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Apoptosis induction potential of bioactive pyrazole scaffold

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Abstract
Pyrazole nucleus is a privileged scaffold in synthetic and medicinal chemistry which has been successfully propelling the interest of researchers towards synthesizing its various derivatives for a broad range of chemotherapeutic activities including its cytotoxicity to induce apoptotic cell death in different human cancer cell lines. Various conjugates bearing pyrazole scaffolds found to be very effective to antagonize proliferation of different human cancer cell lines. The bioactivity of pyrazole scaffold led the opportunity for the rational designing of novel compounds with improved potential of apoptotic induction, subsequently, new potent anticancer drugs for the next generation.

Keywords: pyrazole, apoptosis, anti-cancer

Introduction
Apoptosis [1] is highly regulated and important cellular process for tissue homeostasis and immune defence [2] which pursue programmed cell death upon receiving either extrinsic or intrinsic signals [3]. The extracellular death ligands and cognate death receptors (e.g., Fas, TRAIL, Tumor Necrosis Factor-Receptors [TNFR]) induces extrinsic pathway is induced and lead to the recruitment and activation of caspases such as caspases 3, 8 and 10 [4]. Mitochondrial mediated intrinsic pathway which responds to intracellular stress signaling (e.g., macromolecular damage) and results in activation of the Apoptosis Protease Activating Factor-1 (APAF-1), caspase-9, and caspase-3 [5]. Apoptosis, once triggered by any of physiologic signals may leads to precisely choreographed series of steps involving disruption of membranes, DNA fragmentation, cytoplasmic and nuclear shrinkage, nuclear fragmentation, and other morphological and biochemical changes [6]. Cancer research proved that insufficient apoptosis may cause tumor initiation, progression or metastasis [7] so reported as hallmark of cancer [8-9]. Apoptosis and its regulatory mechanisms affect significantly on the malignant phenotype and proved that drugs, showing potential to restore the normal apoptotic pathways in cancer cells, are found to be effective anticancer agents [10-11]. Consequently in the current scenario, novel synthesized compounds displaying the apoptotic induction pathways may be used as conventional anticancer agents.

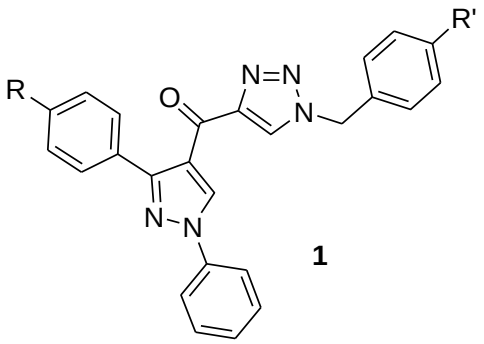
Pyrazole is a privileged scaffold has significant position in the field of synthetic and medicinal chemistry. Owing to its worthy chemotherapeutic potential this scaffold receives much attention of synthetic chemist in the field of drug discovery and development. Pyrazole and its derivatives possess a wide range of pharmacological activities [12-13] such as antiinflammatory, antipyretic, analgesic, antimicrobial, anticancer, sodium channel blocker, antitubercular, antiviral, antihypertensive, antiglaucoma, antioxidant, antidepressant, anxiolytic, neuroprotective and antidiabetic activity. This nucleus is present as the core in a variety of leading marketed drugs such as celebrex, deracoxib, tartrazine, mepiprazole, lonazlac, sildenafil (Viagra), rimonabant and difenamizole.

Pyrazole templet is also considered being associated with its ability to induce apoptosis in a variety of cancer cells including breast, lungs, colon, stomach, prostate [14-15] etc. Consequently, this ring proved to be favourable in the design of drugs targeting cellular apoptosis. This nucleus is a also highly versatile drug-like template that is being used extensively in the design of anti-cancer drugs [16-17].

This article describes the significance of pyrazole nucleus in significantly enhancement apoptotic induction potential of various reported hybrids in different solid tumors and cancer cell lines with the expectation to lead the opportunity to further explore the designing and synthesis of pyrazole based novel compounds bearing improved apoptotic induction potential and can be effective as anticancer agents in different cell lines. Consequently, the recognition of apoptosis inducers is an optimistic approach for the discovery and development of potential anticancer agents.

