Antimycobacterial 1-Aryl-5-benzylsulfanyltetrazoles

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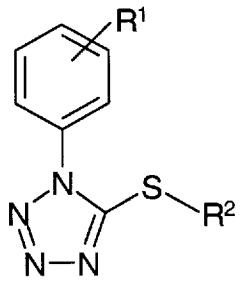
Dedicated to Professor Ing. Jozef Lehotay, DrSc., in honour of his 60th birthday

A group of twenty-two 1-aryl-5-benzylsulfanyltetrazoles and 5-alkylsulfanyl-1-aryltetrazoles was synthesized, and was evaluated for *in vitro* antimycobacterial activity against the strains of *Mycobacterium tuberculosis, Mycobacterium kansasii,* and *Mycobacterium avium*. To describe the structure—antimycobacterial activity relationships the Hansch approach was used. Optimal values of logarithm of partition coefficients were 4.1—4.4 with the exception of *M. avium*. Benzylsulfanyl derivatives were more active than alkylsulfanyl derivatives.

The search for new antimycobacterially active compounds is undoubtedly one of the significant directions of current pharmaceutical chemistry. Some years ago we have found the antimycobacterial activity of 5-alkylsulfanyl-1-aryltetrazoles [1]. In the set under study the benzyl derivatives were not presented. Recently we have found that benzylsulfanyl group increases the activity of some heterocyclic compounds [2, 3]. The goal of this study was to determine the structure—activity relationship of the 1-aryl-5-benzylsulfanyltetrazoles. The selection of substitution modifications on aromatic rings was carried out according to *Topliss* [4].

All the 5-alkylsulfanyl-1-aryltetrazoles (Formula 1) were prepared by alkylation of the corresponding 1-aryltetrazole-1-thiols by alkyl chloride in the toluene—aqueous potassium hydroxide systems by the use of tetrabutylammonium bromide as a phase-transfer catalyst. Structures of the products were proven by NMR and IR spectra and by elemental analysis. The melting points of compounds *X* and *XI* are different from the literature, but their structures were confirmed by the spectral analysis.

The following strains, obtained from the Czech National Collection of Type Cultures (CNCTC), National Institute of Public Health, Prague, were used for the evaluation of *in vitro* antimycobacterial activity: *M. tuberculosis* CNCTC My 331/88, *M. kansasii* CNCTC My 235/80, *M. avium* CNCTC My 330/88, and a clinical isolate of *Mycobacterium kansasii* 6509/96. Antimycobacterial activity of the compounds against these strains was determined in the Šula semisynthetic medium (Sevapharma, Prague). The Šula liquid medium (with bovine serum) is routinely used in the Czech Republic.



	R^1	R^2		R^1	R^2
I	H	$(CH_3)_2CH$	*XII*	4-Cl	$CH_2{=}CH{-}CH_2$
II	2-OCH_3	C_2H_5	*XIII*	H	$C_6H_5CH_2$
III	3-OCH_3	C_2H_5	*XIV*	H	4-$ClC_6H_4CH_2$
IV	4-OCH_3	C_2H_5	*XV*	H	4-$CH_3C_6H_4CH_2$
V	4-OCH_3	C_3H_7	*XVI*	4-Cl	$C_6H_5CH_2$
VI	4-OCH_3	$(CH_3)_2CH$	*XVII*	4-Cl	4-$ClC_6H_4CH_2$
VII	4-OCH_3	$CH_2{=}$ $=CH{-}CH_2$	*XVIII*	4-Cl	4-$CH_3C_6H_4CH_2$
VIII	3-Cl	C_2H_5	*XIX*	4-CH_3	$C_6H_5CH_2$
IX	3-Cl	C_3H_7	*XX*	4-CH_3	4-$ClC_6H_4CH_2$
X	4-Cl	C_2H_5	*XXI*	4-CH_3	4-$CH_3C_6H_4CH_2$
XI	4-Cl	$(CH_3)_2CH$	*XXII*	4-OCH_3	4-$ClC_6H_4CH_2$

Formula 1. Synthesized compounds.

