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Synthesis of Thioxoquinazolin-4(3*H*)-one Derivatives Under Microwave and Ultrasonic Irradiation with Classical Heating

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A series of thioxoquinazolin-4(3*H*)-one derivatives have been synthesized from hydrazide derivatives **1a-f** using different electrophilic reagent, *e.g.*, aryl isothiocyanate derivatives, carbon disulfide and aromatic aldehydes through nucleophilic substitution, condensation and cyclization reactions. Different methods were used to prepare compounds **2-6**, including microwave irradiation, ultrasonic and classical heating. The compounds were characterized using various spectroscopic techniques. The synthesized compounds exhibited antibacterial activity.

Key Words: Thioxoquinazolin-4(3*H*)-one, Sonication, Microwave.

INTRODUCTION

Quinazolinone derivatives have been reported to show a variety of biological properties, such as antimicrobial[1-6], anticonvulsant[7-10], antitumor[11-16], anticoccidial[17], antidepressant[18], antihistaminic[19,20], antiinflammatory[21-24] and antiviral[25,26] activities. Febrifugine and its analogue have been used as an anti malarial treatment[27-29]. In addition, many thioxoquinazolin-4(3*H*)-one derivatives exhibit a considerable variety of activities, such as anticonvulsant[30], anticancer[31,32], antiulcer[33] and antiinflammatory and have been used as therapeutic agents for neuro-protection[34]. Some novel thioxoquinazolinone derivatives have been synthesized using three different methods *i.e.*, conventional synthesis, ultrasonic and microwave irradiation. The structures of these compounds were firmly established by well-defined IR, ^{1}H NMR, ^{13}C NMR, 2D NMR and ESI-MS spectroscopies. These compounds were then examined for antibacterial properties.

EXPERIMENTAL

The melting points (m.p.) were determined using an Electrothermal IA900 digital capillary melting point apparatus. The IR spectra were recorded in KBr discs on a Perkin Elmer 1000 FT-IR spectrophotometer (ν_{max} in cm^{-1}). The ^{1}H NMR, ^{13}C NMR spectra and 2D NMR spectra were collected in DMSO-d_6 or ($CDCl_3$) using a JEOL-ECP-400 and on Bruker 600 MHz spectrometer. The chemical shifts were reported as parts per million (δ ppm) and the coupling constants (J) are given in Hz, tetramethyl silane (TMS) was used as an internal standard. The mass spectra (m/z, %) were obtained on an electro spray ionization (positive mode) LCMS, LCMS-MS and UPLC-MS/MS. The ultrasonic irradiation was performed in a J.P. Selecta with a frequency of 50/60 Hz and a nominal power of 770 W. The microwave experiments were performed in a 1000 W domestic microwave oven. The purity of all compounds was checked by TLC using glass plates coated with silica gel (G) and chloroform/methanol (9:1) as a solvent system. A UV lamp was used as a developing agent. Column chromatography: silica gel (70-230 mesh, Merck). Spectral data (IR, NMR, ^{1}H-^{13}C-COSY (HETCOR), DEPT 135 and mass spectra) confirmed the structures of the synthesized compounds.

The components were synthesized using three different methods: (A) Conventional synthesis, (B) ultrasonic synthesis and (C) microwave irradiation.

2-{[(6- or 7-Substituted-3-(4-substituted phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl) thio]acetyl}-N-(4-substituted phenyl)-hydrazinecarbothioamide (2a-c)

Method A for synthesis of (2a-c): An equimolar amount of compound **1a**, **1b** or **1e** (0.0008 mol) and aryl isothiocyanate derivatives in absolute ethanol (3 mL) comprised the reaction mixture, which was heated under reflux for 1 h. At the end of the reaction (monitored by TLC), the obtained solid was filtered and washed with ethanol. The solid product was pure and did not require recrystallization.

Method B for synthesis of (2a-c): Equimolar amounts of compound **1a**, **1b** or **1e** (0.0008 mol) and aryl isothiocyanate derivatives in absolute ethanol (3 mL) were placed into a 25 mL conical flask, which was then mixed and irradiated in the water bath of an ultrasonic cleaner at 80 ºC for 15 min (TLC). The solid product was pure and did not require recrystallization.

Method C for synthesis of (2a-c): A few drops of absolute ethanol were added to an equimolar amount of compound **1a** or **1e** (0.0002 mol) and aryl isothiocyanate derivatives. Then, the reaction mixture was irradiated in a domestic microwave oven for 5 min (TLC) at a power of 300 W. The solid product was pure and did not require recrystallization.

