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SYNTHESIS, CYTOTOXIC AND ANTIMICROBIAL ACTIVITIES OF NOVEL 1,2,4-TRIAZOLE DERIVATIVES INCORPORATING ARYL SULFONAMIDE MOIETY

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ABSTRACT

In the present study an attempt was made to synthesize various substituted-1,2,4-triazole derivatives, starting from 4-tosylamino benzohydrazide (1) and to investigate their cytotoxic and antimicrobial activities. All the synthesized compounds were confirmed by IR, ^{1}H, ^{13}CNMR, Mass spectrometry and elemental analysis. All spectroscopic data of the new compounds show agreement with the expected values. Some of the newly synthesized compounds were evaluated for their cytotoxic activity against breast carcinoma (MCF7) and colon carcinoma (HCT116) cell lines. The cytotoxic activity showed that compounds 16, 24b have high activity against the two cell lines. Most of the newly prepared compounds were tested for their antimicrobial activity against Gram positive, Gram negative and fungi. The results showed that most of the tested compounds exhibit promising antimicrobial activity.

KEY WORDS

Cytotoxic, Antimicrobial, Synthesis 1,2,4-triazole and Aryl sulfonamide.

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INTRODUCTION

In recent year, nitrogen linked heterocyclic compounds received considerable attention due to their wide application. A large number of heterocyclic compounds containing 1,2,4-triazole moiety are associated with diverse pharmacological properties such as antimicrobial[1-6], anticancer[7-11], anti-inflammatory[12,13], antiviral[14], anticonvulsant[15], antidepressant[16], antioxidant[17], analgesic[18] and hypoglycemic activity[19]. Moreover Schiff base derivatives containing 1, 2, 4-triazole ring were reported as antitumor agents[20].

Among the 1, 2, 4-triazole derivatives, the mercapto- and thione-substituted 1, 2, 4-triazole derivatives were reported to possess a variety of antitumor properties[21].

In addition sulfonamides are important class of drug with several pharmacological properties as antimicrobial[22] and anticancer[23]. In the present work 1, 2, 4-triazole derivatives bearing arylsulfonamide moiety prepared with the aim of obtaining new compounds with interesting biological properties as antimicrobial and cytotoxic activities.

DISCUSSION

A- Chemistry

The reaction sequences employed for synthesis of novel 1,2,4-triazole derivatives are shown in schemes 1,2. In the present work thiosemicarbazide derivatives 2a-e were used as key intermediate for the synthesis of 1,2,4-triazole derivatives. Various thiosemicarbazide derivatives 2a-e were synthesized by condensing isothiocynate derivatives with 4-tosylaminobenzohydrazide 1 *v*ia stirring in dioxane at room temperature overnight. The base catalyzed cyclization of thiosemicarbazide derivatives 2a-e either *v*ia refluxing with 2N sodium hydroxide or hydrazine hydrate in methanol furnished the corresponding 4-substituted-5-(4-tosylamino) phenyl-4H-1,2,4-triazole-3-thiol derivatives 3a-e and 4-amino-3-substitutedamino-5-(4-tosylamino) phenyl-4H-1,2,4-triazoles 4a-d respectively. Compounds 3a-e, when treating with ethyl iodide and aryl chloroacetamide derivatives in ethanol containing potassium hydroxide by stirring at room temperature overnight yielded S-substituted-1,2,4-triazole derivatives 5-20.

Furthermore condensation of triazole derivatives 4a,b with 3,4,5-trimethoxybenzaldehyde by refluxing in ethanol containing acetic acid gave Schiff's base 21,22 (Scheme No.1). The reaction of acid hydrazide 1 with carbon disulphide in ethanolic potassium hydroxide yielded the potassium salt of corresponding dithiocarbazate 23 in quantitave yield. Cyclization of potassium dithiocarbazate 23 upon reaction with hydrazine hydrate (99%) afforded 4-amino-3(4-(tosylamino)phenyl)-4H-1,2,4-triazole-5(1H)thione 24 which was used as starting material in (scheme 2). The amino and mercapto groups are ready-made nucleophilic centers or synthesis of heterocyclic rings. Upon reaction of compound 24 with 4-bromophenacyl bromide *via* refluxing in absolute ethanol containing anhydrous sodium acetate for 6 hrs as an attempt to prepare triazolo [3, 4-b] thiadiazine was unsuccessful. Instead, the S-substituted derivatives 25 was obtained. However a trial was made for cyclization of compound 25 *via* refluxing the previous reaction for long time 25hrs. We obtained the cyclized products-1,2,4-triazolo[3,4-b]1,3,4-thiadiazine derivatives 26a,b. Condensation of compound 24 with aromatic aldehydes namely 3,4,5-trimethoxybenzaldehyde,vanillin,4-methoxybenzaldehyde,4-chlorobenzaldehyde and 4-nitrobenzaldehyde in refluxing ethanol containing acetic acid afforded the corresponding Schiff's base 27 a-e. On the other hand, triazolo [3,4-b] thiadiazole 28 was obtained by the reaction of 24 with carbon disulphide in ethanolic potassium hydroxide. Moreover, the novel S-substituted product 29 was prepared by stirring aminothione 24 with 4-methoxyphenylchloroacetamide in ethanol containing potassium hydroxide at room temperature overnight.

B. Biological activity evaluation

***In-vitro* cytotoxicity screening**[24-26]

Compounds 3b, 4b, 7, 9, 11, 12, 14, 16, 19, 20, 24a and 24b were evaluated for their in vitro cytotoxic activity against two cell lines, namely breast carcinoma cell line (MCF7) and colon carcinoma cell line (HCT116), using Doxorubcin as standard. The results of the cytotoxic activity evaluation of synthesized compounds against breast carcinoma (MCF7) and colon carcinoma (HCT116) cell lines listed in (Table No.1).

The result of cytotoxicity evaluation was summarized in (Table No.1) revealed that:

Compound 16 exhibited highest activity against not only colon carcinoma cell line (IC50=3.7 μg/ml) but also breast carcinoma cell line (IC50=10.8 ug/ml).

Moreover compound 24b Schiff's base showed high cytotoxic activity against the two cell lines, breast

carcinoma cell line (IC50=8.1 ug/ml) and colon carcinoma cell line (IC50=5.3 ug/ml).

Furthermore compounds 9, 20 are less active while compound 12 is the least active one against both cell lines.In addition compounds 4b,14 , 19 and 24a are inactive against the two cell lines.

Compound 4-methoxyphenyl-5-(4-tosylamino phenyl) 4H-1,2,4-triazole-3-thiol 3b showed hiegh activity against breast carcinoma cell line (IC50=14.9 ug/ml), moderate inhibitory activity against colon carcinoma cell line (IC50=34.2 ug/ml). Upon alkylation of compound 3b with 4-methoxy phenyl chloroacetamide lead to S substituted product compound 11 which exhibited increase activity against colon carcinoma cell line (IC50=17.6) but decrease activity against breast carcinoma cell line (IC50-20.3 ug/ml).

Replacement of the two methoxy groups in compound 11 by two halogens (chlorine and bromine) compound 16 lead to increase activity against both cell lines.

Furthermore replacement of 3,4,5-trimethoxybenzylidene (Schiff's base) 24a which completely inactive against both cell lines by 3-hydroxy-4-methoxy benzylidene in compound 24b increase activity against both cell lines, breast carcinoma cell line (IC50=8.1 ug/ml) and colon carcinoma cell line (IC50=5.3 ug/ml).

***In vitro* antimicrobial activity evaluation**

The *in vitro* antimicrobial activity of some newly synthesized compounds was carried out using cup plate diffusion method[27-30]. The antimicrobial activity was screened against Gram positive bacteria (Staphylococcus aureus, Staphylococcus epidermidis), Gram negative bacteria (Pseudomonas aeruginosa, Escherichia coli) and fungi (Candida albicans): Cefotaxime was used as positive control for bacteria and Nystatin for fungi. Dimethyl formamide (DMF) used as solvent. The result of antimicrobial activity of the test compounds are evaluated as shown in (Table No.2) revealed that compounds 2b, 2d, 2e, 3(a-e), 4a,b, 8, 10, 12, 16, 17, 20, 24, 26(b-d) have high activity but compounds 2a, 2c, 6, 13, 14, 19 and 26a have moderate activity against Gram positive (Staphylococcus aureus). Moreover compounds 2b, d, 3a, 3(c-e), 4b, 8, 10, 12, 16, 17, 20, 26b,c have high activity but compounds 2a,c,e, 3b, 4a, 9, 24, 26a, d have moderate activity against Gram positive (Staphylococcus epidermidis). Furthermore compounds 2 (b-e), 3a,d,e, 4a,b, 8, 10, 12, 17, 20, 24, 26 a-d have moderate activity against Gram negative bacteria (Pseudomonas aeruginosa, Escherichia coli). Compounds 2c, 3c have moderate activity against (Candida albicans) but low activity against Gram negative bacteria. In addition compounds 3b, 6 has low activity against Gram negative and fungi. Moreover, compound 7 exhibits high activity against Gram negative (Pseudomonas aeruginosa) low activity against (Escherichia coli) but moderate activity against fungi (Candida albicans). Compound 11 has low activity against Gram positive, Gram negative bacteria but moderate activity against Candida albicans. Finally compounds 13, 14, 19 have moderate activity against Gram positive (Staphylococcus aureus), low activity against (Staphylococcus epidermids) and Gram negative bacteria but high activity against Candida albicans.

