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Pyrazoles as anticancer agents: Recent advances

Nikita Sharma and Mamta Ahuja *

Department of chemistry, Govt. Meera Girls College, Udaipur, Rajasthan, India.

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Abstract

The present review article offers a detailed account of the design strategies employed for the synthesis of nitrogen-containing anticancer agents. The results of different studies described the *N*-heterocyclic ring system as a core structure in many synthetic compounds exhibiting a broad range of anticancer activities.

Keywords: Anticancer activities; Cancer disease; Pyrazoles; Anticancer agents

1. Introduction

Cancer is a disease which severely affects the human population. Anticancer drugs are medicines formulated to treat a wide range of cancer. Cancer is the uncontrolled growth of cells that interfere with the growth of healthy cells. The usual treatments for cancer are surgery, radiation and chemotherapy. Anticancer drugs are targeted to control cancer diseases like Breast cancer, Lung cancer, Head and Neck cancer etc. However, there is a need to develop those anticancer drugs which are specific for malignant cells and show little or no side effect on healthy cells.

Pyrazolines are a class of electron rich nitrogen heterocyclic compounds having versatility in medicinal chemistry and are being reported to exhibit remarkable anticancer effects by inhibiting the enzymes which promote cell division. Pyrazole derivatives are developed by linking pyrimidine, carboxyhydrazide as well as ferrocenyl molecules with the pyrazole cap and all are especially effective against lung cell carcinoma (A549). Therefore, this review discusses the recent advances or research in the field of pyrazoles and their properties which make them targets for potential anticancer treatments.

2. Anticancer activities

Patel et al. synthesized a series of novel pyrazoline scaffolds from coumarin–carbazole chalcones. The synthesized compounds were characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR, DEPT and mass spectroscopic techniques. The in vitro cytotoxicity study of all the synthesized compounds were evaluated against HeLa, NCI-H520 and NRK-52E cell lines. Compounds [1a] and [1b] became the most active compounds and exhibited their potential to arrest the cell cycle progression and induce apoptosis in both the cell lines. In addition, molecular docking studies revealed a higher binding affinity of both the molecules with CDK2 protein. Based on the obtained results, a comprehensive analysis is warranted to establish the role of compounds as promising cancer therapeutic agents.

* Corresponding author: Mamta Ahuja.

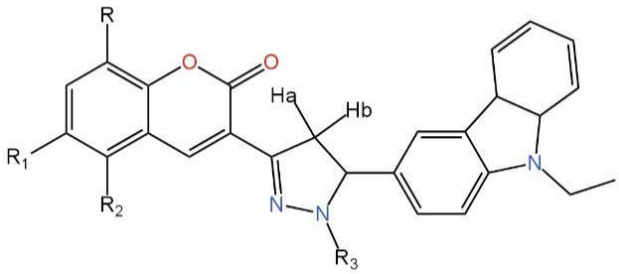

Figure 1 Synthesis of pyrazoline substituted coumarin-carbazole derivatives

a R=H, R_1=H, R_2=H, R_3=CO-NH_2

b R=OCH_3, R_1=H, R_2=H, R_3=3-Cl-C_6H_5

Rana et al. designed and synthesized N-formyl pyrazoline derivatives via Michael addition reaction through cyclization of chalcones with hydrazine hydrate in presence of formic acid. The structural elucidation of N-formyl pyrazoline derivatives was carried out by various spectroscopic techniques such as ^{1}H, ^{13}C NMR, FT-IR, UV–visible spectroscopy, mass spectrometry and elemental analysis. Anticancer activity of the pyrazoline derivatives were evaluated against human lung cancer (A549), fibrosarcoma cell lines (HT1080) and human primary normal lung cells (HFL-1) by MTT assay. The compounds showed moderate to good cytotoxicity and analogs containing Cl & Br groups in the para-substituted benzene ring exhibit excellent cytotoxicity.

Dofe et al. designed and synthesized new active molecules against MCF-7, A549 and HepG2, tetrazole based pyrazoline and isoxazoline derivatives under both conventional and ultrasonic irradiation methods. The structure of newly synthesized compounds was characterized by ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. Several derivatives were found to be excellent cytotoxic agents against MCF-7, A549 and HepG2 cell lines characterized by lower IC50 values (0.78 -- 3.12 μg/mL).

