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Synthesis and antitumor activity of some new N-substituted-sulfonyl, 1,2,4-triazole, N-substituted-benzylidene and pyrrole derivatives attached to 4-(benzo[d]thiazol-2-yl)benzohydrazide

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ABSTRACT

*Some N-substituted-sulfonyl, 1,2,4-triazole, N-substituted-benzylidene and pyrrole derivatives attached to 4-(benzo[d]thiazol-2-yl)benzohydrazide were prepared starting from o-aminothiophenol **1** by reacting with different electrophilic and nucleophilic reagents. Some of the newly synthesized compounds have been evaluated for their potential cytotoxicity against breast cancer cell line (MCF7), compound **12a** exhibited the highest activity.*

Key words: O-Aminothiophenol, 4-(benzo[d]thiazol-2-yl)benzohydrazide, N-substituted-sulfonyl, 1,2,4-triazole, N-substituted-benzylidene, pyrrole, indoline, antibreast cancer activity.

INTRODUCTION

Cancer is a disease of striking significance in the world today. It is the second leading cause of death after cardiovascular disease and it is projected to becoming the primary cause of death within the coming years(1). In a search for new cytotoxic candidates with improved antitumor profiles and encouraged by the marked cytotoxic properties exhibited by some benzothiazoles against various malignant cell types, it deemed of interest to synthesize and investigate the potential antitumor activity of some new benzothiazoles. The small and simple benzothiazole moiety possess interesting biological and industrial activities(2). Many of these compounds showed very intensive antitumor(3-11), antiviral(12-14), antibacterial(15-17), anti-inflammatory, antipyretic(18.19), analgesic(20,21), antioxidant(22), anticonvulsive(23,24) and antidepressant(25) activities. Among the most efficient compounds reported(2) are riluzole(26), sulfathiazole, 2-mercapto benzothiazole and 4-fluoro-2-(4-amino-3-methylphenyl)benzothiazole which revealed neuroprotective, anticonvulsive, antiallergic and antibreast cancer activities(4), respectively.

Compounds containing N-substituted-benzoyl(27), N-substituted-sulfonyl(28,29), 1,2,4-triazole(30-32), N-substituted-benzylidene(33-37), pyrrole and indoline(38-43) nucleus are

associated with diverse pharmacological activities which have made them important chemotherapeutic agents.

Based on the above observations, we report here the synthesis and antibreast cancer activity of some N-substituted-sulfonyl, 1,2,4-triazole, N-substituted-benzylidene and pyrrole derivatives attached to 4-(benzo[d]thiazol-2-yl)benzohydrazide moiety starting from o-aminothiophenol.

MATERIALS AND METHODS

Melting points (˚C) were taken in open capillary tubes using silicon oil on Gallen Kamp apparatus. ^{1}H-NMR Spectra were measured in d_6-DMSO on JEOL-270 Spectrometer with Me_4Si as an internal standard. Mass Spectra were obtained with a Schimadzu GCS-QP1000EX Spectrometer at 70 eV. The IR Spectra were recorded with a Philips Infra cord Spectrophotometer Model PU 9712 in KBr discs. Elemental analysis was performed at the Micro analytical Laboratory of the National Research Center. The antitumor activity of the synthesized compounds was carried out at the National Cancer Institute, Cairo, Egypt.

2-(4-Cyanophenyl)benzo[d]thiazole (2):

4-Cyanobenzaldehye (1.05g, 0.21 mol) and o-aminothiophenol **1** (1 ml, 0.21 mol) were dissolved in ethanol. This mixture was refluxed for 5h. and cooled to room temperature. Then, water was added slowly to the mixture with stirring. The suspension was maintained at -5ºC overnight. The product was washed repeatedly with ethanol-water (1:1) mixture and then recrystallized from acetone. Yield = 1.2g (64%), m.p. = 150-2˚C. Analysis for $C_{14}H_8N_2S$ (236.2): Calcd.: C, 69.0; H, 4.5; N, 12.4; S, 14.2; Fd.: C, 69.2; H, 4.6; N, 12.5; S, 14.3.

4-(Benzo[d]thiazol-2-yl)benzoic acid (3):

A mixture of **2** (2g, 0.01 mol) and 30ml 70% sulfuric acid was stirred in 100 ml three-necked flask at 140ºC for 5h, then suspended in 150 ml water and the resulting precipitate was filtered off. Recrystallization from diluted ethanol afforded white crystals. Yield = 0.8g (74%), m.p. = 250-3˚C. Analysis for $C_{14}H_9NO_2S$ (255.3): Calcd.: C, 65.9; H, 3.6; N, 5.5; S, 12.6; Fd.: C, 66.0; H, 3.6; N, 5.6; S, 12.8. MS: m/z (%):256 (M^++1, 19); 255 (M^+, 100); 238 (12.2); 209 (14.4); 198 (2); 183 (2.5).

Ethyl 4-(benzo[d]thiazol-2-yl)benzoate (4):

To a solution of compound **3** (2g; 0.073 mol) in absolute ethanol, few drops of concentrated sulfuric acid were added and the mixture was refluxed for 4h. The crude product was filtered, air-dried and crystallized from ethanol. Yield = 2.1g (94%), m.p. = 102-6˚C. Analysis for $C_{16}H_{13}NO_2S$ (283.3): Calcd.: C, 67.8; H, 4.6; N, 4.9; S, 11.3; Fd.: C, 68.0; H, 4.6; N, 5.0; S, 11.5. MS: m/z (%): 285 (M^++2, 25); 283 (M^+, 5); 257 (10); 239 (16); 211 (15); 178 (7). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.32 (t, 3H, C<u>H</u>$_3$); 4.32 (q, 2H, C<u>H</u>$_2$CH$_3$); 7.48-8.22 (m, 8H, Ar-H).

4-(Benzo[d]thiazol-2-yl)benzohydrazide (5):

To a solution of ester compound **4** (1g; 0.033 mol) in ethanol, hydrazine hydrate (98%; 2 ml) was added and heated for 5h on a water-bath. The reaction mixture was cooled. The crude product was filtered, washed with water and dried. It was crystallized from ethanol. Yield = 0.8g (84%), m.p. = 234-8˚C. Analysis for $C_{14}H_{11}N_3OS$ (269.3): Calcd.: C, 62.4; H, 4.1; N, 15.6; S, 11.9; Fd.: C, 62.5; H, 4.2; N, 15.7; S, 12.0. IR (cm^{-1}): 3753 (NH), 3414 (NH_2), 1684 (CO). MS: m/z (%): 270 (M^++1, 6); 269 (M^+, 16); 238 (100); 210 (65); 139(12). ^{1}H-NMR: δ, ppm (DMSO-d_6); 7.50-8.24 (m, 8H, Ar-H)**;** 9.96 (s, 2H, N<u>H</u>$_2$); 10.45 (s, 1H, N<u>H</u>).

