CHAPTER-3

NOVEL AND IMPROVED PROCESS FOR THE PREPARATION OF CITALOPRAM AND ITS ANALOGUES CONTAINING TETRAZOLES

This chapter is divided into two sections. Section-A deals with the novel and improved process for the preparation of Citalopram and section-B describes the synthesis & characterization of citalopram analogues containing tetrazoles.

Section-A

NOVEL AND IMPROVED PROCESS FOR THE PREPARATION OF CITALOPRAM

3A.1 INTRODUCTION

This part of the present chapter deals with the novel process for the preparation of citalopram (40), which is an isobenzofuran derivative. The key intermediate, 1-(4-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile (41) of citalopram was prepared using novel intermediates 42, 43, 44, 45, 46, 47 using 2-bromo-4-chlorobenzoylchloride (48) as starting material. The process involves steps such as simple acylation, hydrolysis, and reduction, which can be easily adapted to commercial scale. Synthetic scheme for the preparation of intermediates is depicted in Scheme 3.1
Reagents & Conditions: a) fluorobenzene, AlCl₃, 50-60 °C, 3h. b) CuCN, DMF, 110 °C, 7h. c) H₂SO₄, reflux, 3h. d) SOCl₂, benzene, MeOH, 2h. e) NaBH₄, t-butanol, reflux, 2h. f) PTs-acid, toluene, 2h. g) nickel(II)chloride, triphenylphosphine, Zn, KCN, acetonitrile, reflux, 8h. h) NaH, DMSO, 3-dimethylaminopropylchloride, rt, 1h.

Scheme 3.1

3A.2 LITERATURE SURVEY

Heteroaromatic compounds play a significant role; in particular benzofuran ring is a common moiety in many biologically active natural and therapeutic products [99]. Some of these derivatives of benzofuran, with chiral substituents, represent a very important heterocyclic pharmacophore [100]. Isobenzofurans also have long been recognized as an interesting class of reactive intermediates in organic synthesis. Several excellent reviews on the chemistry of these species have been published [101-110]. Suitably substituted isobenzofurans have served as useful intermediates for the synthesis of natural products such as...
resistomycin [111] and anthracyclinones, [112] inner-functionalized cavity molecules [113,114], steroid analogues [115], oxasteroid analogues [116], azasteroid analogues [117], polycyclic nitrogen heterocycles[118-120] and others[121-124].

Citalopram hydrobromide (40a) is an isobenzofuran derivative, which is Selective Serotonin Reuptake Inhibitor (SSRI) and used for the treatment of depression. Citalopram hydrobromide was invented by Klaus et.al [125]. The chemical name of citalopram is 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (40).

A key intermediate 41 in the synthesis of citalopram (40) is reported by Boegesoe et al [125]. The known process in the literature [125-127] for the preparation of citalopram using this key intermediate 1-(4-fluorophenyl)-1,3-dihydro isobenzofuran-5-carbonitrile (41) is disclosed in Scheme 3.2.
According to the process disclosed in Scheme 3.2, 5-bromophthalide (49) is reacted with p-fluoro-phenylmagnesium bromide (freshly prepared from p-fluoro-bromobenzene and magnesium turnings in THF at reflux) to get the benzophenone derivative 50 which is reduced with lithium aluminium hydride and the resulting dihydroxy compound 51 is cyclised using orthophosphoric acid to get the phthalane derivative 52. The latter intermediate (52) when reacted with copper cyanide in DMF medium affords the cyano derivative 41.

The main drawback in this process are involvement of Grignard reaction and the subsequent reduction with LAH of the benzophenone intermediate. These two reactions cannot be easily adopted for commercial scale due to the risk involved in handling pyrophoric reagents and low yields in Grignard reaction. Often Grignard reaction is also associated with impurity formation. In this particular Grignard
reaction, one major impurity - a bis-Grignard product 53 is formed along with the required product 50, as depicted in Scheme 3.3.

Scheme 3.3

As both the steps involved in making the intermediate 41 are very expensive, the process is not an economically viable one.

3A.3 PRESENT WORK

In present competitive pharmaceutical market, it is necessary to produce a good quality product in higher yield at low cost keeping in view the environmental factors. Safe and hazard-free handling of reagents employing ecofriendly raw materials, at the same time looking into scale up feasibility make commercial process development very challenging.

Keeping in view the obstacles in commercialization of the above-mentioned process for the preparation of citalopram intermediate 41, development of a simple and economically viable process for the preparation of intermediate 41 through new intermediates is aimed at.

3A.4 RESULTS AND DISCUSSION

The present process provides novel and improved process for the preparation of key intermediate 41 of citalopram using novel compounds
42, 43, 44, 45, 46, 47, and process to producing novel compounds mentioned above are fully characterized using advanced spectral data such as FTIR, NMR and MS the same. The present process is described in detail in the experimental section. The synthetic scheme is depicted in scheme 3.1.

Accordingly, the starting material 2-bromo-4-chlorobenzoyl chloride (48) (Prepared from 2-bromo-4-chlorobenzoic acid refluxed with thionylchloride) was reacted with fluorobenzene in the presence of aluminum chloride at 50-60 °C to give benzophenone derivative 2-bromo-4-chloro-4'-fluoro benzophenone (42). Thus its ¹H NMR showed seven aromatic protons in the aromatic region δ7.09-7.87. Its mass spectrum exhibited m/z 312 molecular ion peak corresponding to its base peak as [M-1]⁺. Treating compound 42 with copper (I) cyanide in DMF at 110 °C afforded 2-cyano-4-chloro-4'-fluorobenzophenone (43). The IR (KBr) spectrum exhibited nitrile peak at 2233 cm⁻¹. Its mass spectrum showed molecular mass ion peak at 260[M+1]⁺ corresponding to the molecular mass 259. Hydrolysis of cyano derivative 43 with aqueous sulfuric acid at 150-160 °C gave the benzoic acid derivative 2-(4-fluorobenzoyl)-4-chlorobenzoicacid (44). The compound was characterized by its IR spectrum, which shown the absence of nitrile peak at 2233 cm⁻¹ and presence of hydroxy group at 3288 cm⁻¹. Its mass spectrum exhibited molecular ion peak at m/e 277[M-1]⁺ corresponding to its molecular mass 278. Esterifying the compound 44 with methanol yields methyl-2-
(4-fluorobenzoyl)-4-chlorobenzoate (45). The $^1$H NMR spectrum of compound 45 exhibited singlet at $\delta 3.67$ (s, 3H) assignable to methyl group. Aromatic protons are observed in appropriate region. Compound 45 was reduced with sodium borohydride to afford the dihydroxy compound, 1-(4-chloro-2-hydroxymethylphenyl)-1-(4-fluorophenyl) methanol (46). The compound 46, thus obtained was cyclized in the presence of acid catalyst gives rise to the chloro-phthalane derivative 1-(4-fluorophenyl)-1,3-dihydro-5-chloro-isobenzofuran (47). Thus, its $^1$H NMR showed peak at $\delta 5.2$ (dd, 2H) assignable to methylene (–CH$_2$O–) proton and signal at $\delta 5.3$ (s, 1H) assignable to –CHO– and aromatic protons are observed at appropriate region. Finally the resulting chlorophthalane compound (47) was cyanated to afford the target intermediate 1-(4-fluorophenyl)-1,3-dihydro isobenzofuran-5-carbonitrile (41)[128]

