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SYNTHESIS OF NOVEL N-SUBSTITUTED 3-(AMINOSULFONYL)-2*H*-1-BENZOPYRAN-2-ONE DERIVATIVES AND THEIR BIOLOGICAL ACTIVITY

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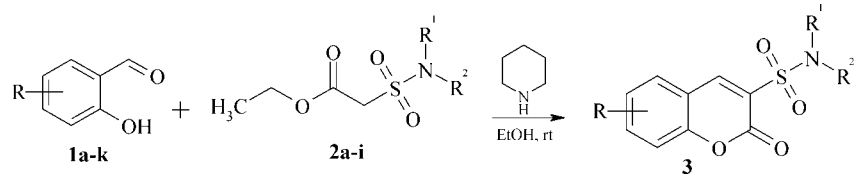
New N-substituted 3-(aminosulfonyl)-2H-1-benzopyran-2-one derivatives were synthesized by the reaction of salicylic aldehydes with N-substituted ethyl 2-(aminosulfonyl)acetates in the Knoevenagel condensation conditions. The structure of obtained compounds was determined through a complete IR- and ^{1}H NMR analysis. The biological activity of some derivatives against protozoan and helminth parasites was studied. Some compounds were active against Onchocerca lienalis.

СИНТЕЗ НОВИХ N-ЗАМІЩЕНИХ ПОХІДНИХ 3-(АМІНОСУЛЬФОНІЛ)-2Н-1-БЕНЗОПІРАН-2-ОНІВ ТА ЇХ БІОЛОГІЧНА АКТИВНІСТЬ
С.С.Коваленко, О.В.Силін, С.М.Коваленко, В.П.Черних, Л.Маес, С.Таунсон, Ф.Юсіф, Ф.Факореде, Р.Бернадет, С.Нвака
Нові N-заміщені похідні 3-(аміносульфоніл)-2Н-1-бензопіран-2-онів були синтезовані за реакцією саліцилових альдегідів з N-заміщеними етил 2-(аміносульфоніл)ацетатами в умовах конденсації за Кньовенагелем. Структуру отриманих сполук було визначено методами ІЧ- та ПМР-спектроскопії. Вивчено біологічну активність отриманих сполук проти протозойних та гельмінтних паразитів. Деякі сполуки виявили високу активність проти Onchocerca lienalis.

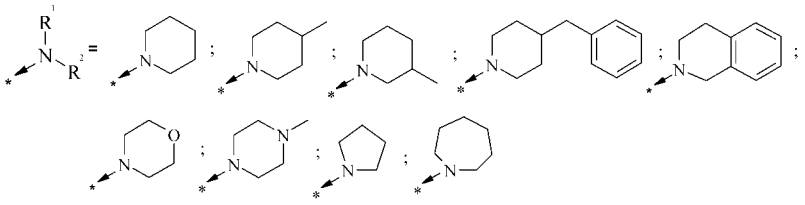
СИНТЕЗ НОВЫХ N-ЗАМЕЩЕННЫХ ПРОИЗВОДНЫХ 3-(АМИНОСУЛЬФОНИЛ)-2Н-1-БЕНЗОПИРАН-2-ОНОВ И ИХ БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ
С.С.Коваленко, А.В.Силин, С.Н.Коваленко, В.П.Черных, Л.Маес, С.Таунсон, Ф.Юсиф, Ф.Факореде, Р.Бернадет, С.Нвака
Новые N-замещенные производные 3-(аминосульфонил)-2Н-1-бензопиран-2-онов были синтезованы реакцией салициловых альдегидов с N-замещенными этил 2-(аминосульфонил)ацетатами в условиях конденсации Кневенагеля. Структура полученных соединений была подтверждена методами ИК- и ПМР-спектроскопии. Изучена биологическая активность полученных соединений против протозойных и гельминтных паразитов. Некоторые соединения проявили высокую активность по отношению к Onchocerca lienalis.

Derivatives of coumarin — *2H*-1-benzopyran-2-one — is an important class of natural and synthetic compounds. It is known that the compounds with coumarine moiety posses a wide range of biological activities [1-16] and are widely used in medicine. The current promising line of investigation in medicinal chemistry is integration of several pharmacophores in one molecule. In view of this the introduction of other biological active moiety — sulfonamide group [17, 18] into position 3 of coumarin in our opinion can lead to a new class of potential biological active substances. The procedure of synthesis of new coumarin 3-(N-aryl)sulfonamides of primary aromatic amines and their anticancer activity was described [8]. Continuing our research work in chemistry of 3-substituted coumarins [19-23] we developed the method that allowed us to synthesize novel 2*H*-1-benzopyran-2-one-3-sulfonamides of secondary aliphatic amines.

