International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.3, No.4, pp 2104-2110, Oct-Dec 2011

Synthesis and Anticonvulsant screening of 4-Phthalimido – N-(4′- substituted Phenyl benzene sulphonamide, 4-Succnimido-N-(4′-substituted Phenyl) benzenesulphonamide

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Abstract: A series of 4-phthalimido-N-(4′-substituted phenyl benzenesulphonamide (**3a-e**) and 4-succnimido-N-(4′-substituted phenyl) benzenesulphonamide (**4a-e**) were synthesized and screened for their anticonvulsant and behavioral activity. The structures of the compound have been elucidated on the basis of their elemental and spectral data. The compounds 3b, 3e, 4a, 4d and 4e were potent anti-MES agents whereas 3b showed good behavioral activity with lowest actophotometer score of 12.6±20.46.

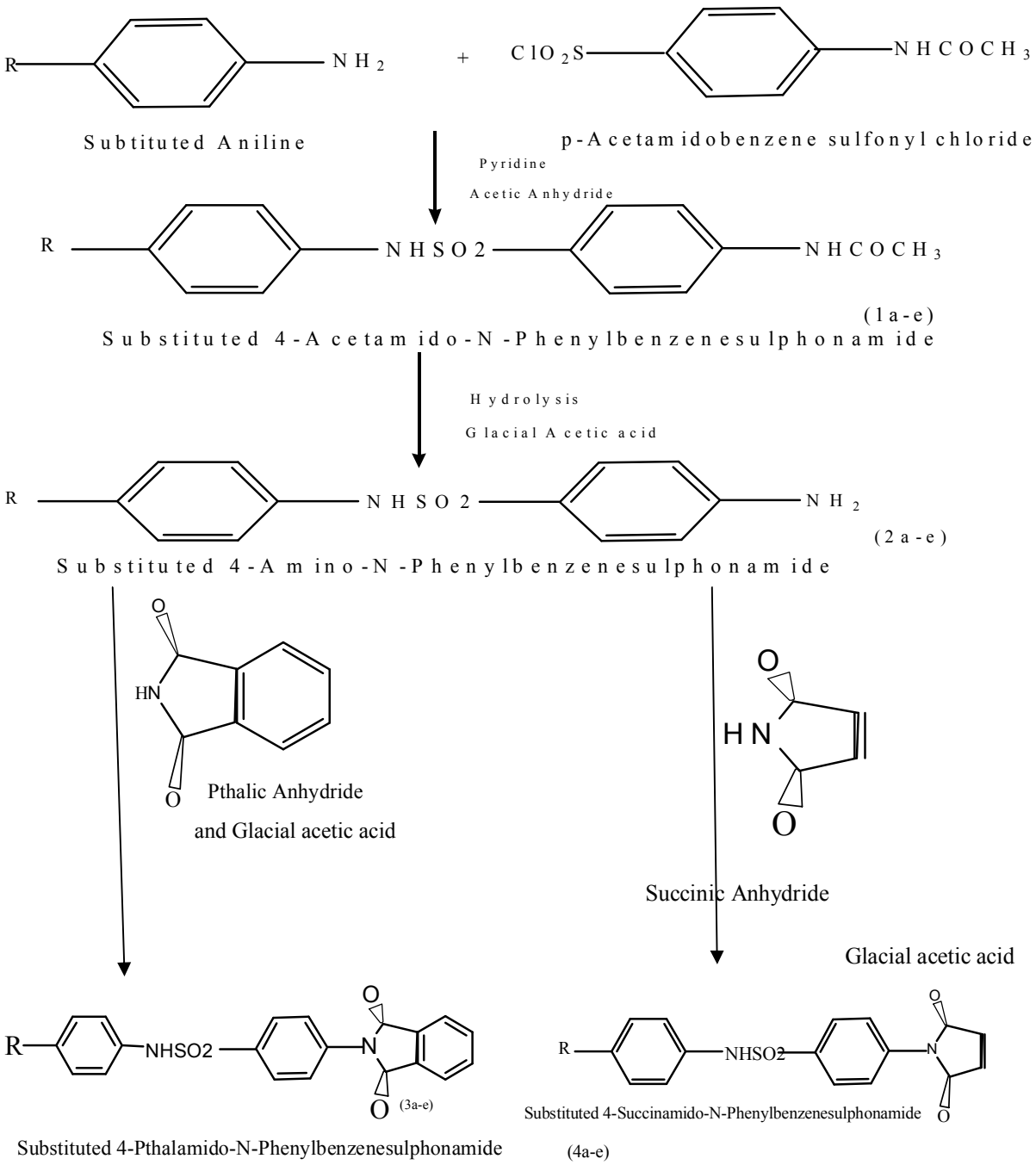
Introduction: Several sulphonamides such as methazolamide, topiramate, acetazolamide and zonisamide were and still used as antiepileptic drug[1], phthalimide[2-4], succinimide[5] were shown to possess anticonvulsant activity. Therefore it was thought worthwhile to synthesize hybrids of substituted phthalimido/succinimido sulphonamide series and screened for potential anticonvulsant activity.

