SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF SOME SUBSTITUTED PYRAZOLYL AND PYRAZOLINYL-1, 3, 4-THIADIAZINO (6,5-b) INDOLES.

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ABSTRACT

Several N-\{5-(1’-phenyl-5’-(substituted aryl)-2’-pyrazol-3’-yl)amino\}-1,3,4-thiadiazol-2-yl methylamino[1,3,4]thiadiazino(6,5-b)indole 8(a-i) and N-\{5-(1’-Acetyl-5’-(substituted aryl)-2’-pyrazolin-3’-yl)-amino\}-1,3,4-thiadiazol-2-yl methyl amino[1,3,4]thiadiazino(6,5-b)indole 9(a-i) have been synthesized from N-\{(5-(Arylidinylacetyl)amino)-1,3,4-thiadiazol-2-yl\} methy lamino]-1,3,4-thiadiazino(6,5-b) indole 7(a-i). All the synthesized compounds have been characterized by elemental and spectral (I.R., \(^1\)H- NMR, Mass) analysis. Furthermore, above said compounds were evaluated for their antifungal and antibacterial activities. Compound 9c was found the most potent one with lesser toxicity in this series.

Keywords: Indoles, antifungal, antibacterial, acute toxicity.

INTRODUCTION

The continual development of antimicrobial drugs represents one of the major medical milestones of the twentieth century. Nevertheless, resistance to commonly used agents has appeared shortly after the introduction of most agents. New infectious diseases and increasing prevalence of drug-resistant pathogens highlight the need for new antimicrobial drugs. Traditional methods of preparation of bioactive agents have been joined by molecular manipulation strategies. Infectious diseases are a clear cut threat to the physical health and economic well-being of the world irrespective of site of residence. Among a number of deferent biological active heterocyclic moieties, the indole nucleus constitutes an important block in numerous natural or synthetic alkaloids\(^1,2\) and in medicinal chemistry.\(^3\) Due to the existence of a vast array of structurally diverse and biologically active indoles, it is not surprising that the indole nucleus is an important feature in many medicinal agents and the most important of all structural classes in drug discovery.\(^4\) The synthesis and reactivity of indole derivatives have been a topic of research interest for well over a century. Bulk of literature evidence revealed wide spectrum of biological activities of indole and its analogs as anti-inflammatory,\(^5-9\) anticonvulsant,\(^10\) antitumour,\(^11\) antimicrobial,\(^12\) antibacterial,\(^13,14\) antifungal.\(^15\) Likewise thiadiazole,\(^16,17\) pyrazole\(^18-21\) and pyrazoline\(^22-23\) congeners have also been found to exhibit various biological properties. These observations encouraged us to design a drug strategy to synthesize several indole derivatives possessing pyrazole and pyrazoline moieties at its 2\(^{nd}\) position. The newly prepared compounds were evaluated for antifungal and antibacterial activities.

EXPERIMENTAL

Materials

All the chemicals used for the preparation of desired derivatives, were obtained from Sisco Research Laboratories (SRL), Mumbai, India; Qualigen Fine Chemicals, Mumbai, India; E. Merck Ltd.,...
New Delhi, India. Reference drugs ampicillin trihydrate and fluconazole were procured from Ind-Swift Pharmaceutical, Panjab, India and Macleods Pharmaceutical, Mumbai, India respectively.

**Equipment**

The melting points of the compounds were determined in open glass capillaries with the help of thermonic melting points apparatus (Campbell Electronics, Mumbai, India) and are uncorrected. The homogeneity of all the newly synthesized compounds were routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber. Elemental analysis was performed in Heraeus CHN rapid analyser. The results were found within the ±0.4% of theoretical values. Infrared spectra were recorded on KBr pellets on a Perkin Elmer system 200 FTIR spectrometer and $^1$H- NMR spectra on Bruker DPX 200 using TMS as internal standard.

**Synthesis**

Compounds 1 and 2 were synthesized according to the earlier reported method.24

### Preparation of 2-Carboethoxymethylamino-1, 3, 4-thiadiazino (6, 5-b) indole (3)

A mixture of compound 2 (0.01 mmol) and chloroethylacetate (0.02 mmol) in dry dioxane was refluxed for 8 h. The reaction mixture was further stirred for 1 h, and poured in water. The resulting mixture was filtered and recrystallized from ethanol to yield compound 3: Yield: 71%, Rf 0.70, m.p. 223°C. Anal. Calcd. for C$_{13}$H$_2$N$_2$O$_2$: S: calcd.C, 49.16; H, 4.16; N, 34.64%. Found: C, 49.04; H, 4.10; N, 34.65%. IR(KBr, cm$^{-1}$): 3148 (C-H aliphatic), 2975 (C-H aliphatic), 1700 (C=O), 1615 (C…C aromatic ring), 1572 (C=N), 1295 (C-N), 1245 (C-N), 715 (CH$_3$), 681 (C-S-C). $^1$H NMR (DMSO-d$_6$, δ / ppm): 3.89 (s, 3H, OCH$_3$), 4.25 (q, 2H-COOCH$_2$), 4.47 (d, 2H, NH-CH$_2$), 7.25 (m, 5H, Ar-H), 7.06 (t, 1H, NH, exchangeable with D$_2$O), 4.55 (d, 2H, NH-CH$_2$). MS (m/z): 288 (M)$^+$.  

