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STRUCTURAL DIVERSITIES AND PRELIMINARY ANTIMICROBIAL STUDIES OF 1-((*E*)-(PENTYLIMINO)METHYL)NAPHTHALEN-2-OL AND ITS METAL COMPLEXES

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Schiff bases and their metal complexes have a number of biological activities such as antidepressant, analgesic, antimicrobial, antiviral, and antitumor. In the present studies, the 1-((*E*)-(pentylimino)methyl)naphthalen-2-ol ligand is prepared by the reaction of 2-hydroxynaphthaldehyde with *n*-amyl amine. The ligand results in CoL_3, NiL_2 and CuL_2 complexes when reacted with the cobalt acetate, nickel acetate, and copper acetate salts respectively. The complexes along with their ligand are fully characterized by X-ray diffraction studies and biologically screened. The ligand structure reveals that it is a zwitterion species where the iminic nitrogen atom is protonated and the C—O bond shows a high double bond character. The cobalt complex has an octahedral geometry around the metal center and each nitrogen atom is in the *trans* position to the oxygen donor site. On the other hand, the copper complex shows a centrosymmetric square planar coordination, and in this case, the nitrogen sites are *trans* to each other. The complexes and the ligand are found to be more potent than the standard drugs used against some microbes in their preliminary biological studies.

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K e y w o r d s: 2-hydroxynaphthaldehyde, *n*-amyl amine, zwitterions, octahedral, centrosymmetric square planar, antimicrobial.

INTRODUCTION

Schiff bases, first prepared by Hugo Schiff in 1864 [1], are one of the most important classes of organic compounds. They contain the azomethine (C=N) functional group and are also known as imines. They are usually prepared by condensing primary amines with carbonyl compounds (aldehydes and ketones) in the presence of an acid or a base as a catalyst or even without a catalyst. Schiff bases have a number of biological activities such as antidepressant and analgesic [2], antimicrobial [3], antiviral [4], and antitumor [5]. Schiff bases are medicinally important molecules and are, therefore, also used for designing other medicinal compounds [6, 7]. The chemical and biological importance of Schiff bases is due to the presence of a lone pair on the nitrogen atom of the azomethine group. The importance becomes twofold when there is one or more additional donor atoms, such as oxygen, ni-

trogen or sulfur in the vicinity of the azomethine group, which may result in an easy chelation with different metals. This chelation makes Schiff bases very important ligands in coordination chemistry. Metals are quite important for maintaining normal activities of the body and treating disorders [8, 9]. They are very selectively shifted to their corresponding sites of action during metabolism where they play their role. Based on the diversified role of metals and metal complexes, they are thought to be the way for the development of future metallopharmaceuticals. The biological activities of Schiff bases may either increase or decrease on complexation with different metal ions [10, 11].

Studies have shown that different Schiff base metal complexes bind strongly to the DNA through different mechanisms promoting DNA cleavage following different pathways [12—14]. This property of transition metal complexes can make them lead compounds for the rational drug design in future. Due to their ability to act as bidentate, tridentate, tetradentate, and hexadentate ligands and associated biological activities, salicylaldehyde and 2-hydroxy-1-naphthaldehyde Schiff bases are becoming very popular. Their complexes with different transition metals are also the topic of the present-day. Keeping in view their importance, we synthesized Co(III), Ni(II)*, and Cu(II) metal complexes of 1-((*E*)-(pentylimino)methyl)naphthalen-2-ol. Their structures were fully characterized using the X-ray diffraction analysis and evaluated for their preliminary biological activities.

EXPERIMENTAL

Synthesis of (1-((*E*)-(pentylimino)methyl)naphthalen-2-ol) (ANSB). The Schiff base was synthesized by condensing a methanolic solution (50 ml) of 2-hydroxy-1-naphthaldehyde (1.70 g, 10 mmol) with a methanolic solution (50 ml) of *n*-amyl amine (1.16 ml, 10 mmol) at room temperature for 1 h. The solvent was removed under vacuum and the product was recrystallized from petroleum ether giving a yellow colored solid product in a quantitative yield.

