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Synthesis and antibacterial activity of substituted indolylthiadiazole derivatives and substituted quinazolinonylthiadiazole derivatives

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ABSTRACT

A mixture of 6-(bromomethyl)-5-(pyridin-4-yl)- [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazole **(3)** with 2-substituted alkyl/aryl-5-substituted-3-amino indoles give 2-(substituted alkyl/aryl)-5-(substituted) -N- [3-(pyridin-4-yl) methyl]-1H indol-3-amino- [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazoles **(4a-4j)**. 2-substituted-3- [3-(pyridin-4-yl)-6 / 6,8-substituted methyl amino] quinazolin-4(3H)-one- [1,2,4] trizolo [3,4-b] [1,3,4] thiadiazoles **(5a-5l)** have been synthesized by 6-(bromomethyl)-5-(pyridin-4-yl)- [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazole **(3)** with 2-substituted 6 / 6,8-substituted 3-amino quinazolinones. All the synthesized compounds were screened for their antibacterial activity and compared with reference drugs ampicillin and gattifloxacin. The compound **(4i)** was the most potent compound of this series. Structure of all the synthesized compounds have been characterized by elemental (C, H, N) and spectral (IR and ^{1}H NMR) analysis.

KEYWORDS

Pyridinylthiadiazole;
Triazolylthiadiazole;
Indolylthiadiazole;
Quinazolinonylthiadiazole.

INTRODUCTION

The chemistry of heterocyclic compounds has attracted attention in recent time due to its increasing importance in the field of pharmaceuticals and industries. Substitution pattern in thiadiazole derivatives play a pivotal role in delineating the biological activities like antibacterial[1,2], antifungal[3,4], anti-inflammatory[5]. Several scientistes have synthesized several thiadiazole derivatives which posses potent antibacterial activity. Further various derivatives of triazole[6] and quinazolinone[7] have also been reported to possess antibacterial activity. In light of above observations it was thought worthwhile to synthesized some new substituted thiadiazole derivatives by incorporation of triazole and quinazolinone moieties with the hope to get better antibacterial agents.

CHEMISTRY

Synthesis routes of thiadiazole derivatives are outlined in Scheme 1. Accordingly reaction of pyridine-4-carboxy hydrazide in methanolic solution with potassium hydroxide and carbon di sulfide afforded 4-amino-3-mercapto-5-pyridin-1,2,4-triazole **(1)**. Compound **(1)** converted into 6-methyl-5-(pyridine-4-yl)-[1,2,4] triazolo[3,4-b] [1,3,4]thiadiazole **(2)** by the reaction of acetic acid in dry phosphorous oxy chloride. 6-(bromomethyl)-5-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole **(3)** on reaction with 2-substituted alkyl/aryl-5-substituted-3-amino indoles yielded 2-

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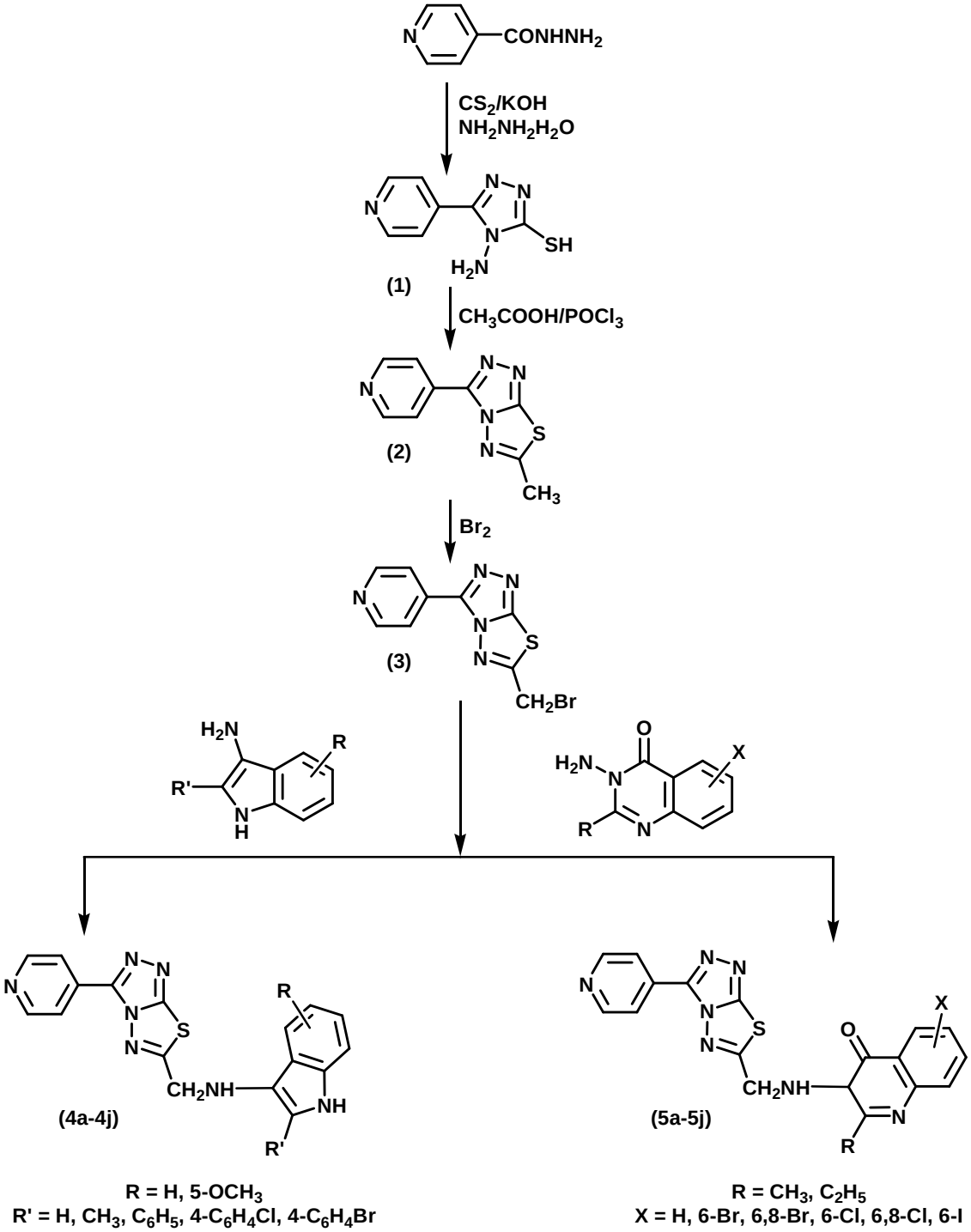


