3.1. Molecular modelling

3.1.1. Softwares/database used

i. Schrodinger suit -2010
ii. Chem Draw ultra-2008
iii. Open Babel 2.3.0
iv. Zinc data base
v. Scifinder Scholar

3.1.2. Method

3.1.2.1. Design of Chemical library

Diphenyl ether derivatives were designed based on the antitubercular activities of compounds synthesized in our laboratory previously. Structure Activity Relationships reports on diphenyl ether based antitubercular agents from published journals were also taken in to consideration. Zinc data base was also mined to collect the structure of diphenyl ether derivatives showing antitubercular activity. Modern medicinal chemistry strategies like Bioisosteric replacement, Scaffold hopping and Label extension techniques were implemented to conduct structural incorporation and modifications in diphenyl ether moiety.

3.1.2.2. Virtual screening for druglikeness

3.1.2.2.1. Ligand preparation

Structures of designed diphenyl ethers were drawn using ChemDraw ultra-08 and converted to sdf file by Open Babel 2.3.0 software. Conversion of the chemical library from 2D to 3D structures and generation of ionization state (through Epik) of the ligands were done by Ligprep tool of Schrodinger-2010. OPLS-2005 force field was used for the energy minimization of 3D structures of the ligands.

3.1.2.2.2. Physicochemical property screening

Prepared ligands were subjected to physicochemical properties screening by QikProp tool of Schrodinifer-2010. Compounds with undesirable features like reactive groups and poor pharmacokinetic properties were removed. Descriptors like lipophilicity (logP), molecular weight, number of nitrogen and oxygen, hydrogen bond donor/ acceptor, solubility, % human absorption, number of rotors, polar surface area (PSA) were taken in to consideration for the virtual screening. Lipinski’s parameter was also considered to select drug-like compounds. About 1200 druggable ligands were selected by virtual screening and subjected to molecular docking study.
3.1.2.3. Molecular docking study

3.1.2.3.1. Preparation of protein

The X-ray structure of *Mycobacterial tuberculosis* ENR (pdb 1P45) was used in all docking experiments. The InhA protein was found to be a heterodimer where the Chain-A was comprised of two Triclosan moieties in the binding site. Among the two ligands, one was showing the required catalytic interactions with the amino acid residues while the other ligand was just lying above, showing some van der Waals interactions. Chain-B contained one Triclosan moiety demonstrating required interactions at the catalytic site of the protein. We chose chain-B for the docking study to get better binding mode. In addition to this, we thought that larger cavity of chain-A would be detrimental for the residual interactions of our active ligand. Thus chain-A was deleted from the protein and only chain-B was optimized through Protein preparation wizard of Schrödinger-2010. Protein was preprocessed by assigning bond order, adding hydrogens and treating disulfide. Water molecules were removed within 5 Å of the binding site. Hydrogen bond was assigned by exhaustive sampling and energy was minimized to RMSD 0.30 Å by OPLS-2005.

3.1.2.3.2. Receptor grid generation

Receptor grid was generated around the co-crystallized ligand (Triclosan) in Schrödinger-2010 suit by using default parameters. Ligand was excluded from the protein and it was confined to the enclosing box at the centroid. The grid was generated to fit the ligands similar in size to Triclosan.

3.1.2.3.3. Ligand docking

Flexible docking study was conducted with standard precision (SP). Epik state penalty was added to the docking score. Docking was limited to the ligands having < 300 atoms and < 50 rotatable bonds. Van der Waal radii of the ligand atoms were scaled to 0.8 and the partial charge cut off was kept less than 0.15. The position of ligand was kept at the center of a 10 Å docking sphere. Default settings were used in Glide for all dockings. At the beginning, co-crystallized ligand (Triclosan) was extracted from the optimized protein and redocked to probe the RMSD and docking parameters. Then all the 1200 ligands qualified in virtual screening were docked with the Mtb InhA protein at the Triclosan binding site. Then all ligand docking results from SP docking was studied. Diphenyl ether derivatives incorporating the features of Triclosan at the Mtb ENR binding site were given priority for synthesis. Molecular docking study afforded
300 virtually druggable diphenyl ether derivatives with similar orientations and interactions as of Triclosan.

3.2. Synthesis and Characterization

3.2.1. Introduction

Before synthesizing the designed diphenyl ether derivatives, their novelty was probed by Scifinder Scholar. Thorough literature search was carried out from chemical abstracts, patents and peer reviewed journals to find the methods for synthesis of structurally similar compounds and the chemistry involved.

3.2.2. Synthetic planning

The synthetic routes for the preparation of target molecules were planned through retrosynthetic approach. Most facile synthetic routes were selected based on the % atom economy of each reaction step. Atom economy of some reaction steps was improved by careful selection of starting materials and catalyst system. While designing the synthetic routes, upmost priority was given for high yielding reproducible reaction steps rather than concentrating on novel synthetic routes and complex chemistry. All the reaction steps even if reported in published literatures were selected based on our inhouse laboratory facilities. Oxygen Index of the planned synthons was calculated to confirm its safety. Handling and disposal of all reagents and catalysts to be used in the reaction steps were studied thoroughly from the corresponding Material Safety Data Sheets (MSDS).

3.2.3. Experimental Section

3.2.3.1. Materials and Methods

All of the chemicals used as starting materials and catalysts in this study were purchased from Aldrich Chemical Co., Spectrochem Ltd., TCI Chemicals and Himedia. All of the solvents used were obtained from S.D. Fine Chemicals Ltd. and Merck. All commercially available reagents procured were used without further purification. Solvents used were distilled and/or dried by standard techniques immediately prior to use and in case of an aqueous work-up, anhydrous magnesium sulfate was used as the drying agent. All moisture-sensitive reactions were carried out under nitrogen atmosphere in anhydrous solvents. Column chromatography was carried out on 100-200 mesh silica gel. Progress of the reactions was monitored by TLC using Aluminum backed sheets of silica gel 60 F24 (Merck). Melting points were recorded
with a laboratory melting point apparatus and are uncorrected. $^1$HNMR and $^{13}$CNMR spectra were recorded on a NMR Spectrometer (AV400 - 400 MHz High Resolution Multinuclear FT-NMR Spectrometer, Bruker) using DMSO-$d_6$ as the solvent. Mass spectroscopy was performed using LC-MS (Agilent 6520 series, Q-TOF LC/MS) and GC-MS (Shimadzu, GCMS-QP5050A). IR spectrum was taken in FT IR Spectrophotometer (IR Affinity-1, Shimadzu) using KBr pallets for solid compounds and chloroform for oils. UV absorbance of the compounds was monitored by UV-Visible spectrophotometer (UV-2450, Shimadzu) and $\lambda_{max}$ was recorded. Compounds designed based on earlier works from our lab, were synthesized in phase-I whereas phase-II compounds were designed and synthesized based on the biological reports of phase-I compounds.

### 3.2.3.21. Method for synthesis of phase-I compounds

#### Scheme-1

![Diagram of reaction scheme]

**Reagents and conditions:**
- (i) ArCOMe, KOH, EtOH, H$_2$O, 25-27 °C, 24h
- (ii) Zn, NH$_4$Cl, EtOH, H$_2$O, 25-27 °C, 4h
- (iii) NaBH$_4$, THF, MeOH, 25-27 °C, 2h

General method for synthesis of 3-(3-phenoxypyphenyl)-1-arylprop-2-en-1-one (1a-n).

To a solution of m-phenox benzaldehyde (1g, 5.044 mmol) and aryl acetphenones (5.044 mmol) in absolute alcohol (25 mL) was added ethanolic solution of KOH (0.282 g, 10.088 mmol) at 25-27 °C. Reaction mixture was stirred at ambient temperature. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the completion of reaction (14h), the reaction mixture was poured into ice cold water (100 mL) with continuous stirring and the residue obtained was extracted with ethyl acetate (3x50 mL). The combined organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO$_4$
and evaporated under vacuum. The crude compound obtained was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compound.

3-(3-phenoxyphenyl)-1-phenylprop-2-en-1-one (1a)

Yield = 1.2 g (79%); mp = 102-104 °C; R_f = 0.64 (hexane: ethyl acetate = 8:2); λ_max = 301.6 nm (MeOH); IR (KBr, cm^{-1}) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym.C-O-C str.), 1149 (Sym.C-O-C str.); ^13CNMR (100.64 MHz, DMSO-d6): 189.61, 157.33, 157.22, 143.67, 137.9, 137.32, 133.70, 130.99, 130.57, 129.26, 129.07, 125.00, 123.92, 123.43, 121.29, 119.63, 118.79; LCMS (+ESI, m/z): 301.114 (M+H)^{+}

3-(3-phenoxyphenyl)-1-p-tolylprop-2-en-1-one (1b)

Yield = 1.12 g (71%); mp = 86-88 °C; R_f = 0.66 (hexane: ethyl acetate = 8:2); λ_max = 305.6 nm (MeOH); IR (KBr, cm^{-1}): 3064 (Ar-H str.), 2918 (C-H str.), 1662 (C=O str.), 1600 (C=C str.), 1572, 1485, 1444 (Ar-C=C str.), 1236 (Asym. C-O-C str.), 1101 (Sym.C-O-C str.); ^1HNMR (400 MHz, DMSO-d6): 8.06 (d, J=8.4 Hz, 2H), 7.94 (d, J=15.6 Hz, 1H), 7.71 (s, 1H), 7.66 (t, J= 6.2 Hz, 1H), 7.45 (t, J= 7.6 Hz, 1H), 7.42-7.39 (m, 2H), 7.36 (d, J= 8 Hz, 2H), 7.14 (t, J= 7.4 Hz, 1H), 7.05-7.01 (m, 3H), 2.39 (s, 3H); LCMS (+ESI, m/z): 315.1476 (M+H)^{+}

3-(3-phenoxyphenyl)-1-m-tolylprop-2-en-1-one (1c)

Yield = 1.08 g (68%); mp = 78-80 °C; R_f = 0.65 (hexane: ethyl acetate = 8:2); λ_max = 299.2 nm (MeOH); IR (KBr, cm^{-1}): 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.).

3-(3-phenoxyphenyl)-1-o-tolylprop-2-en-1-one (1d)

Yield = 1.2 g (76%); mp = 92-94 °C; R_f = 0.68 (hexane: ethyl acetate = 8:2); λ_max = 295 nm (MeOH); IR (KBr, cm^{-1}) = 3032 (Ar-H str.), 1658 (C=O str.), 1602(C=C str.), 1572, 1481, 1452(Ar-C=C str.), 1244(Asym. C-O-C str.), 1149 (Sym.C-O-C str.).

1-(4-methoxyphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1e)

Yield = 1.34 g (81%); mp = 104-106 °C; R_f = 0.66 (hexane: ethyl acetate = 8:2); λ_max = 316.4 nm (MeOH); IR (KBr, cm^{-1}) = 3008 (Ar-H str.), 2927, 2839 (C-H str.), 1662 (C=O str.), 1598 (C=C str.), 1527, 1485, 1418 (Ar-C=C str.), 1261 (Asym. C-O-C str.), 1128 (Sym.C-O-C str.).
1-(3-methoxyphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1f)

Yield=1.12 g (67%); mp = 94-96 °C; Rf = 0.63 (hexane: ethyl acetate = 8:2); λmax =304.4 nm (MeOH); IR (KBr, cm⁻¹) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452(Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.).

1-(2-methoxyphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1g)

Yield= 1.0 g (60%); mp = 98-100 °C; Rf = 0.64 (hexane: ethyl acetate = 8:2); λmax = 297.4 nm (MeOH); IR (KBr, cm⁻¹) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.).

1-(4-hydroxyphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1h)

Yield= 1.35 g (85%); mp = 126-128 °C; Rf = 0.41 (hexane: ethyl acetate = 8:2); λmax = 319.2 nm (MeOH); IR (KBr, cm⁻¹) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.).

1-(4-fluorophenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1i)

Yield= 1.2 g (75%); mp = 78-80 °C; Rf = 0.72 (hexane: ethyl acetate = 8:2); λmax = 304.6 nm (MeOH); IR (KBr, cm⁻¹) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.); LCMS (+ESI, m/z): 319.1153 (M+H)⁺.

1-(3-fluorophenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1j)

Yield= 1.05 g (66%); mp = 58-60 °C; Rf = 0.7 (hexane: ethyl acetate = 8:2); λmax = 278.2 nm (MeOH); IR (KBr, cm⁻¹) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.).

1-(4-chlorophenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1k)

Yield= 1.15 g (68%); mp = 92-94 °C; Rf = 0.74 (hexane: ethyl acetate = 8:2); λmax = 307.11 nm (MeOH); IR (KBr, cm⁻¹) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.).

1-(2,4-dimethylphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1l)

Yield= 1.4 g (85%); mp = 84-86 °C; Rf = 0.72 (hexane: ethyl acetate = 8:2); λmax = 295.8 nm (MeOH); IR (KBr, cm⁻¹) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.); LCMS (+ESI, m/z): 329.3039 (M+H)⁺.
1-(3,4-dimethylphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1m).

Yield = 1.36 g (82%); mp = 72-74 °C; \( R_f = 0.68 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 305.2 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.).

1-(1,5-dimethylphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1n)

Yield = 1.42 g (85%); mp = 70-72 °C; \( R_f = 0.71 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 295.2 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3032 (Ar-H str.), 1658 (C=O str.), 1602 (C=C str.), 1572, 1481, 1452 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1149 (Sym.C-O-C str.).

1-(4-hydroxy-2-methylphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (1o)

Yield = 1.25 g (71%); mp = 81-83 °C; \( R_f = 0.57 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 301 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3030 (Ar-H str.), 2920 (C-H str.), 1683 (C=O str.), 1585, 1485, 1444 (Ar-C=C str.), 1224 (Asym. C-O-C str.), 1153 (Sym.C-O-C str.); \(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 7.969-7.947 (m, 2H), 7.636-7.597 (m, 2H), 7.5 (t, \( J = 8 \) Hz, 2H), 7.38-7.34 (m, 2H), 7.27 (t, \( J = 7.8 \) Hz, 1H), 7.1 (t, \( J = 5.8 \) Hz, 1H), 7.05 (d, \( J = 7.6 \) Hz, 1H), 6.971-6.952 (m, 2H), 6.931-6.912 (m, 1H), 6.871-6.852 (m, 1H), 6.821-6.802 (m, 1H).

General method for synthesis of 3-(3-phenoxyphenyl)-1-arylpropan-1-one (2a-n).

To a solution of chalcones (1a-n) (2 mmol) in absolute alcohol (50 mL) and THF (10 mL) was added with 15 mL saturated aqueous solution of NH\(_4\)Cl (80 mmol) at 25-27 °C. Then the reaction mixture was added with Zn (12 mmol) in four portions at 10 min. interval and stirred for 6h at ambient temperature. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2) as the mobile phase. After the completion of reaction (6h), the reaction mixture was filtered and the filtrate was evaporated under vacuum to remove the volatiles. The residue obtained was added with ice cold water and extracted with ethyl acetate (3x25 mL). The organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO\(_4\) and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compounds.

3-(3-phenoxyphenyl)-1-phenyl propan-1-one (2a)

Yield = 0.54 g (89%); mp = 62-64 °C; \( R_f = 0.74 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 271.4 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3030 (Ar-H str.), 2920 (C-H str.), 1683 (C=O str.), 1585, 1485, 1444 (Ar-C=C str.), 1224 (Asym. C-O-C str.), 1153 (Sym.C-O-C str.); \(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 7.969-7.947 (m, 2H), 7.636-7.597 (m, 2H), 7.5 (t, \( J = 8 \) Hz, 2H), 7.38-7.34 (m, 2H), 7.27 (t, \( J = 7.8 \) Hz, 1H), 7.1 (t, \( J = 5.8 \) Hz, 1H), 7.05 (d, \( J = 7.6 \) Hz, 1H), 6.971-6.952 (m, 2H), 6.931-6.912 (m, 1H), 6.871-6.852 (m, 1H), 6.821-6.802 (m, 1H), 6.801-6.782 (m, 1H), 6.771-6.752 (m, 1H).
Chapter 3

Materials and Method

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2H), 6.794-6.768 (dd, J= 8 Hz and 2 Hz, 1H), 3.36 (t, J= 7.4 Hz, 2H), 2.93 (t, J= 7.4 Hz, 2H).

$^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 29.82, 116.56, 118.89, 119.34, 123.73, 124.13, 128.40, 129.16, 130.26, 130.45, 133.60, 137.07, 144.08, 156.97, 157.20, 199.57; LCMS (+ ESI, m/z): 303.1253 (M+H)+

3-(3-phenoxyphenyl)-1-p-tolylpropan-1-one (2b)

Yield= 0.56 g (87%); mp = 54-56 °C; R$_f$ = 0.82 (hexane: ethyl acetate = 8:2); $\lambda$max = 251.8 nm (MeOH); IR (KBr, cm$^{-1}$) = 3034 (Ar-H str.), 2918 (C-H str.), 1670 (C=O str.), 1579, 1483, 1442 (Ar-C=C str.), 1228 (Asym. C-O-C str.), 1170 (Sym. C-O-C str.). $^1$HNMR (400 MHz, DMSO-$d_6$): 7.85 (d, J=8.4 Hz, 2H), 7.44 (d, J=8 Hz, 2H), 7.27 (t, J=7.8 Hz, 1H), 6.968-6.944 (m, 2H), 6.92-6.86 (m, 2H), 6.864-6.845 (m, 2H), 6.715-6.696 (m, 2H), 3.70 (t, J= 7.4 Hz, 2H), 2.91 (t, J= 7.4 Hz, 2H), 2.35 (s, 3H).

3-(3-phenoxyphenyl)-1-m-tolyl propan-1-one (2c)

Yield= 0.525 g (83%); mp = 64-66 °C; R$_f$ = 0.795 (hexane: ethyl acetate = 8:2); $\lambda$max = 278.4 nm (MeOH); IR (KBr, cm$^{-1}$) = 3022 (Ar-H str.), 2927 (C-H str.), 1685 (C=O str.), 1581, 1485, 1431 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1111 (Sym.C-O-C str.); $^1$HNMR (400 MHz, DMSO-$d_6$): 7.75 (t, J= 6.2 Hz, 2H), 7.45-7.39 (m, 2H), 7.35 (t, J=7.8 Hz, 2H), 7.27 (t, J= 7.8 Hz, 1H), 7.12-7.09 (m, 1H), 7.06 (t, J= 6.2 Hz, 1H), 6.97-6.95 (dd, J= 7.6 Hz and 0.4 Hz, 1H), 6.79-6.76 (dd, J= 8.4 Hz and 2.4 Hz, 1H), 3.34 (t, J= 7.4 Hz, 2H), 2.92 (t, J= 7.6 Hz, 2H), 2.35 (s, 3H).

3-(3-phenoxyphenyl)-1-o-tolylpropan -1-one (2d)

Yield= 0.505 g (80%); mp = 60-62 °C; R$_f$ = 0.783 (hexane: ethyl acetate = 8:2); $\lambda$max = 278.60 nm (MeOH); $^1$HNMR (400 MHz, DMSO-$d_6$): 7.78 (d, J= 8 Hz, 1H), 7.75-7.68 (m, 2H), 7.41-7.37 (m, 2H), 7.36 (t, J=7.8 Hz, 2H), 7.26 (t, J= 7.8 Hz, 1H), 7.18-7.12 (m, 1H), 7.07-7.02 (m, 1H), 6.98-6.91 (m, 1H), 6.66-6.65 (m, 1H), 6.61-6.59 (t, J= 7.8 Hz, 1H), 3.33 (t, J= 7.4 Hz, 2H), 2.92 (t, J= 7.6 Hz, 2H), 2.41 (s, 3H).

1-(4-methoxyphenyl)-3-(3-phenoxyphenyl) propan-1-one (2e)

Yield= 0.6 g (90%); mp = 75-76 °C; R$_f$ = 0.72 (hexane: ethyl acetate = 8:2); $\lambda$max =271.8 nm (MeOH); IR (KBr, cm$^{-1}$) = 3049 (Ar-H str.), 2929 (C-H str.), 1672 (C=O str.), 1591, 1479, 1448(Ar-C=C str.), 1257 (Asym. C-O-C str.), 1157 (Sym.C-O-C str.); $^1$HNMR (400 MHz, DMSO-$d_6$): 7.94 (d, J= 8.8 Hz, 2H), 7.36 (t, J= 8 Hz, 2H), 7.27 (t, J= 8 Hz, 1H), 7.11(t, J= 7.4
Hz, 1H), 7.06-7.00 (m, 4H), 6.96 (d, J= 8.4 Hz, 2H), 6.79-6.77 (dd, J= 8 Hz and 2 Hz, 1H), 3.31-3.29 (dd, J= 7.2 Hz and 5.2 Hz, 2H), 2.91 (t, J= 7.4 Hz, 2H), 3.83 (s, 3H); 13CNMR (100.64 MHz, DMSO-d6): 30.01, 55.96, 114.30, 116.52, 118.88, 119.33, 123.71, 124.11, 130.03, 130.23, 130.43, 130.72, 144.20, 156.96, 157.21, 163.53, 197.87; LCMS (+ESI, m/z): 333.3036 (M+H)+

1-(3-methoxyphenyl)-3-(3-phenoxyphenyl) propan-1-one (2f)

Yield= 0.523 g (79%); Rf = 0.75 (hexane: ethyl acetate = 8:2); λmax = 278.4 nm (MeOH);

1-(2-methoxyphenyl)-3-(3-phenoxyphenyl) propan-1-one (2g)

Yield= 0.53 g (80%); Rf = 0.75 (hexane: ethyl acetate = 8:2); λmax = 271.4 nm (MeOH);

1-(4-hydroxyphenyl)-3-(3-phenoxyphenyl) propan-1-one (2h)

Yield= 0.49 g (77%); mp = 95-97 °C; Rf = 0.64 (hexane: ethyl acetate = 8:2); λmax = 278.4 nm (MeOH); IR (KBr, cm⁻¹) =3313 (O-H str.), 3064 (Ar-H str.), 2916 (C-H str.), 1653 (C=O str.), 1575, 1485, 1444 (Ar-C=C str.), 1219 (Asym. C-O-C str.), 1166 (Sym.C-O-C str.); 1HNMR (400 MHz, DMSO-d6): 10.28 (s, 1H), 7.85-7.81 (m, 2H), 7.37-7.33 (m, 2H), 7.26 (t, J=7.8 Hz, 1H), 7.12-7.08 (m, 1H), 7.05 (d, J = 8 Hz, 1H), 6.97-6.95 (m, 3H), 6.93-6.80 (m, 2H), 6.78-6.75 (dddd, J= 8.4 Hz, 2.8 and 1.2 Hz, 1H), 3.25-3.21 (m, 2H), 2.89 (t, J= 7.6 Hz, 2H).

1-(4-fluorophenyl)-3-(3-phenoxyphenyl) propan-1-one (2i)

Yield= 0.51 g (79%); mp = 42-44 °C; Rf = 0.85 (hexane: ethyl acetate = 8:2); λmax = 303.4 nm (MeOH); 1HNMR (400 MHz, DMSO-d6): 8.06-8.02 (m, 2H), 7.38-7.31 (m, 3H), 7.30-7.25 (m, 2H), 7.13-7.08 (m, 1H), 7.05 (d, J =7.6 Hz, 1H), 6.97-6.94 (m, 3H), 6.79-6.77 (dddd, J= 2.4 Hz and 1.6 Hz, 1H), 3.37-3.33 (m, 2H), 2.92 (t, J= 7.4 Hz, 2H); 13CNMR (100.64 MHz, DMSO-d6): 116.57, 118.88, 119.64, 121.35, 123.92, 124.13, 125.05, 130.25, 131.36, 132.06, 134.58, 137.27, 143.83, 144.00, 156.97, 157.20, 157.31, 164.34, 166.84, 188.11, 198.16.

1-(3-fluorophenyl)-3-(3-phenoxyphenyl) propan-1-one (2j)

Yield= 0.43 g (67%); Rf = 0.81 (hexane: ethyl acetate = 8:2); λmax =292.8 nm (MeOH); LCMS (+ESI, m/z): 321.1284 (M+H)+

1-(4-chlorophenyl)-3-(3-phenoxyphenyl) propan-1-one (2k)

Yield= 0.495 g (74%); mp =61-63 °C; Rf = 0.89 (hexane: ethyl acetate = 8:2); λmax = 240.2 nm (MeOH); IR (KBr, cm⁻¹) = 3020 (Ar-H str.), 2929 (C-H str.), 1683 (C=O str.), 1585, 1485, 1444 (Ar-C=C str.), 1211 (Asym. C-O-C str.), 1170 (Sym.C-O-C str.).
1-(2,4-dimethylphenyl)-3-(3-phenoxyphenyl) propan-1-one (2l)

Yield= 0.56 g (85%); Rf = 0.84 (hexane: ethyl acetate = 8:2); λmax = 251.1 nm (MeOH); 1HNMR (400 MHz, DMSO-d6): 7.67 (d, J = 8 Hz, 2H), 7.37-7.33 (m, 2H), 7.26 (t, J = 7.8 Hz, 1H), 7.12 (t, J = 1.2 Hz, 1H), 7.10-7.07 (m, 2H), 7.01 (d, J = 7.6 Hz, 1H), 6.96-6.94 (m, 2H), 6.91 (t, J = 7.4 Hz, 1H), 6.79-6.77 (dd, J = 8.4 Hz and 2.8 Hz, 1H), 3.22 (t, J = 7.4 Hz, 2H), 2.88 (t, J = 7.4 Hz, 2H), 2.30 (t, J = 4 Hz, 6H).

1-(3,4-dimethylphenyl)-3-(3-phenoxyphenyl) propan-1-one (2m)

Yield= 0.538 (82%); mp = 70-72 °C; Rf = 0.85 (hexane: ethyl acetate = 8:2); λmax = 271.5 nm (MeOH); 1HNMR (400 MHz, DMSO-d6): 7.73 (s, 1H), 7.69-7.67 (dd, J = 8 Hz and 1.6 Hz, 1H), 7.37-7.33 (m, 2H), 7.28-7.23 (m, 2H), 7.12-7.08 (m, 1H), 7.04 (t, J = 8 Hz, 1H), 6.97-6.94 (m, 3H), 6.78-6.76 (dd, J = 8 Hz and 2.4 Hz, 1H), 3.26 (t, J = 7.4 Hz, 2H), 2.90 (t, J = 7.6 Hz, 2H), 2.26 (s, 6H); 13CNMR (100.64 MHz, DMSO-d6): 19.77, 20.01, 29.93, 116.52, 118.88, 119.33, 123.71, 124.12, 126.08, 129.38, 130.16, 130.23, 130.44, 134.98, 137.13, 142.71, 144.17, 156.96, 157.20, 199.17.

1-(1,5-dimethylphenyl)-3-(3-phenoxyphenyl) propan-1-one (2n)

Yield= 0.534 g (81%); mp = 49-50 °C; Rf = 0.872 (hexane: ethyl acetate = 8:2); λmax = 278.6 nm (MeOH);

General method for synthesis of 3-(3-phenoxyphenyl)-1-arylpropan-1-one (3a-n)

To a solution of ketone (2a-n) (0.99 mmol) in methanol (8 mL), THF (4 mL) was added followed by the addition of NaBH₄ (2.97 mmol) in three portions and stirred at ambient temperature. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2) as the mobile phase. After the completion of reaction (2h), the reaction mixture was evaporated under vacuum to remove the volatiles. The residue obtained was treated with ice cold water and extracted with ethyl acetate (3x25 mL). The organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO₄ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compound with quantitative yield.

3-(3-phenoxyphenyl)-1-phenylpropan-1-ol (3a)

Yield= 0.25 g (83%); mp = 47-49 °C; Rf = 0.43 (hexane: ethyl acetate = 8:2); λmax = 272 nm (MeOH); 1HNMR (400 MHz, DMSO-d6): 7.39-7.35 (m, 2H), 7.28 (d, J = 8 Hz, 4H), 7.25 (d,
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3-(3-Phenoxyphenyl)-1-p-tolylpropan-1-ol (3b)

Yield = 0.27 g (85%); mp = 82-84 °C; Rf = 0.52 (hexane: ethyl acetate = 8:2); λmax = 272 nm (MeOH); IR (KBr, cm−1) = 3604 (O-H str.), 3018 (Ar-H str.), 2937 (C-H str.), 1585, 1485, 1448 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1174 (Sym. C-O-C str.); \(^1\)H NMR (400 MHz, DMSO-d6): 7.39-7.35 (dt, J = 8 Hz and 2 Hz, 1H), 7.26 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 8 Hz, 1H), 7.13-7.08 (m, 3H), 6.98-6.93 (m, 3H), 6.78 (d, J = 8.4 Hz, 1H), 5.13 (t, J = 4.4 Hz, 2H), 4.47-4.43 (dd, J = 17.6 Hz and 5.2 Hz, 1H), 2.61-2.55 (m, 2H), 2.25 (s, 3H), 1.86-1.81 (m, 2H);

\(^{13}\)C NMR (100.64 MHz, DMSO-d6): 31.92, 31.96, 40.53, 41.25, 55.47, 71.74, 71.96, 113.89, 116.38, 119.01, 123.72, 123.92, 126.22, 127.42, 129.00, 130.22, 130.41, 138.52, 145.00, 157.16, 157.32, 158.62; LCMS (+ESI, m/z): 318.1855 (M)+

3-(3-Phenoxyphenyl)-1-m-tolyl propan-1-ol (3c)

Yield = 0.24 g (76%); mp = 90-92 °C; Rf = 0.51 (hexane: ethyl acetate = 8:2); λmax = 271.5 nm (MeOH); \(^1\)H NMR (400 MHz, DMSO-d6): 7.40-7.35 (m, 3H), 7.26 (t, J = 7.8 Hz, 1H), 7.18-7.156 (m, 1H), 7.16-7.104 (m, 4H), 6.99-6.94 (m, 3H), 6.85 (t, J = 1.8 Hz, 1H), 6.81-6.78 (dd, J = 7.2 Hz and 1.6 Hz, 1H), 5.09 (d, J = 4.4 Hz, 1H), 4.53-4.41 (m, 1H), 2.59-2.55 (m, 2H), 2.27 (d, J = 4 Hz, 3H), 1.84-1.80 (m, 2H).

3-(3-Phenoxyphenyl)-1-o-tolylpropan-1-ol (3d)

Yield = 0.245 g (77%); Rf = 0.50 (hexane: ethyl acetate = 8:2); λmax = 272.5 nm (MeOH); \(^{1}\)H NMR (400 MHz, DMSO-d6): 7.42 (d, J = 7.2 Hz, 1H), 7.38-7.34 (m, 2H), 7.27 (t, J = 7.8 Hz, 1H), 7.16-7.104 (m, 4H), 6.99-6.94 (m, 3H), 6.85 (t, J = 1.8 Hz, 1H), 6.81-6.78 (dd, J = 7.2 Hz and 1.6 Hz, 1H), 5.09 (d, J = 4.4 Hz, 1H), 4.68-4.64 (d, J = 10.4 Hz and 5.6 Hz, 1H), 2.75-2.60 (m, 2H), 2.13 (s, 3H), 1.76 (t, J = 3.8 Hz, 2H).

