Arabian Journal of Chemistry (2013) **6**, 67–78

King Saud University

Arabian Journal of Chemistry

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ORIGINAL ARTICLE

1st Cancer Update

Synthesis, antimicrobial and anticancer activities of some new *N*-methylsulphonyl and *N*-benzenesulphonyl-3-indolyl heterocycles

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Received 4 October 2011; accepted 2 April 2012
Available online 26 April 2012

KEYWORDS

Indole;
Heterocycles;
Antimicrobial activity;
Anticancer activity

Abstract A series of 1-(*N*-methyl **2a–c** and *N*-benzenesulphonyl-1*H*-indol-3-yl)-3-aryl-prop-2-ene-1-ones **3a–c** were prepared and allowed to react with urea, thiourea or guanidine and gave the pyrimidine derivatives **4a**–**c** to **9a–c**. Base catalyzed reaction of **2a–c** or **3a–c** with ethyl acetoacetate gave cyclohexanone derivatives **10a–c** and **11a–c**, respectively. Reaction of the latter compounds with hydrazine hydrate afforded indazole derivatives **12a–c** and **13a–c**, respectively. On the other hand, condensation of **2c** or **3c** with some hydrazine derivatives namely, hydrazine hydrate, acetyl hydrazine, phenyl hydrazine and benzyl hydrazine hydrochloride gave pyrazole derivatives **14a,b-17a,b**, respectively. Moreover, reaction of **2c** or **3c** with hydroxyl amine hydrochloride gave isoxazole derivatives **18a,b**. The newly synthesized compounds were tested for their antimicrobial activity and showed that, compounds **14a**, **14b**, **15a** and **15b** were found to be the most active ones of all the tested compounds toward *Salmonella typhimurium* (ATCC 14,028) compared to the reference drug chloramphenicol. Eighteen new compounds namely, pyrimidin-2(1*H*)-ones **4a–c** and

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Peer review under responsibility of King Saud University.
http://dx.doi.org/10.1016/j.arabjc.2012.04.003

Production and hosting by Elsevier

5a–**c**, pyrimidin-2(1*H*)-thiones **6a–c and 7a–c** and pyrimidin-2-amines **8a**–c and **9a–c** were tested for their *in vitro* cytotoxicity against human liver carcinoma (HEPG2), human breast cancer (MCF7) and human colon cancer (HCT-116) cell lines and showed that, compounds **4c**, **5c**, **6c**, **8c** and **9c** were found to be the highly active compounds compared to the reference drug doxorubicin.

1. Introduction

Chalcones, one of the major classes of natural products with widespread occurrence in fruits, vegetables, spices and soy-based foodstuff, have been reported to possess several biological activities (Ngameni et al., 2007; Okwu and Ukanwa, 2010). An important feature of chalcones is their ability to act as an intermediate for the synthesis of biologically active heterocyclic compounds *viz*, pyrimidine, cyclohexanone, pyrazole and isoxazole derivatives (Aitmambetov and Menlimuratova, 2003; Flefel et al., 2007; Abdel-Rahman1 et al., 2007; El Shehry et al., 2010; Sreevidya et al., 2010). Additionally, indole which is the potent basic pharmacodynamic nucleus has been reported to possess a wide variety of biological properties *viz*, anti-inflammatory, anti-cancer and antimicrobial activities (George et al., 2008; El-Sawy et al., 2009; Mandour et al., 2007, 2010). Based on the above observation and in continuation of our search (El-Sawy et al., 2009, 2010; Mandour et al., 2007, 2010) herein, we reported the synthesis of some new *N*-substituted sulphonyl-3-indolyl heterocycles and evaluating their antimicrobial and anticancer activities.

2. Experimental

2.1. Chemistry

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 (USA) and were found within ±0.4% of the theoretical values. IR spectra were recorded on a Perkin–Elmer 1600 FTIR (USA) in KBr disks. The ^{1}H NMR spectra were measured with a Bruker Avance digital spectrophotometer 300 MHz in DMSO-d$_6$ and chemical shifts were recorded in δ ppm relative to TMS as internal stander solvent. Mass spectra (EI) were run at SECTOR-FILD MS and GC–MS (single-phase) 200 V (50/60 Hz) 30 A (Germany). *N*-methylsulphonyl (**1a**) and *N*-benzenesulphonyl-3-acetylindoles (**1b**) have been prepared as reported (Mndzhoyan et al., 1969).

2.1.1. Synthesis of N-substituted-3-indolylchalcones 2a–c and 3a–c

To a solution of *N*-substituted-3-acetylindoles **1a** or **1b** (0.001 mol) in ethanol (10 mL) containing aqueous potassium hydroxide solution (5 mL, 25%), the appropriate aldehyde (0.001 mol) was added. The reaction mixture was stirred for 2 h at room temperature, and then left overnight at refrigerator. The reaction mixture was neutralized with diluted hydrochloric acid (1:1) and the solid that formed was filtered off, washed with water, air dried and recrystallized from absolute ethanol.

*2.1.1.1. 1-(N-Methylsulphonyl-1H-indol-3-yl)-3-(m-hydroxyphenyl)-prop-2-ene-1-one (**2c**).* Yield 60%, m.p. 90 dec °C. IR (KBr): ν 3400 (OH), 1686 (C═O), 1614 (C═C), 1342 and 1173 (SO$_2$) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d$_6$, 25 °C, TMS): δ = 10.41 (s, 1H, OH), 8.21 (d, 1H, H-2 indole), 7.89–7.32 (m, 8H, Ar—H), 7.01 and 6.77 (2d, 2H, CH═CH), 2.91 (s, 3H, CH$_3$) ppm. Anal. For $C_{18}H_{15}NO_4S$ (341.38) calcd: C 63.33, H 4.43, N 4.10. Found: C 63.19, H 4.55, N 4.22.

*2.1.1.2. 1-(N-Benzenesulphonyl-1H-indol-3-yl)-3-(m-hydroxyphenyl)-prop-2-ene-1-one (**3c**).* Yield 75%, m.p. 159–61 °C. IR (KBr): ν 3320 (OH), 1700 (C═O), 1617 (C═C), 1342 and 1175 (SO$_2$) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d$_6$, 25 °C, TMS): δ = 12.10 (s, 1H, OH), 8.21 (d, 1H, H-2 indole), 7.89–7.32 (m, 13H, Ar—H), 7.01 and 7.22 (2d, 2H, CH═CH) ppm. Anal. For $C_{23}H_{17}NO_4S$ (403.45), calcd: C 68.47, H 4.25, N 3.47. Found: C 68.33, H 4.0, N, 3.66.

2.1.2. Synthesis of N-substituted-3-indolylpyrimidin-2(1H)-ones 4a–c and 5a–c

A mixture of chalcones **2a–c** or **3a–c** (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 that formed was filtered off, air dried and recrystallized from absolute ethanol.

*2.1.2.1. 4-(N-Methylsulphonyl-1H-indol-3-yl)-6-(p-methoxyphenyl)-pyrimidin-2(1H)-one (**4a**).* Yield 60%, m.p. 163–5 °C. IR (KBr): ν 3140 (NH), 1670 (C═O), 1620 (C═N), 1575 (C═C), 1370 and 1167 (SO$_2$), 1009 (C—O—C) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d$_6$, 25 °C, TMS): δ = 9.90 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 7.78–7.01 (m, 9H, Ar—H), 3.98 (s, 3H, OCH$_3$) 3.32 (s, 3H, CH$_3$) ppm. Anal. For $C_{20}H_{17}N_3O_4S$ (395.43) calcd: C 60.75, H 4.33, N 10.63. Found: C 60.88, H 4.56, N, 10.76.

*2.1.2.2. 4-(N-Methylsulphonyl-1H-indol-3-yl)-6-(p-chlorophenyl)-pyrimidin-2(1H)-one (**4b**).* Yield 50%, m.p. 219–21 °C. IR (KBr): ν 3414 (NH), 1646 (C═O), 1602 (C═N), 1554 (C═C), 1376 and 1150 (SO$_2$), 745 (C—Cl) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d$_6$, 25 °C, TMS): δ = 9.98 (s, 1H, NH), 8.23 (s, 1H, H-2 indole), 7.87–7.21 (m, 9H, Ar—H), 3.32 (s, 3H, CH$_3$) ppm. MS, *m*/*z* (%): 399 (M$^+$, 10), 401 (M$^+$+2, 3), 144 (100). Anal. For $C_{19}H_{14}ClN_3O_3S$ (399.85) calcd: C 57.07, H 3.53, N 10.51. Found: C 57.22, H 3.66, N 10.44.

*2.1.2.3. 4-(N-Methylsulphonyl-1H-indol-3-yl)-6-(m-hydroxyphenyl)-pyrimidin-2(1H)-one (**4c**).* Yield 56%, m.p. 155–7 °C. IR (KBr): ν 3400 (OH), 1678 (C═O), 1612 (C═N), 1577 (C═C), 1366 and 1156 (SO$_2$) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$, 25 °C, TMS): δ = 11.21 (s, 1H, OH), 8.99 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 8.10 (s, 1H, CH—pyrimidine), 7.66–7.12 (m, 8H, Ar—H), 3.33 (s, 3H, CH_3) ppm. Anal. For $C_{19}H_{15}N_3O_4S$ (381.41) calcd: C 59.83, H 3.96, N 11.02. Found: C 60.00, H 4.00, N 11.32.

