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Synthesis of sulfonamides bearing 1,3,5-triarylpyrazoline and 4-thiazolidinone moieties as novel antimicrobial agents

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Abstract: Two series of sulfonamides have been synthesized from 4-hydrazinylbenzenesulfonamide as the key starting material. 1,3,5-triarylpyrazoline sulfonamides (2a-i) were obtained by cyclocondensation of the various chalcones in 53-64 % yields while 4-thiazolidinone derivatives (4a-e) were synthesized by cyclocondensation between mercaptoacetic acid and different phenylhydrazones in 43-62 % yields. The synthesized compounds were characterized on the basis of FTIR, 1H NMR, 13C NMR, and HRMS data. The sulfonamides have been evaluated in vitro antimicrobial activities against four bacterial strains (E. coli, P. aeruginosa, B. subtillis and S. aureus), two filamentous fungal strains (A. niger and F. oxysporum) and two yeast strains (C. albicans and S. cerevisiae). Seven pyrazolines 2a-c and 2e-h exhibited significant inhibition of different microbial strains. Among them, compound 2b displayed good antifungal activity against A. niger (MIC value at 12.5 µg mL−1) over the reference drug.

Keywords: synthesis, sulfonamide, pyrazoline, thiazolidinone, antimicrobial agents

INTRODUCTION

Sulfonamides have been particularly considered as essential scaffolds for developing new medicines. The sulfonamides possess a wide range of biological activities such as anti-inflammatory1, antidepressant2, antimicrobial3,4 and anticancer5. In bacterial cells, antibacterial sulfonamides act as competitive inhibitors of the enzyme, dihydropteroate synthase that involved in folate synthesis6. Several sulfonamide drugs developed from aromatic compounds have been used in the antimicrobial therapeutic application. For instant,

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sulfanilamide and sulfamethoxazole (Figure 1) are the simplest antimicrobial therapy drugs which were commonly used in treatments against Gram-positive and Gram-negative bacteria as well as in the treatments of fungi and protozoa infections. These sulfonamides are selectively toxic in bacteria via blocking the synthesis of folic acid\textsuperscript{7,8}. However, resistance to these sulfonamides has been increased during past years because the susceptible pathogens might develop an ability to take up folic acid from their environment\textsuperscript{9}.

Figure 1. Structures of antimicrobial therapy sulfa drugs

Pyrazolines are one of important heterocycles containing two nitrogen atoms in the five-membered ring. These derivatives have been found to possess a broad spectrum of pharmacological actions such as antimicrobial\textsuperscript{10,11}, anticonvulsant\textsuperscript{12}, anti-inflammatory\textsuperscript{13} and antiviral\textsuperscript{14}. Numerous studies showed the pyrazoline derivatives possessing an interesting antimicrobial activity against many fungal and bacterial strains. For example, Zampieri et al.\textsuperscript{15} reported synthesized pyrazoline derivatives bearing imidazole moieties with high activity against two strains, \textit{C. albicans} and \textit{M. tuberculosis} H37Rv. In particular, 1,3,5-substituted pyrazolines documented as potential antibacterial agents\textsuperscript{16-18}. Additionally, 4-thiazolidinones, derivatives of thiazolidine with a carbonyl group at the 4-position, are an important scaffold known to be associated with many biological applications including anticancer, antimicrobial, antiviral and anti-inflammatory\textsuperscript{19-22}. In connection with our ongoing research program involving synthesis and biological evaluation on heterocycles\textsuperscript{23-25}, biological importance of sulfonamides prompted us to synthesize derivatives bearing pyrazoline and 4-thiazolidinone moieties as well as evaluate their antimicrobial activity.

EXPERIMENTAL

\textit{Chemistry}

All of the materials were purchased from Acros (Belgium) or Aldrich. The other solvents were purchased from Fluka and used without further purification. Melting points were measured with an Electrothermal Model 9200 (England). IR spectra were recorded on BRUKER EQUINOX 55 IR spectrophotometer. The ESI-MS were performed on an Agilent 1100 LC-MSD instrument with MS detector (mass range 100-2000 m/z, energy 3.5 kV, dried gas 8.0 L/min). \textsuperscript{1}H (500 MHz) and \textsuperscript{13}C (125 MHz) NMR were recorded on a BRUKER AVANCE 500 NMR spectrometer using acetone-\textit{d}_6, CDCl\textsubscript{3} and DMSO-\textit{d}_6 as solvents and
tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in $\delta$ relative to TMS.

*General procedure for synthesis of dihydro-$1H$-pyrazol-$1$-ylbenzene sulfonamides (2).*

A stirred solution of chalcones 1 (3 mmol) and 4-hydrazinylbenzenesulfonamide (699 mg; 3 mmol) in anhydrous methanol (30 mL) was refluxed for 12 h, monitoring by TLC. After completion of the reaction, the mixture was cooled overnight at 0 °C. The solid separated was filtered and washed with hexane (30 mL). The residue was purified by recrystallization in ethanol and was dried under the vacuum to afford the pure compounds 2.

*General procedure for synthesis of 4-thiazolidinone sulfonamides (4).*

A stirred mixture of phenylhydrazones (1mmol) and mercaptoacetic acid (1mL) were refluxed for 2h. After completion of the reaction, monitored by TLC, ethyl acetate (10 mL) was added into the mixture. The organic residue was washed with NaHCO$_3$ solution (3 x 20 mL), water and dried by anhydrous Na$_2$SO$_4$. Then the solvent was evaporated and the crude product purified by column chromatography on silica gel with n-hexane/ethyl acetate (30:70, v/v) as the eluent.

