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Synthesis and Antimycobacterial Properties of Fluorinated Benzaldoximes

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ABSTRACT

Full range of fluorsubstituted benzaldoximes were synthesized by reaction of the fluorine-substituted benzaldehydes with hydroxylamine sulphate in the presence of sodium acetate in methanol. Trifluoromethyl- and 4-methoxy-fluorosubstituted benzaldoximes were synthesized also. Antimycobacterial properties of the synthesized compound were studied with the non- pathogenic strain Mycobacterium terrae 15755. The antimycobacterial activity of these substances is comparable to currently used anti-TB agents (pyrazinamide and isoniazide) with MIC ≥200 μg/mL.

Keywords: Benzaldoxime; Antimycobacterialactivity; Fluorine

INTRODUCTION

The tuberculosis in humans is caused by the action of pathogenic mycobacteria [1,2]. Therefore, the main direction in the diseases treatment is associated with antimycobacterial drugs. However, new antimycobacterial drugs development is an important problem now due to the high resistance of mycobacteria to various antibiotics [1-6]. Actively searches carry out among the various classes of organic compounds [2]. Oximes are the derivatives of aldehydes and ketones and these compounds showed high antimycobacterial activity also [3-5]. Oximes are very useful intermediates in organic synthesis. For example, such compounds are widely used for nitrile oxides generation in the synthesis of isoxazoles and 2-isoxazolines [7]. However, the biological properties of oximes themselves are studied seldom, as they only are considered intermediates. There are a few studies of the biological activity of oxime were described, for example in papers [8,9]. We hypothesized that perspective mycobactericides could be obtained based on fluorinated benzaldoximes. It has previously been shown that introduction of fluorine atoms may improve the mycobactericide properties of synthesized compound [10].

EXPERIMENTAL SECTION

Synthesis

Melting points were determined using a Kofler block, VEB Analytic Dresden, Germany and are uncorrected. IR spectra were recorded in potassium bromide tablets (unless otherwise stated) at FT-IR spectrometer Thermo Nicolet Nexus in the area of 4000-400 cm^{-1}. UV spectra were record- ed on Solar PB2201 spectrometer in ethanol. NMR spectra were recorded on Bruker Avance 400 (400 MHz). Chemical shifts are defined in ppm to the internal standard tetramethylsilane (TMS). Progress of reactions and the purity of the obtained compounds were monitored by plates Kieselgel 60 F254 Merck company, Germany. Starting aldehydes 1a-d,g,r,t,x,y, hydroxylamine sulfate and sodium acetate trihydrate were purchased from Sigma-Aldrich, USA. Aldehydes 1e,f,h-q,s,u-w were purchased from ABCR GmbH, Germany. All chemicals were of analytically grade obtained

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from commercial suppliers and used without further purification. Methanol was purchased from commercial sources and was re-distilled under a positive pressure of dry nitrogen atmosphere in the presence of sodium.

General procedure for the synthesis of benzaldoximes (2a-y)

To a boiling solution of 0.045 moles of benzaldehyde in methanol (30 mL) was added dropwise a solution of 0.023 mole of hydroxylamine sulfate and 0.046 mole of sodium acetate trihydrate in water (20 mL). Reaction mixture was heated at reflux for one hour, then cooled to room temperature, water (60 mL) was added and resulting mixture was cooled to 5°C. The precipi- tate was filtered, washed with water (2×50 mL) and dried on air to afford the corresponding oxime. Analytical sample was received after recrystallization from 2-propanol.

4-Fluorobenzaldehyde oxime 2a: Yield 82.7%. Mp 89-90ºC, lit. mp 88.5ºC [11]. IR ($CHCl_3$, cm^{-1}): 3580, 3510-3050 (O-H), 1630 (C = N), 1605, 1505 (C = C). NMR ($(CD_3)_2CO$): 7.15 (2H, t, J 8.8, aromatic protons), 7.66 (2H, dd, J_1 5.4, J_2 8.8, aromatic protons) 8.13 (1H, s, C-H),10.36 (1H, s, NO-H). UV (λ_{max}, nm): 253.

