3

RESULTS AND DISCUSSION

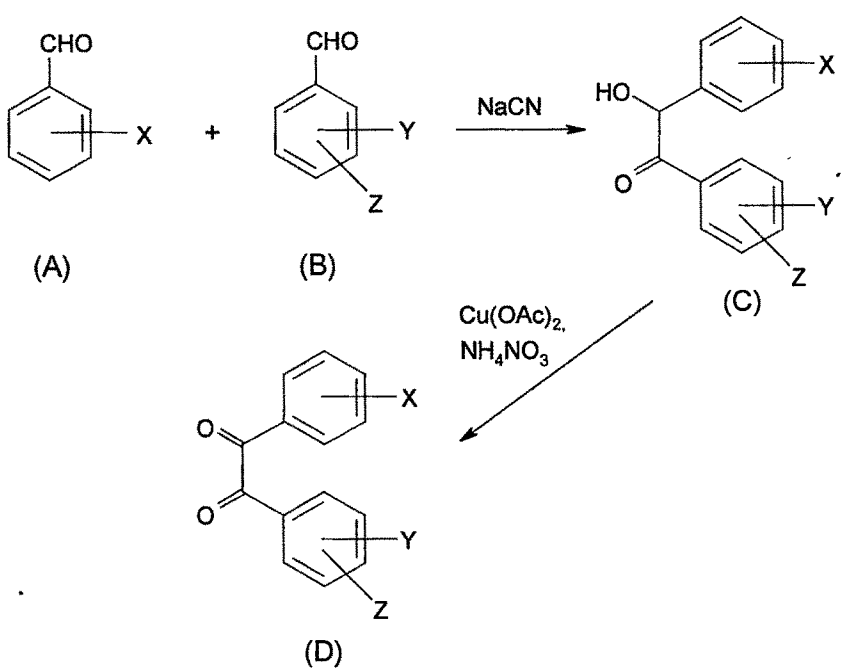
The work carried out has been discussed under the following two main heads:

3.1 Chemical studies and

3.2 Biological studies

3.1 CHEMICAL STUDIES

It was envisaged to synthesize 3,4-diaryl-1,2,5-oxadiazoles as discussed earlier. For preparation of such a system 1,2-diarylethane-1,2-

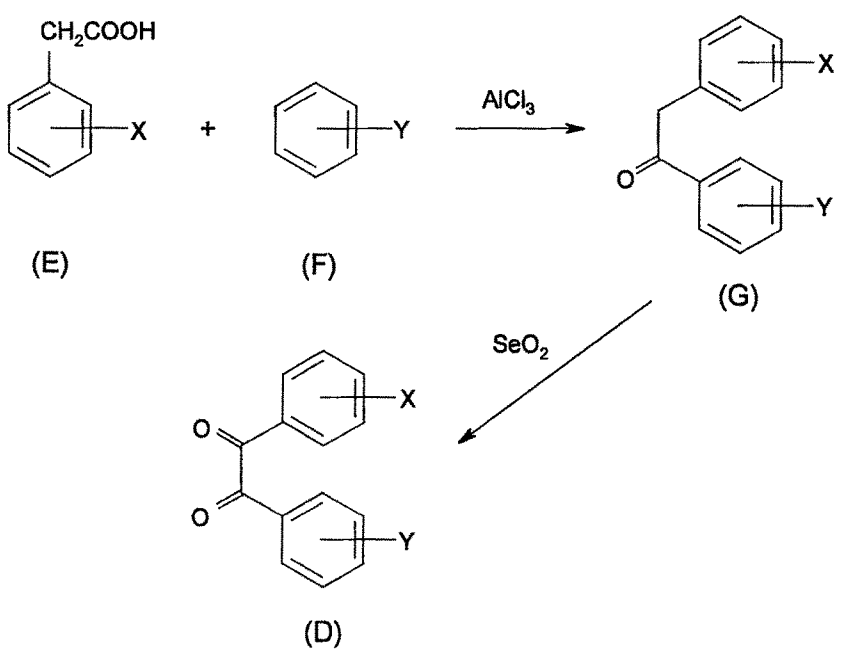


Scheme-1

dione system was required so that the dione could be converted into 1,2-dioximino derivatives which in turn could be cyclized to the desired 1,2,5-oxadiazole heterocyclic system. The simplest route to prepare the

disubstituted 1,2-dione system could be through the preparation of benzoins followed by mild oxidation of the benzoins to benzils. Keeping the above point in mind various benzoins **(C)** were prepared by adopting the well established benzoin condensation. The benzoins **(C)** so obtained were oxidized using a mild oxidizing system like copper acetate-ammonium nitrate to obtain the benzils **(D)** **(Scheme-1).**

Although, the above described route of preparation of various benzils **(D)** offered some benzil derivatives but it was not found to be suitable for certain others because, either a mixture of products were

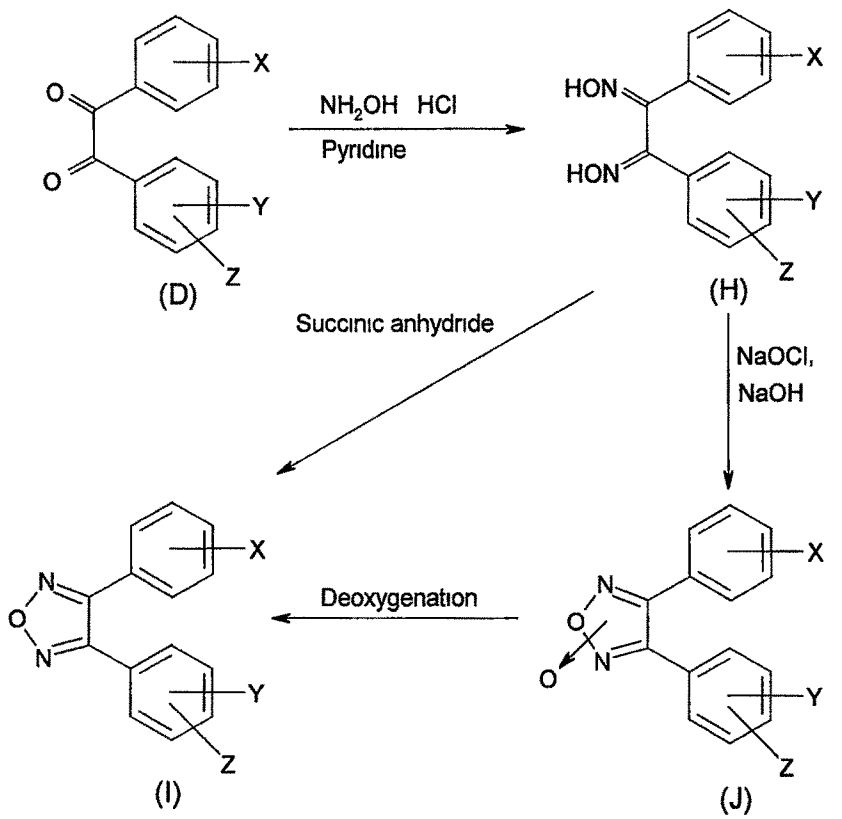


Scheme-2

obtained or the starting substituted benzaldehyde derivatives were not available commercially. To overcome these shortcomings another route **(Scheme-2)** was adopted for preparation of such compounds. In this route, substituted phenylacetic acid as acid chloride was reacted with substituted benzenes through Friedel-Crafts acylation to afford the desoxybenzoins

(G). The desoxybenzoins **(G)** were oxidized to the desired benzils **(D)** using selenium dioxide as the oxidizing agent.

After obtaining the desired benzil derivatives **(D),** it was planned to convert the benzils **(D)** into dioximes **(H)** by their reaction with hydroxylamine. The dioximes **(H)** then could be dehydrated to the desired

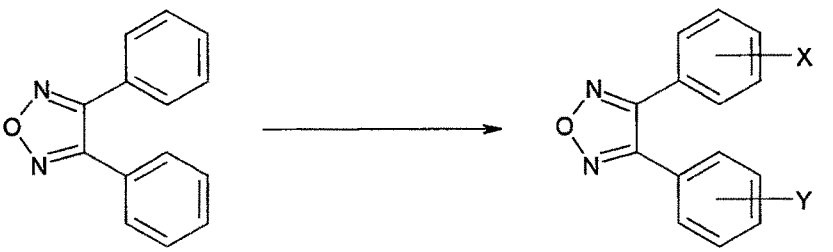


Scheme-3

1,2,5-oxadiazoles **(I)** or could be oxidized to the 1,2,5-oxadiazole N-oxides **(J).** It was also planned to deoxygenate the N-oxides **(J)** into 1,2,5-oxadiazoles **(I)** if the dehydration procedure failed in some specific cases **(Scheme-3).**

Since direct electrophilic aromatic substitution reaction could be possible in the monosubstituted benzene rings of the 3,4-diphenyl-1,2,5-

oxadiazole **(I)**, it was also planned to perform some of these reactions directly into the benzene rings of compound **(I)** **(Scheme–4).**



(I) (K)

Scheme-4

The work carried out has been discussed under the heads:

3.1.1 Syntheses of benzil derivatives **(D)** through benzoin condensation

3.1.2 Syntheses of benzil derivatives **(D)** through Friedel-Crafts acylation

3.1.3 Syntheses of substituted benzil dioximes

3.1.4 Syntheses of 3,4-diaryl-1,2,5-oxadiazoles

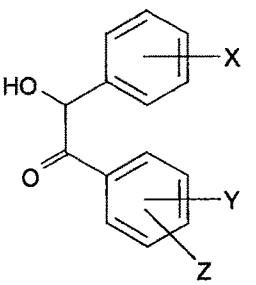
3.1.5 Syntheses of 3,4-diaryl-1,2,5-oxadiazole N-oxides

3.1.1 SYNTHESES OF BENZIL DERIVATIVES (D) THROUGH BENZOIN CONDENSATION

1. Syntheses of benzoin derivatives (C)

Different symmetrically and unsymmetrically substituted benzoins **(C)** were prepared adopting the method of benzoin condensation **(Scheme-1).** Benzaldehyde on condensation in ethanol and sodium cyanide offered the reported benzoin[202-204] **(58).** Anisaldehyde under similar conditions gave anisoin[204] **(59).** Its IR spectrum showed characteristic bands at 3463 (O–H), 1664 (C=O), 1265 (Ar–O–Me, asymmetric) and 1024 cm^{-1} (Ar–O–Me, symmetric). The unsymmetric benzoin **(60)** was obtained by condensing equimolar solution of 2-chlorobenzaldehyde and anisaldehyde[205]. The compound **(60)** showed vibrational bands at 3477

(O–H), 1666 (C=O), 1225 and 1030 (Ar–O–Me) in its IR spectrum. Cross condensation between 2-chlorobenzadehyde and veratraldehyde yielded compound[205] **(61).** Its IR spectrum gave characteristic peaks at 3439, 1662, 1269 and 1027 cm^{-1}. Similarly, reaction between 2-chlorobenzaldehyde and 4-dimethylaminobenzaldehyde offered the



(58) X = Y = Z = H

(59) X = Y = 4 – OCH_3; Z = H

(60) X=2–Cl; Y= 4–OCH_3; Z=H

(61) X = 2–Cl; Y = 4–OCH_3; Z = 3–OCH_3

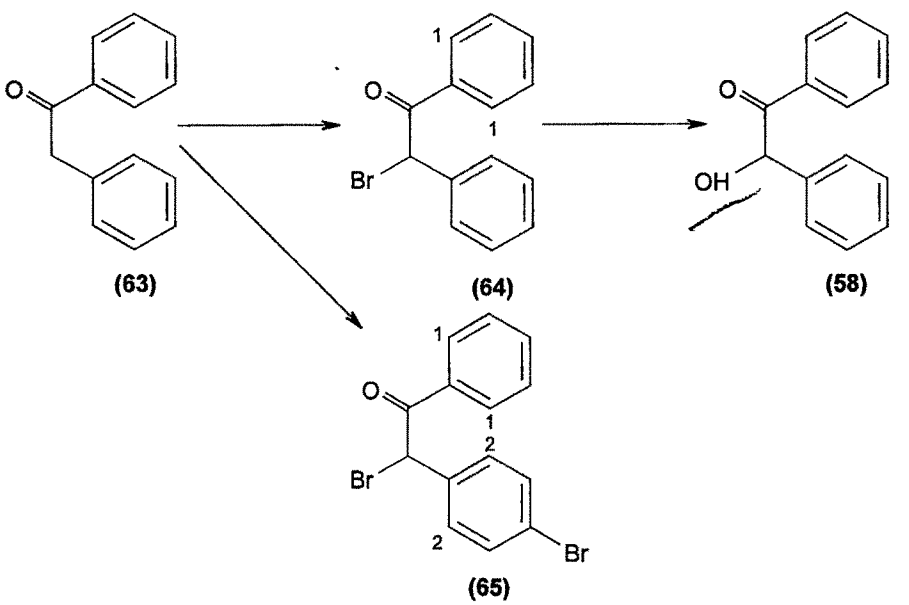
(62) X = 2–Cl; Y = 4–$N(CH_3)_2$; Z = H

disubstituted benzoin[206] **(62).** It gave a broad peak for hydroxyl (O–H) stretching at 3444 cm^{-1} in its IR spectrum.

