3.1 INTRODUCTION

Isoxazolines are an important class of five-membered heterocyclic compounds in which oxygen and nitrogen heteroatoms are present at position-1 and position-2, respectively. The general structure of isoxazole is shown in Figure 1.

Fig.1

Isoxazoline containing compounds were found to exhibit a wide range of bioactivities such as anti-inflammatory, analgesic, antibacterial, anthelmimtic, anticancer and antitubercular [1-4]. Introduction of trifluoromethyl group on the isoxazoline nucleus further resulted in development of many biologically active agents [5-8] (Figure 2).

Fig.2

The synthetic and biological developments made in recent past of some isoxazoline derivatives bearing trifluoromethyl group have been described below.

Synthetic and biological developments

The treatment of substituted phenyl-butane-1,3-dione with hydroxylamine in acetic acid under reflux yielded 3-substitutedphenyl-5-hydroxy-5-trifluoromethylisoxazoline 1 which was used as an intermediate for the synthesis of potent isoxazole containing herbicides 2 and 3 [9] (Scheme-1).

Recently, Aggarwal et al. have reported the synthesis and antimicrobial activity of 3-(2-thienyl)-4-aryazo-5-hydroxy-5-trifluoromethyl-Δ²-isoxazolines 4 and 3-(2-thienyl)-4-aryazo-5-trifluoromethylisoxazoles 5 [8]. 1-(2-Thienyl)-4,4,4-trifluoromethyl-1,3-butanedione on treatment with hydroxylamine yielded 3-(2-
thienyl)-4-arylazo-5-hydroxy-5-trifluoromethyl-Δ2-isoxazolines 4 which on reaction with acetic anhydride or ethanol-sulfuric acid gave corresponding isoxazole derivatives 5. The synthesized compounds 4 and 5 were evaluated for their in vitro antimicrobial activity against pathogenic strains of two Gram-positive B. subtilis and S. aureus, two Gram-negative bacteria P. fluorescens and E. coli, and one fungal strain namely S. cerevisiae. The results revealed that some of the synthesized compounds exhibited potent antimicrobial activity in the MIC range of 5-10 µg/ml against the tested strains (Scheme-2).

Scheme-1

Asymmetric synthesis of some 5-trifluoromethyl-2-isoxazoline N-oxides 9, the promising candidates in pharmaceuticals and agrochemicals, was achieved first time by Kawai et al. [6]. In this strategy, methylhydrazine induced non-metallic aerobic catalytic enantioselective epoxidation of β-trifluoromethyl β,β-disubstituted enone generated epoxide 7 which on chemoselective reduction in the presence of zinc and ammonium chloride using a mixture of ethanol and water was converted into enantio-enriched tertiary alcohols 8. (R)-Alcohols 8 were then efficiently transformed into (R)-5-trifluoromethyl-2-isoxazoline N-oxides 9 (precursors of veterinary medicines)
by reacting with hydroxylamine hydrochloride in pyridine followed by the treatment with [hydroxyl(tosyloxy)iodo]benzene (HTIB) in methanol at room temperature. Finally, deoxygenation of \( \text{9} \) with trimethylphosphite led to the formation of 5-trifluoromethyl-2-isoxazolines \( \text{10} \), which exhibited potent antiparasitic activity against cat fleas and dog ticks (Scheme-3).

\[
\begin{align*}
\text{A} & \quad \text{H}_2\text{NNHMe (1.2 equiv)} \\ & \quad \text{Cs}_2\text{CO}_3 (1.2 \text{ equiv}), \text{air (1 atm)} \\ & \quad \text{methyl tert butyl ether (0.017 M)} \\ & \quad \text{rt, 6 h} \\
\text{F}_3\text{C} & \quad \text{Ar} \end{align*}
\]

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{Ar} \quad \text{Zn (2.0 equiv)} \\ & \quad \text{NH}_4\text{Cl (1.5 equiv)} \\ & \quad \text{EtOH/ H}_2\text{O (1:1)} \\ & \quad \text{reflux, 3 h} \\
\text{O} & \quad \text{N} \\
\text{F}_3\text{C} & \quad \text{Ar} \end{align*}
\]

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{Ar} \quad \text{i) NH}_2\text{OH.HCl (2.0 equiv)} \\ & \quad \text{pyridine, 50 oC, 9 h} \\ & \quad \text{ii) HTIB (1.1 equiv)} \\ & \quad \text{MeOH, rt, 30 min} \\
\text{O} & \quad \text{N} \\
\text{F}_3\text{C} & \quad \text{Ar} \\
\end{align*}
\]

\[\text{A =} \]

\[
\begin{align*}
\text{Ar} & \quad \text{Ph, 4-MePh, 4-OMePh, 4-CIPh, 2-naphthyl} \\
\text{Ar'} & \quad \text{Ph, 4-MePh, 4-CIPh, 4-BrPh, 4-NO}_2\text{Ph, 2-naphthyl}
\end{align*}
\]

Scheme-3

Lahm et al. reported the synthesis of 3,5-disubstituted-5-trifluoromethyl-2-isoxazoline derivatives \( \text{13, 16} \) which were used as precursors for the synthesis of potent insecticides \( \text{14 or 17} \), respectively. These compounds were found to act as potent blockers of insect GABA receptors with an excellent activity against a broad pest range, including Lepidoptera and Hemiptera [7]. Cycloaddition of oxime \( \text{11} \) with 1-trifluoromethyl-1-aryl styrenes \( \text{12} \) in presence of sodium hypochlorite yielded 5-trifluoromethyl-3-(4-fluoromethyl)-5-arylisoxazoline derivatives \( \text{13} \). Displacement of fluorine from \( \text{13} \) by triazole moiety to form 5-trifluoromethyl-3-(4-triazolyl)-5-arylisoxazoline derivatives \( \text{14} \) was easily achieved in presence of potassium carbonate in acetonitrile (Scheme-4). However, styrene \( \text{15} \) underwent cycloaddition with \( \text{11} \) followed by fluorine displacement by triazole to produce 5-(5-(2-chloro-6-(trifluoromethyl)pyridin-4-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile \( \text{17} \) (Scheme-5).

Regio- and -diastereoselective route for the synthesis of 5-trifluoromethyl-4-nitro-2-isoxazolines \( \text{19} \) by trifluoromethylation of aromatic isoxazole \( \text{18} \) via direct
nucleophilic addition has easily been achieved by Kawai et al. [10]. The treatment of 3,5-disubstituted-4-nitro-isoxazole \(18\) (R=substituted phenyl, methyl) with trifluoromethyltrimethylsilane in presence of sodium acetate and cetyltrimethylammonium bromide using DMF at ambient temperature followed by addition of 1M aqueous HCl solution led to the formation of 5-trifluoromethyl-4-nitro-2-isoxazoline \(19\) in 67-97% yield. Moreover, the present protocol also provided a new synthetic route to agrochemically important 3,5-disubstituted-5-trifluoromethyl-2-isoxazoline derivatives \(20\) (R = substituted phenyl) as an efficient class of pest control agents (Scheme-6).

Highly functionalized 5-trifluoromethyl-2-isoxazoline derivatives \(23\) (for agrochemicals) bearing a triflyl group (SO\(_2\)CF\(_3\)) at 4-position were successfully synthesized via a diastereoselective trifluoromethylation and halogenations of isoxazole triflones \(24\) (Scheme-7) [5]. In this strategy, various 3,5-disubstituted-4-trifluoromethanesulfonyl isoxazole derivatives \(21\) were treated with Ruppert-Prakash reagent (Me\(_3\)SiCF\(_3\)) in presence of potassium acetate using DMSO at room temperature to give the desired trifluoromethylated products \(22\) with excellent yields and high diastereoselectivity. Halogenation of trifluoromethylated adducts \(22\) (R = Ph and Ar = Ph with different halogenating agents [Selectfluor®, NBS (N-bromosuccinimide) and NCS (N-chlorosuccinimide)] afforded 4-halo-3,5-diphenyl-4-trifluoromethanesulfonyl isoxazole derivatives \(23\) in excellent yields.

\[
\begin{align*}
R &= H, Me, CF_3, Cl, Br, NO_2, CN, OMe, SO_2Me; \\
R' &= Br, CF_3, Cl; \\
R'' &= H, Cl, F, CN, Me; \\
R''' &= Br, CF_3, Cl, CN, OMe
\end{align*}
\]

\[\text{Scheme-4}\]
3-Amino-5-hydroxy-5-trifluoromethyl-4,5-dihydroisoxazoles 25 have been synthesized regiospecifically by the reaction of (E)-β-ethoxy-β-enamino ketones 24 with hydroxylamine hydrochloride salt in presence of pyridine-methanol in 53-81% yield (Scheme-8) [11]. It was reported that the reaction proceeds through the attack of harder basic site of the binucleophile (i.e O atom) to the carbonyl carbon of enaminone. However, an alternative possibility may be the attack of nitrogen as shown in Scheme-9. The structure of compounds 25 was established on the basis of
A convenient method for the synthesis of 6-(5-trihalomethyl-5-hydroxy-4,5-dihydroisoxazol-3-yl)hexanoates 30 has been reported by Martins et al. [12]. Cyclocondensation of methyl 10,10,10-trihalo-9-oxo-7-methoxydec-7-enoate 29 with hydroxylamine hydrochloride in the presence of pyridine or conc. hydrochloric acid in refluxing methanol afforded the targeted compound 30 in 70% (X = F) and 60% (X = Cl) yields (Scheme-10).

Martins et al. also reported a regiospecific approach for the synthesis of 4,5-dihydroisoxazoles 32 under mild reaction conditions [13]. The treatment of 1,1,1-trifluoro-4,4-diethoxy-3-buten-2-one 31a and 1,1,1,2,2-pentafluoro-4,4-diethoxy-3-penten-2-one 31b with hydroxylamine in pyridine-water afforded the targeted compounds 32a and 32b in 88% and 80% yield, respectively. The mechanistic pathway involved in the reaction includes the nucleophilic attack initially by nitrogen atom of hydroxylamine on the β-carbon of the enone 31 followed by oxygen of hydroxyl group to the α-trifluorocarbonyl centre. Both the compounds 31a and 31b
displayed characteristic doublets at $\delta$ 3.0 and 3.4 ppm corresponding to 4-H protons with geminal coupling constant 17 Hz. In $^{13}$C NMR spectra, the signals of ring carbons C-3, C-4 and C-5 displayed chemical shifts at $\delta$ 166, 41 and 103 ppm, respectively. The C-5 carbon signal appeared as a characteristic quartet in case of 31a or triplet in 31b due to attachment of CF$_2$ group. The trifluoromethyl (CF$_3$) carbon showed a quartet due to one bond carbon-fluorine coupling while pentafluoroethyl group showed a triplet of quartet for the CF$_2$ group and a quartet of triplet for CF$_3$ group (Scheme-11).

![Scheme-11](image)

The treatment of 1,5-anhydro-3,4,6-tri-O-benzyl-2-deoxy-2-trifluoroacetyl-D-arabino-hex-1-enitol 33 with hydroxylamine hydrochloride in ethanol at room temperature afforded 4-(1,2,4-tri-O-benzyl-D-arabino-1,2,3,4-tetra-hydroxybutyl)-5-hydroxy-5-trifluoromethyl-4,5-dihydroisoxazoline 34 (Scheme-12).

![Scheme-12](image)

The compound 34 dehydration to furnished 4-(1,2,4-tri-O-benzyl-D-arabino-1,2,3,4-tetra-hydroxybutyl)-5-trifluoromethylisoxazole 35, by treating 34 with trifluoroacetic anhydride in the presence of pyridine at room temperature [14].

Nenajdenko et al. synthesized 5-hydroxy-5-trifluoromethyl substituted isoxazoline derivatives 37 by treating cyclic-$\beta$-(trifluoroacetyl)enamines 36 with hydroxylamine hydrochloride in refluxing ethanol. Prolonged heating of 37 in concentrated sulfuric
acid at 150 ºC resulted in the formation of isoxazole derivatives 38 in high yield (Scheme-13) [15]. Author proposed that substrate 36 is initially attacked by the oxygen of hydroxylamine instead of first attack by nitrogen on unsaturated ring carbon of pyrrole moiety. However, an alternative possibility may be the attack of nitrogen as shown in Scheme-14.

\[
\begin{align*}
\text{NH}_2\text{OH.HCl, EtOH} & \quad \xrightarrow{\text{reflux}} \quad \text{NH}_2\text{OH.HCl, EtOH} \\
\text{conc. H}_2\text{SO}_4 & \quad \xrightarrow{150 \text{ ºC}} \quad \text{NH}_2\text{OH.HCl, EtOH}
\end{align*}
\]

\[R = \text{Ph, 4-Me}_2\text{NPh, 4-MeOPh}\]

Scheme-13

5-Hydroxy-5-trifluoromethyl-\(\Delta^2\)-isoxazoline 43 was synthesized by the treatment of enol ether 42 with hydroxylamine hydrochloride in tetrahydrofuran [16]. An attempt to prepare the dehydrated product 44 was failed using sulfuric acid. Moreover, treatment of 43 with acetic anhydride under reflux conditions led to the formation of acetoxy derivative 45 instead of 44 (Scheme-15).

\[
\begin{align*}
\text{CF}_3\text{C}==\text{CH}==\text{CH.OEt} & \quad \xrightarrow{\text{NH}_2\text{OH.HCl, H}_2\text{O}} \quad \text{NH}_2\text{OH.HCl, H}_2\text{O} \\
\text{H}_2\text{SO}_4 & \quad \xrightarrow{\text{reflux, 5 h}} \quad \text{H}_2\text{SO}_4}
\end{align*}
\]

Scheme-15

Hamper et al. reported the synthesis of 3-aryl-5-haloalkyl-4-isoxazolecarboxylic ester derivatives 48 which act as precursors for the synthesis of herbicides 51 [17]. In this method, substituted benzohydroximinoyl chloride 46 on treatment with methyl 4-chloro-4,4-difluoro-2-butynoate 47 in presence of sodium hydroxide in dichloromethane gave 48, which further was converted into 4-isoxazolecarboxylic
acid chloride 50 by refluxing it in a mixture of concentrated acetic acid and hydrochloric acid followed by the oxalyl chloride in presence of catalytic amount of DMF in dichloromethane. Finally, ammonlysis of compound 50 with ammonium hydroxide in the presence of 10% aqueous sodium carbonate in diethylether resulted in the formation of the targeted herbicides 51. All compounds synthesized under this investigation were evaluated for preemergent herbicidal activity in the gram per hectare range against morning glory, velvet leaf and barnyardgrass in both greenhouse and field studies. From this study, it was found that compound 51 containing propargyloxy group exhibited excellent herbicidal activity (Scheme-16).

![Scheme-16](image-url)

A highly efficient method for the synthesis of selective COX-1 inhibitor 3-(5-chlorofuran-2-yl)-4-phenyl-5-trifluoromethylisoxazole 56 that affected platelet aggregation in vitro through the inhibition of COX-1-dependent thromboxane (TX) has been reported using 3-(5-chlorofuran-2-yl)-4-phenyl-5-trifluoromethylisoxazoline 55 as a key intermediate [18]. The treatment of 1,1,1-trifluoro-3-phenyl propan-2-one 52 with sodium hydride in THF at 0 °C afforded enolate 53 of 1,1,1-trifluoro-3-phenylpropan-2-one which on treatment with arylnitrile oxide 54 in presence of aqueous ammonium chloride in THF gave 3-(5-chlorofuran-2-yl)-4-phenyl-5-trifluoromethylisoxazoline 55 in 71% yield. Though it seems difficult, finally dehydration of 55 with sodium carbonate in methanol afforded 56 in 65% yield. A
significant inhibitory effect with IC\textsubscript{50} value 0.81 µM for COX-1 and high COX-1 selectivity (\textit{i.e.} COX-2/COX-1 IC\textsubscript{50} ratio of 123.46) has been observed for 56. Moreover, 56 represents the candidate for preclinical development as a novel antithrombotic agent and found to be greater than 1000-fold more potent to inhibit COX-1 than COX-2 and showed a different mechanism of interaction with two COX-enzymes \textit{i.e.} a strong, slowly reversible interaction with the COX-1 and a rapidly reversible with the COX-2 (Scheme-17).

![Scheme-17](image)

Scheme-17

Cyclocondensation of 2-trifluoroacetylcycloalkanones 57 or 58 with hydroxylamine hydrochloride in methanol under reflux afforded regiospecifically 5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazoles 59 or 60, respectively in 80-90% yields [19] (Scheme-18).

![Scheme-18](image)

Scheme-18

Martin \textit{et al.} reported that β-aryl-β-methoxyvinyl ketones 62, obtained from the reaction of the corresponding acetophenone dimethyl acetics 61 with trichloroacetyl chloride or trifluoroacetic anhydride, undergo cyclization with hydroxylamine hydrochloride in refluxing methanol-pyridine to produce 3-aryl-5-hydroxy-5-
trifluoromethylisoxazolines 63 [20]. Finally, dehydration of 63 in the presence of sulfuric acid resulted in the formation of isoxazoles 64 (Scheme-19).

**Scheme-19**

The treatment of 4-methoxy-4-iso-butyl-1,1,1-trifluoro-3-buten-2-one 65 with hydroxylamine hydrochloride in the presence of pyridine in methanol at 45-50 °C afforded the 5-hydroxy-3-iso-butyl-5-trifluoromethyl-4,5-dihydro-isoxazole 66 in 65% yield (Scheme-20) [21]. The 1H NMR spectrum of 66 displayed two doublets corresponding to two methylene protons of isoxazoline ring at δ 3.02 and 3.35 ppm with coupling constant \( J_{\text{H-H}} = 19 \) Hz due to geminal coupling between the diastereotopic protons. A singlet at δ 8.20 ppm was also observed due to the presence of hydroxyl group. The 13C NMR spectrum showed singlets at δ 159.0 and δ 44.56 ppm due to C-3 and C-4 carbon, respectively. The compound displayed two quartets at δ 102.6 (\( J_{\text{C-F}} = 33 \) Hz) and δ 122.7 ppm (\( J_{\text{C-F}} = 284 \) Hz) for C-5 and CF3 carbon, respectively.

