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Antituberculosis activity evaluation of thymol Schiff bases

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Abstract: Thymol, a naturally occurring phenolic compound is a major constituent of essential oils of many plants. It has a wide range of biological and pharmaceutical activities. Keeping in mind the biological importance of thymol a series of forty thymol-Schiff bases was synthesized and evaluated for their antitubercular activity against *M. tuberculosis* H37Rv. Most of the compounds were active and the best active compound was found to have MIC_{99} 6 µg/mL.

Keywords: Thymol, Schiff base, tuberculosis, MIC, H37Rv

Introduction

Tuberculosis (TB) is a contagious and air borne disease caused predominantly by *Mycobacterium tuberculosis* [1]. According to the WHO 2016 report there were about 10.4 million new TB cases and 1.7 million people died from this disease worldwide [2]. A quarter of the World's population is infected by latent TB and may develop active form of TB ever in their lifetime [2, 3]. Immune-compromised individuals, especially those with HIV co-infection, are 20 to 30 times more likely to develop active TB. Although, the TB mortality rate fell by 37% between 2000 and 2016 globally, but the emergence of multi- and extensively-drug resistant (MDR-TB and XDR-TB) [4-6] and more recently totally drug resistant (TDR-TB) [7] strains of *M. tuberculosis* have increased the challenges to eliminate tuberculosis worldwide.

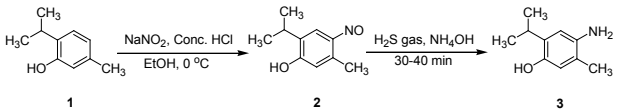
To combat this problem, there is a dire need to develop new antitubercular agents with novel mechanism of action that may act in synergy with already existing drugs to treat MDR-TB and XDR-TB and also shorten the duration of treatment. Although in the last few years several new compounds have been developed as anti-TB agents, only one new drug bedaquiline has been recently approved by FDA [8] for its use in

drug resistant tuberculosis [9].

In continuation with our research work on anti-tubercular agents [10-14] we synthesized a series of thymol-Schiff bases. Thymol (2-*iso*-propyl-5-methylphenol) occurring in the extracts of the plants of thyme species possess a wide range of biological and pharmacological properties [15, 16]. It exhibit antibacterial, antifungal, antiviral, antitumor and anti-inflammatory activities [17-24]. Thymol acts by causing disruption of the bacterial membrane. It also acts as antioxidant agent and free radical scavenger [25, 26]. Thymol is used in medical practice, agriculture, cosmetics and food industry. Thymol has antimicrobial properties and has the ability to reduce bacterial resistance to drugs such as penicillins (synergistic) [27].

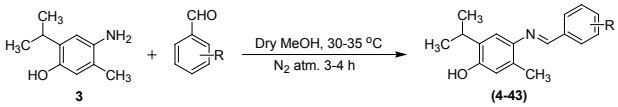
Chemistry

Present investigation deals with the synthesis and antitubercular activity evaluation of thymol-Schiff bases. All the forty synthesized compounds were characterized by spectroscopic techniques. The synthesis of the compounds was carried out according to the procedure shown in schemes 1 and 2. Firstly, 2-iso-propyl-5-methyl-phenol (**thymol/1**) was converted to compound with 4-nitroso substituent (**2**) by treating ethanolic solution of thymol with conc. hydrochloric acid and sodium nitrite at 0 °C. The nitroso compound (**2**) was then reduced in an ammonical solution by passing H_2S gas (scheme 1) [26, 28]. The substituted 4-aminophenol (**3**) obtained is highly unstable and subject to oxidation over a period of time.



Scheme 1

The 4-aminothymol (**3**) prepared according to scheme 1 was condensed with different benzaldehydes as soon as possible due to its instability in air [26,28]. This reaction was carried out at room temperature using dry MeOH as solvent and maintaining inert condition using nitrogen gas. The Schiff bases obtained were characterized by spectroscopic techniques.



