Egypt. J. Chem. **Vol. 66**, No. SI: 13 pp. 1791 - 1800 (2023)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Novel Synthesis and Characterization of Azoles, Azines and Azepines Based on Cinnamoyl Thiourea Derivatives

Islam Ragab

Department of Mathematics, College of Science and Arts, Qassim University, Riyadh Al Khabra, Saudi Arabia

Abstract

(Acryloyl)thioureido)benzoic acid) derivative 3a-c was obtained by reacting cinnamoyl isothiocyanate 2a-c with 2-aminobenzoic acid 1. The cyclization of thiourea 3a-c in dry acetone yielded 2-mercapto-4-oxopyrimidine 4a-c, while in ethoxide, it led to the formation of quinoxaline 5a-c and (Z)-2-(6-(4-nitrophenyl)-4-oxo-5-phenyl-3,4-dihydro-2H-1,3-thiazin-2-ylideneamino)benzoic acid 6c. (E)-2-(3-(2,4-dichlorophenyl)acryloyl)-1-thioxo-2,2a,2a1,4a-tetrahydro-4H-3-oxa-2,9b-diazapentaleno[1,6-ab]naphthalene-4,5(1H)-dione 11a was obtained by reacting thiourea 3a with maleic anhydride. Refluxing thiourea 3a with chloroacetamide resulted in the production of (Z)-2-((4-(2,4-dichlorostyryl)-6-oxo-6,7-dihydro-1,3,5-thiadiazepin-2-yl)amino)benzoic acid 13a and 2-(((Z)-5-carbamoyl-4-((E)-2,4-dichlorostyryl)thiazolidin-2-ylidene)amino)benzoic acid 15a and its isomeric form depending on the base medium. Alkylation of thiourea 3a with ethyl bromoacetate afforded 2-(((Z)-(((E)-3-(2,4-dichlorophenyl)acryloyl)imino)((2-ethoxy-2-oxoethyl)thio)methyl)amino)benzoic acid 16a, which reacted with hydrazine hydrate to yield 12-(2,4-dichlorophenyl)-6,7a-dihydro-7H,10H-benzo[d]pyrazolo[3,4-f]pyrimido[2,1-b][1,3]thiazepine-7,10-dione 17a. Treatment of thiourea 3a with H2O2 in basic and/or acidic medium yielded (E)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)ureido)benzoic acid 18a and (E)-2-(((3-(2,4-dichlorophenyl)acrylamido)methyl)amino)benzoic acid 19a , respectively. The structures of the newly synthesized compounds were verified by analyzing their FT-IR, 13C-NMR, and 1H-NMR spectra.

Keywords: Synthesis (chemical); thiopyrimidin; thiazine; Imidazole; thiazole; pyrimidothiazepine

1. Introduction

Thiourea derivatives have been utilized in the synthesis of a wide range of azole, azine, and azepine heterocyclic compounds [1-7]. Synthesis of heterocyclic with various biological activities using simple reactants has been a prominent goal in organic synthesis [8-11]. Our aim was to expand the chemical space and discover new derivatives by utilizing the reactivity of the thiourea derivative with different reagents to generate novel heterocyclic compounds, through systematic variation of the reaction conditions and reagents.

2. Experimental

The initial components, reagents, and solvents were obtained from Aldrich Chemical Co. and Merck Chemical Co. The melting points were determined on an Electrothermal IA 9100 apparatus and are reported without any corrections. Dry solvents were used in the studies. Recrystallization techniques were employed to obtain pure products. The infrared (IR) spectra were recorded using a Shimadzu FTIR 8101 PC instrument from KBr discs. The 1H and 13C nuclear magnetic resonance (NMR) spectra were measured using a JEOL-JNM-LA 400 MHz spectrometer with dimethyl sulfoxide (DMSO) as the solvent. TMS (tetramethylsilane) was used as the common reference for chemical shifts (δ ppm), and the coupling constants (J) are reported in Hz. Mass spectra were obtained using a Shimadzu QP-2010 plus instrument at an electron energy of 70 eV. TLC was applied [10]. Elemental studies were performed on a PerkinElmer 240 instrument at the

*Corresponding author email: chem_islam82@yahoo.com, is.mohamed@qu.edu.sa.; (Islam Ragab).
EJCHEM use only: Received date 29 October 2023; revised date 22 November 2023; accepted date 05 December 2023
DOI: 10.21608/EJCHEM.2023.243272.8798

Microanalysis Center, Cairo University, Egypt. The instrument was used to determine the elemental composition of the samples under investigation.

2.1. General procedure for compound (3)

A mixture of equimolar amounts of cinnamoyl isothiocyanate **2** and 2-aminobenzoic acid **1** was prepared in 50 ml of dry acetone. The mixture was stirred for 12 hours and/or refluxed for 3 or 6 hours. After the specified reaction time, white yellow crystals were obtained. The crystals were isolated by filtration, dried, and recrystallized from acetic acid (CH3COOH).yielded the compound **3** with an 80% yield.

2.2.(Z)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)thioureido)benzoic acid (3a).

mp 230–237 °C; IR : 3438 (OH), 3256, (NH), 1694 (C=O), 1639 (C=N), 1581 (C=C) cm^{-1} ; ^{1}H-NMR (δ_H): 6.91-6.95 (2H, 2d, J=16 HZ, –CH=CH–Ar), 7.13–8.43 (7H, m, 2(Ar–H)), 10.89 (1H, s, NH), 12.18 (1, s, NH), 13.07 (1H, s, SH), 13..38 (1H, s, OH) ; ^{13}C NMR 118.81 (C=C), 121.57-139.15 (Ar-C), 151.14 (C-SH), 165.00 (C-OH), 167.01 and (C=O) 167.83; m/z (EI, 70 eV) m/z: 393.99 (100.0%), 395.99 (63.9%), 395.00 (18.4%) and 396.99 (11.8%); Elem. Anal. Calcd. (393.99): C, 51.66; H, 3.06; Cl, 17.94; N, 7.09; O, 12.14; S, 8.11. Found: C, 51.42; H, 3.01; N, 7.05%.