***N*-Phenyl-2-({[3-(4-methylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]thio}acetyl)hydrazinecarbothioamide (2a):** White fine scales, m.p. 218 ºC, yield (%) 86[A] 72[B] 36[C]; IR (KBr, ν_{max}, cm^{-1}): 3317, 3278, 3180 (NH), 1687 (C=O_{lactam}), 1659 (C=O_{amide}), 1464 (C=S); ^{1}H NMR (DMSO-d_6): 2.42 (3H, s, CH_3), 4.01 (2H, s, CH_2-S-), 7.16 (1H, t, ^3J = 7.4, H-4'), 7.29-7.41 (8H, m, H-2', 3', 5', 6', 2", 3", 5", 6"), 7.47 (1H, t, ^3J = 8.1, H-6), 7.65 (1H, d, ^3J = 8.1, H-8), 7.80 (1H, t, ^3J = 8.1, H-7), 8.08 (1H, d, ^3J = 8.1, H-5), 9.53, 9.74, 10.37 (3H, br, s. NH groups); ^{13}C NMR spectral data of **2a** were confirmed by 2D NMR ^{1}H-^{13}C-COSY (HETCOR) and DEPT 135 experiments: 20.9 (CH_3), 35.0 (CH_2), 126.2 (C-6), 126.3 (C-8), 126.6 (C-5), 128.1(C-4"), 134.9 (C-7), 157.1 (C=O_{lactam}), 160.8 (C-2), 166.9 (C=O_{amide}), 180.7 (C=S), 119.5, 126.1 (2C), 129.1(2C), 129.2 (2C), 130.1(2C), 133.1, 138.9, 139.8, 147.1 (sp^2 carbons); MS: m/z (%) 476 (13) $[M + H]^+$ ($C_{24}H_{21}N_5O_2S_2$+H), 309 (100) [M+H-$C_7H_8N_3S$-H], 269 (33) [M+H-$C_9H_{10}N_3OS$+H], 208 (24) $[C_9H_{10}N_3OS]^+$, 190 (9) [208-OH-H].

2-{[(7-Chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio]acetyl}-N-4-methylhydrazinecarbothioamide (2b): white fine scales, m.p. 205 ºC, yield (%) 88[A] 54[B], IR (KBr, ν_{max}, cm^{-1}): 3314, 3209, 3115 (NH), 1701 (C=O_{lactam}), 1660 (C=O_{amide}), 1468 (C=S); ^{1}H NMR (DMSO-d_6): 2.28 (3H, s, CH_3), 3.95 (2H, s, CH_2-S-), 7.09-7.20 (4H, m, H-2', 6', 3", 5), 7.48-7.62 (6H, m, H-6, 3', 4', 5', 2", 6"), 7.76 (1H, s, H-8), 8.06 (1H, d, ^3J = 8.8, H-5), 9.44, 9.74, 10.29 (3H, br, s. NH groups); ^{13}C NMR: 20.6 (CH_3), 34.9 (CH_2), 118.4, 125.7, 125.9, 126.3 (2C), 128.6 (2C), 129.4 (2C), 129.7 (2C), 130.2, 134.5, 135.5, 136.3, 139.4, 148.1, 158.8 (C=O_{lactam}), 160.1 (C-2), 166.9 (C=O_{amide}), 180.8 (C=S) [one carbon with the baseline] (sp^2 carbons); MS: m/z (%) 510 (9) $[M + H]^+$ ($C_{24}H_{20}{}^{35}ClN_5O_2S_2$+H), 511 (8) [M+2] ($C_{24}H_{20}{}^{37}ClN_5O_2S_2$), 329 (100) [M+H-$C_8H_{10}N_3$ S-H], 289 (11) [M+H-$C_{10}H_{12}N_3OS$+H], 222 (47) $[C_{10}H_{12}N_3OS]^+$, 204 (13) [222-OH-H].

2-{[(6-Bromo-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio]acetyl}-N-4-methoxyhydrazinecarbothioamide (2c): White bowder, m.p. 204 ºC, yield (%) 99[A] 76[B] 93[C], IR (KBr, ν_{max}, cm^{-1}): 3316, 3243, 3147 (NH), 1699 (C=O_{lactam}), 1654 (C=O_{amide}), 1469 (C=S); ^{1}H NMR (DMSO-d_6): 3.74 (3H, s, OCH_3), 3.98 (2H, s, CH_2-S-), 6.87 (2H, d, ^3J = 8.8, H-3",5", XX' part of AA'XX' system), 7.18 (2H, d, ^3J = 7.7, H-2', 6', AA' part of AA'XX' system), 7.48-7.61 (6H, m, H-8, 3', 4', 5', 2", 6"), 7.94 (1H, d, ^3J = 8.8,H-7), 8.14 (1H, d, ^4J = 1.8, H-5), 9.38, 9.64, 10.29 (3H, br, s. NH groups); ^{13}C NMR: 35.1 (CH_2), 55.3 (OCH_3), 113.4, 118.3, 121.2 (2C), 127.4, 127.7, 128.6, 128.8, 129.4 (2C), 129.8 (2C), 130.3, 131.8 (2C), 135.6, 137.7, 146.2, 157.9 (C=O_{lactam}), 159.7 (C-2), 166.9 (C=O_{amide}), 181.1 (C=S) (sp^2 carbons); MS: m/z (%) 570 (9) $[M+H]^+$ ($C_{24}H_{20}{}^{79}BrN_5O_3S_2$+H), 572 (10) [M+2] ($C_{24}H_{20}{}^{81}BrN_5O_3S_2$+H), 373 (99) [M+H-$C_8H_{10}N_3OS$-H], 333 (11) [M+H-$C_{10}H_{12}N_3O_2S$+H], 238 (100) $[C_{10}H_{12}N_3O_2S]^+$, 220 (25) [238-OH-H].

