ความสัมพันธ์ระหว่างโครงสร้างและฤทธิ์ต้านชักของสารในกลุ่มทาลิมีด

นาย วันชัย ปลื้มภาณุภัทร

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STRUCTURE AND ANTICONVULSANT ACTIVITY RELATIONSHIP OF PHTHALIMIDES

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วันชัย ปลื้มภาณุภัทร : ความสัมพันธ์ระหว่างโครงสร้างและฤทธิ์ต้านชักของสารในกลุ่มทาลิมีด (STURTURE AND ANTICONVULSANT ACTIVITY RELATIONSHIP OF PHTHALIMIDES), อ. ที่ปรึกษา : ผศ.ดร. วรินทร ชวศิริ; 71 หน้า; ISBN 947-347-271-1.

ได้สังเคราะห์สารในกลุ่มทาลิมีด, บิส-ทาลิมีดและสารที่เกี่ยวข้อง และทำการทดสอบฤทธิ์ทางชีวภาพเพื่อค้นหาสารที่แสดงฤทธิ์ต้านชัก โดยอาศัยปฏิกิริยาควบแน่นระหว่างแอนไฮไดรด์ และเอมีนที่สนใจหลายชนิด สามารถประสบความสำเร็จในการเตรียมสารในกลุ่มทาลิมีด 64 ชนิด, บิส-ทาลิมีด 12 ชนิดและสารที่เกี่ยวข้องอีก 6 ชนิด เมื่อนำสารที่สังเคราะห์ได้ทั้งหมดไปทดสอบฤทธิ์ต้านชักโดยวิธี MES (Maximal Electroshock Seizure) ซึ่งเป็นวิธีการทดสอบฤทธิ์ต้านชักเบื้องต้นเปรียบเทียบกับเฟนิโทอิน พบว่า รูปแบบของสารที่แสดงฤทธิ์ต้านชัก จะมีหมู่อะมิโนบนวงเอ็น-เฟนิล และสารที่แสดงฤทธิ์ต้านชักที่ดีที่สุด พบว่าเป็นสารที่มีหมู่แทนที่เป็น 4-อะมิโน, 2-คลอโร-4-อะมิโน และ 2-เมทิล-4-อะมิโน บนวงเอ็น-เฟนิล

ภาควิชา……เคมี……ลายมือชื่อนิสิต……..…….

สาขาวิชา……..เคมี……ลายมือชื่ออาจารย์ที่ปรึกษา……..…….…….

ปีการศึกษา……...2543……..

4272391523 : MAJOR CHEMISTRY
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WANCHAI PLEUMPANUPAT : STRUCTURE AND ANTICONVULSANT ACTIVITY RELATIONSHIP OF PHTHALIMIDE. THESIS ADVISOR : ASSISTANT PROFESSOR WARINTHORN CHAVASIRI, Ph.D. 71 pp. ISBN 947-347-271-1.

Phthalimides, *bis*-phthalimides and analogues were synthesized and screened for the possibility of finding compounds possessing anticonvulsant activity. Condensation reaction between selected anhydrides and various interested amines leads to the accomplishment of the preparation of sixty-four phthalimides, twelve *bis*-phthalimides, six analogues. Synthesized phthalimides were subjected to test with MES (Maximal Electroshock Seizure) test, a preliminary screening test for anticonvulsant activity compared with phenytoin. It was disclosed that the best patterns require amino substitution on the *N*-phenyl moiety. The most potent compounds found were those contained 4-amino, 2-chloro-4-amino and 2-methyl-4-amino, respectively, substituted of the *N*-phenyl ring.

Department……Chemistry…….Student's signature ……
Field of study .....Chemistry…..…Advisor's signature ……..…….
Academic year……2000….....….

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A deep affectionate gratitude is acknowledged to his parents and family members for their love, understanding, encouragement and support throughout the entire course of study. Without them, the author would never have been able to achieve this goal.

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List of Abbreviations

br	broad	mL	milliliter (s)
°C	degree Celsius	m.p.	melting point
cm^{-1}	unit of wavenumber	MW	molecular weight
d	doublet (NMR)	NMR	nuclear magnetic resonance
DMSO	dimethylsulfoxide	ppm	part per million
g	gram (s)	q	quartet (NMR)
hr	hour (s)	qui	quintet (NMR)
Hz	hertz	R_f	retardation factor
IR	infrared	s	strong (IR)
J	coupling constant	s	singlet (NMR)
kg	kilogram	s	second
lit	literature	str.	stretching
m	multiplet (NMR)	t	triplet (NMR)
m	medium (IR)	w	weak (IR)
mA	milliampere (s)	wt	weight
mg	milligram (s)	δ	chemical shift
min	minute (s)	%	percent

CHAPTER I
INTRODUCTION

Epilepsy has been defined as a symptom of excessive temporary neuronal discharge, characterized by discrete recurrent episodes, in which there is a disturbance of movement, sensation, behavior, perception, and/or consciousness. Epileptic seizures vary widely intraindividually and interindividually with respect to magnitude, duration, and frequency of occurrence. It has been estimated that from 0.5 to 1% of the world's population is affected by some forms of epilepsy have more than one type of seizure.[1] In a recent review, Bruni pointed out that with the drugs available today, significant seizure control can be achieved in 70-80% of persons with epilepsy, and complete control can be obtained in 60%. Infantile spasms and complex partial seizures pose the most difficult therapeutic problems. The management of epilepsy is a dynamic process, and orderly changes in antiepileptic drug therapy are often required, and there is still a need for new anticonvulsants with more selective action and fewer toxic effects.

More than four decades have passed since Putnam and Merritt[2] first demonstrated that drugs effective in epilepsy can be distinguished from other organic chemicals by testing their ability to suppress experimentally induced convulsions in normal laboratory animals. During this time, virtually all species of laboratory animals have been subjected to a wide variety of electrical, chemical, and sensory seizure-evoking techniques in anticipation of finding a model that would be representative of the clinical disorder. Ideally, such models should duplicate the human clinical condition. Unfortunately, knowledge of the underlying causes of various types of convulsive disorders is still incomplete, and the development of laboratory models based on etiology is not yet possible. Consequently, most experimental models of epilepsy are designed to simulate in laboratory animals various chemical, electrical, or overt manifestation of the disorder.[3]

Anticonvulsant drug activity can also be determined at various biological levels, such as axons; intact single cell; groups of cells, including pre- and postsynaptic events; suborgan cellular connections, including spinal cord pathways; organ systems, including the whole brain; and modified intact animals in which the

brain has been surgically or chemically altered.[3] Many of these sophisticated procedures are extremely valuable, especially as penultimate tests prior to clinical drug trials and as models for the study of seizure mechanisms. Unfortunately, many of them are also tedious, time consuming, and costly. Consequently, they do not lend themselves to the routine screening of the large numbers of chemicals; one must test in the search for new agents with antiepileptic potential. For these and other reasons, intact normal rodents are preferred for this purpose.[4]

At present, no single laboratory test will in itself establish the presence or absence of anticonvulsant activity in a chemical substance. Therefore, a battery of tests should be employed for identifying and evaluating substances with anticonvulsant potential. These tests should be selected for their ability to detect substances with anticonvulsant activity, to show whether such activity results from the prevention of seizure spread or from the elevation of seizure threshold, and to provide some insight as their mechanisms of action. Since antiepileptic drugs must be taken chronically and, in many instances, throughout the life of the patient, it is equally important to include a battery of toxicity tests in the procedure. The toxicity tests should not only enable the investigator to determine accurately the minimal median neurotoxic dose and the 24 hr median lethal dose but should also provide a profile of the overt toxic manifestations between these two dose levels. A procedure specifically designed to accomplish these objectives will be described in this chapter. During this time, over 5,500 chemical substances have been screened for anticonvulsant activity and neurotoxicity. In addition, more than 900 chemicals show to have activity by the anticonvulsant identification procedure have been subjected to various levels of anticonvulsant quantification and evaluation. Thus, these procedures have been shown to be reliable and reproducible.

1.1 Classification of Epilepsy

Classification of epilepsy is complicated and can be based on etiology, pathology, and age of onset, clinical seizure, electroencephalogram (EEG) findings, or prognosis. A revised classification of individual seizure types was accepted in 1981 by the general Assembly of the International League Against Epilepsy (ILAE)[5,6] (present in term of seizure types in Table 1.1).

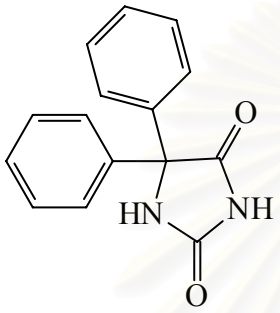
Table 1.1 Classification of epilepsy [6]

I. Partial seizures (Focal, Local seizures) A. Simple partial seizures (consciousness not impaired) 1. With motor symptoms 2. With somatosensory or special sensory symptoms 3. With autonomic symptoms 4. With psychic symptoms B. Complex partial seizures (consciousness impaired) 1. Simple partial onset followed by impaired conscious a. With simple partial feature as in A. 1-4 b. Without automatisms 2. With impairment of consciousness at onset a. With no other features b. With partial feature as in A. 1-4 c. With automatisms C. Partial seizure evolving to secondarily generalized seizures
II. Generalized seizures (Convulsive or Nonconvulsive) A. Absence seizures 1. Absence seizures 2. Atypical absence B. Myoclonic seizures C. Clonic seizures D. Tonic seizures E. Tonic clonic seizures F. Atonic seizures
III. Unclassified epileptic seizures

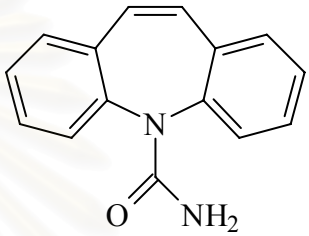
Modified from Commission on Classification of the International League against Epilepsy

1.2 Literature Reviews

Organic chemicals possessing anticonvulsant activity, can be separated into several groups, for instance, hydantoins, iminostilbenes, barbiturates, benzo-diazepines, valproates, imides, oxazolidine-2,4-diones, sulfonamides, phthalimides and miscellaneous agents.[7] Some compounds were developed to commercial anticonvulsant drugs, such as phenytoin **(I)**, carbamazepine **(II)**, ethosuximide **(III)**, valproate **(IV),** clonazepam **(V)** and etc.[8]



(I)



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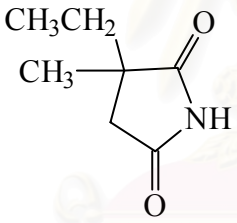

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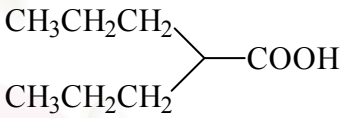

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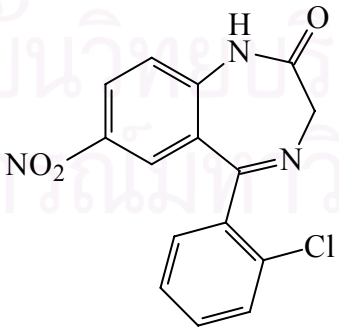


(V)

In order to have a complete control of epilepsy, the appropriate treatment must be selected on the basis of the type of epilepsy and the cause of seizures.[9] The choice of the initial and subsequent drugs considered to be appropriate for each seizure type are given in Table 1.2.

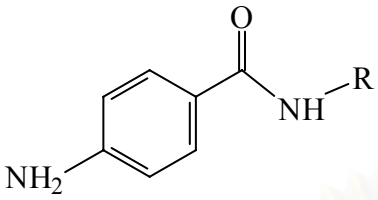
Table 1.2 Appropriate choice of antiepileptic drugs [9]

Seizure type	Initial drugs	Subsequent drugs
Partial seizure		
Simple partial	Carbamazepine	Phenytoin
Complex partial	Carbamazepine	Phenytoin, Valproate
Secondary generalized Tonic-clonic	Carbamazepine	Phenytoin, Valproate
Generalized seizure		
Typical absence	Ethosuximide	Valproate
Atypical absence	Valproate	Clonazepam
Myoclonic	Valproate	Clonazepam
Clonic	Carbamazepine	Valproate
Tonic	Carbamazepine	Valproate
Tonic-clonic	Carbamazepine	Phenytoin, Valproate

Table 1.2, showed the commercial antiepileptic drug specific to seizure type. Every seizure types could not respond to one drug. Sometime, a patient has side effect because at drug toxicity and when used drug more over. After that, the researcher investigated for discovering new compounds, which showed high anticonvulsant activity, no toxicity and used to every seizure types.

The investigation of anticonvulsant activity of phthalimides has been recently reported. For example, in 1984 C. R. Clark and coworkers reported that a series of 4-amino-*N*-substituted-benzamides **(VI)** shown high anticonvulsant activity but high toxicity.[10] After that, in 1985 C. R. Clark and coworkers disclosed significant anticonvulsant potential at 4-aminobenzanilide derivatives. 4-Amino benzanilide derived from 2,6-dimethylaniline (4-amino(2,6-dimethylphenyl)benzamide) **(VII)** was the most potent anti-MES compound with an ED_{50} of 2.60 mg/kg.[11] These compound could not be further developed to a new anticonvulsant because of its high

toxicity. In 1986, C.R. Clark and coworkers exhibited the order of anticonvulsant activity of the aminobenzanilides. It was found that the activity was corresponded to the ring substitution pattern of 4-amino > 3-amino > 2-amino.[12]



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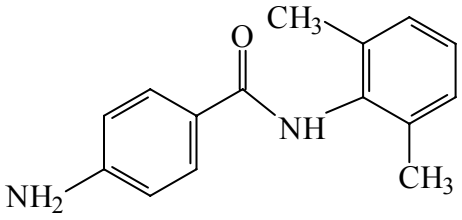
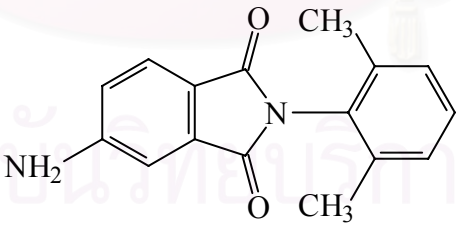


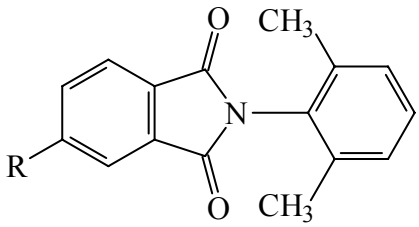
(VII)

In 1994, J. Vamecq and coworkers were interested in the remarkable anticonvulsant properties of 4-aminobenzamide series, claimed by Clark to be highly efficient anticonvulsant drugs in mice and rats. Replacing the benzamide moiety of molecules from the series of Clark with phthalimide affords *N*-phenylphthalimides. 4-amino-*N*-(2,6-dimethylphenyl)phthalimide **(VIII)** was shown high anticonvulsant activity in mice, the order of decreasing anticonvulsant activity in relation to the phthalimide ring substitution pattern was: 4-amino > 4-nitro > 4-methyl ; H > 3-nitro ; 3-amino. Regarding the nature of the 2 and 6 substituents of the *N*-phenyl ring, the anticonvulsant efficiencies may be in ordered as follows : 2,6-dimethyl > 2-methyl > 2-ethyl > 2-ethyl-6-methyl > 2,6-diethyl > unsubstituted phenyl ring.[13]



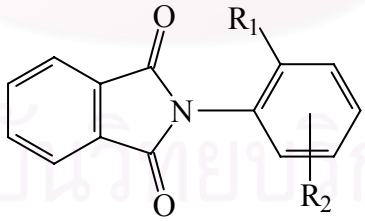
(VIII)

In 1998, J. Vamecq and coworkers studied for anticonvulsant potential in the MES test in mice and rats. After initial screening in mice, phthalimides **(IX)**, **(X)**, **(XI)**, **(XII)** and **(XIII)** exhibited impressive anticonvulsant activity.[14]

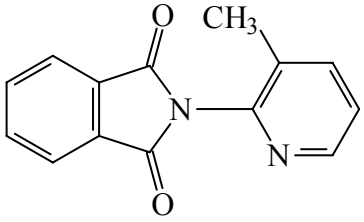


(IX)	R = H
(X)	R = NO_2
(XI)	R = NH_2
(XII)	R = OH
(XIII)	R = Cl

In 2000, J. Vamecq and coworkers investigated a series of *N*-phenyl phthalimide derivatives including methyl, amino, chloro and nitro substituents of *N*-phenyl moiety by devoid of 4-amino substitution. Despite omission of this 4-substituent on phthalimide nucleus, the design results in a series of compounds with highly potent leads active notably in the MES test. After initial screening in mice, phthalimides **(XIV)**, **(XV)**, **(XVI)**, **(XVII)**, **(XVIII)**, **(XIX)** and **(XX)** shown anticonvulsant activity. Some compounds were selected for further testing oral MES evaluation in rats. The resultant ED_{50} values for phthalimides **(XVI)**, **(XVII)** and **(XIX)** were 8.0, 28.3, 5.7 mg/kg, respectively. The comparison of the activity of phthalimide **(XVI)** and succinimide **(XXI)** which having the same substituents in phenyl ring but different in type of anhydride. Phthalimide **(XVI)** was more potent against MES than succinimide **(XXI)**.[15] *N*-Phenylphthalimide derivatives seem to have great potential as candidate anticonvulsant drugs.



(XIV)	R_1 = H, R_2 = 4-NH_2
(XV)	R_1 = H, R_2 = 3-NH_2
(XVI)	R_1 = 2-CH_3, R_2 = 3-NH_2
(XVII)	R_1 = 2-CH_3, R_2 = 6-NH_2
(XVIII)	R_1 = 2-CH_3, R_2 = 3-CH_3
(XIX)	R_1 = 2-Cl, R_2 = 4-NH_2



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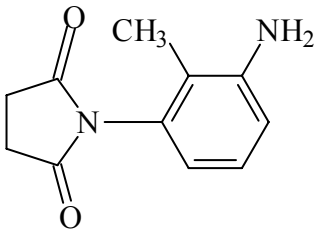


(XXI)

1.3 Synthesis of Phthalimides

Numerous methods applied for the synthesis of phthalimides because of their biological importance to develop new anticonvulsant drugs. The early reported routes to synthesize these compounds are, for instance, the procedure was generally utilized nucleophilic substitution reaction between phthlimides and alkyl- or aryl halides in the presence of anhydrous potassium carbonate at 190°C.[16] Recent reports, methodology used for the synthesis of phthalimides were condensation of phthalic anhydride with interested amines or aniline derivatives in acetic acid at reflux temperature. Most phthalimides were obtained in good yield. This reaction is also a common nucleophilic substitution of phthalic anhydride with a nucleophile (amines). The latter method was more convenient than the former method because various starting materials required are commercially available.[15]

1.4 Goal of This Research

The aim of this research is to investigate and to develop phthalimides that possess anticonvulsant activity. The approach is based upon the assumption that structure-activity relationship (SAR) study is not merely a knowledge of how much their activities are, but also the appropriate match of structures and activities of studied compounds. In addition, the SAR study will permit a logical opportunity to predict relationship of other molecules (analogues of phthalimide) and these activities. Therefore, the goal of this research can be summarized as follows:

1. To synthesize phthalimides and related compounds
2. To study the relationship between phthalimides and related compounds and anticonvulsant activity

CHAPTER II
EXPERIMENTAL

2.1 Instruments and Equipment

Melting points were determined with a Fisher-Johns melting point apparatus or Electrothermal digital melting point apparatus model IA 9100 and are uncorrected. Column chromatography was carried out on silica gel (Merck Kieselgel 60, 70-230 mesh). Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck Kieselgel 60 PF_{254}). The FT-IR spectra were recorded on a Nicolet Fourier Transform Infrared Spectrophotometer model Impact 410: solid samples were incorporated to potassium bromide to form a pellet. The ^{1}H and ^{13}C-NMR spectra were performed in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as an internal reference on a Bruker model ACF 200 Spectrometer which operated at 200.13 MHz for ^{1}H and 50.32 MHz for ^{13}C nuclei.

