Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (7) Issue (1) (2022), (31- 36) **online: ISSN 2356–976x**
http://bjas.journals.ekb.eg

Facile synthesis of quinazoline, oxazine and triazole derivatives as potential antimicrobial agents based on isothiocyanate moiety

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Abstract

A novel series of heterocyclic compounds like quinazoline, triazole, thiazolidine and oxazine derivatives was prepared via treatment of isothiocyanate with nitrogen, sulfur and carbon nucleophiles. The chemical structures of all products were confirmed on the basis of their elemental analyses and spectroscopic data(IR, MS, ^{1}H NMR, ^{13}C NMR).

Keywords: Quinazoline, oxazine, triazole, thiazolidine, isothiocyanate.

1. Introduction

Heteroallenesisothiocyanatesareaninteresting-groupoforganiccompounds that are used asreactive-keyprecursors in the synthesis of heterocyclic molecules due to theirdiversereactionsandalsoto the ireasyavailability. [1-4]

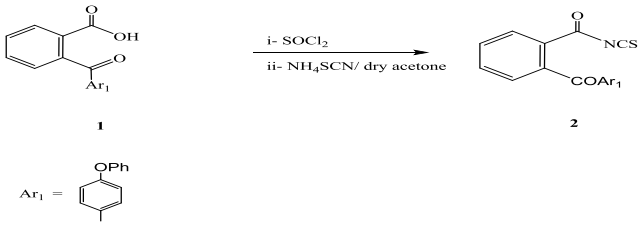
Isothiocyanatesare often prepared from thereactionofaminederivativeswithcarbondisulfide[5-8]orthiophosgene,[9-11] as well as treatmentofthecarboxylicacidderivativeswithammoniumthiocyantes[12-17].

In addition ,is othiocyanates are a class of organic compounds with well-known potent pharmaceutical applications [18,19] and are very popular in drug discovery [20-22]

On the basis of these experiences and in continuation of our ongoing interest in the design of bioactive heterocyclic molecules [23-27], the present work involves a facilesynthesis of a series of five and six-membered heterocyclic compounds as triazole, quinazoline, thiazolidine and oxazine derivatives using 2-(4-phenoxybenzoyl)benzoyl is othiocyanate**(2)**.

2. Results and Discussion:

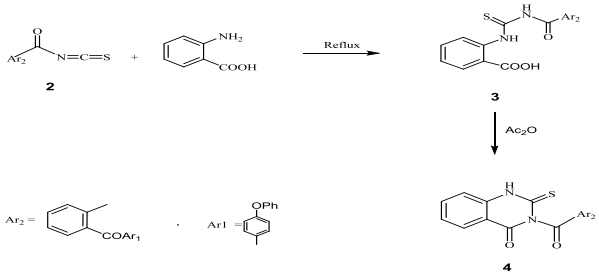
Heating of acid **1**in thionyl chloride under reflux furnished the corresponding acid chloride which in turn reacted with ammonium thiocyanate in dry acetone to give2-(4-phenoxybenzoyl)benzoylisothiocyanate**(2)**.



1 2

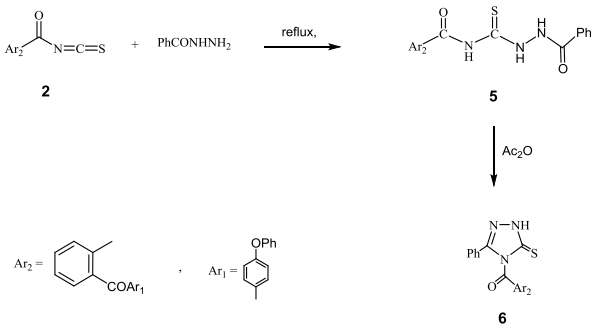
The prepared 2-(4-phenoxybenzoyl)benzoyl isothiocyanate**(2)** was used in situas a reactive key precursor for synthesis of variety of heterocyclic molecules via its reaction with various nucleophiles like-nitrogen nucleophiles, carbon nucleophiles and sulfur nucleophiles.

