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Synthesis and anti-tumor activity of some novel cationic 1,3,4-thiadiazoles as DNA binders

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ABSTRACT

Cationic 2,3-Dihydro-1,3,4-thiadiazoles as hydrochlorides containing benzoxazole or benzothiazole moieties were designed as DNA binders and prepared from the reaction of each of 1-(2-(benzo[*d*]oxazol-2-yl)hydrazono)-1-chloropropan-2-one and 1-(2-(benzo[*d*]thiazol-2-yl)hydrazono)-1-chloropropan-2-one with each of potassium thiocyanate, thiourea and alkyl carbodithioate. All the newly synthesized compounds were confirmed by elemental analysis, spectral data, and alternative route synthesis whenever possible. Some of the newly synthesized compounds were screened toward certain cancer tumors. Docking study was operated to give a hint on their cytotoxic mechanism.

KEYWORDS

Thiadiazoles;
Benzoxazoles;
Cytotoxic activity;
Benzothiazole;
Hydrazonyl halides.

INTRODUCTION

Cytotoxic drugs and chemotherapy still remain the most important area of research. Enhancement and approaches to anticancer drugs seemed to be a major area of investigation, despite the continuous progress of anticancer agents, overall control of cancer is still a dream[1]. Great effort was exerted to develop a new anticancer agents with high toxicity toward cancer cells and with a minimal toxicity against normal cells[2-4]. Drug targeting to DNA specially non covalent minor groove binder are a subject of interest because they interact with DNA selectively so could control cell division[5]. *Minor groove binder* are of four main characters[5]. they all of crescent shape consist of flat aromatic rings or with amide groups connected by flexible links, carry positive charge, have electron donner groups in the concave region and finally they fit in minor groove region with phosphate sugar wall. these drug could interact with A/T base pairs or C/G in minor grooves by hydrogen bonding and van der wall forces. In addition, 2-(4-aminophenyl)-benzothiazole and oxazole and their analogues are a novel class of potent and selective antitumor agents[6–10]. However their mechanism of action is still a glue without distinctive mechanisms. In view of these report and continuation of the previous work[11-16], in our way to investigate their mood of cancer inhibition, Here in we designed some new DNA binders to be interact with C- G region such design was operated using computer aided program for molecular representation showing the synthesized cationic of 9a docked to DNA duplex obtained from protein (10.2210/pdb) with a cationic benzimidazole legend[5] (ID, 3gjj/pdb), using MOE (2008,10, soft ware). These binder formed of a