Cross benzoin condensation between and benzaldehyde failed to give the desired 3,4-dimethoxy-6-nitrobenzoin. Instead, a mixture of benzoin **(58)** and 6-nitroveratraldehyde only could be isolated.

For such benzoins that could not be obtained by the above described route of benzoin condensation it was tried to establish a new route **(Scheme-5)**. Desoxybenzoin **(63)** was prepared by Friedel-Crafts acylation of benzene with phenylacetyl chloride[207]. Bromination of desoxybenzoin using N-bromosuccinimide and visible light irradiation offered a mixture of compounds **(64** and **65).** Compound **(64)** gave a singlet at δ 6.41 (1H; C*H*Br), a doublet at δ 8.00-8.02 (2H; 1-ArC*H*) and a multiplet at δ 7.37–7.56 (8H; ArC*H*) in its PMR spectrum. It gave characteristic keto stretching peak at 1690 cm^{-1} in IR spectrum. Compound **(65)** in the PMR

spectrum showed signals at δ 7.66-7.69 (d, 2H; 2-ArC*H*), 7.75-7.78 (d, 2H; 1-ArC*H*) and 7.27-7.40 (m, 6H; ArC*H* and C*H*Br). Keto stretching peak appeared at 1689 cm^{-1} in its IR spectrum.



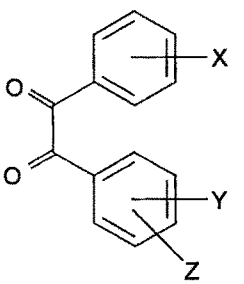
SCHEME-5

Controlled addition of bromine in a carbon tetrachloride solution of desoxybenzoin **(63)** under visible irradiation offered pure bromo derivative **(64)** on repeated crystallizations[208-209]. The bromo derivative **(64)** on alcoholic potassium hydroxide treatment offered benzoin **(58)** but, in poor yields. Facing difficulties in both the steps in **Scheme–5**, it was not pursued for the synthesis of other benzoin derivatives.

2. Syntheses of benzil derivatives (D)

The benzoins were oxidized to benzils using copper acetate-ammonium nitrate system in aqueous acetic acid as per the reported[204] procedure. Benzoin **(58)** provided benzil **(66)** and anisoin **(59)** the anisil **(67).** It offered carbonyl stretching band at 1654 cm^{-1} in its **(67)** IR spectrum. Similarly, other derivatives **(68-70)** were also obtained. Compound **(68)** showed two strong bands at 1673 and 1662 cm^{-1} in

its IR spectrum while, compound (69) showed these bands at 1663 and 1647 cm^{-1}. The dimethylamino derivative **(70)** showed a strong peak at 1679 cm^{-1} in its IR spectrum.



(66) X = Y = Z = H

(67) X = Y = 4–OCH_3; Z = H

(68) X = 2–Cl; Y = 4–OCH_3; Z = H

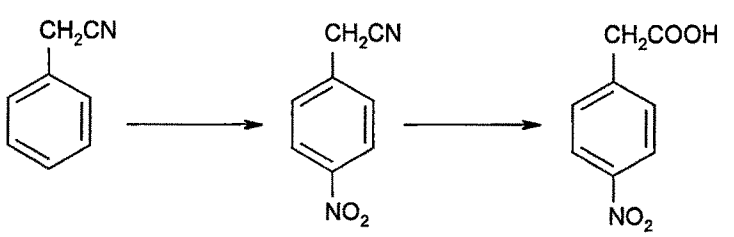
(69) X = 2–Cl; Y = 4–OCH_3; Z = 3–OCH_3

(70) X = 2–Cl; Y = 4–$N(CH_3)_2$; Z = H

3.1.1 SYNTHESES OF BENZIL DERIVATIVES (D) THROUGH FRIEDEL–CRAFTS ACYLATION

1. Syntheses of desoxybenzoin derivatives (G)

For performing Friedel–Crafts acylation reaction, substituted arylacetic acids were required. Some of these acids were available commercially while others were synthesized by the reported procedures[210-215]. 4-Nitrophenylacetic acid **(73)** was prepared by nitrating

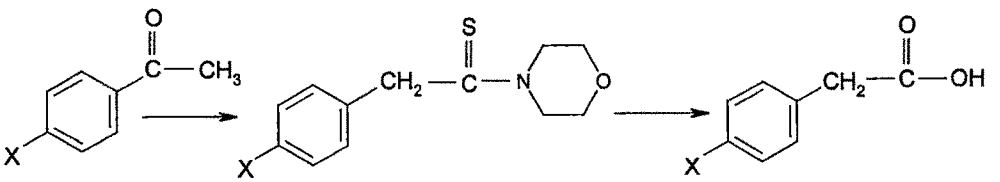


(71) **(72)** **(73)**

phenylacetic acid by the known procedure[210]. Difficulty was encountered in purifying the product (73) so its route of synthesis was changed. Benzyl cyanide **(71)** was nitrated using nitric acid–sulphuric acid mixture to

afford a pure product[210-211] **(72).** Nitrile group was hydrolyzed in acidic medium to the acid **(73)** in pure form. The acid displayed bands at 2900, 1700, 1511 and 1347 cm^{-1} in its IR spectrum.

Other phenylacetic acid derivatives **(74-76)** were prepared using substituted acetophenones through Kindler modified Willgerodt reaction[212-213] **(Scheme-6).** A properly substituted acetophenone derivative



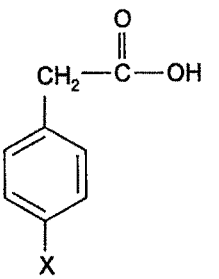
(L) **(M)** **(N)**

SCHEME-6

(L) was refluxed with sulphur in morpholine to afford the thiomorpholide **(M).** The thiomorpholide without further purification and characterization was hydrolyzed in alkaline media to afford the desired phenylacetic acid derivatives **(N).**

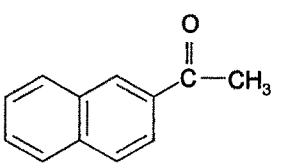
It has been reported[214] that addition of a phase transfer catalyst like triethylbenzylammonium chloride (TEBA) during hydrolysis of thiomorpholide increased the yield and the rate of reaction. However, this observation could not be supplemented in this laboratory. 4-Methylacetophenone offered 4-tolylacetic acid **(74)** while 4-fluoro-phenylacetic acid **(75)** was obtained from 4-fluoroacetophenone. The compound **(74)** showed characteristic peaks at 3000 (O–H) and 1701 cm^{-1} (C=O) while compound **(75)** showed at 3054 (O–H) and 1700 cm^{-1} (C=O) in their IR spectra. For the preparation of biphenylacetic acid **(76)** the required 4-phenylacetophenone was prepared by Friedel-Crafts acylation of biphenyl using acetic anhydride/anhydrous aluminium trichloride. Willgerodt reaction on 4-phenylacetophenone followed by

acidic hydrolysis as per **Scheme-6** afforded the desired biphenylacetic acid[213] **(76).** The compound **(76)** showed characteristic peaks at 3400 and 1690 cm^{-1} in its IR spectrum. Its PMR spectrum gave signals at δ 3.70 (s, 2H; $-CH_2$) and δ 7.25-7.66 (m, 9H; ArC*H*).

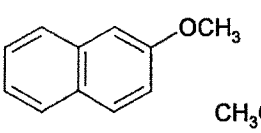


(74) X = CH_3
(75) X = F
(76) X = 

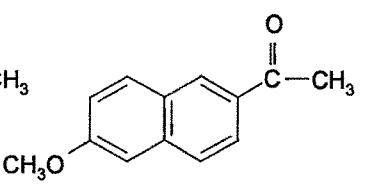
Naphthalene was acetylated by the reported procedure[215] to obtain 2-acetylnaphthalene **(77).** It showed carbonyl stretching vibrations at 1678 cm^{-1} in the IR spectrum. Similarly, 2-acetyl-6-methoxynaphthalene **(79)** was prepared from nerolin[216]**(78).** It **(79)** showed keto stretching vibration



(77)



(78)



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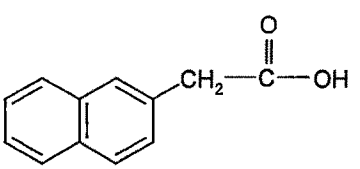
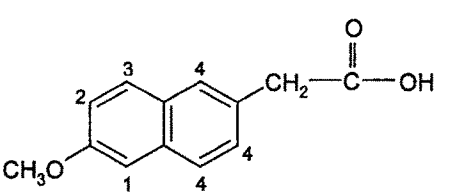


(80)

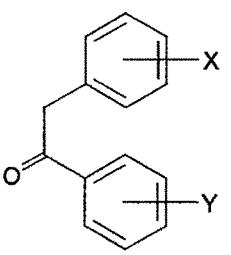


(81)

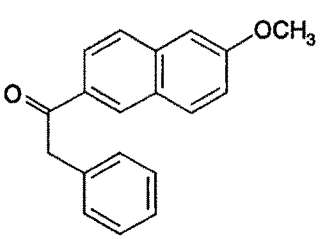
at 1675 cm^{-1} in its IR spectrum. Willgerodt reaction of the compounds **(77** and **79)** followed by hydrolysis yielded 2-naphthylacetic acid[212] **(80)** and 6-methoxy-2-naphthylacetic acid[217] **(81),** respectively. 2-Naphthyl-acetic acid **(80)** displayed characteristic IR bands at 3039 and 1701 cm^{-1}. Compound **(81)** offered IR peaks at 2957 (O–H), 1696 (C=O), 1224

(Ar–O–Me, asymmetric) and 1028 cm^{-1}(Ar–O–Me, symmetric). Its PMR spectrum gave signals at δ 3.78 (s, 2H; –C*H*$_2$), 3.91 (s, 3H; –OC*H*$_3$), 7.11 (s, 1H; 1-ArC*H*), 7.11-7.15 (d, 1H; 2-ArC*H*), 7.34-7.39 (d, 1H; 3-ArC*H*) and 7.66-7.73 (m, 3H; 4-ArC*H*).