Pyrazole-triazole conjugates

A series of thirty pyrazole-triazole conjugates (1-benzyl-1H-1,2,3-triazol-4-yl)(1,3-diphenyl-1H-pyrazol-4-yl) methanones were synthesized and tested for their pro-apoptotic potential against four tumor cell lines, viz. colon (HT-29), prostate (PC-3), lung (A549), and glioblastoma (U87MG) cells. Hybrid compounds 1a-c exhibited more potent cytotoxic activity than the standard 5-Fluorouracil against all the tested cancer cells. In addition, apoptotic induction mechanism in U87MG cells has been studied and reported via mitochondrial pathway through up-regulation of pro-apoptotic (Bax) and down regulation of anti-apoptotic (Bcl-2) gene [18].

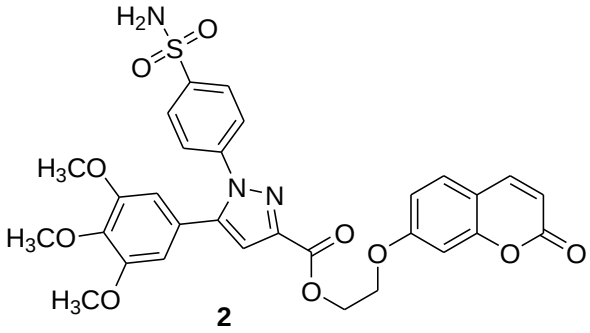


1

a) R = F, R' = 3,4-OCH_3, l) R = Cl, R' = 3,4-OCH_3, m) R = OCH_3, R' = 3,4-OCH_3

Pyrazole-coumarin conjugates

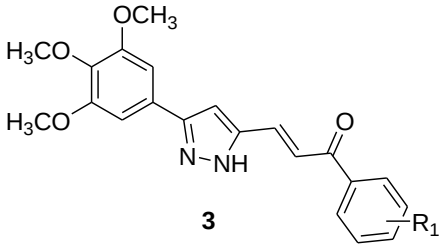
Shen *et al.* [19] designed and synthesized twenty hybrids of pyrazole with substituted coumarin to exhibit in vitro anti-proliferation and cells apoptosis by 5-LOX inhibition in human lung cancer A549 cells. Among them, the hybrid **2** found to be most potent to induce apoptosis in A549 cells by arresting the cell cycle at G2 phase.



2

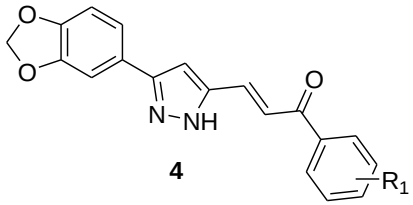
Pyrazol-chalcones conjugates

In other study, Shaik *et al.* [20] synthesized and screened forty pyrazol-chalcone conjugates for their cytotoxic activity against a panel of sixty cancer cell lines. Investigation revealed that fifteen conjugates 3a-g, 4a-b, 5a-c, 6a-b and 7 showed excellent growth inhibition against human breast cancer cell line (MCF-7) by inducing cell cycle arrest, mitochondrial membrane depolarization and apoptosis in MCF-7 cells. In addition, inhibition of PI3K/Akt/mTOR pathway-regulators was also observed in the study.



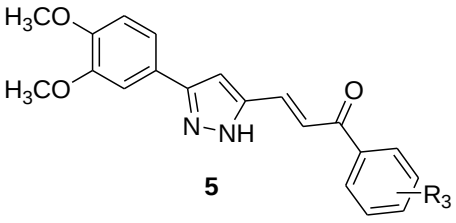
3

a) R_1 = 4-OCH_3, b) R_1 = 3,4$(OCH_3)_2$, c) R_1 = 3,4,5$(OCH_3)_3$, d) R_1 = 3,4(OCH_2O), e) R_1 = 3,4$(Cl)_2$, f) R_1 = 3,4$(F)_2$, g) R_1 = 4-NH_2



