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Synthesis and evaluation of new phenylamino-thiadiazolo-oxadiazolo-1, 3-benzoxazoles for their antifungal and anti-inflammatory activity

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ABSTRACT

In view of various biological activities of benzoxazoles, thiadiazoles and oxadiazole derivatives, it was our interest to prepare benzoxazole derivatives involving 1,3,4-thiadiazole and 1,3,4-oxadiazole nucleus and evaluate them for antifungal and anti-inflammatory activity using carrageenan induced rat paw edema model. The structures of all the synthesized compounds were characterized by IR, ^{1}H-NMR and MASS spectral data. All the synthesized compounds were screened for antifungal and anti-inflammatory activity. Among all the active compounds thiadiazole and oxadiazole derivatives showed good activity.

Key words: Benzoxazoles, thiadiazoles, antifungal agents, anti-inflammatory agents, oxadiazoles.

INTRODUCTION

Heterocycles by far are the largest classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial application ranging for cosmetics, reprography, information storage and plastics are heterocyclic in nature. One striking structural feature inherent to heterocyclic's, which continue to be exploited is their ability to manifest substituent around a core scaffold i.e. benzoxazole.

Benzoxazole and its derivatives are important class of bioactive molecules. Their importance is due to their versatile application in the field of drugs and pharmaceuticals as well as in chemical systems. Zoxazolamine, which is a benzoxazole analogue, is mainly used as skeletal muscle relaxant [1]. Moreover, some benzoxazole derivatives have been demonstrated to be potent antimicrobial [2], anti HIV [3], analgesic [4], anti-inflammatory [4] and anticancer agents [5].

During the last few decades, a considerable attention has been devoted to the synthesis of 1,3,4-thiadiazole, and 1,3,4-oxadiazole derivatives. 1,3,4-thiadiazole derivatives exhibit diverse pharmacological activities possibly due to presence of N=C=S [6] moiety. Moreover, compounds with thiadiazole ring have been produced as anticonvulsant [7], antibacterial [8], anti-inflammatory [9], fungicidal [10] and anticancer agents [11]. Acetazolamide and methazolamide bearing thiadiazole moiety are commonly used as diuretics [12].

1,3,4-Oxadiazoles are a class of heterocycles, which have attracted significant interest in medicine, pesticide chemistry and material science. They are of significant interest in medicinal chemistry in a number of biological targets including, anti-inflammatory [13], human β-tryptase inhibitors [14], anticonvulsant [15], antibacterial and antifungal agents [16].

In recent years, various antitumor drugs have been developed for the treatment of cancer. Among these, compounds incorporating schiff base structure were synthesized as antimicrobial [17] and antitumor [18] agents.

Some of azole derivatives used as common antibiotics such as Amphotericin-B posses a toxic effect on humans. Besides this, although there are antimicrobial agents having different structures are frequently used in the treatment of microbial infections; there is resistance to these drugs. To overcome the development of drug resistance it is crucial to synthesize a new class of antibiotics possessing different chemical properties from those of used commonly. Benzoxazole ring containing a side chain that has thiosemicarbazide structure in it is an ideal heterocyclic for this purpose.

In view of these facts, the aim of present study is the synthesis of benzoxazole derivatives involving 1,3,4-thiadiazole and 1,3,4-oxadiazole nucleus and to obtain benzoxazole derivatives incorporating schiff base as shown in Scheme-I,II,III,IV, and screen them for antifungal and anti-inflammatory activity.

