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Synthesis and biological evaluation of new 2-(4-fluorophenyl) imidazol-5-ones as anticancer agents

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ABSTRACT

Two series of imidazolones were designed, synthesized, and evaluated for their anticancer activity against four cancer cell lines: Hela, MCF-7, PC3, and HCT-116, where four compounds **6**, **25**, **26,** and **29** showed good potency against the whole panel. Compound **30** showed a cytotoxic effect against PC3 cell lines compared to that of the standard doxorubicin with IC_{50} = 8.15µM, while compounds **4** and **18** showed moderate activity with IC_{50} range of 10.58–11.45 µM. Enzyme inhibition assay was implemented against CDK2A and VEGFR-2; where varied activities were obtained. Compound **6** exhibited the highest inhibitory activity against VEGFR-2 with an IC_{50} value of 67 nM and moderate inhibition against CDK2A, while compound **26** achieved the best result against CDK2A with an IC_{50} value of 0.66 µM.

INTRODUCTION

Cancer development process basically results from the uncontrolled growth of mutated or abnormal body cells, whereas normal cells are under strict control of various growth pattern checkpoints, the neoplastic cells typically do not obey these rules and are continuously and uncontrollably proliferating. Normally, during the process of mitosis, any abnormalities during cell division are controlled by a set of physiological processes "apoptosis" ending up in damaged cell death (Spano *et al*., 2016). Nevertheless, if the cells are mutated and not controlled by the programmed cell death and/or acquire the ability to escape several checkpoints, they turn to be malignant cells that are able to invade and metastasize (Kalyanaraman, 2017).

Various compounds have been studied as anticancer agents throughout the work on the different phases of the cell cycle. These compounds include at most the *N*-containing heterocycles (Akhtar *et al*., 2017), among which imidazole ring system represents the main core structure. Imidazole and its derivatives have a great prevalence in both natural products and synthetic molecules. Having the unique structural features with the desirable electron-rich characteristic enables these compounds to readily bind with different enzymes and receptors, thereby exhibiting broad bioactivities (Zhang *et al*., 2014). Various activities including anticancer, anti-inflammatory (Rapolu *et al*., 2013), antimicrobial (Premakumari *et al*., 2014), cardio-activity, and angiotensin-II receptor antagonistic activity have been depicted specifically in compounds containing imidazolone moiety (Padmaja *et al*., 2011). Furthermore, many imidazolones have been used as biotin antagonists capable of inhibiting the growth of malignant tumors like compound **I** (AK *et al*., 2017). For instance, the cytotoxic activity of imidazolone derivatives **I** and **II** against cervical cancer (HeLa), breast cancer (MCF-7), leukemia cells (HL-60), and hepatocellular carcinoma (HepG2) cell lines were characterized *in vitro* (AK *et al*., 2017; Kumar *et al*., 2017). Besides, the 2-aminoimidazolone **III** showed great potency toward HCT116 and H460 cell lines (IC_{50} of 1 and 2 µM, respectively) (Dražić *et al*., 2015) (Fig. 1).

Imidazolones linked to chalcone moiety were shown to have excellent antioxidant and anticancer activities on various cell lines (Mahapatra *et al*., 2015; Mai *et al*., 2014; Ramaiah *et al*., 2011), like compound **IV** (Kamal *et al*., 2010) that possess great

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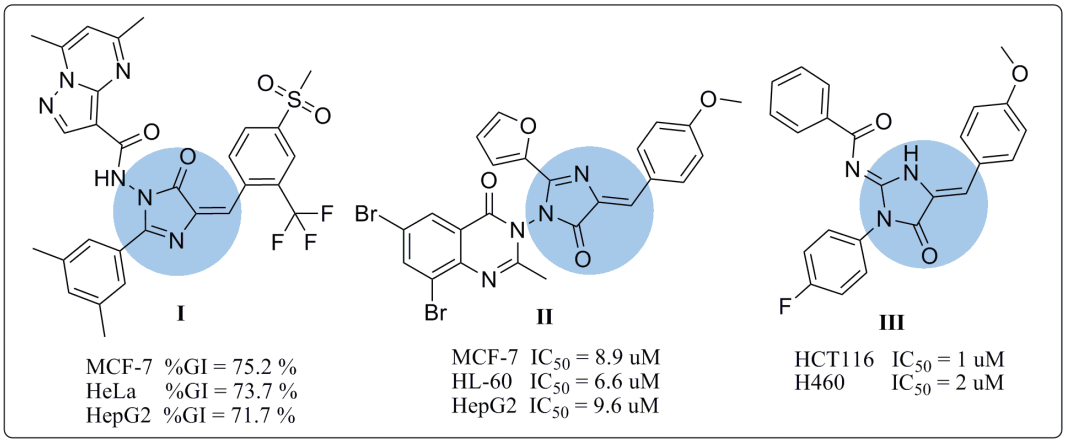


Figure 1. Reported antitumor agents with imidazolone nucleus.

potency against HCT116 and MCF-7 cell lines with GI_{50} values of 1.40 and 1.55 µM, respectively. It has been proved that imidazolone hybridized with chalcone moiety displayed potential antineoplastic activity through different biological mechanisms (Nasir Abbas Bukhari *et al*., 2013). Certain derivatives cause distinctive DNA damage specifically at telomeres and subsequently cause apoptosis (Ramaiah *et al*., 2011). Further mechanisms included assorted protein kinase inhibition (CDK, PLK1, MK-2, and Eg5), Topo (I, II), as well as microtubular inhibition (Akhtar *et al*., 2017). Moreover, they show p21 up-regulation and control damage pathway of DNA (Ramaiah *et al*., 2011; Yin *et al*., 2016).

Based on the preceded data, we aim at functionalizing imidazolone-based scaffold in the design and synthesis of novel derivatives to be evaluated as anticancer agents, and exploring the plausible mechanisms by which they could exert such activity. In the current study, compound **IV** was chosen as the lead compound to design the new imidazolone derivatives. Rational design depended on the maintenance of the basic structural features characterizing the lead compound, mainly the imidazolone core, by replacing the 2-imidazolone ring by 4-substituted-5-imidazolone in all the designed series. Besides, optimizing the whole scaffold throughout either substitution of certain groups or replacement with various moieties, including either five or six-membered heterocyclic moieties, was accomplished to investigate the potential effect on anti-tumoral activity (Fig. 2).

MATERIALS AND METHODS

Melting points (°C) were measured with Fisher–Johns melting point apparatus and are uncorrected. Microanalyses (C, H, and N) were performed in the Microanalytical unit, Cairo University, and all the results were within ±0.5. IR spectra were recorded on Thermo Fisher Scientific Nicolet IS10 spectrometer (ν in cm^{-1}) using KBr disk at Faculty of Pharmacy, Mansoura University. Mass MS (EI) *m/z* analyses were performed on Thermo Scientific DCQII at Faculty of Science, Mansoura University. ^{1}H and ^{13}C-NMR spectra were achieved in dimethyl sulfoxide (DMSO)-d_6 on ASCEND spectrometer (400 MHz) Bruker using TMS (chemical shifts in ppm, δ units) at Georgia State University USA, Kafrelsheikh University, and at Mansoura University. Reaction times were determined using TLC on Silica gel plates 60 F_{254} (E. Merk), and UV (366, 245 nm) was used to visualize the spots.

2-(4-Fluorobenzoylamino) acetic acid (1) was prepared according to the reported procedure. Yield 75% (reported 84%) and mp 168°C–170°C (reported 167°C–169°C) (El-Araby *et al*., 2012).

General procedure for synthesis of compounds 2 and 3

A mixture of compound **1** (1 mmol, 0.197 g), the appropriate heterocyclic aldehyde (1 mmol), and freshly-fused sodium acetate (0.049 g) in acetic anhydride (1.97 ml) was refluxed overnight at 130°C. The obtained crystals were filtered, washed with cold water, followed by aq. EtOH and recrystallized from EtOH.

*2-(4-Fluorophenyl)-4-(furan-2-ylmethylene)oxazol-5(4*H*)-one (2)*

Yield 68%; mp 165°C–167°C; ^{1}H NMR (DMSO d_6): 6.87–7.02 (*m*, 3*H*, Ar-H), 7.44 (*s*, 1*H*, olefinic-H), and 7.61–7.93 (*m*, 4*H*, Ar-H); MS (EI) m/z %: 257 (45.5, M^+); IR cm^{-1}: 1,775 (C=O), 1,650 (C=N); Anal. calcd for $C_{14}H_8FNO_3$: C, 65.37; H, 3.13; and N, 5.45. Found: C, 65.29; H, 3.02; and N, 5.32.

*(*E*)-2-(4-Fluorophenyl)-4-(thiophen-2-ylmethylene)oxazol-5(4*H*)-one (3)*

Yield 70%; mp 173°C–175°C; ^{1}H NMR (DMSO d_6): 7.16–7.28 (*m*, 3*H*, Ar-H), 7.48 (*s*, 1*H*, olefinic-H), and 7.54–7.76 (*m*, 4*H*, Ar-H); MS (EI) m/z %: 274 (2.6, $M^+ + 1$), 273 (4.2, M^+); IR cm^{-1}: 1,780 (C=O), 1,656 (C=N); Anal. calcd for $C_{14}H_8FNO_2S$: C, 61.53; H, 2.95; and N, 5.13. Found: C, 61.11; H, 2.45; and N, 5.11.

General procedure for synthesis of compounds 4–17

A mixture of compound **2** or **3** (1 mmol), the appropriate aromatic amine (1 mmol), and freshly-fused Na-acetate (0.3 g) in glacial acetic acid (7 ml) was refluxed overnight in boiling water bath, maintaining continuous stirring. The product was filtered, then washed with aq. EtOH, and recrystallized from EtOH.