3-Fluorobenzaldehyde oxime 2b: Yield 77.8%. Mp 66-67,5ºC. lit. mp 67-67,5ºC [11]. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1613 (C=N), 1585, 1492 (C=C). UV (EtOH, λ_{max}, nm): 253, 296 (shoulder).

2-Fluorobenzaldehyde oxime 2c: Yield 71.4%. Mp 67-68ºC. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1615 (C=N), 1578, 1492 (C=C). UV (EtOH, λ_{max}, nm): 249, 252, 288, 297 (shoulder).

2,4-Difluorobenzaldehyde oxime 2d: Yield 99,3%. Mp 139-140ºC. IR (KBr, cm^{-1}): 3640-3000 (O–H), 1614 (C=N), 1593, 1507 (C=C). UV (EtOH, λ_{max}, nm): 251, 287.

2,5-Difluorobenzaldehyde oxime 2e: Yield 90,7%. Mp 120,5-122 ºC. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1624 (C=N), 1590, 1497 (C=C), 1253, 1202 (C-F). UV (EtOH, λ_{max}, nm): 251, 294.

2,6-Difluorobenzaldehyde oxime 2f: Yield 76%. Mp 116-117ºC, lit. mp 116-116,5ºC [12]. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1622 (C=N), 1578, 1474 (C=C), 1271, 1209 (C-F). UV (EtOH, λ_{max}, nm): 250.

3,4-Difluorobenzaldehyde oxime 2g: Yield 79.1%. Mp 79-81ºC. IR (KBr, cm^{-1}): 3600- 3000 (O–H), 1639 (C=N), 1602, 1522 (C=C). UV (EtOH, λ_{max}, nm): 252.

3,5-Difluorobenzaldehyde oxime 2h: Yield 73,5%. Mp 87-89ºC. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1620 (C=N), 1590, 1491 (C=C). UV (EtOH, λ_{max}, nm): 255.

2,3,4-Trifluorobenzaldehyde oxime 2i: Yield 70,4%. Mp 137-138ºC. IR (KBr, cm^{-1}): 3630-3000 (O–H), 1631 (C=N), 1604, 1514 (C=C). UV (EtOH, λ_{max}, nm): 252.

2,3,5-Trifluorobenzaldehyde oxime 2j: Yield 46,6%. Mp 128-130ºC. IR (KBr, cm^{-1}): 3630-3000 (O–H), 1630 (C=N), 1590, 1498 (C=C). UV (EtOH, λ_{max}, nm): 254.

2,3,6-Trifluorobenzaldehyde oxime 2k: Yield 85,6%. Mp 152-153,5ºC. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1640 (C=N), 1600, 1503 (C=C). UV (EtOH, λ_{max}, nm): 249.

2,4,5-Trifluorobenzaldehyde oxime 2l: Yield 86,7%. Mp 144-145ºC. IR (KBr, cm^{-1}): 3630-3000 (O–H), 1629 (C=N), 1614, 1512 (C=C). UV (EtOH, λ_{max}, nm): 248, 292.

2,4,6-Trifluorobenzaldehyde oxime 2m: Yield 90,5%. Mp 185-186ºC. IR (KBr, cm^{-1}): 3630-3000 (O–H), 1638 (C=N), 1591, 1498 (C=C). UV (EtOH, λ_{max}, nm): 248.

3,4,5-Trifluorobenzaldehyde oxime 2n: Yield 46,6%. Mp 93-95ºC. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1618 (C=N), 1588, 1533 (C=C), 1353, 1043 (C-F). UV (EtOH, λ_{max}, nm): 253.

2,3,4,5-Tetrafluorobenzaldehyde oxime 2o: Yield 70,1%. Mp 80-82ºC. IR (KBr, cm^{-1}): 3630-3000 (O–H), 1620 (C=N), 1527, 1495 (C=C), 1134, 1077 (C-F). UV (EtOH, λ_{max}, nm): 251.

