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Synthesis and antimicrobial investigation of some 5*H*-pyridazino[4,5-*b*]indoles

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Abstract: Synthesis and in vitro antimicrobial activities are reported for a series of 1,3,5-substituted 4-oxo-3,4-dihydro-5*H*-pyridazino[4,5-*b*]indole derivatives. Corresponding pyridazino[4,5-*b*]indoles were prepared from ethyl 3-formyl-1*H*-indole-2-carboxylate precursors and the functional group in question was installed with hydrazine and its derivatives. The purity and primary structures of pyridazino[4,5-*b*]indole were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analyses. All of the indoles were tested for in vitro antimicrobial activity against 8 isolates of bacteria and a fungus including *Staphylococcus aureus* NRRL B-767, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* NRRL-B123, *Salmonella typhimurium* NRRL B-4420, *Bacillus subtilis* NRRL 744, *Listeria monocytogenes* ATCC 7644, and *Candida albicans* by using broth microdilution test. All of the isolates showed moderate sensitivity against tested indoles and *B. subtilis* NRRL 744 was the most sensitive.

Key words: Pyridazino[4,5-*b*]indole, antimicrobial activity, β-carboline, indole

1. Introduction

Indole has attracted considerable chemical and therapeutic interest as an important building block for many compounds including natural products, alkaloids, and drugs.[1] Among them, 5*H*-pyridazino[4,5-*b*]indole systems **1** (Figure 1) are well known for having notable pharmacological features, such as antihypertensiveness,[2] inhibition of blood platelet aggregation,[3] positive inotropicity,[4] selective thromboxane synthetase inhibition,[2a,2b] HIV-1 reverse transcriptase inhibition,[5] and antiproliferative activities.[6] Pyridazino[4,5-*b*]indoles are also an aza analogue of both β- and γ-carboline alkaloids **2** and **3**, which possess genotoxic, mutagenic, and cytotoxic features due to their high binding ability to DNA.[7,8] In the light of those findings, 1-anilino-5*H*-pyridazino[4,5-*b*]indoles were envisaged as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, and their potent in vitro antiproliferative and antitumor activities against human cancer cell lines were reported.[6,9] A pyridazino[4,5-*b*]indoleacetamide compound, SSR180575 **4** (7-chloro-*N*,*N*,5-trimethyl-4-oxo-3-phenyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indole-1-acetamide), was found to be a highly potent and specific ligand for peripheral benzodiazepine receptor (PBR),[10] recently named as the translocator protein[11] (TSPO, 18 kDa). Hiremath et al. first examined the potent antimicrobial activities of some 11*H*-1,2,4-triazolo[4,3-*b*]pyridazino[4,5-*b*]indoles by cup-plate method, and good results were observed against *E. coli* (20–28 mm).[12]

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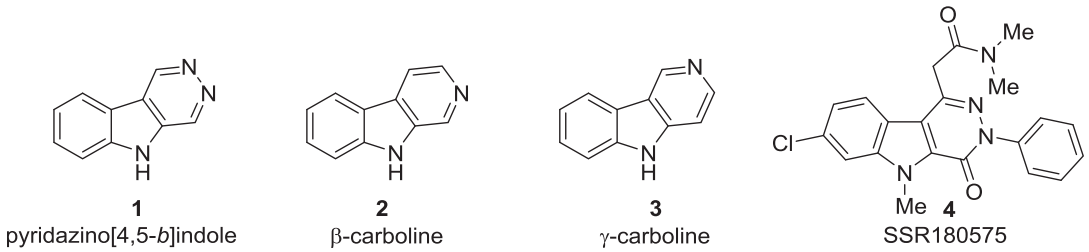
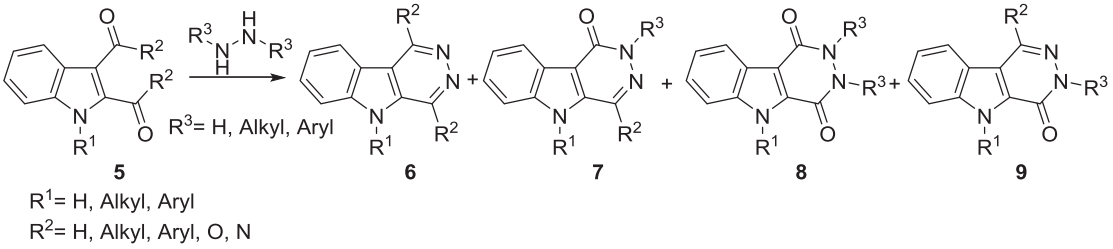


Figure 1. Structures of pyridazino[4,5-*b*]indole **1**, β-carboline **2**, γ-carboline **3**, and SSR180575 **4**.

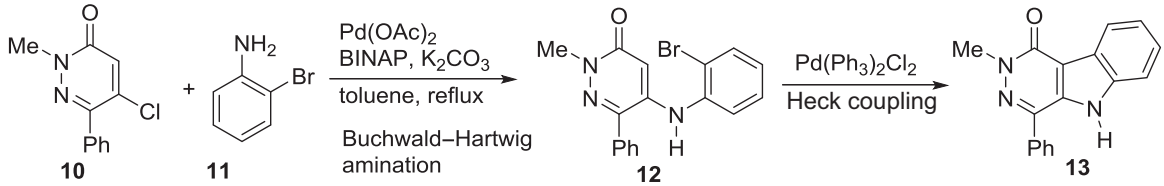
Pyridazino[4,5-*b*]indole ring systems are traditionally prepared through ring closure of di-carbonyls,[2–6,13] palladium-mediated coupling of heterocycles,[14] ring closure of nitrene intermediates,[7a,15] cycloaddition of heterocycles,[16] and cyclization of indole-carbohydrazones.[17]

Pyridazino[4,5-*b*]indoles **6**–**9** are mostly prepared from 2,3-dicarbonylindoles **5** in the presence of hydrazine and its derivatives (Scheme 1).[2–6,13] This method allows the attaining of a large variety of titled compounds in a one-pot procedure from 2,3-dicarbonylindoles **4** depending on the substitutions of hydrazines and indoles (Scheme 1).



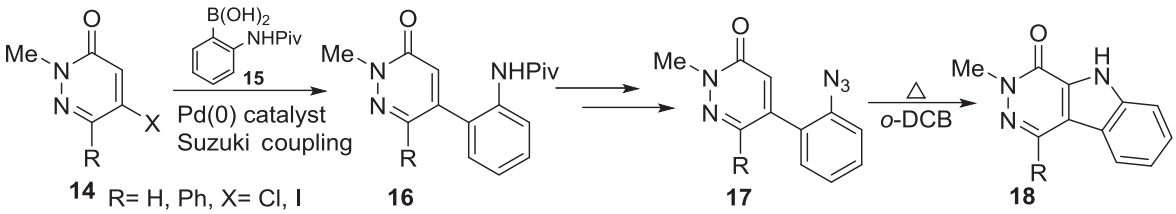
Scheme 1. Synthesis of pyridazino[4,5-*b*]indoles **6**–**9** from 2,3-dicarbonylindoles **5**.

Palladium-mediated coupling reactions are widely used to form C–C and C–N bonds in organic compounds including heterocycles under mild conditions with high efficiencies.[18] The Pd(0)-catalyzed Heck coupling reaction was utilized to form 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one **13** from 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-one **12** obtained via Buchwald–Hartwig amination of 2-methyl-5-halopyridazin-3(2*H*)-one **10** and 2-bromoaniline **11** (Scheme 2).[14]



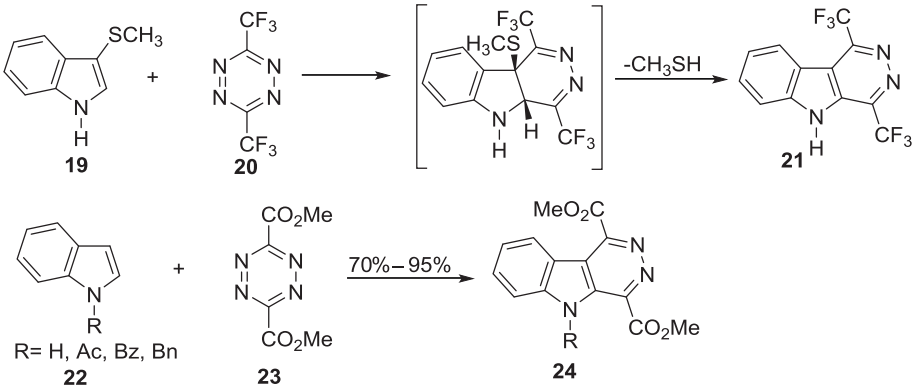
Scheme 2. Synthesis of pyridazino[4,5-*b*]indole **13** from methylpyridazin-3(2*H*)-one **12** via Heck-type ring closure.

Suzuki coupling reaction of 5-halo-2-methyl-6-phenylpyridazin-3(2*H*)-one **14** with *o*-pivaloylaminophenyl boronic acid **15** furnished the corresponding arylated 5-pivaloylaminophenyl derivative **16**, which was transformed into azide form **17** after elimination of pivaloyl protection (Scheme 3).[13a,13c] Ring closure of nitrene intermediate generated in situ from azide adjunct **17** yielded pyridazino[4,5-*b*]indole **18** as a single product (Scheme 3).[7a,15]



Scheme 3. Synthesis of pyridazino[4,5-*b*]indoles **18** via ring closure of nitrene intermediate **17**.

