Chapter 2
Synthesis of Methylene-bis-aldehydes as Linkers for Construction of Macrocyclic Structures
2.1 Introduction

The compounds containing formyl group are very useful in organic synthesis because of their reactivity and diverse products they form. The compounds containing two of this functionality embedded in a molecule can be used as a monomer in polymerization or as a linker in a conducive environment for construction of supermolecules such as cage compounds. Single ring containing two aldehydes e.g. phthalaldehyde, isophthalaldehyde, terephthalaldehyde, pyridine-2,6-dicarbaldehyde, pyrrole-2,5-dicarbaldehyde, furan-2,5-dicarbaldehyde, thiophene-2,5-dicarbaldehyde have been employed as linkers in syntheses of supermolecules.\(^1\)\(^-\)\(^5\)

Rather than employing the compounds containing two formyl groups on same aromatic or hetero-aromatic ring, we looked for the use of methylene linked mono aldehydes as bifunctional linkers for the synthesis of supramolecular structures in context with earlier work reported from our laboratory employing methylene-bis-salicylaldehyde as a linker.\(^6\) The synthesis of 5,5’-methylenedibis-salicylaldehyde from salicylaldehyde and formaldehyde is an example of useful reaction for converting a monoformyl compound to diformyl substrate with an additional ortho functionality present. Methylene-bis-salicylaldehyde has been used for the synthesis of binucleating ligands for the preparation of metal complexes.\(^7\)

These methylene-bis-aldehydes have also been employed as monomers for the synthesis of low cost resins.\(^8\) On reaction with aromatic amines and thioacid they result in antimicrobial and nematicidal agents.\(^8\)-\(^14\) Methylene-bis-salicylaldehydes themselves exhibit tyrosinase inhibitory activity in which the conversion of L-tyrosine to L-DOPA and subsequently to melanine is inhibited.\(^15\)
Formyl group in aromatic ring can be introduced by various well known methods including some famous name reactions.

➢ **The Reimer Tiemann reaction.**\(^{16-18}\)

The Reimer Tiemann reaction is used in the synthesis of 2-hydroxyaldehydes for example, when phenol is subjected to Reimer-Tiemann reaction, it gives salicylaldehyde and 4-hydroxybenzaldehyde in 37% and 9% respectively.

![Chemical structures](attachment:image.png)
The Vilsmeier Haack reaction.

The Vilsmeier Haack reaction is extensively used for synthesis of aromatic aldehydes of activated or conjugated system.\textsuperscript{19,20} The Vilsmeier reagent has also been extensively employed for the synthesis of a variety of heterocyclic compounds often with a formyl group.\textsuperscript{21-23}

Scheme 2.3 : Synthesis of 4-N,N-dimethylaminobenzaldehyde

Formylation using SnCl\textsubscript{4} and paraformaldehyde:

2-Hydroxybenzaldehydes can also be prepared by the use of SnCl\textsubscript{4} as an acid catalyst and tributylamine in nonpolar solvent like toluene by using para-formaldehyde as a formylating agent in good yields.\textsuperscript{24-27}

Scheme 2.4 : Synthesis of 3-methyl-2-hydroxybenzaldehyde.
➢ The Skattebol reaction

A highly regioselective ortho formylation of substituted phenols has been reported by Skattebol and co-workers by using MgCl$_2$ beads, instead of SnCl$_4$ in high yields.$^{28-30}$ The limiting factor here is high cost of MgCl$_2$ beads.

![Scheme 2.5: Synthesis of 3-methyl-2-hydroxybenzaldehyde](image)

Synthesis of this bis-salicylaldehyde involves the use of 1,3,5-trioxane as a source of formaldehyde in presence of catalytic amount of conc. H$_2$SO$_4$ in gl. CH$_3$COOH as a solvent.$^{31}$ (Scheme: 2.6) We also looked for some more methylene-bis-aromatic aldehydes which can be used similarly as linkers for the synthesis of new supramolecular compounds.

![Scheme 2.6: Synthesis of 5,5'-methylenediybis(6-hydroxybenzaldehyde)](image)
Di-formylation of 4,4′-methylene-bis-2-substituted phenols converts them into 5,5′-methylene-bis-3-substituted aldehydes using the duff reaction.

Scheme 2.7: Diformylation of bis phenols.
2.2 Aim and Objectives

In view of usefulness of di-aldehydes in the synthesis of various macrocyclic compounds, as stated earlier, we planned to synthesize methylene-bis-aromatic aldehydes for their application as linkers for the synthesis of some new supramolecular compounds. We visualised that the flexibility or spacer introduced in this bifunctional aldehydes may be advantageous in the formation of supramolecular structure compare to the di-aldehydes with rigid aromatic ring containing the two reactive functionalities. The major differences between the two are the increased distance between the two formyl groups in methylene-bis-aldehydes compared to the dialdehydes and an angle formed between the two reactive functionalities.

The present chapter encompasses the experiments dealing with the synthesis of some aromatic aldehydes and their application in the synthesis of methylene-bis-aldehydes.

The results of these experiments have been included and discussed in this chapter.
2.3 Results and Discussion

We have synthesized or attempted to synthesize a number of methylene-bis-aldehydes starting from various aromatic and hetero-aromatic aldehydes. 5,5’-Methylene-bis-salicylaldehyde has been synthesized and widely employed for various purposes\textsuperscript{1,8-14,33-38} The method employed for the synthesis of methylene-bis-aldehydes was based on the synthesis of bis-salicylaldehyde reported by Marvel and Torkoy in 1957.\textsuperscript{31}

Thus we started with the synthesis of the known methylene-bis-salicylaldehyde following the same procedure. The reaction of salicylaldehyde with trioxane in presence of sulphuric acid results in formation of 5,5’-methylene-bis-salicylaldehyde as a major product. (Scheme: 2.8) Due to the presence of the hydroxyl group in salicylaldehyde, the para position to the hydroxyl group is most reactive but at the same time the ortho position is also activated.

We carefully studied the reaction of salicylaldehyde which was reported to give 5,5’-methylene-bis-salicylaldehyde. In this reaction the ratio of H\textsubscript{2}SO\textsubscript{4} to gl.CH\textsubscript{3}COOH plays an important role. It is also important to adhere to required equivalence of trioxane for getting consistent yields. The reaction temperature was also found to play an important role. At temperature lesser than 90 °C the reaction preceded slowly and conversion was incomplete while with the increased temperature, above 100 °C resulted in multiple product formation as oligomerization was facilitated at higher temperatures. An increased amount of sulphuric acid also resulted in more polar impurities.

