*Review Article*

# Hydrazones as potential anticancer agents: An update

**Diksha Saini, Monika Gupta***

*Department of Pharmaceutical Chemistry, A.S.B.A.S.J.S.M. College of Pharmacy, Bela, 140111(Punjab), India*

https://doi.org/10.31024/ajpp.2018.4.2.4

Received: 9 February 2018 Revised: 7 March 2018 Accepted: 11 March 2018

**Abstract**

Hydrazone derivatives of carbonyl compounds considered to be biologically important class of compounds. Literature studies revealed that hydrazones and various substituted hydrazones are associated with a broad spectrum of biological activities such as antioxidant, antibacterial, antiviral, analgesic, antiplatelet, antimicrobial, and anticancer. The present paper is focused on the overview of the literature findings of the last four years (2014–2017) covering the research on anticancer activity of hydrazone derivatives.

***Keywords:*** Hydrazones, cytotoxicity, Anti proliferative, tubulin polymerization

## Introduction

The hydrocarbons with the structure $R_1R_2C{=}NNH_2$ are categorized as Hydrazones (March, 1985). They contain $NNH_2$ functional group in place of carbonyl oxygen of ketones and aldehydes. They are formed usually by the action of ketones or aldehydes on hydrazine (Stork and Benaim, 1977; Day and Whiting, 1970) (Figure 1). The hydrazones contain C = N bond, which is conjugated with a lone pair of electrons of the nitrogen atom. The carbon atom of the hydrazones has both electrophilic and nucleophilic nature while nitrogen atoms are nucleophilic in nature. The α-hydrogen of hydrazones is more acidic than that of acidic ketones. The combination of hydrazones with other functional group leads to compounds with unique physical and chemical character so they are considered important for the synthesis of heterocyclic compounds.

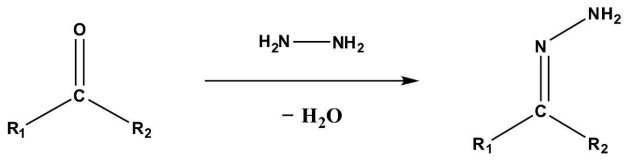



**Figure 1.** Reaction for formation of hydrazone

Hydrazones act as precursor for the synthesis of different heterocyclic scaffolds (Rollas and Kucukguzel, 2007), like 1,3,4-oxadiazolines (Dogan et al., 1998), azetidin-2-ones(Kalsi, et al., 2006), coumarins (Mohareb, et al., 2011), 1,3-thiazolidin-4-ones (Popiolek, et al., 2015; Popiolek, et al., 2016), and 1,3-ben- zothiazin-4-ones (Popiolek, 2016).

The hydrazones exhibit geometrical isomerism (syn and anti) due to the presence of the double bond between C and N. This geometrical isomerism have been reported to play important role in the bioactivity of the acyl hydrazones hence their studies are very crucial to develop synthetic methods for selective synthesis of a particular isomer. The hydrazones have been reported to possess diverse biological activities such as anti-inflammatory, analgesic, anticonvulsant, antituberculosis, antitumor, anti-HIV and antimicrobial activity.

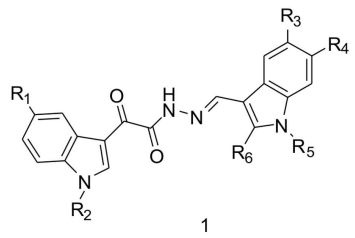
Recent years has witnessed some of the marketed hydrazone derivatives such as **Iproniazide (**Singh, et al., 1992) as antidepressant; **Nifuroxazide and Furazolidone** (Chatterjee, et al., 1979) an oral antibiotic; used in colitis and enteritis treatment respectively, **Nitrofurazone** (Mccalla, et al., 1970) in the treatment of **skin infections** due to **skin grafts** and **Nitrofurantoin** (Munoz-Davila, 2014) in **urinary tract infections**. 2,4-Dinitrophenyl hydrazones of diaryl ketones named 4,4'-Dihydrobenzophenone-2,4-dinitrophenyl-hydrazone (A-007) (Shankar et al., 2017) have been reported in phase II clinical trials. Small molecules like guanylhydrazone (Shankar et al., 2017) have been reported to block estrogen receptor (ER) activity by directly interfering with coactivator binding to agonist-liganded ER.