Kumari et al. synthesized two series of new pyrazoline and isoxazole bridged indole C-glycoside molecular hybrids (n = 36) starting from diverse indole 3-carboxaldehyde derived α, β-unsaturated ketone derivatives of β-D-glucosyl-propan-2-one, β-D-galactosyl-propan-2-one and β-D-mannosyl-propan-2-one, reacting with hydrazine hydrate and hydroxylamine hydrochloride in shorter reaction time (15 min) under microwave assisted condition. Anticancer activity of newly synthesized pyrazoline and isoxazole bridged indole C-glycoside hybrids were determined in detail through cellular assays against MCF-7, MDA-MB-453 and MDA-MB-231 cancer cell lines. The selected library members displayed low micromolar (IC50 = 0.67–4.67 μM) and selective toxicity against breast cancer cell lines (MCF-7). Whereas these compounds were nontoxic towards normal cell lines (MCF-10A). Mechanistic studies showed that active compounds inhibit COX-2 enzyme, which was also supported by molecular docking studies. These findings are expected to provide new leads towards anticancer drug discovery.

Elewa et al. reacted 3-(2-Thienyl)-5-aryl-1-thiocarbamoyl- 2-pyrazolines with chloroacetone derivatives and hydrazonoyl chloride derivatives in ethanol to afford the corresponding thiazolyl pyrazoline derivatives and thiophenylpyrazolyl-5-substituted aryl-diazenyl thiazole derivatives, respectively. The structures of the newly synthesized compounds were elucidated by different elemental and spectral analyses. The antimicrobial and antifungal activities of the newly synthesized compounds were evaluated against four bacterial species and five fungal strains. In addition, the antitumor activities of two of the newly synthesized compounds 1-(2-(5-(4-chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydropyrazol-1-yl)-4-methyl thiazol-5-yl)ethan-1-one and 2-(5-(4-chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)-4-methyl-5-(phenyl-diazenyl)thiazole against HEPG-2, HCT-116, MCF-7, BHK and CACO-2 were evaluated. From the obtained results, found that these two compounds were the most potent candidates towards all gram-positive and gram-negative bacteria, as well as the fungi studied. Also, the same two compounds showed strong antitumor activities against two of the tumor cell lines (HCT-116 and CACO-2).

Wahyuningsih et al. synthesized the novel N-acetyl pyrazoline derivatives [2] containing methoxy groups obtained from veratraldehyde in excellent yield and purity by the cyclocondensation of chalcones and hydrazine hydrate in glacial acetic acid. Cytotoxicity evaluation revealed that the presence of a halogen substituent such as chloro on a pyrazoline derivative [2A] increased its cytotoxic activity against some cancer cell lines, while the presence of hydroxyl substituent [2B and 2C] decreased the anticancer activity. The molecular docking study showed that pyrazoline [2A] could nicely bind to the active site of the EGFR receptor via hydrogen bonding with MET769 and π-cation interaction with LYS721.

Docking study showed the interaction between pyrazolines and EGFR receptors via hydrogen bonds and π-cation interactions.

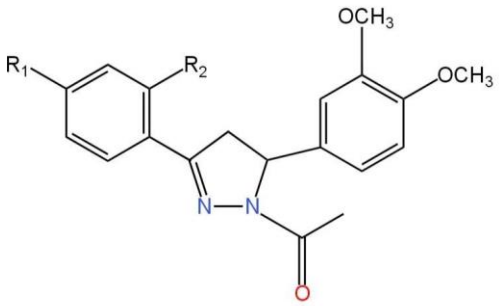

Figure 2 N-acetyl pyrazoline derivatives

A R_1=Cl, R_2=H

B R_1=OH, R_2=H

Cui et al. designed and synthesized a series of 1H-benzofuro [3, 2-c]pyrazole derivatives. The treatment of 6-methoxy benzofuran- 3(2H)-one with LiHMDS in anhydrous tetrahydrofuran (THF) followed by reaction with 3- substituted phenyl isothiocyanate gave the thioamide intermediates, which underwent condensation with hydrazine monohydrate in dioxane / EtOH (1:1) to provide the benzofuropyrazole derivatives as well as the unexpected pyrazole derivatives. In tumor cell growth inhibitory assay, all the benzofuropyrazole derivatives were not active against the breast tumor MCF-7 cell, only was highly active and more potent than ABT-751 against the leukemia K562 and lung tumor A549 cells, while other benzofuropyrazole showed very weak inhibitory activity, In contrast, the pyrazoles were in general more potent than the benzofuropyrazoles. Both pyrazoles [3a] & [3b] exhibited high inhibitory activities against k562, MCF-7 and A549 cells. The most active compound [3a] was much more potent than ABT-751 against K562 and A549 cells with GI50 values of 0.021 and 0.69 Um respectively.