After finding out the best reaction conditions for bridging salicylaldehyde through a methylene carbon the reported product 5,5’-methylene-bis-salicylaldehyde could be obtained on crystallising the crude from acetone. On careful investigation of the filterate obtained from this crystallization, the presence of the other minor compounds was detected as number of spots on TLC. Column chromatography of the residue from the filterate resulted in isolation of two more compounds which have not been reported earlier.
Scheme 2.8: Synthesis of 5,5’-methylene-bis-salicyaldehyde and its derivatives

One of the minor compounds could be assigned as unsymmetrical structure formed by coupling of two salicylaldehyde molecules at para position to phenolic group and the other via the ortho position of the phenolic group resulting in 5,3’-methylene-bis-salicylaldehyde. The proposed structure was confirmed by presence of two distinct aldehyde signals at 9.92δ and 9.86δ and two different signals corresponding to phenolic groups at 11.36δ and 10.91δ in proton NMR spectroscopy. 

Reaching to the structure of the other product just from its NMR, Mass and IR analysis was found to be difficult. Its structure could be realized form the result of single crystal X-ray analysis as the compound was crystalline. It turned out to be interesting combination of the earlier two structure giving rise to coupling of three salicylaldehyde molecules via two methylene bridges with the central ring substituted at both the para and ortho positions available with respect to the phenolic group. Single crystal X-ray analysis was carried out at solid state and the structural chemistry unit IISC Banglore by A. G. Dikundwar from Prof. T. N. Guru Row’s research group.
We also carried out coupling of the other oxygen containing aromatic aldehydes such as 4-hydroxy-3-methoxy-benzaldehyde (vanilline) and 2-hydroxy-3-methoxy-benzaldehyde (o-vanilline) to get the corresponding 5,5’-methylene-bis-benzaldehyde derivatives in low yields. \(^\text{15,40-42}\) (Scheme: 2.9) While the attempts to couple 3,4-dimethoxy-benzaldehyde (veratraldehyde) were not successful, giving a black solution on addition of sulphuric acid.

Scheme 2.9: Synthesis of 5,5’-methylene-bis-o-vanilline and 5,5’-methylene-bis-vanilline
For the synthesis of the other substituted methylene-bis-salicylaldehydes we first targeted at the preparation of alkyl substituted salicylaldehydes. 2-Methylphenol and 2-tert-butylphenol were formylated by using para-formaldehyde and catalytic amount of SnCl₄ in the presence of a base by using toluene as solvent giving good yields. Both the alkylation salicylaldehyde were subjected to the same reaction conditions which were employed for the preparation of 5,5’-methylene-bis-salicylaldehyde. The desired products were isolated and characterized. (Scheme: 2.10)

Scheme 2.10: Synthesis of 5,5’-methylene-bis-(3-alkyl-salicylaldehyde)

2,4-Dihydroxybenzaldehyde is also a good example of activated benzaldehyde derivative which can be subjected to the methylene coupling reaction. The aldehyde was prepared by subjecting resorcinol to the Vilsmeier reaction. The resulting resorcylaldehyde when subjected to the coupling reaction using trioxane, it was found that reaction proceeds even at lower temperatures compared to the earlier experience. Due to higher reactivity of this aldehyde the reaction gave multiple products at room temperature. Careful and repeated column chromatography resulted in isolation of three major
isomeric products which were characterized by subjecting them to spectral and elemental analyses. They were found to be 5,5’-methylene-bis-2,4-dihydroxybenzaldehyde, 3,3’-methylene-bis-2,4-dihydroxybenzaldehyde and 5,3’-methylene-bis-2,4-dihydroxybenzaldehyde, an unsymmetrical methylene-bis-resorcyraldehyde. (Scheme: 2.11)

In mass spectra the molecular ion peak is observed at m/z = 288 for all of them. (Spectra 3.20, 3.22, 3.25) In proton NMR the unsymmetrical isomer could be differentiated because of two distinct signals for the formyl groups at δ 9.73 and 9.81. (Spectrum 3.24) The symmetrical isomer could be differentiated based on proton NMR analysis. 5,5’-isomer shows two singlets for aromatic protons while 3,3’-isomer shows two doublets with $J = 8.4$ Hz. (Spectrum 3.19, 3.21) Elemental analysis of these isomers is in accordance with the expected values.
Scheme 2.11: Synthesis of methylene-bis-resorcyaldehyde

It was observed that change in reaction conditions affect relative ratio of these three isomers. The effect of temperature on this reaction was studied in detail. HPLC technique was used to monitor the reactions. The reactions were carried out at 10 °C, 30 °C, 60 °C, 90 °C and 120 °C (reflux temperature).

At lower temperature reaction doesn’t proceed due to lack of solubility of the β-resorcyaldehyde. The reaction at 30 °C was found to be most conducive for the synthesis of 5,5'-isomer. The higher temperature reactions gave more of the polar products which could not be isolated and characterized. The effect of the available concentration of trioxane in the reaction mixture was also studied at different temperatures. For this slow addition of trioxane was carried out. It did not help in increasing the yield of the desired 5,5'-isomer.

HPLC chromatogram of crude containing mixture of isomeric aldehydes and starting material

Fig: 2.02
2,4-Dihydroxy benzaldehyde being solid, requires a higher quantity of acetic acid to make it soluble because of which the ratio of reactants and catalyst with respect to solvent could not be retained as reported for salicylaldehyde reaction. This led us to an idea of consideration of alternate acid catalyst and solvent. Trifluoroaceticacid (TFA) being a strong organic acid was initially employed only as a catalyst replacing sulphuric acid. While investigating further modifications, the reaction was found to be better when TFA was used as solvent as well as a catalyst, so the reaction was further studied in detail in this medium. The reaction was carried out at lower temperature of 0-5 °C, at R.T. and at 60 °C. Resorcyaldehyde having higher solubility in TFA, the reaction at lower temperature was possible but was not satisfactory. The ratio of isomeric products was found to be different at R.T. and at 60 °C. The higher temperature reaction significantly reduced the generation of 5,5'-isomer. In TFA the 3,3'-isomer was produced in greater amounts compared to that in acetic acid and the 5,5'-isomer was being formed in minor quantities at 60 °C. It was convenient to separate 3,3'-isomer being the major product from this reaction. Purification of the unsymmetrical isomer on column chromatography could not be achieved. The enriched fractions containing this isomer were subjected to preparative reverse phase HPLC to obtain the unsymmetrical product in pure form.