- The method used was cup plate diffusion method.
- Each cup was filled with 100 micro liter from each tested sample.
- Conc. of each sample is 75 mg/ml.
- Conc. of antimicrobial agents (control) is 5 mg/ml.

Experimental

Melting points were determined with a Gallen Kamp melting point apparatus and are uncorrected IR spectra (KBr, cm^{-1}) were recorded in Bruker or Testscan Shimdzu FT8000 spectrometers. ^{1}NMR,^{13}CNMR spectra were recorded on varian Gemini 200, 200 MH_z, varian Mecrcury (300 MH_z) using DMSO-d6 as solvent and (TMS) as internal stander (Chemical shift δ, ppm). Electron impact mass spectra were determined using a GC/MS Mat 112S at 70ev spectrometer. Elemental analyzer, Heraeus and Automatic Elemental analyzer, Model 2400 perkin Elemer at Microanalytical center Al-Azhar University. Thin layer chromatography (TLC) was performed on Silica gel G for TLC (Merck) and

spots were visualized by iodine vapors or by irradiation with ulteraviolet (UV, 254 nm).

Microorganisms

A total of five standard microbial strains were used in this study. They were obtained from the Egyptian Pharmaceutical Industries Company (EPICO), Egypt which were *Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Escherichia coli* ATCC 10536, *Pseudomonas aeruginosa* ATCC 9027 and *Candida albicans* ATCC 10231.

Compound 1 was prepared according to reported procedures[30, 31].

2-[4-(Tosylamino)phenylcarbony]hydrazine-N-substituted carbothioamides 2 (a-e)

To the acid hydrazide 1 (0.610 gm, 0.002 mol) in dioxane (20 ml), substituted isothiocynate (0.002 mol) was added. The reaction mixture was stirred at room temperature overnight. The separated solid product was filtered and crystallized from ethanol Table No.3.

Compound 2a IR (KBr,cm^{-1}): 3303, 3185 (4NH), 3054 (CH, aromatic), 2970, 2916 (CH, aliphatic), 1671 (C=O), 1603 (C=N), 1532 (C=C), 1335 (SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.34 (s, 3H, CH_3) 7.18-7.22(d,2H,J=7.2 Hz , ArH),7.29-7.39(m,7H,ArH) 7.71-7.74(d,2H,J=7.4Hz,ArH)7.81-7.85 (d,2H, J=8.4Hz, ArH) 9.77(s, 2H, 2NH, exchangeable), 10.43 (s, 1H, NH, exchangeable), 10.66 (s, 1H, NH exchangeable).

Ms: m/z (%): 440 (14.88) M^+, 432 (10.98), 377 (18.79), 281 (13.01), 219 (17.74), 165 (13.58), 135 (70.38), 77 (100).

Compound 2b IR (KBr,cm^{-1}): 3315, 3213 (4NH), 3052 (CH, aromatic), 2954,(CH, aliphatic), 1673 (C=O), 1605 (C=N), 1546 (C=C), 1367 (SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.32 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 6.85-6.88 (d, 2H, J=9Hz, ArH), 7.15-7.18 (d, 2H, J=8.7Hz, ArH) 7.23-7.26 (d, 2H, J= 8.4Hz) 7.68-7.71 (d, 2H, J=8.1Hz, ArH) 7.71-7.74 (d, 2H, J=8.7Hz, ArH) 7.78-7.81 (d, 2H, J=8.7Hz, ArH) 9.50 (s, 1H, NH, exchangeable), 9.60 (s, 1H, NH, exchangeable), 10.31 (s, 1H, NH exchangeable), 10.62 (s, 1H, NH, exchangeable).

Ms: m/z (%): 471 (11.06) M^++1, 445 (10.37), 339 (15.93), 274 (30.24), 119 (27.64), 91 (100), 80 (15.93).

Compound 2c (IR, KBr) cm^{-1}: 3301, 3199 (4NH), 3050 (CH, aromatic), 2925, 2866 (CH, aliphatic), 1670 (C=O), 1598 (C=N), 1539 (C=C), 1338 (SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.32 (s, 3H, CH_3), 7.17-7.19 (d, 2H, J=8.7Hz, ArH), 7.22-7.69(m, 6H, ArH) 7.71-7.74 (d, 2H, J=7.8Hz, ArH), 7.78-7.81 (d, 2H, J=8.4Hz, ArH) 9.74 (s, 2H, 2NH, exchangeable), 10.37 (s, 1H, NH, exchangeable), 10.61 (s, 1H, NH exchangeable).

Ms: m/z (%): 520 (21.60)M^++1, 519 (28.40) M^+, 516 (40.80), 494 (28.40), 484 (28), 387 (36.80), 327 (41.20), 274 (45.20), 155 (40.80), 91 (100), 65 (63.60).

Compound 2d IR (KB, cm^{-1}): 3379, 3118, 3184 (4NH), 3058 (CH, aromatic), 2930, 2864 (CH, aliphatic), 1666 (C=O), 1603 (C=N), 1543 (C=C), 1333 (SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.31(s, 3H, CH_3), 4.69 (s, 2H, CH_2), 7.11-7.69 (m, 9H, ArH),7.69-7.70 (d, 2H, J=2.4Hz, ArH), 7.76-7.78 (d, 2H, J=8.4Hz, ArH)8.57(s,1H,NH,exchangeable),9.37(s,1H,NH,exchangeable),10.24(s,1H,NH,exchangeable),10.61(s,1H,NH exchangeable).

Ms: m/z (%): 455(62.71)M^++1, 454 (29.32) M^+, 452 (66.10), 421 (93.22), 389 (73.73), 332 (71.19), 266 (88.98), 249 (91.53), 233 (76.27), 185 (84.75), 141 (100), 128 (61.86), 80 (74.58), 66 (69.49).

Compound 2e IR (KBr,cm^{-1}): 3334, 3171 (4NH), 3050 (CH, aromatic), 2985, 2927 (CH, aliphatic), 1665 (C=O), 1605 (C=N), 1550 (C=C), 1333 (SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.32 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 4.98-4.99 (d, 2H,=CH_2), 5.74-5.79 (m,1H,=CH),7.14-7.17 (d, 2H, J=8.1Hz, ArH), 7.33-7.36 (d, 2H, J=7.8Hz, ArH) 7.65-7.68 (d, 2H, J=8.7Hz, ArH),7.75-7.78(d,2H,J=8.1Hz,ArH) 8.23 (s,1H,NH,exchangeable) 9.31 (s, 1H, NH, exchangeable), 10.23 (s, 1H, NH exchangeable), 10.61 (s, 1H, NH, exchangebale).^{13}C-NMR (DMSO-d6) δppm: 21.15, 113.70, 117.73, 118.10, 126.47, 126.93, 127.36, 128.82, 129.41, 129.88, 136.32, 141.04, 143.58, 165.15.

Ms: m/z(%) : 406(7.02) M^++2, 405(8.91)M^++1, 404 (7.02)M^+, 274 (31.17),155(10.26), 119 (29.42), 99 (34.28), 91 (100), 65 (44.40).

4-Substituted-5-(4-tosylamino) phenyl-4H-1, 2,4-triazole-3-thiols 3(a-e)

General procedure

Solid thiosemicarbazides 2(a-e) (0.002 mol) were added portion wise to (20 ml) 2M NaOH solution. The reaction mixture was refluxed for 10 hrs and completion of the reaction checked by using TLC. After completion of the reaction, the mixture was allowed to cool and then filtered. The filtrate was acidified with acetic acid. The precipitated solid was filtered, washed with water, dried and crystalized from ethanol/H_2O (Table No.4).

Compound 3a IR (KBr, cm^{-1}): 3368 (NH), 3236 (NH), 3050 (CH, aromatic), 2984, 2935 (CH, aliphatic), 1598, 1503 (C=N), 1461 (C=C), 1328 (SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.32 (s, 3H, CH_3), 6.94-7.63 (m, 13H, ArH), 10.55 (s, 1H, NH, exchangeable), 13.96 (s, 1H, NH, exchangeable).

Ms: m/z (%): 422 (45.7) M^+, 267 (74.3), 194 (14.3), 132 (25.7), 91 (100).

Compound 3b IR (KBr, cm^{-1}): 3397 , 3236 (NH), 3052 (CH, aromatic), 2960 (CH, aliphatic), 1616,(C=N), 1510 (C=C), 1331 (SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.33 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.90-7.80 (m, 12H, ArH), 10.56(s, 1H, NH, exchangeable), 13.96 (s, 1H, NH, exchangeable).

Ms: m/z (%): 453 (4) M^++1,452(3)M^+, 402 (20.7), 365 (43.9), 213 (100), 186 (91.9), 153 (87.4), 115 (41.9), 77 (30.8).

Compound 3c IR (KBr, cm^{-1}): 3395 (NH), 3237 (NH), 3085 (CH, aromatic), 2923 (CH, aliphatic), 1613 (C=N), 1509 (C=C), 1330 (SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.34 (s, 3H, CH_3), 7.02-7.80 (m, 12H, ArH), 10.54(s, 1H, NH, exchangeable), 14.06 (s, 1H, NH, exchangeable).

Ms: m/z (%):504(3.4)M^++2, 503(9.1)M^++1,502(30.8)M^+, 501 (29.6) M^+, 347 (45.9), 132 (36.8), 91 (100).

Compound 3d IR (KBr,cm^{-1}):3372(NH),3129 (NH) 3050 (CH, aromatic), 2954, 2926 (CH, aliphatic),1610 (C=N), 1516 (C=C),1338 (SO_2).