Table 1. Minimum Inhibitory Concentrations (MIC) of Synthesized Compounds

Compound	MIC/(μmol dm^{-3}) Incubation 14 days/21 days			
	M. tuberculosis My 331/88	*M. kansasii* 6509/96	*M. kansasii* My 235/80	*M. avium* My 330/88
I	250/500	250/d	250/500	500/500
II	500/d	d/d	d/d	d/d
III	250/500	250/500	500/1000	250/500
IV	d/d	d/d	d/d	d/d
V	125/125	125/d	d/d	250/d
VI	250/d	250/d	250/d	d/d
VII	d/d	d/d	d/d	125/d
VIII	125/250	250/250	125/250	125/250
IX	125/125	125/125	125/250	125/125
X	125/d	250/250	250/d	d/d
XI	d/d	125/250	d/d	250/d
XII	d/d	125/d	d/d	125/d
XIII	16/62.5	32/125	32/125	32/125
XIV	d/d	d/d	d/d	d/d
XV	62.5/125	62.5/250	62.5/125	62.5/250
XVI	16/d	62.5/d	32/d	62.5/d
XVII	d/d	d/>250	d/d	d/>250
XVIII	d/d	d/d	d/d	d/d
XIX	32/125	62.5/d	32/250	62.5/d
XX	d/d	d/d	d/d	d/d
XXI	125/250	32/62.5	125/d	32/62.5
XXII	62.5/d	d/d	32/d	d/d

d – the MIC could not be determined due to a low solubility.

The more details on the microbiological technique are described in our previous paper [5]. In a number of cases, the minimum inhibitory concentration could not be determined due to the limited solubility of the compounds. The values of minimum inhibitory concentration after 14 days and 21 days of incubation correlate. For QSAR study we elected the values of 14 days of incubation. The results are summarized in Table 1.

For structure—antimycobacterial activity analysis we used the Hansch approach. Logarithms of the partition coefficients (log P) were calculated using ChemOffice 5 software. All regression equations were set up using the Multireg H program (Klemera) for Microsoft Excel. Values of logarithms of partition coefficients are summarized in Table 2.

The antimycobacterial activity is a quadratic function of logarithm of partition coefficients (see eqns (*1*—*3*)). The indicator parameter I has the value 1 for compounds with benzyl moiety on sulfur and 0 for another alkyl derivatives. Optimal values of logarithm of partition coefficients are in the interval 4.1—4.4. From this analysis we can conclude that benzylsulfanyl derivatives are more active than other alkylsulfanyl derivatives. The attempt to use the Hansch approach to investigate structure—activity relationship for antimycobacterial activity against *M. avium* was not successful. Eqn (*4*) is not statistically significant. The standard deviations of regression coefficients are greater than the values of regression coefficients (see eqn (*4*)).

M. tuberculosis 331/88

$$\log \mathrm{MIC}_{M.tuber.14\ d} = 0.435(\pm 0.116)(\log P)^2 - 3.563(\pm 0.949)\log P - 0.895(\pm 0.287)\, I + 9.374(\pm 1.926) \quad (1)$$

$$r = 0.918\ s = 0.203\ F = 29.25\ n = 14\ \log P_{\mathrm{opt}} = 4.095$$

M. kansasii 235/80

$$\log \mathrm{MIC}_{M.kans.14\ d} = 0.398(\pm 0.083)(\log P)^2 - 3.397(\pm 0.699)\log P - 0.729(\pm 0.192)\, I + 9.350(\pm 1.457) \quad (2)$$

$$r = 0.964\ s = 0.133\ F = 59.27\ n = 12\ \log P_{\mathrm{opt}} = 4.268$$

Table 2. Logarithm of Partition Coefficients of Synthesized Compounds

Compound	log P	Compound	log P
I	3.47	*XII*	4.07
II	3.03	*XIII*	4.55
III	3.03	*XIV*	5.11
IV	3.03	*XV*	5.04
V	3.51	*XVI*	5.11
VI	3.35	*XVII*	5.67
VII	3.38	*XVIII*	5.59
VIII	3.71	*XIX*	5.04
IX	4.20	*XX*	5.59
X	3.71	*XXI*	5.52
XI	4.03	*XXII*	4.98