MATERIALS AND METHODS

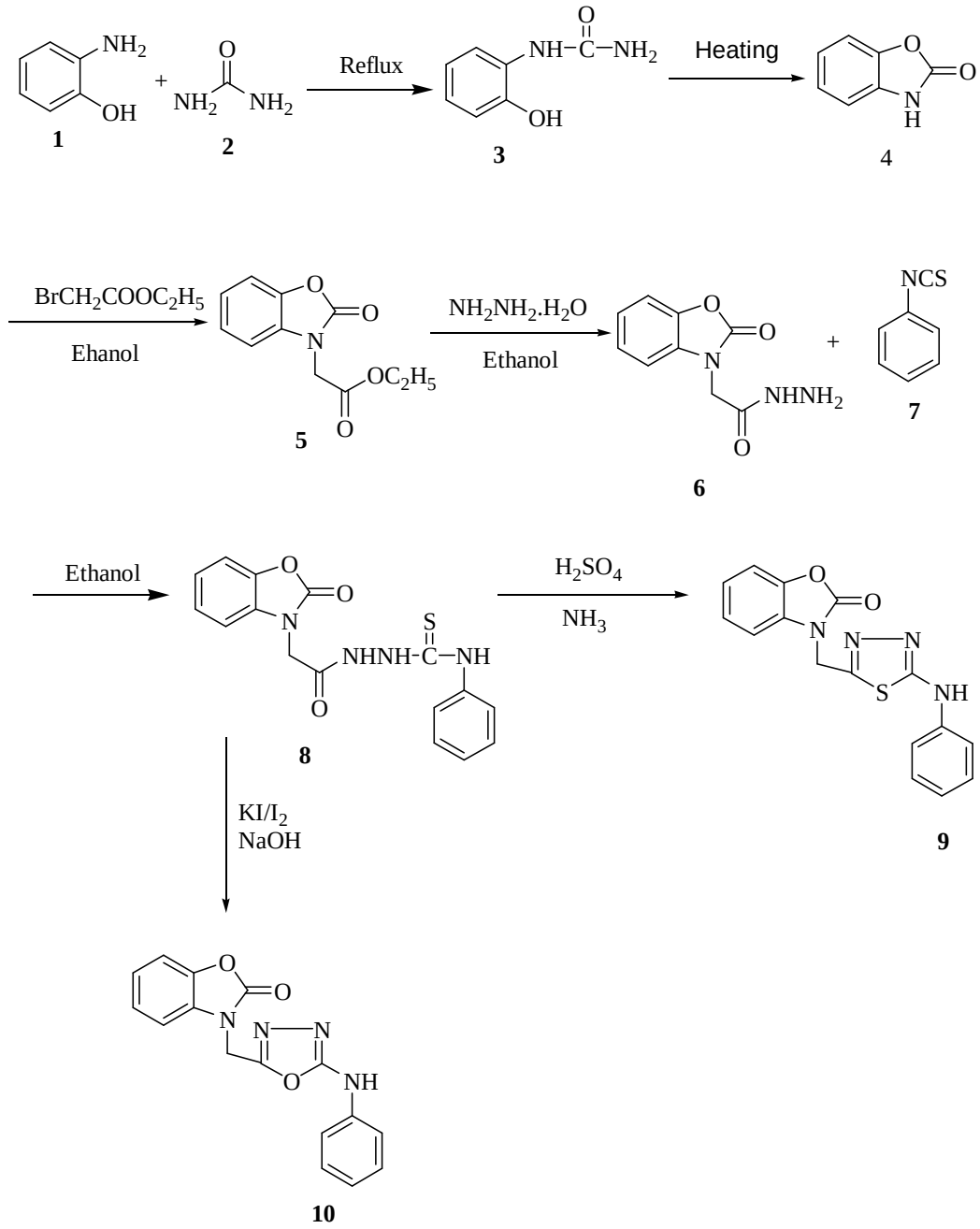
The various synthesized derivatives were characterized by determination of melting point T.L.C, I.R, N.M.R. and MASS. Melting point – By Fischer John's melting point apparatus. T.L.C. – By using Chloroform: methanol (1:1). I.R. - By using Thermo Nicolet Nexus 670 FT-IR. N.M.R. – Bruker 200 spectrospin. MASS – AUTO SPEC-M

Preparation of *o*-hydroxyphenylurea (3):
O-aminophenol (10 g, 91.7mmol) was thoroughly mixed with finely ground urea (10 g, 166.7 mmol) and heated at 160 ^{o}C for 25 min. The melt was allowed to cool and was extracted with 4 M HCl solution (350 ml). This purple acidic solution was in turn extracted with ether (300

ml).The residue resulting from evaporation of dried ether layer was taken up in boiling methanol, decolorized, and the product allowed to crystallize. Yield: 84%, m.p: 130-132 ^{o}C.

Preparation of 3 *H*-benzooxazole-2one (4):

Dry *o*-hydroxyphenylurea (5 g) was placed in round bottom flask and heated at 160 ^{o}C for 15 min. The cooled melts were dissolved in hot methanol, decolorized and the products allowed to crystallize. Yield: 78%, m.p: 135-138 ^{o}C.

