$	*m*-ClC_6H_4	**108**	3-Pyridyl	*o*- $CH_3C_6H_4$
53	*p*-$CH_3C_6H_4$	*p*-FC_6H_4	**109**	3-Pyridyl	*m*- $CH_3C_6H_4$
54	*p*-$CH_3C_6H_4$	*o*-FC_6H_4	**110**	3-Pyridyl	*p*- $OCH_3C_6H_4$
55	*p*-$CH_3C_6H_4$	*m*-FC_6H_4	**111**	3-Pyridyl	*o*- $OCH_3C_6H_4$
56	*p*-$CH_3C_6H_4$	*p*-BrC_6H_4	**112**	3-Pyridyl	*m*- $OCH_3C_6H_4$

While searching *on-the-fly*, conformers were generated, using the Conf Gen method. The matching method used tolerance value of 2.0 Å for each intersite distance in the hypothesis and it has to match on three site points out of three. The compounds containing *ortho* and *meta* substituent having aligned score > 1.2 (do not satisfy criteria set on the alignment, vector, or volume scores), were rejected. Only the compounds having *para* substituent showed satisfactory fitness to the pharmacophore hypothesis, with all sites (three) matching were chosen to synthesize and are shown in table S2. The designed compounds were found to have greater logP than the earlier reported compounds like homoallylamine (QlogPo/w: 4.529). QlogPo/w is the predicted water/octanol partition coefficient (Qikprop) [19].The representative hits of each type of compound to the hypothesis HHR.41 returned are shown in FigureS4.