M. kansasii 6509/96

$$\log MIC_{M.kans.14\ d\ clin.isol.} = 0.189(\pm 0.102)(\log P)^2 - 1.643(\pm 0.844)\log P - 0.810(\pm 0.226)\ I + 5.735\ (\pm 1.746) \quad (3)$$

$r = 0.946\ s = 0.168\ F = 51.09\ n = 15\ \log P_{opt} = 4.357$

M. avium 330/88

$$\log MIC_{M.av.\ 14\ d} = 0.045(\pm 0.129)(\log P)^2 - 0.519(\pm 1.057)\log P - 0.426(\pm 0.281)\ I + 3.582(\pm 2.171) \quad (4)$$

$r = 0.861\ s = 0.213\ F = 14.37\ n = 13\ \log P_{opt} = 5.767$

EXPERIMENTAL

The melting points were determined on a Kofler apparatus. The samples for analysis and antimycobacterial tests were dried over P_4O_{10} at 61 °C and 530 Pa for 24 h. Elemental analyses were performed on a CHNS-O CE elemental analyzer (Fisons EA 1110, Milan) and were within ± 0.4 % of the theoretical values. The IR spectra were measured in $CHCl_3$ on a Nicolet Impact 400 apparatus (for 1-aryl-5-benzylsulfanyltetrazoles), or in KBr pellets (for 5-alkylsulfanyl-1-aryltetrazoles). TLC was performed on silica gel plates precoated with a fluorescent indicator Silufol UV 254 + 366 (Kavalier, Votice, Czech Republic), with petroleum ether—ethyl acetate (φ_r = 9 : 1), or petroleum ether—ether (φ_r = 9 : 1) as the mobile phase. The ^1H NMR and ^{13}C NMR spectra of 1-aryl-5-benzylsulfanyltetrazoles were recorded in DMSO-d_6 solution, or $CDCl_3$-*d* solution at ambient temperature on a Varian Mercury-Vx BB 300 spectrometer operating at 300 MHz. Chemical shifts were recorded as δ and were indirectly referenced to tetramethylsilane *via* the solvent signal (2.49 for ^1H or 39.7 for ^{13}C). The ^1H NMR spectra of 5-alkylsulfanyl-1-aryltetrazoles were recorded in $CDCl_3$-*d* solution at ambient temperature on a Tesla BS 497 spectrometer operating at 100 MHz. Chemical shifts were recorded as δ and were indirectly referenced to tetramethylsilane *via* the solvent signal (2.49 for ^1H).

General Procedure for Preparation of 5-Alkylsulfanyl-1-aryl-1,2,3,4-tetrazoles (*I—XXII*)

Tetrabutylammonium bromide (200 mg; 0.6 mmol) was added to a stirred suspension consisting of 1-aryltetrazole-5-thiol (5 mmol) and alkyl chloride (5 mmol) in toluene (20 cm^3), and 1.1 M-KOH solution (15 cm^3). The mixture was stirred and refluxed for 4 to 12.5 h until the starting thiol disappeared (TLC in toluene—acetone (φ_r = 10 : 1)). The toluene layer was washed with water, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The solid residue was dissolved in methanol, passed through charcoal and recrystallized from ethanol—water or the solid was refined by column chromatography (silica gel, mobil phase petroleum ether—ethyl acetate (φ_r = 9 : 1), or petroleum ether—ether (φ_r = (9 : 1)).