General procedure for the preparation of substituted benzoic acid-N'-(4-benzothiazol-2-yl-benzoyl)hydrazide (6a-b):

To a solution of compound **5** (1g, 0.15 mol) in 10 ml dry DMF, sodium hydride (0.3 mol) was added slowly and the mixture was stirred vigorously for 5 min. at room temperature. To the resulting solution, benzoyl chloride or 4'-methylbenzoyl chloride (0.15 mol) in 2 ml DMF was then added, the mixture was stirred for 6h. at room temperature. The reaction mixture was quenched by addition of water and diluted with ethyl acetate. The organic layer was washed with brine two times and dried over $MgSO_4$. After filtration and concentration, the crude product was purified by crystallization from DMF.

Benzoic acid-N'-(4-benzothiazol-2-yl-benzoyl)hydrazide (6a):

Yield = 1.2g (87%), m.p. = 220-4˚C. Analysis for $C_{21}H_{15}N_3O_2S$ (373.4): Calcd.: C, 67.6; H, 4.1; N, 11.3; S, 8.6; Fd.: C, 67.9; H, 4.2; N, 11.5; S, 8.8. IR (cm^{-1}): 3660-3249 (2NH), 1640 (CO). MS: m/z (%): 373 (M^+, 1); 355 (100); 344 (1); 326 (1); 310 (1); 299 (6.4); 283 (1); 267 (1); 255 (3); 238 (40); 210 (21).

4-Methylbenzoic acid -N'-(4-benzothiazol-2-yl-benzoyl)hydrazide (6b):

Yield = 1.3g (90%), m.p. = above 300˚C. Analysis for $C_{22}H_{17}N_3O_2S$ (387.5): Calcd.: C, 68.2; H, 4.4; N, 10.9; S, 8.3; Fd.: C, 68.2; H, 4.5; N, 11.0; S, 8.5. ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.95 (s, 3H, C$\underline{H}_3$); 2.38 (s, 1H, N$\underline{H}$); 2.50 (s, 1H, N$\underline{H}$); 7.04-8.23 (m, 12H, Ar-H).

General procedure for the preparation of 4-(benzo[d]thiazol-2-yl)-N-substituted-sulfonyl-benzohydrazide (7a-c):

Compound **5** (1g, 0.016 mol) was dissolved in dry acetone (50 ml). Triethylamine (2.5 ml) was added to this solution. Then a solution of benzene sulfonyl chloride, toluene sulfonyl chloride or camphor-10-sulfonyl chloride (0.016 mol) in dry acetone was added and the mixture was stirred for 2h. at room temperature. The solid formed was filtered off and the solvent was removed from the clear solution under reduced pressure. Purification of the product was carried out by preparative thin-layer chromatography using ethyl acetate as eluent. The products were recrystallized from methanol.

4-(Benzo[d]thiazol-2-yl)-N-sulfonylbenzene-benzohydrazide (7a):

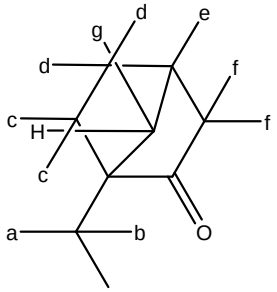
Yield = 1.4g (92%), m.p. = 246-9˚C. Analysis for $C_{20}H_{15}N_3O_3S_2$ (409.5): Calcd.: C, 58.7; H, 3.7; N, 10.3; S, 15.7; Fd.: C, 58.9; H, 3.8; N, 10.5; S, 15.8.

4-(Benzo[d]thiazol-2-yl)-N-tosyl-benzohydrazide (7b):

Yield = 1.3g (83%), m.p. = 273-6˚C. Analysis for $C_{21}H_{17}N_3O_3S_2$ (423.5): Calcd.: C, 59.6; H, 4.1; N, 9.9; S, 15.1; Fd.: C, 59.7; H, 4.2; N, 10.0; S, 15.2. ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.24 (s, 1H, N$\underline{H}$); 3.13 (s, 3H, C$\underline{H}_3$); 7.08-7.43 (m, 12H, Ar-H); 10.43 (s, 1H, N$\underline{H}$).

4-(Benzo[d]thiazol-2-yl)-N-camphorsulfonyl benzohydrazide (7c):

Yield = 1.5g (84%), m.p. = 156-9˚C. Analysis for $C_{24}H_{25}N_3O_4S_2$ (483.6): Calcd.: C, 59.6; H, 5.2; N, 8.7; S, 13.3; Fd.: C, 59.8; H, 5.3; N, 8.9; S, 13.5. IR (cm^{-1}): 3317-3188 (2NH), 1656-1621 (2CO), 1371 (SO_2). MS: m/z (%): 483 (M^+, 1); 481 (M^+-2, 1); 430 (2); 400 (4); 382 (4); 337 (4); 282 (5); 267 (1); 255 (3); 238 (11); 210 (6). ^{1}H-NMR: δ, ppm (DMSO-d_6); 0.83 (s, 3H, $\underline{H}_h$); 1.18 (s, 3H, $\underline{H}_g$); 1.93-1.99 (m, 7H, $\underline{H}_{c-f}$); 4.40 (d, 1H, $\underline{H}_a$); 4.60 (d, 1H, $\underline{H}_b$); 7.47-8.16 (m, 8H, Ar-H) 9.93 (s, 1H, N$\underline{H}$); 10.59 (s, 1H, N$\underline{H}$).



General procedure for the preparation of 4-(benzo[d]thiazol-2-yl)benzoyl-4-phenylthiosemicarbazide/4-(4-chloro phenyl)semicarbazide (8a-b):

A mixture of **5** (1g, 0.01 mol) and arylisothiocyanate or 4'-chloroaryl-isocyanate (0.01 mol) in dry benzene was refluxed for 6h. The solid material obtained on cooling was filtered off and recrystallized from methanol.

4-(Benzo[d]thiazol-2-yl)benzoyl-4-phenylthiosemicarbazide (8a):

Yield = 1.3g (87%), m.p. = 192-5˚C. Analysis for $C_{21}H_{16}N_4OS_2$ (404.5): Calcd.: C, 62.4; H, 4.0; N, 13.9; S, 15.6; Fd.: C, 62.5; H, 4.2; N, 14.0; S, 15.8.

4-(Benzo[d]thiazol-2-yl)benzoyl-4-(4-chloro phenyl)semicarbazide (8b):

Yield = 1.3g (76%), m.p. = 184-7˚C. Analysis for $C_{21}H_{15}ClN_4O_2S$ (422.9): Calcd.: C, 59.6; H, 3.6; N, 13.3; S, 7.6; Fd.: C, 59.8; H, 3.5; N, 13.2; S, 7.8. IR (cm^{-1}): 3295-3228 (3NH), 1670 (CO). ^{1}H-NMR: δ, ppm (DMSO-d_6); 7.28-8.36 (m, 12H, Ar-H); 8.87 (s, 1H, NH); 9.07 (s, 1H, NH); 10.50 (s, 1H, NH).

General procedure for the preparation of 5-[4-(benzo[d]thiazol-2-yl) phenyl]-4-substituted-phenyl-2H-1,2,4-triazol-3(4H)thione/one (9a-b):

A stirring mixture of compound **8a** or **8b** (0.01mol) and sodium hydroxide (40mg, 2N solution) was refluxed for 4h. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered. The product was then crystallized from methanol.

