



Synthesis and Antioxidant activity of New Thioxo Triazinane 2-One Derivatives

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Abstract

4-thioxo, 1, 3, 5-triazinane 2-ones were synthesized by the fusion of aryl isocyanides with 2-amino benzimidazole. All the compounds were screened for their antioxidant activity by determination of DPPH Radical scavenging, Superoxide Scavenging, Nitric oxide methods. Some of the title compounds were proved promising activity against the test organisms, employed. The structures of newly synthesized compounds were established on the basis of spectroscopic analysis.

Keywords

Synthesis, Thioxo- triazinanes, antioxidant activity.

1.0 INTRODUCTION.

Nitrogen containing heterocyclic compounds are attracted great attention because of their wide range of biological activities¹⁻⁵. Triazinanes have occupied a unique position in modern medicinal chemistry⁶⁻⁷ and the derivatives of triazinanes have attracted considerable pharmaceutical interest due to their Antibacterial Activity⁸, antimicrobial agents⁹ antitumor¹⁰, Antiproliferative Activity¹¹. In recent times, triazinanes are not only used in biological point of view also used as Nanocatalyst¹², Molecular Crystals¹³ and Nonlinear Optical Properties¹⁴, Phosphorescent light-emitting diodes¹⁵. Triazinanes have been identified as commercial products which are used as H₂S scavengers in the areas with relatively low concentrations of H₂S and it is inexpensive to use, and which were biodegradable and water soluble¹⁶. Literature survey reports that bi

heterocycles have been a fascinating field in modern medicinal chemistry, because it exhibits enhanced biological profile¹⁷. In view of this potential biological activity, we have planned to synthesize 1,3,5 triazinane thiones linked to benzimidazole ring. Present study is Synthesis of some new substituted 1, 3, 5-triazinane derivatives were carried out by the fusion of aryl isocyanides with 2-amino benzimidazole and the synthesized compounds were evaluated for their antioxidant activity.

2.0 MATERIALS AND METHODS:

Reaction progress was observed by TLC plates, Perkin Elmer BX series FT-IR was used to record IR spectra, Bruker 400 MHz instrument was used to record ¹H NMR spectra in DMSO using TMS as internal standard. Chemical shifts (δ) are expressed in ppm. The mass spectra were measured on a GC/MS-

QP1000EX (EI, 70 eV) mass spectrometer. Elemental analyses were performed on a PerkinElmer 240 CHN analyser.

2.1. Experimental section

2.1.1. Synthesis of *N*-benzylidene-1*H*-benzo[d]imidazol-2-amine (2)

Mixture of Benzaldehyde (0.004 mol) and 2-amino benzimidazole (1) (0.004 mol) were subjected to microwave irradiation for about 3 min. Progress of the reaction was monitored by TLC. After the completion of the reaction, it was cooled, and the product was filtered and recrystallized with methanol to afford the compound Schiff base (2).

2.1.2. Synthesis of *N*-(iso thio cyanato (phenyl) methyl)-1*H*-benzo[d]imidazol-2-amine (3)

To a stirred solution of compound 2 (0.01mole) in glacial acetic acid was added ammonia thiocyanate (0.015mole) in one lot. After stirring for 4 hours *N*-(isothiocyanato (phenyl) methyl)-2-amino benzimidazole (3) was separated out and filtered, washed with water, dried and recrystallized from ethanol.

2.1.3. General procedure for the synthesis of 1-(1*H*-benzo[d]imidazol-2-yl) - substituted phenyl-4-thioxo-1,3,5-triazinan-2-one (4)

To a solution of phenyl isocyanate (0.01mole) in THF was added drop wise to a solution of compound 3(0.01mole) in THF at reflux temperature. The reaction mixture was refluxed for about 8 hours. The solvent on evaporation result in crude product, which was filtered, dried and recrystallized by methanol to afford the compound 4a.