Thus, heating of isothiocyanate **2** withanthranilic acid as a nitrogen nucleophile under reflux at 40 ̊C furnished thiourea derivative **3**. Heating of the latter with acetic anhydrideresulted in the formation of 3-(2-(4-phenoxybenzoyl)benzoyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one**(4)**.

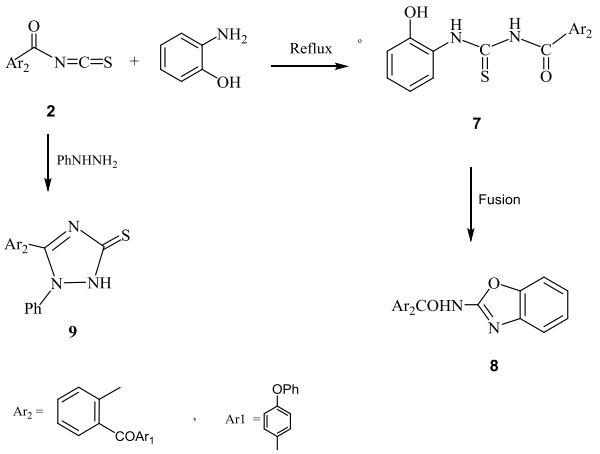


2 3 4

The reactivity of isothiocyanatederivative**2**towards nitrogen nucleophilic reagents was investigated also through its reactionwith benzoylhydrazine.Heating of the reaction mixture under reflux at 40 ̊c gavethiosemicarbazide derivative **5**while its heating at 80 ̊C furnished triazole**(6)**. Formulation of triazole**6**is temperature dependent and proceed via formation of thiosemicarbazide derivative 5 followed by cyclization.

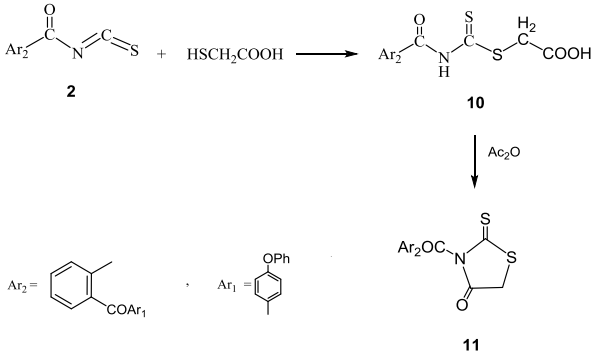


In addition, benzoxazole derivatives are an interesting group of heterocyclic molecules due to their wide range of pharmaceutical applications. This encouraged us to synthesizeN-(benzo[d]oxazol-2-yl)-2-(4-phenoxybenzoyl)benzamide **(8)**in similar way to the previous behaviour ofisothiocyanate**2** toward nitrogen nucleophilesviatreatment of isothiocyanate with o-aminophenol as amphoteric nucleophile in dry acetone under reflux.

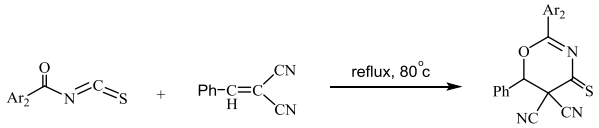


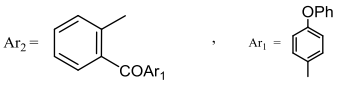
This investigation was extended also to use isothiocyanate as a reactive key precursor for the synthesis of bio-active molecules. Thus, (4-phenoxyphenyl)(2-(2-phenyl-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-3-yl) phenyl) methanone **(9)** was formed viatreatment of isothiocyanate**2** with phenylhydrazine in dry acetone under reflux.

Similarly, 2-(4-phenoxybenzoyl)benzoylisothiocyanate **(2)** reacted with thioglycolic acid as sulfur nucleophile in dry acetone under reflux to give 2-(((2-(4-phenoxybenzoyl) benzoyl) carbamothioyl) thio) acetic acid **(10)**. In addition, thiazolidine **11** can be formed in a good yield upon heating of acid **10** in acetic anhydride under reflux.



