Industrial Engineering Journal
ISSN: 0970-2555
Volume : 53, Issue 5, May : 2024

SYNTHESIS OF N-CONTAINING HETEROCYCLIC COMPOUNDS AND ITS ANTI CANCER ACTIVITY

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ABSTRACT

Mainstream cancer research has continued to place a significant emphasis on the development of new and effective therapeutic candidates to tackle rising treatment resistance and off-target toxicities. Here, a series of novel 3-(substitutedphenyl) -2-(4-(substitutedphenyl) thiazol-2-yl) -2H-pyrazolo(3,4-d) thiazol-5(6H)-one derivatives were synthesized and characterized. The ability of the synthesized compounds to reduce the survival of the human breast cancer cell line MDA-MB 231 was evaluated.

When compared to the reference chemical, 5-fluorouracil, 5b, and 5i showed the highest inhibitory activity (IC50: 550 ± 0.78 μM and 504 ± 0.89 μM respectively) on the viability of MDA-MB 231 cells.

KEYWORDS: Thiazolidione, Heterocyclic compounds, Anticancer activity etc.

INTRODUCTION

Breast cancer is not only the most common cancer in women worldwide, but it also ranks second in terms of the primary causes of mortality for women across the globe (1). It is the most serious health problem of all gynecological cancers, affecting a significant portion of the global population (2). Every year, invasive breast cancer affects an estimated one million women globally. More specifically, in 2017, it was anticipated that there were roughly 40,610 breast cancer deaths among US women, although there were an increasing number of new patients with breast cancer every year in India (3-4). The existing chemotherapy techniques utilized in the

treatment of breast cancers have limitations due to significant target and off-target adverse effects in the face of developing drug resistance to the disease. Early diagnosis, and improved, and safer treatment options are among the interventions and strategies used to lower the prevalence and fatality rates. The problems of existing anticancer medications have spurred research into new, effective breast cancer treatments.

One of the most active components of heterocyclic compounds, pyrazole, and its derivatives exhibit a wide range of pharmacological actions (5-7). Pyrrole exhibits considerable antiviral (8), antimicrobials (9,10), anticancer (11,12), especially antibreast cancer activity (13-16), anticonvulsant (17,18), antitubercular (19,20), analgesics (21), cardiovascular (22) and anti-inflammatory (23,24) activity. The thiazole moiety is one of the most significant heterocyclic compounds and is utilized frequently in pharmaceutical chemistry. It also demonstrates a variety of biological functions, including anti-breast cancer activity, antitubercular activity, analgesic, antiinflammatory, antihypertensive, CNS activity, antioxidant, antiviral, antidiabetics (25), antimicrobial (26), and immunosuppressive activities (27).

The significant inhibitory activity of thiazolone scaffold against anticancer has been thoroughly investigated by numerous research organizations (28-30). A few of the pyrazolothiazolone compounds have been created (1-32), and they have activity against the dengue virus (33) as well as being anti-proliferative (34), anticonvulsant (35), antimicrobial and anti-inflammatory (36), antiviral (37), anti-HIV-1 NNRT inhibitors (38), anticancer (39-40). In an effort to aid in the drive against breast cancer, we screened a number of synthetic compounds incorporating fused heterocycles for possible biological activity.

MATERIAL AND METHOD-

General procedure for the synthesis of 3-(substitutedphenyl)-2-(4-(substitutedphenyl) thiazol-2-yl)-2H-pyrazolo(3,4-d)thiazol-5(6H)-one.

An equimolar quantity of Thiazolidione-2,4-dione (1 mmol) and substituted aromatic aldehydes (1 mmol) were dissolved in a minimum quantity of PEG-400 along with a catalytic amount of Bleaching Earth Clay (pH 12.5 wt %) stirred at 70-80^{o}C for one hour (41). Add excess amount of thiosemicarbazide (1.5 mmol), stir this mixture for another hour, then add 2-bromo-1-(4-substitutedphenyl) ethanone (1 mmol), and stir this reaction mixture for two hours (37). After the reaction is over, it is monitored on Thin Layer Chromatography. The solid catalyst was separated by simple filtration, the mother liquor was poured into crushed ice, stirred for five minutes, and neutralized with diluted HCl if necessary. The separated solid was suction-filtered (water aspirator), washed with ice-cold water, and recrystallized from ethanol to obtained the final products I-III are obtained.

The synthesized compounds are characterized by Elemental analysis, ^{1}H NMR, ^{13}C NMR, Mass Spectroscopy and IR Spectroscopy.

Determination of Anticancer Activities

The MTT assay was used to determine the cytotoxic capability of the chosen drugs against specific cancer cell lines (42). In 96 well culture plates, the cells were inoculated at a density of 1×105 cells/mL. The cells were exposed to various doses of substances dissolved in 0.1% DMSO for 24 hours. Following the initial incubation time, 20 µl of MTT (2 mg/ml) were added to each well, and the cells were then incubated at 37 °C for an additional 4 hours. Further, formazan crystals were dissolved in isopropyl alcohol and therefore the quantity of formazan created was calculable at 570 nm. It has been determined that IC50 represents the concentration.

