

“G-Quadruplex DNA Recognition with New Aldehyde-Alkyl Chain Derivatives”

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ABSTRACT:

DNA is a genetic material with a specialised double-helical structure that is found in both eukaryotic and somatic cells. G-quadruplex is a nucleic acid secondary structure found in guanine-rich sequences of the genome. The G-4 system has been shown to regulate replication, DNA damage repair, and transcription and translation of oncogenes and other cancer-related genes. As a result, targeting G-4 has emerged as a novel and promising anti-cancer strategy. Small molecules that directly bind to the G-quadruplex and molecules that interfere with the binding between the G-quadruplex structures and related binding proteins have all been designed, synthesised, and identified as potential anti-tumor agents. This review will look at the feasibility of G-quadruplex ligands acting as anti-tumor drugs, from the ground up. In the meantime, since Meanwhile, because helicase is the most well-defined G-quadruplex-related protein, the most extensive research on the relationship between helicase and G-quadruplexes, as well as its implications for drug design, is highlighted.

Keywords: G-4(quadruplex), human code TTAGGG, Minor grooves binder, monovalent cation.

INTRODUCTION:

G-quadruplex scaffold

DNA is the genetic material having the specialized double-helical structure it found in eukaryotic as well as in somatic cells [1]. The fundamental function of telomerase to protect the genomic end by the maintaining length [2]. During replication of the cells leads to erosion of telomers approximately 50-200 base pair loss during every single round of somatic cell division [3]. The secondary scaffold of G-quadruplex classified into unimolecular, bimolecular, tri-molecular and tetra-molecular it formed by DNA and RNA based upon the sequence. However it shows the various morphological strand by orienting themselves, it shows variation in their number G strand number of stack central part and length also shows

type variation. In the corresponding to G quadruplex, it includes four parallel or antiparallel direction and its related to the conformational changes and glycosidic torsion angle, in case of parallel G quadruplex all legs in contrary route it has both syn and anti-guanine. G-quadruplex has some promise like, when three legs in the same direction called syn-syn-syn-anti confirmation vice- versa, also known as hybrid mixed G- tetrad core.

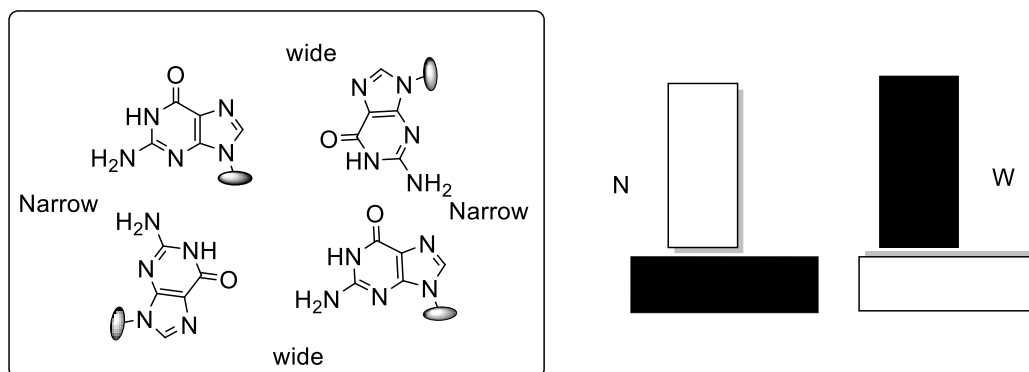


Figure1: Representation of the G-quadruplex core groove.

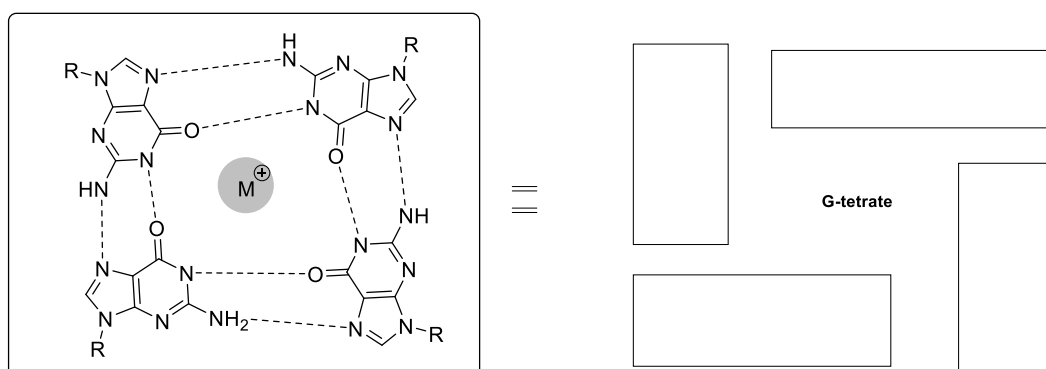


Figure:2 Coplanar representation of G-quadruplex

The secondary scaffold categorizes into unimolecular, bimolecular, trimolecular and tetramolecular it formed by DNA and RNA rely upon the sequence. However it shows the various morphological strand by orienting themselves, its shows variation in their number G strand number of stack central part and length also shows type variation. In the corresponding to G quadruplex, it includes four parallel or antiparallel direction and its related to the conformational changes and glycosidic torsion angle, in case of parallel G quadruplex all legs in contrary route it has both syn and anti guanine. G-quadruplex has some promise like, when three legs in the same direction called syn-syn-syn-anti confirmation vice- versa, also known as hybrid mixed G- tetrad core [4].