Materials and Methods: The compounds (3a-e) and (4f-j) were synthesized according to **scheme 1**. Substituted anilines were condensed with *p*-acetamido benzenesulphonyl chloride in the presence of dry pyridine and acetic anhydride by heating for 2 hours to give substituted 4-Acetamido-N-phenyl benzenesulphonamide, which was further hydrolysed in the presence of glacial acetic acid for 6 hours to give substituted 4-Amino-N-phenyl benzenesulphonamide, and then it was refluxed with phthalic/succinic anhydrides in presence of glacial acetic acid, the yield ranging between 50-65%.

All the compounds showed satisfactory elemental analysis for C, H and N analysis.

Key words: Synthesis ,Anticonvulsant screening, 4-Phthalimido – N-(4′- substituted Phenyl benzene sulphonamide, 4-Succnimido-N-(4′-substituted Phenyl) benzenesulphonamide.

SCHEME : 1


R
NH2
+
ClO2S
NHCOCH3
Subtituted Aniline
p-Acetamidobenzene sulfonyl chloride
Pyridine
Acetic Anhydride
R
NHSO2
NHCOCH3
(1a-e)
Substituted 4-Acetamido-N-Phenylbenzenesulphonamide
Hydrolysis
Glacial Acetic acid
R
NHSO2
NH2
(2a-e)
Substituted 4-Amino-N-Phenylbenzenesulphonamide
O
HN
O
Pthalic Anhydride
and Glacial acetic acid
O
HN
O
Succinic Anhydride
Glacial acetic acid
R
NHSO2
N
O
O
(3a-e)
Substituted 4-Pthalamido-N-Phenylbenzenesulphonamide
R
NHSO2
N
O
O
Substituted 4-Succinamido-N-Phenylbenzenesulphonamide
(4a-e)

Experimental:

The melting points were determined in open glass capillary tubes and are uncorrected. Infrared (IR) spectra were recorded in KBr pellets on FT –761 Jasco. The proton nuclear magnetic resonance (^{1}HNMR) spectra were recorded on a Bruker model dpx 300 (chemical shift in δ ppm). TLC was used to monitor all the reactions and developing solvents were Ethyl acetate : Chloroform, 1:1.

Synthesis of 4-Acetamido-N-phenyl benzene sulphonamide (1a)

Aniline (5.34 g, 0.018 mol) was added in a mixture of 16 ml of dry pyridine and 80 ml of acetic anhydride. To this mixture, *p*-acetamido benzenesulphonyl chloride (5 g, 0.021 mol) was added and the mixture was heated for 2 hours on a water bath. The reaction mixture was poured into crushed ice, and the precipitate obtained was filtered and recrystallized from ethanol to give white crystalline solid.

Similarly compounds **1**a-e were prepared from the same procedure.

4-Amino-N-phenyl benzenesulphonamide (2a)

The compound **1**a (7.50 g, 0.030 mol) was hydrolyzed by boiling with 100 ml of glacial acetic acid for 6 hours and then the reaction mixture was poured into crushed ice, precipitate obtained was filtered and recrystallized from ethanol to give white crystalline solid. Similarly compounds **2**a-e were prepared from **1**a-e.

