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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of N′-arylidene-2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio) acetohydrazides as antidepressants

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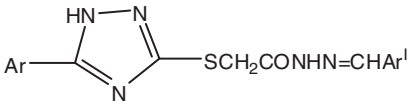
Abstract A series of N′-arylidene-2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio) acetohydrazide were synthesized. Condensation of aromatic aldehydes with 2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio) acetohydrazide gave corresponding N′-arylidene-2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio) acetohydrazide. Spectral and elemental analysis was used for structural elucidation of novel 1, 2, 4-triazole schiff bases. The newly synthesized compounds were screened for their antidepressant activity by using tail suspension test in mice. Compound **4l** showed significant activity among the series.

Graphical Abstract A series of new N′-arylidene-2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio)acetohydrazide have been synthesized and characterized. The results revealed that compound **4l** with bromo substitution exhibited promising antidepressant activity among the series.



Ar - H, Cl, 2, 4-di chloro, 4-CH_3, 2-OH, 4-OH

Ar^1 - H, Cl, Br

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Keywords Antidepressant activity · 1, 2, 4-triazole · Acetohydrazide · Schiff base · Structure-activity relationships

Introduction

Depression is a common mood disorder caused by improper release of monoamine neurotransmitters such as serotonin, noradrenaline, and dopamine in the central nervous system with the dysfunction of dopaminergic, noradrenergic, serotonergic systems. Heterocyclic compounds such as 1, 2, 4-triazoles play a key role in the management of depression for their safety and efficacy (McNamara 2011).

1, 2, 4-Triazoles and their derivatives are possessed by different biological activities such as anticonvulsant (Kamboj et al. 2015; Plech et al. 2013; Song et al. 2011), antimicrobial (Li et al. 2015; Maddila and Jonnalagadda 2012; Mange et al. 2013; Panda and Jain 2014), anticancer (Kamel and Abdo 2014; Flefel et al. 2013; Singh et al. 2013), anti-inflammatory (Sarigol et al. 2015; Jiang et al. 2014). Several compounds containing 1, 2, 4-triazole rings are well known as drugs. For example, fluconazole is used as an antimicrobial drug, while vorozole, letrozole, and anastrozole are non-steroidal drugs used for the treatment of cancer. Loreclezole (anticonvulsant), alprazolam (anxiolytic), rizatriptan (antimigraine), and ribavirin (antiviral) are examples of other drugs with 1, 2, 4-triazole moiety. In addition to 1, 2, 4-triazoles, Schiff base derivatives and their reduced derivatives have been also found to associate with various pharmacological activities (Aouad et al. 2015; Li et al. 2012; Sim et al. 2014).

Literature survey revealed that few reports were established on 1, 2, 4-triazoles Schiff bases with antidepressant

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activity (Jubie et al. 2011). Unsufficient biological data has given a way to synthesize some new 1, 2, 4-triazole Schiff base derivatives. It has been established that introduction of several aromatic aldehydes to 2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio) acetohydrazide have yielded many biologically active Schiff base structures which were screened for antidepressant activity by using tail suspension test in mice. The compounds were characterized by IR, NMR, MS, and elemental analysis.

Materials and methods

Melting points were determined by open capillary using Toshniwal 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 was performed on silicagel G (Merck) pre-coated plates and spots were visualized with ultraviolet light. The chemical shifts are reported in δ p.p.m. 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, N, O, and S were within $\pm$ 0.4% of the theoretical values.

Synthesis of 5-aryl-1H-1, 2, 4-triazole-3-thiol (1)

A mixture of compound aryl thiosemicarbazide (Tozkoparan et al. 2007; Zamani et al. 2003) which was synthesized from thiosemicarbazide and aroylchloride (0.1 mol) and 2M sodium hydroxide was refluxed for 4 h. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered. The precipitate was then recrystallized by using appropriate solvent to get pure compound.

Synthesis of Ethyl 2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio) acetate (2)

Ethyl chloroacetate (0.002 mol) was added to a solution of compound **1** (0.001 mol) in absolute ethanol (20 ml). The mixture was refluxed under stirring for 24 h in the presence of potassium hydroxide (0.001 mol). Then the solvent was removed under reduced pressure to give the solid product. The crude product was recrystallized.

