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Isoxazole-linked 7-hydroxycoumarin–2,6-dimethylheptane conjugates as inhibitors of TDP1 enzyme

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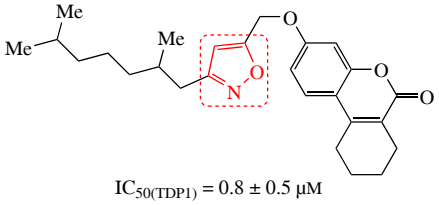
Novel monoterpenoid derivatives of 7-hydroxycoumarine containing an isoxazole linker were synthesized, 2,3-dichloropropene having been the synthetic equivalent of propargyl chloride at the step of isoxazole moiety construction. The conjugates demonstrated promising inhibitory activity against TDP1, an important target for complex anticancer therapy, with IC_{50} values in the low micromolar or submicromolar concentration range.



$IC_{50(TDP1)}$ = 0.8 ± 0.5 μM

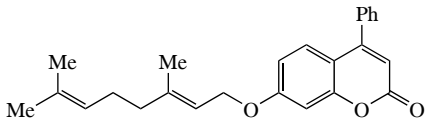
Keywords: coumarin, isoxazole, saturated terpenoids, TDP1, antitumor, synthesis, biological activity.

Polyprenylated coumarins exhibit anticancer,[1,3] anti-inflammatory,[4,5] antiviral (including anti-HIV),[4–6] phosphodiesterase-4 inhibitory,[7] antioxidant[8] and other biological activities.[9–13] Of particular note are conjugates of monoterpenoids and hydroxycoumarins possessing antiviral or anticancer activity.[14–20] Specifically, phenylcoumarin **1** containing geranyloxy fragment showed high inhibitory activity against TDP1, an important target for complex anticancer therapy.[19,21] *In silico* molecular docking against TDP1 catalytic pocket suggested that introducing into compound **1** a linker fragment between coumarin and monoterpene parts capable of acting as a hydrogen bond acceptor may enhance inhibitory activity against TDP1. Additionally, this fragment could reduce the lipophilicity level inherent to conjugates of type **1**. From a biological activity viewpoint, the combination of monoterpenoid and heterocyclic fragments is particularly promising.[22] In this context, a heterocyclic isoxazole fragment may be considered as a suitable linker.

Previous studies demonstrated that isoxazoles containing a chloromethyl group were convenient building blocks for synthesizing biologically active compounds by introducing an isoxazolylmethyl fragment into various molecules.[23,24] The most efficient method for synthesizing 5-(chloromethyl)isoxazoles is a recently developed one-pot procedure involving the reaction of *in situ* generated nitrile oxides with an excess of 2,3-dichloropropene. The latter served both as the reactant, the synthetic equivalent for propargyl chloride, and the solvent.[25,26] This approach avoids the side reaction of nitrile oxide dimerization into furazans and significantly increases the yield of target products, particularly in the case of unstable aliphatic nitrile oxides.[27] The resulting isoxazoles bearing active chloromethyl fragments can be used to synthesize conjugates in reactions with phenols.

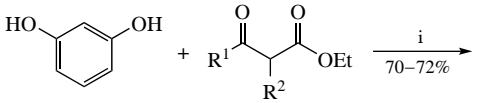
In this work, starting 7-hydroxycoumarins which can be used as O-nucleophiles were obtained by the Pechmann condensation of resorcinol **2** with substituted β-keto esters **3–5** (Scheme 1).[28]

It was found that the reaction of geranial oxime with 2,3-dichloropropene under described conditions[25,26] resulted in intense resinification making isolation of the target product impossible. Therefore, we replaced geranial with its saturated analogue, 3,7-dimethyloctanal (Scheme 2). In the first step, 3,7-dimethyloctanol **9** was oxidized to aldehyde **10**,[29] which was then reacted with hydroxylamine hydrochloride to form the

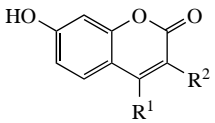


1

IC_{50} = 0.49 ± 0.14 μM



2 **3–5**



6–8

3, **6** $R^1 + R^2 = (CH_2)_4$
4, **7** $R^1 + R^2 = (CH_2)_3$
5, **8** R^1 = Ph, R^2 = H

Scheme 1 *Reagents and conditions*: i, EtOH, H_2SO_4, room temperature.