Unimolecular G-quadruplex

G quadruplex can implement the various kind of the loops namely, the diagonal loop, lateral loop another is the external loop. It can crease into a parallel tetrad with three G-quadruplex

loops [5]. For Instance, human telomeric sequences form crystal structure through the reappearance of the d[AG3(T2AG3)3]. It is also called a hybrid G-quadruplex, by orient themselves in the same and one is a conflicting path, that further agrees to anti-anti-anti-syn confirmation. It also surrounds one narrow and wide external loop. The adaptability of the confirmation depends on their situation and cationic environment. The quadruplex has Watson- crick duplex in a long loop that may a crucial part of the novel target. The identification of that the c-Myc²³⁴⁵, oncogene promoter sequence contains 22 nucleotides and c-Myc¹²⁴⁵, 5'-TGAG3TG4AG3TG4A2-3' both sequences formed the intramolecular G quadruplex, similar to the human telomeric genome. The extend beyond of telomeric DNA compose of a single-stranded duplicate of the TTAGGG unit of something like 100-200 bp in length. In the vitro structure adopt the human telomere below physiologically significant circumstance is still indecisive, however, few reports have not compulsory hybrid structure to be the major conformation under in vivo circumstance [6]. The length of the telomere is maintained by the enzyme telomerase which is overexpressed in 80-85% of cancer cells but not in normal somatic cells. There are an abundance of reports recitation their antitumor, anticancer and antioxidant properties. Describing the role of plant flavonoids, as potential G-quadruplex binding agents. Previously it has been reported through various optical spectroscopy techniques that Quercetin, a naturally taking place in plant flavonoid, interact with monomeric and dimeric G- quadruplex structure from end to end stacking and groove binding mode correspondingly [7]. Another oncogene supporter gene contains the 23-nt bcl-2 promoter sequence 5'-G3CGCG3AG2A2T2G3 CG3- 3' also formed the intramolecular G-quadruplex, its quite similar to the [3+1] G- quadruplex [8,9]. It has also the ability to modulate the gene transcription process. HIV-1 integrase in which the produce small molecular ligand. These are confirmed by means of the CD, NMR, and molecular docking techniques. The interface monomer especially two must be an anti-anti-anti-syn alignment that held guanine both sides from another monomer [3+1type] [10,11]. The various different locked interface interlocked dimeric forms of G-quadruplex are more stable, this is the reason that acts as the biological application, it serves as molecular target canyon of the multimeric protein. The various different locked interface interlocked dimeric forms of G-quadruplex are more stable, this is the reason that acts as the biological application, it serves as molecular target canyon of the multimeric protein [12]. Usually, supplementary of the one type of G-quadruplex hardly ever reported double-stranded G quadruplex twisted by the repeating unit of guanine territory. The oblique loop of the G-quadruplex can be fashioned in the Oxycetrica nova telomeric d(G4T4G4) [13] sequence these in sequence about solution structure and crystal structure obtained by the x-ray crystallography and NMR spectroscopy [14].

The two T4 sequences that formed the in this G-quadruplexes these loops operation as a connector as anti- anti-syn-syn G-tetrads these obliquely cross it top and bottom faced of the G-quadruplex. In the twofold stuck G-quadruplex has one extensive one slender and two intermediate grooves [15].

A. Synthesis of New derivatives of Aldehyde

1. Pentoxybenzaldehyde-

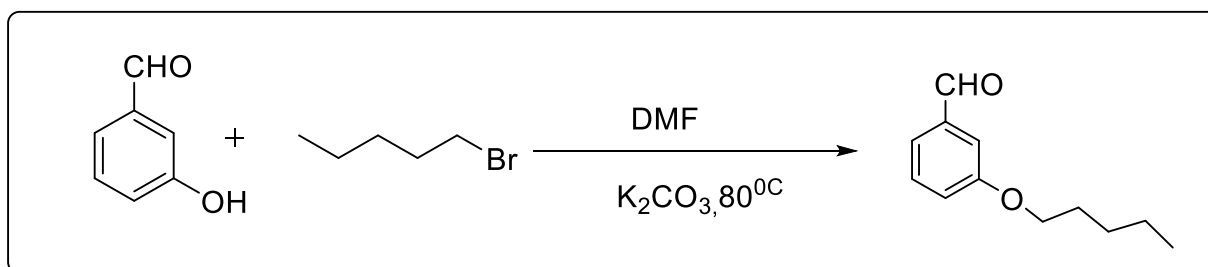


Figure:4 Synthesis of 3-pentoxybenzaldehyde.

Procedure:

To a solution of m-hydroxybenzaldehyde (1.0 g, 8.18 mmol) in DMF (N, N-dimethylformamide, (10 mL) followed by addition of 1-bromopentane (1.13 mL, 8.9 mmol) with potassium carbonate (1.68 g,

12.2 mmol) was added. Refluxed it three hours 80 °C. Progression of the reaction was monitored by the thin layer chromatography with ethyl acetate and hexane solvent system. The reaction was formed it was separated by separating funnel ethylacetate water compound extract in the ethyl acetate layer, and then it was pure by column chromatography, it gives 700 mg. Rf value (0.5 cm.) The percentage yield was found 44.50%. ¹H NMR (400 MHz, DMSO) δ 9.62 (s, 1H), 8.13 (s, 1H), 7.88 – 7.69 (m, 2H), 7.69 – 7.54 (m, 2H), 6.94 (d, J = 8.3 Hz, 1H), 3.90 (s, 3H), 3.34 (s, 6H).

2. Synthesis of 2-(Pentyloxybenzaldehyde)

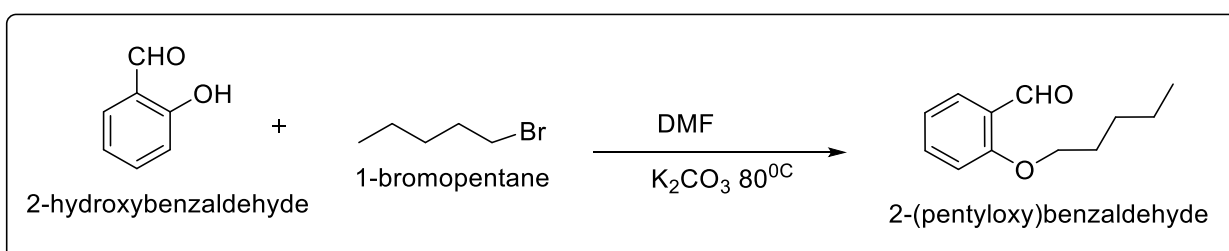


Figure:5 Synthesis of 2-pentyloxybenzaldehyde

Procedure-

To the solution of salicylaldehyde (0.635 mL, 8.18 mmol) in DMF (10 mL) followed by addition of 1-bromopentane (1.13 mL, 8.9 mmol) with potassium carbonate (1.68 g,) was added. Refluxed it four hours 80° C. Progression of the reaction was monitored by the Thin-

layer chromatography with ethyl acetate and hexane solvent system Rf value (0.7cm.). The reaction was completed it was separated by separating funnel ethyl acetate water compound extract in the ethyl acetate layer, then it was purified by column chromatography, to give 660 mg. The percentage yield was found at 41.95%. ¹H NMR (400 MHz, DMSO) δ 10.00 (s, 1H), 8.22 (s, 6H), 8.20 (s, 5H).

