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Ultrasound-assisted one-pot three-component synthesis of new isoxazolines bearing sulfonamides and their evaluation against hematological malignancies

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ABSTRACT

In the present study, following a one-pot two-step protocol, we have synthesized novel sulfonamides-isoxazolines hybrids (**3a-r**) *via* a highly regioselective 1,3-dipolar cycloaddition. The present methodology capitalized on trichloroisocyanuric acid (TCCA) as a safe and ecological oxidant and chlorinating agent for the *in-situ* conversion of aldehydes to nitrile oxides in the presence of hydroxylamine hydrochloride, under ultrasound activation. These nitrile oxides could be engaged in 1,3-dipolar cycloaddition reactions with various alkene to afford the targeted sulfonamides-isoxazolines hybrids (**3a-r**). The latter were assessed for their antineoplastic activity against model leukemia cell lines (Chronic Myeloid Leukemia, K562 and Promyelocytic Leukemia, HL-60).

1. Introduction

Nitrogen-based heterocyclic chemistry is an important and unique class of organic molecules with immense utility in medicinal chemistry [1,2]. A major goal of current medicinal research is to identify new, safer and more effective treatments for a wider range of neoplastic conditions, with the hope of reducing morbidity and mortality. This led to the development of targeted therapies for cancer [3], including differentiation therapies [4]. Nevertheless, the quest for new anti-cancer drugs to combat leukemic cells is still an ongoing field of research [5,6]. In line with this consideration, and in continuation of our recent research in identifying new and original routes to bioactive anticancer agents [7], we synthesized a series of new isoxazoline-linked sulfonamide structures and evaluated their biological activity against CML and APL.

Isoxazoline derivatives are a very important class of *N,O*-containing heterocycles that received significant attention in modern organic chemistry. They are widely present in different biologically active molecules such as anticancer [8], antimicrobial [9], antibacterial [10], anti-inflammatory and analgesics [11]. Additionally, sulfonamides are recurrent motifs in therapeutic agents exhibiting a broad spectrum of biological activities, such as antibacterial [12], antitumor [13], diuretic [14] and hypoglycemic [15] (Fig. 1).

Isoxazolines are frequently synthesized by 1,3-dipolar cycloadditions between an alkene and a nitrile oxide, in the presence of oxidants such as CrO_2 [20], MnO_2 [21], Mg $(OAc)_2$ [22], $Ce^{III}/NaI/I_2$ [23], *N*-chlorosuccinimide [24] and hypervalent iodine reagents [25]. However, all these methods involve the use of either powerful oxidants, toxic solvents or drastic reaction conditions. Thus, we developed a new synthetic

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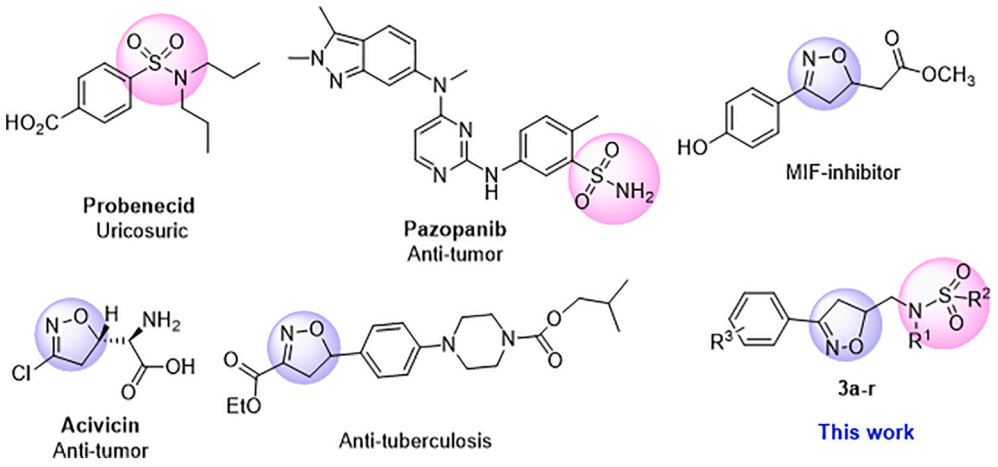
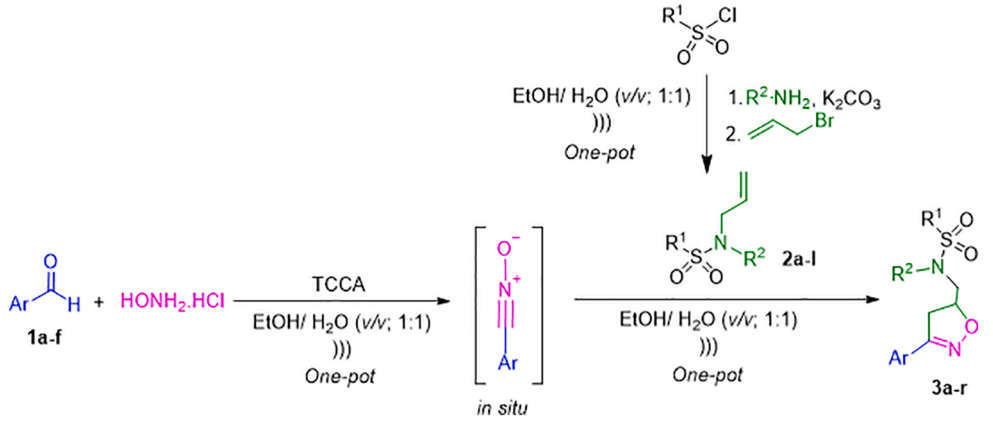


Fig. 1. Selected examples of therapeutic agents containing an isoxazoline or sulfonamide function [16–19].



Scheme 1. One-pot synthesis of sulfonamides 4-substituted-isoxazolines catalyzed by TCCA in ethanol/water under sonication.

method for isooxazoline preparation using an inexpensive, ecological and water-soluble oxidant, namely the trichloroisocyanuric acid (TCCA) [26]. It is coupled with ultrasounds as an efficient activation method as recently disclosed for the synthesis of this type of heterocycle [27]. TCCA was first used as a disinfectant and industrial deodorant, also used in swimming pools. In organic chemistry, TCCA proved efficient in chlorination reactions under mild conditions, as well as oxidation of ethers, thioethers, aldehydes, acetals and alcohols [28]. TCCA was recently used in the heterocyclic synthesis of 2-substituted oxazolines, imidazolines, thiazolines and coumarin, at room temperature [29].

More recently Zhang *et al.* [30] and Bhatt *et al.* [31] reported a novel method for the synthesis of isoxazoles/isoxazolines based on an intramolecular oxidative cyclization using a large excess of TCCA in MeCN or EtOH and long reaction time (*ca.* 10 h). In addition, Aghapour *et al.* [32] successfully used TCCA as a catalyst, in combination with hydroxylamine hydrochloride, for the preparation of oximes starting from tetrahydropyran (THP) ethers under solvent-free conditions at 110 °C.

To our knowledge, there are no reports in the literature on the preparation of isoxazolines in the presence of TCCA under ultrasonic irradiation in water. Inspired by the methods described above for the synthesis of isoxazolines and isoxazoles, we disclose herein the *one-pot* two-step synthesis of novel isoxazoline substituted sulfonamides (**3a-r**) promoted by TCCA at room temperature. It directly starts from aldehydes (**1a-f**) and operates in aqueous medium under ultrasonic irradiation (Scheme 1). The important features of this new method are its ease, straightforwardness and environmentally friendly protocol.

2. Experimental

2.1. Material and methods

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures; all chemicals were purchased from Aldrich, Merck and used without further purification. Analytical thin layer-chromatographies (TLC) have been performed on pre-coated silica gel plates (Kieselgel 60 F_{254}, E. Merck, Germany), and chromatograms were visualized by UV- light irradiation (254 and 360 nm), then by staining with ninhydrin or H_2SO_4/EtOH. Purifications by column chromatography have been performed using silica gel, 100–200 mesh (Merck, Germany). NMR spectroscopies were recorded in dry deuterated solvent (DMSO or chloroform) a Bruker AC 200, or on a Bruker AC 400 spectrometer at 200 MHz or 400 MHz for ^{1}H NMR and 50 MHz or 101 MHz for ^{13}C NMR; δ is expressed in ppm related to TMS (0 ppm) as internal standard. Splitting patterns are designated as follow: s (singlet), d (doublet), t (triplet), m (multiplet), br (broad). Coupling constants (*J* values) are listed in Hertz (Hz). Mass spectra (ESI-MS) were recorded on a Bruker Daltonics Esquire 3000+, and the samples were diluted in methanol. Melting points were measured on a Wagner and Munz Köfler Bench System. The purity of compounds was further verified by HPLC analysis was performed on a Jasco LC-Net II /ADC apparatus using phenomenex columns (conditions: unless otherwise stated: 1.0 mL/min, gradient 75% A/25% B (1 min.) then increasing to 0% A/100% B in 6 min. and a plateau of 3 min. before returning to 75% A/25% B in 1 min. A is water and B is CH_3CN, both containing 1‰ HCOOH). Purity of all compounds was found to be ≥ 95% as determined by HPLC

using UV detection at 254 nm. The ultrasound-assisted reactions were carried out in an "'Elmasonic S 30/S 30H UltraSonic Bath Cleaner", with an effective ultrasound power of 80 W at a frequency of 47 kHz. This ultrasonic cleaner has internal dimensions W/D/H (mm) of 240/137/100 with a liquid retention capacity of 2.75 l. The reactions were carried out in a flask with a capacity of 25 mL in suspension in the center of the cleaning bath, 5 cm below the surface of the liquid. The reaction temperatures were controlled by adding or removing water from the ultrasonic bath.

