PŘIHLÁŠKA VYNÁLEZU

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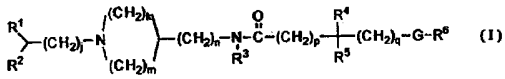
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(I)

(54) Název přihlášky vynálezu:

Sloučenina derivátů cyklických aminů a způsob jejich přípravy

(57) Anotace:

Popisuje se způsob přípravy sloučeniny reprezentované obecným vzorcem I, její farmaceuticky přijatelné soli vzniklé adicí kyseliny nebo její farmaceuticky přijatelné soli vzniklé adicí C_1-C_6alkylové skupiny a jejich medicínské aplikace. Jelikož tyto sloučeniny inhibují aktivitu chemokinů jako jsou MIP-1α a/nebo MCP-1 v cílových buňkách, lze tyto sloučeniny užít jako terapeutická léčiva a/nebo k preventivní léčbě nemocí, jako jsou kornatění tepen, revmatická artritida a nemoci jim podobné, u kterých dochází k infiltraci krevních monocytů a lymfocytů do tkáně.

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Sloučenina derivátů cyklických aminů a způsob jejich přípravy

Oblast techniky

Vynález popisuje nové deriváty cyklických aminů.

Dále vynález také popisuje antagonisty chemokinových receptorů, které mohou být účinné jako terapeutická činidla nebo jako preventivní ochranná agens proti nemocem, jako jsou kornatění tepen, revmatická artritida, lupénka, astma, ulcerózní kolitida, nefritida (nefropatie), skleróza multiplex, plicní fibróza, myokarditida, žloutenka, pankreatitida, sarkoidóza, Crohnova nemoc, endometrióza, selhání srdeční činnosti z městnání, virová meningitida, mozkové příhody, neuropatie, Kawasakiho nemoc a sepse, u kterých infiltrace krevních leukocytů, jako jsou monocyty a lymfocyty, hraje významnou roli v iniciaci, rozvoji či průběhu nemoci.

Dosavadní stav techniky

Chemokiny jsou skupinou imunomodulačních polypeptidových faktorů, které mají molekulovou hmotnost mezi 6 až 15 kD a vyskytují se při zánětech. Chemokiny jsou produkovány v místě zánětu různými typy buněk, jako jsou makrofágy, monocyty, eosinofily, neutrofily, fibroblasty, cévní endotelové buňky, buňky hladkého svalstva a mastocyty.

Chemokiny se rozdělují do dvou hlavních podskupin, CXC chemokiny (neboli α–chemokiny) a CC chemokiny (neboli β - chemokiny), a to podle běžné lokalizace čtyř konzervovaných cysteinových zbytků a podle rozdílů v lokalizaci na chromozomu, který je kóduje. První dva cysteinové zbytky u CXC chemokinů jsou odděleny jedním odlišným aminokyselinovým zbytkem, zatímco tytéž cysteinové zbytky ve skupině chemokinů CC jsou přímo sousedící. Například IL-8 (zkratka je zkratkou pro interleukin – 8) je CXC chemokin, zatímco CC chemokiny zahrnují MIP- 1α/β (zkratky pro makrofágový zánětlivý protein 1 α/β), MCP-1 (zkratka pro monocytární chemoatraktantní protein –1) a RANTES (zkratka pro regulaci za aktivace, normální exprimovaná a sekretovaná T-buňka). Existují však také chemokiny, které nepatří do žádné z uvedených podskupin. Jsou to lymfotaktin, který obsahuje pouze dva cysteinové zbytky a je definován jako C chemokin a dále fractalkin, označovaný jako CX_3C chemokin, který obsahuje chemokinům podobnou doménu v mucinové struktuře, kde jsou však první dva cysteiny odděleny třemi aminokyselinami. Tyto chemokiny

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podporují chemotaxi, migraci buněk, zvyšují expresi buněčných adhesivních molekul, jako jsou integriny a tím buněčnou adhesi. Předpokládá se, že jsou těmi proteinovými faktory, které se úzce zapojují do adhese a infiltrace leukocytů do patogenních míst v zánětlivých pletivech (pro další informace se podívejte například do: Vaddi, K., a další, The Chemokine Facts Book, Academic Press, 1997; Chemoattractant Ligand and Their Receptors, Horuk, R. , Ed. , CRC Press, 1996; Ward, G. W. , a další, Biochem. J., 1998, 333, 457; Luster, A. D., New Engl . J. Med., 1998, 338, 436; Baggiolini, M., Nature, 1998, 392, 565; Rollins, B.J., Blood, 1997, 90, 909; Alam, R., J. Allergy Clin. Immunol., 1997, 99, 273; Hancock, W.W., Am. J. Pathol., 1996, 148, 681; Taub, D.D., Cytokine & Growth Factor Rev., 1996, 7, 335; Strieter, R.M.,a další, J. Immunol., 1996, 156, 3583; Furie, M.B., a další , Am. J. Pathol., 1995, 146, 1287; Schall, T.J., a další , Current Opinion in Immunology, 1994, 6, 865; Edginton, S.M., Biotechnology, 1993, 11, 676).

Dále je známo, že například MIP-1 způsobuje transientní růst koncentrace intracelulárních vápenatých iontů a indukuje migraci T-lymfocytů, B-lymfocytů (pro další informace se podívejte do Taub, D.D., a další, Science, 1993, 260, 355; Schall, T.J.,a další , J. Exp. Med., 1993, 177, 1821), a eosinofílů (pro reference se podívejte do: Rot, A., a další, J. Exp. Med., 1992, 176, 1489), chemotaxi přirozených buněčných zabíječů (viz: Maghazachi, A.A., a další J. Immunol., 1994, 153, 4969), expresi integrínů (viz například: Vaddi, K., a další , J. Immunol. , 1994, 153, 4721), a diferenciaci osteoklastů (pro reference se podívejte například do Kukita, T., a další, Lab. Invest., 1997, 76, 399). MIP-1α/β také zvyšují produkci IgE a IgG4 v B buňkách (pro reference se podívejte například do: Kimata, H., a další, J. Exp. Med., 1996, 183, 2397) a inhibuje proliferaci hematopoietických kmenových buněk (viz například Mayani, H., a další , Exp. Hematol., 1995, 23, 422; Kelley, J.R., a další, Blood, 1994, 84, 2175; Eaves, C.J., a další., Proc. Natl. Acad. Sci. USA, 1993, 90, 12015; Bodine, D.M., a další, Blood, 1991, 78, 914; Broxmeyer, H.E., a další, Blood, 1990, 76, 1110).

Bylo objeveno, že MIP-1α/β , s ohledem na jeho aktivitu in vivo a jeho roli při patogenezi nemoci, působí u králíků jako pyrogen (na další informace se podívejte například do: Davatelis, G., a další, Science, 1989, 243, 1066); dále se ví, že injekce MIP-lα/β do myšího chodidla vyvolá zánětlivou reakci, která je doprovázená infiltrací neutrofilů a monojaderných buněk (na další informace se podívejte například do: Alam, R., a další, J. Immunol., 1994, 152, 1298); je též známo že MIP-lα neutralizující protilátka má ve zvířecích modelech u granulomu inhibiční vliv, či terapeutický účinek (na další informace se podívejte například do Lukacs, N.W., a další , J. Exp. Med., 1993, 177, 1551), či ve spojitosti s astma (pro další informace se podívejte například do: Lukacs, N.W. , a další , Eur. J. Immunol., 1995, 25, 245; Lukacs, N.W., a další, J. Immunol., 1997, 158, 4398), nebo sklerózou multiplex (na další informace se podívejte například do Karpus, W.J., a další, J. Immunol., 1995, 155,

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5003; Karpus, W.J.,a další, J. Leukoc. Biol., 1997, 62, 681), pro idiopatickou plicní fibrosu (na další informace se podívejte například do: Smith, R.E., a další, J. Immunol., 1999, 153, 4704; Smith, R.E., Biol. Signals, 1996, 5, 223), data pro akutní zánět plic jsou například v Shanley, T.P., a další, J. Immunol., 1995, 154, 4793; Standiford, T.J., a další., J. Immunol., 1995, 155, 1515), a pro revmatickou artritidu (Kasama, T., a další, J. Clin. Invest., 1995, 95, 286. Také virem coxsackie vyvolaná myokarditida a herpetická stromalní keratitida jsou u myší inhibovány pomocí narušeného genu pro MIP-1α/β (pro další informace se podívejte například do Cook, D.N. a další., Science, 1995, 269, 1583; Tumpey, T.M., a další , J. Virology, 1998, 72,3705).Výrazně zvýšená exprese pro MIP-1α/β byla také pozorována u pacientů trpících chronickými zánětlivými onemocněními plic (podrobnosti najdete v: Standiford, T.J., a další, J. Immunol. , 1993, 151, 2852) , u pacientů s hypersensitivní pneumonitidou (pro další informaci se podívejte do: Denis, M., Am. J. Respir. Crit. Care Med., 1995, 151, 164), u pacientů s revmatickou artritidou (podrobnosti najdete například v literárním odkaze: Koch, A.E., a další, J. Clin. Invest., 1994, 93, 921), u pacientů s infekční meningitidou (Lahrtz, F., a další, J. Neuroimmunol., 1998, 85, 33) a u pacientů s chronickým zánětem svalů (reference týkající se daného příkladu je například : Adams, E.M., a další, Proc. Assoc. Am. Physicians, 1997, 109, 275). Všechny tyto studie ukazují, že MIP-lα/β je hluboce zapojen v lokálním nashromáždění různých subtypů leukocytů a při iniciaci, průběhu a vývoji choroby ústící do zánětlivé odpovědi.

MCP-1 (také znám pod zkratkou MCAF, což je zkratka pro makrofágový chemotaktický a aktivujícíc faktor nebo JE) je CC chemokin produkovaný monocyty /makrofágy, buňkami hladkého svalstva, fibroblasty a cévními endotelovými buňkami/ a způsobuje buněčnou migraci a buněčnou adhezi monocytů (na podrobnosti se lze podívat například do: Valente, A. J., a další, Biochemistry, 1988, 27, 4162; Matsushima, K., a další , J. Exp. Med., 1989, 169, 1985; Yoshimura, T., a další., J. Immunol., 1989, 142, 1956; Rollins, B.J., a další, Proc. Natl. Acad. Sci. USA, 1988, 85, 3738; Rollins, B.J.,a další, Blood, 1991, 78, 1112; Jiang, Y., a další, J. Immunol., 1992, 148, 2423; Vaddi, K.,a další, J. Immunol., 1994, 153, 4721), paměťových T lymfocytů (na podrobnosti se lze podívat například do: Carr, M.W., a další , Proc. Natl. Acad. Sci. USA, 1994, 91, 3652, Loetscher, P., a další , FASEB J., 1999, 8, 1055) a přirozených buněčných zabijáků (natural killer cells) (na podrobnosti se lze podívat například do: Loetscher, P. , a další , J. Immunol., 1996,156, 322 ; Allavena, P., a další , Eur. J. Immunol., 1994, 24, 3233), dále také zprostředkuje uvolnění histaminu basofily (na podrobnosti se lze podívat například do: Alam, R., a další, J. Clin. Invest., 1992, 89, 723; Bischoff, S.C., a další, J. Exp. Med., 1992, 175, 1271; Kuna, P., a další, J. Exp. Med., 1992, 175, 489).

Co více, vysoká exprese MCP-1 se také uvádí u nemocí, kde akumulace monocytů /makrofágů a/nebo T buněk/ se považuje za důležitou ve spojitosti s iniciací nebo vývojem nemocí, jako je ateroskleróza (na podrobnosti se lze podívat například do: Hayes, I.M., a další, Arterioscler. Thromb. Vasc. Biol., 1998, 18, 397; Takeya, M., a další, Hum. Pathol. , 1993, 24, 534; Yla-Herttuala, S., a další, Proc. Natl. Acad. Sci. USA, 1991, 88, 5252; Nelken, N.A., J. Clin. Invest., 1991, 88, 1121), revmatická artritida (na podrobnosti se lze podívat například do: Koch, A.E., a další, J. Clin. Invest., 1992, 90, 772; Akahoshi, T., a další, Arthritis Rheum., 1993, 36, 762; Robinson, E., a další, Clin. Exp. Immunol., 101, 398), nefritida (na podrobnosti se lze podívat například do: Noris, M., a další., Lab. Invest., 1995, 73, 804; Wada, T.,a další, Kidney Int., 1996, 49, 761; Gesualdo, L., a další, Kidney Int., 1997, 51, 155), nephropatie (pro podrobnosti se lze podívat například do: Saitoh, A., a další, J. Clin. Lab. Anal., 1998, 12, 1; Yokoyama, H., a další, J. Leukoc. Biol., 1998, 63, 493), pulmonarní fibrosa, pulmonarní sarcoidosa (na podrobnosti se lze podívat například do: Sugiyama, Y. ,a další , Internal~Medicine, 1997, 36, 856), astma (na podrobnosti se lze podívat například do: Karina, M., a další, J. Invest. Allergol. Clin. Immunol., 1997, 7, 259; Stephene, T.H., Am. J. Respir. Crit. Care Med., 1997, 15 156, 1377; Sousa, A.R., a další, Am. J. Respir. Cell Mol. Biol., 1994, 10, 142), skleróza multiplex (pro podrobnosti se lze podívat například do: McManus, C., a další, J. Neuroimmunol., 1998, 86, 20), psoriáza (pro podrobnosti se lze podívat například do: Gillitzer, R., et al., J. Invest. Dermatol., 1993, 101, 127), zánětlivá nemoc střev (pro podrobnosti se lze podívat například do: Grimm, M.C., a další , J. Leukoc. Biol., 1996, 59, 804; Reinecker, H. C., a další, Gastroenterology,1995, 106, 40), myokardititida (pro podrobnosti se lze podívat například do: Seino, Y., a další, Cytokine, 1995, 7, 301), endometrióza (pro podrobnosti se lze podívat například do: Jolicoeur, C., a další, Am. J. Pathol., 1998, 152, 125), intraperitoneální adhese (pro podrobnosti se lze podívat například do: Zeyneloglu, H.B., a další , Human Reproduction, 1998, 13, 1194), selhání srdce městnáním (pro podrobnosti se lze podívat například do: Aurust, P., a další , Circulation, 1998, 97, 1136), chronické nemoci jater (pro podrobnosti se lze podívat například do: Marra, F., a další , Am. J. Pathol., 1998, 152, 423), virová meningitida (pro podrobnosti se lze podívat například do: Lahrtz, F., a další, Eur. J. Immunol., 1997, 27, 2484) , Kawasakiho nemoc (pro podrobnosti se lze podívat například do: Wong, M. ; a další , J. Rheumatol., 1997, 24, 1179) a sepse (pro podrobnosti se lze podívat například do: Salkowski, C.A.; a další , Infect. Immun., 1998, 66, 3569). Co více, protilátka generovana proti MCP-1 vykazuje u zvířecích modelů terapeutické účinky v případě revmatické artritidy (pro podrobnosti se lze podívat například do: Schimmer, R. C. , a další , J. Immunol . , 1998, 160, 1466; Schrier, D. J. , J. Leukoc. Biol., 1998, 63, 359; Ogata, H. a další, J. Pathol, 1997, 182, 106), sklerózy multiplex (pro podrobnosti se lze podívat například do: Karpus, W. J., a další, J. Leukoc. Biol., 1997,62, 681), nefritidy (pro podrobnosti se lze podívat například do: Lloyd, C.M., a další, J.

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Exp. Med., 1997, 185, 1371; Wada, T., a další, FASEB J., 1996, 10, 1418), astma (pro podrobnosti se lze podívat například do: Gonzalo, J.A., a další , J. Exp. Med., 1998, 188, 157; Lukacs, N.W., J. Immunol.,1997, 158, 4398), arterosklerózy (pro podrobnosti se lze podívat například do: Guzman, L.A., a další, Circulation, 1993, 88 (dodatek), I-371), opožděného typu hypersensitivity (na podrobnosti se lze podívat například do: Rand, M.L., a další, Am. J. Pathol., 1996, 148, 855), plicní hypertenze (na podrobnosti se lze podívat například do: Kimura, H., a další, Lab. Invest., 1998, 78, 571) a intraperitoneální adheze (na podrobnosti se lze podívat například do: Zeyneloglu, H.B., et al., Am. J. Obstet. Gynecol., 1998, 179, 438). O peptidovém antagonistovi MCP-1, nazvaném MCP-1(9-76) je známo, že v myším modelu inhibuje artritidu (na podrobnosti se lze podívat například do: Gong, J.-H., J. Exp. Med. , 1997, 186, 131) , stejně tak bylo prokázáno ve studiích s MCP-1-deficientními myšmi, že MCP-1 je in vivo nezbytný pro získávání monocytů (Lu,B., a další, J. Exp. Med., 1998, 187, 601; Gu, L., a další, Moll. Cell, 1998, 2, 275).

Tato data naznačují, že chemokiny, jako je MIP-1α a MCP-1 přitahují monocyty a lymfocyty do míst nemocí a zprostředkovávají jejich aktivaci. Tak se obě látky zapojují do iniciace, průběhu a vývoje nemocí, při kterých dochází k velkému zapojení monocytů a lymfocytů, jako je arteroskleróza, revmatická arttritida, lupénka, astma, ulcerózní kolitida, nefritida (nefropatie), skleróza multiplex, plicní fibróza, myokarditititida, žloutenka, pankreatititda, sarkoidóza, Crohnova nemoc, endometrióza, selhání srdeční činnosti z městnání, virová meningitida, mozkové příhody, neuropatie, Kawasakiho nemoc a sepse, (pro podrobnosti se lze podívat například do: Rovin, B.H., a další., Am. J. Kidney.Dis., 1998, 31, 1065; Lloyd, C., a další, Curr. Opin. Nephrol. Hypertens., 1998, 7, 281: Conti, P., a další, Allergy and Asthma Proc., 1998, 19, 121; Ransohoff, R.M., a další, Trends Neurosci., 1998, 21, 154; MacDermott, R.P., a další, Inflammatory Bowel Diseases, 1998, 4, 54). Proto léčiva, která by inhibovala aktivaci chemokinů v cílových buňkách, by byla terapeuticky účinná a mohla by se užívat i jako prevence.

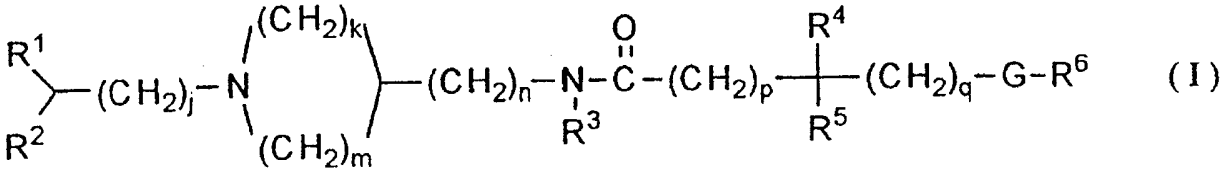
Byly klonovány geny kódující receptory pro specifické chemokiny a bylo zjištěno, že tyto receptory jsou totožné se sedmi G protein vázajícími transmembránovými receptory přítomnými v různých populacích lymfocytů. Doposud bylo identifikováno přinejmenším pět CXC chemokinových receptorů (CXCR1-CXCR5) a osm CC chemokinových receptorů (CCR1-CCR8). Například IL-8 je ligandem pro CXCR1 a CXCR2, MIP-lα je ligandem pro CCRl a CCR5 a MCP-1 je ligandem pro CCR2A a CCR2B (pro další informace se podívejte například do: Holmes, W.E., a další, Science 1991, 253, 1278-1280; Murphy P.M., a další, Science, 253, 1280-1283; Neote, K. a další, Cell, 1993, 72, 415-425; Charo, I.F., a další, Proc. Natl. Acad. Sci. USA, 1994, 91, 2752-2756; Yamagami, S.,a další, Biochem. Biophys. Res. Commun., 1994, 202, 1156-1162; Combadier, C., a další, The Journal of Biological

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Vynález se dále vztahuje k navržení způsobu léčby nemocí, pro které je vazba chemokinů jako jsou MIP-1α a/ nebo MCP-1 k receptorům na cílových buňkách jednou z jejich příčin.

Výsledkem intenzivního studia odborníků předkládajících tento vynález je, že objevili derivát cyklických aminů, který má arylalkylovou skupinu, jeho farmaceuticky přijatelnou sůl vzniklou C_1 - C_6 adicí alkylové skupiny nebo jeho farmaceuticky přijatelnou sůl vzniklou adicí kyseliny, který se vyznačuje vynikající aktivitou inhibovat vazbu chemokinů jako jsou MIP-1α a/ nebo MCP-1 a jim podobných k receptorům cílových buněk, což bylo hlavním cílem vynálezu.

Předmětem vynálezu je sloučenina, jejíž obecný vzorec I je uveden níže:



(I)

její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině,

kde R^1 je fenylová skupina, C_3 – C_8 cykloalkylová skupina, nebo aromatická heterocyklická skupina mající 1 až 3 heteroatomy vybrané ze skupiny obsahující kyslíkový atom, sírový atom a dusíkový atom, nebo kombinací těchto tak, aby se tvořil kondensovaný kruh, a dále fenylová skupina, C_3 – C_8 cykloalkylová skupina, aromatická heterocyklická skupina nebo kondenzovaný kruh jsou substituovány jedním nebo více atomy halogenů, hydroxylovou skupinou, kyanoskupinou, nitroskupinou, karboxylovou skupinou, karbamoylovou skupinou, C_1 – C_6 alkylovou skupinou, C_3 – C_8 cykloalkylovou skupinou , C_2 – C_6 alkenylovou skupinou, C_1 – C_6 alkoxylovou skupinou, C_1 – C_6 alkylthioskupinou , C_3 – C_5 alkylenovou skupinou, C_2 – C_4 alkylenoxyskuplinou, C_1 – C_3 alkylendioxyskupinou, fenylovou skupinou, fenoxyskuplinou, fenylthio skupinou, benzylovou skupinou, benzyloxyskuplinou, benzylaminoskupinou, C_2 – C_7 alkanoylovou skupinou, C_2 – C_7 alkoxykarbonylovou skupinou, C_2 – C_7 alkanoyloxyskupinou, C_2 – C_7 alkanoylaminoskupinou, C_3 - C_7 N-alkylkarbamoylovou skupinou, C_4 – C_9 N-cykloalkylkarbamoylovou skupinou, C_1 – C_6 alkylsulfonylovou skupinou, C_3 – C_3 (alkoxykarbonyl)methylovou skupinou, N-fenylkarbamoylovou skupinou, piperidinkarbonylovou skupinou, morfolinkarbonylovou skupinou, 1-pyrolidinyl-karbonylovou skupinou, bivalentní skupinou reprezentovanou vzorcem: - NH(C=O)O-, bivalentní skupinou reprezentovanou vzorcem: -NH(C=S)O-, aminoskupinou, mono (C_1 – C_6 alkyl)-aminoskupinou, či di(C_1 – C_6 alkyl)amino skupinou, je-li substituentem fenylová skupina, C_3 – C_8

Chemistry, 1995, 270, 16491-16499, Power, C.A., a další, J. Biol. Chem., 1995, 270, 19495-19500; Samson, M.. a daslší, Biochemistry, 1996, 35, 3362-3367; Murphy, P.M., Annual Review of Immunology, 1999, 12, 592-633). Bylo prokázáno, že v CCR1-deficientních myších je zánět plic a tvorba granulonů potlačena (další informace lze nalézt v: Gao, J.L., a další, J. Exp. Med., 1997, 185, 1959; Gerard, C., a další, J. Clin. Invest., 1997, 100, 2022). Dále také bylo prokázáno, že pomnožení makrofágů a tvorba arterosklerotických lezí u CCR2-deficientních myší klesá (Boring, L., a další, Nature, 1998, 394, 894; Kuziel, W.A., a další, Proc. Natl. Acad. Sci., USA, 1997, 99, 12053; Kurihara, T., a další, J. Exp. Med., 1997, 186, 1757; Boring, L., a další, J. Clin. Invest., 1997, 100, 2552). Proto tedy sloučeninu, která inhibuje vazbu chemokinů jako je MIP-1α nebo MCP-1 k těmto receptorům, to znamená antagonistu receptoru, by bylo možno využít jako lék, který inhibuje aktivitu chemokinů jako je MIP-1α nebo MCP-1 v cílových buňkách. Ale doposud nejsou známa žádná léčiva s těmito efekty.

Deriváty cyklických aminů, které jsou předmětem vynálezu, jsou zcela novým přístupem k řešení dané problematiky. Dříve bylo popsáno, že deriváty difenylmetanu (W09729325; Hesselgesser, J., a další, J. Biol. Chem., 1998, 273, 15687), deriváty piperidinu (JP9-249566), deriváty imidazobenzodiazepinu (JP9-249570), deriváty benzazocinu (JP9-255572), tricyklické sloučeniny s cyklickou aminoskupinou (W09804559), deriváty fenothiazinu (Bright, C., a další, Bioorg. Med. Chem. Lett., 1998, B, 771), deriváty piperazinu (WO9744329), deriváty benzimidazolu (W09B06703), analogy distamycinu (Howard, O.M.Z., a další, J. Med. Chem., 1998, 41, 2184), deriváty bis-akridinu (W09830218), spiro-substituované azacykly (W09825604; W09825605), substituované aryl piperaziny (W09825617), deriváty aminochinolinu (Y709827815), deriváty 3-arylpiperidinu (W09831364), deriváty amidů kyseliny kapronové (W09838167) a další malé molekuly (W09744329; W09802151; W09804554) mají antagonistické aktivity vzhledem k chemokinovým receptorům, jako jsou CXCRl, CXCR4, CCR1, CCR2, CCR3 a CCR5. Avšak tyto sloučeniny se liší od sloučenin, které jsou předmětem tohoto vynálezu.

Podstata vynálezu

Vynález popisuje nízkomolekulární sloučeninu, která inhibuje vazbu chemokinů jako jsou MIP-1α a/ nebo MCP-1 k jejich receptorům na cílových buňkách.

Vynález dále popisuje způsob inhibice vazby chemokinů jako jsou MIP-1α a/ nebo MCP-1 k receptorům na cílových buňkách a jejich vliv na cílové buňky.

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cykloalkylová skupina, aromatická heterocyklická skupina nebo je kondenzovaný kruh opticky substituovaný jedním nebo více halogenovými atomy,hydroxlovou skupinou , aminoskupinou, trifluormethylovou skupinou, $C_1 - C_6$ alkylovou skupinou nebo , $C_1 - C_6$ alkoxyskupinou;

R^2 je vodíkový atom, $C_1 - C_6$ alkylová skupina, $C_2 - C_7$ alkoxykarbamoylová skupina, hydroxylová skupina nebo fenylová skupina, kde $C_1 - C_6$ alkylová nebo fenylová skupina je substituována jedním nebo více halogenovými atomy, hydroxyskupinou, $C_1 - C_6$ alkylovou skupinou nebo $C_1 - C_6$ alkoxylovou skupinou, kde je-li $j = 0$, R^2 není hydroxylová skupina;

j reprezentuje celé číslo od 0 do 2;

k reprezentuje celé číslo od 0 do 2;

m reprezentuje celé číslo od 2 do 4;

n reprezentuje 0 nebo 1;

R^3 je vodíkový atom nebo $C_1 - C_6$ alkylová skupina opticky substituovaná jednou nebo dvěma fenylovými skupinami, z nichž každá je substituovaná jedním nebo více halogenovými atomy, $C_1 - C_6$ alkylovou skupinou nebo $C_1 - C_6$ alkoxylovou skupinou;

R^4 a R^5 mohou být buď totožné, nebo každý jiný a může to být vodíkový atom, hydroxyskupina , fenylová skupina, nebo $C_1 - C_6$ alkylová skupina, ve které je $C_1 - C_6$ alkylová skupina opticky substituována jedním nebo více halogenovými atomy, kyanoskupinou, nitroskupinou, karboxylovou skupinou, karbamoylovou skupinou, $C_1 - C_6$ alkylovou skupinou, $C_3 - C_3$ cykloalkylovou skupinou, $C_2 - C_6$ alkenylovou skupinou, $C_1 - C_6$ alkoxylovou skupinou, $C_1 - C_6$ alkylthioskupinou , $C_3 - C_5$ alkylenovou skupinou, $C_2 - C_4$ alkylenoxy-skupinou, $C_1 - C_3$ alkylendioxyskupinou, fenylovou skupinou, fenoxyskupinou, fenylthioskupinou, benzylovou skupinou, benzyloxyskupinou , benzylaminoskupinou, $C_2 - C_7$ alkanoyl skupinou, $C_2 - C_7$ alkoxykarbonyl skupinou, $C_2 - C_7$ alkanoyloxyskuplinou, $C_2 - C_7$ alkanoylaminoskupinou, C_3- C_7 N-alkylkarbamoylovou skupinou, $C_4 - C_9$ N-cykloalkylkarbamoylovou skupinou, $C_1 - C_6$ alkylsulfonylovou skupinou, $C_3 - C_8$ (alkoxykarbonyl)methylovou skupinou, N-fenylkarbamoylovou skupinou, piperidinkarbonylovou skupinou, morfolinkarbonylovou skupinou, 1-pyrolidinylkarbonylovou skupinou, bivalentní skupinou reprezentovanou vzorcem: -NH(C=O)O-, bivalentní skupinou reprezentovanou vzorcem: -NH(C=S)O-, aminoskupinou, mono($C_1 - C_6$ alkyl)amino skupinou, či di($C_1 - C_6$ alkyl)aminoskupinou, je substituentem fenylová skupina, $C_3 - C_8$ cykloalkylová skupina, aromatická heterocyklická skupina nebo kondenzovaný kruh případně substituovaný jedním nebo více halogenovými atomy, hydroxylovou skupinou , aminoskupinou, trifluormethylovou skupinou, $C_1 - C_6$ alkylovou skupinou nebo, $C_1 - C_6$ alkoxyskupinou;

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R^2 je vodíkový atom, C_1 – C_6 alkylová skupina, C_2 – C_7 alkoxykarbamoylová skupina, hydroxylová skupina nebo fenylová skupina, kde C_1 – C_6 alkylová nebo fenylová skupina je substituována jedním nebo více halogenovými atomy, hydroxyskupinou, C_1 – C_6 alkylovou skupinou nebo C_1 – C_6 alkoxylovou skupinou, kde je-li j = 0, R^2 není hydroxylová skupina;

j reprezentuje celé číslo od 0 do 2;

k reprezentuje celé číslo od 0 do 2;

m reprezentuje celé číslo od 2 do 4;

n reprezentuje 0 nebo 1;

R^3 je vodíkový atom nebo C_1 – C_6 alkylová skupina případně substituovaná jednou nebo dvěma fenylovými skupinami, z nichž každá je substituovaná jedním nebo více halogenovými atomy, C_1 – C_6 alkylovou skupinou nebo C_1 – C_6 alkoxylovou skupinou;

R^4 a R^5 mohou být buď totožné, nebo každý jiný a může to být vodíkový atom, hydroxylová skupina , fenylová skupina, nebo C_1 – C_6 alkylová skupina, ve které je C_1 – C_6 alkylová skupina případně substituovaná jedním nebo více halogenovými atomy, hydroxylovou skupinou, kyanoskupinou, nitroskupinou, karboxylovou skupinou, karbamoylovou skupinou, merkaptoskupinou, guanidinovou skupinou, C_3 – C_8 cykloalkylovou skupinou , C_1 – C_6 alkoxylovou skupinou, C_1 – C_6 alkylthioskupinou , fenylovou skupinou, která může být substituována jedním nebo více halogenovými atomy, hydroxylovou skupinou, C_1 – C_6 alkoxylovou skupinou nebo benzyloxyskuplinou, fenoxyskupinou, benzyloxyskupinou, benzyloxykarbonylovou skupinou, C_2 – C_7 alkanoylovou skupinou, C_2 – C_7 alkoxykarbamoylovou skupinou , C_2 –C_7 alkanoyloxyskupinou, C_2 – C_7 alkanoylamino- skupinou, C_2 – C_7 N-alkylkarbamoylovou skupinou C_2 – C_7 alkylsulfonyl skupinou , aminoskupinou, mono(C_1 – C_6 alkyl)aminoskupinou, či di(C_1 – C_6 alkyl)aminoskupinou nebo aromatickou heterocyklickou skupinou, mající jeden až tři heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu, nebo z kombinace předchozích a lze ji případně kondenzovat s benzenovým kruhem, či R^4 a R^5 tvoří dohromady tří až šestičlenný cyklický uhlovodík;

p reprezentuje 0 nebo 1;

q reprezentuje 0 nebo 1;

G je skupina reprezentovaná –CO-, -SO-, -CO-O-, NR-CO-, -CO-NR^7-, -NH-CO-NH-, -NH-CS-NH-, -NR^7–SO_2-, –SO_2-NR^7-, -NH-CO-O- nebo -O-CO-NH-, kde R^7 je vodíkový atom nebo C_1- – C_6 alkylová skupina, nebo R^7 dohromady s R^5 reprezentují C_2 – C_5 alkylenovou skupinu.

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R^6 je fenylová skupina, C_3 – C_8 cykloalkylová skupina, C_3 – C_8 cykloalkenylová skupina, benzylová skupina, nebo aromaticka heterocyklická sloučenina mající jeden až tři heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu nebo z kombinace předchozích a ve kterých fenyl, benzyl nebo aromatický heterocyklus jsou kondenzovány s benzenovým kruhem, či aromatickou hetrocyklickou skupinou mající jeden až tři heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu nebo z kombinace předchozích, tak aby tvořily kondenzovaný kruh, kde fenylová skupina, C_3 – C_8 cykloalkylová skupina, C_3 – C_8 cykloalkenylová skupina, benzylová skupina, nebo aromatická heterocyklická skupina, nebo kondenzovaný kruh mohou být substituovány jedním nebo více halogenovými atomy, hydroxylovou skupinou, merkapto-skupinou, kyanoskupinou , nitroskupinou, thiokyanátovou skupinou, karboxylovou skupinou, karbamoylovou skupinou, trifluormethylovou skupinou, C_1 – C_6 alkylovou skupinou, C_3 – C_6 cykloalkylovou skupinou, C_2 – C_6 alkenylovou skupinou, C_1 – C_6 alkoxylovou skupinou, C_3 – C_8 cykloalkoxylovou skupinou, C_1 – C_6 alkylthioskupinou, C_1 – C_3 alkylendioxyskupinou, fenylovou skupinou, fenoxyskupinou, fenylaminoskupinou, benzylovou skupinou, benzoylovou skupinou, fenylsulfinylovou skupinou, fenylsulfonylovou skupinou, 3-fenylureidoskupinou, C_2 –C_7 alkanoylovou skupinou, C_2 –C_7 alkoxykarbonylovou skupinou, C_2 –C_7 alkanoyloxyskupinou, C_2 –C_7 alkanoylaminoskupinou, C_2 –C_7 N-alkylkarbamoylovou skupinou, C_1 –C_6 alkylsulfonylovou skupinou, fenylkarbamoylovou skupinou, N,N-di(C_1 – C_6 alkyl)sulfamoylovou skupinou, či aminoskupinou, mono(C_1 – C_6 alkyl)aminoskupinou, di(C_1 – C_6 alkyl)aminoskupinou, benzylaminoskupinou, C_2 – C_7 (alkoxykarbonyl)aminoskupinou, C_1 – C_6 (alkylsulfonyl)aminoskupinou nebo bis(C_1 – C_6 alkylsulfonyl)aminoskupinou, kde substituentem pro fenylovou skupinu, C_3 – C_8 cykloalkylovou skupinu, C_3 – C_8 cykloalkenylovou skupinu, benzylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh může být jeden nebo více atomů halogenů, kyanoskupina, hydroxylová skupina, aminoskupina, trifluormethylová skupina, C_1 – C_6 alkylová skupina nebo ,

C_1 – C_6 alkoxyskupina, C_1 – C_6 alkylthioskupina, mono(C_1 – C_6 alkyl)amino skupina nebo di(C_1 –C_6 alkyl)aminoskupina za podminky, že rovná-li se k = 2, m = 2, n = 0 a R^1 je nesubstituovaná fenylová skupina, potom:

C_1 – C_6 alkylová skupina je substituentem pro fenylovou skupinu, C_3 – C_8 cykloalkylová skupina, C_3 – C_8 cykloalkenylová skupinu, benzylová skupina, aromatická heterocyklická skupina nebo kondenzovaný kruh v R^6 není substituovaný aminoskupinou a R^6 není benzylová skupina.

Vynález dále popisuje způsob inhibice vazby chemokinu k receptoru cílové buňky nebo jeho působení na cílové buňky za použití farmaceutického přípravku obsahujícího terapeuticky účinné

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množství sloučeniny reprezentované výše uvedeným vzorcem I, farmaceuticky přijatelnou sůl této sloučeniny vzniklou adicí kyseliny nebo farmaceuticky přijatelnou sůl této sloučeniny vzniklou adicí C_1- C_6 alkylu.

Sloučenina reprezentovaná vzorcem I uvedeným výše aktivně inhibuje vazbu chemokinů jako je MIP-1α a /nebo MCP-1 a podobných k receptoru cílové buňky a dále aktivně inhibuje fyziologické projevy buněk, které jsou způsobeny chemokiny jako jsou MIP-1α a /nebo MCP-1 a jim podobných.

Ve výše zmíněném vzorci I, kde R^1 je fenylová skupina, C_3 – C_8 cykloalkylová skupina nebo aromatická heterocyklická skupina mající 1 až 3 heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu, nebo z kombinace předchozích a ve kterých fenyl nebo aromatická heterocyklická skupina jsou kondenzovány s benzenovým kruhem, či aromatickou hetrocyklickou skupinou mající jeden až tři heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu nebo z kombinace předchozích tak, aby tvořily kondenzovaný kruh, kde fenylová skupina, C_3 – C_8 cykloalkylová skupina, aromatická heterocyklická skupina nebo kondenzovaný kruh mohou být substituovány jedním nebo více halogenovými atomy, hydroxylovou skupinou, kyanoskupinou, nitroskupinou, karboxylovou skupinou, karbamoylovou skupinou, C_1 – C_6 alkylovou skupinou, C_3 – C_8 cykloalkoxylovou skupinou, C_2 - C_6 alkenylovou skupinou, C1 – C_6 alkylthioskupinou, C_3 – C_5 alkylenovou skupinou, C_2 - C_4 alkylenoxyskuplinou, C_1- C_3 alkylendioxyskupinou, fenylovou skupinou, fenoxy- skupinou, fenylthioskupinou, benzylovou skupinou, benzyloxyskupinou, C_2 – C_7 alkanoylovou skupinou, C_2 – C_7 alkoxykarbonylovou skupinou, C_2 – C_7 alkanoyloxyskupinou, C_2 –C_7 alkanoylaminoskupinou, C_2 – C_7 N-alkylkarbamoylovou skupinou, C_4 - C_9 N-cykloalkylkarbamoylovou skupinou, C_1 – C_6 alkylsulfonylovou skupinou, C_3 - C_8 (alkoxykarbonyl)methylovou skupinou, N-fenylkarbamoylovou skupinou, pyperidinkarbonylovou skupinou, morfolinkarbonylovou skupinou, 1--pyrolidinkarbonylovou skupinou, bivalentní skupinou reprezentovanou vzorcem: -NH(C=S)O-, aminoskupinou, mono(C_1 – C_6 alkyl)aminoskupinou, nebo di(C_1 – C_6 alkyl)aminoskupinou.

C_3 - C_8 cykloalkylová skupina pro R^1 znamená cyklickou alkylovou skupinu jako je cyklopropylová, cyklobutylová, cyklopentylová, cyklohexylová, cykloheptylová a cyklooktylová skupina, specificky zahrnující cyklopropylovou, cyklopentylovou a cyklohexylovou skupinu.

V aromatické heterocyklické skupině mající 1 až 3 heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu nebo z kombinace předchozích, je pro R^1 specifická například thienylová, furylová, pyrolilová, imidazolylová, pyrazolylová, oxazolylová, isooxazylová, thiazolylová, isothiazolylpyridylová, pyrimidinylová, triazinylová, triazolylová,

oxidiazolylová (furazanylová), thiadizolylová skupina a další, výhodné provedení zahrnuje thienylovou, furylovou, pyrolylovou, izoxazolylovou a pyridylovou skupinu.

Kondenzovaný kruh v R^1 znamená kruh získaný kondenzací s benzenovým kruhem nebo aromatickou heterocyklickou skupinou mající 1 až 3 heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu z fenylové skupiny nebo z aromatické hetrocyklické sloučeniny mající 1 až 3 heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a /nebo dusíkového atomu, na všech možných místech, například vhodné a specifické jsou naftylová, indolylová, benzofuranylová, benzothienylová, chinolylová, benzimidazolylová, benzoxazylová, benztriazolylová, benzoxadiazolylová benzfurazanylová a benzothiazolylová skupina.

Mezi výše jmenovanými se jeví zvláště výhodné pro R^1 specifické užití fenylové a isoxazolylové skupiny .

Halogenový atom jako substituent pro fenylovou skupinu, C_3- C_8 cykloalkylovou skupinu, .aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1 představuje atom fluoru, atom chloru, atom bromu a atom jodu , ve výhodném provedení atom fluoru, chloru a bromu.

$C_1 - C_6$ alkylová skupina jako substituent pro R^1 znamená přímý nebo větvený řetězec $C_1 - C_6$ alkylových skupin jako jsou : methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-oktyl, isopropyl, isobutyl, sec-butyl, terc-butyl, isopentyl neopentyl, terc-pentyl, isohexyl, 2-methylpentyl, 1--ethylbutyl, ve zvláště výhodném provedení se specificky užívají především methylové, ethylové, propylové a isopropylové skupiny.

C_3- C_8 cykloalkylová skupina jako substituent pro R^1je definovaná stejně, jako výše zmíněná C_3- C_8 cykloalkylová skupina pro R^1, stejné příklady jsou ve výčtu pro výhodné užtití.

C_2 - C_6 alkenylová skupina jako substituent pro R^1 znamená přímý nebo větvený řetězec C_2-C_6 alkylových skupin jako jsou: vynyl, alyl, 1-propenyl, 2-butenyl, 3-butenyl, 2-methyl-1--propenyl, 4-pentenyl, 5-hexenyl, 4-methyl-3-pentenyl a další, ve výhodném provedení vynálezu jsou to vinylová a 2-methyl-1-propenylová skupina.

$C_1 - C_6$ alkoxylová skupina jako substituent pro R^1 znamená skupinu sestávající ze skupin již dříve zmíněných $C_1 - C_6$ alkylových a oxyskupin, ve výhodném provedení například metoxy a etoxyskupina.

$C_1 - C_6$ alkylthioskupina jako substituent pro R^1 znamená skupinu sestávající ze skupin již dříve zmíněných $C_1 - C_6$ alkylových a thioskupin, ve výhodném provedení například methylthio a ethylthioskupina.

$C_3 - C_5$ alkylenová skupina jako substituent pro R^1 znamená $C_3 - C_5$ bivalentní alkylenovou skupinu jako je trimethylen, tetramethylen, pentamethylen a 1-methyltrimethylen, ve výhodném uspořádání trimethylenová a tetramethylenová skupina.

C_2 - C_4 alkylenoxylová skupina jako substituent pro R^1 znamená skupinu sestávající ze skupin již dříve zmíněných pro C_2- C_4 bivalentní alkylenové skupiny a oxyskupiny jako jsou ethylenoxy (-CH_2 CH_2O-), trimethylenoxy (-CH_2 CH_2 CH_2O-), tetramethylenoxy (-CH_2 CH_2 CH_2 CH_2O-) a 1,1--dimethylethylenoxy (-CH_2 $C(CH_3)_2O$-) skupiny, ve výhodnémm provedení ethylenoxy a trimethylenoxy.

C_1- C_3 alkylendioxyskupina jako substituent pro R^1 znamená skupinu sestávající ze skupin C_1- -C_3 bivalentních alkylenových skupin a dvou oxyskuplin jako je methylendioxy (-OCH_2O-), ethylendioxy (-OCH_2CH_2O-), trimethylendioxy (-$OCH_2CH_2CH_2O$-) a propylendioxy (-$OCH_2CH(CH3)O$-) skupiny. Ve výhodném provedení se specificky využívají například methylendioxy a ethylendioxyskupiny.

$C_2 - C_7$ alkanoylová skupina jako substituent pro R^1 znamená přímý nebo větvený řetězec $C_2 - C_7$ alkanoylových skupin jako jsou: acethyl, propanoyl, butanoyl, pentanoyl, hexanoyl, isobutyryl, 3-methylbutanoyl, 2-methylbutanoyl, pivaloyl, 4-methylpentanoyl, 3,3-dimethylbutanoyl, 5-methylhexanoyl a další obdobné, kde se ve výhodném provedení vynálezu používá acetylová skupina.

$C_2 - C_7$ alkoxykarbonylová skupina jako substituent pro R^1 znamená skupinu sestávající ze skupin již dříve zmíněných pro C_1- C_6 alkoxylovou skupinu a karbonylovou skupinu, ve zvláště výhodném provedení vynálezu se používá metoxykarbonylová a etoxykarbonylová skupina.

$C_2 - C_7$ alkanoyloxyskupina jako substituent pro R^1 znamená skupinu sestávající ze skupin již dříve zmíněných pro C_2- C_7 alkanoylovou skupinu a oxyskupinu, ve zvláště výhodném provedení vynálezu se používá acethyloxyskupina.

$C_2 - C_7$ alkanoylaminoskupina jako substituent pro R^1 znamená skupinu sestávající ze skupin již dříve zmíněných pro C_2- C_7 alkanoylovou skupinu a aminoskupinu, ve zvláště výhodném provedení vynálezu se používá acetylaminoskupina.

$C_2 - C_7$ N-alkylkarbamoylová skupina jako substituent pro R^1 znamená skupinu sestávající ze skupin již dříve zmíněných pro C_1- C_6 alkylové skupiny a karbamoylové skupiny, ve zvláště výhodném provedení vynálezu se používá N-methylkarbamoylová a N-ethylkarbamoylová skupina.

$C_2 - C_7$ N-alkylkarbamoylová skupina jako substituent pro R^1 znamená skupinu sestávající ze skupiny již dříve zmíněné pro C_1- C_6 alkylovou skupinu a karbamoylové skupiny, ve zvláště výhodném provedení vynálezu se používá N-methylkarbamoylová a N-ethylkarbamoylová skupina.

$C_4 - C_9$ N-cykloalkylkarbamoylová skupina jako substituent pro R^1 znamená skupinu sestávající ze skupiny již dříve zmíněné pro C_3- C_8 cykloalkylové skupiny a karbamoylové skupiny, ve zvláště výhodném provedení vynálezu se používá N-cyklopentylkarbamoylová a N--cyklohexylkarbamoylová skupina.

$C_1 - C_6$ alkylsulfonylová skupina jako substituent pro R^1 znamená skupinu sestávající ze skupin již dříve zmíněných $C_1 - C_6$ alkylových a sulfonylových skupin, ve výhodném provedení například methylsulfonylová skupina.

$C_3 - C_8$ (alkoxykabonyl)methylová skupina jako substituent pro R^1 znamená skupinu sestávající ze skupin již dříve zmíněných pro C_2- C_7 alkoxylkarbonylovou skupinu a methylovou skupinu, ve zvláště výhodném provedení vynálezu se používá (metoxykarbonyl)methylová a (etoxykarbonyl)methylová skupina.

mono($C_1 - C_6$ alkyl)aminoskupina jako substituent pro R^1 znamená aminoskupinu substituovanou jednou z již dříve zmíněných $C_1 - C_6$ alkylových skupin, ve výhodném provedení například methylamino a ethylamino skupinu.

di($C_1 - C_6$ alkyl)aminoskupina jako substituent pro R^1 znamená aminoskupinu substituovanou dvěma stejnými nebo rozdílnými $C_1 - C_6$ alkylovými skupinami, které byly již dříve zmíněny, ve výhodném provedení například dimethylamino a diethylamino a N-ethyl-N-methylaminoskupinu.

Mezi uvedenými skupinami se s výhodou používají následující skupiny jako substituenty pro fenylové skupiny, $C_3 - C_8$ cykloalkylové skupiny, aromatické heterocyklické skupiny nebo pro kondenzovaný kruh v R^1: hydroxyskupina, $C_1 - C_6$ alkylová skupina ,

$C_2 - C_6$ alkenylová skupina, $C_1 - C_6$ alkoxylová skupina, $C_1 - C_6$ alkylthioskupina, $C_2 - C_4$ alkylenoxyskupina, methylendioxyskupina, N-fenylkarbamoylová skupina, aminoskupina a mono(C_1-C_6 alkyl)aminoskupina a di($C_1 - C_6$ alkyl)aminoskupina.

Mimoto, výše zmíněné substituenty fenylové, $C_3 - C_8$ cykloalkylové skupiny, aromatické heterocyklické skupiny nebo pro kondenzovaný kruh v R^1, jsou volitelně substituované jedním nebo více halogenovými atomy, hydroxylovou skupinou, aminoskupinou a trifluormethylovou skupinou,

$C_1 - C_6$ alkylovou skupinou nebo $C_1 - C_6$ alkoxylovou skupinou. Halogenový atom, $C_1 - C_6$ alkylová a $C_1 - C_6$ alkoxylová skupina jsou tytéž, které byly výše definovány jako substitutenty pro fenylovou

skupinu, C_3 – C_8 cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1. Tytéž příklady lze považovat za příklady výhodného provedení vynálezu.

Ve výše uvedeném vzorci I R^2 reprezentuje vodíkový atom, C_1 – C_6 alkylovou skupinu, C_2 –C_7 alkoxykarbonylovou skupinou, hydroxylovou skupinu nebo fenylovou skupinu, ve kterých C_1 – C_6 alkylová nebo fenylová skupina jsou substituovány jedním nebo více halogenovými atomy, hydroxylovou skupinou, C_1 – C_6 alkylovou skupinou nebo C_1 – C_6 alkoxylovou skupinou. Rovná-li se j = 0, potom R^2 není hydroxyskupina.

C_1 – C_6 alkylová a C_2 – C_7 alkoxykarbonylová skupina jsou pro R^2 tytéž, jako dříve uvedené substituenty pro fenylovou skupinu, C_3 – C_8 cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1. Tytéž příklady lze považovat za příklady výhodného provedení vynálezu.

Halogenový atom, C_1 – C_6 alkylová a C_1 – C_6 alkoxylová skupina jako substituenty pro C_1 – C_6 alkylovou nebo fenylovou skupinu v R^2 jsou tytéž, jako byly výše definovány jako substitutenty pro fenylovou skupinu, C_3 – C_8 cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1. Tytéž příklady lze považovat za příklady výhodného provedení vynálezu.

Ve zvláště výhodném provedení vynálezu se v R^2 z uvedených substituentů preferuje užití vodíkového atomu.

Ve výše uvedeném vzorci I j reprezentuje celé číslo od 0 do 2. Ve zvláště výhodném provedení je j rovno 0.

Ve výše uvedeném vzorci I k reprezentuje celé číslo od 0 do 2 a m reprezentuje celé číslo od 2 do 4. Ve zvláště výhodném provedení vynálezu se používá dvakrát substituovaný pyrolidin, ve kterém k je 0 a m je rovno 3, dále třikrát substituovaný pyrolidin, ve kterém k = 1 a m = 2, nebo třikrát sustituovaný piperidin, ve kterém je k rovno 1 a m je rovno 3, či 4 krát substituovaný piperidin, kde k je rovno 2 a m je rovno 2, nebo třikrát substituovaný hexahydroazepin, kde k = 1 a m = 4.

Ve výše uvedeném vzorci I n reprezentuje 0 nebo 1.

Ve zvláště výhodném uspořádání vynálezu se užívají 3-amidopyrolidiny, kde k je 1, m je rovno 2 a je rovno 0 a dále 4-(amidomethyl)piperidiny, kde k = 2, m = 2 a n = 1.

R^3 ve výše uvedeném vzorci I reprezentuje vodíkový atom nebo C_1 – C_6 alkylovou skupinu, která může být substituována jednou nebo dvěma fenylovými skupinami, z nichž každá může být substituvána jedním nebo dvěma halogenovými atomy, hydroxyskupinou, C_1 – C_6 alkylovou skupinou nebo C_1 – C_6 alkoxylovou skupinou.

