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RESEARCH ARTICLE

Synthesis and Identification of Some New Derivatives of Benzoxazole Bearing Pyrazole and 1, 2, 4-Triazine Rings

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Abstract

In this work, new derivatives of benzoxazole bearing two types of heterocyclic rings; pyrazole and 1,2,4-triazine have been described. This work involved preparation hydrazide derivative **5** as a key material in the synthetic route, which was obtained over five sequence steps. Reaction of 2-aminophenol with CS_2 under basic conditions afforded 2-mercaptobenzoxazole **1** in 61% yield. Michael addition of **1** to ethyl acrylate provided the desired ester **2** in a good yield (74%). Thereafter, hydrolysis of the ester group at **2** using basic conditions yielded the corresponding acid **3**. The acid **3** was then converted to acid chloride **4**, followed by nucleophilic addition of hydrazine hydrate was performed in a one-pot reaction and provided the desired hydrazide **5** in a 71% yield. Pyrazole derivatives **6-11** were then obtained *via* reaction of **5** with 1, 3-dicarbonyl compounds. Whereas, treatment of **5** with 1, 2-dicarbonyl compounds and NH_4OAc in the presence of K_2CO_3 as a base gave the desired 1, 2, 4-triazine derivatives **12-17**.

Keywords: *Benzoxazole, Anticancer, 1, 2, 4-Triazine ring, Heterocyclic.*

Introduction

Benzoxazole is a fused bicyclic heteroaromatic compound has a benzene and oxazole rings. These heterocycles are important synthetic and natural compounds which showed a diverse range of biological [1] antileishmanial [2], anti-inflammatory [3], antimycobacterial [4], anti-HIV [5], antimicrobial [6], analgesic [7], antioxidant [8]. In addition, presence of this bicyclic system was found in many natural products that play an important role in drug discovery. For example, nataxazole showed a significant antitumor activity [9], and caboxamycin, was used as an antibiotic [10]. UK-1 showed a potent cytotoxic activity against HeLa, B16 and P388 cells [11] (Figure 1).

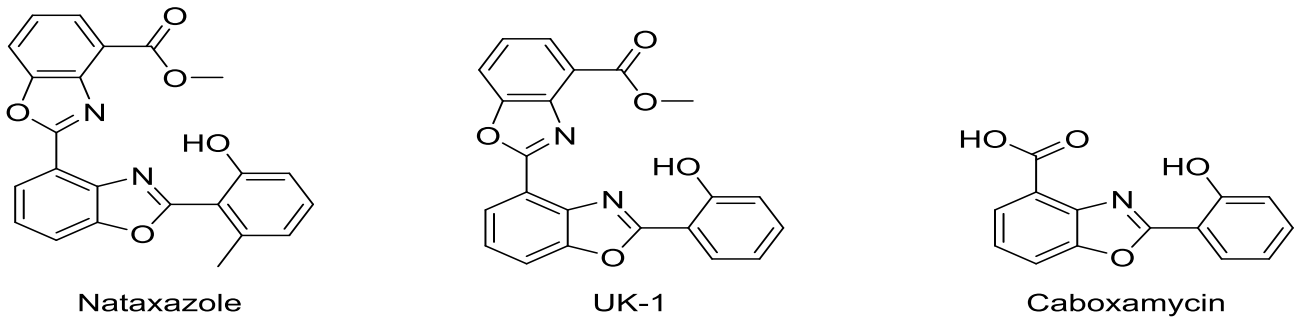


Figure 1: Biologically active natural products containing benzoxazole moiety in their structures

Furthermore, pyrazole and 1, 2, 4-triazine are an important kind of heterocyclic rings bearing nitrogen atoms. Both exhibited a wide range of biological properties, for example, pyrazole derivatives were employed as an anti-inflammatory [12], antitumor [13], antimicrobial [14] and antiviral activities [15].While, 1, 2, 4-triazine derivatives were used as anticancer [16], antithrombotic [17], antimalarial [18], antiplatelet [19] and α-glucosidase inhibition [20]. In our work, the product 3-(benzo[d] oxazol-2-ylthio)

propanehydrazide **5** will be synthesized over five sequence steps starting from commercially available 2-aminophenol. Following this, construction of pyrazole and 1, 2, 4-triazine rings on benzoxazole will performed *via* functionalisation of the hydrazide group at **5**, to afford a new selection of heterocyclic compounds **6-11** and **12-17** (Scheme 1).