2.2. Synthesis

2.2.1. General procedure for the synthesis of allyl-sulfonamides (2a-l)

The primary amine (1 equiv) and K_2CO_3 (2 equiv) were dissolved in EtOH/H_2O (*v/v*, 1:1) (20 mL) and alkyl/phenyl sulfonyl chloride (1.1 equiv) was added dropwise. After completion of the reaction (as monitored *via* TLC), allyl bromide (1.1 equiv) was added dropwise with constant stirring or sonication until complete consumption of the starting material (6–10 h under stirring or 15–20 min under sonication). The salts were then removed by filtration, and filtrate was concentrated under reduced pressure. The crude material was purified on silica gel column chromatography (cyclohexane/ethyl acetate: 9/1 to 6/4), to afford the desired pure products **2a-l**.

2.2.1.1. N-Allyl-N-(4-bromo-phenyl)-benzenesulfonamide ***(2a)***. Brown solid; M_P 63–65 °C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.67$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73–7.64 (m, 1H), 7.58 (d, $J = 4.3$ Hz, 4H), 7.50 (d, $J = 8.8$ Hz, 2H), 7.00 (d, $J = 8.8$ Hz, 2H), 5.76–5.50 (m, 1H), 5.17–4.99 (m, 2H), 4.19 (dd, $J = 6.0$, 1.2 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 133.8, 133.1, 132.3 (2C), 130.8 (2C), 129.8 (2C), 127.7 (2C), 119.6, 52.9; MS (EI): $m/z = 351.99$ $[M + H]^+$.

2.2.1.2. N-Allyl-N-phenyl-methanesulfonamide ***(2b)***. Orange solid; M_P 67–69 °C. TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.58$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45–7.31 (m, 5H), 5.96–5.72 (m, 1H), 5.24–5.12 (m, 2H), 4.34–4.27 (m, 2H), 2.94 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 139.3, 132.8, 129.4 (2C), 128.5 (2C), 128.1, 119.1, 53.7, 38.1; MS (EI): $m/z = 212.07$ $[M + H]^+$.

2.2.1.3. N-Allyl-N-phenyl-benzenesulfonamide ***(2c)***. Beige solid, M_P 80–82 °C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.65$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65–7.55 (m, 3H), 7.47 (t, $J = 7.7$ Hz, 2H), 7.33–7.27 (m, 3H), 7.08–7.02 (m, 2H), 5.84–5.63 (m, 1H), 5.14–5.01 (m, 2H), 4.21 (d, $J = 6.3$ Hz, 2H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 138.9, 138.3, 132.7, 132.7, 128.9 (2C), 128.8 (4C), 127.9, 127.6 (2C), 118.9, 53.6; MS (EI): $m/z = 274.08$ $[M + H]^+$.

2.2.1.4. N-Allyl-N-(4-methoxy-phenyl)-methanesulfonamide ***(2d)***. Black solid, M_P 68–70 °C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.56$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (d, $J = 9.0$ Hz, 2H), 6.91 (d, $J = 9.0$ Hz, 2H), 5.94–5.73 (m, 1H), 5.24–5.06 (m, 2H), 4.33–4.16 (m, 2H), 3.82 (s, 3H), 2.92 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.2, 133.1, 131.7, 130.1(2C), 119.1, 114.5 (2C), 55.4, 53.9, 37.9; MS (EI): $m/z = 242.08$ $[M + H]^+$.

2.2.1.5. N-Allyl-N-(4-methoxy-phenyl)-ethanesulfonamide ***(2e)***. Black solid, M_P 70–72 °C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.40$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (d, $J = 9.0$ Hz, 2H), 6.89 (d, $J = 9.0$ Hz, 2H), 5.90–5.72 (m, 1H), 5.23–5.01 (m, 2H), 4.31–4.18 (m, 2H), 3.80 (s, 3H), 3.04 (q, $J = 7.4$ Hz, 2H), 1.39 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.1, 133.5, 131.6, 130.3 (2C), 118.7, 114.5 (2C), 55.4, 54.4, 45.4, 8.1; MS (EI): $m/z = 256.09$ $[M + H]^+$.

2.2.1.6. N-Allyl-N-propyl-benzenesulfonamide ***(2f)***. Brown oil, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.40$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83–7.79 (m, 2H), 7.57–7.54 (m, 1H), 7.53–7.49 (m, 2H), 5.67–5.56 (m, 1H), 5.21–5.07 (m, 2H), 3.81 (d, $J = 6.4$ Hz, 2H), 3.09 (dd, $J = 8.4$, 6.8 Hz, 2H), 1.53 (dd, $J = 15.0$, 7.5 Hz, 2H), 0.85 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 140.1, 133.1, 132.4, 129.1 (2C), 127.1 (2C), 118.6, 50.5, 49.1, 21.4, 11.1; MS (EI): $m/z = 240.1$ $[M + H]^+$.

2.2.1.7. N-allyl-N-(4-methoxyphenyl) benzenesulfonamide ***(2 g)***. Gray Solid, M_P 91–94 °C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.54$; ^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.66–7.40 (m, 5H), 6.92 (d, $J = 9.1$ Hz, 2H), 6.78 (d, $J = 9.1$ Hz, 2H), 5.87–5.56 (m, 1H), 5.15–4.95 (m, 2H), 4.14 (d, $J = 6.3$ Hz, 2H), 3.78 (s, 3H).^{13}C NMR (50 MHz, Chloroform-*d*) δ 158.9, 138.5, 132.8, 132.5, 131.4, 130.2 (2C), 128.7 (2C), 127.6 (2C), 118.7, 114. (2C), 55.4, 53.9; MS (EI): $m/z = 304,09$ $[M + H]^+$.

2.2.1.8. N-Allyl-N-(4-chloro-phenyl)-benzenesulfonamide ***(2 h)***. Green Solid, M_P 65–67 °C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.6$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65–7.57 (m, 3H), 7.53–7.46 (m, 2H), 7.28 (d, $J = 8.7$ Hz, 2H), 6.98 (d, $J = 8.7$ Hz, 2H), 5.80–5.64 (m, 1H), 5.13–5.03 (m, 2H), 4.18 (d, $J = 6.3$ Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.9, 137.4, 133.7, 132.9, 132.3, 130.1 (2C), 129.1 (2C), 128.9 (2C), 127.6 (2C), 119.3, 53.5; MS (EI): $m/z = 308.04$ $[M + H]^+$.

2.2.1.9. N-Allyl-N-p-tolyl-methanesulfonamide ***(2i)***. Beige Crystals, M_P 67–68 °C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.47$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (d, $J = 8.3$ Hz, 2H), 7.19 (d, $J = 8.2$ Hz, 2H), 5.95–5.78 (m, 1H), 5.21–5.09 (m, 2H), 4.30 (d, $J = 6.3$ Hz, 2H), 2.41 (s, 3H), 2.37 (s, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 140.7, 133.4, 130.8 (2C), 130.2 (2C), 128.6, 21.2, 8.1, 7.8; MS (EI): $m/z = 226.08$ $[M + H]^+$.

2.2.1.10. N-Allyl-N-(4-chloro-phenyl)-ethanesulfonamide ***(2j)***. Green-Yellow Solid, M_P 65–67 °C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f =$ 0.61. MS (EI): $m/z = 259.04$ M ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (d, $J = 8.8$ Hz, 2H), 7.29 (d, $J = 8.8$ Hz, 2H), 5.88–5.73 (m, 1H), 5.18–5.09 (m, 2H), 4.29 (d, $J = 6.4$ Hz, 2H), 3.05 (q, $J = 7.4$ Hz, 2H), 1.38 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.8, 133.5, 132.9, 129.9 (2C), 129.4 (2C), 119.2, 54.1, 45.8, 8.1; MS (EI): $m/z = 260.04$ $[M + H]^+$.

2.2.1.11. N-Allyl-N-p-tolyl-ethanesulfonamide ***(2 k)***. Beige Solid, M_P 66–69 °C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) $R_f = 0.52$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.3$ Hz, 2H), 5.92–5.76 (m, 1H), 5.20–5.08 (m, 2H), 4.30 (d, $J = 6.3$ Hz, 2H), 3.06 (q, $J = 7.4$ Hz, 2H), 2.37 (s, 3H), 1.40 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.8, 136.6, 133.5, 130.8 (2C), 130.2 (2C), 118.6, 49.9, 45.6, 21.2, 7; MS (EI): $m/z = 240.10$ $[M + H]^+$.