\[ \text{o-Anisaldehyde, the methyl ether of salicylaldehyde when subjected to the coupling reaction smoothly resulted in 5,5'-methylenedioxybenzaldehyde and the product was isolated in similar way by crystallising from acetone. Later on, it was found that crystal packing of this bis-aldehyde has been studied, where the 5,5'-methylenedioxybenzaldehyde were prepared by formylating 4,4'-methylenedioxybenzaldehyde using TiCl}_4 \text{ and dichloromethyl methyl ether}. \]^{9,10,12,49} \text{(Scheme:2.12)}

\[
\begin{align*}
\text{CHO} & \xrightarrow{1.66 \text{ eq 1,3,5 Trioxane}} \text{CHO} \\
\text{H}_3\text{CO} & \xrightarrow{0.01\text{wt/v Conc. } \text{H}_2\text{SO}_4} \text{CHO} \\
\text{H}_3\text{CO} & \xrightarrow{5\text{wt/v gl HOAc}} \text{OCH}_3
\end{align*}
\]

\text{Scheme: 2.12 Synthesis of 5,5'-methylenedioxybenzaldehyde}
After exploring compounds with phenolic and alkoxy group activated benzaldehydes, we considered an amino group activated benzaldehyde, 4-(N-dimethylamino-benzaldehyde) which also should undergo similar coupling reaction as per our expectation. This kind of coupling on amino-benzaldehydes has not been reported in literature earlier. Thus 4-(N-dimethylaminobenzaldehyde) was subjected to the coupling reaction with 1,3,5-trioxane in gl. acetic acid in the presence of conc. sulphuric acid which successfully resulted in 3,3’-methylene-bis-(4-dimethylamino-benzaldehyde) as expected though in low yield of 10%. The reaction was found not to go to completion and some of the starting material was recovered (Scheme: 2.13). The newly synthesized compound was characterized with the help of IR, NMR, MASS spectral analysis and elemental analysis. In NMR, the formyl proton is observed at 9.8 δ while the methyl protons give singlet at δ 2.8. Methylene protons are observed at 4.18. The aromatic protons are observed at δ 7.71, 7.49, 7.13 with expected splitting and coupling pattern. (Spectrum 3.31)

![Chemical structure](image)

**Scheme 2.13: Synthesis of 3,3’-Methylene-bis-(4-N,N-dimethylaminobenzaldehyde)**

The bis-aldehyde gave golden yellow crystals form ethanol. The crystals were subjected to single crystal X-ray diffraction analysis at IISc Bangalore with the help of Mr. Amol Dikundwar from Prof. Guru Row’s research group. For the Analysis Bruker Kappa Apex2 CCD area detector and Mo-Kα X-ray radiation source were used. The structure refinement was carried out using SHELXL97. The compound was crystallized with the space group R-3. The orientation of formyl groups of same molecule can attain two different arrangements. Both the arrangements were found to be present in the ORTEP diagram of the given molecule Fig. 2.03.
As such there was no conventional hydrogen bonding found between two or more molecules of the given compound but a soft interaction between hydrogen of N-CH₃ group and aldehyde oxygen of the adjacent molecule was observed. 3,3’-Methylene-bis(4-N-dimethylaminobenzaldehyde) molecules were stacked due to π-π interactions between the aromatic rings. Top view of the crystal packing from space fill model shows the propeller shaped packing of the molecules with hexagonal voids have been generated. (Fig. 2.07) The angle formed between the planes of the two aromatic rings connected via methylene bridge is 64.34°. The angle formed at the methylene bridge carbon connecting the two aromatic rings (C(6)-C(7)-C(8) angle) is found to be 117.38°(Fig. 2.03).

Ortep diagram of 3,3’Methylene-bis-(4-N,N dimethylamino-benzaldehyde)

Fig. 2.03
Single crystal X-ray image showing O----H-CH$_2$N soft Hydrogen bonding of 3,3’-Methylene-bis-(4-N,N dimethylamino-benzaldehyde)

Fig. 2.04

Single crystal X-ray image of 3,3’-Methylene-bis-(4-N,N-dimethylaminobenzaldehyde) showing π-π stacking.

Fig. 2.05
Single crystal X-ray image of 3,3’-Methylene-bis-(4-N,N dimethylamino-benzaldehyde) showing crystal packing pattern.

Fig. 2.06

Single crystal X-ray image of 3,3’-Methylene-bis-(4-N,N dimethylamino-benzaldehyde) showing crystal packing pattern in space-fill pattern.

Fig. 2.07
Crystal parameters of 3,3’-methylene-bis-(4-N-dimethylaminobenzaldehyde) are listed in the Table No. 1

Table No. 1 Crystal data and structure refinement

<p>| | | |</p>
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<td>T(K)</td>
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<td>Crystal system</td>
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<td>6.</td>
<td>Space group</td>
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<td>Z</td>
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<tr>
<td>8.</td>
<td>a Å</td>
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<td>9.</td>
<td>b Å</td>
<td>29.5739(18)</td>
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<tr>
<td>10.</td>
<td>c Å</td>
<td>10.2198(12)</td>
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<td>11.</td>
<td>α (°)</td>
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<td>12.</td>
<td>β (°)</td>
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<tr>
<td>13.</td>
<td>γ (°)</td>
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</tr>
<tr>
<td>14.</td>
<td>goodness of fit</td>
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<td>Calculated density (mg/m$^3$)</td>
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<tr>
<td>16.</td>
<td>Absorption coefficient (mm$^{-1}$)</td>
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</tr>
<tr>
<td>17.</td>
<td>F(000)</td>
<td>2987.5</td>
</tr>
<tr>
<td>18.</td>
<td>θ ranges for data collection</td>
<td>2.15-24.99</td>
</tr>
</tbody>
</table>
| 19. | Index ranges | -35≤ h ≤35  
                 -35≤ k ≤35  
                 -12≤ l ≤12 |
| 20. | Reflection collected | 3024 |
| 21. | R indices | R1=0.0363(2793),  
         wR2=0.0998(3024) |
In order to acquire some more linkers in the form of methylene-bis-aromatic-aldehydes we used 5,5'-methylen bis-salicylaldehyde as a starting material and derivatized the same. Bromination of the bis-aldehyde was carried out in gl. acetic acid at 20 °C with two equivalents of bromine in acetic acid giving 3,3'-dibromo-5,5'-methylen bis-salicylaldehyde in good yield. Similarly the methylene-bis-salicylaldehyde was subjected to nitration by using conc. nitric acid in acetic acid giving the analogous dinitro-bis-aldehyde. (Scheme: 2.14) For both of this reactions a large amount of gl. acetic acid was required to dissolve the starting materials. The use of nitrating mixture or the reaction at greater temperature resulted in formation of picric acid.