*2.1.2.4. 4-(N-Benzenesulphonyl-1H-indol-3-yl)-6-(p-methoxyphenyl)-pyrimidin-2(1H)-one (**5a**).* Yield 55%, m.p. 125–7 °C. IR (KBr): ν 3425 (NH), 1635 (C=O), 1609 (C=N), 1564 (C=C), 1384 and 1163 (SO_2), 1026 (C—O—C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.55 (s, 1H, NH), 8.11 (s, 1H, H-2 indole), 7.99 (s, 1H, CH—pyrimidine), 7.78–7.11 (m, 13H, Ar—H), 3.98 (s, 3H, OCH_3) ppm. Anal. For $C_{25}H_{19}N_3O_4S$ (457.5) calcd: C 65.63, H 4.19, N, 9.18. Found: C 65.44, H 4.33, N 9.00.

*2.1.2.5. 4-(N-Benzenesulphonyl-1H-indol-3-yl)-6-(p-chlorophenyl)-pyrimidin-2(1H)-one (**5b**).* Yield 48%, m.p. 223–5 °C. IR (KBr): ν 3424 (NH), 1641 (C=O), 1602 (C=N), 1545 (C=C), 1395 and 1153 (SO_2), 745 (C—Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 10.21 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 7.71–7.01 (m, 14H, Ar—H) ppm. MS, *m/z* (%): 461 (M^+, 12), 463 ($M^+ + 2$, 4), 281 (100). Anal. For $C_{24}H_{16}ClN_3O_3S$ (461.92) calcd: C 62.34, H 3.49, N, 9.10. Found: C 62.55, H 3.56, N 9.22.

*2.1.2.6. 4-(N-Benzenesulphonyl-1H-indol-3-yl)-6-(m-hydroxyphenyl)-pyrimidin-2(1H)-one (**5c**).* Yield 65%, m.p. 97dec °C. IR (KBr, ν): 3398 (OH), 3140 (NH), 1670 (C=O), 1620 (C=N), 1588 (C=C), 1370 and 1156 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 10.51 (s, 1H, OH), 9.72 (s, 1H, NH), 8.02 (s, 1H, H-2 indole), 7.87–7.23 (m, 14H, Ar—H) ppm. MS, *m/z* (%): 443 (M^+, 10), 144 (100). Anal. For $C_{24}H_{17}N_3O_4S$ (443.47) calcd: C 65.00, H 3.86, N 9.48. Found: C 65.21, H 3.69, N 9.54.

*2.1.3. Synthesis of N-substituted-3-indolylpyrimidin-2(1H)-thiones **6a**–**c** and **7a**–**c***

A mixture of chalcones **2a–c** or **3a–c** (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 that formed was filtered off, air dried and recrystallized from absolute ethanol.

*2.1.3.1. 4-(N-Methylsulphonyl-1H-indol-3-yl)-6-(p-methoxyphenyl)-pyrimidin-2(1H)-thione (**6a**).* Yield 50%, m.p. 138–40 °C. IR (KBr): ν 3162 (NH), 1615 (C=N), 1573 (C=C), 1386 and 1169 (SO_2), 1248 (C=S), 1028 (C—O—C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.87 (1H, s, NH), 8.39 (1H, s, H-2 ind.), 8.22 (1H, s, CH—pyrimidine), 7.81–7.00 (8H, m, Ar—H), 4.32 (3H, s, OCH_3), 3.28 (3H, s, CH_3) ppm. MS, *m/z* (%):411(M^+, 0.01), 277 (100). Anal. For $C_{20}H_{17}N_3O_3S_2$ (411.5) calcd: C 58.38, H 4.16, N 10.21. Found: C 58.42, H 4.30, N 10.44.

*2.1.3.2. 4-(N-Methylsulphonyl-1H-indol-3-yl)-6-(p-chlorophenyl)-pyrimidin-2(1H)-thione (**6b**).* Yield 62%, m.p. 169–71 °C. IR (KBr): ν 3228 (NH), 1612 (C=N), 1567 (C=C), 1378 and 1157 (SO_2), 1244 (C=S), 748 (Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.65 (1H, s, NH), 8.12 (1H, s, H-2 ind.), 7.65–7.01 (9H, m, Ar—H), 3.32 (3H, s, CH_3) ppm. MS, *m/z* (%):415 (M^+, 1), 417 ($M^+ + 2$, 0.01), 281 (100). Anal. For $C_{19}H_{14}ClN_3O_2S_2$ (415.92) calcd: C 54.87, H 3.39, N 10.10. Found: C 54.98, H 3.22, N 10.00.

*2.1.3.3. 4-(N-Methylsulphonyl-1H-indol-3-yl)-6-(m-hydroxyphenyl)-pyrimidin-2(1H)-thione (**6c**).* Yield 50%, m.p. 79–81 °C. IR (KBr): ν 3400 (OH), 3210 (NH), 1645 (C=N), 1370 and 1167 (SO_2), 1240 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 10.54 (s, 1H, OH), 9.51 (1H, s, NH), 8.22 (s, 1H, H-2 indole), 8.00 (s, 1H, CH—pyrimidine), 7.98–7.32 (m, 8H, Ar—H), 3.32 (3H, s, CH_3) ppm. Anal. For $C_{19}H_{15}N_3O_3S_2$ (397.47) calcd: C 57.41, H 3.80, N 10.57. Found: C 57.22, H 3.67, N 10.43.

*2.1.3.4. 4-(N-Benzenesulphonyl-1H-indol-3-yl)-6-(p-methoxyphenyl)-pyrimidin-2(1H)-thione (**7a**).* Yield 55%, m.p. 155dec °C. IR (KBr): ν 3300 (NH), 1637 (C=N), 1608 (C=C), 1386 and 1161 (SO_2), 1250 (C=S), 1099 and 1029 (C—O—C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 12.05 (1H, s, NH), 8.31 (1H, s, H-2 ind.), 8.12 (1H, s, CH—pyrimidine), 7.79–7.00 (13H, m, Ar—H), 4.27 (3H, s, OCH_3) ppm. MS, *m/z* (%):473 (M^+, 0.01), 277 (100). Anal. For $C_{25}H_{19}N_3O_3S_2$ (473.57) calcd: C 63.41, H 4.04, N 8.87. Found C 63.56, H 3.99, N 8.90.

*2.1.3.5. 4-(N-Benzenesulphonyl-1H-indol-3-yl)-6-(p-chlorophenyl)-pyrimidin-2(1H)-thione (**7b**).* Yield 42%, m.p. 200–2 °C. IR (KBr, ν): 3328 (NH), 1641 (C=N), 1563 (C=C), 1236 (C=S), 1395 and 1153 (SO_2), 745 (C—Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.77 (1H, s, NH), 8.22 (1H, s, H-2 ind.), 7.89–7.01 (14H, m, Ar—H) ppm. MS, *m/z* (%):477 (M^+, 12), 479 ($M^+ + 2$, 2), 115 (100). Anal. For $C_{24}H_{16}ClN_3O_2S_2$ (477.99) calcd. C 60.25, H 3.34, N 8.78. Found: C 60.33, H 3.21, N 8.65.

*2.1.3.6. 4-(N-Benzenesulphonyl-1H-indol-3-yl)-6-(m-hydroxyphenyl)-pyrimidin-2(1H)-thione (**7c**).* Yield 68%, m.p. 135–7 °C. IR (KBr): ν 3400 (OH), 3218 (NH), 1645 (C=N), 1577 (C=C), 1375 and 1167 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 11.51(1H, s, OH), 9.87 (1H, s, NH), 8.22 (1H, s, H-2 ind.), 7.78–7.01 (14H, m, Ar—H) ppm. MS, *m/z* (%): 459 (M^+, 1), 144 (100). Anal. For $C_{24}H_{17}N_3O_3S_2$ (459.54) calcd: C 62.73, H 3.73, N 9.14. Found: C 62.88, H 3.55, N 9.34.

*2.1.4. Synthesis of N-substituted-3-indolylpyrimidin-2-amines **8a**–**c** and **9a**–**c***

A mixture of chalcones **2a–c** or **3a–c** (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 that formed was filtered off, air dried and recrystallized from absolute ethanol.

*2.1.4.1. 4-(N-Methylsulphonyl-1H-indol-3-yl)-6-(p-methoxyphenyl)-pyrimidin-2-amine (**8a**).* Yield 75%, m.p. 148–150 °C. IR (KBr): ν 3400 and 3320 (NH_2), 1645 (C=N), 1578 (C=C), 1368 and 1157 (SO_2), 1009 (C—O—C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.91 (s, 2H, NH_2), 8.02 (s, 1H, H-2 indole), 8.00–7.00 (m, 9H, Ar—H), 4.00 (s, 3H, OCH_3) 3.33 (s, 3H, CH_3) ppm. Anal. For $C_{20}H_{18}N_4O_3S$ (394.45) calcd: C 60.90, H 4.60, N 14.20. Found: C 61.01, H 4.76, N 14.36.

