HeterocyclicLetters
Vol. 9| No.1|21-26|Nov-Jan|2019
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF 6-AROYLMETHYLSULFINYL-1,4-DIHYDROPYRIDINES AS POTENTIAL MULTIDRUG RESISTANCE MODULATORS

AivarsKrauze*, Signe Grinberga, IlonaDomracheva and GunarsDuburs

LatvianInstituteofOrganicSynthesis, Riga, Aizkraukles 21, Latvia, LV-1006
E-mail: aivars.krauze@inbox.lv

ABSTRACT
Substituted 6-aroylmethylsulfinyl-1,4-dihydropyridines **3** bearing methoxy-(chloro)phenyl groups at different positions of the ring have been prepared by a selective oxidation of sulfur atom of 6-aroylmethylsulfanyl-1,4-dihydropyridines **2** with oxone. Many oxidizing agents (oxone, *m*-chloroperoxybenzoic acid, cumylhydroperoxide and *t*-butyl hydroperoxide, Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET)) were tested and oxone (mixture of salts $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)was found the most promising. 6-Aroylmethylsulfinyl-1,4-dihydropyridine **3c** bearing trimethoxyphenyl group at positions 4 has revealed pronounced multidrug resistancemodulating (P-glycoprotein inhibition) activity exceeding that of the corresponding 6-aroylmethylsulfanyl-1,4-dihydropyridine **2c** andverapamil.

KEYWORDS
1,4-dihydropyridines; multidrug resistancemodulating activity; P-glycoprotein inhibition; oxidation; oxone; verapamil.

INTRODUCTION
One of the leading causes for the failure of chemotherapeutic agents is the development of resistance to the drug as a result of prolonged treatment. This phenomenon is known as multidrug resistance (MDR). Improving chemotherapy from one side by searching for effective small-molecule drugs that show MDR cancer cell cytotoxicity[i] is on the rise. From the other side the development of MDR modulators, able to increase the intracellular drug levels in co-application with MDR substrates by efflux pump inhibition[ii],is very actual.Substances of different classes have been used as transport protein inhibitors[ii,iii]. Ca^{2+} channel blocker verapamil is the most investigated and often used as a reference compound, but unfortunately cardiotoxicity is also observed in combination with actual anticancer drugs[iv].
Rational approach of drug design – structural analogy with known medicines was used in our research group to develop effective MDR modulators on the basis of thieno[2,3-*b*]pyridines[v].

A pharmacophore model was created assuming one part of verapamil as linker and methoxyphenyl groups as essential for the pharmacophore.