R_f: 0.5 (25 % acetone in hexane); solubility: chloroform, methanol, DMSO; mp: 68—69 °C (68—69 °C) [15]; IR ($\bar{\nu}$, cm^{-1}): 3621, 1616, 1541, 1521, 1354, 1271, 1184, 997, 846, 746; MS (EI, *m*/*z*): 241 [M^+, 88 %], 198, 184 (100 %), 170, 157, 127, 77, 43.

General procedure for the synthesis of metal complexes (ANSM1, ANSM2, ANSM3). A methanolic solution (40 ml) of metal salt (1 mmol) was added dropwise to a methanolic solution (40 ml) of the Schiff base (0.48 g, 2 mmol) with vigorous stirring. The reaction mixture was refluxed for 3 h. The solvent was removed under vacuum and the precipitated product was recrystallized from chloroform in petroleum ether.

ANSM1. Colour: deep green; yield: 0.54 g, 0.69 mmol, 69 %; solubility: chloroform, methanol, DMSO; mp: 162—163 °C; IR ($\bar{\nu}$, cm^{-1}): 1611 (C=N), 1394 (C—O), 505 (Co—N), 486 (Co—O); anal. calcd: for $C_{48}H_{54}CoN_3O_3$ (780): C 73.92, H 6.98, N 5.39, found: C 73.83, H 6.91, N 5.26. AA: Co calculated, 7.56 %; found, 7.44 %.

ANSM2. Colour: green; yield: 0.35 g, 0.65 mmol, 65 %; solubility: chloroform, methanol, DMSO; mp: 178—179 °C; IR ($\bar{\nu}$, cm^{-1}): 1604 (C=N), 1394 (C—O), 513 (Ni—N), 486 (Ni—O): anal. calcd for $C_{32}H_{36}N_2NiO_2$ (539.3): C 71.26, H 6.73, N 5.19; found: C 71.20, H 6.81, N 5.11. AA: Ni calculated, 10.88 %; found, 10.74 %.

ANSM3. Colour: green; yield: 0.25 g, 0.46 mmol, 46 %; solubility: chloroform, methanol, DMSO; mp: 156—158 °C; IR ($\bar{\nu}$, cm^{-1}): 1604 (C=N), 1394 (C—O), 542 (Cu—N), 495 (Cu—O); anal. calcd for $C_{32}H_{36}CuN_2O_2$ (544.2): C 70.63, H 6.67, N 5.15. Found: C 70.51, H 6.81, N 5.19. AA: Cu calculated, 11.68 %; found, 11.81 %.

X-Ray crystallography. Crystallographic analyses were carried out on a Kappa APEX II DUO diffractometer with graphite-monochromated Mo*K*α radiation at a temperature of 200(2) K. The frames were integrated with the Bruker SAINT software package [16]. All data were corrected for Lorentz and polarization effects. The intensities were also corrected for absorption effects using the multi-scan method (SADABS) [17]. The structures were solved by direct methods and refined by full-matrix least-squares methods using the SHELXS and SHELXL97 programs [18]. All non-

* Though it is already known, Ni complex was synthesized for comparative biological studies in the series.