Scheme 1

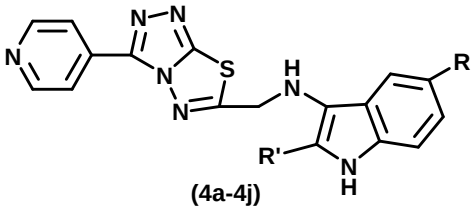
(substituted alkyl/aryl)-5-(substituted)-N-[3-(pyridin-4-yl)methyl]-1H indol-3-amino-[1,2,4] triazolo [3,4-b] [1,3,4] thiadiazoles **(4a-4j)**. 2-substituted-3-[3-(pyridin-4-yl)-6/6,8-substituted methyl amino] quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazoles **(5a-5l)** have been prepared by 6-(bromomethyl)-5-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole **(3)** with 2-substituted 6/6,8-substituted 3-amino quinazolinones.

EXPERIMENTAL

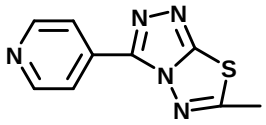
4-amino-3-mercapto-5-pyridin-1,2,4-triazole (1)

In methanolic solution of pyridine-4-carboxy hy-

TABLE 1a : Antibacterial activity of the compounds: 4-amino-3-mercapto-5-pyridin-1,2,4-triazole (1), 6-methyl-5-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole(2), 6-(bromomethyl)-5-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (3), N-((5-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b]-3-aminomethyl-5-substituted-1H-2-substituted indol-3-yl[1,3,4]-thiadiazoles(4a-4j)



(4a-4j)



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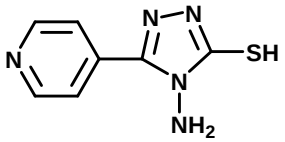

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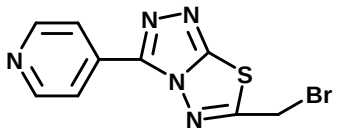

(3)

Compound no.	R	R'	Bacterial growth inhibition (diameter)				ALD_{50} Mg/Kg i.p
			S.aureus	E.coli	P.vulgaris	K.pneumoniae	
1	_	_	5mm	_	_	_	>1000
2	_	_	_	10mm	6mm	_	>1000
3	_	_	_	18mm	_	10mm	>1000
4a	_	H	12mm	14mm	_	15mm	>1000
4b	_	CH_3	_	18mm	_	_	>1000
4c	_	C_6H_5	16mm	20mm	18mm	_	>1000
4d	_	C_6H_4Cl	18mm	_	_	_	>1000
4e	_	C_6H_4Br	18mm	_			>1000
4f	OCH_3	H	20mm	_	19mm	_	>1000
4g	OCH_3	CH_3	_	_	_	_	>1000
4h	OCH_3	C_6H_6	22mm	20mm	_	18mm	>1000
4i	OCH_3	C_6H_4Cl	27mm	_	21mm	_	>2000
4j	OCH_3	$C6H_4Br$	_	24mm	_	22mm	>1000
Ampicillin			20mm	18mm	18mm	14mm	>1000
Gattifloxacin			25mm	22mm	20mm	21mm	>1000

