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Synthesis, Antitumor, Antimicrobial and Anti-Hepatities B Activities of New 3-(4-chlorophenyl)-N-(p-tolyl)acrylamide Chalcone Derivatives

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Abstract

New substituted pyrimidine, pyrazole, pyridine and pyrrole derivatives were synthesized from an unsaturated arylacetylmine key derivative via cyclization reaction with the suitable corresponding reagent and their structures were characterized by elemental and spectral analyses. The synthesised compounds' anticancer, antibacterial, and anti-Hepatitis B efficacy was investigated against a variety of cells and microorganisms. Most of the studied substances had moderate to high activity, according to the data.

Keywords: Pyrimidine, pyridine, pyrazole, antimicrobial, antitumor, antiviral, Anti-Hepatities B

1. Introduction

Chalcones are well known intermediates for the synthesis of numerous heterocycles and are natural biocides [1]. Chalcones, also known as 1,3-diaryl-2-propen-1-ones, are a subclass of flavonoids. They are made up chemically of two aromatic rings connected by a three-carbon α,β-unsaturated carbonyl system in open-chain flavonoids. Chalcones can undergo a number of reactions to synthesize compounds with practical uses. They are the building blocks of the numerous flavonoids and isoflavonoids found in plants [2,3]. One significant scaffold with distinctive biological and therapeutic properties is chalcone. Numerous chalcone-based substances have demonstrated anticancer properties through a wide range of mechanisms of action, such as cell cycle disruption, induction of apoptosis, suppression of angiogenesis, reduction of tubulin polymerization, and antiestrogenic activity [4,5]. By changing the aryl moieties or the enone linker, different structural alterations were made to the chalcones' main structure.

It's interesting to note that these alterations have led to the development of numerous potent anticancer drugs [6,7]. Additionally, a number of heterocyclic chalcones were developed by bioisosterically substituting the aryl groups of chalcones with other heterocyclic rings, such as thiazole, thiophene, indole, chromene, benzothiophene, and imidazole, which had potent and targeted anticancer effects [8–

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11]. Additionally, several chalcone analogues with different heterocyclic rings in place of the enone moiety have been synthesized to provide stiff analogues [12]. Examples of these heterocyclic rings include pyrimidines and fused pyrimidine nuclei, which are known to exhibit extraordinary biological properties such anti-proliferative activity [13–15]. n besides having an inhibitory effect on the proliferation of human leukaemia cells, oxygenated chalcones have potential antimalarial [17], antiplasmodial [18], antiprotozoal, anti-HIV, and antibacterial properties. Chalcones are a group of anticancer substances that have shown promise in the treatment of human tumours. Licochalcone-A, a chalcone derivative derived from Chinese licorice root, has been linked to a number of anticancer properties [20].

Chalcones have also discovered potential uses as medications, agrochemicals, and artificial sweeteners [21]. This class of substances is significant not only for their biological effects but also for the colours they give flowers, which range from yellow to orange. As a result, they attract insects in a way that aids in the pollination of the flower [22]. Additionally, they are a component of various biological macromolecules and the micelle's microenvironment [23]. Chalcone group-containing polymers develop increased photosensitivity and photoconductivity. These polymers serve as materials for negative photo resist [24]. Benkaddour and colleagues [25] recently explored the inhibitory effects of chalcone derivatives on the corrosion of steel in solutions of sulfuric and hydrochloric acids. Additionally, chalcones were extensively exploited for a variety of optical applications, including fluorescent probes for metal ion sensing [26], liquid crystal displays [27], photorefractive polymers, and 45 holographic recording materials. As a result, many researchers have investigated the photophysical characteristics of chalcones that include alkylamino groups as electron donors [28,29].

Chalcone can be used as a starting point for developing various heterocyclic systems. Different uses can be made of these derivatives. As an analgesic, anticancer, antifungal, and antibacterial agent, pyrimidine is one example.

Different configurations with the pyrazole nucleus enable a variety of uses in fields like technology, medicine, and agriculture. They are referred to as antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidant, and antiviral drugs [30,31]. They are also described as protein glycation inhibitors.

Because of their interesting pharmacological characteristics, pyrazole compounds have recently received increased attention as biomolecules. This heterocycle can be found in a number of well-known medications from different sections with a range of therapeutic activity [32–39].

From the above facts and our interest for developing new compounds with potent anticancer activity [40-52], prompted us for the synthesis of new derivatives of 3-(4-chlorophenyl)-*N*-(*p*-tolyl)acrylamide chalcone Derivatives and Evaluation of their Antitumor, Hepatities B and Antimicrobial Activities.

Experimental

Chemistry

Melting points were determined with a Kofler block apparatus and are uncorrected. The IR spectra were recorded on a perkin-Elmer 1720 FTIR spectrometer (cm^{-1}), using KBr disks. ^{1}H-NMR spectra were measured on a varian Gemini spectrometer (300 MHz) using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using Mass spectra were obtained using a CC 2010

Shimadzu Gas chromatography instrument mass spectrometer (70 eV). The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F245. The anticancer activity of the synthesized compounds was carried out at the National Cancer Institute (NCI), Cairo, Egypt. Antiviral activity against HBV was tested at the Liver Institute, Menoufia University, Shebin El-Koam Egypt.

4-(4-chlorophenyl)-6-(*p*-tolylamino)pyrimidin-2-ol (2)

A mixture of compound 1 (0.54 g, 1.9 mmol), urea (0.11g, 1.9 mmol) in ethanol (20 mL) was refluxed for 18h in the presence of sodium ethoxide (0.4 mL). The reaction mixture was cooled and poured into ice water (50mL). The precipitate was collected by filtration and purified by recrystallization from ethanol to give compound 2 as a brown powder in 76% yield, m p (148-152) °C. The IR spectrum of the pyrimidine derivative (2) showed the absorption bands at ν: 3425 (OH), 3294 (NH), 2931 (CH), 1658 (C=N), 1458 (C=S) cm^{-1}; ^1H NMR ppm δ = 2.19 (s, 3H, CH_3), 7.45 (s, 1H, pyrimidine-H), 7.54 (d, 2H, Ar-H), 7.73 (d, 2H, Ar-H), 7.92 (d, 2H, Ar-H), 8.09 (d, 2H, Ar-H), 9.89, 9.90 (br s, 2H, $2NH_{exhangeable}$); Analysis Calcd. For $C_{17}H_{14}ClN_3O$ (M. Wt: 311.77) C, 65.49; H, 4.53; N, 13.48; Found: C, 65.54; H, 4.50; N, 13.50.