Table 1

Crystallographic data for **ANSB**, **ANSM1**, *and* **ANSM3** *complexes*

Parameter	**ANSB**	**ANSM1**	**ANSM3**
Empirical formula	$C_{16}H_{19}NO$	$C_{48}H_{54}CoN_3O_3$	$C_{32}H_{36}CuN_2O_2$
Formula weight	241.32	779.87	544.17
Wavelength, Å		0.71069	
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$	$P\bar{1}$
Unit cell dimensions a, Å; α, deg.	11.117(3)	10.2849(3); 96.530(1)	5.0713(1); 95.715(1)
b Å; β, deg.	8.4604(3); 105.262(1)	11.0906(4); 91.889(1)	16.0691(6); 96.296(1)
c Å; γ, deg.	14.9343(5)	18.2687(6); 101.516(1)	16.9039(6); 90.913(1)
Volume, Å^3	1355.10(8)	2025.32(12)	1361.90(8)
Z	4	2	2
D_{calc}, mg/cm^3	1.183	1.279	1.327
μ, mm^{-1}	0.073	0.469	0.833
F(000)	520	828	574
Crystal size, mm	0.24×0.20×0.10	0.40×0.12×0.04	0.40×0.10×0.02
θ range for data collection, deg.	1.90 to 28.50	1.89 to 30.22	1.22 to 30.51
Index ranges	$-14 \le h \le 14$	$-14 \le h \le 14$	$-7 \le h \le 7$
	$-11 \le k \le 11$	$-15 \le k \le 15$	$-22 \le k \le 22$
	$-20 \le l \le 20$	$-25 \le l \le 25$	$-23 \le l \le 24$
Reflections collected	32055	38801	30975
Unique reflections	3434 (R_{int} = 0.0174)	11968 (R_{int} = 0.0226)	8300 (R_{int} = 0.0231)
Max. and min. transmission	0.9927 and 0.9826	0.9815 and 0.8345	0.9835 and 0.7316
Data / restraints / parameters	3434 / 0 / 164	11968 / 0 / 499	8300 / 0 / 339
GOOF (F^2)	1.082	1.019	1.037
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0397	R_1 = 0.0392	R_1 = 0.0378
	wR_2 = 0.1099	wR_2 = 0.1018	wR_2 = 0.1053
R indices (all data)	R_1 = 0.0467	R_1= 0.0532	R_1 = 0.0549
	wR_2 = 0.1196	wR_2 = 0.1106	wR_2 = 0.1164
Largest diff. peak and role, e/Å^3	0.281 and –0.174	0.741 and –0.331	0.474 and –0.419

hydrogen atoms were refined anisotropically. H atoms attached to C atoms were placed at their calculated positions using the standard geometric criteria. ORTEP views of the molecular structures were drawn using the PLATON software [19]. For the ANSB compound, the hydrogen atom bonded to the nitrogen atom was found from the Fourier difference map and treated with the riding model and its U_{eq} was fixed at 1.2 times U_{iso} of the preceding atom.

Selected crystallographic data are shown in Table 1 and full crystallographic tables (including structure factors) for all three compounds have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1059138-1059140. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Procedure for analyzing antibacterial and antifungal activities. The synthesized compounds were tested in their preliminary studies against five gram negative bacteria (*Klebsiella pneumoniae, Salmonella typhi, Escherichia coli, Erwinia carotovora, Pseudomonas aeruginosa*), three gram positive bacteria (*Staphylococcus aureus, Bacillus atrophaeus, Bacillus subtilis*) and a fungal strain—*Candida albicans*. The nutrient agar and nutrient broth were prepared in distilled water and autoclaved at 120 °C under 1.5 pound pressure for about 30 min. Sterilized agar was poured in sterilized petri

plates in a laminar flow hood and allowed to solidify at room temperature. Bacterial strains were cultured by streaking in these plates and incubated at 37 °C for 24 h. These streaks were then inoculated in a sterilized nutrient broth (20 ml) in conical flasks and incubated in a shaking incubator over night at 200 rpm at 37 °C. Cultures from the flasks were then diluted in test tubes containing a sterilized nutrient broth and standardized by comparing with the McFarland turbidity standard. 50 μL from the standardized cultures were spread on each nutrient agar plate. Whatmann filter paper-1 discs were placed on the agar media. Stock solutions of the Schiff base and the complexes were prepared and applied on discs in a concentration of 1 mg/μL per disc. Experiments were run in duplicate. Petri plates were incubated at 37 °C for 24 h. Inhibition zones were measured in mm. Standard drugs, azithromycin, ciprofloxacin, and clomitrazole were used as the positive control for gram positive bacteria, gram negative bacteria, and the fungal strain respectively.

Metals analysis procedure. Metal analysis was performed on a Hitachi Z-800 (Japan) atomic absorption spectrometer using the wet acid digestion procedure. The metal complexes were separately weighed, digested with aqua regia, and the dilution was made with deionized water. Metal percentages in the complexes were calculated using the formula

