



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]methylamino-1,3,4-thiadiazino(6,5-b) indole 7(a-i). All the synthesized compounds have been characterized by elemental and spectral (I.R., ¹H- 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.

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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 bio-active 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 discovery⁴. 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} pyrazole¹⁸⁻²¹ and pyrazoline²²⁻²³ 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 2nd 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 $\pm 0.4\%$ of theoretical values. Infrared spectra were recorded on KBr pellets on a Perkin Elmer system 2000 FTIR spectrometer and ^1H -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%, R_f 0.70, m.p. 223°C. Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_2\text{S}$: calcd.C, 54.16; H, 4.16; N, 19.44%. Found: C, 54.00; H, 4.10; N=20.00%. IR(KBr, cm^{-1}): 3141 (C-H aromatic), 3185 (N-H), 2950 (C-H aliphatic), 2870 (CH_2), 1695 (C=O), 1612 (C...C of aromatic ring), 1572 (C=N), 1295 (N-N), 1245 (C-N), 715 (CH_3), 681 (C-S-C). ^1H NMR (DMSO- d_6 , δ / ppm): 6.95-7.15 (m, 4H, Ar-H), 6.10 (t, 1H, NH, exchangeable with D_2O), 4.55 (d, 2H, NH- CH_2), 4.25(q, 2H-COOCH $_2$ -CH $_3$), 1.45 (t, 3H, COOCH $_2$ -CH $_3$). 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, dried and recrystallized from methanol to yield compound **4**: Yield 75%, R_f 0.70, m.p. 229°C. Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_7\text{OS}_2$: C, 43.24; H, 3.30; N, 29.42%. Found: C, 43.20; H, 3.32; N=29.48%. IR(KBr, cm^{-1}): 3148(C-H aromatic), 3182 (N-H), 2975(C-H aliphatic), 1700(C=O), 1610 (C...C aromatic ring), 1575 (C=N), 1291 (N-N), 1250(C-N), 688(C-S-C). ^1H NMR (DMSO- d_6 , δ /ppm): 7.32-8.12(m, 4H, NHNHCSNH_2 , exchangeable with D_2O), 6.92-7.20(m, 4H, Ar H), 6.12(t, 1H, NH, exchangeable with D_2O), 4.47(d, 2H, NH- CH_2). 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_2SO_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%, R_f 0.60, m.p. 257 °C. Anal. Calcd. for $\text{C}_{12}\text{H}_9\text{N}_7\text{S}_2$: C, 50.89; H, 3.18; N, 34.63%. Found: C, 50.80; H, 3.18; 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 (N-N), 1245 (C-N), 676 (C-S-C). ^1H 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_2O), 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 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%, R_f 0.80, m.p. 190 °C. Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_7\text{S}_2\text{O}$: C, 47.05; H, 3.08; N, 27.45%. Found: C, 47.00; H, 3.10; N, 27.50%. IR(KBr, cm^{-1}): 3172 (NH), 3145(C...H aromatic), 2962(C-H aliphatic), 2900(CH_2), 1696(C=O), 1612(C...C of aromatic ring), 1570(C=N), 1291(N-N), 1242(C-N), 678(C-S-C). ^1H NMR (DMSO- d_6 , δ /ppm): 8.42

(brs,1H,NHCO),6.98-7.26(m,4H,Ar-H), 5.70 (s,1H,NH, exchangeable with D₂O), 4.50 (d, 2H, NH-CH₂),2.40(s,3H,COCH₃). MS (m/z): 357 (M)⁺.

Preparation of N-[(5-(arylidinylacetyl)amino)-1,3,4-thiadiazol-2-yl]methyl-amino]-1,3,4-thiadiazino(6,5-b)indole 7(a-i)

A methanolic solution of compound **6** (10 mmol) and aromatic aldehydes (10 mmol) in presence of few drops of aq. 2% NaOH solution for 12 h, while progress and completion of reaction was routinely 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%, R_f 0.60, m.p. 199 °C. Anal. Calcd. for C₂₁H₁₅N₇S₂O: C, 56.62; H, 3.37; N, 22.02%. Found: C,56.60;H,3.30;N,22.00%. 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).¹H 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,exchanable with D₂O), 4.60(d, 2H,NH-CH₂). MS (m/z): 445(M)⁺.