2.2 Chemicals

All solvents used in this research were purified prior to use by standard methodology except for those which were reagent grades. The reagents used for synthesizing the precursors, phthalimides and other compounds were purchased from Fluka Chemical Company or otherwise stated and were used without further purification.

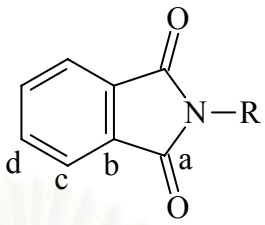
2.3 Synthesis of Phthalimides

General Procedure

A mixture of amine (6 mmol) and phthalic anhydride (5 mmol) in glacial acetic acid (5 mL) was stirred and heated under reflux for 5 hours. The product was precipitated by addition of water, filtered off and washed well with water, and recrystallized with 95% ethanol.

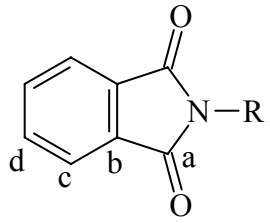
The *bis*-phthalimides were also synthesized by following the above mentioned general procedure using 2 mol equivalents of phthalic anhydride and 1 mol equivalent of diamines.

This research involves the SAR studies of phthalimides and analogues. All studied compounds were further classified into four groups, which are depicted in Figs 2.1-2.4. Compounds **63** and **64** were kindly supplied by W. Munbunjong.



Compound	R
1	—$CH_2CH_2CH_3$
2	—$CH_2(CH_2)_5CH_3$
3	—$CH_2(CH_2)_8CH_3$
4	—$CH_2(CH_2)_{12}CH_3$
5	—$CH_2(CH_2)_{16}CH_3$
6	—$CHCH_3$ CH_3
7	—CH_2CHCH_3 CH_3
8	—CH_2CH_2OH
9	—$CH_2CH_2CH_2OH$
10	—$CH_2CH_2CH_2OCH_3$

Fig 2.1 Structures of synthesized *N*-phthalimides



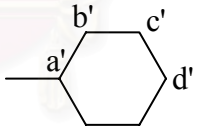
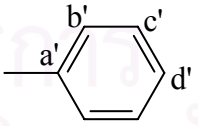
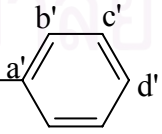
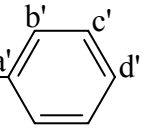
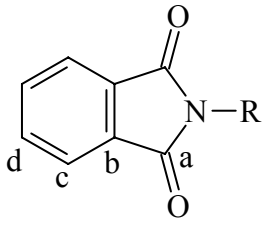
Compound	R
11	—CH_2COOCH_3
12	—CH_2COOH
13	—CHCOOH (+) CH_3
14	—CHCOOH (-) CH_3
15	—CHCOOH CH_3
16	—$CHCH_2COOH$ COOH
17	
18	
19	—CH_2— 
20	—CH_2CH_2— 

Fig 2.1 (cont.)



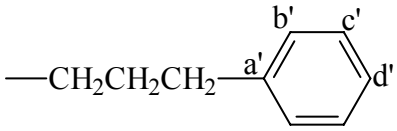
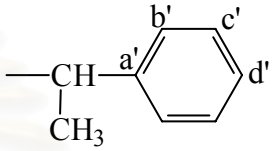
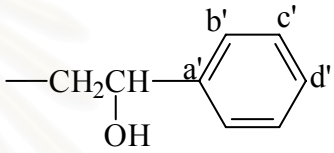
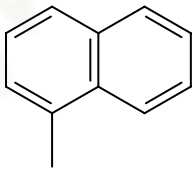
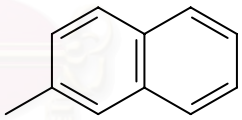
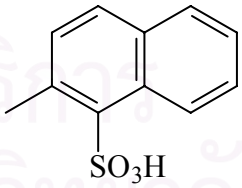
Compound	R
21	
22	
23	
24	
25	
26	

Fig 2.1 (cont.)

N-(Propyl)phthalimide **(1)[17] White crystal (16%), m.p. 64-65°C (95% ethanol), R_f 0.58 (dichloromethane). IR (KBr, cm^{-1}) 3090, 2962, 2935, 1766, 1720, 1608, 1465, 1396, 1384, 1338 and 1049; ^{1}H-NMR (DMSO-d_6) δ (ppm): 0.84 (3H, t, *J* = 6.78 Hz, CH_3), 1.55 (2H, m, CH_2), 3.60 (2H, t, *J* = 7.09 Hz, N-CH_2) and 7.83 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 12.5 (1C, CH_3), 22.4, 37.5 (2C, CH_2), 123.0 (2C, C-c), 131.7 (2C, C-d), 134.1 (2C, C-b) and 167.2 (2C, C-a).**

N-(Heptyl)phthalimide **(2)[18] Colorless liquid (60%), R_f 0.70 (chloroform-ethyl acetate [1:1]). IR (neat, cm^{-1}) 3062, 2927, 2857, 1774, 1716, 1616, 1465, 1438, 1396, 1369 and 1068; ^{1}H-NMR (DMSO-d_6) δ (ppm): 0.81 (3H, t, *J* = 6.70 Hz, CH_3), 1.14-1.25 (10H, m, br, CH_2), 1.51-1.57 (2H, m, N-CH_2-C$\underline{H}_2$), 3.63 (2H, t, *J* = 7.14 Hz, N-CH_2) and 7.82 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 14.0 (1C, CH_3), 22.0, 26.8, 28.4, 31.4, 37.5 (5C, CH_2), 123.1 (2C, C-c), 131.8 (2C, C-d), 134.6 (2C, C-b) and 167.3 (2C, C-a).**

N-(Decyl)phthalimide **(3)[19] White crystal (68%), m.p. 55-56°C (95% ethanol), R_f 0.72 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3108, 3050, 2850, 2915, 1774, 1712, 1612, 1461, 1434, 1403 and 1060; ^{1}H-NMR (DMSO-d_6) δ (ppm): 0.80 (3H, t, *J* = 6.76 Hz, CH_3), 1.17-1.22 (14H, m, br, CH_2), 1.54 (2H, m, N-CH_2-C$\underline{H}_2$), 3.52 (2H, t, *J* = 7.06 Hz, N-CH_2) and 7.81 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 13.8 (1C, CH_3), 22.0, 26.2, 27.8, 28.5, 28.6, 28.8, 31.2, 37.3 (8C, CH_2), 122.9 (2C, C-c), 131.5 (2C, C-d), 134.3 (2C, C-b) and 167.8 (2C, C-a).**

N-(Tetradecyl)phthalimide **(4)[20] White crystal (65%), m.p. 64-66°C (95% ethanol), R_f 0.68 (dichloromethane). IR (KBr, cm^{-1}) 3063, 2954, 1779, 1720, 1602, 1460, 1434, 1399, 1350 and 1067; ^{1}H-NMR (DMSO-d_6) δ (ppm): 0.82 (3H, t, *J* = 6.60 Hz, CH_3), 1.20-1.29 (22H, m, br, CH_2), 1.61 (2H, m, N-CH_2-C$\underline{H}_2$), 3.69 (2H, t, *J* = 7.30 Hz, N-CH_2) and 7.62-7.83 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 13.4 (1C, CH_3), 22.0, 26.3, 26.5, 27.0, 27.8, 28.4, 28.5, 28.6, 28.7, 28.8, 28.9, 31.2, 40.6 (13C, CH_2), 123.5 (2C, C-c), 131.5 (2C, C-d), 134.9 (2C, C-b) and 167.8 (2C, C-a).**

N-(Octadecyl)phthalimide **(5)[21] White crystal (52%), m.p. 76-80°C (95% ethanol) (lit.[21] m.p. 78-80°C), R_f 0.72 (dichloromethane). IR (KBr, cm^{-1}) 3070, 2915, 2850, 1774, 1700, 1616, 1461, 1434, 1334 and 1056; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (3H, t, *J* = 6.65 Hz, CH_3), 1.22-1.29 (30H, m, br, CH_2), 1.64 (2H, m, N-CH_2-C$\underline{H}_2$), 3.65 (2H, t, *J* = 7.38 Hz, N-CH_2) and 7.67-7.84 (4H, m, Ar-H); ^{13}C-**

NMR ($CDCl_3$) δ (ppm): 13.8 (1C, CH_3), 22.0, 26.3, 26.5, 27.0, 27.5, 27.8, 28.4, 28.5, 28.6, 28.6, 28.7, 28.8, 28.8, 28.9, 29.0, 31.2, 40.6 (17C, CH_2), 124.3 (2C, C-c), 132.1 (2C, C-d), 135.0 (2C, C-b) and 168.6 (2C, C-a).

N-(1-methylethyl)phthalimide **(6)[22,23] White crystal (10%), m.p. 79-83°C (95% ethanol), R_f 0.64 (dichloromethane). IR (KBr, cm^{-1}) 3081, 3031, 2999, 2981, 1774, 1697, 1612, 1463, 1388, 1369 and 1041; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.38 (6H, d, *J* = 6.85 Hz, CH_3), 4.36 (1H, m, *J* = 6.92 Hz, CH) and 7.80 (4H, m, br, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 19.8 (2C, CH_3), 42.2 (1C, CH), 122.6 (2C, C-c), 131.4 (2C, C-d), 134.2 (2C, C-b) and 167.8 (2C, C-a).**

N-(2-methylpropyl)phthalimide **(7)[23] White crystal (34%), m.p. 89-90°C (95% ethanol), R_f 0.64 (dichloromethane). IR (KBr, cm^{-1}) 3100, 3031, 2958, 2931, 2873, 1774, 1700, 1612, 1461, 1434, 1400, 1346, 1167 and 1052; ^{1}H-NMR (DMSO-d_6) δ (ppm): 0.82-0.90 (6H, m, CH_3), 1.94 (2H, p, *J* = 6.85 Hz, CH_2), 3.60 (1H, m, CH) and 7.78-7.83 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 19.9 (2C, CH_3), 27.3 (1C, CH_2), 44.7 (1C, CH), 122.9 (2C, C-c), 131.4 (2C, C-d), 134.4 (2C, C-b) and 168.1 (2C, C-a).**

N-(2-hydroxyethyl)phthalimide **(8)[24] White crystal (21%), m.p. 129-131°C (95% ethanol) (lit.[24] m.p. 130-131°C), R_f 0.62 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3465, 2950, 1776, 1738, 1710, 1437, 1395, 1240 and 1037; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.91 (1H, s, br, OH), 3.80 (2H, t, *J* = 5.57 Hz, N-CH_2), 4.20 (2H, t, *J* = 5.54 Hz, O-CH_2) and 7.78-7.87 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 36.7 (1C, N-CH_2), 61.0 (1C, CH_2-O), 123.0 (2C, C-c), 131.4 (2C, C-d), 134.4 (2C, C-b) and 167.6, 170.2 (2×1C, C-a).**

N-(3-hydroxypropyl)phthalimide **(9)[25] Colorless liquid (26%), R_f 0.66 (chloroform-ethyl acetate [1:1]). IR (neat, cm^{-1}) 3600-3250, 3062, 2954, 2896, 1770, 1725, 1465, 1396, 1249 and 1045; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.82 (2H, m, br, CH_2), 3.63 (2H, t, *J* = 6.63, O-CH_2), 3.95 (2H, t, *J* = 6.17 Hz, N-CH_2) and 7.77-7.84 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 26.8 (1C, CH_2), 34.7 (1C, N-CH_2), 61.8 (1C, CH_2-O), 122.9 (2C, C-c), 131.6 (2C, C-d), 134.3 (2C, C-b) and 167.8, 170.2 (2×1C, C-a).**

N-(3-Methoxypropyl)phthalimide **(10)[26] Colorless liquid (32%), R_f 0.64 (chloroform-ethyl acetate [1:1]). IR (neat, cm^{-1}) 3062, 2931, 1770, 1708, 1612,**

1465, 1438, 1396, 1199, 1114 and 1045; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.78 (2H, qui, *J* = 6.65, CH_2), 3.11 (3H, s, CH_3), 3.35 (2H, m, O-CH_2), 3.95 (2H, t, *J* = 6.88 Hz, N-CH_2) and 7.77-7.86 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 28.0 (1C, CH_2), 35.0 (1C, N-CH_2), 57.8 (1C, CH_3), 69.5 (1C, CH_2-O), 122.9 (2C, C-c), 131.6 (2C, C-d), 134.3 (2C, C-b) and 167.8, 170.2 (2×1C, C-a).

***N-(Methylethanoyl)phthalimide* (11)[27] White crystal (43%), m.p. 109-112°C (95% ethanol), R_f 0.70 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3031, 2965, 2915, 1751, 1724, 1612, 1423, 1400, 1373, 1311, 1222 and 1118; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.39 (3H, s, br, CH_3), 4.39 (2H, s, br, CH_2) and 7.84-7.94 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 39.0 (1C, CH_2), 52.5 (1C, CH_3), 123.4 (2C, C-c), 131.3 (2C, C-d), 134.8 (2C, C-b), 167.0 (2C, C-a) and 168.0 (1C, COO).**

***N-(Ethanoyl)phthalimide* (12)[28] White crystal (53%), m.p. 193-196°C (95% ethanol), R_f 0.52 (ethyl acetate-methanol [1:1]). IR (KBr, cm^{-1}) 3300-3000, 3100, 2989, 2935, 1770, 1724, 1608, 1423, 1392, 1319, 1245, 1191 and 1087; ^{1}H-NMR (DMSO-d_6) δ (ppm): 4.30 (2H, s, br, CH_2) and 7.80-7.91 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 38.8 (1C, CH_2), 123.3 (2C, C-c), 131.3 (2C, C-d), 134.7 (2C, C-b), 167.2 (2C, C-a) and 168.9 (1C, COOH).**

***N-(+)-(1-Carboxyethyl)phthalimide* (13)[29] White crystal (68%), m.p. 144-148 °C (95% ethanol), R_f 0.57 (ethyl acetate-methanol [1:1]). IR (KBr, cm^{-1}) 3325-2350, 3032, 2993, 2945, 1780, 1727, 1689, 1606, 1452, 1385, 1332, 1259 and 1045; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.55 (3H, d, *J* = 7.31 Hz, CH_3), 4.86 (1H, q, *J* = 7.11 Hz, CH) and 7.81-7.90 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 14.8 (1C, CH_3), 46.8 (1C, CH), 123.2 (2C, C-c), 131.2 (2C, C-d), 134.7 (2C, C-b), 167.1 (2C, C-a) and 171.1 (1C, COOH).**

***N-(-)-(1-Carboxyethyl)phthalimide* (14)[29] White crystal (81%), m.p. 133-138 °C (95% ethanol), R_f 0.58 (ethyl acetate-methanol [1:1]). IR (KBr, cm^{-1}) 3300-2300, 3030, 2996, 2950, 1774, 1681, 1612, 1454, 1392, 1334, 1265 and 1076; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.54 (3H, d, *J* = 7.32 Hz, CH_3), 4.83 (1H, q, *J* = 7.11 Hz, CH) and 7.80-7.91 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 14.7 (1C, CH_3), 46.8 (1C, CH), 123.2 (2C, C-c), 131.3 (2C, C-d), 134.6 (2C, C-b), 167.2 (2C, C-a) and 171.1 (1C, COOH).**

N-(1-Carboxyethyl)phthalimide **(15)[29] White crystal (75%), m.p. 156-160°C (95% ethanol), R_f 0.56 (ethyl acetate-methanol [1:1]). IR (KBr, cm^{-1}) 3350-2300, 3035, 2996, 2950, 1778, 1730, 1698, 1612, 1465, 1392, 1334, 1265 and 1090; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.55 (3H, d, *J* = 7.30 Hz, CH_3), 4.84 (1H, q, *J* = 7.10 Hz, CH) and 7.81-7.92 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 14.8 (1C, CH_3), 46.9 (1C, CH), 123.2 (2C, C-c), 131.2 (2C, C-d), 134.7 (2C, C-b), 167.1 (2C, C-a) and 171.0 (1C, COOH).**

N-(1,2-Dicarboxyethyl)phthalimide **(16)[29] White crystal (19%), m.p. 226-232 °C (95% ethanol), R_f 0.58 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3500-2300, 3043, 2946, 2923, 1778, 1735, 1608, 1427, 1392, 1299, 1199 and 1110; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.37 (2H, s, br, CH_2), 5.20 (1H, t, *J* = 12.6 Hz, CH), 7.67-7.89 (4H, m, Ar-H), and 11.75 (1H, s, br, COOH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 14.8 (1C, CH_3), 46.9 (1C, CH), 122.9, 125.3 (2×1C, C-c), 128.4, 130.7 (2×1C, C-d), 134.3, 136.1 (2×1C, C-b), 155.9 (2C, C-a) and 170.2 (1C, COOH).**

N-(Cyclohexyl)phthalimide **(17)[30] White crystal (75%), m.p. 162-164°C (95% ethanol) (lit.[30] m.p. 168°C), R_f 0.74 (chloroform-ethyl acetate[1:1]). IR (KBr, cm^{-1}) 3070, 2927, 2854, 1762, 1708, 1612, 1465, 1392, 1376 and 1087; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.36 (6H, m, CH_2), 1.91 (4H, m, CH-C$\underline{H}_2$), 3.95 (1H, m, CH) and 7.72-7.86 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 24.94 (2C, C-c′), 25.4 (1C, C-d′), 29.4 (2C, C-b′), 50.0 (1C, C-a′), 122.8 (2C, C-c), 131.3 (2C, C-d), 134.3 (2C, C-b) and 167.7 (2C, C-a).**

N-(Phenyl)phthalimide **(18)[31] White crystal (71%), m.p. 209-211°C (95% ethanol) (lit.[31] m.p. 211°C), R_f 0.62 (dichloromethane). IR (KBr, cm^{-1}) 3053, 1776, 1705, 1588, 1494, 1456, 1385 and 1122; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.35-7.55 (5H, m, Ar-H) and 7.84-7.94 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 123.4 (1C, C-d′), 127.4 (2C, C-b′), 128.0 (2C, C-c), 128.8 (2C, C-c′), 131.5 (2C, C-d), 131.9 (2C, C-b), 134.7 (1C, C-a′) and 167.5 (2C, C-a).**

N-(1-Phenylmethyl)phthalimide **(19)[32] White needle crystal (59%), m.p. 113-115°C (95% ethanol) (lit.[32] m.p. 116°C), R_f 0.58 (dichloromethane). IR (KBr, cm^{-1}) 3062, 2950, 1767, 1715, 1650, 1428, 1395, 1338 and 1065; ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.83 (2H, s, CH_2), 7.24-7.44 (5H, m, Ar,-H) and 7.66-7.87 (4H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 41.6 (1C, CH_2), 121.7 (1C, C-d′), 124.9 (2C, C-b′),**

127.1 (2C, C-c), 129.2, 129.4 (1C×2, C-c′), 130.2 (2C, C-d), 132.3, 132.4 (1C×2, C-b), 135.5 (1C, C-a′) and 168.0 (2C, C-a).