*(*E*)-2-(4-Fluorophenyl)-4-(furan-2-ylmethylene)-1-phenyl-1*H*-imidazol-5(4*H*)-one (4)*

Yield 68%; mp 148°C–150°C; ^{1}H NMR (DMSO d_6): 6.85 (*s*, 1*H*, olefinic-H), 7.15–7.25 (*m*, 3*H*, Ar-H), 7.35–7.43 (*m*, 5*H*, Ar-H), and 7.75–8.15 (*m*, 4*H*, Ar-H); **MS** (EI) m/z %: 332 (M^+), 333 ($M^+ + 1$); **IR** cm^{-1}: 1,773 (C=O), 1,651 (C=N); Anal. calcd for $C_{20}H_{13}FN_2O_2$: C, 72.28; H, 3.94; and N, 8.43. Found: C, 72.19; H, 3.86; and N, 8.25.

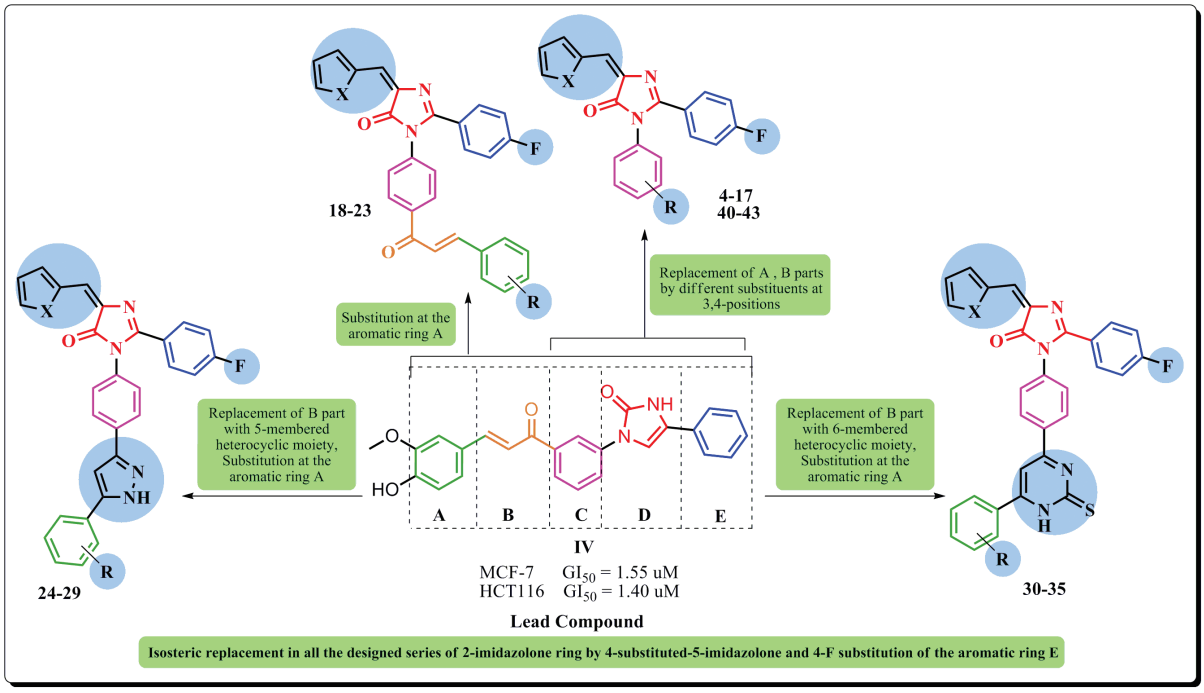


Figure 2. Molecular design of new imidazolones as anticancer agents based on structural modification of the lead compound **IV.**

*(E)-1-(4-Bromophenyl)-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (5)*

Yield 60%; mp 135°C–137°C; ^{1}H NMR (DMSO d_6): 7.15 (*s*, 1*H*, olefinic-H), 7.35–7.78 (*m*, 3*H*, Ar-H), 7.85–8.10 (*m*, 4*H*, Ar-H), and 8.25–8.65 (*m*, 4*H*, Ar-H); **MS** (EI) m/z %: 410 (M^+), 411 (M^+ + 1); **IR** cm^{-1}: 1,768 (C=O), 1,645 (C=N); Anal. calcd for $C_{20}H_{12}BrFN_2O_2$: C, 5841; H, 2.94; and N, 6.81. Found: C, 58.36; H, 2.89; and N, 6.75.

*(E)-2-(4-Fluorophenyl)-4-(furan-2-ylmethylene)-1-(4-methylphenyl)-1*H*-imidazol-5(4*H*)-one (6)*

Yield 55% ; mp 130°C–132°C; ^{1}H NMR (DMSO d_6): 2.45 (*s*, 3*H*, CH_3), 6.85 (*s*, 1*H*, olefinic-H), 7.18–7.35 (*m*, 3*H*, Ar-H), 7.45–7.64 (*m*, 4*H*, Ar-H), and 7.85–8.15 (*m*, 4*H*, Ar-H); **MS** (EI) m/z %: 346 (M^+), 347 (M^+ + 1); **IR** cm^{-1}: 1,759 (C=O), 1,647 (C=N); Anal. calcd for $C_{21}H_{15}FN_2O_2$: C, 72.82; H, 4.37; and N, 8.09. Found: C, 72.75; H, 4.25; and N, 8.15.

*(E)-2-(4-Fluorophenyl)-4-(furan-2-ylmethylene)-1-(3-nitrophenyl)-1*H*-imidazol-5(4*H*)-one (7)*

Yield 70%; mp 145°C–147°C; ^{1}H NMR (DMSO d_6): 7.15 (*s*, 1*H*, olefinic-H), 7.23–7.36 (*m*, 3*H*, Ar-H), 7.65–7.82 (*m*, 4*H*, Ar-H), and 8.43–8.77 (*m*, 4*H*, Ar-H); **MS** (EI) m/z %: 377 (M^+), 378 (M^+ + 1); **IR** cm^{-1}: 1,757 (C=O), 1,644 (C=N); Anal. calcd for $C_{20}H_{12}FN_3O_4$: C, 63.66; H, 3.21; and N, 11.14. Found: C, 63.54; H, 3.15; and N, 11.20.

*(E)-1-(3-Acetylphenyl)-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (8)*

Yield 65%; mp 125°C–127°C; ^{1}H NMR (DMSO d_6): 2.35 (*s*, 3*H*, CH_3), 7.13 (*s*, 1*H*, olefinic-H), 7.18–7.37 (*m*, 3*H*, Ar-H), 7.45–7.87 (*m*, 4*H*, Ar-H), and 7.95–8.15 (*m*, 4*H*, Ar-H); **MS** (EI) m/z %: 374 (M^+), 375 (M^+ + 1); **IR** cm^{-1}: 1,750 (C=O), 1,652 (C=N); Anal. calcd for $C_{22}H_{15}FN_2O_3$: C, 70.58; H, 4.04; and N, 7.37. Found: C, 70.45; H, 4.02; and N, 7.37.

*(E)-1-(4-Acetylphenyl)-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (9)*

Yield 70%; mp 130°C–132°C; ^{1}H NMR (DMSO d_6): 2.54 (*s*, 3*H*, CH_3), 7.12 (*s*, 1*H*, olefinic-H), 7.23–7.36 (*m*, 4*H*, Ar-H), and 7.76–7.89 (*m*, 4*H*, Ar H); **MS** (EI) *m/z* %: 374 (M^+), 375 (M^+ + 1); **IR** cm^{-1}: 1,761 (C=O) imidazolone, 1,685 (C=O) acetyl, 1,658 (C=N); Anal. calcd for $C_{22}H_{15}FN_2O_3$: C, 70.58; H, 4.04; and N, 7.37. Found: C, 70.48; H, 4.02; and N, 7.32.

*(E)-Ethyl 4-[2-(4-fluorophenyl)]-4-(furan-2-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)benzoate (10)*

Yield 65%; mp 170°C–173°C; ^{1}H NMR (DMSO d_6): 1.50 (*t*, 3*H*, CH_3), 4.35 (*q*, 2*H*, CH_2), 7.15 (*s*, 1*H*, olefinic-H), 7.20–7.35 (*m*, 3*H*, Ar-H), 7.44–7.67 (*m*, 4*H*, Ar-H), and 7.78–7.98 (*m*, 4*H*, Ar-H); **MS** (EI) m/z %: 404 (M^+), 405(M^+ + 1); **IR** cm^{-1}: 1,765 (C=O) imidazolone, 1,727 (C=O) ester, 1,657 (C=N); Anal. calcd for $C_{23}H_{17}FN_2O_4$: C, 68.31; H, 4.24; and N, 6.93. Found: C, 68.23; H, 4.18; and N, 6.85.

*(E)-2-(4-Fluorophenyl)-1-phenyl-4-(thiophen-2-ylmethylene)-1H-imidazol-5(4*H*)-one (11)*

Yield 71%; mp 100°C–102°C; ^{1}H NMR (DMSO d_6): 7.14 (*s*, 1*H*, olefinic H), 7.23–7.34 (*m*, 3*H*, Ar-H), 7.45–7.58 (*m*, 5*H*, Ar-H), and 7.75–8.15 (*m*, 4*H*, Ar-H); **MS** (EI) *m/z* %: 348 (M^+), 349 (M^+ + 1); **IR** cm^{-1}: 1,767 (C=O), 1,662 (C=N); Anal. calcd for $C_{20}H_{13}FN_2OS$: C, 68.95; H, 3.76; and N, 8.04. Found: C, 68.85; H, 3.65; and N, 8.02.

