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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).

Keywords

Sulfonamides-Isoxazolines, One-pot synthesis, Radical processes, Ultrasound, Hematological Malignancies.

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] (Figure 1).

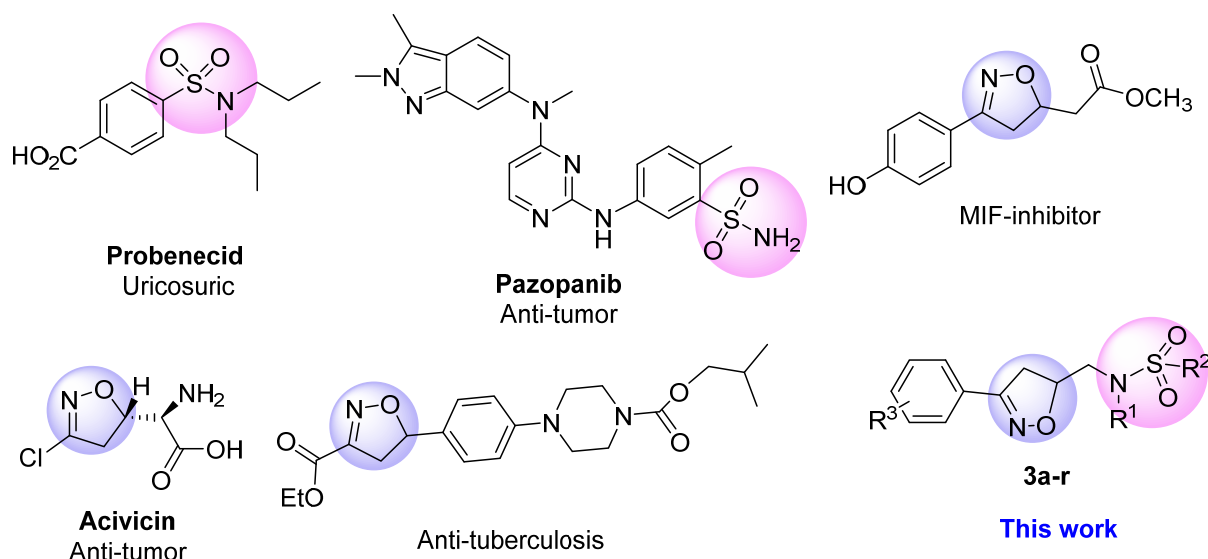
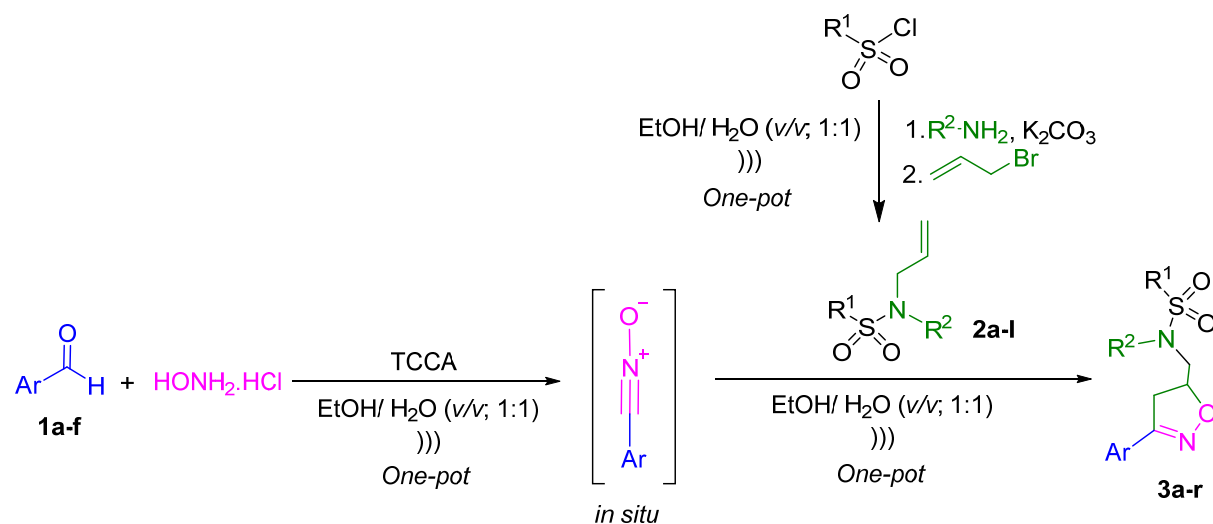


Figure 1. Selected examples of therapeutic agents containing an isoxazoline or sulfonamide function [16-19].

