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(Research Article)

## Eco-friendly Synthesis of Phthalimide Derivatives, their Analgesic Activity and QSAR Studies

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### ABSTRACT

Phthalimide derivatives syntheses were carried out by eco-friendly microwave irradiation methods where, montmorillonite-KSF was used as the reusable clay catalyst. In the context of green chemistry, among the non-conventional methods of reaction activation in organic synthesis, microwave irradiation for reaction activation provides an alternative to the conventional heating for introducing energy into chemical reactions by using the ability of some liquids and solids to transform electromagnetic energy into heat. These compounds were characterized by TLC, melting point determination, and by IR and <sup>1</sup>H NMR spectroscopy. The acute oral toxicity studies of the compounds were carried out using OECD guidelines. The compounds were then screened for analgesic activity using Aspirin as the standard and activity was correlated with FISA (Hydrophilic component of the total accessible surface area). The molecular modeling software, Maestro, from Schrodinger, USA, was used for QSAR studies.

**Key Words:** Phthalimides, Montmorillonite-KSF, Microwave-irradiation, Analgesic activity, QSAR, FISA

### INTRODUCTION

Acylation of amines by phthalic anhydride<sup>1</sup> produces phthalamic acid derivatives, which are organic herbicides. Further cyclization results into the formation of N-substituted imides, which exhibit various biological activities such as analgesic<sup>2</sup>, antimicrobial<sup>3</sup>, antipsychotic<sup>4</sup>, anti-inflammatory<sup>5</sup>, tuberculosis<sup>6</sup>, hypolipidemic<sup>7</sup> and anxiolytic<sup>8</sup>.

Many of these procedures are associated with one or more disadvantages such as long reaction time, low yield, use of hazardous organic solvents, excess reagents or catalysts, and harsh reaction conditions, which leaves scope for further development of new environmentally clean syntheses.

Almost any type of organic reaction, requiring heating or thermal conditions, can be performed by using microwave radiation. Microwave irradiation method, according to the literature, not only reduces the chemical reaction time from hours to minutes but also assists in increasing the yield of products, and reproducibility of the method<sup>9</sup>.

Montmorillonite-KSF is a green chemistry catalyst, which is naturally occurring clay, reusable, non-corrosive, cheap and non-toxic. Use of montmorillonite-KSF is advantageous over the other catalysts and so the process becomes more economical<sup>10</sup>.

Quantitative structure activity relationships (QSAR) are the mathematical relationships between the biological activity of a molecular system and its physicochemical descriptors<sup>9</sup>. In the search of new active molecules, fifteen phthalimides were synthesized and screened for toxicological studies and

analgesic activities. The QSAR studies were undertaken in order to identify the physicochemical property of phthalimides responsible for the particular biological activity<sup>11</sup>.

### MATERIALS AND METHODS

#### Chemistry

The chemicals required for the synthesis of phthalimides were purchased from Merck Specialities Pvt. Ltd., Spectrochem Laboratories, and Rankem Laboratories. Melting points of all the synthesized compounds were determined in open glass capillaries on EXPO-HiTech melting point apparatus and were uncorrected. The purity of compounds was checked by thin layer chromatography (TLC). The structures of all the synthesized compounds were characterized from their IR spectra and confirmed from their <sup>1</sup>H-NMR spectra. The IR spectra were recorded on JASCO FTIR 5300 IR spectrometer using KBr pellet method in the range of 4000–400 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectra were recorded on VNMR-300 and BRUKER-av400 spectrometers, using TMS as an internal standard and carbon tetrachloride and DMSO as the solvents. For microwave irradiation method, microwave synthesizer from CEM Corporation, USA, was used.

#### General Procedure for the Synthesis of Phthalimides

Phthalic anhydride (0.5 g, 0.00337 M) and montmorillonite-KSF (1.0 g) were ground properly to a uniform mixture.

This mixture was exposed to microwave radiation at 700 W with an alkyl or an aryl amine (0.00337 M) using acetic acid (2.5 ml) as the solvent. The completion of the reaction was monitored by TLC. The reaction mixture was allowed to cool to room temperature and the resulting product was extracted in CH<sub>2</sub>Cl<sub>2</sub>/ CHCl<sub>3</sub>. The organic layer was washed with water and the solvent was recovered by distillation. Residue of the crude product was washed with dilute HCl and distilled water and recrystallized from a suitable solvent. Each reaction was carried out at least thrice to standardize the reaction conditions and yield. The spectral data of all the phthalimides are presented in Table 1.