### 2-(Thiosemicarbazido carbonylmethylamino)-1,3,4-thiadiazino (6,5-b) indole (4)

The equimolar mixture (0.01 mmol) of compound 3 and thiosemicarbazide (0.01 mmol) in methanol was refluxed for 8 h. The excess of solvent was distilled off and viscous mass was poured into water, and recrystallized from methanol to yield compound 4: Yield: 75%, Rf 0.70, m.p. 229°C. Anal. Calcd. for C$_{13}$H$_2$N$_2$O$_2$: S: calcd.C, 49.16; H, 4.16; N, 34.64%. Found: C, 49.20; H, 4.32; N, 34.62%. IR(KBr, cm$^{-1}$): 3148 (C-H aromatic), 3185 (N-H), 2950 (C-H aliphatic), 2870 (CH$_3$), 1696 (C=O), 1612 (C…C of aromatic ring), 1572 (C=N), 1295 (C-N), 1245 (C-N), 715 (CH$_3$), 681 (C-S-C). $^1$H NMR (DMSO-d$_6$, δ / ppm): 6.95-7.15 (m, 4H, Ar-H), 6.10 (t, 1H, NH, exchangeable with D$_2$O), 4.47 (d, 2H, NH-CH$_2$), 1.45 (t, 3H, COOCH$_2$-CH$_3$). MS (m/z): 333 (M)$^+$.  

### 2-[(5-Amino-1,3,4-thiadiazol-2-yl)methylamino]-1,3,4-thiadiazino (6,5-b) indole (5)

A mixture of compound 4 (0.01 mmol) and conc. H$_2$SO$_4$ (10 ml) was kept overnight at room temperature, poured into ice-cold water, neutralized with liquid ammonia and filtered. The product thus obtained was recrystallized from ethanol-water to furnish compound 5: Yield 80%, Rf 0.60, m.p. 257°C. Anal. Calcd. for C$_{13}$H$_2$N$_2$O$_2$: S: calcd.C, 49.16; H, 4.16; N, 34.64%. Found: C, 49.20; H, 3.32; N, 34.60%. IR(KBr, cm$^{-1}$): 3370 (NH$_2$), 3178 (NH), 3140(C-H aromatic), 2965 (C-H aliphatic), 1615 (C…C of aromatic ring), 1572 (C=N), 1294 (C-N), 1245 (C-N), 676 (C-S-C). $^1$H NMR (DMSO-d$_6$, δ / ppm): 7.05-7.30 (m, 4H, Ar-H), 6.26 (bs,2H, NH$_2$), 5.75 (s, 1H, NH, exchangeable with D$_2$O), 4.55 (d, 2H, NH-CH$_2$). MS (m/z): 315 (M)$^+$. N-[5-(Acetylamino)-1, 3, 4-thiadiazol-2-yl] methylamino]-1, 3, 4-thiadiazino (6,5-b) indole (6)

To a solution of compound 5 (0.015 mmol) in methanol, acetyl chloride (0.015 mmol) was added drop wise with constant stirring at a temperature of 0-5°C. The reaction mixture was stirred for 4h further at room temperature and then refluxed for 5h. The completion of reaction was checked by TLC and excess of solvent was distilled out. The cooled, refluxed residue was poured into ice-water, filtered, dried and recrystallised from methanol-water to obtain compound 6: Yield 71%, Rf 0.80, m.p. 190°C. Anal. Calcd. for C$_{14}$H$_2$N$_2$O$_2$: C, 47.05; H, 3.08; N, 27.45%. Found: C, 47.00; H, 3.30; N, 27.50%. IR(KBr, cm$^{-1}$): 3172 (NH), 3145(C…H aromatic), 2965 (C-H aliphatic), 1615 (C…C of aromatic ring), 1572 (C=N), 1294 (C-N), 1245 (C-N), 676 (C-S-C). $^1$H NMR (DMSO-d$_6$, δ / ppm): 8.42...
of few drops of aq. 2% NaOH solution for 12 h, while progress and completion of reaction was routinely filtered. The solid mass thus separated out was crystallized from appropriate solvents to give compounds observed by TLC. The reaction mixture was distilled off, cooled then poured onto crushed ice and filtered. The solid mass thus separated out, was crystallized from appropriate solvents to give compounds 7a, 7c, 7d, 7e, 7f, 7g, 7h and 7i.

(7a): Yield 68%. Rf 0.60, m. p. 199 °C. Anal. Calcd. for C$_2$H$_12$N$_2$O: C, 56.62; H, 3.37; N, 22.02%. Found: C, 56.60; H, 3.30; N, 22.06%. IR(KBr, cm$^{-1}$): 3174(NH), 3141(C…H aromatic), 2964 (C-H aliphatic), 1692(C=O), 1610 (C–C of aromatic ring), 1572 (C=N), 1292(N-N), 1240(C-N), 680(C-S-C). $^1$H NMR (DMSO-$d_6$, δ/ppm): 8.45 (brs, 1H, NHCO), 6.60-7.05 (m, 9H, Ar-H), 6.65(d, 1H, CH-R), 6.20(d, 1H, CH-CO), 5.66(s, 1H, NH, exchangeable with D$_2$O), 4.60(d, 2H, NH-CH$_2$). MS (m/z): 437 (M$^+$).

(7b): Yield 60%. Rf 0.72, m. p. 190 °C. Anal. Calcd. for C$_2$H$_14$N$_2$S$_2$OCl: C, 52.55; H, 2.91; N, 20.43%. Found: C, 52.60; H, 2.86; N, 20.40%. IR(KBr, cm$^{-1}$): 3172(NH), 3145(C…H aromatic), 2966 (C-H aliphatic), 1690(C=O), 1613 (C–C of aromatic ring), 1574 (C=N), 1289(N-N), 1240(C-N), 790(C-Cl), 682(C-S-C). $^1$H NMR (DMSO-$d_6$, δ/ppm): 8.42(brs, 1H, NHCO), 6.80-7.30 (m, 8H, Ar-H), 6.66(d, 1H, CH-R), 6.22(d, 1H, CH-CO), 5.66(s, 1H, NH, exchangeable with D$_2$O), 4.60(d, 2H, NH-CH$_2$). MS (m/z): 479.5 (M$^+$).