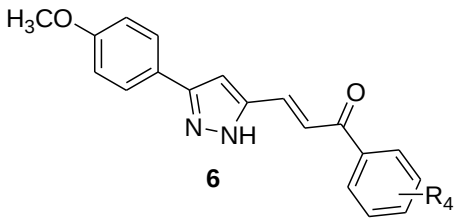
4

a) R_2 = 3,4$(OCH_3)_2$, b) R_2 = 3,4,5$(OCH_3)_3$



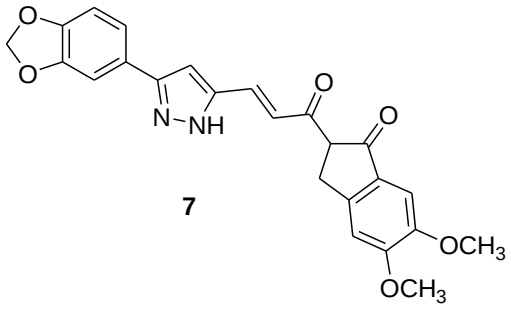
5

a) R_3 = 3,4,5$(OCH_3)_3$, b) R_3 = 3,4(OCH_2O) c) R_3 = 4-NH_2



6

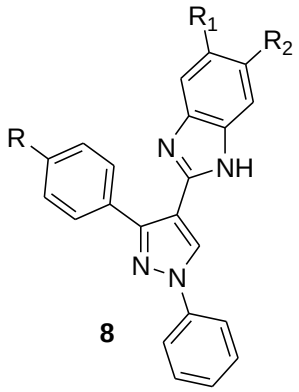
a) R_4 = 3,4(OCH_2O), b) R_4 = 4-NH_2



7

Pyrazole-benzimidazole conjugates

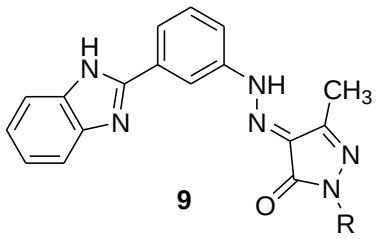
Redddy *et al.* [21] synthesized and investigated forty pyrazole containing benzimidazole hybrids for their potential anti-proliferative activity against three human tumor cell lines viz. lung (A549), breast (MCF-7), and cervical (HeLa). Compounds 8a-c showed potent growth inhibition against all the cell lines tested by arresting cell cycle at G_1 stage.



8

a) R = H, R_1 = Br, R_2 = H,
b) R = F, R_1 = F, R_2 = H,
c) R = Cl, R_1 = Cl, R_2 = H

In another study, Abdelgawad *et al.* [22] also reported the synthesis and screening of some pyrazole- benzimidazole hybrids against for their antiproliferative activity against breast carcinoma (MCF-7) and non-small cell lung cancer (A549) cell lines. Hybrid 9b was found most active compound against both MCF-7 and A549 cell lines.

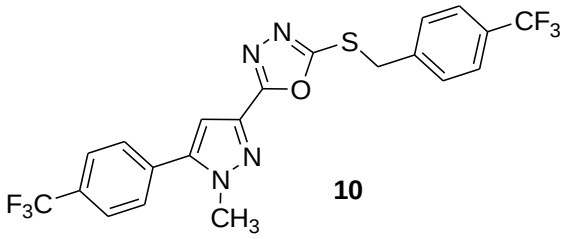


9

a) R = H, b) R = $COCH_3$, c) C_6H_5

Pyrazole-oxadiazole conjugates

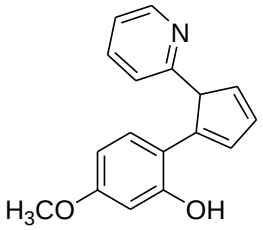
Puthiyapurayil *et al.* [23] synthesized a series of oxadiazole-pyrazole conjugates and evaluated them for in-vitro cytotoxic activity human cancer cells, breast cancer cell line (MCF-7) and alveolar adenocarcinoma cell line (A549). Investigation revealed that compound 10 was found to be the most promising cytotoxic agent among the treated once.



