Chapter 4

Synthesis and Antituberculosis Activity of Thymol Based Schiff Bases and Triazoles


4.1 Introduction

According to the World Health Organization (WHO), six infectious diseases (pneumonia, tuberculosis, diarrhoea, malaria, measles and HIV/AIDS) account for half of all premature deaths worldwide, killing mostly children and young adults.\(^1\) Amongst these, tuberculosis (TB) is a chronic disease that gets transmitted through air. It is caused predominantly by *Mycobacterium tuberculosis* (*M. tb*), while other strains of mycobacteria which can cause TB includes *M. avium* and *M. africanum*.\(^2,3\) Robert Koch was the first scientist who isolated the bacteria, *M. tb* in 1882 and got Nobel Prize for this discovery.\(^4\) Blood stained cough, chest pain, loss of weight, perspiration during night and feeling cold are the main symptoms in a person infected with TB.\(^5\) Three-fourth of the active tuberculosis (TB) cases are pulmonary while in 1/4\(^{th}\) of the cases meninges, lymphatic system, bones, pleura, joints and so on are affected by the bacteria.

The gravity of the situation can be understood from the report published in 2010, by World Health Organisation (WHO) according to which, 9.4 million new tuberculosis cases occurred in 2009. In the same year 1.7 million deaths were reported due to TB, out of which 0.38 million people were infected with both HIV and TB.\(^6\) The situation is even more deplorable than it appears as 0.5 million new cases were due to multidrug resistant (MDR) TB.\(^7\) The alarming estimates exposes that 0.22 billion people may acquire TB and 79 million could die due to TB by the year 2030. According to Denholm *et al* about 33% of the population in the world is at risk of reactivation by latent tuberculosis infection (LTBI) in the future.\(^8\) Moreover the emergence of multi-drug resistance (MDR) and the extensively drug resistant (XDR) TB strains is a serious problem.\(^9\) Recently, India (in 2012) has become the third country after Italy (in 2007)\(^10\) and Iran (in 2009)\(^11\) where totally drug-resistant tuberculosis (TDR-TB) has been reported.\(^12\)
Ninety-five percent of all tuberculosis cases in the world occur in developing countries. Tuberculosis is prevalent in Russia, India, Southeast Asia, Sub-Saharan Africa and parts of Latin America.\textsuperscript{13-15} The main reasons for such a large number of TB cases in developing nations are breakdown in health services, co-infection with HIV/AIDS and the emergence of multidrug-resistant TB.\textsuperscript{16} In 1993, the WHO declared tuberculosis as a global emergency.\textsuperscript{17}

“\textit{If the number of victims which a disease claims is the measure of its significance, then all diseases, particularly the most dreaded infectious diseases, such as bubonic plague, Asiatic cholera, et cetera, must rank far behind tuberculosis.}” \textbf{Robert Koch (1882)}

\section*{4.2 Drugs in Use for Tuberculosis Treatment}

Streptomycin (1) was the first drug used for the treatment of tuberculosis was discovered in 1943(figure 4.1).\textsuperscript{18,19} Later on many other potent drugs were discovered and categorised as first-line, second-line and third-line (figure 4.1).
The first-line antituberculosis drugs are streptomycin (STM/S; 1),20 isoniazid (INH/H; 2),21,22 pyrazinamide (PZA/Z; 3),23 ethambutol (EMB/E; 4)24 and rifampicin (RIF/R; 5).25

Second-line drugs (SLDs) are those which are less effective than the first-line or have some side effects. The unavailability of a drug in many developing countries also makes it second-line drug. Further, the SLDs are divided into six classes; these are (i) aminoglycosides (amikacin/AMK; 6, kanamycin/KM; 7) (ii) polypeptides (capreomycin; 8, viomycin; 9) (iii) fluoroquinolones (ciprofloxacin/CIP; 10) (iv) thioamides (prothionamide; 11, ethionamide; 12) (v) cycloserine (13) and (vi) p-aminosalicylic acid/PAS/P (14). Drugs which are practiced and not included as SLDs are called third-line drugs. The third-line drugs are either not very efficient or their effectiveness is not yet established. This includes linezolid (LZD), rifabutin, macrolides (clarithromycin /CLR), vitamin D, thioacetazone (T), thioridazine and arginine.26 The standard Directly Observed Treatment Short (DOTS) course for TB is a 6 months treatment. This includes the first 2 months of isoniazid (2), pyrazinamide (3), ethambutol (4) and rifampicin (5) in the intensive phase and after isoniazid and rifampicin in the...
continuous phase.\textsuperscript{27} India has a major contribution in the discovery of DOTS programme.\textsuperscript{28}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chemical_structures.png}
\caption{Chemical structures of various TB drugs: 6 (Amikacin), 7 (Kanamycin), 8 (Capreomycin), 9 (Viomycin), 10 (Ciprofloxacin), 11 (Prothionamide), 12 (Ethionamide), 13 (Cycloserine), and 14 (p-Aminosalicylic acid).}
\end{figure}

\subsection*{4.3. Anti-TB Compounds in Clinical Trials}

The determination of \textit{M. tb} H37Rv genome sequence in 1998 was a breakthrough for scientists throughout the world.\textsuperscript{29} Despite the severe outbreak of TB and the rise of multidrug-resistant strains, progress to find a new vaccine or improvement of the BCG (Bacille Calmette-Guerin) vaccine has been very slow.\textsuperscript{30}
Table 4.1: Compounds undergoing clinical trials for tuberculosis treatment

<table>
<thead>
<tr>
<th>Drug Name (Class)</th>
<th>Licensor/Sponsor</th>
<th>Mode of Action</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin (Fluoroquinolone)</td>
<td>Bayer/Global TB Alliance</td>
<td>Inhibition of <em>M. tb</em> DNA topoisomerase II</td>
<td>III</td>
</tr>
<tr>
<td>Gatifloxacin (Fluoroquinolone)</td>
<td>EU/TDR</td>
<td>Inhibition of <em>M. tb</em> DNA topoisomerase II</td>
<td>III</td>
</tr>
<tr>
<td>PA824 (Nitroimidazole)</td>
<td>Global TB Alliance</td>
<td>Inhibition of lipid and protein synthesis, <em>M. tb</em> activated prodrug</td>
<td>II</td>
</tr>
<tr>
<td>TMC207 (Diarylquinoline)</td>
<td>Tibotec/J&amp;J</td>
<td>Target ATP synthase subunit c proton pump</td>
<td>II</td>
</tr>
<tr>
<td>SQ109 (Ethylene diamine)</td>
<td>Sequella</td>
<td>Thought to be cell wall synthesis but different to EMB</td>
<td>II</td>
</tr>
<tr>
<td>OPC67683 (Nitroimidazole)</td>
<td>Otsuka</td>
<td>Inhibits mycolic acid synthesis, prodrug and requires activation</td>
<td>III</td>
</tr>
<tr>
<td>LL3858 (Pyrrole)</td>
<td>Lupin</td>
<td>N/A</td>
<td>I</td>
</tr>
</tbody>
</table>
However, in recent years there are some new drug candidates developed which have reached early stages of clinical trials (table 4.1).\textsuperscript{31} Out of the numerous anti-TB compounds, only a couple of the compounds are in phase I or II clinical trials and three of the compounds have entered phase III clinical trials. The seven new antitubercular drugs, namely moxifloxacin (15), gatifloxacin (16), TMC207 or R207910 (17), OPC67683 (18), PA824 (19), LL3858 (20) and SQ109 (21) are at different stages of clinical development.

\textbf{4.4 Concept of Hybrid Molecules}

In order to overcome the problem of drug resistance several approaches such as targeting bacterial virulence, genome hunting, high-throughput screening (HTS), structure-based drug discovery (SBDD) and combinatorial chemistry have been explored.\textsuperscript{32-34} Sometimes a single drug is not sufficient to completely cure a disease and a combination of drugs is required. A newer concept in the field of drug discovery has come into existence whereby two drug pharmacophores are incorporated in a single molecule to exert dual drug action. One of the hybrid parts may be incorporated to counterbalance the known side effects associated with the other hybrid part, or to amplify its effects through action on another biological target.\textsuperscript{35} These are called “hybrid drugs” which are gaining popularity in medicine and it is anticipated that such approach may solve the problem of drug resistance. Ultimately, no matter how familiar the building blocks may be, hybrid drug molecules may, at their core, become new molecules with identities independent of their precursors.\textsuperscript{36} Using this concept several compounds have been prepared and used for systemic heart disease and malaria. Zatebradine (22, benzazepine and arylalkyl moiety),\textsuperscript{37} reversed chloroquines (23, chloroquine and reversal agent),\textsuperscript{38} PA1103-SAR116242 (24, trioxane and quinine)\textsuperscript{39} are examples of some hybrid molecules.
In order to achieve this goal we turned our attention towards triazole and thymol as both of these classes of compounds have shown very promising anti-TB activity. Triazole based compounds are known for their antibacterial,\textsuperscript{40,41} antifungal,\textsuperscript{42} antiviral,\textsuperscript{43} antimicrobial agents\textsuperscript{44-46} anti-inflammatory,\textsuperscript{47,48} analgesic and antiplatelet activities.\textsuperscript{49} Literature survey revealed that many triazole based compounds have shown promising anti-TB activity as well. In 2011, Shanmugavelan et al reported the \textit{in vitro} activity of some triazoles against \textit{M. tb} H37Rv. The triazole based compound 25, possess MIC 1.56 µg/mL, being 2.08 times more active than the standard drug ethambutol (MIC = 3.25 µg/mL).\textsuperscript{50} Gallardo \textit{et al} had reported the activity of some 1-alkyl-4-phenyl-[1,2,3]-triazoles against \textit{M. tb} H37Rv strain (ATCC 27294, susceptible to rifampicin and isoniazid) using the microplate alamar blue assay (MABA). Five compounds (26a-26e) showed better activity against \textit{M. tb} (MIC = 3.1 µg/mL) than the reference compound ethambutol (MIC = 3.25 µg/mL).\textsuperscript{51} Boecha \textit{et al} synthesized 4-substituted \textit{N}-phenyl-1,2,3-triazole derivatives of isoniazid (27a-27e) and screened them \textit{in vitro} for antimicrobial activity against \textit{M. tb} H37Rv (ATCC 27294) using the alamar blue
susceptibility test. Four compounds (27a-27e) showed activity (MIC = 0.62 µg/mL) better than reference drug rifampcin (1.0 µg/mL).\textsuperscript{52}

Thymol (2-\textit{iso}-propyl-5-methylphenol, 28) is a naturally occurring monoterpenic phenol which is isomeric with carvacrol (29) and has shown antibacterial,\textsuperscript{53} antifungal,\textsuperscript{54} antitumor and anti-inflammatory\textsuperscript{55} activities. It also acts as an antioxidant,\textsuperscript{56} free radical scavenger\textsuperscript{57} and antilipid peroxidative agent.\textsuperscript{58} It is said that thymol acts as biocidal agent by causing disruption of the bacterial membrane. Thymol has antimicrobial properties and has the ability to reduce bacterial resistance to drugs such as penicillins (synergistic). The therapeutic property of thymol is known since centuries, and a preparation from the thyme plant (thymol and carvacrol) was used by ancient Egyptians to preserve mummies. Thymol is an active ingredient of Listerine (mouthwash) and Vicks.

The 4,4′-diaminodiphenylsulfone (DDS, 30) showed inhibition of \textit{M. tb} growth in guinea pigs infected with human type of tubercle bacilli.\textsuperscript{59} But due to toxicity of this drug in humans it is not well suited for the treatment of tuberculosis. But, the diazotization of
DDS (30) and coupling with thymol resulted into 4,4’-bis(6-thymylazo)-diphenylsulfone (DDS-thymol, 31) which is relatively non-toxic. TB patients who do not respond to other treatment showed positive response when treated with DDS-thymol (31).60,61

\[
\begin{align*}
&H_2N\begin{array}{c}
\text{S}\text{O}\\text{N}\text{H}_2
\end{array}

&H_2O\begin{array}{c}
\text{N}\text{H}_2\text{N}\text{O}\text{S}\text{N}\text{O}\text{O}
\end{array}

&H_3C\begin{array}{c}
\text{N}\text{OH}
\end{array}

&H_3C\begin{array}{c}
\text{CH}_3
\end{array}

&H_3C\begin{array}{c}
\text{NH}_3
\end{array}

&\begin{array}{c}
\text{H}_3\text{C}
\end{array}

&\begin{array}{c}
\text{CH}_3
\end{array}

&\begin{array}{c}
\text{CH}_3
\end{array}

&\begin{array}{c}
\text{CH}_3
\end{array}

\end{align*}
\]

30 (4,4’-Diaminodiphenylsulfone) 31 (4,4’-bis(6-Thymylazo)-diphenylsulfone)

### 4.5 Present Investigation

Present investigation deals with the synthesis and antituberculosis activity evaluation of thymol-Schiff bases (34-73) and thymol-triazole hybrids (96-112 and 130-134) (figure 4.2). All the synthesized compounds were characterized by spectroscopic techniques.

![Prototype structures of the present study](image)

### 4.6 Results and Discussion

The strategy of synthesis of thymol derivatives started with the synthesis of 4-aminothymol (33).62 To begin with thymol (28) was first converted to 4-nitrosothymol (32) by treating ethanolic solution of thymol with conc. hydrochloric acid and sodium nitrite at very low temperature (0 °C). The nitroso compound was reduced in an ammonical solution by passing H₂S gas (scheme 4.1). The foul smelling H₂S gas was
generated by treating sodium sulphide flakes with dil. H\textsubscript{2}SO\textsubscript{4}. The 4-aminothymol obtained is highly unstable and subject to oxidation over a period of time.

![Scheme 4.1](image)

The 4-aminothymol (33) prepared according to scheme 4.1 was condensed with different benzaldehydes as soon as possible (scheme 4.2) due to its unstability under air. This reaction was carried out at room temperature using dry MeOH (dried using Mg turnings and I\textsubscript{2}) as solvent and maintaining inert condition using nitrogen balloon. The Schiff bases obtained were characterized by spectroscopic techniques. Interestingly, the NaBH\textsubscript{4} reduction of these Schiff bases were unsuccessful while reduction by Pd/C/H\textsubscript{2} lead to the cleavage of C=N bond.

![Scheme 4.2](image)
In the infrared spectrum compound 39 (figure 4.3) a broad peak beyond 3000 cm\(^{-1}\) was observed which is characteristic of the O–H stretch. Band at 1625 cm\(^{-1}\) was due to N=CH stretch. In the Nuclear Magnetic Resonance spectra of compound 39 (figure 4.4) recorded in CDCl\(_3\) a triplet at \(\delta\) 0.96 was observed for the methyl group of the \(n\)-propyl chain, the other two methylene groups appeared at \(\delta\) 1.67 and 2.64 as sextet and triplet, respectively. Signals appearing as doublet and septet at \(\delta\) 1.27 and 3.18 were assigned to protons of the \textit{iso}-propyl group. A singlet at \(\delta\) 2.30 for three protons was assigned to the methyl group attached with benzene ring. The phenolic OH appeared as broad singlet at \(\delta\) 4.70. Protons of the aromatic ring appeared at \(\delta\) 6.62 and 6.81 as singlet while two doublets at \(\delta\) 7.26-7.28 (merged with solvent peak) and 7.82 were assigned to the \textit{ortho} coupled protons of the aromatic ring. The characteristic peak for the Schiff base appeared at \(\delta\) 8.34 as singlet. The structure of compound 39 was further confirmed by \(^{13}\)C NMR
(figure 4.5) in which a total of seventeen signals appeared. The signals for the carbons of the \( n \)-propyl group appeared at \( \delta \) 13.76, 24.39 and 38.02. The methyl carbon attached directly to the benzene ring appeared at \( \delta \) 17.36. The methyl carbons of \( iso \)-propyl group appeared as an intense signal at \( \delta \) 22.69 while the methine carbon appeared at \( \delta \) 27.0. Signal at \( \delta \) 150.82 was assigned to the aromatic carbon attached to phenolic OH. The most downfield signal at \( \delta \) 157.96 was characteristic of the imine carbon. Remaining peaks at \( \delta \) 115.64, 117.10, 128.54, 128.83, 130.65, 132.46, 134.32, 144.30 and 146.05 were due the aromatic ring carbons. ESI-MS of compound 39 (figure 4.6) showed peak at \( m/z \) 296.23 corresponding to \([M + H]^+\).