2.2.1.12. N-Allyl-N-(4-chloro-phenyl)-methanesulfonamide ***(2 l)***. Green Solid, M_P 97–99 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) $R_f = 0.38$; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (d, $J = 8.3$ Hz, 2H), 7.19 (d, $J = 8.3$ Hz, 2H), 5.96–5.72 (m, 1H), 5.21–5.07 (m, 2H), 4.30 (d, $J = 6.3$ Hz, 2H), 2.37 (s, 3H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 140.7, 133.48, 131.1, 130.8 (2C), 130.2 (2C), 118.6, 49.9, 45.6; MS (EI): $m/z = 246,03$ $[M + H]^+$.

2.2.2. General procedure for the one-pot synthesis of compounds (3a-r)

To a solution of aldehyde (1 equiv) and hydroxylamine hydrochloride (1.5 equiv) in EtOH/H_2O (*v/v*, 1:1) (20 mL) TCCA (0.5 equiv) and allyl-sulfonamides **2a-l** (1 equiv) were added successively and the mixture was sonicated according to the time reported in Table 3. Reactions were then extracted with CH_2Cl_2 (20 mL × 2). The organic phase was washed with water (20 mL) and saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated in vacuum to give the crude

product, which was purified by flash silica gel chromatography (cyclohexane/ EtOAc: 9/1 to 7/3) to afford the pure adducts **3a-r**.

*2.2.2.1. N-(4-Chloro-phenyl)-N-[3-(4-chloro-phenyl)-isoxazolin-5-ylmethyl] benzenesulfonamide **(3a)***. White Solid, Mp 195–197 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.14; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (t, *J* = 7.4 Hz, 3H), 7.60–7.55 (m, 2H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.33–7.27 (m, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 4.88–4.73 (m, 1H), 3.82 (dd, *J* = 13.9, 7.0 Hz, 1H), 3.72 (dd, *J* = 13.9, 4.9 Hz, 1H), 3.52 (dd, *J* = 16.9, 6.6 Hz, 1H), 3.40 (dd, *J* = 16.9, 10.5 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.6, 137.8, 137.3, 136.3, 134.3, 133.2, 129.9 (2C), 129.4 (2C), 129.1 (4C), 128.1 (2C), 127.6 (2C), 127.6, 78.9, 53.2, 37.8; MS (EI): *m/z* = 460.40 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 100 %, t_R = 4.55 min).

*2.2.2.2. N-[3-(3,4-Dichloro-phenyl)-isoxazolin-5-ylmethyl]-N-(4-methoxy-phenyl)-methane sulfonamide **(3b)***. White Solid, M_P 170–172 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.52 ;^{1}H NMR (200 MHz, Chloroform-*d*) δ 7.70–7.64 (m, 1H), 7.42 (d, *J* = 1.4 Hz, 2H), 7.27–7.17 (m, 3H), 6.86 (d, *J* = 9.0 Hz, 2H), 4.87–4.69 (m, 1H), 3.84 (dd, *J* = 14.1, 6.0 Hz, 1H), 3.75 (s, 3H), 3.72 (dd, *J* = 7.3, 2.1 Hz, 1H), 3.64 (dd, *J* = 9.5, 4.6 Hz, 1H), 3.26 ((dd, *J* = 14.1, 6.0 Hz, 1H), 2.89 (s, 3H). ^{13}C NMR (50 MHz, Chloroform-*d*) δ 159.6, 154.8, 134.4, 133.2, 131.5, 130.8, 130.1 (2C), 129.2, 128.5, 125.8, 114.9 (2C), 79.1, 55.5, 53.6, 37.7, 37.5; MS (EI): *m/z* = 429.04 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 100 %, t_R = 4.15 min)

*2.2.2.3. N-(4-Methoxy-phenyl)-N-[3-(3-nitro-phenyl)-isoxazolin-5-ylmethyl]-benzene sulfonamide **(3c)***. White Solid, M_P 145–147 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.5;^{1}H NMR (300 MHz, DMSO-d_6) δ 8.37–8.26 (m, 2H), 8.09–8.02 (m, 1H), 7.78–7.64 (m, 2H), 7.56 (d, *J* = 4.4 Hz, 4H), 6.96–6.84 (m, 4H), 4.81–4.62 (m, 1H), 3.84 (dd, *J* = 14.2, 6.8 Hz, 1H), 3.67 (dd, *J* = 15.9, 11.0 Hz, 1H), 3.54 (dd, *J* = 20.5, 9.8 Hz, 1H), 3.37 (dd, *J* = 12.8, 5.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.2, 156.1, 148.5, 138.2, 133.6, 133.2, 131.8, 131.3, 131.1, 130.7 (2C), 129.7 (2C), 127.8 (2C), 125.1, 121.3, 114.6 (2C), 79.8, 55.7, 54.1, 37.5; MS (EI): *m/z* = 467.12 [M + H] $^+$; IR (KBr, cm^{-1}): 1134 (S = O),1162 (S = O), 732–646 (5HAr-Adjacent), 1506 (N = O), 1420 (Ph-O-C), 3312–2700 (C = CAr); HPLC analysis (luna column, λ = 254 nm, purity 95 %, t_R = 4.11 min).

*2.2.2.4. N-(4-Bromo-phenyl)-N-[3-(3-nitro-phenyl)-isoxazolin-5-ylmethyl]-benzene sulfonamide **(3d)***. White Solid, M_P 167–169 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.57;^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36–8.26 (m, 2H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.79–7.67 (m, 2H), 7.58 (d, *J* = 1.5 Hz, 2H), 7.56 (s, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 4.86–4.68 (m, 1H), 3.88 (dd, *J* = 14.5, 6.7 Hz, 1H), 3.76 (dd, *J* = 14.5, 4.5 Hz, 1H), 3.58 (dd, *J* = 17.3, 10.8 Hz, 1H), 3.34 (dd, *J* = 13.6, 10.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.1, 148.5, 138.9, 137.6, 133.9, 133.2, 132.4 (2C), 131.3, 131.2 (2C), 131.1, 129.8 (2C), 127.7 (2C), 125.1, 121.6, 121.3, 80.1, 53.5, 37.4; MS (ESI +): *m/z* = 516.01 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 95 %, t_R = 4.33 min).

*2.2.2.5. N-(4-Methoxy-phenyl)-N-(3-phenyl-isoxazolin-5-ylmethyl)-benzenesulfonamide **(3e)***. White Solid, M_P 127–129 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.52;^{1}H NMR (300 MHz, DMSO-d_6) δ 7.68 (m, 1H), 7.57 (d, *J* = 4.4 Hz, 4H), 6.91 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 5.66 (ddt, *J* = 17.2, 10.2, 6.0 Hz, 1H), 5.14–4.94 (m, 2H), 4.14 (d, *J* = 6.1 Hz, 2H), 3.71 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.9, 138.3, 133.5, 133.5, 131.5, 130.2 (2C),129.7 (2C), 127.7 (2C), 119.1, 114.4 (2C), 55.7, 53.5; MS (EI): *m/z* = 422.13 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 96 %, t_R = 4.34 min).

*2.2.2.6. N-(4-Chloro-phenyl)-N-[3-(3-nitro-phenyl)-isoxazolin-5-ylmethyl]-benzene sulfonamide **(3f)***. White Solid, Mp 152–154 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.29;^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 1H), 7.67–7.56 (m, 4H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 4.98–4.84 (m, 1H), 3.85 (dd, *J* = 13.9, 6.8 Hz, 1H), 3.76 (dd, *J* = 13.9, 4.9 Hz, 1H), 3.59 (dd, *J* = 16.9, 6.7 Hz, 1H), 3.48 (dd, *J* = 16.9, 10.6 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.9, 148.5, 137.8, 137.3, 134.4, 133.3, 132.3, 130.9, 129.9 (2C), 129.9, 129.5 (2C), 129.1 (2C), 127.6 (2C), 124.7, 121.6, 79.5, 53.2, 37.5; MS (EI): *m/z* = 471.91 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 100 %, t_R = 4.30 min).

*2.2.2.7. N-(4-Chloro-phenyl)-N-(3-phenyl-isoxazolin-5-ylmethyl)-benzenesulfonamide **(3 g)***. White Solid, Mp 148–150 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.34; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.64—7.58 (m, 3H), 7.51–7.41 (m, 5H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 4.84–4.73 (m, 1H), 3.76 (dd, *J* = 20.5, 7.4 Hz, 1H), 3.69 (dd, *J* = 13.5, 4.9 Hz, 1H), 3.55 (dd, *J* = 16.9, 6.5 Hz, 1H), 3.42 (dd, *J* = 16.9, 10.4 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.3, 156.5, 137.8, 132.9, 131.6, 130.2, 129.9 (2C), 129.2, 128.9 (2C), 128.7 (2C), 127.7 (2C), 126.8 (2C), 114.4 (2C), 78.5, 55.4, 53.5, 38.2; MS (EI): *m/z* = 426.92 [M + H] $^+$; IR (KBr, cm^{-1}): 1114 (S = O), 1335 (S = O), 750–690 (5HAr-Adjacent), 685 (C-Cl), 3415–2830 (C = CAr); HPLC analysis (luna column, λ = 254 nm, purity 99 %, t_R = 4.15 min).

