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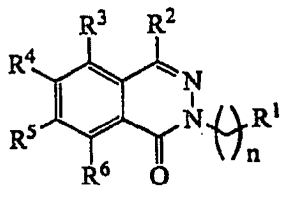
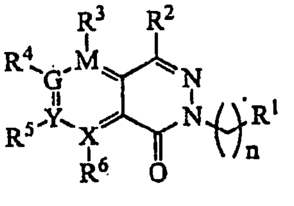


(I)



(II)

(57) **Abstract:** Derivatives of phthalazinone and pyridopyridazonone of formula (I) and (II) having practical application as analgesic and antiinflammatory medicaments, in which n is an integer from 1 to 8 for straight or branched alkyl or alkenyl R1 is -NR7R8-COZ M is nitrogen (N) and G = Y = X = carbon (C); R3 = none; G is nitrogen (N) and M = Y = X = carbon (C); R4 = none; Y is nitrogen (N) and M = G = X = carbon (C); R5 = none; X is nitrogen (N) and M = G = Y = carbon (C); R6 = none and the salts of this compounds.

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BENZO- AND PYRIDOPYRIDAZINONES WITH ANALGESIC AND ANTIINFLAMMATORY ACTIVITY

The invention relates to novel derivatives of benzo- and pyridopyridazinones likewise to pharmaceuticals containing benzo- and pyridopyridazinones. The new compounds stimulates central nervous system exhibiting analgesic and anti-inflammatory activity.

It has been found that compounds with 2*H*-pyridazin-3-ones building block especially condensed with aromatic (phthalazinones) or heteroaromatic ring (pyridopyridazinones) exhibit a number of different biological activities e.g. inhibit uratosis, (T. Hamada, Y. Tsukamoto, H. Shimamura, K. Yoshihara, A. Yamaguchi, M. Ohki Chem. Pharm. Bull. 1981, 29, 3433), as well as platelet aggregation (A. Sugimoto, H. Tanaka, Y. Eguchi, S. Ito, Y. Takashima, M. Ishikawa, J. Med. Chem. 1984, 27, 1300). They also have cardiotonic properties (D. W. Robertson, J. H. Krushinski, E. E. Beedle, V. Wyss, G. D. Pollosk, H. Wilson, R. F. Kanffman, J. S. Hades J. Med. Chem. 1986, 29, 1832) as well as anti-allergic and anti-asthmatic effect (A. Kleemann, J. Engel. B. Kutscher, D. Reichert, Pharmaceutical Substances, third edition, Thieme, Stuttgard, New York, 1999).

In recent years, a lot of attention has been paid to the pyridazinone derivatives that exhibit analgesic and anti-inflammatory activity. (M. P. Giovannoni, C. Vergelli, C. Ghelardini, N. Galeotti, A. Bartolini, V. Dal Piaz, J. Med. Chem. 2003, 46, 1055; V. Dal Piaz, S. Pieretti, C. Vergelli, M. C. Castellana, M. P. Giovannoni, J. Heterocyclic Chem. 2002, 39, 523; M. Takaya, M. Sato, K. Terashima, H. Tanizawa, J. Med. Chem. 1979, 22, 53; V. Dal Piaz, C. Vergelli, M. P. Giovannoni, M. A. Scheiideler, G. Petrone, P. Zaratin Il Farmaco 2003, 58, 1063; S. Pieretti, V. Dal Piaz, R. Matucci, M. P. Giovannoni, A. Galli Life Sciences 1999, 65, 1381; V. Dal Piaz, M. P. Giovannoni, G. Ciciani, D. Barlocco, G. Giardina, G. Petrone, G. D Clarke Eur. J. Med. Chem. 1996, 31, 65; M. Gokce, D. Dogruer, M. F. Sahin Il Farmaco 2001, 56, 233; F. Rohet, C. Rabat, P. Coudert, E. Albuisson, J. Couquelet Chem. Pharm. Bull. 1996, 44, 980; S. Bdavari, Merck and Co. “The Merck Index”, New York, 1989).

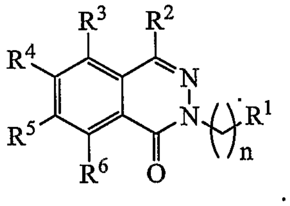
The application and synthesis of this compounds has been widely discussed in a number of publications and patent applications. One of fundamental properties of pyridazinone derivatives is inhibition of phoshodiesterase PDE, the enzyme that acts in the transformation of cyclic nucleotides, which affect hormone functioning, cellular transport and vision.

Recently in our country novel phthalazinones, which could be used as medicaments for treatment of respiratory system diseases, have been protected by the patent specification no. 189418. In this compounds 2*H*-pyridazin-3-one building block is condensed with cyclic non-aromatic system.

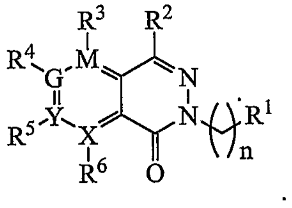
Another patent applications no. 355525, 360909, 363312 and 372926 relate to the compounds and their derivatives having 2H-pyridazin-3-one system condensed with cyclic non-aromatic system with or without substituents that determine their specific properties.

It has been found unexpectedly that derivatives of benzo- and pyridopyridazinones of formulas **I** and **II** have particularly advantageous pharmacological properties, especially analgesic and anti-inflammatory activity as well as low toxicity.

The invention relates to novel phthalazinone and pyridopyridazinone derivatives of formulas **I** and **II** and their pharmaceutically tolerable salts.