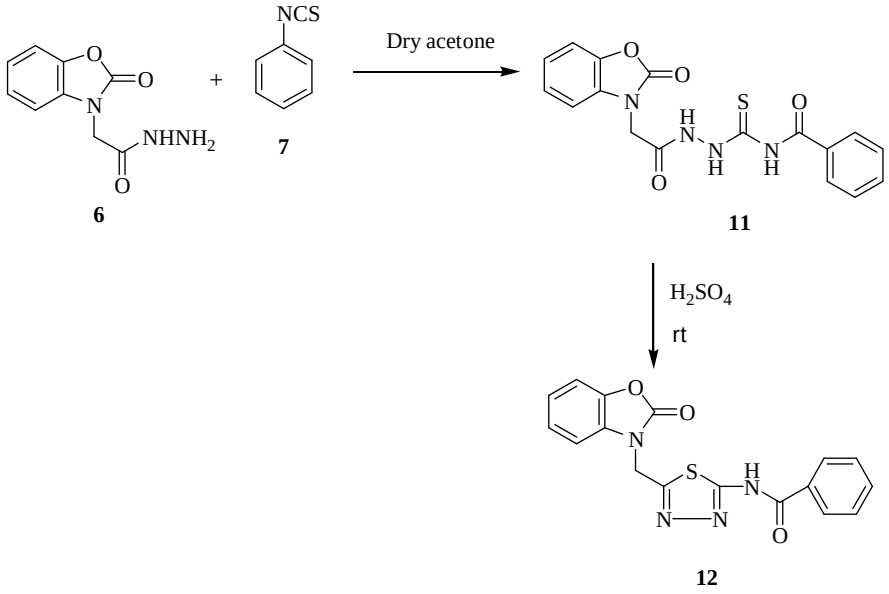


Scheme-I

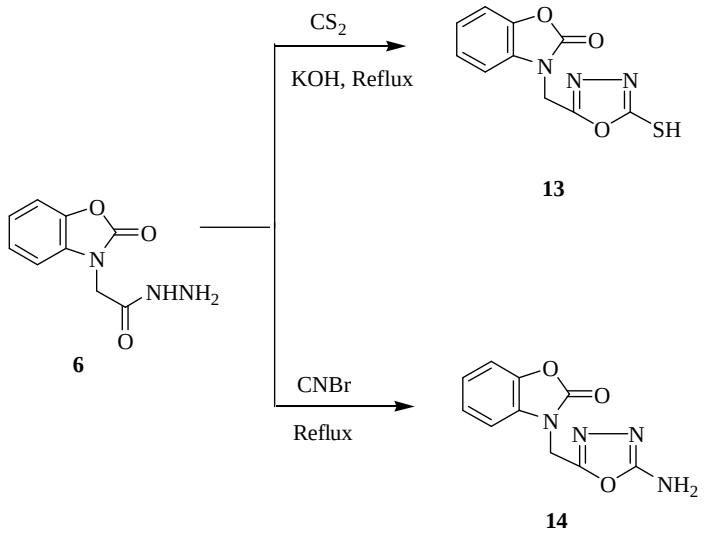
Preparation of (2-Oxobenzooxazol-3-yl) acetic acid ethyl ester (5):
The corresponding 3*H*-Benzooxazol-2-one **4** (5 g, 37 mmol) was refluxed with equivalent amount of sodium in absolute ethanol for 2 h. Then ethyl bromo acetate (6.79 g, 40 mmol) was added and mixture was refluxed for additional 5 h. After concentrating the reaction mixture at 35-40 ^{o}C under reduced pressure a semisolid mass appeared this was recrystalized from ethanol to get the desired compound as a solid. Yield: 78.87%, m.p: 88-90 ^{o}C.

Preparation of (2-oxobenzooxazol-3yl) acetic acid hydrazide (6):
A solution of the corresponding (2-oxobenzooxazol-3yl) acetic acid ethyl ester **5** (3.5 g, 15 mmol) in ethanol was refluxed with hydrazine hydrate (1.9 g, 37 mmol) for 4 h. After concentrating the reaction mixture a white solid mass appeared this was recrystalized from an ethanol to get desired product as a solid. Yield: 55%, m.p.189-190 ^{o}C.

Preparation of 2-(2-(2-Oxobenzo [*d*] oxazol-3 (2*H*)-yl) acetyl)-*N* Phenylhydrazine Carbothioamide (8):
A mixture of corresponding acid hydrazide **6** (0.8 g, 3.8 mmol) and phenyl isothiocynate (0.769 g, 0.5 mmol) was refluxed in ethanol for 8 h. The solution was cooled and a white solid was appeared. This was filtered and recrystalized from ethanol to get desired product as a solid. Yield: 65.89%, m.p. 190-192 ^{o}C.

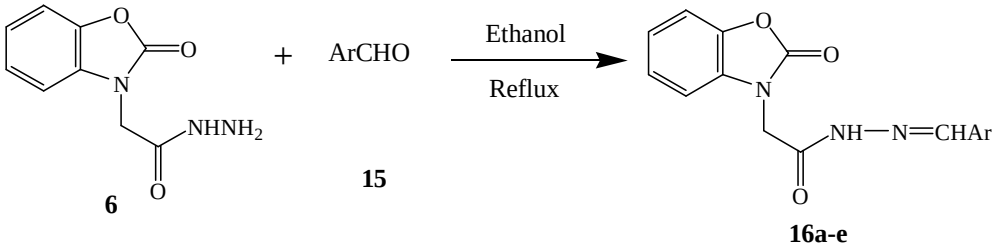


Scheme-II

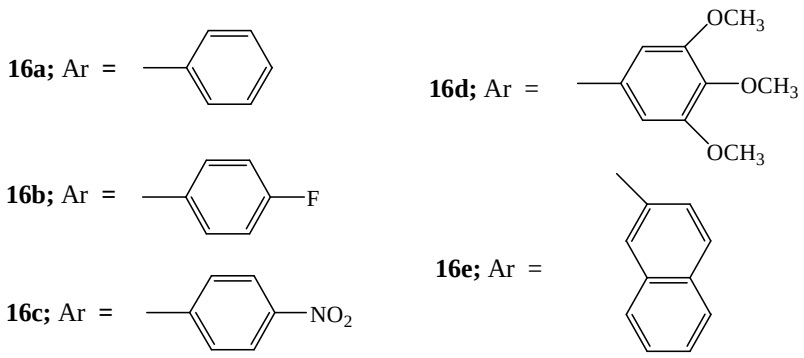


6 **13** **14**

Scheme-III



6 **15** **16a-e**



Scheme-IV

Preparation of 3-(5-Phenylamino- [1,3,4] thiadiazol-2yl methyl)-3*H*-benzooxazol-2-one (9):
A mixture of the corresponding thiosemicarbazide **8** (0.4 g, 1.1 mmol) in cold concentrated sulfuric acid (3.00 ml) was stirred for 10 min. Then the mixture was allowed to room temperature. After stirring for an additional 30 min, the resulting solution was poured into ice-