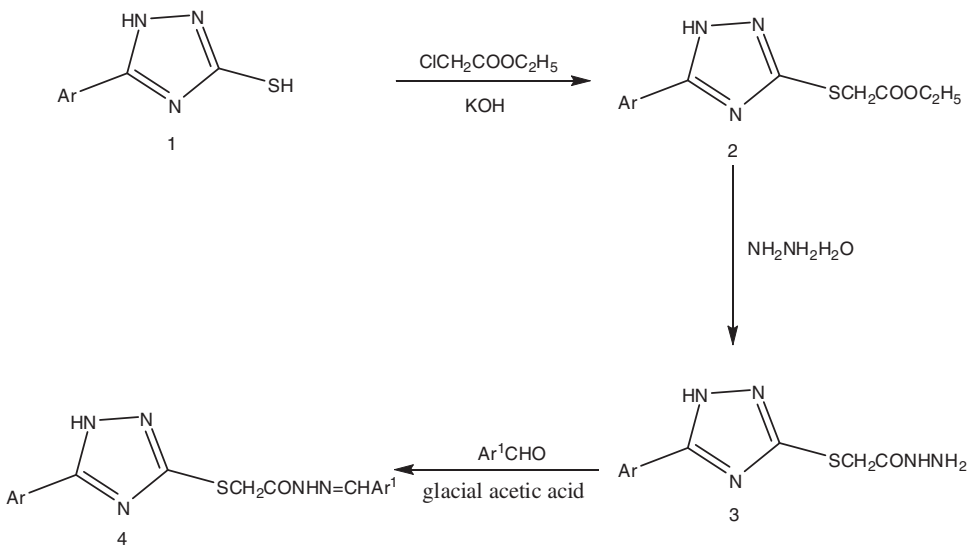
Synthesis of 2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio) acetohydrazide (3)

Eighty percent hydrazine hydrate (0.003 mol) was added to compound **2** (0.002 mol) in ethanol (10 ml) and refluxed for 3 h. After cooling the appeared solid was filtered and recrystallized with appropriate solvent.

Synthesis of N′-arylidene-2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio)acetohydrazide (4a–u)

A solution of **3** (0.001 mol) in ethanol (10 ml) the appropriate aromatic aldehyde (0.001 mol) and 4–5 drops of glacial acetic acid was refluxed for 3 h. The resultant was allowed to cool and poured into cold water. The solid was collected by filtration and recrystallized from ethanol. By using this total 21 compounds **4a–u** were synthesized.

The physical and analytical data of all the synthesized compounds were given in Table 1



Scheme 1 Synthetic pathway of N'-arylidene-2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio) acetohydrazides

Table 1 Physical data of N'-arylidene-2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio)acetohydrazide **(4a–u)**