$C_1 - C_6$ alkylová skupina je pro R^3 taž, jako dříve uvedené substituenty pro fenylovou skupinu, $C_3 - C_8$ cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1. Ve výhodném provedení vynálezu se používají přednostně methylová, ethylová a propylová skupina.

Halogenový atom, $C_1 - C_6$ alkylová a $C_1 - C_6$ alkoxylová skupina jako substituenty pro fenylovou skupinu, která je substituentem pro $C_1 - C_6$ alkylovou skupinu v R^3 jsou tytéž, jako byly výše definovány jako substitutenty pro fenylovou skupinu, $C_3 - C_8$ cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1. Tytéž příklady lze považovat za příklady výhodného provedení vynálezu.

Ve výhodném uspořádání se z výše uvedených substituentů preferuje v R^3 použití vodíkového atomu.

R^4 a R^5 ve výše uvedeném vzorci I a reprezentují dvě stejné nebo rozdílné skupiny, představované vodíkovým atomem, hydroxylovou skupinou, fenylovou skupinou nebo $C_1 - C_6$ alkylovou skupinu, která může být substituována jedním nebo dvěma halogenovými atomy, hydroxylovou skupinou, kyanoskupinou, nitroskupinou, karboxylovou skupinou, karbamoylovou skupinou, merkaptoskupinou, quanidinovou skupinou, $C_3 - C_8$ cykloalkylovou skupinou, $C_1 - C_6$ alkoxylovou skupinou, C_1–C_6 alkylthioskupinou, fenylovou skupinou substituovanou jedním nebo dvěma halogenovými atomy, hydroxyskupinou, $C_1 - C_6$ alkylovou skupinou nebo $C_1 - C_6$ alkoxylovou skupinou, nebo bezyloxyskupinou, fenoxyskupinou, benzyloxyskupinou, benzyloxyskupinou, fenoxyskupinou, benzyloxykarbonylovou skupinou, $C_2 - C_7$ alkanoylovou skupinou, $C_2 - C_7$ alkanoyloxyskupinou, $C_2 - C_7$ alkanoylamino- skupinou, $C_2 - C_7$ N-alkylkarbamoylovou skupinou,

$C_1 - C_6$ alkylsulfonylovou skupinou, aminoskupinou, mono($C_1 - C_6$ alkyl)aminoskupinou, di($C_1 - C_6$ alkyl)aminoskupinou nebo aromatickou hetrocyklickou skupinou mající jeden až tři heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu, nebo z kombinace předchozích, který může být kondenzovaný s benzenovým kruhem, nebo R^4 a R^5 tvoří dohromady tří až šestičlenné cyklické uhlovodíky.

$C_1 - C_6$ alkylová skupina je pro R^4 a R^5 taž, jako dříve uvedené substituenty pro fenylovou skupinu, $C_3 - C_8$ cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1. Tytéž příklady lze považovat za příklady výhodného provedení vynálezu.

Halogenový atom, $C_1 - C_6$ alkoxylová a $C_1 - C_6$ alkylthioskupina, $C_2 - C_7$ alkanoylová skupina, $C_2 - C_7$ alkanoyloxyskupina, $C_2 - C_7$ alkanokarboxylová skupina $C_2 - C_7$ alkanoylaminoskupina,

$C_2 - C_7$ N-alkylkarbamoylová skupina, $C_1 - C_6$ alkylsulfonylová skupina, aminoskupina, mono($C_1 - C_6$ alkyl)aminoskupina, di($C_1 - C_6$ alkyl)aminoskupina jako substituenty pro $C_1 - C_6$ alkylovou skupinu v

R^4 a R^5 jsou tytéž, jako byly výše definovány jako substitutenty pro fenylovou skupinu, $C_3 - C_8$ cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1. Tytéž příklady lze považovat za příklady výhodného provedení vynálezu.

$C_3 - C_8$ cykloalkylová skupina a aromatická heterocyklická skupina mající 1 až 3 heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu, nebo z kombinace předchozích jako substituenty pro $C_1 - C_6$ alkylovou skupinu v R^4 a R^5 jsou tytéž, jako byly výše definovány pro R^1. Tytéž příklady lze považovat za příklady výhodného provedení vynálezu.

Halogenový atom, $C_1 - C_6$ alkylová skupina jako substituenty pro fenylovou skupinu, která je substituentem pro $C_1 - C_6$ alkylovou v R^4 a R^5 jsou tytéž, jako byly výše definovány jako substitutenty pro fenylovou skupinu, $C_3 - C_8$ cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1. Tytéž příklady lze považovat za příklady výhodného provedení vynálezu.

Tří a šestičlenné kruhy sestávající z R^4 a R^5 a sousedního uhlíkatého atomu zahrnují cyklopropan, cyklobutan, cyklopentan a cyklohexan.

Ve výhodném provedení vynálezu se jako R^4 a R^5 využívá vodíkového atomu a $C_1 - C_6$ alkylové skupiny.

Ve výše uvedeném vzorci I je G skupina reprezentovaná -CO-, $-SO_2-$, -CO-O-, $-NR^7$-CO-, $-CO-NR^7-$, -NH-CO-NH-, -NH-CS-NH-, $-NR^7-SO_2-$, $-SO_2-NR^7-$, -NH-CO-O- nebo –O-CO-NH-, kdy R^7 je vodíkový atom $C_1 - C_6$ alkylová skupina, nebo R^5 společně s R^7 reprezentují $C_2 - C_5$ alkylenovou skupinu.

Ve výše uvedeném vzorci –CO- znamená karbonylovou skupinu, $-SO_2-$ sulfonylovou skupinu, -CS-thiokarbonylovou skupinu. Ve výhodném provedení je G skupina vybrána z těch, které jsou reprezentovány vzorci $-NR^7$-CO- a -NH-CO-NH-.

$C_1 - C_6$ alkylová skupiny jsou pro R^7 tytéž, jako dříve uvedené substituenty pro fenylovou skupinu, $C_3 - C_8$ cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh v R^1. Tytéž příklady lze považovat za příklady výhodného provedení vynálezu.

$C_2 - C_5$ alkylenové skupiny sestávající z R^5 a R^7 mají rovný či rozvětvený $C_2 - C_5$ řetězec, jako je u methylenové, propylenové, trimethylenové, tetramethylenové,

1-methyltrimethylenové, pentamethylenové skupiny a dalších obdobných, ve výhodném provedení vhodné a specifické užití zahrnuje ethylenovou, trimethylenovou a tetramethylenovou skupinu.

Ve výhodném provedení se preferuje pro R^7 vodíkový atom.

R^6 ve výše uvedeném vzorci I je reprezentován fenylovou skupinou, $C_3 - C_8$ cykloalkylovou skupinou, $C_3 - C_8$ cykloalkenylovou skupinou, benzylovou skupinou nebo aromatickou heterocyklickou skupinou mající jeden až tři heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu nebo z kombinace předchozích, V R^6 fenylová a aromatická heterocyklická skupina mohou být spojeny s benzenovým kruhem nebo aromatickou heterocyklickou skupinou mající jeden až tři heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu nebo z kombinace předchozích za tvorby kondenzovaných kruhů.

$C_3 - C_8$ cykloalkylovou skupinu, $C_3 - C_8$ cykloalkenylovou skupinu, benzylovou skupinu nebo aromatickou heterocyklickou skupinu či kondenzované kruhy lze substituovat jedním nebo více halogenovými atomy, hydroxylovou skupinou, merkaptoskupinou, kyanoskupinou, nitroskupinou, thiokyanaotvou skupinou, karboxylovou skupinou, karbamoylovou skupinou, trifluormethylovou skupinou, $C_1 - C_6$ alkylovou skupinou, $C_3 - C_6$ cykloalkylovou skupinou, $C_2 - C_6$ alkenylovou skupinou, $C_1 - C_6$ alkoxylovou skupinou, $C_3 - C_8$ cykloalkyoxyskuplinou, $C_1 - C_6$ alkylthioskupinou, $C_1 - C_3$ alkylendioxyskuplinou, fenylovou skupinou, fenoxyskupinou, fenylaminoskupinou, benzylovou skupinou, benzoylovou skupinou, fenylsulfinylovou skupinou, 3-fenylureidoskupinou,

$C_2 - C_7$ alkanoylovou skupinou, $C_2 - C_7$ alkoxykarbonylovou skupinou, $C_2 - C_7$ alkanoyloxyskuplinou, $C_2 - C_7$ alkanoylovou skupinou,$C_2 - C_7$ alkanoylaminoskupinou, $C_2 - C_7$ N-alkylkarbamoylovou skupinou, $C_1 - C_6$ alkylsulfonylovou skupinou, fenylkarbamoylovou skupinou, N,N-di($C_1 - C_6$ alkyl)sulfamoylovou skupinou, aminoskupinou, mono($C_1 - C_6$ alkyl)aminoskupinou,

di($C_1 - C_6$ alkyl)aminoskupinou, benzylaminoskupinou, $C_2 - C_7$ (alkoxykarbonyl)aminoskupinou,

$C_1 - C_6$ (alkylsulfonyl)aminoskupinou nebo bis($C_1 - C_6$ alkylsulfonyl)aminoskupinou.

$C_3 - C_8$ cykloalkylová skupina a aromatická heterocyklická skupina mající 1 až 3 heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu, nebo z kombinace předchozích a kondenzovaný kruh jsou tytéž, jako byly výše definovány pro R^1. Tytéž příklady sloučenin se uvádějí ve výhodném provedení vynálezu.

Halogenový atom, $C_1 - C_6$ alkylová skupina, $C_2 - C_6$ alkenylová skupina, $C_1 - C_6$ alkoxylová skupina, $C_1 - C_6$ alkylthioskupina, $C_1 - C_3$ alkylendioxyskupina, $C_2 - C_7$ alkanoylová skupina, $C_2 - C_7$ alkoxykarbonylová skupina, $C_2 - C_7$ alkanoyloxyskupina, $C_2 - C_7$ alkanoylaminoskupina, $C_2 - C_7$ N--alkylkarbamoylová skupina, $C_1 - C_6$ alkylsulfonylová skupina, mono($C_1 - C_6$ alkyl)aminoskupina a di($C_1 - C_6$ alkyl)aminoskupina jako substiuenty pro fenylovou skupinu, $C_3 - C_8$ cykloalkylovou skupinu, $C_3 - C_8$ cykloalkenylovou skupinu, benzylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh R^6jsou definovány stejně jako shora zmíněné substituenty pro

fenylovou skupinu, C_3 – C_8 cykloalkylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh R^1, také stejné příklady sloučenin jsou uvedeny pro výhodné provedení vynálezu.

C_3 – C_8 cykloalkylová skupina jako substituent pro R^6 je stejná, jako byla definována pro shora zmíněnou C_3 – C_8 cykloalkylovou skupinu pro R^1, stejné příklady jsou také uvedeny v příkladech pro výhodné uspořádání vynálezu.

C_3 – C_8 cykloalkylová skupina jako substituent pro R^6 znamená skupinu obsahující shora zmíněnou C_3 – C_8 cykloalkylovou skupinu a oxyskuplinu, ve výhodném uspořádání hlavně cyklopropyloxy, cyklopentyloxy a cyklohexyloxyskupina.

N,N-di(C_1 – C_6 alkyl)sulfamoylová skupina jako substituent R^6 znamená sulfamoylovou skupinu substituovanou dvěma stejnými nebo rozdílnými C_1 – C_6 alkylovými skupinami zmíněnými shora, přednostně a výhodně hlavně například N,N-dimethylsulfamoylovou, N,N--diethylsulfamoylovou a N-ethyl-N-methylsulfamoylovou skupinou.

C_2 – C_7 (alkoxykarbonyl)aminoskupina jako substituent R^6 znamená skupinu sestávající ze shora zmíněné C_2 – C_7 alkoxykarbonylové skupiny a aminoskupiny, ve výhodném provedení například (methylsulfonyl)aminoskupina.

bis (C_1 – C_6 alkylsulfonyl)aminoskupina. jako substituent R^6 znamená aminoskupinu substituovanou dvěma stejnými nebo rozdílnými C_1 – C_6 alkylsulfonylovými skupinami zmíněnými shora, přednostně a výhodně například bis(methylsulfonyl)aminoskupinu.

Ve výhodném uspořádání jsou substituenty pro fenylovou skupinu, C_3 – C_8 cykloalkylovou skupinu, C_3 – C_8 cykloalkenylovou skupinu, benzylskupinu a aromatickou heterocyklickou skupinu nebo kondenzovaný kruh použity následně: halogenový atom, merkaptoskupina, nitroskupina, thiokyanatoskupina, trifluormethylová skupina, C_1 – C_6 alkylová skupina, C_1 – C_6 alkoxylová skupina, fenylová skupina, fenylsulfonylová skupina, C_2 – C_7 alkanoyl skupina nebo aminoskupina.

Mimoto mohou být výše uvedené substituenty fenylové skupiny, C_3 – C_8 cykloalkylové skupiny, C_3 – C_8 cykloalkenylové skupiny, benzylové skupiny, aromatické heterocyklické skupiny nebo kondenzovaného kruhu v R^6 substituovány jedním nebo více halogenovými atomy, kyanoskupinou, hydroxylovou skupinou, aminoskupinou, trifluormethylovou skupinou, C_1 – C_6 alkylovou skupinou, C_1 – C_6 alkoxylovou skupinou, C_1 – C_6 alkylthioskupinou, mono(C_1 – C_6 alkyl)aminoskupinou.

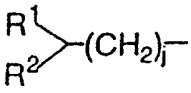
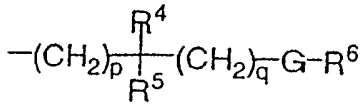
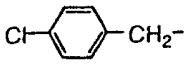
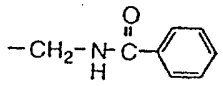
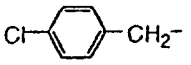
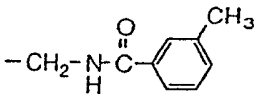
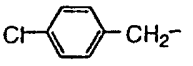
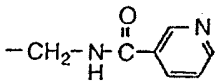
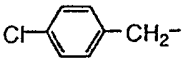
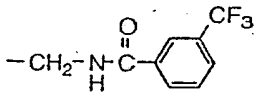
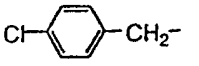
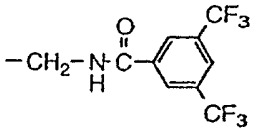
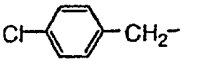
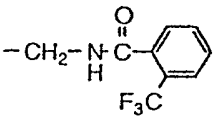
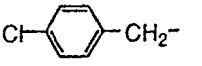
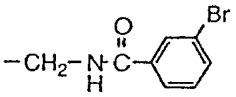
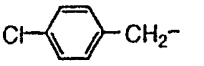
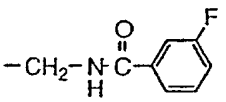
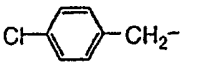
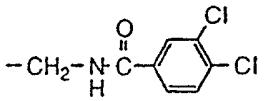
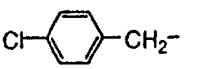
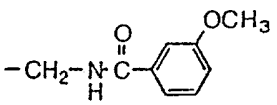
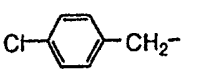
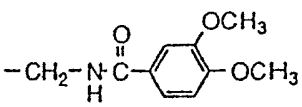
Halogenový atom, C_1 – C_6 alkylová skupina, C_1 – C_6 alkoxylová skupina, C_1 – C_6 alkylthioskupina, mono(C_1 – C_6 alkyl)aminoskupina nebo di(C_1 – C_6 alkyl)aminoskupina jsou stejné, jaké byly definovány v předchozím textu jako substituenty fenylové skupiny, C_3 – C_8 cykloalkylové

skupiny, aromatické heterocyklické skupiny nebo kondenzovaného kruhu v R^1, a proto platí stejné příklady výhodného uspořádání vynálezu.

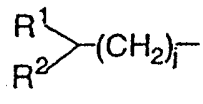
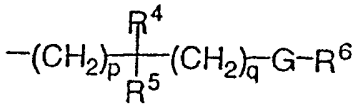
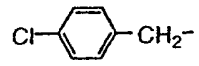
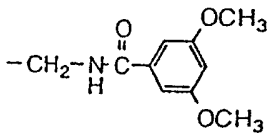
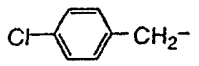
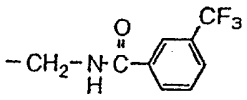
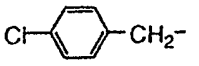
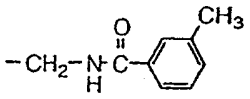
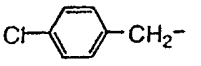
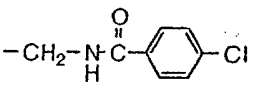
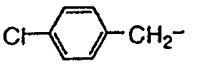
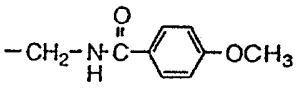
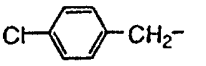
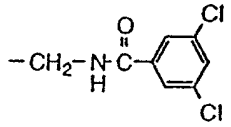
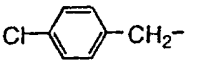
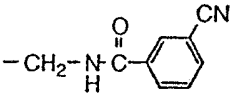
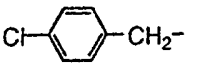
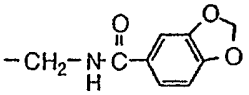
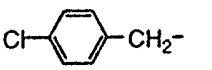
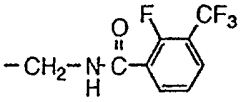
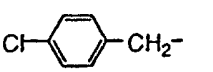
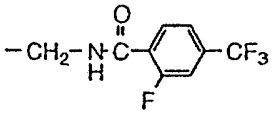
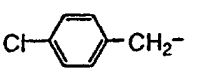
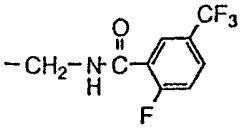
Sloučenina reprezentovaná vzorcem I, který je uveden v předchozím textu, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny k této sloučenině nebo farmaceuticky přijatelná sůl této sloučeniny vzniklá adicí C_1 – C_6 alkylové skupiny je využita k přípravě antagonisty receptoru pro chemokin. Ve vynálezu je definováno terapeuticky účinné množství sloučeniny a nosič/nebo rozpouštědlo použité k přípravě farmaceutického přípravku. Deriváty cyklických aminů reprezentované vzorcem I , jejich farmaceuticky přijatelné soli vzniklé adici kyseliny či C_1 – C_6 alkylové skupiny mohou být podávány buď orálně či parenterálně, například intravenózně , subkutánně, perkutánně nebo intrarektálně.Orální administrace využívá přípravky ve formě tablet, pilulek, granulí, prášku, roztoku, suspenze, kapslí a tak dále.Tablety mohou být například připraveny z plnidla, jako je laktóza, škrob či krystalická celulóza; vazebného nosiče, jako je karboxymethylcelulóza, methylcelulóza a polyvinylpyrolidon; dezintegrátoru jako je alginát sodný, uhličitan sodný a lauryl sulfát a další. Pilulky, prášek a granulované přípravky se připraví pomocí standardních metod pomocí činidel popsaných v předchozím odstavci. Roztok nebo suspenze může být připravena pomocí standardní metody využívající estery glycerinu, jako je trikaprilin a triacetin nebo alkoholů jako je ethanol. Kapsle lze připravit obalením granulí nebo prášku, či roztoku do želatiny, a podobně.Subkutánní, intramuskulární nebo intravenózní injekce se připraví pomocí vodných či nevodných rozpouštědel. Vodný roztok například může obsahovat izotonický roztok chloridu sodného. Nevodné roztoky obsahují například propylenglykol, polyethylenglykol, olivový olej, ethyloleát, a další. Do roztoků jsou přidána antiseptika a stabilizátory. Pro injekční použití jsou sterilizovány pomocí filtrace přes bakteriální filtry nebo kombinací desinfektantů.Perkutanní administrace se děje ve formě mazání či krému, mast se připraví pomocí standardních metod za užití mastných olejů, jako je ricinový a olivový olej, vazelína. Krémy se připraví pomocí masných olejů nebo emulzních činidel, jako je diethylenglykol a sorbitanové estery mastných kyselin.Pro intrarektální administraci lze použít standardní metody přípravy čípků, jako jsou hladké želatinové kapsle, a tak podobně.eriváty cyklických aminů podle vynálezu a jejich farmaceuticky přijatekné soli vzniklé adicí kyseliny nebo C_1- C_6 alkylové skupiny jsou administrovány v dávkách, které závisí na typu onemocnění, cestě administrace, věku a pohlaví pacienta, závažnosti onemocnění, ale v průměru se většinou pohybují v rozmezí 1 až 500mg/den na dospělého pacienta.

Příklady přípravy sloučenin cyklického aminu podle vzorce I zahrnující sloučeniny se všemi substituenty jsou uvedeny v následujících tabulkách 1,1 až 1.201.V tabulkách 1,1 - 1.201. použitý výraz chiralita znamená konfiguraci na asymetrickém uhlíku v cyklickém aminu. R znamená, že asymetrický uhlíkový atom má R konfiguraci, S znamená, že na asymetrickém uhlíkovém atomu je konfigurace S a znakem - je vyznačena existence racemické směsi, nebo to, že sloučenina nemá asymetrický uhlík v kruhu obsahujícím dusíkatý atom.

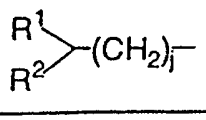
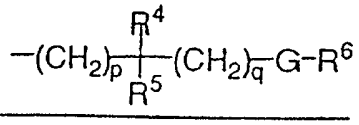
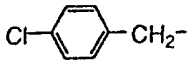
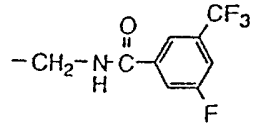
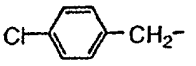
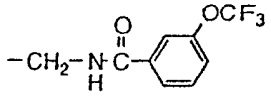
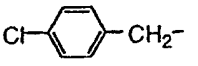
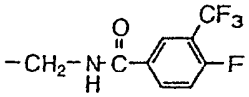
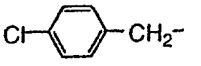
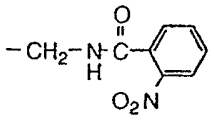
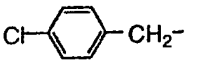
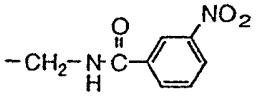
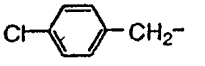
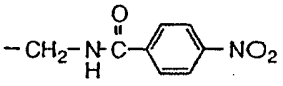
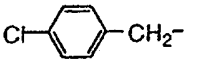
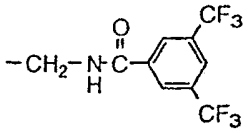
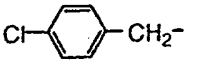
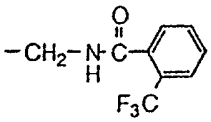
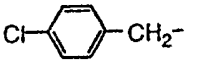
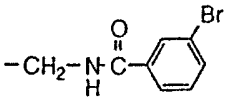
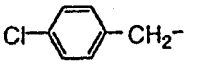
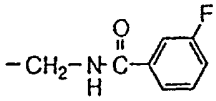
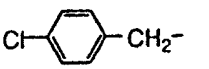
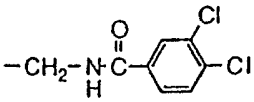
Tabulka 1.1

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4		1	2	0	-	H	
5		1	2	0	S	H	
6		1	2	0	S	H	
7		1	2	0	S	H	
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9		1	2	0	S	H	
10		1	2	0	S	H	
11		1	2	0	S	H	

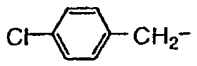
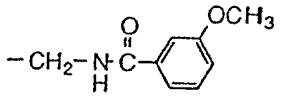
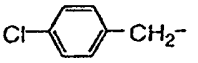
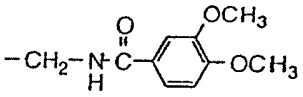
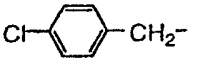
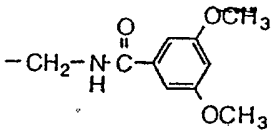
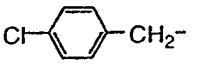
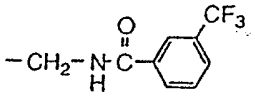
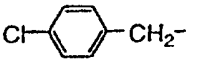
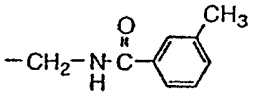
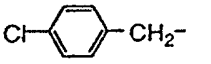
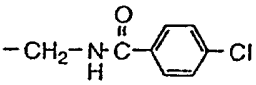
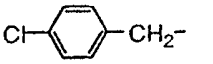
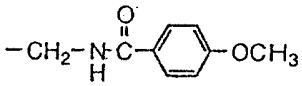
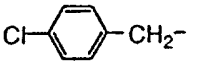
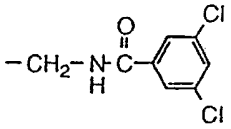
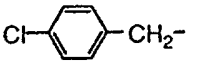
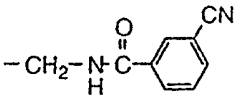
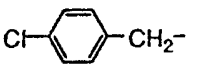
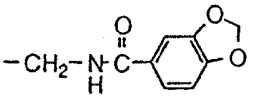
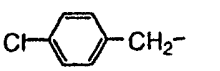
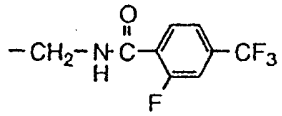
Tabulka 1.2

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15		1	2	0	S	H	
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17		1	2	0	S	H	
18		1	2	0	S	H	
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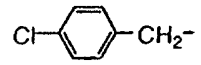
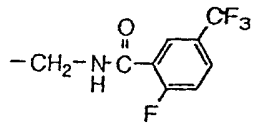
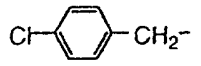
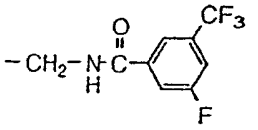
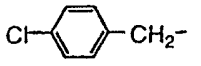
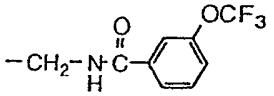
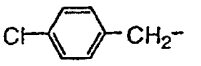
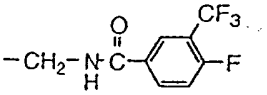
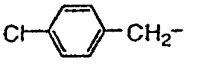
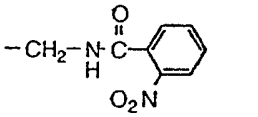
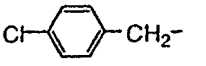
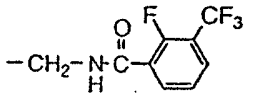
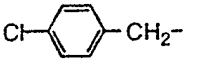
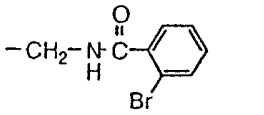
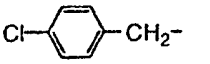
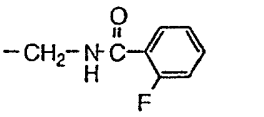
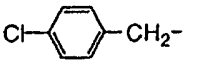
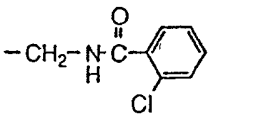
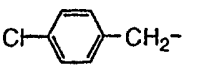
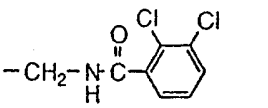
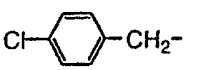
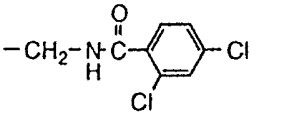
Tabulka 1.3

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27		1	2	0	S	H	
28		1	2	0	S	H	
29		1	2	0	R	H	
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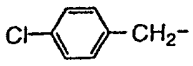
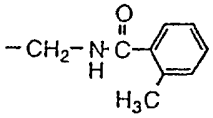
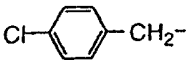
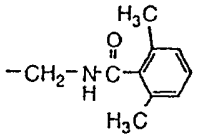
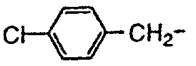
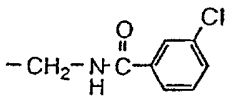
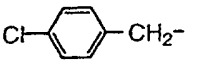
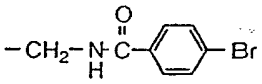
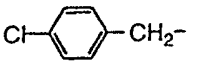
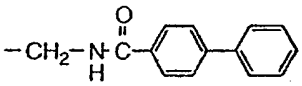
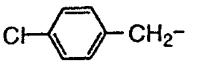
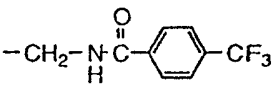
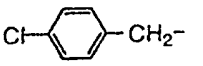
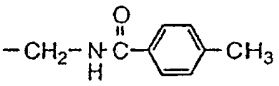
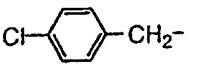
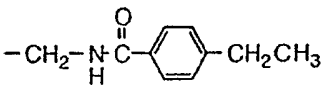
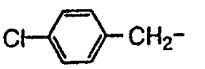
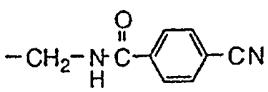
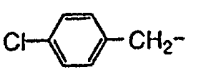
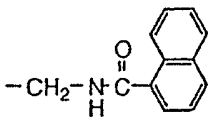
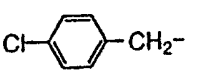
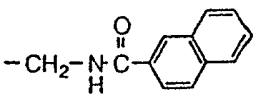
Tabulka 1.4

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35		1	2	0	R	H	
36		1	2	0	R	H	
37		1	2	0	R	H	
38		1	2	0	R	H	
39		1	2	0	R	H	
40		1	2	0	R	H	
41		1	2	0	R	H	
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43		1	2	0	R	H	
44		1	2	0	R	H	

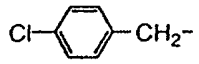
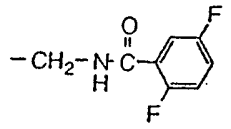
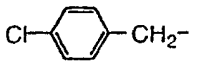
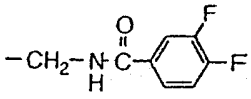
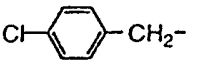
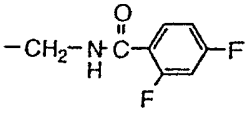
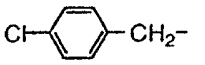
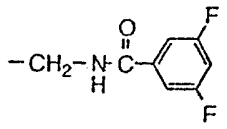
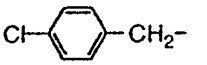
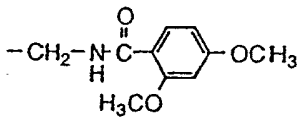
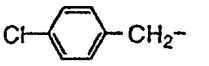
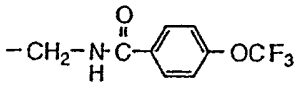
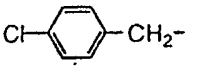
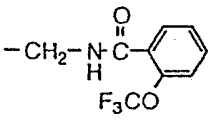
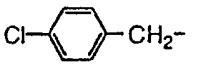
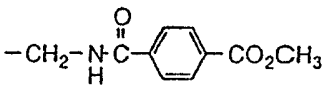
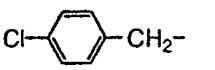
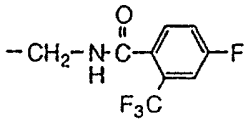
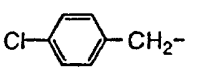
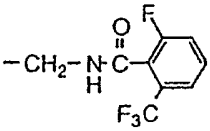
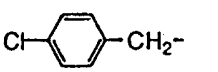
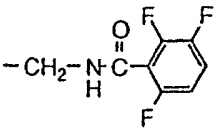
Tabulka 1.5

Sloučč.	R^1, R^2, $(CH_2)_i$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
45		1	2	0	R	H	
46		1	2	0	R	H	
47		1	2	0	R	H	
48		1	2	0	R	H	
49		1	2	0	R	H	
50		1	2	0	R	H	
51		1	2	0	R	H	
52		1	2	0	R	H	
53		1	2	0	R	H	
54		1	2	0	R	H	
55		1	2	0	R	H	

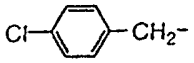
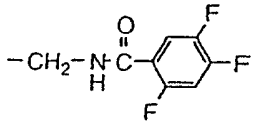
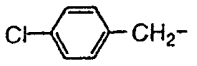
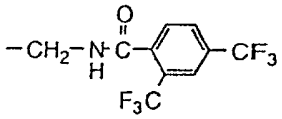
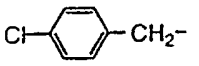
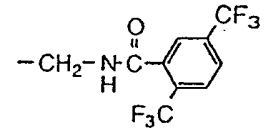
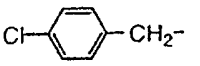
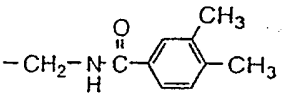
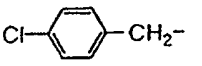
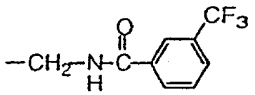
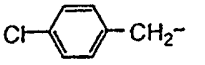
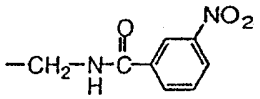
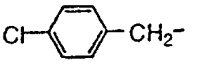
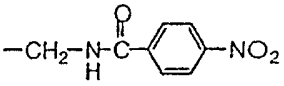
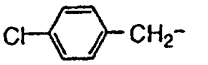
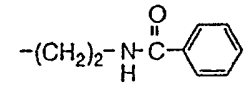
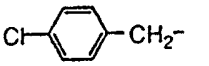
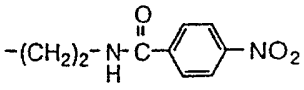
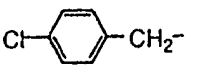
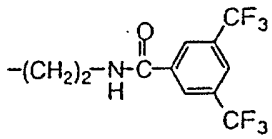
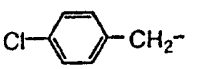
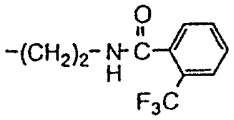
Tabulka 1.6

Slouč.č.	R^1, R^2, $(CH_2)_i$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
56		1	2	0	R	H	
57		1	2	0	R	H	
58		1	2	0	R	H	
59		1	2	0	R	H	
60		1	2	0	R	H	
61		1	2	0	R	H	
62		1	2	0	R	H	
63		1	2	0	R	H	
64		1	2	0	R	H	
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66		1	2	0	R	H	

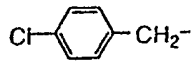
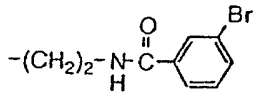
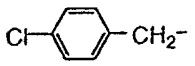
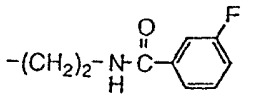
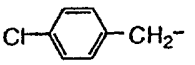
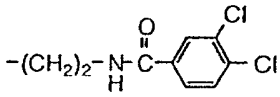
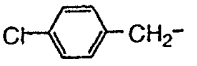
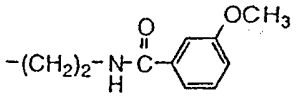
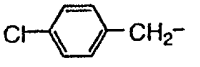
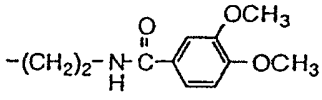
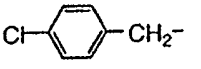
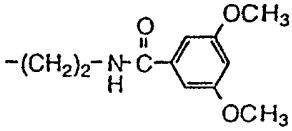
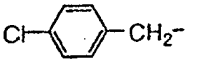
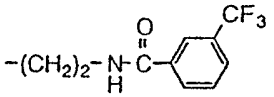
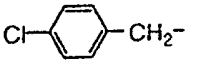
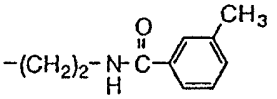
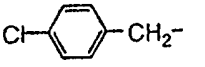
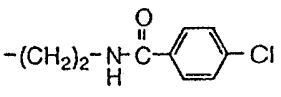
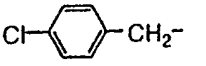
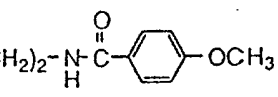
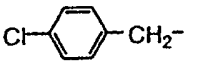
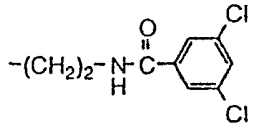
Tabulka 1.7

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
67		1	2	0	R	H	
68		1	2	0	R	H	
69		1	2	0	R	H	
70		1	2	0	R	H	
71		1	2	0	R	H	
72		1	2	0	R	H	
73		1	2	0	R	H	
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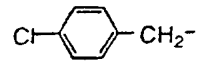
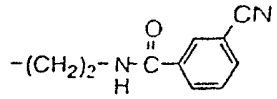
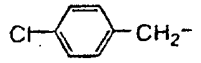
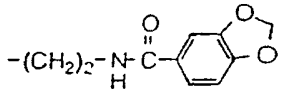
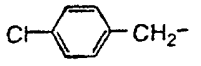
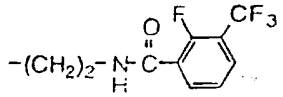
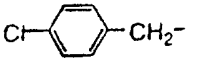
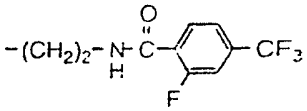
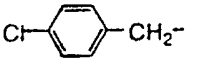
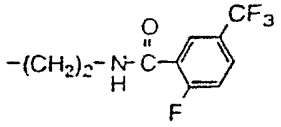
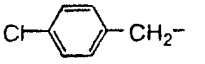
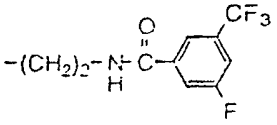
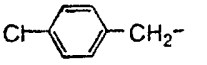
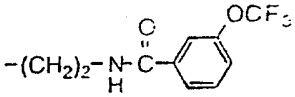
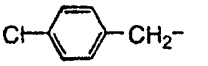
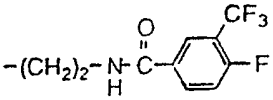
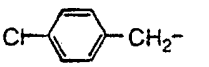
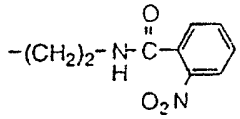
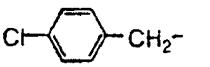
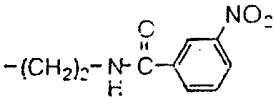
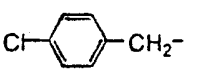
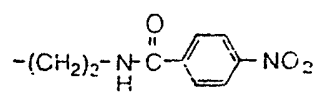
Tabulka 1.8

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
78		1	2	0	R	H	
79		1	2	0	R	H	
80		1	2	0	R	H	
81		1	2	0	R	H	
82		1	2	0	-	$-CH_3$	
83		1	2	0	R	H	
84		1	2	0	R	H	
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86		1	2	0	-	H	
87		1	2	0	S	H	
88		1	2	0	S	H	

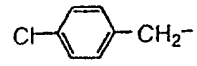
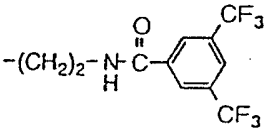
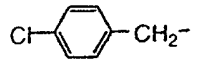
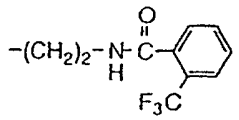
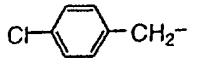
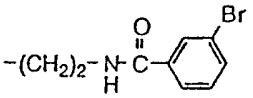
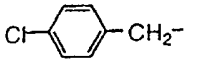
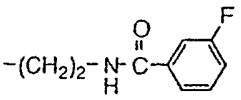
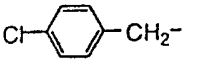
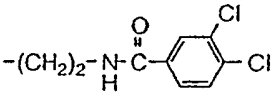
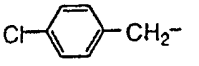
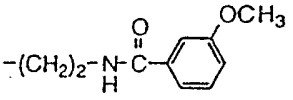
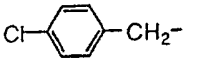
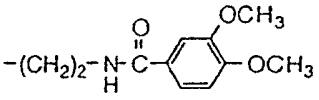
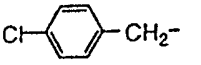
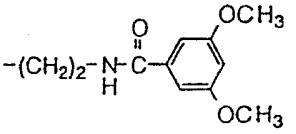
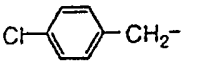
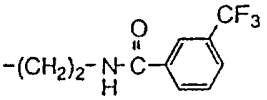
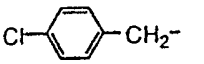
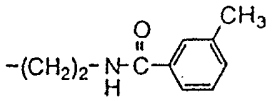
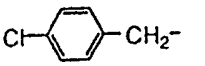
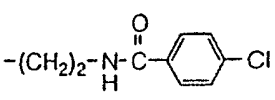
Tabulka 1.9

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
89		1	2	0	S	H	
90		1	2	0	S	H	
91		1	2	0	S	H	
92		1	2	0	S	H	
93		1	2	0	S	H	
94		1	2	0	S	H	
95		1	2	0	S	H	
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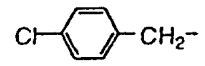
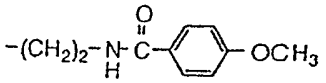
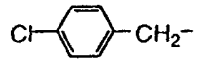
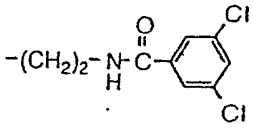
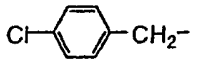
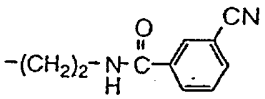
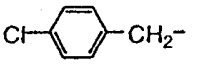
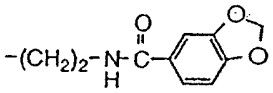
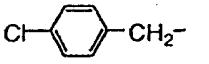
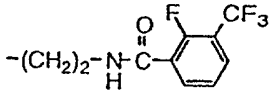
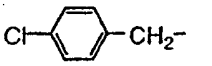
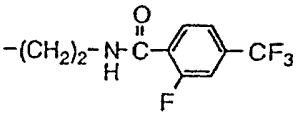
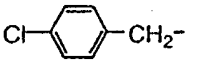
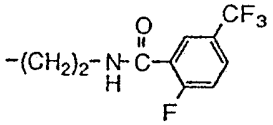
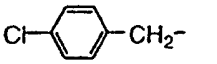
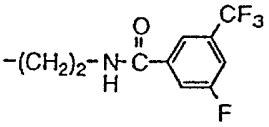
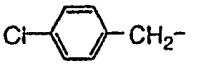
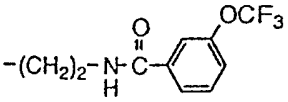
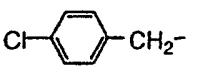
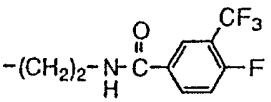
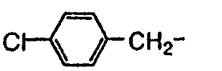
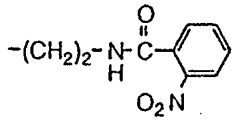
Tabulka 1.10

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
100		1	2	0	S	H	
101		1	2	0	S	H	
102		1	2	0	S	H	
103		1	2	0	S	H	
104		1	2	0	S	H	
105		1	2	0	S	H	
106		1	2	0	S	H	
107		1	2	0	S	H	
108		1	2	0	S	H	
109		1	2	0	S	H	
110		1	2	0	S	H	

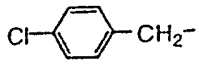
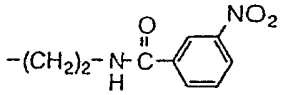
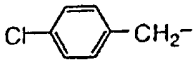
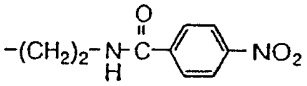
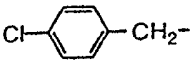
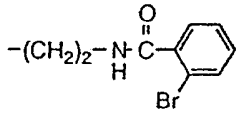
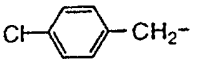
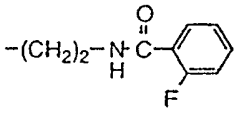
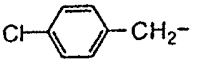
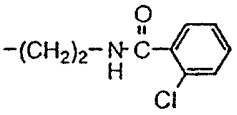
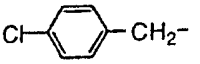
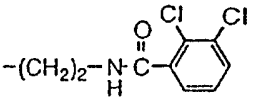
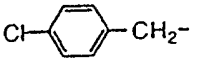
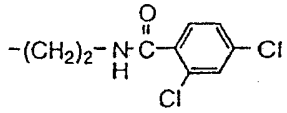
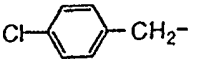
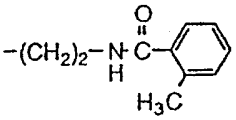
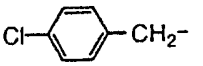
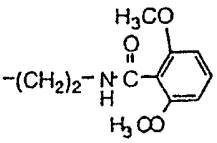
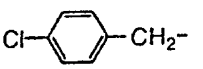
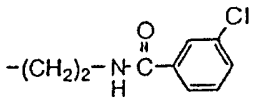
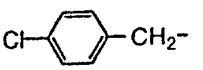
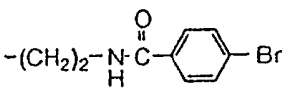
Tabulka 1.11

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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112		1	2	0	R	H	
113		1	2	0	R	H	
114		1	2	0	R	H	
115		1	2	0	R	H	
116		1	2	0	R	H	
117		1	2	0	R	H	
118		1	2	0	R	H	
119		1	2	0	R	H	
120		1	2	0	R	H	
121		1	2	0	R	H	

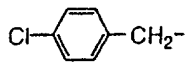
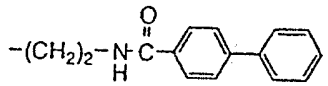
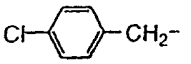
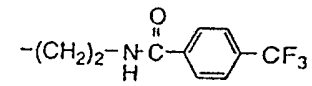
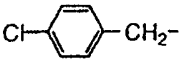
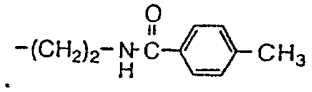
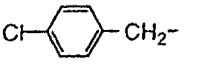
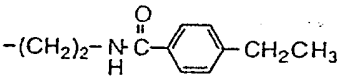
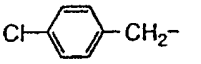
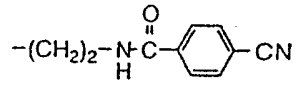
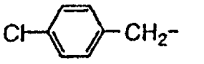
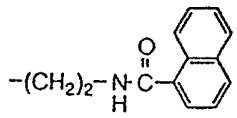
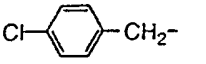
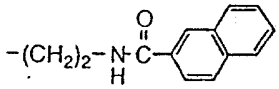
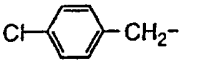
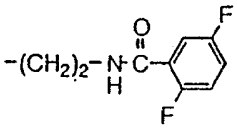
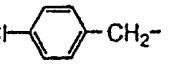
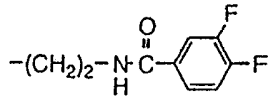
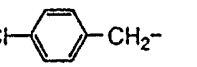
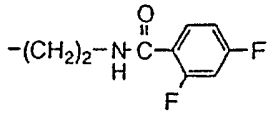
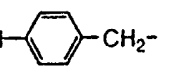
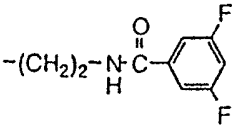
Tabulka 1.12

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
122		1	2	0	R	H	
123		1	2	0	R	H	
124		1	2	0	R	H	
125		1	2	0	R	H	
126		1	2	0	R	H	
127		1	2	0	R	H	
128		1	2	0	R	H	
129		1	2	0	R	H	
130		1	2	0	R	H	
131		1	2	0	R	H	
132		1	2	0	R	H	

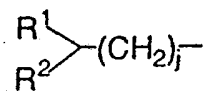
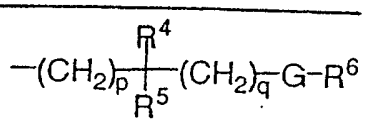
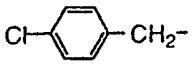
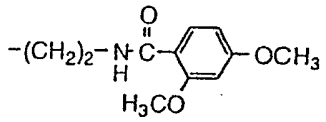
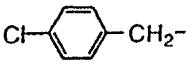
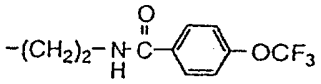
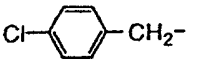
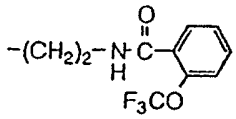
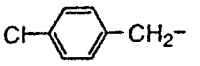
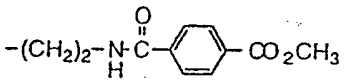
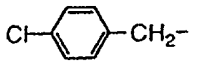
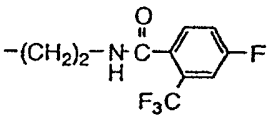
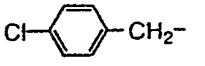
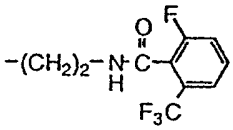
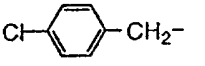
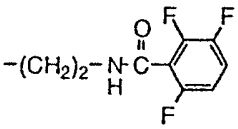
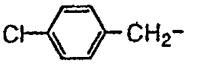
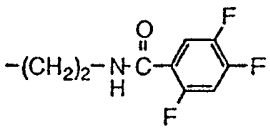
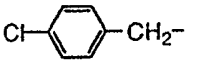
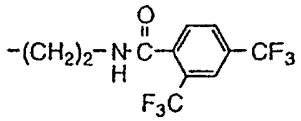
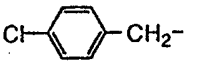
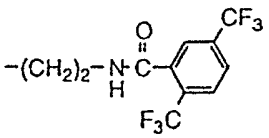
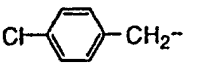
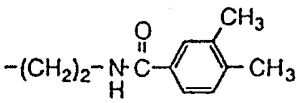
Tabulka 1.13

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
133		1	2	0	R	H	
134		1	2	0	R	H	
135		1	2	0	R	H	
136		1	2	0	R	H	
137		1	2	0	R	H	
138		1	2	0	R	H	
139		1	2	0	R	H	
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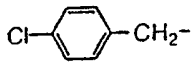
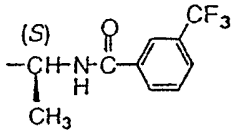
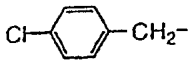
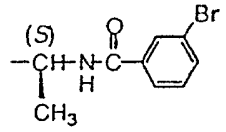
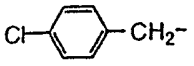
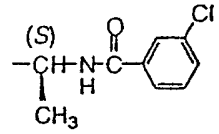
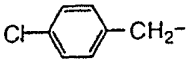
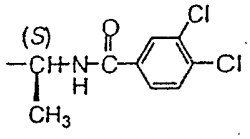
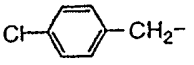
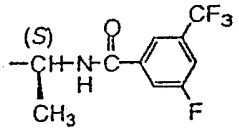
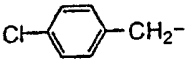
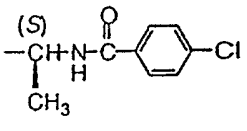
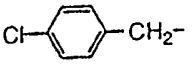
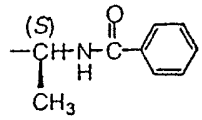
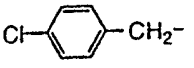
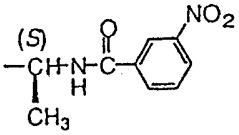
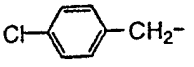
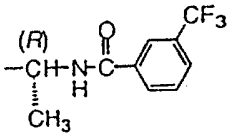
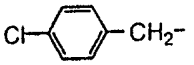
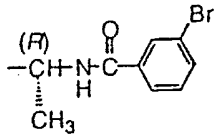
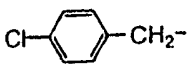
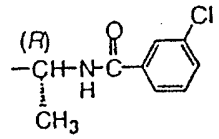
Tabulka 1.14

