Synthesis and Characterization of N-aryl Maleimide Derivatives.

A

Thesis Submitted

in partial fulfillment of the requirements for the award of the degree of

MASTER OF SCIENCE

IN

CHEMISTRY

BY

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Supervisor

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THAPAR UNIVERSITY, PATIALA

JULY, 2013

Certificate

This is to certify that the project entitled **"Synthesis and Characterization of N-Aryl Maleimide Derivatives"** being submitted by Arpan deep Kaur, Roll no. 301102001 in partial fulfillment of the requirements for the award of degree of Master of Science in School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonafide work carried out under my supervision and guidance. The report has not been submitted for the award of any other degree or certificate in this or any other university.

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Candidate's Declaration

I hereby declare that the work which is being presented in the dissertation entitled "**Synthesis and Characterization of N-Aryl Maleimide Derivatives**" in partial fulfillment of the requirements for the award of the degree of master of science in Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala is an authentic record of my own work during a period of six months from January 2013 to July 2013, under the supervision of Dr. Kamaldeep Paul, Assistant Professor, School of Chemistry and Biochemistry, Thapar University, Patiala. The report has not been submitted for the award of any other degree or certificate in this or any other university.

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Place: Patiala

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This is to certify that the above statement given by the candidate is correct and true to the best of our knowledge.

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Acknowledgement

In pursuit of this academic endeavor, I feel that I have been singularly fortunate because insption, guidance, direction, co-operation, love and care all come in my way in abundance and it seems almost an impossible task for me to acknowledge the same in adequate term.

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I thank Ms. Richa Goel, research scholar for their kind cooperation during the project work.

Life at Thapar University would be unforgettable for me throughout my life because I was blessed to spend it with my friends. I thank them all for their great company.

Words fail me to express my thanks to my family for their support, selfless sacrifice, encouragement and heart full blessings that continue to enlighten my life.

Above all I thank almighty God for blessing me with strength and wisdom to complete this project successfully.

Arpan deep Kaur

Arpan deep Kaur

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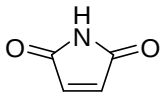
INTRODUCTION AND REVIEW OF LITERATURE

Maleimide is the chemical compound with the formula $C_2H_2(CO)_2NH$. This unsaturated imide is an important building block in organic synthesis. The name is a contraction of maleic acid and imide, the – C(O)NHC(O)- functional groups.



Maleimide [2, 5-Pyrroledione]

Maleimide and its derivatives are prepared from maleic anhydride by treatment with amines followed by dehydration[1]. A special feature of the reactivity of maleimides is their susceptibility to additions across the double bond either by Michael additions or via Diels-Alder reactions. Bismaleimides are a class of compounds with two maleimide groups connected by the nitrogen atoms via a linker, and are used as crosslinking reagents in polymer chemistry. Only a handful of natural maleimides - the cytotoxic showdomycin from *Streptomyces showdoensis,* and pencolide from *Pencoline multicolor* - have been reported[2]. Farinomalein was first isolated in 2009 from the entomopathogenic fungus *Isaria farinosa* (*Paecilomyces farinosus*) - source H599 (Japan) [3].

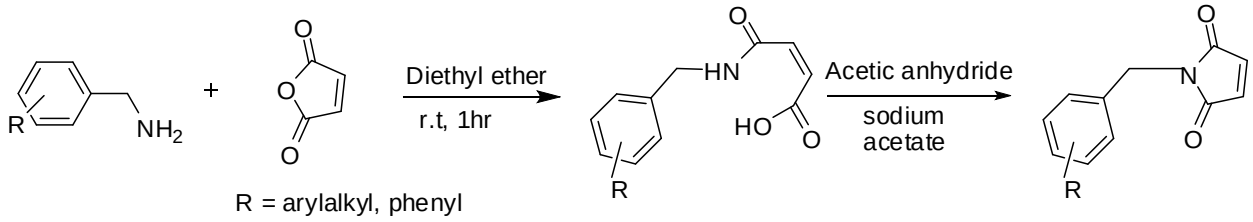
Maleimides linked to polyethylene glycol chains are often used as flexible linking molecules to attach proteins to surfaces. The double bond readily reacts with the thiol group found on cysteine to form a stable carbon-sulfur bond. Attaching the other end of the polyethylene chain to a bead or solid support allows for easy separation of protein from other molecules in solution, provided these molecules do not possess thiol groups. Mono- and bismaleimide-based polymers are used for high temperature applications (up to 250 °C)[4]. Maleimides linked to rubber chains are often used as flexible linking molecules to reinforce the rubber (tire).

The maleimides could present many advantages in pharmaceutical and medicinal chemistry. They can be used as probes; they could give new interesting data about the enzyme's environment, as they react with particular amino acids. It also seems determinant for the enzyme inhibition that the maleimide moiety is substituted by a large lipophilic group (biphenyl) and spaced out from the maleimide ring. This could represent a new horizon in the treatment of diseases where the imbalance of endocannabinoids has been proved to play a

major role, like in CNS diseases and in the treatment of pain and psychiatric disorders (depression, anxiety, etc.).

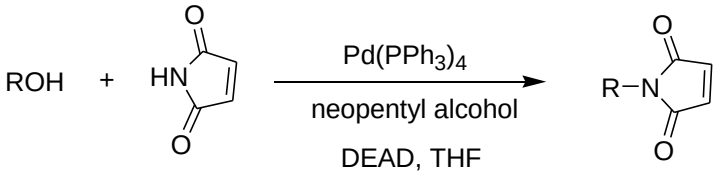
A practical preparation of maleimide by way of carbamylmaleimide has been reported[5]. There are two reactive sites on the maleimide ring- the carboximide function and the double bond. Each exerts an influence upon the reactivity of other, causing maleimide to be somewhat unlike a typical carboximide or cyclic olefin. A variety of methods have been developed for the preparation of some biologically active compounds using maleic anhydride as one of the starting materials[6,7]. The reaction of primary amines with maleic anhydride has been known for many years[8] along with methyl and ethyl amine[9]. The reactions proceed through the malemic acid intermediate to the maleimide and a resinous product.

Few N-substituted malemides has been reported in literature. N-substituted maleimides constitute a promising class of potent and selective monoglyceride lipase (MGL) inhibitors[10]. The N-substituted maleimides were synthesized by two main routes. The first one involves a substituted aniline or an aliphatic amine and maleic anhydride as a building block (**Scheme 1**)[11], whereas the second one requires a primary alcohol and maleimide (**Scheme- 2**)[12]. The N-phenylmaleimides were readily obtained by reacting the desired substituted aniline with maleic anhydride in diethyl ether leading to the corresponding N-phenylmaleanic acid, which was cyclized to N-phenylmaleimide.



Scheme-1

In **scheme 1**, substituted aniline was treated with maleic anhydride in diethyl ether and stirred at room temperature for 1hr leading to N-phenylmaleanic acid. Without any further purification, this open intermediate was subsequently cyclized in acetic anhydride in the presence of sodium acetate (0.5 equv.) to give N-phenylmaleimide.



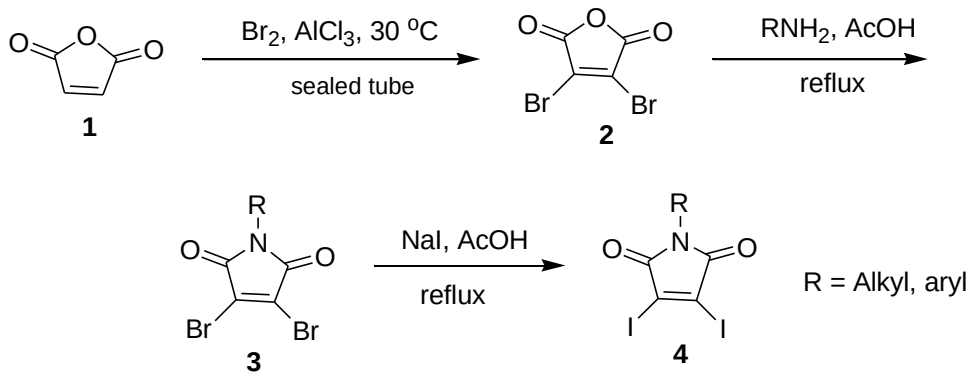
Scheme-2

In **scheme 2**, the alkyl alcohol was stirred overnight with maleimide in the presence of 0.5 equivalent of neopentyl alcohol, 1.0 equivalent of triphenylphosphine (PPh_3) and 1.0 equivalent of diethyldiazodicarboxylate (DEAD) in anhydrous THF. These N-substituted maleimide derivatives can be used as probes and thus they could give new interesting data about the enzyme's environment, as they reacted with particular amino acids.

The olefinic bonds of maleimide and the derivatives were reactive in vinyl type polymerisation under conditions of free radical or anionic initiation. A new N-substituted derivative of maleimide has been prepared in which aliphatic primary amines react exothermally with dichloromaleimide or N-phenyldichloromaleimide yielding N-alkyl-2-alkylamino-3-chloromaleimides. The main factors which determine the remarkable ease of exchange of imide nitrogen are the nucleophilicity of amide nitrogens and inductive effect of chlorine of the chloromaleimides[13].

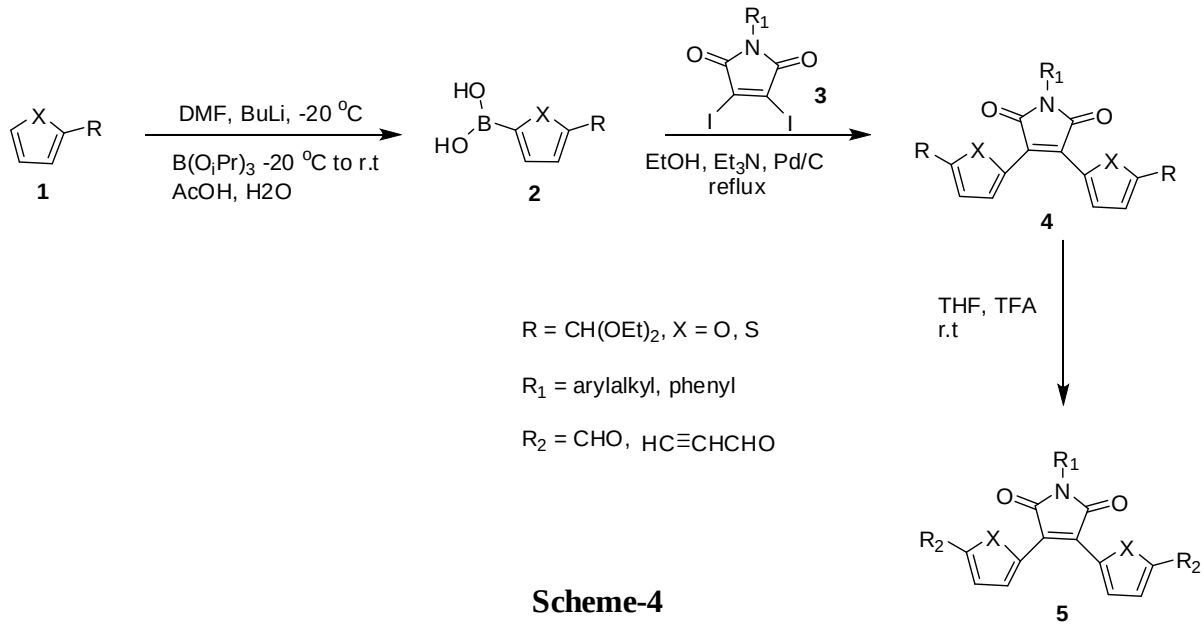
Bisindolylmaleimides, bisazaindolylmaleimides and mixed indolylazaindolylmaleimides along with carbazoles are the most widely described maleimides[14] because of their pharmaceutical interests. They are prepared from their heteroaryl and dihalogenomaleimide precursors, using Grignard reagent (also LiHMDS) and a palladium catalysis (Stille, Suzuki coupling)[15]. Other methods use the reaction between a glyoxalate and an arylacetamide or a homocoupling reaction of 3-arylacetic acid followed by an amidification[16]. Bis(fur-2-yl), bis(fur-3-yl) and bis(thien-2-yl) maleimides with potential antidiabetic properties has also been synthesised[17]. Their synthesis involves, as a key step, a Suzuki cross-coupling between various boron derivatives and the diiodomaleimides.