(7c): Yield 66%, Rf 0.70, m. p. 179 °C. Anal. Calcd. for C$_2$H$_{14}$N$_2$S$_2$OCl: C, 52.55; H, 2.91; N, 20.43%. Found: C, 52.62; H, 2.86; N, 20.41%. IR(KBr, cm$^{-1}$): 3174(NH), 3140(C…H aromatic), 2964 (C-H aliphatic), 1689 (C=O), 1612 (C–C of aromatic ring), 1570 (C=N), 1292(N-N), 1239(N-C), 788(C-Cl), 680(C-S-C). $^1$H NMR (DMSO-$d_6$, δ/ppm): 8.44 (brs, 1H, NHCO), 6.75-7.15 (m, 8H, Ar-H), 6.62(d, 1H, CH-R), 6.25 (d, 1H, CH-CO), 5.60(s, 1H, NH, exchangeable with D$_2$O), 4.62(d, 2H, NH-CH$_2$). MS (m/z): 479.5 (M$^+$).

(7d): Yield 64%, Rf 0.65, m. p. 191 °C. Anal. Calcd. for C$_2$H$_{12}$N$_2$S$_2$O$_2$: C, 55.57; H, 3.57; N, 20.63%. Found: C, 55.60; H, 3.56; N, 20.60%. IR(KBr, cm$^{-1}$): 3170 (NH), 3142 (C…H aromatic), 2962 (C-H aliphatic), 1691(C=O), 1614 (C–C of aromatic ring), 1573 (C=N), 1292(N-N), 1241(C-N), 1170 (C-O-C), 686(C-S-C). $^1$H NMR (DMSO-$d_6$, δ/ppm): 8.41 (brs, 1H, NHCO), 6.70-7.22 (m, 8H, Ar-H), 6.62(d, 1H, CH-R), 6.22(d, 1H, CH-CO), 5.66(s, 1H, NH, exchangeable with D$_2$O), 4.65(d, 2H, NH-CH$_2$), 3.40(s, 3H, ArOCH$_3$). MS (m/z): 475 (M$^+$).

(7e): Yield 68%, R 0.66, m. p. 201 °C. Anal. Calcd. for C$_2$H$_{17}$N$_2$S$_2$O$_2$: C, 55.57; H, 3.57; N, 20.63%. Found: C, 55.61; H, 3.55; N, 20.68%. IR(KBr, cm$^{-1}$): 3175(NH), 3148 (C…H aromatic), 2961 (C-H aliphatic), 1690(C=O), 1612 (C–C of aromatic ring), 1572 (C=N), 1280(N-N), 1240(C-N), 1172 (C-O-C), 680(C-S-C). $^1$H NMR (DMSO-$d_6$, δ/ppm): 8.44 (brs, 1H, NHCO), 6.72-7.24 (m, 8H, Ar-H), 6.60(d, 1H, CH-R), 6.20 (d, 1H, CH-CO), 5.60 (s, 1H, NH, exchangeable with D$_2$O), 4.56(d, 2H, NH-CH$_2$), 3.45(s, 3H, ArOCH$_3$). MS (m/z): 475 (M$^+$).

(7f): Yield 59%, Rf 0.71, m. p. 207 °C. Anal. Calcd. for C$_2$H$_{15}$N$_2$S$_2$O$_2$: C, 54.66; H, 3.25; N, 21.25%. Found: C, 54.60; H, 3.26; N, 21.20%. IR(KBr, cm$^{-1}$): 3410(OH), 3174(NH), 3142 (C…H aromatic), 2964(C-H aliphatic), 1689(C=O), 1610(C–C of aromatic ring), 1575 (C=N), 1282(N-N), 1238(C-N), 685 (C-S-C). $^1$H NMR (DMSO-$d_6$, δ/ppm): 10.00 (s, 1H, ArOH), 8.41 (brs, 1H, NHCO), 6.70-7.30 (m, 8H, Ar-H), 6.64 (d, 1H, CH-R), 6.22 (d, 1H, CH-CO), 5.62 (s, 1H, NH, exchangeable with D$_2$O), 4.61 (d, 2H, NH-CH$_2$). MS (m/z): 461 (M$^+$).

(7g): Yield 58%, Rf 0.68, m. p. 169 °C. Anal. Calcd. for C$_2$H$_{17}$N$_2$S$_2$O$_2$: C, 53.76; H, 3.46; N, 19.95%. Found: C, 53.70; H, 3.46; N, 20.00%. IR(KBr, cm$^{-1}$): 3415(OH), 3174(NH), 3143 (C…H aromatic), 2964 (C-H aliphatic), 1689(C=O), 1612(C–C of aromatic ring), 1575 (C=N), 1282 (N-N), 1238(C-N), 1170 (C-O-C), 685(C-S-C). $^1$H NMR (DMSO-$d_6$, δ/ppm): 10.25(S, 1H, Ar-OH), 8.36(brs, 1H, NHCO), 6.62-7.15(m, 7H, Ar-H), 6.50(d, 1H, CH-R), 6.20(d, 1H, CH-CO), 5.62 (s, 1H, NH, exchangeable with D$_2$O), 4.64 (d, 2H, NH-CH$_2$), 3.40(s, 3H, ArOCH$_3$). MS (m/z): 490 (M$^+$).