After obtaining the required acids, acid chlorides were obtained by reacting the respective acids with thionyl chloride or phosphorous



(63) X = Y = H
(82) X = H; Y= 4 – CH_3
(83) X = H; Y= 4 – OCH_3
(84) X = H; Y = 4 – Cl
(85) X = H; Y = 4 – F
(86) X = H; Y = 4 – Br
(87) X = H; Y = 4 – SCH_3
(88) X = 4 – NO_2; Y = H
(89) X = 4–CH_3; Y = 4–SCH_3
(90) X = 4 – F; Y = 4 – SCH_3
(91) X = 4 – Cl; Y = 4 – CH_3
(92) X = 4 – Cl; Y = 4 – OCH_3
(93) X = 4 – Cl; Y = 4 – F
(94) X = 2 – Cl; Y = H
(95) X = 2 – Cl; Y = 4 – CH_3
(96) X = 4 – Ph; Y = H
(97) X = 4 – Ph; Y = 4 – CH_3



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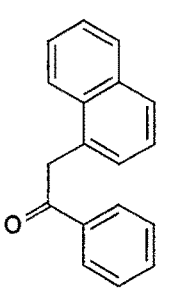
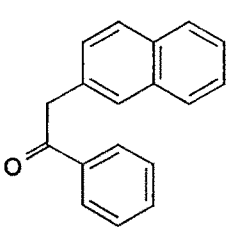


(99)



(100)

trichloride. Reaction of the acid chlorides with benzene/substituted benzenes as per **Scheme-2** offered different desoxybenzoins **(63, 82-100).**

Table 4. Characteristic group frequencies of desoxybenzoins

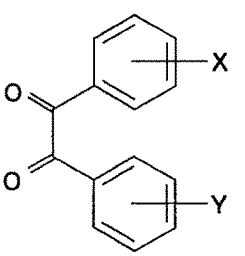
Compound No.	Group frequency (cm^{-1})
63	1685 (C=O)
82	1681 (C=O)
83	1670 (C=O), 1264 (Ar–O–Me, Asymmetric), 1029 (Ar–O–Me, Symmetric)
84	1684 (C=O)
85	1684 (C=O)
86	1684 (C=O)
87	1680 (C=O)
88	1686 (C=O), 1514 (NO_2, Asymmetric), 1352 (NO_2, Symmetric)
89	1679 (C=O)
90	1675 (C=O)
91	1677 (C=O)
92	1675 (C=O), 1260 (Ar–O–Me, Asymmetric), 1024 (Ar–O–Me, Symmetric)
93	1683 (C=O)
94	1692 (C=O)
95	1680 (C=O)
96	1684 (C=O)
97	1687 (C=O)
98	1681 (C=O), 1225 (Ar–O–Me, Asymmetric), 1031 (Ar–O–Me, Symmetric)
99	1712 (C=O)
100	1685 (C=O)

All the synthesized desoxybenzoins were characterized on the basis of their IR spectra (**Table 4**) and their purity was checked by TLC in different solvent systems.

Thioanisole required for the preparation of compounds (**87, 89** and **90**) was prepared in the laboratory by methylating thiophenol with dimethylsulphate/methyl iodide. Friedel-Crafts acylation of thioanisole was carried out at –10 °C. Reaction conditions above 0 °C produced a mixture of products, which were difficult to separate. Similarly, for the preparation of compound (**98**) controlled conditions were given during Friedel–Crafts acylation of nerolin (**78**) with phenylacetic acid.

2. Syntheses of benzil derivatives (D)

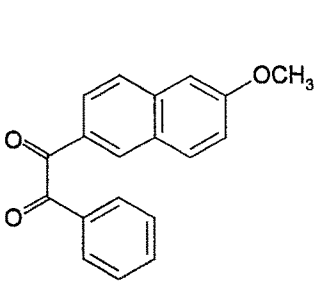
The desoxybenzoins (**63, 82–100**) were converted into respective benzils (**66, 101-119**) using selenium dioxide as the oxidizing agent.



(66)	X = Y = H	**(110)**	X = 4 – Cl; Y = 4 – CH_3
(101)	X = H; Y= 4 – CH_3	**(111)**	X = 4 – Cl; Y = 4 – OCH_3
(102)	X = H; Y= 4 – OCH_3	**(112)**	X = 4 – Cl; Y = 4 – F
(103)	X = H; Y= 4 – Cl	**(113)**	X = 2 – Cl; Y = H
(104)	X = H; Y = 4 – F	**(114)**	X = 2 – Cl; Y = 4 – CH_3
(105)	X = H; Y = 4 – Br	**(115)**	X = 4 – Ph; Y = H
(106)	X = H; Y = 4 – SCH_3	**(116)**	X = 4 – Ph; Y = 4 – CH_3
(107)	X = 4 – NO_2; Y = H	**(117)**	X = H; Y = 4 – SO_2CH_3
(108)	X = 4 – CH_3; Y = 4–SCH_3	**(118)**	X = 4–CH_3; Y = 4–SO_2CH_3
(109)	X = 4 – F; Y = 4 – SCH_3	**(119)**	X = 4 – F; Y = 4 – SO_2CH_3

Selection of solvent for the reaction media proved to be quite an experience in these reactions. Initially, dioxane-water mixture was tried

but the reaction took unusually long time (more then 24 hours) and never culminated in the formation of a pure product. It was found in the literature[218] that acidic medium increased the rate of oxidation so the solvent system was changed to glacial acetic acid. Unfortunately, it was observed that even after refluxing the reaction mixture in glacial acetic acid for 12 long hours, the reaction did not end up with complete oxidation. In order to transfer higher amount of energy to the reaction mixture, it was felt at this stage to choose a solvent having higher boiling point then acetic acid with sufficient solubility for both, the desoxybenzoins and selenium dioxide. Ultimately the choice fell on acetic anhydride as it had both the desired properties. Acetic anhydride proved to be quite a successful solvent as it offered pure products in reasonable timings. All these benzils **(66, 101-116)** were prepared using this system i.e. selenium dioxide in acetic anhydride. A majority of these benzils crystallized out as well defined solids but some **(101, 113)** still remained as oily residues. All the synthesized products were characterized on the basis of their IR Spectra **(Table 5)** and their purity was evaluated on the basis of TLC in different solvent systems.



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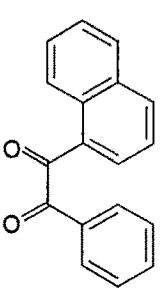

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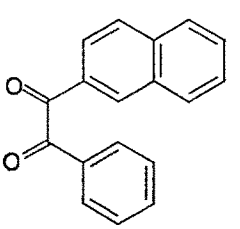


(122)

Another worker in this laboratory, also working on selenium dioxide oxidation of 1,2 diarylethanones, observed that replacement of acetic anhydride with dimethyl sulphoxide reduced the time duration of the reaction, drastically from 6-8 hours to merely 30 seconds. When this solvent system was used for oxidation of compound **(98)** to the dione

Table 5. Characteristic group frequencies of benzil derivatives

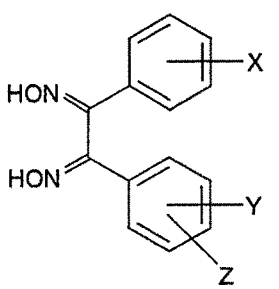
Compound No.	Characteristic group frequency (cm^{-1})
101	1668 (C=O)
102	1675 (C=O), 1651(C=O), 1270 (Ar–O–Me, Asymmetric), 1020 (Ar–O–Me, Symmetric)
103	1666 (C=O)
104	1668 (C=O)
105	1665 (C=O)
106	1662 (C=O)
107	1662 (C=O), 1527 (NO_2, Asymmetric), 1348 (NO_2, Symmetric)
108	1654 (C=O)
109	1667 (C=O), 1652 (C=O)
110	1661 (C=O)
111	1675 (C=O), 1653 (C=O), 1267(Ar–O–Me, Asymmetric), 1029 (Ar–O–Me, Symmetric)
112	1662 (C=O)
114	1671 (C=O)
115	1675 (C=O)
116	1674 (C=O)
117	1682 (C=O), 1668 (C=O), 1325 (SO_2, Asymmetric), 1146 (SO_2, Symmetric)
118	1683 (C=O), 1670 (C=O), 1298 (SO_2, Asymmetric), 1147 (SO_2, Symmetric)
119	1666 (C=O), 1310 (SO_2, Asymmetric), 1151 (SO_2, Symmetric)
120	1675 (C=O), 1652 (C=O), 1263(Ar–O–Me, Asymmetric), 1029 (Ar–O–Me, Symmetric)
121	1718 (C=O)
122	1668 (C=O)

(120), the reaction got completed within 30 seconds with no change in the yield and purity of the compound. Compounds **(121** and **122)** were synthesized by this very method as described for **(120).**

Selenium dioxide did not affect sulphur in thiomethyl derivatives (**106, 108, 109**). In order to make methanesulphonyl derivatives, oxidation of sulphur in these compounds was tried using hydrogen peroxide in acidic medium as described in the literature[219]. Here, sulphoxide derivatives and not sulphonyl derivatives were obtained. Same results were obtained in alkaline medium also. Ultimately, m-chloroperbenzoic acid (mCPBA) afforded the desired sulphones (**117-119**).

3.1.3 SYNTHESES OF SUBSTITUED BENZIL DIOXIMES (H)

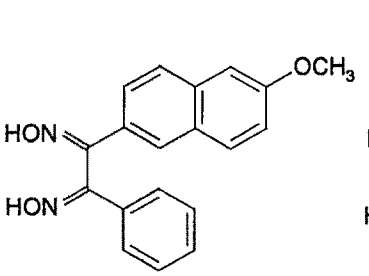
Oximation of the benzil derivatives (**66-70** and **101-122**) was performed using hydroxylamine hydrochloride–pyridine system at



(123) X = Y = Z = H
(124) X = Y = 4 – OCH_3; Z = H
(125) X = 2 – Cl; Y = 4 – OCH_3; Z = H
(126) X=2–Cl; Y=4–OCH_3; Z=3–OCH_3
(127) X = 2–Cl; Y = 4–$N(CH_3)_2$; Z= H
(128) X = Z = H; Y = 4 – CH_3
(129) X = Z = H; Y = 4 – OCH_3
(130) X = Z = H; Y = 4 – Cl
(131) X = Z = H; Y = 4 – F
(132) X = Z = H; Y = 4 – Br
(133) X = Z = H; Y = 4 – SCH_3
(134) X = 4 – NO_2; Y = Z = H
(135) X = 4 – Cl; Y = 4 – CH_3; Z = H
(136) X = 4–Cl; Y = 4–OCH_3; Z = H
(137) X = 4 – Cl; Y = 4 – F; Z = H
(138) X = 2 – Cl; Y = Z = H
(139) X = 2 – Cl; Y = 4 – CH_3; Z = H
(140) X = 4 – Ph; Y = Z = H
(141) X = 4 – Ph; Y = 4 – CH_3; Z = H
(142) X = Z = H; Y = 4 – SO_2CH_3
(143) X=4–CH_3; Y= 4– SO_2CH_3; Z=H
(144) X = 4–F; Y = 4–SO_2CH_3; Z = H

refluxing temperatures. Heating on water bath at 100 °C did not offer good results with a majority of the reactants. For some of the derivatives refluxing time was prolonged to up to 12 hours because the starting benzil

derivative still remained in the reaction mixture as monitored by TLC. For these benzils the refluxing temperature was still increased by changing the solvent system to ethylene glycol but the yields further decreased rather then increasing. All the reactions were monitored by TLC. A majority of the dioximes were isolated as solid compounds.