I



II

in which:

n is an integer from 1 to 8 for straight or branched alkyl or alkenyl

R1 is –**NR7R8**, where **R7**, **R8** are

- hydrogen (H)
- straight or branched alkyl or alkenyl (C1 – C6)
- cycloalkyl (C5 – C7)
- aryl or heteroaryl (e.g. phenyl, pyridyl)
- -C(O)**R9**, where **R9** is
    - straight or branched alkyl (C1 – C6)
    - phenyl
    - benzyl
    - -**OR10**, where **R10** is straight or branched alkyl or alkenyl (C1 – C6)
- -SO$_2$**R11**, where **R11** is
    - alkyl straight or branched (C1 – C4)
    - aryl [phenyl, monosubstitued (2 or 3 or 4 position) or disubstituted (2,3 or 3,4 positions) benzene ring (straight

or branched alkyl (C1 – C6), **R10**O-, where **R10** is straight or branched alkyl (C1-C4), halogen (F, Cl, Br, I);

-CO**Z**, where **Z** is

- hydroxyl (OH)
- -OM, where M is Li^+, Na^+, K^+ or Ca^{2+},
- -N**R13R14**, where **R13**, **R14** is
  - hydrogen (H)
  - straight or branched alkyl or alkenyl (C1-C6)
  - cycloalkyl (C5-C7)
  - aryl (e.g. phenyl, monosubstituted (2 or 3 or 4 position) benzene ring: straight or branched alkyl (C1-C4), **R10**O- (straight or branched alkyl or alkenyl (C1-C6), halogen (F, Cl, Br, I)
- piperidyn-1-yl
- morpholin-4-yl
- 4-(**R12**)piperazin-1-yl, where **R12** is straight or branched alkyl (C1-C6), aryl (substituted in 2 or/and 3 or/and 4 or/and 5 or/and 6position, or halogen (F, Cl, Br, I) poli-substituted benzene ring)

R2 is:

- hydrogen (H)
- straight or branched alkyl or alkenyl (C1-C6)
- benzyl
- phenyl
- benzene ring mono-substituted in 2 or 3 or 4 position [alkyl (C1-C6), **R10**O-, where **R10** is straight or branched alkyl (C1-C6)), halogen (F, Cl, Br, I), hydroxyl (OH)]
- pyridyl (pyrid-2-yl, pyrid-3-yl, pyrid-4-yl)

R3, **R4**

R5, **R6** are

- hydrogen (H)
- straight or branched alkyl or alkenyl (C1-C6)
- cycloalkyl (C5-C7)
- **R10**O- (**R10** is straight or branched alkyl (C1-C6)
- halogen (F, Cl, Br, I)

- benzyl
- hydroxyl (OH)

M is nitrogen (N)
and **G** = **Y** = **X** = carbon (C); **R3** = none;
G is nitrogen (N)
and **M** = **Y** = **X** = carbon (C); **R4** = none;
Y is nitrogen (N)
and **M** = **G** = **X** = carbon (C) ; **R5** = none;
X is nitrogen (N)
and **M** = **G** = **Y** = carbon (C); **R6** = none

The compounds according to the invention containing acidic or basic functional groups can be transformed into water-soluble salts, which are physiologically more useful than starting derivatives. According to the invention lithium, sodium, potassium, calcium magnesium, aluminium and etc. salts of mentioned derivatives are the examples of pharmaceutically tolerable compounds, but not exclusively. The conversion of compounds **I** and **II** into related salts is carried out with one or several equivalents of base or using ion-exchange resins.

Non-toxic addition salts of the compounds according to the invention with inorganic and organic bases e.g. ammonium salts, quaternary ammonium salts and other salts of base containing nitrogen are also acceptable.

Basic group or groups present in the compounds according to the invention can react with non-toxic inorganic acids such as hydrochloric acid, nitric acid, orthophosphoric acid, sulphuric acid, hydrobromic acid, phosphorous acid as well as with non-toxic organic acids such as mono- and dicarboxylic aliphatic acids, phenyl substituted alkanocarboxylic acids, alkanocarboxylic hydroxyacids, alkanodicarboxylic acids, aromatic acids, aliphatic and aromatic sulphonic acids, forming salts, but not exclusively, such as bicarbonates, bisulphates, bitartrates, borates, bromides, iodides, carbonates, chlorides, fluorides, nitrates, phosphates, sulphates, acetates, benzenesulphonates, benzoates, citrates, fumarates, gluconates, glutamates, glucoarsanilates, hexylresorcinates, hydroksynaphthoates, isothiocyanates, lactates, laurynates, malates, clavulanates, maleates, mandelates, mesylates, methylbromides, methylnitrates, methylsulphates, mucates, napsylates, oleates, oxalates, palmitates, pantothenates, polygalactouronates, salicylates, stearates, succinates, tannin salts, tosylates, valeriates. The acids in equimolar quantitative ratio or one differing therefrom are employed in the conversion of compounds of formula **I** and **II** into corresponding salts.

Compounds in the form of free bases or acids differ from corresponding salts in some physical properties e.g. solubility in polar solvents. However for the purpose of the invention the compounds are the equivalents of their salts.

According to the invention some of the compounds can contain one or more chiral centres, so they can exist in optically active form. If the compounds contain alkenyl or alkynyl groups isomers E/Z (*cis*/*trans*) are possible. The invention relates to isomers of absolute configuration R and S, including racemic mixtures, as well as isomers *cis* and *trans* and their mixtures. Additional asymmetric carbon atoms in substituents e.g. alkyl are possible. All this isomers and their mixtures are granted protection.