Synthesis of 4-(hexyloxybenzaldehyde)

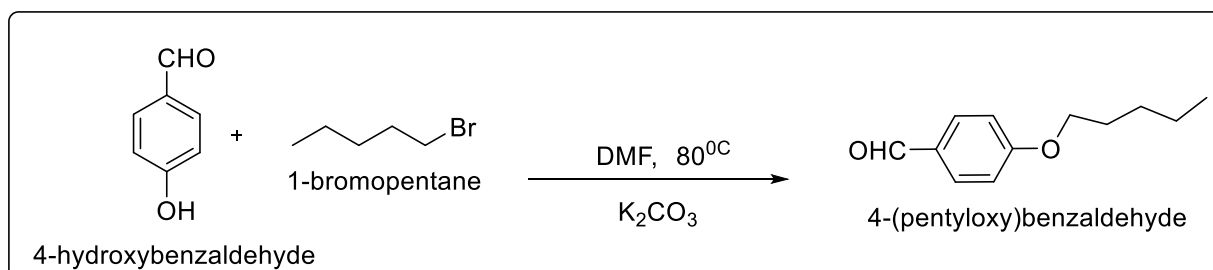


Figure: 6 Synthesis of Pentyloxybenzaldehyde

Procedure—

To the reaction mixture of p-hydroxybenzaldehyde(1.0 g, 8.18 mmol)in DMF(10 mL) followed by the addition of 1-bromopantane (1.13 mL, 8.9 mmol)with potassium carbonate(1.68 g, 12.2 mmol) was added. Refluxed it for two hours at 80°C. Progression of the reaction was monitored by the Thine layer chromatography with ethyl acetate and hexane solvent system. Rf value(0.54 cm.). The reaction was formed it was separated by separating funnel ethylacetate water compound extract in the ethyl acetate layer, then it was purified by column chromatography, to give 950 mg. The percentage yield was found at 60.0%.¹H NMR (400 MHz, DMSO) δ 3.35 (s, 1H), 2.50 (dd, J = 3.4, 1.7 Hz, 1H), 2.08 (s, 1H), 1.28 (s, 1H).

Synthesis of the 2-(propoxybenzaldehyde)

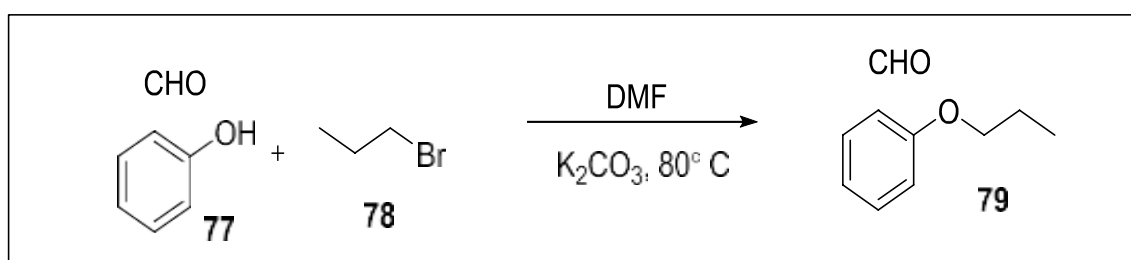


Figure: 27 schematic representations of 2-(propoxybenzaldehyde).

Procedure- To the solution of O-hydroxybenzaldehyde (1 g, 8.18 mmol) in DMF(10 mL) followed by the addition of 1-bromopantane (1.13 mL)with potassium carbonate(1.68 g 12.2 mmol) was added. Refluxed it two hours at 80°C. Progression of the reaction was monitored by the Thin-layer chromatography with ethyl acetate and hexane solvent system. Rf value

(0.54 cm.). The reaction was formed it was separated by separating funnel ethylacetate water compound extract in the ethyl acetate layer, and then it was poured by column chromatography, to give 800 mg. The percentage yield was found at 59.0%. ¹H NMR (300 MHz, MeOD) δ 10.45 (d, J = 0.7 Hz, 1H), 6.94 (s, 4H), 6.92 (s, 2H), 6.89 (d, J = 0.8 Hz, 1H), 5.63 (s, 3H), 5.45 (s, 2H), 1.07 (s, 2H), 1.06 (s, 2H), 1.04 (d, J = 1.1 Hz, 2H), 1.03 (s, 4H).

5. Synthesis of the 3-(propoxybenzaldehyde)

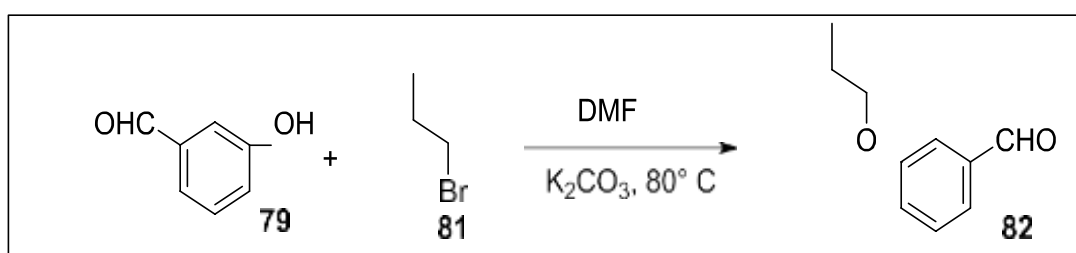


Figure: 28 schematic representation of 3-(propoxybenzaldehyde).