(**7b**): Yield 60%,R_f 0.72,m.p.160 °C. Anal. Calcd. for C₂₁H₁₄N₇S₂OCl: C, 52.55; H, 2.91; N, 20.43;FoundC,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).¹H 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 D₂O), 4.60(d,2H, NH-CH₂). MS (m/z): 479.5(M)⁺.

(**7c**): Yield 66%, R_f 0.70, m.p. 179 °C. Anal. Calcd. for C₂₁H₁₄N₇S₂OCl: 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(C-N),788(C-Cl), 680(C-S-C).¹H 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 D₂O), 4.62 (d,2H,NH-CH₂). MS (m/z): 479.5 (M)⁺.

(**7d**): Yield 64%,R_f 0.65, m.p.191°C.Anal. Calcd. for C₂₂H₁₇N₇S₂O₂: 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).¹H NMR (DMSO-*d*₆, δ / ppm): 8.41 (brs,1H, NH CO),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 D₂O),4.65(d,2H,NH-CH₂),3.40(s,3H,ArOCH₃). MS (m/z): 475 (M)⁺.

(**7e**): Yield 68%, R_f 0.66, m.p. 210°C. Anal. Calcd. for C₂₂H₁₇N₇S₂O₂: 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).¹H 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 D₂O),4.56(d, 2H, NH-CH₂),3.45(s,3H,Ar-OCH₃). MS (m/z): 475 (M)⁺.

(**7f**): Yield 59%, R_f 0.71, m.p. 207°C. Anal. Calcd. for C₂₁H₁₅N₇S₂O₂: 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).¹H 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 D₂O),4.61 (d,2H,NH-CH₂). MS (m/z): 461 (M)⁺.

(**7g**): Yield 58%, R_f 0.68,m.p. 169 °C. Anal. Calcd. for C₂₂H₁₇N₇S₂O₃: 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).¹H 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 D₂O),4.64 (d, 2H,NH-CH₂),3.40(s,3H,Ar-OCH₃). MS (m/z): 490 (M)⁺.

(7h): Yield 60 %, R_f 0.72, m.p. 200°C. Anal. Calcd. for $C_{23}H_{20}N_8S_2O$: C,56.55; H,4.09; N, 22.95%. Found: 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...C of aromatic ring), 1572 (C=N), 1280 (N-N), 1236(C-N), 682(C-S-C). 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-CO), 5.60(s, 1H, NH, exchangeable with D_2O), 4.57(d, 2H, NH- CH_2), 2.90(s, 6H, Ar-N(CH_3) $_2$). MS (m/z): 479.5 (M) $^+$

(7i): Yield 63%, R_f 0.69, m.p. 230°C. Anal. Calcd. for $C_{22}H_{17}N_7S_2O$: 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...C of aromatic ring), 1574 (C=N), 1283(N-N), 1235 (C-N), 686(C-S-C). 1H NMR (DMSO- d_6 , δ / ppm): 8.39 (brs, 1H, NHCO), 6.70-7.25 (m, 8H, ArH), 6.65(d, 1H, CH-R), 6.26(d, 1H, CH-CO), 5.64(s, 1H, NH, exchangeable with D_2O), 4.64 (d, 2H, NH- CH_2), 3.65(s, 3H, Ar- CH_3). 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 (8a-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%, R_f 0.69, m.p. 179 °C. Anal. Calcd. for $C_{27}H_{19}N_9S_2$: 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...C of aromatic ring), 1572(C=N), 1280 (N-N), 1231(C-N), 680(C-S-C). 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 D_2O), 4.50 (d, 2H, NH- CH_2). MS (m/z): 533 (M) $^+$.