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
144		1	2	0	R	H	
145		1	2	0	R	H	
146		1	2	0	R	H	
147		1	2	0	R	H	
148		1	2	0	R	H	
149		1	2	0	R	H	
150		1	2	0	R	H	
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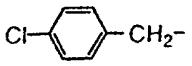
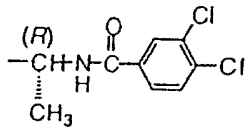
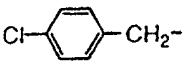
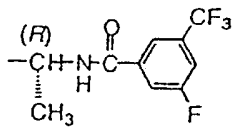
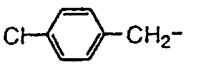
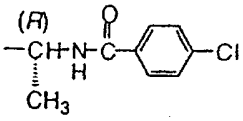
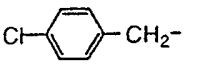
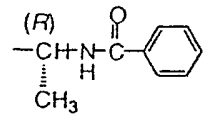
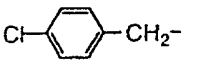
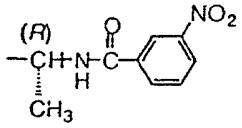
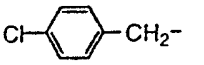
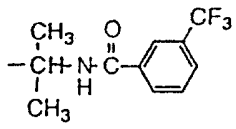
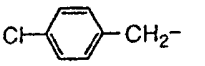
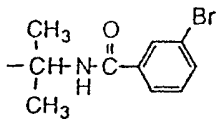
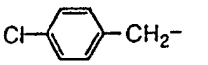
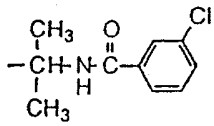
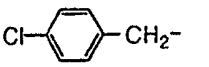
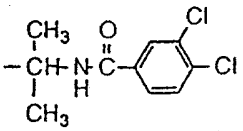
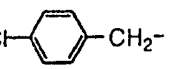
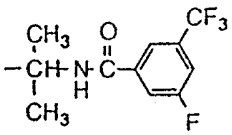
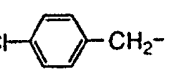
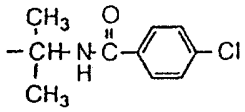
Tabulka 1.15

Sloučč.		k	m	n	chiralita	R^3	
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158		1	2	0	R	H	
159		1	2	0	R	H	
160		1	2	0	R	H	
161		1	2	0	R	H	
162		1	2	0	R	H	
163		1	2	0	R	H	
164		1	2	0	R	H	
165		1	2	0	R	H	

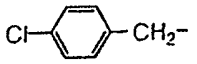
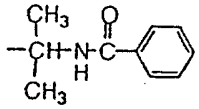
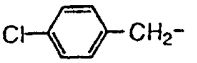
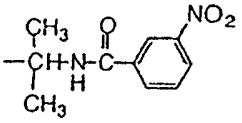
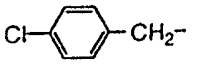
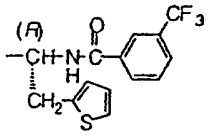
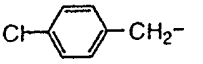
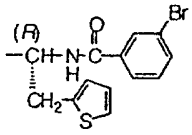
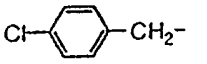
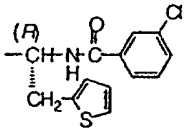
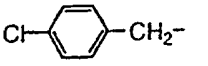
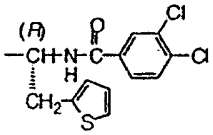
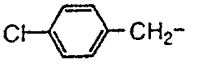
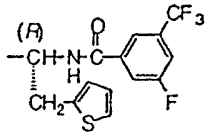
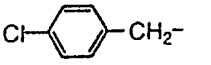
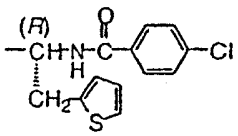
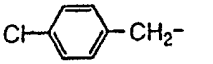
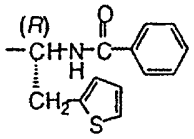
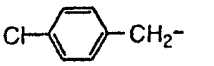
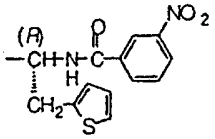
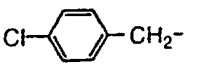
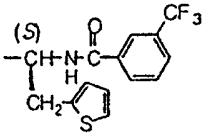
Tabulka 1.16

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
166		1	2	0	R	H	
167		1	2	0	R	H	
168		1	2	0	R	H	
169		1	2	0	R	H	
170		1	2	0	R	H	
171		1	2	0	R	H	
172		1	2	0	R	H	
173		1	2	0	R	H	
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176		1	2	0	R	H	

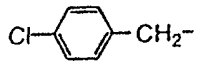
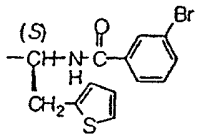
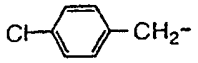
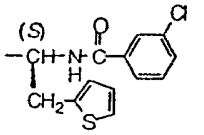
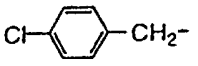
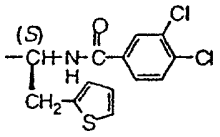
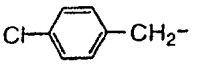
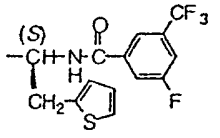
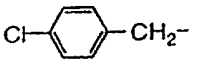
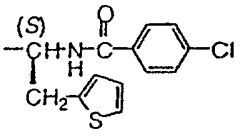
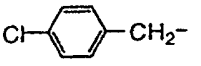
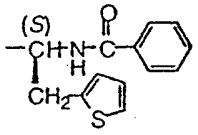
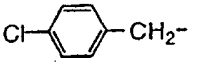
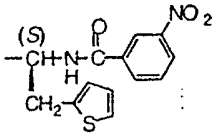
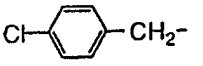
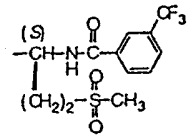
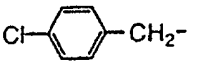
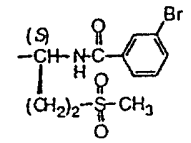
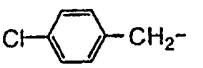
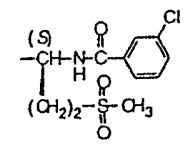
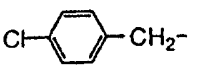
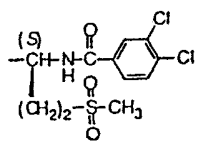
Tabulka 1.17

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
177		1	2	0	R	H	
178		1	2	0	R	H	
179		1	2	0	R	H	
180		1	2	0	R	H	
181		1	2	0	R	H	
182		1	2	0	R	H	
183		1	2	0	R	H	
184		1	2	0	R	H	
185		1	2	0	R	H	
186		1	2	0	R	H	
187		1	2	0	R	H	

Tabulka 1.18

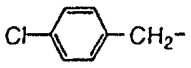
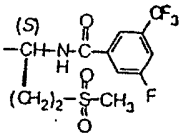
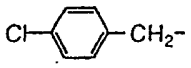
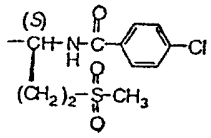
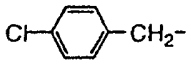
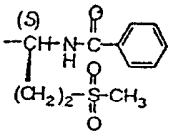
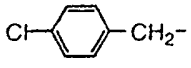
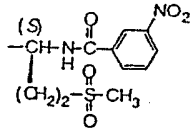
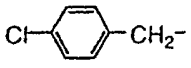
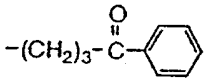
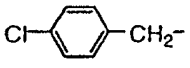
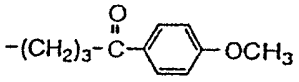
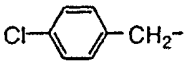
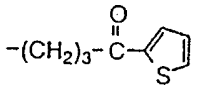
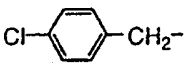
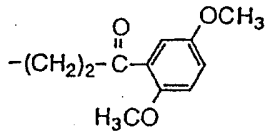
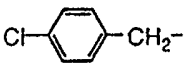
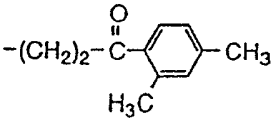
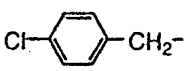
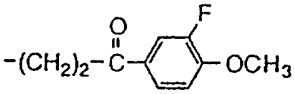
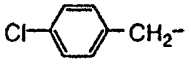
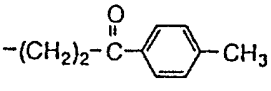
Slouč.č.	R^1, R^2, $-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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189		1	2	0	R	H	
190		1	2	0	R	H	
191		1	2	0	R	H	
192		1	2	0	R	H	
193		1	2	0	R	H	
194		1	2	0	R	H	
195		1	2	0	R	H	
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Tabulka 1.19

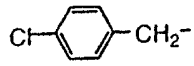
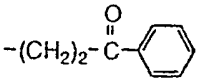
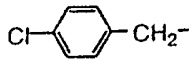
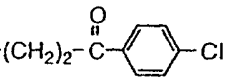
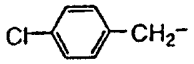
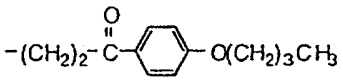
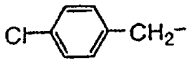
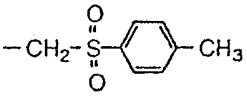
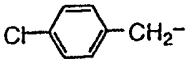
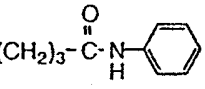
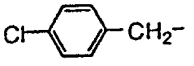
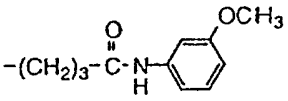
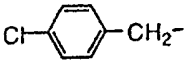
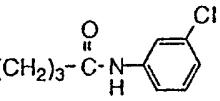
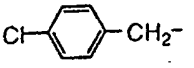
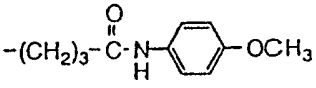
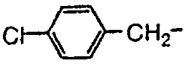
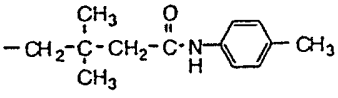
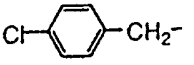
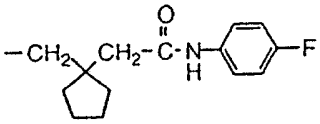
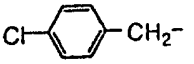
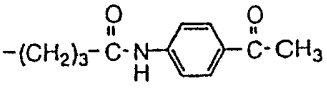
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201		1	2	0	R	H	
202		1	2	0	R	H	
203		1	2	0	R	H	
204		1	2	0	R	H	
205		1	2	0	R	H	
206		1	2	0	R	H	
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03.09.00

Tabulka 1.20

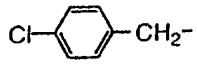
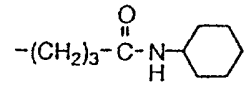
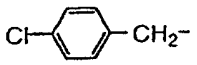
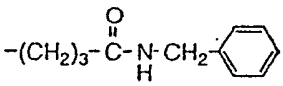
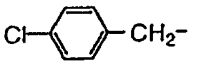
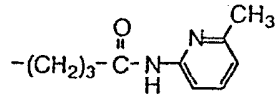
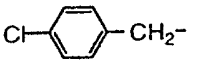
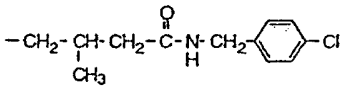
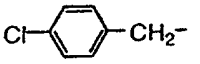
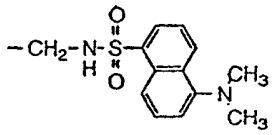
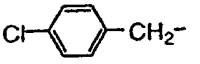
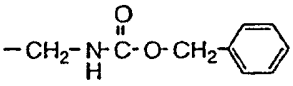
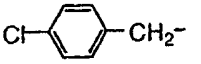
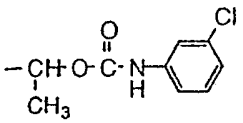
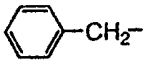
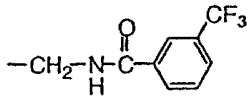
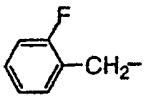
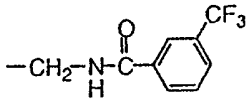
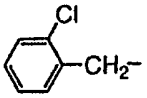
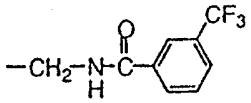
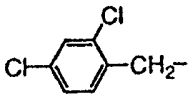
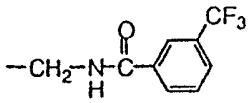
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
210		1	2	0	R	H	
211		1	2	0	R	H	
212		1	2	0	R	H	
213		1	2	0	R	H	
214		1	2	0	-	H	
215		1	2	0	-	H	
216		1	2	0	-	H	
217		1	2	0	-	H	
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219		1	2	0	-	H	
220		1	2	0	-	H	

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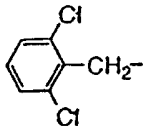
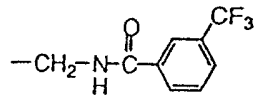
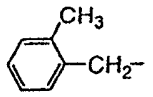
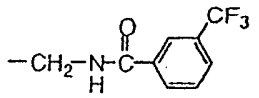
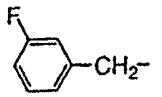
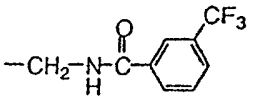
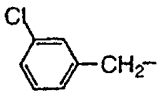
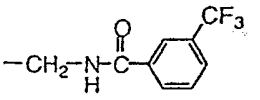
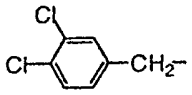
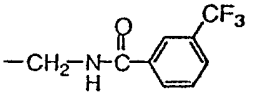
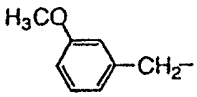
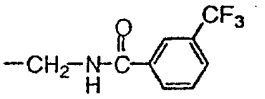
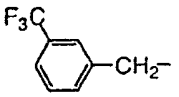
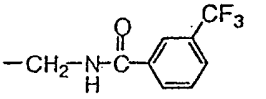
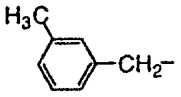
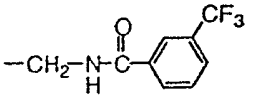
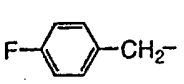
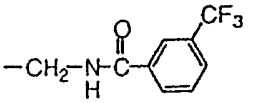
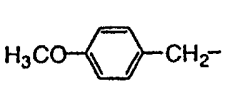
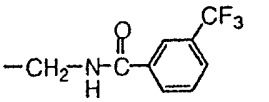
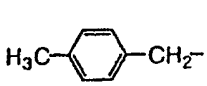
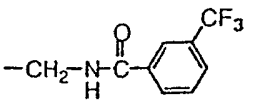
Slouč.č.	R^1, R^2, $(CH_2)_i$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
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222		1	2	0	-	H	
223		1	2	0	-	H	
224		1	2	0	-	H	
225		1	2	0	-	H	
226		1	2	0	-	H	
227		1	2	0	-	H	
228		1	2	0	-	H	
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Tabulka 1.22

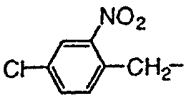
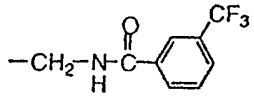
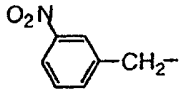
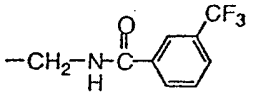
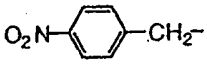
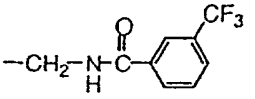
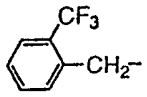
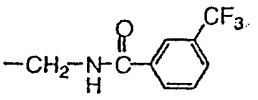
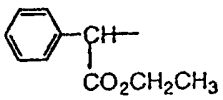
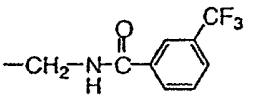
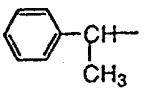
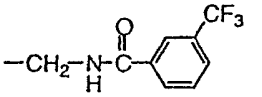
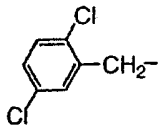
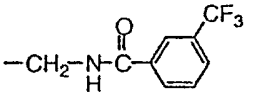
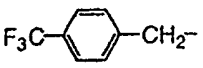
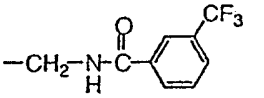
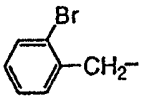
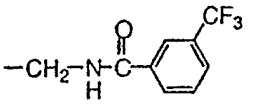
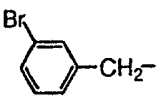
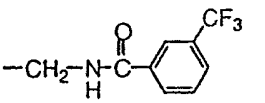
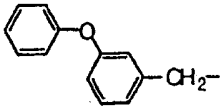
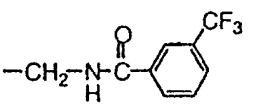
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
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235		1	2	0	-	H	
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237		1	2	0	-	H	
238		1	2	0	-	H	
239		1	2	0	S	H	
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Tabulka 1.23

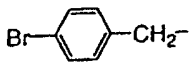
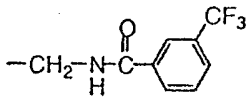
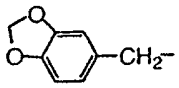
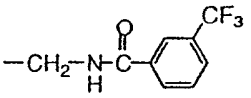
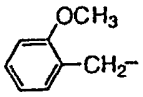
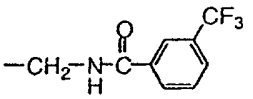
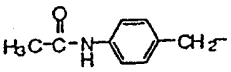
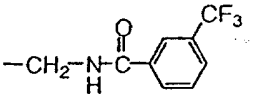
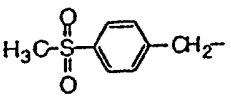
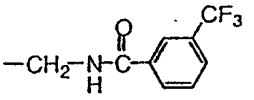
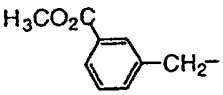
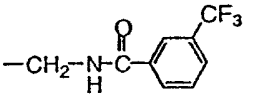
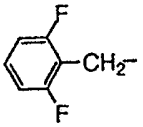
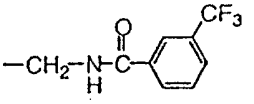
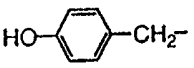
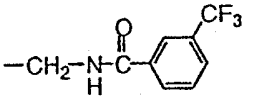
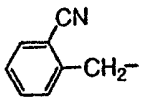
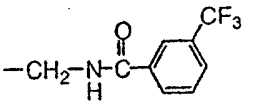
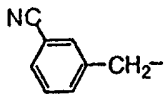
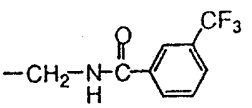
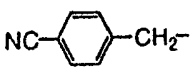
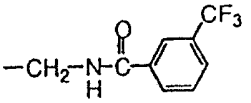
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
243		1	2	0	S	H	
244		1	2	0	S	H	
245		1	2	0	S	H	
246		1	2	0	S	H	
247		1	2	0	S	H	
248		1	2	0	S	H	
249		1	2	0	S	H	
250		1	2	0	S	H	
251		1	2	0	S	H	
252		1	2	0	S	H	
253		1	2	0	S	H	

03.07.00

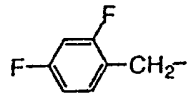
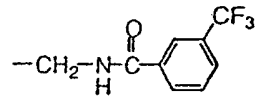
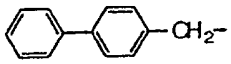
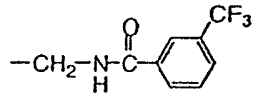
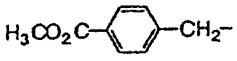
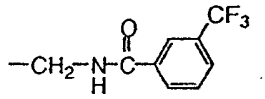
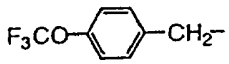
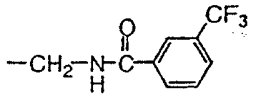
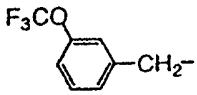
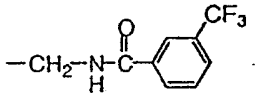
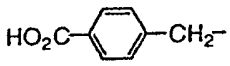
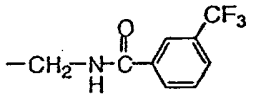
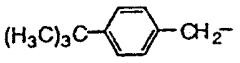
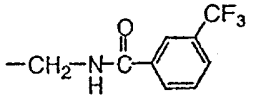
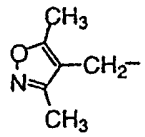
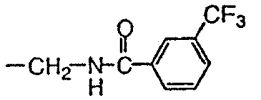
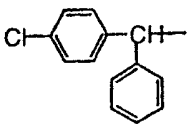
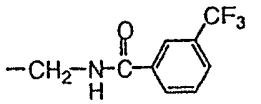
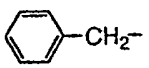
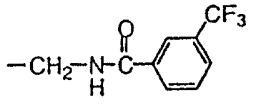
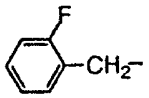
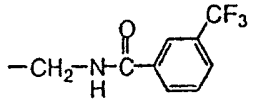
Tabulka 1.24

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
254		1	2	0	S	H	
255		1	2	0	S	H	
256		1	2	0	S	H	
257		1	2	0	S	H	
258		1	2	0	S	H	
259		1	2	0	S	H	
260		1	2	0	S	H	
261		1	2	0	S	H	
262		1	2	0	S	H	
263		1	2	0	S	H	
264		1	2	0	S	H	

Tabulka 1.25

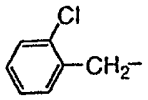
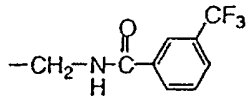
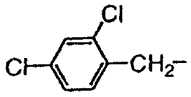
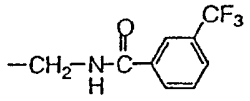
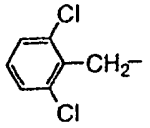
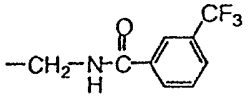
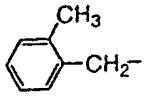
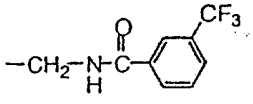
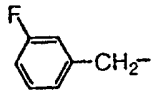
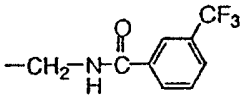
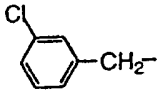
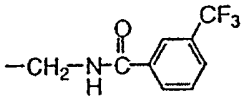
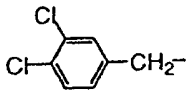
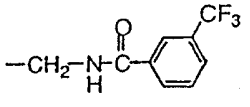
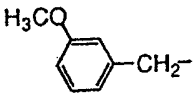
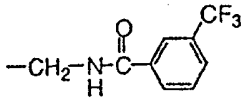
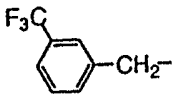
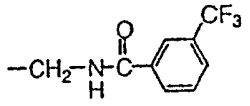
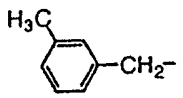
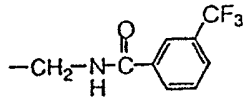
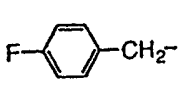
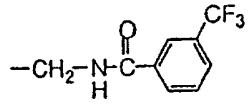
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
265		1	2	0	S	H	
266		1	2	0	S	H	
267		1	2	0	S	H	
268		1	2	0	S	H	
269		1	2	0	S	H	
270		1	2	0	S	H	
271		1	2	0	S	H	
272		1	2	0	S	H	
273		1	2	0	S	H	
274		1	2	0	S	H	
275		1	2	0	S	H	

Tabulka 1.26

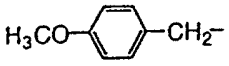
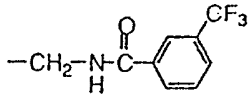
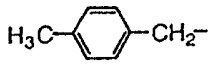
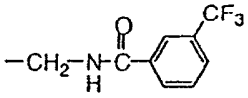
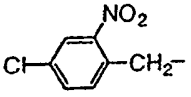
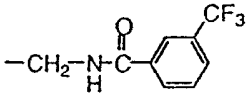
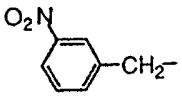
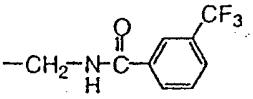
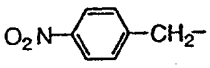
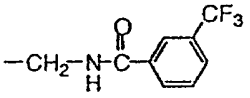
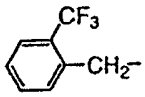
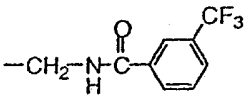
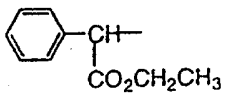
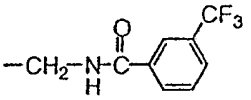
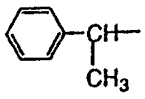
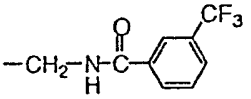
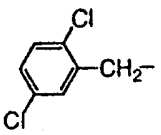
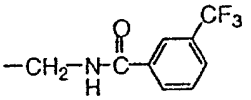
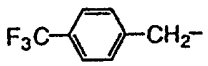
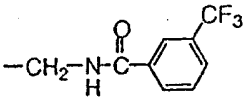
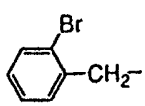
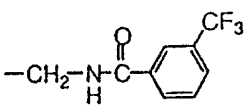
Sloučč.	R^1, R^2, $-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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277		1	2	0	S	H	
278		1	2	0	S	H	
279		1	2	0	S	H	
280		1	2	0	S	H	
281		1	2	0	S	H	
282		1	2	0	S	H	
283		1	2	0	S	H	
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286		1	2	0	R	H	

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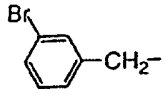
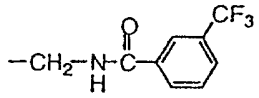
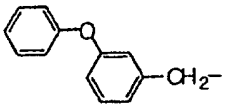
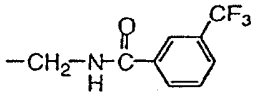
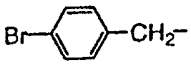
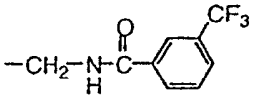
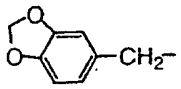
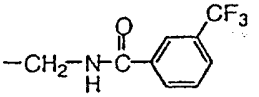
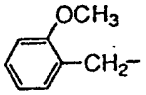
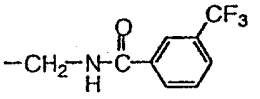
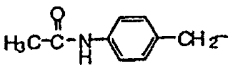
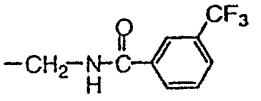
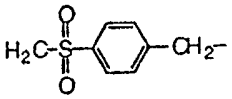
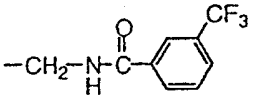
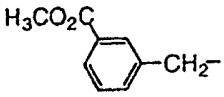
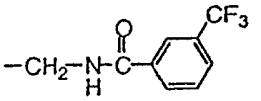
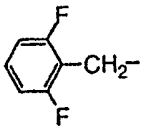
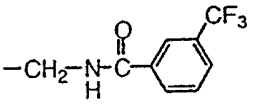
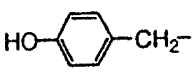
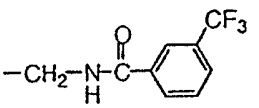
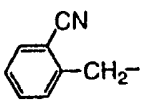
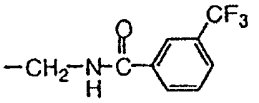
Tabulka 1.27

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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288		1	2	0	R	H	
289		1	2	0	R	H	
290		1	2	0	R	H	
291		1	2	0	R	H	
292		1	2	0	R	H	
293		1	2	0	R	H	
294		1	2	0	R	H	
295		1	2	0	R	H	
296		1	2	0	R	H	
297		1	2	0	R	H	

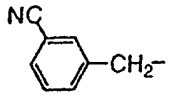
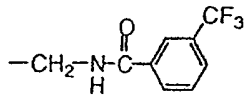
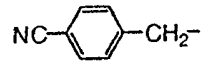
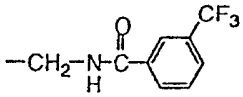
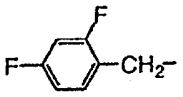
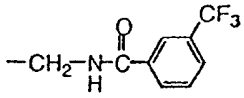
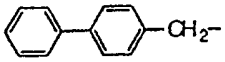
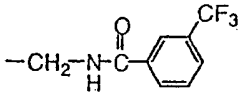
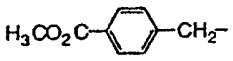
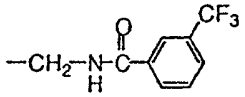
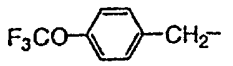
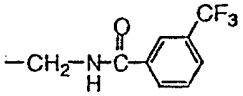
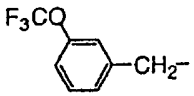
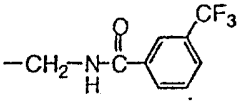
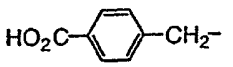
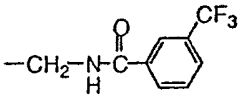
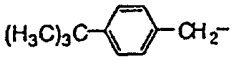
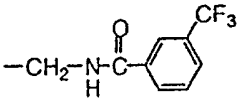
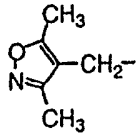
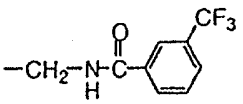
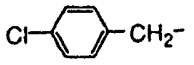
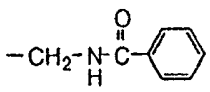
Tabulka 1.28

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
298		1	2	0	R	H	
299		1	2	0	R	H	
300		1	2	0	R	H	
301		1	2	0	R	H	
302		1	2	0	R	H	
303		1	2	0	R	H	
304		1	2	0	R	H	
305		1	2	0	R	H	
306		1	2	0	R	H	
307		1	2	0	R	H	
308		1	2	0	R	H	

Tabulka 1.29

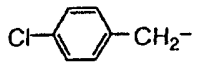
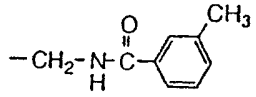
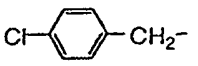
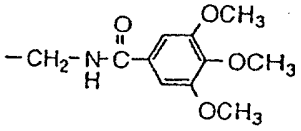
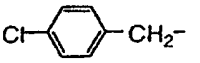
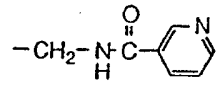
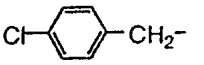
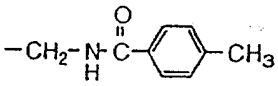
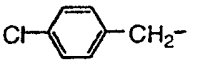
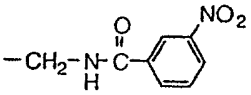
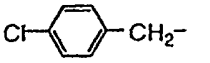
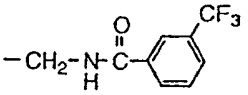
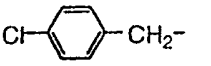
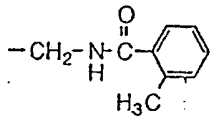
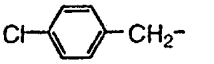
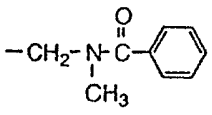
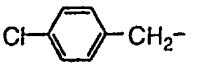
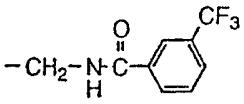
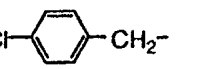
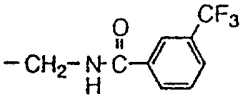
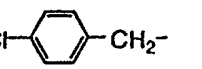
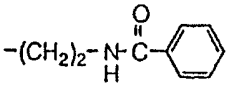
Slouč.č.	R^1, R^2, $(CH_2)_i$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
309		1	2	0	R	H	
310		1	2	0	R	H	
311		1	2	0	R	H	
312		1	2	0	R	H	
313		1	2	0	R	H	
314		1	2	0	R	H	
315		1	2	0	R	H	
316		1	2	0	R	H	
317		1	2	0	R	H	
318		1	2	0	R	H	
319		1	2	0	R	H	

Tabulka 1.30

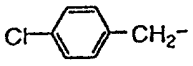
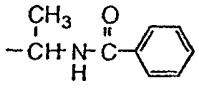
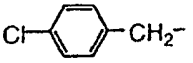
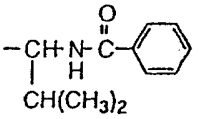
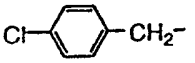
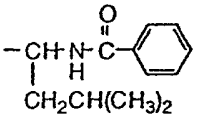
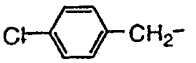
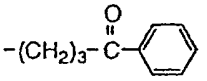
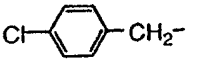
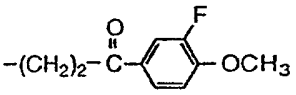
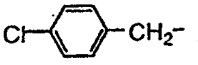
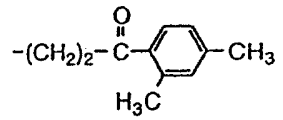
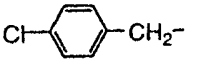
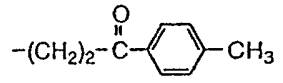
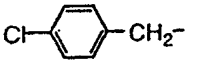
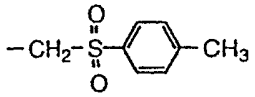
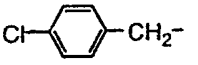
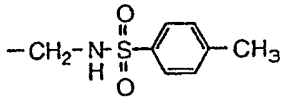
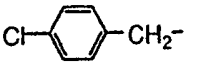
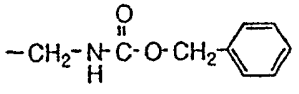
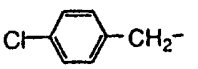
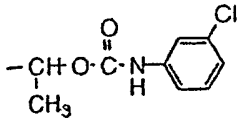
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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321		1	2	0	R	H	
322		1	2	0	R	H	
323		1	2	0	R	H	
324		1	2	0	R	H	
325		1	2	0	R	H	
326		1	2	0	R	H	
327		1	2	0	R	H	
328		1	2	0	R	H	
329		1	2	0	R	H	
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Tabulka 1.31

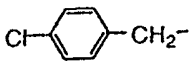
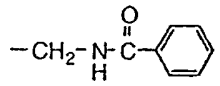
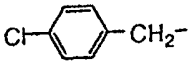
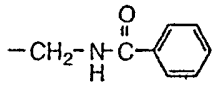
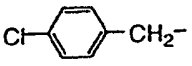
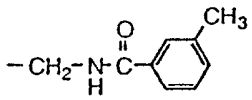
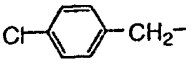
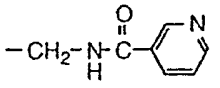
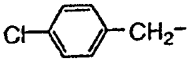
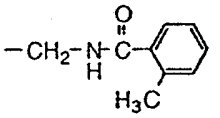
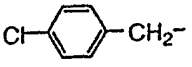
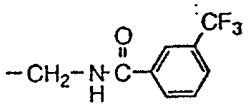
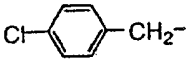
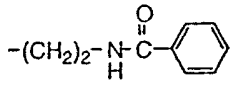
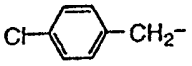
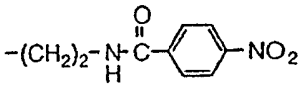
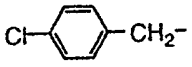
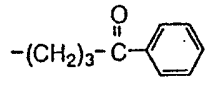
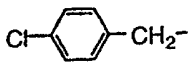
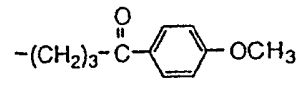
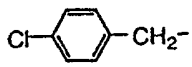
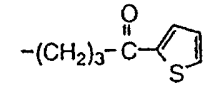
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
331		0	3	1	-	H	
332		0	3	1	-	H	
333		0	3	1	-	H	
334		0	3	1	-	H	
335		0	3	1	-	H	
336		0	3	1	-	H	
337		0	3	1	-	H	
338		0	3	1	-	H	
339		0	3	1	R	H	
340		0	3	1	S	H	
341		0	3	1	-	H	

Tabulka 1.32

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
342		0	3	1	-	H	
343		0	3	1	-	H	
344		0	3	1	-	H	
345		0	3	1	-	H	
346		0	3	1	-	H	
347		0	3	1	-	H	
348		0	3	1	-	H	
349		0	3	1	-	H	
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351		0	3	1	-	H	
352		0	3	1	-	H	

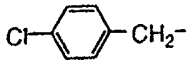
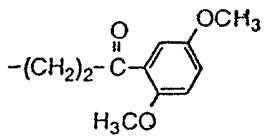
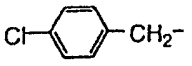
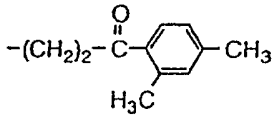
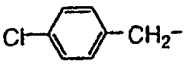
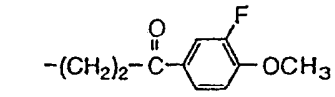
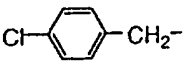
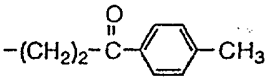
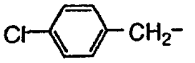
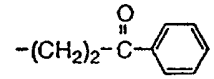
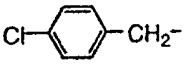
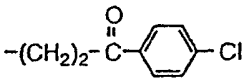
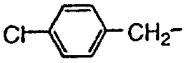
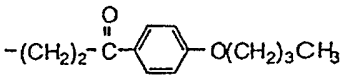
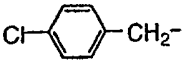
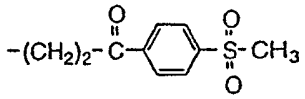
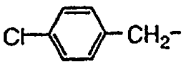
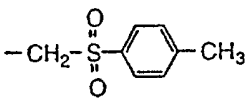
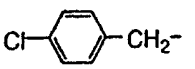
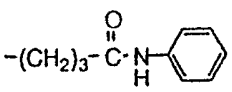
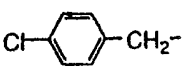
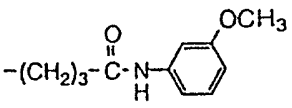
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Tabulka 1.33

Sloučč.	$R^1(R^2)CH(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
353		1	2	1	-	H	
354		1	3	0	-	H	
355		1	3	0	-	H	
356		1	3	0	-	H	
357		1	3	0	-	H	
358		1	3	0	-	H	
359		1	3	0	-	H	
360		1	3	0	-	H	
361		1	3	0	-	H	
362		1	3	0	-	H	
363		1	3	0	-	H	

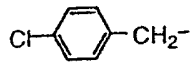
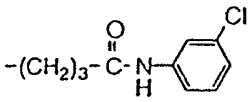
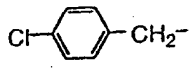
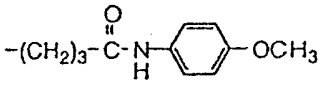
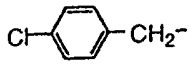
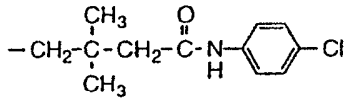
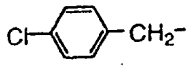
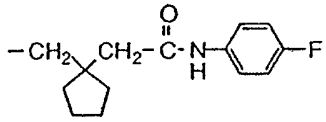
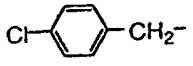
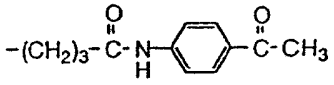
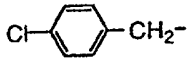
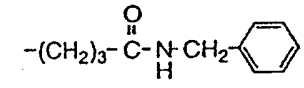
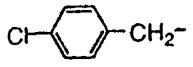
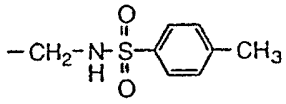
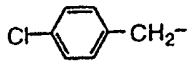
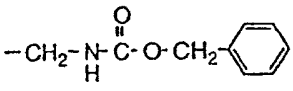
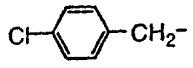
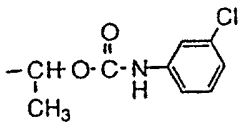
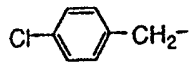
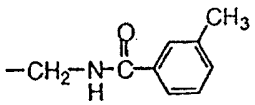
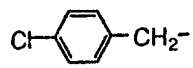
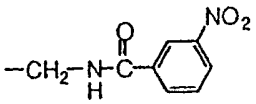
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Tabulka 1.34

Slouč.č.	R^1, R^2, $(CH_2)_i$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
364		1	3	0	-	H	
365		1	3	0	-	H	
366		1	3	0	-	H	
367		1	3	0	-	H	
368		1	3	0	-	H	
369		1	3	0	-	H	
370		1	3	0	-	H	
371		1	3	0	-	H	
372		1	3	0	-	H	
373		1	3	0	-	H	
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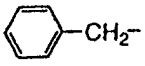
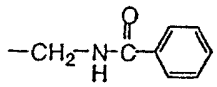
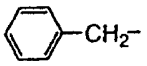
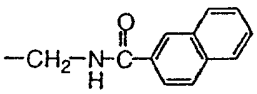
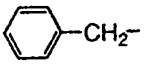
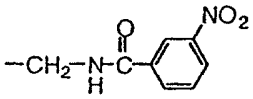
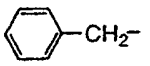
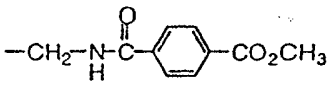
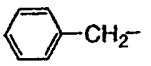
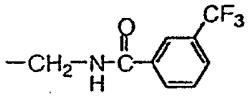
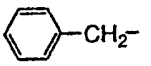
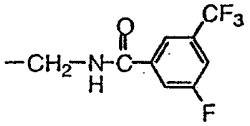
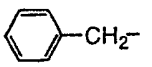
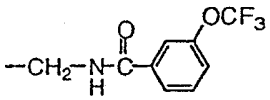
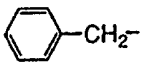
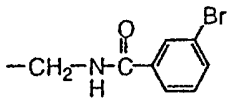
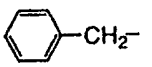
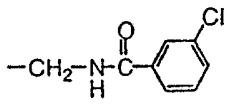
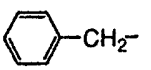
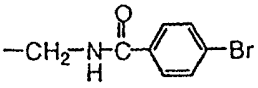
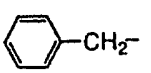
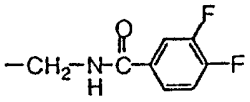
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Tabulka 1.35

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
375		1	3	0	-	H	
376		1	3	0	-	H	
377		1	3	0	-	H	
378		1	3	0	-	H	
379		1	3	0	-	H	
380		1	3	0	-	H	
381		1	3	0	-	H	
382		1	3	0	-	H	
383		1	3	0	-	H	
384		2	2	0	-	H	
385		2	2	0	-	H	

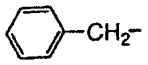
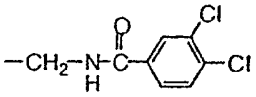
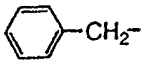
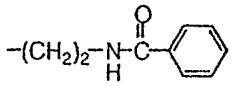
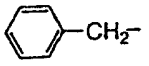
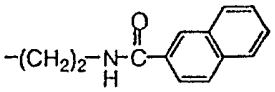
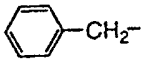
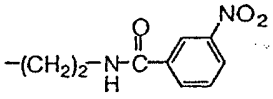
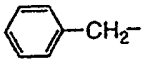
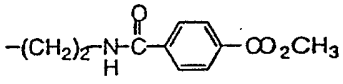
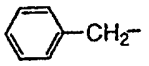
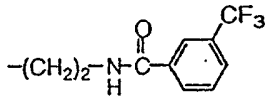
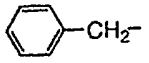
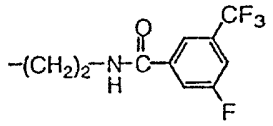
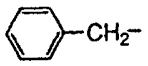
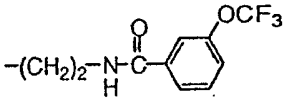
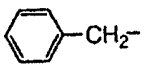
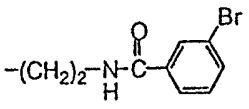
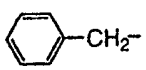
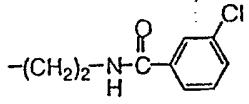
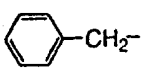
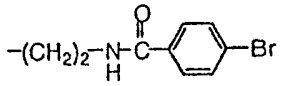
03.07.00

Tabulka 1.36

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
386		2	2	0	-	H	
387		2	2	0	-	H	
388		2	2	0	-	H	
389		2	2	0	-	H	
390		2	2	0	-	H	
391		2	2	0	-	H	
392		2	2	0	-	H	
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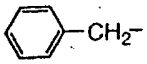
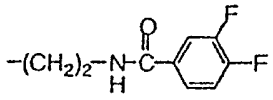
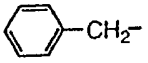
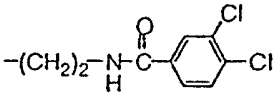
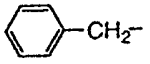
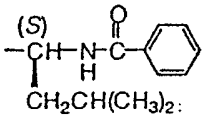
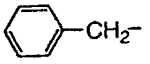
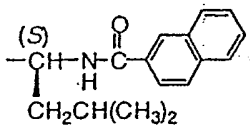
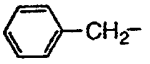
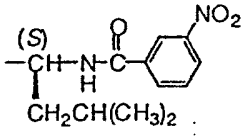
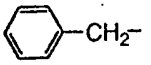
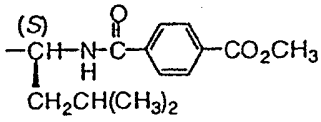
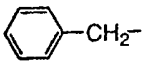
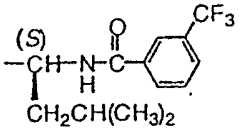
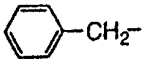
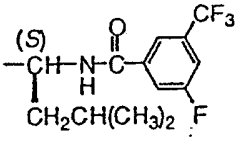
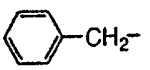
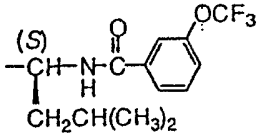
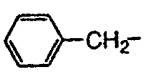
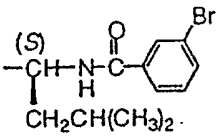
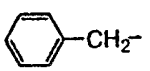
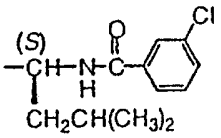
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Tabulka 1.37

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
397		2	2	0	-	H	
398		2	2	0	-	H	
399		2	2	0	-	H	
400		2	2	0	-	H	
401		2	2	0	-	H	
402		2	2	0	-	H	
403		2	2	0	-	H	
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407		2	2	0	-	H	

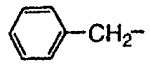
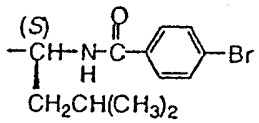
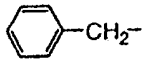
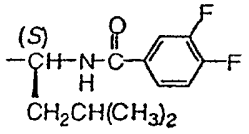
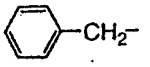
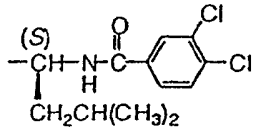
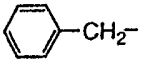
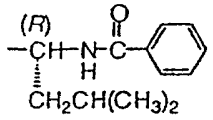
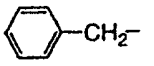
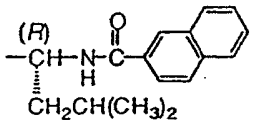
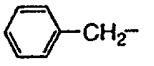
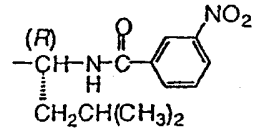
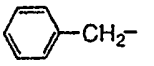
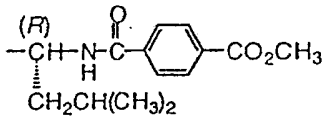
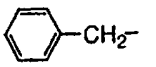
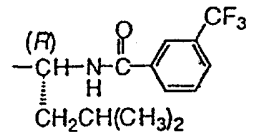
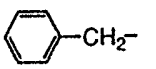
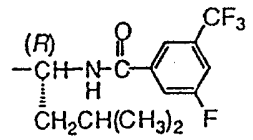
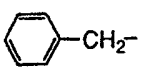
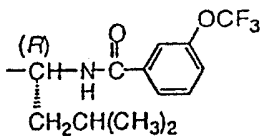
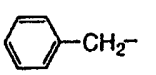
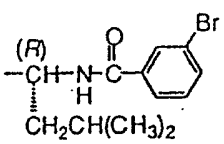
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Tabulka 1.38

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
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409		2	2	0	-	H	
410		2	2	0	-	H	
411		2	2	0	-	H	
412		2	2	0	-	H	
413		2	2	0	-	H	
414		2	2	0	-	H	
415		2	2	0	-	H	
416		2	2	0	-	H	
417		2	2	0	-	H	
418		2	2	0	-	H	

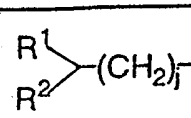
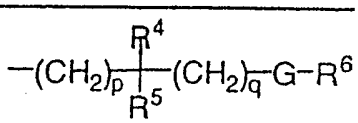
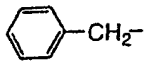
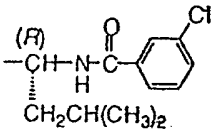
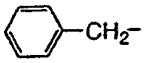
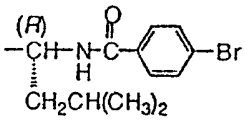
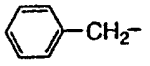
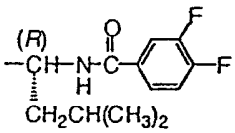
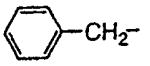
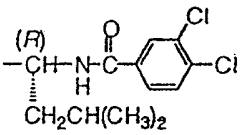
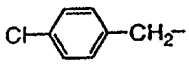
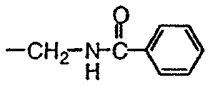
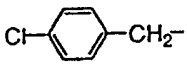
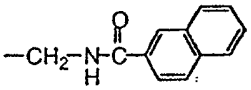
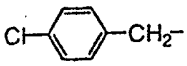
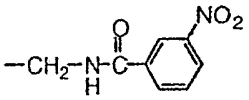
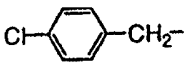
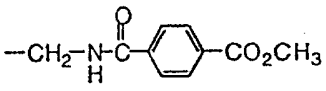
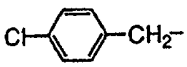
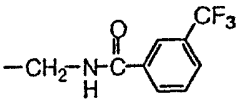
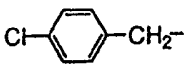
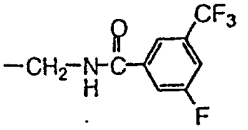
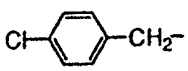
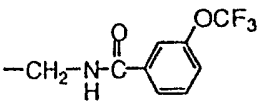
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Tabulka 1.39

