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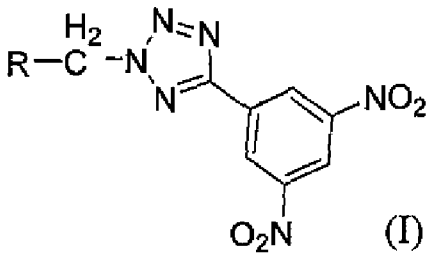
(54) Title: SUBSTITUTED PHENYLTETRAZOLE, ITS USE AND PHARMACEUTICAL PREPARATION CONTAINING IT



(I)

(57) Abstract: A nitro group-substituted phenyltetrazole of general formula (I) wherein R is selected from the group consisting of: H, C_1-C_{11} alkyl, phenyl- or phenyl- substituted in positions 2, 3, 4 or 5 by one or more electron-acceptor groups and/or by one or more electron-donor groups. These compounds can be prepared by easy synthesis and have significant activity against mycobacteria including their multidrug resistant strains. The invention provides also a pharmaceutical preparation having nitro group-substituted phenyltetrazole of formula (I) as the active ingredient, as well as the use of this nitro group-substituted phenyltetrazole as antituberculosis drug.

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Substituted phenyltetrazole, its use and pharmaceutical preparation containing it

TECHNICAL FIELD

The present invention relates to the new antituberculosis agents based on the nitro group-substituted phenyltetrazole, which are active against drug-susceptible and multidrug-resistant strains of mycobacteria.

BACKGROUND ART

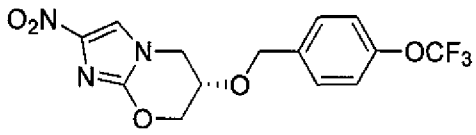
Increasing occurrence of bacterial resistance to antibiotic therapy is one of the main reasons for the development of new antimicrobial active substances. Tuberculosis (TB) is considered as a major global health problem, especially due to the increasing emergence of its multidrug resistant (MDR-TB) and extensively drug resistant (XDR-TB) forms. TB is highly infectious disease caused by *Mycobacterium tuberculosis* (*M.tb.*), which is spread by air from the patients with pulmonary form of TB.

Tuberculosis (TB) caused by *Mycobacterium tuberculosis complex* (MTB), belongs for many years to the most widespread infectious diseases in the world. Nowadays, one third of the world´s population is infected by *M.tb.* In 2013, approximately 9 million people fell ill with TB and 1.5 million people died due to TB (WHO - Global Tuberculosis Report 2014), ranking TB as the second greatest killer worldwide due to a single infectious agent.

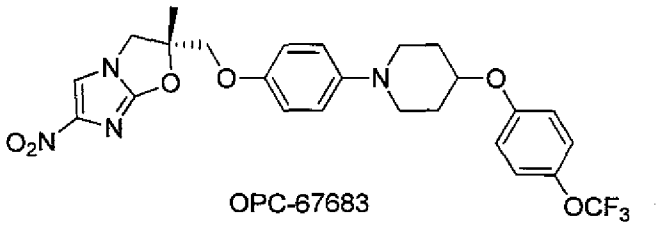
Combinations of drugs with antimycobacterial effect are used for the treatment and they are administered usually for 6 - 9 months. Long period of the treatment leads to the adverse effects, non-compliance of patients and can be unavailable due to its price. Treatment regimen of drug susceptible TB consist of the administration of isoniazid, rifampicin, pyrazinamide a ethambutol for 2 month followed by the administration of isoniazid and rifampicin for 4-6 months. Resistant forms of TB must be treated by second and third line antiTB drugs, such as fluoroquinolones, amikacin, kanamycin, streptomycin, cycloserine, ethionamide, p-aminosalicylic acid, for the period of 18 – 24 months. Another serious complication is a combination of TB with HIV/AIDS, which is usually lethal.

Therefore the development of the compounds that will be active against MDR-TB and latent forms of TB is essential. New antiTB drugs should possess new mechanism of action, which would overcome the possibility of cross resistances with common antiTB drugs. Some of new

active molecules, which are in preclinical and clinical development, contain nitro group. This moiety is essential for their antimycobacterial activity, but several mechanism of action is connected with it. Nitroimidazole-oxazine PA-824 (Stover, C.K.; Warrener, P.; VanDevanter, D. R.; Sherman, D.R.; Arain, T.M.; Langhorne, M.H.; Anderson, S.W.; Towell, J.A.; Yuan, Y.; McMurray, D.N.; Kreiswirth, B.N.; Barry, C.E; Baker W.R. A small-molecule nitrimidazopyran drug candidate for the treatment of tuberculosis. *Nature* 2000, 405, 962-966),

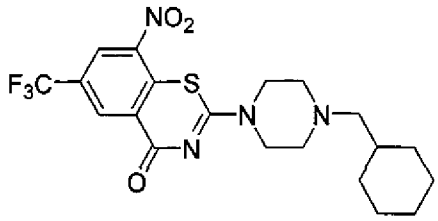


PA-824

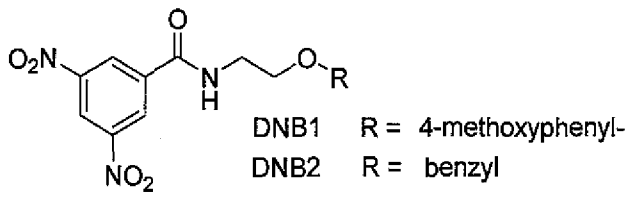


OPC-67683

nitro-dihydro-imidazooxazole OPC-67683 (Matsumoto, M.; Hashizume, H.; Tomishige, T.; Kawasaki, M.; Tsubouchi, H.; Sasaki, H.; Shimokawa, Y.; Komatsu, M. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis *in vitro* and in mice. *PLOS Medicine* 2006, *3*, 2131-2143),