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(7h): Yield 60%, Rf 0.72, m.p. 200°C. Anal. Calcd. for C_{23}H_{20}N_5S_2O: C, 56.60; H, 4.06; N, 22.90%. IR(KBr, cm\(^{-1}\)): 3176 (NH), 3145(C-H aromatic), 2960(C-H aliphatic), 1690(C=O), 1612(C=O of aromatic ring), 1572 (C=N), 1280 (N-N), 1236(C=N), 682(S-C-S). ¹H NMR (DMSO-\(d_6\), δ/ppm): 8.44(brs, 1H, NHCO), 6.70-7.10 (m, 8H, Ar-H), 6.55(d, 1H, CH-R), 6.28(d, 1H, CH-C), 5.60(s, 1H, NH, exchangeable with D₂O), 4.57(d, 2H, NH-CH₂), 3.29(s, 6H, Ar-N(CH₃)₂). MS (m/z): 479.5 (M)⁺

(7i): Yield 63%, Rf 0.69, m.p. 230°C. Anal. Calcd. for C_{22}H_{17}N_5S_2O: C, 57.51; H, 3.70; N, 21.35%. Found: C, 57.60; H, 3.66; N, 21.4%. IR(KBr, cm\(^{-1}\)): 3173(NH), 3142(C-H aromatic), 2962 (C-H aliphatic), 1691(C=O), 1610(C=O of aromatic ring), 1574 (C=N), 1283(N-N), 1235 (C-N), 686(S-C-S). ¹H NMR (DMSO-\(d_6\), δ/ppm): 8.39(brs, 1H, NHCO), 6.70-7.25 (m, 8H, Ar-H), 6.65(d, 1H, CH-R), 6.26(d, 1H, CH-C), 5.64(s, 1H, NH, exchangeable with D₂O), 4.64(d, 2H, NH-CH₂), 3.65(s, 3H, Ar-CH₃). MS (m/z): 459(M)⁺

Preparation of N-[(5-(1'-Phenyl-5'-aryl)-2'-pyrazol-3'-yl)amino]-1,3,4-thiadiazolyl)methylamino-1,3,4-thiadiazino(6,5-b)indole 8(a-i)

Pyridine-bromine complex was prepared by the addition of pure bromine (0.001 mmol) to pyridine (0.001 mmol) at 0-5°C temperature. The complex was added to a solution of compound 7a-7i (0.001 mmol) and phenyl hydrazine hydrochloride (0.002 mmol) in pyridine. The resulting mixture was refluxed for 4-5 hr, cooled, poured in ice-water and washed with 30% acetic acid to remove pyridine and the gummy product, triturated with glacial acetic acid to get products which were crystallized from appropriate solvents to yield compound 8a-8i.

(8a): Yield 65%, Rf 0.69, m.p. 179°C. Anal. Calcd. for C_{27}H_{19}N_5S_2: C, 60.78; H, 3.56; N, 23.63%. Found: C, 60.70; H, 3.50; N, 23.60%. IR(KBr, cm\(^{-1}\)): 3170(NH), 3140 (C-H aromatic), 2960(C-H aliphatic), 1680(C=O), 1611(C=O of aromatic ring), 1572(C=N), 1280 (N-N), 1231(C-N), 680(S-C-S). ¹H NMR (DMSO-\(d_6\), δ/ppm): 6.60-7.36(m, 14H, Ar-H), 6.30(brs, 1H, NH), 6.10(s, 1H, CH of pyrazole ring), 5.65(s, 1H, NH, exchangeable with D₂O), 4.50(d, 2H, NH-CH₂). MS (m/z): 533 (M)⁺

(8b): Yield 56%, Rf 0.66, m.p. 195°C. Anal. Calcd. for C_{22}H_{18}N_5S_2Cl: C, 57.09; H, 3.17; N, 22.20%. Found: C, 57.10; H, 3.20; N, 22.10%. IR(KBr, cm\(^{-1}\)): 3172 (NH), 3145 (C-H aromatic), 2962(C-H aliphatic), 1682(C=O), 1610(C=O of aromatic ring), 1572 (C=N), 1286 (N-N), 1232(C-N), 788(S-CI), 682(S-C-S). ¹H NMR (DMSO-\(d_6\), δ/ppm): 6.50-7.40 (m, 13H, Ar-H), 6.28(brs, 1H, NH), 6.12(s, 1H, CH of pyrazole ring), 5.70(s, 1H, NH, exchangeable with D₂O), 4.60(d, 2H, NH-CH₂). MS (m/z): 567.5 (M)⁺

(8c): Yield 59%, Rf 0.78, m.p. 164°C. Anal. Calcd. for C_{22}H_{18}N_5S_2Cl: C, 57.09; H, 3.17; N, 22.20%. Found: C, 57.00; H, 3.23; N, 22.15%. IR(KBr, cm\(^{-1}\)): 3170(NH), 3144 (C-H aromatic), 2962 (C-H aliphatic), 1683(C=O), 1614(C=O of aromatic ring), 1583 (C=N), 1283 (N-N), 1245(C=N), 786(S-CI), 684(S-C-S). ¹H NMR (DMSO-\(d_6\), δ/ppm): 6.55-7.46(m, 13H, Ar-H), 6.30(brs, 1H, NH), 6.20(s, 1H, CH of pyrazole ring), 5.72(s, 1H, NH, exchangeable with D₂O), 4.63(d, 2H, NH-CH₂). MS (m/z): 567.5 (M)⁺