The first synthesis of substitued bis(fur-2-yl) and bis(thien-2-yl) maleimides via a one-pot Pd/C catalysed Suzuki cross coupling reaction between the diidomaleimides and the [(2-diethoxyalkyl)heteroaryl)]boronic acids has been reported.



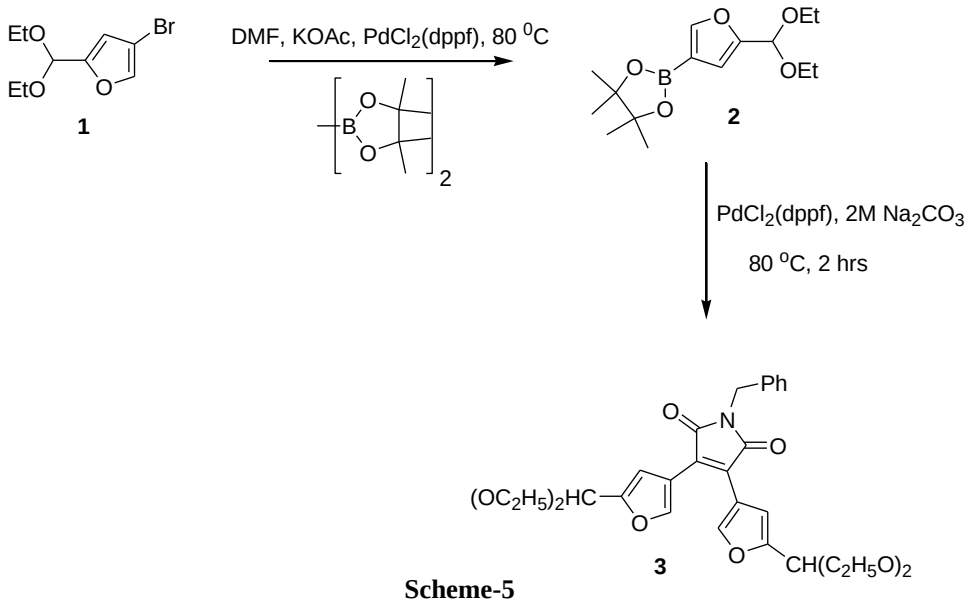
Scheme-3

In **scheme 3**, diidomaleimides has been synthesized from maleic anhydride in three steps. The first step involved bromination in a sealed tube with bromine in the presence of aluminium chloride (catalytic amount) to provide dibromoderivative **(2)**. This dibromo derivative was then treated with different substituted aniline in acetic acid to give corresponding dibromomaleimides **(3)** with moderate yield. Treatment of N-substituted dibromomaleimides with sodium iodide in acetic acid leads to the product **(4)** which is used as coupling reaction.



Scheme-4

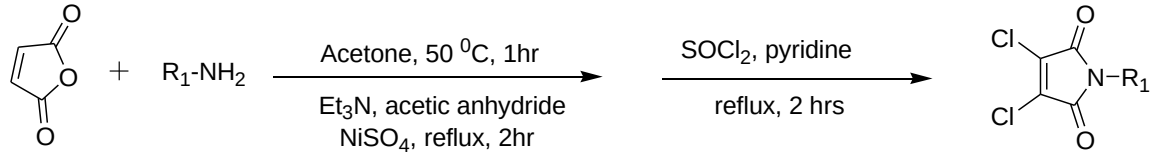
Compound **5** was synthesized by the reaction diiodomaleimide with substituted boronic acids in the presence of palladium catalyst followed by removal of ester group by using trifluoroacetic acids in THF at room temperature (**scheme-4**).



Scheme-5

In **scheme 5**, under an inert atmosphere, (bispinacolato)diborane, potassium acetate, 1,1'-bis(diphenyl phosphinoferrocene)dichloropalladium (II) were added to a stirred solution of 2-diethoxymethyl-4-bromofuraldehyde in dry DMF. The mixture was refluxed under nitrogen with stirring for 2 hrs. After cooling the solution to room temperature, [1,1'bis(diphenyl phosphinoferrocene)dichloropalladium (II) and 2M Na_2CO_3 were added, and then the mixture was stirred at 80 ^{0}C under nitrogen for another 2 hrs. The solution was cooled to room temperature and was extracted with ethyl acetate to obtained compound **3**.

A series of 1,4-benzoxazine-2,3-dicarboximides, which may have potential as anti microbial activities, has been synthesized starting from maleic anhydride and substituted aromatic amines[18]. N-Phenyldichloromaleimide derivatives has been synthesized according to an improved procedure based on reported methods[19,20] using commercially available maleic anhydride and substituted aromatic amines as the starting materials (**Scheme 6**).

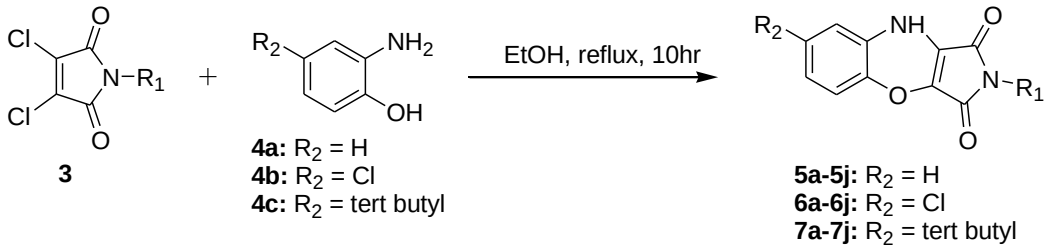


Scheme-6

a, R_1 = phenyl; **b,** R_1 = p-F-phenyl; **c,** R_1 = p-Cl-phenyl; **d,** R_1 = p-CH_3-phenyl; **e,** R_1 = m-CH_3-phenyl; **f,** R_1 = p-NO_2-phenyl; **g,** R_1 = m-NO_2-phenyl; **h,** R_1 = 3,4-dimethoxyphenyl; **i,** R_1 = naphthyl; **j,** R_1 = benzyl.

In **scheme 6**, a solution of aniline **2a** (20 mmol) in 10 ml acetone was added to a suspension of maleic anhydride **1** (20 mmol) in 10ml acetone. After warming it in an oil bath at 55 ^{0}C for 1 hr, Et_3N (2.5mL), acetic anhydride (1 mL), and 15% $NiSO_4$ (0.2 mL) were added. After refluxing in 80 ^{0}C for another 2 hr, the reaction mixture was poured into ice-cold

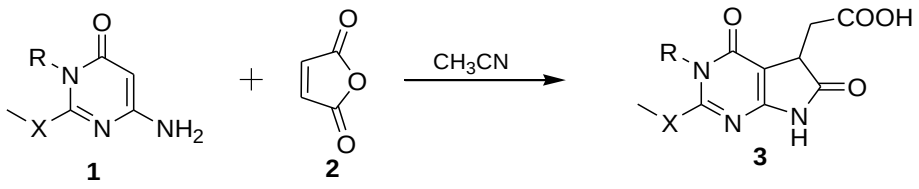
water. The precipitated product was filtered, washed with ice-cold water, and dried under vacuum to give a yellow residue. The obtained residue was dissolved in 15 ml thionyl chloride ($SOCl_2$), then 2 ml pyridine was added dropwise at less than 0 ^{0}C over 15 min. The reaction mixture was allowed to stir for additional 15 min at less than 0 ^{0}C and 30 min at ambient temperature. Then reaction mixture was refluxed at 85 ^{0}C for 2 h. After removing the solvent under vacuum, the residue of the reaction mixture was reconstituted and diluted with ice-cold water. The resulting mixture was then neutralized (pH about 7.0) using sodium bicarbonate solution and extracted with dichloromethane (3-10 ml) to obtain compound **3**. Compound **3** was further used for reaction with 2-aminophenol in ethanol to give 1,4-benzoxazine-2,3-dicarboximide analogue **(5-7)** according to **scheme 7**.



Scheme-7

The condensation reactions of compound **3** with substituted 2-aminophenol (**4)** were studied under different conditions. Initially, reaction of **3a** with **4a** was carried out in methanol or dimethylformamide (DMF) in the presence of CH_3COONa or potassium hydroxide (KOH). However, the reaction was very complex, and the expected product **5a** could not be isolated. After several trials, reaction of **3a** with 2-aminophenol **4a** in ethanol afforded the desired compound **5a** in 71% yield after refluxing for 10 hrs. Such 1,4-benzoxazine derivatives showed interesting biological activities such as antifungal[21] and antimicrobial[22,23] properties. They are also found in the use of herbicides[24] and dyes[25]. Moreover, a number of 1,4-benzoxazine derivatives are developed as antipyretic, analgesic, anti inflammatory and neuroprotective agents[26-28].