#### Acute Oral Toxicity Studies

Acute toxicity studies were performed as per the Organization for Economic Co-operation and Development (OECD) guidelines<sup>12</sup>. Before experimentation, the animals were divided into the *control group* and the *test groups*, each group consisting of six animals. The *control group* received orally, a single dose of 10 ml/kg body weight of a control [1% w/v sodium carboxymethyl cellulose (CMC) suspension]. The test compounds, at different dose levels of 500, 1000 and 2000 mg/kg body weight, were administered orally to the animals present in the *test groups*. After the administration of the test compounds, animals were observed for a period of 14 days for the changes in the skin, fur, eyes and behavioral pattern. Mortality of mice in each group was also observed. A dose leading to these changes or mortality was considered to be a toxic dose.

#### Evaluation of Analgesic Activity

Mice of either sex with a weight between 20 and 25 g were used. For the analgesic activity phthalimides acetic acid in the concentration of 0.6 % w/v was used to produce pain in mice, which resulted in writhes. Writhe is indicated by stretching of the abdomen with simultaneous stretching of at least one hind limb.<sup>13, 14</sup> Acetic acid at the dose of 10 ml/kg body weight of a mouse was injected intraperitoneally, 30 min after the administration of the test compounds. Six animals each, were used for the fifteen *test groups* (a group of mice treated with fifteen phthalimides), the *positive control group* (mice treated with aspirin) and the *negative control group* (mice treated with the CMC). The test compounds were administered orally a dose of 150 mg/kg as a suspension in 0.5 % sodium CMC, 30 min prior to the acetic acid administration. The mice in the *positive control group* were treated with an oral dose of 30 mg/kg of aspirin in the form of a suspension in 0.5 % sodium-CMC. The mice in the *negative control group* were administered orally 0.5 % sodium-CMC (10 ml/kg). The mice were placed individually into cages and then after the injection of acetic acid after five min, the mice were observed for a period of twenty min. The number of writhes was recorded for each animal. The per cent inhibition of writhes is was than calculated using following formula:

$$\text{Per cent inhibition of writhes} = \frac{N - N_t}{N} \times 100$$

Where, N = Average number of writhes in the negative control group

N<sub>t</sub> = Average number of writhes in a test group or in the positive control group

#### Quantitative Structure Activity Relationships (QSAR) Studies

The quantitative structure activity relationships (QSAR) studies were carried out on the synthesized phthalimide derivatives in order to establish the correlation between the physicochemical parameters and their biological activities.

“Maestro” – the molecular modeling software from Schrodinger Inc, USA, was used to develop quantitative structure activity relationships models. The software *LigPrep* was used to get correct conformational structures of the synthesized phthalimides. The software *QikProp* provided different physicochemical parameters of phthalimides. The correlation between the biological activity and physicochemical properties of phthalimides was studied using the program *Strike* from Schrodinger.

#### Statistical Analysis

All the analgesic activity results were expressed as mean ± SEM (Standard Error of Mean) values. The statistical analysis for the analgesic activity of phthalimide derivatives was performed using one-way analysis of variance (ANOVA), followed by Dunnett’s test, for multiple comparison between the control group and the test groups, using the Graphpad software, USA. The ‘p’ values less than 0.05 were considered to be significant.

#### RESULTS AND DISCUSSION

Fifteen phthalimides were synthesized by microwave methods. The reactions involved in the synthesis of phthalimides are presented in Scheme 1. The yield, reaction time, melting point, R<sub>f</sub> and TLC of phthalimides by microwave irradiation methods are listed in Table 2.

Microwave irradiation improved the yield of phthalimides by 5-12% and reduced the reaction time from hours to minutes.

All the fifteen synthesized phthalimides were tested for their toxic effects at different dose levels (500, 1000 and 2000 mg/kg body weight) in mice. The mice were observed for 14 days after the administration of compounds, as per the OECD guidelines. None of the synthesized compounds showed any significant changes in the skin, fur, eyes and other behavioral patterns in mice at any of the tested dose levels. No mortality was observed in the control and the test groups. Thus, these compounds were considered to be safe for administration at all the tested dose levels.