^{1}HNMR (DMDO-d6) δppm: 2.33 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 6.90-7.67 (m, 13H, ArH), 10.54 (s, 1H, NH, exchangeable), 14.06 (s, 1H, NH, exchangeable).

Ms:m/z(%) : 437(4.19)M^++1, 436 (10.40) M^+, 281 (3.14), 219 (2.29), 179 (3.57), 118(4.53), 104 (4.25), 91 (100), 77 (2.97).

Compound 3e IR (KBr, cm^{-1}): 3227(NH),3100 (NH), 3063 (CH, aromatic), 2923 (CH, aliphatic), 1605 (C=N), 1556 (C=C), 1336 (SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.37(s, 3H, CH_3), 4.70 (s, 2H, CH_2), 5.16-5.19 (d, 2H ,=CH_2), 5.89-5.99 (m, 1H, CH), 6.98-7.73 (m, 8H, ArH), 10.52 (s, 1H, NH, exchangeable), 13.92 (s, 1H, NH, exchangeable).

Ms: m/z (%): 387(13.85) M^++1, 386 (19.11) M^+, 91 (100), 65 (41.83).

4-Amino-3-substitutedamino-5-(4-tosylamino)phenyl)-4H-1,2,4-triazoles 4-(a-d)

A mixture of thiosemicarbazides 3(a-d) (0.002 mol) and hydrazine hydrate (0.025 mol) in methanol (20 ml) was refluxed for 10 hrs in water bath. The completion of the reaction was monitored by TLC using silica gel G coated plates by using ethyl acetate: petroleum ether 1:1 as eluent and observed in UV light. The reaction mixture was cooled and poured over crushed ice. Solid was filtered and crystallized from methanol (Table No.5).

Compound 4a: IR (KBr, cm^{-1}): 3353(2NH), 3173, 3100 (NH_2), 3037 (CH, aromatic), 2925, 2856 (CH, aliphatic), 1604(C=N), 1568 (C=C), 1338 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.33 (s, 3H, CH_3), 5.87 (s, 2H, NH_2 exchangeable), 7.18-7.20 (d, 2H, J=8.4Hz, ArH), 7.25-7.27 (d, 2H, J=7.8Hz, ArH), 7.30-7.38 (m, 3H, ArH), 7.70-7.72 (d, 2H, J=8.4H, ArH), 7.74-7.77 (d, 2H, J=8.4Hz, ArH), 7.86-7.88 (d, 2H, J=8.4Hz, ArH), 8.56 (s, 1H, NH, exchangeable), 10.60 (s, 1H, NH, exchangeable).

M.S: m/z (%) 421 (18.8)M^++1, 419 (12.88), 405 (20.45), 104 (28.22), 91 (100), 77 (66.67).

Compound 4b: IR (KBr, cm^{-1}): 3358(NH), 3235, 3105 (NH_2), 3050 (CH, aromatic), 2928 (CH, aliphatic), 1612(C=N), 1547 (C=C), 1334 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.40 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 5.88 (s, 2H, exchangeable), 6.94-7.95 (m, 12H, ArH), 8.39 (s, 1H, NH, exchangeable), 9.90 (s, 1H, NH, exchangeable). ^{13}CNMR (DMSO-d6) δppm: 21.14, 55.24, 114.15, 114.60, 118.22, 118.66, 120.81, 126.44, 126.96, 128.51, 129.87, 136.36, 139.59, 143.56, 150.17, 159.46.

M.S: m/z (%) 452(67.24) M^++2, 451 (69.83)M^++1, 422 (67.24), 411 (72.41), 338 (77.59), 313 (75), 222 (70.69), 201 (79.31), 156 (77.59), 110 (67.24), 91 (51.72), 80 (100).

Compound 4c: IR(KBr,cm^{-1}): 3351, 3238 (2 NH,NH_2), 3050 (CH, aromatic), 2922 (CH, aliphatic), 1605(C=N) , 1563 (C=C),1332 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.33 (s, 3H, CH_3), 5.84 (s, 2H, NH_2, exchangeable), 6.86-7.84 (m, 12H, ArH), 8.74 (s, 1H, NH, exchangeable), 10.40 (s, 1H, NH, exchangeable).

M.S:m/z(%): 500(1.55)M^++2, 498(1.19)M^+, 422(2.19), 420(17.22), 299(2.06), 297(22.84) ,91(100) ,77(22.24).

Compound 4d: IR (KBr, cm^{-1}): 3352 (2 NH), 3270, 3138 (NH_2), 3050 (CH, aromatic), 2936 (CH, aliphatic), 1607 (C=N), 1515 (C=C), 1337 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.30 (s, 3H, CH_3), 5.26 (s, 4H, CH_2, NH_2), 6.92-7.63(m, 13H, ArH), 8.64 (s, 1H, NH, exchangeable), 10.45 (s, 1H, NH, exchangeable).

M.S: m/z (%):436(13.58)M^++2 ,91(100),77(3.17).

4-(5-Ethylthio-4-phenyl-4H-1,2,4-triazol-3-yl)-N-tosylbenzamine(5)

2-[4-Substitued-5-(4-tosylamino)phenyl-4H-1,2,4-triazol-3-ylthio]N-substituted acetamides (6-20)

A mixture of 1,2,4-triazole -3-thiol 3a-e (0.1mol) and appropriate alkyl halid or chloroacetamide derivatives (0.1 mol) in ethanol (30 ml) containing KOH (0.12 mol) was stirred at room temperature overnight. The reaction mixture was poured into ice / water. The separated solid was filtered and crystallized from ethanol (Table No.6).

Compound 5: IR (KBr, cm^{-1}): 3222 (NH), 3051 (CH, aromatic), 2966, 2928 (CH, aliphatic), 1602 (C=N), 1534 (C=C), 1341 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 1.25-1.28 (t, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.06-3.15 (q, 2H, CH_2), 6.82-7.60 (m, 13H, ArH), 10.54 (s, 1H, NH).

Compound 6: IR (KBr, cm^{-1}): 3233(NH) , 3123 (NH), 3057 (CH, aromatic), 2926 (CH, aliphatic), 1673 (C=O), 1609 (C=N), 1543 (C=C), 1333 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.13 (s, 2H, CH_2-), 6.98-7.00 (d, 2H, J=8.4Hz, ArH) 7.09-7.12 (d, 2H, J=8.1Hz, ArH), 7.16-7.19 (d , 2H, J=8.4Hz, ArH), 7.30-7.33 (d, 2H, J=8.7Hz, ArH),7.36-7.55 (m, 7H, ArH), 7.61-7.64 (d, 2H, J=8.1Hz, ArH), 10.22 (s, 1H, NH, exchangeable), 10.50 (s, 1H, NH, exchangeable).

Compound 7: IR (KBr, cm^{-1}): 3230(NH) , 3138 (NH), 3063 (CH, aromatic), 2959, 2929 (CH, aliphatic), 1671 (C=O), 1611 (C=N), 1552 (C=C), 1335 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.32 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2), 6.86-7.64 (m, 17H, ArH), 10.17 (s, 1H, NH, exchangeable), 10.55 (s, 1H, NH, exchangeable).

^{13}CNMR (DMSO-d6) δppm: 21.14, 63.13, 113.67, 118.87, 120.59, 121.48, 127.61, 128.62, 129.86, 131.86, 133.62, 136.43, 139.25, 151.26, 153.84, 155.33, 164.87.

Compound 8: IR (KBr,cm^{-1}): 3255 (NH), 3185 (NH), 3055 (CH, aromatic), 2931 (CH, aliphatic), 1675 (C=O), 1605 (C=N), 1542 (C=C), 1334 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.31 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 6.90-6.92 (d, 2H, J=8.4Hz, ArH), 7.09-7.12 (d, 2H, J=8.4Hz, ArH), 7.26-7.29 (d, 2H, J=8.4Hz, ArH), 7.33-7.62 (m, 11H, ArH),9.80 (s, 1H, NH, exchangeable),10.46 (s, 1H, NH, exchangeable).

MS: m/z (%): 591 (66.6)M^++2, 590 (80.70) M^++1 589 (50) M^+, 543 (76.32), 520 (78.07), 482 (78.07), 436 (78.07), 361 (85.96), 339 (71.93), 275 (78.95), 252 (75.44), 187 (76.32), 166 (100), 127 (83.33), 103 (75.44), 94 (78.95), 66 (83.33).

Compound 9: IR (KBr, cm^{-1}): 3316(NH), 3187 (NH), 3056 (CH, aromatic), 2927 (CH, aliphatic), 1676 (C=O), 1605 (C=N), 1488 (C=C), 1333 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.31 (s, 3H, CH_3), 4.13 (s, 2H, CH_2), 6.96-7.62(m, 17H, ArH), 10.44 (s, 2H,2 NH, exchangeable). MS: m/z (%):

635 (1.06) M^+, 463 (28.31), 267 (20.99), 91 (100), 77(28.52).

Compound 10: IR (KBr, cm^{-1}): 3245 (NH), 3118 (NH),
3036 (CH, aromatic), 2958, 2923 (CH, aliphatic), 1674 (C=O), 1606 (C=N), 1538 (C=C), 1331 (SO_2).
^{1}H NMR (DMSO-d6) δ ppm: 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.80 (s, 3H, O-CH_3), 4.13 (s, 2H, CH_2), 7.00-7.65 (m, 16H, ArH), 10.26 (s, 1H, NH, exchangeable), 10.60 (s, 1H, NH, exchangeable).