5-[4-(Benzo[d]thiazol-2-yl)phenyl]-4-phenyl-2H-1,2,4-triazol-3(4H)thione (9a):

Yield = 0.7g (73%), m.p. = 257-9˚C. Analysis for $C_{21}H_{14}N_4S_2$ (386.5): Calcd.: C, 65.3; H, 3.7; N, 14.5; S, 16.6; Fd.: C, 65.5; H, 4.0; N, 14.4; S, 16.8. ^{1}H-NMR: δ, ppm (DMSO-d_6); 7.02 (s, 1H, NH); 7.17-8.24 (m, 13H, Ar-H).

5-[4-(Benzo[d]thiazol-2-yl)phenyl]-4-(4-chlorophenyl)-2H-1,2,4-triazol-3(4H)one (9b):

Yield = 0.8g (84%), m.p. = 220-2˚C. Analysis for $C_{21}H_{13}ClN_4OS$ (404.8): Calcd.: C, 62.4; H, 4.0; N, 13.9; S, 15.6; Fd.: C, 62.5; H, 4.2; N, 14.0; S, 15.8. MS: m/z (%): 404 (M^+, 1); 369 (3); 325 (4); 297 (4); 266 (5); 239 (5); 196 (6); 168 (8). IR (cm^{-1}): 3212 (NH), 1670 (CO). ^{1}H-NMR: δ, ppm (DMSO-d_6); 7.02 (s, 1H, NH); 7.07-8.24 (m, 12H, Ar-H).

General procedure for the preparation of 2-substituted-5-[4-(benzo[d] thiazol-2-yl)phenyl]-4(4-chlorophenyl)-2H-1,2,4-triazol-3(4H)one (10a-c):

A mixture of compound **9b** (2g; 0.067 mol), appropriate alkyl halide (methyliodide / ethylchloroformate or ethyl-3-bromo propanoate) (0.067 mol), anhydrous sodium carbonate (4g.) and acetone (30 ml) was heated under reflux for 8h. Most of the solvent was distilled off, the residue was diluted with water and the obtained product was collected.

5-[4-(Benzo[d]thiazol-2-yl)phenyl]-4-(4-chlorophenyl)-2-methyl-2H-1,2,4-triazol-3(4H)-one (10a):
Yield = 1.8g (78%), m.p. = 232-6˚C. Analysis for $C_{22}H_{15}ClN_4OS$ (418.9): Calcd.: C, 63.1; H, 3.6; N, 13.4; S, 7.7; Fd.: C, 63.2; H, 3.7; N, 13.5; S, 7.8. IR (cm^{-1}): 1670 (CO). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.50 (s, 3H, $\underline{CH_3}$); 7.07-8.24 (m, 12H, Ar-H).

Ethyl-3-[4-(benzo[d]thiazol-2-yl)phenyl]-4-(4-chlorophenyl)-4,5-dihyro-5-oxo-1,2,4-triazole-1-carbo -xylate (10b):
Yield = 1.8g (78%), m.p. = 264-7˚C. Analysis for $C_{24}H_{17}ClN_4O_3S$ (476.9): Calcd.: C, 60.4; H, 3.6; N, 11.8; S, 6.7; Fd.: C, 60.5; H, 3.8; N, 11.7; S, 6.5. ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.16 (t, 3H, $\underline{CH_3}$); 4.94 (q, 2H, $\underline{CH_2}$); 7.30-8.24 (m, 12H, Ar-H).

Ethyl-3-{3-[4-(benzo[d]thiazol-2-yl) phenyl]-4-(4-chlorophenyl)-4,5-dihyro-5-oxo-1,2,4-triazol-1-yl}propanoate (10c):
Yield = 1.7g (68%), m.p. = 242-5˚C. Analysis for $C_{26}H_{21}ClN_4O_3S$ (504.9): Calcd.: C, 61.8; H, 4.2; N, 11.1; S, 6.4; Fd.: C, 62.0; H, 4.3; N, 10.9; S, 6.6. IR (cm^{-1}): 1731 (COO). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.16 (t, 3H, $\underline{CH_3}$); 3.23 (t, 2H, $\underline{CH_2}$); 3.54 (t, 2H, $\underline{CH_2}$); 4.96 (q, 2H, $\underline{CH_2}$); 7.29-8.36 (m, 12H, Ar-H).

General preocedure for the preparation of N'(substituted-benzylidene)-4-(benzo[d]thiazol-2-yl)benzohydrazide (11a-g):
To the compound **5** (1g; 0.018 mol) dissolved in absolute ethanol (30 ml), the appropriate aromatic aldehydes (benzaldehyde / 4-fluorobenzaldehyde / 4-cyanobenzaldehyde / 4-dimethylaminobenzaldehyde / 4-nitrobenzaldehyde / 4-hydroxy-3-methoxybenzaldehyde or 3,4-dimethoxybenzaldehyde) (0.018 mol) was added and few drops of glacial acetic acid was added then the mixture was refluxed for 6h. Solvent was distilled off, white solid product crystallized from ethylacetate / petroleum ether (95:5).

N'(4-Benzylidene)-4-(benzo[d]thiazol-2-yl)benzohydrazide (11a):
Yield = 1.0g (75%), m.p. = 270-4˚C. Analysis for $C_{21}H_{15}NOS$ (357.4): Calcd.: C, 70.6; H, 4.2; N, 11.8; S, 9.0; Fd.: C, 70.8; H, 4.3; N, 11.8; S, 9.3. IR (cm^{-1}): 3211 (NH), 1634 (CO). MS: m/z (%): 357 (M^+, 7); 356 (M^+-1, 7); 369 (3); 255 (68); 239 (100); 209 (50); 182 (9). ^{1}H-NMR: δ, ppm (DMSO-d_6); 7.43-8.46 (m, 13H, Ar-H); 7.73 (s, 1H, C$\underline{H}$); 11.99 (s, 1H, N$\underline{H}$).

N'(4-Fluorobenzylidene)-4-(benzo[d]thiazol-2-yl)benzohydrazide (11b):
Yield = 1.1g (79%), m.p. = 210-5˚C. Analysis for $C_{21}H_{14}FN_3OS$ (375.4): Calcd.: C, 67.2; H, 3.8; N, 11.2; S, 8.5; Fd.: C, 67.3; H, 4.1; N, 10.9; S, 8.3.

N'(4-Cyanobenzylidene)-4-(benzo[d]thiazol-2-yl)benzohydrazide (11c):
Yield = 1.1g (77%), m.p. = 209-212˚C. Analysis for $C_{22}H_{14}N_4OS$ (382.4): Calcd.: C, 69.1; H, 3.7; N, 14.7; S, 8.4; Fd.: C, 69.3; H, 4.0; N, 14.9; S, 8.3. IR (cm^{-1}): 3216 (NH), 2219 (CN); 1642 (CO).

N'(4-Dimethylaminobenzylidene)-4-(benzo[d]thiazol-2-yl)benzohydrazide (11d):
Yield = 1.2g (80%), m.p. = 202-5˚C. Analysis for $C_{23}H_{20}N_4OS$ (400.5): Calcd.: C, 69.0; H, 5.0; N, 14.0; S, 8.0; Fd.: C, 69.3; H, 5.2; N, 14.2; S, 7.6.