(8d): Yield 52%, Rf 0.72, m.p. 205°C. Anal. Calcd. for C_{23}H_{21}N_5S_2O:C, 59.68; H, 3.73; N, 22.38%. Found: C, 59.70; H, 3.80; N, 22.20%. IR(KBr, cm\(^{-1}\)): 3171(NH), 3144 (C-H aromatic), 2964 (C-H aliphatic), 1682(C=O), 1610(C=O of aromatic ring), 1585 (C=N), 1282 (N-N), 1238(C-N), 1168(C-O-C), 686(S-C-S). ¹H NMR (DMSO-\(d_6\), δ/ppm): 6.72-7.30(m, 13H, Ar-H), 6.30(brs, 1H, NH), 6.17(s, 1H, CH of pyrazole ring), 5.60(s, 1H, NH, exchangeable with D₂O), 4.62(d, 2H, NH-CH₂), 3.32(s, 3H, Ar-OCH₃). MS (m/z): 563(M)⁺

(8e): Yield 61%, Rf 0.68, m.p. 220°C. Anal. Calcd. for C_{28}H_{21}N_5S_2O:C, 59.68; H, 3.73; N, 22.38%. Found: C, 59.74; H, 3.82; N, 22.22%. IR(KBr, cm\(^{-1}\)): 3174(NH), 3140 (C-H aromatic), 2962(C-H aliphatic), 1680(C=O), 1611(C=O of aromatic ring), 1578(C=N), 1280(N-N), 1235 (C-N), 1166(C-O-C), 685(S-C-S). ¹H NMR (DMSO-\(d_6\), δ/ppm): 6.65-7.26(m, 13H, Ar-H), 6.35 (brs, 1H, NH), 6.10 (s, 1H, CH of pyrazole ring), 5.60(s, 1H, NH, exchangeable with D₂O), 4.62(d, 2H, NH-CH₂), 3.32 (s, 3H, Ar-OCH₃). MS(m/z):563(M)⁺

(8f): Yield 58%, Rf 0.63, m.p. 235°C. Anal. Calcd. for C_{27}H_{19}N_5S_2O:C, 59.01; H, 3.46; N, 22.95%. Found: C, 59.10; H, 3.50; N, 22.88%. IR(KBr, cm\(^{-1}\)): 3412(OH), 3172 (NH), 3145(C-H aromatic), 2964 (C-H aliphatic), 1680 (C=O), 1610 (C=O of aromatic ring), 1585(C=N), 1282 (N-N), 1236(C-N), 680(S-C-S). ¹H NMR (DMSO-\(d_6\), δ/ppm): 6.50-7.40(m, 13H, Ar-H), 6.30(brs, 1H, NH), 6.20(s, 1H, CH of pyrazole ring), 5.60(s, 1H, NH, exchangeable with D₂O), 4.62(d, 2H, NH-CH₂), 3.32 (s, 3H, Ar-OCH₃). MS(m/z):563(M)⁺
NMR (DMSO-$d_6$, $\delta$ / ppm): 10.00 (s,1H,Ar-OH), 6.56-7.22 (m,13H,Ar-H), 6.38 (brs, 1H,NH), 6.12 (s,1H,CH of pyrazole ring), 5.66 (s,1H,NH, exchangeable with D$_2$O), 4.60 (d,2H,NH-CH$_2$). MS (m/z): 549 (M$^+$).

(8g): Yield 50%, R$_f$ 0.69, m.p. 213°C. Anal. Calcd. for C$_{28}$H$_{32}$N$_3$O$_2$: C, 58.03; H, 3.62; N, 21.76%. Found C, 58.20;H,3.77;N,21.60%. IR(KBr,cm$^{-1}$): 3408 (OH), 3172 (NH), 3143 (C…H aromatic),2965(C-H aliphatic),1687(C=O),1610(C…C of aromatic ring), 1575 (C=N), 1284(N-N),1238(C-N),1174(C-O-C),683(C-S-C).$^1$H NMR (DMSO-$d_6$, $\delta$ / ppm): 10.10 (s,1H,Ar-OH), 6.60-7.10 (m, 12H,Ar-H), 6.38 (brs,1H,NH), 6.18 (s,1H, CH of pyrazole ring),5.62 (s,1H,NH, exchangeable with D$_2$O), 4.63 (d, 2H,NH-CH$_2$), 3.42 (s,3H,Ar-OCH$_3$). MS (m/z): 579 (M$^+$).

(8h): Yield 65%, R$_f$ 0.60, m.p. 169°C. Anal. Calcd. for (C$_{28}$H$_{32}$N$_3$O)$_2$: calcld,C,60.52;H,4.00;N,24.34%. Found C, 60.40;H,4.11;N,24.25%. IR(KBr,cm$^{-1}$): 3175 (NH),3142(C…H aromatic), 2965(C-H aliphatic), 1683 (C=O), 1614(C…C of aromatic ring), 1581(C=N),1284(N-N),1233(C-N),685(C-S-C). $^1$H NMR (DMSO-$d_6$, $\delta$ / ppm): 6.70-7.16 (m, 12,Ar-H), 6.35 (brs,1H,NH),6.15(s,1H,CH of pyrazole ring), 5.60 (s, 1H, NH, exchangeable with D$_2$O),4.55 (d, 2H,NH-CH$_2$), 2.80 (s,6H,Ar-(CH$_3$)$_2$. MS (m/z): 575(M$^+$).