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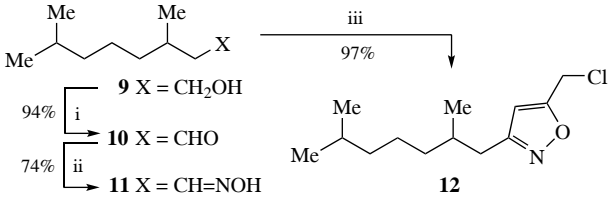
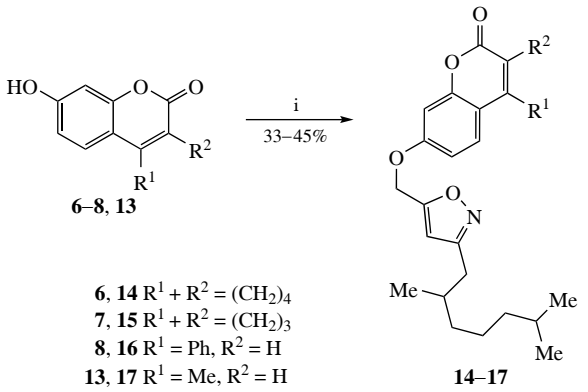


Scheme 2 *Reagents and conditions*: i, pyridinium chlorochromate, CH_2Cl_2, inert atmosphere; ii, $NH_2OH \cdot HCl$, Na_2CO_3, H_2O; iii, $ClCH_2C(Cl)=CH_2$, NCS, Py, Et_3N.



Scheme 3 *Reagents and conditions*: i, compound **12**, K_2CO_3, acetone, 125 °C, p = 6 atm (Anton Paar Monowave 50 reactor).

Table 1 IC_{50} values of compounds **14**–**17**.

Compound	IC_{50}/μM
14	0.8 ± 0.5
15	1.6 ± 0.4
16	2.1 ± 0.2
17	3.1 ± 0.7
Furamidine	1.2 ± 0.3

corresponding oxime **11**.[30] Oxime **11** was subjected to cyclization with 2,3-dichloropropene thus yielding chloromethylisoxazole derivative **12**.[25]

The reaction of compound **12** with herein synthesized 7-hydroxycoumarins **6**–**8** and commercially available 4-methyl-7-hydroxycoumarin **13** in the presence of potassium carbonate in acetone was performed in an Anton Paar Monowave 50 reactor at 125 °C (Scheme 3). The pressure in the reactor rose to 6 atm, and the processing for 4 h[31] afforded the target compounds **14**–**17** with yields ranging from 33 to 45%.

The inhibitory activity of these compounds against TDP1 was determined following the described[32] methodology. Furamidine, the only commercially available TDP1 inhibitor,[32] was used as a positive control. As shown in Table 1, the half-maximal inhibitory concentration (IC_{50}) values were in the low micromolar and submicromolar ranges. Compound **14** was the most active one with an IC_{50} of 0.8 μM, making it the most promising candidate for further evaluation.

In general, the synthetic way to new monoterpene–coumarin conjugates linked through isoxazole fragment was developed. The compounds obtained demonstrated high inhibitory activity against enzyme TDP1, important target for complex antitumor therapy.

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Online Supplementary Materials

Supplementary data associated with this article (syntheses, HRMS, ^1H and ^{13}C NMR spectra of compounds **12**, **14**–**17**, and 2D NMR spectra (COSY, NOESY, HSQC, HMBC) of compound **15**) can be found in the online version at doi: 10.71267/mencom.7704.