Seitz and Mohr first isolated 1,4-bis(trifluoromethyl)pyridazino[4,5-*b*]indole **21** in 26% yield through the cycloaddition/cycloreversion reaction of indole with 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **20**.[16a] Later, the use of 3-methylthioindole **19** in the inverse electron demand Diels–Alder reaction with **20** afforded pyridazino[4,5-*b*]indole **21** in better yield (58%) (Scheme 4).[16b] More recently, Synder and colleagues reported improved methodology using 1,2,4,5-tetrazine-3,6-dicarboxylate **23** to obtain pyridazino[4,5-*b*]indoles **24** in 70%–95% yields (Scheme 4).[16c,16d]

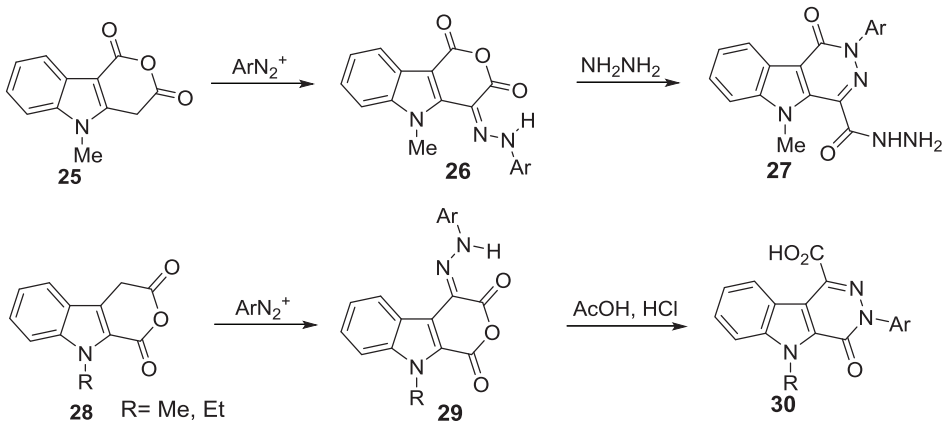


Scheme 4. Synthesis of pyridazino[4,5-*b*]indoles **21** and **24** by inverse electron demand Diels–Alder reaction.

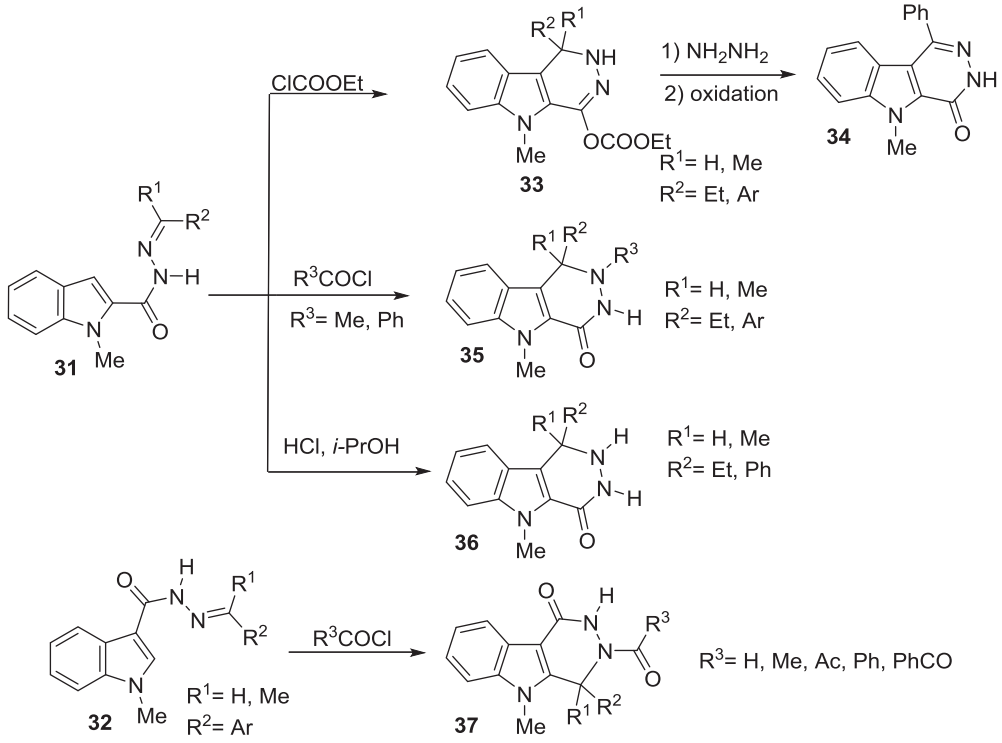
Treatment of aryl diazonium salts with pyrano[4,3-*b*]indole-1,3(4*H*,5*H*)-diones **25**[17a] and/or pyrano[4,3-*b*]indole-1,3(4*H*,9*H*)-diones **28**[17b] and subsequent cyclization of intermediates gave pyridazino[4,5-*b*]indoles **27** and **30** (Scheme 5).

Cyclization of (*N*-methylindole)carbohydrazones **31** and **32** in acidic media is also another synthetic procedure to obtain pyridazino[4,5-*b*]indoles **33**–**37**[17d,19] (Scheme 6).

Herein, the synthesis of a large series of 5*H*-pyridazino[4,5-*b*]indole derivatives including amino, hydrazino, alkyl, and aryl substituents is reported. The structures of the synthesized pyridazino[4,5-*b*]indole were well elucidated by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analyses. Their antimicrobial activities against the variety of selected bacteria and a fungus were investigated and reported as minimum inhibitory concentration (MIC) in order to evaluate the substituent effects of alkyl, aryl, amino, and hydrazino groups attached to the pyridazino[4,5-*b*]indole core.



Scheme 5. Synthesis of pyridazino[4,5-*b*]indoles **27** and **30** from **25** and **28**.



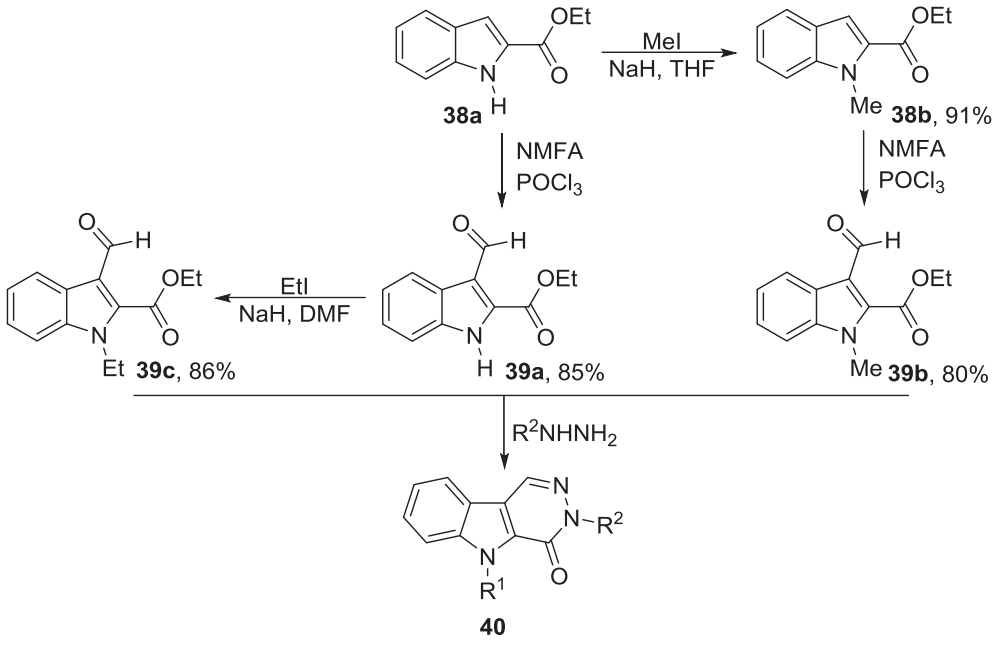
Scheme 6. Synthesis of pyridazino[4,5-*b*]indoles **33**–**37** from **31** and **32**.

2. Results and discussion

Although the synthesis of pyridazino[4,5-*b*]indoles from 2,3-dicarbonylindoles has been applied for a long time, it is still the commonly used approach to attain large varieties of titled compounds in high yields after one-pot procedures without needing long purification steps.

The starting material, ethyl 1*H*-indole-2-carboxylate **38a**, was obtained via Fischer indolization according to previously reported methods (Scheme 7).[20] Vilsmeier–Haack formylation of ethyl 1*H*-indole-2-carboxylate **38a** by $POCl_3$ and *N*-methylformanilide gave ethyl 3-formyl-1*H*-indole-2-carboxylate **39a** (85%). Compound

38a was methylated with MeI under basic conditions to give **38b** (91%), which further underwent formylation reaction to afford **39b** (80%). Ethyl 1-ethyl-1*H*-indole-2-carboxylate **39c** was prepared in 86% yield from **39a** by treatment of ethyl iodide in NaH/DMF, whereas reaction with ethyl 1*H*-indole-2-carboxylate **38a** did not proceed well, due to its low reactivity. Cyclization reactions of **39a**–**39c** with hydrazine or methylhydrazine in 2-ethoxyethanol yielded 3-H and 3-methyl substituted 3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole derivatives **40aa**, **40ab**, **40ba**, **40bb**, **40ca**, and **40cb** in moderate to high yields (41%–91%). 3-Aryl derivatives of 3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indoles **40** were prepared in 38%–95% yields by cyclization reactions of **39a**–**39c** with aryl hydrazines in glacial acetic acid (Scheme 7).



40aa R^1= H, R^2= H, 85%
40ab R^1= H, R^2= Me, 45%
40ac R^1= H, R^2= Ph, 87%
40ad R^1= H, R^2= 3,4-dimethylphenyl, 85%
40ae R^1= H, R^2= 4-methoxyphenyl, 81%
40af R^1= H, R^2= 4-fluorophenyl, 80%
40ag R^1= H, R^2= 4-chlorophenyl, 95%
40ah R^1= H, R^2= 4-bromophenyl, 72%
40ai R^1= H, R^2= 2-ethylphenyl, 48%

40ba R^1= Me, R^2= H, 91%
40bb R^1= Me, R^2= Me, 41%
40bc R^1= Me, R^2= Ph, 78%
40bd R^1= Me, R^2= 3,4-dimethylphenyl, 87%
40be R^1= Me, R^2= 4-methoxyphenyl, 69%
40bf R^1= Me, R^2= 4-fluorophenyl, 84%
40bg R^1= Me, R^2= 4-chlorophenyl, 86%
40bh R^1= Me, R^2= 4-bromophenyl, 76%
40ai R^1= Me, R^2= 2-ethylphenyl, 38%

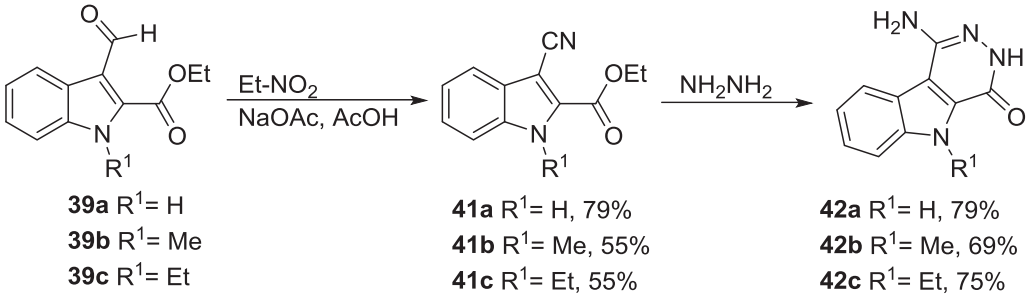
40ca R^1= Et, R^2= H, 82%
40cb R^1= Et, R^2= Me, 68%
40cc R^1= Et, R^2= Ph, 65%
40cd R^1= Et, R^2= 3,4-dimethylphenyl, 85%
40ce R^1= Et, R^2= 4-methoxyphenyl, 69%
40cf R^1= Et, R^2= 4-fluorophenyl, 89%
40cg R^1= Et, R^2= 4-chlorophenyl, 83%
40ch R^1= Et, R^2= 4-bromophenyl, 87%
40ai R^1= Et, R^2= 2-ethylphenyl, 47%

Scheme 7. Synthesis of 3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indoles **40**.