(8i): Yield 58%, R$_f$ 0.71, m.p. 224°C. IR(KBr,cm$^{-1}$): 3171(NH), 3144(C…H aromatic), 2964 (C-H aliphatic),1689(C=O),1612(C…C of aromatic ring), 1579 (C=N),1282(N-N),1237(C-N), 687 (C-S-C). $^1$H NMR (DMSO-$d_6$, $\delta$ / ppm): 6.61-7.10 (m,13H,Ar-H),6.36(brs,1H, NH), 6.10(s,1H,CH of pyrazole ring),5.66 (s,1H,NH, exchangeable with D$_2$O), 4.60 (d, 2H,NH-CH$_2$), 3.55(s,3H,Ar-CH$_3$). MS (m/z): 547(M$^+$).

Preparation of N-[[5-(1’-Acetyl-5’-aryl)-2’-pyrazolin-3’-yl)amino]-1,3,4-thiadiazol-2-yl] methylamino-1,3,4-thiadiazino(6,5-b)indole 9a-i

To a solution of compound 7a-7i (0.001 mmol) in absolute ethanol, hydrazine hydrate (0.001 mmol) was added followed by a few drops of glacial acetic acid and then refluxed for 6-10 h. Excess of solvent was distilled off, remnant of the reaction mixture was cooled and poured on to crushed ice, filtered, dried and finally crystallized from appropriate solvents to furnish compound 9a-9i.

(9a): Yield 54%, R$_f$ 0.64,m.p. 135°C. Anal. Calcd. for C$_{37}$H$_{39}$N$_9$S$_2$O: C, 55.08;H,3.79;N, 25.14%. Found: C, 55.00; H, 3.86;N,25.10%. IR(KBr,cm$^{-1}$): 3175 (NH),3143(C…H aromatic), 2958 (C-H aliphatic),1689(C=O),1615(C…C of aromatic ring), 1579(C=N), 1280 (N-N),1238 (C-N), 790(C-Cl),689(C-S-C). $^1$H NMR (DMSO-$d_6$, $\delta$ / ppm): 6.80-7.05 (m, 9H,Ar-H),6.45(t,1H, CH-CH$_2$ of pyrazoline ring), 5.80(d, 2H,CH$_2$ of pyrazoline ring), 5.60(s,1H,NH,exchangeable with D$_2$O), 5.12(s,1H,NH-CH$_2$),4.54(d,2H,NH-CH$_2$), 2.50 (s,3H,COCH$_3$).MS(m/z): 501(M$^+$).

(9b): Yield 49%, R$_f$ 0.60, m.p.124°C. Anal. Calcd. for C$_{37}$H$_{39}$N$_9$S$_2$OCl: C,51.54; H, 3.36;N,23.52%. Found C, 51.44;H,3.30;N,23.50%. IR(KBr,cm$^{-1}$): 3172(NH), 3145 (C…H aromatic),2960(C-H aliphatic),1684(C=O),1612(C…C of aromatic ring), 1573 (C=N), 1285 (N-N),1244(C-N),792 (C-Cl),686 (C-S-C). $^1$H NMR (DMSO-$d_6$, $\delta$ / ppm): 6.70-7.25(m, 8 H, Ar-H),6.40 (t,1H, CH-CH$_2$ of pyrazoline ring), 5.82(d,2H,CH$_2$ of pyrazoline ring), 5.62 (s,1H,NH,exchangeable with D$_2$O), 5.10(s, 1H, NH), 4.50(d, 2H,NH-CH$_2$), 2.51(s,3H,COCH$_3$). MS (m/z): 535.5(M$^+$).

(9c): Yield50%,R$_f$ 0.62, m.p. 155°C. Anal. Calcd. for C$_{37}$H$_{39}$N$_9$S$_2$OCl: C,51.54; H,3.36; N, 23.52%. Found C,51.42;H,3.34; N,23.60%. IR(KBr,cm$^{-1}$): 3175(NH), 3142(C…H aromatic), 2958 (C-H aliphatic),1682(C=O),1615(C…C of aromatic ring),1575 (C=N), 1280 (N-N),1245(C-N),1166(C-O-C),790(C-Cl),686(C-S-C). $^1$H NMR (DMSO-$d_6$, $\delta$ / ppm): 6.66-7.20(m,8H,Ar-H), 6.45(t,1H,CH-CH$_2$ of pyrazoline ring), 5.80 (d,2H,CH$_2$ of pyrazoline ring), 5.60(s,1H,NH,exchangeable with D$_2$O), 5.12 (s,1H, NH), 4.54(d,2H,NH-CH$_2$), 2.50(s, 3 H,COCH$_3$). MS (m/z): 535.5(M$^+$).

(9d): Yield 46%,R$_f$ 0.68,m.p.147°C. Anal. Calcd. for C$_{37}$H$_{39}$N$_9$S$_2$O$_2$: C,54.23; H,3.95; N, 23.72%. Found C, 54.40; H,3.90; N,23.70%. IR(KBr,cm$^{-1}$): 3173(NH),3140(C…H aromatic), 2956 (C-H aliphatic),1680(C=O),1614(C…C of aromatic ring),1573 (C=N), 1281 (N-N),1238(C-N),788(C-Cl),690(C-S-C). $^1$H NMR (DMSO-$d_6$, $\delta$ / ppm): 6.75-7.25(m,8H, Ar-H), 6.46 (t,1H,CH-CH$_2$ of pyrazoline ring), 5.85(d,2H,CH$_2$ of pyrazoline ring), 5.64(s,1H, NH, exchangeable with D$_2$O), 5.14(s,1H, NH), 4.50(d, 2H,NH-CH$_2$), 2.33(s,3H,COCH$_3$),2.15 (s,3H,Ar-OCH$_3$). MS (m/z): 531(M$^+$).
D

The reaction of indole-2,3-dione with thiosemicarbazide yielded 3-thiosemicarbazidoindole-2-one (9e).