![Figure 4.4: \(^1\)H NMR spectrum of compound 39](image)
Keeping in mind the biological potential of triazole and the recent literature quoting antituberculosis activity of triazoles, some thymol-triazole hybrids were also synthesized as shown in scheme 4.3. The 4-hydroxybenzaldehyde (74) was treated with 1,2-dibromoethane or 1,3-dibromopropane to get compounds 75 and 76 as depicted in scheme 4.3. The bromo group of compounds 75 and 76 was then converted to the azido (77 and 78) by reaction with sodium azide in presence of K$_2$CO$_3$ as base and dimethylformamide as solvent. The cycloaddition of azide group and terminal alkyne via click reaction gave different triazole based compounds (79-95) in which an aldehydic
group was present to carry out further reactions. These compounds were then condensed with 4-aminothymol (33) which was prepared according to scheme 4.1 to get the desired compounds (96-112) in good yields as depicted in scheme 4.3.

Scheme 4.3

The IR spectrum of compound 96 (figure 4.7) showed peaks at 3124, 1620, 1246 and 1054 cm\(^{-1}\) for O–H, N=CH and C–O–C (asymmetrical and symmetrical) stretch, respectively. In the \(^1\)H NMR of compound 96 recorded in DMSO-\(d_6\) (figure 4.8) a triplet at \(\delta\) 0.88, a sextet at \(\delta\) 1.59 and a triplet at \(\delta\) 2.57 of three, two and two protons, respectively were assigned to the protons of \(n\)-propyl group. The \textit{iso}-propyl group
showed a doublet of six protons at $\delta$ 1.16 and septet of one proton at $\delta$ 3.15. Methyl group attached to the phenyl ring appeared at $\delta$ 2.19 as singlet and phenolic OH appeared at $\delta$ 9.11. Two triplets of the proton each at $\delta$ 4.44 and 4.72 were assigned to the methylene groups attached to the nitrogen and oxygen, respectively. Two singlet of one proton each at $\delta$ 6.62 and 6.86 were assigned to protons of the tetra-substituted aromatic ring. Doublets at $\delta$ 7.02 and 7.83 were assigned to the ortho coupled protons of aromatic ring. Singlet at $\delta$ 7.91 was assigned to the CH of triazole ring. The characteristic peak for the Schiff base appeared at $\delta$ 8.40 for N=CH.

$^{13}$C NMR spectrum of compound 96 (figure 4.9) showed twenty-one peaks in all. The most upfield peak at $\delta$ 13.59 was due to the CH$_3$ group of the alkyl chain, peaks for the other two methylene carbons appeared at $\delta$ 22.27 and 27.04. The methyl carbon attached to the aromatic ring appeared at $\delta$ 17.24 and carbons of the iso-propyl group appeared at $\delta$ 22.57 and 26.38. The peaks next to the solvent (DMSO-$d_6$) at $\delta$ 48.76 and 66.39 were
due to the methylene carbons attached to nitrogen and oxygen, respectively. The characteristic peak for N=CH appeared at δ 155.40. The two types of carbons of the triazole nucleus appeared at δ 122.37 and 132.31. The carbon to which phenolic OH is attached appeared at δ 152.55 while the carbon of \textit{para} substituted aromatic ring attached to oxygen appeared most downfield at δ 159.88. Peaks at δ 114.71, 114.88, 116.50, 129.84, 130.16, 130.20, 141.63 and 146.76 were assigned to remaining carbons of aromatic ring. ESI-MS of compound 96 (figure 4.10) showed molecular ion peak at $m/z$ 407.32 [M + H]$^+$. 

![Figure 4.8: $^1$H NMR spectrum of compound 96](image-url)
Using similar synthetic protocol, isomeric triazole derivatives having a methylene linker between the aromatic ring and triazole nucleus were prepared as depicted in scheme 4.4. Firstly, para-hydroxybenzaldehyde (74) was treated with propargyl bromide (113) in the presence of a base and dry DMF as solvent to get compound 114. Different
alky halides (115-119) were then converted to azido compounds (120-124). These azido compounds (120-124) were then reacted with the previously synthesized alkyne (114) to get the triazoles (125-129). Compound 33 was then reacted with these triazoles to get imine linkage and triazole moiety in the same compounds (130-134).

![Scheme 4.4](image)

In the IR spectra of compound 131 (figure 4.11) the peaks for O–H, N=CH and C–O–C stretch appeared at 3102, 1624 and 1251 cm⁻¹, respectively. In the ¹H NMR of compound 131 recorded in DMSO-δ (figure 4.12) a triplet, sextet and triplet of three, two and two protons each at δ 0.82, 1.82 and 4.32, respectively were assigned to n-propyl group. The protons of the iso-propyl group appeared as doublet and septet at δ 1.16 and 3.15, respectively. A singlet at δ 2.20 was assigned for the methyl group attached to benzene ring. The protons of the methylene group attached to oxygen atom appeared downfield at δ 5.20. Two singlet of one proton each at δ 6.62 and 6.86 were assigned to the protons of the tetra-substituted aromatic nucleus. Two distinct doublets at δ 7.13 and
7.85 with $J$ value 8.8 Hz clearly indicates the presence of para-substituted aromatic system. Singlets at $\delta$ 8.25 and 8.41 were characteristic of the proton of triazole nucleus and Schiff base (N=CH), respectively. The most downfield signal at $\delta$ 9.11 was assigned to phenolic OH. In the $^{13}$C NMR of compound 115 (figure 4.13) nineteen signals were observed, though there were twenty types of carbons as two carbons had the same chemical shift. The carbon signals of $n$-propyl group appeared at $\delta$ 10.79, 22.58 and 50.97. The CH$_3$ attached to aromatic ring was assigned peak at $\delta$ 17.27. The carbons of iso-propyl group appeared at $\delta$ 23.18 and 26.41. The methylene carbon attached to oxygen appeared at $\delta$ 61.27. Two signals at $\delta$ 160.08 and 152.56 were assigned for aromatic quartenary carbons attached to oxygen atom. The characteristic peak at $\delta$ 155.47 was due to N=CH carbon.

Figure 4.11: IR spectrum of compound 131
Figure 4.12: $^1$H NMR spectrum of compound 131

Figure 4.13: $^{13}$C NMR spectrum of compound 131
The two carbons of triazole ring appear at δ 129.85 and 141.72. In addition to triazole ring carbon the signal δ 129.85 was also assigned to the aromatic carbon attached to iminic carbon. The remaining peaks at δ 114.88, 116.53, 124.51, 130.02, 130.16, 132.34 and 142.32 belong to aromatic carbons.

4.7 In Vitro Antimycobacterial Activity

The thymol-Schiff bases synthesized (34-73) were screened for their antituberculosis activity against M. tb H37Rv in vitro. All the compounds were dissolved in DMSO at a concentration of 10 mg/mL. M. tuberculosis H37Rv was grown in MB 7H9-tween media (ADC was added as media enrichment) till early-logarithmic phase (A_{600nm} of 0.8) and the cells were subsequently diluted to an A_{600nm} of 0.02 (2 \times 10^6 cfu/mL) in respective media. 1 mL aliquots of this culture were incubated with varying concentrations of the compounds along with the controls (containing appropriate concentrations of DMSO) for 7 days at 37 ºC with constant shaking at 200 rpm. The cultures were serially diluted with MB 7H9 media and CFU was determined by plating on MB 7H11 agar plates after incubation at 37ºC for 3-4 weeks. MIC_{99} value is the concentration of the compound which resulted in 99% inhibition of the growth. Isoniazid and rifampicin were used as standard drugs with MIC 0.1 and 0.125 µg/mL, respectively.

The thymol-Schiff bases (34-73) were found to be moderate to weakly active (table 4.2). Analysis of the data revealed that ten compounds (34, 35, 38, 39, 40, 48, 53, 64, 65 and 67) were active with MIC_{99} value 10 µg/mL. Compound 69 was the best active compound amongst the series with MIC_{99} 6 µg/mL. Alkyl substitution at para position has some contribution to the activity as seen from the MIC values of compounds 37-42. Compounds with 4-Et, 4-n-Pr and 4-i-Pr substituent are better active than methyl or butyl groups. The unsubstituted compound (34) was more active than the methyl substituted compound. The ortho/meta/para NO2 substituted derivatives (43-45) showed
poor activity while presence of OH group as in compound 69 (6 µg/mL) enhances the activity manifold. The di- and tri- fluoro (64 and 65) substituted compounds showed similar activity (10 µg/mL), but in case of chloro substitution the 2,4-Cl (40 µg/mL) was less active than 2,6-Cl (10 µg/mL). Presence of CF$_3$ or di-Me or Cl resulted into compounds with poor activity.

The thymol-triazole hybrids (96-112 and 130-134) showed weak activity with MIC $\geq$50 µg/mL (table 4.3 and 4.4).

### Table 4.2: In vitro antimycobacterial activity of thymol-Shiff bases (34-73)

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>MIC$_{50}$ (µg/mL) H37Rv</th>
<th>Compd</th>
<th>R</th>
<th>MIC$_{50}$ (µg/mL) H37Rv</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>H</td>
<td>10</td>
<td>54</td>
<td>4-Br</td>
<td>20</td>
</tr>
<tr>
<td>35</td>
<td>2-Me</td>
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<td>55</td>
<td>2-CF$_3$</td>
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<tr>
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<td>3-Me</td>
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<td>56</td>
<td>3-CF$_3$</td>
<td>&gt;20</td>
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<tr>
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<td>57</td>
<td>4-CF$_3$</td>
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<tr>
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<td>69</td>
<td>2-OH, 5-NO$_2$</td>
<td>6</td>
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<tr>
<td>50</td>
<td>3-Cl</td>
<td>&gt;20</td>
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<td>2-Pyridyl</td>
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<tr>
<td>51</td>
<td>4-Cl</td>
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<tr>
<td>52</td>
<td>2-Br</td>
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</tr>
<tr>
<td>53</td>
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<td>10</td>
<td>73</td>
<td>2,3-OCH$_3$O</td>
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Table 4.3: *In vitro* antimycobacterial activity of thymol-triazoles (96-112)

<table>
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<th>Compd</th>
<th>MIC$_{99}$ (µg/mL)</th>
<th>Compd</th>
<th>MIC$_{99}$ (µg/mL)</th>
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<tr>
<td>96</td>
<td>2</td>
<td>n-Pr</td>
<td>&gt;50</td>
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<tr>
<td>97</td>
<td>2</td>
<td>n-Bu</td>
<td>&gt;50</td>
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<td>98</td>
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<td>1-Cyclohexanol</td>
<td>&gt;50</td>
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<td>2</td>
<td>CH$_2$OH</td>
<td>50</td>
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<tr>
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<tr>
<td>104</td>
<td>2</td>
<td>CH$_3$O-4-ClPh</td>
<td>&gt;50</td>
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Table 4.4: *In vitro* antimycobacterial activity of thymol-triazoles (130-134)

<table>
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<th>Compd</th>
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<td>n-Bu</td>
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<td>133</td>
<td>n-Pentyl</td>
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<td>134</td>
<td>CH$_3$Ph</td>
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</table>

4.8 Experimental Section

4.8.1 Analytical Methods

All the chemicals were purchased from Sigma-Aldrich. Solvents used for the chemical synthesis were acquired from commercial sources, were of analytical grade and used without further purification unless otherwise stated. Chromatographic purifications were carried out with silica gel (60-120 mesh) and TLC was done on silica gel coated
(Merck Kiesel 60 F254, 0.2 mm thickness) sheets. Spots were visualized by using either UV-lamp, iodine or ninhydrin stain. Melting points were recorded on EZ-Melt automated melting point apparatus, Stanford Research Systems and are uncorrected. The IR spectra were acquired on a Perkin-Elmer FT-IR spectrophotometer using KBr pellets or as film in chloroform. 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded on a Jeol ECX spectrospin using tetramethylsilane (TMS) as internal reference standard dissolving the compounds in CDCl₃ or DMSO-d₆ and the chemical shifts are reported in δ units. Mass data were recorded in Jeol-Accu TOF JMS-T100LC mass spectrometer. The J constant was given in Hz. The letters s, brs, d, t, and q refer to singlet, broad singlet, doublet, triplet and quartet, respectively.

4.8.2 Synthesis and Characterization of Compounds

Synthesis of 2-isopro-pyl-5-methyl-4-nitrosophenol (32): To a stirred solution of 2-isopropyl-5-methylphenol (28; 5 g, 0.03 mol) in ethanol (25 mL), conc. HCl (25 mL) was added. The reaction mixture was cooled to 0 °C and sodium nitrite (3.44 g, 0.04 mol) was added very slowly to this with vigorous stirring. The solid separated was filtered and recrystallized with ethanol. Yield 75%; lit. mp 158 °C62; 1H NMR (400 MHz, CDCl₃) δ: 1.14 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.19 (s, 3H, CH₃), 3.09 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 3.51 (s, 1H, OH), 6.34 (d, J = 1.5 Hz, 1H, ArH), 7.54 (s, 1H, ArH).

Synthesis of 4-amino-2-isopropyl-5-methylphenol (33): To 2-isopropyl-5-methyl-4-nitrosophenol (32; 3.75 g) 30% aq. ammonia (300 mL) was added. The brown solution was filtered and to the clear filtrate hydrogen sulphide gas was passed for 30-40 minutes. The white solid obtained was filtered and recrystallised from ethanol to get amino-2-isopropyl-5-methylphenol (33). Yield 80%; mp 177 °C.
Typical procedure for the synthesis of 4-(benzylideneamino)-2-iso-propyl-5-methylphenol (34) and related compounds (35-73): To a stirred solution of 4-amino-2-iso-propyl-5-methylphenol, (33; 200 mg, 0.012 mmol) in dry MeOH (15 mL), benzaldehyde (128.5 mg, 0.012 mmol) was added and reaction mixture was stirred at 30-35 °C for 3-4 h under nitrogen atmosphere. The completion of reaction was confirmed by TLC. The solvent was removed under reduced pressure and the residue thus obtained was washed with hexane. The crude product was crystallized with MeOH to get compound 34. Yield 50%; mp 146-147 °C; IR (film, cm\(^{-1}\)): 2922, 1618 (C=N), 1408, 1255 (C–O–C), 1181; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ: 1.27 (d, \(J = 7.3\) Hz, 6H, \(\text{CH}(\text{CH}_3)_2\)), 2.31 (s, 3H, \(\text{CH}_3\)), 3.19 (septet, \(J = 7.3\) Hz, 1H, \(\text{CH}(\text{CH}_3)_2\)), 4.68 (s, 1H, \(\text{OH}\)), 6.64 (s, 1H, \(\text{ArH}\)), 6.84 (s, 1H, \(\text{ArH}\)), 7.45-7.47 (m, 3H, \(\text{ArH}\)), 7.91-7.92 (m, 2H, \(\text{ArH}\)), 8.38 (s, 1H, N=CH); ESI-MS (m/z): 254.18 [M + H]+.

2-iso-Propyl-5-methyl-4-(2-methylbenzylideneamino)phenol (35): Yield 43%; mp 139-140 °C; IR (film, cm\(^{-1}\)): 3186 (O–H), 2960, 2924, 2869, 2735, 1621 (C=N), 1508, 1455, 1411, 1256 (C–O–C), 1181, 1039 (C–O–C); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ: 1.28 (d, \(J = 6.6\) Hz, 6H, \(\text{CH}(\text{CH}_3)_2\)), 2.30 (s, 3H, \(\text{CH}_3\)), 2.62 (s, 3H, \(\text{CH}_3\)), 3.19 (septet, \(J = 6.6\) Hz, 1H, \(\text{CH}(\text{CH}_3)_2\)), 4.76 (brs, 1H, \(\text{OH}\)), 6.64 (s, 1H, \(\text{ArH}\)), 6.80 (s, 1H, \(\text{ArH}\)), 7.23 (d, \(J = 7.3\) Hz, 1H, \(\text{ArH}\)), 7.27-7.31 (m, 1H, \(\text{ArH}\)), 7.32-7.36 (m, 1H, \(\text{ArH}\)), 8.04 (d, \(J = 7.3\) Hz, 1H, \(\text{ArH}\)), 8.65 (s, 1H, N=CH); ESI-MS (m/z): 268.22 [M + H]+.