On the other hand, treatmentofisothiocyanate**2** with benzylidenemalononitrile**(12)** as a carbon nucleophilein dry toluene gave2-(2-(4-phenoxybenzoyl)phenyl)-6-phenyl-4-thioxo-4H-1,3-oxazine-5,5(6H)-dicarbonitrile**(13)**via [4+2]cycloadditionmechanism.





Antimicrobial activity

The synthesized molecules were screened and tested in vitro for their antimicrobial activity against Bacillus subtilis and Staphylococcus cocci as Gram-positive bacteria in addition to Klebsiella bacilli and Escherichia coli as Gram-negative bacteria. The products were also evaluated for their antifungal activity against Candida albican and Aspergillusniger. Both of Ampicillin trihydrate and Terbinafine were used as standard drugs to evaluate the potency of the tested products under the same conditions.

Determination of the preliminary antibacterial and antifungal activity was carried out by agar diffusion method[42] and the results were presented for the tested products as the average diameter of inhibition zones (r) of bacterial or fungal growth around the disks in millimeters at 100 µg concentrations in DMSO.

The observed data on the antimicrobial activity of the products and standards are given in Table 1. It aws observed from the results given in Table 1 that most of the synthesized products exhibited varying degrees of inhibition against the tested microorganisms.

Table (1) Antimicrobial activity of products 3-15

compound	B. subtilis	S. cocci	K. bacilli	E. coli	C. albican	A. niger
3	17	16	26	24	20	15
4	33	22	32	39	24	26
5	-	-	17	20	-	-
6	37	29	18	20	36	40
7	33	36	21	23	18	12
8	36	-	31	30	20	16
9	-	-	-	-	30	39
10	31	24	-	-	12	17
11	30	21	37	38	-	-
13	20	-	25	11	20	17
A	36	38	37	40	-	-
T	-	-	-	-	38	41

Note: Numbers in the table represent the inhibition zone diameter (r,mm) of either bacterial or fungal growth for each compound; r> 25 mm, highly active; r > 14 mm, moderately active; r > 10mm, slightly active; (-), no inhibition was observed; A = Ampicillin trihydrate as the standard antibacterial agent and T = Terbinafine as the standard antifungal agent.

It has been observed from data shown in Table 1 most of the synthesized compounds exhibted varying degrees of inhibition against the tested microorganisms in comparison with the standard antibacterial and antifungal. Quinazoline**4** and thiazolidine**11** showed potent ativity against Gram-negative bacteria Escherichia coli while copmound**13** showed the lowest activity. Also, triazole**6** and benzoxazole**8** exhibited the highest activity gainstGram-positive bacteria Bacillus subtilis but other compounds showed moderate activity. On the other hand, triazoles**6** and **9** exhibited high activity against fungal strains Candida Albicanand Aspergillus Niger. Additionally, all the tested compounds showed lower to moderate activity against Candida Albican except triazole**6**.

From the previous results, it was observed that, the presence of triazole moiety in compounds **6** and **9** enhanced their antifungal activity and the presence of quinazoline, benzoxazole and thiazolidine enhanced their antibacterial activity.

Experimental

Meltingpointsweredeterminedbythecapillarytube method and were uncorrected.IR spectra in KBr were recorded using (Perkin – Elmer 298) spectrophotometer. ^{1}H NMR spectra were recorded on a variam-Gemini 400 MHZ instrument. $CDCl_3$ and DMSO- d_6 were used as solvents, chemical shifts (δ) were reported in ppm relative to internal TMS. Mass spectra were obtained by Schimadzu single focusing mass spectrum at abeam energy 70ev. Microanalytical data were obtained from the microanalytical center at Cairo University.

4.2. Synthesis of 2-(4-phenoxybenzoyl)benzoylisothiocyanate (2)

Acid **1**[27] (0.01 mol) in little amount of thionyl chloride was heated under reflux at lower than 70 °C for 2 hrs.Excess of thionyl chloride was removed by evaporation under vacuum to leave solid acid chloride.Solid ammonium thiocyanate (0.01mol) was added to stirred solution of acidchloride in dry acetone (15 ml).The reaction mixture was stirred for 1.5 hrs.at room temperature. The precipitated ammonium chloride was filtered off, then the solvent was removed under vacuum and the crude product was used in the next reaction without purification.