Scheme 3.1.
Reagents & Conditions: a) fluorobenzene, AlCl₃, 50-60 °C, 3h. b) CuCN, DMF, 110 °C, 7h. c) H₂SO₄, reflux, 3h. d) SOCl₂, benzene, MeOH, 2h. e) NaBH₄, t-butanol, reflux, 2h. f) PTs-acid, toluene, 2h. g) nickel(II)chloride, triphenylphosphine, Zn, KCN, acetonitrile, reflux, 8h. h) NaH, DMSO, 3-dimethylaminopropylchloride, rt, 1h.

Scheme 3.1

3A.5 EXPERIMENTAL SECTION

48: Into a 500 ml three-necked RB flask was charged 2-bromo-4-chlorobenzoic acid (45.0 g, 0.2 mol) and 225 ml of toluene. Thionyl chloride (28.0 g, 0.24 mol) was added to the reaction mixture at room temperature. The reaction mixture was slowly heated to reflux temperature and maintained at reflux temperature for 4 h. Toluene and excess thionyl chloride were distilled off from the reaction mixture and finally vacuum was applied to get the required 48 as a residue. This was directly used in next step.
42: Into a clean and dry 500 ml three necked RB flask was added fluorobenzene (22.0 ml), anhydrous aluminum chloride (14 g, 0.15 mol), 48 (22.6 g, 0.09 mol) in fluorobenzene (22 ml) was added to the reaction mixture at 0-5 °C. The reaction temperature was slowly raised to 50-60 °C and maintained for 3h. The reaction mixture was cooled to room temperature and poured into ice-water (200 ml) containing 20 ml of conc. HCl. The reaction mixture was extracted with methylene chloride and the organic layer washed with aqueous sodium bicarbonate. Drying and distillation of solvent gave crude product. The crude compound was distilled under vacuum (200 °C at 3 mm Hg) to get the required 42 (20.0 g, 71.5%). A small sample was recrystallised from isopropanol to get the pure compound. Melting range: 80-81°C. IR (KBr, cm⁻¹): 3081, 1670, 1597, 1582, 1504, 1283, 1243, 1149, 1180, 1044 and 929. ¹H-NMR (CDCl₃); 7.77-7.87 (m, 1H), 7.68 (d, J=1.8Hz, 1H), 7.40-7.44 (m, 1H), 7.29 (d, J=8.4 Hz, 1H) and 7.09-7.21 (m, 2H). MS (ES): m/z 312, [M-1]+.

43: Into a 500ml three-necked RB flask was charged 42 (39.0 g, 0.12 mol), copper (I) cyanide (11.7 g, 0.13 mol), and dry DMF (200 ml). The reaction mixture was slowly heated to 110 °C and maintained at this temperature for 7 h. TLC of the reaction mixture showed the absence of starting bromo compound. The reaction mixture was cooled to room temperature and poured into 500 ml of water. Product was extracted into benzene (3x75ml) and the organic solvent distilled off to get crude compound (35.0 g). The crude product thus obtained was recrystallised
from 100 ml of isopropanol to get 25.0 g (78%) of 43, as an off white crystalline solid. m.p: 114-5 °C. IR (KBr, cm⁻¹): 3075, 2233, 1660, 1599, 1557, 1502, 1286, 1273, 1236, 1153, 932, 854, 842 and 774. ¹H-NMR (CDCl₃): 7.82-7.85 (m, 3H), 7.59-7.70 (m, 2H) and 7.17-7.21 (m, 2H). ¹³C-NMR (CDCl₃): 113.36, 115.60, 115.98, 131.14, 131.91, 132.43, 132.81, 132.90, 133.84, 137.77, 139.24, 164.82, 167.38, 191.02. MS (ES): m/z 260, [M+1]+.

44: Aqueous sulfuric acid (22.5 g, 75% w/w) and 43 (10.0 g, 0.04 mol) were charged into a 100 ml, three necked RB flask and the contents were heated to 160 °C and maintained at this temperature for 3 h. TLC of the reaction mixture showed the absence of starting material and reaction mixture was cooled to room temperature before pouring into ice-water (100 ml). Product was extracted into methylene chloride and the organic layer extracted with 30 ml of 10% aqueous sodium hydroxide solution. The aqueous layer was treated with carbon and filtered. The filtrate was acidified with conc. HCl to get the precipitate. Product was isolated by filtration and dried at 60-70 °C to get 9.7 g (90%) of off white crystalline solid of 44. A small sample was recrystallised from toluene to get white crystalline solid. Melting range: 144-6 °C. IR (KBr, cm⁻¹): 3288, 3114, 1721, 1680, 1598, 1564, 1505, 1288, 1262, 1230, 1199, 1152, 1109, 936, 852 and 763. ¹H-NMR (CDCl₃): 8.67 (br s, 1H, -COOH), 8.06 (d, J=1.8 Hz, 1H, aromatic), 7.71-7.74 (m, 2H, aromatic), 7.63-7.67 (m, 1H, aromatic), 7.30-7.32 (m, 1H, aromatic) and 7.08-7.12 (m, 2H, aromatic).
$^{13}$C-NMR (CDCl$_3$): 115.63, 115.85, 128.89, 129.67, 130.84, 132.00, 133.02, 133.12, 135.86, 140.15, 168.46, 194.79. MS (ES): m/z 277 [M-1]$^+$. 