4-Maleimido-N-phenyl benzenesulphonamide (3a)

Compound **2**a (2.50 g, 0.007 mol) was refluxed with malic anhydride (2.23 g, 0.023 mol) and 20 ml of glacial acetic acid for 5 hours and the reaction mixture was poured into crushed ice, precipitate obtained was filtered and recrystallized from ethanol to give white crystalline solid. Similarly compounds **3**a-e were prepared from **2**a-e.

4-Succinimido-N-phenyl benzenesulphonamide (4a)

Compound **2**a (2.50 g, 0.006 mol) was refluxed with succinic anhydride (1.58 g, 0.016 mol) and 18 ml glacial acetic acid for 5 hours and the reaction mixture was poured into crushed ice, precipitate obtained was filtered and recrystallized from ethanol to give yellow crystalline solid. Similarly compounds **4**f-j were prepared from **2**a-e.

The physical and analytical data of synthesized compound are presented in **Table-1.**

Table 1: Physical data of newly synthesized compounds

Compound	R	M.P. (^{o}C)	Yeild (%)
3a	H	129	65
3b	4-NO_2	130	68
3c	4-Br	125	70
3d	4-Cl	129	73
3e	2-Cl	125	50
4a	H	112	66
4b	4-NO_2	116	67
4c	4-Br	113	66
4d	4-Cl	114	60
4e	2-Cl	115	69

Satisfactory elemental analysis has been obtained for all the synthesized compounds

Anticonvulsant avtivity[6]:

The anticonvulsant activity of the synthesized compounds (3a-e) and (4a-e) were determined by MES (maximal electric shock-induced seizure) method at 10, 25 and 50mg/kg respectively using albino rats. The animals were observed for the convulsive phases flexor, extensor, clonus, stupor and at last recovery or death. Time for each phases was noted by stopwatch. Results were interpreted in terms of abolition or decrease in extensor phase and were compared against phenytoin sodium (25mg/Kg orally) as the standard. Similarly Behavioral test for the synthesized compounds was carried out using actophotometer by Biossier and Simon[7]. The behavior inside photocell was recorded as a digital score. The readings for the test compounds were compared with the standard (phenytoin sodium, 25mg/Kg orally). Lowest actophotometer score suggest good behaviour activity.

Results:

In IR spectra abs bands for aromatic C=C str. appeared in the region 1400-1600. The abs bands for N-H str. of sulphonamide, C=O stretching of phthalimide/succinimide, and aromatic C-N stretching, were observed in the range 3390-3220, 1750-1650 and 1342-1266 respectively.

The ^{1}HNMR spectra of (3a-e) and 4(a-e) in DMSO-d_6 showed in the, range of 7.682-7.055ppm corresponding to the sulphonamide (-$NHSO_2$) proton and 8.823-9.862ppm for 5H proton of phthalimide respectively.

Spectral data of synthesized compounds

1a: FT-IR (KBr) (cm^{-1}) : 3332.43 (N-H str of sulphonamide), 3252.86 (N-H str of amide), 1667.34 (C=O str of amide), 1587.13 (Ring C=C str), 1255.43 (ArC-N str). ^{1}HNMR (DMSO-d_6) (δppm): 7.856-7.765 (m, 5H, ArH), 7.653-7.552 (m, 4H, ArH), 6.729 (s, 1H, -NH of acetamide), 5.704 (s, 1H, -NH of sulphonamide), 2.175 (s, 3H, -CH_3 of acetamide).

2a: IR (KBr) (cm^{-1}): 3355.92 (N-H str of amine), 3301.45 (N-H str of sulphonamide) 1587.13, 14.75.87, 1468.45 (Ring C=C str), 1259.46 (ArC-N str). ^{1}HNMR (DMSO-d_6) (δppm): 7.987-7.969 (m, 5H, ArH), 7.657-7.597 (m, 4H, ArH), 5.675 (s, 1H, -NH of sulphonamide), 5.234 (s, 2H, -NH_2 of amine).