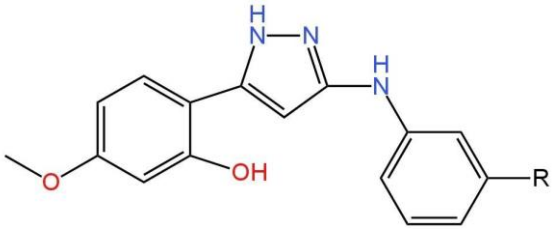

Figure 3 (a) methyl 3-((5-(2-hydroxy-4-methoxyphenyl)-1H-pyrazol-3-yl)amino)benzoate (b)3-((5-(2-hydroxy-4-methoxyphenyl)-1H-pyrazol-3-yl)amino)benzonitrile

R = a = $COOCH_3$, **b** = CN

Madhu et al. designed and synthesized a series of flavanone / chromene derivatives containing pyrazoles with potent anti-leukemic activity. Anti-leukemic activity of novel flavanone derivatives was tested using the K562 cell line. The parental flavanone was selected as the reference compound in identification of analogues with superior anti-leukemic activity. More than two-thirds of the derivatives displayed higher activity than the initial flavanone. Positions of substituents that promoted anti-leukemic activity were identified on both the chromene and pyrazole fragments. Compounds showed the highest activity against the K562 cell line, with IC_{50} values 3.0 and 0.5 uM respectively. Notably, compounds displayed very high selectivity in inhibition of leukemic cells but not of healthy HEK 293 of cells or solid cancer cell lines Hela, MCF7 and BT474.

Wang et al. designed, synthesized and evaluated a new series of pyrazoline derivatives [4] for antiproliferative activity against three cancer cell lines. Additionally NIH/373 cell cytotoxicity were tested and the structure activity relationship were also determined. Among these new derivatives the compounds 3-(4-fluorophenyl)-5-(3,4,5-trimethoxy-

thiophenyl)-4,5-dihydro-1H- pyrazole-1-carbothioamide and 3-(4-chlorophenyl) -5- (3,4,5-trimethoxy thiophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide showed the best activity against HepG-2 cells with IC_{50} values of 6.78 uM and 16.02 uM respectively. They also displayed potent activity against Hela cells, meanwhile, 3-(4-chlorophenyl)-5-(3-bromo-4-hydroxy -5-methoxy-thiophenyl)-4,5-dihydro- 1H-pyrazole 1-carbothioamide and 3-(4-bromo-phenyl)-5-(3-bromo-4-hydroxy-5-methoxythiophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide were also identified as promising anti-cancer agents against A549 cells owing to their notable inhibitory effect, compared with cisplatin. Furthermore, it was also found that compounds [4a & 4b] had low cytotoxicity against NIH/ 3T3 cells and further mechanistic studies revealed that [4a] arrested HepG-2 cells cycle at the G2/M phase at high concentrations and induced apoptosis in HepG-2 cells.

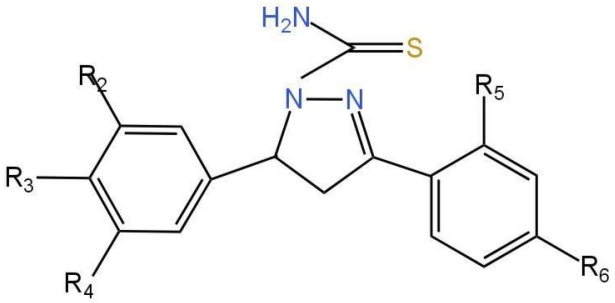

Figure 4 Synthesis of 3,5-Disubstituted-4,5-dihydro-1H-pyrazole-1-carbothioamides