4, R = H
5, R = 2-Me
6, R = 3-Me
7, R = 4-Me
8, R = 4-Et
9, R = 4-*n*-Pr
10, R = 4-*i*-Pr
11, R = 4-*n*-Bu
12, R = 4-*t*-Bu
13, R = 2-NO_2
14, R = 3-NO_2
15, R = 4-NO_2
16, R = 2-F
17, R = 3-F
18, R = 4-F
19, R = 2-Cl
20, R = 3-Cl
21, R = 4-Cl
22, R = 2-Br
23, R = 3-Br
24, R = 4-Br
25, R = 2-CF_3
26, R = 3-CF_3
27, R = 4-CF_3
28, R = 2,3-Me
29, R = 2,4-Me
30, R = 2,5-Me
31, R = 2,6-Me
32, R = 3,4-Me
33, R = 3,5-Me
34, R = 2,5-F
35, R = 2,4,5-F
36, R = 2,4-Cl
37, R = 2,6-Cl
38, R = 3-OMe, 4-OH
39, R = 2-OH, 5-NO_2
40, R = 2-Pyridyl
41, R = 3-Pyridyl
42, R = 2,3,4,5,6-F
43, R = 2,3-Methylenedioxy

Scheme 2

Results and discussions

In Vitro Antitubercular Activity

All thymol-Schiff bases (**4-43**) were screened for their antitubercular activity against *M. tuberculosis* H37Rv *in vitro*. Isoniazid and rifampicin were used as standard drugs with MIC 0.1 and 0.125 µg/mL, respectively.Table 1 represent the MIC values of thymol-Schiff bases against *M. tuberculosis* H37Rv. The thymol-Schiff bases (**4-43**) were found to be moderate to weakly active. Compound **39** with 2-hydroxyl and 5-nitro substituents was the most active compound at MIC_{99} 6 µg/mL against H37Rv.

Analysis of the data revealed that ten compounds (**4, 5, 8, 9, 10, 18, 23, 34, 35 and 37**) were active with MIC_{99} value 10 µg/mL. Compound **4** with no substitution in the benzaldehyde nucleus was active at 10 µg/mL. The unsubstituted compound (**4**) was more active than the methyl substituted compound. Alkyl substitution at *para* position has some good effect on

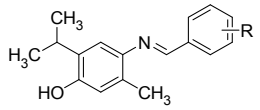
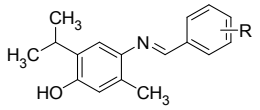
the activity as seen from the MIC values of compounds **7-12**. Replacing H with 4-Me leads to reduced activity, however substitution with 4-Et, 4-*n*-Pr and 4-*i*-Pr has retained activity. Compounds with 4-Et, 4-*n*-Pr and 4-*i*-Pr substituent are better active than methyl or butyl groups. Out of the halo substituents at para position only fluoro substituted compound showed activity at MIC_{99}10 µg/mL.The *ortho*/*meta*/*para* NO_2 substituted derivatives (**13-15**) showed poor activity while presence of OH group as in compound **39** (6 µg/mL) enhanced the activity. The di- and tri- fluoro (**34** and **35**) 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.

Materials and methods

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

Table 1: *In vitro* antimycobacterial activity of thymol-Shiff bases (4-43)

		**MIC_{99} (µg/mL) H37Rv**			**MIC_{99} (µg/mL) H37Rv**
Compd	**R**		**Compd**	**R**	
4	H	10	**24**	4-Br	20
5	2-Me	10	**25**	2-CF_3	>20
6	3-Me	20	**26**	3-CF_3	>20
7	4-Me	20	**27**	4-CF_3	>20
8	4-Et	10	**28**	2,3-Me	>20
9	4-*n*-Pr	10	**29**	2,4-Me	>20
10	4-*i*-Pr	10	**30**	2,5-Me	>20
11	4-*n*-Bu	>20	**31**	2,6-Me	>20
12	4-*t*-Bu	20	**32**	3,4-Me	>20
13	2-NO_2	>20	**33**	3,5-Me	>20
14	3-NO_2	>20	**34**	2,5-F	10
15	4-NO_2	>20	**35**	2,4,5-F	10
16	2-F	20	**36**	2,4-Cl	40
17	3-F	>20	**37**	2,6-Cl	10
18	4-F	10	**38**	3-OCH_3,4-OH	20
19	2-Cl	>20	**39**	2-OH, 5-NO_2	6
20	3-Cl	>20	**40**	2-Pyridyl	40
21	4-Cl	>20	**41**	3-Pyridyl	40
22	2-Br	>20	**42**	2,3,4,5,6-F	50
23	3-Br	10	**43**	2,3-OCH_2O	50

a Perkin-Elmer FT-IR spectrophotometer using KBr pellets or as film in chloroform. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Jeol ECX spectrospin using tetramethylsilane (TMS) as internal reference standard dissolving the compounds in $CDCl_3$ or DMSO-d_6 and the chemical shifts are reported in δ units. Mass data were recorded in Jeol-Accu TOF JMS-T100LC mass spectrometer.