4-(4-chlorophenyl)-6-(*p*-tolylamino)pyrimidine-2(5*H*)-thione (3)

A mixture of compound 1 (0.54 g, 1.9 mmol), thiourea (0.14 g, 1.9 mmol) in ethanol (20 mL) was refluxed for 22h in the presence of Potassium hydroxide (0.4 mL). The reaction mixture was cooled to room temperature and refrigerated overnight. The solid product obtained was filtered and recrystallized from ethanol to give compound 3 as dark gray powder in 76% yield, mp (above 300) °C. IR (KBr ν): 3448 (NH), 2924 (CH), 1635 (C=N) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 2.20 (s, 3H, CH_3), 3.1 (s, 2H, CH_2), 6,68 (d, 2H, Ar-H), 7.12 (s,2H, Ar-H), 7.60 (m, 2H, Ar-H), 7.75 (m, 2H, Ar-H), 9.94 (s, 1H, NH exchangeable) ppm; Analysis Calcd. For $C_{17}H_{14}ClN_3S$ (M. Wt: 327.3) C, 62.28; H, 4.30; N, 12.82; Found: C, 62.50; H, 4.40; N, 12.88.

5-(4-chlorophenyl)-1-phenyl-*N*-(*p*-tolyl)-1*H*-pyrazol-3-amine (4)

A mixture of 1 (0.54 g, 1.9mmol), phenyl hydrazine (0.2 ml, 1.9mmol) in glacial acetic acid (20 ml) was refluxed for 8h. The reaction mixture was cooled and poured into ice water (50 mL). The precipitate was collected by filtration and purified by recrystallization from ethanol to give compound 4 as dark black powder in 80% yield, m p179-182°C. IR (KBr, ν, cm^{-1}): ν: 3410(NH), 2924(CH), 1543(C=N) Cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ = 2.50 (s, 3H, CH_3), 2.19 (s, 2H, CH_2), 6,68 (d, 2H,Ar-H), 7.12 (s,1H, CH), 7.60 (m, 2H, Ar-H), 7.75 (m, 2H, Ar-H), 7.92-8.09 (m, 5H, Ar-H), 9.94 (s, 1H, NH exchangeable) ppm. Analysis Calcd. For $C_{22}H_{18}ClN_3$ (M. Wt: 359.86) C, 73.43; H, 5.04; N, 11.68; Found: C, 73.50; H, 4.46; N, 11.55.

5-(4-chlorophenyl)-*N*-(*p*-tolyl)-1*H*-pyrazol-3-amine (5)

A solution of the corresponding chalcone 1 (0.54 g, 1.9 mmol) in ethanol (10 mL) was refluxed with hydrazine hydrate (0.2 ml, 5.7 mmol) for 5h. The reaction mixture was cooled and the precipitate was filtered then washed with ethanol and di ethyl ether to give 5 as a gray crystalline solid in 79% yield, m p166-170°C. IR (KBr, ν, cm^{-1}): 3448 (NH), 3278(NH), 2924 (CH), 1550 (C=N). ^1H NMR (300 MHz, DMSO-d_6) ppm, δ 1.61 (s, 3H, CH_3), 7.53 (m, 2H, Ar-H), 7.73 (m, 2H, Ar-H), 7.74 (t, 1H,CH), 7,92 (m, 2H, Ar-H), 8.08 (m, 2H, Ar-H), 9.93 (s, 1H, NH exchangeable), 12.50 (s, 1H, NH exchangeable).^{13}C

NMR (75 MHz, DMSO-d_6) δ 23.48, 121.51, 122.72, 125.02, 125.54, 125.71, 125.94, 127.64, 128.08, 133.68, 168.93; Analysis Calcd. For $C_{16}H_{14}ClN_3$ (M. Wt: 283.76) C, 67.73; H, 4.97; N, 14.81; Found: C, 67.50; H, 4.87; N, 14.89.

1-(5-(4-chlorophenyl)-3-(*p*-tolylamino)-1*H*-pyrazol-1-yl)ethan-1-one (6)

A solution of the corresponding chalcone 1 (0.54 g, 1.9 mmol) in glacial acetic acid (10 mL) was refluxed with hydrazine hydrate (0.2 ml, 5.7 mmol) for 5h. Then catalytic amount of HCl (4-5 drops) was added and was refluxed for 30 min. After cooling, 30 mL water was added and the resulting precipitate was filtered, washed with water to give compound 6 as a light brown crystalline solid in74% yield, m p 198-204°C. IR (KBr, cm^{-1}) at ν: 3448 (NH), 2931 (CH), 1681 (C=O), 1597 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.1, 2.50 (2s, 6H, $2CH_3$), 6,68 (d, 2H, Ar-H), 6.68 (d, 2H,Ar-H), 7.12 (s,1H, CH), 7.60 (m, 2H, Ar-H), 7.75 (m, 2H, Ar-H), 9.70 (s, 1H, NH exchangeable) ppm. EI-MS (m/z) = 327 (M^+). Analysis Calcd. For $C_{18}H_{16}ClN_3O$ (M. Wt: 325.80) C, 66.36; H, 4.95; N, 12.90; Found: C, 66.50; H, 4.82; N, 13.00.

2-amino-4-(4-chlorophenyl)-6-(*p*-tolylamino)nicotinonitrile (7)

A mixture of the chalcone 1 (0.54 g, 1.9 mmol), malononitrile (0.13g, 1.9mmol), ammonium acetate (0.30 g, 2 mmol) in ethanol (20 mL) was refluxed for 10h. The reaction mixture was cooled and poured into ice cold water (50 mL). The precipitate was collected by filtration and recrystallized in ethanol to get off compound 7 as a gray powder in80% yield, mp150-152°C. IR (KBr, ν, cm^{-1}): of the resulting compound (7) showed the bands atν: 3448, 3271 (NH_2, NH), 2924 (CH), 2198 (CN), 1590 (C=N); 1H NMR (300 MHz, DMSO-d_6) δ: 2.18 (s, 3H, CH_3), 6.70 (s, 1H, CH pyridine), 6.9 (s, 2H, NH_2 exchangeable), 7.53 (d,2H, Ar-H), 7.72 (d, 2H, Ar-H), 7.91 (d 2H, Ar-H), 8.08 (d, 2H, Ar-H), 9.88 (s, 1H, NH exchangeable) ppm. EI-MS (m/z):334(M^+). ^{13}C NMR (75 MHz, DMSO-d_6) ppm: δ 23.47, 121.50, 122.72, 125.01, 125.53, 125.71, 125.93, 127.65, 128.07, 133.68, 168.92. Analysis Calcd. For $C_{19}H_{15}ClN_4$ (M. W. 334.81); C, 68.16; H, 4.52; N, 16.73; Found: C, 68.20; H, 4.64; N, 16.82.