**Antimicrobial assay**

The antimicrobial activity and the minimal inhibitory concentration (MIC) of synthesized compounds were determined by broth dilution method in 96-well microtiter microplates as reported previously$^{28}$. Briefly, stock solutions of the synthesized compounds at concentration of 2 mg mL$^{-1}$ were prepared by dissolving 2 mg of the test compound in 1 mL dimethyl sulfoxide (DMSO). The stock solutions were serially diluted in 1 mL of sterile medium to obtain concentrations of 12.5 - 50 μg mL$^{-1}$ and inoculated with a suspension (100 μL) of the respective microorganism. Four bacterial strains including two Gram negative bacteria (*Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 25923) and two Gram positive bacteria (*Bacillus subtilis* ATCC 11774 and *Staphylococcus aureus* subsp. *aureus* ATCC 11632) were used for evaluation of antibacterial activity. Two filamentous fungal strains (*Aspergillus niger* 439 and *Fusarium oxysporum* M42) and two yeast strains (*Candida albicans* ATCC 7754 and *Saccharomyces cerevisiae* SH 20) were used for evaluating antifungal properties of the synthesized compounds. Tetracycline, Streptomycin and Nystatin purchased from Sigma Co were used as positive control of the tests with Gram negative, Gram positive bacteria, filamentous fungi and yeast, respectively, and pure DMSO was used as negative control. The MIC value for a sample was expressed as the lowest concentration that inhibits the tested microbial growth.

**RESULTS AND DISCUSSION**

*Chemistry*

In our strategy, the series of triarylpyrazoline sulfonamides contains a benzensulfonamide ring attached to a five-membered pyrazoline ring at position 1 and two aryl rings bearing varied functional groups attached to the pyrazoline ring at positions 3 and 5. These derivatives (2a-i) were synthesized in methanol by cyclocondensation of 4-hydrazinylbenzenesulfonamide and the corresponding chalcones (1a-i) which was prepared from the appropriate aromatic aldehydes and the corresponding ketones in base catalyst/ethanol at room temperature for 5h (Scheme 1). The present results showed that reaction time of the
cyclocondensation (12 h) was much shorter than that of the previous report (36 h)\textsuperscript{13} while the yields were similar (53-64 %).

The structures of triarylpyrazolines were unambiguously characterized by IR, NMR and mass spectral data. The \textsuperscript{1}H NMR spectra showed characteristic singlet around 4.63–6.98 ppm for two protons of -SO\textsubscript{2}NH\textsubscript{2} moiety in the structures. Meanwhile, the appearance of the signals belongs to aliphatic protons of pyrazoline ring, H\textsubscript{a}, H\textsubscript{b} and H\textsubscript{x} (around 3.15-3.27, 3.87-4.09 and 5.33-5.83 ppm, respectively). The other signals are in complete agreement with the assigned structures.

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Scheme 1. Synthesis of 1,3,5-triarylpyrazoline sulphonamides. Reagents: (i) EtOH, KOH aq. (2 %), rt, 4 h; (ii) 4-hydrazinylbenzenesulphonamide, MeOH, reflux, 12 h

Synthetic route of 4-thiazolidinone sulfonamides is illustrated in Scheme 2. The hydrazone derivatives (3a-e) were prepared in good yields (63.0-74.0%) via acid catalyzed condensation of the appropriate aromatic aldehyde and 4-hydrazinylbenzenesulfonamide in methanol for 4h. Cyclocondensation of the appropriate phenylhydrazones (3a-e) with a large excess of mercaptoacetic acid afforded the respective 4-thiazolidinone sulfonamides (4a-e). The IR data of 4a-e showed the bands at around 3270 and 1700 cm\textsuperscript{-1} assigned to NH and CO stretching, respectively. In \textsuperscript{1}H NMR spectra, protons of amines including NH and NH\textsubscript{2} moieties was characterized by singlets around 8.59–8.70 ppm and 7.04-7.06 ppm, respectively while the appearance of signals around 3.74-3.82, 3.84-3.95 and 5.83-5.90 ppm, confirmed aliphatic protons of 4-thiazolidinone ring (H\textsubscript{a}, H\textsubscript{b} and H\textsubscript{x}, respectively).

Scheme 2. Synthesis of 4-thiazolidinone sulfonamides, Reagents: (i) CH3COOH, Methanol, reflux, 4 h; (ii) HSCH2COOH, reflux, 2 h.
Antimicrobial Activity

Pyrazoline and 4-thiazolidinone derivatives were screened for activity against four bacterial strains include two Gram negative (E. coli and P. aeruginosa) and two Gram positive (B. subtilis and S. aureus) bacteria, two filamentous fungal strains (A. niger and F. oxysporum) and two yeast strains (C. albicans and S. cerevisiae). The samples were compared with the standard references including tetracycline, streptomycin and nystatin in the tests of Gram negative, Gram positive bacteria and filamentous fungi and yeast, respectively.

The data in average MIC values is shown in Table 1. It indicated that most of the pyrazoline sulfonamides exhibited high activity against three bacterial strains, E. coli, B. subtilis and S. aureus, both tested fungal strains and a yeast, C. albicans whereas 4-thiazolidinone derivatives do not show antimicrobial activity at the tested concentration (50 μg mL⁻¹).

Table 1. Antimicrobial activity of sulfonamide derivatives

<table>
<thead>
<tr>
<th>Com.</th>
<th>MIC, μg mL⁻¹</th>
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<td>E. coli</td>
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Amongst the synthesized pyrazolines, the compound 2b having 2-hydroxy substitution on benzene ring exhibited similar antibacterial activity to both Gram positive bacteria (MIC values at 12.5 μg mL⁻¹) in comparison with streptomycin and superior antifungal activity to A. niger (MIC value at 12.5 μg mL⁻¹) in respect of nystatin (MIC value at 23.1 μg mL⁻¹). It is noteworthy that only derivatives 2c and 2e containing 4-tolyl substitution attached to the pyrazoline ring at position 5 showed the activity against E. coli (MIC values at 50 and 25 μg mL⁻¹, respectively).
and yeast, *C. albicans* (MIC values at 25 and 50 µg mL⁻¹, respectively) while three pyrazoline compounds 2g, 2h and 2i bearing 4-anisoyl substitution at position 3 did not show antibacterial activity at the tested concentration. The result reveals that substitutions in structure of triarylpyrazoline sulfonamides have important effects on antimicrobial activity. In general, the 4-methyl substitution attached to pyrazoline ring exhibited the activity over the 4-methoxy substitution and the pyrazolines containing hydroxy group can be important antibacterial agents. It is essential for the next researches to prepare new antimicrobial triarylpyrazoline sulfonamides with excellent activity.