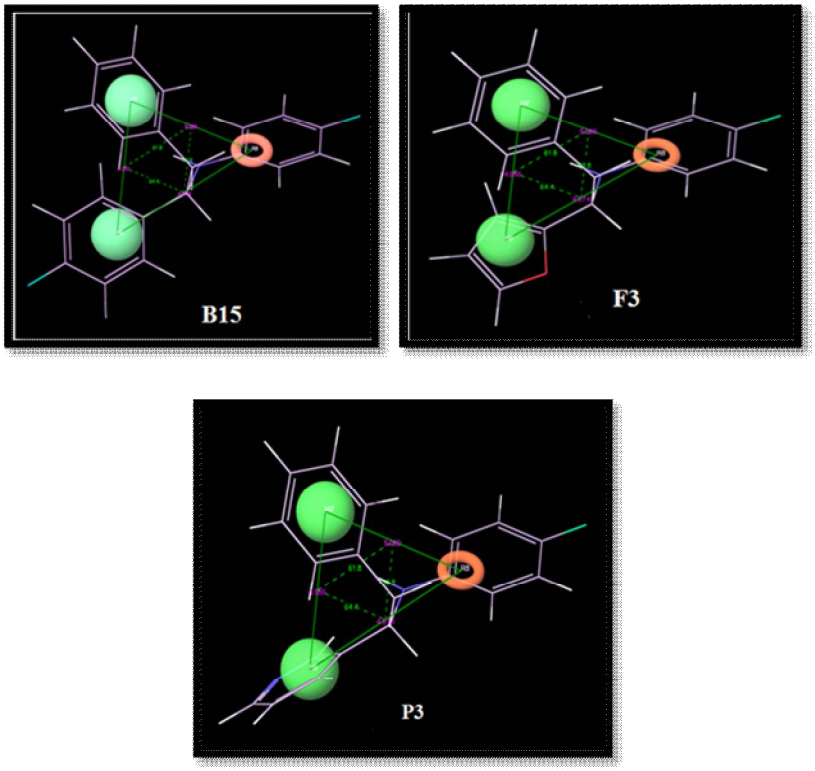
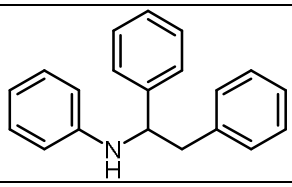
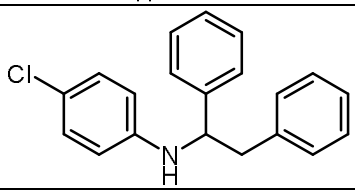
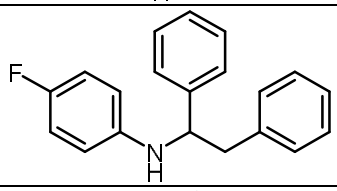
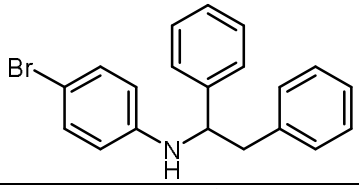
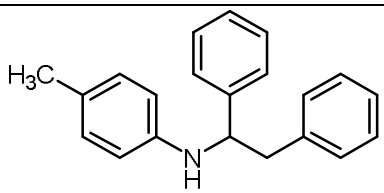
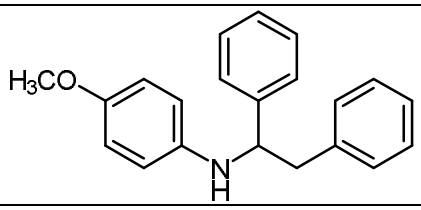
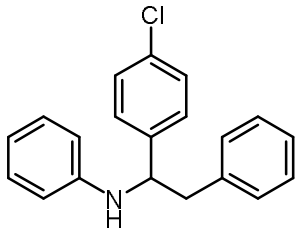
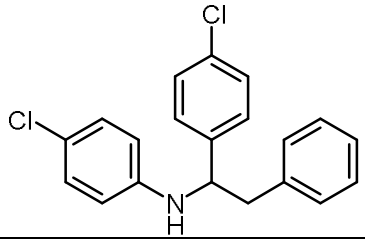
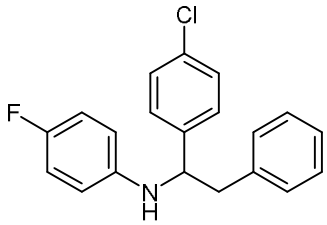
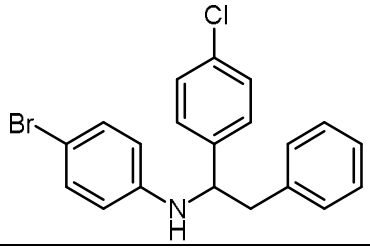
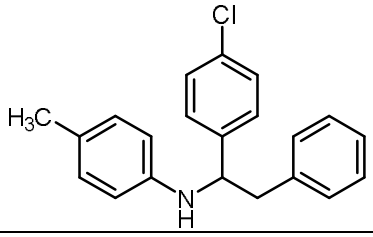
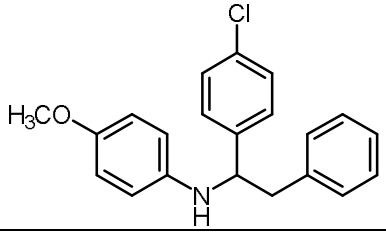
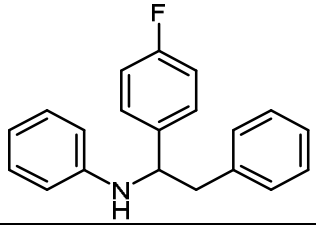
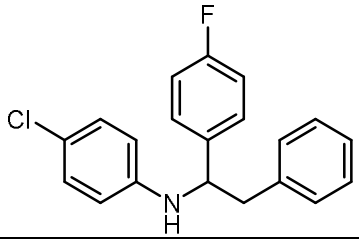
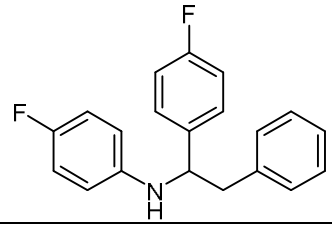
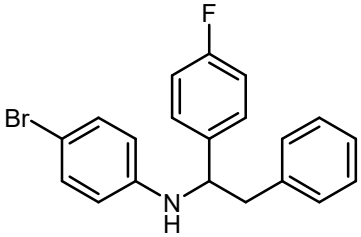
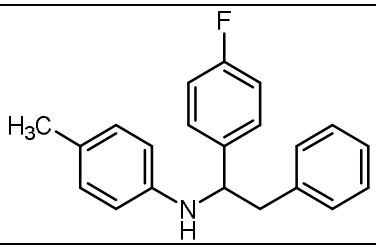
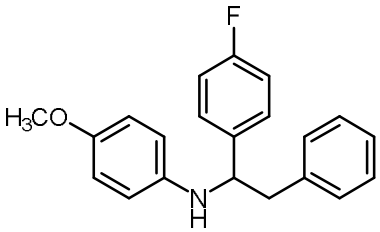
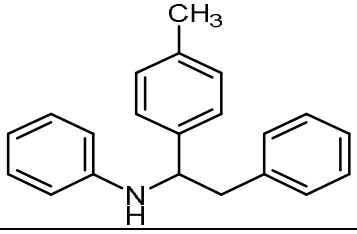