Synthesis of 2-(3-(2-(4-phenoxybenzoyl)benzoyl)thioureido) benzoic acid (3)

A mixture of isothiocyanate **2** (0.01 mol) and anthranilic acid (0.01 mol) in dry acetone was heated under reflux for 4hrs. After the completion of reaction (the reaction progress was monitored by tlc), the prciptated solid was filtered of, dried and recrystallized from toluene.

Yield, 79 %; mp 212°C-214 °C; IR (Cm^{-1}): υmax: 3425-3100(OH, NH), 1687-1660(2CO), 1631(C=N), 1289(C=S); Ms: m/z 496 (M^{+}); ^{1}H NMR(DMSO-d6) δ: 6.89-8.50 (m, 17H, Ar-H), 9.35, 10.10 (2s, 2H, 2NH, exchangeable), 12.12 (s, 1H, OH, exchangeable); ^{13}C NMR: 117.5, 118.3, 118.8, 119.8, 120.9, 121.6, 122.6, 126.5, 127.5, 128.3, 129.5, 130.2, 130.7, 131.3, 135.5, 148.2, 155.2, 161.3, 165.5, 171.4, 178.5, 190.4, Anal.Calcd. for $C_{28}H_{20}N_2O_5S$ (Mol. wt.496): C, 67.73; H, 4.06; N, 5.64 Found: C, 67.66; H, 3.98; N, 5.55%.

4.2. Synthesis of 3-(2-(4-phenoxybenzoyl)benzoyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (4)

Acid 3 (0.01mol)washeatedinaceticanhydride(5ml)underreflu xfor4h. The separated solid was filtered, dried and crystallized from benzene.

Yield, 78 %; mp 185°C- 187 °C; IR (Cm^{-1}): υmax: 3380 (NH), 1617-1690(CO), 1610 (C=N), 1322(C=S); Ms: m/z 478 (M^{+}); ^{1}H NMR (DMSO-d6) δ: 6.70-8.26 (m, 17H, Ar-H), 13.18 (s, 1H, NH, exchangeable); ^{13}C NMR: 118.2, 118.5, 118.9, 120.3, 123.7, 124.5, 125.6, 125.8, 126.1, 127.5, 128.8, 128.9, 130.6, 131.7, 131.9, 134.8, 143.0, 151.3, 152.2, 183.1, 195.2; Anal.Calcd. for $C_{28}H_{18}N_2O_4S$ (Mol. wt. 478): C, 70.28; H, 3.79; N, 5.85; Found: C, 70.18; H, 3.65; N, 5.79%.

4.3. Synthesis of N-(2-benzoylhydrazine-1-carbonothioyl)-2-(4-phenoxybenzoyl) benzamide (5)

A mixture of isothiocyanate **2** (0.01 mol) and benzoylhydrazine (0.01 mol) was heated in dry acetone for 4hrs. After cooling the precipitatedproduct was filtered, dried and recrystallized from ethanol.

Yield, 81 %; mp 193°C- 195 °C; IR (Cm^{-1}): υmax: 3415 (NH) , 3030(CH aromatic), 1685-1664(C=O), 1262(C=S); Ms: m/z 495 (M^{+}); ^{1}H NMR (DMSO-d6) δ: 7.18-8.42 (m, 18H, Ar-H), 9.38, 10.49, 10.82 (3s, 3H, 3NH, exchangeable); ^{13}C NMR: 117.8, 118.3, 118.7, 121.3 122.5, 124.2, 124.8, 126.5, 126.8, 127.2, 127.7, 128.6, 129.8, 130.6, 131.5, 135.7, 148.5, 150.5, 168.7, 170.2 181.5, 192.5; Anal.Calcd. for $C_{28}H_{21}N_3O_4S$ (Mol. wt. 495): C, 67.87; H, 4.27; N, 8.48; Found: C, 67.80; H, 4.18; N, 8.42%.

4.4. Synthesis of (2-(4-phenoxybenzoyl)phenyl)(3-phenyl-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)methanone (6)

The same procedures described for the syntheis of compound **4**. The product was crystallized from methanol.