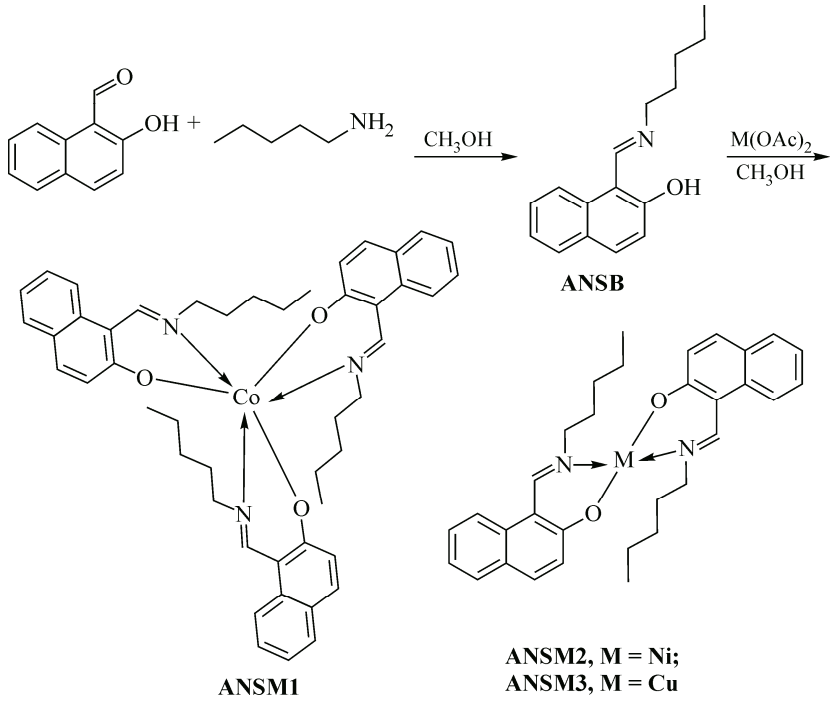
$$\text{Metal (\%)} = \text{AAR} \times \text{V} \times 100/\text{W} \times 1000$$

AAR = Atomic absorption spectrometer reading
V = Volume made for analysis
W = Weight of complex taken for analysis.

RESULTS AND DISCUSSION

The Schiff base (**ANSB**) was obtained in a quantitative yield while treating the methanolic solution of *n*-amyl amine with the methanolic solution of 2-hydroxy naphthaldehyde in equimolecular ratios. The Schiff base **ANSB** was reacted with the metal salts in a 2:1 ratio respectively resulting in the target complexes (**ANSM1**, **ANSM2**, and **ANSM3**) in good yields (Scheme 1).

A peak in the IR spectrum at 3621 cm^{-1} is an indication of the azomethine group formation in the vicinity of the OH group, which results in strong intramolecular hydrogen bonding. The appearance of



Scheme 1. Synthesis of the Schiff base **ANSB** and its metal complexes

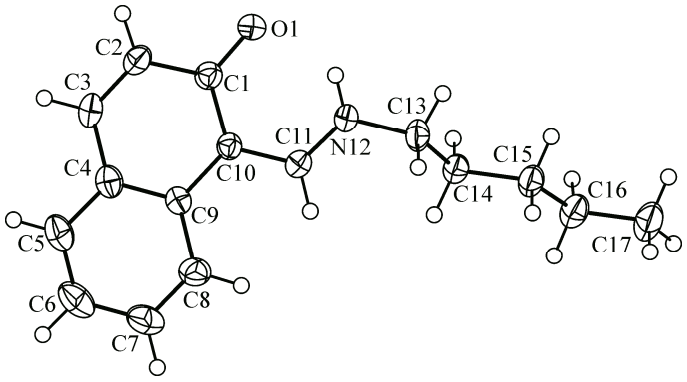


Fig. 1. ORTEP plot of **ANSB**.
Ellipsoids are drawn at a 50 % probability level

the peak at 1616 cm^{-1} for the CH=N moiety and the disappearance of the peaks for the aldehydic and primary amine groups is another indication for the successful synthesis of the Schiff base. Mass spectrometric analysis is in good agreement with the expected structure. The X-ray diffraction analysis stamped well to all the above analyses.

The crystals of the Schiff base were grown from chloroform in hexane. Fig. 1 shows the molecular structure of the Schiff base. The selected crystallographic data have been given in Table 1. The crystal structure revealed that the nitrogen atom of the imine moiety is protonated and this group makes a strong intramolecular N12—H12…O1 hydrogen bond with an N12…O1 distance of 2.5763(10) Å and the N—H…O angle of 134°. This feature induces a great double bond character to C1—O1 and, consequently, the aromatic C—C bonds near the C—O bond are elongated. Also, the distances around N12 are longer than those expected for single and double bonds (Table 2), whereas the aliphatic chain shows a usual extended conformation.