2.3. (E)-2-(3-(3-(3,4-dichlorophenyl)acryloyl)thioureido)benzoic acid(3b).

mp 210–212 °C; IR : 3438 (OH), 3256, (NH), 1694 (C=O), 1639 (C=N), 1581 (C=C)cm^{-1}; ^{1}H-NMR (δ_H): 6.91-6.95 (2H, 2d ,J= 16 HZ, –CH=CH–), 7.03–8.43 (7H, m, ArH), 10.89 (1H, s, NH), 12.18 (1, s, NH), 13.07 (1H, s, SH), 13..38 (1H, s, OH)ppm; ^{13}C NMR (δ_C): 118.81 (C=C), 121.57-139.15 (Ar-C), 151.14 (C-SH), 165.00 (C-OH), 167.01 and 167.83 (C=O) ppm; Elem. Anal. Calcd. (393.99): C, 51.40; H, 3.55; Cl, 17.85; N, 7.05; O, 12.08; S, 8.07. Found: C, 51.66; H, 3.06; Cl, 17.94; N, 7.09; O, 12.14; S, 8.11.65%.

2.4. (E)-2-(3-(3-(3-nitrophenyl)-2-phenylacryloyl)thioureido)benzoic acid (3c).

Mp 154-158 °C; IR : 3445 (OH), 33577, 3162 (2 NH), 1686 (C=O), 1590 (C=C)cm^{-1}; ^{1}H-NMR (δ_H): 7.15–8.43 m (8H, m, CH-Ar and 2Ar–H), 10.89 (1H, s, NH), 13.09 (1H, s, SH), 13..38 (1H, s, OH)ppm. Elem. Anal. Calcd. (371.06): C, 54.98; H, 3.53; N, 11.32; O, 21.54; S, 8.63. Found: C, 54.42; H, 3.51; N, 11.15%.

2.5. General procedure for compound (4)

Cinnamoyl thiourea derivatives 3 (0.01 mol) were dissolved in 50 ml of dry acetone and stirred for 10 hours. After the reaction time, the solvent was removed under reduced pressure, resulting in the formation of white yellow crystals. The crystals were then dried and subjected to recrystallization from ethanol. This recrystallization process yielded the desired product in an 80% yield.

2.6. 2-(6-(2,4-dichlorophenyl)-2-mercapto-4-oxopyrimidin-1(4H)-yl)benzoic acid (tautomeric mixture) (4a).

Mp. 215-217 °C. IR : 3410 (OH), 3162 (2 NH), 1687 (C=O), 1581 (C=C)cm^{-1}; ^{1}H-NMR (δ_H): 7.04–8.15 (7H, m, 2Ar–H), 9.35 (1H, s, NH), 9.37(1H, s, NH), 11.28(1H, s, OH), 11.66 (1H. s, OH), 13.10 (1H, S, SH)ppm. ^{13}C NMR (δ_C): 123.88-137.61 (Ar-C), 164.89 (2 C=O,) 181.70 (C=S)ppm. Elem. Anal. Calcd (391.98): C, 51.92; H, 2.56; Cl, 18.03; N, 7.12; O, 12.21; S, 8.15.

2.7. 2-(6-(3,4-dichlorophenyl)-4-oxo-2-thioxotetrahydropyrimidin-1(2H)-yl)benzoic acid (4b).

Mp 190-192 °C; IR :3400 (OH), 3167 (NH), 1689 (C=O), 1579 (C=C)cm^{-1}; ^{1}H-NMR (δ_H): 2.03,2.05 (2H. d, CH_2 methylene), 3.80 (1H,t,CH-Ar), 7.21–8.61 m (7H, m, 2Ar–H), 10.94 (1H, s, NH), 12.11 (1H, s, OH)ppm; Elem. Anal. Calcd (393.99): C, 51.66; H, 3.06; Cl, 17.94; N, 7.09; O, 12.14; S, 8.11.

2.8. 2-(6-(3-nitrophenyl)-4-oxo-5-phenyl-2-thioxotetrahydropyrimidin-1(2H)-yl)benzoic acid (4c).

Mp. 218-220 °C; IR : 3412 (OH), 3135 (NH), 1670 (C=O), 1622 (C-N), 1585 (C=C)cm^{-1}**;** ^{1}H-NMR (δ_H): 3.32 (1H,d,CH-Ar, CH-Ar_1), 7.05–8.49 m (8H, m, 2Ar–H), 11.95 (1H, s, NH), 13.06 (1H, s, OH)ppm; Elem. Anal. Calcd (371.06): C, 54.98; H, 3.53; N, 11.32; O, 21.54; S, 8.63.

2.9. General procedure for compound (5)

A solution of NaOEt (50 ml) was added to compound **3** (0.01 mol) and refluxed for 2 hours and/or 7 hours. After the specified reflux time, a TLC (thin-layer chromatography) analysis was performed on the reaction mixture. Subsequently, the solvent was removed under reduced pressure, and the resulting alkaline residue was acidified using a 0.01% HCl solution. This acidification step led to the formation of a pale yellow precipitate. The precipitate was then filtered, washed with water, dried, and subjected to recrystallization from ethanol, resulting in the production of pale yellow crystals.

2.10. (E)-3-(3-(2,4-dichlorophenyl)acryloyl)-2-mercapto-5,6-dihydroquinazolin-4(3H)-one (5a) (isomers).

Mp.306-312 °C; 40 % **;** IR: 1686 (C=O), 1615 (C=C), 1590 (C=N)cm^{-1}; ^{1}H-NMR (δ_H): 7.28–7.93 (7H, m, 2Ar–H), 12.44 (1H, s, SH), 12.68 (1H,S, SH)ppm; ^{13}C NMR (δ_C): 119.31-140.89 (Ar-C), 160.01 (2 C=O,) 174.76 (C=S)ppm; Elem. Anal. Calcd (378.00) C, 53.84; H, 3.19; Cl, 18.69; N, 7.39; O, 8.44; S, 8.45.