The present review emphasizes on the anticancer activity of hydrazone derivatives reported in last four years.

## Anticancer activity of Hydrazones

Cancer can be defined as a disease in which a group of abnormal cells grow uncontrollably by disregarding the

*Address for Corresponding Author:
Dr. Monika Gupta
Department of Pharmaceutical Chemistry, A.S.B.A.S.J.S.M. College of Pharmacy, Bela, 140111 (Punjab), India
E-mail: monikaguptaa@gmail.com



1

| S. No. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|---|
| **1a** | H | H | Br | H | H | H |
| **1b** | H | 4-$ClC_6H_4CH_4CH_2$ | $OCH_3$ | H | H | H |
| **1c** | H | H | $OCH_3$ | H | H | H |
| **1d** | H | H | H | $OCH_3$ | H | H |
| **1e** | H | 4-$ClC_6H_4CH_4CH_2$ | H | H | H | H |

**Figure 2.** Bis(indolyl)ketohydrazide-hydrazones

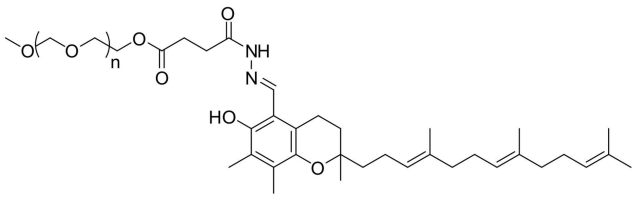


**Figure 3.** γ-T3-mPEG 2000 hydrazone (n= 48 mPEG 2000)

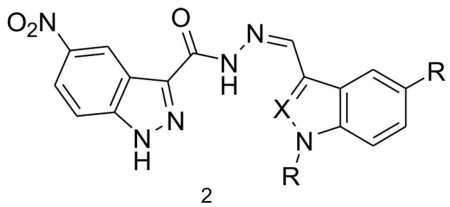
normal rules of cell division. Normal cells are constantly subjected to signals that dictate whether the cell should divide, differentiate into another cell or die. Cancer cells develop a degree of autonomy from these signals, resulting in uncontrolled growth and proliferation. Anticancer agents act on various tumour cells by different mechanisms such as they act by inhibiting protein kinases, cause microtubule dysfunctioning, inhibiting topoisomerase I or II, down regulating oncogenes expression, induce apoptosis and interrupt cell division. Researchers synthesized various substituted hydrazones and screened for their anticancer activity on various cell lines *i.e.* human breast cancer, human colon carcinoma, leukemia, lung cancer, human gastric cancer, human esophageal cancer and pancreatic cancer during last five years. They have been reported to act by inhibiting RNA and DNA synthesis (Kaplanek et al., 2015), inhibiting mitosis (Kaplanek et al., 2015), induced caspase-dependent apoptosis (Tantak et al., 2017), inhibiting tubulin polymerization and cause cell cycle arrests in G2/M phase (Tantak et al., 2017), cancer cycle arrest at sub G1/G0 phase (Senkardes et al., 2016), tumor cell apoptosis (Shen et al., 2017).

Tantak et al. (2017) designed and synthesized bis(indolyl)ketohydrazide-hydrazonescompounds (Tantak et al., 2017) (Figure 2) and evaluated them against multiple cancer cell lines. Among the twenty synthesized compounds, compounds **1a, 1b, 1c, 1d, 1e** exhibited anticancer activity. SAR studies revealed that C-5 methoxy, bromo and N-(4-chlorobenzyl) groups in indole ring are beneficial for the activity Compound **1e** [N'-((1H-Indol-3-yl)methylene)-2-(1-(4-chlorobenzyl)-1H-indol-3-yl)-2-oxoaceto-hydrazide] contains two indole rings present which are critical for the excellent *in vitro* anticancer activity and were found to be the most active against various cell lines, human breast cell lines (MCF-7, MDA-MB-231), human colon carcinoma cell lines (HCT-116) and leukemia cell line (JURKAT). It was also found to be more selectively cytotoxic against tumor cells when compared to normal cells. Mechanism of action studies done by researchers indicated that active compound induced caspase-dependent apoptosis in cells. It arrests cell cycle in G2/M phase by inhibiting of tubulin polymerization.

