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SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SUBSTITUTED OXADIAZOLE AND THIADIAZOLE DERIVATIVES

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Abstract: A series of five membered heterocyclics was synthesized by the reaction between isoniazid and various substituted isothiocyanates and was tested for their anticonvulsant activity by determining their ability to provide protection against convulsions induced by electroconvulsometer. Among the synthesized compounds, **(II_f)** 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole and **(III_f)** 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1, 3, 4-oxadiazole were found promising compounds of the series.

Keywords: anticonvulsant, thiadiazole, oxadiazole

Five membered heterocyclic compounds show various types of biological activities, among them 2,5-disubstituted 1,3,4-thiadiazoles are associated with diverse biological activities, probably by the virtue of –N=C-S- grouping (1), some of them possess antibacterial (2), antifungal (3) and anticonvulsant (4) activities, similarly, 2,5-disubstituted 1,3,4-oxadiazoles also display wide spectrum of activities such as antibacterial (5), antimalarial (6), antiinflammatory (7), antifungal (8) and anticonvulsant (9). The therapeutic importance of these rings prompted us to develop selective molecules in which a substituent could be arranged in a pharmacophoric pattern to display higher pharmacological activities. Derivatives of these nuclei are synthesized from substituted thiosemicarbazides, obtained by reacting isoniazid and different substituted isothiocyanates.

EXPERIMENTAL

The chemicals used during synthesis was supplied by E. Merck (Germany) and S.D. Fine Chemicals (India). Melting points were determined by open capillary tube method and are uncorrected. Purity of the compounds was checked on thin layer chromatography (TLC) plates (Silica gel G) in the solvent system toluene : ethyl acetate : formic acid (5:4:1, v/v/v) and benzene : acetone (8:2, v/v), The spots were located under iodine vapors and UV light. The IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBR pellets). The ^{1}H-NMR spectra were obtained on a Bruker AC 300 MHz spectrometer in DMSO-d_6 using TMS as an internal standard and mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing voltage with a VG Prospec instrument and are presented as m/z.

General method of synthesis of thiosemicarbazides (I_{a-f}) (10, 11)

Substituted phenyl thiosemicarbazides **(I_{a-f})** were synthesized by refluxing isoniazid (0.03 moles) with substituted phenyl isothiocyanates (0.03 moles) in 20 mL of ethanol on a boiling water bath for 5-6 h. After completion of reaction, the reaction mixture was concentrated and kept overnight at room temperature. The needle shaped crystals of thiosemicarbazides so obtained were filtered.

General method of synthesis of 2-(substituted phenyl)amino-5-(4-pyridyl)-4H-1,3,4-thiadiazoles (II_{a-f}) (10)

2-(Substituted phenyl)amino-5-(4-pyridyl)-4H-1,3,4-thiadiazoles **(II_{a-f})** were synthesized by cyclization of substituted phenylthiosemicarbazides of isoniazid (0.004 moles) with sulfuric acid at 0-5^{o}C. After completion of reaction, the mixture was

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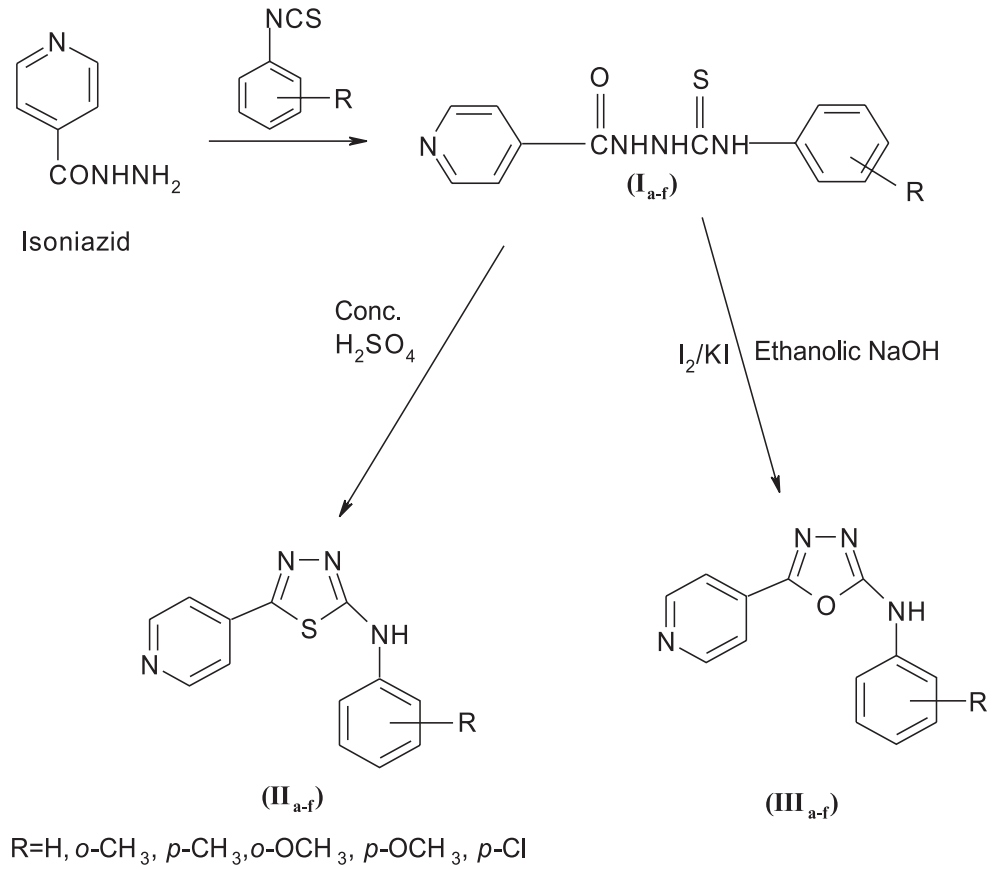
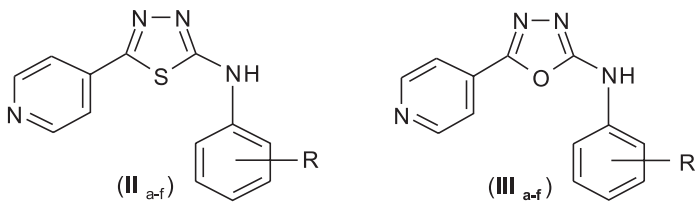