cold water and made alkaline to P^H 8 with ammonia. The precipitated product was filtered and recrystalized from ethanol to get desired product as a solid. Yield: 73.68%, m.p. 223-225 ^oC.

Preparation of 3-(5-phenylamino- [1, 3, 4] oxadiazol-2yl methyl)-3*H*- Benzooxazol-2-one (10):

Thiosemicarbazide **8** (0.15 g, 0.4 mmol) in ethanol was dissolved in aqueous sodium hydroxide (5 N, 1 ml) with cooling and stirring, resulting in a clear solution. To this iodine in potassium iodide solution (5%) was added gradually with stirring till the colour of iodine persisted at room temperature. The reaction mixture was then refluxed for 1 h on oil bath. It was then cooled and poured over crushed ice. The solid mass that separated out was filtered, dried and recrystalized from ethanol to get desired product as a solid. Yield: 57.36%, m.p: 173-175 ^oC.

Preparation of *N*- {*N*- [2-(2-oxo-benzooxazol-3yl)-acetyl]-hydrazinocarbothioyl} benzamide (11):

A mixture of (2-oxobenzooxazol-3yl) acetic acid hydrazide **6** (0.2 g, 0.9 mmol) and phenyl-isothiocynate (0.121 g, 0.8 mmol) in dry acetone (5 ml) was stirred for an hour at room temperature and further washed with water and dried to get desired product as a solid.
Yield: 55.00%, m.p: 190-192 ^oC.

Preparation of *N*- [5-(2-oxobenzooxazol-3yl methyl)-[1,3,4] thiadiazol-2yl] benzamide (12):

A mixture of {*N*-[2-(2-oxobenzooxazol-3yl)-acetyl-hydrazinocarbothioyl] benzamide **11** (0.9 g, 2 mmol) was added to cold conc. sulphuric acid. The mixture was stirred at room temperature for 2 h. The resultant solid mass was poured on to crushed ice with stirring. The product was filtered, washed with water and dried to get as a solid. Yield: 71.50%, m.p:112-115 ^oC.

Preparation of 3-(5-mercapto- [1,3,4] oxadiazol-2yl methyl)- 3*H*-benzooxazol-2-one (13):

A mixture of (2-oxobenzooxazol-3yl) acetic acid hydrazide **6** (0.2 g, 1 mmol), KOH (0.056 g, 1 mmol) and carbon disulphide (1 ml) in ethanol was refluxed on oil bath for 12 h. The solution was then concentrated, cooled and acidified with dilute HCl. The solid mass the separated out was filtered, washed with ethanol, dried and recrystallized from ethanol to get as a solid.
Yield: 57.36%, m.p: 130-132 ^oC.

Preparation of 3-(5-Amino- [1, 3, 4] oxadiazol-2yl methyl) - 3*H*-benzooxazol-2-one (14):

To an ethanolic solution of (2-Oxobenzooxazol-3yl) acetic acid hydrazide **6** (0.3 g, 1 mmol), cynogen bromide (0.106 g, 1 mmol) was added. The reaction mixture was warmed at 55-60 ^oC for 90 min. The resulting solution was cooled and neutralized with sodium bicarbonate solution. The solid thus obtained thus separated out as filtered, washed with water, dried and recrystalized from methanol to get desired product as semisolid. Yield: 65.00%.

Preparation of (2 oxo-benzooxazol-3yl) acetic acid benzylidine hydrazide (16a):

A solution of the corresponding **(**2-oxobenzooxazol-3yl) acetic acid hydrazide (0.050 g, 0.2 mmol) in ethanol was refluxed with benzaldehyde (0.021 g, 0.2 mmol) for 24 h. After cooling to room temperature, a white solid appeared. This crude product was recrystalized from ethanol to get desired product as solid. Yield: 60.97%, m.p.235-240 ^oC.

Preparation of (2-oxo-benzooxazol-3yl) acetic acid (4-fluro benzylidine) - hydrazide (16b):
A solution of the corresponding (2-oxobenzooxazol-3yl) acetic acid hydrazide (0.05 g, 0.2 mmol) in ethanol was refluxed with 4-fluoro benzaldehyde (0.024g, 0.2 mmol) for 24 h. After cooling to room temperature, a white solid appeared. This crude product was recrystalized from ethanol to get desired product as solid. Yield: 94.69%, m.p: 245-250 ^{o}C.

