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Original research paper

Synthesis, antimicrobial and anti-cancer activities of some new *N*-ethyl, *N*-benzyl and *N*-benzoyl-3-indolyl heterocycles

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A series of 1-(*N*-substituted-1*H*-indol-3-yl)-3-arylprop-2--ene-1-ones (**2a,b-4a,b**) were prepared and allowed to react with urea, thiourea or guanidine to give pyrimidine derivatives **5a,b-13a,b**. Reaction of **2a,b-4a,b** with ethyl acetoacetate in the presence of a base gave cyclohexanone derivatives **14a,b-16a,b**. Reaction of the latter compounds with hydrazine hydrate afforded indazole derivatives **17a,b-19a,b**. On the other hand, reaction of **2a,b-4a,b** with some hydrazine derivatives, namely hydrazine hydrate, acetyl hydrazine, phenylhydrazine and benzylhydrazine hydrochloride, led to the formation of pyrazole derivatives **20a,b-31a,b**. Moreover, reaction of **2a,b-4a,b** with hydroxylamine hydrochloride gave isoxazole derivatives **32a,b-34a,b**. The newly synthesized compounds were tested for their antimicrobial activity and showed that 4-(*N*-ethyl-1*H*-indol-3-yl)-6-(*p*-chlorophenyl)-pyrimidine-2-amine (**11b**) was the most active of all the test compounds towards *Candida albicans* compared to the reference drug cycloheximide. Eighteen new compounds, namely pyrimidin-2(1*H*)-ones **5a,b-7a,b**, pyrimidin-2(1*H*)--thiones **8a,b-10a,b** and pyrimidin-2-amines **11a,b-13a,b** derivatives, were tested for their *in vitro* antiproliferative activity against HEPG2, MCF7 and HCT-116 cancer cell lines. 4-(*N*-ethyl-1*H*-indol-3-yl)-6-(*p*-methoxyphenyl)-pyrimidin-2-amine (**11a)** was found to be highly active with IC_{50} of 0.7 μmol L^{-1}.

Keywords: *N*-substituted-3-indolylchalcones, heterocycles, antimicrobial activity, anti-cancer activity

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Chalcones, one of the major classes of natural products with widespread occurrence in fruits, vegetables, spices and soy-based foodstuffs, have been reported to possess several biological activities (1, 2). Chalcones are suitable intermediates for the synthesis of biologically active heterocyclic compounds, *viz*., pyrimidine, cyclohexanone, pyrazole

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and isoxazole derivatives (3–7). In addition, indole derivatives which form potent pharmacodynamic nuclei have been reported to possess a wide variety of biological properties, *viz*., anti-inflammatory, anti-cancer and antimicrobial (8–10). Based on the above observations and in continuation of our research (9, 10), we herein report the synthesis of some new *N*-substituted-3-indolylheterocycles for evaluating their antimicrobial and anti-cancer activities starting from *N*-substituted-3-indolylchalcones.

EXPERMINTAL

Melting points were determined in open capillary tubes on an Electrothermal 9100 digital melting point apparatus (Büchi, Switzerland) and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer (Perkin-Elmer, USA) and were found within ± 0.4 % of the theoretical values. IR spectra were recorded on a Perkin--Elmer 1600 FTIR (Perkin-Elmer) in KBr discs. NMR spectra were measured with a Bruker Avance spectrometer (300 and 125 MHz) (Bruker, Germany) in DMSO-d_6, and chemical shifts were recorded in δ ppm relative to TMS as internal standard solvent. Mass spectra (EI) were run on a sector-field mass spectrometer (AMD M-40, AMD-Intectia GmbH, Germany) and gas chromatograph-mass spectrometer, single phase, 200 V, 50/60 Hz, 30 A (Jeol, Japan). All reagents and solvents were of commercial grade.

N-ethyl (**1a**), *N*-benzyl (**1b**) and *N*-benzoyl-3-acetylindoles (**1c**) were prepared as reported (11).

General synthetic procedures

*1-(*N*-ethyl-1*H*-indol-3-yl)-3-(*p*-methoxyphenyl)prop-2-ene-1-ones (**2a**), 1-(*N*-ethyl-1*H*-indol-3-yl)-3-(*p*-chlorophenyl)prop-2-ene-1-ones (**2b**), 1-(*N*-benzyl-1*H*-indol-3-yl)-3-(*p*-methoxyphenyl)prop-2-ene-1-ones (**3a**), 1-(*N*-benzyl-1*H*-indol-3-yl)-3-(*p*-chlorophenyl)prop-2-ene-1- -ones (**3b**), 1-(*N*-benzoyl-1*H*-indol-3-yl)-3-(*p*-methoxyphenyl)prop-2-ene-1-ones (**4a**) and 1-(*N*- -benzoyl-1*H*-indol-3-yl)-3-(*p*-chlorophenyl)prop-2-ene-1-ones (**4b**).* – To a solution of N-substituted-3-acetylindoles **1a**, **1b** or **1c** (0.001 mol) and *p*-methoxybenzaldehyde or *p*-chlo- robenzaldehyde (0.001 mol) in absolute ethanol (10 mL), an aqueous potassium hydroxide solution (5 mL, 25 %) was added. The reaction mixture was stirred for 2 h at room temperature and then left overnight in refrigerator. The reaction mixture was neutralized with diluted hydrochloric acid (1:1) and the solid formed was filtered off, washed with water, air dried and recrystallized from absolute ethanol.

*4-(*N*-ethyl-1*H*-indol-3-yl)-6-(*p*-methoxyphenyl)pyrimidin-2(1*H*)-ones (**5a**), 4-(*N*-ethyl-1*H*-indol-3-yl)-6-(*p*-chlorophenyl)pyrimidin-2(1*H*)-ones (**5b**), 4-(*N*-benzyl-1*H*-indol-3-yl)-6-(*p*-methoxyphenyl)pyrimidin-2(1*H*)-ones (**6a**), 4-(*N*-benzyl-1*H*-indol-3-yl)-6-(*p*-chlorophenyl)pyrimidin-2(1*H*)-ones (**6b**), 4-(*N*-benzoyl-1*H*-indol-3-yl)-6-(*p*-methoxyphenyl) pyrimidin-2(1*H*)-ones (**7a**) and 4-(*N*-benzoyl-1*H*-indol-3-yl)-6-(*p*-chlorophenyl)pyrimidin-2(1*H*)-ones (**7b**).* – A mixture of chalcones **2a,b**, **3a,b** or **4a,b** (0.01 mol) and urea (0.6 g, 0.01 mol) in dry ethanol (10 mL) containing glacial acetic acid (0.5 mL) was refluxed for 6–8 h. After cooling, the reaction mixture was poured onto ice-water (50 mL) and the solid formed was filtered off, air dried and recrystallized from absolute ethanol.

*4-(*N-*Ethyl-1*H-*indol-3-yl)-6-(*p-*methoxyphenyl)pyrimidin-2(1*H)*-thiones (**8a**)*, *4-(*N-*ethyl-1*H-*indol-3-yl)-6-(*p-*chlorophenyl)pyrimidin-2(1*H)*-thiones (**8b**)*, *4-(*N-*benzyl-1*H-*indol-3-yl)- -6- -(*p-*methoxyphenyl)pyrimidin-2(1*H)*-thiones (**9a**)*, *4-(*N-*benzyl-1*H-*indol-3-yl)-6-(*p-*chlorophenyl) pyrimidin-2(1*H)*-thiones (**9b**)*, *4-(*N-*benzoyl-1*H-*indol-3-yl)-6-(*p-*methoxyphenyl)pyrimidin- -2(1*H)*-thiones (**10a**) and 4-(*N-*benzoyl-1*H-*indol-3-yl)-6-(*p-*chlorophenyl)pyrimidin-2(1*H)*- -thiones (**10b**)*. – A mixture of chalcones **2a,b**, **3a,b** or **4a,b** (0.01 mol) and thiourea (0.76 g, 0.01 mol) in dry ethanol (10 mL) containing glacial acetic acid (0.5 mL) was refluxed for 6–8 h. After cooling, the reaction mixture was poured onto ice-water (50 mL) and the solid formed was filtered off, air dried and recrystallized from absolute ethanol.

*4-(*N-*Ethyl-1*H-*indol-3-yl)-6-(*p-*methoxyphenyl)pyrimidine-2-amines (**11a**)*, *4-(*N-*ethyl-1*H-*indol-3-yl)-6-(*p-*chlorophenyl)pyrimidine-2-amines (**11b**)*, *4-(*N-*benzyl-1*H-*indol-3-yl)-6-(*p-*methoxyphenyl)pyrimidine-2-amines (**12a**)*, *4-(*N-*benzyl-1*H-*indol-3-yl)-6-(*p-*chlorophenyl)pyrimidine-2-amines (**12b**)*, *4-(*N-*benzoyl-1*H-*indol-3-yl)-6-(*p-*methoxyphenyl) pyrimidine-2-amines (**13a**) and 4-(*N-*benzoyl-1*H-*indol-3-yl)-6-(*p-*chloro-phenyl)pyrimidine-2-amines (**13b**)*. – A mixture of chalcones **2a,b**, **3a,b** or **4a,b** (0.01 mol), guanidine hydrochloride (0.96 g, 0.01 mol) and anhydrous sodium acetate (0.82 g, 0.01 mol) in dry ethanol (15 mL) was refluxed for 2–3 h. After cooling, the solid formed was filtered off, air dried and recrystallized from absolute ethanol.