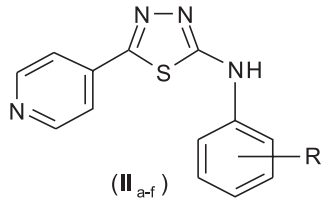
Scheme 1.

Table 1. Physical constants of newly synthesized thiadiazole and oxadiazole derivatives

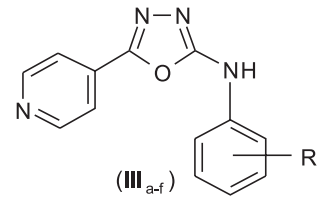


Compound	R	Yield (%)	M.p. (°C)	Mol. formula	Mol. wt.
II$_a$	H	90	136-38	$C_{13}H_{10}N_4S$	254.31
II$_b$	*o*-CH_3	80	166-68	$C_{14}H_{12}N_4S$	268.33
II$_c$	*p*-CH_3	82	140-42	$C_{14}H_{12}N_4S$	268.33
II$_d$	*o*-OCH_3	87	138-40	$C_{14}H_{12}N_4OS$	284.33
II$_e$	*p*-OCH_3	89	168-70	$C_{14}H_{12}N_4OS$	284.33
II$_f$	*p*-Cl	78	152-54	$C_{13}H_9Cl\ N_4S$	288.75
III$_a$	H	66	266-68	$C_{13}H_{10}N_4O$	238.24
III$_b$	*o*-CH_3	86	276-78	$C_{14}H_{12}N_4O$	252.27
III$_c$	*p*-CH_3	79	278-80	$C_{14}H_{12}N_4O$	252.27
III$_d$	*o*-OCH_3	68	236-38	$C_{14}H_{12}N_4O_2$	268.27
III$_e$	*p*-OCH_3	87	280-82	$C_{14}H_{12}N_4O_2$	268.27
III$_f$	*p*-Cl	76	238-40	$C_{13}H_9ClN_4O$	272.69

Table 2. Anticonvulsant activity of thiadiazoles and oxadiazoles on albino mice



(II_{a-f})



(III_{a-f})

Compound	Dose (mg/kg)	Anticonvulsant activity (MES) (% protection)
II_a	25	83.33
II_b	25	49.99
II_c	25	49.99
II_d	25	33.33
II_e	25	66.66
II_f	25	100
III_a	25	83.33
III_b	25	33.33
III_c	25	66.66
III_d	25	49.99
III_e	25	66.66
III_f	25	100
Phenytoin sodium	25	100

poured onto crushed ice, the solid so separated was filtered, washed with water and recrystallization from methanol yielded the pure compound.

2-Phenylamino-5-(4-pyridyl)-1,3,4-thiadiazole (II_a)

IR (KBr, cm^{-1}): 3380 (NH), 1615 (C=N), 1069 (N-N), 700 (C-S-C); ^1H NMR (DMSO-d_6, δ, ppm)**:** 7.4 - 7.7 (5H, m, aromatic), 8.4 and 8.9 (2H each, 2 × d, pyridine *J* = 5.50 Hz, 5.56 Hz), 7.9 (1H, s, NH); MS (m/z): 254 (M^+).