2-iso-Propyl-5-methyl-4-(3-methylbenzylideneamino)phenol (36): Yield 40%; IR (film, cm\(^{-1}\)): 2922, 2852, 1624 (C=N), 1586, 1450, 1409, 1257 (C–O–C), 1196; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ: 1.27 (d, \(J = 6.6\) Hz, 6H, \(\text{CH}(\text{CH}_3)_2\)), 2.30 (s, 3H, \(\text{CH}_3\)), 2.42 (s, 3H, \(\text{CH}_3\)), 3.18 (septet, \(J = 6.6\) Hz, 1H, \(\text{CH}(\text{CH}_3)_2\)), 4.73 (brs, 1H, \(\text{OH}\)), 6.63 (s, 1H, \(\text{ArH}\)), 6.81 (s, 1H, \(\text{ArH}\)), 7.25-7.28 (m, 1H, \(\text{ArH}\)), 7.33-7.37 (m, 1H, \(\text{ArH}\)), 7.68 (d, \(J = 7.3\) Hz, 1H, \(\text{ArH}\)).
2-iso-Propyl-5-methyl-4-(4-methylbenzylideneamino)phenol (37): Yield 45%; mp 148-149 °C; IR (film, cm⁻¹): 3026, 2960, 2924, 2869, 1623 (C=N), 1609, 1572, 1514, 1413, 1284, 1255 (C–O–C), 1110, 1039 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 1.26 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.29 (s, 3H, CH₃), 2.41 (s, 3H, CH₃), 3.19 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.86 (brs, 1H, OH), 6.61 (s, 1H, ArH), 6.81 (s, 1H, ArH), 7.26 (d, J = 8 Hz, 2H, ArH), 7.80 (d, J = 8 Hz, 2H, ArH), 8.34 (s, 1H, N=CH); ESI-MS (m/z): 268.23 [M + H]⁺.

4-(4-Ethylbenzylideneamino)-2-iso-propyl-5-methylphenol (38): Yield 51%; mp 141-142 °C; IR (film, cm⁻¹): 2962, 2926, 2868, 1609 (C=N), 1411, 1255 (C–O–C), 1174, 899; ¹H NMR (400 MHz, CDCl₃) δ: 1.25-1.29 (m, 9H), 2.29 (s, 3H, CH₃), 2.71 (q, J = 7.3 Hz, 2H, CH₂CH₃), 3.18 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.72 (s, 1H, OH), 6.62 (s, 1H, ArH), 6.81 (s, 1H, ArH), 7.29 (d, J = 8 Hz, 2H, ArH), 7.83 (d, J = 8 Hz, 2H, ArH), 8.34 (s, 1H, N=CH); ESI-MS (m/z): 282.24 [M + H]⁺.

2-iso-Propyl-5-methyl-4-(4-propylbenzylideneamino)phenol (39): Yield 48%; mp 131-133 °C; IR (film, cm⁻¹): 2960, 2930, 2871, 1625 (C=N), 1608, 1513, 1454, 1415, 1256 (C–O–C), 1175, 1040 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 0.96 (t, J = 7.3 Hz, 3H, CH₂CH₃), 1.27 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 1.67 (sextet, J = 7.3 Hz, 2H, CH₂CH₂CH₃), 2.30 (s, 3H, CH₃), 2.64 (t, J = 7.3 Hz, 2H, CH₂CH₂CH₃), 3.18 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.70 (brs, 1H, OH), 6.62 (s, 1H, ArH), 6.81 (s, 1H, ArH), 7.26-7.28 (m, 2H, ArH), 7.82 (d, J = 8 Hz, 2H, ArH), 8.34 (s, 1H, N=CH); ¹³C NMR (100 MHz, CDCl₃) δ: 13.76, 17.36, 22.69, 24.39, 27.0, 38.02, 115.64, 117.10, 128.54, 128.83, 130.65, 132.46, 134.32, 144.30, 146.05, 150.82, 157.96; ESI-MS (m/z): 296.23 [M + H]⁺.
2-iso-Propyl-4-(4-iso-propylbenzylideneamino)-5-methylphenol (40): Yield 49%; mp 154-156 °C; IR (film, cm⁻¹): 2954, 2923, 2868, 1624 (C=N), 1609, 1407, 1255 (C–O–C), 1180, 1055 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 1.26-1.29 (m, 12H, 2CH(CH₃)₂), 2.29 (s, 3H, CH₃), 2.96 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 3.18 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.68 (s, 1H, OH), 6.62 (s, 1H, ArH), 6.80 (s, 1H, ArH), 7.32 (d, J = 8 Hz, 2H, ArH), 7.84 (d, J = 8 Hz, 2H, ArH), 8.34 (s, 1H, N=CH); ESI-MS (m/z): 296.26 [M + H]⁺.

4-(4-Butylbenzylideneamino)-2-iso-propyl-5-methylphenol (41): Yield 46%; mp 140-141 °C; IR (film, cm⁻¹): 3082, 2953, 2924, 2857, 1625 (C=N), 1609, 1406, 1255 (C–O–C), 1179, 1040 (C–O–C), 907; ¹H NMR (400 MHz, CDCl₃) δ: 0.93 (t, J = 7.3 Hz, 3H, CH₂CH₂CH₂CH₃), 1.26 (d, J = 7.3 Hz, 6H, CH(CH₃)₂), 1.62 (pentet, J = 7.3 Hz, 2H, CH₂CH₂CH₂CH₂CH₃), 2.30 (s, 3H, CH₃), 3.18 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.67 (s, 1H, OH), 6.62 (s, 1H, ArH), 6.81 (s, 1H, ArH), 7.26-7.28 (m, 2H, ArH), 7.82 (d, J = 8 Hz, 2H, ArH), 8.34 (s, 1H, N=CH); ESI-MS (m/z): 310.26 [M + H]⁺.

4-(4-tert-Butylbenzylideneamino)-2-iso-propyl-5-methylphenol (42): Yield 42%; mp 127-130 °C; IR (film, cm⁻¹): 2960, 2924, 1618 (C=N), 1411, 1255 (C–O–C), 1177, 1106; ¹H NMR (400 MHz, CDCl₃) δ: 1.27 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 1.35(s, 9H, C(CH₃)₃), 2.29 (s, 3H, CH₃), 3.18 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.68 (brs, 1H, OH), 6.63 (s, 1H, ArH), 6.80 (s, 1H, ArH), 7.49 (d, J = 8 Hz, 2H, ArH), 7.84 (d, J = 8.8 Hz, 2H, ArH), 8.35 (s, 1H, N=CH); ESI-MS (m/z): 310.26 [M + H]⁺.

2-iso-Propyl-5-methyl-4-(2-nitrobenzylideneamino)phenol (43): Yield 50%; mp 149-151 °C; IR (film, cm⁻¹): 3102 (O=H), 2959, 2868, 1609 (C=N), 1524 (O=N=O), 1438, 1412, 1340(O=N=O), 1258 (C–O–C), 1183, 1042 (C–O–C); ¹H NMR (400 MHz, CDCl₃)
δ: 1.28 (d, J = 6.6 Hz, 6H, CH(CH$_3$)$_2$), 2.35 (s, 3H, CH$_3$), 3.18 (septet, J = 6.6 Hz, 1H, CH(CH$_3$)$_2$), 4.90 (s, 1H, OH), 6.65 (s, 1H, ArH), 6.93 (s, 1H, ArH), 7.56-7.60 (m, 1H, ArH), 7.70-7.73 (m, 1H, ArH), 8.04 (d, J = 7.3 Hz, 1H, ArH), 8.31 (dd, J = 8, 1.5 Hz, 1H), 8.84 (s, 1H, N=CH); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 17.38, 22.56, 27.09, 115.72, 117.21, 124.42, 129.74, 130.62, 131.51, 131.82, 132.73, 133.36, 142.99, 149.15, 151.94, 152.60; ESI-MS (m/z): 299.19 [M + H]$^+$.

2-iso-Propyl-5-methyl-4-(3-nitrobenzylideneamino)phenol (44): Yield 56%; mp 160-161 °C; IR (film, cm$^{-1}$): 2923, 1528 (O–N=O), 1350 (O–N=O), 1255 (C–O–C), 1178, 913; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.28 (d, J = 7.3 Hz, 6H, CH(CH$_3$)$_2$), 2.35 (s, 3H, CH$_3$), 3.28 (septet, J = 7.3 Hz, 1H, CH(CH$_3$)$_2$), 4.91 (s, 1H, OH), 6.66 (s, 1H, ArH), 6.90 (s, 1H, ArH), 7.62-7.66 (m, 1H, ArH), 8.25-8.31 (m, 2H, ArH), 8.48 (s, 1H, N=CH); ESI-MS (m/z): 299.19 [M + H]$^+$.

2-iso-Propyl-5-methyl-4-(4-nitrobenzylideneamino)phenol (45): Yield 45%; mp 102-103 °C; IR (film, cm$^{-1}$): 3449 (O–H), 2923, 2852, 1518 (O–N=O), 1342 (O–N=O), 1255 (C–O–C), 1176, 1107; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.28 (d, J = 7.3 Hz, 6H, CH(CH$_3$)$_2$), 2.35 (s, 3H, CH$_3$), 3.20 (septet, J = 7.3 Hz, 1H, CH(CH$_3$)$_2$), 4.86 (s, 1H, OH), 6.66 (s, 1H, ArH), 6.92 (s, 1H, ArH), 8.07 (d, J = 8.8 Hz, 2H, ArH), 8.31 (d, J = 8.8 Hz, 2H, ArH), 8.49 (s, 1H, N=CH); ESI-MS (m/z): 299.20 [M + H]$^+$.

4-(2-Fluorobenzylideneamino)-2-iso-propyl-5-methylphenol (46): Yield 46%; mp 144-146 °C; IR (film, cm$^{-1}$): 3118 (O–H), 2953, 1617 (C=N), 1406, 1255 (C–O–C), 1232, 1196, 1180, 905; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.28 (d, J = 6.6 Hz, 6H, CH(CH$_3$)$_2$), 2.32 (s, 3H, CH$_3$), 3.18 (septet, J = 6.6 Hz, 1H, CH(CH$_3$)$_2$), 4.73 (s, 1H, OH), 6.64 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.10-7.15 (m, 1H, ArH), 7.22 (d, J = 8 Hz, 1H,
ArH), 7.40-7.45 (m, 1H, ArH), 8.18-8.22 (m, 1H, ArH), 8.69 (s, 1H, N=CH); ESI-MS (m/z): 272.24 [M + H]^+.

4-(3-Fluorobenzylideneamino)-2-iso-propyl-5-methylphenol (47): Yield 50%; mp 121-123 °C; IR (film, cm⁻¹): 2961, 2924, 2852, 1617 (C=N), 1425, 1255 (C–O–C), 1182; ¹H NMR (400 MHz, CDCl₃) δ: 1.27 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.32 (s, 3H, CH₃), 3.19 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.74 (s, 1H, OH), 6.64 (s, 1H, ArH), 6.85 (s, 1H, ArH), 7.12-7.17 (m, 1H, ArH), 7.40-7.45 (m, 1H, ArH), 7.63 (d, J = 8 Hz, 1H, ArH), 7.68 (dd, J = 8.8 Hz, 2.2 Hz, 1H, ArH), 8.36 (s, 1H, N=CH); ESI-MS (m/z): 272.25 [M + H]^+.

4-(4-Fluorobenzylideneamino)-2-iso-propyl-5-methylphenol (48): Yield 40%; mp 139-140 °C; IR (film, cm⁻¹): 2961, 2924, 2852, 1625 (C=N), 1603, 1512, 1455, 1417, 1380, 1290, 1234 (C–O–C), 1182, 1155, 1041 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 1.27 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.30 (s, 3H, CH₃), 3.19 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.81 (brs, 1H, OH), 6.63 (s, 1H, ArH), 6.82 (s, 1H, ArH), 7.12-7.17 (m, 2H, ArH), 7.91 (dd, J = 8.8, 5.9 Hz, 2H, ArH), 8.34 (s, 1H, N=CH); ESI-MS (m/z): 272.24 [M + H]^+.

4-(2-Chlorobenzylideneamino)-2-iso-propyl-5-methylphenol (49): Yield 53%; mp 140-141 °C; IR (film, cm⁻¹): 3080 (O=H), 2958, 2923, 2853, 1611 (C=N), 1415, 1333, 1274 (C–O–C), 1185, 1036 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 1.28 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.32 (s, 3H, CH₃), 3.19 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.73 (s, 1H, OH), 6.51 (s, 1H, ArH), 6.87 (s, 1H, ArH), 7.35-7.37 (m, 2H, ArH), 7.41-7.43 (m, 1H, ArH), 8.24-8.27 (m, 1H, ArH), 8.82 (s, 1H, N=CH); ESI-MS (m/z): 288.16 [M + H]^+, 290.18 [M + 2]^+. 
4-(3-Chlorobenzylideneamino)-2-iso-propyl-5-methylphenol (50): Yield 55%; mp 142-143 °C; IR (film, cm⁻¹): 3329 (O–H), 2961, 2925, 1617 (C=N), 1411, 1255 (C–O–C), 1182, 1039 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 1.27 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.32 (s, 3H, CH₃), 3.19 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.75 (s, 1H, OH), 6.64 (s, 1H, ArH), 6.84 (s, 1H, ArH), 7.37-7.43 (m, 2H, ArH), 7.75 (d, J = 6.6 Hz, 1H, ArH), 7.94 (s, 1H, ArH), 8.34 (s, 1H, N=CH); ESI-MS (m/z): 288.17 [M + H]⁺, 290.16 [M + 2]⁺.

4-(4-Chlorobenzylideneamino)-2-iso-propyl-5-methylphenol (51): Yield 40%; mp 144-145 °C; IR (film, cm⁻¹): 3088 (O–H), 2962, 2924, 2870, 1618 (C=N), 1595, 1412, 1287, 1257 (C–O–C), 1184, 1088 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 1.27 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.31 (s, 3H, CH₃), 3.19 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.78 (s, 1H, OH), 6.63 (s, 1H, ArH), 6.84 (s, 1H, ArH), 7.43 (d, J = 8 Hz, 2H, ArH), 7.85 (d, J = 8 Hz, 2H, ArH), 8.34 (s, 1H, N=CH); ESI-MS (m/z): 288.15 [M + H]⁺, 290.16 [M + 2]⁺.

4-(2-Bromobenzylideneamino)-2-iso-propyl-5-methylphenol (52): Yield 41%; mp 143-144 °C; IR (film, cm⁻¹): 3078 (O–H), 2958, 2924, 2870, 1618 (C=N), 1415, 1333, 1273 (C–O–C), 1184, 1034 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 1.28 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.32 (s, 3H, CH₃), 3.19 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.79 (s, 1H, OH), 6.64 (s, 1H, ArH), 6.87 (s, 1H, ArH), 7.27-7.31 (m, 1H, ArH), 7.37-7.41 (m, 1H), 7.61 (dd, J = 8, 1.5 Hz, 1H, ArH), 8.24 (dd, J = 7.3 Hz, 1.5 Hz, 1H, ArH), 8.75 (s, 1H, N=CH); ESI-MS (m/z): 332.13 [M + H]⁺, 334.13 [M + 2]⁺.