Yield, 74 %; mp 157°C- 159 °C; IR (Cm^{-1}): υmax: 3380 (NH) , 3030(CH aromatic), 1692-1670(C=O), 1315(C=S); Ms: m/z 477 (M^{+}); ^{1}H NMR (DMSO-d6) δ: 7.13-8.36 (m, 18H, Ar-H), 12.82 (s, H, NH, exchangeable); ^{13}C NMR: 118.2, 118.5, 119.3, 121.5 121.8, 124.6, 125.5, 126.2, 126.9, 127.5, 128.3, 128.8, 129.2, 131.1, 131.7, 135.5, 148.2, 155.4, 170.3, 182.2, 189,5; Anal.Calcd. for $C_{28}H_{19}N_3O_3S$ (Mol. wt. 477): C, 70.43; H, 4.01; N, 8.80 Found: C, 70.29; H, 3.92; N, 8.73%.

4.5. Synthesis of N-((2-hydroxyphenyl)carbamothioyl)-2-(4-phenoxybenzoyl) benzamide (7)

Heat a mixture of isothiocyanate **2** (0.01 mol) and o-anminophenol (0.01 mol) in dry acetonefor 3hrs. After cooling the precipitated product was filtered, dried and recrystallized from benzene.

Yield, 77 %; mp 181°C- 183 °C; IR (Cm^{-1}): υmax: 3430 – 3180 (OH , NH) , 3035 (CH-aromatic), 1683-1660 (C=O),1306 (C=S); Ms: m/z 468 (M^{+}); ^{1}H NMR (DMSO-d6) δ: 6.98-8.13 (m, 17H, Ar-H), 10.34 (s, H, OH, exchangeable), 11.51, 12.82 (2s, 2H, 2NH, exchangeable); ^{13}C NMR: 118.4, 118.6, 118.9, 121.3 122.5, 123.3, 126.5, 127.3 127.7, 128.2, 128.7, 129.4, 130.5, 131.5, 133.4, 134.2, 150.3, 154.7, 168.5, 173.1, 184.5; Anal.Calcd. for $C_{27}H_{20}N_2O_4S$ (Mol. wt. 468): C, 69.22; H, 4.30; N, 5.98; Found: C, 69.28; H, 4.42; N, 5.93%.

4.6. Synthesis of N-(benzo[d]oxazol-2-yl)-2-(4-phenoxybenzoyl)benzamide (8)

Heat compound 7 above its melting point for 2hrs., the product was recrystallized from cyclohexane.

Yield, 68 %; mp 172°C- 174 °C; IR (Cm^{-1}): υmax: 3400 (NH), 3013 (CH-aromatic), 1690-1673 (C=O), 1240 (C=S); Ms: m/z 434 (M^{+}); ^{1}H NMR ($CDCl_3$) δ: 5.64 (s, 1H, NH, exchangeable), 6.89-7.95 (m, 18H, Ar-H). Anal.Calcd. for $C_{27}H_{18}N_2O_4$ (Mol. wt. 434): C, 74.65; H, 4.18; N, 6.45; Found: C, 74.58; H, 4.10; N, 6.37

4.7. Synthesis of (4-phenoxyphenyl)(2-(2-phenyl-5-thioxo-2,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl)methanone (9)

A mixture of isothiocyanate **2** (0.01 mol) and phenylhydrazine (0.01 mol) in dry acetone was heated under reflux for 4hrs. After cooling the precipitated product was filtered, dried and recrystallized from ethanol.

Yield, 80 %; mp 179°C- 181 °C; IR (Cm^{-1}): υmax: 3348 (NH), 3050 (CH-aromatic), 1686 (C=O), 1295 (C=S); Ms: m/z 449 (M^{+}); ^{1}H NMR (DMSO-d6) δ: 6.67-7.89 (m, 17H, Ar-H), 7.54 (s, 1H, NH, exchangeable); ^{13}C NMR: 118.3, 118.7, 119.8, 121.7, 124.3, 124.6, 126.6, 129.1, 129.2, 129.3, 129.6, 137.8, 138.4, 140.8, 152.6, 156.6 (Ar-C), 172.4, 179.1 (CO, CS); Anal.Calcd. for $C_{27}H_{19}N_3O_2S$ (Mol. wt. 449): C, 72.14; H, 4.26; N, 9.35; Found: 72.03; H, 4.17; N, 9.28%.