**Scheme-20**

An efficient method for the regioselective synthesis of 5-hydroxy-3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)-4,5-dihydroisoxazole 68 has been reported by Bonacorso et al. [22]. The reaction of α,β-unsaturated-β-diketones 67 with hydroxylamine hydrochloride in presence of pyridine-methanol under reflux furnished the desired product 68 in 71% yield. The structure was well established on the basis of spectral data. The 1H NMR spectrum of 68 showed two characteristic doublets at δ 3.33 ppm and 2.94 ppm with geminal coupling constant \( J = 18 \) Hz while in 13C NMR spectrum, two singlets at δ 157.9 ppm and 44.0 ppm for C-3 and C-4 carbon atom,
respectively were observed. However, characteristic quartets at $\delta$ 101.4 ppm ($J = 32$ Hz) and 122.5 Hz ($J = 284$ Hz) for C-5 and CF$_3$ carbon atoms, respectively suggested the presence of 5-hydroxy-5-(trifluoromethyl)-4,5-dihydroisoxazole 68. Dehydration of 68 to produce 3-(S,S-dimethylsulfoximido)-5-(trifluoromethyl)isoxazole 69 in 51% yield was achieved by treating 68 with thionyl chloride in the presence of pyridine using benzene as a solvent. A characteristic singlet for isoxazole 4-H proton at $\delta$ 6.35 ppm was found to be appeared in the $^1$H NMR spectrum while in the $^{13}$C NMR spectrum, singlet signals at $\delta$ 162.9 and 102.5 ppm for C-3 and C-4 carbon atom, respectively and two quartets at $\delta$ 158 ppm ($J = 42$ Hz) and 117 ppm ($J = 270$ Hz) for C-5 and CF$_3$ carbon, respectively were appeared (Scheme-21).

\[ \text{Scheme-21} \]

One pot and regiospecific synthesis of 3-hydroxy-3-trifluoromethyl-3,4-dihydro-cycloalkan[c]isoxazoles 71 was achieved by the treatment of 2-trifluoro-1-methoxycycloalkenes 70 with hydroxylamine hydrochloride in the presence of pyridine-water with 45-85% yield [23]. The reaction proceeds via the Michael addition of amino group of hydroxylamine to the $\beta$-carbon atom of enones 70 to produce addition product (i.e aminoether) which is unstable in pyridine-water system, and methoxy group is eliminated as methanol followed by intermolecular cyclization involving the nucleophilic attack of oxygen atom on the carbonyl group to give 71 (Scheme-22).

A regioselective approach for the synthesis of 5-hydroxy-5-trifluoromethyl isoxazoline 73 has been reported by Sosnovskikh et al. [24]. In this method, 2-hydroxy-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyranone 72a and 2-hydroxy-5,5-pentamethylene-2-trifluoromethyltetrahydro-4-pyranone 72b were allowed to react with hydroxylamine hydrochloride in presence of 0.5 N solution of hydrochloric acid in a mixture of ethanol and water under reflux conditions to furnish 5-hydroxy-3-
(2-hydroxy-1,1-dimethylethyl)-5-trifluoromethyl-$\Delta^2$-isoxazoline 73a and 5-hydroxy-
3-(2-hydroxy-1,1-pentamethylene)-5-trifluoromethyl-$\Delta^2$-isoxazoline 73b, respectively
(Scheme-23). However, 3-tert-butyl-5-hydroxy-5-trifluoromethyl-$\Delta^2$-isoxazoline 75
has been synthesized under similar reaction conditions, when pivaloyltrifluoroacetone
74 was treated with hydrochloride (Scheme-24).

Nitrone 77 generated by removal of water from nitrone hydrate 76 on cycloaddition
with monosubstituted and disubstituted acetylene derivatives 78 and 79 in benzene
produced exclusively 3-trifluoromethylisoxazoline derivatives 80 and 82, respectively
[25]. In case of alkyne 78 (R = COOMe), along with desired product 80, regioisomer
81 was also obtained (Scheme-25).
For compounds (78, 80, 81) \( R = \text{Ph, } p\text{-CH}_3\text{Ph, } n\text{-C}_8\text{H}_{13}, \text{COOMe} \)

(79, 82) \( R = \text{Me, COOMe} \)

\( R' = \text{Ph, Me, COOMe} \)

Scheme-25
3.2 RESULTS AND DISCUSSION

3.2A Chemistry

As already discussed, trifluoromethyl substituted isoxazoline derivatives have gained significance importance in the field of medicinal and synthetic chemistry. Moreover, halo substitution on isoxazoline moiety resulted in many potent anticancer agents [26-29]. It has been reported that azoles having arylazo group at position-4 were known as efficient class of antimicrobial, antibacterial, anti-staphylococcal, analgesic, antioxidant, cytotoxic and CDK2-cyclin E inhibiting agents [30-37]. Prompted from the above facts it was planned to synthesize some novel isoxazoline derivatives having haloarylazo group at position-4 and explore their biological potential with an expectation to find new class of biologically active agents.

In order to synthesize some novel \((E)-4\)-(aryl diazenyl)-3-aryl-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol derivatives 89, initially starting precursors were synthesized according to literature method. Claisen condensation of arylmethylketones 83 with 4,4,4-ethyltrifluoroacetate 84 in the presence of sodium ethoxide in dry benzene afforded aryl-4,4,4-trifluoromethyl-\(\beta\)-diketones 85 (Scheme-26) [38]. Various primary amines 86 on diazotization followed by coupling with 85 in the presence of sodium acetate further afforded 87 in good yields (Scheme-27) [39].

\[
\text{Ar} \text{CH}_3 + \text{CF}_3\text{COOEt} \xrightarrow{\text{NaOEt, dry benzene, stir}} \text{Ar} \text{O} \text{O} \text{CF}_3
\]

For compds (83, 85)

\(\text{Ar} = p\text{-Cl-Ph, p-Br-Ph, p-F-Ph, p-OCH}_3, 2\text{-naphthyl, 1-naphthyl}\)

Scheme-26 Synthesis of trifluoromethyl-\(\beta\)-diketones 85
Scheme-27 Synthesis of (E)-1-(4-aryl)-4,4,4-trifluoro-2-(4-aryldiazenyl)butane-1,3-diones 87

The synthesis of some novel (E)-4-(aryldiazenyl)-3-aryl-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol derivatives 89 has been accomplished according to the reaction sequence shown in Scheme-28.

Scheme-28 Synthesis of (E)-4-(aryldiazenyl)-3-aryl-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol derivatives 89
To achieve the target compound 89a, (E)-1-(4-chlorophenyl)-4,4,4-trifluoro-2-((4-iodophenyl)diazenyl)butane-1,3-dione 87a was treated with hydroxylamine hydrochloride 88 in the presence of sodium acetate using ethanol under reflux conditions. The structure of 89a was established on the basis of a combined use of IR, NMR (∫H, 13C and 19F) spectroscopy and mass spectrometry. In IR spectrum, two absorption bands due to NH and OH str. at 3292 and 3005 cm⁻¹ were appeared. The ∫H NMR spectroscopy is not a useful tool to distinguish between compounds 87 and 89 (Figure 4). In 13C NMR spectrum of 89a, carbon-5 resonated as a quartet at δ 98.52 ppm (2J_C-F = 35.21 Hz) while C-4 and C-3 resonated as singlets at δ 131.95 and 154.60 ppm, respectively (Figure 5). The carbonyl carbon peaks, C-1 at δ 189.68 and C-3 at 175.32 ppm (2J_C-F = 33.20 Hz) in the starting precursor 87a were found to be disappeared in the product. A sharp signal in 19F NMR spectrum at δ -78.86 ppm also provides a firm evidence in support of the structure of isoxazoline (Figure 6) [39]. Further confirmation of 89a was supported by the mass spectral data which showed a molecular ion peak at m/z = 495.9 (M⁺) in conformity with molecular formula C16H10ClF3IN3O2. The probable mechanism for the formation of 89 is given in Scheme-29.

![Scheme-29](image)

Scheme-29 The probable mechanism of formation of (87, 89)
Fig. 3 The $^1$H NMR spectrum of the compound 89a

Fig. 4 The $^{13}$C NMR spectrum of the compound 89a
Fig. 5 The $^{19}$F NMR spectrum of the compound 89a

3.2B Biological Evaluation

3.2B.1 Effects of compounds on plasmid DNA under UV-irradiation (89a-n and 89aa-an)

To explore the potential of 89a-n and 89aa-an for the DNA damage protecting activity, agarose gel electrophoresis was used (Figure 6, 7). It has been reported in literature that when the single strand break occurs the supercoiled (SC) form changes into the more relaxed open circular (OC) form, however, when there is double strand break occurs the SC form transforms into the linear (LC) form. In the present investigation, it has been observed that in the absence of UV-irradiation, plasmid DNA existed in SC form (lane 1) but on exposure to UV light, most of it was transformed into OC form along with a very less intense LC form as shown in lane-2. The protecting potential of the test compounds was assessed by comparing the appearance of bands and their intensities appeared in control (C) and test compounds in presence of UV-irradiation.

In this study, it has been found that all the compounds 89a-n and 89aa-an displayed very high DNA damage protecting ability from the effect of UV radiation at 60 µg
concentration because they prevented the DNA degradation and preserved the initial supercoiled conformation when compared with control.

**Fig. 6** Effects of compounds on plasmid DNA under UV-irradiation (89a-n):
Lane-1: A = DNA + DMSO without UV, Lane-2: C = DNA + DMSO + UV, Lane-3: DNA + 87a + UV, Lane-4: DNA + 87b + UV, Lane-5: DNA + 87c + UV, Lane-6: DNA + 87d + UV, Lane-7: DNA + 87e + UV, Lane-8: DNA + 87f + UV, Lane-9: DNA + 87g + UV, Lane-10: DNA + 87h + UV, Lane-11: DNA + 87i + UV, Lane-12: DNA + 87j + UV, Lane-13: DNA + 87k + UV, Lane-14: DNA + 87l + UV, Lane-15: DNA + 87m + UV, Lane-15: DNA + 87n + UV

**Fig. 7** Effects of compounds on plasmid DNA under UV-irradiation (89aa-n):
Lane-1: A = DNA + DMSO without UV, Lane-2: C = DNA + DMSO + UV, Lane-3: DNA + 89aa + UV, Lane-4: DNA + 89ab + UV, Lane-5: DNA + 89ac + UV, Lane-6: DNA + 89ad + UV, Lane-7: DNA + 89ae + UV, Lane-8: DNA + 89af + UV, Lane-9: DNA + 89ag + UV, Lane-10: DNA + 89ah + UV, Lane-11: DNA + 89ai + UV, Lane-12: DNA + 89aj + UV, Lane-13: DNA + 89ak + UV, Lane-14: DNA + 89al + UV, Lane-15: DNA + 89am + UV, Lane-15: DNA + 89an + UV

**3.2C Conclusion**
In conclusion, some novel (E)-4-(aryldiazenyl)-3-aryl-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol derivatives 89a-n and 89aa-an have been synthesized and their structures were established on the basis of rigorous analysis of IR, NMR (1H and 13C), mass spectral data. The effects of compounds on DNA were studied under UV
irradiation. It has been found that all compounds 89a-n and 89aa-an displayed a very high level of DNA damage protecting potential as they prevent the SC form from degradation or its interconversion into other forms in comparison with control. Therefore, the compounds 89a-n and 89aa-an can act as template for the synthesis of potent DNA damage protecting agents which may serve as potent anti-UV materials in the future.
3.3 EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. The FT-IR spectra of the compounds were recorded on FT-Infra-Red Spectrometer Model RZX (Perkin Elmer) using KBr pellets. The $^1$H and $^{13}$C NMR spectra were recorded on Bruker Advance II 400 NMR Spectrometer at 400 MHz and 100 MHz, respectively; chemical shifts are expressed on $\delta$-scale downfield from TMS as an internal standard. $^{19}$F NMR spectra were run on DRX 400 at 376 MHz using DMSO as a solvent. Mass spectra were recorded on Waters Micromass Q-Tof Micro Mass spectrometer equipped with electronization (ESI) and atmospheric pressure chemical ionization sources having mass range of 4000 amu in quadruple and 20000 amu in ToF. Thermo Scientific (FLASH 2000) CHN Elemental Analyser was used to determine percentages of C, H and N with an accuracy of 0.3%.

3.3A Chemistry

3.3A.1 Synthesis of (E)-4-(aryldiazenyl)-3-aryl-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ols 89

Synthesis of 1-aryl-4,4,4-trifluoromethyl-1,3-butanedione 85 [38]

General procedure: To a stirred mixture of sodium ethoxide (0.1 mol) and ethyl trifluoroacetate (0.06 mol) in dry benzene, added appropriate arylmethylketone (0.06 mol) in 20 ml of benzene dropwise at 5-10 °C. The reaction mixture was continued to be stirred for 8 h under calcium chloride guard tube at room temperature. The mixture was treated with 500 ml of water when the two layers separated. The aqueous layer was drawn off and acidified with 10% hydrochloric acid. The mixture was extracted thrice with diethyl ether. The combined extracts were dried using anhydrous Na$_2$SO$_4$ and solvent was evaporated to give 85.

Table 1 Physical data of 1-aryl-4,4,4-trifluoromethyl-1,3-butanediones 85

<table>
<thead>
<tr>
<th>Compds</th>
<th>m.p. (°C)</th>
<th>Lit. m.p. (°C) [Ref]</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>85a</td>
<td>62</td>
<td>61 [38]</td>
<td>76</td>
</tr>
<tr>
<td>85b</td>
<td>52</td>
<td>50-52 [38]</td>
<td>75</td>
</tr>
<tr>
<td>85c</td>
<td>39</td>
<td>39-40 [38]</td>
<td>68</td>
</tr>
<tr>
<td>85d</td>
<td>50</td>
<td>42-45 [38]</td>
<td>74</td>
</tr>
<tr>
<td>85e</td>
<td>58</td>
<td>55-57 [40, 41]</td>
<td>73</td>
</tr>
<tr>
<td>85f</td>
<td>80</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>85g</td>
<td>Low melting point</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Synthesis of (E)-1-(4-aryl)-4,4,4-trifluoro-2-(4-aryldiazenyl)butane-1,3-diones [40]

General Procedure: Aniline / substituted aniline (0.02 mol) was dissolved in a mixture of conc. HCl and water (20 ml, 1:1). It was cooled to 0 °C and a cold aq. solution of sodium nitrite (0.02 mol in 10 ml water) was added to it slowly by maintaining the temperature upto 5°C. The cold diazotized solution was added dropwise to a cooled mixture of 1-aryl-4,4,4-trifluorobutane-1,3-dione (0.02 mol) and sodium acetate (0.06 mol) in 20 ml of 50% ethanol. The stirring was continued for 1 h and the crystals separated were filtered, washed with water, dried and recrystallized from ethanol to obtain the product.

(E)-1-(4'-Chlorophenyl)-4,4,4-trifluoro-2-((4''-iodophenyl)diazenyl)butane-1,3-dione (87a)

**Yield:** 85%, **m.p.** 121 °C

**IR** (ν<sub>max</sub>, cm<sup>-1</sup>): 1698 (CO str.), 3208 (OH str.), 3378 (NH str.)

**<sup>1</sup>H NMR** (400 MHz; CDCl<sub>3</sub> + DMSO-<sup>d6</sup>, δ<sub>H</sub>): 7.28 (d, 2H, 2'', 6'' -H, <sup>3</sup>J<sub>H-H</sub> = 8.82 Hz), 7.60 (d, 2H, 3', 5'-H, <sup>2</sup>J<sub>H-H</sub> = 8.56 Hz), 7.74 (d, 2H, 3'', 5'' -H, <sup>3</sup>J<sub>H-H</sub> = 8.72 Hz), 7.80 (d, 2H, 2', 6'-H, <sup>3</sup>J<sub>H-H</sub> = 8.84 Hz), 12.50 (s, 1H, NH or OH, D<sub>2</sub>O exchangeable)

**<sup>13</sup>C NMR** (100 MHz; CDCl<sub>3</sub> + DMSO-<sup>d6</sup>, δ<sub>C</sub>): 89.59 (C-4''), 116.93 (q, 4-CF<sub>3</sub>, <sup>1</sup>J<sub>C-F</sub> = 292.77 Hz), 118.25 (C-2'', 6''), 129.06 (C-3', 5''), 130.50 (C-2', 6''), 131.13 (C-2), 134.30 (C-1), 138.08 (C-3'', 5''), 139.45 (C-4'), 141.72 (C-1''), 175.32 (C-3, <sup>2</sup>J<sub>C-F</sub> = 33.20 Hz), 189.68 (C-1)

**<sup>19</sup>F NMR** (DMSO-<sup>d6</sup>, δ<sub>F</sub>): - 69.19 (s, 3F, CF<sub>3</sub>)

**MS:** m/z 508 (M<sup>+</sup>)

**Anal. Calcd** for C<sub>18</sub>H<sub>13</sub>ClF<sub>3</sub>IN<sub>2</sub>O<sub>2</sub> (%): C, 42.50; H, 2.58; N, 5.51. Found (%): C, 42.47; H, 2.53; N, 5.47
(E)-1-(4′-Bromophenyl)-4,4,4-trifluoro-2-((4′′-iodophenyl)diazenyl)butane-1,3-dione (87b)

**Yield:** 89%, **m.p.** 123 °C

**IR** ($v_{\text{max}}$, cm$^{-1}$): 1692 (CO str.), 3209 (OH str.), 3375 (NH str.)

**$^1$H NMR** (400 MHz; CDCl$_3$ + DMSO-$d_6$, $\delta_H$): 7.27-7.83 (m, 8H, 2′, 3′, 5′, 6′, 2″, 3″, 5″, 6″-$H$), 12.50 (s, 1H, NH or OH, D$_2$O exchangeable)