drazide (1.0 mole), potassium hydroxide (1.5 mole) and carbon di sulfide (1.0 mole) were added and stirred for 4 hr. After stirrring excess of hydrazine hydrate was added and the mixture was further refluxed for 5 hr. The completion of the reaction was checked by TLC. The cooled reaction mixture was poured into ice water and neutralized with concentrate HCl. Thus obtained product was filtered, washed with water and recrystallized from methanol to yield compound 1 (95%), m.p.: 257°C; IR (KBr) ν_{max} in cm^{-1}: 3380 (NH_2), 3132 (aromatic CH stretching), 2585 (SH), 1612 (C = C of aromatic ring), 1608 (C = N), 1281 (N-N). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 11.65 (s, 1H, SH exchangeable with D_2O), 7.70-8.50 (m, 4H, Ar-H), 8.72 (s, 2H, NH_2 exchangeable with D_2O). Anal. Calcd. for $C_7H_7N_5S$: C, 43.51; H, 3.65; N, 36.24; Found: C, 43.45; H, 3.94; N, 36.49%; MS: $[M]^+$ at m/z 193.23.

6-methyl-5-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (2)

An equimolar mixture of triazole (1) (0.02 mole), acetic acid (0.02 mole) in dry phosphorous oxy chloride (10 ml) was refluxed for 7 hr. The reaction mixture cooled to room temperature and than gradually poured onto chrushed ice with stirring. Finally powdered potassium carbonate solid potassium hydroxide were added till PH of the mixture was raised to 8, to remove the excess of phosphorous oxycloride. The mixture was allowed to stand overnight and solid was separated. It was filtered, washed thoroughly with cold water, dry

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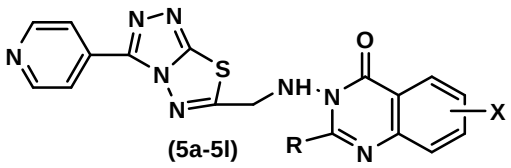
TABLE 1b : Antibacterial activity of the compounds: 2-Substituted-3-[3-(pyridin-4-yl)-6/6,8-substituted methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b][1,3,4]thiadiazoles (5a-5l)



(5a-5l)

Comp. no.	R	X	Bacterial growth inhibition (diameter)				ALD_{50} Mg/Kg i.p
			S.aureus	E.coli	P.vulgaris	K.pneumoniae	
5a	CH_3	H	-	16mm	-	-	>1000
5b	CH_3	6-Br	-	-	-	19mm	>1000
5c	CH_3	6,8-Br	17mm	18mm	17mm	-	>1000
5d	CH_3	6-Cl	25mm	18mm	20mm	21mm	>1000
5e	CH_3	6,8-Cl	19mm	-	-	-	>1000
5f	CH_3	6-I	16mm	15mm	17mm	16mm	>1000
5g	C_2H_5	H	-	12mm	-	-	>1000
5h	C_2H_5	6-Br	14mm	17mm	-	-	>1000
5i	C_2H_5	6,8-Br	-	15mm	-	16mm	>1000
5j	C_2H_5	6-Cl	18mm	-	-	15mm	>1000
5k	C_2H_5	6,8-Cl	17mm	-	16mm	-	>1000
5l	C_2H_5	6-I	12mm	-	13mm	-	>1000
Ampicillin			20mm	18mm	18mm	14mm	>1000
Gattifloxacin			25mm	22mm	20mm	21mm	>1000

and recystallized from ethanol to yield compound **(2)** (92%), m.p.: 265°C; IR (KBr) ν_{max} in cm^{-1}: 3134 (aromatic CH stretching), 1613 (C = C of aromatic ring), 1609 (C = N), 1507 (C-N), 1283 (N-N), 680 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.71-8.49 (m, 4H, Ar-H), 2.12 (s, 3H, CH_3). Anal. Calcd. for $C_9H_7N_5S$ C, 49.76; H, 3.25; N, 32.24; Found: C, 49.45; H, 3.44; N, 32.49% ; MS: $[M]^+$ at m/z 217.25.

6-(bromomethyl)-5-(pyridin-4-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole (3)

A mixture of compound **(2)** (0.1 mole), was suspended glacial acetic acid and bromine (0.2 mole) was added dropwise. After complete addition of bromine the reaction mixture was stirred for 4 hr and poured into cold water then left overnight at room temperature. The solid thus obtained was filtered, washed excess of with water, dried and recystallized from acetone to yield compound **(3)** (90%), m.p.: 276°C; IR (KBr) ν_{max} in cm^{-1}: 3130 (aromatic CH stretching), 1615 (C = C of aromatic ring), 1607 (C = N), 1285 (N-N), 1509 (C-N), 684 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.70-8.51 (m, 4H, Ar-H), 3.09 (s, 2H, CH_2Br). Anal. Calcd. for $C_9H_6BrN_5S$: C, 36.50; H, 2.04; N, 23.65; Found: C, 36.65; H, 2.24; N, 23.59% ; MS: $[M]^+$ at m/z 296.15.