N'(4-Nitrobenzylidene)-4-(benzo[d]thiazol-2-yl)benzohydrazide (11e):
Yield = 1.2g (80%), m.p. = 110-4˚C. Analysis for $C_{21}H_{14}N_4O_3S$ (402.4): Calcd.: C, 62.7; H, 3.5; N, 13.9; S, 8.0; Fd.: C, 62.9; H, 3.8; N, 14.0; S, 8.3. MS: m/z (%): 402 (M^+, 4); 293 (100); 279 (28); 254 (25); 238 (71); 210 (38).

N'(4-Hydroxy-3-methoxybenzylidene)-4-(benzo[d]thiazol-2-yl)benzo hydrazide (11f):
Yield = 1.1g (73%), m.p. = 222-5˚C. Analysis for $C_{22}H_{17}N_3O_3S$ (403.5): Calcd.: C, 65.5; H, 4.3; N, 10.4; S, 8.0; Fd.: C, 65.3; H, 4.1; N, 10.9; S, 8.3. IR (cm^{-1}): 3780-3225 (OH, NH), 1645 (CO). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.94 (s, 1H, OH); 3.71 (s, 3H, OCH_3); 7.50-8.24 (m, 11H, Ar-H); 7.60 (s, 1H, CH); 9.96 (s, 1H, NH).

N'(3,4-Dimethoxybenzylidene)-4-(benzo[d]thiazol-2-yl)benzohydrazide (11g):
Yield = 1.3g (84%), m.p. = 240-5˚C. Analysis for $C_{23}H_{19}N_3O_3S$ (417.5): Calcd.: C, 66.2; H, 4.6; N, 10.1; S, 7.7; Fd.: C, 66.7; H, 4.7; N, 10.0; S, 7.6. ^{1}H-NMR: δ, ppm (DMSO-d_6); 3.63 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3); 7.50-8.24 (m, 11H, Ar-H); 7.60 (s, 1H, CH); 9.96 (s, 1H, NH).

General procedure for the preparation of 4-(benzo[d]thiazol-2-yl)-N'[(2R, 3S, 4R) / (2R, 3R, 4R, 5R) / (2R, 3R, 4S, 5R)-2,3,4,5-tetrahyroxy pentylidene/2,3,4,5,6-pentahydroxyhexylidene]benzohydrazide (12a-c):
To a solution of compound **5** (1g, 0.1 mol) in 50 ml ethanol, the respective sugar [D(+)xylose, D(+)glucose or D(+)galactose] (0.1 mol) and 0.1 ml acetic acid were added. The mixture was heated under reflux on a water-bath for 2h. The solid that separated on cooling was filtered, washed with ethanol and crystallized from the appropriate solvent.

4-(Benzo[d]thiazol-2-yl)-N'[(2R,3S,4R)- 2,3,4,5-tetrahyroxy pentylidene benzohydrazide (12a):
Yield = 1.0g (67%), m.p. = 206-9˚C. Analysis for $C_{19}H_{19}N_3O_5S$ (401.4): Calcd.: C, 56.9; H, 4.8; N, 10.5; S, 8.0; Fd.: C, 57.0; H, 4.7; N, 10.5; S, 7.8. IR (cm^{-1}): 3755-3220 (OH, NH), 1669 (CO). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.49-2.53 (s, 4H, OH); 3.29 (m, 1H, $^{'}H_5$); 4.10 (m, 1H, $^{''}H_5$); 4.20 (t, 1H, $^1H_2$); 4.31 (t, 1H, $^1H_4$); 5.16 (t, 1H, $^1H_3$); 5.95 (d, 1H, CH); 7.51 (s, 1H, NH); 7.56-8.25 (m, 8H, Ar-H). ^{13}C-NMR δ, ppm (DMSO-d_6): showed the presence of 19 signals correspond to the 19 different carbon groups, signals appeared at δ 64.50 (CH_2OH), 66.50-74.50 (3CHOH), 122.49-130.70 (Ar-8CH), 134.72 (C=C), 137.07 (CS), 153.51 (CH=N), 154.38 (C-N), 164.57 (C=C), 165.74 (C=N) and 167.50 (CO).

4-(Benzo[d]thiazol-2-yl)-N'[(2R,3R,4R,5R)-2,3,4,5,6-pentahydroxy hexylidene]benzohydrazide (12b):
Yield = 1.2g (75%), m.p. = 210-2˚C. Analysis for $C_{20}H_{21}N_3O_6S$ (431.5): Calcd.: C, 55.7; H, 4.9; N, 9.7; S, 7.4; Fd.: C, 56.0; H, 4.8; N, 9.7; S, 7.5. IR (cm^{-1}): 3652-3265 (OH, NH), 1637 (CO). MS: m/z (%): 433 (M^++2, 4); 431 (M^+, 10); 419 (3); 376 (6); 337 (7); 321 (11); 304 (3); 266 (19); 238 (71); 210 (5). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.30 (s, 5H, OH); 3.13 (m, 1H, $^{'}H_6$); 3.29 (m, 1H, $^{''}H_6$); 4.20 (t, 1H, $^1H_2$); 4.31 (t, 1H, $^1H_4$); 4.89 (m, 1H, $^1H_5$); 5.16 (t, 1H, $^1H_3$); 5.95 (d, 1H, CH); 7.55-8.16 (m, 8H, Ar-H); 10.22 (s, 1H, NH). ^{13}C-NMR δ, ppm (DMSO-d_6): showed the presence of 20 signals correspond to the 20 different carbon groups, signals appeared at δ 64.50 (CH_2OH), 66.50-78.02 (4CHOH), 122.49-130.70 (Ar-8CH), 134.72 (C=C), 137.07 (CS), 153.51 (CH=N), 154.38 (C-N), 164.57 (C=C), 165.74 (C=N) and 167.50 (CO).

4-(Benzo[d]thiazol-2-yl)-N'[(2R,3R,4S,5R)- 2,3,4,5,6-pentahydroxy hexylidene] benzohydrazide (12c):
Yield = 1.1g (69%), m.p. = 192-5˚C. Analysis for $C_{20}H_{21}N_3O_6S$ (431.5): Calcd.: C, 55.7; H, 4.9; N, 9.7; S, 7.4; Fd.: C, 56.0; H, 4.8; N, 9.7; S, 7.5. IR (cm^{-1}): 3380-3200 (OH, NH), 1658 (CO). MS: m/z (%): 432 (M^++1, 19); 419 (6); 279 (19); 254 (87); 238 (100); 210 (57); 183 (21). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.48-2.53 (s, 5H, OH); 3.36 (m, 1H, $^{'}H_6$); 3.51 (m, 1H, $^{''}H_6$); 3.67 (t, 1H, $^1H_2$); 4.23 (t, 1H, $^1H_4$); 4.46 (m, 1H, $^1H_5$); 4.91 (t, 1H, $^1H_3$); 6.95 (d, 1H, CH); 7.52 (s, 1H, NH); 7.55-8.16 (m, 8H, Ar-H).

