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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antidepressant activity of di substituted-5-aryl-1,2,4-triazoles

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Abstract A series of 5-aryl-1H-1,2,4-triazole-3-thiol (**3**) were synthesized. Alkylation of thiol group with *N*,*N*-dimethyl/diethyl/dicyclo hexyl-(2-chloro ethyl) amine gave compounds *N*,*N*-disubstituted-2-(5-aryl-1H-1,2,4-triazol-3-ylthio)ethanamine (**4**). These compounds were characterized on the basis of IR, ^{1}H NMR, Mass spectral data, and elemental analysis. The newly synthesized compounds were screened for their antidepressant activity by using tail suspension test in mice.

Keywords 1,2,4-Triazole · Thiol · Antidepressant activity · Aroyl thiosemicarbazide

Introduction

1,2,4-triazole and their derivatives constitute an important class of heterocyclic organic compounds with diverse pharmacological and biological activities including antimicrobial, sedative, anticonvulsant, anti-inflammatory, antidepressant, antihypertensive etc. (Monazza *et al.*, 2009; Hussain *et al.*, 2005; Loredana *et al.*, 2004; Katica *et al.*, 2001; Mohammad *et al.*, 2006; Aniket Kshirsagar *et al.* 2009).

Literature survey reveals that *N*,*N*-di alkyl ethyl chain is important for antidepressant activity. For instance, tricyclic antidepressants like Imipramine, Amitriptyline, Clomipramine, Doxepin which are used for the treatment of depression, contain *N*,*N*-di alkyl ethyl side chain in their structures (Foye, 1989; John *et al.*, 2005). Keeping these observations in view, we incorporated this side chain in the 1,2,4-triazole ring and we report the synthesis of *N*,*N*-disubstituted-2-(5-aryl-1H-1,2,4-triazol-3-ylthio)ethanamine and their antidepressant screening studies. Among the synthesized compounds, compound **4l** has shown most promising activity.

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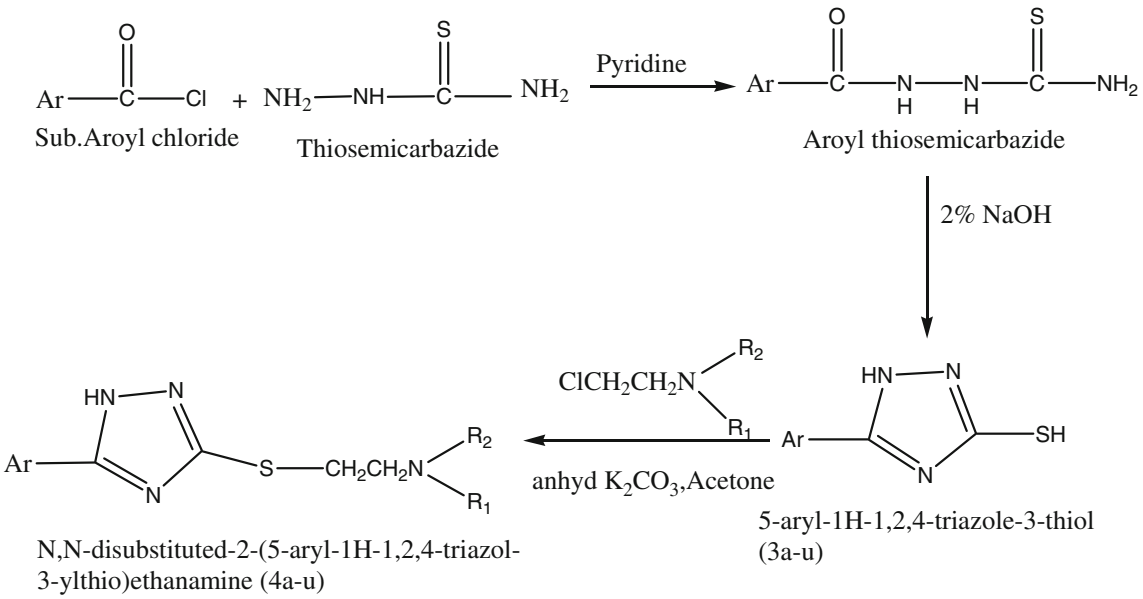
Chemistry

Aroyl thiosemicarbazide (**2**) was obtained by the reaction of Aroyl chloride with thiosemicarbazide (Plumitallo *et al.*, 2004). The cyclization of compound (**2**) in the presence of 2 M NaOH resulted in the formation of 5-aryl-1H-1,2,4-triazole-3-thiol (**3**) (Khosrow *et al.*, 2003; Birsen *et al.*, 2007). These were reacted in acetone in the presence of anhydrous K_2CO_3 and a catalytic amount of KI with dimethyl (2-chloro ethyl) amine/di ethyl (2-chloro ethyl) amine/di cyclo hexyl (2-chloro ethyl) amine to give desired products (**4**). (Scheme 1).