**$^{13}$C NMR** (100 MHz; CDCl$_3$ + DMSO-$d_6$, $\delta_C$): 89.55 (C-4), 116.93 (q, 4-CF$_3$, $^1J_{C-F} = 291.77$ Hz), 118.28 (C-2″, 6″), 128.54 (C-4′), 130.47 (C-2′, 6′), 131.01 (C-2), 131.96 (C-3′,5′), 134.72 (C-1′), 138.05 (C-3′,5″), 141.70 (C-1″), 175.13 (C-3, $^2J_{C-F} = 33.20$ Hz), 189.87 (C-1)

**$^{19}$F NMR** (DMSO-$d_6$, $\delta_F$): - 69.22 (s, 3F, CF$_3$)

**MS:** m/z 524 (M$^+$)

**Anal. Calcd** for C$_{16}$H$_9$BrF$_3$IN$_2$O$_2$ (%): C, 36.60; H, 1.73; N, 5.34. Found (%): C, 36.50; H, 1.69; N, 5.32

(E)-4,4,4-Trifluoro-2-((4′-iodophenyl)diazenyl)-1-phenylbutane-1,3-dione (87c)

**Yield:** 81%, **m.p.** 121 °C

**IR** ($v_{\text{max}}$, cm$^{-1}$): 1690 (CO str.), 3212 (OH str.), 3379 (NH str.)

**$^1$H NMR** (400 MHz; CDCl$_3$ + DMSO-$d_6$, $\delta_H$): 7.27 (d, 2H, 2″, 6″-$H$, $^3J_{H-H} = 8.88$ Hz), 7.58-7.62 (m, 2H, 3′, 5′-$H$), 7.73-7.76 (m, 1H, 4′-$H$), 7.79 (d, 2H, 3″, 5″-$H$, $^3J_{H-H} = 8.76$ Hz), 7.84 (d, 2H, 2′, 6′-$H$, $^3J_{H-H} = 7.40$ Hz), 12.41 (s, 1H, NH or OH, D$_2$O exchangeable)

**$^{13}$C NMR** (100 MHz; CDCl$_3$ + DMSO-$d_6$, $\delta_C$): 89.59 (C-4″), 116.93 (q, 4-CF$_3$, $^1J_{C-F} = 291.77$ Hz), 128.40 (C-2″, 6″), 128.87 (3″,5″-C), 129.15 (C-2″, 6″), 132.23 (C-2), 134.67 (C-4″), 135.36 (C-1′), 138.24 (C-3″, 5″), 141.87 (C-1″), 175.32 (C-3, $^2J_{C-F} = 33.20$ Hz), 191.00 (C-1)

**$^{19}$F NMR** (DMSO-$d_6$, $\delta_F$): - 69.20 (s, 3F, CF$_3$)

**MS:** m/z 446 (M$^+$)

**Anal. Calcd** for C$_{16}$H$_{10}$F$_3$IN$_2$O$_2$ (%): C, 43.07; H, 2.26; N, 6.28. Found (%): C, 43.02; H, 2.23; N, 6.24
(E)-4,4,4-Trifluoro-1-(4'-fluorophenyl)-2-((4''-iodophenyl)diazenyl)butane-1,3-dione (87d)

Yield: 82%, m.p. 119 °C

IR (νmax, cm⁻¹): 1692 (CO str.), 3209 (OH str.), 3375 (NH str.)

¹H NMR (400 MHz; CDCl₃ + DMSO-d₆, δH): 7.27 (d, 2H, 2'', 6''-H, ³JH-H = 8.76 Hz), 7.36-7.41 (m, 2H, 3', 5'-H), 7.76 (d, 2H, 3'', 5''-H, ³JH-H = 8.56 Hz), 7.90-7.93 (m, 2H, 2', 6'-H), 12.40 (s, 1H, NH or OH, D₂O exchangeable)

¹³C NMR (100 MHz; CDCl₃ + DMSO-d₆, δC); 89.50 (C-4''), 116.88 (q, 4-CF₃, ¹JC-F = 291.77 Hz), 116.23 (d, 3', 5'-C, ²JC-F = 23.14 Hz), 118.15 (C-2'', 6''), 131.74 (d, C-1', ⁴JC-F = 3.02 Hz), 131.98 (d, 2', 6'-C, ³JC-F = 10.06 Hz), 132.23 (C-2), 138.13 (3'', 5''-C), 141.82 (C-1''), 165.75 (d, C-4', ¹JC-F = 254.54 Hz), 175.30 (C-3, ²JC-F = 33.20 Hz), 189.35 (C-1)

¹⁹F NMR (DMSO-d₆, δF): - 69.25 (s, 3F, CF₃), 109.33 (s, 3F, 4''-F)

MS: m/z 464 (M⁺)

Anal. Calcd for C₁₆H₉F₄IN₂O₂ (%): C, 41.40; H, 1.95; N, 6.04. Found (%): C, 41.36; H, 1.92; N, 6.01

(E)-4,4,4-Trifluoro-2-((4''-iodophenyl)diazenyl)-1-(4'-methoxyphenyl)butane-1,3-dione (87e)

Yield: 83%, m.p. 121-122 °C

IR (νmax, cm⁻¹): 1683 (CO str.), 3217 (OH str.), 3372 (NH str.)

¹H NMR (400 MHz; CDCl₃ + DMSO-d₆, δH): 7.09 (d, 2H, 3', 5'-H, ²JH-H = 8.76 Hz), 7.25 (d, 2H, 2'', 6''-H, ³JH-H = 8.76 Hz), 7.72 (d, 2H, 3'', 5''-H, ³JH-H = 8.80 Hz), 12.15 (s, 1H, NH or OH, D₂O exchangeable)

¹³C NMR (100 MHz; CDCl₃ + DMSO-d₆, δC); 88.80 (C-4''), 114.40 (C-3', 5'), 116.90 (q, 4-CF₃, ¹JC-F = 292.77 Hz), 117.93 (C-2'', 6''), 128.15 (C-1''), 131.47 (C-2', 6')
132.96 (C-2), 138.01 (C-3'', 5''), 142.03 (C-1''), 164.48 (C-4), 175.33 (q, C-3, \(J_{C,F} = 33.20\) Hz), 188.93 (C-1)

**19F NMR** (DMSO-\(d_6\), \(\delta_F\)) \(\delta : -69.26\) (s, 3F, CF\(_3\))

**MS**: \(m/z\) 476 (M\(^+\))

**Anal. Caled** for C\(_{17}\)H\(_{12}\)F\(_3\)IN\(_2\)O\(_3\) (%): C, 42.88; H, 2.54; N, 5.88. Found (%): C, 42.83; H, 2.49; N, 5.86

**(E)-4,4,4-Trifluoro-2-((4''-iodophenyl)diazenyl)-1-(naphthalen-2'-yl)butane-1,3-dione (87f)**

Yield: 86%, m.p. 111 °C

**IR** (\(\nu_{max}, \text{cm}^{-1}\)): 1698 (CO str.), 3215 (OH str.), 3379 (NH str.)

**1H NMR** (400 MHz; CDCl\(_3\), \(\delta_H\)): 7.28 (d, 2H, 2'', 6''-H, \(J_{H-H} = 8.80\) Hz), 7.45-8.00 (m, 7H, 1', 3', 4', 5', 6', 7', 8'-H), 7.78 (d, 2H, 3'', 5''-H, \(J_{H-H} = 8.72\) Hz), 14.61 (s, 1H, NH or OH, D\(_2\)O exchangeable)

**13C NMR** (100 MHz; CDCl\(_3\), \(\delta_C\)): 91.72 (C-4''), 117.13 (q, 4-CF\(_3\), \(J_{C,F} = 292.78\) Hz), 118.82 (C-2'',6''), 124.16, 124.62, 126.14, 126.61, 127.66, 128.85, 129.59, 129.77, 132.01, 133.59 (C-2), 135.88, 138.98 (C-3'',5''), 140.46 (C-1''), 176.32 (C-3, \(J_{C,F} = 33.20\) Hz), 194.35 (C-1)

**19F NMR** (DMSO-\(d_6\), \(\delta_F\)) \(\delta : -69.30\) (s, 3F, CF\(_3\))

**MS**: \(m/z\) 476 (M\(^+\))

**Anal. Caled** for C\(_{20}\)H\(_{12}\)F\(_3\)IN\(_2\)O\(_2\) (%): C, 48.41; H, 2.44; N, 5.65. Found (%): C, 48.39; H, 2.44; N, 5.65

**(E)-4,4,4-Trifluoro-2-((4''-iodophenyl)diazenyl)-1-(naphthalen-1'-yl)butane-1,3-dione (87g)**

Yield: 78%, m.p. 109 °C

**IR** (\(\nu_{max}, \text{cm}^{-1}\)): 1697 (CO str.), 3215 (OH str.), 3372 (NH str.)

**1H NMR** (400 MHz; CDCl\(_3\) + DMSO-\(d_6\), \(\delta_H\)): 7.25 (d, 2H, 2'', 6''-H, \(J_{H-H} = 8.80\) Hz), 7.46-8.00 (m, 7H, 2', 3', 4', 5', 6', 7', 8'-H), 7.72 (d, 2H, 3'', 5''-H, \(J_{H-H} = 8.72\) Hz), 14.56 (s, 1H, NH or OH, D\(_2\)O exchangeable)

**13C NMR** (100 MHz; CDCl\(_3\) + DMSO-\(d_6\), \(\delta_C\)): 91.70
(C-4''), 117.12 (q, 4-CF₃, $^1J_{C-F} = 292.78$ Hz), 118.76 (C-2'', 6''), 123.16, 124.71, 126.15, 126.67, 127.68, 128.87, 129.71, 129.80, 132.05, 133.62 (C-2), 135.89, 138.96 (C-3'', 5''), 140.48 (C-1''), 176.32 (C-3, $^2J_{C-F} = 33.20$ Hz), 194.31 (C-1)

$^{19}F$ NMR (DMSO-$d_6$, δF) δ : -69.27 (s, 3F, CF₃)

**MS:** m/z 476 (M⁺)

**Anal. Calcd** for C₂₀H₁₂F₃IN₂O₂ (%): C, 48.41; H, 2.44; N, 5.65. Found (%): C, 48.39; H, 2.44; N, 5.65

(E)-2-((4''-Bromophenyl)diazenyl)-1-(4'-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (87h)

**Yield:** 86%, **m.p.** 119 °C

**IR** ($\nu_{max}$, cm⁻¹): 1688 (CO str.), 3212 (OH str.), 3379 (NH str.)

$^1H$ NMR (400 MHz; CDCl₃ + DMSO-$d_6$, δH): 7.40-7.81 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6'')

$^{13}C$ NMR (100 MHz; CDCl₃ + DMSO-$d_6$, δC): 117.16 (q, 4-CF₃, $^1J_{C-F} = 292.77$ Hz), 117.64 (C-4''), 118.04 (C-2'', 6''), 129.01 (C-3', 5'), 130.43 (C-2', 6'), 131.04 (C-2), 132.20 (C-3'', 5''), 134.34 (C-1'), 139.46 (C-4''), 141.18 (C-1''), 175.73 (q, C-3, $^2J_{C-F} = 33.20$ Hz), 189.64 (C-1)

$^{19}F$ NMR (DMSO-$d_6$, δF) δ : -69.29 (s, 3F, CF₃)

**MS:** m/z 434 (M⁺)

**Anal. Calcd** for C₁₆H₉BrClF₃N₂O₂ (%): C, 44.32; H, 2.09; N, 6.46. Found (%): C, 44.29; H, 2.03; N, 6.42

(E)-1-(4'-Bromophenyl)-2-((4''-bromophenyl)diazenyl)-4,4,4-trifluorobutane-1,3-dione (87i)

**Yield:** 79%, **m.p.** 118-119 °C

**IR** ($\nu_{max}$, cm⁻¹): 1693 (CO str.), 3211 (OH str.), 3375 (NH str.)

$^1H$ NMR (400 MHz; CDCl₃, δH): 7.35-7.60 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H)

1H NMR (400 MHz; CDCl₃, δH): 7.35-7.60 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H), 13.98 (s, 1H, NH or OH, D₂O exchangeable)
$^{13}$C NMR (100 MHz; CDCl$_3$, $\delta_C$): 117.18 (q, 4-CF$_3$, $^1J_{C\cdot F} = 291.77$ Hz), 118.49 (C-2",6"), 120.67 (C-4"), 128.34 (C-2'), 128.30 (C-4'), 129.86 (C-2', 6'), 131.71 (C-3', 5'), 133.09 (C-3",5"), 136.26 (C-1'), 139.61 (C-1''), 176.81 (C-3, $^2J_{C\cdot F} = 33.20$ Hz), 191.17 (C-1)

$^{19}$F NMR (DMSO-$d_6$, $\delta_F$) $\delta$: -69.27 (s, 3F, CF$_3$)

MS: m/z 478 (M$^+$)

Anal. Calcd for C$_{16}$H$_9$Br$_2$F$_3$N$_2$O$_2$ (%): C, 40.18; H, 1.86; N, 5.86. Found (%): C, 40.14; H, 1.82; N, 5.82

$^{(E)}$-2-((4"-Bromophenyl)diazenyl)-4,4,4-trifluoro-1-phenylbutane-1,3-dione (87j)

$^{13}$C NMR (100 MHz; CDCl$_3$, $\delta_C$): 117.22 (q, 4-CF$_3$, $^1J_{C\cdot F} = 292.77$ Hz), 118.37 (C-2", 6"), 120.30 (C-4"), 128.38 (C-3', 5'), 128.40 (C-2',6'), 128.78 (C-2), 133.03 (C-3",5"), 133.20 (C-4), 137.47 (C-1'), 139.75 (C-1''), 176.84 (C-3, $^2J_{C\cdot F} = 33.20$ Hz), 191.17 (C-1)

$^{19}$F NMR (DMSO-$d_6$, $\delta_F$) $\delta$: -69.22 (s, 3F, CF$_3$)

MS: m/z 400 (M$^+$)

Anal. Calcd for C$_{16}$H$_{10}$BrF$_3$N$_2$O$_2$ (%): C, 48.14; H, 2.53; N, 7.02. Found (%): C, 48.11; H, 2.49; N, 7.01

$^{(E)}$-2-((4"-Bromophenyl)diazenyl)-1-(4'-chlorophenyl)-4,4,4-trifluorobutane-1,3-dione (87k)

$^{13}$C NMR (100 MHz; CDCl$_3$, $\delta_C$): 116.23 (q, 4-CF$_3$, $^1J_{C\cdot F} = 292.77$ Hz), 118.37 (C-2", 6"), 120.30 (C-4"), 128.38 (C-3', 5'), 128.40 (C-2',6'), 128.78 (C-2), 133.03 (C-3",5"), 133.20 (C-4), 137.47 (C-1'), 139.75 (C-1''), 176.84 (C-3, $^2J_{C\cdot F} = 33.20$ Hz), 191.17 (C-1)

$^{19}$F NMR (DMSO-$d_6$, $\delta_F$) $\delta$: -69.22 (s, 3F, CF$_3$)

MS: m/z 400 (M$^+$)

Anal. Calcd for C$_{16}$H$_{10}$BrF$_3$N$_2$O$_2$ (%): C, 48.14; H, 2.53; N, 7.02. Found (%): C, 48.11; H, 2.49; N, 7.01
\[ J_{C-F} = 23.14 \text{ Hz} \], 117.23 (q, 4-CF\(_3\), \( J_{C-F} = 292.77 \text{ Hz} \)), 118.36 (C-2\(^\prime\), 6\(^\prime\)), 120.33 (C-4\(^\prime\)), 128.76 (C-2), 131.76 (d, C-1\(^\prime\), \( J_{C-F} = 3.02 \text{ Hz} \)), 131.97 (d, 2\(^\prime\), 6\(^\prime\)-C, \( J_{C-F} = 10.06 \text{ Hz} \)), 133.03 (C-3\(^\prime\), 5\(^\prime\)), 139.72 (C-1\(^\prime\)), 165.71 (d, C-4\(^\prime\), \( J_{C,F} = 254.54 \text{ Hz} \)), 176.84 (C-3, \( J_{C,F} = 33.20 \text{ Hz} \)), 191.19 (C-1)

\[ \delta_{\text{F}} : -69.25 \text{ (s, 3F, CF}_3\text{)}, -103.33 \text{ (s, 1F, 4''-F)} \]

**MS:** m/z 416 (M\(^+\))

**Anal. Calcd** for C\(_{16}\)H\(_9\)BrF\(_4\)N\(_2\)O\(_2\) (%): C, 46.07; H, 2.17; N, 6.72. Found (%): C, 46.01; H, 2.11; N, 6.70

\((E)-2-((4''-\text{Bromophenyl})\text{diazenyl})-4,4,4-\text{trifluoro-1-(4'-methoxyphenyl)}\text{butane-1,3-dione (87l)}\)

**Yield:** 83\%, **m.p.** 113 °C

**IR** (\(\nu_{\text{max}}, \text{cm}^{-1}\)): 1697 (CO str.), 3190 (OH str.), 3378 (NH str.)

\[ \delta_{\text{H}} : 3.88 \text{ (s, 3H, OMe)}, 6.91-7.66 \text{ (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H)}, 14.61 \text{ (s, 1H, NH or OH, D\(_2\)O exchangeable)} \]

**13C NMR** (100 MHz; CDCl\(_3\), \(\delta_{\text{C}}\)): 55.58 (4'-OMe), 113.81 (C-3',5'), 117.23 (q, 4-CF\(_3\), \( J_{C-F} = 292.77 \text{ Hz} \)), 118.12 (C-2\(^\prime\), 6\(^\prime\)), 119.78 (C-4\(^\prime\)), 129.34 (C-1\(^\prime\)), 129.66 (C-2), 131.40 (C-2\(^\prime\), 6\(^\prime\)), 132.94 (C-3',5'), 139.89 (C-1\(^\prime\)), 164.14 (C-4\(^\prime\)), 176.92 (C-3, \( J_{C,F} = 33.20 \text{ Hz} \)), 189.83 (C-1)

\[ \delta_{\text{F}} : -69.26 \text{ (s, 3F, CF}_3\text{)} \]