4-(3-Bromobenzylideneamino)-2-iso-propyl-5-methylphenol (53): Yield 40%; mp 131-132 °C; IR (film, cm⁻¹): 3154 (O–H), 2961, 1618, 1413, 1381, 1256 (C–O–C), 1184, 1070 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 1.27 (d, J = 6.6 Hz, 6H,
CH(CH$_3$)$_2$), 2.32 (s, 3H, CH$_3$), 3.19 (septet, $J = 6.6$ Hz, 1H, CH(CH$_3$)$_2$), 6.63 (s, 1H, ArH), 6.83 (s, 1H, ArH), 7.31-7.35 (m, 1H, ArH), 7.56-7.58 (m, 1H, ArH), 7.80 (d, $J = 8$ Hz, 1H, ArH), 8.09 (d, $J = 2.2$ Hz, 1H, ArH), 8.32 (s, 1H, N=CH); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 17.37, 22.66, 26.99, 115.37, 117.20, 122.94, 127.25, 130.16, 131.09, 131.28, 132.64, 133.59, 138.65, 143.29, 151.44, 155.76; ESI-MS ($m/z$): 332.10 [M + H]$^+$, 334.11 [M + 2]$^+$.

4-(4-Bromobenzylideneamino)-2-iso-propyl-5-methylphenol (54): Yield 42%; mp 152-153 °C; IR (film, cm$^{-1}$): 3085 (O–H), 2960, 1618 (C=N), 1588, 1413, 1286, 1257 (C–O–C), 1183, 1069 (C–O–C); $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.27 (d, $J = 7.3$ Hz, 6H, CH(CH$_3$)$_2$), 2.30 (s, 3H, CH$_3$), 3.19 (septet, $J = 7.3$ Hz, 1H, CH(CH$_3$)$_2$), 4.75 (s, 1H, OH), 6.62 (s, 1H, ArH), 6.84 (s, 1H, ArH), 7.59 (d, $J = 8.8$ Hz, 2H, ArH), 7.78 (d, $J = 8.8$ Hz, 2H, ArH), 8.33 (s, 1H, N=CH); ESI-MS ($m/z$): 332.13 [M + H]$^+$, 334.13 [M + 2]$^+$.

2-iso-Propyl-5-methyl-4-(2-(trifluoromethyl)benzylideneamino)phenol (55): Yield 35%; mp 158-160 °C; IR (film, cm$^{-1}$): 3076 (O–H), 2960, 1607, 1578, 1417, 1245 (C–O–C), 1173, 1120, 1059 (C–O–C); $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.28 (d, $J = 7.3$ Hz, 6H, CH(CH$_3$)$_2$), 2.33 (s, 3H, CH$_3$), 3.18 (septet, $J = 7.3$ Hz, 1H, CH(CH$_3$)$_2$), 4.77 (s, 1H, OH), 6.65 (s, 1H, ArH), 6.85 (s, 1H, ArH), 7.52-7.55 (m, 1H, ArH), 7.62-7.66 (m, 1H, ArH), 7.72 (d, $J = 8$ Hz, 1H, ArH), 8.45 (d, $J = 7.3$ Hz, 1H, ArH), 8.73 (q, $J = 2.2$ Hz, 1H, N=CH); ESI-MS ($m/z$): 322.21 [M + H]$^+$.

2-iso-Propyl-5-methyl-4-(3-(trifluoromethyl)benzylideneamino)phenol (56): Yield 64%; mp 145-146 °C; IR (film, cm$^{-1}$): 3154 (O–H), 2962, 2924, 1610, 1413, 1330, 1272 (C–O–C), 1184, 1163, 1128, 1075 (C–O–C); $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.27 (d, $J = 6.6$ Hz, 6H, CH(CH$_3$)$_2$), 2.33 (s, 3H, CH$_3$), 3.19 (septet, $J = 6.6$ Hz, 1H, CH(CH$_3$)$_2$), 4.77 (s, 1H, OH), 6.65 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.57-7.60 (m, 1H, ArH), 7.70 (d, $J = 8$ Hz,
1H, ArH), 8.10 (d, J = 8 Hz, 1H, ArH), 8.17 (s, 1H, ArH), 8.43 (s, 1H, N=CH); ESI-MS (m/z): 322.22 [M + H]^+.

2-iso-Propyl-5-methyl-4-(4-(trifluoromethyl)benzylideneamino)phenol (57): Yield 65%; mp 160-161 °C; IR (film, cm\(^{-1}\)): 3069 (O–H), 2963, 1624 (C=N), 1582, 1413, 1324, 1287, 1259 (C–O–C), 1182, 1162, 1129, 1114, 1065 (C–O–C); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ: 1.28 (d, J = 6.6 Hz, 6H, CH\(_2\)(CH\(_3\))\(_2\)), 2.33 (s, 3H, CH\(_3\)), 3.19 (septet, J = 6.6 Hz, 1H, CH\(_2\)(CH\(_3\))\(_2\)), 4.76 (s, 1H, OH), 6.65 (s, 1H, ArH), 6.87 (s, 1H, ArH), 7.71 (d, J = 8 Hz, 2H, ArH), 8.02 (d, J = 8.05 Hz, 2H, ArH), 8.44 (s, 1H, N=CH); \(^13\)C NMR (100 MHz, CDCl\(_3\)) δ: 17.35, 22.66, 27.03, 115.26, 117.24, 122.60, 125.31, 125.59, 125.63, 128.64, 131.62, 132.02, 132.34, 132.65, 139.78, 143.23, 151.60, 155.56; ESI-MS (m/z): 322.21 [M + H]^+.

4-(2,3-Dimethylbenzylideneamino)-2-iso-propyl-5-methylphenol (58): Yield 42%; mp 172-173 °C; IR (film, cm\(^{-1}\)): 2925, 1706, 1611 (C=N), 1407, 1255 (C–O–C), 1183; \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ: 1.28 (d, J = 6.6 Hz, 6H, CH\(_2\)(CH\(_3\))\(_2\)), 2.30 (s, 3H, CH\(_3\)), 2.34 (s, 3H, CH\(_3\)), 2.50 (s, 3H, CH\(_3\)), 3.19 (septet, J = 6.6 Hz, 1H, CH\(_2\)(CH\(_3\))\(_2\)), 4.70 (s, 1H, CH\(_2\)(CH\(_3\))\(_2\)), 4.76 (s, 1H, OH), 6.64 (s, 1H, ArH), 6.78 (s, 1H, ArH), 7.17-7.21 (m, 1H, ArH), 7.24 (s, 1H, ArH), 7.92 (d, J = 8 Hz, 1H, ArH), 8.72 (s, 1H, N=CH); ESI-MS (m/z): 282.14 [M + H]^+.

4-(2,4-Dimethylbenzylideneamino)-2-iso-propyl-5-methylphenol (59): Yield 30%; mp 116-117 °C; IR (film, cm\(^{-1}\)): 3368 (O–H), 2959, 2923, 2853, 1610 (C=N), 1458, 1411, 1255 (C–O–C), 1183, 1037 (C–O–C); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ: 1.27 (d, J = 6.6 Hz, 6H, CH\(_2\)(CH\(_3\))\(_2\)), 2.29 (s, 3H, CH\(_3\)), 2.36 (s, 3H, CH\(_3\)), 2.58 (s, 3H, CH\(_3\)), 3.18 (septet, J = 6.6 Hz, 1H, CH\(_2\)(CH\(_3\))\(_2\)), 4.68 (brs, 1H, OH), 6.63 (s, 1H, ArH), 6.78 (s, 1H, ArH), 7.05 (s, 1H, ArH), 7.10 (d, J = 8 Hz, 1H, ArH), 7.93 (d, J = 8 Hz, 1H, ArH), 8.60 (s, 1H, N=CH); ESI-MS (m/z): 282.23 [M + H]^+. 

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4-(2,5-Dimethylbenzylideneamino)-2-iso-propyl-5-methylphenol (60): Yield 42%; mp 114-115 °C; IR (film, cm\(^{-1}\)): 2959, 2922, 2851, 1616 (C=N), 1437, 1256 (C–O–C), 1182; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.27 (d, \(J = 7.3\) Hz, 6H, CH\((CH_3)_2\)), 2.30 (s, 3H, CH\(_3\)), 2.37 (s, 3H, CH\(_3\)), 2.56 (s, 3H, CH\(_3\)), 3.19 (septet, \(J = 7.3\) Hz, 1H, CH\((CH_3)_2\)), 6.64 (s, 1H, Ar\(H\)), 6.78 (s, 1H, Ar\(H\)), 7.11-7.12 (m, 2H, Ar\(H\)), 7.86 (s, 1H, Ar\(H\)), 8.61 (s, 1H, N=CH); ESI-MS (m/z): 282.24 [M + H]\(^+\).

4-(2,6-Dimethylbenzylideneamino)-2-iso-propyl-5-methylphenol (61): Yield 44%; mp 154-155 °C; IR (film, cm\(^{-1}\)): 2963, 2922, 1621 (C=N), 1409, 1288, 1258 (C–O–C), 1243, 1185, 1036 (C–O–C); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.28 (d, \(J = 6.6\) Hz, 6H, CH\((CH_3)_2\)), 2.30 (s, 3H, CH\(_3\)), 2.57 (s, 6H, 2CH\(_3\)), 3.20 (septet, \(J = 6.6\) Hz, 1H, CH\((CH_3)_2\)), 4.76 (s, 1H, OH), 6.65 (s, 1H, Ar\(H\)), 6.80 (s, 1H, Ar\(H\)), 7.10 (d, \(J = 7.3\) Hz, 2H, Ar\(H\)), 7.17-7.21 (m, 1H, Ar\(H\)), 8.75 (s, 1H, N=CH); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 17.82, 21.23, 22.62, 27.10, 115.48, 117.12, 128.85, 129.26, 130.61, 132.45, 133.69, 134.51, 137.0, 140.01, 144.50, 150.65, 158.12; ESI-MS (m/z): 282.24 [M + H]\(^+\).

4-(3,4-Dimethylbenzylideneamino)-2-iso-propyl-5-methylphenol (62): Yield 46%; mp 159-160 °C; IR (film, cm\(^{-1}\)): 3368 (O–H), 2960, 2923, 2854, 1683, 1623 (C=N), 1608, 1572, 1509, 1452, 1414, 1284, 1255 (C–O–C), 1192, 1120, 1022 (C–O–C); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.26 (d, \(J = 6.6\) Hz, 6H, CH\((CH_3)_2\)), 2.30 (s, 3H, CH\(_3\)), 2.32 (s, 3H, CH\(_3\)), 3.18 (septet, \(J = 6.6\) Hz, 1H, CH\((CH_3)_2\)), 4.67 (brs, 1H, OH), 6.63 (s, 1H, Ar\(H\)), 6.80 (s, 1H, Ar\(H\)), 7.22 (d, \(J = 7.3\) Hz, 1H, Ar\(H\)), 7.61 (d, \(J = 7.3\) Hz, 1H, Ar\(H\)), 7.71 (s, 1H, Ar\(H\)), 8.31 (s, 1H, N=CH); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 17.38, 19.71, 19.92, 22.69, 27.0, 115.64, 117.05, 126.38, 129.36, 129.93, 130.61, 132.36, 134.51, 137.0, 140.01, 144.50, 150.65, 158.12; ESI-MS (m/z): 282.23 [M + H]\(^+\).
4-(3,5-Dimethylbenzylideneamino)-2-iso-propyl-5-methylphenol (63): Yield 58%; mp 161-162 °C; IR (film, cm\(^{-1}\)): 2959, 2923, 2854, 1604 (C=N), 1410, 1255 (C–O–C), 1196; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.26 (d, \(J = 7.3\) Hz, 6H, CH\((CH_3)_2\)), 2.30 (s, 3H, CH\(_3\)), 2.38 (s, 6H, 2CH\(_3\)), 3.18 (septet, \(J = 7.3\) Hz, 1H, CH\((CH_3)_2\)), 4.75 (s, 1H, OH), 6.62 (s, 1H, ArH), 6.80 (s, 1H, ArH), 7.10 (s, 1H, ArH), 7.26 (s, 1H, ArH), 7.52 (s, 1H), 8.31 (s, 1H, N=CH); ESI-MS (m/z): 282.23 [M + H]\(^+\).

4-(2,5-Difluorobenzylideneamino)-2-iso-propyl-5-methylphenol (64): Yield 40%; mp 154-155 °C; IR (film, cm\(^{-1}\)): 3140 (O–H), 2962, 1623 (C=N), 1488, 1406, 1255 (C–O–C), 1194, 1178; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.27 (d, \(J = 6.6\) Hz, 6H, CH\((CH_3)_2\)), 2.33 (s, 3H, CH\(_3\)), 3.19 (septet, \(J = 6.6\) Hz, 1H, CH\((CH_3)_2\)), 4.83 (brs, 1H, OH), 6.64 (s, 1H, ArH), 6.88 (s, 1H, ArH), 7.02-7.12 (m, 2H, ArH), 7.86-7.90 (m, 1H, ArH), 8.64 (s, 1H, N=CH); ESI-MS (m/z): 290.20 [M + H]\(^+\).

2-iso-Propyl-5-methyl-4-(2,4,5-trifluorobenzylideneamino)phenol (65): Yield 40%; mp 159-160 °C; IR (film, cm\(^{-1}\)): 2922, 1507, 1437, 1219, 1219, 889; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.27 (d, \(J = 6.6\) Hz, 6H, CH\((CH_3)_2\)), 2.32 (s, 3H, CH\(_3\)), 3.18 (septet, \(J = 6.6\) Hz, 1H, CH\((CH_3)_2\)), 4.72 (s, 1H, OH), 6.64 (s, 1H, ArH), 6.86 (s, 1H, ArH), 6.96-7.02 (m, 1H, ArH), 7.99-8.06 (m, 1H, ArH), 8.58 (s, 1H, N=CH); ESI-MS (m/z): 308.25 [M + H]\(^+\).

4-(2,4-Dichlorobenzylideneamino)-2-iso-propyl-5-methylphenol (66): Yield 52%; mp 122-124 °C; IR (film, cm\(^{-1}\)): 2958, 1584, 1408, 1256 (C–O–C), 1176, 1098, 1022 (C–O–C); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.28 (d, \(J = 7.3\) Hz, 6H, CH\((CH_3)_2\)), 2.32 (s, 3H, CH\(_3\)), 3.18 (septet, \(J = 7.3\) Hz, 1H, CH\((CH_3)_2\)), 4.72 (s, 1H, OH), 6.64 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.33 (dd, \(J = 8, 2.2\) Hz, 1H, ArH), 7.44 (d, \(J = 2.2\) Hz, 1H, ArH), 8.20 (d, \(J = 8.8\) Hz, 1H, ArH), 8.75 (s, 1H, N=CH); \(^1^3\)C NMR (100 MHz, CDCl\(_3\))

4-(2,6-Dichlorobenzylideneamino)-2-iso-propyl-5-methylphenol (67): Yield 48%; mp 161-162 °C; IR (film, cm⁻¹): 3131 (O–H), 2959, 1605, 1411, 1341, 1258, 1182, 1093; ¹H NMR (400 MHz, CDCl₃) δ: 1.29 (d, J = 6.6 Hz, 6H, CH(CH₃)₂), 2.34 (s, 3H, CH₃), 3.19 (septet, J = 6.6 Hz, 1H, CH(CH₃)₂), 4.77 (s, 1H, OH), 6.64 (s, 1H, ArH), 6.89 (s, 1H, ArH), 7.23-7.27 (m, 1H, ArH), 7.39 (d, J = 8 Hz, 2H, ArH), 8.60 (s, 1H, N=CH); ESI-MS (m/z): 322.15 [M + H]+, 324.15 [M + 2]+, 326.13 [M + 4]+.