*2.2.2.8. N-[3-(3,4-Dichloro-phenyl)-isoxazolin-5-ylmethyl]-N-phenyl-benzenesulfonamide **(3 h)***. White Solid, Mp 148–150 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.34;^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 1.7 Hz, 1H), 7.66–7.56 (m, 3H), 7.53–7.46 (m, 4H), 7.37–7.33 (m, 3H), 7.08–7.04 (m, 2H), 4.89–4.75 (m, 1H), 3.84 (dd, *J* = 13.7, 7.8 Hz, 1H), 3.74 (dd, *J* = 13.7, 4.8 Hz, 1H), 3.54 (dd, *J* = 16.9, 6.5 Hz, 1H), 3.38 (dd, *J* = 16.9, 10.6 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.8, 139.1, 137.6, 134.3, 133.1, 133.1, 130.8, 129.3 (2C), 129.2, 128.9 (2C), 128.6 (2C), 128.5 (2C), 127.7 (2C), 125.8, 79.1, 53.1, 37.7; MS (EI): *m/z* = 461.36 [M + H] $^+$; IR (KBr, cm^{-1}): 1171 (S = O), 1309 (S = O), 895–826 (2HAr-Adjacent), 757 (C-Cl), 688 (C-Cl), 3415–2830 (C = CAr) and (C-HAr) elongation; HPLC analysis (luna column, λ = 254 nm, purity 96 %, t_R = 4.55 min).

*2.2.2.9. N-Phenyl-N-(3-p-tolyl-isoxazolin-5-ylmethyl)-benzenesulfonamide **(3i)***. White Solid, Mp 148–150 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.34; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63–7.55 (m, 5H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.37–7.32 (m, 3H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.10–7.05 (m, 2H), 4.83–4.71 (m, 1H), 3.83 (dd, *J* = 13.5, 7.9 Hz, 1H), 3.73 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.53 (dd, *J* = 16.9, 6.4 Hz, 1H), 3.40 (dd, *J* = 16.8, 10.4 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.5, 140.5, 139.2, 137.7, 133.0, 129.4 (2C), 129.2 (2C), 128.9 (2C), 128.7 (2C), 128.4, 127.7 (2C), 126.8 (2C), 126.3, 78.3, 53.2, 38.3, 21.5; MS (EI): *m/z* = 406.50 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 100 %, t_R = 4.28 min).

*2.2.2.10. N-Phenyl-N-[3-(3,4,5-trimethoxy-phenyl)-isoxazolin-5-ylmethyl]-benzene sulfonamide **(3j)***. White Solid, Mp 175–177 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.55; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64–7.55 (m, 3H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.35–7.32 (m, 3H), 7.09–7.05 (m, 2H), 4.83–4.72 (m, 1H), 3.91 (s, *J* = 3.1 Hz, 6H), 3.90 (s, 3H), 3.85 (dd, *J* = 13.6, 8.0 Hz, 1H), 3.70 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.56 (dd, *J* = 16.8, 6.3 Hz, 1H), 3.40 (dd, *J* = 16.8, 10.4 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.5, 153.3, 139.9, 139.1, 137.6, 133.1, 129.2 (2C), 128.95 (2C), 128.9 (2C), 128.4, 127.6 (2C), 124.6, 104.1 (2C), 78.5, 60.9, 56.3(2CH_3), 53.1, 38.2; MS (EI): *m/z* = 482.15 [M + H] $^+$; IR (KBr, cm^{-1}): 1320 (S = O), 1186 (S = O), 784–650 (5HAr-Adjacent), 1454 (Ph-O-C), 1387 (Ph-O-C), 1119 (Ph-O-C), 3362–2794

(C = CAr) and (C-HAr) elongation ; HPLC analysis (luna column, λ = 254 nm, purity 100 %, t_R = 4.02 min).

*2.2.2.11. N-[3-(3,4-Dichloro-phenyl)-isoxazolin-5-ylmethyl]-N-propyl-benzenesulfonamide **(3 k)***. Monocrystal, Mp 115–116 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.34; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85–7.80 (m, 2H), 7.78 (d, *J* = 1.7 Hz, 1H), 7.65–7.59 (m, 1H), 7.58–7.49 (m, 4H), 5.12–4.78 (m, 1H), 3.54 (dd, *J* = 14.8, 5.8 Hz, 1H), 3.46 (dd, *J* = 17.0, 7.7 Hz, 1H), 3.39 (dd, *J* = 17.0, 10.4 Hz, 1H), 3.29 (t, *J* = 6.2 Hz, 1H), 3.27–3.23 (m, 1H), 3.11 (dd, *J* = 14.8, 6.9 Hz, 1H), 1.65–1.55 (m, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.3, 139.2, 134.3, 133.1, 132.8, 130.8, 129.2 (2C), 129.2, 128.5, 127.1 (2C), 125.8, 80.7, 51.9, 50.9, 37.7, 21.8, 11.1; MS (EI): *m/z* = 427.34 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 100%, t_R = 4.53 min).

*2.2.2.12. N-[3-(3,4-Dichloro-phenyl)-soxazolin-5-ylmethyl]-N-phenyl-methanesulfonamide **(3 l)***. White Solid, Mp 135–137 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.14; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (s, 1H), 7.53–7.47 (m, 2H), 7.47–7.43 (m, 2H), 7.42–7.39 (m, 3H), 4.92–4.80 (m, 1H), 3.97 (dd, *J* = 14.2, 6.0 Hz, 1H), 3.86 (dd, *J* = 14.2, 6.3 Hz, 1H), 3.37 (dd, *J* = 13.2, 5.6 Hz, 1H), 3.34–3.25 (m, 1H), 2.99 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.9, 139.1, 134.3, 133.1, 130.8, 129.8 (2C), 129.1, 128.7, 128.7 (2C), 128.5, 125.8, 79.1, 53.4, 37.8, 37.5. MS (EI): *m/z* = 399.30 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 95 %, t_R = 4.13 min).

*2.2.2.13. N-(4-Methoxy-phenyl)-N-[3-(3,4-dichloro-phenyl)-isoxazolin-5-ylmethyl]-benzene sulfonamide **(3 m)***. White Solid, M_P 109–111 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.59; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81 (d, *J* = 1.8 Hz, 1H), 7.72–7.64 (m, 2H), 7.61 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.56 (d, *J* = 4.3 Hz, 4H), 6.93 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 9.1 Hz, 2H), 4.75–4.61 (m, 1H), 3.81 (dd, *J* = 14.1, 6.8 Hz, 1H), 3.72 (s, 3H), 3.66 (dd, *J* = 14.2, 4.9 Hz, 1H), 3.48 (dd, *J* = 17.3, 10.8 Hz, 1H), 3.24 (dd, *J* = 17.3, 6.9 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.2, 155.6, 138.2, 133.6, 133.1, 132.2, 131.8, 131.5, 130.4 (2C), 130.3, 129.7 (2C), 128.7, 127.8 (2C), 127.1, 114.6 (2C), 79.7, 55.7, 54.1, 37.5; MS (EI): *m/z* = 491.05 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 98 %, t_R = 4.55 min)

*2.2.2.14. N-(4-Methoxy-phenyl)-N-[3-(3-nitro-phenyl)-isoxazolin-5-ylmethyl]-ethane sulfonamide **(3n)***. White Solid, Mp 136–138 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.28; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 7.7 Hz, 2H), 7.44–7.41 (m, 2H), 7.35 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 4.88–4.73 (m, 1H), 3.92 (dd, *J* = 14.6, 6.6 Hz, 1H), 3.86 (dd, 1H), 3.84 (s, 3H), 3.41 (dd, *J* = 14.7, 7.7 Hz, 1H), 3.35 (dd, *J* = 14.7, 5.4 Hz, 1H), 3.12 (qd, *J* = 7.2, 1.9 Hz, 2H), 1.42 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.4, 156.6, 131.6, 130.3 (2C), 130.2, 129.2, 128.8 (2C), 126.8 (2C), 114.8 (2C), 78.5, 55.5, 54.2, 45.3, 38.1, 8.1; MS (EI): *m/z* = 419.45 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 95 %, t_R = 3.86 min).

*2.2.2.15. N-(4-Chloro-phenyl)-N-(3-phenyl-isoxazolin-5-yl)methyl)-ethanesulfonamide **(3o)***. White Solid, Mp 98–100 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.29; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69–7.64 (m, 2H), 7.46–7.41 (m, 3H), 7.37 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 11.1 Hz, 2H), 4.89–4.78 (m, 1H), 3.41 (dd, *J* = 16.8, 10.3 Hz, 1H), 3.33 (dd, *J* = 16.9, 7.0 Hz, 1H), 3.13 (dd, *J* = 7.4, 1.9 Hz, 1H), 3.10 (dd, *J* = 7.4, 1.8 Hz, 1H), 1.42 (t, *J* = 7.4 Hz, 3H), 1.33 (q, *J* = 30.9, 10.6 Hz, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.6, 137.9, 134.3, 130.3, 130.1 (2C), 129.8 (2C), 129.1, 128.7 (2C), 126.7 (2C), 78.6, 54.2, 45.7, 37.9, 8.1; MS (EI): *m/z* = 378.45 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity100 %, t_R = 4.03 min).