Procedure-

To a solution of m-hydroxybenzaldehyde (1.0 g, 8.18 mmol) in DMF (10 mL) was added n-propyl bromide (0.814 mL) with potassium carbonate (1.68 g, 12.2 mmol). It was refluxed overnight at 80°C. Thin-layer chromatography with ethyl acetate and hexane solvent system was used to monitor the reaction's progress. The R_f value (0.6 cm.). The reaction was separated by separating funnel ethyl acetate and water, compound extract in the ethyl acetate layer, then pure by column chromatography, yielding 700 mg. The percentage yield was discovered to be 52.08%. ¹H NMR (300 MHz, MeOD) δ 9.93 (s, 1H), 7.48 (dd, J = 3.6, 1.1 Hz, 1H), 7.46 - 7.43 (m, 1H), 7.40 (dd, J = 1.8, 0.9 Hz, 1H), 5.48 (s, 1H), 3.99 (t, J = 6.5 Hz, 2H), 5.48 (s, 1H),

6. Synthesis of the 4- propoxybenzaldehyde

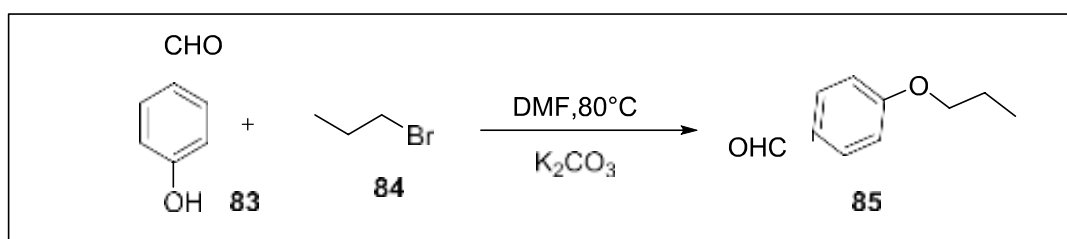


Figure: 29 synthetic scheme of the 4- propoxybenzaldehyde

Procedure- The reaction mixture of p-hydroxybenzaldehyde (1.0 g, 8.18 mmol) in DMF (10 mL) was then followed by the addition of 1-bromopropan (0.82 mL, 8.9 mmol) and potassium carbonate (1.68 g, 12.2 mmol). It was refluxed for six hours at 80°C. Thin layer chromatography with ethyl acetate and hexane solvent system was used to monitor the

reaction's progress. The Rf value (0.54 cm.). The reaction was separated by separating funnel ethylacetate water compound extract in the ethyl acetate layer, and then purified by column chromatography to yield 690 mg. The percentage yield was discovered to be 51.33%.

7. Synthesis of the 4-butoxybenzaldehyde

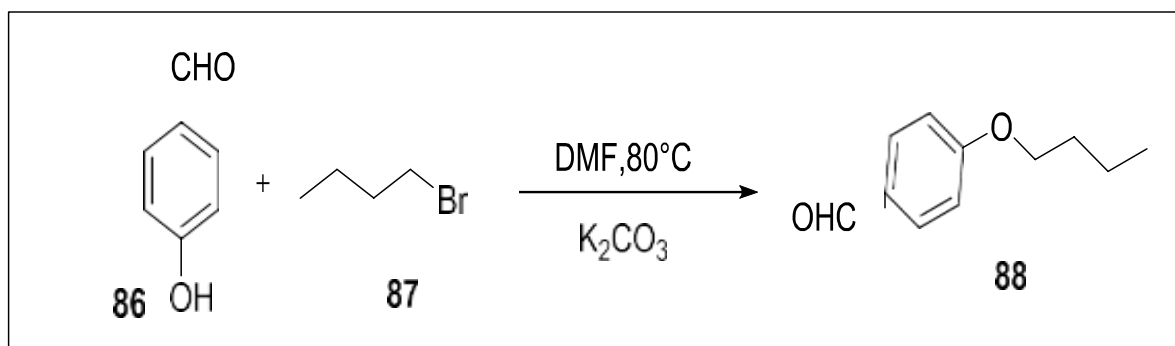


Figure 30: synthetic scheme of the 4- butoxybenzaldehyde.

Procedure— A reaction mixture of p-hydroxybenzaldehyde (1.0 g, 8.18 mmol) in DMF (10 mL) was added, followed by n-butyl bromide (0.82 mL, 8.9 mmol) and potassium carbonate (1.68 g, 12.2 mmol). It was refluxed for six hours at 80°C. Thin-layer chromatography with ethyl acetate and hexane solvent system was used to monitor the reaction's progress. The Rf value (0.5 cm.). The reaction was separated by separating funnel ethylacetate water compound extract in the ethyl acetate layer, and then purified by column chromatography to yield 600 mg. The percentage yield was discovered to be 60.0%.

8. Synthesis of the 2-butoxybenzaldehyde

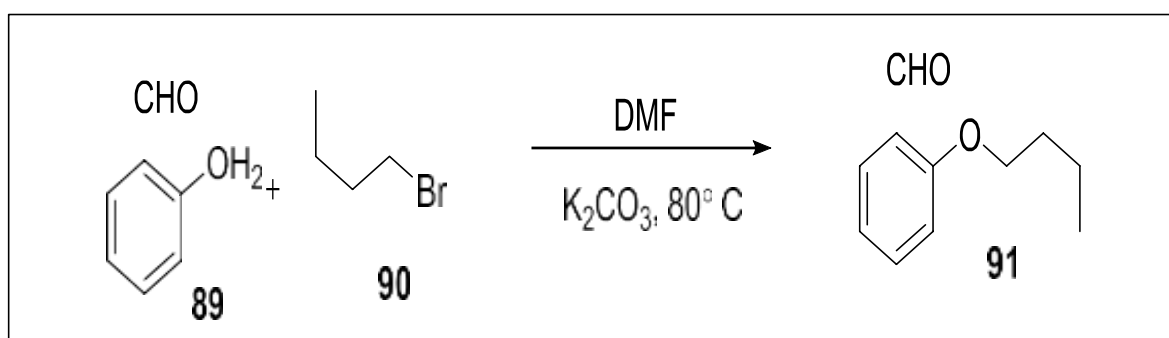


Figure: 31. Synthetic scheme of the 2- butoxybenzaldehyde.