4-(4-Hydroxy-3-methoxybenzylideneamino)-2-iso-propyl-5-methylphenol (68): Yield 42%; mp 183-184 °C; IR (film, cm⁻¹): 3369 (O–H), 2919, 2850, 1593, 772; ¹H NMR (400 MHz, CDCl₃) δ: 1.26 (d, J = 7.3 Hz, 6H, CH(CH₃)₂), 2.29 (s, 3H, CH₃), 3.18 (septet, J = 7.3 Hz, 1H, CH(CH₃)₂), 3.99 (s, 3H, OCH₃), 4.67 (s, 1H, OH), 5.92 (brs, 1H, OH), 6.62 (s, 1H, ArH), 6.79 (s, 1H, ArH), 6.98 (d, J = 8 Hz, 1H, ArH), 7.29 (d, J = 1.5 Hz, 1H, ArH), 7.61 (d, J = 2.2 Hz, 1H, ArH), 8.25 (s, 1H, N=CH); ESI-MS (m/z): 300.21 [M + H]+.

(E)-4-(2-Hydroxy-5-nitrobenzylideneamino)-2-iso-propyl-5-methylphenol (69): Yield 82%; mp 224-225 °C; IR (film, cm⁻¹): 3062 (O=H), 2961, 2877, 2750, 1613 (C=N), 1551, 1429, 1328, 1301, 1271, 1257 (C–O–C), 1099, 1027 (C–O–C); ¹H NMR (400 MHz, DMSO-d₆) δ: 1.20 (d, J = 7.3 Hz, 6H, CH(CH₃)₂), 2.27 (s, 3H, CH₃), 3.19 (septet, J = 7.3 Hz, 1H, CH(CH₃)₂), 6.72 (s, 1H, ArH), 6.98 (d, J = 8.8 Hz, 1H, ArH), 7.40 (s, 1H, ArH), 8.18 (dd, J = 9.5, 2.9 Hz, 1H, ArH), 8.62 (d, J = 2.9 Hz, 1H, ArH), 9.21 (s, 1H), 9.68 (s, 1H), 15.75 (s, 1H); ¹³C NMR (100 MHz, DMSO-d₆) δ: 17.36, 22.47, 26.34, 115.45, 115.56, 117.22, 127.55, 129.36, 129.60, 131.60, 132.32, 132.62, 136.04, 136.92, 143.49, 151.60, 152.58; ESI-MS (m/z): 322.13 [M + H]+, 324.14 [M + 2]+, 326.14 [M + 4]+.
116.78, 117.65, 118.93, 127.88, 129.11, 130.61, 133.60, 137.89, 154.75, 157.69, 169.52; ESI-MS (m/z): 315.19 [M + H]+.

**(E)-2-iso-Propyl-5-methyl-4-(pyridin-2-ylmethyleneamino)phenol (70):** Yield 69%; mp 131-132 °C; IR (film, cm⁻¹): 3067 (O–H), 2961, 2742, 1623 (C=N), 1592, 1568, 1472, 1438, 1421, 1285, 1252 (C–O–C), 1193, 1184, 1147, 1045 (C–O–C); ¹H (400 MHz, CDCl₃) δ: 1.25 (d, J = 6.6 Hz, 6H, CH(CH₃)₃), 2.34 (s, 3H, CH₃), 3.19 (septet, J = 6.6 Hz, 1H, CH(CH₃)₃), 5.43 (s, 1H, OH), 6.65 (s, 1H, ArH), 6.98 (s, 1H, ArH), 7.34-7.37 (m, 1H, ArH), 7.79-7.83 (m, 1H, ArH), 8.26 (d, J = 8 Hz, 1H, ArH), 8.57 (s, 1H, N=CH), 8.69 (d, J = 5.1 Hz, 1H, ArH); ¹³C (100 MHz, CDCl₃) δ: 17.38, 22.62, 26.89, 115.46, 117.15, 121.51, 124.80, 131.90, 133.19, 137.0, 148.99, 155.06, 156.48; ESI-MS (m/z): 255.26 [M + H]+.

**(E)-2-iso-Propyl-5-methyl-4-(pyridin-3-ylmethyleneamino)phenol (71):** Yield 71%; mp 182-183 °C; IR (film, cm⁻¹): 3064 (O–H), 2958, 2925, 2746, 1623 (C=N), 1606, 1430, 1291, 1253 (C–O–C), 1198, 1184, 1030 (C–O–C); ¹H (400 MHz, CDCl₃) δ: 1.28 (d, J = 7.3 Hz, 6H, CH(CH₃)₃), 2.33 (s, 3H, CH₃), 3.24 (septet, J = 7.3 Hz, 1H, CH(CH₃)₃), 6.15 (brs, 1H, OH), 6.68 (s, 1H, ArH), 6.90 (s, 1H, ArH), 7.41-7.44 (m, 1H, ArH), 8.30-8.33 (m, 1H, ArH), 8.45 (s, 1H, N=CH), 8.68 (dd, J = 4.4, 1.5 Hz, 1H, ArH), 9.04 (d, J = 1.5 Hz, 1H, ArH); ESI-MS (m/z): 255.21 [M + H]+.

**(E)-2-iso-Propyl-5-methyl-4-(perfluorobenzylideneamino)phenol (72):** Yield 74%; mp 128-129°C; IR (film, cm⁻¹): 3171 (O–H), 2963, 2925, 2874, 1618 (C=N), 1524, 1498, 1411, 1257 (C–O–C), 1157, 1138, 1039 (C–O–C); ¹H (400 MHz, CDCl₃) δ: 1.27 (d, J = 6.6 Hz, 6H, CH(CH₃)₃), 2.31 (s, 3H, CH₃), 3.18 (septet, J = 6.6 Hz, 1H, CH(CH₃)₃), 4.82 (s, 1H, OH), 6.64 (s, 1H, ArH), 6.87 (s, 1H, ArH), 8.50 (s, 1H, N=CH); ESI-MS (m/z): 344.13 [M + H]+.
(E)-4-(Benzo[d][1,3]dioxol-5-ylmethyleneamino)-2-iso-propyl-5-methylphenol (73): Yield 77%; mp 160-161°C; IR (film, cm⁻¹): 3079 (O–H), 2964, 2925, 1620 (C=N), 1598, 1501, 1449, 1414, 1337, 1277, 1261 (C–O–C), 1210, 1190, 1179, 1038 (C–O–C); ¹H (400 MHz, CDCl₃) δ: 1.26 (d, J = 6.6 Hz, 6H, CH(CH₃)₃), 2.28 (s, 3H, CH₃), 3.18 (septet, J = 6.6 Hz, CH(CH₃)₃), 4.76 (brs, 1H, OH), 6.03 (s, 2H, OCH₂O), 6.60 (s, 1H, ArH), 6.80 (s, 1H, ArH), 6.87 (d, J = 8 Hz, 1H, ArH), 7.25-7.27 (m, 1H, ArH), 7.56 (d, J = 1.5Hz, 1H, ArH), 8.25 (s, 1H, N=CH); ESI-MS (m/z): 298.22 [M + H]⁺.

**Typical procedure for the synthesis of 4-(2-bromoethoxy)benzaldehyde (75)⁶³,⁶⁴ and related compound (76):** A mixture of 4-hydroxy benzaldehyde (2.5 g, 0.02 mol), 1,2-dibromoethane (12.5 g, 0.061 mol) and K₂CO₃ (8.5 g, 0.061 mmol) in dry DMF (70 mL) was stirred at 35-40°C for 10-12 h. The reaction mixture was diluted with H₂O (250 mL) after cooling to room temperature and extracted with CHCl₃ (3 x 30 mL). The organic layer was washed thrice with water (3 x 100 mL) to remove DMF. The organic phase was dried over Na₂SO₄ and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography using EtOAc:hexane as eluent to get compound 75. Yield 60 % (white solid); ¹H NMR (CDCl₃) δ: 3.65 (t, J = 12 Hz, 2H), 4.36 (t, J = 12 Hz, 2H), 7.00 (d, J = 9 Hz, 2H, ArH), 7.83 (d, J = 11 Hz, 2H, ArH), 9.82 (s, 1H, CHO); ¹³C NMR (CDCl₃) δ: 53.0, 67.0, 115.2, 130.6, 132.4, 164.1, 191.0.

4-(3-Bromopropoxy)benzaldehyde (76)⁶⁴: Yield 61% (pale yellow oil); IR (film, cm⁻¹): 2940, 2880, 2828, 1688, 1600, 1468,1159; ¹H NMR (300 MHz, CDCl₃) δ: 2.36 (quintet, J = 6 Hz, 2H), 3.62 (t, J = 6 Hz, 2H), 4.20 (t, J = 6 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H, ArH), 7.69 (d, J = 8.5 Hz, 2H, ArH), 9.89 (s, 1H, CHO); ¹³C NMR (125 MHz, CDCl₃) δ: 25.7, 29.9, 66.0, 115.2, 130.6, 132.4, 164.1, 191.2.
Typical procedure for the synthesis of 4-(2-azidoethoxy)benzaldehyde (77)\textsuperscript{64} and related compound (78): To a well stirred solution of compound 65 (2.8 g, 0.012 mol) and K$_2$CO$_3$ (5.0 g, 0.035 mol) in dry DMF (40 mL), NaN$_3$ (2.4 g, 0.035 mol) was added slowly. The reaction mixture was stirred at 50 °C for 4-5 h. After cooling down to ambient temperature, the solution was extracted from CHCl$_3$ (3 x 40 mL). The organic layer was washed several times with water to remove DMF. The organic phase was dried over Na$_2$SO$_4$ and solvent was distilled off under reduced pressure. The residue was purified by column chromatography using EtOAc:Hexane as eluent to get compound 77. Yield 80 % (white solid); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 3.57 (t, $J = 10$ Hz, 2H), 4.15 (t, $J = 10$ Hz, 2H), 6.99 (d, $J = 9$ Hz, 2H, ArH), 7.79 (d, $J = 11$ Hz, 2H, ArH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 48.9, 67.1, 114.6, 129.2, 131.6, 162.8, 190.

4-(3-Azidopropoxy)benzaldehyde (78)\textsuperscript{65}: Yield 99% (colorless oil); $^1$H NMR (CDCl$_3$) $\delta$: 2.0-2.15 (m, 2H), 3.58 (t, $J = 6.4$ Hz, 2H), 4.17 (t, $J = 5.8$ Hz, 2H), 6.98 (d, $J = 8.5$ Hz, 2H, ArH), 7.81 (d, $J = 8.5$ Hz, 2H, ArH), 9.85 (s, 1H), $^{13}$C NMR (CDCl$_3$) $\delta$: 28.5, 48.0, 64.9, 114.7, 130.0, 131.9, 163.7, 190.6.

Typical procedure for the synthesis of 4-(2-(4-propyl-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde (79) and related compounds (80-95): 4-(2-Azidoethoxy)benzaldehyde, (77; 300 mg, 1.56 mmol), 1-pentyne (108 mg, 1.56 mmol), CuSO$_4$.5H$_2$O (78.2 mg, 0.318 mmol) and sodium ascorbate (124 mg, 0.627 mmol) were successively added to a reaction flask. A mixture of H$_2$O/tBuOH (1:1) (20 mL) was then added and the reaction flask was warmed to 35-40 °C. After stirring at this temperature for 2-3 h, the reaction mixture was then extracted with EtOAc. The organic layer was dried over Na$_2$SO$_4$ and filtered. The solvent was removed under pressure and purified by column chromatography. The corresponding triazole (79) was obtained which was used for next reaction. Yield 82%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.89 (t, $J = 7.3$ Hz, 3H,
4-(2-(4-Butyl-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde (80): Yield 85%; IR (film, cm⁻¹): 2957, 2937, 2871, 2860, 2741, 1690 (C=O), 1602, 1580, 1312, 1254, 1217, 1162, 1045; ¹H NMR (400 MHz, CDCl₃) δ: 0.92 (t, J = 7.3 Hz, 3H, CH₂CH₃), 1.37 (sextet, J = 7.3 Hz, 2H, CH₂CH₂CH₂CH₃), 1.64 (pentet, J = 7.3 Hz, 2H, CH₂CH₂CH₂CH₂CH₃), 2.71 (t, J = 7.3 Hz, 2H, CH₂CH₂CH₂CH₃), 4.45 (t, J = 5.8 Hz, 2H, NCH₂), 4.76 (t, J = 5.1 Hz, 2H, OCH₂), 6.97 (d, J = 8.8 Hz, 2H, ArH), 7.44 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 260.24 [M + H]+.

4-(2-(4-(1-Hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde (81): Yield 78%; IR (film, cm⁻¹): 3394 (O–H), 2929, 2854, 1680 (C=O), 1601, 1254, 1161, 1053, 907; ¹H NMR (400 MHz, CDCl₃) δ: 1.18 (s, 1H), 1.26-1.32 (m, 1H), 1.47-1.49 (m, 2H), 1.54-1.56 (m, 1H), 1.66-1.69 (m, 2H), 1.82 (s, 2H), 1.89-1.91 (m, 2H), 2.32 (brs, 1H, OH), 4.39 (t, J = 5.1 Hz, 2H, NCH₂), 4.71 (t, J = 5.1 Hz, 2H, OCH₂), 6.90 (d, J = 8.0 Hz, 2H, ArH), 7.59 (s, 1H), 7.76 (d, J = 8.8 Hz, 2H, ArH), 9.81 (s, 1H, CHO); ESI-MS (m/z): 316.21 [M + H]+.

4-(2-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde (82): Yield 74%; IR (film, cm⁻¹): 3364 (O–H), 2925, 2853, 1677 (C=O), 1600, 1578, 1508, 1311, 1252, 1162, 1042; ¹H NMR (400 MHz, CDCl₃) δ: 2.37 (brs, 1H, CH₂OH), 4.46 (t, J = 5.1 Hz, 2H, NCH₂), 4.81 (t, J = 5.1 Hz, 4H), 6.98 (d, J = 8.8 Hz, 2H, ArH), 7.32(s, 1H), 7.84 (d, J = 8.8 Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 248.21 [M + H]+.
(1-(2-(4-Formylphenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl propionate (83): Yield 86%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.12 (t, $J = 7.3$ Hz, 3H, COCH$_2$CH$_3$), 2.34 (q, $J = 7.3$ Hz, 2H, COCH$_2$CH$_3$) 4.46 (t, $J = 5.1$ Hz, 2H, NCH$_2$), 4.81 (t, $J = 5.1$ Hz, 2H, OCH$_2$), 5.22 (s, 2H, CH$_2$OCO) 6.98 (d, $J = 8.8$ Hz, 2H, ArH), 7.80 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 304.27 [M + H]$^+$. 

4-(2-(4-(Pyridin-2-yl)-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde (84): Yield 65%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 4.51 (t, $J = 5.1$ Hz, 2H, NCH$_2$), 4.88 (t, $J = 5.1$ Hz, 2H, OCH$_2$), 7.01 (d, $J = 8.8$ Hz, 2H, ArH), 7.23-7.25 (m, 1H, ArH), 7.76-7.81 (m, 1H, ArH), 7.83 (d, $J = 8.8$ Hz, 2H, ArH), 8.18 (d, $J = 7.3$ Hz, 1H, ArH), 8.35 (s, 1H), 8.59 (d, $J = 5.1$ Hz, 1H, ArH), 9.88 (s, 1H, CHO); ESI-MS (m/z): 295.23 [M + H]$^+$. 

4-(2-(4-(Phenoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde (85): Yield 70%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 4.45 (t, $J = 5.1$ Hz, 2H, NCH$_2$), 4.80 (t, $J = 5.1$ Hz, 2H, OCH$_2$), 5.22 (s, 2H, CH$_2$OPh), 6.94-6.99 (m, 5H, ArH), 7.26-7.30 (m, 2H, ArH), 7.79 (s, 1H), 7.82 (d, $J = 8.8$ Hz, 2H, ArH), 9.88 (s, 1H, CHO); ESI-MS (m/z): 324.21 [M + H]$^+$. 

4-(2-(4-((p-Tolyloxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde (86): Yield 78%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 2.28 (s, 3H, CH$_3$), 4.45 (t, $J = 5.1$ Hz, 2H, NCH$_2$), 4.80 (t, $J = 5.1$ Hz, 2H, OCH$_2$), 5.19 (s, 2H, CH$_2$OPh), 6.87 (d, $J = 8.8$ Hz, 2H, ArH), 6.95 (d, $J = 8.8$ Hz, 2H, ArH), 7.07 (d, $J = 8.8$ Hz, 2H, ArH), 7.78 (s, 1H), 7.82 (d, $J = 8.8$ Hz, 2H, ArH), 9.88 (s, 1H, CHO); ESI-MS (m/z): 338.27 [M + H]$^+$. 

