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DESIGN, SYNTHESIS AND ANTICONVULSANT ACTIVITY OF SOME 1, 3, 4-THIADIAZOL DERIVATIVES

ARVIND K. SINGH*, R. PARTH SARTHY and M. LOHANI

NIMS University, JAIPUR (Raj.) INDIA
Kamla Nehru Institute on Management and Technology (Faculty of Pharmacy),
SULTANPUR – 228001 (U.P.) INDIA

ABSTRACT

A series of five membered heterocyclic's were synthesized from [N-(5-phenyl) 1,3,4-thiadiazole-2-yl]-benzamide and reacts with 4-amino-benzene sulfonyl chloride to derived seven different (a_1-a_7) compounds. The structures of these synthesized compounds were confirmed by IR, ^{1}H NMR and Mass spectral data. All spectral data shows good peaks. 2, 5-disubstituted 1, 3, 4-thiadiazoles have various biological activities such as anticonvulsant activity. The anticonvulsant activity has been evaluated by using maximal electroshock method (MES). All the reported compounds showed good anticonvulsant activity. Among the compounds (a_1) 4-amino- [N- (5-phenyl-1, 3, 4-thiadiazole-2-yl]-benzene sulfonamide and (a_4) 4-amino-N-[5-(4-chlorophenyl)-1, 3, 4-thiadiazole-2-yl]-benzene sulfomide has good activity but compound (a_2) 4-amino-[N-5(2-chlorophenyl) 1, 3, 4-thiadiazole-2-yl]-benzenesulfonamide and (a_5) 4-amino-[N-(2-Nitrophenyl)-1, 3, 4-thiadiazole-2-yl]-benzenesulfonamide moderate activity. These compounds shows potent anticonvulsant activity against phenytoin sodium used as the standard drug.

Key words: 1, 3, 4-thiadiazoles, 4-aminobenzene sulfonylchloride, Anticonvulsant activity.

INTRODUCTION

Five membered heterocyclic compounds show various type of biological activities among the 2, 5-disubstituted 1, 3, 4-thiadiazoles are associated with diverse biological activities.[1] Various biological activities like antimicrobial, anti-tubercular, anti-inflammatory, anticonvulsant[2], hypnotic, anesthetic activity[3]. 1, 3, 4-thiadiazoles showed antibacterial properties similar to those of well known sulfonamide drugs. The thiadiazole nucleus with N=C–S linkage exhibits a large number of pharmacological activities[4]. Sulfone derivatives containing heterocyclic moiety are known for their interesting antifungal bioactivities and have attracted considerable attention in pesticide and medicinal formulation. A large number of reports on their synthesis and biological activities have appeared during the last three

*Author for correspondence; E-mail: adi_arv26@rediffmail.com

years[5]. 1, 3, 4-thadiazoles represents an important hetrocyclic system due to their pharmacological activity[6]. We have obtained several 1, 3, 4-thiadiazole sulfonamides and determined their crystal structure[7].

EXPERIMENTAL

Material and methods

General preparation of acid chloride (A)

1 : 1 (molar ratio) of aromatic acid and phosphorous penta chloride were taken in round bottom flask fitted with air condenser and calcium chloride guard tube. This mixture was heated gently to melt with vigorous shaking at around 50°C. After 30 minute excess $POCl_3$ was distilled out through steam distillation apparatus.

General preparation of 1, 3, 4-thiadiazole (B)

(0.01 mole) thiosemicarbazide was added to the respective acid chloride and refluxed for 4-5 hours. Then excess benzene was distilled out, neutralized with aq. $NaHCO_3$ and the compound was extracted with $CHCl_3$ (25 x 4 mL). The crude sample was obtained by distillation of $CHCl_3$ under reduced pressure.

General preparation for the (a_1–a_7) derivatives

Compound B was hydrolyzed with sodium hydraoxide (3 M) and heated on boiling water bath. After 10 minutes, vapors from the tube was smelled and tested with moist red litmus paper to identify the evolved ammonia. Then added 1.91 g (0.01 m) 4-aminobenzene sulfonylchloride and refluxed with pyridine for 4-5 hrs. and finally neutralized with $NaHCO_3$. Reaction mixture was checked by thin layer-chromatography. Solvent system decided ethyl acetate : Pet. Ether : methanol (4:18:2 drops). The actual fraction was collected by regular checking by TLC.