PBTZ169

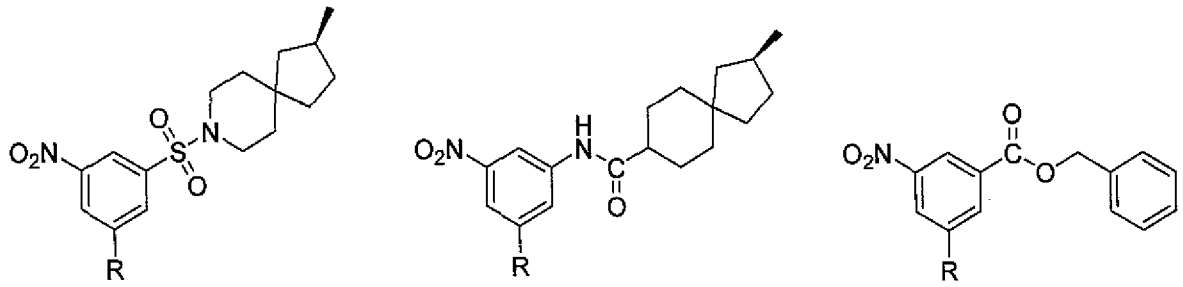


dinitrobenzamides

and benzothiazinone PBTZ169 (Makarov, V.; Manina, G.; Mikusova, K.; Möllmann, U.; Ryabova, O.; Saint-Joanis, B.; Dhar, N.; Pasca, M.R.; Buroni, S.; Lucarelli, A.P.; Milano, A.; De Rossi, E.; Belanova, M.; Bobovska, A.; Dianiskova, P.; Kordulakova, J.; Sala, C.; Fullnm, E.; Schneder, P.; McKinney, J.D.; Brodin, P.; Christophe, T.; Waddell, S.; Butcher, P.; Albrethesen, J.; Rosenkrands, I.; Brosch, R.; Nandi, V.; Bharath, S.; Gaonkar, S.; Shandil, R.K.; Balasubramanian, V.; Balganesh, T.; Tyagi, S.; Grosset, J.; Riccardi, G.; Cole, S.T. Benzothiazinones kill *Mycobacterium tuberculosis* by blocking arabinan synthesis. *Science* 2009, *324*, 801-804) can be mentioned as the expamples.

Another antiTB active nitro group-bearing compounds are dinitrobenzamides (Christophe, T.; Jackson, M.; Jeon, H.K.; Fenistein, D.; Contreras-Dominguez, M.; Kim, J.; Genovesio, A.; Carralot, J.P.; Ewann, F.; Kim, E.H.; Lee, S.Y.; Kang, S.; Seo, M.S.; Park, E.J.; Škovierová, H.; Pham, H.; Riccardi, G.; Nam, J.Y.; Marsollier, L.; Kempf, M.; Joly-Guillou, M.L.; Oh, T.; Shin, W.K.; No, Z.; Nehrbass, U.; Brosch, R.; Cole, S.T.; Brodin, P. High content screening

identifies decaprenyl-phosphoribose 2′epimerase as a target for intracellular antimycobacterial inhibitors. *PLOS Pathog* **2009**, *5*, 1-10) and nitroaromates derived from benzothiazinones (Tiwari, R.;Möllmann, U.; Sanghyun, Ch.; Franzblau, S.G.; Miller, P.A.; Miller M.J. Design and syntheses of anti-tuberculosis agents inspired by BTZ043 using a scaffold simplification strategy. *ACS Medicinal Chemistry Letters* 2014, 5, 587-591).



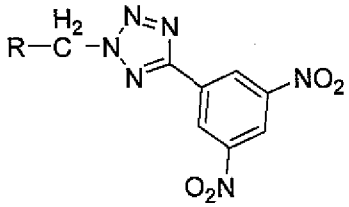
nitroaromates

R = CF_3, NO_2

SUMMARY OF THE INVENTION

New substituted phenyltetrazoles of general formula (I) show significant activity against *Mycobacterium tuberculosis*, against non-tuberculous mycobacteria and also against clinically isolated multidrug resistant strains of *M. tuberculosis*.

Compounds of general formula (I)



I

wherein

R is selected from the group consisting of: H, C_1–C_{11} alkyl, phenyl-, or phenyl- substituted in positions 2, 3, 4 or 5, with one or more electron-acceptor groups comprising -NO_2, -N^+(C_1-C_4 alkyl)$_3$, -CF_3, CCl_3, -CN, -COOH, -COO(C_1-C_4 alkyl), -COOAryl, -CHO, -CO(C_1-C_4 alkyl), -COAryl, -F, -Cl, -Br, -I, and/or by one or more electron-donor groups comprising -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)$_2$, -OH, -O(C_1-C_4 alkyl), -OAryl, -$NHCOCH_3$, -NHCO(C_1-C_4 alkyl), -NHCOaryl, -(C_1-C_4 alkyl), -phenyl or -naphtyl.

The term „electron-donor groups“ as used herein, refers to substituents that increase electron density on the phenyl substituent R. Examples of electron-donor groups include

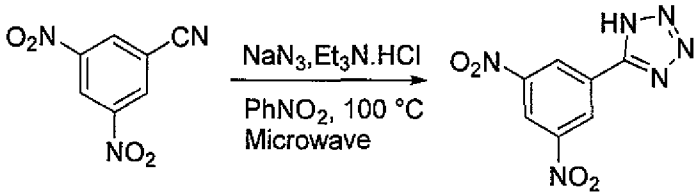
especially -NH_2, -NHAlk, -$NAlk_2$, -OH, -OAlk, -OAr, -$NHCOCH_3$, -NHCOAlk, -NHCOAr, -Alk, -Ar, wherein Alk = alkyl, Ar = aryl, wherein aryl = phenyl or phenyl substituted in position 2, 3, 4, and 5 by one or more electron-acceptor groups and/or by one or more electron-donor groups, naphtyl or pyridyl.

The term „electron-acceptor groups" as used herein, refers to substituents that decrease electron density on the phenyl substituent R. Examples of electron-donor groups include - NO_2, -$NAlk_3$, -CF_3, CCl_3, -CN, -COOH, -COOAlk, -COOAr, -CHO, -COAlk, -COAr, -F, -Cl, -Br, -I, wherein Alk = alkyl, Ar = aryl, wherein aryl = phenyl or phenyl substituted in position 2, 3, 4, and 5 by one or more electron-acceptor groups and/or by one or more electron-donor groups, naphtyl or pyridyl. (Source: (a) John McMurry: Organic Chemistry, Sixth edition, 2004, Brooks/Cole, a Thomson Learning Company; b) L. G. Wade, Jr.: Organic Chemistry, Sixth edition, 2006, Pearson Prentice Hall Inc.; c) J. Clayden, N. Greeves, S. Warren, P. Wothers: Organic Chemistry, 2001, Oxford University Press).

Another aspect of the invention is the use of the above mentioned nitro group-substituted phenyltetrazole of general formula (I) according to the current invention as antituberculosis agent.

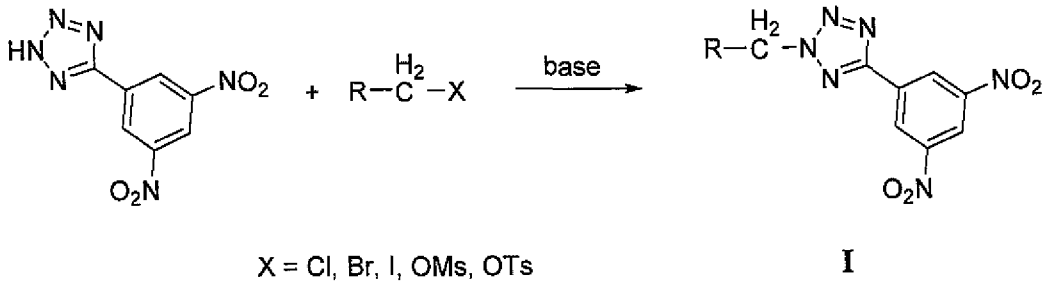
Further aspect of the invention also relates to a pharmaceutical preparation containing the nitro group-substituted phenyltetrazole of general formula (I) as the active ingredient.

