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EXPLORING THE BOUNDLESS POTENTIAL OF TETRAZOLE HYBRIDS: A REVIEW OF ITS ANTICANCER ACTIVITY

Meera Rajendran*[1], Sreelekshmi S. S.[1], Asim Mohamed P[2]. and Akash Marathakam[3]

National College of Pharmacy, Kozhikode.

***Corresponding Author: Meera Rajendran**

National College of Pharmacy, Kozhikode.

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ABSTRACT

For the treatment of different malignancies, anticancer medicines are essential, but the majority of those currently available on the market are not specific, leading to a variety of chemotherapy side effects. However, in recent decades, the crisis of cancer medication resistance has already reached frightening proportions. In this work we focused on the anticancer activity of tetrazole hybrids with combining of different pharmacophores.

KEYWORDS: Anticancer, Pharmacophores, Tetrazole.

INTRODUCTION

One of the most significant classes of five-membered heterocycles is tetrazole (the bioisoster of carboxylic acid) (fig.1), and its derivatives have demonstrated a variety of biological activities, including antibacterial,[1,2] antimalarial,[3,4] antifungal,[5,6] antitubercular,[7,8] and antimutagenic,[9] properties. As further evidence of the therapeutic potential of tetrazole derivatives, numerous tetrazole-based medications, including Cilostazol, Cefamandole, and Irbesartan, have already been employed in clinical practise to treat a variety of disorders,[10] There have been significant attempts over the past two decades to find tetrazole compounds with comparable or enhanced anticancer activity and reduced toxicity. There have been significant attempts over the past two decades to find tetrazole compounds with comparable or enhanced anticancer activity and reduced toxicity.[11] Due to several carcinogenic causes, cancer, which is characterised by abnormal cell and tissue proliferation, is a frequently leading cause of death worldwide. Many anticancer drugs are currently offered for sale on the international market. Researchers are becoming increasingly interested in creating newer novel possible anticancer medicines, meanwhile, as a result of their resistance and expense.[12]

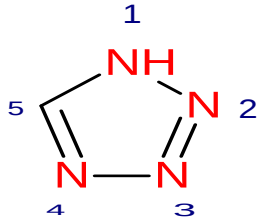


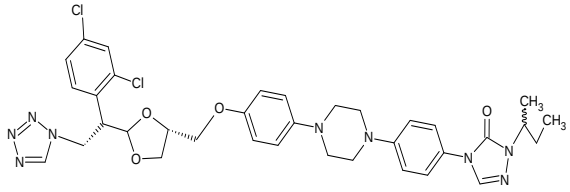
Fig. 1: Structure of tetrazole.

Tetrazole Hybrids

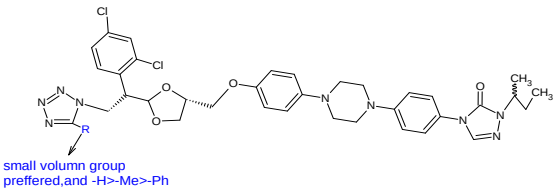
Relative to the parent medications, hybrid compounds may increase effectiveness, combat drug resistance, and lessen toxicity.[13] As a result, combining tetrazole with pharmacophores that have anticancer capabilities is a possible way to create new anticancer candidates.

1. Tetrazole Azole Hybrids

Azoles are five-membered heterocyclic compounds with one or more nitrogen atoms in the ring, and it has been shown that various medicinal qualities can be obtained from their derivatives.[14,15] Moreover, azoles are the most prevalent drug fragment, and several anticancer medications, like Crizotinib and Lorlatinib, have an azole moiety.[16,17] Hence, using tetrazole and azoles to hybridise new anticancer candidates is a rational technique. Phase II clinical trials for the antifungal drug itraconazole are being conducted for the treatment of basal cell carcinoma, non-small cell lung cancer, prostate cancer, and other malignancies.[18,19]