*(*E*)-1-(4-Bromophenyl)-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (12)*

Yield 65%; mp 140°C–142°C; ^{1}H NMR (DMSO d_6): 7.19 (*s*, 1*H*, olefinic H), 7.43–7.78 (*m*, 3*H*, Ar-H), 7.87–8.10 (*m*, 4*H*, Ar-H), and 8.36–8.65 (*m*, 4*H*, Ar-H); **MS (**EI) *m/z* %: 425 (M^+), 426 ($M^+ + 1$); **IR** cm^{-1}: 1,762 (C=O), 1,671 (C=N); Anal. calcd for $C_{20}H_{12}BrFN_2OS$: C, 56.22; H, 2.83; and N, 6.56. Found: C, 56.15; H, 2.74; and N, 6.45.

*(*E*)-2-(4-Fluorophenyl)-4-(thiophen-2-ylmethylene)-1-(4-methylphenyl)-1*H*-imidazol-5(4*H*)-one (13)*

Yield 75% ; mp 163°C–167°C; ^{1}H NMR (DMSO d_6): 2.35 (*s*, 3*H*, CH_3), 6.88 (*s*, 1*H*, olefinic), 7.23–7.35 (*m*, 3*H*, Ar-H), 7.56–7.64 (*m*, 4*H*, Ar-H), and 7.85–8.12 (*m*, 4*H*, Ar-H); **MS (**EI) *m/z* %: 362 (M^+), 363 ($M^+ + 1$); **IR** cm^{-1}: 1,762 (C=O), 1,669 (C=N); Anal. calcd for $C_{21}H_{15}FN_2OS$: C, 69.59; H, 4.17; and N, 7.73. Found: C, 69.4; H, 4.20; and N, 7.67.

*(*E*)-2-(4-Fluorophenyl)-1-(3-nitrophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (14)*

Yield 68%; mp 142°C–145°C; ^{1}H NMR (DMSO d_6): 7.15 (*s*, 1*H*, olefinic H), 7.23–7.45 (*m*, 3*H*, Ar-H), 7.65–7.82 (*m*, 4*H*, Ar-H), and 8.36–8.77 (*m*, 4*H*, Ar-H); **MS (**EI) *m/z* %: 393 (M^+), 394 ($M^+ + 1$); **IR** cm^{-1}: 1,765 (C=O), 1,666 (C=N); Anal. calcd for $C_{20}H_{12}FN_3O_3S$: C, 61.06; H, 3.07; and N, 10.68. Found: C, 61.15; H, 3.11; and N, 10.54.

*(*E*)-1-(3-Acetylphenyl)-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (15)*

Yield 71%; mp 120°C–122°C; ^{1}H NMR (DMSO d_6): 2.53 (*s*, 3*H*, CH_3), 6.98 (*s*, 1*H*, olefinic-H), 7.02–7.14 (*m*, 3*H*, Ar H), 7.34–7.56 (*m*, 4*H*, Ar H), and 7.75–7.91 (*m*, 4*H*, Ar H); **MS (**EI) *m/z* %: 390 (M^+), 391 ($M^+ + 1$); **IR** cm^{-1}: 1,768 (C=O), 1,684 (C=O) acetyl, 1,657 (C=N); Anal. calcd for $C_{22}H_{15}FN_2O_2S$: C, 67.68; H, 3.87; and N, 7.18. Found: C, 67.54; H, 3.75; and N, 7.11.

*(*E*)-1-(4-Acetylphenyl)-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (16)*

Yield 75%; mp 132°C–134°C; ^{1}H NMR (DMSO d_6): 2.52 (*s*, 3*H*, CH_3), 6.92 (*s*, 1*H*, olefinic-H), 7.23–7.41 (*m*, 8*H*, Ar-H), and 7.93–8.11 (*m*, 3*H*, Ar-H); ^{13}C NMR (DMSO d_6): δ 20.7, 89.4, 100.6, 110.5, 117.0, 120.3, 122.5, 127.5, 130.5, 132.3, 137.3, 140.8, 144.6, 148.3, 153.9, 156.2, 158.0, 166.0, 169.6, 177.6, and 190.1; **MS (**EI) *m/z* %: 390 (M^+), 391 ($M^+ + 1$); **IR** cm^{-1}: 1,768 (C=O) imidazolone, 1,687 (C=O) acetyl, 1,655 (C=N); Anal. calcd for $C_{22}H_{15}FN_2O_2S$: C, 67.68; H, 3.87; and N, 7.18. Found: C, 67.58; H, 3.45; and N, 7.09.

*(*E*)-Ethyl 4-[2-(4-fluorophenyl)-5-oxo-4-(thiophen-2-ylmethylene)-4,5-dihydro-1*H*-imidazol-1-yl]benzoate (17)*

Yield 69%; mp 167°C–170°C; ^{1}H NMR (DMSO d_6): 1.21 (*t*, 3*H*, CH_3), 4.27 (*q*, 2*H*, CH_2), 6.96 (*s*, 1*H*, olefinic-H), 7.08–7.28 (*m*, 4*H*, Ar H), and 7.43–7.98 (*m*, 7*H*, Ar H); ^{13}CNMR (DMSO d_6): δ 10.7, 25.4, 100.2, 113.5, 114.3, 117.4, 118.5, 120.6, 123.7, 124.2, 125.7, 126.5, 127.4, 130.3, 133.5, 142.3, 147.4, 152.7, 153.9, 155.3, 160.4, 166.7, and 200.0, **MS (**EI) *m/z* %: 420 (17.5, M^+); **IR** cm^{-1}: 1,759 (C=O) imidazolone, 1,725 (C=O) ester, 1,649 (C=N); Anal. calcd for $C_{23}H_{17}FN_2O_3S$: C, 65.70; H, 4.08; and N, 6.66. Found: C, 65.45; H, 4.02; and N, 6.55.

General procedure for synthesis of compounds 18–23

A mixture of compound **9** or **19** (1 mmol) and different aromatic aldehydes (1 mmol) was stirred in ethanolic sodium hydroxide solution (5%, 10 ml) in ice bath for 4 hours, then the resulted precipitate was filtered, washed with aq. EtOH, and recrystallized from EtOH.

*(*E*)-2-(4-Fluorophenyl)-4-(furan-2-ylmethylene)-1-[4-(3-phenylprop-2-enoyl)phenyl]-1*H*-imidazol-5(4*H*)-one (18)*

Yield 50%; mp 118°C–120°C; ^{1}H NMR (DMSO d_6): 6.89 (*s*, 1*H*, oleifinic H), 7.18–7.23 (*m*, 3*H*, Ar-H), 7.50 (*d*, 1*H*, C<u>H</u>=CH), 7.78 (*d*, 1*H*, CH=C<u>H</u>), 8.12–8.23 (*m*, 4*H*, Ar-H), 8.35–8.47 (*m*, 4*H*, Ar-H), and 8.76–9.11 (*m*, 5*H*, Ar-H); **MS (**EI) *m/z* %: 462.14 (M^+), 463 ($M^+ + 1$); **IR** cm^{-1}: 1,765 (C=O), 1,655 (C=N); Anal. calcd for $C_{29}H_{19}FN_2O_3$: C, 75.32; H, 4.14; and N, 6.06. Found: C, 75.32; H, 4.25; and N, 6.15.

*(*E*)-{4-[3-(3-Bromophenyl)prop-2-enoyl]phenyl}-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (19)*

Yield 65%; mp 115°C–117°C; ^{1}H NMR (DMSO d_6): 7.14 (*s*, 1*H*, oleifinic H), 7.32–7.45 (*m*, 3*H*, Ar-H), 7.64 (*d*, 1*H*, C<u>H</u>=CH), 7.85 (*d*, 1*H*, CH=C<u>H</u>), 8.32–8.45 (*m*, 4*H*, Ar-H), 8.67–8.98 (*m*, 4*H*, Ar-H), and 9.00–9.10 (*m*, 4*H*, Ar-H); **MS (**EI) *m/z* %: 540 **(**M^+), 541 ($M^+ + 1$); **IR** cm^{-1}: 1,750 (C=O), 1,661 (C=N); Anal. calcd for $C_{29}H_{18}BrFN_2O_3$: C, 64.34; H, 3.35; and N, 5.17. Found: C, 64.25; H, 3.15; and N, 5.26.

*(*E*)-{4-[3-(4-Chlorophenyl)prop-2-enoyl]phenyl}-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (20)*

Yield 69%; mp 120°C–122°C; ^{1}H NMR (DMSO d_6): 7.04 (*s*, 1*H*, oleifinic-H), 7.27–7.36 (*m*, 3*H*, Ar-H), 7.78 (*d*, 1*H*, C<u>H</u>=CH), 7.98 (*d*, 1*H*, CH=C<u>H</u>), 8.15–8.34 (*m*, 4*H*, Ar-H), 8.48–8.67 (*m*, 4*H*, Ar-H), and 8.78–9.89 (*m*, 4*H*, Ar-H); **MS (**EI) *m/z* %: 496.10 (M^+), 497 ($M^+ + 1$); **IR** cm^{-1}: 1,755 (C=O), 1,660 (C=N); Anal. calcd for $C_{29}H_{18}ClFN_2O_3$: C, 70.09; H, 3.65; and N, 5.64. Found: C, 70.45; H, 3.45; and N, 5.87.

*(*E*)-2-(4-Fluorophenyl)-4-(thiophen-2-ylmethylene)-1-[4-(3-phenylprop-2-enoyl)phenyl]-1*H*-imidazol-5(4*H*)-one (21)*

Yield 55%; mp 125°C–127°C; ^{1}H NMR (DMSO d_6): 7.36 (*s*, 1*H*, oleifinic-H), 7.43 (*d*, 1*H*, C<u>H</u>=CH), 8.16 (*d*, 1*H*, CH=C<u>H</u>), 8.32–8.45 (*m*, 4*H*, Ar-H), 8.67–8.98 (*m*, 4*H*, Ar-H), and 9.01–9.10 (*m*, 5*H*, Ar-H); **MS** (EI) *m/z* %: 478.54 (M^+); **IR** cm^{-1}: 1,757 (C=O), 1,656 (C=N); Anal. calcd for $C_{29}H_{19}FN_2O_2S$: C, 72.79; H, 4; and N, 5.85. Found: C, 72.45; H, 4.15; and N, 5.45.