N-(2-Phenylethyl)phthalimide **(20)[32] White crystal (74%), m.p. 129-133°C (95% ethanol) (lit.[32] m.p. 131-132°C), R_f 0.70 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3104,3027, 2969, 2935, 1770, 1708, 1616, 1496, 1461, 1427, 1396 and 1103; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.90 (2H, t, *J* = 7.60 Hz, CH_2), 3.79 (2H, t, *J* = 1.29 Hz, N-CH_2), 7.12-7.27 (5H, m, Ar-H) and 7.75-7.84 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 33.6 (1C, CH_2-Ph), 40.7 (1C, N-CH_2), 122.9 (1C, C-d′), 126.4 (2C, C-c), 128.3 (2C, C-b′), 128.4, 128.6 (1C×2, C-c′), 131.4 (2C, C-d), 134.4 (2C, C-b), 138.1 (1C, C-a′) and 167.6 (2C, C-a).**

N-(3-Phenylpropyl)phthalimide **(21)[33] Colorless liquid (67%), R_f 0.71 (chloroform-ethyl acetate [1:1]). IR (neat, cm^{-1}) 3085, 3027, 2938, 2861, 1774, 1716, 1612, 1438, 1396, 1369 and 1018; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.88 (2H, m, CH_2), 2.50 (2H, t, *J* = 8.09 Hz, CH_2-Ph), 3.58 (2H, t, *J* = 7.08 Hz, N-CH_2), 7.11-7.24 (5H, m, Ar-H) and 7.79-7.84 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 29.4 (1C, CH_2), 32.4 (1C, CH_2-Ph), 37.2 (1C, N-CH_2), 122.9 (1C, C-d′), 125.7 (2C, C-c), 128.1 (2C, C-b′), 128.2 (2C, C-c′), 131.6 (2C, C-d), 134.3 (2C, C-b), 141.1 (1C, C-a′) and 167.9 (2C, C-a).**

N-(1-Phenylethyl)phthalimide **(22)[34] Colorless liquid (53%), R_f 0.71 (chloroform-ethyl acetate [1:1]). IR (neat, cm^{-1}) 3062, 3031, 2981, 2938, 1774, 1708, 1612, 1454, 1388, 1357, 1330 and 1049; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.83 (3H, d, *J* = 7.25 Hz, CH_3), 5.44 (1H, q, *J* = 7.25 Hz, CH), 7.18-7.40 (5H, m, Ar-H) and 7.75-7.85 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 17.4 (1C, CH_3), 48.7 (1C, CH_2), 123.0 (1C, C-d′), 126.5 (2C, C-b′), 127.2 (2C, C-c), 128.4 (2C, C-c′), 131.3 (2C, C-d), 134.5 (2C, C-b), 140.6 (1C, C-a′) and 167.7 (2C, C-a).**

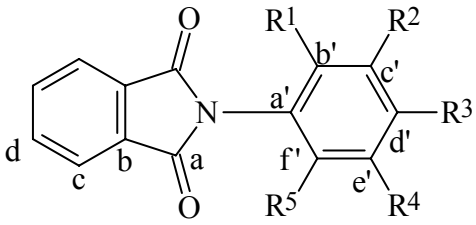
N-(2-Hydroxy-2-phenylethyl)phthalimide **(23)[35] White crystal (52%), m.p. 163-166°C (95% ethanol) (lit.[35] m.p. 160-161°C), R_f 0.62 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3456, 3071, 3034, 2940, 2903, 1767, 1701, 1611, 1498, 1428, 1400, 1315, 1131 and 1070; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.64 (2H, m, CH_2), 4.91 (1H, qui, *J* = 4.40 Hz, CH), 5.64 (1H, d, *J* = 4.34 Hz, OH), 7.24-7.35 (5H, m, Ar-H) and 7.78-7.87 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 45.5 (1C, CH_2), 69.5 (1C, CH), 122.9 (1C, C-d′), 125.9 (2C, C-c), 126.3 (2C, C-b′),**

127.3, 128.1 (1C×2, C-c′), 131.6 (2C, C-d), 134.3 (2C, C-b), 142.4 (1C, C-a′) and 167.7 (2C, C-a).

N-(1-Naphthyl)phthalimide **(24)[36,37] White crystal (56%), m.p. 178-180°C (95% ethanol) (lit.[36,37] m.p. 180-181°C), R_f 0.60 (dichloromethane). IR (KBr, cm^{-1}) 3053, 1771, 1710, 1597, 1400, 1367 and 1108; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.55-7.74 (5H, m, Ar-H) and 7.92-8.08 (6H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 122.8, 123.6, 125.6, 126.6, 127.1, 127.4, 128.3, 128.5 (8C, naphthyl moiety), 129.5 (2C, C-c), 130.1 (2C, C-d), 131.8 (2C, C-b), 133.7, 134.7 (2C, naphthyl moiety) and 167.6 (2C, C-a).**

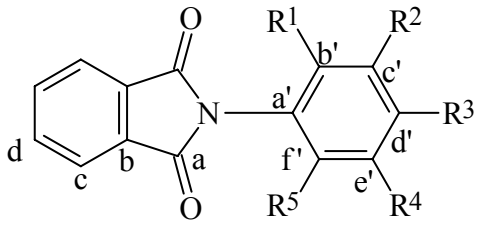
N-(2-Naphthyl)phthalimide **(25)[37] White crystal (70%), m.p. 215-219°C (95% ethanol) (lit.[37] m.p. 218°C), R_f 0.76 (chloroform-ethyl acetate [1:1]). IR (cm^{-1})(KBr) 3051, 1779, 1715, 1616, 1402, 1360 and 1093; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.52-7.68 (3H, m, Ar-H) and 7.94-8.02 (8H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 123.4, 125.2, 126.0, 126.7, 126.8, 127.6, 127.7 (7C, naphthyl moiety), 127.9 (2C, C-c), 128.4 (1C, naphthyl moiety), 129.4 (2C, C-d), 131.5 (2C, C-b), 132.6, 134.8 (2C, naphthyl moiety) and 167.1 (2C, C-a).**

N-(2-(1-Sulfonyl)naphthyl)phthalimide **(26)[38] White crystal (46%), m.p. 230-235°C (95% ethanol), R_f 0.62 (dichloromethane). IR (KBr, cm^{-1}) 3053, 1771, 1705, 1602, 1470, 1385, 1108 and 1080; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.52 (1H, s, br, SO_3H) and 7.16-8.08 (10H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 119.7, 123.7, 125.2, 126.5, 127.6, 127.7, 127.9, (7C, naphthyl moiety), 128.4 (2C, C-c), 129.4, 131.5 (2C, naphthyl moiety) 132.1 (2C, C-d), 132.6 (2C, C-b), 134.8 (1C, naphthyl moiety) and 167.1 (2C, C-a).**



Compound	R^1	R^2	R^3	R^4	R^5
27	NO_2	H	H	H	H
28	H	NO_2	H	H	H
29	H	H	NO_2	H	H
30	NO_2	H	NO_2	H	H
31	NH_2	H	H	H	H
32	H	NH_2	H	H	H
33	H	H	NH_2	H	H
34	NH_2	H	NH_2	H	H
35	H	Cl	H	H	H
36	H	H	Cl	H	H
37	Cl	Cl	H	H	H
38	Cl	H	Cl	H	H
39	Cl	H	H	Cl	H
40	H	Cl	Cl	H	H
41	H	Cl	H	Cl	H
42	H	Br	H	H	H
43	H	H	Br	H	H
44	NO_2	H	Cl	H	H
45	H	NO_2	Cl	H	H
46	Cl	H	NO_2	H	H
47	Cl	H	H	NO_2	H
48	H	NH_2	Cl	H	H
49	Cl	H	NH_2	H	H
50	Cl	H	H	NH_2	H
51	NO_2	H	CH_3	H	H
52	NO_2	H	OCH_3	H	H

Fig 2.2 Structures of synthesized *N*-phenylphthalimides



Compound	R^1	R^2	R^3	R^4	R^5
53	CH_3	H	NO_2	H	H
54	CH_3	H	NH_2	H	H
55	CH_3	H	H	H	CH_3
56	$CH(CH_3)_2$	H	H	H	$CH(CH_3)_2$
57	OCH_3	H	H	CH_3	H
58	OH	H	H	H	H
59	H	OH	H	H	H
60	H	H	OH	H	H
61	COOH	H	H	H	H
62	H	H	$COOC_2H_5$	H	H
63	OCH_2COOH	H	H	H	H
64	H	H	OCH_2COOH	H	H

Fig 2.2 (cont.)

N-(2-Nitrophenyl)phthalimide **(27)[37,41] Yellow powder (32%), m.p. 200-201°C (95% ethanol) (lit.[37] m.p. 202-203°C), R_f 0.59 (dichloromethane). IR (KBr, cm^{-1}) 3093, 1789, 1716, 1604, 1523, 1484, 1376 and 1103; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.24-7.97 (8H, m, Ar-H) and 8.19 (1H, d, *J* = 8.15 Hz, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 122.3 (1C, C-f′), 122.8 (1C, C-c′), 123.8 (1C, C-d′), 130.5 (2C, C-c), 131.5 (2C, C-d), 133.5 (2C, C-b), 133.6 (1C, C-a′), 134.8 (1C, C-e′), 147.5 (1C, C-b′) and 166.8 (2C, C-a).**

N-(3-Nitrophenyl)phthalimide **(28)[37, 41] White crystal (77%), m.p. 244-247°C (95% ethanol) (lit.[37] m.p. 244°C), R_f 0.59 (dichloromethane). IR (KBr, cm^{-1}) 3100, 1781, 1721, 1608, 1531, 1469, 1384, 1353 and 1106; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.83-8.03 (7H, m, Ar-H) and 8.26-8.41 (2H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 122.0 (1C, C-b), 122.7 (1C, C-d′), 123.6 (1C, C-f′), 130.3 (2C, C-c), 131.5 (1C, C-e′), 133.0 (2C, C-d), 133.7 (2C, C-b), 134.9 (1C, C-a′), 147.8 (1C, C-c′) and 166.6 (2C, C-a).**

N-(4-Nitrophenyl)phthalimide **(29)[37,41] White crystal (79%), m.p. 267-269°C (95% ethanol) (lit.[37] m.p. 268°C), R_f 0.62 (dichloromethane). IR (KBr, cm^{-1}) 3102, 1781, 1731, 1608, 1519, 1496, 1380, 1346 and 1079; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.80 (2H, m, Ar-H), 7.90-8.03 (4H, m, Ar-H) and 8.36-8.43 (2H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 123.6 (2C, C-b′ and f ′), 124.1 (2C, C-c′ and e′), 127.7 (2C, C-c), 131.4 (2C, C-d), 134.9 (2C, C-b), 138.2 (1C, C-d′), 138.9 (1C, C-a′), and 166.4 (2C, C-a).**

N-(2,4-Dinitrophenyl)phthalimide **(30)[39] Yellow powder (51%), m.p. 178-181 °C (95% ethanol), R_f 0.58 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3108, 1770, 1631, 1585, 1519, 1492, 1427, 1388, 1334, 1257 and 1064; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.09 (2H, d, *J* = 9.44 Hz, Ar-H), 8.11-8.14 (3H, m, Ar-H), 8.36 (1H, s, br, Ar-H) and 8.76 (2H, d, *J* = 2.64 Hz, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 119.7 (1C, C-c′), 123.3 (1C, C-f ′), 128.62 (2C, C-c), 129.3 (1C, C-e′), 135.1 (2C, C-d), 136.5 (2C, C-b), 139.2 (1C, C-a′), 145.5 (1C, C-b′), 149.8 (1C, C-d′) and 161.3 (2C, C-a).**

N-(2-Aminophenyl)phthalimide **(31)[40] Reduction of Compound 27 (5 mmol) was performed using iron powder (15 mmol) in a mixture of methanol (6 mL) and glacial acetic acid (4.5 mL). The mixture was heated for 2 hours at 80 °C. Upon completion of the reaction, the mixture was poured into ice-water, the solid was filtered off and dried. The resulting compound was recrystallized with 95% ethanol to yield red powder (14%), m.p. 187-188°C (ethanol-water [1:1]) (lit.[40] m.p. 189°C), R_f 0.38 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3446, 3146, 3043, 1781, 1720, 1644, 1456 and 1070; ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.30 (2H, s, br, NH_2), 6.64 (3H, m, Ar-H), 7.05 (1H, t, *J* = 6.12 Hz, Ar-H) and 7.84 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 112.0 (1C, C-c′), 112.9 (1C, C-e′), 113.6 (1C, C-f ′), 123.8 (1C, C-a′), 124.2 (1C, C-d′), 129.0 (2C, C-c), 132.4 (2C, C-d), 132.9 (2C, C-b), 144.9 (1C, C-b′) and 166.9 (2C, C-a).**

N-(3-Aminophenyl)phthalimide **(32)[37] Reduction of Compound 28: Brown crystal (35%), m.p. 188-191°C (ethanol-water [1:1]) (lit.[37] m.p. 190°C), R_f 0.54 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3428, 3343, 3050, 1780, 1705, 1602, 1494 and 1117; ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.32 (2H, s, br, NH_2), 6.56 (3H, m, Ar-H), 7.11 (1H, t, *J* = 6.02 Hz, Ar-H) and 7.89 (4H, m, Ar-H); ^{13}C-NMR**

(DMSO-d_6) δ (ppm): 112.6 (1C, C-b′), 113.5 (1C, C-f ′), 114.5 (1C, C-d′), 123.3 (2C, C-c), 129.0 (1C, C-e′), 131.4 (2C, C-d), 132.4 (2C, C-b), 134.6 (1C, C-a′), 149.2 (1C, C-c′) and 167.0 (2C, C-a).

N-(4-Aminophenyl)phthalimide **(33)[37] Reduction of Compound 29: Yellow brown crystal (9%), m.p. 250-252°C (ethanol-water [1:1]) (lit.[37] m.p. 250°C), R_f 0.52 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3475, 3381, 3240, 1710, 1630, 1465 and 1178; ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.34 (2H, s, br, NH_2), 6.63 (2H, d, *J* = 7.58 Hz, Ar-H), 6.98 (2H, d, *J* = 6.48 Hz, Ar-H) and 7.88 (4H, s, br, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 113.5 (2C, C-c′ and e′), 119.5 (2C, C-a′ and f ′), 123.1 (2C, C-c), 128.2 (1C, C-a′), 131.5 (2C, C-d), 134.5 (2C, C-b), 148.8 (1C, C-d′) and 167.6 (2C, C-a).**

N-(2,4-Diaminophenyl)phthalimide **(34)[39] Reduction of Compound 30: Red powder (33%), m.p. 166-172°C (95% ethanol), R_f 0.36 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3378, 3340, 3220, 3097, 3077, 1760, 1635, 1469, 1438, 1330 and 1120; ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.05 (2H, NH_2, s, br), 6.03 (2H, s, br, NH_2), 6.48 (1H, m, br, Ar-H), 7.11 (2H, s, br, Ar-H) and 7.79 (4H, m, br, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 106.5 (1C, C-c′), 110.3 (1C, C-e′), 119.8 (1C, C-a′), 122.0 (1C, C-f ′) 124.5 (2C, C-c), 132.5 (2C, C-d), 133.7 (2C, C-b), 145.5 (1C, C-b′), 148.8 (1C, C-d′) and 167.9 (2C, C-a).**

N-(3-Chlorophenyl)phthalimide **(35)[41,42] White crystal (73%), m.p. 161-164°C (95% ethanol) (lit.[42] m.p. 163-164°C), R_f 0.70 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3073, 1762, 1720, 1589, 1446, 1106 and 725; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.52-7.58 (4H, m, Ar-H) and 7.91-7.96 (4H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 122.5 (1C, C-f ′), 126.1 (1C, C-b′), 127.2 (1C, C-d′), 127.9 (2C, C-c), 130.4 (1C, C-e′), 131.5 (2C, C-d), 132.8 (2C, C-b), 133.3 (1C, C-c′), 134.7 (1C, C-a′) and 166.6 (2C, C-a).**

N-(4-Chlorophenyl)phthalimide **(36)[41] White crystal (65%), m.p. 198-200°C (95% ethanol) (lit.[41] m.p. 194-195°C), R_f 0.64 (dichloromethane). IR (KBr, cm^{-1}) 3062, 1789, 1743, 1712, 1612, 1465, 1087 and 720; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.36-7.49 (4H, m, Ar-H) and 7.74-7.98 (4H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 123.8 (2C, C-b′ and f ′), 127.7 (2C, C-c), 129.3 (2C, C-c′ and e′), 131.3 (1C, C-d′), 132.4 (2C, C-d), 132.8 (2C, C-b), 134.6 (1C, C-a′) and 166.8 (2C, C-a).**

N-(2,3-Dichlorophenyl)phthalimide **(37)[42] White crystal (66%), m.p. 190-194 °C (95% ethanol) (lit.[42] m.p. 195-196°C), R_f 0.56 (hexane-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3097, 1778, 1716, 1608, 1461, 1084 and 722; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.28-7.60 (2H, m, Ar-H), 7.59 (1H, m, Ar-H) and 7.75-8.16 (4H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 124.0 (1C, C-f′), 127.7 (1C, C-d′), 128.9 (1C, C-b′), 131.5 (2C, C-c), 131.8 (1C, C-e′), 132.3 (2C, C-d), 132.7 (2C, C-b), 134.3 (1C, C-c′), 134.7 (1C, C-a′) and 166.3 (2C, C-a).**

N-(2,4-Dichlorophenyl)phthalimide **(38)[43] White crystal (50%), m.p. 152-156 °C (95% ethanol) (lit.[43] m.p. 155°C), R_f 0.68 (dichloromethane). IR (KBr, cm^{-1}) 3090, 1790, 1752, 1720, 1614, 1494, 1108 and 714; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.20-7.41 (2H, m, Ar-H), 7.56 (1H, m, Ar-H) and 7.75-7.97 (4H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 124.0 (1C, C-f′), 128.1 (1C, C-b′), 128.3 (1C, C-e′), 130.4 (2C, C-c), 131.4 (1C, C-c′), 131.7 (1C, C-d′), 134.1 (2C, C-d), 134.6 (2C, C-b), 136.0 (1C, C-a′) and 166.4 (2C, C-a).**

N-(2,5-Dichlorophenyl)phthalimide **(39)[42,44] White crystal (79%), m.p. 203-204°C (95% ethanol) (lit.[42] m.p. 206-207°C), R_f 0.66 (dichloromethane). IR (KBr, cm^{-1}) 3097, 3077, 1785, 1770, 1724, 1612, 1473, 1411, 1373, 1095 and 1079; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.52-7.88 (3H, m, Ar-H) and 7.92-8.05 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 123.8 (1C, C-f′), 130.9 (1C, C-b′), 131.0 (1C, C-d′), 131.1 (2C, C-c), 131.2 (1C, C-c′), 131.3 (2C, C-d), 131.4 (1C, C-e′), 132.0 (2C, C-b), 135.2 (1C, C-a′) and 165.9 (2C, C-a).**

N-(3,4-Dichlorophenyl)phthalimide **(40)[42] White crystal (57%), m.p. 192-195°C (95% ethanol) (lit.[42] m.p. 195-196°C), R_f 0.70 (dichloromethane). IR (KBr, cm^{-1}) 3089, 3058, 1770, 1716, 1602, 1477, 1095, 1083 and 715; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.24-7.37 (1H, m, Ar-H), 7.52-7.62 (2H, m, Ar-H) and 7.76-7.96 (4H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 123.9 (1C, C-f′), 125.5 (1C, C-b′), 128.1 (2C, C-c), 130.7 (1C, C-d′), 131.0 (1C, C-e′), 131.4 (2C, C-d), 132.0 (2C, C-b), 134.7 (1C, C-c′), 136.4 (1C, C-a′) and 166.6 (2C, C-a).**

N-(3,5-Dichlorophenyl)phthalimide **(41)[42,45] White crystal (71%), m.p. 205-208°C (95% ethanol) (lit.[42] m.p. 203-204°C), R_f 0.71 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3090, 3057, 1770, 1716, 1592, 1477, 1095, 1083 and 710; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.60 (2H, d, *J* = 1.98 Hz, Ar-H), 7.72 (1H, m, Ar-**

H) and 7.95 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 123.6 (2C, C-b′ and f ′), 126.1 (1C, C-d′), 127.7 (2C, C-c), 131.4 (2C, C-d), 133.9 (1C, C-b), 134.2 (2C, C-c′ and e′), 134.9 (1C, C-a′) and 166.3 (2C, C-a).