3a: FT-IR (KBr) (cm^{-1}): 3335.43 (N-H str of sulphonamide), 1689.34 (C=O str of maleimide), 1587.13 (Ring C=C str), 1268.30 (ArC-N str). ^{1}HNMR (DMSO-d_6) (δppm): 7.997 - 7.968 (m, 5H, ArH), 7.543 - 7.503 (d, 2H, -CH=CH of maleimide), 7.497-7.257 (m, 4H, ArH), 5.368 (s, 1H, -NH of sulphonamide).

4a: FT-IR (KBr) (cm^{-1}): 3273.57 (N-H str of sulphonamide), 1605.98, 1497.82, 1468.41 (Ring C=C str), 1679.69 (C=O str of succinimide), 1293.69 (ArC-N str). ^{1}HNMR (DMSO-d_6) (δppm): 8.231-8.201 (m, 4H, ArH), 7.710-7.681 (m, 4H, ArH), 6.473 (s, 1H, -NH of sulphonamide), 2.245 (m, 4H, CH_2-CH_2 of succinimide).

Discussion

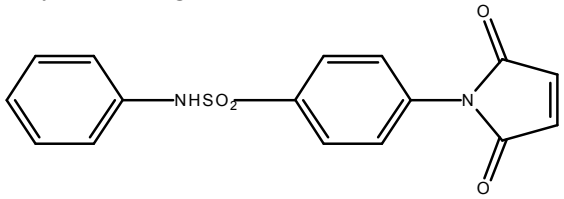
CHEMICAL

The work carried out is discussed under the fallowing heads :

4-MALEIMIDO-N-PHENYL BENZENESULPHONAMIDE (25)

The explainatory work was first carried out with aniline and maleimide, and 4 - Maleimido - N - phenyl benzenesulphonamide was prepared.

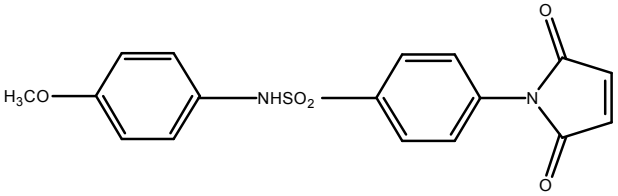
4-Maleimido-N-phenyl benzenesulphonamide 25, (C=O stretching of maleimide at 1689.34 and doublet of -CH=CH at 7.543-7.503ppm was obtained by condensation of 23 and 24 in the presence of maleic anhydride and glacial acetic acid.



(25)

4 - MALEIMIDO - N - (4′ - METHOXY PHENYL) BENZENE SULPHONAMIDE (28)

4-Maleimido-N-(4′-methoxyphenyl) benzenesulphonamide 28 (C=O stretching of maleimide at 1644.02 and doublet of -CH=CH at 6.994-6.965ppm) was obtained by condensation of 26 and 27 in the presence of maleic anhydride and glacial acetic acid.

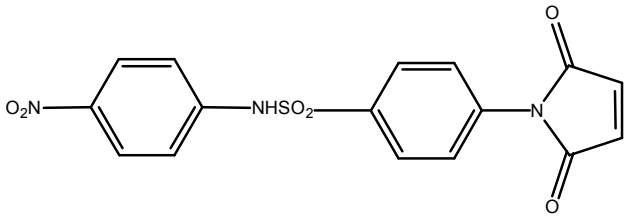


(28)

4 - MALEIMIDO - N - (4′ - NITRO PHENYL) BENZENE SULPHONAMIDE (31)

4-Maleimido-N-(4′-nitrophenyl) benzenesulphonamide 31 (C=O stretching of maleimide at 1680.66 and doublet of -CH=CH at 7.262ppm) was obtained by

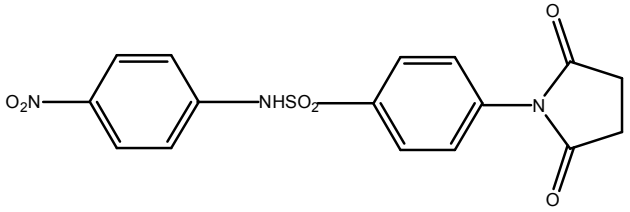
condensation of 29 and 30 in the presence of maleic anhydride and glacial acetic acid.