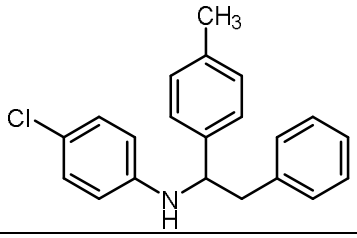
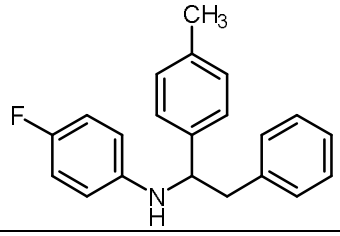
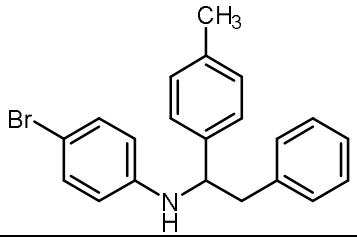
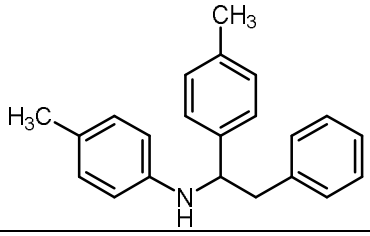
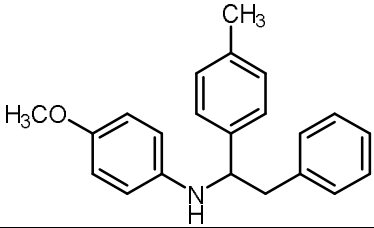
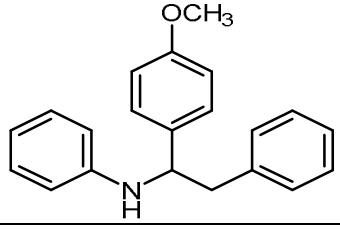
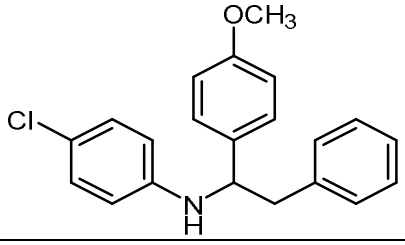
Figure S4. Returned Hits to the hypothesis HHR.41