Compounds of general formula (I) can be obtained by routine methods of organic synthesis. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole for synthesis of the compounds of general formula (I) were prepared by synthetic procedures as described in „Roh, J.; Artamonova, T. V.; Vavrova, K.; Koldobskii, G. I.; Hrabalek, A.:*Synthesis* **2009,**(13), 2175-2178." (Scheme 1)



Scheme 1.

The final products of general formula (I) were prepared by Williamson synthesis from the 5-(3,5-dinitrophenyl)-1*H*-tetrazole with the appropriate alkylating agent (Scheme 2). The synthetic route is very simple and raw materials for them are easily accessible and also cheap.



Scheme 2.

The prepared compounds corresponding to general formula (I) were evaluated in Regional Institute of Public Health, Ostrava (Department for Diagnostic of Mycobacteria, Partyzánské náměstí 7, 702 00 Ostrava) in *in vitro* conditions in Šula´s semisynthetic liquid medium (SEVAC, Prague) and the minimum inhibitory concentrations (MIC) were determined. The antimycobacterial activity was tested against Czech National Collection strains *Mycobacterium tuberculosis* CNCTC My 331/88, *M. avium* CNCTC My 330/88, and *M. kansasii* CNCTC My 235/80, and a clinical isolate *M. kansasii* 6509/96. Isoniazid (INH) was used as a standard in each assay. The results are shown in Table 2.

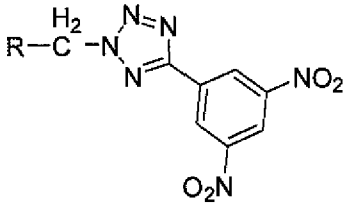
The most active compounds of general formula (I) were also evaluated for their activity against multidrug resistant strains of *Mycobacterium tuberculosis* (MDR strains). The strains are labelled as *M. tuberculosis 234/2005, M. tuberculosis 9449/2007, M. tuberculosis 8666/2010, M. tuberculosis Praha 1, M. tuberculosis Praha 4 and M. tuberculosis Praha 131 M. tuberculosis 7357/1998.* These strains were clinically isolated from patients and are deposited in Regional Institute of Public Health, Ostrava (Department for Diagnostic of Mycobacteria, Partyzánské náměstí 7, 702 00 Ostrava). The sensitivity/resistance of the mentioned clinically isolated strains to common antituberculotics and antibiotics used are summarized in Table 3. The activity of compounds of general formula (I) was expressed as minimum inhibitory concentration (MIC). The results were obtained under the same conditions as described above. Isoniazid (INH) was used as a standard in each assay. The results are shown in Table 4.

Substituent -CH_2-R on the heterocycle plays a crucial role in the antimycobacterial activity. When the substituent -CH_2-R is replace by hydrogen atom – i.e. in the case of 5-(3,5-dinitrophenyl)-1*H*-tetrazole – the antimycobacterial activity disappear.

Accordingly, the subject matter of the present invention comprises a highly antimycobacterially active low molecular weight tetrazole based compounds with a combination of a substituent -CH_2-R in the position 2 and 3,5-dinitrophenyl moiety bound in the position 5 of tetrazole.

Examples:

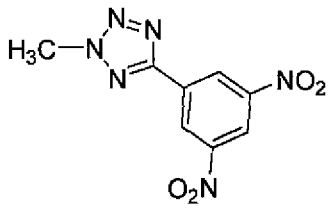
The following examples describe how to prepare nitro group-substituted phenyltetrazoles of general formula (I)



(I)

wherein R has the above mentioned meaning.

Example 1: 5-(3,5-dinitrophenyl)-2-methyl-2*H*-tetrazole (**1**)



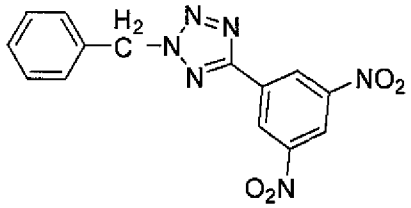
1

Compound **1** was prepared according to Scheme 2. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole (0.2 g, 0.85 mmol) was stirred with dimethyl sulfate (0.083 mL, 0.76 mmol) in the system CH_2Cl_2 (10 mL) and water (10 mL) in the presence of tetrabutylammonium bromide

(0.01 g; 0.032 mmol) and NaOH (0.038 g, 0.85 mmol) at room temperature for 50 hours. Upon completion, the reaction was diluted with 30 mL of CH_2Cl_2. The organic phase was washed with 5% Na_2CO_3 (3 x 20 mL) and 20% NaCl (1 x 20 mL). The organic phase was dried over Na_2SO_4 and evaporated. Compound **1** was isolated and purified by column chromatography (mobile phase: hexane/ethyl acetate 2.5:1).

The starting dimethyl sulfate is a commercially available compound. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1 (Roh, J.; Artamonova, T. V.; Vavrova, K.; Koldobskii, G. I.; Hrabalek, A.:*Synthesis* **2009,** (13), 2175-2178).

Example 2: 2-benzyl-5-(3,5-dinitrophenyl)-2*H*-tetrazole (**2**)

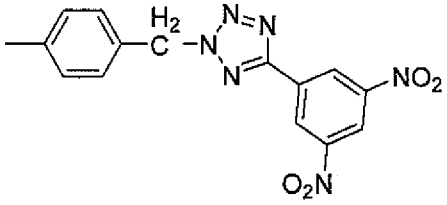


2

Compound **2** was prepared according to Scheme 2. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole (0.2 g, 0.85 mmol) was stirred with benzyl bromide (0.091 mL, 0.76 mmol) and triethylamine (0.12 mL, 0.85 mmol) in acetonitrile (10 mL) at 90 °C for 4 hours. Upon completion, the reaction mixture was evaporated and diluted with 30 mL of ethyl acetate. The organic phase was washed with 10% Na_2CO_3 (2 x 20 mL) and 20% NaCl (1 x 20 mL). The organic phase was dried over Na_2SO_4 and evaporated. Compound **2** was isolated and purified by column chromatography (mobile phase: hexane/ethyl acetate 6:1).

The starting benzyl bromide is a commercially available compound. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1 (Roh, J.; Artamonova, T. V.; Vavrova, K.; Koldobskii, G. I.; Hrabalek, A.:*Synthesis* **2009,** (13), 2175-2178).

Example 3: 5-(3,5-dinitrophenyl)-2-(4-methylbenzyl)-2*H*-tetrazole (**3**)



3

Compound 3 was prepared according to Scheme 2. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole (0.1 g, 0.42 mmol) was stirred with 4-methylbenzyl bromide (0.050 mL, 0.38 mmol) and triethylamine (0.058 mL, 0.42 mmol) in acetonitrile (10 mL) at 90 °C for 5 hours. Upon completion, the reaction mixture was evaporated and diluted with 30 mL of ethyl acetate. The organic phase was washed with 10% Na_2CO_3 (2 x 20 mL) and 20% NaCl (1 x 20 mL). The organic phase was dried over Na_2SO_4 and evaporated. Compound **3** was isolated and purified by column chromatography (mobile phase: hexane/ethyl acetate 15:1).