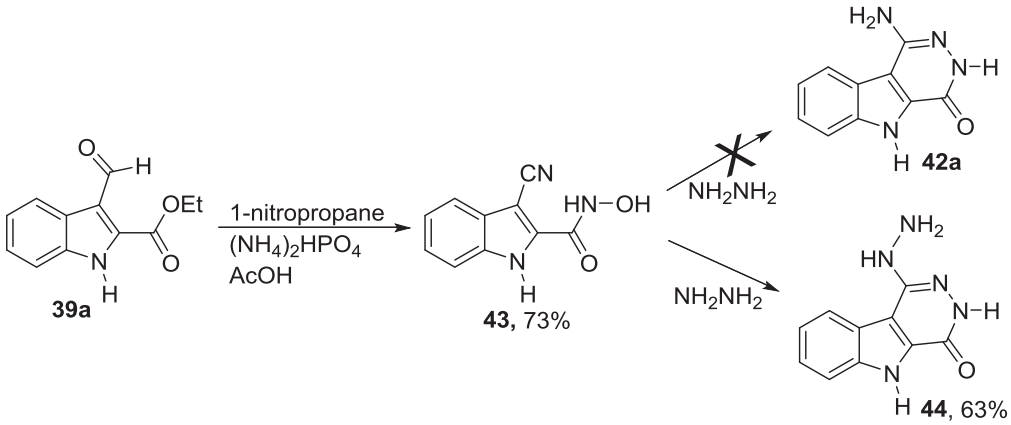
Ethyl 3-cyano-1*H*-indole-2-carboxylates **41** were obtained in 55%–79% yields from corresponding formyl indoles **39** by treatment with an in situ hydroxylamine-producing buffer consisting of acetic acid, sodium acetate and nitroethane.[21] Ethyl 3-cyano-1*H*-indole-2-carboxylates **41** were subsequently treated with hydrazine to obtain 1-amino-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indoles **42** in 69%–79% yields (Scheme 8).

Blatter et al. previously reported the preparation of 3-cyanoindole from indole-3-carboxaldehyde by treatment with another buffer consisting of diammonium hydrogen phosphate, acetic acid, and 1-nitropropane.[22] Herein, the treatment of 3-formyl-1*H*-indole-2-carboxylate **39a** with this high boiling buffer gave 3-cyano-1*H*-indole-2-hydroxamic acid **43** in 73% yield (Scheme 9). In contrast to the expected formation of **42a**, the reaction

of **43** with unsubstituted hydrazine gave 3,4-dihydro-1-hydrazino-4-oxo-5*H*-pyridazino[4,5-*b*]indole **44** in 63% yield (Scheme 9). Compound **44** was reformed from hydroxamic acid derivative **43** in several other attempts under the same conditions.

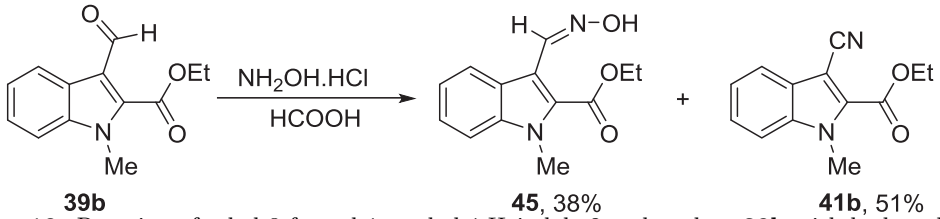


Scheme 8. Synthesis of 1-amino-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indoles **42**.



Scheme 9. Synthesis of 1-hydrazino-4-oxo-5*H*-pyridazino[4,5-*b*]indole **44**.

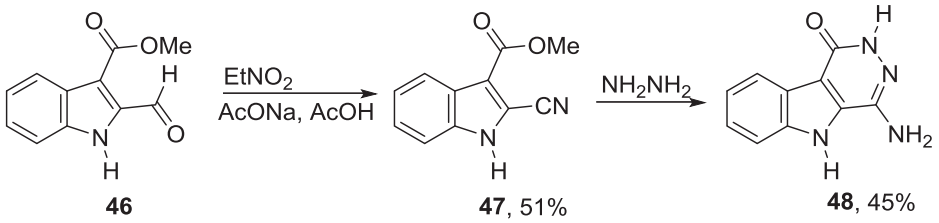
Another approach to install cyano functionality (Scheme 10) is the treatment of formyl functionalized indoles with hydroxylamine in formic acid. Nevertheless, reaction of **39b** with hydroxylamine resulted in the formation of 2 different products, ethyl 3-(*N*-hydroxyiminomethyl)-1-methyl-1*H*-indole-2-carboxylate **45** and ethyl 3-cyano-1-methyl-1*H*-indole-2-carboxylate **41b**, in moderate yields (Scheme 10). Compounds **45** and **41b** were separated by column chromatography.



Scheme 10. Reaction of ethyl 3-formyl-1-methyl-1*H*-indole-2-carboxylate **39b** with hydroxylamine.

4-Amino-1,2-dihydro-1-oxo-5*H*-pyridazino[4,5-*b*]indole **48** (Scheme 11) was obtained in 45% yield from the cyclization of hydrazine and methyl 2-cyano-1*H*-indole-3-carboxylates **47**, which were prepared from corresponding 2-formylindole **46** by treatment with nitroethane buffer (Scheme 11).[23] Compound **48** and its

reversed isomer **42a** showed almost identical ^{1}H NMR spectra, where **42a** had clear singlets at 12.66 ppm (indole-NH) and 11.79 ppm (pyridazine-NH) and compound **48** gave singlets at 11.89 ppm (indole-NH) and 11.43 ppm (pyridazine-NH).



Scheme 11. Synthesis of 4-amino-1,2-dihydro-1-oxo-5*H*-pyridazino[4,5-*b*]indole **48**.

2.1. Antimicrobial activity

MICs are defined as the minimum concentration of an active compound necessary to inhibit the growth of tested microorganisms. All tested compounds showed antibacterial and antifungal activity as compared to the reference drugs (Table).

The antibacterial assessment revealed that the compounds possess significant activity. The MIC values are generally within the range of 31.25–250 μg/mL against all evaluated strains. In comparing their MIC values with chloramphenicol (reference antibacterial), compounds **41a**, **41b**, **41c**, **42a**, **42b**, **42c**, **43**–**45**, **38a**, **40bc**, **40bd**, **40be**, **40bf**, **40bg**, **40cb**, **40ce**, **40cf**, **40cg**, **40ch**, and **40bi** had MIC values of 15.6–31.25 μg/mL, which is the range of the reference antibacterial. *Bacillus subtilis* **F**, a gram-positive bacteria, was the most sensitive microorganism against the compounds tested. The results in the Table show various activities against *Bacillus subtilis* **F**, suggesting that there is a variation in the growth of this microorganism depending on the substituents attached to pyridazino[4,5-*b*]indole. Those substituents that increase the target molecules' lipophilicity, having alky functionality on the 5-position or having an aryl functionality on the 3-position of pyridazino[4,5-*b*]indole, increase the antimicrobial activity against *Bacillus subtilis* **F**. For example, compound **40bc**, which has 5-methyl, 3-phenyl substitutions, showed better activity (MIC = 31.25 μg/mL) against *Bacillus subtilis* **F** than compound **40ac** (MIC = 125 μg/mL) with 5-H, 3-phenyl substitutions and also unsubstituted 5*H*-pyridazino[4,5-*b*]indole **40aa** (MIC = 250 μg/mL). Moreover, amino and hydrazino on the 1-position of pyridazino[4,5-*b*]indole (**42** and **44**) comparatively reduce the bacteria growth. Compound **42b** showed the highest MIC value (15.6 μg/mL) on *Bacillus subtilis*. Nevertheless, halogen substitution on the aryl ring attached on the 3-position did not provide a significant variance in antimicrobial activity against the selected microorganisms.

When compared with ketoconazole, only compounds **41a** showed closer activity against *Candida albicans* **H**, whereas all other compounds showed a moderate level of activities (MIC = 250 μg/mL). However, *S. aureus* **A** was the second most sensitive organism against compounds **42a** and **42c** (MIC = 62.5 μg/mL). Therefore, these compounds may be evaluated for the synthesis of novel antibacterials.

In conclusion, we report the synthesis and antimicrobial activities of a long series of amino, hydrazino, alkyl, and aryl substituted 5*H*-pyridazino[4,5-*b*]indoles. All prepared compounds showed moderate levels of antimicrobial activities against the variety of selected bacteria and a fungus. Compound **42b** exhibited the highest MIC value (15.6 μg/mL) against *Bacillus subtilis*, which was the most sensitive microorganism to the tested compounds.

Table. Antimicrobial activities of tested compounds (μg/mL).