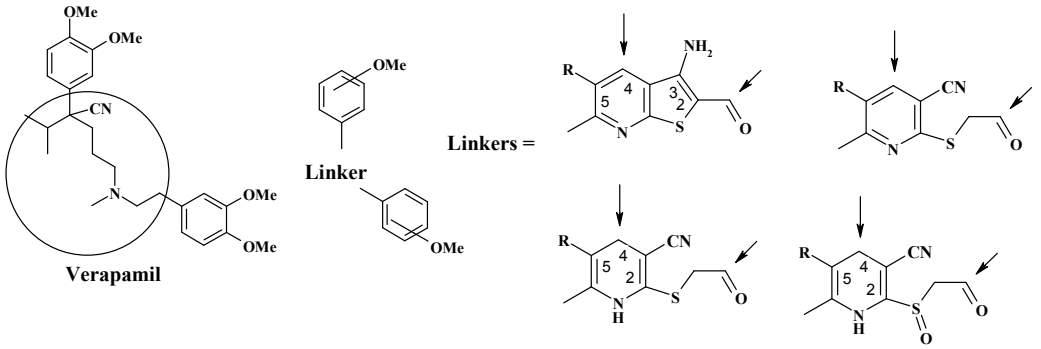


Figure 1. Pharmacophoreapproachwithmodifiedlinker

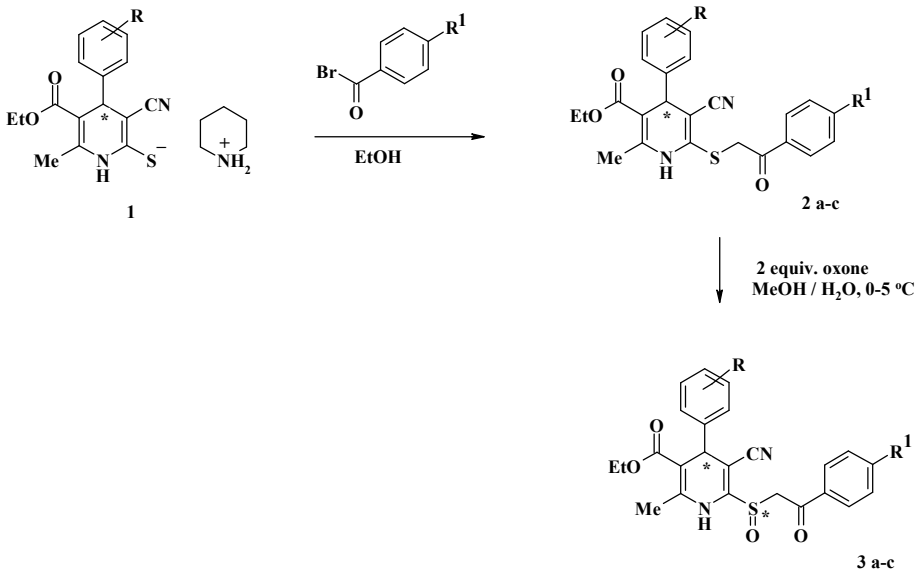
We have shown that decoration of 3-aminothieno[2,3-*b*]pyridine-5-carboxylate or pyridine-5-carboxylate scaffolds with methoxyphenyl groups (hydrophobic aryl groups and methoxy groups as hydrogen bond acceptors) in position 2 and 4 lead to potent P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP1) and breast cancer resistance protein (BCRP1) inhibitors which significantly exceed the activity of Verapamil, MK-571 and Reversan[v]. In the case of pyridine derivatives[vi] activities were comparable, but in the case of 1,4-dihydropyridine (DHP) derivatives[vii]slightly lower activities to verapamil were observed. As it was mentioned inliterature[vii]DHP could serve as prodrugs of more potent pyridines and thienopyridines.

There are a lot of publications in the last years in which DHPs as Ca^{2+} channel blockers are investigated as promising MDR reversal agents[viii,ix]. It is known that modification of substituent on theDHP ring can lead to the loss of calcium antagonistic properties[viii]which in this case is a positive result. So, DHP as a privilege structure is promising for the design of MDR modulators.

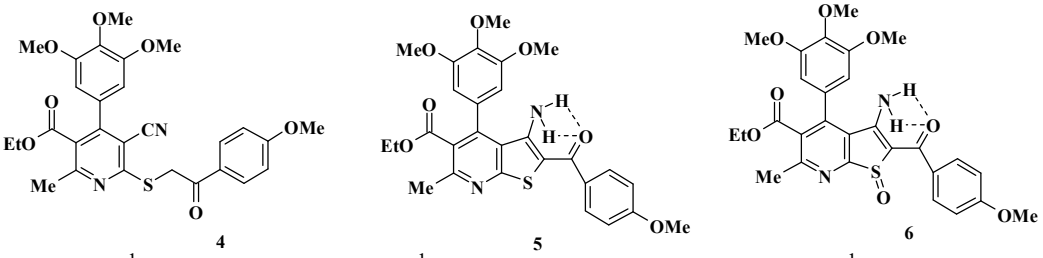
Results and discussion

In continuation of our research we used the above mentioned pharmacophore approach with DHP as linker. We succeeded to carry out selective oxidation on sulfur and the target benzoylmethylsulfinyl-1,4-dihydropyridines **3** bearing hydrophobic aryl groups and methoxy groups as hydrogen bond acceptors were obtained. Selective oxidation on the sulfur atom allows the introduction of an additional sulfinyl group as hydrogen bond acceptorin the molecule.

DHPs **2** were prepared in 82-88% yields by treatment of thiolates**1**[x]with substituted 2-bromoacetophenone. It is worth to mention that DHPs are good antioxidants[xi]. So, selective oxidation of sulfur atom while preserving untouched the hydrogenated DHP ring is a very challenging task[xii]. By treatment of 6-alkylsulfanyl-1,4-dihydropyridines **2** with two equivalents of oxone 6-alkylsulfinyl-1,4-dihydropyridines **3** were preparedin 54-68% yield. Many oxidizing agents (oxone, *m*-chloroperoxybenzoic acid, cumylhydroperoxide and *t*-butyl hydroperoxide, Ti(O*i*-Pr)$_4$/(*R*,*R*)-DET)) were tested[xii] and oxone (mixture of salts $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)was found the most promising to carry out selective oxidation and reaching highest yields. By making use of column chromatography the minor 6-alkylsulfonyl-1,4-dihydropyridines were separated.