4a R_2=OCH_3, R_3=OCH_3, R_4=OCH_3, R_5=H, R_6=F

4b R_2=OCH_3, R_3=OCH_3, R_4=OCH_3, R_5=H, R_6=Cl

Hafez synthesized a series of novel pyrazole derivatives bearing pyran, pyridine, pyrazole, imidazol, 1,3-oxazole and 1,3,4-thiadiazole. 2-amino-4-(3-methyl-1-phenyl-1H-pyrazol-4-yl)-4H-benzo chromene-3-carbonitrile derivatives under microwave irradiation. The structure of the newly synthesized compounds was elucidated on the basis of analytical and spectral analyses. All the synthesized compounds screened for the anticancer activity against three tumor cell lines using doxorubicin as standard compounds had excellent cytotoxic agents against the three tumor cell lines, which is more potent than the activity of doxo-rubicin.

Xu et al. synthesized a series of novel pyrazoline derivatives and evaluated for cytotoxic effects on HepG-2 (human liver hepatocellular carcinoma cell line) and primary hepatocytes. Benzo[b]thiophen-2-yl-[5-(4-hydroxy-3,5-dimethoxy-phenyl)-3-(2-hydroxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-methanone [5] was the most effective anticancer agent against HepG-2 cells owing to its notable inhibitory effect on HepG-2 with an IC_{50} value of 3.57 uM when compared with cisplatin (IC_{50} =8.45 uM) and low cytotoxicity against primary heptacytes.

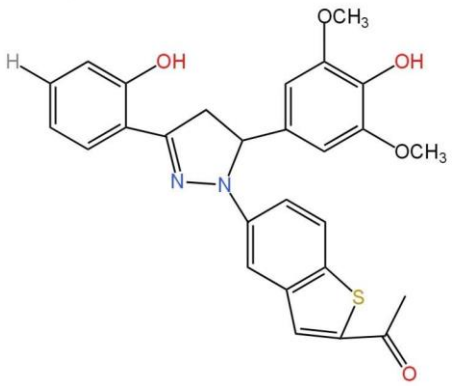

Figure 5 Benzo[b]thiophen-2-yl-[5-(4-hydroxy-3,5-dimethoxy-phenyl)-3-(2-hydroxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-methanone

Fahmy et al. synthesized a novel series of polysubstituted pyrazole derivatives linked to different nitrogenous heterocyclic ring systems at the C-4 position through different chemical reactions and characterized by means of

spectral and elemental analyses and their antiproliferative activity against 60 different human tumor cell lines was validated by the U.S. National Cancer Institute using a two stage process. The in vitro anticancer evaluation revealed that compound [6] showed increased potency toward most human tumor cell lines with GI_{50}MG-MID = 3.59 μM, as compared to the standard drug sorafenib (GI_{50} MG-MID = 1.90 μM).

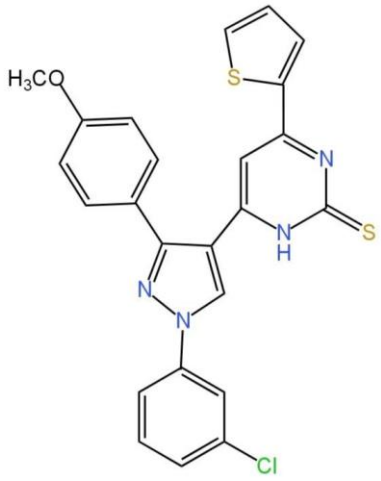

Figure 6 Polysubstituted pyrazole derivative

Belal and Abdelgawad designed and synthesized ten new hybrids, their chemical structures were confirmed through spectral and elemental analysis. The new hybrids were screened against lung, breast and liver cancer cell lines (A549, MCF7 and Hep3B), in addition to normal fibroblast cells. Compound [7a] was the most active and selective one on the lung cancer cell line (A549), its IC_{50} and S.I. values were 2.4 μM and 83.2 μM, respectively. Compound [7b] was active on MCF7 with the best selectivity towards this cell line. The new derivatives were screened for their inhibitory activity against COX enzymes; the obtained results revealed that compounds [7a] & [7b] were more active inhibitors for COX-2 than celecoxib. This finding encourages us to consider COX-2 inhibitory activity as a proposed mechanism for their anticancer activity.