#### Analgesic Activity

The analgesic activity is expressed as the mean of the number of writhes ± SEM (Standard Error of Mean) and the per cent inhibition of writhes. Out of 15 synthesized compounds, 13 compounds showed reduction in number of writhes in mice when compared with the number of writhes produced in mice treated with aspirin and thus showed statistically significant analgesic activity, which is listed in Table 7.

The per cent protection provided by aspirin against the writhes was 46.3 and that provided by most of the test compounds was more than that. Compounds 2, 4, 7, 9 and 11 produced % protection greater than 90, compounds 3, 5, 6 and 10 produced % protection in the range of 70-82 and compounds 8, 12, 13 and 14 showed per cent protection in the range of 50-66. Compounds 1 and 15 showed analgesic activity lesser than that of aspirin, whereas compound 4 had the highest analgesic activity (95.5 %) as compared to all the

other synthesized compounds. The graph showing analgesic activity is presented in Fig. 1.

**Development and Validation of QSAR Models**

The best QSAR model for the analgesic activity of fifteen phthalimides was developed and validated by using 9 phthalimides in the *training set* and 5 phthalimides in the *test set*, and is represented by equation 2.

$$\text{Log (\% inhibition of writhes)} = 2.1185 - 0.0019 \text{ FISA} \dots \text{eq. 2}$$

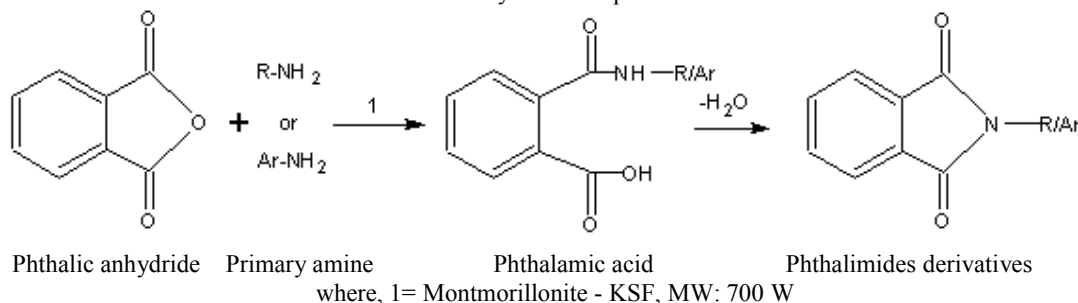
$$n = 9, r^2 = 0.80, s = 0.047, F = 29.3$$

The correlation between the observed and predicted analgesic activities for the *training* and *test set* compounds is shown graphically in Figures 2 and 3 respectively.

