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Synthesis and Reactions of Some New Substituted Benzoxazin-4-One and Quinazolin-4-One

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Abstract. The reaction of 3,4-dichlorobenzoyl chloride with 3,5-dibromo anthranilic acid yielded benzoxazine derivative **(1)**, whose reaction with primary and secondary amines such as benzyl amine, *p*-chloroaniline, *p*-anisidine, *p*-toluidine, piperidine and morpholine in boiling ethanol yielded six (3,5-dibromo-2-(3,4-dichlorobenzoylamino)-N-substituted benzamides **(2-7)**. Reaction of the derivative **(1)** with hydrazine hydrate (1:1 molar proportions) gave the unexpected product 6,8-dibromo-2-(3,4-dichlorophenyl)-3-(2-(3,4-dichlorobenzoylamino)-3,5-dibromobenzamido) quinazolin-4-one **(8)**.

Keywords: benzoxazine derivatives, quinazoline derivatives, 3-thia-1-azabutane-2,4-dione

Introduction

The present investigation deals with synthesis of some new benzoxazine and quinazolinone derivatives bearing a bulky moiety at position -2 in order to study the stability and reactivity of their nucleus towards different nucleophiles. Here we report reactions of 6,8-dibromo-2-(3,4-dichlorophenyl)-*4H*-benzo[d][1,3]oxazin-4-one **(1)** with nitrogen and carbon nucleophiles, aiming to synthesize condensed and non-condensed heterocyclic systems involving quinazoline moiety due to its significant biological activities as anticonvulsant (Dandia *et al*., 2005) as well as antihistamic agents, (Amine *et al.*, 1996), inhibition of cathepsin (Gutschow *et al.*, 2002), besides other antihyperglycemic activities (Ram *et al.*, 2003) and in continuation of other investigations directed towards the synthesis and reaction of some benzoxazine and quinazoline derivatives (Ma *et al*., 2006; Zheng *et al.*, 2006).

Materials and Methods

Melting points are uncorrected. IR spectra were recorded on a Pay-Unicam SP3-2000 spectrophotometer using KBr wafer technique. The ^{1}H-NMR spectra 200 MHz were determined on a Varian Gemini using TMS as internal reference (chemical shifts are expressed as δ, ppm). Micro-analytical data (C, H, N) were obtained from the Microanalytical Center at Cairo University. The physical data are listed in Table 1.

6,8-Dibromo-2-(3,4-dichlorophenyl)-*4H*-benzo [d] [1,3] oxazin-4-one (1). To a solution of 3,5-dibromoanthranilic acid (0.01mol) in dry 50 ml pyridine, 3,4-dichlorobenzoyl chloride was added dropwise with stirring.The reaction mixture was heated on water bath for 2 h, and then poured onto acidified cold water, The separated solid was filtered off, dried and crystallized from benzene to give compound **1** as yellow crystals. IR: 1773 cm^{-1} (C=O lactone), 1622 cm^{-1} (C=N) and 1600 cm^{-1} (C=C); ^{1}H NMR (DMSO): δ 7.63-7.90 (m, 3H) and 8.07-8.45 (m, 2H).

3,5-Dibromo-2-(3,4-dichlorobenzoylamino)-N–substituted benzamides (2-7). A mixture of **1** (4.49 g, 0.01 mol) and primary amines and/or secondary amines namely benzyl amine, *p*-chlroaniline, *p*-anisidine, *p*-toluidine, piperidine and morpholine (0.01 mol) in 50 ml ethanol was refluxed for 3 h. The solid obtained, while heating and after concentration of solvent was filtered off and recrystallized from a suitable solvent to give compounds **2-7**.

3,5-Dibromo-2-(3,4-dichlorobenzoylamino)-N-benzyl benzamide (2). IR: 3270 cm^{-1} (NH) and 1650 cm^{-1} (C=O); ^{1}H NMR (DMSO): δ 4.52(m, 2H), 7.18-7.22 (m, 5H phenyl ring), 7.72-8.13(m, 5H halogenated rings), 8.93-8.97(s, 1H) and 10.38-10.40(s, 1H).