Comp-a_1 : 4-Amino-N-[(5-phenyl)-1, 3, 4-thiadiazole-2-yl]-benzene sulfonamide

Yield: 72%, mp: 148-149°C: IR (KBr cm^1): 3324 (NH_2), 3272 (NH), 1632 (C=N), 1247-1333 (SO_2): ^{1}H NMR ($CDCl_3$, δ, ppm); 8.12 (S, 2H, -NH_2), 7.92 (m, 9H, -aromatic), MS (m/z%): Anal. Calculated for $C_{14}H_{12}O_2N_4S$: C = 56.12, H = 3.81, N = 18.66 Found: C = 56.25, H = 3.9, N = 19.2

Comp-a_2 : 4-Amino-N-[5(2-chlorophenyl)1, 3, 4-thiadiazole-2-yl]benzene sulfonamide

Yield: 71%, mp : 147-149°C, IR (KBr) cm^1 : 3321 (NH_2), 3275 (NH), 1628 (C=N),

1305 (SO_2), ^{1}H NMR ($CDCl_3$): 7.62 (s, 2H, NH_2), 7.47 (m, 9H, aromatic), ms (m/z %); Anal. calculated, C = 50.22, H = 3.28, N = 16.74, Found; C = 50.12, H = 3.25, N = 17.21.

Comp-a_3 : 4-Amino-N-[5-(3-chlorophenyl)-1, 3, 4-thiadiazole-2-yl]-benzenesulfonamide

Yield: 69%, mp; 148-149^{o}C, IR (KBr) cm^1 : 3350 (NH_2), 3250 (NH), 1620 (C=N), 1309 (SO_2), ^{1}H NMR ($CDCl_3$): 7.76 (d, 2H, NH_2), 7.41 (Q, 9H, aromatic), ms (m/z %); Anal. Calculated, C = 50.23, H = 3.28, N = 16.74, Found; C = 50.14, H = 3.259, N = 17.91.

Comp-a_4 : 4-Amino-N-[5-(4-chlorophenyl)-1, 3, 4-thiadiazole-2-yl]-benzene sulfonamide

Yield: 77%, mp; 148-149^{o}C, IR (KBr cm^1): 3280 (NH_2), 3269 (NH), 1621 (C=N), 1249 (SO_2), ^{1}H NMR ($CDCl_3$): 7.92 (s, 2H, NH_2), 7.91 (m, 9H, aromatic), ms (m/z %); Anal. Calculated, C = 50.23, H = 3.28, N = 16.74, Found; C = 50.44, H = 3.29, N = 18.21.

Comp-a_5 : 4-Amino-N-[5-(2-Nitrophenyl)-1, 3, 4-thiadiazole,-2-yl-]-benzene sulfonamide

Yield: 78%, mp; 142-149^{o}C, IR (KBr) cm^1: 3272 (NH_2), 3242 (NH), 1618 (C=N), 1332 (SO_2), ^{1}H NMR ($CDCl_3$): 7.78 (s, 2H, NH_2), 7.72 (m, 9H, aromatic), ms (m/z %); Anal. Calculated, C = 48.69.23, H = 3.18, N = 16.742, Found; C = 49.44, H = 3.21, N = 17.21.

Comp-a_6 : 4-Amino-N-[5-(3-Nitrophenyl)-1, 3, 4-thiadiazole-2-yl-]-benzene sulfonamide

Yield: 70%, mp; 148-150^{o}C, IR (KBr) cm^1: 3268 (NH_2), 3239 (NH), 1619 (C=N), 1333 (SO_2), ^{1}H NMR ($CDCl_3$): 7.73 (s, 2H, NH_2), 7.46 (M, 9H, aromatic), ms (m/z %); Anal. Calculated, C = 48.61.23, H = 3.28, N = 17.74, Found; C = 49.41, H = 3.24, N = 17.21.

Comp-a_7 : 4-Amino-N-[5-(4-Nitro-phenyl)-1, 3, 4-thiadiazole-2-yl-]-benzene sulfonamide

Yield: 62%, mp; 146-150^{o}C, IR (KBr cm^1): 3261 (NH_2), 3241 (NH), 1621 (C=N), 1340 (SO_2), ^{1}H NMR ($CDCl_3$) : 7.82 (d, 2H, NH_2), 7.56 (m, 9H, aromatic), ms (m/z%); Anal. Calculated, C = 48.51.23, H = 3.20, N = 17.79, Found; C = 49.41, H = 3.24, N = 17.21.