*2.1.4.2. 4-(N-Methylsulphonyl-1H-indol-3-yl)-6-(p-chlorophenyl)-pyrimidin-2-amine (**8b**).* Yield 85%, m.p. 236–8 °C. IR (KBr): ν 3310 and 3218 (NH_2), 1645 (C=N), 1578 (C=C), 1368 and 1157 (SO_2), 746 (Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ 9.99 (s, 2H, NH_2), 8.22 (s, 1H, H-2 indole), 8.01–7.21 (m, 9H, Ar—H), 3.31 (s, 3H, CH_3) ppm. Anal. For $C_{19}H_{15}ClN_4O_2S$ (398.87) calcd: C 57.21, H 3.79, N 14.05. Found: C 57.44, H 3.60, N 14.22.

*2.1.4.3. 4-(N-Methylsulphonyl-1H-indol-3-yl)-6-(m-hydroxyphenyl)-pyrimidin-2-amine (**8c**).* Yield 79%, m.p. 201–2 °C. IR (KBr): ν 3400 (OH), 3218 and 3100 (NH_2), 1635 (C=N), 1566 (C=C), 1368 and 1157 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ 11.65 (s, 2H, OH), 8.21 (s, 1H, H-2 indole), 7.65–7.01 (m, 9H, Ar—H), 6.65 (s, 2H, NH_2), 3.32 (s, 3H, CH_3) ppm. MS, *m/z* (%): 380 (M^+, 20), 142 (100). Anal. For $C_{19}H_{16}N_4O_3S$ (380.42) calcd: C 59.99, H 4.24, N 14.37. Found: C 60.02, H 4.39, N 14.10.

*2.1.4.4. 4-(N-Benzenesulphonyl-1H-indol-3-yl)-6-(p-methoxyphenyl)-pyrimidin-2-amine (**9a**).* Yield 81%, m.p. 155–7 °C. IR (KBr): ν 3300 and 3220 (NH_2), 1635 (C=N), 1545 (C=C), 1368 and 1157 (SO_2), 1010 (C—O—C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 8.99 (s, 2H, NH_2), 8.22 (s, 1H, H-2 indole), 8.12 (s, 1H, CH—pyrimidine), 8.00–7.10 (m, 13H, Ar—H), 3.98(s, 3H, OCH_3) ppm. Anal. For $C_{25}H_{20}N_4O_3S$ (456.52) calcd: C 65.77, H 4.42, N 12.27. Found: C 65.98, H 4.57, N 12.44.

*2.1.4.5. 4-(N-Benzenesulphonyl-1H-indol-3-yl)-6-(p-chlorophenyl)-pyrimidin-2-amine (**9b**).* Yield 77%, m.p. 237–240 °C. IR (KBr): ν 3220 and 3180 (NH_2), 1635 (C=N), 1565 (C=C), 1368 and 1157 (SO_2), 757 (Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 8.76 (s, 2H, NH_2), 8.32 (s, 1H, H-2 indole), 8.21 (s, 1H, CH—pyrimidine), 7.98–7.10 (m, 13H, Ar—H) ppm. Anal. For $C_{24}H_{17}ClN_4O_2S$ (460.94) calcd: C 62.54, H 3.72, N 12.16. Found: C 62.35, H 3.56, N 12.44.

*2.1.4.6. 4-(N-Benzenesulphonyl-1H-indol-3-yl)-6-(m-hydroxyphenyl)-pyrimidin-2-amine (**9c**).* Yield 70%, m.p. 233–5 °C. IR (KBr): ν 3450 (OH), 3300 and 3218 (NH_2), 1645 (C=N), 1535 (C=C), 1368 and 1157 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 12.01 (s, 1H, OH), 9.21 (s, 2H, NH_2), 8.22 (s, 1H, H-2 indole), 8.01 (s, 1H, CH—pyrimidine), 7.87–7.10 (m, 13H, Ar—H) ppm. Anal. For $C_{24}H_{18}N_4O_3S$ (442.49) calcd: C 65.14, H 4.10, N 12.66. Found: C 65.32, H 4.22, N 12.56.

*2.1.5. Synthesis of N-substituted-3-indolylcyclohexanones **10a–c** and **11a–c***

A mixture of chalcones **2a–c** or **3a–c** (0.01 mol) and ethyl acetoacetate (1.30 mL, 0.01 mol) in absolute ethanol (10 mL) containing aqueous potassium hydroxide solution (1 mL, 10%). The reaction mixture was refluxed for 2 h and then left overnight at room temperature. The solid that formed was filtered off, air dried and recrystallized from absolute ethanol.

*2.1.5.1. Ethyl-4-(N-methylsulphonyl-1H-indol-3-yl)-6-(p-methoxyphenyl)-2-oxo-cyclohexa-3-enecarboxylate (**10a**).* Yield 30%, m.p. 177dec °C. IR (KBr): ν 1702 and 1688 (C=O), 1567 (C=C), 1367 and 1156 (SO_2), 1001 (C—O—C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 8.21 (s, 1H, H-2 indole), 7.87–7.01 (m, 8H, Ar—H), 6.68 (s, 1H, CH=C), 4.42 (q, 2H, CH_2—CO), 4.12 (s, 3H, OCH_3), 3.65 (s, 3H, CH_3), 3.45–2.99 (m, 4H, —CH—CH—CH_2 cyclohexanone), 1.91 (t, 3H, CH_3CH_2CO) ppm. Anal. For $C_{25}H_{25}NO_6S$ (467.53) calcd: C 64.22, H 5.39, N 3.00. Found: C 64.45, H 5.45, N 2.89.

*2.1.5.2. Ethyl-4-(N-methylsulphonyl-1H-indol-3-yl)-6-(p-chlorophenyl)-2-oxo-cyclohexa-3-enecarboxylate (**10b**).* Yield 32%, m.p. 151–3 °C. IR (KBr): ν 1703 and 1678 (C=O), 1577 (C=C), 1367 and 1156 (SO_2), 750 (Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 8.22 (s, 1H, H-2 indole), 7.77–7.01 (m, 8H, Ar—H), 6.67 (s, 1H, CH=C), 4.44 (q, 2H, CH_2—CO), 3.75 (s, 3H, CH_3), 3.45–2.99 (m, 4H, —CH—CH—CH_2 cyclohexanone), 1.61 (t, 3H, CH_3CH_2CO) ppm. Anal. For $C_{24}H_{22}ClNO_5S$ (471.95) calcd: C 61.08, H 4.70, N 2.97. Found: C 61.22, H 4.82, N 3.01.

*2.1.5.3. Ethyl-4-(N-methylsulphonyl-1H-indol-3-yl)-6-(m-hydroxyphenyl)-2-oxo-cyclohexa-3-enecarboxylate (**10c**).* Yield 32%, m.p. 211–3 °C. IR (KBr): ν 3450 (OH), 1712 and 1698 (C=O), 1557 (C=C), 1367 and 1156 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 10.21 (s, 1H, OH), 8.21 (s, 1H, H-2 indole), 7.67–7.21 (m, 8H, Ar—H), 6.66 (s, 1H, CH=C), 4.41 (q, 2H, CH_2—CO), 3.67 (s, 3H, CH_3), 3.54–2.91 (m, 4H, —CH—CH—CH_2 cyclohexanone), 1.61 (t, 3H, CH_3CH_2CO) ppm. Anal. For $C_{25}H_{23}NO_6S$ (453.51) calcd: C 63.56, H 5.11, N 3.09. Found: C 63.77, H 5.33, N 3.21.

*2.1.5.4. Ethyl-4-(N-benzenesulphonyl-1H-indol-3-yl)-6-(p-methoxyphenyl)-2-oxo-cyclohexa-3-enecarboxylate (**11a**).* Yield 32%, m.p. 168–170. IR (KBr): ν 1710 and 1698 (C=O), 1567 (C=C), 1367 and 1156 (SO_2), 1011 (C—O—C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 8.21 (s, 1H, H-2 indole), 7.87–7.01 (m, 13H, Ar—H), 6.68 (s, 1H, CH=C), 4.42 (q, 2H, CH_2—CO), 4.21(s, 3H, OCH_3), 3.55–2.69 (m, 4H, —CH—CH—CH_2 cyclohexanone), 2.91 (t, 3H, CH_3CH_2CO) ppm. Anal. For $C_{30}H_{27}NO_6S$ (529.60) calcd: C 68.04, H 5.14, N 2.64. Found: C 68.33, H 5.34, N 2.53.

*2.1.5.5. Ethyl-4-(N-benzenesulphonyl-1H-indol-3-yl)-6-(p-chlorophenyl)-2-oxo-cyclohexa-3-enecarboxylate (**11b**).* Yield 32%, m.p. 102–4 °C. IR (KBr): ν 1710 and 1668 (C=O), 1557 (C=C), 1367 and 1156 (SO_2), 748 (Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 8.11 (s, 1H, H-2 indole), 7.77–7.21 (m, 13H, Ar—H), 6.66 (s, 1H, CH=C), 4.44 (q, 2H, CH_2—CO), 3.45–2.89 (m, 4H, —CH—CH—CH_2 cyclohexanone), 2.61 (t, 3H, CH_3CH_2CO) ppm. MS, *m/z* (%): 534 (M^+, 12), 536 ($M^+ + 2$, 2), 56 (100). Anal. For $C_{29}H_{24}ClNO_5S$ (534.02) calcd: C 65.22, H 4.53, N 2.62. Found: C 65.44, H 4.35, N 2.78.