**45:** Into a 250ml, three-necked RB flask was charged 100ml of dry benzene, 10g (0.036 mol) of **44**, and 7.0ml of thionyl chloride. The reaction mixture was heated to reflux temperature and maintained for 3h. Excess of thionyl chloride and benzene were removed from the reaction mass under vacuum to get a crude product. And to the above crude compound was added 30ml of methanol and stirred for 2h at room temperature. Methanol was distilled off from the reaction mixture under vacuum and the residue was recrystallized from ethyl acetate–hexane to get 9.0g (85.6 % yield) of white crystalline solid, **45**. Melting range: 78-80 °C. IR (KBr, cm$^{-1}$): 3074, 2956, 1724, 1671, 1599, 1298, 1147, 931, 823 and 756. $^1$H-NMR (200MHz, CDCl$_3$); 8.02 (d, J=1.8Hz, 1H aromatic), 7.74-8.03 (m, 2H, aromatic), 7.60-7.63 (dd, J=1.8Hz, 8.1Hz, 1H, aromatic), 7.26-7.34 (m, 1H), 7.09-7.17 (m, 2H, aromatic) and 3.67 (s, 3H, COOCH$_3$). $^{13}$C-NMR (100MHz, CDCl$_3$): 52.45, 115.67, 128.96, 130.09, 130.65, 131.66, 131.76, 132.37, 133.22, 135.76, 139.52, 164.37, 164.97, 166.91, 194.27; MS (ES): m/z 293, [M+1]$^+$. 

**46:** Into a 250 ml, three-necked, RB flask was charged **45** (5.0 g, 0.017 mol), t-butanol (50ml) and sodium borohydride (3.0g, 0.08mol). The reaction mixture was heated to reflux temperature and methanol (10.0 ml) was added in 4 lots over a period of 8h. After maintaining for 2h at
reflux temperature after the last lot addition, reaction was found to be completed by TLC. The reaction mixture was quenched by adding acetic acid (4.0ml) and the solvents distilled off under vacuum. To the residue, water (50.0ml) was added and the product extracted into methylene chloride (3x50.0ml). Methylene chloride layer dried over sodium sulfate, and the solvent distilled off to get 4.0g (88% yield) of crude dihydroxy compound, 46 as syrup. This was directly used in next step after checking its IR. ¹H-NMR (400 MHz, CDCl₃): 7.01-7.34 (m, 7H, aromatic), 5.98 (s, 1H, -CH-OH), 4.27-4.50 (m, 2H, -CH₂-OH), and 3.72 (br, s, 2H, -CHOH-, CH₂OH). ¹³C-NMR (400MHz, CDCl₃): 62.3, 74, 116.3, 127.4, 128.5, 129.6, 130.3, 132.2, 139.2, 142.6, 160; MS (ES): m/z 268.5, [M+2]⁺.

47: Into a 250 ml, three-necked, RB flask was charged benzene (25ml), 2.4g (0.01mol) of 46, and p-toluenesulfonic acid (0.63g, 0.004mol). The reaction mixture was heated to reflux under azeotropic conditions using Dean Stark apparatus to remove water formed in the reaction. After refluxing for 2h, reaction was found to be completed by TLC. The reaction mixture was cooled to room temperature. Water (100ml) was added to the reaction mixture and the product extracted into benzene. Benzene layer was washed with 5% sodium bicarbonate, water (50ml) and dried over sodium sulfate. Solvent was removed on rotavapour to get 2.0g (89%) of 47 as oil. Purity by HPLC was found to be >96%. Chromatographic purification over a column of silica gel gave the title
compound as pure product. IR (neat, cm$^{-1}$): 3072, 2923, 2855, 1605, 1509, 1476, 1419, 1341, 1225, 1156, 1039, 1015, 828, 813, 782 and 699. $^1$H-NMR (400MHz, CDCl$_3$): 7.20-7.29 (m, 4H, aromatic), 6.09-7.06 (m, 3H, aromatic), 5.30 (s, 1H, -CHO-) and 5.20 (dd, J=1.8Hz, 12.8Hz and 28.6Hz, 2H, -CH$_2$O-). $^{13}$C-NMR (400MHz, CDCl$_3$): 72.59, 85.13, 116.3, 127.4, 128.7, 129.4, 129.8, 131.9, 140.4, 141.2, 142.2, 160.6; MS (ES): m/z 248 [M]$^+$. 

**41**: Into a 250ml three-necked RB flask was charged nickel (II) chloride (0.031g, 0.003mol), triphenyl phosphine (0.25g, 0.0012mol), acetonitrile (25ml). The reaction mixture was heated to reflux temperature and treated with 0.2g of zinc powder. After stirring for 30min at room temperature, a solution of 47 (1.5g, 0.006mol) in acetonitrile (25ml) was added to the reaction mixture. After stirring for 30min at RT, potassium cyanide (0.22g, 0.003mol) was added to the reaction mixture and heated the contents to reflux temperature. After maintaining for 8 h at reflux, reaction mixture was diluted with di-isopropyl ether (200ml) and filtered on hyflow bed. The filtrate was distilled off on rotavapour and the residue chromatographed over a silica gel column to get (86%) of 41 as off white crystalline solid. Melting range: 94-5 °C. HPLC purity of this material was found to be 95% with respect to the compound prepared by the known process. $^1$H-NMR (400MHz, CDCl$_3$): 5.19-5.36 (dd, 2H), 6.16 (bs, 1H), 7.04-7.6(m, complex, 7H); $^{13}$C-NMR (400MHz, CDCl$_3$): δ 72.41, 85.19,
Into a 250ml three-necked RB flask was charged DMSO (90ml), NaH (2.1g, 60% dispersion in paraffin oil) under nitrogen atmosphere. A solution of 41 (9.6g) in DMSO (15ml) was added to the reaction mixture. After stirring for 10min at room temperature, a solution of 3-dimethylaminopropylchloride (5.3 g) in DMSO (2.5ml) was added to the reaction mixture and the contents were heated to 40 °C for 50min. The reaction mixture was poured into ice-cold water and extracted with ether (2x20ml). The ether layer was extracted with 10% aq acetic acid. The aq. acetic acid layer was neutralized with aq. ammonia and the liberated citalopram base is extracted into isopropyl ether. The extracts were dried and evaporated under vacuum to get residue as an oil product (5.6g) of 40. The residue was crystallized from isopropyl ether to get crystalline citalopram base. \(^1\)H-NMR (400MHz, CDCl\(_3\)): 1.30-1.33 (m, 1H), 1.43-1.46 (m, 1H), 2.13-2.15 (bs, 6H), 2.16-2.24 (m, 4H), 5.13-5.21 (q, 2H), 6.98-7.0 (m, 2H), 7.37-7.44 (m, 3H), 7.5 (bs, 1H), 7.5-7.6 (m, 1H). \(^13\)C-NMR (400MHz, CDCl\(_3\)): δ 22.0, 38.76, 45.20, 59.25, 71.11, 90.93, 111.46, 114.98, 115.19, 118.47, 122.58, 125.01, 126.54, 126.62, 131.63, 139.45, 140.14, 149.30, 160.57, 163.02. MS (ES): m/z 325[M+1]^+. 
Section-B