6-Bromo-3-phenyl-2-{[4-(4-methoxyphenyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]thio}quinazolin-4(3*H*)-one (3)

Method A for synthesis of (3): Synthesis was conducted according to the procedures in the literature[35-37].

Method B for synthesis of (3): A solution of compound **2c** (0.1 g, 0.0002 mol) in a sodium hydroxide solution (4 %) was placed into a 25 mL conical flask, mixed and irradiated in the water bath of an ultrasonic cleaner at 80 ºC for 1.5 h. The mixture was cooled, filtered and acidified with hydrochloric acid (37 %) to a pH of 5-7. The resulting solid was filtered, washed with water and recrystallized from ethanol. A yellowish white powder was obtained; m.p. 280 ºC, yield (%) 99[A] 22[B], IR (KBr, ν_{max}, cm^{-1}): 3306 (NH), 1659 (C=O), 1249 (C=S); ^{1}H NMR ($CDCl_3$:DMSO-d_6): 3.88 (2H, s, CH_2-S-), 3.90 (3H, s, OCH_3), 7.11(1H, d, ^3J = 8.4, H-8), (2H, d, ^3J = 8.4, H-3',5', XX' part of AA'XX' system), 7.27 (2H, d, ^3J = 7.5, H-3",5", XX' part of AA'XX' system), 7.36 (1H, d, ^3J = 8.4, H-7), 7.45 (1H, t, ^3J = 8.4, H-4'), 7.52 (2H, d, ^3J = 7.5, H-2", 6", AA' part of AA'XX' system), 7.69 (2H, d, ^3J = 8.4, H-2', 6', AA' part of AA'XX' system), 8.12 (1H, d, ^4J = 1.8, H-5), 10.87 (1H, br, s, NH); ^{13}C NMR spectral data of **3** were confirmed by 2D NMR ^{1}H-^{13}C-COSY (HETCOR) and DEPT 135 experiments: 29.5 (CH_2), 55.5 (OCH_3), 115.2 (C-8), 117.6 (2C-3', 5'), 128.4 (2C-3", 5"), 128.6 (C-4'), 129.2 (2C-2", 6"), 130.0 (C-5), 130.2 (C-7), 137 (2C-2', 6'), 161.6 (C=O_{lactam}), 165.4 (C-2), 169.5 (C=S), 116.1, 134.9, 138.8, 140.8, 147.4, 150.5, 160.4 (sp^2 carbons). MS: m/z (%) 552 (39) $[M+H]^+$ ($C_{24}H_{18}{}^{79}BrN_5O_2S_2$+H), 553 (8) [M+2] ($C_{24}H_{18}{}^{81}BrN_5O_2S_2$+H), 521 (6) [M+H-$OCH_3$], 507 (76) [M+H-CS-H], 463 (20) [M+H-NC_6H_5+2H], 445 (9) [M+H-$OCH_3C_6H_4$].

Synthesis of potassium-2-({[6 or 7-substituted 3-(4-substituted phenyl)-4-oxo-3,4-dihydroquinaazolin-2-yl]thio}-acetyl)hydrazinecarbodithioate (4a-b): Synthesis was conducted according to the procedures in the literature[38]. Note that **4** was not detected in this reaction pathway.

2-{[(4-Amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]thio} 6- or 7-substituted 3-(4-substituted phenyl)-quinazolin-4(3*H*)-one (5a-b)

Method A for synthesis of (5a-b): A mixture of the potassium salt **4a** or **4b** (0.0002 mol), hydrazine hydrate 99 % (0.3 mL) and water (1 mL) was heated under reflux for 1 h, diluted with (3 mL) cold water, neutralized with hydrochloric acid (37 %) to a pH of 5-7 and then filtered. The solid was washed with water and purified by silica gel column chromatography (70-230 mesh) using chloroform/ethanol (9:1) as the eluent to yield the pure product (**5a-b**).