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], $\text{MgO}(\text{Ac})_2$ [22], $\text{Ce}^{\text{III}}/\text{NaI}/\text{I}_2$ [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 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.



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

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 F₂₅₄, E. Merck, Germany), and chromatograms were visualized by UV- light irradiation (254 and 360 nm), then by staining with ninhydrin or $\text{H}_2\text{SO}_4/\text{EtOH}$. 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 ^1H 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 CH₃CN, both containing 1% HCOOH). Purity of all compounds was found to be $\geq 95\%$ as determined by HPLC using UV detection at 254 nm. The ultrasound-assisted reactions were carried out in an “Elmasonic S 30 / S 30 H 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 K₂CO₃ (2 equiv) were dissolved in EtOH/H₂O (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; ¹H 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). ¹³C 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; ¹H 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). ¹³C 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; ¹H 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). ¹³C 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; ¹H 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). ¹³C 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; ¹H 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). ¹³C 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; ¹H 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). ¹³C 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 (2g)*: Gray Solid, M_P 91-94°C, TLC (cyclohexane/AcOEt, 6/4, *v/v*) R_f = 0.54; ¹H 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). ¹³C 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 (**2h**): Green Solid, M_P 65-67°C, TLC (cyclohexane/AcOEt, 6/4, v/v) R_f = 0.6; ¹H 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). ¹³C 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; ¹H 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). ¹³C 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 ¹H 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). ¹³C 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 (**2k**): Beige Solid, M_P 66-69°C, TLC (cyclohexane/AcOEt, 6/4, v/v) R_f = 0.52; ¹H 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). ¹³C 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 (**2l**) : Green Solid, M_P 97-99°C, TLC (cyclohexane/AcOEt, 8/2, v/v) R_f = 0.38; ¹H 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). ¹³C 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/H₂O (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 CH₂Cl₂ (20 mL x 2). The organic phase was washed with water (20 mL) and saturated brine solution (20 mL), dried over MgSO₄ 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; ¹H 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). ¹³C 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 = 4.55min).

2.2.2.2. *N*-[3-(3,4-Dichloro-phenyl)-isoxazolin-5-ylmethyl]-*N*-(4-methoxy-phenyl)-methane

sulfonamide (3b): White Solid, Mp 170-172°C, TLC (cyclohexane/AcOEt, 8/2, v/v) R_f = 0.52; ¹H 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). ¹³C 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 = 4.15min)

2.2.2.3. *N*-(4-Methoxy-phenyl)-*N*-[3-(3-nitro-phenyl)-isoxazolin-5-ylmethyl]-benzene

sulfonamide (3c): White Solid, Mp 145-147°C, TLC (cyclohexane/AcOEt, 8/2, v/v) R_f = 0.5; ¹H 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). ¹³C 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 = 4.11min).

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; ¹H 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). ¹³C 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 = 4.33min).

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; ¹H 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). ¹³C 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, M_P 152-154°C, TLC (cyclohexane/AcOEt, 8/2, v/v) R_f = 0.29; ¹H 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). ¹³C 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 (3g):

White Solid, M_P 148-150°C, TLC (cyclohexane/AcOEt, 8/2, v/v) R_f = 0.34; ¹H 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). ¹³C 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, $\lambda = 254 \text{ nm}$, purity 99 %, $t_R = 4.15 \text{ min}$).

2.2.2.8. *N*-[3-(3,4-Dichloro-phenyl)-isoxazolin-5-ylmethyl]-*N*-phenyl-benzenesulfonamide (**3h**): White Solid, Mp 148-150°C, TLC (cyclohexane/AcOEt, 8/2, v/v) $R_f = 0.34$; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, $J = 1.7 \text{ Hz}$, 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, $J = 13.7, 7.8 \text{ Hz}$, 1H), 3.74 (dd, $J = 13.7, 4.8 \text{ Hz}$, 1H), 3.54 (dd, $J = 16.9, 6.5 \text{ Hz}$, 1H), 3.38 (dd, $J = 16.9, 10.6 \text{ Hz}$, 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, $\lambda = 254 \text{ nm}$, purity 96 %, $t_R = 4.55 \text{ min}$).