Compound 11: IR (KBr, cm^{-1}): 3200 (NH), 3100 (NH), 3050 (CH, aromatic), 2932, 2841 (CH, aliphatic), 1671 (C=O), 1607 (C=N), 1555 (C=C), 1333 (SO_2).
^{1}H NMR (DMSO-d6) δ ppm: 2.34 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.69-7.62 (m, 16H, ArH), 10.24 (s,2H,2NH, exchangeable).
^{13}CNMR(DMSO-d6) δ ppm: 18.75, 55.25, 70.86, 113.36, 113.66, 114.05, 115.14, 119.45, 120.60, 126.00, 126.73, 128.20, 128.81, 131.91, 138.82, 144.07, 150.38, 155.37, 159.75, 165.10.

Compound 12: IR (KBr, cm^{-1}): 3262 (NH), 3186 (NH), 3061 (CH, aromatic), 2931 (CH, aliphatic), 1675 (C=O), 1606 (C=N), 1541 (C=C), 1334 (SO_2).
^{1}H NMR (DMSO-d6) δppm: 2.40 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.21 (s, 2H, CH_2), 7.08-7.73 (m, 16H, ArH), 10.53 (s, 2H, 2NH, exchangeable).
MS: m/z (%): 621 (45.03)M^++2, 620 (49.01) M^++1, 619 (36.42) M^+, 586 (69.54), 313 (68.21), 197 (62.25), 154 (66.23), 91 (60.93), 64 (100).

Compound 13: IR (KBr, cm^{-1}): 3250(NH), 3150 (NH), 3050 (CH, aromatic), 2925 (CH, aliphatic), 1674 (C=O), 1606 (C=N), 1536 (C=C), 1331 (SO_2).
^{1}H NMR (DMSO-d6) δppm: 2.25 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.03 (s, 2H, CH_2), 6.62-7.70 (m, 16H, ArH), 10.14 (s, 2H, 2NH, exchangeable).
MS: m/z (%): 649 (0.77) M^+, 271 (10.59), 107 (97.64),91 (100), 77(44.51).

Compound 14: IR (KBr, cm^{-1}): 3240 (NH), 3136 (NH), 3063 (CH, aromatic), 2933 (CH, aliphatic), 1670 (C=O), 1612 (C=N), 1556 (C=C), 1336 (SO_2).
^{1}H NMR (DMSO-d6) δppm: 2.33 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 6.86-7.72 (m, 16H, ArH), 10.15 (s, 1H, NH, exchangeable), 10.48 (s, 1H, NH, exchangeable).
^{13}CNMR(DMSO-d6) δ ppm: 21.14, 55.24, 69.80, 113.67, 114.055, 118.59, 119.04, 120.62, 121.28, 123.22, 126.44, 126.80, 128.86, 129.20, 129.63, 129.84, 131.82, 132.93, 136,41, 139.37, 143.47, 164.82.
MS: m/z (%): 667 (54.05)M^++2, 666 (59.46) M^++1, 665 (100) M^+, 649 (75.68), 607 (71.17), 563 (78.38), 397 (71.17), 257 (77.48), 113 (77.48), 91 (75.68), 77 (100).

Compound 15: IR (KBr, cm^{-1}): 3347(NH), 3136 (NH), 3054 (CH, aromatic), 2924 (CH, aliphatic), 1671 (C=O), 1599 (C=N), 1535 (C=C), 1330 (SO_2).
^{1}HNMR (DMSO-d6) δppm: 2.19 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 4.16 (s, 2H, CH_2), 7.07-7.35 (m,10H, ArH), 7.41-7.44 (d, 2H, J=7.8Hz, ArH), 7.63-7.65 (d, 2H, J=7.8Hz, ArH), 7.71-7.73 (d, 2H, J=8.4Hz, ArH), 9.67 (s, 1H, NH, exchangeable), 10.48 (s, 1H, NH, exchangeable).

Compound 16: IR (KBr, cm^{-1}): 3264(NH) ,3188 (NH), 3062 (CH, aromatic), 2931 (CH, aliphatic), 1677 (C=O), 1606 (C=N), 1541 (C=C), 1333 (SO_2).
^{1}H NMR (DMSO-d6) δppm: 2.41 (s, 3H, CH_3), 4.22 (s, 2H, CH_2), 7.10- 7.13 (d, 2H, J=8.4Hz, ArH), 7.26-7.29 (d, 2H, J=8.7Hz, ArH), 7.39-7.42 (d, 2H, J=8.7Hz, ArH), 7.45-.7.68 (m, 6H, ArH), 7.70-7.72 (d, 2H, J=8.1Hz, ArH), 7.77-7.80 (d, 2H, J=8.4Hz, ArH).
10.52 (s, 1H, NH, exchangeable), 10.56 (s, 1H, NH, exchangeable).
MS: m/z (%): 671 (45.24)M^++2), 670 (57.94) M^++1, 669 (74.60) M^+, 545 (73.02), 471 (74.60), 316 (74.60), 291 (76.98), 290 (75.40), 284 (75.40), 232 (89.68), 189 (73.02), 91 (65.08), 80 (100), 64 (94.44).

Compound 17: IR (KBr, cm^{-1}): 3313(NH),3237 (NH), 3058 (CH, aromatic),2925 (CH, aliphatic), 1678 (C=O), 1605 (C=N), 1537 (C=C), 1331 (SO_2).
MS:m/z(%):715(0.48)M^++2, 713(0.94)M^+, 502 (32.28), 500 (28.54), 346 (38.77), 344(36.64), 171(33.69), 99(100),77 (16.01).

Compound 18: IR (KBr, cm^{-1}): 3393(NH), 3253 (NH), 3046 (CH, aromatic), 2925 (CH, aliphatic), 1670 (C=O), 1609 (C=N), 1461 (C=C), 1334 (SO_2).
^{1}H NMR (DMSO-d6) δppm: 2.14 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 5.22(s, 2H, CH_2),

6.90-7.67 (m, 17H, ArH), 9.65 (s, 1H, NH, exchangeable), 10.50 (s, 1H, NH, exchangeable).

Compound 19: IR (KBr,cm^{-1}): 3397 (2 NH), 3050 (CH, aromatic), 2929 (CH, aliphatic), 1673 (C=O), 1609 (C=N), 1559 (C=C), 1346 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.24 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.03 (s, 2H, CH_2), 5.19 (s, 2H, CH_2), 6.71-7.55(m, 17H, ArH), 10.14 (s, 2H, 2NH, exchangeable).^{13}CNMR(DMSO-d6) δppm: 21.14, 55.24, 69.80, 113.07, 113.66, 114.04, 119.83, 120.63, 125.77, 125.95, 126.19, 127.78, 128.17, 128.58, 131.84, 135.91, 138.60, 152.93, 155.35, 156.40, 165.12.

Compound 20: IR (KBr, cm^{-1}): 3253(NH), 3195 (NH), 3056 (CH, aromatic),2928, 2840 (CH, aliphatic), 1668 (C=O), 1609 (C=N), 1544 (C=C),1334 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.31(s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.08 (s, 2H, CH_2), 4.57-4.58 (d, 2H, CH_2), 5.20-5.22 (d, 2H,=CH_2), 5.80-6.00 (m, 1H, =CH), 6.84-7.96 (m, 12H, ArH), 10.141 (s, 2H, 2NH, exchangeable).

^{13}CNMR (DMSO-d6) δppm: 21.15, 55.24, 69.80, 113.67, 114.07, 118.91, 119.26, 120.61, 121.72, 126.42, 126.88, 129.08, 129.67, 131.83, 136.58,139.74, 143.41, 150.39, 154.63, 155.35, 165.036.

4-(3,4,5-Trimethoxybenzylidene amino) -3-substituted amino-5-[4-(tosyl amino) phenyl-4H-1,2,4-triazoles (21,22).

To a solution of triazoles 4(a,b) (0.01 mol) in absolute ethanol(20 ml) containing 3 drops of acetic acid,3,4,5-trimethoxybenzaldehyde (0.012 mol) was added .The reaction mixture was heated under reflux for 8 hrs. The formed solid after cooling was filtered off and crystalized from ethanol to give compounds 21,22 respectively.

Compound 21: mp 248-250C^o, yield 68%, IR(KBr,cm^{-1}):

3235 (2NH), 3077 (CH, aromatic), 2926, 2845 (CH, aliphatic), 1607 (C=N),1509 (C=C), 1333 (SO_2). ^{1}HNMR (DMSO-d6) δppm: 2.31 (s, 3H, CH_3),3.84 (s, 3H, OCH_3), 3.86 (s, 6H, $2OCH_3$), 6.86-7.89 (m,15H, ArH), 8.65 (s, 1H, HC=N), 10.47 (s,1H, NH, exchangeable), 14.02 (s,1H, NH, exchangeable). Microanlysis for C_{31} H_{30} N_6O_5S(598): Calcd %C, 62.19; H,5.05; N,14.04 Found % C, 62.38; H, 5.11; N,14.21.

Compound 22: mp 258-260C^o, yield % 65, IR (KBr, cm^{-1}): 3271 (NH), 3173(NH),3018 (CH, aromatic), 2952 (CH, aliphatic), 1586 (C=N), 1501 (C=C), 1330 (SO_2).