10

Pyrazole-pyridine conjugates

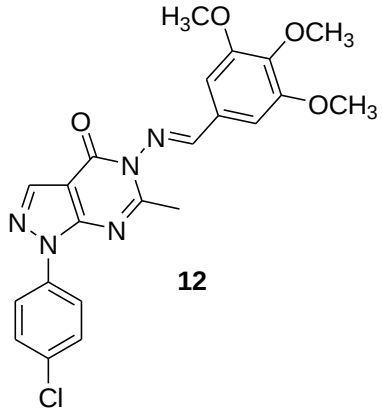
Babli *et al.* [24] synthesized thirty-six novel pyrazole derivatives bearing pyridine ring and investigated their antiproliferative activity in human ovarian adenocarcinoma A2780 cells, human lung carcinoma A549 cells, and murine P388 leukemia cells. Results analysed that compound 11 induced apoptosis and arrested cell cycle.



11

Pyrazole-pyrimidine conjugates

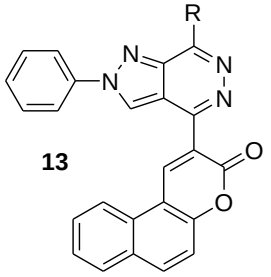
Hassan *et al.* [25] have reported the synthesis of two series of N'-(4-chlorophenyl) pyrazolo [3,4-d] pyrimidines and N'-(4-chlorophenylsulfonyl) pyrazolo [3,4-d] pyrimidines and screened all the synthesized hybrids for their cytotoxic activity against human breast cancer MCF-7 cell lines. Mostly treated compounds possessed potential to inhibit growth of cancer cell lines. In particular, compound 12 exhibit better potency to the reference drug cisplatin to induce apoptois and inhibit growth of MCF-7 cell lines.



12

Pyrazole-pyridazine conjugates

In this study, antitumor activity of three pyrazolo [3,4-*d*] pyridazine derivatives 13 were investigated against A549 (lung cancer cell line); HCT-116 (colorectal carcinoma cell line); HEPG2 (liver carcinoma cell line), HFB4 (normal human skin melanocyte cell line) and WI-38 (human embryonic lung fibroblasts). Compound 13a exhibited remarkable cytotoxic activity on all treated cancer cell lines, with the highest anti-tumor activity on A549. The result also revealed that compound 13a was capable to activate apoptosis by cell cycle arrest at the Sub G1 and the G2/M phase. Furthermore, the study also demonstrated that compound 13a induced apoptosis possible through intrinsic mitochondria-dependent pathway by disruption of the Bcl-2/ BAX balance in lung cancer cell lines [26].

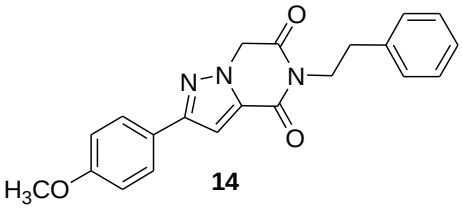


13

a) R = OH, b) R = CH_3, c) R = C_6H_5

Pyrazole-pyrazine conjugates

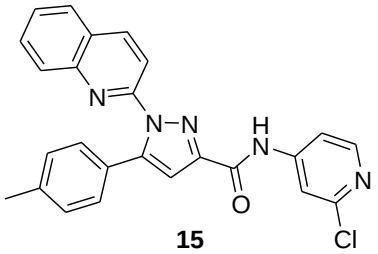
Lv *et al.* [27] synthesized a series of novel substituted 5-benzyl-2-phenylpyrazolo [1, 5-a] pyrazin-4,6 (5H,7H)-dione derivatives and evaluate the them for their ability to induce apoptosis in A549 and H322 lung cancer cell growth. Results showed that the compound 14 inhibited selectively much more proliferation of H322 lung cancer cells.



14

Pyrazole-quinoline conjugate

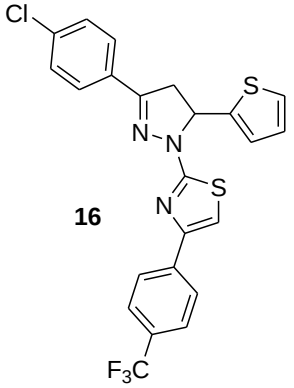
Pirol *et al.* [28] synthesized a series of pyrazole-quinoline hybrids and assessed their antiproliferative activities against three human cancer cell lines (Huh7, human liver; MCF7, breast and HCT116, colon carcinoma cell lines). Results revealed that hybrid 15 exhibited promising cytotoxic activity against all treated cell lines and induced apoptotic cell death by arresting cell cycle at SubG1/G1 phase.



