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Synthesis, antibacterial and anticancer activities of some novel imidazoles

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Abstract

Amino group of thiazole moiety (**1**) have been treated with various aromatic aldehydes gave corresponding Schiff's bases (**2-12**). These Schiff's bases have been reacted with benzil and ammonium acetate (NH_4OAc) to get corresponding novel imidazoles (**2a-12a**). Structures of all the newly synthesized compounds were confirmed by IR, ^1H NMR, mass spectral data and elemental analysis. The synthesized compounds were evaluated for their antibacterial and short-term anticancer activity. All the synthesized substituted imidazoles have shown good antibacterial activity against gram negative bacterial strains *Klebsiella pneumoniae* and *Escherichia coli*. The synthesized imidazole derivative possessed significant cytotoxic activity against Dalton's Lymphoma Ascites (DLA) and Ehrlich's Ascites Carcinoma (EAC) cell lines.

Keywords: Thiazoles, Imidazoles, antibacterial activity, anticancer activity.

INTRODUCTION

Imidazoles are useful structural units in the field of the medicinal chemistry and have been reported to exhibit a variety of biological activity such as antibacterial [1], antirheumatoid arthritis [2], antitubercular [3], antiviral [4], antiepileptic [5], anti-inflammatory [6], anticancer [7-9] and antifungal [10] etc. Various substituted novel imidazoles have been synthesized and examined for antibacterial and anticancer activity.

In the present study, various N-(4-{2-[2-(Substituted-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide were synthesized and screened for their antibacterial, antitubercular and anticancer activity. Starting compound *p*-acetamidoacetophenone was obtained by treating *p*-aminoacetophenone with acetic anhydride. The required substituted 2-aminothiazole was obtained according to the reported method [11]. Substituted 2-aminothiazole was treated with various aromatic aldehyde in methanol to get 2-[(substituted-benzylidene) amino]-4-(4'-acetanilido)-thiazoles (**2-12**) and these compounds on reaction with benzil produced N-(4-{2-[2-(Substituted-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (**2a-12a**).

MATERIALS AND METHODS

Experimental

The analytical grade chemicals and reagents of SIGMA ALDRICH were used to synthesize all the reported compounds. The melting points were determined in open capillaries and are uncorrected. The temperatures were expressed in °C and are uncorrected. The IR spectra of compounds were recorded on Perkin-Elmer infrared-283 FTIR spectrometer by KBr pellet technique and are expressed in cm^{-1} . $^1\text{H-NMR}$ spectra were recorded on Bruker DRX-300 (300 MHz, FT NMR) spectrophotometer using TMS as an internal standard, CDCl_3 and DMSO-d_6 as solvents. Mass spectrum was obtained using LC-MS (Schimadzu-2010AT) under Electro Spray Ionization (ESI) technique and elemental analysis was performed using Elemental Vario EL III, Carlo-Erba 1108. TLC was performed to monitor the reactions and to determine the purity of the products on a precoated aluminum plates using 10% methanol in chloroform or 20% ethyl acetate in chloroform as a mobile phase.