**MS:** m/z 428 (M\(^+\))

**Anal. Calcd** for C\(_{17}\)H\(_{12}\)BrF\(_3\)N\(_2\)O\(_3\) (%): C, 47.57; H, 2.82; N, 6.53. Found (%): C, 47.52; H, 2.76; N, 6.52

\((E)-2-((4''-\text{Bromophenyl})\text{diazenyl})-4,4,4-\text{trifluoro-1-(naphthalen-2'-yl)}\text{butane-1,3-dione (87m)}\)

**Yield:** 99\%, **m.p.** 112 °C

**IR** (\(\nu_{\text{max}}, \text{cm}^{-1}\)): 1695 (CO str.), 3217 (OH str.), 3378 (NH str.)

\[ \delta_{\text{H}} : 7.00-7.66 \text{ (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H)}, 7.70-8.27 \text{ (m, 7H, 1', 3', 4', 5', 6', 7', 8'-H)}, 14.52 \text{ (s, 1H, NH or OH, D\(_2\)O exchangeable)} \]
OH, D₂O exchangeable)

**¹³C NMR** (100 MHz; CDCl₃ + DMSO-d₆, δ_C): 117.23 (q, 4-CF₃, ¹J_C-F = 292.77 Hz), 118.12 (C-2\(^{''}\), 6\(^{''}\)), 119.78 (C-4\(^{''}\)), 124.18, 124.60, 126.16, 126.63, 127.69, 128.87, 129.60, 129.66 (C-2), 129.77, 132.06, 132.94 (C-3\(^{''}\),5\(^{''}\)), 135.84, 139.89 (C-1\(^{''}\)), 175.92 (C-3, ²J_C-F = 33.20 Hz), 191.83 (C-1)

**¹⁹F NMR** (DMSO-d₆, δ_F): δ: -69.29 (s, 3F, CF₃)

**MS**: m/z 448 (M⁺)

**Anal. Calcd** for C₂₀H₁₂BrF₃N₂O₂ (%): C, 53.47; H, 2.69; N, 6.24. Found (%): C, 53.42; H, 2.63; N, 6.21

(E)-2-((4''-Bromophenyl)diazenyl)-4,4,4-trifluoro-1-(naphthalen-1'yl)butane-1,3-dione (87n)

Yield: 82%, m.p. 114 °C

**IR** (ν\(_{max}\), cm\(^{-1}\)): 1699 (CO str.), 3220 (OH str.), 3380 (NH str.)

**¹H NMR** (400 MHz; CDCl₃ + DMSO-d₆, δ_H): 7.11-7.66 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6'' -H), 7.70-8.27 (m, 7H, 1', 3', 4', 5', 6', 7', 8'-H), 14.48 (s, 1H, NH or OH, D₂O exchangeable)

**¹³C NMR** (100 MHz; CDCl₃, δ_C): 117.21 (q, 4-CF₃, ¹J_C-F = 292.77 Hz), 118.16 (C-2'', 6''), 119.80 (C-4''), 119.80 (C-4'''), 123.17, 124.72, 126.16, 126.70, 127.72, 128.90, 129.74, 129.82, 132.07, 132.94 (C-3'',5''), 135.90, 139.91 (C-1''), 175.93 (C-3, ²J_C-F = 33.20 Hz), 192.85 (C-1)

**¹⁹F NMR** (DMSO-d₆, δ_F): δ: -69.27 (s, 3F, CF₃)

**Anal. Calcd** for C₂₀H₁₂BrF₃N₂O₂ (%): C, 53.47; H, 2.69; N, 6.24. Found (%): C, 53.42; H, 2.63; N, 6.21

**MS**: m/z 448 (M⁺)

(E)-1-(4'-Chlorophenyl)-2-((4''-chlorophenyl)diazenyl)-4,4,4-trifluorobutane-1,3-dione (87aa)
Yield: 81%, m.p. 121-123 °C
IR (ν_max, cm⁻¹): 1692 (CO str.), 3218 (OH str.), 3379 (NH str.)

^1H NMR (400 MHz; CDCl₃, δ_H): 7.40-7.54 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6'') - 13.98 (s, 1H, NH or OH, D₂O exchangeable)

^13C NMR (100 MHz; CDCl₃, δ_C): 117.21 (q, 4-CF₃, J_C-F = 292.78 Hz), 118.21 (C-2", 6"), 128.28 (C-2), 128.73 (C-3', 5'), 129.82 (C-2', 6'), 130.14 (C-3", 5"), 132.86 (C-4"), 135.82 (C-1'), 139.15 (C-1''), 139.58 (C-4'), 176.79 (q, C-3, J_C-F = 32.20 Hz), 190.96

^19F NMR (DMSO-d₆, δ_F): - 69.27 (s, 3F, CF₃)

MS: m/z 388 (M⁺)

Anal. Calcd for C₁₆H₁₉Cl₂F₃N₂O₂ (%): C, 49.38; H, 2.33; N, 7.20. Found (%): C, 49.32; H, 2.31; N, 7.18

(E)-1-(4'-Bromophenyl)-2-((4''-chlorophenyl)diazenyl)-4,4,4-trifluorobutane-1,3-dione (87ab)

Yield: 83%, m.p. 125 °C
IR (ν_max, cm⁻¹): 1695 (CO str.), 3210 (OH str.), 3376 (NH str.)

^1H NMR (400 MHz; CDCl₃, δ_H): 7.43-7.60 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6'') - 14.00 (s, 1H, NH or OH, D₂O exchangeable)

^13C NMR (100 MHz; CDCl₃, δ_C): 117.23 (q, 4-CF₃, J_C-F = 292.78 Hz), 118.22 (C-2", 6"), 128.29 (C-2), 128.58 (C-4"), 130.17 (C-3", 5"), 130.46 (C-2', 6'), 131.97 (C-3', 5'), 132.86 (C-4"), 134.72 (C-1'), 139.16 (C-1''), 176.79 (q, C-3, J_C-F = 33.20 Hz), 190.96 (C-1)

^19F NMR (DMSO-d₆, δ_F): - 69.24 (s, 3F, CF₃)

MS: m/z 434 (M⁺)

Anal. Calcd for C₁₆H₉ClF₃N₂O₂ (%): C, 44.32; H, 2.09; N, 6.46. Found (%): C, 44.30; H, 2.02; N, 6.42

(E)-2-((4'-Chlorophenyl)diazenyl)-4,4,4-trifluoro-1-phenylbutane-1,3-dione (87ac)
Yield: 85%, \textbf{m.p.} 112 °C

\textbf{IR} (ν\textsubscript{max}, cm\textsuperscript{-1}): 1688 (CO str.), 3211 (OH str.), 3380 (NH str.)

\textbf{\textsuperscript{1}H NMR} (400 MHz; CDCl\textsubscript{3}, δ\textsubscript{H}): 7.42-7.65 (m, 9H, 2', 3', 4', 5', 6', 2'', 3'', 5'', 6''-H), 13.90 (s, 1H, NH or OH, D\textsubscript{2}O exchangeable)

\textbf{\textsuperscript{13}C NMR} (100 MHz; CDCl\textsubscript{3}, δ\textsubscript{C}); 117.24 (q, 4-CF\textsubscript{3}, \textsuperscript{1}J\textsubscript{C-F} = 292.78 Hz), 118.09 (C-2", 6"), 128.38 (C-2', 3', 5', 6'), 128.71 (C-2), 130.08 (C-3", 5"'), 132.54 (C-4"), 133.16 (C-4'), 137.49 (C-1'), 139.29 (C-1''), 176.82 (q, C-3, \textsuperscript{2}J\textsubscript{C-F} = 32.20 Hz), 192.22 (C-1)

\textbf{\textsuperscript{19}F NMR} (DMSO-\textit{d}_6, δ\textsubscript{F}): - 69.28 (s, 3F, CF\textsubscript{3})

\textbf{MS}: m/z 354 (M\textsuperscript{+})

\textbf{Anal. Caled} for C\textsubscript{16}H\textsubscript{10}ClF\textsubscript{3}N\textsubscript{2}O\textsubscript{2} (%): C, 54.18; H, 2.84; N, 7.90. Found (%): C, 54.12; H, 2.82; N, 7.90

(E)-2-((4''-Chlorophenyl)diazenyl)-4,4,4-trifluoro-1-(4'-fluorophenyl)butane-1,3-dione (\textit{87ad})

Yield: 85%, \textbf{m.p.} 119 °C

\textbf{IR} (ν\textsubscript{max}, cm\textsuperscript{-1}): 1692 (CO str.), 3210 (OH str.), 3377 (NH str.)

\textbf{\textsuperscript{1}H NMR} (400 MHz; CDCl\textsubscript{3}, δ\textsubscript{H}): 7.11-7.65 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H), 13.88 (s, 1H, NH or OH, D\textsubscript{2}O exchangeable)

\textbf{\textsuperscript{13}C NMR} (100 MHz; CDCl\textsubscript{3}, δ\textsubscript{C}); 115.69 (d, 3', 5'-C, \textsuperscript{3}J\textsubscript{C-F} = 22.13 Hz), 117.24 (q, 4-CF\textsubscript{3}, \textsuperscript{1}J\textsubscript{C-F} = 292.78 Hz), 118.14 (C-2", 6"), 128.41 (C-2), 130.12 (C-3", 5"'), 131.24 (C-2', 6'-C, \textsuperscript{3}J\textsubscript{C-F} = 9.05 Hz), 132.73 (C-4"), 133.69 (C-1', \textsuperscript{4}J\textsubscript{C-F} = 3.02 Hz), 139.19 (C-1''), 165.72 (d, C-4', \textsuperscript{1}J\textsubscript{C-F} = 255.55 Hz), 176.89 (q, C-3, \textsuperscript{2}J\textsubscript{C-F} = 45.27 Hz), 190.53 (C-1)

\textbf{\textsuperscript{19}F NMR} (DMSO-\textit{d}_6, δ\textsubscript{F}): - 69.29 (s, 3F, CF\textsubscript{3}), -103.36 (s, 1F, 4''-F)

\textbf{MS}: m/z 372 (M\textsuperscript{+})

\textbf{Anal. Caled} for C\textsubscript{16}H\textsubscript{9}ClF\textsubscript{4}N\textsubscript{2}O\textsubscript{2} (%): C, 51.56; H, 2.43; N, 7.52. Found (%): C, 51.56; H, 2.43; N, 7.52

(E)-2-((4''-Chlorophenyl)diazenyl)-4,4,4-trifluoro-1-(4'-methoxyphenyl)butane-1,3-dione (\textit{87ae})

Yield: 85%, \textbf{m.p.} 119 °C

\textbf{IR} (ν\textsubscript{max}, cm\textsuperscript{-1}): 1692 (CO str.), 3210 (OH str.), 3377 (NH str.)

\textbf{\textsuperscript{1}H NMR} (400 MHz; CDCl\textsubscript{3}, δ\textsubscript{H}): 7.11-7.65 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H), 13.88 (s, 1H, NH or OH, D\textsubscript{2}O exchangeable)

\textbf{\textsuperscript{13}C NMR} (100 MHz; CDCl\textsubscript{3}, δ\textsubscript{C}); 115.69 (d, 3', 5'-C, \textsuperscript{3}J\textsubscript{C-F} = 22.13 Hz), 117.24 (q, 4-CF\textsubscript{3}, \textsuperscript{1}J\textsubscript{C-F} = 292.78 Hz), 118.14 (C-2", 6"), 128.41 (C-2), 130.12 (C-3", 5"'), 131.24 (C-2', 6'-C, \textsuperscript{3}J\textsubscript{C-F} = 9.05 Hz), 132.73 (C-4"), 133.69 (C-1', \textsuperscript{4}J\textsubscript{C-F} = 3.02 Hz), 139.19 (C-1''), 165.72 (d, C-4', \textsuperscript{1}J\textsubscript{C-F} = 255.55 Hz), 176.89 (q, C-3, \textsuperscript{2}J\textsubscript{C-F} = 45.27 Hz), 190.53 (C-1)

\textbf{\textsuperscript{19}F NMR} (DMSO-\textit{d}_6, δ\textsubscript{F}): - 69.29 (s, 3F, CF\textsubscript{3}), -103.36 (s, 1F, 4''-F)

\textbf{MS}: m/z 372 (M\textsuperscript{+})

\textbf{Anal. Caled} for C\textsubscript{16}H\textsubscript{9}ClF\textsubscript{4}N\textsubscript{2}O\textsubscript{2} (%): C, 51.56; H, 2.43; N, 7.52. Found (%): C, 51.56; H, 2.43; N, 7.52

(E)-2-((4''-Chlorophenyl)diazenyl)-4,4,4-trifluoro-1-(4'-methoxyphenyl)butane-1,3-dione (\textit{87ae})
RESULTS AND DISCUSSION

**Yield:** 87%, **m.p.** 123 °C

**IR** ($\nu_{\text{max}}$, cm⁻¹): 1697 (CO str.), 3209 (OH str.), 3376 (NH str.)

**$^1$H NMR** (400 MHz; CDCl₃, $\delta_H$): 7.45-7.60 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H), 14.00 (s, 1H, NH or OH, D₂O exchangeable)

**$^{13}$C NMR** (100 MHz; CDCl₃, $\delta_C$); 55.56 (4'-OMe), 113.80 (C-3',5'), 117.25 (q, 4-CF₃, $^1J_{C-F} = 292.78$ Hz), 118.11 (C-2'', 6''), 124.82 (C-2), 129.32 (C-1'), 131.42 (C-2', 6'), 130.12 (C-3', 5''), 132.77 (C-4''), 139.19 (C-1''), 176.89 (q, C-3, $^2J_{C-F} = 45.27$ Hz), 190.53 (C-1)

**$^{19}$F NMR** (DMSO-d₆, $\delta_F$) δ: -69.27 (s, 3F, CF₃)

**MS:** m/z 384 (M⁺)

**Anal. Calcd** for C₁₇H₁₂ClF₃N₂O₃ (%): C, 53.07; H, 3.12; N, 7.28. Found (%): C, 53.02; H, 3.08; N, 7.23

**$(E)$-2-((4''-Chlorophenyl)diazenyl)-4,4,4-trifluoro-1-(naphthalen-2'-yl)butane-1,3-dione (87af)**

---

**Yield:** 78%, **m.p.** 110 °C

**IR** ($\nu_{\text{max}}$, cm⁻¹): 1699 (CO str.), 3215 (OH str.), 3375 (NH str.)

**$^1$H NMR** (400 MHz; CDCl₃ + DMSO-d₆, $\delta_H$): 7.41-7.65 (m, 9H, 2', 3', 4', 5', 6', 2'', 3'', 5'', 6''-H), 7.69-8.32 (m, 7H, 1', 3', 4', 5', 6', 7', 8'-'H), 13.90 (s, 1H, NH or OH, D₂O exchangeable)

**$^{13}$C NMR** (100 MHz; CDCl₃ + DMSO-d₆, $\delta_C$): 117.25 (q, 4-CF₃, $^1J_{C-F} = 292.78$ Hz), 118.11 (C-2'', 6''), 124.16, 124.62, 126.14, 126.61, 127.66, 128.42 (C-2), 128.89, 129.59, 129.77, 130.12 (C-3'', 5''), 132.01, 132.77 (C-4''), 135.88, 139.19 (C-1''), 176.89 (q, C-3, $^2J_{C-F} = 45.27$ Hz), 190.53 (C-1)

**$^{19}$F NMR** (DMSO-d₆, $\delta_F$): -69.22 (s, 3F, CF₃)

**MS:** m/z 404 (M⁺)

**Anal. Calcd** for C₂₀H₁₂ClF₃N₂O₂ (%): C, 59.35; H, 2.99; N, 6.92. Found (%): C, 59.34; H, 2.95; N, 6.90
(E)-2-((4”-Chlorophenyl)diazenyl)-4,4,4-trifluoro-1-(naphthalen-1’-yl)butane-1,3-dione (87ag)

**Yield:** 76%, **m.p.** 100 °C

**IR** \( (\nu_{\text{max}}, \text{cm}^{-1}) \): 1699 (CO str.), 3217 (OH str.), 3375 (NH str.)

**\(^1\text{H NMR}\)** (400 MHz; CDCl\(_3\) + DMSO-\(d_6\), \(\delta_H\)): 7.31-7.65 (m, 9H, 2’, 3’, 4’, 5’, 6’, 2”, 3”, 5”, 6”-H), 7.70-8.44 (m, 7H, 2’, 3’, 4’, 5’, 6’, 7’, 8’-H), 13.82 (s, 1H, NH or OH, D\(_2\)O exchangeable)

**\(^{13}\text{C NMR}\)** (100 MHz; CDCl\(_3\) + DMSO-\(d_6\), \(\delta_C\)): 117.30 (q, 4-CF\(_3\), \(J_{C-F} = 292.78 \text{ Hz}\)), 118.17 (C-2”, 6”), 123.20, 124.75, 126.19, 126.74, 127.71, 128.44 (C-2), 128.92, 129.76, 129.86, 130.14 (C-3”, 5”), 132.09, 132.77 (C-4”), 135.99, 139.20 (C-1”), 176.91 (q, C-3, \(J_{C-F} = 45.27 \text{ Hz}\)), 190.51 (C-1)

**\(^{19}\text{F NMR}\)** (DMSO-\(d_6\), \(\delta_F\)): -69.30 (s, 3F, CF\(_3\))

**MS:** m/z 404 (M\(^+\))

**Anal. Calcd** for C\(_{20}\)H\(_{12}\)ClF\(_3\)N\(_2\)O\(_2\) (%): C, 59.35; H, 2.99; N, 6.92. Found (%): C, 59.34; H, 2.95; N, 6.90

\( (E)\)-1-(4’-Chlorophenyl)-4,4,4-trifluoro-2-((4”'-fluorophenyl)diazenyl)butane-1,3-dione (87ah)

**Yield:** 87%, **m.p.** 103 °C, **Lit m.p.** 104 °C [39]

**IR** \( (\nu_{\text{max}}, \text{cm}^{-1}) \): 1694 (CO str.), 3210 (OH str.), 3377 (NH str.)

**\(^1\text{H NMR}\)** (300 MHz; CDCl\(_3\), \(\delta_H\)): 7.13-7.23 (m, 2H, 3”, 5”-H), 7.44 (d, 2H, 3’, 5’-H, \(J_{H-H} = 8.40 \text{ Hz}\)), 7.48-7.52 (m, 2H, 2”, 6”-H), 7.55 (d, 2H, 2’, 6’-H, \(J_{H-H} = 8.40 \text{ Hz}\)) (Hz), 14.17 (bs, 1H, NH or OH, D\(_2\)O exchangeable)

**\(^{13}\text{C NMR}\)** (75 MHz; CDCl\(_3\), \(\delta_C\)): 117.01 (q, C-3”, 5”, \(J_{C-F} = 23.25 \text{ Hz}\)), 117.25 (q, 4-CF\(_3\), \(J_{C-F} = 290.25 \text{ Hz}\)), 118.76 (q, C-2”, 6”, \(J_{C-F} = 8.25 \text{ Hz}\)), 128.65 (C-3’, 5’), 129.78 (C-2’, 6’), 131.81 (C-1’, C-2), 136.82 (q, C-1”, \(J_{C-F} = 3.0 \text{ Hz}\)), 139.64 (C-4’), 161.54 (q, C-4”, \(J_{C-F} = 247.5 \text{ Hz}\)), 176.74 (q, C-3, \(J_{C-F} = 33 \text{ Hz}\)), 191.04 (C-1)

**\(^{19}\text{F NMR}\)** (DMSO-\(d_6\), \(\delta_F\)): -69.26 (s, 3F, CF\(_3\)), -103.35 (s, 1F, 4”-F)

**MS:** m/z 372 (M\(^+\))
Anal. Calcd for C_{16}H_{9}ClF_{4}N_{2}O_{2} (%): C, 51.56; H, 2.43; N, 7.52. Found (%): C, 51.54; H, 2.42; N, 7.49

\((E)-1-(4'-\text{Bromophenyl})-4,4,4\text{-trifluoro-2-}((4'\text{-fluorophenyl})\text{diazenyl})\text{butane-1,3-dione} (87\text{ai})\)

Yield: 83\%, m.p. 102 °C, Lit m.p. 101-102 °C [39]

IR \((\nu_{\text{max}}, \text{cm}^{-1})\): 1698 (CO str.), 3210 (OH str.), 3375 (NH str.)