Preparation of (2-oxo-benzooxazol-3yl) acetic acid (4-nitro benzylidine)-hydrazide (16c):
A solution of the corresponding (2-oxobenzooxazol-3yl) acetic acid hydrazide (0.05 g, 0.2 mmol) in ethanol was refluxed with 4-nitro benzaldehyde (0.03 g, 0.2 mmol) for 24 h. After cooling to room temperature, a white solid appeared. This crude product was recrystalized from ethanol to get desired product as solid. Yield: 88.95%, m.p: 275-280 ^{o}C.

Preparation of (2-oxo-benzooxazol-3yl) acetic acid (3, 4, 5-trimethoxy benzylidine)-hydrazide (16d):
A solution of the corresponding (2-oxobenzooxazol-3yl) acetic acid hydrazide (0.05 g, 0.2 mmol) in ethanol was refluxed with 3,4,5-trimethoxy benzaldehyde (0.03 g, 0.2 mmol) for 24 h. After cooling to room temperature, a white solid appeared. This crude product was recrystalized from ethanol to get desired product as solid. Yield: 65.73%, m.p: 235-240 ^{o}C.

Preparation of (2-oxo-benzooxazol-3yl) acetic acid naphthalene 1-yl methylene hydrazide (16e):
A solution of the corresponding (2-oxobenzooxazol-3yl) acetic acid hydrazide (0.05 g, 0.2 mmol) in ethanol was refluxed with 4-nitro benzaldehyde (0.031 g, 0.2 mmol) for 24 h. After cooling to room temperature, a white solid appeared. This crude product was recrystalized from ethanol to get desired product as solid. Yield: 74.35%, m.p.220-225 ^{o}C.

3-(5-Phenylamino- [1,3,4] thiadiazol-2yl methyl)-3*H*-benzooxazol-2-one (9)
IR (KBr): υ_{max} 3301 (NH), 1736 (lactone C=O), 1544 (C=N) cm^{-1}. ^{1}HNMR (200 MHz, DMSO-d_6): δ 5.4 (s, 2H, NCH_2), 6.95-7.62 (m, 9H, Ar-H). EI-MS: $m/_Z$ = 324 (M^+)

3-(5-phenylamino- [1, 3, 4] oxadiazol-2yl methyl)-3*H*- Benzooxazol-2-one (10):
IR (KBr): υ_{max} 3369-3437 (NH), 1775 (lactone C=O), 1488 (C=N) cm^{-1}.^{1}HNMR (200 MHz, DMSO-d_6): δ 5.02 (s, 2H, NCH_2), 6.9-7.62 (m, 9H, Ar-H), 10.2 (s, 1H, NH). EI-MS: $m/_Z$ = 308 (M^+).

***N*- {*N*- [2-(2-oxo-benzooxazol-3yl)-acetyl]-hydrazinocarbothioyl} benzamide (11):**
IR (KBr): υ_{max} 3136-3261 (3NH), 1757 (amide C=O), 1483 (C=S) cm^{-1}. ^{1}HNMR (200 MHz, DMSO-d_6): δ 4.65 (s, 2H, NCH_2), 6.82-7.75 (m, 9H, Ar-H), 9.5 (s, 1H, CONH). EI-MS: $m/_Z$ = 370 (M^+).

***N*- [5-(2-oxobenzooxazol-3yl methyl)-[1,3,4] thiadiazol-2yl] benzamide (12):**
IR (KBr): υ_{max} 3431 (NH), 1741 (lactone C=O), 1491 (C=N) cm^{-1}. ^{1}HNMR (200 MHz, DMSO-d_6): δ 5.40 (s, 2H, NCH_2), 6.90-8 (m, 9H, Ar-H), 10.10 (s, 1H, NH). EI-MS: $m/_Z$ = 352 (M^+).

3-(5-mercapto- [1,3,4] oxadiazol-2yl methyl)- 3*H*-benzooxazol-2-one (13):
IR (KBr): υ_{max} 1757 (lactone C=O), 1483 (C=N), $cm^{-.1}$HNMR (200 MH_Z, DMSO-d_6): δ 5.15 (s, 2H, NCH_2), 7.05-7.03 (m, 1H, Ar-H), EI-MS: $m/_Z$ = 249 (M^+) .

3-(5-Amino- [1, 3, 4] oxadiazol-2yl methyl) - 3*H*-benzooxazol-2-one (14):
IR (Neat): υ_{max} 3447 (NH_2), 1769 (lactoneC=O), 1458 (C=N), 1489 (C=N) cm^{-1}. ^{1}HNMR (200 MHz, DMSO-d_6): δ 4.70 (s, 2H, $NCH_)$, 6.00 (s, 2H, NH_2), 6.70-7.40 (m, 4H, Ar-H). EI-MS: $m/_Z$ = 232 (M^+).