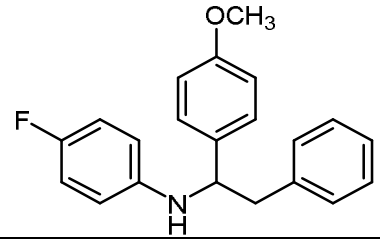
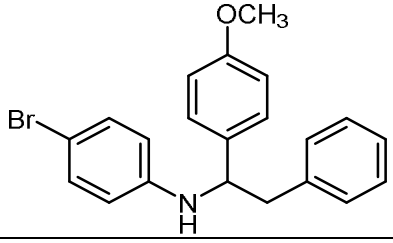
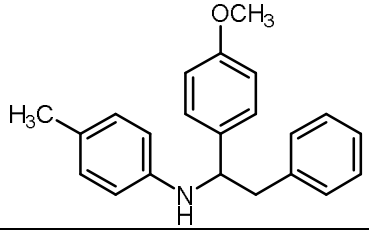
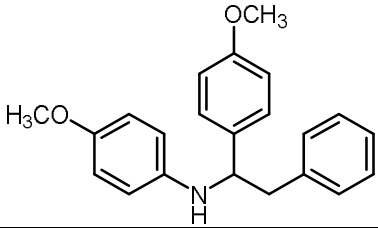
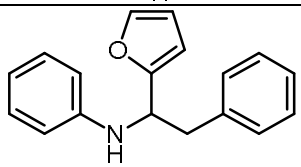
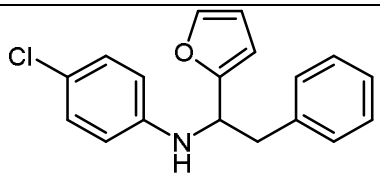
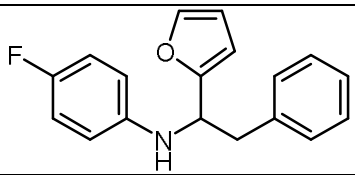
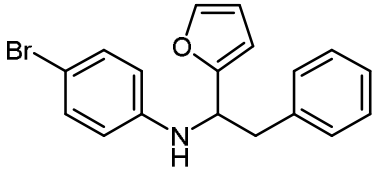
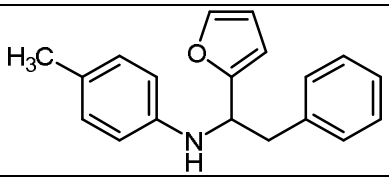
Table S4. Screened compounds

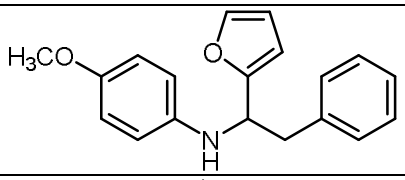
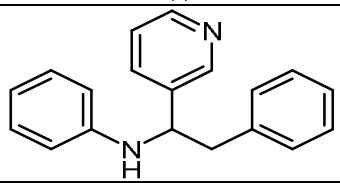
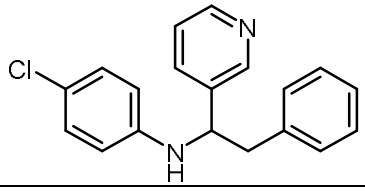
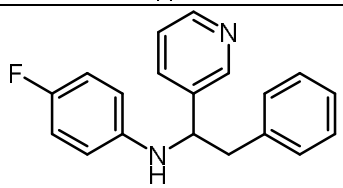
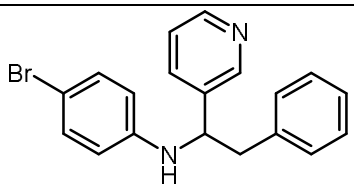
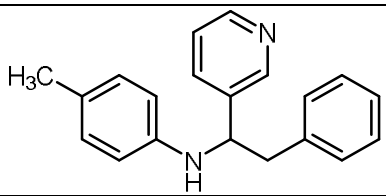
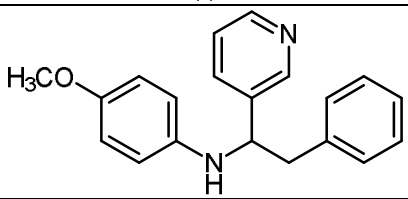
Compound	Structure	Fitness score	QlogPo/w[a]
B1		1.93	5.5
B2		1.69	6.05
B3		1.81	5.79
B4		1.91	6.1
B5		1.91	5.84