![Scheme 2.14: Synthesis of 5,5'-methylen bis-(3-bromosalicylaldehyde) and 5,5'-methylen bis-(3-nitrosalicylaldehyde)](image)

Following the synthesis of a number of methylene-bis-aldehydes as linkers we decided to synthesize methylene-bis-acetophenone which may also be used as a linker for the synthesis of macrocyclic structures. Thus 2-hydroxy-acetophenone was subjected to the coupling reaction using 1,3,5-trioxane under the conditions which were employed for coupling of benzaldehyde derivatives. (Scheme: 2.15) Resulting methylene-bis-acetophenone was characterized by using spectral analysis.
With the success in coupling of the acetophenone derivative it was planned to extend the same coupling reaction is extended for coupling of hetero-aromatic aldehydes and in particular five member heterocyclic aldehydes. This should result in linkers with hetero atoms included in them. Furfural, pyrrole-2-carbaldehyde and thiophene-2-carbaldehyde were subjected to the same coupling reaction using paraformaldehyde and sulphuric acid (Scheme: 2.16). The hetero-aromatic rings were found to be too sensitive to the acid catalysed coupling reactions and were resulting in dark reaction mixture without indication of any product on TLC. We also subjected these aldehydes to mild acid catalysed reactions for which Lewis acids such as AlCl₃ and Amberlyst-15 were employed. The coupling was also attempted by replacing paraformaldehyde by dimethoxymethane (methylal). All these attempts didn’t meet with success. The coupling reactions were also attempted on the other aromatic aldehydes such as benzaldehyde, p-hydroxy-benzaldehyde, veratraldehyde and 2-hydroxy-1-naphthaldehyde but were unsuccessful. (Scheme: 2.17)

Scheme 2.15: Synthesis of 2,2’-dihydroxy-5,5’-methylene-bis-acetophenone

Scheme 2.16: Attempted synthesis of heterocyclic linkers.
2.4 Conclusion

Several bifunctional linking agents useful in the synthesis of supramolecular structures have been synthesized by employing acid catalyzed coupling of aromatic aldehydes using the help of formaldehyde in acetic acid. Modification in synthetic methodology has also been studied. During the synthesis of bifunctional linking agents, several new compounds were isolated and characterized. Thus this chapter is comprised of a practical synthetic methodology leading to a library of several useful bifunctional linking agents for construction of supramolecular assemblies.

Scheme 2.17: Attempted synthesis of some other Methylene-bis-derivatives as linkers.
2.5 Experimental

General Remarks

All the chemicals and reagents were purchased from Sigma-Aldrich, Merck, or Spectrochem. All solvents were distilled before use. Column chromatography was carried out using silicagel (60-120 mesh). Thin layer chromatography was performed on pre-coated silicagel 60F254 (Merck) aluminium sheets.

Infrared spectra were recorded on Perkin-Elmer FT-IR 16PC spectrophotometer as KBr pellets. $^1$H NMR and $^{13}$C NMR were recorded on Bruker 200 or 400 MHz NMR spectrophotometer in CDCl$_3$, DMSO or D$_2$O. Elemental analyses were carried out at different places (ZRC, SPARC and CSMCRI). ESI mass were recorded on Shimadzu LC-MS 2010-A and EI and CI mass were recorded on Thermo Fisher DSQ II mass spectrometer. HPLC was carried out using Shimadzu LC-10AT and UFLC using Shimadzu LC-20AD. Melting points were measured in open capillaries and are uncorrected.
2.5.1 Synthesis of 2,4-dihydroxybenzaldehyde$^{23,48}$

In a 500 ml beaker, resorcinol (50g, 0.45 mol) was dissolved in dimethyl formamide (36 ml, 0.44 mole). The solution mixture was cooled to 10 °C in ice bath. POCl$_3$ (60g, 0.39 mole) was added drop wise over 45 minutes with stirring. Reaction mixture became sticky near the completion of addition of POCl$_3$ and needed to stir manually. An exotherm was observed after 30 minutes of stirring which was followed by precipitation of white solid. The reaction mixture was poured in to a cold solution of sodium acetate (50%) in water with stirring. A yellowish solution was filtered and kept in refrigerator for crystallization. White needle shaped crystals were obtained. Crystals were filtered and washed with cold water. It was necessary to cool solution of sodium acetate as decomposition of white solid was exothermic. At higher temperature (~ 80 °C) yellowish undersirable product precipitated out.

Yield: 25g (40%)

M.P. = 135 °C (135-137 °C)

IR (KBr disc, cm$^{-1}$): 3129 (phenol, $\nu$(O-H)), 1891, 1633 (aldehyde, $\nu$(O-C-H)), 1582, 1498 (aromatic ring, $\nu$(C=C)), 1444(phenol, $\delta$(O-H)), 1395(aldehyde, $\delta$(O-C-H)) 1329 (phenol, $\delta$(O-H)), 1231 (phenol, $\nu$(C-O)), 1166 (out of plane, $\delta$(C-H)), 1130 (phenol, $\nu$(C-O)), 974, 856, 823 (aromatic, out of plane, $\delta$(C-O)), 746, 695, 635, 460, 427 (aromatic ring, $\delta$(C=C)).
2.5.2 Synthesis of 3-alkyl-2-hydroxybenzaldehydes\textsuperscript{24-27} 6,7

\[ \text{HO-R-HO} \xrightarrow{\text{para-formaldehyde, Toluene}} \xrightarrow{\text{SnCl}_4, (n\text{-Bu})_3N, 100^\circ C} \text{CHO} \]

3-alkyl-2-hydroxybenzaldehyde

\[ R= -\text{CH}_3 \quad 93\% \text{ yield} \]
\[ R= -\text{C(CH}_3)_3 \quad 55\% \text{ yield} \]

General procedure:

2-Alkyl phenol (0.23 mol), tri n-butylamine (0.09 mol) and 2v/v toluene was placed in a 250 ml three necked round bottom flask equipped with a condenser and an addition funnel under N\textsubscript{2} atmosphere. To a stirred mixture SnCl\textsubscript{4} (0.02 mol) was added dropwise over 30 minutes at room temperature (30 \(^\circ\)C) with stirring. After this time paraformaldehyde (0.5 mol) was added in single portion. The reaction mixture was heated to reflux for 8hrs (TLC). The reaction mixture was poured in to aqueous HCl (5\%, 600ml) solution and was extracted with diethyl ether (3x100ml). Combined organic layers were washed with water, brine and were dried over Na\textsubscript{2}SO\textsubscript{4}. Diethyl ether was removed using rotary evaporator. Brownish oil was subjected to column chromatography using Pet-ether : dichloromethane (gradient) was done using pet-ether:MDC mixtures. Pure product was separated as yellowish oil which solidified later.
**3-Methyl-2-hydroxybenzaldehyde**<sup>24,26</sup> 6

2-Methylphenol (24 ml, 0.23 mol), paraformaldehyde (15 g, 0.5 mol), SnCl<sub>4</sub> (2.7 ml, 0.02 mol) and tri-n-butylamine (22.1 ml, 0.09 mol) were reacted in toluene (50 ml) to give compound 6 as yellow oil which partially solidifies on standing.