(2 oxo-benzooxazol-3yl) acetic acid benzylidine hydrazide (16a):
IR (KBr): υ_{max} 3188 (NH), 1770 (lactone C=O), 1679 (amide C=O), 1679 (amide C=O) 1489 (C=N) cm^{-1}. ^{1}HNMR (200 MHz, DMSO-d_6): δ 5 (s, 2H, CH_2), 6.95- 7.8 (m, 9H, Ar-H), 8 (s, 1H, CH), 11.69 (s, 1H, NH). EI-MS: $m/_Z$ = 295 (M^+).

(2-oxo-benzooxazol-3yl) acetic acid (4-fluro benzylidine) - hydrazide (16b):
IR (KBr): υ_{max} 3190 (NH), 1777 (lactone C=O), 1677 (amide C=O), 1492 (C=N) cm^{-1} .^{1}HNMR (200 MHz, DMSO-d_6): δ 5.1 (s, 2H, CH_2), 7.15- 7.85 (m, 8H, Ar-H), 8.1 (s, 1H, CH), 11.8 (s, 1H, NH). EI-MS: $m/_Z$ = 313 (M^+).

(2-oxo-benzooxazol-3yl) acetic acid (4-nitro benzylidine)-hydrazide (16c):
IR (KBr): υ_{max} 3322 (NH), 1783 (lactone C=O), 1677 (amide C=O), 1593 (C=N) cm^{-1}. ^{1}HNMR (200 MHz, DMSO-d_6): δ 5.15 (s, 2H, CH_2), 6.80 - 7.25 (m, 4H, Ar-H), 8.25 (d, 2H, NO_2-Ar-H), 12.10 (s, 1H, NH). EI-MS: $m/_Z$ = 340 (M^+).

(2-oxo-benzooxazol-3yl) acetic acid (3, 4, 5-trimethoxy benzylidine)-hydrazide (16d):
IR (KBr): υ_{max}1772 (lactone C=N), 1681 (amide C=O), 1582 (C=N) cm^{-1}. ^{1}HNMR (200 MHz, DMSO-d_6): δ 3.90-3.95 (2s, 9H, 3-OCH_3), 5.06 (s, 2H, CH_2), 6.85- 7.25 (m, 6H, Ar-H), 7.95 (s, 1H, CH), 11.68 (s, 1H, NH). EI-MS: $m/_Z$ =385 (M^+)

(2-oxo-benzooxazol-3yl) acetic acid naphthalene 1-yl methylene hydrazide (16e):
IR (KBr): υ_{max} 3181 (NH), 1775 (lactone C=O), 1679 (amide C=O), 1489 (C=N) cm^{-1}. ^{1}HNMR (200 MHz, DMSO-d_6): δ 5.50 (s, 2H, N-CH_2), 7.00- 8.00 (m, 11H, Ar-H), 8.70 (s, 1H, N=CH), 8.25 (d, 2H, NO_2-Ar-H). EI-MS: $m/_Z$ = 345 (M^+).

Table-I: Physico-Chemical data of the synthesized compounds

Compound code	Mol. Formula	M. Wt	M.P. ^oC	% Yield
9	$C_{16}H_{12}N_4O_2$	324	223-225	73.68
10	$C_{16}H_{12}N_4O_3$	308	173-175	57.36
11	$C_{17}H_{14}N_4O_4S$	370	190-192	55.00
12	$C_{17}H_{12}N_4O_3S$	352	112-115	71.50
13	$C_{10}H_7N_3O_3S$	249	130-132	57.36
14	$C_{10}H_8N_4O_3$	332	Liquid	65.00
16a	$C_{16}H_{13}N_3O_3$	295	238-240	60.97
16b	$C_{16}H_{12}N_3O_3F$	313	248-250	94.69
16c	$C_{16}H_{12}N_4O_5$	340	277-280	88.95
16d	$C_{19}H_{19}N_3O_6$	385	238-240	65.73
16e	$C_{20}H_{15}N_3O_3$	345	222-225	74.35

RESULTS AND DISCUSSION

Antifungal activity:

The antifungal activity of the test compounds were tested by agar diffusion method (cup-plate method) [19, 20] taking drug at a concentration of 100 µg/ml and 150 µg/ml against five fungi. The area of zone of inhibition (ZOI) was taken as a parameter of antifungal activity. The ZOI of the test compound is compared to that of the standard drug *i.e.*, Amphotericin-B.

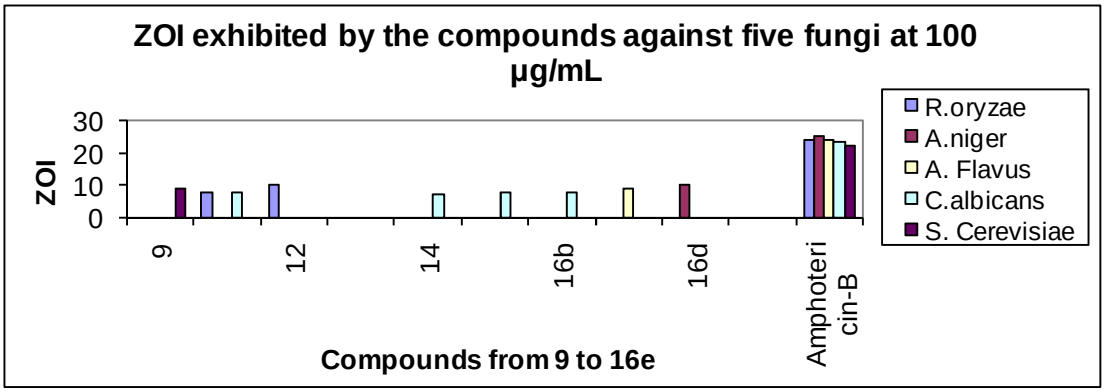
The compounds when screened at 100 µg/ml showed different ZOI against five fungi. At 100 µg/ml compounds were screened against five fungi. Among the compounds screened the maximum zone of inhibition was observed against *R. oyrzae*, *A. flavus* and *C. albicans*.