The peak in the IR spectra due to the hydrogen atom of the OH group was not observed in any of the complexes. Alternatively, new peaks appeared at 505 cm^{-1} (Co—N), 486 cm^{-1} (Co—O) for **ANSM1**, 513 cm^{-1} (Ni—N), 486 cm^{-1} (Ni—O) for **ANSM2** and 542 cm^{-1} (Cu—N), 495 cm^{-1} (Cu—O)

T a b l e 2

Selected bond lengths (Å) *and angles* (deg.)

ANSB		**ANSM1**			
C1—O1	1.2735(12)	Co1—O21	1.8838(10)	O1—Co1—N12	90.68(5)
C11—N12	1.3046(12)	Co1—O1	1.8985(10)	N52—Co1—N12	92.77(5)
C10—C11	1.4118(12)	Co1—N52	1.9381(12)	C21—O21—Co1	125.78(9)
C13—N12	1.4657(12)	Co1—O41	1.8893(10)	O21—Co1—O1	90.50(5)
O1—C1—C10	122.68(8)	Co1—N32	1.9364(12)	O21—Co1—N32	92.45(5)
C11—N12—C13	124.00(8)	Co1—N12	1.9411(11)	O1—Co1—N32	85.81(5)
N12—C11—C10	124.09(9)	O21—Co1—O41	174.35(4)	O41—Co1—N52	91.53(5)
ANSM3		O41—Co1—O1	86.95(4)	N32—Co1—N52	90.80(5)
Cu1—O1	1.8215(12)	O41—Co1—N32	92.39(5)	O41—Co1—N12	89.73(5)
Cu1—N12	1.9150(14)	O21—Co1—N52	91.32(5)	N32—Co1—N12	175.80(5)
O1—Cu1—N12^{i}	87.85(6)	O1—Co1—N52	176.22(5)	C1—O1—Co1	122.88(8)
O1—Cu1—N12	92.15(6)	O21—Co1—N12	85.26(5)	C41—O41—Co1	125.52(9)

Symmetry code: ^{i} $-x+1, -y, -z+1$.

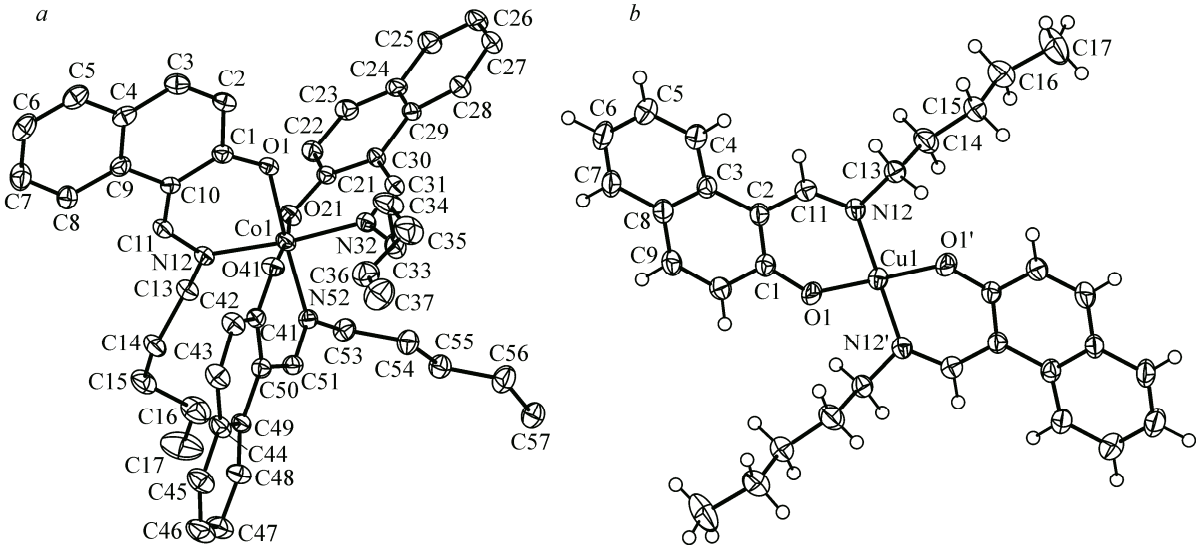


Fig. 2. ORTEP plots of **ANSM1** (*a*) and **ANSM3** (*b*).
Ellipsoids are drawn at a 40 % probability level. Hydrogen atoms for **ANSM1**were omitted for clarity

