Synthesis and Anticancer Molecular Docking Studies of Phenothiazine Derivatives

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Abstract: **Phenothiazine incorporated pyran derivatives are prepared by using N-alkyl-phenothiazine-3-carbaldehydes under ultrasonic/reflux condition by one step synthesis. Improvement in yield is observed when the reaction is carried out under ultrasonic condition compared to classical synthetic method. The synthesized compounds are characterized by using FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Anticancer docking studies are carried out for the synthesized compounds and different cancer target proteins namely lung cancer, colon cancer, breast cancer and pancreatic cancer and the results are reported.**

***Index Terms*— Phenothiazine, Pyran, Anticancer docking and Ultrasonic Irradiation.**

I. Introduction

Hetero aromatic compound containing Nitrogen and Sulfur atom in their backbone is being pursued as a thrust area of research in Chemistry due to its potential applications of these derivatives are used in pharma field. The combination of two or more pharmacophores in one molecule is an idea involved in designing of new biologically active chemical compound including natural alkaloids. Phenothiazine, a hetero aromatic tricyclic compound containing nitrogen and sulfur hetero atom in their ring has been well known for a period of hundred years. The first parent compound of unsubstituted phenothiazine was synthesized in 1883 by a synthetic chemist Bernthsen.

These derivatives were used in treatment of psychopathy for the first time and to get better results. Phenothiazine is a heterocyclic compound of possess lots of pharmaceutical applications such as antifungal [1], antibacterial [2-3], anti-inflammatory [4], anti-malarial [5], anti-psychotropic [6], antimicrobial [7], antitubercular [8-9] activities. It is reported that these derivatives have a few significant anticancer activities. These characteristics have generated a great interest in formulating and synthesizing new phenothiazine to investigate their anticancer activities. [10-11].

Phenothiazine derivatives also act as human cholinesterase inhibitors and on several occasions, these derivatives have been characterized as multidrug resistance (MDR) reversal agents [12-13]. The literature reports have shown that the anticancer activity of phenothiazine derivatives are determined by the substituents linked to Carbon-2 position of phenothiazine ring, extent of alkyl group connecting nitrogen atom attached at position (N-10) of the cyclic ring, also the terminal N-H group present in ring [14-15]. This activity is firmly bound to the nature of substituents attached to phenothiazine ring rather than nature of side chain present [16].

Phenothiazine derivatives are used as neuroleptic drugs because they cross the blood brain barrier possess a strong affinity to lipid-rich tissues and lipid bilayers in neurons because of high degree of lipophilicity of phenothiazine derivatives [17]. In order to get active neuroleptic agents containing hydrogen atoms attached to nitrogen N-10 carbon-2 atoms are replaced by different groups attached at N-10 position such, as piperidin, aliphatic side chain and piperazine derivatives are given in literature [18]. They are also used as antipsychotic drugs because of their easily interaction with various receptors in central nervous system particularly which blocks the dopaminergic receptors [19].

A. Experimental procedure

General: All the chemicals were purchased from SD Fine Chemicals (India), Sisco Research Laboratory and Sigma-Aldrich (USA). Open capillary tubes were used to determine melting point of reported compound by a Buchi-530 melting point apparatus and the results were uncorrected. Perkin Elmer of FT-IR 1600 RX1 spectrophotometer used for recording FT-Infra Red spectra and potassium bromide used as discs. Proton and Carbon NMR were recorded using AV-400MHz and Bruker DPX 400 MHz spectrometer using deuterated chloroform and dimethyl sulphoxide a solvent by using an internal reference of Tetramethylsilane (TMS). Mass spectra were obtained using HR mass spectrometer and the compounds were dried under vacuum before analysis.