Thiadiazole derivative 12 oxadiazole derivative 10 (Table- II) were active against *Rhizopus oryzae*. Among the active compounds thiadiazole derivative 12 showed maximum zone of inhibition (10mm) oxadiazole derivative 10 showed zone of inhibition (8mm). Only compound 16d was active against *Aspergillus Niger* and showed zone of inhibition (10mm). The compound 16c (Table- II) was active against *Aspergillus flavus* and showed zone of inhibition (9mm). Thiadiazole derivative 10, Oxadiazole derivatives 14 (Table- II) and schiff base derivatives 16a and 16b were active against *Candida albicans*. Among all the active compounds 10,16a and 16b showed equal zone of inhibition (8mm), compound 14 showed zone of inhibition (7mm) (Table-II). Thiadiazole derivative 9 was active against *Staphyllococcus cerevisiae*, showed zone of inhibition (9mm).

Table-II: Antifungal activity of compounds at 100 µg/ml

ZONE OF INHIBITION (mm)					
Compound Code	***R.oryzae***	***A.niger***	***A. Flavus***	***C.albicans***	***S. Cerevisiae***
9	-	-	-	-	9
10	8	-	-	8	-
12	10	-	-	-	-
13	-	-	-	-	-
14	-	-	-	7	-
16a	-	-	-	8	-
16b	-	-	-	8	-
16c	-	-	9	-	-
16d	-	10	-	-	-
16e	-	-	-	-	-
Amphotericin-B	24	25	24	23.5	22

Graph I: ZOI exhibited by compounds at 100 µg/ml



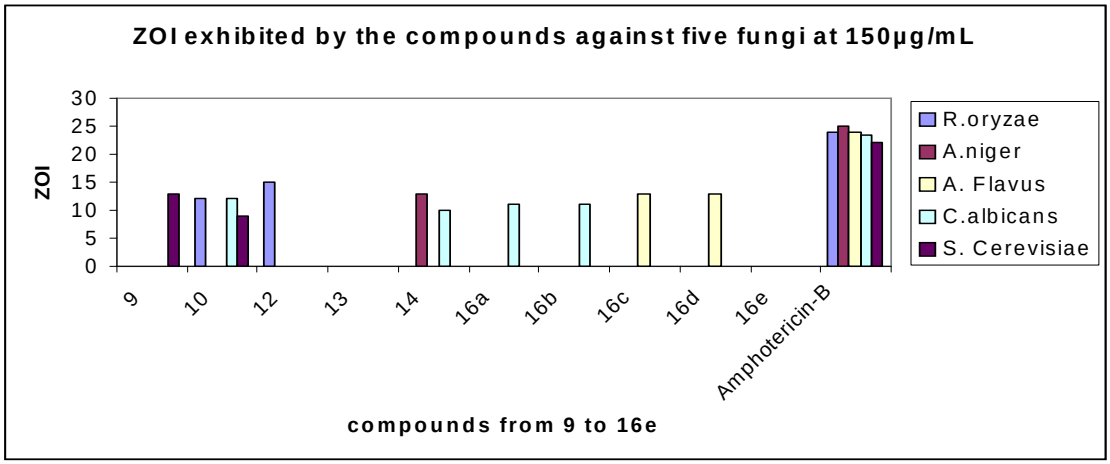
At 150 µg/ml the compounds were screened against five fungi. Among the active compounds the maximum zone of inhibition was observed against *Rhizopus oryzae*, *Aspergillus Niger* and *Candida albicans*. Oxadiazole derivative 10 thiadiazole derivative 12 and were active against *Rhizopus oryzae*. Among all the active compounds oxadiazole derivatives 10 showed maximum zone of inhibition (12mm), Thiadiazole derivative 12 showed zone of inhibition (15mm).

Only 14 was active against *Aspergillus Niger* and showed zone of inhibition (13mm). Schiff base derivative 16c and 16d (Table- III) were active against *Aspergillus flavus*. The compounds 16c and 16d (Table- III) showed an equal zone of inhibition (13mm). Oxadiazole derivatives 10 and 14 and schiff base derivative 16a and 16b (Table- III) were active against *Candida albicans*. Among the active compounds maximum zone of inhibition (12mm) was shown by 10. The compounds 16a and 16b showed an equal zone of inhibition (11mm), 14 showed zone of inhibition (10mm) (Table- III). Thiadiazole derivative 9 and oxadiazole derivative 10 were active against *Staphylococcus cerevisiae*. Between these compounds 9 showed maximum zone of inhibition (13mm) and compound 10 showed zone of inhibition (9mm).