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419		2	2	0	-	H	
420		2	2	0	-	H	
421		2	2	0	-	H	
422		2	2	0	-	H	
423		2	2	0	-	H	
424		2	2	0	-	H	
425		2	2	0	-	H	
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427		2	2	0	-	H	
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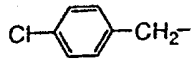
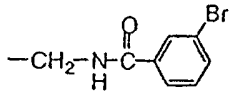
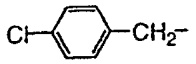
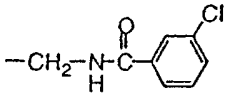
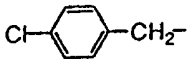
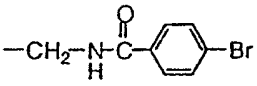
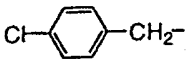
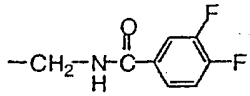
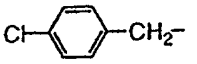
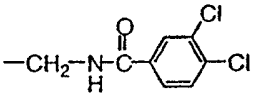
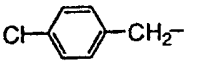
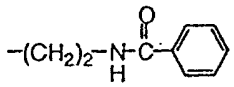
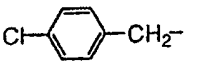
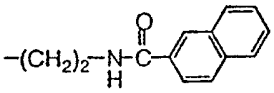
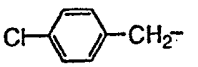
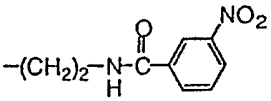
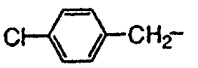
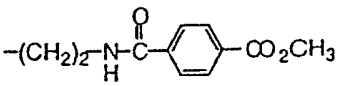
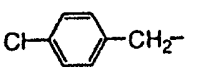
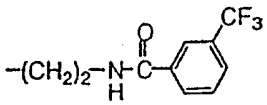
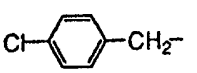
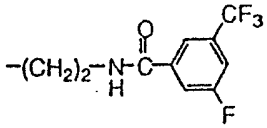
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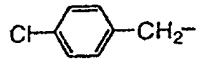
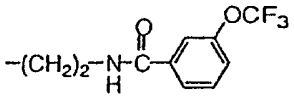
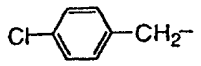
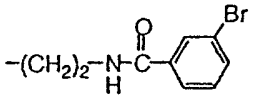
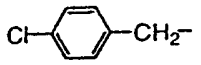
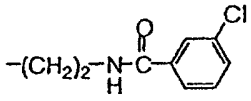
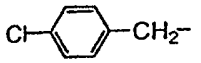
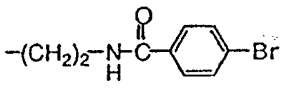
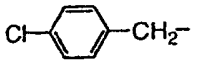
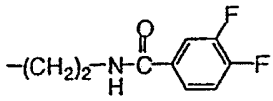
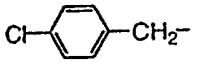
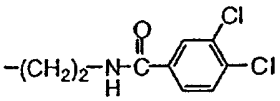
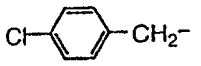
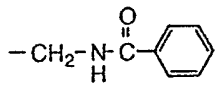
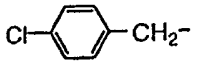
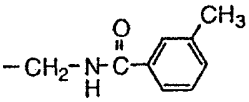
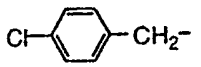
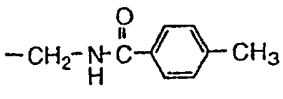
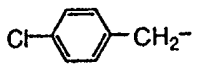
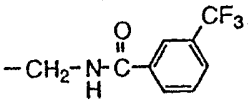
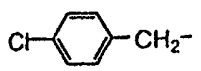
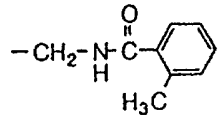
Slouč.č.		k	m	n	chiralita	R³	
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433		2	2	0	-	H	
434		1	3	1	-	H	
435		1	3	1	-	H	
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Tabulka 1.41

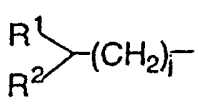
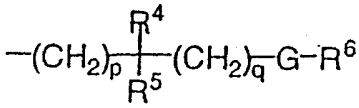
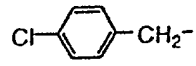
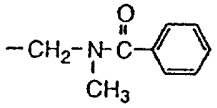
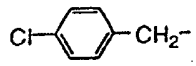
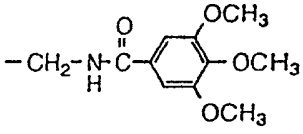
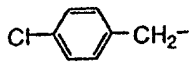
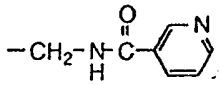
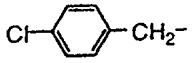
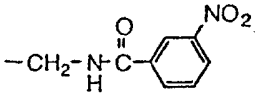
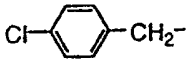
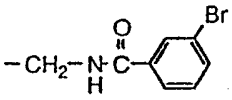
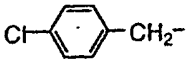
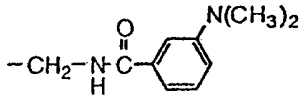
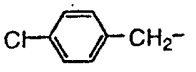
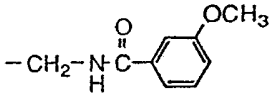
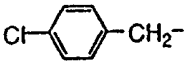
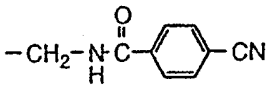
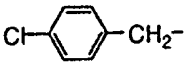
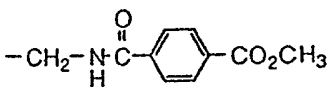
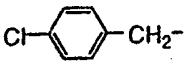
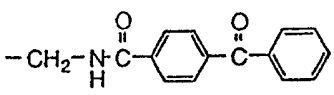
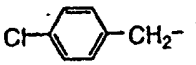
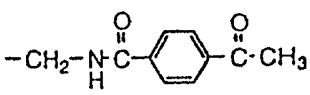
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
441		1	3	1	-	H	
442		1	3	1	-	H	
443		1	3	1	-	H	
444		1	3	1	-	H	
445		1	3	1	-	H	
446		1	3	1	-	H	
447		1	3	1	-	H	
448		1	3	1	-	H	
449		1	3	1	-	H	
450		1	3	1	-	H	
451		1	3	1	-	H	

Tabulka 1.42

Sloučč.	R^1, R^2, $(CH_2)_i$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
452		1	3	1	-	H	
453		1	3	1	-	H	
454		1	3	1	-	H	
455		1	3	1	-	H	
456		1	3	1	-	H	
457		1	3	1	-	H	
458		2	2	1	-	H	
459		2	2	1	-	H	
460		2	2	1	-	H	
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462		2	2	1	-	H	

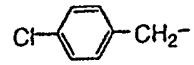
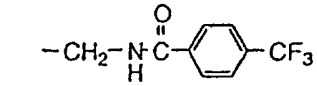
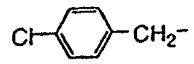
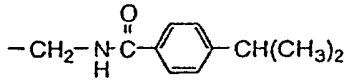
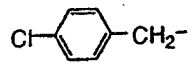
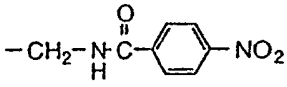
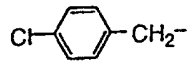
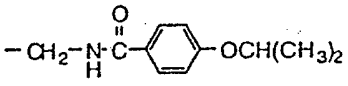
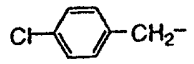
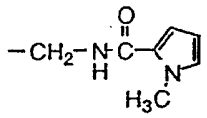
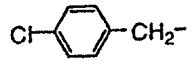
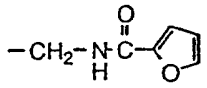
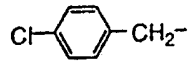
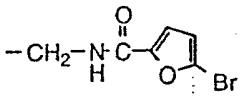
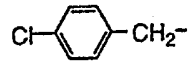
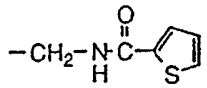
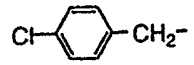
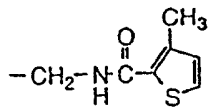
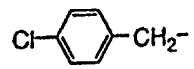
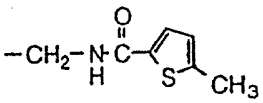
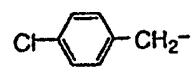
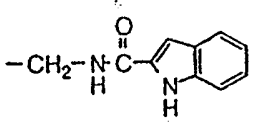
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Tabulka 1.43

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465		2	2	1	-	H	
466		2	2	1	-	H	
467		2	2	1	-	H	
468		2	2	1	-	H	
469		2	2	1	-	H	
470		2	2	1	-	H	
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472		2	2	1	-	H	
473		2	2	1	-	H	

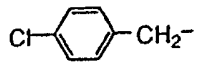
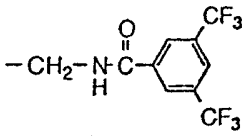
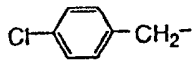
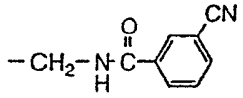
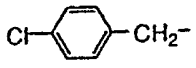
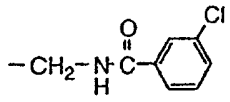
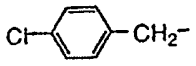
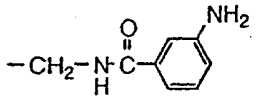
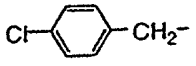
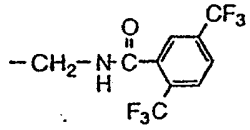
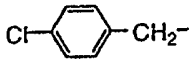
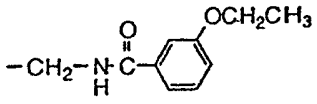
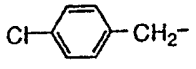
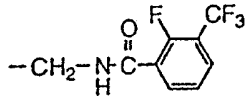
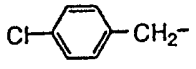
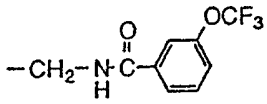
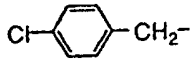
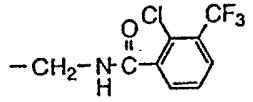
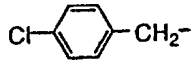
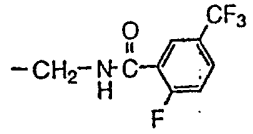
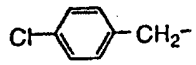
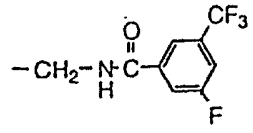
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Tabulka 1.44

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
474		2	2	1	-	H	
475		2	2	1	-	H	
476		2	2	1	-	H	
477		2	2	1	-	H	
478		2	2	1	-	H	
479		2	2	1	-	H	
480		2	2	1	-	H	
481		2	2	1	-	H	
482		2	2	1	-	H	
483		2	2	1	-	H	
484		2	2	1	-	H	

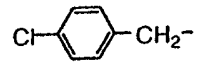
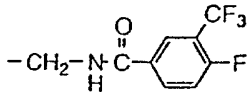
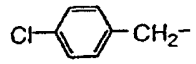
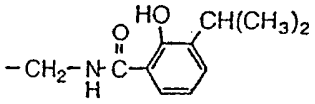
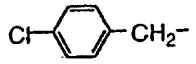
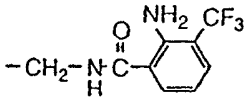
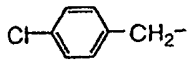
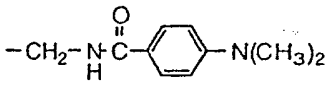
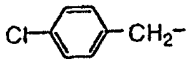
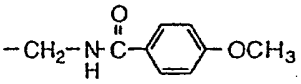
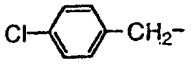
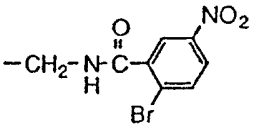
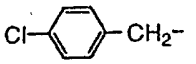
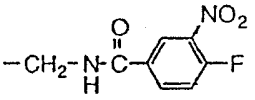
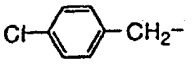
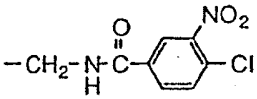
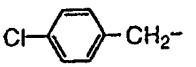
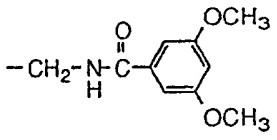
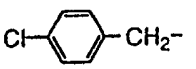
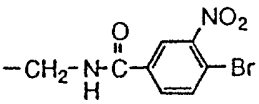
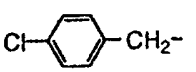
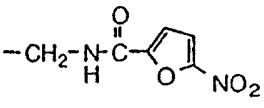
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Tabulka 1.45

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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486		2	2	1	-	H	
487		2	2	1	-	H	
488		2	2	1	-	H	
489		2	2	1	-	H	
490		2	2	1	-	H	
491		2	2	1	-	H	
492		2	2	1	-	H	
493		2	2	1	-	H	
494		2	2	1	-	H	
495		2	2	1	-	H	

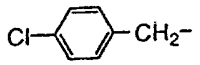
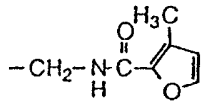
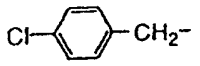
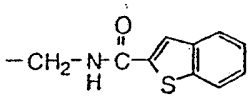
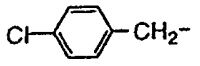
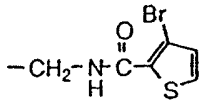
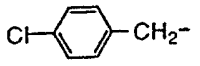
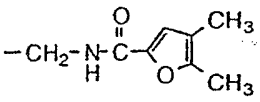
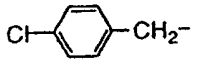
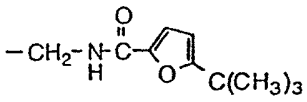
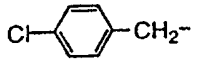
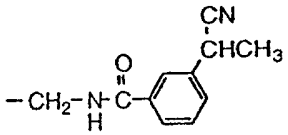
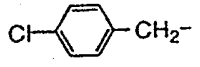
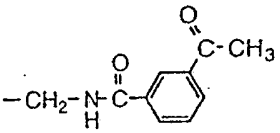
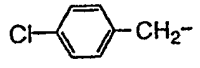
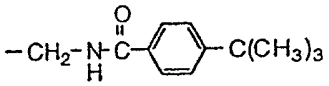
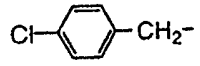
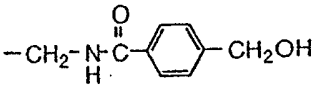
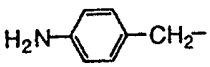
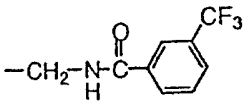
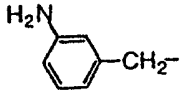
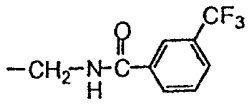
03.07.00

Tabulka 1.46

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
496		2	2	1	-	H	
497		2	2	1	-	H	
498		2	2	1	-	H	
499		2	2	1	-	H	
500		2	2	1	-	H	
501		2	2	1	-	H	
502		2	2	1	-	H	
503		2	2	1	-	H	
504		2	2	1	-	H	
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506		2	2	1	-	H	

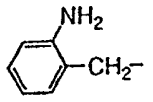
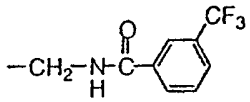
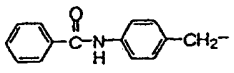
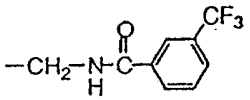
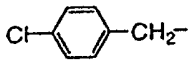
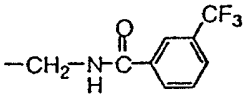
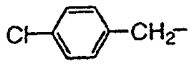
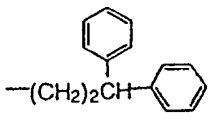
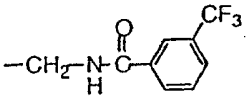
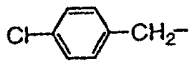
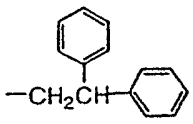
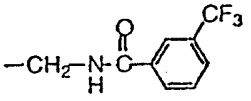
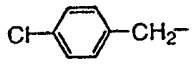
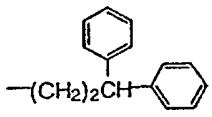
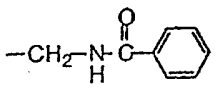
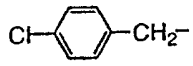
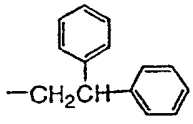
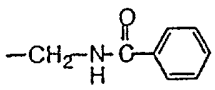
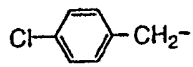
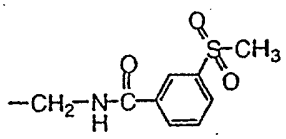
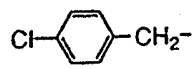
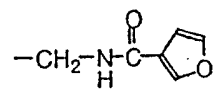
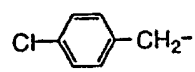
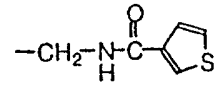
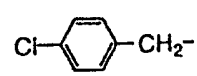
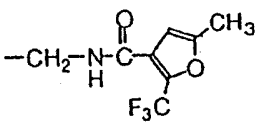
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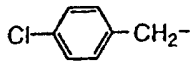
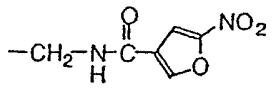
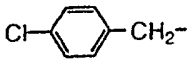
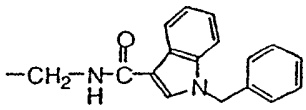
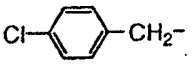
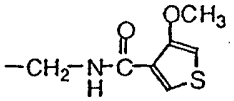
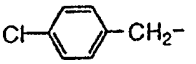
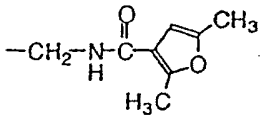
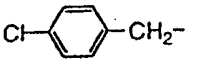
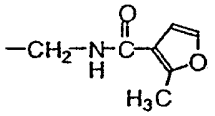
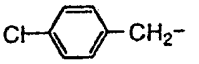
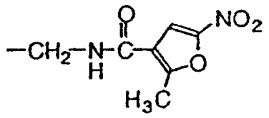
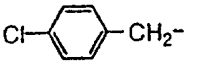
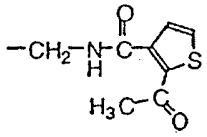
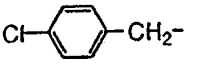
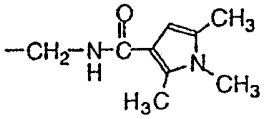
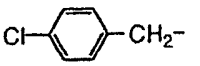
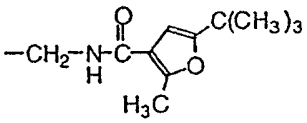
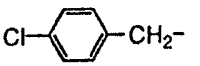
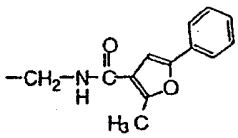
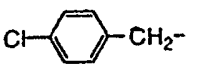
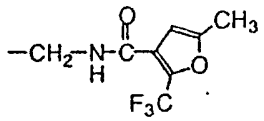
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511		2	2	1	-	H	
512		2	2	1	-	H	
513		2	2	1	-	H	
514		2	2	1	-	H	
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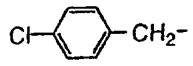
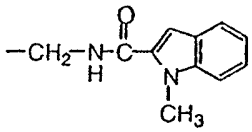
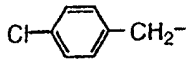
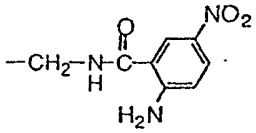
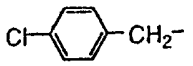
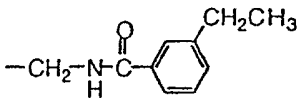
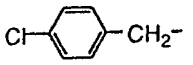
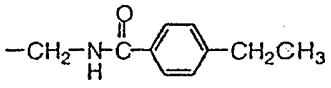
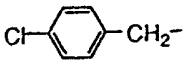
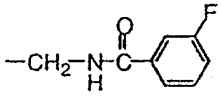
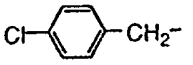
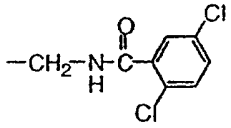
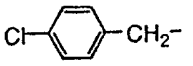
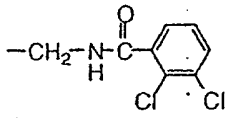
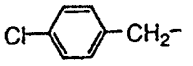
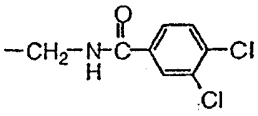
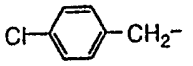
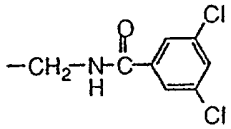
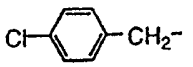
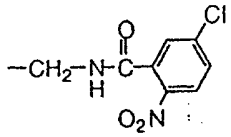
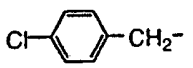
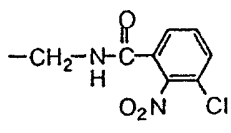
.Tabulka 1.48

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
518		2	2	1	-	H	
519		2	2	1	-	H	
520		2	2	1	-	$-CH_3$	
521		2	2	1	-		
522		2	2	1	-		
523		2	2	1	-		
524		2	2	1	-		
525		2	2	1	-	H	
526		2	2	1	-	H	
527		2	2	1	-	H	
528		2	2	1	-	H	

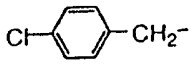
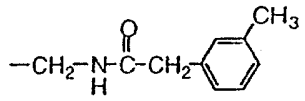
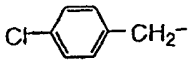
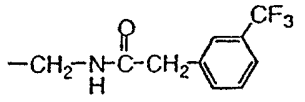
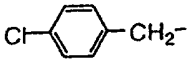
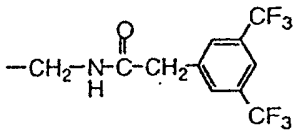
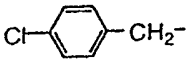
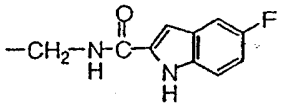
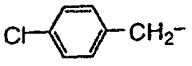
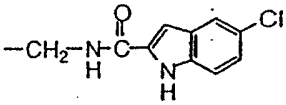
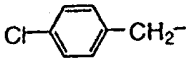
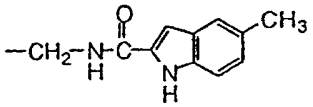
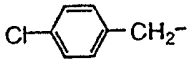
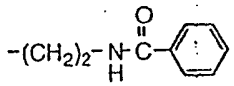
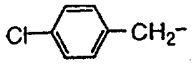
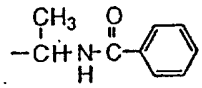
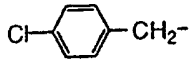
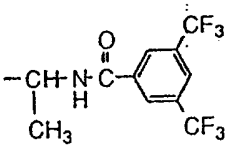
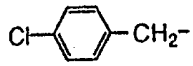
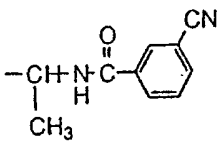
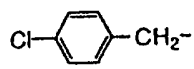
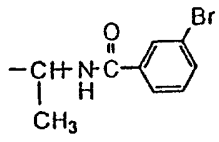
Tabulka 1.49

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
529		2	2	1	-	H	
530		2	2	1	-	H	
531		2	2	1	-	H	
532		2	2	1	-	H	
533		2	2	1	-	H	
534		2	2	1	-	H	
535		2	2	1	-	H	
536		2	2	1	-	H	
537		2	2	1	-	H	
538		2	2	1	-	H	
539		2	2	1	-	H	

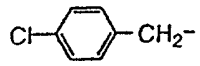
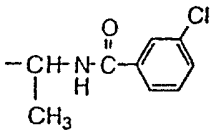
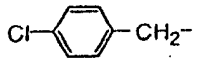
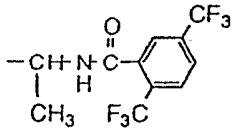
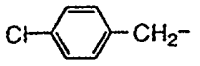
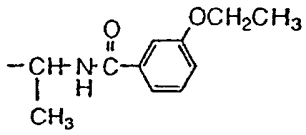
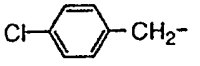
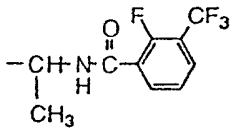
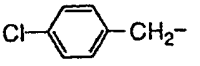
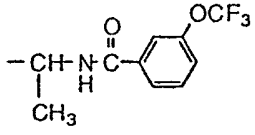
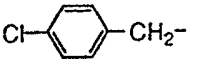
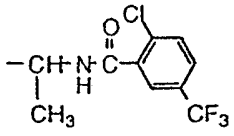
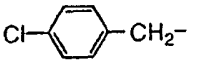
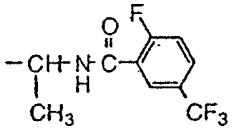
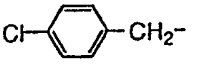
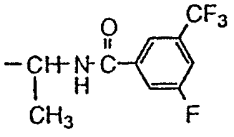
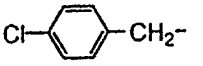
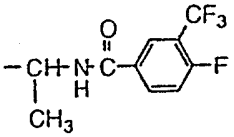
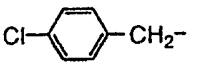
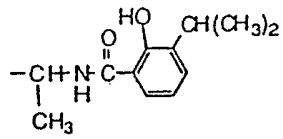
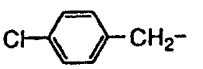
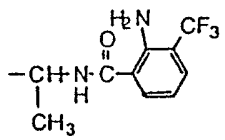
Tabulka 1.50

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
540		2	2	1	-	H	
541		2	2	1	-	H	
542		2	2	1	-	H	
543		2	2	1	-	H	
544		2	2	1	-	H	
545		2	2	1	-	H	
546		2	2	1	-	H	
547		2	2	1	-	H	
548		2	2	1	-	H	
549		2	2	1	-	H	
550		2	2	1	-	H	

Tabulka 1.51

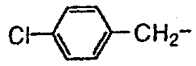
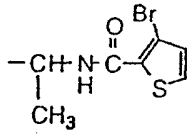
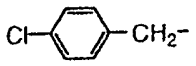
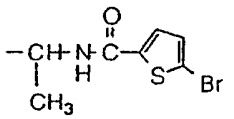
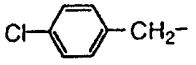
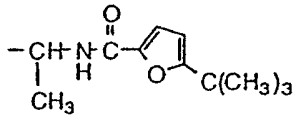
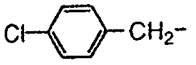
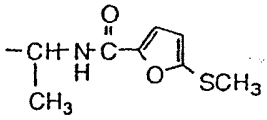
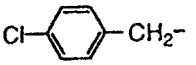
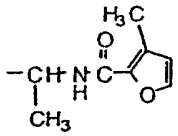
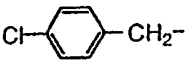
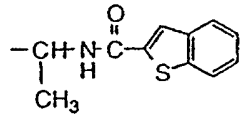
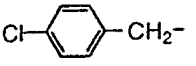
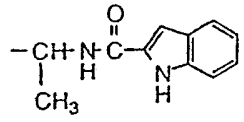
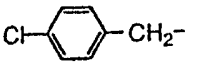
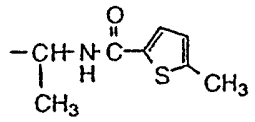
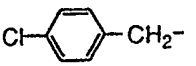
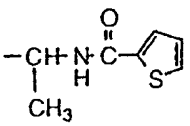
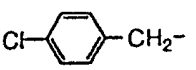
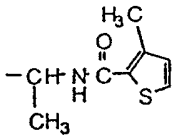
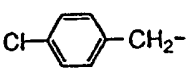
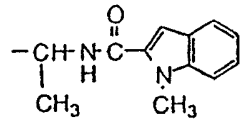
Slouč.č.	$R^1(R^2)CH(CH_2)_i-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
551		2	2	1	-	H	
552		2	2	1	-	H	
553		2	2	1	-	H	
554		2	2	1	-	H	
555		2	2	1	-	H	
556		2	2	1	-	H	
557		2	2	1	-	H	
558		2	2	1	-	H	
559		2	2	1	-	H	
560		2	2	1	-	H	
561		2	2	1	-	H	

Tabulka 1.52

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
562		2	2	1	-	H	
563		2	2	1	-	H	
564		2	2	1	-	H	
565		2	2	1	-	H	
566		2	2	1	-	H	
567		2	2	1	-	H	
568		2	2	1	-	H	
569		2	2	1	-	H	
570		2	2	1	-	H	
571		2	2	1	-	H	
572		2	2	1	-	H	

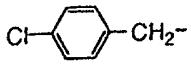
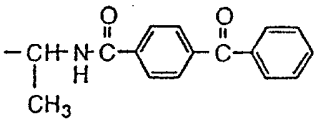
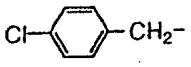
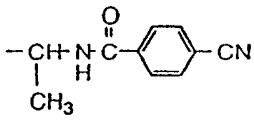
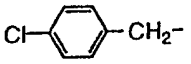
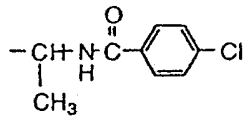
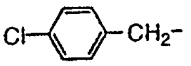
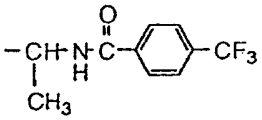
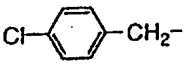
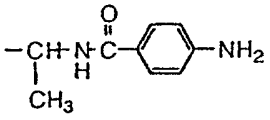
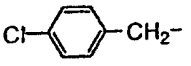
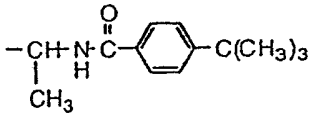
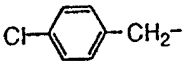
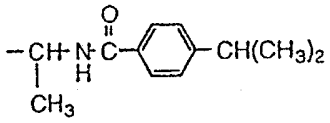
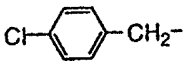
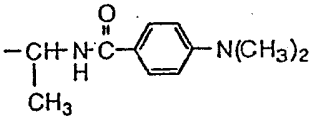
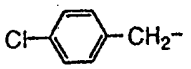
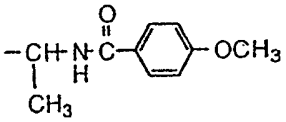
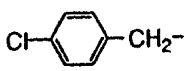
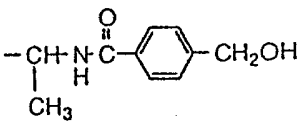
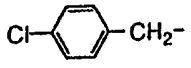
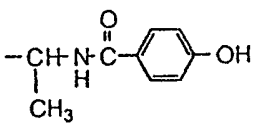
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Tabulka 1.53

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CH(R^4)(R^5)-(CH_2)_q-G-R^6$
573		2	2	1	-	H	
574		2	2	1	-	H	
575		2	2	1	-	H	
576		2	2	1	-	H	
577		2	2	1	-	H	
578		2	2	1	-	H	
579		2	2	1	-	H	
580		2	2	1	-	H	
581		2	2	1	-	H	
582		2	2	1	-	H	
583		2	2	1	-	H	

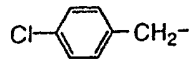
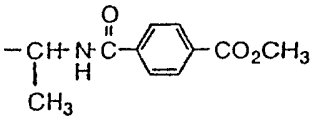
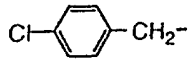
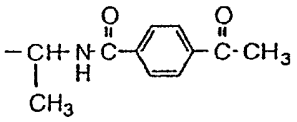
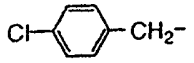
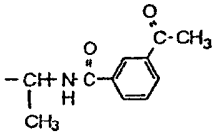
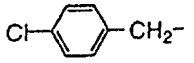
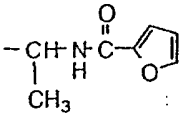
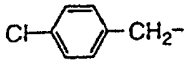
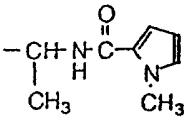
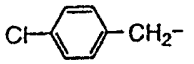
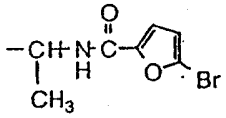
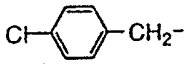
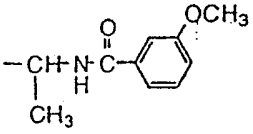
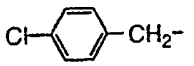
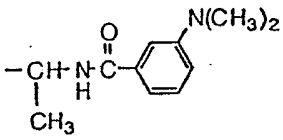
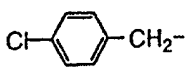
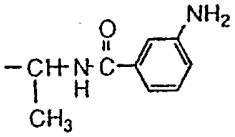
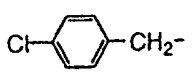
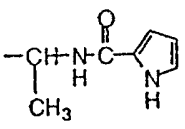
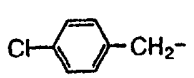
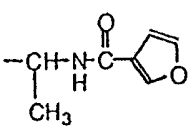
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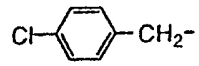
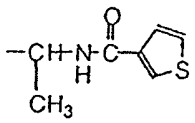
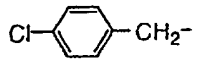
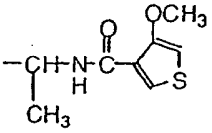
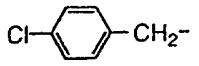
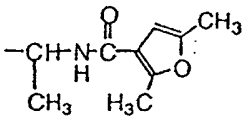
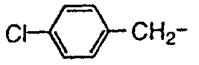
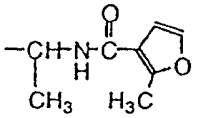
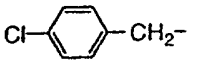
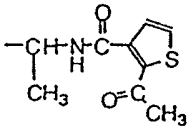
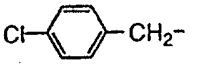
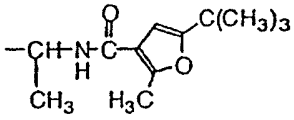
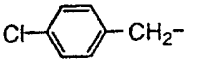
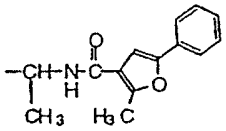
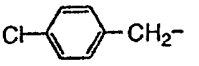
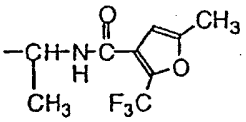
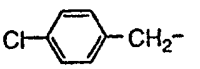
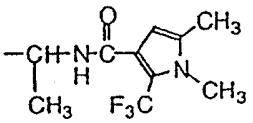
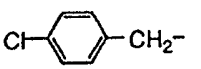
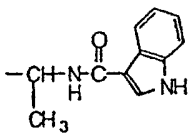
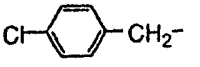
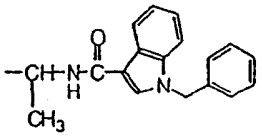
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585		2	2	1	-	H	
586		2	2	1	-	H	
587		2	2	1	-	H	
588		2	2	1	-	H	
589		2	2	1	-	H	
590		2	2	1	-	H	
591		2	2	1	-	H	
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Tabulka 1.55

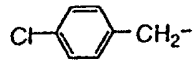
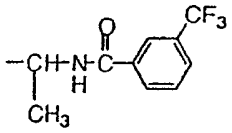
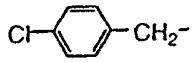
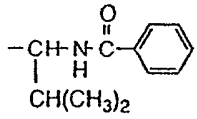
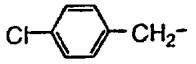
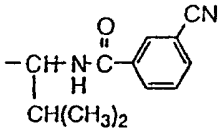
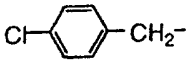
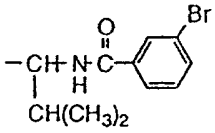
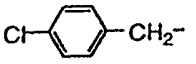
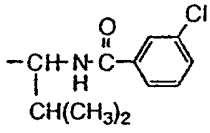
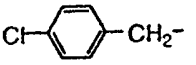
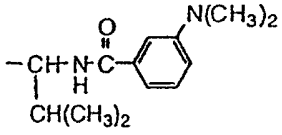
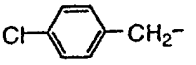
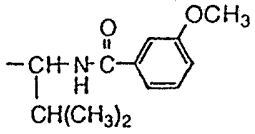
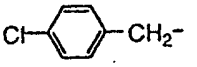
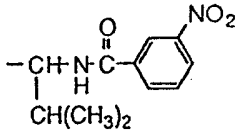
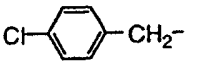
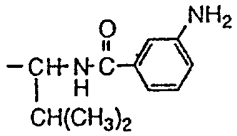
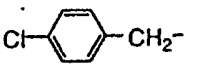
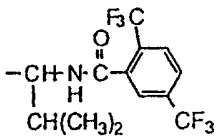
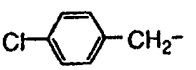
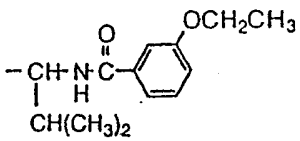
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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599		2	2	1	-	H	
600		2	2	1	-	H	
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Tabulka 1.56

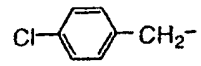
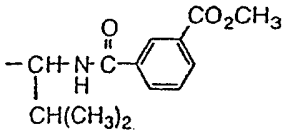
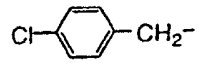
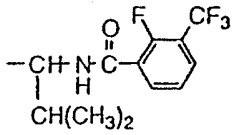
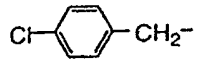
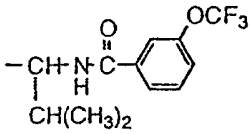
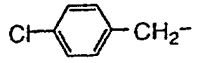
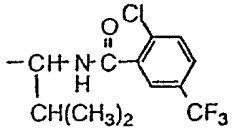
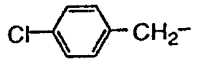
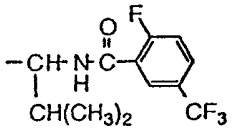
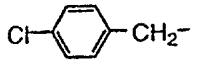
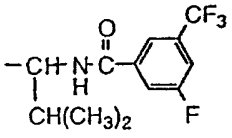
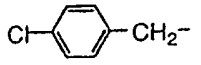
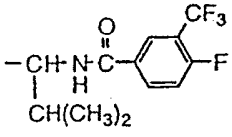
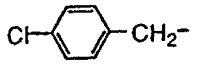
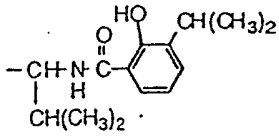
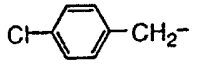
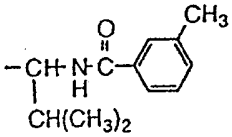
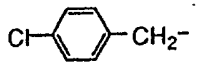
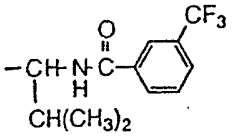
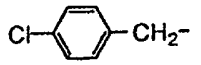
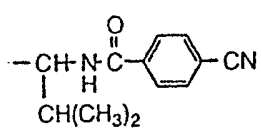
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
606		2	2	1	-	H	
607		2	2	1	-	H	
608		2	2	1	-	H	
609		2	2	1	-	H	
610		2	2	1	-	H	
611		2	2	1	-	H	
612		2	2	1	-	H	
613		2	2	1	-	H	
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615		2	2	1	-	H	
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03.07.00

Tabulka 1.57

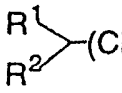
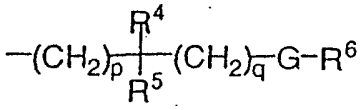
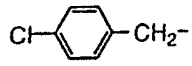
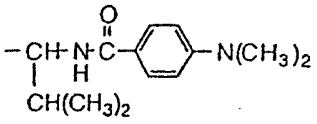
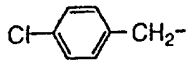
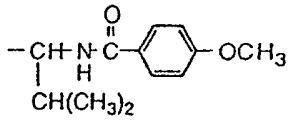
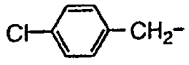
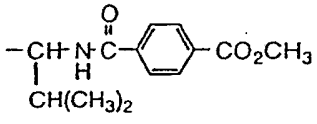
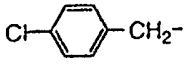
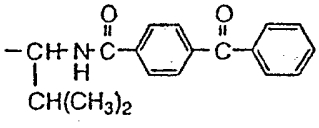
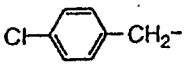
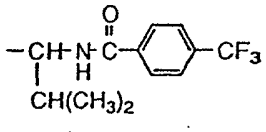
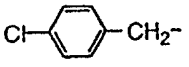
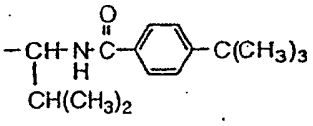
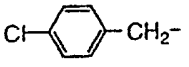
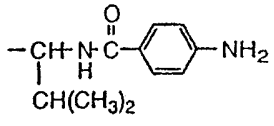
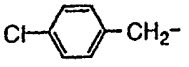
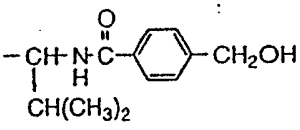
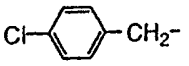
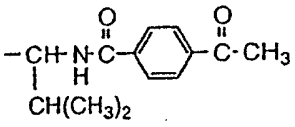
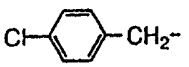
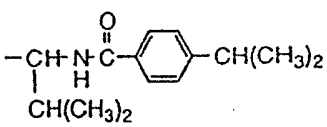
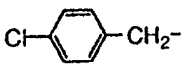
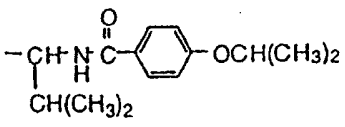
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
617		2	2	1	-	H	
618		2	2	1	-	H	
619		2	2	1	-	H	
620		2	2	1	-	H	
621		2	2	1	-	H	
622		2	2	1	-	H	
623		2	2	1	-	H	
624		2	2	1	-	H	
625		2	2	1	-	H	
626		2	2	1	-	H	
627		2	2	1	-	H	

Tabulka 1.58

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
628		2	2	1	-	H	
629		2	2	1	-	H	
630		2	2	1	-	H	
631		2	2	1	-	H	
632		2	2	1	-	H	
633		2	2	1	-	H	
634		2	2	1	-	H	
635		2	2	1	-	H	
636		2	2	1	-	H	
637		2	2	1	-	H	
638		2	2	1	-	H	

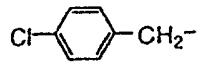
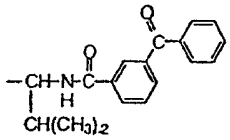
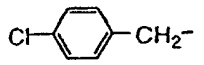
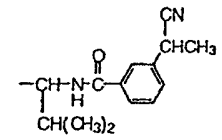
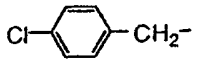
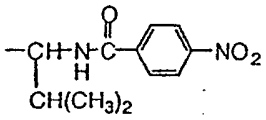
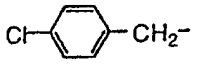
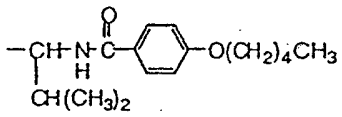
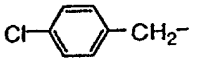
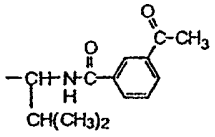
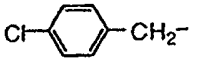
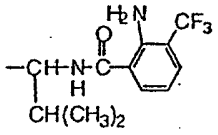
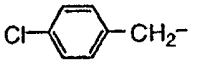
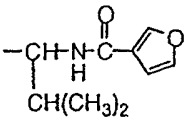
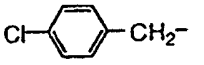
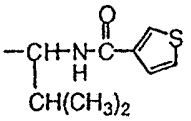
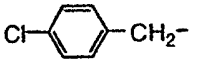
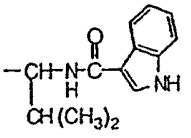
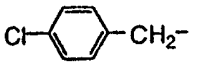
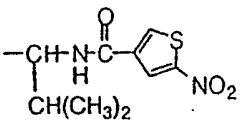
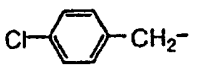
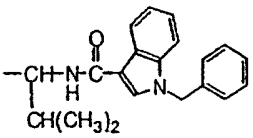
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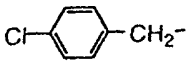
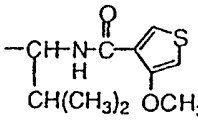
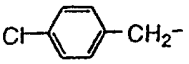
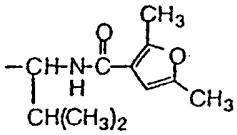
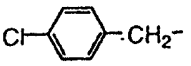
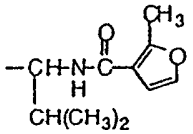
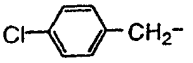
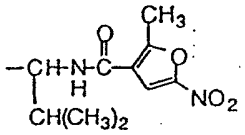
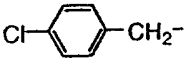
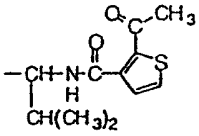
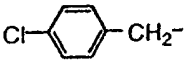
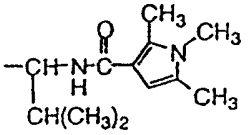
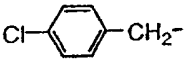
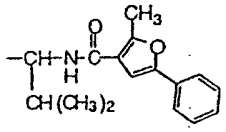
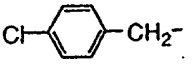
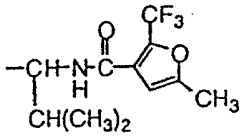
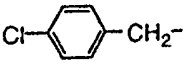
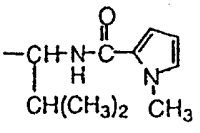
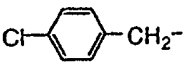
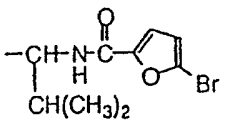
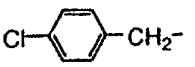
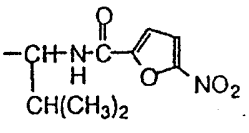
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Tabulka 1.60

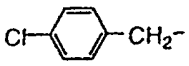
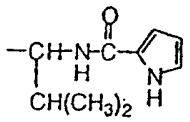
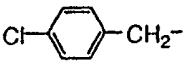
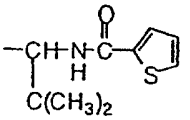
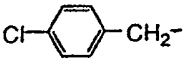
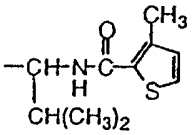
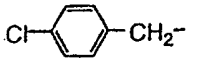
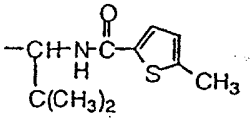
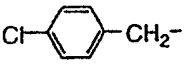
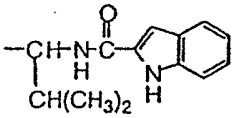
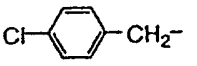
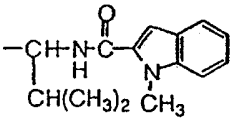
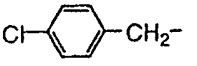
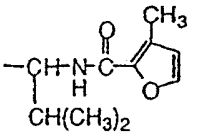
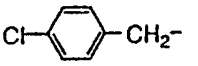
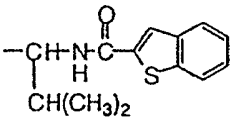
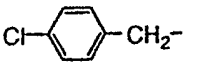
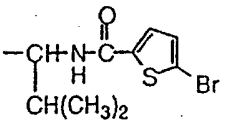
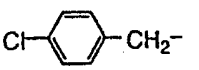
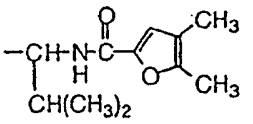
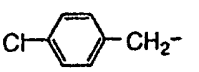
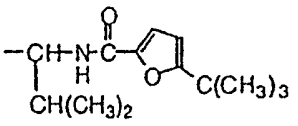
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
650		2	2	1	-	H	
651		2	2	1	-	H	
652		2	2	1	-	H	
653		2	2	1	-	H	
654		2	2	1	-	H	
655		2	2	1	-	H	
656		2	2	1	-	H	
657		2	2	1	-	H	
658		2	2	1	-	H	
659		2	2	1	-	H	
660		2	2	1	-	H	

Tabulka 1.61

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$(CH_2)_p$, R^4, R^5, $(CH_2)_q$, G, R^6
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662		2	2	1	-	H	
663		2	2	1	-	H	
664		2	2	1	-	H	
665		2	2	1	-	H	
666		2	2	1	-	H	
667		2	2	1	-	H	
668		2	2	1	-	H	
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670		2	2	1	-	H	
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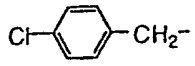
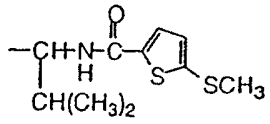
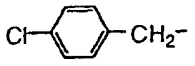
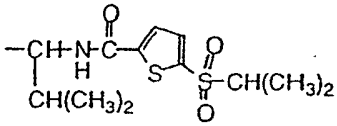
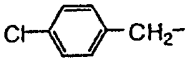
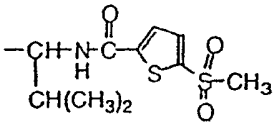
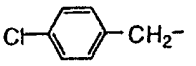
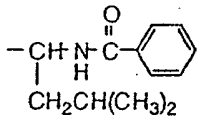
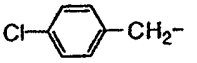
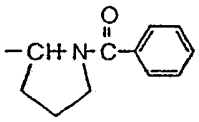
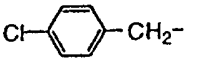
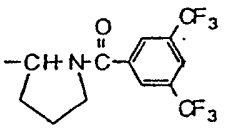
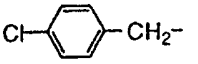
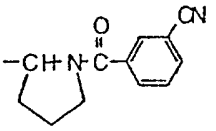
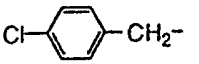
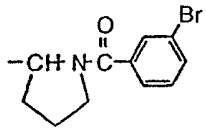
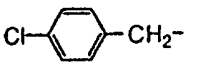
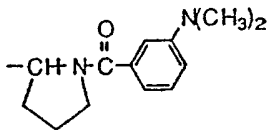
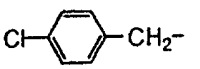
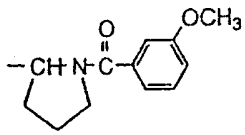
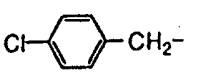
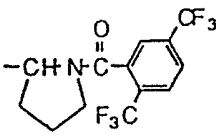
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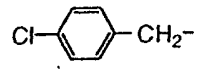
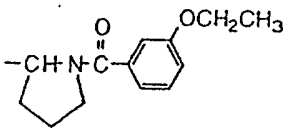
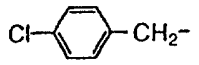
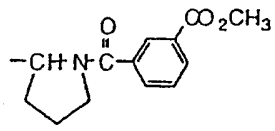
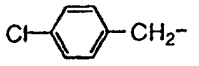
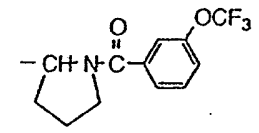
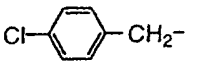
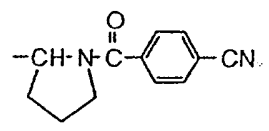
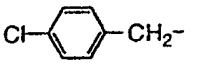
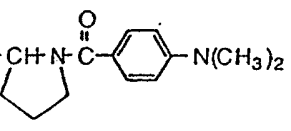
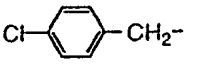
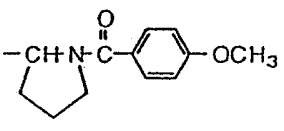
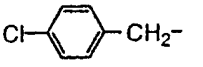
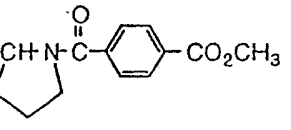
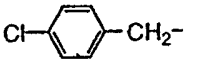
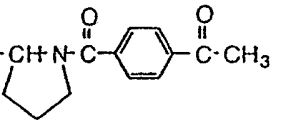
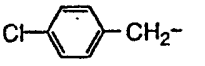
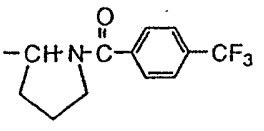
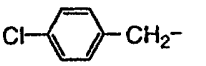
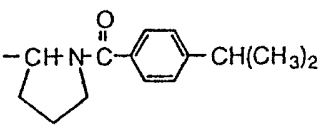
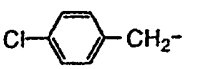
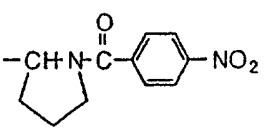
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673		2	2	1	-	H	
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675		2	2	1	-	H	
676		2	2	1	-	H	
677		2	2	1	-	H	
678		2	2	1	-	H	
679		2	2	1	-	H	
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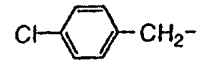
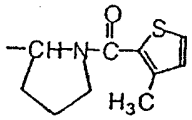
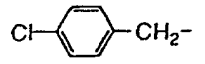
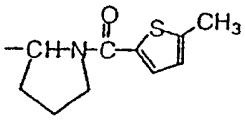
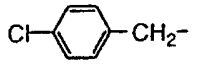
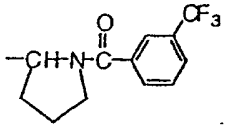
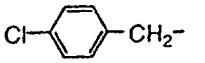
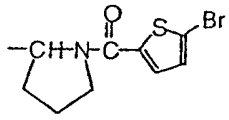
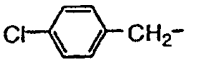
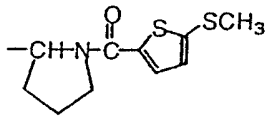
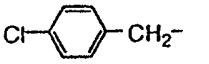
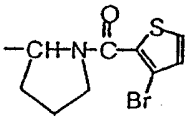
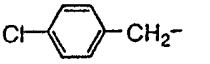
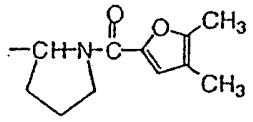
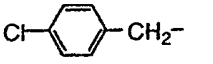
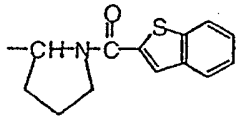
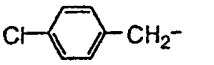
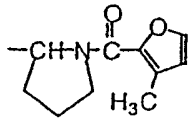
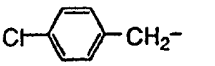
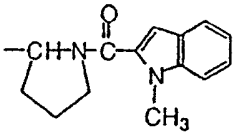
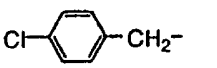
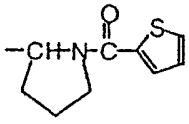
Tabulka 1.63