2-(Substituted alkyl/aryl)-5-(substituted)-N-[3-(pyridin-4-yl)methyl]-1H indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (4a-4j)

A mixture of 6-(bromomethyl)-5-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole compound **(3)** (0.01 mole) and 2-substituted alkyl/aryl-5-substituted-3-amino indoles (0.01 mole) was refluxed in suitable solvent. The mixtures were poured into water. The solid thus obtained was filtered,washed with water, dried and recrystallized from appropriate solvents to yield compounds **(4a-4j)**.

N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4a)

Yield (87%), m.p.: 203°C; IR (KBr) ν_{max} in cm^{-1}: 3365 (NH), 3133 (aromatic CH stretching), 1613 (C = C of aromatic ring), 1608 (C = N), 1284 (N-N), 1508 (C-N), 683 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.80 (s, 1H, CH_2NH), 7.68-8.50 (m, 8H, Ar-H), 7.20 (s, 1H, NH exchangeable with D_2O), 7.10 (s, 1H, CH of indole), 3.11 (s, 2H, CH_2NH). Anal. Calcd. for $C_{17}H_{13}N_7S$: C, 58.77; H, 3.77; N, 28.22; Found: C, 58.45; H, 3.54; N, 28.49%; MS: $[M]^+$ at m/z 347.40.

2-methyl-N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (4b)

Yield 84%, (Petroleum ether), m.p.: 213°C; IR (KBr) ν_{max} in cm^{-1}: 3368 (NH), 3134 (aromatic CH stretching), 1614 (C = C of aromatic ring), 1607 (C = N), 1282 (N-N), 1506 (C-N), 681 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.90 (s, 1H, NH of indole), 7.71-8.51 (m, 8H, Ar-H), 7.21 (s, 1H, NH exchangeable with D_2O), 3.10 (s, 2H, CH_2NH), 2.13 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{15}N_7S$: C, 59.82; H, 4.18; N, 27.13; Found: C, 59.65; H, 4.34; N, 27.29% ; MS: $[M]^+$ at m/z 361.42.

2-phenyl-N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4c)

Yield 82%, (Ethanol), m.p.: 190°C; IR (KBr) ν_{max} in cm^{-1}: 3367 (NH), 3136 (aromatic CH stretching),

1616 (C = C of aromatic ring), 1609 (C = N), 1508 (C-N), 1284 (N-N), 683 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.85 (s, 1H, NH of indole), 7.72-8.50 (m, 13H, Ar-H), 7.24 (s, 1H, NH exchangeable with D_2O), 3.05 (s, 2H, CH_2NH). Anal. Calcd. for $C_{23}H_{17}N_7S$ C, 65.23; H, 4.05; N, 23.15; Found: C, 65.45; H, 4.24; N, 23.29% ; MS: $[M]^+$ at m/z 423.49.

2-(4-chlorophenyl)-N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4d)

Yield 80%, (DMF-water), m.p.: 215°C; IR (KBr) ν_{max} in cm^{-1}: 3362 (NH), 3131 (aromatic CH stretching), 1611 (C = C of aromatic ring), 1604 (C = N), 1503 (C-N), 1279 (N-N), 759 (C-Cl), 678 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.87 (s, 1H, NH of indole), 7.68-8.50 (m, 12H, Ar-H), 7.18 (s, 1H, NH exchangeable with D_2O), 3.03 (s, 2H, CH_2NH). Anal. Calcd. for $C_{23}H_{16}ClN_7S$: C, 60.32; H, 3.52; N, 21.41; Found: C, 60.55; H, 3.74; N, 21.69%; MS: $[M]^+$ at m/z 457.94.

2-(4-bromophenyl)-N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4e)

Yield 79%, (Acetone), m.p.: 228°C; IR (KBr) ν_{max} in cm^{-1}: 3368 (NH), 3137 (aromatic CH stretching), 1617 (C = C of aromatic ring), 1610 (C = N), 1509 (C-N), 1285 (N-N), 684 (C-S-C), 613 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.82 (s, 1H, NH of indole), 7.73-8.51 (m, 12H, Ar-H), 7.23 (s, 1H, NH exchangeable with D_2O), 3.04 (s, 2H, CH_2NH). Anal. Calcd. for $C_{23}H_{16}BrN_7S$: C, 54.99; H, 3.21; N, 19.52; Found: C, 54.69H, 3.11N, 19.29%; MS: $[M]^+$ at m/z 502.39.

5-methoxy-N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4f)

Yield 76%, (Methanol), m.p.: 222°C; IR (KBr) ν_{max} in cm^{-1}: 3363 (NH), 3132 (aromatic CH stretching), 1612 (C = C of aromatic ring), 1605 (C = N), 1504 (C-N), 1280 (N-N), 1227 (OCH_3), 679 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.82 (s, 1H, NH of indole), 7.69-8.50 (m, 7H, Ar-H), 7.29 (s, 1H, NH exchangeable with D_2O), 7.04 (s, 1H, CH of indol), 3.36 (s, 3H, OCH_3), 3.05 (s, 2H, CH_2NH). Anal. Calcd. for $C_{18}H_{15}N_7OS$ C, 57.28; H, 4.01; N, 25.98; Found: C, 57.55H, 4.24N, 25.59% ; MS: $[M]^+$ at m/z 377.42.