2.11. (E)-3-(3-(3,4-dichlorophenyl)acryloyl)-2-mercapto-5,6-dihydroquinazolin-4(3H)-one (5b).

mp. 170-178 ˚C; 70% ; IR: 1686 (C=O), 1615 (C=C), 1590 (C=N)cm^{-1}; ^{1}H-NMR (δ_H): 6.91-6.95 (2H, 2d, J = 16 Hz, –CH=CH–Ar), 7.15–8.43 m (7H, m, 2Ar–H), 10.89, 11.82 (2H, 2 s, 2NH), 13.09 (1H, s, SH), 13..38 (1H, s, OH)ppm; Elem. Anal. Calcd (378.00) C, 53.84; H, 3.19; Cl, 18.69; N, 7.39; O, 8.44; S, 8.45.

2.12. 2-(3-nitrophenyl)-3-phenyl-[1,3]thiazino[2,3-b]quinazoline-4,6-dione (5c).

mp. 242-244 ˚C; 80% ; IR : 1686 (C=O), 1615 (C=C), 1590 (C=N)cm^{-1}. ^{1}H-NMR (δ_H): 7.51–7.62 m (7H, m, 2Ar–H)ppm; Elem. Anal. Calcd (353.05), C, 57.79; H, 3.14; N, 11.89; O, 18.11; S, 9.07

2.13. (Z)-2-(6-(4-nitrophenyl)-4-oxo-5-phenyl-3,4-dihydro-2H-1,3-thiazin-2-ylideneamino)benzoic acid (6c).

Cinnamoyl thiourea derivative 3 (0.01 mol) was mixed with NaOEt solution (50 ml) and stirred for 2 or 7 hours at room temperature. After the specified reaction time, a TLC (thin-layer chromatography) analysis was performed on the mixture. The solvent was removed under reduced pressure, and the resulting alkaline residue was acidified using a 0.01% HCl solution. This acidification step led to the formation of a pale yellow precipitate. The precipitate was then filtered, washed with water, dried, and subjected to recrystallization from acetic acid. The recrystallization process from acetic acid yielded pale yellow crystals in an 80% yield; mp. 170-172 ◦C; IR :3455 (OH), 1691 (C=O), 1614 (C=C), 1528 (C=N)cm-1. 1H-NMR (δH): 7.71–8.06 (12H, m, 3Ar–H), 8.07 (1H, s, NH), 12.9 (1H, s, OH)ppm; Elem. Anal. Calcd (353.05) C, 57.79; H, 3.14; N, 11.89; O, 18.11; S, 9.07.

2.14. (E)-2-(3-(2,4-dichlorophenyl)acryloyl)-1-thioxo-2,2a,2a1,4a-tetrahydro-4H-3-oxa-2,9b-diazapentaleno[1,6-ab]naphthalene-4,5(1H)-dione (11a):

Cinnamoyl isothiocyanate **3** (0.01 mol) and Maleic anhydride (0.01 mol) in sod. Acetate (0.01 mol) were mixed and fused for 1h. The brown crystals produced by collecting it, washing it with water, drying it, and recrystallizing it from butanol with an 85% Yield.; mp >360; IR: 1686 (C=O), 1584 (C=N)cm^{-1}; ^{1}H-NMR (δ_H): 1.90 (1H, t, CH-CH-N), 2.72 (1H,d, CH-C=O) ,2.88 (1H, d, CH-O), 7.157.48–7.95 m (7H, m, 2Ar–H) ppm; ^{13}C NMR (δ_C):35.79 (C-C), 119.31-140.89 (Ar-C), 162.28 (2 C=O)ppm; Elem. Anal. Calcd (457.99) C, 54.92; H, 2.63; Cl, 15.44; N, 6.10; O, 13.93; S, 6.98.

2.15. (Z)-2-((4-(2,4-dichlorostyryl)-6-oxo-6,7-dihydro-1,3,5-thiadiazepin-2-yl)amino)benzoic acid (13a):

Cinnamoyl isothiocyanate **3** (0.01 mol)**,** chloro acetamide (0.01 mol) and pot. Carbonate (0.01 mol) in ethanol (50 ml) was mixed and refluxed for 7h. HCl solution (0.01%) was used to acidify the alkaline residue. Pale yellow crystals were produced by filtering the generated product, washing it with water, drying it, and recrystallizing it from acetic acid in 80% Yield; mp 245-247 ˚C; IR : 1682 (C=O), 1580 (C=N) cm^{-1}; ^{1}H-NMR (δ_H): 6.91(2H, 2d, J = 16 Hz, –CH=CH–Ar), 6.95 (2H, 2d, J = 16 Hz, –CH=CH–Ar), 7.15–8.43 m (7H, m, 2Ar–H), 10.90 (H, s, NH), 10.96 (H, s, NH), 12.08 (H, s, NH), 12.18 (H, s, NH), 13..38 (1H, s, OH) ppm; ^{13}C NMR (δ_C): 118.81-139.15 (Ar-C), 151.13 (C-S), 164.99,167.83 (2 C=O)ppm; Elem. Anal. Calcd (433.01) C, 52.55; H, 3.02; Cl, 16.33; N, 9.68; O, 11.05; S, 7.38.

2.16. 2-(((Z)-5-carbamoyl-4-((E)-2,4-dichlorostyryl)thiazolidin-2-ylidene)amino)benzoic acid (15a):

NaOEt solution (50 ml) mixed with compound **3** (0.01 mol) and chloro acetamide (0.01 mol) refluxed for 7h. TLC was then performed on the mixture. Under reduced pressure, the solvent was removed and HCl solution (0.01%) was used to acidify the alkaline residue. Pale yellow crystals were produced by filtering the generated product, washing it with water, drying it, and recrystallizing it from acetic acid in **85% yield; mp 222-225;** IR : 1685 (C=O), 1581 (C=N) cm^{-1}; ^{1}H-NMR (δ_H): : 6.91(2H, 2d, J=16 Hz, –CH=CH–Ar), 6.95 (2H, 2d, J =16 1 Hz, –CH=CH–Ar), 7.14–8.43 m (7H, m, 2Ar–H), 10.90 (2H, s, NH_2), 11.66 (H, s, NH), 12.18 (H, s, NH), 13.07 (H, s, OH), 13..39 (1H, s, OH)ppm; ^{13}C NMR (δ_C): 118.81-139.15 (Ar-C), 151.13 (C-S), 165,167.83 (2 C=O)ppm; Elem. Anal. Calcd (436.31) C, 52.30; H, 3.47; Cl, 16.25; N, 9.63; O, 11.00; S, 7.35.

