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Anticancer Activity of Some Mercapto Substituted 4-amino-1, 2, 4-Triazoles : A Review

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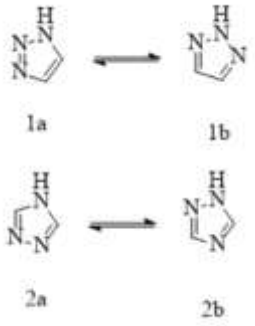
ABSTRACT: Cancer is a life threatening disease and remains a major health problem around the globe. It is the second most occurring disease after cardiovascular diseases. Thus, the development of potent and effective novel antineoplastic drugs is one of the most intenselypersuaded goals of contemporary medicinal chemistry.Nitrogen-containing five-membered heterocycles plays a vital role in drug discovery to identify novel chemical entities of immense therapeutic potential. The present review aims to summarize the anticancer properties of mercapto substituted 4-amino-1,2,4-triazoles, one of the emerging scaffold, as antifungal, antibacterial, anticancer, anticonvulsant, antituberculosis, antiviral, antiparasitic, analgesic and anti-inflammatory agents, etc. along with structure-activity relationship. This compilation of work carried out since 2015, will provide insight into various ligand-receptor interactions and advancement of novel potential drug having mercapto substituted 4-amino-1,2,4-triazoles nucleus having better efficacy and selectivity.

KEYWORDS: Azoles, Mercapto substituted 4-amino-1,2,4-triazoles, Anticancer properties

I. INTRODUCTION

Triazoles are a versatile class of heterocyclic compounds with three nitrogen atoms positioned in a five membered aromatic ring. 1,2,3-Triazole (1) and 1,2,4-triazole (2).[1]



The chemistry involving triazoles has a significant role due to their medicinal and industrial properties as drugs and intermediates respectively in various areas. The differently substituted 1,2,4-triazole derivatives are reported to possess wide range of bioactivities including antifungal, antimicrobial, antibacterial, anti-inflammatory, anti-tubercular, hypoglycaemic, antidiabetic, antidepressant, anticonvulsant, anti-malarial, analgesic, anti-migraine, arthritis, antihypertensive, antiviral, antileishmanial, potassium channel activators, antiplatelet and antioxidant. [2-9]

Among these heterocycles, the mercapto and thione substituted 1,2,4-triazole ring systems have been well studied and so far a variety of biological activities have been reported for a large number of their derivatives such as anticancer, antitubercular, diuretic, antibacterial, antifungal, antimycobacterial, and hypoglycemic etc. [11, 12]

There are a number of reviews written on the chemistry of triazole derivatives describing its synthesis and various bioactivities. In the present review, we focused on current publications since 2015 on the study of the anticancer properties of compounds containing the mercapto substituted 4-amino-1,2,4-triazole ring. This review article is based on chemical structure of ligand with triazole nucleus. It is expected that this review article will provide insight into various ligand-receptor interactions and help in the rational design and

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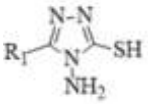
development of novel 1,2,4-triazole based anti-cancer drugs with improved selectivity for cancer cells.

II. REVIEW



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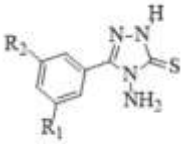
4-Amino-1,2,4-triazole (**3**) nucleus and its derivatives proved to be indispensable scaffold in drug discovery and development possessing plethora of bioactivities. Plausible reason for its broad biological profile is small and stable cyclic ring structure wherein the nitrogen atoms can act both as hydrogen bond donor and acceptors at the active site of the receptor. In addition, the triazole ring may be involved in other interactions such as coordination with metals at the receptor sites and pi-pi stacking. Due to its polar nature, the triazole nucleus endowing its derivatives with increased water solubility, bioavailability and bioactivities that in turn improve thepharmacokinetic and pharmacodynamic profile of the drug. This ring can also coordinate with a number of metal ions forming organometallic compounds possessing various bioactivities. Various mechanistic studies have also confirmed that 4-amino-1,2,4-triazole nucleus coordinate with haem present at the receptorsite that result in anticancer activity.