Novel N-substituted 3-(aminosulfonyl)-2*H*-1-benzopyran-2-one derivatives **3** were obtained in the Knoevenagel condensation conditions according to Scheme.



R = H, 6-F, 6-Cl, 6-Br, 6,8-di-C(CH$_3$)$_3$, 6-COOMe, 6-Me, 6-OMe, 7-OMe, 8-OMe, 8-OEt (in the molecule of coumarine);



Scheme

Initial N-substituted ethyl 2-(aminosulfonyl)acetates (**2a-i**) were prepared by interaction of N-substituted aminosulfonylmethan with excess of diethylcarbonate and NaH in dioxane. The reaction of salicylic aldehydes (**1a-k**) with N-substituted ethyl 2-(aminosulfonyl)acetates (**2a-i**) gave the novel N-substituted 3-(aminosulfonyl)-2*H*-1-benzopyran-2-one derivatives (**3**). The condensation was conducted under reflux in methanol in the presence of catalytic amount of piperidine for 20-40 minutes. Products of these reactions were obtained as crystals after the cooling of reaction mixture.

The purity and individuality of the synthesized compounds were determined by thin layer chromatography (TLC). The structure of compounds was assigned on the basis of complete analysis of IR- and ^{1}H NMR spectra.

^{1}H NMR spectra of compounds (**3**) showed characteristic signals of proton in the position 4 of the coumarin system at δ 8.71-8.74 ppm (singlet, 1H) and other aromatic protons of the correspondent aromatic system in the range of δ 6.99-8.13 ppm. All these spectra also contained signals of aliphatic protons of sulphonamide substituents (in the range of 1.38-3.38 ppm). IR spectra of compounds (**3**) contain several specific absorption bands. There are the strong bands of C=O group of coumarin ring at 1720-1754 cm^{-1}. The absorption bands of the C=C group of aromatic rings appear in the range from 1557 to 1611 cm^{-1}.

There is a continuing need for new and improved treatments for neglected tropical diseases particularly those caused by protozoan and helminth parasites. Thus, discovering new compounds with potential to become usable drugs using parasite targeted assays is an important undertaking. There is precedence for coumarins in the area of infectious diseases [1] so we focused our efforts on evaluating of activity of synthesised compounds in this field.

The new compounds in this series (n = 5) were tested *in vitro* against protozoan targets (*Trypanosoma cruzi, Trypanosoma brucei, Leishmania donovani* and *Plasmodium falciparum*) and helminth targets (*Onchocerca lienalis* and *Schistosoma mansoni*). None of the compounds were active *in vitro* against the protozoan parasites and *Schistosoma mansoni.* However, two compounds, (**3a**) and (**3d**), were active at 12.5 uM concentration against *O. lienalis*, exhibiting a % motility reduction of microfilaria at 66.7% and 100%, respectively (the reference standard drug, melarsomine, immobilizes microfilaria down to a concentration of 3.1×10^{-6} M).). None of the compounds were cytotoxic to the human lung fibroblast cell line, MRC-5. Further testing of these compounds *in vivo* is warranted.

Experimental

Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). The solvent system for the TLC method is ethyl acetate: toluene (1:1 or 1:2). IR spectra were recorded on FT-IR Bruker Tensor-27 spectrometer in KBr. ^{1}H NMR spectra were recorded on Varian Mercury-200 spectrometer in DMSO-d$_6$ using TMS as an internal standard. Chemical shifts were expressed in δ (ppm) relative to TMS as internal standard and coupling constants (J) in Hz. Elemental analysis were within±0.4% of the theoretical value.

General Procedure for Synthesis of N-substituted 3-(aminosulfonyl)-2*H*-1-benzopyran-2-one derivatives (3)

A mixture of salicylic aldehyde (**1a-k**) (5 mmol) and corresponding N-substituted ethyl 2-(aminosulfonyl)acetate (**2a-i**) (5 mmol) was dissolved at heating (30-40°C) in 50 mL of methanol. To the obtained solution 2-3 drops of piperidine was added and has been refluxed during 20-40 min. The reaction mixture was cooled and diluted with 50 mL of water. The precipitate was filtered off and recrystallized from methanol or its mixture with water.