Results and Discussion

The synthesis of 3-(benzo[d]oxazol-2-ylthio)-1-(1H-pyrazol -1-yl) propan-1-one derivatives 6-11 and 2-((2-(1, 2, 4-triazin-3-yl) ethyl)thio)benzo[d] oxazole derivatives 12-17 was described in Scheme 1. Table 1 displays some physical properties of the prepared products 1-17. Initially, the preparation of benzoxazole 1 was achieved successfully according to the literature procedure by Wang *et al* [21]. This was done *via* treatment of 2-aminophenol with CS_2 in the presence of KOH gave the desired product 1 in a 61% yield. This product 1 was confirmed by disappearance of stretching absorptions of OH and NH_2 groups at 2-aminophenol and appearance bands at 1665 cm^{-1} and 2590 cm^{-1}, which due to C=N and S-H stretching of the desired product 1 as shown in the Table 2.

All the starting material was consumed within 6 hours. Thereafter, nucleophilic addition of 1 to ethyl acrylate thermodynamically provided the corresponding ester derivative 2 in a good yield (74%). Fortunately, only single product 2 was formed and the undesired kinetic product was not detected. The FT-IR spectrum of 2 showed absorption band at 1747 cm^{-1}, which belong to the C=O of the ester group. Meanwhile, the absorption of the SH group was disappeared in the product 2 as expected. Following this, hydrolysis of the ester group at 2 under basic conditions (NaOH 1.0 N, THF) gave the desired carboxylic acid **3** in an excellent yield (98%).

The conversion to acid **3** was monitored by TLC easily due to high polarity of the carboxyl group at **3**. The solvent was then removed carefully, and the crude material used in the next step without further purification. Reaction of the acid **3** with $SOCl_2$ yielded the corresponding acid chloride derivative **4**, which was then directly treated with hydrazine hydrate (99%) in a one-pot reaction due to the instability of 4.

This afforded hydrazide derivative 5 in a very good yield (71%). The FT-IR spectrum of acid hydrazide 5 showed two absorption bands at 3272 cm^{-1} attributed to NH_2 group, and at 3141 cm^{-1} belong to NH group. The product 5 was then used as a key intermediate for the synthesis of pyrazole derivatives 6-11 and 1, 2, 4-triazine derivatives 12-17.

The heterocyclisation of hydrazide 5 to the pyrazole derivatives 6-11 was carried out successfully *via* reaction with 1,3-dicarbonyl compounds in glycerol-water [22]. The desired products 6-11 were obtained in moderate to good yields (59-72%). The products 6-11 were confirmed by FT-IR spectroscopy that showed absorptions between 1640-1644 cm^{-1} and 1572-1591 cm^{-1} attributed to C=N and C=C groups of the pyrazole ring.

In addition, the absorptions of NH_2, NH and C=O stretching bands of the hydrazide group at the starting material 5 were completely disappeared at the products 6-11. ^1H NMR spectrum of product 6 showed two singlet signals at 2.20 and 2.42 ppm attributed to the two CH_3 groups at the pyrazole ring, and multiple signals between 3.18 and 3.50 ppm were assigned to the two CH_2 groups. Singlet signal at 6.22 ppm belong to the CH of the pyrazole ring.