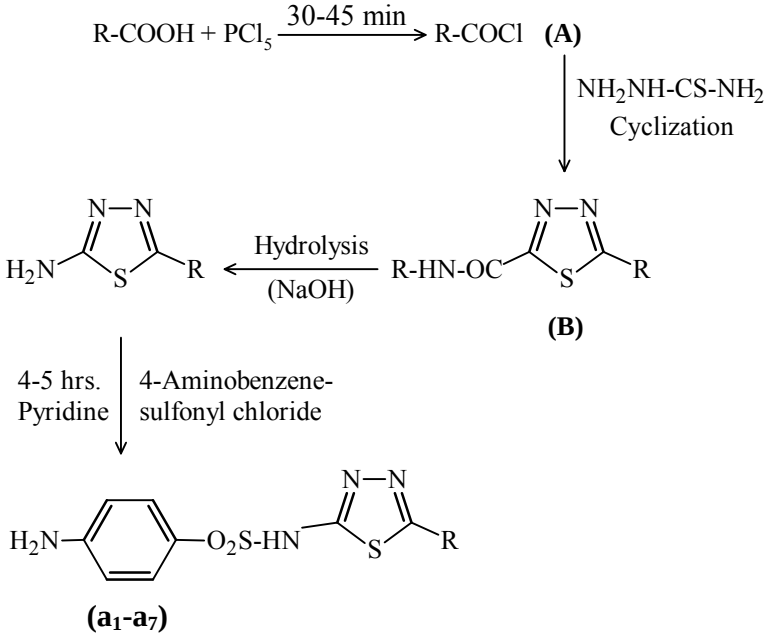
Anticonvulsant activity[1]

Anticonvulsant activity of the synthesized derivatives (a_1-a_7) was determined by their ability to provide protection from convulsions in albino mice. All mice have weighted to 30-35 grams. 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 the administration of 20 mg/Kg of test compounds; phenytoin sodium (20 mg/Kg) was used as a standard. The abolition of the hind limb tonic extensor spasm was recorded as a measured (% protection) of anticonvulsant activity.

RESULTS AND DISCUSSION

Chemistry

After the experiment, it was concluded that the compounds were synthesized in the project was good yield. The synthesize thiadiazole compounds 4-amino-N-(5-phenyl-1, 3, 4-thiadiazole-2-yl-benzenesulfonamide (a_1), 4-amino-N-[5-(2-chlorophenyl)-1, 3, 4-thiadiazole-2-yl]-benzenesulfonamide (a_2), 4-amino-N-[5-(3-chlorophenyl)-1, 3, 4-thiadiazole, 2-yl]-benzenesulfonamide (a_3), 4-amino-N-[5-(4-chlorophenyl)-1, 3, 4-thiadiazole-2-yl]-benzene-sulfonamide (**a_4**), 4-amino-N-[5-(2-Nitrophenyl)-1,3,4-thiadiazole-2-yl]-benzenesulfonamide (a_5) identified and characterize by IR, ^{1}H NMR and Mass spectral.



Scheme

Anticonvulsant activity

All the newly synthesized compounds were evaluated for their anticonvulsant activity by MES method. All the compounds showed activity in the range of 45.67-84.33 % in compare with the standard drug phenytoin which completely inhibited the convulsions produced by Electroconvulsometer in albino mice. Compounds a_1 and a_4 showed good activity and compounds a_2 and a_5 showed moderate activity.

Table 1: Physical characteristics of synthesized compounds (a_1-a_7)

Compounds	R	Yield (%)	MP (^oC)	Molecular formula	Molecular weight
a_1	-C_6H_5	72	148-149	$C_{14}H_{12}O_2N_4S$	332.0
a_2	o-ClC_6H_5	71	147-149	$C_{14}H_{11}ClO_2N_4S$	366.5
a_3	m-ClC_6H_5	69	148-149	$C_{14}H_{11}ClO_2N_4S$	366.5
a_4	p-ClC_6H_5	77	146-149	$C_{14}H_{11}ClO_2N_4S$	366.5
a_5	O-$NO_2C_6H_5$	78	142-149	$C_{14}H_{11}O_4N_5S$	377.2
a_6	m- $NO_2C_6H_5$	70	148-150	$C_{14}H_{11}O_4N_5S$	377.2
a_7	p- $NO_2C_6H_5$	62	146-150	$C_{14}H_{11}O_4N_5S$	377.2

Table 2: Anticonvulsant activity of thiadiazoles derivatives (a_1-a_7).

Compound	Dose (mg/Kg)	Anticonvulsant activity (MES) (% protection)
a_1	20	82.33
a_2	20	68.97
a_3	20	49.99
a_4	20	84.33
a_5	20	65.66
a_6	20	45.67
a_7	20	58.33
Phenytoin sodium	20	100

Dose; 20 mg/Kg

Standard drug: Phenytoin sodium

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