The invention relates also to pharmaceuticals containing as active component novel phthalazinone and pyridopyridazinone derivatives as well as pharmaceuticals with additives and/or media or solvents that are pharmaceutically tolerable according to the invention.

The invention relates also to the application of the newly synthesised benzo- and pyridopyridazinones, described in the invention as analgesic and anti-inflammatory drugs.

The compounds no. **3**, **4**, **5**, **6**, **8**, **9** and **10** according to the invention are profitable and they were biologically tested:

(**3**) Dimethyl-[2-(1-oxo-4-phenyl-1*H*-phthalazin-2-yl)-ethyl]-ammonium chloride
(**4**) Dimethyl-[2-(1-oxo-1*H*-pyrido[3, 4-*d*]pyridazin-2-yl)-ethyl]-ammonium chloride
(**5**) 4,*N*-Dimethyl-*N*-[2-(1-oxo-1*H*-phthalazin-2-yl)-ethyl]-benzenesulfonamide
(**6**) *N*-{2-[1-(2-methoxyphenyl)-4-oxo-4*H*-pyrido[3,4-*d*]pyridazin-3-yl]ethyl} -4,*N*-dimethylbenzenesulphonamide
(**8**) *N*-Methyl-[2-(1-oxo-1*H*-phthalazin-2-yl)ethyl]-ammonium chloride
(**9**) 2-[2-(1-Oxo-1*H*-phthalazin-2-yl)-ethyl]-isoindole-1,3-dione
(**10**) Methyl-[2-(1-oxo-4-phenyl-1*H*-phthalazin-2-yl)-ethyl]-carbamic acid *tert*-butyl ester

Compounds of formula **I** or **II** are the active components of pharmaceutic composition, while typical solids like lactose, calcium sulphate, saccharose, talc, gelatine, agar, pectin, magnesium stearate, cellulose derivatives can be used as useful carriers. Water, syrup, fatty acids and olive oil can serve as solvents.

Pharmaceutic compositions comprise the compounds according to the invention are obtained using typical techniques described in Remington's Pharmaceutical Sciences.

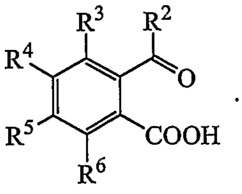
Compounds described in the invention can be synthesised in the following ways:

a) reacting corresponding phthalazinone or pyridopyridazinone with selected alkylating agents of formula **Z**-(CH_2)$_n$-**R1**, in which **R1** has the abovementioned meaning and **Z** stands for a leaving group to give further compounds of formula **I** or **II**, in which **R1**, **R2**, **R3**, **R4**, **R5**, **R6** have the abovementioned meanings. The reactions are carried out in the manner known by a person skilled in the art. Examples of suitable leaving groups which may be mentioned are halogen atoms, especially chlorine or bromine, as well as hydroxyl group activated by esterification (for example with *p*-toluenesulphonic acid). In the first step hydrogen atom of the NH- group present in starting phthalazinone or pyridopyridazinone is removed by a base such as potassium carbonate, sodium hydroxide, sodium hydride, sodium methoxide, sodium ethoxide in a suitable solvents such as dimethylsulphoxide, dimethylformamide, tetrahydrofuran.

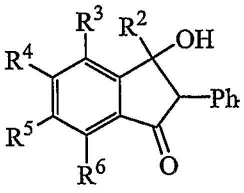
b) reacting corresponding phthalazinone or pyridopyridazinone with selected amino alcohol derivatives of formula HO-(CH_2)$_n$-**NR7R8**, in which R7, R8 have the abovementioned meaning, in the presence of reactive phosphanes and azodicarboxylic acid derivatives to give compounds **I** or **II**, in which **R2**, **R3**, **R4**, **R5**, **R6**, **R7**, **R8** have the abovementioned meanings. Reactions are carried out in the range of temperatures between –30°C and 25°C and in solvents such as tetrahydrofuran or dimethylformamide.

Starting 2*H*-phthalazin-1-ones and pyridopyridazinones, necessary for the synthesis of compounds **I** or **II** are obtained according to one of the known methods (J. Z. Brzeziński, J. Epsztajn, A. D. Bakalarz, A. Łajszczak, Z. Malinowski *Synth. Commun.* 1999, 29, 457; J. Epsztajn, Z. Malinowski, J. Z. Brzeziński, M. Karzatka Synthesis, 2001, 14, 2085; J. Epsztajn, A. Jóźwiak, A. K. Szcześniak Synth. Commun. 1994, 24, 1789; J. Epsztajn, Z. Malinowski, P. Urbaniak, G. Andrijewski Synth. Commun. 2005, 35, 181).

In order to synthesise starting 2*H*-phthalazin-1-ones and pyridopyridazinones corresponding ketoacids, 3-hydroxyisoindolinones as well as azaisoindolinones react with hydrazine hydrate, which simultaneously can be used as solvent. It is possible, however, to use auxiliary solvents such as ethanol, propan-1-ol, acetic acid. The reaction times are preferably between 1 and 46 hours. The reaction is carried out at the boiling point of appropriate solvent.



III



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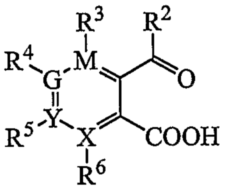
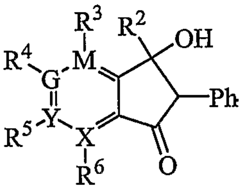


V



VI

If it is necessary, one or more functional groups present in compounds **I**, **II**, **III**, **IV**, **V** or **VI** may be transformed into another functional group, using known methods.

The conversions of compounds according to the invention are carried out analogous to known methods described in the literature, for example in the manner, which is described in the following examples. The substances (products and substrates) according to the invention are isolated and purified in manners known *per se*, e. g. subjecting to column chromatography on a suitable support material, recrystallizing from a suitable solvent as well as vacuum distillation. The salts of corresponding compounds are obtained by dissolving the free compound in a low molecular weight aliphatic alcohol, e.g. methanol, which contains the desired acid or base, or to which the desired acid or base is then added. Evaporating the solvent, precipitating with a non-solvent for the additional salt, reprecipitating or filtering, allow to isolate the salts. The salts obtained can be transformed by basification or by acidifying into the free compounds, in turn, can be converted into salts pharmacologically tolerable.

The following examples illustrate the invention in greater detail, without restricting it. Further compounds of formula **I** and **II**, of which the preparation is not described, can be prepared in an analogous way or in a way, which is known by a person skilled in the art using conventional preparation methods.

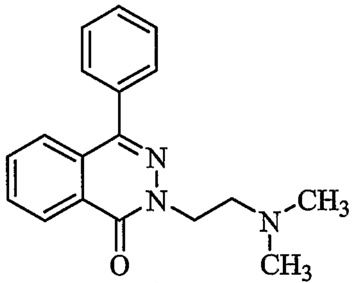
EXAMPLES

1. Synthesis of *N*-[2-(dimethylamino)ethyl]- derivatives of 2*H*-phtalazin-1-ones and pyridopyridazinones

To the solution of sodium methoxide (0,0148 mol of Na) in dry methanol (20 ml) was added 4-phenyl-2*H*-phthalazin-1-on (0,0070 mol). The mixture was stirred and refluxed for 30 minutes, then cooled to ambient temperature and (2-chloroethyl)-dimethylammonium chloride was added. Afterwards the reaction mixture was heated and refluxed for 6 hours. After cooling to room temperature, the inorganic material was collected by filtration and the filtrate was evaporated to dryness. The residue was triturated with hydrochloric acid (20 ml, c = 2 mol/dm^3). The filtrate was neutralised with aqueous solution of sodium hydroxide and extracted with dichloromethane (3x20ml). The combined extracts were dried over anhydrous $MgSO_4$ and vacuum concentrated till dryness. The residue was subjected to column chromatography (silica gel, eluent: MeOH – ethyl acetate = 1 : 1)

2-[2-(Dimethylamino)ethyl]-4-phenyl-2*H*-phthalazin-1-one (compound no. **1**)

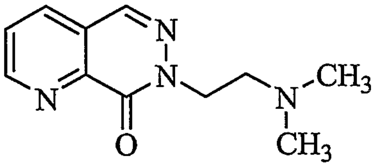
Yield 65%;
m.p.: 99-102°C;
FT-IR (KBr): 1653 (C=O);
^{1}H NMR ($CDCl_3$) δ: 8.49-8.54 (m, 1H, 8-ArH), 7.70-7.80 (m, 3H, ArH), 7.49-7.60 (m, 5H, ArH), 4.48 (t, 2H, CH_2, *J*=6.8), 2.84 (t, 2H, CH_2, *J*=6.8), 2.35 (s, 3H, Me);
^{13}C NMR ($CDCl_3$) δ: 159.1 (C=O), 147.0, 135.2, 132.7, 131.3, 129.4, 129.1, 128.6, 128.2, 127.2, 126.6, 57.1 (CH_2), 48.6 (CH_2), 45.4 (Me);
Elemental Analysis:
Calculated for $C_{18}H_{19}N_3O$ M = 293. 37 g/mol: C 73.70, H 6.53, N 14.32;
Found: C 73.52; H 6.55, N 14.29.



1

7-[2-(Dimethylamino)ethyl]-7*H*-pyrido[2,3-d]pyridazin-8-one (compound no. **2**)

Yield 65%;
m.p.: 77-79°C; R_F = 0,4 (eluent: AcOEt-MeOH=1:1);
FT-IR (KBr): cm^{-1} 1655;
^{1}H NMR ($CDCl_3$) δ: 9.13 (dd, 1H, PyH, *J* = 4.2, 1.6), 8.2 (s, 1H, PyH), 8.08 (dd, 1H, PyH, *J*=8.2, 1.6), 7.74 (dd, 1H, PyH, *J*=7.7, 4.9), 4.46 (t, 2H, CH_2, *J*=6.6), 2.85 (t, 2H, CH_2, *J*=6.6), 2.36 (s, 6H, Me);
^{13}C NMR ($CDCl_3$) δ: 158.3 (C=O), 153.7, 135.8, 133.9, 127.1, 125.5, 57.0 (CH_2), 49.0 (CH_2), 45.4 (Me);
Elemental Analysis:
Calculated for $C_{11}H_{14}N_4O$ = 218.26 g/mol C 60.53, H 6.47, N 25.67;
Found: C 60.51; H 6.67, N 25.42.



2

2. The conversion of *N*-[2-(dimethylamino)ethyl]- derivatives of 2*H*-phtalazin-1-ones and pyridopyridazinones into hydrochlorides

To the solution of compound **1** or **2** (0,0102 mol) in methanol (15 ml) stoichiometric amount of hydrochloric acid (2 mol/dm^3) was added. The mixture was held in ambient temperature for 12 hours. Then solvents were evaporated and the obtained hydrochloride was dried in desiccator.

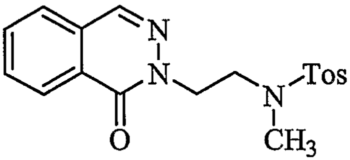
Dimethyl-[2-(1-oxo-4-phenyl-1*H*-phthalazin-2-yl)-ethyl]-ammonium chloride
(compound no. **3**)
m.p.: 246-249.5°C

Dimethyl-[2-(1-oxo-1*H*-pyrido[3, 4-*d*]pyridazin-2-yl)-ethyl]-ammonium chloride
(compound no. **4**)
m.p.: 240-245°C

3. Synthesis of *N*-tosyl-derivatives of *N*-[2-(methylamino)ethyl]benzo- and pyridopyridazinones

To the solution of sodium methoxide (0,0165 mol of Na) in dry methanol (70 ml) was added 2*H*-phthalazin-1-on (0,0153 mol). The mixture was stirred and refluxed for 30 minutes, then cooled to ambient temperature and bis-tosyl-derivative of 2-methylaminoethanol (0.0230 mol) was added. Afterwards the reaction mixture was heated and refluxed for 10 hours. After cooling to room temperature the product was filtrated and recrystalized. If the product was well soluble in reaction solvent, the solvent was first evaporated and to the residue water (20ml) was added. The aqueous layer was extracted with chloroform (3x20ml). The combined extracts were dried over anhydrous MgSO4 and vacuum concentrated till dryness. The residue was purified by column chromatography (silica gel).

4,N-Dimethyl-N-[2-(1-oxo-1*H*-phthalazin-2-yl)-ethyl]-benzenesulfonamide
(compound no **5**)

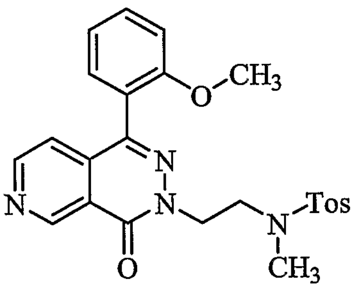


5

Yield 45%;
m.p.: 136-139°C;
FT-IR (KBr): 1651 (C=O), 1338, 1165 (=SO_2);
^{1}H NMR ($CDCl_3$) δ: 8.39 (d, 1H, 5-ArH, , *J*=7.1), 8.15 (s, 1H, 4-ArH), 7.66-7.86 (m, 3H, 6,7,8-ArH), 7.61 (d, 2H, TosH, *J*=8.2) 7.18 (d, 2H, TosH, *J*=8.0) 4.41 (t, 2H, CH_2, *J*=6.2),

3.51 (t, 2H, CH$_2$, *J*=6.3), 2.90 (s, 3H, N-Me), 2.34 (s, 3H, Tos-Me);
^{13}C NMR (CDCl$_3$) δ: 159.3 (C=O), 143.0, 137.8, 134.9, 133.7, 133.0, 131.5, 129.5, 129.4, 127.0, 126.5, 125.9, 48.4 (N(C=O)-CH$_2$), 48.1 (N(Me-CH$_2$), 35.0 (N-Me), 21.4 (Tos-Me)
Elemental Analysis:
Calculated for $C_{18}H_{19}N_3O_3S$ M = 357. 43 g/mol:
C 60.49, H 5.36, N 11.76, S 8,97;
Found: C 60.39; H 5.42, N 11.63, S 9.08.

N-{2-[1-(2-Methoxy-phenyl)-4-oxo-4*H*-pyrido[3,4-d]pyridazin-3-yl]-ethyl}-4,N-dimethyl-benzenesulfonamide (compound no **6**)



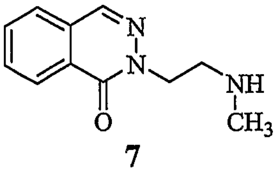
6

Yield 64%;
m.p.: 157-159°C (isopropanol); R$_F$ = 0.38 (acetone-chloroform = 2:8)
FT-IR (KBr): 1666 (C=O), 1333, 1154 (=SO$_2$);
^{1}H NMR (CDCl$_3$) δ: 9.66 (s, 1H, PyH), 8.85 (d, 1H, PyH *J*=5.6) 7.35-7.70 (m, 4H, ArH), 6.98-7.24 (m, 5H, ArH and PyH), 4.55-4.85 (m, 1H, CH$_2$), 4.10-4.36 (m, 1H, CH$_2$
3.75 (s, 3H, O-Me), 3.40-3.70 (m, 2H, CH$_2$), 2.91(s, 3H, N
Elemental Analysis:
Calculated for $C_{24}H_{24}N_4O_4S$ M = 464.54 g/mol:
C 62.05, H 5.21, N 12.06, S 6,90;
Found: C 61.83; H 5.18, N 12.07, S 6.95.

4. Synthesis of 2-[2(methylamino)ethyl]-2*H*-phthalazin-1-ones

In a round-bottomed flask *N*-tosyl-derivative of 2-[2-(methylamino)ethyl]-2*H*-phthalazin-1-on (0,0106 mol) and sulphuric acid (0,0318 mole, c=98%) were placed and the whole lot was heated for 6 hours at 100-110°C. After cooling to ambient temperature the reaction mixture was alkalised with 20% NaOH and then extracted with methlene chloride (3x30 ml). The combined extracts were dried over anhydrous MgSO$_4$ and vacuum concentrated till dryness. The residue was purified by column chromatography (silica gel, eluent ethyl acetate – methanol 1:1, and then ethyl acetate – methanol 1:2)

2-(2-Methylamino-ethyl)-2*H*-phthalazin-1-one (compound no.7)



7

Yield 81%;
R$_F$ = 0(ethyl acetate-methanol 1:1)
FT-IR (film): 1652 (C=O), 3316 (N-H);
^{1}H NMR (CDCl$_3$) δ: 8.46-8.42 (m, 1H, Ar-H) 8.19 (s,1H, Ar-H), 7.87-7.69 (m, 3H, ArH), 4.41 (t, 2H, *J*=6,0Hz, CH$_2$), 3.09 (t, 2H, *J*=6,0Hz, CH$_2$), 2.48 (s, 3H, Me), 2.37 (s, 1H, N-H));

^{13}CHNMR (CDCl$_3$): δ = 153 (C=O), 137.7, 132.8,
131.4, 129.3, 127.6, 126.4, 125.7, 50.1 (CH$_2$);
50 (CH$_2$), 36.0
HRMS:
Calculated for $C_{11}H_{13}N_3O$: 103,10586
Found: 203,10597

4. The conversion of 2-[(2-methylamino)-ethyl)-2*H*-phthalazin-1-one into hydrochloride

To the solution of **7** (0,0045 mol) in methanol (10 ml) stoichiometric amount of hydrochloric acid (2 mol/dm^3) was added. The mixture was held in ambient temperature for 12 hours. Then solvents were evaporated and the obtained hydrochloride was dried in desiccator.

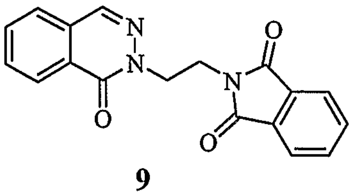
N-methyl-[2-(1-oxo-1*H*-phthalazin-2-yl)-ethyl]-ammonium chloride
(compound no. **8**)
m.p.: 199-204°C

5. Synthesis of 2-phthalimidoethyl-derivatives of benzopyridazinones

To the solution of sodium methoxide (0,0151 mol of Na in dry methanol 40 ml) was added 2*H*-phthalazin-1-on (0,01368 mol). The mixture was stirred and heated at reflux for 30 minutes. Then solvent was evaporated and the obtained sodium salt of phthalazinone was dried in vacuum dessicator. To the dried salt anhydrous dimethylformamide (20 ml) and N-2-bromoethyl)phthalimide (0,01505 mol) were added and the mixture was refluxed for 6 hours. After cooling to ambient temperature water (100 ml) was added to the reaction mixture. The product was filtrated and purified by recrystallization.

2-[2-(1-Oxo-1H-phthalazin-2-yl)-ethyl]-isoindole-1,3-dione (compound no. **9**)

Yield 25%;
m.p.: 205-208°C (AcOEt-hexane)
FT-IR (KBr): 1719, 1656 (C=O);
^{1}H NMR (DMSO-*d$_6$*) δ: 8.29 (s, 1H, 4-ArH), 8.18 (d, 1H, 5-ArH), *J*=7.7) 7.80-7.95 (m, 7H, ArH), 4.39 (t, 2H, CH$_2$, *J*=5.2), 4.02 (t, 2H, CH$_2$, *J*=5.2)
^{13}C NMR (DMSO-*d$_6$*) δ: 167.9, 159.5, 137.7, 133.8, 133.7, 132.9, 131.9, 131.5, 129.4, 127.6, 126.5, 125.9, 123.2, 123.1, 49.5, 36.6;
Elemental Analysis:
Calculated for $C_{18}H_{13}N_3O_3$ M = 319.32 g/mol: C 67.71, H 4.10, N 13.16;



9

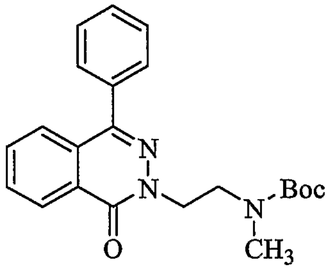
Found: C 67.65; H 4.15, N 13.19.

6. Synthesis of acyl-derivatives of benzo- and pyridopyridazinones.

The reaction was performed in atmosphere of argon. To triphenyphosphine (0.0102 mol) stirred in THF (10 ml) at –10°C the solution of diethyl azodicarboxylate (0.0102 mol, c ≈ 40%) in toluene was added dropwise, followed by the solution of phthalazinone (0.0068 mol) in THF (44 ml). After 15 minutes at –10°C the solution of corresponding N-acyl-derivative of N-methylethanoloamine (0.00748 mol) in THF (5 ml) was added. The reaction mixture after 2 hours at –10°C was warmed up to ambient temperature and kept at this temperature for 20 hours with vigorous stirring. Then all volatile materials were removed under reduced pressure and to the residue diethyl ether (20 ml) was added. The mixture was stirred at ambient temperature for 20 minutes. Afterwards the white solid was filtered off and the filtrate was concentrated and subjected to column chromatography. The product was purified by crystallization.

Methyl-[2-(1-oxo-4-phenyl-1H-phthalazin-2-yl)-ethyl]-carbamic acid tert-butyl ester (compound no. **10**)

Yield 50%;
m.p.: 169-170°C (methanol-water);
R_F = 0.42 (CH_2Cl_2-acetone 9:1);
FT-IR (KBr): 1690, 1645 (C=O);
^{1}H NMR ($CDCl_3$; rotamer mixture) δ: 8.57-8.54 (m, 1H, ArH), 7.77 (m, 3H, ArH), 7.61-7.53 (m, 5H, ArH), 4.47 (t, 2H, CH_2, *J*=6.0), 3.75 (t, 2H, CH_2, *J*=6.0), 2.95 (s, 3H, Me-N, rotamer II), 2.89 (s, 3H, Me-N, rotamer I), 1.27 (s, 9H, Me-Boc, rotamer I), 1.13 (s, 9H, Me-Boc, rotamer II)



10

^{13}C NMR ($CDCl_3$; rotamer mixture) δ: 158.9 (C=O), 155.4, 146.6, 134.9, 132.7, 131.1, 129.4, 128.9, 128.5, 127.0, 126.5, 79.2, 48.9, 47.1 (CH_2), 46.8 (CH_2), 34.9 (Me-N, 34.2 (Me-N, rotamer II), 28.0 (Me-Boc)
Elemental Analysis:
Calculated for $C_{22}H_{25}N_3O_3$ M = 279. 46 g/mol: C 69.64, H 6.64, N 11.07;
Found: C 69.57; H 6.77, N 11.09.

Biological Investigations

In the investigation of acute pain inhibition, the mechanism of supraspinal, spinal and peripheral structures of antinociceptive system is ascribe particular importance. Decreasing sensitivity to the pain stimulus, realized by employing one or more above-mentioned structures, is the measure of analgesic activity of the compound.

The investigating of anti-inflammatory activity consists in estimation of decreasing in inflammatory state, caused by pro-inflammatory agent. Karagenine is quite often used agent causing paw inflammatory oedema.

The investigating of analgesic activity of the compounds coordinated by supraspinal structures, was carried out according to the methodology of Eddy and Leimbach (W. B. Eddy, D. Limbach; *J. Pharmacol. Exp. Ther.* **1953**, *107*, 385).

The influence of the compounds on the spinal structures was investigated applying the methodology of D'Amour and Smith (F. E. D'Amour, D. L. Smith; *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74).

To determine the influence of the compounds on the peripheral structure the methodology of Collie and co-workers was applied (H. O. J. Collier, L. C. Dinnen, A. Chistine, A. Johnson, C. Schneider; *Br. J. Pharmacol. Chemother.* **1968**, *32*, 295).

Analgesic activity of the investigated compounds was tested on Balb/c male mice and was compared with the strong analgesic, which is metamizole.

The investigating of inflammatory and suppressing paw oedema activity was carried out on Wistar rats according to Ferreira methodology (S. H. Ferreira, *J. Pharm. Pharmacol.* **1971**, *31*, 648). Indometacine was used as reference material in order to compare the activity of tested compounds.

Compounds no. **3** and **4** demonstrated a strong analgesic activity. It was connected with influence on supraspinal structures. The analgesic activity was comparable and stronger then metamizole. Compounds **3**, **4**, **5**, **6**, **8**, **9** and **10** demonstrated an analgesic activity on spinal structures, as well as on peripheral structures (compounds **3**, **4** and **5**), comparable or stronger then metamizole.

Table 1. Analgesic activity of tested compounds

Type of activity	Tested compounds							
	3	4	5	6	8	9	10	Metamizole
Supraspinal	+++++	++	-	-	-	-	-	+++
Spinal	+++	+++	++	+++	+++	++	++++	+++
Peripheral	++	++	+++	-	-	-	-	+++

Where ++ - moderate activity; +++ - strong activity; ++++ and more – very strong activity;

Anti-inflammatory activity stronger then indometacine, was found for compound **9**.

The compounds according to the invention have useful pharmacological properties, which make them industrially utilizable.

The acute toxicity is the strong toxic effect, which occurs in a short time after giving the tested compound in a single dose or during 24 hours after giving the multiple dose. This kind of tests, performed on animals, should give the answers to several basic questions: (a) What dose of the compound is needed to cause death of an animal? (b) What organs are damaged in strong intoxication? (c) Has the tested compound allergenic or irritating activity?

The acute toxicity is usually tested on mice and rats. The experiments on male and female animals are recommended in the first evaluation. The acute toxicity is determined quantitatively as the medial lethal dose DL_{50}, i.e. dose causing dead of 50% of the animals subjected to the experiments.

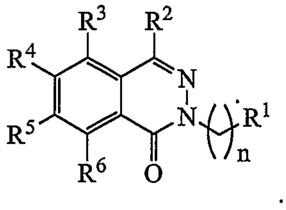
The acute toxicity of the tested compounds was evaluated according to the classification obligatory in the countries of The European Union and recommended by OECD. The acute toxicity of the compounds was compared with the toxicity of metamizole, which is the active component of commonly used analgetic medicament. The LD_{50} values for tested compounds were given in Table 2.

Table 2. The LD_{50} (mg/kg) of the compounds (p.o. administration) for mice.

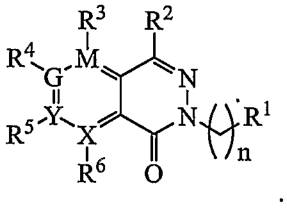
tested compounds							
3	**4**	**5**	**6**	**8**	**9**	**10**	Metamizole
200	300	>2000	>2000	200	1900	>2000	>2000

Patent claims

1. Derivatives of phthalazinone and pyridopyridazonone of formula **I** and **II**



I



II

in which:

n is an integer from 1 to 8 for straight or branched alkyl or alkenyl

R1 is –NR7R8, where **R7**, **R8** are

- hydrogen (H)
- straight or branched alkyl or alkenyl (C1 – C6)
- cycloalkyl (C5 – C7)
- aryl or heteroaryl (e.g. phenyl, pyridyl)
- -C(O)**R9**, where **R9** is
    - straight or branched alkyl (C1 – C6)
    - phenyl
    - benzyl
    - -**OR10**, where **R10** is straight or branched alkyl or alkenyl (C1 – C6)
- -SO_2**R11**, where **R11** is
    - alkyl straight or branched (C1 – C4)
    - aryl [phenyl, monosubstitued (2 or 3 or 4 position) or disubstituted (2,3 or 3,4 positions) benzene ring (straight or branched alkyl (C1 – C6), **R10O**-, where **R10** is straight or branched alkyl (C1-C4), halogen (F, Cl, Br, I);

-CO**Z**, where **Z** is

- hydroxyl (OH)
- -OM, where M is Li^+, Na^+, K^+ or Ca^{2+},
- -**NR13R14**, where **R13**, **R14** is

    - hydrogen (H)
    - straight or branched alkyl or alkenyl (C1-C6)
    - cycloalkyl (C5-C7)
    - aryl (e.g. phenyl, monosubstituted (2 or 3 or 4 position) benzene ring: straight or branched alkyl (C1-C4), **R10**O- (straight or branched alkyl or alkenyl (C1-C6), halogen (F, Cl, Br, I)
- piperidyn-1-yl
- morpholin-4-yl
- 4-(**R12**)piperazin-1-yl, where **R12** is straight or branched alkyl (C1-C6), aryl (substituted in 2 or/and 3 or/and 4 or/and 5 or/and 6position, or halogen (F, Cl, Br, I) poli-substituted benzene ring)

R2 is:

- hydrogen (H)
- straight or branched alkyl or alkenyl (C1-C6)
- benzyl
- phenyl
- benzene ring mono-substituted in 2 or 3 or 4 position [alkyl (C1-C6), **R10**O-, where **R10** is straight or branched alkyl (C1-C6)), halogen (F, Cl, Br, I), hydroxyl (OH)]
- pyridyl (pyrid-2-yl, pyrid-3-yl, pyrid-4-yl)

R3, R4

R5, R6 are

- hydrogen (H)
- straight or branched alkyl or alkenyl (C1-C6)
- cycloalkyl (C5-C7)
- **R10**O- (**R10** is straight or branched alkyl (C1-C6)
- halogen (F, Cl, Br, I)
- benzyl
- hydroxyl (OH)

M is nitrogen (N)

and **G** = **Y** = **X** = carbon (C); **R3** = none;

G is nitrogen (N)

and **M** = **Y** = **X** = carbon (C); **R4** = none;

Y is nitrogen (N)

and **M** = **G** = **X** = carbon (C) ; **R5** = none;

X is nitrogen (N)

and **M** = **G** = **Y** = carbon (C); **R6** = none
and the salts of this compounds.

2. Pharmaceutical composition which comprises the compounds of claim **1** as active ingredients as well as pharmaceutically acceptable carriers, auxiliaries or solvents.

3 Application of benzo- and pyridopyridazonones of claim **1** as analgesic and antiinflammatory medicine.

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2008/000070

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/06 C07D471/04 C07D487/04 A61P29/00 A61K31/502
A61K31/5025

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 808 636 A (CASSELLA FARBWERKE MAINKUR AG) 11 February 1959 (1959-02-11) Therapeutic acitivity: see page 1, lines 71-74 claims 8,9,11,14; examples 1,3,8	1-3
X	WO 93/07146 A (SYNTEX INC [US]) 15 April 1993 (1993-04-15) page 132, line 31 - line 32 page 133, line 10 - line 11	1-3

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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search 25 February 2009	Date of mailing of the international search report 13/03/2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Lange, Tim

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GALVEZ J ET AL: "TOPOLOGICAL APPROACH TO ANALGESIA" JOURNAL OF CHEMICAL INFORMATION AND COMPUTER SCIENCES, AMERICAN CHEMICAL SOCIETY, COLOMBUS,OHIO, US, vol. 34, no. 5, 1 January 1994 (1994-01-01), pages 1198-1203, XP000907050 ISSN: 0095-2338 commercial drug Talestine, falling into scope of claim 1 page 1201; table 4 -----	1-3
X	DENIZ S. DOGRUERA, ESRA KUPELIB, ERDEM YESILADAB, M. FETHI SAHINA: "Synthesis of New 2-[1(2H)-Phthalazinon-2-yl]-acetamide and 3-[1(2H)-Phthalazinon-2-yl]-propanamide Derivatives as Antinociceptive and Anti-inflammatory Agents" ARCH. PHARM. PHARM. MED. CHEM., vol. 337, no. 6, 2 June 2004 (2004-06-02), pages 303-310, XP002516615 tables 2,3; compounds 2A-2E, 4A-4E -----	1-3
X	EP 0 309 765 A (PENNWALT CORP [US]) 5 April 1989 (1989-04-05) page 6; examples 1,step,b -----	1
X	EP 0 242 173 A (PFIZER LTD [GB]) 21 October 1987 (1987-10-21) page 18, line 20; example 17 -----	1
X	NICOLETTA CESARI, CLAUDIO BIANCALANI, CLAUDIA VERGELLI, VITTORIO DAL PIAZ, ALESSIA GRAZIANO,: "Arylpiperazinylalkylpyridazinones and Analogues as Potent and Orally Active Antinociceptive Agents: Synthesis and Studies on Mechanism of Action" JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 26, 6 December 2006 (2006-12-06), pages 7826-7835, XP002516616 see Table 3 for antinociceptive/analgesic activity of compounds compounds 15A-15D, 18 -----	1-3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/PL2008/000070

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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