*2.2.2.16. N-(4-chlorophenyl)-N-((3-phenyl-isoxazolin-5-yl)methyl)-methanesulfonamide **(3p)***. White Solid, Mp 160–162 °C, TLC (cyclohexane/AcOEt, 80/20, *v/v*) R_f = 0.27; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.45–7.41 (m, 3H), 7.41 (s, 2H), 7.37 (d, *J* = 8.9 Hz, 2H), 4.93–4.80 (m, 1H), 3.94 (dd, *J* = 14.4, 6.5 Hz, 1H), 3.85 (dd, *J* = 14.4, 5.4 Hz, 1H), 3.42 (dd, *J* = 16.9, 10.4 Hz, 1H), 3.31 (dd, *J* = 16.9, 6.8 Hz, 1H), 3.01 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.6, 137.8, 134.5, 130.4, 130.1 (2C), 129.9 (2C), 128.9 (2C), 128.8, 126.79(2C), 78.3, 78.1, 53.8, 38.2, 37.9. MS (EI): *m/z* = 365.06 [M + H] $^+$; HPLC analysis (luna column, λ = 254 nm, purity 100 %, t_R = 3.95 min).

*2.2.2.17. N-[3-(3-Nitro-phenyl)-isoxazolin-5-ylmethyl]-N-p-tolyl-methanesulfonamide **(3q)***. White Solid, Mp 177–179 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.27; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 8.28 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 4.98–4.85 (m, 1H), 3.98 (dd, *J* = 14.2, 5.9 Hz, 1H), 3.86 (dd, *J* = 14.2, 6.4 Hz, 1H), 3.43 (d, *J* = 8.7 Hz, 2H), 2.98 (s, 3H), 2.39 (s, *J* = 10.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.1, 148.4, 138.9, 136.4, 132.3, 131.1, 130.4 (2C), 129.8, 128.4 (2C), 124.7, 121.5, 79.3, 53.4, 37.7, 37.5, 21.2; MS (EI): *m/z* = 389.10 [M + H] +; HPLC analysis (luna column, λ = 254 nm, purity 98 % , t_R = 3.87 min).

*2.2.2.18. N-((3-(3-Nitro-phenyl)-isoxazolin-5-yl)methyl)-N-propyl-benzenesulfonamide **(3r)***. White Solid, Mp 102–104 °C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) R_f = 0.25; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (t, *J* = 1.8 Hz, 1H), 8.33–8.26 (m, 1H), 8.08–8.04 (m, 1H), 7.85–7.80 (m, 2H), 7.66–7.59 (m, 2H), 7.58–7.52 (m, 2H), 5.10–5.01 (m, 1H), 3.57 (dd, *J* = 14.9, 5.7 Hz, 1H), 3.53–3.42 (m, 2H), 3.31 (dd, *J* = 10.5, 4.3 Hz, 1H), 3.27 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.13 (dd, *J* = 14.8, 7.1 Hz, 1H), 1.61 (q, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.4, 148.5, 139.2, 132.8, 132.3, 131.1, 129.8, 129.2 (2C), 127.1 (2C), 124.6, 121.6, 80.9, 51.9, 50.9, 37.6, 21.8, 11.1; MS (EI): *m/z* = 403.12 [M + H] $^+$; IR (KBr, cm^{-1}): 1336 (S = O), 1188 (S = O), 1046 (Propyl),1500 (N = O), 3312–2700 (C = CAr) and (C-HAr) elongation 818–670 (3HAr-Adjacent); HPLC analysis (luna column, λ = 254 nm, purity 99 %, t_R = 4.12 min).

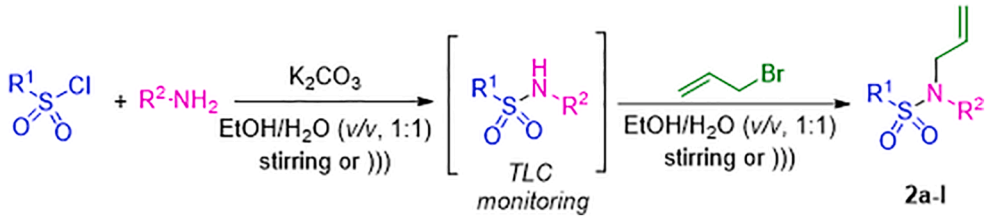
2.2.3. General procedure for the radical trapping experiment

To a solution of *p*-chlorobenzaldehyde **1a** (1.0 equiv, 70 mg) and hydroxylamine hydrochloride (1.5 equiv, 52. 1 mg) in EtOH/H_2O (*v/v*, 1:1) (10 mL) TCCA (0.5 equiv, 58.1 mg), TEMPO (0.5 equiv, 78.1 mg) and alkene **2 h** (1 equiv, 153.5 mg) were added successively and the mixture was sonicated for 20 min using ultrasonic bath (47 kHz) at 25 °C (the temperature of the reaction has been maintained by the addition of crushed ice). After completion of the reaction (TLC), the reaction mixture was concentrated under pressure to remove ethanol and then extracted with CH_2Cl_2 (20 mL). The organic phase was washed with water (20 mL) and saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated in vacuum. The resulting residue was then purified by silica gel column chromatography (cyclohexane/ EtOAc: 9/1 to 7/3) to afford the pure **3a** (≈ 125 mg), with inseparable mixture of trapped-TEMPO products.

2.3. Crystallography

One crystal suitable for X-ray diffraction analysis was coated with dry perfluoropolyether, mounted on glass fiber, and fixed in a cold nitrogen stream to the goniometer head. Data collection was performed on a Bruker D8 VENTURE Super DUO diffractometer, using graphite monochromatized Mo radiation (Mo *K*α radiation, l = 0.71073 Å). The data were reduced (SAINT) and corrected for absorption effects by the multiscan method (SADABS). The corresponding crystallographic data were deposited with the Cambridge Crystallographic Data Centre as

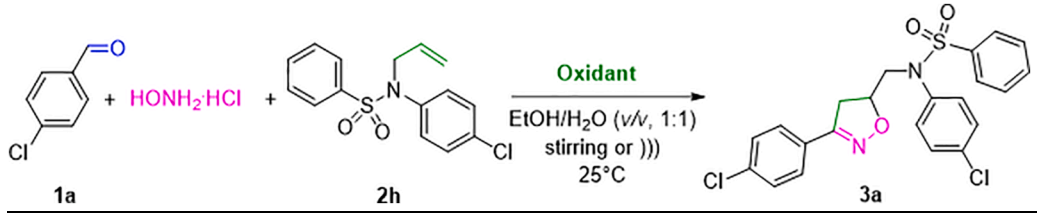
Table 1
One-pot synthesis of allyl-sulfonamides under sonication. **2a-l**.



Entry [a]	Allyl	R^1	R^2	Conventional stirring		Sonication	
				Time (h)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	**2a**	Ph	4-Br C_6H_4	11	70	27	75
2	**2b**	Me	C_6H_5	9	60	18	66
3	**2c**	Ph	C_6H_5	12	75	25	79
4	**2d**	Me	4-MeO C_6H_4	8	56	16	65
5	**2e**	Et	4-MeO C_6H_4	10	78	17	81
6	**2f**	Ph	C_3H_7	6	66	19	69
7	**2 g**	Ph	4-MeO C_6H_4	10.5	75	21	83
8	**2h**	Ph	4-Cl C_6H_4	14	55	26	69
9	**2i**	Me	4-Me C_6H_4	9.5	60	15	69
10	**2j**	Et	4-Cl C_6H_4	8.5	64	21	68
11	**2k**	Et	4-Me C_6H_4	9	72	18	76
12	**2l**	Me	4-Cl C_6H_4	13	77	22	86

[a] Phenyl/alkyl sulfonyl chloride (1.1 mmol), primary amine (1.0 mmol), K_2CO_3 (2.0 mmol) in EtOH/H_2O (20 mL, 1:1) at 25 °C, then allyl bromide (1.1 mmol). [b] Isolated yield after purification.

Table 2
Optimization of the reaction conditions for the '*one-pot*' synthesis of sulfonamide-isoxazolines under sonication.