The structures of compounds **4** were established on the basis of IR, NMR, mass spectral data and C, H, N analysis. The physical data and analytical data was given in Table 1.

Results and discussion

The IR spectrum of compound **3a** showed an absorption band at 3450.8 cm^{-1} indicating the presence of NH stretching. The absorption band at 2,360 cm^{-1} indicating the presence of SH functional group. When compound **3** was converted to alkyl derivative **4** the SH peak disappeared, while new signal due to C–S group was observed at 1010.2 cm^{-1}.



Scheme 1 Synthesis of *N*,*N*-disubstituted-2-(5-aryl-1H-1,2,4-triazol-3-ylthio)ethanamine

In the ^{1}H NMR spectra of compound **3a**, NH signal was observed at 13.6 ppm. Additional signals (**5H**) belonging to phenyl ring were observed in the aromatic region at 7.3 to 8.0 ppm. The signal due to –SH group was observed at 13.2 ppm in the ^{1}H NMR spectra of compound **3a**. When compound **3a** is converted to alkyl derivative **4a** the SH signal disappeared. In compound **4a** the additional signals were observed at 2.9 to 3.0 (S–CH_2), 3.2 (N–CH_2) and 2.4 (aliphatic **6H**) ppm integrating for two protons, two protons, and six protons, respectively.

The molecular ion (M + 1) for compound **3a** was recorded at m/z 178.3 while compound **4a** was recorded at m/z 249.4.

Acute toxicity studies

All the test compounds have been found to be free from toxicity as well as toxic symptoms even at high dose of 2,000 mg/kg (b.w).

Gross behavioral studies

The gross behavioral studies reveal that all the compounds have shown alertness.

Tail suspension test in mice

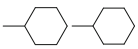
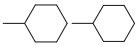
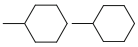
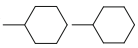
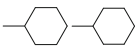
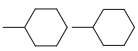
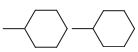
The test compounds were screened for antidepressant activity by using tail suspension method in mice and the duration of immobility was recorded for a period of 5 min. Some of the test compounds have shown significant ($P < 0.001$) decrease in immobility time when compared with the control group animals. This significant reduced immobility time displayed by mice indicates that the investigational compounds having the potential anti-depressant properties. Compound **4l** with 2,4-di chloro and dicyclohexyl substitution showed most significant activity as compared to other test compounds and are comparable with standard drug (imipramine 10 mg/kg). Compound **4i** with 4-chloro substitution, compound **4o** with 4-methoxy substitution, compound **4j** with 2,4-dichloro substitution also showed good activity. Compounds **4a**, **4b**, **4c**, **4g**, **4h**, **4k**, **4m**, **4n** showed slight activity. Compounds **4d**, **4e**, **4f**, **4p**, **4q** showed no activity. From above results it is revealed that compound with dicyclohexyl substitution have shown good activity due to lipophilic nature of the dicyclohexyl group. (Table 2).

Pharmacology

Acute toxicity study

Healthy and adult female albino Swiss mice weighing between 20 and 25 g were used in this investigation. The test compounds suspended in 0.1% sodium carboxy methyl cellulose (CMC) were administered by i.p, in doses up to 2,000 mg/kg-body weight. The control group animals received only vehicle (0.1% sodium CMC). The animals were observed for 1 month from the time of administration of test compound to record the mortality.