Yield: 29.0g (93%)

**M.P.** = 204 °C (730 mm of Hg) (Reported)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 11.27 (s, 1H), 9.78 (s, 1H), 7.31 (d, J = 7.6 Hz, 2H), 6.86 (t, J = 7.6 Hz, 1H), 2.22 (s, 1H)

**<sup>13</sup>C NMR** (400 MHz, CDCl<sub>3</sub>): δ 196.7, 159.8, 137.7, 131.3, 126.6, 119.9, 119.3, 14.9

**3-tert-Butyl-2-hydroxybenzaldehyde**<sup>27</sup> 7

2-<i>tert</i>-Butylphenol (25.6 ml, 0.17 mole), paraformaldehyde (11 g, 0.37 mole), SnCl<sub>4</sub> (2.0 ml, 0.02 mol) and tri-n-butylamine (15.9 ml, 0.07 mole) were reacted in toluene 50 ml to give the 7 as yellowish oil.

Yield: 16.0g (55%)

**B.P.** = 78-79 °C (1mm of Hg) (Reported)

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 11.30 (s, 1H), 7.53 (dd, J = 1.6 Hz, J = 7.6 Hz, 1H), 7.44 (dd, J = 1.6 Hz, J = 7.6 Hz, 1H), 6.86 (t, J = 7.6 Hz, 1H), 1.48 (s, 1H)

**<sup>13</sup>C NMR** (400 MHz, CDCl<sub>3</sub>): δ 204.2, 161.0, 138.6, 132.9, 131.6, 120.1, 117.8, 35.1, 29.4
### 2.5.3 5,5′-Methylene-bis(3-substituted-salicylaldehyde)

![Chemical structure]

General Procedure\(^{31}\):

3-Substituted-salicylaldehyde (0.39 mol), 1,3,5-trioxane (0.06 mol) and gl. CH\(_3\)COOH (1v/v) were placed in a 250 ml round bottom flask equipped with a condenser and N\(_2\) balloon. Reaction mixture was warmed to 90 °C. A solution of conc. H\(_2\)SO\(_4\) (0.01v/v) in gl. CH\(_3\)COOH (0.05v/v) was added drop wise using a syringe to the magnetically stirred reaction mixture maintained at 90°C under N\(_2\) atmosphere. The stirring was continued at 90 °C for 5hrs. (TLC). The Reaction mixture was poured in to ice-water (1L). Yellowish semi solid was obtained after decantation of water which was washed with pet.ether (3x 100ml) and recrystallized from acetone to give off white product.
2.5.4 Preparation of 5,5’-Methylene-bis-salicylaldehyde

Salicylaldehyde (41ml, 0.39 mol), 1,3,5-trioxane (5.9g, 0.06 mol) and conc. H$_2$SO$_4$ (0.4ml, 0.01v/v) in 41ml gl. HOAc (1v/v) were reacted as per the general procedure (2.5.3) to yield title compound 1 as off white solid.

Yield= 12 g (25%) M.P.= 149 °C.

The residue obtained from concentrating mother liquor after crystallization from acetone was subjected to column chromatography using pet-ether ethyl acetate solvent system in gradient manner. Compound 2 and 3 were obtained successively as white crystals.

Compound 2 : 0.1g (0.2% yield)
Compound 3 : 2.5g (5% yield), M.P.= 141 °C.
**5,5’-Methylene-bis-salicylaldehyde 1**

$^1$H NMR (400 MHz, CDCl$_3$): δ 10.95 (s, 1H), 9.86 (s, 1H), 7.34-7.38 (m, 2H), 6.65 (d, 1H), 3.98 (s, 1H)

$^{13}$C NMR (400 MHz, CDCl$_3$): δ 196.4, 160.2, 137.6, 133.2, 131.9, 120.4, 117.9, 39.4

IR (KBr disc, cm$^{-1}$): 3424 (phenol, $\nu$(O-H)), 2915, 2858, 2744 (Fermiresonance, $\nu$(CHO), 2364, 1656(aldehyde, $\nu$(C-H), 1590, 1483 (aromatic ring, $\nu$(C=C)), 1440 (phenol, $\delta$(O-H)), 1376 (aldehyde, $\delta$(C-H)) 1332 (phenol, $\delta$(O-H)), 1277 (phenol, $\nu$(C-O)), 1199(out of plane, $\delta$(C-H)), 956, 896, 844, 811 (aromatic, out of plane, $\delta$(C-O)), 768, 718, 617, 553, 423 (aromatic ring, $\delta$(C=C)).

CHN: 70.39 %C, 4.69 %H (Theoretical cal value: 70.31 %C, 4.72 %H)

Mass: 256m/z

**5,3’-Methylene-bis-salicylaldehyde 2**

$^1$H NMR (400 MHz, CDCl$_3$): δ 11.36 (d, $J = 6.8$ Hz, 1H), 10.91 (d, $J = 12$ Hz, 1H), 9.92(d, $J = 6$ Hz, 1H), 9.86 (d, $J = 6$ Hz, 1H), 7.33-7.48 (m, 4H), 6.91-7.00(m, 2H), 3.99 (s, 1H)

$^{13}$C NMR (400 MHz, CDCl$_3$): δ 196.8, 196.6, 160.1, 159.5, 137.8, 137.3, 133.5, 132.3, 131.5, 129.4, 120.5, 120.4, 119.8, 117.7, 33.9

IR (KBr disc, cm$^{-1}$): 3420 (phenol,$\nu$(O-H)), 1652(aldehyde, $\nu$(C-H), 1568, 1482 (aromatic ring, $\nu$(C=C)), 1436 (phenol, $\delta$(O-H)), 1373 (aldehyde, $\delta$(C-H)) 1319 (phenol, $\delta$(O-H)), 1274 (phenol, $\nu$(C-O)), 1148(out of plane, $\delta$(C-H)), 995, 904, 841, 811 (aromatic, out of plane, $\delta$(C-O)), 737, 673, 656, 458 (aromatic ring, $\delta$(C=C)).