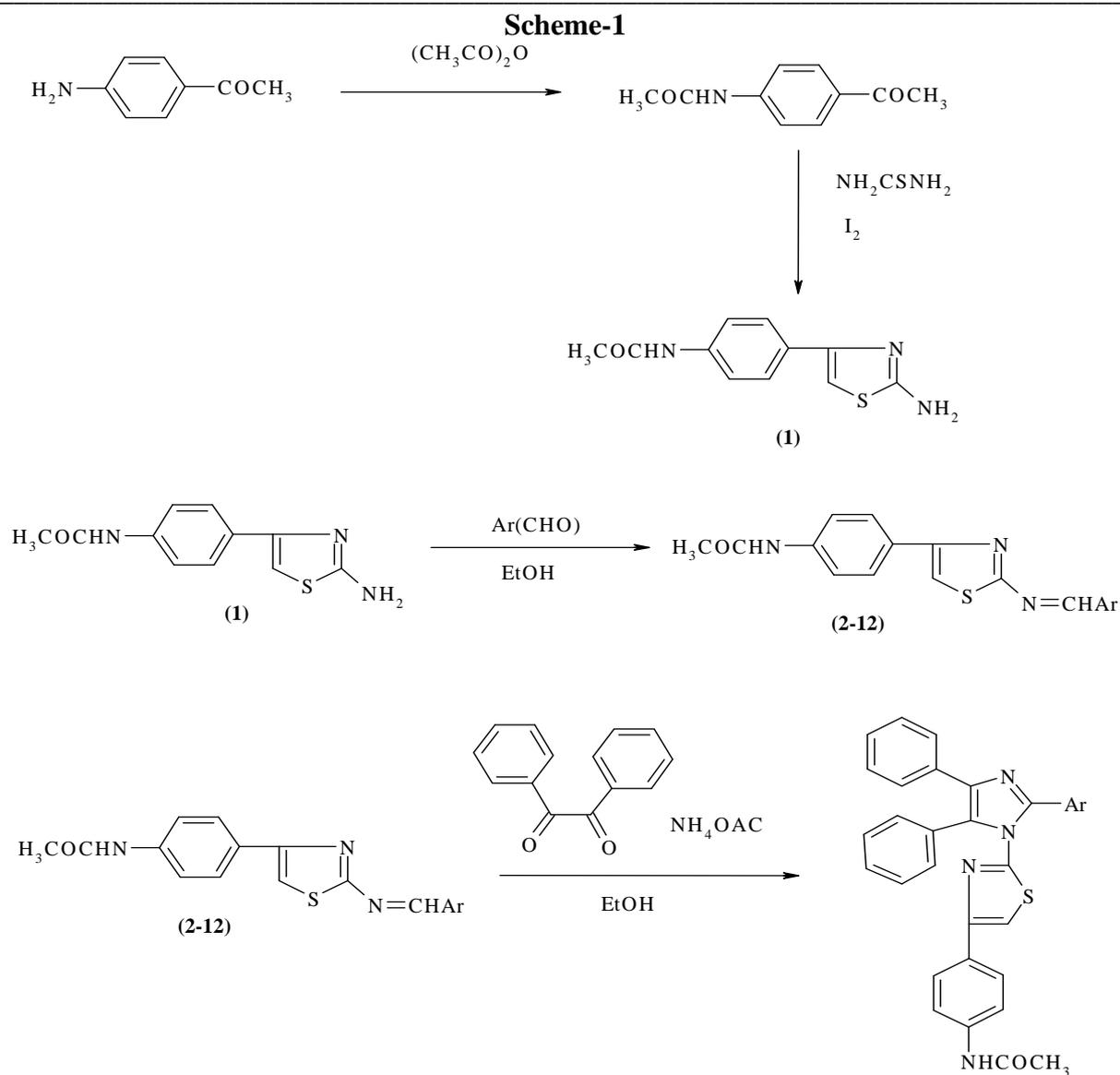
***p*-Acetamidoacetophenone:** A mixture of *p*-aminoacetophenone (0.076 mole) and acetic anhydride (30 ml) was taken in a beaker. The reaction mixture was heated on a steam bath for 50 minutes and allowed to stand for 2 hours. The solid obtained was filtered, dried and purified by recrystallization from ethanol.

IR (KBr) (ν , cm^{-1}): 3298 (NH), 1745 (C=O, aromatic), 1672 (C=O, amide).

2-Amino-4-(4'-acetanilido)-thiazole (1): A mixture of iodine (0.033 mole) and thiourea (0.066 mole) was triturated and the mixture was poured in to a conical flask containing *p*-acetamidoacetophenone (0.033 mole). The reaction mixture was heated for 9 hours on a water bath with occasional stirring. The solid obtained was washed with diethyl ether to remove any unreacted *p*-acetamidoacetophenone, after which it was washed with sodium thiosulfate to remove unreacted iodine. Finally, it was washed with water and the residue was filtered and dried. Purification was done by dissolving in hot water, filtered and dilute ammonia was added to the filtrate to precipitate and was purified by recrystallization from distilled water.