RESULT AND DISCUSSION

2-(4-(4-chlorophenyl)thiazol-2-yl)-3-(4-nitrophenyl)-2H-pyrazolo (3,4d) thiazol-5(6H)-one (C19H10ClN5O3S2) (I)

This compound was obtained in 90% yield, mp 210-220°C; IR (KBr) cm-1:3294(NH stretching), 1670(>C=O stretching), 1581(aromatic C=N stretching),; 1H NMR (400 MHz, DMSO-d6): δ

12.6(s,1H, NH), 7.4-7.4(d, 2H), 7.8-7.9(m, 2H), 8.1(s, 1 H,), 8.2-8.2(d, 2H),; 13C NMR (400 MHz, DMSO-d6) ppm: δ 168.44, 148.52, 140.40, 133.67, 133,14, 128.83, 127.83, 126.26, 124.01, 108.64,; ms (EI): m/z (M+) 455.5. Anal. calcd. for: C, 50.00; H, 2.37; Cl, 7.70; N, 15.45; O, 10.32; S, 14.16. Found: C, 50.06; H, 2.21; Cl, 7.78; N, 15.36; O, 10.52; S, 14.07.

3-(4-chlorophenyl)-2-(4-(4-chlorophenyl)thiazol-2-yl)-2H-pyrazolo(3,4d)thiazol-5(6H)-one (C19H10Cl2N4OS2) (II)

This compound was obtained in 92% yield, mp 210-220°C; IR (KBr) cm-1:3294(NH stretching), 1670(>C=O stretching), 1581(aromatic C=N stretching),; 1H NMR (400 MHz, DMSO-d6): δ 12.6(s,1H, NH), 7.4-7.4(d, 2H), 7.8-7.9(m, 2H), 8.1(s, 1 H,), 8.2-8.2(d, 2H),; 13C NMR (400 MHz, DMSO-d6) ppm: δ168.12, 148.52, 146.18, 140.54, 140.40, 133.54, 133.24, 131.87, 129.43, 128.81,128.52, 128.22, 127.76, 127.14 104.56,; ms (EI): m/z (M+) 445 Anal. calcd. for: C,51.20; H, 2.27; Cl, 15.92; N, 12.58; O, 03.61; S, 14.41. Found: C, 51.24; H, 2.26; Cl, 15.92; N, 12.58; O, 03.59; S, 14.40.

3-(4-chlorophenyl)-2-(4-(4-nitrophenyl)thiazol-2-yl)-2H-pyrazolo(3,4d)thiazol-5(6H)-one (C19H10ClN5O3S2) (III)

This compound was obtained in 90% yield, mp 210-220°C; IR(KBr) cm-1:3355(NH stretching), 1670(>C=O stretching), 1589(aromatic C=N stretching),; 1H NMR (400 MHz, DMSO-d6): δ 12.3(s,1H, NH), 7.4-7.4(d, 2H), 7.8-7.9(m, 2H), 8.1(s, 1 H,), 8.2-8.2(d, 2H),; 13C NMR (400 MHz, DMSO-d6) ppm: δ167.78,149.40,147.05, 140.67, 138.68, 133.27, 131,98, 128.54, 127.15, 126.87, 124.01, 123.72, 105.16,; ms (EI): m/z (M+) 455.5 Anal. calcd. for: C, 50.08; H, 2.34; Cl, 7.76; N, 15.34; O, 10.41; S, 14.07. Found: C, 50.06; H, 2.21; Cl, 7.78; N, 15.36; O, 10.53; S, 14.07.

By using FTIR, 1H NMR, 13C NMR, mass spectrum analysis, and elemental analysis, the structures of all the newly synthesized compounds (I-III) were confirmed. The IR spectrum of compounds (I-III) revealed the presence of the >C=O stretching band at 1700-1660 cm^{-1} of

thiazolone. The characteristic band at near 1650-1580 cm^{-1} is due to –C=N stretching, while the characteristic band is due to –NH stretching at 3500-3300 m^{-1}. The NMR spectra of the compounds revealed a characteristic signal around δ 12.2-12.7 ppm due to -NH proton. Aromatic protons appeared as multiplate around δ 7.4-8.2 ppm. The most distinguishing signal in the ^{13}C NMR spectrum data of the title compounds is associated with the carbonyl carbon and is located between 167.78 – 168.44 ppm, while all aromatic carbons of the compounds exhibit signals between 104.56 to 155.59 ppm. The anticipated M+ peak, which corresponds to the actual molecular mass, can be found in the mass spectra of all substances.

Biology: Anticancer Activities

The growth inhibitory effect was assessed using the human breast cancer cell line MDA MB-231. The results are summarized and expressed as the IC50 values. 5-fluorouracil was used as a positive control. Compounds II and III showed significant anti-breast cancer activity (IC50 - 550 ± 0.78, 504 ± 0.89 μM respectively) as shown, while the remaining compound I showed moderate activity against breast cancer cell lines. From IC50 values, we can assume that the synthesized derivatives exhibited good to moderate cytotoxic activity against the examined breast cancer cell line.

CONCLUSIONS

Compounds II and III are the most potent drug for breast cancer cell line MDM-MB-231 has validated this. The biological test results the following conclusions can be reached about their structure-activity relationships, incorporation of a substituted electron withdrawing group into 3-(substitutedphenyl) and 4-(substitutedphenyl) of the 3-(substitutedphenyl)-2-(4-(substitutedphenyl)thiazol-2-yl)-2H-pyrazolo(3,4-d)thiazol-5(6H)-one ring appears to increase anticancer activity and further investigations are in process.

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