4.8. Synthesis of 2-(((2-(4-phenoxybenzoyl) benzoyl)carbamothioyl)thio)acetic acid (10)

A mixture of isothiocyanate **2** (0.01 mol) and thioglycolic acid (0.01 mol) in dry acetone was heated under reflux for 4hrs. After cooling, the precipitatedproduct was filtered, dried and recrystallized from ethanol.

Yield, 76 %; mp 203°C- 205 °C; IR (Cm^{-1}): υmax: 3450-3215 (OH, NH), 3038 (CH-aromatic), 2938, 2850 (CH- aliphatic), 1710-1670(CO), 1290 (C=S); Ms: m/z 451 (M^{+}); ^{1}H NMR (DMSO-d6) δ: 2.32 (s, 2H, SCH_2), 6.93-7.86 (m, 13H, Ar-H), 9.83 (s, 1H, NH, exchangeable), 10.40 (s, 1H, OH, exchangeable); ^{13}C NMR: 41.5 (SCH_2), 118.1, 118.5, 119.3, 121.3, 126.2, 128.7, 129.1, 129.6, 130.4, 135.2, 140.8, 148.5, 155.3, 155.5 (Ar-C), 168.5, 177.6, 185.5, 190.7 (CO, CS); Anal. Calcd. for$C_{23}H_{17}NO_5S_2$ (Mol. wt. 451): C, 61.18; H, 3.80; N, 3.10 Found: C, 61.11; H, 3.73; N, 2.98 %.

4.9. Synthesis of 3-(2-(4-phenoxybenzoyl)benzoyl)-2-thioxothiazolidin-4-one (11)

Acid 3 (0.01mol) was heatedinaceticanhydride (5ml)underrefluxfor4h. The separated solid was filtered, dried and recrystallized from ethanol.

Yield, 74 %; mp 184°C- 186°C; IR (Cm^{-1}): υmax: 3050 (CH-aromatic), 2915, 2875 (CH- aliphatic), 1740-1685(CO), 1310 (C=S); Ms: m/z 433 (M^{+}); ^{1}H NMR (DMSO-d6) δ: 4.19 (s, 2H, SCH_2), 7.11-7.81 (m, 13H, Ar-H); ^{13}C NMR: 38.8 (SCH_2), 117.5, 118.2, 118.4, 122.3, 127.6, 128.2, 128.6, 129.8, 131.3, 133.5, 142.4, 148.1, 154.6, 156.2 (Ar-C), 170.3, 173.5, 187.3, 192.6 (CO, CS); Anal. Calcd. for $C_{23}H_{15}NO_4S_2$ (Mol. wt. 433): C, 63.73; H, 3.49; N, 3.23 Found: C, 63.65; H, 3.39; N, 3.16 %.

4.10. Synthesis of 2-(2-(4-phenoxybenzoyl)phenyl)-6-phenyl-4-thioxo-4H-1,3-oxazine-5,5-(6H)-dicarbonitrile (13).

A mixture of isothiocyanate **2** (0.01 mol) and benzylidenemalononitrile **(12)** (0.01 mol) in dry toluene was heated under reflux for 4hrs. After cooling, the precipitatedproduct was filtered, dried and recrystallized from benzene.

Yield, 78 %; mp 213°C- 215 °C; IR (Cm^{-1}): υmax: 3007 (CH- aromatic), 2248 (C≡N), 1603 (C=N), 1267 (C=S); Ms: m/z 513 (M^{+}); ^{1}H NMR (DMSO-d6) δ: 4.87 (s, 1H, CH), 7.32-8.18 (m, 18H, Ar-H); Anal.Calcd. for $C_{31}H_{19}N_3O_3S$ (Mol. wt. 513.57): C, 72.50; H, 3.73; N, 8.18; Found: C, 72.42; H, 3.61; N, 8.07 %.

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