5-Isopropylsulfanyl-1-phenyl-1,2,3,4-tetrazole (*I*)

White crystals. Yield 92 %; m.p. = 60—62 °C (Ref. [6] gives m.p. = 65—66 °C). IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1600 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1040, 1112, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2880, 2940, 2980. ^1H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.55 (bs, 5H, H-2, H-3, H-4, H-5, H-6), 4.16 (m, 1H, CHS), 1.51 (d, 6H, J = 7.0 Hz, CH_3).

5-Ethylsulfanyl-1-(2-methoxyphenyl)-1,2,3,4-tetrazole (*II*)

White crystals. Yield 98 %; m.p. = 75—76 °C. IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1610 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1040, 1115, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2860, 2950, 2990. For $C_{10}H_{12}N_4OS$ (M_r = 236.3) w_i(calc.): 50.83 % C, 5.12 % H, 23.71 % N, 13.57 % S, 6.77 % O; w_i(found): 50.74 % C, 5.13 % H, 23.91 % N, 13.45 % S. ^1H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.56 (td, 1H, J = 8.4 Hz, J = 8.4 Hz, H-4), 7.41 (dd, 1H, J = 8.1 Hz, J = 8.0 Hz, H-6), 7.10 (m, 2H, H-3, H-5), 3.83 (s, 3H, OCH_3), 3.33 (q, 2H, J = 7.2 Hz, SCH_2), 1.44 (t, 3H, J = 7.4 Hz, CH_3).

5-Ethylsulfanyl-1-(3-methoxyphenyl)-1,2,3,4-tetrazole (*III*)

White crystals. Yield 51 %; m.p. = 32—37 °C. IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1610 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1020, 1118, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2865, 2950, 2990. For $C_{10}H_{12}N_4OS$ (M_r = 236.3) w_i(calc.): 50.83 % C, 5.12 % H, 23.71 % N, 13.57 % S, 6.77 % O; w_i(found): 50.78 % C, 5.12 % H, 23.97 % N. ^1H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.50 (m, 1H, H-5), 7.19 (m, 3H, H-2, H-4, H-6), 3.87 (s, 3H, OCH_3), 3.42 (q, 2H, J = 7.0 Hz, SCH_2), 1.50 (t, 3H, J = 7.4 Hz, CH_3).

5-Ethylsulfanyl-1-(4-methoxyphenyl)-1,2,3,4-tetrazole (*IV*)

White crystals. Yield 94 %; m.p. = 87 °C (Ref. [6] gives m.p. = 88—90 °C). IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1610 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1030, 1110, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2895, 2950, 2990. ^1H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.47 (d, 2H, J = 9.0 Hz, H-3, H-5), 7.04 (d, 2H, J = 8.7 Hz, H-2, H-6), 3.88 (s, 3H, OCH_3), 3.39 (q, 2H, J = 7.0 Hz, SCH_2), 1.49 (t, 3H, J = 7.3 Hz, CH_3).

1-(4-Methoxyphenyl)-5-propylsulfanyl-1,2,3,4-tetrazole (*V*)

White crystals. Yield 83 %; m.p. = 46 °C. IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1610 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1030, 1108, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2895, 2950, 2980. For $C_{11}H_{14}N_4OS$ (M_r = 250.3) w_i(calc.): 52.78 % C, 5.64 % H, 22.38 % N, 6.39 % O, 12.81 % S; w_i(found): 52.61 % C, 5.52 % H, 22.29 % N. ^{1}H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.45 (d, 2H, J = 9.0 Hz, H-2, H-6), 7.03 (d, 2H, J = 9.0 Hz, H-3, H-5), 3.88 (s, 3H, OCH_3), 3.37 (t, 2H, J = 7.0 Hz, SCH_2), 1.83 (m, 2H, CH_2), 1.06 (t, 3H, J = 7.3 Hz, CH_3).