(8b): Yield 56%, R_f 0.66, m.p. 195 °C. Anal. Calcd. for $C_{27}H_{18}N_9S_2Cl$: 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...C of aromatic ring), 1572 (C=N), 1286 (N-N), 1232(C-N), 788(C-Cl), 682(C-S-C). 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 D_2O), 4.60(d, 2H, NH- CH_2). MS (m/z): 567.5 (M) $^+$.

(8c): Yield 59%, R_f 0.78, m.p. 164 °C. Anal. Calcd. for $C_{27}H_{18}N_9S_2Cl$: 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...C of aromatic ring), 1583 (C=N), 1283 (N-N), 1245(C-N), 786(C-Cl), 684(C-S-C). 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 D_2O), 4.63(d, 2H, NH- CH_2). MS (m/z): 567.5 (M) $^+$.

(8d): Yield 52%, R_f 0.72, m.p. 205°C. Anal. Calcd. for $C_{28}H_{21}N_9S_2O$: 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...C of aromatic ring), 1585 (C=N), 1282 (N-N), 1238(C-N), 1168(C-O-C), 686(C-S-C). 1H NMR (DMSO- d_6 , δ /ppm): 6.72-7.30(m, 13H, ArH), 6.30(brs, 1H, NH), 6.17(s, 1H, CH of pyrazole ring), 5.60(s, 1H, NH, exchangeable with D_2O), 4.62(d, 2H, NH- CH_2), 3.32(s, 3H, Ar-O CH_3). MS (m/z): 563(M) $^+$.

(8e): Yield 61%, R_f 0.68, m.p. 220°C. Anal. Calcd. for $C_{28}H_{21}N_9S_2O$: 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...C of aromatic ring), 1578(C=N), 1280(N-N), 1235 (C-N), 1166(C-O-C), 685(C-S-C). 1H NMR (DMSO- d_6 , δ /ppm): 6.65-7.26(m, 13H, ArH), 6.35 (brs, 1H, NH), 6.10 (s, 1H, CH of pyrazole ring), 5.60(s, 1H, NH, exchangeable with D_2O), 4.62(d, 2H, NH- CH_2), 3.32 (s, 3H, Ar-O CH_3). MS(m/z): 563 (M) $^+$.

(8f): Yield 58%, R_f 0.63, m.p. 235°C. Anal. Calcd. for $C_{27}H_{19}N_9S_2O$: 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...C of aromatic ring), 1585(C=N), 1282 (N-N), 1236(C-N), 680(C-S-C). 1H

NMR (DMSO- d_6 , δ / 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 D₂O),4.60(d,2H,NH-CH₂). MS (m/z): 549 (M)⁺.

(8g): Yield 50%, R_f 0.69, m.p. 213^oC. anal. Calcd. for C₂₈H₂₁N₉S₂O₂: 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). ¹H NMR (DMSO- d_6 , δ / ppm): 10.10 (s,1 H,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 D₂O),4.63(d, 2H,NH-CH₂),3.42(s,3H,Ar-OCH₃). MS (m/z): 579 (M)⁺.

(8h): Yield 65%, R_f 0.60, m.p. 169 ^oC. Anal. Calcd. for Elemental analysis (C₂₉H₂₃N₁₀S₂); calcd.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). ¹H NMR (DMSO- d_6 , δ / ppm): 6.70-7.16 (m, 12H,Ar-H),6.35 (brs,1H, NH),6.15(s,1H,CH of pyrazole ring), 5.60 (s, 1H, NH, exchangeable with D₂O),4.55 (d, 2H,NH-CH₂), 2.80(s,6H,Ar-N(CH₃)₂). MS (m/z): 575(M)⁺.