**CONCLUSION**

In summary, the 1,3,5-triarylpyrazoline and 4-thiazolidinone sulfonamides were prepared from 4-hydrazinylbenzenesulfonamide in good yields. All synthesized sulfonamides including novel compounds 2f, 2h, 4c and 4d, were well characterized by spectral analyses and investigated for antimicrobial activity. Seven pyrazoline sulfonamides 2a-c and 2e-h exhibited high activity against the different strains whereas 4-thiazolidinone derivatives did not display antimicrobial activity at the tested concentration. Among them, compound 2b was found as a potential antibacterial and antifungal agent compared with the references, streptomycin and nystatin, respectively.

**SUPPLEMENTARY MATERIAL**

Experimental data for synthesis of compounds 1a-i and 3a-e. NMR and HRMS spectral data and copy of compounds 2 and 4. Supplementary Material are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

**Disclosure statement:** No potential conflict of interest was reported by the authors

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SYNTHESIS OF ANTIMICROBIAL SULFONAMIDES

lidinoн derivati (4a-e) добијени реакцијом циклокондензације 2-тиол-сирћетне киселине са различитим фенилхидразонима у приносу 43-62 %. Синтетисана јединиња су окарактерисана FTIR, 1H NMR, 13C NMR и масеним спектрама. Испитана је in vitro антимикробна активност према четири бактерије (E. coli, P. aeruginosa, B. subtillis и S. aureus), два филаментна соја гљивица и два соја квасца (C. albicans и S. cerevisiae). Седам пиразолина 2a-c и 2e-h показују значајну инхибицију различитих микробних сојева. Од њих, јединиње 2b показује добру антифунгалну активност према A. Niger (MIC 12.5 μg mL^-1), у поређењу са референтним леком.


REFERENCES


SUPPLEMENTARY MATERIAL TO
Synthesis of sulfonamides bearing 1,3,5-triarylpyrazoline and 4-thiazolidinone moieties as novel antimicrobial agents

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GENERAL PROCEDURE FOR SYNTHESIS OF CHALCONES (1A-1)

To a stirred solution of acetophenones (0.215 mol) and aldehydes (0.215 mol) in methanol (60 mL) was slowly added 100 mL of aqueous sodium hydroxide solution (2.8 M) and mixed occasionally for 4h at room temperature, monitoring by TLC. After completion of the reaction, the mixture was cooled overnight at 0°C. The solid separated was filtered and washed water (10 mL) and cooled ethanol (10 mL). The solid was dried under the vacuum. It was purified by recrystallization in ethanol to afford the pure chalcones.

Benzalacetophenone (1a).

Yellow powder. Yield 80.8 %. 1H NMR (500 MHz, acetone-d6, δ, ppm): 8.16-8.14 (m, 2H, -CH), 7.89 (d, 1H, J = 15.5, -CO-CH=CH), 7.86-7.83 (m, 2H, -CH), 7.81 (d, 1H, J = 15.5, -CO-CH=CH), 7.67-7.64 (m, 1H, -CH), 7.59-7.55 (m, 2H, -CH), 7.49-7.45 (m, 1H, CH).

(2E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one (1b).

Orange powder. Yield 82.3 %. 1H NMR (500 MHz, acetone-d6, δ, ppm): 8.23-8.19 (d, 1H, J 15.5 Hz, -CO-CH=CH), 8.17-8.14 (d, 1H, J = 15.5, -CO-CH=CH), 8.09-8.06 (m, 2H, CH), 7.57-7.54 (m, 1H, CH), 7.52-7.46 (m, 3H, -CH), 7.07-7.00 (m, 2H, -CH), 6.48-6.45 (m, 1H, CH).

(2E)-3-(4-methylphenyl)-1-phenylprop-2-en-1-one (1c).

Orange powder. Yield 81.0 %. 1H NMR (500 MHz, CDCl3, δ, ppm): 7.77 (d, 1H, J = 15.5, -CO-CH=CH), 8.01-7.97 (m, 2H, -CH), 7.86-7.57 (m, 2H, -CH),
7.52-7.50 (m, 1H, -CH), 7.48-7.44 (m, 2H, -CH), 7.42 (d, 1H, J = 15.5, -CO-CH=CH), 7.16-7.12 (m, 1H, CH). (2E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (1d).

Orange powder. Yield 81.0 %. 1H NMR (500 MHz, CDCl3, δ, ppm): 8.00-7.98 (m, 2H, CH), 7.78 (d, 1H, J = 15.5, -CO-CH=CH), 7.88-7.55 (m, 2H, -CH), 7.54-7.52 (m, 1H, -CH), 7.48-7.45 (m, 2H, -CH), 7.41 (d, 1H, J = 15.5, -CO-CH=CH), 6.92-6.89 (m, 2H, -CH), 3.80 (s, 3H, OCH3).

(2E)-1-(4-fluorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (1e).

Pale yellow powder. Yield 65.0 %. 1H NMR (500 MHz, CDCl3, δ, ppm): 8.01-8.00 (m, 2H, CH), 7.79 (d, 1H, J = 15.5, -CO-CH=CH), 7.53 (d, 2H, J = 8.0, -CH), 7.46 (d, 1H, J = 15.5, -CO-CH=CH), 7.21-7.20 (m, 2H, -CH), 7.17-7.12 (m, 2H, -CH), 2.37 (s, 3H, CH3).

(2E)-1-(4-fluoroethyl)-3-(4-methoxyphenyl)prop-2-en-1-one (1f).

Pale yellow powder. Yield 76.0 %. 1H NMR (500 MHz, CDCl3, δ, ppm): 8.03-8.00 (m, 2H, CH), 7.77 (d, 1H, J = 15.5, -CO-CH=CH), 7.57 (d, 2H, J = 8.5, -CH), 7.37 (d, 1H, J = 15.5, -CO-CH=CH), 7.15-7.11 (m, 2H, -CH), 6.92-6.89 (m, 2H, -CH), 3.81 (s, 3H, OCH3).

(2E)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (1g).