**3,5-bis(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde 3**

$^1$H NMR (400 MHz, CDCl$_3$): δ 11.27(s, 1H), 10.91 (d, 1H), 9.84 (s, 1H), 7.39(t, $J = 9.6$ Hz, 2H), 7.33(t, $J = 9.6$ Hz, 2H), 7.20 (dd, $J = 9.6$ Hz, 2H), 6.90-6.96 (m, 2H), 3.94 (d, 2H)
$^{13}$C NMR (400 MHz, CDCl$_3$): δ 196.6, 196.5, 196.4, 160.3, 160.1, 158.2, 137.9, 137.7, 137.6, 133.4, 133.3, 131.9, 131.8, 131.7, 129.9, 120.5, 120.4, 120.3, 118.0, 117.7, 39.4, 33.9

IR (KBr disc, cm$^{-1}$): 3059 (phenol,$\nu$(O-H)), 2923, 2834, 2364, 1683(aldehyde, $\nu$(C-H)), 1591, 1554 (aromatic ring, $\nu$(C=C)), 1436 (phenol, $\delta$(O-H)), 1324 (phenol, $\delta$(O-H)), 1275 (phenol, $\nu$(C-O)), 1193(out of plane, $\delta$(C-H)), 916, 896, 833, 800 (aromatic, out of plane, $\delta$(C-O)), 768, 736, 675, 544, 420 (aromatic ring, $\delta$(C=C)).

CHN: 70.67%C, 4.60%H (Theoretical cal value: 70.76 %C, 4.65 %H)

**2.5.5 5,5’-Methylene-bis-(3-methoxy-salicylaldehyde)$^{15,40,41}$**

![Chemical Structure](image)

o-Vaniline (20g, 0.23mol), 1,3,5-trioxane (2g, 0.02mol) and H$_2$SO$_4$ (0.2ml, 0.01v/wt) were reacted in 100 ml gl. HOAc (5v/wt) using similar procedure as that of 5,5’methylene-bis-(3-substituted-salicylaldehyde) (2.5.3) to yield the title compound 4 as light brown powder.

Yield= 4g (20%)

**M.P.** = 151 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.82 (s, 1H), 6.76 (d, 1H), 6.59 (d, 1H), 5.23 (s, 1H), 3.47(s, 3H), 3.39 (s, 1H)
The compound 5 was synthesized using similar procedure as that of 5,5’-methylene-bis-(3-substituted-salicylaldehyde) (2.5.3) Vanilline (7.6g, 0.05 mol), 1,3,5-trioxane (0.75g, 0.01 mol) and H₂SO₄ (0.07ml, 0.01wt/v) in 8ml gl. HOAc (1wt/v) were reacted at 95 °C to yield the title compound 5

Yield: 1.2 g (15%)

M.P.= 276 °C

¹H NMR (400 MHz, CDCl₃): δ 9.71 (s, 1H), 9.00 (s, 1H), 7.67 (s, 2H), 3.95 (s, 1H), 3.06 (s, 3H)

IR (KBr disc, cm⁻¹) : 3203 (phenol, ν(O-H)), 2966 (methyl, ν(C-H)), 2934 (CH₂, asymmetric ν(C-H)), 2832, 2725 (aldehyde, fermiresonance, ν(CHO)), 2367, 2345, 1666 (aldehyde, ν(CHO)), 1591, 1498 (aromatic ring, ν(C=C)), 1469 (δ(CH₂)), 1427 (phenol, δ(O-H)), 1368 (aldehyde, δ(CHO)), 1321 (phenol, δ(O-H)), 1276 (δ(CH₂)), 1261 (ether, νas(C-O)), 1145, 1091(ether, νs(C-O)), 998, 958, 930, 875, 850, 813, 782, 694, 616, 588 (out of plane, δ(C-H))
2.5.7 5,5'-Methylene-bis-(3-methyl-salicylaldehyde)\textsuperscript{43-45} 8

![Chemical structure of 5,5'-Methylene-bis-(3-methyl-salicylaldehyde)](image)

Compound 8 was synthesized using the general procedure described earlier (2.5.3). 3-Methylsalicylaldehyde (10g, 0.07mol), 1,3,5-trioxane (1.1g, 0.01mol) and H\textsubscript{2}SO\textsubscript{4} (0.1ml, 0.01wt/v) in 10 ml gl. HOAc (1wt/v) were reacted to yield the title compound 8 as yellow crystals.

Yield= 8.26 g (79.12%)

**M.P.**= 150 °C.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 11.19 (s, 1H), 9.83 (s, 1H), 7.23 (s, 1H), 7.19 (d, 1H), 3.90 (s, 1H), 2.25 (s, 3H)

\textsuperscript{13}C NMR (400 MHz, CDCl\textsubscript{3}): δ 196.1, 147.4, 158.6, 138.6, 131.7, 130.8, 127.2, 119.8, 39.6
2.5.8 5,5′-Methylene-bis-(3-tert-butyl-salicylaldehyde)\(^{36,43-47}\)

Compound 9 was synthesized using similar procedure as that of 5,5′-methylene-bis-(3-substituted-salicylaldehyde) (2.5.3). 3-tert-Butyl-salicylaldehyde (10g, 0.06mol), 1,3,5-trioxane (0.84g, 0.01mol) and \(\text{H}_2\text{SO}_4\) (0.1ml, 0.01wt/v) in 10 ml gl. HOAc (1wt/v) were reacted to yield title compound 9 as light yellow crystals.

Yield= 3.24 g (31%)

M.P.= 105 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 11.74 (s, 1H), 9.84 (s, 1H), 7.40 (d, \(J = 2\) Hz, 1H), 7.17 (d, \(J = 2\) Hz, 1H), 3.97 (s, 1H), 1.43 (s, 9H)

\(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \(\delta\) 197.1, 159.8, 138.6, 135.0, 131.3, 131.2, 120.5, 40.1, 34.9, 29.2
2.5.9 Synthesis of 5,5’-methylene-bis-resorcyaldehyde\textsuperscript{15} \textit{11}

![Chemical structure diagram](image)

Compound \textit{11} was synthesized using similar procedure as that of 5,5’-methylene-bis-(3-substituted-salicylaldehyde)(2.5.3). Resorcyaldehyde (14 g, 0.10mol), 1,3,5-trioxane (1.5 g, 0.02 mol) and H\textsubscript{2}SO\textsubscript{4} (0.14 ml, 0.01wt/v) in 84 ml gl. acetic acid (6 wt/v) were reacted at 25 °C to yield title compound \textit{11}

Yield= 4g (30% ) (HPLC)

M.P.= 260 °C (d)

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}+DMSO): δ 11.28 (s, 1H), 10.35 (s, 1H), 9.60 (s, 1H), 7.20 (s, 1H), 6.44 (s, 1H), 3.79 (s, 1H)

IR (KBr disc, cm\textsuperscript{-1}): 3175 (phenol,ν(O-H)), 2848, 1636 (aldehyde, ν(C-H), 1515 (aromatic ring, ν(C=C)), 1424 (phenol, δ(O-H)), 1386 (aldehyde, δ(C-H)) 1354 (phenol, δ(O-H)), 1247 (phenol, ν(C-O)), 1130 (out of plane, δ(C-H)), 935, 888, 864, 805 (aromatic, out of plane, δ(C-O)),751, 687, 625, 560, (aromatic ring, δ(C=C)).