Method B for synthesis of (5a-b): A suspension of the potassium salt of **4a** or **4b** (0.0006 mol), hydrazine hydrate 99 % (0.3 mL) and water (9 mL) in a 25 mL conical flask was mixed and irradiated in the water bath of an ultrasonic cleaner

at 80 ºC for 45 min, diluted with (3 mL) cold water, neutralized with hydrochloric acid (37 %) to a pH of 5-7 and filtered. The solid was washed with water and recrystallized from ethanol (**5b**) or purified by column chromatography using chloroform/ethanol (9:1) as the eluent (**5a-b**).

2-{[(4-Amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]thio}-7-chloro-3-(4-methoxyphenyl)quinazolin-4(3*H*)-one (5a): White powder, m.p. 240 ºC, yield (%) 56[A] 62[B], IR (KBr, ν_{max}, cm^{-1}): 3349 (NH), 3301, 3181 (NH_2), 1690 (C=O), 1461 (C=S); ^{1}H NMR (DMSO-d_6): 3.84 (1H, s, OCH_3), 3.97 (1H, s, CH_2),4.31 (2H, br, s, NH_2), 7.11 (2H, d, ^3J = 8.8, H-3',5', XX' part of AA'XX' system), 7. 38 (2H, d, ^3J = 8.8, H-2', 6', AA' part of AA'XX' system), 7.47-7.61 (2H, m, H-5, 8), 8.06 (1H, dd, ^3J = 8.4, ^4J = 2.6, H-6), 10.31 (1H, br, s, NH); ^{13}C NMR: 34.6 (CH_2), 54.7 (OCH_3), 113.9 (2C), 117.6, 124.2, 125.2, 125.3, 128.0, 129.7 (2C), 138.5, 147.3, 150.5, 155.6, 159.5, (C=O_{lactam}), 162.4 (C-2), 167.8 (C=S) (sp^2 carbons).

2-{[(4-Amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]thio}-6-bromo-3-(4-methylphenylphenyl) quinazolin-4(3*H*)-one (5b): Pale gray powder, m.p. 195 ºC, (from ethanol); yield (%) 50[A], 59[B], IR (KBr, ν_{max}, cm^{-1}): 3349 (NH), 3301, 3181 (NH_2), 1690 (C=O), 1461 (C=S); ^{1}H NMR ($CDCl_3$:DMSO-d_6): 2.46 (1H, s, CH_3), 3.82 (1H, s, CH_2), 4.09 (2H, br, s, NH_2), 7.23 (2H, d, ^3J = 8.1, H-3',5', XX' part of AA'XX' system), 7.36 (2H, d, ^3J = 8.1, H-2', 6', AA' part of AA'XX' system), 7.56 (1H, d, ^3J = 9, H-8), 7.83 (1H, dd, ^3J = 9, ^4J = 2.4, H-7),8.24 (1H, d, ^4J = 2.4, H-5), 9.81 (1H, br, s, NH); ^{13}C NMR spectral data of **5b** were confirmed by 2D NMR ^{1}H-^{13}C-COSY (HETCOR) and DEPT 135 experiments: 21.2 (CH_3), 34.4 (CH_2), 128.2 (C-8), 128.7 (2C-3', 5'), 129.1 (C-5), 130.2 (2C-2', 6'), 137.5 (C-7), 157.7 (C=O_{lactam}), 160.1 (C-2), 167.4 (C=S), 118.6, 121.1, 132,5, 140.2, 146.2 [one carbon with the baseline] (sp^2 carbons).

2-[(6 or 7-Substituted (4-substituted phenyl)-4-oxo-3,4-dihydrequinazolin-2-yl)thio]-N'-(3,4 substituted benzylidene)-acetohydrazide (6a-d)

Method A for synthesis of (6a-c): Equimolar quantities of hydrazide **1b** or **1e** or **1f** and the substities aldehydes (0.0002 mol) were refluxed in absolute ethanol for 2 h (TLC), the reactions were filtered and the products were dried and recrystallized from benzene.

Method B for synthesis of (6a,c-d): A solution of the hydrazides **1b**, **1e** or **1g** and the substituted aldehyde (0.0002 mol) in absolute ethanol was irradiated in the water bath of an ultrasonic cleaner for 15-45 min (TLC). The reactions were filtered and the products were dried and recrystallized from benzene.

Method C for synthesis of (6c-d): A few drops of absolute ethanol were added to an equimolar amount of hydrazide **1e** or **1g** and the substituted aldehyde (0.0002 mol). This solution was irradiated in a microwave for 5-15 min (TLC). The solid product was treated with ethanol, filtered, dried and recrystallized from benzene.

2-[(7-Chloro-3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]-N'-(3,4-dimethoxybenzylidene)acetohydrazide (6a): Beige scales, m.p. 269 ºC, yield (%) 83[A], 36[B], IR (KBr, ν_{max}, cm^{-1}): 3167(NH), 1678 (C=O_{lactam}), 1656 (C=O_{amide}); MS: m/z (%) 509 (7) $[M+H]^+$ ($C_{25}H_{21}{}^{35}ClN_4O_4S$+H), 510 (3) [M+2] ($C_{25}H_{21}{}^{37}ClN_4O_4S$), 329 (100) [M+H-$C_9H_{11}N_2O_2$-H], 301 (5) [329-CO], 180 (4) [M+H-$C_{16}H_{10}{}^{35}ClN_2O_2S$+H].