Comp	Ar	Ar[1]	M.F	M.wt	M.P	% Yield	Elemental analysis Calc.(found)			
							C	H	N	S
4a	Phenyl	Phenyl	$C_{17}H_{15}N_5SO$	337	282	76	60.52 (60.50)	4.48 (4.50)	20.76 (20.75)	9.50 (9.48)
4b	Phenyl	4-Chloro Phenyl	$C_{17}H_{14}N_5SOCl$	371	>300	59	54.91 (54.90)	3.79 (3.80)	18.83 (18.84)	8.62 (8.60)
4c	phenyl	4-Bromo Phenyl	$C_{17}H_{14}N_5SOBr$	416	290	69	49.05 (49.03)	3.39 (3.40)	16.82 (16.82)	7.70 (7.72)
4d	4-Methyl phenyl	Phenyl	$C_{18}H_{17}N_5SO$	351	290	72	61.52 (61.50)	4.88 (4.90)	19.93 (19.91)	9.12 (9.10)
4e	4-Methyl phenyl	4-Chloro Phenyl	$C_{18}H_{16}N_5SOCl$	385	>300	55	56.03 (56.04)	4.18 (4.18)	18.15 (18.16)	8.31 (8.30)
4f	4-Methyl phenyl	4-Bromo Phenyl	$C_{18}H_{16}N_5SOBr$	430	294	58	50.24 (50.23)	3.75 (3.76)	16.27 (16.28)	7.45 (7.43)
4g	4-Chloro Phenyl	Phenyl	$C_{17}H_{14}N_5SOCl$	371	>300	67	54.91 (54.90)	3.79 (3.80)	18.83 (18.83)	8.62 (8.62)
4h	4-Chloro Phenyl	4-Chloro Phenyl	$C_{17}H_{13}N_5SOCl_2$	406	>300	57	50.26 (50.28)	3.23 (3.24)	17.24 (17.25)	7.89 (7.90)
4i	4-Chloro Phenyl	4-Bromo Phenyl	$C_{17}H_{13}N_5SOBrCl$	450	>300	55	45.30 (45.30)	2.91 (2.90)	15.54 (15.53)	7.11 (7.11)
4j	2, 4-Dichloro phenyl	Phenyl	$C_{17}H_{13}N_5SOCl_2$	406	>300	60	50.26 (50.27)	3.23 (3.24)	17.24 (17.25)	7.89 (7.90)
4k	2, 4-Dichloro phenyl	4-Chloro Phenyl	$C_{17}H_{12}N_5SOCl_3$	440	>300	65	46.33 (46.32)	2.74 (2.75)	15.89 (15.90)	7.28 (7.30)
4l	2, 4-Dichloro phenyl	4-Bromo Phenyl	$C_{17}H_{12}N_5SOBrCl_2$	419	>300	58	42.08 (42.10)	2.49 (2.50)	14.43 (14.44)	6.61 (6.62)
4m	4-methoxy phenyl	Phenyl	$C_{18}H_{17}N_5SO_2$	367	298	50	58.84 (58.85)	4.66 (4.67)	19.06 (19.08)	8.73 (8.74)
4n	4-methoxy phenyl	4-Chloro Phenyl	$C_{17}H_{16}N_5SO_2Cl$	401	>300	52	53.80 (53.82)	4.01 (4.00)	17.43 (17.45)	7.98 (8.00)
4o	4-methoxy phenyl	4-Bromo Phenyl	$C_{18}H_{16}N_5SO_2Br$	446	>300	65	48.44 (48.43)	3.61 (3.61)	15.69 (15.69)	7.18 (7.19)
4p	2-Hydroxy	Phenyl	$C_{17}H_{15}N_5SO_2$	353	semisolid	70	57.78 (57.80)	4.28 (4.29)	19.82 (19.80)	9.07 (9.08)
4q	2-Hydroxy	4-Chloro Phenyl	$C_{17}H_{14}N_5SO_2Cl$	387	semisolid	72	52.65 (52.66)	3.64 (3.65)	18.06 (18.07)	8.27 (8.28)
4r	2-Hydroxy	4-Bromo Phenyl	$C_{17}H_{14}N_5SO_2Br$	432	semisolid	62	47.23 (47.22)	3.26 (3.25)	16.20 (16.22)	7.42 (7.43)
4s	4-Hydroxy	Phenyl	$C_{17}H_{15}N_5SO_2$	353	semisolid	64	57.78 (57.79)	4.28 (4.29)	19.82 (19.81)	9.07 (9.08)
4t	4-Hydroxy	4-Chloro Phenyl	$C_{17}H_{14}N_5SO_2Cl$	387	semisolid	69	52.65 (52.65)	3.64 (3.66)	18.06 (18.05)	8.27 (8.28)
4u	4-Hydroxy	4-Bromo Phenyl	$C_{17}H_{14}N_5SO_2Br$	432	semisolid	70	47.23 (47.22)	3.26 (3.25)	16.20 (16.20)	7.42 (7.44)

*N′-benzylidene-2-(5-phenyl-1H-1,2,4-triazol-3-ylthio) acetohydrazide (**4a**)*

Yield 81%; m.p. 282 °C FT-IR (KBr) cm^{-1}: 3460(NH), 1639(C=O), 1515(C=N), 1018(C–S) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ p.p.m.:7.3–8.2(m,10H, ArH),4.06(s,2H, S–CH_2), 10.6 (s,1H, CONH), 8.39 (s,1H, N=CH), 13.17 (s,1H, Ar–NH); ^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.1 and 159.5(C_3 and C_5 triazole ring), 127.4–133.2(aromatic), 40.1 (SCH_2),172.4 (C=O), 143.8(N–CH);MS (70 eV) *m/z*: 338 (M^+).

*N′-(4-chlorobenzylidene)-2-(5-phenyl-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4b**)*

Yield 79%; m.p. > 300 °C FT-IR (KBr) cm^{-1}:3349 (NH), 3093(aromatic C–H str),1639(C=O), 1590(C=N), 1019 (C–S), 742(C–Cl); ^{1}H NMR ($CDCl_3$) δ p.p.m.: 7.2–8.2 (m,9H, ArH),4.15(s,2H, S–CH_2), 8.29 (s, 1H, N=CH), 11.0 (s,1H, CONH), 13.2 (s,1H,Ar–NH); ^{13}C NMR ($CDCl_3$) δ p. p.m.:160.5 and 159.2(C_3 and C_5 triazole ring), 126.8–132.6 (aromatic), 40.6 (SCH_2),172.3 (C=O), 143.7(N–CH), 136.9 (C–Cl); MS (70 eV) *m/z*: 372 (M^+).