2,3,5,6-Tetrafluorobenzaldehyde oxime 2p: Yield 95,9%. Mp 186-187ºC. IR (KBr,cm^{-1}): 3630-3000 (O–H), 1610 (C=N), 1496 (C=C), 1262, 1176 (C-F). UV (EtOH, λ_{max}, nm): 250.

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2,3,4,5,6-Pentafluorobenzaldehyde oxime 2q: Yield 79,4%. Mp 140-141,5ºC. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1652 (C=N), 1527, 1498 (C=C), 1160, 1136, 1027 (C-F). UV (EtOH, λ_{max}, nm): 249.

2-(Trifluoromethyl)benzaldehyde oxime 2r Yield 85.1%. Mp 54-55ºC, lit. mp 54-55ºC [13]. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1627 (C=N), 1577, 1495 (C=C), 1177, 1119 (C-F). UV
(EtOH, λ_{max}, nm): 255.

3-(Trifluoromethyl)benzaldehyde oxime 2s Yield 23.9%. Mp 47-48,5ºC. Lit. bp 102- 104ºC/12 torr [14]. IR (KBr,cm^{-1}): 3600-3000 (O–H), 1625 (C=N), 1474 (C=C), 1207, 1174, 1122 (C-F). UV (EtOH, λ_{max}, nm): 253.

4-(Trifluoromethyl)benzaldehyde oxime 2t Yield 93.8%. Mp 101,5-102,5ºC. lit. mp 100- 101,5ºC [13]. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1618 (C=N), 1469, 1413 (C=C). UV (EtOH, λ_{max}, nm): 257.

4-Methoxy-2-fluorobenzaldehyde oxime 2u Yield 95,9%. Mp 102-104ºC. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1623 (C=N), 1573, 1510 (C=C), 1266 (C-O), 1160, 1092 (C-F). UV (EtOH, λ_{max}, nm): 263, 294.

3-Fluoro-4-methoxybenzaldehyde oxime 2v Yield 99%. Mp 123-124.5ºC. IR (KBr, cm^{-1}): 3475–3150 (O-H), 1615 (C=N). NMR ($(CD_3)_2CO$): 3.82 (3H, s, OCH_3), 7.14 (1H, t, J 8.4, aromatic protons), 7.33 (2H, d, J 8.4, aromatic protons), 7.41 (1H, dd, J_1 2.0, J_2 12.0, aromatic pro- tons), 8.06 (1H, s, CH), 10.30 (1H, s, OH). UV (EtOH, λ_{max}, nm): 264.

4-Methoxy-3,5-difluorobenzaldehyde oxime 2w Yield 84,6%. Mp 104-105ºC. IR (KBr, cm^{-1}): 3630-3000 (O–H), 1575 (C=N), 1524, 1433 (C=C), 1344, 1040 (C-F). UV (EtOH, λ_{max}, nm): 263.

Benzaldehyde oxime 2x Yield 87,6%. Mp 32-34ºC, lit. mp 33-35ºC [15]. IR (KBr, cm^{-1}): 3630-3000 (O–H), 1638 (C=N), 1494, 1445 (C=C). UV (EtOH,λ_{max},nm): 254.

4-Methoxybenzaldehyde oxime 2y. Yield 80.9%. Mp 63-65ºC. lit. mp 63-65ºC [16], 63- 64ºC [674I]. IR (KBr, cm^{-1}): 3600-3000 (O–H), 1609 (C=N), 1575, 1515 (C=C), 1252. UV (EtOH, λ_{max}, nm): 267.

