4.1. Introduction:

Natural products play a significant role in the treatment of cancer, because of their excellent pharmacological activity and less toxicity. Curcumin is one such product and detail literature on curcumin described in introductory part of this chapter. Curcumin is dietary phytochemicals extracted from rhizomes of plant curcuma longa. It is a popular Indian spice used in herbal medicines for the treatment of various diseases since it functions as antioxidant, anti-inflammatory, antiproliferative, anti-tumor, anti-malarial, anti-bacterial etc. Curcumin and its analogues play a prominent role in the treatment of various types of cancer [1–6]. The pharmacological activity of curcumin is explored by many researchers and it was described to possess anticarcinogenic property because of its ability to modulate signaling pathways and it was found to exhibit potential inhibition on the activation of various transcription factors including activated proteins, nuclear factor-kB (NF-kB), activator and transducer of transcription (STAT) proteins and β-catenin.

Curcumin and their derivatives are well known as anticancer agents with vast literature. A few examples are described in this chapter as follows.

4.2. Curcumin derivatives against ovarian cancer:

Ovarian cancer is a malignant type of cancer. It is the seventh most common cancer among all the types and it is the eight most common cancer leading to death. An average of 152,000 deaths/year occur from ovarian cancer alone and it is most common disease in America, Europe and Africa [7].

Curcumin and their analogues have been found to display multifunctional pathways of anticancer activity. Although the prospect of curcuminoids as anticancer agents in the treatment of ovarian cancer appears to be challenging, the modification in the basic moiety of curcumin may promise to be effective in clinical studies.
Selvendiran et al., [8] reported studies of anticancer activity (breast, colon, neck, prostate and ovarian cancer) of diarylidenylpipiridone (DAPs). They have synthesized four different analogues of curcumin namely H-4073, HO-4200, HO-3867 and H-4318 (1-4, Fig-1). All four compounds display satisfactory activity, whereas HO-3867 and HO-4200 are found to display lower cytotoxicity towards noncancerous cells. The same group [9] reported the effective inhibition of the growth of cisplatin resistant ovarian cancer cells in-vitro by using synthetic compound EF24 5 (Fig-1). They have demonstrated that EF24 enhances the G2/M cell cycle arrest.

Saladini and co-workers [10] have synthesized the glycosilated curcumin analogues 6 and screened for their cytotoxicity towards human ovarian cancer. The glucosilated curcuminoid 6 exhibits improvement of cDDP efficacy with selectivity towards cancer cells.

4.3. Curcuminoinds against Lung cancer:

Francesco Caruso et al., [11] reported curcumin with ruthenium-arene complex in the 7 (Fig-2). The curcumin ruthenium complex is found to exhibit a
potent activity towards breast cancer (MCF7), lung cancer (A549) and ovarian cancer (A2780) cell lines.

![Figure 2](image)

Fig.2

Inhibition of lung cancer cells by curcumin was reported by Pillai et al., [12]. They have selected the lung cancer cell lines A549 and H1299 as a model system to study the effect of curcumin on the growth of cancerous cells. They have observed the induction of apoptosis in human lung cancer.

4.4. Curcuminoids in the treatment of colon cancer:

Ferrari et al., [13] reported improved activity of new curcumin derivatives 8 (Scheme 3) against colon carcinoma and ovarian cancer. The new derivatives show significant cytotoxicity against human carcinoma cells LoVo and HCT116 as well as ovarian carcinoma cell A2780 and C13. Similarly, Wagner and co-workers [14] have reported the synthesis of halogenated curcumin derivatives 9-14 (Fig-3) and their biological studies towards human colon cancer.
Fig. 3

4.5. Curcumin analogues in the treatment of breast cancer:

Breast cancer is the most common malignant cancer and it is clinically considered as heterogeneous disease and the malignant cells are found in the breasts of mammals. Approximately 25% of women will be diagnosed with breast cancer every year. The detection of this disease is more common in women than in men and is diagnosed one in every eight women [15]. Larsen and group [16] have described the synthesis of various heterocyclic cyclohexanone curcumin analogues and screened for their activity towards breast cancer. They have selected the breast cancer cell line MBA-MB-231 for the cytotoxicity studies. Among eighteen heterocyclic analogues of curcumin, the analogues 15-19 (Fig-4) were found to display significant activity.