Mass: 289.13 (M+H)

**Elemental Analysis:** Calculated for \textit{C}_{15}\textit{H}_{12}\textit{O}_{6}: C= 62.50\%, H= 4.20\%

Found: C= 62.07\%, H= 4.37\%
2.5.10 3,3’-methylene-bis-resorcylaldehyde 12 and Unsymmetrical methylene-bis-resorcylaldehyde 13

Resorcylaldehyde (1g, 0.007mol), 1,3,5-trioxane (0.11 g, 0.001 mol) and TFA (10 ml, 1wt/v) were placed in a 50ml round bottom flask equipped with a condenser, N2 balloon and warmed to 60 °C. The stirring was continued at 60 °C for 3hrs (TLC). Reaction mixture was poured in 1L ice-water. The solid obtained was filtered and washed with distilled water (10x20ml) to yield pinkish solid giving a mixture of compound 12 (23%, by HPLC), 13 (40%, by HPLC) and some more polar impurities. The crude mixture was subjected to column chromatography using petether-ethylacetate. (gradient). Pure compound 12 was obtained as white crystalline solid and compound 13 was obtained with some contamination of 12. The compound 13 was then purified using preparative HPLC.

Yield : 0.9 g (Crude mixture (12+13))
Yield of Compoud 12: 23% (HPLC),
M.P.= 205 °C (d)
Yield of Compoud 13: 40% (HPLC),
M.P.= 215 °C
3,3’-Methanediylbis(2,4-dihydroxybenzaldehyde) 12

**1H NMR** (400 MHz, DMSO-d$_6$): δ 11.67 (s, 2H), 10.64 (s, 2H), 9.72 (s, 2H), 7.45 (d, $J = 8.4$ Hz, 2H), 6.51 (d, $J = 8.4$ Hz, 2H), 3.87 (s, 2H)

**13C NMR** (400 MHz, CDCl$_3$): δ 194.8, 163.4, 159.9, 134.1, 114.4, 112.3, 111.3, 15.1

Mass: 289.02(M+H)

**Elemental Analysis:** Calculated for C$_{15}$H$_{12}$O$_6$: C= 62.50%, H= 4.20%

Found: C= 62.44%, H= 4.17%

**IR** (KBr disc, cm$^{-1}$): 3348 (phenol, $\nu$(O-H)), 2922, 2852, 1689 (aldehyde, $\nu$(OC-H), 1617 (aromatic ring, $\nu$(C=C)), 1429 (phenol, $\delta$(O-H)), 1391 (aldehyde, $\delta$(OC-H)) 1301 (phenol, $\delta$(O-H)), 1220 (phenol, $\nu$(C-O)), 1080 (out of plane, $\delta$(C-H)), 832, (aromatic, out of plane, $\delta$(C-O)), 756, 640, 536, (aromatic ring, $\delta$(C=C)).

3-(5-formyl-2,4-dihydroxybenzyl)-2,4-dihydroxybenzaldehyde 13

**1H NMR** (400 MHz, DMSO-d$_6$): δ 11.59 (s, 1H), 10.76 (s, 2H), 10.62 (s, 1H), 9.81 (s, 1H), 9.74 (s, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 6.83 (s, 1H), 6.61 (d, $J = 8.8$ Hz, 1H), 6.40 (d, 1H) 3.67 (s, 2H)

**13C NMR** (400 MHz, CDCl$_3$): δ 195.7, 190.3, 164.3, 163.5, 162.1, 161.9, 134.6, 128.9, 119.5, 115.2, 114.6, 112.5, 108.8

Mass: 287.9 M$^+$

**IR** (KBr disc, cm$^{-1}$): 3256 (phenol, $\nu$(O-H)), 2928, 2837, 2754 (fermiresonance,$\nu$CHO), 1612 (aldehyde, $\nu$(OC-H), 1501 (aromatic ring, $\nu$(C=C)), 1439 (phenol, $\delta$(O-H)), 1385 (aldehyde, $\delta$(OC-H)) 1331 (phenol, $\delta$(O-H)), 1252 (phenol, $\nu$(C-O)), 1113 (out of plane, $\delta$(C-H)), 982, 872,841, 802 (aromatic, out of plane, $\delta$(C-O)),784, 700, 636, 540, (aromatic ring, $\delta$(C=C)).
2.5.11 5,5’-Methylene-bis-anisaldehyde\textsuperscript{9,12} \textbf{14}

\begin{center}
\begin{tikzpicture}
\node[draw,shape=rectangle](img){\includegraphics[width=\textwidth]{image.png}};
\end{tikzpicture}
\end{center}

The compound \textbf{14} was synthesized using similar procedure as that of 5,5’-methylene-bis-salicylaldehyde (2.5.3). Anisaldehyde (10 g, 0.05 mol), 1,3,5-trioxane (0.69 g, 0.01 mol) and H\textsubscript{2}SO\textsubscript{4} (0.1 ml, 0.01 wt/v) in 50 ml gl. HOAc (5 wt/v) were reacted at 90\textdegree C to yield the compound \textbf{14}

Yield : 3 g (30% )

\textbf{M.P.} = 135 \textdegree C.

\textsuperscript{1}HNMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 10.40 (s, 1H), 7.60 (d, \(J = 2.4\) Hz, 1H), 7.32 (dd, \(J = 2.4\) Hz, \(J = 8.4\) Hz, 1H), 6.89 (d, \(J = 8.4\) Hz, 1H), 3.87 (s, 1H)

\textsuperscript{13}CNMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 189.8, 160.5, 136.3, 133.1, 128.3, 124.6, 112.0, 55.7, 39.6

\textbf{IR} (KBr disc, cm\textsuperscript{-1}) : 3031(aromatic,\(\nu\)(C-H)), 2964 (methyl, \(\nu\)(C-H)), 2915 (CH\textsubscript{2}, asymmetric \(\nu\)(C-H)), 2876, 2773 (aldehyde, fermiresonance, \(\nu\)(CHO)), 2334, 2359, 1676 (aldehyde, \(\nu\)(CHO)), 1606, 1494 (aromatic ring, \(\nu\)(C=C)), 1445 (CH\textsubscript{2}, \(\delta\)), 1401, 1257, 1215, 1192 (ether, \(\nu_{as}(C-O)\)), 1112, 1027 (ether, \(\nu_s(C-O)\)), 976, 965, 907, 888, 837, 824, 814, 792, 749, 648, 552, 473 (out of plane, \(\delta\)(C-H))
Compound 15 was synthesized using similar procedure as described for 5,5’-methylene-bis-(3-substituted-salicylaldehyde) (2.5.3).