IR (KBr) (ν , cm^{-1}): 3407 (NH_2), 3299 (NH), 3121 (CH_3), 1673 cm^{-1} (C=O); $^1\text{H NMR}$ (DMSO-d_6 , δ ppm): δ 2.16 (s, 3H, COCH_3), 7.21-7.50 (m, 4H, Ar-H), 7.51 (s, 1H, CH at C_5 of thiazole), 9.48 (s, 2H, NH_2); MS: m/z 232.9 (M^+), 191, 162 and 80.

2-[(Substituted-benzylidene)amino]-4-(4'-acetanilido)-thiazole (2-12): A mixture containing 2-amino-4-(4'-acetanilido) thiazole (0.02 mole) and substituted aromatic aldehyde (0.02 mole) in 40 ml of ethanol along with glacial-acetic acid (2-3 drops), was refluxed for 2 hours. The reaction mixture was cooled. The solid obtained was filtered, washed with ethanol, dried and recrystallized from DMF: water (1:1) mixture.



2 & 2a, Ar = 4-chloro phenyl; **3 & 3a**, Ar = 4-hydroxy phenyl; **4 & 4a**, Ar = 3,4,5-trimethoxyphenyl; **5 & 5a**, Ar = 4-Methoxy phenyl; **6 & 6a**, Ar = 4-Dimethylamino phenyl; **7 & 7a**, Ar = 2-Chloro-phenyl; **8 & 8a**, Ar = 4-Hydroxy-3-methoxy phenyl; **9 & 9a**, Ar = 3-Nitro phenyl; **10 & 10a**, Ar = 2,6-Dichloro phenyl; **11 & 11a**, Ar = 2-Nitro phenyl; **12 & 12a**, Ar = 2-Methoxy phenyl.

N-(4-{2-[2-(Substituted-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (2a-12a): An equimolar amounts of Schiff's base (0.01 mole) and benzil (0.01 mole) were transferred along with excess of ammonium acetate (2 mole) in to a 250 ml round bottom flask containing 30 ml of methanol. The mixture was refluxed for about 12 hours. Then, the reaction mixture was washed with 25 ml of water, twice to remove ammonium acetate and dried over magnesium sulphate. Then, the reaction mixture was washed with 5 ml of benzene, twice to remove traces of any unreacted benzil, further purified by recrystallization with ethyl acetate.

N-(4-{2-[2-(4-Chloro-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (2a): mp 191 °C; yield 59%; IR (KBr) (ν , cm^{-1}): 3294 (NH), 3123 (CH_3), 3054 (Ar C-H), 1673 (C=O), 1595 (C=C), 1594 (N=CH), 1253 (C-N), 760 (C-Cl); $^1\text{H NMR}$ (DMSO- d_6 , δ ppm): δ 2.11 (s, 3H,

COCH₃), 6.94-7.75 (m, 18H, Ar-H), 7.35 (s, 1H, CH at C₅ of thiazole), 7.39 (s, 1H, NH); MS: m/z 547.23 (M⁺); Anal. Calcd for C₃₂H₂₃ClN₄OS: C, 70.26; H, 4.24; Cl, 6.48; N, 10.24, O, 2.92, S, 5.86; Found: C, 70.20; H, 4.14; Cl, 6.30; N, 10.19; O, 2.98; S, 5.89.

N-(4-{2-[2-(4-Hydroxy-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (3a): mp 195 °C; yield 62%; IR (KBr) (ν , cm⁻¹): 3287 (OH), 3181 (NH), 3123 (CH₃), 3056 (Ar C-H), 1674 (C=O), 1598 (C=C), 1596 (N=CH), 1252 (C-N); ¹H NMR (DMSO-d₆, δ ppm): δ 2.11 (s, 3H, COCH₃), 6.82-7.81 (m, 18H, Ar-H), 7.35 (s, 1H, CH at C₅ of thiazole), 7.38 (s, 1H, NH); MS: m/z 528.43 (M⁺); Anal. Calcd for C₃₂H₂₄N₄O₂S: C, 72.71; H, 4.58; N, 10.60; O, 6.05; S, 6.07; Found: C, 72.69; H, 4.65; N, 10.45; O, 6.11; S, 6.27.