1 2 a-c 3 a-c



4 5 6

a) R = 3-Cl, R^1 = 4-Cl; b) R = 3-Cl, R^1 = 4-OMe; c) R = 3,4,5-$(OMe)_3$, R^1 = 4-OMe

Scheme 1

The structures of compounds **2** and **3**were proved by spectroscopic methods. In their IR spectra characteristic absorption bands for $\nu_{C\equiv N}$ at 2198-2202 cm^{-1} and for $\nu_{C=O}$ at 1683-1710 cm^{-1} are seen. In the ^1H NMR spectra of **2** and **3** the most characteristic are the H_4singlets at 4.60-4.67 ppm for sulfanyl derivatives **2** and at 4.68-4.72 and 4.74-4.79 ppm for sulfinyl derivatives **3.** 6-Alkylsulfinyl-1,4-dihydropyridines **3** are formed as mixture of diastereomerssince the molecule contains two chiral centres: carbon atom in position 4 and sulfinyl group attached to the hydrogenated boat shaped ring. In case of **3a** and **3b**, diastereomer ratio is 1:1, but in case of **3c** it is 7:3. The AB-doublets of the SCH_2 group (compounds **2**) have J = 16.0 Hz, but AB-doublets of $SOCH_2$ group (compounds **3**) have J = 14.0 Hz.

Measurement of P-gp inhibition activity was carried out according to the procedure described inpublication[v].

Table 1.MDR modulating activity of tested compounds **2** - **5**and verapamil.

Compound	MDR, P-gp EC_{50}, μM
Verapamil	7.1 ± 2.0
2c	22.8 ± 2.3
3c	5.1 ± 0.7
4[vi]	9.1 ± 1.2
5[v]	0.3 ± 0.1

As shown in table, 6-alkylsulfinyl-DHP **3c** P-gp inhibition activity more than three times exceeds the corresponding 6-alkylsulfanyl-DHP **2c** and activity is **s**lightly higher than that of verapamil.

Our results confirm, that decoration of linker – N,S-containing heterocycle with methoxyphenyl groups (hydrophobic aryl groups and methoxy groups as hydrogen bond acceptors) in position 2 and 4 lead to potent P-glycoprotein inhitors. Introduction of sulfinyl group (additional hydrogen bond acceptor) in the molecule leads to the enhancement of P-gp inhibition activity in the DHPseries.

As it was mentioned DHPs are good antioxidants and they usually undergo further transformations in living organism.Pyridines and thieno[2,3-b]pyridines can be considered as their potential metabolites. So,compounds**2**and**3**could serve asprodrugsofthecorresspondingpyridinesandthieno[2,3-b]pyridines. As seen in table 1 activity rises by transformation of DHP **2c** via pyridine **4** to thienopyridine**5.** A challenging task in the future could be the preparation and investigation of MDR modulating activity of 1-oxothieno[2,3-b]pyridines**6**.

Conclusion

6-Aroylmethylsulfinyl-1,4-dihydropyridines **3** bearing 3,4,5-trimethoxyphenyl or 4-chlorophenyl group at positions 4 of the ring have been prepared by a selective oxidation of 6-aroylmethylsulfanyl-1,4-dihydropyridines**2**. Multidrug resistancemodulating (P-glycoprotein inhibition) activity of 6-aroylmethylsulfinylderivative **3c** exceeding that of the corresponding 6-aroylmethylsulfanyl-1,4-dihydropyridine **2c** andverapamil has been revealed.

Experimental

Melting points were determined on OptiMelt MPA100 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury BB 400 MHz spectrometer using $CDCl_3$ as the solvents. The chemical shifts of the atoms are reported in ppm relatively to $CDCl_3$ (δ:7.26).The IR spectra have been recorded on Shimadzu IR Prestige-21 spectrometer in nujol and peak positions are expressed as ν/cm. The course of the reactions and the individuality of substances were monitored using silica gel 60 F_{254} plates (Merck) methylchloride – benzene – acetone (9 : 7 : 1) as eluent. Synthesis of **2c** are described in[vii], **4**in[vi] and **5** in[v].