Paola et al., [17] explored the effect of isoxazole derivatives of curcumin and screened for their multidrug resistant. The analogue 18 (Fig-18) was found to display
significant cancerous cell inhibition. Adams and co-workers [18] reported curcumin analogues as anticancer agents based on in-vitro and in-vivo screening of anticancer and anti-angiogenesis study of 3,5-Bis-(2-fluorobenzylidene)-piperidin-4-one, acetic acid salt (Fig-4). The piperidone salt 19 effectively reduced the growth of human breast tumor.

Simoni et al., [19] synthesized derivatives of curcumin 20-22 (Fig-5) using the concept of bioisosterism. The inhibition of cell growth and apoptosis inducing effect of these derivatives were studied in vitro by using heaptocellular carcinoma VGH/HA22T cells, breast cancer cell line MCF-7 and MCF-7R cell line.
4.6. Curcuminoids against bone and liver cancer:

Junko et al., [20] have synthesized fifty-eight analogues of curcumin 23-27 (Figure 8) and all the compounds were screened for the activity against bone cancer (HOS). Compound 27 shows significant activity in the inhibition of bone cancer cells. It is evaluated for in-vitro cytotoxicity against bone cancer (HOS) with ED 50 value 0.97 μg/mL.

Xiaolin and co-workers [21] reported the synthesis of ruthenium-arene complex containing curcumin ligand 28. The synthesized compounds were characterized by NMR spectroscopic analysis and the structures were determined by single crystal XRD techniques. These curcuminod ligands were evaluated for the in-vitro antiproliferative activity against human liver cancer cell lines (SMMC-7721).
4.7. Curcuminoids as anti-prostate cancer agent:

Prostate cancer is a complex heterogeneous disease and is common among males of western countries. In an effort towards the design and synthesis of potential anti-prostate cancer drug molecules Qian et al., [22] synthesized twelve analogues of curcumin 29-31 (Figure 9) and evaluated their cytotoxicity against two prostate cancer cell lines androgen-independent PC-3 and androgen-dependent LNCaP. Among all synthesized compounds, the molecule 29, a conjugate of methylcurcumin, was found to exhibit more potential against both the cancer cell lines with IC$_{50}$ values of 39.1 μM (for PC-3) and 41.8 μM (for LNCaP).

![Figure 7](image)

In another approach [23] by the same group, they have synthesized over forty new curcumin analogues 32-37 (Fig-8) and evaluated for the prostate tumor inhibition against PC-3 and LNCaP cell lines. The molecules 57 display significant cytotoxicity.
Xingchan and co-workers [24] have synthesized sixty one curcumin related molecules and evaluated their anticancer activity. On the basis of MTT assay, the compounds 38-41 (Fig-9) shows inhibition of pancreas cancer cell (Panc-1) and prostate cancer cell (PC-3) with IC$_{50}$. 

4.8.1. Synthesis of bisdemethoxycurcumin isoxazole:

Bisdemethoxycurcumin 42 was reacted with hydroxylamine hydrochloride in the presence of catalytic amount of acetic acid in ethanol at 80 ºC for 3 h to afford the corresponding isoxazole curcumin derivative 43 in 95 % yield (Scheme 1).

4.8.2. Synthesis of tetrahydrocurcumin isoxazole:

Finally the tetrahydrocurcumin was treated with hydroxylamine hydrochloride in the presence of catalytic amount of acetic acid in refluxing ethanol for four hours to afford the corresponding isoxazole derivative of tetrahydrocurcumin 44 (Scheme 2) in 96 % yield.

4.8.3. Synthesis of bisdemethoxycurcumin pyrazoles:

In another approach the bisdemethoxycurcumin 42 was treated with various aryl hydrazines in the presence equimolar quantity of glacial acetic acid and ethanol for 3-6 h at 80 ºC to afford the corresponding curcumin analogue of pyrazoles 62a-g in overall 80-95 % yield (Scheme 3).
Scheme 3

142
4.9. Experimental procedure:

- **Synthesis of 4,4’-((1E,1’E)-isoxazole-3,5-diylbis(ethene-2,1-diyl))diphenol 43:**