*Ethyl-4-(*N-*ethyl-1*H-*indol-3-yl)-6-(*p-*methoxyphenyl)-2-oxocyclohexa-3-enecarboxylate (**14a**)*, *ethyl-4-(*N-*ethyl-1*H-*indol-3-yl)-6-(*p-*chlorophenyl)-2-oxocyclohexa-3-enecarboxylate (**14b**)*, *ethyl- -4-(*N-*benzyl-1*H-*indol-3-yl)-6-(*p-*methoxyphenyl)-2-oxocyclohexa-3-enecarboxylate (**15a**)*, *ethyl- -4-(*N-*benzyl-1*H-*indol-3-yl)-6-(*p-*chlorophenyl)-2-oxocyclohexa-3-enecarboxylate (**15b**)*, *ethyl- -4-(*N-*benzoyl-1*H-*indol-3-yl)-6-(*p-*methoxyphenyl)-2-oxocyclohexa-3-enecarboxylate (**16a**) and ethyl-4-(*N-*benzoyl-1*H-*indol-3-yl)-6-(*p-*chlorophenyl)-2-oxocyclohexa-3-enecarboxylate (**16b**)*. – A mixture of chalcones **2a,b**, **3a,b** or **4a,b** (0.01 mol) and ethyl acetoacetate (1.30 mL, 0.01 mol) in absolute ethanol (15 mL) containing aqueous potassium hydroxide solution (1 mL, 10 %) was refluxed for 2 h and then left overnight at room temperature. The solid formed was filtered off, air dried and recrystallized from absolute ethanol.

*4,5-Dihydro-4-(*p-*methoxyphenyl)-6-(*N-*ethyl-1*H-*indol-3-yl)-2*H-*indazol-3(*H*)ones (**17a**)*, *4,5-dihydro-4-(*p-*chlorophenyl)-6-(*N-*ethyl-1*H-*indol-3-yl)-2*H-*indazol-3(*H*)ones (**17b**)*, *4,5-dihydro-4-(*p-*methoxyphenyl)-6-(*N-*benzyl-1*H-*indol-3-yl)-2*H-*indazol-3(*H*)ones (**18a**)*, *4,5-dihydro- -4-(*p-*chlorophenyl)-6-(*N-*benzyl-1*H-*indol-3-yl)-2*H-*indazol-3(*H*)ones (**18b**)*, *4,5-dihydro-4-(*p- -methoxyphenyl)-6-(*N-*benzoyl-1*H-*indol-3-yl)-2*H-*indazol-3(*H*)ones (**19a**) and 4,5-dihydro-4-(*p- -chlorophenyl)-6-(*N-*benzoyl-1*H-*indol-3-yl)-2*H-*indazol-3(*H*)ones (**19b**)*. – A mixture of compound **14a,b**, **15a,b** or **16a,b** (0.1 mol) and hydrazine hydrate 99 % (5 mL, 0.1 mol) in absolute ethanol (15 mL) containing glacial acetic acid (0.5 mL) was refluxed for 2 h. After cooling, the solid formed was filtered off, air dried and recrystallized from chloroform.

*4,5-Dihydro-3-(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)pyrazoles (**20a**)*, *4,5-dihydro-3- -(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl) pyrazoles (**20b**)*, *4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)pyrazoles (**21a**)*, *4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)pyrazoles (**21b**)*, *4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)pyrazoles (**22a**) and 4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)pyrazoles (**22b**)*. – To a solution of compound **2a,b**, **3a,b** or **4a,b** (0.01 mol) in absolute ethanol (10 mL) containing glacial acetic acid (0.5 mL), hydrazine hydrate 99 % (1 mL, 0.02 mol) was added. The

reaction mixture was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice-water (50 mL) and the solid formed was filtered off, air dried and recrystallized from absolute ethanol.

*4,5-Dihydro-3-(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)*-N-*acetyl-pyrazoles (**23a**), 4,5-dihydro-3-(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl*-N-*acetylpyrazoles (**23b**), 4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)*-N-*acetylpyrazoles (**24a**), 4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)*-N-*acetylpyrazoles (**24b**) 4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)*-N-*acetylpyrazoles (**25a**) and 4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)*-N-*acetylpyrazoles (**25b**). – Method A.* – To a solution of compound **2a,b**, **3a,b** or **4a,b** (0.01 mol) in a mixture of (15 mL) acetic anhydride and glacial acetic acid (2:1), hydrazine hydrate 99 % (1 mL, 0.02 mol) was added. The reaction mixture was refluxed for 6-8 h. After cooling, the reaction mixture was poured onto ice-water (50 mL) and the solid formed was filtered off, air dried and recrystallized from aqueous ethanol. *Method B.* – A mixture of compound **2a,b**, **3a,b** or **4a,b** (0.01 mol) and acetyl hydrazine (0.74 g, 0.01 mol) in absolute ethanol (10 mL) containing glacial acetic acid (0.5 mL) was refluxed for 2 h. After cooling, the solid formed was filtered off, air dried and recrystallized from aqueous ethanol.

*4,5-Dihydro-3-(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)*-N-*phenylpyrazoles (**26a**), 4,5-dihydro-3-(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)*-N-*phenylpyrazoles (**26b**), 4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)*-N-*phenylpyrazoles (**27a**), 4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)*-N-*phenylpyrazoles (**27b**) 4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)*-N-*phenylpyrazoles (**28a**) and 4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)*-N-*phenylpyrazoles (**28b**).* – A mixture of compound **2a,b**, **3a,b** or **4a,b** (0.01 mol) and phenylhydrazine (1.08 mL, 0.01 mol) in absolute ethanol (10 mL) containing glacial acetic acid (0.5 mL) was refluxed for 2 h. After cooling, the solid formed was filtered off, air dried and recrystallized from absolute ethanol.

*4,5-Dihydro-3-(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)*-N-*benzyl-pyrazoles (**29a**), 4,5-dihydro-3-(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)*-N-*benzylpyrazoles (**29b**), 4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)*-N-*benzylpyrazoles (**30a**), 4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)*-N-*benzylpyrazoles (**30b**), 4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)*-N-*benzylpyrazoles (**31a**) and 4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)*-N-*benzylpyrazoles (**31b**).* – A mixture of compound **2a,b**, **3a,b** or **4a,b** (0.01 mol), benzylhydrazine hydrochloride (1.95 g, 0.01 mol) and anhydrous sodium acetate (0.67 g, 0.015 mol) in dry ethanol (15 mL) was refluxed for 2–3 h. After cooling, the solid formed was filtered off, air dried and recrystallized from absolute ethanol.

*4,5-Dihydro-3-(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)isoxazoles (**32a**), 4,5-dihydro-3-(*N-*ethyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl) isoxazoles (**32b**), 4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)isoxazoles (**33a**), 4,5-dihydro-3-(*N-*benzyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)isoxazoles (**33b**), 4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*methoxyphenyl)-isoxazoles (**34a**) and 4,5-dihydro-3-(*N-*benzoyl-1*H-*indol-3-yl)-5-(*p-*chlorophenyl)isoxazoles (**34b**).* – A mixture of compound **2a,b**, **3a,b** or **4a,b** (0.01 mol), hydroxylamine hydrochloride (0.69 g, 0.01 mol) and anhydrous sodium acetate (0.67 g, 0.01 mol) in absolute ethanol (10 mL) was refluxed for 6–8 h. After cooling, the reaction mixture was poured onto ice-water (50 mL). The solid that formed was filtered off, air dried and recrystallized from absolute ethanol.

Biological assay

Antimicrobial evaluation. – Antimicrobial activity of the synthesized compounds was determined *in vitro* by the disc diffusion method (12) against a variety of pathogenic microorganisms: *Salmonella typhimurium* (ATCC 14028), *Pseudomonas fluorescens* (S 97) (Gram-positive bacteria), *Staphylococcus aureus* (ATCC 25923), *Bacillus subtilis* (ATCC 6635) (Gram-negative bacteria) and two strains of fungi, *Candida albicans* (ATCC 10231) and *Aspergillus fumigatus* (identified microscopically according to Moubasher (13). Antimicrobial activities of the tested compounds were estimated by placing presterilized filter paper discs (6 mm in diameter) impregnated with two doses of test compounds (10 and 20 μg per disc) on Nutrient and MacConky agar media for bacteria and on Sabouraud dextrose agar for fungus. Dimethyl formamide (DMF) was used as a solvent for impregnation. Inhibition zones (IZ) of the test compounds were measured after 24–48 h incubation at 37 °C for bacteria and after 5 days incubation at 28 °C for fungi. Chloramphenicol and cephalothin were used as a reference drugs for bacteria, whereas, cycloheximide (Sigma-Aldrich, USA) was used as reference drug for fungi.

Cell culture. – HEPG2 (human liver carcinoma), MCF7 (human breast cancer) and HCT-116 (human colon cancer) cell lines were obtained from the Karolinska Institute, Stockholm, Sweden. All cells were maintained in RPMI 1640 medium, except for the MCF7 cancer cells which were maintained in DMEM medium (Lonza Biowahittkar, Belgium). All the media were supplemented with 1 % antibiotic-antimycotic mixture (10,000 U mL^{-1} potassium penicillin, 10,000 μg mL^{-1} streptomycin sulfate, 25 μg mL^{-1} amphotericin B and 1 % L-glutamine (Biowest, USA).