The starting 4-methylbenzyl bromide is a commercially available compound. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1 (Roh, J.; Artamonova, T. V.; Vavrova, K.; Koldobskii, G. I.; Hrabalek, A.:*Synthesis* **2009,** (13), 2175-2178).

Numerous other compounds of general formula (I) (compounds **4** - **19**) can be prepared using the above mentioned synthetic procedures.

Compound **4** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 4-bromobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 4-Bromobenzyl chloride is a commercially available compound.

Compound **5** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 3,5-dinitrobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 3,5-Dinitrobenzyl chloride is a commercially available compound.

Compound **6** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 4-chlorobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 4-Chlorobenzyl chloride is a commercially available compound.

Compound **7** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 4-nitrobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-

1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 4-Nitrobenzyl chloride is a commercially available compound.

Compound **8** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 3,4-dichlorobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 3,4-Dichlorobenzyl chloride is a commercially available compound.

Compound **9** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 4-methoxybenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 4-Methoxybenzyl chloride is a commercially available compound.

Compound **10** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and propyl bromide. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. Propyl bromide is a commercially available compound.

Compound **11** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and dodecyl bromide. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. Dodecyl bromide is a commercially available compound.

Compound **12** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 4-fluorobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 4-Fluorobenzyl chloride is a commercially available compound.

Compound **13** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 3,4-difluorobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 3,4-Difluorobenzyl chloride is a commercially available compound.

Compound **14** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 3,5-difluorobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 3,5-Difluorobenzyl chloride is a commercially available compound.

Compound **15** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 2-chloro-6-fluorobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 2-Chloro-6-fluorobenzyl chloride is a commercially available compound.

Compound **16** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 3-fluorobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1.

3-Fluorobenzyl chloride is a commercially available compound.

Compound **17** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 3-bromobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1.

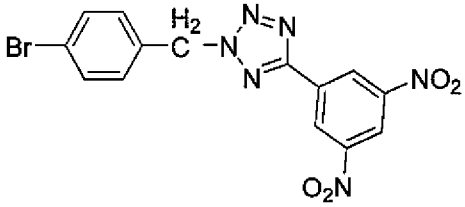
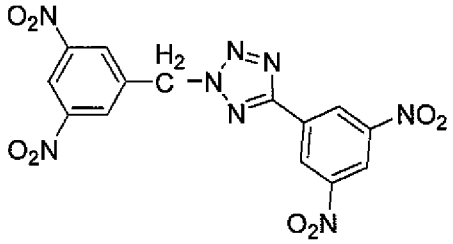
3-Bromobenzyl chloride is a commercially available compound.

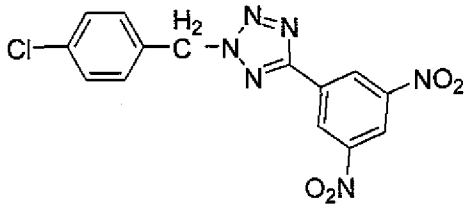
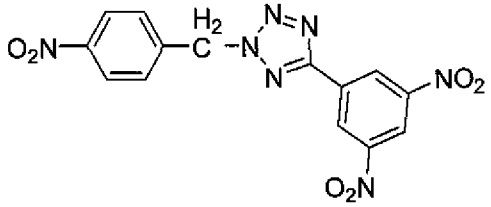
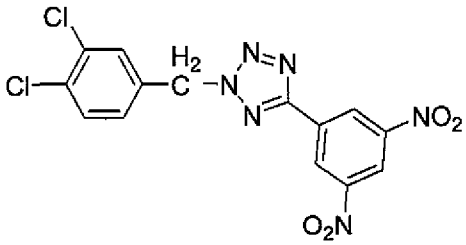
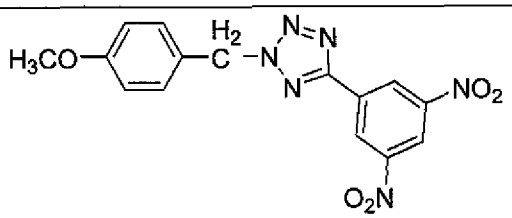
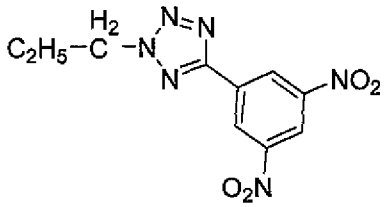
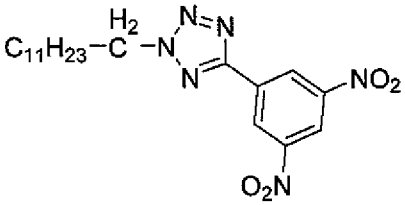
Compound **18** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 3-methoxybenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1. 3-Methoxybenzyl chloride is a commercially available compound.

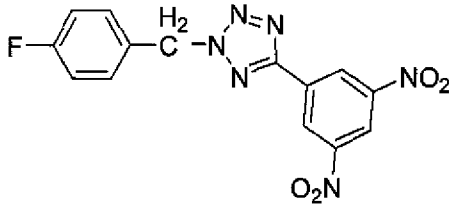
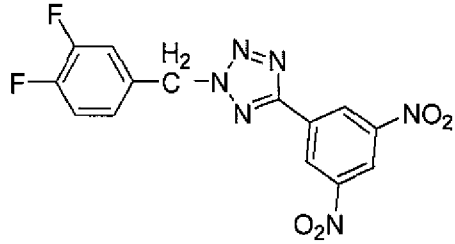
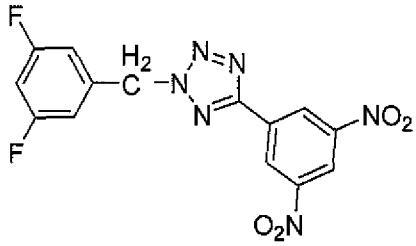
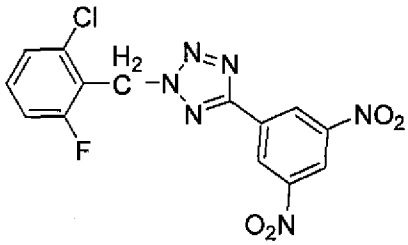
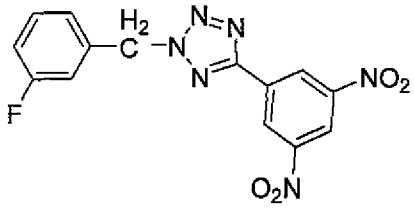
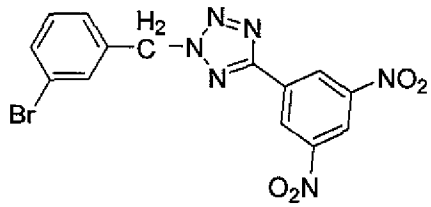
Compound **19** was prepared using the above mentioned synthetic procedures from 5-(3,5-dinitrophenyl)-1*H*-tetrazole and 3-chlorobenzyl chloride. The starting 5-(3,5-dinitrophenyl)-1*H*-tetrazole was prepared according to published procedure shown in Scheme 1.