4-(4-chlorophenyl)-2-oxo-6-(*p*-tolylamino)-1,2-dihydropyridine-3-carbonitrile (8)

A mixture of the chalcone 1 (0.54 g, 1.9 mmol), ethyl cyanoacetate (0.22 mL, 1.9 mmol), ammonium acetate (0.30 g, 1.9mmol) in ethanol (20 mL) was refluxed for 8h. The reaction mixture was cooled and poured into ice-cold water (50 mL). The precipitate was collected by filtration and recrystallized from ethanol to get off compound 8 as a gray powder in 70% yield, mp164-166 °C. IR spectrum (KBr, ν, cm^{-1}): 3448 (NH), 2924 (CH), 2075 (CN),1651 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6) ppm: δ 2.18 (s, 3H, CH3), 5.24 (s, 1H, CH pyridone), 7.53 (d, 2H, Ar-H), 7.73 (d, 2H, Ar-H), 7,92 (d, 2H, Ar-H), 8.08 (d, 2H, Ar-H), 9.88 (s, 1H, NH exchangeable), 11.19 (s, 1H, NH exchangeable), ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.45, 121.48, 122.72, 125, 125.52, 125.69, 125.93, 127.61, 128.07, 133.68, 168.90. Analysis Calcd. For $C_{21}H_{14}ClN_3O$ (M. W. 335.08); C, 67.96; H, 4.20; N, 12.51; Found: C, 67.85; H, 4.50; N, 12.60.

6-(4-chlorophenyl)-N^2, N^4-di-p-tolylpyridine-2,4-diamine (9)

A mixture of the chalcone 1 (0.54 g, 1.9 mmol), ammonium acetate (0.30 g, 1.9 mmol) in glacial acetic acid (10 mL) was refluxed for 6h. The reaction mixture was cooled and poured into-ice cold water (50 ml). The precipitate was collected by filtration and recrystallized from ethanol to get off compound9 as a dark gray powder in 72% yield, m. p. 150-152°C. IR (KBr, ν, cm^{-1}): 3271 (NH), 2924 (CH),1715

(C=O) 1590 (C=N). ^{1}H NMR (300 MHz, DMSO-d6) ppm: δ 2.1, 2.30 (2s, 6H, $2CH_3$), 5.44, 6.90 (2s, 2H, CH pyridine), 7.11 (s, 1H, NH exchangeable), 7.23-7.24 (m, 6H, Ar-H), 7.53 (d,2H, Ar-H), 7.73 (d, 2H, Ar-H), 8.30 (d, 2H, Ar-H), 8.36 (d, 1H, NH exchangeable), EI-MS (m/z): 398 (M+); Analysis Calcd. For $C_{25}H_{22}ClN_3$ (M. W. 399.92); C, 75.08; H, 5.55; N, 10.51; Found: C, 75.12; H, 5.57; N, 10.65.

Ethyl 4'-chloro-3-oxo-5-(p-tolylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (10)

A mixture of the chalcone 1 (0.54 g, 1.9 mmol), ethyl acetoacetate (0.2 mL, 1.9 mmol) in ethanol (20 ml), 0.2 ml (10% NaOH) was added and refluxed for 4h. The reaction mixture was cooled to room temperature and the solid product obtained was filtered and recrystallized from ethanol to get of 10 as a light brown powder in 75% yield, m p 150-152°C. IR spectrum (KBr, ν, cm^{-1}): 3271 (NH), 2924 (CH), 1643 (C=O).1H NMR (300 MHz, DMSO-d6) δ 1.1 (t,3H, CH_3), 2.21 (s,3H,CH_3), 2.30, 2.35 (dd,2H,CH_2), 3.37 (q,1H,CH), 3.67 (d, 1H, CH), 4.1(q, 2H, CH_2) 5.50 (s, 1H, CH), 7.52 (d,2H, Ar-H), 7.72 (d, 2H,Ar-H), 7.92 (d, 2H, Ar-H), 8.13 (d, 2H, Ar-H), 10.10 (s, 1H, NH).^{13}C NMR (75 MHz, DMSO-d6) δ 23.47, 121.51, 122.86, 124.86, 125.51, 125.66, 125.9, 127.34, 127.70, 127.84, 128.03, 128.17, 131, 133.67 133.81, 134.23, 137.54, 169.03.EI-MS (m/z): 383 (M^+). Analysis Calcd. For $C_{22}H_{22}ClNO_3$ (M. W. 383.87) C, 68.84; H, 5.78; N, 3.65; Found: C, 68.87; H, 5.80; N, 3.67.

4'-Chloro-2-(1-hydroxyethylidene)-5-(*p*-tolylamino)-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (11)

A mixture of the chalcone 1 (0.54 g, 1.9 mmol), acetyl acetone (0.2 mL, 1.9 mmol) in ethanol (25 mL) was refluxed for 6h in the presence of 10% NaOH solution (0.2 mL). The reaction mixture was cooled to room temperature and the solid product that obtained was filtered and recrystallized from ethanol to get compound 11 as black crystals in 85% yield, mp (150-152) °C. IR spectrum (KBr, ν, cm^{-1}): 3479 (OH), 3333 (NH), 2924 (CH), 1635 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: δ 2.29, 2.30 (2s,6H,$2CH_3$), 2.17, 2.40 (2d, 2H, CH_2), 3.49, 5.84 (2s, 2H, 2CH), 7.05 (d,2H, Ar-H), 7.30 (d, 2H, Ar-H), 7.52 (d,2H, Ar-H), 7.72 (d, 2H,Ar-H), 12.90 (s, 1H, NH exchangeable), 16.72 (s, 1H, OH); EI-MS (m/z): 353 (M^+). Analysis Calcd. For $C_{21}H_{20}ClNO_2$ (M. W. 353.85); C, 71.28; H, 5.70; Cl, 10.02; N, 3.96; Found: C, 71.30; H, 5.75; Cl, 10.02; N, 3.90.

2-(4-chlorophenyl)-*N*-(*p*-tolyl)-2,3-dihydro-1H-benzo[*b*][1,4]diazepin-4-amine (12)

In the absence of sunlight, a solution of the chalcone 1 (0.54 g, 1.9 mmol), 1.2 – diaminobenzene (0.2g, 1.9 mmol) in absolute ethanol (15ml) was refluxed in the presence of tri ethyl amine (0.6ml) for 15h. The reaction mixture was cooled to °C and left overnight. The precipitate formed was filtered off and recrystallized from ethanol affording 12 as dark black crystals in 73% yield, mp 160-165°C. IR spectrum (KBr, ν, cm^{-1}): 3371 (NH), 3325 (NH), 2939 (CH). 1H NMR (300 MHz, DMSO-d_6) ppm: δ 2.30 (s,3H,CH_3), 2.60, 2.90 (2t, 2H, CH_2), 3.65 (q, 1H, CH, J = 5.2 ppm), 5.8 (s, 1H, NH exchangeable), 6.6 (d, 2H, Ar-H), 6.9-7.1 (m, 4H, Ar-H), 7.30 (d, 2H, Ar-H), 7.52 (d,2H, Ar-H), 7.72 (d, 2H,Ar-H), 9.90 (s, 1H, NH exchangeable), EI-MS (m/z): 346 (M^+). Analysis Calcd. for $C_{22}H_{20}ClN_3$ (M. W.: 361.87): C, 73.02; H, 5.57; N, 11.61; Found: 72.90; H, 5.55; N, 11.58.