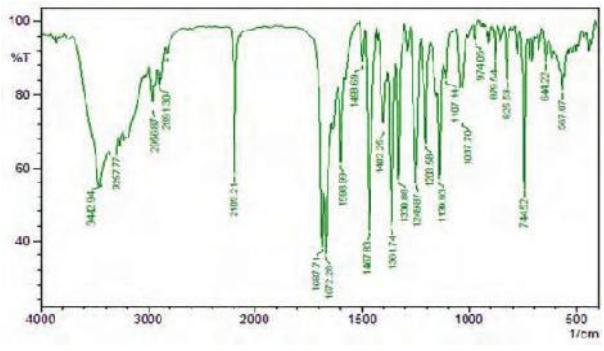


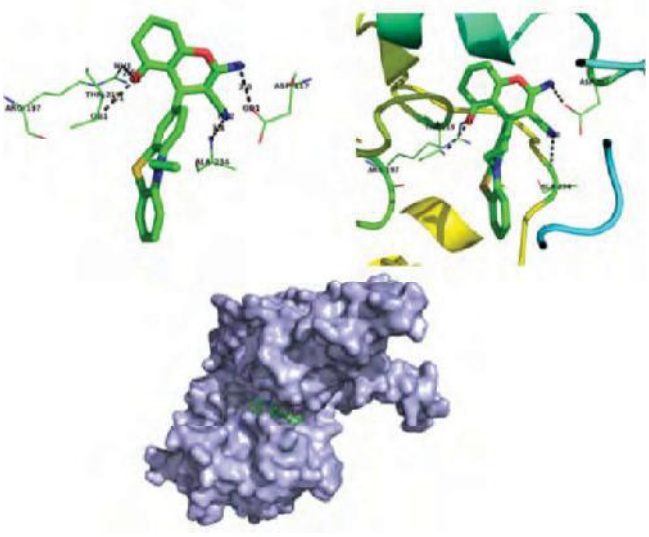
Figure 1. IR spectrum of compound **4a**.

B. Docking Analysis

Geometry optimized structures for all new synthesized derivatives were obtained using iGEMDOCK automated docking program. The 3-dimensional coordinates of different target cancer proteins were selected from protein

DOI:10.32377/cvrjst1221

data bank (PDB). The PDB id of pancreatic cancer (1SVC), lung cancer (1MOX), colon cancer (4FLH), and breast cancer (2DSQ) were chosen for docking study. The 3D structure of ligand molecules and therapeutic target proteins were executed through GEMDOCK graphical interface. Before starting docking analysis, the output path was set. The default parameters were included such as population size (n=200), number of solutions (s=10) and generation (g=70) to compute the feasible binding mechanism of ligand moiety for each target protein. The docking run was initiated through GEMDOCK scoring function.



Figur. 2. Active sites of Rho-associated protein kinase 1 of compound **4d** by docking studies.

The binding pose of every ligand molecule was observed after docking analysis and their affinity with target proteins were analyzed. Binding geometries are predicted by visual examination which contributes essentially further development of a new compound. The best binding pose and total energy of each ligand molecules were analyzed using post docking analysis and the details were saved in output folder. Pymol automated docking software used to analyzed and visualized the protein-ligand binding site [20-21].

Protocol for the preparation of compound 2(a-b):

In a 50 mL two-necked RB flask a mixture of Phenothiazine (1.0 mmol), ethyl or methyl iodide (3.0 mmol) and DMF (25 mL) were taken. The solution was heated in an oil bath at 75°C, potassium tert-butoxide was added (1.5 mmol) and stirred for 24 hours. Completion of reaction was observed through thin layer chromatography, and cooled to room temperature and transferred into ice cooled water, the reaction mixture was extracted using chloroform and dried using sodium sulphate salt to get crude product. The impure products were subjected to column chromatography using hexane/ethyl ethanoate (4.5:0.5) to get pure compound as a colourless solid (yield: 81-83%).

Spectral data of compound 2a: mp. 96-98 ºC; IR (KBr) νmax: 1130, 1280, 1327, 1384, 1440, 1483, 1570, 1591, 1788, 1899, 2826, 2937, 2981, 3053 3053, cm^{-1}; ^1H NMR (500 MHz, ppm, $CDCl_3$), δ_H 3.40 (s, 3H, CH_3), 6.84 (d, 2H, *J* 8.0 Hz, C_3, C_6- Ph-H), 6.95-7.28 (m, 6H, Ph-H); ^{13}C NMR (125.787 MHz, ppm, $CDCl_3$), δ_C 35.3, 114.0, 122.4, 123.4, 127.4, 145.8; Mass (EI): *m/z* [M^+] calculated for $C_{13}H_{11}NS$: 212.0612; obtained: 212.2038.