4-(2-(4-(4-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde (87): Yield 75%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 4.45 (t, $J = 5.1$ Hz, 2H, NCH$_2$), 4.81 (t, $J = 5.1$ Hz, 2H, OCH$_2$), 5.19 (s, 2H, CH$_2$OPh), 6.90 (d, $J = 9.5$ Hz, 2H, ArH), 6.94 (d, $J = 8.8$ Hz, 2H, ArH), 7.22 (d, $J = 8.8$ Hz, 2H, ArH), 7.79 (s, 1H), 7.82 (d, $J = 8.8$ Hz, 2H, ArH), 9.88 (s, 1H, CHO); ESI-MS (m/z): 358.19 [M + H]$^+$, 360.16 [M + H]$^+$. 

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4-(3-(4-Propyl-1H-1,2,3-triazol-1-yl)propoxy)benzaldehyde (88): Yield 85%; IR (film, cm\(^{-1}\)): 3137, 3076, 2960, 2873, 2837, 1688, 1601, 1578, 1510, 1313, 1257, 1161, 1049; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 0.94 (t, \(J = 7.3\) Hz, 3H, CH\(_2\)CH\(_3\)), 1.66 (sextet, \(J = 7.3\) Hz, 2H, CH\(_2\)CH\(_3\)), 2.43 (pentet, \(J = 6.6\) Hz, 2H, OCH\(_2\)CH\(_2\)CH\(_2\)N), 2.68 (t, \(J = 5.9\) Hz, 2H, NCH\(_2\)), 2.68 (t, \(J = 6.6\) Hz, 2H, OCH\(_2\)), 3.98 (d, \(J = 8.8\) Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 274.28 [M + H]\(^+\).

4-(3-(4-Butyl-1H-1,2,3-triazol-1-yl)propoxy)benzaldehyde (89): Yield 80%; IR (film, cm\(^{-1}\)): 2950, 1685, 1603, 1251, 1041, 806; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 0.91 (t, \(J = 7.3\) Hz, 3H, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.35 (sextet, \(J = 7.3\) Hz, 2H, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 1.62 (pentet, \(J = 7.3\) Hz, 2H, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 2.43 (pentet, \(J = 6.6\) Hz, 2H, OCH\(_2\)CH\(_2\)CH\(_2\)N), 4.03 (t, \(J = 5.9\) Hz, 2H, NCH\(_2\)), 4.56 (t, \(J = 6.6\) Hz, 2H, OCH\(_2\)), 6.98 (d, \(J = 8.8\) Hz, 2H, ArH), 7.27 (s, 1H), 7.84 (d, \(J = 8.8\) Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 288.25 [M + H]\(^+\).

4-(3-(4-(1-Hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)propoxy)benzaldehyde (90): Yield 75%; IR (film, cm\(^{-1}\)): 3394 (O–H), 2933, 2857, 1686 (C=O), 1600, 1577, 1509, 1256, 1218, 1160, 1047; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.31-1.36 (m, 1H), 1.50-1.55 (m, 2H), 1.59-1.64 (m, 1H), 1.67-1.78 (m, 2H), 1.82-1.86 (m, 2H), 1.92-1.95 (m, 2H), 2.04 (s, 1H, OH), 2.45 (pentet, \(J = 5.9\) Hz, 2H, OCH\(_2\)CH\(_2\)CH\(_2\)N), 4.07 (t, \(J = 5.9\) Hz, 2H, NCH\(_2\)), 4.57 (t, \(J = 6.6\) Hz, 2H, OCH\(_2\)), 6.98 (d, \(J = 8.8\) Hz, 2H, ArH), 7.45 (s, 1H), 7.83 (d, \(J = 8.0\) Hz, ArH), 9.88 (s, 1H, CHO); ESI-MS (m/z): 330.10 [M + H]\(^+\).

4-(3-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)propoxy)benzaldehyde (91): Yield 77%; IR (film, cm\(^{-1}\)): 3370, 2926, 2853, 1686 (C=O), 1601, 1577, 1509, 1313, 1258, 1218, 1161, 1045; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 2.10 (s, 1H, OH), 2.45 (pentet, \(J = 6.6\) Hz, ArH), 9.88 (s, 1H, CHO); ESI-MS (m/z): 330.10 [M + H]\(^+\).
2H, OCH$_2$CH$_2$CH$_2$N), 4.07 (t, J = 5.9 Hz, 2H, NCH$_2$), 4.60 (t, J = 6.6 Hz, 2H, OCH$_2$), 4.78 (s, 2H, CH$_2$OH), 6.98 (d, J = 8.8 Hz, 2H, ArH), 7.56 (s, 1H), 7.83 (d, J = 8.8 Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 262.23 [M + H]$^+$. 

(1-(3-(4-Formylphenoxy)propyl)-1H,1,2,3-triazol-4-yl)methyl propionate (92): Yield 79%; $^1$H NMR (400 MHz, CDCl$_3$) δ: 1.12 (t, J = 5.8 Hz, 3H, COCH$_2$CH$_3$), 2.34 (pentet, J = 7.3 Hz, 2H, OCH$_2$CH$_2$CH$_2$N), 2.45 (q, J = 5.8 Hz, 2H, OCH$_2$CH$_3$), 4.07 (t, J = 5.8 Hz, 2H, NCH$_2$), 4.59 (t, J = 6.6 Hz, 2H, OCH$_2$), 5.21 (s, 2H, CH$_2$OCO), 6.98 (d, J = 8.8 Hz, 2H, ArH), 7.61 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 318.31 [M + H]$^+$. 

4-(3-(4-(Phenoxymethyl)-1H,1,2,3-triazol-1-yl)propoxy)benzaldehyde (93): Yield 74%; $^1$H NMR (400 MHz, CDCl$_3$) δ: 2.45 (pentet, J = 5.6 Hz, 2H, OCH$_2$CH$_2$CH$_2$N), 4.06 (t, J = 5.1 Hz, 2H, OCH$_2$CH$_2$CH$_2$N), 4.60 (t, J = 6.6 Hz, 2H, OCH$_2$), 5.21 (s, 2H, CH$_2$OPh), 6.96 (d, J = 8 Hz, 5H, ArH), 7.29 (d, J = 7.3 Hz, 2H, ArH), 7.62 (s, 1H), 7.82 (d, J = 8.8 Hz, 2H, ArH), 9.88 (s, 1H, CHO); ESI-MS (m/z): 338.11 [M + H]$^+$. 

4-(3-(4-(p-Tolyloxymethyl)-1H,1,2,3-triazol-1-yl)propoxy)benzaldehyde (94): Yield 76%; $^1$H NMR (400 MHz, CDCl$_3$) δ: 2.28 (s, 3H, CH$_3$), 2.45 (pentet, J = 6.6 Hz, 2H, OCH$_2$CH$_2$CH$_2$N), 4.06 (t, J = 5.9 Hz, 2H, NCH$_2$), 4.60 (t, J = 6.6 Hz, 2H, OCH$_2$), 5.17 (s, 2H, CH$_2$OPh), 6.85 (d, J = 8.8 Hz, 2H, ArH), 6.96 (d, J = 8.8 Hz, 2H, ArH), 7.07 (d, J = 8.8 Hz, 2H, ArH), 7.61 (s, 1H), 7.82 (d, J = 8.8 Hz, 2H, ArH), 9.88 (s, 1H, CHO); ESI-MS (m/z): 352.26 [M + H]$^+$. 

4-(3-(4-((4-Chlorophenoxy)methyl)-1H,1,2,3-triazol-1-yl)propoxy)benzaldehyde (95): Yield 72%; $^1$H NMR (400 MHz, CDCl$_3$) δ: 2.46 (pentet, J = 5.9 Hz, 2H, OCH$_2$CH$_2$CH$_2$N), 4.05 (t, J = 5.9 Hz, 2H, NCH$_2$), 4.61 (t, J = 6.6 Hz, 2H, OCH$_2$), 5.17 (s, 2H, CH$_2$OPh), 6.89 (d, J = 9.5 Hz, 2H, ArH), 6.95 (d, J = 8.8 Hz, 2H, ArH), 7.22 (d, J =
Typical procedure for the synthesis of (E)-2-iso-propyl-5-methyl-4-(4-(2-(4-propyl-1H-1,2,3-triazol-1-yl)ethoxy)benzylideneamino)phenol (96) and related compounds (97-112): A mixture of 4-amino-2-iso-propyl-5-methylphenol (33; 200 mg, 1.21 mmol) and 4-(2-(4-propyl-1H-1,2,3-triazol-1-yl)ethoxy)benzaldehyde, (79; 313 mg, 1.21 mmol) in dry MeOH was stirred at ambient temperature (30-35 °C) for 3-4 h under inert atmosphere. The separated solid was filtered and washed with cold MeOH to get compound 96. Yield 73%; mp 187-188 °C; IR (KBr, cm⁻¹): 3124 (O–H), 3072, 2961, 2926, 2869, 1620 (C=N), 1605, 1573, 1513, 1455, 1424, 1393, 1309, 1286, 1246 (C–O–C), 1169, 1054 (C–O–C); ¹H NMR (400 MHz, DMSO-d$_6$) δ: 0.88 (t, J = 7.3 Hz, 3H, CH$_2$CH$_2$CH$_3$), 1.16 (d, J = 7.3 Hz, 6H, CH(CH$_3$)$_2$), 1.59 (sextet, J = 7.3 Hz, 2H, CH$_2$CH$_2$CH$_3$), 2.19 (s, 3H, CH$_3$), 2.57 (t, J = 7.3 Hz, 2H, CH$_2$CH$_2$CH$_3$), 3.15 (septet, J = 7.3 Hz, 1H, CH(CH$_3$)$_2$), 4.44 (t, J = 5.1 Hz, 2H, NCH$_2$), 4.72 (t, J = 5.1 Hz, 2H, OCH$_2$), 6.62 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.02 (d, J = 8.8 Hz, 2H, ArH), 7.83 (d, J = 8.8 Hz, 2H, ArH), 7.91 (s, 1H), 8.40 (s, 1H, N=CH), 9.11 (s, 1H, OH); ¹³C NMR (100 MHz, DMSO-d$_6$) δ: 13.59, 17.24, 22.27, 22.57, 26.38, 27.04, 48.76, 66.39, 114.71, 114.88, 116.50, 122.37, 129.84, 130.16, 130.20, 132.31, 141.63, 146.76, 152.55, 155.40, 159.88; ESI-MS (m/z): 407.32 [M + H]$^+$.

(E)-4-(4-(2-(4-Butyl-1H-1,2,3-triazol-1-yl)ethoxy)benzylideneamino)-2-iso-propyl-5-methyl-phenol (97): Yield 77%; mp 178-179 °C; IR (KBr, cm⁻¹): 3069 (O–H), 2958, 2925, 2863, 1620 (C=N), 1606, 1576, 1513, 1422, 1245 (C–O–C), 1227, 1168, 1043 (C–O–C); ¹H NMR (400 MHz, DMSO-d$_6$) δ: 0.87 (t, J = 7.3 Hz, 3H, CH$_2$CH$_3$), 1.16 (d, J = 6.6 Hz, 6H, CH(CH$_3$)$_2$), 1.29 (sextet, J = 7.3 Hz, 2H, CH$_2$CH$_2$CH$_3$), 1.55 (pentet, J = 7.3 Hz, 2H, CH$_2$CH$_2$CH$_2$CH$_3$), 2.19 (s, 3H, CH$_3$), 2.59 (t, J = 7.3 Hz, 2H,
CH$_2$CH$_2$CH$_3$), 3.15 (septet, $J = 6.6$ Hz, 1H, CH(CH$_3$)$_2$), 4.44 (t, $J = 5.1$ Hz, 2H, NCH$_2$), 4.72 (t, $J = 5.1$ Hz, 2H, OCH$_2$), 6.63 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.01 (d, $J = 8.8$ Hz, 2H, ArH), 7.83 (d, $J = 8.8$ Hz, 2H, ArH), 7.91 (s, 1H), 8.40 (s, 1H, N=CH), 9.11 (s, 1H, OH); ESI-MS (m/z): 421.35 [M + H$^+$].

(E)-4-(4-(2-(4-(1-Hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzylidene amino)-2-iso-propyl-5-methylphenol (98): Yield 54%; mp 192-193 °C; IR (KBr, cm$^{-1}$): 3277 (O–H), 2937, 2862, 1621 (C=N), 1609, 1509, 1458, 1449, 1420, 1303, 1252 (C–O–C), 1237, 1165, 1154, 1044 (C–O–C); $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.16 (d, $J = 7.3$ Hz, 6H, CH(CH$_3$)$_2$), 1.20-1.29 (m, 1H), 1.39-1.40 (m, 2H), 1.48 (br, 1H), 1.60-1.62 (m, 1H), 1.66-1.69 (m, 3H), 1.81-1.82 (m, 1H), 1.84-1.87 (m, 1H), 2.19 (s, 3H, CH$_3$), 3.15 (septet, $J = 7.3$ Hz, 1H, CH(CH$_3$)$_2$), 4.46 (t, $J = 5.1$ Hz, 2H, NCH$_2$), 4.74 (t, $J = 5.1$ Hz, 2H, OCH$_2$), 4.85 (brs, 1H, OCH$_2$), 6.62 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.02 (d, $J = 8.8$ Hz, 2H, ArH), 7.83 (d, $J = 8.8$ Hz, 2H, ArH), 7.94 (s, 1H), 8.41 (s, 1H, N=CH), 9.11 (s, 1H, OH); ESI-MS (m/z): 463.37 [M + H$^+$].

(E)-4-(4-(2-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzylideneamino)-2-iso-propyl-5-methylphenol (99): Yield 60%; mp 156-158 °C; IR (KBr, cm$^{-1}$): 3143 (O–H), 2961, 2928, 2873, 1623 (C=N), 1606, 1576, 1514, 1453, 1306, 1248 (C–O–C), 1174, 1042 (C–O–C); $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.15 (d, $J = 7.3$ Hz, 6H, CH(CH$_3$)$_2$), 2.19 (s, 3H, CH$_3$), 3.14 (septet, $J = 7.3$ Hz, 1H, CH(CH$_3$)$_2$), 4.45 (t, $J = 5.1$ Hz, 2H, NCH$_2$), 4.50 (s, 2H, CH$_2$OH), 4.76 (t, $J = 5.1$ Hz, 2H, OCH$_2$), 5.17 (brs, 1H, CH$_2$OH), 6.62 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.03 (d, $J = 8.8$ Hz, 2H, ArH), 7.83 (d, $J = 8.8$ Hz, 2H, ArH), 8.04 (s, 1H), 8.40 (s, 1H, N=CH), 9.11 (s, 1H, OH); ESI-MS (m/z): 394.36 [M + H$^+$].
(E)-(1-(2-(4-(4-Hydroxy-5-iso-propyl-2-methylphenylimino)methyl)phenoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl propionate (100): Yield 40%; mp 120-121 °C; IR (film, cm⁻¹): 3151 (O–H), 2959, 1736, 1604, 1512, 1421, 1244 (C–O–C), 1168, 1046 (C–O–C); ¹H NMR (400 MHz, DMSO-d₆) δ: 1.0 (t, J = 7.3 Hz, 3H, COCH₂CH₃), 1.16 (d, J = 5.8 Hz, 6H, CH(CH₃)₂), 2.19 (s, 3H, CH₃), 2.30-2.32 (m, 2H, OCH₂), 3.15 (septet, J = 7.3 Hz, 1H, CH(CH₃)₂), 4.47 (brs, 2H, NCH₂), 4.79 (brs 2H, OCH₂), 5.12 (s, 2H, CH₂OCO), 6.62 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.02 (d, J = 6.6 Hz, 2H, ArH), 7.83 (d, J = 6.6 Hz, 2H, ArH), 8.22 (s, 1H), 8.41 (s, 1H, N=CH), 9.11 (s, 1H, OH); ESI-MS (m/z): 451.33 [M + H]+.