*(*E*)-{4-[3-(3-Bromophenyl)prop-2-enoyl]phenyl}-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (22)*

Yield 60%; mp 114°C–116°C; ^{1}H NMR (DMSO d_6): 7.36 (*s*, 1*H*, oleifinic-H), 7.59 (*d*, 1*H*, C<u>H</u>=CH), 8.23 (*d*, 1*H*, CH=C<u>H</u>), 8.33–8.46 (*m*, 4*H*, Ar-H), 8.68–8.88 (*m*, 4*H*, Ar-H), and 9.00–9.12 (*m*, 4*H*, Ar-H); **MS (**EI) *m/z* %: 557.43 (M^+); **IR** cm^{-1}:

1,761 (C=O), 1,650 (C=N); Anal. calcd for $C_{29}H_{18}BrFN_2O_2S$: C, 62.48; H, 3.25; and N, 5.03. Found: C, 62.35; H, 3.15; and N, 5.15.

*(*E*)-{4-[3-(4-Chlorophenyl)prop-2-enoyl]phenyl}-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (23)*

Yield 67%; mp 124°C–126°C; ^{1}H NMR (DMSO d_6): 7.09 (*s*, 1*H*, olefinic-H), 7.87 (*d*, 1*H*, C<u>H</u>=CH), 8.43 (*d*, 1*H*, CH=C<u>H</u>), 8.32–8.45 (*m*, 4*H*, Ar-H), 8.67–8.98 (*m*, 4*H*, Ar-H), and 9.02–9.10 (*m*, 4*H*, Ar-H); **MS (**EI) *m/z* %: 512.98 (M^+); **IR** cm^{-1}: 1,755 (C=O), 1,657 (C=N); Anal. calcd for $C_{29}H_{18}ClFN_2O_2S$: C, 67.9; H, 3.54; and N, 5.46. Found: C, 67.85; H, 3.34; and N, 5.67.

General procedure for synthesis of compounds 24–29

A mixture of the appropriate chalcone **18**–**23** (1mmol) and hydrazine hydrate 98% (1 mmol, 0.03 ml) in abs. EtOH (5 ml) was refluxed overnight followed by evaporation of the solvent, and then the product was neutralized with dil. HCl. The precipitated product was filtered and dried after washing thoroughly with water.

*(*E*)-2-(4-Fluorophenyl)-4-(furan-2-ylmethylene)-1-[4-(5-phenyl-1*H*-pyrazol-3-yl)phenyl]-1*H*-imidazol-5(4*H*)-one (24)*

Yield 50%; mp 217°C–220°C; ^{1}H NMR (DMSO d_6): 6.51 (*s*, 1*H*, pyrazole-H), 6.89 (*s*, 1*H*, olefinic-H), 7.12–7.32 (*m*, 3*H*, Ar-H), 7.84–8.11 (*m*, 4*H*, Ar-H), 8.38–8.76 (*m*, 4*H*, Ar-H), 8.89–9.10 (*m*, 5*H*, Ar-H), and 12.45 (*s*, 1*H*, NH); ^{13}CNMR (DMSO d_6): δ 89.5, 110.4, 112.2, 114.5, 115.4, 117.7, 119.5, 120.5, 121.7, 122.9, 123.4, 125.4, 126.6, 127.9, 128.5, 129.8, 130.0, 132.4, 135.0, 136.4, 138.4, 139.6, 144.7, 146.3, 148.5, 152.0, 153.9, 166.4, and 170.5; **MS** (EI) *m/z* %: 474 (M^+), 475 (M^+ + 1); **IR** cm^{-1}: 3,340 (NH), 1,750 (C=O), 1,661 (C=N); Anal. calcd for $C_{29}H_{19}FN_4O_2$: C, 73.41; H, 4.04; and N, 11.81. Found: C, 73.35; H, 4.15; and N, 11.72.

*(*E*)-1-{4-[5-(3-Bromophenyl)-1*H*-pyrazol-3-yl]phenyl}-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (25)*

Yield 55%; mp 198°C–200°C; ^{1}H NMR (DMSO d_6): 6.87 (*s*, 1*H*, pyrazole-H), 7.14 (*s*, 1*H*, olefinic-H), 7.24–7.65 (*m*, 3*H*, Ar-H), 7.95–8.23 (*m*, 4*H*, Ar-H), 8.48–8.76 (*m*, 4*H*, Ar-H), 8.89–9.10 (*m*, 4*H*, Ar-H), 12.45 (*s*, 1*H*, NH), and 12.64 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 552 (M^+), 553 (M^++1); **IR** cm^{-1}: 3,410 (NH), 1,759 (C=O), 1,655 (C=N); Anal. calcd for $C_{29}H_{18}BrFN_4O_2$: C, 62.94; H, 3.28; and N, 10.12. Found: C, 62.87; H, 3.15; and N, 10.15.

*(*E*)-1-{4-[5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl]phenyl}-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (26)*

Yield 56%; mp 158°C–160°C; ^{1}H NMR (DMSO d_6): 7.04 (*s*, 1*H*, pyrazole-H), 7.23 (*s*, 1*H*, olefinic-H), 7.35–7.75 (*m*, 3*H*, Ar-H), 7.98–8.34 (*m*, 4*H*, Ar-H), 8.48–8.76 (*m*, 4*H*, Ar-H), 8.89–9.10 (*m*, 4*H*, Ar-H), 12.45 (*s*, 1*H*, NH), 12.64 (*s*, 1*H*, NH), and 12.77 (*s*, 1*H*, NH); ^{13}CNMR (DMSO d_6): δ 87.5, 111.4, 112.3, 113.2, 115.9, 116.9, 118.5, 119.5, 120.8, 121.9, 124.7, 125.9, 126.5, 127.9, 128.3, 129.5, 130.4, 132.4, 135.0, 137.4, 138.4, 139.6, 143.7, 145.3, 147.5, 152.0, 153.9, 166.4, and 170.5; **MS** (EI) *m/z* %: 508 (M^+), 509 (M^++1); **IR** cm^{-1}: 3,310 (NH), 1,755 (C=O), 1,661 (C=N); Anal. calcd for $C_{29}H_{18}ClFN_4O_2$: C, 68.44; H, 3.56; and N, 11.01. Found: C, 68.65; H, 3.45; and N, 11.15.

*(*E*)-2-(4-Fluorophenyl)-1-[4-(5-phenyl-1*H*-pyrazol-3-yl)phenyl]-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (27)*

Yield 56%; mp 200°C–202°C; ^{1}H NMR (DMSO d_6): 6.45 (*s*, 1*H*, pyrazole-H), 7.12 (*s*, 1*H*, olefinic-H), 7.23–7.56 (*m*, 3*H*, Ar-H), 7.84–8.11 (*m*, 4*H*, Ar-H), 8.38–8.76 (*m*, 4*H*, Ar-H), 8.89–9.10 (*m*, 5*H*, Ar-H), 12.45 (*s*, 1*H*, NH), and 12.45 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 490 (M^+), 491 (M^+ + 1); **IR** cm^{-1}: 3,410 (NH), 1,754 (C=O), 1,656 (C=N); Anal. calcd for $C_{29}H_{19}FN_4OS$: C, 71; H, 3.9; and N, 11.42. Found: C, 71.15; H, 3.75; and N, 11.32.

*(*E*)-1-{4-[5-(3-Bromophenyl)-1*H*-pyrazol-3-yl]phenyl}-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (28)*

Yield 59%; mp 208°C–210°C; ^{1}H NMR (DMSO d_6): 6.65 (*s*, 1*H*, pyrazole-H), 6.87 (*s*, 1*H*, olefinic-H), 7.24–7.65 (*m*, 3*H*, Ar-H), 7.95–8.23 (*m*, 4*H*, Ar-H), 8.48–8.76 (*m*, 4*H*, Ar-H), 8.89–9.10 (*m*, 4*H*, Ar-H), 12.45 (*s*, 1*H*, NH), 12.64 (*s*, 1*H*, NH), and 12.64 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 569.45 (M^+); **IR** cm^{-1}: 3,330 (NH), 1,758 (C=O), 1,655 (C=N); Anal. calcd for $C_{29}H_{18}BrFN_4OS$: C, 61.17; H, 3.19; and N, 9.84. Found: C, 61.23; H, 3.15; and N, 9.78.

*(*E*)-1-{4-[5-(4-Chlorophenyl)-1H-pyrazol-3-yl]phenyl}-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (29)*

Yield 58%; mp 160°C–162°C; ^{1}H NMR (DMSO d_6): 7.04 (*s*, 1*H*, pyrazole-H), 7.23 (*s*, 1*H*, olefinic-H), 7.35–7.75 (*m*, 3*H*, Ar-H), 7.95–8.23 (*m*, 4*H*, Ar-H), 8.48–8.76 (*m*, 4*H*, Ar-H), 8.89–9.10 (*m*, 4*H*, Ar-H), 12.45 (*s*, 1*H*, NH), 12.64 (*s*, 1*H*, NH), and 12.77 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 524 (M^+), 525 (M^+ + 1); **IR** cm^{-1}: 3,350 (NH), 1,757 (C=O), 1,662 (C=N); Anal. calcd for $C_{29}H_{18}ClFN_4OS$: C, 66.35; H, 3.46; and N, 10.67. Found: C, 66.15; H, 3.24; and N, 10.87.