3'-(4-chlorophenyl)-3-oxo-*N*-(*p*-tolyl)spiro[indoline-2,2'-pyrrolidine]-4'-carboxamide (13)

A mixture of the chalcone 1 (0.54 g, 1.9 mmol), glycine (0.2 g, 2.4 mmol), isatine (0.3 g, 1.9 mmol) was refluxed in ethanol (25 mL) for 24h. The reaction mixture was cooled then acidified with dilute HCl,

The solid obtained was filtered off dried and then recrystallized from ethanol to get 13 as a black powder in 85% yield, mp 150-152°C. IR (KBr, ν, cm^{-1}): 3333 (NH), 3294 (NH), 2938 (CH), 1730 (C=O), 1635 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: δ 2.0 (s, 1H, NH exchangeable), 2.30 (s,3H,CH3), 2.90, 3.23 (m, 3H, CH_2, CH), 3.07, 3.65 (d, 1H, CH), 6.9-7.7 (m, 5H, Ar-H, NH exchangeable), 7.05 (d,2H, Ar-H), 7.30 (d, 2H, Ar-H), 7.52 (d,2H, Ar-H), 7.72 (d, 2H,Ar-H), 9.90 (s, 1H, NH exchangeable), EI-MS (m/z): 431 (M+). Analysis Calcd. for $C_{25}H_{22}ClN_3O_2$ (M. W.: 431.92): C, 69.52; H, 5.13; Cl, 8.21; N, 9.73; Found: 70.0; H, 5.23; N, 9.83.

3-(4-chlorophenyl)-3-(2-oxocyclohexyl)-*N*-(*p*-tolyl)propanamide (14)

A mixture of the chalcone1 (0.54 g, 1.9 mmol), cyclohexanone (0.2 ml, 1.9 mmol) was refluxed in ethanol (25 ml) for 24h. The reaction mixture was cooled then acidified with dilute HCl and the solid obtained was filtered off, dried and recrystallized from ethanol to give 14 as black crystals in 70% yield, m p 150-152°C. IR spectrum (KBr, ν, cm^{-1}): 3348 (NH), 2939 (CH), 1635 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: δ 1.3-2.2 (m, 8H, 4CH2), 2.30 (s,3H,CH3), 2.41, 2.45 (dd, 2H, CH2), 2.5 (t, 1H, CH), 3.2 (q, 1H, CH), 7.05 (d,2H, Ar-H), 7.30 (d, 2H, Ar-H), 7.52 (d,2H, Ar-H), 9.90 (s, 1H, NH exchangeable), EI-MS (m/z): 369 (M^+); Analysis Calcd. for $C_{22}H_{24}ClNO_2$ (M. W.: 369.89): C, 71.44; H, 6.54; N, 3.79; Found: 71.50; H, 6.53; N, 3.66.

6-{[1-(4-chlorophenyl)-3-oxo-3-(*p*-tolylamino)propyl]thio}acetic acid (15)

A mixture of chalcone 1 (0.54 g, 1.9mmol), thioglycolic acid (0.2 ml, 1.9 mmol) was refluxed in pyridine (25 ml) for 15h. The reaction mixture was cooled then acidified with dilute HCl and the solid obtained was filtered off, dried then recrystallized from ethanol to give 15 as black powder in 85%yield, m p 167-172°C. IR (KBr) ν, cm^{-1}: 3341 (OH), 3226 cm^{-1} (NH), cm-1 3043 (CH Ar) cm-1 1626 cm-1(C=O amide).); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: δ 2.30 (s,3H,CH_3), 2.80, 3.0 (d, 2H, CH_2,), 3.40 (s, 2H, CH_2), 4.12 (t, 1H, CH), 7.05 (d,2H, Ar-H), 7.30 (d, 2H, Ar-H), 7.52 (d, 2H, Ar-H), 7.72 (d, 2H,Ar-H), 9.90 (s, 1H, NH exchangeable), 12.0 (s, 1H, OH); EI-MS (m/z): 362 (M^+). Analysis Calcd. for $C_{18}H_{18}ClNO_3S$ (M. Wt: 363.86) C, 59.42; H, 4.99; N, 3.85; Found: C, 59.56; H, 4.69; N, 3.76.

Results and Discussion

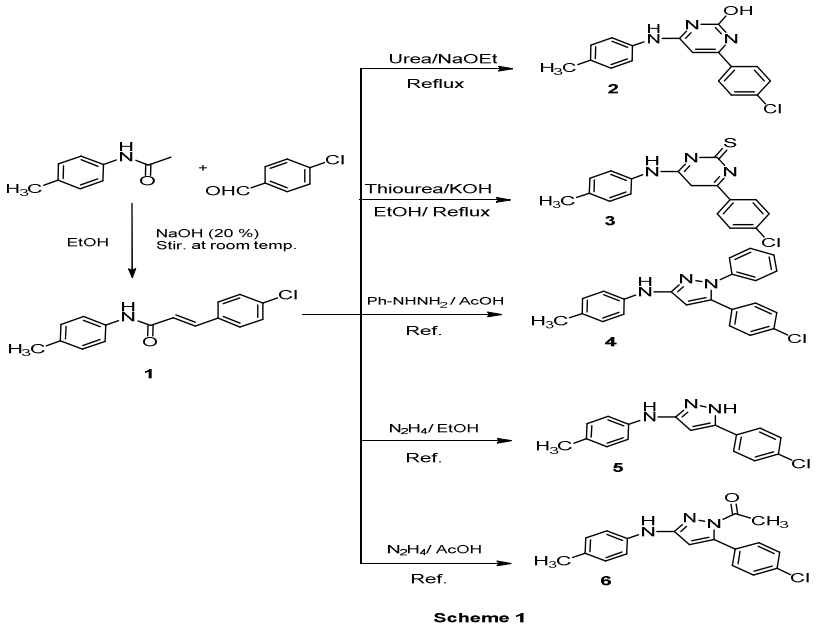
In the present study, the substituted 3-(4-chlorophenyl)-*N*-(*p*-tolyl)- acrylamide (1) was first prepared via Claisen-Schmidt condensation reaction of *N*-(p-tolyl)acetamide with *P*-chlorobenzaldehyde in ethanol in a basic solution (10 mL, 20%) [*c.f.*(Scheme 1)]. The IR spectrum of compound 1 revealed strong absorption bands for NH, CH and C=O groups at ν 3271, 2933 and 1651 Cm^{-1}. The mass spectrum of compound 1 showed EI-MS (m/z): 271 (M^+). The ^{1}H NMR spectrum of the same compound revealed the signals at δ 2.19 for the methyl in addition to the aryl protons signals and the NH at 9.94 ppm.