(E)-2-iso-Propyl-5-methyl-4-(4-(2-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)ethoxy)benzylideneamino)phenol (101): Yield 45%; mp 113-115 °C; IR (KBr, cm⁻¹): 3140 (O–H), 3023, 2959, 2927, 1701, 1654, 1627 (C=N), 1605, 1513, 1457, 1424, 1309, 1243 (C–O–C), 1175, 1038 (C–O–C); ¹H NMR (400 MHz, DMSO-d₆) δ: 1.14 (d, J = 7.3 Hz, 6H, CH(CH₃)₃), 2.18 (s, 3H, CH₃), 3.14 (septet, J = 7.3 Hz, 1H, CH(CH₃)₂), 4.53-4.56 (m, 2H, NCH₂), 4.85-4.89 (m, 2H, OCH₂), 6.61 (s, 1H, ArH), 6.85 (s, 1H, ArH), 7.04 (d, J = 8.8 Hz, 1H, ArH), 7.12 (d, J = 8.8 Hz, 1H, ArH), 7.31-7.34 (m, 1H, ArH), 7.82-7.86 (m, 2H, ArH), 7.87-7.90 (m, 1H), 8.0-8.03 (m, 1H), 8.40 (s, 1H, N=CH), 8.58-8.59 (m, 1H, ArH), 8.69 (s, 1H, ArH), 9.10 (s, 1H, OH); ESI-MS (m/z): 442.32 [M + H]+.

(E)-2-iso-Propyl-5-methyl-4-(4-(2-(4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzylideneamino)phenol (102): Yield 56%; mp 125-126 °C; IR (film, cm⁻¹): 3140 (O–H), 3023, 2959, 2927, 1701, 1654, 1627 (C=N), 1605, 1513, 1457, 1424, 1309, 1243 (C–O–C), 1175, 1038 (C–O–C); ¹H NMR (400 MHz, CDCl₃) δ: 1.26 (d, J = 7.3 Hz, 6H, CH(CH₃)₃), 2.29 (s, 3H, CH₃), 3.19 (septet, J = 7.3 Hz, 1H, CH(CH₃)₂), 4.43 (t, J = 5.1 Hz, 2H, NCH₂), 4.89 (brs, 1H, OH), 5.23 (s, 2H, CH₂OPh), 6.63 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.92 (d, J = 9.1 Hz, 2H, ArH), 6.96-6.99 (m, 2H, ArH), 7.0 (s, 1H),
7.27-7.31 (m, 2H, ArH), 7.82 (s, 1H, ArH), 7.84 (d, \( J = 8.8 \) Hz, 2H, ArH), 8.30 (s, 1H, N=CH); ESI-MS (m/z): 471.15 [M + H]⁺.

(\( E \))-2-iso-Propyl-5-methyl-4-(4-(2-(4-(p-toloyxymethyl)-1H,1,2,3-triazol-1-yl)ethoxy)benzylideneamino)phenol (103): Yield 62%; mp 81-82 °C; IR (film, cm⁻¹): 3146 (O–H), 2959, 2871, 1686, 1603, 1510, 1458, 1288, 1243 (C–O–C), 1166, 1045 (C–O–C); \(^1\)H (400 MHz, CDCl₃) δ: 1.26 (d, \( J = 6.6 \) Hz, 6H, CH(CH₃)₂), 2.28 (s, 6H, 2(CH₃)), 3.20 (septet, \( J = 6.6 \) Hz, 1H, CH(CH₃)₂), 4.41 (t, \( J = 4.4 \) Hz, 2H, OCH₂), 4.78 (t, \( J = 4.4 \) Hz, 2H, OCH₂), 5.20 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.87-6.89 (m, 4H, ArH), 7.07 (d, \( J = 8 \) Hz, 2H, ArH), 7.80-7.83 (m, 2H, ArH), 7.85 (s, 1H), 8.29 (s, 1H, N=CH); ESI-MS (m/z): 485.36 [M + H]⁺.

(\( E \))-4-(4-(2-(4-((4-Chlorophenoxy)methyl)-1H,1,2,3-triazol-1-yl)ethoxy)benzylideneamino)-2-iso-propyl-5-methylphenol (104): Yield 65%; mp 110-111 °C; IR (film, cm⁻¹): 3150 (O–H), 2960, 2872, 1624 (C=N), 1603, 1512, 1491, 1422, 1242 (C–O–C), 1168, 1046 (C–O–C); \(^1\)H (400 MHz, CDCl₃) δ: 1.26 (d, \( J = 6.6 \) Hz, 6H, CH(CH₃)₂), 2.27 (s, 3H, CH₃), 3.21 (septet, \( J = 7.3 \) Hz, 1H, CH(CH₃)₃), 4.42-4.45 (m, 2H, NCH₂), 4.78-4.80 (m, 2H, OCH₂), 5.19 (s, 2H, CH₂OPh), 5.55 (s, 1H, OCH), 6.63 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.89-6.92 (m, 4H, ArH), 7.22 (d, \( J = 8.8 \) Hz, 2H, ArH), 7.81 (s, 1H), 7.84 (d, \( J = 8.8 \) Hz, 2H, ArH), 8.30 (s, 1H, N=CH); ESI-MS (m/z): 505.31 [M + H]⁺.

(\( E \))-2-iso-Propyl-5-methyl-4-(4-(3-(4-propyl-1H,1,2,3-triazol-1-yl)propoxy)benzylideneamino)phenol (105): Yield 73% (pale yellow solid); mp 138-139 °C; IR (film, cm⁻¹): 3139 (O–H), 2959, 2872, 1687, 1605, 1577, 1514, 1423, 1339, 1307, 1251 (C–O–C), 1166, 1044 (C–O–C); \(^1\)H NMR (400 MHz, CDCl₃) δ: 0.94 (t, \( J = 7.3 \) Hz, 3H, CH₂CH₂CH₃), 1.26 (d, \( J = 6.6 \) Hz, 6H, CH(CH₃)₂), 1.67 (sextet, \( J = 7.3 \) Hz, 2H,
(E)-4-(4-(3-(4-(1-Hydroxycyclohexyl)-1H-1,2,3-triazol-1-yl)propoxy)benzylideneamino)-2-iso-propyl-5-methylphenol (106): Yield 50% (pale yellow solid); mp 124-126 °C; IR (film, cm⁻¹): 2922, 1693, 1605, 1515, 1436, 1256 (C–O–C), 1164, 1110, 1047 (C–O–C); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 0.91 (t, \(J = 7.3\) Hz, 3H, \(CH_2CH_3\)), 1.26 (d, \(J = 6.6\) Hz, 6H, \(CH(CH_3)_2\)), 1.35 (sextet, \(J = 7.3\) Hz, 2H, \(CH_2CH_2CH_3\)), 1.62 (pentet, \(J = 7.3\) Hz, 2H, \(CH_2CH_2CH_2CH_3\)), 2.28 (s, 3H, \(CH_3\)), 2.42 (pentet, \(J = 6.6\) Hz, 2H, OCH\(_2CH_2CH_2N\)), 2.70 (t, \(J = 7.3\) Hz, 2H, \(CH_2CH_2CH_2CH_3\)), 3.21 (septet, \(J = 6.6\) Hz, 1H, \(CH(CH_3)_2\)), 3.49 (s, 1H, \(OH\)), 4.01 (t, \(J = 5.8\) Hz, 2H, NCH\(_2\)), 4.56 (t, \(J = 6.6\) Hz, 2H, OCH\(_2\)), 6.64 (s, 1H, \(ArH\)), 8.30 (s, 1H, \(N=CH\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 13.72, 17.35, 22.18, 22.71, 25.12, 26.83, 29.74, 31.43, 46.81, 64.10, 114.44, 115.44, 117.14, 121.27, 130.13, 130.37, 132.82, 132.94, 148.32, 151.61, 151.86, 156.76, 160.49; ESI-MS (m/z): 435.36 [M + H]\(^+\).

(\(E\))-4-(4-(3-(4-Butyl-1H-1,2,3-triazol-1-yl)propoxy)benzylideneamino)-2-iso-propyl-5-methylphenol (107): Yield 42% (buff coloured solid); mp 143-144 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 1.16 (d, \(J = 6.6\) Hz, 6H, CH(CH\(_3\))\(_2\)), 1.24-1.29 (m, 1H), 1.38-1.39 (m, 2H), 1.47 (brs, 1H), 1.59-1.69 (m, 4H), 1.81-1.87 (m, 2H), 2.20 (s, 3H, \(CH_3\)), 2.28 (pentet, \(J = 5.8\) Hz, 2H, OCH\(_2CH_2CH_2N\)), 3.15 (septet, \(J = 6.6\) Hz, 1H,
CH(CH$_3$)$_2$), 4.03 (t, $J$ = 5.8 Hz, 2H, NCH$_2$), 4.49 (t, $J$ = 6.6 Hz, 2H, OCH$_2$), 4.82 (s, 1H, OH), 6.63 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.01 (d, $J$ = 8.8 Hz, 2H, ArH), 7.84 (d, $J$ = 8.0 Hz, 2H, ArH), 7.91 (s, 1H), 8.41 (s, 1H, N=CH), 9.10 (s, 1H, OH); ESI-MS (m/z): 477.39 [M + H]$^+$. 

\[(E)-4-(4-(3-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)propoxy)benzylideneamino)-2-iso-propyl-5-methylphenol (108):\] Yield 40% (buff coloured solid); mp 137-138 °C; IR (KBr, cm$^{-1}$): 3140 (O–H), 2957, 2870, 1618 (C=N), 1603, 1508, 1420, 1243 (C–O–C), 1166, 1040 (C–O–C); $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.15 (d, $J$ = 7.3 Hz, 6H, CH(CH$_3$)$_2$), 2.19 (s, 3H, CH$_3$), 2.28 (pentet, $J$ = 6.6 Hz, 2H, OCH$_2$CH$_2$CH$_2$N), 3.14 (septet, $J$ = 7.3 Hz, 1H, CH(CH$_3$)$_2$), 4.03 (t, $J$ = 5.8 Hz, 2H, NCH$_2$), 4.48-4.53 (m, 4H), 5.16 (t, $J$ = 5.1 Hz, 1H, CH$_2$OH), 6.62 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.01 (d, $J$ = 8.8 Hz, 2H, ArH), 7.83 (d, $J$ = 8.8 Hz, 2H, ArH), 8.0 (s, 1H), 8.40 (s, 1H, N=CH), 9.10 (s, 1H, OH); ESI-MS (m/z): 409.15 [M + H]$^+$. 

\[(E)-(1-(3-(4-((4-Hydroxy-5-iso-propyl-2-methylphenylimino)methyl)phenoxy)propyl)-1H-1,2,3-triazol-4-yl)methylpropionate (109):\] Yield 60% (light purple solid); mp 125-126 °C; IR (KBr, cm$^{-1}$): 3139 (O–H), 2965, 1727, 1625 (C=N), 1604, 1517, 1413, 1260 (C–O–C), 1169, 1038 (C–O–C); $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 1.0 (t, $J$ = 7.3 Hz, 3H, OCH$_2$CH$_3$), 1.15 (d, $J$ = 7.3 Hz, 6H, CH(CH$_3$)$_2$), 2.19 (s, 3H, CH$_3$), 2.26-2.33 (m, 4H), 3.14 (septet, $J$ = 7.3 Hz, 1H, CH(CH$_3$)$_2$), 4.03 (t, $J$ = 5.8 Hz, 2H, OCH$_2$), 4.54 (t, $J$ = 6.6 Hz, 2H, NCH$_2$), 5.10 (s, 2H, CH$_2$OCO), 6.62 (s, 1H, ArH), 6.85 (s, 1H, ArH), 6.99 (d, $J$ = 8.8 Hz, 2H, ArH), 7.83 (d, $J$ = 8.8 Hz, 2H, ArH), 8.10 (s, 1H), 8.40 (s, 1H, N=CH), 9.10 (s, 1H, OH); ESI-MS (m/z): 465.34 [M + H]$^+$. 

\[(E)-2-iso-Propyl-5-methyl-4-(4-(3-(4-(phenoxymethyl)-1H-1,2,3-triazol-1-yl)propoxy)benzylideneamino)phenol (110):\] Yield 70%; mp 113-114 °C; IR (film, cm$^{-1}$): 3148 (O–
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H), 2959, 2926, 1623 (C=N), 1603, 1513, 1496, 1244 (C–O–C), 1166, 1033 (C–O–C); $^1$H (400 MHz, CDCl$_3$) δ: 1.26 (d, $J = 6.6$ Hz, 6H, CH(CH$_3$)$_3$), 2.29 (s, 3H, CH$_3$), 2.44 (pentet, $J = 6.6$ Hz, 2H, OCH$_2$CH$_2$CH$_2$N), 3.20 (septet, $J = 6.6$ Hz, 1H, CH(CH$_3$)$_3$), 4.02 (t, $J = 5.9$ Hz, 2H, NCH$_2$), 4.61 (t, $J = 6.6$ Hz, 2H, OCH$_2$), 5.07 (brs, 1H, OH), 5.21 (s, 2H, OCH$_2$Ph), 6.63 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.92 (s, 1H, ArH), 6.94-6.96 (m, 3H, ArH), 6.98 (s, 1H, ArH), 7.26-7.30 (m, 2H, ArH), 7.62 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H, ArH), 8.30 (s, 1H, N=CH); ESI-MS (m/z): 485.14 [M + H]$^+$.  

(E)-2-iso-Propyl-5-methyl-4-(4-(3-(4-(p-tolyloxymethyl)-1H-1,2,3-triazol-1-yl)propoxy)benzylideneamino)phenol (111): Yield 75%; mp 128-129 °C; IR (film, cm$^{-1}$): 3142 (O–H), 2959, 2925, 2870, 1604, 1510, 1244 (C–O–C), 1166, 1041 (C–O–C); $^1$H (400 MHz, CDCl$_3$) δ: 1.26 (d, $J = 7.3$ Hz, 6H, CH(CH$_3$)$_3$), 2.27 (s, 3H, CH$_3$), 2.29 (s, 3H, CH$_3$), 2.44 (pentet, $J = 7.3$ Hz, 2H, OCH$_2$CH$_2$CH$_2$N), 3.19 (septet, $J = 7.3$ Hz, 1H, CH(CH$_3$)$_3$), 4.03 (t, $J = 5.9$ Hz, 2H, NCH$_2$), 4.61 (t, $J = 6.6$ Hz, 2H, OCH$_2$), 4.98 (brs, 1H, OH), 5.18 (s, 2H, CH$_2$OPh), 6.63 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.86 (d, $J = 8$ Hz, 2H, ArH), 6.93 (d, $J = 8.8$ Hz, 2H, ArH), 7.07 (d, $J = 8$ Hz, 2H, ArH), 7.61 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H, ArH), 8.30 (s, 1H, N=CH); ESI-MS (m/z): 499.35 [M + H]$^+$.  

(E)-4-(4-(3-(4-(4-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)propoxy)benzylideneamino)-2-iso-propyl-5-methylphenol (112): Yield 77%; mp 124-126 °C; IR (film, cm$^{-1}$): 3145 (O–H), 2959, 2871, 1623 (C=N), 1604, 1513, 1490, 1421, 1243 (C–O–C), 1166, 1041 (C–O–C); $^1$H (400 MHz, CDCl$_3$) δ: 1.26 (d, $J = 7.3$ Hz, 6H, CH(CH$_3$)$_3$), 2.29 (s, 3H, CH$_3$), 2.44 (pentet, $J = 6.6$ Hz, 2H, OCH$_2$CH$_2$CH$_2$N), 3.19 (septet, $J = 7.3$ Hz, 1H, CH(CH$_3$)$_3$), 4.01 (t, $J = 5.9$ Hz, 2H, NCH$_2$), 4.62 (t, $J = 6.6$ Hz, 2H, OCH$_2$), 4.96 (s, 1H, OH), 5.18 (s, 2H, CH$_2$OPh), 6.63 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.89 (d, $J = 9.5$ Hz, 2H, ArH), 6.92 (d, $J = 8.8$ Hz, 2H, ArH), 7.21 (d, $J = 8.8$, 2H, ArH), 7.60 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H, ArH), 8.30 (s, 1H, N=CH); ESI-MS (m/z): 519.31 [M + H]$^+$.  