2-methyl-5-methoxy-N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4g)

Yield 73%, (DMF-water), m.p.: 235°C; IR (KBr) ν_{max} in cm^{-1}: 3368 (NH), 3137 (aromatic CH stretching), 1617 (C = C of aromatic ring), 1609 (C = N), 1509 (C-N), 1285 (N-N), 1231 (OCH_3), 684 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.83 (s, 1H, NH of indole), 7.71-8.52 (m, 7H, Ar-H), 7.23 (s, 1H, NH exchangeable with D_2O), 3.35 (s, 3H, OCH_3), 3.04 (s, 2H, CH_2NH), 2.11 (s, 3H, CH_3). Anal. Calcd. for $C_{19}H_{17}N_7OS$: C, 58.30; H, 4.38; N, 25.05; Found: C, 58.75; H, 4.74; N, 25.29% ; MS: $[M]^+$ at m/z 391.45.

2-phenyl-5-methoxy-N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4h)

Yield 72%, (Petroleum ether), m.p.: 224°C; IR (KBr) ν_{max} in cm^{-1}: 3363 (NH), 3132 (aromatic CH stretching), 1612 (C = C of aromatic ring), 1605 (C = N), 1504 (C-N), 1280 (N-N), 1227 (OCH_3), 680 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.89 (s, 1H, NH of indole), 7.70-8.50 (m, 12H, Ar-H), 7.20 (s, 1H, NH exchangeable with D_2O), 3.36 (s, 3H, OCH_3), 3.10 (s, 2H, CH_2NH). Anal. Calcd. for $C_{24}H_{19}N_7OS$ C, 63.56; H, 4.22; N, 21.62; Found: C, 63.75; H, 4.44; N, 21.89% ; MS: $[M]^+$ at m/z 453.52.

2-(4-chlorophenyl)-N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4i)

Yield 70%, (Ethanol), m.p.: 240°C; IR (KBr) ν_{max} in cm^{-1}: 3365 (NH), 3134 (aromatic CH stretching), 1614 (C = C of aromatic ring), 1607 (C = N), 1282 (N-N), 1506 (C-N), 760 (C-Cl) ,681 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.90 (s, 1H, NH of indole), 7.71-8.52 (m, 11H, Ar-H), 7.21 (s, 1H, NH exchangeable with D_2O), 3.39 (s, 3H, OCH_3), 3.02 (s, 2H, CH_2NH). Anal. Calcd. for $C_{24}H_{18}ClN_7OS$ C, 59.07; H, 3.72; N, 20.09; Found: C, 59.35; H,

3.94; N, 20.29% ; MS: $[M]^+$ at m/z 487.96.

2-(bromophenyl)-N-[5-(pyridin-4-yl)methyl]-1H-indol-3-amino-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (4j)

Yield 69%, (Acetone), m.p.: 246°C; IR (KBr) ν_{max} in cm^{-1}: 3361 (NH), 3130 (aromatic CH stretching), 1610 (C = C of aromatic ring), 1603 (C = N), 1502 (C-N), 1278 (N-N), 678 (C-S-C), 611 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 8.86 (s, 1H, NH of indole), 7.68-8.50 (m, 11H, Ar-H), 7.19 (s, 1H, NH exchangeable with D_2O), 3.35 (s, 3H, OCH_3), 3.09 (s, 2H, CH_2NH). Anal. Calcd. for $C_{24}H_{18}BrN_7OS$ C, 54.14; H, 3.41; N, 18.42; Found: C, 54.45; H, 3.24; N, 18.29% ; MS: $[M]^+$ at m/z 532.42.

2-Substituted-3-[3-(pyridin-4-yl)-6/6,8-substituted methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo [3,4-b][1,3,4]thiadiazoles (5a-5l)

A mixture of 6-(bromomethyl)-5-(pyridin-4-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole\ **(3)** (0.01 mole) and 2-substituted 6/6,8-substituted 3-amino quinazolinones (0.01 mole) were refluxed in dry benzene (50ml) in the presence of potassium carbonate. The mixtures were poured into water and the solid thus obtained was filtered, washed with water and dried recrystallized from appropriate solvents to yield compounds **(5a-5l)**.