Compound/m.o.	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**
38a	250	250	250	125	250	31.25	125	250
38b	250	250	250	125	250	125	125	250
39a	250	250	250	125	250	125	125	250
39b	250	250	250	125	250	125	125	250
39c	250	250	250	125	250	125	125	250
40aa	250	250	250	250	250	250	125	250
40ab	250	250	250	250	250	250	125	250
40ac	250	250	250	250	250	125	125	250
40ad	250	250	250	125	250	62.5	125	250
40ae	250	250	250	250	250	250	125	250
40af	250	250	250	250	250	125	125	250
40ag	250	250	250	250	250	125	250	250
40ah	250	250	250	250	250	250	250	250
40ai	250	250	250	125	250	62.5	125	250
40ba	250	250	250	250	250	250	250	250
40bb	250	250	250	250	250	250	125	250
40bc	250	250	250	125	250	31.25	125	250
40bd	250	250	250	125	250	31.25	125	250
40be	250	250	250	125	250	31.25	125	250
40bf	250	250	250	250	250	31.25	125	250
40bg	250	250	250	125	250	31.25	125	250
40bh	250	250	250	125	250	62.5	125	250
40bi	250	250	250	250	250	31.25	125	250
40ca	250	250	250	125	250	62.5	125	250
40cb	250	250	250	125	250	31.25	125	250
40cc	250	250	250	250	250	62.5	125	250
40cd	125	250	250	250	250	62.5	125	250
40ce	250	250	250	125	250	31.25	125	250
40cf	250	250	250	250	250	31.25	125	250
40cg	250	250	250	125	250	31.25	125	250
40ch	250	250	250	125	250	31.25	125	250
40ci	250	250	250	250	250	62.5	125	250
41a	250	250	250	125	250	31.25	125	125
41b	250	250	250	125	250	31.25	125	250
41c	250	250	250	125	250	31.25	125	250
42a	62.5	125	250	250	250	31.25	125	250
42b	125	250	250	250	250	15.6	125	250
42c	62.5	250	250	125	250	31.25	125	250
43	250	250	250	125	250	31.25	125	250
44	125	250	250	125	250	31.25	125	250
45	250	250	250	250	250	31.25	125	250
Ch	31.25	15.6	15.6	31.25	31.25	31.25	31.25	-
KC	-	-	-	-	-	-	-	3.9

m.o.: Microorganisms, **A:** *Staphylococcus aureus* NRRL B-767, **B:** *Escherichia coli* ATCC 25922, **C:** *Pseudomonas aeruginosa* ATCC 27853, **D:** *Proteus vulgaris* NRRL-B123, **E:** *S. typhimurium* NRRL B-4420, **F:** *B. subtilis* NRRL 744, **G:** *L. monocytogenes* ATCC 7644, **H:** *Candida albicans*, **Ch:** chloramphenicol, **KC:** ketoconazole. **-:** not tested.

3. Experimental

All chemicals used in the present study were of analytical grade and purchased from commercial suppliers. Melting points were determined with a Sanyo Gallenkamp MPD350 apparatus and were uncorrected. Infrared spectra were recorded using potassium bromide disks on a Jasco FT/IR-300E infrared spectrophotometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker Biospin 500 MHz apparatus in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard. The data are reported as follows: chemical shift in parts per million (ppm, δ units) and spin-spin coupling J (Hz). Elemental analyses were performed on a Vario EL III CHNOS elemental analyzer. Combustion analyses agreed with the calculated data within $\pm 0.4\%$. DMF was dried and distilled over CaH_2, whereas THF was used after distillation over Na/benzophenone. Compounds **38a**[20] and **46**[23] were prepared according to literature procedures.

3.1. Ethyl 1-methyl-1*H*-indole-2-carboxylate (38b)

Compound **38a** (9.45 g, 50 mmol) was added portionwise to a cooled solution of NaH (2.2 g, 55 mmol) in dry THF (250 mL). After the mixture was stirred for 30 min, MeI (4 mL, 60 mmol) was added dropwise via syringe. The mixture was stirred for 6 h at room temperature, and then $H_2C_2O_4 \cdot 2H_2O$ salt was added for neutralization and THF was evaporated. The residue was washed with excess water and dissolved in DCM. The solvent was evaporated after the solution was dried over $MgSO_4$. The crude product was recrystallized from EtOH and dried under high vacuum to afford ethyl 1-methyl-1*H*-indole-2-carboxylate **38b** (9.23 g, 91%) as pale yellowish microcrystals. Yield 91%, mp 61.5–62 °C (lit.[24] 62–63 °C).

3.2. Synthesis of ethyl 3-formyl-1*H*-indole-2-carboxylate (39a) and ethyl 3-formyl-1-methyl-1H-indole-2-carboxylate (39b)

A mixture of *N*-methyl formanilide (NMFA) (8.68 g, 63.5 mmol) and $POCl_3$ (9.85 g, 63.5 mmol) in 1,2-dichloroethane (30 mL) was mixed under nitrogen atmosphere at room temperature. After 1 h, a solution of **38a** or **38b** (58 mmol) in 1,2-dichloroethane (30 mL) was added dropwise to this solution. The reaction mixture was kept at reflux temperature for 2 h. The reaction mixture was then neutralized by pouring onto a sodium acetate/ice mixture. The mixture was extracted with diethyl ether, washed with brine, and dried over $MgSO_4$. After evaporation of solvent, the crude was recrystallized from EtOH and dried under high vacuum. Ethyl 3-formyl-1*H*-indole-2-carboxylate **39a** (10.71 g, 85%) was obtained as pale yellow microcrystals. Yield: 85%, mp 191–192 °C (lit.[25] 187–188 °C). Ethyl 3-formyl-1-methyl-1H-indole-2-carboxylate **39b** (10.70 g, 80%) was obtained as pale yellow microcrystals. Yield: 80%, mp 111 °C (lit.[25] 108 °C).

3.3. Ethyl 1-ethyl-3-formyl-1*H*-indole-2-carboxylate (39c)

NaH in mineral oil (0.24 g, 6.0 mmol) was added portionwise into a cooled solution of **39a** (1.0 g, 4.6 mmol) in dry DMF (10 mL). After the mixture was stirred for 1 h at room temperature, EtI (0.5 mL, 6 mmol) was added via syringe. The mixture was stirred for 7 h. Crushed ice-water (30 g) and 1 N HCl (1.5 mL) were added for quenching. The precipitate that was formed was collected by filtration and washed with water. The residue was recrystallized from EtOH and dried under high vacuum to afford ethyl 1-ethyl-3-formyl-1*H*-indole-2-carboxylate **39c**. Yield: 86%: mp 109–111 °C (lit.[2c] 95–96 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.44 (s, 1H, -C*H*O), 8.32 (d, J = 8.0 Hz, 1H, H-4), 7.77 (d, J = 8.4 Hz, 1H, H7), 7.47 (t, J = 7.7 Hz, 1H, H-6), 7.36

(t, J = 7.5 Hz, 1H, H-5), 4.59 (q, J = 7.1 Hz, 2H, -OCH_2-), 4.49 (q, J = 7.1 Hz, 2H, OCH_2-), 1.36–1.43 (m, 6H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.98, 160.68, 137.15, 134.41, 126.46, 124.37, 124.33, 122.96, 118.96, 112.01, 62.67, 40.79, 15.85, 14.38. Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.40; H, 6.26; N, 5.70.

3.4. General procedure for the synthesis of 3-alkyl-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indoles (40aa, 40ab, 40ba, 40bb, 40ca, 40cb)

A suspension of **39a**–**39c** (4 mmol) and hydrazine monohydrate (1 mL) or methyl hydrazine (1.5 mL) in 2-ethoxyethanol (10 mL) or glycerin (8 mL) with 1–2 drops of acetic acid was boiled at reflux temperature for several hours. After a white precipitate was formed, it was cooled to ambient temperature. Cold water was added (50 mL) for quenching. White precipitate was collected by filtration. Residue was washed with water and cold ethyl alcohol. It was dried under high vacuum. An analytical sample was prepared by further recrystallization from the appropriate solvent.

3.4.1. 3,4-Dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40aa)

Reaction mixture was boiled at reflux temperature for 4 h in 2-ethoxyethanol. Residue was washed with ethyl alcohol to afford **40aa** (0.63 g, 85%) as pale white microcrystals. Yield: 85%, mp 326–327 °C (lit.[2c] 324–326 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.84 (s, 1H, NH, indole), 12.74 (s, 1H, NH), 8.76 (s, 1H, H-1), 8.17 (d, J = 8.0 Hz, 1H, H-9), 7.63 (d, J = 8.3 Hz, 1H, H-6), 7.51 (t, J = 7.6 Hz, 1H, H-7), 7.33 (t, J = 7.5 Hz, 1H, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.20, 139.37, 133.76, 132.14, 127.45, 121.92, 121.79, 121.25, 117.97, 113.45. Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.43; H, 3.75; N, 22.59.

3.4.2. 3,4-Dihydro-3-methyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ab)

Reaction mixture was boiled at reflux temperature for 4 h in glycerin. Residue was washed with ethyl alcohol to afford **40ab** (0.21 g, 45%) as pale white microcrystals. Yield: 45%, mp 279–281 °C (lit.[23] 282–283 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.77 (s, 1H, NH), 8.76 (s, 1H, H-1), 8.17 (d, J = 8.0 Hz, 1H, H-9), 7.62 (d, J = 8.2 Hz, 1H, H-6), 7.51 (t, J = 7.6 Hz, 1H, H-7), 7.33 (t, J = 7.5 Hz, 1H, H-8), 3.83 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.10, 139.66, 133.15, 131.92, 127.46, 121.92, 121.85, 121.20, 117.72, 113.47, 39.24. Anal. Calcd. for $C_{11}H19_7N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.71; H, 4.91; N, 20.98.

3.4.3. 3,4-Dihydro-5-methyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ba)

Reaction mixture was boiled at reflux temperature for 5 h in 2-ethoxyethanol. Residue was recrystallized from 2-ethoxyethanol to afford **40ba** (0.725 g, 91%) as white microcrystals. Yield: 91%, mp 282–283 °C (lit.[23] 282–283 °C). IR (KBr, cm^{-1}): 3161–2850 broad, 1673, 1519, 950, 739; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.82 (s, 1H, NH), 8.76 (s, 1H, H-1), 8.21 (d, J = 8.0 Hz, 1H, H-9), 7.76 (d, J = 8.4 Hz, 1H, H-6), 7.62–7.58 (m, 1H, H-7), 7.39 (t, J = 7.3 Hz, 1H, H-8), 4.28 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.78, 140.44, 133.81, 130.66, 127.62, 122.18, 121.93, 120.37, 117.59, 111.69, 31.89. Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.37; H, 4.27; N, 21.07.

3.4.4. 3,4-Dihydro-3,5-dimethyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40bb)

Reaction mixture was boiled at reflux temperature for 4 h in glycerin. Residue was recrystallized from ethyl alcohol to afford **40bb** (0.35 g, 41%) as pale white microcrystals. Yield: 41%, mp 216–217 °C (lit.[23] 211 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 1H, H-1), 8.21 (d, J = 8.0 Hz, 1H, H-9), 7.76 (d, J = 8.4 Hz, 1H, H-6), 7.61 (t, J = 7.7 Hz, 1H, H-7), 7.40 (t, J = 7.5 Hz, 1H, H-8), 4.29 (s, 3H, -CH_3), 3.80 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.55, 140.71, 133.05, 127.65, 122.27, 121.91, 120.22, 117.43, 111.77, 39.34, 31.88. Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.74; H, 5.59; N, 19.39.