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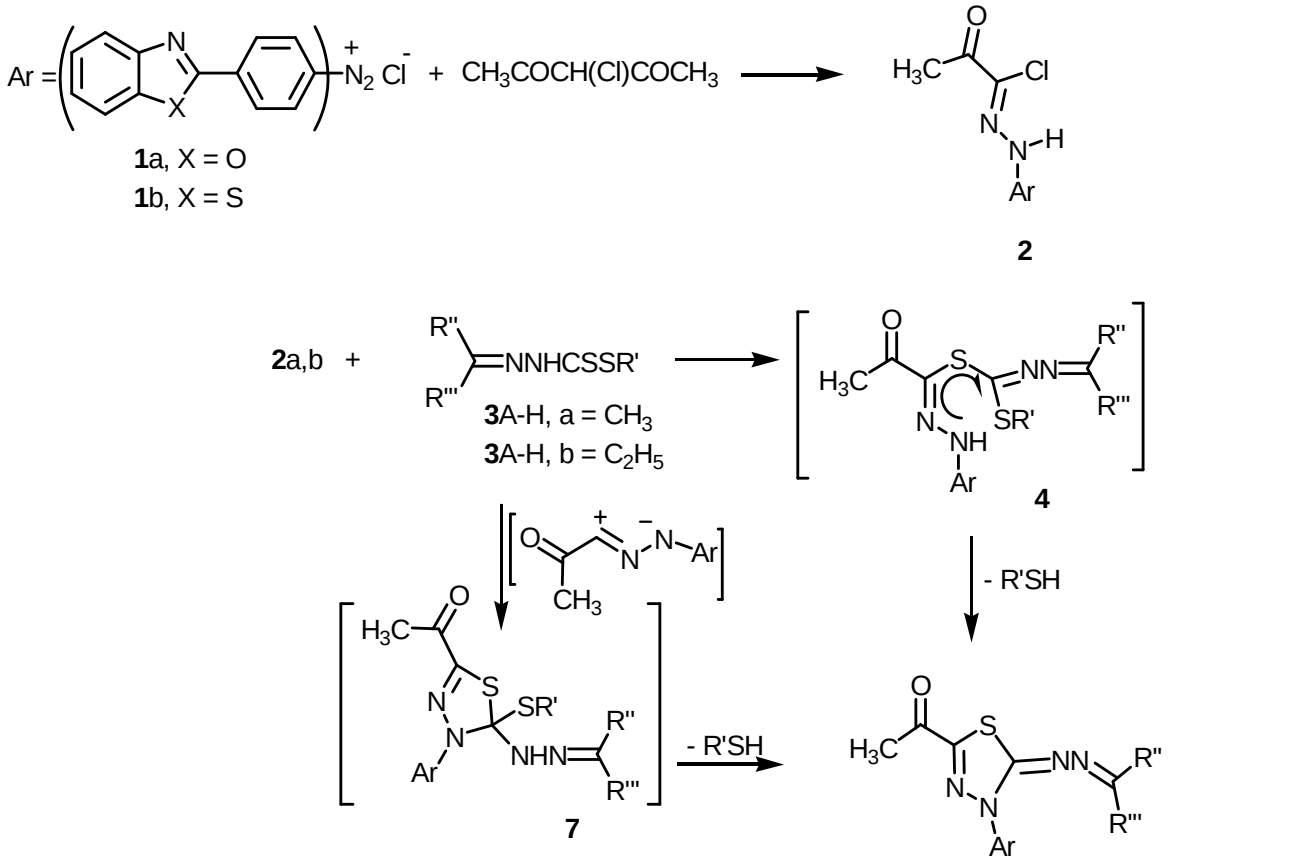


3A, R'' = H, R''' = C_6H_5
B, R'' = H, R''' = 2-C_4H_3S
C, R'' = H, R''' = 4-$(CH_3)_2CHC_6H_4$
D, R'' = CH_3, R''' = C_6H_5
E, R'' = CH_3, R''' = 2-C_4H_3O
F, R''= H, R''' = 2,3-$C_6H_3OCH_2O$
G, R''-R''' = 1, 2-C_6H_4(NHCOC=)
H, R''-R''' = 1, 2-C_6H_4(COC=CO)

a, R' = CH_3
b, R' = C_2H_5

5a, R'' = H, R''' = C_6H_5, X = O
b, R'' = H, R''' = 2-C_4H_3S, X = O
c, R'' = H, R''' = 4-$(CH_3)_2CHC_6H_4$, X = O
d, R'' = CH_3, R''' = C_6H_5, X = O
e, R'' = CH_3, R''' = 2-C_4H_3O, X = O
f, R''= H, R''' = 2,3-$C_6H_3OCH_2O$, X = O
g, R''-R''' = 1,2-C_6H_4(NHCOC=), X = O
h, R''-R''' = 1,2-C_6H_4(COC=CO), X = O

6a, R'' = H, R''' = C_6H_5, X = S
b, R'' = H, R''' = 2-C_4H_3S, X = S
c, R'' = H, R''' = 4-$(CH_3)_2CHC_6H_4$, X = S
d, R'' = CH_3, R''' = C_6H_5, X = S
e, R'' = CH_3, R''' = 2-C_4H_3O, X = S
f, R''= H, R''' = 2,3-$C_6H_3OCH_2O$, X = S
g, R''-R''' = 1,2-C_6H_4(NHCOC=), X = S
000 h, R''-R''' = 1,2-C_6H_4(COC=CO), X = S