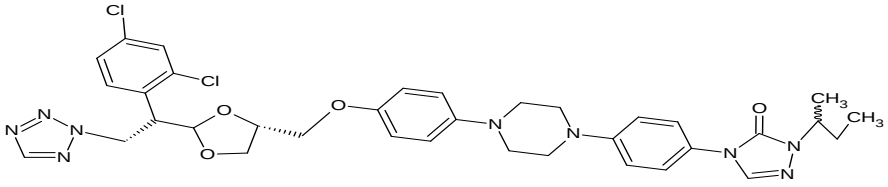


1a



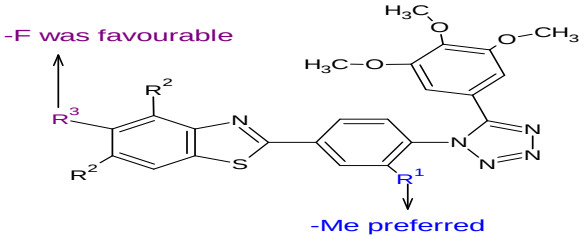
compound 1a-c

The Regio-isomer of compound 1a, compound 1d, was discovered to be less active than 1a, indicating that the linking pattern has a significant impact on the activity.



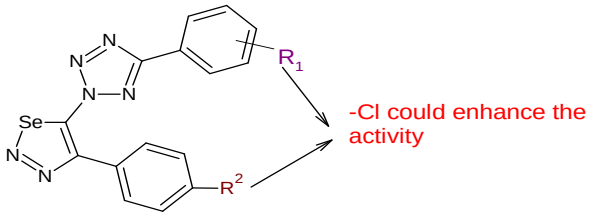
Compound 1d.

Additional research revealed that the most active chemical 1a (IC50: 73 nm.) may induce the Niemann-Pick C phenotype (NPC phenotype) and block AMPK/mechanistic target of rapamycin signalling without having a significant impact on CYP3A4 (EC50: >20 mM). These findings suggested that compound 1a is a viable anticancer candidate and might be utilised in combination with the majority of other anticancer medications now on the market. The reference combretastatin A-4 was more effective than the tetrazole-benzothiazole hybrids 2 (IC50: 0.24e31.62 mM), although they were less effective against human prostate (DU-145), cervix (HeLa), lung adenocarcinoma (A549), liver (HepG2), and breast (MCF-7) cancer cells (CA-4, IC50: 0.005e0.069 mM).[20]



Compound 2

The SAR suggested that the methyl group at R1 and the fluoro at R3 positions could greatly boost the activity. The bulk of tetrazole 1,2,3-selenadiazole hybrids 3 were inert against Hep G2 and MCF-7 cell lines by MTT assay, however three of them 3a-c with IC50 values of 43.19e74.78 mM demonstrated substantial activity.[21] The SAR indicated that chloro at R1 and R2 positions could enhance the activity, and the most active hybrid 3b (IC50: 43.19 and 47.15 mM) was no inferior to the reference Cisplatin (IC50: 33.69 and 21.69 mM).

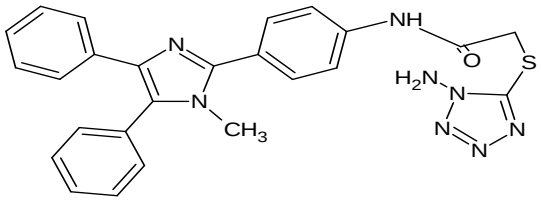


3a: R_1 =H, R_2 =Cl
3b: R_1=4-Cl, R_2=Cl
3c: R_1=2-Cl, R_2=Cl
3d: R_1=4-Me, R_2=Cl

3e: R_1=H, R_2= OMe
3f: R_1=4-Cl, R_2=OMe
3g: R_1=2-Cl, R_2=OMe
3h: R_1=4-Me, R_2=OMe

Compound 3

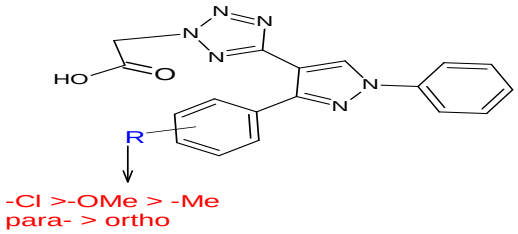
Tetrazole-imidazole 4 was shown to have anti-proliferation action against MCF-7 and HT-29 cells that was comparable to Cisplatin (IC50: 2.6 and 1.7 mg/mL) (IC50: 4.5 and 1.6 mg/mL)[22] Several tetrazole-benzimidazole hybrids were evaluated for their anticancer activity, and while some of them demonstrated notable in vitro and in vivo potency, the bulk of them were less potent than standards.