3.4.5. 5-Ethyl-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ca)

Reaction mixture was boiled at reflux temperature for 5 h in 2-ethoxyethanol. Residue was recrystallized from DMF to afford **40ca** (0.70 g, 82%) as pale white microcrystals. Yield: 82%, mp 242–244 °C (lit.[2c] 226–227 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.83 (s, 1H, NH), 8.76 (s, 1H, H-1), 8.21 (d, J = 8.0 Hz, 1H, H-9), 7.81 (d, J = 8.4 Hz, 1H, H-6), 7.59 (t, J = 7.7 Hz, 1H, H-7), 7.38 (t, J = 7.5 Hz, 1H, H-8), 4.83 (q, J = 7.0 Hz, 2H, -CH_2-), 1.37 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 156.44, 139.29, 133.67, 130.10, 127.65, 122.09, 120.59, 117.92, 111.65, 16.41. Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.37; H, 5.04; N, 19.72.

3.4.6. 5-Ethyl-3,4-dihydro-3-methyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40cb)

Reaction mixture was boiled at reflux temperature for 5 h in glycerin. Residue was recrystallized from DMF–water to afford **40cb** (0.62 g, 68%) as pale white microcrystals. Yield: 68%, mp 285–287 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (s, 1H, H-1), 8.21 (d, J = 7.9 Hz, 1H, H-9), 7.81 (d, J = 8.4 Hz, 1H, H-6), 7.59 (t, J = 7.7 Hz, 1H, H-7), 7.38 (t, J = 7.5 Hz, 1H, H-8), 4.84 (q, J = 7.0 Hz, 2H, -CH_2-), 3.81 (s, 3H, -CH_3), 1.36 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.22, 139.55, 132.95, 129.80, 127.68, 122.20, 122.07, 120.42, 117.74, 111.71, 39.36, 16.39. Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.72; N, 18.49. Found: C, 68.65; H, 5.34; N, 18.51.

3.5. General procedure for the synthesis of 3-aryl-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indoles (40ac–40ai, 40bc–40bi, 40cc–40ci)

A mixture of ethyl 3-formyl-1*H*-indole-2-carboxylates **39a–c** (2 mmol) and phenylhydrazines (2 mmol) in glacial acetic acid (8 mL) was boiled at reflux temperature for several hours. An equivalent amount of anhydrous AcONa (0.165 g, 2 mmol) was added to the reaction mixture if phenyl hydrazine.HCl salts were used. The mixture was then cooled to room temperature. The solvent was removed under vacuum. The residue was washed with 1 M Na_2CO_3 solution and water. Subsequent crystallization from solvent gave pure products of **40ac–40ai**, **40bc–40bi**, and **40cc–40ci**.

3.5.1. 3,4-Dihydro-4-oxo-3-phenyl-5*H*-pyridazino[4,5-*b*]indole (40ac)

Reaction mixture was boiled at reflux temperature for 2 h in acetic acid. Residue was recrystallized from DMF–water to afford **40ac** (0.45 g, 87%) as pale yellowish microcrystals. Yield: 87%, mp 323–325 °C (lit.[15b] 323–324 °C). IR (KBr, cm^{-1}): 3150, 1654, 1532, 736; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.96 (s, 1H, NH), 8.95 (s, 1H, H-1), 8.23 (d, J = 8.0 Hz, 1H, H-9), 7.63–7.67 (m, 3H, HAr), 7.58–7.51 (m, 3H, HAr), 7.44 (t, J = 7.4

Hz, 1H, H7), 7.38 (t, J = 7.5 Hz, 1H, H8); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.94, 142.43, 139.88, 134.30, 132.25, 129.01, 128.06, 127.70, 126.78, 122.14, 122.05, 121.22, 117.40, 113.58. Anal. Calcd. for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08; Found: C, 73.01; H, 3.97; N, 15.92.

3.5.2. 3,4-Dihydro-3-(3,4-dimethylphenyl)-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ad)

Reaction mixture was boiled at reflux temperature for 3 h in acetic acid. Residue was washed with water and ethyl alcohol and recrystallized from DMF to afford **40ad** (0.49 g, 85%) as pale white microcrystals. Yield: 85%, mp 289–291 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.89 (s, 1H, NH), 8.90 (s, 1H, H-1), 8.22 (d, J = 8.0 Hz, 1H, H-9), 7.65 (d, J = 8.3 Hz, 1H, H-6), 7.54 (t, J = 7.6 Hz, 1H, H-7), 7.40–7.25 (m, 4H, HAr), 2.30 (s, 6H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 154.93, 140.29, 139.86, 136.93, 136.22, 133.96, 132.29, 129.82, 139.62, 139.58, 124.03, 122.07, 122.00, 121.23, 117.35, 113.57, 19.85, 19.52. Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52; Found: C, 74.75; H, 5.02; N, 14.53.

3.5.3. 3,4-Dihydro-3-(4-methoxyphenyl)-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ae)

Reaction mixture was boiled at reflux temperature for 3 h in acetic acid. Residue was washed with water and ethyl alcohol and recrystallized from DMF–water to afford **40ae** (0.47 g, 81%) as pale white microcrystals. Yield: 81%, mp 292–294 °C decomp. IR (KBr, cm^{-1}): 3146, 3084, 1644, 1510, 1251, 736; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.92 (s, 1H, NH), 8.91 (s, 1H, H-1), 8.22 (d, J = 8.0 Hz, 1H, H-9), 7.65 (d, J = 8.4 Hz, 1H, H-6), 7.56–7.54 (m, 3H, H-7, HAr), 7.39–7.35 (m, 1H, H-8), 7.07 (d, J = 9.0 Hz, 2H, HAr), 3.84 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.82, 154.97, 139.85, 135.41, 134.01, 132.29, 139.94, 139.63, 122.07, 122.02, 121.23, 117.35, 114.10, 113.55, 55.88. Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; N, 14.42. Found: C, 69.94; N, 14.38.

3.5.4. 3-(4-Fluorophenyl)-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40af)

Reaction mixture was boiled at reflux temperature for 3 h in acetic acid. Residue was washed with water and ethyl alcohol and recrystallized from DMF to afford **40af** (0.45 g, 80%) as pale yellowish microcrystals. Yield: 80%, mp >330 °C decomp. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.96 (s, 1H, NH), 8.94 (s, 1H, H-1), 8.23 (d, J = 7.98 Hz, 1H, H-9), 7.73–7.68 (m, 2H, HAr), 7.66 (d, J = 8.4 Hz, 1H, H-6), 7.55 (t, J = 7.6 Hz, 1H, H7), 7.35–7.40 (m, 3H, H-8, HAr); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.97, 139.89, 134.37, 132.19, 128.91, 128.84, 127.73, 122.17, 122.04, 121.24, 117.45, 115.87, 115.69, 113.60. Anal. Calcd. for $C_{16}H_{10}FN_3O$: C, 68.81; H, 3.61; N, 15.05; Found: C, 69.07; H, 3.63; N, 15.02.

3.5.5. 3-(4-Chlorophenyl)-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ag)

Reaction mixture was boiled at reflux temperature for 6 h in acetic acid. Residue was washed with water and ethyl alcohol and recrystallized from DMF to afford **40ag** (0.56 g, 95%) as pale yellowish microcrystals. Yield: 95%, mp 337–338 °C (lit.[26]). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.98 (s, 1H, NH), 8.96 (s, 1H, H-1), 8.23 (d, J = 8.0 Hz, 1H, H-9), 7.70–7.40 (m, 2H, HAr), 7.66 (d, J = 8.3 Hz, 1H, H-6), 7.58–7.62 (m, 2H, HAr), 7.55 (t, J = 7.7 Hz, 1H, H-7), 7.38 (t, J = 7.5 Hz, 1H, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 154.91, 141.213, 139.91, 134.63, 132.34, 132.13, 128.97, 128.45, 127.77, 122.21, 122.05, 121.23, 117.43, 113.61. Anal. Calcd. for $C_{16}H_{10}ClN_3O$: C, 64.98; H, 3.41; N, 14.21; Found: C, 65.26; H, 3.56; N, 14.20.

3.5.6. 3-(4-Bromophenyl)-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ah)

Reaction mixture was boiled at reflux temperature for 6 h in acetic acid. Residue was washed with water and ethyl alcohol and recrystallized from DMF to afford **40ah** (0.49 g, 72%) as pale yellowish microcrystals. Yield: 72%, mp 325–327 °C decomp. (lit.[26]). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.97 (s, 1H, N*H*), 8.95 (s, 1H, H-1), 8.23 (d, J = 7.99 Hz, 1H, H-9), 7.75–7.72 (m, 2H, *H* Ar), 7.68–7.64 (m, 3H, H-6, *H* Ar), 7.55 (t, J = 7.64 Hz, 1H, H7), 7.38 (t, J = 7.5 Hz, 1H, H-8); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.87, 141.63, 139.91, 134.65, 132.12, 131.92, 128.75, 127.77, 122.21, 122.04, 121.23, 120.78, 117.43, 113.61. Anal. Calcd. for $C_{16}H_{10}BrN_3O$: C, 56.49; H, 2.96; N, 12.35; Found: C, 56.93; H, 3.02; N, 12.57.

3.5.7. 3-(2-Ethylphenyl)-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ai)

Reaction mixture was boiled at reflux temperature for 8 h in acetic acid. Residue was washed with water and recrystallized from 2-ethoxy ethanol–water to afford **40ai** (0.27 g, 48%) as pale yellowish microcrystals. Yield: 48%, mp 290–291 °C decomp. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.96 (s, 1H, NH), 8.92 (s, 1H, H-1), 8.24 (d, J = 8.0 Hz, 1H, H-9), 7.66 (d, J = 8.3 Hz, 1H, H-6), 7.56 (t, J = 7.7 Hz, 1H, H-7), 7.47–7.42 (m, 2H, *H* Ar), 7.41–7.33 (m, 3H, *H* Ar), 2.41 (q, J = 7.54 Hz, 2H, -CH_2-), 1.04 (t, J = 7.6 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.16, 141.27, 141.05, 139.80, 133.89, 132.14, 129.45, 129.31, 128.63, 127.70, 127.02, 122.14, 122.02, 121.29, 117.66, 113.57, 24.14, 14.59. Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52; Found: C, 74.33; H, 5.48; N, 14.18.