CITALOPRAM ANALOGUES CONTAINING TETRAZOLES

3B.1 INTRODUCTION

This section describes the synthesis of novel isobenzofuran derivatives containing tetrazole moiety developed from 5-cyanophthalide. The synthesized compounds are analogues of citalopram (1-[3-(dimethylamino)propyl]-1-(4-flurophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile).

3B.2 LITERATURE SURVEY

Tetrazole derivatives possess a unique physico-chemical, chemical, biological and other properties making them promising entities for fundamental studies and for a wide range of applications. For the last 10-12 years, compounds of this class find new applications in medicine, biochemistry, agriculture, photography and other fields [129]. The 1,5-disubstituted tetrazole ring is very important for cis-amide bonds and a valuable tool in the design of peptidic receptor probes [130-134]. Tetrazoles are an increasingly popular functionality [135], often used as metabolically stable surrogates for a carboxylic acid group [136]. They are treated as precursors to a variety of nitrogen-containing heterocycles [137] and act as convenient lipophilic spacers in pharmaceuticals. Wadsworth and co-workers [138] reported the synthesis and anti-muscarine activity of quinaldin-3-yl tetrazole derivatives (49). It was also
reported that the compound (50) was identified as leukothiene [139] (LT) receptor model and listed for inhibition of LTD4.

![Chemical structures](49)\(\text{(49)}\)\(\text{(50)}\)

**Preparations of tetrazoles: Literature survey:**

The most convenient method for preparation of 5-substituted 1-H-tetrazole (53) is the reaction of nitriles (51) with azide ion (52) [140] Scheme 3.4.

![Reaction scheme](51)\(\text{(51)}\) + \(\text{M+N}_3^-\) → \(\text{R-CN} \text{N-N-H}\)\(\text{(52)}\)\(\text{(53)}\)

**Scheme 3.4**

The Schmidt reaction [141] is another general route for the preparation of 1,5-disubstituted tetrazoles (55) from ketones (54) Scheme 3.5.

![Reaction scheme](54)\(\text{(54)}\) \(\text{R}_1\text{O}=\text{N}^+\text{R}_2\) → \(\text{R}_1\text{R}_2\text{N}_3\) → \(\text{R}_1\text{R}_2\text{N}_3\) → \(\text{R}_1\text{N-N-R}_2\)\(\text{(55)}\)

**Scheme 3.5**
Butler et al. [142,143] reported that the synthesis of 1,5-disubstituted tetrazoles culminate in the 1,5-heterocyclation of imino azide species (56)

Scheme 3.6.

\[
\begin{align*}
\text{R}_1\text{N} & \text{NR}_2 \xrightarrow{+ \text{N}_3^-} \text{R}_1\text{N} & \text{NR}_2 \\
\text{X} & \xrightarrow{-\text{X}^-} \text{N}_3\text{NR}_2 & \text{N} = \text{N} \\
\text{(56)} & \text{(55)}
\end{align*}
\]

Scheme 3.6

Ding and weber [144] have improved the synthesis of 1,5-substituted tetrazoles (57) under solid liquid phase-transfer catalysed reaction conditions (Scheme 3.7).

\[
\begin{align*}
\text{C}_{6}\text{H}_5\text{N} & \text{C:N} \xrightarrow{\text{NaN}_3} \text{C}_{6}\text{H}_5\text{N} & \text{O} \\
\text{n-Bn}_4\text{NCl} & \text{(57)}
\end{align*}
\]

Scheme 3.7

A fused tetrazole (58) was synthesized by sharples and Demko [145] via intramolecular [2+3] cyclo addition reaction of compounds containing both nitrile and azide moieties Scheme 3.8.

\[
\begin{align*}
\text{N} & \xrightarrow{[\text{2+3}]} \text{N} & \text{N} \xrightarrow{z} \text{N} \\
\text{(58)}
\end{align*}
\]

Scheme 3.8
3B.3 PRESENT WORK

The present work comprises the synthesis and characterization of a series of tetrazole derivatives as novel analogs of Citalopram. The novel analogues of citalopram of present work consists of tetrazole derivatives having functional variants in the aryl fragment other than the phthalane ring. The novel analogues of citalopram are designated as 63 and their tetrazole derivatives are designated as 64 and the synthetic scheme for the preparation of these compounds is depicted in Scheme 3.9.

Scheme 3.9
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3B.4 RESULTS AND DISCUSSION

Process for the preparation of the key intermediate 5-cyanophthalalane derivative 62 starts from 5-cyanophthalide (59). Compound 59 was reacted with 4-methyl-phenylmagnesiumbromide (freshly prepared from 4-methyl-phenylbromide and Mg turnings in THF medium at reflux) in THF medium at –10°C to –15°C afforded 4-cyano-2-Hydroxymethyl benzophenone derivative 60 (ie.60, R=4-Me C₆H₄), which was not isolated. The product 60 was however characterized by spectral data (IR). Thus its IR (neat) (Fig. 3.1) showed a very sharp band of strong
intensity in the region 1759 cm\(^{-1}\) assignable to \(-\text{C}=\text{O}\) and a sharp peak at 2232 cm\(^{-1}\) indicating the presence of \(-\text{CN}\) group. Reduction of this benzophenone derivative 60 with sodiumborohydride at room temperature gave the 1-\((4\text{-cyano-2-hydroxymethylphenyl})-1\text{-}(4\text{-methylphenyl})\text{methanol}\) (61) (Scheme 3.10).

