HETEROCYCLES, Vol. 94, No. 3, 2017, pp. 523 - 530. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 17th January, 2017, Accepted, 28th February, 2017, Published online, 14th March, 2017
DOI: 10.3987/COM-17-13654

NOVEL *O*-BENZYL OXIME ETHERS OF 1-(THIOPHEN-2-YL)ETHAN-1-ONE – SYNTHESIS, STRUCTURE AND ANTIMICROBIAL ACTIVITY

Tomasz Kosmalski,[1]* Jolanta Kutkowska,[2] Izabela Dwojak,[1] Renata Studzińska,[1] Adam Sikora,[3] Bożena Modzelewska-Banachiewicz,[1] and Andrzej Gzella[4]

[1] Department of Organic Chemistry, Collegium Medicum, Nicolaus Copernicus University, Jurasza 2, 85-094 Bydgoszcz, Poland, *E-mail: tpkos@wp.pl
[2] Department of Genetic and Microbiology, Faculty of Biology and Biotechnology, Sklodowska-Curie University, Akademicka 19, 20-033 Lublin, Poland
[3] Medicinal Chemistry Department, Collegium Medicum, Nicolaus Copernicus University, Jurasza 2, 85-094 Bydgoszcz, Poland
[4] Department of Organic Chemistry, Poznan University of Medical Sciences, Grunwaldzka 6, 60-780 Poznan, Poland

Abstract – In this study, new *O*-benzyl oxime ethers of (2-thienyl)ethan-1-one were synthesized and tested for their antimicrobial activity. First, we prepared, in a pure form, (*E*)-oxime of (2-thienyl)ethan-1-one. Then, we obtained eight final products with good yields and purities. The structure elucidation of the titled compounds was performed by ^{1}H NMR, ^{13}C NMR and mass spectrum. X-Ray analysis was carried out to the compound **7**. The compounds were tested to its antimicrobial activities against *C. albicans*, *S. aureus*, and *E. coli*.

The study of oxime ethers derivatives has aroused much interest in recent years because of the broad spectrum of, e.g., antimicrobial, antidepressant, anticonvulsant, and β-adrenoceptor activities of the compounds.[1-6] Heterocyclic compounds containing an oxime, or an oxime ether function, and complexes of oximes with metals were found to be active antimicrobial, antitubercular, antilepral, antiviral, and antimalarial drugs.[7,8] Oxiconazole (**1**), an azole *O*-benzyl oxime ether, is an antifungal drug used to treat skin mycoses (shown in Figure 1).

The increasing number of multidrug resistant pathogen infections lead to finding new antimicrobial drugs with activity against resistant clinical isolates.

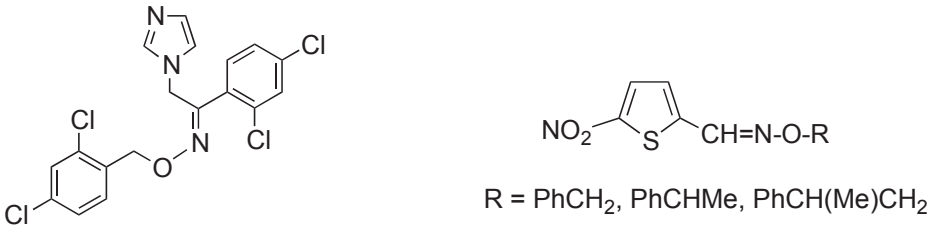

Figure 1. Biological active *O*-benzyl oximes ethers

Aromatic *O*-benzyl oxime ethers containing β-methoxyacylate moiety have high fungicidal activity.[9] Oxime ethers of heterocycles with nitrogen, oxygen, or sulfur exhibited promise more activity than standard drugs,[10] and some *O*-benzyl pyrazole oxime ethers display acaricidal activity.[11] *O*-Benzyl ether of (dinaphtho[2,1-*b*]furan-2-yl)methanone oxime has shown antimicrobial activity.[12]

It was described to influence halogenes, substituted phenyl ring, inversion of the methyleneaminoxy group, C=N-O, and increasing of the steric hindrance to its activity.[13] All these factors are crucial to its antimicrobial activity. The presence of the *O*-benzyl substituted group plays an important role in the structure and activity of these molecules.