2-[(7-Chloro-3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]-N'-(4-nitrobenzylidene)acetohydraazide (6b): Yellowish white fine needles, m.p. 240 ºC, yield (%) 77[A], IR (KBr, ν_{max}, cm^{-1}): 3126 (NH), 1689 (C=O_{lactam}), 1666 (C=O_{amide}); ^{1}H NMR ($CDCl_3$:DMSO-d_6): 448 (1H, s, CH_2), 7.38-7.47 (3H, m, H-3', 4', 5'), 7.47 (1H, d, ^4J = 1.8, H-8), 7.59-7.60 (3H, m, H-6, 2', 6'), 7.92 (2H, d, ^3J = 8.4, H-2", 6", XX' part of AA'XX' system), 8.08 (2H, d, ^3J = 8.4, H-5), 8.16 (1H, s, =CH), 8.25 (2H, d, ^3J = 8.4, H-3", 5", XX' part of AA'XX' system),11.93 (1H, br, s, NH); ^{13}C NMR spectral data of **6b** were confirmed by 2D-NMR ^{1}H-^{13}C-COSY (HETCOR) and DEPT 135 experiments: 34.1 (CH_2), 123.2 (2C-3", 5"), 125.1 (C-8), 125.8 (C-4'), 127.3 (2C-2",6"), 128.2 (C-5), 128.8 (2C-3', 5'), 129.3 (2C-2', 6'), 129.7 (C-6), 160.1 (C=O_{lactam}), 164.1 (C-2), 168.9 (C=O_{amide}), 117.9, 135.1, 140.1, 145.5, 147.9, 158.3 (sp^2 carbons); MS: m/z (%) 494 (4) $[M+H]^+$ ($C_{23}H_{16}{}^{35}ClN_5O_4S$+H), 495 (2) [M+2] ($C_{23}H_{16}{}^{37}ClN_5O_4S$), 329 (100) [M+H-$C_7H_6N_3O_2$-H], 301 (10) [329-CO], 128 (3 %) [301-Ph-N=C=O], 166 (4) [M+H-$C_{16}H_{10}{}^{35}ClN_2O_2S$+H].

N'-(4-Bromobenzylidene)-2-[(6-bromo-3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl) thio]acetohydrazide (6c): White scales, m.p. 257 ºC, yield (%) 99[A], 75[B], 99[C], IR (KBr, ν_{max}, cm^{-1}): 3180 (NH), 1696 (C=O_{lactam}), 1673 (C=O_{amide}); MS: m/z 571 (7) $[M + H]^+$ ($C_{23}H_{16}{}^{79}Br_2N_4O_2S$+H), 573 (16) [M+2] ($C_{23}H_{16}{}^{79,81}Br_2N_4O_2S$+H), 575 (7) [M+4] ($C_{23}H_{16}{}^{81}BrN_4O_2S$+H), 373 (100) [M+H-$C_7H_6{}^{79}BrN_2$], 345 (15) [373-CO], 210 (13) [M+H-$C_9H_8{}^{79}BrN_2O$-Ph-N=C=O-2H].

2-[(6-Iodo-(4-methoxyphenyl)-4-oxo-3,4-dihydro-quinazolin-2-yl)thio]-N'-(4-nitrobenzylidene)aceto-hydrazide (6d): White scales, m.p. 264 ºC, yield (%) 84[A], 71[B], 99[C], IR (KBr, ν_{max}, cm^{-1}): 3178 (NH), 1680 (C=O_{lactam}), 1680 (C=O_{amide}); MS: m/z (%) 616 (24) $[M+H]^+$ ($C_{24}H_{18}IN_5O_5S$+H), 451 (100) [M+H-$C_7H_6N_3O_2$-H], 423 (2) [451-CO].

Antibacterial activity: The *in vitro* antibacterial activity of some compounds was determined using the cup-plate diffusion method[39]. The nearest zone of inhibition was measured in mm. The concentration (100 µg/mL) of the test compounds was adjusted by dissolving the compounds in dimethyl sulfoxide. The antibiotic gentamycin was used as a standard (100 µg/mL) antibacterial agent. The antibacterial activity was screened against two gram-negative bacteria (*Escherichia coli* ATCC25922 and *Pseudomonas aeruginosa* ATCC27853) and two gram-positive bacteria (*Bacillus subtilis* ATCC6633 and *Staphylococcus aureus* ATCC25923), the bacterial cultures were adjusted to 0.5 McFarland turbidity standard.