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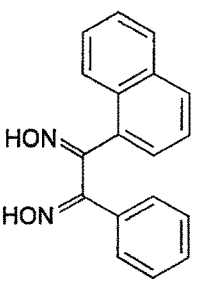

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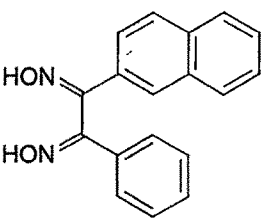


(147)

Their IR spectra indicated **(Table 6)** absence of keto stretching bands. Since there is a possibility of formation of syn and anti products[220], no efforts were made to isolate these geometric isomers and used as such for the next step.

Table 6. Characteristic IR group frequencies of dioximes

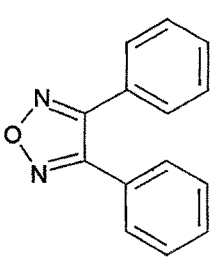
Compound No.	Group frequency (cm^{-1})
123	3279 (OH), 1443 (C=N)
124	3275 (OH), 1513 (C=N), 1247 (Ar–O–Me, Asymmetric), 1029 (Ar–O–Me, Symmetric)
125	3241 (OH), 1511 (C=N), 1248 (Ar–O–Me, Asymmetric), 1080 (Ar–O–Me, Symmetric)
126	3245 (OH), 1240 (Ar–O–Me, Asymmetric), 1060 (Ar–O–Me, Symmetric)

Contd..

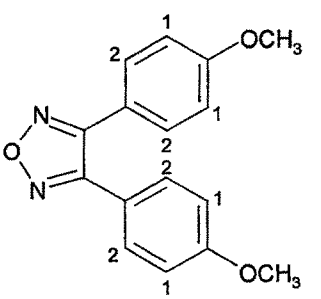
128	3184 (OH), 1541 (C=N)
129	3326 (OH), 1514 (C=N), 1250 (Ar–O–Me, Asymmetric), 1025 (Ar–O–Me, Symmetric)
130	3190 (OH)
131	3231 (OH), 1506 (C=N)
132	3190 (OH), 1488 (C=N)
133	3332 (OH), 1592 (C=N)
134	3275 (OH), 1527 (NO_2, Asymmetric), 1350 (NO_2, Symmetric)
135	3289 (OH)
136	3272 (OH), 1513 (C=N), 1250 (Ar–O–Me, Asymmetric), 1022 (Ar–O–Me, Symmetric)
137	3408 (OH), 1510 (C=N)
138	3365 (OH)
139	3268 (OH), 1512 (C=N)
140	3341 (OH)
141	3231 (OH), 1601(C=N)
142	3378 (OH), 1591 (C=N), 1310 (SO_2, Asymmetric), 1143 (SO_2, Symmetric)
143	3377 (OH), 1302 (SO_2, Asymmetric), 1142 (SO_2, Symmetric)
144	3380 (OH), 1510 (C=N), 1300 (SO_2, Asymmetric), 1141 (SO_2, Symmetric)
145	3340 (OH), 1203 (Ar–O–Me, Asymmetric), 1025 (Ar–O–Me, Symmetric)
146	3259 (OH), 1487 (C=N)
147	3217 (OH)

3.1.4 SYNTHESES OF 3,4-DIARYL-1,2,5-OXADIAZOLES (I)

For cyclization of the 1,2-dioxime into 1,2,5-oxadiazole ring, preliminary investigations were carried out using 1,2-diphenylethanedione dioxime **(123).** Different reaction conditions conducive for dehydration of the dioxime **(123)** to the required 1,2,5-oxadiazole were tried. Basic conditions involving heating of the dioxime **(123)** in presence of potassium hydroxide and diethylene glycol/ethylene glycol/ 1-propanol/ethanol failed to provide the desired product. Refluxing the dioxime with acetic anhydride offered the diacetate while refluxing with thionyl chloride degraded the starting dioxime to some unknown compound, which could not be isolated. Ultimately, an intimate admixture of the dioxime **(123)** with succinic anhydride on heating at 180 to 200 °C offered the desired product **(148)** although, not in a very satisfactory yield. Vibrational bands appeared at 1577 (C=N–O), 1367 (N–O) and 893 cm^{-1} (heterocyclic ring) in its IR spectrum in agreement with the literature[221]. PMR spectrum showed signals only in the aromatic region at δ 7.37–7.56 as a multiplet. Quasi molecular ion peak (M+H) was obtained at 223 (m/z)



(148)



(149)

in its mass spectrum. Other peaks were at 192, 119, 103, 89 and 30 as explained in **(Fig. 9).** After standardizing the cyclization conditions for the benzil dioxime **(123),** same conditions were used throughout the course of the work for the preparation of the 1,2,5–oxadiazole derivatives.

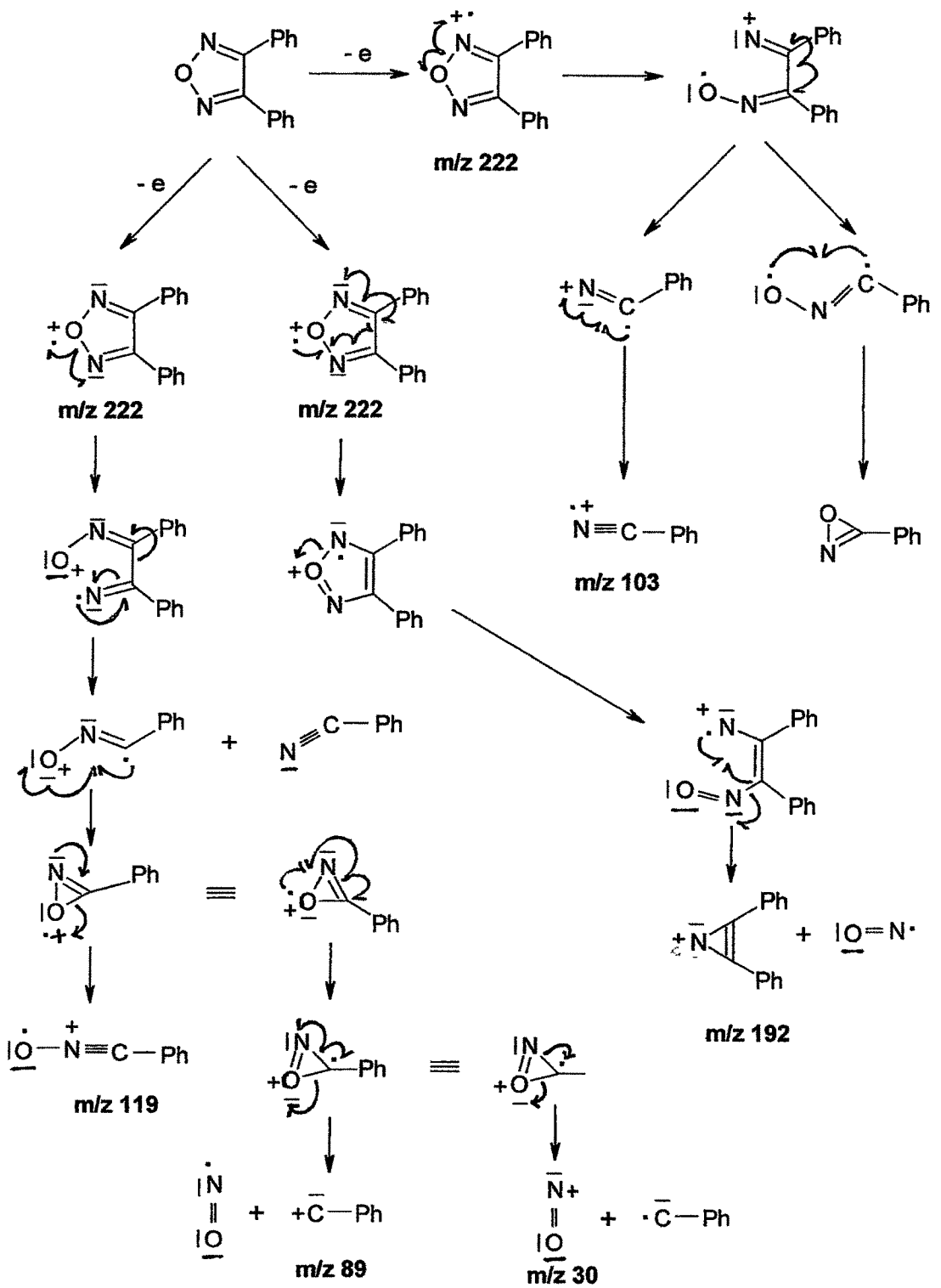
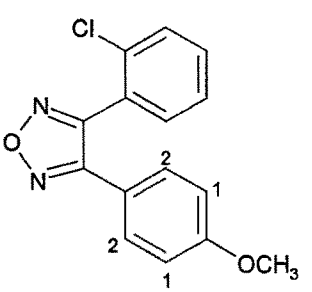


Fig. 9. Mass fragmentation of 3,4-Diphenyl-1,2,5-oxadiazole (148)

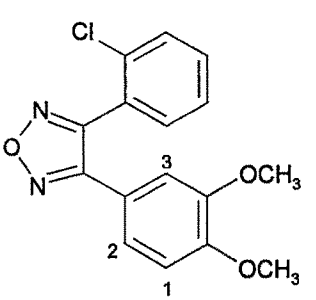
Anisil dioxime **(124)** under similar conditions offered the desired product **(149).** The compound **(149)** gave peaks at 1612 (C=N–O), 1444, (N–O), 1257 (Ar–O–Me, Asymmetric) and 1026 cm^{-1} (Ar–O–Me, Symmetric) in its IR spectrum. PMR spectrum offered peaks at δ 3.86 (s, 6H; –OC*H*$_3$), 6.92-6.96 (d, 4H; 1-ArC*H*) and 7.45-7.50 (d, 4H; 2-ArC*H*). The compound **(149)** offered M+H peak at 283 (m/z) in FAB mode. Other peaks appeared at 252, 149, 133 and 119 (m/z) in its mass spectrum.

3-(2-Chlorophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole **(150)** gave characteristic IR signals at 1611, 1437, 1253 and 1029 cm^{-1}. In the PMR spectrum, signals were obtained at δ 3.80 (s, 3H; –OC*H*$_3$), 6.84-6.87 (d, 2H; 1-ArC*H*; J = 8.7 Hz), 7.41-7.44 (d, 2H; 2-ArC*H*; J = 8.7 Hz) and 7.44–7.51 (m, 4H). Molecular ion peak (M+H) was obtained at 287 (m/z) in its mass spectrum.

Compound **(151)** showed characteristic peaks at 1605 (C=N–O), 1256 (Ar–O–Me, asymmetric) and 1019 cm^{-1} (Ar–O–Me, symmetric) in the IR spectrum. The PMR spectrum displayed two singlets each integrating for three protons at δ 3.71 and 3.87 (–OC*H*$_3$), a doublet at



(150)

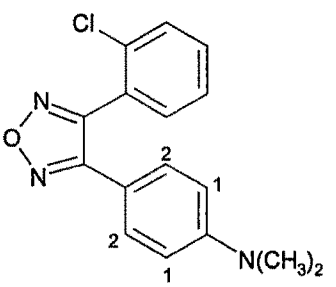


(151)

δ 6.78-6.81 (1H, 3-ArC*H*), a double doublet at δ 6.98-7.02 (1H, 1-ArC*H*) and a doublet at δ 7.08-7.087 (1H, 2-ArC*H*). A multiplet was observed at 7.43-7.52 for the remaining four aromatic protons of 2-chlorophenyl ring. In mass spectrum, the molecular ion peak was observed at 316 (m/z) and other peaks appeared at 286, 179, 163 and 137 (m/z).