Shen et al. (2017) synthesized complex (E)-N'-(1-(pyridin-2-yl)ethylidene) nicotinohydrazide (penh) and metals complex such as [Co (penh)2], [Cu(penh)2], [Cd(penh)2], [Mn(penh)2] (Shen et al, 2017). All complexes were able to markedly decrease the proliferation rate of various types of tumor cell, including the human lung cancer cell line A549, human gastric cancer cell line BGC823 and human esophageal cancer cell line Eca109, in a concentration-dependent manner. Furthermore, the complexes promoted tumor cell apoptosis.

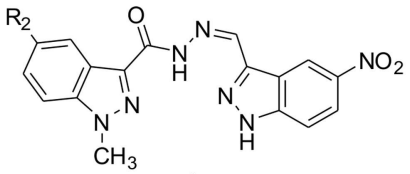
The anticancer activity of water soluble methoxy polyethylene glycol (mPEG) derivatives of tocotrienol (T3) isomers of vitamin E was previously found to be reduced when compared to the parent free isomers. This could be due to the ester bond formation between the mPEG and the 6-OH group on the chroman moiety of the T3 isomer. To further investigate Fayyad et al. (2017) synthesized, physiochemical characterized, stable amide and hydrazone conjugates between mPEG and carbon-5 on the chroman moiety of T3(Fayyad et al., 2017) (Figure 3) and examined the cytotoxicity of the newly synthesized mPEG conjugates against breast (MCF-7 and MDA- MB-231) and pancreatic (BxPC-3 and PANC-1) cancer cells. Conjugates were synthesized by direct conjugation of succinyl chloride derivatives of mPEG to the α-tocopherol and γ-tocotrienol isomers of vitamin E. The hydrolysis of the hydrazone conjugate was pH dependent with highest release at acidic (pH 5.5) conditions, whereas the amide conjugate was stable in all tested media. The amide conjugate nonetheless showed greater cytotoxicity than the hydrazone conjugate, which suggested that maintaining solubility and the presence of free 6-OH group are important for γ-T3 to exert anticancer activity in vitro.

In another study a series of ten novel Hydrazide–hydrazones linked indole and indazole moieties were



2

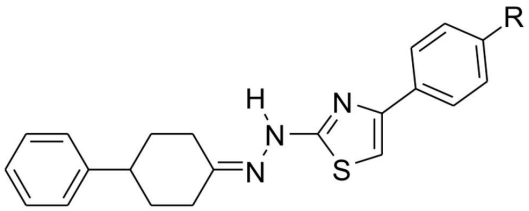
| S. No. | R | $R_1$ | X |
|---|---|---|---|
| **2a** | H | H | CH |
| **2b** | H | $CH_3$ | CH |
| **2c** | Br | H | CH |



3

| S. No. | R1 |
|---|---|
| **3a** | H |
| **3b** | Br |

**Figure 4.** Hydrazide–hydrazones linked indole and indazole moieties



4

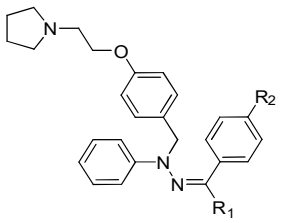
| S. No. | R |
|---|---|
| **4a.** | $O_2SCH$ |
| **4b.** | Cl |
| **4c.** | CN |

**Figure 5.** Thiazolyl hydrazone

synthesized **(**Sreenivasulu et al, 2017) (Figure 4) and evaluated for their cytotoxicity against four human cancer cell lines *i.e.* HeLa (cervical cancer cells), MDA-MB-231, MCF-7 (human breast adenocarcinoma cells) and A549 (human alveolar adenocarcinoma cells). The docking studies performed by suggested that the presence of the indole ring plays a critical role in the cytotoxicity of the compounds. Three of the synthesized compounds **2a, 2b, and 2c** showed a comparatively promising cytotoxicity on different cell lines. Compound 2b showed promising cytotoxic effect on HeLa and A549 cancer cell lines. The compound 2c showed promising cytotoxic effect on MCF-7 cancer cell lines. While, compound 2a showed a promising cytotoxic effect on A549 and HeLa cancer cell lines with. Further, compounds **3a** and **3b** showed promising cytotoxicity towards MCF cell line.