*N′-(4-bromobenzylidene)-2-(5-phenyl-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4c**)*

Yield 76%; m.p. 290 °C FT-IR (KBr) cm^{-1}:3291 (NH), 3024.2 (aromatic C–H str), 1629(C=O), 1580 (C=N),1028 (C–S),690.3(C–Br);^{1}H NMR ($CDCl_3$) δ p.p.m.:7.3–8.2 (m,9H, ArH), 3.97 (s,2H, S–CH_2), 10.9 (s,1H, CONH), 8.38 (s,1H, N=CH), 13.0 (s,1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.8 and 159.9(C_3 and C_5 triazole ring), 127.7–133.1(aromatic), 40.3 (SCH_2),172.1(C=O), 143.2 (N–CH), 124.6 (C–Br); MS (70 eV) *m/z*: 417 (M^+).

*(N′-benzylidene-2-(5-p-tolyl-1H-1,2,4-triazol-3-ylthio) acetohydrazide (**4d**)*

Yield 78%; m.p. 291 °C FT-IR (KBr) cm^{-1}: 3316 (NH), 3074(aromatic C–H str), 1647(C=O), 1591(C=N), 1023 (C–S);^{1}H NMR ($CDCl_3$) δ p.p.m.: 7.2–8.2(m,9H, ArH), 2.33 (s, 3H, CH_3), 3.87 (s,2H, S–CH_2), 11.2 (s,1H, CONH), 8.52 (s,1H, N=CH), 13.3 (s,1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.4 and 159.1(C_3 and C_5 triazole ring), 127.4–133.5(aromatic), 40.2 (SCH_2),172.7 (C=O), 143.1 (N–CH), 21.5(CH3); MS (70 eV) *m/z*: 352 (M^+).

*N′-(4-chlorobenzylidene)-2-(5-p-tolyl-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4e**)*

Yield 72%; m.p. > 300 °C FT-IR (KBr) cm^{-1}: 3275(NH), 3082(aromatic C–H str), 1754(C=O), 1570(C=N), 1010 (C–S),738(C–Cl); ^{1}H NMR ($CDCl_3$) δ p.p.m.:7.5–8.3 (m,8H, ArH), 2.47 (s, 3H, CH_3), 3.62(s,2H, S–CH_2), 11.5 (s,1H, CONH), 7.89(s,1H, N=CH), 13.4 (s,1H,Ar–NH); ^{13}C NMR ($CDCl_3$) δ p.p.m.:160.7 and 159.8(C_3 and C_5 triazole ring), 126.5–132.9(aromatic), 40.4 (SCH_2),172.1 (C=O), 143.7(N–CH), 136.2(C–Cl),21.6(CH3); MS (70 eV) *m/z*: 386 (M^+).

*N′-(4-bromobenzylidene)-2-(5-p-tolyl-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4f**)*

Yield 81%; m.p. 294 °C FT-IR (KBr) cm^{-1}:3197(NH), 3094(aromatic C–H str), 1654(C=O), 1560(C=N), 1109 (C–S),682(C–Br); ^{1}H NMR ($CDCl_3$) δ p.p.m.:7.3–8.0(s,8H, ArH), 3.4(s,2H, S–CH_2), 10.5 (s, 1H, CONH), 7.9(s, 1H, N=CH), 2.51 (s, 3H, CH_3), 13.1(s,1H,Ar–NH); ^{13}C NMR ($CDCl_3$) δ p.p.m.:159.9 and 159.6(C_3 and C_5 triazole ring), 127.2–133.7(aromatic), 40.5 (SCH_2),172.2 (C=O), 143.8 (N–CH), 21.3(CH3),123.9(C–Br); MS (70 eV) *m/z*:431 (M^+).

*N′-benzylidene-2-(5-(4-chlorophenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4g**)*

Yield 75%; m.p. > 300 °C FT-IR (KBr) cm^{-1}: 3250(NH), 3094(aromatic C-H str),1670(C=O), 1551(C=N), 1020(C-S),743(C–Cl); ^{1}H NMR ($CDCl_3$) δ p.p.m.: 7.5–8.3(m,9H, ArH), 3.6 (s,2H, S–CH_2), 10.6 (s,1H, CONH), 8.1(s,1H, N=CH), 13.4 (s,1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ p.p.m.: 161.4 and 159.8(C_3 and C_5 triazole ring), 127.9–136.6 (aromatic), 40.0 (SCH_2),172.7 (C=O), 143.1(N–CH),137.8 (C–Cl); MS (70 eV): $m/z = 372$ (M^+).