Entry [a]	Oxidant	Base	Conventional stirring		Sonication	
	(1 equiv)	(1.2 equiv)	Time (h)	Yield (%) [b]	Time (min)	Yield (%) [b]
1	None	–	12	nr	30	nr
2	NCS	–	6	<10	20	15
3	NCS	Et_3N	5	50	16	65
4	*p*-Chloranil	–	4	<5	15	10
5	*p*-Chloranil	K_2CO_3	4	45	12	52
6	Chloramine-T	–	6	20	17	36
7	Chloramine-T	K_2CO_3	5	49	22	61
8	CAN	K_2CO_3	6	56	20	75
9	TCCA	–	4	72	12	87
10	TCCA	K_2CO_3	4	70	12	86
11[c]	TCCA	–	4	71	12	89
12 [d]	TCCA	–	4	53	20	62

[a] aryl aldehyde/ $HONH_2$.HCl (1/1.5 mmol), in EtOH/H_2O (*v/v*, 1:1) at 25 °C.
[b] Pure isolated yield under stirring and sonication (ultrasonic bath, 47 kHz).
[c] Reaction conditions with 0.5 equiv of TCCA.
[d] Reaction performed with 0.3 equiv of TCCA.

supplementary publications. CCDC 2,040,890 **3 k**. The data can be obtained free of charge via: https://www.ccdc.cam.ac.uk/structures/.

3. Results and discussion

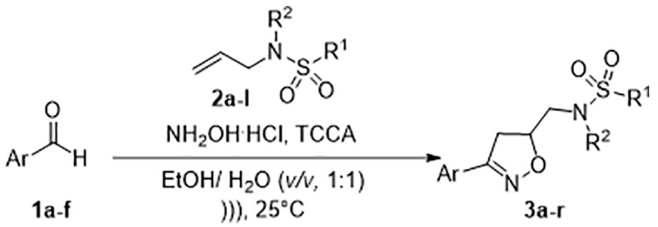
3.1. Effect of sonication on one-pot, tandem synthesis of allyl sulfonamides

Firstly, we synthesize different allyl-sulfonamides **2a-l** directly from phenyl/alkyl sulfonyl chloride and a primary amine in presence of potassium carbonate, and subsequently allyl bromide is added; this process was performed in a *one-pot* under ultrasound activation. The results presented in Table 1 clearly show the effect of ultrasound on the acceleration of the reaction rate (15–27 min) compared with conventional agitation (6–13 h). Of note, both methods afforded the expected allyl-sulfonamides (**2 a-l**) in comparable yields.

3.2. Effect of sonication and different oxidant on one-pot synthesis of sulfonamides 4-substituted-isoxazolines

Next, we examined the reactivity of *p*-chlorobenzaldehyde **1a** (1.0 equiv1) with hydroxylamine hydrochloride (1.5 equiv), and alkene **2 h**

Table 3
Generalization of the *one-pot* two-steps procedure under sonication.



Entry [a]	Isoxazoline	R^1	R^2	Ar	Time (min)	Yield (%)[b]
1	**3a**	Ph	4-Cl C_6H_4	4-Cl C_6H_4	17	86
2	**3b**	Me	4-MeO C_6H_4	3,4-di Cl C_6H_3	18	77
3	**3c**	Ph	4-MeO C_6H_4	3-NO_2 C_6H_4	20	81
4	**3d**	Ph	4-Br C_6H_4	3-NO_2 C_6H_4	22	63
5	**3e**	Ph	4-MeO C_6H_4	C_6H_5	16	68
6	**3f**	Ph	4-Cl C_6H_4	3-NO_2 C_6H_4	21	81
7	**3g**	Ph	4-Cl C_6H_4	C_6H_5	16	59
8	**3h**	Ph	C_6H_5	3,4-di Cl C_6H_3	16	75
9	**3i**	Ph	C_6H_5	4-Me C_6H_4	14	85
10	**3j**	Ph	C_6H_5	3,4,5-tri MeO C_6H_2	12	67
11	**3k**	Ph	C_3H_7	3,4-di Cl C_6H_3	16	65
12	**3l**	Me	C_6H_5	3,4-di Cl C_6H_3	14	84
13	**3m**	Ph	4-MeO C_6H_4	3,4-di Cl C_6H_3	16	70
14	**3n**	Et	4-MeO C_6H_4	3-NO_2 C_6H_4	18	86
15	**3o**	Et	4-Cl C_6H_4	C_6H_5	19	58
16	**3p**	Me	4-Cl C_6H_4	C_6H_5	18	53
17	**3q**	Me	4-Me C_6H_4	3-NO_2 C_6H_4	19	52
18	**3r**	Ph	C_3H_7	3-NO_2 C_6H_4	17	60

[a] Reactions carried out with (1 mmol) of aldehyde, (1.5 mmol) $NH_2OH.HCl$, (0.5 mmol) TCCA and (1 mmol) alkene, in EtOH/H_2O (10 mL, 1 :1) at 25 °C under sonication (ultrasonic bath, 47 kHz).
[b] Yield of products after purification.

(1.0 equiv) as the benchmark reaction for the 1,3-dipolar cycloaddition under oxidative condition leading to sulfonamides 4-substituted-isoxazolines (Table 2). For this purpose, different oxidizing agents were screened, with or without base, under conventional stirring or sonication, at room temperature (25 °C).

First, we proceeded to the optimization of the *one-pot* two steps conversion of the aldehyde **1a** to the corresponding nitrile oxide, using different oxidants (1,0 equiv.) with or without base, and its cycloaddition with the model *N*-allyl compound **2 h** (Table 2, entries 2–7). We first confirmed that the presence of an oxidant is mandatory (entry 1). Therefore, we subsequently assessed different oxidants (*N*-chlorosuccinimide, chloranil and chloramine-T), in the presence/absence of a base. It appeared that the reaction performs poorly when the base is omitted. Low yields of isolated product **3a** were obtained under such conditions (10–36%, Table 2, entries 2, 4, 6). However, once the base is added the reactions proceed more smoothly and the isolated yields were improved. For instance, a 40% yield increase was observed with *p*-Chloranil in the presence of K_2CO_3 (Table 2, entries 4 and 5). Similarly, a 50% yield increase was observed for *N*-chlorosuccinimide in the presence of Et_3N (Table 2, entries 2 and 3). Of note, the combination of ceric ammonium nitrate (CAN) as the oxidant, and K_2CO_3 [33] afforded the expected product **3a** in good yield (75%, entry 8).

We then pursued our investigation using TCCA as the oxidant. While the other oxidants required presence of a base, TCCA could be used alone, without affecting the isolated yields. In fact, the desired product **3a** was obtained in excellent yield, up to 87%, and short reaction time (Table 2, entries 9 and 10). It is noteworthy that the ultrasound assistance speeded up the reaction by 20-fold (12 min vs 4 h) compared with conventional stirring.

Afterwards, we focused on reducing the quantity of TCCA, decreasing from 1.0 equiv to 0.5 equiv promoted the reaction similarly in terms of yield and reaction time (Table 2, entry 11; 89 %). Although, a further decrease in the amount of TCCA (from 0.5 to 0.3 equiv.) induced a reduction in yield (Table 2, entry 12; 65%).