Spectral data of compound 2b: mp. 102-104ºC; IR (KBr) νmax: 1107, 1136, 1163, 1259, 1286, 1330, 1456, 1489, 1568, 2816, 2879, 2960, 3055 cm-1; 1H NMR (500 MHz, ppm, $CDCl_3$), δ_H 1.46 (t, 3H, *J* 5.4Hz, CH_3), 3.96 (d, 2H, *J* 5.7Hz, CH_2), 6.90-7.28 (m, 8H, Ph-H); ^{13}C NMR (125.787 MHz, ppm, $CDCl_3$), δ_C 13.7, 41.6, 115.1, 122.3, 124.5, 127.2, 127.4, 145.0; Mass (EI): m/z [M^+] calculated. for $C_{14}H_{13}NS$: 227.0769; obtained: 227.1685.

Protocol for the preparation of compound 3(a-b):

In a two necked RB flask a solution of $POCl_3$ (4.1 mmol) and freshly distilled dry DMF (4.7 mmol) was added drop wise at 0°C under inert or nitrogen atmospheric condition. The compound **2(a-b)** (1.0 mmol) dissolved in 40 mL of DCM and the solution was added dropwise to the $POCl_3$/DMF complex at 30°C. The reaction mixture was stirred at 80°C in an oil bath for 16 hours. Completion of the reaction was monitored through thin layer chromatography and then cooled to room temperature and poured it to 200 grams of ice crystals. The reaction mixture was neutralized by adding sodium bicarbonate solution, then extracted with chloroform, dried using sodium sulphate salt and the excess solvent was evaporated using vacuum distillation to get crude product. The impure product was subjected to column chromatography hexane/ethyl ethanoate solvent; to get pure yellow coloured compound, yield obtained was 79-82%.

Spectral data of compound 3a: mp. 106-108 ºC; IR (KBr) νmax: 1036, 1144, 1288, 1327, 1566, 1595, 1641, 1678, 2884, 3056 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$), δ_H 3.37 (s, 3H, CH_3), 7.00-7.74 (m, 7H, Ph-H), 9.79 (s, 1H, CHO); ^{13}C NMR (100.602 MHz, ppm, $CDCl_3$), δ_C 35.6, 114.5, 115.4, 121.1, 122.3, 123.5, 126.9, 127.2, 128.0, 130.4, 130.8, 143.6, 150.4, 190.6; Mass (EI): *m/z* [M+] calculated. for $C_{14}H_{11}NOS$: 241.0351; obtained: 241.0187.

Spectral data of compound 3b: mp. 109-111 ºC; IR (KBr) νmax: 1042, 1135, 1199, 1238, 1310, 1466, 1552, 1572, 1669, 2738, 2827, 2931, 2977, 3057 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$), δ_H 1.45 (d, 3H, *J* 6.4Hz, CH_3), 3.97 (d, 2H, *J* 6.4Hz, CH_2), 7.62 (d, 1H, *J* 8.4Hz, C_7-Ph-H), 7.56 (s, 1H, C8- Ph-H), 6.89-7.26 (m, 5H, Ph-H), 9.78 (s, 1H, CHO); ^{13}C NMR (100.602 MHz, ppm, $CDCl_3$), δ_C 12.8, 42.4, 114.4, 115.6, 123.2, 124.4, 127.6, 128.2, 130.2, 143.0, 150.3, 190.0; Mass (EI): *m/z* [M^+] calculated. for $C_{15}H_{13}NOS$: 255.1688; obtained: 255.1798.

Protocol for the preparation of compound 4(a-d).

Conventional method: In a 100 mL RB flask a mixture of compound **3a-b** (1.0 mmol), 1,3-diketone (1.0 mmol), malononitrile 1.0 mmol, K_3PO_4 (15 mmol%) and 20% ethanol (5 ml) were refluxed with constant stirring at 80°C in an oil bath for the period of time listed in Table. 1 (completion of reaction monitored by thin layer chromatography using hexane/ethyl ethanoate as eluent). The reaction mixture on cooling to get precipitated crude

DOI:10.32377/cvrjst1221

product and the solid obtained was filtered and recrystallization process was done by using ethanol solvent to get pure product.