Pale yellow powder. Yield 78.0 %. 1H NMR (500 MHz, DMSO-d6, δ, ppm): 8.15-8.13 (m, 2H, -CH), 7.84-7.82 (m, 2H, -CH), 7.80 (d, 1H, J = 15.5, -CO-CH=CH), 7.69 (d, 1H, J = 15.5, -CO-CH=CH), 7.08-7.06 (m, 2H, -CH), 7.02-7.00 (m, 2H, -CH), 3.81 (s, 3H, OCH3).

(2E)-1-(4-methoxyphenyl)-3-(4-methylphenyl)prop-2-en-1-one (1h).

Pale yellow powder. Yield 70.0 %. 1H NMR (500 MHz, DMSO-d6, δ, ppm): 8.17-8.13 (m, 2H, -CH), 7.88 (d, 1H, J = 15.5, -CO-CH=CH), 7.77-7.75 (d, 2H, J = 8.0, -CH), 7.69 (d, 1H, J = 15.5, -CO-CH=CH), 7.27 (d, 2H, J = 8.0, -CH), 7.09-7.06 (m, 2H, -CH), 3.86 (s, 3H, OCH3), 2.35 (s, 3H, -CH3).

(2E)-1-(4-methoxyphenyl)-3-(4-methylphenyl)prop-2-en-1-one (1i).

Yellow powder. Yield 65.0 %. 1H NMR (500 MHz, DMSO-d6, δ, ppm): 8.15-8.13 (m, 2H, -CH), 7.84-7.82 (m, 2H, -CH), 7.80 (d, 1H, J = 15.5 Hz, -CO-CH=CH), 7.69 (d, 1H, J = 15.5, -CO-CH=CH), 7.08-7.06 (m, 2H, -CH), 7.02-7.00 (m, 2H, -CH), 3.86 (s, 3H, OCH3), 3.81 (s, 3H, OCH3).

SPECTRA DATA OF DIHYDRO-1H-PYRAZOL-1-YLBENZENE SULFONAMIDES (2a-2l) 4-(3.5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)benzene sulfonamide (2a).

Pale yellow powder, m.p. 209-210 °C. Yield 61.0 %. IR (KBr, cm⁻¹): 3389 (NH3), 3279 (NH2), 3070, 3028 (>C=H, benzene), 2875, 2617, 1958, 1881, 1755, 1592 (benzene), 1555, 1503, 1449 (benzene), 1397, 1328 (-SO2), 1247, 1153 (-SO3), 1096, 1025, 895, 869, 817, 757, 728, 694. 1H NMR (500 MHz, CDCl3, δ, ppm):
SUPPLEMENTARY MATERIAL

Pale yellow powder, m.p. 255-257 °C (lit. [26] 266-268 °C). Yield 60.0 %.
IR (KBr, νmax cm⁻¹): 3449 (-OH), 3387 (-NH₂), 3272 (-NH₂), 1592 (benzene),
1504 (benzene), 1453 (benzene), 1400, 1335 (-SO₂), 1303, 1215, 1145 (-SO₂),
1093, 906, 874, 820, 751, 690. ¹H NMR (500 MHz, acetone-d₆, δ ppm): 7.84 (d,
2H, J = 7.5, -CH), 7.66 (d, 2H, J = 9.0 Hz, -CH), 7.45-7.36 (m, 3H, -CH), 7.13-
7.09 (m, 3H, -CH), 6.98-6.95 (m, 2H, -CH), 6.76 (t, 1H, J = 7.5, -CH), 6.23 (s,
2H, NH₂), 5.83 (dd, 1H, J₁ = 12.0, J₂ = 5.5 Hz, CH₂-CH), 4.03 (dd, 1H, J₁ = 17.5
J₂ = 12.0, -CH₂), 3.22 (dd, 1H, J₁ = 17.5, J₂ = 5.5, -CH₂) ¹³C NMR (125 MHz,
acetone-d₆, δ ppm): 154.1, 150.0, 146.8, 132.9, 132.6, 128.7, 128.6, 127.5,
127.4, 126.3, 126.0, 120.1, 115.7, 114.4, 111.9, 57.6, 41.9. ESI-MS (m/z):

4-(5-(2-hydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2b).

Pale yellow powder, m.p. 211-212 °C. Yield 57.0 %. IR (KBr, νmax cm⁻¹):
3363 (-NH₂), 3264 (-NH₂), 3057, 3024, 2914, 1592 (benzene), 1506 (benzene),
1443 (benzene), 1401, 1337 (-SO₂), 1238, 1152 (-SO₂), 1095, 910, 871, 818, 755,
687. ¹H NMR (500 MHz, CDCl₃, δ ppm): 7.75 (d, 2H, J = 8.0, -CH), 7.71 (d,
2H, J₁ = 9.0, -CH), 7.43-7.37 (m, 3H, -CH), 7.14 (br, 4H, -CH), 7.10 (d, 2H, J =
9.0, -CH), 5.35 (dd, 1H, J₁ = 12.5, J₂ = 5.5, CH₂-CH), 4.60 (s, 2H, NH₂), 3.91
(dd, 1H, J₁ = 17.5, J₂ = 7.5, -CH₂), 3.22 (dd, 1H, J₁ = 17.5, J₂ = 5.5, -CH₂), 2.32
(s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃, δ ppm): 149.6, 147.4, 138.2, 137.9,
132.0, 130.2, 130.1, 129.4, 128.7, 128.1, 126.1, 125.6, 112.6, 63.4, 43.7, 21.0.

4-(5-(4-methylphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2c).

Pale yellow powder, m.p. 215-217 °C. Yield 55.0 %. IR (KBr, νmax cm⁻¹):
3387 (-NH₂), 3263 (-NH₂), 1592 (benzene), 1506 (benzene), 1402, 1336 (-SO₂), 1300, 1220, 1148 (-SO₂), 1095, 908, 872, 820, 754, 690. ¹H NMR (500 MHz, CDCl₃, δ ppm): 7.75 (dd, 2H, J₁ = 8.0, J₂ = 15 Hz, -CH), 7.69
(dd, 2H, J₁ = 9.0, -CH), 7.42-7.37 (m, 3H, -CH), 7.17-7.15 (m, 2H, -CH), 7.09 (d,
2H, J = 9.0, -CH), 6.86-6.84 (m, 2H, -CH), 5.33 (dd, 1H, J₁ = 12.0, J₂ = 5.5,
CH₂-CH), 4.70 (s, 2H, NH₂), 3.89 (dd, 1H, J₁ = 17.0, J₂ = 12.0, -CH₂), 3.77 (s,
3H, -OCH₃), 3.20 (dd, 1H, J₁ = 17.0, J₂ = 5.5, -CH₂) ¹³C NMR (125 MHz,
CDCl₃, δ ppm): 159.3, 149.5, 147.4, 133.2, 132.0, 130.3, 129.4, 128.7, 128.0,
126.9, 126.1, 114.8, 112.6, 63.1, 55.3, 43.7. ESI-MS (m/z): 406.1229 [M - H] calcld for C_{22}H_{30}N_3O_5S ([M - H]^+ = 406.1225).