B6		1.91	5.64
B7		1.91	6.08
B8		1.93	6.59
B9		1.94	6.33
B10		1.94	6.66
B11		2.01	6.39
B12		2.01	6.01

B13		1.95	5.75
B14		1.93	6.32
B15		1.99	5.99
B16		1.93	6.33
B17		1.94	6.08
B18		1.99	5.86
B19		1.95	5.83

B20		1.93	6.21
B21		1.94	6.07
B22		2.01	6.46
B23		2.01	6.21
B24		2.01	5.84
B25		1.92	5.54
B26		1.93	6.04

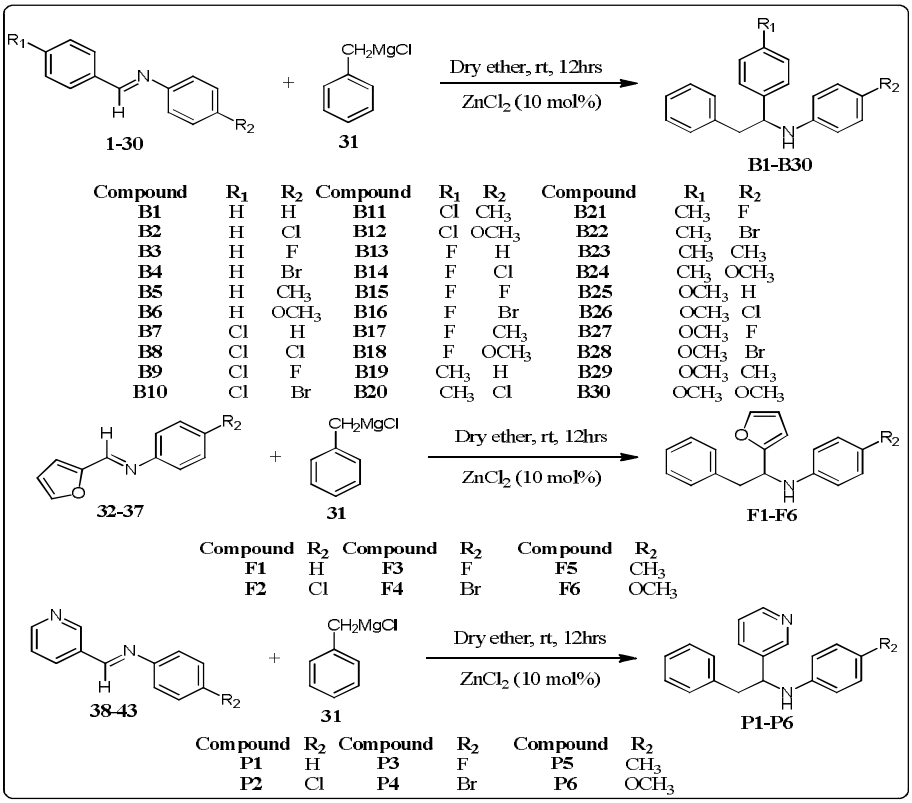
B27		1.91	5.61
B28		1.90	6.12
B29		1.93	5.70
B30		1.90	5.58
F1		2.017	4.93
F2		2.017	5.42
F3		2.08	5.16
F4		1.99	5.49
F5		2.17	5.24

F6		1.99	4.75
P1		2.07	4.42
P2		1.98	4.92
P3		1.98	4.65
P4		1.98	4.99
P5		1.98	4.74
P6		1.97	4.70

QlogPo/w[a]= Predicted water/octanol partition coefficient by using Qikprop[12].

Chemistry

Benzenamine derivatives were obtained from *N*-aryl aldimines[10, 20-23]. Benzenamines were synthesized by nucleophilic addition of benzyl magnesium chloride at -C=N of *N*-aryl aldimines under Grignard conditions (Figure 5). In principle, aldimines are less reactive due to their weak electrophilic nature, and alkylation with Grignard reagents was not been easy. As expected, the alkylation of **1**with only Grignard reagent at room temperature was slow. In contrast, $ZnCl_2$ promoted the alkylation, to get the desired amines **B1-B30, F1-F6** and **P1-P6**in good yield (61-72%) for 12 h[24].