![Scheme 3.10](image)

The IR spectrum of 61 (ie.61, \(R=4\text{-Me C}_6\text{H}_4\)) (Fig. 3.2) showed a very broad band of strong intensity in the region 3385 cm\(^{-1}\) assignable to \(-\text{OH}\) and a strong sharp peak at 2232 cm\(^{-1}\) indicating the presence of nitrile group, the absence of 1759 cm\(^{-1}\) indicated the completion of reduction of the carbonyl function to hydroxy moiety.

Dehydrating the dihydroxy compound 1-\((4\text{-cyano-2-hydroxymethylphenyl})-1\text{-}(4\text{-methylphenyl})\text{methanol}\) (61) with \(p\)-TsOH in toluene under azeotropic conditions afforded the 1-\((4\text{-methylphenyl})\text{-1,3-dihydroisobenzofuran-5-carbonitrile}\) (62) (ie.28, \(R=4\text{-Me C}_6\text{H}_4\)) (Scheme 3.11), which was characterized on the basis of its spectral data.
The absence of the peak at 3385 cm\(^{-1}\) indicated the absence of hydroxy group in the compound and the band at 2226 cm\(^{-1}\) indicated in the IR spectrum (Fig 3.3) the presence of nitrile functionality. Its \(^1\)H NMR (Fig 3.4) showed signal at δ 2.33 (s, 3H) assignable to methyl group, signal at δ 5.12-5.27 as double doublet that is assignable to –CH\(_2\)-in phthalane ring, singlet at δ 6.45 is assignable to –CH-O in phthalane ring. Signals in the region δ 7.05 to 7.9 represent aromatic protons. Its \(^{13}\)C NMR (Fig 3.5) showed a signal at δ 18.8 assignable to CH\(_3\) group. Signals at δ 71 and 82 are assignable to aliphatic carbons (-CH\(_2\)- and >CH-) present in phthalane ring and signal at δ 146 is assignable to nitrile carbon and aromatic carbons are showed in the region δ110-140.

5-cyano-isobenzofuran derivative 62 (ie.62, R= 4-Me C\(_6\)H\(_4\)) was reacted with 3-N,N-dimethyl aminopropylchloride (freshly isolated from neutralization of its HCl salt form) in the presence of NaH in DMSO to afford citalopram analogues 1-[3-(dimethylamino)propyl-1-(4-methyl phenyl)-1,3-dihydro-5-isobenzofurancarbonitrile (63i) (ie.63, R = 4-Me C\(_6\)H\(_4\), R\(_1\)=CH\(_3\), R\(_2\)=CH\(_3\)) (Scheme 3.12), which were characterized on the basis of spectral data.
Thus its IR (Fig 3.6) showed peak at 2229 cm\(^{-1}\) assignable to nitrile group. Its \(^1\)H NMR (Fig 3.7) exhibited signal at 62.13 (s, 6H) assignable to two methyl protons and signal at 5.13-5.21 (q, 2H) assignable to –CH\(_2\)- in phthalane ring protons. Aromatic and aliphatic protons are observed at appropriate region.

The citalopram analogues having nitrile group 63e (ie.63, R= 4-F \(\text{C}_6\text{H}_4\), R1=CH\(_3\), R2=CH\(_3\)) was treated with sodium azide, ammonium chloride in the presence of DMF at 130-140 \(^\circ\)C gave the tetrazole derivative of 64e (ie.64, R=4-F \(\text{C}_6\text{H}_4\), R1=CH\(_3\), R2=CH\(_3\)) (Scheme 3.13), which have characterized on the basis of spectral data. Thus, its IR (Fig 3.8) showed mainly absence of nitrile peak at 2200 cm\(^{-1}\) and presence of NH at 3406 cm\(^{-1}\). Its \(^1\)H NMR equals to compound 63 (some times NH protons are disappeared in proton NMR). Fig (3.9) showed signal at 6 2.6 (s, 6H) representing two methyl protons, signal at 5.13-5.23 (q, 2H) representing –CH\(_2\)- protons in phthalane ring. Aromatic protons are observed in the region 7.1-7.9.

\[
\begin{align*}
\text{(63)} & \quad \text{\overset{\text{NaN_3, NH_4Cl,}}{\overset{\text{DMF}}{\longrightarrow}}} \quad \text{\text{(64)}}
\end{align*}
\]

Scheme 3.13

The above Schemes 3.10 - 3.13 was found to be a general one and has been found to occur with other derivatives of 64 [63,64 (a to x)]. The
structures of the products **61, 62, 63, and 64** thus obtained were confirmed on the basis of spectral data (Experimental Section).

### 3B.5 EXPERIMENTAL SECTION

**General procedure for the preparation of 61:**

To a stirred solution of **59** (0.05mole) in THF (50ml) was added freshly prepared arylmagnesiumbromide (0.06mole) in THF [from arylbromide and magnesium turninigs in THF at reflux] at –10 to –15 °C. The reaction mass was maintained at –10 to –15 °C for 1h and the reaction was monitored by TLC. After the completion of the reaction, the reaction mass temperature was raised to 0-5 °C. To the reaction mass was then added sodiumborohydride and allowed the reaction mass temperature to 25 °C during 5-6 h. The reaction mass was quenched with water and extracted with toluene. The solvent was distilled off completely under vacuum to get the product as syrupy liquid corresponding dihydroxy compound **61**.

**61a** (i.e., **61**, R = C₆H₅) Yield 9.75g (82%). IR (neat, cm⁻¹): 3395, 2231, 1604, 1493, 1451, 1244, 1035, 732, 700.

**61b** (i.e., **61**, R = 4-F C₆H₄) Yield 11.4g (89%). IR (neat, cm⁻¹): 3389, 2237, 1597, 1503, 1455, 1029, 821, 740, 593, 551, 529.

**61c** (i.e., **61**, R = 2-CH₃ C₆H₄) Yield 10.45g (83%). IR (neat, cm⁻¹): 3394, 2921, 2231, 1604, 1488, 1460, 1021, 896, 851, 730, 695, 465.