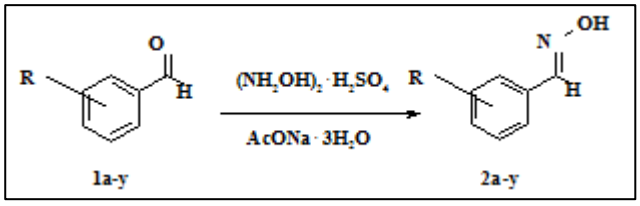
Microbiological studies

Antimycobacterial properties of the synthesized compounds were studied with the non- pathogenic strain *Micobacterium terrae 15755*. Antimycobacterial properties of the compounds evaluated on the basis of the minimum inhibitory concentration (MIC, μg/mL) and are listed in the table. Well-known anti-TB drugs (pyrazinamide, isoniazid) were used as standards. The experi- ments were performed by serial dilutions in solid medium in Petri dishes. Synthesized compound solution in DMSO with starting concentration 2 g/L was added to Middlebrook 7H9 medium with glycerol to obtain the required concentrations (200, 100, 50, 25, 12.5 and 6.25 μg/mL). All samples were incubated three weeks at 37°C. The mycobacteria growth lack in Petri dish correspond the minimum inhibitory concentration. All experiments were performed three times.

RESULTS AND DISCUSSION

Chemistry

Synthesis was performed by reaction of a fluorine-substituted benzaldehydes 1a-y with hy- droxylamine sulphate in the presence of sodium acetate in methanol according to the next scheme 1.



Scheme 1: Synthesis of the desired oximes

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Oxime formation was confirmed by the IR spectra analysis. The broad band in the 3600- 3000 cm^{-1} area corresponds to the vibrations of the O-H group and confirms the formation of oxime. The melting point satisfactory correspondence for substances that are described in the litera- ture (2a, 2b, 2f, 2r, 2t, 2x, 2y) confirms the formation of the desired products as well.

Antimycobacterial activity

Antimycobacterial properties of the synthesized compounds are shown in the table.

Table 1: Antimycobacterial properties of the synthesized compounds

Compound	MIC,μg/mL	Compound	MIC,μg/mL	Compound	MIC,μg/mL
2a	>200	**2j**	200	**2s**	>200
2b	200	**2k**	200	**2t**	200
2c	200	**2l**	200	**2u**	200
2d	200	**2m**	200	**2v**	200
2e	>200	**2n**	200	**2w**	200
2f	>200	**2o**	200	**2x**	>200
2g	>200	**2p**	200	**2y**	200
2h	200	**2q**	200	**Pyra- zinamide**	200
2i	200	**2r**	200	**Isoniazid**	200

As could be seen from the table the fluorosubstituted oximes 2a-w possess antimycobacterial activity which comparable to the currently used anti-TB agents (MIC ≥200 μg/mL). It should be noted that activity of fluorinated oximes increases slightly in comparison with unsubstituted benzaldehyde oxime 2x. For example, 4-fluorobenzaldoxime 2a is the less active compound among the mono-fluorosubstituted benzaldoximes 2a-c. Compounds 2e, 2f and 2g have the lowest activity among di-fluorosubstituted benzaldoximes. Increasing the number of fluorine atoms from three to five in compounds 2i-q results in improving activity compared with the unsubstituted benzaldoxime 2x. 3-(Trifluoromethyl)benzaldoxime 2s is the less active compound among the oximes 2r-t with trifluoromethyl group. It should be noted that the presence of the methoxy group in the structure of fluoro-substituted oximes 2u-w slightly affects the mycobactericidal activity.

It should be noted that increasing the number of fluorine atoms in the molecule increases the lipophilicity of the compound. This can improve the transport of substances in vivo, and enhance their activity. The results obtained in this study complement the previously studied by other authors [17-19], and further use of the compounds 2a-y for antimycobacterial compounds synthesis will be informed later.

CONCLUSION

Fluorinated benzaldoximes were synthesized by the reaction of the corresponding aldehydes with hydroxylamine sulphate in the presence of sodium acetate in methanol. Antimycobacterial properties of the synthesized compounds were studied. It was shown that the antimycobacterial activity of these substances was comparable to currently used anti-TB agents (pyrazinamide, isoniazid).

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