3.5.8. 3,4-Dihydro-5-methyl-4-oxo-3-phenyl-5*H*-pyridazino[4,5-*b*]indole (40bc)

Reaction mixture was boiled at reflux temperature for 5 h in acetic acid. Residue was washed with water and recrystallized from ethyl alcohol to afford **40bc** (0.43 g, 78%) as pale white microcrystals. Yield: 78%, mp 174–175 °C, (lit.[17b] 169 °C). IR (KBr, cm^{-1}): 3030, 1656, 1530, 1300, 955, 737; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H, H-1), 8.25 (d, J = 8.0 Hz, 1H, H-9), 7.79 (d, J = 8.4 Hz, 1H, H-6), 7.69–7.38 (m, 6H, *H* Ar), 4.29 (s, 3H, -NCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.43, 142.42, 140.92, 134.12, 130.62, 128.99, 128.11, 127.86, 126.94, 122.54, 122.0, 120.19, 117.15, 111.88, 32.07. Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 73.56; H, 4.52; N, 15.18.

3.5.9. 3,4-Dihydro-5-methyl-3-(3,4-dimethylphenyl)-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40bd)

Reaction mixture was boiled at reflux temperature for 2 h in acetic acid. Residue was washed with water and cold ethyl alcohol and recrystallized from DMF–water to afford **40bd** (0.52 g, 87%) as pale white microcrystals. Yield: 87%, mp 164–165 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (s, 1H, H-1), 8.24 (d, J = 7.9 Hz, 1H, H-9), 7.78 (d, J = 8.4 Hz, 1H, H-6), 7.63 (t, J = 8.1 Hz, 1H, H-7), 7.42 (t, J = 7.4 Hz, 1H, H-8), 7.36 (s, 1H, HAr), 7.32–7.25 (m, 2H, *H* Ar), 4.29 (s, 3H, -NCH_3), 2.30 (s, 6H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.43, 140.93, 140.19, 136.89, 136.22, 133.81, 130.68, 129.82, 127.81, 127.69, 124.11, 122.48, 121.97, 120.21, 117.11, 111.84, 32.03, 19.82, 19.52. Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.24; H, 5.37; N, 13.80.

3.5.10. 3,4-Dihydro-3-(4-methoxyphenyl)-5-methyl-4-oxo-5H-pyridazino[4,5-*b*]indole (40be)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and recrystallized from DMF–water to afford **40be** (0.42 g, 69%) as pale white microcrystals. Yield: 69%, mp 177–178 °C (lit.[17b] 170 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (s, 1H, H1), 8.25 (d, J = 7.9 Hz, 1H, H-9), 7.79 (d, J = 8.5 Hz, 1H, H-6), 7.63 (t, J = 7.3, 1H, H-7), 7.51 (d, J = 8.9 Hz, 2H, *H* Ar), 7.43 (t, J = 7.5 Hz, 1H, H-8), 7.06 (d, J = 8.9, 2H, *H* Ar), 4.30 (s, 3H, -NCH_3), 3.83 (s, 3H, -OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.83, 155.49, 140.91, 135.37, 133.85, 130.67, 128.07, 127.81, 122.49, 121.98, 120.21, 117.12, 114.07, 111.87, 55.87, 32.04. Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.91; H, 4.55; N, 13.85.

3.5.11. 3-(4-Fluorophenyl)-3,4-dihydro-5-methyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40bf)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and cold ethyl alcohol and recrystallized from DMF–water to afford **40bf** (0.49 g, 84%) as pale white microcrystals. Yield: 84%, mp 205–206 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H, H-1), 8.26 (d, J = 7.9 Hz, 1H, H-9), 7.80 (d, J = 8.4 Hz, 1H, H-6), 7.69–7.61 (m, 3H, H-7, *H* Ar), 7.44 (t, J = 7.5 Hz, 1H, H-8), 7.39–7.33 (m, 2H, HAr), 4.30 (s, 3H, -NCH$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.42, 160.47, 155.48, 140.95, 138.71, 134.20, 130.60, 129.07, 129.00, 127.91, 122.58, 122.00, 120.23, 117.21, 115.85, 115.67, 111.90, 32.07. Anal. Calcd. for $C_{17}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found: C, 69.83; H, 4.32; N, 14.24.

3.5.12. 3-(4-Chlorophenyl)-3,4-dihydro-5-methyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40bg)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and cold ethyl alcohol and recrystallized from DMF to give **40bg** (0.53 g, 86%) as pale yellowish microcrystals. Yield: 86%, mp 247–249 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 1H, H-1), 8.27 (d, J = 7.9 Hz, 1H, H-9), 7.82 (d, J = 8.4 Hz, 1H, H-6), 7.73–7.51 (m, 5-H), 7.45 (t, J = 7.5 Hz, 1H, H-8), 4.31 (s, 3H, -NCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.43, 141.21, 141.0, 134.48, 132.40, 130.60, 128.96, 128.65, 127.97, 122.64, 122.04, 120.25, 117.21, 111.95, 32.12. Anal. Calcd. for $C_{17}H_{12}ClN_3O$: C, 65.92; H, 3.90; N, 13.57. Found: C, 65.92; H, 3.73; N, 13.50.

3.5.13. 3-(4-Bromophenyl)-3,4-dihydro-5-methyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40bh)

Reaction mixture was boiled at reflux temperature for 5 h in acetic acid. Residue was washed with water and cold ethyl alcohol and recrystallized from DMF to give **40bh** (0.54 g, 76%) as pale white microcrystals. Yield: 76%, mp 244–245 °C, (lit.[17b] 245 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (s, 1H, H-1), 8.27 (d, J = 7.9 Hz, 1H, H-9), 7.82 (d, J = 8.4 Hz, 1H, H-6), 7.73 (d, J = 8.6 Hz, 2H, *H* Ar), 7.68–7.60 (m, 3H, H7-HAr), 7.44 (t, J = 7.52 Hz, 1H, H8), 4.31 (s, 1H, -NCH$_3$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.40, 141.64, 141.00, 134.51, 131.91, 130.59, 128.96, 127.97, 122.64, 122.04, 120.84, 120.24, 117.20, 111.95, 32.13. Anal. Calcd. for $C_{17}H_{12}BrN_3O$: C, 57.65; H, 3.41; N, 11.86. Found: C, 57.87; H, 3.28; N, 11.89.

3.5.14. 3-(2-Ethylphenyl)-3,4-dihydro-5-methyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40bi)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and recrystallized from ethyl alcohol to afford **40bi** (0.23 g, 38%) as pale yellowish microcrystals. Yield: 38%, mp

295–296 °C decomp. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H, H-1), 8.27 (d, J = 7.9 Hz, 1H, H-9), 7.80 (d, J = 8.4 Hz, 1H, H-6), 7.65 (t, J = 7.72 Hz, 1H, H-7), 7.48–7.30 (m, 3H, H-8, *H* Ar), 7.39–7.31 (m, 2H, *H* Ar), 4.30 (s, 3H, -NCH_3), 2.41 (q, J = 7.0 Hz, 2H, -CH_2-), 1.06 (t, J = 7.6 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 155.62, 141.26, 141.05, 140.87, 133.79, 130.61, 129.39, 129.29, 128.59, 127.89, 126.99, 122.56, 121.00, 120.30, 117.35, 111.90, 32.06, 24.10, 14.60. Anal. Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.08; H, 5.47; N, 13.70.

3.5.15. 5-Ethyl-3,4-dihydro-3-phenyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40cc)

Reaction mixture was boiled at reflux temperature for 8 h in acetic acid. Residue was washed with water and recrystallized from ethyl alcohol to afford **40cc** (0.37 g, 65%) as pale white microcrystals. Yield: 65%, mp 138–139 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (d, J = 8.3 Hz, 1H, H-1), 8.26 (d, J = 7.9 Hz, 1H, H-9), 7.85 (d, J = 8.44 Hz, 1H, H-6), 7.66–7.59 (m, 3H, *H* Ar), 7.53 (t, J = 7.5 Hz, 2H, *H* Ar), 7.47–7.39 (m, 2H, *H* Ar), 4.85 (q, J = 6.9 Hz, 2H, -CH_2-), 1.38 (t, J = 7.0 Hz, 3H, -CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 155.09, 142.43, 139.81, 134.03, 130.07, 128.95, 128.08, 127.92, 126.93, 122.48, 122.16, 120.41, 117.47, 111.82, 16.41. Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.85; H, 5.79; N, 14.50.

3.5.16. 5-Ethyl-3,4-dihydro-3-(3,4-dimethylphenyl)-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40cd)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and recrystallized from ethyl alcohol to afford **40cd** (0.37 g, 85%) as pale yellowish microcrystals. Yield: 85%, mp 159–160 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (s, 1H, H-1), 8.25 (d, J = 8.0 Hz, 1H, H-9), 7.84 (d, J = 8.5 Hz, 1H, H-6), 7.64–7.59 (m, 1H, H-7), 7.41 (t, J = 7.5 Hz, 1H, H-8), 7.38 (d, J = 1.7 Hz, 1H, *H* Ar), 7.31 (dd, J = 8.0, 2.1 Hz, 1H, *H* Ar), 7.26 (d, J = 8.1 Hz, 1H, *H* Ar), 4.85 (q, J = 7.0 Hz, 2H, -CH_2-), 2.30 (s, 6H, -CH_3), 1.38 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.07, 140.20, 139.78, 136.86, 136.18, 133.74, 130.10, 129.77, 127.84, 127.68, 124.13, 122.41, 122.14, 120.41, 117.41, 111.79, 19.81, 19.52, 16.40. Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.72; H, 5.48; N, 13.13.

3.5.17. 5-Ethyl-3,4-dihydro-3-(*p*-methoxyphenyl)-4-oxo-5H-pyridazino[4,5-*b*]indole (40ce)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and recrystallized from ethyl alcohol to afford **40ce** (0.44 g, 69%) as pale white microcrystals. Yield: 69%, mp 172–173 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (s, 1H, H1), 8.25 (d, J = 7.9 Hz, 1H, H9), 7.84 (d, J = 8.4 Hz, 1H, H6), 7.61 (t, J = 7.7 Hz, 1H, H7), 7.52 (d, J = 8.8 Hz, 2H, HAr), 7.41 (t, J = 7.5 Hz, 1H, H-8), 7.06 (d, J = 8.8 Hz, 2H, *H* Ar), 4.85 (q, J = 6.9 Hz, 2H, -NCH_2-), 3.83 (s, 3H, -OCH_3), 1.38 (t, J = 7.0 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.83, 155.13, 139.78, 135.40, 133.74, 130.11, 128.05, 127.84, 122.41, 122.12, 120.42, 117.42, 114.05, 111.78, 55.88, 16.39. Anal. Calcd. for $C_{19}H_{12}N_3O_2$: C, 71.46; N, 13.16. Found: C, 71.74; N, 13.14.