4-N,N-dimethylaminobenzaldehyde (20 g, 0.13mol), 1,3,5-trioxane (2 g, 0.02mol) and H$_2$SO$_4$ (0.6 ml,0.03wt/v) in 60 ml gl. Acetic acid (3wt/v) were reacted at 95 °C to yield compound 15. Here 50% of the starting material was recovered from water work up.

Yield: 2g (20% on recovery base)
M.P.= 104 °C

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.79 (s, 1H), 7.71 (dd, $J_1 = 1.9$Hz, $J_2 = 8.3$ Hz, 1H), 7.50 (d, $J = 1.7$ Hz, 1H), 7.13 (d, $J = 8.3$ Hz, 1H), 4.15 (s, 1H), 2.80 (s, 6H)

Mass: 311.18 (M+H)

Elemental Analysis: Calculated for C$_{19}$H$_{22}$O$_2$N$_2$: C= 73.52%, H= 7.14%, N= 9.03%

Found: C= 72.47%, H= 7.07%, N= 9.67 %

IR (KBr disc, cm$^{-1}$): 2954 (methylene, $v_{as}$(C-H)), 2840 (methylene, $v_s$(C-H)), 2798, 2723 (aldehyde, fermiresonance, $v$(CHO)), 2365, 2345, 1681 (aldehyde, $v$(CHO)), 1595, 1499 (aromatic ring, $v$(C=C)), 1469 ($\delta$(CH$_2$)), 1378 (aldehyde, $\delta$(CHO)), 1340 (aromatic, $v$(C-N)), 1317 ($\delta$(CH$_2$)), 1243 (aromatic, $v$(C-N)), 1221, 1188, 1170, 1084, 1052 (aliphatic, $v$(C-N)), 980, 952, 931, 876, 826, 799, 754, 645, 616, 582, 475 (out of plane, $\delta$(C-H))
2.5.13 Synthesis of 5,5’-methylene-bis(3-bromo-salicylaldehyde)\(^{50}\) \(\text{16}\)

5,5’-Methylene-bis-salicylaldehyde \(\text{1} \) (5 g, 0.02 mol) and gl. acetic acid (350 ml, 70 wt/v) were placed in a 500ml round bottom flask equipped with addition funnel. Reaction mixture was cooled to 20 \(^{\circ}\)C. Bromine (2.1ml, 6.2 g, 0.03mole) in 10ml gl. acetic acid was added dropwise at 20 \(^{\circ}\)C over 30 min. Allowed to come at R.T. (TLC). Reaction mixture was poured into 1L ice-water. Off white solid was filtered and washed with distilled water (4x100ml) to remove trapped acid. The crude product was recrystallized from absolute alcohol to yield pure compound \(\text{16}\).

Yield : 4g (54% )

M.P.=188 \(^{\circ}\)C.

\(^{1}\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 11.11 (s, 1H), 10.03 (s, 1H), 7.86 (d, \(J = 2\) Hz, 1H), 6.46 (d, \(J = 2\) Hz, 1H), 3.94 (s, 1H)

\(^{13}\)C NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 195.2, 155.6, 139.9, 134.4, 131.7, 123.3, 111.7, 38.0
2.5.14 Synthesis of 5,5’-methylene-bis(3-nitro-salicylaldehyde)\textsuperscript{50} 17

5,5’-Methylene-bis-salicylaldehyde 1 (5g, 0.02 mol, 1eq) and gl. HOAc (350 ml, 50wt/v) were placed in a 500 ml round bottom flask equipped with addition funnel carrying CaCl\textsubscript{2} guard tube. Reaction mixture was cooled to 20\textdegree C and solution of conc. HNO\textsubscript{3} (119 ml, 17 wt/v) in 140 ml gl. acetic acid was added dropwise at 20\textdegree C over 30 min. Reaction mixture was allowed to warm to R.T. (TLC). Reaction mixture was poured in 1L ice-water. Yellow solid obtained. The solid was filtered and washed with distilled water (4x 100 ml) to remove trapped acid. The crude product was recrystallized from MDC:EtOAc :: 50:50 to yield compound 17

Yield: 5 g (54%)

M.P.=218 \textdegree C.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textasciitilde 11.31 (s, 1H), 10.44 (s, 1H), 8.18 (d, \textit{J} = 2.4 Hz, 1H), 7.94 (d, \textit{J} = 2.4 Hz, 1H), 4.09 (s, 1H)

\textsuperscript{13}C NMR (400 MHz, DMSO-d\textsubscript{6}): \textasciitilde 191.0, 153.6, 138.3, 136.0, 132.2, 131.7, 126.3, 37.6
2.5.15 Synthesis of 5,5′-methylene-bis-acetophenone

The title compound 18 was synthesized using general procedure as described for synthesis of 5,5′-methylene-bis-(3-substituted-salicylaldehyde) derivatives. (2.5.3)

2-Hydroxyacetophenone (44 ml, 50g, 0.37 mole), 1,3,5-trioxane (5.5g, 0.06 mol) and H₂SO₄ (0.5ml, 0.01wt/v) in 50ml gl. acetic acid (1wt/v) were reacted at 95 °C to yield compound 18

Yield: 10g (20%)

M.P. = 139°C.

¹H NMR (400 MHz, CDCl₃) δ 12.20 (s, 1H), 7.53 (d, J = 2 Hz, 1H), 7.30 (dd, J = 2 Hz, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 3.93 (s, 1H), 2.62 (s, 3H)

¹³C NMR (400 MHz, CDCl₃) δ 204.4, 161.0, 137.1, 131.0, 130.4, 119.5, 118.8, 39.9, 26.7
2.6 Analytical Data:

Spectrum 2.1

Spectrum 2.2

1H NMR
Spectrum 2.3

$^{13}$C NMR

Spectrum 2.4

$^1$H NMR
Spectrum 2.7

**1H NMR**

![1H NMR spectrum with labeled peaks]

Spectrum 2.8

**13C NMR**

![13C NMR spectrum with labeled peaks]
Spectrum 2.10-c

DEPT 90

Spectrum 2.10-d

DEPT 135
Spectrum 2.11-a

13 CNMR

DEPT 90

Spectrum 2.11-b
Spectrum 2.14

\[ ^1H \text{NMR} \]

CDCl$_3$ + DMSO-d$_6$

Spectrum 2.15

\[ ^1H \text{NMR} \]
**Spectrum 2.24-a**

**13C NMR**

![13C NMR Spectrum](image)

**Spectrum 2.24-b**

**DEPT 90**

![DEPT 90 Spectrum](image)
Spectrum 2.24-c

DEPT 135

Spectrum 2.25

Mass
Chromatogram 2.26

HPLC

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Spectrum 2.27

IR
2. 7 References