*N′-(4-chlorobenzylidene)-2-(5-(4-chlorophenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4h**)*

Yield 71%; m.p. > 300 °C FT-IR (KBr) cm^{-1}: 3270(NH), 1650(C=O), 3096(aromatic C-H str), 1564(C=N), 1100 (C–S),741(C–Cl); ^{1}H NMR ($CDCl_3$) δ p.p.m.: 7.4–8.2 (m,8H, ArH), 3.5 (s,2H, S–CH_2), 10.1 (s,1H, CONH), 7.8 (s,1H, N=CH), 13.8 (s,1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ p. p.m.: 160.3 & 159.6(C_3 and C_5 triazole ring), 128.8–136.5 (aromatic), 40.3 (SCH_2),172.9 (C=O), 143.5(N–CH),137.6 (C–Cl); MS (70 eV) *m/z*: 407 (M^+).

*N′-(4-bromobenzylidene)-2-(5-(4-chlorophenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4i**)*

Yield 78%; m.p. > 300 °C FT-IR (KBr) cm^{-1}: 3260 (NH), 3086(aromatic C–H str), 1654(C=O), 1559(C=N), 1107 (C–S), 684(C–Br),747(C–Cl);^{1}H NMR ($CDCl_3$) δ p.p. m.:7.5–8.0(m,8H, ArH), 3.2(s,2H, S–CH_2), 10.8(s,1H, CONH), 7.7(s,1H, N=CH), 13.1(s,1H,Ar–NH) p.p.m.;^{13}C

NMR ($CDCl_3$) δ p.p.m.:160.4 and 159.(C_3 and C_5 triazole ring), 125.4–134.2 (aromatic), 40.3 (SCH_2),171.9 (C=O), 143.8(N–CH),135.7(C–Cl),123.9(C–Br); MS (70 eV) *m/z*: 451 (M^+).

*N′-benzylidene-2-(5-(2,4-dichlorophenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4j**)*

Yield 69%; m.p. > 300 °C FT-IR (KBr) cm^{-1}: 3210 (NH), 3192(aromatic C–H str), 1657(C=O), 1562(C=N), 1103 (C–S),741(C–Cl); ^1H NMR ($CDCl_3$) δ p.p.m.: 7.4–7.9 (m,8H, ArH), 3.3(s,2H, S–CH_2), 10.7(s,1H, CONH), 6.9 (s,1H, N=CH), 13.2(s,1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ: 160.1 and 159.4(C_3 and C_5 triazole ring), 127.5–136.7 (aromatic), 40.5 (SCH_2),172.7 (C=O), 143.4(N–CH),137.5 (C–Cl);MS (70 eV) *m/z*: 407 (M^+).

*N′-(4-chlorobenzylidene)-2-(5-(2,4-dichlorophenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4k**)*

Yield 73%; m.p. > 300 °C FT-IR (KBr) cm^{-1}: 3209(NH), 3087(aromatic C–H str), 1651(C=O), 1567(C=N), 1110 (C–S),752(C–Cl);^1H NMR ($CDCl_3$) δ p.p.m.: 7.3–7.8 (m,7H, ArH), 3.6(s,2H, S–CH_2), 10.7(s,1H, CONH), 7.4 (s,1H, N=CH), 13.0(s,1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ p.p.m.:160.8 and 159.4(C_3 and C_5 triazole ring), 127.3–135.6 (aromatic), 40.7 (SCH_2),172.0 (C=O), 143.7(N–CH),137.2 (C–Cl);MS (70 eV) *m/z*: 441 (M^+).

*N′-(4-bromobenzylidene)-2-(5-(2,4-dichlorophenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4l**)*

Yield 81%; m.p. > 300 °C FT-IR (KBr) cm^{-1}: 3346 (NH), 3106(aromatic C–H str), 1654 (C=O), 1564(C=N), 1105 (C–S),691(C–Br),742(C–Cl); ^1H NMR ($CDCl_3$) δ p.p.m.:7.4–7.8(m,7H, ArH), 3.7(s,2H, S–CH_2), 10.3(s,1H, CONH), 7.8(s,1H, N=CH), 13.0(s,1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.1 and 159.4(C_3 and C_5 triazole ring),127.4–136.7 (aromatic), 40.7 (SCH_2),172.5 (C=O), 143.8(N–CH), 136.8(C–Cl),128.1(C–Br); MS (70 eV) *m/z*: 420 (M^+).