Assay for *in vitro* antitubercular activity

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 x 10^6cfu/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 37 ºC for 3-4 weeks. MIC_{99} value is the concentration of the compound which resulted in 99% inhibition of the growth.

Experimental section

Synthesis of 2-*iso*-propyl-5-methyl-4-nitrosophenol (2) [26, 28]**:** To a stirred solution of 2-*iso*-propyl-5-methylphenol (**1**; 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 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14 (d, J = 6.6 Hz, 6H, CH(CH_3)$_2$), 2.19 (s, 3H, CH_3), 3.09 (septet, J = 6.6 Hz, 1H, CH(CH_3)$_2$), 3.51 (s, 1H, *OH*), 6.34 (d, J = 1.5 Hz, 1H, Ar*H*), 7.54 (s, 1H, Ar*H*).

Synthesis of 4-amino-2-*iso*-propyl-5-methylphenol (3) [26]**:** To 2-*iso*-propyl-5-methyl-4-nitrosophenol (**2**;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 (**3**). Yield 80%; mp 177 °C.

Typical procedure for the synthesis of 4-(benzylideneamino)-2-*iso*-propyl-5-methylphenol (4) and related compounds (5-43) [26]**:** To a stirred solution of 4-amino-2-*iso*-propyl-5-methylphenol, (**3**; 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, CH(CH_3)$_2$), 2.31 (s, 3H, CH_3), 3.19 (septet, J = 7.3 Hz, 1H, CH(CH_3)$_2$), 4.68 (s, 1H, *OH*), 6.64 (s, 1H, Ar*H*), 6.84 (s, 1H, Ar*H*), 7.45-7.47 (m, 3H, Ar*H*), 7.91-7.92 (m, 2H, Ar*H*), 8.38 (s, 1H, N=*CH*); ESI-MS (*m/z*): 254.18 [M + H]$^+$.

2-*iso*-Propyl-5-methyl-4-(2-methylbenzylideneamino)phenol (5): 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, CH(CH_3)$_2$), 2.30 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 3.19 (septet, J = 6.6

Hz, 1H, *CH*(CH_3)$_2$), 4.76 (brs, 1H, *OH*), 6.64 (s, 1H, Ar*H*), 6.80 (s, 1H, Ar*H*), 7.23 (d, *J* = 7.3 Hz, 1H, Ar*H*), 7.27-7.31 (m, 1H, Ar*H*), 7.32-7.36 (m, 1H, Ar*H*), 8.04 (d, *J* = 7.3 Hz, 1H, Ar*H*), 8.65 (s, 1H, N=*CH*); ESI-MS (*m/z*): 268.22 $[M + H]^+$.

2-*iso*-Propyl-5-methyl-4-(3-methylbenzylideneamino)phenol (6): 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, CH*(*CH_3*)*$_2$), 2.30 (s, 3H, *CH*$_3$), 2.42 (s, 3H, *CH*$_3$), 3.18 (septet, *J* = 6.6 Hz, 1H, *CH*(CH_3)$_2$), 4.73 (brs, 1H, *OH*), 6.63 (s, 1H, Ar*H*), 6.81 (s, 1H, Ar*H*), 7.25-7.28 (m, 1H, Ar*H*), 7.33-7.37 (m, 1H, Ar*H*), 7.68 (d, *J* = 8 Hz, 1H, Ar*H*), 7.75 (s, 1H, Ar*H*), 8.34 (s, 1H, N=*CH*); ESI-MS (*m/z*): 268.23 $[M + H]^+$.

2-*iso*-Propyl-5-methyl-4-(4-methylbenzylideneamino)phenol (7): 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); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (d, *J* = 6.6 Hz, 6H, CH*(*CH_3*)*$_2$), 2.29 (s, 3H, *CH*$_3$), 2.41 (s, 3H, *CH*$_3$), 3.19 (septet, *J* = 6.6 Hz, 1H, *CH*(CH_3)$_2$), 4.86 (brs, 1H, *OH*), 6.61 (s, 1H, Ar*H*), 6.81 (s, 1H, Ar*H*), 7.26 (d, *J* = 8 Hz, 2H, Ar*H*), 7.80 (d, *J* = 8 Hz, 2H, Ar*H*), 8.34 (s, 1H, N=*CH*); ESI-MS (*m/z*): 268.22 $[M + H]^+$.