Kaplancikli et al. (2017) synthesized Thiazolyl hydrazone **(**Kaplancikli et al., 2017) (Figure 5) from the reaction of 1-(4-Phenylcyclohexylidene)thiosemicarbazide with 2-Bromoacetophenone derivatives and evaluated for their anticancer activity on A549 human lung adenocarcinoma, HepG2 human liver hepatocellular carcinoma and C6 rat glioma cell lines. **Compound 4a[**4-(4-Methylsulfonylphenyl)-2-(2-(4-phenylcyclohexylidene) hydrazinyl) thiazole] was found to be the most promising anticancer agent against HepG2 cell line**. Compounds 4b and 4c** also exhibited cytotoxic effects on HepG2 cell line.

Shankar et al. (2017) designed and synthesized a series of triaryl-substituted hydrazones (Shankar et al., 2017) (Figure 6) and screened for anti-proliferative activity against breast and uterine cancer cell lines. Two compounds **5a** and **5b** were found to be the most active, 5a showed the maximum inhibition of both functional estrogen receptor containing Michigan cancer foundation-7 cells and Ishikawa cells by its estrogen receptor antagonistic effect. Compound 5b was selectively most active against ER-negative MD Anderson metastatic breast-231 cells.



5

| S. No. | $R_1$ | $R_2$ |
|---|---|---|
| **5a** | $CH_2CH_3$ | H |
| **5b** | $CH_3$ | $OCH_3$ |

**Figure 6.** Triaryl-substituted hydrazones

Senkardes et al.(2016) designed and synthesized a number of 2',4'-Difluoro-4-hydroxy-N'-(arylmethylidene) biphenyl-3-carbohydrazide (Senkardes et al., 2016) (Figure 7) as anti-HCV and anticancer agents. Compound 2',4'-Difluoro-4-hydroxy-N'-[(pyridin-2-yl) methylidene]biphenyl-3-carbohydrazide **(6a)** with 2-pyridinyl group in the hydrazone part exhibited promising cytotoxic activity against liver cell lines *i.e.* Huh7, HepG2, Hep3B, Mahlavu, FOCUS and SNU-475cells, respectively, and produced dramatic cell cycle arrest at SubG1/G0 phase as an indicator of apoptotic cell death induction.