Ethyl 5-cyano-6-[2-(4-chlorophenyl)-2-oxoethanesulfanyl]-2-methyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3-carboxylate (2a)

To a solution of piperidinium 4-(3-chlorophenyl)-3-cyano-5-etoxycarbonyl-6-ethyl-1,4-dihydropyridine-2-tiolate **1** [7] (0.84 g, 2 mmol) in 10 mL of ethanol 2-bromo-1-(4-chlorophenyl)ethanone (0.47 g, 2 mmol) was added and reaction mixture was shortly refluxed and stirred at room temperature for 30 min. The precipitated crystals were separated by filtration and purified by washing with ethanol and water during the filtration to give 88% of DHP **2a.** Colourless crystals; mp 142-144 ^{o}C; IR (ν/cm): 1683 (C=O), 2200 (CN), 3070, 3277 (NH); ^{1}H NMR ($CDCl_3$): δ 1.06 un 3.96 (t and q, 3H and 2H, *J*=7.0 Hz, COOEt), 2.36 (s, 3H, 2-Me), 4.02 and 4.33 (d un d, 1H un 1H, *J*=16 Hz, SCH_2), 4.60 (s, 1H, 4-H), 7.05-7.83 (complex, 8H, $2C_6H_4$), 8.03 (s, 1H, NH). Anal. Calcd. for $C_{24}H_{20}O_3N_2Cl_2S$: C, 59.14; H, 4.14; N, 5.75. Found: C, 58.87; H, 4.09; N, 5.69.

Ethyl 5-cyano-6-[2-(4-methoxyphenyl)-2-oxoethanesulfanyl]-2-methyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3-carboxylate (2b)

Colourless crystals; yield 88%; mp 121-123^{o}C; IR (ν/cm): 1637, 1695 (C=O), 2198 (CN), 3068, 3265 (NH); ^{1}H NMR ($CDCl_3$): δ 1.15 un 4.06 (t and q, 3H and 2H, *J*=7.0 Hz, COOEt), 2.44 (s, 3H, 2-Me), 3.91 (s, 3H, OMe), 4.00 and 4.38 (d un d, 1H un 1H, *J*=16 Hz, SCH_2), 4.67 (s, 1H, 4-H), 6.99-7.97 (complex, 8H, $2C_6H_4$), 8.67 (s, 1H, NH). Anal. Calcd. for $C_{25}H_{23}O_4N_2ClS$: C, 62.17; H, 4.80; N, 5.80. Found: C, 62.08; H, 4.78; N, 5.73.

General procedure for synthesis of 4-aryl-6-(2-aryl-2-oxoethyl)sulfinyl-5-cyano-2-methyl-1,4-dihydropyridine-3-carboxylates (3)

Oxone (1,23 g, 2 mmol) was dissolved in 100 ml of water and cooled to 0 ^{o}C. DHP **2** (1 mmol) was dissolved in 5 ml of methanol and during 2 h was added to oxone solution under temperature 0-5 ^{o}C. Reaction mixture was extracted with methylchloride and purified by making use column chromatography, eluent methylchloride, benzene, acetone, 9 : 7 : 1. Recrystallization from ethanol give pure 6-benzoylmethylsulfinilpyridines **3**.

Ethyl 5-cyano-6-[2-(4-chlorophenyl)-2-oxoethanesulfinyl]-2-methyl-4-(3-chloroxyphenyl)-1,4-dihydropyridine-3-carboxylate (3a)

Colourless crystals; yield 54%; mp157-159 °C;IR (ν/cm): 1710 (C=O), 2200 (C≡N), 3038, 3250 (NH);^{1}H NMR ($CDCl_3$): δ 1.16 un 4.07 (d, t and m, 3H and 2H, *J*=7.0 Hz, COOEt), 2.36 un 2.46 (s, 3H, 2-Me), 4.42 and 4.54 (d and d, 2H, *J*=14 Hz, SCH_2), 4.72 and 4.79 (s and s,1H, 4-H), 7.10 and 7.17 (br.s and br.s, 1H, NH), 7.12-7.91 (complex, 8H, $2C_6H_4$). Anal. Calcd. for $C_{24}H_{20}O_4N_2SCl_2$: C, 57.26; H, 4.00; N, 5.56. Found: C, 57.23; H, 4.12; N, 5.45.

Ethyl 5-cyano-6-[2-(4-methoxyphenyl)-2-oxoethanesulfinyl]-2-methyl-4-(3-chloroxyphenyl)-1,4-dihydropyridine-3-carboxylate (3b)

Colourless crystals; yield 68%; mp 146-148 °C;IR (ν/cm): 1702 (C=O), 2202 (C≡N), 3076, 3242 (NH);^{1}H NMR ($CDCl_3$): δ 1.16 un 4.08 (d, t and m, 3H and 2H, *J*=7.0 Hz, COOEt), 2.35 un 2.46 (s, 3H, 2-Me), 3.89 and 3.90 (s, 3H, OMe), 4.41 un 4.51 (d and d, 2H, *J*=14 Hz, SCH_2), 4.71 un 4.79 (s and s,1H, 4-H), 6.94-7.96 (complex, 8H, $2C_6H_4$), 7.14 un 7.19 (s and s, 1H, NH). Anal. Calcd. for $C_{25}H_{23}O_5N_2SCl$: C, 60.18; H, 4.65; N, 5.61. Found: C, 60.10; H, 4.54; N, 5.43.