4-(4-Benzothiazol-2-yl)-N-{2-[(1R, 2S, 3R, 4S)-1,2,3,4,5-pentahydroxy-pentyl)-4-oxothiazolidin-3-yl} benzamide (13):

A mixture of compound **12b** (1g, 0.002 mol), 2-mercaptoacetic acid (0.21 ml, 0.002 mol) and 20 ml of dry benzene was heated under reflux on a water-bath for 6h., cooled and filtered. The residue was dried and recrystallized from DMF/ethanol. Yield = 0.8g (69%), m.p. = 274-7˚C. Analysis for $C_{22}H_{21}N_3O_7S_2$ (503.5):Calcd.: C, 52.5; H, 4.2; N, 8.3; S, 12.7. Fd.: C, 52.9; H, 4.0; N, 8.5; S, 12.7. IR (cm^{-1}): 3786-3208 (OH), 1637-1602 (CO). MS: m/z (%): 503 (M^+, 4); 491 (19); 361 (19); 254 (23); 238 (28); 210 (22). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.30 (s, 5H, O<u>H</u>); 3.13 (m, 1H, $^{'}H_6$); 3.29 (m, 1H, $^{''}H_6$); 3.76 (s, 2H, C<u>H</u>$_2$); 4.20 (t, 1H, $^1H_2$); 4.31 (t, 1H, $^1H_4$); 4.76 (d, 1H, C<u>H</u>); 4.89 (m, 1H, $^1H_5$); 5.16 (t, 1H, $^1H_3$); 7.55-8.16 (m, 8H, Ar-H).

{[4-(Benzo[d]thiazol-2-yl)phenyl]-3,5-dimethyl-1H-pyrazol-1-yl}methanone (14):

A mixture of compound **5** (1g, 0.005 mol) and acetylacetone (0.37 ml, 0.005 mol) in absolute ethanol (25 ml) was boiled under reflux for 3h. until all the starting material had disappeared as indicated by TLC. Then the reaction mixture was concentrated under vacuum, whereby the resulted oily product was triturated with petroleum ether. The formed solid product was filtered off, dried and crystallized from methanol. Yield = 0.7g (57%), m.p. = 268-272˚C. Analysis for $C_{19}H_{15}N_3OS$ (333.4): Calcd.: C, 68.5; H, 4.5; N, 12.6; S, 9.6. Fd.: C, 68.7; H, 4.2; N, 12.8; S, 9.7. IR (cm^{-1}): 1679 (CO). MS: m/z (%): 333 (M^+, 1); 291 (4); 270 (2); 255 (100); 238 (13); 210 (18). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.44 (s, 6H, 2C<u>H</u>$_3$); 5.93 (s, 1H, <u>CH</u>); 7.47-8.19 (m, 8H, Ar-H).

General procedure for the preparation of 4-[(benzo[d]thiazol-2-yl)-N-(2,5-dioxo-2H-pyrrol-1(5H)-yl)/(2,5-dioxopyrrolidin-1-yl)/(1,3-dioxoisoindolin-2-yl)]benzamide (15a-c):

To a stirred solution of the hydrazide **5** (1g; 0.017 mol) in glacial acetic acid (10 ml), acid anhydride (maleic anhydride / succinic anhydride or phthalic anhydride) (0.0348 mol) was added. The mixture was heated under reflux with stirring for 8h. The precipitate formed was filtered, washed with water and the crude product was crystallized from ethanol.

4-[(Benzo[d]thiazol-2-yl)-N-(2,5-dioxo-2H-pyrrol-1(5H)-yl)]benzamide (15a):

Yield = 0.8g (62%), m.p. = 250-3˚C. Analysis for $C_{18}H_{11}N_3O_3S$ (349.4): Calcd.: C, 61.9; H, 3.2; N, 12.0; S, 9.2. Fd.: C, 62.0; H, 3.2; N, 12.2; S, 9.4. IR (cm^{-1}): 3226 (NH); 1719 (CO); 1640 (CO). MS: m/z (%): 349 (M^+, 2); 348 (M^+-1, 2); 317 (3); 293 (15); 256 (45); 240 (100); 213 (53); 209 (20); 175 (40). ^{1}H-NMR: δ, ppm (DMSO-d_6); 6.29 (d, 1H, C<u>H</u>=); 6.32 (d, 1H, C<u>H</u>=); 7.47-8.17 (m, 8H, Ar-H); 9.93 (s, 1H, N<u>H</u>).

4-[(Benzo[d]thiazol-2-yl)-N-(2,5-dioxopyrrolidin-1-yl)]benzamide (15b):

Yield = 0.7g (54%), m.p. = 270-2˚C. Analysis for $C_{18}H_{13}N_3O_3S$ (351.4): Calcd.: C, 61.5; H, 3.7; N, 12.0; S, 9.1. Fd.: C, 61.7; H, 3.8; N, 12.3; S, 8.9. IR (cm^{-1}): 3203 (NH); 1704 (CO); 1620 (CO). ^{1}H-NMR: δ, ppm (DMSO-d_6); 2.34 (t, 2H, C<u>H</u>$_2$); 2.41 (t, 2H, C<u>H</u>$_2$); 7.47-8.23 (m, 8H, Ar-H); 9.76 (s, 1H, N<u>H</u>).

4-[(Benzo[d]thiazol-2-yl)-N-(1,3-dioxoisoindolin-2-yl)]benzamide (15c):

Yield = 1.0g (67%), m.p. = 296-9˚C. Analysis for $C_{22}H_{13}N_3O_3S$ (399.4): Calcd.: C, 66.2; H, 3.3; N, 10.5; S, 8.0. Fd.: C, 66.3; H, 3.4; N, 10.1; S, 8.3. IR (cm^{-1}): 3200 (NH); 1719 (CO); 1682 (CO).

General procedure for the preparation of 4-(benzo[d]thiazol-2-yl)-N-substituted ketone-benzohydrazide (16a-c):

To the compound **5** (1g; 0.018 mol) dissolved in absolute ethanol (30 ml), the respective ketone (4-methylpentan-2-one/ cyclohexane-1,4-dione or 5-nitro isatin) (0.018 mol) and few drops of

glacial acetic acid were added then the mixture was refluxed for 6h. Solvent was distilled off, white solid product crystallized from ethylacetate / petroleum ether (95:5).

4-(Benzo[d]thiazol-2-yl)-N-(4-methylpentan-2-ylidene)benzohydrazide (16a):
Yield = 0.9g (69%), m.p. = 280-3˚C. Analysis for $C_{20}H_{21}N_3OS$ (351.4): Calcd.: C, 68.4; H, 6.0; N, 12.0; S, 9.1. Fd.: C, 68.5; H, 6.2; N, 12.1; S, 9.4. IR (cm^{-1}): 3426 (NH); 1681 (CO). MS: m/z (%): 351 (M^+, 1); 344 (1); 329 (1); 315 (3); 293 (2); 268 (32); 255 (100); 238 (31); 210 (22); 183 (2).