The compounds (4b-j) were prepared by similar procedure with minor changes in reaction conditions 1-(1*H*-benzo[d]imidazol-2-yl)-3,6-diphenyl-4-thioxo-1,3,5-triazinan-2-one (4a).

Yield:82%, IR (KBr, cm^{-1}): 3325 (NH), 1558(C=N), 1675 (C=O), 1235(C=S); ^1H NMR (DMSO- d_6 , 400MHz, δ in ppm): 6.5(s,1H,NH), 7.12(d,2H, Ar-H), 7.22 (d,2H, Ar-H), 7.35-7.51(m,5H, Ar-H), 4.1(s,1H,CH), 7.65-7.74 (m,5H, Ar-H), 9.85 (bs, 1H,NH). MS, m/z (%), 399 (M^+); Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_5\text{OS}$: C, 66.15; H, 4.29; N, 17.53%. Found: C, 66.05; H, 4.04; N, 17.23%.

1-(1*H*-benzo[d]imidazol-2-yl)-6-phenyl-4-thioxo-3-(*p*-tolyl)-1,3,5-triazinan-2-one(4b).

Yield:80%, IR (KBr, cm^{-1}): 3334 (NH), 1568(C=N), 1678(C=O), 1251 (C=S); ^1H NMR (DMSO- d_6 , 400MHz, δ in ppm): 2.85(s,3H,CH₃), 4.1(s,1H,CH), 7.12 (d,2H,Ar-H), 7.20 (d,2H, Ar-H), 7.34(d,2H,Ar-H), 7.43(d,2H,Ar-H), 7.58(m,5H, Ar-H), 10.05(bs, 1H, NH). MS, m/z (%), 413 (M^+); Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{N}_5\text{OS}$: C, 66.81; H, 4.63; N, 16.94%. Found: C, 66.31; H, 4.23; N, 16.44%.

1-(1*H*-benzo[d]imidazol-2-yl)-3-(4-methoxyphenyl)-6-phenyl-4-thioxo-1,3,5-triazinan-2-one (4c).

Yield:81%, IR (KBr, cm^{-1}): 3085(C-H), 3351 (NH), 1568(C=N), 1688 (C=O), 1241(C=S); ^1H NMR(DMSO- d_6 ,400MHz, δ inppm):3.45(s,3H,OCH₃),5.85 (s,1H,NH), 4.23(s,1H,CH), 7.18 (d,2H, Ar-H), 7.26(d,2H,Ar-H),7.44(d,2H,Ar-H),7.53(d,2H,Ar-H),7.69 (m,5H, Ar-H), 9.95(bs, 1H, NH). MS, m/z (%), 429 (M^+); Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{N}_5\text{O}_2\text{S}$: C, 64.32; H, 4.46; N, 16.31%. Found: C, 64.02; H, 4.16; N, 16.11%.

1-(1*H*-benzo[d]imidazol-2-yl)-3-(4-nitrophenyl)-6-phenyl-4-thioxo-1,3,5-triazinan-2-one(4d).

Yield:78%, IR (KBr, cm^{-1}): 3340 (NH), 1572(C=N), 1523 (NO₂), 1685 (C=O), 1238(C=S); ^1H NMR (DMSO- d_6 ,400MHz, δ in ppm): 5.65 (s,1H,NH), 4.33(s,1H,CH), 7.15 (d,2H,Ar-H),7.31(d,2H,Ar-H),7.88(d,2H,Ar-H),8.14(d,2H,Ar-H),7.53(m,5H,Ar-H),10.15 (bs, 1H,NH).MS, m/z (%),444(M^+);Anal. Calcd for $\text{C}_{22}\text{H}_{16}\text{N}_6\text{O}_3\text{S}$: C, 59.45; H, 3.63; N, 18.91%. Found: C, 59.15; H, 3.23; N, 18.41%.

1-(1*H*-benzo[d]imidazol-2-yl)-3-(4-hydroxyphenyl)-6-phenyl-4-thioxo-1,3,5-triazinan-2-one (4e).