(8i): Yield 58%, R_f 0.71, m.p. 224^oC. 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). ¹H NMR (DMSO- d_6 , δ / 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 D₂O),4.60(d, 2H,NH-CH₂),3.55(s,3H,Ar-CH₃). 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 9(a-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^oC. Anal. Calcd. for C₂₃H₁₉N₉S₂O: 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),1682(C=O),1615(C...C of aromatic ring), 1575(C=N), 1280 (N-N),1238 (C-N),790(C-Cl),689(C-S-C). ¹H NMR (DMSO- d_6 , δ / ppm): 6.80-7.05 (m, 9H,Ar-H),6.45(t,1H, CH-CH₂ of pyrazoline ring), 5.80(d, 2H,CH₂ of pyrazoline ring), 5.60(s,1H,NH,exchangeable with D₂O), 5.12(s,1H,NH-CH₂),4.54(d,2H,NH-CH₂), 2.50 (s,3H,COCH₃).MS(m/z): 501(M)⁺.

(9b): Yield 49%, R_f 0.60, m.p.124^oC. Anal. Calcd. for C₂₃H₁₈N₉S₂OCl: 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). ¹H NMR (DMSO- d_6 , δ / ppm):6.70-7.25(m, 8 H, Ar-H),6.40 (t,1H, CH-CH₂ of pyrazoline ring), 5.82(d,2H,CH₂ of pyrazoline ring), 5.62 (s, 1H,NH,exchangeable with D₂O), 5.10(s, 1H, NH), 4.50(d, 2H,NH-CH₂),2.51(s,3H,COCH₃). MS (m/z): 535.5(M)⁺.

(9c): Yield50%,R_f 0.62,m.p. 155^oC. Anal. Calcd. for C₂₃H₁₈N₉S₂OCl: 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). ¹H NMR (DMSO- d_6 , δ / ppm): 6.66-7.20(m,8H,Ar-H),6.45(t,1H,CH-CH₂ of pyrazoline ring),5.80 (d,2H,CH₂ of pyrazoline ring),5.60(s,1H,NH,exchangeable with D₂O),5.12 (s,1H, NH),4.54(d,2H,NH-CH₂),2.50(s, 3 H,COCH₃). MS (m/z): 535.5(M)⁺.

(9d): Yield 46%,R_f 0.68,m.p.147^oC. Anal. Calcd. for C₂₄H₂₁N₉S₂O₂: 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). ¹H NMR (DMSO- d_6 , δ / ppm): 6.75-7.25(m,8H, Ar-H), 6.46 (t,1H,CH-CH₂ of pyrazoline ring),5.85(d,2H,CH₂ of pyrazoline ring),5.64(s,1H, NH, exchangeable with D₂O),5.14(s,1H, NH), 4.50(d, 2H,NH-CH₂),2.33(s,3H,COCH₃),2.15 (s,3H,Ar-OCH₃). MS (m/z): 531(M)⁺.

(9e): Yield 44%, R_f 0.63, m.p. 159⁰C. Anal. Calcd. for C₂₄H₂₁N₉S₂O₂: C, 54.23; H, 3.95; N, 23.72%. Found C, 54.30; H, 3.98; N, 23.76%. 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), 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), 6.45 (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), 2.18 (s, 3H, Ar-OCH₃). MS (m/z): 531 (M)⁺.

(9f): Yield 42%, R_f 0.60, m.p. 174⁰C. Anal. Calcd. for C₂₃H₁₉N₉S₂O₂: C, 53.38; H, 3.67; N, 24.37%. Found C, 53.40; H, 3.70; N, 24.40%. IR (KBr, cm⁻¹): 3412(OH), 3176(NH), 3142(C...H aromatic), 2960(C-H aliphatic), 1681(C=O), 1615(C...C of aromatic ring), 1575 (C=N), 1284 (N-N), 1235(C-N), 788(C-Cl), 687(C-S-C). ¹H NMR (DMSO-*d*₆, δ/ppm): 10.00(s, 1H, Ar-OH), 6.65-7.05(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), 4.50(d, 2H, NH-CH₂), 2.55(s, 3 H, COCH₃). MS (m/z): 517 (M)⁺.