Ethyl 5-cyano-6-[2-(4-methoxyphenyl)-2-oxoethanesulfinyl]-2-methyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3-carboxylate (3c)

Colourless crystals; yield 58%; mp>140 °C(decomp.); IR (ν/cm): 1696 (C=O), 2198 (CN), 3183 (NH); ^{1}H NMR ($CDCl_3$): δ 1.14-1.20 and 4.03-4.12 (m and m, 5H, COOEt), 2.34 and 2.45 (s and s, 2H and 1H, 2-Me),3.83-3.90 (m,12H, $C_6H_2\underline{(OMe)_3}$ and $C_6H_4\underline{OMe}$), 4.21 and 4.61, 4.45 and 4.59 (d and d, d and d, 0.3H and 0.3H, 0.7H and 0.7H, *J*=14 Hz, $SOCH_2$), 4.68 and 4.74 (s and s, 0.7H and 0.3H, 4-H), 6.42 and 6.52 (s and s, 1.4H and 0.6H, $\underline{C_6H_2}(OMe)_3$), 6.94 and 7.82, 6.98 and 7.94 (d and d, d and d, 0.6H and 0.6H, 1.4H and 1.4H, *J*=9 Hz,

C_6H_4OMe), 7.03 and 7.08 (s and s, 0.3H and 0.7H, NH). Anal. Calcd. for $C_{28}H_{30}N_2O_8S$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.15; H, 5.66; N, 4.95.

Acknowledgments

This work waspartly funded by the Latvian National Research Programme BIOMEDICINE 2014 – 2018.

References

i. James, D.A.; Koya, K.; Li, H.; Liang, G.; Xia, Z.; Ying, W.; Wu, Y.; Sun,L. *Bioorg. Med. Chem. Lett.* **2008**, 18, 1784.
ii. Szakács, G.; Paterson, J. K, Ludwig, J. A.; Booth-Genthe, C.; Gottesman, M. M. *Nat. Rev. Drug Disc.* **2006**,5, 219.
iii. Colabufo, N. A.; Berardi, F.; Cantore, M.; Contino, M.; Inglese, C.; Niso, M.; Perrone, R. *J.Med. Chem.***2010**, 53, 1883.
iv. Pennock, G. D.; Dalton, W. S.; Roeske W. R.; Appleton C. P.; Mosley, K.;Plezia, P.; Miller, T. P.; Salmon, S. E. *J. Natl. Cancer Inst.* **1991,** 83, 105.
v. Krauze, A.; Grinberga, S.; Krasnova, L.; Adlere, I.; Sokolova, Domracheva, Shestakova, I.; Andzans, Z.; Duburs G. *Bioorg.Med. Chem*. **2014**, 22, 5860.
vi. Krauze, A.; Grinberga, S.; Sokolova E.; Domracheva, I.; Shestakova, I.; Duburs G. *Heterocycl.Commun*.**2015**, 21, 93.
vii. Krauze, A.; Krasnova, L.; Grinberga, S; Sokolova, E.; Domracheva, I.;Shestakova, I.; Duburs, G. *Heterocycl. Commun*.**2016**, 22, 157.
viii. Miri, R.; Mehdipour, A. *Bioorg. Med.Chem.* **2008**, 16, 8329.
ix. Baumert, C.; Gunthel, M.; Krawczyk, S.; Hemmer, M.; Wersig, T.; Langner A.; Molnar, J.; Lage, H.; Hilgeroth, A.*Bioorg.Med. Chem*. **2013**, 21, 166.
x. Krauze, A.A.; Liepinsh E.E.; PelcherYu.E.; Kalme Z.A.; Dipan I.V.; Dubur, G.Ya. *Chem. Heterocycl. Comp.*1**985**, 21, 95.
xi. Velena, A.; Zarkovic, N.; Troselj, K.G.; Bisenieks,E.; Krauze, A.;Poikans, J.; Duburs,G.*Oxidative Medicine and Cellular Longevity***2016**, 1.
xii. Krasnova, L.; Krauze, A.; Belyakov, S.; Duburs, G. *Chem. Heterocycl. Comp.***2012**, 48, 10, 1482.

Received on January 21, 2019.