Yield:81%, IR (KBr, cm^{-1}): 3514(OH), 3346 (NH), 1568 (C=N),1685 (C=O), 1238(C=S); ^1H NMR (DMSO- d_6 ,400MHz, δ in ppm): 5.43 (s,1H,NH), 4.56(s,1H,CH),7.18(d,2H,Ar-H),7.29(d,2H,Ar-H),7.83(d,2H,Ar-H),7.94(d,2H,Ar-H),7.65(m, 5H, Ar-H), 9.45 (bs, 1H, NH),11.25(s, 1H,OH), ;MS, m/z (%), 415 (M^+); Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_5\text{O}_2\text{S}$: C, 63.60; H, 4.12; N, 16.86%. Found: C, 63.23; H, 4.04; N, 16.32%.

1-(1*H*-benzo[d]imidazol-2-yl)-3-(4-chlorophenyl)-6-phenyl-4-thioxo-1,3,5-triazinan-2-one (4f):

Yield:80%, IR(KBr, cm^{-1}):3366(NH), 1561(C=N),1694 (C=O), 875(C-Cl); ^1H NMR (DMSO- d_6 ,400MHz, δ in ppm):5.64 (s,1H,NH),4.77 (s,1H,CH),7.28 (d,2H,Ar-H),7.35 (d,2H, Ar-H),7.73 (d,2H,Ar-H),7.98 (d,2H,Ar-H),7.47(m,5H,Ar-H), 9.55 (bs, 1H, NH), MS, m/z (%), 433 (M^+) 435(M^{++}) ; Anal. Calcd for $\text{C}_{22}\text{H}_{16}\text{ClN}_5\text{OS}$: C, 60.90; H, 3.72; N, 16.14%. Found: C, 60.24; H, 3.43; N, 16.04%.

1-(1*H*-benzo[d]imidazol-2-yl)-3-(4-bromophenyl)-6-phenyl-4-thioxo-1,3,5-triazinan-2-one (4g)

Yield:79%, IR (KBr, cm^{-1}): 3328 (NH), 1562 (C=N),1676(C=O); ^1H NMR (DMSO- d_6 ,400MHz, δ in ppm): 5.44 (s,1H,NH), 4.57(s,1H,CH), 7.12 (d,2H,Ar-H), 7.25 (d,2H, Ar-H),7.63 (d,2H,Ar-H),7.84 (d,2H,Ar-H),7.35 (m,5H,Ar-H), 9.65 (bs, 1H, NH), MS, m/z (%), 477 (M^+) 478(M^{++}) ; Anal. Calcd for $\text{C}_{22}\text{H}_{16}\text{BrN}_5\text{OS}$: C, 55.24; H, 3.37; N, 14.64%. Found: C, 54.94; H, 3.04; N, 14.18.

1-(1*H*-benzo[d]imidazol-2-yl)-3-(4-(dimethylamino) phenyl)-6-phenyl-4-thioxo-1,3,5-triazinan-2-one (4h)

Yield:82%,IR (KBr, cm^{-1}): 3328 (NH), 1562 (C=N),1676(C=O), 1238(C=S); ^1H NMR (DMSO-

δ , 400MHz, δ in ppm): 3.22(s, 6H, $-\text{N}(\text{CH}_3)_2$), 5.84 (s, 1H, NH), 4.86 (s, 1H, CH), 7.22 (d, 2H, Ar-H), 7.35 (d, 2H, Ar-H), 7.83 (d, 2H, Ar-H), 8.04 (d, 2H, Ar-H), 7.55 (m, 5H, Ar-H), 9.55 (bs, 1H, NH), MS, m/z (%), 442 (M^+); Anal. Calcd for $\text{C}_{24}\text{H}_{22}\text{N}_6\text{O}_3\text{S}$: C, 59.45; H, 3.63; N, 18.91%. Found: C, 59.08; H, 3.26; N, 18.32%.

