Research Paper

Synthesis and Preliminary Antiproliferative Activity of Novel 4-Substituted Phenylsulfonyl Piperazines with Tetrazole Moiety

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Kommula *et al.*: Synthesis and Antiproliferative Activity of Tetrazole-piperazinesulfonamide Hybrids

A series of 1-substituted-1H-tetrazole-5-thiol building blocks were synthesized (6a–h) and coupled by S-alkylation with 2-bromo-1-(4-(substituted phenylsulfonyl)piperazin-1-yl)ethanone (4a–c) using triethylamine in ethanol under reflux conditions. The structures of newly synthesized compounds were characterised by nuclear magnetic resonance and mass spectral data. Further, the hybrid compounds (7a–x) were screened for *in vitro* inhibitory effect on human cervical carcinoma (SiHA), breast adenocarcinoma (MDA-MB-235) and human pancreatic carcinoma (PANC-1) cell lines using sulforhodamine B assay. Antiproliferative assay revealed that most of the target compounds exhibited significant growth inhibitory activity (GI_{50}≤0.1 µM) against all tested cancer cell lines compared to the reference drug. The most promising active compounds in this series were 7e and 7n, which displayed antiproliferative activity with GI_{50}≤0.2 µM against the SiHa and MIDA-MB-231 cancer cell lines, whereas compounds 7g, 7l, 7p, 7s and 7t exhibited antiproliferative activity with GI_{50}≤0.1 µM against the PANC-1 cell line. Thus the tetrazole-piperazinesulfonamide hybrid compounds could be potential leads for the development of new antiproliferative agents.

Key words: Tetrazoles, N-substituted sulfonyl piperazine, hybrid, antiproliferative activity

Cancer is a major cause of death around the world from decades. The WHO estimated 12 million deaths by cancer with current therapeutics by 2030. Among all the characterized cancers, only lung, stomach, liver, colon, and breast cancers are main cause of cancer mortality worldwide[1]. There probable causes for the difficulty in the control and treatment cancer could be the genetic instability and poor prognosis of cancer[2]. Among all types of cancer treatment, chemotherapy is an important option. Cancer cells become simultaneously resistant to different structural types of chemotherapeutic agents due to the multidrug resistance. Hence, the development of efficient, selective and less toxic anticancer agents are necessary to overcome the multidrug resistance of cancer cells[3].

The tetrazoles are five-membered ring 6π-heterocycles, containing four contiguous nitrogen atoms and these are not found in nature, but there is scarce data available on their biological activity[4]. Further, 5-sulfenyl tetrazoles are congeners of tetrazoles that can be found as a distinguished scaffold in active pharmaceutical ingredients, such as cefamandol, latamoxef and cilostazol[5] (fig. 1). In addition, tetrazole derivatives displayed interesting pharmacological and biological properties such as antibacterial[6], antiinflammatory[6], anticonvulsant[7] and anticancer[8]. Moreover, tetrazoles commonly used in pharmaceuticals as lipophilic spacers and carboxylic acid surrogates[9].

On the other hand, sulfonamides are a very important class of compounds in the pharmaceutical industry and a key pharmacophore in many marketed drugs (fig. 2)[10]. In addition, sulfonamide derivatives possess very interesting diversified pharmacological and biological properties, like antifungal[11], antiviral[12], antitumor[13], antiinflammatory[14] and as a carbonic anhydrase inhibitors[15]. Moreover, the sulfonamides

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combined with trimethoprim were established to significantly enhance their antibacterial efficacy. It was commonly well-known that sulfamethoxazole in combination with trimethoprim is a potent pharmaceutical compound and has been broadly used for the treatment of urinary tract and pneumonia bacterial infections, toxoplasmosis[16] and pneumocystis in HIV infected patients[17]. Numerous research reports indicated that the sulfanilamide moiety (-SO_2NH-) retaining the structural feature, which was incorporated into nitrogen containing aromatic heterocyclic groups exhibited stronger anticancer or antitumor activity than the corresponding sulfanilamide precursor[11-14,18]. Thus, above results revealed that modification of sulfanilamide with nitrogen containing aromatic heterocyclic groups leads to the enhancement of antiproliferative activity and improve their potency.

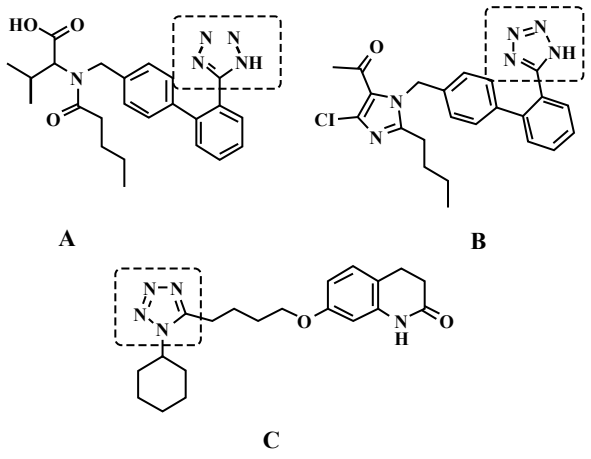


Fig. 1: Some important tetrazole containing drugs
A: Valsartan; B: losartan; C: cilostazol