4-(3-(4-fluorophenyl)-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2e).

Pale yellow needle, m.p. 158-160 °C. Yield 53.0 %. IR (KBr, ν_{max} cm\(^{-1}\)):
3371 (-NH\(_2\)), 3259 (-NH\(_2\)), 1594 (benzene), 1502 (benzene), 1414 (benzene),
1396, 1338 (-SO\(_2\)), 1309, 1226, 1154 (-SO\(_2\)), 1094, 960, 871, 820, 748, 708. \(^1\)H NMR (500 MHz, CDCl\(_3\), δ, ppm): 7.73-7.70 (m, 2H, -CH\(_2\)), 7.69 (d, 2H, J = 9.0, -CH\(_2\)), 7.13-7.11 (m, 4H, -CH\(_2\)), 7.09-7.06 (m, 4H, -CH\(_2\)). 5.34 (dd, 1H, J\(_1\) = 12.0, J\(_2\) = 6.0, CH\(_2\)-CH\(_2\)), 4.67 (s, 2H, NH\(_2\)). 3.88 (dd, 1H, J\(_1\) = 17.0, J\(_2\) = 12.0, -CH\(_3\)). 3.19 (dd, 1H, J\(_1\) = 17.5, J\(_2\) = 6.0, -CH\(_2\)). 2.32 (s, 3H, -CH\(_3\)). \(^{13}\)C NMR (125 MHz, CDCl\(_3\), δ, ppm): 163.5 (C-F, J\(_{CF}\) = 250 Hz), 147.9 (C-F, J\(_{CF}\) = 151.3Hz), 138.0 (C-F, J\(_{CF}\) = 21.2Hz), 112.6, 63.5, 43.8, 21.1. ESI-MS (m/z): 408.1182 [M - H] calcld for C\(_{22}\)H\(_{30}\)N\(_3\)O\(_5\)S ([M - H] = 408.1182).

4-(3-(4-fluorophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2f)

Pale yellow needle, m.p. 195-197 °C. Yield 63.0 %. IR (KBr, ν_{max} cm\(^{-1}\)):
3351 (-NH\(_2\)), 3218 (-NH\(_2\)), 1594 (benzene), 1504 (benzene), 1415 (benzene),
1397, 1330 (-SO\(_2\)), 1295, 1247, 1152 (-SO\(_2\)), 1096, 962, 867, 832, 736. \(^1\)H NMR (500 MHz, CDCl\(_3\), δ, ppm): 7.73-7.70 (m, 2H, -CH\(_2\)), 7.69 (d, 2H, J = 8.5, -CH\(_2\)), 7.16 (d, 2H, J = 9.0, -CH\(_2\)). 7.11-7.06 (m, 4H, -CH\(_2\)). 6.86 (d, 2H, J = 8.5, -CH\(_2\)). 5.33 (dd, 1H, J\(_1\) = 12.0, J\(_2\) = 6.0 Hz, CH\(_2\)-CH\(_2\)), 4.76 (s, 2H, NH\(_2\)). 3.87 (dd, 1H, J\(_1\) = 17.0, J\(_2\) = 12.0, -CH\(_3\)). 3.77 (s, 3H, -OCH\(_3\)). 3.17 (dd, 1H, J\(_1\) = 17.5, J\(_2\) = 6.0, -CH\(_2\)). \(^{13}\)C NMR (125 MHz, CDCl\(_3\), δ, ppm): 163.5 (C-F, J\(_{CF}\) = 250 Hz), 159.4, 147.9 (C-F, J\(_{CF}\) = 151.3Hz), 133.1, 130.4, 128.6, 128.04, 127.99, 127.9, 126.9, 115.8 (C-F, J\(_{CF}\) = 21.2Hz), 114.8, 112.6, 63.2, 55.3, 43.8. ESI-MS (m/z): 424.1129 [M - H] calcld for C\(_{22}\)H\(_{30}\)N\(_3\)O\(_5\)S ([M - H] = 424.1131).

4-(3-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2g)

Orange powder, m.p. 202-203 °C. Yield 57.0 %. IR (KBr, ν_{max} cm\(^{-1}\)):
3351 (-NH\(_2\)), 3218 (-NH\(_2\)), 1594 (benzene), 1504 (benzene), 1415 (benzene),
1397, 1330 (-SO\(_2\)), 1295, 1247, 1152 (-SO\(_2\)), 1096, 962, 867, 832, 736. \(^1\)H NMR (500 MHz, DMSO-d\(_6\), δ, ppm): 7.74 (d, 2H, J = 9.0, -CH\(_2\)), 7.58 (d, 2H, J = 9.0, -CH\(_2\)). 7.36-7.33 (m, 2H, -CH\(_2\)), 7.27-7.24 (m, 3H, -CH\(_2\)). 7.05 (d, 2H, J = 9.0, -CH\(_2\)). 7.02 (d, 2H, J = 9.0, -CH\(_2\)). 6.99 (s, 2H, NH\(_2\)). 5.60 (dd, 1H, J\(_1\) = 12.0, J\(_2\) = 5.0 , CH\(_2\)-CH\(_2\)). 3.97 (dd, 1H, J\(_1\) = 17.0, J\(_2\) = 12.0, -CH\(_3\)). 3.80 (s, 3H, -OCH\(_3\)). 3.17 (dd, 1H, J\(_1\) = 17.5, J\(_2\) = 5.5, -CH\(_3\)). \(^{13}\)C NMR (125 MHz, DMSO-d\(_6\), δ, ppm): 160.3, 149.6, 146.0, 141.7, 132.6, 129.1, 127.7, 127.5, 127.1, 125.7, 124.3, 114.2, 111.7, 62.2, 55.3, 43.2. ESI-MS (m/z): 406.1228 [M-H] calcld for C\(_{22}\)H\(_{30}\)N\(_3\)O\(_5\)S ([M-H] = 406.1225).
4-(3-(4-methoxyphenyl)-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2h).