*N′-benzylidene-2-(5-(4-methoxyphenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4m**)*

yield 73%; m.p. 298 °C FT-IR (KBr) cm^{-1}: 3334 (N–H str), 3072 (aromatic C–H str), 1641 (C=O), 1517(C=N), 1018 (C–S);^1H NMR ($CDCl_3$) δ p.p.m.: 7.2–8.0 (m, 9H, ArH), 3.8 (s, 3H, OCH_3), 4.1 (s, 2H, S–CH_2), 8.3 (s, 1H, N=CH), 10.8 (s, 1H, CONH), 13.0(s, 1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.0 and 158.9(C_3 and C_5 triazole ring), 114.4–160.7(aromatic), 40.1 (SCH_2),172.7 (C=O), 143.6 (N–CH), 55.8 (OCH_3); MS (70 eV) *m/z*: 368 (M^+).

*N′-(4-chlorobenzylidene)-2-(5-(4-methoxyphenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4n**)*

Yield 79%; m.p. > 300 °C FT-IR (KBr) cm^{-1}: 3294(NH), 3091 (aromatic C–H str),1648(C=O), 1562(C=N), 1107 (C–S),739(C–Cl); ^1H NMR ($CDCl_3$) δ p.p.m.: 7.1–7.9 (m,8H, ArH), 3.7(s,3H,OCH_3), 4.2(s,2H, S–CH_2), 10.5 (s,1H, CONH), 8.1(s,1H, N=CH), 13.1(s,1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.5 and 159.6(C_3 and C_5 triazole ring), 114.9–160.6 (aromatic), 40.2 (SCH_2),172.6 (C=O), 143.9(N–CH), 55.7 (OCH_3),139.2(C–Cl); MS (70 eV) *m/z*: 402 (M^+).

*N′-(4-bromobenzylidene)-2-(5-(4-methoxyphenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4o**)*

Yield 73%; m.p. > 300 °C FT-IR (KBr) cm^{-1}: 3256 (NH), 3085 (aromatic C–H str),1653(C=O), 1549(C=N), 1094 (C–S),675(C–Br);^1H NMR ($CDCl_3$) δ p.p.m.: 7.0–8.1 (m,8H, ArH), 3.5(s,3H,OCH_3), 4.2(s,2H, S–CH_2), 10.2 (s,1H, CONH), 7.8(s,1H, N=CH), 13.3(s,1H,Ar–NH);^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.5 and 159.6(C_3 and C_5 triazole ring), 114.2–160.2 (aromatic), 40.4 (SCH_2),172.7 (C=O), 143.9(N–CH), 55.2 (OCH_3),126.3(C–Br); MS (70 eV) *m/z*: 447 (M^+).

*N′-benzylidene-2-(5-(2-hydroxyphenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4p**)*

Yield 76%; Semisolid FT-IR (KBr) cm^{-1}: 3750(OH), 3360 (NH), 3085 (aromatic C–H str), 1554(C=N),1103(C–S); ^1H NMR ($CDCl_3$) δ p.p.m.: 7.1–7.9(m, 9H, ArH),4.1(s,2H, S–CH_2), 10.4(s,1H, CONH), 8.1(s,1H, N=CH), 13.1(s,1H, Ar–NH), 9.6(s,1H,OH); ^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.1 and 159.5(C_3 and C_5 triazole ring), 117.9–154.6 (aromatic), 40.0 (SCH_2),172.5 (C=O), 143.8(N–CH) p.p.m.; MS (70 eV) *m/z*: 354 (M^+).

*N′-(4-chlorobenzylidene)-2-(5-(2-hydroxyphenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4q**)*

Yield 83%; Semisolid FT-IR (KBr) cm^{-1}: 3769(OH),3275 (NH), 3076 (aromatic C–H str), 1641(C=O), 1559(C=N), 1101(C–S),739(C–Cl); ^1H NMR ($CDCl_3$) δ p.p.m.: 7.0–7.7 (m,8H, ArH), 3.5(s,2H, S–CH_2), 10.5(s,1H, CONH), 7.2 (s,1H, N=CH), 13.4(s,1H,Ar–NH), 9.4(s,1H,OH);^{13}C NMR ($CDCl_3$) δ p.p.m.:160.7 and 159.2(C_3 and C_5 triazole ring), 117.0–136.6 (aromatic), 40.7 (SCH_2),172.6 (C=O), 143.9(N–CH),137.6(C–Cl); MS (70 eV) *m/z*:388 (M^+).

*N′-(4-bromo benzylidene)-2-(5-(2-hydroxy phenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4r**)*

Yield 76%; Semisolid FT-IR (KBr) cm^{-1}: 3709(OH), 3260 (NH), 3060(aromatic C–H str), 1649(C=O), 1541(C=N), 1123(C–S),662(C–Br); ^{1}H NMR ($CDCl_3$) δ p.p.m.: 7.1–7.8 (m,8H, ArH), 3.2(s,2H, S–CH_2), 10.2(s,1H, CONH), 7.8 (s,1H, N=CH), 13.4(s,1H,Ar–NH), 9.5(s,1H,OH);^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.1 and 158.9(C_3 and C_5 triazole ring), 117.7–154.3 (aromatic), 40.3 (SCH_2),172.3 (C=O), 143.1(N–CH),126.9(C–Br); MS (70 eV) *m/z*:433 (M^+).