\(^{1}H \text{ NMR} (300 \text{ MHz}; \text{CDCl}_3, \delta_H): 7.16-7.68 (m, 8H, 2', 3', 5', 6', 2'' , 3'', 5'', 6'') , 14.19 (bs, 1H, NH or OH, D\text{2}O exchangeable)\)

\(^{13}C \text{ NMR} (75 \text{ MHz}; \text{CDCl}_3, \delta_C): 116.40 \text{ (q, C-3'}, 5'', J_{C-F} = 23.25 \text{ Hz}), 116.61 \text{ (q, 4-CF}_3, J_{C-F} = 290.25 \text{ Hz}), 118.08 \text{ (q, C-2', 6''}, J_{C-F} = 8.25 \text{ Hz}), 127.25 \text{ (C-4')}, 129.16 \text{ (C-3'}, 5''), 130.95 \text{ (C-2', 6''), 131.25 (C-2), 135.75 (C-1'), 136.18 (q, C-1', J_{C-F} = 3.0 Hz), 160.91 \text{ (q, C-4''}, J_{C-F} = 247.5 \text{ Hz}), 176.08 \text{ (q, C-3}, 2J_{C-F} = 33.0 \text{ Hz}), 190.59 \text{ (C-1)}\)

\(^{19}F \text{ NMR} (\text{DMSO-d}_6, \delta_F): -69.26 \text{ (s, 3F, CF}_3), -103.39 \text{ (s, 1F, 4''-F)}\)

MS: m/z 418 (M\(^+\))

Anal. Calcd for C_{16}H_{9}BrF_{4}N_{2}O_{2} (%): C, 46.07; H, 2.17; N, 6.72. Found (%): C, 46.03; H, 2.15; N, 6.70

\((E)-4,4,4\text{-Trifluoro-2-}((4''\text{-fluorophenyl})\text{diazenyl})\text{-1-phenylbutane-1,3-dione} (87\text{aj})\)

Yield: 86\%, m.p. 100 °C, Lit m.p. 101-102 °C [39]

IR \((\nu_{\text{max}}, \text{cm}^{-1})\): 1693 (CO str.), 3210 (OH str.), 3375 (NH str.)

\(^{1}H \text{ NMR} (300 \text{ MHz}; \text{CDCl}_3, \delta_H): 7.15-7.28 (m, 9H, 2', 3', 4', 5', 6', 2'', 3'', 5'', 6''-H) , 14.07 (bs, 1H, NH or OH, D\text{2}O exchangeable)\)

\(^{13}C \text{ NMR} (75 \text{ MHz}; \text{CDCl}_3, \delta_C): 116.91 \text{ (q, C-3'}, 5'', J_{C-F} = 23.25 \text{ Hz}), 117.31 \text{ (q, 4-CF}_3, J_{C-F} = 290.25 \text{ Hz}), 118.56 \text{ (q, C-2', 6''}, J_{C-F} = 8.25 \text{ Hz}), 128.28 \text{ (C-3'}, 5''), 130.46 \text{ (C-1'), 133.10 \text{ (C-2'), 133.14 (C-2), 137.00 (q, C-1', J_{C-F} = 2.25 \text{ Hz}), 137.61 \text{ (C-4'}, 161.39 \text{ (q, C-4''}, J_{C-F} = 246.75 \text{ Hz}), 176.75 \text{ (q, C-3}, 2J_{C-F} = 33 \text{ Hz}), 192.29 \text{ (C-1)}\)

\(^{19}F \text{ NMR} (\text{DMSO-d}_6, \delta_F): -69.30 \text{ (s, 3F, CF}_3), -103.37 \text{ (s, 1F, 4''-F)}\)

MS: m/z 338 (M\(^+\))
**Anal. Calcd** for C$_{16}$H$_{10}$F$_{4}$N$_{2}$O$_{2}$ (%): C, 56.81; H, 2.98; N, 8.28. Found (%): C, 56.74; H, 2.92; N, 8.24

(E)-4,4,4-Trifluoro-1-(4'-fluorophenyl)-2-((4''-fluorophenyl)diazenyl)butane-1,3-dione (87ak)

**Yield:** 83%,  **m.p.** 98-99 °C,  **Lit. m.p.** 99 °C [39]

**IR** ($\nu_{\text{max}}$, cm$^{-1}$): 1697 (CO str.), 3219 (OH str.), 3375 (NH str.)

**$^1$H NMR** (300 MHz; CDCl$_3$, $\delta_{\text{H}}$): 6.97-7.56 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6'' -H), 14.02 (bs, 1H, NH or OH, D$_2$O exchangeable)

**$^{13}$C NMR** (100 MHz; CDCl$_3$, $\delta_{\text{C}}$): 98.97 (q, C-5, $^2J_{C-F}$ = 36.00 Hz), 114.93 (d, C-2'', 6'', $^3J_{C-F}$ = 7.50 Hz), 115.65 (C-3', 5'), 116.06 (d, C-3'', 5'', $^2J_{C-F}$ = 23.25 Hz), 122.13 (q, 4-CF$_3$, $^1J_{C-F}$ = 287.25 Hz), 123.23 (C-1'), 129.91 (C-2', 6'), 133.27 (C-4), 138.79 (d, C-1'', $^4J_{C-F}$ = 3.0 Hz), 154.52 (C-3), 158.59 (d, C-4'', $^1J_{C-F}$ = 240.75 Hz), 164.02 (C-4')

**$^{19}$F NMR** (DMSO-d$_6$, $\delta_{\text{F}}$): -69.29 (s, 3F, CF$_3$), 103.33 (s, 1F, 4''-F)

**MS:** m/z 356 (M$^+$)

**Anal. Calcd** for C$_{16}$H$_9$F$_5$N$_2$O$_2$ (%): C, 53.94; H, 2.55; N, 7.86. Found (%): C, 53.92; H, 2.49; N, 7.82

(E)-4,4,4-Trifluoro-2-((4''-fluorophenyl)diazenyl)-1-(4'-methoxyphenyl)butane-1,3-dione (87al)

**Yield:** 78%,  **m.p.** 120 °C,  **Lit. m.p.** 121 °C [39]

**IR** ($\nu_{\text{max}}$, cm$^{-1}$): 1692 (CO str.), 3219 (OH str.), 3375 (NH str.)

**$^1$H NMR** (300 MHz; CDCl$_3$, $\delta_{\text{H}}$): 7.16–7.68 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6''-H), 14.19 (bs, 1H, NH or OH, D$_2$O exchangeable)

**$^{13}$C NMR** (75 MHz; CDCl$_3$, $\delta_{\text{C}}$): 55.51 (4'-OCH$_3$), 113.61 (C-3', 5'), 116.45 (q, C-3'', 5'', $^2J_{C-F}$ = 23.25 Hz), 117.27 (q, 4-CF$_3$, $^1J_{C-F}$ = 290.25 Hz), 118.26 (q, C-2'', 6'', $^3J_{C-F}$ = 8.25 Hz), 128.80 (C-1'), 131.21 (C-2', 6'), 131.32 (C-2), 137.11 (q, C-1'', $^4J_{C-F}$ = 3 Hz), 161.11 (q, C-4'', $^1J_{C-F}$ = 246.75 Hz), 163.98 (C-4'), 176.35 (q, C-3, $^2J_{C-F}$ = 33),
RESULTS AND DISCUSSION

189.92 (C-1)

$^{19}$F NMR (DMSO-$d_6$, $\delta_F$): -69.31 (s, 3F, CF$_3$), 103.39 (s, 1F, 4"-F)

**MS:** m/z 368 (M$^+$)

**Anal. Calcd** for C$_{17}$H$_{12}$F$_4$N$_2$O$_3$ (%): C, 55.44; H, 3.28; N, 7.61. Found (%): C, 55.42; H, 3.27; N, 7.54

(E)-4,4,4-Trifluoro-2-((4''-fluorophenyl)diazenyl)-1-(naphthalen-2'-yl)butane-1,3-dione (**87am**)

Yield: 87%, **m.p.** 103 °C

**IR** ($\nu_{max}$, cm$^{-1}$): 1692 (CO str.), 3212 (OH str.), 3379 (NH str.)

$^1$H NMR (300 MHz; CDCl$_3$, $\delta_H$): 7.12-7.69 (m, 8H, 2', 3', 5', 6', 2'', 3'', 5'', 6'')-H), 7.71-8.27 (m, 7H, 1', 3', 4', 5', 6', 7', 8'-H), 14.19 (bs, 1H, NH or OH, D$_2$O exchangeable)

$^{13}$C NMR (75 MHz; CDCl$_3$, $\delta_C$): 116.49 (q, $^2J_{C-F}$ = 23.25 Hz), 117.29 (q, 4-CF$_3$, $^1J_{C-F}$ = 290.25 Hz), 118.27 (q, C-2", 6", $^3J_{C-F}$ = 8.25 Hz), 124.18, 124.65, 126.18, 126.67, 127.69, 128.90, 129.60, 129.78, 131.32 (C-2), 132.01, 135.88, 137.11 (q, C-1", $^4J_{C-F}$ = 3.0 Hz), 161.11 (q, C-4", $^1J_{C-F}$ = 246.75 Hz), 176.35 (q, C-3, $^2J_{C-F}$ = 33 Hz), 189.92 (C-1)

**MS:** m/z 388 (M$^+$)

$^{19}$F NMR (DMSO-$d_6$, $\delta_F$): -69.25 (s, 3F, CF$_3$), 103.35 (s, 1F, 4"-F)

**Anal. Calcd** for C$_{20}$H$_{12}$F$_4$N$_2$O$_2$ (%): C, 61.86; H, 3.11; N, 7.21. Found (%): C, 61.82; H, 3.05; N, 7.19

(E)-2-((4"-Chlorophenyl)diazenyl)-4,4,4-trifluoro-1-(naphthalen-1'-yl)butane-1,3-dione (**87an**)

Yield: 76%, **m.p.** 100 °C

**IR** ($\nu_{max}$, cm$^{-1}$): 1696 (CO str.), 3219 (OH str.), 3373 (NH str.)

$^1$H NMR (300 MHz; CDCl$_3$, $\delta_H$): 7.15-7.70 (m, 8H, 2', 3', 5', 6', 2", 3", 5", 6"-H), 7.81-8.27 (m, 7H, 2', 3', 4', 5', 6', 7', 8'-H), 14.25 (bs, 1H, NH or OH, D$_2$O exchangeable)

$^{13}$C NMR (75 MHz; CDCl$_3$, $\delta_C$): 116.51 (q, $^2J_{C-F}$ =23.25 Hz), 117.25 (q, 4-CF$_3$, $^1J_{C-F}$...
RESULTS AND DISCUSSION

= 290.25 Hz), 118.22 (q, C- 2'', 6'', 3 J_C-F = 8.25 Hz), 123.21, 124.76, 126.20, 126.76, 127.75, 128.94, 129.78, 129.88, 131.34 (C-2), 132.19, 135.99, 137.12 (q, C-1'', 4 J_C-F = 3.0 Hz), 161.12 (q, C-4'', 1 J_C-F = 246.75 Hz), 176.37 (q, C-3, 2 J_C-F = 33 Hz), 189.94 (C-1)

19F NMR (DMSO-d6, δ_F): - 69.27 (s, 3F, CF3), 103.38 (s, 1F, 4''-F)

MS: m/z 388 (M+)

Anal. Caled for C20H12F4N2O2 (%): C, 61.86; H, 3.11; N, 7.21. Found (%): C, 61.82; H, 3.05; N, 7.19

Synthesis of (E)-4-(aryldiazenyl)-3-aryl-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ols

89

General procedure: An ethanolic solution (25ml) of hydroxylamine hydrochloride salt (5 mmol) and sodium acetate (5 mmol) was refluxed on water bath for 15 minutes (pH = 6.7). Aryl-1,1,1-trifluorobutane-2,4-dione (5 mmol) was subsequently added and solution was refluxed further for 4 hr. The reaction was monitored by TLC. The solvent was evaporated and residue obtained was extracted with chloroform. The organic phase was dried over anhydrous sodium sulphate and chloroform was distilled off in order to obtain the product 89.

(E)-3-(4'-Chlorophenyl)-4-((4''-iodophenyl)diazenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89a)

Yield: 87%, m.p. 200-201 °C

IR (v_max, cm⁻¹): 3005 (OH str.), 3292 (NH str.)

1H NMR (400 MHz; DMSO-d6, δ_H): 7.26 (d, 2H, 2'', 6''-H, 1 J_H-H = 8.80 Hz), 7.65 (d, 2H, 3', 5', 3'', 5'' -H, 1 J_H- H = 7.92 Hz), 7.98 (d, 2H, 2', 6'-H, 1 J_H-H = 8.56 Hz), 9.86 (bs, 1H, OH, D2O exchangeable), 10.45 (bs, 1H, NH, D2O exchangeable)

13C NMR (100 MHz; DMSO-d6, δ_C): 85.72 (C-4''), 98.52 (q, C-5, 2 J_C-F = 35.21 Hz), 117.00 (C-2'', 6''), 122.05 (q, 5-CF3, 1 J_C-F = 288.75 Hz), 125.60 (C-1''), 129.03 (C-3', 5'), 129.40 (C-2', 6'), 131.95 (C-4), 135.56 (C-4''), 137.75 (C-3'', 5''), 143.12 (C-1''), 154.60 (C-3)

19F NMR (DMSO-d6, δ_F): - 78.87 (s, 3F, CF3)

MS: m/z 493 (M+)

Anal. Caled for C16H10ClF3IN3O2 (%): C, 38.77; H, 2.03; N, 7.15. Found (%): C,
38.72; H, 2.01; N, 7.12

\((E)-3-(4'-\text{Bromophenyl})-4-((4''-\text{iodophenyl})\text{diazenyl})-5-(\text{trifluoromethyl})-4,5-\text{dihydroisoxazol}-5-\text{ol (89b)}\)

**Yield:** 88%,  **m.p.** 202 °C  
**IR** \((\nu_{\text{max}}, \text{cm}^{-1})\): 3009 (OH str.), 3292 (NH str.)  
**\(\text{\textsuperscript{1}H NMR}\)** (400 MHz; CDCl\(_3 + \text{DMSO-}d_6\), \(\delta_H\)): 7.14 (d, 2H, 2'', 6''-H, \(J_{H-H} = 8.76\) Hz), 7.54 (d, 2H, 3'', 5''-H, \(J_{H-H} = 8.72\) Hz), 7.64 (d, 2H, 3', 5'-H, \(J_{H-H} = 8.56\) Hz), 7.86 (d, 2H, 2', 6'-H, \(J_{H-H} = 8.52\) Hz), 9.64 (bs, 1H, OH, D\(_2\text{O}\) exchangeable), 10.16 (bs, 1H, NH, D\(_2\text{O}\) exchangeable)  
**\(\text{\textsuperscript{13}C NMR}\)** (100 MHz; CDCl\(_3 + \text{DMSO-}d_6\), \(\delta_C\)): 90.32 (C-4''), 103.40 (q, C-5, \(J_{C-F} = 35.21\) Hz), 121.88 (C-2'', 6''), 126.93 (q, 5-CF\(_3\), \(J_{C-F} = 288.75\) Hz), 129.61 (C-4'), 131.19 (C-1'), 131.61 (C-4), 134.53 (C-2', 6'), 136.86 (C-3', 5'), 142.81 (C-3'', 5''), 148.15 (C-1''), 159.66 (C-3)  
**\(\text{\textsuperscript{19}F NMR}\)** (DMSO-\(d_6\), \(\delta_F\)) \(\delta\): -78.85 (s, 3F, CF\(_3\))

**MS:** m/z 539 (M\(^+\))

**Anal. Calcd** for \(\text{C}_{16}\text{H}_{10}\text{BrF}_{3}\text{IN}_{3}\text{O}_{2}\) (%): C, 35.58; H, 1.87; N, 7.78. Found (%): C, 35.52; H, 1.86; N, 7.73

\((E)-4-((4''-\text{Iodophenyl})\text{diazenyl})-3-\text{phenyl}-5-(\text{trifluoromethyl})-4,5-\text{dihydroisoxazol}-5-\text{ol (89c)}\)

**Yield:** 83%,  **m.p.** 187 °C  
**IR** \((\nu_{\text{max}}, \text{cm}^{-1})\): 3009 (OH str.), 3297 (NH str.)  
**\(\text{\textsuperscript{1}H NMR}\)** (400 MHz; DMSO-\(d_6\), \(\delta_H\)): 7.13 (d, 2H, 2'', 6''-H, \(J_{H-H} = 8.76\) Hz), 7.45-7.47 (m, 3H, 3', 4', 5'-H), 7.52 (d, 2H, 3'', 5''-H, \(J_{H-H} = 8.76\) Hz), 7.90-7.92 (m, 2H, 2', 6'-H), 9.62 (bs, 1H, OH, D\(_2\text{O}\) exchangeable), 10.11 (bs, 1H, NH, D\(_2\text{O}\) exchangeable)  
**\(\text{\textsuperscript{13}C NMR}\)** (100 MHz; DMSO-\(d_6\), \(\delta_C\)): 84.90 (C-4''), 98.39 (q, C-5, \(J_{C-F} = 35.21\) Hz), 116.48 (C-2'', 6''), 121.93 (q, 5-CF\(_3\), \(J_{C-F} = 287.74\) Hz), 126.23 (C-1'), 127.54 (C-3', 5'), 128.45 (C-2', 6'), 132.77 (C-4), 130.44 (C-3'', 5''), 137.54 (C-3'', 5''), 142.97 (C-1''), 155.21 (C-3)  
**\(\text{\textsuperscript{19}F NMR}\)** (DMSO-\(d_6\), \(\delta_F\)): -78.89 (s, 3F, CF\(_3\))

212
MS: m/z 461 (M⁺)

**Anal. Calcd** for C₁₆H₁₁F₃IN₃O₂ (%): C, 41.67; H, 2.40; N, 9.11. Found (%): C, 41.62; H, 2.38; N, 9.03

(E)-3-(4'-Fluorophenyl)-4-(4''-iodophenyl)diazenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89d)

Yield: 83%, m.p. 190-191 °C

IR (ν<sub>max</sub>, cm<sup>-1</sup>): 3008 (OH str.), 3292 (NH str.)