2-(2-Methylphenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole (II_b)

IR (KBr, cm^{-1}): 2853 (NH), 1559 (C=N), 1008 (N-N), 672 (C-S-C); ^1H NMR (DMSO-d_6, δ, ppm): 2.5 (3H, s, CH_3), 7.1 - 7.7 (4H, m, aromatic), 8.3 and 8.9 (2H each, 2 × d, pyridine *J* = 5.406 Hz, 5.57 Hz), 7.9 (1H, s, NH); MS (m/z): 268 (M^+).

2-(4-Methylphenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole (II_c)

IR (KBr, cm^{-1}): 2996 (NH), 1606 (C=N), 1006 (N-N), 659 (C-S-C); ^1H NMR (DMSO-d_6, δ, ppm)**:** 2.5 (3H, s, CH_3), 7.2 and 7.5 (2H each, 2 × d, aromatic *J* = 7.76 Hz, 7.79 Hz), 8.4 and 8.97 (2H each, 2 × d, pyridine *J* = 5.658 Hz, 5.703 Hz), 7.7 (1H, s, NH); MS (m/z): 268 (M^+).

2-(2-Methoxyphenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole (II_d)

IR (KBr, cm^{-1})**:** 3120 (NH), 1596 (C=N), 1033 (N-N), 686 (C-S-C); ^1H NMR (DMSO-d_6, δ, ppm)**:** 3.9 (3H, s, OCH_3), 7.0 - 7.3 (4H, m, aromatic), 8.3 and 8.5 (2H each, 2 × d, pyridine *J* = 5.65 Hz, 5.91 Hz), 7.5 (1H, s, NH); MS (m/z): 284 (M^+).

2-(4-Methoxyphenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole (II_e)

IR (KBr, cm^{-1}): 3073 (NH), 1613 (C=N), 1006 (N-N), 712 (C-S-C); ^1H NMR (DMSO-d_6, δ, ppm): 3.9 (3H, s, OCH_3), 6.9 and 7.5 (2H each, 2 × d, aromatic *J* = 8.25 Hz, 8.52 Hz), 8.3 and 8.9 (2H each, 2 × d, pyridine *J* = 5.50 Hz, 5.56 Hz), 7.7 (1H, s, NH); MS (m/z): 284 (M^+).

2-(4-Chlorophenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole (II_f)

IR (KBr, cm^{-1}): 3396 (NH), 1632 (C=N), 1071 (N-N), 665 (C-S-C); ^1H NMR (DMSO-d_6, δ, ppm): 7.4 and 7.7 (2H each, 2 × d, aromatic *J* = 8.559 Hz, 5.56 Hz), 8.4 and 8.9 (2H each, 2 × d, pyridine *J* = 5.718 Hz, 5.76 Hz), 8.0 (1H, s, NH); MS (m/z): 289 (M^++1).

General method of synthesis of 2-(substituted phenyl)amino-5-(4-pyridyl)-4H-1,3,4-oxadiazoles (III_{a-f}) (11)

A solution of substituted phenylthiosemicarbazide (0.004 mole) and NaOH (5 M, 2 mL) in 25 mL of absolute ethanol was cooled with continuous stirring for half an hour. To this mixture, iodine in KI (5%) was added dropwise, till the color of iodine persisted at room temperature and the mixture was refluxed for 2 h on a water bath. After completion of reaction, the mixture was poured onto crushed ice and the solid so separated was filtered and washed with water. The recrystallisation from petroleum ether : diethyl ether mixture (8:2, v/v) gave the pure compounds.

2-Phenylamino-5-(4-pyridyl)-1, 3, 4-oxadiazole (III_a)

IR (KBr, cm^{-1}): 3446 (NH), 1645 (C=N), 1235 (C-O-C), 1072 (N-N) ^1H NMR (DMSO-d_6, δ, ppm): 7.0 - 7.5 (5H, m, aromatic), 8.3 - 8.6 (4H, m, pyridine), 7.9 (1H, s, NH); **MS** (m/z): 238 (M^+).

2-(2-Methylphenyl)amino-5-(4-pyridyl)-1,3,4-oxadiazole (III_b)

IR (KBr, cm^{-1}): 3052 (CH, aromatic), 2854 (NH), 1606 (C=N), 1236 (C-O-C), 1096 (N-N); ^1H NMR (DMSO-d_6, δ, ppm): 2.7 (3H, s, CH_3), 7.2 - 7.4 (2H each, m, aromatic), 8.5 and 8.7 (2H each, 2 × d, pyridine J = 4.45 Hz, 4.48 Hz), 7.6 (1H, s, NH); MS (m/z): 252 (M^+).