15

Pyrazole-thiazole-thiophene conjugates

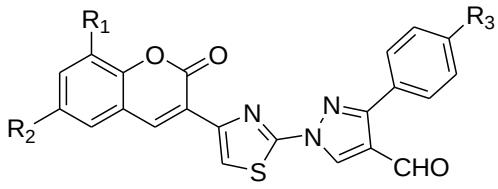
Zhao *et al.* [29] designed and synthesized a series of pyrazole derivatives containing thiazole and thiophene moieties as potential V600E mutant BRAF kinase (BRAFV600E) inhibitors and evaluated *in vitro* for anticancer activities against WM266.4 human melanoma cell line and breast cancer MCF-7 cell line. Biological active data revealed that mostly synthesized compounds showed effective BRAFV600E inhibitory activity and antiproliferative activity against WM266.4 and MCF- 7 cell lines. Furthermore, hybrid 16 found the most potent agent to show BRAFV600E inhibitory activity along with antiproliferative activity for WM266.4 and MCF- 7 cell lines.



16

Pyrazole-coumarin-thiazole conjugates

Vaarla *et al.* [30] have synthesized a series of coumarin substituted thiazolyl-3-aryl-pyrazole-4-carbaldehydes 17 and were screened for their *in vitro* cytotoxic activity against human cancer cell lines viz. MCF-7, DU-145 and HeLa cell lines. Results showed that compounds 17a and 17b exhibited significant cytotoxic activity through apoptosis induction against HeLa cell line.

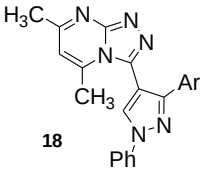


17

a) R_1 = Cl, R_2 = Cl, R_3 = CH_3,
b) R_1 = Br, R_2 = Br, R_3 = CH_3

Pyrazole-triazole-pyrimidine conjugates

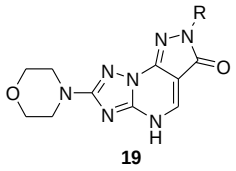
Kamal *et al.* [31] reported the synthesis and screening of ten 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)- 5,7- dimethyl- [1,2,4] triazolo [4,3-a] pyrimidines 18a-j for their *in vitro* ability to induce apoptosis in testicular germ cells of *Capra hircus*. All screened compounds were found to have potent cytotoxicity associated with them to induce apoptotic cell death.



18

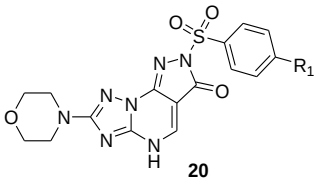
Ar = a) C_6H_5, b) 4-CH_3-C_6H_4, c) 4-OCH_3-C_6H_4, d) 2-OCH_3-C_6H_4, e) 4-NO_2-C_6H_4, f) 3-NO_2-C_6H_4, g) 4-Cl-C_6H_4, h) 4-Br-C_6H_4, i) 4-F-C_6H_4, j) $C_{10}H_7$

Hassan *et al.* [32] synthesized and evaluated a series of pyrazolotriazolopyrimidine hybrids 19a-e and 20a-b for their *in vivo* antitumor activity against Ehrlich ascite carcinoma in mice. Results revealed that all evaluated compounds shown potential to induce apoptosis as anti-tumor agents.



19

a) R = H, b) R = C_6H_5, c) R = 4-ClC_6H_4, d) R = 4-$CH_3OC_6H_4$, e) R = 2,4$(NO_2)_2C_6H_3$



20

a) R_1 = H, b) R_1 = CH_3

Conclusions

In this review, an overview of the different conjugates of pyrazole with different moieties such as triazole, coumarin, chalcone, benzimidazole, oxadiazole, pyridine, pyrimidine, pyridazine, pyrazine, quinoline, thiazole, thiophene etc have been highlighted and discussed. These observations will be beneficial for the development of novel compounds bearing pyrazole scaffold as potent apoptotic inducer which subsequently can be effective anticancer agents in different cancer cell lines.

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Conflict of Interest: The author has declared no conflict of interest.

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