1-(1H-benzo[d]imidazol-2-yl)-3-(2-nitrophenyl)-6-phenyl-4-thioxo-1,3,5-triazinan-2-one(4i)

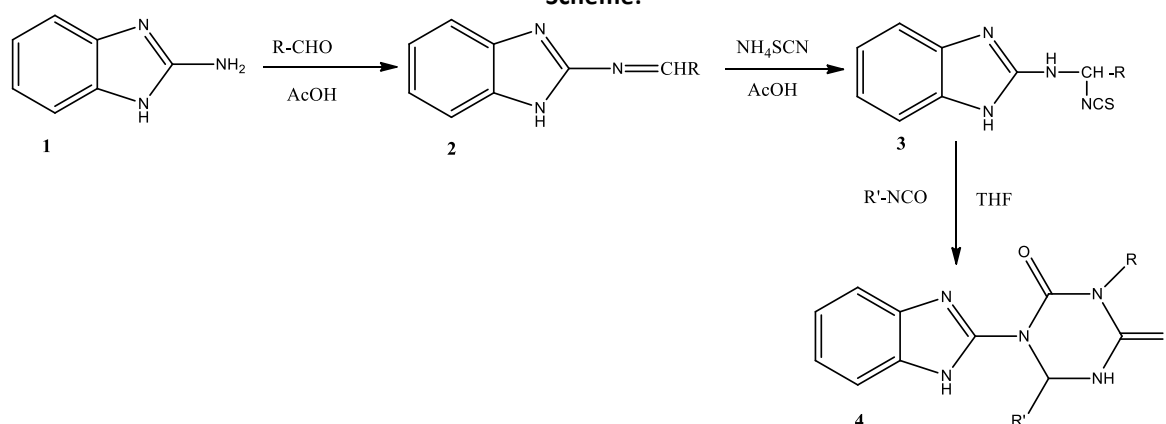
Yield: 80%, IR (KBr, cm^{-1}): 3342 (NH), 1575 (C=N), 1531 (NO_2), 1686 (C=O), 1232 (C=S); ^1H NMR (DMSO- d_6 , 400MHz, δ in ppm): 5.65 (s, 1H, NH), 4.35 (s, 1H, CH), 7.10 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H), 7.48 (m, 5H, Ar-H), 7.78 (d, 2H, Ar-H), 8.12 (d, 2H, Ar-H), 10.12 (bs, 1H, NH),

MS, m/z (%), 444 (M^+); Anal. Calcd for $\text{C}_{24}\text{H}_{16}\text{N}_6\text{O}_3\text{S}$: C, 59.45; H, 3.63; N, 18.91%. Found: C, 59.08; H, 3.26; N, 18.32%.

(1H-benzo[d]imidazol-2-yl)-3-(2-methoxyphenyl)-6-phenyl-4-thioxo-1,3,5-triazinan-2-one(4j)

Yield: 80%, IR (KBr, cm^{-1}): 3085 (C-H), 3351 (NH), 1568 (C=N), 1688 (C=O), 1241 (C=S); ^1H NMR (DMSO- d_6 , 400MHz, δ in ppm): 3.43 (s, 3H, OCH_3), 5.81 (s, 1H, NH), 4.25 (s, 1H, CH), 7.16 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.56 (d, 2H, Ar-H), 7.72 (m, 5H, Ar-H), 9.98 (bs, 1H, NH). MS, m/z (%), 429 (M^+); Anal. Calcd for $\text{C}_{23}\text{H}_{19}\text{N}_5\text{O}_2\text{S}$: C, 64.32; H, 4.46; N, 16.31%. Found: C, 63.92; H, 4.15; N, 16.08%.