**¹H NMR** (400 MHz; DMSO-d₆, δ<sub>H</sub>): 7.25 (d, 2H, 2'', 6''-H, J<sub>H-H</sub> = 8.84 Hz), 7.38-7.44 (m, 2H, 3', 5'-H), 7.64 (d, 2H, 3'', 5''-H, J<sub>H-H</sub> = 8.84 Hz), 8.00-8.05 (m, 2', 6'-H), 9.84 (bs, 1H, OH, D₂O exchangeable), 10.42 (bs, 1H, NH, D₂O exchangeable)

**¹³C NMR** (100 MHz; DMSO-d₆, δ<sub>C</sub>): 85.65 (C-4''), 98.40 (q, C-5, J<sub>C-F</sub> = 35.21 Hz), 116.01 (d, C-3', 5', J<sub>C-F</sub> = 21.13 Hz), 116.95 (C-2'', 6''), 122.05 (q, 5-CF₃, J<sub>C-F</sub> = 288.75 Hz), 123.25 (d, C-1', 4', J<sub>C-F</sub> = 3.02 Hz), 130.08 (d, C-2', 6', J<sub>C-F</sub> = 9.05 Hz), 132.24 (C-4), 137.23 (C-3'', 5''), 143.14 (C-1''), 154.60 (C-3), 163.45 (d, C-4', J<sub>C-F</sub> = 248.51 Hz)

**¹⁹F NMR** (DMSO-d₆, δ<sub>F</sub>): -78.89 (s, 3F, CF₃), 109.33 (s, 1F, 4''-F)

MS: m/z 473 (M⁺)

**Anal. Calcd** for C₁₆H₁₀F₄IN₃O₂ (%): C, 40.11; H, 2.10; N, 8.77. Found (%): C, 40.08; H, 2.02; N, 8.76

(E)-4-((4''-Iodophenyl)diazenyl)-3-(4'-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydro isoxazol-5-ol (89e)

Yield: 81%, m.p. 182 °C

IR (ν<sub>max</sub>, cm<sup>-1</sup>): 3002 (OH str.), 3297 (NH str.)

**¹H NMR** (400 MHz; DMSO-d₆, δ<sub>H</sub>): 3.79 (s, 3H, 4'-OMe), 7.02 (d, 2H, 3', 5'-H, J<sub>H-H</sub> = 8.76 Hz), 7.17 (d, 2H, 2'', 6''-H, J<sub>H-H</sub> = 8.68 Hz), 7.55 (d, 2H, 2', 6'-H, J<sub>H-H</sub> = 8.64 Hz), 7.87 (d, 2H, 2', 6'-H, J<sub>H-H</sub> = 8.64 Hz), 9.64 (bs, 1H, OH, D₂O exchangeable), 10.17 (bs, 1H, NH, D₂O exchangeable)

**¹³C NMR** (100 MHz; DMSO-d₆, δ<sub>C</sub>): 55.07 (4'-OMe), 85.08 (C-4''), 98.40 (q, C-5,
$^2J_{C,F} = 35.21 \text{ Hz}$, 114.13 (C-3', 5'), 116.69 (C-2'', 6''), 119.00 (C-1'), 122.05 (q, 5-CF$_3$, $^1J_{C,F} = 288.75 \text{ Hz}$), 129.09 (C-2', 6'), 131.61 (C-4), 137.63 (C-3'', 5''), 143.17 (C-1''), 154.67 (C-5), 161.09 (C-4')

$^{19}$F NMR (DMSO-$d_6$, δ$_F$): -78.89 (s, 3F, CF$_3$)

MS: m/z 491 (M$^+$)

Anal. Caled for C$_{16}$H$_{13}$F$_4$IN$_3$O$_3$ (%): C, 41.57; H, 2.67; N, 8.55. Found (%): C, 41.52; H, 2.62; N, 8.52

(E)-4-((4''-Iodophenyl)diazenyl)-3-(naphthalen-2'-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89f)

Yield: 78%, m.p. 201 °C

IR ($\nu_{\text{max}}$, cm$^{-1}$): 3011 (OH str.), 3299 (NH str.)

$^1$H NMR (400 MHz; CDCl$_3$ + DMSO-$d_6$, δ$_H$): 7.22 (d, 2H, 2'', 6''-H, $^1J_{H-H} = 8.60 \text{ Hz}$), 7.53-8.00 (m, 8H, 3'', 5'', 3', 4', 5', 6', 7', 8'-H), 8.62 (s, 1'-H), 9.73 (bs, 1H, OH, D$_2$O exchangeable), 10.27 (bs, 1H, NH, D$_2$O exchangeable)

$^{13}$C NMR (400 MHz; CDCl$_3$ + DMSO-$d_6$, δ$_H$): 85.08 (C-4''), 98.40 (q, C-5, $^2J_{C,F} = 35.21 \text{ Hz}$), 116.69 (C-2'', 6''), 122.05 (q, 5-CF$_3$, $^1J_{C,F} = 288.75 \text{ Hz}$), 124.18, 124.60, 126.16, 126.63, 127.69, 128.87, 129.60, 129.77, 131.95 (C-4), 132.06, 135.84, 137.63 (C-3'', 5''), 143.17 (C-1''), 154.67 (C-5)

$^{19}$F NMR (DMSO-$d_6$, δ$_F$): -78.82 (s, 3F, CF$_3$)

MS: m/z 513 (M$^+$)

Anal. Caled for C$_{20}$H$_{13}$F$_3$IN$_3$O$_2$ (%): C, 46.99; H, 2.56; N, 8.22. Found (%): C, 46.92; H, 2.56; N, 8.20
(E)-4-((4"-Iodophenyl)diazenyl)-3-(naphthalen-1'-yl)-5-(trifluoromethyl)-4,5-dihydro isoxazol-5-ol (89g)

Yield: 78%, m.p. 170 °C

IR (νmax, cm⁻¹): 3007 (OH str.), 3295 (NH str.)

1H NMR (400 MHz; CDCl₃ + DMSO-d₆, δH): 6.28 (d, 2H, 2'', 6''-H, JH-H = 8.80 Hz), 7.34 (d, 2H, 3'', 5''-H, JH-H = 8.76 Hz), 7.46-8.08 (m, 7H, 2', 3', 4', 5', 6', 7, 8'-H), 9.65 (bs, 1H, OH, D₂O exchangeable), 10.19 (bs, 1H, NH, D₂O exchangeable)

13C NMR (100 MHz; CDCl₃ + DMSO-d₆, δC): 85.09 (C-4''), 98.42 (q, C-5, JCF = 35.21 Hz), 116.70 (C-2'', 6''), 122.07 (q, 5-CF₃, JCF = 288.75 Hz), 123.18, 123.60, 124.16, 126.63, 127.70, 128.89, 129.62, 129.79, 131.95 (C-4), 132.08, 135.86, 137.69 (C-3'', 5''), 143.17 (C-1''), 154.67 (C-5)

19F NMR (DMSO-d₆, δF): - 78.83 (s, 3F, CF₃)

MS: m/z 513 (M⁺)

Anal. Calcd for C₂₀H₁₃F₃IN₃O₂ (%): C, 46.99; H, 2.56; N, 8.22. Found (%): C, 46.92; H, 2.56; N, 8.20

(89h)

Yield: 87%, m.p. 178 °C

IR (νmax, cm⁻¹): 3005 (OH str.), 3293 (NH str.)

1H NMR (400 MHz; CDCl₃ + DMSO-d₆, δH): 7.34 (d, 2H, 2'', 6''-H, JH-H = 8.96 Hz), 7.43 (d, 2H, 3'', 5''-H, JH-H = 8.92 Hz), 7.57 (d, 2H, 3', 5'-H, JH-H = 8.56 Hz), 8.00 (d, 2H, 2', 6'-H, JH-H = 8.60 Hz), 9.72 (bs, 1H, OH, D₂O exchangeable), 10.27 (bs, 1H, NH, D₂O exchangeable)

13C NMR (100 MHz; CDCl₃ + DMSO-d₆, δC): 98.52 (q, C-5, JCF = 36.21 Hz), 114.11 (C-4''), 116.23 (C-2'', 6''), 121.89 (q, 5-CF₃, JCF = 288.75 Hz), 125.54 (C-1'), 128.70 (C-3', 5'), 129.09 (C-2', 6'), 131.72 (C-3'', 5''), 132.22 (C-4), 135.72 (C-4'), 142.36 (C-1''), 154.36 (C-3)

19F NMR (DMSO-d₆, δF): - 78.84 (s, 3F, CF₃)

MS: m/z 449 (M⁺)
Anal. Calcd for C_{16}H_{10}BrClF_{3}N_{3}O_{2} (%): C, 42.84; H, 2.25; N, 9.37. Found (%): C, 42.82; H, 2.22; N, 9.32

\( (E) \)-3-(4'-Bromophenyl)-4-((4''-bromophenyl)diazenyl)-5-(trifluoromethyl)-4,5-dihydro isoxazol-5-ol (89i)

Yield: 89%, m.p. 174 °C
IR (ν_{max}, cm^{-1}): 3006 (OH str.), 3296 (NH str.)
\(^1\)H NMR (400 MHz; CDCl\(_3\) + DMSO-\(d_6\), δ\(_H\)): 7.36 (d, 2H, 2'', 6''-H, \(^1\)J\(_{H-H} = 8.92\) Hz), 7.45 (d, 2H, 3'', 5''-H, \(^1\)J\(_{H-H} = 8.88\) Hz), 7.73 (d, 2H, 3', 5'-H, \(^1\)J\(_{H-H} = 8.56\) Hz), 7.93 (d, 2H, 2', 6'-H, \(^1\)J\(_{H-H} = 8.56\) Hz), 9.77 (bs, 1H, OH, D\(_2\)O exchangeable), 10.35 (bs, 1H, NH, D\(_2\)O exchangeable)
\(^13\)C NMR (100 MHz; CDCl\(_3\) + DMSO-\(d_6\), δ\(_C\)): 98.54 (q, C-5, \(^2\)J\(_{C-F} = 36.21\) Hz), 114.10 (C-4''), 116.38 (C-2'', 6''), 121.93 (q, 5-CF\(_3\), \(^1\)J\(_{C-F} = 288.75\) Hz), 124.35 (C-4'), 125.97 (C-1'), 129.39 (C-2', 6'), 131.72 (C-3', 5'), 131.76 (C-3'', 5''), 132.06 (C-4), 142.46 (C-1''), 154.53 (C-3)
\(^1^9\)F NMR (DMSO-\(d_6\), δ\(_F\)): -78.83 (s, 3F, CF\(_3\))
MS: m/z 493 (M\(^+\))

Anal. Calcd for C_{16}H_{10}BrF_{3}N_{3}O_{2} (%): C, 38.97; H, 2.04; N, 8.52. Found (%): C, 38.92; H, 2.02; N, 8.49

\( (E) \)-4-((4'-Bromophenyl)diazenyl)-3-phenyl-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89j)

Yield: 86%, m.p. 172 °C
IR (ν_{max}, cm^{-1}): 3002 (OH str.), 3294 (NH str.)
\(^1\)H NMR (400 MHz; CDCl\(_3\) + DMSO-\(d_6\), δ\(_H\)): 7.35 (d, 2H, 2'', 6''-H, \(^1\)J\(_{H-H} = 8.88\) Hz), 7.44 (d, 2H, 3'', 5''-H, \(^1\)J\(_{H-H} = 8.88\) Hz), 7.52-7.56 (m, 3H, 3', 4', 5'-H), 7.96-7.99 (m, 2H, 2', 6'-H), 9.73 (bs, 1H, OH, D\(_2\)O exchangeable), 10.30 (bs, 1H, NH, D\(_2\)O exchangeable)
\(^13\)C NMR (100 MHz; CDCl\(_3\) + DMSO-\(d_6\), δ\(_C\)): 98.38 (q, C-5, \(^2\)J\(_{C-F} = 36.22\) Hz), 113.98 (C-4''), 116.22 (C-2'', 6''), 121.99 (q, 5-CF\(_3\), \(^1\)J\(_{C-F} = 287.74\) Hz), 126.84 (C-1''), 127.59 (C-3', 5'), 128.56 (C-2', 6'), 130.52 (C-4'), 131.75 (C-3'', 5''), 132.59 (C-4), 142.54 (C-1''), 155.33 (C-3)
F NMR (DMSO-\textit{d}_6, \delta_F): -78.89 (s, 3F, CF\textsubscript{3})

**MS:** m/z 415 (M\textsuperscript{+})

**Anal. Calcd** for C\textsubscript{16}H\textsubscript{11}BrF\textsubscript{3}N\textsubscript{3}O\textsubscript{2} (%): C, 46.40; H, 2.68; N, 10.15. Found (%): C, 46.37; H, 2.62; N, 10.12

\((E)-3-(4'-Fluorophenyl)-4-((4''-iodophenyl)diazenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89k)

**Yield:** 85%, **m.p.** 176 °C

**IR** (\(\nu_{\text{max}}, \text{cm}^{-1}\)): 3007 (OH str.), 3295 (NH str.)

**1H NMR** (400 MHz; CDCl\textsubscript{3} + DMSO-\textit{d}_6, \delta_H): 7.31-7.36 (m, 4H, 3', 5', 2'', 6'' -H, \(1\text{J}_{\text{H-H}} = 8.80 \text{ Hz}\)), 7.44 (d, 3'', 5''-H, \(1\text{J}_{\text{H-H}} = 8.84 \text{ Hz}\)), 8.02-9.05 (m, 2', 6' -H), 9.73 (bs, 1H, OH, D\textsubscript{2}O exchangeable), 10.31 (bs, 1H, NH, D\textsubscript{2}O exchangeable)

**13C NMR** (100 MHz; CDCl\textsubscript{3} + DMSO-\textit{d}_6, \delta_C): 98.41 (q, C-5, \(2\text{J}_{\text{C-F}} = 36.22 \text{ Hz}\)), 114.04 (C-4''), 115.70 (d, 3', 5'-C, \(2\text{J}_{\text{C-F}} = 22.13 \text{ Hz}\)), 116.28 (C-2'', 6''), 121.94 (q, 5-CF\textsubscript{3}, \(1\text{J}_{\text{C-F}} = 288.75 \text{ Hz}\)), 123.21 (d, C-1', \(4\text{J}_{\text{C-F}} = 4.02 \text{ Hz}\)), 129.87 (d, C-2', 6', \(3\text{J}_{\text{C-F}} = 9.05 \text{ Hz}\)), 131.73 (C-3''', 5'''), 132.40 (C-4), 142.46 (C-1''), 154.40 (C-3), 163.43 (d, C-4', \(1\text{J}_{\text{C-F}} = 249.51 \text{ Hz}\))

\(^{19}\text{F NMR}\) (DMSO-\textit{d}_6, \delta_F): \(-78.89\) (s, 3F, CF\textsubscript{3}), \(-109.38\) (s, 1F, 4''-F)

**MS:** m/z 431 (M\textsuperscript{+})

**Anal. Calcd** for C\textsubscript{16}H\textsubscript{10}BrF\textsubscript{4}N\textsubscript{3}O\textsubscript{2} (%): C, 44.47; H, 2.33; N, 9.72. Found (%): C, 44.43; H, 2.32; N, 9.70

\((E)-4-((4''-Bromophenyl)diazenyl)-3-(4'-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89l)