RESULTS AND DISCUSSION

The condensation of the hydrazide derivative **1a,b,e** with aryl isothiocyanate derivatives resulted in the formation of **2a-c**. Different methods were used to prepare **2a-c**, in good yield, including the traditional methods, microwave and ultrasound irradiation methodologies. The structures of **2a-c** were assigned on the basis of the spectroscopic analyses. The IR spectrum of compound **2a** exhibited bands at 3317, 3278 and 3180 cm^{-1} due to NH stretching and the lactam C=O stretching of the quinazolinone ring and amide C=O stretching

were observed at 1686 and 1659 cm^{-1}, respectively. The ^1H NMR spectrum of **2a** exhibited a singlet at δ 2.42 ppm, which corresponded to the methyl protons and a singlet at δ 4.01 ppm, which corresponded to the methylene group. A triplet signal was also observed at δ 7.15 ppm (J = 7.4 Hz), which was assigned to H-4'. This spectrum also displayed a multiplet signal at δ 7.29-7.41 ppm, which integrated to eight protons and was assigned to protons C-2', 3', 5', 6', 2", 3", 5" and 6-H, whereas the doublet signal at δ 7.47 ppm (J = 8.1 Hz) was assigned to H-6. Two doublet signals were observed at δ 7.65 ppm and δ 8.08 ppm (J = 8.1 Hz), which were assigned to the protons at positions 8 and 5, respectively (**Scheme-I**) and the doublet signal at δ 7.80 ppm (J = 8.1 Hz) was assigned to H-7. Furthermore, the presence of singlet signals at δ 9.53, 9.74 and 10.34 ppm, which are exchangeable with D_2O, were assigned to the NH groups. The ^{13}C NMR spectrum of **2a** displayed signals at δ 20.9 ppm for the methyl carbon, 35.0 ppm for the methylene group carbon, 126.2 ppm for C-6, 126.3 ppm for C-8, 126.6 ppm for C-5, 134.9 ppm for C-7, 128.3 ppm for C-4", 157.1 ppm for (C=O lactam), 160.8 ppm for C-2, 166.9 ppm for (C=O amide), 180.7 ppm for (C=S) and 9 lines at δ 119.5, 133.1, 138.9, 139.8, 147.1, 126.1 (2C), 129.1 (2C), 129.2 (2C), 130.1 (2C) for other aromatic carbons. The assignment of all protons and carbons in **2a** were verified by the analysis with DEPT and ^1H-^{13}C Cosy techniques. The mass spectrum of **2a** exhibited a molecular ion peak $[M+H]^+$ at m/z 476 which is in agreement with its assigned structure.

Compound **2c** was used in the cyclization reaction with sodium hydroxide under reflux and produced the triazolthione **3**, which was also obtained following ultrasound irradiation under the same conditions in moderate yield. The IR spectrum of **3** exhibited an absorption band at 3306 cm^{-1} for NH group, the strong absorption at 1659 cm^{-1} is due to the (C=O lactam) stretching vibration and the absorption with strong intensity at 1249 cm^{-1} corresponds to a C=S stretching vibration.

The ^1H NMR spectrum of **3** revealed two singlet signals in the aliphatic region at δ 3.88 and δ 3.90, which were integrated for 2 and 3 protons, respectively and attributed to the CH_2 and OCH_3 groups. All other aromatic protons in this spectrum appeared at their expected chemical shifts. The ^{13}C NMR data of **3** were fully consistent with its structure. The ^{13}C chemical shift values of some carbons assigned by the 2D NMR ^1H-^{13}C-COSY(HETCOR) and DEPT 135 data are shown in Fig. 1. The mass spectrum of **3** revealed $[M+H]^+$ at m/z 552 and at m/z 553 with almost equal intensity, as expected for bromine isotopes.

The cyclisation of the potassium salts of **4a-b** with 99 % hydrazine hydrate, either using the conventional method or by ultrasoincation, under the conditions stated in (**Scheme-I**) produced the S-triazoles **5a-b** in good-moderate yields. The IR spectrum of compound **5b** exhibited absorption bands at 3241, 3263 and 3202 cm^{-1}, which were assignable to NH/NH_2, in addition to the presence of a strong absorption band at 1670 cm^{-1} due to a carbonyl group and C=S stretching frequencies at 1466 cm^{-1}. The ^1H NMR in (DMSO-d_6:$CDCl_3$) displayed **3** singlet signals at δ 2.46, 3.82 and 9.18 ppm which are characteristic of a methyl group, methylene protons and a NH proton, respectively. Although the signal from the NH_2 group appeared weak, the aromatic protons appeared as a pair of doublets at