MTT cytotoxicity assay. – Cell viability was investigated using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (Bio Basic Canada Inc., Canada) assay (14). This reaction depends on the mitochondrial reduction of yellow MTT into purple formazan. All the preceding steps were carried out in a sterile laminar air flow cabinet Biosafety class II level (Baker, SG403INT, USA). All incubations were done at 37 °C in 5 % CO_2 incubator in humidified atmosphere (Sheldon, TC2323, USA). Cells were seeded into 96-well microtiter plastic plates at a concentration of (10^4 cells per well) and allowed to adhere for 24 hours. Medium was aspirated and fresh medium (without serum) was added to the cells with various concentrations of test compounds (10, 5, 2.5 and 1.25 μg mL^{-1} in DMSO) and incubated for 48 hours. Medium was aspirated and 40 μL MTT salt (2.5 μg mL^{-1}) was added to each well and incubated for further 4 hours. To stop the reaction and dissolve any formed formazan crystals, 200 μL of 10 % sodium dodecyl sulfate (SDS) was added to each well and incubated overnight at 37 °C. The amount of formazan producted was measured at 595 nm with a reference wavelength of 620 nm as background using a microplate reader (Bio-Rad Laboratories, model 3350, USA). For untreated cells (negative control), medium was added instead of test compounds. A positive control Adrinamycin® (doxorubicin) (M_r = 579.9) was used as a known cytotoxic natural agent giving 100 % inhibition. Dimethyl sulfoxide (DMSO) was the vehicle used for dissolution of the tested compound and its final concentration on the cells was less than 0.2 %.

IC_{50} was calculated for the samples and negative control (cells with vehicle) by the probit analysis method using a simple *t*-test (SPSS statistical analysis software package/ version 11.0, SPPS Inc., (IL), Chicago, USA).

RESULTS AND DISCUSSION

Chemistry

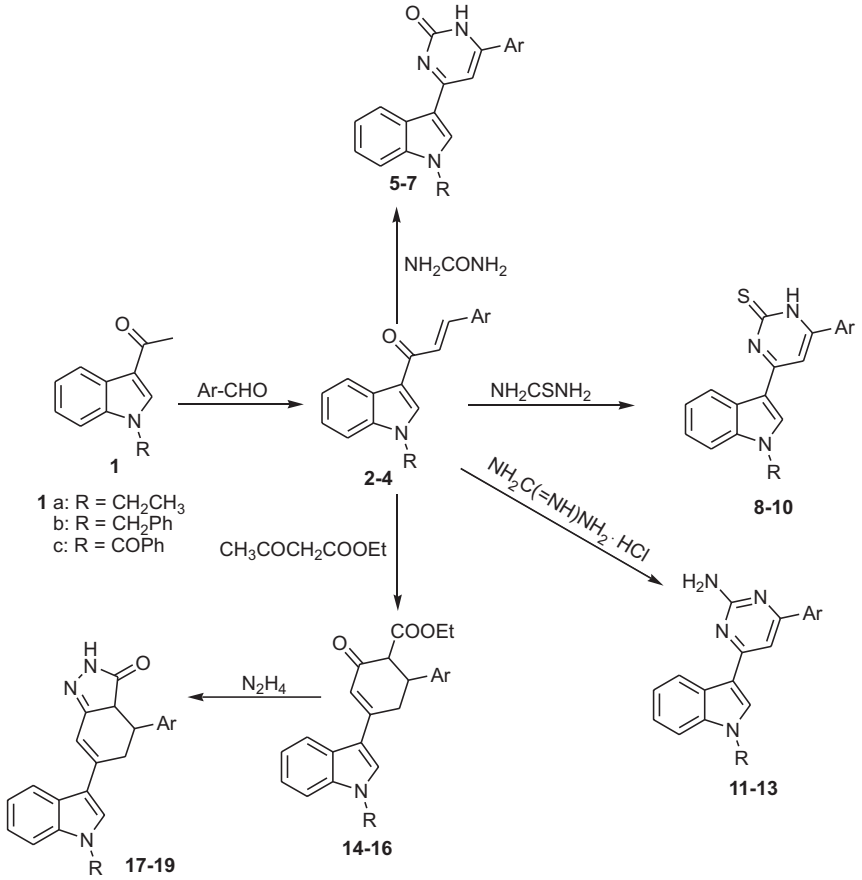
The starting chalcones, namely, 1-(*N*-ethyl-1*H*-indol-3-yl)-3-arylprop-2-ene-1-ones (**2a,b**), 1-(*N*-benzyl-1*H*-indol-3-yl)-3-arylprop-2-ene-1-ones (**3a,b**) and 1-(*N*-benzoyl-1*H*-indol-3-yl)-3-arylprop-2-ene-1-ones (**4a,b**), were synthesized *via* the Claisen-Schmidt reaction of *N*-ethyl (**1a**), *N*-benzyl (**1b**) and *N*-benzoyl-3-acetylindoles (**1c**), respectively, with *p*-methoxybenzaldehyde and/or *p*-chlorobenzaldehyde in ethanol and in the presence of aqueous potassium hydroxide 25 % (Scheme 1).

Cyclocondensation of chalcones **2a,b**, **3a,b** or **4a,b** with urea in dry ethanol and in the presence of glacial acetic acid as a catalyst gave 4-(*N*-substituted-1*H*-indol-3-yl)-6--arylpyrimidin-2(1*H*)-ones (**5a,b**), (**6a,b**) and (**7a,b**), respectively. Similarly, the reaction of chalcones **2a,b**, **3a,b** or **4a,b** with thiourea gave pyrimidin-2(1*H*)-thiones **8a,b**, **9a,b** and **10a,b**, respectively. Moreover, the reaction of chalcones **2a,b**, **3a,b** or **4a,b** with guanidine hydrochloride in dry ethanol and in the presence of anhydrous sodium acetate yielded 4-(*N*-substituted-1*H*-indol-3-yl)-6-aryl-pyrimidine-2-amines (**11a,b**), (**12a,b**) and (**13a,b**), respectively (Scheme 1).

It was reported previously that the base catalyzed reaction of chalcone with ethyl acetoacetate gave rise to cyclohexanone (7, 15). In the present work and under the above mentioned conditions, the new chalcones **2a,b**, **3a,b** or **4a,b** were allowed to react with ethyl acetoacetate (1:1) in the presence of aqueous potassium hydroxide 10 % to give new compounds, namely ethyl-4-(*N*-substituted-1*H*-indol-3-yl)-6-aryl-2-oxocyclohexa-3-ene--carboxylates (**14a,b**), (**15a,b**) and (**16a,b**), respectively (Scheme 1).

Reaction of compound **14a** with hydrazine hydrate under reflux in ethanol in the presence of glacial acetic acid gave a compound with molecular ion peak at *m/z* = 385 (7 %). Its IR (KBr) spectrum showed characteristic absorption bands at 3210 (NH), 1645 (C=O), 1620 (C=N), 1577 (C=C) and 1009 cm^{-1} (C-O-C). Its ^1H NMR (DMSO-d_6) lacked the signals at 4.42 and 1.61 ppm of COO$\mathbf{CH_2CH_3}$ and revealed signals at 9.21 (s, 1H, NH), 8.02 (s, 1H, H-2 indole), 7.97–7.01 (m, 8H, ArH), 6.16 (s, 1H, CH=C), 4.21 (q, 2H, $CH_3\mathbf{CH_2}N$), 3.91 (s, 3H, OCH_3), 2.90 and 3.31 (2d, 2H, CHCH), 2.13 and 2.45 (dd, 2H, $CH\mathbf{CH_2}$), 1.30 ppm (t, 3H, $\mathbf{CH_3}CH_2N$). Its ^{13}C NMR (DMSO-d_6) revealed signals at 177.3 (C=O), 111.1–152.1 (ArC), 52.6 (CH_2), 42.6 (CH) and 15.1 ppm (CH_3).

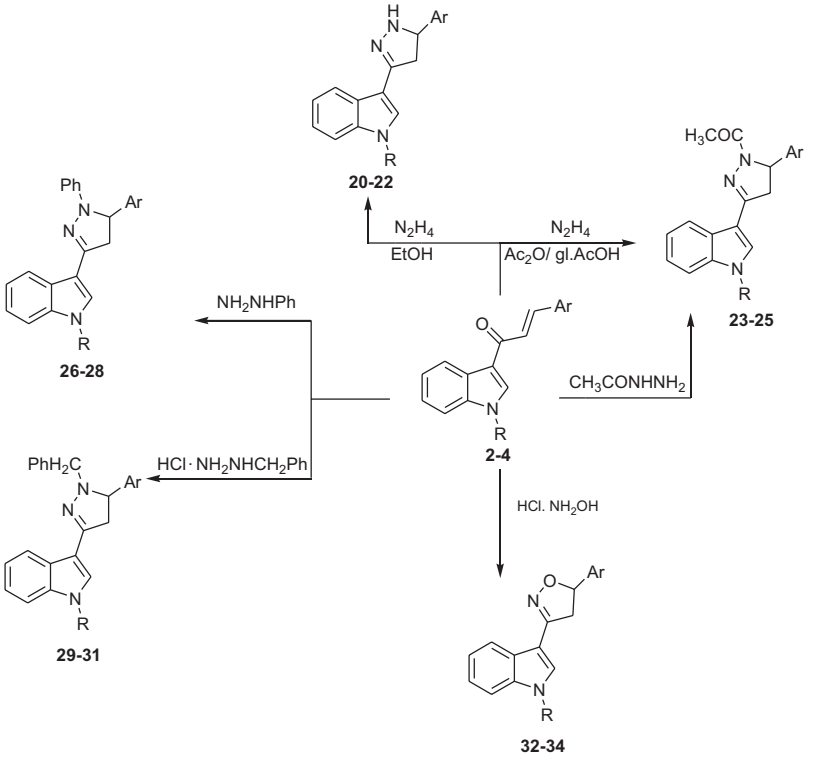
Based on these data, the assigned structure of the product was proposed as 4,5-dihydro-4-(*p*-methoxyphenyl)-6-(*N*-ethyl-1*H*-indol-3-yl)-2*H*-indazol-3(*H*)one (**17a**) (Scheme 1). The reaction may have proceeded through condensation between C=O of cyclohexanone and NH_2 of hydrazine, followed by cyclization by loosing a molecule of ethanol. Similarly, reaction of **14b**, **15a,b** or **16a,b** with hydrazine hydrate under the above mentioned conditions led to the formation of 4,5-dihydro-4-aryl-6-(*N*-substituted-1*H*-indol-3-yl)-2*H*--indazol-3(H)one **17b**, **18a,b**, and **19a,b** (Scheme 1).