Orange powder, m.p. 210-212 °C. Yield 54.0 %. IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 3415 (-NH$_2$), 3277 (-NH$_2$), 1589 (benzene), 1504 (benzene), 1423 (benzene), 1400, 1331 (-SO$_2$), 1307, 1246, 1156 (-SO$_2$), 1096, 941, 863, 830, 734. $^1$H NMR (500 MHz, DMSO-$d_6$, $\delta$, ppm): 7.74-7.72 (m, 2H, -CH), 7.57 (d, 2H, J = 9.0, -CH), 7.15-7.13 (m, 4H, -CH), 7.27-7.24 (m, 3H, -CH), 7.04-7.00 (m, 4H, -CH), 6.97 (s, 2H, NH$_2$), 5.56 (dd, 1H, $J_1 = 12.0$, $J_2 = 5.0$, CH$_2$-CH), 3.95 (dd, 1H, $J_1 = 18.0$, $J_2 = 12.0$, -CH$_2$), 3.80 (s, 3H, -OCH$_3$), 3.15 (dd, 1H, $J_1 = 17.5$, $J_2 = 5.5$, -CH$_3$), 2.24 (s, 3H, -CH$_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$, $\delta$, ppm): 160.2, 149.6, 146.0, 138.7, 136.7, 132.5, 129.6, 127.6, 127.0, 125.6, 124.4, 114.2, 111.7, 61.7, 55.3, 43.2, 20.6. ESI-MS (m/z): 422.1382 [M + H]$^+$ calc for C$_{23}$H$_{23}$N$_2$O$_5$S (M + H)$^+$ = 422.1528.

4-(3-(4-methoxyphenyl)-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2i).

Orange powder. M.p. 213-215 °C. Yield 60.0 %. IR (KBr, $\nu_{\text{max}}$ cm$^{-1}$): 3342 (-NH$_2$), 3258 (-NH$_2$), 1592 (benzene), 1505 (benzene), 1421 (benzene), 1399, 1339 (-SO$_2$), 1309, 1242, 1154 (-SO$_2$), 1095, 927, 871, 832, 744. $^1$H NMR (500 MHz, DMSO-$d_6$, $\delta$, ppm): 7.74-7.72 (m, 2H, -CH), 7.57 (d, 2H, J = 9.0, -CH), 7.18-7.16 (m, 2H, -CH), 7.27-7.24 (m, 3H, -CH), 7.05-7.00 (m, 4H, -CH), 6.98 (s, 2H, NH$_2$), 6.90-6.88 (m, 2H, -CH), 5.55 (dd, 1H, $J_1 = 12.0$, $J_2 = 5.0$, CH$_2$-CH), 3.93 (dd, 1H, $J_1 = 18.0$, $J_2 = 12.0$, -CH$_2$), 3.80 (s, 3H, -OCH$_3$), 3.70 (s, 1H, -OCH$_3$), 3.15 (dd, 1H, $J_1 = 17.5$, $J_2 = 5.0$, -CH$_3$). $^{13}$C NMR (125 MHz, DMSO-$d_6$, $\delta$, ppm): 160.2, 158.5, 149.6, 146.0, 133.6, 132.5, 127.6, 127.0, 124.4, 114.4, 114.2, 111.7, 61.7, 55.3, 55.0, 43.2. ESI-MS (m/z): 436.1327 [M - H]$^-$ calc for C$_{23}$H$_{23}$N$_2$O$_4$S ([M - H]$^-$ = 436.1331).

GENERAL PROCEDURE FOR SYNTHESIS OF PHENYLHYDRAZONES (3A-E)

To a stirred solution of 4-hydrazinylbenzene sulfonamide hydrochloride (2.5 mmol) and benzaldheydes (2.5 mmol) in methanol (30 mL) was added one drop of acetic acid. The mixture was refluxed under stirring at for 4 h with a Dean-Stark equipment. The solvent was evaporated under vacuum and the residue was recrystallized in appropriate solvents to afford pure phenylhydrazones.

4-(2-Benzylidenedihydrayzyl)benzene sulfonamide (3a).

Recrystallization in EtOAc. Pale yellow powder, m.p. 174-175 °C. Yield 63.0 %. $^1$H NMR (500 MHz, DMSO-$d_6$, $\delta$, ppm): 10.77 (s, 1H, =N-NH$_2$), 7.95 (s, 1H, -CH$_2$N-, 7.70 (t, 4H, J = 9.0 Hz, -CH), 7.43 (t, 2H, J = 7.5 Hz, -CH$_3$), 7.35 (t, 1H, =N =N-H), 7.16 (d, 2H, J = 8.5 Hz, -CH), 7.06 (s, 2H, -SO$_2$NH$_2$).

4-(2-4-Methylbenzylidene)hydrazyl)benzene sulfonamide (3b).

Recrystallization in EtOH. Yellow powder, m.p. 213-214 °C. Yield 67.0 %. $^1$H NMR (500 MHz, DMSO-$d_6$, $\delta$, ppm): 10.68 (s, 1H, =N-NH$_2$), 7.91 (s, 1H, -
4-(2-(4-Methoxybenzylidene)hydrazinyl)benzene sulfonamide (3c).

Recrystallization in EtOH. Yellow needle, m.p. 225-226 °C. Yield 74.0 %.

1H NMR (500 MHz, DMSO-d6, δ, ppm): 10.59 (s, 1H, =N-NH-), 7.90 (s, 1H, -CH=N-), 7.65 (t, 4H, J = 8.5, -CH), 7.12 (d, 2H, J = 9.0, -CH), 7.03 (s, 2H, J = 8.0, SO2NH2), 6.99 (d, 2H, J = 9.0, CH), 3.79 (s, 3H, OCH3).