Another interesting group that determines the diverse biological activity of the molecules is a thiophene ring. Many 5-nitrothiophene derivatives have antibacterial and bacteriostatic activity.[14] Abele and Lukevics described many thienyl ether oximes and their biological activities.[15] Anti-inflammatory and antidepressant activity in the *O*-alkyloximes of 2-acetyl-5-arylthiophene was observed.[16] *O*-Benzyloximes of the thiophene series **2** (as shown in Figure 1) have antibacterial activity against *Escherichia coli*.[17,18]

In our previous publication, we showed some (benzofuran-2-yl)ethan-1-one oxime ethers. The presence of the benzofuran-2-yl ring gave low antimicrobial activity.[19] Following the above reports, we supposed that, if heterocyclic – 2-thienyl ring and substituted *O*-benzyl group would be in the ether oxime, it causes more antimicrobial activity. In this publication, we present some new substituted *O*-benzyl oxime ethers of (2-thienyl)ethan-1-one and their antimicrobial activity.

The new oxime ethers **4**-**11** were synthesised as outlined in Figure 2. The (*E*)-oxime **3** was prepared in reaction of the 1-(2-thienyl)ethan-1-one with hydroxylamine hydrochloride in the presence of sodium acetate.[20] In these conditions, isomers *E* and *Z* (about 15%) of oxime were observed and recrystallizated from ethanol, giving the pure *E* isomer (**3**).

Oxime **3** reacted with appropriate substituted benzyl bromides or chlorides with good yields. Oxime ethers are obtained in the reaction of oximes with alkyl or benzyl halides in a basic medium, in the presence of sodium or sodium methanolate.[3,21] We used the potassium carbonate as a mild base in acetone.

Use of K_2CO_3 enables its easy removal from the reaction mixture. In this study, 8 new oxime ethers were obtained in high yields, 65-78% (as shown in Table 1).

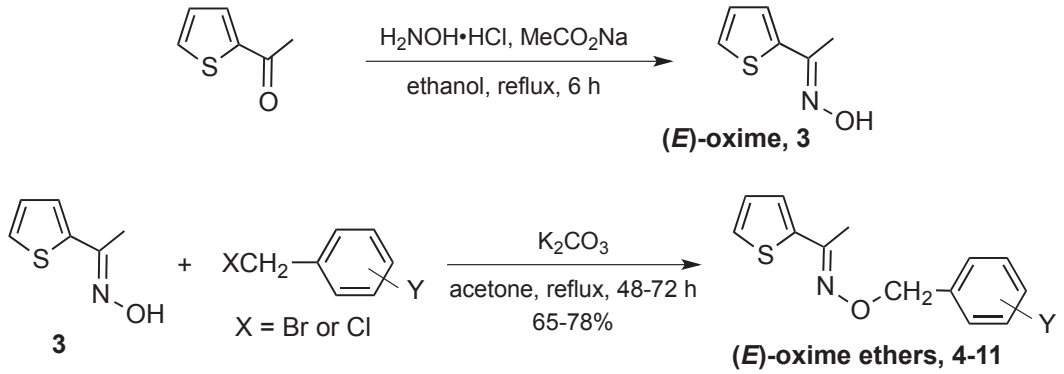

Figure 2. Synthesis of the oxime **3** and the final products **4-11**

Table 1. Structure of new ether oximes, compounds **4-11**

No.	Y	Yield [%]	mp [°C]
4	4-NO_2	69	98.5-100.0
5	2,4-diCl	77	54.0-55.0
6	5-MeO-2-NO_2	70	117.0-118.5
7	4-Br	78	53.5-54.5
8	4-CF_3	75	54.5-56.0
9	4-Cl	78	oil
10	2,6-diF	65	47.5-49
11	4-Br-2-F	69	oil

The final products were crystallized from ethanol. Compounds **9** and **11** were obtained as oils (shown in Table 1). No isomers *Z* were observed in the final products. An X-ray crystallography was performed on exemplified compound **7** to confirm the expected stereoisomer. Single crystal X-ray structure determination corroborated the *E* configuration of the molecule of **7** as shown in Figure 3.