2-methyl-3-[5-(pyridin-4-yl) methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b][1,3,4]thiadiazoles (5a)

Yield (67%), m.p.: 193°C; IR (KBr) ν_{max} in cm^{-1}: 3365 (NH), 3134 (aromatic CH stretching), 1614 (C = C of aromatic ring), 1607 (C = N), 1506 (C-N), 1282 (N-N), 681 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.71-8.50 (m, 8H, Ar-H), 7.21 (s, 1H, NH exchangeable with D_2O), 3.12 (s, 2H, CH_2NH), 2.10 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{14}N_8OS$: C, 55.37; H, 3.61; N, 28.70; Found: C, 55.65; H, 3.94; N, 28.99% ; MS: $[M]^+$ at m/z 390.42.

2-methyl-3-[5-(pyridin-4-yl)-6-bromo methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazoles (5b)

Yield 66%, (Petroleum ether), m.p.: 195°C; IR (KBr) ν_{max} in cm^{-1}: 3362 (NH), 3131 (aromatic CH stretching), 1611 (C = C of aromatic ring), 1604 (C = N), 1503 (C-N), 1279 (N-N), 678 (C-S-C). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.69-8.51 (m, 7H, Ar-H), 7.19 (s, 1H, NH exchangeable with D_2O), 3.10 (s, 2H, CH_2NH), 2.10 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{13}BrN_8OS$: C, 46.07; H, 2.79; N, 23.88; Found: C, 46.15; H, 2.54; N, 23.69%; MS: $[M]^+$ at m/z 469.32.

2-methyl-3-[5-(pyridin-4-yl)-6,8-dibromo methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b][1,3,4]thiadiazoles (5c)

Yield 65%, (ethanol), m.p.: 201°C; IR (KBr) ν_{max} in cm^{-1}: 3366 (NH), 3134 (aromatic CH stretching), 1638 (C = O), 1610 (C = C of aromatic ring), 1606 (C = N), 1505 (C-N), 1278 (N-N), 679 (C-S-C), 611 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.68-8.49 (m, 6H, Ar-H), 7.18 (s, 1H, NH exchangeable with D_2O), 3.11 (s, 2H, CH_2NH), 2.09 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{12}Br_2N_8OS$: C, 39.44; H, 2.21; N, 20.44; Found: C, 39.27; H, 2.52; N, 20.60%; MS: $[M]^+$ at m/z 548.21.

2-methyl-3-[5-(pyridin-4-yl)-6-chloro methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazoles (5d)

Yield 63%, (acetone), m.p.: 190°C; IR (KBr) ν_{max} in cm^{-1}: 3365 (NH), 3134 (aromatic CH stretching), 1643 (C = O), 1615 (C = C of aromatic ring), 1609 (C = N), 1506 (C-N), 1280 (N-N), 681 (C-S-C), 612 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.71-8.50 (m, 7H, Ar-H), 7.22 (s, 1H, NH exchangeable with D_2O), 3.04 (s, 2H, CH_2NH), 2.10 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{13}ClN_8OS$: C, 50.88; H, 3.08; N, 26.37; Found: C, 41.57; H, 2.35; N, 21.66%; MS: $[M]^+$ at m/z 424.87.

2-methyl-3-[5-(pyridin-4-yl)-6,8-dichloro methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazoles (5e)

Yield 61%, (ethanol), m.p.: 198°C; IR (KBr) ν_{max} in cm^{-1}: 3369 (NH), 3135 (aromatic CH stretching), 1646 (C = O), 1619 (C = C of aromatic ring), 1611 (C = N), 1511 (C-N), 1290 (N-N), 685 (C-S-C), 762 (C-Cl). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.69-8.51 (m, 6H, Ar-H), 7.20 (s, 1H, NH exchange-

able with D_2O), *3.05* (s, 2H, CH_2NH), 2.09 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{12}Cl_2N_8OS$: C, 47.07; H, 2.63; N, 24.40; Found: C, 50.57; H, 3.32; N, 26.57%; MS: $[M]^+$ at m/z 459.31.

2-methyl-3-[5-(pyridin-4-yl)-6-iodo methyl amino] quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazole (5f)

Yield 58%, (DMF-water), m.p.: 212°C; IR (KBr) ν_{max} in cm^{-1}: 3364 (NH), 3131 (aromatic CH stretching), 1638 (C = O), 1616 (C = C of aromatic ring), 1605 (C = N), 1505 (C-N), 1283 (N-N), 679 (C-S-C), 768 (C-Cl). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.70-8.50 (m, 7H, Ar-H), 7.19 (s, 1H, NH exchangeable with D_2O), 3.02 (s, 2H, CH_2NH), 2.11 (s, 3H, CH_3). Anal. Calcd. for $C_{18}H_{13}IN_8OS$: C, 41.87; H, 2.54; N, 21.70; Found: C, 41.57; H, 2.45; N, 21.52%; MS: $[M]^+$ at m/z 516.32.