4-(Benzo[d]thiazol-2-yl)-N-(4-oxocyclohexylidene)benzohydrazide (16b):
Yield = 0.8g (59%), m.p. = above 300˚C. Analysis for $C_{20}H_{17}N_3O_2S$ (363.4): Calcd.: C, 66.1; H, 4.7; N, 11.6; S, 8.8. Fd.: C, 66.3; H, 4.8; N, 11.3; S, 8.9. IR (cm^{-1}): 3199 (NH); 1654 (CO). MS: m/z (%): 365 (M^++2, 1); 363 (M^+, 2); 351 (2); 344 (2); 327 (2); 311 (12); 293 (100); 279 (5); 268 (32); 254 (31); 238 (69); 210 (34); 183 (9). ^{1}H-NMR: δ, ppm (DMSO-d_6); 1.90 (t, 4H, 2C$\underline{H}_2$); 2.49 (t, 4H, 2C$\underline{H}_2$); 7.48 (s, 1H, N$\underline{H}$); 7.50-8.23 (m, 8H, Ar-H).

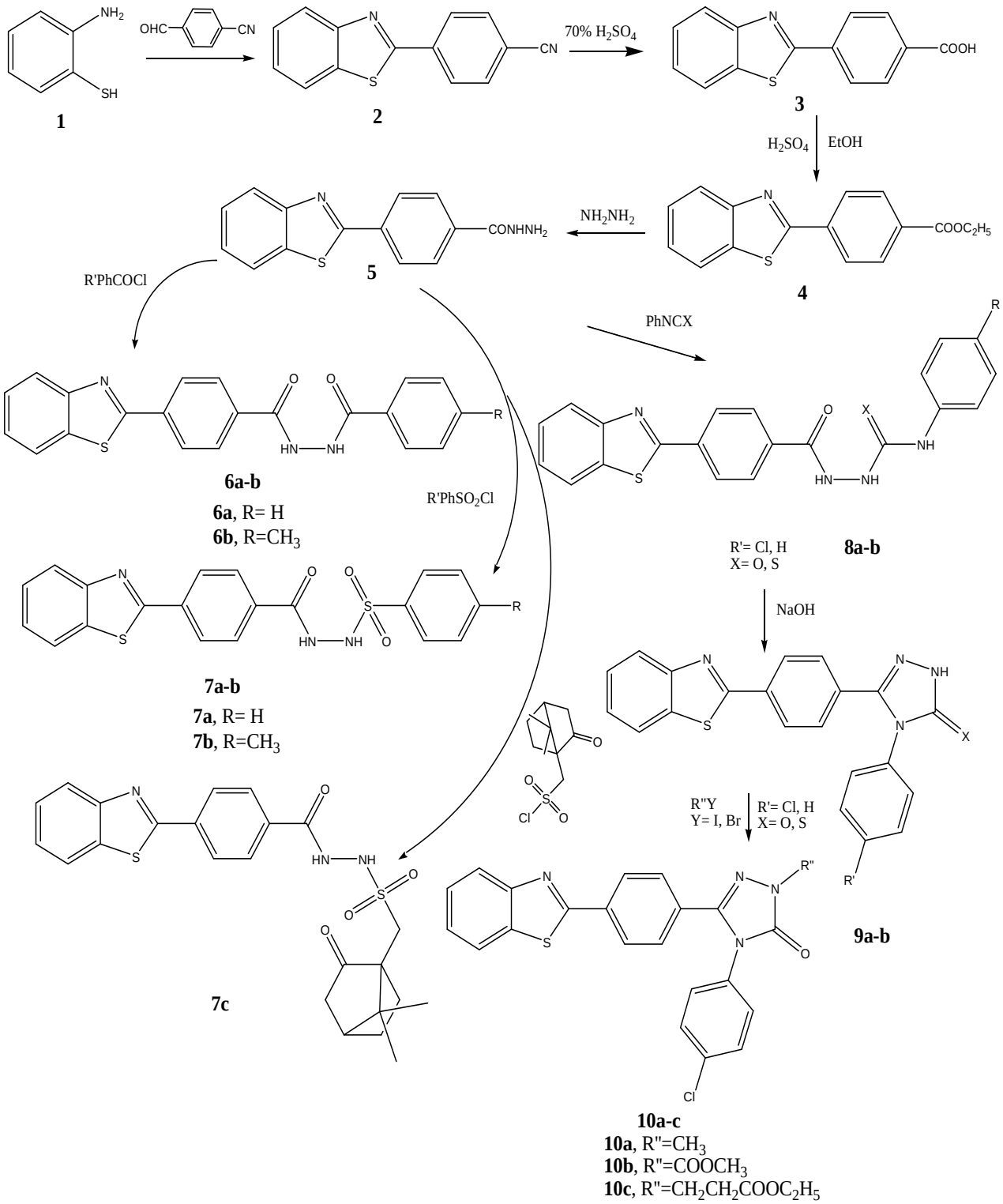
4-(Benzo[d]thiazol-2-yl)-N-(5-nitro-2-oxoindolin-3-ylidene)benzohydrazide (16c):
Yield = 1.3g (79%), m.p. = above 300˚C. Analysis for $C_{22}H_{13}N_5O_4S$ (443.4): Calcd.: C, 59.6; H, 3.0; N, 15.8; S, 7.2. Fd.: C, 59.8; H, 3.1; N, 15.9; S, 7.3. IR (cm^{-1}): 3404-3149 (2NH); 1671-1623 (CO); 1605 (C=N). MS: m/z (%): 445 (M^++2, 4); 443 (M^+, 3); 140 (4); 127 (8). ^{1}H-NMR: δ, ppm (DMSO-d_6); 7.04-8.25 (m, 11H, Ar-H); 11.83 (s, 1H, N$\underline{H}$); 12.31 (s, 1H, N$\underline{H}$).