General procedure for synthesis of compounds 30–35

To the solution of thiourea (1 mmol, 0.076 g) and sodium ethoxide in ethanol (5 ml), the appropriate chalcone**18–23** (1 mmol) was added. The mixture was refluxed overnight. After cooling and evaporation of the solvent, the mixture was neutralized with dil. HCl and the precipitate was filtered and washed thoroughly with water.

*(*E*)-2-(4-Fluorophenyl)-4-(furan-2-ylmethylene)-1-[4-(6-phenyl-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)]-1*H*-imidazol-5(4*H*)-one (30)*

Yield 53%; mp 215°C–217°C; ^{1}H NMR (DMSO d_6): 6.23 (*s*, 1*H*, pyrazole-H), 7.13 (*s*, 1*H*, olefinic-H), 7.34–7.65 (*m*, 3*H*, Ar-H), 7.75–7.89 (*m*, 4*H*, Ar-H), 8.15–8.23 (*m*, 4*H*, Ar-H), 8.38–8.45 (*m*, 5*H*, Ar-H), 12.45 (*s*, 1*H*, NH), 12.64 (*s*, 1*H*, NH), and 13.65 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 518 (M^+), 519 (M^+ + 1);

IR cm^{-1}: 3,310 (NH), 1,760 (C=O), 1,654 (C=N); Anal. calcd for $C_{30}H_{19}FN_4O_2S$: C, 69.48; H, 3.69; and N, 10.08. Found: C, 69.54; H, 3.59; and N, 10.76.

*(*E*)-1-{4-[6-(3-Bromophenyl)-2-sulfanylidene-1,2-dihydropyrimidin-4-yl]phenyl}-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (31)*

Yield 56%; mp 218°C–220°C; ^{1}H NMR (DMSO d_6): 6.65 (*s*, 1*H*, pyrazole-H), 7.25 (*s*, 1*H*, olefinic-H), 7.34–7.78 (*m*, 3*H*, Ar-H), 7.89–8.14 (*m*, 4*H*, Ar-H), 8.33–8.68 (*m*, 4*H*, Ar-H), 8.79–8.89 (*m*, 4*H*, Ar-H), and 13.45 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 596 (M^+), 597 ($M^+ + 1$); **IR** cm^{-1}: 3,310 (NH), 1,758 (C=O), 1,652 (C=N); Anal. calcd for $C_{30}H_{18}BrFN_4O_2S$: C, 60.31; H, 3.04; and N, 9.38. Found: C, 60.25; H, 3.54; and N, 9.48.

*(*E*)-1-{4-[6-(4-Chlorophenyl)-2-sulfanylidene-1,2-dihydropyrimidin-4-yl]phenyl}-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (32)*

Yield 56%; mp 162°C–164°C; ^{1}H NMR (DMSO d_6): 7.02 (*s*, 1*H*, pyrazole-H), 7.35 (*s*, 1*H*, olefinic-H), 7.44–7.78 (*m*, 3*H*, Ar-H), 7.98–8.17 (*m*, 4*H*, Ar-H), 8.37–8.58 (*m*, 4*H*, Ar-H), 8.79–8.89 (*m*, 4*H*, Ar-H), and 13.45 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 552 (M^+), 553 ($M^+ + 1$); **IR** cm^{-1}: 3,310 (NH), 1,762 (C=O), 1,659 (C=N); Anal. calcd for $C_{30}H_{18}ClFN_4O_2S$: C, 65.16; H, 3.28; and N, 10.13. Found: C, 65.25; H, 3.15; and N, 10.27.

*(*E*)-2-(4-Fluorophenyl)-1-[4-(6-phenyl-2-sulfanylidene-1,2-dihydropyrimidin-4-yl)phenyl]-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (33)*

Yield 55%; mp 200°C–203°C; ^{1}H NMR (DMSO d_6): 6.23 (*s*, 1*H*, pyrazole-H), 7.13 (*s*, 1*H*, olefinic-H), 7.34–7.65 (*m*, 3*H*, Ar-H), 7.75–7.89 (*m*, 4*H*, Ar-H), 8.15–8.23 (*m*, 4*H*, Ar-H), 8.38–8.45 (*m*, 5*H*, Ar-H), and 13.65 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 534 (M^+), 544 ($M^+ + 1$); **IR** cm^{-1}: 3,320 (NH), 1,757 (C=O), 1,665 (C=N); Anal. calcd for $C_{30}H_{19}FN_4OS_2$: C, 67.4; H, 3.58; and N, 10.48. Found: C, 67.65; H, 3.45; and N, 10.35.

*(*E*)-1-{4-[6-(3-Bromophenyl)-2-sulfanylidene-1,2-dihydropyrimidin-4-yl]phenyl}-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (34)*

Yield 59%; mp 215°C–217°C; ^{1}H NMR (DMSO d_6): 6.65 (*s*, 1*H*, pyrazole-H), 7.25 (*s*, 1*H*, olefinic-H), 7.34–7.78 (*m*, 3*H*, Ar-H), 7.89–8.14 (*m*, 4*H*, Ar-H), 8.33–8.68 (*m*, 4*H*, Ar-H), 8.79–8.89 (*m*, 4*H*, Ar-H), and 13.45 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 612 (M^+), 613 ($M^+ + 1$); **IR** cm^{-1}: 3,310 (NH), 1,753 (C=O), 1,651 (C=N); Anal. calcd for $C_{30}H_{18}BrFN_4OS$: C, 58.73; H, 2.96; and N, 9.13. Found: C, 58.65; H, 2.45; and N, 9.15.

*(*E*)-1-{4-[6-(4-Chlorophenyl)-2-sulfanylidene-1,2-dihydropyrimidin-4-yl)]phenyl}-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (35)*

Yield 58%; mp 168°C–170°C; ^{1}H NMR (DMSO d_6): 7.02 (*s*, 1*H*, pyrazole-H), 7.35 (*s*, 1*H*, olefinic-H), 7.44–7.78 (*m*, 3*H*, Ar-H), 7.98–8.17 (*m*, 4*H*, Ar-H), 8.37–8.58 (*m*, 4*H*, Ar-H), 8.79–8.89 (*m*, 4*H*, Ar-H), and 13.45 (*s*, 1*H*, NH); **MS** (EI) *m/z* %: 568 (M^+), 569 ($M^+ + 1$); **IR** cm^{-1}: 3,310 (NH), 1,760 (C=O), 1,662 (C=N); Anal. calcd for $C_{30}H_{18}ClFN_4OS$: C, 67.10; H, 3.38; and N, 10.43. Found: C, 67.23; H, 3.28; and N, 10.41.

General procedure for synthesis of compounds 36–39

A solution of the appropriate acetyl derivative (**8**, **9**, **15**, **16**) (1 mmol) in glacial acetic acid (15 ml) was heated to 80°C–90°C with stirring. Bromine (1 mmol, 0.159 g) was added drop by drop over 30 minutes to the hot mixture with stirring at 80°C–90°C. After completion of bromine addition, the mixture continued to stir at room temperature for further 1 hour till evolution of hydrogen bromide gas was ceased. Then, it was poured over ice where the formed product was filtered, washed thoroughly with water, and recrystallized from 70% EtOH.

*(*E*)-1-[3-(2-Bromoacetyl)phenyl]-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (36)*

Yield 69%; mp 133°C–137°C; ^{1}H NMR (DMSO d_6): 4.54 (*s*, 2*H*, CH_2), 7.27 (*s*, 1*H*, olefinic-H), 7.56–7.90 (*m*, 3*H*, Ar-H), and 8.00–8.11 (*m*, 8*H*, Ar H); **MS** (EI) *m/z* %: 452 (M^+), 453 ($M^+ + 1$); **IR** cm^{-1}: 1,765 (C=O), 1,652 (C=N); Anal. calcd for $C_{22}H_{14}BrFN_2O_3$: C, 56.3; H, 3.01; and N, 5.97. Found: C, 65.25; H, 3.53; and N, 5.65.

*(*E*)-1-[4-(2-Bromoacetyl)phenyl]-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (37)*

Yield 68%; mp 125°C–128°C; ^{1}H NMR (DMSO d_6): 4.67 (*s*, 2*H*, CH_2), 7.27 (*s*, 1*H*, olefinic-H), 7.56–7.78 (*m*, 3*H*, Ar-H), and 7.92–8.11 (*m*, 8*H*, Ar H); **MS** (EI) *m/z* %: 452 (M^+), 453 ($M^+ + 1$); **IR** cm^{-1}: 1,761 (C=O), 1,654 (C=N); Anal. calcd for $C_{22}H_{14}BrFN_2O_3$: C, 58.3; H, 3.11; and N, 6.18. Found: C, 58.25; H, 3.15; and N, 6.17.

*(*E*)-1-[3-(2-Bromoacetyl)phenyl]-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (38)*

Yield 73%; mp 130°C–133°C; ^{1}H NMR (DMSO d_6): 4.5 (*s*, 2*H*, CH_2), 7.45 (*s*, 1*H*, olefinic H), 7.56–7.67 (*m*, 3*H*, Ar-H), and 7.88–8.23 (*m*, 8*H*, Ar H); ^{13}CNMR (DMSO d_6): δ 29.4, 107.6, 114.7, 115.9, 118.7, 124.9, 125.9, 127.5, 129.5, 131.5, 132.9, 133.0, 134.7, 135.9, 136.5, 138.5, 139.3, 140.5, 158.4, 166.4, 168.2, and 200.5; **MS** (EI) *m/z* %: 467 (M^+), 468 ($M^+ + 1$); **IR** cm^{-1}: 1,750 (C=O), 1,656 (C=N); Anal. calcd for $C_{22}H_{14}BrFN_2O_2S$: C, 56.3; H, 3.01; and N, 5.97. Found: C, 65.25; H, 3.53; and N, 5.65.