Mavrova et al. in 2019 investigated the initial biological screening in vitro of the studied compounds (**4**) and observed their high cytotoxicity against thymocytes and low cytotoxicity against blood lymphocytes, derived from sexually mature hamsters.

After treatment of the experimental animals with a dose of the tested compounds at and following estimation of the cytotoxicity in vitro, the results showed increase in the cytotoxicity of compounds these compounds against thymocytes. IC_{50} values were in the range 0.46- $1.0*10^{-6}$µM. With respect to blood lymphocytes, the most cytotoxic was compound **4b**, IC_{50} was 0.012 µM. The PFC, LIF and the migration tests' study indicated that the compounds revealeda general stimulating effect on the B cells' response. Compound **4a** exhibited a general stimulation regarding blood lymphocytes, LIF - 1.654, whilecompound **4b** showed the highest value number of PFC, which surpasses 29 timesthan that of the control cells. The above results also confirmed the hypothesis that the introduction of a 5-phenylthiophene-2- and tetrahydrobenzothiophene-2-substituent at 5th position in the structure of 3- mercapto-1,2,4-triazoles is auspicious to the interaction of these molecules with the biological targets.



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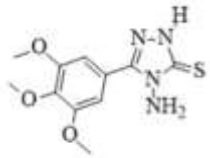
4a = R_1/R_2; $-(CH_2)_4$,
4b = R_1 = H; R_2 = $-C_6H_5$

Ameri A. et. al in 2016 evaluated the in vitro cytotoxic effects of compound**5** against HT1080, HepG2, HT29, MCF-7, and A549 cancer cell lines by MTT assay. The compounds inhibited the abovementioned cell lines by mean IC_{50}_S.E. of 167.85_14.04, 34.05_2.57, 43.48_1.58, 9.09_0.81, 19.44_2.07, and 41.89_1.54mM, respectively [14].



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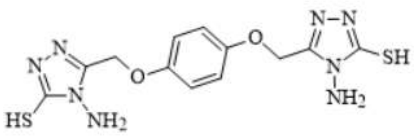
Holla et.al in 2020 synthesized bis-[4-amino-5-mercapto-1,2,4-triazol-3-lmethyleneoxy]phenylenes (**6**) starting from corresponding unsubstituted/substituted 1,4-quinols in a one pot reaction. These newly synthesised compounds were screened for their anticancer activity against a panel of 60 cell lines derived from seven cancer types namely, lung, colon, melanoma, renal, ovarian, CNS and leukemia. Some of the tested compounds showed promising anticancer properties [15].



6

R_1/R_2 = H, Cl, ^{t}Bu

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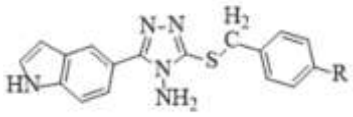
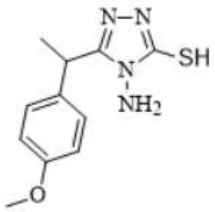
A series of triazole/oxime hybrids were evaluated by Aziz et.al in 2018 for their antiproliferative, anti-inflammatory activity and ulcerogenic liability. The selected compounds were screened against NCI 60 cell linesand it was found that the unsubstituted 1,2-diphenyl triazole 6 was found to be the most potent in the series against renal cancer A498 cell lines.[16]



7

R= H, Cl, Br, C_6H_5, $pCH_3C_6H_4$

A series of non-carboxylic naproxen analogues, bearing triazole ring **8** was synthesized by El-Husseiny et al, among which arylidene derivatives exhibited potent antitumor activities against cell lines MCF-7, MDA-231, HeLa, and HCT-116, with IC_{50} in the range of 4.83-12.07 µM. Compound also exhibited the most potent COX-2 inhibitory activity with IC_{50} value of 0.40 µM and selectivity index (SI) value of >62.50 and showed strong interactions at the COX-2 binding site. [17]



