Amongst different heterocyclic compounds the development of five membered heterocycles from readily available chemicals is one of the major challenges in organic synthesis. Indeed, the chemistry of 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole constitute immensely important members of the heterocycle family due to their presence in a myriad of bioactive natural products as privileged pharmacophores. In this perspective, the present work “A study on some nitrogen containing heterocycles” has been taken up.

INTRODUCTION

A brief introduction on the importance of five membered heterocycles and the methods of syntheses of 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole and their derivatives were presented. Apart from this, the actual scope and objectives of the work were also mentioned.

PRESENT WORK

The exploitation of simple molecules with different functionalities for the synthesis of a variety of bis heterocycles having 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole moieties adopting simple, facile and elegant synthetic methodologies is a worthwhile contribution in the field of synthetic organic chemistry particularly heterocyclic chemistry. In this perspective, the author did considerable work on the synthesis and antioxidant activity of symmetrical bis heterocycles viz., bis(oxadiazoles), bis(thiadiazoles) and bis(triazoles). The results were presented in four chapters.
CHAPTER - I

The chapter-I deals with the synthesis and antioxidant activity of bis(5-aryl-1,3,4-oxadiazol-2-ylmethyl)sulfone, bis(5-aryl-1,3,4-thiadiazol-2-ylmethyl)sulfone and bis(4-amino-5-aryl-1,2,4-triazol-3-ylmethyl)sulfone.

The above mentioned bis heterocycles were prepared from the reactive intermediates sulfonyldiacetic acid (2) and aryl acid hydrazide (5). Oxidation of thiodiacetic acid (1) in the presence of hydrogen peroxide in glacial acetic acid resulted in 2. The reaction of aryl acid (3) with methanol in the presence of conc. H₂SO₄ produced aryl methyl ester (4). The treatment of compound 4 with hydrazine hydrate in methanol in the presence of pyridine yielded aryl acid hydrazide (5) (Scheme I.1).

![Scheme 1.1](image_url)

The cyclocondensation of one mole of sulfonyldiacetic acid (2) two with two moles of aryl acid hydrazide (5) in the presence of POCI₃ afforded bis(5-aryl-1,3,4-oxadiazol-2-ylmethyl)sulfone (6) (Scheme I.2).
Interconversion of oxadiazole to thiadiazole was effected by treating 6 with thiourea in tetrahydrofuran to get bis(5-aryl-1,3,4-thiadiazol-2-ylmethyl)sulfone (7). On the other hand, the reaction of 6 with hydrazine hydrate in the presence of KOH in n-butanol furnished bis(4-amino-5-aryl-1,2,4-triazol-3-ylmethyl)sulfone (8) (Scheme I.3).
Antioxidant activity

The compounds 6, 7 and 8 were evaluated for antioxidant activity by 2,2-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide (NO) and hydrogen peroxide (H₂O₂) methods at three concentrations (50, 75 and 100 μM). In all the three methods Ascorbic acid is used as the standard. The aim of the study is to identify the potential heterocyclic compound as antioxidant agent. The results of antioxidant activity revealed that bis(5-aryl-1,3,4-oxadiazol-2-ylmethyl)sulfone (6) and bis(4-amino-5-aryl-1,2,4-triazol-3-ylmethyl)sulfone (8) exhibited higher antioxidant activity than bis(5-aryl-1,3,4-thiadiazol-2-ylmethyl)sulfone (7). Amongst 6 and 8, the compound 6 showed good radical scavenging activity than 8. It was also noticed that unsubstituted and methyl substituted compounds displayed higher antioxidant activity than the corresponding chloro substituted ones. Besides, the perusal of results indicated that radical scavenging activity increases with increase in concentration in all the three methods.

CHAPTER - II

The chapter II describes the synthesis and antioxidant activity of bis(5-aryl sulfonylmethyl-1,3,4-oxadiazol-2-ylmethyl)sulfone, bis(5-aryl sulfonylmethyl-1,3,4-thiadiazol-2-ylmethyl)sulfone and bis(4-amino-5-aryl sulfonylmethyl-1,2,4-triazol-3-ylmethyl)sulfone.