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Procedure for synthesis of 4-(prop-2-ynyloxy)benzaldehyde (114)\textsuperscript{66}: To a mixture of \textit{para}-hydroxybenzaldehyde (2 g, 0.016 mol) and anhydrous K\textsubscript{2}CO\textsubscript{3} (6.7 g, 0.049 mol) in dry DMF (25 mL), a solution of propargyl bromide (2.3 g, 0.019 mol) in dry DMF (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 10-12 h. The progress of the reaction was monitored by thin layer chromatography and after completion, the reaction mixture was poured into ice cold water and extracted thrice with chloroform (3 x 30 mL). The organic layer was washed thrice with cold water (3 x 70 mL) to remove DMF. The chloroform layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and excess of solvent was removed under reduced pressure. The crude product thus obtained was purified over silica gel column using EtOAc:Hexane as an eluent to afford compound 114 as a white solid. Yield 86%; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 2.55-2.57 (m, 1H, C≡CH), 4.78 (s, 2H, OCH\textsubscript{2}), 6.94-6.97 (d, 2H, ArH), 7.84-7.87 (d, 2H, ArH), 9.90 (s, 1H, CHO); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\): 56.3, 76.7, 78.4, 115.6, 131.0, 132.3, 162.8, 191.2.

Typical procedure for the syntheses of 1-azidopropane (121) and related compounds (120-124): Sodium azide (286 mg, 6.09 mmol) was added to a solution of 1-bromopropane (250 mg, 2.03 mmol) and K\textsubscript{2}CO\textsubscript{3} (510 mg, 6.09 mmol) in dry DMF (15 mL). The mixture was stirred for 2-3 h at 50 °C. Afterward, water (30 mL) was added to dissolve the excess sodium azide and reaction mixture was extracted with CHCl\textsubscript{3} (3 x 20 mL). The organic layer was washed with water (5 x 40 mL) to remove DMF. The resulting organic layer was dried in Na\textsubscript{2}SO\textsubscript{4} and solvent was removed under vacuum to get compound 121. bp 81-82 °C.\textsuperscript{67}

1-Azidobutane (122)\textsuperscript{68}: Yield 80% (colorless liquid); bp 106-108 °C; IR (neat, cm\textsuperscript{-1}): 2962, 2934, 2874, 2097, 1633, 1465, 1380, 1351, 1279, 1262, 1215, 1116; \textsuperscript{1}H NMR (300
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299 MHz, CDCl\(_3\)) \(\delta\): 0.95 (t, \(J= 7.5\) Hz, 3H), 1.41 (m, 2H), 1.83 (m, 2H), 3.25 (t, \(J = 6.9\) Hz, 2H); \(^{13}\)C NMR (300 MHz, CDCl\(_3\)) \(\delta\): 13.5, 19.7, 32.6, 50.1.

(Azidomethyl)benzene (124): Yield 95.4% (colorless oil); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 4.19 (s, 2H, CH\(_2\)), 7.18-7.26 (m, 5 H, ArH).

Typical procedure for the synthesis of 4-((1-propyl-1\(^1\)H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (126) and related compounds (125-129): 4-(Prop-2-ynyloxy)benzaldehyde (114; 300 mg, 1.87 mmol), 1-azidopropane (121; 230.4 mg, 1.87 mmol), CuSO\(_4\).5H\(_2\)O (93.5 mg, 0.375 mmol) and sodium ascorbate (148.5 mg, 0.375 mmol) were added to a 1:1 (v/v) solution of \textit{tert}-butanol (10 mL) and water (10 mL). The reaction mixture was stirred at 30-35 °C for 2-3 h. The product was extracted with ethyl acetate. The organic layer was washed with water, dried with Na\(_2\)SO\(_4\), filtered and concentrated. The crude was purified by column chromatography to get compound 126. Yield 88%; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 0.97 (t, \(J= 7.3\) Hz, 3H, CH\(_3\)CH\(_3\)), 1.96 (sextet, \(J = 7.3\) Hz, 2H, NCH\(_2\)CH\(_2\)), 4.34 (t, \(J = 7.3\) Hz, 2H, NCH\(_2\)), 5.30 (s, OCH\(_2\), 2H), 7.12 (d, \(J = 8.8\) Hz, 2H, ArH), 7.63 (s, 1H), 7.84 (d, \(J = 8.8\) Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 246.28 [M + H]

4-((1-iso-Propyl-1\(^1\)H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (125): Yield 90%; IR (film, cm\(^{-1}\)) : 2982, 2928, 2852, 1689, 1600, 1578, 1508, 1311, 1247, 1215, 1161, 1110; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.60 (d, \(J = 6.6\) Hz, 6H, CH(CH\(_3\))\(_2\)), 4.85 (septet, \(J = 6.6\) Hz, 1H, CH(CH\(_3\))\(_2\)), 5.29 (s, 2H, OCH\(_2\)), 7.12 (d, \(J = 8.8\) Hz, 2H, ArH), 7.67 (s, 1H), 7.84 (d, \(J = 8.8\) Hz, 2H, ArH), 9.89 (s, 1H, OH); ESI-MS (m/z): 246.25 [M + H]

4-((1-Butyl-1\(^1\)H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (127): Yield 85%; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 0.95 (t, \(J = 7.3\) Hz, 3H, CH\(_3\)), 1.36 (sextet, \(J = 7.3\) Hz, 2H, CH\(_2\)CH\(_3\)), 1.90 (pentet, \(J = 7.3\) Hz, 2H, NCH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 4.37 (t, \(J = 7.3\) Hz, 2H,
NCH$_2$), 5.30 (s, 2H, OCH$_2$), 7.11 (d, $J = 8.8$ Hz, 2H, ArH), 7.63 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 260.31 [M + H]$^+$. 

4-((1-Pentyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (128): Yield 90%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.89 (t, $J = 7.3$ Hz, 3H, CH$_3$), 1.32-1.35 (m, 4H), 1.92 (pentet, $J = 7.3$ Hz, 2H, NCH$_2$CH$_2$), 4.36 (t, $J = 7.3$ Hz, 2H, NCH$_2$), 5.30 (s, 2H, OCH$_2$), 7.11 (d, $J = 8.8$ Hz, 2H, ArH), 7.62 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H, ArH), 9.89 (s, 1H, CHO); ESI-MS (m/z): 274.41 [M + H]$^+$. 

4-((1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (129): Yield 92%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 5.19 (s, 2H, OCH$_2$), 5.47 (s, 2H, NCH$_2$Ph), 7.01 (d, $J = 8.8$ Hz, 2H, ArH), 7.19-7.22 (m, 2H, ArH), 7.29-7.33 (m, 3H, ArH), 7.48 (s, 1H), 7.75 (d, $J = 8.8$ Hz, 2H, ArH), 9.81 (s, 1H, CHO); ESI-MS (m/z): 294.26 [M + H]$^+$. 

**Typical procedure for the synthesis of (E)-2-iso-propyl-5-methyl-4-(4-((1-propyl-1H-1,2,3-triazol-4-yl)methoxy)benzylideneamino)phenol (131) and related compounds (130-134):** A mixture of 4-amino-2-iso-propyl-5-methylphenol (33; 200 mg, 1.21 mmol) and 4-((1-propyl-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde, (126; 297 mg, 1.21 mmol) in dry MeOH were stirred at 30-35 °C for 3-4 h under nitrogen atmosphere. The precipitated solid was filtered and washed with cold MeOH to get the desired product (131) in good yield. Yield 50% (yellow solid); mp 138-139 °C; IR (KBr, cm$^{-1}$): 3102 (O–H), 2952, 2866, 1624 (C=N), 1609, 1583, 1514, 1405, 1251(C–O–C), 1175, 1050 (C–O–C); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 0.82 (t, $J = 7.3$ Hz, 3H, CH$_2$CH$_3$), 1.16 (d, $J = 6.6$ Hz, 6H, CH(CH$_3$)$_2$), 1.82 (sextet, $J = 7.3$ Hz, 2H, CH$_2$CH$_2$CH$_3$), 2.20 (s, 3H, CH$_3$), 3.15 (septet, $J = 7.3$ Hz, 1H, CH(CH$_3$)$_2$), 4.32 (t, $J = 7.3$ Hz, 2H, NCH$_2$CH$_2$), 5.20 (s, 2H, OCH$_2$), 6.62 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.13 (d, $J = 8.8$ Hz, 2H, ArH), 7.85 (d, $J = 8.8$ Hz, 2H, ArH), 8.25 (s, 1H), 8.41 (s, 1H), 9.11 (s, 1H).
OH); $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 10.79, 17.27, 22.58, 23.18, 26.41, 50.97, 61.27, 114.88, 116.53, 124.51, 129.85, 130.02, 130.16, 132.34, 141.72, 142.32, 152.56, 155.47, 160.08; ESI-MS (m/z): 393.34 [M + H]$^+$. 

**(E)-2-iso-Propyl-4-((1-iso-propyl-1H-1,2,3-triazol-4-yl)methoxy)benzylideneamino)-5-methylphenol** (130): Yield 45% (yellow solid); mp 142-143 °C; IR (KBr, cm$^{-1}$): 3232 (O–H), 2957, 2870, 1638 (C=N), 1605, 1512, 1424, 1307, 1238 (C–O–C), 1191, 1171, 1060 (C–O–C), 1011; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 1.16 (d, J = 6.6 Hz, 6H, CH(CH$_3$)$_2$), 1.49 (d, J = 6.6 Hz, 6H, NCH(CH$_3$)$_2$), 2.20 (s, 3H, CH$_3$), 3.15 (septet, J = 6.6 Hz, 1H, CH(CH$_3$)$_2$), 4.82 (septet, J = 6.6 Hz, 1H, NCH(CH$_3$)$_2$), 5.19 (s, 2H, OCH$_2$), 6.63 (s, 1H, ArH), 6.87 (s, 1H, ArH), 7.14 (d, J = 8.8 Hz, 2H, ArH), 7.86 (d, J = 8.8 Hz, 2H, ArH), 8.32 (s, 1H), 8.42, (s, 1H), 9.11 (s, 1H, OH); ESI-MS (m/z): 393.28 [M + H]$^+$. 

**(E)-4-(4-((1-Butyl-1H-1,2,3-triazol-4-yl)methoxy)benzylideneamino)-2-iso-propyl-5-methylphenol** (132): Yield 65% (white solid); mp 141-142 °C; IR (KBr, cm$^{-1}$): 3143 (O–H), 2960, 2872, 1623 (C=N), 1604, 1512, 1411, 1246 (C–O–C), 1166, 1040 (C–O–C); $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 0.88 (t, J = 7.3 Hz, 3H, CH$_2$CH$_3$), 1.70 (d, J = 6.6 Hz, 6H, CH(CH$_3$)$_2$), 1.23 (sextet, J = 7.3 Hz, 2H, CH$_2$CH$_2$CH$_3$), 1.79 (pentet, J = 7.3 Hz, 2H, NCH$_2$CH$_2$CH$_2$CH$_3$), 2.20 (s, 3H, CH$_3$), 3.16 (septet, J = 6.6 Hz, 1H, CH(CH$_3$)$_2$), 4.36 (t, J = 7.3 Hz, 2H, NCH$_2$CH$_2$), 5.20 (s, 2H, OCH$_2$), 6.63 (s, 1H, ArH), 6.87 (s, 1H, ArH), 7.14 (d, J = 8.8 Hz, 2H, ArH), 7.86 (d, J = 8.8 Hz, 2H, ArH), 8.26 (s, 1H), 8.42 (s, 1H), 9.12 (s, 1H, OH); $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 13.28, 17.26, 19.07, 22.58, 26.39, 31.70, 49.09, 61.27, 114.89, 116.51, 124.51, 129.84, 130.01, 130.13, 132.31, 141.70, 142.30, 152.52, 155.48, 160.06; ESI-MS (m/z): 407.32 [M + H]$^+$. 

**(E)-2-iso-Propyl-5-methyl-4-((1-pentyl-1H-1,2,3-triazol-4-yl)methoxy)benzylidene amino)phenol** (133): Yield 90% (white solid); mp 162-164 °C; IR (KBr, cm$^{-1}$):
3402 (O–H), 2960, 1655 (C=O), 1245 (C=O–C), 1026 (C=O–C), 1007; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 0.83 (t, \(J = 7.3\) Hz, 3H, CH\(_2\)CH\(_3\)), 1.16 (d, \(J = 7.3\) Hz, 6H, CH(CH\(_3\))\(_2\)), 1.17-1.21 (m, 2H, CH\(_2\)CH\(_2\)CH\(_3\)), 1.27 (pentet, \(J = 6.6\) Hz, 2H, NCH\(_2\)CH\(_2\)CH\(_2\)), 1.80 (pentet, \(J = 7.3\) Hz, 2H, NCH\(_2\)CH\(_2\)CH\(_2\)), 2.20 (s, 3H, CH\(_3\)), 3.15 (septet, \(J = 7.3\) Hz, 1H, CH(CH\(_3\))\(_2\)), 4.34 (t, \(J = 6.6\) Hz, 2H, NCH\(_2\)CH\(_2\)), 5.20 (s, 2H, OCH\(_2\)), 6.63 (s, 1H, Ar\(H\)), 6.86 (s, 1H, Ar\(H\)), 7.13 (d, \(J = 8.8\) Hz, 2H, Ar\(H\)), 7.85 (d, \(J = 8.8\) Hz, 2H, Ar\(H\)), 8.25 (s, 1H), 8.41 (s, 1H), 9.10 (s, 1H, O\(H\)); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 13.76, 17.24, 21.50, 22.57, 26.38, 27.99, 29.39, 49.35, 61.25, 114.89, 116.50, 124.49, 129.82, 130.0, 130.12, 132.30, 141.70, 142.29, 152.52, 155.45, 160.03; ESI-MS (m/z): 421.32 [M + H]\(^+\).

\((E)-4-(4-(1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy)benzylideneamino)-2-iso-propyl-5-methylphenol (134): Yield 64% (brown solid); mp 144-145 °C; IR (KBr, cm\(^{-1}\)): 3167 (O–H), 2954, 2928, 2868, 1605, 1578, 1512, 1423, 1304, 1242 (C=O–C), 1191, 1161, 1033 (C=O–C); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 1.16 (d, \(J = 7.3\) Hz, 6H, CH(CH\(_3\))\(_2\)), 2.20 (s, 3H, CH\(_3\)), 3.15 (septet, \(J = 7.3\) Hz, 1H, CH(CH\(_3\))\(_2\)), 5.20 (s, 2H, OCH\(_2\)), 5.61 (s, 2H, NCH\(_2\)Ph), 6.63 (s, 1H, Ar\(H\)), 6.86 (s, 1H, Ar\(H\)), 7.12 (d, \(J = 8.8\) Hz, 2H, Ar\(H\)), 7.30 (brs, 1H, Ar\(H\)), 7.31-7.32 (m, 2H, Ar\(H\)), 7.33-7.39 (m, 2H, Ar\(H\)), 7.84 (d, \(J = 8.8\) Hz, 2H, Ar\(H\)), 8.30 (s, 1H), 8.41 (s, 1H), 9.11 (s, 1H, O\(H\)); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 17.28, 22.60, 26.41, 52.88, 61.21, 114.91, 116.54, 124.82, 127.97, 128.18, 128.79, 129.85, 130.04, 130.17, 132.36, 135.99, 141.73, 142.74, 152.56, 155.50, 160.05; ESI-MS (m/z): 441.31 [M + H]\(^+\).
Chapter 4
Synthesis and Antituberculosis Activity of Thymol Based Schiff Bases and Triazoles

References


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