Ultrasonic method: In a 25 mL beaker, a mixture of compound **3a-b** (1.0 mmol), 1,3-diketones 1.0 mmol, malononitrile (1.0 mmol) in the presence of K_3PO_4 catalyst 15 mmol% and 20% ethanol (5 ml) were sonicated using ultrasonic probe at frequency range of 22 kHz for the given periods of time listed in Table. Completion of the reaction observed by thin layer chromatography, the precipitate obtained was filtered using funnel and washed with large amount of water and purified by recrystallization process using ethanol solvent.

Spectral data of compound 4a: mp. 194-196 ºC; IR (KBr) νmax: 1037, 1103, 1203, 1249, 1330, 1361, 1402, 1467, 1598, 2189, 2891, 2958, 3257, 3442 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$), δ_H 0.97 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.37 (q, 2H, *J* 7.8Hz, CH_2), 3.27 (s, 3H, N-CH_3), 4.25 (s, 1H, CH) 4.49 (s, 2H, NH_2), 6.67 (d, 1H, *J* 7.6Hz, C_4- Ph-H), 2.14 (q, 2H, *J* 6.6Hz, CH_2), 6.71 (d, 1H, *J* 7.6Hz, C_2-Ar-H), 6.84-7.20 (m, 5H, Ph-H); ^{13}C NMR (100.602 MHz, ppm, $CDCl_3$), δ_C 27.8, 28.6, 32.2, 34.6, 35.2, 40.4, 50.7, 63.2, 113.7, 118.5, 122.3., 123.0, 123.5, 125.8, 127.2, 127.4, 137.5, 144.8, 145.7, 157.4, 161.3, 195.8; Mass (EI): *m/z* [M^+] calculated for $C_{25}H_{23}N_3O_2S$: 429.1511, obtained: 429.1514.

Spectral data of compound 4b: mp. 161-163 ºC; IR (KBr) νmax: 1035, 1215, 1251, 1385, 1485, 1606, 1680, 2191, 2933, 2958, 3170, 3255, 3352 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$), δ_H 0.99 (s, CH_3, 3H), 1.03 (s, CH_3, 3H), 1.32 (s, 3H, CH_3), 2.15 (s, 2H, CH_2), 2.37 (q, 2H, *J* 7.6Hz, CH_2), 3.82 (s, 2H, N-CH_2), 4.24 (s, 1H, CH), 4.45 (s, 2H, NH_2), 6.82-7.20 (m, 5H, Ph-H), 6.71 (d, 1H, *J* 7.3Hz, C_2-Ar-H), 6.75 (d, 1H, *J* 6.8Hz, C_2-Ar-H); ^{13}C NMR (100.602 MHz, ppm, $CDCl_3$), δ_C 12.9, 27.9, 28.6, 32.2, 34.5, 40.6, 41.7, 50.6, 63.4, 113.3, 14.8, 118.5, 122.1, 124.0, 126.1, 126.9, 127.1, 137.3, 144.1, 144.8, 157.3, 161.3, 195.8; Mass (EI): *m/z* [M^+] calculated for $C_{26}H_{25}N_3O_2S$: 443.1667, obtained: 443.1663.

Spectral data of compound 4c: mp. 150-152 ºC; IR (KBr) νmax: 1125, 1260, 1334, 1365, 1485, 1566, 1606, 1647, 1680, 2191, 2203, 2922, 3360 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$), δ_H 2.02-2.20 (m, CH_2, 2H), 2.28-2.35 (m, 2H, CH_2), 2.40-2.59 (m, CH_2, 2H), 3.32 (s, 3H, *N*-CH_3), 4.34 (s, 1H, CH), 4.52 (s, 2H, NH_2), 6.74 (d, 1H, *J* 7.2Hz, 4- Ph-H), 6.85 (d, 1H, *J* 7.5Hz, C_2- Ph-H), 6.91-7.23 (m, 6H, Ph-H); ^{13}C NMR (100.602 MHz, ppm, $CDCl_3$), δ_C 20.0, 26.8, 35.9, 36.7, 401., 60.5, 114.0, 114.5, 121.9, 122.3, 124.1, 124.3, 125.3, 125.8, 127.3, 127.8, 129.0, 131.6, 143..2, 151.2, 157.4, 194.2; Mass (EI): *m/z* [M^+] calculated for $C_{23}H_{19}N_3O_2S$: 401.1198, obtained: 401.1192.