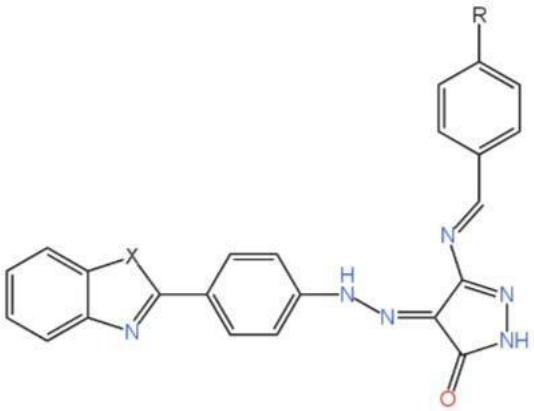

Figure 7 Benzothiazole and benzoxazole pyrazole hybrids

a X=O, R=NO_2, **b** X=S, R=Cl

El-Gaby et al. synthesized the structure of the newly compounds that were confirmed on the basis of analytical and spectral data. The utility of 4-isothiocyanato-N-(1-phenyl-1H-pyrazol-5-yl)benzene sulfonamide [8] in the synthesis of some novel thiosemicarbazide, carbothioate,1,3,4-thiadiazole, azomethine, thiourea, bis thiourea and imidazole derivatives is reported. Some of the prepared compounds were evaluated for their in vitro anticancer activity against Ehrlich ascites carcinoma cells (EAC). It was found that the corresponding 2-acetyl-N-(4-(N-(1-phenyl-1H-pyrazol-5-yl) sulfamoyl)phenyl) hydrazinecarbothioamide with IC50 value (2.14 μg/ml) showed better activity than doxorubicin with IC50 value (43.6 μg/ml) as reference drug.

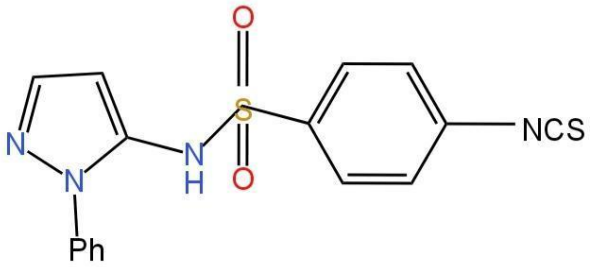

Figure 8 4-isothiocyanato-N-(1-phenyl-1H-pyrazol-5-yl)benzene sulfonamide

Chaudhary et al. designed and synthesized a series of Knoevenagel condensation by clubbing pyrazole carbaldehydes at the active methylene carbon atom of the curcumin backbone. Molecular docking studies were carried out to target the proposed derivatives on human kinase β (IKKβ), a potential anti-cancer target. The chloro derivative displayed five hydrogen bond interactions with a docking score of −11.874 kcal/mol higher than curcumin (docking score = −7.434 kcal/mol). The screened compounds were synthesized, characterized and evaluated in vitro for cytotoxicity against cervical cancer cell line, HeLa using standard cell proliferation assay. Chloro derivative and bromo analog demonstrated IC50 (half maximal inhibitory concentration) value of 14.2 and 18.6 μg/ml, respectively, significantly lower than 42.4 μg/ml of curcumin and higher than 0.008 μg/ml of paclitaxel. In conclusion, chloro and bromo derivatives must be evaluated under a set of stringent *in vitro* and *in vivo* parameters for translating into a clinically viable product.

Salem et al. studied chemical reactivity of 4-((6-chloro-4-oxo-4H-chromen-3-yl)methylene)-2-phenyloxazol-5(4H)-one towards nitrogen and sulfur nucleophiles, as well as bidentate nucleophiles under various conditions. The investigated nucleophilic reactions result in formation of heterocyclic systems, namely pyrazolyl oxazolone, pyrazole dihydro triazinone, chromanyl imidazolone, chromonyl imidazole, and chromonylbenzo[d]imidazole and chromonyloxathiazepine derivatives. All the synthesized products were screened for their anticancer activity against two cell lines, namely human colon (HCT-116) and mammary gland breast cancer (MCF-7) using the MTT assay. Some of the investigated compounds showed remarkable cytotoxic activities against HCT-116 (IC50 7.74–82.49 μg/mL) and MCF-7 (IC50 4.98–92.62 μg/mL) cells in comparison to the standard anticancer drug doxorubicin (IC50 5.23 and 4.17 μg/mL, respectively). Among the tested compounds, pyrazole benzamide and pyrazole dihydro triazinone derivatives were the most significant antiproliferative efficacy against the two cell lines. Our findings suggested that the designed compounds may be considered promising antiproliferative agents.