Scheme 1.

On the other hand, condensation of chalcones **2a,b**, **3a,b** or **4a,b** with hydrazine hydrate in absolute ethanol and in the presence of a few drops of glacial acetic acid afforded 4,5-dihydro-3-(*N*-substituted-1*H*-indol-3-yl)-5-arylpyrazoles **20a,b**, **21a,b** and **22a,b**, respectively (Scheme 2), whereas reaction of **2a,b**, **3a,b** or **4a,b** with hydrazine hydrate under reflux in a mixture of acetic anhydride and glacial acetic acid (2:1) afforded the corresponding *N*-acetylpyrazole derivatives **23a,b**, **24a,b** and **25a,b**, respectively (Scheme 2). Also, compounds **23a,b**, **24a,b** and **25a,b** were obtained *via* the reaction of **2a,b**, **3a,b** or **4a,b** with acetyl hydrazine in refluxing absolute ethanol, which showed no depression in admixed melting points with that previously obtained (Scheme 2).

In addition, reaction of **2a,b**, **3a,b** or **4a,b** with phenylhydrazine gave *N*-phenylpyrazole derivatives **26a,b**, **27a,b** and **28a,b**, respectively (Scheme 2). Also, reaction of **2a,b**, **3a,b** or **4a,b** with benzylhydrazine hydrochloride in the presence of anhydrous sodium acetate gave *N*-benzylpyrazole derivatives **29a,b**, **30a,b** and **31a,b**, respectively (Scheme 2).



Scheme 2.

Furthermore, reaction of **2a,b**, **3a,b** or **4a,b** with hydroxylamine hydrochloride in the presence of anhydrous sodium acetate led to the formation of 4,5-dihydro-3-(*N*-substituted-1*H*-indol-3-yl)-5-aryl-isoxazoles (**32a,b**), (**33a, b**) and (**34a,b**), respectively (Scheme 2).

Structures of the newly synthesized compounds were confirmed on the basis of elemental analyses (Table I) as well as IR, NMR, and MS spectral data (Table II).

Biological activity

All the newly synthesized compounds were tested for their antimicrobial activity against a variety of pathogenic microorganisms using the disk diffusion method (12) at two doses of 10 and 20 μg per disc (Table III). None of the test compounds showed antimicrobial activity at the dose of 10 μg per disc, whereas at the dose of 20 μg per disc compound 4-(*N*-ethyl-1*H*-indol-3-yl)-6-(*p*-chlorophenyl) pyrimidine-2-amine (**11b**) was found to be the most active of all the test compounds, with of 33 mm against *Candida albicans*, compared to the reference drug cycloheximide (39 mm).

Eighteen new compounds, namely pyrimidin-2(1*H*)-ones **5a,b**-**7a,b**, pyrimidin-2(1*H*)--thiones **8a,b**-**10a,b** and pyrimidin-2-amines **11a,b**-**13a,b** were preliminarily screened for

Table I. Physical and analytical properties of the newly synthesized compounds

Compd.	R	Ar	Formula (M_r)	M. p. (°C)	Yield (%)	Analysis (calcd./found) (%)		
						C	H	N
2a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{20}H_{19}NO_2$ (305.37)	60–2	69	78.66/7.56	6.27/6.32	4.59/4.60
2b	CH_2CH_3	C_6H_4Cl-*p*	$C_{19}H_{16}ClNO$ (309.79)	179–81	60	73.66/73.44	5.21/5.42	4.52/4.32
3a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{25}H_{21}NO_2$ (367.44)	81–3	50	81.72/81.88	5.76/5.66	3.81/4.00
3b	CH_2Ph	C_6H_4Cl-*p*	$C_{24}H_{18}ClNO$ (371.86)	161–3	65	77.52/77.42	4.88/5.01	3.77/3.54
4a	COPh	$C_6H_4OCH_3$-*p*	$C_{25}H_{19}NO_3$ (381.42)	157–9	45	78.72/78.99	5.02/4.99	3.67/3.75
4b	COPh	C_6H_4Cl-*p*	$C_{24}H_{16}ClNO_2$ (385.84)	218–20	76	74.71/74.65	4.18/4.32	3.63/3.55
5a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{21}H_{19}N_3O_2$ (345.39)	116–8	80	73.03/72.89	5.54/5.65	12.17/12.33
5b	CH_2CH_3	C_6H_4Cl-*p*	$C_{20}H_{16}ClN_3O$ (349.81)	136–8	30	68.67/68.55	4.61/4.54	12.01/12.22
6a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{26}H_{21}N_3O_2$ (407.46)	69–71	40	76.64/76.76	5.19/5.00	10.31/10.55
6b	CH_2Ph	C_6H_4Cl-*p*	$C_{25}H_{18}ClN_3O$ (411.88)	88–90	35	72.90/73.00	4.40/4.22	10.20/10.45
7a	COPh	$C_6H_4OCH_3$-*p*	$C_{26}H_{19}N_3O_3$ (421.45)	136–8	58	74.10/74.33	4.54/4.62	9.97/10.01
7b	COPh	C_6H_4Cl-*p*	$C_{25}H_{16}ClN_3O_2$ (425.87)	226–8	37	70.51/70.66	3.79/3.57	9.87/9.66
8a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{21}H_{19}N_3OS$ (361.46)	124–6	55	69.78/69.89	5.30/5.53	11.63/11.45
8b	CH_2CH_3	C_6H_4Cl-*p*	$C_{20}H_{16}ClN_3S$ (365.88)	125–7	82	65.65/65.43	4.14/4.22	11.48/11.65
9a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{26}H_{21}N_3OS$ (423.53)	99–101	72	73.73/73.86	5.00/4.88	9.92/10.10
9b	CH_2Ph	C_6H_4Cl-*p*	$C_{25}H_{18}ClN_3S$ (427.95)	183–5	45	70.16/70.33	4.24/4.01	9.82/9.77
10a	COPh	$C_6H_4OCH_3$-*p*	$C_{26}H_{19}N_3O_2S$ (437.51)	170–2	70	71.38/71.55	4.38/4.42	9.60/9.77
10b	COPh	C_6H_4Cl-*p*	$C_{25}H_{16}ClN_3OS$ (441.93)	255–7	50	67.94/68.01	3.65/3.82	9.51/9.33
11a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{21}H_{20}N_4O$ (344.41)	200–2	82	73.23/73.45	5.85/6.00	16.27/16.45
11b	CH_2CH_3	C_6H_4Cl-*p*	$C_{20}H_{17}ClN_4$ (348.83)	133–5	85	68.86/68.67	4.91/5.00	16.06/16.23
12a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{26}H_{22}N_4O$ (406.48)	84–6	80	76.63/76.70	5.46/5.65	13.78/13.88

Table I. continued

12b	CH_2Ph	C_6H_4Cl-*p*	$C_{25}H_{19}ClN_4$ (410.90)	196–8	80	73.08/72.89	4.66/4.54	13.64/13.54
13a	COPh	$C_6H_4OCH_3$-*p*	$C_{26}H_{20}N_4O_2$ (420.46)	172–5	82	74.27/74.45	4.79/4.61	13.33/13.55
13b	COPh	C_6H_4Cl-*p*	$C_{25}H_{17}ClN_4O$ (424.88)	175–7	78	70.67/70.88	4.03/3.98	13.19/13.33
14a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{26}H_{27}NO_4$ (417.50)	60–2	65	74.80/74.65	6.52/6.63	3.35/3.55
14b	CH_2CH_3	C_6H_4Cl-*p*	$C_{25}H_{24}ClNO_3$ (421.92)	127–9	60	71.17/71.33	5.73/5.88	3.32/3.45
15a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{31}H_{29}NO_4$ (479.57)	86–8	45	77.64/77.87	6.10/6.33	2.92/3.00
15b	CH_2Ph	C_6H_4Cl-*p*	$C_{30}H_{26}ClNO_3$ (483.99)	189–191	46	74.45/74.65	5.41/5.61	2.89/3.01
16a	COPh	$C_6H_4OCH_3$-*p*	$C_{31}H_{27}NO_5$ (493.55)	169–171	36	75.44/75.66	5.51/5.32	2.84/2.65
16b	COPh	C_6H_4Cl-*p*	$C_{30}H_{24}ClNO_4$ (497.97)	146–8	40	72.36/72.55	4.86/5.00	2.81/2.98
17a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{24}H_{23}N_3O_2$ (385.46)	75–9	60	74.78/74.66	6.01/5.89	10.90/11.00
17b	CH_2CH_3	C_6H_4Cl-*p*	$C_{23}H_{20}ClN_3O$ (389.88)	133–5	54	70.85/70.90	5.17/5.01	10.78/10.88
18a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{29}H_{25}N_3O_2$ (447.53)	220–2	46	77.83/77.65	5.63/5.78	9.39/9.55
18b	CH_2Ph	C_6H_4Cl-*p*	$C_{28}H_{22}ClN_3O$ (451.95)	201–3	56	74.41/74.65	4.91/5.01	9.30/9.11
19a	COPh	$C_6H_4OCH_3$-*p*	$C_{29}H_{23}N_3O_3$ (461.51)	322–4	55	75.47/75.56	5.02/5.33	9.10/9.33
19b	COPh	C_6H_4Cl-*p*	$C_{28}H_{20}ClN_3O_2$ (465.93)	196–8	52	72.18/72.33	4.33/4.65	9.02/8.99
20a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{20}H_{21}N_3O$ (319.4)	188–90	44	75.21/75.45	6.63/6.81	13.16/13.33
20b	CH_2CH_3	C_6H_4Cl-*p*	$C_{19}H_{18}ClN_3$ (323.82)	197–9	86	70.47/70.55	5.60/5.76	12.98/13.00
21a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{25}H_{23}N_3O$ (381.47)	235–7	50	78.71/78.85	6.08/5.99	11.02/10.98
21b	CH_2Ph	C_6H_4Cl-*p*	$C_{24}H_{20}ClN_3$ (385.89)	206–8	98	74.70/74.66	5.22/5.01	10.89/11.01
22a	COPh	$C_6H_4OCH_3$-*p*	$C_{25}H_{21}N_3O_2$ (395.45)	289–91	30	75.93/76.00	5.35/5.55	10.63/10.77
22b	COPh	C_6H_4Cl-*p*	$C_{24}H_{18}ClN_3O$ (399.87)	161–3	90	72.90/72.76	4.54/4.67	10.51/10.66
23a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{22}H_{23}N_3O_2$ (361.44)	109–11	56	73.11/73.33	6.41/6.65	11.63/11.77
23b	CH_2CH_3	C_6H_4Cl-*p*	$C_{21}H_{20}ClN_3O$ (365.86)	132–4	40	68.94/68.76	5.51/5.67	11.49/11.56