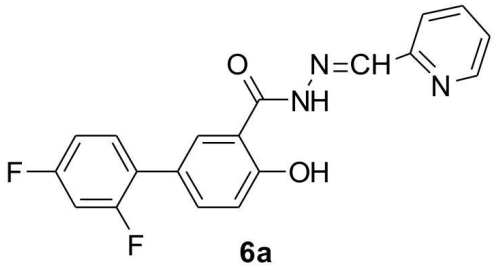



**Figure 7.** 2',4'-Difluoro-4-hydroxy-N'-[(pyridin-2-yl)methylidene]biphenyl-3-carbohydrazide

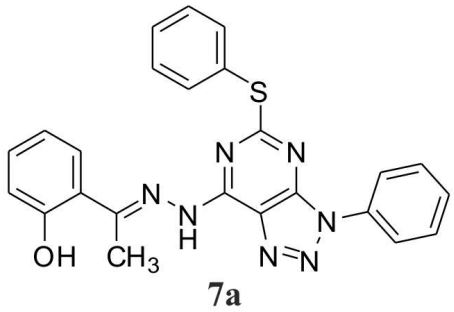



**Figure 8.** 2-(1-(2-(3-Phenyl-5-(phenylthio)-3H-[1,2,3]triazolo [4,5-d]pyrimidin-7-yl)hydrazono)ethyl)phenol

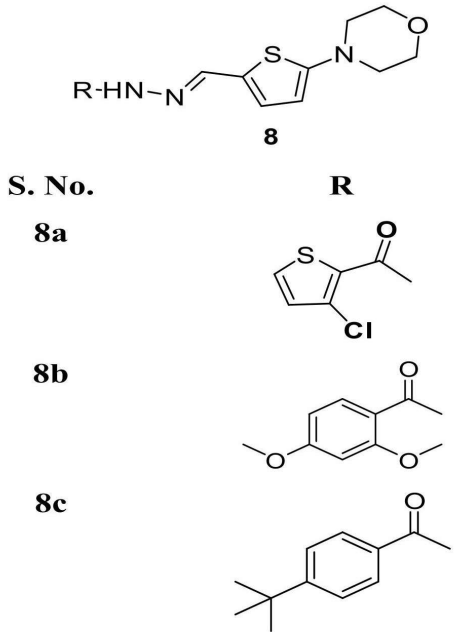



**Figure 9.** Morpholinothiophene hydrazone derivatives

Li et al. (2016) designed and synthesized a series of [1,2,3]Triazolo[4,5-d]pyrimidine derivatives bearing a hydrazone moiety (Li et al., 2016) (Figure 8) and biologically evaluated for their antiproliferative activity. Among all the synthesized compounds, compound **7a** exhibited more potent inhibition against the tested cancer cells such as MGC-803 (human gastric cancer cell line), MCF-7 (human breast cancer cell line) and EC-109 (human esophageal cancer cell line) by inducing apoptosis. Mechanism investigation showed that compound **7a** can inhibit the colony formation and induce morphological changes and lead to apoptosis with the decrease of mitochondrial membrane potential in MGC-803 cells.

Taha et al. (2016) synthesized a series of Morpholine derivatives (Taha et al., 2016) (Figure 9). Small series of morpholinothiophene hydrazones were synthesized by treating 5-Morpholinothiophene-2-carbaldehyde with different Aryl hydrazides and evaluated for their in vitro anticancer potential against two human cell lines like MCF-7 (breast carcinoma) and HepG2 (liver carcinoma). The results showed morpholine derivatives showed strong growth inhibitory effect on MCF-7 cell by encouraging cancer cell apoptosis. Compounds **8a** and **8b** were found to be outstanding inhibitors for MCF-7 cell. Compound **8c** showed potent inhibition against HepG2 cell. The molecular docking studies were performed to understand the binding interaction of the active compounds.

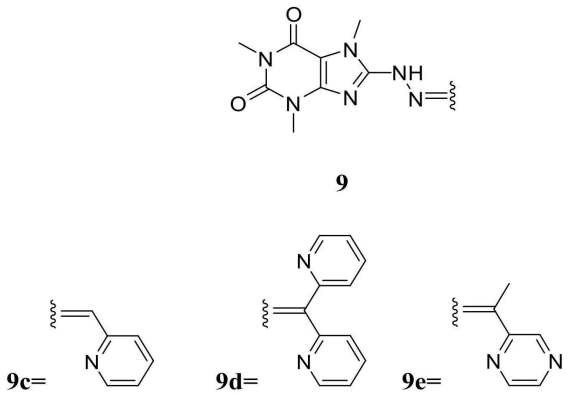



**Figure 10.** Caffeine- hydrazone

Some novel anticancer agents based on Caffeine-hydrazones bearing 2-hydroxyaryl or 2-N-heteroaryl moiety were also synthesized (Kaplanek et al., 2015) (Figure 10). Anticancer activity evaluation done by using nine cell lines, seven were cancer cell lines and two were non-malignant cell lines. Six compounds (**9a, 9b, 9c, 9d, 9e and 9f**) show high cytotoxic activity. The best results were obtained for compounds possessed 2-N-heterocyclic moiety (**9c, 9d and 9e**) which show superior selectivity against malignant versus non-malignant cells. Majority of tested compounds exhibits dose dependent inhibition of both RNA and DNA synthesis, mitosis and induced apoptosis.

Another hydrazone derivatives based on a Troger's base skeleton were synthesized (Kaplanek et al., 2015) (Figure 11) and biologically evaluated against anticancer and antimicrobial activity. The anticancer activity of the prepared hydrazones was tested on nine cell lines. Compounds **10a, 10b, 10c, 10d** and **10e** showed excellent selectivity against leukaemic cells. Compounds 10b, 10c