**61d** (i.e., **61**, R = 4-CH₃ C₆H₄) Yield 8.9g (71%).
61e) (i.e., 61, R = 4-OCH₃ C₆H₄) Yield 10.5g (78%). IR (neat, cm⁻¹): 3406, 2231, 1609, 1511, 1251, 1174, 1031, 833, 733, 599.

61f) (i.e., 61, R = C₁₀H₇) Yield 14.7g (86%). IR (neat, cm⁻¹): 3382, 2231, 1594, 1509, 1389, 1022, 780, 481.

**General procedure for the preparation of 62:** The dihydroxy compound 61 (0.03mole), toluene (150ml) and p-toluenesulfonic acid (0.012mol) were charged into a four necked RB flask. The reaction mixture was heated to reflux under azeotropic conditions using Dean Stark apparatus to remove water formed in the reaction. After refluxing for 2-3h, reaction was found to be completed (TLC). The reaction mixture was cooled to 25 °C and water (100ml) was added and the product was extracted into toluene. The toluene layer was washed with 5% sodium bicarbonate followed by water and dried over sodium sulfate. The solvent was removed on rotavapour to get compound 62.

62a) (i.e., 62, R = C₆H₅) Yield 2.14g (97%). IR (neat, cm⁻¹): 2870, 2226, 1454, 1423, 1340, 1274, 1233, 1020, 901, 759, 696, 625, 531, 448.

**¹H NMR (CDCl₃):** 5.21-5.38 (dd, 2H, -CH₂-O), 6.18 (s, 1H, >CH-O), 7.29-7.38 (m, 5H, aromatic H), 7.53 (d, J=7.6, 1H, aromatic H), 7.59 (s, 1H, aromatic H).

**¹³C NMR δ:** 72.53, 85.90, 111.53, 118.63, 123.15, 124.89, 126.73, 128.44, 128.66, 131.66, 140.27, 140.60, 147.09.
62b) (i.e., 62, R = 4-F C₆H₄) Yield 2.21g (93%). Melting range: 94-5 °C; IR (KBr, cm⁻¹): 2869, 2226, 1601, 1509, 1423, 1222, 1048, 1030, 820, 590, 554, 532.

¹H-NMR(CDCl₃) δ: 5.19-5.36(dd, 2H, -CH₂O-), 6.16 (s, 1H, >CHO-), 7.04-7.11(m complex, 3H, aromatic H), 7.25-7.29 (m complex, 2H, aromatic H), 7.54-7.60 (m, 2H, aromatic H).

62c) (i.e., 62, R = 2-CH₃ C₆H₄) Yield 2.38g (85%). m.p: 119.9 °C; IR (KBr, cm⁻¹): 3062, 2233, 1486, 1466, 1351, 1039, 921, 812, 753, 622, 581, 463.

¹H NMR (DMSO d₆) δ : 2.34(s, 3H, -CH₃), 512-5.27 (dd, 2H, -CH₂O-), 6.45 (s, 1H, >CH-O), 7.05-7.23 (m complex, 5H, aromatic), 7.72 (d, J=7.6, 1H, aromatic), 7.90 (s, 1H, aromatic).

¹³C NMR δ: 18.81, 71.76, 82.79, 110.42, 118.86, 123.14, 125.50, 126.01, 127.54, 128.14, 130.72, 131.83, 135.82, 138.73, 140.85, 146.85.

62d) (i.e., 62, R = 4-CH₃ C₆H₄) Yield 2.44g (87%). m.p: 89.1 °C; IR (KBr, cm⁻¹): 2232, 1759, 1465, 1354, 1276, 1205, 1053, 1001, 852, 774, 680, 438.

62e) (i.e., 62, R = 4-OCH₃ C₆H₄) Yield 2.7g (90%). m.p: 65.5 °C IR (KBr, cm⁻¹): 2224, 1611, 1511, 1242, 1175, 1057, 1028, 807, 591, 529.
$^{1}$H-NMR(DMSO d$_6$) δ: 3.74 (s, 3H, -OCH$_3$), 5.101-5.30 (dd, 2H, -CH$_2$-O), 6.18 (s, 1H, -CH-O), 6.92 (d, J=8.8, 2H, aromatic H), 7.19-7.25 (q, 3H, aromatic H), 7.71 (d, J=7.6, 1H, aromatic H), 7.88 (s, 1H, aromatic H).

$^{13}$C NMR (DMSO d$_6$) δ: 55.06, 71.87, 84.54, 110.37, 113.91, 118.89, 123.28, 125.52, 128.05, 131.78, 133.45, 140.33, 147.56, 159.13.

62f (i.e., 62, R = C$_{10}$H$_7$) Yield:3.01g (93%). Melting range: 140-1 °C; IR (KBr, cm$^{-1}$): 2853, 2228, 1613, 1509, 1066, 1012, 896, 822, 796, 773. $^{1}$H NMR (DMSO d$_6$): 5.23-5.38 (dd, 2H, -CH$_2$-O), 7.03 (s, 1H), 7.19 (d, J=7.6, 1H, aromatic), 7.39 (d, J=6.8), 7.48 (t, 1H, aromatic), 7.58 (m, 2H, aromatic), 7.69 (d, J=7.6, 1H, aromatic), 7.91-8.00 (m, 3H, aromatic), 8.2 (bs, 1H).

$^{13}$C NMR (DMSO d$_6$): 71.85, 82.40, 110.54, 118.82, 123.11, 123.73, 124.85, 125.40, 125.69, 125.89, 126.45, 128.64, 128.71, 130.50, 131.82, 133.60, 136.36, 140.688, 147.02.

**General procedure for the preparation of 63:**

To a stirred a solution of DMSO (70ml) in NaH (0.03mole) was added compound 62 (0.025mole) in DMSO (20ml) under nitrogen atmosphere. Stirred for 10min at room temperature. To the reaction mass was added a solution of 3-N,N-disubstitutedaminopropyl chloride (0.031mole) in DMSO. The temperature of the reaction mass was raised to 40 °C over 50 min. Aliquots were followed by TLC. The reaction mixture was poured
into ice cold water and extracted with ether. The ether layer was extracted with 10% aq acetic acid and the aq. acetic acid layer was neutralized with aq. ammonia. The liberated product (63) as base is extracted into isopropyl ether. The combined extracts were dried over Na$_2$SO$_4$ and evaporated under vacuum to get residue as oily products (63). The residue was crystallized from isopropyl ether to get crystalline compound 63.