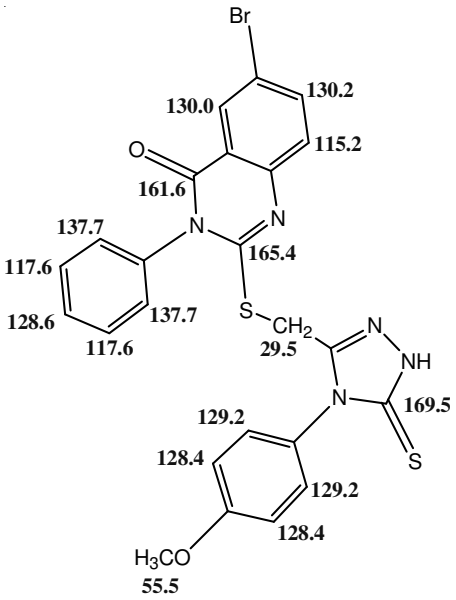


Fig. 1. Structure and ^{13}C NMR data of some carbon atoms in **3**

δ 7.23 ppm (H-3', 5') and δ 7.36 ppm (H-2', 6') with J = 8.1 Hz and the other aromatic protons in this spectrum appeared at their expected chemical shifts. Further, the ^{13}C NMR data of **5b** is fully consistent with its assigned structure (Fig. 2).

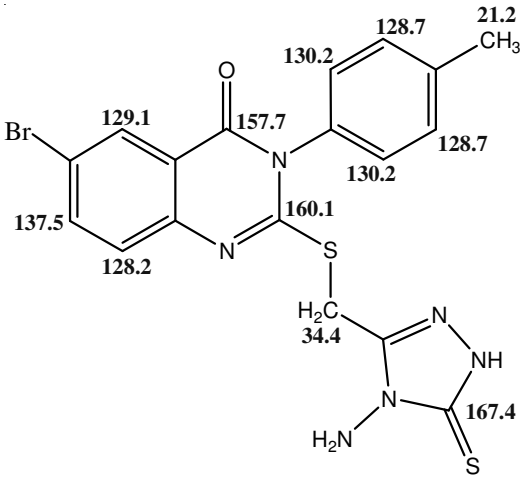
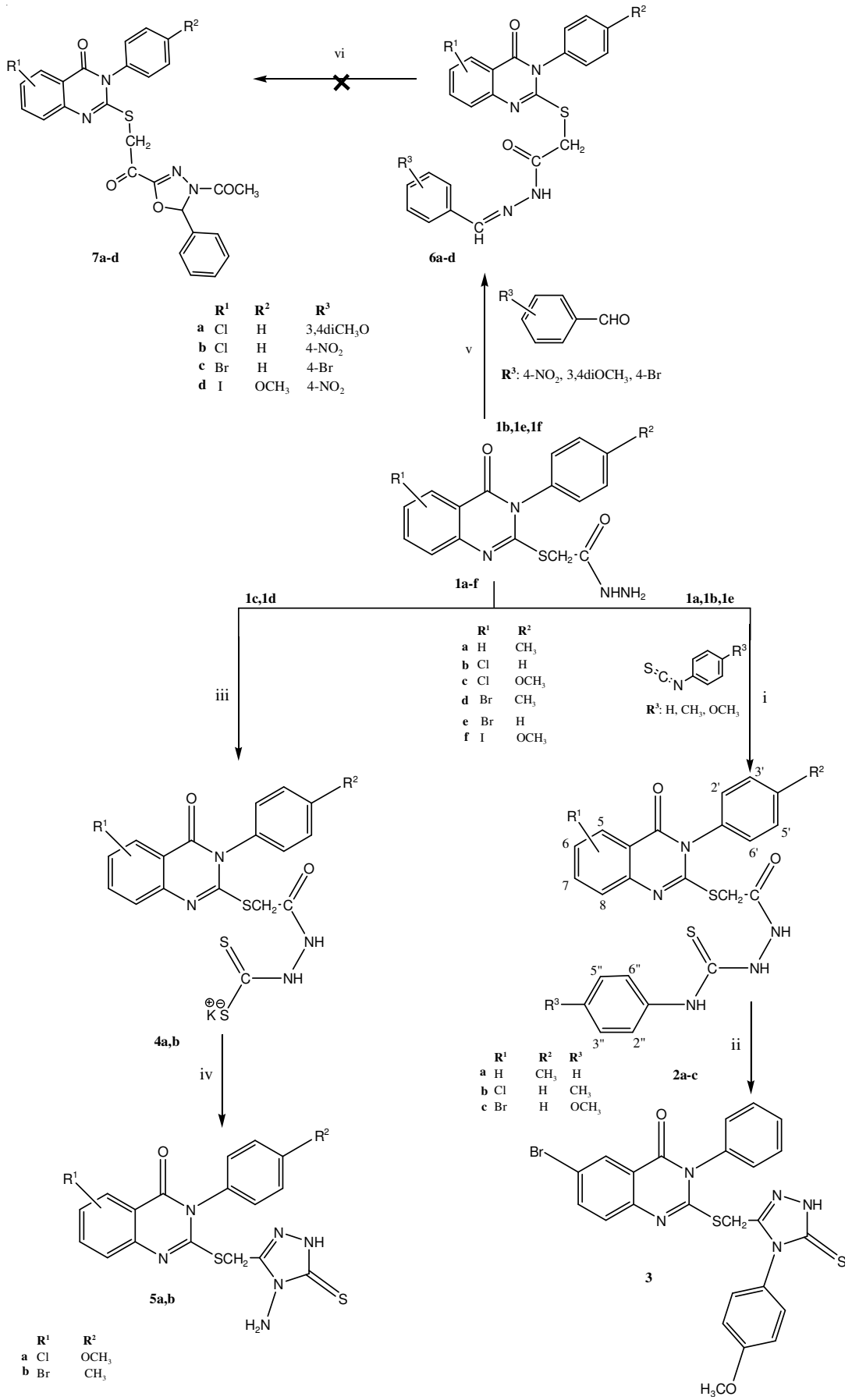