References

1 G. Li, J. Wang, X. Li, J. Xu, Z. Zhang and J. Si, *Arch. Pharm. Res*., 2018, **41**, 646; https://doi.org/10.1007/s12272-018-1028-0.
2 M. Iranshahi, A. Sahebkar, M. Takasaki, T. Konoshima and H. Tokuda, *Eur. J. Cancer Prev*., 2009, **18**, 412; https://doi.org/10.1097/CEJ.0b013e32832c389e.
3 C. Bocca, L. Gabriel, F. Bozzo and A. Miglietta, *Planta Med*., 2002, **68**, 1135; https://doi.org/10.1055/s-2002-36342.
4 Y.-P. Liu, G. Yan, Y.-T. Xie, T.-C. Lin, W. Zhang, J. Li, Y.-J. Wu, J.-Y. Zhou and Y.-H. Fu, *Bioorg. Chem*., 2020, **97**, 103699; https://doi.org/10.1016/j.bioorg.2020.103699.
5 Y.-P. Liu, G. Yan, J.-M. Guo, Y.-Y. Liu, Y.-J. Li, Y.-Y. Zhao, L. Qiang and Y.-H. Fu, *J. Agric. Food Chem*., 2019, **67**, 11942; https://doi.org/10.1021/acs.jafc.9b04326.
6 M. Z. Hassan, H. Osman, M. A. Ali and M. J. Ahsan, *Eur. J. Med. Chem*., 2016, **123**, 236; https://doi.org/10.1016/j.ejmech.2016.07.056.
7 T.-T. Lin, Y.-Y. Huang, G.-H. Tang, Z. Cheng, X. Liu, H. Luo and S. Yin, *J. Nat. Prod*., 2014, **77**, 955; https://doi.org/10.1021/np401040d.
8 S. A. Popova, O. G. Shevchenko, I. Y. Chukicheva and A. V. Kutchin, *Chem. Biodiversity*, 2019, **16**, e1800317; https://doi.org/10.1002/cbdv.201800317.
9 R. R. Kurdelas, B. Lima, A. Tapia, G. E. Feresin, M. G. Sierra, M. V. Rodríguez, S. Zacchino, R. D. Enriz and M. L. Freile, *Molecules*, 2010, **15**, 4898; https://doi.org/10.3390/molecules15074898.
10 M. Monti, M. Pinotti, G. Appendino, F. Dallocchio, T. Bellini, F. Antognoni, F. Poli and F. Bernardi, *Biochim. Biophys. Acta*, 2007, **1770**, 1437; https://doi.org/10.1016/j.bbagen.2007.06.013.
11 M. Iranshahi, A. Jabbari, A. Orafaie, R. Mehri, S. Zeraatkar, T. Ahmadi, M. Alimardani and H. Sadeghian, *Eur. J. Med. Chem*., 2012, **57**, 134; https://doi.org/10.1016/j.ejmech.2012.09.006.
12 S. C. Baek, M.-G. Kang, J.-E. Park, J. P. Lee, H. Lee, H. W. Ryu, C. M. Park, D. Park, M.-L. Cho, S.-R. Oh and H. Kim, *Bioorg. Med. Chem. Lett*., 2019, **29**, 839; https://doi.org/10.1016/j.bmcl.2019.01.016.
13 N. S. Li-Zhulanov, K. Yu. Ponomarev, S. Sari, D. Gülmez, S. Arikan-Akdagli, V. I. Krasnov, E. V. Suslov, K. P. Volcho and N. F. Salakhutdinov, *Mendeleev Commun*., 2024, **34**, 119; https://doi.org/10.1016/j.mencom.2024.01.036.
14 T. M. Khomenko, V. V. Zarubaev, I. R. Orshanskaya, R. A. Kadyrova, V. A. Sannikova, D. V. Korchagina, K. P. Volcho and N. F. Salakhutdinov, *Bioorg. Med. Chem. Lett*., 2017, **27**, 2920; https://doi.org/10.1016/j.bmcl.2017.04.091.
15 A. K. Zhanataev, A. V. Kulakova, O. A. Luzina, T. M. Khomenko, K. P. Volcho, N. F. Salakhutdinov and A. D. Durnev, *Bull. Exp. Biol. Med*., 2024, **177**, 30; https://doi.org/10.1007/s10517-024-06125-9.
16 T. M. Khomenko, A. A. Shtro, A. V. Galochkina, Y. V. Nikolaeva, G. D. Petukhova, S. S. Borisevich, D. V. Korchagina, K. P. Volcho and N. F. Salakhutdinov, *Molecules*, 2021, **26**, 7493; https://doi.org/10.3390/molecules26247493.
17 T. M. Khomenko, A. L. Zakharenko, T. E. Kornienko, A. A. Chepanova, N. S. Dyrkheeva, A. O. Artemova, D. V. Korchagina, C. Achara, A. Curtis, J. Reynisson, K. P. Volcho, N. F. Salakhutdinov and O. I. Lavrik, *Int. J. Mol. Sci*., 2023, **24**, 9155; https://doi.org/10.3390/ijms24119155.
18 T. M. Khomenko, A. A. Shtro, A. V. Galochkina, Y. V. Nikolaeva, A. V. Garshinina, S. S. Borisevich, D. V. Korchagina, K. P. Volcho and N. F. Salakhutdinov, *Molecules*, 2023, **28**, 2673; https://doi.org/10.3390/molecules28062673.
19 T. M. Khomenko, A. L. Zakharenko, A. A. Chepanova, E. S. Ilina, O. D. Zakharova, V. I. Kaledin, V. P. Nikolin, N. A. Popova, D. V. Korchagina, J. Reynisson, R. Chand, D. M. Ayine-Tora, J. Patel, I. K. H. Leung, K. P. Volcho, N. F. Salakhutdinov and O. I. Lavrik, *Int. J. Mol. Sci.*, 2020, **21**, 126; https://doi.org/10.3390/ijms21010126.
20 S. Kuranov, M. Marenina, D. Ivankin, M. Blokhin, S. Borisov, T. Khomenko, O. Luzina, M. Khvostov, K. Volcho, T. Tolstikova and N. Salakhutdinov, *Molecules*, 2022, **27**, 8663; https://doi.org/10.3390/molecules27248663.
21 T. Dexheimer, S. Antony, C. Marchand and Y. Pommier, *Anti-Cancer Agents Med. Chem*., 2008, **8**, 381; https://doi.org/10.2174/187152008784220357.