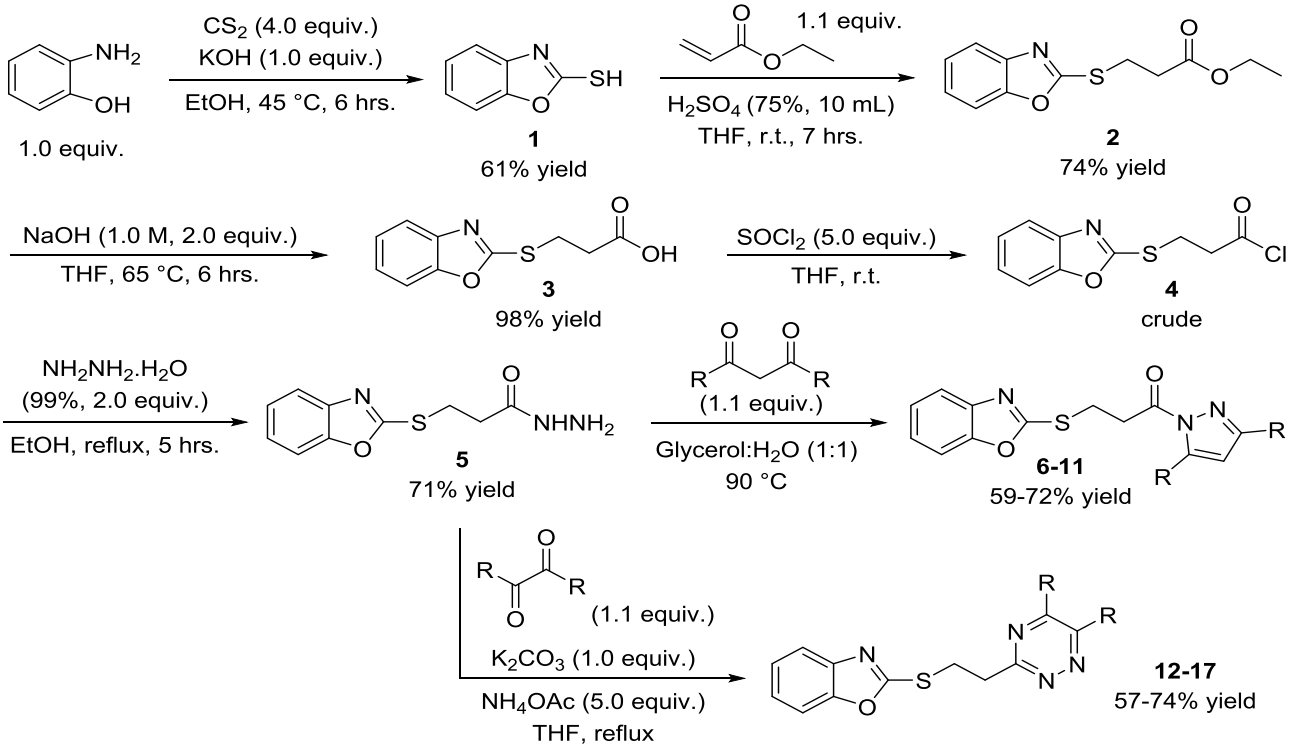
Multiple signals between 7.24 and 7.51 ppm attributed to the four protons of the benzene ring. While, ^{13}C NMR spectrum of **6** showed two peaks at 13.1 and 13.9 ppm for two CH_3 groups, and two peaks at 29.6 and 31.8 ppm for two CH_2 groups. Nine peaks from 105.7 to 152.8 ppm attributed to the aromatic carbons of the benzene and pyrazole rings. Finally, two peaks at 170.5 and 180.3 ppm due to the carbonyl of amide and imine groups respectively. ^1H NMR spectrum of compound **9** showed a singlet signal at 2.31 ppm attributed to the CH_3 group at the pyrazole ring. Two groups of CH_2 were appeared between 2.80 and 3.44 ppm, and the proton of the pyrazole ring was appeared at 5.78 ppm.

Multiple signals between 7.17-8.34 ppm are belong to the aromatic protons. ^{13}C NMR showed the desired peaks of the product **9** as described in the Table 3. In addition, the product **10** was confirmed by ^1H- and ^{13}C NMR spectroscopy, ^1H NMR spectrum showed singlet signal at 2.3 ppm attributed to the CH_3 group of pyrazole ring, and two at

2.79 and 3.37 ppm due to the four aliphatic protons of two CH_2 groups at 10. Two singlet signals at 3.79 and 3.94 ppm belong to the two OCH_3 groups. Singlet signal at 6.31 ppm for CH of the pyrazole ring. Multiple signals between 7.17 and 7.79 ppm belong to the aromatic protons. While, the desired 1, 2, 4-triazine derivatives 12-17 were prepared in a one-pot reaction according to the modified literature procedure by Rostamizadeh and Sadeghi [23]. This was performed by reaction of 6 with 1, 2-dicarbonyl compounds and NH_4OAc in the presence of K_2CO_3 as a base provided 12-17 in yields ranging from 57 to 74% (Scheme 1).