Compound 4

The anti-proliferation SAR of tetrazole-pyrazole hybrids 5 (IC50: 6.43e86.26 mM) demonstrated that in comparison with unsubstituted conjugate 5a (IC50: 86.26 and 70.25 mM), implementation of either electron-withdrawing chloro (5b,c, IC50: 6.43e18.23 mM) or

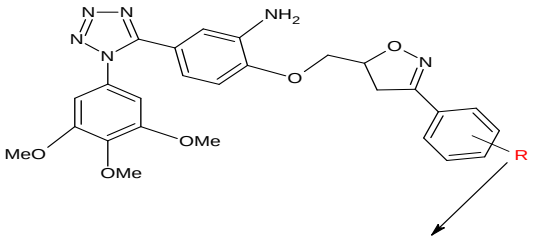
electron-donating methyl and methoxy (5d-f, IC50: 7.23e48.34 mM) could improve its efficacy against HT-29 (colon) and PC-3 (prostate) cell lines, and the relative participation order was chloro > methoxy > methyl.[23] The effectiveness is greatly influenced by the position of substituents, and para-position was preferable to ortho-position.



Compound 5

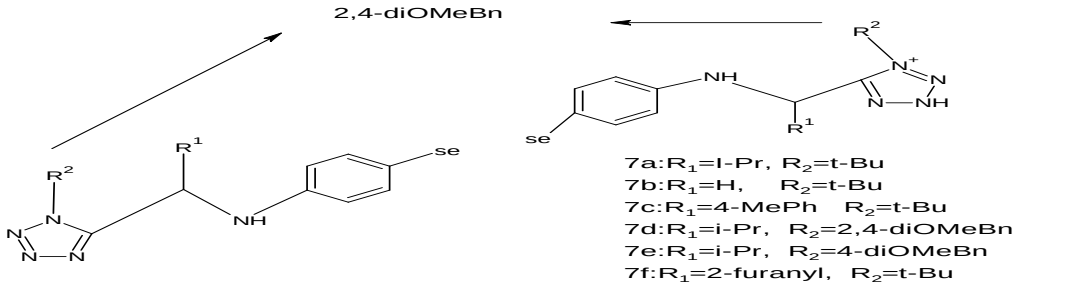
5a: R =H 5b: R=2-Cl 5c: R =4-Cl 5d: R=4-Me 5e: R =2-Ome 5f: R=-OMe

The IC50 values for the tetrazole-isooxazoline hybrids 6 (Fig. 1) against MDA-MB-231 (breast adenocarcinoma) and A549 (lung adenocarcinoma) ranged from 1.22 to 3.22 mM, however they were less effective than the reference CA4 (IC50: 0.55 and 0.1 mM)[24] In comparison to their analogues 6a-h (IC50: 1.51e3.62 mM), the hybrids 6i-k (IC50: 1.22e2.40 mM) with the electron-withdrawing groups fluoro, chloro, and trifluoromethyl on the phenyl ring demonstrated greater activity.



6a: R=3-OMe-4-OH 6b: R=3-OH-4-OMe 6c: R=3,4-diOMe 6d: R=2,5-diOMe
6e: R=3,4,5-triOMe 6f: R=2,3,4-triOMe 6g: R=3-NH_2-4-OMe 6h: R=2-F-5-OMe
6i: R=2-F 6j: R=3-Cl 6k: R=4-CF_3
Compound 6

Many series of tetrazole dimers were tested for their in vitro anticancer activity, and some of them showed appreciable antiproliferative effects.[25] The diselenide tethered tetrazole dimers 7 were more active than the reference 5-Fluorouracil (IC50: 3e8 mM) in their ability to kill HepG2, MCF-7, and WI-38 cells. They also showed selective cytotoxicity to these cells. The SAR showed that adding either an alkyl or aromatic ring to the R1 position or changing the branching alkyl iso-propyl and tert-butyl groups to cyclohexyl at the R2 position did not appear to improve the activity, however adding 2,4-dimethoxyphenyl to the R2 position did.