3,5-Dibromo-2-(3,4-dichlorobenzoylamino)-N-(4-chlorophenyl)benzamide (3). IR:3250 cm^{-1} (NH) and 1660 cm^{-1} (C=O).

3,5-Dibromo-2-(3,4-dichlorobenzoylamino)-N-(4-methoxyphenyl) benzamide (4). IR:3240 cm^{-1} (NH) and 1660 cm^{-1} (C=O).

3,5-Dibromo-2-(3,4-dichlorobenzoylamino)-N-(4-methylphenyl) benzamide (5). IR:3260 cm^{-1} (NH) and 1650 cm^{-1} (C=O).

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Table 1. Characterization and physical data of synthesized compounds

Compound nos.	M.p.(°C)	Solvent (yield%)	M.F (M. Wt.)	Calc.% (found%) C	H	N
1	187-188	B	$C_{14}H_5Br_2Cl_2NO_2$	37.37	1.12	3.11
		80	449.91	36.96	1.97	2.98
2	269-270	D	$C_{21}H_{14}Br_2Cl_2N_2O_2$	45.27	2.53	5.03
		70	557.06	45.21	2.51	4.90
3	281-282	B/EtOH	$C_{20}H_{11}Br_2Cl_3N_2O_2$	41.59	1.92	4.85
		80	577.48	41.27	1.73	4.84
4	271-272	B/EtOH	$C_{21}H_{14}Br_2Cl_2N_2O_3$	44.01	2.46	4.88
		80	573.06	43.86	2.34	4.80
5	234-235	D	$C_{21}H_{14}Br_2Cl_2N_2O_2$	45.27	2.53	5.03
		80	557.06	45.94	2.81	4.96
6	130-132	Pet. (80/100)/B	$C_{19}H_{16}Br_2Cl_2N_2O_2$	42.65	3.01	5.23
		70	535.05	42.34	2.87	5.08
7	252-254	D	$C_{18}H_{14}Br_2Cl_2N_2O_3$	40.25	2.63	5.22
		70	533.87	40.72	2.09	4.96
8	254-256	D	$C_{28}H_{12}Br_4Cl_4N_4O_3$	36.80	1.32	6.13
		90	913.85	36.33	1.23	5.98
9	Over300	DMF	$C_{14}H_6Br_2Cl_2N_2O_2$	36.16	1.30	6.02
		60	464.92	37.56	1.28	5.56
10	230-232	D	$C_{14}H_7Br_2Cl_2N_3O$	35.53	1.59	11.05
		70	463.94	35.80	1.30	10.07
11	250-252	D	$C_{15}H_8Br_2Cl_2N_4O_2$	36.24	1.52	9.06
		80	506.96	36.09	1.42	8.97
12	191-192	D	$C_{29}H_{12}Br_4Cl_4N_4O_4S$	35.76	1.24	5.75
		60	973.92	34.98	1.21	5.72
13	211-212	B/EtOH	$C_{17}H_7Br_2Cl_2NO_5$	38.09	1.32	2.61
		40	535.95	38.12	1.51	2.59
14	220-221	B/EtOH	$C_{14}H_7Br_2Cl_2NO_3$	35.93	1.51	2.99
		50	467.92	35.67	1.55	2.92
15	Over300	DMF	$C_{14}H_7Br_2Cl_2N_2O$	37.45	1.35	6.25
		80	448.93	37.34	1.24	6.00
16	191-192	Pet. (80/100)/B	$C1_{14}H6Br_2C_{12}N4O_2$	34.11	1.22	11.36
		70	492.94	33.98	1.12	11.23

EtOH =ethanol; B = benzene; D = 1,4-dioxane; DMF = N,N-dimethylformamide; Pet. = petroleum ether

3,4-Dichloro-N-(2,4-dibromo-6-(piperidine-1-carbonyl) phenyl)benzamide (6). IR: 3230 cm^{-1} (NH) and 1660 cm^{-1} (C=O).