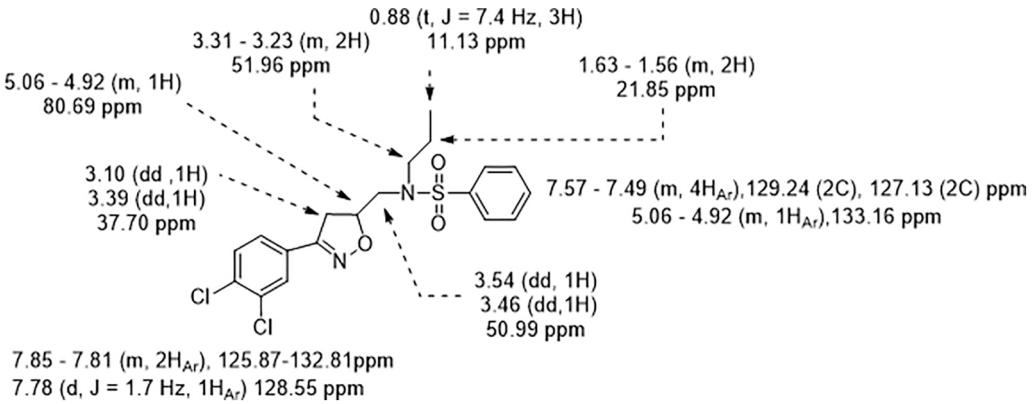


Fig. 2. Characteristic ^1H, ^{13}C NMR of **3 k.**

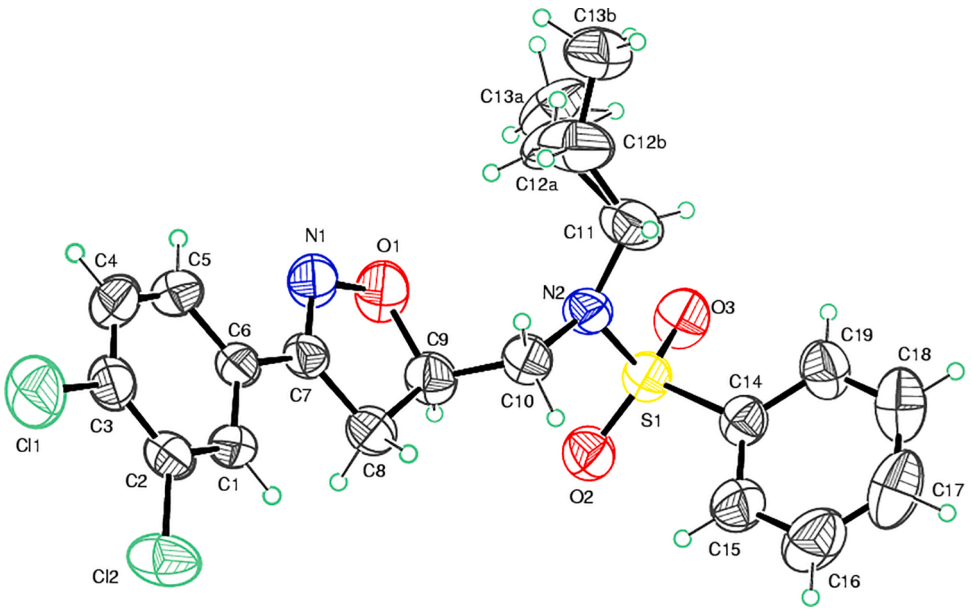
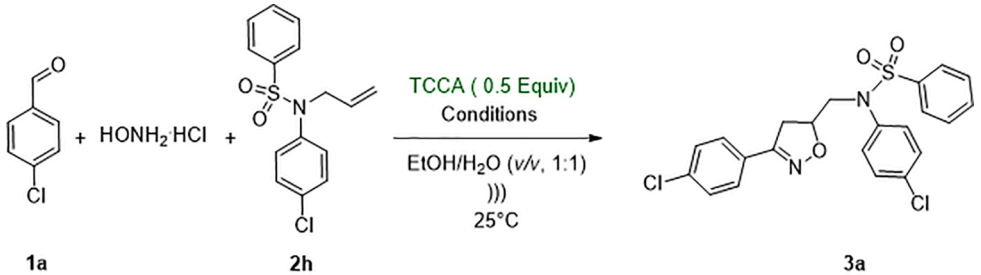


Fig. 3. The ORTEP diagram of novel single crystal of product **(3 k).**



Conditions	3a yield		
a. TEMPO (0.5 equiv), 20 min	55 %	+	TEMPO-trapped unidentified products
b. O_2, 15 min	90 %		
c. air, 15 min	89 %		

Scheme 2. Radical scavenging and control experiments.

3.3. High efficiency synthesis of sulfonamides 4-substituted-isoxazolines 3a-r under sonication

After optimizing the experimental conditions, we explored the scope of this new *one-pot* reaction to synthesize a series of isoxazolines (Table 3).

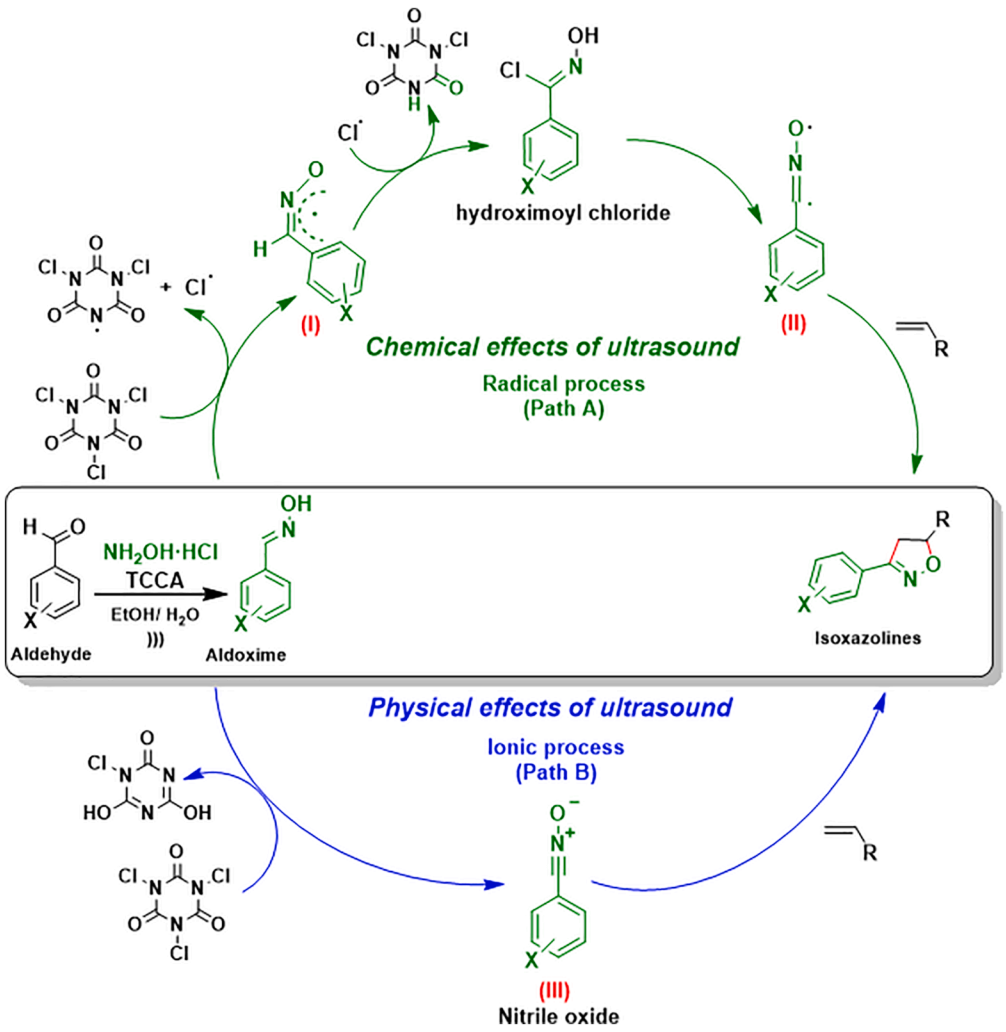
All experiments were performed in short overall reaction time (12–22 min) and isolated yields ranged between 52 and 86% (Table 3). A variety of aldehyde substituents were explored first, by using either electron-donating groups such as methoxy and methyl or electron-withdrawing groups such as chlorine, bromine and nitro. All these substitutions were well tolerated. The corresponding cycloadducts were obtained in good yields (Table 3, entries 1–4, 11–14 and 17–18). In addition, the substrates with an electron donor or acceptor group all reacted well to generate the desired isoxazolines (**3a-r**) with good to high yields.

The isoxazolines (**3a-r**), were fully characterized by IR, ^{1}H, ^{13}C NMR, 2D NMR, MS and their HPLC traces were acquired. For example, the ^{1}H NMR spectrum of *N-[3-(3,4-Dichloro-phenyl)-isoxazolin-5-ylmethyl]-N-propyl-benzenesulfonamide* **3 k** showed a multiplet with a chemical shift δ = 5.06–4.92 ppm for the *H*-isoxazolinic proton, two doublets appear at δ = 3.10 and 3.39 ppm characteristic of the two CH_2-isoxazolinic protons, two other signals in the form of doublets at δ = 3.54 and 3.46 ppm correspond to the two protons of methylene, thus the presence of the signals between 4.92 and 7.85 ppm attributable to the different aromatic protons. The ^{13}C NMR spectrum showed characteristic signals at 11.13 ppm (CH_2-CH_2-**CH_3**), 21.85 ppm (CH_2-**CH_2**-CH_3), 37.70 ppm (**$CH_{2isoxazoline}$**), 51.96 ppm (**CH_2**-CH_2-CH_3), 50.99 ppm (N-**CH_2**-CH), 80.69 ppm (**$CH_{isoxazoline}$**) and 125.87–132.81, 127.13, 128.55, 129.24, 133.16 ppm attributable for aromatic carbons (Fig. 2).

The regioselectivity of the cycloaddition was further ascertained by X-ray diffraction of single crystal of **3 k.** The single crystals were obtained by slow evaporation from a saturated ethanolic solution (Fig. 3). The crystallographic data (see ESI) relative to the structure of **3 k** has been deposited with the Cambridge Crystallographic Data Centre [34].

3.4. The study of acceleration mechanism under sonication

In this work, the remarkable acceleration and yield improvement observed under US can be explained by the simultaneous coexistence of chemical and mechanical effects of ultrasound [35]; the chemical effects generating free radicals with a high propensity to react due to the



Scheme 3. Plausible mechanism of the isoxazoline formation under heterogeneous ultrasound conditions.

implosion of microbubbles and the mechanical effects that enhance heterogeneous solid–liquid or liquid–liquid reactions due to microjets formed during cavitation [36]. In fact, cavitation accelerates much more easily mass transport between the two phases such as alkene and aldehyde that are poorly soluble at the beginning of the reaction. The 1,3-dipolar cycloaddition reaction can take place in both concerted or radical mechanism [37]. Depending on the reaction conditions used, TCCA can release either an electrophilic chlorine atom (Cl^+) or a chlorine radical ($Cl^{\cdot}$) selectively promoting two plausible concerted and /or radical mechanistic approaches [38].