RESULTS AND DISCUSSION

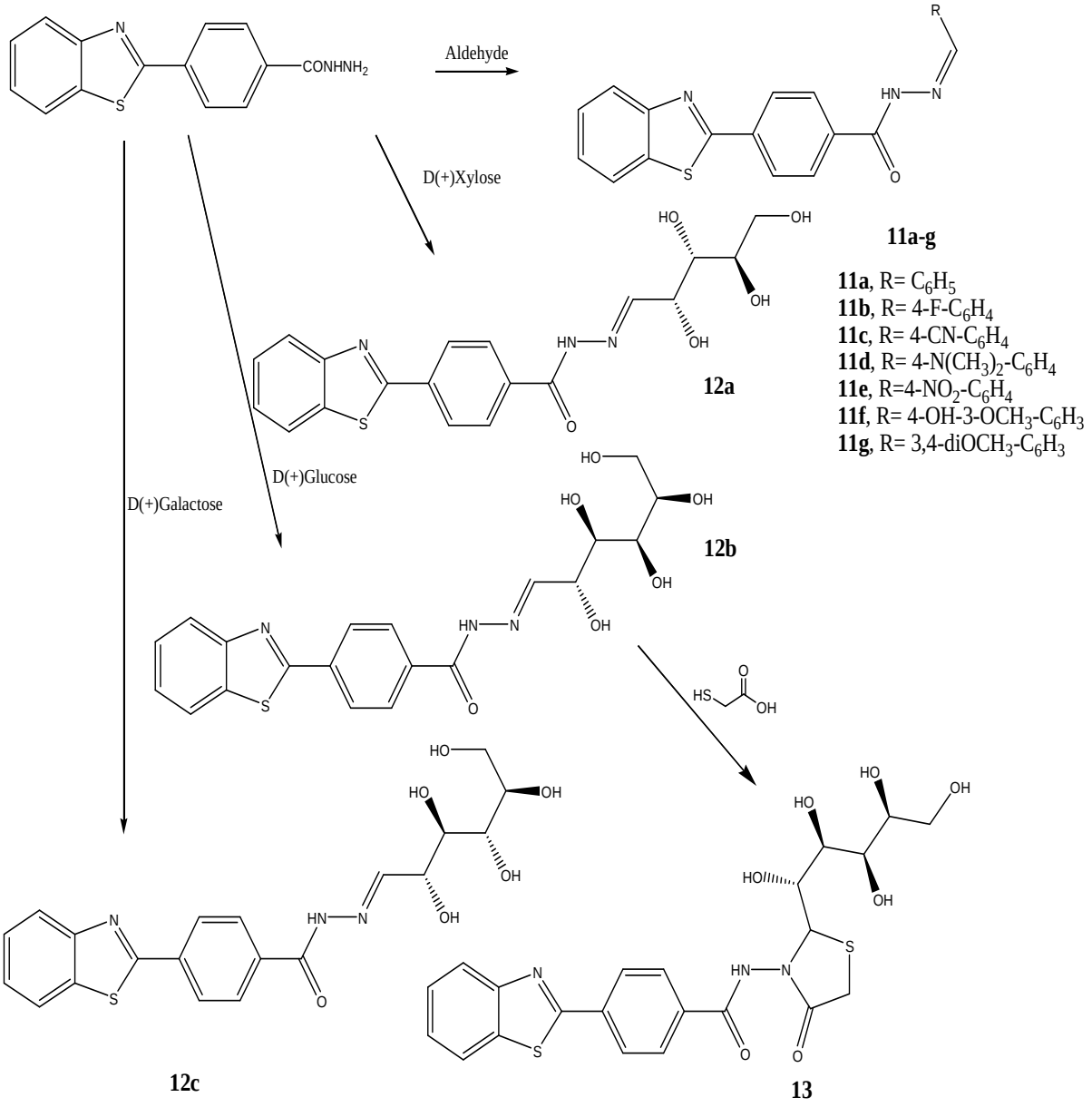
Chemistry:

2-(4-Cyanophenyl)benzo[d]thiazole **2** was prepared from reacting o-aminothiophenol **1** with 4-cyanobenzaldehyde in absolute ethanol according to reported procedure[(3)]. Acid oxidation of carbonitrile group by stirring with 70% sulfuric acid to give 4-(benzo[d]thiazol-2-yl) benzoic acid **3** followed by esterification and reacting with hydrazine hydrate to form the corresponding 4-(benzo[d]thiazol-2-yl)benzohydrazide **5**.

Reacting **5** with benzoyl chloride or 4'-methylbenzoyl chloride, few drops of triethylamine in 10 ml dry benzene was then added to form the following products: benzoic acid-N'-(4-benzothiazol-2-yl-benzoyl)hydrazide **6a** and 4-methylbenzoic acid-N'-(4-benzothiazol-2-yl-benzoyl)hydrazide **6b**, in addition, stirring benzohydrazide **5** with sulfonyl chloride, toluene sulfonyl chloride or camphor-10-sulfonyl chloride in dry acetone and triethylamine, yielded the following compounds 4-(benzo[d]thiazol-2-yl)-N-sulfonylbenzene-benzo-hydrazide **7a**, 4-(benzo[d]thiazol-2-yl)-N-tosyl-benzohydrazide **7b** and 4-(benzo[d]thiazol-2-yl)-N-camphorsulfonylbenzohydrazide **7c**, respectively.


NH2
SH
OHC
CN
1
2
70% H2SO4
COOH
3
H2SO4
EtOH
COOC2H5
4
NH2NH2
CONHNH2
5
R'PhCOCl
PhNCX
6a-b
6a, R= H
6b, R=CH3
R'PhSO2Cl
8a-b
R'= Cl, H
X= O, S
NaOH
7a-b
7a, R= H
7b, R=CH3
R''Y
Y= I, Br
R'= Cl, H
X= O, S
9a-b
7c
10a-c
10a, R''=CH3
10b, R''=COOCH3
10c, R''=CH2CH2COOC2H5