4-(4-Ethylbenzylideneamino)-2-*iso*-propyl-5-methylphenol (8): Yield 51%; mp 141-142 °C; IR (film, cm^{-1}): 2962, 2926, 2868, 1609 (C=N), 1411, 1255 (C–O–C), 1174, 899; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25-1.29 (m, 9H), 2.29 (s, 3H, *CH*$_3$), 2.71 (q, *J* = 7.3 Hz, 2H, *CH*$_2$CH$_3$), 3.18 (septet, *J* = 6.6 Hz, 1H, *CH*(CH_3)$_2$), 4.72 (s, 1H, *OH*), 6.62 (s, 1H, Ar*H*), 6.81 (s, 1H, Ar*H*), 7.29 (d, *J* = 8 Hz, 2H, Ar*H*), 7.83 (d, *J* = 8 Hz, 2H, Ar*H*), 8.34 (s, 1H, N=*CH*); ESI-MS (*m/z*): 282.24 $[M + H]^+$.

2-*iso*-Propyl-5-methyl-4-(4-propylbenzylideneamino)phenol (9): 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); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (t, *J* = 7.3 Hz, 3H, CH$_2$*CH*$_3$), 1.27 (d, *J* = 6.6 Hz, 6H, CH*(*CH_3*)*$_2$), 1.67 (sextet, *J* = 7.3 Hz, 2H, CH$_2$*CH*$_2$CH$_3$), 2.30 (s, 3H, *CH*$_3$), 2.64 (t, *J* = 7.3 Hz, 2H, *CH*$_2$CH$_2$CH$_3$), 3.18 (septet, *J* = 6.6 Hz, 1H, *CH*(CH_3)$_2$), 4.70 (brs, 1H, *OH*), 6.62 (s, 1H, Ar*H*), 6.81 (s, 1H, Ar*H*), 7.26-7.28 (m, 2H, Ar*H*), 7.82 (d, *J* = 8 Hz, 2H, Ar*H*), 8.34 (s, 1H, N=*CH*); ^{13}C NMR (100 MHz, $CDCl_3$) 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 (10): 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); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26-1.29 (m, 12H, 2CH*(*CH_3*)*$_2$), 2.29 (s, 3H, *CH*$_3$), 2.96 (septet, *J* = 6.6 Hz, 1H, *CH*(CH_3)$_2$), 3.18 (septet, *J* = 6.6 Hz, 1H, *CH*(CH_3)$_2$), 4.68(s, 1H, *OH*), 6.62 (s, 1H, Ar*H*), 6.80 (s, 1H, Ar*H*), 7.32 (d, *J* = 8 Hz, 2H, Ar*H*), 7.84 (d, *J* = 8 Hz, 2H, Ar*H*), 8.34 (s, 1H, N=*CH*); ESI-MS (*m/z*): 296.26 $[M + H]^+$.

4-(4-Butylbenzylideneamino)-2-*iso*-propyl-5-methylphenol (11): 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, *J* = 7.3 Hz, 3H, CH$_2$CH$_2$CH$_2$*CH*$_3$), 1.26 (d, *J* = 7.3 Hz, 6H, CH*(*CH_3*)*$_2$), 1.37 (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$_3$), 2.30 (s, 3H, *CH*$_3$), 2.67 (t, *J* = 7.3 Hz, 2H, *CH*$_2$CH$_2$CH$_2$CH$_3$), 3.18 (septet, *J* = 6.6 Hz, 1H, *CH*(CH_3)$_2$), 4.67 (s, 1H, *OH*), 6.62 (s, 1H, Ar*H*), 6.81 (s, 1H, Ar*H*), 7.26-7.28 (m, 2H, Ar*H*), 7.82 (d, *J* = 8 Hz, 2H,

Ar*H*), 8.34 (s, 1H, N=*CH*); ESI-MS (*m/z*): 310.26 $[M + H]^+$.

4-(4-*tert*-Butylbenzylideneamino)-2-*iso*-propyl-5-methylphenol (12): 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, $CDCl_3$) δ: 1.27 (d, *J* = 6.6 Hz, 6H, CH*(CH$_3$)$_2$*), 1.35(s, 9H, C(*CH$_3$*)$_3$), 2.29 (s, 3H, *CH$_3$*), 3.18 (septet, *J* = 6.6 Hz, 1H, *CH*(CH_3)$_2$), 4.68 (brs, 1H, *OH*), 6.63 (s, 1H, Ar*H*), 6.80 (s, 1H, Ar*H*), 7.49 (d, *J* = 8 Hz, 2H, Ar*H*), 7.84 (d, *J* = 8.8 Hz, 2H, Ar*H*), 8.35 (s, 1H, N=*CH*); ESI-MS (*m/z*): 310.26 $[M + H]^+$.