Several nucleosidic and heterocyclic purine structural analogues such as pyrrolo[2,3-d]pyrimidines have shown a wide range of biological applications. Such pyrrolo[2,3-d]pyrimidines derivatives have been synthesized from reactions of 6-aminopyrimidines and maleic acid derivatives[29] as in **scheme 8**:

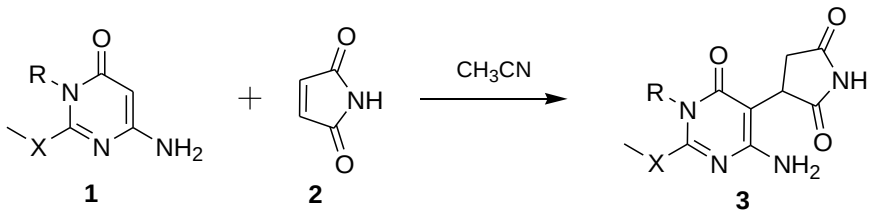


R = H, CH_3, X = O, S

Scheme-8

According to **scheme 8**, to the suspension of 6-aminopyrimidine-4(*3H*)-one in dry acetonitrile (4ml/mmol) was added maleic anhydride (molar ratio 2:1) and the mixture was stirred under reflux for several hours. Then the solid was precipitated, filtered off and washed with fresh acetonitrile to obtain compound **3**.

Reaction of 6-aminopyrimidin-4(3-*H)*-ones derivatives with maleimide is as shown in **scheme 9**



R = H, CH_3, X = O, S

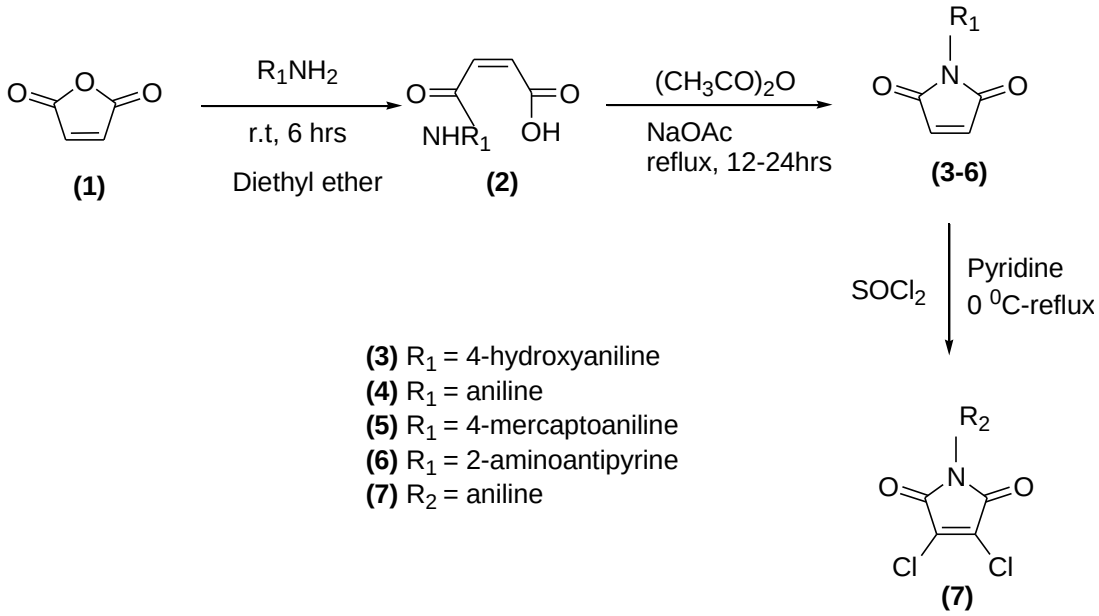
Scheme-9

To a suspension of 6-aminopyrimidine-4(*3H*)-one in dry acetonitrile was added maleimide (molar ratio 1:2) and the mixture was stirred overnight. Then the solid precipitated was filtered off and washed with fresh acetonitrile. The results showed the higher reactivity of maleic anhydride as compared to maleimide, because of prevention by Michael adducts and also due to longer reaction time achieved in the case of maleimide.

Literature reports proved that maleimide moieties when combined with heterocyclic moieties exhibits potent biological activitiy, thus we developed new methodology for the synthesis of these biological active N-aryl maleimide derivatives with separation of intermediate and then chlorination of maleimide.

RESULTS AND DISCUSSION

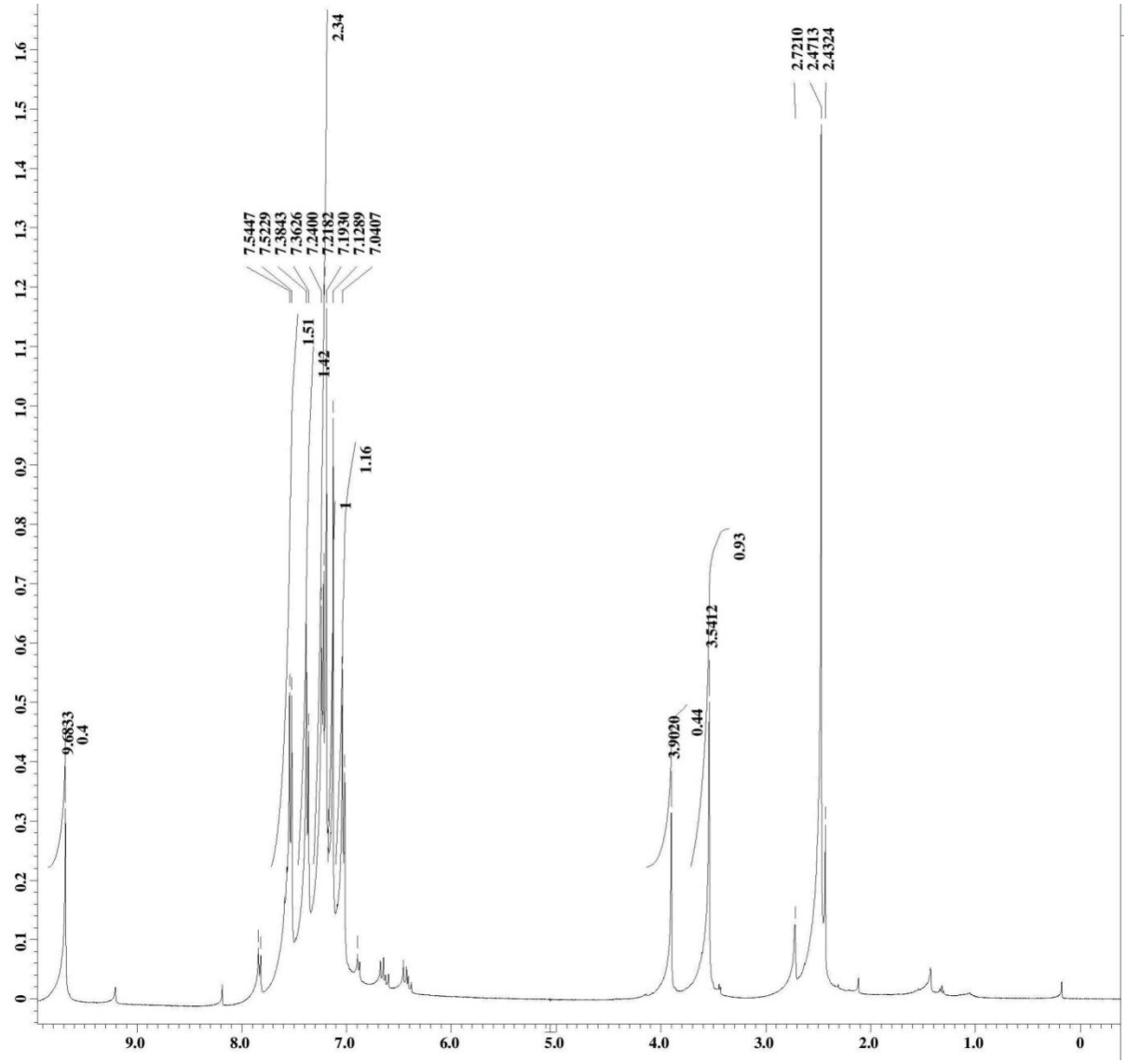
General scheme for synthesis of compounds 3-7



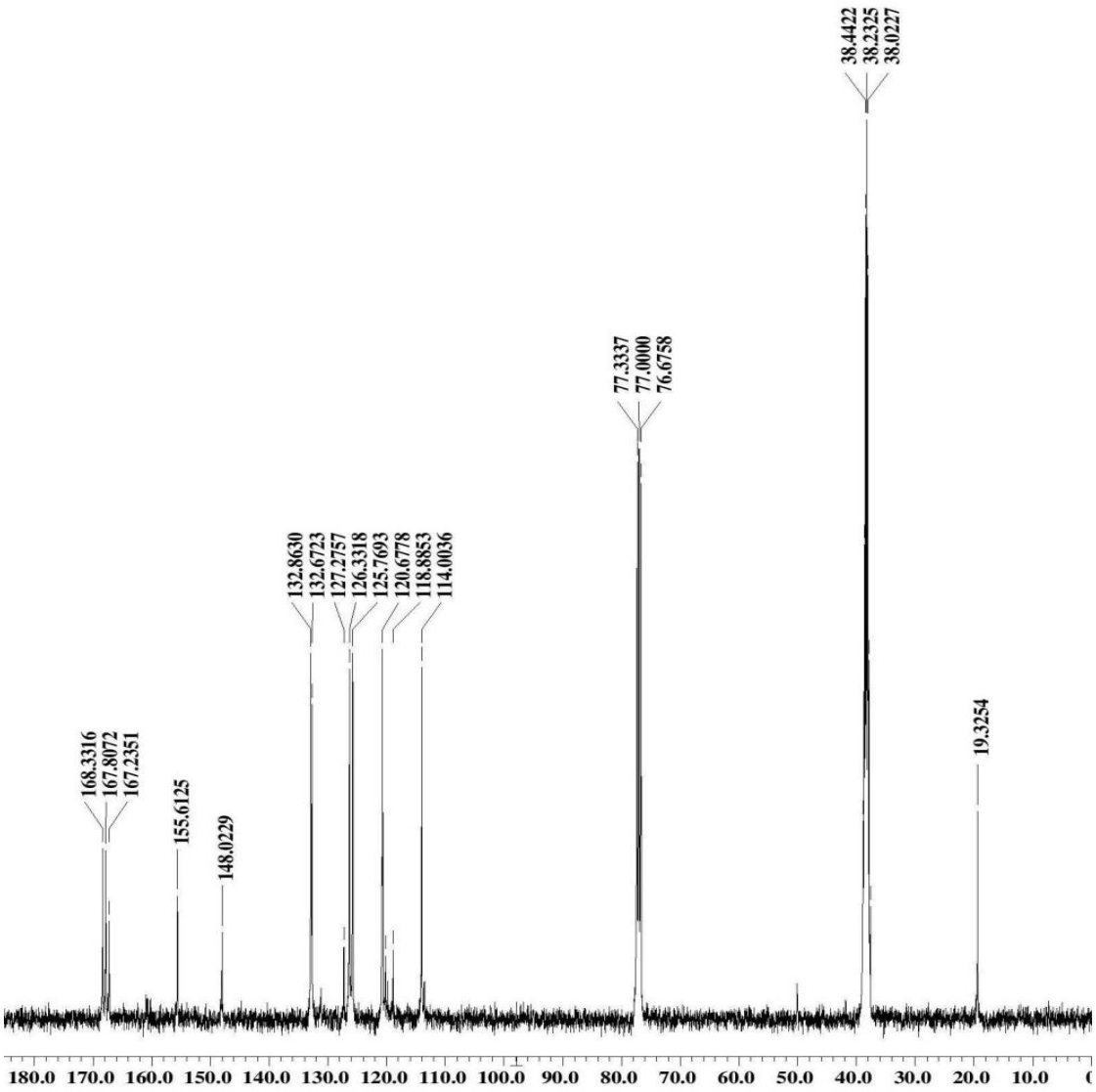
Scheme-10

Compounds **3-7** were synthesized according to **Scheme-10**. A mixture of maleic anhydride **(1)** and 1 eq. of primary amine (R_1NH_2) in diethyl ether/THF was stirred for 6-12 hrs at room temperature. After the completion of reaction, monitored by TLC, intermediate **(2)** has been separated out**.** This intermediate was filtered out, washed with diethyl ether and dried to get pure compound.