Fig. 2. ^{13}C chemical shift values some of carbons are assigned by ^1H-^{13}C-COSY and DEPT 135 data of **5b**

The hydazide derivatives **1b,e-f** easily condensed with aromatic aldehydes such as 4-bromo benzaldehyde, 3,4 dimethoxyl benzaldehyde and 4-nitro benzaldehyde under different reactions conditions, *e.g.*, microwave irradiation, ultrasonication and classical heating, to produce **6a-d** in excellent yields. The IR spectrum of **6b** exhibited absorption band at 3126 cm^{-1} for the NH group, a band at 1689 cm^{-1} due to $C=O_{(lactam)}$ and a band in the 1666 cm^{-1} region from C=O (amide) stretching. The chemical shifts of all the protons absorptions in the ^1H NMR spectrum of **6b** and the carbon signals in the ^{13}C NMR spectrum were fully consistent with its structure. The mass spectrum of compound **6b** revealed a molecular ion peak at m/z = 494 ($[M+H]^+$, 18 %) and a base peak was observed in the spectrum at m/z = 329 (100 %), which is compatible with its molecular formula of $C_{23}H_{16}{}^{35}ClN_5O_4$+H.



Scheme-I: (i) A: Absolute EtOH, reflux, 1 h (**2a-c**); B: US, 15 min (**2a-c**); C: MW, 5 min (**2a,c**). (ii) A: NaOH (4 %), HCl (37 %), reflux, 3 h; B: US, 1.5 h. (iii) KOH/absolute EtOH, CS_2, dry. ether, stirring, 14 h. (iv) A: H_2O, $N_2H_4{\cdot}H_2O$ 99 %, HCl (37 %), reflux, 1 h; B: US, 45 min. (v) A: absolute EtOH, reflux, 2 h (**6a-d**); B: US, 15-45 min (**6a,c-d**); C: MW, 5-15 min (**6c-d**). (vi) A: acetaic anhydride, reflux, 1-6 h (**7a-d**); B: US, 2 h; C: MW, 1 h

Mallikarjuna *et al*.[40] reported that refluxing a mixture of hydrazones **6a-d** and acetic anhydride afforded the oxadiazole **7a-d**, also we used microwave and ultrasonic irradiation methods, but when performing the same reaction we did not isolate **7a-d**.

Antibacterial activity: The results of the antibacterial activity are shown in (Table-1). Compounds **2a**, **2b**, **2c** and **5b** exhibited good activities against gram-positive bacterial *S. aureus* whereas compounds **3** and **5a** displayed good activity against the gram-negative bacterial *P. aeruginosa*. Compound **6b** also exhibited good activity against the gram-positive bacterial *B. asubtilis* whereas all compounds showed good to moderate activity against the gram-negative bacterial *E. coli*. All of the compounds possessed moderate to poor activities compared to gentamycin.

TABLE-1
ANTIBACTERIAL ACTIVITY AT A CONCENTRATION OF 100 µg/mL

Test organisms compound	Zone of inhibition in diameter (mm)			
	Gram-negative		Gram-positive	
	E. coli	*P. aeruginosa*	*S. aureus*	*B. asubtilis*
2a	11	14	15	9
2b	14	13	17	10
2c	14	11	15	11
3	13	16	0	12
5a	11	16	12	9
5b	11	9	15	9
6b	13	0	10	15
Gentamycin	23	36	27	34

*Diameter of well (bore size) = 5 mm.

Conclusion

The syntheses of some new thioxoquinazolin-4(3*H*)-one derivatives using microwave, ultrasonic and classical heating have been described. The structures of compounds **2-6** were confirmed through spectral data (IR, ^{1}H NMR, ^{13}C NMR, 2D NMR and ESI-MS). The results indicated that the compounds exhibited good to poor antibacterial activity.

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