(31)

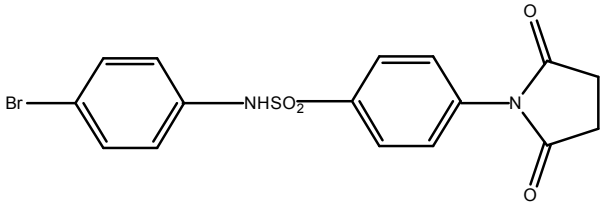
4 – SUCCINIMIDO – N - (4′ - NITRO PHENYL) BENZENE SULPHONAMIDE (32)

4 – Succinimido – N - (4′-nitrophenyl) benzenesulphonamide 32 (C=O stretching of succinimide at 1679.69 and multiplet of CH_2-CH_2 at 2.245ppm) was obtained by condensation of 29 and 30 in the presence of succinic anhydride and glacial acetic acid.



(32)

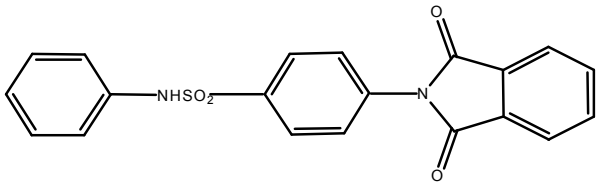
4 - SUCCINIMIDO - N - (4′ - BROMO PHENYL) BENZENE SULPHONAMIDE (35) 4-Succinimido-N-(4′-bromophenyl) benzenesulphonamide 35 (C=O stretching of succinimide at 1688.27 and multiplet of CH_2-CH_2 at 2.249 ppm) was obtained by condensation of 33 and 34 in the presence of succinic anhydride and glacial acetic acid.



(35)

4-PHTHALIMIDO-N-PHENYL BENZENESULPHONAMIDE (36)

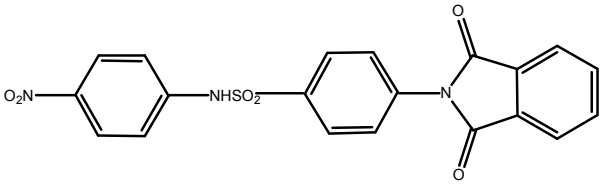
4-Phthalimido-N-phenyl benzenesulphonamide 36 (C=O stretching of phthalimide at 1778.25 and multiplet of ArH at 6.486ppm) was obtained by condensation of 23 and 24 in the presence of phthalic anhydride and glacial acetic acid.



(36)

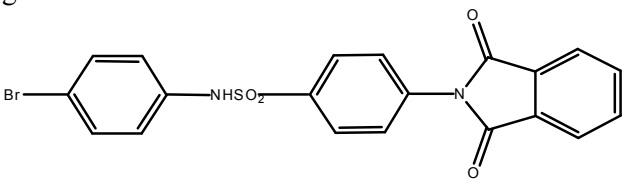
4 - PHTHALIMIDO - N - (4′ - NITRO PHENYL) BENZENE SULPHONAMIDE (37)

4-Phthalimido-N - (4′-nitrophenyl) benzenesulphonamide 37 (C=O stretching of phthalimide at 1760.73 and multiplet of ArH at 7.258ppm) was obtained by condensation of 29 and 30 in the presence of phthalic anhydride and glacial acetic acid.



(37)

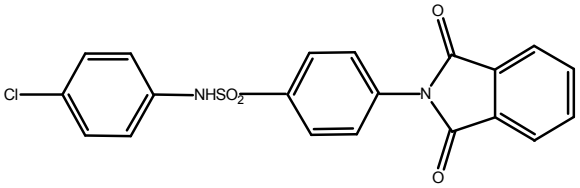
4 – PHTHALIMIDO – N - (4′ - BROMO PHENYL) BENZENE SULPHONAMIDE (38) 4-Phthalimido-N-(4′-bromophenyl) benzenesulphonamide 38 (C=O stretching of phthalimide at 1744.98 and multiplet of ArH at 7.257ppm) was obtained by condensation of 33 and 34 in the presence of phthalic anhydride and glacial acetic acid.