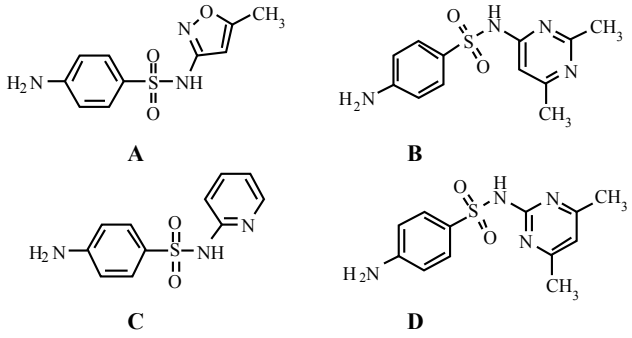


Fig. 2: Some important sulfonamide containing drugs
A: Sulfamethoxazole; B: sulfisomedine; C: sulfapyridine; D: sulfadimidine

Prompted by the aforementioned important medicinal properties of tetrazole and piperazine sulfonamides, an attempt has been made to incorporate the structural features of piperazine sulfonamides and tetrazole by aiming at the discovery of new drug candidates with potent antiproliferative activity. The synthesis of aforesaid conjugates was done by a pharmacophore hybrid approach adopted in which piperazine sulfonamide incorporated with tetrazole were hybridized in one structure (fig. 3) often lead to synergistic effects[19-21]. Herein, a new series of 2-((1-substituted phenyl-1*H*-tetrazol-5-yl)thio)-1-(4-(substituted phenylsulfonyl)piperazin-1-yl) ethanone (7a-x) were synthesized by combining the two vital pharmacophores; sulfonamides and tetrazole with a view to create promising antiproliferative agent.

MATERIALS AND METHODS

All the reagents and starting materials were obtained from commercial sources (Aldrich Chemicals, Spectrochem and Alfa-aesar) and were used without further purification. The progress of reactions was determined by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated plates, and a UV lamp and I2 stain for visualization of the TLC plates. Column chromatography was done using Merck 60-120 sized mesh silica gel using chloroform and methanol as eluents. ^{1}H nuclear magnetic resonance

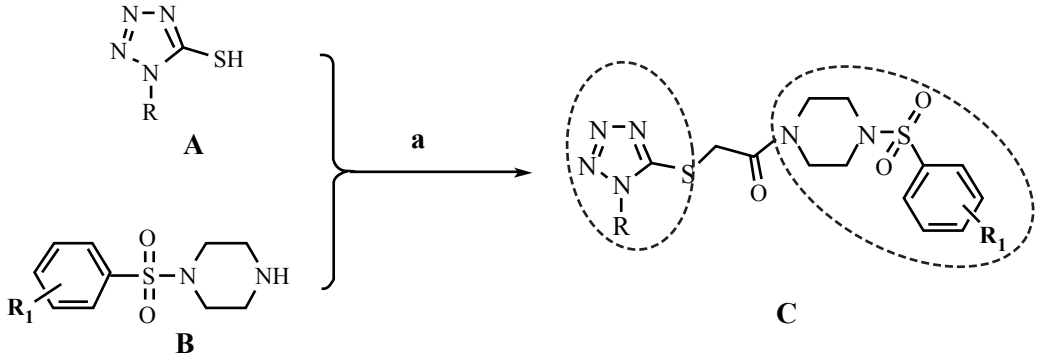


Fig. 3: Rational design of tetrazole-piperazine sulfonamide hybrids
A: Tetrazole residue; B: piperazine sulfonamide; C: tetrazole-piperazine sulfonamide hybrids; a: incorporation, molecular hybridization

(NMR) spectra (300 and 500 MHz) and ^{13}C NMR spectra (75, 101 and 126 MHz) were recorded on a Bruker Avance spectrometer using $CDCl_3$ or DMSO-D_6 as solvents and tetramethylsilane (TMS) as internal standard. Chemical shifts were reported in parts per million (ppm, δ) downfield from TMS. The following abbreviations are used for NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets. ESI-high resolution mass spectrometry (HRMS) spectra were recorded on "high-resolution QSTAR XL hybrid MS/MS system using methanol as a solvent. Melting points (MPs) were recorded on a Buchi R-535 apparatus and are uncorrected.

General procedure for the synthesis of 1-((4-substitutedphenyl)sulfonyl)piperazine (3a–c):

4-substituted aryl sulfonyl chloride (2a–c; 1.4 mmol) was added drop-wise over 4 min to a solution of piperazine (1.4 mmol) in tetrahydrofuran (THF, 3 ml) at 10-15°. The reaction mixture was stirred for 10 min and then zinc dust (2.8 mmol) was added to the reaction mixture and stirred at room temperature for 20 min. After the completion of reaction (confirmed by TLC), the reaction mixture was filtered and the filtrate was concentrated to give the crude product. The product was washed with ether and purified by crystallization using methanol to yield pure 1-((4-substitutedphenyl) sulfonyl)piperazine (3a–c).

General procedure for the synthesis of 2-bromo-1-(4-(substituted phenylsulfonyl) piperazin-1-yl) ethanone (4a–c):

A mixture of substituted 1-((4-substitutedphenyl) sulfonyl)piperazine (3a–c; 10 mmol) and bromoacetylchloride (11.5 mmol) in dichloromethane were stirred at 0° for 30-45 min. Completion of reaction indicated by TLC, the compound was extracted with CH_2Cl_2. The organic layers were collected, washed with saturated brine solution, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resultant crude was purified by column chromatograph (EtOAc and n-hexane, 3:6) to get the corresponding 2-bromo-1-(4-(substituted phenylsulfonyl)piperazin-1-yl) ethanone (4a–c).