^{1}H NMR spectrum of compound **2** show 1H singlet at δ 9.68 for NH (exchangeable with D_2O), 1H doublet at δ 7.54 for CH, 1H doublet at δ 7.38 for CH, 4H multiplet at δ 7.24-7.04 for ArH and 1H singlet at δ 3.54 for OH (exchangeable with D_2O). ^{13}C NMR spectrum shows peaks at δ 168.3, 167.8, 155.6, 148.0, 132.6, 126.3, 125.7, 120.6, 114.0. ^{1}H and ^{13}C NMR spectra of compound **2** confirmed the structure of intermediate 4-(4-hydroxyphenylamino)-4-oxobut-2-enoic acid**.**



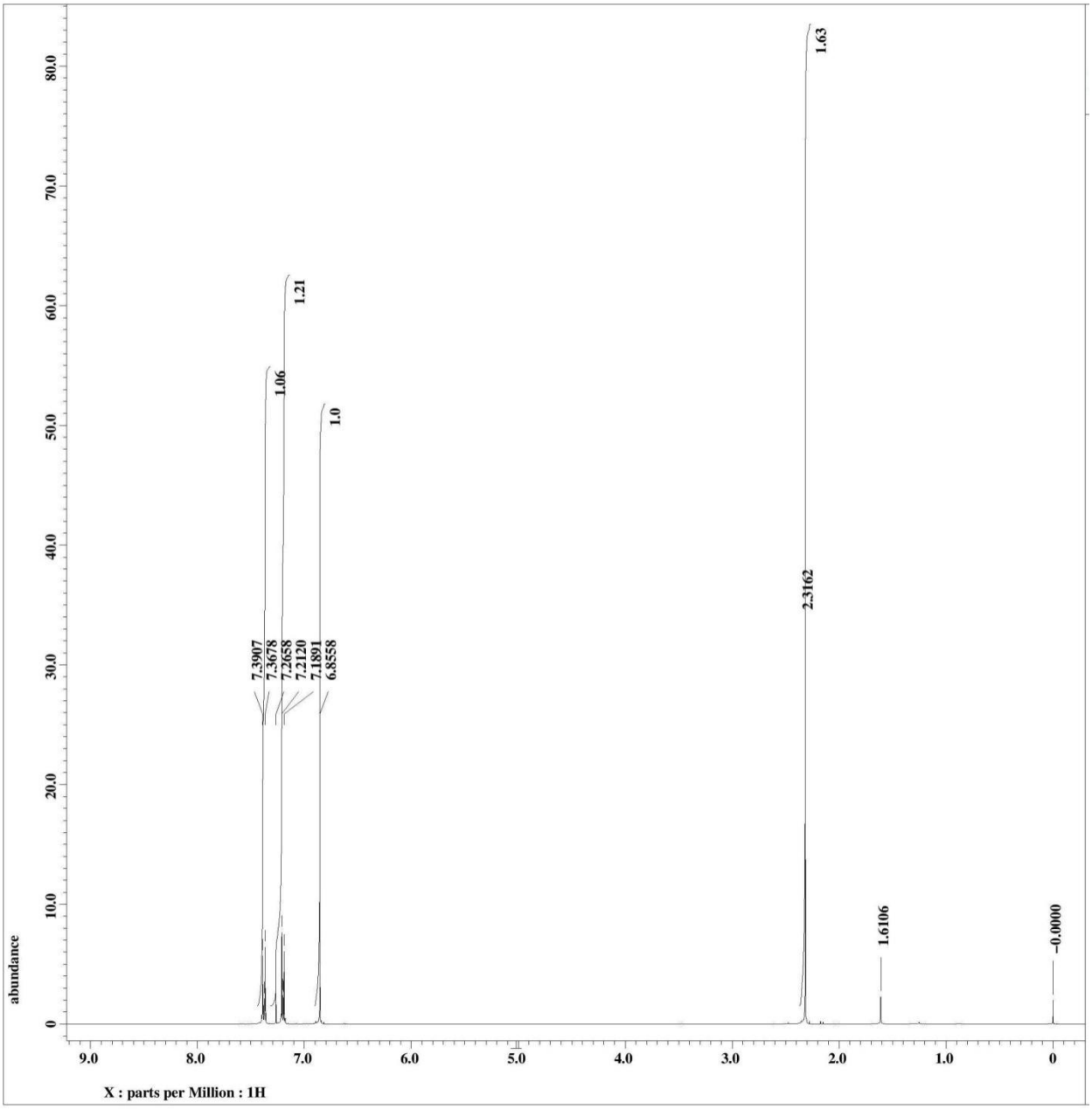
^{1}H NMR spectrum of 4-(4-hydroxyphenylamino)-4-oxobut-2-enoic acid (2).



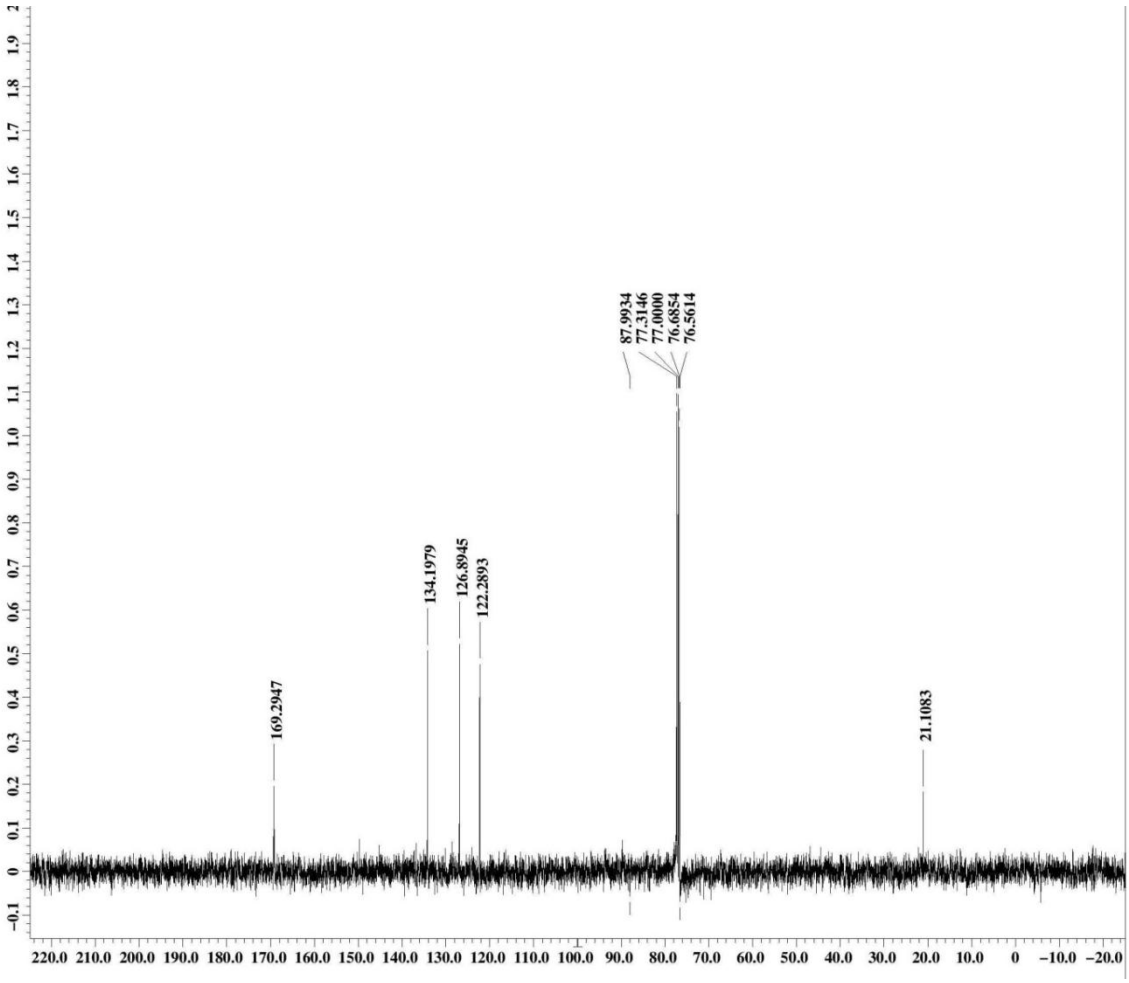
^{13}C NMR spectrum of 4-(4-hydroxyphenylamino)-4-oxobut-2-enoic acid (2).

The intermediate **2** was refluxed with 1 mole equivalent of sodium acetate and 0.5 ml/mmol acetic anhydride for 12-24 hrs. After the completion of reaction (monitored by TLC), the crude product was purified by column chromatography using hexane:ethylacetate as eluents.

^{1}H NMR spectrum of compound **3** shows 2H doublet at δ 7.37 for aromatic-H, 2H doublet at δ 7.19 for aromatic-H and 2H singlet at δ 6.85 for CH. ^{13}C NMR spectrum shows peaks at δ 169.2, 134.1, 126.8, 122.2. Disappearance of singlets of NH and OH at δ 9.68 and 3.54 respectively and appearance of 2H singlet at δ 6.85 of CH confirmed the cyclization of compound **2.** ^{1}H and ^{13}C NMR spectra confirmed the structure of 1-(4-hydroxyphenyl)-*1H*-pyrrole-2,5-dione (**3**).