The torsion angle found assumes C2—C6—N8—O9 of 176.7(2)°. The S1 and C5 atoms of the thiophene are disordered in the crystal and take two alternative positions *a* and *b* (Figure 3), both with site occupancy factors of 0.5. The mean planes of the both thiophene rings are almost perpendicular to the plane of the phenyl ring [dihedral angle for S1*a*,C2—C4,C5*a*/C11—C16: 83.45(14)°, for S1*b*,C2—C4,C5*b*/C11—C16: 88.86(15)°]. The supplementary crystallographic data of **7** have been deposited at the Cambridge Crystallography Data Centre (CCDC) as supplementary publication CCDC 1498391.

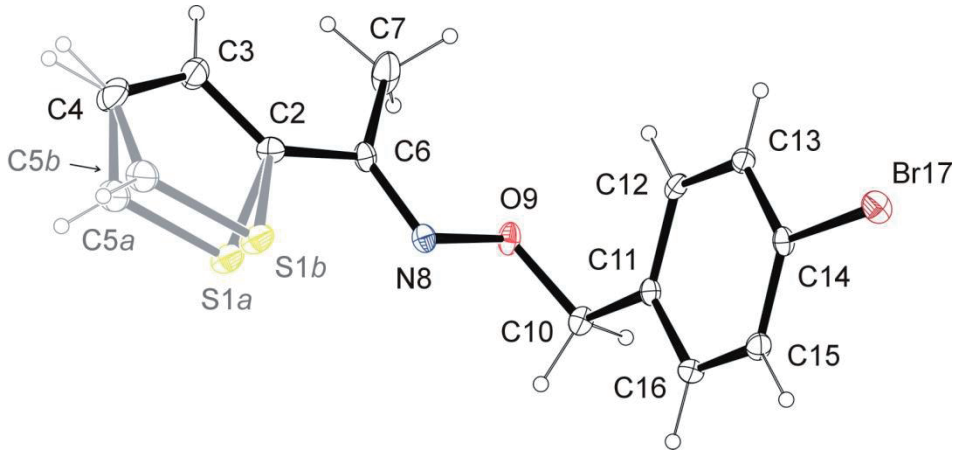

Figure 3. ORTEP view of **7** showing the atomic labelling scheme. Non-H atoms are drawn as 30% probability displacement ellipsoids, and H atoms are drawn as spheres of an arbitrary radius. The disordered part of the molecule is coloured grey.

Antimicrobial activity

The MIC values of oxime ethers derivatives **4-11** obtained against the tested microorganisms are presented in Table 2. The strongest antifungal activity was shown by compound **3** (oxime) at a concentration of 32 μg/mL, although it was less active than the reference drug itraconazole (MIC 2 μg/mL). Oxime ethers **7**, **8**, and **11** were effective against *C. albicans* at a concentration of 128 μg/mL. Compounds **5**, **6**, and **9** showed lower activity against *Candida* with twofold higher (256 μg/mL) MIC values.

Growth inhibition of *S. aureus* was observed at the concentration of 256 μg/mL of oxime ethers **7**, **9**, and **11** and at the dose of 128 μg/mL of derivative **8**. Compounds **3**, **5**, and **7** exhibited relatively high antibacterial potency against *E. coli* at the MIC values of 128 μg/mL, whereas derivative **9** was less active against *E. coli* and inhibited bacterial growth at the concentration of 256 μg/mL. The MICs of standard drug ampicillin for the *E. coli* and *S. aureus* strains used were 8 μg/mL. The weakest antimicrobial effect was observed for compounds **4** and **10** (MIC ≥ 512 μg/mL).