N-(3-Bromophenyl)phthalimide **(42)[37] White crystal (51%), m.p. 170-172°C (95% ethanol) (lit.[37] m.p. 172-173°C), R_f 0.72 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3089, 1762, 1708, 1612, 1427 and 1076; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.50 (2H, m, Ar-H), 7.61-7.71 (2H, m, Ar-H) and 7.87-7.99 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 121.1 (1C, C-f ′), 123.5 (1C, C-c′), 126.5 (1C, C-b′), 130.0 (1C, C-d′), 130.7 (2C, C-c), 130.8 (1C, C-e′), 131.4 (2C, C-d), 133.4 (2C, C-b), 134.8 (1C, C-a′) and 166.6 (2C, C-a).**

N-(4-Bromophenyl)phthalimide **(43)[42] White crystal (67%), m.p. 205-208°C (95% ethanol) (lit.[42] m.p. 204-206°C), R_f 0.70 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3062, 1789, 1739, 1708, 1612, 1465 and 1010; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.40 (2H, d, *J* = 7.80 Hz, Ar-H), 7.73 (2H, d, *J* = 7.99 Hz, Ar-H) and 7.87-7.99 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 120.9 (1C, C-d′), 123.5 (2C, C-b′ and f ′), 129.3 (2C, C-c), 131.2 (2C, C-d), 131.5 (1C, C-b), 131.8 (2C, C-c′ and e′), 134.7 (1C, C-a′) and 166.7 (2C, C-a).**

N-(4-Chloro-2-nitrophenyl)phthalimide **(44)[46] Yellow crystal (21%), m.p. 198-201°C (acetic acid-water [1:1]), R_f 0.68 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3108, 3060, 1781, 1731, 1608, 1535, 1483, 1348, 1089 and 722; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.49 (1H, m, Ar-H), 7.70-7.97 (5H, m, Ar-H) and 8.15 (1H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 122.7 (1C, C-f ′), 124.2 (1C, C-c′), 127.4 (2C, C-c), 131.4 (1C, C-a′), 130.3 (1C, C-d′) 132.0 (2C, C-d), 132.4 (2C, C-b), 135.2 (1C, C-e′), 141.7 (1C, C-b′), and 166.4 (2C, C-a).**

N-(4-Chloro-3-nitrophenyl)phthalimide **(45)[42] Brown powder (84%), m.p. 212-215°C (95% ethanol) (lit.[42] m.p. 212-213°C), R_f 0.69 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3090, 1786, 1740, 1607, 1536, 1480, 1348, 1089 and 714; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.69-8.04 (6H, m, Ar-H) and 8.25 (1H, s, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 123.7 (1C, C-b′), 124.0 (1C, C-d′), 124.4 (2C, C-c), 131.4 (1C, C-f ′), 131.7 (1C, C-e′), 132.2 (2C, C-d), 132.4 (2C, C-b), 135.0 (1C, C-a′), 147.3 (1C, C-b′), and 166.3 (2C, C-a).**

N-(2-Chloro-4-nitrophenyl)phthalimide **(46)[15] Yellow crystal (43%), m.p. 181-183°C (95% ethanol) (lit.[15] m.p. 180-182°C), R_f 0.70 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3112, 1785, 1731, 1589, 1523, 1481, 1338, 1083 and 721; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.55 (1H, d, *J* = 8.67 Hz, Ar-H), 7.81-7.99 (4H, m, Ar-H), 8.25 (1H, m, Ar-H) and 8.43 (1H, s, br, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 121.9 (1C, C-e′), 122.7 (1C, C-f ′), 124.3 (1C, C-c′), 126.6 (1C, C-b′), 127.3 (2C, C-c), 132.2 (2C, C-d), 132.5 (2C, C-b), 144.7 (1C, C-a′), 145.4 (1C, C-d′) and 166.4 (2C, C-a).**

N-(2-Chloro-5-nitrophenyl)phthalimide **(47)[42] White crystal (81%), m.p. 193-195°C (95% ethanol) (lit.[42] m.p. 197°C), R_f 0.54 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3108, 1781, 1727, 1608, 1527, 1477, 1349, 1080 and 717; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.72-8.00 (5H, m, Ar-H) and 8.25-8.32 (2H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 116.9 (1C, C-f ′), 120.7 (1C, C-d′), 127.5 (2C, C-c), 130.0 (1C, C-c′), 131.8 (1C, C-b′), 132.2 (2C, C-d), 132.6 (2C, C-b), 139.7 (1C, C-a′), 146.7 (1C, C-e′) and 166.6 (2C, C-a).**

N-(3-Amino-4-chlorophenyl)phthalimide **(48)[42] Reduction of Compound 45: Yellow crystal (67%), m.p. 183-185°C (95% ethanol) (lit.[41] m.p. 180-181°C), R_f 0.66 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3428, 3334, 3049, 1782, 1724, 1635, 1437, 1084 and 718; ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.58 (2H, s, br, NH_2), 6.57 (1H, d, *J* = 8.46 Hz, Ar-H), 6.82 (1H, s, br, Ar-H), 7.30 (1H, d, *J* = 8.41 Hz, Ar-H) and 7.85-7.96 (4H, m, br, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 113.9 (1C, C-b′), 115.5 (1C, C-f ′), 116.5 (1C, C-d′), 129.1 (2C, C-c), 131.2 (1C, C-e′), 131.4 (2C, C-d), 131.5 (2C, C-b), 134.6 (1C, C-a′), 145.0 (1C, C-c′) and 166.7 (2C, C-a).**

N-(4-Amino-2-chlorophenyl)phthalimide **(49)[15,42] Reduction of Compound 46: Yellow crystal (66%), m.p. 204-206°C (95% ethanol) (lit.[15] m.p. 205-207°C), R_f 0.60 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3432, 3351, 3235, 3043, 1778, 1758, 1724, 1704, 1600, 1465, 1106 and 717; ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.74 (2H, s, br, NH_2), 6.62 (1H, d, *J* = 8.22 Hz, Ar-H), 6.75 (1H, s, br, Ar-H), 7.12 (1H, d, *J* = 8.34 Hz, Ar-H) and 7.92 (4H, s, br, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 112.6 (1C, C-e′), 113.2 (1C, C-c′), 113.9 (1C, C-f ′), 116.1 (1C, C-b′), 123.5**

(2C, C-c), 131.3 (1C, C-a′), 132.3 (2C, C-d), 134.8 (2C, C-b), 151.0 (1C, C-d′) and 167.0 (2C, C-a).

***N-(5-Amino-2-chlorophenyl)phthalimide* (50)[42] Reduction of Compound 47: Pale Brown powder (53%), m.p. 182-186°C (95% ethanol) (lit.[42] m.p. 182-183°C), R_f 0.50 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3478, 3386, 3232, 3062, 1785, 1766, 1731, 1619, 1450, 1083 and 719; ^{1}H-NMR (DMSO-d_6) δ (ppm): 5.55 (2H, s, br, NH_2), 6.65 (2H, m, Ar-H), 7.21 (1H, d, *J* = 8.99 Hz, Ar-H) and 7.94 (4H, s, br, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 115.7 (1C, C-f ′), 115.9 (1C, C-d′), 117.0 (1C, C-b′), 123.6 (2C, C-c), 129.6 (1C, C-c′), 131.3 (2C, C-d), 132.2 (1C, C-b), 134.9 (1C, C-a′), 148.7 (1C, C-e′) and 166.4 (2C, C-a).**

***N-(4-Methyl-2-nitrophenyl)phthalimide* (51)[42] Yellow crystal (42%), m.p. 186-188°C (95% ethanol) (lit.[42] m.p. 185-186°C), R_f 0.66 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3090, 2954, 1785, 1762, 1731, 1608, 1535, 1465, 1380, 1349 and 1079; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.45 (3H, s, br, CH_3), 7.34-7.57 (2H, m, Ar-H) and 7.73-7.96 (5H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.1 (1C, CH_3), 122.8 (1C, C-f ′), 124.0 (1C, C-c′), 126.1 (2C, C-c), 130.6 (1C, C-a′), 131.8 (2C, C-d) 134.7 (2C, C-b), 134.8 (1C, C-d′), 140.7 (1C, C-e′), 145.3 (1C, C-b′), and 166.5 (2C, C-a).**

***N-(4-Methoxy-2-nitrophenyl)phthalimide* (52)[40] Yellow crystal (21%), m.p. 145-148°C (95% ethanol) (lit.[40] m.p. 146°C), R_f 0.64 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3104, 3031, 2958, 1781, 1735, 1716, 1619, 1535, 1465, 1442, 1384, 1349, 1241 and 1029; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.90 (3H, s, CH_3), 7.22-7.54 (2H, m, Ar-H) and 7.67-7.94 (5H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 56.2 (1C, CH_3), 110.8 (1C, C-c′), 117.9 (1C, C-e′), 120.1 (1C, C-f ′), 124.0 (1C, C-a′), 127.8 (2C, C-c) 131.9 (2C, C-d), 134.6 (2C, C-b), 146.2 (1C, C-b′), 160.1 (1C, C-d′), and 166.7 (2C, C-a).**

***N-(2-Methyl-4-nitrophenyl)phthalimide* (53)[15,42] White crystal (69%), m.p. 190-193°C (95% ethanol) (lit.[15] m.p. 193-195°C), R_f 0.68 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3108, 3058, 2981, 1781, 1727, 1616, 1519, 1492, 1369, 1342 and 1079; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.31 (3H, s, br, CH_3), 7.36 (1H, d, *J* = 8.56 Hz, Ar-H), 7.78-8.00 (4H, m, Ar-H) and 8.12-8.23 (2H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 10.8 (1C, CH_3), 120.8 (1C, C-e′), 121.2 (1C, C-f ′),**

124.5 (1C, C-c′), 127.5 (2C, C-c), 130.5 (1C, C-b′), 131.3 (2C, C-d), 132.3 (2C, C-b), 143.8 (1C, C-d′), 145.0 (1C, C-a′) and 166.7 (2C, C-a).

N-(4-Amino-2-methylphenyl)phthalimide **(54)[15,42] Reduction of Compound 53: Pale brown powder (63 %), m.p. 177-180°C (95% ethanol) (lit.[15] m.p. 179-181°C), R_f 0.52 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3455, 3370, 3232, 3062, 3027, 2923, 1778, 1758, 1724, 1700, 1623, 1465, 1388, 1324 and 1112; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.91 (3H, s, CH_3) 5.28 (2H, s, br, NH_2), 6.64-6.65 (2H, m, Ar-H), 6.87 (1H, d, *J* = 8.28 Hz, Ar-H), and 7.90 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 17.5 (1C, CH_3), 111.6 (1C, C-e′), 114.9 (1C, C-c′), 118.5 (1C, C-f ′), 123.3 (2C, C-c), 129.5 (1C, C-a′), 131.5 (1C, C-b′), 134.5 (2C, C-d), 136.3 (2C, C-b), 149.4 (1C, C-d′) and 167.7 (2C, C-a).**

N-(2,6-Dimethylphenyl)phthalimide **(55)[15] Small white crystal (26%), m.p. 203-205°C (95% ethanol) (lit.[15] m.p. 205-208°C), R_f 0.62 (hexane-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3062, 2931, 1776, 1738, 1710, 1480, 1442 and 1112; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.09 (6H, s, CH_3), 7.16-7.24 (3H, m, Ar-H) and 7.77-7.97 (4H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 18.1 (2C, CH_3), 121.5 (1C, C-d′), 123.8 (2C, C-c′ and e′), 128.5 (2C, C-c), 129.5 (1C, C-b′ and f ′), 131.9 (2C, C-d) 134.3 (2C, C-b), 136.8 (2C, C-a′) and 167.2 (2C, C-a).**

N-(2,6-(Di-(1-methylethyl)phenyl)phthalimide **(56)[48] Pale brown crystal (69%), m.p. 160-165°C (95% ethanol) (lit.[48] m.p. 172°C), R_f 0.74 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3034, 2950, 1776, 1720, 1602, 1461, 1371 and 1080; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.05 (12H, d, *J* = 6.64 Hz, CH_3), 2.64 (2H, m, br, CH), 7.32-7.47 (3H, m, Ar-H) and 7.94-7.99 (4H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 23.6 (4C, CH_3), 28.7 (2C, CH), 123.8 (1C, C-d′), 126.8 (2C, C-c′ and e′), 127.5 (2C, C-c), 130.0 (2C, C-d), 131.0 (2C, C-b) 135.2 (1C, C-a′), 146.9 (2C, C-b′ and f ′) and 167.8 (2C, C-a).**

N-(2-Methoxy-5-methylphenyl)phthalimide **(57)[42] Black crystal (61%), m.p. 197-199°C (95% ethanol) (lit.[42] m.p. 230-231°C), R_f 0.54 (haxane-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3093, 3008, 2977, 2919, 1778, 1724, 1608, 1469, 1446, 1110 and 1029; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.31 (3H, s, br, CH_3), 3.74 (3H, s, br, O-CH_3), 6.90-7.24 (3H, m, Ar-H) and 7.72-7.94 (4H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ**

(ppm): 20.4 (1C, CH_3), 55.9 (1C, O-CH_3), 112.0 (1C, C-c′), 119.8 (1C, C-f ′), 123.6 (1C, C-a′), 125.8 (1C, C-d′), 130.4 (2C, C-c), 131.1 (1C, C-e′), 132.3 (2C, C-d), 134.0 (2C, C-b), 153.2 (1C, C-b′) and 167.5 (2C, C-a).

N-(2-Hydroxyphenyl)phthalimide **(58)[42] Pale orange crystal (68%), m.p. 223-225°C (95% ethanol) (lit.[42] m.p. 223°C), R_f 0.65 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3500-3100, 3089, 3046, 1785, 1700, 1627, 1469, 1388, 1226 and 1099; ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.86-7.00 (2H, m, Ar-H), 7.22-7.34 (2H, m, Ar-H), 7.86-7.98 (4H, m, Ar-H) and 9.84 (1H, s, br, OH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 116.5 (1C, C-c′), 118.8 (1C, C-e′), 119.1 (1C, C-f ′), 123.3 (1C, C-a′), 125.5 (1C, C-d′), 130.3 (2C, C-c), 131.8 (2C, C-d), 134.6 (2C, C-b), 153.9 (1C, C-b′) and 167.1 (2C, C-a).**

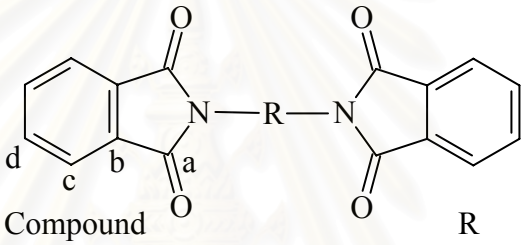
N-(3-Hydroxyphenyl)phthalimide **(59)[42] White crystal (49%), m.p. 230-233°C (95% ethanol) (lit.[42] m.p. 230-231°C), R_f 0.70 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3325, 3071, 1776, 1701, 1607, 1461, 1268 and 1122; ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.79-6.87 (3H, m, Ar-H), 7.28 (1H, t, *J* = 6.48 Hz, Ar-H), 7.86-7.97 (4H, m, Ar-H) and 9.74 (1H, s, br, OH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 110.6 (1C, C-b′), 113.0 (1C, C-f ′), 114.3 (1C, C-d′), 127.3 (2C, C-c), 130.1 (1C, C-e′), 131.3 (2C, C-d), 132.8 (2C, C-b), 139.6 (1C, C-a′), 157.5 (1C, C-c′) and 166.7 (2C, C-a).**

N-(4-Hydroxyphenyl)phthalimide **(60)[42] Gray crystal (75%), m.p. 296-299°C (95% ethanol) (lit.[42] m.p. 295-296°C), R_f 0.72 (ethyl acetate). IR (KBr, cm^{-1}) 3409, 3060, 1775, 1715, 1607, 1437, 1207 and 1117; ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.68-6.93 (2H, m, Ar-H), 7.16-7.24 (2H, m, Ar-H), 7.84-7.95 (4H, m, Ar-H) and 9.83 (1H, s, OH); ^{13}C-NMR (DMSO-d_6) δ (ppm): 115.9 (2C, C-c′ and e′), 121.8 (2C, C-b′ and f ′), 127.6 (2C, C-c), 130.9 (1C, C-a′), 132.4 (2C, C-d), 132.3 (2C, C-b), 153.4 (1C, C-d′) and 166.7 (2C, C-a).**

N-(2-Carboxyphenyl)phthalimide **(61)[42, 48] White crystal (53%), m.p. 215-218 °C (95% ethanol) (lit.[42] m.p. 216-217°C), R_f 0.78 (methanol). IR (KBr, cm^{-1}) 3184, 3081, 1715, 1701, 1602, 1461, 1400, 1249 and 1127; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.52-8.07 (8H, m, Ar-H) and 13.08 (1H, s, br, COOH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 123.5 (1C, C-f ′), 124.2 (1C, C-b′), 125.6 (1C, C-d′), 130.6 (2C, C-c), 131.0**

(1C, C-d′), 131.4 (2C, C-d), 131.7 (2C, C-b), 133.0 (1C, C-e′), 134.8 (1C, C-a′), 166.1 (2C, C-a) and 167.1 (1C, COOH).