Sloučč.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
683		2	2	1	-	H	
684		2	2	1	-	H	
685		2	2	1	-	H	
686		2	2	1	-	H	
687		2	2	1	-	H	
688		2	2	1	-	H	
689		2	2	1	-	H	
690		2	2	1	-	H	
691		2	2	1	-	H	
692		2	2	1	-	H	
693		2	2	1	-	H	

Tabulka 1.64

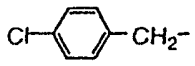
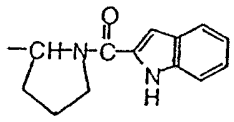
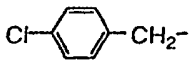
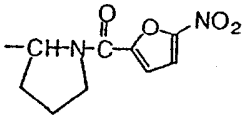
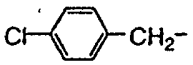
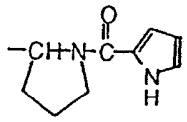
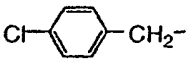
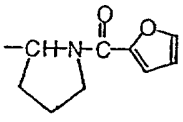
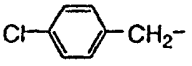
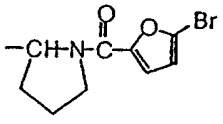
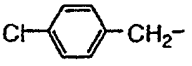
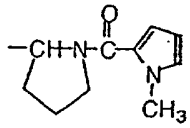
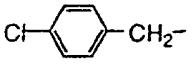
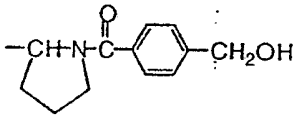
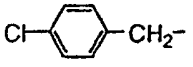
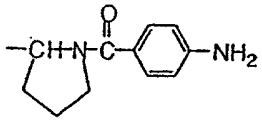
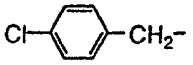
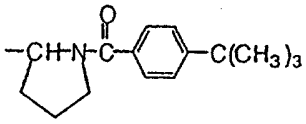
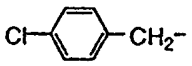
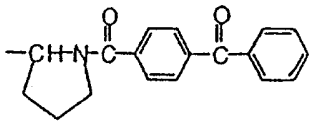
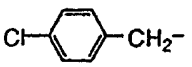
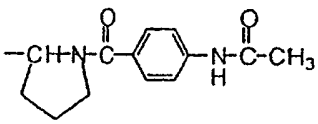
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
694		2	2	1	-	H	
695		2	2	1	-	H	
696		2	2	1	-	H	
697		2	2	1	-	H	
698		2	2	1	-	H	
699		2	2	1	-	H	
700		2	2	1	-	H	
701		2	2	1	-	H	
702		2	2	1	-	H	
703		2	2	1	-	H	
704		2	2	1	-	H	

Tabulka 1.65

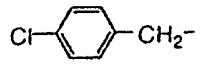
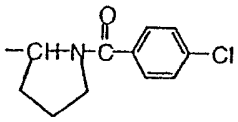
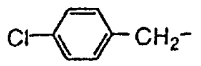
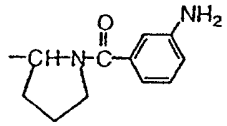
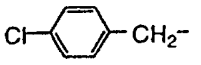
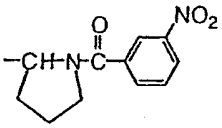
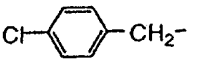
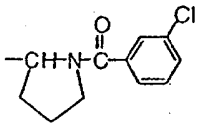
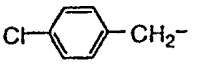
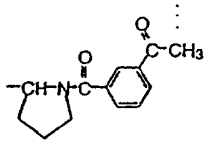
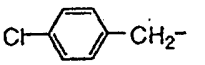
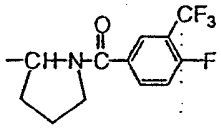
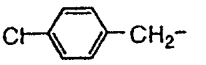
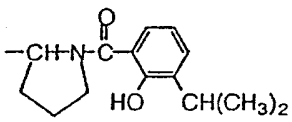
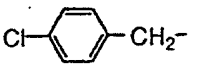
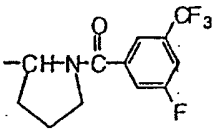
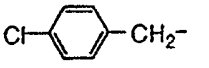
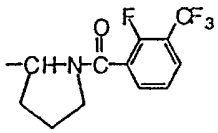
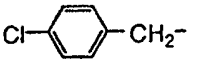
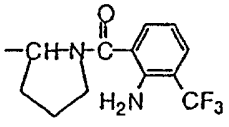
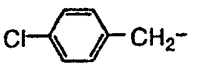
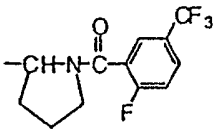
Sloučč.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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706		2	2	1	-	H	
707		2	2	1	-	H	
708		2	2	1	-	H	
709		2	2	1	-	H	
710		2	2	1	-	H	
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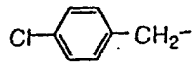
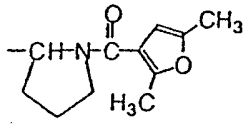
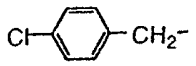
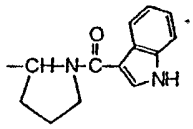
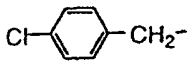
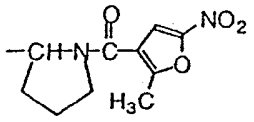
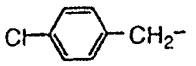
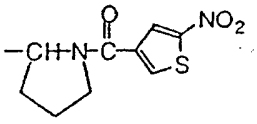
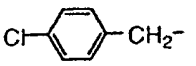
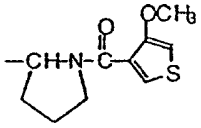
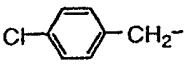
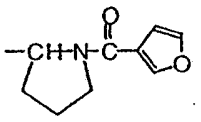
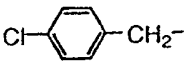
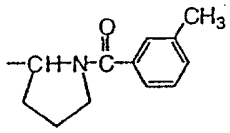
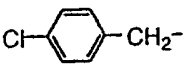
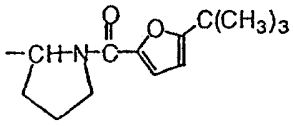
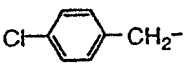
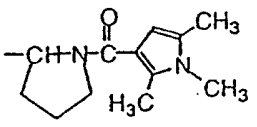
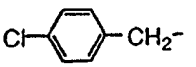
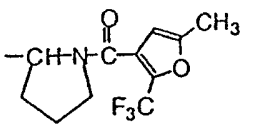
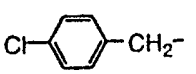
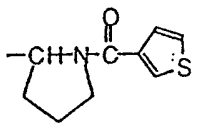
Tabulka 1.66

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
716		2	2	1	-	H	
717		2	2	1	-	H	
718		2	2	1	-	H	
719		2	2	1	-	H	
720		2	2	1	-	H	
721		2	2	1	-	H	
722		2	2	1	-	H	
723		2	2	1	-	H	
724		2	2	1	-	H	
725		2	2	1	-	H	
726		2	2	1	-	H	

Tabulka 1.67

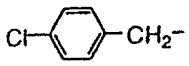
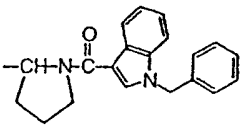
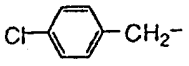
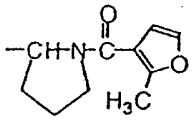
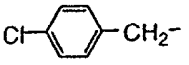
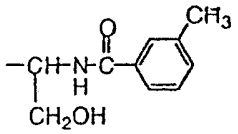
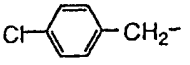
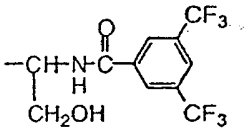
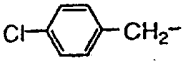
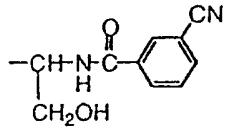
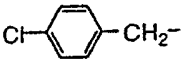
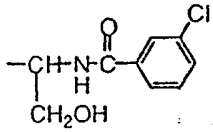
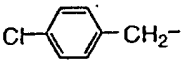
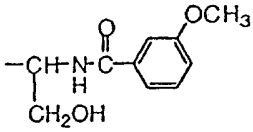
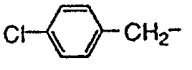
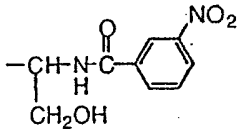
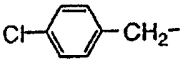
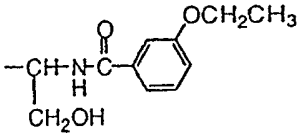
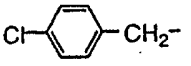
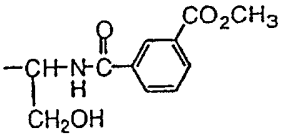
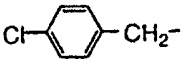
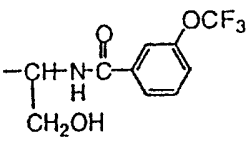
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
727		2	2	1	-	H	
728		2	2	1	-	H	
729		2	2	1	-	H	
730		2	2	1	-	H	
731		2	2	1	-	H	
732		2	2	1	-	H	
733		2	2	1	-	H	
734		2	2	1	-	H	
735		2	2	1	-	H	
736		2	2	1	-	H	
737		2	2	1	-	H	

Tabulka 1.68

Sloučč.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
738		2	2	1	-	H	
739		2	2	1	-	H	
740		2	2	1	-	H	
741		2	2	1	-	H	
742		2	2	1	-	H	
743		2	2	1	-	H	
744		2	2	1	-	H	
745		2	2	1	-	H	
746		2	2	1	-	H	
747		2	2	1	-	H	
748		2	2	1	-	H	

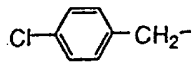
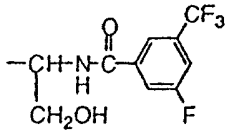
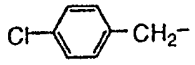
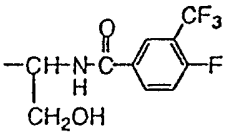
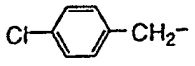
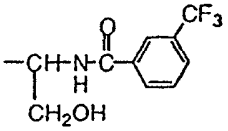
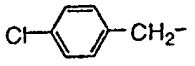
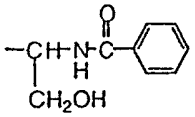
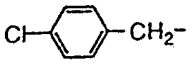
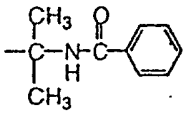
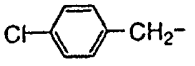
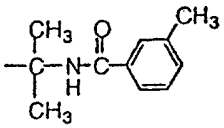
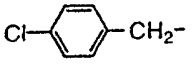
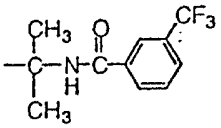
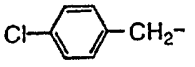
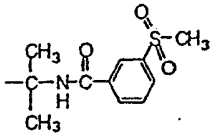
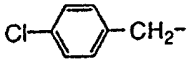
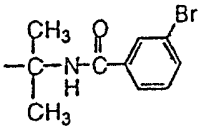
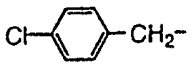
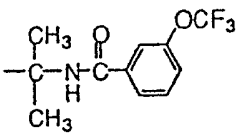
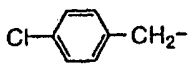
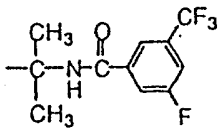
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Tabulka 1.69

Sloučenina č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CH(R^4)(R^5)-(CH_2)_q-G-R^6$
749		2	2	1	-	H	
750		2	2	1	-	H	
751		2	2	1	-	H	
752		2	2	1	-	H	
753		2	2	1	-	H	
754		2	2	1	-	H	
755		2	2	1	-	H	
756		2	2	1	-	H	
757		2	2	1	-	H	
758		2	2	1	-	H	
759		2	2	1	-	H	

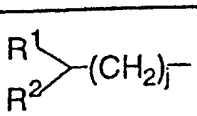
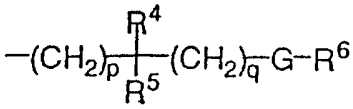
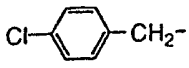
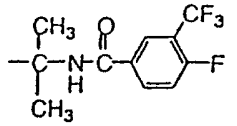
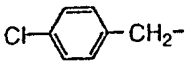
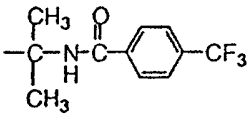
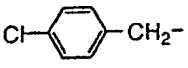
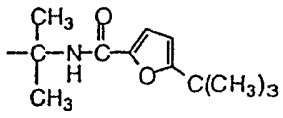
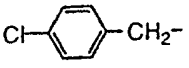
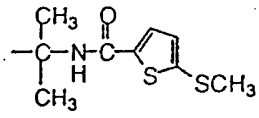
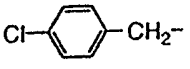
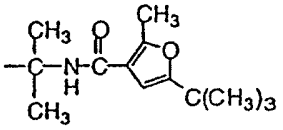
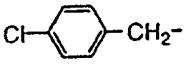
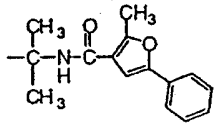
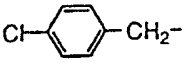
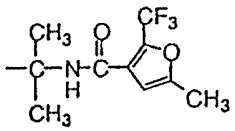
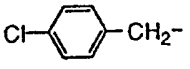
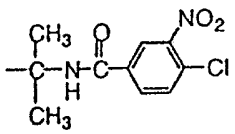
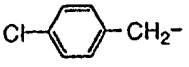
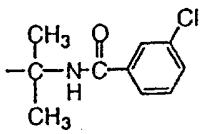
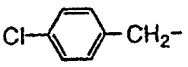
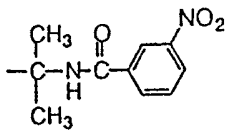
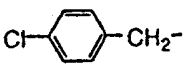
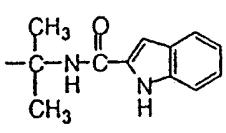
03.07.00

Tabulka 1.70

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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761		2	2	1	-	H	
762		2	2	1	-	H	
763		2	2	1	-	H	
764		2	2	1	-	H	
765		2	2	1	-	H	
766		2	2	1	-	H	
767		2	2	1	-	H	
768		2	2	1	-	H	
769		2	2	1	-	H	
770		2	2	1	-	H	

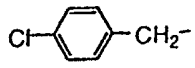
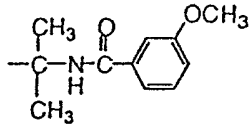
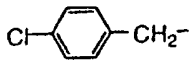
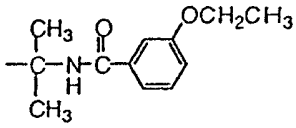
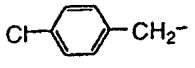
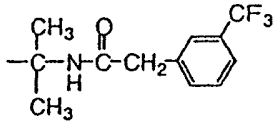
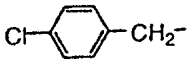
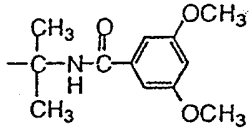
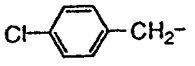
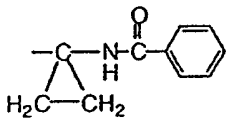
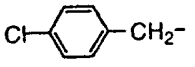
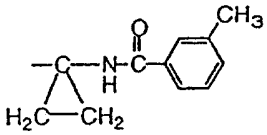
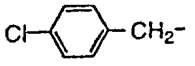
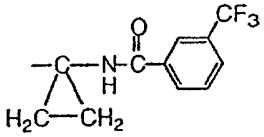
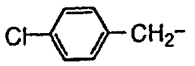
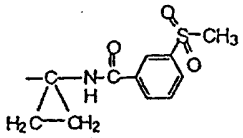
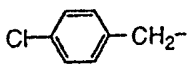
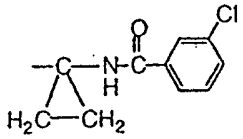
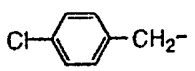
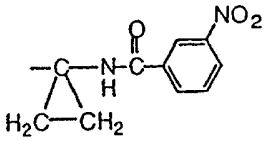
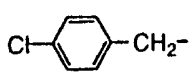
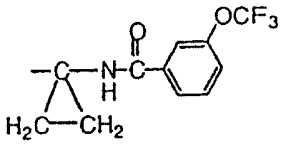
03.07.00

Tabulka 1.71

Slouč.č.		k	m	n	chiralita	R³	
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772		2	2	1	-	H	
773		2	2	1	-	H	
774		2	2	1	-	H	
775		2	2	1	-	H	
776		2	2	1	-	H	
777		2	2	1	-	H	
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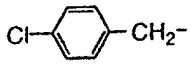
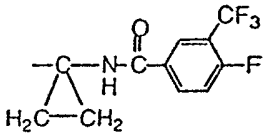
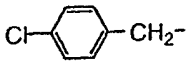
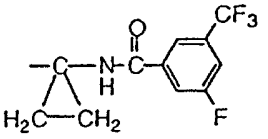
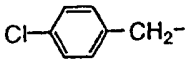
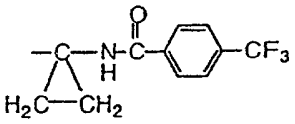
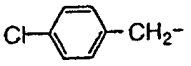
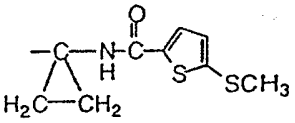
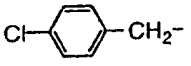
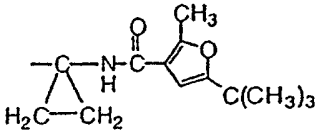
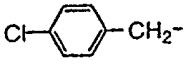
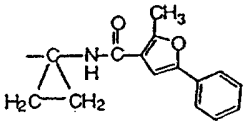
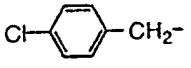
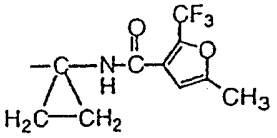
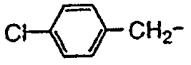
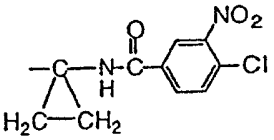
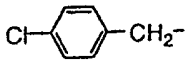
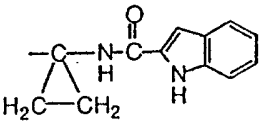
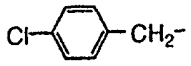
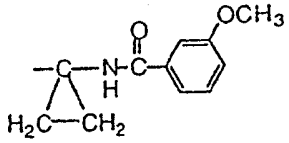
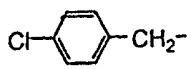
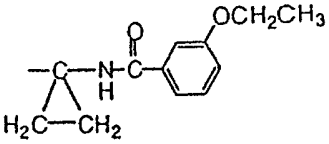
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Tabulka 1.72

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783		2	2	1	-	H	
784		2	2	1	-	H	
785		2	2	1	-	H	
786		2	2	1	-	H	
787		2	2	1	-	H	
788		2	2	1	-	H	
789		2	2	1	-	H	
790		2	2	1	-	H	
791		2	2	1	-	H	
792		2	2	1	-	H	

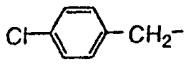
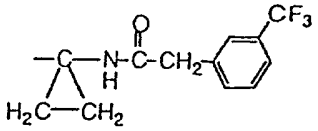
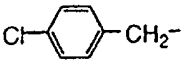
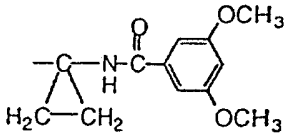
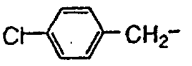
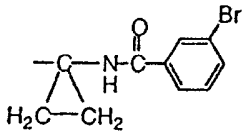
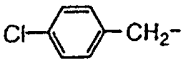
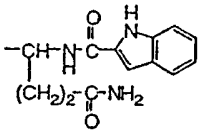
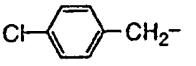
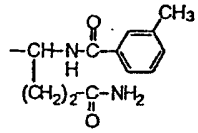
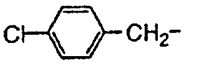
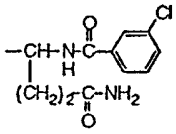
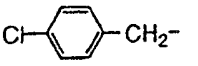
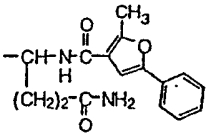
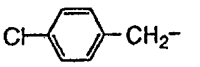
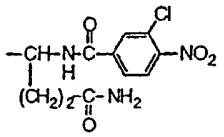
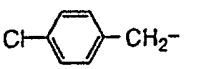
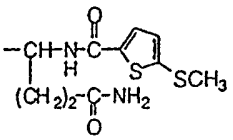
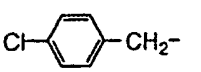
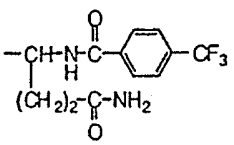
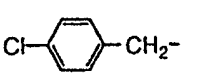
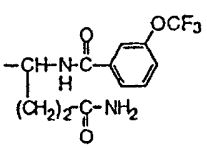
03.07.00

Tabulka 1.73

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
793		2	2	1	-	H	
794		2	2	1	-	H	
795		2	2	1	-	H	
796		2	2	1	-	H	
797		2	2	1	-	H	
798		2	2	1	-	H	
799		2	2	1	-	H	
800		2	2	1	-	H	
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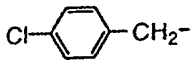
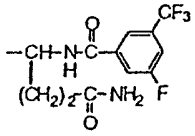
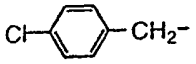
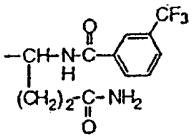
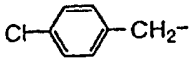
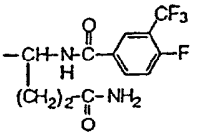
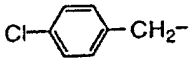
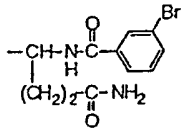
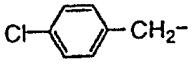
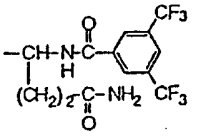
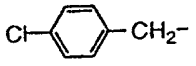
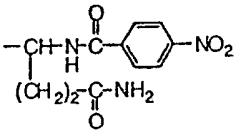
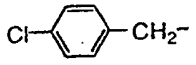
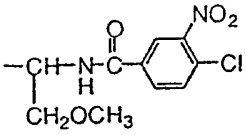
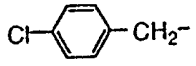
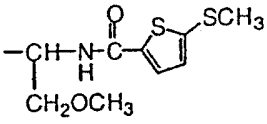
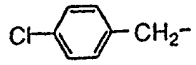
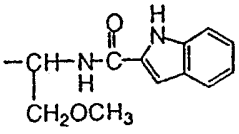
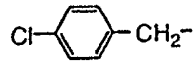
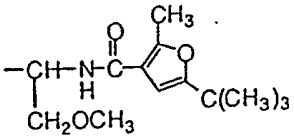
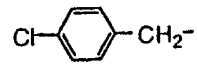
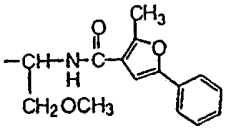
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Tabulka 1.74

Sloučč.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
804		2	2	1	-	H	
805		2	2	1	-	H	
806		2	2	1	-	H	
807		2	2	1	-	H	
808		2	2	1	-	H	
809		2	2	1	-	H	
810		2	2	1	-	H	
811		2	2	1	-	H	
812		2	2	1	-	H	
813		2	2	1	-	H	
814		2	2	1	-	H	

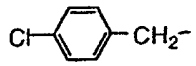
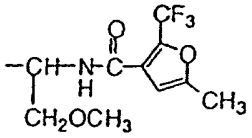
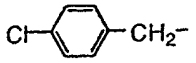
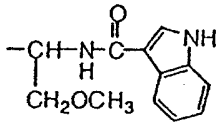
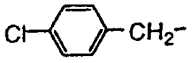
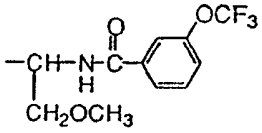
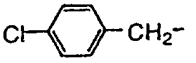
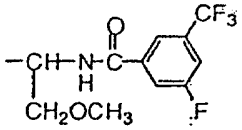
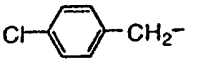
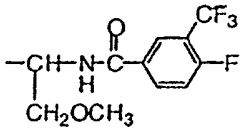
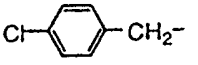
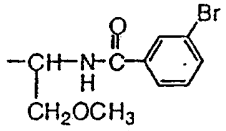
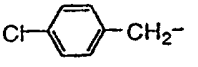
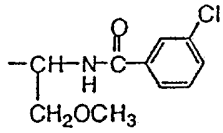
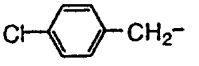
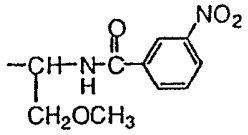
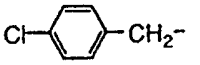
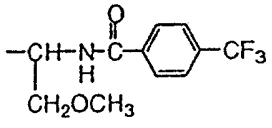
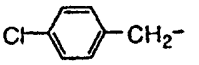
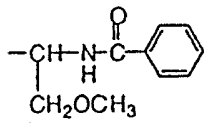
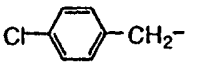
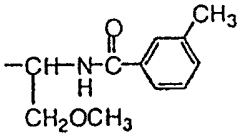
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Tabulka 1.75

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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816		2	2	1	-	H	
817		2	2	1	-	H	
818		2	2	1	-	H	
819		2	2	1	-	H	
820		2	2	1	-	H	
821		2	2	1	-	H	
822		2	2	1	-	H	
823		2	2	1	-	H	
824		2	2	1	-	H	
825		2	2	1	-	H	

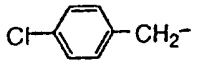
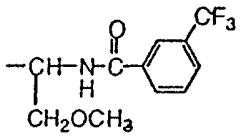
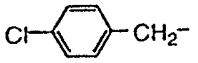
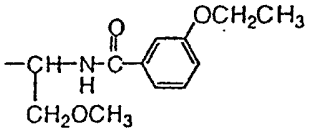
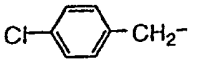
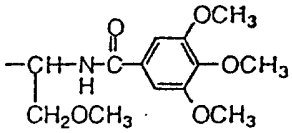
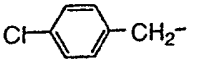
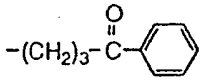
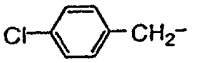
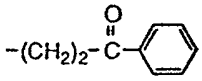
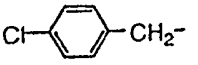
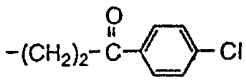
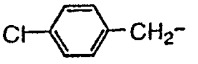
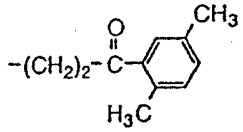
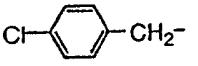
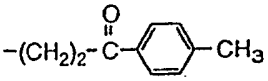
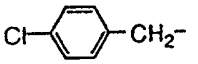
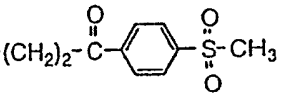
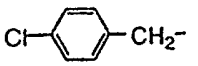
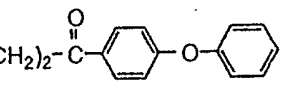
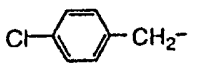
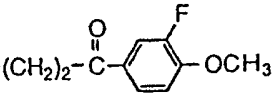
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Tabulka 1.76

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
826		2	2	1	-	H	
827		2	2	1	-	H	
828		2	2	1	-	H	
829		2	2	1	-	H	
830		2	2	1	-	H	
831		2	2	1	-	H	
832		2	2	1	-	H	
833		2	2	1	-	H	
834		2	2	1	-	H	
835		2	2	1	-	H	
836		2	2	1	-	H	

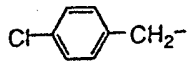
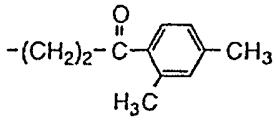
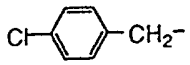
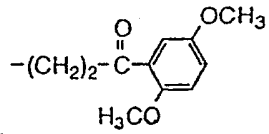
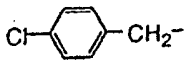
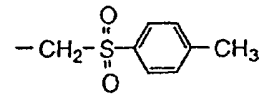
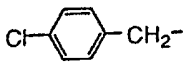
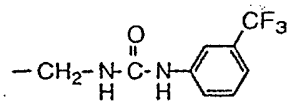
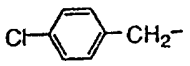
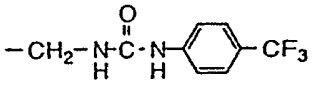
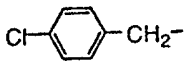
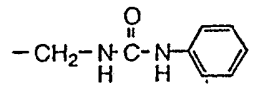
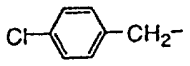
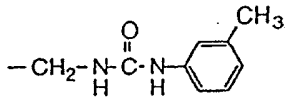
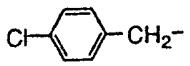
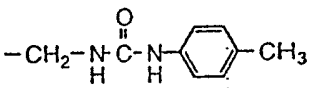
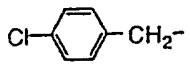
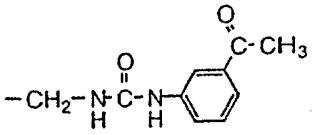
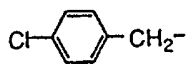
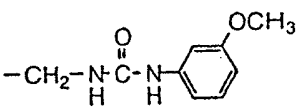
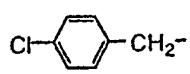
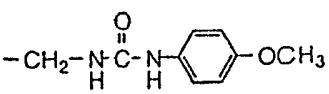
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Tabulka 1.77

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838		2	2	1	-	H	
839		2	2	1	-	H	
840		2	2	1	-	H	
841		2	2	1	-	H	
842		2	2	1	-	H	
843		2	2	1	-	H	
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845		2	2	1	-	H	
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847		2	2	1	-	H	

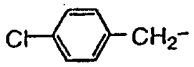
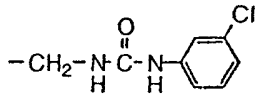
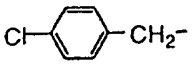
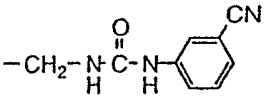
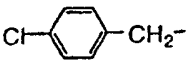
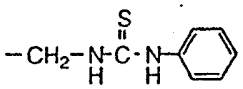
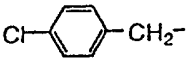
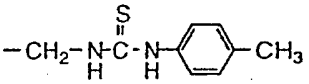
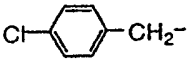
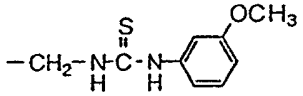
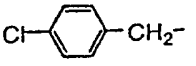
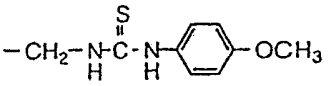
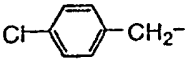
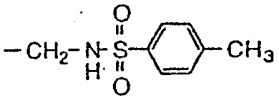
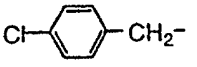
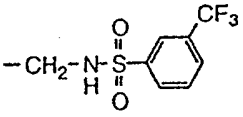
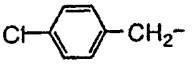
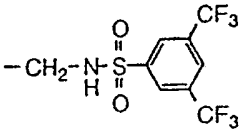
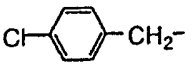
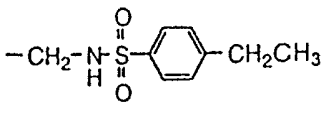
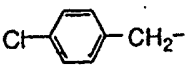
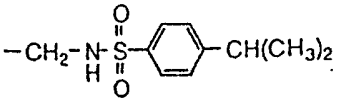
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Tabulka 1.78

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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849		2	2	1	-	H	
850		2	2	1	-	H	
851		2	2	1	-	H	
852		2	2	1	-	H	
853		2	2	1	-	H	
854		2	2	1	-	H	
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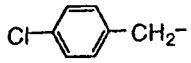
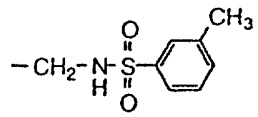
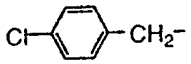
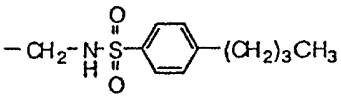
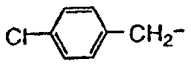
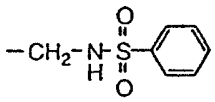
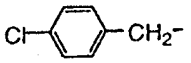
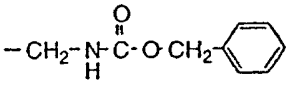
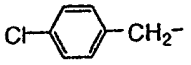
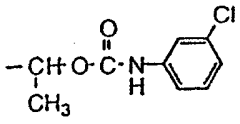
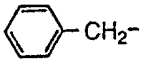
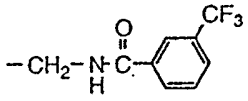
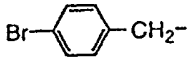
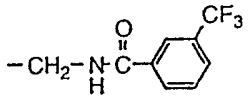
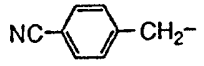
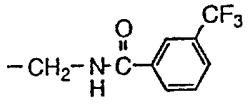
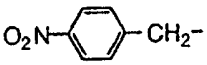
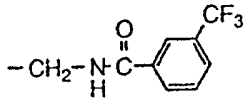
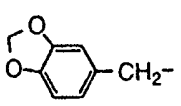
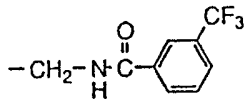
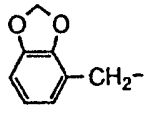
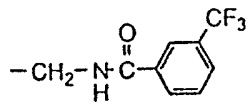
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Tabulka 1.79

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859		2	2	1	-	H	
860		2	2	1	-	H	
861		2	2	1	-	H	
862		2	2	1	-	H	
863		2	2	1	-	H	
864		2	2	1	-	H	
865		2	2	1	-	H	
866		2	2	1	-	H	
867		2	2	1	-	H	
868		2	2	1	-	H	
869		2	2	1	-	H	

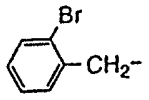
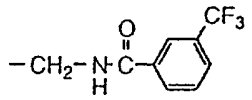
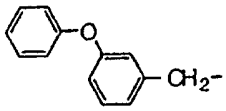
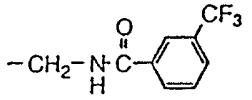
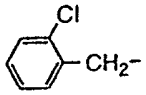
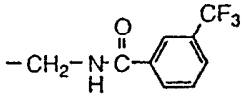
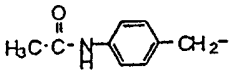
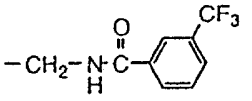
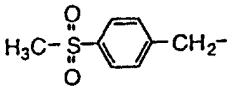
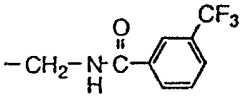
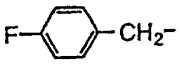
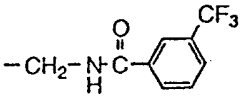
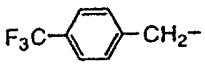
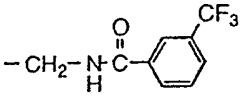
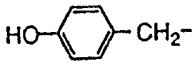
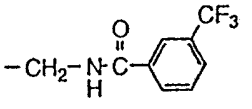
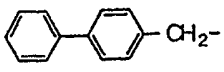
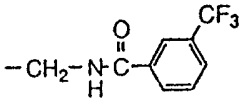
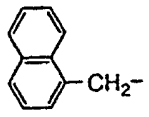
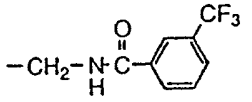
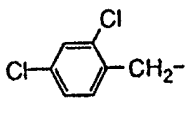
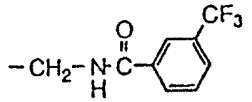
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Tabulka 1.80

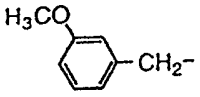
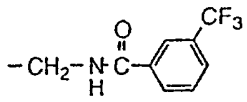
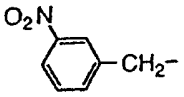
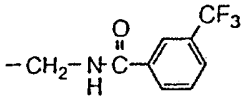
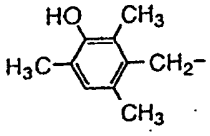
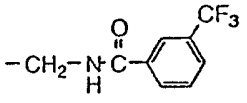
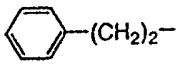
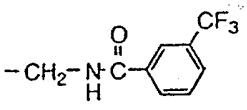
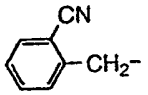
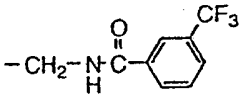
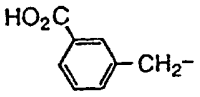
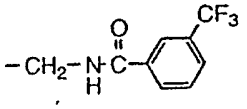
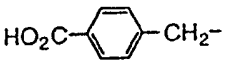
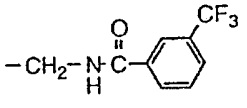
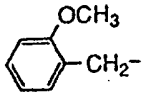
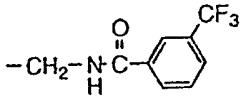
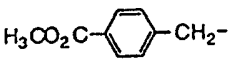
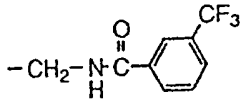
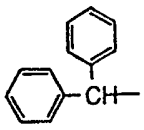
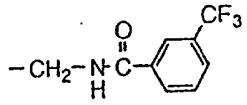
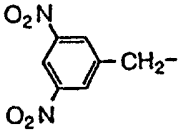
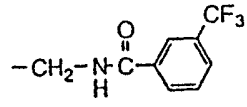
Sloučč.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
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873		2	2	1	-	H	
874		2	2	1	-	H	
875		2	2	1	-	H	
876		2	2	1	-	H	
877		2	2	1	-	H	
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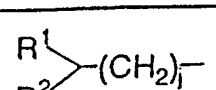
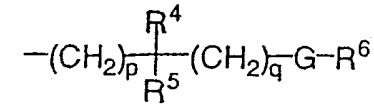
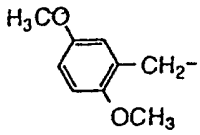
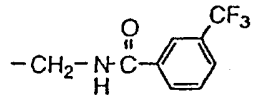
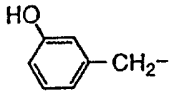
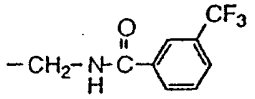
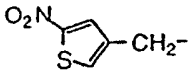
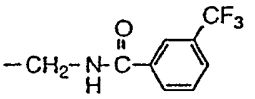
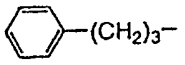
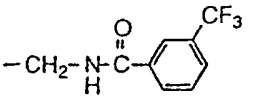
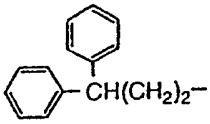
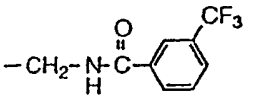
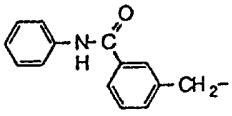
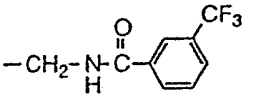
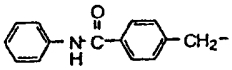
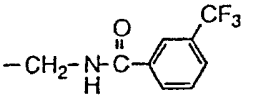
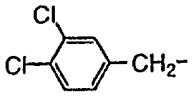
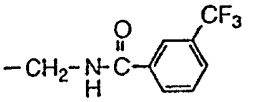
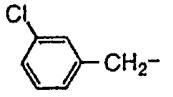
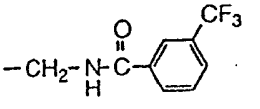
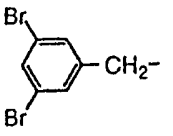
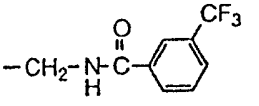
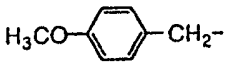
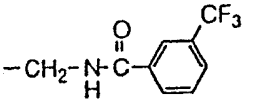
Tabulka 1.81

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
881		2	2	1	-	H	
882		2	2	1	-	H	
883		2	2	1	-	H	
884		2	2	1	-	H	
885		2	2	1	-	H	
886		2	2	1	-	H	
887		2	2	1	-	H	
888		2	2	1	-	H	
889		2	2	1	-	H	
890		2	2	1	-	H	
891		2	2	1	-	H	

Tabulka 1.82

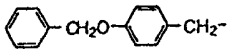
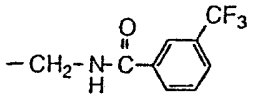
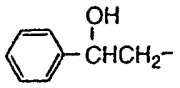
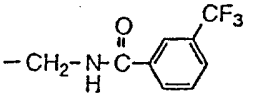
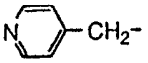
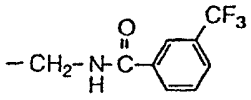
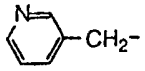
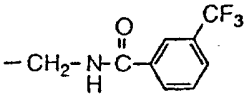
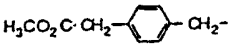
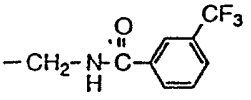
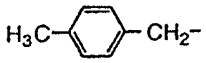
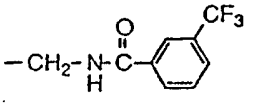
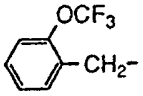
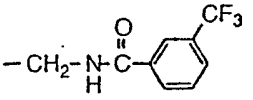
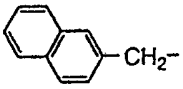
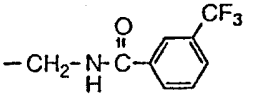
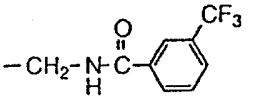
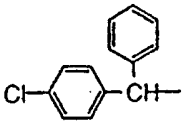
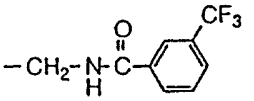
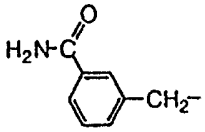
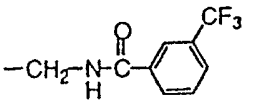
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
892		2	2	1	-	H	
893		2	2	1	-	H	
894		2	2	1	-	H	
895		2	2	1	-	H	
896		2	2	1	-	H	
897		2	2	1	-	H	
898		2	2	1	-	H	
899		2	2	1	-	H	
900		2	2	1	-	H	
901		2	2	1	-	H	
902		2	2	1	-	H	

Tabulka 1.83

Slouč.č.		k	m	n	chiralita	R^3	
903		2	2	1	-	H	
904		2	2	1	-	H	
905		2	2	1	-	H	
906		2	2	1	-	H	
907		2	2	1	-	H	
908		2	2	1	-	H	
909		2	2	1	-	H	
910		2	2	1	-	H	
911		2	2	1	-	H	
912		2	2	1	-	H	
913		2	2	1	-	H	

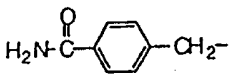
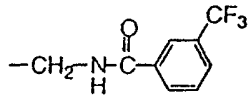
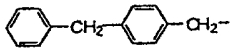
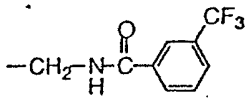
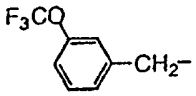
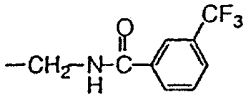
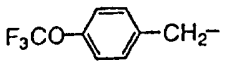
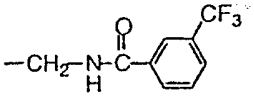
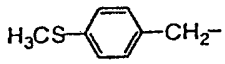
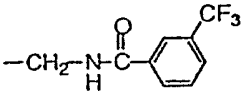
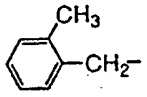
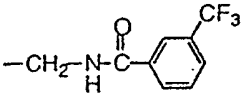
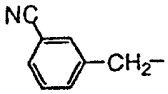
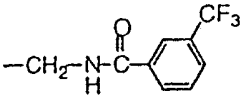
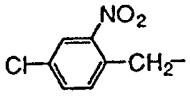
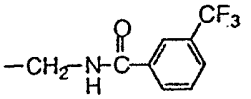
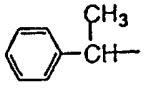
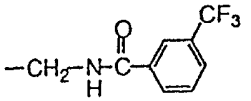
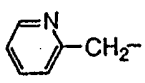
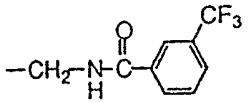
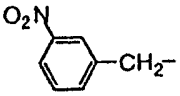
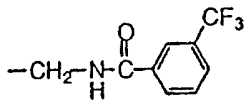
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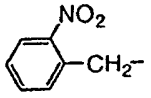
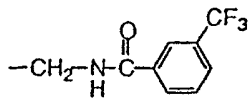
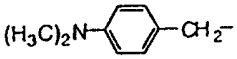
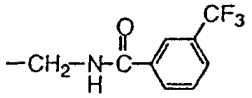
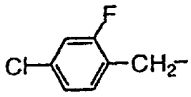
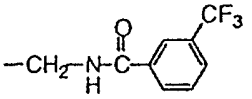
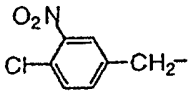
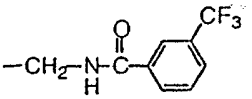
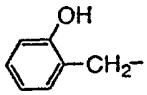
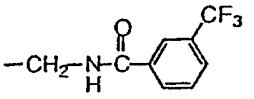
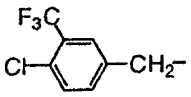
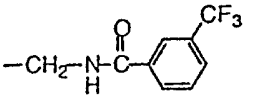
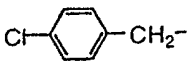
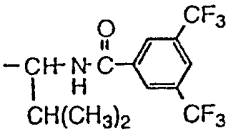
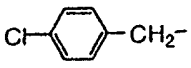
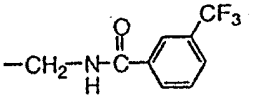
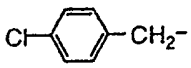
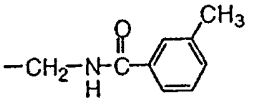
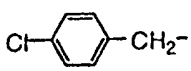
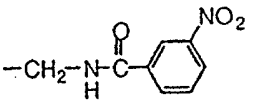
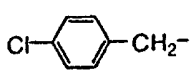
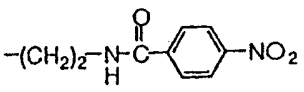
Sloučenina č.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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915		2	2	1	-	H	
916		2	2	1	-	H	
917		2	2	1	-	H	
918		2	2	1	-	H	
919		2	2	1	-	H	
920		2	2	1	-	H	
921		2	2	1	-	H	
922		2	2	1	-	H	
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924		2	2	1	-	H	

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Tabulka 1.85

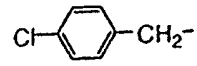
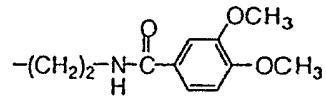
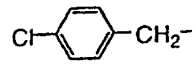
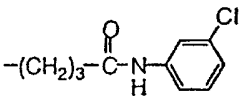
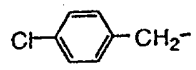
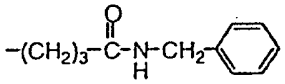
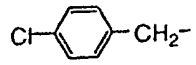
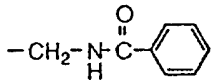
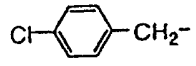
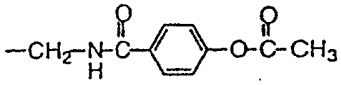
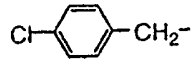
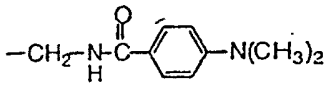
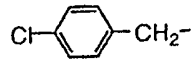
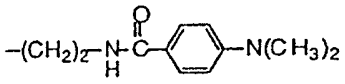
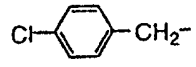
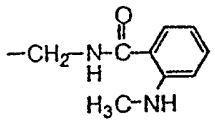
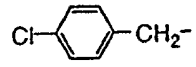
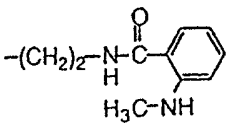
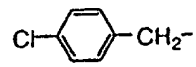
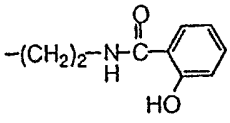
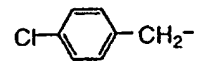
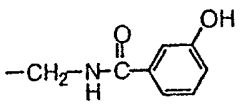
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
925		2	2	1	-	H	
926		2	2	1	-	H	
927		2	2	1	-	H	
928		2	2	1	-	H	
929		2	2	1	-	H	
930		2	2	1	-	H	
931		2	2	1	-	H	
932		2	2	1	-	H	
933		2	2	1	-	H	
934		2	2	1	-	H	
935		2	2	1	-	H	