63a) (i.e., 63, R = C$_6$H$_5$, R$_1$, R$_2$ = CH$_3$); Yield 2.01g (69%). IR (KBr, cm$^{-1}$): 3054, 2958, 2852, 2706, 2228, 1471, 1446, 1198, 1027, 774, 702, 466.

63b) (i.e., 63, R = C$_6$H$_5$, R$_1$, R$_2$ = C$_2$H$_5$); Yield 2.08g (65%). IR (neat, cm$^{-1}$): 3051, 2922, 2813, 1709, 2233, 1468, 1200, 1030, 790, 704, 469.

63c) (i.e., 63, R = C$_6$H$_5$, R$_1$, R$_2$ = piperidine); Yield 2.12 (61%). MS (ES): m/z: 347 [M-2]

63d) (i.e., 63, R = C$_6$H$_5$, R$_1$, R$_2$ = morpholine); Yield 2.42g (70%). IR (neat, cm$^{-1}$): MS (ES): m/z: 349 [M+1]

63e) (i.e., 63, R = 4-F C$_6$H$_4$, R$_1$, R$_2$ = CH$_3$); Yield 1.95g (63%). IR (KBr, cm$^{-1}$): 2980, 2941, 2847, 2813, 2756, 2230, 1595, 1504, 1456, 1264, 1221, 1157, 1061, 1025, 848, 729, 597.

$^1$H NMR: 1.30-1.33 (m complex, 1H, aliphatic), 1.43-1.46 (m complex, 1H, aliphatic), 2.13 (s, 6H, 2xCH$_3$), 2.15-2.20 (m, 1H, aliphatic), 2.20-
2.24 (m, 3H, aliphatic), 5.13-5.21 (q, 2H, -CH₂O-), 6.98-7.02 (t, 2H, aromatic), 7.37-7.60 (m, 5H, aromatic).

$^{13}$C NMR (CDCl₃): 22.01, 38.76, 45.20, 59.25, 71.11, 90.93, 111.46, 114.98, 115.19, 118.47, 122.58, 125.01, 126.54, 126.62, 131.63, 139.45, 140.14, 149.30, 160.57, 163.02.

63f) (i.e., 63, R = 4-F C₆H₄, R₁, R₂ = C₂H₅); Yield 2.0g (59%); m.p: (oxalate): 142 °C

63g) (i.e., 63, R = 4-F C₆H₄, R₁, R₂ = piperidine); Yield 2.49g (68%); m.p: 132.4 °C

63h) (i.e., 63, R = 4-F C₆H₄, R₁, R₂ = morpholine); Yield 2.43g (67%); m.p: (oxalate): 139.4 °C; IR (neat, cm⁻¹): 2954, 2854, 2810, 2229, 1600, 1507, 1457, 1226, 1117, 1069, 1033, 838, 598.

63i) (i.e., 63, R = 4-CH₃ C₆H₄ , R₁,R₂ = CH₃); Yield 2.2g (72%); IR (KBr, cm⁻¹): 2948, 2807, 2773, 2229,1510,1463, 1270, 1035, 815, 598.

63j) (i.e., 63, R = 4-CH₃ C₆H₄ , R₁,R₂ = C₂H₅); Yield 2.53g (76%). As syrup. m.p (oxalate): 151.4 °C

63k) (i.e., 63, R = 4-CH₃ C₆H₄ , R₁,R₂ = piperidine); Yield 2.64g (73%).

63l) (i.e., 63, R = 4-CH₃ C₆H₄ , R₁,R₂ = morpholine); Yield 2.84g (79%).

63m) (i.e., 63, R = 2-CH₃ C₆H₄ , R₁,R₂ = CH₃); Yield 2.23g (73%).
63n) (i.e., 63, R = 2-CH$_3$ C$_6$H$_4$, R$_1$, R$_2$ = C$_2$H$_5$); Yield 2.5g (75%). As syrup. m.p (oxalate): 133.4 °C

63o) (i.e., 63, R = 2-CH$_3$ C$_6$H$_4$, R$_1$, R$_2$ = piperidine); Yield 2.53g (70%); m.p: 111.3 °C

63p) (i.e., 63, R = 4-CH$_3$ C$_6$H$_4$, R$_1$, R$_2$ = morpholine); Yield 2.66g (74%).

63q) (i.e., 63, R = 4-OMe C$_6$H$_4$, R$_1$, R$_2$ = CH$_3$); Yield 2.15g (67%); m.p: 168 °C; IR (KBr, cm$^{-1}$): 2949, 2228, 1610, 1510, 1464, 1250, 1176, 1033, 830, 801.

63r) (i.e., 63, R = 4-OMe C$_6$H$_4$, R$_1$, R$_2$ = C$_2$H$_5$); Yield 2.24g (64%); m.p: (oxalate): 139.7 °C

63s) (i.e., 63, R = 4-OMe C$_6$H$_4$, R$_1$, R$_2$ = piperidine); Yield 2.6g (69%); m.p: (oxalate): 99.5 °C

63t) (i.e., 63, R = 4-OMe C$_6$H$_4$, R$_1$, R$_2$ = morpholine); Yield 2.44g (65%). IR (neat, cm$^{-1}$): 2957, 2854, 2811, 2229, 1509, 1458, 1251, 1117, 1034; m.p: (oxalate): 163.6 °C

63u) (i.e., 63, R = C$_{10}$H$_7$, R$_1$, R$_2$ = CH$_3$); Yield 2.46g (72%). Melting range: 129-31 °C. IR (KBr, cm$^{-1}$): 3340, 2945, 2860, 2228, 1654, 1463, 1377, 1246, 1038, 800, 779, 731, 695; $^1$H NMR: 3.06-3.48(m, 10 H, aliphatic), 4.9 (s, 1H, aliphatic); 5.2-5.4 (m, 2H, aliphatic), 7.36-7.96 (m complex, 10H, aromatic); MS (ES): m/z: 357 [M+1]$^+$. 
63v) (i.e., 63, R = C_{10}H_{7}, R_1, R_2 = C_2H_5); Yield 2.51g (68%). Melting range: 99-101 °C

63w) (i.e., 63, R = C_{10}H_{7}, R_1, R_2 = piperidine); Yield 2.82g (71%). Melting range: 121-23 °C

63x) (i.e., 63, R = C_{10}H_{7}, R_1, R_2 = morpholine); Yield 3.0g (76%); IR (neat, cm^{-1}): 2954, 2854, 2811, 1655, 1116, 861, 781. ^1H NMR: 2.37 (bs, 8H, morpholine Hs), 3.55-3.58 (m, 6H, aliphatic Hs), 6.9-8.2 (m complex, 10H, aromatic Hs); MS (ES): m/z: 400[M+2]+.