3,4-Dichloro-N-(2,4-dibromo-6-(morpholine-4-carbonyl)phenyl) benzamide (7). IR:3240 cm^{-1} (NH) and 1680 cm^{-1} (C=O).

6,8-Dibromo-2-(3,4-dichlorophenyl)-3-(2-(3,4-dichloro-benzoylamino)-3,5-dibromobenzamido)quinazolin-4-one (8). A mixture of compound **1** (4.49 g,0.01 mol) and hydrazine hydrate (0.5 g, 0.01mol) in 50 ml. ethanol was refluxed for one h. The solid that separated while refluxing was filtered off and recrystallized from 1,4-dioxane to give compound **8** as white crystals. IR: 3300-3500 cm^{-1} (NH) or enolic (OH), 1645 cm^{-1} (CO); ^{1}H NMR (DMSO): δ 8.50 (d, 1H), 8.45 (d, 1H), 8.36 (s, 1H), 7.91 (m, 4H), and 5.71 (br, 1H, NH).

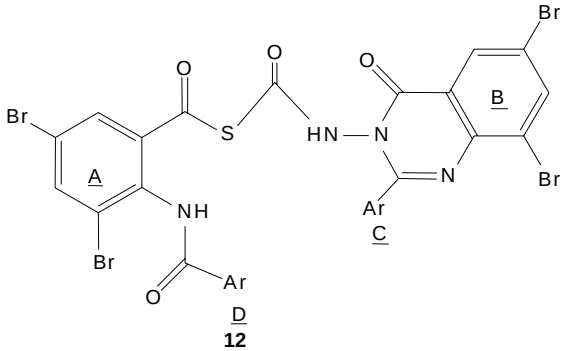
6,8-Dibromo-2-(3,4-dichlorophenyl)-3-N-substituted quinazolin-4-one (9,10, 11). A mixture of compound **1** (4.49 g, 0.01 mol) and primary amines, namely, hydrazine hydrate, hydroxylamine hydrochloride and/or semicarbazide hydrochloride (0.01 mol) was refluxed in 50 ml *n*-butanol for 4 h. The solid that formed while refluxing was filtered off and recrystallized from a suitable solvent to give comounds **9, 10,** and **11**.

6,8-Dibromo-2-(3,4-dichlorophenyl)-3-hydroxyquinazoline-4-(3H)-one (9). IR: 3440 cm^{-1} (NH), 1684cm^{-1} (CO).

3-Amino-6,8-dibromo-2-(3,4-dichlorophenyl)quinazoline-4-(3H)-one (10). IR: 3200 cm^{-1} (NH), 3450-3315 cm^{-1} (NH_2) and 1688 cm^{-1} (C=O).

1-(6,8-Dibromo-2-(3,4-dichlorophenyl)-4-oxoquinazolin-3-(4H)-yl)urea (11). IR: 3211 cm^{-1} (NH), 3330-3260 cm^{-1} (NH_2) and 1672 cm^{-1} (C=O).

1-(6,8-Dibromo-2-(3,4-dichlorophenyl)quinazolin-4-one-3-yl)-4-(2-(3,4-dichlorobenzoylamino)-3,5-dibromophenyl)-3-thia-1-azabutane-2,4-dione (12). A mixture of compound **1** (4.49 g, 0.01 mol) and thiosemicarbazide (0.91 g, 0.01 mol) in 50 ml ethanol was refluxed for 4 h. The solid that separated was filtered off and recrystallized from 1, 4-dioxane to give compound **12** as colourless crystals. IR: 3220-3370 cm^{-1} (NH/OH) 1685 cm^{-1} (CO) and 1610-1590 cm^{-1} C=N/C=C); ^{1}H NMR (DMSO): δ 7.65 (s, 1H, CONH), 7.84-8.05 (m, 4 H aromatic A & B), 8.22-8.39 (m, 3H aromatic C), 8.062-8.063 (m, 3H aromatic D) and 10.45 (s, NH exchangeable with D_2O).