2-*iso*-Propyl-5-methyl-4-(2-nitrobenzylideneamino)phenol (13): 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, $CDCl_3$) 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, Ar*H*), 6.93 (s, 1H, Ar*H*), 7.56-7.60 (m, 1H, Ar*H*), 7.70-7.73 (m, 1H, Ar*H*), 8.04 (d, *J* = 7.3 Hz, 1H, Ar*H*), 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 (14): 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; ^1H 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, Ar*H*), 6.90 (s, 1H, Ar*H*), 7.62-7.66 (m, 1H, Ar*H*), 8.25-8.31 (m, 2H, Ar*H*), 8.48 (s, 1H, N=*CH*), 8.72-8.73 (m, 1H, ArH); ESI-MS (*m/z*): 299.19 $[M + H]^+$.

2-*iso*-Propyl-5-methyl-4-(4-nitrobenzylideneamino)phenol (15): 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; ^1H 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, Ar*H*), 6.92 (s, 1H, Ar*H*), 8.07 (d, *J* = 8.8 Hz, 2H, Ar*H*), 8.31 (d, *J* = 8.8 Hz, 2H, Ar*H*), 8.49 (s, 1H, N=*CH*); ESI-MS (*m/z*): 299.20 $[M + H]^+$.

4-(2-Fluorobenzylideneamino)-2-*iso*-propyl-5-methylphenol (16): 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; ^1H 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, Ar*H*), 6.86 (s, 1H, Ar*H*), 7.10-7.15 (m, 1H, Ar*H*), 7.22 (d, *J* = 8 Hz, 1H, Ar*H*), 7.40-7.45 (m, 1H, Ar*H*), 8.18-8.22 (m, 1H, Ar*H*), 8.69 (s, 1H, N=*CH*); ESI-MS (*m/z*): 272.24 $[M + H]^+$.

4-(3-Fluorobenzylideneamino)-2-*iso*-propyl-5-methylphenol (17): 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, $CDCl_3$) 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)$_2$), 4.74 (s, 1H, *OH*), 6.64 (s, 1H, Ar*H*), 6.85 (s, 1H, Ar*H*), 7.12-7.17 (m, 1H, Ar*H*), 7.40-7.45 (m, 1H, Ar*H*), 7.63 (d, *J* = 8 Hz, 1H, Ar*H*), 7.68 (dd, *J* = 8.8 Hz, 2.2 Hz, 1H, Ar*H*), 8.36 (s, 1H, N=*CH*); ESI-MS (*m/z*): 272.25 $[M + H]^+$.

4-(4-Fluorobenzylideneamino)-2-*iso*-propyl-5-methylphenol (18): 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, $CDCl_3$) δ: 1.27 (d, *J* = 6.6 Hz,

6H, CH*(CH$_3$)$_2$*), 2.30 (s, 3H, *CH$_3$*), 3.19 (septet, *J* = 6.6 Hz, 1H, *CH*(CH$_3$)$_2$), 4.81 (brs, 1H, *OH*), 6.63 (s, 1H, Ar*H*), 6.82 (s, 1H, Ar*H*), 7.12-7.17 (m, 2H, Ar*H*), 7.91 (dd, *J* = 8.8, 5.9 Hz, 2H, Ar*H*), 8.34 (s, 1H, N=*CH*); ESI-MS (*m/z*): 272.24 $[M + H]^+$.