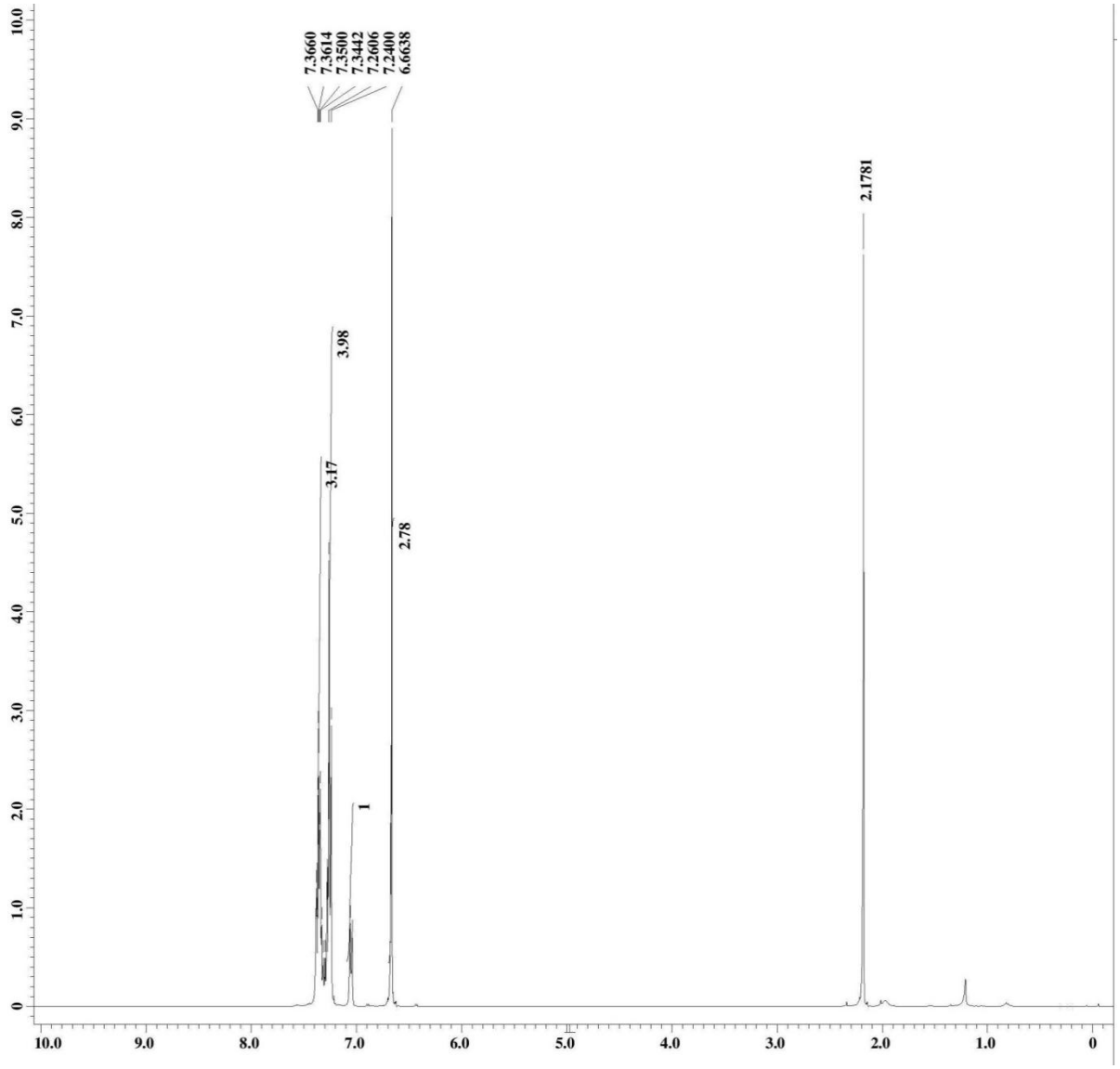


^{1}H NMR spectrum of 1-(4-hydroxyphenyl)-*1H*-pyrrole-2,5-dione (3)

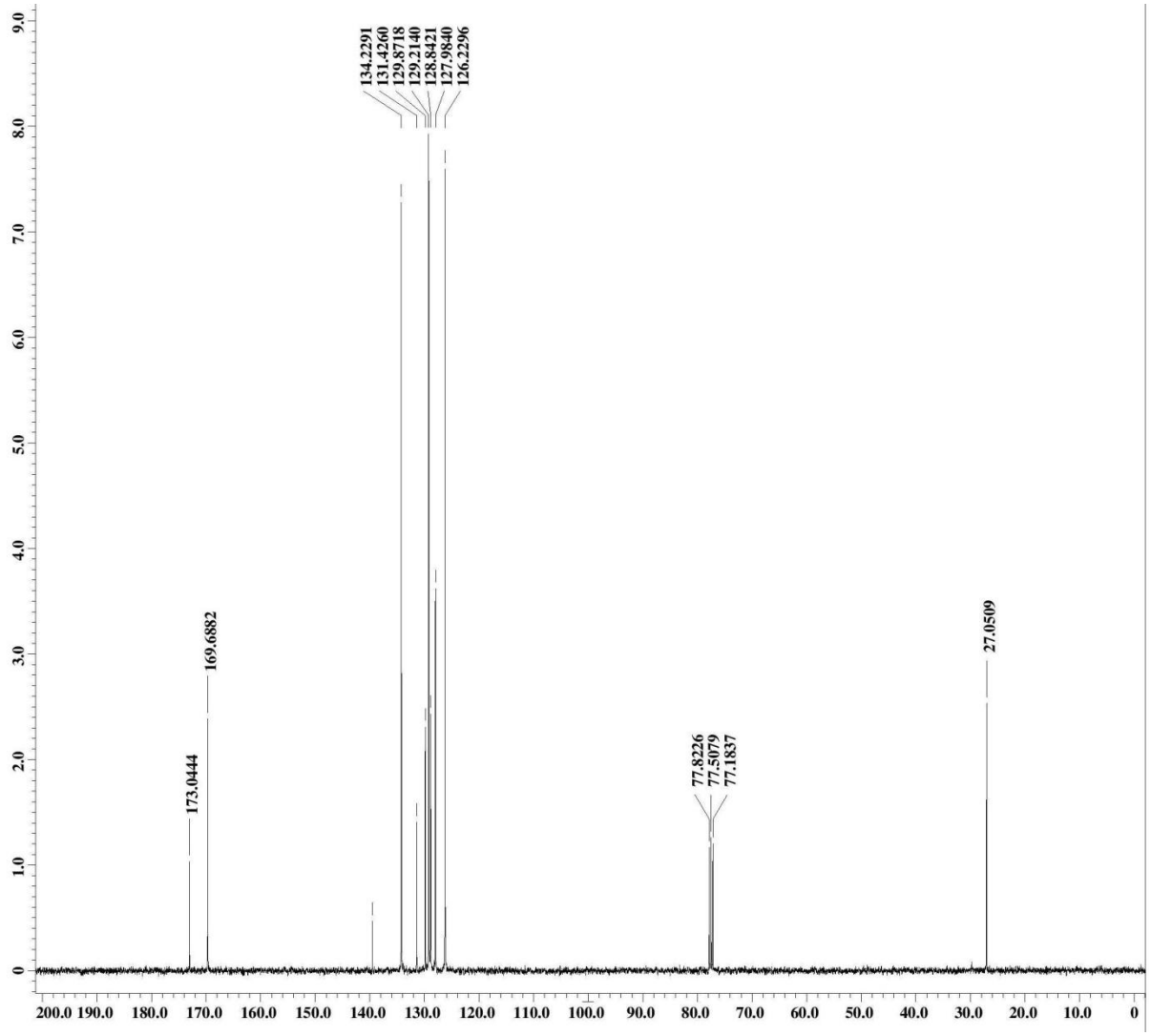


^{13}C NMR spectrum of 1-(4-hydroxyphenyl)-*1H*-pyrrole-2,5-dione (3)

Similarly, maleic anhydride was also treated with aniline, 4-mercaptoaniline and 2-aminoantipyrine in the same reaction conditions to obtained compound **4-6** respectively. ^{1}H NMR spectrum of compound **4** (reaction of maleic anhydride and aniline) shows 3H multiplet at δ 7.38-7.33 for aromatic-H, 2H multiplet at δ 7.27-7.24 for aromatic-H and 2H singlet at δ 6.66 for CH. **^{13}**C NMR spectrum shows peaks at δ 173.0, 169.6, 134.2, 130.0, 129.8, 129.2, 128.8, 127.9, 126.2. ^{1}H and ^{13}C NMR spectra confirmed the structure of 1-phenyl -*1H*-pyrrole-2,5-dione **(4)**.

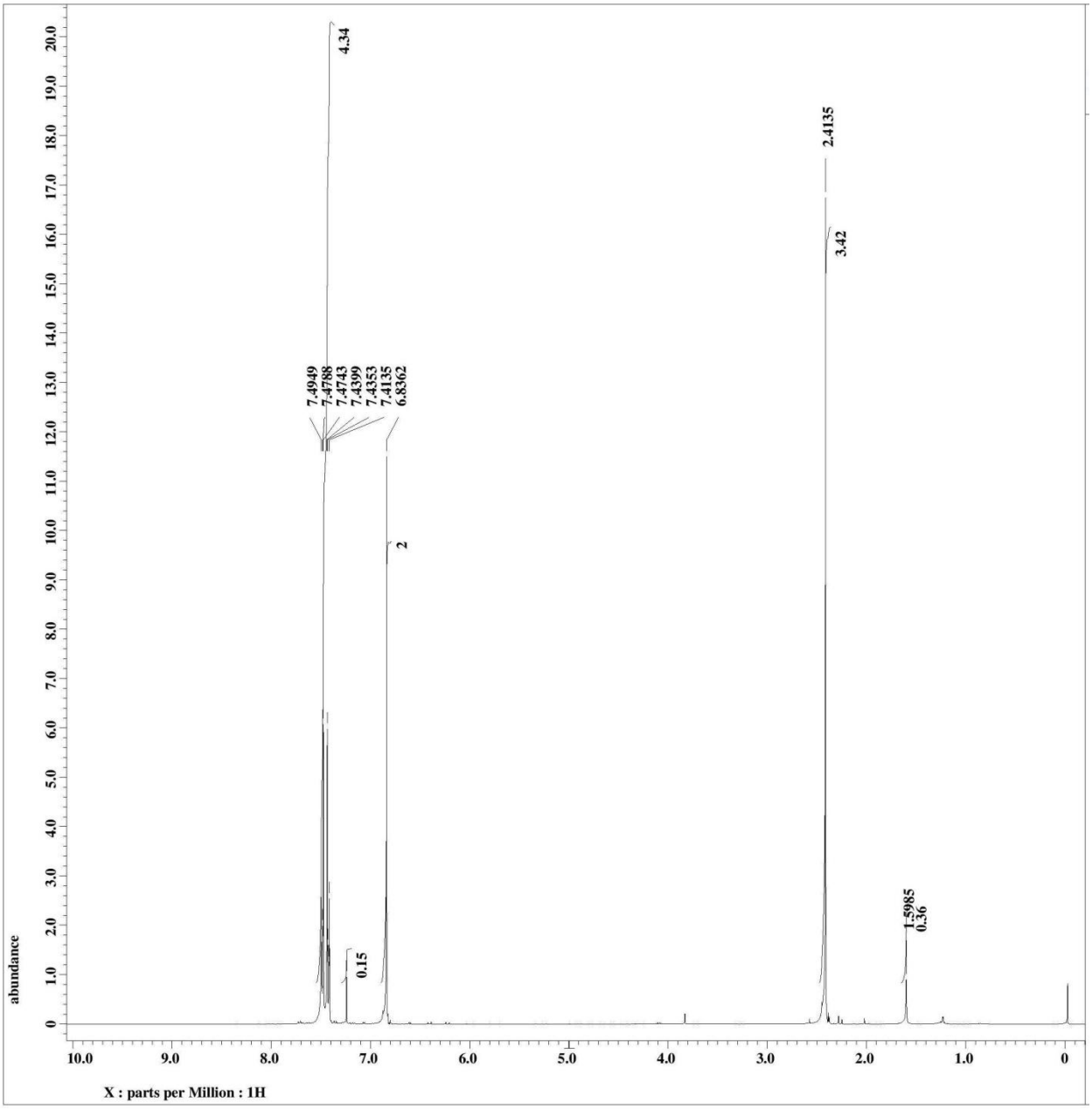


^{1}H NMR spectrum of 1-phenyl -*1H*-pyrrole-2,5-dione (4)