12

2-(6,8-Dibromo-2-(3,4-dichlorophenyl)-*4H*-benzo [d] [1,3] oxazin-4-ylidene) malonic acid (13) and 3,5-Dibromo-2-(3,4-dichlorobenzamido) benzoic acid (14). A mixture of compound **1** (4.49 g, 0.01 mol) and active methylene compounds namely, ethyl cyanoacetate and /or diethyl malonate (0.01 mol) in 10 ml. dry pyridine was refluxed for 10 h. The reaction mixture was poured onto crushed ice and acidified with 10% HCl, 20 ml; the precipitate was filtered off, washed with water and dried. Products **13** and **14** were separated by fractional crystallization using benzene and ethyl alcohol, respectively.

2-(6, 8-Dibromo-2-(3, 4-dichlorophenyl)-4 H-benzo [d] [1,3] oxazin-4-ylidene) malonic acid (13). IR: 1610cm^{-1}(CN) 1700 cm^{-1} (CO) and 3350-3500 cm^{-1} (OH); ^{1}H NMR (DMSO): δ 7.93-8.08 (m, 3H aromatic 8.29-8.34 (m, 2H aromatic) and 10.55(s, 2H, 2COOH)].

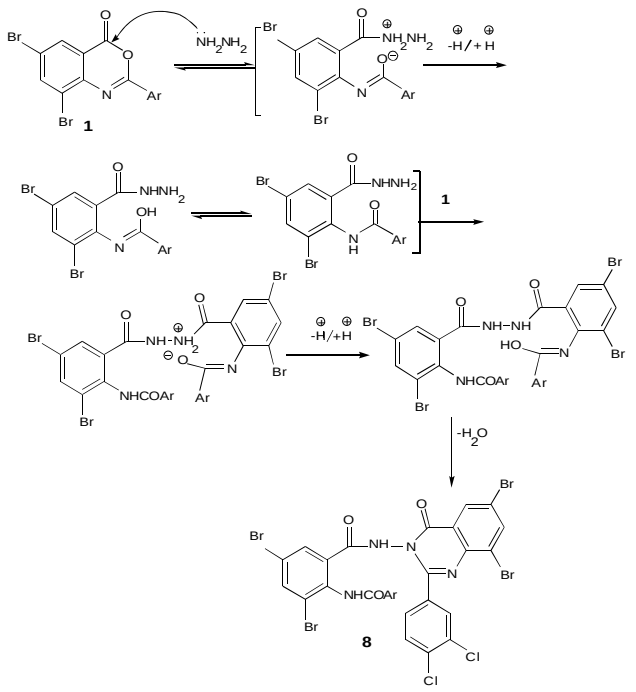
3,5-Dibromo-2-(3,4-dichlorobenzamido) benzoic acid (14). IR: 1680 cm^{-1} (amido CO) 1690 cm^{-1} (CO), 3270 cm^{-1}(NH) 3570 cm^{-1} (OH); ^{1}H NMR (DMSO): δ 7.92-8.08 (m, 3H aromatic) 8.28-8.34 (m, 2H aromatic) and 10.56 (*s*, 2H, COOH, NHCO).

6,8-Dibromo-2-(3, 4-dichlorophenyl)quinazoline-4*(3H)*-one (15). A mixture of compound **1** (4.49 g, 0.01 mol) and 20 ml formamide and/or amm. acetate (0.73 g, 0.01 mol) was fused on oil bath at 190 °C for an h. The reaction mixture was poured onto cold water and the solid formed was filtered off, washed with water, dried and recrystallized from *N*, *N* dimethlyformamide to give compound **15** as pale yellow crystals. IR:1684 cm^{-1} (CO), 3445 cm^{-1} (NH), 1610 cm^{-1} (C=N); ^{1}H NMR (DMSO): δ 13.12 (s, 1H NH or OH, exchangeable with D_2O) and 7.92-8.34 (m, 5H, aromatic).