4-(2-Chlorobenzylideneamino)-2-*iso*-propyl-5-methylphenol (19): Yield 53%; mp 140-141 ^oC; IR (film, cm^{-1}): 3080 (O–H), 2958, 2923, 2853, 1611 (C=N), 1415, 1333, 1274 (C–O–C), 1185, 1036 (C–O–C); ^{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$_3$*), 3.19 (septet, *J* = 6.6 Hz, 1H, *CH*(CH$_3$)$_2$), 4.73(s, 1H, *OH*), 6.51 (s, 1H, Ar*H*), 6.87 (s, 1H, Ar*H*), 7.35-7.37 (m, 2H, Ar*H*), 7.41-7.43 (m, 1H, Ar*H*), 8.24-8.27 (m, 1H, Ar*H*), 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 (20): Yield 55%; mp 142-143 ^oC; IR (film, cm^{-1}): 3329 (O–H), 2961, 2925, 1617 (C=N), 1411, 1255 (C–O–C), 1182, 1039 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) 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$_3$)$_2$), 4.75 (s, 1H, *OH*), 6.64 (s, 1H, Ar*H*), 6.84 (s, 1H, Ar*H*), 7.37-7.43 (m, 2H, Ar*H*), 7.75 (d, *J* = 6.6 Hz, 1H, Ar*H*), 7.94 (s, 1H, Ar*H*), 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 (21): Yield 40%; mp 144-145 ^oC; 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); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (d, *J* = 6.6 Hz, 6H, CH*(CH$_3$)$_2$*), 2.31 (s, 3H, *CH$_3$*), 3.19 (septet, *J* = 6.6 Hz, 1H, *CH*(CH$_3$)$_2$), 4.78 (s, 1H, *OH*)6.63 (s, 1H, Ar*H*), 6.84 (s, 1H, Ar*H*), 7.43 (d, *J* = 8 Hz, 2H, Ar*H*), 7.85 (d, *J* = 8 Hz, 2H, Ar*H*), 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 (22): Yield 41%; mp 143-144 ^oC; IR (film, cm^{-1}): 3078 (O–H), 2958, 1610 (C=N), 1415, 1333, 1273 (C–O–C), 1184, 1034 (C–O–C); ^{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$_3$*), 3.19 (septet, *J* = 6.6 Hz, 1H, *CH*(CH$_3$)$_2$), 4.79 (s, 1H, *OH*), 6.64 (s, 1H, Ar*H*), 6.87 (s, 1H, Ar*H*), 7.27-7.31 (m, 1H, Ar*H*), 7.37-7.41 (m, 1H), 7.61 (dd, *J* = 8, 1.5 Hz, 1H, Ar*H*), 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 (23): Yield 40%; mp 131-132 ^oC; IR (film, cm^{-1}): 3154 (O–H), 2961, 1618, 1413, 1381, 1256 (C–O–C), 1184, 1070 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) 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, Ar*H*), 6.83 (s, 1H, Ar*H*), 7.31-7.35(m, 1H, ArH), 7.56-7.58 (m, 1H, ArH), 7.80 (d, *J* = 8 Hz, 1H, Ar*H*), 8.09 (d, *J* = 2.2 Hz, 1H, Ar*H*), 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 (24): Yield 42%; mp 152-153 ^oC; 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, Ar*H*), 6.84 (s, 1H, Ar*H*), 7.59 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.78 (d, *J* = 8.8 Hz, 2H, Ar*H*), 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 (25): Yield 35%;mp 158-160 ^oC; 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, Ar*H*), 6.85 (s, 1H, Ar*H*), 7.52-7.55 (m, 1H, Ar*H*), 7.62-7.66 (m, 1H, Ar*H*), 7.72 (d, *J* = 8 Hz, 1H, Ar*H*), 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 (26): 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, Ar*H*), 6.86 (s, 1H, Ar*H*), 7.57-7.60 (m, 1H, Ar*H*), 7.70 (d, *J* = 8 Hz, 1H, Ar*H*), 8.10 (d, *J* = 8 Hz, 1H, Ar*H*), 8.17 (s, 1H, Ar*H*), 8.43 (s, 1H, N=*CH*); ESI-MS (*m/z*): 322.22 $[M + H]^+$.

2-*iso*-Propyl-5-methyl-4-(4-(trifluoromethyl) benzylideneamino)phenol (27): 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*(CH$_3$)$_2$*), 2.33 (s, 3H, *CH$_3$*), 3.19 (septet, *J* = 6.6 Hz, 1H, *CH*(CH_3)$_2$), 4.76 (s, 1H, *OH*), 6.65 (s, 1H, Ar*H*), 6.87 (s, 1H, Ar*H*), 7.71 (d, *J* = 8 Hz, 2H, Ar*H*), 8.02 (d, *J* = 8.05 Hz, 2H, Ar*H*), 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 (28): 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*(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*(CH_3)$_2$), 4.70 (s, 1H, *OH*), 6.64 (s, 1H, Ar*H*), 6.78 (s, 1H, Ar*H*), 7.17-7.21 (m, 1H, ArH), 7.24 (s, 1H, Ar*H*), 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 (29): 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), 1182, 1037 (C–O–C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (d, *J* = 6.6 Hz, 6H, CH*(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*(CH_3)$_2$), 4.68 (brs, 1H, *OH*), 6.63 (s, 1H, Ar*H*), 6.78 (s, 1H, Ar*H*), 7.05 (s, 1H, ArH), 7.10 (d, *J* = 8 Hz, 1H, Ar*H*), 7.93 (d, *J* = 8 Hz, 1H, Ar*H*), 8.60 (s, 1H, N=*CH*); ESI-MS (*m/z*): 282.23 $[M + H]^+$.