(9g): Yield 41%; R_f 0.65; m.p. 232⁰C. Anal. Calcd. for C₂₄H₂₁N₉S₂O₃: 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(C-H 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, 1 H, NH), 4.50(d, 2H, NH-CH₂), 3.30(s, 3H, Ar-OCH₃), 2.55(s, 3H, COCH₃). MS (m/z): 547(M)⁺.

(9h): Yield 54%, R_f 0.68, m.p. 205⁰C. Anal. Calcd. for C₂₅H₂₃N₁₀S₂O: 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(C-H 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), 4.54(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%, R_f 0.64, m.p. 162⁰C. Anal. Calcd. for C₂₄H₂₁N₉S₂O: 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 (C-H 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), 4.50(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'-aminothiadiaazol-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

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} ($>\text{C}=\text{O}$ of amide). In the $^1\text{H-NMR}$ spectra of compound **5**, the peak was observed at δ 6.26 ppm due to NH_2 . In the IR spectra of compound **5**, the band at 3370 cm^{-1} (NH_2) 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 CH_2 and $\text{C}=\text{O}$ respectively. Appearance of signal at δ 2.40 ($-\text{CH}_3$) 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 $^1\text{H-NMR}$ spectra. The structures of above prepared substituted pyrazolines **9a-9i** were confirmed by appearance of signal at δ 5.80-5.90 (CH_2 of pyrazoline ring) in $^1\text{H-NMR}$ 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*, *Klasiella pneumoniae* and *Proteus vulgaris*. Disk diffusion method²⁵⁻²⁶ 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 $140\text{ }^\circ\text{C}$ 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 for placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at $37\text{ }^\circ\text{C}$ 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 ($\mu\text{g/mL}$) 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.^{27,28} 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 $37\text{ }^\circ\text{C}$ for 1 h. Using an agar punch wells were made into each well labeled. A control was also prepared in triplicate and maintained at $37\text{ }^\circ\text{C}$ for 3-4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. The MIC ($\mu\text{g/ml}$) values of the tested compounds against the tested fungal strains are recorded in Table 1.

Acute toxicity study

Lethal dose (LD_{50}) of most potent test compound was determined by the method of Carrol²⁹ in albino mice. After 24 hr of drug administration, percent mortality in each group was observed from the data obtained LD_{50} . Data revealed that compound **9c** does not show any toxicity upto 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.