N-(4-{2-[2-(4,5-Diphenyl-2-(3,4,5-trimethoxy-phenyl)-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (4a): mp 201 °C; yield 67%; IR (KBr) (ν , cm⁻¹): 3199 (NH), 3123 (CH₃), 3051 (Ar C-H), 1641 (C=O), 1592 (C=C), 1542 (N=CH), 1251 (C-N); ¹H NMR (DMSO-d₆, δ ppm): δ 2.60 (s, 3H, COCH₃), 3.21 (s, 9H, {OCH₃}₃), 6.61-7.71 (m, 18H, Ar-H), 7.35 (s, 1H, NH), 7.43 (s, 1H, CH at C₅ of thiazole); MS: m/z 602.31 (M⁺); Anal. Calcd for C₃₅H₃₀N₄O₄S: C, 69.75; H, 5.02; N, 9.30; O, 10.62; S, 5.32; Found: C, 69.79; H, 5.12; N, 9.22; O, 10.72; S, 5.19.

N-(4-{2-[2-(4-Methoxy-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide(5a): mp 181 °C; yield 72%; IR (KBr) (ν , cm⁻¹): 3201 (NH), 3132 (CH₃), 3050 (Ar C-H), 1642 (C=O), 1592 (C=C), 1540 (N=CH), 1251 (C-N); ¹H NMR (DMSO-d₆, δ ppm): δ 2.71 (s, 3H, COCH₃), 3.11 (s, 3H, OCH₃), 6.75-7.72 (m, 18H, Ar-H), 7.35 (s, 1H at C₅ of thiazole), 7.45 (s, 1H, NH); MS: m/z 542.34 (M⁺); Anal. Calcd for C₃₃H₂₆N₄O₂S: C, 73.04; H, 4.83; N, 10.32; O, 5.90; S, 5.91; Found: C, 73.11; H, 4.89; N, 10.22; O, 5.89; S, 5.82.

N-(4-{2-[2-(4-Dimethylamino-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (6a): mp 211 °C; yield 70%; IR (KBr) (ν , cm⁻¹): 3144 (NH), 3052 (Ar C-H), 2961 (CH₃), 1670 (C=O), 1597 (C=C), 1250 (C-N); ¹H NMR (DMSO-d₆, δ ppm): δ 2.31 (s, 3H, CH₃), 2.41 (s, 3H, COCH₃), 6.61-7.41 (m, 18H, ArH), 7.12 (s, 1H, CH at C₅ of thiazole), 7.49 (s, 1H, NH); MS: m/z 555.45 (M⁺); Anal. Calcd for C₃₄H₂₉N₅OS: C, 73.49; H, 5.26; N, 12.60; O, 2.88; S, 5.77; Found: C, 73.35; H, 5.25; N, 12.45; O, 2.82; S, 5.71.

N-(4-{2-[2-(2-Chloro-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (7a): mp 187 °C; yield 69%; IR (KBr) (ν , cm⁻¹): 3294 (NH), 3123 (CH₃), 3051 (Ar C-H), 1673 (C=O), 1595 (C=C), 760 (C-Cl); ¹H NMR (DMSO-d₆, δ ppm): δ 2.11 (s, 3H, COCH₃), 6.75-7.69 (m, 18H, Ar-H), 7.39 (s, 1H, CH at C₅ of thiazole), 7.45 (s, 1H, NH); MS: m/z 546.56 (M⁺); Anal. Calcd for C₃₂H₂₃ClN₄OS: C, 70.26; H, 4.24; Cl, 6.48; N, 10.24; O, 2.92; S, 5.86; Found: C, 70.25; H, 4.19; Cl, 6.18; N, 10.31; O, 2.85; S, 5.89.