4-(2,5-Dimethylbenzylideneamino)-2-*iso*-propyl-5-methylphenol (30): 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, $CDCl_3$) δ: 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 (31): 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, $CDCl_3$) δ: 1.28 (d, *J* = 6.6 Hz, 6H, CH*(CH$_3$)$_2$*), 2.30 (s, 3H, *CH$_3$*), 2.57 (s, 6H, 2*CH$_3$*), 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, $CDCl_3$) δ: 17.82, 21.23, 22.62, 27.10, 115.48, 117.12, 128.85, 129.26, 130.61, 132.45, 133.69, 138.19, 145.26, 150.91, 158.60; ESI-MS (*m/z*): 282.24 $[M + H]^+$.

4-(3,4-Dimethylbenzylideneamino)-2-*iso*-propyl-5-methylphenol (32): 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, $CDCl_3$) δ: 1.26 (d, *J* = 6.6 Hz, 6H, CH*(CH$_3$)$_2$*), 2.30 (s, 3H, *CH$_3$*), 2.32 (s, 3H, *CH$_3$*), 2.33 (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, $CDCl_3$) δ: 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 (33): 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, $CDCl_3$) δ: 1.26 (d, *J* = 7.3 Hz, 6H, CH*(CH$_3$)$_2$*), 2.30 (s, 3H, *CH$_3$*), 2.38 (s, 6H, 2*CH$_3$*), 3.18 (septet, *J* = 7.3 Hz, 1H, *CH*$(CH_3)_2$), 4.75 (s, 1H, *OH*), 6.62 (s, 1H, Ar*H*), 6.80 (s, 1H, Ar*H*), 7.10 (s, 1H, Ar*H*), 7.26 (s, 1H, Ar*H*), 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 (34): 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, $CDCl_3$) 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*$(CH_3)_2$), 4.83 (brs, 1H, *OH*), 6.64 (s, 1H, Ar*H*), 6.88 (s, 1H, Ar*H*), 7.02-7.12 (m, 2H, Ar*H*), 7.86-7.90 (m, 1H, Ar*H*), 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 (35): Yield 40%; mp 159-160 °C; IR (film, cm^{-1}): 2922, 1507, 1437, 1219, 1219, 889; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 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, Ar*H*), 6.86 (s, 1H, Ar*H*), 6.96-7.02 (m, 1H, Ar*H*), 7.99-8.06 (m, 1H, Ar*H*), 8.58 (s, 1H, N=*CH*); ESI-MS (*m/z*): 308.25 $[M + H]^+$.

4-(2,4-Dichlorobenzylideneamino)-2-*iso*-propyl-5-methylphenol (36): 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, $CDCl_3$) δ: 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, Ar*H*), 6.86 (s, 1H, Ar*H*), 7.33 (dd, *J* = 8, 2.2 Hz, 1H, Ar*H*), 7.44 (d, *J* = 2.2 Hz, 1H, Ar*H*), 8.20 (d, *J* = 8.8 Hz, 1H, Ar*H*), 8.75 (s, 1H, N=*CH*); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.40, 22.61, 27.10, 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 $[M + 4]^+$.

4-(2,6-Dichlorobenzylideneamino)-2-*iso*-propyl-5-methylphenol (37): Yield 48%; mp 161-162 °C; IR (film, cm^{-1}): 3131 (O–H), 2959, 1605, 1411, 1341, 1258, 1182, 1093; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (d, *J* = 6.6 Hz, 6H, CH*(CH$_3$)$_2$*), 2.34 (s, 3H, CH_3), 3.19 (septet, *J* = 6.6 Hz, 1H, *CH*$(CH_3)_2$), 4.77 (s, 1H, *OH*), 6.64 (s, 1H, Ar*H*), 6.89 (s, 1H, Ar*H*), 7.23-7.27 (m, 1H, Ar*H*), 7.39 (d, *J* = 8 Hz, 2H, Ar*H*), 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 (38): Yield 42%;