3-(2-Chlorophenyl)-4-(4-dimethylaminophenyl)-1,2,5-oxadiazole **(152),** showed infrared bands at 1619 and at 1430 cm^{-1}, characteristic bands of the oxadiazole ring system. In PMR spectrum, a singlet for six protons was observed at δ 2.97 (–N(CH_3)$_2$). Two doublets appeared at δ 6.60-6.63 (2H, 1-ArC*H*; *J*=9 Hz) and 7.34-7.37 (2H, 2-ArC*H*; *J*=9 Hz). A multiplet for the four aromatic protons of 2-chlorophenyl was observed at δ 7.38-7.51. The molecular ion peak (M+H) was observed at 300 (m/z) in its mass spectrum.

3-Phenyl-4-(4-tolyl)-1,2,5-oxadiazole **(153)** showed vibrational bands at 1605 and 1450 cm^{-1} in the IR spectrum. A singlet at δ 2.40 for three protons (–CH_3) and a multiplet at δ 7.20-7.53 for nine aromatic



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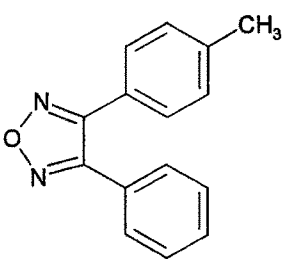
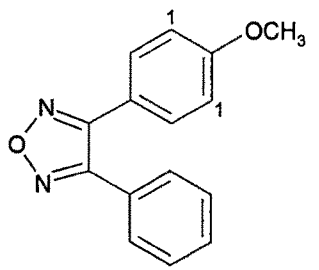


(153)

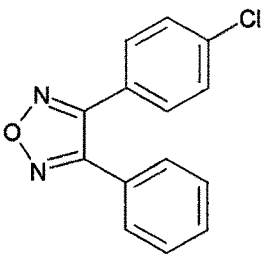
protons were observed in PMR spectrum. The title compound **(153)** gave the molecular ion peak at 236 (m/z) in mass spectrum. Other peaks were at 206, 133, 119, 103 and 89 (m/z).

Compound **(154)** showed a sharp peak for (C=N–O) at 1613 cm^{-1} and peaks at 1250 and 1025 cm^{-1} for (Ar–O–Me, asymmetric) and (Ar–O–Me, symmetric) respectively, in the IR spectrum. A singlet at δ 3.82 for three protons of (–OCH_3) and a doublet at δ 6.88-6.91 for two shielded aromatic protons (1-ArC*H*) were observed in its PMR spectrum. A multiplet appeared at δ 7.37-7.55 for seven aromatic protons. It gave the

molecular ion peak at 252 (m/z) in the mass spectrum. Other peaks appeared at 222, 149, 133, 119, 103 and 89 (m/z).



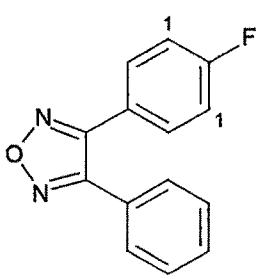
(154)



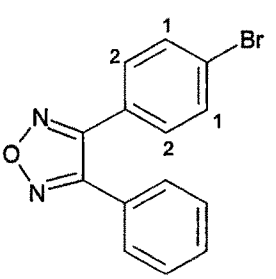
(155)

3-(4-Chlorophenyl)-4-phenyl-1,2,5-oxadiazole **(155)** displayed stretching bands at 1597 (C=N=O) and 1447 cm^{-1} (N–O) in the IR spectrum. The PMR spectrum showed a multiplet for the nine aromatic protons at δ 7.42-7.49. In mass spectrum, it gave the molecular ion peak at 256 (m/z) and other peaks were observed at 226, 153, 137, 119, 103 and 89 (m/z).

3-(4-Fluorophenyl)-4-phenyl-1,2,5-oxadiazole **(156)** gave vibrational bands at 1605 (C=N–O) and 1227 cm^{-1} (C–F) in the IR spectrum. The PMR spectrum showed signals at δ 7.12 (m, 2H, 1-ArC*H*)



(156)

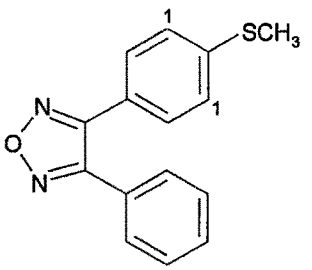


(157)

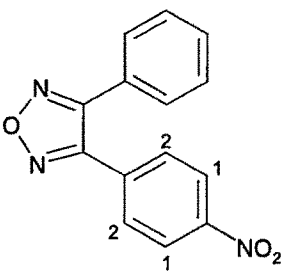
and 7.40-7.56, (m, 7H, ArC*H*). In mass spectrum, it gave the molecular ion peak at 240 (m/z). Peaks for other prominent ions appeared at 210, 37, 119, 107, 95 and 89 (m/z).

3-(4-Bromophenyl)-4-phenyl-1,2,5-oxadiazole **(157)** showed characteristic absorption peaks at 1596 (C=N–O) and 1407 cm^{-1} (N–O) in the IR spectrum. In PMR spectrum, signals appeared at δ 7.39-7.42 (d, 2H; 2-ArC*H*), 7.55-7.56 (d, 2H; 1-ArC*H*) and 7.45-7.52 (m, 4H, ArC*H*). The compound gave a molecular ion peak at 302 (m/z) in the mass spectrum. Other peaks were present at 272, 199, 169, 119 and 89 (m/z).

A characteristic stretching band at 1602 cm^{-1} for (C=N–O) appeared in the IR spectrum of the compound **(158)**. The PMR spectrum showed



(158)



(159)

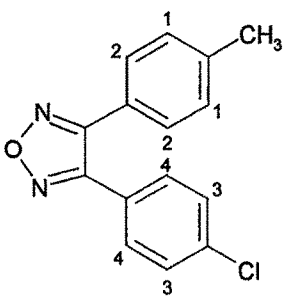
signals at δ 2.50 (s, 3H; –SCH_3), 7.24-7.26 (d, 2H; 1-ArC*H*) and 7.40-7.54 (m, 7H; Ar*CH*). It offered the M+H peak at 268 (m/z) in the mass spectrum.

In IR spectrum 3-nitrophenyl-4-phenyl-1,2,5-oxadiazole **(159)** showed vibrational bands at 1600 (C=N–O), 1520 (NO_2, asymmetric) and 1349 cm^{-1} (NO_2, symmetric). The PMR spectrum displayed signals at δ 7.47- 7.50 (m, 5H; ArC*H*), 7.74-7.77 (d, 2H; 2-ArC*H*; J=8.7 Hz) and 8.28-8.31 (d, 2H; 1-ArCH; J=8.7 Hz). It gave the molecular ion peak at 267 (m/z) in the mass spectrum.

Compound **(160)** showed infrared bands at 1612 (C=N–O), 1408 (N–O) and 1091 cm^{-1} (C–Cl). In PMR spectrum, signals were obtained at δ 2.46 (s, 3H; CH_3), 7.34-7.37 (d, 2H; 1-ArC*H*; J=8.1 Hz), 7.47-7.50 (d, 2H; 4-ArC*H*; J=8.7 Hz), 8.08-8.11 (d, 2H; 2-ArC*H*; J=8.1 Hz) and

8.10-8.13 (d, 2H; 3-ArC*H*; J=8.7 Hz). The compound gave the molecular ion peak at 270 (m/z) in its mass spectrum.

3-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole **(161)** gave characteristic IR signals at 1614 (C=N–O), 1253 (Ar–O–Me, asymmetric), 1090 (C–Cl) and 1027 cm^{-1} (Ar–O–Me, symmetric). The PMR spectrum displayed signals at δ 3.86 (s, 3H; –OC*H*$_3$), 6.94-6.97



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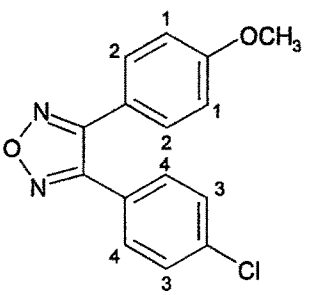
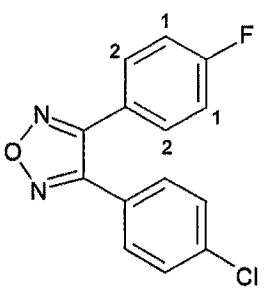


(161)



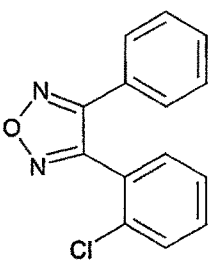
(162)

(d, 2H; 1-ArC*H*; J=8.7 Hz), 7.40-7.43 (d, 2H; 4-ArC*H*; d, J=9 Hz), 7.43-7.46 (d, 2H; 3-ArC*H*; d, J=9 Hz) and 7.48-7.51 (d, 2H; 2-ArC*H*; J=8.7 Hz).

In the IR spectrum, 3-(4-chlorophenyl)-4-(4-fluorophenyl)-1,2,5-oxadiazole **(162)** displayed characteristic absorption bands at 1601 (C=N–O), 1225 (C–F) and 1090 cm^{-1} (C–Cl). In PMR spectrum, a double doublet was observed at δ 7.12-7.18 (2H; 1-ArC*H*) due to coupling of 1-ArC*H* with adjacent 2-ArC*H* and with fluorine atom. A multiplet

appeared at δ 7.44-7.46 for four aromatic protons (4-chlorophenyl). A multiplet was also observed at δ 7.49-7.54 (2H; 2-ArC*H*).

3-(2-Chlorophenyl)-4-phenyl-1,2,5-oxadiazole **(163)** gave characteristic IR signals at 1600 (C=N–O), 1434 (N–O) and 1062 cm^{-1} (C–Cl). A multiplet at δ 7.34-7.51 for aromatic protons was observed in its PMR spectrum.



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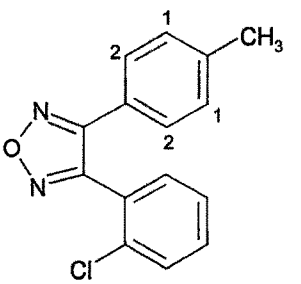
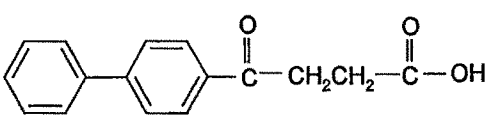


(164)

Characteristic absorption bands appeared at 1613 (C=N–O), 1435 (N–O) and 1060 cm^{-1} (C–Cl) in the IR spectrum of 3-(2-chlorophenyl)-4-(4-tolyl)-1,2,5-oxadiazole **(164)**. The PMR signals were observed at δ 2.35 (s, 3H; –C*H*$_3$), 7.13-7.16 (d, 2H; 1-ArC*H*; J=8.1 Hz), 7.33-7.36 (d, 2H; 2-ArC*H*; J=8.1 Hz) and 7.39-7.51 (m, 4H, ArC*H*).

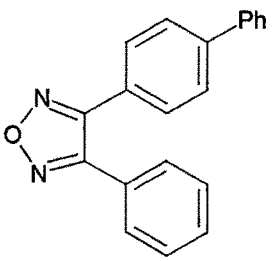
4-Biphenylacetic acid **(76)** is an active metabolite of fenbufen **(165)** with three times more activity than the parent drug but is also considerably more ulcerogenic than it or its other metabolites[222].



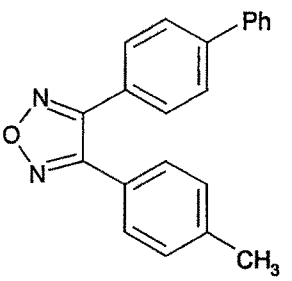
(165)

Considering its higher activity it was thought to synthesize such type of compounds having biphenyl ring as one of the aryl group attached to the 1,2,5-oxadiazole ring moiety.