Compound	R_1	R_2	Compound	R_1	R_2	Compound	R_1	R_2
B1	H	H	**B11**	Cl	CH_3	**B21**	CH_3	F
B2	H	Cl	**B12**	Cl	OCH_3	**B22**	CH_3	Br
B3	H	F	**B13**	F	H	**B23**	CH_3	CH_3
B4	H	Br	**B14**	F	Cl	**B24**	CH_3	OCH_3
B5	H	CH_3	**B15**	F	F	**B25**	OCH_3	H
B6	H	OCH_3	**B16**	F	Br	**B26**	OCH_3	Cl
B7	Cl	H	**B17**	F	CH_3	**B27**	OCH_3	F
B8	Cl	Cl	**B18**	F	OCH_3	**B28**	OCH_3	Br
B9	Cl	F	**B19**	CH_3	H	**B29**	OCH_3	CH_3
B10	Cl	Br	**B20**	CH_3	Cl	**B30**	OCH_3	OCH_3

Compound	R_2	Compound	R_2	Compound	R_2
F1	H	**F3**	F	**F5**	CH_3
F2	Cl	**F4**	Br	**F6**	OCH_3

Compound	R_2	Compound	R_2	Compound	R_2
P1	H	**P3**	F	**P5**	CH_3
P2	Cl	**P4**	Br	**P6**	OCH_3

Figure 5. Synthesis of benzenamine derivatives

B1-B30, F1-F6 and **P1-P6** structures were established using IR, NMR spectroscopy, and mass spectrometry. Spectral analysis (IR, NMR & Mass) of the compounds satisfactorily supported the structures of the synthesized compounds. The IR spectrum of benzenamines showed the presence of strong -NH stretching vibration band in the region of 3408-3194 cm^{-1}, and -NH bending vibration band in the region of 1560-1502 cm^{-1}. The absence of any band assignable for –C=N function in the region of 1628-1620 cm^{-1} supports the formation of benzenamine. In the ^1H NMR spectra of these compounds the broad singlet of NH appeared in region 4.00 ppm, whereas triplets signal of HC- appeared in a region 4.47 ppm, and the protons of CH_2-group appeared in the region 3.11 ppm as two multiplets (H^A and H^B are diastereotopic).

Molecular ion peaks and fragmentation pattern of the synthesized benzenamine compounds obtained on the mass spectrum adequately corresponded with their structures (FigureS3 and S4). This spectral data satisfactorily supports the formation of benzenamine compounds.

Antifungal activity

For preliminary screening,the synthesized benzenamines **B1-B30, F1-F6** and **P1-P6**were subjected to antifungal tests by disc-diffusion method at 100µg/mL. Nystatin (100U/mL) was used as a positive control in the disc diffusion method. The yeast cell suspension for *Candida albicans*and*Saccharomyces cerevisiae*, fungal suspension for *Aspergillus niger and Aspergillus flavus* were spread on sterile YPG (yeast extract, 0.3%, peptone, 0.5%, and glucose, 1%) and PDA (potato, 20% dextrose, 2%) agar plates separately. The entire synthesized compounds were found to be active against the tested fungi (Table S5).

Table S5. *In vitro* antifungal activity detection by using disc-diffusion method

Compound	Zone of inhibition (mm) (mean±SD)			
	S. cerevisiae	***C. albicans***	***A. niger***	***A. flavus***
B1	8.38±0.24	7.44±0.24	8.58±0.41	8.38±0.31
B2	8.81±0.19	9.86±0.27	8.90±0.35	8.79±0.36
B3	9.68±0.34	9.82±0.22	8.97±0.22	9.17±0.27
B4	9.48±0.43	9.13±0.55	9.96±0.22	10.06±0.22
B5	8.62±0.35	8.60±0.37	8.83±0.19	8.93±0.49
B6	7.70±0.46	7.23±0.29	8.48±0.25	8.58±0.25
B7	10.66±0.31	9.58±0.31	9.03±0.19	8.93±0.39
B8	13.64±0.38	12.61±0.38	10.70±0.29	10.11±0.49
B9	11.62±0.37	12.47±0.31	10.60±0.31	10.43±0.32