3.5.18. 5-Ethyl-3-(*p*-fluorophenyl)-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40cf)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and recrystallized from ethyl alcohol to afford **40cf** (0.54 g, 89%) as pale white microcrystals. Yield: 89%, mp 162–164 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 1H, H-1), 8.27 (d, J = 7.9 Hz, 1H, H-9), 7.86 (d, J =

8.4 Hz, 1H, H-6), 7.68 (dd, J = 8.7, 5.0 Hz, 2H, H Ar), 7.63 (t, J = 7.7 Hz, 1H, H-7), 7.43 (t, J = 7.5 Hz, 1H, H-8), 7.36 (t, J = 8.7 Hz, 2H, H Ar), 4.85 (q, J = 6.8 Hz, 2H, -CH_2-), 1.39 (t, J = 7.0 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.40, 160.46, 155.12, 139.82, 138.73, 134.13, 130.04, 129.08, 129.01, 127.95, 122.52, 122.18, 120.43, 117.51, 115.82, 115.63, 111.85, 16.40. Anal. Calcd. for $C_{18}H_{14}FN_3O$: C, 70.35; H, 4.59; N, 13.67. Found: C, 69.87; H, 4.40; N, 13.68.

3.5.19. 3-(*p*-Chlorophenyl)-5-ethyl-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40cg)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and recrystallized from ethyl alcohol to afford **40cg** (0.53 g, 83%) as pale white microcrystals. Yield: 83%, mp 147–149 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 1H, H-1), 8.26 (d, J = 7.9 Hz, 1-H, H9), 7.85 (d, J = 8.4 Hz, 1H, H-6), 7.69 (d, J = 8.7 Hz, 2H, H Ar), 7.64–7.60 (m, 1H, H-7), 7.59 (d, J = 8.7 Hz, 2H, H Ar), 7.42 (t, J = 7.4 Hz, 1H, H-8), 4.84 (q, J = 6.9 Hz, 2H, -CH_2-), 1.38 (t, J = 7.0 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.04, 141.20, 139.83, 134.37, 132.34, 129.97, 128.90, 128.61, 127.97, 122.54, 122.17, 120.41, 117.48, 111.84, 16.39. Anal. Calcd. for $C_{18}H_{14}ClN_3O$: C, 66.77; H, 4.36; N, 12.98. Found: C, 66.72; H, 3.81; N, 12.84.

3.5.20. 3-(*p*-Bromophenyl)-5-ethyl-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ch)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and recrystallized from ethyl alcohol to afford **40ch** (0.64 g, 87%) as pale yellowish microcrystals. Yield: 87%, mp 167–168 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 1H, H-1), 8.26 (d, J = 8.0 Hz, 1H, H-9), 7.85 (d, J = 8.5 Hz, 1H, H-6), 7.72 (d, J = 8.7 Hz, 2H, H Ar), 7.65–7.59 (m, 3H, H-7, H Ar), 7.42 (t, J = 7.5 Hz, 1H, H-8), 4.84 (q, J = 7.0 Hz, 2H, -CH_2-), 1.38 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.00, 141.63, 139.83, 134.39, 131.85, 129.97, 128.92, 127.97, 122.54, 122.16, 120.77, 120.41, 117.47, 111.84, 16.39. Anal. Calcd. for $C_{18}H_{14}BrN_3O$: C, 58.71; H, 3.83; N, 11.41. Found: C, 58.72; H, 3.73; N, 11.39.

3.5.21. 5-Ethyl-3-(2-ethylphenyl)-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (40ci)

Reaction mixture was boiled at reflux temperature for 4 h in acetic acid. Residue was washed with water and recrystallized from ethyl alcohol to afford **40ci** (0.30 g, 47%) as pale yellowish microcrystals. Yield: 47%, mp 275–277 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H, H-1), 8.28 (d, J = 7.8 Hz, 1H, H-9), 7.8 (d, J = 8.4 Hz, 1H, H-6), 7.63 (t, J = 7.6 Hz, 1H, H-7), 7.47–7.41 (m, 3H, H Ar), 7.40–7.33 (m, 2H, H Ar), 4.90–4.80 (m, 2H, -NCH_2-), 2.41 (q, 6.8 Hz, 2H, -CH_2-), 1.37 (t, J = 6.8 Hz, 3H, -CH_3), 1.05 (t, J = 7.5 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.26, 141.26, 141.03, 139.73, 133.70, 130.02, 129.42, 129.28, 128.62, 127.92, 127.00, 122.49, 122.17, 120.49, 117.70, 111.84, 24.14, 16.47, 14.57. Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.53; H, 5.62; N, 13.07.

3.6. Ethyl 3-cyano-1*H*-indole-2-carboxylate (41a)

A mixture of compound **39a** (1.08 g, 5 mmol), anhydrous AcONa (1.65 g, 20 mmol), glacial acetic acid (5 mL), and nitroethane (3 mL) was boiled at reflux temperature for 12 h. After cooling of the dark brown suspension, all volatile material was removed under reduced pressure. Water was added to the residue. The precipitated product was collected by filtration and washed well with concentrated $NaHCO_3$ solution. The crude product

was recrystallized from EtOH–water and gave **41a** (0.83 g, 79%) as pale yellowish microcrystals. Yield: 79%, mp 164.5–166 °C (lit.[5] 167 °C). IR (KBr, cm^{-1}): 3285, 2986, 2221, 1694, 1265, 1016, 744. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.12 (s, 1H, NH), 7.75 (d, J = 8.1 Hz, 1H, H-4), 7.61 (d, J = 8.3 Hz, 1H, H-7), 7.46 (t, J = 7.6 Hz, 1H, H-6), 7.35 (t, J = 7.5 Hz, 1H, H-5), 4.44 (q, J = 7.1 Hz, 2H, -CH_2-), 1.39 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.42, 136.17, 132.70, 127.80, 126.86, 123.56, 120.18, 115.02, 114.33, 89.17, 62.29, 14.50. Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.05; H, 4.67; N, 13.06.

3.7. Ethyl 3-cyano-1-methyl-1*H*-indole-2-carboxylate (41b)

A mixture of compound **39b** (1.15 g, 5 mmol), anhydrous NaOAc (1.65 g, 20 mmol), glacial acetic acid (5 mL), and nitroethane (3 mL) was boiled at reflux temperature for 11 h. After cooling of the dark brown suspension, volatile material was removed under reduced pressure. Water was added to the residue. The precipitated product was collected by filtration and washed well with concentrated $NaHCO_3$ solution. The crude product was recrystallized from EtOH–water and gave **41b** (0.63 g, 55%) as pale yellowish microcrystals. Yield: 55%, mp 141–143 °C (lit.[27] 128–129 °C). IR (KBr, cm^{-1}): 2998, 2223, 1715, 1259, 757. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.76 (d, J = 8.5 Hz, 1H, H-4), 7.71 (d, J = 8.1 Hz, 1H, H-7), 7.50 (t, J = 7.7 Hz, 1H, H-6), 7.39–7.34 (m, 1H, H-5), 4.41 (q, J = 7.1 Hz, 2H, -CH_2-), 4.05 (s, 3H, -NCH_3), 1.39 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.45, 138.01, 132.66, 126.86, 126.49, 123.87, 120.15, 114.97, 112.81, 90.53, 62.30, 33.07, 14.28. Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.37; H, 5.32; N, 12.29.

3.8. Ethyl 3-cyano-1-ethyl-1*H*-indole-2-carboxylate (41c)

A mixture of compound **39c** (0.610 g, 2.5 mmol), anhydrous AcONa (0.85 g, 10 mmol), glacial acetic acid (2.5 mL), and nitroethane (1.5 mL) was boiled at reflux temperature for 11 h. After cooling of the dark brown suspension, volatile material was removed under reduced pressure and water was added to the residue. The precipitated product was collected by filtration and washed well with concentrated $NaHCO_3$ solution. It was recrystallized from EtOH–water and gave **40c** (0.36 g, 60%) as pale yellowish microcrystals. For further purification, use of a column chromatograph (20%, AcOEt–hexane) gave **41c** (0.33 g, 55%). Yield: 55%, mp 145–146 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.84 (d, J = 8.5 Hz, 1H, H-4), 7.76 (d, J = 8.1 Hz, 1H, H-7), 7.55–7.50 (m, 1H, H-6), 7.39 (t, J = 7.5 Hz, 1H, H-5), 4.66 (q, J = 7.1 Hz, 2H, -NCH_2-), 4.45 (q, J = 7.1 Hz, 2H, -OCH_2-), 1.40 (t, J = 7.1 Hz, 3H, -CH_3), 1.35 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.27, 137.09, 131.97, 127.05, 126.74, 123.98, 120.39, 114.99, 112.77, 90.95, 62.40, 40.99, 15.82, 14.26. Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.95; H, 5.80; N, 11.13.

3.9. 1-Amino-3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole (42a)

A mixture of compound **41a** (0.215 g, 1 mmol) and hydrazine monohydrate (2 mL) was boiled at reflux temperature for 5 h. After reaction the mixture was cooled to room temperature and water (10 mL) was added. The precipitated product was collected by filtration and washed with water and EtOH. It was dried under vacuum to afford **42a** (0.160 g, 79%) as pale white microcrystals. Yield: 79%, mp >330 °C decomp. IR (KBr, cm^{-1}): 3265, 3166, 3078, 2964, 1657, 1627, 1435, 734; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.66 (s, 1H, NH (indole)), 11.79 (s, 1H, NH (pyridazine)), 8.31 (d, J = 8.1 Hz, 1H, H-9), 7.61 (d, J = 8.3 Hz, 1H, H-6), 7.47

(t, J = 7.4 Hz, 1H, H-7), 7.29 (t, J = 7.3 Hz, 1H, H-8), 5.79 (s, 2H, -NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.79, 146.69, 138.89, 132.83, 126.44, 122.59, 121.38, 121.18, 113.16, 110.64. Anal. Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.64; H, 3.97; N, 28.11.