Table 1 Physical and analytical data of *N*,*N*-disubstituted-2-(5-aryl-1H-1,2,4-triazol-3-ylthio)ethanamine **4a–u**

Compd	Ar	R1	R2	Mol. formula	Mol. wt.	M.P. (°C)	% Yield	Elemental analysis calc. (found)		
								C	H	N
4a	Phenyl	CH_3	CH_3	$C_{12}N_4H_{16}S$	248	210–212	87	58.06 (58.03)	6.45 (6.47)	22.51 (22.52)
4b	Phenyl	C_2H_5	C_2H_5	$C_{14}N_4H_{20}S$	276	216–218	82	60.86 (60.85)	7.24 (7.22)	20.28 (20.29)
4c	Phenyl			$C_{22}N_4H_{32}S$	384	288–290	75	68.75 (68.73)	8.33 (8.30)	14.58 (14.56)
4d	4-methyl phenyl	CH_3	CH_3	$C_{13}N_4H_{18}S$	262	234–236	68	59.54(59.55)	6.87 (6.85)	21.37 (21.35)
4e	4-methyl phenyl	C_2H_5	C_2H_5	$C_{15}N_4H_{22}S$	290	242–244	62	62.06(62.03)	7.58 (7.55)	19.31 (19.34)
4f	4-methyl phenyl			$C_{23}N_4H_{34}S$	398	>300	73	69.34(69.35)	8.54 (8.56)	14.07 (14.09)
4g	4-chloro phenyl	CH_3	CH_3	$C_{12}N_4H_{15}SCl$	282	257–258	79	51.06 (51.09)	5.31 (5.30)	19.85 (19.88)
4h	4-chloro phenyl	C_2H_5	C_2H_5	$C_{14}N_4H_{19}SCl$	310	262–264	73	58.74(58.78)	6.64 (6.63)	19.58 (19.57)
4i	4-chloro phenyl			$C_{22}N_4H_{31}SCl$	418	298–299	80	63.15 (63.17)	7.41 (7.42)	13.39 (13.40)
4j	2,4-di chloro phenyl	CH_3	CH_3	$C_{12}N_4H_{14}SCl_2$	316	266–268	65	66.66 (66.69)	6.48 (6.47)	25.92 (25.93)
4k	2,4-di chloro phenyl	C_2H_5	C_2H_5	$C_{14}N_4H_{18}SCl_2$	344	270–272	60	68.85 (68.88)	7.37 (7.38)	22.95 (22.96)
4l	2,4-di chloro phenyl			$C_{22}N_4H_{30}SCl_2$	452	>300	72	58.40 (58.38)	6.63 (6.65)	12.38 (12.40)
4m	4-methoxy phenyl	CH_3	CH_3	$C_{13}N_4OH_{18}S$	278	236–238	62	56.11 (56.10)	6.47 (6.48)	20.14 (20.13)
4n	4-methoxy phenyl	C_2H_5	C_2H_5	$C_{15}N_4OH_{22}S$	306	240–241	63	58.82 (58.83)	7.18 (7.21)	18.30 (18.34)
4o	4-methoxy phenyl			$C_{23}N_4OH_{34}S$	414	>300	53	66.66 (66.68)	8.21 (8.23)	13.52 (13.55)
4p	2-OH phenyl	CH_3	CH_3	$C_{12}N_4OH_{16}S$	264	198–200	67	54.54 (54.55)	6.06 (6.04)	21.21 (21.25)
4q	2-OH phenyl	C_2H_5	C_2H_5	$C_{14}N_4OH_{20}S$	292	194–196	65	57.53 (57.55)	6.84 (6.87)	19.17 (19.16)
4r	2-OH phenyl			$C_{22}N_4OH_{30}S$	400	188–190	59	66 (66.03)	8 (8.02)	14 (13.97)
4s	4-OH phenyl	CH_3	CH_3	$C_{12}N_4OH_{16}S$	264	170–172	75	54.54 (54.53)	6.06 (6.04)	21.21 (21.23)
4t	4-OH phenyl	C_2H_5	C_2H_5	$C_{14}N_4OH_{20}S$	292	174–176	70	57.53 (57.51)	6.84 (6.85)	19.17 (19.14)
4u	4-OH phenyl			$C_{22}N_4OH_{30}S$	400	178–180	68	66 (66.02)	8 (7.97)	14 (14.03)

IR (KBr, cm^{-1}): **4a**, 3307.9 (NH str), 3072 (aromatic CH str), 2941.7 (aliphatic CH str), 1010.2 (C–S str) **4b**: 3400(NH str), 1033 (C–S str), 800 (Ar–H str) **4f**: 3490 (NH str), 2792 (CH str), 1030 (C–S), 810 (Ar–H str)