The structures of 12-17 were confirmed by the disappearance of the NH_2, NH and C=O stretching bands of the hydrazide group as shown in the Table 2.

^1H NMR spectrum of compound 16 showed multiple signals between 1.36 and 1.31 ppm attributed to the CH_3 of the ethyl group at the triazine ring. Six protons for three CH_2 groups were appeared between 2.99 and 3.29 ppm, and multiple signals at 7.26-7.59 ppm are belong to the four protons of the benzene ring. Finally, two protons for furan ring were appeared between 7.77 and 8.14 ppm. Whereas, ^{13}C NMR showed the characteristic peaks of the product 16 as shown in the Table 3.

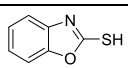
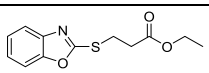


Scheme 1: Outline of the synthesis of benzoxazole derivatives bearing heterocyclic rings

Conclusion

This article has demonstrated the preparation of new derivatives of benzoxazole containing pyrazole and 1, 2, 4-triazine rings over six steps. The key step is functionalising the hydrazide group with 1, 3- and 1, 2-dicarbonyl compounds to provide the desired products. The pyrazole derivatives were isolated in moderate to goods yields (57-72%). Whereas, 1, 2, 4-triazine derivatives were obtained in yields ranging from 57 to 74%.

Table 1: Physical properties of the prepared compounds 1-17

Compound structure	Compound number	Color	m.p. (^{0}C)	Yield (%)	Solvent of recrystallization
	**1**	Yellow	191-931	61	Ethanol
	**2**	Pale yellow	175-177	74	Ethyl acetate

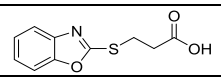
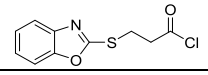
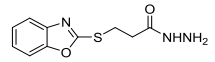
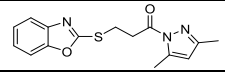
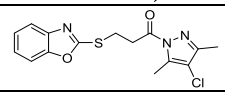
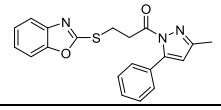
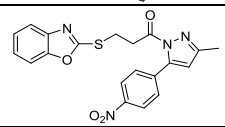
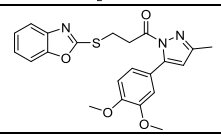
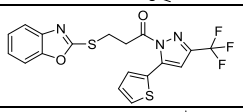
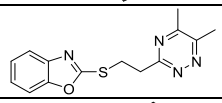
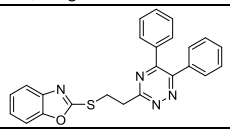
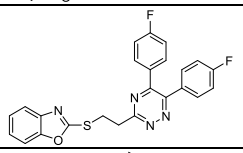
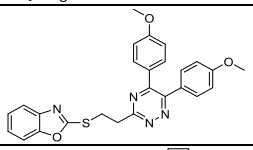
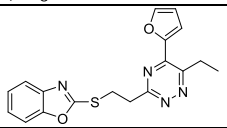
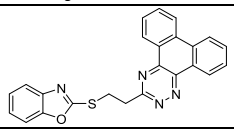
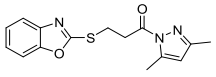
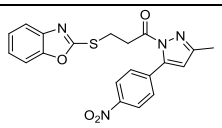
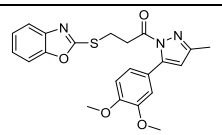
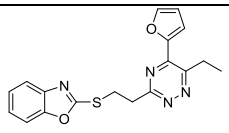
	**3**	Yellow	167-169	98	Without purification
	**4**	Pale yellow	-	crude	Without purification
	**5**	Dark yellow	157-159	71	Ethanol
	**6**	Pale yellow	137-139	65	Ethanol
	**7**	Pale yellow	123-125	68	Ethanol
	**8**	Pale yellow	176-178	70	Ethanol
	**9**	Yellow	175-177	59	Ethanol
	**10**	Yellow	113-115	72	Ethanol
	**11**	Pale red	101-103	60	Ethyl acetate
	**12**	Pale yellow	119-121	72	Ethyl acetate
	**13**	Pale yellow	144-146	74	Ethyl acetate
	**14**	Pale yellow	188-190	69	Ethyl acetate
	**15**	Yellow	176-178	71	Ethanol
	**16**	Pale yellow	153-155	57	Ethanol
	**17**	Pale yellow	213-215	66	Ethanol