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) $R_f = 0.34$; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.55 (m, 5H), 7.48 (t, $J = 7.7 \text{ Hz}$, 2H), 7.37 – 7.32 (m, 3H), 7.23 (d, $J = 7.9 \text{ Hz}$, 2H), 7.10 – 7.05 (m, 2H), 4.83 – 4.71 (m, 1H), 3.83 (dd, $J = 13.5, 7.9 \text{ Hz}$, 1H), 3.73 (dd, $J = 13.6, 4.8 \text{ Hz}$, 1H), 3.53 (dd, $J = 16.9, 6.4 \text{ Hz}$, 1H), 3.40 (dd, $J = 16.8, 10.4 \text{ Hz}$, 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, $\lambda = 254 \text{ nm}$, purity 100 %, $t_R = 4.28 \text{ min}$).

2.2.2.10. *N*-Phenyl-*N*-[3-(3,4,5-trimethoxy-phenyl)-isoxazolin-5-ylmethyl]-benzenesulfonamide (**3j**): White Solid, Mp 175-177°C, TLC (cyclohexane/AcOEt, 8/2, v/v) $R_f = 0.55$; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.55 (m, 3H), 7.48 (t, $J = 7.7 \text{ Hz}$, 2H), 7.35 – 7.32 (m, 3H), 7.09 – 7.05 (m, 2H), 4.83 – 4.72 (m, 1H), 3.91 (s, $J = 3.1 \text{ Hz}$, 6H), 3.90 (s, 3H), 3.85 (dd, $J = 13.6, 8.0 \text{ Hz}$, 1H), 3.70 (dd, $J = 13.6, 4.8 \text{ Hz}$, 1H), 3.56 (dd, $J = 16.8, 6.3 \text{ Hz}$, 1H), 3.40 (dd, $J = 16.8, 10.4 \text{ Hz}$, 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 (2CH₃), 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=C_{Ar}) and (C-H_{Ar}) elongation ; HPLC analysis (luna column, $\lambda = 254$ nm, purity 100 %, $t_R = 4.02$ min).

2.2.2.11. *N*-[3-(3,4-Dichloro-phenyl)-isoxazolin-5-ylmethyl]-*N*-propyl-benzenesulfonamide (**3k**): Monocrystal, Mp 115-116°C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) $R_f = 0.34$; ¹H 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). ¹³C 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, $\lambda = 254$ nm, purity 100%, $t_R = 4.53$ min).

2.2.2.12. *N*-[3-(3,4-Dichloro-phenyl)-soxazolin-5-ylmethyl]-*N*-phenyl-methanesulfonamide (**3l**): White Solid, Mp 135-137°C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) $R_f = 0.14$; ¹H 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). ¹³C 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, $\lambda = 254$ 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 (**3m**) : White Solid, Mp 109-111°C, TLC (cyclohexane/AcOEt, 8/2, *v/v*) $R_f = 0.59$; ¹H 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). ¹³C 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, $\lambda = 254$ 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*) $R_f = 0.28$; ¹H 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): $m/z = 419.45$ [$\text{M} + \text{H}$] $^{+}$; HPLC analysis (luna column, $\lambda = 254$ nm, purity 95 %, $t_{\text{R}} = 3.86$ 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*) $R_{\text{f}} = 0.29$; ^1H 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): $m/z = 378.45$ [$\text{M} + \text{H}$] $^{+}$; HPLC analysis (luna column, $\lambda = 254$ nm, purity 100 %, $t_{\text{R}} = 4.03$ 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*) $R_{\text{f}} = 0.27$; ^1H 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): $m/z = 365.06$ [$\text{M} + \text{H}$] $^{+}$; HPLC analysis (luna column, $\lambda = 254$ nm, purity 100 %, $t_{\text{R}} = 3.95$ 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*) $R_{\text{f}} = 0.27$; ^1H 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): $m/z = 389.10$ [$\text{M} + \text{H}$] $^{+}$; HPLC analysis (luna column, $\lambda = 254$ nm, purity 98 %, $t_{\text{R}} = 3.87$ 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*) $R_{\text{f}} = 0.25$; ^1H 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): $m/z = 403.12$ [$\text{M} + \text{H}$] $^+$; IR (KBr, cm^{-1}): 1336 (S=O), 1188 (S=O), 1046 (Propyl), 1500 (N=O), 3312-2700 (C=C_{Ar}) and (C-H_{Ar}) elongation 818-670 (3H_{Ar}-Adjacent); HPLC analysis (luna column, $\lambda = 254$ nm, purity 99 %, $t_{\text{R}} = 4.12$ 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/H₂O (*v/v*, 1:1) (10 mL) TCCA (0.5 equiv, 58.1 mg), TEMPO (0.5 equiv, 78.1 mg) and alkene **2h** (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 CH₂Cl₂ (20 mL). The organic phase was washed with water (20 mL) and saturated brine solution (20 mL), dried over MgSO₄ 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