**Table 1:** The spectral data of phthalimide derivatives

Comp No.	IR Wave numbers (cm <sup>-1</sup> )	H <sup>1</sup> NMR Chemical shift values (δ ppm)
1	1385, C-N str 1494, Ar, C=C str 1707, C=O str 3076, C-H str	7.26-7.54 (m, 5H, Ar- H <sub>5</sub> , H <sub>6</sub> , H <sub>7</sub> , H <sub>8</sub> , H <sub>9</sub> ) 7.81 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 7.98 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> )
2	715, C-Cl str 1381, C-N str 1487, Ar, C=C str 1718, C=O str	7.26-7.61 (m, 4H, Ar-H <sub>5</sub> , H <sub>6</sub> , H <sub>7</sub> , H <sub>8</sub> ) 7.83 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 8.0 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> )
3	1392 C-N str 1602, Ar, C=C str 1705 C=O str	1.20-1.45 (m, 6H, Ar-H <sub>7</sub> , H <sub>8</sub> , H <sub>9</sub> , H <sub>10</sub> , H <sub>11</sub> , H <sub>12</sub> ) 1.45-1.89 (t, 2H, Ar-H <sub>3</sub> , H <sub>4</sub> ) 2.14-2.2 (t, 2H, Ar-H <sub>5</sub> , H <sub>6</sub> ) 7.7 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 8.1 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> )
4	1373, C-N str 1464, Ar, C=C str 1714, C=O str 3057, C-H str	7.45-8.01 (m, 11H, Ar-H <sub>1</sub> , H <sub>2</sub> , H <sub>3</sub> , H <sub>4</sub> , H <sub>5</sub> , H <sub>6</sub> , H <sub>7</sub> , H <sub>8</sub> , H <sub>9</sub> , H <sub>10</sub> , H <sub>11</sub> )
5	1319, C-N str 1462, Ar, C=C str 1620, N-H ben 1712, C=O str 3454, N-H str	3.96 (d, 2H, NH <sub>2</sub> ) 4.32 (d, 2H, H <sub>5</sub> , H <sub>6</sub> ) 7.75 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 7.8 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> )
6	1385, C-N str 1494, Ar, C=C str 1602, N-H ben 1707, C=O str 3400, N-H str 3076, C-H str	6.98-7.966 (m, 8H, Ar-H <sub>1</sub> , H <sub>2</sub> , H <sub>3</sub> , H <sub>4</sub> , H <sub>5</sub> , H <sub>6</sub> , H <sub>7</sub> , H <sub>8</sub> ) 3.33 (s, 2H, NH <sub>2</sub> )
7	1305, C-N str 1419, 1452, 1493, Ar, C=C str 1637, C=O str	2.21 (s, 3H, 1xCH <sub>3</sub> ) 7.1 (d, 1H, Ar-H <sub>5</sub> ) 7.31-7.39 (m, 3H, Ar-H <sub>6</sub> , H <sub>7</sub> , H <sub>8</sub> ) 7.81 (d, 2H, Ar-H <sub>2</sub> , Ar-H <sub>3</sub> ) 7.97 (d, 2H, Ar-H <sub>1</sub> , Ar-H <sub>4</sub> )
8	1300, C-N str 1491, 1556, 1591, Ar, C=C str 1720, C=O str	2.42 (s, 3H, 1xCH <sub>3</sub> ) 7.21-7.26 (m, 3H, Ar-H <sub>5</sub> , H <sub>6</sub> , H <sub>7</sub> ) 7.40 (s, 1H, Ar-H <sub>8</sub> ) 7.79 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 7.96 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> )
9	1388, C-N str 1516, 1547, Ar, C=C str 1718, C=O str	2.41 (s, 3H, 1xCH <sub>3</sub> ) 7.26 (d, 2H, Ar-H <sub>5</sub> , H <sub>8</sub> ) 7.31 (d, 2H, Ar-H <sub>6</sub> , H <sub>7</sub> ) 7.79 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 7.96 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> )
10	597, C=O str 1344, C-N str 1464, 1489, 1527, 1597, Ar, C=C str	3.80 (s, 3H, 1xOCH <sub>3</sub> ) 7.04 (d, 1H, H <sub>5</sub> ) 7.08 (d, 1H, H <sub>8</sub> ) 7.26 (t, 1H, H <sub>7</sub> ) 7.44 (t, 1H, H <sub>6</sub> ) 7.78 (d, 2H, H <sub>2</sub> , H <sub>3</sub> ) 7.95 (d, 2H, H <sub>1</sub> , H <sub>4</sub> )
11	1302, C-N str 1516, Ar, C=C str 1655, C=O str	3.85 (s, 3H, 1xOCH <sub>3</sub> ) 7.03 (d, 2H, Ar-H <sub>6</sub> , H <sub>7</sub> ) 7.73 (d, 2H, Ar-H <sub>5</sub> , H <sub>8</sub> ) 7.79 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 7.95 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> )
12	1346, C-N str 1466, 1496, Ar, C=C str 1521, NO <sub>2</sub> str 1597, 1732, C=O str	7.77 (d, 2H, Ar-H <sub>6</sub> , H <sub>7</sub> ) 7.86 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 8.01 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> ) 8.38 (d, 2H, Ar-H <sub>5</sub> , H <sub>8</sub> )
13	1300, 1531, -NO <sub>2</sub> str 1352, C-N str 1467, 1485, 1531, 1726, Ar, C=C str 1726, C=O str	7.70 (t, 1H, Ar-H <sub>6</sub> ) 7.85 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 7.87 (d, 1H, Ar-H <sub>5</sub> ) 8.01 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> ) 8.26 (d, 1H, Ar-H <sub>7</sub> ) 8.44 (s, 1H, Ar-H <sub>8</sub> )
14	1354, C-N str 1467, 1485, 1531, Ar, C=C str 1335, NO <sub>2</sub> str 1583, 1726, C=O str 2918, C-H str	7.70 (t, 1H, Ar-H <sub>6</sub> ) 7.86 (d, 2H, Ar- H <sub>2</sub> , H <sub>3</sub> ) 7.89 (d, 1H, Ar-H <sub>5</sub> ) 8.01 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> ) 8.28 (d, 1H, Ar-H <sub>8</sub> ) 8.44 (t, 1H, Ar-H <sub>7</sub> )
15	1329, 1348, C-N str 1493, 1556, Ar, C=C str 1601, C=O str 1660, N-H ben 2900, N-H str 2916, C-H str	7.89 (d, 2H, Ar-H <sub>2</sub> , H <sub>3</sub> ) 8.06 (d, 2H, Ar-H <sub>1</sub> , H <sub>4</sub> ) 11.52 (s, 2H, NH <sub>2</sub> )