Table 2: Characteristic absorption bands of FT-IR spectra of the compounds 1-17

Compound number	FTIR spectral data (cm^{-1})						
	υ(C=O) Carbonyl	**υ(C-H) Aromatic**	**υ(C-H) Aliphatic**	**υ(C=C) Aromatic**	**υ(C=N) Imine**	**υ(C-O-C) Ether**	**Others (υ)**
1	-	3077 3051	-	1553	1665	1240 1105	2590 (S-H)
2	1747	3075 3045	2945 2834	1590	1663	1239 1109	-
3	1724	3078 3043	2950 2832	1571	1664	1237 1101	-
4	1792	3075 3052	2947 2830	1587	1663	1249 1106	-

5	1680	3074 3039	2949 2830	1568	1660	1241 1111	3272, 3141 ($NHNH_2$) hydrazide
6	1666	3071 3040	2947 2822	1572	1663 1641	1247 1112	2966 (C-H) olefinic
7	1669	3079 3040	2953 2820	1581	1667 1642	1241 1113	1089 (C-Cl) aromatic
8	1671	3072 3042	2946 2824	1591	1671 1644	1230 1115	2959 (C-H) olefinic
9	1667	3075 3033	2949 2825	1587	1672 1640	1239 1110	1541, 1342 ($C-NO_2$) 2960 (C-H) olefinic
10	1665	3076 3043	2947 2827	1586	1670 1643	1237 1109	2967 (C-H) olefinic
11	1668	3070 3037	2957 2825	1577	1670 1644	1239 1100	1122 (C-F) aliphatic 2968, 2981 (C-H) olefinic
12	-	3075 3037	2953 2833	1572	1668 1647	1241 1114	-
13	-	3081 3042	2951 2843	1589	1663 1641	1240 1113	-
14	-	3076 3035	2950 2623	1588	1672 1647	1241 1110	1203 (C-F) aromatic
15	-	3079 3033	2942 2838	1592	1675 1646	1242 1114	-
16	-	3080 3023	2949 2848	1590	1673 1647	1237 1099	2969 (C-H) olefinic
17	-	3076 3039	2946 2848	1596	1674 1643	1246 1114	-