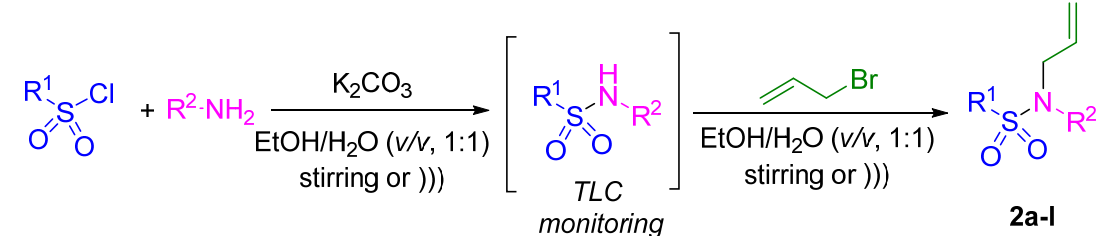
One crystal suitable for X-ray diffraction analysis was coated with dry perfluoropolyether, mounted on glass fiber, and fixed in a cold nitrogen stream to the goniometer head. Data collection was performed on a Bruker D8 VENTURE Super DUO diffractometer, using graphite monochromatized Mo radiation (Mo $K\alpha$ radiation, $\lambda = 0.71073$ 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 supplementary publications. CCDC 2040890 **3k**. 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 [32]. 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.

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 ₆ H ₄	11	70	27	75
2	2b	Me	C ₆ H ₅	9	60	18	66
3	2c	Ph	C ₆ H ₅	12	75	25	79
4	2d	Me	4-MeO C ₆ H ₄	8	56	16	65
5	2e	Et	4-MeO C ₆ H ₄	10	78	17	81
6	2f	Ph	C ₃ H ₇	6	66	19	69
7	2g	Ph	4-MeO C ₆ H ₄	10.5	75	21	83
8	2h	Ph	4-Cl C ₆ H ₄	14	55	26	69
9	2i	Me	4-Me C ₆ H ₄	9.5	60	15	69
10	2j	Et	4-Cl C ₆ H ₄	8.5	64	21	68
11	2k	Et	4-Me C ₆ H ₄	9	72	18	76
12	2l	Me	4-Cl C ₆ H ₄	13	77	22	86

^a Phenyl/alkyl sulfonyl chloride (1.1 mmol), primary amine (1.0 mmol), K₂CO₃ (2.0 mmol) in EtOH/H₂O (20 ml, 1:1) at 25°C, then allyl bromide (1.1 mmol). ^b Isolated yield after purification.

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 equiv) with hydroxylamine hydrochloride (1.5 equiv), and alkene **2h** (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).

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

Reaction scheme: **1a** + **HONH₂HCl** + **2h** $\xrightarrow[\text{EtOH/H}_2\text{O (v/v, 1:1), 25}^\circ\text{C, stirring or sonication}]{\text{Oxidant}}$ **3a**

Entry ^a	Oxidant (1 equiv)	Base (1.2 equiv)	Conventional stirring		Sonication	
			Time (h)	Yield (%) ^b	Time (min)	Yield (%) ^b
1	None	--	12	nr	30	nr
2	NCS	--	6	<10	20	15
3	NCS	Et ₃ N	5	50	16	65
4	<i>p</i> -Chloranil	--	4	<5	15	10
5	<i>p</i> -Chloranil	K ₂ CO ₃	4	45	12	52
6	Chloramine-T	--	6	20	17	36
7	Chloramine-T	K ₂ CO ₃	5	49	22	61
8	CAN	K ₂ CO ₃	6	56	20	75
9	TCCA	--	4	72	12	87

10	TCCA	K ₂ CO ₃	4	70	12	86
11 ^c	TCCA	--	4	71	12	89
12 ^d	TCCA	--	4	53	20	62

^a aryl aldehyde/ HONH₂.HCl (1/1.5 mmol), in EtOH/H₂O (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.