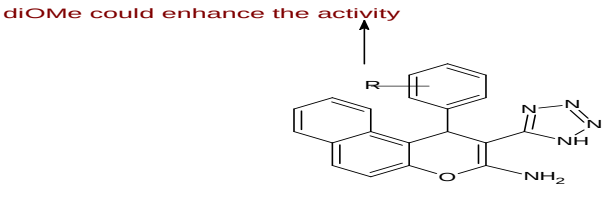
7a:R_1=I-Pr, R_2=t-Bu
7b:R_1=H, R_2=t-Bu
7c:R_1=4-MePh R_2=t-Bu
7d:R_1=i-Pr, R_2=2,4-diOMeBn
7e:R_1=i-Pr, R_2=4-diOMeBn
7f:R_1=2-furanyl, R_2=t-Bu
7g:R_1=2-furanyl,R_2=2,4-diOMeBn
7h:R_1=2-furanyl,R_2=cyclohexyl
7i:R_1=H, R_2=cyclohexyl
7j:R_1=4-MePh, R_2=cyclohexyl
7k:R_1=i-Pr, R_2=cyclohexyl
7l:R_1=i-Pr, R_2=Bn
7m:R_1=4-MePh, R_2=2,4-diOMePh

Compound 7

2. Tetrazole-Benzochromene Hybrids

The compounds of benzochromene have a variety of major pharmacological characteristics, making it a potentially advantageous pharmacophore. Tetrazole-benzochromene hybrids 8 were discovered to be less powerful than 5-Fluorouracil (IC50: 10e17 mM) against human breast (MCF-7 and SKBR-3), colorectal (Caco-2), and cervical cancer (HeLa) cells.[26] Their IC50 values ranged from 15 to 87 mm. The anticancer activity of the hybrids could be improved by adding dimethoxy at ortho-, meta-, and para positions of the phenyl ring, and the potency order was dimethoxy > methoxy > fluoro > chloro > bromo.

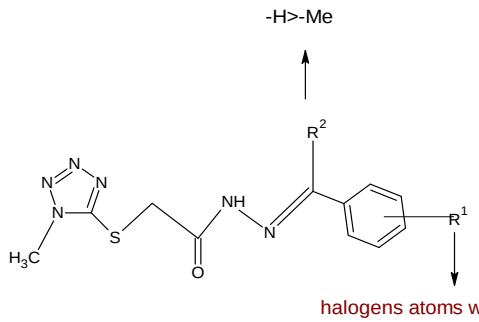
All of the examined cell lines were sensitive to the broad-spectrum anticancer activity of the most potent hybrid 8f (IC50: 15e26 mM), and this activity was on par with 5-Fluorouracil.



8a: R=2-OMe 8b: R=4-OMe 8c: R =4-Br 8d: R=2,5-diOMe 8e: R=2,3-diOMe
8f: R=2,4-diOMe 8g: R=3-OH 8h: R=2-Cl 8i: R=4-Cl 8j: R=2-F 8k: R= 4-Et
Compound 8

3. Tetrazole-Imine/Urea/Thiosemicarbazide Hybrids

Many medications contained imine fragments such hydrazone, amidine, and carbamidine, and some of these chemicals had significant anticancer action.[27,28] The tetrazole-hydrazone hybrids 9 had marginal to marginally significant cytotoxic effects on A549 cells. The IC50 values for the derivatives 9a through h were discovered to be in the micromolar range (100–800 mM), although they were found to be less powerful than the reference cisplatin (IC50: 31.6 mM). When compared to analogues without substituents, the SAR showed that attaching methyl at the R2 position was detrimental to the activity. The activity of hybrids with halogen atoms at the phenyl ring (R1) was higher than that of hybrids with other substituents, but it could be decreased by adding a second halogen atom.