*2.1.5.6. Ethyl-4-(N-benzenesulphonyl-1H-indol-3-yl)-6-(m-hydroxyphenyl)-2-oxo-cyclohexa-3-enecarboxylate (**11c**).* Yield 32%, m.p. 122–4 °C. IR (KBr): ν 3410 (OH), 1722 and 1678 (C=O), 1577 (C=C), 1367 and 1156 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.97 (s, 1H, OH), 8.35 (s, 1H, H-2 indole), 7.97–7.01 (m, 13H, Ar—H), 6.67 (s, 1H, CH=C), 4.24 (q, 2H, CH_2—CO), 3.45–2.99 (m, 4H, —CH—CH—CH_2 cyclohexanone), 2.91 (t, 3H, CH_3CH_2CO)ppm. MS, *m/z* (%):515 (M^+, 12), 255 (100). Anal. For $C_{29}H_{25}NO_6S$ (515.58) calcd: C 67.56, H 4.89, N 2.72. Found: C 67.43, H 4.77, N 2.92.

*2.1.6. Synthesis of N-substituted-3-indolylindazoles **12a–c** and **13a–c***

A mixture of compounds **10a–c** or **11a–c** (0.01 mol) and hydrazine hydrate 99% (5 mL, 0.01 mol) in absolute ethanol (15 mL) containing glacial acetic acid (0.5 mL) was refluxed for 2 h. After cooling, the solid that formed was filtered off, air dried and recrystallized from chloroform.

*2.1.6.1. 4,5-Dihydro-4-(p-methoxyphenyl)-6-(N-methylsulphonyl-1H-indol-3-yl)-2H-indazol-3(H)one (**12a**).* Yield 51%, m.p. 220–2 °C. IR (KBr): ν 3218 (NH), 1665 (C=O), 1620 (C=N), 1557 (C=C), 1367 and 1156 (SO_2), 1001 (C—O—C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.50 (s, 1H, NH), 8.12 (s, 1H, H-2 indole), 7.67–7.01 (m, 8H, Ar—H), 6.66 (s, 1H, CH=C), 3.98 (s, 3H, OCH_3), 3.88 (s, 3H, CH_3), 2.81 and 3.35 (2d, 2H, CH—CH) 2.33 and 2.35 (dd, 2H, CH_2)ppm. MS, *m/z* (%):453 (M^+, 3), 144 (100). Anal. For $C_{23}H_{21}N_3O_4S$ (435.13) calcd: C 63.43, H 4.86, N 9.65. Found: C 63.58, H 4.62, N 9.34.

*2.1.6.2. 4,5-Dihydro-4-(p-chlorophenyl)-6-(N-methylsulphonyl-1H-indol-3-yl)-2H-indazol-3(H)one (**12b**).* Yield 48%, m.p. 100–2 °C. IR (KBr): ν 3218 (NH), 1665 (C=O), 1620 (C=N), 1557 (C=C), 1367 and 1156 (SO_2), 752 (Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.67 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 7.65–7.00 (m, 8H, Ar—H), 6.66 (s, 1H, CH=C), 3.41 (s, 3H, CH_3), 3.32 and 2.81 (2d, 2H, CH—CH), 2.31 and 2.21 (dd, 2H, CH_2)ppm. MS, *m/z* (%):457 (M^+, 1), 459 ($M^+ + 2$, 0.2), 65 (100). Anal. For $C_{22}H_{18}ClN_3O_3S$ (439.91) calcd: C 60.07, H 4.12, N 9.55. Found: C 60.22, H 4.30, N 9.31.

*2.1.6.3. 4,5-Dihydro-4-(m-hydroxyphenyl)-6-(N-methylsulphonyl-1H-indol-3-yl)-2H-indazol-3(H)one (**12c**).* Yield 51%, m.p. 144–6 °C. IR (KBr): ν 3400 (OH), 3218 (NH), 1665 (C=O), 1620 (C=N), 1557 (C=C), 1367 and 1156 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 10.51 (s, 1H, OH), 8.57 (s, 1H, NH), 8.12 (s, 1H, H-2 indole), 7.97–7.01 (m, 8H, Ar—H), 6.66 (s, 1H, CH=C), 3.71 (s, 3H, CH_3), 2.81 and 3.35 (2d, 2H, CH—CH) 2.33 and 2.35 (dd, 2H, CH_2) ppm. Anal. For $C_{22}H_{19}N_3O_4S$ (421.47) calcd: C 62.69, H 4.54, N 9.97. Found: C 62.33, H 4.75, N 9.63.

*2.1.6.4. 4,5-Dihydro-4-(p-methoxyphenyl)-6-(N-benzenesulphonyl-1H-indol-3-yl)-2H-indazol-3(H)-one (**13a**).* Yield 62%, m.p. 211–3 °C. IR (KBr): ν 3218 (NH), 1665 (C=O), 1620 (C=N), 1557 (C=C), 1367 and 1156 (SO_2), 1001 (C—O—C) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 8.91 (s, 1H, NH), 8.22 (s, 1H, H-2 indole), 7.87–7.01 (m, 13H, Ar—H), 6.66 (s, 1H, CH=C), 3.98 (s, 3H, OCH_3), 2.81 and 3.35 (2d, 2H, CH—CH) 2.33 and 2.35 (dd, 2H, CH—CH_2) ppm. MS, *m/z* (%): 497 (M^+, 3), 142 (100). Anal. For $C_{28}H_{23}N_3O_4S$ (497.56) calcd: C 67.59, H 4.66, N 8.45. Found: C 67.41, H 4.45, N 8.32.

*2.1.6.5. 4,5-Dihydro-(p-chlorophenyl)-6-(N-benzenesulphonyl-1H-indol-3-yl)-2H-indazol-3(H)-one (**13b**).* Yield 70%, m.p. 98–100 °C. IR (KBr): ν 3100 (NH), 1685 (C=O), 1620 (C=N), 1567 (C=C), 1367 and 1156 (SO_2), 748 (Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 9.21 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 7.76–7.31(m, 13H, Ar—H), 6.66 (s, 1H, CH=C), 3.35 and 2.81 (2d, 2H, CH—CH), 2.31 and 2.21 (dd, 2H, CH_2)ppm. MS, *m/z* (%): 501 (M^+, 1), 503 ($M^+ + 2$, 0.2), 77 (100). Ana. For $C_{27}H_{20}ClN_3O_3S$ (501.98) calcd: C 64.60, H 4.26, N 8.08. Found: C 62.45, H 4.44, N 8.22.

*2.1.6.6. 4,5-Dihydro-(m-hydroxyphenyl)-6-(N-benzenesulphonyl-1H-indol-3-yl)-2H-indazol-3(H)-one (**13c**).* Yield 65%, m.p. 115–7 °C. IR (KBr): ν 3420 (OH), 3220 (NH), 1675 (C=O), 1618 (C=N), 1557 (C=C), 1367 and 1156 (SO_2) cm $^{-1}$. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 12.10 (s, 1H, OH), 8.75 (s, 1H, NH), 8.22 (s, 1H, H-2 indole), 7.97–7.01 (m, 13H, Ar—H), 6.76 (s, 1H, CH=C), 2.81 and 3.35 (2d, 2H, CH—CH) 2.33 and 2.35 (dd, 2H, CH—CH_2) ppm. Anal. For $C_{27}H_{21}N_3O_4S$ (483.54) calcd: C 67.07, H 4.38, N 8.69. Found: C 67.25, H 4.52, N 8.32.

*2.1.7. Synthesis of N-substituted-3-indolylpyrazoles **14a** and **14b***

To a solution of compound **2c** or **3c** (0.01 mol) in absolute ethanol (10 mL) containing few drops of glacial acetic acid, 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 that formed was filtered off, air dried and recrystallized from absolute ethanol.

*2.1.7.1. 4,5-Dihydro-3-(N-methylsulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-pyrazole (**14a**).* Yield 65%, m.p. 105–7 °C. IR (KBr): ν 3340 (OH), 3210 (NH), 1645 (C=N), 1567 (C=C), 1376 and 1156 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 12.01 (s, 1H, OH), 8.78 (s, 1H, NH), 8.21 (s, 1H, H-2 indole), 7.76–7.21 (m, 8H, Ar—H), 4.51 (dd, 1H, CH—pyrazoline), 3.88 (1H, dd, CH_2—pyrazoline equatorial), 3.44 (dd, 1H, CH—pyrazoline axial), 3.22 (s, 3H, CH_3) ppm. Anal. For $C_{18}H_{17}N_3O_3S$ (355.41) calcd: C 60.83, H 4.82, N 11.82. Found: C 60.67, H 5.00, N 11.65.

*2.1.7.2. 4,5-Dihydro-3-(N-benzenesulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-pyrazole (**14b**).* Yield 75%, m.p. 223–5 °C. IR (KBr): ν 3300 (OH), 3100 (NH), 1619 (C=N), 1566 (C=C), 1375 and 1156 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 11.01 (s, 1H, OH), 8.57 (s, 1H, NH), 8.01 (s, 1H, H-2 indole), 7.81–7.01 (m, 13H, Ar—H), 4.51 (dd, 1H, CH—pyrazoline), 3.98 (1H, dd, CH_2—pyrazoline equatorial), 3.44 (dd, 1H, CH—pyrazoline axial) ppm. Anal. For $C_{23}H_{19}N_3O_3S$ (417.48) calcd: C 66.17, H 4.59, N 10.07. Found: C 66.33, H 4.44, N 9.97.