Table I. continued

24a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{27}H_{25}N_3O_2$ (423.51)	182–4	71	76.57/76.66	5.95/6.01	9.92/10.00
24b	CH_2Ph	C_6H_4Cl-*p*	$C_{26}H_{22}ClN_3O$ (427.93)	150–2	68	72.97/73.05	5.18/5.22	9.82/9.66
25a	COPh	$C_6H_4OCH_3$-*p*	$C_{27}H_{23}N_3O_3$ (437.49)	130–2	59	74.12/74.33	5.30/5.55	9.60/9.44
25b	COPh	C_6H_4Cl-*p*	$C_{26}H_{20}ClN_3O_2$ (441.91)	189–91	37	70.67/70.55	4.56/4.67	9.51/9.72
26a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{26}H_{25}N_3O$ (395.5)	221–3	46	78.96/79.11	6.37/6.52	10.62/10.84
26b	CH_2CH_3	C_6H_4Cl-*p*	$C_{25}H_{22}ClN_3$ (399.92)	121–3	60	75.08/75.22	5.54/5.67	10.51/10.70
27a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{31}H_{27}N_3O$ (457.57)	148–150	64	81.37/81.55	5.59/6.03	9.18/9.33
27b	CH_2Ph	C_6H_4Cl-*p*	$C_{30}H_{24}ClN_3$ (461.98)	194–6	70	77.99/78.11	5.24/5.44	9.10/9.33
28a	COPh	$C_6H_4OCH_3$-*p*	$C_{31}H_{25}N_3O_2$ (471.55)	157–9	65	78.96/78.76	5.34/5.54	8.91/9.00
28b	COPh	C_6H_4Cl-*p*	$C_{30}H_{22}ClN_3O$ (475.97)	178–180	66	75.70/75.85	4.66/4.44	8.83/8.65
29a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{27}H_{27}N_3O$ (409.52)	59–61	57	79.19/79.33	6.65/6.45	10.26/10.45
29b	CH_2CH_3	C_6H_4Cl-*p*	$C_{26}H_{24}ClN_3$ (413.94)	152–4	60	75.44/75.22	5.84/6.00	10.15/10.33
30a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{32}H_{29}N_3O$ (471.59)	82–4	60	81.50/81.75	6.20/6.45	8.91/9.00
30b	CH_2Ph	C_6H_4Cl-*p*	$C_{31}H_{26}ClN_3$ (476.01)	212–4	64	78.22/78.44	5.51/5.66	8.33/8.55
31a	COPh	$C_6H_4OCH_3$-*p*	$C_{32}H_{27}N_3O_2$ (485.58)	167–9	54	79.15/79.22	5.60/5.44	8.65/8.47
31b	COPh	C_6H_4Cl-*p*	$C_{31}H_{24}ClN_3O$ (489.99)	170–2	57	75.99/76.12	4.94/5.11	8.58/8.44
32a	CH_2CH_3	$C_6H_4OCH_3$-*p*	$C_{20}H_{22}N_2O_2$ (320.38)	58–60	40	74.98/74.85	6.29/6.45	8.74/8.54
32b	CH_2CH_3	C_6H_4Cl-*p*	$C_{19}H_{17}ClN_2O$ (324.8)	60–2	80	70.26/70.45	5.28/5.45	8.62/8.44
33a	CH_2Ph	$C_6H_4OCH_3$-*p*	$C_{25}H_{22}N_2O_2$ (382.45)	113–5	46	78.51/78.65	5.80/5.72	7.32/7.55
33b	CH_2Ph	C_6H_4Cl-*p*	$C_{24}H_{19}ClN_2O$ (386.87)	135–7	96	74.51/74.66	4.96/5.01	7.24/7.45
34a	COPh	$C_6H_4OCH_3$-*p*	$C_{25}H_{20}N_2O_3$ (396.44)	169–71	57	75.74/75.55	5.08/4.99	7.07/7.22
34b	COPh	C_6H_4Cl-*p*	$C_{24}H_{17}ClN_2O_2$ (400.86)	173–5	74	71.91/71.75	4.27/4.55	6.99/7.11

Table II. Spectral characterization of the newly synthesized compounds

Compd.	IR (ν_{max}, cm^{-1})	^1H and ^{13}C NMR (δ, ppm)	Mass (*m/z*, %)
2a	1634 (C=O), 1570 (C=C), 1025 (C-O-C)		
2b	1641 (C=O), 1617 (C=C), 746 (C-Cl)	^1H NMR: 8.35 (s, 1H, H-2 indole), 7.89–7.78 (m, 4H, ArH indole), 7.63 & 7.51 (2d, 2H, CH=CH), 7.31–7.23 (m, 4H, ArPh), 4.35 (q, 2H, CH_2), 1.51 (t, 3H, CH_3)	
3a	1739 (C=O), 1634 (C=C), 1017 (C-O-C)	^1H NMR: 8.21 (s, 1H, H-2 indole), 7.01–7.65 (m, 13H, ArH), 7.00 & 6.91 (2d, 2H, CH=CH), 5.6 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3)	
3b	1738 (C=O), 1638 (C=C), 735 (C-Cl)		
4a	1742 & 1674 (C=O), 1570 (C=C), 1020 (C-O-C)	^1H NMR: 8.28 (s, 1H, H-2 indole), 8.15 & 7.46 (2d, 2H, CH=CH), 7.22–7.13 (m, 13H, ArH), 3.82 (s, 3H, OCH_3)	
4b	1693 & 1635 (C=O), 1570 (C=C), 748 (C-Cl)		
5a	3429 (NH), 1639 (C=O), 1572 (C=N), 1554 (C=C), 1024 (C-O-C)		345 (M^+, 21), 315 (20), 238 (10), 143 (100), 117 (50), 109 (17)
5b	3480 (NH), 1643 (C=O), 1585 (C=N), 1545 (C=C), 739 (C-Cl)	^1H NMR: 8.75 (s, 1H, NH), 8.33 (s, 1H, H-2 indole), 7.87–7.24 (m, 9H, ArH), 4.31 (q, 2H, CH_2), 1.48 (t, 3H, CH_3)	
6a	3445 (NH), 1638 (C=O), 1605 (C=N), 1568 (C=C), 1020 (C-O-C)		407 (M^+, 1), 206 (2), 202 (1), 191 (1), 115 (30), 91 (100)
6b	3327 (NH), 1624 (C=O), 1602 (C=N), 1557 (C=C), 751 (C-Cl)	^1H NMR: 8.98 (s, 1H, NH), 8.56 (s, 1H, H-2 indole), 8.37 (d, 1H, H-7 indole), 7.90–7.20 (m, 13H, ArH), 5.55 (s, 2H, CH_2) ^{13}C NMR: 157.6 (C=O), 137.8–109.6 (ArC), 61.6 (CH_2N)	411 (M^+, 5), 413 (M^++2, 0.15), 373 (35), 371 (100), 343 (46), 217 (26)
7a	3457 (NH), 1744 (C=O), 1614 (C=N), 1571 (C=C), 1021 (C-O-C)	^1H NMR: 11.87 (s, 1H, NH), 8.68 (s, 1H, H-2 indole) 8.29 (d, 1H, H-7 indole), 7.81–7.00 (m, 13H, ArH), 3.82 (s, 3H, OCH_3)	
7b	3390 (NH), 1742 & 1638 (C=O), 1600 (C=N), 1563 (C=C), 747 (C-Cl)		425 (M^+, 0.02), 427 (M^++2, 0.006), 283 (34), 281 (100), 144 (76), 117 (29), 116 (43)
8a	3417 (NH), 1638 (C=N), 1572 (C=C), 1249 (C=S), 1055 (C-O-C)		361 (M^+, 2), 316 (20), 238 (10), 142 (100), 116 (50), 77 (17)