Tabulka 1.86

Sloučč.	$R^1R^2CH(CH_2)_j$–	k	m	n	chirali	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
936		2	2	1	-	H	
937		2	2	1	-	H	
938		2	2	1	-	H	
939		2	2	1	-	H	
940		2	2	1	-	H	
941		2	2	1	-	H	
942		2	2	1	-	H	
943		1	4	0	-	H	
944		1	4	0	-	H	
945		1	4	0	-	H	
946		1	4	0	-	H	

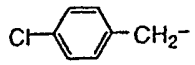
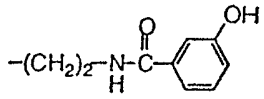
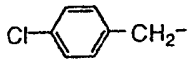
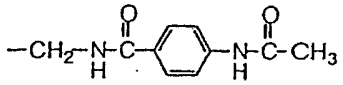
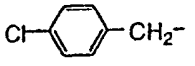
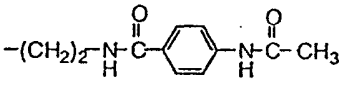
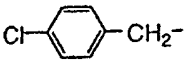
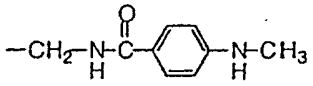
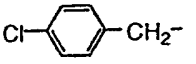
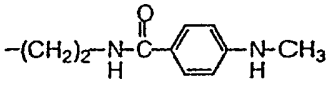
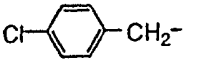
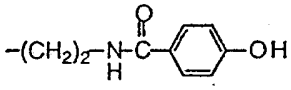
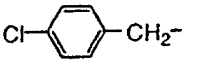
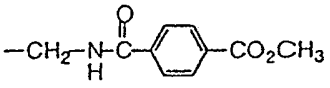
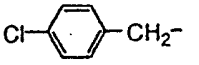
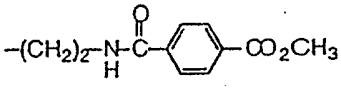
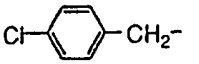
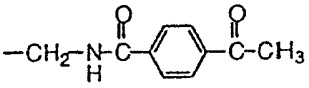
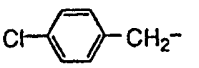
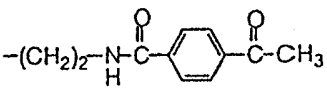
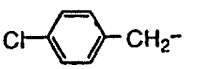
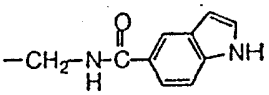
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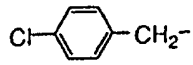
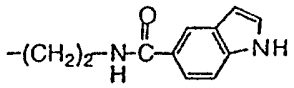
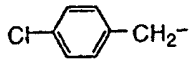
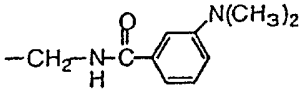
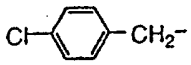
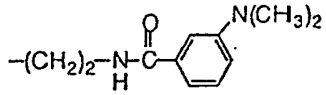
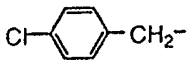
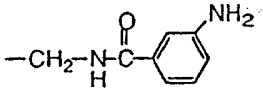
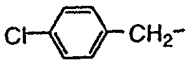
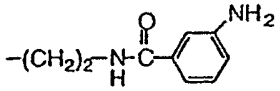
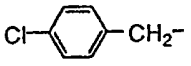
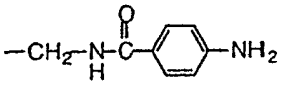
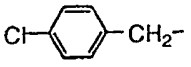
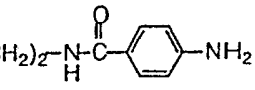
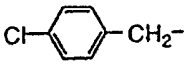
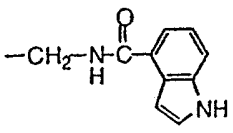
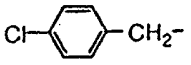
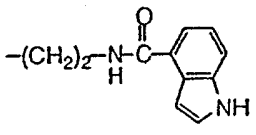
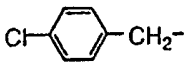
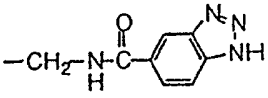
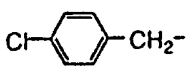
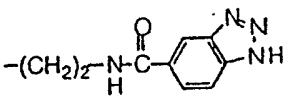
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948		1	4	0	-	H	
949		1	4	0	-	H	
950		0	4	1	-	H	
951		1	2	0	R	H	
952		1	2	0	R	H	
953		1	2	0	R	H	
954		1	2	0	R	H	
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956		1	2	0	R	H	
957		1	2	0	R	H	

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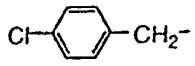
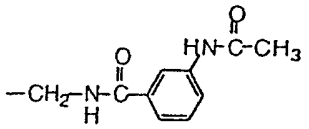
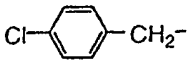
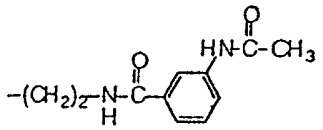
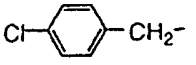
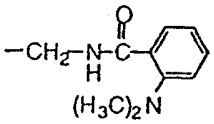
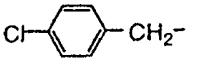
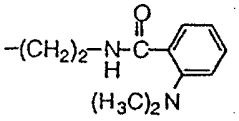
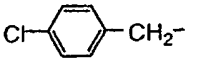
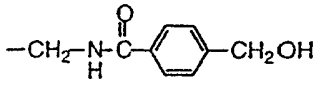
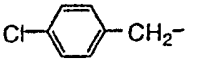
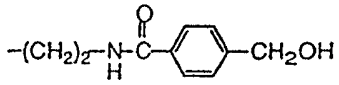
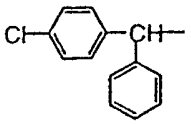
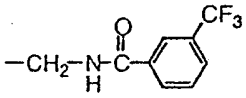
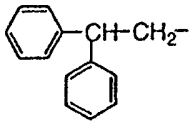
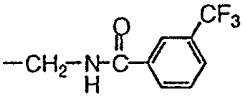
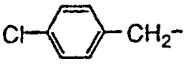
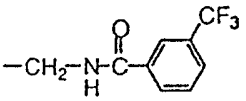
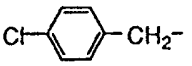
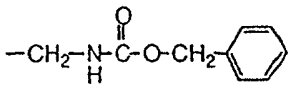
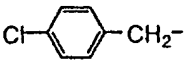
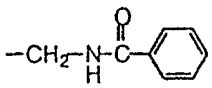
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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959		1	2	0	R	H	
960		1	2	0	R	H	
961		1	2	0	R	H	
962		1	2	0	R	H	
963		1	2	0	R	H	
964		1	2	0	R	H	
965		1	2	0	R	H	
966		1	2	0	R	H	
967		1	2	0	R	H	
968		1	2	0	R	H	

Tabulka 1.89

Sloučenina č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
969		1	2	0	R	H	
970		1	2	0	R	H	
971		1	2	0	R	H	
972		1	2	0	R	H	
973		1	2	0	R	H	
974		1	2	0	R	H	
975		1	2	0	R	H	
976		1	2	0	R	H	
977		1	2	0	R	H	
978		1	2	0	R	H	
979		1	2	0	R	H	

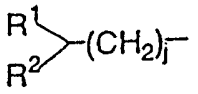
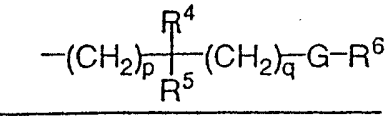
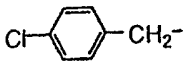
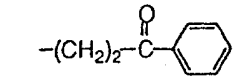
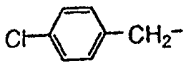
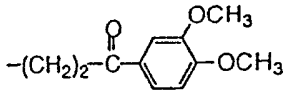
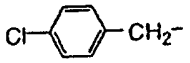
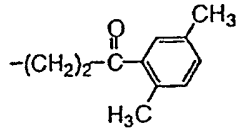
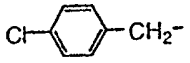
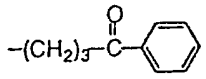
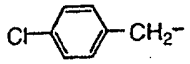
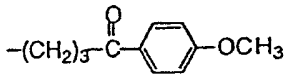
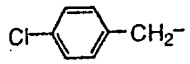
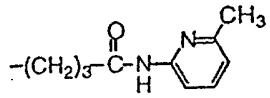
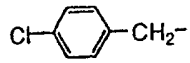
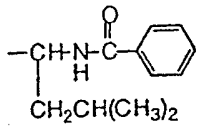
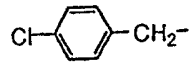
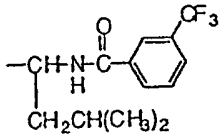
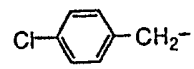
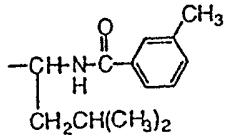
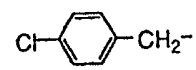
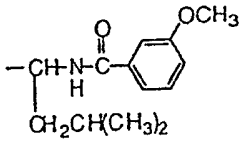
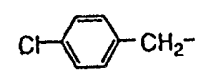
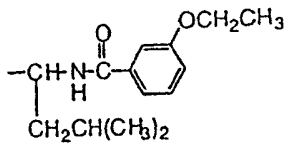
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Tabulka 1.90

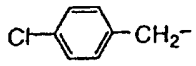
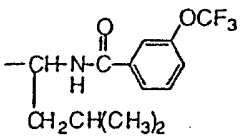
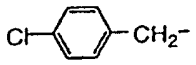
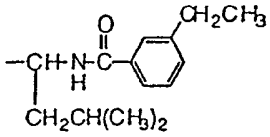
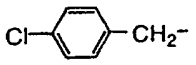
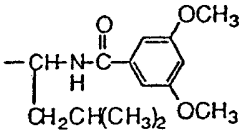
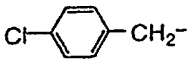
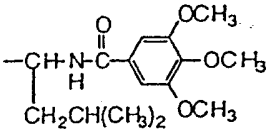
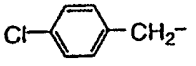
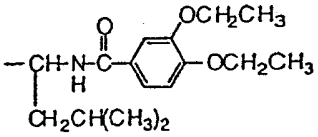
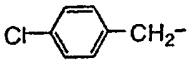
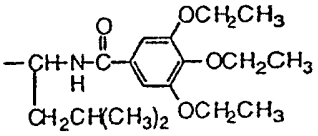
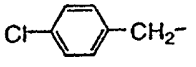
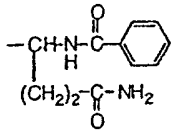
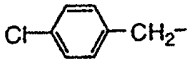
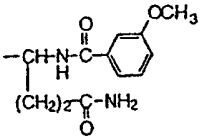
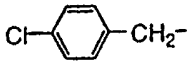
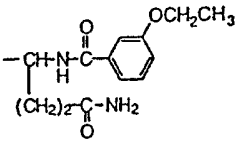
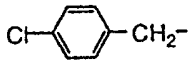
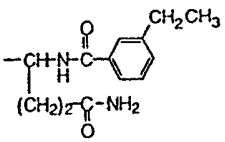
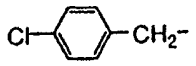
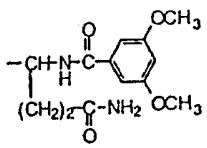
Slouč.č.	$R^1(R^2)CH-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
980		1	2	0	R	H	
981		1	2	0	R	H	
982		1	2	0	R	H	
983		1	2	0	R	H	
984		1	2	0	R	H	
985		1	2	0	R	H	
986		1	2	0	R	H	
987		2	2	1	-	H	
988		1	4	0	-	H	
989		1	4	0	-	H	
990		1	4	0	-	H	

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Tabulka 1.91

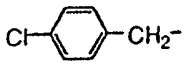
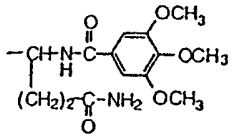
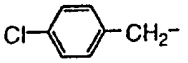
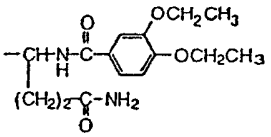
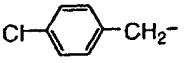
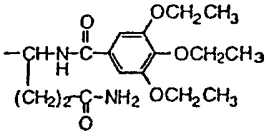
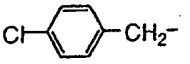
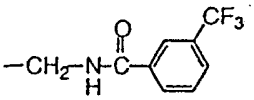
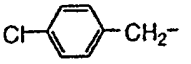
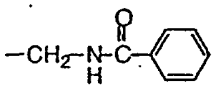
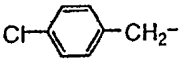
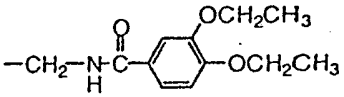
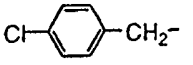
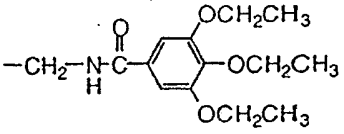
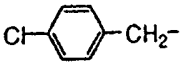
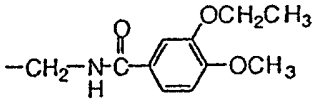
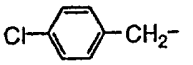
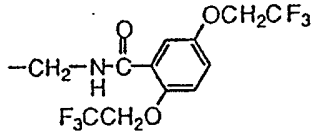
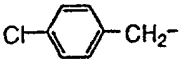
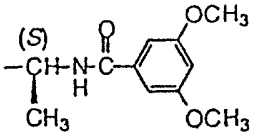
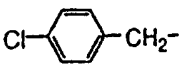
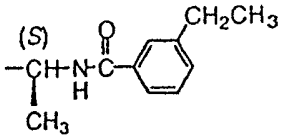
Slouč.č.		k	m	n	chiralita	R^3	
991		1	4	0	-	H	
992		1	4	0	-	H	
993		1	4	0	-	H	
994		1	4	0	-	H	
995		1	4	0	-	H	
996		1	4	0	-	H	
997		2	2	1	-	H	
998		2	2	1	-	H	
999		2	2	1	-	H	
1000		2	2	1	-	H	
1001		2	2	1	-	H	

Tabulka 1.92

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1002		2	2	1	-	H	
1003		2	2	1	-	H	
1004		2	2	1	-	H	
1005		2	2	1	-	H	
1006		2	2	1	-	H	
1007		2	2	1	-	H	
1008		2	2	1	-	H	
1009		2	2	1	-	H	
1010		2	2	1	-	H	
1011		2	2	1	-	H	
1012		2	2	1	-	H	

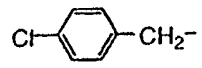
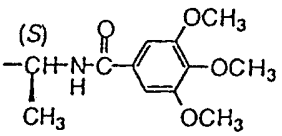
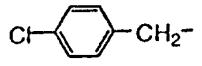
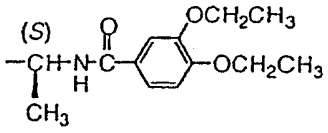
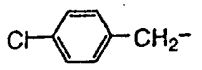
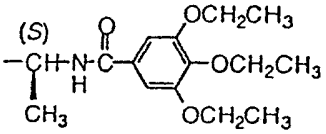
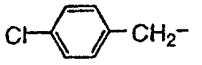
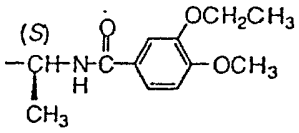
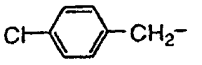
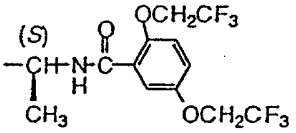
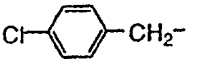
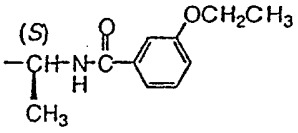
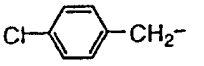
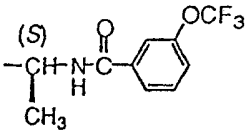
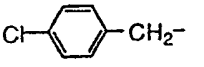
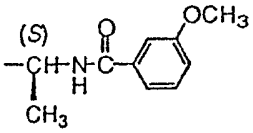
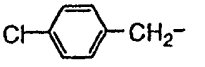
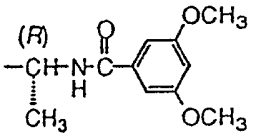
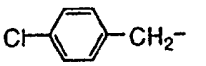
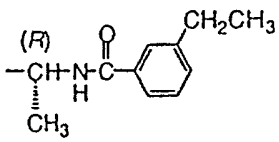
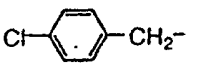
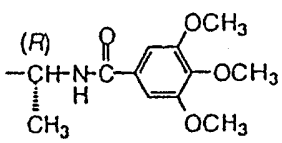
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Tabulka 1.93

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1013		2	2	1	-	H	
1014		2	2	1	-	H	
1015		2	2	1	-	H	
1016		2	2	0	-	H	
1017		2	2	0	-	H	
1018		2	2	1	-	H	
1019		2	2	1	-	H	
1020		2	2	1	-	H	
1021		2	2	1	-	H	
1022		2	2	1	-	H	
1023		2	2	1	-	H	

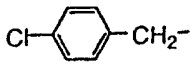
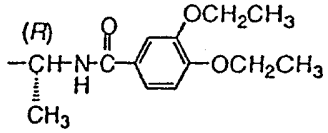
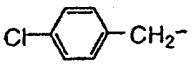
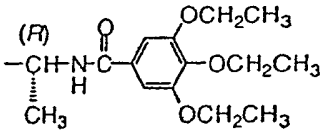
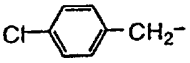
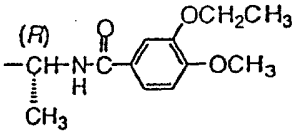
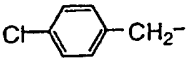
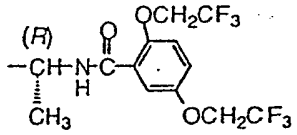
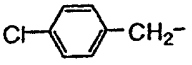
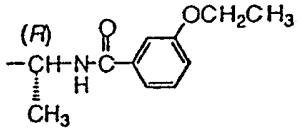
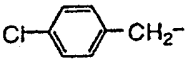
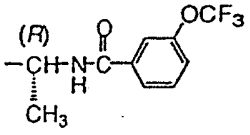
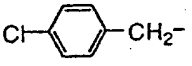
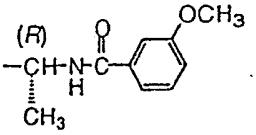
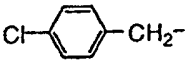
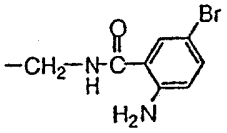
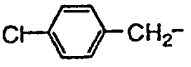
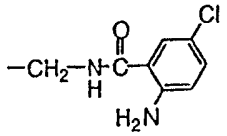
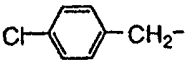
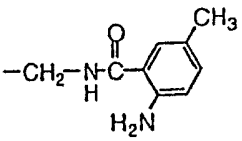
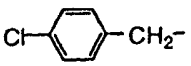
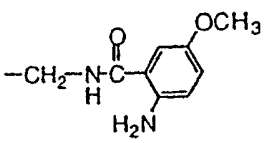
03.07.00

Tabulka 1.94

Sloučeník	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1024		2	2	1	-	H	
1025		2	2	1	-	H	
1026		2	2	1	-	H	
1027		2	2	1	-	H	
1028		2	2	1	-	H	
1029		2	2	1	-	H	
1030		2	2	1	-	H	
1031		2	2	1	-	H	
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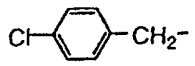
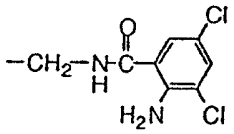
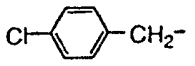
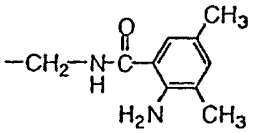
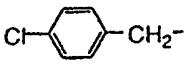
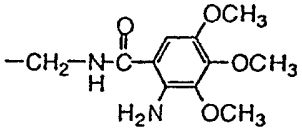
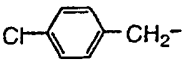
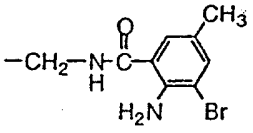
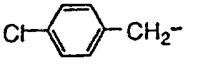
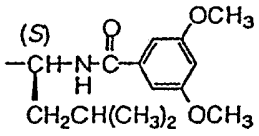
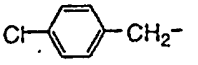
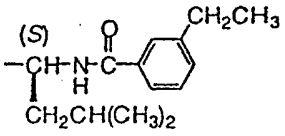
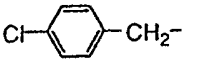
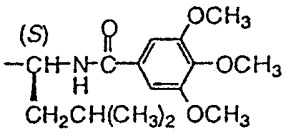
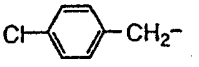
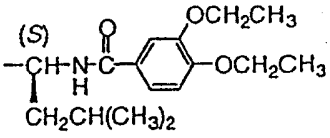
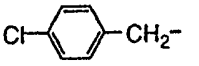
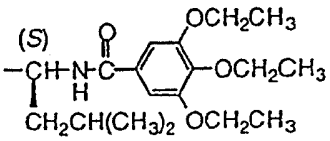
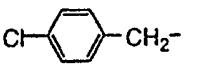
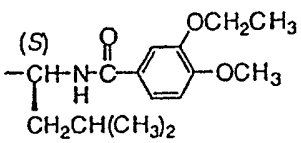
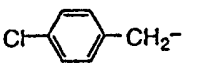
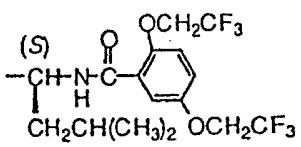
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Tabulka 1.95

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1035		2	2	1	-	H	
1036		2	2	1	-	H	
1037		2	2	1	-	H	
1038		2	2	1	-	H	
1039		2	2	1	-	H	
1040		2	2	1	-	H	
1041		2	2	1	-	H	
1042		2	2	1	-	H	
1043		2	2	1	-	H	
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1045		2	2	1	-	H	

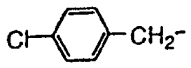
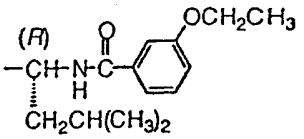
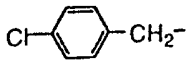
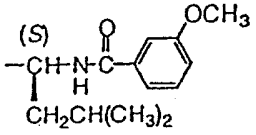
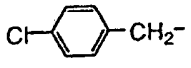
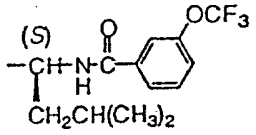
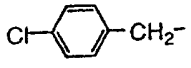
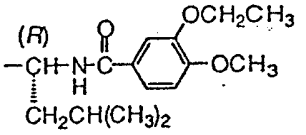
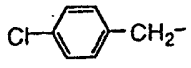
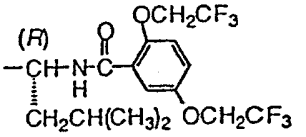
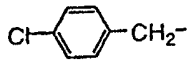
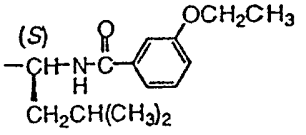
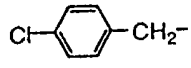
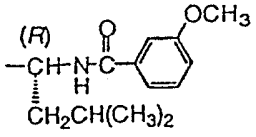
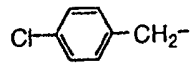
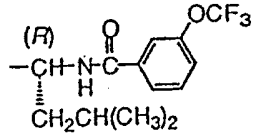
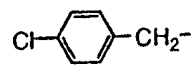
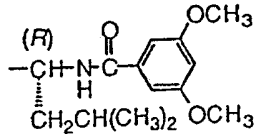
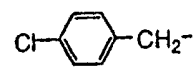
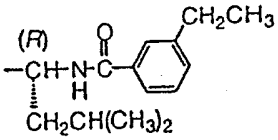
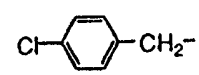
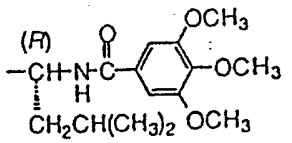
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Tabulka 1.96

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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1047		2	2	1	-	H	
1048		2	2	1	-	H	
1049		2	2	1	-	H	
1050		2	2	1	-	H	
1051		2	2	1	-	H	
1052		2	2	1	-	H	
1053		2	2	1	-	H	
1054		2	2	1	-	H	
1055		2	2	1	-	H	
1056		2	2	1	-	H	

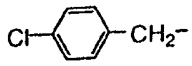
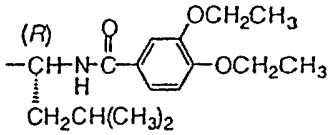
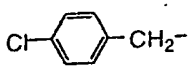
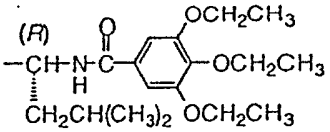
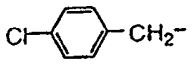
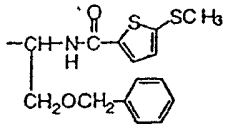
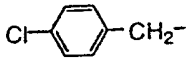
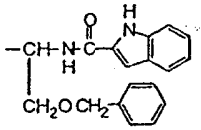
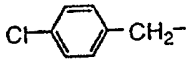
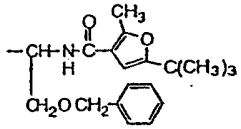
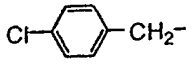
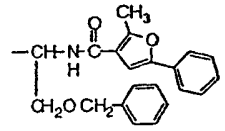
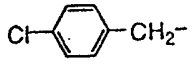
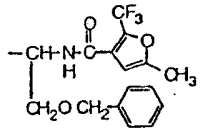
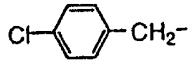
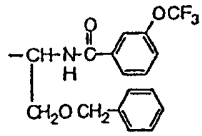
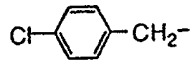
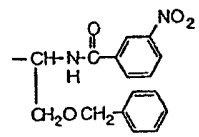
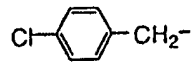
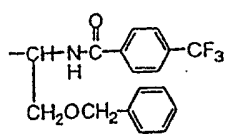
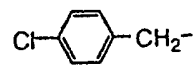
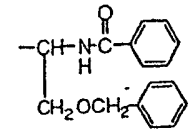
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Tabulka 1.97

Sloučč.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1057		2	2	1	-	H	
1058		2	2	1	-	H	
1059		2	2	1	-	H	
1060		2	2	1	-	H	
1061		2	2	1	-	H	
1062		2	2	1	-	H	
1063		2	2	1	-	H	
1064		2	2	1	-	H	
1065		2	2	1	-	H	
1066		2	2	1	-	H	
1067		2	2	1	-	H	

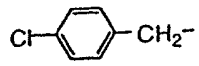
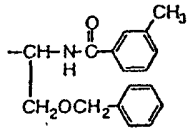
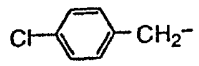
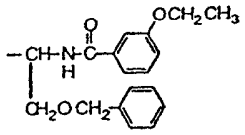
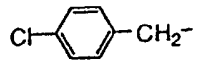
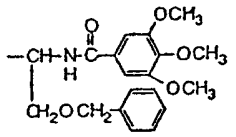
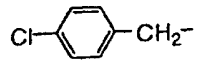
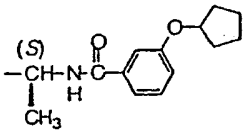
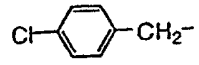
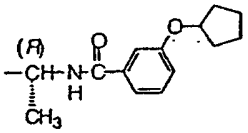
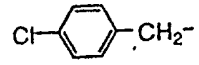
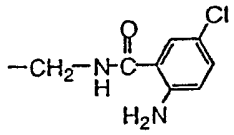
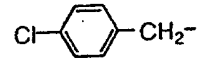
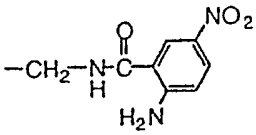
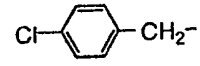
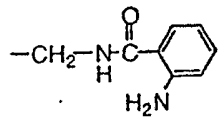
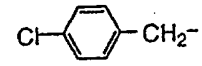
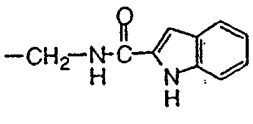
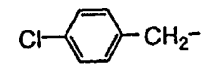
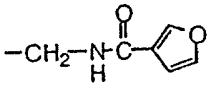
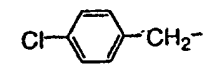
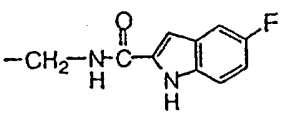
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Tabulka 1.98

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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1069		2	2	1	-	H	
1070		2	2	1	-	H	
1071		2	2	1	-	H	
1072		2	2	1	-	H	
1073		2	2	1	-	H	
1074		2	2	1	-	H	
1075		2	2	1	-	H	
1076		2	2	1	-	H	
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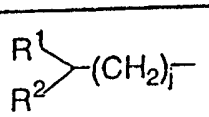
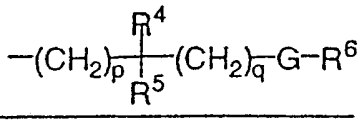
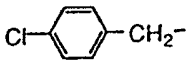
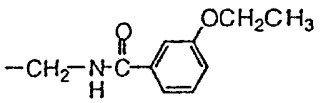
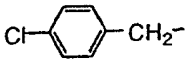
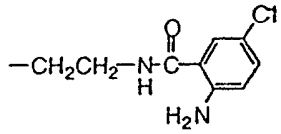
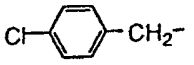
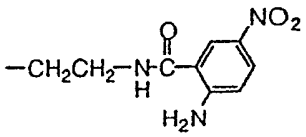
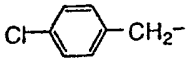
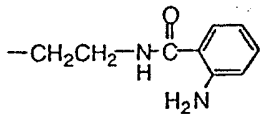
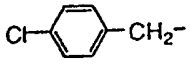
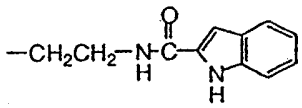
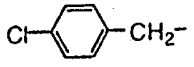
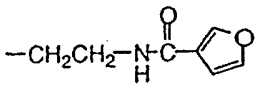
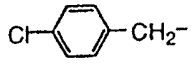
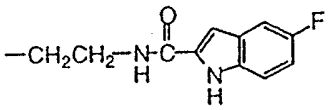
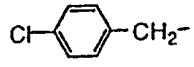
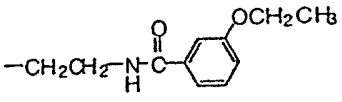
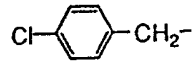
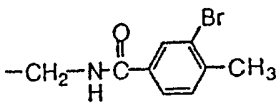
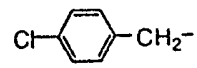
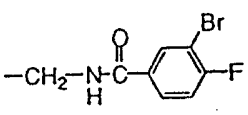
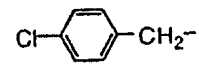
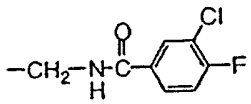
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Tabulka 1.99

Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
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1080		2	2	1	-	H	
1081		2	2	1	-	H	
1082		2	2	1	-	H	
1083		2	2	1	-	H	
1084		1	2	0	R	H	
1085		1	2	0	R	H	
1086		1	2	0	R	H	
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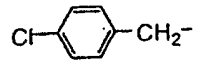
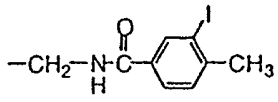
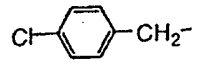
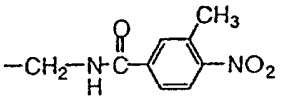
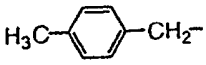
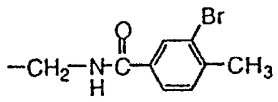
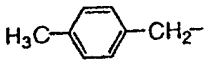
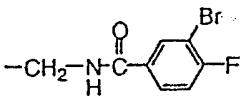
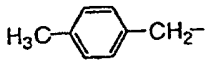
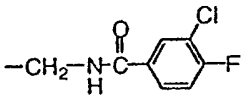
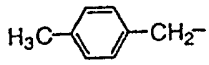
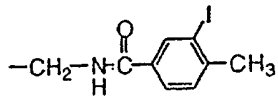
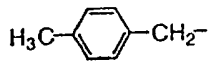
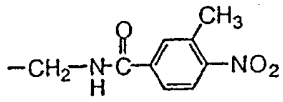
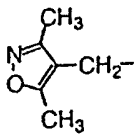
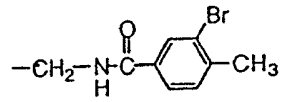
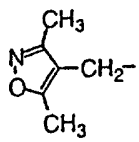
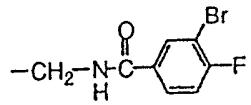
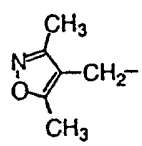
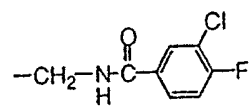
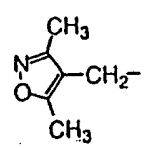
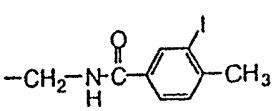
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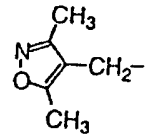
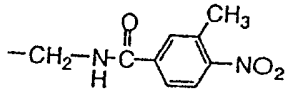
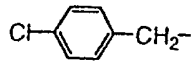
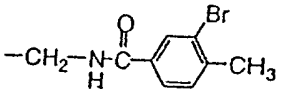
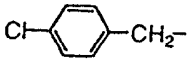
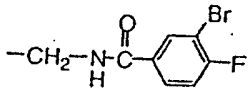
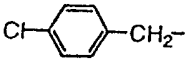
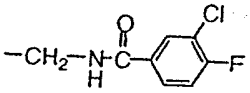
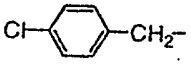
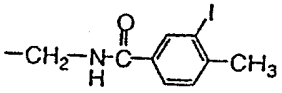
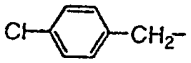
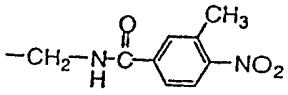
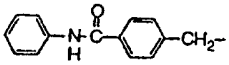
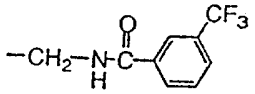
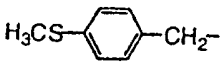
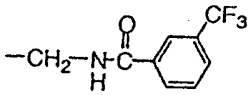
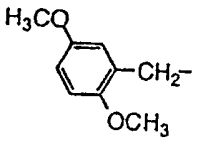
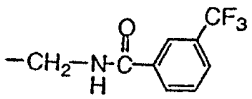
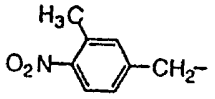
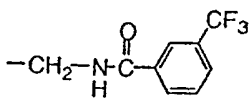
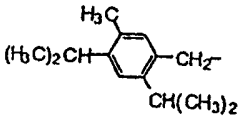
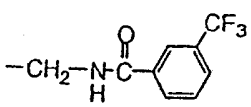
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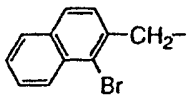
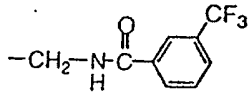
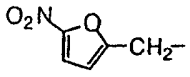
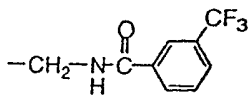
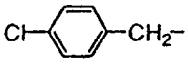
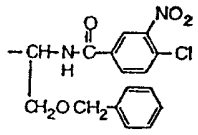
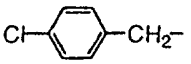
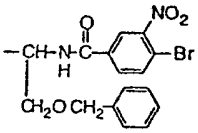
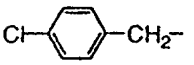
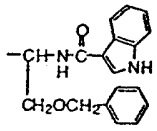
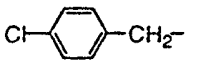
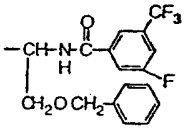
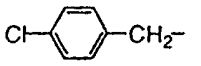
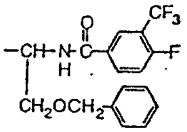
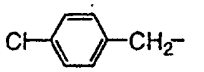
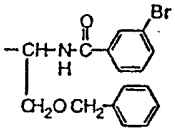
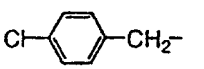
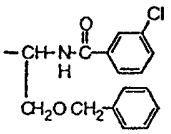
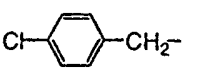
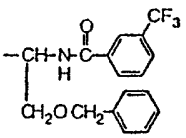
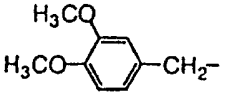
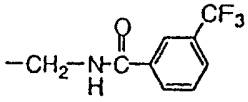
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1101		1	2	0	R	H	
1102		1	2	0	R	H	
1103		1	2	0	R	H	
1104		1	2	0	R	H	
1105		1	2	0	R	H	
1106		1	2	0	R	H	
1107		1	2	0	R	H	
1108		1	2	0	R	H	
1109		1	2	0	R	H	
1110		1	2	0	R	H	
1111		1	2	0	R	H	

Tabulka 1.102

Sloučč.	$R^1R^2CH-(CH_2)_l-$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1112		1	2	0	R	H	
1113		2	2	1	-	H	
1114		2	2	1	-	H	
1115		2	2	1	-	H	
1116		2	2	1	-	H	
1117		2	2	1	-	H	
1118		1	2	0	R	H	
1119		1	2	0	R	H	
1120		1	2	0	R	H	
1121		1	2	0	R	H	
1122		1	2	0	R	H	

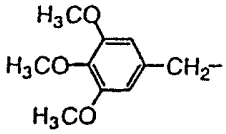
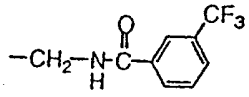
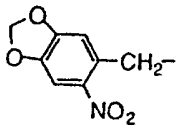
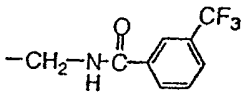
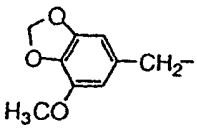
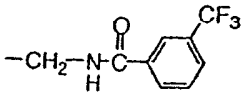
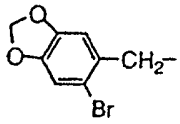
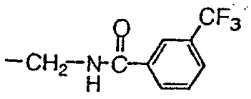
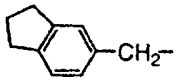
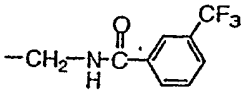
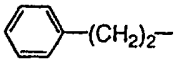
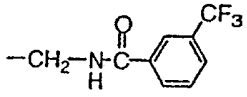
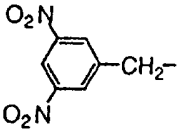
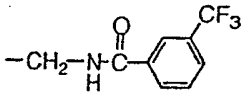
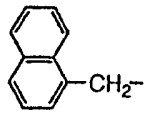
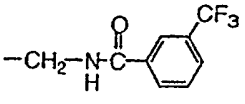
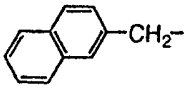
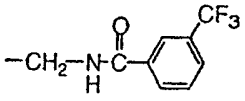
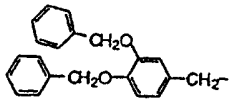
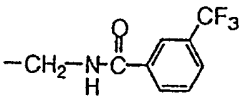
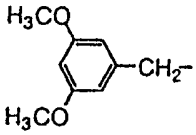
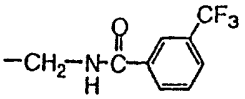
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Tabulka 1.103

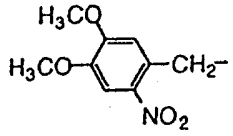
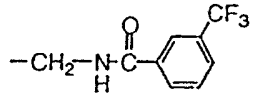
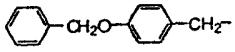
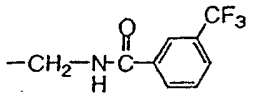
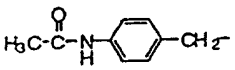
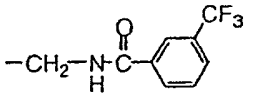
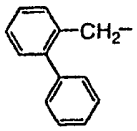
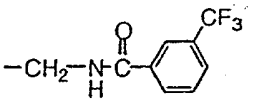
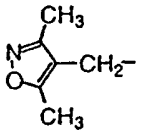
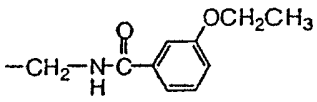
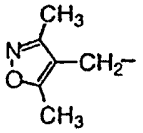
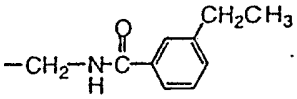
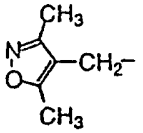
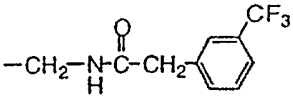
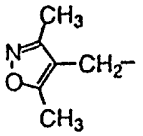
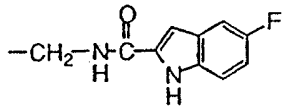
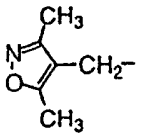
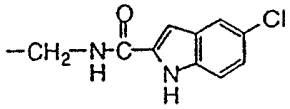
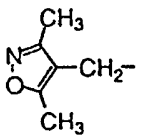
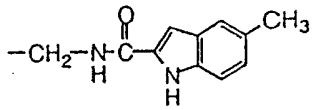
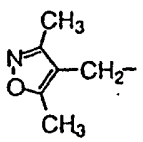
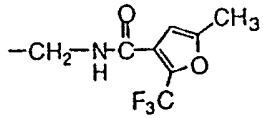
Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1123		1	2	0	R	H	
1124		1	2	0	R	H	
1125		2	2	1	-	H	
1126		2	2	1	-	H	
1127		2	2	1	-	H	
1128		2	2	1	-	H	
1129		2	2	1	-	H	
1130		2	2	1	-	H	
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1132		2	2	1	-	H	
1133		1	2	0	R	H	

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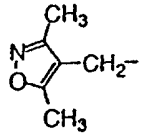
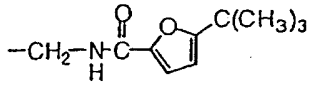
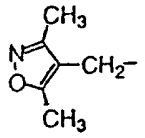
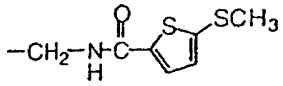
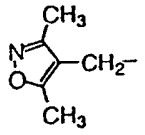
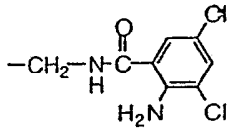
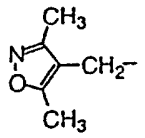
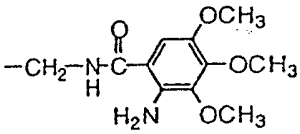
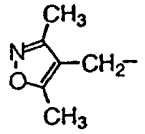
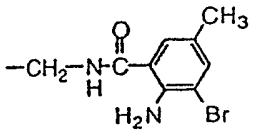
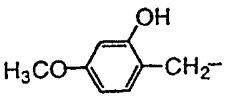
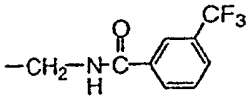
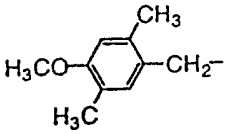
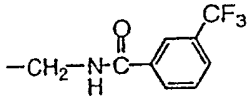
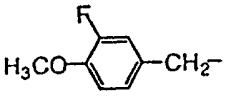
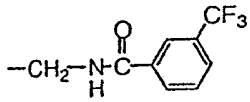
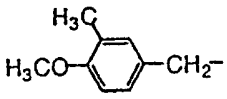
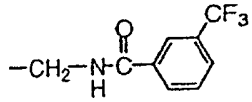
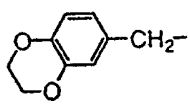
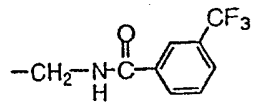
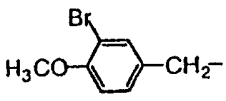
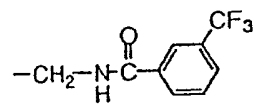
Tabulka 1.104

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1134		1	2	0	R	H	
1135		1	2	0	R	H	
1136		1	2	0	R	H	
1137		1	2	0	R	H	
1138		1	2	0	R	H	
1139		1	2	0	R	H	
1140		1	2	0	R	H	
1141		1	2	0	R	H	
1142		1	2	0	R	H	
1143		1	2	0	R	H	
1144		1	2	0	R	H	

Tabulka 1.105

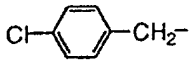
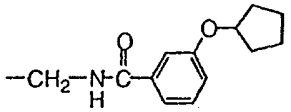
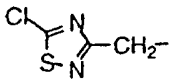
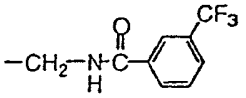
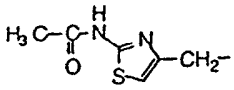
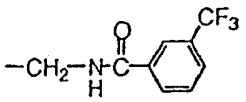
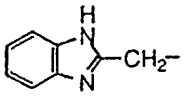
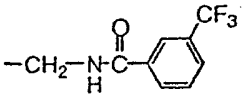
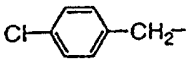
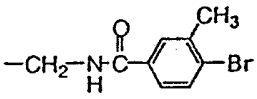
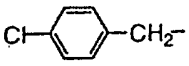
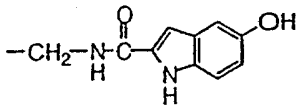
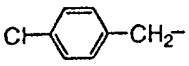
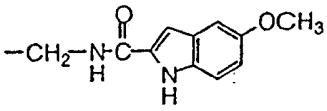
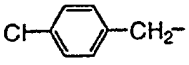
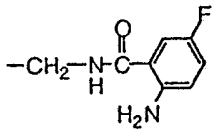
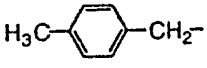
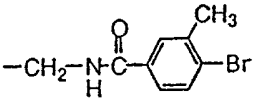
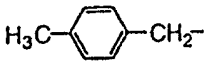
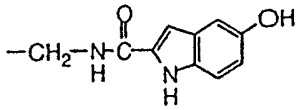
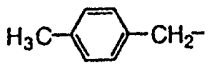
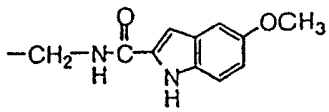
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1145		1	2	0	R	H	
1146		1	2	0	R	H	
1147		1	2	0	R	H	
1148		1	2	0	R	H	
1149		1	2	0	R	H	
1150		1	2	0	R	H	
1151		1	2	0	R	H	
1152		1	2	0	R	H	
1153		1	2	0	R	H	
1154		1	2	0	R	H	
1155		1	2	0	R	H	

Tabulka 1.106

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1156		1	2	0	R	H	
1157		1	2	0	R	H	
1158		1	2	0	R	H	
1159		1	2	0	R	H	
1160		1	2	0	R	H	
1161		1	2	0	R	H	
1162		1	2	0	R	H	
1163		1	2	0	R	H	
1164		1	2	0	R	H	
1165		1	2	0	R	H	
1166		1	2	0	R	H	

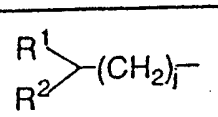
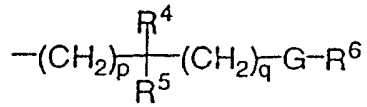
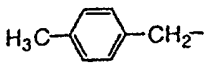
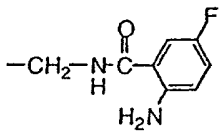
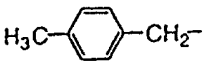
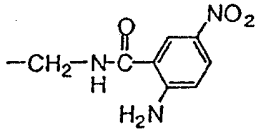
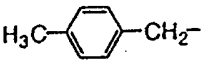
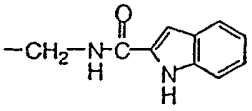
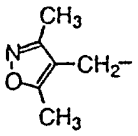
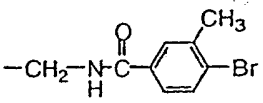
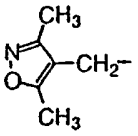
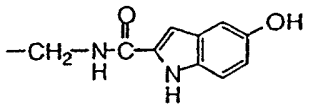
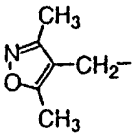
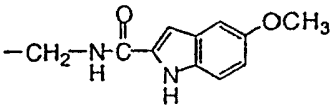
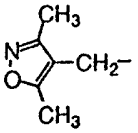
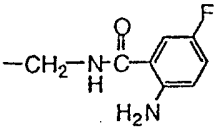
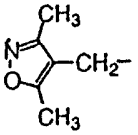
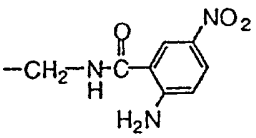
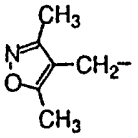
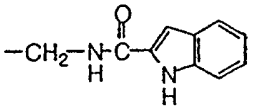
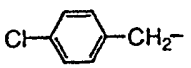
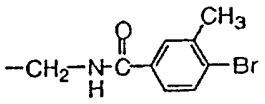
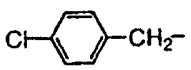
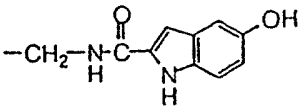
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Tabulka 1.107

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1167		2	2	1	-	H	
1168		1	2	0	R	H	
1169		1	2	0	R	H	
1170		1	2	0	R	H	
1171		1	2	0	R	H	
1172		1	2	0	R	H	
1173		1	2	0	R	H	
1174		1	2	0	R	H	
1175		1	2	0	R	H	
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1177		1	2	0	R	H	

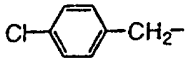
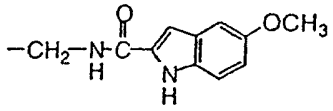
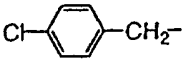
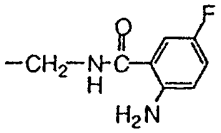
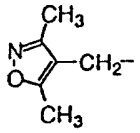
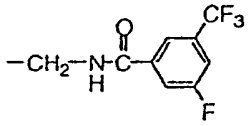
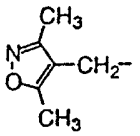
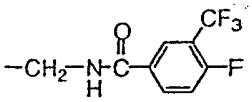
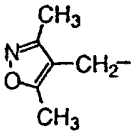
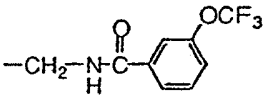
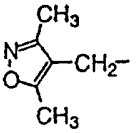
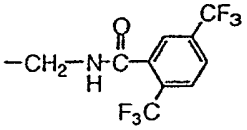
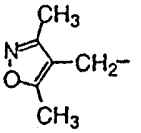
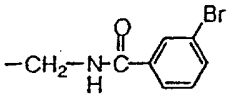
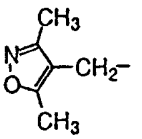
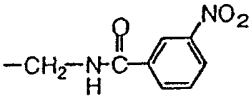
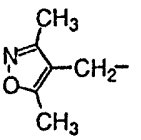
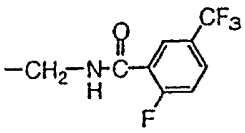
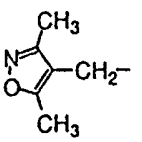
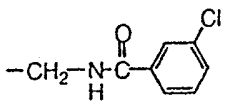
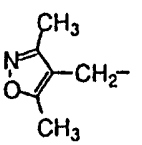
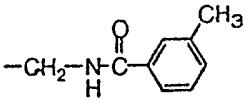
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Tabulka 1.108

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1179		1	2	0	R	H	
1180		1	2	0	R	H	
1181		1	2	0	R	H	
1182		1	2	0	R	H	
1183		1	2	0	R	H	
1184		1	2	0	R	H	
1185		1	2	0	R	H	
1186		1	2	0	R	H	
1187		2	2	1	-	H	
1188		2	2	1	-	H	