General procedure for the synthesis of 2-((1-substituted phenyl-1*H*-tetrazol-5-yl)thio)-1-(4-(substituted phenylsulfonyl)piperazin-1-yl) ethanone (7a–x):

To a solution of 1- substituted phenyl-1*H*-tetrazole-5-thiol (6a–h; 0.9819 mmol) in ethanol (4 ml) and triethylamine (0.27 ml, 1.9638 mmol; 0.0981 mmol) were added at room temperature under N_2 atmosphere. To the resultant mixture, 2-bromo-1-(4-(substituedsulfonyl)piperazin-1-yl)ethanone (3a–c; 0.9819 mmol) was added and heated at 80°. Completion of reaction indicated by TLC, ethanol was evaporated *in vacuo*. The compound was extracted with CH_2Cl_2. The organic layers were collected, washed with saturated brine solution, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resultant crude was purified by column chromatograph (EtOAc and n-hexane, 3:7) to get the title compound.

2-((1-ethyl-1*H*-tetrazol-5-yl)thio)-1-(4-(phenyl sulfonyl)piperazin-1-yl)ethanone (7a):

White solid; MP: 121-123°. ^1H NMR (500 MHz, $CDCl_3$) δ 7.80-7.69 (m, 2H), 7.68-7.51 (m, 5H), 4.34 (s, 3H), 4.28 (q, J=7.3 Hz, 3H), 3.79-3.63 (m, 4H), 3.17-2.98 (m, 7H), 1.51 (t, J=7.3 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 152.5, 135.2, 133.3, 129.3, 127.6, 46.0, 45.4, 42.7, 41.7, 37.2, 13.9; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{15}H_{21}O_3N_6S_2$: 397.11124, found: 397.11065.

2-((1-ethyl-1*H*-tetrazol-5-yl)thio)-1-(4-((4-methoxy phenyl)sulfonyl)piperazin-1-yl)ethanone (7b):

Yellow solid; MP: 138-140°. ^1H NMR (500 MHz, $CDCl_3$) δ 7.72-7.63 (m, 2H), 7.04-6.97 (m, 2H) 4.34 (s, 2H), 4.27 (q, J=7.2 Hz, 2H), 3.88 (s, 3H) 3.77-3.64 (m, 4H), 3.10-2.95 (m, 4H), 1.50 (t, J=7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 163.4, 152.6, 129.8, 126.5, 114.5, 55.7, 46.0, 45.6, 42.8, 41.7, 37.3, 13.9; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{16}H_{23}O_4N_6S_2$: 427.12205, found: 427.12178.

2-((1-ethyl-1*H*-tetrazol-5-yl)thio)-1-(4-((4-(trifluoro methyl)phenyl)sulfonyl)piperazin-1-yl)ethanone (7c):

White solid; MP: 160-162°. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81-7.69 (m, 2H), 7.68-7.51 (m, 2H), 4.34 (s, 2H), 4.27 (q, J=7.3 Hz, 2H), 3.78-3.66 (m, 4H), 3.08 (m, 4H), 1.51 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 152.5, 138.8, 128.2, 126.5, 45.4, 42.8, 41.6, 37.2, 14.1; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{16}H_{20}O_3N_6F_3S_2$: 465.09864, found: 465.09828.

2-((1-phenyl-1*H*-tetrazol-5-yl)thio)-1-(4-(phenyl sulfonyl)piperazin-1-yl)ethanone (7d):

White solid; MP: 157-159°. ^1H NMR (500 MHz, $CDCl_3$) δ 7.78-7.74 (m, 3H), 7.67-7.61 (m, 2H), 7.60-

7.51 (m, 5H), 4.38 (s, 2H), 3.79-3.57 (m, 4H), 3.19-3.07 (m, 2H), 3.01-2.95 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 153.5, 135.2, 133.3, 130.3, 129.9, 129.3, 127.7, 123.6, 46.0, 45.6, 41.7, 37.4; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{19}H_{21}O_3N_6S_2$: 445.11134, found: 445.11105.

1-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)-2-((1-phenyl-1*H*-tetrazol-5-yl)thio)ethanone (7e):

White solid; MP: 131-134°. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, J=6.7, 4.9 Hz, 2H), 7.61-7.51 (m, 5H), 7.02 (d, J=8.9 Hz, 2H), 4.39 (s, 2H), 3.88 (s, 3H), 3.80-3.75 (m, 4H), 3.14-2.96 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 163.4, 153.5, 133.4, 130.3, 129.9, 126.5, 123.6, 114.5, 55.7, 46.0, 45.5, 41.7, 37.5; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{20}H_{23}O_4N_6S_2$: 475.12215, found: 475.12190.

2-((1-phenyl-1*H*-tetrazol-5-yl)thio)-1-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)ethanone (7f):

White solid; MP: 165-167°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.72 (m, 4H), 7.66-7.42 (m, 5H), 4.37 (s, 2H), 3.92-3.62 (m, 4H), 3.30-2.89 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3, 150.9, 136.4, 130.8, 127.8, 127.4, 125.6, 124.0, 121.1, 43.4, 43.0, 39.1, 34.7; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{20}H_{20}O_3N_6F_3S_2$: 513.09889, found: 513.09854.