2.17. 2-(((Z)-(((E)-3-(2,4-dichlorophenyl)acryloyl)imino)((2-ethoxy-2-oxoethyl)thio)methyl)amino)benzoic acid (16a):

A mixture of equimolar amounts of cinnamoyl isothiocyanate **3** (0.01 mol) **and** ethyl bromo acetate (0.01 mol) in NaOEt solution (50 ml) was mixed and refluxed for 6h. TLC was then performed on the mixture. HCl solution (0.01%) was used to acidify the alkaline residue. Pale yellow crystals were produced by filtering the generated product, washing it with water, drying it, and recrystallizing it from acetic acid in **85% yield; mp 213-215;** IR: 3114 (NH) 1689 (C=O), 1634 (C=C),1583 (C=N) cm^{-1}; ^{1}H-NMR (δ_H): 1.33,1.34, 1.36, 1.90 (3H, t, CH_3), 4.34, 4.35, 4.37, 4.39 (2H, q,CH_2CH_3 + CH_2-S), 6.91(2 H, 2d, J = 16 Hz, –CH=CH–Ar), 6.95 (2H, 2d, J = 16 Hz, –CH=CH–Ar), 7.15–8.43 m (7H, m, 2Ar–H), 10.90 (H, s, NH), 10.96 (H, s, NH), 12.08 (H, s, NH), 12.19 (H, s, NH), 13..38 (1H, s, OH)ppm. Elem. Anal. Calcd (480.03) C, 52.40; H, 3.77; Cl, 14.73; N, 5.82; O, 16.62; S, 6.66

2.18. 12-(2,4-dichlorophenyl)-6,7a-dihydro-7H,10H-benzo[d]pyrazolo[3,4-f]pyrimido[2,1-b][1,3]thiazepine-7,10-dione (17a):

Compound **16a** (0.01 mol) **and** hydrazine hydrate (0.01 mol) in ethanol (50ml) was mixed and refluxed for 6h. TLC was then performed on the mixture. Pale yellow crystals were produced by filtering the generated product, washing it with water, drying it, and recrystallizing it from acetic acid in **80% yield; mp 335-337;** IR :3114 (NH) 1662 (C=O), 1634 (C=C),1544 (C=N) cm^{-1}; ^{1}H-NMR (δ_H): 7.09–8.09 (H, m, 2Ar–H), 18.11 (1H, s, NH)ppm. Elem. Anal. Calcd (427.99) C, 53.16; H, 2.35; Cl, 16.52; N, 13.05; O, 7.45; S, 7.47.

2.19. (E)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)ureido)benzoic acid (18a):

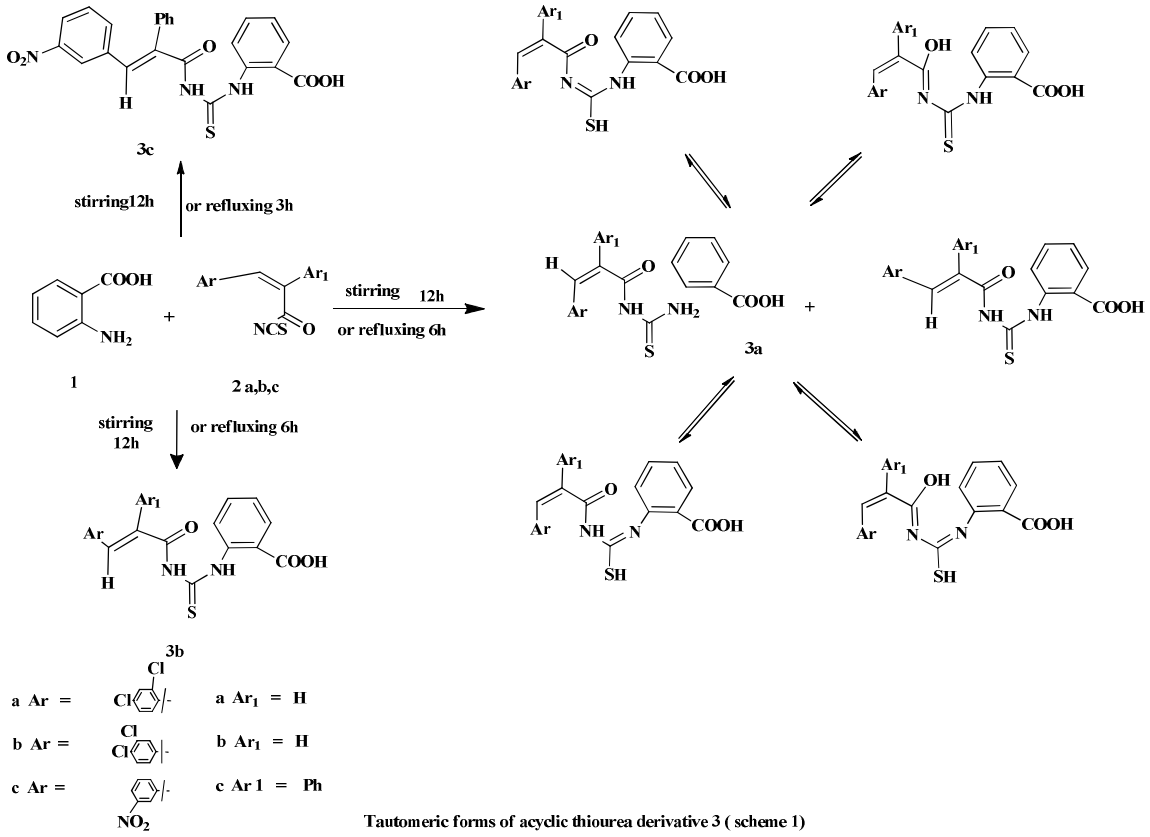
Compound **3** (0.01 mol) and H_2O_2 (60 ml) in NaOH solution (20 ml/ 5%) was stirred for 2 h. HCl solution (0.01%) was used to acidify the alkaline residue. Pale yellow crystals (85% yield) were produced by filtering the generated product, washing it with water, drying it, and recrystallizing it from acetic acid. ; mp 251-253◦C; IR: 1682 (C=O), 1634 (C=C),1581 (C=N) cm^{-1}; ^{1}H-NMR (δ_H): 6.91(2 H, 2d, J = 16 Hz, –CH=CH–Ar), 6.95 (2H, 2 d, J = 16 Hz, –CH=CH–Ar),7.15–8.43 m (7H, m, 2Ar–H), 10.90 (H, s, NH), 12.81 (1H, s, SH), 13..39 (1H, s, OH) ppm; Elem. Anal. Calcd (378.02) C, 53.85; H, 3.19; Cl, 18.70; N, 7.39; O, 16.88.