Compound **(166)** displayed characteristic IR stretching peaks at 1612 (C=N–O) and 1411 cm^{-1} (N–O). A multiplet at δ 7.36-7.62 for fourteen aromatic protons was observed in its PMR spectrum.



(166)



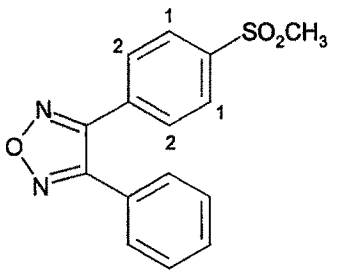
(167)

Compound **(167)** showed infrared bands at 1614 (C=N–O) and 1401 cm^{-1} (N–O). A singlet at δ 2.42 (–C*H*$_3$) and a multiplet at δ 7.22-7.63 for thirteen aromatic protons were observed in the PMR spectrum.

Difference in volume (space) of the binding sites of a particular enzyme, is exploited for the rational designing of selective enzyme inhibitors. Clinically used selective COX-II inhibitors have either a SO_2Me or SO_2NH_2 group substituted at the para position of one of the phenyl rings. These groups can interact with secondary pocket amino acid residues such as His 90, Gln 192, Phe 518 and Arg 513[140]. Keeping in view the importance of these groups, it was envisaged to synthesize compounds bearing these groups in one phenyl ring along with certain other substituents in the second phenyl ring.

Compound **(168)** displayed characteristic peaks at 1600 (C=N–O), 1408 (N–O), 1308 (SO_2, asymmetrical) and 1149 cm^{-1} (SO_2, symmetrical) in the IR spectrum. The PMR spectrum exhibited signals at δ 3.11 (s, 3H; –SO_2CH_3), 7.47-7.50 (m, 5H; Ar*CH*), 7.76-7.78 (d, 2H; 2-Ar*CH*; 8.6 Hz) and 8.00-8.03 (d, 2H; 1-ArCH; 8.6 Hz).

3-(4-Methanesulphonylphenyl)-4-(4-tolyl)-1,2,5-oxadiazole **(169)** showed characteristic IR peaks at 1610 (C=N–O), 1407 (N–O), 1307 (SO_2, asymmetric) and 1150 cm^{-1} (SO_2, symmetric). The PMR spectrum



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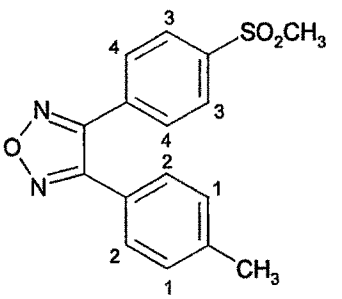
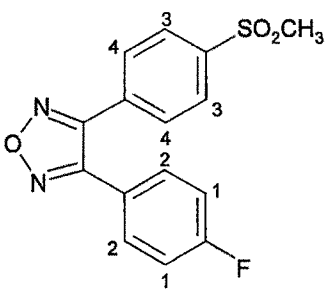


(169)

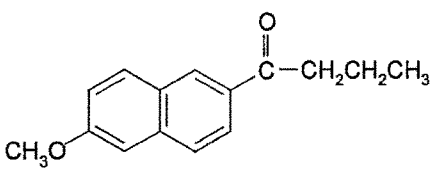


(170)

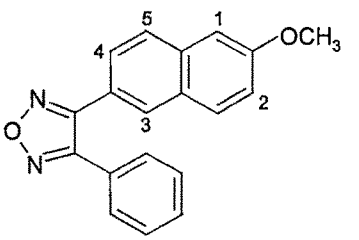
displayed signals at δ 2.43 (s, 3H; –C*H*$_3$), 3.10(s, 3H; –SO_2C*H*$_3$),7.25-7.28 (d, 2H; 1-ArC*H*; J=8.1 Hz), 7.37-7.39 (d, 2H; 2-ArC*H*; J=8.1 Hz), 7.76-7.78 (d, 2H; 4-ArC*H*; J=8.6 Hz) and 8.00-8.02 (d, 2H; 3-ArC*H*; J=8.6 Hz).

Structure-activity relationship (SAR) studies[140] have shown that for optimum COX-II selectivity and inhibitory potency presence of a SO_2Me substituent at the *para-* position of one phenyl ring and a *p*-F substituent on the other phenyl ring improves *in vivo* activity. It was therefore thought to synthesize such a compound **(170).** Compound **(170)** gave characteristic IR signals at 1606 (C=N–O), 1402 (N–O), 1310 (SO_2, asymmetric), 1225 (C–F) and 1151 cm^{-1} (SO_2, symmetric). In the PMR spectrum, signals appeared at δ 3.12 (s, 3H; –SO_2C*H*$_3$), 7.15-7.20 (dd, 2H; 1-ArC*H*; J^1_{HH}=8.4 Hz; J^1_{FH}=8.4 Hz), 7.49-7.53 (m, 2H; 2-ArC*H*), 7.75-7.77 (d, 2H; 4-ArC*H*; J=8.3 Hz) and 8.02-8.05 (d, 2H; 3-ArC*H*; J=8.3 Hz).

6-Methoxy-2-naphthylacetic acid (6-MNA) **(81)** an active metabolite of nabumetone **(171)** is a potent anti-inflammatory agent. Taking the structure of 6-MNA **(81)** into consideration it was planned



(171)

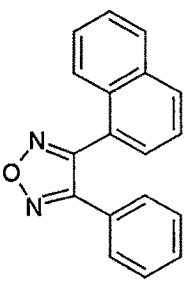


(172)

to have naphthyl ring as one of the aryl group attached to the 1,2,5-oxadiazole ring moiety. The dioxime **(145)** was cyclized adopting the standardized cyclization method using succinic anhydride to obtain the desired product **(172).** Characteristic IR peaks were present at 1627 (C=N–O), 1388 (N–O), 1210 (Ar–O–Me, asymmetric) and 1031 cm^{-1} (Ar–O–Me, symmetric). PMR signals appeared at δ 3.93 (s, 3H; $-OCH_3$), 7.16 (s, 1H; 1-ArC*H*), 7.16-7.19 (m, 1H; 2-ArC*H*), 7.39-7.58 (m, 6H; ArC*H*), 7.66-7.68 (d, 1H; 4-ArC*H*), 7.75-7.78 (d, 1H; 5-ArC*H*) and 7.96 (s, 1H; 3-ArC*H*). The compound **(172)** gave M+H peak at 303 (m/z) in LC-MS.

In order to obtain the 1-naphthylsubstituted oxadiazole **(173),** the dioxime **(146)** was fused with succinic anhydride as per the established method. It was astonishing to isolate the acid **(174)** although in a very poor yield of around 9 %. Electrophilic aromatic substitution was not expected because no Lewis acid was added into the reaction mixture. The compound **(174)** exhibited characteristic peaks at 3200 (O–H), 1701 (C=O of COOH) and 1676 cm^{-1} (C=O, aryl keto) in its IR spectrum. It offered a sodiated peak at 395.1 in LC-MS. Electrophilic

substitution has been indicated to take place at position-5 in structure **(174)** on mechanistic basis and no effort has been done to establish it.



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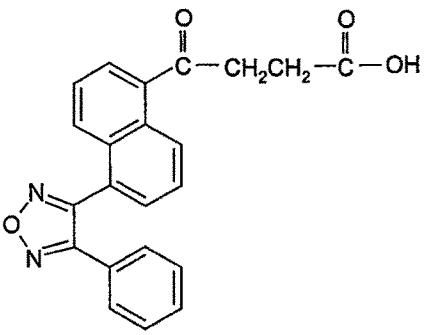

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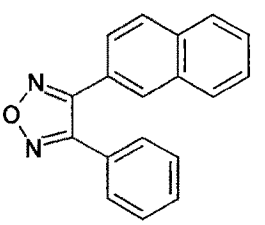
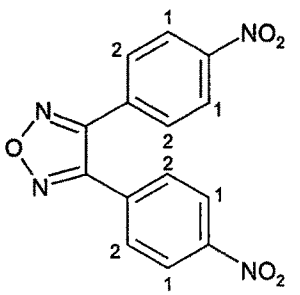


(175)

Similarly, the dioxime **(147)** was cyclized with the expectation to obtain the desired compound **(175)** but unfortunately no such compound could be isolated from the reaction mixture. A sticky material isolated showed a sharp peak at 2225 cm^{-1} (C≡N) indicating breakdown of the dioxime **(147).**

Friedel–Crafts acylation was not possible theoretically to be performed on some of the aromatic substrates containing electron withdrawing groups (e.g. NO_2). To synthesize compounds having these groups, electrophilic aromatic substitution reactions were performed directly on the preformed 3,4-diphenyl-1,2,5-oxadiazole **(148).** When compound **(148)** was treated with nitrating mixture, two spots were obtained in the TLC of the product. Fractional crystallization in methanol

separated both the products (**176** and **177**). Nitro stretching vibrations appeared at 1527 and 1346 cm^{-1} in the IR spectrum of compound **(176).**



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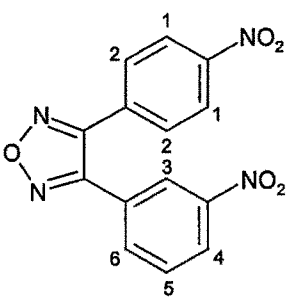
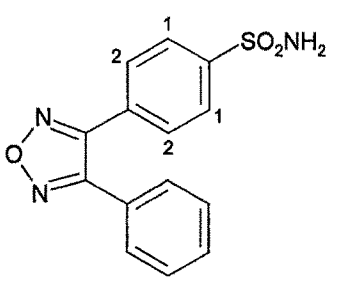


(177)

It offered PMR signals at δ 7.72-7.75 (d, 4H; 2-ArC*H*) and 8.33-8.36 (d, 4H; 1-ArC*H*). Compound **(177)** gave IR characteristic peaks at 1540 and 1349 cm^{-1} for the nitro group. PMR signals appeared at δ 8.41-8.45 (m, 2H; 3-ArC*H* and 4-ArC*H*), 8.32-8.37 (d, 2H; 1-ArC*H*), 7.84-7.87 (m, 1H; 6-ArC*H*), 7.75-7.78 (d, 2H; 2-ArC*H*) and 7.70-7.79 (m, 1H; 5-ArC*H*). It offered a molecular ion peak at 312 (m/z) in its mass spectrum. Other prominent peaks were at 282, 164 and 134 (m/z).



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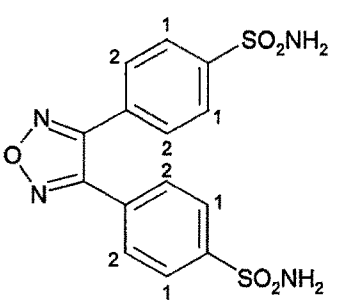


(179)

Controlled reaction of compound **(148)** with chlorosulphonic acid in dry chloroform followed by strong ammonia treatment offered the mono substituted sulphonamide **(178).** It showed two characteristic absorption bands at 3368 and 3177 (N–H) and two bands at 1354 and 1159 cm^{-1} (SO_2) in its IR spectrum. PMR signals appeared at δ 7.37 (b, NH_2),

7.47-7.55 (m, 5H; ArC*H*), 7.65-7.68 (d, 2H; 2-ArC*H*; *J*=8.4 Hz) and 7.99-8.01 (d, 2H; 1-ArC*H*; *J* = 8.4 Hz). Reaction of the starting material **(148)** with excess of chlorosulphonic acid followed by ammonia treatment offered the disubstituted sulphonamide **(179).** It gave characteristic peaks at 3355, 3266, 1332 and 1159 cm^{-1} in its IR spectrum. PMR spectrum offered signals at δ 7.34 (b, NH_2), 7.64-7.67 (d, 4H; 2-ArC*H*) and 7.98-8.00 (d, 4H; 1-ArC*H*). The molecular ion peak appeared at 380 (m/z) in the mass spectrum. Other prominent peaks appeared at 350 and 198 (m/z).