(E)-1-[4-(2-Bromoacetyl)phenyl]-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1H-imidazol-5(4H)-one (39)

Yield 70; mp 115°C–120°C; ^{1}H NMR (DMSO d_6): 4.3 (*s*, 2*H*, CH_2), 7.45 (*s*, 1*H*, olefinic-H), 7.52–7.77 (*m*, 3*H*, Ar-H), and 7.89–8.19 (*m*, 8*H*, Ar H); **MS** (EI) *m/z* %: 467 (M^+), 468 ($M^+ + 1$); **IR** cm^{-1}: 1,762 (C=O), 1,657 (C=N); Anal. calcd for $C_{22}H_{14}BrFN_2O_2S$: C, 56.3; H, 3.01; and N, 5.97. Found: C, 65.25; H, 3.53; and N, 5.65.

General procedure for synthesis of compounds 40–43

To a solution of the appropriate bromo derivative (**36–39**) (1 mmol) in abs. EtOH (20 ml), thiourea was added (1 mmol, 0.076 g). The mixture was refluxed overnight, then it was cooled, followed by the addition of ammonium hydroxide. The precipitate was filtered and washed several times with water.

*(*E*)-1-[3-(2-Aminothiazol-4-yl)phenyl]-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (40)*

Yield 60%; mp 260°C–262°C; ^{1}H NMR (DMSO d_6): 7.11 (*s*, 2*H*, NH_2), 7.77–8.11 (*m*, 8*H*, Ar H), and 7.36 (*s*, 1*H*, olefinic-H); **MS** (EI) *m/z* %:430 (% M^+), 431 (M^+ + 1); **IR** cm^{-1}: 3,470 (NH_2), 1,753 (C=O), 1,655 (C=N); Anal. calcd for $C_{23}H_{15}FN_4O_2S$: C, 61.87; H, 3.39; and N, 12.55. Found: C, 61.74; H, 3.14; and N, 12.45.

*(*E*)-1-[4-(2-Aminothiazol-4-yl)phenyl]-2-(4-fluorophenyl)-4-(furan-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (41)*

Yield 69%; mp 243°C–245°C; ^{1}H NMR (DMSO d_6): 7.24 (*s*, 2*H*, NH_2), 7.74–8.11 (*m*, 8*H*, Ar H), and 7.36 (*s*, 1*H*, olefinic-H); **MS** (EI) *m/z* %: 430 (% M^+), 431 (M^+ + 1); **IR** cm^{-1}: 3,468 (NH_2), 1,761 (C=O), and 1,659 (C=N); Anal. calcd for $C_{23}H_{15}FN_4O_2S$: C, 64.87; H, 3.51; and N, 13.02. Found: C, 64.25; H, 3.45; and N, 13.15.

*(*E*)-1-[3-(2-Aminothiazol-4-yl)phenyl]-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (42)*

Yield 55%; mp 255°C–257°C; ^{1}H NMR (DMSO d_6): 7.17 (*s*, 2*H*, NH_2), 7.89–8.11 (*m*, 8*H*, Ar H), and 7.36 (*s*, 1*H*, olefinic-H); **MS** (EI) *m/z* %: 446 (% M^+), 447(M^+ + 1); **IR** cm^{-1}: 3,482 (NH_2), 1,763 (C=O), 1,655 (C=N); Anal. calcd for $C_{23}H_{15}FN_4OS_2$: C, 61.87; H, 3.39; and N, 12.55. Found: C, 61.74; H, 3.14; and N, 12.45.

*(*E*)-1-[4-(2-Aminothiazol-4-yl)phenyl]-2-(4-fluorophenyl)-4-(thiophen-2-ylmethylene)-1*H*-imidazol-5(4*H*)-one (43)*

Yield 73%; mp 256°C–258°C; ^{1}H NMR (DMSO d_6): 7.65 (*s*, 2*H*, NH_2), 7.75–8.11 (*m*, 8*H*, Ar H), and 7.36 (*s*, 1*H*, olefinic-H); **MS** (EI) *m/z* %: 446 (% M^+), 447 (M^+ + 1); **IR** cm^{-1}: 3,475 (NH_2), 1,761 (C=O), and 1,656 (C=N); Anal. calcd for $C_{23}H_{15}FN_4OS_2$: C, 61.87; H, 3.39; and N, 12.55. Found: C, 61.74; H, 3.14; and N, 12.45.

Biological evaluation

Preliminary in vitro cytotoxic screening

Cell lines: Four human tumor cell lines, namely, Epithelioid carcinoma (Hela), breast cancer (MCF-7), prostate cancer (PC3), and colorectal carcinoma (HCT-116) were obtained from ATCC through Holding company for biological products and vaccines (VACSERA), Cairo, Egypt.

Chemicals and reagents: The reagents used were RPMI-1640 medium, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and DMSO (Sigma co., St. Louis, USA), and Fetal Bovine Serum (GIBCO, UK). Doxorubicin was used as a standard anticancer drug for comparison.

MTT assay

Cytotoxicity of the target compounds was determined *via* MTT assay on different cell lines. The assay depends on the conversion of yellow tetrazolium bromide (MTT) to a purple formazan derivative by mitochondrial succinate dehydrogenase. The process is initiated by culturing the cells in fetal bovine serum (10%) mixed with RPMI-1640 medium. Both penicillin (100 units/ml) and streptomycin (100 µg/ml) were added in a 5% CO_2 incubator, at a temperature of 37°C. Cells were grown at a density of 1.0×10^4 cells/well at 37°C under 5% CO_2 in a 96-well plate for 48 hours. Cells were treated with various concentrations of the tested compounds after incubation, where they were further incubated for 24 hours. Thereafter, 20 µl of MTT at 5 mg/ml was added and incubated for 4 hours. The dissolution of the purple formazan formed was achieved by the addition of 100 µl of DMSO into each well. The colorimetric assay was performed and recorded at 570 nm *via* a microplate reader (EXL 800, USA). % Cell viability was then calculated as previously reported (Denizot and Lang, 1986; Mosmann, 1983).

CDK2A enzyme assay

Seven wells for standard and one well for blank were prepared. Add 100 µl each of dilutions of standard (read reagent preparation), blank, and samples into the appropriate wells. Cover with the plate sealer. Incubate for 2 hours at 37°C. Then, the liquid of each well was removed. After that, 100 µl of detection reagent was added to each well and incubated for 1 hour at 37°C after covering with the plate sealer, followed by washing of each well with 350 µl of the washing solution and left for 1–2 minutes. The remaining liquid was completely removed from all wells by snapping the plate onto absorbent paper, totally washed for three times, after which, any remaining wash buffer was removed, followed by plate inversion and blotting against absorbent paper. The previous process was repeated again using 100 µl of detection reagent B working solution. Ninety miroliter of substrate solution was added to each well, covered with a new plate sealer and incubated for 15–25 minutes at 37°C. The liquid was turned blue by the addition of substrate solution. Then, the microplate reader was run and measurement was conducted at 450 nm immediately. Results were calculated by determination of the duplicate reading average for each standard, control, and samples, where the average zero standard optical density was subtracted. Then, construction of the standard curve was performed by plotting the mean O.D. and concentration for each standard, and a best-fit curve was drawn through the points on the graph or standard curve on log-log graph paper with CDK2 concentration on the *Y*-axis and absorbance on the *X*-axis was created.

VEGFR-2 enzyme assay

All reagents and samples were used at room temperature (18°C–25°C). Both the standards and samples were run in duplicate, then 100 µl of each standard and sample was added to the appropriate wells and incubated overnight at 4°C with gentle shaking. The solution was washed four times with the washing solution, where any remaining wash buffer was removed. Plate inversion was performed, and then it was blotted. Each well was subjected to the addition of the biotinylated antibody (100 µl) and then incubated for 1 hour at room temperature. After washing, the addition of the streptavidin solution (100 µl) was made, followed by incubation for 45 minutes at room temperature. Also, 100 µl of TMB (Item H) was added and then incubated for 30 minutes in the dark. Finally, 50 µl of stop solution was added and read at 450 nm. The mean absorbance for each set of duplicate standards, controls, and samples was calculated, and the average zero standard optical density was subtracted. Standard curve was drawn using Sigma

plot software and then the best-fit straight line was drawn through the standard points.

RESULTS AND DISCUSSION

Chemistry

Imidazolone ring has a particular synthetic interest rather than the unique biological value owing to synthetic accessibility and structural variability. Besides, it constitutes the core structure of several natural compounds like histamine, histidine, biotin, alkaloids, and nucleic acids. It has been reported to be prepared by several methods, including the condensation of substituted azalactone with primary amines under anhydrous conditions (Kortiwala *et al*., 2016). In the present work, the synthetic pathways adopted for the preparation of the target new imidazolone derivatives are illustrated in Schemes 1–3.

4-Fluorobenzoyl chloride was subjected to nucleophilic condensation reaction with glycine in aq. NaOH to afford hippuric acid derivative **1** as the starting material. Oxazolone derivatives **2** and **3** were synthesized *via* Erlenmeyer condensation (El-Mekabaty, 2013; Erlenmeyer, 1900) of compound **1** with different heterocyclic aldehydes in acetic anhydride and glacial acetic acid. Disappearance of the broad band signal at 2,970 cm^{-1}; that corresponds to the (OH) of compound **1**; in the IR spectrum of both compounds **2** and **3**, in addition to the replacement of the (C=O) band at 1,720 cm^{-1} with 1,775-1,780 cm^{-1} confirmed the formation of the oxazolone ring. Subsequent reaction with different aromatic amines yielded the required imidazolone derivatives **4**–**17** (Scheme 1).

Chalcones **18**–**23** were synthesized from the acetyl derivatives **9** and **16** throughout Aldol condensation reaction with the proper aromatic aldehyde using 5% NaOH. The ^{1}H-NMR spectrum reveals the appearance of two doublet peaks in the range of 7.50–8.06 ppm that correspond to the resulting olefinic protons.