N-(4-{2-[2-(4-Hydroxy-3-methoxy-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (8a): mp 209 °C; yield 57%; IR (KBr) (ν , cm⁻¹): 3285 (OH), 3179 (NH), 3125 (CH₃), 3057 (Ar C-H), 1672 (C=O), 1255 (C-N); ¹H NMR (DMSO-d₆, δ ppm): δ 2.75 (s, 3H, COCH₃), 3.12 (s, 3H, OCH₃), 6.64-7.71 (m, 17H, Ar-H), 7.32 (s, 1H, CH at C₅ of thiazole), 7.52 (s, 1H, NH); MS: m/z 558.24 (M⁺); Anal. Calcd for C₃₃H₂₆N₄O₃S: C, 70.95; H, 4.69; N, 10.03; O, 8.59; S, 5.74; Found: C, 70.89; H, 4.61; N, 10.13; O, 8.45; S, 5.59.

N-(4-{2-[2-(3-Nitro-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (9a): mp 198 °C; yield 55%; IR (KBr) (ν , cm⁻¹): 3292 (NH), 3129 (CH₃), 3058 (Ar C-H), 1672 (C=O), 1594 (C=C), 1257 (CN); ¹H NMR (DMSO-d₆, δ ppm): δ 2.11 (s, 3H, COCH₃), 6.74-7.71 (m, 18H, Ar-H), 7.31 (s, 1H, CH at C₅ of thiazole), 7.41 (s, 1H, NH); MS: m/z 557.25 (M⁺); Anal.

Calcd for C₃₂H₂₃N₅O₃S: C, 68.93; H, 4.16; N, 12.56; O, 8.61; S, 5.75; Found: C, 68.87; H, 4.25; N, 12.28; O, 8.56; S, 5.79.

N-(4-{2-[2-(2,6-Dichloro-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (10a): mp 202 °C; yield 55%; IR (KBr) (ν , cm⁻¹): 3294 (NH), 3123 (CH₃), 3055 (Ar C-H), 1660 (C=O), 1590 (C=C), 762 (C-Cl); ¹H NMR (DMSO-d₆, δ ppm): δ 2.22 (s, 3H, COCH₃), 6.79-7.70 (m, 18H, ArH), 7.32 (s, 1H, CH at C₅ of thiazole) 7.42 (s, 1H, NH); MS: m/z 581.34 (M⁺); Anal. Calcd for C₃₂H₂₂Cl₂N₄OS: C, 66.09; H, 3.81; Cl, 12.19; N, 9.63; O, 2.75; S 5.51; Found: C, 66.21; H, 3.95; Cl, 12.25; N, 9.31; O, 2.85; S, 5.39.

N-(4-{2-[2-(2-Nitro-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (11a): mp 203 °C; yield 61%; IR (KBr) (ν , cm⁻¹): 3290 (NH), 3130 (CH₃), 3055 (Ar C-H), 1675 (C=O), 1592 (C=C), 1252 (C-N); ¹H NMR (DMSO-d₆, δ ppm): δ 2.23 (s, 3H, COCH₃), 6.74-7.69 (m, 18H, ArH), 7.35 (s, 1H, CH at C₅ of thiazole), 7.39 (s, 1H, NH); MS: m/z 557.56 (M⁺); Anal. Calcd for C₃₂H₂₃N₅O₃S: C, 68.93; H, 4.16; N, 12.56; O, 8.61; S, 5.75; Found: C, 68.81; H, 4.31; N, 12.60; O, 8.59; S, 5.69.

N-(4-{2-[2-(2-Methoxy-phenyl)-4,5-diphenyl-imidazol-1-yl]-thiazol-4-yl}-phenyl)-acetamide (12a): mp 176 °C; yield 69%; IR (KBr) (ν , cm⁻¹): 3208 (NH), 3122 (CH₃), 3054 (Ar C-H), 1650 (C=O), 1589 (C=C), 1545 (N=CH), 1249 (C-N); ¹H NMR (DMSO-d₆, δ ppm): δ 2.71 (s, 3H, COCH₃), 3.22 (s, 3H, OCH₃), 6.75-7.80 (m, 18H, Ar-H), 7.35 (s, 1H, NH), 7.41 (s, 1H at C₅ of thiazole); MS: m/z 542.12 (M⁺); Anal. Calcd for C₃₃H₂₆N₄O₂S: C, 73.04; H, 4.83; N, 10.32; O, 5.90; S, 5.91, Found: C, 73.23; H, 4.79; N, 10.25; O, 5.81; S, 6.01.