5-Isopropylsulfanyl-1-(4-methoxyphenyl)-1,2,3,4-tetrazole (*VI*)

White crystals. Yield 98 %; m.p. = 58—61.5 °C (Ref. [6] gives m.p. = 68—69 °C). IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1610 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1030, 1110, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2895, 2950, 2990. For $C_{11}H_{14}N_4OS$ (M_r = 250.3) w_i(calc.): 52.78 % C, 5.64 % H, 22.38 % N, 6.39 % O, 12.81 % S; w_i(found): 52.46 % C, 5.68 % H, 22.22 % N. ^{1}H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.45 (d, 2H, J = 9.0 Hz, H-2, H-6), 7.04 (d, 2H, J = 9.0 Hz, H-3, H-5), 4.12 (m, 1H, CHS), 3.87 (s, 3H, OCH_3), 1.49 (d, 6H, J = 6.3 Hz, CH_3).

5-Allylsulfanyl-1-(4-methoxyphenyl)-1,2,3,4-tetrazole (*VII*)

White crystals. Yield 67 %; m.p. = 42—47.5 °C. IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1610 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1030, 1110, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2860, 2950, 2980. For $C_{11}H_{12}N_4OS$ (M_r = 248.3) w_i(calc.): 53.21 % C, 4.87 % H, 22.56 % N, 12.91 % S, 6.44 % O; w_i(found): 53.11 % C, 4.65 % H, 22.37 % N. ^{1}H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.43 (d, 2H, J = 8.6 Hz, H-2, H-6), 7.03 (d, 2H, J = 8.4 Hz, H-3, H-5), 6.00 (m, 1H, CH), 5.30 (m, 1H, $_{cis}$H CH=), 5.16 (m, 1H, $_{trans}$H CH=), 3.94 (d, 2H, J = 7.1 Hz, SCH_2).

1-(3-Chlorophenyl)-5-ethylsulfanyl-1,2,3,4-tetrazole (*VIII*)

White crystals. Yield 69 %; m.p. = 44.5—46 °C. IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1600 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1030, 1110, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2895, 2950. For $C_9H_9ClN_4S$ (M_r = 240.7) w_i(calc.): 44.91 % C, 3.77 % H, 14.73 % Cl, 23.28 % N, 13.32 % S; w_i(found): 44.85 % C, 3.52 % H, 23.14 % N. ^{1}H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.62 (m, 1H, H-5), 7.52 (bs, 3H, H-2, H-4, H-6), 3.44 (q, 2H, J = 7.2 Hz, SCH_2), 1.52 (t, 3H, J = 7.3 Hz, CH_3).

1-(3-Chlorophenyl)-5-propylsulfanyl-1,2,3,4-tetrazole (*IX*)

White crystals. Yield 71 %; m.p. = 58—59 °C. IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1600 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1030, 1120, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2895, 2950, 2990. For $C_{10}H_{11}ClN_4S$ (M_r = 254.7) w_i(calc.): 47.53 % C, 3.59 % H, 14.03 % Cl, 22.17 % N, 12.69 % S; w_i(found): 47.19 % C, 3.67 % H, 22.13 % N. ^{1}H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.64 (m, 1H, H-5), 7.53 (bs, 3H, H-2, H-4, H-6), 3.40 (t, 2H, J = 7.5 Hz, SCH_2), 1.84 (m, 2H, CH_2), 1.07 (t, 3H, J = 7.7 Hz, CH_3).

1-(4-Chlorophenyl)-5-ethylsulfanyl-1,2,3,4-tetrazole (*X*)

White crystals. Yield 31 %; m.p. = 45—52 °C (Ref. [6] gives m.p. = 79—80 °C). IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1600 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1030, 1110, $\tilde{\nu}$ (C—H)$_{arom}$ 3010 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2895, 2950. For $C_9H_9ClN_4S$ (M_r = 240.7) w_i(calc.): 44.91 % C, 3.77 % H, 14.73 % Cl, 23.28 % N, 13.32 % S; w_i(found): 44.86 % C, 3.52 % H, 22.99 % N. ^{1}H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.51 (bs, 4H, H-2, H-3, H-5, H-6), 4.09 (q, 2H, J = 7.2 Hz, SCH_2), 1.51 (t, 3H, J = 7.5 Hz, CH_3).