*N′-benzylidene-2-(5-(4-hydroxyphenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4s**)*

Yield 71%; Semisolid FT-IR (KBr) cm^{-1}: 3735(OH),3249 (NH), 3059 (aromatic C–H str), 1643 (C=O), 1562(C=N), 1100(C–S); ^{1}H NMR ($CDCl_3$) δ p.p.m.: 7.1–7.9(m,8H, ArH), 3.4(s,2H, S–CH_2), 10.3 (s,1H, CONH), 7.6(s,1H, N=CH), 13.0(s,1H,Ar–NH), 9.8(s,1H,OH) p.p.m.; ^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.1 and 159.6(C_3 and C_5 triazole ring), 116.2–158.3 (aromatic), 40.2 (SCH_2),170.8 (C=O), 143.2(N–CH); MS (70 eV) *m/z*:354 (M^+).

*N′-(4-chlorobenzylidene)-2-(5-(4-hydroxyphenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4t**)*

Yield 76%; Semisolid FT-IR (KBr) cm^{-1}: 3765(OH),3280 (NH), 3074 (aromatic C–H str), 1621(C=O), 1574(C=N), 1128(C–S),741(C–Cl);^{1}H NMR ($CDCl_3$) δ p.p.m.: 6.8–7.9 (m,8H, ArH), 4.1(s,2H, S–CH_2), 9.5(s,1H, CONH), 7.9 (s,1H, N=CH), 13.1(s,1H,Ar–NH), 9.4(s,1H,OH);^{13}C NMR ($CDCl_3$) δ p.p.m.:160.5 and 159.3(C_3 and C_5 triazole ring), 116.7–158.9 (aromatic), 40.4 (SCH_2),170.8 (C=O), 143.3(N–CH),124.9(C–Cl); MS (70 eV) *m/z*: 388 (M^+).

*N′-(4-bromobenzylidene)-2-(5-(4-hydroxyphenyl)-1H-1,2,4-triazol-3-ylthio)acetohydrazide (**4u**)*

Yield 83%; Semisolid FT-IR (KBr) cm^{-1}:3760(OH),3292 (NH), 3097 (aromatic C–H str), 1654(C=O), 1531 (C=N),1112(C–S); ^{1}H NMR ($CDCl_3$) δ p.p.m.: 6.9–8.0 (m,8H, ArH), 3.2(s,2H, S–CH_2), 9.6 (s,1H, CONH), 8.1 (s,1H, N=CH), 13.8(s,1H,Ar–NH), 9.6(s,1H,OH); ^{13}C NMR ($CDCl_3$) δ p.p.m.: 160.3 and 159.6(C_3 and C_5 triazole ring), 116.2–158.3 (aromatic), 40.7 (SCH_2),172.4 (C=O), 143.1(N–CH), 129.3(C–Br); MS (70 eV) *m/z*: 433 (M^+).

Pharmacology

The synthesized compounds were evaluated for anti-depressant activity by tail suspension test in mice.

Tail suspension test in mice

Healthy adult male or female mice weighing between 20–25 g were used as experimental animals. Animals were fasted for overnight 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 (0.1% Sodium CMC-Sodium Carboxy Methyl Cellulose) were administered to the mice by intraperitoneal injection. The tail suspension test was conducted in a silent experimental room in which tail of the mouse was hanged to a horizontal wooden bar located inside a yellow plastic box (40 × 46 × 40 cm) just above 35 cm from the floor. The mouse was fixed to the bar with the help of adhesive tape placed 1–1.5 cm from the tip of the tail, such that the mouse's head was laid about 20 cm above the floor. The subject was observed with the help of video camera through a perspex plastic coverage of the box allowed observation of the subject with the aid of a video camera. The trial was conducted for 5 min (300 s) during which a blinded observer scored the total duration of immobility. The mouse was considered immobile only when it hung 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 (Cryan et al. 2005).

Results and discussion

Chemistry

IR spectrum of the compound **1a** exhibited NH stretching at 3450.8 cm^{-1}, the absorption band at 2360 cm^{-1} indicating the presence of SH group. When triazole Schiff base was prepared from compound **1** the SH peak was disappeared. In the series **4**, the absence of signals in the region 2300–2600 cm^{-1} (SH str) in IR spectral data and the presence of signal in the region of 1010–1050 cm-1 (C–S str) and 1600–1700 cm^{-1} (C=O) indicates the formation of compounds for the series **4**.