Scheme 1

benzothiazole-phenyl -thiadiazole cationic head (flat aromatic), having an acetyl group instead of an ester group[16] in pervious work and quaternary nitrogen mimic that of cytosine to interact with guanine DNA base also include 2- phenyl benzoxazole and thiazole side chain such group with a free rotation around c2- of

oxazole or thiazole and c-1 of 2-phenyl. This free rotation enable them to be embedded inside DNA strands major groves. Also they have the crescent shape with an electron donner sites in this region we have herein synthesized new derivatives of Cationic 1,3,4-thiadiazoline derivatives and evaluated for their co-adherent cytotoxic properties against breast cancer (MCF-7).

RESULTS AND DISCUSSION

Chemistry

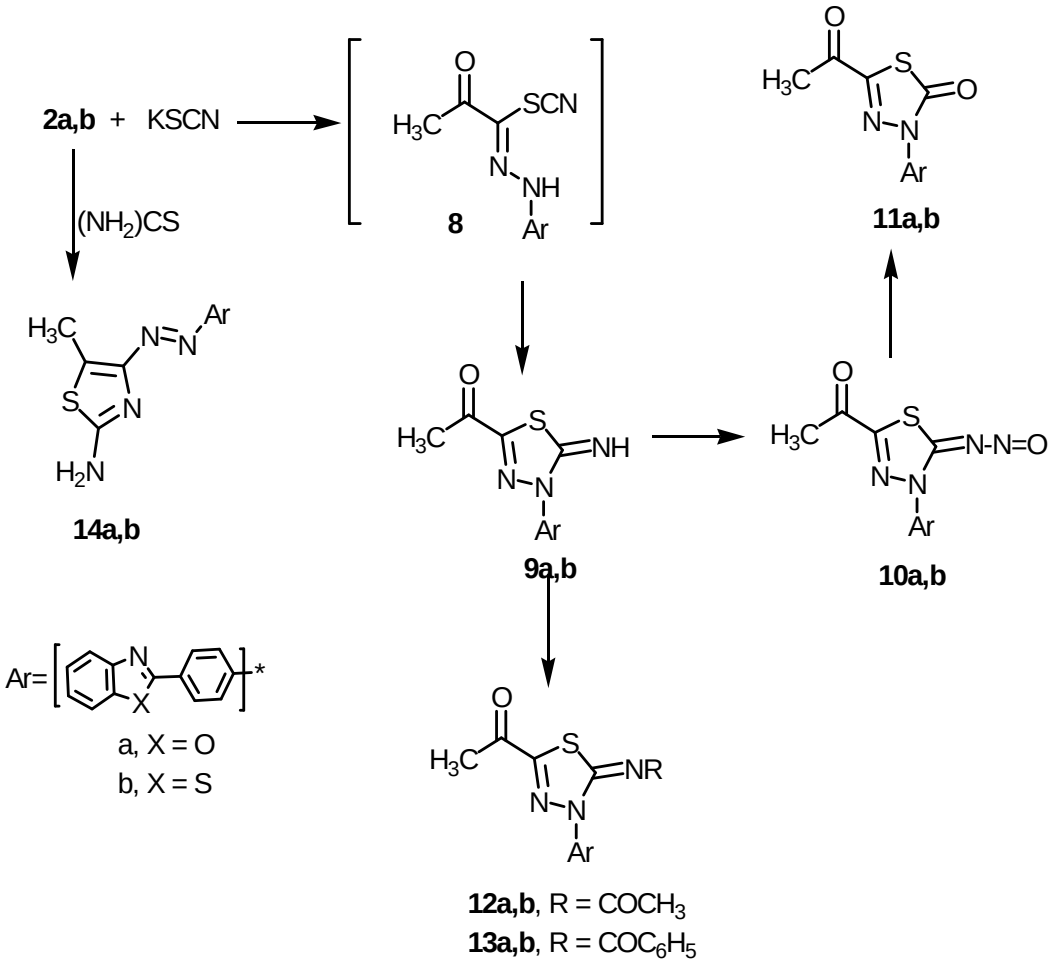
Treatment of each diazotized [4-(1,3-benzoxazol-2-yl)phenyl]amine (1a)[6] and diazotized [4-(1,3-benzothiazol-2-yl)phenyl]amine (1b)[9] with 2-chloro-2,4-pentandione in ethanolic sodium acetate gave 1-(2-(benzo[d]oxazol-2-yl)hydrazono)-1-chloropropan-2-one (2a) and 1-(2-(benzo[d]thiazol-2-yl)hydrazono)-1-chloropropan-2-one (2b). Structure 2 was elucidated by elemental analysis and spectral data. ^{1}H NMR spectrum of 2a showed signals at δ = 2.10 (s, 3H, CH_3CO), 7.40 (d, 2H, J = 8Hz, ArH's), 7.50 (d, 2H, J = 8Hz, ArH's), 8.00 (d, 2H, J = 8Hz, ArH's), 8.07 (d, 2H, J = 8Hz, ArH's) and 10.89 (s, br., 1H, NH). Thus, compound 2a reacted with the alkyl carbodithioates 3Aa[17,18] to give 1-[4-(4-benzooxazol-2-yl-phenyl)-5-(benzylidene-hydrazono)-4,5-dihydro-[1,3,4]thiadiazol-2-yl]-ethanone (5a).