Table II. continued

8b	3414 (NH), 1644 (C=N), 1585 (C=C), 1240 (C=S), 775 (C-Cl)	^{1}H NMR: 12.09 (s, 1H, NH), 8.36 (s, 1H, H-2 indole), 7.86–7.23 (m, 9H, ArH), 4.33 (q, 2H, CH_2), 1.51 (t, 3H, CH_3)	365 (M^+, 1), 367 (M^++2, 0.015), 309 (24), 311 (8), 281 (38), 144 (28), 116 (20) 91 (100)
9a	3445 (NH), 1637 (C=N), 1606 (C=C), 1251 (C=S), 1020 (C-O-C)		423(M^+, 10), 367 (40), 276 (18), 204 (11), 91 (100)
9b	3383 (NH), 1637 (C=N), 1572 (C=C), 1226 (C=S), 736 (C-Cl)		427 (M^+, 10), 429 (M^++2, 3), 371 (100), 345 (13), 343 (37), 207 (5), 115 (3)
10a	3158 (NH), 1705 (C=O), 1614 (C=N), 1571 (C=C), 1245 (C=S), 1020 (C-O-C)	^{1}H NMR: 8.71 (s, 1H, NH), 8.35 (s, 1H, H-2 indole), 8.19 (d, 1H, H-7 indole), 7.82 (d, 1H, H-4 indole), 7.71–7.01 (m, 12H, ArH), 3.82 (s, 3H, OCH_3) ^{13}C NMR: 192.6 (C=O), 182.7 (C=S), 167.4 (C=N), 160.2–110.0 (ArC), 54.8 (OCH_3)	437 (M^+, 1), 277 (100), 249 (12), 144 (40), 117 (12), 116 (14)
10b	3212 (NH), 1709 (C=O) 1643 (C=N), 1578 (C=C), 1238 (C=S), 773 (C-Cl)	^{1}H NMR: 8.75 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 7.87–7.01 (m, 14H, ArH)	
11a	3440 (NH_2), 1620 (C=N), 1578 (C=C), 1009 (C-O-C)	^{1}H NMR: 10.50 (s, 2H, NH_2), 8.22 (s, 1H, H-2 indole), 8.01–7.00 (m, 9H, ArH), 4.45 (q, 2H, CH_2), 3.94 (s, 3H, OCH_3), 1.96 (t, 3H, CH_3) ^{13}C NMR: 161.4 (C=N), 160.2–110.0 (ArC), 54.8 (CH_2), 42.4 (OCH_3), 15.7 (CH_3)	
11b	3445 (NH_2), 1621 (C=N), 1588 (C=C), 745 (Cl)		348 (M^+, 10), 350 (M^++2, 3), 144 (100), 116 (60), 111 (50), 77 (70)
12a	3300 (NH_2), 1621 (C=N), 1590 (C=C), 1019 (C-O-C)	^{1}H NMR: 9.55 (s, 2H, NH_2), 8.02 (s, 1H, H-2 indole), 8.00–7.00 (m, 14H, ArH), 5.65 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3) ^{13}C NMR: 161.4 (C=N), 161.0–111.0 (ArC), 56.7 (CH_2), 42.1 (CH_3)	
12b	3445 (NH_2), 1621 (C=N), 1575 (C=C), 748 (Cl)		410 (M^+, 17), 412 (M^++2, 9), 142 (100), 115 (60), 111 (50), 77 (70)
13a	3330 (NH_2), 1660 (C=O), 1621 (C=N), 1597 (C=C), 1010 (C-O-C)	^{1}H NMR: 9.71 (s, 2H, NH_2), 8.02 (s, 1H, H-2 indole), 7.70–7.00 (m, 14H, ArH), 3.94 (s, 3H, OCH_3) ^{13}C NMR: 182.0 (C=O), 157.4 (C=N), 155.7–111.0 (ArC), 41.1 (CH_3)	

Table II. continued

13b	3345 (NH_2), 1678 (C=O), 1621 (C=N), 1575 (C=C), 748 (Cl)		424 (M^+, 11), 426 (M^++2, 3), 193 (10), 144 (100), 115 (60), 111 (50), 77 (70)
14a	1703 & 1687 (2C=O), 1599 (C=C), 1009 (C-O-C)	^{1}H NMR: 8.21 (s, 1H, H-2 indole), 7.87–7.01 (m, 8H, ArH), 6.68 (s, 1H, CH=C), 4.42 (q, 2H, CH_2CO), 4.21 (q, 2H, CH_2-N), 3.91 (s, 3H, OCH_3), 3.55–2.69 (m, 4H, -CHCHCH$_2$ cyclohexanone), 1.61 (t, 3H, **CH$_3$**CH$_2$CO), 1.30 (t, 3H, **CH$_3$**CH$_2$N) ^{13}C NMR: 182.1 & 177.3 (2C=O), 111.1–152.1 (ArC), 61.3 (**CH$_2$**CO), 52.6 (**CH$_2$**N), 42.6 (CH), 15.1 (2CH$_3$)	
14b	1736 & 1701 (2C=O), 1557 (C=C), 747 (Cl)	^{1}H NMR: 8.21 (s, 1H, H-2 indole), 7.81–7.01 (m, 8H, ArH), 6.66 (s, 1H, CH=C), 4.44 (q, 2H, CH_2CO), 4.21 (q, 2H, CH_2-N), 3.57–2.61 (m, 4H, CHCHCH$_2$ cyclohexanone), 1.61 (t, 3H, **CH$_3$**CH$_2$CO), 1.21 (t, 3H, **CH$_3$**CH$_2$N)	
15a	1721 & 1699 (2C=O), 1578 (C=C), 1010 (C-O-C)	^{1}H NMR: 8.21 (s, 1H, H-2 indole), 7.81–7.01 (m, 13H, ArH), 6.68 (s, 1H, CH=C), 5.55 (s, 2H, CH_2), 4.43 (q, 2H, CH_2CO), 3.99 (s, 3H, OCH_3), 3.56–2.67 (m, 4H, CHCHCH$_2$ cyclohexanone), 1.9 (t, 3H, **CH$_3$**CH$_2$CO)	
15b	1707 & 1689 (2C=O), 1566 (C=C), 745 (Cl)	^{1}H NMR: 8.11 (s, 1H, H-2 indole), 7.81–7.01 (m, 13H, ArH), 6.68 (s, 1H, CH=C), 5.56 (s, 2H, CH_2), 4.43 (q, 2H, CH_2CO), 3.88–2.51 (m, 4H, CHCHCH$_2$ cyclohexanone), 1.9 (t, 3H, **CH$_3$**CH$_2$CO)	
16a	1721, 1703 & 1689 (3C=O), 1577 (C=C), 1008 (C-O-C)	^{1}H NMR: 8.21 (s, 1H, H-2 indole), 7.81–7.01 (m, 13H, ArH), 6.68 (s, 1H, CH=C), 4.43 (q, 2H, CH_2CO), 3.99 (s, 3H, OCH_3), 3.56–2.67 (m, 4H, CHCHCH$_2$ cyclohexanone), 1.9 (t, 3H, **CH$_3$**CH$_2$CO)	
16b	1723, 1705 & 1678 (3C=O), 1588 (C=C), 748 (Cl)	^{1}H NMR: 8.11 (s, 1H, H-2 indole), 7.81–7.01 (m, 13H, ArH), 6.66 (s, 1H, CH=C), 4.42 (q, 2H, CH_2CO), 3.88–2.51 (m, 4H, CHCHCH$_2$ cyclohexanone), 1.61 (t, 3H, **CH$_3$**CH$_2$CO)	

Table II. continued

17a	3340 (NH), 1645 (C=O), 1620 (C=N), 1577 (C=C), 1009 (C-O-C)	^{1}H NMR: 9.21 (s, 1H, NH), 8.02 (s, 1H, H-2 indole), 7.97–7.01 (m, 8H, ArH), 6.16 (s, 1H, CH=C), 4.21 (q, 2H, CH_2N), 3.91 (s, 3H, OCH_3), 2.90 & 3.31 (2d, 2H, CHCH), 2.13 & 2.45 (2dd, 2H, CH**CH_2**), 1.30 (t, 3H, **CH_3**CH_2N) ^{13}C NMR: 177.3 (C=O), 111.1–152.1 (ArC), 52.6 (CH_2), 42.6 (CH), 15.1 (CH_3)	385 (M^+, 7), 350 (10), 308 (30), 141 (100), 117(18), 77 (60)
17b	3300 (NH), 1665 (C=O), 1621 (C=N), 1578 (C=C), 745 (Cl)		389 (M^+, 7), 391 (M^++2, 1), 144 (100), 142 (10), 117 (60), 111 (50), 77 (70)
18a	3320 (NH), 1660 (C=O), 1643 (C=N), 1567 (C=C), 1018 (C-O-C)	^{1}H NMR: 8.71 (s, 1H, NH), 8.02 (s, 1H, H-2 indole), 7.77–7.01 (m, 13H, ArH), 6.22 (s, 1H, CH=C), 5.56 (s, 2H, CH_2-N), 3.91 (s, 3H, OCH_3), 2.81 & 3.43 (2d, 2H, CHCH) 2.11 & 2.55 (2dd, 2H, CH**CH_2**)	
18b	3218 (NH), 1675 (C=O), 1621 (C=N), 1577 (C=C), 754 (Cl)		451 (M^+, 10), 453 (M^++2, 2), 142 (10), 117 (60), 111 (50), 91 (100), 77 (70)
19a	3298 (NH), 1687 (C=O), 1621 (C=N), 1567 (C=C), 1019 (C-O-C)	^{1}H NMR: 8.71 (s, 1H, NH), 8.02 (s, 1H, H-2 indole), 7.77–7.01 (m, 13H, ArH), 6.22 (s, 1H, CH=C), 3.98 (s, 3H, OCH_3), 2.81 & 3.43 (2d, 2H, CHCH) 2.11 & 2.55 (2dd, 2H, CH**CH_2**)	
19b	3200 (NH), 1678 (C=O), 1619 (C=N), 1587 (C=C), 745 (Cl)		465 (M^+, 10), 467 (M^++2, 2), 193 (100), 142 (10), 111 (50), 77 (70)
20a	3332 (NH), 1583 (C=N), 1523 (C=C), 1013 (C-O-C)	^{1}H NMR: 8.52 (s, 1H, H-2 ind.), 8.03 (s, 1H, NH), 7.82–7.17 (m, 8H, ArH), 4.31(q, 2H, CH_2N), 3.81 (s, 3H, OCH_3), 3.74 (dd, 1H, CH-pyrazoline), 2.58 (dd, 1H, **CH_2**-pyrazoline equatorial), 1.44 (dd, 1H, **CH_2**-pyrazoline axial), 1.05 (t, 3H, CH_3)	319 (M^+, 12), 317 (11), 172 (100), 170 (31), 156 (12), 145 (23), 115 (18)
20b	3255 (NH), 1618 (C=N), 1523 (C=C), 746 (C-Cl)		323 (M^+, 2), 325 (M^++2, 0.01), 144 (100), 130 (12), 116 (31), 111 (9)