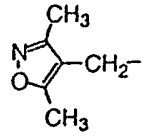
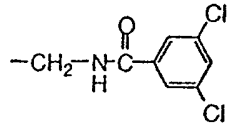
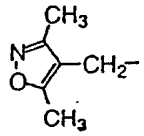
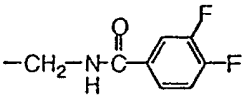
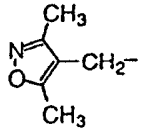
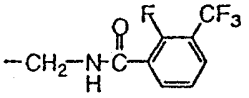
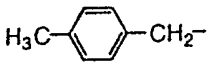
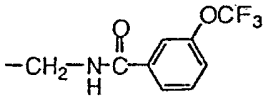
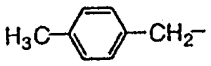
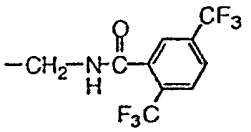
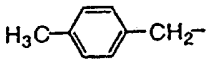
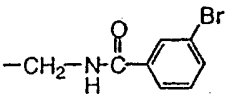
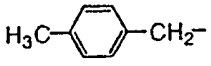
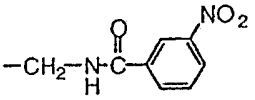
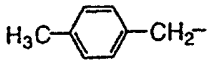
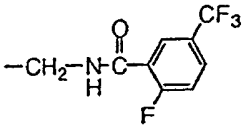
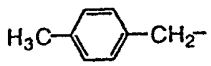
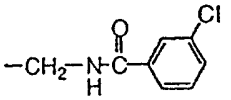
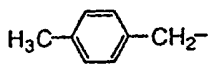
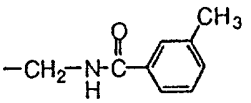
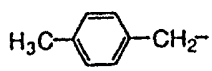
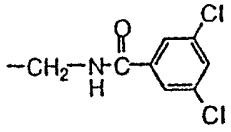
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Tabulka 1.109

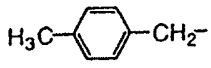
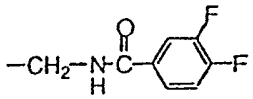
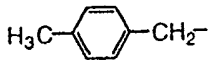
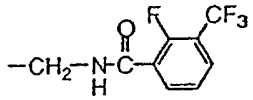
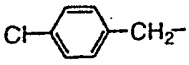
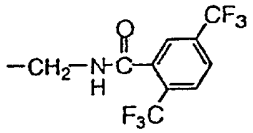
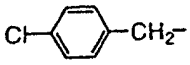
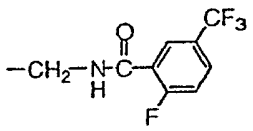
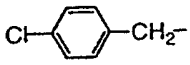
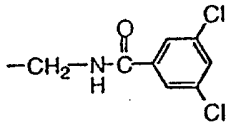
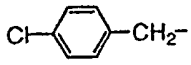
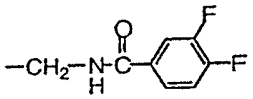
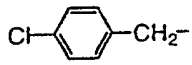
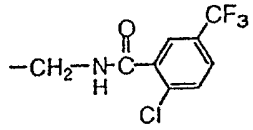
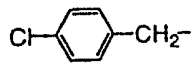
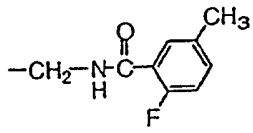
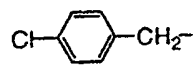
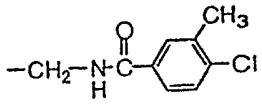
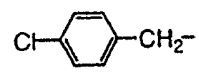
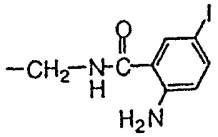
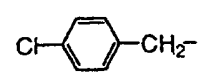
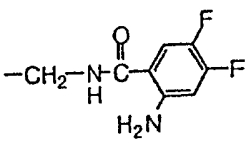
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1189		2	2	1	-	H	
1190		2	2	1	-	H	
1191		1	2	0	R	H	
1192		1	2	0	R	H	
1193		1	2	0	R	H	
1194		1	2	0	R	H	
1195		1	2	0	R	H	
1196		1	2	0	R	H	
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Tabulka 1.110

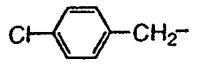
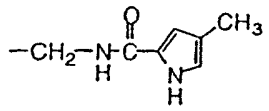
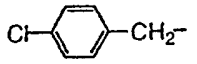
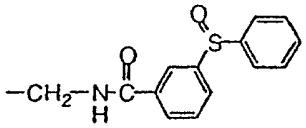
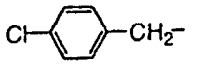
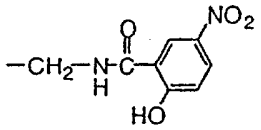
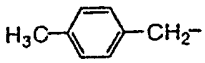
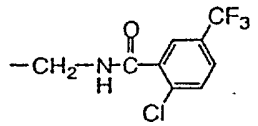
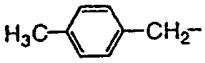
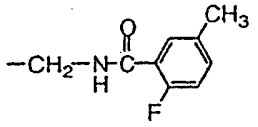
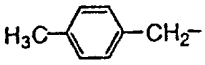
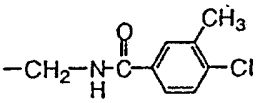
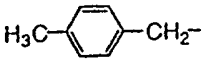
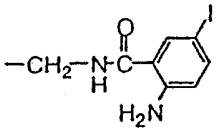
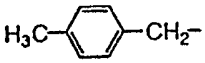
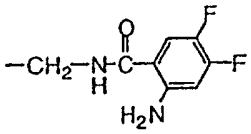
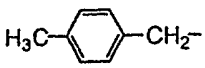
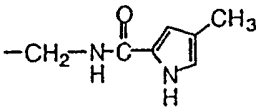
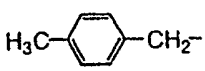
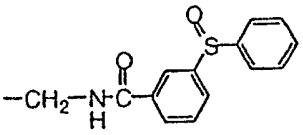
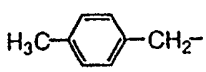
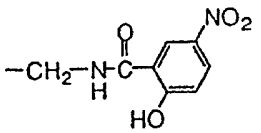
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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1201		1	2	0	R	H	
1202		1	2	0	R	H	
1203		1	2	0	R	H	
1204		1	2	0	R	H	
1205		1	2	0	R	H	
1206		1	2	0	R	H	
1207		1	2	0	R	H	
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Tabulka 1.111

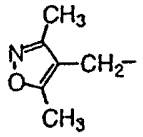
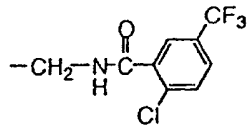
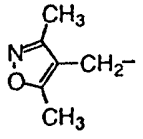
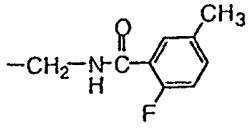
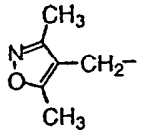
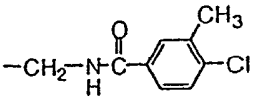
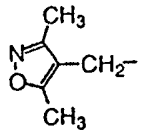
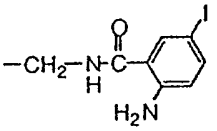
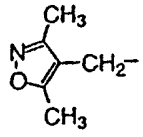
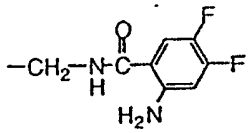
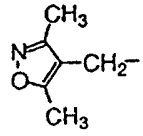
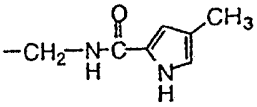
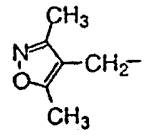
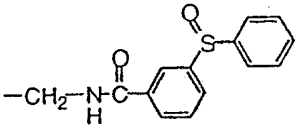
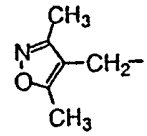
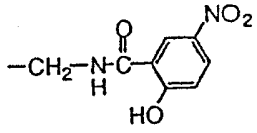
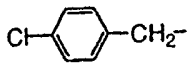
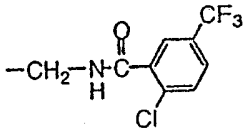
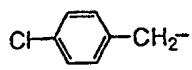
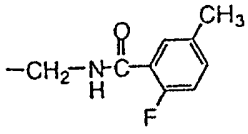
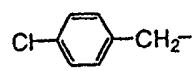
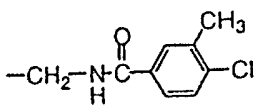
Sloučenina č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1211		1	2	0	R	H	
1212		1	2	0	R	H	
1213		2	2	1	-	H	
1214		2	2	1	-	H	
1215		2	2	1	-	H	
1216		2	2	1	-	H	
1217		1	2	0	R	H	
1218		1	2	0	R	H	
1219		1	2	0	R	H	
1220		1	2	0	R	H	
1221		1	2	0	R	H	

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Tabulka 1.112

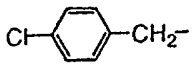
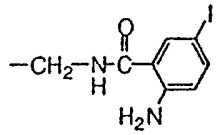
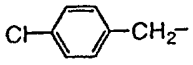
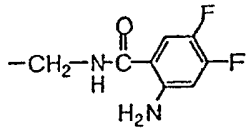
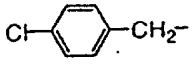
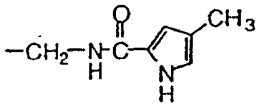
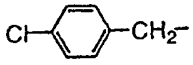
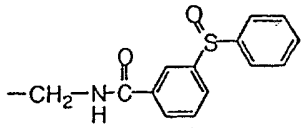
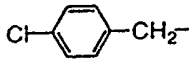
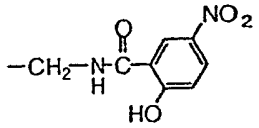
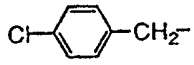
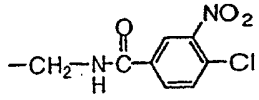
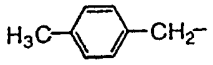
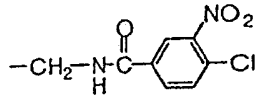
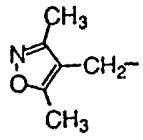
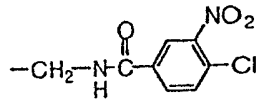
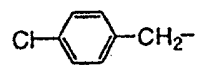
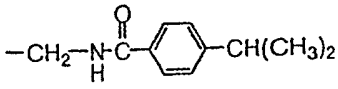
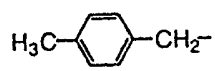
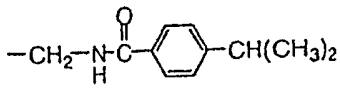
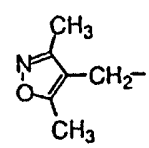
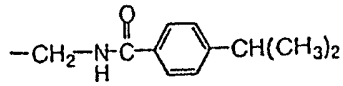
Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CHR^4R^5-(CH_2)_q-G-R^6$
1222		1	2	0	R	H	
1223		1	2	0	R	H	
1224		1	2	0	R	H	
1225		1	2	0	R	H	
1226		1	2	0	R	H	
1227		1	2	0	R	H	
1228		1	2	0	R	H	
1229		1	2	0	R	H	
1230		1	2	0	R	H	
1231		1	2	0	R	H	
1232		1	2	0	R	H	

Tabulka 1.113

Slouč.č.	R^1, R^2, $-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1233		1	2	0	R	H	
1234		1	2	0	R	H	
1235		1	2	0	R	H	
1236		1	2	0	R	H	
1237		1	2	0	R	H	
1238		1	2	0	R	H	
1239		1	2	0	R	H	
1240		1	2	0	R	H	
1241		2	2	1	-	H	
1242		2	2	1	-	H	
1243		2	2	1	-	H	

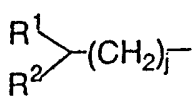
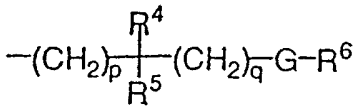
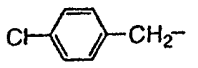
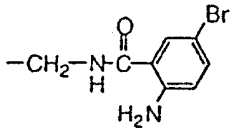
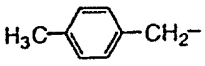
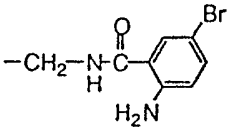
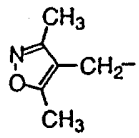
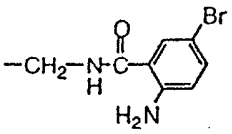
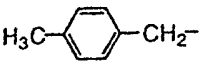
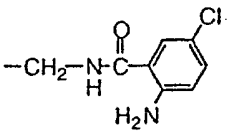
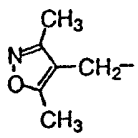
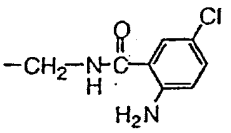
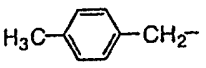
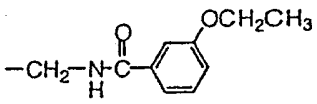
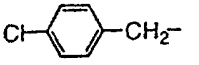
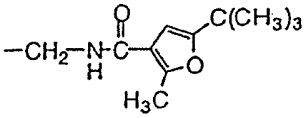
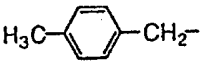
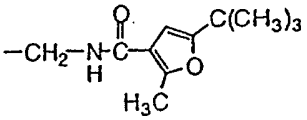
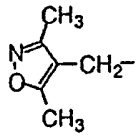
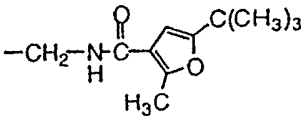
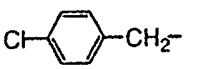
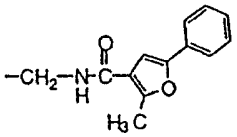
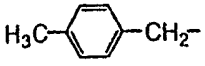
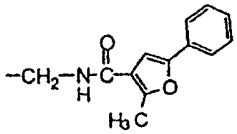
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Tabulka 1.114

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1244		2	2	1	-	H	
1245		2	2	1	-	H	
1246		2	2	1	-	H	
1247		2	2	1	-	H	
1248		2	2	1	-	H	
1249		1	2	0	R	H	
1250		1	2	0	R	H	
1251		1	2	0	R	H	
1252		1	2	0	R	H	
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1254		1	2	0	R	H	

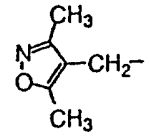
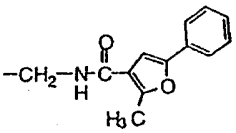
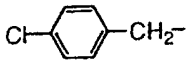
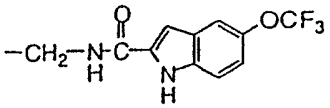
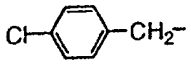
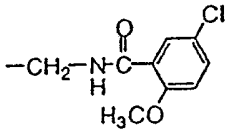
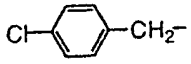
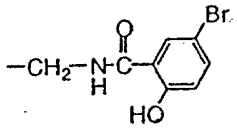
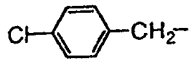
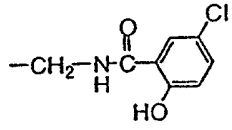
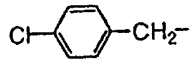
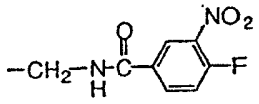
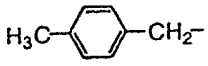
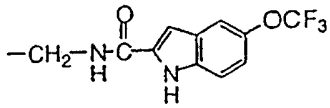
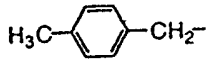
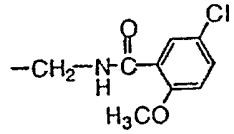
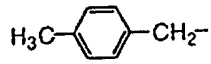
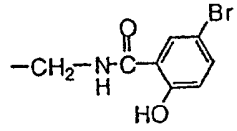
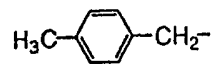
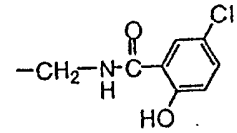
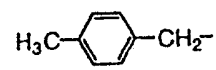
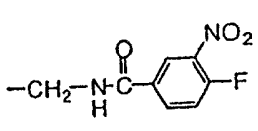
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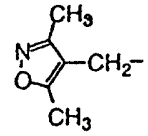
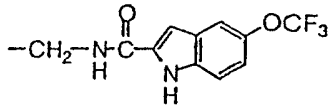
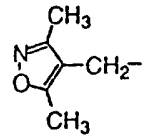
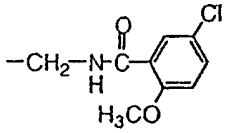
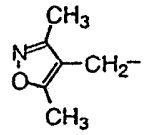
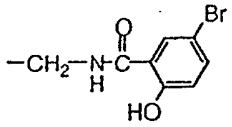
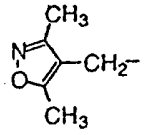
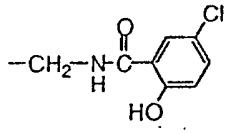
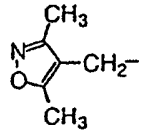
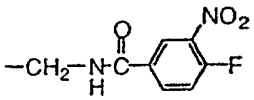
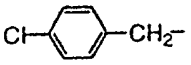
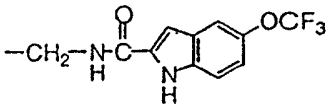
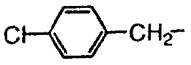
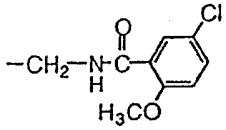
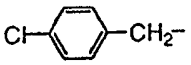
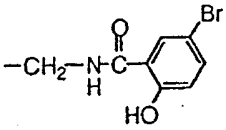
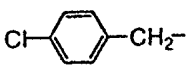
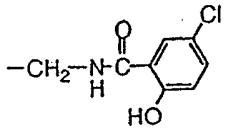
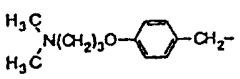
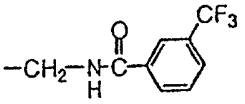
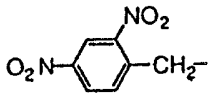
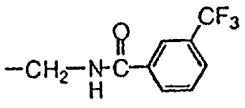
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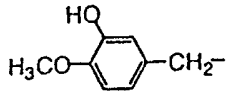
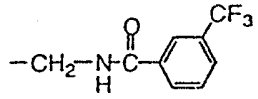
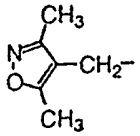
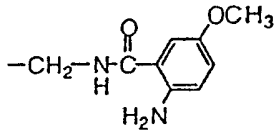
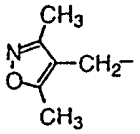
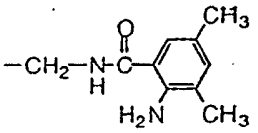
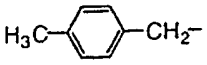
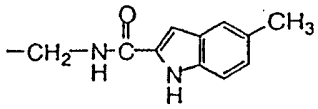
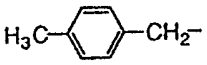
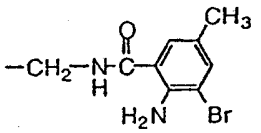
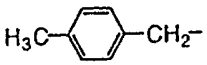
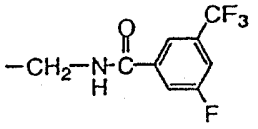
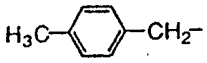
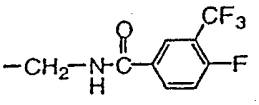
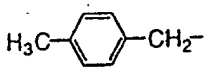
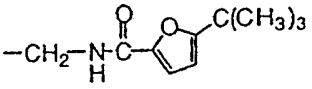
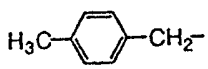
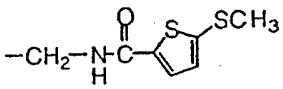
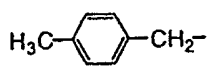
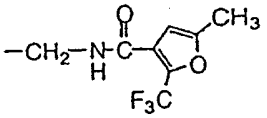
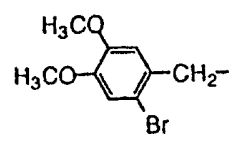
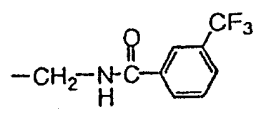
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1266		1	2	0	R	H	
1267		1	2	0	R	H	
1268		1	2	0	R	H	
1269		1	2	0	R	H	
1270		1	2	0	R	H	
1271		1	2	0	R	H	
1272		1	2	0	R	H	
1273		1	2	0	R	H	
1274		1	2	0	R	H	
1275		1	2	0	R	H	
1276		1	2	0	R	H	

Tabulka 1.117

Sloučč.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1277		1	2	0	R	H	
1278		1	2	0	R	H	
1279		1	2	0	R	H	
1280		1	2	0	R	H	
1281		1	2	0	R	H	
1282		2	2	1	-	H	
1283		2	2	1	-	H	
1284		2	2	1	-	H	
1285		2	2	1	-	H	
1286		1	2	0	R	H	
1287		1	2	0	R	H	

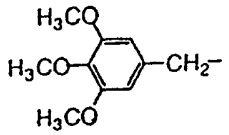
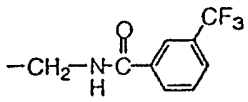
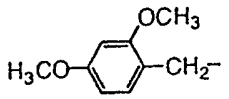
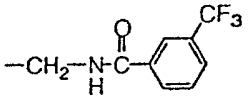
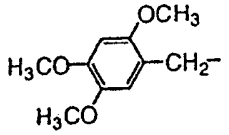
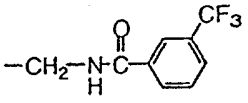
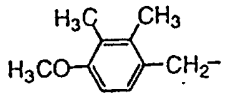
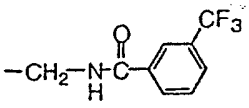
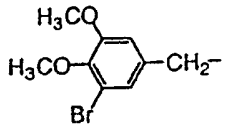
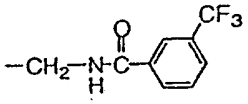
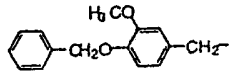
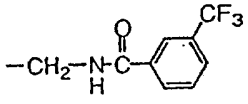
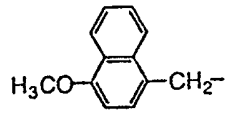
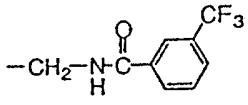
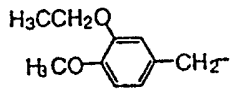
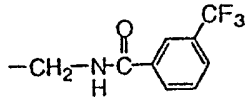
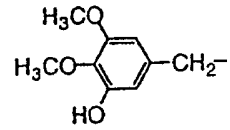
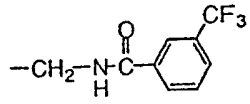
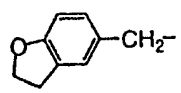
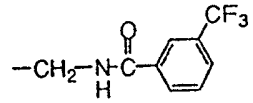
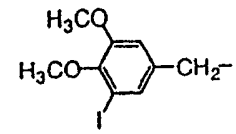
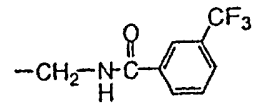
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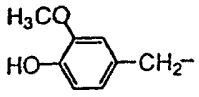
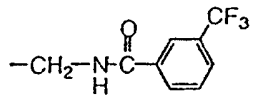
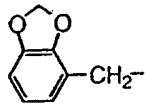
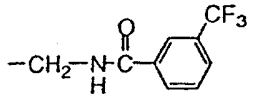
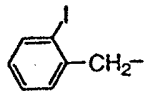
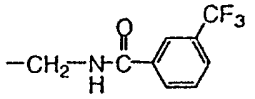
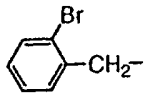
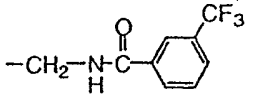
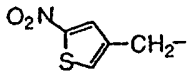
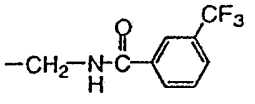
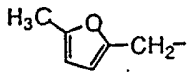
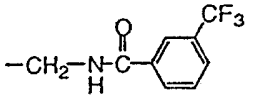
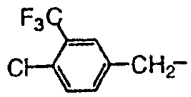
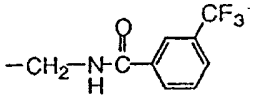
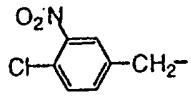
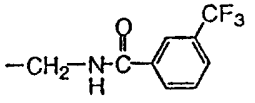
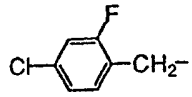
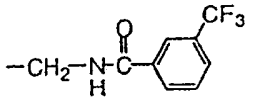
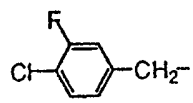
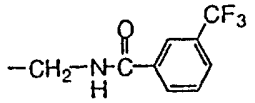
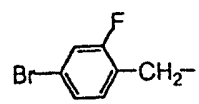
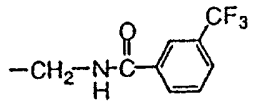
Slouč.č.	R^1, R^2, $-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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1289		1	2	0	R	H	
1290		1	2	0	R	H	
1291		1	2	0	R	H	
1292		1	2	0	R	H	
1293		1	2	0	R	H	
1294		1	2	0	R	H	
1295		1	2	0	R	H	
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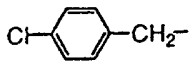
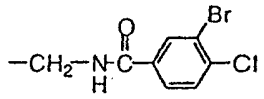
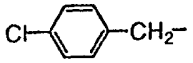
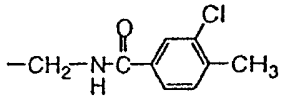
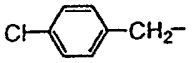
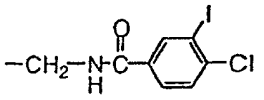
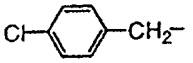
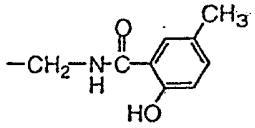
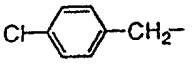
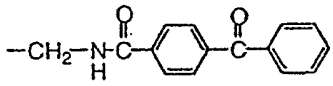
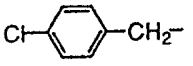
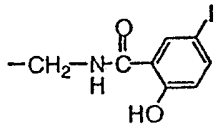
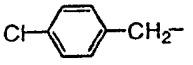
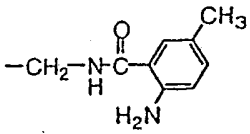
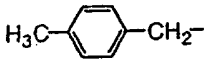
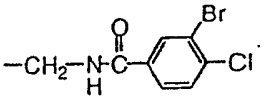
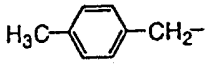
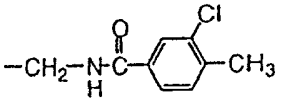
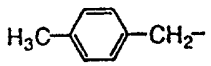
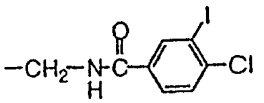
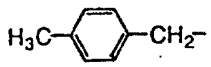
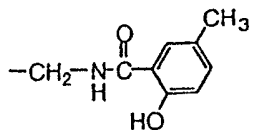
Tabulka 1.119

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1299		1	2	0	R	H	
1300		1	2	0	R	H	
1301		1	2	0	R	H	
1302		1	2	0	R	H	
1303		1	2	0	R	H	
1304		1	2	0	R	H	
1305		1	2	0	R	H	
1306		1	2	0	R	H	
1307		1	2	0	R	H	
1308		1	2	0	R	H	
1309		1	2	0	R	H	

Tabulka 1.120

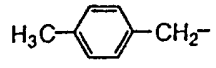
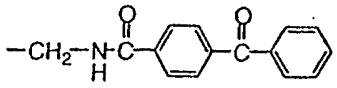
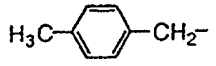
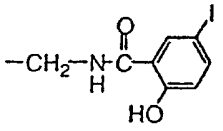
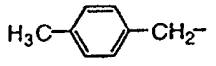
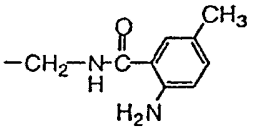
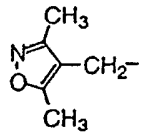
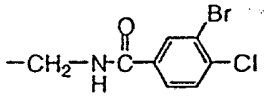
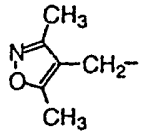
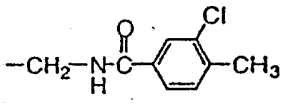
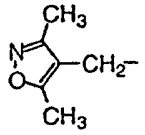
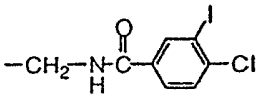
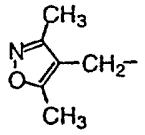
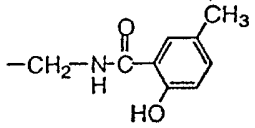
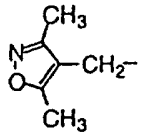
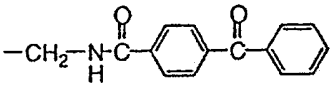
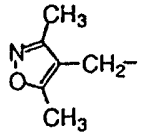
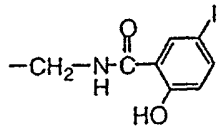
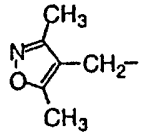
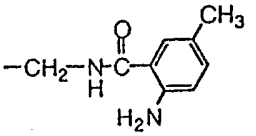
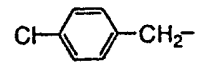
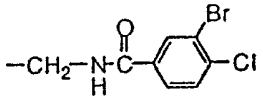
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1310		1	2	0	R	H	
1311		1	2	0	R	H	
1312		1	2	0	R	H	
1313		1	2	0	R	H	
1314		1	2	0	R	H	
1315		1	2	0	R	H	
1316		1	2	0	R	H	
1317		1	2	0	R	H	
1318		1	2	0	R	H	
1319		1	2	0	R	H	
1320		1	2	0	R	H	

Tabulka 1.121

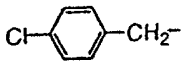
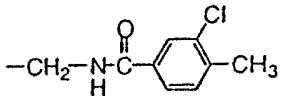
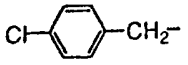
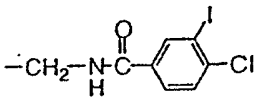
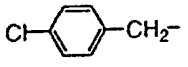
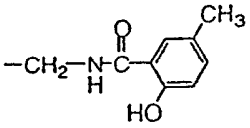
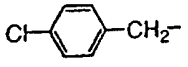
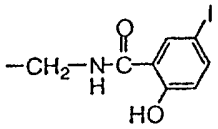
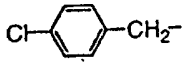
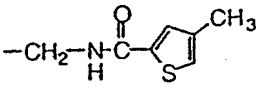
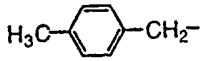
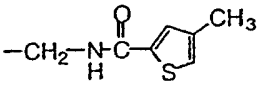
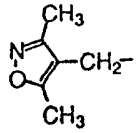
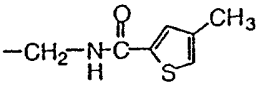
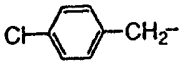
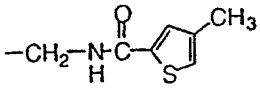
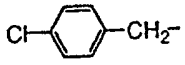
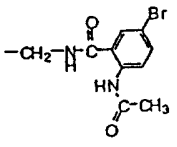
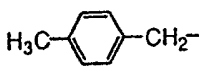
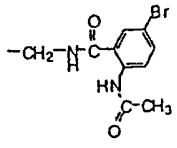
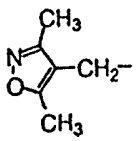
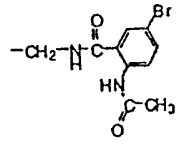
Sloučč.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1321		1	2	0	R	H	
1322		1	2	0	R	H	
1323		1	2	0	R	H	
1324		1	2	0	R	H	
1325		1	2	0	R	H	
1326		1	2	0	R	H	
1327		1	2	0	R	H	
1328		1	2	0	R	H	
1329		1	2	0	R	H	
1330		1	2	0	R	H	
1331		1	2	0	R	H	

03.07.00

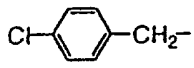
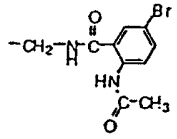
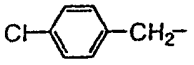
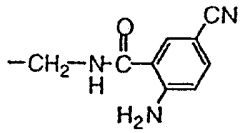
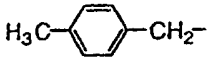
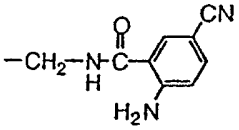
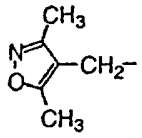
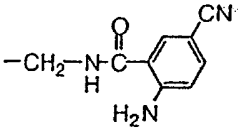
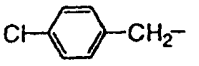
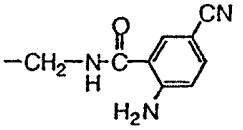
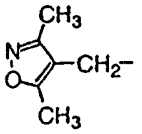
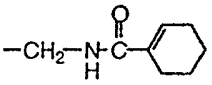
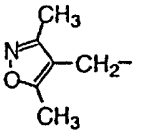
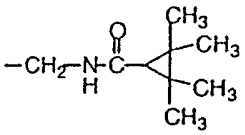
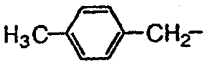
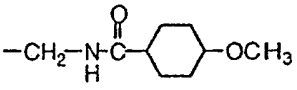
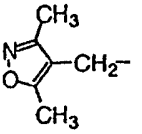
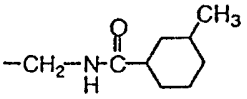
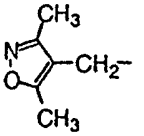
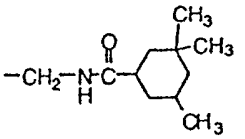
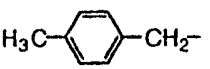
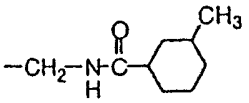
Tabulka 1.122

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1332		1	2	0	R	H	
1333		1	2	0	R	H	
1334		1	2	0	R	H	
1335		1	2	0	R	H	
1336		1	2	0	R	H	
1337		1	2	0	R	H	
1338		1	2	0	R	H	
1339		1	2	0	R	H	
1340		1	2	0	R	H	
1341		1	2	0	R	H	
1342		2	2	1	-	H	

Tabulka 1.123

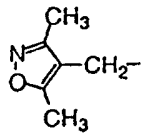
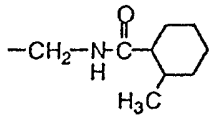
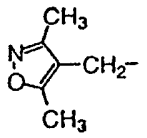
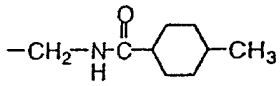
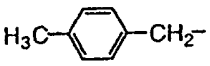
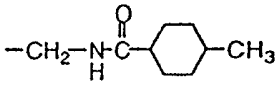
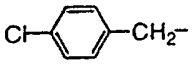
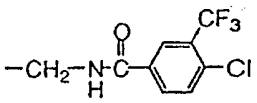
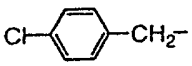
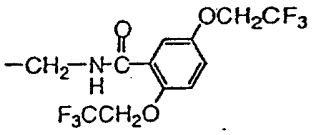
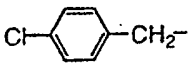
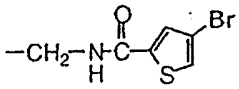
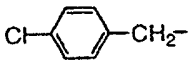
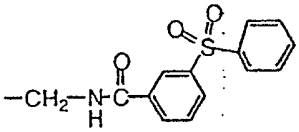
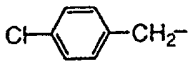
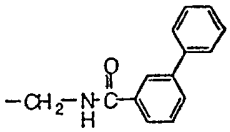
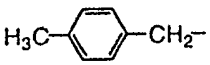
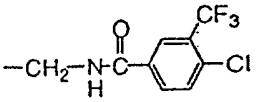
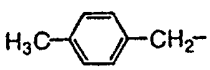
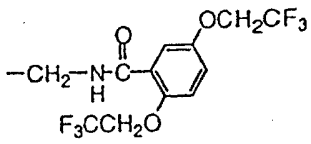
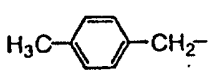
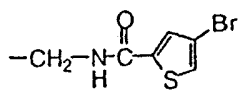
Slouč.č.	$R^1R^2CH(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1343		2	2	1	-	H	
1344		2	2	1	-	H	
1345		2	2	1	-	H	
1346		2	2	1	-	H	
1347		1	2	0	R	H	
1348		1	2	0	R	H	
1349		1	2	0	R	H	
1350		2	2	1	-	H	
1351		1	2	0	R	H	
1352		1	2	0	R	H	
1353		1	2	0	R	H	

Tabulka 1.124

Sloučč.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1354		2	2	1	-	H	
1355		1	2	0	R	H	
1356		1	2	0	R	H	
1357		1	2	0	R	H	
1358		2	2	1	-	H	
1359		1	2	0	R	H	
1360		1	2	0	R	H	
1361		1	2	0	R	H	
1362		1	2	0	R	H	
1363		1	2	0	R	H	
1364		1	2	0	R	H	

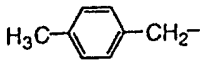
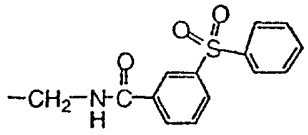
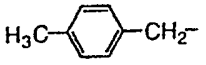
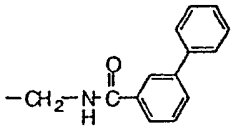
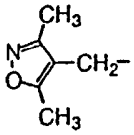
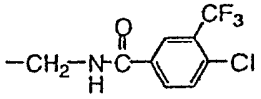
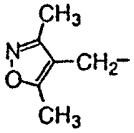
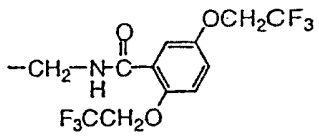
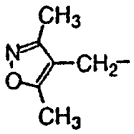
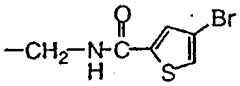
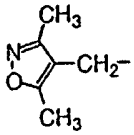
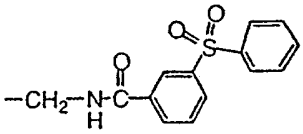
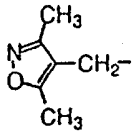
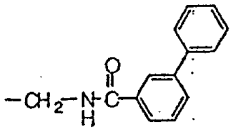
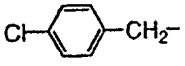
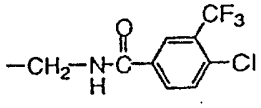
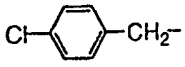
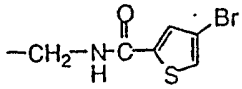
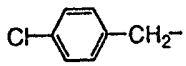
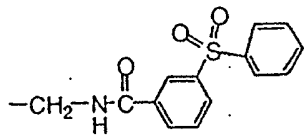
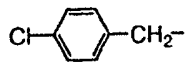
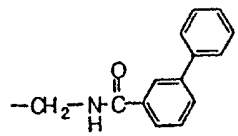
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Tabulka 1.125

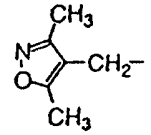
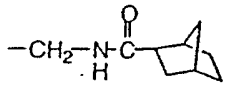
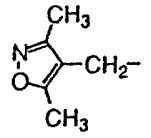
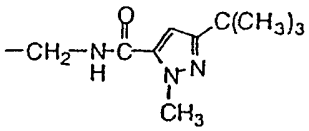
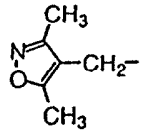
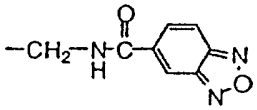
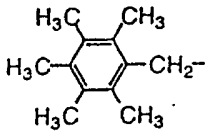
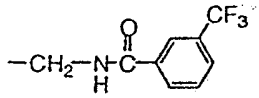
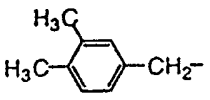
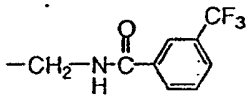
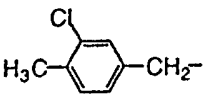
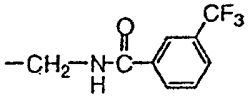
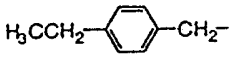
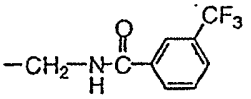
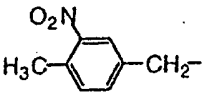
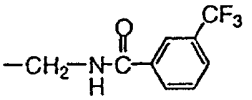
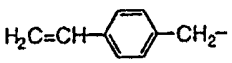
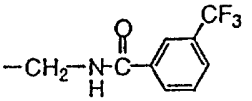
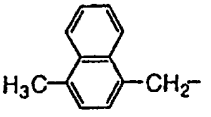
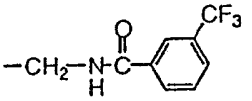
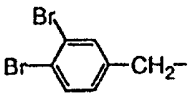
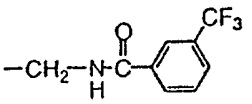
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1366		1	2	0	R	H	
1367		1	2	0	R	H	
1368		1	2	0	R	H	
1369		1	2	0	R	H	
1370		1	2	0	R	H	
1371		1	2	0	R	H	
1372		1	2	0	R	H	
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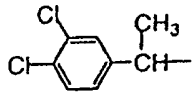
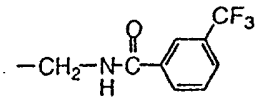
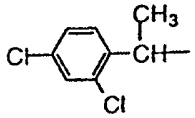
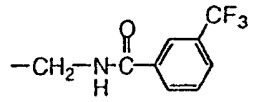
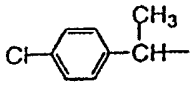
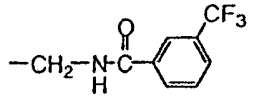
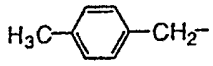
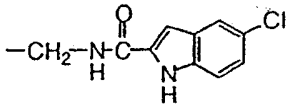
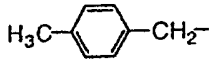
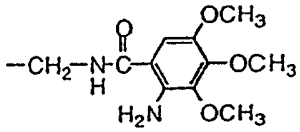
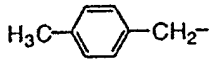
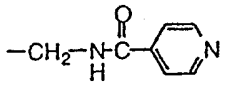
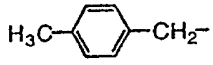
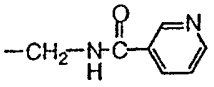
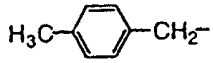
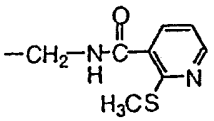
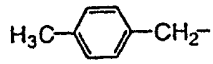
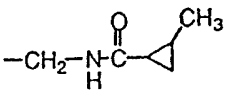
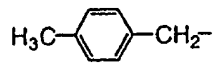
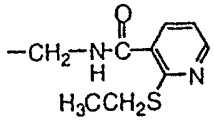
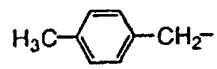
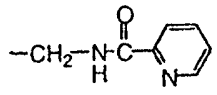
Tabulka 1.126

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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1377		1	2	0	R	H	
1378		1	2	0	R	H	
1379		1	2	0	R	H	
1380		1	2	0	R	H	
1381		1	2	0	R	H	
1382		1	2	0	R	H	
1383		2	2	1	-	H	
1384		2	2	1	-	H	
1385		2	2	1	-	H	
1386		2	2	1	-	H	

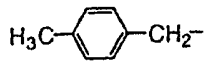
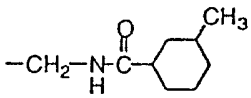
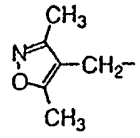
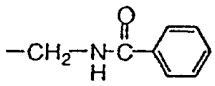
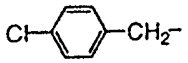
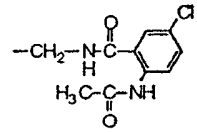
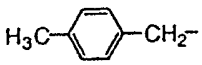
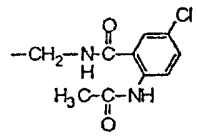
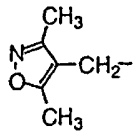
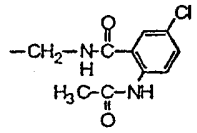
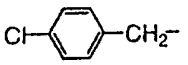
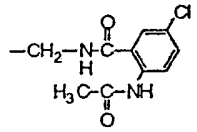
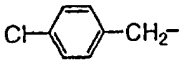
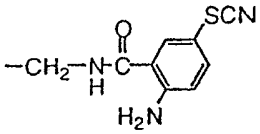
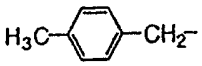
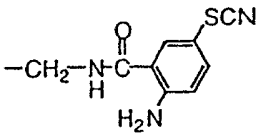
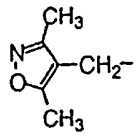
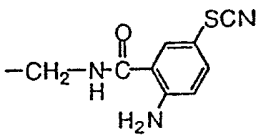
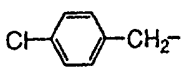
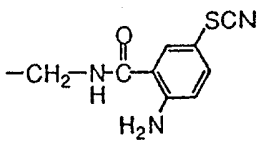
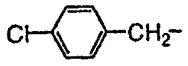
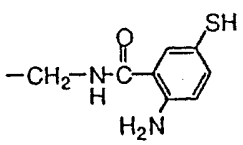
Tabulka 1.127

Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1387		1	2	0	R	H	
1388		1	2	0	R	H	
1389		1	2	0	R	H	
1390		1	2	0	R	H	
1391		1	2	0	R	H	
1392		1	2	0	R	H	
1393		1	2	0	R	H	
1394		1	2	0	R	H	
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1396		1	2	0	R	H	
1397		1	2	0	R	H	

Tabulka 1.128

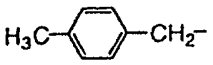
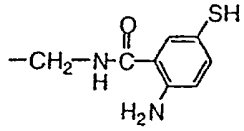
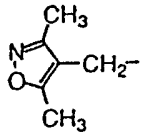
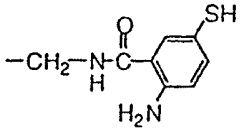
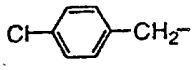
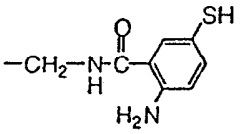
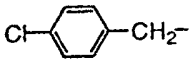
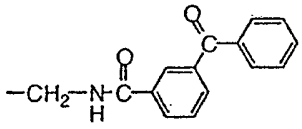
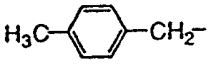
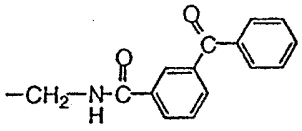
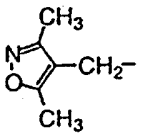
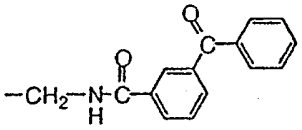
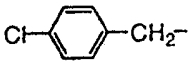
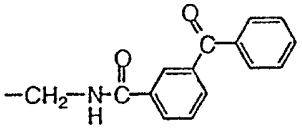
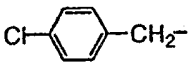
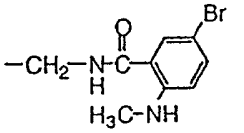
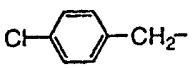
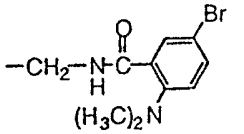
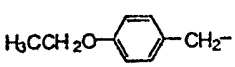
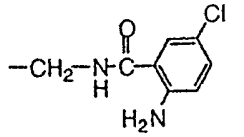
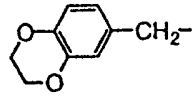
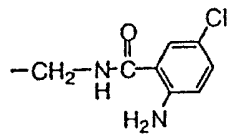
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1398		1	2	0	R	H	
1399		1	2	0	R	H	
1400		1	2	0	R	H	
1401		1	2	0	R	H	
1402		1	2	0	R	H	
1403		1	2	0	R	H	
1404		1	2	0	R	H	
1405		1	2	0	R	H	
1406		1	2	0	R	H	
1407		1	2	0	R	H	
1408		1	2	0	R	H	

Tabulka 1.129

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1409		1	2	0	R	H	
1410		1	2	0	R	H	
1411		1	2	0	R	H	
1412		1	2	0	R	H	
1413		1	2	0	R	H	
1414		2	2	1	-	H	
1415		1	2	0	R	H	
1416		1	2	0	R	H	
1417		1	2	0	R	H	
1418		2	2	1	-	H	
1419		1	2	0	R	H	

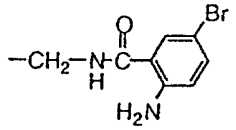
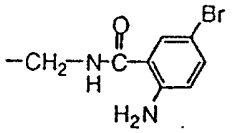
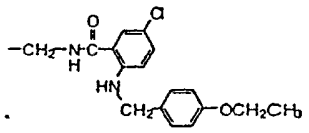
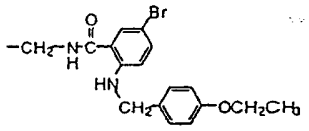
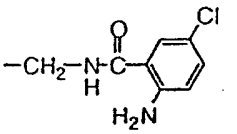
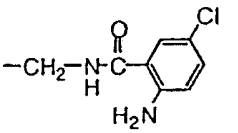
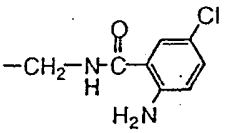
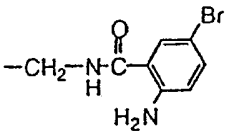
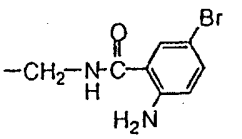
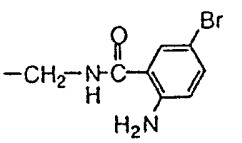
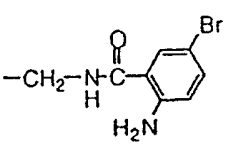
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Tabulka 1.130

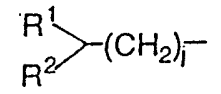
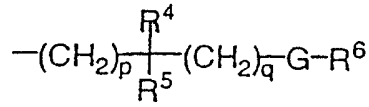
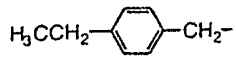
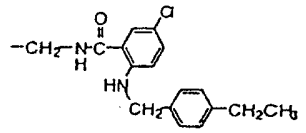
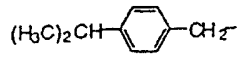
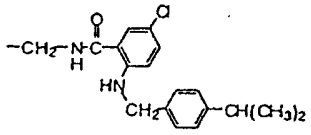
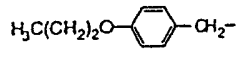
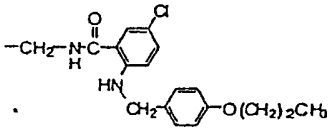
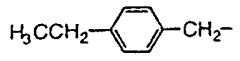
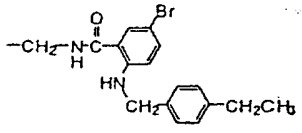
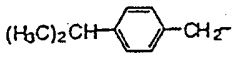
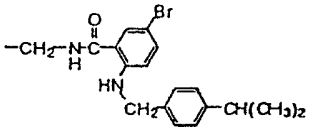
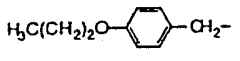
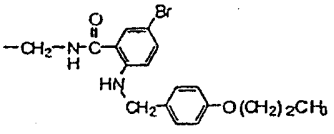
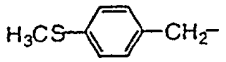
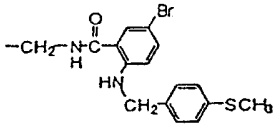
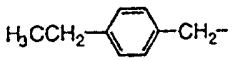
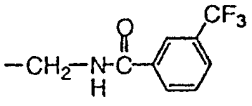
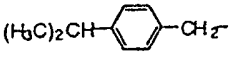
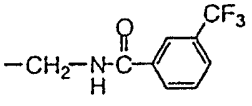
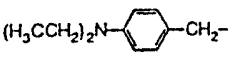
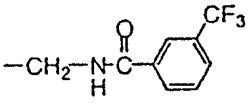
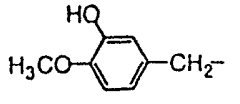
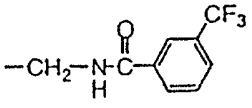
Sloučč.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1420		1	2	0	R	H	
1421		1	2	0	R	H	
1422		2	2	1	-	H	
1423		1	2	0	R	H	
1424		1	2	0	R	H	
1425		1	2	0	R	H	
1426		2	2	1	-	H	
1427		2	2	1	-	H	
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1430		2	2	1	-	H	