B10	10.67±0.40	9.89±0.23	9.36±0.2	9.28±0.23
B11	9.48±0.61	11.59±0.31	10.27±0.26	10.17±0.16
B12	7.38±0.15	11.49±0.15	9.44±0.29	9.24±0.39
B13	9.42±0.35	9.46±0.25	8.35±0.67	8.15±0.41
B14	10.41±0.28	11.58±0.42	10.55±0.39	10.41±0.61
B15	12.69±0.28	11.14±0.34	10.85±0.41	10.71±0.23
B16	13.55±0.46	9.72±0.19	9.92±0.32	10.00±0.32
B17	9.31±0.23	10.83±0.19	10.74±0.21	10.34±0.33
B18	7.20±0.58	7.64±0.22	8.40±0.21	8.21±0.31
B19	8.65±0.20	8.91±0.17	8.93±0.3	9.13±0.2
B20	10.61±0.37	7.61±0.20	9.60±0.36	9.27±0.46
B21	10.62±0.41	9.55±0.31	10.24±0.28	10.14±0.58
B22	10.47±0.45	9.33±0.30	10.22±0.15	9.97±0.43
B23	10.92±0.18	8.26±0.27	10.67±0.28	10.57±0.48
B24	8.57±0.38	7.56±0.33	9.57±0.25	9.73±0.35
B25	9.65±0.33	8.58±0.28	9.96±0.36	10.16±0.25
B26	12.95±0.28	8.83±0.21	9.70±0.28	9.47±0.37
B27	10.70±0.23	9.03±0.45	7.45±0.22	7.67±0.41
B28	10.32±0.22	9.98±0.34	9.48±0.54	9.54±0.36
B29	10.55±0.40	7.44±0.23	9.63±0.33	9.51±0.21
B30	9.74±0.21	7.72±0.26	9.95±0.28	10.21±0.39
F1	10.60±0.36	9.79±0.46	10.61±0.42	10.15±0.32
F2	10.59±0.43	9.88±0.33	10.15±0.34	10.51±0.41
F3	10.42±0.31	9.56±0.37	10.55±0.49	10.75±0.69
F4	10.24±0.25	9.50±0.23	10.56±0.45	10.16±0.34
F5	8.63±0.33	9.55±0.33	8.92±0.14	8.71±0.49
F6	10.58±0.40	8.55±0.29	9.57±0.24	9.07±0.64
P1	9.55±0.29	8.51±0.27	9.06±0.2	8.96±0.4
P2	13.60±0.36	12.52±0.28	13.30±0.23	12.90±0.43
P3	13.63±0.41	12.49±0.24	13.46±0.23	12.46±0.27
P4	10.58±0.34	10.46±0.22	10.54±0.27	10.24±0.17
P5	9.94±0.42	9.53±0.38	9.60±0.41	8.99±0.31
P6	9.62±0.46	8.54±0.31	8.77±0.49	9.17±0.29
Nyastatin (100 U/mL)	9.53±0.41	9.53±0.32	9.53±0.26	9.55±0.45

The synthesized benzenamines **B1-B30, F1-F6** and **P1-P6** were evaluated for antifungal activity (MIC) using the broth dilution method against *Candida albicans 3471, Saccharomyces cerevisiae 3046*, *Aspergillus niger 545 and Aspergillus flavus 524.* Amphotericin B and ketoconazole were taken as a positive control because the antifungal efficacy of nikkomycin Z is low[25].Concentrations up to 1000µg/mL of each compound were incorporated into the growth media according to reported procedures (Table 6).

Table 6. Minimum inhibitory concentration values of the compounds against the fungal species using broth dilution method

Compound	Minimum Inhibitory Concentration (µg/mL)			
	S. cerevisiae	***C. albicans***	***A. niger***	***A. flavus***
B1	512	256	512	512
B2	64	32	128	256
B3	16	32	128	128
B4	128	256	64	32
B5	512	128	512	256
B6	512	512	256	256
B7	16	16	32	32
B8	2	2	8	16
B9	2	2	16	32
B10	2	32	64	128
B11	256	8	512	512
B12	512	4	128	128
B13	128	256	512	512