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 **2h** (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 K₂CO₃ (Table 2, entries 4 and 5). Similarly, a 50% yield increase was observed for *N*-chlorosuccinimide in the presence of Et₃N (Table 2, entries 2 and 3). Of note, the combination of ceric ammonium nitrate (CAN) as the oxidant, and K₂CO₃ [32] afforded the expected product **3a** in good yield (75%, entry 8).

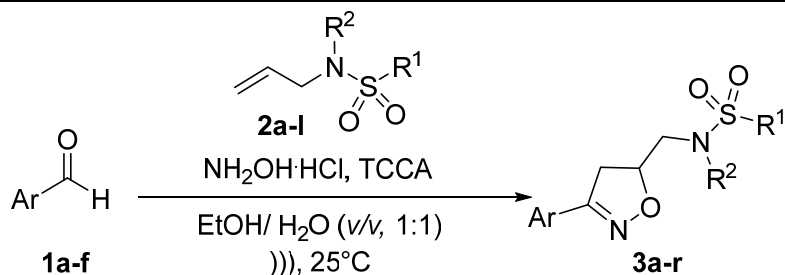
We then pursued our investigation using TCCA as the oxidant. While the other oxidants required presence of a base, TCCA could be used alone, without affecting the isolated yields. In fact, the desired product **3a** was obtained in excellent yield, up to 87%, and short reaction time (Table 2, entries 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%).

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).

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 ₆ H ₄	4-Cl C ₆ H ₄	17	86
2	3b	Me	4-MeO C ₆ H ₄	3,4-di Cl C ₆ H ₃	18	77
3	3c	Ph	4-MeO C ₆ H ₄	3-NO ₂ C ₆ H ₄	20	81
4	3d	Ph	4-Br C ₆ H ₄	3-NO ₂ C ₆ H ₄	22	63
5	3e	Ph	4-MeO C ₆ H ₄	C ₆ H ₅	16	68
6	3f	Ph	4-Cl C ₆ H ₄	3-NO ₂ C ₆ H ₄	21	81
7	3g	Ph	4-Cl C ₆ H ₄	C ₆ H ₅	16	59
8	3h	Ph	C ₆ H ₅	3,4-di Cl C ₆ H ₃	16	75
9	3i	Ph	C ₆ H ₅	4-Me C ₆ H ₄	14	85
10	3j	Ph	C ₆ H ₅	3,4,5-tri MeO C ₆ H ₂	12	67
11	3k	Ph	C ₃ H ₇	3,4-di Cl C ₆ H ₃	16	65
12	3l	Me	C ₆ H ₅	3,4-di Cl C ₆ H ₃	14	84
13	3m	Ph	4-MeO C ₆ H ₄	3,4-di Cl C ₆ H ₃	16	70
14	3n	Et	4-MeO C ₆ H ₄	3-NO ₂ C ₆ H ₄	18	86
15	3o	Et	4-Cl C ₆ H ₄	C ₆ H ₅	19	58
16	3p	Me	4-Cl C ₆ H ₄	C ₆ H ₅	18	53
17	3q	Me	4-Me C ₆ H ₄	3-NO ₂ C ₆ H ₄	19	52
18	3r	Ph	C ₃ H ₇	3-NO ₂ C ₆ H ₄	17	60

^a Reactions carried out with (1 mmol) of aldehyde, (1.5 mmol) NH₂OH.HCl, (0.5 mmol) TCCA and (1 mmol) alkene, in EtOH/H₂O (10 ml, 1 : 1) at 25°C under sonication (ultrasonic bath, 47 kHz).

^b Yield of products after purification.