2-((1-benzyl-1*H*-tetrazol-5-yl)thio)-1-(4-(phenylsulfonyl)piperazin-1-yl)ethanone (7g):

Yellow solid; MP: 133-135°. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81-7.52 (m, 5H), 7.43-7.17 (m, 5H), 5.55 (s, 2H), 4.42 (s, 2H), 3.58-3.49 (m, 4H) 3.06-2.83 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 153.3, 135.2, 133.3, 132.6, 129.3, 129.1, 128.2, 127.6, 51.2, 45.9, 45.6, 41.7, 37.5; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{20}H_{23}O_3N_6S_2$: 459.12703, found: 459.12659.

2-((1-benzyl-1*H*-tetrazol-5-yl)thio)-1-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)ethanone (7h):

White solid; MP: 123-125°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.63 (m, 2H), 7.37-7.31 (m, 4H), 7.28-7.10 (m, 2H), 7.06-6.96 (m, 2H), 5.42 (s, 2H), 4.29 (s, 2H), 3.88 (s, 3H), 3.74-3.60 (m, 4H), 3.10-2.93 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 153.1, 139.0, 134.8, 132.5, 129.1, 128.2, 126.5, 124.4, 121.7, 51.2, 45.9, 45.6, 41.7, 37.2; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{21}H_{25}O_4N_6S_2$: 489.13756, found: 489.13703.

2-((1-benzyl-1*H*-tetrazol-5-yl)thio)-1-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)ethanone (7i):

White solid; MP: 135-137°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00-7.76 (m, 4H), 7.39-7.15 (m, 5H), 5.41 (s, 2H), 4.27 (s, 2H), 3.84-3.56 (m, 4H), 3.19-2.93 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 153.3, 139.1, 134.8, 132.5, 129.1, 128.2, 126.5, 124.0, 122.1, 51.2, 45.6, 41.7, 37.3; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{21}H_{22}O_3N_6F_3S_2$: 527.11456, found: 527.11402.

2-((1-(4-bromophenyl)-1*H*-tetrazol-5-yl)thio)-1-(4-(phenylsulfonyl)piperazin-1-yl)ethanone (7j):

White solid; MP: 154-156°. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.39 (m, 9H), 4.38 (s, 2H), 3.84-3.60 (m, 4H), 3.22-2.96 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 153.5, 135.1, 133.2, 132.3, 129.3, 127.7, 125.2, 124.4, 46.0, 45.6, 41.7, 37.6; ESI-HRMS (*m/z*): $[M+H]^+$. Calcd. for $C_{19}H_{20}O_3N_6BrS_2$: 523.02189, found: 523.02104.

2-((1-(4-bromophenyl)-1*H*-tetrazol-5-yl)thio)-1-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)ethanone (7k):

White solid; MP: 155-157°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74-7.65 (m, 4H), 7.52-7.46 (m, 2H), 7.08-6.97 (m, 2H), 4.39 (s, 2H), 3.88 (s, 3H), 3.78-3.67 (m, 4H), 3.14-3.06 (m, 2H), 3.02-2.92 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 163.4, 153.5, 133.2, 132.3, 129.8, 126.5, 125.1, 124.4, 114.5, 55.7, 46.0, 45.5, 41.7, 37.7; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{20}H_{22}O_4N_6BrS_2$: 553.03228, found: 553.03173.

2-((1-(4-bromophenyl)-1*H*-tetrazol-5-yl)thio)-1-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)ethanone (7l):

White solid; MP: 140-142°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J=8.5 Hz, 2H), 7.73-7.66 (m, 3H), 7.50-7.43 (m, 3H), 4.37 (s, 2H), 3.82-3.70 (m, 4H), 3.22-3.14 (m, 2H), 3.12-3.01 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 153.4, 139.0, 133.2, 132.3, 128.2, 126.6, 125.0, 124.4, 45.9, 45.6, 41.8, 37.3; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{20}H_{19}O_3N_6BrF_3S_2$: 591.00905, found: 591.00838.

2-((1-(4-nitrophenyl)-1*H*-tetrazol-5-yl)thio)-1-(4-(phenylsulfonyl)piperazin-1-yl)ethanone (7m):

Yellow solid; MP: 145-147°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (t, J=10.8 Hz, 2H), 7.91 (t, J=10.8 Hz, 2H), 7.76-7.72 (m, 2H), 7.69-7.53 (m, 3H), 4.45 (s, 2H), 3.80-3.68 (m, 4H), 3.19-3.00 (m, 4H); ^{13}C

NMR (75 MHz, $CDCl_3$+DMSO) δ 169.3, 158.9, 152.7, 142.9, 139.9, 138.1, 134.1, 132.3, 130.2, 129.0, 50.7, 50.1, 46.4, 42.8; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{19}H_{20}O_5N_7S_2$: 490.09662, found: 490.09611.

1-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)-2-((1-(4-nitrophenyl)-1*H*-tetrazol-5-yl)thio)ethanone (7n):

Yellow solid; MP: 161-163°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48-8.40 (m, 2H), 7.92-7.87 (m, 2H), 7.72-7.62 (m, 2H), 7.06-6.96 (m, 2H), 4.45 (s, 2H), 3.89 (s, 3H), 3.79-3.67 (m, 4H), 3.16-2.98 (m, 4H); ^{13}C NMR (126 MHz, DMSO-D_6) δ 159.5, 158.5, 149.1, 143.2, 133.3, 125.0, 121.6, 120.6, 119.3, 109.7, 50.9, 41.1, 40.8, 36.8, 33.2; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{15}H_{21}O_3N_6S_2$: 520.10713, found: 520.10640.