3,5-Dibromo-2-(5-(3,4-dichlorophenyl)-*1H*-tetrazol-1-yl) benzoic acid (16). A mixture of compound **1** (4.49 g, 0.01 mol) and sod. azide (0.65 g, 0.02 mol) in acetic acid (20 ml) was refluxed for 12 h. The solvent was removed and the residue was washed with water (3x20 ml), filtered off, dried and crystallized from pet. ether (80-100)/benzene mixture to give compound **16** as light yellow crystals. IR:3445cm^{-1} (OH) and 1690 cm^{-1} of (CO); ^{1}H NMR (DMSO): δ 11.1 (s, 1H COOH, exchangeable with D_2O) and 7.92-8.30 (m, 5H aromatic).

Results and Discussion

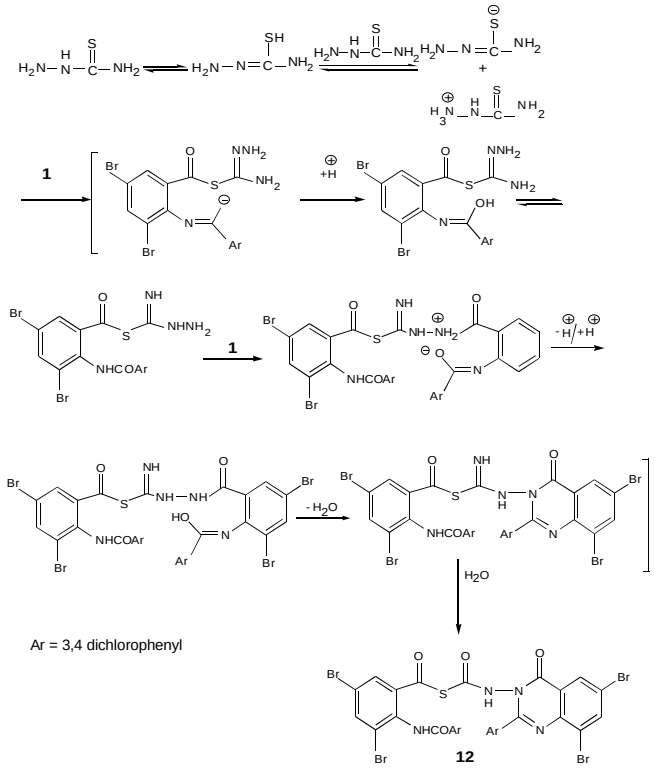
The benzoxazine derivative **(1)** was prepared in situ by the reaction of 3,4-dichlorobenzoyl chloride with 3,5-dibromo anthranilic acid. Reaction of compound **1** with primary and secondary amines such as benzyl amine, *p*-chloroaniline, *p*-anisidine, *p*-toluidine, piperidine and morpholine in boiling ethanol yielded (3,5-dibromo-2-(3,4-dichlorobenzoylamino)-N–substituted benzamides (compounds **2-7**) (scheme 1). Also reaction of compound **1** with hydrazine hydrate (1:1 molar proportion) gave the unexpected product 6,8-dibromo-2-(3,4-dichlorophenyl)-3-(2-(3,4-dichlorobenzoylamino)-3,5-dibromobenzamido)quinazolin-4-one (**8**). Formation of compound **8** take place probably according to the following mechanism:

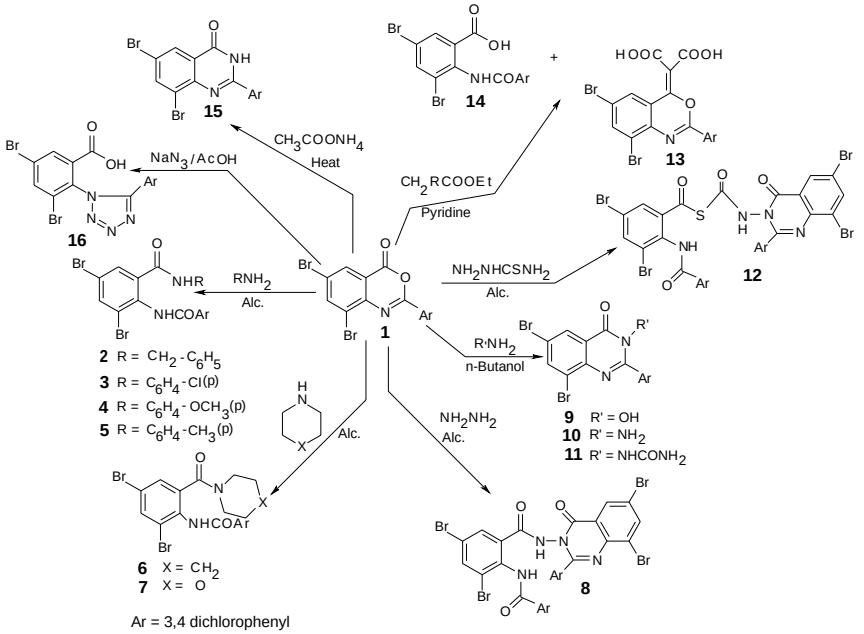


On the other hand, reaction of compound **1** with hydrazine hydrate, hydroxylamine hydrochloride and/or semicarbazide hydrochloride in boiling *n*-butanol gave 6, 8-dibromo 2-(3′,4′-dichlorophenyl)quinazolin-4-one derivatives. (**9,10,11**).

According to our interests in developing new condensed and non condensed heterocyclic systems, (El-Ziaty and Shiba, 2007), compound **1** was treated with thiosemicarbazide in boiling ethanol giving 1-(6,8-dibromo-2-(3, 4-dichlorophenyl) quinazolin-4-one-3-yl)-4-(2-(3,4-dichlorobenzoylamino)-3,5-dibromophenyl)-3-thia-1-azabutane-2,4-dione **(12)** as unexpected product in contrary to that previously reported, by Nassar and Aly (2002) and Mohamed *et al.* (1981) (scheme 1).

Formation of compound **12** probably takes place according to the following mechanism:

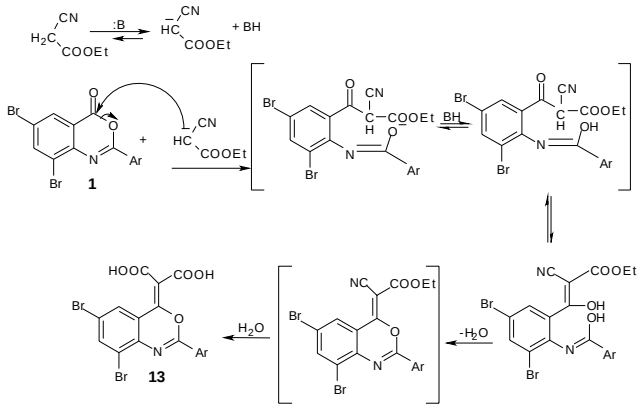




Scheme 1

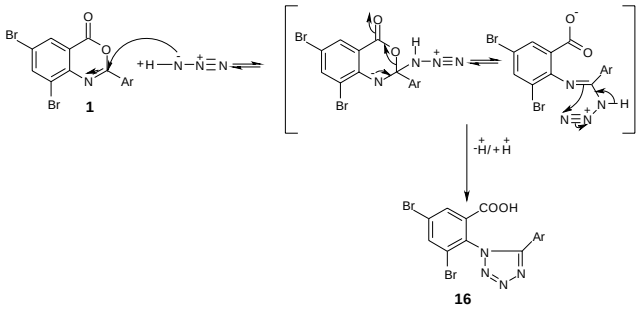
By studying reaction of compound **1** with active methylene compounds, namely, ethyl cyanoacetate and/or diethyl malonate in pyridine afforded 2-(6,8-dibromo-2-(dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-ylidene)malonic acid **(13)** and 3,5-dibromo-2-(3,4-dichlorobenzamido)benzoic acid **(14),** the open form of **1**, respectively.