3.10. 1-Amino-3,4-dihydro-5-methyl-4-oxo-5*H*-pyridazino[4,5-*b*]indole (42b)

A mixture of compound **41b** (0.38 g, 1.6 mmol) and hydrazine monohydrate (2.5 mL) was boiled at reflux temperature for 5 h. After the reaction mixture was cooled to room temperature, water (10 mL) was added. The precipitated product was collected by filtration and washed with water and EtOH. It was dried under vacuum to afford **42b** (0.23 g, 69%) as pale white microcrystals. Yield: 69%, mp >350 °C decomp. IR (KBr, cm^{-1}): 3412, 3329, 3222, 3153, 2975, 2883, 1654, 1617, 1538, 1453, 736; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.76 (s, 1H, NH (pyridazine)), 8.33 (d, J = 8.0 Hz, 1H, H-9), 7.73 (d, J = 8.4 Hz, 1H, H-6), 7.56 (t, J = 7.6 Hz, 1H, H-7), 7.36 (t, J = 7.5 Hz, 1H, H-8), 5.75 (s, 2H, -NH_2), 4.29 (s, 3H, -NCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.35, 146.72, 140.01, 131.01, 126.63, 122.71, 121.80, 120.17, 111.35, 110.42, 31.52. Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.46; H, 4.60; N, 26.39.

3.11. 1-Amino-3,4-dihydro-5-ethyl-4-oxo-5*H*-pyridazino[4,5-*b*]indoles (42c)

A mixture of compound **41c** (0.24 g, 1.0 mmol) and hydrazine monohydrate (2.5 mL) was boiled at reflux temperature for 6 h. After the reaction mixture was cooled to room temperature, water (10 mL) was added. The precipitated product was collected by filtration and washed with water and EtOH. It was dried under vacuum to afford **42c** (0.18 g, 75%) as pale white microcrystals. Yield: 75%, mp >300 °C decomp. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.76 (s, 1H, -NH (pyridazine)), 8.33 (d, J = 8.1 Hz, 1H, H-9), 7.79 (d, J = 8.4 Hz, 1H, H-6), 7.55 (t, J = 7.4 Hz, 1H, H-7), 7.35 (t, J = 7.6 Hz, 1H, H-8), 5.74 (s, 2H, -NH_2), 4.87 (q, J = 7.0 Hz, 2H, -CH_2-), 1.35 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ155.03, 146.64, 138.83, 130.50, 126.64, 122.88, 121.71, 120.41, 111.30, 110.72, 39.39, 16.31. Anal. Calcd. for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.19; H, 4.95; N, 24.40.

3.12. 3-Cyano-1*H*-indole-2-hydroxamic acid (43)

A mixture of compound **41a** (2.18 g, 10 mmol), $(NH_4)_2HPO_4$ (7.0 g, 53 mmol), glacial acetic acid (10 mL), and 1-nitropropane (30 mL) was boiled at reflux temperature for 13 h. After cooling the suspension, volatile material was removed under reduced pressure. Water (50 mL) was added to the residue. The precipitated product was collected by filtration. The crude product was recrystallized from EtOH to give compound **43** (1.46 g, 73%) as pale white microcrystals. Yield: 73%, mp 291–293 °C. IR (KBr, cm^{-1}): 3284, 3190, 3085, 2922, 2221, 1573, 1455, 728; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (d, J = 7.8 Hz, 1H, H-4), 7.49 (d, J = 8.1 Hz, 1H, H-7), 7.25 (t, J = 7.4 Hz, 1H, H-6), 7.18 (t, J = 7.4 Hz, 1H, H-5); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.22, 145.52, 134.84, 128.65, 123.95, 121.75, 119.14, 117.36, 113.65, 84.36. Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.42; H, 3.84; N, 20.58.

3.13. 3,4-Dihydro-1-hydrazino-4-oxo-5*H*-pyridazino[4,5-*b*]indole (44)

A mixture of compound **43** (0.370 g, 1.85 mmol) and hydrazine monohydrate (2 mL) was boiled at reflux temperature for 5 h. After the reaction mixture was cooled to room temperature, water (10 mL) was added.

The precipitated product was collected by filtration and washed with water and EtOH. It was dried under vacuum to afford **44** (0.25 g, 63%) as pale white microcrystals. Yield: 63%, mp 312–316 °C decomp. IR (KBr, cm^{-1}): 3267, 3158, 2899, 1634, 1619, 1532, 738; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.70 (s, 1H, N*H* (indole)), 12.03 (s, 1H, N*H* (pyridazine)), 8.26 (d, J = 7.7 Hz, 1H, H-9), 7.60 (d, J = 8.0 Hz, 1H, H-6), 7.50–7.43 (m, 2H, -N*H* and H-7), 7.28 (t, J = 7.0 Hz, 1H, H-8), 4.16 (s, 2H, -NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ155.06, 148.78, 138.88, 132.48, 126.49, 123.32, 121.51, 120.66, 113.12, 109.74. Anal. Calcd. for $C_{10}H_9N_5O$: C, 55.81; H, 4.22; N, 32.54. Found: C, 56.03; H, 3.78; N, 32.09.

3.14. Ethyl 3-(*N*-hydroxyiminomethyl)-1-methyl-1*H*-indole-2-carboxylate (45)

A mixture of compound **39b** (2.0 g, 8.6 mmol), $NH_2OH.HCl$ (0.78 g, 10 mmol), and formic acid (8 mL) was boiled at reflux temperature for 1 h. Reaction was monitored with TLC (pet.ether, ethyl acetate (2:1)). After the reaction mixture was cooled to room temperature, the mixture was poured into icy water (100 mL) and neutralized with 1 N NaOH. The mixture was extracted with diethyl ether (3 × 20 mL). The organic phase was collected and dried over $MgSO_4$. Solvent was removed under vacuum. The products (**41b** and **45**) were separated by column chromatograph (pet.ether, ethyl acetate (2:1)). Compound **41b** (0.98 g, 51%) was obtained as a white microcrystals, mp 141.5–143 °C. Compound **45** (0.80 g, 38%) was obtained as a yellow microcrystals, mp 192–193 °C decomp. IR (KBr, cm^{-1}): 3422, 2982, 1684, 1257, 966, 743; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.18 (s, 1H, -O*H*), 8.77 (s, 1H, -C*H* =N), 8.23 (d, J = 8.0 Hz, 1H, H-4), 7.64 (d, J = 8.4 Hz, 1H, H-7), 7.42 (t, J = 7.6 Hz, 1H, H-6), 7.23 (t, J = 7.4 Hz, 1H, H-5), 4.41 (q, J = 7.0 Hz, 2H, -CH_2-), 3.98 (s, 3H, -NCH_3), 1.38 (t, J = 7.0 Hz, 3H, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.59, 145.49, 138.94, 127.70, 126.15, 124.18, 123.59, 122.16, 114.98, 111.54, 61.68, 32.71, 14.55. Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.56; H, 5.75; N, 11.39.

3.15. Methyl 2-cyano-1*H*-indole-3-carboxylate (47)

The mixture of methyl 2-formyl-1*H*-indole-3-carboxylate **46** (0.51 g, 2.5 mmol), anhydrous AcONa (0.82 g, 10 mmol), glacial acetic acid (2.5 mL), and nitroethane (1.5 mL) was boiled at reflux temperature for 10 h. After cooling of the dark brown suspension to room temperature, volatile material was removed under reduced pressure. Water (15 mL) was added to the residue. The precipitated product was collected by filtration and washed well with concentrated $NaHCO_3$ solution. The crude product was recrystallized from EtOH–water to give **47** (0.25 g, 51%) as pale yellowish microcrystals. Yield: 51%, mp 150–151 °C. IR (KBr, cm^{-1}): 3245, 2950, 2230, 1673, 1449, 754; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.42 (s, 1H, N*H* (indole)), 8.09 (d, J = 8.1 Hz, 1H, H-4), 7.57 (d, J = 8.4 Hz, 1H, H-7), 7.48–7.43 (m, 1H, H-6), 7.38–7.33 (m, 1H, H-5), 3.92 (s, 3H, -OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.20, 137.09, 126.71, 124.76, 123.79, 122.22, 121.99, 113.53, 113.32, 52.19. Anal. Calcd. for $C_{11}H_8N_2O_2$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.87; H, 4.76; N, 14.17.

3.16. 4-Amino-1,2-dihydro-1-oxo-5*H*-pyridazino[4,5-*b*]indole (48)

A mixture of compound **47** (0.082 g, 0.4 mmol) and hydrazine monohydrate (1.5 mL) was boiled at reflux temperature for 7 h. After reaction, the mixture was cooled to room temperature and water (5 mL) was added. The precipitated product was collected by filtration and washed with water and EtOH. The product was dried under reduced pressure to afford **48** (0.036 g, 45%) as pale white microcrystals. Yield: 45%, mp >350 °C. IR

(KBr, cm^{-1}): 3396, 3235, 3159, 1625, 1561, 735; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.89 (s, 1H, NH (indole)), 11.43 (s, 1H, NH (pyridazine)), 8.17 (d, J = 7.8 Hz, 1H, H-9), 7.69 (d, J = 8.2 Hz, 1H, H-6), 7.46 (t, J = 7.5 Hz, 1H, H-7), 7.30 (t, J = 7.4 Hz, 1H, H-8), 5.79 (s, 2H, -NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.12, 140.52, 137.77, 131.23, 126.10, 123.32, 121.93, 121.82, 113.05, 112.19. Anal. Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.03; N, 27.99. Found: C, 59.51; H, 3.87; N, 27.73.

3.17. Antimicrobial activity

Antimicrobial activities of the compounds against gram-positive bacteria, namely *Staphylococcus aureus* NRRL B-767, *Bacillus subtilis* NRRL 744, *Listeria monocytogenes* ATCC 7644; gram-negative bacteria, namely *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* NRRL-B123, and *Salmonella typhimurium* NRRL B-4420; and a fungus, namely *Candida albicans*, were expressed as MICs. The standard bacteria strains were obtained from the US Department of Agriculture (Peoria, IL, USA). *Candida albicans* was obtained from a patient in Eskişehir Osmangazi University Hospital in Turkey.

The MIC values were determined by the microdilution testing protocol.[28] The stock solutions of the compounds were prepared in DMSO. Chloramphenicol was used as the standard antibacterial agent and ketoconazole was used as an antifungal agent. The observed data on the antimicrobial activity of the compounds and control drugs as MIC values, in μg/mL, are given in the Table.

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