The reaction of 1 with urea in ethanol at reflux temperature in the presence of sodium ethoxide afforded 4-(4-chlorophenyl)-6-(*p*-tolylamino)pyrimidin-2-ol (2) in 76 % yield. Its IR spectrum of the pyrimidine derivative (2) showed the absorption bands at 3425 for the OH, 3294 for the NH. Its ^{1}H NMR indicated the presence of the signals at δ 2.19 ppm for the CH_3 in addition to 7.45 – 8.09 ppm for the aryl and pyrimidine signals and at 9.89 ppm for the NH groups.

On the other hand, 4-(4-chlorophenyl)-6-(*p*-tolylamino)pyrimidine-2(5*H*)-thione (3) was formed

in 76 % yield by the reaction of 3-(4-chlorophenyl)-*N*-(p-tolyl)acrylamide (1) with thiourea in ethanolic KOH solution at reflux temperature (Scheme 1). The IR spectrum of the substituted thiopyrimidine 3 showed the absorption bands at ν: 3448 (NH), 2924 (CH), 1635 (C=N) cm^{-1}. while, ^1H NMR indicated the presence of the signals at δ 3.1 ppm for the CH_2 and at 9.9 ppm for the NH groups which in agreement with the assigned structure. Reaction of 3-(4-chlorophenyl)-N-(*p*-tolyl)acrylamide (1) with phenyl hydrazine in glacial acetic acid gave 5-(4-chlorophenyl)-1-phenyl-*N*-(*p*-tolyl)-1*H*-pyrazol-3-amine (4) in 80% yield (Scheme 3). The structure of imidazolidine product was proved by IR and NMR spectra which are in accordance with the assigned structure. The 1*H*-pyrazol-3-amine (5) derivative was formed in 79% yield by reacting a solution of the corresponding *N*-(p-tolyl)acrylamide derivative 1 with hydrazine hydrate in ethanol. The IR spectrum of 5 showed the signals at ν: 3448 and 3278 cm^{-1} for the NH bands and the ^1H NMR showed the assigned signals for the CH_3 and CH protons as well as the aryl signals and NH (D_2O exchangeable) groups, respectively. [*c.f.* Scheme 2 & Experimental part].

On the other hand, 1-(5-(4-chlorophenyl)-3-(*p*-tolylamino)-1*H*-pyrazol-1-yl)ethan-1-one (6) was prepared in 74% by refluxing the *N*-(p-tolyl)acrylamide derivative 1 with hydrazine hydrate in presence of glacial acetic acid for 5h (Scheme 1). The IR spectrum of the substituted imidazolidine derivative 6 showed the absorption bands at ν: 3448 (NH), 2931 (CH), 1681 (C=O), 1597 (C=N) cm^{-1}. Its ^1H NMR indicated the presence of the signals at δ 2.50 ppm for the acetyl CH_3 and at 9.70 ppm for the NH groups (D_2O exchangeable) and its Mass spectrum EI-MS (m/z) showed the presence of the molecular ion peak equal to 327 (M^+) which is in agreement with the assigned structure.



Scheme 1: Synthesis of compound (1-6)

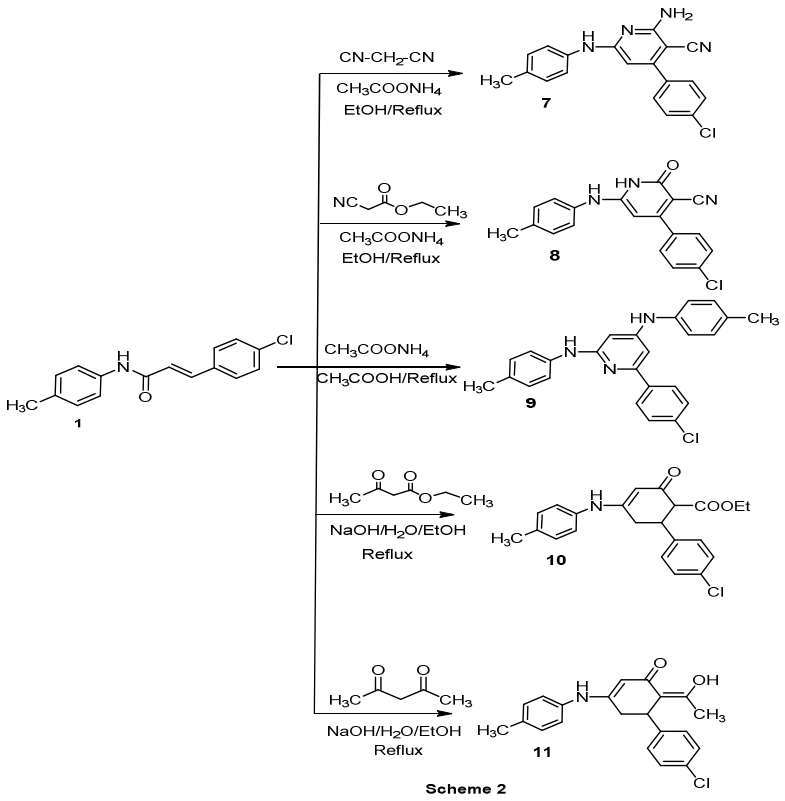
Formation of 2-amino-4-(4-chlorophenyl)-6-(*p*-tolylamino)nicotinonitrile (7) was consistent in 80% yield by reaction of the key compound *N*-(p-tolyl)acrylamide 1 with malononitrile and ammonium acetate in ethanol (Scheme 2). The IR spectrum of the resulting compound 7 showed the bands at ν: 3448, 3271 (NH_2, NH), 2924 (CH), 2198 (CN), 1590 (C=N) cm^{-1}. The ^1H NMR of the aminopyridine compound 7 revealed the presence of the signals at δ 6.7 ppm for pyridine CH and 7.53-8.08 ppm for the aryl signals and at 9.88 ppm for the NH proton in addition to a singlet at 6.9 for NH_2 group (D_2O exchangeable). The ^{13}C NMR revealed signals at δ = 23.47, 121.50, 122.72, 125.01, 125.53, 125.71, 125.93, 127.65, 128.07, 133.68, 168.92 ppm. Its Mass spectrum EI-MS (m/z) showed the presence of the molecular ion peak equal to 334 (M^+) in agreement with the assigned structure (Scheme 2)