The structure of 5a was confirmed by elemental analysis, spectral data, and alternative synthetic route. ^{1}H NMR spectrum of 5a showed signals at δ = 2.10 (s, 3H, CH_3), and 7.54-8.53 (m, 11H, ArH's), 8.40 (d, 2H, ArH's) and 8.52 CH (vinyl)). Also, treatment of 2a with each of 3Ab in ethanolic triethylamine gave a product identical in all respects (mp, mixed mp, and spectra) with 5a. Products 5a was assumed to be formed via elimination of alkanethiol (R\SH) from the corresponding cycloadduct 7, which formed from 1,3-dipolar cycloaddition (or 1,3-addition) of nitrile imide (generated in situ from 2 and triethylamine) to C=S 3 (Scheme 1). Analogously, treatment of the appropriate 2a, b with the appropriate 13a-h in ethanolic triethylamine gave the thiadiazoles 5a-h and 6a-h, respectively (Scheme 1).

Also, treatment of the appropriate 2a, b with potassium thiocyanate gave 1-(4-(benzo[d]oxazol-2-yl)-4,5-dihydro-5-imino-1,3,4-thiadiazol-2-yl) ethanone (9a) and 1-(4-(benzo[d]thiazol-2-yl)-4,5-dihydro-5-imino-1,3,4-thiadiazol-2-yl) ethanone (9b), respectively (Scheme 2). The structures of 9a and 9b were elucidated on the basis of elemental analyses, spectral data, and its chemical transformation. These results indicate that hydrazone 8, is not the final products and that 8 readily gave 9 by cyclization (Scheme 2). Nitrosation of each 9a and 9b with saturated sodium nitrite in acetic acid at 0–5æ%C gave 1-(4-(benzo[d]oxazol-2-yl)-4,5-dihydro-5-nitrosoimino-1,3,4-thiadiazol-2-yl) ethanone (10a) and 1-(4-(benzo[d]thiazol-2-yl)-4,5-dihydro-5-nitrosoimino-1,3,4-thiadiazol-2-yl) ethanone (10b), respectively. 5-acetyl-3-(benzo[d]oxazol-2-yl)-1,3,4-thiadiazol-2(3H)-one (11a) and 5-acetyl-3-(benzo[d]thiazol-2-yl)-1,3,4-thiadiazol-2(3H)-one (11b) were prepared by thermolysis of 10a and 10b in boiling xylene. IR spectra of 11a and 11b revealed a band near ν = 1685 cm^{-1} (CO). Acylation of 9a with acetic anhydride or with benzoyl chloride in pyridine afforded *N*-(5-acetyl-3-(benzo[d]oxazol-2-yl)-1,3,4-thiadiazol-2(3H)-ylidene) acetamide (12a) and *N*-(5-acetyl-3-(benzo[d]oxazol-2-yl)-1,3,4-thiadiazol-2(3H)-ylidene) benzamide (13a), respectively. ^{1}H NMR spectrum of 12a showed signals at δ = 2.10 (s, 3H, CH_3CO), 2.40 (s, 3H, CH_3CON), 7.40 (d, 2H, J = 8Hz, ArH's), 7.50 (d, 2H, J = 8Hz, ArH's), 8.00 (d, 4H, J = 8Hz, ArH's).