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, ^1H , ^{13}C NMR, 2D NMR, MS and their HPLC traces were acquired. For example, the ^1H NMR spectrum of *N*-[3-(3,4-Dichlorophenyl)-isoxazolin-5-ylmethyl]-*N*-propyl-benzenesulfonamide **3k** showed a multiplet with a chemical shift $\delta = 5.06 - 4.92$ ppm for the *H*-isoxazolinic proton, two doublets appear at $\delta = 3.10$ and 3.39 ppm characteristic of the two CH_2 -isoxazolinic protons, two other signals in the form of doublets at $\delta = 3.54$ and 3.46 ppm correspond to the two protons of methylene, thus the presence of the signals between 4.92-7.85 ppm attributable to the different aromatic protons. The ^{13}C NMR spectrum showed characteristic signals at 11.13 ppm ($\text{CH}_2\text{-CH}_2\text{-CH}_3$), 21.85 ppm ($\text{CH}_2\text{-CH}_2\text{-CH}_3$), 37.70 ppm (CH_2 isoxazoline), 51.96 ppm ($\text{CH}_2\text{-CH}_2\text{-CH}_3$), 50.99 ppm ($\text{N-CH}_2\text{-CH}$), 80.69 ppm (CH isoxazoline) and 125.87-132.81, 127.13, 128.55, 129.24, 133.16 ppm attributable for aromatic carbons.

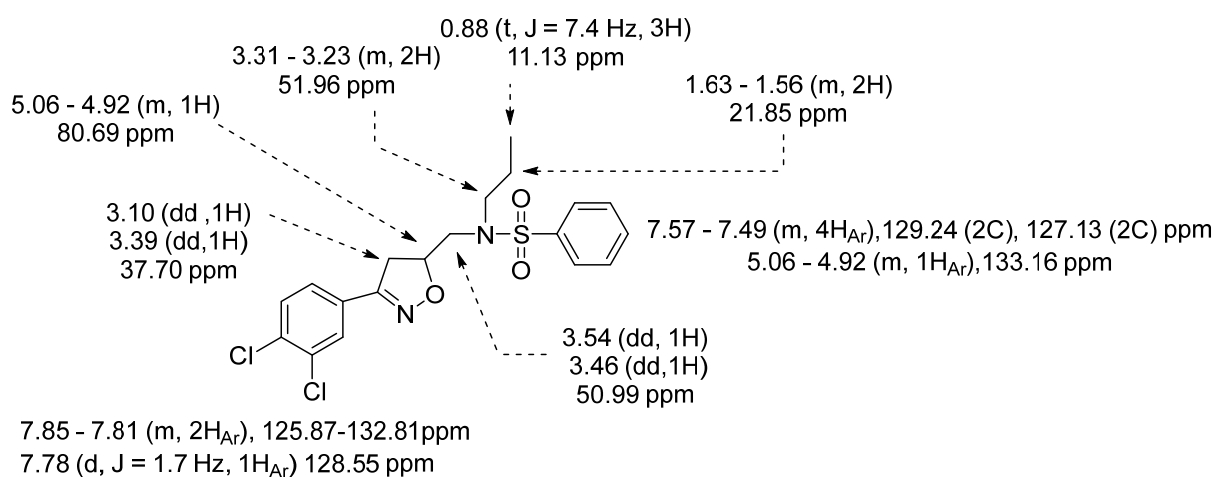


Figure 2 Characteristic ^1H , ^{13}C NMR of **3k**.