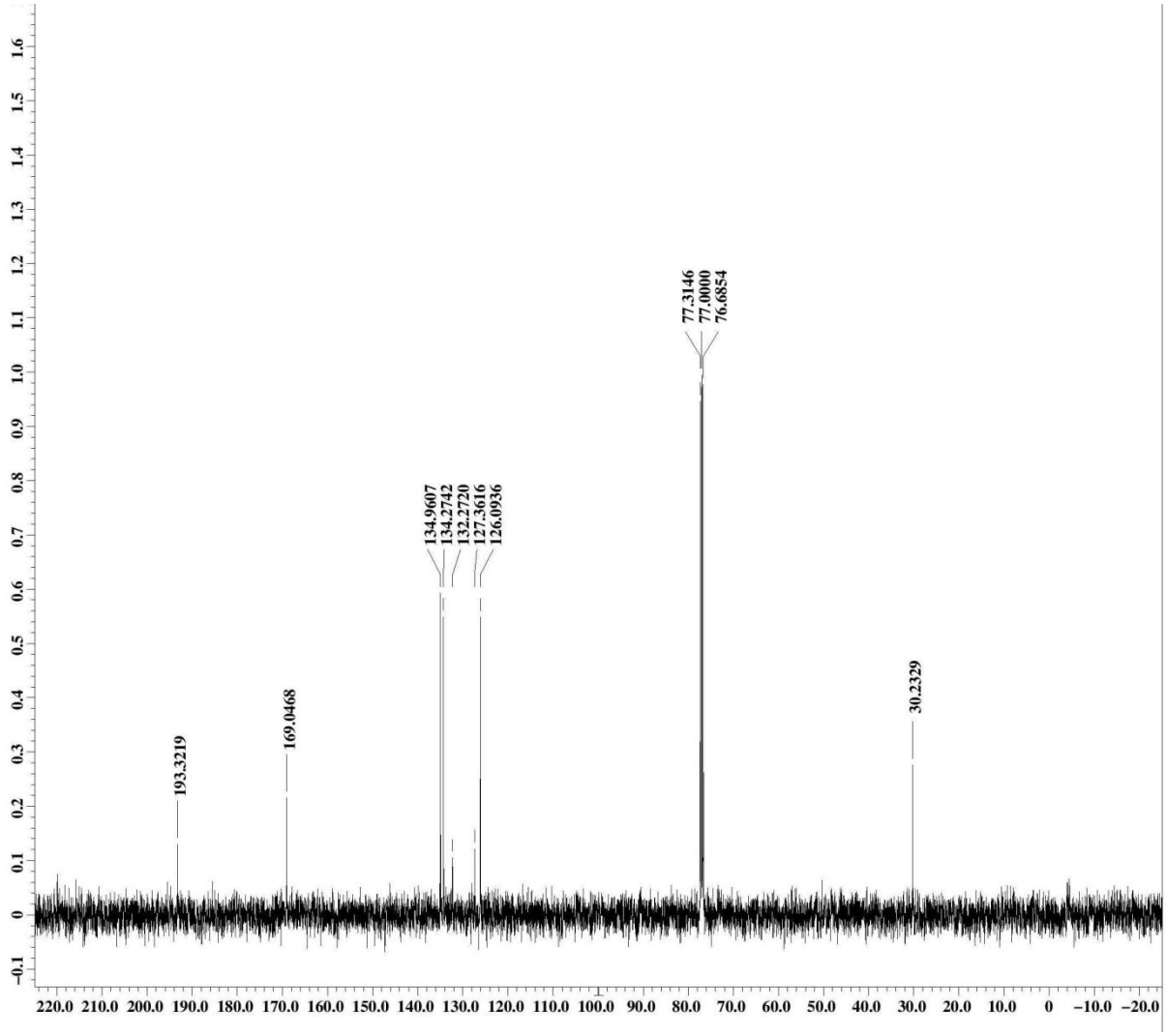


^{13}C NMR spectrum of 1-phenyl -*1H*-pyrrole-2,5-dione (4)

^{1}H NMR spectrum of compound **5** (reaction of maleic anhydride and 4-mercaptoaniline) shows 4H multiplet at δ 7.49-7.41 for aromatic-H and 2H singlet at δ 6.83 for CH. ^{13}C NMR spectrum shows peaks at δ 193.3, 169.0, 134.9, 134.2, 132.2, 127.3, 126.0. ^{1}H and ^{13}C NMR spectra confirmed the structure of 1-(4-mercaptophenyl)-*1H*-pyrrole-2,5-dione (**5**).

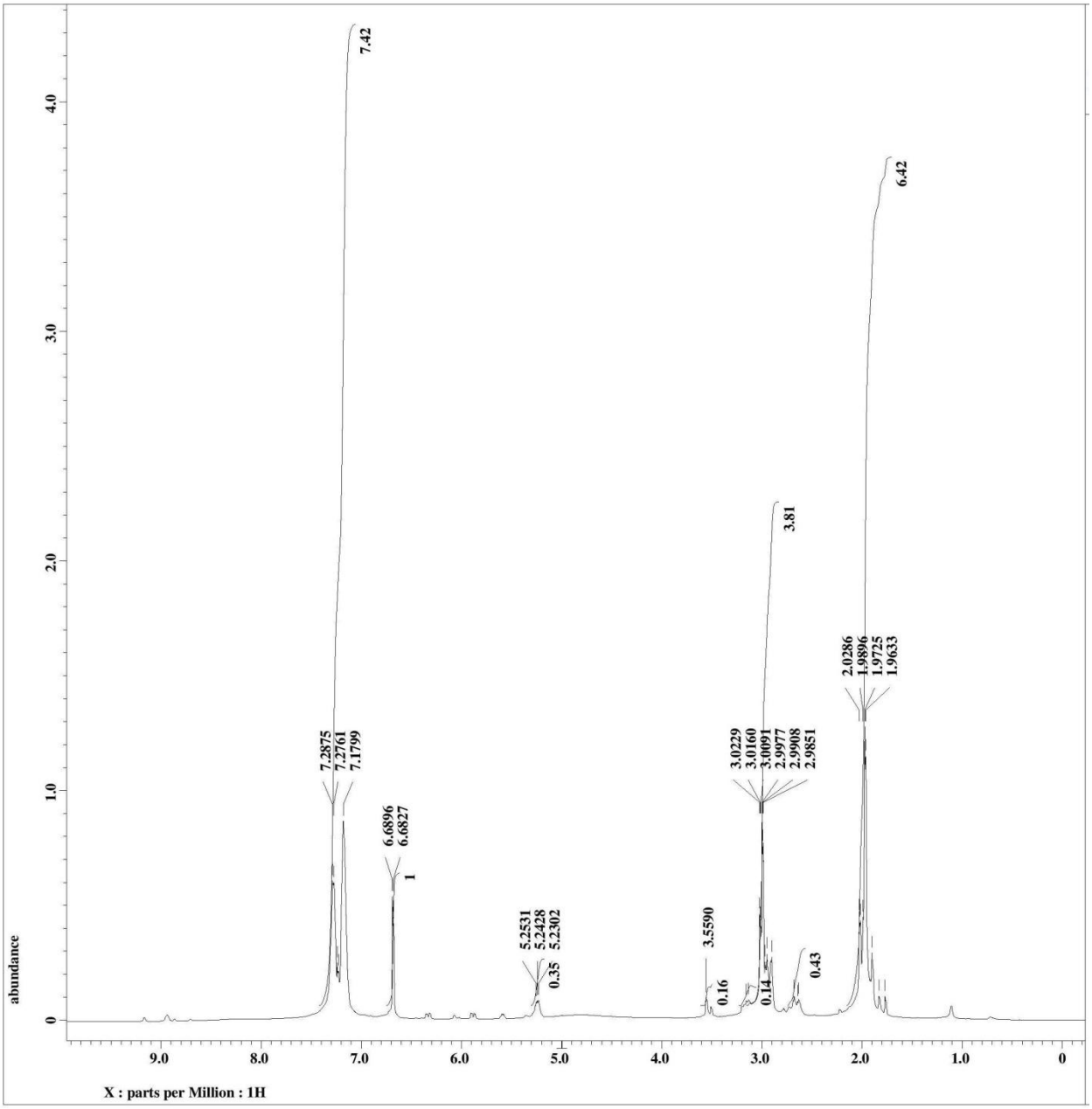


^{1}H NMR spectrum of 1-(4-mercaptophenyl)-*1H*-pyrrole-2,5-dione (5).