Replacement of the benzofuran system with the thiophene ring in oxime ethers in most cases caused an activity increase against microorganisms or not influenced the activity of the compounds. In case of two fluorine atoms on the phenyl ring (compound **10**) the decrease in activity was observed.[19] In case of compounds with substituents 4-Br, 4-Br-2-F, and 4-CF_3 in the phenyl ring (compounds **7**, **8**, **11**) the increase of activity against *C. albicans* to the thiophene derivatives was observed. In case of substituents 2,4-diCl and 4-Br (compounds **5**, **7**) the activity against *E. coli* increased. The change of heterocyclic system did not affect significantly the activity against *S. aureus.*

Table 2. Minimum inhibitory concentration (MIC) of the compounds **3-11** used in the study against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*

Strain	MIC [μg/mL]										
	Compound										
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Amp.**	**Itr.**
C. albicans	32	>512	256	256	128	128	256	>512	128	-	2
S. aureus	>512	>512	512	>512	256	128	256	>512	256	8	-
E. coli	128	512	128	>512	128	512	256	512	512	8	-

Each value is the mean ± SD of three independent measurements. Amp. = ampicillin, Itr. = itraconazole.

EXPERIMENTAL

General information

Hydroxylamine hydrochloride, sodium acetate, potassium carbonate, magnesium sulfate, anhydrous ethanol, ethyl acetate and acetone were commercially available (Avantor, Poland). Organic reagents, 1-(2-thienyl)ethan-1-one, benzyl bromides, or chlorides were commercially available (Sigma-Aldrich); oxime of 1-(2-thienyl)ethan-1-one and final products were synthesized following the procedures described in the literature. All NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer, using $CDCl_3$ as solvent, with TMS as an internal standard. Mass spectra were recorded on a Shimadzu LC-MS 8030 spectrometer (triple quadrupole). HRMS were recorded on QTOF (Impact HD, Bruker) spectrometer. Melting points were determined using an DigiMelt MPA161 digital melting point apparatus and were uncorrected.

Preparation of (*E*)-1-(2-thienyl)ethan-1-one oxime (3)[20]

The 1-(2-thienyl)ethan-1-one (25.20 g, 0.20 mol), hydroxylamine hydrochloride (15.65 g, 0.225 mol) and sodium acetate (22.96 g, 0.28 mol) were refluxed in anhydrous EtOH for 6 h. The reaction mixture was allowed to stand overnight. The raw product was filtered and recrystallised (EtOH), afforded colourless solid, 11.55 g (41%) **3**; mp 113.5-115 °C, (lit.[22] mp 113-114 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.35 (s, 3H, CH_3), 7.05 (dd, J = 4.0 Hz, J = 5.2 Hz, 1H, CH), 7.28 (dd, J = 1.2 Hz, J = 4.0 Hz, 1H, CH), 7.31 (dd, J = 1.2 Hz, J = 5.2 Hz, 1H, CH), 8.0-9.3 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 12.34 (CH_3), 126.49 (CH), 126.81 (CH), 127.12 (CH), 141.03 (C), 151.85 (C).

General procedure for preparation of the oxime ethers 4-11[20]

A mixture of oxime ketone **3** (6 mmol), benzyl bromide (6 mmol), and potassium carbonate (10 mmol) were refluxed in acetone (20 mL) for 48 h. Products **9-11** were prepared using benzyl chlorides and time of the reactions were longer – 72 h. The solvent was evaporated, and the residue was treated with EtOAc,

washed with water and dried with anhydrous magnesium sulfate. Raw products were crystallized from anhydrous EtOH; compounds **9** and **11** were oils.

(E)-1-(2-Thienyl)ethan-1-one O-(4-nitrobenzyl) oxime (**4**): yield: 69%, mp 98.5-100.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.33 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), 7.03 (dd, J = 3.6 Hz, J = 5.2 Hz 1H, CH), 7.26 (dd, J = 1.2 Hz, J = 3.6 Hz, 1H, CH), 7.29 (dd, J = 1.2 Hz, J = 5.2 Hz, 1H, CH), 7.58 (dd, J = 0,8 Hz, J = 4.0 Hz, 2H, 2×CH), 8.23 (dd, J = 0.8 Hz, J = 4.0 Hz, 2H, 2×CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.15 (CH_3), 74.77 (CH_2), 123.61 (2×CH), 126.63 (CH), 127.04 (CH), 127.20 (CH), 128.38 (2×CH), 139.82 (C), 145.60 (C), 147.50 (C), 151.81 (C); MS (ESI) *m/z*: 277.1 $(M+H)^+$, 141, 136, 124 (100%), 106; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}N_2O_3S$ $[M+H]^+$ 277.0641, Found 277.0650.