^{1}HNMR(DMSO-d6)δppm:2.33(s,3H,CH_3),3.71(s,3H,OCH_3),3.86 (s,6H, $2OCH_3$), 3.87 (s, 3H, OCH_3), 6.90-7.93 (m, 14H, ArH), 9.88 (s, 1H, HC=N), 10.55 (s, 1H, NH, exchangeable),13.97 (s, 1H, NH, exchangeable).

Microanalysis for $C_{32}H_{32}N_6O_6S$ (628) Calcd%C, 61.13; H, 5.13; N, 13.37.

Found %C, 61.32; H, 5.21; N, 13.45.

Potassium 2-[4-(tosylamino)phenyl carbonyl hydrazine carbodithionate(23)

Carbon disulphide (0.15 mol) was added dropwise to an ice cooled solution of potassium hydroxide (0.15 mol) in absolute ethanol (20 ml) containing the acid hydrazide (1) (0.1 mol). The reaction mixture was stirred at room temperature overnight.Dry ether 200ml was added, the separated solid washed with ether (20 ml). The product used in the next step without further purification. Yield nearly quantitative.

4-Amino-3-(4-(tosylamino) phenyl) 4H-1,2,4-triazole-5-(1H) thione (24)

A Suspension of potassium dithiocarbazate (23) (0.01 mol), hydrazine hydrate (0.02 mol) in ethanol (20 ml) was heated under reflux for 8 hrs.The colour of the reaction mixture changed to deep green colour with evolution of hydrogen sulfide gas then cooled to room temperature. Cold distilled water was added, neutralized with dil HCl .The precipitate solid was filtered washed with water and crystallized from ethanol mp286-288C^o, yield 68%. Microanalysis for $C_{15}H_{15}N_5O_2S_2$ (361) Calcd% C, 49.84; H, 4.18; N, 19.38. Found % C, 49.92; H, 4.22; N, 19.51.

IR (KBr, cm^{-1}): 3239 (NH_2), 3136 (2NH), 3038 (CH, aromatic), 2969 (CH, aliphatic), 1612(C=N), 1509 (C=C), 1335 (SO_2).

^{1}HNMR(DMSO-d6)δppm:2.34(s,3H,CH_3),5.60(s,2H,NH_2,exchangea

ble) 7.21-7.24(d,2H,J=8.7Hz,ArH),7.36-7.38(d,2H, J=7.8Hz,.ArH),7.71-7.74(d,2H, J=8.1Hz,ArH),7.87-7.90(d,2H,J=9Hz,ArH),10.70 (s, 1H, NH, exchangeable), 13.90 (s, 1H, NH, exchangeable).
Ms: m/z (%) 361 (11) M^+, 154 (39), 91 (100), 77 (17).

5-[4-(Tosylamino) phenyl] -3-(4-bromophenacylthio)-4-amino-4H-1,2,4-triazole (25)

A mixture of triazole 24 (0.5 gm., 0.001 mol), 4-bromophenacyl bromide(0.38 gm., 0.001 mol) and anhydrous sodium acetate(0.001 mol) in absolute ethanol (20 ml) was heated under reflux for 6 hrs then cooled, poured into ice-cold water. The solid product was precipitated, then Filter, washed with water, crystallized from ethanol to afford componnd 25 mp178-180 C^o Yield (0.5gm,65%).
IR(KBr,cm^{-1}): 3262, 3207 (NH, NH_2), 3091 (CH, aromatic), 2916, 2857 (CH, aliphatic), 1641 (C=O), 1590 (C=N), 1461 (C=C), 1331(SO_2).
^{1}HNMR (DMSO-d6) δppm: 2.32 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 5.26 (s, 2H, NH_2, exchangeable),7.20-7.23 (d, 2H, J=7.8Hz, ArH), 7.32-7.34 (d, 2H, J=7.5Hz, ArH), 7.69-7.85 (m, 6H, ArH), 7.91-7.94 (d, 2H, J=7.8Hz, ArH),10.20 (s, 1H, NH, exchangeable). Microanalysis for $C_{23}H_{20}BrN_5O_3S_2$(557) Calcd: %C,49.46; H ,3.61 ; N ,12.54.
Found: %C, 49.64; H, 3.68;N,12.68.

4-[6-(4-Substituted phenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl]N-tosylbenzamine.26a,b

A mixture of triazole 24 (0.5 gm., 0.001 mol) , 4-Substituted phenacyl bromide(0.001 mol) and anhydrous sodium acetate(0.001 mol) in absolute ethanol (20 ml) was heated under reflux for 25 hrs then cooled. And poured into ice-cold water. The solid product was precipitated, then Filter,washed with water,crystallized from CH_2Cl_2/hexane to afford compounds 26a,b.

Compound26a: mp 206-208 ^oC, yield 70%, IR (KBr, cm^{-1}): 3293(NH), 3050 (CH,aromatic),2922,2852(CH, aliphatic), 1611(C=N),1588(C=C),1333 (SO_2).
^{1}HNMR (DMSO-d6)δppm: 2.30 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 7.01-7.04 (d, 2H, J= 7.5Hz, ArH) 7.23-7.26 (d, 2H, J=8.1Hz, ArH), 7.64-7.67 (d, 2H, J=8.7Hz, ArH), 7.71-7.74 (d, 2H, J=7.5Hz, ArH), 7.77-7.80 (d, 2H, J=8.7Hz, ArH) 7.84-7.87 (d, 2H, J=8.4Hz, ArH) 10.22 (s, 1H, NH, exchangeable).
Ms:m/z (%) 496(1.26) M^++1,495(1.69) M^+,91(100).
Microanalysis for $C_{23}H_{18}ClN_5O_2S_2$ (495) Calcd %C, 55.69; H, 3.66; N,14.12. Found % C,55.86; H,3.69 ; N,14.37.

Compound 26b: mp,210-212C^o yield 68%, IR (KBr, cm^{-1}): 3281(NH),3060(CH,aromatic),2980,2929(CH,aliphatic),1582(C=N),1464(C=C),1333(SO_2).
^{1}HNMR (DMSO-d6) δppm: 2.28 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 6.91-6.94 (d, 2H, J=8.1Hz, ArH), 7.16-7.18 (d, 2H, J=6.9Hz, ArH), 7.58-7.61 (d, 2H, J=8.7Hz, ArH), 7.64-7.94 (m, 4H, ArH), 7.98-8.00 (d, 2H, J=7.8Hz, ArH), 10.23 (s, 1H, NH, exchangeable). Microanalysis for $C_{23}H_{18}BrN_5O_2S_2$ (539). Calcd %C, 51.11; H ,3.36; N,12.96. Found %C,51.38 ; H,3.34 ;N,13.08.

4-(Substituted benzylidenamino) 5-[4-(tosyl-amino) phenyl] -4H-1,2,4-triazole-3-thiols 27 (a-e).

A mixture of triazole 24 (0.001 mole,0.361gm) and the corresponding aldehydes (0.001 mole) in ethanol (20 ml) containing acetic acid (1.5 ml) and refluxed for 8 hrs. The reaction mixture was cooled, filtered and purified by crystallization from ethanol/H_2O Table No.7.

Compound 27a: IR (KBr,cm^{-1}): 3250 (2NH), 3072 (CH, aromatic), 2941, 2840 (CH, aliphatic), 1607 (C=N), 1580 (C=C), 1328 (SO_2).
^{1}H NMR (DMSO-d6) δppm: 2.31 (s, 3H, CH_3), 3.76(s, 3H, OCH_3), 3.86 (s, 6H, $2OCH_3$), 7.18-7.21 (d,2H,J=6.9Hz, ArH),7.23-7.35(m,4H,ArH),7.68-7.70(d,2H,J=8.4Hz,ArH),7.74-7.77(d,2H,J=9Hz,ArH), 9.58 (s, 1H,N=CH), 10.63 (s, 1H, NH, exchangeable), 14.09 (s, 1H, NH, exchangeable).
MS: m/z (%): 539 (0.49)M^+, 346 (33.70), 205 (17.05), 193 (100), 191 (56.35), 178 (64.21), 150 (26.20), 135 (36.43), 120 (29.08), 91 (49.93), 77 (11.29).

^{13}CNMR(DMSO-d6) δppm: 21.14, 55.84, 56.15, 60.04, 105.82, 106.16, 118.43, 118.74, 120.36, 126.44, 126.66, 127.26, 129.86, 136.43, 139.99, 141.37, 143.53, 148.01, 153.26.

Compound 27b: IR (KBr, cm^{-1}): 3194 (NH, OH), 3051 (CH, aromatic), 2938 (CH, aliphatic), 1606 (C=N), 1510 (C=C), 1334 (SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.30 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.20-7.90 (m, 11H, ArH), 9.68 (s, 1H,N=CH), 10.60 (s, 1H, NH, exchangeable), 13.80 (s, 1H, OH, exchangeable), 14.20 (s, 1H, NH, exchangeable).

Compound27c: IR(KBr,cm^{-1}): 3316(NH), 3252(NH), 3018(CH,aromatic), 2957(CH,aliphatic), 1605(C=N), 1509 (C=C),1330(SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.326 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.99-7.91 (m, 12H, ArH), 9.48 (s, 1H,N=CH), 10.56 (s, 1H, NH, exchangeable), 14.01 (s, 1H, NH, exchangeable).

Compound27d:IR(KBr,cm^{-1}): 3271(NH), 3176(NH), 3019(CH,aromatic), 2952 (CH,aliphatic), 1588(C=N),1502(C=C),1331(SO_2).