  Bisdemethoxycurcumin (1 mmol, 0.5g) was taken in a round bottom flask equipped with magnetic stirrer and water cooling condenser. The bisdemethoxycurcumin was dissolved in ethyl alcohol (15 mL) and glacial acetic acid (2-5 mL). Hydroxylamine hydrochloride (1.5 mmol) was added to the solution of bisdemethoxycurcumin solution followed by the addition of base sodium acetate (2 mmol). The reaction mixture was refluxed for six hours at 80 °C. The progress of the reaction was monitored by TLC. After completion of the reaction the solvent was removed under reduced pressure. The residue was poured into ice cold water and neutralized with ammonium hydroxide solution to produce dark grey colored precipitate. Then the precipitate was extracted with ethylacetate (3 x 10 mL) and washed with water (3 x 10 mL), dried under sodium sulphate, concentrated using rotaevaporator to afford dark semisolid which was purified by column chromatography (pet ether/EtOAc, 6:4) to afford the pure compound 4,4’-((1E,1’E)-isoxazole-3,5-diylbis(ethene-2,1-diyl))diphenol (59).

- **Synthesis of 4,4’-(isoxazole-3,5-diylbis(ethane-2,1-diyl))bis(2-methoxyphenol) 45:**

  Tetrahydrocurcumin (1 mmol) was taken in a round bottom flask equipped with magnetic stirrer and water cooling condenser. The tetrahydrocurcumin was dissolved in ethyl alcohol (15 mL) and glacial acetic acid (2-5 mL). Hydroxylamine hydrochloride (1.5 mmol) was added to the solution of tetrahydrocurcumin solution followed by the addition of base sodium acetate (2 mmol). The reaction mixture was refluxed for five and half hours at 80 °C. The progress of the reaction was monitored...
by TLC. After completion of the reaction the solvent was removed under reduced pressure. The residue was poured into ice cold water and neutralized with ammonium hydroxide solution to produce dark grey colored precipitate. Then the precipitate was extracted with ethylacetate (3 x 10 mL) and washed with water (3 x 10 mL), dried under sodium sulphate, concentrated using rotaevaporador to afford dark semisolid which was purified by column chromatography (pet ether/EtOAc, 6:4) to afford the pure compound 4,4'-(isoxazole-3,5-diylbis(ethane-2,1-diyl))bis(2-methoxyphenol) (61).

- **Synthesis of 4,4'-(1E,1'E)-(1-substituted-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))diphenol 46a-g:**

  Bisdemethoxycurcumin (1 mmol, 0.5g) was dissolved in ethanol (15 mL) and glacial acetic acid (2-5 mL). The appropriate arylhydrazines hydrochloride (1.2 mmol) was added followed by addition of sodium acetate (2 mmol) to the solution of bisdemethoxy curcumin. The mixture of solution was refluxed for 6-8 hours at 80 °C. The completion of the reaction was confirmed by TLC techniques and the solvent was removed under reduced pressure to produced orange red precipitate. The precipitate was extracted with ethyl acetate (10 x 3) and washed with water (10 x 3) to get the crude solid product. Produced solid was purified by column chromatography (pet ether/EtOAc, 6:4) to afford the corresponding 4,4'-(1E,1'E)-(1-aryl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))diphenol (60a-h).

### 4.10. Cytotoxic activity of curcumin, tetrahydrocurcumin-isoxazole, bisdemethoxy curcumin-isoxazole and bis-demethoxycurcumin pyrazoles

The cytotoxicity of the synthesized bis-demethoxycurcumin pyrazoles and isoxazole were examined using four human cancer cell lines (skin, pancreatic, lung and oral) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)
assay after 72h observation. All compounds were compared with naturally occurring curcumin, bis-demethoxycurcumin 42, bis-demethoxycurcumin-isoxazole 43 and the standard cisplatin drug (chemotherapy agent) during 72h treatment. Most of the synthesized compounds showed comparable activity with respect to standard cisplatin. Among the tested compounds 46d and 46f exhibited excellent cell growth inhibition against all cancer cell lines with an IC50 value ranges from 0.715 - 2.211 and 0.473 - 1.945 µg/mL respectively (Table 1). Similarly, compounds 46a, 46e and 46g curcumin-pyrazole hybrids showed better activity than reference drug with an IC50 value ranges from 1.116 - 2.645 µg/mL. Whereas, bisdemethoxy curcumin analogues such as 46b and 46c exhibited moderate and considerable cytotoxic effect on all four cancer cell lines. On the other hand, cytotoxic effect of mother compound curcumin, bisdemethoxy curcumin 42 and synthesized bis-demethoxy curcumin-isoxazole 43 showed comparable activity as standard cisplatin drug with an IC50 value ranges from 1.681 - 2.740 µg/mL.