(38)

4 – PHTHALIMIDO – N - (4′ - CHLORO PHENYL) BENZENE SULPHONAMIDE (41)

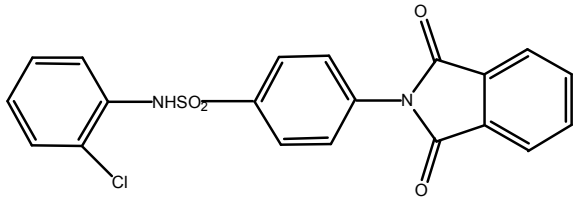
4-Phthalimido-N-(4′-chlorophenyl) benzenesulphonamide 41 (C=O stretching of phthalimide at 1688.37 and multiplet of ArH at 7.257-7.450ppm) was obtained by condensation of 39 and 40 in the presence of phthalic anhydride and glacial acetic acid.



(41)

4 – PHTHALIMIDO – N - (2′ - CHLORO PHENYL) BENZENE SULPHONAMIDE (44)

4-Phthalimido-N-(2′-chlorophenyl) benzenesulphonamide 44 (C=O stretching of phthalimide at 1718.52 and multiplet of ArH at 7.283ppm) was obtained by condensation of 42 and 43 in the presence of phthalic anhydride and glacial acetic acid.



(44)

3.2 BIOLOGICAL

Anticonvulsant screening

All newly synthesized compounds were tested *in vivo* in order to evaluate for their anticonvulsant activity. The biological data of all the synthesized compounds of substituted maleimido/phthalimido/succinimido sulphonamide series have been reported in Table 2.5. The compounds were screened for their anticonvulsant activity against maximal electric shock induced seizures tested at 10, 25 and 50mg/kg respectively. The MES test is most widely employed models for the early identification and high throughput screening of investigational antiepileptic drugs. At the three doses tested, all compounds exhibited anticonvulsant activity but compounds 31, 32, 37, 41 and 44 showed significant activity by their ability to prevent seizure spread and the mechanism may involve blockage of neuronal voltage-dependent Na+ channels.

In the MES screen substituted maleimido sulphonamide series aniline derivative 25 and 4-methoxy 28 derivative was found to be less active at all the three doses, but the 4-nitro 31 derivative was found to be more potent at 25, 50mg/Kg respectively by showing reduction in all phases, significantly of extensor phase.

In the substituted succinimido sulphonamide series 4-nitro derivative 32 was found to be effective at 25, 50mg/Kg respectively than 4-bromo derivative 35. Also in substituted phthalimido sulphonamide series aniline derivative 36 was found to be least active in all the three doses, but 4-nitro derivative 37 was found to be effective at 10, 25, 50 mg/Kg respectively than chloro derivatives, 2-chloro 41 and 4-chloro 44 derivatives were found to be effective at 25, 50mg/Kg respectively.

Therefore considering the results of compounds of all the series, it may be concluded that electron withdrawing nitro derivatives 32, 31, and 37 were found to be effective at 25, 50mg/Kg except 37 which is also effective at 10mg/Kg, than electron donating aniline derivatives 25, 36 which were found to be ineffective in all the three doses. It can be also reported that substituted Phthalimido sulphonamide derivatives were more potent than substituted succinimido/maleimido sulphonamide derivatives

Behavioral test

In behavioral despair test the compounds except 25, 28, 32, 35, 36, 38, 44 showed decreased motor activity as indicated by actophotometer scores Table 2.6. The compound with 4-nitro phthalimido group 37 showed maximum motor impairment activity with lowest actophotometer score of 12.6 ± 20.46.

Therefore it can be concluded that 4-nitro derivative 37 showed significant anticonvulsant and motor activity.

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