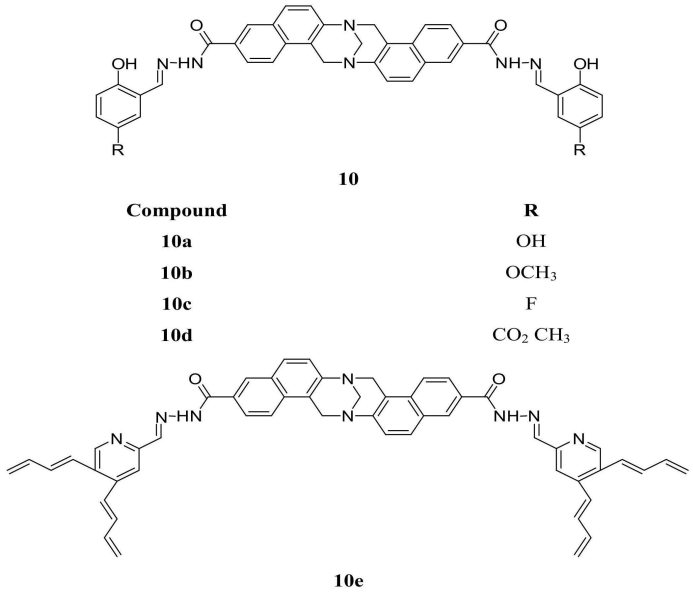



**Figure 11.** Hydrazone derivatives based on a Troger's base skeleton

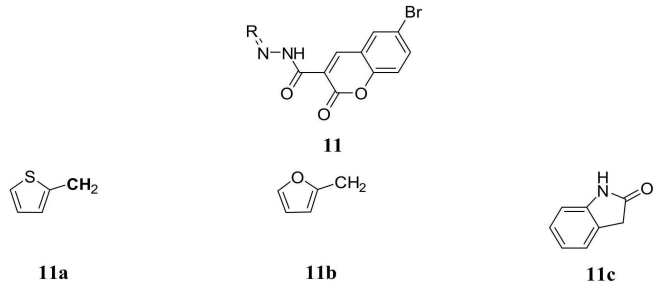



**Figure 12.** 6-Brominated coumarin hydrazide-hydrazone

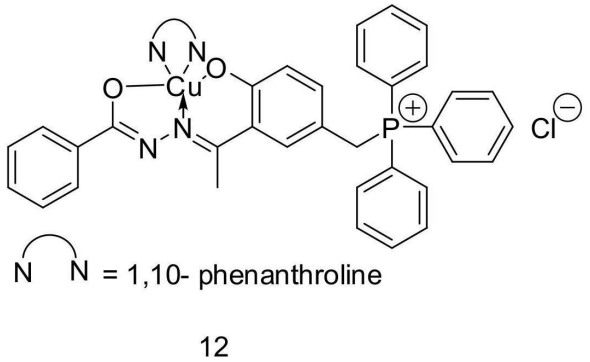



**Figure 13.** Cu(II) complexes of hydrazone ligand containing triphenylphosphonium moiety

and 10e showed superior selectivity for all leukaemic and cancer cell lines compared to healthy cell lines. The prepared compounds did not show any antimicrobial activity. Complexation studies with biologically important metal ions demonstrated that these compounds could bind to the $Co^{2+}$, $Cu^{2+}$, $Fe^{3+}$, $Ni^{2+}$ and $Zn^{2+}$ ions. DNA interaction studies showed that the compounds do not interact with DNA alone, but their metallocomplexes with $Co^{2+}$, $Cu^{2+}$, $Fe^{3+}$, $Ni^{2+}$ and $Zn^{2+}$ interact, probably through intercalation into DNA. Results demonstrate that hydrazones with Troger's base skeletons are a promising class of potent cytostatic agents with high selectivity toward leukaemia and cancer cells.

Nasar et al. (2014) designed and synthesized sixteen Coumarins bearing hydrazide-hydrazone moiety (Nasar et al., 2014) (Figure 12) and evaluated them against human drug-resistant pancreatic carcinoma (Panc-1) cells and drug-sensitive (hepatic carcinoma; Hep-G2 and leukemia; CCRF) cell lines in vitro. The most potent compounds were 6-brominated coumarin hydrazide-hydrazone derivatives BCHHD's **11a, 11b** and **11c**. **BCHHD 10a** showed significant cytotoxicity against all tested cells, whereas **BCHHD's 11b** and **11c** showed significant antiproliferative activity only against resistant Panc-1cells. All the BCHHD's were able to activate caspases 3/7 and they could induce apoptosis in resistant Panc-1 cells. The microarray result showed that BCHHD 11a induced the expression of apoptosis and cell cycle arrest in G2/M phase. Moreover, BCHHD 11a induced the up-regulation of CDKN1A, DDIT4, GDF-15 and down-regulation of CDC2, CDC20, CDK2 genes. 11a could be a potent anticancer drug to overcome drug resistance in cancer and it could be highly beneficial for patients in the clinic.