4-(2-(Hydroxybenzylidene)hydrazinyl)benzene sulfonamide (3d).

Recrystallization in 1-propanol. Yellow needle, m.p. 254-255 °C. Yield 71.0 %.

1H NMR (500 MHz, DMSO-d6, δ, ppm): 10.78 (s, 1H, OH), 10.23 (s, 1H, =N-NH-), 7.93 (s, 1H, -CH=N-), 7.72 (d, 2H, J = 8.5, -CH), 7.67 (d, 2H, J = 8.5, -CH), 7.07-7.05 (m, 4H, -CH and SO2NH2), 6.90-6.86 (m, 2H, CH).

4-(2-(4-Chlorobenzylidene)hydrazinyl)benzene sulfonamide (3e).

Recrystallization in dichloromethane. Pale yellow needle, m.p. 210-211 °C. Yield 66.0 %. 1H NMR (500 MHz, DMSO-d6, δ, ppm): 10.85 (s, 1H, =N-NH-), 7.93 (s, 1H, -CH=N-), 7.72 (d, 2H, J = 8.5, -CH), 7.67 (d, 2H, J = 8.5, -CH), 7.47 (d, 2H, J = 9.0, -CH), 7.16 (d, 2H, J = 8.5, -CH), 7.07 (m, 2H, CH).

SPECTRA DATA OF 4-THIAZOLIDINONE SULFONAMIDES (4A-4E)

2-Phenyl-3-(4-aminosulfonylphenylamino)-4-thiazolidinone (4a)

White needle, m.p. 179-181 °C (lit. [26] 181°C). Yield 62.0 %. IR (KBr, νmax cm⁻¹): 3265 (NH), 2925, 2854, 1714 (C=O), 1599, 1461, 1378, 1331 (SO2), 1273, 1157 (SO2), 1045, 833, 797, 698. 1H NMR (500 MHz, DMSO-d6, δ, ppm): 8.67 (s, 1H, -NH), 7.59 (d, 1H, J = 8.0, -CH), 7.42-7.39 (m, 2H, -CH), 7.39-7.34 (m, 3H, -CH), 7.05 (s, 2H, -SO2NH2), 6.74 (d, 2H, J= 8.5, -CH), 5.88 (s, 1H, S-CH), 3.95 (d, 1H, J = 15.5, -CH3), 3.81 (d, 1H, J = 15.5, -CH3). 13C NMR (125 MHz, DMSO-d6, δ, ppm): 169.1, 149.3, 134.2, 128.8, 128.7, 127.2, 111.3, 59.8, 28.9. ESI-MS (m/z): 350.0487 [M + H]⁺ celled for C15H16N3O2S2 [M + H]⁺ 350.0633.

2-(4-Methylphenyl-3-(4-aminosulfonylphenylamino))-4-thiazolidinone (4b)

Pale yellow needle, m.p. 173-175 °C (lit. [26] 159 °C). Yield 52.0 %. IR (KBr, νmax cm⁻¹): 3264 (NH), 2924, 2854, 1690 (C=O), 1598, 1509, 1459, 1410, 1331 (SO2), 1266, 1216, 1155 (SO2), 1097, 1040, 902, 826, 704. 1H NMR (500 MHz, DMSO-d6, δ, ppm): 8.63 (s, 1H, -NH), 7.60 (d, 1H, J = 8.0, -CH), 7.32 (br, 2H, -CH), 7.20 (d, 2H, J = 8.0, -CH), 7.05 (s, 2H, -SO2NH2), 6.75 (d, 2H, J = 8.5, -CH), 5.85 (s, 1H, S-CH), 3.94 (d, 1H, J = 15.5, -CH3), 3.82 (d, 1H, J = 15.5, -CH3), 2.31 (s, 3H, CH3). 13C NMR (125 MHz, DMSO-d6, δ, ppm): 170.3, 149.3, 138.2, 134.1, 129.1, 127.1, 111.3, 59.7, 28.8, 20.7, 14.0. ESI-MS (m/z): 362.0636 [M - H]⁻ celled for C16H16N3O2S2 [M - H]⁻ = 362.0633.
2-(4-Methoxyphenyl)-3-(4-aminosulfonylphenylamino)-4-thiazolidinone (4e)

Yellow needle, m.p. 186-187 °C. Yield 49.0 %. IR (KBr, νmax cm⁻¹): 3265 (NH), 3097, 2929, 2855, 2364, 1689 (C=O), 1598, 1512, 1462, 1407, 1332 (SO₂), 1249, 1155 (SO₂), 1098, 1027, 901, 829, 734, 708, 676. ¹H NMR (500 MHz, DMSO-d₆, δ, ppm): 8.59 (s, 1H, -NH), 7.58 (d, 1H, J = 7.5, -CH), 7.36 (br, 2H, -CH), 7.04 (s, 2H, -SO₂NH₂), 6.93 (d, 2H, J = 8.0, -CH), 6.73 (d, 2H, J = 9.0, -CH), 5.83 (s, 1H, S-CH), 3.93 (d, 1H, J = 16.0, -CH₂), 3.81 (d, 1H, J = 16.0, -CH₂), 3.75 (s, 3H, OCH₃). ¹³C NMR (125 MHz, DMSO-d₆, δ, ppm): 168.8, 159.6, 149.4, 134.1, 129.1, 127.1, 126.7, 113.9, 111.2, 59.7, 55.2, 28.9. ESI-MS (m/z): 378.0580 [M - H]⁺ calecd for C₁₆H₁₄N₂O₃S₂ ([M - H]⁺ = 378.0582).