The substituted 4-(4-chlorophenyl)-2-oxo-6-(*p*-tolylamino)-1,2-dihydro pyridine-3-carbonitrile (8) was prepared in 70 % yield via the reaction of *N*-(p-tolyl)acrylamide (1) with ethyl cyanoacetate and ammonium acetate in ethanol (Scheme 2). The structure of compound 8 was supported by correct elemental analyses and spectral data. The IR spectrum of compound 8 showed bands at ν 3448 (NH), 2924 (CH), 2075 (CN), 1651 (C=O) cm^{-1}. The ^1H NMR spectrum of the substituted pyridine 8 showed the signals at δ: 5.24, 9.88 and 11.19 ppm for (s, CH pyridone) and (2s, 2NH exchangeable) respectively. While, ^{13}C NMR (75 MHz, DMSO-d6) showed δ 23.45, 121.48, 122.72, 125, 125.52, 125.69, 125.93, 127.61, 128.07, 133.68, 168.90 ppm.

Reaction of the starting compound *N*-(p-tolyl)acrylamide (1) with ammonium acetate in glacial acetic acid gave the corresponding 6-(4-chlorophenyl)-N^2,N^4-di-*p*-tolylpyridine-2,4-diamine (9) in 72% (Scheme 2). The structure of the product 9 was proved by IR spectrum which showed bands at ν: 3271 (NH), 2924 (CH), 1715 (C=O), 1590 (C=N) cm^{-1}. The ^1H NMR spectrum of 9 inferred two singlet signals at δ: 5.44, 6.90 ppm for CH pyridine and at δ: 7.11, 8.36 ppm for 2NH groups (D_2Oexchangeable), The mass spectrum of compound 9 showed EI-MS (m/z) the molecular ion peak at 398 (M^+) (Scheme 2 & Exp. part). Ethyl 4'-chloro-3-oxo-5-(*p*-tolylamino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (10) was formed in 75 % yield by the reaction of *N*-(*p*-tolyl)acrylamide derivative (1) with ethyl acetoacetate in ethanol in the presence of NaOH (10% solution) (Scheme 2). The IR spectrum of the ester derivative 10 showed strong bands at ν: 3271 (NH), 2924 (CH), 1643 (C=O) Cm^{-1}. ^1H NMR of 10 showed signals at δ 1.1 and 2.21 ppm for two methyl groups in addition to signals at 2.30, 2.35 (dd), 3.37, 3.67, 4.1 and 5.50 ppm for two CH_2 and two CH groups respectively. While, ^{13}C NMR (75 MHz, DMSO-d_6) shows signals at δ 23.47, 121.51, 122.86, 124.86, 125.51, 125.66, 125.9, 127.34, 127.70, 127.84, 128.03, 128.17, 131, 133.67, 133.81, 134.23, 137.54, 169.03 ppm. The mass spectrum of the latter compound revealed in its molecular ion peak at 383 (M^+) in consistent with the assigned structure.

(*Z*)-4'-chloro-2-(1-hydroxyethylidene)-5-(*p*-tolylamino)-1,6-dihydro-[1,1'-biphenyl]-3(2*H*)-one (11) was formed in 85% yield by reacting a solution of the corresponding *N*-(p-tolyl)acrylamide derivative 1 with acetyl acetone in ethanol (Scheme 5). The IR spectrum of compound 11 showed the absorption bands at ν: 3479 (OH), 3333 (NH), 2924 (CH), 1635 (C=O) cm^{-1}. Its ^1H NMR showed signals at δ 2.29, 2.30, 2.17, 2.40, 3.49 and 5.84 ppm for two $2CH_3$, CH_2 and 2CH groups respectively in addition to singlet signal at δ 16.72 ppm for OH group. In addition, the mass spectrum of the same compound showed EI-MS (m/z): 353 (M^+) corresponding to the

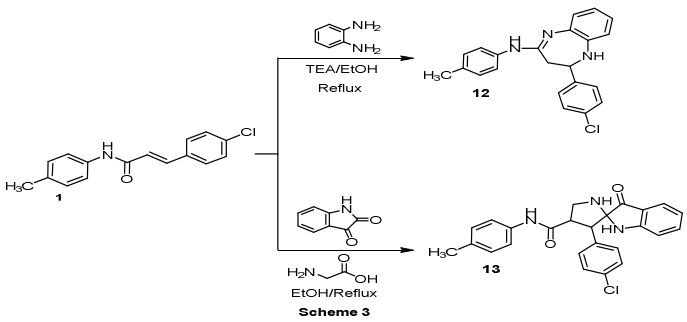
molecular ion peak of the assigned structure. (Scheme 2)



Scheme 2: Synthesis of compound (**7**-**11**)

Formation of 2-(4-chlorophenyl)-*N*-(*p*-tolyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepin-4-amine (12) was consistent in 73% yield by refluxing the *N*-(p-tolyl)acrylamide derivative 1 with *o*-phenylene diamine in absolute ethanol in the presence of few drops of triethyl amine (Scheme 3). The IR spectrum of the resulting compound showed strong absorption bands at ν: 3371, 3325 (2NH), 2939 (CH) Cm^{-1}. ^1H NMR spectrum of 12 showed two triplet signals at δ 2.60, 2.90 ppm for CH_2 in addition to signals at 3.65 and 5.8 ppm for CH and NH (D_2Oexchangeable) groups respectively. Furthermore, the mass spectrum of the diazipine derivative 12 showed EI-MS (m/z): 346 (M^+) agreeing with the assigned structure.