^{1} H NMR (DMSO): **4a**, 7.4 to 8.1 (m, 5H, ArH), 2.9 to 3.0 (s, 2H, S–CH_2), 3.2 (s, 2H, N–CH_2), 2.4 (m, aliphatic 6H). **4c**, 7.7–7.9 (m, 5H, Ar H), 3.0 (s, 2H, S–CH_2), 3.4 (s, 2H, N–CH_2), 6.3–6.9 (m, 11H of cyclohexyl). **4g**, 7.01–8.0 (m, 4H of *p*-chlorophenyl), 3.2 (S–CH_2), 3.2 (N–CH_2), 2.5 (aliphatic 6H). **4m**, 7.27–7.7 (m, 5H Ar H), 3.9 (s, 3H, OCH_3), 2.7 (s, 2H, S–CH_2), 3.0 (s, N–CH_2), 2.3 (m, aliphatic 6H). **4a**, m/z 249.4

Gross behavioral studies

All the compounds were tested for the gross behavioral changes continuously for 3 h starting from the administration of test compound and 48 h intermittently and compared with that of control group of mice. In the behavioral profile the test animals were observed for alertness, visual placing, vocalization, restlessness, irritability, fearfulness, reactivity, touch response, and pain responses.

Tail suspension test in mice

Healthy adult male mice weighing between 20 and 25 g were used as experimental animals. Animals were fasted for over night and divided into groups of six animals each. Standard drug (10 mg/kg of Imipramine), test compound (10, 30 and 100 mg/kg), and control vehicles (1% Sodium CMC) were administered to the mice by intraperitoneal injection 60 min before testing. Mice were suspended on the edge of a shelf 58 cm above a table top by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was recorded for a period of 5 min. Mice were considered immobile when they were passively and completely motionless for at least 1 min. The responses were noted at 60 min after the injection of the test compound. The results were compared with control and standard drug.

Conclusions

This study reports the synthesis of some *N*,*N*-disubstituted-2-(5-aryl-1H-1,2,4-triazol-3-ylthio)ethanamine. The antidepressant

Table 2 Antidepressant activity of test compounds by tail suspension test in mice

Compound name	Dose (mg/kg)	Immobility (s)
Control	0.1 ml of 1% sodium CMC	169.8 ± 13.0
Imipramine	10	95.8 ± 11.6*
4a	10	117.2 ± 10.5*
	30	110.3 ± 8.1*
	100	102.0 ± 9.3*
4b	10	145.8 ± 14.1
	30	120.7 ± 12.5*
	100	108.3 ± 6.9*
4c	10	117.0 ± 9.1*
	30	109.7 ± 6.7*
	100	101.7 ± 9.0*
4d	10	172.8 ± 5.9
	30	168.2 ± 8.7
	100	152.8 ± 13.2
4e	10	178.3 ± 7.7
	30	168.2 ± 8.0
	100	151.2 ± 10.9
4f	10	165.0 ± 11.6
	30	151.3 ± 11.4
	100	150.0 ± 8.5
4g	10	109.2 ± 6.8*
	30	102.2 ± 4.9*
	100	96.0 ± 11.0*
4h	10	129.7 ± 8.6*
	30	115.0 ± 11.5*
	100	103.8 ± 12.3*
4i	10	96.8 ± 10.7*
	30	94.8 ± 11.0*
	100	89.2 ± 12.2*
4j	10	109.0 ± 7.5*
	30	101.8 ± 4.7*
	100	96.2 ± 11.7*
4k	10	121.8 ± 9.0*
	30	110.0 ± 10.9*
	100	103.2 ± 12.2*
4l	10	96.5 ± 11.8*
	30	94.5 ± 11.7*
	100	90.5 ± 10.8*
4m	10	116.3 ± 9.5*
	30	111.0 ± 5.5*
	100	103.8 ± 6.0*
4n	10	139.0 ± 10.9*
	30	118.5 ± 9.4*
	100	103.8 ± 4.5*
4o	10	101.3 ± 5.8*
	30	96.3 ± 14.5*
	100	94.8 ± 12.8*
4p	10	164.8 ± 14.8
	30	150.8 ± 13.6
	100	150.0 ± 9.1
4q	10	173.8 ± 12.2
	30	163.5 ± 9.4
	100	137.3 ± 12.8
4r	10	162.5 ± 13.3
	30	149.3 ± 12.0
	100	150.0 ± 9.1
4s	10	161.2 ± 13.1
	30	150.3 ± 13.0
	100	149.0 ± 8.5
4t	10	171.8 ± 10.1
	30	167.3 ± 9.2
	100	151.8 ± 13.5
4u	10	157.5 ± 16.8
	30	126.2 ± 11.4*
	100	112.7 ± 11.9*

$N = 6$

* $P < 0.001$ Compared with control

activity revealed that all the compounds screened showed good to moderate antidepressant activities, except compounds **4d**, **4e**, **4f**, **4p**, **4q**. Among all the compounds, compound **4l** which contains dicyclohexyl ring in its structure displayed significant activity due to high lipophilic nature.