Procedure- The reaction mixture of O-hydroxybenzaldehyde (1.0 g, 8.18 mmol) in DMF (10 mL) was followed by the addition of n-butyl bromide (0.972 mL) with potassium carbonate (1.68 g, 12.2 mmol). It was refluxed three times at 80°C. Thin-layer chromatography with ethyl acetate and hexane solvent system was used to monitor the reaction's progress. The Rf value (0.6 cm.). The reaction was separated by separating funnel ethyl acetate and water, compound extract in the ethyl acetate layer, and then purified by

column chromatography, yielding 650 mg. The percentage yield was discovered to be 43.18%.

9. Synthesis of 3-butoxybenzaldehyde

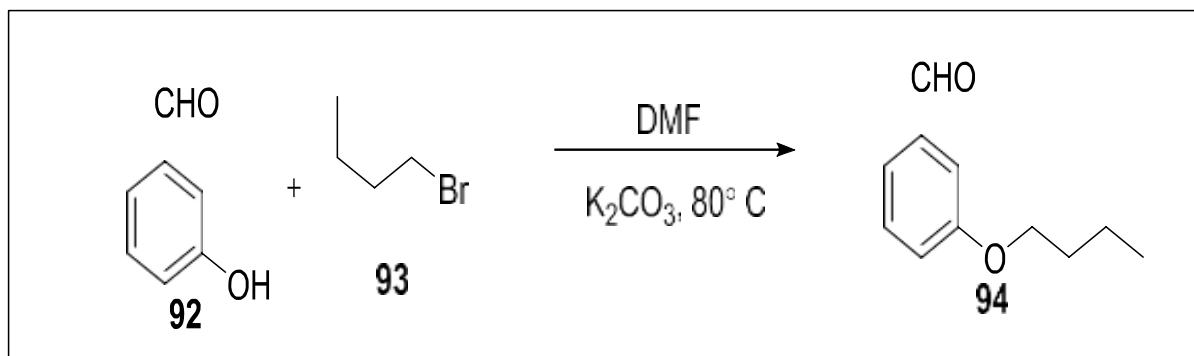


Figure: 32 synthetic scheme of 3-butoxybenzaldehyde.

Procedure- A solution of m-hydroxybenzaldehyde (1.0 g, 8.18 mmol) in DMF (N, N-dimethylformamide, (10 mL) was prepared, followed by the addition of n-butyl bromide (0.97 mL, 8.9 mmol) and potassium carbonate (1.68 g, 12.2 mmol). Refluxed it three hours later at 80 °C. The reaction's progression was monitored using thin layer chromatography with an ethyl acetate and hexane solvent system. After the reaction was formed, it was separated by separating funnel ethylacetate water compound extract in the ethyl acetate layer and then purified by column chromatography, yielding 800 mg. Rf value (0.5 cm.) The percentage yield was discovered to be 53%.

10. Synthesis of 6-heloxybenzaldehyde

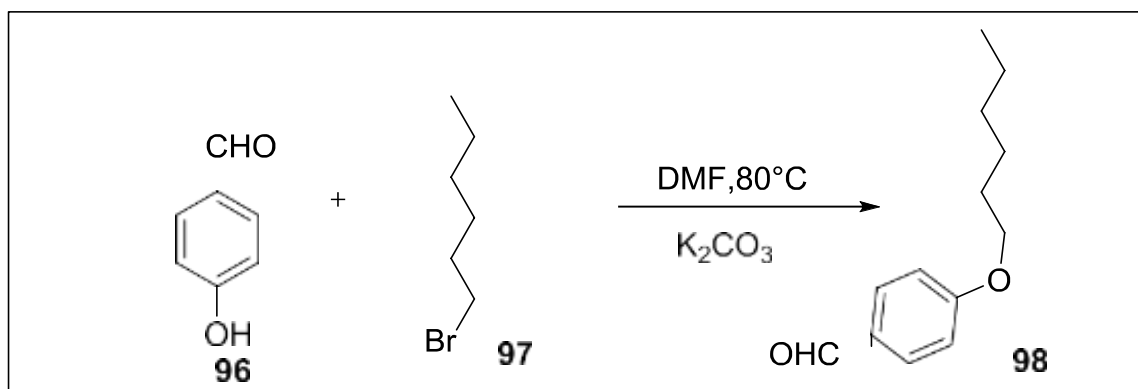


Figure : 33 synthetic scheme of the 6-heloxybenzaldehyde.

Procedure-- To the reaction of p-hydroxybenzaldehyde (1.0 g, 8.18 mmol) in DMF (10 mL) followed by the addition of 1-bromohexane (0.82 mL, 8.9 mmol) with potassium carbonate (1.68 g, 12.2 mmol) was added. Refluxed it to 23 hours at 80°C. Progression of the reaction was monitored by the Thin-layer chromatography with ethyl acetate and hexane

solvent system. R_f value(0.6 cm.). The reaction was formed it was separated by separating funnel ethylacetate water compound extract in the ethyl acetate layer, then it was purified by column chromatography, to give 890 mg. The percentage yield was found at 53%.

11. Synthesis of the m-pentoxybenzaldehyde

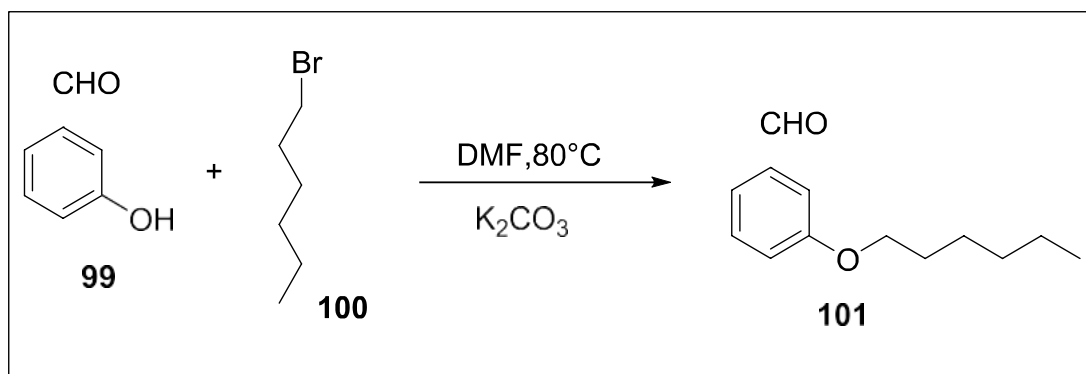


Figure:34. Synthetic scheme of m-pentoxybenzaldehyde.