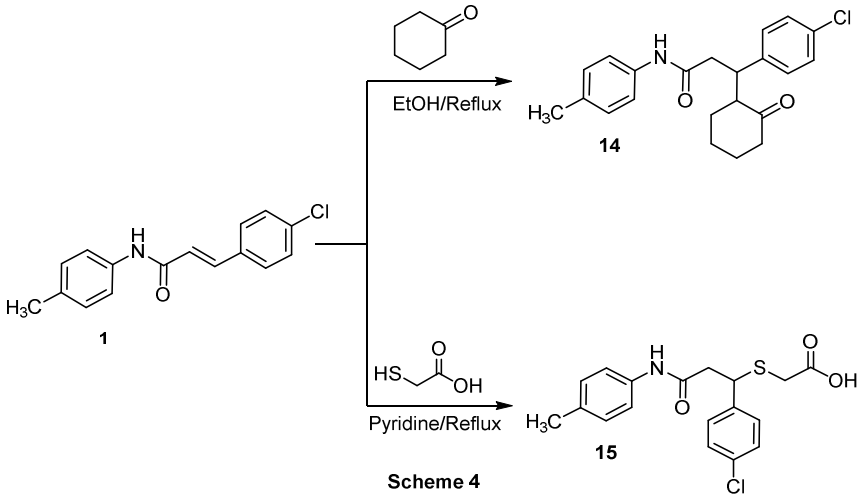
The substituted 3'-(4-chlorophenyl)-3-oxo-*N*-(*p*-tolyl)spiro[indoline-2,2'-pyrrolidine]-4'-carboxamide (13) was prepared in 85% yield by means of reaction of the key compound *N*-(p-tolyl)acrylamide) derivative 1, glycine and isatine in ethanol (Scheme 3). The structure of the resulting product 13 was supported by its correct elemental analyses and spectral data. Its IR spectrum showed the absorption bands at ν: 3333, 3294 (2NH), 2938 (CH), 1730, 1635 (2C=O) cm^{-1}. ^1H NMR spectrum of 13 showed a singlet signal at δ 2.0 for NH group in addition to signals at 2.90, 3.23 and 3.07 ppm for CH_2 and CH and a doublet at 3.65 ppm for CH groups for the two pyrrolidine moieties. While, its mass spectrum showed EI-MS (m/z) = 430 (M^+) which was proven to agree with the assigned structure. (Scheme 3 & Experimental section)



Scheme 3: Synthesis of compound (**12,13**)

On the other hand, The reaction of the *N*-(p-tolyl)acrylamide derivative 1 with cyclohexanone in ethanol gave the corresponding 3-(4-chlorophenyl)-3-(2-oxocyclohexyl)-*N*-(*p*-tolyl)propanamide (14) in 70% yield (Scheme 4). The structure of the amide product 14 was confirmed by its IR spectrum which showed the strong absorption bands at 3348 (NH), 2939 (CH), 1635 (C=O) cm^{-1} Its ^1H NMR spectrum inferred signals at δ 1.3-2.2 (m, $4CH_2$ of the cyclohexanone), 2.41, 2.45 (dd, CH_2), 2.5 (t, CH), 3.2 (q, CH). In addition to its corresponding mass spectrum showed the peak corresponding to the molecular ion peak at 369 (M^+) as shown by the assigned structure.

The reaction of the starting compound (1) with thioglycolic acid in dry pyridine gave 6-{[1-(4-chlorophenyl)-3-oxo-3-(*p*-tolylamino)propyl]thio}acetic acid (15) in 85 % yield (Scheme 4). The IR spectrum of compound 15 showed the strong absorption bands at 3341 (NH), 3226 (CH Ar), 3043 (CH =CH), 1626 (C=O amide) cm^{-1} (Scheme 4). Its ^1H NMR spectrum inferred signals at δ 2.80, 3.0 (dd, CH_2,), 3.40 (s, CH_2), 4.12 ppm (t, CH) and a singlet signal at 12.0 ppm for OH group. In addition to its corresponding mass spectrum showed the peak corresponding to the molecular ion peak at 362 (M^+) as shown by the assigned structure.



Scheme 3: Synthesis of compound (**14,15**)

ANTITUMOR ACTIVITY

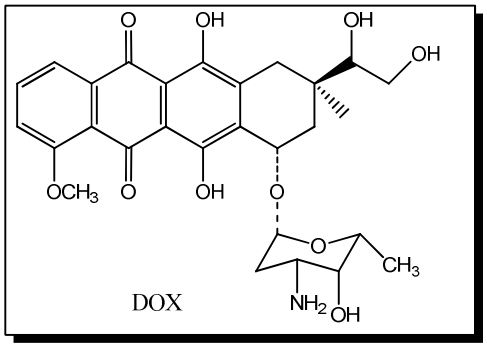
In vitro Antitumor Activity

Measurement of Potential Cytotoxicity by SRB assay

Using the Skehan and Storeng approach, some of the recently synthesised compounds were assessed for their potential cytotoxicity tests against breast cancer (MCF7). [53] Before treatment with the compounds, cells were plated in 96-multiwell plates (104 cells/well) for 24 hours to allow for cell adhesion to the plate wall. Triplicate wells were made for each individual dose and different concentrations of the substance under test (0, 1, 2.5, 5, and 10 g/ml) were applied to the cell monolayer. At 37 degrees Celsius and with a 5% CO_2 environment, monolayer cells were exposed to the chemicals for 48 hours. Cells were fixed, cleaned, and stained with Sulfo-Rhodamine-B dye after 48 hours. Acetic acid was used to remove extra stain, and Tris EDTA buffer was used to recover any attached stain. Using an ELISA reader, colour intensity was evaluated. To determine the survival curve of each tumour cell line following exposure to a particular substance, the relationship between surviving fraction and drug concentration is displayed. For the different active substances, the IC50 percent control of infected and uninfected response values were determined and given in Table 1. The positive standard utilised was doxirubsin (DOX). Compounds with an IC50 5 g/ml are thought to be potentially active and are subjected to additional in vivo testing.

Table 1 The IC_{50} (µg/mL) of some of the selected new compounds against Breast cancer cell line (**MCF7**)

Compound	IC_{50} µg/ml	Compound	IC_{50} µg/ml
DOX	2.97	**DOX**	2.97
1	4.03	**9**	4.10
2	4.34	**10**	4.39
3	4.70	**11**	4.20
4	6.30	**12**	4.60
5	4.50	**13**	4.10
6	4.00	**14**	4.22
7	4.60	**15**	4.40
8	3.60		



DOX

HEPATITIS B ACTIVITY

Acute hepatitis is brought on by the DNA virus known as the hepatitis B virus (HBV), which can also cause chronic hepatitis, liver cirrhosis, and hepatocellular cancer. [54] More than one million deaths worldwide are reported each year as a result of problems connected to HBV, and there are around 300 million HBV carriers worldwide [55]. Despite

the effectiveness of effective immunization in preventing HBV infection, the need for the availability of drugs that specifically target HBV replication remains. [56] There have been several medications considered, but only alpha interferon has shown any clinical benefit in some patients. [57,58]

The stage of the HBV life cycle known as reverse transcription may be a potential target for antiviral treatment. Reverse transcription of the progenome employing the endogenous viral reverse transcriptase produces the minus strand of HBV. It has been demonstrated that the reverse transcriptase enzyme leads to a more effective incorporation of nucleotide analogues than the cellular DNA polymerase. [59] These nucleotide analogues compete with the nucleosides pool in the cell's cytoplasm to block reverse transcriptase during minus strand synthesis.