22 V. N. Charushin, E. V. Verbitskiy, O. N. Chupakhin, D. V. Vorobyeva, P. S. Gribanov, S. N. Osipov, A. V. Ivanov, S. V. Martynovskaya, E. F. Sagitova, V. D. Dyachenko, I. V. Dyachenko, S. G. Krivokolysko, V. V. Dotsenko, A. V. Aksenov, D. A. Aksenov, N. A. Aksenov, A. A. Larin, L. L. Fershtat, V. M. Muzalevskiy, V. G. Nenajdenko, A. V. Gulevskaya, A. F. Pozharskii, E. A. Filatova, K. V. Belyaeva, B. A. Trofimov, I. A. Balova, N. A. Danilkina, A. I. Govdi, A. S. Tikhomirov, A. E. Shchekotikhin, M. S. Novikov, N. V. Rostovskii, A. F. Khlebnikov, Yu. N. Klimochkin, M. V. Leonova, I. M. Tkachenko, V. A. Mamedov, V. L. Mamedova, N. A. Zhukova, V. E. Semenov, O. G. Sinyashin, O. V. Borshchev, Yu. N. Luponosov, S. A. Ponomarenko, A. S. Fisyuk, A. S. Kostyuchenko, V. G. Ilkin, T. V. Beryozkina, V. A. Bakulev, A. S. Gazizov, A. A. Zagidullin, A. A. Karasik, M. E. Kukushkin, E. K. Beloglazkina, N. E. Golantsov, A. A. Festa, L. G. Voskressensky, V. S. Moshkin, E. M. Buev, V. Ya. Sosnovskikh, I. A. Mironova, P. S. Postnikov, V. V. Zhdankin, M. S. Yusubov, I. A. Yaremenko, V. A. Vil', I. B. Krylov, A. O. Terent'ev, Yu. G. Gorbunova, A. G. Martynov, A. Yu. Tsivadze, P. A. Stuzhin, S. S. Ivanova, O. I. Koifman, O. N. Burov, M. E. Kletskii, S. V. Kurbatov, O. I. Yarovaya, K. P. Volcho, N. F. Salakhutdinov, M. A. Panova, Ya. V. Burgart, V. I. Saloutin, A. R. Sitdikova, E. S. Shchegravina and A. Yu. Fedorov, *Russ. Chem. Rev*., 2024, **93**, RCR5125; https://doi.org/10.59761/RCR5125.

23 E. V. Kondrashov, L. A. Belovezhets, N. S. Shatokhina, A. N. Shilova, Y. A. Kostyro, Y. A. Markova, M. K. Borovskaya and G. B. Borovskii, *Bioorg. Chem*., 2023, **138**, 106644; https://doi.org/10.1016/j.bioorg.2023.106644.

24 S. N. Adamovich, E. V. Kondrashov, I. A. Ushakov, N. S. Shatokhina, E. N. Oborina, A. V. Vashchenko, L. A. Belovezhets I. B. Rozentsveig and F. Verpoort, *Appl. Organomet. Chem*., 2020, **34**, e5976; https://doi.org/10.1002/aoc.5976.

25 E. V. Kondrashov and N. S. Shatokhina, *Chem. Heterocycl. Compd*., 2019, **55**, 1228; https://doi.org/10.1007/s10593-019-02606-2.

26 A. N. Shilova, N. S. Shatokhina and E. V. Kondrashov, *Russ. J. Org. Chem*., 2022, **58**, 1554; https://doi.org/10.1134/S1070428022100268.

27 C. Grundmann and S. K. Datta, *J. Org. Chem*., 1969, **34**, 2016; https://doi.org/10.1021/jo01258a125.

28 Ya. L. Garazd, T. N. Panteleimonova, M. M. Garazd and V. P. Khilya, *Chem. Nat. Compd*., 2003, **39**, 330; https://doi.org/10.1023/B:CONC.0000003410.74701.dc.

29 V. N. Odinokov, G. Yu. Ishmuratov, R. Ya. Kharisov, S. I. Lomakina and G. A. Tolstikov, *Russ. Chem. Bull*., 1989, **38**, 1768; https://doi.org/10.1007/BF00956974.

30 R. T. Dahill, Jr., *Patent US 3637533A*, 1972; https://patents.google.com/patent/US3637533A/en.

31 C. Gnerre, M. Catto, F. Leonetti, P. Weber, P.-A. Carrupt, C. Altomare, A. Carotti and B. Testa, *J. Med. Chem*., 2000, **43**, 4747; https://doi.org/10.1021/jm001028o.

32 A. Zakharenko, T. Khomenko, S. Zhukova, O. Koval, O. Zakharova, R. Anarbaev, N. Lebedeva, D. Korchagina, N. Komarova, V. Vasiliev, J. Reynisson, K. Volcho, N. Salakhutdinov and O. Lavrik, *Bioorg. Med. Chem*., 2015, **23**, 2044; https://doi.org/10.1016/j.bmc.2015.03.020.

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