RESULTS AND DISCUSSION

The structures of all the newly synthesized compounds have been established on the basis of their spectral data analysis. The appearance of primary amino group band at 3407 cm⁻¹ in the IR spectrum, the NMR signal for thiazole proton at δ 7.51, the molecular ion peak at m/z 232.9 and fragmentation peaks at m/z 191, 162 and 80 confirmed the formation of compound (1). Compounds 2 to 12 showed -N=CH- band in IR between 1530-1600 cm⁻¹. The NMR spectra of the compounds 2 to 12 exhibited absence of amino group signal of thiazole at δ 9.46 and appearance of sharp signal of -N=CH- between δ 8.71-9.42 which indicated the formation of schiff's bases. Compounds 2a to 12a showed =N-C group band between 1249-1257 cm⁻¹ in IR spectra, and their NMR spectrum Showed the absence of -N=CH- proton signal between δ 8.71-9.42. Mass of representative compounds 2a to 12a exhibited molecular ion peak at m/z 547.23, 528.43, 602.31, 542.34, 555.45, 546.56, 558.24, 557.25, 581.34, 557.56 & 542.12 along with their fragmentation peaks.

All the synthesized imidazoles incorporated with chemotherapeutic pharmacophores were evaluated for their in vitro antibacterial activity against two-gram positive bacteria such as Bacillus subtilis and Staphylococcus aureus and two gram negative bacteria Such as Escherichia coli and Klebsiella pneumoniae. Almost all the newly synthesized substituted imidazoles showed good antibacterial activity against gram negative bacterial strains Escherichia coli and Klebsiella pneumonia. The results of antibacterial studies are presented in Table 1.

Anticancer activity of the synthesized compounds was evaluated by determining the percentage growth inhibition of Dalton's Lymphoma Ascites (DLA) cells and Erlich's Ascites Carcinoma (EAC) cells by trypan blue dye exclusion technique. Compounds 3a and 8a showed good anticancer activity with CTC₅₀ (cytotoxic concentration). Presence of phenolic group in

compound **3a** and **8a** significantly affect activity due to the binding capability to the cytoplasmic hormone receptors. While compounds **9a** and **11a** least potency due to presence of NO₂ group which stabilize the lone pair of electron due to negative inductomeric effect. The CTC₅₀ values of the newly synthesized imidazoles are shown in Table 2.

Biological activity studies

Antibacterial activity

The synthesized imidazole derivatives were screened for their antibacterial activity against two gram positive bacterial strains *B. subtilis* (NCIM 2063), *S. aureus* (NCIM 2079) and two gram negative bacterial strains *K. pneumoniae* (NCIM 2087), *E. coli* (NCIM 2065) by using modified Kirby-Bauer disc diffusion method. MIC values of test compounds were determined by tube dilution technique. All the synthesized compounds were dissolved separately to prepare a stock solution of 1 mg ml⁻¹ using DMF. Stock solution was aseptically transferred and suitably diluted with sterile broth medium to have seven different concentrations of each test compound ranging from 200 to 3.1 µg ml⁻¹ in different test tubes. All the tubes were inoculated with one loopful of one of the test bacteria. The process was repeated with different test bacteria and different samples. Tubes inoculated with bacterial cultures were incubated at 37 °C for 18 h and the presence/absence of growth of the bacteria was observed. From these results, MIC of each test compound was determined against each test bacterium. A spore suspension in sterile distilled water was prepared from five-days-old culture of the test bacteria growing on nutrient broth media. About 20 ml of the growth medium was transferred into sterilized petri plates and inoculated with 1.5 ml of the spore suspension (spore concentration 6 X 10⁴ spores ml⁻¹). Filter paper disks of 6 mm diameter and 2 mm thickness were sterilized by autoclaving at 121 °C (15 psi) for 15 min. Each petri plate was divided into five equal portions along the diameter to place one disc. Three discs of test sample were placed on three portions together with one disc with reference drug ciprofloxacin and a disk impregnated with the solvent (DMF) as negative control. Test sample and reference drugs were tested at the concentration of 10 µg ml⁻¹.