3-Chlorobenzyl chloride is a commercially available compound.

Table 1. Examples of compounds of general formula (I) (compounds **4 - 19**)

	R	**Name and Structure**
4	4-BrC_6H_4	 2-(4-bromobenzyl)-5-(3,5-dinitrophenyl)-2*H*-tetrazole
5	3,5-$(NO_2)_2C_6H_3$	 2-(3,5-dinitrobenzyl)-5-(3,5-dinitrophenyl)-2*H*-tetrazole

6	4-ClC_6H_4	 2-(4-chlorobenzyl)-5-(3,5-dinitrophenyl)-2*H*-tetrazole
7	4-$NO_2C_6H_4$	 5-(3,5-dinitrophenyl)-2-(4-nitrobenzyl)-2H-tetrazole
8	3,4-$Cl_2C_6H_3$	 2-(3,4-dichlorobenzyl)-5-(3,5-dinitrophenyl)-2*H*-tetrazole
9	4-$CH_3OC_6H_4$	 5-(3,5-dinitrophenyl)-2-(4-methoxybenzyl)-2*H*-tetrazole
10	C_2H_5	 5-(3,5-dinitrophenyl)-2-propyl-2*H*-tetrazole
11	n-$C_{11}H_{23}$	 5-(3,5-dinitrophenyl)-2-dodecyl-2*H*-tetrazole

12	4-FC_6H_4	 5-(3,5-dinitrophenyl)-2-(4-fluorobenzyl)-2*H*-tetrazole
13	3,4-$F_2C_6H_3$	 2-(3,4-difluorobenzyl)-5-(3,5-dinitrophenyl)-2*H*-tetrazole
14	3,5-$F_2C_6H_3$	 2-(3,5-difluorobenzyl)-5-(3,5-dinitrophenyl)-2*H*-tetrazole
15	2-Cl-6-FC_6H_3	 2-(2-chloro-6-fluorobenzyl)-5-(3,5-dinitrophenyl)-2*H*-tetrazole
16	3-FC_6H_4	 5-(3,5-dinitrophenyl)-2-(3-fluorobenzyl)-2*H*-tetrazole
17	3-BrC_6H_4	

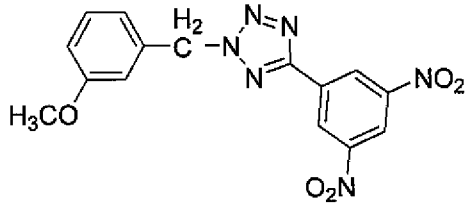
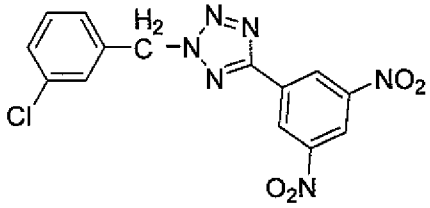
		2-(3-bromobenzyl)-5-(3,5-dinitrophenyl)-2*H*-tetrazole
18	3-$CH_3OC_6H_4$	 5-(3,5-dinitrophenyl)-2-(3-methoxybenzyl)-2*H*-tetrazole
19	3-ClC_6H_4	 2-(3-chlorobenzyl)-5-(3,5-dinitrophenyl)- 2*H*-tetrazole

Table 2. The minimum inhibitory concentration *in vitro* (expressed in μmol.l^{-1}) of compounds of general formula (I) (micromethod for determination of minimum inhibitory concentration in Šula´s semisynthetic medium on plastic P-microplates; MICs determined after incubation at 37 °C for 14 and 21 days for *M. tuberculosis* and *M. avium*, for 7, 14 and 21 days for *M. kansasii).*

	M.tuberculosis My 331/88	**M. avium My 330/88**	**M. kansasii My 235/80**	**M. kansasii 6509/96**
1	32 / 32	62,5 / 125	62,5 / 125 / 125	62,5 / 62,5 / 62,5
2	0.5 / 1	8 / 8	1 / 2 / 2	1 / 2 / 2
3	0.125 / 0.125	8 / 16	0.5 / 1 / 1	0.25 / 0.5 / 0.5
4	0.25 / 0.25	4 / 8	0.25 / 1 / 1	0.25 / 1 / 1
5	1 / 1	4 / 4	1/2/2	2/4/4
6	0.25 / 0.25	8 / 8	0.25 / 1 / 2	0.5 / 1 / 2
7	1 / 1	4 / 4	0.5 / 1 / 2	2 / 4 / 4
8	0.125 / 0.125	4 / 8	0.25 / 0.5 / 1	0.25 / 0.5 / 0.5
9	0.03 / 0.03	4 / 8	0.125 / 0.125 / 0.25	0.06 / 0.06 / 0.125
10	8 / 16	32 / 62.5	16 / 32 / 32	16 / 32 / 32

11	1 / 2	8 / 16	4 / 8 / 8	2 / 4 / 4
12	0.25 / 0.5	8 / 8	1 / 2 / 2	1 / 2 / 4
13	0.25 / 0.5	4 / 8	1 / 2 / 4	1 / 2 / 2
14	0.25 / 0.5	8 / 16	1 / 2 / 4	1 / 2 / 4
15	0.5 / 0.5	4 / 8	0.5 / 1 / 1	0.5 / 1 / 1
16	1 / 1	8 / 16	1 / 2 / 2	0.5 / 1 / 2
17	0.25 / 0.25	4 / 8	1 / 2 / 2	0.5 / 1 / 2
18	1 / 1	4 / 8	1 / 2 / 4	1 / 2 / 2
19	0.5 / 0.5	4 / 8	1 / 2 / 2	0.5 / 1 / 2
INH	**0.5/1**	**>250**	**>250**	**4/4/4**

Table 3. The minimum inhibitory concentration *in vitro* (expressed in $\mu mol.l^{-1}$) of selected antibiotics and antituberculotics (micromethod for determination of minimum inhibitory concentration in Šula´s semisynthetic medium on plastic P-microplates after incubation for 14 and 21 days) for multidrug resistant strains of *M. tuberculosis*