6-Chloro-3-(piperidin-1ylsulfonyl)-2H-1-benzopyran-2-one (3a)

Yield — 83%. M.p. — 165-166°C; IR (cm^{-1}): 3066, 2943, 1754, 1611, 1560; ^{1}H NMR, δ, ppm: 1.41-1.58 (m, 6H, 3CH$_2$), 3.23 (m, 4H, 2NCH$_2$), 7.50 (d, J = 8.9 Hz, 1H, H-8), 7.78 (dd, J = 8.9 Hz, J = 2.6 Hz,

1H, H-7), 8.13 (d, J = 2.6 Hz, 1H, H-5), 8.71 (s, 1H, H-4). Calc. for $C_{14}H_{14}ClNO_4S$: C, 51.30, H, 4.31, N, 4.27; found: C, 51.34, H, 4.29, N, 4.30.

8-Methoxy-3-(piperidin-1ylsulfonyl)-2H-1-benzopyran-2-one (3b)

Yield — 87%. M.p. — 175-177°C; IR (cm^{-1}): 3105, 3055, 3018, 2943, 2858, 1723, 1606, 1569; ^{1}H NMR, δ, ppm: 1.38-1.58 (m, 6H, $3CH_2$), 3.22 (m, 4H, $2NCH_2$), 3.90 (s, 3H, OCH_3), 7.29-7.53 (m, 3H, H-5,6,7), 8.71 (s, 1H, H-4). Calc. for $C_{15}H_{17}NO_5S$: C, 55.72, H, 5.30, N, 4.33; found: C, 55.71, H, 5.34, N, 4.36.

6-Chloro-3-(pyrrolidin-1-ylsulfonyl)-2H-1-benzopyran-2-one (3c)

Yield — 66%. M.p. — 212-213°C; IR (cm^{-1}): 3075, 3051, 2987, 2898, 1744, 1611, 1557; ^{1}H NMR, δ, ppm: 1.78 (m, 4H, $2CH_2$), 3.38 (m, 4H, $2NCH_2$), 7.52 (d, J = 8.9 Hz, 1H, H-8), 7.80 (dd, J = 8.9 Hz, J = 2.8 Hz, 1H, H-7), 8.13 (d, J = 2.8 Hz, 1H, H-5), 8.74 (s, 1H, H-4). Calc. for $C_{13}H_{12}ClNO_4S$: C, 49.77, H, 3.86, N, 4.46; found: C, 49.81, H, 3.83, N, 4.42.

7-Methoxy-3-(pyrrolidin-1-ylsulfonyl)-2H-1-benzopyran-2-one (3d)

Yield — 63%. M.p. — 203-204°C; IR (cm^{-1}): 3094, 3055, 3016, 2983, 2952, 2876, 1720, 1606, 1569; ^{1}H NMR, δ, ppm: 1.77 (m, 4H, $2CH_2$), 3.36 (m, 4H, $2NCH_2$), 3.89 (s, 3H, OCH_3), 6.99-7.14 (m, 2H, H-6,8), 7.91 (d, J = 8.7 Hz, 1H, H-5), 8.71 (s, 1H, H-4). Calc. for $C_{14}H_{15}NO_5S$: C, 54.36, H, 4.89, N, 4.53; found: C, 54.37, H, 4.88, N, 4.49.

8-Methoxy-3-[(4-methylpiperazin-1-yl)sulfonyl]-2H-1-benzopyran-2-one (3e)

Yield — 58%. M.p. — 197-198°C; IR (cm^{-1}): 3095, 3054, 3020, 3004, 2963, 2934, 2798, 1724, 1605, 1568; ^{1}H NMR, δ, ppm: 2.14 (s, 3H, NCH_3), 2.31 (t, J = 5.0 Hz, 4H, $(CH_2)_2NCH_3$), 3.25 (m, 4H, $(CH_2)_2NSO_2$), 3.90 (s, 3H, OCH_3), 7.28-7.55 (m, 3H, H-5,6,7), 8.72 (s, 1H, H-4). Calc. for $C_{15}H_{18}N_2O_5S$: C, 53.24, H, 5.36, N, 8.28; found: C, 53.28, H, 5.34, N, 8.26.