4.11. Structure activity relationship

The functional group modification was carried out on different position of phenyl ring substituted at 1st nitrogen of pyrazole-bisdemethoxycurcumin ring. The cytotoxic potency was increased in the presence of fluro and chloro (46d and 46f) functional group at meta position of phenyl ring. Correspondingly, compound unsubstituted phenyl ring 46a, fluro and chloro (46e and 46g) functional group at ortho position of phenyl ring showed better activity than cisplatin drug. Likewise, para substituted functional groups like fluro and methyl (46b and 46c) on phenyl ring compounds exhibited activity as cisplatin. In the same way, lead compound curcumin, lead compound bisdemethoxy curcumin 42 and bisdemethoxy curcumin-isoxazole 43 compounds also showed good activity. Overall, structural modification on curcumin
and bisdemethoxy curcumin improves the cytotoxic effect than standard cisplatin drug and parent compounds. Therefore, bis-demethoxycurcumin pyrazole analogues can be used as potential cytotoxic agents.

### Table 1: Cytotoxic assay of bis-demethoxycurcumin pyrazole analogues against human skin, pancreatic, lung and oral cancer cell lines (IC\text{50} value in µg/mL).

<table>
<thead>
<tr>
<th></th>
<th>SKIN (A-431)</th>
<th>PAC创ATIC (MIAPACA)</th>
<th>LUNG (A549)</th>
<th>ORAL (KB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>1.968</td>
<td>2.242</td>
<td>1.784</td>
<td>2.375</td>
</tr>
<tr>
<td>42</td>
<td>1.911</td>
<td>2.471</td>
<td>2.740</td>
<td>1.681</td>
</tr>
<tr>
<td>43</td>
<td>2.178</td>
<td>1.673</td>
<td>1.018</td>
<td>1.825</td>
</tr>
<tr>
<td>46a</td>
<td>1.854</td>
<td>1.346</td>
<td>1.766</td>
<td>2.645</td>
</tr>
<tr>
<td>46b</td>
<td>2.534</td>
<td>2.028</td>
<td>1.939</td>
<td>3.266</td>
</tr>
<tr>
<td>46c</td>
<td>1.855</td>
<td>2.259</td>
<td>2.031</td>
<td>2.882</td>
</tr>
<tr>
<td>46d</td>
<td>1.881</td>
<td>1.301</td>
<td>0.715</td>
<td>2.211</td>
</tr>
<tr>
<td>46e</td>
<td>1.896</td>
<td>1.905</td>
<td>2.443</td>
<td>2.036</td>
</tr>
<tr>
<td>46f</td>
<td>1.422</td>
<td>1.038</td>
<td>0.473</td>
<td>1.945</td>
</tr>
<tr>
<td>46g</td>
<td>2.025</td>
<td>1.716</td>
<td>1.116</td>
<td>2.489</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>3.562</td>
<td>2.128</td>
<td>2.753</td>
<td>3.029</td>
</tr>
</tbody>
</table>

#### 4.12. Protocol- Cytotoxicity

We performed cytotoxicity by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. All four cell lines were procured from National Centre for Cell Science, Pune, India. The cell line was cultured in DMEM medium (Invitrogen) which was supplemented with 10 % FBS (Gibco, Invitrogen) and 1 % Antibiotic – Antimycotic 100X solution (Thermofisher
Scientific, Cat No-15240062). The cells were seeded at a density of approximately $5 \times 10^3$ cells/well in 100 μL of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10 % fetal bovine serum (FBS, Gibco, Invitrogen, Cat No - 10270106) plated in 96-well flat-bottom micro plate (NEST-Biotechnology) and maintained at 37 °C in 95 % humidity and 5 % CO$_2$ for overnight. Further, 100 μL of different concentration of (200, 100, 50, 25, 12.5, 6.25, 3.125 µg/mL) compounds were treated to cell lines. The cells were incubated for another 72 hours. The cells in well were washed twice with phosphate buffer solution, and 50 μL of the MTT staining solution (5mg/ml in phosphate buffer solution) was added to each well and plate was incubated at 37 °C. The cells treated with DMSO (2%) alone were used as vehicle controls and after 4h the absorbance was recorded with a 570 nm using micro plate reader.