N-((4-Ethyl methanoyl)phenyl)phthalimide **(62)[49] White crystal (75%), m.p. 158-160°C (95% ethanol), R_f 0.76 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3113, 3059, 2966, 2911, 1794, 1734, 1712, 1604, 1473, 1415, 1373, 1280 and 1114; ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.29 (3H, t, *J* = 7.08 Hz, CH_3), 4.34 (2H, q, *J* = 7.10 Hz, CH_2), 7.62 (2H, d, *J* = 1.83 Hz, Ar-H), 7.88-8.00 (4H, m, Ar-H) and 8.10 (2H, d, *J* = 1.90 Hz, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 14.1 (1C, CH_3), 60.9 (1C, CH_2), 123.5 (2C, C-b′ and f ′), 127.1 (1H, C-d′), 128.9 (2C, C-c), 129.6 (2C, C-c′ and e′), 131.4 (2C, C-d), 134.8 (2C, C-b) 136.1 (1C, C-a′), 165.1 (2C, C-a and 167.8 (1C, COO).**



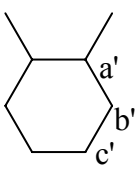
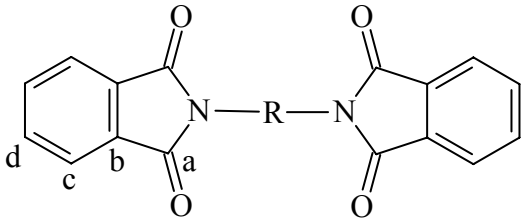
Compound	R
65	—CH_2CH_2—
66	—$CH_2CH_2CH_2$—
67	—$CH_2(CH_2)_2CH_2$—
68	—$CH_2(CH_2)_4CH_2$—
69	—$CH_2(CH_2)_6CH_2$—
70	—$CH_2CH(CH_3)(CH_2)_2CH_2$—
71	

Fig 2.3 Structures of synthesized *bis*-phthalimides



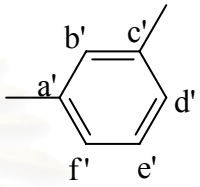
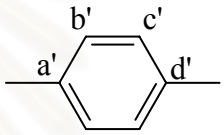
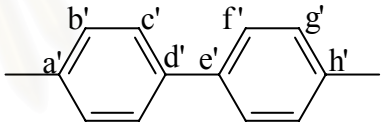
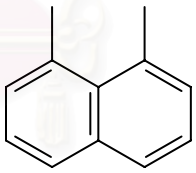
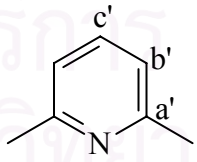
Compound	R
72	
73	
74	
75	
76	

Fig 2.3 (cont.)

***N,N'-Ethane-1,2-diyl-bis-phthalimide* (65)[50] White crystal (59%), m.p. 234-238°C (95% ethanol) (lit.[50] m.p. 232-235°C), R_f 0.32 (dichloromethane). IR (KBr, cm^{-1}) 3071, 2959, 1776, 1705, 1616, 1470, 1447, 1359 and 1061; ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.02 (4H, t, *J* = 6.20 Hz, CH_2) and 7.74-7.98 (8H, m, Ar-H); ^{13}C-NMR**

($CDCl_3$) δ (ppm): 36.8 (1C, CH_2), 123.3 (4C, C-c), 131.9 (4C, C-d), 134.0 (4C, C-b) and 168.2 (4C, C-a).

N,N′-Propane-1,3-diyl-bis-phthalimide **(66)[51] White crystal (56%), m.p. 190-195°C (95% ethanol) (lit.[51] m.p. 198-199°C), R_f 0.62 (ethyl acetate). IR (KBr, cm^{-1}) 3069, 2950, 1771, 1701, 1607, 1470, 1437, 1367 and 1023; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.08 (2H, m, CH_2), 3.75 (4H, t, *J* = 0.25 Hz, N-CH_2) and 7.64-7.79 (8H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 27.66 (1C, CH_2), 35.7 (2C, N-CH_2), 123.3 (4C, C-c), 131.7 (4C, C-d), 133.9 (4C, C-b) and 168.4 (4C, C-a).**

N,N′-Butane-1,4-diyl-bis-phthalimide **(67)[52] White crystal (64%), m.p. 223-226°C (95% ethanol) (lit.[52] m.p. 222-223°C), R_f 0.26 (dichloromethane). IR (KBr, cm^{-1}) 3090, 2940, 1767, 1720, 1607, 1465, 1437, 1367 and 1070; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.71 (4H, m, CH_2), 3.68 (4H, m, N-CH_2) and 7.65-7.91 (8H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 26.1, 42.4 (4C, CH_2), 120.3 (4C, C-c), 129.5 (4C, C-d), 132.8 (4C, C-b) and 166.2 (4C, C-a).**

N,N′-Hexane-1,6-diyl-bis-phthalimide **(68)[53] White crystal (68%), m.p. 171-175°C (95% ethanol) (lit.[53] m.p. 178-179°C), R_f 0.34 (dichloromethane). IR (KBr, cm^{-1}) 3094, 2931, 1771, 1715, 1607, 1465, 1437, 1362 and 1070; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.32 (4H, m, CH_2), 1.62 (4H, m, N-CH_2-C$\underline{H}_2$), 3.65 (4H, t, *J* = 8.12 Hz, N-CH_2) and 7.65-7.78 (8H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 27.8, 29.5, 41.7 (6C, CH_2) 124.2 (4C, C-c), 131.6 (4C, C-d), 132.4 (4C, C-b) and 166.9 (4C, C-a).**

N,N′-Octane-1,8-diyl-bis-phthalimide **(69)[54] White crystal (71.0%), m.p. 136-138°C (95% ethanol) (lit.[54] m.p. 138°C), R_f 0.44 (dichloromethane). IR (KBr, cm^{-1}) 3081, 2921, 1761, 1710, 1607, 1465, 1442, 1362 and 1061; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.31 (8H, m, CH_2), 1.68 (4H, m, N-CH_2-C$\underline{H}_2$), 3.67 (4H, t, *J* = 8.21 Hz, N-CH_2) and 7.65-7.80 (8H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 27.4, 29.2, 30.1, 41.6 (8C, CH_2) 127.4 (4C, C-c), 132.0 (4C, C-d), 132.2 (4C, C-b) and 165.9 (4C, C-a).**

N,N′-(2-Methyl)pentane-1,5-diyl-bis-phthalimide **(70) White crystal (52%), m.p. 133-135°C (95% ethanol), R_f 0.66 (ethyl acetate). IR (KBr, cm^{-1}) 3075, 2940, 1771, 1701, 1611, 1461, 1395, 1362 and 1061; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.85 (3H, d, *J* = 6.73 Hz, CH_3), 1.18-1.80 (5H, m, CH, CH_2), 3.48 (2H, m, N-C$\underline{H}_2$-CH),**

3.62 (2H, t, *J* = 7.23 Hz, N-CH_2) and 7.63-7.79 (8H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 17.3 (1C, CH_3), 25.8, 32.3, 37.9, 43.8 (4C, CH_2), 31.3 (1C, CH), 123.1, 123.2 (2×2C, C-c), 132.0, 132.1 (2×2C, C-d), 133.8, 133.8 (2×2C, C-b) and 168.3, 168.5 (2×2C, C-a). The IR, ^{1}H-NMR and ^{13}C-NMR spectra are presented in Figs 1-3, respectively.

N,N′-Cyclohexane-1,2-diyl-bis-phthalimide **(71)[53] White crystal (49%), m.p. 248-250°C (95% ethanol), R_f 0.68 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3082, 2940, 1767, 1724, 1611, 1475, 1372 and 1108; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.54 (4H, m, br, CH_2), 1.85 (4H, m, br, CH-C$\underline{H}_2$), 4.97 (2H, m, br, CH) and 7.59-7.67 (8H, m, br, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 19.8 (2C, C-c′), 24.1 (2C, C-b′), 45.6 (2C, C-a′), 118.0 (4C, C-c), 126.0 (4C, C-d), 128.6 (4C, C-b) and 162.7 (4C, C-a).**

N,N′-Phenylene-1,3-diyl-bis-phthalimide **(72)[55] White powder (86%), m.p. > 300°C, R_f 0.64 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3059, 1776, 1720, 1607, 1461 and 1070; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.50-7.75 (4H, m, Ar-H) and 7.85-8.10 (8H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 112.3 (1C, C-b′), 116.0 (2C, C-d′ and f ′), 127.5 (4C, C-c), 128.9 (1C, C-e′), 132.2 (4C, C-d), 132.8 (4C, C-b), 138.5 (2C, C-a′ and c′) and 168.2 (4C, C-a).**

N,N′-Phenylene-1,4-diyl-bis-phthalimide **(73)[56] Black powder (71%), m.p. > 300°C (lit.[56] m.p. 356°C), R_f 0.66 (ethyl acetate). IR (KBr, cm^{-1}) 3029, 2931, 1715, 1608, 1465 and 1023; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.55-7.65 (4H, m, Ar-H) and 7.80-8.15 (8H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 120.6 (4C, C-b′ and c′), 127.2 (4C, C-c), 132.4 (4C, C-d), 132.8 (4C, C-b), 133.9 (2C, C-a′ and c′) and 163.4 (4C, C-a).**

N,N′-Biphenyl-4,4′-diyl-bis-phthalimide **(74)[57] Brown powder (26%), m.p. > 300°C (lit.[57] m.p. 406°C), R_f 0.67 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3053, 1785, 1767, 1705, 1663, 1472 and 1122; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.46-7.75 (8H, m, Ar-H) and 7.79-8.15 (8H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 120.9 (4C, C-b′ and g′), 127.4 (4C, C-c), 127.9 (4C, C-c′ and f ′), 131.9 (2C, C-d′ and e′), 132.0 (4C, C-d), 132.4 (4C, C-b), 137.1 (2C, C-a′ and h′) and 163.2 (4C, C-a).**

N,N′-Naphthalene-1,8-diyl-bis-phthalimide **(75) Red black powder (51%), m.p. > 300°C, R_f 0.50 (chloroform). IR (KBr, cm^{-1}) 3090, 1724, 1649, 1456 and 1103; ^{1}H-NMR (DMSO-d_6) δ (ppm): 6.22-6.65 (2H, m, Ar-H) and 7.04-8.34 (12H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 108.8, 121.4, 122.5, 123.5 (7C, naphthyl moiety), 128.4 (4C, C-c), 130.6 (4C, C-d), 133.0 (4C, C-b), 133.8, 134.8 (3C, naphthyl moiety) and 164.2 (2C, C-a). The IR, ^{1}H-NMR and ^{13}C-NMR spectra are presented in Figs 4-6, respectively.**

N,N′-Pyridine-2,6-diyl-bis-phthalimide **(76)[58] Brown powder (68%), m.p. > 300°C (lit.[58] m.p. 354°C), R_f 0.62 (ethyl acetate). IR (KBr, cm^{-1}) 3090, 1790, 1734, 1592, 1456 and 1070; ^{1}H-NMR (DMSO-d_6) δ (ppm): 7.22 (2H, d, *J* = 7.30 Hz, Ar-H) 7.91-8.02 (7H, m, Ar-H) and 8.15 (2H, d, *J* = 7.66 Hz, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 113.5 (2C, C-b′), 123.7 (4C, C-c), 131.2 (4C, C-d), 135.1 (4C, C-b), 140.6 (1C, C-c′), 155.9 (2C, C-a′) and 169.5 (4C, C-a).**

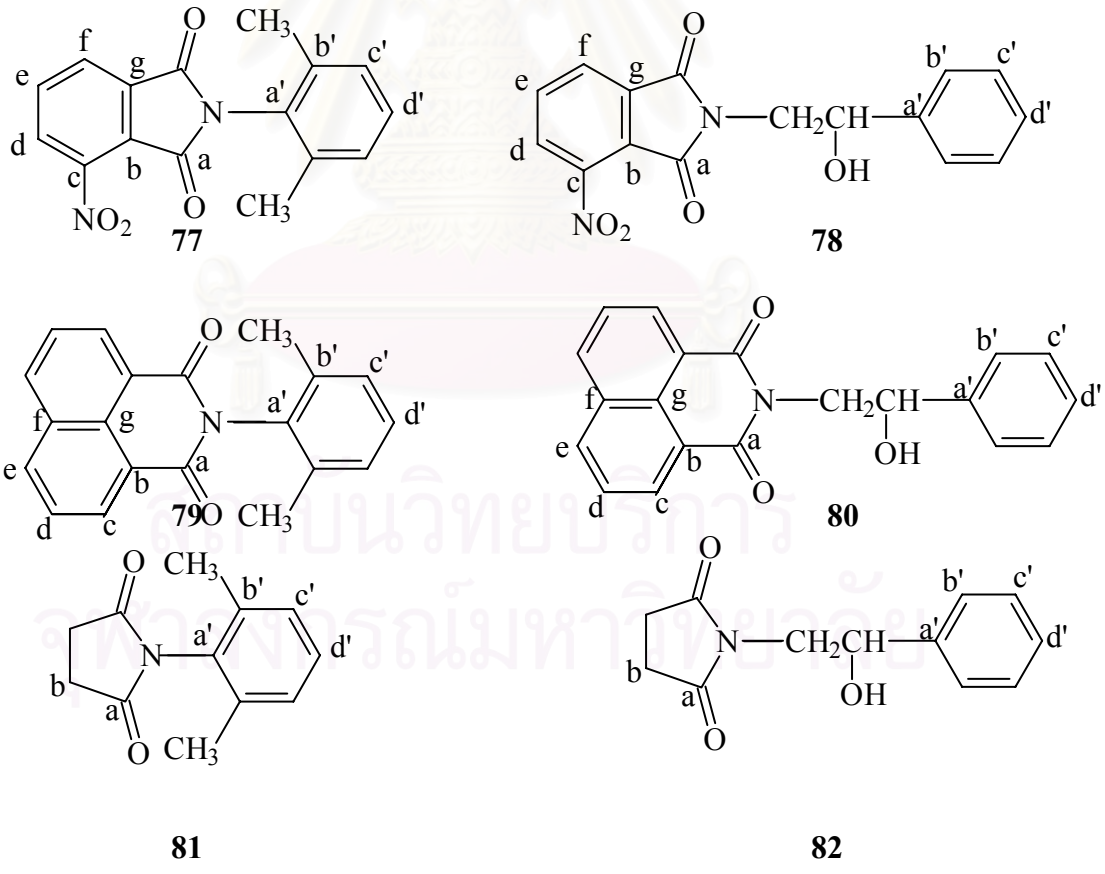


Fig 2.4 Structures of other synthesized analogues

3-Nitro-N-(2,6-dimethylphenyl)phthalimide **(77)[13] Yellow crystal (76 %), m.p. 170-172°C (95% ethanol) (lit.[13] m.p. 172-174°C), R_f 0.58 (dichloromethane). IR (KBr, cm^{-1}) 3097, 3035, 2962, 2927, 1781, 1731, 1616, 1550, 1442, 1369 and 1118; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.14 (6H, s, CH_3), 7.12-7.34 (3H, m, Ar-H) and 7.79-8.17 (3H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 18.1 (2C, CH_3), 123.6 (1C, C-d′), 127.5 (2C, C-c′ and e′), 128.6 (1C, C-d), 128.9 (1C, C-b), 129.1 (2C, C-b′ and c′), 129.8 (1C, C-e), 133.9 (1C, C-g), 135.8 (1C, C-f), 136.6 (1C, C-a′), 145.4 (1C, C-c) and 161.6, 164.7 (1C×2, C-a).**

3-Nitro-N-(2-hydroxy-2-phenylethyl)phthalimide **(78)[46] Yellow crystal (29%), m.p. 190-195°C (95% ethanol), R_f 0.61 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3475, 3390, 3100, 3043, 2940, 1771, 1705, 1621, 1536, 1461, 1400, 1352, 1075 and 1004; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.64 (2H, m, CH_2), 4.89 (1H, qui, *J* = 4.35 Hz, CH), 5.65 (1H, d, *J* = 4.32 Hz, OH), 7.24-7.40 (5H, m, Ar-H) and 8.01-8.30 (3H, m, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 46.1 (1C, CH_2), 69.2 (1C, CH), 122.8 (1C, C-d), 125.2 (2C, C-b′ and f′), 125.9 (1C, C-b), 126.7 (1C, C-d′), 128.3 (2C, C-c′ and e′), 133.5 (1C, C-e), 136.2 (1C, C-g), 142.0 (1C, C-f), 144.3 (1C, C-a′), 156.8 (1C, C-c) and 163.3, 165.8 (1C×2, C-a).**

N-(2,6-Dimethylphenyl)-1,8-naphthalimide **(79)[36] White crystal (75%), m.p. 224-227°C (95% ethanol), R_f 0.51 (dichloromethane). IR (KBr, cm^{-1}) 3050, 2919, 1789, 1700, 1623, 1473, 1434, 1346 and 1029; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.15 (6H, s, CH_3), 7.12-7.30 (3H, m, Ar-H) 7.79 (2H, t, *J* = 8.04 Hz, Ar-H), 8.28 (2H, d, *J* = 8.25 Hz, Ar-H) and 8.86 (2H, d, *J* = 7.32 Hz, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 17.9 (2C, CH_3), 122.7 (1C, C-d′), 127.0 (2C, C-b), 128.5 (1C, C-g), 128.8 (2C, C-c′ and e′), 131.7 (2C, C-d), 131.8 (2C, C-b′ and f′), 134.3 (1C, C-f), 135.5 (2C, C-e), 137.5 (2C, C-c), 139.6 (1C, C-a′) and 163.5 (2C, C-a).**

N-(2-hydroxy-2-phenylethyl)-1,8-naphthalimide **(80)[59] Pale Brown crystal (13%), m.p. 245-247°C (95% ethanol), R_f 0.66 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3475, 3071, 2962, 1771, 1734, 1614, 1442, 1404, 1130 and 1028; ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.68 (2H, m, CH_2), 4.82 (1H, p, *J* = 4.46, CH), 5.54 (1H, d, *J* = 4.32 Hz, OH), 7.15-7.32 (3H, m, Ar-H) 7.60 (2H, t, *J* = 8.08 Hz, Ar-H), 7.99 (2H, d, *J* = 8.24 Hz, Ar-H) and 8.05 (2H, d, *J* = 7.40 Hz, Ar-H); ^{13}C-NMR (DMSO-d_6) δ (ppm): 50.9 (1C, CH_2), 73.2 (1C, CH), 125.6 (2C, C-b), 126.4 (1C,**

C-g), 127.3 (2C, C-b′ and f ′), 127.4 (1C, C-d′), 128.0 (2C, C-d), 128.7 (2C, C-c′ and e′), 130.6 (1C, C-f), 137.6 (2C, C-e), 138.0 (2C, C-c), 140.6 (1C, C-a′) and 165.9 (2C, C-a).

***N-(2,6-Dimethylphenyl)succinimide* (81)[60] White crystal (43%), m.p. 184-188 °C (95% ethanol) (lit.[60] m.p. 187°C), R_f 0.64 (ethyl acetate). IR (KBr, cm^{-1}) 3045, 2992, 2915, 1774, 1700, 1473, 1434, 1376 and 1187; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.09 (6H, s, CH_3), 2.94 (4H, m, CH_2 (succinimide ring)) and 7.10-7.24 (3H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 17.8 (2C, CH_3), 28.7 (2C, C-b), 125.9 (1C, C-d′), 128.6 (2C, C-c′ and e′), 129.5 (2C, C-b′ and f ′) 135.6 (1C, C-a′) and 176.0 (2C, C-a).**

***N-(2-hydroxy-2-phenylethyl)succinimide* (82)[61] White crystal (7%), m.p. 159-164°C (95% ethanol), R_f 0.33 (chloroform-ethyl acetate [1:1]). IR (KBr, cm^{-1}) 3381, 3006, 2931, 1767, 1687, 1432, 1400, 1324, 1174 and 1070; ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.54 (4H, m, CH_2 (succinimide ring)), 3.55 (2H, m, CH_2), 4.81 (1H, qui, *J* = 4.38 Hz, CH), 5.48 (1H, d, *J* = 4.36 Hz, OH) and 7.22-7.34 (5H, m, Ar-H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 27.9 (2C, C-b), 45.9 (1C, CH_2), 70.9 (1C, CH), 125.8 (2C, C-b′ and f ′), 127.3 (1C, C-d′), 128.2 (2C, C-c′ and e′) 142.4 (1C, C-a′) and 177.6 (2C, C-a).**

2.4 Anticonvulsant Experiment

In MES (Maximal Electroshock Seizure) test, the equipment (Electroshock apparatus with corneal electrode) and some chemicals were kindly supplied by Associate Professor Dr. Boonyong Tantisira and Assistant Professor Dr. Mayuree Tantisira (Department of Physiology and Department of Pharmacology, respectively, Faculty of Pharmaceutical Sciences, Chulalongkorn University).