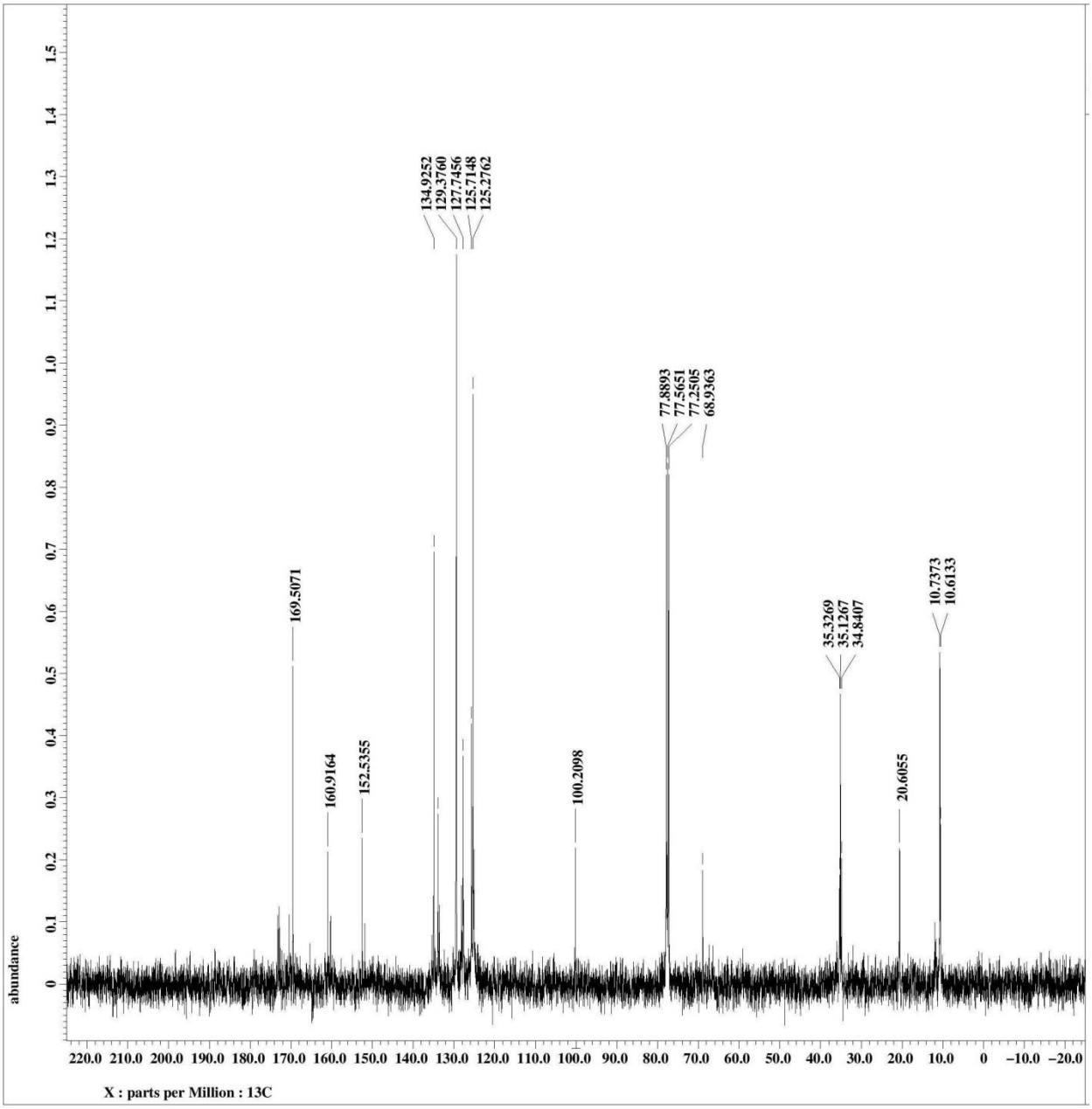


^{13}C NMR spectrum of 1-(4-mercaptophenyl)-*1H*-pyrrole-2,5-dione (5).

^{1}H NMR spectrum of compound **6** (reaction of maleic anhydride and aminoantipyrine) shows 5H multiplet at δ 7.28-7.27 for aromatic H, 1H singlet at δ 7.17 for NH, 2H singlet at δ 6.68 for CH, 3H singlet at δ 2.99 for N-CH_3 and 3H singlet at δ 1.96 for CH_3. ^{13}C NMR shows peaks at δ 169.5, 165.4, 160.9, 152.5, 134.9, 132.5, 129.3, 127.7, 126.4, 125.2, 100.2, 68.9, 35.1, 10.7. These NMR spectra confirmed the structure of 1-(2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-*1H*-pyrazol-4-yl)-*1H*-pyrrole-2,5-dione (**6**)



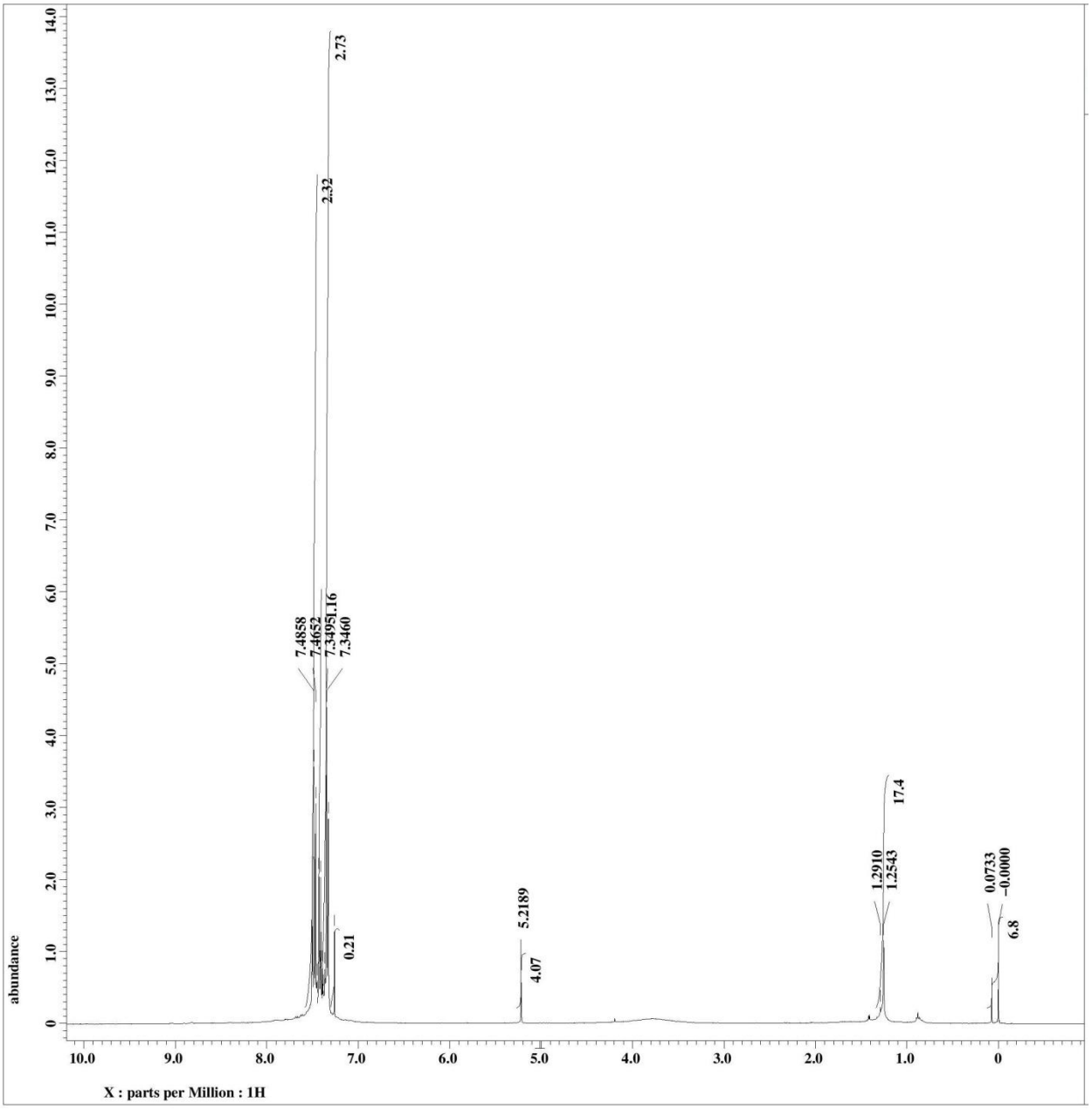
^{1}H NMR spectrum of 1-(2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-*1H*- pyrazol-4-yl)-*1H*-pyrrole-2,5-dione(6)



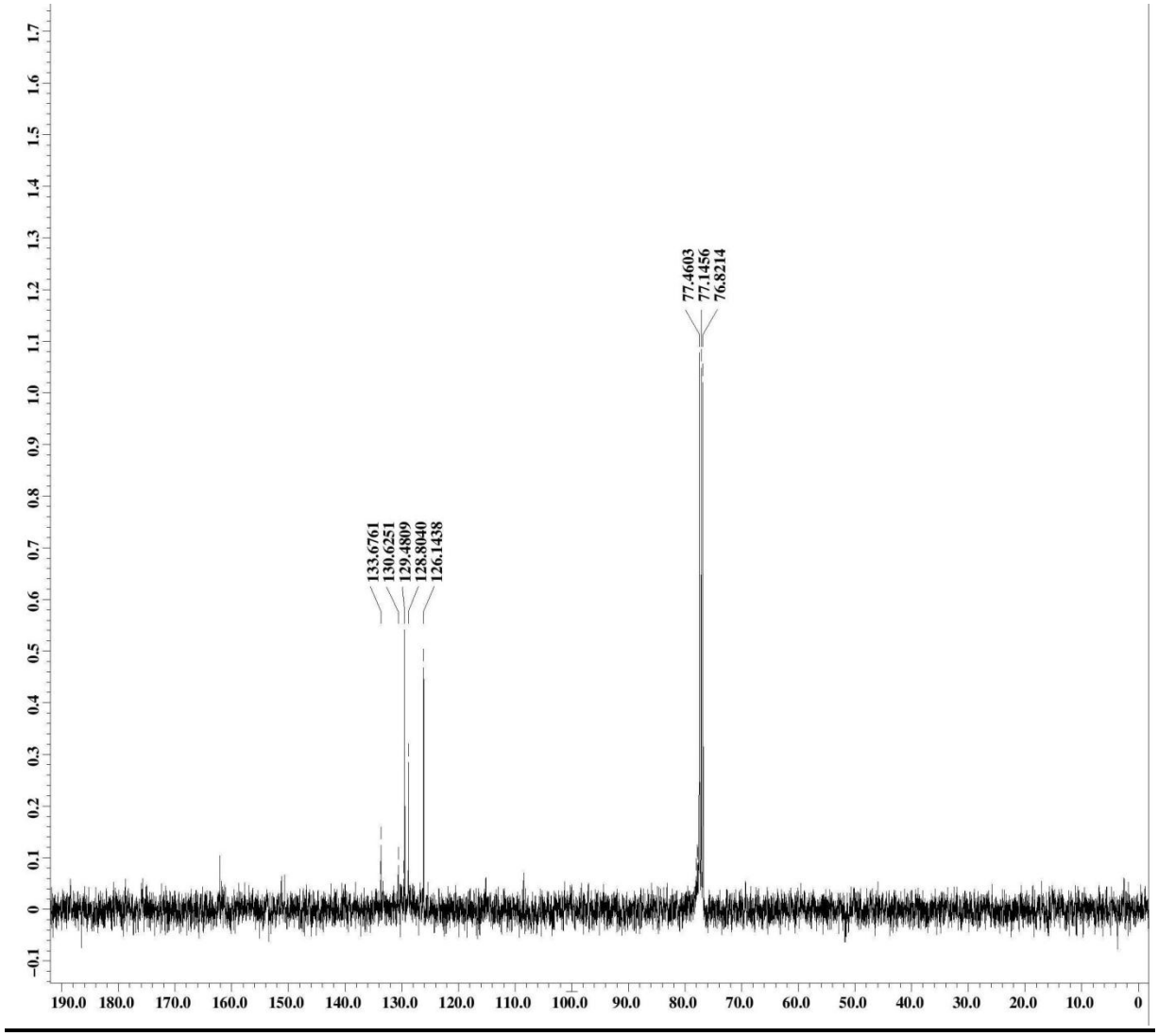
^{13}C NMR spectrum of 1-(2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-*1H*- pyrazol-4-yl)-*1H*-pyrrole-2,5-dione (6)