In contrast treatment of the appropriate 2a, b with thiourea in boiling ethanol gave 4-(2-(benzo[d]oxazol-2-yl) diazenyl)-5-methylthiazol-2-amine (14a) and 4-(2-(benzo[d]thiazol-2-yl)diazenyl)-5-methylthiazol-2-amine (14b). Spectral data and elemental analyses confirmed their structures. ^{1}H NMR spectrum of 14a showed signals at δ = 2.54 (s, 3H, thiazole 4-CH_3), 5.60 (s, br, 2H, NH_2), 7.57-7.66 (m, 6H, ArH's) and 8.43 (d, 2H, J = 8H, ArH's).

Treatment of 2b with methyl benzoylhydrazinecarbodithioate (15a) in ethanolic triethylamine gave 2,3-dihydro-1,3,4-thiadiazole 17 (Scheme 3). Its structure was elucidated on the basis of elemental analysis, spectral data, and alternative synthetic route. ^{1}H NMR spectrum of 17 showed signals at δ = 2.15 (s, 3H, CH_3), 7.42–8.35 (m, 13H, ArH's), 11.42 (s, br., 1H, NH); Thus, treatment of 2b with each



Scheme 2

of 15b or 5-phenyl-1,3,4-oxadiazole-2-thione (18) gave products identical in all respects (mp, mixed mp, and spectra) with 17a (Scheme 4). Similarly, treatment of the appropriate 2a, b with the 19 gave thiadiazoles 20a and 20b, respectively.

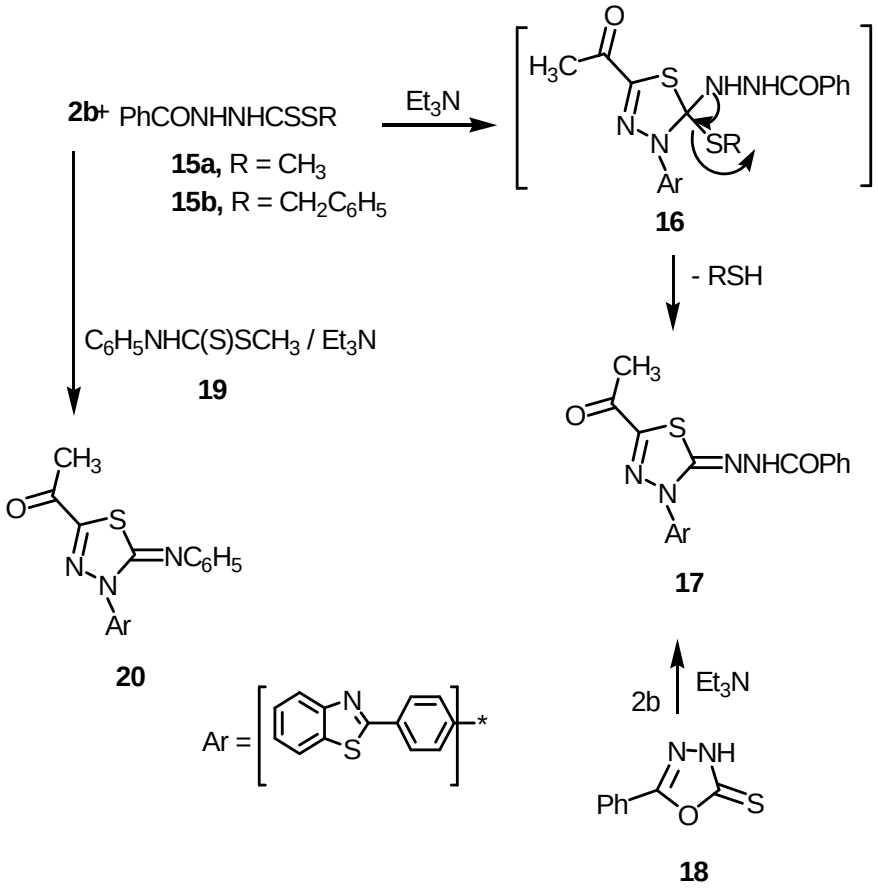
Theoretical evaluation of DNA binding affinity (docking)