^{1}H NMR (DMSO-d6) δppm: 2.33 (s, 3H, CH_3), 7.19-7.90(m, 12H, ArH), 8.69 (s, 1H,N=CH), 11.68 (s, 1H, NH, exchangeable), 13.90 (s, 1H, NH, exchangeable).

Ms: m/z(%): 485 (13.34)M^++2, 483 (13.84)M^+, 117 (25.21), 91 (100), 77 (9.06), 65 (48.93).

Compound 27e: IR (KBr) cm^{-1}: 3325(NH), 3277 (NH), 3050 (CH, aromatic), 2938 (CH, aliphatic), 1606 (C=N), 1495 (C=C), 1589, 1338 (NO_2).

^{1}H NMR (DMSO-d6) δppm: 2.32 (s, 3H, CH_3), 7.23-8.37 (m, 12H, ArH), 9.84(s,1H, N=CH), 10.66 (s, 1H, NH, exchangeable),14.22 (s, 1H, NH, exchgangeable).

3-(4-Tosylamino)phenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole 6(5H) -thione (28)

Compound 24 (0.5 gm, 0.001 mol) was dissolved in a solution of potassium hydroxide (0.015 mol) in absolute ethanol (20 ml). Carbon disulfide (5 ml) was then added and the reaction mixture was heated under reflux for 10hrs. The reaction mixture was concentrated under reduced pressure and the residue was poured into an ice-water mixture with stirring. The solid product obtained was filtered, washed with water and recrystalized from ethanol to yield compound 28 (0.4 gm,72%), mp 265-267C^o.

IR(KBr, cm^{-1}): 3316(NH), 3193 (NH), 3051 (CH, aromatic), 2959 (CH, aliphatic), 1612 (C=N), 1514 (C=C),1337 (SO_2).

^{1}HNMR (DMSO, d6) δppm: 2.33 (s, 3H, CH_3), 7.21-7.24 (d, 2H, J=8.7Hz, ArH), 7.35-7.38 (d, 2H, J=7.5, ArH), 7.70-7.73 (d, 2H, J=8.7, ArH), 7.88-7.90 (d, 2H, J=7.5Hz, ArH), 10.61 (s, 1H, NH, exchangeable), 13.81 (s, 1H, NH, exchangeable). Microanalysis for$C_{16}H_{13}N_5O_2S_2$(403) Calcd% C,47.63; H,3,35;N,17.36, Found %C,47.80; H,3.23 ; N,17.51.

2-[4-Amino-5-(4-tosylamino) phenyl-1,2,4-triazol-3-ylthio] N-(4-methoxyphenyl) acetamide (29)

To a solution of triazol 24(0.5gm,0.001mol) in ethanol (20ml) containing KOH (0.012mol), 4-methoxychloroacetamide (0.28gm, 0.001mol) was added.

The reaction mixture was stirred at room temperature overnight,then poured into ice-water mixture with stirring. The solid product obtained was filtered washed with water and crystalized from ethanol to yield compound 29 (0.5 gm,71%), mp 198-200 ^{o}C.

IR(KBr,cm^{-1}): 3285, 3181 (NH, NH_2), 3042 (CH, aromatic), 2927 (CH, aliphatic), 1658 (C=O), 1609 (C=N),1538 (C=C),1333(SO_2).

^{1}HNMR (DMSO-d6) δppm: 2.33 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.08 (s, 2H, CH_2), 6.10 (s, 2H, NH_2, exchangeable), 6.86-6.89 (d, 2H, J=8.4Hz, ArH), 7.19-7.21 (d, 2H, J=8.1Hz, ArH), 7.35-7.37 (d, 2H, J=8.1Hz, ArH), 7.45-7.48 (d, 2H, J=8.4Hz, ArH), 7.70-7.72 (d, 2H, J=7.8Hz, ArH), 7.83-7.86 (d, 2H, J=8.1Hz, ArH), 10.17 (s, 1H, NH, exchangeable),10.45 (s, 1H, NH, exchangeable).

Microanalysis for $C_{24}H_{24}N_6O_4S_2$(524) :Calcd%C,54,95; H,4.61; N,16.02.

Found %C, 55.11; H, 4.66; N, 16.17.

Biological studies

1- Cytotoxic activity evaluation[24-26]

Some of the newly synthesized compounds 3b, 4b, 7, 9, 11, 12, 14, 16, 19, 20, 24a ,b were evaluated for their *in vitro* cytotoxic activity against two cell

lines, namely breast carcinoma (MCF7) And colon carcinoma (HCT116) cell lines . Doxrubcin used as a stander, and the data was represented in (Table No.1).

Cell line

The cell lines were obtained from the American Type Culture Collection (ATCC, Rockville, MD). The cells were grown on RPMI-1640 medium supplemented with 10% inactivated fetal calf serum and 50µg/ml gentamycin. The cells were maintained at 37ºC in a humidified atmosphere with 5% CO_2 and were subcultured two to three times a week.

Evaluation of the antitumor activity

The antitumor activity was evaluated on carcinoma cell lines at the Regional center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt. Briefly, the cell lines was grown as monolayers in growth medium supplemented with 10% inactivated fetal calf serum and 50µg/ml gentamycin. The monolayers of 10,000 cells adhered at the bottom of the wells in a 96-well Microtiter plate (Falcon, NJ, USA) incubated for 24h at 37ºC in a humidified incubator with 5% CO_2. The monolayers were then washed with sterile phosphate buffered saline (0.01 M pH 7.2) and simultaneously the cells were treated with 100 µl from different dilutions of tested compounds in fresh maintenance medium and incubated at 37ºC. A control of untreated cells was made in the absence of the tested compounds. Three wells were used for each concentration of the test sample. Every 24 h the observation under the inverted microscope was made. The number of the surviving cells was determined by staining the cells with crystal violet followed by cell lysing using 33% glacial acetic acid and read the absorbance at 590nm using ELISA reader after well mixing. The absorbance values from untreated cells were considered as 100% proliferation and the percentage of viability was calculated as [1-(ODt/ODc)]x100% where ODt is the mean optical density of wells treated with the tested.

2- Antimicrobial activity[27-30]

Most of the newly synthesized compounds 2 (a-e), 3 (a-e), 4a, 4b, 6-14, 16, 17, 19, 20, 24 and 26 (a-d) were evaluated for *in vitro* antimicrobial activity against Gram positive such as Staphylococcus aureus and Staphlyococcus epidermidis, Gram negative bacteria such as Pseudomonas aeruginosa and Escherichia coli and Fungi such as Candida albicans at concentration 75 mg/ml by Cup diffusion method[27-30] using DMF as solvent control, nutrient agar was employed as culture media. Mueller-Hinton agar plates were surface-inoculated with the tested strains suspensions adjusted to match 0.5 McFarland standard and the inocula were spread over the surfaces of plates using sterile cotton swabs. After drying of the plates, cups (10 mm diameter) were punched in the agar and 100 µl of the samples in DMF or the antimicrobial agents were added into the wells. The plates were incubated at 37 ºC for 24 hours. The antibacterial activity was determined by measuring the diameter of the zone of inhibition. The test was repeated three times and the mean inhibition zones were calculated.

The activity was compared with cefotaxim as positive control for bacteria and Nystatin for fungi and data was represented in Table No.2.

Table No.1: Cytotoxicity evaluation of the synthesized compounds against breast carcinoma (MCF7) and colon carcinoma (HCT116) cell lines

S.No	Compound No	IC50[a] (µg/ml)	
		Breast carcinoma (MCF7) cell line	Colon carcinoma (HCT-116) cell line
1	3b	14.9	34.2
2	4b	>50	>50
3	7	>50	40.9
4	9	42.2	40.8
5	11	20.3	17.6
6	12	46.1	43.5
7	14	>50	>50
8	16	10.8	3.7
9	19	>50	>50
10	20	43.5	42.9
11	24a	>50	>50
12	24b	8.1	5.3
13	Doxrubcin stander	0.426	0.469

[a]IC50 is a dose required to inhibit the cell growth by 50%.

Table No.2: Antimicrobial activity of synthesized compounds by cup plate diffusion method[27-30]

Tested Samples	Diameter (mm) of inhibition zones against the corresponding standard strains of different microorganisms				
	Gm +ve bacteria		Gm -ve bacteria		Fungi
	Staphylococcus aureus ATCC 6538	*Staphylococcus epidermidis* ATCC 12228	*Pseudomonas aeruginosa* ATCC 9027	*Escherichia coli* ATCC 10536	*Candida albicans* ATCC 10231
2a	27	24	18	20	20
2b	30	26	23	25	25
2c	27	23	20	22	23
2d	31	27	25	27	30
2e	29	25	24	26	30
3a	30	27	24	26	26
3b	28	24	20	22	21
3c	30	26	19	21	22
3d	30	26	23	25	28
3e	31	27	25	27	29
4a	30	25	24	25	28
4b	29	26	24	26	28
6	25	21	18	20	20
7	27	25	28	20	21
8	29	26	23	25	26
9	27	24	20	21	28
10	29	27	24	26	27
11	21	18	15	17	24
12	29	27	22	24	25
13	25	20	18	19	28
14	25	21	17	19	28
16	30	28	26	28	30
17	30	26	24	26	28
19	25	21	18	19	27
20	29	26	23	24	27

24	28	24	22	24	30
26a	27	24	23	24	24
26b	29	26	23	25	25
26c	30	27	24	26	27
26d	28	24	23	24	25
Cefotaxime (5 mg/ml) (control)	32	30	33	36	-
Nystatin (5 mg/ml) (control)	-	-	-	-	26
DMF (control)	-	-	-	-	-