2-((1-(4-nitrophenyl)-1*H*-tetrazol-5-yl)thio)-1-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)ethanone (7o):

Yellow solid; MP: 154-156°. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64-8.22 (m, 4H), 8.16-7.54 (m, 6H), 4.47 (s, 2H), 3.85-3.48 (m, 4H), 3.34-2.94 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 153.7, 148.1, 138.1, 136.7, 130.8, 130.2, 128.2, 125.5, 124.6, 124.0, 121.7, 45.9, 45.6, 41.8, 37.7, 29.7; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{20}H_{19}O_5N_7F_3S_2$: 558.08395, found: 558.08339.

1-(4-(phenylsulfonyl)piperazin-1-yl)-2-((1-(4-(trifluoromethyl)phenyl)-1*H*-tetrazol-5-yl)thio)ethanone (7p):

White solid; MP: 175-177°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.68 (m, 6H), 7.64-7.57 (m, 3H), 4.43 (s, 2H), 3.85-3.58 (m, 4H), 3.24-2.92 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 153.7, 136.2, 135.2, 133.3, 129.3, 127.6, 127.24, 123.8, 46.0, 45.5, 41.7, 37.9; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{20}H_{20}O_3N_6F_3S_2$: 513.09878, found: 513.09834.

1-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)-2-((1-(4-(trifluoromethyl)phenyl)-1*H*-tetrazol-5-yl)thio)ethanone (7q):

White solid; MP: 175-177°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J=8.6 Hz, 2H), 7.78 (d, J=8.5 Hz, 2H), 7.73-7.66 (m, 2H), 7.07-6.98 (m, 2H), 4.42 (s, 2H), 3.88 (s, 3H), 3.79-3.65 (m, 4H), 3.14-3.07 (m, 2H), 3.05-2.98 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 163.4, 153.7, 136.2, 129.8, 127.2, 126.5, 123.8, 114.5, 55.7, 46.0, 45.5, 41.7, 37.9; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{21}H_{22}O_4N_6F_3S_2$: 543.10946, found: 543.10901.

2-((1-(4-(trifluoromethyl)phenyl)-1*H*-tetrazol-5-yl)thio)-1-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)ethanone (7r):

White solid; MP: 175-177°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94-7.88 (m, 4H), 7.85 (d, J=8.9 Hz, 2H), 7.78 (d, J=8.4 Hz, 2H), 4.40 (s, 2H), 3.76-3.69 (m, 4H), 3.22-3.14 (m, 2H), 3.12-3.04 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 153.5, 139.0, 136.2, 128.2, 127.2, 126.5, 123.7, 45.9, 45.6, 41.8, 37.4; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{21}H_{19}O_3N_6F_6S_2$: 581.08618, found: 581.08575.

1-(4-(phenylsulfonyl)piperazin-1-yl)-2-((1-(2,3,4-trifluorophenyl)-1*H*-tetrazol-5-yl)thio)ethanone (7s):

White solid; MP: 144-146°. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.47 (m, 6H), 7.41-7.09 (m, 2H), 4.39 (s, 2H), 3.80-3.60 (m, 4H), 3.12-2.98 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 155.7, 135.1, 133.4, 129.3, 127.6, 122.1, 113.0, 45.9, 45.6, 41.7, 37.9; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{19}H_{18}O_3N_6F_3S_2$: 499.08303, found: 499.08259.

1-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)-2-((1-(2,3,4-trifluorophenyl)-1*H*-tetrazol-5-yl)thio)ethanone (7t):

White solid; MP: 175-177°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.05-6.97 (m, 4H), 4.39 (s, 2H), 3.88 (s, 3H), 3.76-3.64 (m, 4H), 3.14-3.06 (m, 2H), 3.03-2.97 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 163.4, 155.7, 129.8, 126.4, 122.3, 118.1, 114.5, 113.2, 113.0, 55.7, 46.0, 45.6, 41.6, 37.9; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{20}H_{20}O_4N_6F_3S_2$: 529.09372, found: 529.09318.

1-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)-2-((1-(2,3,4-trifluorophenyl)-1*H*-tetrazol-5-yl)thio)ethanone (7u):

White solid; MP: 143-145°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01-7.80 (m, 4H), 7.31-7.12 (m, 2H), 4.38 (s, 2H), 3.82-3.65 (m, 4H), 3.25-2.97 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 153.6, 139.1, 136.2, 128.2, 127.2, 126.6, 123.7, 45.9, 45.6, 41.8, 37.5; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{20}H_{17}O_3N_6F_6S_2$: 567.07058, found: 567.07005.

1-(4-(phenylsulfonyl)piperazin-1-yl)-2-((1-(3,4,5-trimethoxyphenyl)-1*H*-tetrazol-5-yl)thio)ethanone (7v):

White solid; MP: 145-148°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.71 (m, 2H), 7.67-7.52 (m, 3H), 6.76 (s, 2H), 4.37 (s, 2H), 3.90 (s, 9H), 3.77-3.68 (m, 4H), 3.18-3.14 (m, 2H), 3.07-3.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 153.9, 138.9, 130.8, 130.3, 128.2, 127.2, 126.5, 123.8, 101.4, 61.0, 56.4, 45.9, 45.6, 41.7, 37.6; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{22}H_{27}O_6N_6S_2$: 535.14306, found: 535.14268.