Nassar et al. prepared 4-(4-Chlorobenzylidene)-2,5-diphenyl-2,3-dihydro-3H-pyrazol-3-one and 4-(3,4-dimethoxybenzylidene)-5-phenyl-2,3-dihydro-3H-pyrazol-3-one and were reacted with phenylhydrazine, thiosemicarbazide, hydroxylamine hydrochloride, ethyl acetoacetate, diethyl malonate, malononitrile, ethyl cyanoacetate, and thiourea yielding fused pyrazole derivatives. Some of the new compounds were reacted with cyclic and acyclic sugars to produce new S-, O-, and N-glycoside derivatives. The antitumor activity against the human breast cancer cells (MCF-7) was assessed. Four of the new compounds showed IC50 values less than those of the positive control, indicating that these four compounds are better anticancer agents than doxorubicin.

Nossier et al. prepared and characterized a series of novel 1,3,4-triarylpyrazoles containing different heterocycles and screened for their in vitro antiproliferative activity against HePG-2, MCF-7, PC-3, A549 and HCT-116 cancer cell lines. The biological results revealed that compound [9] showed the highest anticancer activity so it was subjected to a kinase assay study where it reduced the activity of several protein kinases including AKT1, AKT2, BRAF V600E, EGFR, p38α and PDGFRβ at 100 μM using the radiometric or ADP-Glo assay method. Molecular docking simulation supported the initial kinase assay and suggested a common mode of interaction at the ATP-binding sites of these kinases, which demonstrates that compound [9] is a potential agent for cancer therapy deserving further research.

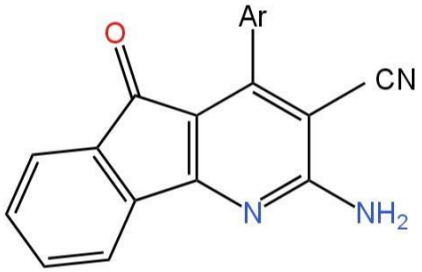

Figure 9 5-oxo-5*H*-indeno-[1,2-b]pyridine-3-carbonitrile

Du et al. synthesized a series of novel sugar-based pyrazole derivatives with good anticancer activity under microwave irradiation in eco-friendly water. Most of the new compounds displayed good inhibitory activity against HepG2 cells or A549 cells. The in vitro anti-proliferation assay and IC_{50} values supported our design and ensured these sugar- based pyrazole derivatives were promising lead compounds for the discovery of new anticancer drugs.

Akhmetova et al. synthesized new N,N′-mononuclear bi-ligand Pd(II) and tri-ligand Pt(II)complexes bearing sulfanyl(phenyl, benzyl, cyclohexyl, 4-hydroxyphenyl)3,5-dimethyl-1H-pyrazole ligands. The obtained compounds were studied for apoptosis-inducing activity and effect on the cell cycle for Jurkat, K562, and U937 neoplastic cell cultures and conditionally normal human embryonic kidney HEK293 cells. The cells showed the highest sensitivity to platinum and palladium complexes in comparison with ligands and cisplatin. The cytotoxic properties were enhanced for compounds with cyclohexyl substituents at the S-atom in sulfanyl pyrazoles and complexes.

Akhtar et al. synthesized a new series of benzimidazole linked pyrazole derivatives by cyclocondensation reaction through one-pot multicomponent reaction in absolute ethanol. All the synthesized compounds were tested for their in vitro anticancer activities on five human cancer cell lines including MCF-7, HaCaT, MDA-MB231, A549 and HepG2. EGFR receptor inhibitory activities were carried out for all the compounds. Majority of the compounds showed potent antiproliferative activity against the tested cancer cell lines. Compound [10] showed the most effective activity against the lungs cancer cell lines (IC50 = 2.2 µM) and EGFR binding (IC50 = 0.97 µM) affinity as compared to other members of the series. Compound [10] inhibited growth of A549 cancer cells by inducing a strong G2/M phase arrest. In addition, the same compound inhibited growth of A549 cancer cells by inducing apoptosis.