2-(4-Methylyphenyl)amino-5-(4-pyridyl)-1,3,4-oxadiazole (III_c)

IR (KBr, cm^{-1}): 3151 (NH), 3052 (CH, aromatic), 1609 (C=N), 1230 (C-O-C), 1093 (N-N); ^1H NMR (DMSO-d_6, δ, ppm): 2.5 (3H, s, CH_3), 7.2 - 7.5 (4H each, m, aromatic), 8.5 and 8.7 (2H each, 2 × d, pyridine J = 4.32 Hz, 4.35 Hz), 7.76 (1H, s, NH); MS (m/z): 252 (M^+).

2-(2-Methoxyphenyl)amino-5-(4-pyridyl)-1,3,4-oxadiazole (III_d)

IR (KBr, cm^{-1}): 3053 (CH, aromatic), 2890 (NH), 1605 (C=N), 1230 (C-O-C), 1096 (N-N); ^1H NMR (DMSO-d_6, δ, ppm): 3.5 (3H, s, OCH_3), 7.2 - 7.5 (4H, m, aromatic), 8.2 and 8.5 (2H each, 2 × d, pyridine J = 4.42 Hz, 4.45 Hz), 7.7 (1H, s, NH); MS (m/z): 268 (M^+).

2-(4-Methoxyphenyl)amino-5-(4-pyridyl)-1,3,4-oxadiazole (III_e)

IR (KBr, cm^{-1}): 3436 (NH), 1612 (C=N), 1239 (C-O-C), 1059 (N-N); ^1H NMR (DMSO-d_6, δ, ppm): 3.8 (3H, s, OCH_3), 6.8 -7.3 (4H, m, aromatic), 8.3 and 8.6 (2H each, 2 × d, pyridine J = 4.45 Hz, 4.48 Hz), 7.6 (1H, s, NH); MS (m/z): 268 (M^+).

2-(4-Chlorophenyl)amino-5-(4-pyridyl)-1,3,4-oxadiazole (III_f)

IR (KBr, cm^{-1}): 3267 (NH), 1611 (C=N), 1242 (C-O-C), 1054 (N-N), 724 (C-Cl); ^1H NMR (DMSO-d_6, δ, ppm): 7.4 and 7.6 (2H each, 2 × d, aromatic J = 8.52 Hz, 8.55 Hz), 7.8 and 8.8 (2H each, 2 × d, pyridine J = 4.32 Hz, 4.38 Hz), 7.5 (1H, s, NH); MS (m/z): 273 (M^++1)

Biological evaluation

Anticonvulsant activity

Anticonvulsant activity of the synthesized compounds was determined by their ability to provide protection from convulsions in albino mice. Supra maximal electroshock of current intensity of 50 mA, 60 Hz for 0.2 s duration was given to the various groups of mice after administration of 25 mg/kg of test compounds; phenytoin sodium (25 mg/kg) was used as a standard. The abolition of the hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity (12).

RESULTS AND DISCUSSION

Chemistry

A series of 2-(substituted phenyl)amino-5-(4-pyridyl)-4H-1,3,4-thiadiazole (II_{a-f}) and 2-(substituted phenyl)amino-5-(4-pyridyl)-4H-1,3,4-oxadiazole (III_{a-f}) was prepared from isoniazid and substituted phenyl isothiocyanates derived thiosemicarbazides (Scheme 1). The structure of newly synthesized compounds was confirmed by spectral and analytical data. In general, the IR spectra of newly synthesized compounds revealed NH, C=N, N-N, C-S-C (thiadiazole) and C-O-C (oxadiazole) peaks near 3396, 1632, 1071, 665 and 1235 cm^{-1}, respectively. In the ^1H-NMR spectra, signals of respective protons of newly synthesized compounds showed the peaks for -CH_3, -OCH_3, NH and aromatic protons near δ 2.3, 3.9, 7.8 and 6.8-8.6, respectively. The general mass fragmentation pattern for the compounds showed the m/z peaks. Both analytical and spectral data (IR, ^1H-NMR, mass) of all the synthesized compounds were in full agreement with the proposed structures. Physical data of all the newly synthesized compounds are presented in Table 1.

Anticonvulsant activity

All the newly synthesized compounds were evaluated for their anticonvulsant activity by MES method (12). All the compounds showed activity in the range of 33-100 % in comparison to phenytoin which completely inhibited the convulsions produced by electroconvulsometer in albino mice. Compounds II_f and III_f showed maximal activity whereas compounds II_a and III_a showed good activity.

CONCLUSION

Among the synthesized compounds, those with electron withdrawing substituents: **(II_f)** 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1,3,4-thiadiazole and **(III_f)** 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1,3,4-oxadiazole showed excellent anticonvulsant activity, whereas compounds with unsubstituted phenyl ring showed good activity. It may be assumed that further modifications may produce compounds of better activity with less toxic effects.

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