1-(4-Methoxyphenyl)-3-(3-Phenoxyphenyl) propan-1-ol (3e)

Yield = 0.285 g (92%); Rf = 0.5 (hexane: ethyl acetate = 8:2); λmax = 272.5 nm (MeOH); \(^{13}\)C NMR (100.64 MHz, DMSO-d6): 31.92, 41.25, 55.35, 72.02, 111.74, 112.55, 116.41, 118.49, 123.74, 123.96, 129.48, 130.27, 130.45, 144.93, 148.32, 157.10, 157.25, 159.64; LCMS (+ESI, m/z): 334.1793 (M)+
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Yield= 0.28 g (90%); \( R_f = 0.52 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 271.5 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3604 (O-H str.), 3020 (Ar-H str.), 2947 (C-H str.), 1589, 1485, 1442 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1157 (Sym.C-O-C str.); \(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 7.39-7.73 (m, 2H), 7.27-7.24 (m, 1H), 7.21-7.18 (dd, \( J = 8.8 \) Hz and \( 2.8 \) Hz , 2H), 7.13-7.09 (m, 1H), 6.99-6.93 (m, 3H), 6.86-6.83 (dd, \( J = 6.8 \) Hz and 2 Hz, 2H), 6.79-6.77 (m, 2H), 5.09 (d, \( J = 4.8 \) Hz, 1H), 4.46-4.41 (m, 1H), 3.71 (s, 3H), 2.61-2.53 (m, 2H), 1.87-1.78 (m, 2H); LCMS: (+ESI, m/z): 334.1793 (M)+

1-(3-methoxyphenyl)-3-(3-phenoxyphenyl) propan-1-ol (3f)

Yield= 0.28 g (90%); \( R_f = 0.52 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 271 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3604 (O-H str.), 3020 (Ar-H str.), 2947 (C-H str.), 1589, 1485, 1442 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1157 (Sym.C-O-C str.); \(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 7.42-7.34 (m, 2H), 7.29 (d, \( J = 4.4 \) Hz, 3H), 7.26-7.24 (m, 1H), 7.15-7.09 (m, 1H), 6.96 (t, \( J = 9 \) Hz, 2H), 6.94-6.87 (m, 1H), 6.81-6.77 (m, 2H), 5.22 (d, \( J = 4.4 \) Hz, 1H), 4.51-4.47 (dd, \( J = 12 \) Hz and 5.6 Hz, 1H), 3.73 (s, 3H), 2.67-2.52 (m, 2H), 1.87-1.80 (m, 2H).

1-(2-methoxyphenyl)-3-(3-phenoxyphenyl) propan-1-ol (3g)

Yield= 0.282 g (90%); \( R_f = 0.49 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 271 \) nm (MeOH); \(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 7.42-7.34 (m, 2H), 7.29 (d, \( J = 4.4 \) Hz, 3H), 7.26-7.24 (m, 1H), 7.22-7.18 (m, 1H), 7.15-7.09 (m, 1H), 6.96 (t, \( J = 9 \) Hz, 2H), 6.94-6.87 (m, 1H), 6.81-6.77 (m, 2H), 5.22 (d, \( J = 4.4 \) Hz, 1H), 4.51-4.47 (dd, \( J = 12 \) Hz and 5.6 Hz, 1H), 3.73 (s, 3H), 2.67-2.52 (m, 2H), 1.87-1.80 (m, 2H).

1-(4-hydroxyphenyl)-3-(3-phenoxyphenyl) propan-1-ol (3h)

Yield= 0.245 g (77%); mp = 78-80 °C; \( R_f = 0.38 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 258.8 \) nm (MeOH)

1-(4-fluorophenyl)-3-(3-phenoxyphenyl) propan-1-ol (3i)

Yield= 0.26 g (81%); \( R_f = 0.52 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 278 \) nm (MeOH); \(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 7.38-7.30 (m, 4H), 7.26 (t, \( J = 7.8 \) Hz, 1H), 7.13-7.10 (m, 1H), 7.09-7.07 (m, 2H), 6.99-6.93 (m, 2H), 6.81-6.76 (m, 2H), 5.26-5.21 (dd, \( J = 17.2 \) Hz and 4.4 Hz, 1H), 4.52-4.48 (dd, \( J = 12.4 \) Hz and 5.6 Hz, 1H), 2.64-2.49 (m, 2H), 1.86-1.80 (m, 2H); \(^1\)CNMR (100.64 MHz, DMSO-\(d_6\)): 31.83, 41.24, 71.40114.32, 115.02, 115.22, 115.34, 116.41, 118.94, 119.12, 119.27, 123.78, 123.94, 127.40, 128.06, 128.14, 128.32, 130.30, 130.52, 142.66, 142.69, 144.82, 157.11, 157.22, 160.31, 162.71; LCMS (+ESI, m/z): 324.2133 (M+2)+

1-(3-fluorophenyl)-3-(3-phenoxyphenyl) propan-1-ol (3j)

Yield= 0.21 g (66%); \( R_f = 0.54 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 271.6 \) nm (MeOH); \(^1\)CNMR (100.64 MHz, DMSO-\(d_6\)): 42.17, 42.57, 45.86, 115.33, 115.54, 117.41, 119.46, 123.71, 124.45, 130.04, 130.12, 130.70, 131.02, 137.09, 137.12, 138.80, 156.62, 157.60, 174.28.
1-(4-chlorophenyl)-3-(3-phenoxyphenyl) propan-1-ol (3k)

Yield = 0.23 g (69%); mp = 48-50 °C; Rf = 0.6 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 271.6 \text{ nm} \) (MeOH); IR (KBr, cm\(^{-1}\)) = 3416 (O-H str.), 3061 (Ar-H str.), 2920 (C-H str.), 1668 (C-O str.), 1583, 1483, 1442 (Ar-C=C str.), 1242 (Sym. C-O-C str.), 1163 (Sym.C-O-C str.). LCMS (+ ESI, m/z): 338.1319 (M+2)\(^+\)

1-(2,4-dimethylphenyl)-3-(3-phenoxyphenyl) propan-1-ol (3l)

Yield = 0.28 g (86%); Rf = 0.65 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 271.4 \text{ nm} \) (MeOH); IR (KBr, cm\(^{-1}\)) = 3606 (O-H str.), 3020 (Ar-H str.), 2927 (C-H str.), 1585, 1487, 1444 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1160 (Sym.C-O-C str.).

1-(3,4-dimethylphenyl)-3-(3-phenoxyphenyl) propan-1-ol (3m)

Yield = 0.3 g (92%); mp = 49-51 °C; Rf = 0.52 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 272.2 \text{ nm} \) (MeOH); \(^{13}\)CNMR (100.64 MHz, DMSO-d\(_6\)): 157.27, 157.09, 144.99, 143.90, 135.98, 134.72, 130.44, 130.25, 129.52, 127.48, 123.95, 123.73, 123.67, 118.98, 116.39, 71.92, 41.31, 31.97, 19.50; LCMS (+ESI, m/z): 332.202 (M)

1-(2,6-dimethylphenyl)-3-(3-phenoxyphenyl) propan-1-ol (3n)

Yield = 0.305 g (94%); mp = 68-70 °C; Rf = 0.53 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 271.6 \text{ nm} \) (MeOH); \(^1\)HNMR (400 MHz, DMSO-d\(_6\)): 7.38-7.34 (m, 2H), 7.28 (d, \( J = 8 \text{ Hz} \), 1H), 7.24 (d, \( J = 8 \text{ Hz} \), 1H), 7.53 (s, 1H), 7.52-7.48 (m, 2H), 7.39-7.35 (m, 2H), 7.71 (t, \( J = 7.8 \text{ Hz} \), 1H), 7.24 (d, \( J = 7.8 \text{ Hz} \), 1H), 7.12-7.08 (m, 1H), 6.97 (t, \( J = 8 \text{ Hz} \), 3H), 6.92-6.89 (m, 2H), 6.86 (d, \( J = 8.8 \text{ Hz} \), 1H), 6.81-6.78 (dd, \( J = 8.08 \text{ Hz} \) and 1.2 Hz, 1H), 5.06 (d, \( J = 4.4 \text{ Hz} \), 1H), 4.65-4.60 (dd, \( J = 11.2 \text{ Hz} \) and 5.6 Hz, 1H), 3.23-3.18 (dd, \( J = 17.6 \text{ Hz} \) and 4.4 Hz, 1H), 2.73-2.61 (m, 2H), 2.23 (s, 3H), 2.07 (s, 3H), 1.78-1.72 (dd, \( J = 14 \text{ Hz} \) and 7.6 Hz, 2H);

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**Scheme-2**

![Scheme-2](image)

1a. R=H, 1b. R=4-Me, 1e. R=4-OMe, 1f. R=3-OMe, 1g. R=2-OMe, 1i. R=4-F, 1j. R=4-Cl, 1k. R=2,4-Me, 1m. R=2,6-Me, 1o. R=4-OH, 2-Me

4a. R=H, 4b. R=4-Me, 4c. R=4-OMe, 4d. R=3-OMe, 4e. R=2-OMe, 4f. R=4-F, 4g. R=4-Cl, 4h. R=2,4-Me, 4i. R=2,6-Me, 4j. R=4-OH, 2-Me

5a. R=H, 5b. R=4-Me, 5c. R=4-OMe, 5d. R=3-OMe, 5e. R=2-OMe, 5f. R=4-F, 5g. R=4-Cl, 5h. R=2,4-Me, 5i. R=2,6-Me, 5j. R=4-OH, 2-Me

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*Reagents and conditions:* (i). Cyanohydrin acetone, TBMAH, K\(_2\)CO\(_3\), Me\(_2\)CO, H\(_2\)O, 55-27 °C, 14h; (ii). H\(_2\)O\(_2\), K\(_2\)CO\(_3\), DMSO, 5 °C to 25-75 °C, 2h.
General method for synthesis of 4-(3-phenoxyphenyl)-2-arylbutanenitrile (4a-j)

To a solution of chalcone (1.16 mmol) in acetone (15 mL) and water (1 mL), cyanohydrins acetone (2.32 mmol), TBMAH (1.16 mmol) and K$_2$CO$_3$ (2.32 mmol) were added. The resulting reaction mixture was refluxed at 57-58 °C for 14h. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2) as the mobile phase. After the completion of reaction (14h), solvent was evaporated under vacuum. The residue obtained was treated with ice cold water and extracted with ethyl acetate (3x25 mL). The organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO$_4$ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compound.

4-(3-phenoxyphenyl)-2-phenylbutanenitrile (4a)

Yield = 0.332 g (87%); mp = 84-86 °C; R$_f$ = 0.48 (hexane: ethyl acetate = 8:2); λ$_{max}$ = 275.6 nm (MeOH); IR (KBr, cm$^{-1}$) = 3051 (Ar-H str.), 2924 (C-H str.), 2237 (C-N str.), 1680 (C=O str.), 1585, 1485, 1444 (Ar-C=C str.), 1242 (Asym. C-O-C str.), 1161 (Sym.C-O-C str.); $^1$HNMR (400 MHz, DMSO-d$_6$): 8.01-7.99 (m, 2H), 7.68-7.64 (m, 1H), 7.55-7.51 (m, 2H), 7.44-7.37 (m, 3H), 7.30 (d, J = 8 Hz, 1H), 7.24 (t, J = 2 Hz, 1H), 7.16-7.14 (m, 1H), 7.03-7.01 (m, 2H), 4.66-4.61 (dd, J = 9.2 Hz and 5.2 Hz, 2H), 4.02-3.96 (dd, J = 18.4 Hz and 9.2 Hz, 1H), 3.76-3.70 (dd, J = 18.4 Hz and 5.2 Hz, 1H); $^{13}$CNMR (100.64 MHz, DMSO-d$_6$): 31.46, 43.11, 118.26, 118.66, 119.20, 121.61, 123.21, 124.18, 128.61, 129.25, 130.59, 131.01, 134.19, 136.17, 138.39, 156.71, 157.40, 196.46; LCMS (+ESI, m/z): 328.135 (M)$^+$

4-(3-phenoxyphenyl)-2-p-tolylbutanenitrile (4b)

Yield = 0.354 g (90%); R$_f$ = 0.62 (hexane: ethyl acetate = 8:2); λ$_{max}$ = 254.4 nm (MeOH); LCMS (+ESI, m/z): 344.1071(M)$^+$

2-(4-methoxyphenyl)-4-(3-phenoxyphenyl) butanenitrile (4c)

Yield = 0.35g (85%); mp = 58-60 °C; R$_f$ = 0.75 (hexane: ethyl acetate = 8:2); λ$_{max}$ = 277.2 nm (MeOH); LCMS (+ESI, m/z): 358.3069 (M)$^+$

2-(3-methoxyphenyl)-4-(3-phenoxyphenyl) butanenitrile (4d)

Yield = 0.32 g (77%); R$_f$ = 0.72 (hexane: ethyl acetate = 8:2); λ$_{max}$ = 280.6 nm (MeOH)

2-(2-methoxyphenyl)-4-(3-phenoxyphenyl) butanenitrile (4e)

Yield = 0.336 g (81%); mp = 62-64 °C; R$_f$ = 0.72 (hexane: ethyl acetate = 8:2); λ$_{max}$ = 307 nm (MeOH)
2-(4-fluorophenyl)-4-(3-phenoxyphenyl) butanenitrile (4f)

Yield = 0.328 g (82%); mp = 76-78 °C; R\textsubscript{f} = 0.72 (hexane: ethyl acetate = 8:2); λ\textsubscript{max} = 239.4 nm (MeOH)

2-(4-chlorophenyl)-4-(3-phenoxyphenyl) butanenitrile (4g)

Yield = 0.365 g (87%); mp = 84-86 °C; R\textsubscript{f} = 0.76 (hexane: ethyl acetate = 8:2); λ\textsubscript{max} = 253 nm (MeOH); \textsuperscript{1}HNMR (400 MHz, DMSO-\textit{d}6): 7.97 (d, J = 8.4 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.53 (d, J = 3.6 Hz, 1H), 7.49 (t, J = 7.2 Hz, 2H), 7.39-7.35 (m, 2H), 7.31 (t, J = 7.8 Hz, 1H), 7.17-7.12 (m, 2H), 7.10 (t, J = 1.8 Hz, 1H), 6.98 (d, J = 7.6 Hz, 2H), 6.84-6.81 (dd, J = 8 Hz and 1.2 Hz, 2H), 4.08-4.05 (dd, J = 10 Hz and 4.4 Hz, 1H), 3.86-3.79 (dd, J = 18 Hz and 10 Hz, 1H), 3.23-3.18 (dd, J = 18 Hz and 4.4 Hz, 1H).

2-(2,4-dimethylphenyl)-4-(3-phenoxyphenyl) butanenitrile (4h)

Yield = 0.345 g (84%); R\textsubscript{f} = 0.74 (hexane: ethyl acetate = 8:2); λ\textsubscript{max} = 255.4 nm (MeOH)

2-(2,6-dimethylphenyl)-4-(3-phenoxyphenyl) butanenitrile (4i)

Yield = 0.328 g (80%); R\textsubscript{f} = 0.79 (hexane: ethyl acetate = 8:2); λ\textsubscript{max} = 237.4 nm (MeOH)

2-(4-hydroxy-2-methylphenyl)-4-(3-phenoxyphenyl) butanenitrile (4j)

Yield = 0.35 g (84%); mp = 90-92 °C; R\textsubscript{f} = 0.63 (hexane: ethyl acetate = 8:2); λ\textsubscript{max} = 274.4 nm (MeOH)

General method for synthesis of 4-oxo-2- (3-phenoxyphenyl)-4-arylbutanamide (5a-j).

To a solution of 4-(3-phenoxyphenyl)-2-arylanitrile (4a-j) (0.76 mmol) in DMSO (8 mL) and anhydrous K\textsubscript{2}CO\textsubscript{3} (1.52 mmol), hydrogen peroxide solution (1.52 mmol) was added dropwise at 5-10 °C. The resulting reaction mixture was stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2) as the mobile phase. After the completion of reaction (2h), the reaction mixture was poured into ice cold water and the precipitate obtained was extracted with ethyl acetate (3x25 mL). The organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO\textsubscript{4} and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (5:5) as the mobile phase to afford the target compound with good yield.
4-oxo-2-(3-phenoxypheynyl)-4-phenylbutanamide (5a)

Yield= 0.19 (81%); mp = 98-100 °C; Rf = 0.22 (hexane: ethyl acetate =5:5); λmax = 272 nm (MeOH); IR (KBr, cm⁻¹) = 3437, 3350 (N-H str.), 3063 (Ar-H str.), 2962, 2858 (C-H str.), 1678 (C=O str.), 1581, 1483, 1444(Ar-C=C str.), 1236(Asym. C-O-C str.), 1159 (Sym.C-O-C str.); ¹HNMR (400 MHz, DMSO-d₆): 7.98-7.96 (dd, J = 7.2 Hz and 5.2 Hz, 2H), 7.64-7.60 (m, 1H), 7.53 (s, 1H), 7.52-7.48 (m, 2H), 7.39-7.35(m, 2H), 7.71 (t, J = 7.8 Hz, 1H), 7.17-7.14 (m, 1H), 7.12-7.04 (m, 2H), 6.99-6.97 (m, 2H), 6.84-6.81 (m, 2H), 4.06 (d, J = 5 Hz, 1H), 3.86-3.79 (dd, J = 17.6 Hz and 9.6 Hz, 1H), 3.23-3.18 (dd, J = 17.6 Hz and 4.4 Hz, 1H), 2.61-2.53 (m, 2H), 1.87-1.78 (m, 2H); ¹³CNMR (100.64 MHz, DMSO-d₆): 41.96, 46.58, 117.17, 118.74, 118.98, 123.38, 123.86, 128.40, 129.14, 130.28, 130.50, 133.65, 136.99, 143.27, 156.91, 157.02, 174.11, 198.51; LCMS (+ESI, m/z): 346.2309 (M⁺)

4-oxo-2-(3-phenoxypheynyl)-4-p-tolylbutanamide (5b)

Yield = 0.21 g (77%); mp = 72-74 °C; Rf = 0.24 (hexane: ethyl acetate =5:5); λmax = 251.4 nm (MeOH); ¹HNMR (400 MHz, DMSO-d₆): 7.86 (d, J = 8 Hz, 2H), 7.52 (s, 1H), 7.39-7.35 (m, 2H), 7.32-7.28 (m, 3H), 6.98 (d, J = 8 Hz, 2H), 6.83-6.81 (q, 2H), 4.07-4.03 (dd, J = 9.6 Hz and 4.4 Hz, 1H), 3.82-3.75 (dd, J = 9.6 Hz and 4.4 Hz, 1H), 1.87-1.78 (m, 2H); ¹³CNMR (100.64 MHz, DMSO-d₆): 21.61, 41.83, 46.58, 117.14, 118.73, 118.97, 123.38, 123.85, 128.52, 129.67, 130.26, 130.50, 134.55, 143.33, 143.96, 156.89, 157.02, 174.13, 197.97; LCMS (+ESI, m/z): 360.1428 (M⁺)

4-(4-methoxyphenyl)-4-oxo-2-(3-phenoxypheynyl) butanamide (5c)

Yield= 0.22 g (85%); mp = 104-106 °C; Rf = 0.22 (hexane: ethyl acetate =5:5); λmax = 271.6 nm (MeOH); ¹³CNMR (100.64 MHz, DMSO-d₆): 42.57, 46.64, 55.99, 114.28, 117.13, 118.72, 118.98, 123.38, 123.86, 129.99, 130.26, 130.50, 134.55, 143.33, 143.96, 156.89, 157.02, 174.13, 196.82.

4-(3-methoxyphenyl)-4-oxo-2-(3-phenoxypheynyl) butanamide (5d)

Yield = 0.2 g (76%); mp = 96-98 °C; Rf = 0.21 (hexane: ethyl acetate =5:5); λmax = 271.8 nm (MeOH)

4-(2-methoxyphenyl)-4-oxo-2-(3-phenoxypheynyl) butanamide (5e)

Yield= 0.198 g (76%); mp = 74-76 °C; Rf = 0.22 (hexane: ethyl acetate =5:5); λmax = 279.8 nm (MeOH); ¹HNMR (400 MHz, DMSO-d₆): 7.54-7.48 (m, 3H), 7.39-7.35 (m, 2H), 7.29 (t,
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Materials and Method

Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal.

J= 7.8 Hz, 1H), 7.15-7.12 (m, 2H), 7.09 (d, J= 7.6 Hz, 1H), 7.01-6.97 (m, 4H), 6.84-6.82 (dd, J= 8 Hz and 1.6 Hz, 1H), 6.80 (s, 1H), 4.03-3.99 (dd, J= 14.4 Hz and 5.2 Hz, 1H), 3.83 (s, 3H), 3.65-3.59 (dd, J= 17.6 Hz and 9.2 Hz, 1H), 3.18-3.12 (dd, J= 18 Hz and 5.2 Hz, 1H).

4-(4-fluorophenyl)-4-oxo-2-(3-phenoxyphenyl) butanamide (5f)
Yield= 0.212 g (78%); mp = 101-103 °C; Rf = 0.26 (hexane: ethyl acetate =5:5); \( \lambda_{\text{max}} = 272 \) nm (MeOH); \(^1\)HNMR (400 MHz, DMSO-\( d_6 \)): 8.06-8.04 (dd, J= 8.8 Hz and 5.6 Hz, 2H), 7.53 (s, 1H), 7.37 (t, J= 8 Hz, 2H), 7.34-7.29 (m, 3H), 7.16 (d, J= 8 Hz, 1H), 7.13 (d, J= 7.2 Hz, 1H), 7.09 (s, 1H), 6.98 (d, J= 8 Hz, 2H), 6.83 (d, J= 8 Hz, 2H), 4.07-4.03 (dd, J= 10 Hz and 4 Hz, 1H), 3.86-3.79 (dd, J= 17.6 Hz and 10 Hz, 1H), 3.22-3.16 (dd, J= 17.6 Hz and 4 Hz, 1H).

4-(4-chlorophenyl)-4-oxo-2-(3-phenoxyphenyl) butanamide (5g)
Yield= 0.23 g (80%); mp = 118-120 °C; Rf = 0.27 (hexane: ethyl acetate =5:5); \( \lambda_{\text{max}} = 273.8 \) nm (MeOH)

4-(2,4-dimethylphenyl)-4-oxo-2-(3-phenoxyphenyl) butanamide (5h)
Yield= 0.22 g (78%); mp = 104-106 °C; Rf = 0.28 (hexane: ethyl acetate =5:5); \( \lambda_{\text{max}} = 271.8 \) nm (MeOH); \(^1\)HNMR (400 MHz, DMSO-\( d_6 \)): 8.71 (d, J= 7.6 Hz and 5.6 Hz, 1H), 7.50 (s, 1H), 7.38-7.34 (m, 2H), 7.29 (t, J= 7.8 Hz, 1H), 7.12 (t, J= 7.4 Hz, 3H), 7.08-7.03 (m, 2H), 6.97 (d, J= 8.4 Hz, 2H), 6.84-6.81 (dd, J= 8.8 Hz and 2.4 Hz, 2H), 4.03-4.01 (dd, J= 14.8 Hz and 4.8 Hz, 1H), 3.67-3.61 (dd, J= 17.2 Hz and 9.6 Hz, 1H), 3.13-3.07 (dd, J= 17.2 Hz and 4.8 Hz, 1H), 2.29 (d, J= 4.4 Hz, 6H).

4-(2,6-dimethylphenyl)-4-oxo-2-(3-phenoxyphenyl) butanamide (5i)
Yield= 0.235 (83%); mp = 80-82 °C; Rf = 0.28 (hexane: ethyl acetate =5:5); \( \lambda_{\text{max}} = 271.6 \) nm (MeOH)

4-(4-hydroxy-2-methylphenyl)-4-oxo-2-(3-phenoxyphenyl) butanamide (5j)
Yield = 0.225 g (79%); mp = 95-97 °C; Rf = 0.18 (hexane: ethyl acetate =5:5); \( \lambda_{\text{max}} = 271.8 \) nm (MeOH); \(^1\)HNMR (400 MHz, DMSO-\( d_6 \)): 10.04 (s, 1H), 7.77 (d, J= 8.4 Hz, 1H), 7.48 (s, 1H), 7.36 (t, J= 8 Hz, 2H), 7.29 (t, J= 8 Hz, 1H), 7.12 (t, J= 6.8 Hz, 2H), 7.03 (s, 1H), 7.15 (d, J= 7.6 Hz, 1H), 7.13-7.10 (m, 1H), 7.07 (d, J= 7.6 Hz, 1H), 7.00-6.96 (m, 1H), 6.96 (d, J= 8 Hz, 2H), 4.04-4.02 (dd, J= 14.6 Hz and 4.4 Hz, 1H), 3.65-3.55 (dd, J= 16.2 Hz and 9.0 Hz, 1H), 3.12-3.08 (dd, J= 16 Hz and 4.4 Hz, 1H), 2.98 (s, 3H).
Synthesis of 3-phenoxybenzaldehyde (6)

To the stirred solution of 4-hydroxy-3-methoxy-acetophenone (3g, 22.02 mmol) in anhydrous dichloromethane (120 mL), was added with activated molecular sieves (4Å, 3g), phenylboronic acid (4.02 g, 33.18 mmol), copper (II) acetate (7.98 g, 44.04 mmol) and anhydrous pyridine (3.48 g, 44.04 mmol, 3.51 mL) successively. The resulting suspension was stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (9:1). After the completion of reaction (72h), the reaction mixture was diluted with dichloromethane (100 mL) and filtered under vacuum. The filtrate was washed with dilute aqueous hydrochloric acid solution (2M, 75 mL), followed by water (75 mL), dried over anhydrous MgSO₄ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (9:1) as the mobile phase to afford the target compound with good yield.

Yield= 2.25 g (48%); Rf = 0.95 (hexane: ethyl acetate = 9:1); λmax = 301 nm (MeOH);

¹HNMR (400 MHz, DMSO-d₆): 7.47-7.72 (m, 1H), 7.55-7.51 (m, 1H), 7.47-7.46 (m, 1H), 7.43-7.39 (m, 2H), 7.28-7.26 (ddd, J = 8 Hz, 2.8 Hz and 0.8 Hz, 1H), 7.20-7.16 (m, 2H), 7.06-7.03 (m, 2H), 2.55 (s, 3H); GCMS(EI, m/z): 212 (M)⁺, 197 (M−CH₃)⁺, 169 (M−COCH₃)⁺
General method for the synthesis of 3-((3-phenoxyphenyl)-1-arylprop-2-en-1-one (7a-h).

Compounds 7a-h were synthesized by following the method described for synthesis of compounds 1a-o. 4-hydroxy-3-methoxy-acetophenone (1 g, 4.71 mmol) was used as the starting material.

1-(3-phenoxyphenyl)-3-phenylprop-2-en-1-one (7a)

Yield = 1.1 g (78%); mp = 72-74 ºC; Rf = 0.66 (hexane: ethyl acetate = 8:2); λmax = 309.8 nm (MeOH); LCMS (+ESI, m/z): 301.1069 (M+H)+

1-(3-phenoxyphenyl)-3-p-tolylprop-2-en-1-one (7b)

Yield= 1.0 g (68%); mp = 58-60 ºC; Rf = 0.8 (hexane: ethyl acetate = 8:2); λmax = 321.4 nm (MeOH); LCMS (+ESI, m/z): 315.1473 (M+H)+

3-(4-methoxyphenyl)-1-(3-phenoxyphenyl) prop-2-en-1-one (7c)

Yield = 1.2 g (77%); mp = 80-82 ºC; Rf = 0.6 (hexane: ethyl acetate = 8:2); λmax= 343.2 nm (MeOH); LCMS (+ESI, m/z): 331.2903 (M+H)+

3-(3-methoxyphenyl)-1-(3-phenoxyphenyl) prop-2-en-1-one (7d)

Yield= 1.15 g (74%); mp = 79-81 ºC; Rf = 0.60 (hexane: ethyl acetate = 8:2); λmax = 306.6 nm (MeOH).

3-(2-methoxyphenyl)-1-(3-phenoxyphenyl) prop-2-en-1-one (7e)

Yield= 1.2 g (77%); mp = 55-57 ºC; Rf = 0.71 (hexane: ethyl acetate = 8:2); λmax = 316.4 nm (MeOH);

3-(4-fluorophenyl)-1-(3-phenoxyphenyl) prop-2-en-1-one (7f)

Yield= 1.1 g (67%); mp = 68-70 ºC; Rf = 0.71 (hexane: ethyl acetate = 8:2); λmax = 310.2 nm (MeOH); LCMS (+ESI, m/z): 319.1206 (M+H)+
3-(4-chlorophenyl)-1-(3-phenoxyphenyl) prop-2-en-1-one (7g)

Yield = 1.12 g (72%); mp = 77-79 °C; Rf = 0.84 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 305.4 \) nm (MeOH)

3-(2-chloro-6-fluorophenyl)-1-(3-phenoxyphenyl) prop-2-en-1-one (7h)

Yield = 1.1 g (66%); mp = 106-108 °C; Rf = 0.79 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 296.4 \) nm (MeOH)

3-(4-(dimethylamino) phenyl)-1-(3-phenoxyphenyl) prop-2-en-1-one (7i)

Yield = 1.25 g (77%); mp = 122-124 °C; Rf = 0.45 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 256.8 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3400 (O-H str.), 3062 (Ar-H str.), 2912 (C-H str.), 1639 (C=O str.), 1603 (C=C str.), 1529, 1458, 1420 (Ar-C=C str.), 1269 (Asym. C-O-C str.), 1182 (Sym. C-O-C str.)

3-(furan-2-yl)-1-(3-phenoxyphenyl) prop-2-en-1-one (7j)

Yield = 0.95 g (70%); mp = 52-54 °C; Rf = 0.59 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 270.3 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3073 (Ar-H str.), 2920, 2850 (C-H str.), 1662 (C=O str.), 1593 (C=C str.), 1556, 1485, 1435 (Ar-C=C str.), 1253 (Asym. C-O-C str.), 1157 (Sym. C-O-C str.)

General method for synthesis of 3-(3-phenoxyphenyl)-1-arylpropan-1-one (8a-g).

Compounds 8a-g were synthesized following the method described for synthesis of compounds 2a-n.

1-(3-phenoxyphenyl)-3-phenylprop-1-one (8a)

Yield = 0.52 g (82%); Rf = 0.75 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 299.8 \) nm (MeOH); LCMS (+ESI, m/z): 304.1271 (M+H)

1-(3-phenoxyphenyl)-3-p-tolylpropan-1-one (8b)

Yield = 0.5 g (80%); Rf = 0.84 (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 301.4 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3022 (Ar-H str.), 2927 (C-H str.), 1685 (C=O str.), 1581, 1485, 1431 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1153 (Sym. C-O-C str.); \(^1\)HNMR (400 MHz, DMSO-d\(_6\)):

7.77-7.74 (m, 1H), 7.52 (t, \( J = 7.8 \) Hz, 1H), 7.48 (t, \( J = 2 \) Hz, 1H), 7.44-7.39 (m, 2H), 7.28-7.26 (m, 1H), 7.20-7.16 (m, 1H), 7.15 (d, \( J = 8 \) Hz, 2H), 7.07-7.03 (m, 4H), 3.30 (t, \( J = 7.4 \) Hz, 2H), 2.86 (t, \( J = 7.4 \) Hz, 2H), 3.2 (s, 3H); LCMS (+ESI, m/z): 317.1547 (M+H)
3-(4-methoxyphenyl)-1-(3-phenoxyphenyl) propan-1-one (8c)

Yield = 0.56 g (84%); mp = 50–52 °C; R_f = 0.72 (hexane: ethyl acetate = 8:2); λ_max = 283.8 nm (MeOH); ^1HNMR (400 MHz, DMSO-d_6): 7.76-7.73 (m, 1H), 7.54-7.50 (dt, J = 8 Hz and 1.2 Hz, 1H), 7.47-7.46 (m, 1H), 7.43-7.39 (m, 2H), 7.27-7.25 (dd, J = 8.4 Hz, 2.8 and 1.2 Hz, 1H), 7.20-7.14 (m, 3H), 7.05-7.02 (m, 2H), 6.82-6.80 (dd, J = 8.4 Hz and 1.2 Hz, 2H), 3.69 (s, 3H), 3.27 (t, J = 3.8 Hz, 2H), 2.84 (m, J = 7.4 Hz, 2H); LCMS (+ESI, m/z): 333.1478 (M)^+

3-(3-methoxyphenyl)-1-(3-phenoxyphenyl) propan-1-one (8d)

Yield = 0.515 g (77%); R_f = 0.75 (hexane: ethyl acetate = 8:2); λ_max = 271.6 nm (MeOH); ^1HNMR (400 MHz, DMSO-d_6): 7.76-7.74 (m, 1H), 7.47-7.46 (m, 1H), 7.43-7.39 (m, 2H), 7.28-7.25 (dd, J = 8.4 Hz, 2.8 and 1.2 Hz, 1H), 7.19-7.14 (m, 2H), 7.05-7.02 (m, 2H), 6.81 (d, J = 7.2 Hz, 2H), 6.74-6.71 (m, 1H), 3.70 (s, 3H), 3.34 (t, J = 7.6 Hz, 2H), 2.87 (m, J = 7.4 Hz, 2H); ^13CNMR (100.64 MHz, DMSO-d_6): 29.10, 115.20, 115.41, 117.57, 119.43, 119.49, 121.09, 123.61, 124.47, 129.71, 130.70, 131.03, 138.92, 143.17, 156.58, 157.64, 159.73, 199.11.