1-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)-2-((1-(3,4,5-trimethoxyphenyl)-1*H*-tetrazol-5-yl)thio) ethanone (7w):

White solid; MP: 159-161°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J=8.7 Hz, 2H), 7.04 (d, J=8.6 Hz, 2H), 6.78 (s, 2H), 4.39 (s, 2H), 3.91 (s, 9H), 3.83-3.78 (m, 4), 3.24-2.87 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.7, 163.4, 153.9, 153.6, 139.3, 129.8, 128.6, 126.5, 114.5, 101.5, 61.0, 56.5, 55.7, 46.0, 45.6, 41.7, 37.4; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{23}H_{29}O_7N_6S_2$: 565.15371, found: 565.15323.

1-(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)-2-((1-(3,4,5-trimethoxyphenyl)-1*H*-tetrazol-5-yl)thio)ethanone (7x):

White solid; MP: 155-157°. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-7.84 (m, 3H), 7.74-7.70 (m, 1H), 6.76 (s, 2H), 4.36 (s, 2H), 3.92 (s, 9H), 3.83-3.69 (m, 4H), 3.25-3.19 (m, 2H), 3.14-3.01 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 153.9, 153.6, 139.3, 136.7, 130.8, 130.2, 130.0, 128.6, 124.5, 101.4, 61.0, 56.5, 45.9, 45.6, 41.7, 37.1; ESI-HRMS (m/z): $[M+H]^+$. Calcd. for $C_{23}H_{26}O_6N_6F_3S_2$: 603.13056, found: 603.13009.

***In vitro* antiproliferative activity:**

The cell lines, SiHa, MDA-MB-231 and PANC1, which were used in this study, were procured from American Type Culture Collection (ATCC), United States. The synthesized tetrazole-arylpiperazinesulfonamide hybrid compounds were evaluated for *in vitro* antiproliferative activity against these three human cancer cell lines. A protocol of 48-h continuous drug exposure was used, and the sulforhodamine B (SRB) cell proliferation assay was used to estimate cell viability or growth[21,22]. All cell lines were grown in Dulbecco's modified Eagle's medium containing 10 % fetal bovine serum in a humidified atmosphere of 5 % CO_2 at 37°. Cells were trypsinized when sub-confluent from T25 flasks/60-mm dishes and seeded in 96-well plates in 100 µl aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37°, 5 % CO_2, 95 % air, and 100 % relative humidity for 24 h prior to addition of experimental drugs and were incubated for 48 h with different doses (0.01, 0.1, 1, 10, 100 µM) of the prepared derivatives. After 48-h incubation at 37°, cell monolayers were fixed by the addition of 10 % (wt/vol) cold trichloroacetic acid, incubated at 4° for 1 h, and then stained with 0.057 % SRB dissolved in 1 % acetic acid for 30 min at room temperature. Unbound SRB was washed with 1 % acetic acid. The protein-bound dye was dissolved in 10 mM Tris base solution for OD determination at 510 nm using a microplate reader (Enspire, Perkin Elmer, USA). Using the seven absorbance measurements, time zero, (Tz), control growth (C), and test growth in the presence of drug at the five concentration levels (Ti), the percent growth was calculated at each level of the drug concentration. Percent growth inhibition was calculated as; [(Ti-Tz)/(C-Tz)]×100 for concentrations for which Ti>/=Tz; [(Ti-Tz)/Tz]×100 for concentrations for which Ti<Tz.

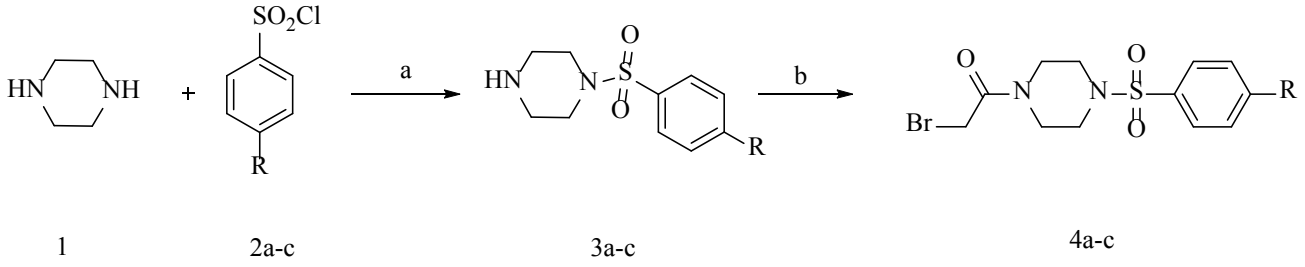
The dose-response parameters were calculated for each experimental agent. Growth inhibition of 50 % (GI_{50}) was calculated from [(Ti−Tz)/(C−Tz)]×100 = 50, which is the drug concentration resulting in a 50 % reduction in the net protein increase (as measured by SRB staining) in control cells during incubation with the test or standard agents. The values were calculated for this parameter if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.

RESULTS AND DISCUSSION

The 1-substituted-1*H*-tetrazole-5-thiols (6a–h) coupled with substituted phenylsulfonyl piperazine acetamide derivatives (3a–c) were synthesized by a converging synthesis route that requires the preparation of the 4-substituted phenylsulfonylpiperazines and 1-substituted-1*H*-tetrazole-5-thiol precursors independently that can be subsequently coupled together. Initially, 4-substituted phenylsulfonylpiperazines (3a–c) were prepared by starting with the appropriate arylsulfonyl chloride (2) reacted with simple piperazine in THF solvent using zinc dust under mild and neutral conditions at room temperature[23]. The excess piperazine was removed by washing with saturated aq. $NaHCO_3$ solution to afford the required product with good yields. Then, the substituted phenylsulfonyl piperazines (3a–c) were treated with bromoacetyl bromide in CH_2Cl_2 solvent at 0° to room temperature