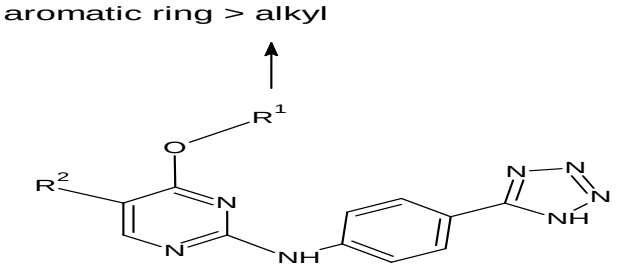


9a; R1= 4-NO2, R2=H 9b: R1= 4-Cl, R2=H 9c: R1=4-iPr, R2=H 9d: R1=4-NMe2,
R2=H 9e: R1=3-Br, R2=H 9f: R1=2,3-diCl, R2=H 9g: R1=2,4-diCl, R2=H
9h: R1=2,4-diCl, R2=Me
Compound 9

4. Tetrazole Pyrimidine Hybrids

All cells require pyrimidines as important metabolites, and the survival of the cell depends on the de novo pyrimidine synthesis pathway. Tetrazole-pyrimidine hybrids' rational design may provide candidates for anti-cancer therapy.

Aurora kinase A (AKA) is overexpressed in many malignancies, including colorectal, glioma, breast, ovarian, and pancreatic cancers.[29,30] AKA is typically up-regulated in the G2/M phase of the cell cycle. AKA inhibitors can therefore act as a starting point for the development of anticancer medications. The SAR showed that the tetrazole-pyrimidine hybrids 10b-d (IC50: 0.012e0.068 nm.) with a phenyl ring at R1 position were more powerful than the alkyl counterpart 10a (IC50: 0.438 nm.)[31] These hybrids showed substantial inhibition against AKA with IC50 values ranging from 0.012 to 0.438 nm. The hybrid 10d, which has an IC50 of 0.012 nm. against AKA, may serve as a lead for additional research.

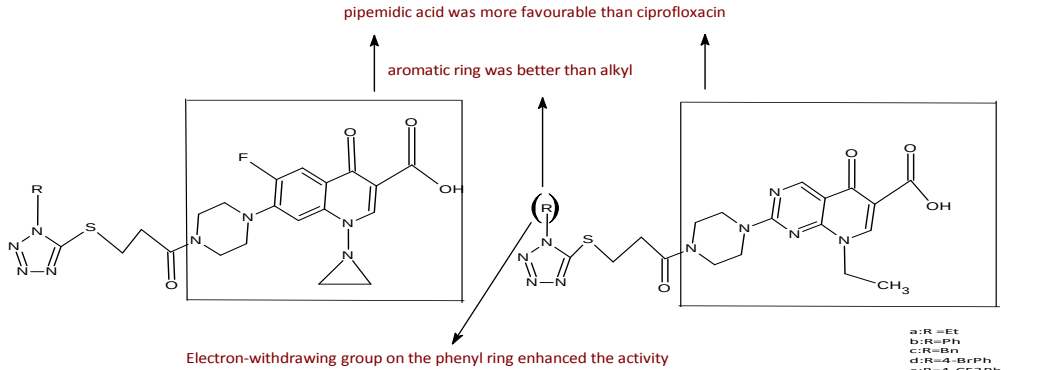


10a: R1=iPr, R2=Me 10b: R1=4-OMePh, R2=Cl 10c: R1=4-FPh, R2=Cl 10d: R1=2-FPh,
R2=Cl Compound 10

5. Tetrazole-Quinoline/Quinolones Hybrids

Quinoline/quinolones offer a wide range of pharmacological properties, and some of them, such as Voreloxin and Quarfloxin, have already been employed in clinics or in clinical studies to treat different tumour.[32]