Conclusions

A facile approach to N-substituted 3-(aminosulfonyl)-2*H*-1-benzopyran-2-one derivatives (**3**) has been developed. A series of novel compounds were synthesized and characterized. All the compounds obtained are perspective biologically active substances. *In vitro* assays against agents of different tropical diseases showed that (**3a**) and (**3d**) could be perspective agents for treatment of onchocercosis and were recommended for further investigations.

References

1. *Reyes-Chilpa R., Estrada-Muniz E., Vega-Avila E. et al. // Mem. Inst. Oswaldo Cruz. — 2008. — Vol. 103 (5). — P. 431-436.*
2. *Spino C., Dodier M., Sotheeswaran S. // Bioorg. Med. Chem. Lett. — 1998. — Vol. 8 (24). — P. 3475-3478.*
3. *Madhavan G.R., Balraju V., Mallesham B. et al. // Bioorg. Med. Chem. Lett. — 2003. — Vol. 13 (15). — P. 2547.*
4. *Kontogiorgis C., Hadjipavlou-Litina D. // J. Enzym. Inhib. Med. Chem. — 2003. — Vol. 18 (1). — P. 63-69.*
5. *Hoult J.R.S., Paya M. // Gen. Pharmacol. — 1996. — Vol. 27. — P. 713-722.*
6. *Pochet L., Frederick R., Masereel B. // Curr. Pharm. Design. — 2004. — Vol. 10 (30). — P. 3781-3796.*
7. *Kempen I., Papapostolou D., Thierry N. et al. // Brit. J. Cancer. — 2003. — Vol. 88. — P. 1111-1118.*
8. *Reddy N.S., Mallireddigari M.R., Cosenza S. et al. // Bioorg. Med. Chem. Lett. — 2004. — Vol. 14 (15). — P. 4093-4097.*
9. *Pochet L., Doucet C., Dive G. et al. // Bioorg. Med. Chem. — 2000. — Vol. 8. — P. 1489-1501.*
10. *Wouters J., Huygens M., Pochet L. et al. // Bioorg. Med. Chem. Lett. — 2002. — Vol. 12. — P. 1109-1112.*
11. *Mor A., Maillard J., Favreau C., Reboud-Ravaux M. // Biochim. Biophys. Acta. — 1990. — Vol. 1038 (1). — P. 119-124.*
12. *Doucet C., Pochet L., Thierry N. et al. // J. Med. Chem. — 1999. — Vol. 42. — P. 4161-4171.*
13. *Egan D., O'Kennedy E., Moran E. et al. // Drug. Metab. Rev. — 1990. — Vol. 22 (5). — P. 503-529.*
14. *Nicolaides D.N., Fylaktakidou K.C., Litinas K.E., Hadjipavlou-Litina D.J. // J. Heterocyd. Chem. — 1996. — Vol. 33 (3). — P. 967-971.*
15. *Brenzan M.A., Nakamura C.V., Dias Filho B.P. et al. // Biomed. Pharmacother. — 2008. — Vol. 62 (9). — P. 651-658.*
16. *Zavrsnik D., Muratovic S., Spirtovic S. et al. // Bosn. J. Basic Med. Sci. — 2008. — Vol. 8 (3). — P. 277-281.*
17. *Shan B., Medina J.C., Santha E. et al. // Proc. Natl. Acad. Sci. U.S.A. — 1999. — Vol. 96. — P. 5686-5691.*
18. *Medina J.C., Shan B., Beckmann H. et al. // Bioorg. Med. Chem. Lett. — 1998. — Vol. 8 (19). — P. 2653-2656.*
19. *Zhuravel' I.O., Kovalenko S.M., Vlasov S.V., Chernykh V.P. // Molecules. — 2005. — Vol. 10. — P. 444-456.*
20. *Kovalenko S.M., Vlasov S.V., Chernykh V.P. // Synthesis. — 2006. — Vol. 5. — P. 847-852.*
21. *Kovalenko S.M., Vlasov S.V., Chernykh V.P. // Heteroat. Chem. — 2007. — Vol. 18 (4). — P. 341-346.*
22. *Zhuravel' I.O., Kovalenko S.M., Ivashchenko A.V. et al. // Synthetic Commun. — 2005. — Vol. 35. — P. 1641-1647.*
23. *Zhuravel' I.O., Kovalenko S.M., Ivashchenko A.V. et al. // J. Heterocyclic Chem. — 2004. — Vol. 41. — P. 517-524.*

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