These chalcones underwent different cyclization reactions either with hydrazine hydrate in absolute ethanol to afford the pyrazole derivatives **24**–**29** or with thiourea in the presence of sodium ethoxide to give the pyrimidines **30**–**35**. The most diagnostic aspects in the ^{1}HNMR spectrum that confirmed the pyrazole ring cyclization were the disappearance of the two olefinic protons' signals and the appearance of a distinguishing singlet that corresponds to pyrazolyl ring proton at 6.5 ppm (Scheme 2).

Compounds **8**, **9**, **15** and **16** were subjected to bromination in glacial acetic acid to afford compounds **36**–**39**, which were treated with thiourea in the presence of absolute ethanol to give compounds **40**–**43**. IR spectrum was characterized by the presence of NH band at 3,400 cm^{-1}. In addition, ^{1}HNMR spectra were distinguish by the presence of a singlet signal at 7.11–7.65 ppm, corresponding to the protons of the NH_2 group (Scheme 3).

Biological evaluation

Preliminary in vitro *cytotoxic screening*

In vitro cytotoxicity of all the synthesized imidazolone-derivatives was evaluated against four tumor cell lines: Hela, MCF-7, PC3, and HCT-116, taking Doxorubicin (DOX.) as a control, where IC_{50} values were determined and listed in Table 1. Compounds **6**, **25**, **26,** and **29** were shown to have the highest anticancer activities in the four cell lines in comparison to DOX. Concerning PC3 cell lines, compound **30** showed a cytotoxic effect compared to that of the standard with IC_{50} values of 8.15 ± 0.9 µM, while compounds **4** and **18** showed moderate activity with IC_{50} range of 10.58–11.45 µM. Regarding Hela and HCT-116 cell lines, compound **25** achieved the maximum cytotoxic activity with IC_{50} values of 7.34 ± 0.5 µM and 4.87 ± 0.3 compared to IC_{50} values of 5.57 ± 0.4 µM and 5.23 ± 0.2 µM for DOX, respectively. On the other hand, compound **29** depicted the maximum effectiveness in MCF-7 and PC-3 cell lines with IC_{50} values of 6.27 ± 0.4 µM and 5.31 ± 0.5 µM, respectively, whereas compound **6** reported the least anti-neoplastic activity among the four compounds. Interestingly, compound **29** was approximately twice as potent as Dox in PC3 cell line, while compound **25** was marginally better than the control in the HCT-116 cell line (Fig. 3).

CDK2A inhibition assay

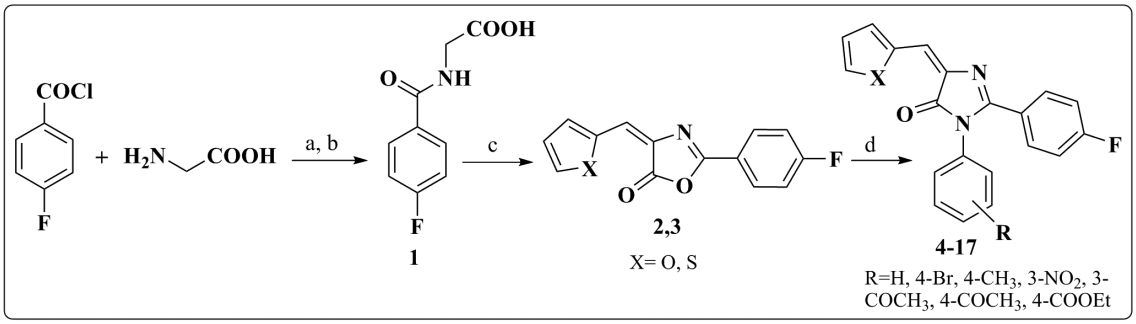
To evaluate the possible mode of action of the synthesized imidazolones as anticancer agents, compounds **6, 25, 26,** and **29** were tested for both CDK2A and VEGFR-2 inhibitory activity using sorafenib as a reference drug. All substrates apart from **29** depicted a marginal rise in IC_{50} compared to sorafenib with compound **26** achieving the best result, followed by compounds **25** and **6**. On the other hand, the IC_{50} of compound **29** skyrocketed up to 3.5 µM making it the least effective (Table 2). These results indicated that CDK2A may be a possible target for the designed hybrids for their antineoplastic activity.

VEGFR-2 enzyme assay

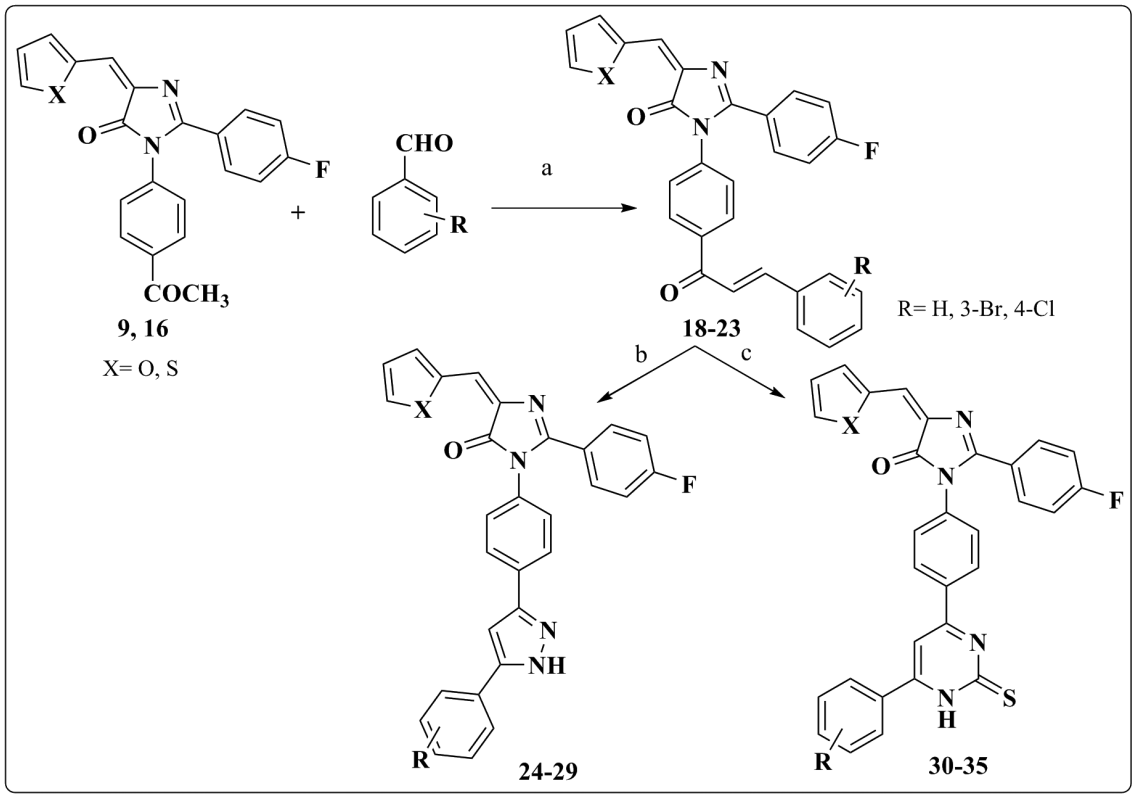
Evaluating the inhibitory effect of compounds **6**, **25**, **26,** and **29** on VEGFR-2 revealed excessively higher IC_{50} in comparison to sorafenib. IC_{50} ranged from as low as treble that of sorafenib in compound **6**, up to approximately 8 folds in compound **29** (Table 2).

SAR discussion

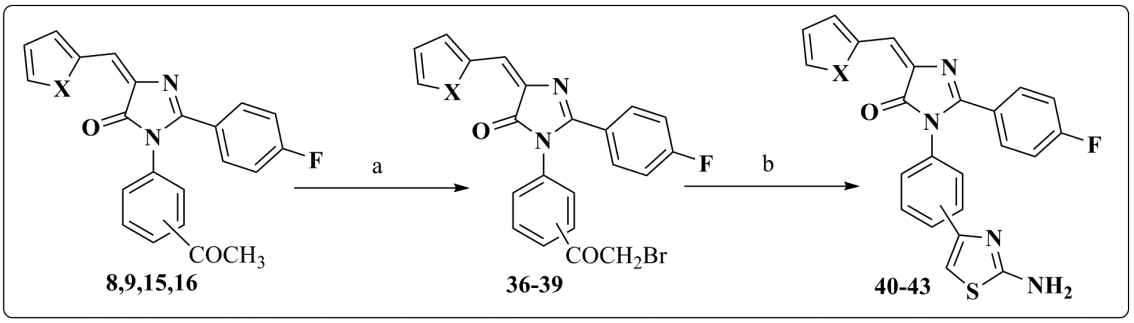
Several imidazolone hybrids were synthesized and evaluated for their cytotoxicity against four cancer cell lines, namely, Hela, MCF-7, PC3, and HCT-116. Enzyme inhibitory activity against CDK2A as well as VEGFR-2 was also investigated. Two compounds from the first series which embraces furanylmethylene-imidazolone **4**–**10** showed considerable cytotoxic activity, where the unsubstituted phenyl derivative **4** exhibited moderate activity against PC3 cell lines with an IC_{50} value of 11.45 ± 1.2 µM, while the 4-methylphenyl derivative **6** showed good and broad-spectrum activity against the tested cell lines. The thiophenyl methylene-imidazolone series **11**–**17** exhibited weak to no activity. Regarding the imidazolone hybrids containing chalcone moiety **18**–**23**, compound **18** showed moderate activity against PC3 cell lines with an IC_{50} value of 10.85 ± 1.1 µM. The series that involves the pyrazolyl derivatives **24**–**29** was the most promising regarding the anticancer activity with three potent compounds **25**, **26,** and **29**, having broad activity against all cell lines. On the other hand, hybrids containing the pyrimidinethione derivatives **30**–**35** provided compound **30** with anticancer activity compared to that of the standard DOX against PC3 cell lines. The



Scheme 1. Synthesis of compounds **2**–**17**. Reagents and Conditions: (a) 10% NaOH, stirring, 2 hours; (b) conc. HCl; (c) the appropriate heterocyclic aldehyde, NaOAc, glacial acetic acid, reflux; (d) the appropriate aromatic amine, NaOAc/glacial acetic acid, heat/water bath.