It makes sense to combine quinoline/quinolone and tetrazole to create potential new cancer treatment candidates. The sulforhodamine B (SRB) assay was used to investigate a range of ciprofloxacin-tetrazoles 11 and pipemidic acid-tetrazoles 12 for their in vitro antiproliferative activity against cervix (SiHa), breast (MDAMB-231) and pancreatic cancer cell lines.[33-35] Among them, 5 showed stronger reduction of cell growth than the reference drug tamoxifen against the SiHa cancer cell line, 11 against the MDA-MB-231 cancer cell line, and 1 against the PANC-1 cancer cell line35. Pipemidic acid-tetrazoles 20 were more effective than the comparable ciprofloxacin analogues, according to the SAR. The GI50 values for hybrids 11b and 11c with an unsubstituted phenyl moiety on the tetrazole ring against various cancer cells ranged from 0.085 to 1.15 mM, while hybrids 11d-g and 12d-g (GI50: 0.066e1.3 mM) with various substituents on the tetrazole ring demonstrated increased growth inhibition. While electron-donating groups were typically bad for the activity, hybrids 11d and 12d with electron-withdrawing bromo onto phenyl rings improved growth inhibition against all of the evaluated cancer cell types. Particularly, pipemidic acid-tetrazole conjugate 12d (GI50: 0.08, 0.22, and 0.07 mM) was much more effective than Tamoxifen (GI50: 0.12, 0.24, and 0.15 mM) against SiHa, MDA-MB231 and PANC-1 cancer cell lines. It was also extremely active against all other cancer cell lines examined.

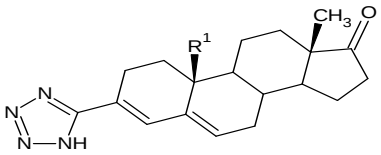


Compound 11 Compound 12

6. Tetrazole -Steroid Hybrids

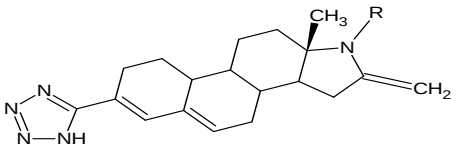
The production of steroids encourages the aggressiveness of cancer cells, and steroids are crucial in the development of many diseases.[36-38] The development of new anticancer prospects may be made possible through the hybridization of steroids and tetrazole.

The most frequent benign tumour in older people is benign prostatic hyperplasia, and 5a-reductase inhibitors are crucial for treating it.[39,40] Aggarwal et al. evaluated a group of tetrazole-steroid hybrids 13 for their potential as 5a-reductase inhibitors, and preliminary findings revealed that all hybrids shown excellent effectiveness against 5a-reductase type 2 with an IC50 in the nanomolar range.[41,42] The SAR showed that the steroid fragment significantly affected activity, with hybrid 13c (IC50: 15.6 nm.) > 13a, b (IC50: 83.8 nm.) > 13d-f (IC50: 157-273 nm.) being the most effective molecule against 5areductase type 2 [42]. Finasteride (IC50: 204.20 mg/mL) was marginally less effective against DU-145 cancer cells than the hybrids 13b, 13e, and 13f, which had IC50 values of 174.40–195.10 mg/mL.