4.13. Materials and methods

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>CELL LINES</th>
<th>MEDIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SKIN (A-431)</td>
<td>DMEM with high glucose (Cat No- 11965-092)</td>
</tr>
<tr>
<td>2</td>
<td>PACREATIC (MIAPACA)</td>
<td>DMEM (Cat No- 11965-092)</td>
</tr>
<tr>
<td>3</td>
<td>LUNG (A549)</td>
<td>Ham's F12K (Cat No- 11765054)</td>
</tr>
<tr>
<td>4</td>
<td>ORAL (KB)</td>
<td>MEM (E) with NEAA</td>
</tr>
</tbody>
</table>
4.14. Conclusions:

Analogous showed a fascinating cytotoxicity against human cancer cell lines namely skin, pancreatic, lung and oral. MTT assay study showed prominent cytotoxic activity. Mother compound curcumin, bisdemethoxy curcumin 42 and synthesized bis-demethoxy curcumin-isoxazole 43 showed comparable activity as standard cisplatin drug with an IC$_{50}$ value ranges from 1.681 - 2.740 µg/mL whereas no apparent cytotoxicity was observed towards MCF-10A normal mammary epithelial cells up to 1mg/mL.

4.15. Analytical data for the synthesized compounds:

- **4,4'-(1E,1'E)-isoxazole-3,5-diylbis(ethene-2,1-diyl))diphenol 43:**
  
  **Obtained yield:** 95 %; m.p:255-259 °C; **IR** (KBr, cm$^{-1}$): 168.3, 162.0, 158.5, 158.2, 135.6, 134.4, 128.4, 126.8, 126.4, 115.8, 112.3, 109.7; **$^1$HNMR (400MHz, DMSO-$d_6$):** $\delta$ 9.81 (s, 1H), 9.75 (s, 1H), 7.50 - 7.46 (t, 4H), 7.26-7.25 (d, $J$ = 16Hz, 2H), 7.01-6.94 (m, 2H), 6.85 (s, 1H), 6.80 - 6.75 (m, 4H); **$^{13}$C NMR (100 MHz, CDCl$_3$):**3332.3, 3133.9, 3022.4, 1603.6, 1563.0, 1449, 1253.5, 835.0; HRMS for C$_{19}$H$_{15}$NO$_3$, m/z = 306.1085 (Calculated), m/z = 306.1131[M+H]$^+$ (Found).

- **4,4'-(isoxazole-3,5-diylbis(ethane-2,1-diyl))bis(2-methoxyphenol) 45:**
  
  **Obtained yield:** 92 %; Solid. m.p: 210-214 °C; **$^1$HNMR (400MHz, DMSO-$d_6$):** $\delta$ 2.87-2.91 (m, 6H), 2.96 (m, 2H), 3.82- 3.83 (s, 6H), 5.50-5.51 (s, 2H), 5.67(s, 1H), 6.61-6.67 (m, 4H), 6.80 -6.81 (d, J
= 7.8 Hz, 2H). \(^1\)HRMS for C\(_{21}\)H\(_{23}\)NO\(_5\), m/z = 370.1610 (Calculated), m/z = 370.0438 [M+H]\(^+\) (Found).

- **4,4’-((1E,1’E)-(1-phenyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))diphenol 46a:**

  **Obtained yield:** 90 %; m.p:190-194 °C;
  **IR (KBr):** 157.8, 157.3, 151.2, 142.5, 139.3, 132.2, 130.3, 129.0, 127.9, 125.0, 117.1, 112.0 cm\(^{-1}\). \(^1\)H NMR (400MHz, DMSO-\(d_6\)): \(\delta\) 9.66 (s, 1H), 9.57 (s, 1H), 7.57-7.49 (m, 5H), 7.44-7.39 (m, 2H), 7.18-6.91 (m, 4H), 6.77-6.67 (m, 5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)):157.9, 157.3, 151.2, 142.5, 139.3, 132.2, 130.3, 127.9, 127.4, 125.0, 117.1, 112.0 ; HRMS for C\(_{25}\)H\(_{20}\)N\(_2\)O\(_2\), m/z = 381.1558 (Calculated), m/z = 381.1603[M+H]\(^+\) (Found).