3.1.5 SYNTHESES OF 3,4-DIARYL-1,2,5-OXADIAZOLE N-OXIDES (J)

For preparation of 1,2,5-oxadizole N-oxides **(J)**, dioximes **(H)** were oxidized with sodium hypochlorite to obtain the desired N-oxides except for compound **(192)** which was synthesized by oxidation of 1,2,5-oxadiazole **(158)** with potassium permanganate solution (3 %) in acidic medium. In unsymmetrically substituted aryl groups there are chances of formation of two isomeric N-oxides. No efforts were made to resolve such isomers, if formed in those cases.

The N-oxides were prepared with a view to provide changed electronic environment in the five membered heterocyclic ring and these may also act as precursors of nitric oxide (vasodilatory effect) which would have a favorable cardiovascular profile. This type of compounds could provide an edge over the other classes of selective COX-II inhibitors.

The dioxime **(123)** on sodium hypochlorite treatment afforded the desired N-oxide **(180)** in reasonably good yields. It showed IR absorption peaks at 1592 ($C=N^+-O^-$), 1419 ($=N^+(O^-)-O$), 1309 (N–O) and 835 cm^{-1} (heterocyclic ring) in agreement with literature[223]. PMR spectrum gave a multiplet at δ 7.35–7.55 for the aromatic protons. Quasi molecular ion

peak was observed at 239 (m/z) in the mass spectrum. Other peaks were at 222, 208, 178 and 119 (m/z) as explained in **(Fig.10).**

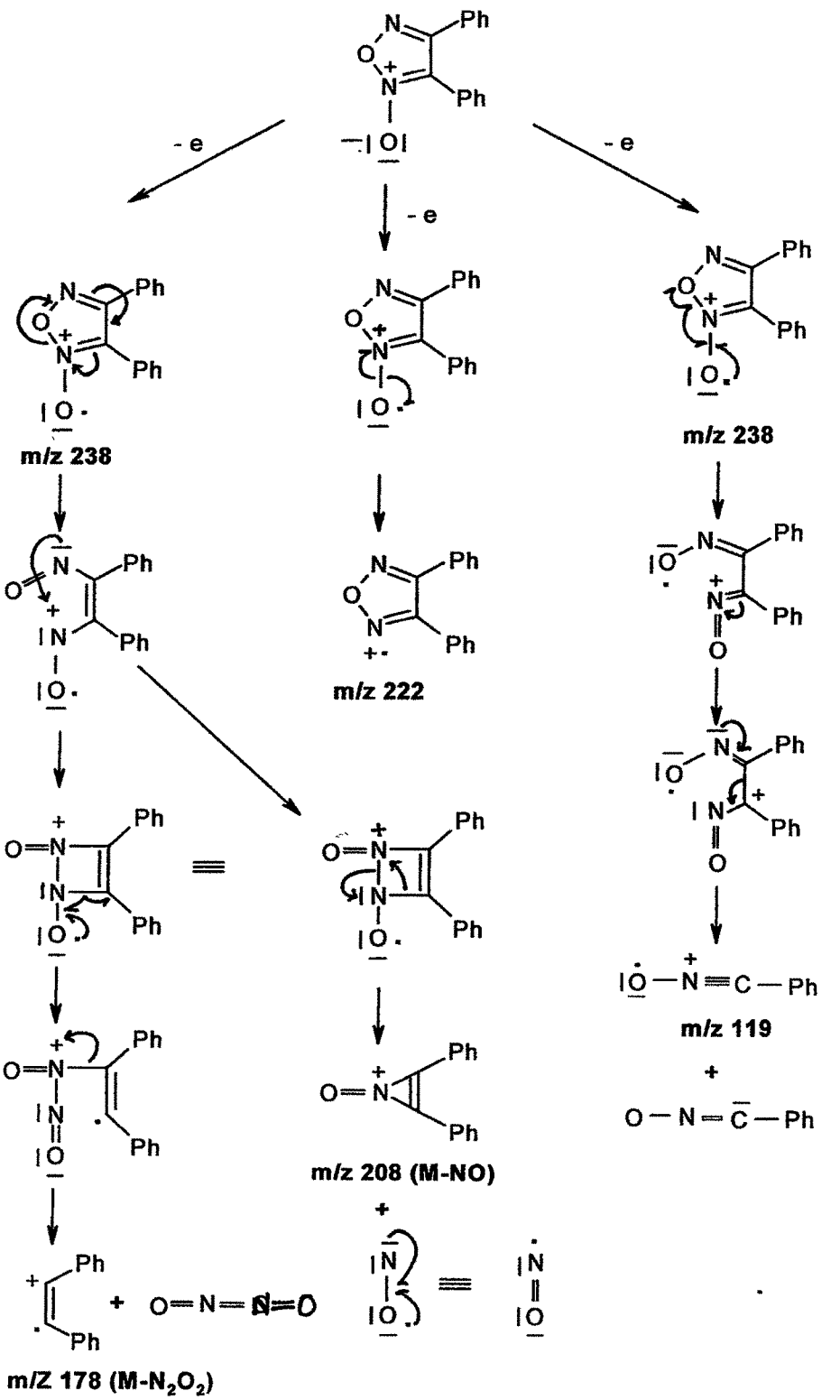
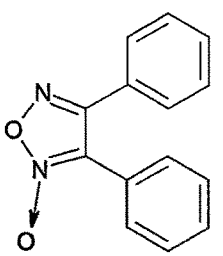


Fig. 10. Mass fragmentation of 3,4-Diphenyl-1,2,5-oxadiazole N-oxide (180)

Similar treatment of anisil dioxime **(124)** offered the title compound **(181)**. It offered characteristics IR peaks at 1600 ($C=N^{+}-O^{-}$), 1443 ($=N^{+}(O^{-})-O$), 1299 (N–O), 1261 (Ar–O–Me, asymmetric) and 1022 cm^{-1} (Ar–O–Me, symmetric). In the PMR spectrum two singlets appeared at δ 3.84 and 3.85 (6H; $-OCH_3$), 6.93-6.96 (d, 2H; 3-Ar*CH*), 6.94-6.97 (d, 2H;



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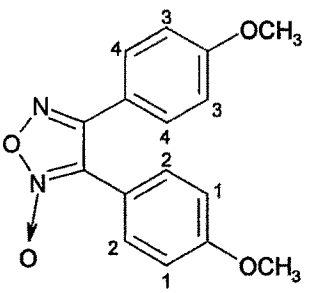

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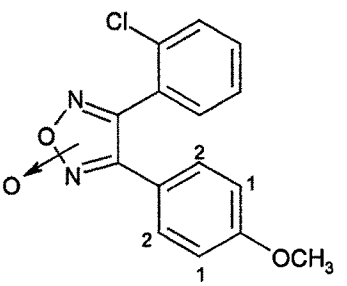


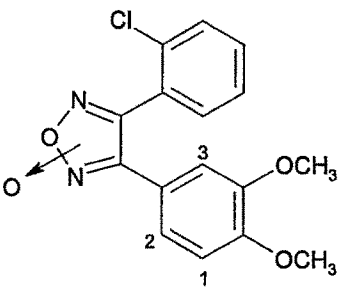
(182)

1-Ar*CH*), 7.44-7.47 (d, 2H; 4-Ar*CH*) 7.46-7.49 (d, 2H; 2-Ar*CH*). Compound **(181)** gave the molecular ion peak at 299 (m/z) in FAB mode of its mass spectrum. Other peaks at 282, 238 and 119 (m/z) were also observed.

Compound **(182)** showed vibrational bands at 1590 (C=N–O), 1426 ($=N^{+}(O^{-})-O$), 1253 (Ar–O–Me, asymmetric) and 1029 cm^{-1} (Ar–O–Me, symmetric) in the IR spectrum. Its PMR spectrum showed two singlets at δ 3.80 and 3.81 for three protons of ($-OCH_3$) which could be due to a mixture of two isomers (2' N-oxide and 5' N-oxide). However, TLC showed only one spot and attempts to separate the isomers were not made. Two doublets were observed at δ 6.85-6.86 (2H, 1-Ar*CH*; J=8.7 Hz) and

7.43-7.46 (2H, 2-Ar*CH*; J=8.7 Hz). A multiplet at δ 7.37-7.57 appeared for the remaining aromatic protons in the PMR spectrum.

3-(2-Chlorophenyl)-4-(3,4-dimethoxyphenyl)-1,2,5-oxadiazole N-oxide **(183)** offered stretching bands at 1601 (C=N–O), 1264 (Ar–O–Me, asymmetric) and 1025 cm^{-1} (Ar–O–Me, symmetric) in its IR spectrum. The characteristic singlets for (–O*CH*$_3$) were observed at δ 3.63, 3.72 and 3.87 for six protons accounting for the presence of two isomers of N- oxide.



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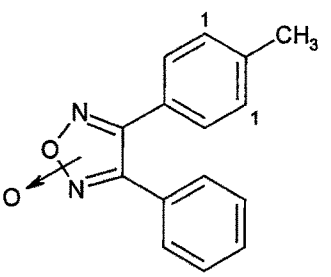

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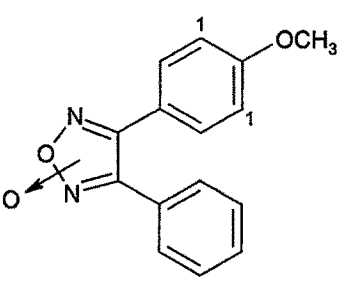


(185)

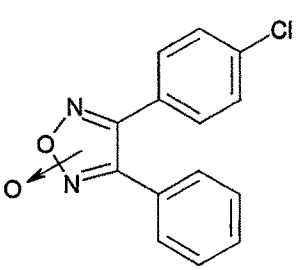
Other signals appeared at δ 6.78-6.84 (m, 1H; 1-Ar*CH*), 7.04-7.07 (m, 1H; 3-Ar*CH)* 7.14-7.17 (m, 1H; 2-Ar*CH*) and 7.42-7.59 (m, 4H; 2-chloro-phenyl) in PMR spectrum.

3-Phenyl-4-(4-tolyl)-1,2,5-oxadiazole N-oxide **(184)** showed characteristic IR peaks at 1600 (C=N–O), 1429 (=$N^+(O^-)$–O) and 1309 cm^{-1} (N–O). In PMR spectrum, it showed two characteristic singlets at δ 2.40 and 2.42 for three protons (–*CH*$_3$) indicating isomeric mixture of N-oxides. A doublet was observed at δ 7.21-7.24 for two aromatic protons (1-Ar*CH*) and a multiplet at δ 7.38-7.51 for the remaining seven aromatic

protons. The compound **(184)** gave the molecular ion peak at 252 and base peak at 196 (m/z) in the mass spectrum.

Compound **(185)** displayed characteristic absorption bands at 1591 (C=N–O), 1252 (Ar–O–Me, asymmetric) and 1026 cm^{-1} (Ar–O–Me, symmetric) in the IR spectrum. The PMR spectrum of **(185)** showed two singlets at δ 3.83 and 3.84 for three protons (–OC*H*$_3$). A doublet for two shielded aromatic protons (1-ArC*H*) at δ 6.90-6.93 and a multiplet for seven aromatic protons at δ 7.40-7.54 were also observed.