M. tuberculosis	Praha 1	Praha 4	Praha 131	9449/2007	234/2005	7357/1998	8666/2010
Streptomycin	13.7 R	>27.5 R	>27.5 R	>27.5 R	27.5 R	>27.5 R	>27.5 R
Isoniazid	14.6 R	14.6 R	14.6 R	58.3 R	14.6 R	14.6 R	29.2 R
Etambutol	39.2 R	19.6 R	39.2 R	9.8 C	19.6 R	19.6 R	19.6 R
Rifampicin	>9.7 R	>9.7 R	>9.7 R	>9.7 R	>9.7 R	>9.7 R	>9.7 R
Ofloxacin	1.38 C	>22.2 R	22.2 R	2.75 C	0.69 C	11.1 R	11.1 R
Gentamicin	1.05 C	0.52 C	>8.37 R	1.05 C	0.26 C	1.05 C	2.09 C
Clofazimine	0.53 R	0.53 R	0.26 C	0.13 C	0.06 C	0.13 C	2.11 R
Amikacin	0.43 C	0.85 C	>27.2 R	0.43 C	0.43 C	0.85 C	1.7 C

R - strain resistant to mentioned antituberculosis drug

C - strain sensitive to mentioned antituberculosis drug

Table 4. The minimum inhibitory concentration *in vitro* (expressed in $\mu mol.l^{-1}$) of compounds by general formula (I) (micromethod for determination of minimum inhibitory concentration in Šula´s semisynthetic medium on plastic P-microplates) after incubation at

37 °C for 14 and 21 days for multidrug resistant strains of *M. tuberculosis*

	M.tuberculosis (MDR kmeny)						
	PRAHA 1	**PRAHA 4**	**PRAHA 131**	**9449/2007**	**234/2005**	**7357/1998**	**8666/2010**
2	1 / 1	1 / 1	1 / 1	1 / 1	1 / 1	1 / 1	n.d.
16	1 / 1	1 / 1	1 / 1	1 / 1	1 / 1	1 / 1	1 / 1
3	0.125/0.25	0.125/ 0.125	0.125/ 0.125	0.125/ 0.125	0.125/ 0.125	0.125/ 0.125	0.125/ 0.125
9	0.03/0.03	0.03/0.03	0.03/ 0.03	0.03/ 0.03	0.03/ 0.06	0.03/ 0.03	0.03/ 0.03
17	0.5/0.5	0.5/1	0.5/1	0.25/0.5	0.25/0.5	0.5/0.5	0.25/0.5
12	1/1	0.5/1	0.5/1	0.25/0.5	0.5/1	0.5/0.5	0.5/0.5

Tabulka 5. Melting points and NMR spectra of compounds of general formula (I).

	Melting point [°C]	^{1}H NMR	^{13}C NMR
1	144-145	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (d, *J* = 2.1 Hz, 2H), 9.12 (t, *J* = 2.1 Hz, 1H), 4.50 (s, 3H).	^{13}C NMR (75 MHz, $CDCl_3$) δ 161.76, 149.07, 130.99, 126.55, 119.76, 39.99.
2	113-114	^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (d, *J* = 2.1 Hz, 2H), 9.10 (t, *J* = 2.1 Hz, 1H), 7.51 – 7.38 (m, 5H), 5.87 (s, 2H).	^{13}C NMR (75 MHz, $CDCl_3$) δ 161.94, 148.99, 132.47, 131.01, 129.38, 129.20, 128.61, 126.62, 119.74, 57.47.
3	109-110	^{1}H NMR (500 MHz, Acetone) δ 9.18 (d, *J* = 2.1 Hz, 2H), 9.04 (t, *J* = 2.1 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.00 (s, 2H), 2.31 (s, 3H)	^{13}C NMR (126 MHz, Acetone) δ 162.74, 150.09, 139.64, 131.62, 131.54, 130.38, 129.49, 126.96, 120.55, 57.67, 21.09.

4	144-145	^{1}H NMR (500 MHz, Acetone) δ 9.18 (d, J = 2.1 Hz, 2H), 9.05 (t, J = 2.1 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 6.08 (s, 2H).	^{13}C NMR (126 MHz, Acetone) δ 162.90, 150.13, 133.96, 132.91, 131.65, 131.45, 127.02, 123.46, 120.65, 57.09
5	136-138	^{1}H NMR (300 MHz, Acetone) δ 9.19 (d, J = 2.1 Hz, 2H), 9.06 (t, J = 2.1 Hz, 1H), 8.98 (t, J = 2.1 Hz, 1H), 8.89 (d, J = 2.1 Hz, 2H), 6.51 (s, 2H).	^{13}C NMR (75 MHz, Acetone) δ 163.14, 150.16, 149.75, 130.35 (2C), 127.07 (2C), 120.83, 119.95, 56.06
6	136-137	^{1}H NMR (500 MHz, Acetone) δ 9.19 (d, J = 2.1 Hz, 2H), 9.05 (t, J = 2.1 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 6.09 (s, 2H)	^{13}C NMR (126 MHz, Acetone) δ 162.90, 150.14, 135.30, 133.51, 131.46, 131.39, 129.91, 127.02, 120.66, 57.04
7	168-169	^{1}H NMR (500 MHz, Acetone) δ 9.20 (d, J = 2.1 Hz, 2H), 9.06 (t, J = 2.1 Hz, 1H), 8.30 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 8.7 Hz, 2H), 6.30 (s, 2H)	^{13}C NMR (126 MHz, Acetone) δ 163.08, 150.16, 149.19, 141.57, 131.35, 130.70, 127.06, 124.84, 120.76, 56.82
8	162-163	^{1}H NMR (500 MHz, DMSO) δ 9.03 (d, J = 2.1 Hz, 2H), 8.94 (t, J = 2.1 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.46 (dd, J = 8.3, 2.1 Hz, 1H), 6.13 (s, 2H)	^{13}C NMR (126 MHz, DMSO) δ 161.72, 148.93, 134.60, 131.83, 131.59, 131.29, 130.95, 129.55, 129.22, 126.34, 120.15, 55.27
9	104-105	^{1}H NMR (500 MHz, Acetone) δ 9.18 (d, J = 2.1 Hz, 2H), 9.04 (t, J = 2.1 Hz, 1H), 7.49 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 5.98 (s, 2H), 3.79 (s, 3H)	^{13}C NMR (126 MHz, Acetone) δ 162.74, 161.19, 150.14, 131.60, 131.16, 126.97, 126.48, 120.56, 115.14, 57.50, 55.62