NMR (DMSO-d_6, δ/ppm): 3.17 (s, 1H, NH, exchangeable with D2O), 3.63 (s, 2H, CH2 of pyrazoline ring), 6.51 (s, 1H, NH, exchangeable with D2O), 6.54 (d, 2H, NH-CH2), 3.30 (s, 3H, Ar-OCH3), 2.18 (s, 3H, Ar-OCH3). MS (m/z): 531 (M)+.

(9f): Yield 42%. Rf 0.60, m.p. 174°C. Anal. Calcd. for C_{24}H_{23}N_{3}O_{2}: C, 53.38; H, 3.67; N, 24.37%. Found C, 54.30; H, 3.70; N, 24.40%. IR (KBr, cm-1): 3412 (OH), 3176 (NH), 3142 (C-H aromatic), 2960 (CH aliphatic), 1681 (C=O), 1615 (C-C of aromatic ring), 1575 (C=N), 1280 (N-N), 1235 (C-N), 790 (C-Cl), 689 (C-S-C). 1H NMR (DMSO-d_6, δ/ppm): 6.70-7.27 (m, 8H, Ar-H), 4.45 (t, 1H, CH-CH2 of pyrazoline ring). 5.88 (d, 2H, CH2 of pyrazoline ring), 5.61 (s, 1H, NH, exchangeable with D2O), 5.12 (s, 1H, NH), 4.54 (d, 2H, NH-CH2), 3.30 (s, 3H, COCH3). MS (m/z): 547 (M)+.

(9g): Yield 41%; Rf 0.65, m.p. 232°C. Anal. Calcd. for C_{24}H_{23}N_{3}O_{2}: C, 52.65; H, 3.83; N, 23.03%. Found: C, 52.40; H, 3.90; N, 23.10%. IR (KBr, cm-1): 3175 (NH), 3145 (C-H aromatic), 2958 (CH aliphatic), 1680 (C=O), 1611 (C-C of aromatic ring), 1572 (C=N), 1280 (N-N), 1238 (C-N), 1161 (C-O-C), 790 (C-Cl), 689 (C-S-C). 1H NMR (DMSO-d_6, δ/ppm): 9.95 (s, 1H, ArOH), 6.60-6.90 (m, 7H, Ar-H), 6.44 (t, 1H, CH-CH2 of pyrazoline ring), 5.90 (d, 2H, CH2 of pyrazoline ring), 5.60 (s, 1H, NH, exchangeable with D2O), 5.13 (s, 1H, NH), 4.50 (d, 2H, NH-CH2), 3.30 (s, 3H, Ar-OCH3), 2.55 (s, 3H, COCH3). MS (m/z): 587 (M)+.

(9h): Yield 54%. Rf 0.68, m.p. 205°C. Anal. Calcd. for C_{24}H_{23}N_{3}O_{2}: C, 55.24; H, 4.23; N, 25.78%. Found: C, 55.30; H, 4.20; N, 25.70%. IR (KBr, cm-1): 3170 (NH), 3142 (C-H aromatic), 2958 (CH aliphatic), 1680 (C=O), 1613 (C-C of aromatic ring), 1574 (C=N), 1280 (N-N), 1238 (C-N), 790 (C-Cl), 689 (C-S-C). 1H NMR (DMSO-d_6, δ/ppm): 6.70-6.96 (m, 7H, Ar-H), 6.45 (t, 1H, CH-CH2 of pyrazoline ring), 5.86 (d, 2H, CH2 of pyrazoline ring), 5.60 (s, 1H, NH, exchangeable with D2O), 5.12 (s, 1H, NH), 4.45 (d, 2H, NH-CH2), 3.52 (s, 3H, Ar-N(CH3)2), 2.52 (s, 3H, COCH3). MS (m/z): 543 (M)+.

(9i): Yield 50%. Rf 0.64, m.p. 162°C. Anal. Calcd. for C_{24}H_{23}N_{3}O_{2}: C, 55.92; H, 4.07; N, 24.46%. Found: C, 55.90; H, 3.96; N, 24.60%. IR (KBr, cm-1): 3173 (NH), 3141 (C-H aromatic), 2956 (CH aliphatic), 1682 (C=O), 1615 (C-C of aromatic ring), 1575 (C=N), 1281 (N-N), 1237 (C-N), 788 (C-Cl), 691 (C-S-C). 1H NMR (DMSO-d_6, δ/ppm): 6.70-7.00 (m, 8H, Ar-H), 6.40 (t, 1H, CH-CH2 of pyrazoline ring), 5.81 (d, 2H, CH2 of pyrazoline ring), 5.64 (s, 1H, NH, exchangeable with D2O), 5.10 (s, 1H, NH), 4.45 (d, 2H, NH-CH2), 3.66 (s, 3H, Ar-CH3), 2.42 (s, 3H, COCH3). MS (m/z): 515 (M)+.

RESULTS AND DISCUSSION

The reaction of indole-2,3-dione with thiosemicarbazide yielded 3-thiosemicarbazidoindole-2-one 1. Amino-1, 3, 4-thiadiazino (6,5-b) indole-2 was prepared by the cyclization of compound 1 with cold conc. sulphuric acid. Furthermore, compound 2 reacted with chloroethylacetate to yield 2-carboethoxymethylamino-1,3,4-thiadiazino (6,5-b) indole 3. The latter compound on reaction with thiosemicarbazide resulted into the formation of 2-(thiosemicarbazido carbonyl methyl amino)-1,3,4-thiadiazino (6,5-b) indole 4. Treatment of compound 4 with conc. H2SO4 and followed by neutralization with liquid NH3 gave 2-[5'-aminothiadiazol-2'-ylmethylamino]-1,3,4-thiadiazino (6,5-b) indole 5 which on further reaction with acetyl chloride in the presence of dry benzene yielded the desired compound 6. Condensation reaction of compound 6 and aromatic aldehydes furnished different chalcones 7a-7i. Cyclization of the 7a-7i with pyridine-bromine complex and phenyl hydrazine acid afforded substituted pyrazole compounds 8a-8i. Reaction of 7a-7i with hydrazine hydrate and a few drops of glacial acetic acid undergo cyclization to give substituted pyrazolines 9a-9i.