2-(2-Hydroxyphenyl)-3-(4-aminosulfonylphenylamino)-4-thiazolidinone (4d)

Yellow needle, m.p. 209-210 °C. Yield 55.0 %. IR (KBr, νmax cm⁻¹): 3266 (NH), 3099, 2986, 2929, 2602, 1908, 1682 (C=O), 1598, 1502, 1459, 1398, 1329 (SO₂), 1153 (SO₂), 1098, 1042, 900, 885, 829, 757, 708, 682. ¹H NMR (500 MHz, DMSO-d₆, δ, ppm): 9.95 (s, 1H, OH), 8.70 (s, 1H, -NH), 7.62 (d, 2H, J = 7.5, -CH), 7.22-7.21 (m, 1H, -CH), 7.18 (dt, 1H, J₁ = 8.0, J₂ = 1.5, -CH), 7.07 (s, 2H, -SO₂NH₂), 6.84 (d, 2H, J = 8.0, -CH), 6.79 (d, 2H, J = 9.0, -CH), 5.99 (s, 1H, S-CH), 3.84 (d, 1H, J = 15.5, -CH₂), 3.74 (d, 1H, J = 16.0, -CH₂). ¹³C NMR (125 MHz, DMSO-d₆, δ, ppm): 169.6, 155.1, 149.5, 134.2, 129.4, 127.3, 119.1, 111.5, 111.2, 59.7, 28.8. ESI-MS (m/z): 364.0421 [M - H]⁺ calecd for C₁₅H₁₂N₂O₃S₂ ([M - H]⁺ = 364.0425).

2-(4-Chlorophenyl)-3-(4-aminosulfonylphenylamino)-4-thiazolidinone (4e)

Pale yellow needle, m.p. 178-181 °C (lit. [27] 163°C). Yield 43.0 %. IR (KBr, νmax cm⁻¹): 3281 (NH), 3095, 2925, 2854, 2364, 2342, 1873, 1693 (C=O), 1598, 1493, 1411, 1388, 1330 (SO₂), 1264, 1220, 1155 (SO₂), 1094, 1014, 902, 828, 790, 760, 739, 707. ¹H NMR (500 MHz, DMSO-d₆, δ, ppm): 8.68 (s, 1H, -NH), 7.79 (d, 2H, J = 8.0, -CH), 7.45-7.43 (m, 4H, -CH), 7.06 (s, 2H, -SO₂NH₂), 6.73 (d, 2H, J = 8.5 Hz, -CH), 5.90 (s, 1H, S-CH), 3.93 (d, 1H, J = 15.5, -CH₂), 3.82 (d, 1H, J = 16.0, -CH₂). ¹³C NMR (125 MHz, DMSO-d₆, δ, ppm): 170.3, 169.0, 149.9, 149.2, 134.3, 133.3, 128.7, 127.2, 111.4, 59.8, 28.8. ESI-MS (m/z): 382.0085 [M-H]⁺ calecd for C₁₅H₁₃N₂O₃S₂Cl ([M - H]⁺ = 382.0086).
Fig. S1. $^1$H NMR Spectrum of compound 2a (Acetone-d$_6$)

Fig. S2. $^{13}$C NMR Spectrum of compound 2a (Acetone-d$_6$)

Fig. S3. HR-MS Spectrum of compound 2a
Fig. S4. $^1$H NMR Spectrum of compound 2b (Acetone-$d_6$)

Fig. S5. $^{13}$C NMR Spectrum of compound 2b (Acetone-$d_6$)

Fig. S6. HR-MS Spectrum of compound 2b
Fig. S7. $^1$H NMR Spectrum of compound 2e (CDCl$_3$)

Fig. S8. $^{13}$C NMR Spectrum of compound 2e (CDCl$_3$)

Fig. S9. HR-MS Spectrum of compound 2e
Fig. S10. $^1$H NMR Spectrum of compound 2d (CDCl$_3$)

Fig. S11. $^{13}$C NMR Spectrum of compound 2d (CDCl$_3$)

Fig. S12. HR-MS Spectrum of compound 2d
Fig. S13. $^1$H NMR Spectrum of compound 2e (CDCl$_3$)

Fig. S14. $^{13}$C NMR Spectrum of compound 2e (CDCl$_3$)

Fig. S15. HR-MS Spectrum of compound 2e
Fig. S16. $^1$H NMR Spectrum of compound 2f (CDCl$_3$)

Fig. S17. $^{13}$C NMR Spectrum of compound 2f (CDCl$_3$)
Fig. S18. DEPT Spectra of compound 2f (CDCl₃)

Fig. S19. HR-MS Spectrum of compound 2f
Fig. S20. $^1$H NMR Spectrum of compound 2g (DMSO)

Fig. S21. $^{13}$C NMR Spectrum of compound 2g (DMSO)

Fig. S22. HR-MS Spectrum of compound 2g
Fig. S23. $^1$H Spectrum of compound 2h (DMSO)

Fig. S24. $^{13}$C Spectrum of compound 2h (DMSO)
**Fig. S24.** DEPT Spectra of compound 2h (DMSO)

**Fig. S25.** HR-MS spectrum of compound 2h
Fig. S26. $^1$H Spectrum of compound 2i (DMSO)

Fig. S27. $^{13}$C Spectrum of compound 2i (DMSO)

Fig. S28. HR-MS spectrum of compound 2i
Fig. S29. $^1$H Spectrum of compound 4a (DMSO)

Fig. S30. $^{13}$C Spectrum of compound 4a (DMSO)
Fig. S31. HR-MS spectrum of compound 4a

Fig. S32. $^1$H Spectrum of compound 4b (DMSO)

Fig. S33. $^{13}$C Spectrum of compound 4b (DMSO)
Fig. S34. HR-MS spectrum of compound 4b

Fig. S35. $^1$H Spectrum of compound 4c (DMSO)
Fig. S36. $^{13}$C Spectrum of compound 4c (DMSO)

DEPT90

CH$_2$CH$_3$

CH$_2$

C$_{13}$CPD

Fig. S37. DEPT Spectra of compound 4c (DMSO)

Fig. S38. HR-MS spectrum of compound 4c
Fig. S39. $^1$H Spectrum of compound 4d (DMSO)

Fig. S40. $^{13}$C Spectrum of compound 4d (DMSO)
Fig. S41. DEPT Spectra of compound 4d (DMSO)

Fig. S42. HR-MS spectrum of compound 4d
Fig. S43. $^1$H Spectrum of compound 4e (DMSO)

Fig. S44. $^{13}$C Spectrum of compound 4e (DMSO)

Fig. S45. HR-MS spectrum of compound 4e (DMSO)