A significant advance in the study of selective antiviral activity has been made recently with the creation of heterocyclic analogues. Lamivudine, one of these medications, inhibits retroviruses. [60] Both in vitro and in vivo, it inhibits HBV replication.

Preparation and culture of Hep G2 2.2.15 cells

The required cell line was made by transfection of Hep G2-cells with a plasmid containing multiple tandem copies of HBV genome (subtype ayw). The 2.2.15 cell line was maintained in RPMI-1640 (Glutamic) culture media containing 100 IU/ml nystatin and 380 µg/ml G418 (geneticin). A tissue culture flask containing the transferred HEP G2-2.2.15 cell line was maintained at 37°C with 5% CO_2. After a week, subcultures were established by aspirating the media from the culture flask and twice washing the cells in PBS. The cells were treated for 1 minute at 37°C with a 10% versine/trypsin solution after being introduced.

For the comparative studies, the medication Lamivudine, which is a strong, selective inhibitor of HBV replication [61], has been chosen as the gold standard.

DNA Extraction

HBV-DNA was extracted by combining 10 l of diluted supernatant (1:5 with PBS) with 10 l of 0.2 M NaOH in a reaction tube and incubating at 37 °C for an hour. 9.6 l of 0.2 M HCl and 90 l of TE buffer solution were carefully added.

PCR-Elisa

The PCR reaction mixture contained 14 µl extracted supernatant, 4 mmol/l MgCl2, 10 µmol/l DIG-11-dUTP, 190 µmol/l dTTP, 200 µmol/l dATP, dGTP, dCTP, 1.5 U Taq polymerase, 20 mmol/l HCl (pH 8.4), 50 mmol/l KCl, 1 µmol/l HCID-1 primer (5′GGA AAG AAG TCA GAA GGC A3′) and 1 µmol/l HCID-2 (5′TTG GGG GAG GAG ATT AGG TT3′), in total volume 50 µl. PCR reaction conditions were 32 cycles of 1 min. at 94oC, 30 sec. at 58oC and 30 sec. at 72^{o}C + 3 sec. for each cycle in a thermal circler as described in literature.[62].

Cytotoxicity Assay

The colourless substrate 3-(3,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), which is converted to colourful product by any living cells but not by dead cells or tissue culture medium, was used in a colorimetric assay for living cells. By cultivating the Hep G2-2.2.15 cells in the presence of the compounds and performing an MTT-assay, the cytotoxic effect of the compounds was determined. [63]

Calculation of IC_{50}, CC_{50} and SI

By extrapolating from plots of DNA copy number versus antiviral medication concentration, the 50% inhibitory concentration of antiviral medicines (IC50)

was discovered. In order to determine the 50% cytotoxic impact (CC50), the average cell viability at the drug concentration was used. The CC50/IC50 formula can be used to compute the selective index (SI). [63]

Testing

Selected compounds exhibited some compounds demonstrated moderate viral replication suppression and minor cytotoxicity, according to the results of the viral screening against HBV.

Results of chosen compounds' viral screening against HBV revealed that the majority of the tested compounds exhibited strong viral replication inhibition and minimal cytotoxicity (Table 2).

TABLE 2 CYTOTOXIC EFFECT (CC_{50}), INHIBITORY CONCENTRATION (IC_{50}) AND SELECTIVE INDEX (SI) OF SELECTED COMPOUNDS

COMPD.	HBV DNA IC_{50} (MM)	HEP G2 2.2.15 CC_{50} (MM)	SI
Lamivudine	<0.1	>100	>1000
1	0.16	>100	>625
2	0.25	>100	>400
3	0.27	>100	>370
4	0.27	>100	>370
5	0.25	>100	>400
6	0.16	>100	>625
7	0.27	>100	>370
8	0.16	>100	>625
9	0.25	>100	>400
10	0.27	>100	>370
11	0.25	>100	>400
12	0.16	>100	>625
13	0.27	>100	>370
14	0.27	>100	>370
15	0.20	>100	>500

ANTIMICROBIAL ACTIVITY

The screening procedure used the agar diffusion method described by Cruickshank et al. [64]. On Czapek's-Dox agar and nutrition agar, respectively, the bacteria and fungi were kept alive. When the assay medium flasks containing 50 mL of Czapek's-Dox agar medium for fungi and nutritional agar for bacteria correspondingly reached 40–50o C, they were injected with 0.5 mL of the test organism cell suspension.

The flasks were thoroughly combined before being each emptied into a Petri dish (15 x 2 cm) and given time to set. After solidification, sterile cork pokes were used to create holes (0.6 cm in diameter) in the agar plate (diameter 6 mm). Each of the produced target substances was dissolved in 2 mL of DMSO. 100 1 of each compound were inserted into these holes using an automated micropipette.

To allow samples to diffuse through the agar medium and slow the growth of the test organism, the Petri dishes were kept at 5 °C for 1 hour. For 24 hours at 30 ^{o}C for bacteria and 72 hours at 28^{o}C for fungus, plates were incubated. There were no inhibitory zones in DMSO. Zone of inhibition diameters were measured, compared to the standard, and the results were tabulated. Fusidic acid [67] and ciprofloxacin

[65,66] (50 g/mL each) were employed as standards for antibacterial and antifungal activities, respectively. Table 3 displays the observed zones of inhibition.

Table 3 In vitro antimicrobial activity by agar diffusion method of the tested compounds

Compound No.	Zone of Inhibition (mm) of Microorganisms			
	Bacillus subtilis	*Escherichia coli*	*Candida albicans*	*Aspergillus flavus*
Penicillin	50	45	17	46
1	40	25	16	35
2	40	37	15	36
3	39	34	14	35
4	29	35	15	38
5	38	30	10	39
6	35	26	12	37
7	33	34	12	33
8	39	25	14	29
9	38	26	15	30
10	36	30	13	32
11	30	30	13	30
12	39	34	14	35
13	30	20	13	20
14	35	30	12	33
15	32	22	12	36

Aspergillus flavus, *Candida albicans* NRRL Y-477, *Bacillus subtilis* NRRL B-543, and *Escherichia coli* NRRL B-210 (Gram ¯ve bacteria) were used as test organisms for the synthesized compounds' antibacterial properties [56–67]. (Fungi).

Zone of inhibition diameters was measured, compared to the standard, and the results were tabulated. Tetracycline was employed as a reference for the antibacterial activity, and Table 3 shows the observed zone of inhibition.

Overall, the results showed that examined compounds did not exhibit strong activity against the bacteria under investigation (*Escherichia coli* and *Bacillus subtilis*), although several compounds did exhibit strong activity against fungus. All novel compounds had antimicrobial activity.

Conclusion

The antimicrobial screening results indicate that all the recently synthesized compounds shown moderate to good effectiveness against the examined species.

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