Procedure- The solution of m-hydroxybenzaldehyde (1.0 g, 8.18 mmol) in DMF (10 mL) was followed by the addition of 1-bromohexane (1.2 mL) with potassium carbonate (1.68 g, 12.2 mmol). It was refluxed for five hours at 80°C. Thin-layer chromatography with ethyl acetate and hexane solvent system was used to monitor the reaction's progress. The R_f value (0.67 cm.). The reaction was separated by separating funnel ethyl acetate and water, compound extract in the ethyl acetate layer, and then purified by column chromatography, yielding 900 mg. The percentage yield was discovered to be 52%.Synthesis of the 2-(hexyloxybenzaldehyde)

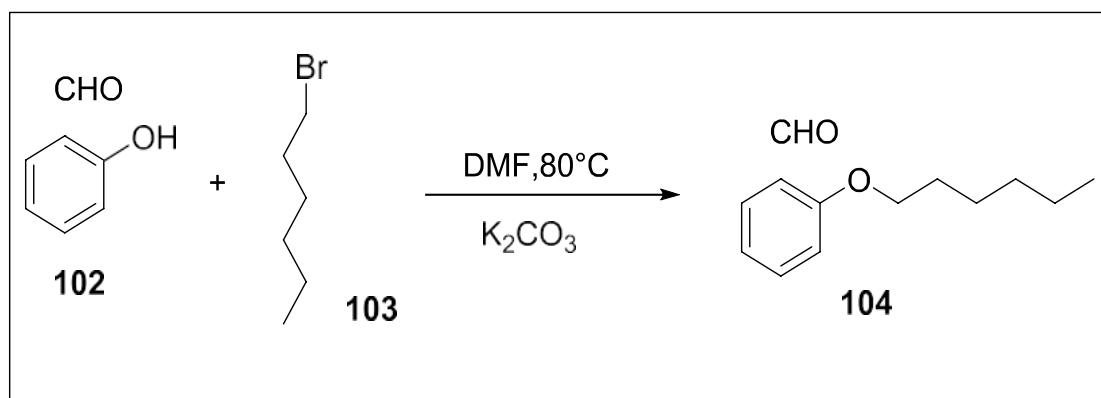


Figure35. Synthetic scheme of O-hexyloxybenzaldehyde.

Procedure- To the solution of O-hydroxybenzaldehyde (1.0 g, 8.18 mmol) in DMF(10 mL) followed by the addition of 1-bromohexane (0.972 mL)with potassium carbonate(1.68 g, 12.2 mmol)was added. Refluxed it five at 80°C. Progression of the reaction was monitored by the Thin-layer chromatography with ethyl acetate and hexane solvent system. R_f value (0.6 cm.).

1. Pentoxybenzaldehyde-

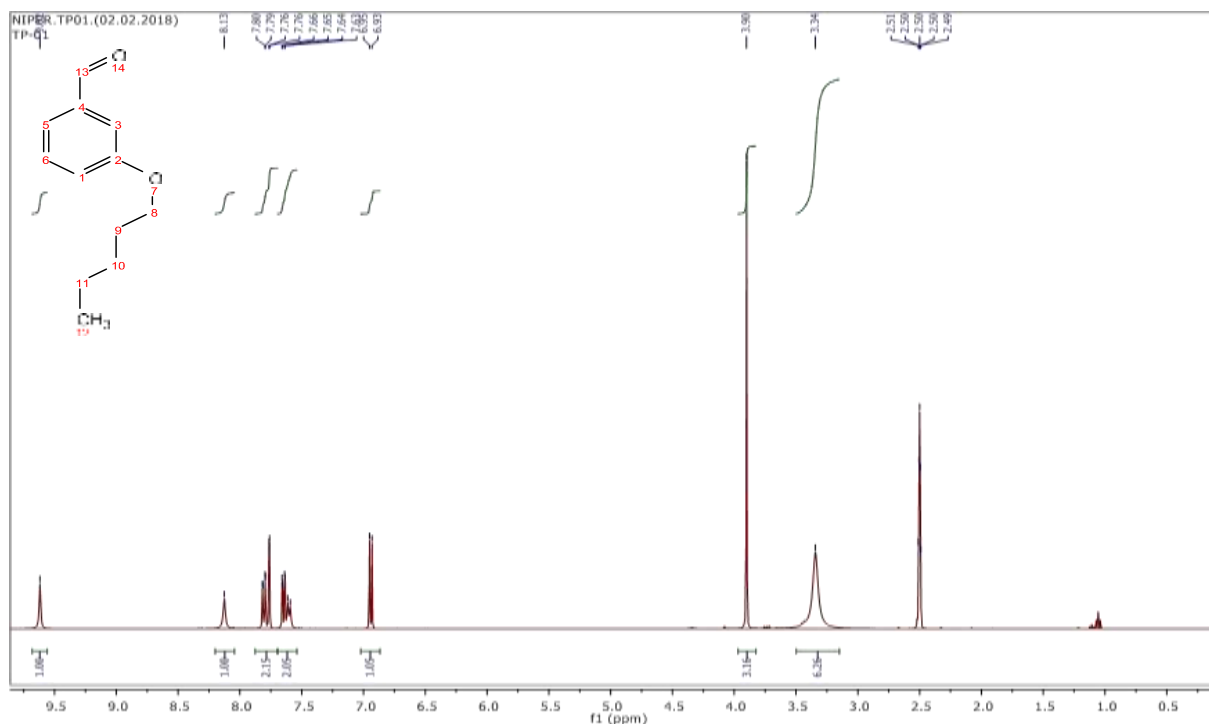


Figure:49 ¹H NMR of 3-(pentoxybenzaldehyde).

2. Synthesis of 2-(Pentoxybenzaldehyde)

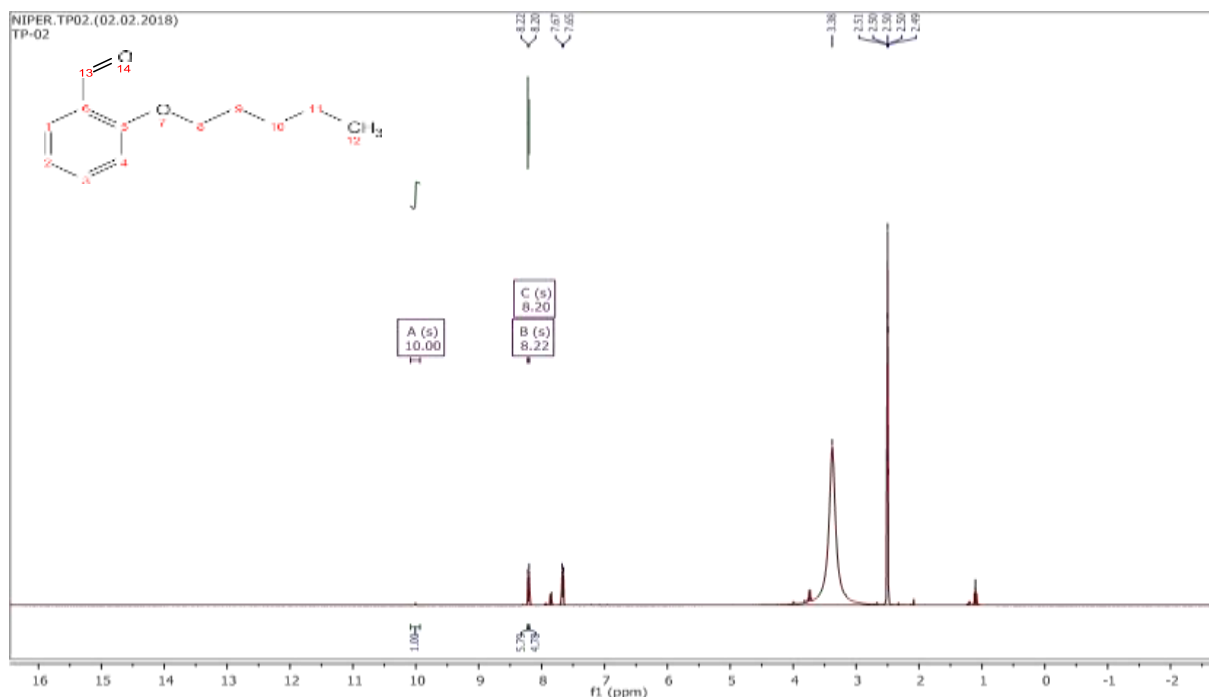
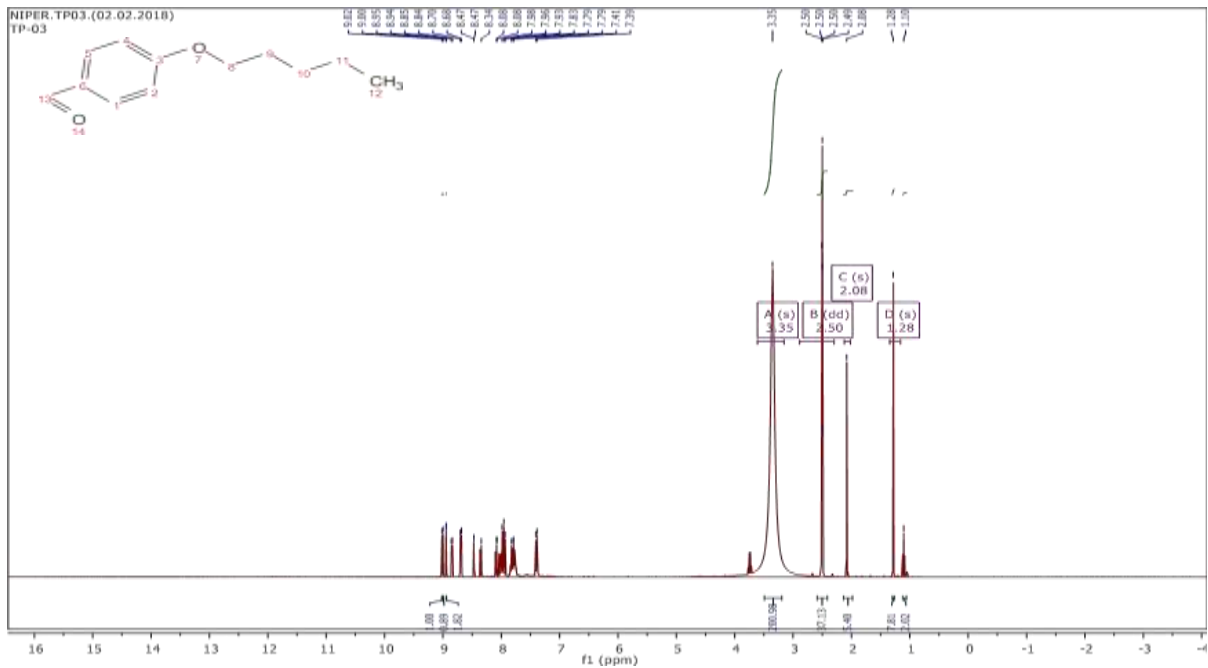
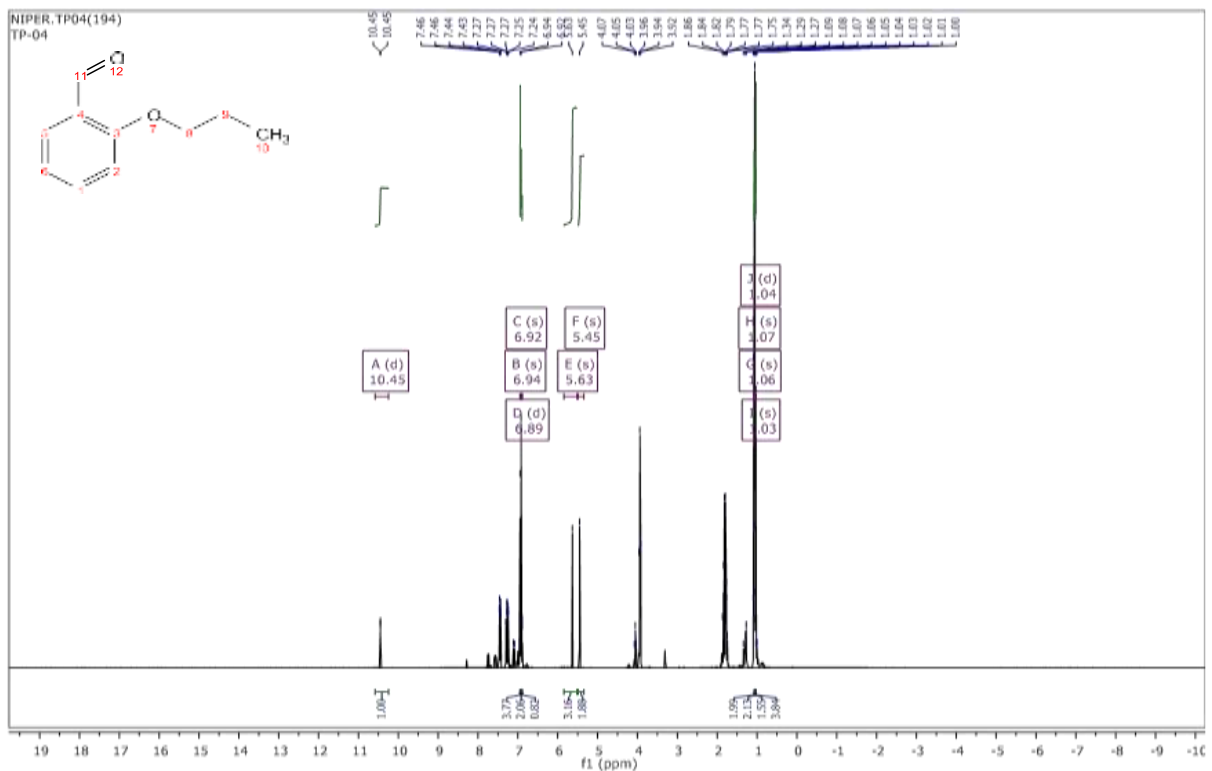