Table 3: ^{1}H NMR and ^{13}C NMR data for 6, 9, 10 and 16

Compound number	Compound structure	^{1}H and ^{13}C NMR data
6		^{1}H NMR δ_H = 7.51-7.46 (2H, m, Ar-H), 7.34-7.24 (2H, m, Ar-H), 6.22 (1H, s, pyarzole-H), 3.50-3.46 (2H, m, CH_2), 3.25-3.18 (2H, m, CH_2), 2.42 (3H, s, CH_3), 2.20 (3H, s, CH_3); ^{13}C NMR δ_C = 180.3 (C=N), 170.5 (C=O), 152.8 (Ar-C), 148.3 (Ar-C), 143.5 (Ar-C), 131.4 (Ar-C), 125.3 (Ar-C), 123.9 (Ar-C), 110.7 (Ar-C), 110.2 (Ar-C), 105.7 (Ar-C), 31.8 (CH_2), 29.6 (CH_2), 13.9 (CH_3), 13.1 (CH_3).
9		^{1}H NMR δ_H = 8.34-8.24 (2H, m, Ar-H), 8.01-7.94 (2H, Ar-H), 7.51-7.46 (1H, m, Ar-H), 7.27-7.17 (3H, m, Ar-H), 5.78 (1H, s, pyrazole-H), 3.43-3.33 (2H, m, CH_2), 2.89-2.80 (2H, m, CH_2), 2.31 (3H, s, CH_3); ^{13}C NMR δ_C = 181.1 (C=N), 170.3 (C=O), 151.7 (Ar-C), 148.6 (Ar-C), 145.2 (Ar-C), 141.1 (Ar-C), 131.4 (Ar-C), 129.0 (Ar-C), 128.1 (Ar-C), 125.4 (Ar-C), 124.0 (Ar-C), 122.2 (Ar-C), 119.3 (Ar-C), 110.7 (Ar-C), 110.2 (Ar-C), 31.7 (CH_2), 29.7 (CH_2), 13.9 (CH_3).
10		^{1}H NMR δ_H = 7.79-7.67 (3H, m, Ar-H), 7.50-7.45 (1H, Ar-H), 7.29-7.17 (3H, m, Ar-H), 6.31 (1H, s, pyrazole-H), 3.94 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.37-3.28 (2H, m, CH_2), 2.89-2.79 (2H, m, CH_2), 2.3 (3H, s, CH_3); ^{13}C NMR δ_C = 179.8 (C=N), 171.1 (C=O), 147.8 (Ar-C), 135.0 (Ar-C), 133.8 (Ar-C), 133.5 (Ar-C), 130.8 (Ar-C), 129.1 (Ar-C), 128.4 (Ar-C), 126.9 (Ar-C), 124.8 (Ar-C), 123.4 (Ar-C), 122.6 (Ar-C), 120.7 (Ar-C), 110.1 (Ar-C), 109.6 (Ar-C), 105.1 (Ar-C), 56.7 (OCH_3), 56.1 (OCH_3), 31.8 (CH_2), 29.1 (CH_2), 13.5 (CH_3).
16		^{1}H NMR δ_H = 8.14-8.11 (1H, m, furan-H), 7.81-7.77 (1H, m, furan-H), 7.59-7.50 (1H, m, Ar-H), 7.44-7.26 (4H, m, Ar-H), 3.29-3.19 (4H, m, $2CH_2$), 3.09-2.99 (2H, m, CH_2), 1.36-1.31 (3H, s, CH_3);^{13}C NMR δ_C = 179.8 (C=N), 166.1 (C=O), 157.3 (Ar-C), 155.2 (Ar-C), 153.3 (Ar-C), 151.5 (Ar-C), 150.3 (Ar-C), 147.8 (Ar-C), 146.2 (Ar-C), 130.8 (Ar-C), 124.8 (Ar-C), 123.4 (Ar-C), 110.1 (Ar-C), 109.6 (Ar-C), 36.2 (CH_2), 34.0 (CH_2), 24.7 (CH_2), 12.3 (CH_3).

Materials and Methods

General Experimental Procedures

All reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm pre-coated silica-gel F_{254} plates, spots were detected with iodine vapour. The FT-IR spectra were recorded on SHIMDZU FT-IR 8400 spectrophotometer; the samples were run in KBr discs. Melting points are uncorrected and were recorded in open capillary tubes using Gallenkamp meting point apparatus. ^{1}H and ^{13}C NMR spectral data were recorded using a Bruker AV(III)400HD spectrometer at university of Nottingham. Chemical shifts are quoted in ppm downfield from tetramethylsilane (TMS) as internal standard or DMSO-d_6 either in ^{1}H NMR or ^{13}C NMR as reference (δ_H 2.50 ppm or δ_C 39.52 ppm respectively).

Preparation of benzo[d]oxazole-2-thiol (1)

This compound was prepared according to the literature procedure [21]. To a mixture of 2-aminophenol (10 g, 91.6 mmol, 1.0 equiv.) and KOH (5.1 g, 91.6 mmol, 1.0 equiv.) in absolute ethanol (100 mL), CS_2 (28 g, 367 mmol, 4.0 equiv.) was then added carefully and stirred at 45 ^{0}C for 6 hours, after which TLC indicated the consumption of the starting material. Then the solvent was evaporated, and the crude material poured to ice cold water, followed by addition HCl (10%, 60 mL). The organic layer was then extracted with ethyl acetate (2 × 25 mL) and dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo* to provide the crude material, which was recrystallized from ethanol to afford **1** (8.5 g, 55.9 mmol, 61%).