**Scheme-1:** Synthesis of phthalimides



**Table 2:** The reaction time and yield of phthalimides obtained by microwave (MW) irradiation methods with mp and TLC

Compound No.	Reaction Time MW(min)	% Yield MW	Melting Point (°C)	Thin Layer Chromatography	
				R <sub>f</sub>	Mobile Phase
1	11	75.1	207-208	0.75	Benzene:Ethyl acetate (3:1)
2	14	91.1	140-143	0.57	Cyclohexane:Ethyl acetate (3:1)
3	18	60.4	164-168	0.84	Methanol:Benzene (3:1)
4	13	90.1	180-184	0.79	Benzene:Ethyl acetate (3:1)
5	6	51.6	89-90	0.71	Mthanol:Benzene (3:1)
6	10	50.4	150-154	0.63	Benzene:Acetone (2.5:1)
7	14	73.3	182-184	0.82	Benzene:Ethyl acetate (3:0.5)
8	8	86.0	175-177	0.80	Benzene:Ethyl acetate (2:0.5)
9	10	60.7	203-204	0.80	Hexane:Ethyl acetate (2:1.5)
10	9	85.3	158-160	0.81	Benzane:Ethyl acetate (3:0.5)
11	10	91.6	164-168	0.79	Hexane:Ethyl acetate (2:1)
12	5	73.1	264-266	0.82	Benzene:Acetone (2.5:0.5)
13	14	89.1	247-256	0.80	Benzene:Ethyl acetate (2.5:0.5)
14	49	51.1	245-246	0.62	Hexane:Ethyl acetate (4:1)
15	11	42.2	289-292	0.63	Hexane:Ethyl acetate (4:1)

**Table 3:** Mean number of writhes and the % protection against writhes for phthalimides and the standard, Aspirin

Compound No.	Mean no. of writhes ± SEM	% Protection against writhes
1	47.5 ± 2.36* ##	29.1
2	6 ± 0.68***	91.0
3	12 ± 1.18**##	82.0
4	3 ± 0.51***	95.5
5	18.5 ± 1.17*##	72.4
6	12 ± 1.03*##	82.0
7	6.5 ± 0.67*##	90.3
8	23 ± 1.31*##	65.7
9	4 ± 0.36***	94.0
10	12.5 ± 1.25*##	81.3
11	5.5 ± 0.42***	91.8
12	32 ± 3.43##	52.2
13	28 ± 1.94**	58.2
14	30 ± 1.82##	55.2
15	38.5 ± 2.42##	42.5
<b>Standard (Aspirin)</b>	36 ± 2.42	46.3
<b>Control</b>	67 ± 2.38	-

(\*) Denotes values is significant at p < 0.05 whereas,

(\*\*) denotes values are significant at p < 0.01 when compared with the standard used (aspirin).

(##) Denotes values is significant at p < 0.01 when compared with control.

**CONCLUSION**

Microwave irradiation provided higher yield and required shorter reaction time for the synthesis of phthalimides as compared to the traditional method of synthesis. None of the compounds was found to be toxic up to 2000 mg/kg body weight of a mouse.