3-(4-Chlorophenyl)-4-phenyl-1,2,5-oxadiazole N-oxide **(186)** gave an intense peak at 1591 cm^{-1} for (C=N–O) stretching and a strong peak at



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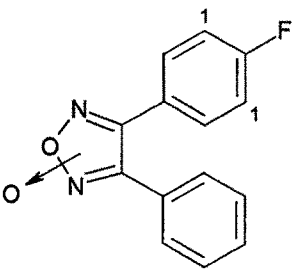
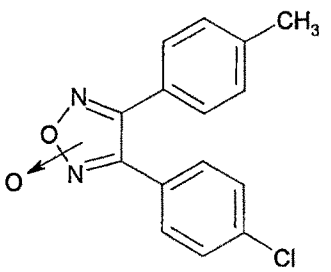


(187)

1093 cm^{-1} for C–Cl stretching in the IR spectrum. The compound **(186)** showed a multiplet for nine aromatic protons at δ 7.42-7.49 in the PMR spectrum.

Compound **(187)** offered infrared bands at 1588 (C=N–O) and 1228 cm^{-1} (C-F). A double doublet was observed at δ 7.10-7.15 (2H, 1-ArC*H*), which could be due to coupling of 1-ArC*H* with 2-ArC*H* and with fluorine atom. A multiplet at δ 7.44-7.55 for seven aromatic protons appeared in the PMR spectrum. The compound gave the molecular ion peak at 256 and base peak at 196 (m/z) (EI mode) in its mass spectrum.

Characteristic infrared bands for compound **(188)** were observed at 1589 (C=N–O), 1436 (=$N^+(O^-)$–O) and 1091 cm^{-1} (C–Cl). In PMR spectrum, two characteristic singlets appeared at δ 2.40 and 2.42 for three protons (–CH_3). A doublet at δ 7.24-7.27 appeared for the two aromatic protons adjacent to N-oxide ring. The remaining six aromatic protons showed a multiplet at δ 7.37-7.47. Molecular ion peak (286 m/z) and base peak (226 m/z) were observed in its mass spectrum.



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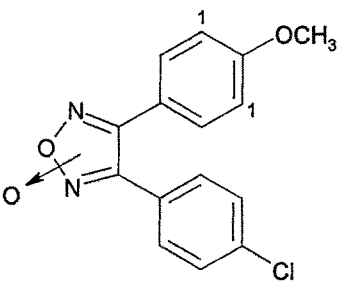
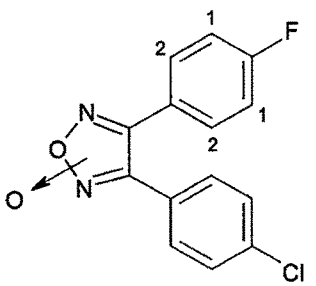


(189)

3-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole N-oxide **(189)** showed characteristic IR peaks at 1591 (C=N–O), 1450 (=$N^+(O^-)$–O) 1254 (Ar–O–Me, asymmetric), 1088 (C–Cl) and 1025 (Ar–O–Me, symmetric). Two characteristic singlets were observed at δ 3.85 and 3.86 for three protons (–OCH_3) in the PMR spectrum. A doublet at δ 6.94-6.97 for two protons (1-ArC*H*) and a multiplet at 7.40-7.51 for the remaining six aromatic protons were also observed.

Compound **(190)** showed characteristic vibrational bands at 1605 (C=N–O) and 1400 cm^{-1} (=$N^+(O^-)$–O) in its IR spectrum. A double doublet was observed at δ 7.16 (2H, 1-ArC*H*). A multiplet at δ 7.48-7.54 appeared for two aromatic protons (2-ArC*H*). A multiplet at δ 7.44-7.46 for remaining aromatic protons was also observed. The compound **(190)** gave the molecular ion peak at 290 (m/z) and base peak at 230 (m/z) in its mass spectrum.

In IR spectrum, 3-(2-chlorophenyl)-4-(4-tolyl)-1,2,5-oxadiazole N-oxide **(191)** offered characteristic peaks at 1592 (C=N–O), 1306 (N–O) and 1056 cm^{-1} (C–Cl). Its PMR spectrum displayed two characteristic



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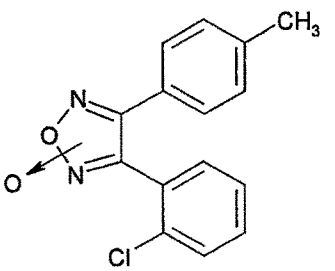

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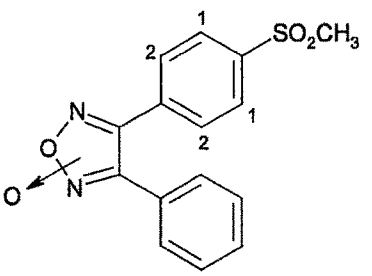

(192)

singlets at δ 2.34 and 2.36 for three protons (–C*H*$_3$). A complex multiplet for the aromatic protons was observed at δ 7.12-7.52 indicating that N-oxide has affected the chemical shift of aromatic protons.

1-(4-Methylthiophenyl)-2-phenylethanedione dioxime **(133)** was oxidized with potassium permanganate solution (3 %) in glacial acetic acid to afford the compound **(192).** The vibrational bands were observed at 1594 (C=N–O), 1307 (SO_2, asymmetric) and 1150 cm^{-1} (SO_2, symmetric) in its IR spectrum. The PMR spectrum of compound **(192)** showed two characteristic singlets for three protons at δ 3.09 and 3.11, confirming the formation of two isomeric N-oxides. A multiplet for five protons (Ar*CH*) was observed at δ 7.47- 7.58. Two doublets at δ 7.75-7.78 (2H, 2-ArC*H*; J=8.4 Hz) and 8.00-8.03 due to deshielded aromatic protons (2H, 1-ArC*H*; J=8.4 Hz) were observed in its PMR spectrum. The compound **(192)** gave

the molecular ion peak at 316 (m/z). Other peaks appeared at 300, 256, 119 and 89 (m/z) in the mass spectrum.

Since cyclization of the dioximes **(H)** to 1,2,5-oxadiazoles **(I)** using succinic anhydride as dehydrating agent has not provided very good yields, it was planned to deoxygenate the N-oxides **(J)** to respective oxadiazoles **(I)** as shown in **Scheme-3.** This route cold gain importance since the yields of the N-oxides **(J)** in a majority of the cases has remained reasonably good. To establish this route of synthesis of 1,2,5-oxadiazoles, 3,4-diphenyl-1,2,5-oxadiazole N-oxide **(180)** was utilized for further experimentation. The N-oxide **(180)** was refluxed with reagents like triphenyl phosphite/phosphorous trichloride for deoxygenation purpose. All these experiments failed to yield the desired product **(148)** and the started material **(180)** only could be isolated every time. This route was abandoned after successive failures in isolating the desired 1,2,5-oxadiazole **(148).**

3.2 BIOLOGICAL STUDIES

As the aim of the current study was to prepare selective COX-II inhibitors, the synthesized compounds were evaluated for their COX-II selectivity by *in vitro* receptor binding studies on COX-I and COX-II enzymes.

COX-I AND COX-II INHIBITION ASSAYS

The ability of the synthesized compounds to inhibit COX-I and COX-II enzyme activity was examined using the Cayman COX-I and COX-II colorimetric screening kit (Cayman Chemical company, MI, USA). The kit includes purified ovine COX-I and COX-II enzymes. Indomethacin was used as the positive control for COX-I inhibition; Valdecoxib was used as the positive control for COX-II inhibition. Test

drugs were dissolved in DMSO and diluted in the assay buffer before use. The assays were run according to the manufacturer's instructions.

This assay analyzes the heme-catalyzed peroxidase activity of the enzymes. The peroxidase activity was assayed colorimetrically by monitoring the appearance of oxidized N,N,N',N'-tetramethyl-*p*-phenylenediamine (TMPD) at 590 nm[1]. TMPD is an easily oxidizable compound that serves as a reducing co-substrate for heme peroxidase. Higher oxidation states produced a highly colored product that absorbs at 590 nm. The absorbance at 590 nm was noted and the average absorbance was determined for all the samples. The % inhibition of COX-I or COX-II were calculated by the formula as given below.

$$\% \text{ Inhibition} = \frac{(\text{Mean absorbance of control} - \text{Mean absorbance of test}) \times 100}{(\text{Mean absorbance of Control})}$$

The results are indicated as the % COX-II and COX-I inhibition in following **Table 4** and **5** respectively.

Table 4. COX-II inhibition activity of the synthesized drugs.

Sr. No.	Compound No.	COX-II	
		Concentration (μ M)	% Inhibition
	Valdecoxib **(40)** (Control)	22.0	87.2
		5.5	77.1
		1.375	80.1
		0.344	76.7
		0.086	62.9
		0.0276	30.9
		0.00532	14.2
1	**148**	22.0	5.1
2	**149**	22.0	26.1

Contd...

3	**150**	22.0	9.0
4	**151**	22.0	4.6
5	**152**	22.0	**87.2**
		5.5	57.0
		1.375	22.8
		0.344	7.2
		0.086	2.7
6	**153**	22.0	7.9
7	**154**	22.0	17.2
8	**155**	22.0	0.0
9	**156**	22.0	0.0
10	**157**	22.0	0.0
11	**158**	22.0	4.8
12	**159**	22.0	0.0
13	**160**	22.0	0.0
14	**161**	22.0	4.3
15	**162**	22.0	0.0
16	**163**	22.0	0.0
17	**164**	22.0	0.0
18	**166**	22.0	4.18
19	**167**	22.0	0.0
20	**168**	22.0	0.0
21	**169**	22.0	0.0
22	**170**	22.0	3.84
23	**176**	22.0	0.0
24	**177**	22.0	0.0
25	**178**	22.0	0.0
26	**179**	22.0	10.2
27	**180**	22.0	0.0
28	**181**	22.0	**53.9**
		5.5	52.9

Contd...

29	**182**	22.0	6.0
30	**183**	22.0	3.7
31	**184**	22.0	0.0
32	**185**	22.0	20.7
33	**186**	22 0	0.0
34	**187**	22.0	2.6
35	**188**	22.0	0.0
36	**189**	22.0	19.8
37	**190**	22.0	0.0
38	**191**	22.0	0.0
39	**192**	22.0	10.5

Table 5. COX-I Inhibition activity of some of the synthesized drugs.

Sr. No.	**Compound No.**	**COX-I**	
		Concentration (μ M)	**% Inhibition**
	Indomethacin **(2)** (Control)	1.375	94.23
		0.344	87.82
		0.086	62.82
		0.0215	20.42
1	**149**	88	53.13
2	**152**	88	84.38
		22	77.34
3	**181**	88	44.53
4	**185**	88	54.69
5	**189**	88	53.13

Test for *in vitro* COX-II inhibition activity for compound **(172 and 174)** couldn't perform.

3-(2-Chlorophenyl)-4-(4-dimethylaminophenyl)-1,2,5-oxadiazole **(152)** was as equipotent as valdecoxib (control) in enzyme inhibition in similar dose. It showed significant COX-II inhibition even at low concentration. 3,4-Di(4-methoxyphenyl)-1,2,5-oxadiazole N-oxide **(181)** also showed significant COX-II inhibition while 3,4-di(4-methoxyphenyl)-1,2,5-oxadiazole **(149),** 3-(4-methoxyphenyl)-4-phenyl-1,2,5-oxadiazole **(154),** 3-(4-methoxyphenyl)-4-phenyl-1,2,5-oxadiazole N-oxide **(185)** and 3-(4-chlorophenyl)-4-(4-methoxyphenyl)-1,2,5-oxadiazole N-oxide **(189)** exhibited reasonable COX-II inhibition suggesting that *para* substitution of one or both phenyl rings with methoxy group increases the COX-II selectivity.