Compound 13 a,b

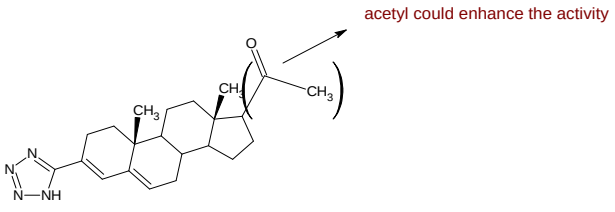
13a:R=H
13b:R=Me



Compound 13d-f

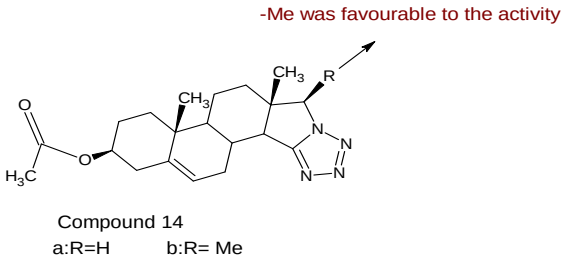
13d:R=H
13e:R=Me
13f: R=allyl

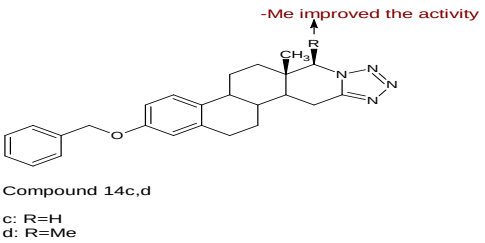
In invitro, Hybrid 13c (IC50: 547 and 15.6 nm.) exhibited activity similar to Finasteride (IC50: 453 and 40 nm.) and was shown to be a powerful dual inhibitor for 5a-reductase type 1 and type 2 isozymes. The weight of the rat prostate tumour was significantly reduced by hybrid 13c, according to an in vivo 5a-reductase inhibitory investigation. These data suggest that hybrid 13c might serve as a starting point for more research.



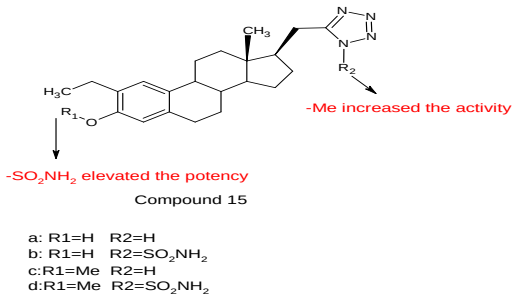
Compound 13c

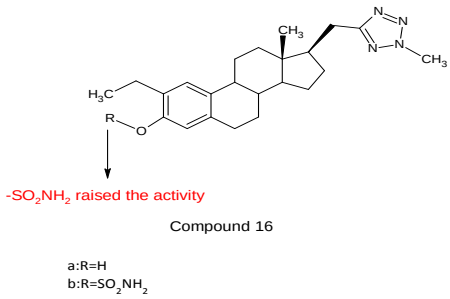
The tetrazole-steroid hybrids 14 (IC50: 4.58->100 mM) displayed weak to moderate activity against the majority of the tested cells, including breast cancer (MDA-MB-231 and MCF-7), prostate cancer (PC3), human cervical carcinoma (HeLa), myelogenous leukaemia 35 (K562), colon cancer (HT-29), and normal foetal lung fibroblast (MRC-5) cells.[43] The SAR showed that adding methyl to the R position was advantageous to the activity. Against MCF-7, hybrids 14a and b were more effective than their analogues 14c and d (IC50: 56.23 and 25.45 mM), whereas the latter were more effective than the former (IC50: 65.45->100 mM) against PC3 and K562 cancer cells. One of them, hybrid 14c, was 6.2 times more effective than doxorubicin (IC50: 95.61 mM) against the PC3 cancer cell line and was worthy of further optimisation.





The antineoplastic SAR of tetrazole-steroid varieties 15 (GI50: 0.34- >100 mM) and 16 (GI50: 0.8e47.0 mM) showed that hybrids 16 were generally more active than hybrids 15, and incorporation of sulphonamide into phenyl ring was beneficial to the activity against MCF-7, DU-145, and MDA-MB 231 breast cancer cells.[44] Tetrazole moiety methylation for hybrid 15 may enhance activity. The most potent of them, hybrid 15d (GI50: 0.34e0.55 mM), was very effective against the three cancer cell lines that were examined.[45]





CONCLUSION

The pharmacological and biological properties of tetrazole derivatives are very advantageous. Many biological actions have been documented for them. Tetrazoles play a significant role in the creation of novel medications because they have a wide range of chemotherapeutic properties, including anticancer activity. Tetrazole moiety hybridization with different anticancer pharmacophores has the potential to boost anticancer activity, get around drug resistance, and lessen side effects. In recent years, a variety of tetrazole hybrids have been created and tested for their anticancer properties, and several of them have demonstrated promising effectiveness against both drug-susceptible and drug-resistant cancer cell lines. This review discusses the most current developments in tetrazole hybrids, such as those involving azoles, benzo chromes, Imines, quinolones/quinolines, steroids as potential anticancer agents.

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