2.4.1 Experimental Animal

Preliminary anticonvulsant evaluation of *N*-substituted phthalimide derivatives was conducted by following the Anticonvulsant Drug Development (ADD) Program protocol.[8,62] Experiments were performed on adult male Swiss albino mice weighing 18-25 g which were obtained from National Laboratory Animal Center, Mahidol University, Salaya, Nakornpathom, Thailand. The mice were allowed free access to

food and water, except when they were removed from their cages for the experimental procedures.

2.4.2 Sample Preparations

a) For solid compounds

The preliminary screening was done at doses of test compounds at 300 mg/kg. Samples were prepared by grinding together 60 mg of finely powdered test compound and 2-3 drops of glycerol in a mortar. After that, the mixture was suspended in 2 mL of 0.5% methylcellulose/water mixture. (This preparation for 20 g body weight of mice).

b) For liquid compounds

The test compound (60 mg) were dissolved in 30% polyethylene glycol 400 (PEG 400) 2 mL. (This preparation for 20 g body weight of mice).

2.4.3 Injection of Test Compounds

The volume employed in mice is 0.01 mL/g body weight to mice. Test compounds were administered to mice by intraperitoneal route 30 min or 4 hr before performing MES test. In this test, one test compound was used to 2 mice/dose. Comparison with data recorded under the same conditions on phenytoin, the reference prototype antiepileptic drug.

2.4.4 Maximal Electroshock Seizure Test (MES test) [8, 13]

A drop of electrolyte solution (0.9% sodium chloride solution) is applied to the eyes of mice, the corneal electrodes are applied to the eyes, and the electrical stimulus (50 mA in mice; 60 Hz) is delivered for 0.2 second. The animals are retrained only by hand and are released at the moment of stimulation in order to permit observation of the seizure throughout its entire course. Abolition of the hindleg tonic extensor component after sample treatment is considered abolished if the hindleg tonic extension does not exceed a 90° angle with the plane of the body and indicates that the test substance has the ability to present seizure spread.

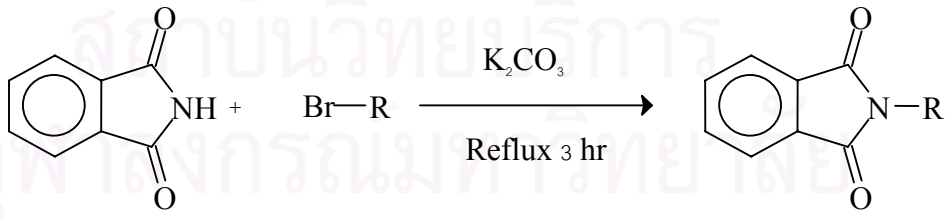
CHAPTER III
RESULTS AND DISCUSSION

Eighty-two compounds including sixty-four phthalimides, twelve *bis*-phthalimides and six analogues were synthesized. These compounds were subjected to the MES test to observe the effects of phthalimide structure on anticonvulsant activity.

3.1 Synthesis of Phthalimides and Analogues

A series of *N*-substituted phthalimides was synthesized employing mainly two routes as shown in Fig 3.1. The first procedure (method I) was generally utilized the nucleophilic substitution between phthalimides and aryl- or alkyl halides in the presence of anhydrous potassium carbonate.[16] The other procedure (method II) was employed the reaction between phthalic anhydride and amines in acetic acid at reflux temperature. The product was precipitated by addition of water.[15] In this research, method II was selected for the synthesis of phthalimides because the procedure was not complicated and the desired products were normally gained in moderate to high yield. The amino derivatives were obtained by reducing the nitro precursors through hydrogenation at reflux temperature using iron powder, glacial acetic acid and methanol as a solvent.

Method I



Method II

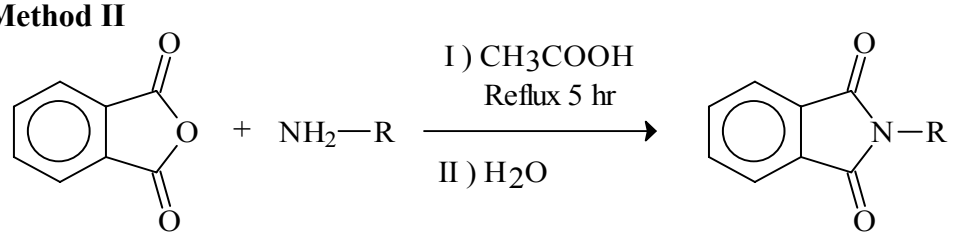
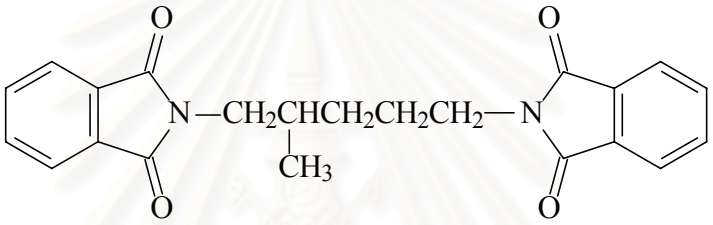


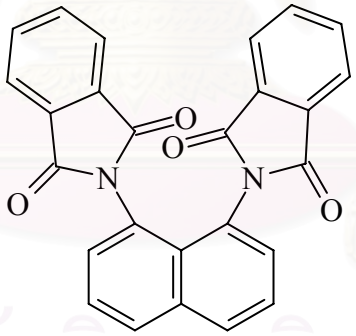
Fig 3.1 General synthesis of phthalimides

A class of *N*-phthalimide contained a linkage between two phthalimides at *N*-position is called *bis*-phthalimide. In this research, these compounds were synthesized by the aforementioned general procedure, but 2 mol equivalents of phthalic anhydride and 1mol equivalent of diamine were used.

Among eighty-two compounds synthesized, two compounds (**70** and **75**) were disclosed to be new substances based upon no report of those compounds available in chemical literature (structure shown below). Structures of all synthesized compounds were well characterized using various spectroscopic techniques including IR, ^{1}H- and ^{13}C-NMR. The physical properties of all synthetic compounds are tabulated in Tables 3.1 and 3.2.



(**70**)



(**75**)

Table 3.1 Physical properties and % yield of phthalimides

Compound	Physical Properties		% Yield
	Appearance	m.p. (°C)	
1	white crystal	64-65	16
2	colorless liquid	-	61
3	white crystal	55-56	69
4	white crystal	64-66	65
5	white crystal	76-80	52
6	white crystal	79-83	10
7	white crystal	89-90	34
8	white crystal	129-131	21
9	colorless liquid	-	26
10	colorless liquid	-	32
11	white crystal	109-112	43
12	white crystal	193-196	53
13	white crystal	144-148	68
14	white crystal	133-138	81
15	white crystal	156-160	75
16	white crystal	226-232	19
17	white crystal	162-164	75
18	white crystal	209-211	71
19	white needle crystal	113-115	59
20	white crystal	129-133	74
21	colorless liquid	-	67
22	colorless liquid	-	53
23	white crystal	163-166	52
24	white crystal	178-180	56
25	white crystal	215-219	70
26	white crystal	230-235	47
27	yellow powder	200-201	32
28	white crystal	244-247	77

Table 3.1 (cont.)

Compound	Physical Properties		% Yield
	Appearance	m.p. (°C)	
29	white crystal	267-269	79
30	yellow powder	178-181	51
31	red powder	187-188	14
32	brown crystal	188-191	35
33	yellow brown crystal	250-252	9
34	red powder	166-167	33
35	white crystal	161-164	73
36	white crystal	198-200	65
37	white crystal	190-194	66
38	white crystal	152-156	50
39	white crystal	203-204	79
40	white crystal	192-195	57
41	white crystal	205-208	71
42	white crystal	170-172	51
43	white crystal	205-208	67
44	yellow crystal	198-201	21
45	brown powder	212-215	84
46	yellow crystal	181-183	43
47	white crystal	193-195	81
48	yellow crystal	183-185	67
49	yellow crystal	204-206	66
50	pale brown powder	182-186	53
51	yellow crystal	186-188	42
52	yellow crystal	145-148	21
53	white crystal	190-193	69
54	pale brown powder	177-180	63
55	small white crystal	203-205	26
56	pale brown crystal	160-165	69

Table 3.1 (cont.)

Compound	Physical Properties		% Yield
	Appearance	m.p. (°C)	
57	black crystal	197-199	61
58	pale orange crystal	223-225	68
59	white crystal	230-233	49
60	gray crystal	296-299	75
61	white crystal	215-218	53
62	white crystal	158-160	75

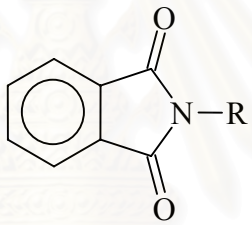
Table 3.2 Physical properties and % yield of *bis*-phthalimides and analogues

Compound	Physical Properties		% Yield
	Appearance	m.p. (°C)	
65	white crystal	234-238	59
66	white crystal	190-195	56
67	white crystal	223-226	64
68	white crystal	171-175	68
69	white crystal	136-138	71
70	white crystal	133-135	52
71	white crystal	248-250	49
72	white powder	> 300	86
73	black powder	> 300	71
74	brown powder	> 300	26
75	red black powder	> 300	51
76	brown powder	> 300	68
77	yellow crystal	170-172	76
78	yellow crystal	190-195	29
79	white crystal	224-227	75
80	pale brown crystal	245-247	13
81	white crystal	184-188	43
82	white crystal	159-164	7

The derived products between phthalic anhydride and aliphatic amines (Compounds **1-17**) were generally found to achieve in low to moderate yield (16-68%) except for Compounds **14**, **15** and **17** which obtained in high yield (75-81%). Melting points of most aliphatic phthalimides were below 150°C, except for those of Compounds **12** and **15-17**. For phthalimides which were synthesized from interested aromatic amines (Compounds **18-64**), moderate to high yield were gained (42-81%) except for Compounds **27**, **31-33**, **44**, **52** and **55** which were obtained in low yield (9-35%). Melting points of most aromatic phthalimides were over 150°C. The yield of *bis*-phthalimides and analogues (Compounds **65-82**) was found to be moderate to high yield. Most of these compounds had melting point over 150°C.

3.2 Spectroscopy of Phthalimides and Analogues

Infrared Spectroscopy (IR)

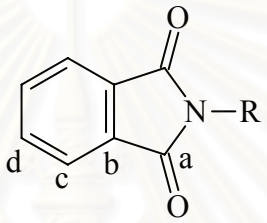


The IR absorption pattern for all phthalimides and *bis*-phthalimides showed the characteristic of common functional group. To illustrate this, the C-H stretching vibration of aromatic moiety at 3108-3030 cm^{-1} and that of aliphatic at 2993-2850 cm^{-1} were detected. C=O Stretching vibration of phthalimide ring at 1779-1698 cm^{-1} and that of C=C ring stretching at 1498-1437 cm^{-1} were also observed. The C-N stretching vibration was found at 1122-1037 cm^{-1}. The FT-IR absorption band assignments of new synthetic phthalimides are tabulated in Table 3.3.

Table 3.3 The FT-IR absorption band assignments of new synthetic phthalimides

Compound	Wave number (cm^{-1})				
	C-H str. (aromatic)	C-H str. (aliphatic)	C=O str.	C=C str.	C-N str.
70	3075 (w)	2940 (w)	1771, 1701 (s)	1461 (m)	1061 (s)
75	3090 (w)	-	1724 (s)	1456 (m)	1103 (s)

Nuclear Magnetic Resonance Spectroscopy (NMR)



^{1}H-NMR

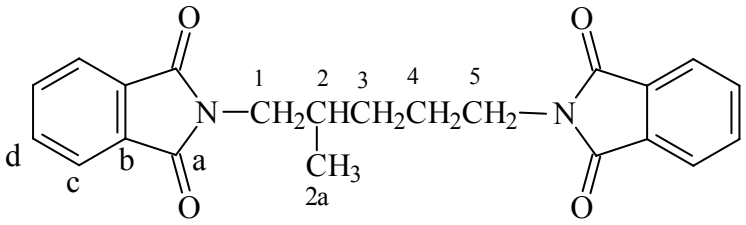
^{1}H-NMR spectra of phthalimides and *bis*-phthalimides generally exhibited a multiplet signal with 4H integration around 7.67-8.43 ppm which could be assigned for aromatic protons.

^{13}C-NMR

^{13}C-NMR spectra of main skeleton of phthalimides and *bis*-phthalimides revealed total of four signals. The remaining 4 C signals were aromatic carbons as C-a, C-b, C-c and C-d detected around 166.3-168.9, 132.9-135.0, 123.5-128.9 and 126.0-134.5 ppm, respectively.

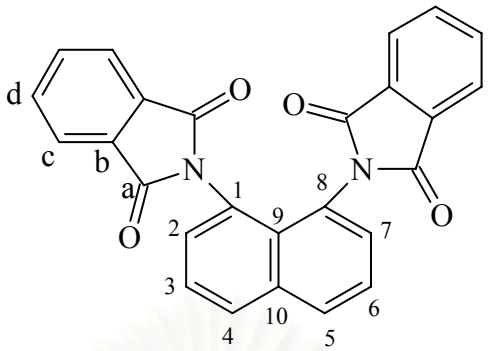
The ^{1}H- and ^{13}C-NMR spectral assignments of new synthetic phthalimides are exhibited in Table 3.4-3.5.

Table 3.4 ^{1}H- and ^{13}C-NMR spectral assignments of Compound **70**



Position	Chemical shift (ppm)	
	^{1}H-NMR	^{13}C-NMR
1	3.48 (m)	43.8
2	1.18 (m)	31.3
2a	0.85 (d, J = 6.73 Hz)	17.3
3	1.18-1.82 (m)	32.3
4		25.8
5	3.62 (t, J = 7.32 Hz)	37.9
a	7.63-7.79 (m)	168.3, 168.5
b		133.8
c		123.1, 123.2
d		132.0, 132.1

Table 3.5 ^{1}H- and ^{13}C-NMR spectral assignments of Compound **75**



Position	Chemical shift (ppm)	
	^{1}H-NMR	^{13}C-NMR
1	-	133.8
2	6.22-6.65(m), 7.04-8.34 (m)	108.8
3		123.5
4		122.5
5		122.5
6		123.5
7		108.8
8	-	133.8
9	-	121.4
10	-	134.8
a	7.04-8.34 (m)	164.2
b		133.0
c		128.4
d		130.6

3.3 Anticonvulsant Activity

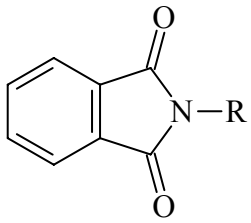
Animal seizure tests included one electrically and one chemically induced seizure episode test and were conducted according to the Anticonvulsant Drug Development (ADD) Program protocol.[8,62] The electrical test employed was the Maximal Electroshock Seizure (MES) pattern test. In MES test, maximal seizures are elicited in mice by a 60 Hz alternating current of 50 mA delivered for 0.2 s *via* corneal electrodes. This amount of current is approximately 6 times the threshold and reveals the ability of the compound to prevent seizure spread. A drop of an anesthetic solution instilled in each eye prior to application of the electrodes ensures adequate electrical contact; it also reduces the incidence of fatalities to near zero. Maximal seizures are produced in virtually all normal mice. The maximal seizure typically consists of a short period of initial tonic flexion and a prolonged period of tonic extension (especially of the hind limbs), followed by terminal clonus. The typical seizure lasts approximately 22 s. Failure to extend the hind limbs to an angle with the trunk greater than 90° is defined as protection.[13]

For the chemically induced convulsant test, pentylenetetrazol was dissolved in sufficient 0.9% sodium chloride solution to allow subcutaneous injections to mice and rats in volumes of 0.01 mL/g of body weight and 0.02 mL/10 g body weight, respectively. The animals given subcutaneous pentylenetetrazol (scPtz) were observed for at least 30 min for the presence or absence of a seizure.

In this research, the MES method was used to investigate anticonvulsant activity. Initial anticonvulsant evaluation of phthalimides, *bis*-phthalimide and analogues were conducted by using dose of 300 mg/kg. All compounds were administered to mice by intraperitoneal route 30 min before evaluation of their activities in these tests. Comparison with data recorded under the same conditions on 0.5% methylcellulose and phenytoin, the reference prototype antiepileptic drug, are further provided.

Generally, the position and type of substituents were major factors to influence the biological activity. To make the SAR study more understandable, the comparison of various substituents of eighty-two compounds prepared could be summarized as shown below. Preliminary anticonvulsant activity data for *N*-aliphatic phthalimides is reported in Table 3.6.

Table 3.6 Anticonvulsant screening data in mice of *N*-aliphatic phthalimides



Compound	R	MES
		30 min
1	$-CH_2CH_2CH_3$	
2	$-CH_2(CH_2)_5CH_3$	
3	$-CH_2(CH_2)_8CH_3$	
4	$-CH_2(CH_2)_{12}CH_3$	
5	$-CH_2(CH_2)_{16}CH_3$	
6	$-CH(CH_3)CH_3$	
7	$-CH_2CH(CH_3)CH_3$	
8	$-CH_2CH_2OH$	
9	$-CH_2CH_2CH_2OH$	
10	$-CH_2CH_2CH_2OCH_3$	
11	$-CH_2COOCH_3$	
12	$-CH_2COOH$	
13	$-CH(CH_3)COOH$ (+)	
14	$-CH(CH_3)COOH$ (-)	
15	$-CH(CH_3)COOH$	
16	$-CH(COOH)CH_2COOH$	
17	-Cyclohexyl	
0.5% Methylcellulose	-	
Phenytoin	-	

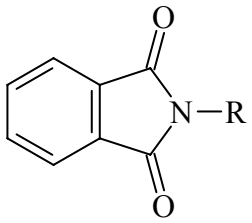
Note : Activity at 300 mg/kg

No activity at 300 mg/kg

Compounds **1-5** were prepared and subjected to MES tests with the aims to observed the effects of side chain on anticonvulsant activity. Unfortunately, no activity was found for these compounds. Similar results were observed for Compounds **8-11** which included alkyl alcohol, alkyl ether and alkyl ester side chain. Moreover, a series of compounds derived from amino acid starting materials such as glycine, (D)-alanine, Compounds **12-16** was manipulated. However, these compounds did not exhibit anticonvulsant activity. Compound **17** containing a cyclohexane ring substituent did also not express activity similar to all mentioned alkyl substituent phthalimides.