Table 1. Data of newly synthesized tetraaryl imidazoles compounds screened against bacterial strains

Compound	Diameter of zone of inhibition (mm) Bacterial strains			
	Gram (+ve)		Gram (-ve)	
	<i>S.aureus</i>	<i>B.subtilis</i>	<i>E.coli</i>	<i>K.pneumoniae</i>
2a	6.1 (100)	7.9 (50)	9.2 (25)	10.6 (12.5)
3a	4.8 (100)	4.6 (100)	8.1 (50)	11.8 (6.2)
4a	9.0 (50)	8.6 (50)	11.3 (12.5)	12.1 (25)
5a	11.0 (25)	11.3 (50)	11.8 (6.2)	11.2 (12.5)
6a	8.1 (50)	7.8 (100)	10.5 (50)	9.2 (50)
7a	10.5 (25)	10.1 (25)	10.9 (25)	10.6 (12.5)
8a	7.5 (25)	7.3 (25)	9.2 (12.5)	9.9 (12.5)
9a	10.9 (50)	11.3 (50)	11.9 (25)	10.9 (50)
10a	7.1 (100)	6.8 (50)	10.8 (25)	10.3 (25)
11a	6.0 (100)	5.4 (100)	9.2 (50)	9.9 (25)
12a	11.8 (50)	10.7 (25)	11 (50)	11.8 (12.5)
Control	-	-	-	-
Ciprofloxacin	18 (12.5)	19 (6)	19 (12.5)	16 (6)

The petri plates inoculated with bacterial cultures were incubated at 37 °C for 18 h. Diameters of the zones of inhibition (mm) were measured and the average diameters for test sample were

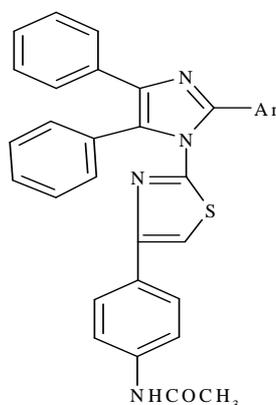
calculated in triplicate sets. The diameters obtained for the test sample were compared with that produced by the standard drug ciprofloxacin. Result can be correlated to Table 1.

Anticancer activity

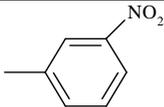
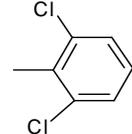
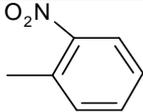
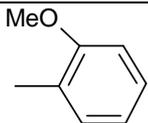
Anticancer activities of the synthesized compounds were assessed by determining the percentage inhibition of DLA cells and EAC cells by trypan blue dye exclusion technique according to the standard procedure. We checked anticancer activity of all the synthesized compounds at the concentration of 500, 250, 125, 62.5, 31.25 $\mu\text{g/ml}$. The percentage growth inhibition was calculated by using the following formula: % Growth inhibition = [(Total cells – Live cells) \times 100]/Total cells.

The CTC_{50} values were calculated by plotting the graph between concentration versus percentage growth inhibition and by bisecting concentration at the 50% growth inhibition. The synthesized aryl imidazoles and their CTC_{50} values are as shown in Table 2.

Table 2. List of synthesized imidazoles and there *in vitro* anticancer activity results



Compounds	Ar	DLA cells CTC_{50} $\mu\text{g/ml}$	EAC Cells CTC_{50} $\mu\text{g/ml}$
2a		190.26	110.25
3a		102.86	31.25
4a		320.00	290.25
5a		304.56	340.95
6a		480.25	425.24
7a		440.56	402.56
8a		138.50	31.25

9a		>500	500
10a		355.56	345.67
11a		450.50	490
12a		150.26	94.63

CTC_{50} = The cytotoxic concentration (which inhibited 50% of total cells).

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