*2.1.8. Synthesis of N-substituted-3-indolyl-N-acetylpyrazoles **15a** and **15b***

Method A: To a solution of compound **2c** or **3c** (0.01 mol) in a mixture of (10 mL) acetic anhydride and glacial acetic acid (2:1) was added hydrazine hydrate 99% (1 mL, 0.02 mol). The reaction mixture was refluxed for 6–8 h. After cooling, the reaction mixture was poured onto ice-water (50 mL), and the solid that formed was filtered off, air dried and recrystallized from aqueous ethanol.

Method B: A mixture of compound **2c** or **3c** (0.01 mol), acetic acid hydrazide (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 that formed was filtered off, air dried and recrystallized from aqueous ethanol.

*2.1.8.1. 4,5-Dihydro-3-(N-methylsulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-N-acetylpyrazole (**15a**).* Yield 75%, m.p. 178–180 °C. IR (KBr): ν 3218 (OH), 1678 (C=O), 1619 (C=N), 1567 (C=C), 1367 and 1167 (SO_2) cm^{-1}. ^1H NMR spectrum (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 10.05 (s, 1H, OH), 8.23 (s, 1H, H-2 indole), 7.76–7.01 (m, 8H, Ar—H), 4.55 (dd, 1H, CH—pyrazoline), 3.98 (s, 3H, $COCH_3$), 3.78 (1H, dd, CH_2—pyrazoline equatorial), 3.44 (dd, 1H, CH—pyrazoline axial), 3.10 (s, 3H, CH_3) ppm. Anal. For $C_{20}H_{19}N_3O_4S$ (397.45) calcd: C 60.44, H 4.82, N 10.57. Found: C, 60.19, H 5.00, N 10.37.

*2.1.8.2. 4,5-Dihydro-3-(N-benzenesulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-N-acetylpyrazole (**15b**).* Yield 71%, m.p. 201–3 °C. IR (KBr): ν 3320 (OH), 1688 (C=O), 1618 (C=N), 1545 (C=C), 1357 and 1167 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 11.01 (s, 1H, OH), 8.01 (s, 1H, H-2 indole), 7.81–7.01 (m, 13H, Ar—H), 4.51 (dd, 1H, CH-pyrazoline), 3.98 (s, 3H, $COCH_3$), 3.68 (1H, dd, CH_2—pyrazoline equatorial), 3.24 (dd, 1H, CH—pyrazoline axial) ppm. Anal. For $C_{25}H_{21}N_3O_4S$ (459.52) calcd: C 65.34, H 4.61, N 9.14. Found: C 65.18, H 4.54, N 19.28.

*2.1.9. Synthesis of N-substituted-3-indolyl-N-phenylpyrazoles **16a** and **16b***

A mixture of compound **2c** or **3c** (0.01 mol), 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 that formed was filtered off, air dried and recrystallized from absolute ethanol.

*2.1.9.1. 4,5-Dihydro-3-(N-methylsulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-N-phenylpyrazole (**16a**).* Yield 70%, m.p. 161–3 °C. IR (KBr): ν 3218 (OH), 1620 (C=N), 1567 (C=C), 1367 and 1157 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 11.71(s, 1H, OH), 8.21 (s, 1H, H-2 indole), 7.67–7.01 (m, 13H, Ar—H), 4.56 (dd, 1H, CH—pyrazoline), 3.71 (1H, dd, CH_2—pyrazoline equatorial), 3.32 (s, 3H, CH_3), 3.21 (dd, 1H, CH—pyrazoline axial) ppm. MS, *m/z* (%): 431 (M^+, 15), 144 (100). Anal. For $C_{24}H_{21}N_3O_3S$ (431.51) calcd: C 66.80, H 4.91, N 9.74. Found: C 67.00, H 5.01, N 9.54.

*2.1.9.2. 4,5-Dihydro-3-(N-benzenesulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-N-phenylpyrazole (**16b**).* Yield 55%, m.p. 179–181 °C. IR (KBr): ν 3320 (OH), 1635 (C=N), 1545 (C=C), 1357 and 1157 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 12.51(s, 1H, OH), 8.21 (s, 1H, H-2 indole), 7.56–7.00 (m, 18H, Ar—H), 4.55 (dd, 1H, CH—pyrazoline), 3.66 (1H, dd, CH_2—pyrazoline equatorial), 3.32 (dd, 1H, CH—pyrazoline axial) ppm. MS, *m/z* (%): 493 (M^+, 7), 142 (100). Anal. For $C_{29}H_{23}N_3O_3S$ (493.58) calcd: C 70.57, H 4.70, N 8.51. Found: C 70.43, H 4.57, N 8.65.

2.1.10. Synthesis of N-substituted-3-indolyl- N-benzylpyrazoles 17a and 17b

A mixture of compound **2c** or **3c** (0.01 mol), benzylhydrazine hydrochloride (1.95 g, 0.01 mol), anhydrous sodium acetate (0.67 g, 0.02 mol) in dry ethanol (15 mL) was refluxed for 2–3 h. After cooling, the solid that formed was filtered off, air dried and recrystallized from absolute ethanol.

2.1.10.1. 4,5-Dihydro-3-(N-methylsulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-N-benzylpyrazole (17a). Yield 55%, m.p. 87–9 °C. IR (KBr): ν 3100 (OH), 1622 (C=N), 1547 (C=C), 1367 and 1167 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 12.05 (s, 1H, OH), 8.23 (s, 1H, H-2 indole), 7.76–7.01 (m, 13H, Ar—H), 5.56 (s, 2H, N—CH_2), 4.55 (dd, 1H, CH—pyrazoline), 3.78 (dd, 1H, CH_2—pyrazoline equatorial), 3.44 (dd, 1H, CH_2—pyrazoline axial), 3.10 (s, 3H, CH_3) ppm. Anal. For $C_{25}H_{23}N_3O_3S$ (445.53) calcd: C 67.40, H 5.20, N 9.43. Found: C 67.56, H 5.37, N 9.65.

*2.1.10.2. 4,5-Dihydro-3-(N-benzenesulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-N-benzylpyrazole (**17b**).* Yield 64%, m.p. 148–150 °C. IR (KBr): ν 3212 (OH), 1645 (C=N), 1555 (C=C), 1357 and 1151 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 11.01 (s, 1H, OH), 8.01 (s, 1H, H-2 indole), 7.91–7.01 (m, 18H, Ar—H), 5.56 (s, 2H, N—CH_2), 4.51 (dd, 1H, CH—pyrazoline), 3.68 (1H, dd, CH_2—pyrazoline equatorial), 3.24 (dd, 1H, CH—pyrazoline axial) ppm. Anal. For $C_{30}H_{25}N_3O_3S$ (507.60) calcd: C 70.98, H 4.96, N 8.28. Found: C 71.01, H 5.02, N 8.11.

*2.1.11. Synthesis of N-substituted-3-indolylisoxazoles **18a** and **18b***

To a solution of compounds **2c** and **3c** (0.01 mol) in absolute ethanol (10 mL) were added hydroxylamine hydrochloride (0.69 g, 0.01 mol) and anhydrous sodium acetate (0.67 g, 0.01 mol). The reaction mixture was refluxed for 6–8 h. After cooling, the reaction mixture was poured onto ice-water (50 ml) and the solid that formed was filtered off, air dried and recrystallized from absolute ethanol.

*2.1.11.1. 4,5-Dihydro-3-(N-methylsulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-isoxazole (**18a**).* Yield 70%, m.p. 168–170 °C. IR (KBr): ν 3218 (OH), 1626 (C=N), 1557 (C=C), 1367 and 1147 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 12.23 (s, 1H, OH), 8.22 (s, 1H, H-2 indole), 7.78–7.01 (m, 8H, Ar—H), 4.51 (dd, 1H, CH—isoxazole), 3.78 (1H, dd, CH_2—isoxazole equatorial), 3.56 (dd, 1H, CH—isoxazole axial), 3.31 (s, 3H, CH_3)ppm. MS, *m/z* (%): 356 (M^+, 20), 144 (100). Anal. For $C_{18}H_{16}N_2O_4S$ (356.40) calcd: C 60.66, H 4.53, N 7.86. Found: C 60.88, H 4.42, N 7.64.

*2.1.11.2. 4,5-Dihydro-3-(N-benzenesulphonyl-1H-indol-3-yl)-5-(m-hydroxy-phenyl)-isoxazole (**18b**).* Yield 70%, m.p. 145–7 °C. IR (KBr): ν 3200 (OH), 1615 (C=N), 1545 (C=C), 1357 and 1157 (SO_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, 25 °C, TMS): δ = 11.77 (s, 1H, OH), 8.21 (s, 1H, H-2 indole), 7.54–7.07 (m, 13H, Ar—H), 4.54 (dd, 1H, CH—isoxazole), 3.87 (1H, dd, CH_2—isoxazole equatorial), 3.41 (dd, 1H, CH—isoxazole axial)ppm. MS, *m/z* (%): 418 (M^+, 1), 144 (100). Anal. For $C_{23}H_{18}N_2O_4S$ (418.47) calcd: C 66.01, H 4.34, N 6.69. Found: C 66.22, H 4.50, N 6.54.