2-ethyl-3-[5-(pyridin-4-yl) methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b][1,3,4]thiadiazole (5g)

Yield 54%, (Petroleum ether), m.p.: 176°C; IR (KBr) ν_{max} in cm^{-1}: 3368 (NH), 3139 (aromatic CH stretching), 1649 (C = O), 1615 (C = C of aromatic ring), 1609 (C = N), 1281 (N-N), 1503 (C-N), 680 (C-S-C), 610 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.70-8.51 (m, 8H, Ar-H), 7.21 (s, 1H, NH exchangeable with D_2O), 3.01 (s, 2H, CH_2NH), 2.21 (m, 2H, CH_2), 2.09 (t, 3H, CH_3). Anal. Calcd. for $C_{19}H_{16}N_8OS$: C, 56.42; H, 3.99; N, 27.71; Found: C, 50.66; H, 3.87; N, 27.50%; MS: $[M]^+$ at m/z 404.45.

2-ethyl-3-[5-(pyridin-4-yl)-6-bromo methyl amino] quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazole (5h)

Yield 52%, (methanol), m.p.: 182°C; IR (KBr) ν_{max} in cm^{-1}: 3363 (NH), 3136 (aromatic CH stretching), 1648 (C = O), 1614 (C = C of aromatic ring), 1602 (C = N), 1281(N-N), 1506 (C-N), 681 (C-S-C), 612 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.71-8.50 (m, 7H, Ar-H), 7.24 (s, 1H, NH exchangeable with D_2O), 3.01 (s, 2H, CH_2NH), 2.20 (m, 2H, CH_2), 2.08 (t, 3H, CH_3). Anal. Calcd. for $C_{19}H_{15}BrN_8OS$ C, 47.21; H, 3.13; N, 23.18; Found: C, 47.36; H, 3.27; N, 23.39%; MS: $[M]^+$ at m/z 483.34.

2-ethyl-3-[5-(pyridin-4-yl)-6,8-dibromo methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazole (5i)

Yield 48%, (acetone), m.p.: 192°C; IR (KBr) ν_{max} in cm^{-1}: 3367 (NH), 3139 (aromatic CH stretching), 1646 (C = O), 1612 (C = C of aromatic ring), 1607 (C = N), 1282 (N-N), 1508 (C-N), 683 (C-S-C), 610 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.69-8.48 (m, 6H, Ar-H), 7.25 (s, 1H, NH exchangeable with D_2O), 3.03 (s, 2H, CH_2NH), 2.22 (m, 2H, CH_2), 2.09 (t, 3H, CH_3). Anal. Calcd. for $C_{19}H_{14}Br_2N_8OS$: C, 40.59; H, 2.51; N, 19.93; Found: C, 40.68; H, 2.47; N, 19.76%; MS: $[M]^+$ at m/z 562.24.

2-ethyl-3-[5-(pyridin-4-yl)-6-chloro methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazole (5j)

Yield 45%, (Petroleum ether), m.p.: 187°C; IR (KBr) ν_{max} in cm^{-1}: 3364 (NH), 3138 (aromatic CH stretching), 1648 (C = O), 1614 (C = C of aromatic ring), 1608 (C = N), 1280 (N-N), 1502 (C-N), 680 (C-S-C), 611 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.71-8.50 (m, 7H, Ar-H), 7.21 (s, 1H, NH exchangeable with D_2O), 3.01 (s, 2H, CH_2NH), 2.25 (m, 2H, CH_2), 2.10 (t, 3H, CH_3). Anal. Calcd. for $C_{19}H_{15}ClN_8OS$: C, 52.00; H, 3.44; N, 25.53; Found: C, 52.21; H, 3.67; N, 25.48%; MS: $[M]^+$ at m/z 438.89.

2-ethyl-3-[5-(pyridin-4-yl)-6,8-dichloro methyl amino]quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazole (5k)

Yield 41%, (ethanol), m.p.: 192°C; IR (KBr) ν_{max} in cm^{-1}: 3369 (NH), 3134 (aromatic CH stretching), 1646 (C = O), 1616 (C = C of aromatic ring), 1605 (C = N), 1281 (N-N), 1509 (C-N), 684 (C-S-C), 610 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.70-8.52 (m, 6H, Ar-H), 7.24 (s, 1H, NH exchangeable with D_2O), 3.05 (s, 2H, CH_2NH), 2.23 (m, 2H, CH_2), 2.08 (t, 3H, CH_3). Anal. Calcd. for $C_{19}H_{14}Cl_2N_8OS$: C, 48.21; H, 2.98; N, 23.67; Found: C, 48.35; H, 2.77; N, 23.49%; MS: $[M]^+$ at m/z 473.34.

2-ethyl-3-[5-(pyridin-4-yl)-6-iodo methyl amino] quinazolin-4(3H)-one-[1,2,4]trizolo[3,4-b] [1,3,4]thiadiazole (5l)

Yield 37%, (DMF-water), m.p.: 198°C; IR (KBr) ν_{max} in cm^{-1}: 3364 (NH), 3133 (aromatic CH stretching), 1649 (C = O), 1617 (C = C of aromatic ring), 1602 (C = N), 1284 (N-N), 1504 (C-N), 682 (C-S-C), 612 (C-Br). ^{1}HNMR ($CDCl_3$ + DMSO-d_6) δ in ppm: 7.71-8.51 (m, 7H, Ar-H), 7.20 (s, 1H, NH exchangeable with D_2O), 3.01 (s, 2H, CH_2NH), 2.22 (m, 2H, CH_2), 2.06 (t, 3H, CH_3). Anal. Calcd. for $C_{19}H_{15}IN_8OS$: C, 43.03;H, 2.85; N, 21.13; Found: C, 43.16; H, 2.65; N, 21.29%; MS: $[M]^+$ at m/z 530.34.