Preliminary anticonvulsant evaluation of compounds containing an aromatic ring (Compounds **18-26**) in an amine component of phthalimide is reported in Table 3.7. These results clearly indicated that the introduction of an aromatic ring provided an optimal activity. Compound **19** showed good preliminary anticonvulsant activity, exhibiting greater potency than any *N*-aliphatic phthalimides. It was noteworthy that when increasing a bridge carbon chain in a target molecule such as Compound **20**, similar activity was observed as that found in Compound **19**. However, the addition of three-carbon linkage between phthalimide and phenyl ring as Compound **21**, no activity was detected. Moreover Compound **23**, a derivative of Compound **20**, appeared to show promising anticonvulsant activity. Replacement of a phenyl ring in Compound **18** with 1-naphthyl or 2-naphthyl moieties as in Compounds **24-26**, no activity was observed.

Table 3.7 Anticonvulsant screening data in mice of *N*-aromatic phthalimides



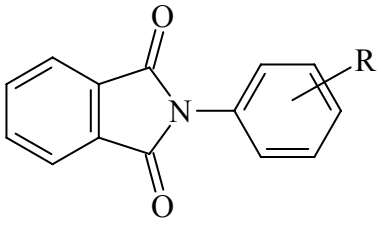
Compound	R	MES
		30 min
18	$-C_6H_5$	
19	$-CH_2C_6H_5$	
20	$-CH_2CH_2C_6H_5$	
21	$-CH_2CH_2CH_2C_6H_5$	
22	$-CH(CH_3)C_6H_5$	
23	$-CH_2CH(OH)C_6H_5$	
24	1-Naphthyl	
25	2-Naphthyl	
26	2-(1-SO_3H)- Naphthyl	
0.5% Methylcellulose	-	
Phenytoin	-	

Note : Activity at 300 mg/kg

No activity at 300 mg/kg

The results reported in Table 3.8 were obtained from the study of a series of phthalimide derivatives including chloro, bromo, amino, nitro, methyl, hydroxy and other substituents of *N*-phenylphthalimide. To gain more information for discussion, *N*-phenylphthalimides were classified according to their substituents into five groups as follows:

Table 3.8 Anticonvulsant screening data in mice of *N*-phenylphthalimides



Compound	R	MES
		30 min
27	2-NO_2	
28	3-NO_2	
29	4-NO_2	
30	2,4-$(NO_2)_2$	
31	2-NH_2	
32	3-NH_2	
33	4-NH_2	
34	2,4-$(NH_2)_2$	
35	3-Cl	
36	4-Cl	
37	2,3-$(Cl)_2$	
38	2,4-$(Cl)_2$	
39	2,5-$(Cl)_2$	
40	3,4-$(Cl)_2$	
41	3,5-$(Cl)_2$	
42	3-Br	
43	4-Br	
44	2-NO_2-4-Cl	
45	3-NO_2-4-Cl	
46	2-Cl-4-NO_2	
47	2-Cl-5-NO_2	
48	3-NH_2-4-Cl	
49	2-Cl-4-NH_2	
50	2-Cl-5-NH_2	

Table 3.8 (cont.)

Compound	R	MES
		30 min
51	2-NO_2-4-CH_3	
52	2-NO_2-4-OCH_3	
53	2-CH_3-4-NO_2	
54	2-CH_3-4-NH_2	
55	2,6-$(CH_3)_2$	
56	2,6-$(CH_2CH_3)_2$	
57	2-OCH_3-5-CH_3	
58	2-OH	
59	3-OH	
60	4-OH	
61	2-COOH	
62	4-$COOC_2H_5$	
63	2-OCH_2COOH	
64	4-OCH_2COOH	
0.5% Methylcellulose	-	
Phenytoin	-	

Note : Activity at 300 mg/kg

No activity at 300 mg/kg

1. Nitro and amino substituents

Compounds **27**-**29** containing a nitro substituent at 2- 3- and 4-positions of a phenyl ring. These compounds, however, did not exhibit anticonvulsant activity at 300 mg/kg. Compound **30** bearing 2,4-dinitro moiety also did not show the activity. It was noteworthy that the transformation of a nitro group to an amino moiety in certain positions significantly enhanced the activity. To illustrate this, Compounds **32** and **33** which contained an amino group at 3- and 4-position on phenyl ring exhibited the activity. However, Compound **34** which contained two amino groups at 2- and 4-

position, no activity was observed. Thus, an amino substituent particularly present at 3- or 4-position was active in anticonvulsant activity more than a nitro group.

2. Chloro and bromo substituents

Compounds **35-41** contained chloro- and dichloro substituents at various positions were synthesized and examined for anticonvulsant activity. It was observed that these compounds did not display anticonvulsant activity. Similar results were observed when bromo substituents at 3- or 4-position (Compounds **42** and **43**) were investigated. Thus, halide substituent of phthalimides did not reveal anticonvulsant activity.

3. Nitro-chloro and amino-chloro substituents

Compounds **44-47** belonged to a series of compounds having the same substituents (nitro-chloro), but different in positions on a phenyl ring. These compounds, however, did not show any activity. Transforming a nitro group to an amino group by reduction reaction of these compounds yielding Compounds **48-50**. Anticonvulsant activity was observed in Compounds **49** and **50**. This result clearly confirmed that an amino substituent displayed a profound effect prevailing to a nitro group. However, the addition of chloro group at 4-position in Compound **48** caused the loss of potency comparing with Compound **32**.

4. Methyl-containing substituents

Among seven compounds be classified in this group, two compounds were found to be active. For example, Compound **54** contained substituted methyl and amino at 2- and 4-position on a phenyl ring, respectively. In contrast to Compound **53**, where an amino group was replaced by a nitro group, no activity was observed. Similar trend of results was visualized when the same substituents were present, but at different positions. To illustrate this, Compound **55** which consisted of two methyl groups at 2- and 6-positions on a phenyl ring exhibited activity. However, changing a methyl group to an isopropyl group, the activity was lessen.

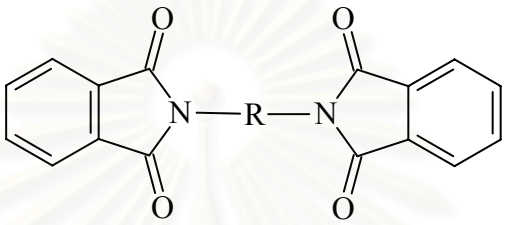
5. Other substituents

Compounds **58-60** contained a hydroxy group at 2-, 3- and 4-position at a phenyl ring did not reveal anticonvulsant activity. Other compounds in this group

including carboxy or ester substituents as in Compounds **61**-**64** also did not exhibit this interested activity.

A series of twelve *bis*-phthalimides was prepared and evaluated for anticonvulsant activity. The results of initial anticonvulsant activity of these compounds are reported in Table 3.9.

Table 3.9 Anticonvulsant screening data in mice of *bis*-phthalimides



Compound	R	MES
		30 min
65	$-CH_2CH_2-$	
66	$-CH_2CH_2CH_2-$	
67	$-CH_2(CH_2)_2CH_2-$	
68	$-CH_2(CH_2)_4CH_2-$	
69	$-CH_2(CH_2)_6CH_2-$	
70	$-CH_2CH(CH_3)(CH_2)_2CH_2-$	
71	1,2-Cyclohexyl	
72	$1,3\text{-}C_6H_4$	
73	$1,4\text{-}C_6H_4$	
74	$1,1'\text{-}(C_6H_4)_2$	
75	1,8-Naphthyl	
76	2,6-Pyridyl	
0.5% Methylcellulose	-	
Phenytoin	-	

Note : Activity at 300 mg/kg

No activity at 300 mg/kg

The variation of the numbers of carbon atoms between two phthalimides of alkyl group at *N*,*N*′-position was also investigated. It was found that in a series of Compounds **65-69** which carbon atoms increased from 2, 3, 4, 6 and 8, these compounds were essentially inactive for anticonvulsant activity. The similar result was observed for Compounds **70** and **71**, where a side chain was of an alkyl branch chain and cyclohexyl substituents, respectively. Compounds **72-74** which contained phenyl or biphenyl ring between two phthalimides did not show activity. Replacement of a phenyl ring in Compound **73** with 1,8-naphthyl or 2,6-pyridinyl ring in Compounds **75-76** not reveal activity. From these results, *bis*-phthalimides (Compounds **65-76**) were not of anticonvulsant activity.

According to the data gained from previous table, Compounds **23** and **55** composed of two parts: phthalic anhydride and amines (2-hydroxy-2-phenyl ethylamine and 2,6-dimethyl aniline) exhibited activity observed at 300 mg/kg. This group of compounds (Compound **77-82**) was synthesized to extend the knowledge on structures of anhydride-derived portion and anticonvulsant activity. Phthalic anhydride was changed to 3-nitrophthalic anhydride, 1,8-naphthalic anhydride and succinic anhydride. The results are tabulated as shown in Table 3.10.

Table 3.10 Anticonvulsant screening data in mice of analogues

Compound		R	MES
			30 min
77	3-Nitrophthalimide	*N*-2,6-$(CH_3)_2C_6H_4$	
78	3-Nitrophthalimide	*N*-$CH_2CH(OH)C_6H_5$	
79	1,8-Naphthalimide	*N*-2,6-$(CH_3)_2C_6H_4$	
80	1,8-Naphthalimide	*N*-$CH_2CH(OH)C_6H_5$	
81	Succinamide	*N*-2,6-$(CH_3)_2C_6H_4$	
82	Succinamide	*N*-$CH_2CH(OH)C_6H_5$	
0.5% Methylcellulose		-	
Phenytoin		-	

Note : Activity at 300 mg/kg

No activity at 300 mg/kg

Whereas Compounds **77-80** derived from the replacement of phthalic anhydride with 3-nitrophthalic anhydride and 1,8-naphthalic anhydride, no activity was showed, the alternation of phthalic anhydride with succinic anhydride in Compounds **81-82** gave good results exhibiting anticonvulsant activity.

Among eighty-two compounds synthesized and subjected to preliminary screened, eleven compounds, i.e., Compounds **19**, **20**, **23**, **32**, **33**, **49**, **50**, **54**, **55**, **81** and **82** were found to be of activity in the MES test. These compounds were further selected for quantitative evaluation of anticonvulsant activity in mice dosed (30, 100 and 300 mg/kg) at route 30 min or 4 hr. The results of these evaluations are given in Table 3.11.

Table 3.11 Anticonvulsant screening data in mice dosed intraperitoneally with selected active compounds.

Compound	MES	
	30 min	4 hr
19	++	-
20	+	-
23	++	+
32	+	-
33	+++	-
49	+++	-
50	++	-
54	+++	++
55	++	-
81	+	-
82	+	-
0.5% Methylcellulose	-	-
Phenytoin	+++	++

Note : +++ Signify activity at 30 mg/kg
++ Signify activity at 100 mg/kg
+ Signify activity at 300 mg/kg
- No activity observed at 300 mg/kg

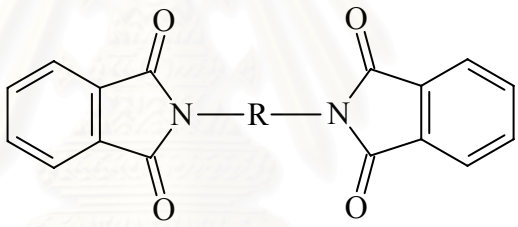
All of these compounds showed activity against MES-induced convulsions at 300 mg/kg 30 min after administration with most compounds, maintaining at least minimal anti-MES activity 4 hour after administration. Almost compounds showed activity against MES-induced convulsions at 30 min; however, the activity had essentially disappeared at 4 hour. Compound **19** showed some activity against MES seizures at 100 mg/kg. However, the addition of one carbon atom as in Compound **20** drastically decreases the anticonvulsant effects. Compound **23** which was a derivative of Compound **20**, showed activity at 30 min interval after administration of a dose of 100 mg/kg, and observed activity was still remained at 4 hour administration of 300 mg/kg. The comparison of the activity of Compounds **32** and **33** which contained the amino group at 3 and 4-position, respectively was examined. Compound **32** showed anticonvulsant activity at 300 mg/kg whereas Compound **33** protected at dose of 30 mg/kg. Thus, the relationship between anticonvulsant activity and relative position of the amino group for these *N*-phenyl phthalimides is 4-amino > 3-amino > 2-amino.

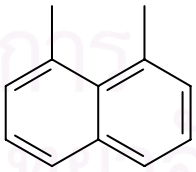
Compounds **49** and **50** showed the most potent anticonvulsant activity at 30 and 100 mg/kg, respectively. These compounds having the same substituents but different in the position of phenyl ring. It was found that 2-chloro-4-amino substituent expressed more potency than 2-chloro-5-amino substituent in the anticonvulsant screening test. When chloro group at 2-position in Compound **49** was replaced with methyl group as in Compound **54**, activity was showed at 30 mg/kg and observed activity still remained at 4 hour administration of 100 mg/kg. Thus, the compounds included an amino portion at 4-position and chloro or amino at 2-position, were of the most potent anticonvulsant activity. From these results, the compounds contained an amino group at 4-position displayed higher activity than other positions. Compound **55** was found to possess activity at 100 mg/kg. When the same combined substitutions of the *N*-phthalimides are associated with succinimide (Compounds **81** and **82**) instead of phthalimide (Compounds **23** and **55**, respectively), the anticonvulsant activity was found to be decreased.

Compared with phenytoin, a prototype anticonvulsant drug largely utilized in human clinic, Compounds **33**, **49** and **54** was found to exhibit the activity at least the same as phenytoin in all determinations performed in mice.

CHAPTER IV
CONCLUSION

During the course of this research, phthalimides, *bis*-phthalimides and analogues were synthesized and screened for the possibility of finding active compounds possessing anticonvulsant activity. The synthesized of these compounds was simple: selected anhydride was condensed with various amines to provide sixty-four phthalimides, twelve *bis*-phthalimides and six analogues. All structures were well-characterized using their physical properties and spectroscopic techniques such as IR, ^{1}H- and ^{13}C-NMR was also performed. Two compounds: Compounds **70** and **75** have not been reported in chemical literatures. The structures of new compounds are shown below:



Compound	R
70	—$CH_2CH(CH_3)CH_2CH_2CH_3$—
75	

In this research, phthalimides were tested with MES test, which was selected as the preliminary screening test for anticonvulsant activity studies. For phthalimides, the compounds containing an aromatic ring, such as Compounds **19**, **20**, **23**, **32**, **33**, **49, 50, 54** and **55** displayed anticonvulsant activity.

From SAR studies on these compounds, the best patterns require an amino substitution of the *N*-phenyl moiety. Combination of amino, amino-chloro and amino-methyl substitutions of the *N*-phenyl group gave apparently more potent compounds

with optimal anti-MES properties conveyed by Compounds **32**, **33**, **49**, **50**, **54** and **55**. The most potent compound might be Compounds **33**, **49** and **54**. It combines 4-amino, 2-chloro-4-amino and 2-methyl-4-amino, respectively, substitutions of the *N*-phenyl ring. Thus, an amino group at 4-position of *N*-phenylphthalimides displayed high potent in anticonvulsant activity.

The intent of this research is not only try find out the new chemicals to use as drug, but also to look for the relationship between the structures of phthalimides and anticonvulsant activity. These results could surely be utilized for further development as the application for antiepileptic drugs or discovery high active compounds.

Propose for the Future work

From this study, the results of anticonvulsant activity with MES test of phthalimides displayed the relationship of the anticonvulsant activity and phthalimide structures. Other functional groups substituted on these structures were still attractive to be searched for more potent compound and attained the relationship between structures and anticonvulsant activity. The possibly further work related to this research would be finding out the role of phthalimides in anticonvulsant activity for the truth being revealed.

The further research would be the study of phthalimide structure and these activity by the other methods, such as subcutaneous pentylenetetrazol (scPtz) for discovered new compound, which showed high anticonvulsant activity.