Scheme:



3.0. Antioxidant activity

3.1.0. DPPH free radical scavenging assay

The antioxidant activity of compounds was measured in terms of hydrogen donating or radical scavenging ability using the stable free radical DPPH according to the method (18). 200 μl aliquots of sample at different concentrations were mixed with 1.8 ml of the DPPH solution (0.5 mM). The reaction mixture was allowed to stand at room temperature for 30 minutes and absorbance was measured at 517 nm using UV-VIS spectrophotometer. Control solution consisting of DPPH and DMSO without compounds was used as blank. Ascorbic acid was used as standard. The percentage inhibition of DPPH radical was calculated by comparing the results of the test with those of the control.

3.1.1. Nitric oxide scavenging activity

Nitric oxide scavenging activity was determined by the method (19). Briefly, 5 mM sodium nitroprusside was prepared in phosphate buffered saline and mixed with different concentrations of compounds (50, 75 and 100 $\mu\text{g}/\text{ml}$) followed by incubation at 25°C for 30 min. A control without the samples but with equivalent amounts of methanol was taken. After 30 min, 1.5 ml of incubated solution was removed and diluted with 1.5 ml of Griess reagent. The absorbance

of the chromophore formed during diazotization of the nitrite with sulphanilamide and subsequent coupling with N-1-naphthyl ethylenediamine dihydrochloride was measured at 546 nm and percentage scavenging activity was measured with reference standard.

3.1.2. Super oxide radical scavenging activity

The super oxide radical scavenging activity was measured by the method (20-21). 1 ml of each compounds of various concentrations (50 and 100 $\mu\text{g}/\text{ml}$) were mixed with 1 ml of nitro blue tetrazolium (NBT) solution (156 mM NBT in phosphate buffer of pH 7.4) and 1 ml NADH in phosphate buffer of pH 7.4. The reaction was initiated by adding 100 μl of phenazine methosulfate (PMS) solution (60 mM PMS in phosphate buffer, pH 7.4) to the mixture. The reaction mixture was incubated at 25°C for 5 min and the absorbance was measured at 560 nm against blank sample and compared with standards. Decreased absorbance of reaction mixture indicated increased superoxide anion scavenging activity.

The percentage of inhibition radical was calculated by comparing the results of the test with those of the control.

4.0. RESULT AND DISCUSSION:

In the present study, It has been discussed that the synthesis of Thioxo Triazinanes linked with benzimidazole using aryl isocyanates with appreciable yield. In this investigation the compound **2** (Schiff base) is synthesized using 2-aminobenzimidazole with Benzaldehyde under microwave irradiation. The reaction of compound **2** with ammonium thiocyanate in acetic acid under reflux for about 4 hours afforded the compound **3** in good yield. Cyclization of *N*-(isothiocyanates (phenyl) methyl-aminobenzimidazole was treated with aryl isocyanates in THF at reflux temperature to afford the title compounds Thioxo triazinanes with excellent yield (4a-j). The chemical structure of title compounds was established on the basis of spectral and analytical data. IR spectrum showed strong

absorption bands at 3366 cm^{-1} for (NH), 1568 cm^{-1} for (C=N), 1241 cm^{-1} for (C=S), 1680 cm^{-1} for (C=O) respectively. ^1H NMR spectra of test compounds displayed singlet signals at 4.2, and 9.55 ppm for CH and NH protons, aromatic protons as a multiplet in the range of 7.10-8.12 ppm. Mass spectrum of title compounds showed a corresponding molecular ion peak at m/z with respect to their molecular weights. The newly synthesized compounds were evaluated for antioxidant activity using DPPH free radical, super oxide radical scavenging and Nitric oxide scavenging methods. The compounds were dissolved in DMSO (50 $\mu\text{g}/\text{ml}$, 100 $\mu\text{g}/\text{ml}$). It was observed that the activity was concentration dependent and the compounds exhibited variability in their which are summarized in Table 2.