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

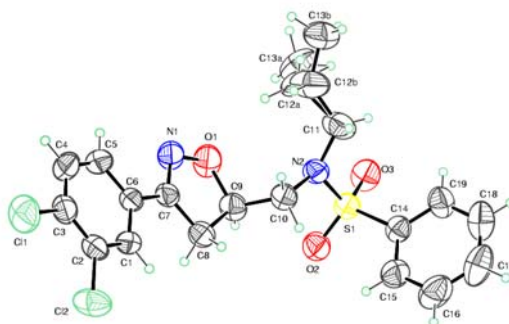


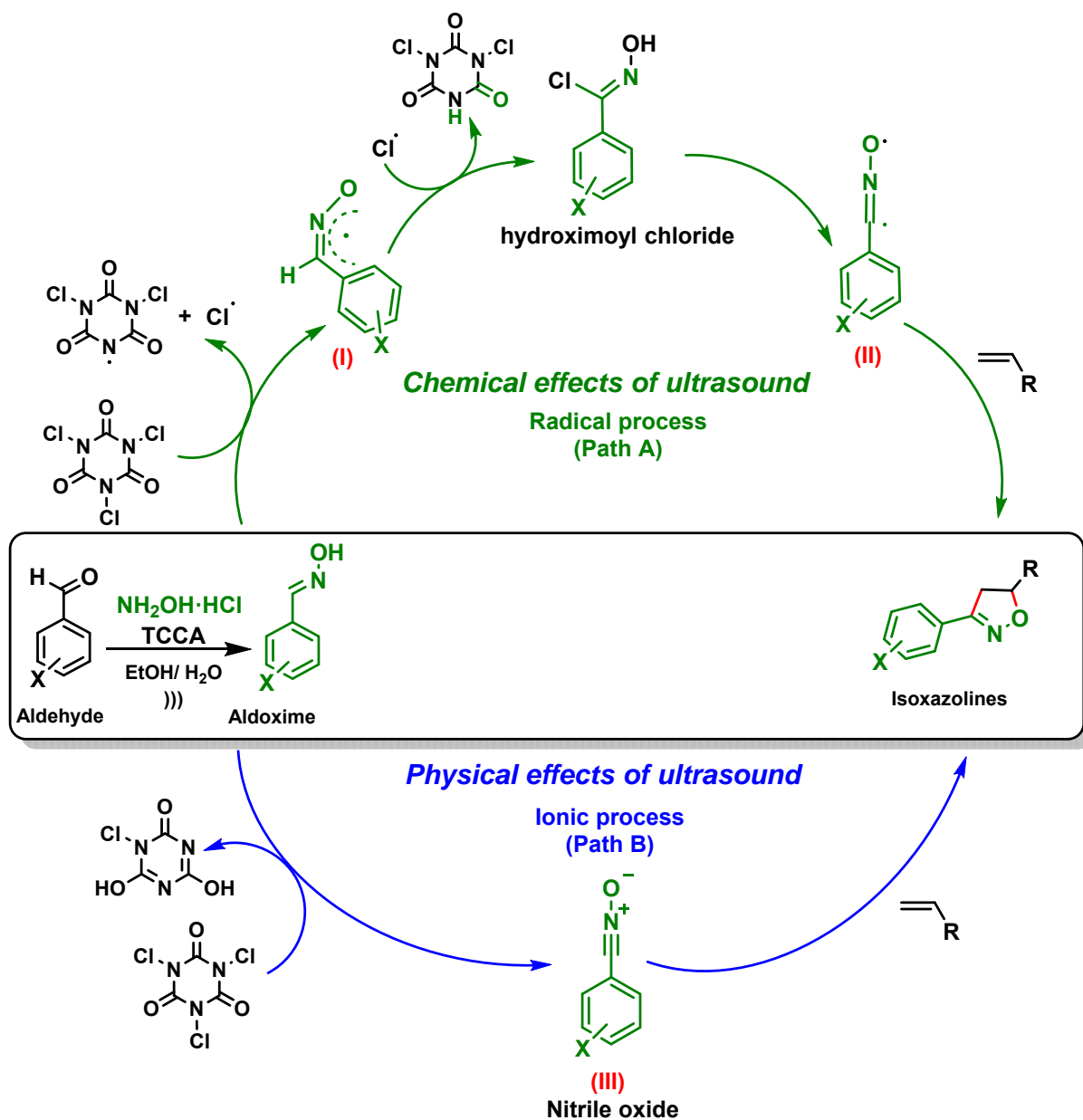
Figure 3. The ORTEP diagram of novel single crystal of product (**3k**).

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 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 ($\text{Cl}\cdot$) 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 the investigated conditions. When a radical scavenger, TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), was added under sonication, a significant decrease in yield of **3a** ($\approx 55\%$) 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 according 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).

isoxazolines [45]. In fact, the acceleration observed in this reaction is maybe due to the cooperative effect of ultrasound activation and the TCCA catalytic capacity.



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

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 (**3h** and **3l**) decreases the cell viability between 10 and 50 μM . Thus, we decided to investigate further the biological

effect of **3h**. It is interesting to note that these two compounds share the same structure except for the sulfonamide part ($R^1 = \text{Ph}$ for **3h** and $R^1 = \text{CH}_3$ for **3l**).