2.20. (E)-2-(((3-(2,4-dichlorophenyl)acrylamido)methyl)amino)benzoic acid (19a):

Compound **3** (0.01 mol) , H_2O_2 (30 ml) in CH_3COOH (20 ml) was mixed and stirred for 2 h. Pale yellow crystals (85% yield) were produced by filtering the generated product, washing it with water, drying it, and recrystallizing it from acetic acid; mp 245-248◦C;.IR : 2985 (CH2), 1683 (C=O), 1634 (C=C),1580 (C=N) cm^{-1}; ^{1}H-NMR (δ_H): 2.67 (2H,t, CH_2), 6.91(2H, 2d, J = 15.6 Hz, –CH=CH–Ar), 6.95 (2 H, 2d, J = 15.6 Hz, –CH=CH–Ar),7.17–8.43 m (7H, m, 2Ar–H), 10.90 (H, s, NH), 12.81 (1H, s, NH), 13..39 (1H, s, OH) ppm; Elem. Anal. Calcd (364.04) C, 55.91; H, 3.86; Cl, 19.41; N, 7.67; O, 13.14.

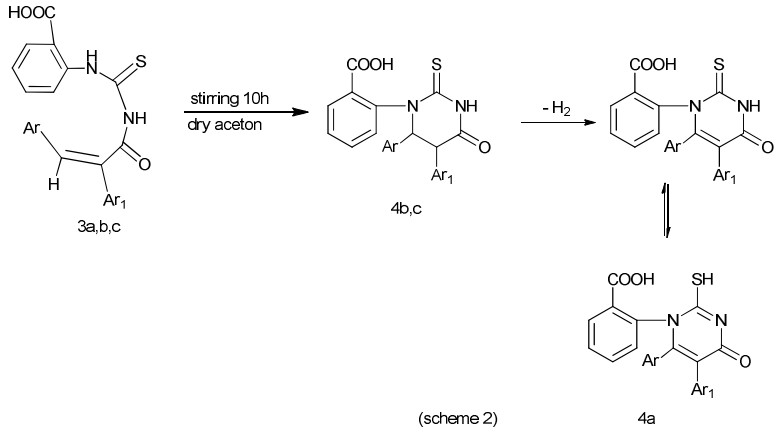
3. Dissection

When cinnamoyl isothiocyanate 2a-c reacted with 2-aminobenzoic acid 1 , an acyclic thiourea derivative mixture 3a-c was formed through the aza Michael addition of nucleophilic nitrogen to electrophilic cation of N=C=S. The tautomeric mixture obtained depended on the reaction time,, with approximately equal amounts obtained after stirring for 12h. The thione derivative was predominantly formed when the reaction was carried out for 3 to 6 hours. (Scheme1). The tautomeric mixture exhibited absorption peaks corresponding to stretching vibrations of SH, NH, C=O, and C=S. Compound 3 displayed downfield signals for COOH, SH, OH, and NH, which varied depending on the reaction time.



Tautomeric forms of acyclic thiourea derivative 3 (scheme 1)

2-Mercapto-4-oxopyrimidine 4a-c and its isomeric form were obtained by keeping the thiourea derivative **3a-c** in dry acetone for 10 hours **(Scheme2).** 2-Mercapto-4-oxopyrimidine 4a-c showed stretching absorption peaks for NH, OH and 2 C=O, with proton signals for SH, NH, OH and absence of cinnamoyl proton. ^{13}C signals at 181.70 and 164.89 respectively.