(E)-1-(2-Thienyl)ethan-1-one O-(2,4-dichlorobenzyl) oxime (**5**): yield: 77%, mp 54.0-55.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 7.03 (dd, J = 3.6 Hz, J = 5.2 Hz, 1H, CH), 7.25 (ddd, J = 1.2 Hz, J = 3.6 Hz, J = 6.0 Hz, 2H, 2×CH), 7.30 (dd, J = 1.2 Hz, J = 3.2 Hz, 1H, CH), 7.42 (dd, J = 3.2 Hz, J = 5.2 Hz, 2H, 2×CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.11 (CH_3), 72.68 (CH_2), 126.44 (CH), 126.99 (CH), 127.07 (CH), 129.18 (CH), 130.62 (CH), 133.96 (C), 134.01 (C), 134.42 (C), 140.07 (C), 151.59 (C), 160.50 (C); MS (ESI) *m/z*: 299.9 $(M+H)^+$, 159 (100%), 124; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}Cl_2NOS$ $[M+H]^+$ 300.0011, Found 300.0020.

(E)-1-(2-Thienyl)ethan-1-one O-(5-methoxy-2-nitrobenzyl) oxime (**6**): yield: 70%, mp 117.0-118.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 5.28 (s, 2H, CH_2), 6.95 (d, J = 8.8 Hz, 1H, CH), 7.03 (dd, J = 3.6 Hz, J = 8.8 Hz, 1H, CH), 7.26 (dd, J = 1.2 Hz, J = 4.0 Hz, 1H, CH), 7.28 (dd, J = 1.2 Hz, J = 4.0 Hz, 1H, CH), 8.23 (dd, J = 2.8 Hz, J = 8.8 Hz, 2H, 2×CH), 8.30 (d, J = 2.8 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.22 (CH_3), 56.16 (CH_2), 70.14 (CH_2), 109.81 (CH), 124.06 (CH), 125.07 (CH), 126.51 (CH), 127.00 (CH), 127.07 (CH), 127.91 (C), 140.04 (C), 141.39 (C), 151.68 (C), 161.80 (C); MS (ESI) *m/z*: 307.1 $(M+H)^+$, 166, 124 (100%), 90; HRMS (ESI) *m/z* calcd for $C_{14}H_{15}N_2O_4S$ $[M+H]^+$ 307.0747, Found 307.0757.

(E)-1-(2-Thienyl)ethan-1-one O-(4-bromobenzyl) oxime (**7**): yield: 78%, mp 53.5-54.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.28 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 7.03 (dd, J = 3.6 Hz, J = 5.2 Hz, 1H, CH), 7.24 (dd, J = 1.2 Hz, J = 3.6 Hz, 1H, CH), 7.28 (dd, J = 1.2 Hz, J = 5.2 Hz, 1H, CH), 7.30 (spin system AA`, dt, $J$ = 1.2 Hz, $J$ = 6.0 Hz, 2H, 2×CH), 7.51 (spin system BB`, dt, J = 1.2 Hz, J = 6.0 Hz, 2H, 2×CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.10 (CH_3), 75.47 (CH_2), 121.81 (C), 126.31 (CH), 126.93 (CH), 126.97 (CH), 123.91 (CH), 129.98 (2×CH), 131.48 (2×CH), 136.91 (C), 140.25 (C), 151.20 (C); MS (ESI) *m/z*: 312.0 $(M+H)^+$, 171 (100%), 124, 90.

(E)-1-(2-Thienyl)ethan-1-one O-(4-trifluoromethylbenzyl) oxime (**8**): yield: 75%, mp 54.5-56.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.31 (s, 3H, CH_3), 5.26 (s, 2H, CH_2), 7.03 (dd, J = 3.6 Hz, J = 5.2 Hz, 1H, CH), 7.25 (dd, J = 1.2 Hz, J = 3.6 Hz, 1H, CH), 7.29 (dd, J = 1.2 Hz, J = 5.2 Hz, 1H, CH), 7.53 (d, J

= 8.0 Hz, 2H, 2×CH), 7.63 (d, *J* = 8.0 Hz, 2H, 2×CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.11 (CH_3), 75.33 (CH_2), 122.84 (C), 125.30 (q, J_{CF} = 14.4 Hz, CF), 126.46 (CH), 127.00 (CH), 127.03 (CH), 128.18 (2×CH), 129.93 (q, J_{CF} = 129.2 Hz, 2×CH), 140.10 (C), 142.03 (C), 151.44 (C); ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) -62.49 (3F, CF_3); MS (ESI) *m/z*: 300.1 $(M+H)^+$, 159 (100%), 109; HRMS (ESI) *m/z* calcd for $C_{14}H_{13}F_3NOS$ $[M+H]^+$ 300.0664, Found 300.0673.