Compound **4** was further used for the chlorination at the carbon-carbon double bond. Compound **4** was dissolved in 1 ml of pyridine. To this solution, 4 ml of $SOCl_2$ was added dropwise at 0 °C and then refluxed at 60 °C for 24 hrs. The resulted product was then purified by column chromatography using hexane:ethylacetate as eluents to get yellow coloured liquid of 3,4-dichloro-1-phenyl-*1H*-pyrrole-2,5-dione. ^{1}H NMR spectrum of compound **7** shows 5H multiplet at δ 7.48-7.34 for aromatic-H. ^{13}C NMR shows peaks at δ 161.9, 133.5, 129.3, 128.6, 125.9. Disappearance of peak of 2H singlet at δ 6.66 for CH confirmed the

chlorination of carbon-carbon double bond. NMR spectra confirmed the structure of 3,4-dichloro-1-phenyl-*1H*-pyrrole-2,5-dione(**7**).



^{1}H NMR spectrum of 3,4-dichloro-1-phenyl-*1H*-pyrrole-2,5-dione(7).



^{13}C NMR spectrum of 3,4- dichloro-1-phenyl-*1H*-pyrrole-2,5-dione (7).

We have also tried the reactions of maleic anhydride with another amines viz. *o*-phenylenediamine, bromopyridine, *o*-mercaptoaniline and 2-aminopyridine at different reaction conditions but only starting materials was recovered.

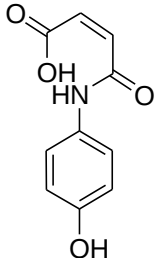
EXPERIMENTAL

All reactions were carried out in oven-dried glassware. Hydroxyaniline and 4-mercaptoaniline were purchased from Sigma Aldrich and rest of the chemicals and solvents were purchased from Merck, Loba, SD Fine and Spectrochem. Thin layer chromatography (TLC) was performed on glass plates coated with silica gel purchased from Merck Inc. Purification was carried out by column chromatography using hexane:ethylacetate (70:30) as eluents using 60-120 mesh silica gel. ^{1}H and ^{13}C NMR spectra were obtained from Jeol 400

MHz spectrometer with use of chloroform–d and dimethylsulfoxide-d_6 as solvents. Chemical shifts were recorded in parts per million (ppm, δ) and were reported relative to the solvent peak or TMS. Multiplicities are recorded with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (hertz).

Synthesis of intermediate 4-(hydroxyphenylamino)-4-oxobut-2-enoic acid (2)

The intermediate of compound **2** was synthesised by stirring of maleic anhydride (0.5 g,

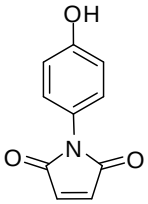


0.005 mmol) with 4-hydroxyaniline (0.56 g, 0.005 mmol) in diethyl ether (40 mL) at room temperature for 10 hrs. This resulted semisolid was filtered, washed with diethyl ether and then dried. Green coloured solid of 4-(4-hydroxyphenylamino)-4-oxobut-2-enoic acid **(2)** was obtained; m.p.-181 ^{0}C; yield-84.7%; ^{1}H NMR ($CDCl_3$): δ 9.68 (s, 1H, NH), 7.54 (d, 1H, *J* = 8.72, CH), 7.38 (d, 1H, *J* = 8.68, CH), 7.24-7.04 (m, 4H, ArH), 3.54 (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 168.3, 167.8, 155.6, 148.0, 132.6, 126.3, 125.7, 120.6, 114.

General procedure for synthesis of compounds 3-6

1-(4-hydroxyphenyl)-*1H*-pyrrole-2,5-dione (3)

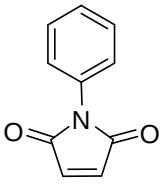
To the compound **2**, sodium acetate (1 mole eq.) and acetic anhydride (0.5 ml/mmol) were



added. The mixture was refluxed for 24 hrs and the reaction was monitored by TLC. After the completion of reaction, the product was purified by column chromatography using hexane:ethylacetate as eluents. Yellow coloured liquid of 1-(4- hydroxyphenyl)-*1H*-pyrrole-2,5-dione was obtained; yield-84.6%; ^{1}H NMR ($CDCl_3$): δ 7.37 (d, 2H, *J* = 9.16 Hz, ArH), 7.19 (d, 2H, *J* = 9.16 Hz, ArH), 6.85 (s, 2H, CH); ^{13}C NMR ($CDCl_3$): δ 169.2, 134.1, 126.8, 122.2, 21.1.

1-phenyl-*1H*-pyrrole-2,5-dione (4)

A mixture of maleic anhydride (0.5 g, 0.005 mmol) and 1eq. of aniline (0.47 g, 0.005 mmol)

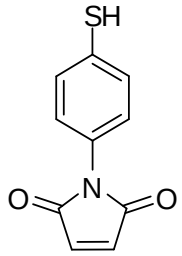


in diethyl ether (40 ml) was stirred for 6 hrs at room temperature. The mixture was then filtered and washed with diethyl ether. This intermediate was used without further purification for next reaction. To filtered product, sodium acetate (1 mole eq.) and acetic anhydride (0.5 ml/mmol) was

added. The mixture was refluxed for 12 hrs. The resulted product was then purified using column chromatography. White fine powder of 1-phenyl-*1H*-pyrrole-2,5-dione was obtained; m.p-181.5 ^{0}C; yield-80.2%; ^{1}H NMR ($CDCl_3$): δ 7.38-7.33 (m, 3H, ArH), 7.27-7.24 (m, 2H, ArH), 6.66 (s, 2H, 2CH); ^{13}C NMR ($CDCl_3$): δ 173.0, 169.6, 134.2, 130.0, 129.8, 129.2, 128.8, 127.9, 126.2.

1-(4-mercaptophenyl)-*1H*-pyrrole-2,5-dione (5)

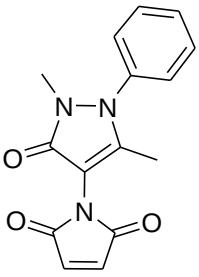
A mixture of maleic anhydride (0.5g, 0.005 mmol) and 1eq. of 4-mercaptoaniline (0.64g, 0.005



mmol) in diethyl ether (40 ml) was stirred for 10 hrs at r.t. The mixture was then filtered and washed with diethyl ether. To filtered product, sodium acetate (1 mole eq.) and acetic anhydride (0.5 ml/mmol) was added. The mixture was refluxed for 24 hrs. The resulted product was purified by column chromatography. White fine powder of 1-(4-mercaptophenyl)-*1H*-pyrrole-2,5-dione obtained; m.p-179 ^{0}C; yield-76%; ^{1}H NMR ($CDCl_3$): δ 7.49-7.41 (m, 4H, ArH), 6.83 (s, 2H, CH); ^{13}C NMR ($CDCl_3$): δ 193.3, 169.0, 134.9, 1343.2, 132.2, 127.3, 126.0.

1-(2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-*1H*-pyrazol-4-yl)-*1H*-pyrrole-2,5-dione (6)

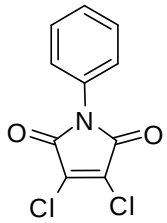
A mixture of maleic anhydride (0.5g, 0.005 mmol) and 1.1eq. of 2-aminoantipyrine (1.15g,



0.0056mmol) in THF (40 ml) was stirred for 5 hrs at room temperature.. The mixture was then filtered. To filtered product, sodium acetate (1 mole eq., 42 mg) and acetic anhydride (0.5 ml/mmol) was added. The mixture was refluxed for 12 hrs. The resulted product was then purified using column chromatography. Yellow coloured semisolid of 1-(2,5-dimethyl-3-oxo-1-phenyl-2, 3-dihydro-*1H*-pyrazol-4-yl)-*1H*-pyrrole-2,5-dione was obtained; yield-81.5%, ^{1}H NMR ($CDCl_3$): δ 7.28-7.27 (m, 5H, ArH), δ 7.17 (s, 1H, NH), 6.68 (s, 2H, CH), 2.99 (s, 3H, N-CH_3), 1.96 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 169.5, 165.4, 160.9, 152.5, 134.9, 132.5, 129.3, 127.7, 125.7, 126.4, 125.2, 100.2, 68.9, 35.1, 10.7.

General procedure for the synthesis of 3,4-dichloro-1-phenyl-*1H*-pyrrole-2,5-dione (7)

Compound **3** was dissolved in pyridine (1ml) and $SOCl_2$ (4 ml) was added dropwise at 0°C



and then refluxed at 60°C for 24 hrs. The resulted product was then purified by column chromatography using hexane:ethylacetate as eluents. Yellow coloured liquid of 3,4-dichloro-1-phenyl-*1H*-pyrrole-2,5-dione was obtained; yield-77%; ^{1}H NMR ($CDCl_3$): δ 7.48-7.34 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$): δ 161.9, 133.5, 129.3, 128.6, 125.9.

CONCLUSION

1. Novel compounds of 1-(4-hydroxyphenyl)-*1H*- pyrrole-2,5-dione (**3**), 1-phenyl-*1H*-pyrrole-2,5-dione (**4**), 1-(4-mercaptophenyl)-*1H*-pyrrole-2,5-dione (**5**), 1-(2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-*1H*-pyrazol-4-yl)-*1H*-pyrrole-2,5-dione**(6),** 3,4-dichloro-1-phenyl-*1H*-pyrrole-2,5-dione **(7)** were synthesized in moderate to high yield. These compounds were well characterized by ^{1}H and ^{13}C NMR experiments.
2. Intermediate 4-(4-hydroxyphenylamino)-4-oxobut-2-enoic acid was synthesized and isolated from reaction mixture and characterized by NMR experiments.
3. Chlorination of 1-phenyl-*1H*-pyrrole-2,5-dione with thionyl chloride and pyridine gave good yield of product.

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