**Yield:** 84%, **m.p.** 172-173 °C

**IR** (\(\nu_{\text{max}}, \text{cm}^{-1}\)): 3009 (OH str.), 3295 (NH str.)

**1H NMR** (400 MHz; CDCl\textsubscript{3} + DMSO-\textit{d}_6, \delta_H): 7.06 (d, 2H, 3', 5'-H, \(1\text{J}_{\text{H-H}} = 8.88 \text{ Hz}\)), 7.32 (d, 2H, 2'', 6'' -H, \(1\text{J}_{\text{H-H}} = 8.88 \text{ Hz}\)), 7.43 (d, 2H, 3'', 5''-H, \(1\text{J}_{\text{H-H}} = 8.88 \text{ Hz}\)), 7.95 (d, 2H, 2', 6'-H), 9.46 (bs, 1H, OH, D\textsubscript{2}O exchangeable), 10.15 (bs, 1H, NH, D\textsubscript{2}O exchangeable)

**13C NMR** (100 MHz; CDCl\textsubscript{3} + DMSO-\textit{d}_6, \delta_C): 55.07 (4'-OMe), 98.13 (q, C-5, \(2\text{J}_{\text{C-F}} = \))
35.21 Hz), 113.87 (C-4''), 113.92 (C-3', 5'), 116.01 (C-2'', 6''), 118.98 (C-1'), 121.94 (q, 5-CF₃, \(^{1}J_{C,F} = 287.74\) Hz), 129.00 (C-2', 6'), 131.70 (C-3'', 5''), 133.18 (C-4), 142.44 (C-1''), 154.57 (C-3), 161.03 (C-4'')

\(^{19}\)F NMR (DMSO-\(d_6, \delta_F\)): - 78.89 (s, 3F, CF₃)

**MS**: m/z 445 (M')

**Anal. Calcd** for C₁₇H₁₃BrF₃N₃O₃ (%): C, 45.97; H, 2.95; N, 9.46. Found (%): C, 45.93; H, 2.93; N, 9.42

\((E)-4-((4''-Bromophenyl)diazenyl)-3-(naphthalen-2'-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89m)\)

\[\text{Yield: 79\% , m.p. 179} ^\circ\text{C}\]

**IR** (v\(_{\text{max}}, \text{cm}^{-1}\)): 3009 (OH str.), 3299 (NH str.)

\(^{1}\)H NMR (400 MHz; CDCl₃ + DMSO-\(d_6, \delta_H\)): 7.40 (m, 2H, 2'', 6''-H, \(^{1}J_{H-H} = 8.92\) Hz), 7.48 (d, 2H, 3'', 5''-H, \(^{1}J_{H-H} = 8.88\) Hz), 7.58-8.21 (m, 6H, 3', 4', 5', 6', 7', 8'-H), 8.68 (s, 1H, 1'-H), 9.78 (bs, 1H, OH, D₂O exchangeable), 10.39 (bs, 1H, NH, D₂O exchangeable)

\(^{13}\)C NMR (100 MHz; CDCl₃ + DMSO-\(d_6, \delta_C\)): 98.16 (q, C-5, \(^{2}J_{C,F} = 35.21\) Hz), 113.89 (C-4''), 116.06 (C-2'', 6''), 121.98 (q, 5-CF₃, \(^{1}J_{C,F} = 287.74\) Hz), 124.17, 124.62, 126.18, 126.69, 127.71, 128.87, 129.60, 129.77, 131.70 (C-3'', 5''), 132.06, 133.18 (C-4), 135.84, 142.44 (C-1''), 154.57 (C-3)

\(^{19}\)F NMR (DMSO-\(d_6, \delta_F\)): - 78.89 (s, 3F, CF₃)

**MS**: m/z 463 (M')

**Anal. Calcd** for C₂₀H₁₃BrF₃IN₃O₂ (%): C, 51.74; H, 2.82; N, 9.05. Found (%): C, 51.72; H, 2.80; N, 9.02

\((E)-4-((4''-Bromophenyl)diazenyl)-3-(naphthalen-1'-yl)-5-(trifluoromethyl)-4,5-dihydro isoxazol-5-ol (89n)\)

\[\text{Yield: 73\% , m.p. 170} ^\circ\text{C}\]

**IR** (v\(_{\text{max}}, \text{cm}^{-1}\)): 3009 (OH str.), 3296 (NH str.)

\(^{1}\)H NMR (400 MHz; CDCl₃ + DMSO-\(d_6, \delta_H\)): 7.04 (d, 2'', 6''-H, \(^{1}J_{H-H} = 8.92\) Hz), 7.27 (d, 3'', 5''-H, \(^{1}J_{H-H} = 8.88\) Hz), 7.57-8.12 (m, 7H, 2', 3', 4', 5', 6', 7', 8'-H), 9.76 (bs, 1H, OH, D₂O exchangeable), 10.38 (bs, 1H, NH, D₂O exchangeable)
\[ ^{13}\text{C NMR} \ (100 \text{ MHz}; \text{CDCl}_3 + \text{DMSO-}d_6, \delta_C) : 98.18 \text{ (q, C-5, } ^2J_{C-F} = 35.21 \text{ Hz)}, \\
113.91 \text{ (C-4''), 116.09 \text{ (C-2'', 6''), 121.99 \text{ (q, 5-CF}_3, \ ^1J_{C-F} = 287.74 \text{ Hz)}, 123.20,} \\
123.62, 124.18, 126.69, 127.70, 128.79, 129.62, 129.79, \ 131.72 \text{ (C-3'', 5''), 132.08,} \\
133.19 \text{ (C-4), 135.86, 142.44 \text{ (C-1''), 154.60 \text{ (C-3)}} \]

\[ ^{19}\text{F NMR} \ (\text{DMSO-}d_6, \delta_F) : -78.83 \text{ (s, 3F, CF}_3) \]

\textbf{MS: m/z 463 (M\textsuperscript{+})}

\textbf{Anal. Calcd} for C\textsubscript{20}H\textsubscript{13}BrF\textsubscript{3}IN\textsubscript{3}O\textsubscript{2} (%): C, 51.74; H, 2.82; N, 9.05. Found (%): C, 51.72; H, 2.80; N, 9.02

\[(E)-3-(4'-\text{Chlorophenyl})-4-((4''-\text{chlorophenyl})\text{diazenyl})-5-(\text{trifluoromethyl})-4,5\text{-dihydroisoxazol}-5\text{-ol (89aa)}\]

\textbf{Yield: 89 \%}, \textbf{m.p. 169 \degree C}

\textbf{IR (}\nu_{\text{max}}, \text{ cm}^{-1}): 2995 \text{ (OH str.), 3293 \text{ (NH str.)}}

\[ ^1\text{H NMR} \ (400 \text{ MHz}; \text{CDCl}_3 + \text{DMSO-}d_6, \delta_H) : 7.33 \text{ (d, 2H, 2'', 6''-H, } ^1J_{H-H} = 8.92 \text{ Hz)}, 7.43 \text{ (d, 2H, 3'', 5''-H,} \\
^1J_{H-H} = 8.88 \text{ Hz)}, 7.61 \text{ (d, 2H, 3', 5'-H, } ^1J_{H-H} = 8.52 \text{ Hz)}, 8.00 \text{ (d, 2H, 2', 6'-H, } ^1J_{H-H} = 8.56 \text{ Hz)}, 9.80 \text{ (bs,} \\
1\text{H, OH, D}_2\text{O exchangeable), 10.41 \text{ (bs, 1H, NH, D}_2\text{O exchangeable)}}

\[ ^{13}\text{C NMR} \ (100 \text{ MHz}; \text{CDCl}_3 + \text{DMSO-}d_6, \delta_C) : 98.52 \text{ (q, C-5, } ^2J_{C-F} = 35.21 \text{ Hz)}, \\
116.00 \text{ (C-2'', 6''), 121.99 \text{ (q, 5-CF}_3, \ ^1J_{C-F} = 288.75 \text{ Hz)}, 125.60 \text{ (C-1'), 126.28 \text{ (C-4),} } \\
128.85 \text{ (C-3', 5'), 128.92 \text{ (C-3'', 5''), 129.25 \text{ (C-2', 6'), 131.91 \text{ (C-4'')}}, 135.62 \text{ (C-4')}}, \\
142.10 \text{ (C-1''), 154.50 \text{ (C-3)}} \]

\[ ^{19}\text{F NMR} \ (\text{DMSO-}d_6, \delta_F) : -78.89 \text{ (s, 3F, CF}_3) \]

\textbf{MS: m/z 405 (M\textsuperscript{+})}

\textbf{Anal. Calcd} for C\textsubscript{16}H\textsubscript{10}Cl\textsubscript{2}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2} (%): C, 47.55; H, 2.49; N, 10.40. Found (%): C,
(E)-3-(4'-Bromophenyl)-4-((4''-chlorophenyl)diazenyl)-5-(trifluoromethyl)-4,5-dihydro isoxazol-5-ol (89ab)

**Yield:** 90%, **m.p.** 170 °C

**IR** ($\nu_{\text{max}}$, cm$^{-1}$): 2997 (OH str.), 3295 (NH str.)

**$^1$H NMR** (400 MHz; CDCl$_3$ + DMSO-$d_6$, $\delta_H$): 7.32 (d, 2H, 2'', 6''-H, $^1J_{H-H} = 8.92$ Hz), 7.42 (d, 2H, 3'', 5'-H, $^1J_{H-H} = 8.56$ Hz), 7.75 (d, 2H, 3', 5'-H, $^1J_{H-H} = 8.56$ Hz), 7.92 (d, 2H, 2', 6'-H, $^1J_{H-H} = 8.52$ Hz), 9.79 (bs, 1H, OH, D$_2$O exchangeable), 10.40 (bs, 1H, NH, D$_2$O exchangeable)

**$^{13}$C NMR** (100 MHz; CDCl$_3$ + DMSO-$d_6$, $\delta_C$): 98.34 (q, C-5, $^2J_{C-F} = 36.21$ Hz), 116.00 (C-2'', 6''), 121.93 (q, 5-CF$_3$, $^1J_{C-F} = 288.75$), 124.34 (C-4'), 125.98 (C-1'), 126.27 (C-4), 128.92 (C-3'', 5''), 129.44 (C-2', 6'), 131.77 (C-3', 5'), 131.83 (C-4''), 142.08 (C-1''), 154.58 (C-3)

**$^{19}$F NMR** (DMSO-$d_6$, $\delta_F$): -78.81 (s, 3F, CF$_3$)

**MS:** m/z 449 (M$^+$)

**Anal. Calcd** for C$_{16}$H$_{10}$BrClF$_3$N$_3$O$_2$ (%): C, 42.84; H, 2.25; N, 9.37. Found (%): C, 42.82; H, 2.22; N, 9.31

(E)-4-((4''-Chlorophenyl)diazenyl)-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-isoxazol-5-ol (89ac)

**Yield:** 80%, **m.p.** 165°C

**IR** ($\nu_{\text{max}}$, cm$^{-1}$): 2998 (OH str.), 3293 (NH str.)

**$^1$H NMR** (400 MHz; CDCl$_3$ + DMSO-$d_6$, $\delta_H$): 7.30 (d, 2H, 2'', 6''-H, $^1J_{H-H} = 8.56$ Hz), 7.39 (d, 2H, 3'', 5''-H, $^1J_{H-H} = 8.56$ Hz), 7.55 (appeared as singlet, 3H, 3', 4', 5'-H), 7.98-7.99 (m, 2H, 2', 6'-H), 9.74 (bs, 1H, OH, D$_2$O exchangeable), 10.27 (bs, 1H, NH, D$_2$O exchangeable)

**$^{13}$C NMR** (100 MHz; CDCl$_3$ + DMSO-$d_6$, $\delta_C$): 98.34 (q, C-5, $^2J_{C-F} = 36.21$ Hz), 116.00 (C-2'', 6''), 121.93 (q, CF$_3$, $J = 288.75$), 128.92 (C-3'', 5''), 131.83 (C-4''), 142.08 (C-1''), 154.58 (C-3)

**$^{19}$F NMR** (DMSO-$d_6$, $\delta_F$): -78.84 (s, 3F, CF$_3$)
CHAPTER-3 RESULTS AND DISCUSSION

MS: m/z 369 (M⁺)

**Anal. Calcd** for C₁₆H₁₁ClF₃N₃O₂ (%): C, 51.98; H, 3.0; N, 11.37. Found (%): C, 51.90; H, 2.98; N, 11.34

**Yield:** 81%, **m.p.** 162 °C

**IR** (ν_{max}, cm⁻¹): 2998 (OH str.), 3297 (NH str.)

**¹H NMR** (400 MHz; CDCl₃ + DMSO-d₆, δH): 7.30-7.37 (m, 4H, 3', 5', 2'', 6''-H), 7.41 (d, 2H, 3'', 5''-H, ¹J_H-H = 8.76 Hz), 8.02-8.05 (m, 2H, 2', 6'-H), 9.77 (bs, 1H, OH, D₂O exchangeable), 10.34 (bs, 1H, NH, D₂O exchangeable)

**¹³C NMR** (100 MHz; CDCl₃ + DMSO-d₆, δC): 98.40 (q, C-5, ²J_C-F = 35.21 Hz), 115.75 (d, C-3', 5', ³J_C-F = 22.13 Hz), 115.89 (C-2'', 6''), 121.99 (q, 5-CF₃, ¹J_C-F = 288.75 Hz), 123.24 (d, C-1', ⁴J_C-F = 3.02 Hz), 126.24 (C-4), 128.88 (C-3'', 5''), 129.90 (d, C-2', 6', ³J_C-F = 8.05 Hz), 132.23 (C-4''), 142.08 (C-1''), 154.44 (C-3), 163.43 (d, C-4', ¹J_C-F = 249.51 Hz)

**¹⁹F NMR** (DMSO-d₆, δF): - 78.81 (s, 3F, CF₃), 109.39 (s, 1F, 4''-F)

**MS:** m/z 387 (M⁺)

**Anal. Calcd** for C₁₆H₁₀ClF₄N₃O₂ (%): C, 49.56; H, 2.60; N, 10.84. Found (%): C, 49.52; H, 2.54; N, 10.82

**Yield:** 83%, **m.p.** 165 °C

**IR** (ν_{max}, cm⁻¹): 2995 (OH str.), 3299 (NH str.)

**¹H NMR** (400 MHz; CDCl₃ + DMSO-d₆, δH): 7.09 (d, 2H, 3', 5'-H, ¹J_H-H = 8.76 Hz), 7.32 (d, 2H, 2'', 6''-H, ¹J_H-H = 8.80 Hz), 7.41 (d, 2H, 3'', 5''-H, ¹J_H-H = 8.84 Hz), 7.95 (d, 2H, 2', 6'-H), 9.71 (bs, 1H, OH, D₂O exchangeable), 10.41 (bs, 1H, NH, D₂O exchangeable)

**¹³C NMR** (100 MHz; CDCl₃ + DMSO-d₆, δC): 55.15 (OMe), 98.14 (q, C-5, ²J_C-F = 35.21 Hz), 114.06 (C-3', 5'), 119.01 (C-1'), 122.06 (q, CF₃, ¹J_C-F = 288.75 Hz), 123.24 (d, C-1', ⁴J_C-F = 3.02 Hz), 126.24 (C-4), 128.88 (C-3'', 5''), 129.90 (d, C-2', 6', ³J_C-F = 8.05 Hz), 132.23 (C-4''), 142.08 (C-1''), 154.44 (C-3), 163.43 (d, C-4', ¹J_C-F = 249.51 Hz)

**D₂O exchangeable**, 10.41 (bs, 1H, NH, D₂O exchangeable)

**¹³C NMR** (100 MHz; CDCl₃ + DMSO-d₆, δC): 55.15 (OMe), 98.14 (q, C-5, ²J_C-F = 35.21 Hz), 114.06 (C-3', 5'), 119.01 (C-1'), 122.06 (q, CF₃, ¹J_C-F = 35.21 Hz)
287.74 Hz), 126.07 (C-4), 128.89 (C-3'', 5''), 129.06 (C-2', 6'), 132.92 (C-4''), 142.17 (C-1''), 154.66 (C-3), 161.05 (C-4')

\(^{19}\text{F NMR}\) (DMSO-\(d_6\), \(\delta_F\)): - 78.87 (s, 3F, CF\(_3\))

**MS:** m/z  399 (M\(^+\))

**Anal. Calcd** for C\(_{17}\)H\(_{13}\)ClF\(_3\)N\(_3\)O\(_3\) (%): C, 51.08; H, 3.28; N, 10.51. Found (%): C, 51.03; H, 3.27; N, 10.48

\((E)-4-((4''-\text{Chlorophenyl})\text{diazenyl})-3-(\text{naphthalen}-2'-yl)-5-(\text{trifluoromethyl})-4,5-\text{dihydroisoxazol}-5-\text{ol} \ (89af)\)

![Diagram](image)

**Yield:** 76% ,  **m.p.** 162 \(^\circ\)C

**IR** (\(\nu_{\text{max}}, \text{cm}^{-1}\)): 2999 (OH str.), 3299 (NH str.)

\(^1\text{H NMR}\) (400 MHz; CDCl\(_3\) + DMSO-\(d_6\), \(\delta_H\)): 7.35 (d, 2H, 2'', 6'', \(J_{H-H} = 8.84\) Hz), 7.47 (d, 2H, 2'', 6''-H, \(J_{H-H} = 8.92\) Hz), 7.59-8.22 (m, 6H, 3', 4', 5', 6', 7', 8'-H), 8.69 (s, 1H, 1'-H), 9.79 (bs, 1H, NH, D\(_2\)O exchangeable), 10.40 (bs, 1H, NH, D\(_2\)O exchangeable)

\(^{13}\text{C NMR}\) (100 MHz; CDCl\(_3\) + DMSO-\(d_6\), \(\delta_C\)): 98.16 (q, C-5, \(J_{C-F} = 35.21\) Hz), 115.77 (C-2'', 6''), 122.09 (q, 4-CF\(_3\), \(J_{C-F} = 287.74\) Hz), 124.19, 124.63, 126.09 (C-4), 126.19, 126.70, 127.72, 128.87, 128.89 (C-3'', 5''), 129.61, 129.77, 132.06, 132.92 (C-4''), 135.84, 142.17 (C-1''), 154.67 (C-3)

\(^{19}\text{F NMR}\) (DMSO-\(d_6\), \(\delta_F\)): - 78.91 (s, 3F, CF\(_3\))