(E)-1-(2-Thienyl)ethan-1-one O-(4-chlorobenzyl) oxime (**9**): yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.29 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 7.03 (dd, *J* = 3.6 Hz, *J* = 5.2 Hz, 1H, CH), 7.25 (dd, *J* = 1.2 Hz, *J* = 4.0 Hz, 1H, CH), 7.29 (dd, *J* = 1.2 Hz, *J* = 4.0 Hz, 1H, CH), 7.34-7.39 (m, 4H, 4×CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.11 (CH_3), 75.46 (CH_2), 126.33 (CH), 126.94 (CH), 127.00 (CH), 128.54 (CH), 129.69 (CH), 133.67 (C), 136.42 (C), 140.29 (C), 151.18 (CH); MS (ESI) *m/z*: 265.9 $(M+H)^+$, 125 (100%), 89; HRMS (ESI) *m/z* calcd for $C_{13}H_{13}ClNOS$ $[M+H]^+$ 266.0401, Found 266.0407.

(E)-1-(2-Thienyl)ethan-1-one O-(2,6-difluorobenzyl) oxime (**10**): yield: 65%, mp 47.5-49.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.23 (s, 3H, CH_3), 5.29 (s, 2H, CH_2), 6.91-6.95 (m, 2H, 2×CH), 7.01 (dd, *J* = 3.6 Hz, *J* = 5.2 Hz, 1H, CH), 7.22 (dd, *J* = 1.2 Hz, *J* = 3.6 Hz, 1H, CH), 7.25-7.35 (m, 2H, 2×CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 12.85 (CH_3), 63.39 (t, J_{CF} = 2.6 Hz, CH_2), 111.20 (dd, J_{CF} = 6.2 Hz, J_{CF} = 19 Hz, CH), 126.20 (CH), 126.88 (2C, 2×CH), 126.93 (2C, 2×CH), 130.32 (t, J_{CF} = 10.3 Hz, 1H, C), 140.40 (C), 151.26 (C), 162.25 (dd, J_{CF} = 7.9 Hz, J_{CF} = 249.5 Hz, 2C, 2×C-F); ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) -114.28 (t, *J* = 6.4 Hz, 2F, 2×C-F); MS (ESI) *m/z*: 268.1 $(M+H)^+$, 127 (100%), 124, 101; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}F_2NOS$ $[M+H]^+$ 268.0602, Found 268.0611.

(E)-1-(2-Thienyl)ethan-1-one O-(4-bromo-2-fluorobenzyl) oxime (**11**): yield: 69%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.27 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 7.03 (dd, *J* = 3.6 Hz, *J* = 4.8 Hz, 1H, CH), 7.24 (dd, *J* = 1.2 Hz, *J* = 3.6 Hz, 1H, CH), 7.25-7.33 (m, 3H, 3×CH), 7.35 (d, *J* = 7.6 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 13.04 (CH_3), 69.16 (CH_2), 119.00 (d, J_{CF} = 24.7 Hz, CH), 126.40 (CH), 126.98 (CH), 127.04 (CH), 129.82 (CH), 130.85 (CH), 131.80 (C), 131.85 (C), 140.13 (C), 151,45 (C), 160.67 (d, J_{CF} = 251 Hz, C); ^{19}F NMR (376 MHz, $CDCl_3$): δ (ppm) -115.50 (t, *J* = 7.9 Hz, 1F, CF); MS (ESI) *m/z*: 330.0 $(M+H)^+$, 189 (100%), 124, 108; HRMS (ESI) *m/z* calcd for $C_{13}H_{12}{}^{79}BrFNOS$ $[M+H]^+$ 327.9801, Found 327.9811.