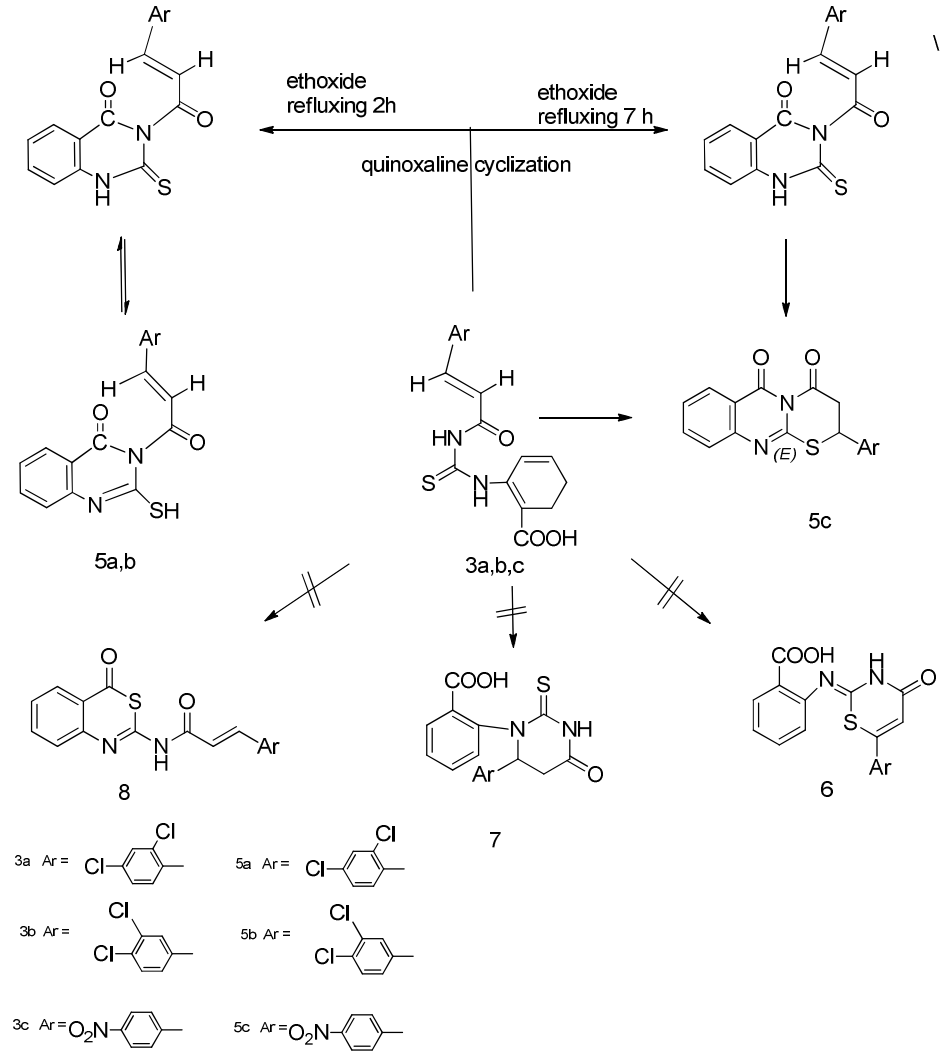


(scheme 2)

The cyclization of cinnamoyl thiourea 3a-c to yield quinoxaline 5a-c and (Z)-2-(6-(4-nitrophenyl)-4-oxo-5-phenyl-3,4-dihydro-2H-1,3-thiazin-2-ylideneamino)benzoic acid 6c was achieved by refluxing and/or stirring in ethoxide (Scheme 3). In the case of quinoxaline 5a,b, the attack of the nucleophilic nitrogen to the electrophilic carboxylic carbon was observed, while no addition of thiol or nitrogen to the cinnamoyl moiety was observed. On

the other hand, thiazine **6c** was formed through the addition of the thiol to the cinnamoyl moiety. 2-(3-nitrophenyl)-3-phenyl-[1,3]thiazino[2,3-b]quinazoline-4,6-dione **5c** was formed through the attack of both the nucleophilic nitrogen to the carboxylic carbon and the addition of thiol to the cinnamoyl moiety.

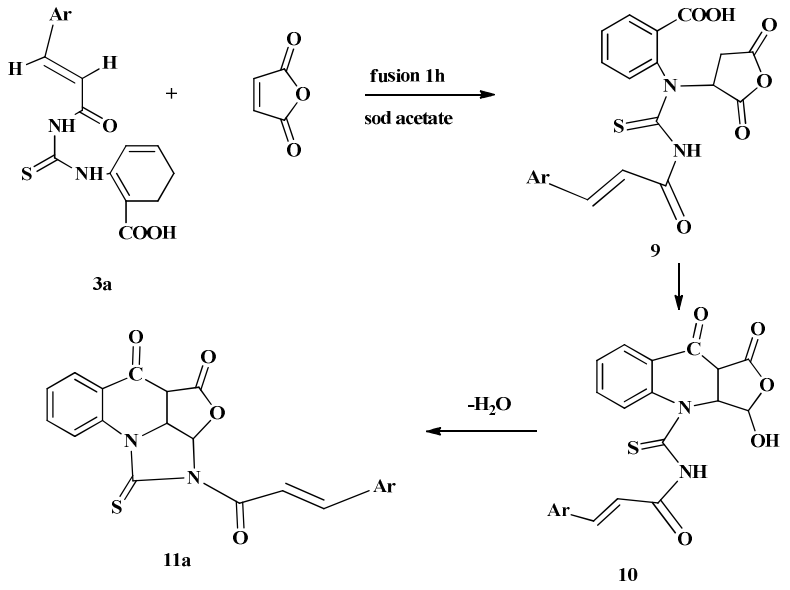
The reaction was confirmed by the presence of absorption peaks corresponding to C=N, NH, C=O, and C=S groups. Additionally, the trans cinnamoyl proton signals were observed, along with downfield shifts of SH and NH protons in compounds **5a**,**b**. In the case of 2-(3-nitrophenyl)-3-phenyl-[1,3]thiazino[2,3-b]quinazoline-4,6-dione **5c**, the absence of the cinnamoyl proton, NH, and SH proton signals confirmed its structure. Carbon signals were observed at 174.76 and 168.10 ppm for C=S and C=O sp^2 carbons, respectively.



Bas mediated heterocyclization of 3 (scheme 3)

(Z)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)thioureido)benzoic acid **3a** underwent nucleophilic addition of the nitrogen to the polarized double bond of maleic anhydride, followed by cyclization to form quinolineol and subsequent dehydration to form the imidazole ring, resulting in the formation of (E)-2-(3-(2,4-dichlorophenyl)acryloyl)-1-thioxo-2,2a,2a1,4a-tetrahydro-4H-3-oxa-2,9b-diazapentaleno[1,6-ab]naphthalene-4,5(1H)-dione **11**a (Scheme 4).

(E)-2-(3-(2,4-dichlorophenyl)acryloyl)-1-thioxo-2,2a,2a1,4a-tetrahydro-4H-3-oxa-2,9b-diazapentaleno[1,6-ab]naphthalene-4,5(1H)-dione **11a** exhibited a carbonyl absorption band. However, it lacked any SH or NH proton signals. Carbon signals were observed at 168.10 and 35.76 ppm for C=O sp^2 and C-C carbons, respectively.