10	103-104	^{1}H NMR (500 MHz, Acetone) δ 9.21 (d, J = 2.1 Hz, 2H), 9.06 (t, J = 2.1 Hz, 1H), 4.81 (t, J = 7.0 Hz, 2H), 2.19 – 2.07 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H)	^{13}C NMR (126 MHz, Acetone) δ 162.47, 150.16, 131.74, 126.94, 120.52, 55.92, 23.40, 11.08
11	68-69	^{1}H NMR (500 MHz, Acetone) δ 9.21 (d, J = 2.1 Hz, 2H), 9.06 (t, J = 2.1 Hz, 1H), 4.85 (t, J = 7.0 Hz, 2H), 2.15 – 2.07 (m, 2H), 1.45 – 1.34 (m, 4H), 1.34 – 1.21 (m, 14H), 0.88 – 0.84 (m, 3H)	^{13}C NMR (126 MHz, Acetone) δ 162.44, 150.17, 131.74, 126.92, 120.52, 54.40, 32.59, 30.29, 30.18, 30.05, 30.02, 29.95, 29.88, 29.54, 26.93, 23.28, 14.30.
12	151-152	^{1}H NMR (500 MHz, Acetone) δ 9.18 (d, J = 2.2 Hz, 2H), 9.05 (t, J = 2.2 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.23 – 7.16 (m, 2H), 6.08 (s, 2H).	^{13}C NMR (126 MHz, Acetone) δ 163.84 (d, J = 245.9 Hz), 162.86, 150.14, 131.94 (d, J = 8.6 Hz), 131.49, 130.80 (d, J = 3.2 Hz), 127.01, 120.64, 116.62 (d, J = 22.0 Hz), 57.07.
13	213-214	^{1}H NMR (500 MHz, Acetone) δ 9.19 (d, J = 2.1 Hz, 2H), 9.05 (t, J = 2.1 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.48 – 7.35 (m, 2H), 6.11 (s, 2H).	^{13}C NMR (126 MHz, Acetone) δ 162.95, 151.29 (dd, J = 247.8, 12.2 Hz), 150.94 (dd, J = 247.0, 12.5 Hz), 150.14, 132.01 (dd, J = 6.1, 3.9 Hz), 131.44, 127.05, 126.71 (dd, J = 6.9, 3.7 Hz), 120.68, 119.07 – 118.66 (m, 2C), 56.62 (d, J = 1.6 Hz).
14	122-123	^{1}H NMR (500 MHz, Acetone) δ 9.69 – 9.62 (m, 2H), 9.53 – 9.48 (m, 1H), 7.68 – 7.64 (m, 2H), 7.57 – 7.49 (m, 1H), 6.61 (s, 2H)	^{13}C NMR (126 MHz, Acetone) δ 164.01 (dd, J = 248.2, 13.0 Hz), 163.05, 150.15, 138.65 (t, J = 9.8 Hz), 131.43, 127.11, 120.71, 112.65 (dd, J = 20.1, 6.4 Hz), 105.02 (t, J = 25.8 Hz), 56.60 (t, J = 2.1 Hz).
15	137-138	^{1}H NMR (500 MHz, Acetone) δ 9.16 (d, J = 2.1 Hz, 2H), 9.05 (t, J = 2.1 Hz, 1H), 7.62 – 7.53 (m, 1H), 7.46 – 7.42 (m, 1H), 7.36 –	^{13}C NMR (126 MHz, acetone) δ 162.06 (d, J = 251.6 Hz), 161.81, 149.28, 135.87 (d, J = 4.5 Hz), 132.38 (d, J = 10.0 Hz), 130.51,

		7.28 (m, 1H), 6.23 (d, J = 1.5 Hz, 2H).	126.16, 125.95 (d, J = 3.4 Hz), 119.81, 119.32 (d, J = 17.3 Hz), 114.82 (d, J = 22.2 Hz), 48.34 (d, J = 4.4 Hz).
16	145-148	^{1}H NMR (500 MHz, Acetone) δ 9.20 (d, J = 2.1 Hz, 2H), 9.05 (t, J = 2.1 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.38 – 7.35 (m, 1H), 7.34 – 7.30 (m, 1H), 7.20 – 7.15 (m, 1H), 6.12 (s, 2H)	^{13}C NMR (126 MHz, acetone) δ 163.66 (d, J = 245.3 Hz), 162.93, 150.14, 137.14 (d, J = 7.8 Hz), 131.85 (d, J = 8.3 Hz), 131.47, 127.06, 125.45 (d, J = 3.1 Hz), 120.66, 116.58 (d, J = 21.1 Hz), 116.32 (d, J = 22.7 Hz), 57.10
17	128-129	^{1}H NMR (500 MHz, Acetone) δ 9.19 (d, J = 2.1 Hz, 2H), 9.06 (t, J = 2.1 Hz, 1H), 7.77 – 7.73 (m, 1H), 7.61 – 7.57 (m, 1H), 7.57 – 7.52 (m, 1H), 7.42 – 7.38 (m, 1H), 6.11 (s, 2H).	^{13}C NMR (126 MHz, Acetone) δ 162.94, 150.13, 137.05, 132.82, 132.44, 131.83, 131.44, 128.53, 127.06, 123.13, 120.66, 56.98.
18	92-94	1H NMR (500 MHz, acetone) δ 9.19 (d, J = 2.1 Hz, 2H), 9.05 (t, J = 2.1 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.97 – 6.93 (m, 1H), 6.03 (s, 2H), 3.79 (s, 3H).	^{13}C NMR (126 MHz, acetone) δ 162.81, 161.01, 150.12, 135.98, 131.52, 130.95, 127.01, 121.41, 120.59, 115.15, 115.01, 57.74, 55.60.
19	140-143	^{1}H NMR (500 MHz, acetone) δ 9.19 (d, J = 2.1 Hz, 2H), 9.05 (t, J = 2.1 Hz, 1H), 7.60 – 7.59 (m, 1H), 7.51 – 7.42 (m, 3H), 6.11 (s, 2H)	^{13}C NMR (126 MHz, acetone) δ 162.94, 150.13, 136.82, 135.06, 131.58, 131.44, 129.84, 129.49, 128.09, 127.06, 120.66, 57.03

Tabulka 6. Elemental analysis of compounds of general formula (I).

	calculated	found
1	C, 38.41; H, 2.42; N, 33.59;	C, 38.15; H, 2.33; N, 33.78;
2	C, 51.54; H, 3.09; N, 25.76;	C, 51.81; H, 3.26; N, 25.48;
3	C, 52.94; H, 3.55; N, 24.70;	C, 53.17; H, 3.19; N, 24.50;
4	C, 41.50; H, 2.24; N, 20.74;	C, 41.39; H, 2.07; N, 21.03;
5	C, 40.40; H, 1.94; N, 26.92;	C, 40.08; H, 2.14; N, 27.06;
6	C, 46.62; H, 2.52; N, 23.30;	C, 46.34; H, 2.41; N, 23.07;
7	C, 45.29; H, 2.44; N, 26.41;	C, 44.98; H, 2.27; N, 26.17;
8	C, 42.55; H, 2.04; N, 21.27;	C, 42.19; H, 1.87; N, 20.92;
9	C, 50.57; H, 3.39; N, 23.59;	C, 50.35; H, 3.57; N, 23.48;
10	C, 43.17; H, 3.62; N, 30.21;	C, 42.95; H, 3.32; N, 30.01;
11	C, 56.42; H, 6.98; N, 20.78;	C, 56.80; H, 7.21; N, 21.59;
12	C, 48.84; H, 2.64; N, 24.41;	C, 48.75; H, 2.70; N, 24.40;
13	C, 46.42; H, 2.23; N, 23.20;	C, 46.30; H, 1.92; N, 23.10;
14	C, 46.42; H, 2.23; N, 23.20;	C, 46.78; H, 2.32; N, 23.07;
15	C, 44.40; H, 2.13; N, 22.19;	C, 44.52; H, 2.19; N, 22.15;
16	C, 48.84; H, 2.64; N, 24.41;	C, 48.97; H, 2.80; N, 24.49;
17	C, 41.50; H, 2.24; N, 20.74;	C, 41.29; H, 2.47; N, 21.02;
18	C, 50.57; H, 3.39; N, 23.59;	C, 50.51; H, 3.52; N, 23.93;
19	C, 46.62; H, 2.52; N, 23.30;	C, 46.92; H, 2.29; N, 23.15;

Examples of the pharmaceutical compositions - tablets

In manufacture of solid dosage forms, the technology common in the given art is used, i.e., dry or wet granulation, which is well-known to a person skilled in the art. There are used routine and well proven excipients and suitable additives that give to the dosage form the desired physical characteristics.