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APPENDIX

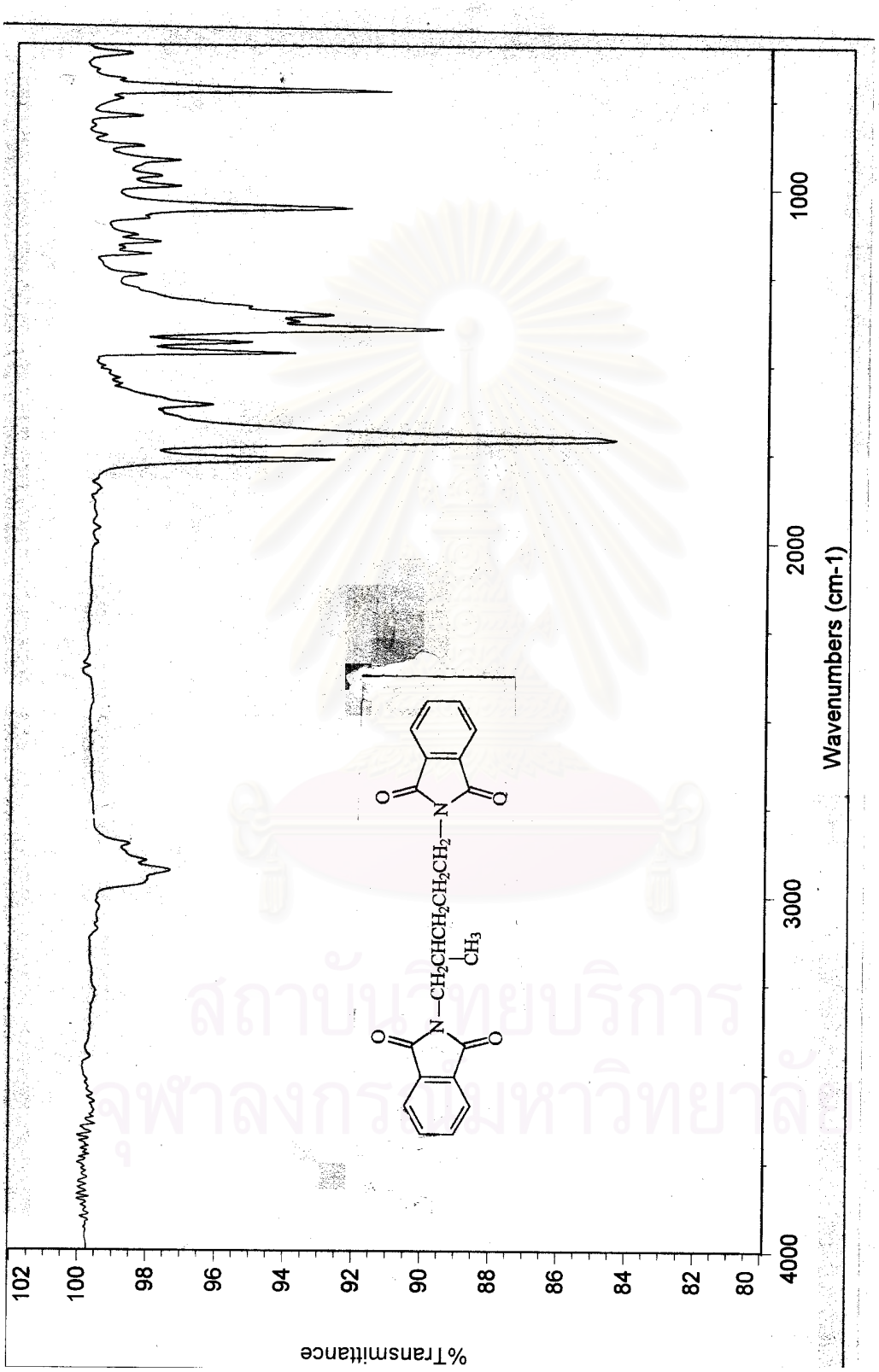

Fig 1 The IR spectrum of Compound **70**

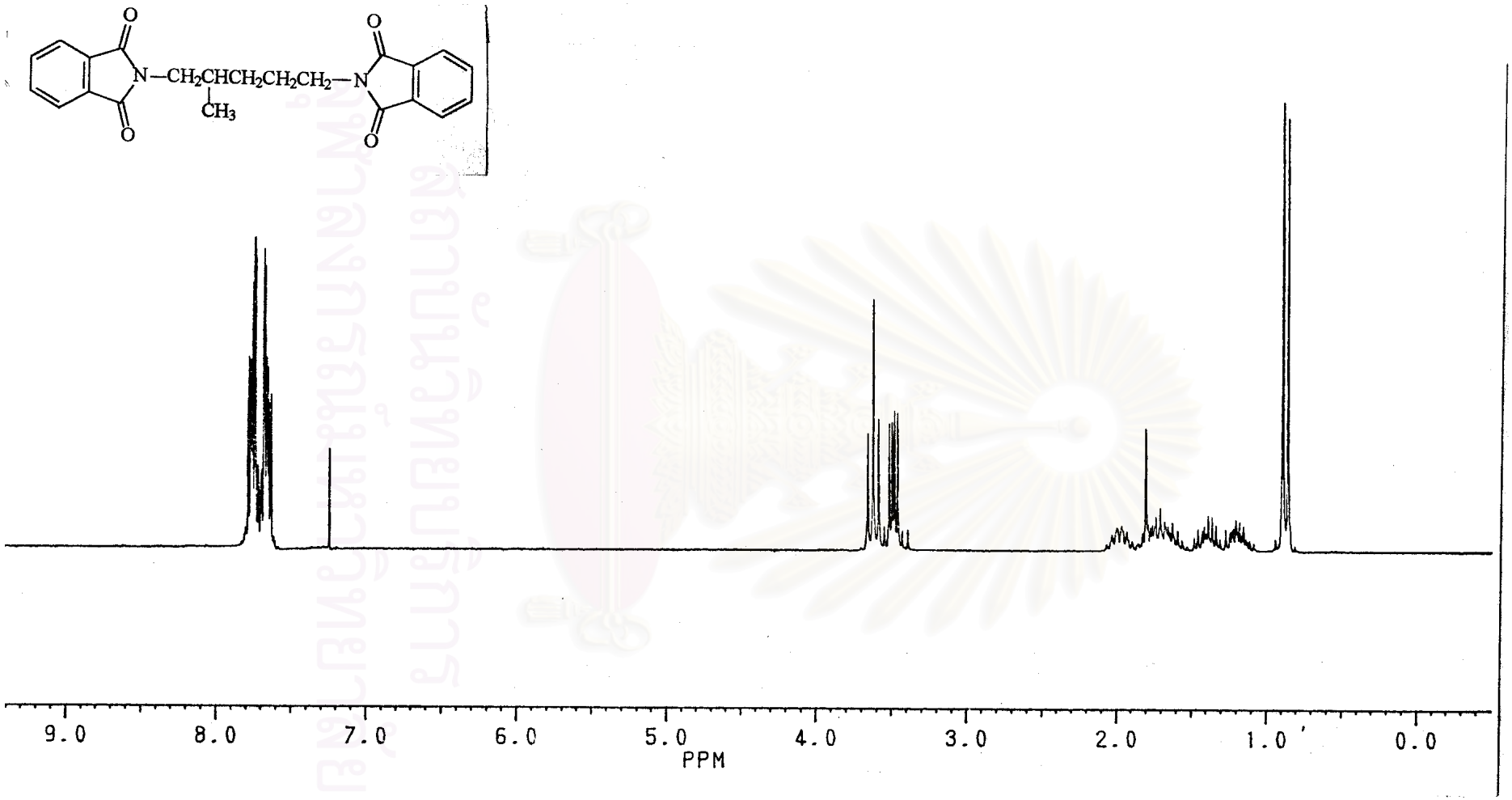

Fig 2 The ^{1}H-NMR spectrum of Compound **70**

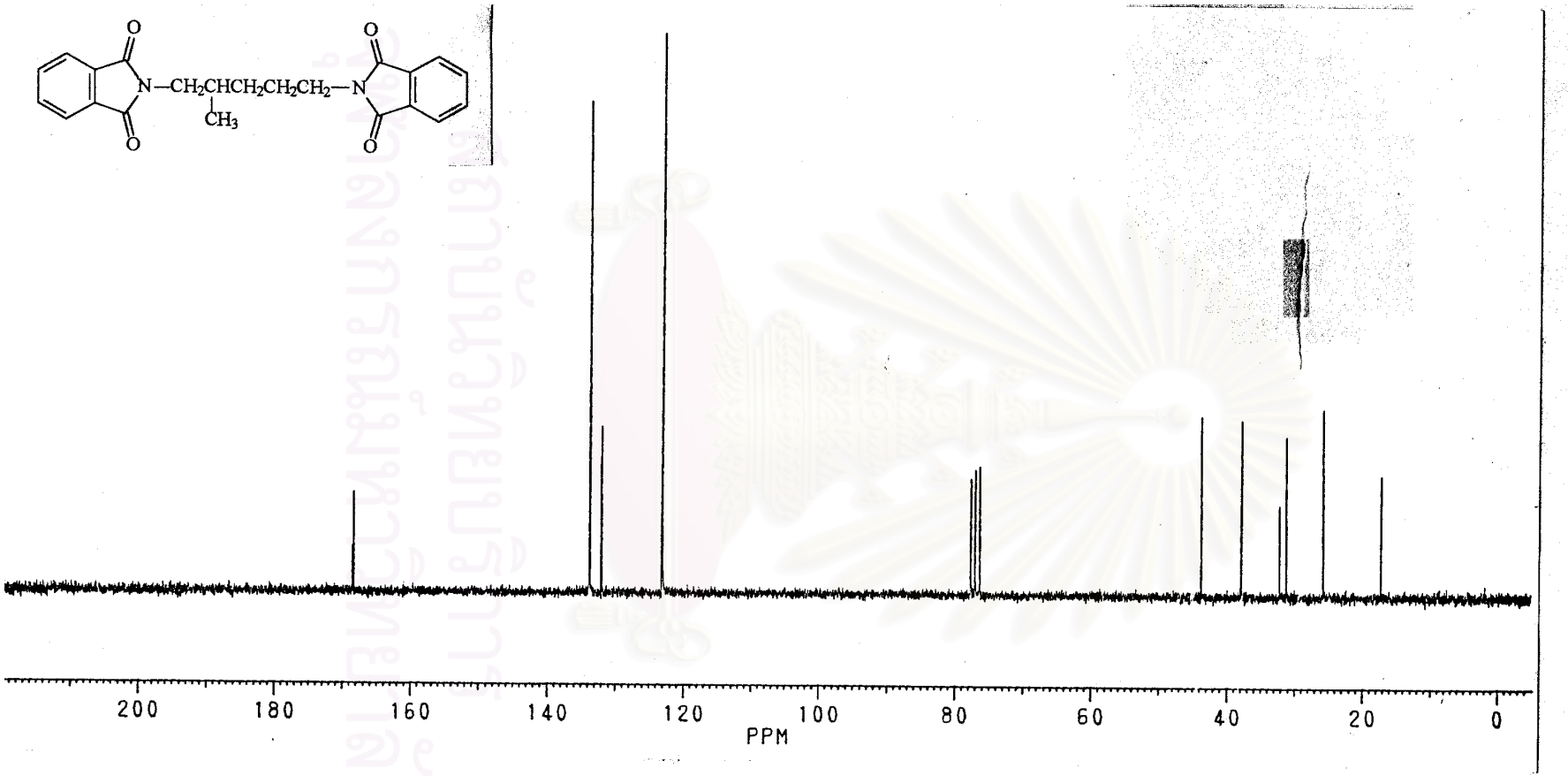

Fig 3 The ^{13}C-NMR spectrum of Compound **70**

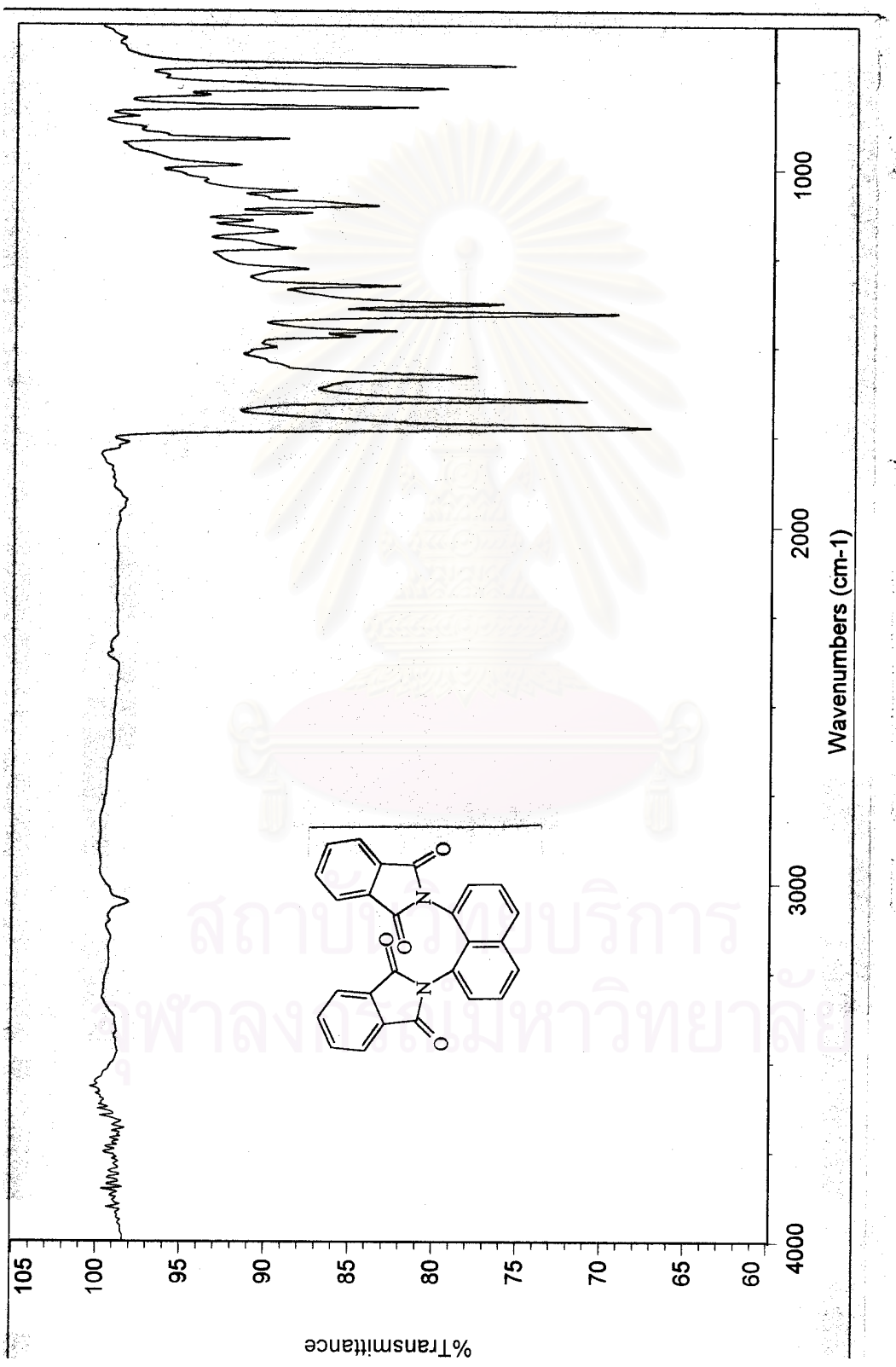

Fig 4 The IR spectrum of Compound **75**

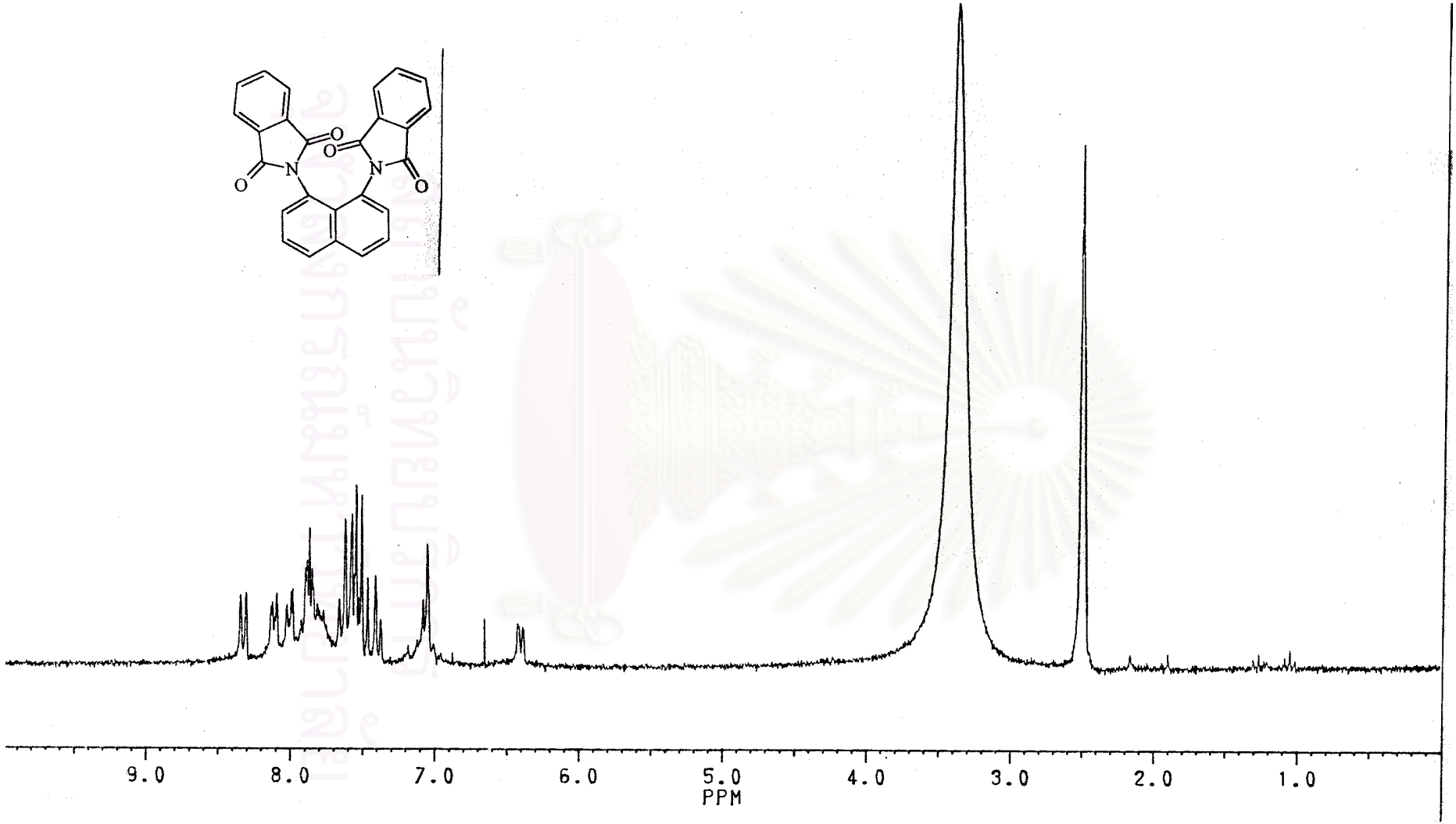

Fig 5 The ^{1}H-NMR spectrum of Compound **75**

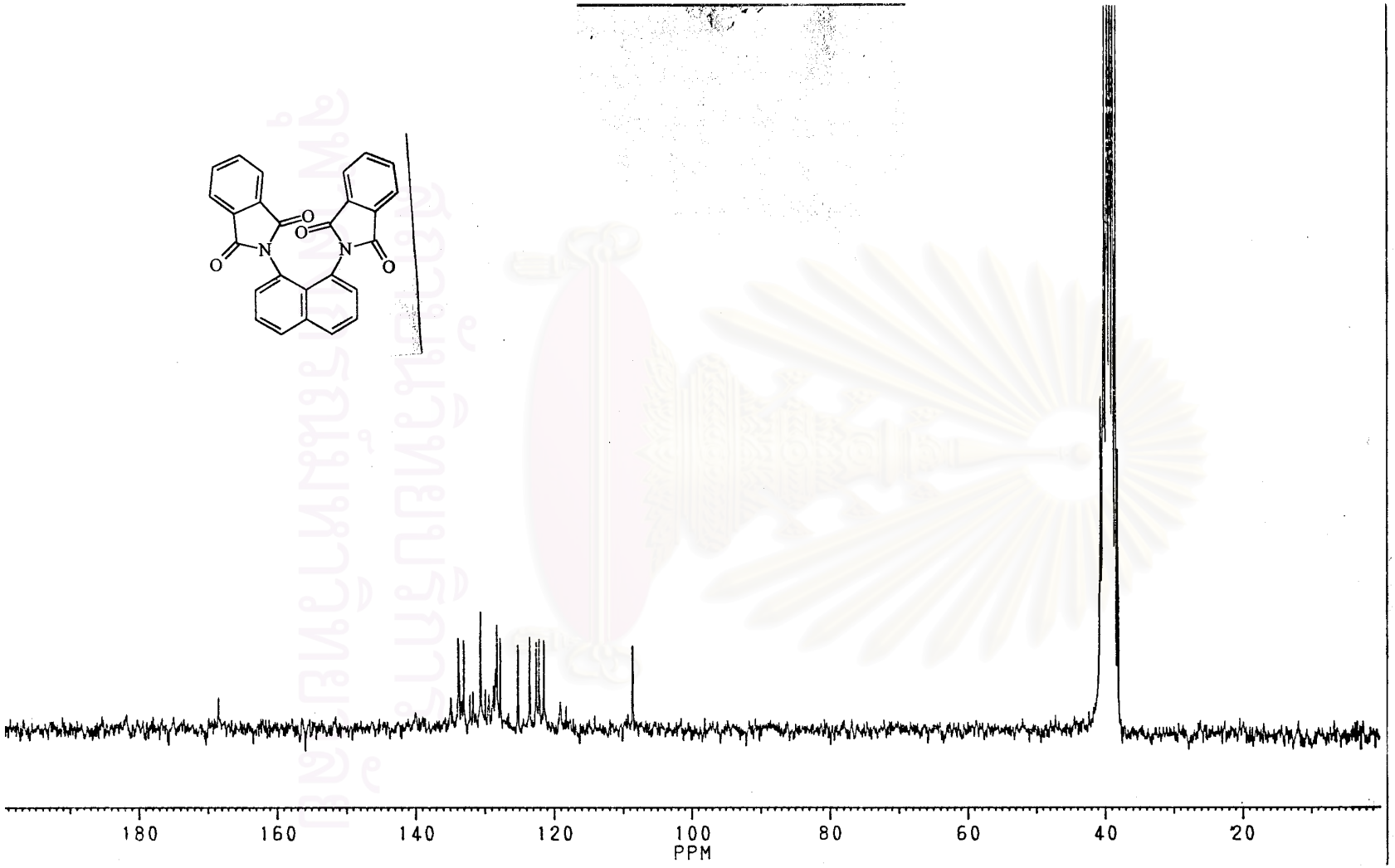

Fig 6 The ^{13}C-NMR spectrum of Compound **75**

VITA

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