3-(4-fluorophenyl)-1-(3-phenoxyphenyl) propan-1-one (8e)

Yield = 0.41 g (64%); mp = 52-54 °C; R_f = 0.83 (hexane: ethyl acetate = 8:2); λ_max = 271.6 nm (MeOH); ^1HNMR (400 MHz, DMSO-d_6): 7.76-7.74 (m, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 2 Hz, 1H), 7.43-7.39 (m, 2H), 7.30-7.25 (m, 1H), 7.11-6.99 (m, 3H), 3.33 (t, J = 7.6 Hz, 2H), 2.89 (t, J = 7.4 Hz, 2H); ^13CNMR (100.64 MHz, DMSO-d_6): 29.10, 115.20, 115.41, 117.57, 119.43, 123.56, 124.39, 130.55, 130.62, 130.94, 137.65, 137.68, 138.99, 156.67, 157.66, 198.94; LCMS (+ESI, m/z): 321.129 (M+H)^+

3-(2-chloro-6-fluorophenyl)-1-(3-phenoxyphenyl) propan-1-one (8f)

Yield = 0.5 g (71%); mp = 46-48 °C; R_f = 0.89 (hexane: ethyl acetate = 8:2); λ_max = 271.4 nm (MeOH); ^1HNMR (400 MHz, DMSO-d_6): 7.76-7.73 (m, 1H), 7.52 (t, J = 8 Hz, 1H), 7.49-7.48 (m, 2H), 7.43-7.39 (m, 3H), 7.27-7.26 (dd, J = 2.8 Hz and 1.2 Hz, 1H), 7.20-7.15 (m, 2H), 7.05-7.02 (m, 2H), 3.26-3.22 (dt, J = 7.8 Hz and 3.4 Hz, 2H), 3.01-3.05 (dt, J = 7.8 Hz and 1.6 Hz, 2H)

3-(4-(dimethylamino) phenyl)-1-(3-phenoxyphenyl) propan-1-one (8g)

Yield = 0.52 g (74%); mp = 60-62 °C; R_f = 0.68 (hexane: ethyl acetate = 8:2); λ_max = 248.2 nm (MeOH)
General method for synthesis of 1-(3-phenoxyphenyl)-3-arylpropan-1-ol (9a-g)

Compounds 9a-g were synthesized by following the method described for synthesis of compounds 3a-n.

1-(3-phenoxyphenyl)-3-phenylprop-1-ol (9a)

Yield = 0.23 g (76%); Rf = 0.5 (hexane: ethyl acetate = 8:2); λmax = 273.6 nm (MeOH); IR (KBr, cm⁻¹) = 3604 (O-H str.), 3020 (Ar-H str.), 2929 (C-H str.), 1587, 1485, 1444 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1160 (Sym. C-O-C str.); ¹HNMR (400 MHz, DMSO-d₆): 7.39-7.36 (m, 2H), 7.31 (t, J = 7 Hz, 1H), 7.26-7.22 (m, 2H), 7.15 (d, J = 7.6 Hz, 3H), 7.13-7.10 (m, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.00-6.96 (m, 3H), 6.86-6.84 (ddd, J = 8 Hz, 2.4 Hz and 0.8 Hz, 1H), 5.28 (d, J = 4.4 Hz, 1H), 4.53-4.48 (dd, J = 10.8 Hz and 6 Hz, 1H), 2.64-2.53 (m, 2H), 1.87-1.81 (m, 2H); LCMS (+ESI, m/z): 304.1546 (M)+

3-(4-methoxyphenyl)-1-(3-phenoxyphenyl) propan-1-ol (9c)

Yield = 0.26 g (84%); Rf = 0.52 (hexane: ethyl acetate = 8:2); λmax = 278 nm (MeOH); ¹HNMR (400 MHz, DMSO-d₆): 7.42-7.40 (dd, J = 7.6 Hz and 2 Hz, 2H), 7.38 (t, J = 4.4 Hz, 1H), 7.16 (t, J = 1.2 Hz, 1H), 7.14-7.07 (m, 3H), 7.02-6.98 (m, 3H), 6.889-6.881 (dd, J = 2.4 Hz and 0.8 Hz, 1H), 6.86-6.81 (m, 2H), 5.26 (d, J = 4 Hz, 1H), 4.53-4.48 (dd, J = 10.8 Hz and 6 Hz, 1H), 3.71 (s, 3H), 2.60-2.55 (dd, J = 14.4 Hz and 6 Hz, 2H), 1.85-1.80 (m, 2H); LCMS (+ESI, m/z): 334.1804 (M)+

3-(3-methoxyphenyl)-1-(3-phenoxyphenyl) propan-1-ol (9d)

Yield = 0.242 g (78%); Rf = 0.53 (hexane: ethyl acetate = 8:2); λmax = 272.2 nm (MeOH); ¹HNMR (400 MHz, DMSO-d₆): 7.39-7.34 (m, 2H), 7.31 (t, J = 7.8 Hz, 1H), 7.16-7.11 (m, 2H),
7.10-7.07 (m, 2H), 7.00-6.95 (m, 3H), 6.86-6.83 (ddd, J= 8 Hz, 2.4 and 0.8 Hz, 1H), 6.73-6.69 (m, 3H), 5.27 (d, J= 4.8 Hz, 1H), 4.52-4.48 (dd, J= 11.2 Hz and 6 Hz, 1H), 3.70 (s, 3H), 2.64-2.54 (m, 2H), 2.23 (s, 2H), 1.86-1.81 (dd, J= 14 Hz and 8 Hz, 2H).

3-(4-fluorophenyl)-1-(3-phenoxyphenyl) propan-1-ol (9e)

Yield = 0.263 g (82%); mp = 48-50 °C; R_f = 0.59 (hexane: ethyl acetate = 8:2); λ_max = 272.2 nm (MeOH); IR (KBr, cm^{-1}) = 3604 (O-H str.), 3020 (Ar-H str.), 2931, 2864 (C-H str.), 1587, 1485, 1433 (Ar-C=C str.), 1215 (Sym.C-O-C str.), 1152 (Sym.C-O-C str.); LCMS (+ESI, m/z): 322.1602 (M)^{+}.

3-(2-chloro-6-fluorophenyl)-1-(3-phenoxyphenyl) propan-1-one (9f)

Yield = 0.218 g (62%); R_f = 0.65 (hexane: ethyl acetate = 8:2); λ_max = 272.2 nm (MeOH); ^1HNMR (400 MHz, DMSO-d_6): 7.39-7.35 (m, 2H), 7.34-7.29 (m, 1H), 7.25-7.21 (m, 1H), 7.25-7.21 (m, 1H), 7.25-7.21 (m, 1H), 7.13-7.08 (m, 2H), 7.08-7.05 (m, 1H), 7.00-6.96 (m, 3H), 6.88-6.84 (m, 1H), 5.27 (d, J= 4.4 Hz, 1H), 4.56 (d, J= 5.6 Hz, 1H), 3.98-3.93 (m, 2H), 1.86-1.77 (m, 2H).

3-(4-(dimethylamino) phenyl)-1-(3-phenoxyphenyl) prop-2-en-1-one (9g)

Yield = 0.23 g (67%); mp = 51-52 °C; R_f = 0.35 (hexane: ethyl acetate = 8:2); λ_max = 278.6 nm (MeOH)

![Scheme-4](image)

Reagents and conditions: (i). Cyanohydrin acetone, TMBH, K_2CO_3, Me_2CO, H_2O, 55-27 °C, 14h; (ii). H_2O_2, K_2CO_3, DMSO, 5 °C to 25-27 °C, 2h.

General method for synthesis of 4-oxo-4-(3-phenoxyphenyl)-2-arylbutanenitrile (10a-g).

Compounds 10a-g were synthesized by following the method given for synthesis of compounds 4a-j.

4-oxo-4-(3-phenoxyphenyl)-2-phenylbutanenitrile (10a)

Yield = 0.32 g (84%); mp = 62-64 °C; R_f = 0.47 (hexane: ethyl acetate = 8:2); λ_max = 224.4 nm (MeOH); ^1HNMR (400 MHz, DMSO-d_6): 8.02-7.98 (td, J= 9.2 Hz, 2.2 Hz and 2.4 Hz,
2H), 7.16 (t, J = 1 Hz, 1H), 7.17-7.12 (m, 1H), 7.02-6.94 (m, 2H), 6.92-6.91 (dd, J = 8.8 Hz and 1.2 Hz, 1H), 4.62-4.59 (dd, J = 8.8 Hz and 5.2 Hz, 1H), 4.01-3.95 (dd, J = 18.4 Hz and 4.8 Hz, 1H); 13CNMR (100.64 MHz, DMSO-d6): 21.09, 31.17, 43.34, 117.71, 119.43, 121.87, 123.82, 124.20, 124.49, 128.10, 129.87, 130.71, 131.12, 133.13, 137.76, 138.01, 156.57, 157.62, 196.03; LCMS (+ ESI, m/z): 328.1341 (M+4 - oxo-4 -(3-phenoxyphenyl)-2-p-tolylbutanenitrile (10b)

Yield = 0.365 g (93%); Rf = 0.62 (hexane: ethyl acetate = 8:2); λmax = 300 nm (MeOH); LCMS (+ ESI, m/z): 342.1492 (M+2 -(4-methoxyphenyl)-4-oxo-4-(3-phenoxyphenyl) butanenitrile (10c)

Yield = 0.348 g (84%); mp = 52-54 ºC; Rf = 0.70 (hexane: ethyl acetate = 8:2); λmax = 254.4 nm (MeOH)

2-(2-methoxyphenyl)-4-oxo-4-(3-phenoxyphenyl) butanenitrile (10d)

Yield = 0.33 g (80%); mp = 58-60 ºC; Rf = 0.71 (hexane: ethyl acetate = 8:2); λmax = 271 nm (MeOH)

2-(4-fluorophenyl)-4-oxo-4-(3-phenoxyphenyl) butanenitrile (10e)

Yield = 0.342 g (85%); mp = 60-62 ºC; Rf = 0.84 (hexane: ethyl acetate = 8:2); λmax = 303 nm (MeOH)

2-(4-chlorophenyl)-4-oxo-4-(3-phenoxyphenyl) butanenitrile (10f)

Yield = 0.35 g (83%); mp = 69-71 ºC; Rf = 0.86 (hexane: ethyl acetate = 8:2); λmax = 295.4 nm (MeOH)

2-(furan-2-yl)-4-oxo-4-(3-phenoxyphenyl) butanenitrile (10g)

Yield = 0.24 g (65%); Rf = 0.65 (hexane: ethyl acetate = 8:2); λmax = 304.2 nm (MeOH)

General method for synthesis of 4-oxo-2-(3-phenoxyphenyl)-4-arylbutanamide (11a-g)

Compounds 11a-g were synthesized by following the method given for synthesis of compounds 5a-j.

4-oxo-4-(3-phenoxyphenyl)-2-phenylbutanenitrile (11a)

Yield = 0.165 g (70%); mp = 165-167 ºC; Rf = 0.21 (hexane: ethyl acetate = 6:4); λmax = 295.8 nm (MeOH); 1HNMR (400 MHz, DMSO-d6): 7.78 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 8 Hz,
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1H), 7.48-7.47 (m, 2H), 7.43-7.39 (m, 2H), 7.38-7.36 (m, 2H), 7.30-7.25 (m, 3H), 7.21-7.15 (m, 2H), 6.79 (s, 1H), 4.06-4.02 (dd, J = 10 Hz and 4.4 Hz, 1H), 3.86-3.79 (dd, J = 17.6 Hz and 4 Hz, 1H); 13CNMR (100.64 MHz, DMSO-d6): 42.18, 46.70, 117.36, 119.48, 123.70, 124.45, 127.16, 128.24, 128.76, 130.70, 131.02, 138.85, 140.96, 156.61, 157.61, 174.34, 198.08; LCMS (+ESI, m/z): 346.3793 (M+H)+.

4-oxo-4-(3-phenoxypyphenyl)-2-p-tolylbutanamide (11b)

Yield = 0.2 g (73%); mp = 139-141 °C; Rf = 0.25 (hexane: ethyl acetate = 6:4); λmax = 299 nm (MeOH); 1HNMR (400 MHz, DMSO-d6): 7.78-7.76 (dd, J = 6.4 Hz and 1.2 Hz, 1H), 7.52 (t, J = 8 Hz, 1H), 7.46 (t, J = 2 Hz, 1H), 7.43-7.39 (m, 3H), 7.28-7.27 (dd, J = 2.4 Hz and 0.8 Hz, 1H), 7.26-7.23 (m, 2H), 7.19-7.15 (m, 1H), 7.09 (d, J = 8 Hz, 2H), 7.05-7.03 (m, 2H), 6.75 (s, 1H), 4.01-3.97 (dd, J = 10 Hz and 4.4 Hz, 1H), 3.83-3.76 (dd, J = 18 Hz and 10 Hz, 1H), 3.14-3.09 (dd, J = 18 Hz and 4 Hz, 1H), 2.24 (s, 3H); 13CNMR (100.64 MHz, DMSO-d6): 21.08, 42.19, 42.57, 46.29, 117.32, 119.49, 123.67, 124.46, 128.08, 129.29, 130.70, 131.02, 137.94, 156.60, 157.62, 174.49, 198.12; LCMS (+ESI, m/z): 360.1588 (M+H)+.

2-(4-methoxyphenyl)-4-oxo-4-(3-phenoxypyphenyl) butanamide (11c)

Yield = 0.2 g (77%); mp = 102-104 °C; Rf = 0.21 (hexane: ethyl acetate = 6:4); λmax = 273.8 nm (MeOH); 1HNMR (400 MHz, DMSO-d6): 7.77 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 8 Hz, 1H), 7.46 (s, 1H), 7.41 (t, J = 8 Hz, 3H), 7.27 (d, J = 8.4 Hz, 3H), 7.17 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 1H), 6.74 (s, 1H), 3.98 (d, J = 6 Hz, 1H), 3.82-3.75 (dd, J = 17.6 Hz and 9.2 Hz, 1H), 3.70 (s, 3H), 3.16-3.12 (dd, J = 18 Hz and 4 Hz, 1H); 13CNMR (100.64 MHz, DMSO-d6): 42.57, 55.52, 114.16, 117.31, 119.49, 123.67, 124.47, 129.21, 130.70, 131.02, 137.94, 156.60, 157.62, 174.49, 198.12; LCMS (+ESI, m/z): 360.1588 (M+H)+.

2-(2-methoxyphenyl)-4-oxo-4-(3-phenoxypyphenyl) butanamide (11d)

Yield = 0.18 g (70%); mp = 153-155 °C; Rf = 0.24 (hexane: ethyl acetate = 6:4); λmax = 272 nm (MeOH); 1HNMR (400 MHz, DMSO-d6): 7.76 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.46 (s, 1H), 7.39 (t, J = 8.8 Hz, 2H), 7.28-7.25 (dd, J = 1.6 Hz and 8 Hz, 1H), 7.23-7.17 (m, 3H), 7.17-7.12 (m, 1H), 7.04 (d, J = 7.6 Hz, 2H), 6.98 (d, J = 8 Hz, 1H), 6.89 (t, J = 7.6 Hz, 2H), 6.82 (s, 1H), 4.43-4.39 (dd, J = 10 Hz and 3.6 Hz, 1H), 3.78 (s, 3H), 3.76-3.66 (m, 1H), 3.01-2.95 (m, 1H).

2-(4-fluorophenyl)-4-oxo-4-(3-phenoxypyphenyl) butanamide (11e)

Yield = 0.19 g (70%); mp = 130-132 °C; Rf = 0.27 (hexane: ethyl acetate = 6:4); λmax = 271 nm (MeOH); 1HNMR (400 MHz, DMSO-d6): 7.78 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8 Hz, 1H),
7.49 (d, J= 8.8 Hz, 2H), 7.43-7.39 (m, 4H), 7.28-7.26 (dd, J= 8 Hz and 2 Hz, 1H), 7.17 (t, J= 7.2 Hz, 1H), 7.11 (t, J= 7.6 Hz, 1H), 7.04 (d, J= 7.6 Hz, 2H), 6.81 (s, 1H), 4.07-4.03 (dd, J= 10.8 Hz and 4 Hz, 1H), 3.85-3.78 (dd, J= 18 Hz and 10 Hz, 1H), 3.19-3.14 (dd, J= 17.6 Hz and 4.4 Hz, 1H); LCMS (+ESI, m/z): 364.134 (M+H)^+

2-(4-chlorophenyl)-4-oxo-4-(3-phenoxyphenyl) butanamide (11f)

Yield = 0.205 g (71%); mp = 105-107 °C; R_f = 0.29 (hexane: ethyl acetate = 6:4); λmax = 274.5 nm (MeOH);

2-(furan-2-yl)-4-oxo-4-(3-phenoxyphenyl) butanamide (11g)

Yield = 0.163 g (64%); mp = 69-71 °C; R_f = 0.16 (hexane: ethyl acetate = 6:4); λmax = 270 nm (MeOH).
3.2.1.3.3. Spectra

$^1$H NMR (400 MHz, DMSO-$d_6$): 7.969-7.947 (m, 2H), 7.636-7.597 (m, 2H), 7.5 (t, $J=8$ Hz, 2H), 7.38-7.34 (m, 2H), 7.27 (t, $J=7.8$ Hz, 1H), 7.1 (t, $J=5.8$ Hz, 1H), 7.05 (d, $J=7.6$ Hz, 1H), 6.971-6.952 (m, 2H), 6.794-6.768 (dd, $J=8$ Hz and 2 Hz, 1H), 3.36 (t, $J=7.4$ Hz, 2H), 2.93 (t, $J=7.4$ Hz, 2H)

Figure 13.1. $^1$H NMR (400 MHz, DMSO-$d_6$) spectrum of compound 2a

$^{13}$C NMR (100.64 MHz, DMSO-$d_6$): 29.82, 116.56, 118.89, 119.34, 123.73, 124.13, 128.40, 129.16, 130.26, 130.45, 133.60, 137.07, 144.08, 156.97, 157.20, 199.57.

Figure 13.2. $^{13}$C NMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 2a

Figure 13.3. LCMS spectrum of compound 2a
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Figure 14.1. $^1$HNMR (400 MHz, DMSO-$d_6$) spectrum of compound 3a

Figure 14.2. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 3a

Figure 14.3. LCMS spectrum of compound 3a
Figure 15. UV-Vis spectra of compounds 1a, 2a and 3a in methanol.

Figure 16.1. $^1$HNMR (400 MHz, DMSO-$d_6$) spectrum of compound 5a
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Figure 16.2. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 5a

Figure 16.3. LCMS spectrum of compound 5a
Figure 17. UV-Visible spectrum of compound 1a, 4a and 5a.

\[ \text{1H NMR (400 MHz, DMSO-\textit{d}_6): 7.76-7.74 (td, } J = 7.6 \text{ Hz and 1.2 Hz, 1H), 7.52 (t, } J = 8 \text{ Hz, 1H), 7.48 (t, } J = 2 \text{ Hz, 1H), 7.43-7.38 (m, 3H), 7.30-7.25 (m, 1H), 7.11-6.99 (m, 3H), 3.33 (t, } J = 7.6 \text{ Hz, 2H), 2.89 (t, } J = 7.4 \text{ Hz, 2H)} \]

Figure 18.1. \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) spectrum of compound 8e
Figure 18.2. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 8e

$$^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 29.95, 55.36, 111.79, 114.55, 117.43, 119.49, 121.09, 123.61, 124.47, 129.71, 130.70, 131.03, 138.92, 143.17, 156.58, 157.64, 159.73, 199.11

Figure 18.3. LCMS spectrum of compound 8e

Figure 19.1. $^1$HNMR (400 MHz, DMSO-$d_6$): 7.39-7.36 (m, 2H), 7.31 (t, $J = 7$ Hz, 1H), 7.26-7.22 (m, 2H), 7.15 (d, $J = 7.6$ Hz, 3H), 7.13-7.10 (m, 1H), 7.07 (d, $J = 7.6$ Hz, 1H), 7.00-6.96 (m, 3H), 6.86-6.84 (dd, $J = 8$ Hz, 2.4 Hz and 0.8 Hz, 1H), 5.28 (d, $J = 4.4$ Hz, 1H), 4.53-4.48 (dd, $J = 10.8$ Hz and 6 Hz, 1H), 2.64-2.53 (m, 2H), 1.87-1.81 (m, 2H)
**Figure 19.2.** $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 9a

$^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 31.94, 40.61, 68.17, 71.76, 116.38, 117.36, 119.03, 121.40, 123.80, 126.09, 128.70, 128.74, 130.04, 130.08, 130.48, 142.48, 149.11, 157.00, 157.20, 157.24

**Figure 19.3.** LCMS spectrum of compound 9a

**Figure 20.** UV-Visible spectrum of compounds 7b, 6b and 9b in methanol.
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1^HNMR (400 MHz, DMSO-d$_6$): 7.78 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 8 Hz, 1H), 7.48-7.47 (m, 2H), 7.43-7.39 (m, 2H), 7.38-7.36 (m, 2H), 7.30-7.25 (m, 3H), 7.21-7.15 (m, 2H), 6.79 (s, 1H), 4.06-4.02 (dd, J = 10 Hz and 4.4 Hz, 1H), 3.86-3.79 (dd, J = 17.6 Hz and 10 Hz, 1H), 3.18-3.13 (dd, J = 17.6 Hz and 4 Hz, 1H);

Figure 2.1 $^1$HNMR (400 MHz, DMSO-d$_6$) spectrum of compound 11a

$^{13}$CNMR (100.64 MHz, DMSO-d$_6$): 42.18, 46.70, 117.36, 119.48, 124.45, 127.16, 128.24, 128.76, 130.70, 131.02, 138.85, 140.96, 123.70, 156.61,

Figure 2.2 $^{13}$CNMR (100.64 MHz, DMSO-d$_6$) spectrum of compound 11a

LCMS spectrum of compound 11a

Figure 2.3 LCMS spectrum of compound 11a
Figure 22. UV-Visible spectrum of compounds 9a, 10a and 11a
3.2.3.2II. Method for the synthesis of phase-II compounds

Novel compounds designed by computer assisted structure based drug design approach were synthesized in phase-II.

**Synthesis of 1-(3-methoxy-4-phenoxyphenyl) ethanone (12)**

To the stirred solution of 4-hydroxy-3-methoxy-acetophenone (3 g, 18.05 mmol) in anhydrous dichloromethane (90 mL), was added with activated molecular sieves (4Å, 3 g). Phenylboronic acid (4.49 g, 36.82 mmol), copper (II) acetate (7.36 g, 40.58 mmol) and anhydrous pyridine (5.70 g, 72.15 mmol, 5.82 mL) were added successively to the reaction mixture. The resulting suspension was stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the completion of reaction (72h), the reaction mixture was diluted with dichloromethane (40 mL) and filtered through under vacuum. The filtrate was washed with dilute aqueous hydrochloric acid solution (2 M, 50 mL), followed by water (50 mL), dried over anhydrous MgSO₄ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compound as white crystalline solid.

Yield= 4.12 g (94%); mp = 82-84 °C Rf = 0.9 (hexane: ethyl acetate = 8:2); λmax = 269.6 nm (MeOH); IR (KBr, cm⁻¹) = 3051 (Ar-H str.), 2928 (C-H str.), 1674 (C=O str.), 1583, 1489,
1413 (Ar-C=C str.), 1276 (Asym. C-O-C str.), 1134 (Sym. C-O-C str.); $^1$HNMR (400 MHz, DMSO-$d_6$): 7.60 (d, $J = 8$ Hz, 2H), 7.36 (t, $J = 7.8$ Hz, 2H), 7.12 (t, $J = 7.2$ Hz, 1H), 7.00 (d, $J = 8$ Hz, 1H), 6.94 (d, $J = 8$ Hz, 2H), 3.83 (s, 3H), 2.56 (s, 3H).

Synthesis of 1-(3-hydroxy-4-phenoxyphenyl) ethanone (13)

To a solution of 1-(3-methoxy-4-phenoxyphenyl) ethanone (12) (4 g, 16.52 mmol) in anhydrous dichloromethane (60 mL) was added with BBr$_3$ (1M, 8.28 g, 33.04 mmol) at -78 °C in presence of N$_2$. Reaction mixture was stirred for 2h at -78 °C and then the temperature of the reaction mixture was allowed to increase up to 10 °C and stirred continuously. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (6h), the reaction was quenched by pouring it into ice cold aqueous sodium bicarbonate with continuous stirring. The organic layer was separated, washed with water, brine, dried over anhydrous MgSO$_4$ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound as white crystalline compound.

Yield= 3.6 g (96%); mp = 87-89 °C; R$_f$ = 0.63 (hexane: ethyl acetate = 6:4); $\lambda_{\text{max}}$ = 269.4 nm (MeOH); $^1$HNMR (400 MHz, DMSO-$d_6$): 9.89 (s, 1H), 7.51 (d, $J = 2$ Hz, 1H), 7.45-7.43 (dd, $J = 8.4$ Hz and 2.4 Hz, 1H), 7.37-7.33 (m, 2H), 7.11-7.07 (m, 1H), 6.96 (s, 1H), 6.94-6.92 (m, 2H), 2.50 (s, 3H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 27.02, 116.81, 117.90, 120.57, 121.27, 123.51, 130.33, 134.03, 148.15, 149.23, 157.17, 197.14; LCMS (+ESI, m/z): 229.085 (M+H)$^+$

Synthesis of 5-(1-hydroxyethyl)-2-phenoxyphenol (14)

To the solution of compound 13 (0.2 g, 0.877 mmol) in methanol (4 mL) and THF (2 mL), NaBH$_4$ (0.99 g, 2.63 mmol) was added in three portions and stirred for 2h at ambient temperature. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4) as the mobile phase. After the completion of reaction (1h), the reaction mixture was evaporated under vacuum to remove the volatiles. The residue obtained was added to ice cold water and extracted with ethyl acetate (3x25 mL). The organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO$_4$ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound as white crystalline solid.

Yield= 0.18 g (90%); mp = 67-69 °C; R$_f$ = 0.44 (hexane: ethyl acetate = 6:4); $\lambda_{\text{max}}$ = 278.4 nm (MeOH); IR (KBr, cm$^{-1}$) = 3414 (O-H str.), 3064 (Ar-H str.), 2972, 2926 (C-H str.), 1591,
1496, 1398 (Ar-C=C str.), 1219 (Asym. C-O-C str.), 1163 (Sym. C-O-C str.); $^1$HNMR (400 MHz, DMSO-$d_6$): 9.43 (s, 1H), 7.28 (t, $J = 7.8$ Hz, 2H), 6.99 (d, $J = 5.6$ Hz, 2H), 6.89 (d, $J = 8$ Hz, 1H), 6.81 (d, $J = 8$ Hz, 2H), 6.77 (d, $J = 8$ Hz, 1H), 5.13 (d, $J = 4$ Hz, 1H), 4.65 (t, $J = 5.2$ Hz, 1H), 1.31 (d, $J = 6.4$ Hz, 3H).

**General method for synthesis of 1-(3-hydroxy-4-phenoxyaryl) ethanone (15a-f).**

1-(3-hydroxy-4-phenoxyphenyl) ethanone (13) (1g, 4.38 mmol) and aryl acetophenone (4.38 mmol) were dissolved in absolute alcohol (25 mL). Saturated ethanolic solution of KOH (0.98 g, 17.5 mmol) was added to it at 25-27 °C. Reaction mixture was stirred for 24h at ambient temperature. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (24h), the reaction mixture was poured into ice cold water with continuous stirring and neutralized to pH 7 by adding dil. HCl. The suspension formed was extracted with ethyl acetate (3x50 mL). The organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO$_4$ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound with good yield.

**1-(3-hydroxy-4-phenoxyphenyl)-3-phenylprop-2-en-1-one (15a)**

Yield= 1 g (72%); mp = 94-96 °C; R$_f$ = 0.61 (hexane: ethyl acetate = 6:4); $\lambda$max = 322.2 nm (MeOH); IR (KBr, cm$^{-1}$) = 3414 (O-H str.), 3026 (Ar-H str.), 2943, 2891 (C-H str.), 1668 (C-O str.), 1581, 1485, 1440 (Ar-C=C str.), 1255 (Asym. C-O-C str.), 1157 (Sym. C-O-C str.); $^1$HNMR (400 MHz, DMSO-$d_6$): 9.98 (s, 1H), 7.71 (d, $J = 7.6$ Hz, 1H), 7.68 (t, $J = 2.4$ Hz, 2H), 7.44 (t, $J = 2.6$ Hz, 3H), 7.36 (t, $J = 7.8$ Hz, 2H), 7.10 (t, $J = 7.4$ Hz, 1H), 7.01-6.94 (m, 3H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 117.27, 118.00, 120.51, 121.40, 121.56, 123.56, 129.32, 130.03, 130.35, 132.47, 134.71, 135.18, 144.05, 148.36, 149.50, 157.15, 188.40; LCMS (+ESI, m/z): 317.1157 (M+H)$^+$

**1-(3-hydroxy-4-phenoxyphenyl)-3-p-tolylprop-2-en-1-one (15b)**

Yield= 0.8 g (55%); mp = 152-153 °C; R$_f$ = 0.82 (hexane: ethyl acetate = 6:4); $\lambda$max = 321.8 nm (MeOH); $^1$HNMR (400 MHz, DMSO-$d_6$): 9.91 (s, 1H), 7.81 (s, 1H), 7.76 (t, $J = 7.4$ Hz, 1H), 7.70-7.67 (dd, $J = 8.4$ Hz and 2.4 Hz, 2H), 7.66 (d, $J = 2.4$ Hz, 1H), 7.38-7.34 (td, $J = 7$ Hz and 2 Hz , 2H ), 7.26 (d, $J = 8$ Hz, 2H), 7.12-7.08 (m, 1H), 7.00-6.95 (m, 3H), 2.34 (s, 3H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 117.22, 117.98, 120.52, 121.40, 121.56, 123.56, 129.32, 130.03, 130.35, 132.47, 134.84, 141.10, 144.13, 148.24, 149.44, 157.17, 188.35; LCMS (+ESI, m/z): 331.1348 (M+H)$^+$
1-(3-hydroxy-4-phenoxycyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (15c)

Yield= 0.94 g (62%); mp = 138-140 °C; Rf = 0.70 (hexane: ethyl acetate = 6:4); λmax = 352.4 nm (MeOH); $^1$HNMR (400 MHz, DMSO-d$_6$): 9.89 (s, 1H), 7.83-7.80 (dd, J= 8.8 Hz and 1.6 Hz, 2H), 7.70 (d, J= 3.6 Hz, 2H), 7.66-7.65 (m, 1H), 7.38-7.34 (m, 2H), 7.12-7.08 (m, 1H), 7.01-6.97 (m, 3H), 6.96-6.94 (m, 2H), 3.81 (s, 3H); LCMS (+ESI, m/z): 347.1256 (M+H)$^+$

3-(4-fluorophenyl)-1-(3-hydroxy-4-phenoxycyphenyl) prop-2-en-1-one (15d)

Yield= 1 g (68%); mp = 127-129 °C; Rf = 0.80 (hexane: ethyl acetate = 6:4); λmax = 310.6 nm (MeOH); $^1$HNMR (400 MHz, DMSO-d$_6$): 9.87 (d, J= 2.8 Hz, 1H), 7.95-7.92 (dd, J= 8.4 Hz and 5.6 Hz, 2H), 7.81 (d, J= 15.6 Hz, 2H), 7.71-7.66 (m, 2H), 7.36 (t, J= 8 Hz, 2H), 7.10 (t, J= 7.6 Hz, 1H), 7.00-6.95 (dd, J= 12.4 Hz and 8.4 Hz, 2H); LCMS (+ESI, m/z): 335.2502 (M+H)$^+$

3-(4-chlorophenyl)-1-(3-hydroxy-4-phenoxycyphenyl) prop-2-en-1-one (15e)

Yield= 1.13 (73%); mp = 141-143 °C; Rf = 0.81 (hexane: ethyl acetate = 6:4); λmax = 351.0708 (M+H)$^+$

3-(furan-2-yl)-1-(3-hydroxy-4-phenoxycyphenyl) prop-2-en-1-one (15f)

Yield= 0.89 g (66%); mp = 134-136 °C; Rf = 0.55 (hexane: ethyl acetate = 6:4); λmax = 307.0916 (M+H)$^+$

General method for synthesis of 1-(3-hydroxy-4-phenoxycyphenyl)-3-aryl propan-1-one (16a-f)

Compounds 16a-f were synthesized by following the method described for synthesis of compounds 2a-n.