Experimental

Chemistry

Melting points were determined by open capillary using toshiwal melting point apparatus and are uncorrected. IR spectra were recorded in potassium bromide KBr on FTIR 8400 Shimadzu spectrophotometer. ^{1}H NMR spectra were recorded on 300 MHz Bruker DPX using $CDCl_3$ and Mass spectra were recorded on LC–MS/MS. Elemental analysis was performed on Perkin–Elmer series 2400.

All chemicals used in synthesis were purchased from E.Merck and Aldrich. Thin layer chromatography (TLC) was performed on silicagel G (Merck) pre-coated plates and spots were visualized with ultraviolet light. The chemical shifts are reported in δ ppm scale. The splitting pattern abbreviations are as follows: s, singlet; t, triplet; m, multiplet. The synthetic pathway is given in Scheme 1. Elemental data for C, H, and N were within ±0.4% of the theoretical values.

*Synthesis of aroyl thiosemicarbazide (**2**)*

Thiosemicarbazide (0.1 mol) was suspended in dry pyridine (100 ml). The reaction mixture was cooled down to −5°C and the appropriate Aroylchloride (0.1 mol) was added dropwise, maintaining temperature under 0°C. The reaction was stirred overnight. The crude precipitate was filtered off, washed several times with water, and recrystallized.

*Synthesis of 5-aryl-1H-1,2,4-triazole-3-thiol (**3a–u**) (Khosrow et al., 2003; Birsen et al. 2007)*

A mixture of compound **2** (0.1 mol) and 2 M sodium hydroxide was refluxed for 4 h. After cooling, the solution was acidified with hydrochloric acid and the ppt was filtered. The ppt was then recrystallized by using appropriate solvent to get TLC pure compound **3a**–**u**.

*5-phenyl-1H-1,2,4-triazole-3-thiol (**3a**)* Yield 76%; m.p. 261–265°C; FT-IR (KBr) cm^{-1}: 3450.8 (NH), 3053 (aromatic CH), 1563.3, 1508.9, 1481.2 (C=C), 2360 (SH); ^{1}H NMR (DMSO-d6) δ ppm: 7.3–8.0(m, 5H, ArH), 13.6 (s, 1H, NH), 13.2 (s, 1H, SH).

Mass spectrum of the compound (**3a**, $R = C_6H_5$) was recorded its molecular ion (M + 1) at m/z 178.3.

*Synthesis of N,N-disubstituted-2-(5-aryl-1H-1,2,4-triazol-3-ylthio)ethanamine (**4a–u**)*

To a mixture of 3 (0.1 mol), a solution of dimethyl-(2-chloro ethyl)amine (0.1 mol) or diethyl-(2-chloro ethyl)amine (0.1 mol) or dihexyl-(2-chloro ethyl)amine (0.1 mol) in 10 ml of acetone and anhydrous Potassium carbonate (K_2CO_3) (0.1 mol) in 25 ml of acetone was added. The reaction was refluxed for 6 h. After cooling, the ppt was filtered. The ppt was then recrystallized from acetone.

*N,N-dimethyl-2-(5-phenyl-1H-1,2,4-triazol-3-ylthio)ethanamine (**4a**)* Yield 87%; m.p. 210–212°C FT-IR (KBr) cm^{-1}: 3307.9 (NH), 3072 (aromatic CH), 2941.7, 2865.2, 2785.9 (aliphatic CH), 1464.8 (CH), 1010.2 (C–S); ^{1}H NMR (DMSO-d6) δ ppm: 7.4 to 8.1 (m, 5H, ArH), 2.9 to 3.0 (s, S-CH_2), 3.2 (s, N-CH_2), 2.4 (m, aliphatic 6H); $C_{12}N_4H_{16}S$; Calc. N 22.51; Found N 22.52.

Mass spectrum of the compound (**4a**, $R = C_6H_5$) was recorded its molecular ion (M + 1) at m/z 249.4.

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