REFERENCES

1. C. Ramalingan, Y. T. Park, and S. Kabilan, *Eur. J. Med. Chem.*, 2006, **41**, 683.
2. M. I. Attia, A. S. Zakaria, M. S. Almutairi, and S. W. Ghoneim, *Molecules*, 2013, **18**, 12208.
3. M. Abid, K. Husain, and A. Azam, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4375.
4. O. Bozdağ, B. Gümüşel, R. Demirdamar, E. Büyükbingöl, Y. Rolland, and R. Ertan, *Eur. J. Med. Chem.*, 1998, **33**, 133.

5. J. S. Knutsen, K. E. Andersen, J. Lau, B. F. Lundt, R. F. Henry, H. E. Morton, L. Naerum, H. Peterson, H. Stephenson, P. D. Suzdak, M. D. B. Swedberg, Ch. Thomsen, and P. O. Sørensen, *J. Med. Chem.*, 1999, **42**, 3447.
6. H. A. Ghabbour, E. R. El-Bendary, M. B. El-Ashmawy, and M. M. El-Kerdawy, *Molecules*, 2014, **19**, 3417.
7. L. Milanese, N. Giaccheè, F. Schiaffella, A. Vecciarelli, A. Macchiarulo, and R. Fringuelli, *ChemMedChem*, 2007, **2**, 1208.
8. A. Barve, M. Noolvi, N. Subhedar, V. D. Gupta, and G. Bhatia, *Eur. J. Chem.*, 2011, **2**, 388.
9. Z.-B. Hu, H.-A. Luo, X.-G. Wang, M.-Z. Huang, L. Huang, H.-L. Pang, C.-H. Mao, H. Pei, C.-Q. Huang, J. Sun, P.-L. Liu, and A.-P. Liu, *Bull. Korean Chem. Soc.*, 2014, **35**, 1073.
10. P. Parthiban, G. Aridoss, P. Rathika, V. Ramkumar, and S. Kabilan, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2981.
11. H. Dai, J. Chen, H. Li, B. Dai, H. He, Y. Fang, and Y. Shi, *Molecules*, 2016, **21**, 276.
12. C. Kilirmiş, M. Koca, S. Servi, and S. Gür, *Turk. J. Chem*., 2009, **33**, 375.
13. A. Rossello, S. Bertini, A. Lapucci, M. Macchia, A. Martinelli, S. Rapposelli, E. Herreros, and B. Macchia, *J. Med. Chem.*, 2002, **45**, 4903.
14. F. M. Riccieri, F. Gualtiri, and B. Babudieri, *Farmaco. Ed. Sci.*, 1965, **20**, 707.
15. E. Abele and E. Lukevics, *Chem. Heterocycl. Compd.*, 2001, **37**, 141.
16. R. Shridhar, C. V. Reddy Sastry, S. C. Chaturvedi, R. Gurumurthy, P. P. Singh, R. C. Seshagiri, and A. Y. Junnarka, *Indian J. Chem.*, 1984, **23B**, 692.
17. J. R. Nicolaus and E. Testa, B.P. 1964, 964,721 (*Chem. Abstr.*, 1964, **61**, 9467).
18. J. R. Nicolaus, G. Pagani, and E. Testa, *Helv. Chim. Acta*, 1962, **45**, 1381.
19. T. Kosmalski, J. Kutkowska, A. K. Gzella, and A. Nowakiewicz, *Acta Pol. Pharm.*, 2015, **72**, 289.
20. Ş. Demirayak, Ü. Uçucu, K. Benkli, N. Gündoğdu-Karaburun, A. Karaburun, D. Akar, M. Karabacak, and N. Kiraz, *Il Farmaco*, 2002, **57**, 609.
21. A. Karakurt, S. Dalkaraa, M. Özalp, S. Özbey, E. Kendi, and J. P. Stables, *Eur. J. Med. Chem.*, 2001, **36**, 421.
22. P. B. Fabrichnyi, V. N. Bulgakova, and L. Y. Goldfarb, *Chem. Heterocycl. Compd*., 1985, **21**, 401.