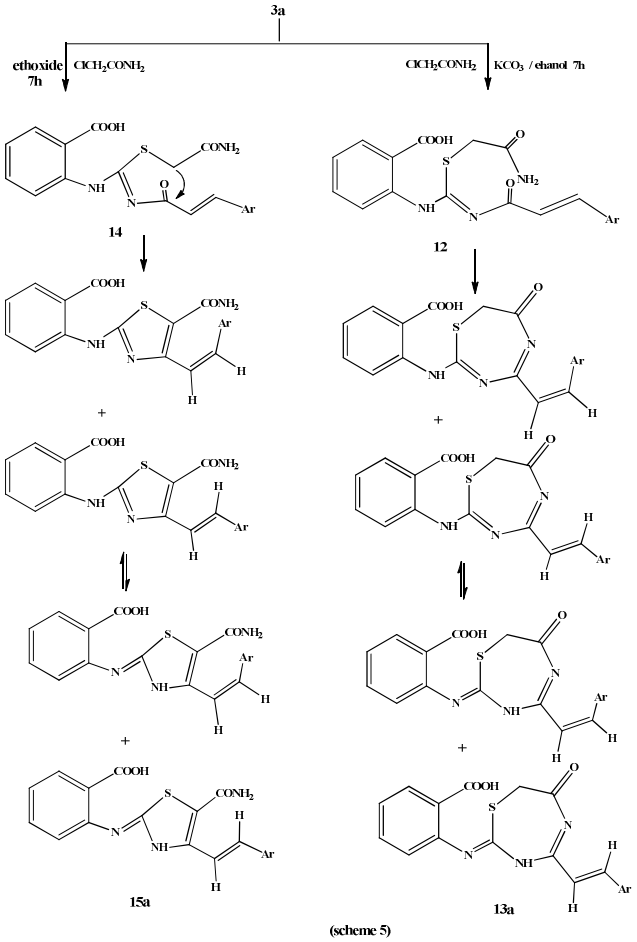
scheme 4

(Z)-2-((4-(2,4-dichlorostyryl)-6-oxo-6,7-dihydro-1,3,5-thiadiazepin-2-yl)amino)benzoic acid **13**a was obtained through the thia addition of (Z)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)thioureido)benzoic acid **3a.** By chloroacetamide, followed by cyclodehydration via the attack of nitrogen to the carbonyl group (C=O) of the cinnamoyl moiety **(Scheme 5**).

(Z)-2-((4-(2,4-dichlorostyryl)-6-oxo-6,7-dihydro-1,3,5-thiadiazepin-2-yl)amino)benzoic acid 13a exhibited absorption peaks at 3085 cm-1 for OH, 1682 cm-1 for C=O, and 1580 cm-1 for C=C. It displayed two downfield signals at 13.38 and 12.23 ppm for COOH and NH protons, respectively. The carbon signals in diazepin 13a were observed at 167.83 and 164.99 ppm, corresponding to the carbon atoms involved in the C=O group.

Contrary to the previous cyclization chloroacetamide undergo thiazole cyclization with thiourea 3a involving the activated CH2 group in cyclization in a basic medium, resulting in the formation of 2-(((Z)-5-carbamoyl-4-((E)-2,4-dichlorostyryl)thiazolidin-2-ylidene)amino)benzoic acid 15a and its isomeric form.

The IR spectrum of 2-(((Z)-5-carbamoyl-4-((E)-2,4-dichlorostyryl)thiazolidin-2-ylidene)amino)benzoic acid 15a exhibited peaks at 3010 cm-1 for OH, 1689 cm-1 for CO, and 1581 cm-1 for C=S. The proton signals for OH, NH, and NH2 were detected at chemical shifts of 13.39, 12.87, 11.66, and 10.96, respectively. The carbon signals for the sp2 carbonyl carbon were observed at 167.83 and 165.00 ppm.



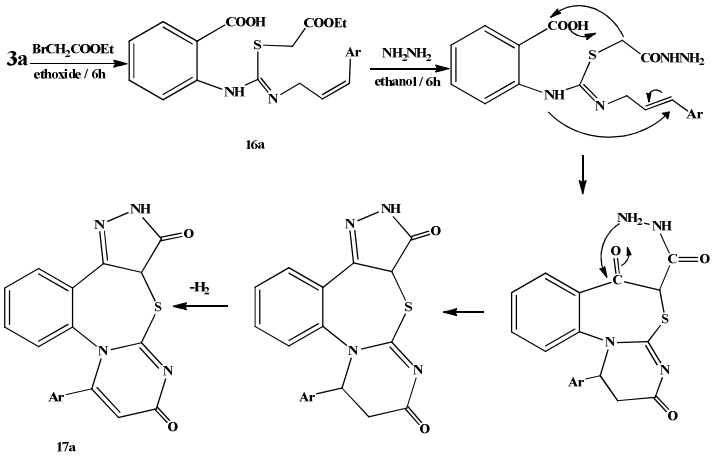
(scheme 5)

(Z)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)thioureido)benzoic acid 3a undergo alkylation with ethylbormoacetate resulting in the formation ofa tautomeric mixture of 2-(((Z)-(((E)-3-(2,4-dichlorophenyl)acryloyl)imino)((2-ethoxy-2-oxoethyl)thio)methyl)amino)benzoic acid **16**a (**Scheme 6**).

2-(((Z)-(((E)-3-(2,4-dichlorophenyl)acryloyl)imino)((2-ethoxy-2-oxoethyl)thio)methyl)amino)benzoic acid **16**a exhibits peaks corresponding to NH, C=O, and C=C groups in its IR spectrum, as well as broad signals for two COOH and two NH protons in its NMR spectrum.

The cyclization of 2-(((Z)-(((E)-3-(2,4-dichlorophenyl)acryloyl)imino)((2-ethoxy-2-oxoethyl)thio)methyl)amino)benzoic acid **16a** to form 12-(2,4-dichlorophenyl)-6,7a-dihydro-7H,10H-benzo[d]pyrazolo[3,4-f]pyrimido[2,1-b][1,3]thiazepine-7,10-dione **17a** is achieved by refluxing in an excess amount of hydrazine hydrate (**Scheme 6**).