Table No.3: 2[4-Tosylamino) phenyl carbonyl]hydrazine-N-substituted carbothioamides 2(a-e)

Comp.No	R	m.p °C	Yield %	M.F. (M.W)	Analysis of C, H, N Calcd/found			
						C	H	N
2a	C_6H_5-	198-200°C	85	$C_{21}H_{20}N_4O_3S_2$ (440)	Calcd Found	57.57 57.39	4.58 4.64	12.72 12.89
2b	4-H_3COC6H4-	200-202°C	90	$C_{22}H_{22}N_4O_4S_2$ (470)	Calcd Found	56.15 56.24	4.71 4.78	11.91 12.04
2c	4-BrC_6H_4-	206-208°C	88	$C_{21}H_{19}BrN_4O_3S_2$(519)	Calcd Found	48.56 48.62	3.69 3.74	10.79 10.92
2d	C_6H_5-CH_2-	223-225°C	88	$C_{22}H_{22}N_4O_3S_2$(454)	Calcd Found	58.13 58.21	4.88 4.90	12.33 12.47
2e	H_2C=CH-CH_2-	203-205°C	84	$C_{18}H_{20}N_4O_3S_2$(404)	Calcd Found	53.45 53.53	4.98 4.96	13.85 13.96

Table No.4: 4-Substituted-5-[4-(tosylamino) phenyl-4H-1,2,4-triazole-3-thiols 3(a-e)

Comp.No.	R	m.p °C	Yield %	M.F. (M.W)	Analysis of C, H, N Calcd/found			
						C	H	N
3a	C_6H_5-	295-300°C	88	$C_{21}H_{18}N_4O_2S_2$ (422)	Calcd Found	59.69 59.83	4.29 4.35	13.26 13.41
3b	4H_3CO-C_6H_4-	265-268°C	91	$C_{22}H_{20}N_4O_3S_2$ (452)	Calcd Found	58.39 58.48	4.45 4.43	12.38 12.49
3c	4-BrC_6H_4-	290-293°C	90	$C_{21}H_{17}BrN_4O_2S_2$ (502)	Calcd Found	50.30 50.47	3.42 3.43	11.17 11.19
3d	C_6H_5-CH_2-	230-235°C	89	$C_{22}H_{20}N_4O_2S_2$ (436)	Calcd Found	60.53 60.62	4.62 4.66	12.83 12.91
e	H_2C=CH-CH_2-	245-248°C	88	$C_{18}H_{18}N_4O_2S_2$ (386)	Calcd Found	55.95 56.12	4.69 4.69	14.50 14.67

Table No.5: 4-Amino-3-substituted amino-5-[4-(tosylamino)phenyl-4H-1,2,4-triazoles 4(a-d)

Comp.No.	R	m.p°C	Yield %	M.F. (M.W)	Analysis of C, H, N Calcd/found			
						C	H	N
4a	C_6H_5-	238-40°C	73	$C_{21}H_{20}N_6O_2S$ (420)	Calcd Found	59.98 60.07	4.79 4.83	19.99 20.06
4b	4-H_3CO-C_6H_4-	228-230°C	84	$C_{22}H_{22}N_6O_3S$ (450)	Calcd Found	58.65 58.79	4.92 4.98	18.65 18.81
4c	4-Br-C_6H_4-	248-250°C	72	$C_{21}H_{19}BrN_6O_2S$ (499)	Calcd Found	50.51 50.69	3.83 3.81	16.83 17.04
4d	C_6H_5-CH_2-	210-212°C	68	$C_{22}H_{22}N_6O_2S$ (434)	Calcd Found	60.81 60.97	5.10 5.17	19.34 19.48

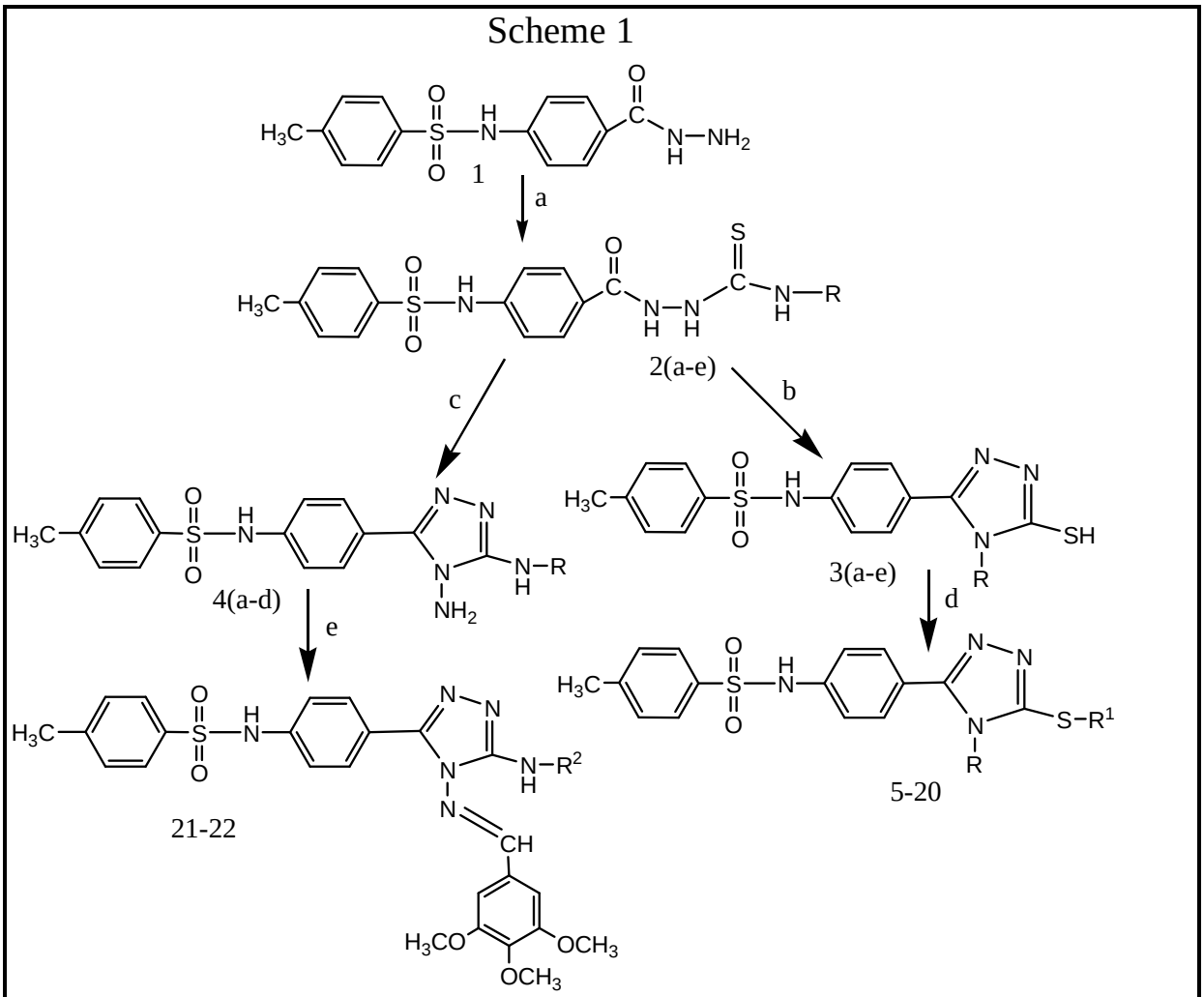
Table No.6: 4-(5-Ethylthio-4-phenyl-4H-1,2,4-triazol-3-yl)-N-toslylbenzamine(5) 2-[4-Substitued-5-(4-tosylamino)phenyl-4H-1,2,4-triazol-3-ylthio]N-substituted acetamides (6-20)