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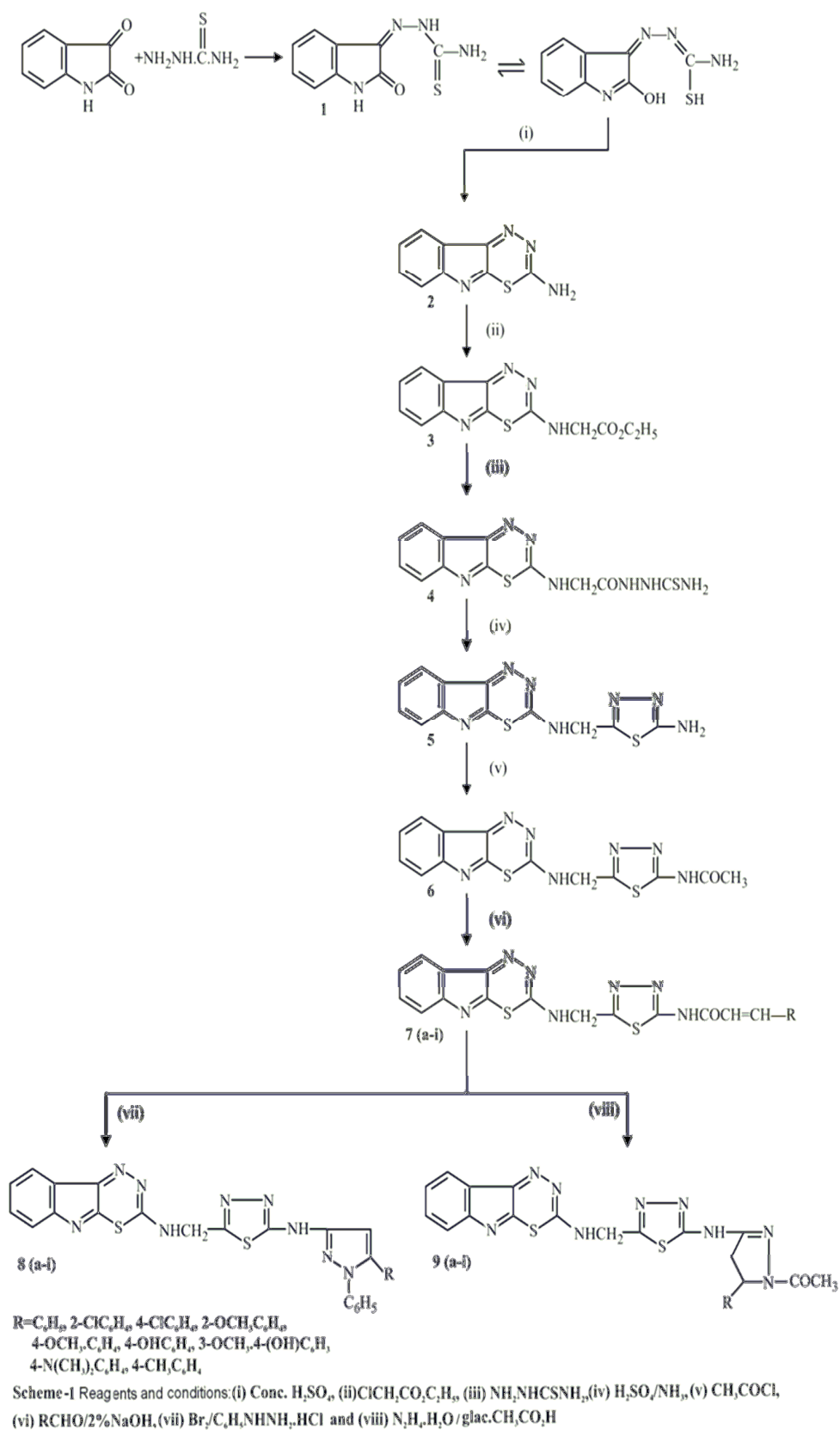


Table 1. Antibacterial and antifungal data for the synthesized compounds.

Comp. no.	Antibacterial activity data in MIC (µg/ml)				Antifungal activity data in MIC (µg/ml)			
	<i>S. aureus</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. vulgaris</i>	<i>A. fumigatus</i>	<i>C. glabrata</i>	<i>C. albicans</i>	<i>C. krusei</i>
7a	-	-	-	-	-	-	-	-
7b	5	-	-	5	-	6	5	-
7c	-	5	-	6	-	8	-	4
7d	-	4	4	-	5	4	4	-
7e	4	-	4	-	-	-	-	-
7f	4	-	4	-	4	6	5	-
7g	-	5	4	-	-	-	7	7
7h	6	-	6	-	-	-	-	-
7i	-	7	-	5	4	4	5	-
8a	4	4	-	-	-	5	6	5
8b	8	8	6	-	-	-	7	7
8c	10	12	12	10	-	10	5	5
8d	6	8	8	10	12	10	6	8
8e	8	-	-	12	-	8	10	12
8f	12	8	8	10	10	5	6	-
8g	-	10	6	8	8	10	6	-
8h	8	6	6	5	8	8	10	6
8i	-	-	7	8	5	-	8	10
9a	8	8	10	12	6	8	5	6
9b	13	14	12	15	10	10	6	5
9c	18	20	19	20	18	14	10	8
9d	13	10	12	10	-	8	8	7
9e	12	13	6	10	8	-	-	7
9f	10	12	10	12	-	10	6	6
9g	8	14	8	10	6	8	12	7
9i	12	10	14	8	-	9	7	9
Ampicillin trihydrate (std.)	16	20	20	20	-	-	-	-
Fluconazole (std.)	-	-	-	-	20	15	16	15
DMF (control)	-	-	-	-	-	-	-	-

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