Scheme 2. Synthesis of compounds **18**–**35**. Reagents and Conditions: (a) 5% ethanolic NaOH, stirring, ice bath, 4h; (b) $NH_2NH_2.H_2O$, abs. EtOH, reflux; (c) thiourea, NaOEt, reflux.



Scheme 3. Synthesis of compounds **36**–**43**. Reagents and Conditions: (a) Br_2, glacial acetic acid, 80°C–90°C; (b) thiourea, abs. EtOH, reflux.

Table 1. IC_{50} of the target compounds against Hela, MCF-7, PC3, and HCT-116cell lines.

Comp. no.	IC_{50} (µM)				Comp. no.	IC_{50} (µM)			
	Hela	MCF-7	PC3	HCT-116		Hela	MCF-7	PC3	HCT-116
2	97.81 ± 5.3	47.84 ± 3.2	43.79 ± 3.2	>100	24	14.83 ± 1.1	11.72 ± 1.2	16.89 ± 1.5	13.70 ± 1.1
4	16.28 ± 1.3	10.36 ± 1.1	11.45 ± 1.2	14.56 ± 1.3	25	7.34 ± 0.5	7.58 ± 0.6	6.64 ± 0.6	4.87 ± 0.3
5	36.12 ± 2.2	15.81 ± 1.4	17.50 ± 1.6	38.63 ± 2.0	26	8.86 ± 0.8	7.83 ± 0.7	7.26 ± 0.7	6.81 ± 0.6
6	10.11 ± 0.9	8.67 ± 0.7	9.80 ± 1.1	7.55 ± 0.8	27	24.51 ± 1.7	20.16 ± 1.6	30.80 ± 2.4	22.43 ± 1.6
7	94.67 ± 4.9	95.37 ± 5.1	>100	>100	28	13.07 ± 1.1	9.70 ± 1.0	15.01 ± 1.4	11.42 ± 0.9
8	46.56 ± 3.1	22.87 ± 1.8	21.57 ± 1.9	52.83 ± 2.5	29	7.91 ± 0.6	6.27 ± 0.4	5.31 ± 0.5	5.93 ± 0.6
9	>100	93.62 ± 4.8	>100	>100	30	21.35 ± 1.6	9.48 ± 0.9	8.15 ± 0.9	17.36 ± 1.5
10	60.41 ± 3.5	29.84 ± 2.4	37.47 ± 2.9	64.62 ± 3.1	31	19.35 ± 1.4	23.61 ± 1.8	31.85 ± 2.5	16.49 ± 1.3
11	91.49 ± 4.8	88.25 ± 4.2	86.91 ± 4.4	97.18 ± 5.7	32	38.24 ± 2.4	13.66 ± 1.3	12.71 ± 1.3	41.95 ± 2.0
12	84.59 ± 4.4	90.50 ± 4.5	>100	91.74 ± 4.9	33	65.14 ± 3.8	50.10 ± 3.3	59.84 ± 3.7	73.74 ± 3.5
13	63.82 ± 3.6	61.06 ± 3.4	64.08 ± 3.8	68.11 ± 3.2	34	81.56 ± 4.3	80.41 ± 3.8	69.47 ± 3.9	87.83 ± 4.7
14	51.34 ± 3.0	37.08 ± 2.8	48.60 ± 3.4	54.49 ± 2.7	35	57.19 ± 3.4	25.81 ± 1.9	13.43 ± 1.3	62.31 ± 2.9
15	43.87 ± 2.6	32.62 ± 2.5	33.32 ± 2.8	44.90 ± 2.3	36	79.47 ± 4.2	28.13 ± 2.3	25.04 ± 2.3	85.19 ± 4.1
16	71.20 ± 3.9	39.57 ± 2.9	41.50 ± 3.1	78.16 ± 3.8	37	>100	>100	>100	>100
17	68.01 ± 3.8	82.62 ± 4.0	78.53 ± 4.2	77.25 ± 3.6	38	87.21 ± 4.6	56.92 ± 3.4	51.62 ± 3.5	92.80 ± 5.0
18	46.10 ± 2.9	12.59 ± 1.2	10.58 ± 1.1	50.76 ± 2.4	39	>100	>100	>100	>100
19	29.23 ± 1.8	15.37 ± 1.4	16.97 ± 1.5	32.01 ± 1.7	40	31.40 ± 1.9	17.63 ± 1.5	18.61 ± 1.7	34.55 ± 1.8
20	33.58 ± 2.0	18.85 ± 1.6	19.83 ± 1.8	36.78 ± 1.9	41	40.53 ± 2.5	26.49 ± 2.0	35.06 ± 2.8	42.72 ± 2.1
21	54.72 ± 3.3	27.50 ± 2.1	22.39 ± 1.9	57.08 ± 2.8	42	74.48 ± 4.0	34.81 ± 2.7	45.31 ± 3.3	82.81 ± 3.9
22	76.36 ± 4.1	45.42 ± 3.1	55.91 ± 3.5	83.97 ± 4.2	43	27.03 ± 1.8	22.03 ± 1.7	24.78 ± 2.1	28.64 ± 1.7
23	89.40 ± 4.7	72.65 ± 3.8	75.12 ± 3.9	96.02 ± 5.3	DOX	5.57 ± 0.4	4.17 ± 0.2	8.87 ± 0.6	5.23 ± 0.2

DOX: Doxorubicin.
Data are presented as the mean ± SDs of three independent experiments.

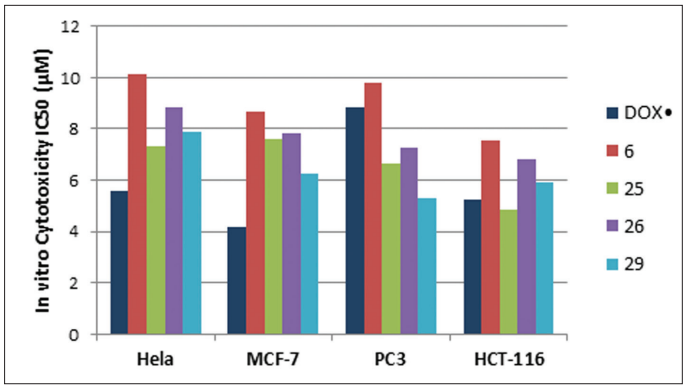


Figure 3. Cytotoxic activity of compounds **6**, **25**, **26**, and **29** compared to Dox.

last series **36**–**43** with the aminothiazole substitution showed low activity.

Concerning the enzyme inhibitory activity against both CDK2A and VEGFR-2, compounds **6**, **25**, **26,** and **29** showed various activities, related to the structural features characterizing them. İnvestigation into the SAR of the target compounds revealed that furanylmethylene-imidazolone hybrids **6**, **25,** and **26** exhibited considerable enzyme inhibition rather than the thiophenyl methylene-imidazolone hybrid **29**, where compound **26** showed an IC_{50} value of 92 ± 1.57 nM (for VEGFR-2) and 0.66 ± 0.03 µM (for CDK2A) on HCT116 cell line, respectively. Likewise, compound **6** with an IC_{50} value of 67 ± 0.89 nM (for VEGFR-2) and compound **25** with an IC_{50} value of 0.83 ± 0.04 µM (for CDK2A) came next. It was observed that compound **6** demonstrated the highest inhibitory effect when compared to other compounds on VEGFR-2 and moderate effect on CDK2A enzyme. On the other hand, compound **29** yielded the lowest inhibitory activity on both tested enzymes. Conversely, when thiophene ring of compound **29** was replaced by furfural ring and the 3-bromophenyl group substituted the 4-chlorophenyl group in compound **25**, the inhibitory effect was moderate against CDK2A enzyme. Interestingly, as 3-bromophenyl moiety was replaced by 4-chlorophenyl moiety in the presence of furfural ring in compound **26**, the inhibitory effect was demonstrated on both VEGFR-2 and CDK2A enzymes suggesting a powerful anti-cancer effect.

To sum up, compounds **25** and **26** are more likely to produce their effects on the molecular enzymatic level rather than inhibiting cell surface receptors.

Table 2. CDK2A and VEGFR-2 IC_{50} of compounds **6**, **25**, **26,** and **29** compared to sorafenib.

Enzyme	Comp.				
	6	25	26	29	Sorafinib
VEGFR-2 (Cell line: HCT116) IC_{50} (nM)	67 ± 0.89	158 ± 0.87	92 ± 1.57	177 ± 1.15	21 ± 0.72
CDK2A (Cell line: HCT116) IC_{50} (µM)	1.14 ± 0.14	0.83 ± 0.04	0.66 ± 0.03	3.55 ± 0.09	0.37 ± 0.02

Data are presented as the mean ± SDs of three independent experiments.

CONCLUSION

Compounds **6**, **25**, **26,** and **29** were shown to have the highest anticancer activities in the four cell lines in comparison to DOX. Concerning PC3 cell lines, compound **30** showed a cytotoxic effect comparable to that of the standard. Compounds **6**, **25**, and **26** depicted a marginal rise in IC_{50} compared to sorafenib, with compound **26** achieving the best result regarding CDK2A and VEGFR-2 inhibitory activity.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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