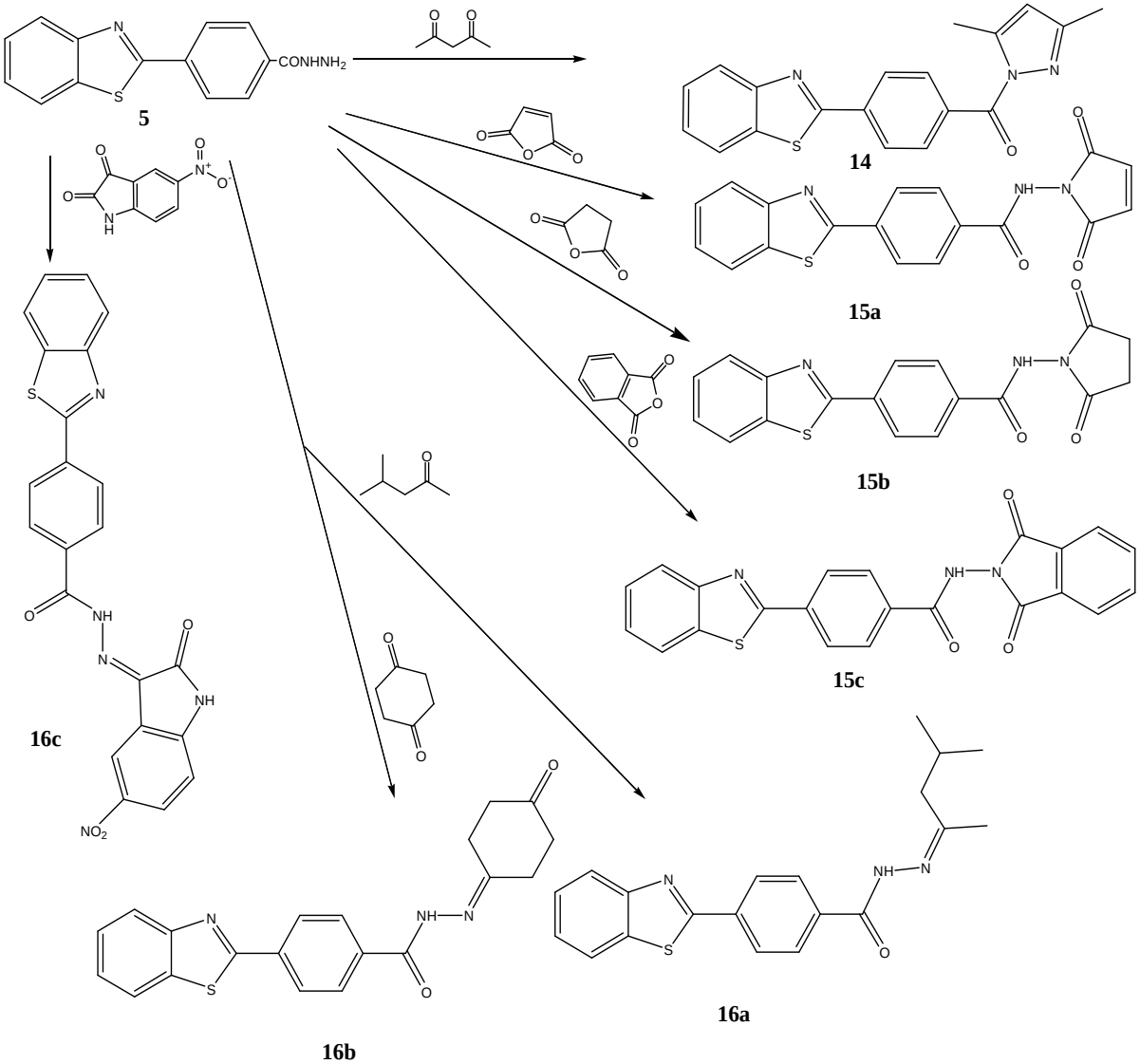
Scheme 1



Scheme 2

Compounds **8a-b** were synthesized via the reaction of benzohydrazide **5** with arylisothiocyanate or 4'-chloroarylisocyanate in dry benzene followed by refluxing the mixture of compound **8a** or **8b** and sodium hydroxide for 4hrs., afforded the corresponding compounds 5-[4-(benzo[d] thiazol-2-yl)phenyl]-4-phenyl-2H-1,2,4-triazol-3(4H)thione **9a** and 5-[4-(benzo[d]thiazol-2-yl)phenyl]-4-(4-chlorophenyl)-2H-1,2,4-triazol-3(4H)one **9b**, respectively. Condensing **9b** with the required alkylhalide (methyliodide / ethylchloroformate or ethyl-3-bromopropanoate) in the presence of anhydrous sodium carbonate as acid halide abstract and acetone as solvent. The products **10a-c** were obtained mostly in pure state (***Scheme 1***). In addition, benzohydrazide **5** was refluxed with the appropriate aromatic aldehydes (benzaldehyde / 4-fluorobenzaldehyde / 4-cyanobenzaldehyde / 4-dimethyl aminobenzaldehyde / 4-nitrobenzaldehyde / 4-hydroxy-3-methoxybenzaldehyde or 3,4-dimethoxybenzaldehyde) in the presence of ethanol and few drops of glacial acetic acid to give the corresponding N'-(substituted-benzylidene)-4-(benzo[d]thiazol-2-yl)benzo-hydrazides **11a-g**. Also, refluxing compound **5** with the appropriate sugar [D(+)xylose, D(+)glucose or D(+)galactose] yielded the following products: 4-(benzo[d]thiazol-2-yl)-N'[(2R,3S,4R)-2,3,4,5-tetrahyroxypentylidenebenzo- hydrazide **12a**, 4-(benzo[d]thiazol-2-

yl)-N'[(2R,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexylidene] benzohydrazide **12b** and 4-(benzo[d]thiazol-2-yl)-N'[(2R,3R,4S,5R)-2,3,4,5,6-pentahydroxyhexylidene]benzohydrazide **12c**, respectively. Compound **13** was prepared via the reaction of compound **12b** and mercaptoacetic acid in dry benzene (***Scheme 2***). {[4-(Benzo[d]thiazol-2-yl) phenyl]-3,5-dimethyl-1H-pyrazol-1-yl}methanone **14** was synthesized through refluxing benzohydrazide **5** with acetylacetone in ethanol. Products **15a-c** formed via the reaction of benzohydrazide **5** with the appropriate acid anhydride (maleic anhydride / succinic anhydride or phthalic anhydride). 4-(Benzo[d]thiazol-2-yl)-N-(4-methylpentan-2-ylidene)benzohydrazide **16a**, 4-(benzo[d]thiazol-2-yl)-N-(4-oxocyclohexylidene)benzohydrazide **16b** and 4-(benzo[d]thiazol-2-yl)-N-(5-nitro-2-oxoindolin-3-ylidene)benzohydrazide **16c** were prepared through the reaction of benzohydrazide **5** with the following reagents: 4-methylpentan-2-one, cyclohexane-1,4-dione or 5-nitroisatin, respectively (***Scheme 3***).



Scheme 3

In *Vitro* Antitumor Activity:

Measurement of potential cytotoxicty by SRB assay:

Some of the newly synthesized compounds have been evaluated for their potential cytotoxicity testing against breast cancer (MCF7) using the method of Skehan et al.[44]. Cells were plated in 96-multiwell plate (10^4 cell/well) for 24hrs before treatment with the compounds to allow

attachment of cell to the wall of the plate. Different concentration of the compound 0, 5, 12.5, 25 and 50 µg/ml were added to the cell monolayer triplicate wells were prepared for each individual dose and left to attach to the plates for 24 hrs. After 24 hrs, cells were incubated with the appropriate concentration ranges of drugs, completed to total of 200 µl volume/well using fresh medium and incubation was continued for 24, 48 and 72 hrs. Control cells were treated with vehicle alone. For each drug concentration, 4 wells were used. Following 24, 48 and 72 hrs treatment, the cells were fixed with 50 µl cold 50 % trichloroacetic acid for 1 hr at 4 ^{0}C. Wells were washed 5 times with distilled water and stained for 30 min at room temperature with 50 µl 0.4 % SRB dissolved in 1 % acetic acid. The wells were then washed 4 times with 1 % acetic acid.The plates were air-dried and the dye was solubilized with 100 µl/well of 10 mM tris base (ph 10.5) for 5 min on a shaker at 1600rpm. The optical density (O.D.) of each well was measured spectrophotometrically at 564nm with an ELISA micro plate reader. The mean background absorbances was automatically subtracted and mean values of each drug concentration was calculated. The relation between surviving fraction and drug concentration is plotted to get the survival curve of each tumor cell line for the specified compound. The IC_{50} percent control of infected and uninfected response values were calculated for the various active compounds were reported in Table 1.

Table 1: IC_{50} (µg/ml) of some selected new compounds against Breast cancer cell line (MCF7)

Compound	IC_{50} (µg/ml)
DOX	4.5
7c	15
9b	12
10a	19.5
12a	7.05
12b	13.2
11e	17
14	21.2
15a	23.1
16a	18.3

Doxirubsin (DOX) was used as positive standard. Compounds having IC_{50} less than 15 are considered potentially active and exposed to further in *vivo* studies.

The results obtained in table 1 show that compounds **12a**, **9b** and **12b** possess high significant effect against breast cancer cell line (MCF7) and this is might be due to the presence of D(+)xylose, 1,2,4-triazole or D(+)glucose attached to 4-(benzo[d]thiazol-2-yl)benzohydrazide moiety. The other compounds show less effect against breast cancer cell line.

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