- **4,4’-((1E,1’E)-(1-(p-tolyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))diphenol 46b:**

  **Obtained yield:** 92 %; m.p:180-184 °C;
  **IR (KBr):** 3018.2, 2806.0, 2679.0, 1606.7, 1588.8, 1510.2, 1254.9, 820.9 cm\(^{-1}\).
  \(^1\)HNMR (400MHz, DMSO-\(d_6\)): \(\delta\) 9.65 (s, 1H), 9.57 (s, 1H), 7.44-7.42 (m, 6H), 7.29-7.17 (m, 4H), 7.14-6.73 (m, 4H), 6.71-6.66 (m, 5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)):157.8, 157.3, 151.0, 142.5, 139.2, 130.2, 128.7, 128.1, 127.5, 122.1, 117.1, 115.7, 112.0; HRMS for C\(_{26}\)H\(_{22}\)N\(_2\)O\(_2\), m/z = 395.1715 (Calculated), m/z = 395.1751[M+H]\(^+\) (Found).
- **4,4’-((1E,1’E)-(1-(4-fluorophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))diphenol 46c:**

  Obtained yield: 85 %; m.p: 185-189 °C; IR (KBr): 3368.6, 3120.0, 1606.9, 1586.9, 1510.7, 1223.3, 1102.3, 822.8 cm\(^{-1}\).

  \(^1\)HNMR (400MHz, DMSO-\(d_6\)): \(\delta\) 9.66 (s, 1H), 9.57 (s, 1H), 7.56-7.52 (m, 2H), 7.41-7.37 (m, 4H), 7.36-7.30 (d, \(J=8.8\) Hz, 2H), 7.17-6.89 (m, 5H), 6.77-6.72 (t, 4H), 6.67-6.63 (d, \(J=15.6\)Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 157.9, 157.3, 142.7, 132.6, 130.5, 127.9, 126.9, 116.9, 116.0, 115.3, 111.6; HRMS for C\(_{25}\)H\(_{19}\)FN\(_2\)O\(_2\), m/z = 399.1461 (Calculated), m/z = 399.1509[M+H]\(^+\) (Found).

- **4,4’-((1E,1’E)-(1-(3-fluorophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))diphenol 46d:**

  Obtained yield: 95 %; m.p: 105-109 °C; IR (KBr, cm\(^{-1}\)): 3526.5, 3126.3, 1608.8, 1537.1, 1272.3, 1170.6, 821.9 cm\(^{-1}\).

  \(^1\)HNMR (400MHz, DMSO-\(d_6\)): \(\delta\) 9.68 (s, 1H), 9.59 (s, 1H), 7.61-7.55 (m, 1H), 7.42-7.27 (m, 8H), 7.19-7.04 (m, 4H), 6.95-6.88 (m, 1H), 6.77-6.73 ( m, 5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 157.9, 157.4, 151.9, 144.1, 132.6, 130.7, 130.4, 129.8, 128.0, 127.6, 124.8, 116.8, 115.7, 111.0; HRMS for C\(_{25}\)H\(_{19}\)FN\(_2\)O\(_2\), m/z = 399.1461 (Calculated), m/z = 399.1506[M+H]\(^+\) (Found).
• 4,4’-((1E,1’E)-(1-(2-fluorophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))diphenol 46e:

\[
\begin{align*}
\text{Obtained yield: } & 80 \% \text{; m.p: } 210-214 \, ^\circ \text{C;} \\
\text{IR (KBr): } & 3529.3, \, 3010.6, \, 2802.5, \, 1607.4, \, 1509.9, \, 1231.7, \, 759.0 \, \text{cm}^{-1}. \\
\text{\textsuperscript{1}HNMR (400MHz, DMSO-} & \text{d}_6): \, \delta \, 7.19 \\
\text{d, (1H), 7.20 (t, 1H), 7.12 (d, 1H), 7.21 (s, 1H), 6.6 (t, 2H), 5.2 (br s, 1H), 6.42 (s, 2H), 3.28 (t, 2H), 2.72 (t, 2H), 3.76 (s, 2H), 3.78 (s, 2H); } \\
\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3): & 157.9, \, 157.4, \, 151.9, \, 144.1, \, 132.6, \, 130.7, \, 130.4, \, 129.8, \, 128.0, \, 127.6, \, 124.8, \, 116.8, \, 115.7, \, 111.0; \text{HRMS for C}_{25}\text{H}_{19}\text{FN}_2\text{O}_2, \, m/z = 399.1461 \text{ (Calculated), m/z = 399.1509[M+H]}^+ \text{ (Found).}
\end{align*}
\]