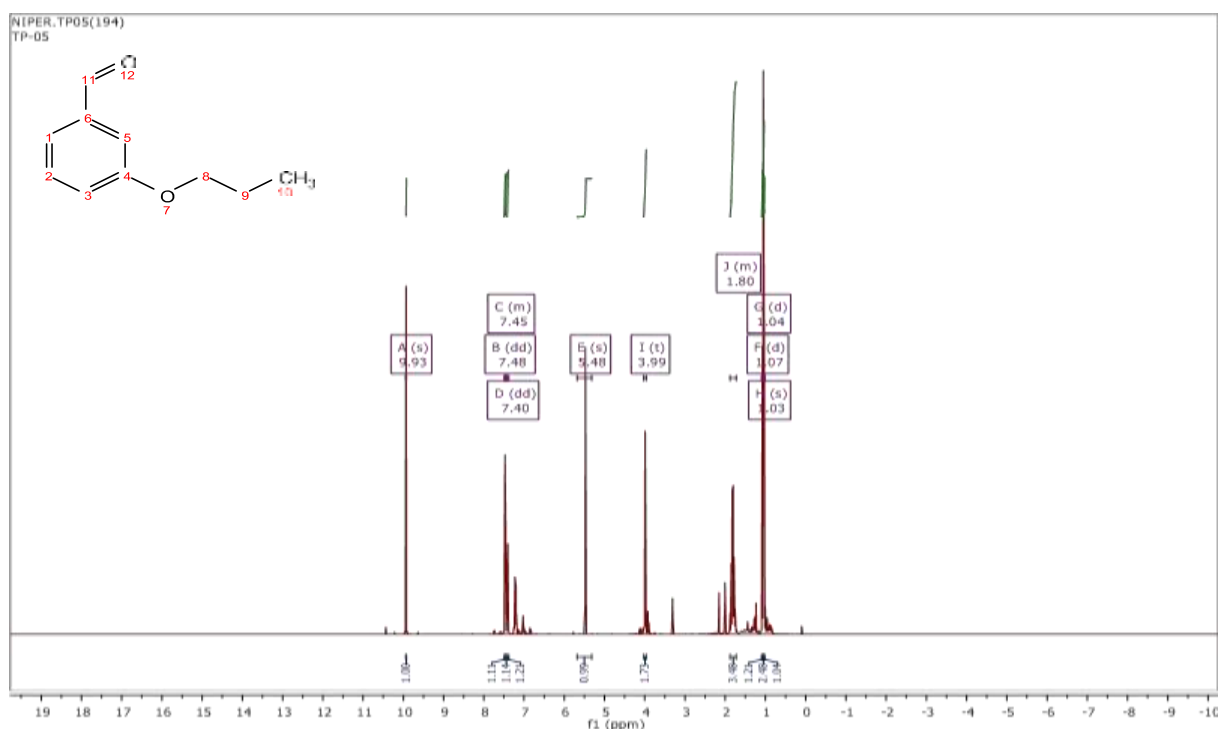
Figure:50 ¹H NMR of 2-(pentoxybenzaldehyde).

3. Synthesis of 4-Pentoxybenzaldehyde



2-(propoxybenzaldehyde)



3-(propoxybenzaldehyde)**CONCLUSION:**

The new aldehyde-alkyl halide hybrid molecules were synthesised in steps and characterised to the best of our ability. We make aldehydes from various alkyl chain derivatives. The reaction of various substituted aldehydes yields a high yield and is purified using column chromatography. The solvents used in the purification of the alkyl substituted aldehydes were ethyl acetate and hexane, after we collected spectroscopic data from several aldehyde hybrid analogues, particularly proton NMR, and discovered that it was purely synthesised with a high percentile of yields.

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