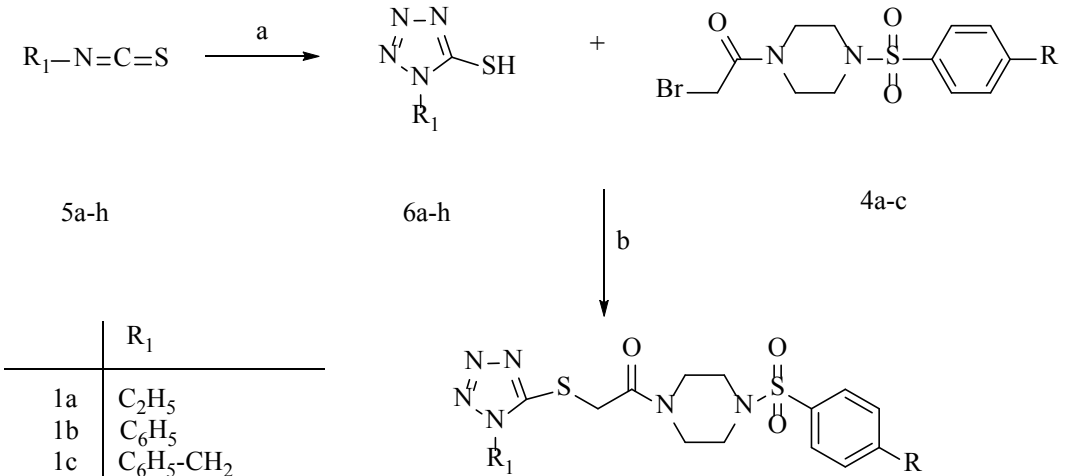
stirring for 90-120 min to afford the 2-bromo-1-(4-(substitutedsulfonyl)piperazin-1-yl)ethanone (4a–c) with excellent yield range from 85-90 %, the overall reaction sequence described in fig. 4.

On the other hand, 1-substituted 5-mercaptotetrazoles[24] (6a–h) derivatives were synthesized by the reaction of NaN_3 with isocyanates (5a–g) in water at 80° for 3 h. To obtain final compounds (7a–x), the compounds 2-bromo-1-(4-(substituted sulfonyl)piperazin-1-yl) ethanone (3a–c) and 1-substituted 5-mercaptotetrazoles (6a–h) were refluxed with ET_3N in ethanol to afford corresponding compounds yields ranging from 79 to 88 % (Table 1, fig. 5). The formation of *S*-alkylated products (7a–x) were confirmed by the presence of *S*–CH_2 characteristic peak appeared at δ 41.2-41.7 ppm in ^{13}C NMR and appearance of signal as a singlet for the methylene group at δ 3.39-3.47 ppm in ^1H NMR spectrum, which is typical for connectivity. The spectroscopic data of all the newly synthesized compounds are in full accordance with their depicted structures. The detailed general synthesis procedure of the compounds is mentioned in the experimental section.



	R
2a	H
2b	OMe
2c	CF_3

Fig. 4: Preparation of 2-bromo-1-(4-(substituted sulfonyl)piperazin-1-yl)ethanone (4a–c)
Reagents and conditions: a) NaN_3, H_2O, 80°. b) Et_3N, ethanol, reflux, 4 h



	R_1
1a	C_2H_5
1b	C_6H_5
1c	C_6H_5-CH_2
1d	4-Br-C_6H_5
4e	4-NO_2-C_6H_5
4f	4-CF_3-C_6H_5
4g	2,3,4-tri-F-C_6H_5
1h	3,4,5-tri-OCH_3-C_6H_5

Fig. 5: Preparation of 2-((1-substituted phenyl-1*H*-tetrazol-5-yl)thio)-1-(4-(substituted phenylsulfonyl)piperazin-1-yl)ethanone
Reagents and conditions, a) Zn, THF, rt, 30 min, b) 2-bromoacetyl bromide, dichloromethane, 0°, 1-2 h

The novel target compounds (7a–x) were tested *in vitro* for inhibitory effect on human cancer cell lines, cervix (SiHa), breast (MDA-MB-231) and pancreatic carcinoma (PANC-1) using the SRB assay method. The GI_{50} values are listed in Table 2. From the screening results in Table 2, it was observed that all the compounds showed antiproliferative activities against these cell lines in a concentration-dependent manner.

Among the tested cell lines, compounds such as 7d, 7e and 7n showed 1-2 fold greater activity than reference drug (GI_{50}=0.12 μM), as evidenced by GI_{50} values of 0.071-0.098 μM against SiHa cancer cell line. On the other hand, compounds 7a, 7c, 7e and 7n showed comparable activity (GI_{50}=0.193-0.239 μM) than reference drug (GI_{50}=0.24 μM) against MIDA-MB-231 cancer cell line, while the compounds 7h, 7s and 7m showed equal activity (GI_{50}=0.072-0.15 μM) to that of the reference drug (GI_{50}=0.15 μM) against PANC-1 cancer cell line

Different substituents such as alkyl, phenyl, benzyl, electron-withdrawing Br, CF_3, F, NO_2 and electron-donating OCH_3 on a phenyl ring were applied on tetrazole moiety as well as different substituents (CF_3, OCH_3) were employed on sulfonylpiperazines to investigate antiproliferative activity. However the interesting inhibitory behaviour of these compounds is relatively dependent on electronic nature of substituents on the tetrazole and sulfonylpeparazine hybrids (7a–x). The overall results of antiproliferative activity indicated that the compounds bearing methoxy group (OCH_3) sulfonylpeparazine attached to the tetrazole which were having unsubstituted phenyl (7d and 7e) and substituted electron withdrawing (NO_2, F) groups (7n, 7s and 7t) showed 50 % inhibition at a concentrations ranges from 0.071-0.22 μM against various tested cancer cell lines. From the obtained results it revealed that compounds bearing methoxy group (OCH_3) sulfonylpeparazine attached to the tetrazole, which were having either unsubstituted phenyl or substituted electron withdrawing (NO_2, F) groups contributed to the promising antiproliferative activity.