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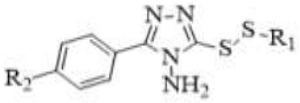
Compound **9**was found to have the highest potency with IC_{50} values of 0.37, 2.94 and 31.31 µM against HCT116, HeLa and PC-3, respectively. Mechanistic studies demonstrated that it not only induces cell cycle arrest in a dose-dependent manner in HeLa cells at G2/M phase but also induced apoptosis. [18]

9

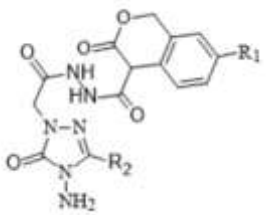
Wang et al synthesized nonsymmetricaldisulfides bearing 1,2,4-triazole moiety **10** andevaluated their antiproliferative activity against human cancer cell lines SMMC-7721, HeLa, A549, and normal cell lines L929 by CCK-8 assay. Most of the tested compounds exhibited better activity than positive control 5-fluorouracil. These compounds exhibited the best inhibition against A549 cells (IC50: 2.79 µM) and found to be the most potent against SMMC-7721 cells (IC50: 2.97 µM). [19,20]



R_1= H/Cl
R_2 = C_2H_5, C_3H_7, C_4H_9, C_6H_{11}, $CH_2C_6H_5$, $CH_2C_6H_4$(4-Cl)

10

Antitumor activity of coumarin-triazole hybrids **11** (IC_{50}: 3.1-37.9 µg/mL) was evaluated against four cancer cell lines (BT-20, SK-Mel-128, DU-145 and A549, MTT assay) by Kahveci et al. [21]. Hybrids showed better selectivity index value (SI: 5.2 and 2.7) against BT-20 cell line than cisplatin (SI: 2).



11

(a) R_1 = 6-Cl, R_2 = 3,4-diClBn;
(b) R_1 = 6,8-diCl, R_2 = 4-ClBn;
(c) R_1 = 6,8-diCl, R_2 = 4-BrBn;
(d) R_1 = 6,8-diCl, R_2 = 2-BrBn;
(e) R_1 = 7-NEt$_2$, R_2 = Me

Ya-Ping Hou et al., have screened a series of 1,2,4-triazole derivatives**12** containing 1,4 benzodioxanfor their ability to anti proliferative activity against HEPG2, HELA, SW1116 and BGC823 [22]. The tested compounds show potent activities against HEPG2 than other three cancer cell lines. Analysis of structure-activity relationship (SAR) indicated that compounds with electron-withdrawing group show stronger activity than that with electron-donating group, with all the IC_{50}

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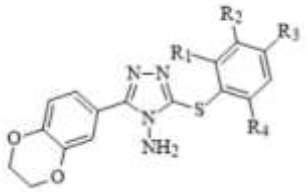
values below 50 lM against HEPG2. Compounds with different electron-withdrawing groups, are ableto portray different antitumor activities, and the potency order follows F (fluorine) >Cl (chlorine) > Br (bromine)> NO_2 (nitro-group). With regard to the F-substituted compounds, monosubstitution is preferred over di-substitution. The placement of substituents based ontheir effects is ortho- > meta- >para-. The work is continued with MetAP2 inhibitory assay, apoptosis assay, and Western-blot assay.



12

R_1, R_2, R_3, R_4 = H, CH_3, OCH_3, Cl, NO_2

III CONCLUSIONS

1,2,4-triazole derivatives are the preferred structuralmoieties in the development of new drugs with a wide range of pharmacological activity, as evidenced by severalreviews.This is due to the fact that the triazole ring can beconsidered a bioisostere of an amide, ester, or carboxylgroups. Relatively low toxicity, good pharmacokinetic andpharmacodynamic properties of triazole, its resistanceto metabolic degradation are another advantages.

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