Examples for dry granulation:

Example 1 (content of active substance 100 mg)

Active ingredient of general formula (I) **1**	100.0 mg
Cellulose, microcrystaline	75.0 mg
Sodium carboxymethylstarch	3.5 mg
Magnesium Stearate	0.5 mg
Silicon Dioxide, Colloidal	0.5 mg

Example 2 (content of active substance 200 mg)

Active ingredient of general formula (I) **13**	200.0 mg
Cellulose, microcrystaline	95.0 mg
Sodium carboxymethylstarch	7.0 mg
Magnesium Stearate	1.0 mg
Silicon Dioxide, Colloidal	1.0 mg

Example 3 (content of active substance 300 mg)

Active ingredient of general formula (I) **9**	300.0 mg
Cellulose, microcrystaline	115.0 mg
Sodium carboxymethylstarch	10.5 mg
Magnesium Stearate	1.5 mg
Silicon Dioxide, Colloidal	1.5 mg

Example 4 (content of active substance 400 mg)

Active ingredient of general formula (I) **5**	400.0 mg
Cellulose, microcrystaline	130.0 mg
Sodium carboxymethylstarch	14.5 mg

Magnesium Stearate	2.0 mg
Silicon Dioxide, Colloidal	2.0 mg

Example 5 (content of active substance 500 mg)

Active ingredient of general formula (I) **2**	500.0 mg
Cellulose, microcrystaline	140.0 mg
Sodium carboxymethylstarch	17.5 mg
Magnesium Stearate	2.5 mg
Silicon Dioxide, Colloidal	2.5 mg

The active ingredient is mixed together with other individual excipients and the obtained mixture is compressed by regular manner using a conventional tablet machine.

Examples for wet granulation

Example 6 (content of active substance 100 mg)

Active ingredient of general formula (I) **19**	100.0 mg
Potato starch	48.0 mg
Lactose	27.0 mg
Povidone	3.0 mg
Sodium carboxymethylstarch	4.0 mg
Magnesium Stearate	0.2 mg
Talc	1.8 mg

Example 7 (content of active substance 200 mg)

Active ingredient of general formula (I) **6**	200.0 mg
Potato starch	60.8 mg
Lactose	34.2 mg
Povidone	6.0 mg
Sodium carboxymethylstarch	8.0 mg
Magnesium Stearate	0.4 mg
Talc	3.6 mg

Example 8 (content of active substance 300 mg)

Active ingredient of general formula (I) **7**	300.0 mg

Potato starch	73.6 mg
Lactose	41.4 mg
Povidone	9.0 mg
Sodium carboxymethylstarch	12.0 mg
Magnesium Stearate	0.6 mg
Talc	5.4 mg

Example 9 (content of active substance 400 mg)

Active ingredient of general formula (I) **3**	400.0 mg
Potato starch	82.3 mg
Lactose	46.8 mg
Povidone	12.0 mg
Sodium carboxymethylstarch	16.0 mg
Magnesium Stearate	0.8 mg
Talc	7.2 mg

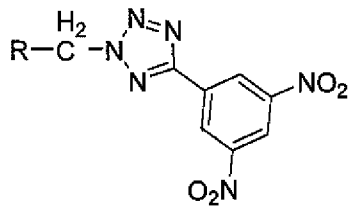
Example 10 (content of active substance 500 mg)

Active ingredient of general formula (I) **1**	500.0 mg
Potato starch	96.0 mg
Lactose	54.0 mg
Povidone	15.0 mg
Sodium carboxymethylstarch	20.0 mg
Magnesium Stearate	1.0 mg
Talc	9.0 mg

The therapeutically effective compound is mixed with lactose, potato starch and this mixture is granulated with povidone. The dried granulate is mixed then with sodium carboxymethyl-starch, magnesium stearate, and talc. The obtained mixture is compressed by regular manner using a conventional tablet machine.

CLAIMS

1. A nitro group-substituted phenyltetrazole of general formula (I)



(I)

wherein

R is selected from the group consisting of: H, C_1–C_{11} alkyl, phenyl- or phenyl-substituted in positions 2, 3, 4 or 5 by one or more electron-acceptor groups comprising $-NO_2$, $-N^+(C_1\text{-}C_4\ \text{alkyl})_3$, $-CF_3$, CCl_3, -CN, -COOH, $-COO(C_1\text{-}C_4\ \text{alkyl})$, -COOaryl, -CHO, $-CO(C_1\text{-}C_4\ \text{alkyl})$, -COaryl, -F, -Cl, -Br, -I, and/or by one or more electron-donor groups comprising $-NH_2$, $-NH(C_1\text{-}C_4\ \text{alkyl})$, $-N(C_1\text{-}C_4\ \text{alkyl})_2$, -OH, $-O(C_1\text{-}C_4\ \text{alkyl})$, -Oaryl, $-NHCOCH_3$, $-NHCO(C_1\text{-}C_4\ \text{alkyl})$; -NHCOaryl; $-(C_1\text{-}C_4\ \text{alkyl})$, -phenyl or -naphtyl.

2. The nitro group-substituted phenyltetrazole of general formula (I) according to claim 1 for use as antituberculosis drug.

3. A use of the nitro group-substituted phenyltetrazole of general formula (I) according to any claim 1 for the manufacture of a medicament for the treatment of tuberculosis.

4. A pharmaceutical preparation characterized in that it contains the nitro group-substituted phenyltetrazole of formula (I) according to claim 1 as the active ingredient.

5. The pharmaceutical preparation according to claim 4, characterized in that it contains one or more pharmaceutically acceptable excipients.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2015/000126

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D257/04 A61K31/41 A61P31/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/161516 A1 (UNIVERZITA KARLOVA V PRAZE FARMACEUTICKA FAKULTA V HRADCI KRALOVE [CZ]) 9 October 2014 (2014-10-09) the whole document -----	1-5
A	WO 2010/003533 A2 (PASTEUR INSTITUT KOREA [KR]; INST NAT SANTE RECH MED [FR]; BRODIN PRIS) 14 January 2010 (2010-01-14) the whole document -----	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2016	21/01/2016

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2015/000126

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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