B14	16	4	2	4
B15	2	4	4	8
B16	16	64	32	32
B17	128	64	64	64
B18	512	512	512	512
B19	32	512	512	256
B20	4	512	8	16
B21	4	512	64	64
B22	8	256	16	32
B23	2	256	128	128
B24	1025	512	256	128
B25	64	512	512	256
B26	8	256	128	256
B27	4	128	512	512
B28	16	256	256	128
B29	32	512	128	128
B30	64	512	128	64
F1	64	64	32	64
F2	2	8	8	4
F3	2	8	4	4
F4	32	16	16	32
F5	128	128	32	32
F6	1025	512	256	256
P1	16	64	32	64
P2	0.5	0.5	1	1
P3	1	0.5	2	2
P4	4	16	8	16
P5	8	32	16	16
P6	16	64	64	64
Amphotericin B	0.25	0.25	0.5	0.25
Ketoconazole	0.125	0.25	0.25	0.25
Nikkomycin Z[19]	--	<0.5–32	>64	--

All the designed benzenamines were found to be active against the selected and formulated panel of human pathogenic fungi as compared to earlier reported homoallylamines and related compounds[10]. This may be due to the hydrophobic group, e.g. phenyl ring increasing the lipophilicity of molecules, as per the predictions of the developed pharmacophore model. The activity data did not show any correlation with the fitness score, probably because a pharmacophore based QSAR cannot account for factors beyond the pharmacophore model itself, such as possible steric clashes with the receptor. This requires consideration of the entire molecular structure, i.e., an atom-based QSAR[26].

The structures **B8, B9**, **B14, B15**, **F2, F3, P2** and **P3** (MICs <100 µg/mL) containing halogen substituent has displayed significant activity against all tested organisms.

Compounds **B11, B12, B17, P5**and**P6**containing methyl and methoxy group on ring A (Figure2) has shown activity against *C. albicans.* It is interesting to note that when methoxy group changes from ring A to B (compound **B19-B30**) activity resides against *S. cerevisiae.* The structures containing halogen atoms on both rings (Compound **B8, B9**, **B14, B15**, **F2, F3, P2** and **P3**) were found to have better activity as compared to nonsubstituted analog (Compound **B1**).

After replacing the phenyl ring (ring B) with 3-pyridyl/ 2-furyl ring it was found that compounds **F1-F6** and **P1-P6** has displayed a broad spectrum of activity, inhibiting all the tested fungi at low concentrations. The benzenamines with 2-furyl moieties, structured with a halogen in the *p*-position (**F2, F3**) displayed good antifungal activities (MICs 2.0-8.0 µg/mL) and with 3-pyridyl moieties, structured with a halogen in the *p*-position (**P2, P3**) displayed good antifungal activities (MICs 0.5-2.0 µg/mL).

The most active antifungal compounds were tested for their capacity to inhibit *in vitro* chitin synthase. Results of the *in vitro* assays are listed in Table 2. Nikkomycin Z (Chitin synthase inhibitor) was used as a positive control. Chitin synthase inhibition activity from *S. cerevisiae* was estimated with compounds (4 µg/mL), and without also, using a nonradioactive chitin synthase assay according to *Lucero et al*[27]. It

was found that compound **P2,P3** inhibited 91 % and 92 %, chitin synthase activity respectively. The rest of the compounds showed the considerable percentage of inhibition in the range of 71-84 %, except compound **B2** and **B20** (49 & 45 % inhibition, respectively).

Table 7. Chitin synthase inhibition activity of compounds.

Compound	Percent inhibition(mean±SD)
B2	49±0.34
B8	71±0.47
B9	84±0.21
B14	76±0.53
B15	80±0.61
B20	56±0.16
B26	69±0.32
F2	70±0.55
F3	72±0.35
P2	91±0.19
P3	92±0.23
Nikkomycin Z	100

Cytotoxicity test

The most active compounds **P2** and **P3** were subjected to cytotoxicity test. The pharmacological results of these compounds were summarized in TableS5. It is observed that designated compounds were less toxic.

CONCLUSIONS

In the present study, fourty two benzenamine derivatives were designed and synthesized. The benzenamines (**P2, P3**) containing heteroaryl group as part of their structures showed best antifungal activity along with chitin synthase enzyme inhibition.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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