mp 183-184 °C; IR (film, cm^{-1}): 3369 (O–H), 2919, 2850, 1593, 772; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.26 (d, *J* = 7.3 Hz, 6H, CH*(CH$_3$)$_2$*), 2.29 (s, 3H, *CH$_3$*), 3.18 (septet, *J* = 7.3 Hz, 1H, *CH*(CH$_3$)$_2$), 3.99 (s, 3H, O*CH$_3$*), 4.67 (s, 1H, *OH*), 5.92 (brs, 1H, *OH*), 6.62 (s, 1H, Ar*H*), 6.79 (s, 1H, Ar*H*), 6.98 (d, *J* = 8 Hz, 1H, Ar*H*), 7.29 (d, *J* = 1.5 Hz, 1H, Ar*H*), 7.61 (d, *J* = 2.2 Hz, 1H, Ar*H*), 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 (39): 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 Mz, DMSO-*d$_6$*) δ: 1.20 (d, *J* = 7.3 Hz, 6H, CH*(CH$_3$)$_2$*), 2.27 (s, 3H, *CH$_3$*), 3.19 (septet, *J* = 7.3 Hz, 1H, *CH*(CH$_3$)$_2$), 6.72 (s, 1H, Ar*H*), 6.98 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.40 (s, 1H, Ar*H*), 8.18 (dd, *J* = 9.5, 2.9 Hz, 1H, Ar*H*), 8.62 (d, *J* = 2.9 Hz, 1H, Ar*H*), 9.21 (s, 1H), 9.68 (s, 1H), 15.75 (s, 1H); ^{13}C NMR (100 MHz, DMSO-*d$_6$*) δ: 17.36, 22.47, 26.34, 115.45, 116.78, 117.65, 118.93, 127.88, 129.11, 130.61, 133.60, 134.13, 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 (40): 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, $CDCl_3$) δ: 1.25 (d, *J* = 6.6 Hz, 6H, CH*(CH$_3$)$_2$*), 2.34 (s, 3H, *CH$_3$*), 3.19 (septet, *J* = 6.6 Hz, 1H, *CH*(CH$_3$)$_2$), 5.43 (s, 1H, *OH*), 6.65 (s, 1H, Ar*H*), 6.98 (s, 1H, Ar*H*), 7.34-7.37 (m, 1H, Ar*H*), 7.79-7.83 (m, 1H, Ar*H*), 8.26 (d, *J* = 8 Hz, 1H, Ar*H*), 8.57 (s, 1H, N=*CH*), 8.69 (d, *J* = 5.1 Hz, 1H, Ar*H*); ^{13}C (100 MHz, $CDCl_3$) 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 (41): 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, $CDCl_3$) δ: 1.8 (d, *J* = 7.3 Hz, 6H, CH*(CH$_3$)$_3$*), 2.33 (s, 3H, CH_3), 3.24 (septet, *J* = 7.3 Hz, 1H, *CH*(CH$_3$)$_3$), 6.15 (brs, 1H, *OH*), 6.68 (s, 1H, Ar*H*), 6.90 (s, 1H, Ar*H*), 7.41-7.44 (m, 1H, Ar*H*), 8.30-8.33 (m, 1H, Ar*H*), 8.45 (s, 1H, N=*CH*), 8.68 (dd, *J* = 4.4, 1.5 Hz, 1H, Ar*H*), 9.04 (d, *J* = 1.5 Hz, 1H, Ar*H*); ESI-MS (*m/z*): 255.21 $[M + H]^+$.

(*E*)-2-*iso*-Propyl-5-methyl-4-(perfluorobenzylideneamino)phenol (42): 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, $CDCl_3$) δ: 1.27 (d, *J* = 6.6 Hz, 6H, CH*(CH$_3$)$_3$*), 2.31 (s, 3H, *CH$_3$*), 3.18 (septet, *J* = 6.6 Hz, 1H, *CH*(CH$_3$)$_3$), 4.82 (s, 1H, *OH*), 6.64 (s, 1H, Ar*H*), 6.87 (s, 1H, Ar*H*), 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 (43): 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, $CDCl_3$) δ: 1.26 (d, *J* = 6.6 Hz, 6H, CH*(CH$_3$)$_3$*), 2.28 (s, 3H, *CH$_3$*), 3.18 (septet, *J* = 6.6 Hz, *CH*(CH$_3$)$_3$), 4.76 (brs, 1H, *OH*), 6.03 (s, 2H, O*CH$_2$*O), 6.60 (s, 1H, Ar*H*), 6.80 (s, 1H, Ar*H*), 6.87 (d, *J* = 8 Hz, 1H, Ar*H*), 7.25-7.27 (m, 1H, Ar*H*), 7.56 (d, *J* = 1.5Hz, 1H, Ar*H*), 8.25 (s, 1H, N=*CH*); ESI-MS (*m/z*): 298.22 $[M + H]^+$.

Conclusion

A series of forty thymol-Schiff bases were synthesised and evaluated for their anti-TB

activity. These compounds exhibited moderate to weak activity against *M.tb* H37Rv. The best active compound **39** can be further modified to develop new anti-TB agents.

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