In the ^{1}H NMR spectra of compound **1a**, NH signal was observed at 13.6 p.p.m. Additional signals (5H) belonging to phenyl ring were observed in the aromatic region at 7.3 to 8.0 p.p.m. The signal due to –SH group was observed at 13.2 p.p.m. in the ^{1}H NMR spectra of compound **1a**. When compound **1** is converted to Schiff base **4** the SH signal was disappeared. In compound **4a** the additional signals were observed at 3.0 (2H, S–CH_2), 8.6 (1H, CONH), 6.5 (1H, N=CH).

Mass spectrum of the compound (**4a**, R = C_6H_5) was recorded at molecular ion (M + 1) i.e. *m/z* 338.

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

Compound Name	Dose (mg/kg)	Immobility (in seconds)
Control	0.1 ml of 0.1% Sodium CMC	173.8 ± 10.2
Imipramine	10	96.8 ± 11.5*
4a	10	176.8 ± 10.8
	30	167.5 ± 8.2
	100	155.5 ± 9.4
4b	10	172.2 ± 5.7
	30	167.7 ± 12.5
	100	158.5 ± 9.7
4c	10	156.3 ± 9.5
	30	146.0 ± 14.1
	100	121.3 ± 12.8*
4d	10	177.0 ± 9.9
	30	163.0 ± 8.5
	100	137.2 ± 11.7
4e	10	173.3 ± 11.5
	30	166.3 ± 6.3
	100	155.3 ± 9.6
4f	10	158.0 ± 16.3
	30	117.7 ± 6.7*
	100	111.8 ± 7.7*
4g	10	168.2 ± 15.1
	30	152.0 ± 16.2
	100	149.7 ± 11.2*
4h	10	118.2 ± 11.0*
	30	112.8 ± 7.8*
	100	102.8 ± 6.5*
4i	10	104.0 ± 5.1*
	30	98.7 ± 12.0*
	100	95.7 ± 9.6*
4j	10	165.8 ± 11.8
	30	152.5 ± 10.9
	100	145.5 ± 10.4
4k	10	117.2 ± 11.2*
	30	108.0 ± 8.1*
	100	100.7 ± 10.1*
4l	10	97.2 ± 11.9*
	30	95.2 ± 11.7*
	100	91.0 ± 10.0*
4m	10	167.0 ± 12.9
	30	16.0.5 ± 13.4
	100	151.2 ± 12.5
4n	10	132.7 ± 8.7*
	30	117.0 ± 9.6*
	100	102.5 ± 10.2*
4o	10	131.5 ± 13.8
	30	116.8 ± 9.3*
	100	111.0 ± 7.6*
4p	10	167.2 ± 11.2
	30	154.3 ± 11.6
	100	147.0 ± 14.6
4q	10	121.5 ± 7.6*
	30	113.5 ± 8.6*
	100	102.2 ± 9.2*
4r	10	118.8 ± 13.7*
	30	105.2 ± 4.3*
	100	96.0 ± 13.8*
4s	10	166.2 ± 11.1
	30	155.0 ± 10.0
	100	153.2 ± 8.2
4t	10	128.2 ± 9.9*
	30	118.0 ± 8.7*
	100	109.0 ± 8.7*
4u	10	119.8 ± 8.4*
	30	109.7 ± 10.2*
	100	102.5 ± 9.9*

$N = 6$

*$P < 0.001$ Compared with control

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 antidepressant properties. Compound **4l** with 4-bromo and 2, 4-dichloro substitution showed most significant activity as compared to other test compounds and is comparable with standard drug (imipramine 10 mg/kg). Compounds **4f, 4h, 4i, 4k, 4n, 4q, 4r, 4t, 4u** showed moderate activity. Compounds **4a, 4b, 4d, 4e, 4j, 4m,** and **4p** showed no activity. From above results it is revealed that compound with bromo substitution have shown good activity due to lipophilicity and high-molecular weight. (Table 2).

Conclusions

This study reports the synthesis of N′-arylidene-2-(5-aryl-1H-1, 2, 4-triazol-3-ylthio) acetohydrazides. Twenty one compounds were successfully synthesized. The antidepressant activity revealed that all the compounds that were screened showed good to moderate antidepressant

activities, except compounds **4a, 4b, 4d, 4e, 4j, 4m,** and **4p**. Among all the compounds, compound **4l** displayed significant activity due to high-lipophilic nature.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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