Table-III: Antifungal activity of compounds at 150 µg/ml

ZONE OF INHIBITION (mm)					
Compound Code	***R.oryzae***	***A.niger***	***A. Flavus***	***C.albicans***	***S. Cerevisiae***
9	-	-	-	-	13
10	12	-	-	12	9
12	15	-	-	-	-
13	-	-	-	-	-
14	-	13	-	10	-
16a	-	-	-	11	-
16b	-	-	-	11	-
16c	-	-	13	-	-
16d	-	-	13	-	-
16e	-	-	-	-	-
Amphotericin-B	24	25	24	23.5	22

Graph II: ZOI exhibited by compounds at 150 µg/ml



Anti-inflammatory activity:

Among the synthesized compounds, three compounds 9, 12, 13 were screened for anti-inflammatory activity by the Carrageenan induced paw edema assay [21] in rats at a dose of 100 mg/kg body weight, orally. The data is presented in (Table-IV).

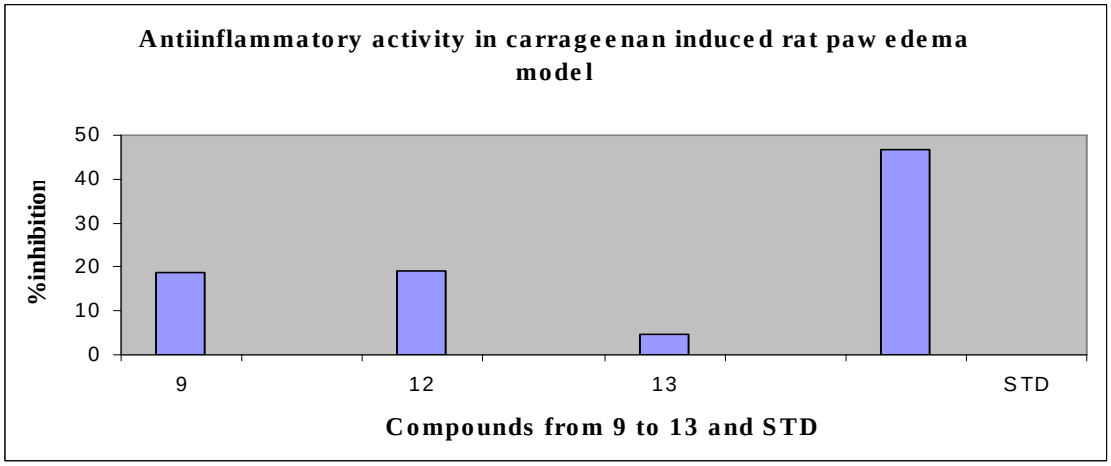
Thiadiazole derivative 12 showed more activity and % of inhibition was found to be 19.20. Whereas thiadiazole derivative 9 showed 18.60 and oxadiazole derivative 13 showed mild activity and % of inhibition for these compounds was found to be at 4.57 respectively.

Table-IV: Anti-inflammatory activity in carrageenan induced rat paw edema model

Rat No.	Group	0 hr	3rd hr	Difference in Paw volume	% of inhibition
1	CONTROL	1.18	2.46	1.28	
2		1.13	2.40	1.27	
3		1.22	2.51	1.29	
4		1.13	2.24	1.11	
Mean ± SE				1.23 ± 0.04	
5	9	1.17	2.21	1.04	15.40
6		1.20	2.21	0.92	25.00
7		1.13	2.17	1.04	15.40
Mean ± SE					18.60±3.20
8	12	1.11	2.16	1.05	14.60
9		1.12	1.14	1.02	17.00
10		1.17	2.08	0.91	26.00
Mean ± SE					19.20±3.47
11	13	1.32	2.51	1.19	1.60
12		1.23	2.24	1.11	9.70
13		1.26	2.46	1.20	2.40
Mean ± SE					4.57± 2.58
14	STD	1.30	1.90	0.60	48.20
15		1.26	1.89	0.63	45.60
16		1.20	1.82	0.62	46.50
Mean ± SE					46.77±0.76

Compound dose: 100 mg/ Kg *Standard (Indomethacin) : 10 mg / Kg*

Graph III: Antiinflammatory activity in carrageenan induced rat paw edema model



CONCLUSION

The proposed benzoxazole derivatives i.e. thiadiazoles, oxadiazoles, and schiff bases were synthesized successfully. All the compounds were evaluated for antifungal and anti-inflammatory activity. The compounds were found to have good activity, among all the active compounds of thiadiazole and oxadiazole derivatives, *N*- [5-(2-oxobenzooxazol-3yl methyl)-[1,3,4] thiadiazol-2yl] benzamide (12) showed good anti-inflammatory activity.

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