2.2. Antimicrobial evaluation

The antimicrobial activity of the newly synthesized compounds was determined *in vitro* using the disk diffusion method (Bauer et al., 1966) 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* (isolated from clinical samples and identified to the species level according to different API 20E system (Analytab Products) (bioMerieux, Australia). The antimicrobial activities of the tested compounds were estimated by placing presterilized filter paper disks (6 mm in diameter) impregnated with 20 and 10 $\mu g\ disk^{-1}$ in Nutrient and MacConky agar media for bacteria and on Sabouraud dextrose agar for fungus. Dimethyl formamide (DMF) which showed no inhibition zone was used as a solvent for impregnation. The inhibition zones (IZ) of the tested compounds were measured after 24–48 h incubation at 37 °C for bacteria and after 5 days incubation at 28 °C for fungi. Chloramphenicol (C1863, Sigma–Aldrich) and cephalothin (C3050, Sigma–Aldrich) were used as reference drugs for bacteria. Whereas, cycloheximide (C7698, Sigma–Aldrich) was used as reference drug for fungi.

2.3. Anticancer evaluation

2.3.1. Cell culture

HEPG2 (human Liver carcinoma), MCF7 (Human Breast Cancer) and HCT-116 (Human Colon Cancer) cell lines were obtained from Karolinska Institute, Stockholm, Sweden. All cells were maintained in RPMI 1640 (Lonza Biowahittkar) medium, except for MCF7 cancer cells that were maintained in DMEM medium (Lonza Biowahittkar). All the media were supplemented with 1% antibiotic–antimycotic mixture (10,000 U per mL Potassium Penicillin (Biowest), 10,000 $\mu g\ mL^{-1}$ Streptomycin Sulfate (Biowest), 25 $\mu g\ mL^{-1}$ Amphotericin B (Biowest) and 1% L-glutamine (Biowest).

2.3.2. MTT cytotoxicity assay

The cell viability was investigated using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay (Mosmann, 1983). This reaction depends on the mitochondrial dependant reduction of yellow MTT into purple formazan. All the preceding steps were carried out in sterile laminar air flow cabinet Biosafty class II level (Baker, SG403INT, Sanford, ME, USA). All incubations were done at 37 °C in 5% CO_2 incubator in humidified atmosphere (Sheldon, TC2323, Cornelius, OR, USA). Cells were seeded into 96-well microtiter plastic plates at the concentration of (10^4 cells per well) and allowed to adhere for 24 h. Media were aspirated and fresh medium (without serum) was added to the cells with various concentrations of the tested compounds (10, 5, 2.5 and 1.25 $\mu g\ mL^{-1}$) and incubated for 48 h. For the untreated cells (negative control), media were added instead of the tested compounds. A positive control Adrinamycin (Doxorubicin) [Mw = 579.99] was used as a known cytotoxic natural agent which gives 100% inhibition. Medium was aspirated and 40 μL MTT salt (2.5 $\mu g\ mL^{-1}$) (Biobasic Inc) was added to each well and incubated for further 4 h. To stop the reaction and dissolve any formed formazan crystals, 200 μL of 10% sodium dodicyl sulfate (SDS) was added to each well and incubated overnight at 37 °C. The amount of formazan product was measured at 595 nm and a reference wave length of 620 nm as a background using a microplate reader (Bio-Rad Laboratories Inc., model 3350, Hercules, California, USA). The percentage of change in viability was calculated according to the formula:

$$\left[\frac{\text{Absorbance of tested compounds}}{\text{Absorbance of negative control}}\right] - 1 \times 100$$

A statistical significance was tested between samples and negative control (cells with vehicle) using independent *t*-test by SPSS 11 program. Dimethyl Sulfoxide (DMSO) is the vehicle used for dissolution of tested compound and its final concentration on the cells was less than 0.2%. A probate analysis was carried out for IC_{50} determination using SPSS 11 program

3. Results and discussion

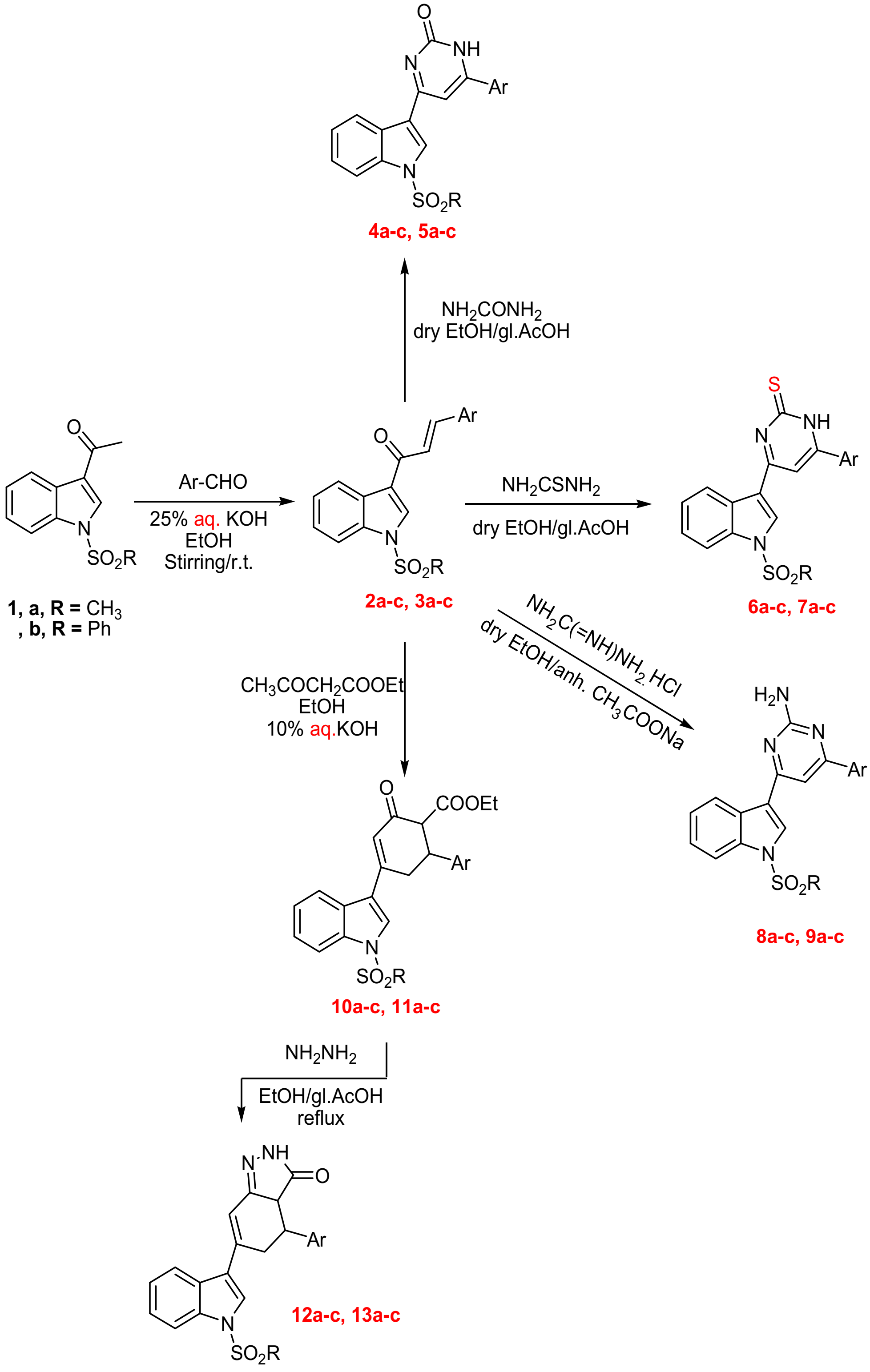
3.1. Chemistry

The reaction routes for the synthesis of the title compounds were described, as shown in Schemes 1 and 2. Claisen–Schmidt reaction of *N*-methylsulphonyl-3-acetylindole (**1a**) and *N*-benzenesulphonyl-3-acetylindole (**1b**) with some aromatic aldehydes namely, *p*-methoxy, *p*-chloro or *m*-hydroxybezaldehydes in ethanol in the presence of aqueous potassium hydroxide (25%) led to the formation of 1-(*N*-methylsulphonyl-1*H*-indol-3-yl)-3-aryl-prop-2-ene-1-ones (**2a–c**) and 1-(*N*-benzenesulphonyl-1*H*-indol-3-yl)-3-aryl-prop-2-ene-1-ones (**3a–c**), respectively (Scheme 1). Compounds **2a**,**b** and **3a**,**b** are previously reported (El-Sawy et al., 2009), and the newly compounds **2c** and **3c** were confirmed by their correct elemental analyses and spectral data (c.f. Experimental section).

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

It was reported that, reaction of chalcone with ethyl acetoacetate in the presence of aqueous potassium hydroxide (10%) gives rise to cyclohexanone (Sreevidya et al., 2010). In the present work and under the above mentioned conditions, chalcones **2a–c** or **3a–c** reacted with ethyl acetoacetate (1:1) and gave the newly compounds namely, ethyl-4-(*N*-substituted-1*H*-indol-3-yl)-6-aryl-2-oxo-cyclohexa-3-enecarboxylates (**10a–c**) and (**11a–c**), respectively (Scheme 1).