Comp.No	R	R\	m.p °C	Yield %	M.F. (M.W)	Analysis of C, H, N Calcd/found			
							C	H	N
5	C_6H_5-	C_2H_5-	264-266	70	$C_{23}H_{22}N_4O_2S_2$m (450)	Calcd Found	61.31 61.39	4.92 4.96	12.43 12.56
6	C_6H_5-	4-H_3C-$C_6H_4NCOCH_2$-	278-280	80	$C_{30}H_{27}N_5O_3S_2$ (569)	Calcd Found	63.25 63.36	4.78 4.81	12.29 12.47
7	C_6H_5-	4-$H_3COC_6H_4NHCOCH_2$-	244-246	87	$C_{30}H_{27}N_5O_4S_2$ (585)	Calcd Found	61.52 61.59	4.65 4.68	11.96 12.03
8	C_6H_5-	4-$ClC_6H_4NHCOCH_2$-	258-260	80	$C_{29}H_{24}ClN_5O_3S_2$ (589)	Calcd Found	59.02 59.13	4.10 4.13	11.87 11.98
9	C_6H_5-	4-$BrC_6H_4NHCOCH_2$-	270-272	67	$C_{29}H_{24}BrN_5O_3S_2$ (635)	Calcd Found	54.89 **55.03**	3.81 3.78	11.04 11.21
10	4-$H_3COC_6H_4$-	4-H_3C-$C_6H_4NHCOCH_2$-	268-270	79	$C_{31}H_{29}N_5O_4S_2$ (599)	Calcd Found	62.08 62.21	4.87 4.90	11.68 11.81
11	4-$H_3COC_6H_4$-	4-$H_3COC_6H_4NHCOCH_2$-	232-235	77	$C_{31}H_{29}N_5O_5S_2$ (615)	Calcd Found	60.47 60.56	4.75 4.80	11.37 11.49
12	4-$H_3COC6H4$-	4-$ClC_6H_4NHCOCH_2$-	276-278	70	$C_{30}H_{26}ClN_5O_4S_2$ (619)	Calcd Found	58.10 58.23	4.23 4.25	11.29 11.42
13	4-BrC_6H_4-	4-H_3C-$C_6H_4NHCOCH_2$-	247-249	77	$C_{30}H_{26}BrN_5O_3S_2$ (649)	Calcd Found	55.55 55.73	4.04 4.12	10.80 10.93
14	4-BrC_6H_4-	4-$H_3COC_6H_4NHCOCH_2$-	250-252	83	$C_{30}H_{26}BrN_5O_4S_2$ (665)	Calcd Found	54.22 54.37	3.94 3.92	10.54 10.68
15	4-BrC_6H_4-	2-$H_3CC_6H_4NHCOCH_2$-	244-246	75	$C_{30}H_{26}BrN_5O_3S_2$ (649)	Calcd Found	55.55 55.78	4.04 4.12	10.80 10.94
16	4-BrC_6H_4-	4-$ClC_6H_4NHCOCH_2$-	287-290	83	$C_{29}H_{23}BrClN_5O_3S_2$ (669)	Calcd Found	52.06 52.18	3.47 3.44	10.47 10.61
17-	4-BrC_6H_4-	4-$BrC_6H_4NHCOCH_2$-	274-276	64	$C_{29}H_{23}BrN_5O_3S_2$ (713)	Calcd Found	48.82 48.97	3.25 3.26	9.82 9.95
18	C_6H_5-CH_2⁻	2-$H_3CC_6H_4NHCOCH_2$-	-	62	$C_{31}H_{29}N_5O_3S_2$ (583)	Calcd Found	63.79 63.94	5.01 5.09	12.00 12.17
19	C_6H_5-CH_2⁻	4-$H_3COC_6H_4NHCOCH_2$-	196-198	65	$C_{31}H_{29}N_5O_4S_2$ (599)	Calcd Found	62.08 62.23	4.87 4.91	11.68 11.85
20	H_2C=CH–CH_2-	4-$H_3COC_6H_4NHCOCH_2$-	188-190	64	$C_{27}H_{27}N_5O_4S_2$ (549)	Calcd Found	59.00 59.16	4.95 5.03	12.74 12.89

Table No.7: 4-(Substituted benzylidenamino)5-[4-tosylamino)phenyl]-4H-1,2,4-triazole-3-thiols 27(a-e)

Comp. No.	Ar	m.p °C	Yield %	M.F. (M.W)	Analysis of C, H, N Calcd/found			
						C	H	N
27a	3,4,5-tri-H_3CO-C_6H_2	244-246	72	$C_{25}H_{25}N_5O_5S_2$ (539)	Calcd Found	55.64 55.72	4.67 4.62	12.98 13.05
2b	4-OH,3-H_3CO-C_6H_3	252-254	66	$C_{23}H_{21}N_5O_4S_2$ (495)	Calcd Found	55.75 55.89	4.24 4.30	14.14 14.21
27c	4-H_3CO-C_6H_4	236-238	76	$C_{23}H_{21}N_5O_3S_2$ (479)	Calcd Found	57.60 57.72	4.41 4.48	14.60 14.69
27d	4-Cl-C_6H_4	272-274	68	$C_{22}H_{18}ClN_5O_2S_2$ (483)	Calcd Found	54.59 54.73	3.75 3.79	14.47 14.63
27e	4-$NO_2C_6H_4$	270-282	73	$C_{22}H_{18}N_6O_4S_2$ (494)	Calcd Found	53.44 53.62	3.64 3.74	17.00 17.23

Scheme 1



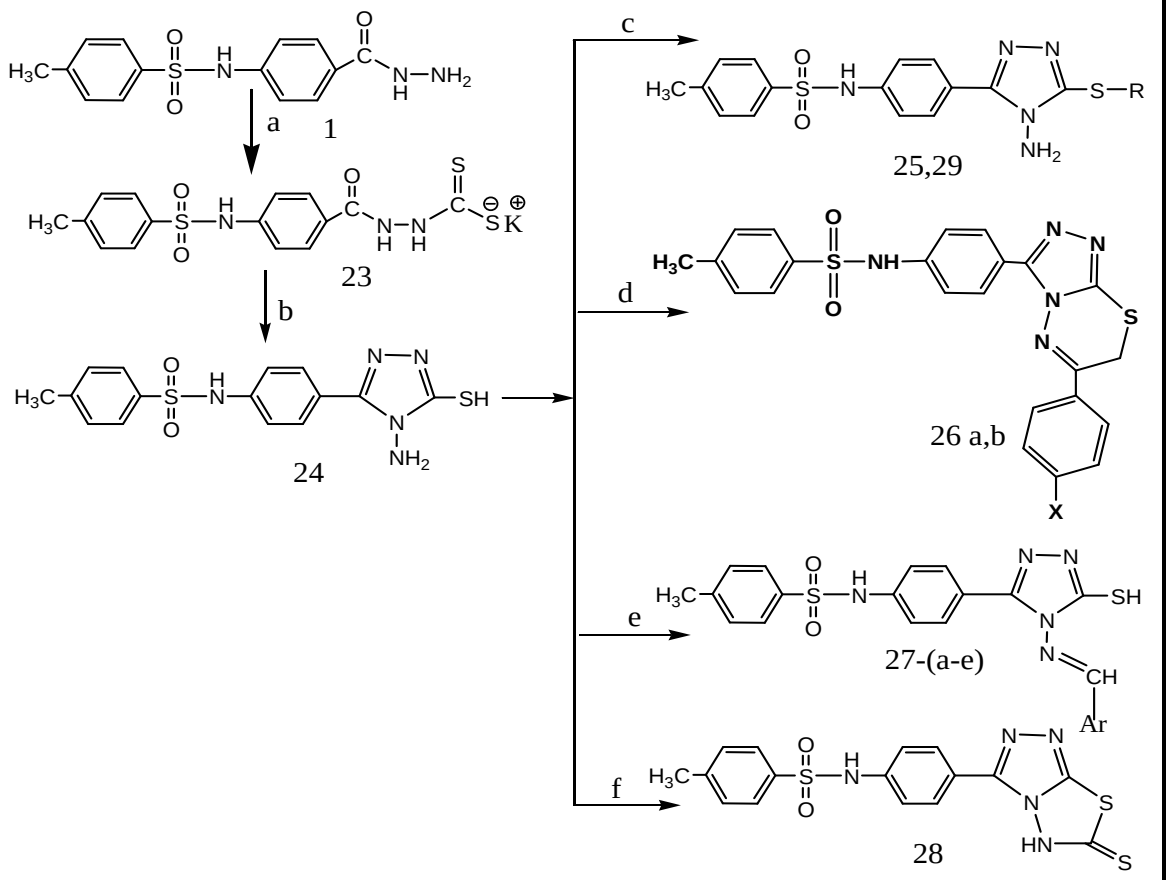
R = C_6H_5- ,4-H_3CO-C_6H_4- ,4-Br-C_6H_4- ,C_6H_5-CH_2- , $H_2C{=}\underset{H}{C}{-}CH_2$-

R^1 = C_2H_5- ,4-H_3C-$C_6H_4NHCOCH_2$- ,2-H_3C-$C_6H_4NHCOCH_2$- ,4-H_3CO-$C_6H_4NHCOCH_2$- , 4-Cl-$C_6H_4NHCOCH_2$- & 4-Br-$C_6H_4NHCOCH_2$-

X=I ,Cl R^2 = C_6H_5- ,4-H_3CO-C_6H_4-

a- R-NCS /Dioxane b- 2M, NaOH / reflux c- H_2N-NH_2 / MeOH / reflux
d- R_1-X /KOH/EtOH e- 3,4,5-Trimethoxybenzaldehyde /EtOH /HOAc /reflux

Scheme 2



a- EtOH/KOH/CS_2/rt. b- NH_2NH_2/EtOH /reflux c-RX/ NaOAc/EtOH/reflux or R-X /KOH./EtOH /r.t
d- RX/NaOAc/EtOH /reflux25h e-Ar-COH/EtOH/HOAc/reflux f-EtOH/CS_2/KOH/reflux

R= 4-X-$C_6H_4COCH_2$- , 4-H_3CO-C_6H_4-$NHCOCH_2$- , X= Cl,Br

Ar =3,4,5- $(H_3CO)_3C_6H_2$- ,4-OH,3-H_3CO-C_6H_3- ,4-H_3CO-C_6H_4-, 4-Cl-C_6H_4 ,4-NO_2-C_6H_4-

CONCLUSION

New derivatives of substituted 1,2,4-triazole bearing aryl sulfonamide moiety were synthesized. All the synthesized compounds were characterized by spectral data. Some of the newly synthesized triazole derivatives were evaluated for their cytotoxic activity against breast carcinoma (MCF7) and colon carcinoma (HCT116) cell lines. The cytotoxic activity showed that compounds 16 and 24b have high activity against the two cell lines. Most of the newly prepared compounds were screened for their antimicrobial activity against Gram positive S. aureus and S. epidermidis, Gram negative P. aeruginosa, E. coli and fungi C. albicans using cup diffusion method The results showed that most of the newly prepared -1,2,4-derivatives Shown significant antibacterial and antifungal activities.

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