for **ANSM3**. Also the peak in the Schiff base **ANSB** for the CH=N moiety at 1616 cm^{-1} was shifted to a lower frequency at 1611 cm^{-1}, 1604 cm^{-1}, and 1604 cm^{-1} in the **ANSM1**, **ANSM2**, and **ANSM3** complexes respectively, which strongly suggests the participation of the CH=N moiety in the complex formation. The elemental data were quite consistent with the expected structures. Further confirmation was made by X-ray diffraction analyses.

The crystals of the complexes were grown from chloroform in hexane. A very distinct and interesting difference was observed among the complexes (Fig. 2). Ni [20] and Cu complexes crystallize in the $P\bar{1}$ space group with two centrosymmetric molecules in the unit cell. These complexes are isostructural, showing a square planar coordination, where iminic nitrogen and oxygen atoms are in the *trans* positions with respect to same species. The cobalt complex shows a distorted octahedral geometry around the metal ion with three ligand molecules coordinated in a bidentate fashion through both nitrogen and oxygen donor sites. In this octahedral arrangement, all three nitrogen atoms are in *trans* positions to the oxygen atoms. The aliphatic side chain of the ligand shows an extended conformation in the square planar complexes, while steric effects in the cobalt complex induces the alkyl chains to take a somehow curled spatial conformation. Selected bond lengths and angles for the complexes are also presented in Table 2.

Antibacterial and antifungal activities. Antibacterial and antifungal activities were tested as preliminary studies following the procedure given in EXPERIMENTAL. The results are listed in Table 3.

The Schiff base showed moderate activities for the gram positive and gram negative bacteria but excellent activity against the fungal strain—*Candida albicans*. It was found to be even more potent than the standard drug clomitrazole which showed an inhibition zone of 25 mm compared to the inhibition zone of 28 mm offered by the Schiff base. The **ANSM1** complex was found to be more potent against *Klebsiella pneumonia*, *Erwinia carotovora*, and *Pseudomonas aeruginosa* compared to the standard drug used. The **ANSM3** complex showed almost comparable results for *Pseudomonas aeruginosa* and *Bacillus subtilis* compared to the standard drugs. In most of the other cases, the ligand and the complexes displayed very good results, too.

CONCLUSIONS

The ligand and its complexes were synthesized and fully characterized using different spectroanalytical techniques, especially the X-ray diffraction technique. A diversity of the structures of the complexes was found using the single crystal X-ray diffraction analysis. The X-ray diffraction studies

Table 3

Antibacterial and antifungal activities of the ligand and its complexes

S. No	Microbe	**ANSB**	**ANSM1**	**ANSM2**	**ANSM3**	Standard
01	*Klebsiella pneumonia*	—	21	16	—	18
02	*Salmonella typhi*	16	14	19	—	32
03	*Escherichia coli*	13	13	18	16	26
04	*Erwinia carotovora*	14	29	—	20	26
05	*Pseudomonas aeruginosa*	16	17	13	16	16
06	*Staphylococcus aureus*	12	15	12	18	27
07	*Bacillus atrophaeus*	14	14	15	18	29
08	*Bacillus subtilis*	15	12	11	25	27
09	*Candida albicans*	28	13	13	21	25

showed the ligand structure to be a zwitterion species where the nitrogen atom of the imine group is protonated and where the C—O bond displayed a strong double bond character. Following the same studies, the cobalt complex displayed an octahedral geometry around the metal center where each nitrogen atom was in the *trans* position to the oxygen donor site. On the other hand, the copper complex shows a centrosymmetric square planar coordination, and in this case, nitrogen sites are *trans* to each other. All the synthesized compounds were just scanned against different microbes as preliminary studies and found to be more potent than the standard drugs used against some microbes. They can be thought to be the alternative future drugs against these microbes after performing all the required pharmacological and clinical studies.

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