Reaction of compound **10a** with hydrazine hydrate under reflux in absolute ethanol in the presence of glacial acetic acid as a catalyst afforded **12a**. Its IR spectrum showed absorption band at 3218, 1665, 1620 for NH, C=O and C=N groups successively. Its ^1H NMR (DMSO-d_6) lacks the signals at δ 4.48 and 1.69 ppm of $COOCH_2CH_3$ and showed 1H, singlet signal (D_2O exchangeable) at δ 9.50 ppm which can be attributed to the proton of NH group besides the signals at δ 8.12 (s, 1H, H-2 indole), 7.67–7.01 (m, 8H, Ar—H), 6.66 (s, 1H, CH=C), 3.98 (s, 3H, OCH_3), 3.88 (s, 3H, CH_3), 2.81 and 3.35 (2d, 2H, CH—CH) 2.33 and 2.35 ppm (dd, 2H, CH—CH_2). Its mass spectrum showed a molecular ion peak at m/z 453 (3%) (c.f. Experimental section). The structure of compound **12a** was actually identified by the IR, ^1H NMR and MS spectra as, 4,5-dihydro-4-(*p*-methoxyphenyl)-6-(*N*-methylsulphonyl-1*H*-indol-3-yl)-2*H*-indazol-3(H)one (Scheme S1). The reaction may be proceded through condensation between C=O of cyclohexanone and NH_2 of hydrazine, followed with cyclization by loosing a molecule of ethanol. Similarly, reaction of **10b**,**c** or **11a–c** with hydrazine hydrate under the above mention condition led to the formation of 4,5-dihydro-4-aryl-6-



Scheme 1 Synthetic route for the preparation of *N*-substituted sulphonyl-3-indolyl chalcone, pyrimidine and cyclohexanone derivatives.

(*N*-substituted sulphonyl-1*H*-indol-3-yl)-2*H*-indazol-3(H)ones (**12b**,**c**) and (**13a–c**), respectively (Scheme 1) (See Scheme S2).

On the other hand, condensation of chalcones **2c** or **3c** with hydrazine hydrate in absolute ethanol in the presence of few drops of glacial acetic acid gave 4,5-dihydro-3-(*N*-substituted-1*H*-indol-3-yl)-5-(*m*-hydroxy-phenyl)pyrazoles (**14a**) and (**14b**), respectively (Scheme 2). whereas, reaction of **2c** or **3c** with hydrazine hydrate under reflux in a mixture of acetic anhydride and glacial acetic acid (2:1) afforded the corresponding *N*-acetylpyrazole derivatives **15a** and **15b** (Scheme 2). Incidentally, compounds **15a** and **15b** were obtained *via* the reaction of **2c** and **3c** with acetic acid hydrazide in refluxing ethanol which showed no depression in a dmixed m.p.s with that previously obtained (Scheme 2).

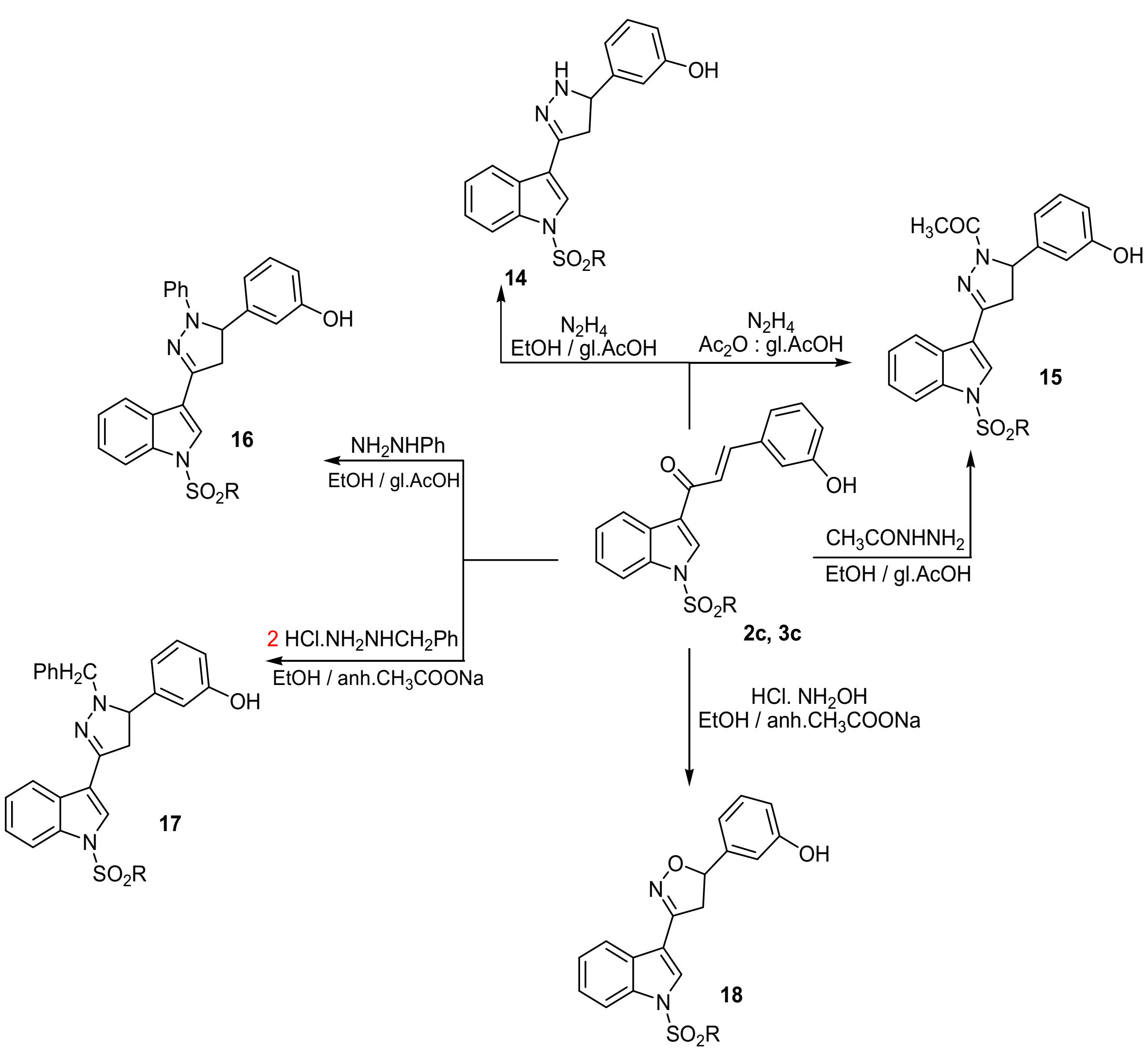
Additionally, reaction of **2c** or **3c** with phenylhydrazine gave *N*-phenylpyrazole derivatives **16a** and **16b**. While, reaction of **2c** or **3c** with benzylhydrazine hydrochloride in the presence of anhydrous sodium acetate gave *N*-benzylpyrazole derivatives **17a** and **17b** (Scheme 2).

Moreover, reaction of **2c** or **3c** with hydroxyl amine 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-(*m*-hydroxyphenyl)isoxazoles (**19a**) and (**19b**) (Scheme 2).

The structures of the newly synthesized compounds were confirmed on the bases of elemental analyses as well as spectral data (IR, ^{1}H NMR, and MS spectra) (c.f. Experimental section).

3.2. Antimicrobial activity

All the newly synthesized compounds were tested for their antimicrobial activities against a variety of pathogenic microorganisms: *S. typhimurium* (ATCC 14028), *P. fluorescens* (S 97) (Gram-positive bacteria), *S. aureus* (ATCC 25923), *B. subtilis* (ATCC 6635) (Gram-negative bacteria) and two strains of fungi *C. albicans* (ATCC 10231) and *A. fumigatus* (isolated from clinical samples and identified to the species level according to different API 20E system (Analytab Products) (bio-Merieux, Australia) using the disk diffusion method at concentrations of 10 and 20 µg disk^{-1} (Table 1). The results showed that, compounds **14a**, **14b**, **15a** and **15b** were found to be the most active of all the tested compounds, with inhibition zones of 30, 35, 31 and 30 mm, respectively, against *S.*



Scheme 2 Synthetic route of the preparation of *N*-substituted sulphonyl-3-indolyl pyrazole and isoxazole derivatives; compounds **14–18**, R, *a* = CH3; *b* = Ph.

Table 1 Antimicrobial activity[a] of the newly synthesized compounds.