Table II. continued

21a	3400 (NH), 1587 (C=N), 1545 (C=C), 1021 (C-O-C)	^{1}H NMR: 10.22 (s, 1H, NH), 8.53 (s, 1H, H-2 indole), 7.51–7.17 (m, 13H, ArH), 5.55 (s, 2H, CH_2), 3.86 (dd, 1H, CH-pyrazoline), 3.74 (s, 3H, OCH_3), 2.57 (dd, 1H, **CH_2**-pyrazoline equatorial), 1.55 (dd, 1H, **CH_2**-pyrazoline axial) ^{13}C NMR: 157.6 (C=N), 136.6–109.9 (ArC), 40.6 (CH_2N), 15.5 (CH_3)	381(M^+, 62), 366 (1), 91 (100), 77 (6), 65 (16)
21b	3265 (NH), 1606 (C=N), 1580 (C=C), 734 (C-Cl)	^{1}H NMR: 10.21 (s, 1H, NH), 8.20 (s, 1H, H-2 indole), 7.75–7.12 (m, 13H, ArH), 5.51 (s, 2H, CH_2), 5.42 (dd, 1H, CH-pyrazoline), 4.76 (dd, 1H, **CH_2**-pyrazoline equatorial), 2.58 (dd, 1H, **CH_2**-pyrazoline axial) ^{13}C NMR: 139.5–110.6 (ArC), 41.2 (CH_2Ph), 15.0 ($CH_{2)}$	
22a	3392 (NH), 1664 (C=O), 1582 (C=N), 1545 (C=C), 1012 (C-O-C)		395 (M^+, 1), 314 (100), 144 (3), 142 (23), 117 (5), 89 (11)
22b	3391 (NH), 1722 (C=O), 1618 (C=N), 1521 (C=C), 747 (C-Cl)		399 (M^+, 2), 401 (M^++2, 0.15), 295 (30), 293 (100), 258 (5)
23a	1719 (C=O), 1640 (C=N), 1572 (C=C), 1042 (C-O-C)		361 (M^+, 1), 305 (42), 277 (13), 172 (100), 145 (19),130 (7), 116 (20)
23b	1725 C=O), 1648 (C=N), 1614 (C=C), 783 (C-Cl)		365 (M^+, 1), 367 (M^++2, 0.015),313 (34), 309 (100), 281 (53), 172 (58), 144 (20), 117 (3)
24a	1741 (C=O), 1639 (C=N), 1604 (C=C), 1023 (C-O-C)		423 (M^+, 0.01) and 249 (100) Diagram 37
24b	1723 (C=O), 1639 (C=N), 1575 (C=C), 736 (C-Cl)	^{1}H NMR: 8.56 (s, 1H, H-2 indole), 8.37 (d, 1H, H-7 indole), 8.21 (d, 1H, H-4 indole), 7.91–7.15 (m, 11H, ArH), 5.55 (s, 2H, CH_2N), 5.51 (dd, 1H, CH-pyrazoline), 2.51 (dd, 1H, **CH_2**-pyrazoline equatorial), 1.23 (dd, 1H, **CH_2**-pyrazoline axial), 1.19 (s, 3H, CH_3) ^{13}C NMR: 182.8 (C=O), 138.1–110.7 (ArC), 41.2 (CH_2), 15.1 (CH_3)	427 (M^+, 0.01), 429 (M^++2, 0.003), 372 (34), 371 (89), 345 (14), 115 (7), 91 (100)

Table II. continued

25a	1724 (C=O), 1647 (C=N), 1615 (C=C), 1028 (C-O-C)		437 (M^+, 1), 367 (32), 333 (13), 277 (100), 91 (80), 57 (25)
25b	1723 C=O), 1646 (C=N), 1590 (C=C), 777 (C-Cl)		441 (M^+, 13), 443 (M^++2, 4), 298 (43), 296 (100), 261 (13), 186 (13)
26a	1620 (C=N), 1589 (C=C), 1009 (C-O-C)	^{1}H NMR: 8.01 (s, 1H, H-2 indole), 7.97–7.00 (m, 13H, ArH), 5.45 (dd, 1H, CH-pyrazoline), 4.42 (q, 2H, CH_2), 3.98 (s, 3H, OCH_3), 3.88 (dd, 1H, **CH_2**-pyrazoline equatorial), 3.02 (dd, 1H, **CH_2**-pyrazoline axial), 1.90 (t, 3H, CH_3)	
26b	1621 (C=N), 1577 (C=C), 754 (Cl)	^{1}H NMR: 8.21 (s, 1H, H-2 indole), 7.99–7.12 (m, 13H, ArH), 5.40 (dd, 1H, CH-pyrazoline), 4.45 (q, 2H, CH_2), 3.78 (dd, 1H, **CH_2**-pyrazoline equatorial), 3.32 (dd, 1H, **CH_2**-pyrazoline axial), 1.90 (t, 3H, CH_3)	
27a	1621 (C=N), 1567 (C=C), 1016 (C-O-C)	^{1}H NMR: 8.02 (s, 1H, H-2 indole), 7.68–7.10 (m, 18H, ArH), 5.53 (s, 2H, CH_2), 5.00 (dd, 1H, CH-pyrazoline), 3.99 (s, 3H, OCH_3), 3.88 (dd, 1H, **CH_2**-pyrazoline equatorial), 3.32 (dd, 1H, **CH_2**-pyrazoline axial)	
27b	1623 (C=N), 1576 (C=C), 740 (Cl)		461 (M^+, 10), 463 (M^++2, 4), 144 (40), 105 (60), 91(100)
28a	1687 (C=O), 1645 (C=N), 1587 (C=C), 1010 (C-O-C)		471 (M^+, 3), 394 (30), 193 (30), 117 (20), 77 (35)
28b	1670 (C=O), 1621 (C=N), 1566 (C=C), 754 (Cl)	^{1}H NMR: 8.02 (s, 1H, H-2 indole), 8.01–7.10 (m, 18H, ArH), 4.39 (dd, 1H, CH-pyrazoline), 3.88 (dd, 1H, **CH_2**-pyrazoline equatorial), 3.32 (dd, 1H, **CH_2**-pyrazoline axial)	
29a	1621 (C=N), 1576 (C=C), 1009 (C-O-C)	^{1}H NMR: 8.23 (s, 1H, H-2 indole), 8.01–7.10 (m, 13H, ArH), 5.65 (s, 2H, CH_2), 4.45 (q, 2H, CH_2), 4.39 (dd, 1H, CH-pyrazoline), 3.99 (s, 3H, OCH_3), 3.88 (dd, 1H, **CH_2**-pyrazoline equatorial), 3.32 (dd, 1H, **CH_2**-pyrazoline axial), 1.91 (t, 3H, CH_3)	
29b	1618 (C=N), 1569 (C=C), 750 (Cl)		

Table II. continued

30a	1630 (C=N), 1567 (C=C), 1009 (C-O-C)	^{1}H NMR: 8.21 (s, 1H, H-2 indole), 7.99–7.10 (m, 18H, ArH), 5.65 (s, 2H, CH_2), 5.53 (s, 2H, CH_2), 4.99 (dd, 1H, CH-pyrazoline), 4.01 (s, 3H, OCH_3), 3.88 (dd, 1H, **CH_2**-pyrazoline equatorial), 3.32 (dd, 1H, **CH_2**-pyrazoline axial)	
30b	1621 (C=N), 1577 (C=C), 745 (Cl)		
31a	1678 (C=O), 1621 (C=N), 1576 (C=C), 1009 (C-O-C)		
31b	1698 (C=O), 1632 (C=N), 1566 (C=C), 754 (Cl)		
32a	1602 (C=N), 1575 (C=C), 1021 (C-O-C)		320 (M^+, 1), 212 (12), 202 (100), 145 (7), 130 (38), 117 (11)
32b	1634 (C=N), 1594 (C=C), 741 (C-Cl)		324 (M^+, 1), 326 (M^++2, 0.16), 294 (1), 184 (1), 130 (3), 71 (38), 57 (100).
33a	1608 (C=N), 1517 (C=C), 1182 & 1138 & 1104 (C-O-C)		382 (M^+, 1), 264 (31), 207 (12), 131 (5), 115 (5), 91 (100)
33b	1635 (C=N), 1572 (C=C), 736 (C-Cl)	^{1}H NMR: 8.29 (s, 1H, H-2 indole), 8.01–7.12 (m, 13H, ArH), 5.53 (s, 2H, CH_2), 5.40 (dd, 1H, CH-isoxazole), 3.78 (dd, 1H, **CH_2**-isoxazole equatorial), 3.32 (dd, 1H, **CH_2**-isoxazole axial)	386 (M^+, 10), 388 (M^++2, 3), 264 (43), 207 (19), 115 (5), 91 (100)
34a	1738 (C=O), 1615 (C=N), 1567 (C=C), 1022 (C-O-C)	^{1}H NMR: 8.21 (s, 1H, H-2 indole), 8.13 (d, 1H, H-7 indole), 7.67–7.00 (m, 12H, ArH), 3.88 (s, 3H, OCH_3), 3.71 (dd, 1H, CH-isoxazole), 2.44 (dd, 1H, **CH_2**-isoxazole equatorial), 2.16 (dd, 1H, **CH_2**-isoxazole axial)	396 (M^+, 1), 290 (14), 277 (62), 262 (15), 144 (100), 105 (10), 91 (46)
34b	1738 (C=O), 1633 (C=N), 1575 (C=C), 746 (C-Cl)		400 (M^+, 10), 402 (M^++2, 3), 296 (17), 281 (83), 144 (100), 117 (35), 89 (44), 77 (19)