1-(4-Chlorophenyl)-5-isopropylsulfanyl-1,2,3,4-tetrazole (*XI*)

White crystals. Yield 69 %; m.p. = 64—65.5 °C (Ref. [6] gives m.p. = 53—54 °C). IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1620 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1030, 1115, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2890, 2950, 2995. For $C_{10}H_{11}ClN_4S$ (M_r = 254.74) w_i(calc.): 47.15 % C, 4.35 % H, 13.92 % Cl, 21.99 % N, 12.59 % S; w_i(found): 47.36 % C, 4.38 % H, 22.27 % N, 12.32 % S. ^{1}H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.54 (bs, 4H, H-2, H-3, H-5, H-6), 4.17 (m, 1H, CHS), 1.53 (d, 6H, J = 7.0 Hz, CH_3).

5-Allylsulfanyl-1-(4-chlorophenyl)-1,2,3,4-tetrazole (*XII*)

White crystals. Yield 88 %; m.p. = 58.5—59 °C. IR spectrum (KBr), $\tilde{\nu}$ (skeletal vibrations of phenyl ring) 1620 cm^{-1}, $\tilde{\nu}$ (skeletal vibrations of tetrazole ring)/cm^{-1}: 1030, 1115, $\tilde{\nu}$ (C—H)$_{arom}$ 3020 cm^{-1}; $\tilde{\nu}$ (C—H)$_{alif}$/cm^{-1}: 2865, 2940. For $C_{10}H_9ClN_4S$ (M_r = 252.7) w_i(calc.): 47.53 % C, 3.59 % H, 14.03 % Cl, 22.17 % N, 12.69 % S; w_i(found): 47.68 % C, 3.67 % H, 22.42 % N, 12.85 % S. ^{1}H NMR spectrum (100 MHz, $CDCl_3$), δ: 7.55 (bs, 4H, H-2, H-3, H-5, H-6), 5.95 (m, 1H, CH), 5.47 (m, 1H, $_{cis}$H CH=), 5.25 (m, 1H, $_{trans}$H CH=), 4.05 (d, 2H, J = 6.9 Hz, SCH_2).

5-Benzylsulfanyl-1-phenyl-1,2,3,4-tetrazole (*XIII*)

White crystals. Yield 41 %; m.p. = 67—70 °C (Ref. [7] gives m.p. = 70—71 °C). IR spectrum ($CHCl_3$): $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/cm^{-1}: 1500, 1598. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ: 7.49—7.55 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.39—7.45 (m, 2H, H-2′′, H-6′′), 7.28—7.36 (m, 3H, H-3′′, H-4′′, H-5′′), 4.63 (s, 2H, SCH_2). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 153.8, 135.2, 133.5, 130.1, 129.7, 129.2, 129.0, 128.8, 128.1, 123.7, 37.6.

5-(4-Chlorobenzyl)sulfanyl-1-phenyl-1,2,3,4-tetrazole (*XIV*)

White crystals. Yield 29 %; m.p. = 97—99 °C. IR spectrum ($CHCl_3$), $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/cm^{-1}: 1500, 1598. For $C_{14}H_{11}ClN_4S$ (M_r = 302.7) w_i(calc.): 55.54 % C, 3.66 % H, 11.71 % Cl, 18.50 % N, 10.59 % S; w_i(found): 55.87 % C, 3.72 % H, 18.56 % N, 10.46 % S. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ: 7.48—7.59 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.32—7.40 (m AA′, BB′, 2H, H-3′′, H-5′′), 7.22—7.30 (m AA′, BB′, 2H, H-2′′, H-6′′), 4.58 (s, 2H, SCH_2). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 134.0, 133.9, 133.4, 130.6, 130.2, 130.1, 129.8, 128.9, 123.7, 36.7.