Chew et al. (2014) synthesized Mononuclear Cu(II) complexes of hydrazone ligand containing triphenyl-phosphonium moiety (Chew et al., 2014) (Figure 13). The cytotoxicity and topoisomerase I (topo I) inhibition activities of these compounds were studied. Complex 12 *i.e.* (1,10'-phenanthroline)[5-(triphenylphosphoniummethyl)-salicylaldehydebenzoylhydrazonato] copper(II) monohydrate ethanol exhibits the highest activity against human prostate adenocarcinoma cell line (PC-3) with the IC50 value of 3.2 mM. The addition of N,N-ligands to the copper(II) complex lead to the enhancement in the cytotoxicity of the compounds, especially against human prostate adenocarcinoma cell line. All the compounds can inhibit topo I upon complexation through the binding to DNA and the enzyme.

## Conclusion

The present work gives an overview of the anticancer activity of diverse hydrazone derivatives. The hydrazone moiety has been an indispensable pharmacophore for various bioactive molecules. During last five years, hydrazones have occupied a significant position in anticancer research by exhibiting variety of mechanism of action and possessing *in vitro* growth inhibition activity against various cancer cell lines. This work can act as an aid to the researchers for the development of novel anti cancer hydrazones. Based upon the reported pharmcophores; the scientific community can utilize hydrazones as lead and explore further to get safer and

effective compounds.

**Conflict of interest**

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

**References**

Ahmad AF, Sami S. 2017. Synthesis, physiochemical characterization, and in vitro antitumor activity of the amide and pH cleavable hydrazone conjugates of γ-tocotrienol isomer of vitamin E with methoxy-poly(ethylene) glycol. International Journal of Pharmaceutics, 529:75-86.

Chatterjee SN, Ghosh S. 1979. Mechanism of action of furazolidone: inter-strand cross-linking in DNA & liquid holding recovery of Vibrio cholerae cells. Indian Journal of Biochemistry & Biophysics, 16:125-130.

Chew ST, Lo KM, Lee SK, Heng MP, Teoh WY, Sim KS, Tan KW. 2014. Copper complexes with phosphonium containing hydrazone ligand:Topoisomerase inhibition and cytotoxicity study. European Journal of Medicinal Chemistry, 76:397-407.

Day AC, Whiting MC. 1970. Acetone hydrazone. Organic Synthesis, 6:10.

Dogan HN, Duran A, Rollas S, Sener G, Armutak Y, Keyer-Uysal M. 1998. Synthesis and structure elucidation of some new hydrazones and oxadiazolines anticonvulsant activities of 2-(3-acetyloxy-2-naphtyl)-4-acetyl-5-substituted-1,3,4-oxadiazolines. Medicinal Science Research, 26:755-758.

Kalsi R, Shrimali M, Bhalla TN, Barthwal JP. 2006. Synthesis and anti-inflammatory activity of indolyl azetidinones. Indian Journal of Pharmaceutical Sciences, 41:353-359.

Kaplancıkl ZA, Sever B, Altıntop MD, Atl O, Baysal M, Ozdemir A. 2017. Synthesis and Evaluation of New Thiazolyl Hydrazone Derivatives as Potential Anticancer Agents. Letters in Drug Design & Discovery, **14:672- 677.**

Kaplanek R, Havlik M, Dolensky B, Rak J, Dzubak P, Konecny P, Hajduch M, Kralova J, Kral V. 2015. Caffeine-hydrazones as anticancer agents with pronounced selectivity toward T-lymphoblastic leukaemia cells Bioorganic & Medicinal Chemistry, 23:1651-1659.

Kaplanek R, Jakubek M, Rak J, Kejik Z, Havlik M, Dolensky B, Frydrych I, Hajduch M, Kolar M, Bogdanova K, Kralova J, Dzubak P, Kral V. 2015. Caffeine-hydrazones as anticancer agents with pronounced selectivity toward T-lymphoblastic leukaemia cells. Bioorganic Chemistry, 60:19-29.

Li ZH, Yang DX, Geng PF, Zhang J, Wei HM, Hu B, Guo Q, Zhang XH, Guo WG, Zhao P, Yu P. 2016. Design, synthesis and biological evaluation of [1,2,3]triazolo[4,5-d]pyrimidine derivatives possessing a hydrazone moiety as antiproliferative agents. European Journal of Medicinal Chemistry, 124:967-980.