Preparation of ethyl 3-(benzo[d]oxazol-2-yloxy)propanoate (2)

A solution of compound **1** (8.1 g, 53.6 mmol, 1.0 equiv.) and ethyl acrylate (6.3 mL, 59 mmol, 1.1 equiv.) in anhydrous THF (75 mL), was added H_2SO_4 (75%, 10 mL) slowly over 30 minutes. After completion of the addition, the reaction mixture was then stirred at ambient temperature for 7 hours. Then, a saturated solution of aqueous $NaHCO_3$ (25 mL) was added and the organic layers were extracted with chloroform (2 × 25 mL). The combined organic layers were then dried over anhydrous Mg_2SO_4 and concentrated to give crude of the ester, which was recrystallized from ethanol to provide the desired product **2** (9.3 g, 39.7 mmol, 74%).

3-(benzo[d]oxazol-2-ylthio)propanoic acid (3)

To a solution of ester **2** (9 gm, 38.3 mmol, 1.0 equiv.) in anhydrous THF (75 mL) at room temperature, NaOH (1.0 M, 76.6 mL, 76.6 mmol, 2.0 equiv.) was added. The reaction mixture was heated at 65 °C for 6 hours. A solution of aqueous NH_4Cl (1.0 M, 75 mL) was then added and the organic layers were extracted with diethyl ether (2 × 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was then evaporated and the crude material of acid **3** (8.4 g, 37.5 mmol, 98%) used in the next step without further purification.

3-(benzo[d]oxazol-2-ylthio) propane hydrazide (4) [24]

To a solution of the crude acid **3** (8.4 g, 37.5 mmol, 1.0 eq.) in anhydrous THF (50 mL) at room temperature. $SOCl_2$ (13.8 mL, 187.5 mmol, 5.0 eq.) was then added slowly to the reaction mixture. After completion of the addition, the mixture was stirred at ambient temperature. The reaction was monitored by TLC (MeOH/hexane) until no starting material **3** remained.

Then, the solvent was removed under reduce pressure to afford the desired acid chloride **4** (8.7 g, 36 mmol, 96%). The crude **4** was then used in the next step without further purification. Acid chloride **4** (8.7 g, 36 mmol, 1.0 equiv.) in ethanol (50 mL) was added to **3**, then hydrazine hydrate (99%, 3.8 mL, 75 mmol, 2.0 equiv.) was added slowly at room temperature. The mixture was then refluxed for 5 hours. Ethyl acetate (25 mL) was added before the layers were separated, and the aqueous layer was washed with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo*. The crude residue was recrystallized from chloroform to give the hydrazide derivative **5** (6.1 g, 25.6 mmol, 71%).

General Procedure for the Preparation of 3-(benzo[d]oxazol-2-ylthio)-1-(1H-pyrazol-1-yl) propan-1-one Derivatives 6-11

The hydrazide product **5** (237 mg, 1 mmol, 1.0 equiv.) was dissolved in THF (10 mL) in a 25 mL round bottom flask. Glycerol: H_2O (1:1) (10 mL) was then added and the resulting mixture stirred at room temperature for 30 minutes. A solution of 1, 3-dicarbonyl compound (1.2 mmol, 1.1 equiv.) in THF (5 mL) was added dropwise. The reaction mixture was heated to reflux until no starting material **5** remained. Ethyl acetate (15 mL) was added before the layers were separated, then the combined organic layers were dried over anhydrous $MgSO_4$ before filtration and concentrating *in vacuo*. The crude residue was recrystallized from chloroform to give the title compounds **6-11** (59-72% yield).

General Procedure for the Preparation of 2-((2-(1, 2, 4-triazin-3-yl) ethyl)thio) benzo [d]oxazole Derivatives 12-17

To a solution of hydrazide 5 (237 mg, 1 mmol, 1.0 equiv.) and K_2CO_3 (1.0 equiv.) in anhydrous THF (10 mL) at room

temperature. A suspension of 1,2-dicarbonyl compounds (1.2 mmol, 1.1 eq.) and in anhydrous THF (5 mL) was then added slowly to the reaction mixture. After completion of the addition, the mixture was heated to 50 ^{0}C for 10 minutes. Thereafter, NH_4OAc (385 mg, 5.0 mmol, 5.0 equiv.) in THF (5 mL) was added slowly to the reaction mixture and heated to reflux until no hydrazide material **5** remained. The organic solvent was evaporated under reduce pressure and the organic layers were washed with H_2O followed by the brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude products were then recrystallized from ethanol or ethyl acetate to provide the desired products **12-17** (57-74% yield).

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