The synthetic intermediate arylsulfonylacetic acid hydrazide (13) was used for the synthesis of above mentioned heterocycles. The compound 13 was prepared by the treatment of arylsulfonylacetic acid methyl ester (12) with hydrazine hydrate in the presence of pyridine. The compound 12 in turn was obtained by esterification of arylsulfonylacetic acid (11). The latter compound was prepared by the condensation of thiophenol (9) with chloroacetic acid followed by oxidation of the resultant arylmercaptoacetic acid (10) with hydrogen peroxide in acetic acid (Scheme II.1).
The bis(5-arylsulfonfylmethyl-1,3,4-oxadiazol-2-ylmethyl)sulfone (14) was prepared by the reaction of one mole of sulfonyldiacetic acid (2) with two moles of arylsulfonylacetic acid hydrazide (13) in the presence of POCl₃ (Scheme II.2).
Moreover, bis(5-arylsulfonylmethyl-1,3,4-thiadiazol-2-ylmethyl)sulfone (15) was synthesized by the treatment of compound 14 with thiourea in tetrahydrofuran (Scheme II.3).

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\text{Scheme II.3}
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In addition to these, bis(4-amino-5-arylsulfonylmethyl-1,2,4-triazol-3-ylmethyl)sulfone (16) was obtained by the treatment of compound 14 with hydrazine hydrate in the presence of KOH in n-butanol (Scheme II.4).

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\text{Scheme II.4}
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Antioxidant activity

The compounds 14, 15 and 16 were assayed for antioxidant activity by DPPH, NO and H$_2$O$_2$ methods at 50, 75 and 100 µM concentrations. The results of antioxidant activity indicated that the compounds having oxadiazole moiety 14 showed higher radical scavenging activity when compared with those having thiadiazole 15 and triazole 16 units. Further, it was noticed that methyl substituted and unsubstituted compounds displayed higher antioxidant activity than the chloro substituted compounds. In fact, the compound 14b exhibited greater antioxidant activity than the standard Ascorbic acid. It was also observed that the compounds 14a, 15a, 15b, 16a and 16b exhibited good antioxidant activity whereas the other compounds displayed least activity. Moreover, the results indicated that radical scavenging activity increases with increase in concentration in all the three methods.

CHAPTER III

The chapter III concerns with the synthesis and antioxidant activity of bis(5-arylmethanesulfonylmethyl-1,3,4-oxadiazol-2-ylmethyl)sulfone (22), bis(5-arylmethanesulfonylmethyl-1,3,4-thiadiazol-2-ylmethyl)sulfone (23) and bis(4-amino-5-arylmethanesulfonylmethyl-1,2,4-triazol-3-ylmethyl)sulfone (24).

To achieve the above mentioned heterocycles, arylmethanesulfonylacetic acid hydrazide (21) was utilized as synthon. The compound 21 was obtained by the reaction of arylmethanesulfonylacetic acid methyl ester (20) with hydrazine hydrate in methanol. The latter compound 20 in turn was prepared by the reaction of arylmethane chloride (17) with thioglycolic acid in the presence of sodium hydroxide in methanol. The resulting arylmethanethioacetic acid (18) were oxidized to arylmethanesulfonylacetic acid (19) with hydrogen peroxide in glacial acetic acid. The compound 19 on esterification with methanol in the presence of concentrated sulfuric acid resulted in 20 (Scheme III.1).
The reaction of one mole of sulfonidyldiacetic acid (2) with two moles of arylmethanesulfonylacetic acid hydrazide (21) in the presence of POCl₃ yielded bis(5-arylmethanesulfonylmethyl-1,3,4-oxadiazol-2-ylmethyl)sulfone (22) (Scheme III.2).

Apart from these, bis(5-arylmethanesulfonylmethyl-1,3,4-thiadiazol-2-ylmethyl)sulfone (23) was synthesized by the treatment of compound 22 with thiourea in tetrahydrofuran (Scheme III.3).
Furthermore, bis(4-amino-5-arylmethanesulfonylmethy1-1,2,4-triazol-3-ylmethyl) sulfone (24) was prepared by the reaction of the compound 22 with hydrazine hydrate in the presence of KOH in n-butanol (Scheme III.4).
Antioxidant activity

The compounds 22, 23 and 24 were tested for antioxidant activity by DPPH, NO and \( \text{H}_2\text{O}_2 \) methods at three different concentrations. The compound 22 showed greater radical scavenging activity than the other compounds 23 and 24. Amongst all the tested compounds 22b exhibited significant antioxidant activity. The structure-activity relationship of the tested compounds revealed that arylmethanesulfonylethane linked oxadiazole derivatives displayed greater radical scavenging activity than corresponding thiadiazole and triazole derivatives. Moreover, it was observed that compounds having electron donating substituent on the phenyl ring enhances the activity when compared with the electron withdrawing substituent.