Compd. no.	Inhibition zone (mm)											
	Gram-positive bacteria				Gram-negative bacteria				Fungi			
	S. typhimurium (ATCC 14028)		*P. fluorescens* (S 97)		*S. aureus* (ATCC 25923)		*B. subtilis* (ATCC 6635)		*C. albicans* (ATCC 10231)		*A. fumigatus*[b]	
	Concentration μg											
	20	10	20	10	20	10	20	10	20	10	20	10
4a	14	9	14	9	14	9	14	9	–	–	–	–
4b	14	9	14	9	14	9	14	9	–	–	–	–
4c	14	9	14	9	14	9	14	9	–	–	–	–
5a	14	9	14	9	14	9	14	9	–	–	–	–
5b	14	9	14	9	14	9	14	9	–	–	–	–
5c	14	9	14	9	14	9	14	9	–	–	–	–
6a	14	9	14	9	14	9	14	9	–	–	–	–
6b	14	9	14	9	14	9	14	9	–	–	–	–
6c	14	9	14	9	14	9	14	9	–	–	–	–
7a	14	9	14	9	14	9	14	9	–	–	–	–
7b	14	9	14	9	14	9	14	9	–	–	–	–
7c	14	9	14	9	14	9	14	9	–	–	–	–
8a	17	8	17	8	14	9	14	9	–	–	–	–
8b	17	8	17	8	14	9	14	9	–	–	–	–
8c	17	8	17	8	14	9	14	9	–	–	–	–
9a	17	8	17	8	14	9	14	9	–	–	–	–
9b	17	8	17	8	14	9	14	9	–	–	–	–
9c	17	8	17	8	14	9	14	9	–	–	–	–
10a	17	8	17	8	14	9	14	9	–	–	–	–
10b	17	8	17	8	14	9	14	9	–	–	–	–
10c	17	8	17	8	14	9	14	9	–	–	–	–
11a	17	8	17	8	14	9	14	9	–	–	–	–
11b	17	8	17	8	14	9	14	9	–	–	–	–
11c	17	8	17	8	14	9	14	9	–	–	–	–
12a	–	–	–	–	–	–	–	–	–	–	–	–
12b	–	–	–	–	–	–	–	–	–	–	–	–
12c	–	–	–	–	–	–	–	–	–	–	–	–
13a	–	–	–	–	–	–	–	–	–	–	–	–
13b	–	–	–	–	–	–	–	–	–	–	–	–
13c	–	–	–	–	–	–	–	–	–	–	–	–
14a	30	20	28	19	17	9	20	11	–	–	–	–
14b	35	20	26	19	17	9	20	11	–	–	–	–
15a	31	20	27	19	17	9	21	11	–	–	–	–
15b	30	20	26	19	17	9	21	11	–	–	–	–
16a	28	18	28	18	18	10	22	11	–	–	–	–
16b	28	18	28	18	18	10	22	11	–	–	–	–
17a	27	17	26	17	18	10	20	11	–	–	–	–
17b	27	17	26	17	18	10	20	11	–	–	–	–
18a	–	–	–	–	–	–	–	–	–	–	–	–
18b	–	–	–	–	–	–	–	–	–	–	–	–
Stander a	42	28	37	31	–	–	–	–	–	–	–	–
Stander b	–	–	–	–	38	29	38	30	–	–	–	–
Stander c	–	–	–	–	–	–	–	–	39	28	40	31

Stander a: chloramphenicol; reference drug for Gram-positive bacteria; **stander b**: cephalothin; reference drug for Gram-negative bacteria; **stander c**: cycloheximide; reference drug for fungi.

[a] Disk diffusion method.

[b] Isolated from clinical samples and identified to the species level according to different API 20E system (Analytab Products) (bioMerieux, Australia).

typhimurium (ATCC 14028) compared to the reference drug chloramphenicol (42 mm) at 20 μg disk^{-1}, and showed inhibition zones of 20 mm against *S. typhimurium* (ATCC 14028) compared to the reference drug chloramphenicol (28 mm) at 10 μg disk^{-1}. The rest of the tested compounds were non-active against all microorganisms (Table 1).

Table 2 Anticancer screening of the eighteen new synthesized compounds against human liver (HEPG2), human breast (MCF7) and human colon carcinoma (HCT-116) cell lines at a concentration of 10 μg ml^{-1}.

Compd. no.	HEPG-2	MCF7	HCT-116
	Inhibition growth %		
4a	63.5	47.3	43.0
4b	63.5	26.7	37.6
4c	99.6	100.7	100.0
5a	36.1	35.0	16.4
5b	3.1	50.9	11.5
5c	94.3	84.6	97.4
6a	24.8	14.3	26.0
6b	16.23	23.2	19.5
6c	94.2	99.0	100.3
7a	65.1	23.2	23.8
7b	19.5	13.7	4.8
7c	70.3	73.9	85.4
8a	46.0	64.2	28.1
8b	51.6	32.8	27.8
8c	95.1	100.3	99.3
9a	37.0	35.0	43.5
9b	22.6	18.9	14.9
9c	96.3	85.0	90.1

Table 3 IC_{50} of the highly cytotoxic active compounds against human liver carcinoma (HEPG2), human breast cancer (MCF7) and human colon cancer (HCT-116) cell lines.

Compd. no.	IC_{50} (μg/ml)		
	HEPG2	MCF7	HCT-116
4c	1.6	2.1	3.7
5c	2.9	–	5.1
6c	3.1	2.6	4.7
8c	2.4	1.8	3.5
9c	1.7	–	2.8
Doxorubicin	24.47	38.2	37.6

IC_{50}: compound concentration required to inhibit the cell viability by 50%.

3.3. Anticancer activity

Eighteen new compounds namely, pyrimidin-2(1*H*)-ones **4a**–**c** and **5a–c**, pyrimidin-2(1*H*)-thiones **6a–c** and **7a–c** and pyrimidin-2-amines **8a**–c and **9a–c** were primary screened for their *in vitro* cytotoxicity against (HEPG2), (MCF7) and (HCT-116) cell lines at a concentration of 10 μg mL^{-1} (Table 2). Compounds **4c**, **6c** and **8c** were found to be the highly active compounds with cytotoxicity of 99.6, 94.2 and 95.1%, respectively, against HEPG2, and showed activity of 100.7, 99.0 and 100.3%, respectively, against MCF7 and also, showed activity of 100.0, 100.3 and 99.3%, respectively, against HCT-116. While, compounds **5c** and **9c** showed activity of 94.3 and 96.3%, respectively, against HEPG2 and showed activity of 97.4 and 90.1%, respectively, against HCT-116 (Table 2).

The compounds that gave cytotoxicity more than 90% at 10 μg mL^{-1} were used to calculate their IC_{50} value, which corresponds to the concentration required for 50% inhibition of all cell viability. Doxorubicin is one of the most effective anticancer agents used as reference drug (Table 3). In case of HEPG2 cancer cell line, compounds **4c**, **5c**, **6c**, **8c** and **9c** showed more potent activity with IC_{50} = 1.6, 2.9, 3.1, 2.4 and 1.7 μg mL^{-1}, respectively, than the reference drug doxorubicin (IC_{50} = 24.47 μg mL^{-1}). In case of MCF7 cancer cell line, compounds **4c**, **6c** and **8c** showed more potent activity with IC_{50} = 201, 2.6 and 1.8 μg mL^{-1}, respectively, than the reference drug doxorubicin(IC_{50} = 38.2 μg mL^{-1}) (Table 3). In case of HCT-116 cancer cell line, compounds **4c**, **5c**, **6c**, **8c** and **9c** showed more potent activity with IC_{50} = 3.7, 5.1, 4.7, 3.5 and 2.8 μg mL^{-1}, respectively, than the reference drug doxorubicin (IC_{50} = 37.6 μg mL^{-1}) (Table 3).

Interpretation of the obtained results and considering the structure activity relationship (SAR) of the tested compounds showed that, compounds **4c**, **5c**, **6c**, **8c** and **9c** that contain hydroxyl group at *p*-position of phenyl moiety at pyrimidine ring are associated with remarkable cytotoxicity against all cancer cell lines under investigation HEPG2, MCF7 and HCT-116.

4. Conclusion

A new series of pyrimidin-2(1*H*)ones **4a–c** and **5a–c**, pyrimidin-2(1*H*)-thiones **6a–c** and **7a–c**, pyrimidin-2-amines **8a–c** and **9a–c**, cyclohexanones **10a–c and 11a**–**c**, indazoles **12a–c** and **13a–c**, pyrazoles **14a,b–17a**,**b** and isoxazoles **18a,b** derivatives incorporated to *N*-substituted sulphonyl indoles at their 3-positions were prepared. The newly synthesized compounds were tested for their *in vitro* antimicrobial and anti-cancer activities, and interpretation of the obtained results with considering the structure activity relationship (SAR) of the tested compounds showed that:

1. Compounds **14a**, **14b**, **15a** and **15b** which contain pyrazole ring at 3-position of *N*-substituted sulphonyl indole were found to be the most active of all the tested compounds toward *S. typhimurium* (ATCC 14028) compared to the reference drug chloramphenicol.
2. Compounds **4c**, **5c**, **6c**, **8c** and **9c** that contain hydroxyl group at *p*-position of phenyl moiety at pyrimidine ring are associated with remarkable cytotoxicity against all cancer cell lines under investigation HEPG2, MCF7 and HCT-116.

Acknowledgments

The authors thank Ibrahim Hassan Mohamed Tolba, Department of Agriculture Botany, Faculty of Agriculture, Al-Azher University, Cairo, Egypt, for carrying out the antimicrobial activity screening. Also, the authors are grateful to Micro analytical Unit, National Research Centre, Cairo, Egypt for carrying out elemental analyses and IR H NMR and Mass spectra.

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