**General procedure for the preparation of tetrazole derivative (64):**

To a stirred solution of 63 (0.01mole) in DMF (30.0ml) was added Sodium azide (NaN_3, 0.03mole) and ammonium chloride (NH_4Cl, 0.016mole), the temperature of the reaction mass was raised to 130 °C. The reaction mass temperature was maintained at 130-140 °C for 4-5h and the reaction course was monitored by TLC. After completion of the reaction, the reaction mass was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and the obtained residue was quenched with water (100ml). The slurry obtained was filtered and washed with water. The material was dried at 60-65 °C to get the tetrazole derivative 64.

64a) (i.e., 64, R = C_6H_5, R_1, R_2 = CH_3); Yield 2.8g (80%). Purity (HPLC): 96%
64b) (i.e., 64, R = C₆H₅, R₁, R₂ = C₂H₅); Yield 2.95g (76%). Purity (HPLC): 93%

64c) (i.e., 64, R = C₆H₅, R₁, R₂ = piperidine); Yield 3.5g (83%). Purity (HPLC): 91%. IR (neat, cm⁻¹): 3043, 2998, 2878, 2747, 2653, 1604, 1518.

64d) (i.e., 64, R = C₆H₅, R₁, R₂ = morpholine); Yield 3.27g (79%). Purity (HPLC): 95%

64e) (i.e., 64, R = 4-F C₆H₄, R₁, R₂ = CH₃); Yield 3.14g (83%). Purity (HPLC): 99.61%; m.p: 213 °C;

IR (KBr, cm⁻¹): 3051, 2980, 2891, 2808, 2729, 2635, 1600, 1505, 1422, 1213, 1159, 1030, 839, 590, 532.

¹H-NMR(DMSO-d₆) δ: 1.42-1.53 (m complex, 2H, -CH₂-), 2.188 (t, 2H, -CH₂-), 2.60 (s, 6H, 2xCH₃), 2.93 (t, 2H, -CH₂-), 7.16 (t, 2H, aromatic H), 7.51 (d, J=8, 1H, aromatic H), 7.58-7.62 (q, 2H, aromatic H), 7.87 (1H, aromatic H), 7.93 (d, J=8 aromatic H).

¹³C NMR (DMSO d₆) δ: 19.62, 37.57, 42.48, 56.95, 71.54, 90.00, 114.88, 115.09, 118.68, 121.89, 125.58, 126.84, 126.92, 131.42, 138.90, 141.36, 142.80, 159.93, 160.14, 162.35.

64f) (i.e., 64, R = 4-F C₆H₄, R₁, R₂ = C₂H₅); Yield 2.8g (69%). Melting range: 210-11 °C; IR (KBr, cm⁻¹): 3058, 2983, 2901, 2812, 2731, 2642, 1604, 1509, 1422, 1213, 1159, 1030, 839, 590, 532.
64g) (i.e., 64, R = 4-F C₆H₄, R₁, R₂ = piperidine); Melting range: 198-99 °C; Yield 3.3g (76%).

64h) (i.e., 64, R = 4-F C₆H₄, R₁, R₂ = morpholine); Yield 3.37g (78%). Purity (HPLC): 91%;

IR (KBr, cm⁻¹): 3328, 2958, 2918, 1666, 1506, 1393, 1264, 1224, 1160, 1012, 838, 592.

64i) (ie. 64 R = 4-CH₃ C₆H₄; R₁,R₂ = CH₃) Yield 3.26g (87%); m.p: 156 °C; IR (neat, cm⁻¹): 3407, 2953, 1654, 1570, 1420, 1031, 815, 765.

64j) (ie. 64 R = 4-CH₃ C₆H₄; R₁,R₂ = C₂H₅); Yield 3.1g (91%). Purity (HPLC): 89%; m.p: 179 °C

64k) (ie. 64 R = 4-CH₃ C₆H₄; R₁,R₂ = piperidine); Yield 3.36g (78%); m.p: 206 °C

64l) (ie. 64 R = 4-CH₃ C₆H₄; R₁,R₂ = morpholine); Yield 3.73g (87%); m.p: 189 °C

64m) (ie. 64 R = 2-CH₃ C₆H₄; R₁,R₂ = CH₃) ; Yield 2.43g (65%); m.p: 203 °C

64n) (ie. 64 R = 2-CH₃ C₆H₄; R₁,R₂ = C₂H₅); Yield 3.1g (77%); m.p: 146 °C

64o) (ie. 64 R = 2-CH₃ C₆H₄; R₁,R₂ = piperidine); Yield 2.54g (59%); m.p: 203 °C
64p) (ie. 64 R = 2-CH₃ C₆H₄; R₁,R₂ = morpholine); Yield 2.91g (68%).

64q) (ie. 64 R = 4-OCH₃ C₆H₄; R₁,R₂ = CH₃); Yield 2.89g (74%). Purity (HPLC): 94%. Melting range: 199-200 °C.

64r) (ie. 64 R = 4-OCH₃ C₆H₄; R₁,R₂ = C₂H₅); Yield 3.18g (76%).

64s) (ie. 64 R = 4-OCH₃ C₆H₄; R₁,R₂ = piperidine); Yield 3.57g (80%).

64t) (ie. 64 R = 4-OCH₃ C₆H₄; R₁,R₂ = morpholine); Yield 2.9g (66%); m.p: 173 °C

64u) (i.e., 64, R = C₁₀H₇, R₁,R₂ = CH₃); Yield 3.2g (78%); m.p: 163 °C

64v) (i.e., 64, R = C₁₀H₇, R₁,R₂ = C₂H₅); Yield 3.16g (72%); m.p: 142 °C

64w) (i.e., 64, R = C₁₀H₇, R₁,R₂ = piperidine); Yield 2.94g (63%); m.p: 211°C

64x) (i.e., 64, R = C₁₀H₇, R₁,R₂ = morpholine); Yield 3.2g (69%); m.p: 200 °C.