1-(3-hydroxy-4-phenoxycyphenyl)-3-phenylpropan-1-one (16a)

Yield= 0.42 g (69%); mp = 86-88 °C; Rf = 0.67 (hexane: ethyl acetate = 6:4); λmax = 269 nm (MeOH); IR (KBr, cm$^{-1}$) = 3414 (O-H str.), 3026 (Ar-H str.), 2943, 2891 (C-H str.), 1668 (C=O str.), 1585, 1485, 1427 (Ar=C=C str.), 1246 (Asym. C-O-C str.), 1163 (Sym.C-O-C str.); $^1$HNMR (400 MHz, DMSO-d$_6$): 9.87 (s, 1H), 7.53 (d, J= 2 Hz, 1H), 7.49-7.46 (dd, J= 8.4 Hz and 2 Hz, 1H), 7.37-7.33 (m, 2H), 7.26 (d, J= 8.8 Hz, 4H), 7.18-7.15 (m, 1H), 7.11-7.07 (m,
1H), 6.95-6.92 (m, 3H), 3.29-3.26 (dd, J = 9.6 Hz and 5.66 Hz, 2H), 2.91 (t, J = 7.6 Hz, 2H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 30.07, 116.67, 117.93, 120.56, 120.93, 123.52, 126.32, 128.73, 128.84, 130.33, 133.73, 141.75, 148.14, 149.26, 157.15, 198.31; LCMS (+ ESI, m/z): 319.1235 (M+H)$^+$

1-(3-hydroxy-4-phenoxyphenyl)-3-p-tolylpropan-1-one (16b)

Yield = 0.425 (70%); mp = 118-120 °C; R$_f$ = 0.82 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 269 nm (MeOH); IR (KBr, cm$^{-1}$) = 3385 (O-H str.), 3047 (Ar-H str.), 2941, 2875 (C-H str.), 1672 (C=O str.), 1585, 1487, 1433 (Ar-C=C str.), 1166 (Sym.C-O-C str.); $^{1}$HNMR (400 MHz, DMSO-$d_6$): 9.87 (s, 1H), 7.52 (d, J = 2 Hz, 1H), 7.47-7.45 (dd, J = 8.4 Hz and 2 Hz, 1H), 7.37-7.32 (m, 2H), 7.14-7.11 (m, 2H), 7.09-7.05 (m, 3H), 6.94-6.92 (m, 3H), 3.25-3.22 (dd, J = 11.2 Hz and 7.2 Hz, 2H), 2.86 (t, J = 7.4 Hz, 2H), 2.24 (s, 3H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 21.08, 24.02, 29.68, 31.03, 35.01, 116.67, 117.93, 120.56, 120.90, 123.52, 128.63, 128.70, 129.29, 130.33, 133.75, 133.88, 135.20, 138.61, 148.12, 149.26, 157.16, 198.36; LCMS (+ ESI, m/z): 333.1393 (M+H)$^+$

1-(3-hydroxy-4-phenoxyphenyl)-3-(4-methoxyphenyl) propan-1-one (16c)

Yield = 0.42 g (69%); mp = 88-90 °C; R$_f$ = 0.78 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 270 nm (MeOH); IR (KBr, cm$^{-1}$) = 3419 (O-H str.), 3045 (Ar-H str.), 2951, 2833 (C-H str.), 1676 (C=O str.), 1587, 1517, 1429 (Ar-C=C str.), 1163 (Sym.C-O-C str.); $^{1}$HNMR (400 MHz, DMSO-$d_6$): 9.93 (s, 1H), 7.35 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 7.2 Hz, 2H), 7.11 (d, J = 7.2 Hz, 1H), 6.94 (d, J = 7.6 Hz, 4H), 6.83 (d, J = 8.4 Hz, 2H), 3.70 (s, 3H), 3.24 (t, J = 7.4 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 29.25, 55.44, 114.16, 116.67, 117.93, 120.56, 120.91, 123.52, 128.70, 129.29, 130.33, 133.75, 133.88, 135.20, 138.61, 148.12, 149.26, 157.16, 198.36; LCMS (+ ESI, m/z): 349.1346 (M+H)$^+$

3-(4-fluorophenyl)-1-(3-hydroxy-4-phenoxyphenyl) propan-1-one (16d)

Yield = 0.4 g (66%); mp = 62-64 °C; R$_f$ = 0.83 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 271.8 nm (MeOH); IR (KBr, cm$^{-1}$) = 3392 (O-H str.), 3045 (Ar-H str.), 2939, (C-H str.), 1670 (C=O str.), 1591, 1500, 1435 (Ar-C=C str.), 1253 (Asym. C-O-C str.), 1163 (Sym.C-O-C str.); $^{1}$HNMR (400 MHz, DMSO-$d_6$): 9.88 (s, 1H), 7.53 (d, J = 2 Hz, 1H), 7.47-7.46 (dd, J = 8.4 Hz and 2 Hz, 1H), 7.37-7.32 (m, 2H), 7.09 (t, J = 7.4 Hz, 1H), 6.96-6.93 (m, 3H), 3.23 (t, J = 7.2 Hz, 2H), 2.93 (t, J = 7.2 Hz, 2H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 29.21, 115.24, 115.45, 116.69,
117.93, 120.54, 120.91, 123.52, 129.76, 130.32, 130.57, 130.65, 133.71, 137.84, 137.87, 148.16, 149.27, 157.16, 159.93, 162.33, 198.24; LCMS (+ESI, m/z): 337.1142 (M+H)^+ 

3-(4-chlorophenyl)-1-(3-hydroxy-4-phenoxyphenyl) propan-1-one (16e) 

Yield = 0.396 (65%); mp = 82-84 °C; R_f = 0.85 (hexane: ethyl acetate = 6:4); λmax = 269.6 nm (MeOH); IR (KBr, cm⁻¹) = 3371 (O-H str.), 3074 (Ar-H str.), 2943, (C-H str.), 1670 (C=O str.), 1585, 1494, 1435 (Ar-C=C str.), 1253 (Asym. C-O-C str.), 1174 (Sym.C-O-C str.); ^1HNMR (400 MHz, DMSO-d_6): 9.88 (s, 1H), 7.52 (d, J= 2.4 Hz, 1H), 7.48-7.45 (dd, J= 8.4 Hz and 2 Hz, 1H), 7.40 (s, 1H), 7.35 (t, J= 8 Hz, 2H), 7.30-7.27 (m, 3H), 7.09 (t, J= 7.4 Hz, 1H), 6.94-6.92 (m, 3H), 3.28 (t, J= 6.4 Hz, 2H), 2.90 (t, J= 7.2 Hz, 2H); LCMS (+ESI, m/z): 353.0841 (M+H)^+ 

3-(furan-2-yl)-1-(3-hydroxy-4-phenoxyphenyl) propan-1-one (16f) 

Yield= 0.378 g (63%); mp = 81-83 °C; R_f = 0.6 (hexane: ethyl acetate = 6:4); λmax = 269.8 nm (MeOH); IR (KBr, cm⁻¹) = 3388 (O-H str.), 3074 (Ar-H str.), 2912 (C-H str.), 1670 (C=O str.), 1587, 1496, 1433 (Ar-C=C str.), 1253 (Asym. C-O-C str.), 1163 (Sym.C-O-C str.); ^1HNMR (400 MHz, DMSO-d_6): 9.89 (s, 1H), 7.54 (d, J= 2 Hz, 1H), 7.50-7.48 (dd, J= 8.4 Hz and 2 Hz, 2H), 7.37-7.33 (dt, J= 7.2 Hz and 2 Hz, 2H), 7.09 (t, J= 7.4 Hz, 1H), 6.96-6.93 (m, 3H), 3.23 (t, J= 7.2 Hz, 2H), 2.93 (t, J= 7.2 Hz, 2H); ^13CNMR (100.64 MHz, DMSO-d_6): 22.50, 36.37, 105.67, 110.86, 116.67, 117.95, 120.55, 120.94, 123.54, 130.34, 133.59, 141.72, 148.23, 149.27, 155.15, 157.14, 197.70; LCMS (+ESI, m/z): 309.103 (M+H)^+ 

General method for synthesis of 5-(1-hydroxy-3-phenylpropyl)-2-phenoxyphenol (17a-f) 

To the solution of compounds 1-(3-hydroxy-4-phenoxyphenyl)-3-aryl propan-1-one (16a-f) (0.75 mmol) in methanol (4 mL) and THF (2 mL), NaBH₄ (3.0 mmol) dissolved in aq. NaOH (4N, 1mL) was added in three portions and stirred at ambient temperature. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4) as the mobile phase. After the completion of reaction (2h), the reaction mixture quenched with sat. NH₄Cl solution (5 mL) and evaporated under vacuum to remove the volatiles. The residue obtained was added into ice cold water, neutralized to pH 7 (by adding dil. HCl) and extracted with ethyl acetate (3x25 mL). The organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO₄ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compounds.
1-(3-hydroxy-4-phenoxyphenyl)-3-phenylpropan-1-ol (17a)

Yield = 0.215 (89%); mp = 76-78 °C; Rf = 0.54 (hexane: ethyl acetate = 6:4); \( \lambda_{\text{max}} \) = 276.2 nm (MeOH); IR (KBr, cm\(^{-1} \)) = 3525, 3265 (O-H str.), 3049 (Ar-H str.), 2943, 2912 (C-H str.), 1598, 1487, 1436 (Ar-C=C str.), 1236 (Asym. C-O-C str.), 1163 (Sym.C-O-C str.); \(^1\)HNMR (400 MHz, DMSO-\( d_6 \)): 9.38 (s, 1H), 7.29-7.24 (m, 4H), 7.19-7.13 (m, 3H), 6.99 (d, \( J = 7.2 \) Hz, 1H), 6.95 (d, \( J = 2 \) Hz, 1H), 6.88 (d, \( J = 8 \) Hz, 1H), 6.81 (d, \( J = 8.4 \) Hz, 2H), 6.76-6.73 (dd, \( J = 8 \) Hz and 1.6 Hz, 1H), 5.21 (d, \( J = 4.4 \) Hz, 1H), 4.46-4.42 (dd, \( J = 12 \) Hz and 5.6 Hz, 1H), 2.68-2.61 (m, 2H), 1.88-1.85 (dd, \( J = 12 \) Hz and 5.6 Hz, 2H); \(^{13}\)CNMR (100.64 MHz, DMSO-\( d_6 \)): 32.04, 41.50, 71.71, 115.15, 116.42, 117.50, 121.98, 122.16, 126.09, 128.74, 129.97, 141.38, 142.59, 144.15, 149.46, 158.66; LCMS (-ESI, m/z): 319.103 (M-H)

1-(3-hydroxy-4-phenoxyphenyl)-3-p-tolylpropan-1-ol (17b)

Yield = 0.224 g (93%); mp = 69-71 °C; Rf = 0.56 (hexane: ethyl acetate = 6:4); \( \lambda_{\text{max}} \) = 274.2 nm (MeOH); IR (KBr, cm\(^{-1} \)) = 3479, 3375 (O-H str.), 3064 (Ar-H str.), 2943 (C-H str.), 1591, 1496, 1446 (Ar-C=C str.), 1217 (Asym. C-O-C str.), 1163 (Sym.C-O-C str.); \(^1\)HNMR (400 MHz, DMSO-\( d_6 \)): 9.37 (s, 1H), 7.71 (d, \( J = 8 \) Hz, 1H), 7.49 (s, 1H), 7.38-7.34 (dt, \( J = 7 \) Hz and 2 Hz, 2H), 7.29 (t, \( J = 7.8 \) Hz, 1H), 7.14-7.10 (m, 1H), 7.08 (d, \( J = 4.8 \) Hz, 1H), 7.03 (t, \( J = 4 \) Hz, 1H), 6.98-6.95 (td, \( J = 7.6 \) Hz and 1.2 Hz, 2H), 6.84-6.81 (m, 2H), 4.03-4.00 (dd, \( J = 9.6 \) Hz and 4.8 Hz, 1H), 3.68-3.61 (dd, \( J = 17.6 \) Hz and 10 Hz, 1H), 2.98 (t, \( J = 2 \) Hz, 1H), 2.49 (t, \( J = 1.8 \) Hz, 1H), 2.67-2.56 (m, 2H), 2.29-2.28 (m, 6H); \(^{13}\)CNMR (100.64 MHz, DMSO-\( d_6 \)): 31.11, 41.73, 55.41, 71.68, 114.17, 115.15, 116.39, 117.56, 121.97, 122.22, 128.59, 129.33, 129.99, 134.96, 139.37, 141.39, 144.04, 149.39, 158.60; LCMS (-ESI, m/z): 333.1639 (M-H)

1-(3-hydroxy-4-phenoxyphenyl)-3-(4-methoxyphenyl) propan-1-ol (17c)

Yield = 0.2 g (83%); mp = 54-56 °C; Rf = 0.53 (hexane: ethyl acetate = 6:4); \( \lambda_{\text{max}} \) = 272 nm (MeOH); IR (KBr, cm\(^{-1} \)) = 3479, 3375 (O-H str.), 3064 (Ar-H str.), 2943 (C-H str.), 1600, 1502, 1452(Ar-C=C str.), 1217 (Asym. C-O-C str.), 1165 (Sym.C-O-C str.); \(^{13}\)CNMR (100.64 MHz, DMSO-\( d_6 \)): 31.11, 41.73, 55.41, 71.68, 114.17, 115.15, 116.42, 117.50, 121.96, 122.16, 129.63, 129.97, 134.40, 141.36, 144.21, 149.46, 157.78, 158.67; LCMS (-ESI, m/z): 349.1821 (M-H)

1-(3-hydroxy-4-phenoxyphenyl)-3-(4-fluorophenyl) propan-1-ol (17d)

Yield = 0.22 g (91%); mp = 62-64 °C; Rf = 0.60 (hexane: ethyl acetate = 6:4); \( \lambda_{\text{max}} \) = 272 nm (MeOH); \(^1\)HNMR (400 MHz, DMSO-\( d_6 \)): 9.38 (s, 1H), 7.27 (t, \( J = 7.6 \) Hz, 2H), 7.23-7.19 (dd,
Chapter 3

Materials and Method

Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal.

\[ J = 8 \text{ Hz and } 6 \text{ Hz, } 2H \], 7.06 (t, \( J = 8.6 \text{ Hz, } 2H \)), 6.99 (d, \( J = 7.2 \text{ Hz, } 1H \)), 6.95 (s, \( 1H \)), 6.88 (d, \( J = 8.4 \text{ Hz, } 1H \)), 6.80 (d, \( J = 8 \text{ Hz, } 2H \)), 6.75-6.73 (dd, \( J = 8 \text{ Hz and } 1.6 \text{ Hz, } 1H \)), 5.21-5.16 (dd, \( J = 16 \text{ Hz and } 4.4 \text{ Hz, } 1H \)), 4.45-4.41 (dd, \( J = 10.4 \text{ Hz and } 5.2 \text{ Hz, } 1H \)), 2.69-2.48 (m, \( 2H \)), 1.87-1.81 (dd, \( J = 15.2 \text{ Hz and } 8 \text{ Hz, } 2H \)); \(^{13}\)CNMR (100.64 MHz, DMSO-\( d_6 \)): 31.20, 41.52, 71.63, 114.67, 115.15, 115.26, 116.43, 117.48, 121.97, 122.16, 129.62, 129.96, 130.38, 134.28, 138.67, 141.40, 144.23, 149.48, 157.04, 158.66, 159.79, 162.19; LCMS (- ESI, m/z): 337.1351 (M-H)⁻

3-(4-chlorophenyl)-1-(3-hydroxy-4-phenoxypyphenyl) propan-1-ol (17e)

Yield= 0.218 g (90%); mp = 78-80 °C; \( R_f = 0.62 \) (hexane: ethyl acetate: 6:4); \( \lambda_{\text{max}} = 276.2 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3603, 3550 (O-H str.), 3020 (Ar-H str.), 2943 (C-H str.), 1593, 1496, 1450 (Ar=C=C str.), 1215 (Asym. C-O-C str.), 1162 (Sym.C-O-C str.); \(^{1}\)HNMR (400 MHz, DMSO-\( d_6 \)): 9.39 (d, \( J = 4 \text{ Hz, } 1H \)), 7.31-7.25 (m, \( 2H \)), 7.21 (d, \( J = 8 \text{ Hz, } 1H \)), 6.95 (s, \( 1H \)), 6.88 (d, \( J = 8.4 \text{ Hz, } 1H \)), 6.95 (s, \( 1H \)), 6.80 (d, \( J = 8 \text{ Hz, } 1H \)), 6.75-6.73 (dd, \( J = 8 \text{ Hz and } 2 \text{ Hz, } 1H \)), 5.21(d, \( J = 4.4 \text{ Hz, } 1H \)), 4.43 (d, \( J = 6 \text{ Hz, } 1H \)), 2.67-2.56 (m, \( 2H \)), 1.87-1.81 (m, \( 2H \)); \(^{13}\)CNMR (100.64 MHz, DMSO-\( d_6 \)): 31.34, 71.58, 115.12, 117.47, 121.97, 122.17, 128.64, 129.97, 130.63, 141.40, 141.60, 144.04, 149.47, 158.64; LCMS (- ESI, m/z): 353.1117 (M-H)⁻

3-(furan-2-yl)-1-(3-hydroxy-4-phenoxypyphenyl) propan-1-ol (17f)

Yield= 0.198 g (82%); mp = 60-62 °C; \( R_f = 0.44 \) (hexane: ethyl acetate: 6:4); \( \lambda_{\text{max}} = 276.4 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3550, 3452 (O-H str.), 3018 (Ar-H str.), 2927, 2864 (C-H str.), 1730 (-C-O str.), 1593, 1496, 1458 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1153 (Sym.C-O-C str.); \(^{1}\)HNMR (400 MHz, DMSO-\( d_6 \)): 9.39 (d, \( J = 12.4 \text{ Hz, } 1H \)), 7.47 (s, \( 1/2H \)), 7.27 (t, \( J = 7.6 \text{ Hz, } 1H \)), 6.98 (t, \( J = 7.2 \text{ Hz, } 1H \)), 6.87 (t, \( J = 7.2 \text{ Hz, } 1H \)), 6.80 (t, \( J = 7.6 \text{ Hz, } 2H \)), 6.75 (d, \( J = 8 \text{ Hz, } 1H \)), 6.32 (d, \( J = 1.6 \text{ Hz, } 1/2H \)), 6.07 (d, \( J = 2.4 \text{ Hz, } 1/2H \)), 5.24 (d, \( J = 4.4 \text{ Hz, } 1/2H \)), 5.08 (d, \( J = 4 \text{ Hz, } 1/2H \)), 4.63 (t, \( J = 5.2 \text{ Hz, } 1/2H \)), 4.48 (d, \( J = 4.8 \text{ Hz, } 1/2H \)), 2.65-2.60 (dd, \( J = 14.4 \text{ Hz and } 7.6 \text{ Hz, } 1H \)), 1.89-1.83 (dd, \( J = 14.8 \text{ Hz and } 8 \text{ Hz, } 1H \)), 1.29 (d, \( J = 6 \text{ Hz, } 2H \)); \(^{13}\)CNMR (100.64 MHz, DMSO-\( d_6 \)): 37.92, 71.50, 105.36, 110.78, 114.71, 115.11, 116.43, 117.01, 117.46, 121.98, 122.13, 122.18, 129.96, 141.24, 141.45, 143.83, 145.39, 149.45, 149.48, 155.95, 158.64; LCMS (-ESI, m/z): 309.1348 (M-H)⁻
General method for synthesis of 4-(3-hydroxy-4-phenoxyphenyl)-4-oxo-2-aryl butanenitrile (18a-c).

To a solution of chalcone (15a-c) (1.10 mmol) in acetone (15 mL) and water (1.5 mL), were added cyanohydrin acetone (2.20 mmol), TBMAH (3.30 mmol) and K$_2$CO$_3$ (6.60 mmol). The resulting reaction mixture was refluxed at 57-58 °C for 14h. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4) as the mobile phase. After the completion of reaction (14h), solvent from the reaction mixture was evaporated under vacuum. The residue obtained was added into ice cold water and extracted with ethyl acetate (3x25 mL). The organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO$_4$ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compounds.

4-(3-hydroxy-4-phenoxyphenyl)-4-oxo-2-phenyl butanenitrile (18a)

Yield= 0.3 g (80%); mp = 81-82 °C; R$_f$ = 0.28 (hexane: ethyl acetate = 6:4); λmax = 275.4 nm (MeOH); $^1$HNMR (400 MHz, DMSO-d$_6$): 9.94 (s, 1H), 7.54-7.47 (m, 4H), 7.42-7.33 (m, 5H), 7.20 (d, J= 8 Hz, 1H), 7.10 (t, J= 7.4 Hz, 1H), 6.94 (d, J= 8 Hz, 3H), 4.59-4.49 (m, 1H), 3.92-3.81 (m, 1H), 3.65-3.56 (m, 1H); $^{13}$CNMR (100.64 MHz, DMSO-d$_6$): 21.10, 31.29, 31.69, 43.10, 116.70, 118.09, 120.39, 121.27, 121.83, 123.68, 128.07, 128.22, 128.42, 129.37, 129.88, 130.37, 132.76, 132.78, 133.26, 136.29, 137.74, 143.76, 149.27, 157.00, 195.14; LCMS (+ESI, m/z): 344.1294 (M+H)$^+$

4-(3-hydroxy-4-phenoxyphenyl)-4-oxo-2-p-tolylbutanenitrile (18b)

Yield= 0.33 g (83%); mp = 60-62 °C; R$_f$ = 0.32 (hexane: ethyl acetate = 6:4); λmax = 274.8 nm (MeOH); $^1$HNMR (400 MHz, DMSO-d$_6$): 9.97 (s, 1H), 7.52 (d, J= 2.4 Hz, 1H), 7.49-7.46 (dd, J= 8.4 Hz and 2.4 Hz, 1H), 7.38-7.33 (m, 4H), 7.19 (d, J= 7.6 Hz, 2H), 7.12-7.07 (tt, J=...
7.4 Hz and 1 Hz, 1H), 6.95-6.92 (m, 3H), 4.52-4.49 (dd, J= 8.8 Hz and 5.2 Hz, 1H), 3.87-3.80 (dd, , J= 18.8 Hz and 9.2 Hz, 1H), 3.61-3.55 (dd, J= 18 Hz and 5.6 Hz, 1H), 2.28 (s, 3H); LCMS (+ESI, m/z): 358.1448 (M+H)^+

4-(3-hydroxy-4-phenoxyphenyl)-2-(4-methoxyphenyl)-4-oxobutanenitrile (18c)

Yield= 0.305 g (81%); mp = 52-54 °C; R_f = 0.31 (hexane: ethyl acetate = 6:4); λmax = 274.8 nm (MeOH); LCMS (+ESI, m/z): 374.1396 (M+H)^+

General method for synthesis of 4-(3-hydroxy-4-phenoxyphenyl)-4-oxo-2-aryl butanamide (19a-c).

To a solution of compounds 18a-c (0.728 mmol) in DMSO (8 mL), anh. K_2CO_3 (2.912 mmol) was added followed by dropwise addition of hydrogen peroxide (1.456 mmol) at 5-10 °C. The resulting reaction mixture was stirred at 25-27 °C for 3h. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4) as the mobile phase. After the completion of reaction (2h), reaction mixture was poured into ice cold water and the precipitate obtained was extracted with ethyl acetate (3x25 mL). The organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO_4 and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compounds.

4-(3-hydroxy-4-phenoxyphenyl)-4-oxo-2-phenylbutanamide (19a)

Yield = 0.215 g (82%); mp = 143-145 °C; R_f = 0.09 (hexane: ethyl acetate = 5:5); λmax = 269.4 nm (MeOH); IR (KBr, cm^{-1}) = 3390 (O-H str.), 3334, 3320 (N-H str.), 3047 (Ar-H str.), 2926 (C-H str.), 1670 (C=O str.), 1583, 1494, 1421 (Ar-C=C str.), 1271 (Asym. C-O-C str.), 1192 (Sym.C-O-C str.); ^1HNMR (400 MHz, DMSO-d_6): 9.87 (s, 1H), 7.51 (t, J= 5 Hz, 1H), 7.50-7.46 (m, 2H), 7.43 (s, 1H), 7.38-7.34 (m, 3H), 7.33-7.30 (m, 2H), 7.28-7.20 (m, 1H), 7.09 (t, J= 7.2 Hz, 1H), 6.95-6.92 (dd, J= 8.4 Hz and 5.2 Hz, 3H), 6.80-6.76 (m, 1H), 4.07-4.04 (dd, J= 10 Hz and 4 Hz, 1H), 3.81-3.74 (m, 1H), 3.13-3.07 (dd, J= 18 Hz and 4.4 Hz, 1H); ^13CNMR (100.64 MHz, DMSO-d_6): 41.89, 46.73, 116.65, 117.88, 120.62, 120.90, 123.49, 127.14, 128.05, 128.20, 128.20, 129.30, 130.33, 133.75, 141.13, 148.08, 149.25, 157.20, 174.41, 197.28; LCMS (+ESI, m/z): 362.1562 (M+H)^+

4-(3-hydroxy-4-phenoxyphenyl)-4-oxo-2-p-tolylbutanamide (19b)

Yield = 0.235 g (86%); mp = 135-137 °C; R_f = 0.12 (hexane: ethyl acetate = 5:5); λmax = 269.6 nm (MeOH); IR (KBr, cm^{-1}) = 3437 (O-H str.), 3332, 3316 (N-H str.), 3047 (Ar-H str.), 2920 (C-H str.), 1680 (C=O str.), 1583, 1500, 1436 (Ar-C=C str.), 1269 (Asym. C-O-C str.),
1176 (Sym. C-O-C str.); $^1$HNMR (400 MHz, DMSO-$d_6$): 9.87 (s, 1H), 7.52 (d, $J= 2$ Hz, 1H), 7.48-7.46 (dd, $J= 8.4$ Hz and 2 Hz, 1H), 7.43 (s, 1H), 7.36-7.32 (m, 2H), 7.24 (d, $J= 8$ Hz, 2H), 7.10 (d, $J= 7.2$ Hz, 1H), 6.95-6.92 (m, 2H), 6.76 (s, 1H), 4.02-3.99 (dd, $J= 10$ Hz and 4.4 Hz, 1H), 3.78-3.71 (dd, $J= 17.6$ Hz and 11.2 Hz, 1H), 3.09-3.03 (dd, $J= 17.6$ Hz and 4.8 Hz, 1H), 2.25 (s, 3H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 21.09, 41.89, 42.57, 46.32, 116.64, 117.88, 120.63, 120.89, 123.49, 128.05, 129.31, 130.33, 133.77, 136.17, 138.11, 148.07, 149.24, 157.19, 174.59, 197.34; LCMS (+ESI, m/z): 376.1511 (M+H)$^+$

4-(3-hydroxy-4-phenoxyphenyl)-2-(4-methoxyphenyl)-4-oxobutanamide (19c)

Yield = 0.23 g (81%); mp = 123-125 °C; $R_f$ = 0.11 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 270.6 nm (MeOH); IR (KBr, cm$^{-1}$) = 3471 (O-H str.), 3398, 3360 (N-H str.), 3045 (Ar-H str.), 2930 (C-H str.), 1678 (C=O str.), 1583, 1500, 1436 (Ar-C=C str.), 1269 (Asym. C-O-C str.), 1147 (Sym. C-O-C str.); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 41.99, 42.58, 45.86, 55.52, 114.18, 116.66, 117.88, 120.63, 120.89, 123.49, 129.17, 130.32, 133.09, 133.79, 148.07, 149.24, 157.20, 158.56, 174.78, 197.39; LCMS (+ESI, m/z): 392.135 (M+H)$^+$

Synthesis of methyl 4-hydroxy-3-methoxybenzoate (20)

To a solution of vanillyl acid (2.5 g, 14.88 mmol) in methanol (25 mL), conc. H$_2$SO$_4$ (0.25 mL) was added and refluxed at 65-67 °C for 4h. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the completion of reaction (4h), the reaction mixture was evaporated and the residue obtained was added to ice cold water (50 mL). Then it was extracted with ethyl acetate (3x50 mL) and the organic layers were separated, washed with water, brine, dried over anhydrous MgSO$_4$ and evaporated under vacuum. The crude compound obtained was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compound as pale yellow crystalline solid.

Yield = 2.6 g (96%); mp = 64-65 °C; $R_f$ = 0.58 (hexane: ethyl acetate = 8:2); $\lambda_{max}$ = 256 nm (MeOH).

Synthesis of methyl 3-methoxy-4-phenoxybenzoate (21)

To the stirred solution of methyl 4-hydroxy-3-methoxybenzoate (2 g, 10.98 mmol) in anhydrous dichloromethane (60 mL), activated molecular sieves (4A°, 1 g), phenylboronic acid (2 g, 16.48 mmol), copper (II) acetate (3 g, 16.48 mmol) and anhydrous pyridine (3.47 g, 43.92 mmol, 3.55 mL) were added successively. The resulting suspension was stirred at 25-27 °C for 72h. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2).
After the completion of reaction (48 h), the reaction mixture was diluted with dichloromethane (30 mL) and filtered under vacuum. The filtrate was washed with dilute aqueous hydrochloric acid (2 M, 40 mL), followed by water (100 mL), dried over anhydrous MgSO₄ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compound as white crystalline solid.

Yield = 2.2 g (78%); mp = 68-70 °C; Rf = 0.86 (hexane: ethyl acetate = 8:2); λmax = 257.8 nm (MeOH); IR (KBr, cm⁻¹) = 3053 (Ar-H str.), 2939, 2873 (C-H str.), 1720 (C=O str.), 1587, 1496, 1415 (Ar-C=C str.), 1294 (Asym. C-O-C str.), 1184 (Sym. C-O-C str.).

**Synthesis of 3-methoxy-4-phenoxybenzoic acid (22)**

To the solution of methyl 4-hydroxy-3-methoxybenzoate (2.1 g, 8.139 mmol) in methanol (15 mL) and water (15 mL), KOH (1.82 g, 32.55 mmol) was added and refluxed at 65-67 °C for
1h. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (8h), the reaction mixture was evaporated under vacuum to remove excess methanol. The residue obtained was added to ice cold water (75 mL) and acidified to pH 3–4 using dil. HCl. The precipitate obtained was filtered under vacuum, washed twice with cold water and dried. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compound as white crystalline solid.

Yield = 1.86 g (94%); mp = 178-180 °C; Rf = 0.25 (hexane: ethyl acetate = 6:4); λmax = 249.6 nm (MeOH); 1H NMR (400 MHz, DMSO-d6): 12.91 (s, 1H), 7.72 (d, J = 1.6 Hz, 1H), 7.56-7.53 (dd, J = 8 Hz and 1.6 Hz, 1H), 7.37-7.33 (m, 2H), 7.12-7.08 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.94-6.92 (m, 2H), 3.81 (s, 3H); 13C NMR (100.64 MHz, DMSO-d6): 56.20, 114.05, 117.96, 120.09, 123.32, 123.74, 127.58, 130.44, 148.85, 150.94, 156.99, 167.24; LCMS (+ESI, m/z): 245.0692 (M+H)+

Synthesis of 3-hydroxy-4-phenoxybenzoic acid (23)

To the stirred solution of 3-methoxy-4-phenoxybenzoic acid (22) (1.7 g, 6.96 mmol) in glacial AcOH (20 mL), HBr (48%v/v, 10 mL) was added. Resulting reaction mixture was refluxed at 112-115 °C for 14 h. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (8h), reaction mixture was cooled to room temperature and poured in to ice cold water (50 mL) with continuous stirring. The precipitate obtained was washed with water and dried in a desiccator. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound as off white crystalline solid.

Yield = 1.2 g (75%); mp = 142-144 °C; Rf = 0.14 (hexane: ethyl acetate = 6:4); λmax = 253.4 nm (MeOH); IR (KBr, cm−1) = 3267 (O–H str.), 3078 (Ar–H str.), 1697 (C=O str.), 1587, 1489, 1436 (Ar–C=C str.), 1209 (Asym. C-O-C str.), 1130 (Sym. C-O-C str.); 1H NMR (400 MHz, DMSO-d6): 12.737 (s, 1H), 9.86 (s, 1H), 7.53 (d, J = 2 Hz, 2H), 7.40-7.37 (dd, J= 8 Hz and 2 Hz, 1H), 7.36-7.32 (m, 2H), 7.10-7.06 (m, 1H), 6.94-6.91 (m, 3H); 13C NMR (100.64 MHz, DMSO-d6): 117.76, 118.39, 120.76, 121.75, 123.37, 127.63, 130.30, 147.64, 149.11, 157.29, 167.31; LCMS (+ESI, m/z): 231.0575 (M+H)+

Synthesis of alkyl 3-hydroxy-4-phenoxybenzoate (24a-b).

To the solution of 3-hydroxy-4-phenoxybenzoic acid (23) (1.8 mmol) in methanol (for 24a)/ethanol (for 24b) (15 mL), conc. H2SO4 (0.15 mL) was added and refluxed for 4h.
Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the completion of reaction (4h), the reaction mixture was evaporated and the residue obtained was added to ice cold water (50 mL). The precipitate obtained was filtered under vacuum, washed twice with cold water and dried. Crude compound was recrystallized in abs. alcohol to afford the desired compound as off white crystalline solid.

**Methyl 3-hydroxy-4-phenoxybenzoate (24a)**

Yield = 93%; mp = 61-63 °C; Rf = 0.80 (hexane: ethyl acetate = 6:4); λmax = 256.8 nm (MeOH); IR (KBr, cm⁻¹) = 3369 (O-H str.), 3078 (Ar-H str.), 2954 (C-H str.), 1695 (C=O str.), 1589, 1496, 1415 (Ar=C=C str.), 1041 (Sym. C-O-C str.); ¹HNMR (400 MHz, DMSO-d₆): 9.95 (s, 1H), 7.55 (s, 1H), 7.42-7.39 (dd, J= 8.4 Hz and 1.4 Hz, 1H), 7.35 (t, J= 7.6 Hz, 2H), 7.09 (t, J= 7.4 Hz, 1H), 6.96-6.92 (dd, J= 8.4 Hz and 4.8 Hz, 3H), 3.81 (s, 3H); ¹³CNMR (100.64 MHz, DMSO-d₆): 52.52, 117.96, 118.14, 120.68, 121.61, 123.55, 126.30, 130.34, 148.16, 149.20, 157.09, 166.23; LCMS (+ESI, m/z): 245.0787 (M+H)⁺

**Ethyl 3-hydroxy-phenoxybenzoate (24b)**

Yield = 90%; mp = 66-68 °C; Rf = 0.95 (hexane: ethyl acetate = 6:4); λmax = 257.6 nm (MeOH); IR (KBr, cm⁻¹) = 3454 (O-H str.), 3057 (Ar-H str.), 2968 (C-H str.), 1720 (C=O str.), 1558, 1481, 1438 (Ar=C=C str.), 1251 (Asym. C-O-C str.), 1147 (Sym. C-O-C str.); ¹³CNMR (100.64 MHz, DMSO-d₆): 14.68, 56.27, 61.26, 113.81, 118.06, 120.07, 123.21, 123.86, 126.59, 130.47, 149.23, 151.02, 156.85, 165.66; LCMS (+ESI, m/z): 256.2636 (M+H)⁺

**Synthesis of 3-hydroxy-4-phenoxybenzohydrazide (25)**

Hydrazine hydrate (0.065 g, 1.625 mmol, 0.063 mL) was added to a solution of ethyl 3-hydroxy-4-phenoxybenzoate (24b) (0.2 g, 0.774 mmol) in abs. alcohol (20 mL) and refluxed at 80-82 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (2h), the reaction mixture was evaporated and the residue obtained was recrystallized using abs. alcohol to afford the desired compound as off white crystalline solid.

Yield = 1.6 g (85%); mp = 171-172 °C; Rf = 0.04 (hexane: ethyl acetate = 6:4); λmax = 254 nm (MeOH); IR (KBr, cm⁻¹) = 3284 (O-H str.), 3051 (Ar-H str.), 1627 (C=O str.), 1589, 1514, 1435 (Ar=C=C str.), 1257 (Asym. C-O-C str.), 1145 (Sym. C-O-C str.); ¹HNMR (400 MHz, DMSO-d₆): 9.72 (s, 1H), 9.62 (s, 1H), 7.42 (s, 1H), 7.32 (t, J= 8 Hz, 2H), 7.26 (d, J= 8.4 Hz, 1H), 7.05 (t, J= 7.2 Hz, 1H), 6.93-6.87 (m, 2H), 6.83-6.81 (dd, J= 8.4 Hz and 2 Hz, 1H), 4.43 (s, 2H); LCMS (+ESI, m/z): 245.0927 (M+H)⁺
Synthesis of 5-(hydroxymethyl)-2-phenoxyphenol (26)

To the solution of methyl 3-hydroxy-4-phenoxybenzoate (24a, 0.2 g, 0.818 mmol) in methanol (8 mL), NaBH₄ (0.093 g, 2.454 mmol) was added and stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (1h), the reaction mixture was quenched by adding aq. NH₄Cl and evaporated to remove excess methanol. The residue obtained was added to ice cold water (25 mL). The precipitate obtained was filtered under vacuum, washed twice with cold water and dried to afford the target compound as pale yellow solid. Compound was further purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to obtain the desired compound as white crystalline solid.

Yield = 0.158 g (89%); mp = 90-92 °C; Rf = 0.38 (hexane: ethyl acetate = 6:4); λmax = 276.4 nm (MeOH); IR (KBr, cm⁻¹) = 3437 (O-H str.), 3045 (Ar-H str.), 2812 (C-H str.), 1591, 1494, 1415 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1134 (Sym. C-O-C str.); LCMS (+ESI, m/z): 215.0738 (M-H)

Synthesis of 3-hydroxy-4-phenoxybenzamide (27)

To the solution of methyl 3-hydroxy-4-phenoxybenzoate (24a, 0.2 g, 0.818 mmol) in methanol (15 mL), NH₃ (g) was purged at 0 °C for 1h. Then the reaction was kept aside at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (14h), the reaction mixture was evaporated to remove excess methanol. The residue obtained was added to ice cold water (50 mL). The precipitate obtained was filtered under vacuum, washed twice with cold water and dried in a desiccator. Compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (5:5) as the mobile phase to obtain the desired compound as off white crystalline solid.

Yield = 0.142 g (76%); mp = 168-170 °C; Rf =0.07 (hexane: ethyl acetate = 6:4); λmax = 252.6 nm (MeOH); ¹HNMR (400 MHz, DMSO-d₆): 9.70 (s, 1H), 7.82 (s, 1H), 7.46 (d, J= 2 Hz, 1H), 7.34-7.30 (m, 3H), 7.21 (s, 1H), 7.05 (t, J= 7.4 Hz, 1H), 6.92 (d, J= 8.4 Hz, 1H), 6.88 (d, J= 7.6 Hz, 2H); LCMS (+ESI, m/z): 230.0724 (M+H)+

General method for synthesis of amide derivatives of 3-hydroxy-4-phenoxybenzoic acid (28a-i).

Amine (1.08 mmol) was added to a mixture of 3-hydroxy-4-phenoxybenzoic acid (23) (0.25 g, 1.08 mmol), dichloromethane (10 mL), HOBT. H₂O (0.25 g, 1.63 mmol), EDC.HCl (0.25 g 1.30 mmol), triethyl amine (0.22 g, 2.17 mmol, 0.305 mL) and stirred at 25-27 °C. Progress of
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the reaction was monitored by TLC, using hexane: ethyl acetate (6:4) as the mobile phase. After the completion of reaction (30 min.), the reaction mixture quenched with water and the organic layer was separated, diluted with dichloromethane (10 mL), washed with water, brine, dried over anhydrous MgSO$_4$ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound.

3-hydroxy-N, N-dimethyl-4-phenoxybenzamide (28a)

Yield = 62%; mp = 158-160 °C; R$_f$ = 0.38 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 285.2 nm (MeOH); IR (KBr, cm$^{-1}$) = 3267 (O-H str.), 3051 (Ar-H str.), 2931 (C-H str.), 1581, 1485, 1402 (Ar-C=C str.), 1220 (Asym. C-O-C str.), 1128 (Sym. C-O-C str.); $^1$HNMR (400 MHz, DMSO-d$_6$): 9.76 (s, 1H), 7.34-7.30 (dt, $J$ = 7 Hz and 2 Hz, 2H), 7.06-7.02 (m, 1H), 6.96 (d, $J$ = 2 Hz, 1H), 6.94 (d, $J$ = 8 Hz, 1H), 6.90-6.87 (m, 2H), 6.83-6.81 (dd, $J$ = 8.4 Hz and 2 Hz, 1H), 2.94 (s, 6H); LCMS (+ESI, m/z): 258.1092 (M+H)$^+$

(3-hydroxy-4-phenoxyphenyl) (piperidin-1-yl) methanone (28b)

Yield = 58%; mp = 148-150 °C; R$_f$ = 0.25 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 268.4 nm (MeOH); IR (KBr, cm$^{-1}$) = 3224 (O-H str.), 3043 (Ar-H str.), 2943 (C-H str.), 1676 (C=O str.), 1591, 1469, 1419 (Ar-C=C str.), 1234 (Asym. C-O-C str.), 1159 (Sym. C-O-C str.); LCMS (+ESI, m/z): 266.2399 (M+H)$^+$

(3-hydroxy-4-phenoxyphenyl)(4-(trifluoromethyl) piperidin-1-yl) methanone (28c)

Yield = 65%; mp = 156-158 °C; R$_f$ = 0.34 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 268.2 nm (MeOH); IR (KBr, cm$^{-1}$) = 3305 (O-H str.), 3045 (Ar-H str.), 1645 (C=O str.), 1591, 1481, 1413 (Ar-C=C str.), 1217 (Asym. C-O-C str.), 1188 (Sym. C-O-C str.); $^1$HNMR (400 MHz, DMSO-d$_6$): 9.79 (s, 1H), 7.32 (t, $J$ = 8 Hz, 2H), 7.04 (t, $J$ = 7.4 Hz, 1H), 7.32 (t, $J$ = 2.4 Hz, 1H), 6.94 (s, 1H), 6.89 (t, $J$ = 7.6 Hz, 2H), 6.84-6.82 (dd, $J$ = 8 Hz and 2 Hz, 1H), 4.47 (s, 1H), 3.92 (s, 1H), 3.1-2.8 (m, 2H), 2.63 (d, $J$ = 4.4 Hz, 1H), 1.85 (d, $J$ = 11.2 Hz, 2H), 1.44-1.33 (m, 2H); LCMS (+ESI, m/z): 339.2022 (M+H)$^+$

tert-Butyl 4-(3-hydroxy-4-phenoxybenzoyl) piperazine-1-carboxylate (28d)

Yield = 63%; mp = 176-178 °C; R$_f$ = 0.2 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 286 nm (MeOH); IR (KBr, cm$^{-1}$) = 3414 (O-H str.), 3007 (Ar-H str.), 1689, 1629 (C=O str.), 1581, 1462, 1436 (Ar-C=C str.), 1213 (Asym. C-O-C str.), 1168 (Sym. C-O-C str.); LCMS (+ESI, m/z): 399.1024 (M+H)$^+$
(3-hydroxy-4-phenoxyphenyl)(4-(2-hydroxyethyl) piperazin-1-yl) methanone (28e)

Yield = 60%; mp = 104-106 °C; Rf = 0.096 (hexane: ethyl acetate = 6:4); λmax = 292.2 nm (MeOH); IR (KBr, cm⁻¹) = 3479 (O-H str.), 3084 (Ar-H str.), 2939 (C-H str.), 1635 (C=O str.), 1587, 1481, 141 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1141 (Sym. C-O-C str.); ¹HNMR (400 MHz, DMSO-d₆): 9.78 (s, 1H), 7.33-7.29 (m, 2H), 7.04 (t, J = 7.2 Hz, 1H), 6.95 (t, J = 1.8 Hz, 1H), 6.93 (s, 1H), 6.88-6.72 (dd, J = 2 Hz and 1.2 Hz, 2H), 6.81-6.78 (dd, J = 8 Hz and 2 Hz, 1H), 4.40 (t, J = 5.2 Hz, 1H), 3.52-3.47 (m, 4H), 3.52-2 (m, 2H), 2.63 (d, J = 4.4 Hz, 1H), 1.85 (d, J = 11.2 Hz, 2H), 1.44-1.33 (m, 2H); LCMS (+ESI, m/z): 343.1654 (M+H)⁺

N-cyclopropyl-3-hydroxy-4-phenoxybenzamide (28f)

Yield = 72%; mp = 119-120 °C; Rf = 0.12 (hexane: ethyl acetate = 6:4); λmax = 285.6 nm (MeOH); ¹³CNMR (100.64 MHz, DMSO-d₆): 23.51, 116.99, 117.25, 119.11, 121.02, 122.97, 130.19, 131.93, 145.74, 149.19, 157.76, 167.46; LCMS (+ESI, m/z): 270.1127 (M+H)⁺

3-hydroxy-4-phenoxy-N-(piperidin-4-ylmethyl) benzamide (28g)

Yield = 76%; mp = 98-100 °C; Rf = 0.11 (hexane: ethyl acetate = 6:4); λmax = 249 nm (MeOH); IR (KBr, cm⁻¹) = 3354 (O-H str.), 3269 (N-H str.), 3045 (Ar-H str.), 2914 (C-H str.), 1625 (C=O str.), 1587, 1496, 1415 (Ar-C=C str.), 1269 (Asym. C-O-C str.), 1145 (Sym. C-O-C str.); ¹HNMR (400 MHz, DMSO-d₆): 9.78 (s, 1H), 8.39 (t, J = 5.6 Hz, 1H), 7.44 (d, J = 2 Hz, 1H), 7.06-7.02 (m, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.89-6.87 (m, 2H), 6.81-6.78 (dd, J = 8.4 Hz and 2 Hz, 1H), 4.35 (s, 1H), 3.77 (t, J = 15.2 Hz, 1H), 3.40-3.34 (m, 1H), 3.16 (s, 2H), 1.82 (d, J = 16.4 Hz, 1H), 1.70 (s, 2H), 1.37 (s, 2H), 1.08 (d, J = 7 Hz, 2H); LCMS (+ESI, m/z): 325.156 (M+H)⁺

3-hydroxy-4-phenoxy-N-(1H-tetrazol-5-yl) benzamide (28h)

Yield = 62%; mp = 154-156 °C; Rf = 0.09 (hexane: ethyl acetate = 6:4); λmax = 260.6 nm (MeOH); IR (KBr, cm⁻¹) = 3545 (O-H str.), 3051 (N-H str.), 2914 (C-H str.), 1625 (C=O str.), 1587, 1496, 1424 (Ar-C=C str.), 1269 (Asym. C-O-C str.), 1145 (Sym. C-O-C str.); LCMS (-ESI, m/z): 296.082 (M-H)⁻

2,2,2-trifluoro-1-(1-(3-hydroxy-4-phenoxybenzoyl)-1H-pyrrol-2-yl) ethanone (28i)

Yield = 62%; mp = 124-126 °C; Rf = 0.51 (hexane: ethyl acetate = 6:4); λmax = 265.2 nm (MeOH); IR (KBr, cm⁻¹) = 3400 (O-H str.), 3038 (Ar-H str.), 1747, 1643 (C=O str.), 1541, 1496, 1440 (Ar-C=C str.), 1228 (Asym. C-O-C str.), 1145 (Sym. C-O-C str.); ¹HNMR (400 MHz, DMSO-d₆): 9.59 (s, 1H), 8.18 (d, J = 2 Hz, 1H), 8.11-8.08 (dd, J = 8 Hz and 2 Hz, 1H), 7.95 (s, 1H), 7.04-6.98 (m, 2H), 6.89-6.85 (dd, J = 8 Hz and 2 Hz, 1H), 4.35 (s, 1H), 3.77 (t, J = 15.2 Hz, 1H), 3.40-3.34 (m, 1H), 3.16 (s, 2H), 1.82 (d, J = 16.4 Hz, 1H), 1.70 (s, 2H), 1.37 (s, 2H), 1.08 (d, J = 7 Hz, 2H); LCMS (+ESI, m/z): 325.156 (M+H)⁺
8.06-8.05 (m, 2H), 7.98-7.95 (m, 3H), 7.43-7.38 (m, 2H), 7.21-7.16 (m, 1H), 7.11-7.07 (m, 1H); LCMS (+ESI, m/z): 364.1482 (M+H)⁺

General method for synthesis of amino acid ester derivatives of 3-hydroxy-4-phenoxybenzoic acid (29a-i)

Amine ester (2.17 mmol) was added to a mixture of 3-hydroxy-4-phenoxybenzoic acid (23) (0.5 g, 2.17 mmol), dichloromethane (10 mL), HOBT. H₂O (0.5 g, 3.22 mmol), EDC.HCl (0.5 g, 2.60 mmol), triethyl amine (0.878 g, 8.78 mmol, 1.22 mL) and stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4) as the mobile phase. After the completion of reaction (30 min.), the reaction mixture quenched with water. The organic layer was separated, diluted with dichloromethane (10 mL), washed with water, brine, dried over anhydrous MgSO₄ and evaporated under vacuum. The crude compound was
purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound.

**Methyl 2-(3-hydroxy-4-phenoxybenzamido) acetate (29a)**

Yield = 78%; mp = 80-82 °C; R$_f$ = 0.28 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 253.6 nm (MeOH); $^1$HNMR (400 MHz, DMSO-$d_6$): 9.80 (s, 1H), 8.80 (t, J = 5.6 Hz, 1H), 7.47 (d, J = 2 Hz, 1H), 7.35-7.31 (m, 3H), 7.06 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 7.6 Hz, 2H), 3.97 (d, J = 5.6 Hz, 2H)

**Methyl 3-(3-hydroxy-4-phenoxybenzamido) propanoate (29b)**

Yield = 71%; mp = 74-75 °C; R$_f$ = 0.32 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 253 nm (MeOH); $^1$HNMR (400 MHz, DMSO-$d_6$): 9.74 (s, 1H), 8.41 (t, J = 5.4 Hz, 1H), 7.42 (d, J = 2 Hz, 3H), 7.34-7.30 (m, 2H), 7.28-7.25 (dd, J = 8.4 Hz and 2 Hz, 1H), 7.07-7.03 (m, 1H), 6.94 (d, J = 8 Hz, 1H), 6.89-6.87 (td, J = 8 Hz, 1.6 Hz and 1.2 Hz, 2H), 3.59 (s, 3H), 3.48-3.43 (q, 2H), 2.56 (t, J = 7 Hz, 2H)

**Methyl 2-(3-hydroxy-4-phenoxybenzamido) propanoate (29c)**

Yield = 75%; mp = 68-70 °C; R$_f$ = 0.3 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 254.4 nm (MeOH)

**Methyl 4-(3-hydroxy-4-phenoxybenzamido) butanoate (29d)**

Yield = 72%; mp = 73-75 °C; R$_f$ = 0.34 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 253.6 nm (MeOH); IR (KBr, cm$^{-1}$) = 3352 (O-H str.), 3194 (N-H str.), 3064 (Ar-H str.), 2949, 2852 (C-H str.), 1735, 1616 (C=O str.), 1585, 1492, 1440 (Ar-C=C str.), 1215 (Asym. C-O-C str.), 1103 (Sym. C-O-C str.); $^1$HNMR (400 MHz, DMSO-$d_6$): 9.77 (s, 1H), 8.35 (t, J = 5.4 Hz, 1H), 7.44 (d, J = 1.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 2H), 7.30-7.27 (m, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8 Hz, 2H), 3.57 (s, 3H), 3.29-3.21 (m, 2H), 2.35 (t, J = 7.4 Hz, 2H), 1.79-1.72 (m, 2H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 34.04, 35.97, 51.85, 116.99, 117.28, 119.09, 121.09, 123.00, 130.19, 131.78, 145.87, 149.24, 157.74, 166.27, 172.25; LCMS (+ESI, m/z): 330.1388 (M+H)$^+$

**Methyl 1-(3-hydroxy-4-phenoxybenzoyl) pyrrolidine-2-carboxylate (29e)**

Yield = 69%; mp = 111-113 °C; R$_f$ = 0.56 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 246.8 nm (MeOH); $^1$HNMR (400 MHz, DMSO-$d_6$): 9.80 (s, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.40-7.37 (dd, J = 8.4 Hz and 2 Hz, 1H), 7.20-7.12 (m, 2H), 7.10-7.02 (m, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8 Hz, 2H), 3.55 (s, 3H), 3.29-3.19 (m, 2H), 2.32 (t, J = 7.4 Hz, 2H), 1.79-1.71 (m, 2H); $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 34.08, 35.97, 51.85, 116.99, 117.28, 119.09, 121.09, 123.00, 130.19, 131.78, 145.87, 149.24, 157.74, 166.27, 172.25; LCMS (+ESI, m/z): 330.1388 (M+H)$^+$
$J$ = 8.4 Hz and 2 Hz, 1H), 7.12 (s, 1H), 7.09 (d, $J$ = 7.2 Hz, 1H), 7.06-7.03 (m, 2H), 6.99 (t, $J$ = 7.6 Hz, 2H), 4.47-4.44 (dd, $J$ = 8.4 Hz and 5.2 Hz, 1H), 3.65 (s, 3H), 3.54 (d, $J$ = 5.4 Hz, 2H), 2.27 (d, $J$ = 7.4 Hz, 1H), 1.87 (d, $J$ = 85.2 Hz, 3H); $^{13}$CNMR (100.64 MHz, DMSO-d$_6$): 25.53, 50.18, 52.31, 59.41, 116.79, 117.75, 118.39, 119.30, 120.77, 121.74, 122.96, 123.36, 130.19, 133.12, 144.89, 149.11, 157.77, 168.10, 172.89; LCMS (+ESI, m/z): 342.1186 (M+H)$^+$(R)

(R)-Methyl 1-(3-hydroxy-4-phenoybenzoyl) pyrrolidine-2-carboxylate (29f)

Yield = 72%; mp = 108-113 °C; $R_f$ = 0.59 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 245.2 nm (MeOH).

(2S)-Methyl 4-hydroxy-1-(3-hydroxy-4-phenoybenzoyl)pyrrolidine-2-carboxylate (29g)

Yield = 65%; mp = 168-170 °C; $R_f$ =0.35 (hexane: ethyl acetate = 6:4); $\lambda_{max}$ = 248.6 nm (MeOH). $^1$HNMR (400 MHz, DMSO-d$_6$): 9.83 (s, 1H), 7.33 (t, $J$ = 7.8 Hz, 2H), 7.33 (t, $J$ = 7.8 Hz, 2H), 77.13 (s, 1H), 7.05 (t, $J$ = 7.4 Hz, 1H), 7.00-6.94 (m, 2H), 6.90 (d, $J$ = 8 Hz, 2H), 5.07 (d, $J$ = 2.8 Hz, 1H), 4.55 (t, $J$ = 8.4 Hz, 1H), 4.28 (s, 1H), 3.73-3.69 (dd, $J$ = 11.2 Hz and 3.6 Hz, 1H), 3.65 (s, 3H), 3.39 (t, $J$ = 10.2 Hz, 1H), 2.18 (t, $J$ = 9.8 Hz, 1H), 1.98-1.93 (m, 1H)

General method for synthesis of amino acid derivatives of 3-hydroxy-4-phenoybenzoic acid (30a-g).

To the solution of compound (29a-g) (0.597 mmol) in methanol (6 mL) and water (4 mL), NaOH (2.39 mmol) was added and heated to reflux at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (5:5) as the mobile phase. After the completion of reaction (1h), the reaction mixture was evaporated to remove excess volatiles and the residue obtained was added to cold water (25 mL) and neutralized to pH 4 using dil. HCl. Then it was extracted with ethyl acetate (2x25 mL) and the organic layers were separated, pooled, washed with water, brine, dried over anhydrous MgSO$_4$ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (5:5) as the mobile phase to afford the target compound.

2-(3-hydroxy-4-phenoybenzamido) acetic acid (30a)

Yield = 90%; mp = 135-137 °C; $R_f$ = 0.04 (hexane: ethyl acetate = 5:5); $\lambda_{max}$ = 252.6 nm (MeOH); IR (KBr, cm$^{-1}$) = 3545 (O-H str.), 3311 (N-H str.), 3046 (Ar-H str.), 2941 (C-H str.), 1703, 1633 (C=O str.), 1579, 1490, 1433 (Ar=C=C str.), 1247 (Asym. C-O-C str.), 1161 (Sym. C-O-C str.); 12.54 (s, 1H), 9.78 (s, 1H), 8.66 (t, $J$ = 6 Hz, 1H), 7.47 (d, $J$ = 2 Hz, 1H), 7.34-7.30
(m, 3H), 7.05 (t, J= 7.4 Hz, 1H), 6.97 (d, J= 8.4 Hz, 1H), 6.91-6.88 (dd, J= 8.8 Hz and 0.8 Hz, 2H), 3.87 (d, J= 6 Hz, 2H); LCMS (+ESI, m/z): 288.0737 (M+H)

3-(3-hydroxy-4-phenoxybenzamido) propanoic acid (30b)

Yield = 87%; mp = 92-94 °C; Rf = 0.12 (hexane: ethyl acetate = 5:5); λmax = 252 nm (MeOH); LCMS (+ESI, m/z): 302.0885 (M+H)

2-(3-hydroxy-4-phenoxybenzamido) propanoic acid (30c)

Yield = 85%; mp = 100-102 °C; Rf = 0.03 (hexane: ethyl acetate = 5:5); λmax = 254.6 nm (MeOH); 1H NMR (400 MHz, DMSO-d6): 12.47 (s, 1H), 9.73 (s, 1H), 8.24 (d, J= 7.2 Hz, 1H), 7.48 (d, J= 2 Hz, 1H), 7.36-7.30 (m, 3H), 7.05 (t, J= 7.2 Hz, 1H), 6.96 (d, J= 8.4 Hz, 1H), 6.90-6.88 (dd, J= 8 Hz and 0.8 Hz, 2H), 4.41-4.33 (m, 1H).

4-(3-hydroxy-4-phenoxybenzamido) butanoic acid (30d)

Yield = 92%; mp = 130-132 °C; Rf = 0.18 (hexane: ethyl acetate = 5:5); λmax = 252.4 nm (MeOH); 13CNMR (100.64 MHz, DMSO-d6): 25.04, 31.68, 117.04, 117.24, 119.05, 121.10, 122.96, 130.18, 132.10, 145.72, 149.24, 157.79, 166.21, 174.78; LCMS (+ESI, m/z): 316.1035 (M+H)

(S)-1-(3-hydroxy-4-phenoxybenzoyl) pyrrolidine-2-carboxylic acid (30e)

Yield = 84%; mp = 134-136 °C; Rf = 0.31 (hexane: ethyl acetate = 5:5); λmax = 243.6 nm (MeOH); IR (KBr, cm⁻¹) = 3365 (O-H str.), 3167 (N-H str.), 3039 (Ar-H str.), 2879 (C-H str.), 1735, 1620 (C=O str.), 1587, 1489, 1450 (Ar=C=C str.), 1244 (Asym. C-O-C str.), 1163 (Sym. C-O-C str.); 1H NMR (400 MHz, DMSO-d6): 12.51 (s, 1H), 9.83 (s, 1H), 7.32 (t, J= 7.6 Hz, 1H), 7.14 (s, 1H), 7.05 (t, J= 7.2 Hz, 1H), 6.96 (s, 2H), 6.89 (d, J= 7.6 Hz, 2H), 5.06 (s, 1H), 4.47 (t, J= 8.2 Hz, 1H), 4.27 (s, 1H), 3.68 (d, J= 8 Hz, 1H), 3.36 (d, J= 11.2 Hz, 1H), 2.18 (t, J= 9.8 Hz, 1H), 1.95 (d, J= 8.8 Hz, 1H); 13CNMR (100.64 MHz, DMSO-d6): 25.02, 25.33, 25.52, 28.45, 28.96, 29.40, 46.71, 50.16, 50.40, 58.31, 59.46, 116.62, 116.78, 117.13, 119.21, 121.37, 122.87, 130.17, 133.48, 144.68, 149.29, 157.84, 173.80; LCMS (+ESI, m/z): 328.1032 (M+H)

(R)-1-(3-hydroxy-4-phenoxybenzoyl) pyrrolidine-2-carboxylic acid (30f)

Yield = 87%; mp = 158-160 °C; Rf = 0.21 (hexane: ethyl acetate = 5:5); λmax = 276 nm (MeOH); 1H NMR (400 MHz, DMSO-d6): 12.42 (s, 1H), 9.81 (s, 1H), 7.32 (t, J= 7.6 Hz, 2H), 7.10 (t, J= 7.8 Hz, 1H), 7.04 (d, J= 6.8 Hz, 1H), 6.96 (t, J= 5 Hz, 2H), 6.87 (d, J= 6 Hz, 2H),
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Materials and Method

Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal.

Yield = 79%; mp = 205-207 °C; R_f = 0.19 (hexane: ethyl acetate = 5:5); λ_max = 245.4 nm (MeOH); LCMS (+ESI, m/z): 344.0992 (M+H)^+

General method for synthesis of amino acid amide derivatives of 3-hydroxy-4-phenoxybenzoic acid (31a-g).

To a solution of methyl 3-hydroxy-4-phenoxybenzoate (29a-g, 0.626 mmol) in methanol (15 mL), was purged with NH_3 gas at 0 °C for 2h. Then the reaction was kept aside at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (24h), the reaction mixture was evaporated to remove excess methanol. The residue obtained was added to ice cold water (50 mL). The precipitate obtained was filtered under vacuum, washed twice with cold water and dried in a desiccator. Compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (5:5) as the mobile phase to obtain the desired compound.

N-(2-amino-2-oxoethyl)-3-hydroxy-4-phenoxybenzamide (31a)

Yield = 65%; mp = 124-126 °C; R_f = 0.03 (hexane: ethyl acetate = 5:5); λ_max = 258.6 nm (MeOH);

N-(3-amino-3-oxopropyl)-3-hydroxy-4-phenoxybenzamide (31b)

Yield = 67%; mp = 156-158 °C; R_f = 0.14 (hexane: ethyl acetate = 5:5); λ_max = 252.4 nm (MeOH); ^1HNMR (400 MHz, DMSO-d_6): 9.71 (s, 1H), 8.35 (s, 1H), 7.44 (s, 1H), 7.31 (t, J= 8 Hz, 3H), 7.26 (d, J= 8.4 Hz, 1H), 7.04 (t, J= 7 Hz, 1H), 6.93 (d, J= 8 Hz, 1H), 6.87 (d, J= 7.6 Hz, 2H), 6.81 (s, 1H), 3.39 (dd, J= 6.4 Hz, 2H), 2.32 (t, J= 7 Hz, 2H); LCMS (+ESI, m/z): 301.1217 (M+H)^+

N-(1-amino-1-oxopropan-2-yl)-3-hydroxy-4-phenoxybenzamide (31c)

Yield = 62%; mp = 180-182 °C; R_f = 0.22 (hexane: ethyl acetate = 5:5); λ_max = 254 nm (MeOH); ^1HNMR (400 MHz, DMSO-d_6): 9.73 (s, 1H), 8.24 (d, J= 7.2 Hz, 1H), 7.47 (d, J= 2 Hz, 1H), 7.37-7.30 (m, 3H), 7.35-7.30 (m, 3H), 7.07-7.03 (m, 1H), 6.95 (d, J= 8.4 Hz, 2H), 6.89-6.87 (dd, J= 8.4 Hz and 0.8 Hz, 2H), 4.41-4.30 (m, 1H), 1.30 (d, J= 3.6 Hz, 3H).
N-(4-amino-4-oxobutyl)-3-hydroxy-4-phenoxybenzamide (31d)

Yield = 70%; mp = 117-119 °C; R_f = 0.23 (hexane: ethyl acetate = 5:5); λ_max = 252.4 nm (MeOH); IR (KBr, cm⁻¹) = 3408 (O-H str.), 3311, 3205 (N-H str.), 3051 (Ar-H str.), 2939 (C-H str.), 1689, 1649 (C=O str.), 1552, 1492, 1458 (Ar-C=C str.), 1222 (Asym. C-O-C str.), 1165 (Sym. C-O-C str.); ¹HNMR (400 MHz, DMSO-d₆): 11.96 (s, 1/2H ), 9.75 (s, 1H), 8.35 (s, 1H), 7.44 (s, 3H), 7.34-7.28 (m, 3H), 7.05 (t, J= 7.4 Hz, 1H), 6.94 (d, J= 8 Hz, 1H), 6.88 (d, J= 8 Hz, 2H), 6.72 (s, 1/2H), 6.72 (s, 1/2H), 3.29-3.19 (m, 2H), 2.25 (t, J= 7.2 Hz, 1H), 2.09 (t, J= 7.4 Hz, 1H), 1.76-1.69 (m, 2H); ¹³CNMR (100.64 MHz, DMSO-d₆): 25.05, 25.61, 31.79, 33.16, 117.04, 117.24, 119.04, 121.10, 122.95, 130.18, 132.10, 132.14, 145.71, 149.25, 157.79, 166.20, 174.56; LCMS (+ESI, m/z): 315.1197 (M+H)⁺

(S)-1-(3-hydroxy-4-phenoxybenzoyl) pyrrolidine-2-carboxamide (31e)

Yield = 68%; mp = 70-72 °C; R_f = 0.34 (hexane: ethyl acetate = 5:5); λ_max = 248 nm (MeOH); ¹HNMR (400 MHz, DMSO-d₆): 9.75 (s, 1H), 8.35 (s, 1H), 7.44 (s, 1H), 7.34-7.28 (m, 3H), 7.05 (t, J= 7.4 Hz, 1H), 6.94 (d, J= 8 Hz, 1H), 6.88 (d, J= 8 Hz, 2H), 6.72 (s, 1H), 3.29-3.19 (m, 2H), 2.25 (t, J= 7.2 Hz, 1H), 2.09 (t, J= 7.4 Hz, 1H), 1.76-1.69 (m, 2H); ¹³CNMR (100.64 MHz, DMSO-d₆): 25.05, 25.61, 31.79, 33.16, 117.04, 117.24, 119.04, 121.10, 122.95, 130.18, 132.10, 132.14, 145.71, 149.25, 157.79, 166.20, 174.56; LCMS (+ESI, m/z): 327.123 (M+H)⁺

(2S)-4-hydroxy-1-(3-hydroxy-4-phenoxybenzoyl) pyrrolidine-2-carboxamide (31f)

Yield = 64%; mp = 178-180 °C; R_f = 0.21 (hexane: ethyl acetate = 5:5); λ_max = 247.2 nm (MeOH)

Synthesis of ((2S)-4-hydroxy-2-(hydroxymethyl) pyrrolidin-1-yl) (3-hydroxy-4-phenoxyphenyl) methanone (32).

To the solution compound 29g (0.15 g, 0.419 mmol) in methanol (3 mL) and THF (2 mL), NaBH₄ (0.047 g, 1.259 mmol) was added and stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (5:5). After the completion of reaction (1h), the reaction mixture was quenched by using aq. NH₄Cl. The reaction mixture was evaporated to remove excess methanol. The residue obtained was added with ice cold water (25 mL). The precipitate obtained was filtered under vacuum, washed twice with cold water and dried to afford the target compound with quantitative yield as pale yellow solid. Compound was further purified by column chromatography over silica 100-200 with hexane: ethyl acetate (5:5) as the mobile phase to obtain the desired product as white crystalline solid.
Yield = 1.2 g (87%); mp = 196-198 °C; R_f = 0.37 (hexane: ethyl acetate = 5:5); λ_max = 286.4 nm (MeOH).

**Synthesis of 3-methoxy-4-(4-nitrophenoxy) benzaldehyde (33)**

1-fluoro-4-nitrobenzene (5 g, 35.43 mmol) was dissolved in dry DMF (50 mL) and anhydrous K_2CO_3 (12.12 g, 87.85) was to it. To the suspension, vanillin (5.9 g, 38.81 mmol) and 18-crown-6 (0.018 g, 0.069 mmol) were added and stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the completion of reaction (14h), the reaction mixture was added to ice cold water (50 mL) and extracted with ethyl acetate (3x25 mL). The organic layers were separated, washed with water (50 mL), 1N NaOH (10 mL), water (25 mL), brine, dried over anhydrous MgSO_4 and evaporated under vacuum to afford the target compound as pale yellow solid. Compound was further purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to obtain light yellow crystalline solid.

Yield = 8.4 g (87%); mp = 88-89 °C; R_f = 0.88 (hexane: ethyl acetate 8:2); λ_max = 308.8 nm (MeOH).

**2.8.2.34. Synthesis of 3-methoxy-4-(4-nitrophenoxy) benzoic acid (34)**

To a mixture of 3-methoxy-4-(4-nitrophenoxy) benzaldehyde (0.4 g, 1.46 mmol) in water (15 mL) were added with NaOH (0.116 g, 2.92 mmol) and KMnO_4 (0.462 g, 2.92 mmol). The
reaction mixture was heated at 80 °C with stirring. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (1h), the reaction mixture was filtered at hot condition and then acidified using dil. HCl to pH 3. Then it was extracted with ethyl acetate (3x25 mL). The organic layers were separated, washed with water (50 ml), brine, dried over anhydrous MgSO₄ and evaporated under vacuum to afford the target compound with quantitative yield. Crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford white crystalline solid.

Yield = 0.36 g (85%); mp = 204-206 °C; Rf = 0.36 (hexane: ethyl acetate = 8:2); λmax = 300.2 nm; LCMS (+ESI, m/z): 290.0549 (M+H)⁺

**Synthesis of 3-hydroxy-4-(4-nitrophenoxy) benzoic acid (35)**

To the stirred solution of compound **34** (0.325 g, 1.12 mmol) in glacial AcOH (4 mL), HBr (48% v/v, 8 mL) was added. Resulting reaction mixture was refluxed at 112-115 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (48h), it was cooled to room temperature and poured in to ice cold water (40 mL) with vigorous stirring. The precipitate obtained was washed with water and dried. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford white crystalline solid.

Yield = 0.25 g (74%); mp = 210-212 °C; Rf = 0.16 (hexane: ethyl acetate = 6:4); λmax = 303.2 nm (MeOH); IR (KBr, cm⁻¹) = 3450, 3313 (O-H str.), 3062 (Ar-H str.), 1697 (C=O str.), 1602 (N-O str.), 1504, 1450, (Ar-C=C str.), 1242 (Asym. C-O-C str.), 1112 (Sym. C-O-C str.); ¹³CNMR (100.64 MHz, DMSO-d₆): 116.59, 117.78, 123.04, 124.29, 126.48, 129.16, 140.98, 142.41, 154.21, 163.39, 166.9; LCMS (-ESI, m/z): 274.0399 (M-H)

**Synthesis of 4-(4-aminophenoxy)-3-hydroxybenzoic acid (36)**

To the mixture of 3-hydroxy-4-(4-nitrophenoxy) benzoic acid (35) (0.15 g, 0.545 mmol) in refluxing H₂O (15 mL), Fe powder (0.121 g, 2.18 mmol) and FeSO₄.7H₂O (0.303 g, 1.091 mmol) were added. The reaction mixture was refluxed at 100 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4) as the mobile phase. After the completion of the reaction (14h), it was filtered and washed thoroughly with ethyl acetate (45 mL). The organic layer was separated from the filtrate, dried over anhydrous MgSO₄ and evaporated under vacuum to afford the corresponding amine. The crude compound was purified by
column chromatography over silica 100-200 with hexane: ethyl acetate (5:5) as the mobile phase to afford the target compound.

Yield = 0.08 g (60%); mp = 216-218 °C; R_f = 0.04 (hexane: ethyl acetate =5:5); λ_max = 248.4 nm (MeOH); IR (KBr, cm^{-1}) = 3487, 3414 (O-H str.), 3178, 3126(N-H str.), 3062 (Ar-H str.), 1668 (C=O str.), 1602 (N-O str.), 1512, 1450 (Ar-C=C str.), 1238 (Asym. C-O-C str.), 1124 (Sym. C-O-C str.); LCMS (ESI, m/z): 334.0833 (M+H)^+

Synthesis of (3-methoxy-4-(4-nitrophenoxy) phenyl) methanol (37)

To the solution of 3-methoxy-4-(4-nitrophenoxy) benzaldehyde 33 (5 g, 18.31 mmol) in methanol (15 mL) and THF (10 mL), NaBH_4 (1.35 g, 35.89 mmol) was added and stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (2h), the reaction mixture was quenched using aq. NH_4Cl and evaporated to remove excess methanol. The residue obtained was added with ice cold water (50 mL). The precipitate obtained was filtered under vacuum, washed twice with cold water and dried to afford the target compound as pale yellow solid. Compound was further purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to obtain the desired product

Yield = 4.5 g (89%); mp = 100-102 °C; R_f = 0.20 (hexane: ethyl acetate =6:4); λ_max = 303.6 nm (MeOH)

Synthesis of (4-(4-aminophenoxy)-3-methoxyphenyl) methanol (38)

Compound 38 was synthesized by following the method given for synthesis of compound 36. (3-methoxy-4-(4-nitrophenoxy) phenyl) methanol (37) (4.4 g, 16 mmol) was used as the starting material.

Yield = 3.2 g (82%); mp = 63-65 °C; R_f = 0.16 (hexane: ethyl acetate = 6:4); λ_max = 296.4 nm (MeOH).

Synthesis of 4-(chloromethyl)-1-(4-chlorophenoxo)-2-methoxybenzene (39)

A solution of compound 38 (3.1 g, 12.64 mmol) in glacial AcOH (10 ml) was added to a stirred mixture of NaNO_2 (1.31 g, 18.958 mmol) and concentrated HCl (8 ml) maintained at -5 °C. Stirring was continued for 1h at temperature below 0 °C. The reaction mixture was added to a mixture of CuCl (2.5 g, 25.278 mmol) and CuCl_2 (4.32 g, 25.278 mmol) in concentrated HCl (20 ml) at -5 °C. The reaction mixture was stirred at 0-5 °C for 1h and then 14h at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the
completion of reaction (14h), the reaction mixture was quenched using saturated solution of NH₄Cl in NH₄OH until the blue color persisted. Then it was extracted with dichloromethane (2x25 mL). The organic layers were separated, washed with water (2x25 mL), dried over anhydrous MgSO₄ and evaporated under vacuum to afford the desired compound. Crude compound was further purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford yellow oil.

Yield = 0.6 g (19%); Rf = 0.79 (hexane: ethyl acetate = 8:2)

**Synthesis of 4-(4-chlorophenoxy)-3-methoxybenzaldehyde (40).**

To the solution of compound 39 (0.55 g, 1.94 mmol) in water (10 ml) were added K₂Cr₂O₇ (1.13 g, 3.88 mmol), Na₂CO₃ (0.411 g, 3.88 mmol) and 18-crown-6 (0.01 g, 0.02 mmol). The resulting reaction mixture was heated to reflux at 100-102 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2) as the mobile phase. After the completion of reaction (12h), the reaction mixture was filtered and the filtrate was extracted with dichloromethane (2x25 mL). The organic layers were separated, washed with water (25 mL), dried over anhydrous MgSO₄ and evaporated under vacuum to afford the desired compound. Crude compound was further purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford colourless oil.

Yield = 0.503 g (98%); Rf = 0.64 (hexane: ethyl acetate = 8:2)

**Synthesis of 4-(4-chlorophenoxy)-3-methoxybenzoic acid (41)**

Compound 41 was synthesized by following the method given for synthesis of compound 34. 4-(4-chlorophenoxy)-3-methoxybenzaldehyde (40) (0.45 g, 1.713 mmol) was used as the starting material.

Yield = 0.37 g (75%); mp = 134-136 °C; Rf = 0.36 (hexane: ethyl acetate = 6:4); λmax = 248.1 nm (MeOH);

2.8.2.42. Synthesis of 4-(4-chlorophenoxy)-3-hydroxybenzoic acid (42)

Compound 42 was synthesized by following the method given for synthesis of compound 35. 4-(4-chlorophenoxy)-3-methoxybenzoic acid (41) (0.32 g, 1.14 mmol) was used as the starting material.

Yield = 0.23 g (76%); mp = 204-206 °C, Rf = 0.22 (hexane: ethyl acetate = 6:4); λmax = 251.2 nm (MeOH); IR (KBr, cm⁻¹) = 3348, 3271 (O-H str.), 3062 (Ar-H str.), 1695 (C=O str.), 1600 (N-O str.), 1521, 1485, 1442 (Ar-C=C str.), 1213 (Asym. C-O-C str.), 1097 (Sym. C-O-C str.);
13CNMR (100.64 MHz, DMSO-d$_6$): 118.52, 119.12, 121.38, 121.79, 126.91, 128.23, 130.06, 146.95, 149.24, 156.38, 167.25; LCMS (+ESI, m/z): 265.142 (M+H)$^+$

2.8.2.43. Synthesis of N-benzyl-4-(4-nitrophenoxy)-3-hydroxybenzamide (43)

Compound 43 was synthesized by following the method given for synthesis of compounds 28a-i.

Yield = 0.142 g (71%); mp = 192-194 °C, R$_f$ = 0.38 (hexane: ethyl acetate = 6:4); λmax = 254.8 nm (MeOH); LCMS (ESI, m/z): 365.0812 (M+H)$^+$

**Scheme-10**

**Reagents and conditions:** (i). Morpholin, S, 135-140 ºC, 7h; (ii). HCl (4N), 100 ºC, 4h (iii). BBR$_3$ (1M CH$_2$Cl$_2$), CH$_2$Cl$_2$, -10 ºC to 25-27 ºC, 12h; (iv).MeOH, Conc. H$_2$SO$_4$ (Cat.), 65-67 ºC, 4h; (v). NaBH$_4$, THF, MeOH, 25-27 ºC, 2h; (vi). Amines, EDC.HCl, HOBT, H$_2$O, Et$_3$N, CH$_2$Cl$_2$, 25-27 ºC, 30 min.

**Synthesis of 2-(3-methoxy-4-phenoxyphenyl) acetic acid (45)**

To the mixture of 1-(3-methoxy-4-phenoxyphenyl) ethanone (1.8 g, 7.96 mmol) in morpholin (1.73 g, 19.9 mmol, 1.739 mL), sulphur (0.51 g, 15.93 mmol) was added and heated at 140 ºC. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the completion of reaction (12h), the reaction mixture was diluted with ethyl acetate (35 mL) and treated with activated charcoal and filtered. The filtrate obtained was washed with dil. HCl (10 mL) and evaporated under vacuum to afford pale yellow colour oil. To it aq. KOH (1N, 20 mL) was added and refluxed at 100-102 ºC. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (12h), the reaction mixture was filtered and extracted with diethyl ether (50 mL). The aqueous layer was separated, acidified with dil. HCl and extracted with ethyl acetate (2x50 mL). The organic layers were separated, washed with water (25 mL), dried over anhydrous MgSO$_4$ and evaporated under vacuum. Crude compound obtained was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford white crystalline solid.
Synthesis of 2-(3-hydroxy-4-phenoxyphenyl) acetic acid (46)

To the solution of 2-(3-methoxy-4-phenoxyphenyl) acetic acid (45) (1g, 3.87 mmol) in anhydrous dichloromethane (25 mL), BBr3 (1M, 1.94 g, 7.74 mmol) was added at -10 °C in presence of N2. Reaction mixture was stirred for 1h at -10 °C and then the temperature of the reaction mixture was allowed to reach 25-27 °C and stirring was continued. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (3h), the reaction was quenched by pouring it into ice cold aqueous sodium bicarbonate with continuous stirring. The aqueous layer was separated and acidified to pH 4-5 by dil. HCl. Then it was extracted with ethyl acetate (2x45 mL) and the separated organic layers were washed with water, brine, dried over anhydrous MgSO4 and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound as white crystalline solid.

Yield = 0.9 g (95%); mp = 115-117 °C; Rf = 0.18 (hexane: ethyl acetate = 6:4); λmax = 276.6 nm (MeOH); IR (KBr, cm⁻¹) = 3424, 3271 (O-H str.), 3062 (Ar-H str.), 2846 (C-H str.), 1701 (C=O str.), 1591, 1485, 1411 (Ar-C=C str.), 1224 (Asym. C-O-C str.), 1165 (Sym. C-O-C str.); 13CNMR (100.64 MHz, DMSO-d6): 116.48, 118.65, 121.07, 122.16, 122.26, 130.00, 132.67, 141.59, 149.50, 158.52, 173.16; LCMS (ESI, m/z): 245.0717 (M+H)+

Synthesis of methyl 2-(3-hydroxy-4-phenoxyphenyl) acetate (47)

To the solution of 2-(3-hydroxy-4-phenoxyphenyl) acetic acid (46, 0.4 g, 1.63 mmol) in methanol (15 mL), conc. H2SO4 (0.05 mL) was added and refluxed at 65-67 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the completion of reaction (4h), the reaction mixture was evaporated and the residue obtained was treated with ice cold water (50 mL). Then it was extracted with ethyl acetate (2x25 mL) and the combined organic layer was washed with water, brine, dried over anhydrous MgSO4 and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compound as an colourless oil.
Yield = 0.385 g (91%); \( R_f = 0.75 \) (hexane: ethyl acetate = 8:2); \( \lambda_{\text{max}} = 276.6 \) nm (MeOH)

**Synthesis of 5-(hydroxymethyl)-2-phenoxyphenol (48)**

To the solution of methyl 2-(3-hydroxy-4-phenoxyphenyl) acetate (46, 0.2 g, 0.774 mmol) in methanol (6 mL) and THF (3 mL), NaBH\(_4\) (0.087 g, 2.323 mmol) was added and stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (1h), the reaction mixture was quenched using aq. NH\(_4\)Cl and the reaction mixture was evaporated to remove excess methanol. The residue obtained was added with ice cold water (25 mL). The precipitate obtained was filtered under vacuum, washed twice with cold water and dried to afford a white solid product. Crude solid was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to obtain the desired product as white crystalline solid.

Yield = 0.152 g (85%); mp = 75-77 °C; \( R_f = 0.36 \) (hexane: ethyl acetate = 6:4); \( \lambda_{\text{max}} = 276.6 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3527, 3192 (O-H str.), 3057 (Ar-H str.), 2883 (C-H str.), 1672 (C-O str.), 1558, 1487, 1460 (Ar-C=C str.), 1274 (Asym. C-O-C str.), 1180 (Sym. C-O-C str.);

\(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)): 62.60, 116.37, 118.21, 120.52, 122.10, 122.17, 129.95, 137.42, 140.90, 149.44, 158.70; LCMS (ESI, m/z): 231.1015 (M+H)

**General method for synthesis of amide derivatives of 2-(3-hydroxy-4-phenoxyphenyl) acetic acid (49a-c)**

Amine (0.819 mmol) was added to a mixture of 2-(3-hydroxy-4-phenoxyphenyl) acetic acid (45, 0.2 g, 0.819 mmol), dichloromethane (10 mL), HO\(\text{Bt.H}_2\)\(\text{O}\) (0.188 g, 1.22 mmol), EDC.HCl (0.188 g, 0.98 mmol), triethyl amine (0.165 g, 1.63 mmol, 0.23 mL) and stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4) as the mobile phase. After the completion of reaction (30 min.) the reaction mixture quenched with water and the organic layer was separated, diluted with dichloromethane (10 mL), washed with water, brine, dried over anhydrous MgSO\(_4\) and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound.

**N, N-diethyl-2-(3-hydroxy-4-phenoxyphenyl) acetamide (49a)**

Yield = 0.182 g (74%); mp = 148-150 °C; \( R_f = 0.30 \) (hexane: ethyl acetate = 6:4); \( \lambda_{\text{max}} = 239.4 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3452 (O-H str.), 3057 (Ar-H str.), 2937, 2883 (C-H str.), 1624 (C-O str.), 1583, 1487, 1400 (Ar-C=C str.), 1219 (Asym. C-O-C str.), 1147 (Sym. C-O-C str.)
\(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)): 13.47, 14.70, 42.25, 116.42, 118.10, 120.59, 122.21, 129.98, 133.90, 141.30, 149.58, 158.58, 169.73; LCMS (+ESI, m/z): 300.1563 (M+H)^+  

**N-cyclopropyl-2-(3-hydroxy-4-phenoxyphenyl) acetamide (49b)**  
Yield = 0.165 g (72%); mp = 105-107 °C; R_f = 0.33 (hexane: ethyl acetate = 6:4); \(\lambda_{\text{max}} = 276.6 \text{ nm (MeOH)}\); \(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)): 6.15, 22.89, 42.19, 116.42, 118.20, 120.64, 122.14, 122.19, 129.97, 134.13, 141.34, 149.46, 158.59, 171.63; LCMS (+ESI, m/z): 284.1269 (M+H)^+  

2-(3-hydroxy-4-phenoxyphenyl)-N-(piperidin-4-ylmethyl) acetamide (49c)  
Yield = 0.186 g (67%); mp = 117-119 °C; R_f = 0.08 (hexane: ethyl acetate = 6:4); \(\lambda_{\text{max}} = 276.8 \text{ nm (MeOH)}\); LCMS (+ESI, m/z): 339.1703 (M)^+  

**Synthesis of 3-methoxy-4-phenoxybenzaldehyde (50)**  
To the stirred solution of vanillin (5 g, 32.89 mmol) in anhydrous dichloromethane (60 mL), activated molecular sieves (4Å, 2.5 g), phenylboronic acid (6.01 g, 49.33 mmol), copper (II) acetate (8.96 g, 49.33 mmol) and anhydrous pyridine (5.19 g, 64.78 mmol) were added successively. The resulting suspension was stirred at 25-27 °C for 72h. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the completion of reaction (72h), the reaction mixture was diluted with dichloromethane (40 mL) and filtered under vacuum. The filtrate was washed with dilute aqueous hydrochloric acid solution (2 M, 50 mL), followed by water (50 mL), dried over anhydrous MgSO\(_4\) and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (8:2) as the mobile phase to afford the target compound.  
Yield = 5 g (67%); mp = 40-42 °C; R_f = 0.83 (hexane: ethyl acetate = 8:2); \(\lambda_{\text{max}} = 275.2 \text{ nm (MeOH)}\).  

**Synthesis of 3-(3-methoxy-4-phenoxyphenyl) acrylic acid (51)**  
To the solution of 3-methoxy-4-phenoxybenzaldehyde (50) (4.5 g, 19.73 mmol) and malonic acid (3.08 g, 29.6 mmol) in pyridine (15 mL), catalytic amount of piperidine (0.1 mL) was added. The resulting reaction mixture was heated at stirred at 100 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (4h), the reaction mixture was cooled to room temperature, poured in to ice cold water (50 mL) and acidified to pH 3 using dil. HCl. The precipitate formed was filtered, washed with water
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(25 mL) and dried. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound as off white crystalline solid

Yield = 4.8 g (91%); mp = 171-173 °C; Rf = 0.28 (hexane: ethyl acetate = 6:4); \( \lambda_{\text{max}} = 277.4 \) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3454 (O-H str.), 3057 (Ar-H str.), 2951, 2810 (C-H str.), 1689 (C=O str.), 1604 (C≡C str.), 1558, 1527, 1448 (Ar-C=C str.), 1232 (Asym. C-O-C str.), 1178 (Sym. C-O-C str.); \(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 12.3 (s, 1H), 7.57 (d, \( J = 16 \) Hz, 1H), 7.50 (s, 1H), 7.32 (t, \( J = 8 \) Hz, 2H), 7.25 (d, \( J = 8 \) Hz, 1H), 7.08-7.04 (dt, \( J = 7.4 \) Hz and\(0.8 \) Hz, 1H), 6.97 (d, \( J = 8 \) Hz, 1H), 6.88 (d, \( J = 8.4 \) Hz, 2H), 6.54 (d, \( J = 16 \) Hz, 1H). 3.79 (s, 3H); \(^{13}\)C NMR (100.64 MHz, DMSO-\(d_6\)): 56.32, 112.82, 117.22, 119.28, 121.37, 122.48, 123.18, 130.29, 131.91, 143.97, 146.19, 151.75, 157.61, 168.16; LCMS (+ESI, m/z): 271.0848 (M+H)+

Synthesis of 3-(3-methoxy-4-phenoxyphenyl) propanoic acid (52)

To 3-(3-methoxy-4-phenoxyphenyl) acrylic acid (51, 2 g, 7.4 mmol) dissolved in aqueous NaOH (2.5M, 50 mL), PdCl\(_2\) (0.197 g, 1.11 mmol) was added, followed by drop wise addition

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\*Reagents and conditions: (i). PdBr\(_2\)(OH)$_2$, Cu(OAc)$_2$, C\(_6\)H\(_5\)N, CH\(_2\)Cl\(_2\), 25-27 °C, 48 h; (ii). CH\(_2\)COOH, C\(_6\)H\(_5\)N, C\(_6\)H\(_5\)N, 100 °C, 4h; (iii). PdCl\(_2\), HCOOH, NaOH, H\(_2\)O, 100 °C, 14h; (iv). BBr\(_3\) (1M CH\(_2\)Cl\(_2\)), CH\(_2\)Cl\(_2\), -10 °C to 25-27 °C, 14h; (v). MeOH, Conc. H\(_2\)SO\(_4\) (Cat.), 65-67 °C, 4h; (vi). NaBH\(_4\), THF, MeOH, 25-27 °C, 2h; (vii). Amine, EDC.HCl, HOBt. H\(_2\)O, Et\(_3\)N, CH\(_2\)Cl\(_2\), 25-27 °C, 30 min.
of formic acid (2.65 g, 57.77 mmol). The resulting reaction mixture was heated at 80 °C with stirring. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (14h), the reaction mixture was cooled to 5-10 °C and acidified by dil. HCl to pH 3. Then it was extracted with ethyl acetate (3x25 mL) and the organic layers were separated, washed with water, brine, dried over anhydrous MgSO₄ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound as white crystalline solid.

Yield = 1.88 g (94%); mp = 90-92 °C; Rf = 0.26 (hexane: ethyl acetate = 6:4); λmax = 276.6 nm (MeOH); IR (KBr, cm⁻¹) = 3455 (O-H str.), 3022 (Ar-H str.), 2939 (C-H str.), 1701 (C=O str.), 1500, 1487, 1417 (Ar-C=C str.), 1217 (Asym. C-O-C str.), 1102 (Sym. C-O-C str.);

¹HNMR (400 MHz, DMSO-d₆): 12.12 (s, 1H), 7.29-7.25 (m, 2H), 7.04 (d, J = 1.6 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 8 Hz, 1H), 6.82-6.77 (m, 3H), 3.70 (s, 3H), 2.82 (t, J = 7.6 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H);

¹³CNMR (100.64 MHz, DMSO-d₆): 30.68, 35.73, 56.03, 113.95, 116.20, 121.08, 122.09, 122.31, 130.08, 139.07, 141.93, 151.63, 158.56, 174.29;

LCMS (+ESI, m/z): 273.1004 (M+H)+

Synthesis of 3-(3-hydroxy-4-phenoxophenyl) propanoic acid (53)

To the solution of compound 52 (1.7 g, 6.25 mmol) in anhydrous dichloromethane (25 mL) maintained at -10 °C under N₂, BBr₃ (1M, 3.13 g, 12.5 mmol) was added in a dropwise manner. Resulting reaction mixture was stirred for 1h at -10 °C. Temperature of the reaction mixture was allowed to 25-27 °C and stirring was continued. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4). After the completion of reaction (14h), the reaction was quenched by pouring it into ice cold aqueous sodium bicarbonate with continuous stirring. The aqueous layer was separated and acidified to pH 4-5 using dil. HCl. Then it was extracted with ethyl acetate (2x45 mL) and the organic layers were separated, washed with water, brine, dried over anhydrous MgSO₄ and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound.

Yield= 1.25 g (70%); mp = 150-152 °C; Rf = 0.37 (hexane: ethyl acetate =6:4); λmax = 277 nm (MeOH); IR (KBr, cm⁻¹) = 3450, 3373 (O-H str.), 3062 (Ar-H str.), 2904 (C-H str.), 1683 (C=O str.), 1519, 1485, 1435 (Ar-C=C str.), 1217 (Asym. C-O-C str.), 1112 (Sym. C-O-C str.);

¹HNMR (400 MHz, DMSO-d₆): 1212.12 (s, 1H), 9.37 (s, 1H), 7.30-7.25 (m, 2H), 6.97 (t, J=
7.4 Hz, 1H), 6.84 (d, J= 8 Hz, 1H), 6.81-6.78 (m, 3H), 6.66-6.64 (dd, J= 8 Hz and 2 Hz, 1H),
2.74 (t, J= 7.6 Hz, 2H), 2.50 (t, J= 5.2 Hz, 2H); \(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)): 30.34,
35.67, 116.40, 116.86, 117.34, 117.57, 118.72, 119.83, 120.74, 121.79, 122.15, 122.29,
123.02, 129.97, 130.20, 138.72, 141.00, 144.04, 149.55, 158.64, 174.25; LCMS (+ESI, m/z):
258.3559 (M+H) +

**Synthesis of methyl 3-(3-hydroxy-4-phenoxyphenyl) propanoate (54)**

To the solution of compound 53 (0.28 g, 1.028 mmol) in methanol (10 mL), catalytic amount
of conc. H\(_2\)SO\(_4\) (0.05 mL) was added and refluxed at 65-67 °C. Progress of the reaction was
monitored by TLC, using hexane: ethyl acetate (8:2). After the completion of reaction (4h), the
reaction mixture was evaporated and the residue obtained was treated with ice cold water (50 mL).
The precipitate obtained was filtered under vacuum, washed twice with cold water and
dried. Crude compound was recrystallized using abs. alcohol to afford the desired compound
as off white crystalline solid.

Yield = 0.253 g (86%); mp = 78-80 °C; Rf =0.54 (hexane: ethyl acetate =8:2); \(\lambda\)max = 277.4
nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3402 (O-H str.), 3062 (Ar-H str.), 2956 (C-H str.), 1716 (C=O
str.), 1541, 1491, 1417 (Ar=C=C str.), 1244 (Asym. C-O-C str.), 1124 (Sym. C-O-C str.);
\(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 9.39 (s, 1H), 7.34-7.25 (m, 1H), 7.18-7.16 (dd, J= 8.4 Hz and
2 Hz, 1H), 7.06 (t, J= 7.2 Hz, 1H), 6.98 (t, J= 7.4 Hz, 2H), 6.93-6.98 (m, 2H), 6.66-6.63 (dd, J= 8
Hz and 2 Hz, 1H), 3.55 (s, 3H), 2.77 (t, J= 7.6 Hz, 2H), 2.59 (t, J= 7.4 Hz, 2H); LCMS
(+ESI, m/z): 273.1138 (M+H) +

**Synthesis of 5-(3-hydroxypropyl)-2-phenoxyphenol (55)**

To the stirred solution of compound 54 (0.18 g, 0.661 mmol) in methanol (6 mL) and THF (4
mL), NaBH\(_4\) (0.075 g, 1.98 mmol) was added at 25-27 °C and stirring was continued. Progress
of the reaction was monitored by TLC, using hexane: ethyl acetate (8:2). After the completion
of reaction (2h), the reaction mixture was quenched using aq. NH\(_4\)Cl and evaporated to remove
excess methanol. The residue obtained was treated with ice cold water (30 mL). The precipitate
obtained was filtered under vacuum, washed twice with cold water and dried. Crude compound
was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as
the mobile phase to obtain white crystalline solid.

Yield = 0.14 g (87%); mp = 82-84 °C; Rf = 0.37 (hexane: ethyl acetate =6:4); \(\lambda\)max = 270.2
nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3543 (O-H str.), 3056 (Ar-H str.), 2941 (C-H str.), 1635 (C-O
str.), 1558, 1558, 1406 (Ar=C=C str.), 1228 (Asym. C-O-C str.), 1134 (Sym. C-O-C str.);
\(^{1}\)HNMR (400 MHz, DMSO-\(d_6\)): 9.32 (s, 1H), 7.29-7.24 (m, 2H), 6.99-6.95 (m, 1H), 6.82 (d, \(J = 8.4\) Hz, 1H), 6.81-6.79 (dd, \(J = 8.8\) Hz and 1.2 Hz, 2H), 6.78 (d, \(J = 2\) Hz, 1H), 6.63-6.61 (dd, \(J = 8.4\) Hz and 2 Hz, 1H), 4.42 (t, \(J = 5.2\) Hz, 1H), 3.43-3.38 (q, 2H), 2.52 (t, \(J = 7.8\) Hz, 2H), 1.72-1.65 (m, 2H); \(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)): 31.65, 34.69, 60.57, 116.35, 117.56, 119.92, 122.09, 122.27, 129.95, 140.04, 140.66, 149.53, 158.72; LCMS (+ESI, m/z): 245.0906 (M+H)

**Synthesis of amide derivatives of 3-(3-hydroxy-4-phenoxyphenyl) propanoic acid (56a-f)**

Amine (0.696 mmol) was added to a mixture of compound 53 (0.18 g, 0.58 mmol), dichloromethane (10 mL), HOBt, H\(_2\)O (0.133 g, 0.878 mmol), EDC.HCl (0.133g, 0.697 mmol), triethyl amine (0.117 g, 1.16 mmol, 0.162 mL) and stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (6:4) as the mobile phase. After the completion of reaction (30 min.), the reaction mixture was quenched with water and the organic layer was separated, diluted with dichloromethane (10 mL), washed with water, brine, dried over anhydrous MgSO\(_4\) and evaporated under vacuum. The crude compound was purified by column chromatography over silica 100-200 with hexane: ethyl acetate (6:4) as the mobile phase to afford the target compound with quantitative yield.

**N, N-diethyl-3-(3-hydroxy-4-phenoxyphenyl) propanamide (56a)**

Yield = 1.5 g (82%); mp = 108-110 °C; \(R_f = 0.6\) (hexane: ethyl acetate = 6:4); \(\lambda_{\text{max}} = 276.6\) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3454 (O-H str.), 3059 (Ar-H str.), 2935 (C-H str.), 1635 (C=O str.), 1541, 1485, 1404 (Ar-C=C str.), 1228 (Asym. C-O-C str.), 1136 (Sym. C-O-C str.); \(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)): 13.58, 14.73, 31.07, 34.35, 41.78, 116.40, 117.82, 119.98, 121.11, 122.23, 129.91, 139.38, 140.97, 149.52, 158.73, 170.75; LCMS (+ESI, m/z): 314.3209 (M+H)

**3-(3-hydroxy-4-phenoxyphenyl)-1-(piperidin-1-yl) propan-1-one (56b)**

Yield = 0.128 g (68%); mp = 130-132 °C; \(R_f = 0.51\) (hexane: ethyl acetate = 6:4); \(\lambda_{\text{max}} = 277\) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3446 (O-H str.), 3051 (Ar-H str.), 2860 (C-H str.), 1653 (C=O str.), 1541, 1483, 1408 (Ar-C=C str.), 1225 (Asym. C-O-C str.), 1109 (Sym. C-O-C str.); \(^{1}\)HNMR (400 MHz, DMSO-\(d_6\)): 9.33 (s, 1H), 7.29-7.24 (m, 2H), 6.97 (t, \(J = 7.4\) Hz, 1H), 6.84 (d, \(J = 8\) Hz, 2H), 6.80 (d, \(J = 8\) Hz, 2H), 6.68-6.65 (dd, \(J = 8.4\) Hz and 2 Hz, 1H), 3.41 (t, \(J = 5.4\) Hz, 2H), 3.35 (t, \(J = 5.4\) Hz, 2H), 2.72 (t, \(J = 7.6\) Hz, 2H), 2.56 (t, \(J = 7.6\) Hz, 2H), 1.57-1.51 (m, 2H), 1.39 (d, \(J = 3.2\) Hz, 4H); LCMS (+ESI, m/z): 326.1758 (M+H)

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3-(3-hydroxy-4-phenoxyphenyl)-1-(4-(2-hydroxyethyl)piperazin-1-yl)propan-1-one (56c)

Yield = 0.165 g (77%); mp = 75-77 °C; R_f = 0.19 (hexane: ethyl acetate = 6:4); λmax = 277 nm (MeOH); LCMS (+ESI, m/z): 371.1936(M+H)^+

N-cyclopropyl-3-(3-hydroxy-4-phenoxyphenyl) propanamide (56d)

Yield = 0.125 g (74%); mp = 108-110 °C; R_f = 0.14 (hexane: ethyl acetate =6:4); λmax = 282.2 nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3410 (O-H str.), 3255 (N-H str.), 3041 (Ar-H str.), 2935 (C-H str.), 1649 (C=O str.), 1554, 1496, 1417 (Ar-C=C str.), 1222 (Asym. C-O-C str.), 1159 (Sym. C-O-C str.); \(^{13}\)CNMR (100.64 MHz, DMSO-d$_6$): 23.01, 31.38, 37.36, 56.01, 56.14, 112.52, 113.88, 116.17, 117.08, 121.71, 122.10, 122.17, 122.29, 123.05, 130.05, 132.67, 138.36, 139.52, 141.84, 145.39, 151.59, 157.78, 158.61, 166.51, 172.87; LCMS (+ESI, m/z): 298.1436 (M+H)^+

3-(3-hydroxy-4-phenoxyphenyl)-N-(piperidin-4-ylmethyl) propanamide (56e)

Yield = 0.156 g (76%); mp = 84-86 °C; R_f = 0.17 (hexane: ethyl acetate =6:4); λmax = 277.4 nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3471 (O-H str.), 3282 (N-H str.), 3039 (Ar-H str.), 2931, 2854 (C-H str.), 1647 (C=O str.), 1554, 1487, 1408 (Ar-C=C str.), 1220 (Asym. C-O-C str.), 1125 (Sym. C-O-C str.)

3-(3-hydroxy-4-phenoxyphenyl)-N-(3-methylisoxazol-5-yl) propanamide (56f)

Yield = 0.121 (62%); mp = 112-114 °C; R_f =0.29 (hexane: ethyl acetate =6:4); λmax = 241.2 nm (MeOH); LCMS (+ESI, m/z): 339.154 (M+H)^+

Synthesis of 3-(3-hydroxy-4-phenoxyphenyl) acrylic acid (57)

Compound 57 was synthesized by following the method given for synthesis of compound 53. 3-(3-methoxy-4-phenoxyphenyl) acrylic acid (51) (2 g, 7.40 mmol) was used as the starting material.

Yield= 1.24 g (66%); mp = 208-210 °C; R_f = 0.18 (hexane: ethyl acetate =6:4); λmax = 278 nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3348 (O-H str.), 3062 (Ar-H str.), 2848 (C-H str.), 1674 (C=O str.), 1618 (C=C str.), 1517, 1487, 1429 (Ar-C=C str.), 1219 (Asym. C-O-C str.), 1165 (Sym. C-O-C str.); \(^{1}\)HNMR (400 MHz, DMSO-d$_6$): 12.31 (s, 1H), 9.72 (s, 1H), 7.49 (d, J = 15.6 Hz, 1H), 7.32 (t, J = 8 Hz, 2H), 7.20 (d, J = 8.6 Hz, 3H), 7.13 (d, J = 8 Hz, 1H), 7.05 (t, J = 7.4 Hz, 3H), 6.90 (t, J = 7.4 Hz, 3H), 6.32 (d, J = 16 Hz, 1H); \(^{13}\)CNMR (100.64 MHz, DMSO-d$_6$):
116.85, 117.34, 118.74, 120.73, 121.79, 123.02, 130.20, 131.64, 144.02, 145.37, 149.71, 157.73, 168.03; LCMS (+ESI, m/z): 257.1863 (M+H)

**Synthesis of methyl 3-(3-hydroxy-4-phenoxyphenyl) acrylate (58)**

Compound 58 was synthesized by following the method given for synthesis of compound 54. 3-(3-hydroxy-4-phenoxyphenyl) acrylic acid (57) (0.25 g, 7.40 mmol) was used as the starting material.

Yield = 0.24 g (91%); mp = 118-120 °C; R_f = 0.6 (hexane: ethyl acetate =6:4); λmax = 290.4 nm (MeOH); IR (KBr, cm^-1) = 3296 (O-H str.), 3060 (Ar-H str.), 2954 (C-H str.), 1705 (C=O str.), 1618 (C=C str.), 1547, 1476, 1419 (Ar=C=C str.), 1242 (Asym. C-O-C str.), 1130 (Sym. C-O-C str.); ^1^HNMR (400 MHz, DMSO-d_6): 9.73 (s, 1H), 7.56 (d, J = 5.8 Hz, 1H), 7.32 (t, J = 8 Hz, 2H), 7.23 (d, J = 1.6 Hz, 1H), 7.18-7.15 (dd, J = 8.4 Hz and 2 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.91 (t, J = 7.4 Hz, 3H), 6.43 (d, J = 15.6 Hz, 1H), 0.70 (s, 3H); ^13^CNMR (100.64 MHz, DMSO-d_6): 51.90, 117.05, 117.29, 117.42, 120.92,, 121.69, 123.09, 130.21, 131.36, 144.65, 145.68, 149.69, 157.65, 167.14; LCMS (+ESI, m/z): 271.0875 (M+H)

**Synthesis of 5-(3-hydroxyprop-1-enyl)-2-phenoxyphenol (59)**

Compound 59 was synthesized by following the method given for synthesis of compound 55. Methyl 3-(3-hydroxy-4-phenoxyphenyl) acrylate (58) (0.15 g, 0.555 mmol) was used as the starting material.

Yield = 0.112 g (84%); mp = 76-78 °C; R_f = 0.34 (hexane: ethyl acetate =8:2); λmax = 260.2 nm (MeOH); IR (KBr, cm^-1) = 3460 (O-H str.), 3060 (Ar-H str.), 2808 (C-H str.), 1681 (C-O str.), 1610 (C=C str.), 1543, 1485, 1409 (Ar=C=C str.), 1274 (Asym. C-O-C str.), 1176 (Sym. C-O-C str.); ^1^HNMR (400 MHz, DMSO-d_6): 9.48 (s, 1H), 7.31-7.25 (m, 2H), 7.00 (t, J = 7.4 Hz, 2H), 6.89-6.86 (m, 2H), 6.84 (d, J = 8 Hz, 2H), 6.45 (d, J = 16 Hz, 1H), 6.24-6.17 (m, 1H), 4.80 (t, J = 5.6 Hz, 1H), 4.10-4.07 (m, 2H); ^13^CNMR (100.64 MHz, DMSO-d_6): 31.65, 34.69, 60.57, 61.93, 115.02, 116.35, 116.65, 118.26, 122.34, 122.40, 128.48, 129.96, 130.04, 130.62, 134.81, 142.32, 149.77, 158.40; LCMS (+ESI, m/z): 243.1027 (M+H)

**Synthesis of amide derivatives of 3-(3-hydroxy-4-phenoxyphenyl) acrylic acid (60a-f)**

Compounds 60a-f were synthesized by following the method given for synthesis of compound 56a-f. 3-(3-hydroxy-4-phenoxyphenyl) acrylic acid (57) (0.15 g, 0.585 mmol) was used as the starting material.
N,N-diethyl-3-(3-hydroxy-4-phenoxyphenyl)acrylamide (60a)

Yield = 0.132 g (73%); mp = 170-172 °C; Rf = 0.41 (hexane: ethyl acetate = 6:4); λmax = 290.6 nm (MeOH); IR (KBr, cm⁻¹) = 3213 (O-H str.), 3086 (Ar-H str.), 2974 (C-H str.), 1639 (C=O str.), 1600 (C=C str.), 1521, 1485, 1427 (Ar-C=C str.), 1247 (Asym. C-O-C str.), 1162 (Sym. C-O-C str.); LCMS (+ESI, m/z): 313.374 (M+H)+

3-(3-hydroxy-4-phenoxyphenyl)-1-(piperidin-1-yl) prop-2-en-1-one (60b)

Yield = 0.126 g (69%); mp = 186-188 °C; Rf = 0.5 (hexane: ethyl acetate = 6:4); λmax = 291.2 nm (MeOH); IR (KBr, cm⁻¹) = 3282 (O-H str.), 3043 (Ar-H str.), 2935 (C-H str.), 1647 (C=O str.), 1608 (C=C str.), 1515, 1465, 1419 (Ar-C=C str.), 1253 (Asym. C-O-C str.), 1160 (Sym. C-O-C str.); 1HNMR (400 MHz, DMSO-d6): 9.59 (s, 1H), 7.37 (s, 1H), 7.33-7.29 (m, 2H), 7.22 (d, J= 2.4 Hz, 1H), 7.18-7.15 (dd, J= 8.4 Hz and 2 Hz, 1H), 7.09 (m, 1H), 7.06-7.02 (m, 1H), 6.92 (s, 1H), 6.90-6.87 (m, 1H), 3.60-3.52 (m, 4H), 1.62-1.48 (m, 6H); LCMS (+ESI, m/z): 324.1604 (M+H)+

N-cyclopropyl-3-(3-hydroxy-4-phenoxyphenyl) acrylamide (60c)

Yield = 0.13 g (76%); mp = 140-142 °C; Rf = 0.14 (hexane: ethyl acetate = 6:4); λmax = 288 nm (MeOH); IR (KBr, cm⁻¹) = 3381 (O-H str.), 3282 (O-H str.), 3055 (Ar-H str.), 2933 (C-H str.), 1660 (C=O str.), 1608 (C=C str.), 1593 (C=C str.), 1548, 1487, 1427 (Ar-C=C str.), 1259 (Asym. C-O-C str.), 1168 (Sym. C-O-C str.); 13CNMR (100.64 MHz, DMSO-d6): 6.35, 22.99, 115.95, 116.15, 117.16, 120.15, 121.63, 122.06, 122.85, 130.06, 130.16, 132.43, 138.46, 144.57, 149.79, 157.90, 166.52; LCMS (+ESI, m/z): 296.1291 (M+H)+

3-(3-hydroxy-4-phenoxyphenyl)-N-(piperidin-4-ylmethyl) acrylamide (60d)

Yield = 0.115 g (56%); mp = 102-104 °C; Rf = 0.11 (hexane: ethyl acetate = 6:4); λmax = 277.2 nm (MeOH); LCMS (+ESI, m/z): 352.1815 (M+H)+

3-(3-hydroxy-4-phenoxyphenyl)-N-(3-methylisoxazol-5-yl) acrylamide (60e)

Yield = 0.125 g (64%); mp = 120-122 °C; Rf = 0.30 (hexane: ethyl acetate = 6:4); λmax = 295.2 nm (MeOH); IR (KBr, cm⁻¹) = 3496 (O-H str.), 3400 (N-H str.), 3043 (Ar-H str.), 2920 (C-H str.), 1631 (C=O str.), 1541, 1498, 1440 (Ar-C=C str.), 1263 (Asym. C-O-C str.), 1049 (Sym. C-O-C str.); LCMS (+ESI, m/z): 337.158 (M+H)+
Synthesis of 3-(3-methoxy-4-(4-nitrophenoxy) phenyl) acrylic acid (61)

Compound 61 was synthesized by following the method described for synthesis of compound 51. 3-methoxy-4-(4-nitrophenoxy) benzaldehyde (33) (0.5 g, 1.29 mmol) was used as the starting material.

Yield = 0.49 g (85%); mp = 222-224 °C; Rf = 0.51 (hexane: ethyl acetate =6:4); λmax = 312 nm (MeOH); LCMS (+ESI, m/z): 316.0674 (M+H)+

2.8.2.62. Synthesis of 3-(4-(4-chlorophenoxy)-3-methoxyphenyl) acrylic acid (62)

Compound 62 was synthesized by following the method described for synthesis of compound 51. 4-(4-chlorophenoxy)-3-methoxybenzaldehyde (42) (0.5 g, 1.29 mmol) was used as the starting material.

Yield = 0.51 g (88%); mp = 204-206 °C; Rf = 0.54 (hexane: ethyl acetate =6:4); λmax = 292 nm (MeOH).

Synthesis of 3-(3-hydroxy-4-(4-nitrophenoxy) phenyl) acrylic acid (63)

Compound 63 was synthesized by following the method given for synthesis of compound 53. 3-(3-methoxy-4-phenoxyphenyl) acrylic acid (61) (0.4 g, 1.268 mmol) was used as the starting material.

Yield = 0.32 g (84%); mp = 212-214 °C (decomposed); Rf = 0.20 (hexane: ethyl acetate =6:4); λmax = 281.6 nm (MeOH); IR (KBr, cm⁻¹) = 3450, 3350 (O-H str.), 3062 (Ar-H str.), 2846 (C-H str.), 1668 (C=O str.), 1614 (C=C str.), 1598 (N-O str.), 1512, 1433 (Ar-C=C str.), 1263 (Asym. C-O-C str.), 1166 (Sym. C-O-C str.); ¹³CNMR (100.64 MHz, DMSO-d₆): 116.42, 117.23, 119.64, 120.81, 123.12, 126.44, 127.16, 128.02, 133.42, 143.68, 149.95, 151.84, 163.55, 167.93, 168.23; LCMS (-ESI, m/z): 300.0561 (M-H)−
Synthesis of 3-(4-(4-chlorophenoxy)-3-hydroxyphenyl) acrylic acid (64)

Synthesized by following the method given for synthesis of compound 53. 3-(4-(4-chlorophenoxy)-3-methoxyphenyl) acrylic acid (62) (0.35 g, 1.148 mmol) was used as the starting material.

Yield = 0.272 g (82%); mp = 206-208 °C; \( R_f = 0.24 \) (hexane: ethyl acetate =6:4); \( \lambda_{\text{max}} = 286.6 \) nm (MeOH); IR (KBr, \( \text{cm}^{-1} \)) = 3383, 3304 (O-H str.), 3062 (Ar-H str.), 2842 (C-H str.), 1683 (C=O str.), 1620 (C=C str.), 1500, 1484, 1410 (Ar-C=C str.), 1219 (Asym. C-O-C str.), 1125 (Sym. C-O-C str.); LCMS (+ESI, m/z): 296.1135 (M+H)+

Synthesis of 3-(4-(4-aminophenoxy)-3-hydroxyphenyl) acrylic acid (65)

Compound 65 was synthesized by following the method given for synthesis of compound 36. 3-(3-hydroxy-4-(4-nitrophenoxy) phenyl) acrylic acid (63) (0.2 g, 0.663 mmol) was used as the starting material.

Yield = 0.125 g (69%); mp = 230 °C (decomposed); \( R_f = 0.08 \) (hexane: ethyl acetate =6:4); \( \lambda_{\text{max}} = 262.6 \) nm (MeOH); IR (KBr, \( \text{cm}^{-1} \)) = 3452, 3414 (O-H str.), 3311, 3271 (N-H str.), 3062 (Ar-H str.), 2846 (C-H str.), 1678 (C=O str.), 1620 (C=C str.), 1502, 1487, 1413 (Ar-C=C str.), 1211 (Asym. C-O-C str.), 1109 (Sym. C-O-C str.); LCMS (+ESI, m/z): 272.0616 (M+H)+

Synthesis of 3-hydroxy-4-phenoxybenzaldehyde (66)

Compound 66 was synthesized by following the method given for synthesis of compound 53. 3-methoxy-4-phenoxybenzaldehyde (50, 0.4 g, 1.75 mmol) was used as the starting material.

Yield = 0.226 g (60%); mp = 82-84 °C; \( R_f = 0.59 \) (hexane: ethyl acetate =6:4); \( \lambda_{\text{max}} = 275 \) nm (MeOH); IR (KBr, \( \text{cm}^{-1} \)) = 3452 (O-H str.), 3057 (Ar-H str.), 1680 (C=O str.), 1527, 1483, 1413, 1211 (Ar-C=C str.), 1109 (Sym. C-O-C str.), 1084 (Sym. C-O-C str.); LCMS (+ESI, m/z): 272.0616 (M+H)+

Scheme-13a

Reagents and conditions: (i). HBr (48% v/v), Gla. AcOH, 110-112 °C, 24h; (ii). L-Cysteine, EtOH, 25-27 °C, 2h.
1440 (Ar-C=C str.), 1245 (Asym. C-O-C str.), 1132 (Sym. C-O-C str.); \(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 10.08 (s, 1H), 9.85 (s, 1H), 7.42 (d, \(J = 1.6\) Hz, 1H), 7.39-7.35 (m, 3H), 7.14-7.10 (m, 1H), 7.01-7.26 (d, \(J = 8\) Hz, 1H), 6.98-6.96 (td, \(J = 8\) Hz and 1.6 Hz, 2H); LCMS (+ESI, m/z): 215.069 (M+H)\(^+\)

**Synthesis of 3-hydroxy-4-(4-nitrophenoxy) benzaldehyde (67)**

Compound 67 was synthesized by following the method given for synthesis of compound 53. 3-methoxy-4-(4-nitrophenoxy) benzaldehyde (42) (0.4 g, 1.46 mmol) was used as the starting material.

Yield= 0.217 g (57%); mp = 138-140 °C; R\(_f\) = 0.61 (hexane: ethyl acetate =6:4); \(\lambda_{\text{max}} = 301.4\) nm (MeOH); \(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)): 116.98, 117.14, 123.28, 123.52, 126.49, 135.19, 146.61, 150.36, 162.78, 192.55; LCMS (+ESI, m/z): 260.0525 (M+H)\(^+\)

**Synthesis of 2-(3-hydroxy-4-phenoxyphenyl) thiazolidine-4-carboxylic acid (68)**

To a stirred solution of compound 66 (0.15 g, 0.7 mmol) in abs. alcohol (2.5 mL), L-Cysteine (0.085 g, 0.7 mmol) was added. Resulting reaction mixture was stirred at 25-27 °C. Progress of the reaction was monitored by TLC, using hexane: ethyl acetate (5:5) as the mobile phase. After the completion of reaction (2h), the reaction mixture was maintained at 0 °C for 4h. The precipitate formed was filtered, washed with cold abs. ethanol and dried. The crude compound was triturated with diethyl ether to afford the target compound as white crystalline solid.

Yield= 0.18 g (81%); mp = 105-107 °C; R\(_f\) = 0.15 (hexane: ethyl acetate =5:5); \(\lambda_{\text{max}} = 276.4\) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3487, 3414 (O-H str.), 3111 (N-H str.), 3062 (Ar-H str.), 2904 (C-H str.), 1631 (C=O str.), 1529, 1487, 1427 (Ar-C=C str.), 1244 (Asym. C-O-C str.), 1157 (Sym. C-O-C str.); LCMS (+ESI, m/z): 318.197 (M+H)\(^+\)

**Synthesis of 2-(3-hydroxy-4-(4-nitrophenoxy)phenyl) thiazolidine-4-carboxylic acid (69).**

Compound 69 was synthesized by following the method given for synthesis of compound 68. 3-hydroxy-4-(4-nitrophenoxy) benzaldehyde (67) (0.13 g, 0.501 mmol) was used as the starting material.

Yield= 0.16 g (88%); mp = 136-138 °C; R\(_f\) = 0.15 (hexane: ethyl acetate =5:5); \(\lambda_{\text{max}} = 303.4\) nm (MeOH); IR (KBr, cm\(^{-1}\)) = 3487, 3414 (O-H str.), 3111 (N-H str.), 3062 (Ar-H str.), 2904 (C-H str.), 1625 (C=O str.), 1591 (N-O str.), 1514, 1485, 1435 (Ar-C=C str.), 1259 (Asym. C-O-C str.), 1163 (Sym. C-O-C str.); \(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)): 116.80, 118.90, 119.38, 122.81, 123.10, 126.43, 138.22, 140.93, 141.03, 142.12, 149.40, 163.76, 173.36; LCMS (+ESI, m/z): 363.0618 (M+H)\(^+\)
3.2.3.2II.1.Spectra

Figure 23.1. $^1$HNMR (400 MHz, DMSO-$d_6$) spectrum of compound 16a

![HNMR spectrum](image)

$^1$HNMR (400 MHz, DMSO-$d_6$): 9.87 (s, 1H), 7.53 (d, $J=2$ Hz, 1H), 7.49-7.46 (dd, $J=8.4$ Hz and 2 Hz, 1H), 7.37-7.33 (m, 2H), 7.26 (d, $J=8.8$ Hz, 4H), 7.18-7.15 (m, 1H), 7.11-7.07 (m, 1H), 6.95-6.92 (m, 3H), 3.29-3.26 (dd, $J=9.6$ Hz and 5.66 Hz, 2H), 2.91 (t, $J=7.6$ Hz, 2H)

Figure 23.2. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 16a

![CNMR spectrum](image)

$^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 30.07, 116.67, 117.93, 120.56, 120.93, 123.52, 126.32, 128.73, 128.84, 130.33, 135.73, 141.75, 148.14, 149.26, 157.85, 198.31

Figure 23.3. LCMS spectrum of compound 16a

![LCMS spectrum](image)

LCMS (+ ESI, m/z): 319.1235 (M+H)$^+$
Figure 23.4. FTIR (KBr, cm⁻¹) spectrum of compound 16a

![FTIR spectrum of compound 16a](image)

Figure 24.1. \(^1\)HNMR (400 MHz, DMSO-\(d_6\)) spectrum of compound 17a

![\(^1\)HNMR spectrum of compound 17a](image)

\(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 9.38 (s, 1H), 7.29-7.24 (m, 4H), 7.19-7.13 (m, 3H), 6.99 (d, \(J = 7.2\) Hz, 1H), 6.95 (d, \(J = 2\) Hz, 1H), 6.88 (d, \(J = 8\) Hz, 1H), 6.81 (d, \(J = 8.4\) Hz, 2H), 6.76-6.73 (dd, \(J = 8\) Hz and 1.6 Hz, 1H), 5.21 (d, \(J = 4.4\) Hz, 1H), 4.46-4.42 (dd, \(J = 12\) Hz and 5.6 Hz, 1H), 2.68-2.61 (m, 2H), 1.88-1.85 (dd, \(J = 12\) Hz and 5.6 Hz, 2H)

Figure 24.2. \(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)) spectrum of compound 17a

![\(^{13}\)CNMR spectrum of compound 17a](image)

\(^{13}\)CNMR (100.64 MHz, DMSO-\(d_6\)): 32.04, 41.50, 71.71, 115.15, 116.42, 117.50, 121.98, 122.16, 126.09, 128.74, 129.97, 141.38, 142.59, 144.15, 149.46, 158.66
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Figure 24.3. LCMS spectrum of compound 17a

Figure 24.4. FTIR (KBr, cm⁻¹) spectrum of compound 17a

Figure 25. UV-Visible spectrum of compound 15a, 16a and 17a in methanol

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**Figure 26.1.** $^1$HNMR (400 MHz, DMSO-$d_6$) spectrum of compound 19b

$^1$HNMR (400 MHz, DMSO-$d_6$): 9.87 (s, 1H), 7.52 (d, $J= 8.4$ Hz and 2 Hz, 1H), 7.43 (s, 1H), 7.36-7.32 (m, 2H), 7.24 (d, $J= 8$ HZ, 2H), 7.10 (d, $J= 7.2$ Hz, 1H), 6.95-6.92 (m, 2H), 6.76 (s, 1H), 4.02-3.99 (dd, $J= 10$ Hz and 4.4 Hz, 1H), 3.78-3.71 (dd, $J= 17.6$ Hz and 11.2 Hz, 1H), 3.09-3.03 (dd, $J= 17.6$ Hz and 4.8 Hz, 1H), 2.25 (s, 3H)

**Figure 26.2.** $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 19b

$^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 21.09, 41.89, 42.57, 46.32, 116.64, 117.88, 120.63, 120.89, 123.49, 128.05, 129.31, 130.33, 133.77, 136.17, 138.11, 148.07, 149.24, 157.19, 174.59, 197.34

**Figure 26.3.** LCMS spectrum of compound 19b

- Molecular Weight: 375.42
- LCMS (+ESI, m/z): 376.1511 (M+H)$^+$
- 356.1242
- 213.0528

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Figure 26.4. FTIR (KBr, cm\(^{-1}\)) spectrum of compound 19b

Figure 27. UV-Visible spectrum of compound 15c, 18c and 19c in methanol

\(^1\)HNMR (400 MHz, DMSO-\(d_6\)): 12.737 (s, 1H), 9.86 (s, 1H), 7.53 (d, \(J= 2\) Hz, 2H), 7.40-7.37 (dd, \(J= 8\) Hz and 2 Hz, 1H), 7.36-7.32 (m, 2H), 7.10-7.06 (m, 1H), 6.94-6.91 (m, 3H)

Figure 28.1. \(^1\)HNMR (400 MHz, DMSO-\(d_6\)) spectrum of compound 23
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Figure 28.2. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 23

![CNMR Spectrum](image)

Figure 28.3. LCMS spectrum of compound 23

![LCMS Spectrum](image)

Figure 29. UV-Visible spectrum of compound 23, 24a and 26 in methanol

![UV-Visible Spectrum](image)
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Figure 30.1. $^1$HNMR (400 MHz, DMSO-$d_6$) spectrum of compound 29d

$^1$HNMR (400 MHz, DMSO-$d_6$): 9.77 (s, 1H), 8.35 (t, $J$ = 5.4 Hz, 1H), 7.44 (d, $J$ = 1.6 Hz, 1H), 7.33 (d, $J$ = 7.6 Hz, 2H), 7.30-7.27 (m, 1H), 7.05 (t, $J$ = 7.4 Hz, 1H), 6.94 (d, $J$ = 8.4 Hz, 1H), 6.88 (d, $J$ = 8 Hz, 2H), 3.57 (s, 3H), 3.29-3.21 (m, 2H), 2.35 (t, $J$ = 7.4 Hz, 2H), 1.79-1.72 (m, 2H)

Figure 30.1. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 34.04, 35.97, 51.85, 116.99, 117.28, 119.09, 121.09, 123.00, 130.19, 131.78, 145.87, 149.24, 157.74, 166.27, 172.25

Figure 30.2. LCMS spectrum of compound 29d

Molecular Weight: 329.35
LCMS (+ESI, m/z): 330.1388 (M+H)$^+$

Counts vs. Mass-to-Charge (m/z)

ESI Scan (0.159 min) Frag = 110.0V SSK-83.d

$^*330.1388$

$^*213.0653$

368.0721

542.1561
1HNMR (400 MHz, DMSO-$d_6$): 12.51 (s, 1H), 9.83 (s, 1H), 7.32 (t, $J=7.6$ Hz, 1H), 7.14 (s, 1H), 7.05 (t, $J=7.2$ Hz, 1H), 6.96 (s, 2H), 6.89 (d, $J=7.6$ Hz, 2H), 5.06 (s, 1H), 4.47 (t, $J=8.2$ Hz, 1H), 4.27 (s, 1H), 3.68 (d, $J=8$ Hz, 1H), 3.36 (d, $J=11.2$ Hz, 1H), 2.18 (t, $J=9.8$ Hz, 1H), 1.95 (d, $J=8.8$ Hz, 1H);

**Figure 31.1.** 1HNMR (400 MHz, DMSO-$d_6$) spectrum of compound 30e

13CNMR (100.64 MHz, DMSO-$d_6$): 25.02, 25.33, 25.52, 28.46, 28.96, 29.40, 46.71, 50.16, 50.40, 58.31, 59.46, 116.62, 116.78, 117.13, 119.21, 121.37, 122.87, 130.17, 133.48, 144.68, 149.29, 157.84, 173.80

**Figure 31.2.** 13CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 30e

LCMS (+ESI, m/z): 328.1032 (M+H)+

**Figure 31.3.** LCMS spectrum of compound 30e
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Figure 32.1. $^1$HNMR (400 MHz, DMSO-$d_6$) spectrum of compound 31d

$^1$HNMR (400 MHz, DMSO-$d_6$): 11.96 (s, 1/2H), 9.75 (s, 1H), 8.35 (s, 1H), 7.44 (s, 3H), 7.34-7.28 (m, 3H), 7.05 (t, $J$ = 7.4 Hz, 1H), 6.94 (d, $J$ = 8 Hz, 1H), 6.88 (d, $J$ = 8 Hz, 2H), 6.72 (s, 1/2H), 3.29-3.19 (m, 2H), 2.25 (t, $J$ = 7.2 Hz, 1H), 2.09 (t, $J$ = 7.4 Hz, 1H), 1.76-1.69(m, 2H);

Figure 31.2. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$), 25.05, 25.61, 31.79, 33.16, 117.04, 117.24, 119.04, 121.10, 122.95, 130.18, 132.10, 132.14, 145.71, 149.25, 157.79, 166.20, 174.56

Figure 31.3. LCMS spectrum of compound 31d

Molecular Weight: 314.34
LCMS (+ESI, $m/z$): 315.1197 (M+H)$^+$

$^+$ESI Scan (0.191 min) Frag=110.0V SSK-84 d

[Data Points]

Counts vs. Mass-to-Charge (m/z)

[Graph]

[Label]
Figure 32. UV-Visible spectrum of compound 23, 29d, 30d and 31d in methanol

Figure 33.1. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 35

Figure 33.1. LCMS spectrum of compound 35
Figure 34.1. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 42

Figure 34.2. LCMS spectrum of compound 42

Figure 35. UV-Visible spectrum of compound 35, 36 and 42 in methanol


**Figure 36.1.** $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 46

**Figure 36.2.** LCMS spectrum of compound 46

**Figure 37.** UV-Visible spectrum of compound 46, 47, 48 and 49b in methanol
Figure 38.1. $^1$HNMR (400 MHz, DMSO-d$_6$) spectrum of compound 53

$^1$HNMR (400 MHz, DMSO-d$_6$): 1212.12 (s, 1H), 9.37 (s, 1H), 7.30-7.25 (m, 2H), 6.97 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 8 Hz, 1H), 6.81-6.78 (m, 3H), 6.66-6.64(dd, J = 8 Hz and 2 Hz, 1H), 2.74 (t, J = 7.6 Hz, 2H), 2.50 (t, J = 5.2 Hz, 2H)

Figure 38.2. $^{13}$CNMR (100.64 MHz, DMSO-d$_6$): 30.34, 35.67, 116.40, 116.86, 117.34, 117.57, 118.72, 119.83, 120.74, 121.79, 122.15, 122.29, 123.02, 129.97, 130.20, 138.72, 141.00, 144.04, 149.55, 158.64, 174.25

Figure 38.3. LCMS spectrum of compound 53

Molecular Weight: 258.27
LCMS (+ESI, m/z): 258.3559 (M+H)+
$^1$HNMR (400 MHz, DMSO-$d_6$): 12.31 (s, 1H), 9.72 (s, 1H), 7.49 (d, $J = 15.6$ Hz, 1H), 7.32 (t, $J = 8$ Hz, 2H), 7.20 (d, $J = 8.6$ Hz, 3H), 7.13 (d, $J = 8$ Hz, 1H), 7.05 (t, $J = 7.4$ Hz, 3H), 6.90 (t, $J = 7.4$ Hz, 3H), 6.32 (d, $J = 16$ Hz, 1H)

Figure 39.1. $^1$HNMR (400 MHz, DMSO-$d_6$) spectrum of compound 57

$^{13}$CNMR (100.64 MHz, DMSO-$d_6$): 116.85, 117.34, 118.74, 120.73, 121.79, 123.02, 130.20, 131.64, 144.02, 145.37, 149.71, 157.73, 168.03

Figure 39.2. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 57

Figure 39.3. LCMS spectrum of compound 57
Figure 40. UV-Visible spectrum of compound 23, 46, 53 and 57 in methanol

Figure 41.1. $^{13}$CNMR (100.64 MHz, DMSO-$d_6$) spectrum of compound 63

Figure 41.2. LCMS spectrum of compound 63
Figure 42. UV-Visible spectrum of compound 63, 64 and 65 in methanol.
3.3. Biological evaluations

3.3.1. In Vitro Antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv

3.3.1.1. Introduction

There are many methods available for the Drug Susceptibility Test (DST) of *Mycobacterium tuberculosis* H37Rv. Among them Microplate Alamar Blue Assay (MABA) is the most widely used indirect colorimetric DST method for the determination of MICs of AntiTB agents. The principle of this assay is based on the reduction of nonfluorescent indicator Alamar blue to fluorescent pink colored compound in the presence of Mycobacterial growth. MABA is a rapid, economic and nonhazardous method through which even reading can be taken without using any analytical instrument. This assay is reported to be conducted inexpensively in the most basic biocontainment level 2 laboratories.

3.3.1.2. Materials and Method

MABA assay was performed as per the reported literature methods.

3.3.1.2.1. Preparation of Media

Alamar blue was procured from Invitrogen. Media-I was prepared using Difco Middlebrook 7H9 (HIMEDIA), Bactocasitone (BD Bioscience), Difcoglycerol (Dickinson and Company), and OADC (BD Bioscience). Media-II was prepared from Middlebrook 7H9 broth (BD Bioscience), Bactocasitone (BD Bioscience), Difco polysorbate-80 (Becton, Dickinson and Company) and OADC (BD Bioscience).

3.3.1.2.2. Preparation of Mycobacterial inoculum

The frozen stock culture suspension of *Mycobacterium tuberculosis* H37Rv (ATTC 27294) from Lowenstein–Jensen slants in complete 7H9 broth were vortexed, adjusted to a turbidity equivalent to that of a 1 McFarland standard (3x10^8 cfu/mL). It was further diluted with media-I to concentration of 2x10^5 cfu/mL and used as inoculum in the MABA assay.

3.3.1.2.3. Preparation of the Standard and Test sample stock/ working solutions

Test samples and standard compounds (Isoniazid and Rifampicin) were dissolved in DMSO and sterilized by filtering through syringe driven filters (0.22 µm, 13 mm, Himedia) to prepare stock solutions of concentration 20,000 µg/mL. The stock solutions were diluted serially with media-II to afford working solutions of 4X strength.
3.3.1.2.4. Method

Serial dilutions of the test compounds were done by using a multi channel micropipette. Inoculum (100 μL, 2x10^5 cfu/mL) was added to each well. Final drug concentrations tests were 1.56–100 μg/mL. Isoniazid and Triclosan were used as standards and DMSO as blank.

Positive control (only inoculum) and negative control (only media) were also applied in the plate. Then the plates were incubated at 37 °C under aeration. On the seventh day of incubation, 12.5 μL of 20% Tween-80 and 20 μL of Alamar blue were added to each wells of the plate and incubated further at 37 °C. A change in color from blue to pink was considered as the growth of the Mycobacterium at that concentration of the drug. For better interpretation of the results, the color was compared to the color present in the growth control wells. The MICs were defined as the lowest concentration of drug that inhibited bacterial.

Primary screening was conducted at six concentrations, ranging from 100 to 1.56 μg/mL. Test compounds which showed MIC ≤ 25 μg/mL against *Mycobacterium tuberculosis* H37Rv were evaluated further with a narrow range of concentration. Their MICs represent an average of two individual measurements.

3.3.2. In Vitro Antitubercular screening against Resistant strains of *Mycobacterium tuberculosis* H37Rv

3.3.2.1. Introduction

Recently, various fully automated, continuously monitoring, nonradiometric systems have been developed to detect the mycobacterium growth. Assay using Mycobacterial Growth Indicator Tube (MGIT) is considered to be a reliable method for the screening of antitubercular agents.\(^{86,87}\) MGIT assay is considered to be safer than the microplate Alamar Blue (MABA) assay as far as the handling of drug resistant strains of *Mycobacterium tuberculosis* is concerned.\(^{88,89}\)

Mycobacterial Growth Indicator Tube (MGIT) contains a fluorescent compound (oxygen-sensitive ruthenium metal complex) whose emissions are quenched by the dissolved oxygen present in the broth. When the mycobacterium grows in the tube, it consumes the dissolved oxygen and allows the fluorescence to be detected. Tubes entered into the instrument
are continuously incubated at 37 °C and monitored every 60 min. for increasing fluorescence. Analysis of the fluorescence by the BACTEC MGIT 960 instrument determines if the test sample in the tube contains viable organisms or not.  

3.3.2.1. Materials and Method  

MGIT assay was performed as per the reported literature methods.  

3.3.2.1.1. Preparation of Mycobacterial inoculum  

**Preparation of the Inoculum for Test samples:** Isoniazid Resistant/ Multi Drug Resistant *Mycobacterium tuberculosis* strain (clinical isolate) suspension was prepared as per the literature method.  

**Preparation of the Inoculation for Growth Control tubes:** Using the INH resistant/Multi Drug Resistant *Mycobacterium tuberculosis* (clinical isolate) strain suspension, 1:100 Growth Control suspension was prepared.  

3.3.2.1.2. Preparation of the Test sample stock/working solutions  

Test samples were dissolved in DMSO to prepare stock solutions of concentration 10,000 µg/mL. The stock solutions were diluted to afford working solutions. First line antitubercular drugs were used as standard.  

3.3.2.1.2. Method  

Mycobacteria Growth Indicator Tubes containing the drug solution and the growth media were placed inside the BACTEC MGIT-900 instrument at 37°C for 12-14 days. The BACTEC MGIT-960 instrument monitored the fluorescence of the MGITs and the results are reported. The Result was analyzed by comparing the fluorescence of test sample tube and growth control tube. The MIC was defined as the lowest concentration of drug that inhibited bacterial growth.
3.3.3. In Vitro Cytotoxicity screening against Vero cells

3.3.3.1. Introduction

To estimate the risk of specific compounds to humans, many toxicity studies are done using animals. However, because of species differences, there is a need for reliable human test system. Therefore, to reduce the use of animals for toxicity assays, cell culture models have been established. A number of methods have been developed to study the cell cytotoxicity of NCEs. Microplate assay using MTT is the most convenient method implemented widely in modern drug discovery. MTT Cell Assay is a safe, sensitive, in vitro colorimetric assay for the measurement of cell viability. Basic principle of this assay is based on enzyme (cytoplasmic NADH/ NADPH and succinate-tetrazolium reductase of mitochondrial respiratory chain) mediated reduction of yellow tetrazolium compound MTT (3-[4, 5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) to formazan, a purple dye by the viable cells. The optical density of formazan is directly proportional to the number of living cells in the culture. Vero cells are the most common mammalian continuous cell lines used to study the cytotoxicity of NCEs. They are nothing but the kidney epithelial cells of African green monkey (Cercopithecus aethiops). 

3.3.3.2. Materials and Method

MTT assay against Vero cells was performed as per the published literature methods. 

3.3.3.2.1. Preparation of Reagents and Media

DMEM was prepared by adding 4.7 g of Dulbeco Modified Eagle Media (AT007, 10x1L, HIMEDIA) and 3.7 g of sodium bicarbonate to MiliQ water and diluted to 1L. pH of the media was adjusted to 7.4. Then the media was filtered aseptically through a membrane filter (0.22 μm) and 10 mL antibiotic solution (a mixture of Penicillin, Streptomycin and Clarithromycin) was added. Saline Phosphate Buffer (1L, pH 7.4) was prepared as per the method described in Indian Pharmacopoeia-2010. MTT reagent (2 mg/mL) was prepared by dissolving 200 mg of Thiazolyl Blue Tetrazolium Bromide (MTT) in 100 mL sterile Saline Phosphate buffer (PBS).

3.3.3.2.2. Propagation of Vero Cell culture

Cryovial containing Vero cells (procured from NCCLS, Pune) was quickly thawed and reconstituted with 5 mL of Dulbeco Modified Eagle Media (DMEM) supplemented with 10% Fetal Bovine Serum (FBS). Then Vero cell (5 mL) suspension was transferred to a tissue culture flask (25 cm²) with vented cap and incubated at 37°C with 5% CO₂. The growth and taxonomy of the cells were monitored daily under microscope and media was changed every 3
days. When it reached >90% confluent monolayer, cells were passaged into new tissue culture flask.

3.3.3.2.3. Inoculation of Vero cells in 96 well Microplate

Cells present in the trypsinated (Trypsin-EDTA) suspension of Vero cells were counted using Hemocytometer and then diluted using DMEM supplemented with 10% Fetal Bovine Serum (FBS) to achieve a final concentration of 1x10⁵ cells/mL. Then 100 µL of cell suspension was added to each well in a 96 well microplate except the outer perimeter (which were filled with 200 µL sterile water) and kept for incubation at 37°C with 5% CO₂ for 24h.

3.3.3.2.4. Preparation of the Test sample stock and working solutions

Test samples were dissolved in DMSO and sterilized by filtering through syringe filters (0.22 µm, HIMEDIA) to prepare stock solutions of concentration 20,000 µg/mL. Stock solution of test samples was diluted with DMEM (without FBS) in a 96 deep well plate to afford working solutions of concentrations 300, 250, 200, 150, 100, 100 and 50 µg/mL. Final concentration of DMSO was kept ≤ 0.1%.

3.3.3.3. Method

Outer perimeter wells of the 96 well plate were filled with sterile deionized water to prevent dehydration in test wells during incubation. Test sample dilutions were distributed at a volume of 100 µL to each wells containing monolayer of Vero cells in a 96-well plate. The plate was incubated at 37 °C with 5% of CO₂ inside an incubator. DMSO was used as blank. Positive control (only inoculum) and negative control (only media) were also maintained in the plate. After 72 h of incubation, supernant was removed from the wells and added with 50 µL of MTT (2 mg/mL) in dark. It was further incubated at 37°C for 3h. After the incubation, supernant was removed carefully from each well. 50 µL of sterile DMSO (filtered through 0.22 µm syringe filter) was added to each well. The plate was transferred to an incubator and kept at 37°C for 2h. Then the plate was placed in an Elisa Reader and the optical density (OD) of the wells was measured at 540 nm.

Optical Density (OD) readings from each well were entered in to the equations below to determine % Cell Viability and % Cell Inhibition.

\[
\% \text{ Cell Viability} = \left( \frac{\text{Optical Density of Test}}{\text{Optical Density of Control}} \right) \times 100
\]

\[
\% \text{ Cell Inhibition} = 100 - \% \text{ Cell Viability}
\]
The CC$_{50}$ values were determined using a curve-fitting program. The CC$_{50}$ values represent an average of two individual measurements.

3.3.4. In Vitro Hepatotoxicity screening against HepG2 cells

3.3.4.1. Introduction

Drug-induced hepatotoxicity is the most common side effect of current antitubercular drugs. It is also one of the chief contributors to high attrition rates during preclinical and clinical drug development. Hepatotoxicity screening of NCEs at the early phase of drug discovery can provide a better idea about the safety profile as most of the drugs metabolized by liver. Determination of human hepatotoxicity using traditional screening methods is not reliable due to the poor assay and reagent specificity, insufficient numbers of endpoints, and an inability to detect early stages of hepatotoxicity. However, microplate assay using MTT against cultures of HepG2 is the most efficient method reported to be used for in vitro hepatotoxicity screening. This is an easy to handle reliable assay method which can provide more accurate human toxicity data by avoiding species variations and less time consuming than animal models.

3.3.4.2. Materials and Method

MTT assay against HepG2 cells was performed by following the same method described for in vitro cytotoxicity screening against Vero cells. HepG2 cells added to each well at a concentration of 7,00,000 cells/mL. MTT was added after 24h and 48h of incubation to visualize the morphological changes. CC$_{50}$ was calculated from following equations.

\[
\% \text{ Cell Viability} = \frac{\text{Optical Density of Test}}{\text{Optical Density of Control}} \times 100
\]

\[
\% \text{ Cell Inhibition} = 100 - \% \text{ Cell Viability}
\]

The CC$_{50}$ values were determined using a curve-fitting program. The CC$_{50}$ values represent an average of two individual measurements.
3.5. Evaluation of drug-like properties

3.5.1. Determination of log P

3.5.1.1. Introduction

The complex lipoglycan calyx on the Mycobacterial cell wall provides a significant natural barrier to the penetration of many intracellular-acting antibiotics. Lipophilic drugs like Quinolones and Rifampicin can cross this hydrophobic thick cell wall by passive diffusion. However hydrophilic drugs can not cross the membrane by passive diffusion. They usually enter through less abundant porin channel which leads to their lesser uptake. Hence antitubercular activity has been observed to be better in more lipophilic compounds (ClogP = 4), although the ClogP values between 2 and 3 are often considered optimal for oral drugs. The majority of current TB drugs still have logP values ranging from 2.5 to 4.38.

Chromatographic methods and in particular reverse phase liquid chromatography (RPLC) methods for octanol/water logP (or logD) values based on capacity factors are widely used and recognized method for the determination of logP. Hence Reverse phase HPLC method was applied to determine the logP (lipophilicity) of our synthesized NCEs. Basic principle of this experiment is based on the retention of a compound in reversed-phase liquid chromatography which governs its lipophilicity. In fact, there exists a co-relationship between logP (P = 1-octanol/water partition coefficient) and logk’ (k’ = retention factor derived from reversed phase liquid chromatography) with aqueous methanol solutions as the mobile phase. Chromatography technique using ODS-4 column and MOPS buffer-octanol system provides better simulation for biological partition/distribution process.

3.5.1.2. Materials and Method

HPLC grade methanol and 1-octanol were purchased from Fisher Scientific. 3-morpholinopropane-1-sulfonic acid (MOPS) was obtained from Spectrochem ltd. MilliQ water was used in preparation of buffer. All the chromatographic runs were conducted on a Shimadzu HPLC at room temperature using ODS-4 (Intersil ODS-4, 5 µm, 4.6 x 150 mm, GL Science Inc.) column and UV-Visible detector. Numerical analysis and data processing were done with Lab solution-2013 software.

Buffer preparation

MilliQ water (1 L) was stirred with 1-octanol (250 mL) at 25-27 °C for 14h. Then the aqueous layer was separated using separating funnel. MOPS (4.18 g) was dissolved in 900 mL MilliQ water and the volume was made up to 1L. pH of the buffer was adjusted to 7.4.
Test sample preparation

Synthesized compounds were dissolved in methanol to prepare test sample concentration of 10 µg/mL.

Chromatographic conditions

Different HPLC methods were developed to run samples to obtain precise data. The flow rate was kept at 1 mL/min for moderately polar compounds and 2 mL/min for comparatively more nonpolar compounds. A mixture of methanol (0.25% v/v octanol) and buffer was used in gradient as mobile phase. Methanol: buffer at the ratio of 60:40, 65:45, 70:30, 75:25, 80:20 and 85:15 were used to elute the samples. Signals were detected at λmax 243, 256, and 270 nm. Sample run time was kept in between 15 min. to 1h.

Chromatographic run

5 µL of test sample solutions were injected using autosampler. As a non-retained compound, methanol was used as blank. While switching over from one method to other, column was kept for equilibration for 2h under new condition.

Table 2. Chromatographic conditions applied for the determination logP

<table>
<thead>
<tr>
<th>Compounds</th>
<th>% Methanol used in mobile phase</th>
<th>Flow rate/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
<td>55</td>
</tr>
<tr>
<td>2a-n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a-n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5a-c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8a-f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9a-f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11a-c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16a, 16b, 16d, 16e</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16c, 16f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17a, 17b, 17c, 17d, 17e</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19a, 19b, 19c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24a, 47, 54, 56b, 56d, 58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26, 28b, 28c, 28f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46, 48, 49b, 60c, 68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53, 55, 56c, 56f, 57, 59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60a, 60e, 60b</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Calculation

Capacity factor \((k')\) was calculated for each run by using the equation given below.

\[ k' = \frac{t_R - t_0}{t_0} \]

Where \(t_R\) is retention time of sample, \(t_0\) is the retention time of blank. The logarithm of \(k'\) was extrapolated to a 0% concentration of methanol in the graph plotted by taking \(\log k'\) in y axis and % methanol (3-4 percentage concentrations) in x-axis. Regression equation was generated from the graph for each sample. From the regression equation, \(\log k'\) at 0% methanol was calculated as the logP of the test compound. In all the cases \(R^2\) was observed to be > 0.99. Obtained experimental logP values were compared with the ClogP calculated virtually using ChemDraw Ultra-08.

3.5.2. Determination of pKa

3.5.2.1. Introduction

Most of the drugs exist in a neutral or charged state, depending on the pH of the body fluids. Ionization of a compound is depicted by pKa (ionization constant). It is observed that neutral compounds are more lipophilic than the ionized one. Even logD, permeability and solubility of a drug depend on its pKa. Hence pKa of a drug is crucial as it influences its pharmacokinetics and toxicity. Therefore, modern approaches to the search for new drugs require ready access to the pKa data of drug candidates.

Reverse phase HPLC method was applied to determine the pKa (Ionization constant) of the synthesized NCEs. The principle behind the determination of pKa value by RPHPLC is based on the relationship between capacity factors and the pH values of the mobile phase. The retention of an ionizable compound in Reverse phase HPLC is different from the retention of neutral compound. Study of the change in retention time of the compound with the change in pH of the mobile phase will give an idea to calculate the pKa of the corresponding compound.

3.5.2.2. Materials and Method\(^{117,118}\)

HPLC grade acetonitrile was purchased from Fisher Scientific. Phosphoric acid, glacial acetic acid, and boric acid were purchased from Spectrochem. All the chromatographic runs were conducted on a Shimadzu HPLC at room temperature using C18 column (Gemini 5 µ
C18 110 A, 4.6 x 150 mm, Phenomenex) and UV-Visible detector. Numerical analysis and data processing were done with Lab solution-2013 software.

**Buffer preparation**

**Universal buffer I**: Phosphoric acid (1.96 g), glacial acetic acid (1.2 g, 1.14 mL) and boric acid (1.36 g) were dissolved in MilliQ water and volume was made up to 5 L.

**Universal buffer I**: 0.02 M NaOH solution was prepared by dissolving 0.8 g of NaOH in MilliQ water (1L).

**Mobile phase preparation**

Acetonitrile was used as the organic modifier in the mobile phase system. Buffers of different pH (pH 2, 5, 7.4 and 10) were prepared by adding universal buffer II to I at different proportions.

**Test sample preparation**

Stock solution of synthesized compounds (10 µg/mL) was prepared using methanol as the solvent.

**Chromatographic conditions**

Different HPLC methods were developed to run samples to achieve precision. Chromatographic measurements were done at 25-27 °C with eluent flow rate of 1 mL/min. Each compound was eluted using buffer of pH 2, 5, 7.4 and 10 and acetonitrile in gradient run. Acetonitrile: buffer at the ratio of 50:50 and 30:70 were used to elute apparently nonpolar and polar samples respectively. Signals were detected at λmax 270 nm. Sample run time was kept in between 15 min. to 1h. Sample injection volume was kept 3 µL and samples were injected using an autosampler. Retention time (RT) of acetonitrile was used as t0. While switching over from one method to other, column was kept for equilibration for at least 2h under new condition.

**Chromatographic run**

pH gradient run was applied with a fixed concentration of organic modifier at the pH range providing complete suppression of ionization of the test sample at the beginning of the gradient and its full ionization at its end. The retention time values, \( t_R \) of each compounds were determined from three separate injections.
Calculation

Capacity factor \((k')\) was calculated for each run by using the equation given below.

\[
k' = \frac{t_R - t_0}{t_0}
\]

Where \(t_R\) is retention time of sample, \(t_0\) is the retention time of blank (acetonitrile). \(pK_a\) was calculated by putting data in the following equation.

\[
pK_a = \text{pH} - \log \frac{kHA - k}{k - kA}
\]

Where \(k\) is the retention factor at a given pH of the compound investigated, \(kHA\) and \(kA\) are the retention factors of unionized and fully ionized form.

A graph was plotted by taking \(\log k'\) (y axis) against different pH (y axis) for each compound and \(pK_a\) was calculated from the slope.\(^{119}\)

The \(pK_a\) values obtained experimentally were compared with the virtually calculated \(pK_a\) of the compounds from SPARC \(pK_a\) predictor.

3.5.3. Evaluation of Protein binding

3.5.3.1. Introduction

Human serum albumin (HSA, 66 kDa) is the most abundant protein in plasma with a concentration of 0.6–0.7 mM.\(^{120}\) This protein has many potential drug binding sites which helps in transportation and distribution of drugs.\(^{121}\) Binding affinities of drugs to plasma proteins are dependent on their hydrophobicity. Thus the basic principle of chromatographic retention was used to measure the extent of protein binding of selected synthesized compounds. HSA column was used to simulate the Human Serum Albumin of plasma.

3.5.3.2. Materials and Method\(^{122,123}\)

HPLC grade isopropyl alcohol was purchased from Fisher Scientific. All the chromatographic runs were conducted on a Shimadzu HPLC at room temperature using Thermo-HSA column (4.6 x 150 mm, 5 µm/ 025) and UV-Visible detector. Numerical analysis and data processing were done with Lab solution-2012 software.

Buffer preparation

Potassium phosphate buffer (0.067 M, pH 7.4) was prepared as per the method given in Indian Pharmacopoeia-2010.
Mobile phase preparation

Mobile phase contained Isopropyl alcohol as the organic modifier and Potassium phosphate buffer (0.067 M, pH 7.4) as the aqueous system.

Test sample preparation

Synthesized compounds were dissolved in isopropyl alcohol to prepare test sample concentration of 10 µg/mL.

Chromatographic conditions

Different HPLC methods were developed to run samples to achieve precision. Chromatographic measurements were done at 25-27 °C with eluent flow rate of 1-2 mL/min.

Table 3. Chromatographic conditions.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mobile phase</th>
<th>Flow rate/min.</th>
<th>Compound</th>
<th>Mobile phase</th>
<th>Flow rate/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Buffer</td>
<td>IPA*</td>
<td></td>
<td>Buffer</td>
<td>IPA*</td>
</tr>
<tr>
<td>16a</td>
<td>90</td>
<td>10</td>
<td>1 mL</td>
<td>29d</td>
<td>80</td>
</tr>
<tr>
<td>16f</td>
<td>80</td>
<td>20</td>
<td>2 mL</td>
<td>29e</td>
<td>80</td>
</tr>
<tr>
<td>17a</td>
<td>90</td>
<td>10</td>
<td>1 mL</td>
<td>46</td>
<td>80</td>
</tr>
<tr>
<td>17b</td>
<td>80</td>
<td>20</td>
<td>2 mL</td>
<td>53</td>
<td>80</td>
</tr>
<tr>
<td>17f</td>
<td>80</td>
<td>20</td>
<td>2 mL</td>
<td>57</td>
<td>80</td>
</tr>
<tr>
<td>19b</td>
<td>80</td>
<td>20</td>
<td>2 mL</td>
<td>60c</td>
<td>80</td>
</tr>
<tr>
<td>23</td>
<td>80</td>
<td>20</td>
<td>2 mL</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*IPA= Isopropyl alcohol

Chromatographic run

The HSA column retention characteristics were calibrated using Verapamil and Metoprolol. Selected synthesized compounds were then eluted using buffer and acetonitrile in gradient run at the ratio of 95:5 and 90:10. Signals were detected at λmax 256 nm. Sample run time was kept in between 15 min. to 1h. Sample injection volume was kept 3 µL and samples were injected using an autosampler. Retention time (RT) of isopropanol (IPA) was used as t₀. While switching over from one method to other, column was kept for equilibration for at least 2h under new condition. The retention time values, tᵣ of each compounds were determined from three separate injections.
Calculation

Capacity factor ($k'$) was calculated for each run by using the equation given below.

$$k' = \frac{t_R - t_0}{t_0}$$

Where $t_R$ is retention time of sample, $t_0$ is the retention time of blank (acetonitrile). Capacity factor ($k'$) is used to calculate the percentage of protein binding. The % protein binding (P) is calculated by:

$$P = 100 \left(\frac{k'}{k' + 1}\right)$$

Where $k'$ is the capacity factor

3.5.4. Evaluation of Human Liver Microsome Stability

3.5.4.1. Introduction

In vitro screening assays using human liver microsomes represent the most effective approach to identify chemical structures with most appropriate stability upon hepatic metabolism.\textsuperscript{124,125} Metabolic stability assay was performed to evaluate the stability of selected synthesized compounds by incubating them with human liver microsomes. Reverse phase HPLC method was applied to quantify the microsomal stability of the test compounds. A reduction in the HPLC peak area of the test compound with time indicates liver microsomal activity. Assays were conducted at 10 mM concentration in duplicate. A concentration of 10 mM was chosen for the one-point assay, because it is the industry standard for initial microsomal screening.

3.5.4.2. Materials and Method

Solvents: HPLC grade acetonitrile was purchased from Fisher Scientific. Acetonitrile (molecular biology grade) and Dimethyl sulfoxide (DMSO) (molecular biology grade) were obtained from Sigma. Testosterone was purchased from TCI Chemicals.

Enzyme: Pooled human liver microsomes (protein content: 20 mg/mL) were obtained from BD Biosciences. All human liver microsomes should be stored at -80 °C and thawed rapidly in a 37 °C water bath and then stored on wet ice prior to use.

NADPH generating agents: Solution A (Cat. No. 451220) and Solution B (Cat. No. 451200) were procured from BD Biosciences.
**Buffer**: Potassium phosphate buffer (0.5 M, pH 7.4) was used in the present study.

**Test sample preparation**: Synthesized compounds were dissolved in DMSO to prepare test sample concentration of 5 mM.

**Incubation of the compounds with HLM**

The study was performed as per literature method. The test compounds were incubated with liver microsomes in presence of NADPH and placed inside an incubator at 37 °C water bath. After 0, 15, 30, 60 and 120 minutes of incubation, 100 µL of the mixture was withdrawn and analyzed by HPLC.

A positive control (Testosterone) was used to confirm that the assay is working properly. A negative control for each test compound was used to detect problems such as nonspecific protein binding or heat instability.

**Chromatographic analysis**

All the chromatographic runs were conducted on a Shimadzu HPLC at room temperature using C18 column (Gemini 5 µ C18 110 A, 4.6 x 150 mm, Phenomenex) and UV-Visible detector. Numerical analysis and data processing were done with Lab solution-2012 software.

**Mobile phase preparation**: Mobile phase contained acetonitrile as the organic modifier and Buffer (0.1% v/v formic acid).

**Chromatographic conditions**

Different HPLC methods were developed to run samples to achieve precision. Chromatographic measurements were done at 25-27 °C with eluent flow rate of 1 mL/min. Each compound was eluted using buffer and acetonitrile in gradient run. Acetonitrile: buffer at
the ratio of 60:40, 50:50 and 40:60 were used to elute the test samples. Signals were detected at λ\text{max} 272 nm. Sample run time was kept in between 15 min. to 1h.

**Chromatographic run**

Sample injection volume was kept 50 µL and samples were injected using an autosampler. Retention time (RT) of acetonitrile was used as t₀. While switching over from one method to other, column was kept for equilibration for at least 2h under new condition.

**Calculation**

The percentage of compound remaining after 15, 30, 60 and 120 min. of incubation was calculated as:

\[
\text{% remaining} = 100 \times \left( \frac{\text{mean \ PAR}_R}{\text{mean \ PAR}_0} \right)
\]

Where PAR = Peak area of analyte/IS peak area ratio

The log peak area ratio (mean PAR_R/mean PAR_0) was plotted against time, and the elimination rate constant \[k = (-2.303) \text{ slope}\] was calculated from the slope. The half-life was calculated as \[t_{1/2} = 0.693/k\].

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