Table III. Antimicrobial activity of some synthesized compounds (20 μg per disc)

Compd.	Inhibition zone (mm)					
	S. typhimurium	P. *fluorescens*	*S. aureus*	*B. subtilis*	*C. albicans*	*A. fumigatus*
11b	–	17	14	14	33	–
12a	–	–	–	–	14	–
12b	–	–	–	14	–	–
13a	8	8	14	–	14	–
13b	–	8	–	–	14	–
14a	8	8	14	–	14	15
15a	–	–	–	–	9	–
15b	–	–	–	–	–	–
16a	–	14	14	14	9	–
16b	10	–	–	–	–	–
20b	–	14	14	–	14	–
22a	–	14	–	–	–	–
22b	–	14	14	–	14	–
23b	–	–	–	–	14	–
24a	–	–	–	–	14	–
24b	–	–	–	–	14	–
25a	–	–	–	–	14	–
25b	14	–	14	–	14	9
26a	–	–	–	–	–	–
26b	–	–	–	–	14	–
28a	14	14	14	–	9	–
28b	–	14	14	–	14	9
29a	–	14	14	–	14	–
30b	–	–	–	–	9	–
31a	–	15	14	–	–	–
31b	–	14	–	–	15	–
32a	–	14	14	–	15	–
33a	–	–	14	–	–	–
34a	–	14	14	–	14	–
34b	14	–	14	–	14	–
Chloramphenicol	42	37	–	–	–	–
Cephalothin	–	–	38	38	–	–
Cycloheximide	–	–	–	–	39	40

Inhibition zones: 3–12 mm – low activity, 13–21 mm – moderate activity, > 22 mm – high activity

their *in vitro* antiproliferative activity against human liver carcinoma HEPG2, (MCF7) and human colon cancer (HCT-116) cell lines at a concentration of 10 μg mL^{-1} (Table IV). Compound **11a** was the most active one with antiproliferative activity of 97.6, 100.5 and 99.6 % against HEPG2, MCF7 and HCT-116 cancer cell lines, respectively, whereas compound **11b** showed activity of 94.3 % against the HCT-116 cancer cell line and compound **12a** of 95.7 % against the MCF7 cancer cell line.

Compounds that showed antiproliferative activity higher than 90 % at concentration of 10 μg mL^{-1} were used to calculate their IC_{50} value, which corresponds to the concentration required for 50 % inhibition of cell viability. Doxorubicin, one of the most effective anticancer agents, was used as a reference drug (Table V). In case of the HEPG2 cancer cell line, compound **11a** was shown to be more potent with IC_{50} of 0.7 μmol L^{-1} than doxorubicin with IC_{50} of 40 μmol L^{-1}, for MCF7 cancer cell line, both **11a** and **12a** were found to be more potent with IC_{50} of 0.7 μmol L^{-1} *vs*. 0.07 μmol mL^{-1}, whereas in case of the HCT-116 cancer cell line, again compounds **11a** and **11b** were found to be more potent than doxorubicin (IC_{50} of 60 μmol L^{-1}) with IC_{50} of 0.7 μmol L^{-1}.

Table IV. Antiproliferative activity of the newly synthesized compounds against human carcinoma cell lines

Compd.[a]	Inhibition growth (%)		
	HEPG2	MCF7	HCT-116
5a	17.5	7.6	2.1
5b	42.2	6.2	0
6a	61.4	3.9	34.0
6b	27.9	7.8	5.4
7a	42.1	0.65	37.4
7b	57.2	12.9	20.6
8a	47.8	7.7	4.3
8b	0	14.1	0
9a	53.2	19.6	12.5
9b	41.2	18.9	2.9
10a	1.5	22.5	5.0
10b	65.7	25.9	26.6
11a	97.6	100.5	99.6
11b	56.1	60.0	94.3
12a	29.2	95.7	84.2
12b	71.8	28.2	34.9
13a	39.7	6.6	46.7
13b	46.6	0	64.9
Doxorubicin	100.0	100.0	100.0

[a] Concentration of test compounds and positive control (doxorubicin) 10 μg mL^{-1}
[b] Untreated cells in DMSO and its final concentration on the cells was less than 0.2 %.

Table V. Antiproliterative activity against human cancer cell lines

Compd.	IC_{50} (μmol mL^{-1})		
	HEPG2	MCF7	HCT-116
11a	0.0007	0.0007	0.0007
11b	–	–	0.0007
12a	–	0.0007	–
Doxorubicin	0.04	0.07	0.06

IC_{50} – Concentration required to inhibit cell viability by 50 %.

Structure activity relationship (SAR)

From the data obtained it is clear that compound **11a** was the most active compound and its activity may be due to the presence of the ethyl donating group at the position-1 of indole nucleus and the methoxy withdrawing group at the *p*-position of phenyl moiety. The presence of the withdrawing chlorine atom at the *p*-position of phenyl moiety in **11b** is associated with the remarkable antiproliferative activity against the HCT-116 cancer cell line only, whereas the presence of the benzyl withdrawing moiety as in **12a** is associated with the remarkable antiproliferative activity against the MCF7 cancer cell line.

CONCLUSIONS

A series of pyrimidin-2(1*H*)ones **5a,b-7a,b**, pyrimidin-2(1*H*)-thiones **8a,b-10a,b**, pyrimidin-2-amines **11a,b-13a,b**, cyclohexanone derivatives **14a,b-16a,b,** indazole derivatives **17a,b-19a,b**, pyrazole derivatives **20a,b-31a,b** and isoxazole derivatives **32a,b-34a,b** incorporated into *N*-alkylindole at their 3-positions were prepared. 4-(*N*-Ethyl-1*H*-indol--3-yl)-6-(*p*-chlorophenyl)-pyrimidin-2-amine (**11b**) was found to be the most active of all test compounds towards *Candida albicans*, whereas compound 4-(*N*-ethyl-1*H*-indol-3-yl)--6-(*p*-methoxyphenyl)-pyrimidin-2-amine (**11a)** was found to be the most active one against HEPG2, MCF7 and HCT-116 cancer cell lines with IC_{50} values of 0.7 μmol L^{-1}.

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S A Ž E T A K

Sinteza, antimikrobno i antitumorsko djelovanje nekoliko novih *N*-etil, N-benzil i *N*-benzoil-3-indolil heterocikličkih spojeva

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Sintetizirana je serija 1-(*N*-supstituiranih-1*H*-indol-3-il)-3-arilprop-2-en-1-ona (**2a,b-4a,b**) i podvrgnuta reakciji s ureom, tioureom ili gvanidinom, pri čemu su nastali derivati pirimidina **5a,b**–**13a,b**. Reakcijom **2a,b-4a,b** s etil-acetoacetatom u prisutnosti baze nastali su derivati cikloheksanona **14a,b-16a,b**. Njihovom reakcijom s hidrazin hidratom dobiveni su derivati indazola **17a,b-19a,b**. S druge strane, reakcijom **2a,b-4a,b** s određenim derivatima hidrazina, tj. s hidrazin hidratom, acetil hidrazinom, fenilhidrazinom i benzilhidrazin hidrokloridom, nastali su derivati pirazola **20a,b-31a,b**. Nadalje, reakcijom **2a,b-4a,b** s hidroksilamin hidrokloridom dobiveni su derivati izoksazola **32a,b-34a,b**. Pripravljeni spojevi ispitani su na antimikrobno djelovanje. Pokazalo se da je 4-(*N*-etil-1*H*-indol-3-il)-6-(*p*-klorfenil)-pirimidin-2-amin (**11b**) najaktivniji spoj za *Candida albicans* (ATCC 10231) uz cikloheksimid kao poredbeni lijek. Testirano je antitumorsko djelovanje *in vitro* osamnaest novih spojeva, tj. pirimidin-2(1*H*)-ona **5a,b-7a,b**, pirimidin-2(1*H*)-tiona **8a,b-10a,b** i pirimidin-2-amina **11a,b-13a,b** na tumorske stanice HEPG2, MCF7 i HCT-116. Najaktivniji spoj bio je 4-(*N*-etil-1*H*-indol-3-il)-6-(*p*-metoksifenil)-pirimidin-2-amin (**11a)** uz IC_{50} 0,7 μmol L^{-1}.

Ključne riječi: *N*-supstituirani-3-indolilkalkoni, heterociklički spojevi, antimikrobno djelovanje, antitumorsko djelovanje

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