**MS:** m/z  419 (M\(^+\))

**Anal. Calcd** for C\(_{20}\)H\(_{10}\)ClF\(_4\)N\(_3\)O\(_2\) (%): C, 57.22; H, 3.12; N, 10.01. Found (%): C, 57.19; H, 3.13; N, 9.98

\((E)-4-((4''-\text{Chlorophenyl})\text{diazenyl})-3-(\text{naphthalen}-1'-yl)-5-(\text{trifluoromethyl})-4,5-\text{dihydroisoxazol}-5-\text{ol} \ (89ag)\)

![Diagram](image)

**Yield:** 73% ,  **m.p.** 160 \(^\circ\)C

**IR** (\(\nu_{\text{max}}, \text{cm}^{-1}\)): 2994 (OH str.), 3298 (NH str.)

\(^1\text{H NMR}\) (400 MHz; CDCl\(_3\) + DMSO-\(d_6\), \(\delta_H\)): 7.00-8.18 (m, 11H, 2', 3', 4', 5', 6', 7', 8', 3'', 5'', 2'', 6''-H), 9.66 (bs, 1H, OH, D\(_2\)O exchangeable), 10.24 (bs, 1H, NH or OH, D\(_2\)O exchangeable)

\(^{13}\text{C NMR}\) (400 MHz; CDCl\(_3\) + DMSO-\(d_6\), \(\delta_H\)): 98.16 (q, 2''-C, \(J_{C-C} = 35.21\) Hz), 115.77 (C-2', 6'), 122.09 (q, 4-CF\(_3\), \(J_{C-C} = 287.74\) Hz), 124.19, 124.63, 126.09 (C-4), 126.19, 126.70, 127.72, 128.87, 128.89 (C-3', 5'), 129.61, 129.77, 132.06, 132.92 (C-4''), 135.84, 142.17 (C-1''), 154.67 (C-3)
(q, C-5, $^2J_{C,F} = 35.21$ Hz), 115.77 (C-2'', 6''), 122.09 (q, 4-CF$_3$, $^1J_{C,F} = 287.74$ Hz), 123.20, 123.62, 124.18, 126.09 (C-4), 126.69, 127.70, 128.89 (C-3'', 5''), 128.91, 129.62, 129.79, 132.08, 132.92 (C-4''), 135.86, 142.17 (C-1''), 154.67 (C-3)

$^{19}$F NMR (DMSO-$d_6$, $\delta_F$): - 78.90 (s, 3F, CF$_3$)

MS: m/z 419 (M$^+$)

Anal. Calcd for C$_{20}$H$_{10}$ClF$_4$N$_3$O$_2$ (%): C, 57.22; H, 3.12; N, 10.01. Found (%): C, 57.19; H, 3.13; N, 9.98

(E)-3-(4''-Chlorophenyl)-4-((4'-fluorophenyl)diazenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol ($89ah$)

Yield: 86 %, m.p. 140 °C, Lit m.p. 140-141 °C [39]

IR ($\nu_{max}$, cm$^{-1}$): 3128 (OH str.), 3318 (NH str.)

$^1$H NMR (300 MHz; CDCl$_3$, $\delta_H$): 3.78 (bs, 1H, OH, D$_2$O exchangeable), 6.95–6.97 (m, 4H, 2'', 3'', 5'' and 6''-H), 7.30 (d, 2H, 3', 5'-H, $J = 7.8$ Hz), 7.77 (d, 2H, 2', 6'-H, $J = 7.5$ Hz), 9.15 (bs, 1H, NH, D$_2$O exchangeable)

$^{13}$C NMR (100 MHz; CDCl$_3$, $\delta_C$): 98.53 (q, C-5, $^2J_{C,F} = 38.25$ Hz), 115.26 (d, C-2'', 6'', $^3J_{C,F} = 8.25$ Hz), 116.38 (d, C-3'', 5'', $^2J_{C,F} = 23.25$ Hz), 121.73 (q, CF$_3$, $^1J_{C,F} = 287.25$ Hz), 124.59 (C-1''), 128.94 (C-3', 5'), 129.34 (C-2', 6'), 131.28 (C-4), 137.35 (C-4''), 138.18 (d, C-1'', $^4J_{C,F} = 3.00$ Hz), 155.05 (C-3), 159.17 (d, C-4'', $^1J_{C,F} = 240.75$ Hz)

$^{19}$F NMR (DMSO-$d_6$, $\delta_F$): - 78.90 (s, 3F, CF$_3$), 109.36 (s, 1F, 4''-F)

MS: m/z 387 (M$^+$)

Anal. Calcd for C$_{16}$H$_{10}$ClF$_4$N$_3$O$_2$ (%): C, 49.56; H, 2.60; N, 10.84. Found (%): C, 49.51; H, 2.52; N, 10.82

(E)-3-(4''-Bromophenyl)-4-((4'-fluorophenyl)diazenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol ($89ai$)
Yield: 89%, m.p. 165 °C, Lit m.p. 166 °C [39]
IR (ν_{max}, cm^{-1}): 3129 (OH str.), 3320 (NH str.)

\(^1\)H NMR (300 MHz; CDCl\(_3\), δ\(_{H}\)): 3.78 (bs, 1H, OH, D\(_2\)O exchangeable), 7.03-7.10 (m, 4H, 2'', 3'', 5'' and 6''-H), 7.56 (d, 2H, 3', 5'-H, \(^1\)J\(_{H-H} = 8.1 \text{ Hz}\)), 7.80 (d, 2H, 2', 6'-H, \(^1\)J\(_{H-H} = 8.4 \text{ Hz}\)), 9.21 (bs, 1H, NH, D\(_2\)O exchangeable)

\(^13\)C NMR (100 MHz; CDCl\(_3\), δ\(_{C}\)): 98.75 (q, C-5, \(^2\)J\(_{C-F} = 38.25 \text{ Hz}\)), 115.27 (d, C-2'', 6'', \(^3\)J\(_{C-F} = 8.25 \text{ Hz}\)), 116.43 (d, C-3'', 5'', \(^2\)J\(_{C-F} = 23.25 \text{ Hz}\)), 121.75 (q, CF\(_3\), \(^1\)J\(_{C-F} = 285.75 \text{ Hz}\)), 125.12 (C-4'), 125.77 (C-1'), 129.54 (C-2', 6'), 131.32 (C-4), 131.93 (C-3', 5'), 138.18 (d, C-1'', \(^4\)J\(_{C-F} = 3 \text{ Hz}\)), 155.13 (C-3), 159.18 (d, C-4'', \(^1\)J\(_{C-F} = 240.75 \text{ Hz}\))

\(^19\)F NMR (DMSO-\(d_6\), δ\(_{F}\)): -78.89 (s, 3F, CF\(_3\)), 109.37 (s, 1F, 4''-F)

MS: m/z 433 (M\(^+\))

Anal. Calcd for C\(_{16}\)H\(_{10}\)BrF\(_4\)N\(_3\)O\(_2\) (%): C, 44.47; H, 2.33; N, 9.72. Found (%): C, 44.42; H, 2.32; N, 9.71

\((E)-4-((4''-Fluorophenyl)diazenyl)-3-phenyl-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89aj)\)
(d, C-1', $^4J_{C-F} = 285.75$), 128.58 (d, C-2', 6', $^3J_{C-F} = 8.25$ Hz), 128.16 (d, 3', 5'-H, $^2J_{C-F} = 21.75$ Hz), 130.98 (d, C-4', $^1J_{C-F} = 249.75$ Hz), 132.11 (C-4), 138.45 (d, C-1'', $^4J_{C-F} = 3.00$ Hz), 156.02 (C-3), 158.96 (C-4'')

$^{19}$F NMR (DMSO-$d_6$, $\delta_F$): -78.81 (s, 3F, CF$_3$), 109.36 (s, 1F, 4''-F)

**MS:** m/z 353 (M$^+$)

**Anal. Caled** for C$_{16}$H$_{11}$F$_4$N$_3$O$_2$ (%): C, 54.40; H, 3.14; N, 11.89. Found (%): C, 54.32; H, 3.12; N, 11.82

(E)-3-(4'-Fluorophenyl)-4-((4'-fluorophenyl)diazenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89ak)

Yield: 78%, m.p. 169-170 °C, Lit m.p. 170 °C [39]

**IR** ($\nu_{max}$, cm$^{-1}$): 3130 (OH str.), 3328 (NH str.)

$^1$H NMR (300 MHz; CDCl$_3$, $\delta_H$): 3.82 (bs, 1H, OH, D$_2$O exchangeable) 7.06-7.18 (m, 6H, 3', 5', 2'', 3'', 5'', 6''-H), 7.97 (dd, 2H, 2', 6'-H, $^1J_{H-H} = 7.6$ Hz, $^4J_{H-F} = 3.3$ Hz), 9.23 (bs, 1H, NH, D$_2$O exchangeable)

$^{13}$C NMR (100 MHz; CDCl$_3$, $\delta_C$): 98.97 (q, C-5, $^2J_{C-F} = 36.00$ Hz), 114.93 (d, C-2'', 6'', $^3J_{C-F} = 7.50$ Hz), 115.65 (C-3', 5'), 116.06 (d, C-3'', 5'', $^2J_{C-F} = 23.25$ Hz), 122.13 (q, CF$_3$, $^1J_{C-F} = 287.25$ Hz), 123.23 (C-1'), 129.91 (C-2', 6'), 133.27 (C-4), 138.79 (d, C-1'', $^4J_{C-F} = 3.0$ Hz), 154.52 (C-3), 158.59 (d, C-4'', $^1J_{C-F} = 240.75$ Hz), 164.02 (C-4'')

$^{19}$F NMR (DMSO-$d_6$, $\delta_F$): -78.89 (s, 3F, CF$_3$), 109.36 (s, 1F, 4''-F)

**MS:** m/z 371 (M$^+$)

**Anal. Caled** for C$_{16}$H$_{10}$F$_5$N$_3$O$_2$ (%): C, 51.76; H, 2.71; N, 11.32. Found (%): C, 51.72; H, 2.64; N, 11.30

(E)-4-((4''-Fluorophenyl)diazenyl)-3-(4'-methoxyphenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89al)
RESULTS AND DISCUSSION

Yield: 80 %, m.p. 143 °C, Lit m.p. 145-146 °C [39]
IR (v<sub>max</sub>, cm<sup>-1</sup>): 3123 (OH str.), 3320 (NH str.)

<sup>1</sup>H NMR (300 MHz; CDC<sub>3</sub>, δ<sub>H</sub>): 3.81 (bs, 1H, OH, D<sub>2</sub>O exchangeable), 3.83 (s, 3H, OCH<sub>3</sub>), 6.92 (d, 2H, 3', 5'-H, J<sub>H-H</sub> = 8.4 Hz), 7.02-7.05 (m, 4H, 2'', 3'', 5'' and 6''-H), 7.90 (d, 2H, 2', 6'-H, J<sub>H-H</sub> = 8.4 Hz), 9.22 (bs, 1H, NH, D<sub>2</sub>O exchangeable)

<sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>, δ<sub>C</sub>): 55.32 (4''-OMe), 98.86 (q, C-5, J<sub>C-F</sub> = 36 Hz), 113.99 (C-3', 5'), 115.11 (d, C-2'', 6'', J<sub>C-F</sub> = 7.5 Hz), 116.20 (d, C-3'', 5'', J<sub>C-F</sub> = 22.25 Hz), 118.71 (C-1'), 122.08 (q, CF<sub>3</sub>, J<sub>C-F</sub> = 285.75), 129.60 (C-2', 6'), 132.44 (C-4), 138.53 (d, C-1'', J<sub>C-F</sub> = 3 Hz), 155.15 (C-3), 158.77 (d, C-4'', J<sub>C-F</sub> = 240.75 Hz), 161.61 (C-4')

<sup>19</sup>F NMR (DMSO-<sup>d</sup><sub>6</sub>, δ<sub>F</sub>): - 78.85 (s, 3F, CF<sub>3</sub>), 109.37 (s, 1F, 4''-F)
MS: m/z 383 (M<sup>+</sup>)


(E)-4-(((4''-Fluorophenyl)diazenyl)-3-(naphthalen-2'-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89am)

Yield: 78%, m.p. 159 °C
IR (v<sub>max</sub>, cm<sup>-1</sup>): 3129 (OH str.), 3323 (NH str.)

<sup>1</sup>H NMR (300 MHz; CDC<sub>3</sub>, δ<sub>H</sub>): 3.81 (bs, 1H, OH, D<sub>2</sub>O exchangeable), 7.02-7.05 (m, 4H, 2'', 3'', 5'' and 6''-H), 7.53-8.00 (m, 7H, 2', 3', 4', 5', 6', 7', 8'-H), 8.62 (s, 1'-H), 9.27 (bs, 1H, NH, D<sub>2</sub>O exchangeable)

<sup>13</sup>C NMR (100 MHz; CDCl<sub>3</sub>, δ<sub>C</sub>): 98.86 (q, C-5, J<sub>C-F</sub> = 36 Hz), 115.11 (d, C-2'', 6'', J<sub>C-F</sub> = 7.5 Hz), 116.20 (d, C-3'', 5'', J<sub>C-F</sub> = 22.25 Hz), 122.08 (q, 5-CF<sub>3</sub>, J<sub>C-F</sub> = 285.75), 124.17, 124.62, 126.18, 126.69, 127.71, 128.87, 129.60, 129.77, 132.06, 132.44 (C-4), 138.53 (d, C-1'', J<sub>C-F</sub> = 3 Hz), 135.84, 155.15 (C-3), 158.77 (d, C-4'', J<sub>C-F</sub> = 240.75 Hz)

<sup>19</sup>F NMR (DMSO-<sup>d</sup><sub>6</sub>, δ<sub>F</sub>): - 78.90 (s, 3F, CF<sub>3</sub>), 109.37 (s, 1F, 4''-F)
MS: m/z 405 (M<sup>+</sup>)

Anal. Calcd for C<sub>20</sub>H<sub>13</sub>F<sub>4</sub>N<sub>3</sub>O<sub>2</sub> (%): C, 59.56; H, 3.25; N, 10.42. Found (%): C, 59.52; H, 3.22; N, 10.41
(E)-4-((4'-Fluorophenyl)diazenyl)-3-(naphthalen-2'-yl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-5-ol (89an)

Yield: 72%, m.p. 149 °C

IR (ν_max, cm⁻¹): 3128 (OH str.), 3320 (NH str.)

¹H NMR (300 MHz; CDCl₃, δ_H): 3.86 (bs, 1H, OH, D₂O exchangeable), 7.02-7.07 (m, 4H, 2", 3", 5" and 6"-H), 7.53-8.00 (m, 7H, 2', 3', 4', 5', 6', 7', 8'-H), 9.29 (bs, 1H, NH, D₂O exchangeable)

¹³C NMR (100 MHz; CDCl₃, δ_C): 98.86 (q, C-5, ²J_C-F = 36 Hz), 115.11 (d, C-2", 6", ³J_C-F = 7.5 Hz), 116.20 (d, C-3", 5", ²J_C-F = 22.25 Hz), 122.08 (q, 5-CF₃, ¹J_C-F = 285.75), 123.20, 123.62, 124.18, 126.69, 127.70, 128.89, 129.62, 129.79, 132.08, 132.44 (C-4), 135.86, 138.53 (d, C-1", ⁴J_C-F = 3 Hz), 155.15 (C-3), 158.77 (d, C-4", ¹J_C-F = 240.75 Hz)

¹⁹F NMR (DMSO-d₆, δ_F): - 78.92 (s, 3F, CF₃), 109.38 (s, 1F, 4"-F)

MS: m/z 405 (M⁺)

Anal. Caled for C₂₀H₁₃F₄N₃O₂ (%): C, 59.56; H, 3.25; N, 10.42. Found (%): C, 59.52; H, 3.22; N, 10.41

3.3B Biological Evaluation

3.3B.1 Effects of compounds on plasmid DNA under UV-irradiation

Treatment of plasmid DNA with the samples

The stock solutions for all tested compounds were prepared by dissolving 0.005 g of compound in 0.5 ml of DMSO. All synthesized compounds (60 µg) in DMSO were added separately to volume of 2µl containing plasmid DNA in TE (Tris 10 mM, EDTA 0.01 mM, pH 8.0) buffer. The same volume of DMSO as used to make the solution of the test compounds was added into A and control C. The reaction volumes except A were held in caps of polyethylene microcentrifuge tubes, which were irradiated directly on the surface of a trans-illuminator (8000 mW/cm) at 360 nm for 1 h at room temperature. After that A, control (C) and test samples were incubated at 37 °C for 0.5 h.

Agarose gel electrophoresis

After the treatment, electrophoresis was done according to the given procedure mentioned below [42].
To a 2 ml 50X tris-acetate EDTA buffer (TAE) (40 mM Tris, 20 mM acetic acid, 1 mM EDTA, pH: 8.0), added 98 ml of autoclaved water to make it 1X TAE buffer. Agarose (0.8 g) was dissolved by boiling to the resultant mixture. When the gel attained 55 ºC temperature, 10 mg/ml of ethidium bromide (ETBR) was added. The treated DNA sample mixed with 6X loading dye (0.25%) bromophenol blue added and then it was poured into gel cassette fitted with a comb. The gel was then allowed to solidify. The comb was carefully removed and the gel was placed over electrophoresis chamber flooded with tris-acetate EDTA buffer (40 mM Tris, 20 mM acetic acid, 1 mM EDTA, pH: and 30% glycerol) was carefully loaded into the wells along with control (C) and A, and electrophoresis was carried out at 5V/cm for 2.0 h and the bands were observed under UV transilluminator.
REFERENCES


[8] R. Aggarwal, A. Bansal, A. Mittal, Synthesis and antimicrobial activity of 3-(2-thienyl)-4-arylazo-5-hydrxy-5-trifluoromethyl-∆2-isoxazolines and 3-(2-


[34] M. Shukla, D.S. Seth, H. Kulshreshtha, Green chemical approach to synthesize 1-(N-substituted aniline malonyl)-3,5-dimethyl-4-(3,4-difluoro phenyl azo) pyrazoles and their antimicrobial evaluation, JOAC. 2 (2013) 1484-1488.