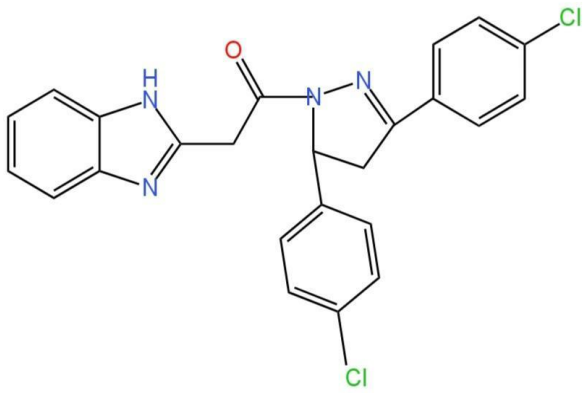

Figure 10 Benzimidazole derivative

Mahal et al. synthesized a series of new pyrazole derivatives of THC as potent anticancer agents. Direct condensation of THC with various substituted hydrazines leads to new pyrazole derivatives of THC [11]. The prepared compounds had been evaluated via in vitro MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay for their cell proliferation-inhibitory activity against human lung adenocarcinoma (A549), human cervical carcinoma (HeLa) and

human breast carcinoma (MCF-7) cells. Most derivatives showed significantly higher anticancer activity against all three tested cancer cell lines than the parent compound THC. Several compounds displayed promising anticancer activity against MCF-7 cell lines with IC50 values ranging from 5.8 to 9.3 μM. The most active compound was substituted with 4-bromophenyl group at the pyrazole ring and inhibits the growth of all three tested cancer cell lines with an IC50 values of (8.0 μM, A549), (9.8 μM, HeLa) and (5.8 μM, MCF-7). The obtained compounds can be a good starting point for the development of new lead molecules in the fight against cancer.

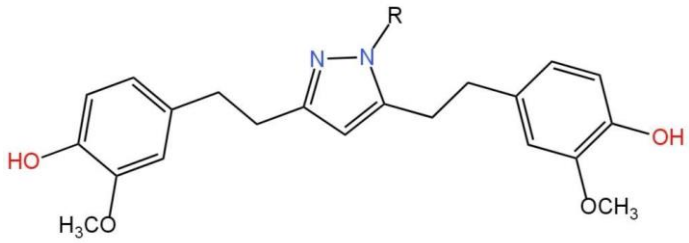

Figure 11 Pyrazole derivative of THC

Shi et al. designed and synthesized 12 novel scopoletin-isoxazole and scopoletin-pyrazole hybrids and their chemical structures were confirmed by HR-MS, IR, ^{1}H NMR and ^{13}C NMR spectra. The anticancer activities of the newly synthesized compounds were evaluated in vitro against three human cancer cell lines including HCT-116, Hun7 and SW620 by MTT assay. The screening results showed that six compounds exhibited potent cytotoxic activities with IC50 values below 20 μM. Besides, we have further evaluated the growth inhibitory activities of six compounds against the human normal tissue cell lines HFL-1. Especially, compound [12] displayed significant anti-proliferative activity with IC50 values ranging from 8.76 μM to 9.83 μM and weak cytotoxicity with IC50 value of 90.9 μM on normal cells HFL-1, which suggested that isoxazole-based hybrids of scopoletin were an effective chemical modification to improve the anticancer activity of scopoletin.

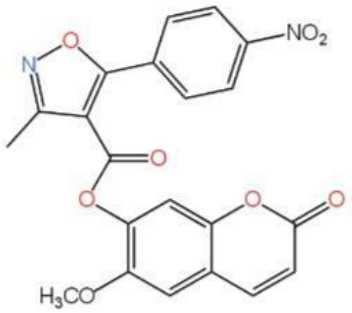

Figure 12 Scopoletin-pyrazole hybrid

Lv et al. synthesized fourty two thiazolyl-pyrazoline derivatives to screen for their EGFR kinase inhibitory activity. Compound 4-(-4-chlorophenyl) -2- (3- (3,4-di-methylphenyl) -5-p-tolyl-4,5-dihydro-1H-pyrazol -1- yl) thiazole displayed the most potent EGFR TK inhibitory activity with IC_{50} of 0.06uM, which was comparable to the positive Control. Molecular docking results indicated that the compound was nicely bound to the EGFR kinase. Compound also showed significant antiproliferative activity against MCF-7 with IC_{50} of 0.07uM, which would be a potential anticancer agent.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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