Formation of compound **13** probably takes place according to the following mechanism:



Fusion of compound **1** with ammonium acetate and/or formamide yielded the corresponding 6,8-dibromo-2-(3,4-dichlorophenyl) quinazolin-4-(*3H*)-one **(15)** as previously reported (Nassar and Aly, 2002). Ring opening of **1** with hydrazoic acid gave 3,5-dibromo-2-(5-(3,4-dichlorophenyl)-*1H*-tetrazol-1-yl) benzoic acid **(16)** (scheme 1).

Formation of compound **16** probably takes place according to the following mechanism:



References

Amine, M.S., Nassar, S.A., EL-Hashash, M.A., Essawy, S.A., Hashish, A.A. 1996. Synthesis and characterization of some biologically active pyrimidine derivatives containing sulphur-Part 1. *Indian. J. Chem.* **35B:** 388-391.

Dandia, A., Singh, R., Sarawgi, P. 2005. Green chemical multi-component one-pot synthesis of fluorinated 2,3-disubstituted quinazolin-4*(3H)*-ones under solvent-free conditions and their anti-fungal activity. *J. Fluor. Chem.* **126:** 307-312.

El-Ziaty, A.K., Shiba, S.A. 2007. Antibacterial activities of new (E) 2-cyano-3-(3′,4′dimethoxyphenyl)-2-propenoylamide derivatives. *Synth. Comm.* **37:** 4043-4057.

Gutschow, M., Kuerschner, L., Pietsch, M., Ambrozak, A., Newmann, U., Gunther, R., Hofmann, H. J. 2002. Inhibition of cathepsin G by 2-amino-3,1-benzoxazin-4-ones: Kinetic investigation and docking studies. *Arch. Biochem. Biophy.* **402:** 180-191.

Mohamed, M.M., EL-Hashash, M.A., Essawy, A., Shaban, M. E. 1981. Reactions of 2-cyanomethyl-3,1-benzoxazin-4(*H*)-one with nucleophilic reagent, acid anhydride and acid amides. *Indian J. Chem.* **20B:** 718-719.

Nassar, S.A., Aly, A. A. 2002. Synthesis of some new substituted β-(quinazolin-2-yl) acrylic acid derivatives of expected biological activity. *Egypt. J. Chem.* **45:** 205-217.

Ram, V.J., Farhanullah, Tripathi, B.K., Srivastava, A.K. 2003. Synthesis and antihyperglycemic activity of suitably functionalized 3H-quinazoline-4-one. *Bioorganic Med. Chem.* **11:** 2439-2444.

Ma, S., Li, J., Sun, Y., Zhao, J., Zhao, X.,Yang, X., Zhang, L., Wang, L., Zhou, Z. 2006. Synthesis of 1,2-dihydro-4*H*-3,1-benzoxazine derivatives via $ZnCl_2$ catalyzed cyclocondensation reaction. *Tetrahedron* **62:** 7999-8005.

Zheng, X., Hodgetts, K.J., Brielmann, H., Hutchison, A., Burkamp, F., Brian Jones A., Blurton, P., Clarkson, R., Chandrasekhar, J., Bakthavatchalam, R., De Lombaert, S., Crandall, M., Cortright, D., Blum, C.A. 2006. From arylureas to biarylamides to aminoquinazolines: Discovery of a novel, potent TRPV1 antagonist. *Bioorg. Med. Chem. Lett.* **16:** 5217-5221.