• 4,4’-((1E,1’E)-(1-(3-chlorophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))diphenol 46f:

\[
\begin{align*}
\text{Obtained yield: } & 90 \% \text{; m.p: } 170-174 \, ^\circ \text{C;} \\
\text{IR (KBr): } & 3365.0, \, 3020.8, \, 1591.3, \, 1510.0, \, 1227.3, \, 1169.8, \, 821.9 \, \text{cm}^{-1}. \\
\text{\textsuperscript{1}HNMR (400MHz, DMSO-} & \text{d}_6): \, \delta \, 7.24 (s, 1H), \, 7.21 (s, 1H), \, 6.91-6.70 (m, 9H), \, 6.54-6.64 (m, 3H), \, 6.46-6.43 (m, 2H), \, 6.32-6.28 (m, 5H); \, \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3): } \, 158.0, \, 157.4, \, 151.6, \, 142.7, \, 140.3, \, 134.5, \, 132.8, \, 130.8, \, 127.9, \, 127.2, \, 124.9, \, 122.9, \, 116.7, \, 111.4; \text{HRMS for C}_{25}\text{H}_{19}\text{ClN}_2\text{O}_2, \, m/z = 414.1135 \text{ (Calculated), m/z = 415.1214[M+H]}^+ \text{ (Found).}
\end{align*}
\]
**4,4’-((1E,1’E)-(1-(2-chlorophenyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))diphenol 46g:**

- **Obtained yield:** 88 %; m.p: 95-99 °C; **IR (KBr):** 3366.4, 3340.5, 3033.7, 1606.6, 1587.8, 1239.2, 1169.7, 821.8 cm⁻¹.

  1H NMR (400MHz, DMSO-d₆): δ 9.65 (s, 1H), 9.57 (s, 1H), 7.72-7.70 (d, J = 8Hz, 1H), 7.60-7.51 (m, 3H), 7.45-7.35 (m, 2H), 7.35-7.20 (d, J = 15.2Hz, 2H), 7.18-7.02 (m, 3H), 6.93-6.88 (d, J = 16.4Hz, 1H), 6.77-6.75 (d, J = 8Hz, 2H), 6.71-6.69 (d, J = 8Hz, 2H), 6.30-6.62 (d, J = 16.4Hz, 1H);

  13C NMR (100 MHz, CDCl₃): 157.9, 157.4, 151.6, 144.0, 136.7, 132.5, 130.6, 129.8, 127.9, 116.9, 115.7, 111.1; HRMS for C₂₅H₁₉ClN₂O₂, m/z = 414.1135 (Calculated), m/z = 415.1217[M+H⁺] (Found).
4.16. References:


4.17. Appendices

$^1$H NMR spectrum of compound 43:

$^{13}$C NMR spectrum of compound 43:
Chapter 4

Mass spectrum of compound 43:

[Mass spectrum image]

IR Spectrum of compound 43:

[IR spectrum image]
Mass spectrum of compound 45:

$^1$H NMR spectrum of compound 46a:
13C NMR spectrum of compound 46a:

Mass spectrum of compound 46a:
Chapter 4

IR spectrum of compound 46a:

[Image of IR spectrum]

$^1$H NMR spectrum of compound 46c:

[Image of NMR spectrum]
$^{13}$C NMR spectrum of compound 46c:

Mass spectrum of compound 46c:
$^1$H NMR spectrum of compound 46d:

$^{13}$C NMR spectrum of compound 46d:
Mass spectrum of compound 46d:

\[ \text{Mass spectrum image} \]

\[ \text{H NMR spectrum of compound 46g:} \]

\[ \text{H NMR spectrum image} \]
$^{13}$C Spectrum of compound 46g:

Mass spectrum of compound 46g: