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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW DERIVATIVES OF ISOINDOLINE-1,3-DIONES AS NON-STEROIDAL ANALGESICS

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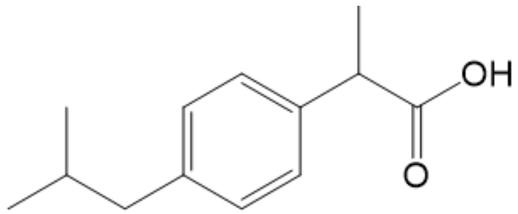
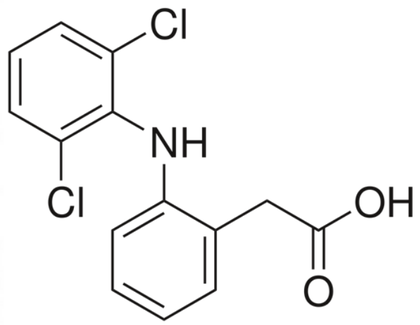
Introduction

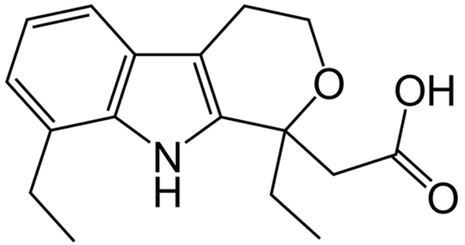
Today, there are many pain relievers available, but the search continues for more effective and less toxic organic molecules of non-steroidal structure



Ibuprofen



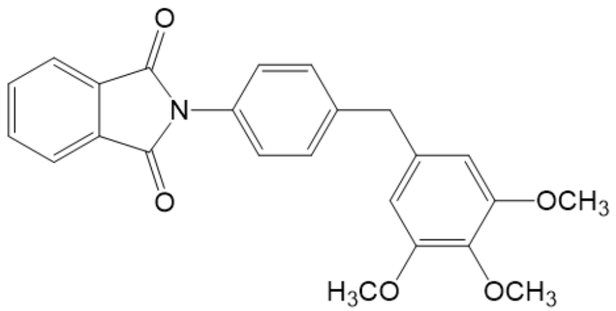
Diclofenac



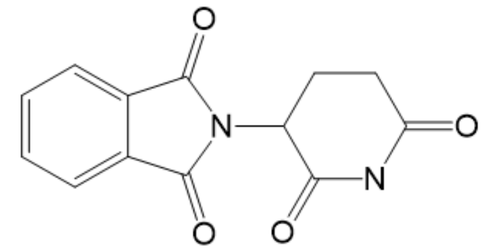
Etodolac

Introduction

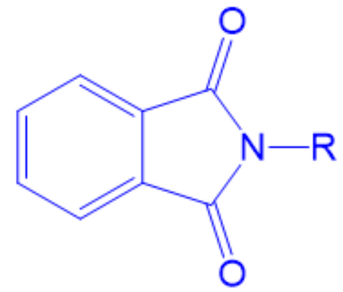
As a result of the literature review, it was decided to synthesize a molecule containing a substituted *N*-phthalimide fragment in its structure, which is present in the molecule of drugs such as thalidomide, lenalidomide, amphotalide and talmethoprim

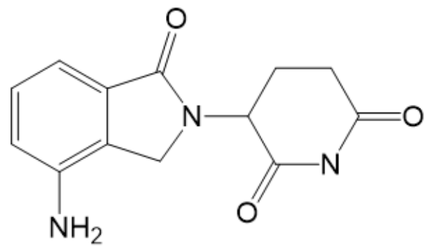


talmethoprim

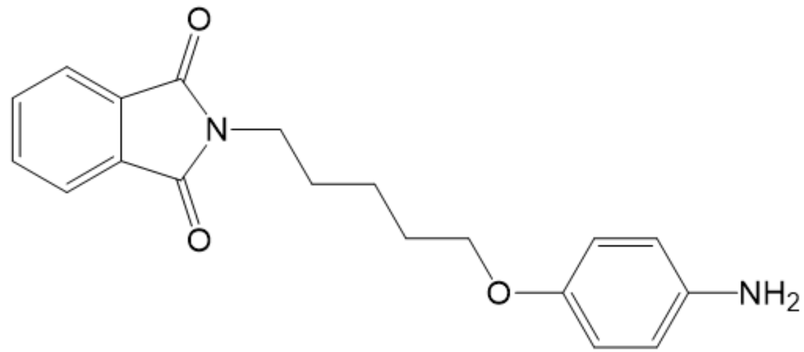


thalidomide





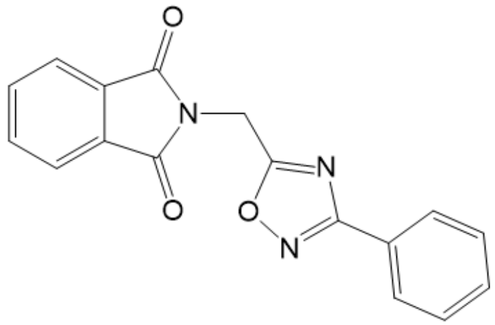
lenalidomide



amphotalide

Introduction

Known *N*-substituted derivatives of phthalimide, which have analgesic [1,2], hypolipidemic [3], anti-inflammatory [4], anticonvulsant [5] activities.



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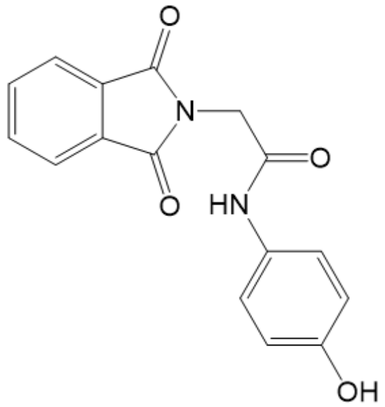

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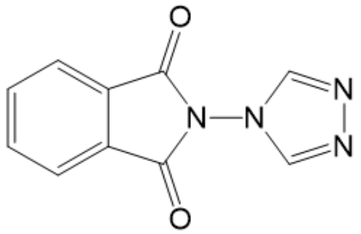
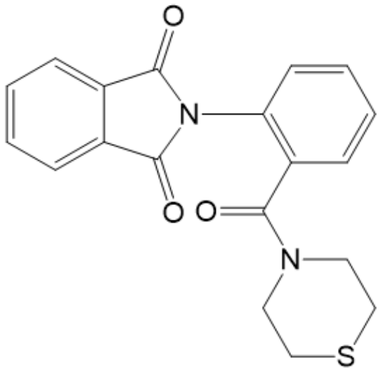
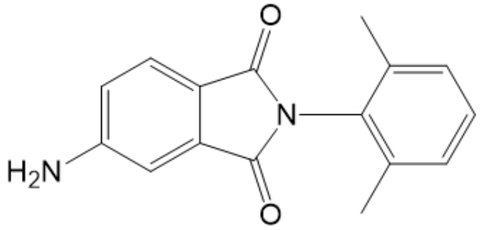


[3]



[4]

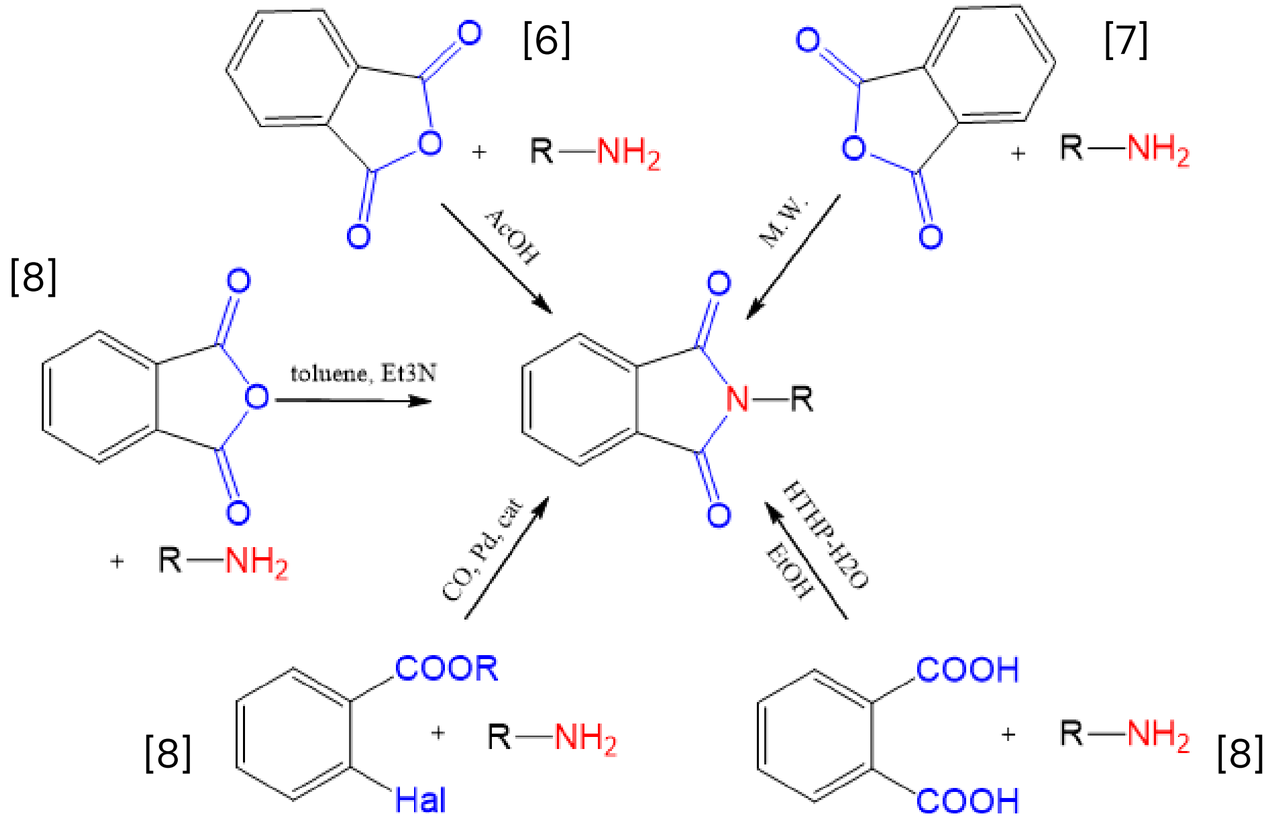


[5]

1.Antunes R.,J. Mol. Struct. 2003; 660(1-3): 1-13. DOI:10.1016/S0022-2860(03)00418-6
2.Reddy Y.D., Indian J. Chemistry. 2013; 52B: 691-693. ISSN: 0376-4699
3.Sena V.L., Farm. 2003; 58(12): 1283-1288. DOI:10.1016/S0014-827X(03)00185-X
4.Machado A. L, 2005; 15(4): 1169–1172. DOI: 10.1016/j.bmcl.2004.12.012
5. Bailleux V., Epilepsia. 1995; 36(6): 559-565. DOI:10.1111/j.1528-1157.1995.tb02567.x

Introduction

There are several approaches to the preparation of *N*-substituted phthalimide derivatives



6.Vamecq J, Journal of Medicinal Chemistry. 2000; 43(7): 1311–1319. DOI: 10.1021/jm990068t

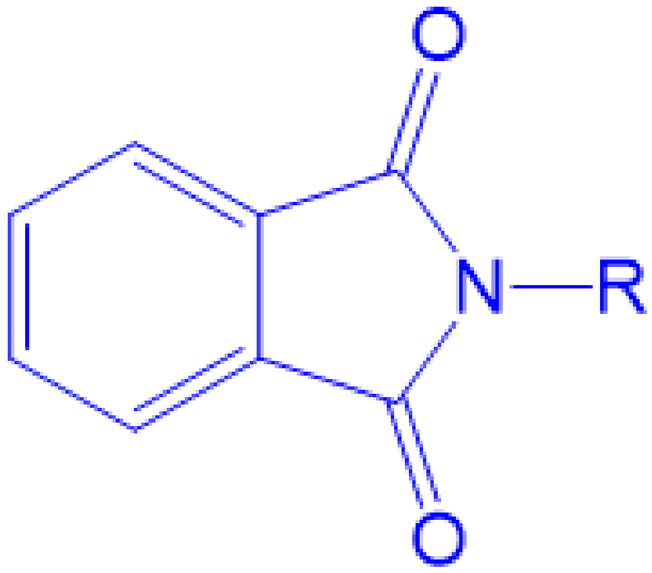
7. Omran Fhid, Der Pharma Chemica, 2014, 6(2):234-238. ISSN 0975-413X

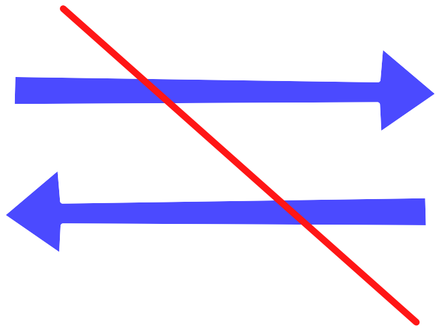
8. Sharma U., Med Chem. 2010; 10(8): 678-704. DOI:10.2174/138955710791572442

Purpose

Development of a simple method for the synthesis of new analgesics containing in their structure an *N*-substituted phthalimide fragment

Particular attention was paid to the absence of tautomerism and chirality of the target molecule





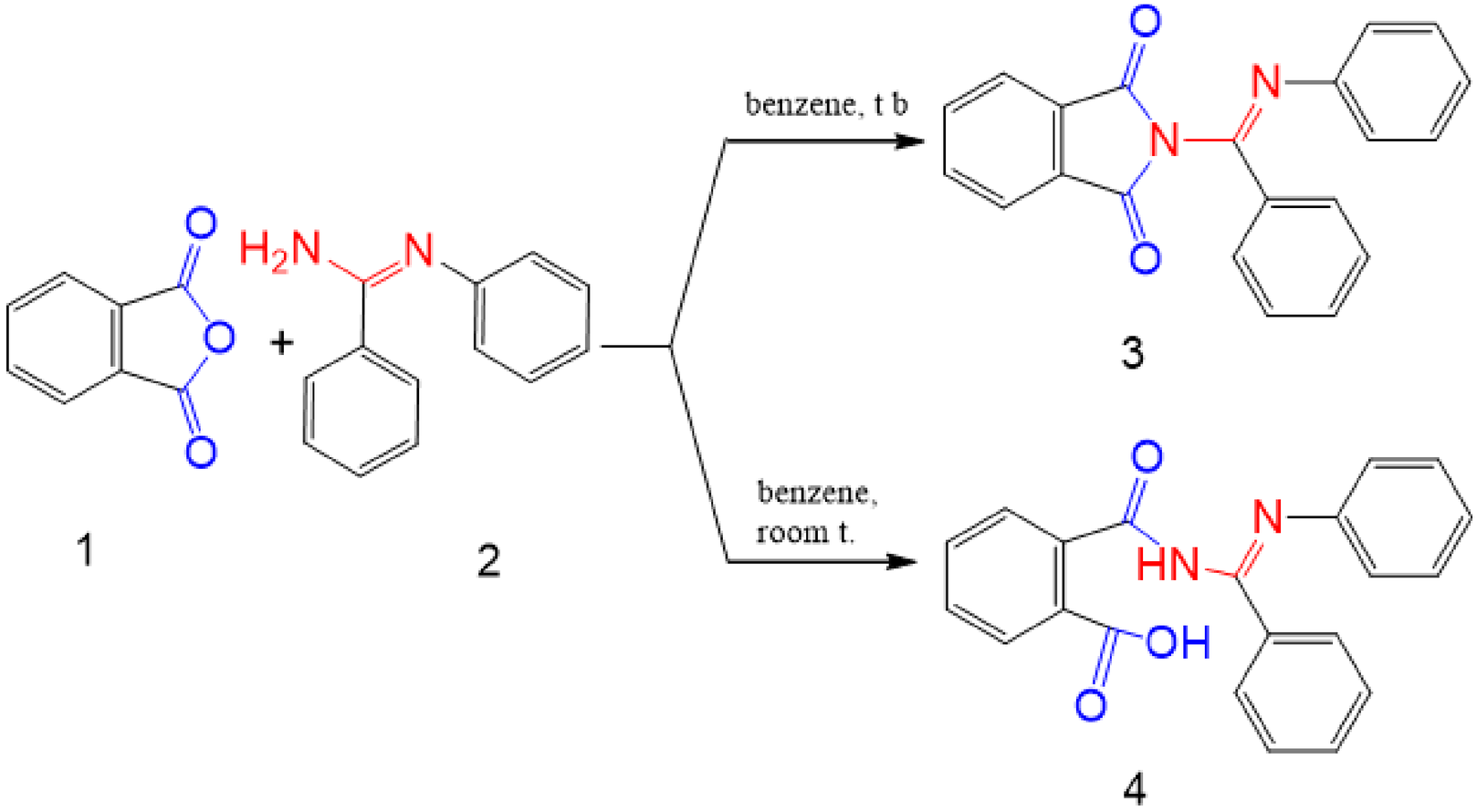
tautomer

or

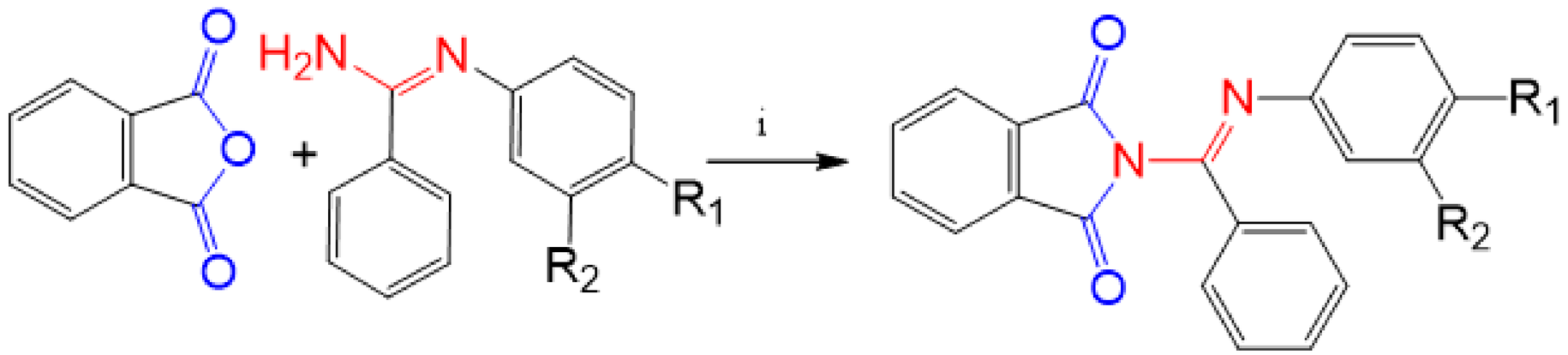
enantiomer

Results and discussion

The starting reagents were phthalic anhydride **1** and *N*-phenylbenzenecarboximidamide **2**. The target product (substituted *N*-phthalimide) could be obtained only by refluxing in benzene. Intermediate **4** was obtained without heating



Results and discussion



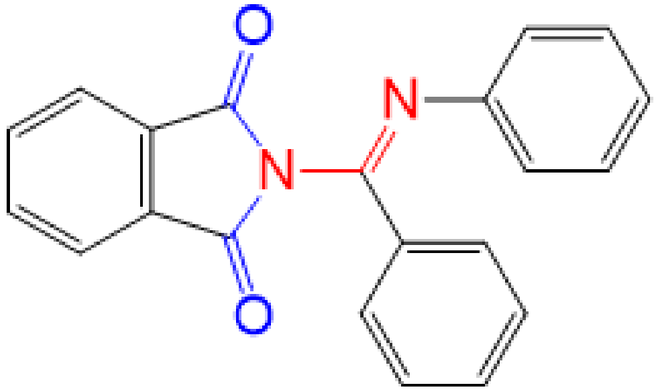
1 **2a–e** **3a–e**

Compounds number	R_1	R_2	Yield (%)
3a	H	H	84
3b	OMe	H	75
3c	Me	H	94
3d	Br	H	78
3e	H	Cl	78

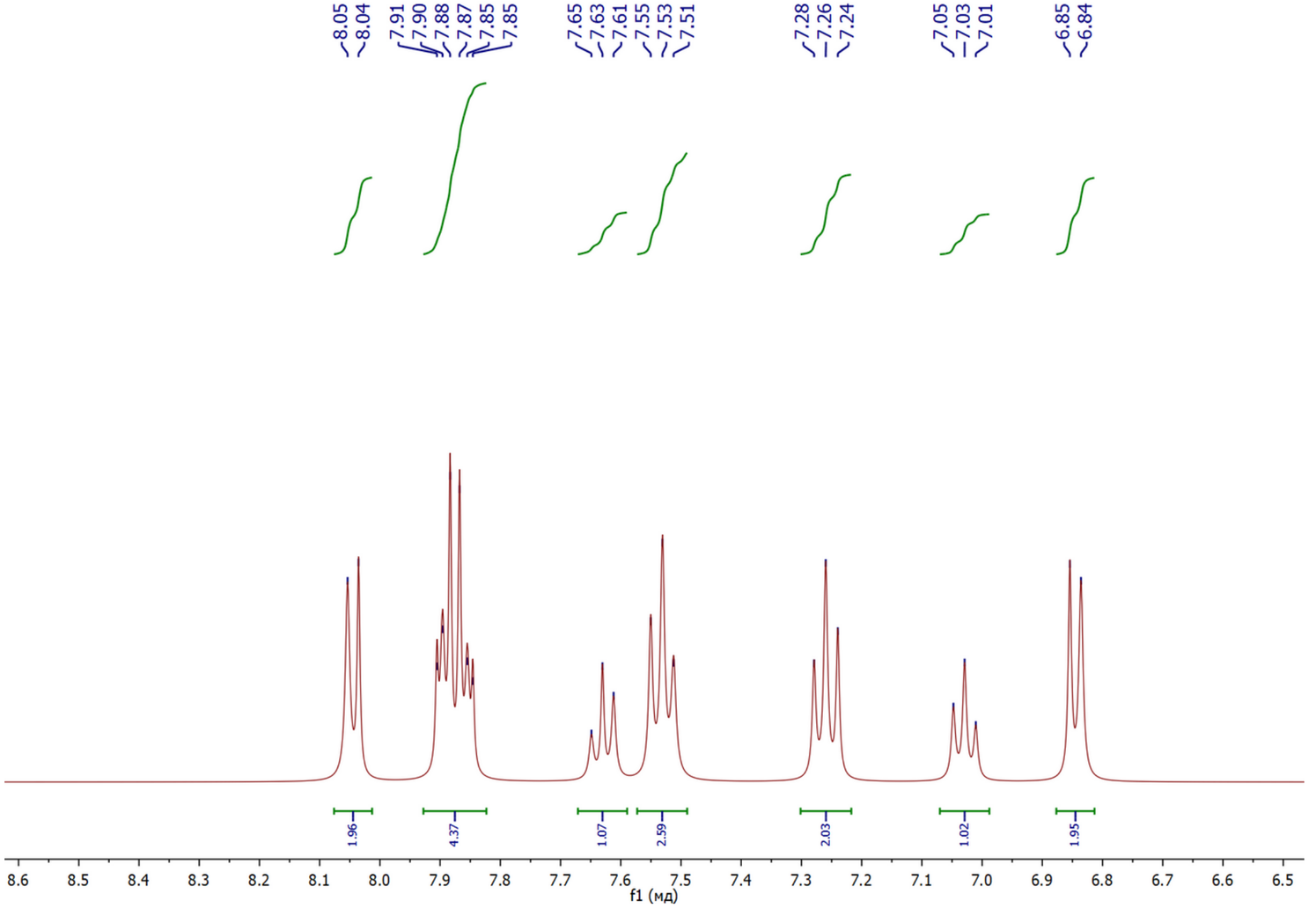
Conditions: i, benzene, Δ, 4–7 hours.

Results and discussion

Typical 1H NMR spectrum for compounds **3a-e** by the example of 1H NMR spectrum for **3a**. The spectrum was recorded in DMSO-d6 (400 MHz) relatively tetramethylsilane as internal standard

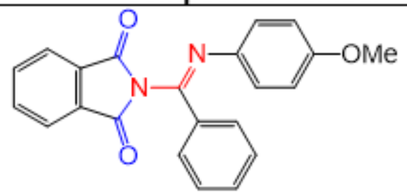
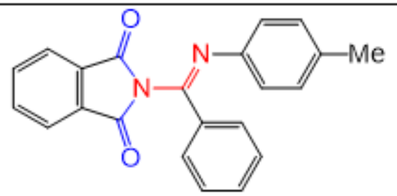


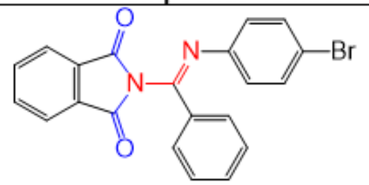
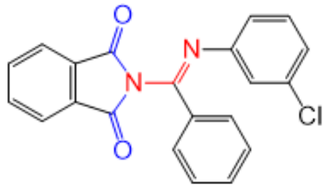
1H NMR (400 MHz, DMSO-d6)
δ 6.85 (d, J = 7.4 Hz, 2H),
7.03 (t, J = 7.4 Hz, 1H),
7.26 (t, J = 7.9 Hz, 2H),
7.53 (t, J = 7.6 Hz, 3H),
7.63 (t, J = 7.4 Hz, 1H),
7.93 – 7.82 (m, 4H),
8.04 (d, J = 7.3 Hz, 2H).



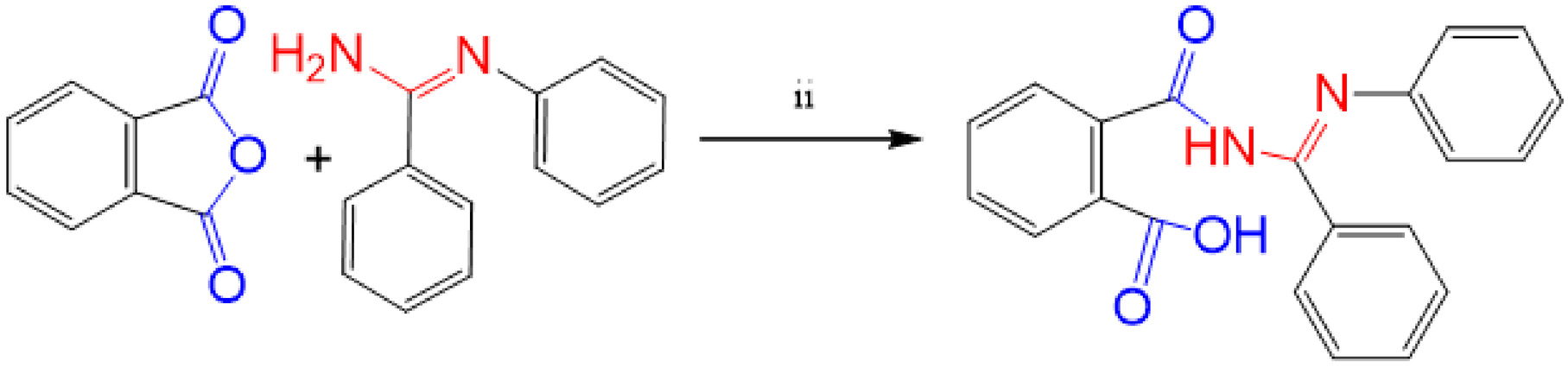
Results and discussion

Spectral characteristics of compounds **3b-e** (DMSO-d6, 400 MHz) relatively tetramethylsilane as internal standard

Compounds number	δ, ppm
 **3b**	3.64 (s, 3H), 6.80 (m, 4H), 7.51 (t, 2H, J=7.6 Hz), 7.61 (t, 1H, J=7.4 Hz), 7.91 (m, 4H), 7.98 (d, 2H, J=7.4 Hz)
 **3c**	2.16 (s, 3H), 6.73 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 7.52 (t, J = 7.6 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.89 (q, J = 4.4 Hz, 4H),8.00 (d, J = 7.4 Hz, 2H)

Compounds number	δ, ppm
 **3d**	6.80 (d, 2H, J=8.6 Hz), 7.46 (d, 2H, J=8.6 Hz), 7.53 (t, 2H, J=7.7 Hz), 7.64 (t, 1H, J=7.4 Hz), 7.90 (m, 4H), 8.03 (d, 2H, J=7.3 Hz)
 **3e**	6.76 (d, 1H, J=7.9 Hz), 6.90 (s, 1H), 7.10 (d, 1H, J=8.0 Hz), 7.27 (t, 1H, J=8.0 Hz), 7.54 (t, 2H, J=7.7 Hz), 7.65 (t, 1H, J=7.3 Hz), 7.90 (m, 4H), 8.04 (d, 2H, J=7.6 Hz)

Results and discussion



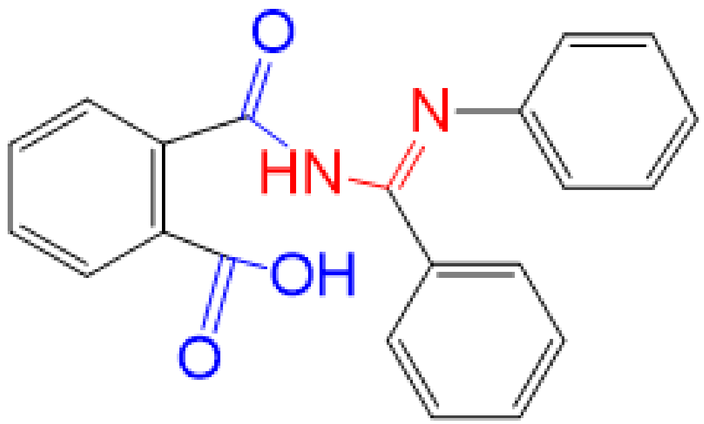
1 **2a** **4**

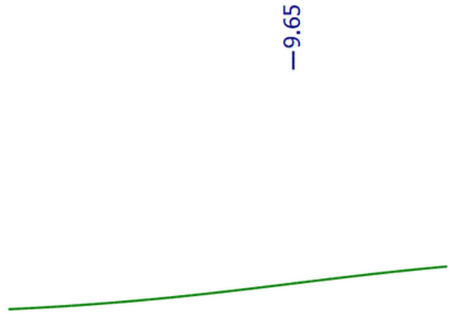
yield 97%

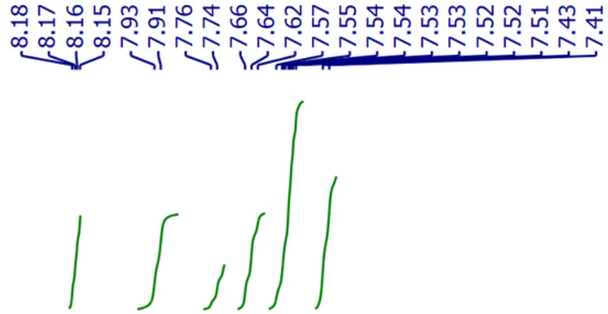
Conditions: ii, benzene, 25 °C, 4 hours

Results and discussion

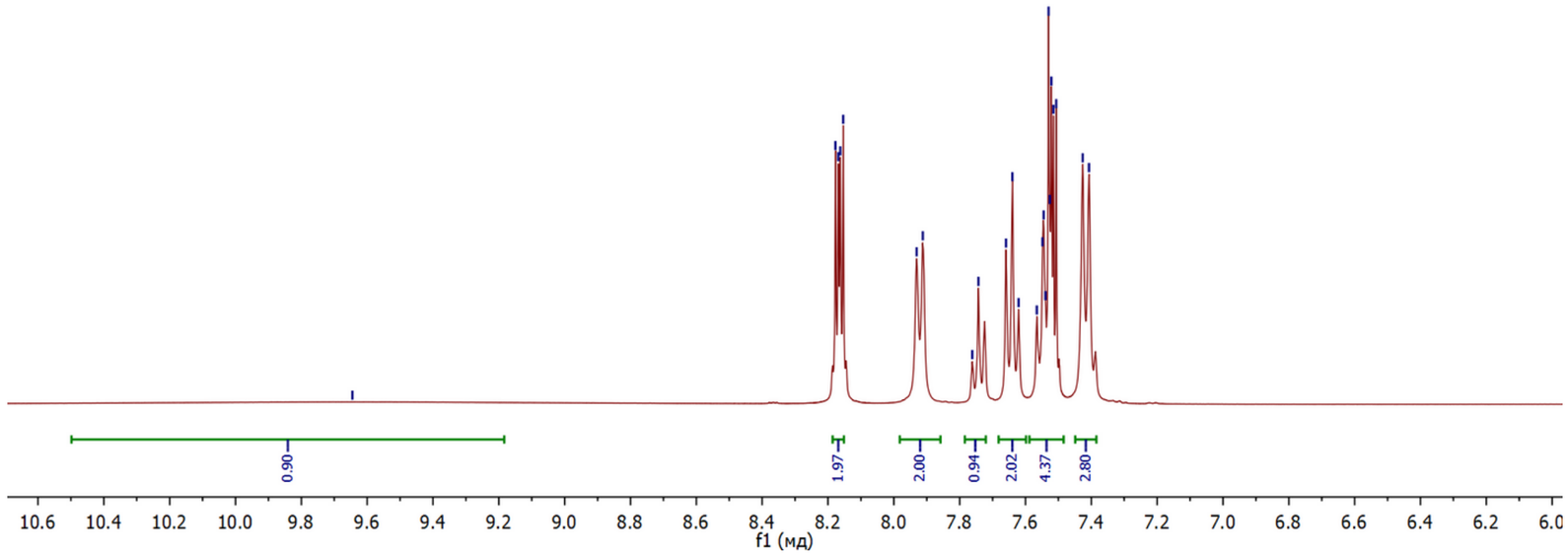
1H NMR spectrum for compounds **4.** The spectrum was recorded in DMSO-d6 (400 MHz) relatively tetramethylsilane as internal standard





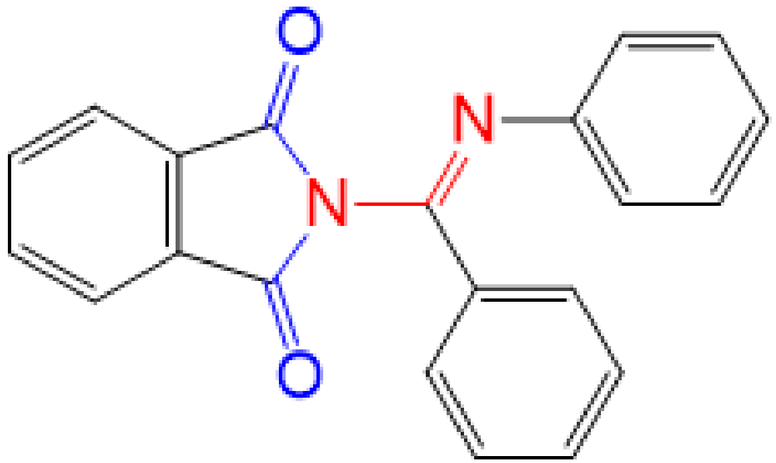


1H NMR (400 MHz, DMSO-d6)
δ 7.42 (d, J = 7.7 Hz, 3H),
7.56 – 7.48 (m, 4H),
7.64 (t, J = 7.7 Hz, 2H),
7.74 (t, J = 7.5 Hz, 1H),
7.92 (d, J = 7.7 Hz, 2H),
8.17 (dd, J = 6.0, 3.5 Hz, 2H),



Results and discussion

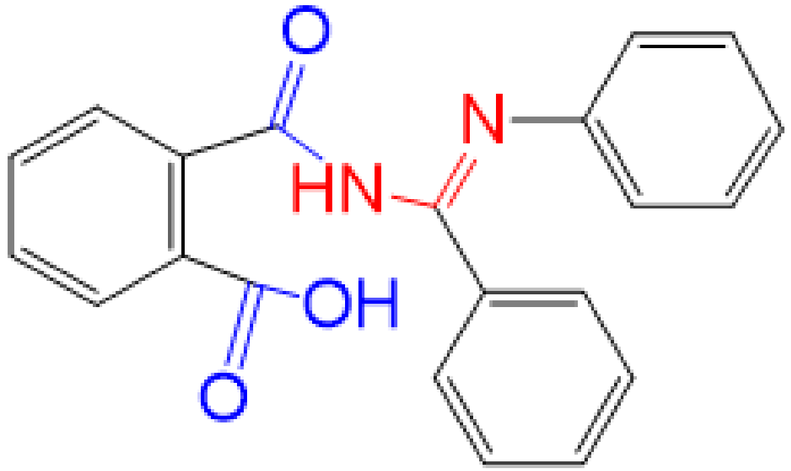
According to the results of an acute toxicity study *in vivo* in laboratory mice, it was found that compounds **3a** and **4** are practically non-toxic when administered intraperitoneally. Compound **4** was found to be less toxic in comparison with **3a**, which correlates with the *in siliko* data obtained using the online program GUSAR



3a

LD50 (in vivo)=1270,0 mg/kg

LD50 (in silico)=722,6 mg/kg



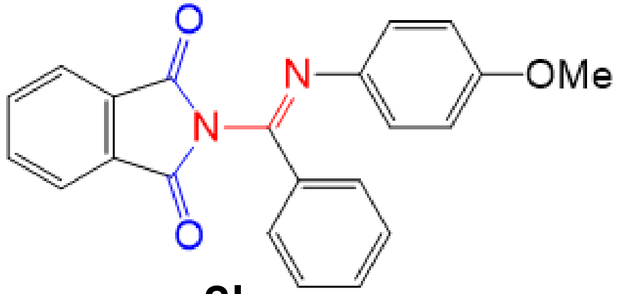
4

LD50 (in vivo)=1440,0 mg/kg

LD50 (in silico)=861,5 mg/kg

Results and discussion

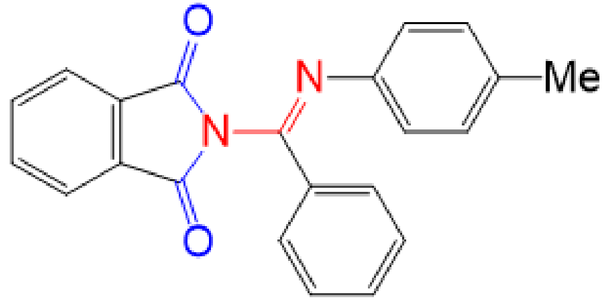
According to the results of an acute toxicity study *in vivo* in laboratory mice, it was found that compounds **3b-e** are practically non-toxic when administered intraperitoneally. Experimental data are comparable to results the *in siliko* data obtained using the online program GUSAR



3b

LD50 (in vivo)=1020,0 mg/kg

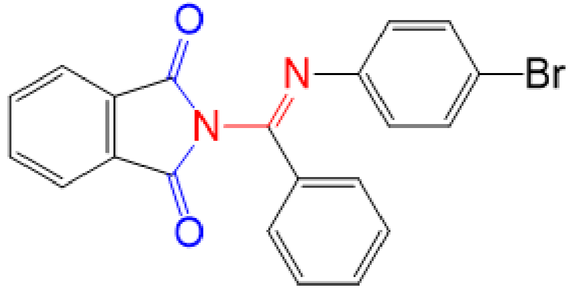
LD50 (in silico)=572,4 mg/kg



3c

LD50 (in vivo)=930,0 mg/kg

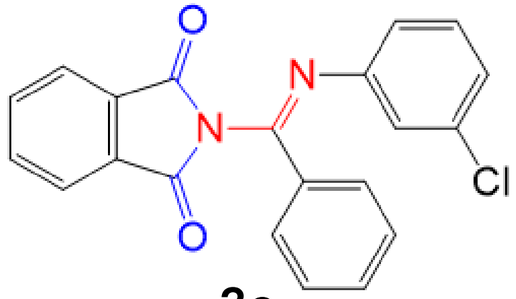
LD50 (in silico)=407,6 mg/kg



3d

LD50 (in vivo)=1160,0 mg/kg

LD50 (in silico)=658,7 mg/kg



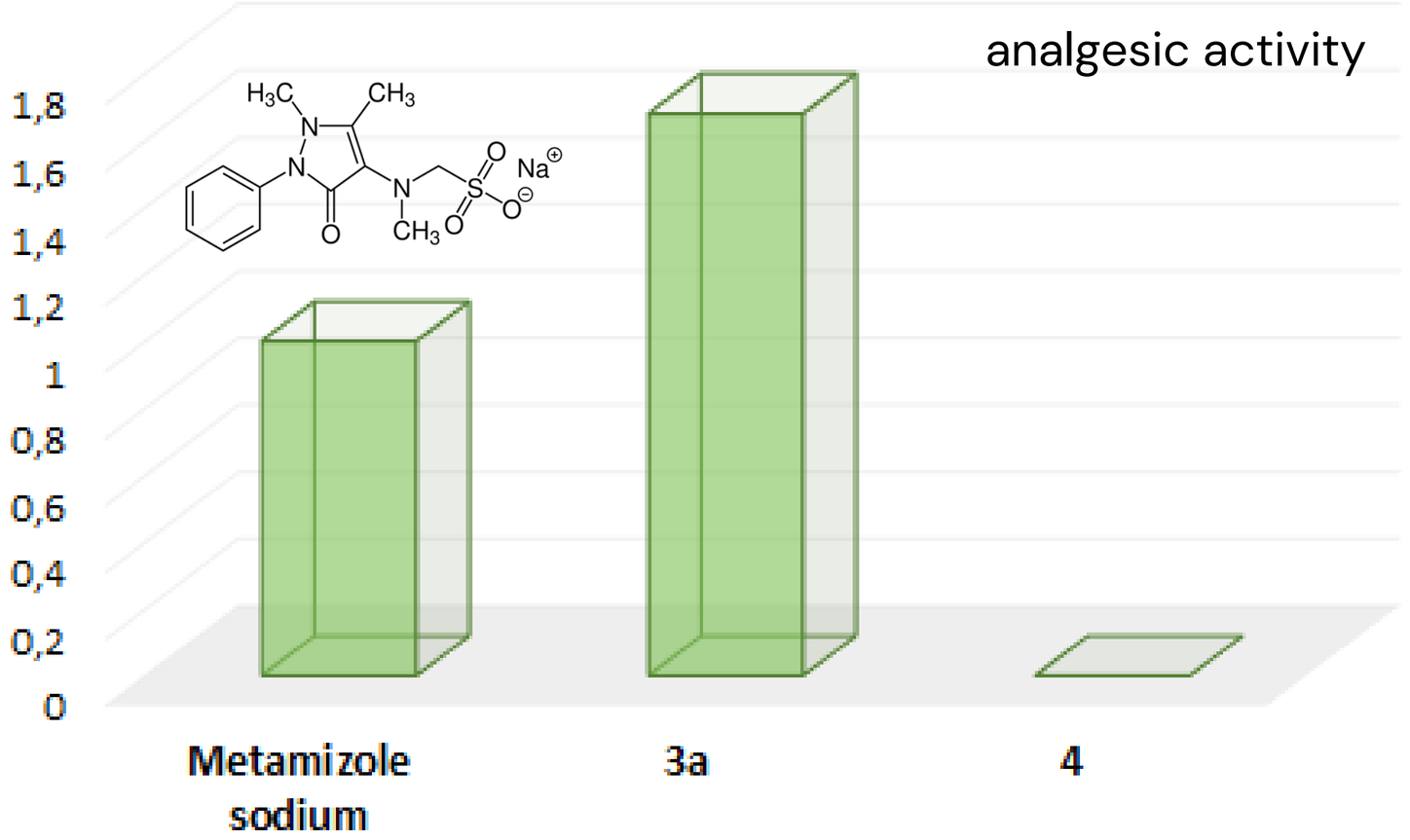
3e

LD50 (in vivo)=1270,0 mg/kg

LD50 (in silico)=724,2 mg/kg

Results and discussion

The study of analgesic activity in vivo on laboratory mice showed that compound **3a** exhibits pronounced analgesic activity, which is 1.6 times higher than the activity of the reference drug (metamizole sodium). In turn, compound **4** has no analgesic activity. The obtained data correlate with the results of *in silico* analysis obtained using the Pass-online program



Conclusion

- A simple method has been developed for the synthesis of five new substituted isoindoline-1,3-diones **3a-e**, consisting in the interaction of *N*-arylbenzenecarboxymidamides **2a-e** with phthalic anhydride **1** in a benzene medi-um during boiling.
- It was found that carrying out the reaction without heating leads to the formation of 2-((phenyl(phenylimino)methyl)carbamoyl)benzoic acid **4**.
- The structure of all isolated substances was proved using 1H and 13C NMR spectroscopy.
- Acute toxicity study *in vivo* in laboratory mice showed low toxicity of all compounds, which is comparable to the results *in silico* (GUSAR online software package). Using the PASS online software package, it was predicted that isoindoline-1,3-diones **3a-e** have analgesic activity with a probability of 40-80 %, while for 2-((phenyl(phenylimino)methyl)carbamoyl)benzoic acid **4**, this activity was not predicted.
- For the most bioactive compound - 2-(phenyl(phenylimino)methyl)isoindoline-1,3-dione **3a** and for 2-((phenyl(phenylimino)methyl)carbamoyl)benzoic acid **4**, the analgesic activity *in vivo* was studied in laboratory mice. It was found that compound **3a** has a high analgesic activity, 1.6 times higher than the activity of the reference drug metamizole sodium, while compound **4** does not. The obtained experimental data are fully consistent with computer forecasts

Conclusion

Thank you for your attention!

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