The use of direct-ultrasonic irradiation, the radical or radical-ion intermediates are generated more possibly in water [39]. For the present hypothesis, a series of control experiments were carried out (Scheme 2). The reaction yields have dramatically changed under different conditions. When a radical scavenger, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), was added under sonication, a significant decrease in yield of **3a** (≈ 55 %) was observed along with the formation of other non-identified products trapped by TEMPO (Scheme 2, a), which suggests that the reaction under ultrasonication evolves the two mechanisms *i.e.*, radical and ionic. This observation was supported with other experiments under O_2 or air as the radical initiator, without TEMPO under suitable conditions. The reaction gave the isoxazoline product **3a** with excellent yields, 90% and 89% respectively (Scheme 2, b and c).

Based on the above-mentioned experimental observations, a plausible mechanism has been propozed as shown in scheme 3. Firstly, the chlorine radical atom ($Cl^{\cdot}$) and dichloroisocyanuric acid radical were generated by the homolytic cleavage of *N*–Cl bond in TCCA assisted by ultrasound [40]. The amidyl radical *N*-centered will then react as a proton acceptor during the first step of reaction with hydroxylamine hydrochloride to provide the aldoxime (not isolated) [32], which is then converted to hydroximoyl chloride with TCCA [41,42]. The latter was subsequently oxidized to unstable bi-radical nitrile oxide (II) [43], promoted by the chemical effect of ultrasound, followed by a rapid 1,3-cycloaddition reaction with allyl-sulfonamide **2**, to deliver the corresponding isoxazoline product (Path A, Scheme 3).

Following similar approach, an electrophilic chlorine atom (Cl^+) and cyanurate anion were generated from TCCA the mechanical effect of ultrasound that promotes an ionic process through the generation of nitrile oxide (III) which reacts with the alkene to give the corresponding isoxazoline by 1,3-cycloaddition reaction (Path B, scheme 3).

Taking into account all these considerations, we suggested that the mechanistic outcome of this heterogeneous reaction might be explained by a switch from a radical mechanism (Path A, scheme 3) to a concerted mechanism (Path B, scheme 3) upon sonication [44]. In both pathways the reaction affords only one regiosiomer 4-substituted isoxazoline. This high regioselectivity can be explained by considering the steric interactions that prevents the formation of C5-substituted isoxazolines in favor of the exclusive formation of C4-substituted isoxazolines [45]. In fact, the acceleration observed in this reaction is maybe due to the cooperative effects of ultrasound activation and the TCCA catalytic capacity.

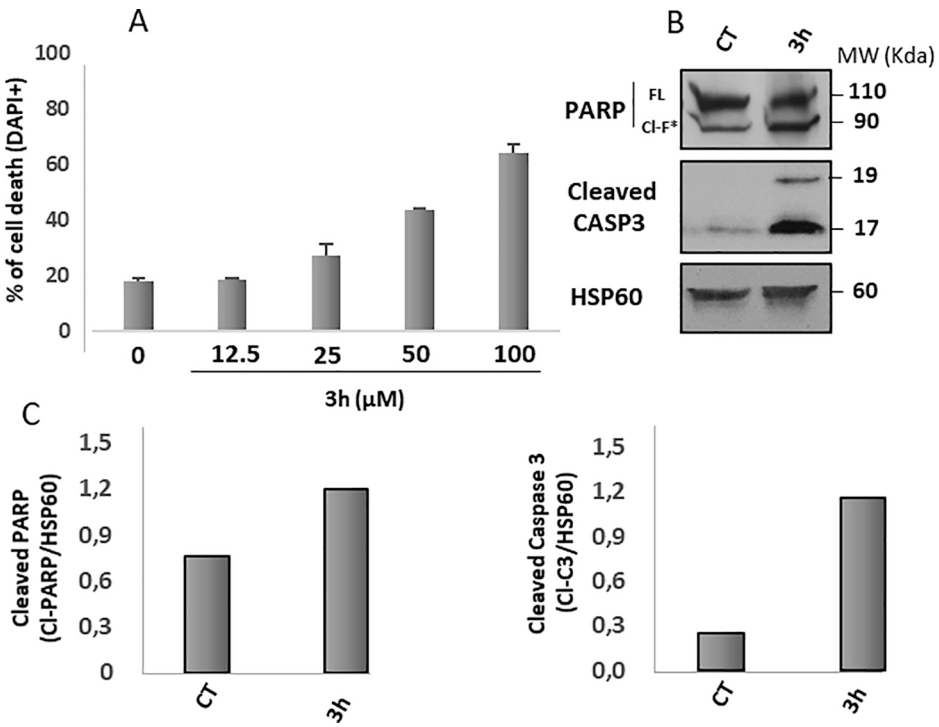


Fig. 4. *Upper-left panel (A)* HL-60 cells were treated with increasing doses (12.5–100 µM) of **3 h** and cell viability was evaluated after 48 h with DAPI staining and flow cytometry analysis. *Upper-right panel (B)* HL-60 cells were treated with 94 µM of **3 h** (48 h), and expression of cleaved forms of PARP and caspase 3 were analyzed by Western blot. HSP60 was used as loading control. *Lower panel (C)* Quantification of the cleaved form of PARP and caspase 3, normalized against loading control HSP60.

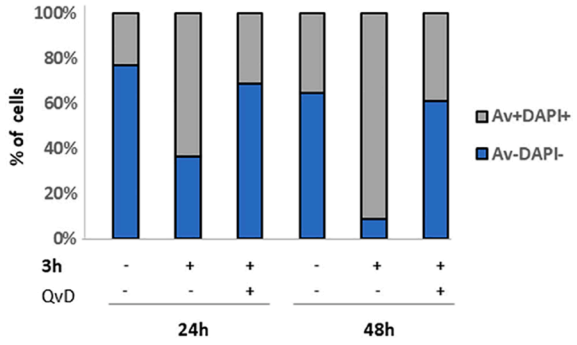


Fig. 5. HL-60 cells were treated during 24 h or 48 h with 94 µM of **3 h** in presence or absence of QvD (Av = Annexin V).

4. Biology

All these newly synthesized isooxazoline **3a-r**, were evaluated for their anti-cancer activity against K562 cell line (CML) at 1 µM 10 µM and 50 µM (48 h) using XTT and DAPI assays. This first screening against K562 cells revealed a couple of compounds (**3 h** and **3 l**) decreases the cell viability between 10 and 50 µM. Thus, we decided to investigate further the biological effect of **3 h**. It is interesting to note that these two compounds share the same structure except for the sulfonamide part (R^1 = Ph for **3 h** and $R^1 = CH_3$ for **3 l**).

Next, we evaluated the dose–response effect of **3 h** (12.5–100 µM) on HL-60 cell line (APL, Fig. 4-A). This was performed in a DAPI assay by flow cytometry. The percentage of HL-60 DAPI positive cells (dead cells) increased from 18% in the untreated control population (and at the dose of 12.5 µM) to 31, 44 and 67% in cultures treated by **3 h** for 48 h with respectively 25, 50 and 100 µM doses. The determined value of EC_{50} (i.e. the concentration leading to a cell viability rate of 50%) of the compound **3 h** on HL-60 cell was found at 62 ± 2 µM. In addition, to get insights into the mode of action of this new compound (**3 h**), we had a look at cell death mechanism induced by **3 h**. HL-60 cells were treated for 48 h with 94 µM of **3 h** and PARP (poly ADP-ribose polymerase, marker of apoptosis) and caspase 3 (apoptosis-related cysteine peptidase) cleavage were analyzed by Western blot (Fig. 4-B, 3-C). Compound **3 h** display a strong induction of apoptosis when HL60 cells were treated at the EC_{50} concentration as suggested by cleavage of PARP and more evidently caspase 3.

To confirm that **3 h** induced a caspase dependent apoptotic cell death, we performed an AV/DAPI labeling in the presence of a pan-caspsae inhibitor (QvD) on HL60 cell line at 24 and 48 h (Fig. 5). While **3 h** alone induced a significant drop in the cell viability, the co-treatment with QvD completely restored it. In fact, the co-treatment induced a cell viability comparable with control experiment (untreated cells). This experiment shows us in a formal way that the death induced by compound **3 h** is a caspases-dependent process at 24 and 48 h, thus confirming the first results obtained by western blot (Fig. 4).

5. Conclusion

In summary, we reported the synthesis, chemical characterization and anticancer activity of a novel functionalized 3,5-disubstituted sulfonamide-isoxazoline series. These molecules were synthesized using a new, versatile and efficient "two-step one-pot" methodology through a 1,3-dipolar cycloaddition reaction. This environmentally friendly process was carried out efficiently in an aqueous medium. It is based on the use of inexpensive and environmentally friendly TCCA as an oxidant to generate nitrile oxides in-situ. In addition, the use of a cooperative effect of ultrasound activation and TCCA catalytic capacity allows significant reaction rate acceleration. Among this series of isoxazoline analogues one compound, **3 h**, impairs the cell viability of leukemia K562 and HL-60 cells. In addition, **3 h** behaved as an apoptotic cell death inducer. Altogether, these results clearly demonstrated the potential of this class of molecules for the optimization of apoptosis inducer owing to their ease of synthesis the herein report two-step one-pot strategy.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ultsonch.2021.105748.

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ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Tel. +44 1223 336 408; Fax: +44 1223 336 033; or e-mail. deposit@ccdc.cam.ac.uk).

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