Next, we evaluated the dose-response effect of **3h** (12.5-100 μM) on HL-60 cell line (APL, Figure 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 **3h** for 48 hours 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 **3h** on HL-60 cell was found at 62 ± 2 μM . In addition, to get insights into the mode of action of this new compound (**3h**), we had a look at cell death mechanism induced by **3h**. HL-60 cells were treated for 48 h with 94 μM of **3h** and PARP (poly ADP-ribose polymerase, marker of apoptosis) and caspase 3 (apoptosis-related cysteine peptidase) cleavage were analyzed by Western blot (Figure 4-B, 3-C). Compound **3h** 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.

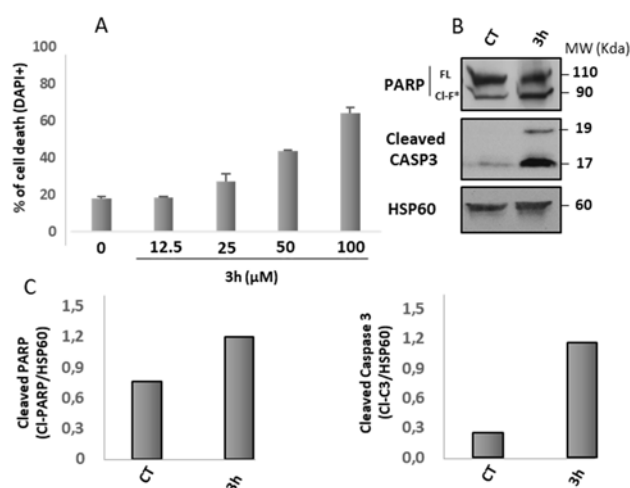


Figure 4. Upper-left panel (A) HL-60 cells were treated with increasing doses (12.5-100 μM) of **3h** and cell viability was evaluated after 48 h with DAPI staining and flow cytometry analysis. Upper-right panel (B) HL-60 cells were treated with 94 μM of **3h** (48 h), and expression of cleaved forms 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.

To confirm that **3h** induced a caspase dependent apoptotic cell death, we performed an AV/DAPI labeling in the presence of a pan-caspase inhibitor (QvD) on HL60 cell line at 24 and

48 h (Figure 5). While **3h** 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 **3h** is a caspases-dependent process at 24 and 48 h, thus confirming the first results obtained by western blot (Figure 4).

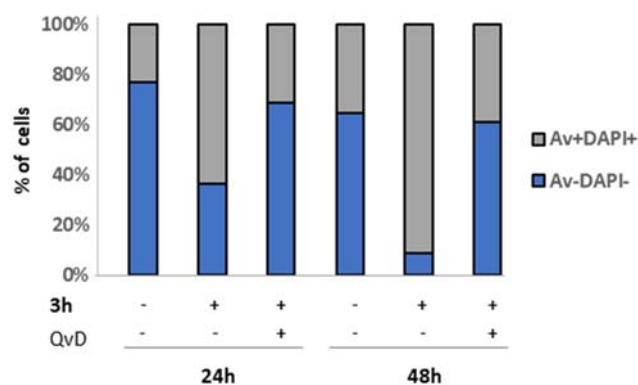


Figure 5. HL-60 cells were treated during 24 h or 48 h with 94 μ M of **3h** in presence or absence of QvD (Av = Annexin V).

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, 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, **3h**, impairs the cell viability of leukemia K562 and HL-60 cells. In addition, **3h** 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.

CRedit authorship contribution statement

Aicha Talha: Conceptualization, Methodology, Writing, **Cécile Favreau:** biology studies **Maxence Bourgoïn:** biology studies, **Guillaume Robert:** biology studies, **Patrick Auburger:** Supervision biology studies, **Lahcen EL Ammari:** Software, Validation, **Mohamed Saadi:**

Software, Validation, **Rachid Benhida**: Supervision, review, **Anthony R. Martin**: Supervision, Writing - review & editing, **Khalid Bougrin**: Supervision, Project administration, Writing - review & editing.

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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.

Supporting Information

Supplementary data include the experimental procedures for the synthesis of all the compounds, their spectroscopic characterization (NMR, IR, and HPLC), representative spectra and additional biological assays.

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