5-(4-Methylbenzyl)sulfanyl-1-phenyl-1,2,3,4-tetrazole (*XV*)

White crystals. Yield 58 %; m.p. = 59.5—61.5 °C. IR spectrum ($CHCl_3$), $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/cm^{-1}: 1500, 1598. For $C_{15}H_{14}N_4S$ (M_r = 282.3) w_i(calc.): 63.81 % C, 5.00 % H, 19.84 % N, 11.36 % S; w_i(found): 63.73 % C, 4.95 % H, 19.90 % N, 11.33 % S. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ: 7.49—7.55 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.28—7.35 (m AA′, BB′, 2H, H-2′′, H-6′′), 7.09—7.17 (m AA′, BB′, 2H, H-3′′, H-5′′), 4.60 (s, 2H, SCH_2), 2.33 (s, 3H, CH_3). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 154.0, 138.1, 133.6, 132.1, 130.0, 129.7, 129.5, 129.1, 123.8, 37.4, 21.1.

5-Benzylsulfanyl-1-(4-chlorophenyl)-1,2,3,4-tetrazole (*XVI*)

White crystals. Yield 76 %; m.p. = 68.5—70 °C. IR spectrum ($CHCl_3$): $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/cm^{-1}: 1498, 1602. For $C_{14}H_{11}ClN_4S$ (M_r = 302.7) w_i(calc.): 55.54 % C, 3.66 % H, 11.71 % Cl, 18.50 % N, 10.59 % S; w_i(found): 55.61 % C, 3.61 % H, 18.43 % N, 10.50 % S. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ: 7.47—7.51 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.38—7.44 (m, 2H, H-2′′, H-6′′), 7.29—7.37 (m, 3H, H-3′′, H-4′′, H-5′′), 4.63 (s, 2H, SCH_2). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 136.2, 135.1, 130.0, 129.2, 128.9, 128.3, 125.0, 122.7, 118.5, 37.8.

5-(4-Chlorobenzyl)sulfanyl-1-(4-chlorophenyl)-1,2,3,4-tetrazole (*XVII*)

White crystals. Yield 48 %; m.p. = 112—114 °C. IR spectrum ($CHCl_3$), $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/cm^{-1}: 1497, 1598. For $C_{14}H_{10}Cl_2N_4S$ (M_r = 337.2) w_i(calc.): 49.86 % C, 2.99 % H, 21.03 % Cl, 16.61 % N, 9.51 % S; w_i(found): 49.86 % C, 2.98 % H, 16.54 % N, 21.22 % Cl. ^1H NMR spectrum (300 MHz, DMSO), δ: 7.38—7.49 (m, 6H, H-2′, H-3′, H-5′, H-6′, H-3′′, H-5′′), 7.18—7.25 (m, 2H, H-2′′, H-6′′), 4.95 (s, 2H, SCH_2). ^{13}C NMR spectrum (75 MHz, DMSO), δ: 138.7, 133.9, 133.2, 130.1, 129.8, 129.1, 127.8, 117.9, 113.2, 51.6.

1-(4-Chlorophenyl)-5-(4-methylbenzyl)sulfanyl-1,2,3,4-tetrazole (*XVIII*)

White crystals. Yield 42 %; m.p. = 99—102 °C. IR spectrum ($CHCl_3$), $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/cm^{-1}: 1498, 1615. For $C_{15}H_{13}ClN_4S$ (M_r = 316.8) w_i(calc.): 56.87 % C, 4.14 % H, 11.19 % Cl, 17.68 % N, 10.12 % S; w_i(found): 57.12 % C, 4.13 % H, 17.38 % N, 11.19 % Cl. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ: 7.44—7.53 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.27—7.33 (m AA′, BB′, 2H, H-2′′, H-6′′), 7.10—7.16 (m AA′, BB′, 2H, H-3′′, H-5′′), 4.60 (s, 2H, SCH_2), 2.33 (s, 3H, CH_3). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 154.0, 138.2, 136.1, 132.0, 131.9, 129.9, 129.5, 129.1, 125.0, 37.6, 21.1.