March J. 1995. Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (3rd ed.). New York: Wiley, ISBN 0-471-85472-7.

McCalla DR, Reuvers A, Kaiser C. 1970. Mode of Action of Nitrofurazone. Journal of Bacteriology, 104:1126-1134.

Mohareb RM, Fleita, DH, Sakka OK. 2011. Novel synthesis of hydrazide–hydrazone derivatives and their utilizaiton in the synthesis of coumarin, pyridine, thiazole and thiopehene derivatives with antitumor activity. Molecules, 16:16-27.

Munoz-Davila MJ. 2014. Role of Old Antibiotics in the Era of Antibiotic Resistance. Highlighted Nitrofurantoin for the Treatment of Lower Urinary Tract Infections. Antibiotics, 3:39-48.

Nasr T, Bondock S, Youns M, Eur J. 2014. Anticancer activity of new coumarin substituted hydrazide-hydrazone derivatives. European Journal of Medicinal Chemistry, 76:539-548.

Popiolek L, Biernasiuk A, Malm A. 2015. Synthesis and antimicrobial activity of new 1,3-thiazolidin-4-one derivatives obtained from carboxylic acid hydrazides. Phosphorus, Sulfur, and Silicon and the Related Elements, 190:251-260.

Popiolek L, Biernasiuk A, Malm A. 2016. Design, synthesis, and in vitro antimicrobial activity of new Furan/Thiophene-1,3-Benzothiazin-4-one hybrids. Journal of Heterocyclic Chemistry, 53:479-486.

Popiolek L, Stefanska J, Kielczykowska M, Musik I, Biernasiuk A, Malm A, Wujec M. 2016. Synthesis, dissociation constants, and antimicrobial activity of novel 2,3-disubstituted-1,3-Thiazolidin-4-one derivatives. Journal of Heterocyclic Chemistry, 53:393-402.

Rollas S, Kucukguzel SG. 2007. Biological activities of hydrazone derivatives. Molecules, 12:1910-1939.

Senkardes S, Basu NK, Durmaz I, Manvar D, Basu A, Atalay R, Kucukguzel SG. 2016. Synthesis of Novel Diflunisal Hydrazide-Hydrazones as Anti-Hepatitis C Virus Agents and Hepatocellular Carcinoma Inhibitors. European Journal of Medicinal Chemistry, 108:301-308.

Shankar R, Rawal RK, Singh US, Chaudhary P, Konwar R, Hajela K. 2017. Design, synthesis and biological evaluation of hydrazone derivatives as anti-proliferative agents. Medicinal Chemistry Research,

26:1459-1468.

Shen S, Chen H, Zhu T, Ma X, Xu J, Zhu W, Chen R, Xie J, Ma T, Jia L, Wang Y, Peng C. 2017. Synthesis, characterization and anticancer activities of transition metal complexes with a nicotinohydrazone ligand. Oncology. Letters, 13:3169-3176.

Singh V, Srivastava VK, Palit G, Shankar K. 1992. Coumarin congeners as antidepressants. Arzneimittelforschung, Drug Research**,** 42:993- 996**.**

Sreenivasulu R, Sujitha P, Jadav SS, Ahsan MJ, Kumar CG, Raju RR. 2016. Synthesis, antitumor evaluation, and molecular docking studies of indole–indazolyl hydrazide–hydrazone derivatives. Monatshefte Fur Chemie, 148:305-314.

Stork G, Benaim J. 1997. Monoalkylation of α,β-Unsaturated Ketones via Metalloenamines: 1-butyl-10-methyl-Δ1(9)-2-octalone. Organic Synthesis, 6:242.

Taha M, Shah SAA, Afifi M, Zulkeflee M, Sultan S, Wadood A, Rahim F, Ismail NH. 2016. Morpholine hydrazone scaffold: synthesis, anticancer activity and docking studies, Chinese Chemical Letters, 28:607-611.

Tantak MP, Klingler L, Arun L, Kumar A, Sadana R, Kumar D. 2017. Design and synthesis of bis(indolyl)ketohydrazide-hydrazones: Identification of potent and selective novel tubulin inhibitors. European Journal of Medicinal Chemistry, 136:184-194.