RESULTS AND DISCUSSION

Various substituted derivatives of thiadiazol were synthesized and screened for their anti bacterial activity. The pharmacological results of the compounds have been reported in TABLE 1a-b. Compound **(1)** exhibited zone of inhibition 5mm against *S.aureus*. Compound **(2)** obtained by the cyclization of compound **(1)**. It was found that compound **(1)** resulted in to increase of antibacterial activity as shown by compound **(2)**. Compound **(3)** showed zone of inhibition diameter of 18mm against *E.coli*, 10mm against *K.pneumoniae*.

The addition of various 3-amino-5-substituted 1H indoles with thiadiazole nucleus yielded compounds **(4a-4j)**. Among the compounds **(4a-4j)**, compounds **(4a)** and **(4b)** showed moderate antibacterial activity. Compound **(4c)** exhibited zone of inhibition 16mm against *S.aureus*, 20mm against *E.coli* and 18mm against *P.vulgaris*. Presense of OCH_3 gp. at 5 position of indole in compounds **(4f-4j)** enhances the antibacterial activity. Compound **(4f)** exhibited zone of inhibition 20mm against *S.aureus*, 19mm against *P.vulgaris*. Compound **(4h)** exhibited zone of inhibition 22mm against *S.aureus*, 20mm against *E.coli*, 18mm against *K.pneumoniae*. The compounds **(4i)** and **(4j)** showed better antibacterial activity than standard drugs by showing inhibition zone of defferent diameter as 27mm (*S.aureus*), 21mm (*P.vulgaris*) and 24mm (*E.coli*), 22mm (*K.Pneumoniae*).

The addition of various mono/di substituted quinazolines with thiadiazole nucleus yielded compounds **(5a-5l)**. Among the compounds **(5a-5f)** having CH_3 gp. at 2 position of quinazoline, compound **(5d)** was found to exhibited equipotent antibacterial activity than reference drug. Compounds **(5a)**, **(5b)**, **(5c)**, **(5e)** and **(5f)** showed moderate zone of inhibition against various used pathogens. The compounds **(5g-5l)** having C_2H_5 gp. at 2 position of quinazoline have shown less antibacterial activity than compounds **(5a-5f)**. The synthesized compounds were also tested for approximate lethal dose ALD_{50} and were found to exhibit a higher value of ALD_{50} i.e. more than 1000mg/kg i.p. except compound **(4i)** which exhibited ALD_{50} of more than 2000mg/kg i.p. (maximum dose tested). As these compounds have shown high value of ALD_{50} thus indicating good safety margin.

While considering all the newly synthesized compounds of this series we may concluded that:

1 Compounds **(4f-4j)** having OCH_3 gp.at 5 position of indole had shown good antibacterial activity.
2 Presence of electronegative(i.e chlorine) atoms at 4 positions of indole ring in general beneficial for antibacterial activity.
3 Compounds **(4i)** and **(4j)** showed better antibacterial activity than standard drugs.
4 Compound **(5d)** exhibited equipotent antibacterial activity than reference drug.

PHARMACOLOGICAL EVALUATION (ANTIBACTERIAL ACTIVITY)

All the synthesized compounds were tested for their antibacterial activity. The effect of unknown compounds were compared with the standard drug Ampicillin and Gattifloxacin and propylene glycol treated group served as control. All the newly synthesized compounds were also screened for their approximate lethal dose (ALD_{50}).

Cup-Plate Method (CUPS): This activity was performed by following the method of Chuinckshank et. al.[8] in albino rats. Nutrient agar was poured onto the sterilized petri dishes (20-25mL each pertri dish). The poured material was allowed to set (1-1.5 h) and thereafter the "CUPS" (10 mm diameter) were made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into these cups the test compound solution was added with the help of sterile syringe. The plates were incubated at

37°C for 48 hr and the results were noted. A solvent control (10% DMSO in methanol) was also run to not the activity of the blank (solvent). The above said standard drugs were also screened under similar conditions for comparison.

Approximate lethal dose (ALD_{50}): The LD_{50} was determined in albino rats weighing 100-120gm of either sex by the method of Smith[9]. The test compounds were administered by i.p. route in one group and the same volume of propylene glycol in another group of animals consisting six rats in graded doses. The animals were allowed to take food and water adlibidum. After 24 h of drug administration percent mortality in each group was observed. From the data obtained ALD_{50} was calculated.

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