5-Benzylsulfanyl-1-(4-methylphenyl)-1,2,3,4-tetrazole (*XIX*)

White pin-like crystals. Yield 68 %; m.p. = 75—77 °C (Ref. [8] gives m.p. = 75 °C). IR spectrum ($CHCl_3$), $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/cm^{-1}: 1515, 1603.

5-(4-Chlorobenzyl)sulfanyl-1-(4-methylphenyl)-1,2,3,4-tetrazole (*XX*)

White crystals. Yield 59 %; m.p. = 101—104 °C. IR spectrum ($CHCl_3$), $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/cm^{-1}: 1515, 1598. For $C_{15}H_{13}ClN_4S$ (M_r = 316.8) w_i(calc.): 56.87 % C, 4.14 % H, 11.19 % Cl, 17.68 % N, 10.12 % S; w_i(found): 56.71 % C, 4.04 % H, 17.56 % N, 11.20 % Cl, 9.95 % S. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ: 7.25—7.40 (m, 8H, H-2′, H-3′, H-5′, H-6′, H-2′′, H-3′′, H-5′′, H-6′′), 4.56 (s, 2H, SCH_2), 2.43 (s, 3H, CH_3). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 153.5, 140.6, 134.0, 134.0, 130.9, 130.6, 130.3, 128.9, 123.6, 36.7, 21.2.

5-(4-Methylbenzyl)sulfanyl-1-(4-methylphenyl)-1,2,3,4-tetrazole (*XXI*)

White crystals. Yield 22 %; m.p. = 33—34 °C. IR spectrum ($CHCl_3$), $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/

cm^{-1}: 1515, 1615. For $C_{16}H_{16}N_4S$ (M_r = 296.40) w_i(calc.): 64.84 % C, 5.44 % H, 18.90 % N, 10.82 % S; w_i(found): 64.82 % C, 5.39 % H, 18.71 % N, 10.84 % S. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ: 7.36—7.42 (m, 2H, H-2′, H-6′), 7.28—7.34 (m, 4H, H-3′, H-5′, H-2′′, H-6′′), 7.10—7.15 (m, 2H, H-3′′, H-5′′), 4.58 (s, 2H, SCH_2), 2.42 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 153.9, 140.4, 138.0, 132.1, 130.2, 129.5, 129.3, 129.1, 123.6, 37.4, 21.2, 21.1.

5-(4-Chlorobenzyl)sulfanyl-1-(4-methoxyphenyl)-1,2,3,4-tetrazole (*XXII*)

White crystals. Yield 29 %; m.p. = 72—74 °C. IR spectrum ($CHCl_3$), $\tilde{\nu}$ (skeletal vibrations of phenyl ring)/ cm^{-1}: 1516, 1609. For $C_{15}H_{13}ClN_4OS$ (M_r = 332.81) w_i(calc.): 54.13 % C, 3.94 % H, 10.65 % Cl, 16.83 % N, 4.81 % O, 9.63 % S; w_i(found): 54.25 % C, 3.96 % H, 16.67 % N, 9.36 % S. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ: 7.32—7.42 (m, 4H, H-2′, H-6′, H-3′′, H-5′′), 7.24—7.30 (m, 2H, H-2′′, H-6′′), 6.97—7.04 (m, 2H, H-3′, H-5′), 4.54 (s, 2H, SCH_2), 3.85 (s, 3H, OCH_3). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 160.7, 153.6, 134.0, 134.0, 130.5, 128.9, 126.1, 125.4, 114.8, 55.6, 36.6.

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