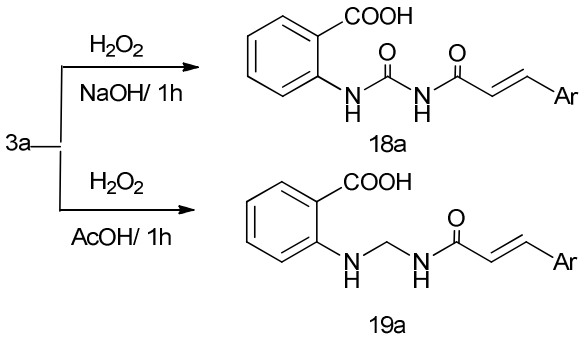
12-(2,4-dichlorophenyl)-6,7a-dihydro-7H,10H-benzo[d]pyrazolo[3,4-f]pyrimido[2,1-b][1,3]thiazepine-7,10-dione **17a** displays peaks corresponding to NH and CO groups in its IR spectrum, while the OH and cinnamoyl proton signals are absent.



(scheme 6)

The oxidation of (Z)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)thioureido)benzoic acid **3**a was carried out by treating it with H_2O_2 in NaOH, resulting in the formation of (E)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)ureido)benzoic acid **18a** (**Scheme 7**). On the other hand, dichlorophenyl)acrylamido)methyl)amino)benzoic acid **19a** was obtained through the desulfurization of (Z)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)thioureido)benzoic acid **3**a using H_2O_2 in acetic acid.

(E)-2-(3-(3-(2,4-dichlorophenyl)acryloyl)ureido)benzoic acid**18a** exhibited absorption peaks in the IR spectrum corresponding to NH and CO groups, as well as proton signals for OH and 2NH groups. dichlorophenyl)acrylamido)methyl)amino)benzoic acid **19a** also displayed absorption peaks for NH and CO groups in the IR spectrum, along with proton signals for OH, 2NH, and CH_2 groups.



(scheme 7)

4. Conclusions

In our study, the reaction of cinnamoyl thiourea derivatives with various simple reagents as maleic anhydride, chloroacetamide, ethyl bromoacetate, hydrazine hydrate and hydrogen peroxide led to the synthesis of various azoles, azines, and azepines, including thiopyrimidine, quinoxaline, thiazine, imidazole, thiazapine, thiazole, isothiourea, pyrimidothiazepine, cinnamoyl urea derivative, and cinnamamide derivative. The characterization of the synthesized compounds was confirmed through various analytical techniques such as FT-IR, ^{13}C-NMR, and ^{1}H-NMR spectroscopy.

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

Qassim University is the funding source.

7. Author Contributions

I.R: supervision, project administration, conceptualization, investigation, writing-original draft, visualization, formal analysis, data curation, writing- review.

8. Acknowledgements:

Researcher would like to thank the Deanship of Scientific Research, Qassim University for funding publication of this project.

9. Reference

[1] A. A Ghoneim, M. G Assy, E.K. Mohamed, I. Ragab, Design, synthesis and anticancer evaluation of novel thiazine, pyrimidine and pyridine derivatives, Iranian chemical communication, 5 (2017) 195-206.

[2] R.A. Haggam, M.G. Assy, M.H. Sherif, M.M. Galahom, Facile synthesis of some condensed 1, 3-thiazines and thiazoles under conventional conditions: Antitumor activity, Research on Chemical Intermediates, 43 (2017) 6299-6315.

[3] R.A. Haggam, E.A. Soylem, M.G. Assy, M.F. Arastiedy, Synthesis and antimicrobial evaluation of new series of quinazolin-5-one derivatives, Journal of the Iranian Chemical Society, 17 (2020) 1715-1723.

[4] P. Sharma, R. Makkar, A REVIEW: THIAZINES DERIVATIVES TREATED AS POTENTIAL ANTIMICROBIAL AGENTS, Asian Journal of Pharmaceutical and Clinical Research, 10 (2016) 43.

[5] M.H. Abd El-Azim, M.G. Assy, M.I. Khalil, Y.A. Selim, Cyclization of thiosemicarbazide derivative: As a source of novel synthesis of some azoles and azines, Journal of Heterocyclic Chemistry, 57 (2020) 3153-3160.

[6] L.A. Siddig, M.A. Khasawneh, A. Samadi, H. Saadeh, N. Abutaha, M.A. Wadaan, Synthesis of novel thiourea-/urea-benzimidazole derivatives as anticancer agents, Open Chemistry, 19 (2021) 1062-1073.

[7] A. Ghoneim, M. Assy, E. Mohamed, I. Ragab, Cycloaddition involving activated isothiocyanate: Synthesis and antimicrobial activities of thiazine, pyrimidine and pyridine derivatives, Int. J. Chem, Pharm, Sci., 3 (2015) 1637-1642.

[8] I. Ragab, Y.A. Selim, M.H. Abd El-Azim, Synthesis of some New Dihydropyrimidines Derivatives by Cyclization of Polarized Unsaturated Systems, Journal of Heterocyclic Chemistry, 55 (2018) 2727-2731.

[9] M. Abd El-Azim, M. Assy, M. Elmesalmy, Y. Selim, Heterocyclization and Biological Evaluation of Malonic Hydrazide; Novel Synthesis of Some Azoles and Azines, Egyptian Journal of Chemistry, 66 (2023) 479-482.

[10] F.M. Sroor, W.M. Basyouni, W.M. Tohamy, T.H. Abdelhafez, M.K. El-awady, Novel pyrrolo [2, 3-d] pyrimidine derivatives: Design, synthesis, structure elucidation and in vitro anti-BVDV activity, Tetrahedron, 75 (2019) 130749.

[11] M.G. Assy, E.K. Mohamed, A.A. Ghoneim, I. Ragab, Enamines as a precursor for synthesized of some azoles and azines with expected biological activity, organic chimistry An Indian Journal, Volume 9 (2013) 295 300.