Spectral data of compound 4d: mp. 143-145 ºC; IR (KBr) νmax: 1120, 1271, 1365, 1483, 1576, 1600, 1648, 1679, 2190, 2922, 3268, 3382 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$), δ_H 1.25 (s, CH_3, 3H), 1.46-1.55 (m, CH_2, 2H), 2.02 (m, 2H, CH_2), 2.57 (q, 2H, *J* 6.6Hz, CH_2), 3.48 (s, 2H, N-CH_2), 4.33 (s, 1H, CH), 4.50 (s, 2H, NH_2), 6.74 (d, 1H, *J* 8.1Hz, C_4- Ph-H), 6.82 (d, 1H, *J* 8.1Hz, C_2- Ph-H), 6.93-7.25 (m, 5H, Ph-H); ^{13}C NMR (100.602 MHz, ppm, $CDCl_3$), δ_C 13.1, 20.2, 27.1, 36.9, 41.8, 42.8, 59.8, 114.5, 114.9, 115.3, 124.2, 127.3, 127.6, 127.9, 129.4, 131.6, 144.2, 150.4, 157.5, 194.4; Mass (EI): *m/z* [M^+] calculated for $C_{24}H_{21}N_3O_2S$: 415.1534, obtained: 415.1530.

II. RESULTS AND DISCUSSION

Phenothiazine (1) was treated with methyl, ethyl iodide using potassium tertiary but-oxide catalyst and dry DMF used as a solvent and heated in an oil bath around 80 ºC for 24 hours to yield alkyl substituted phenothiazine **2a-b** (Scheme 1). The compound **2a** showed a singlet peak at δ 3.40 ppm in ^1H NMR spectrum of corresponds to methyl group which is an evidence for the compound **2a** formation. The disintegration of N-H band at 3420 cm^{-1} in IR spectra of **2a** supporting the formation of alkyl phenothiazine. The compound **2b** showed a quartet peak at δ 3.96 ppm and triplet peak at δ 1.47 ppm in ^1H NMR spectrum indicating the formation of CH_2 and CH_3 protons which is an evidence for compound **2b** formation. The compound **2b** showed peaks at δ 41.76 and 14.09 ppm in ^{13}C NMR spectrum indicated the presence of CH_3 and CH_2 carbons in compound **2b**.

TABLE I
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

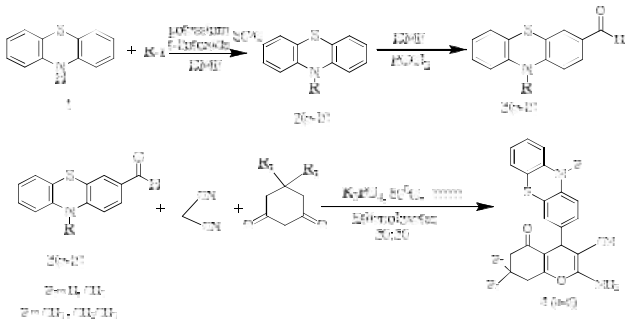
Compound	R	R_1	Reaction Time [a] (min)	Yield[a,b](%)	m.p. (°C)
4a	CH_3	CH_3	165/7	85/87	195-197
4b	CH_2-CH_3	CH_3	170/8	83/86	160-162
4c	CH_3	H	175/8	84/86	152-155
4d	CH_2-CH_3	H	180/9	81/83	145-147