Table 1: Table .1: Substituents of compound 4(a-j)

S.No	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j
R	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph
R'	Ph	4-CH ₃ -Ph	4-OCH ₃ -Ph	4-NO ₂ -Ph	4-OH-Ph	4-Cl-Ph	4-Br-Ph	4-N(CH ₃) ₂ Ph	2-NO ₂ -Ph	2-OCH ₃ -Ph

Table: 2 Antioxidant activity of synthesized compounds (4a-j)

Compounds	Conc $\mu\text{g}/\text{mL}$	DPPH	Nitric oxide	Superoxide
4a	50	2.54 $\pm$ 0.1	2.82 $\pm$ 0.1	3.66 $\pm$ 0.1
	100	2.18 $\pm$ 0.1	1.66 $\pm$ 0.5	2.63 $\pm$ 0.1
	50	1.94 $\pm$ 0.3	1.88 $\pm$ 0.2	2.91 $\pm$ 0.2
4b	100	1.17 $\pm$ 0.1	1.09 $\pm$ 0.1	1.55 $\pm$ 0.1
	50	1.88 $\pm$ 0.2	1.60 $\pm$ 0.4	2.36 $\pm$ 0.1
	100	0.93 $\pm$ 0.2	1.06 $\pm$ 0.2	1.23 $\pm$ 0.1
4c	50	1.13 $\pm$ 0.1	1.48 $\pm$ 0.5	1.41 $\pm$ 0.2
	100	0.60 $\pm$ 0.1	0.54 $\pm$ 0.1	0.68 $\pm$ 0.3
	50	0.71 $\pm$ 0.3*	0.85 $\pm$ 0.2*	1.40 $\pm$ 0.1*
4e	100	49 $\pm$ 0.2*	0.47 $\pm$ 0.1*	0.51 $\pm$ 0.2*
	50	1.12 $\pm$ 0.1*	1.38 $\pm$ 0.1*	2.11 $\pm$ 0.2*
	100	0.60 $\pm$ 0.3*	0.70 $\pm$ 0.2*	1.10 $\pm$ 0.3*
4f	50	0.95 $\pm$ 0.2*	1.20 $\pm$ 0.2*	1.88 $\pm$ 0.2*
	100	0.55 $\pm$ 0.2*	0.62 $\pm$ 0.2*	0.83 $\pm$ 0.1*
	50	1.26 $\pm$ 0.5*	1.77 $\pm$ 0.1*	1.21 $\pm$ 0.2*
4g	100	0.98 $\pm$ 0.1*	0.86 $\pm$ 0.2*	1.08 $\pm$ 0.1*
	50	3.36 $\pm$ 0.3	3.51 $\pm$ 0.2	4.41 $\pm$ 0.2
	100	3.29 $\pm$ 0.2	2.69 $\pm$ 0.1	3.51 $\pm$ 0.3
4i	50	2.91 $\pm$ 0.2	3.01 $\pm$ 0.3	3.84 $\pm$ 0.1
	100	2.88 $\pm$ 0.1	2.40 $\pm$ 0.3	3.21 $\pm$ 0.1
	10	0.21 $\pm$ 0.5*	0.38 $\pm$ 0.1*	0.27 $\pm$ 0.2*
Ascorbic acid	10			

Results are shown in Standard Error of the Mean and Standard Deviation (SEM $\pm$ SD). $P < 0.05$

Among the compounds tested 4d, 4e, 4f and 4g exhibited significant activity comparing to other compounds. Perhaps the activity of 4d, 4e, 4f and 4g is directly proportional to electronegative functional groups, nitro, hydroxyl, choro and bromo groups present on the molecules respectively.

The compound 4c have been found to be active than 4b. The +ve inductive effect of methoxy group might be a discussion point for its high activity of 4c comparing to that of methyl group as a substitute on 4b molecule. Based on the results, we have observed that compounds scavenged DPPH, HNO₃ and superoxide radicals in a significant manner as compared to the standard drug ascorbic acid.

5.0. CONCLUSION:

With the experimental results, It has been concluded that a new series of thioxo triazinanes containing benzimidazole nucleus and derivatives (4a-j) were found to be exhibiting antioxidant activity and scavenged all the free radicals tested in the study.

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