Out of 15 phthalimides, 13 were found to be good analgesic agents. The negative sign associated with the hydrophilic component of the total accessible surface area (FISA) in equation 2 indicated that the compounds with lower FISA can show higher analgesic activity. New phthalimide derivatives showing higher analgesic activities can be

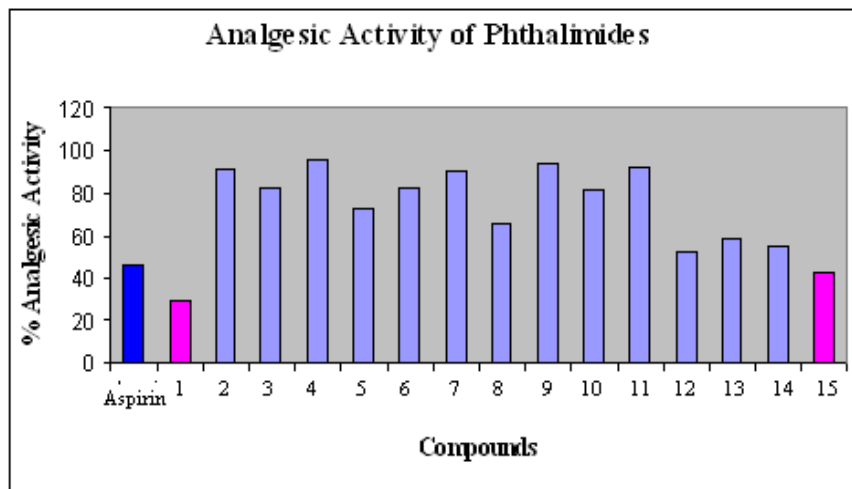
designed and synthesized using the results obtained from the QSAR studies.

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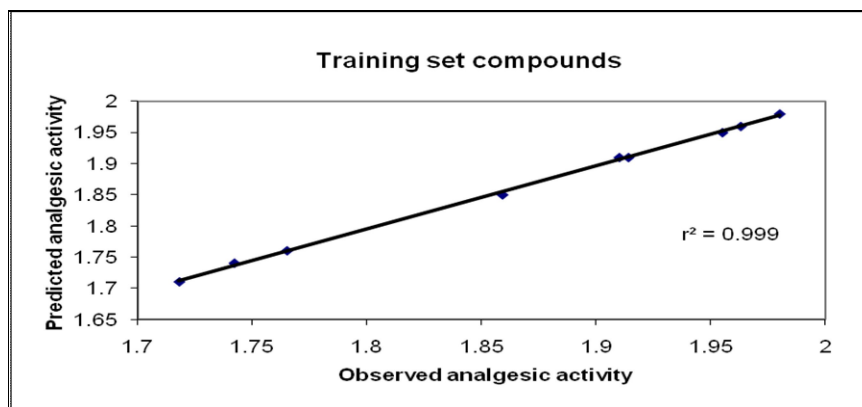
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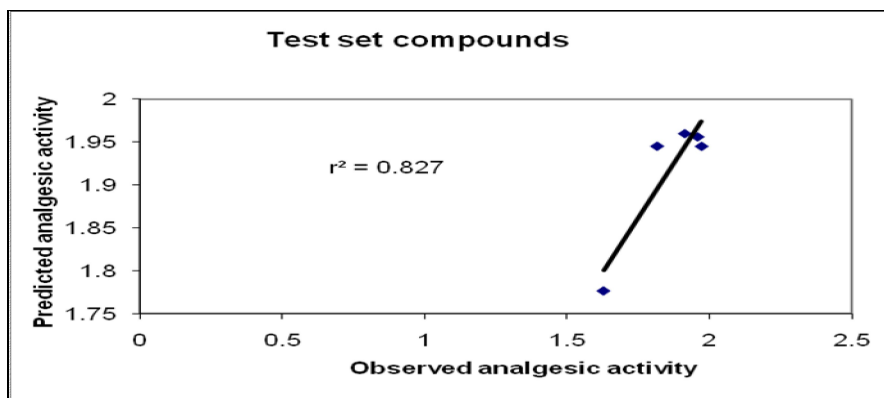
**Fig 1:** Analgesic activity of phthalimides and aspirin



**Fig. 2:** Correlation of the observed and the predicted analgesic activity (% inhibition of writhes) of the *training set* compounds



**Fig. 3:** Correlation of the observed and the predicted analgesic activity (% inhibition of writhes) of the *test set* compounds



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