Analytic and spectral characterization

The structures of the prepared compounds were confirmed using elemental analysis, IR, 1H-NMR and mass spectrometry. In the 1H-NMR spectra of compound 3, the peak at δ 1.45 and 4.25 ppm were observed due to CH3 and CH2, respectively in –COOCH2CH3 gp. Furthermore in the IR spectra, the absorption bands at 1695 cm⁻¹ due to ester (C=O) and 2915, 2870, 1423, 715 cm⁻¹ (CH2 and CH3) also confirmed the formation of compound 3. The formation of compound 4 was evidenced by the appearance

SOME SUBSTITUTED INDOLES

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of peak at δ 6.12 ppm were observed due to CONH, it was also confirmed by the IR spectral band at 1700 cm⁻¹ (>C=O of amide). In the 1H-NMR spectra of compound 5, the peak was observed at δ 6.26 ppm due to NH₂. In the IR spectra of compound 5, the band at 3370 cm⁻¹ (NH₂) also confirms its preparation. Existence of compound 6 was confirmed by the presence of IR spectral bands at 2900 and 1696 cm⁻¹ due to CH₂ and C=O respectively. Appearance of signal at δ 2.40 (-CH₃) confirmed the existence of compound 6. Appearance of signals at δ 6.60-6.80 (CH-Ar) and 6.20-6.30(CH-CO) ppm confirm the evidence of the chalcones 7a-7i. Pyrazole preparation was confirmed by the presence of signal at δ 6.10-6.20 ppm (CH of pyrazole ring) in 1H-NMR spectra. The structures of above prepared substituted pyrazolines 9a-9i were confirmed by appearance of signal at δ 5.80-5.90 (CH₂ of pyrazoline ring) in 1H-NMR spectra of compounds 9a-9i.

**Antimicrobial tests**

All the newly synthesized compounds were screened for their antibacterial and antifungal activity. Microorganisms employed antibacterial studies were Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae and Proteus vulgaris. Disk diffusion method was used for determination of the preliminary antibacterial activity. Disks measuring 6.25 mm in diameter were punched from Whatman no. 1 filter paper. Batches of 100 disks were dispensed to each screw-capped bottle and sterilized by dry heat at 140 °C for an hour. The test compounds were prepared with different concentrations using DMF. One milliliter containing 100 times the amount of chemical in each disk was added to each bottle, which contained 100 disks. Disks of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 °C for 24 h. Ampicillin trihydrate was used as a standard drug. Solvent and growth controls were kept and zones of inhibition were noted. The MIC (µg/mL) values of the tested compounds against the tested bacteria strains are recorded in Table 1. On the other hand, the newly prepared compounds were screened for their in vitro antifungal activity against Aspergillus fumigatus (plant isolate), Candida glabrata, Candida albicans and Candida krusei in DMSO by the serial plate dilution method. All the fungal strains were clinical isolates, identified with conventional morphological and biochemical methods. Fluconazole (antifungal) was used as reference drug. Sabouraud’s agar media were prepared by dissolving peptone (1 g), D-glucose (4 g), and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of the spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of the corresponding species. Agar media (20 ml) was poured into each petri dish. Excess suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch wells were made into each well labeled. A control was also prepared in triplicate and maintained at 37 °C for 3-4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. The MIC (µg/ml) values of the tested compounds against the tested fungal strains are recorded in Table 1.

**Acute toxicity study**

Lethal dose (LD₅₀) of most potent test compound was determined by the method of Carrol in albino mice. After 24 hr of drug administration, percent mortality in each group was observed from the data obtained LD₅₀. Data revealed that compound 9c does not show any toxicity up to dose of 9.75 mg/ml body weight in mice.

**CONCLUSION**

Hence it is cleared from the study of biological activity data and may be concluded that cyclization of chalcones 7a-7i into respective pyrazoles 8a-8i and pyrazolines 9a-9i enhance antifungal and antibacterial activities. Presence of chloro group as substituent brought remarkable increase in biological activities. Compound 9c was the most potent compound with lesser amount of toxicity and deserve further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed.

**ACKNOWLEDGEMENTS**

We are thankful for SAIF, Punjab University, India for spectral, elemental analysis and L.L.R.M. Medical College, India for biological activities.
Scheme 1: Reagents and conditions: (i) Conc. H$_2$SO$_4$, (ii) CH$_3$CO$_2$H, (iii) NH$_2$CONH$_2$, (iv) H$_2$SO$_4$/NH$_3$, (v) CH$_2$Cl$_2$, (vi) RCHO/2% NaOH, (vii) Br$_2$/C, HNHNH$_2$/HCl, and (viii) N$_2$, H$_2$, O/glac. CH$_2$Cl$_2$.
Table 1. Antibacterial and antifungal data for the synthesized compounds.

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**Antibacterial activity data in MIC (µg/ml)**

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**Antifungal activity data in MIC (µg/ml)**

REFERENCES


[RJC-786/2011]

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