CHAPTER - IV

The chapter IV consists of the synthesis and antioxidant activity of bis(5-arylaminosulfonylmethyl-1,3,4-oxadiazol-2-ylmethyl)sulfone (31), bis(5-arylaminosulfonylmethyl-1,3,4-thiadiazol-2-ylmethyl)sulfone (32) and bis(4-amino-5-arylaminosulfonylmethyl-1,2,4-triazol-3-ylmethyl)sulfone (33).

Encouraged by the results of our approach towards the synthesis of a new class of symmetrical bis heterocycles, arylaminosulfonylacetic acid hydrazide (30) was used as synthetic intermediate and prepared as follows. The treatment of methyl bromoacetate (25) with sodium sulfite gave sodium methylsulfoacetate (26). This in the presence of phosphorus (V) chloride produced methyl 2-(chlorosulfonyl)acetate (27). The reaction of latter compound with substituted aniline (28) in the presence of triethylamine in benzene resulted in arylaminosulfonylacetate (29) which on treatment with hydrazine hydrate furnished compound 30 (Scheme IV.I).
The reaction of one mole of sulfonyldiacetic acid (2) with two moles of arylaminosulfonylacetic acid hydrazide (30) in the presence of POCl₃ provided bis(5-arylaminosulfonylmethyl-1,3,4-oxadiazol-2-ylmethyl)sulfone (31) (Scheme IV.2).

**Scheme IV.1**

(i) Na₂SO₄ / H₂O / MeOH  
(ii) POCl₃ / Δ  
(iii) Et₃N / C₆H₆  
(iv) NH₂NH₂·H₂O / Pyridine / MeOH  

**Scheme IV.2**

(i) POCl₃  

R = a) H  
b) Me  
c) Cl
Treatment of bis(5-arylaminosulfonylmethyl-1,3,4-oxadiazol-2-ylmethyl)-sulfone (31) with thiourea in tetrahydrofuran afforded bis(5-arylaminosulfonylmethyl-1,3,4-thiadiazol-2-ylmethyl)sulfone (32) (Scheme IV.3).

\[
31 
\xrightarrow{\text{NH,CSONH$_2$ / THF}} 
32 
\]

(i) NH$_2$CSNH$_2$ / THF

R = a) H  
b) Me  
c) Cl

SCHEME IV.3

On the other hand, the reaction of bis(5-arylaminosulfonylmethyl-1,3,4-oxadiazol-2-ylmethyl)sulfone (31) with hydrazine hydrate led to the formation of bis(4-amino-5-arylaminosulfonylmethyl-1,2,4-triazol-3-ylmethyl)sulfone (33) (Scheme IV.4).

\[
31 
\xrightarrow{\text{NH$_2$NH$_2$,H$_2$O / KOH / n-Butanol}} 
33 
\]

(i) NH$_2$NH$_2$,H$_2$O / KOH / n-Butanol

R = a) H  
b) Me  
c) Cl

SCHEME IV.4
Antioxidant activity

The compounds 31, 32 and 33 were evaluated for antioxidant property in three (DPPH, NO and H₂O₂) methods using Ascorbic acid as the standard. The results of antioxidant activity indicated that the compound 31 displayed higher radical scavenging activity than the compounds 32 and 33. Further, it was noticed that unsubstituted and methyl substituted compounds showed greater antioxidant activity than the corresponding chloro substituted ones. Amongst all the tested compounds bis(5-(4-methylphenylaminosulfonylmethyl)-1,3,4-oxadiazol-2-ylmethyl)sulfone (31b) exhibited higher antioxidant activity than the standard Ascorbic acid. It was observed that with increasing number of chromophoric groups the antioxidant activity increases. In fact, the presence of sulfonamide linked oxadiazole displayed promising activity. Besides, the results indicated that the radical scavenging activity increases with increasing concentration in all the three methods.