[a]At reflux temperature/ ultrasonic irradiation; [b]Isolated yields

The compound **2a-b** on treatment with Vilsmeier Hack reaction to get compound **3a-b** with a yield of 78-80%. The compound **3a** and **3b** showed a singlet peak at δ 9.76 and 9.78 ppm observed in ^1H NMR spectra indicating the formation of aldehyde hydrogen and the peaks at δ 190.68 and 190.10 ppm in ^{13}C NMR spectra also confirming the presence of aldehyde carbon. The compound **3a** and **3b** showed the absorption peak at 1679 and 1665 cm^{-1} in IR spectra indicated the presence of aldehyde carbonyl group which is also an evidence for the formation of **3a** and **3b**.
The compound **4(a-d)** was prepared by one step multi constituent reaction of dimedone, malono nitrile, **3(a-b)** and K_3PO_4 catalyst were heated at 100 °C with equal ratio of Et-OH and water was used as a solvent for a given period of time listed in table and the same reaction was carried out using ultra sonication. The compound **4a** showed absorption frequency at 3432 and 3263 cm^{-1} in IR spectra due to amine group at 2187 cm^{-1} due to CN and 1686 cm^{-1} (Figure. 1) due to ketonic group which is also supporting the compound **4a** formation.

DOI:10.32377/cvrjst1221

SCHEME I
SYNTHETIC PROTOCOL OF COMPOUND **4a-d**.



The compound **4a** shows two singlet peaks at δ 1.02, 0.98 ppm corresponds to CH_3 hydrogens of cyclomethone, while CH_2 hydrogen of cyclomethone appeared as quartet peak δ 2.39, 2.13 and CH_3 hydrogen attached to nitrogen appeared at δ 3.29 as a singlet. The peak at δ 4.25 ppm belongs to benzylic methyl hydrogen and the singlet peak at δ 4.49 ppm belongs to -NH_2 hydrogen and which is clearly indicating the compound **4a** formation. The structures of all the synthesized derivatives were conformed through spectral techniques such as IR, ^1H, ^{13}C NMR and mass spectra. The physical data of all the newly reported derivatives were summarized in Table 1.

C. Molecular docking studies

Docking studies of synthesized pyran derivatives have been studied to find out the best drug moiety giving an insight into substituted and configurational needs for perfect receptor pit which cause the evolution of best pharmacophore moiety. These models are achieved to get more precise and consistent picture of the potentially active biological molecules at the atomic level and also produce new insights that could be used to develop new therapeutic agents.

In anticancer docking results, only best conformers were chosen and dock value for every ligand listed in Table 2. Most stable receptor ligand complex form is the one which has low dock value. The best docked conformer of every ligand and receptor were joined together and their complexes were optimized energetically after docking execution by define a radius of 10A° measured from the docked ligand. Step by step optimization energy was done by using first hydrogen, side chains attached and finally the backbone of receptor molecule.

Fig. 2, shows the binding relationship between compound **4d** and protein kinase 1 active site residues interact with Arg 197, Thr 219, Asp117 and Ala 234.

TABLE II
DOCKING SCORES OF THE SYNTHESIZED COMPOUNDS.

Compound	Docking score (Binding energy)			
	Breast Cancer	Colon Cancer	Lung Cancer	Pancreatic Cancer
4a	-93.04	-86.24	-90.09	-83.87
4b	-93.55	-92.00	-83.92	-83.54
4c	-97.29	-94.78	-78.13	-78.34
4d	-104.89	-89.55	-91.56	-86.26

Important hydrogen bonding interaction takes place between Thr 219 and the (C=O) oxygen atom of pyran ring, another strong bonding takes place between Asp117 and Ala 234 and the nitrogen atom attached to the pyran ring.

III. CONCLUSIONS

In conclusion, it is found that a simple and efficient method for the synthesis of phenothiazine substituted different pyran derivatives under conventional heating and ultrasonic method. The main advantages of ultrasonic irradiation are those which include yield improvement, short reaction times, easy reaction set-up and use of very little amount of solvents or without solvents. The synthesized phenothiazine derivatives were subjected to anticancer molecular docking studies using four dissimilar cancer target proteins. The results of anticancer docking studies showed that the synthesized compound **4d** possess significant binding energy with breast cancer when comparing with other compound.

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DOI:10.32377/cvrjst1221

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DOI:10.32377/cvrjst1221