In summary, a straightforward synthetic strategy was developed for the preparation of novel 2-((1-substitued phenyl-1*H*-tetrazol-5-yl)thio)-1-(4-(substituted phenyl

TABLE 1: SYNTHESIS OF 2-((1-SUBSTITUTED PHENYL-1H-TETRAZOL-5-YL)THIO)-1-(4-(SUBSTITUTED PHENYLSULFONYL)PIPERAZIN-1-YL)ETHANONE

S. No.	R	R_1	Yield[a] (%)
7a	H	C_2H_5	84
7b	OCH_3	C_2H_5	85
7c	CF_3	C_2H_5	82
7d	H	Ph	86
7e	OCH_3	Ph	87
7f	CF_3	Ph	83
7g	H	Ph-CH_2	88
7h	OCH_3	Ph-CH_2	86
7i	CF_3	Ph-CH_2	83
7j	H	4-Br-Ph	86
7k	OCH_3	4-Br-Ph	87
7l	CF_3	4-Br-Ph	82
7m	H	4-NO_2-Ph	83
7n	OCH_3	4-NO_2-Ph	84
7o	CF_3	4-NO_2-Ph	79
7p	H	4-CF_3-Ph	82
7q	OCH_3	4-CF_3-Ph	84
7r	CF_3	4-CF_3-Ph	79
7s	H	2,3,4-tri-F-Ph	83
7t	OCH_3	2,3,4-tri-F-Ph	82
7u	CF_3	2,3,4-tri-F-Ph	80
7v	H	3,4,5-tri-OMe-Ph	88
7w	OCH_3	3,4,5-tri-OMe-Ph	90
7x	CF_3	3,4,5-tri-OMe-Ph	81

'[a]'After purification by column chromatography

TABLE 2: *IN VITRO* ANTIPROLIFERATIVE ACTIVITY (GI_{50} μM)[a] OF THE SYNTHESIZED COMPOUNDS[b]

Compound No	SiHA	MDA-MB-231	PANC-1
7a	0.685±0.02	0.239±0.01	0.491±0.01
7b	0.731±0.04	0.858±0.03	0.681±0.01
7c	3.365±0.07	0.102±0.05	0.228±0.03
7d	0.073±0.002	1.877±0.06	0.42±0.02
7e	0.098±0.003	0.229±0.03	0.827±0.05
7f	12.527±0.06	11.47±0.09	9.77±0.06
7g	3.675±0.02	3.627±0.05	0.483±0.01
7h	0.2±0.01	7.783±0.06	0.2±0.03
7i	2.234±0.05	2.395±0.02	0.375±0.03
7j	1.765±0.06	1.632±0.01	0.642±0.02
7k	0.948±0.02	2.394±0.03	0.334±0.07
7l	1.641±0.02	2.021±0.04	0.678±0.04
7m	1.883±0.03	1.885±0.06	0.154±0.03
7n	0.071±0.002	0.193±0.02	1.967±0.06
7o	8.182±0.09	10±0.05	0.388±0.01
7p	0.582±0.02	1.24±0.01	0.155±0.03
7q	0.817±0.04	1.833±0.03	0.884±0.05
7r	0.221±0.01	0.496±0.02	0.2±0.01
7s	0.639±0.03	2.761±0.01	0.072±0.002
7t	9.961±0.08	2.845±0.06	0.1±0.01
7u	0.991±0.02	0.571±0.03	0.261±0.03
7v	2.482±0.06	2.363±0.05	2.92±0.04
7w	5.982±0.06	1.627±0.02	1.1±0.03
7x	0.699±0.03	0.223±0.01	1.15±0.01
Tamoxifen	0.12±0.01	0.24±0.01	0.15±0.02

'[a]'GI_{50} was defined as the concentration resulting in 50 % growth inhibition. Data are means±SD of three independent experiments. '[b]'All compounds were characterized by NMR and mass spectroscopy

sulfonyl)piperazin-1-yl)ethanone derivatives (7a–x) with good yields and evaluated for their *in vitro* antiproliferative studies. The preliminary studies revealed that a few of the synthesized hybrids were active on all the tested cancer cell lines with GI_{50} values less than 1.5 μM. The growth inhibition of cancer cell lines profile revealed that compounds 7e and 7n displayed broader spectrum of antiproliferative activity with $GI_{50} \leq 0.2$ μM against the SiHa and MIDA-MB-231 cell lines compared to reference drug whereas compounds 7g, 7l, 7p, 7s and 7t exhibited antiproliferative activity with $GI_{50} \leq 0.1$ μM against the PANC-1 cell lines. Overall, these findings proposed that tetrazole-containing substituted phenylsulfonylpiperazine hybrids have the potential to be developed as lead molecule and further structural modification might create promising new antiproliferative agents.

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Conflict of interest:

There is no conflict of interest among authors.

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