Several benzothiazole and oxazoles have found to be antitumor agent scince they are structurally analogues of purine bases. These analogues could interact with DNA replication or its functions. This interaction with DNA occurred through hydrogen bonding as being either electron donor or acceptor moities in presence of water or metal ion as zinc or magnesium and also through ring stacking. These interactions were investigated to increase the anticipation of reactivity and potency of expected drug. We previously described a co-simillar series of potent benzothiazole and oxazoles as anticancer agent[16]. Such evaluation was maintained using computer aided program MOE, 2008,10, soft ware. The synthesized compounds were docked into DNA duplex obtained from protein (10.2210/pdb) [5] with a benzimidazole legend I (ID, 3gjj/pdb).

From benzimidazole ligand 9(Hoechst 33258)[5] X-crystal DNA complex (C-G-C-G-A-T-T-C-G-C-G) structure At 2.2 A^{o} resolution using data collected at room temperature by teng etal at 1998. The binding affinity of any active legand with DNA bases is usually satisfied through hydrogen bonding with the following DNA bases DG822 and DCA9 as that reported for the active benzimidazole ligand[5]and the result of newly synthesized compounds are listed in table.

Antitumor activity

The newly synthesized cationic compounds were evaluated for their *in vitro* cytotoxic activity against human breast cell line (MCF7) using doxorubicin as



Scheme 3

the reference drug according to the method described as reported[19]. The cytotoxicity was assessed at concentrations 1,2.5,5, 10 µg/mL. The relation between surviving fraction and drug concentration was plotted to obtain the survival curve of MCF7 tumor cell line after addition of the specified compound. The parameter used here is IC_{50}, which corresponds to the concentration required for 50% inhibition of cell viability. The IC_{50} of the synthesized compounds compared to the reference drug.

The obtained data revealed that most of the newly synthesized compounds showed potent antitumor activity.

CONCLUSION

Docking experiment showed that compounds 5c,5g, and 17 exhibit the same lead interactions. Compounds 5g and 6g with R"-R"'= 2,3-C_6H_4(NHCOC=) increase their affinity to recptor pocket by two hydrogen bonding and 5g showed a cytotoxic activity with $IC_{50}$of (1.75 µg). On the other hand the other compounds e.g. 5h and 6h, were interact to different residue and all of them showed higher binding scores than lead compound. their fitting to receptor is not sufficient hence they show lower molecular impactation to receptor. that the R"-R"'= 1,2-C_6H_4(COC=CO) moiety faced one of the hydrogen bonding areas mean no interaction at this site and this result was going in coincidence with the biological activities as they all showed negative result. Generally all compounds of Scheme 2 show good affinity to receptor especially compounds 9a and 9b. Both of them interact with DNA at D (CTACCT) with two hydrogen bonds and also interact with DT819 residue showing best fitting in DNA duplex. Compound cationic 9a was showed to be the least binding energy score When compared with lead compound and it was showing the best cytotoxic activity with IC_{50} of (o.98 µg) against MCF7 tumor cell line.

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