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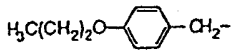
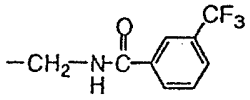
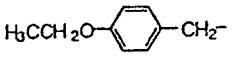
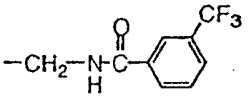
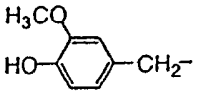
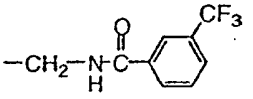
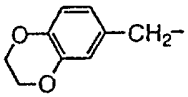
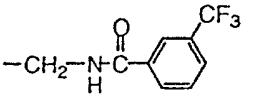
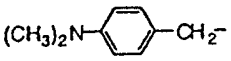
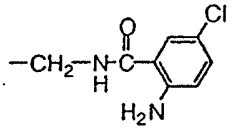
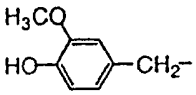
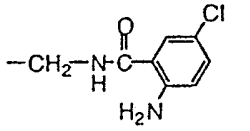
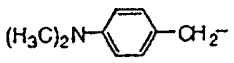
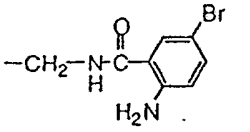
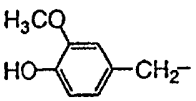
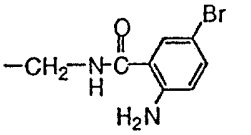
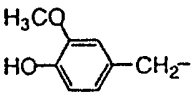
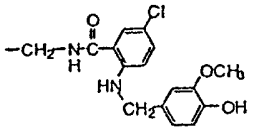
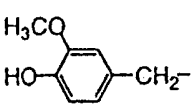
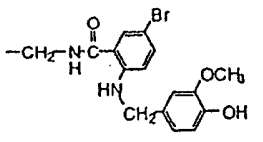
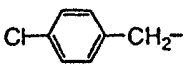
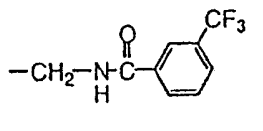
Tabulka 1.131

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1431	H_3CCH_2O-Ph-CH_2-	2	2	1	-	H	
1432	1,4-benzodioxan-CH_2-	2	2	1	-	H	
1433	H_3CCH_2O-Ph-CH_2-	2	2	1	-	H	
1434	H_3CCH_2O-Ph-CH_2-	2	2	1	-	H	
1435	H_3CCH_2-Ph-CH_2-	2	2	1	-	H	
1436	$(H_3C)_2CH$-Ph-CH_2-	2	2	1	-	H	
1437	$H_3C(CH_2)_2O$-Ph-CH_2-	2	2	1	-	H	
1438	H_3CCH_2-Ph-CH_2-	2	2	1	-	H	
1439	$(H_3C)_2CH$-Ph-CH_2-	2	2	1	-	H	
1440	$H_3C(CH_2)_2O$-Ph-CH_2-	2	2	1	-	H	
1441	H_3CS-Ph-CH_2-	2	2	1	-	H	

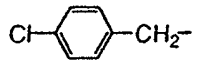
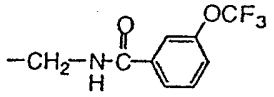
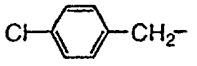
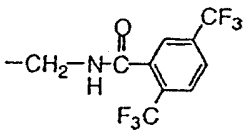
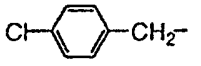
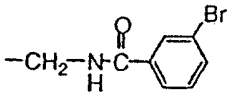
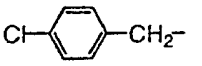
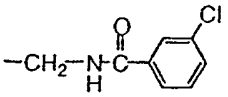
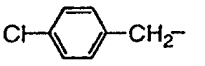
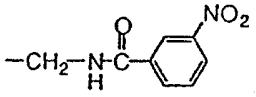
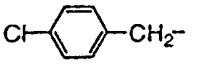
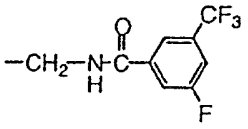
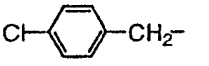
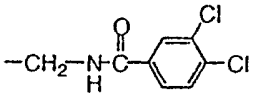
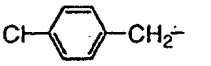
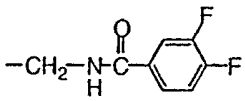
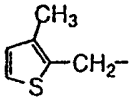
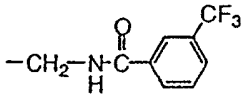
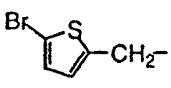
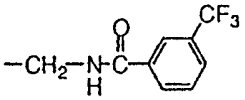
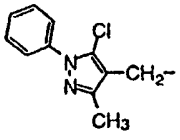
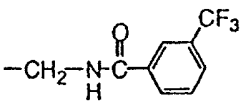
Tabulka 1.132

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1443		2	2	1	-	H	
1444		2	2	1	-	H	
1445		2	2	1	-	H	
1446		2	2	1	-	H	
1447		2	2	1	-	H	
1448		2	2	1	-	H	
1449		2	2	1	-	H	
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1451		2	2	1	-	H	
1452		2	2	1	-	H	

Tabulka 1.133

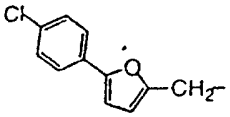
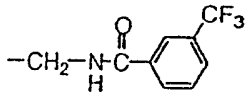
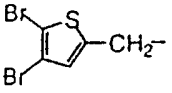
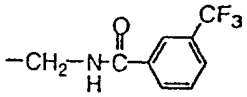
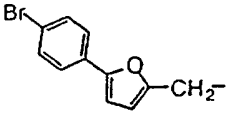
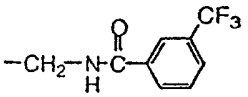
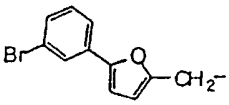
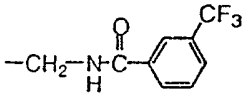
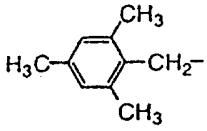
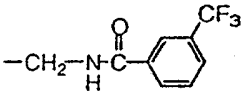
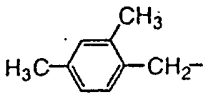
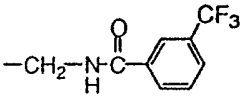
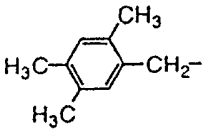
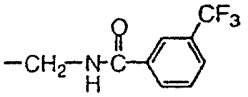
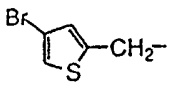
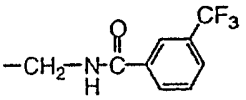
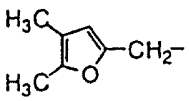
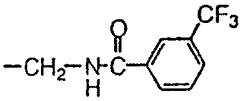
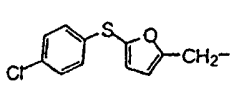
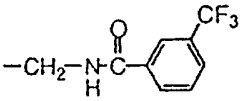
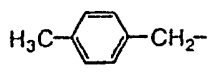
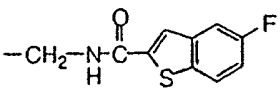
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1453		2	2	1	-	H	
1454		2	2	1	-	H	
1455		2	2	1	-	H	
1456		2	2	1	-	H	
1457		2	2	1	-	H	
1458		2	2	1	-	H	
1459		2	2	1	-	H	
1460		2	2	1	-	H	
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1463		2	1	1	-	H	

Tabulka 1.134

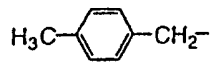
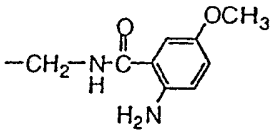
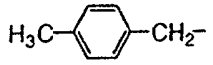
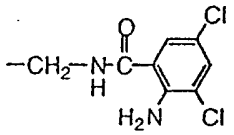
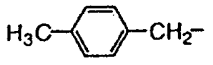
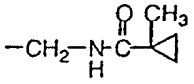
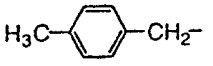
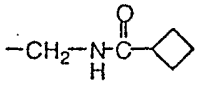
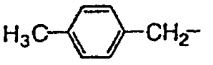
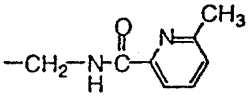
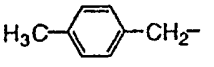
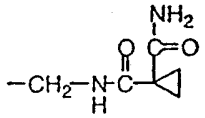
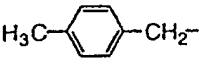
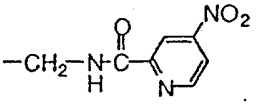
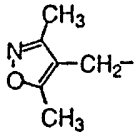
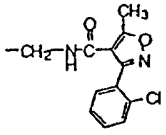
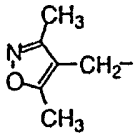
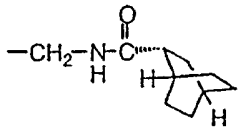
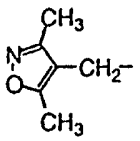
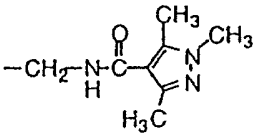
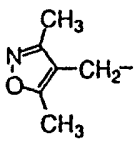
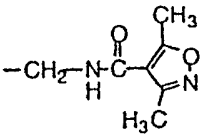
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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1465		2	1	1	-	H	
1466		2	1	1	-	H	
1467		2	1	1	-	H	
1468		2	1	1	-	H	
1469		2	1	1	-	H	
1470		2	1	1	-	H	
1471		2	1	1	-	H	
1472		1	2	0	R	H	
1473		1	2	0	R	H	
1474		1	2	0	R	H	

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Tabulka 1.135

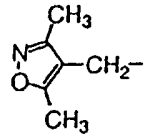
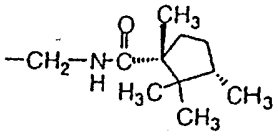
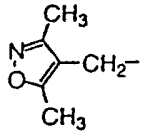
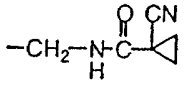
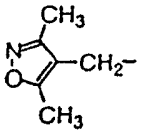
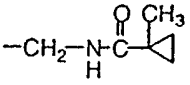
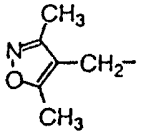
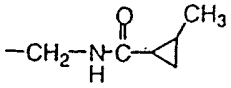
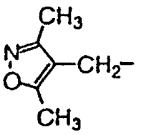
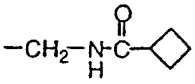
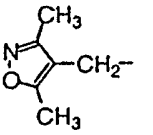
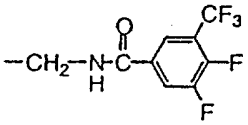
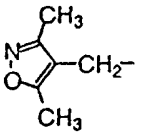
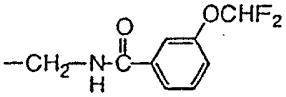
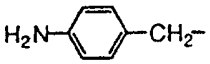
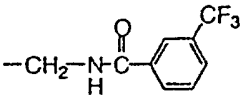
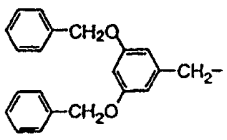
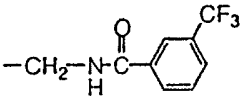
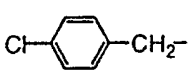
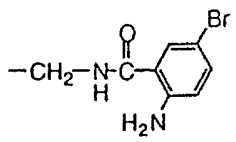
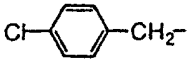
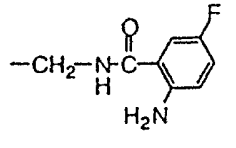
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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1476		1	2	0	R	H	
1477		1	2	0	R	H	
1478		1	2	0	R	H	
1479		1	2	0	R	H	
1480		1	2	0	R	H	
1481		1	2	0	R	H	
1482		1	2	0	R	H	
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1484		1	2	0	R	H	
1485		1	2	0	R	H	

Tabulka 1.136

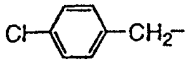
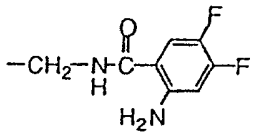
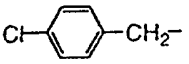
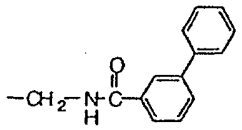
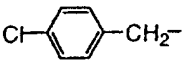
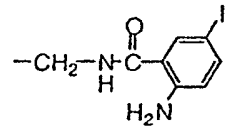
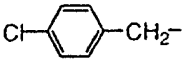
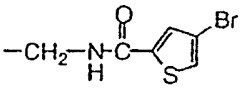
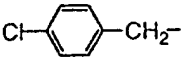
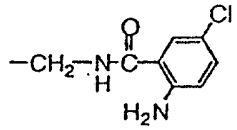
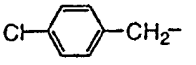
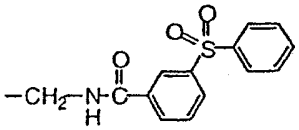
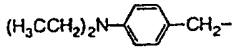
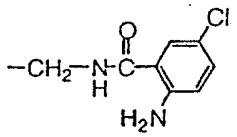
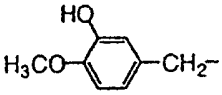
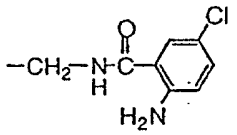
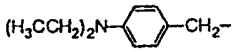
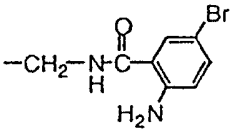
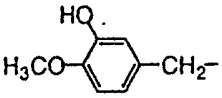
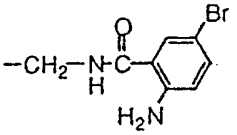
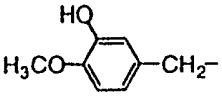
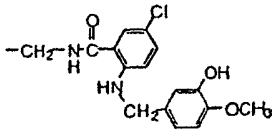
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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1487		1	2	0	R	H	
1488		1	2	0	R	H	
1489		1	2	0	R	H	
1490		1	2	0	R	H	
1491		1	2	0	R	H	
1492		1	2	0	R	H	
1493		1	2	0	R	H	
1494		1	2	0	R	H	
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1496		1	2	0	R	H	

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Tabulka 1.137

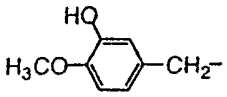
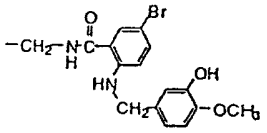
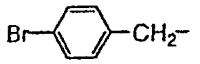
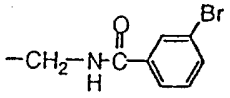
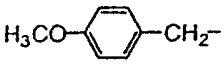
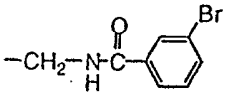
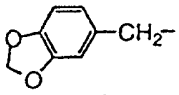
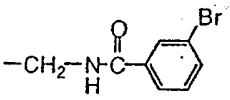
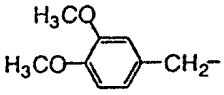
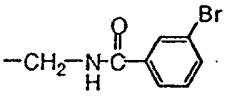
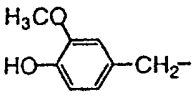
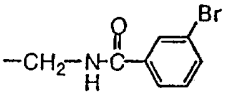
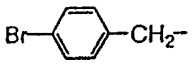
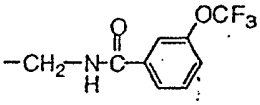
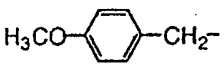
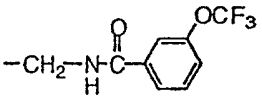
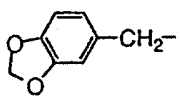
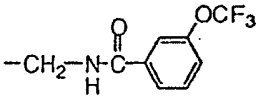
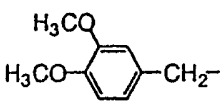
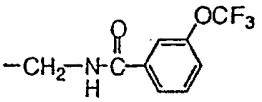
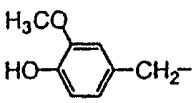
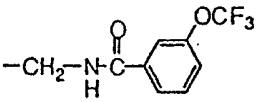
Slouč.č.	R^1, R^2, $(CH_2)_i$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1497		1	2	0	R	H	
1498		1	2	0	R	H	
1499		1	2	0	R	H	
1500		1	2	0	R	H	
1501		1	2	0	R	H	
1502		1	2	0	R	H	
1503		1	2	0	R	H	
1504		1	2	0	R	H	
1505		1	2	0	R	H	
1506		2	1	1	-	H	
1507		2	1	1	-	H	

Tabulka 1.138

Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1508		2	1	1	-	H	
1509		2	1	1	-	H	
1510		2	1	1	-	H	
1511		2	1	1	-	H	
1512		2	1	1	-	H	
1513		2	1	1	-	H	
1514		2	2	1	-	H	
1515		2	2	1	-	H	
1516		2	2	1	-	H	
1517		2	2	1	-	H	
1518		2	2	1	-	H	

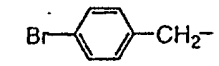
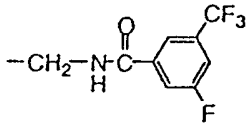
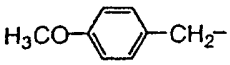
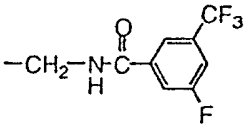
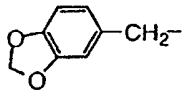
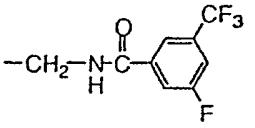
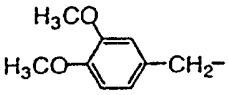
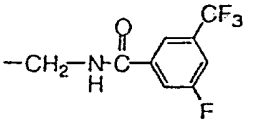
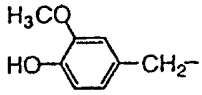
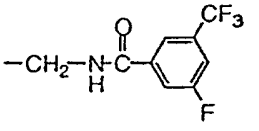
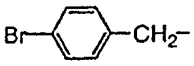
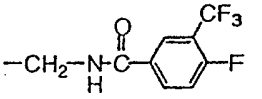
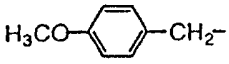
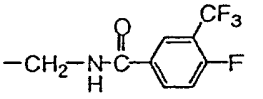
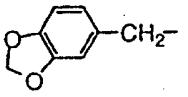
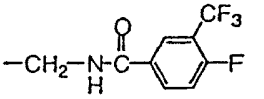
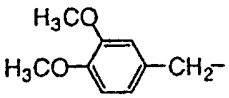
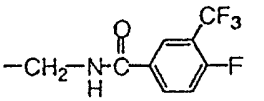
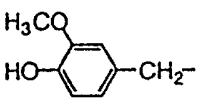
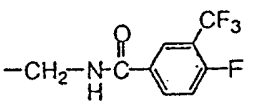
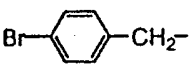
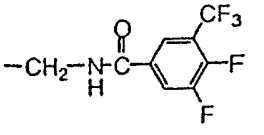
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Tabulka 1.139

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1519		2	2	1	-	H	
1520		1	2	0	R	H	
1521		1	2	0	R	H	
1522		1	2	0	R	H	
1523		1	2	0	R	H	
1524		1	2	0	R	H	
1525		1	2	0	R	H	
1526		1	2	0	R	H	
1527		1	2	0	R	H	
1528		1	2	0	R	H	
1529		1	2	0	R	H	

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Tabulka 1.140

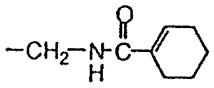
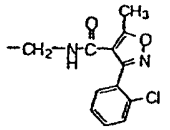
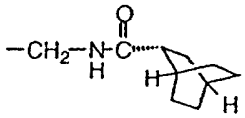
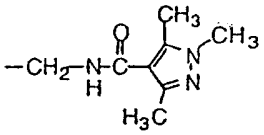
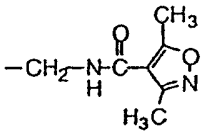
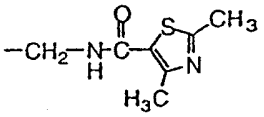
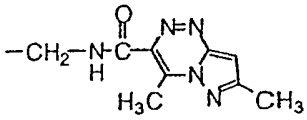
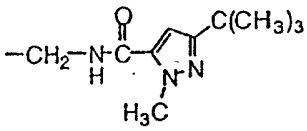
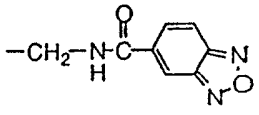
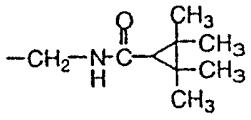
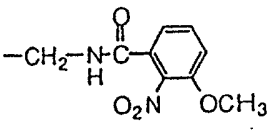
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1530		1	2	0	R	H	
1531		1	2	0	R	H	
1532		1	2	0	R	H	
1533		1	2	0	R	H	
1534		1	2	0	R	H	
1535		1	2	0	R	H	
1536		1	2	0	R	H	
1537		1	2	0	R	H	
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1539		1	2	0	R	H	
1540		1	2	0	R	H	

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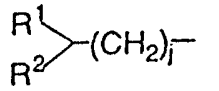
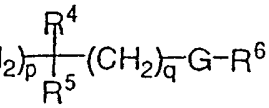
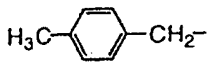
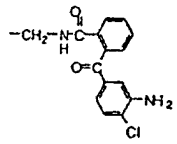
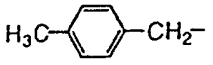
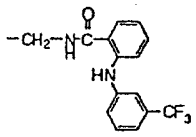
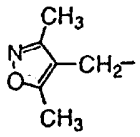
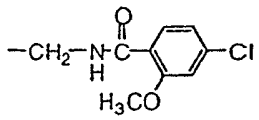
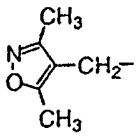
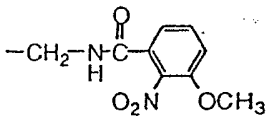
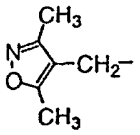
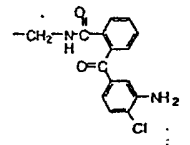
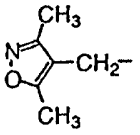
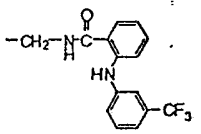
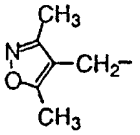
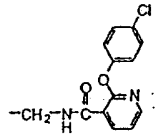
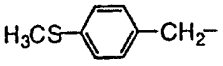
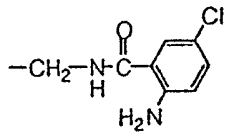
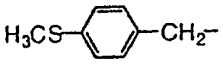
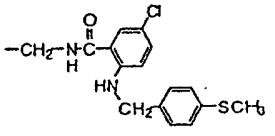
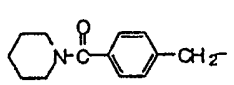
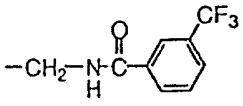
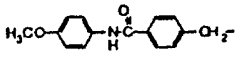
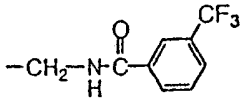
Tabulka 1.141

Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1541	H_3CO-Ph-CH_2–	1	2	0	R	H	–CH_2–NH–C(=O)–Ph(3-CF_3, 4-F, 5-F)
1542	1,3-benzodioxol-5-CH_2–	1	2	0	R	H	–CH_2–NH–C(=O)–Ph(3-CF_3, 4-F, 5-F)
1543	2,3-dimethoxybenzyl	1	2	0	R	H	–CH_2–NH–C(=O)–Ph(3-CF_3, 4-F, 5-F)
1544	2-hydroxy-3-methoxybenzyl	1	2	0	R	H	–CH_2–NH–C(=O)–Ph(3-CF_3, 4-F, 5-F)
1545	2-chloro-5-thienyl-CH_2–	1	2	0	R	H	–CH_2–NH–C(=O)–Ph(3-CF_3)
1546	2,3,5,6-tetrafluoro-4-methoxybenzyl	1	2	0	R	H	–CH_2–NH–C(=O)–Ph(3-CF_3)
1547	2,6-dibromo-4-methoxybenzyl	1	2	0	R	H	–CH_2–NH–C(=O)–Ph(3-CF_3)
1548	H_3C-Ph-CH_2–	1	2	0	R	H	–CH_2–NH–C(=O)–(1-CH_3, 2,2-$(CH_3)_2$, 3-CH_3 cyclopentyl)
1549	H_3C-Ph-CH_2–	1	2	0	R	H	–CH_2–NH–C(=O)–(2-$CH=C(CH_3)_2$, 3,3-$(CH_3)_2$ cyclopropyl)
1550	H_3C-Ph-CH_2–	1	2	0	R	H	–CH_2–NH–C(=O)–Ph(3-NH–C(=O)–NH–Ph(2-OCH_3, 3-Cl, 4-OCH_3))
1551	H_3C-Ph-CH_2–	1	2	0	R	H	–CH_2–NH–C(=O)–Ph(3-$SO_2N(CH_2CH_2OH)_2$)

Tabulka 1.142

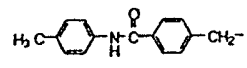
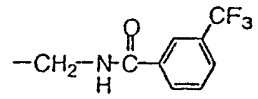
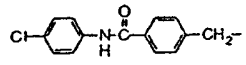
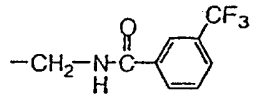
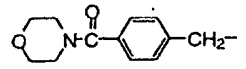
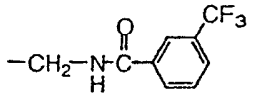
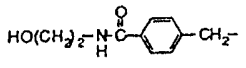
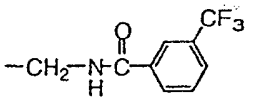
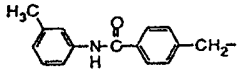
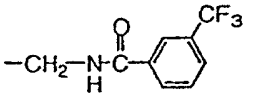
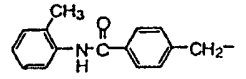
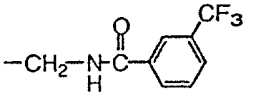
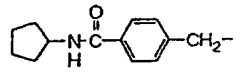
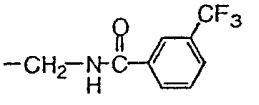
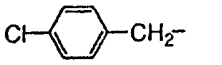
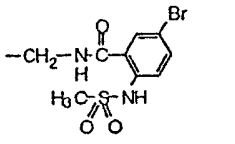
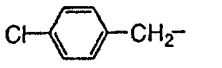
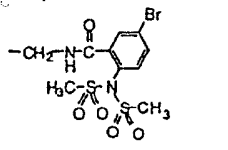
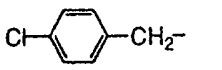
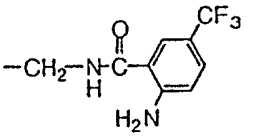
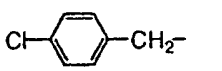
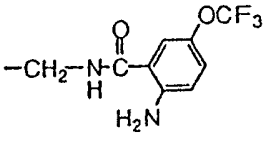
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1552	H_3C, CH_2	1	2	0	R	H	
1553	H_3C, CH_2	1	2	0	R	H	
1554	H_3C, CH_2	1	2	0	R	H	
1555	H_3C, CH_2	1	2	0	R	H	
1556	H_3C, CH_2	1	2	0	R	H	
1557	H_3C, CH_2	1	2	0	R	H	
1558	H_3C, CH_2	1	2	0	R	H	
1559	H_3C, CH_2	1	2	0	R	H	
1560	H_3C, CH_2	1	2	0	R	H	
1561	H_3C, CH_2	1	2	0	R	H	
1562	H_3C, CH_2	1	2	0	R	H	

Tabulka 1.143

Slouč.č.		k	m	n	chiralita	R^3	
1563		1	2	0	R	H	
1564		1	2	0	R	H	
1565		1	2	0	R	H	
1566		1	2	0	R	H	
1567		1	2	0	R	H	
1568		1	2	0	R	H	
1569		1	2	0	R	H	
1570		2	2	1	-	H	
1571		2	2	1	-	H	
1572		2	2	1	-	H	
1573		2	2	1	-	H	

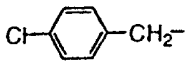
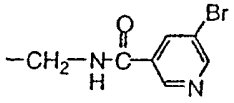
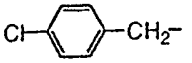
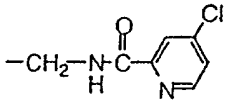
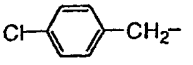
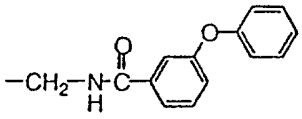
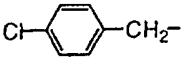
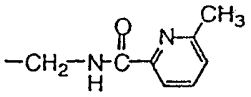
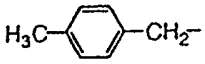
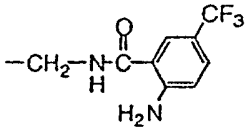
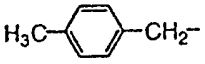
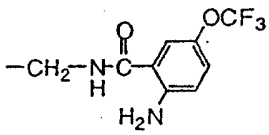
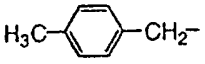
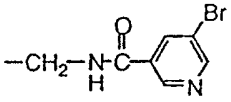
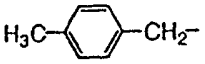
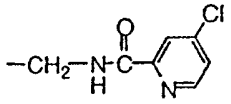
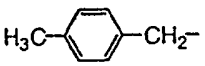
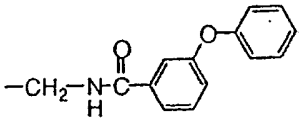
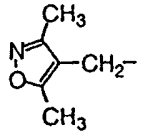
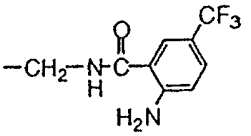
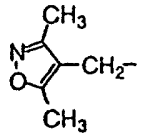
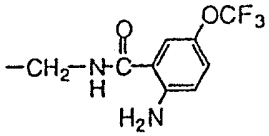
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Tabulka 1.144

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1574		2	2	1	-	H	
1575		2	2	1	-	H	
1576		2	2	1	-	H	
1577		2	2	1	-	H	
1578		2	2	1	-	H	
1579		2	2	1	-	H	
1580		2	2	1	-	H	
1581		2	2	1	-	H	
1582		2	2	1	-	H	
1583		1	2	0	R	H	
1584		1	2	0	R	H	

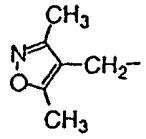
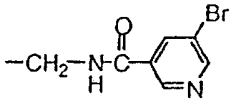
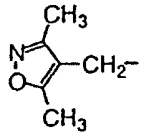
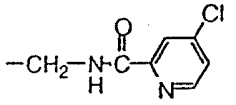
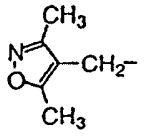
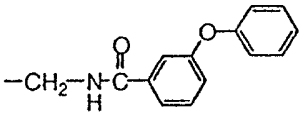
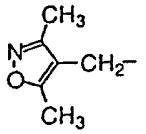
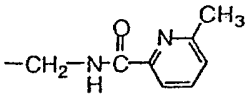
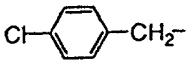
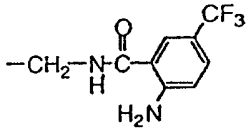
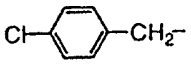
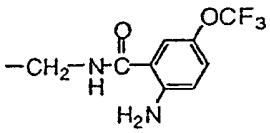
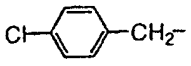
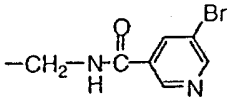
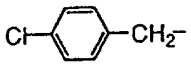
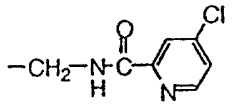
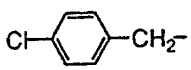
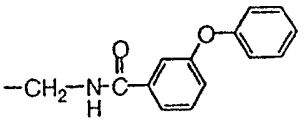
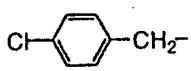
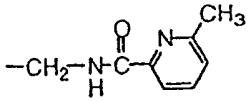
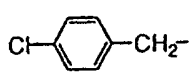
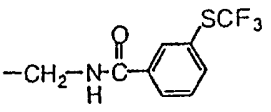
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Tabulka 1.145

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1585		1	2	0	R	H	
1586		1	2	0	R	H	
1587		1	2	0	R	H	
1588		1	2	0	R	H	
1589		1	2	0	R	H	
1590		1	2	0	R	H	
1591		1	2	0	R	H	
1592		1	2	0	R	H	
1593		1	2	0	R	H	
1594		1	2	0	R	H	
1595		1	2	0	R	H	

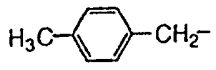
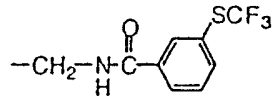
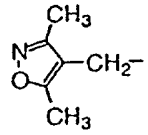
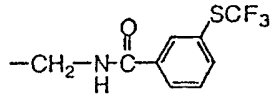
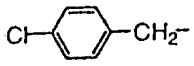
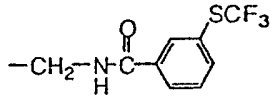
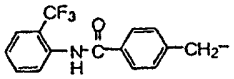
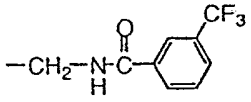
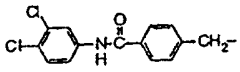
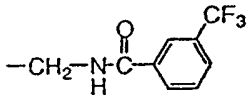
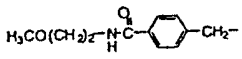
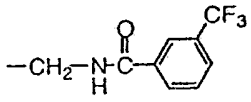
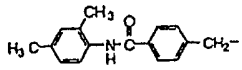
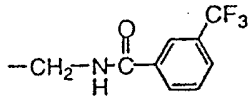
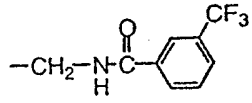
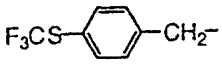
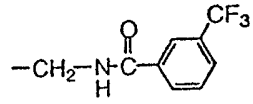
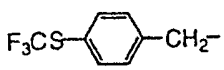
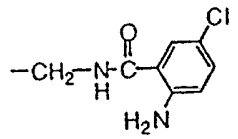
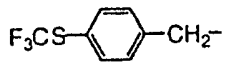
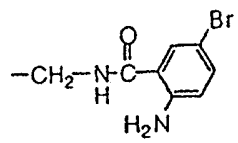
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Tabulka 1.146

Slouč.č.	R^1, R^2, $-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1596		1	2	0	R	H	
1597		1	2	0	R	H	
1598		1	2	0	R	H	
1599		1	2	0	R	H	
1600		2	2	1	-	H	
1601		2	2	1	-	H	
1602		2	2	1	-	H	
1603		2	2	1	-	H	
1604		2	2	1	-	H	
1605		2	2	1	-	H	
1606		1	2	0	R	H	

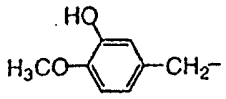
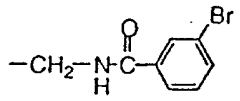
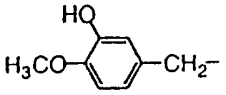
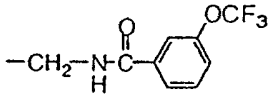
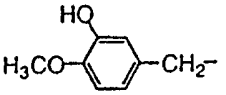
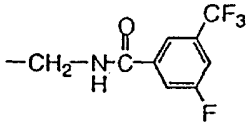
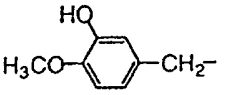
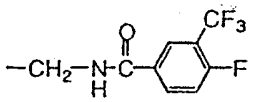
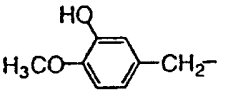
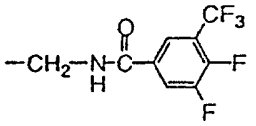
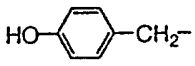
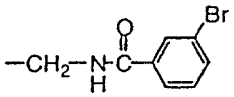
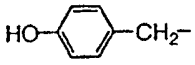
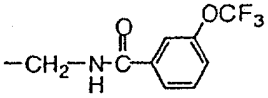
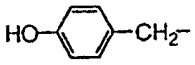
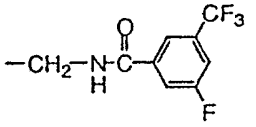
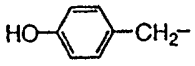
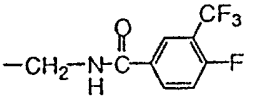
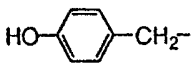
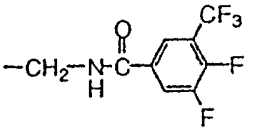
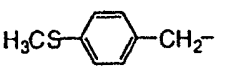
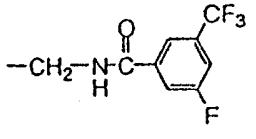
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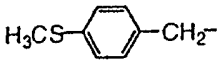
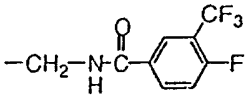
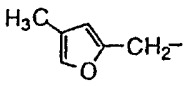
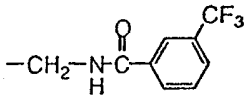
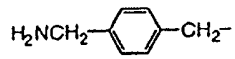
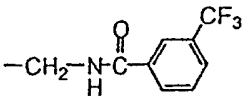
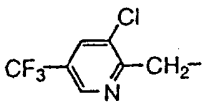
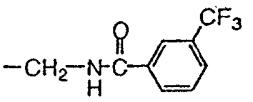
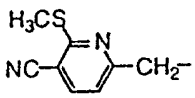
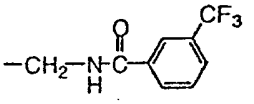
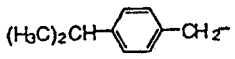
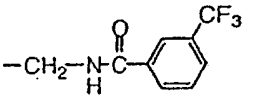
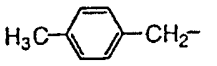
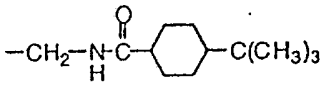
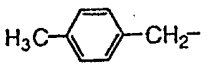
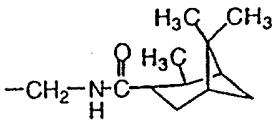
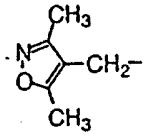
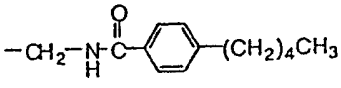
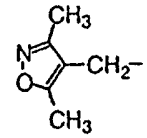
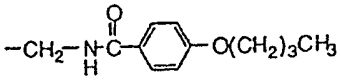
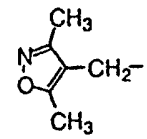
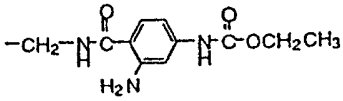
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1607		1	2	0	R	H	
1608		1	2	0	R	H	
1609		2	2	1	-	H	
1610		2	2	1	-	H	
1611		2	2	1	-	H	
1612		2	2	1	-	H	
1613		2	2	1	-	H	
1614		1	2	0	R	H	
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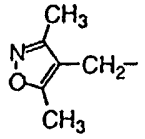
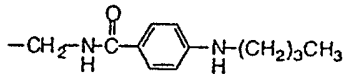
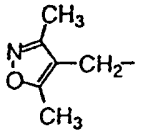
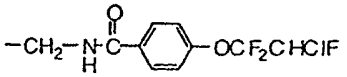
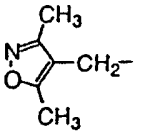
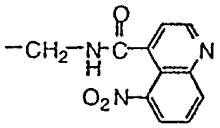
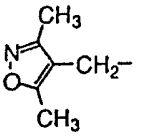
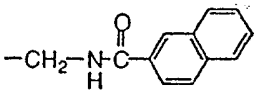
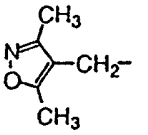
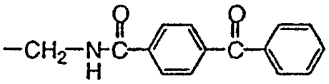
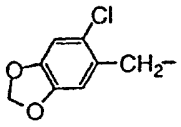
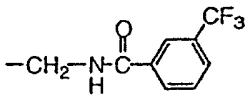
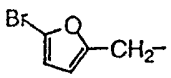
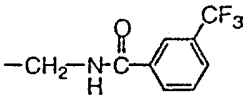
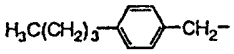
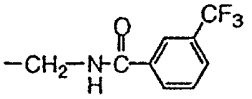
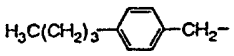
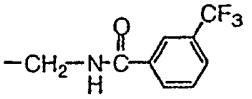
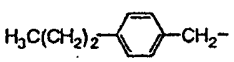
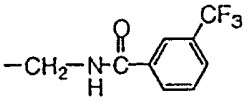
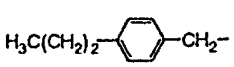
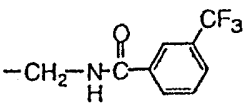
Sloučč.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1618		1	2	0	R	H	
1619		1	2	0	R	H	
1620		1	2	0	R	H	
1621		1	2	0	R	H	
1622		1	2	0	R	H	
1623		1	2	0	R	H	
1624		1	2	0	R	H	
1625		1	2	0	R	H	
1626		1	2	0	R	H	
1627		1	2	0	R	H	
1628		1	2	0	R	H	

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Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1629		1	2	0	R	H	
1630		1	2	0	R	H	
1631		1	2	0	R	H	
1632		1	2	0	R	H	
1633		1	2	0	R	H	
1634		1	2	0	R	H	
1635		1	2	0	R	H	
1636		1	2	0	R	H	
1637		1	2	0	R	H	
1638		1	2	0	R	H	
1639		1	2	0	R	H	

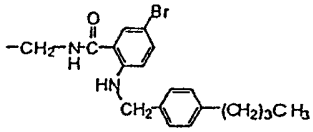
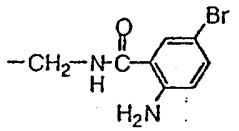
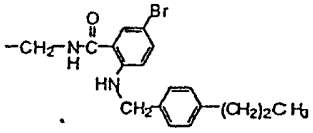
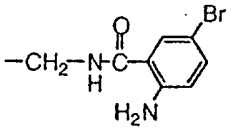
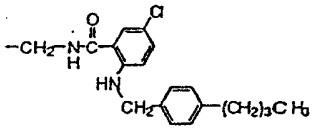
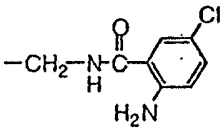
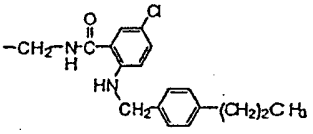
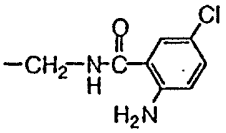
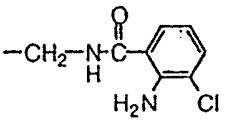
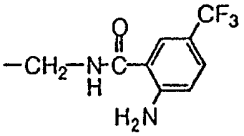
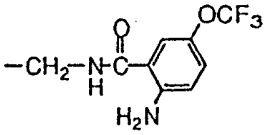
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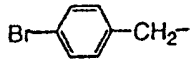
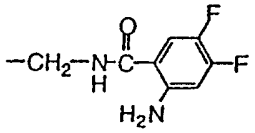
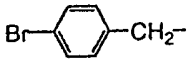
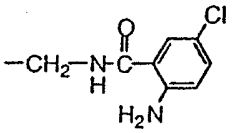
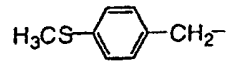
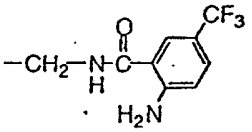
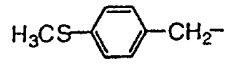
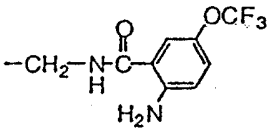
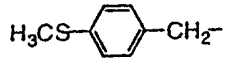
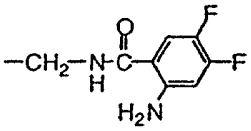
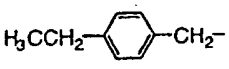
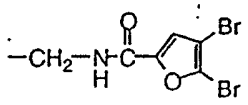
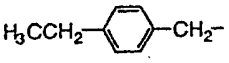
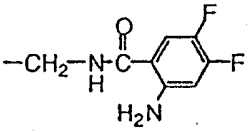
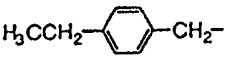
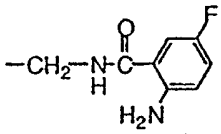
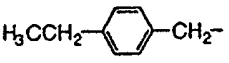
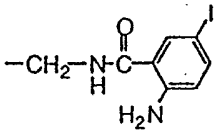
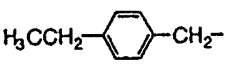
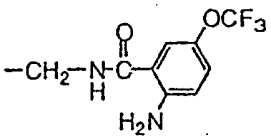
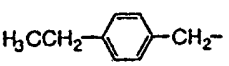
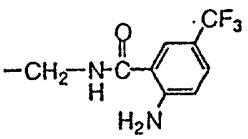
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1640		1	2	0	R	H	
1641		1	2	0	R	H	
1642		1	2	0	R	H	
1643		1	2	0	R	H	
1644		1	2	0	R	H	
1645		1	2	0	R	H	
1646		1	2	0	R	H	
1647		2	2	1	-	H	
1648		1	2	0	R	H	
1649		2	2	1	-	H	
1650		1	2	0	R	H	

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Slouč.č.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1651	$H_3C(CH_2)_3-C_6H_4-CH_2-$	2	2	1	-	H	
1652	$H_3C(CH_2)_3-C_6H_4-CH_2-$	2	2	1	-	H	
1653	$H_3C(CH_2)_2-C_6H_4-CH_2-$	2	2	1	-	H	
1654	$H_3C(CH_2)_2-C_6H_4-CH_2-$	2	2	1	-	H	
1655	$H_3C(CH_2)_3-C_6H_4-CH_2-$	2	2	1	-	H	
1656	$H_3C(CH_2)_3-C_6H_4-CH_2-$	2	2	1	-	H	
1657	$H_3C(CH_2)_2-C_6H_4-CH_2-$	2	2	1	-	H	
1658	$H_3C(CH_2)_2-C_6H_4-CH_2-$	2	2	1	-	H	
1659	$Cl-C_6H_4-CH_2-$	2	2	1	-	H	
1660	$Br-C_6H_4-CH_2-$	1	2	0	R	H	
1661	$Br-C_6H_4-CH_2-$	1	2	0	R	H	

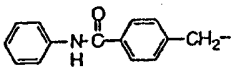
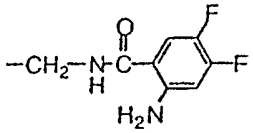
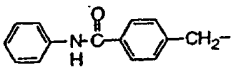
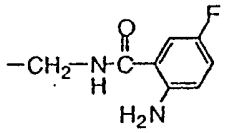
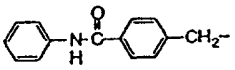
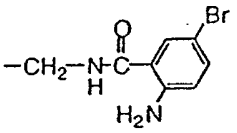
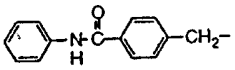
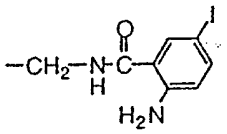
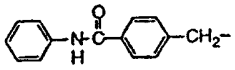
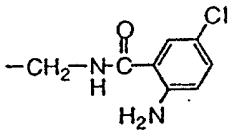
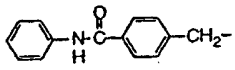
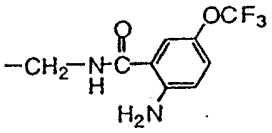
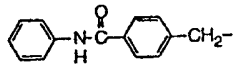
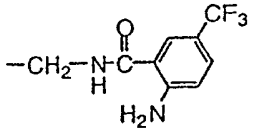
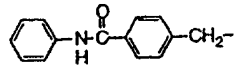
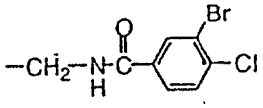
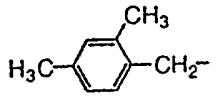
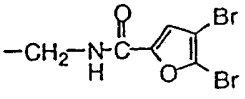
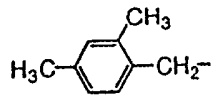
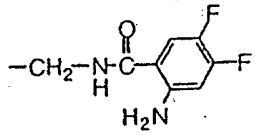
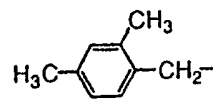
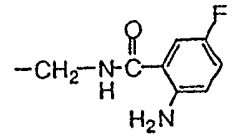
Tabulka 1.152

Slouč.č.	$R^1R^2CH(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1662		1	2	0	R	H	
1663		1	2	0	R	H	
1664		2	2	1	-	H	
1665		2	2	1	-	H	
1666		2	2	1	-	H	
1667		2	2	1	-	H	
1668		2	2	1	-	H	
1669		2	2	1	-	H	
1670		2	2	1	-	H	
1671		2	2	1	-	H	
1672		2	2	1	-	H	

Tabulka 1.153

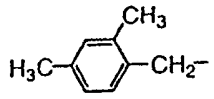
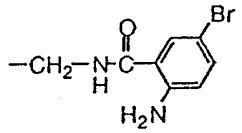
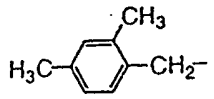
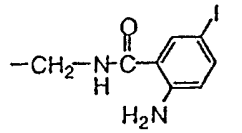
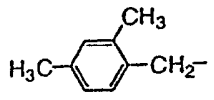
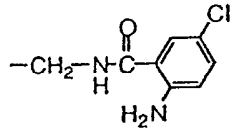
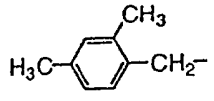
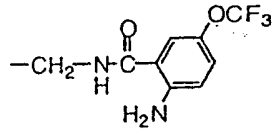
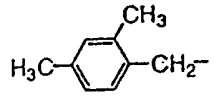
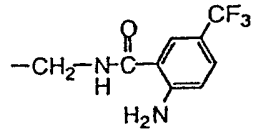
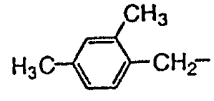
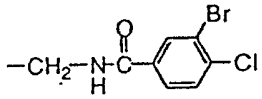
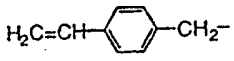
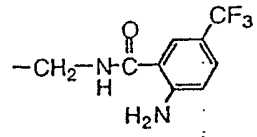
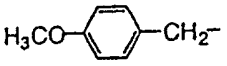
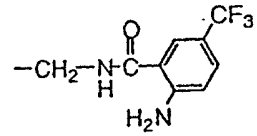
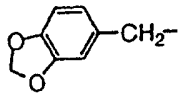
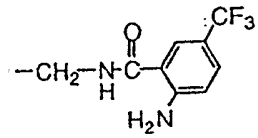
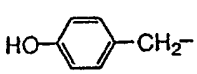
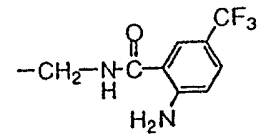
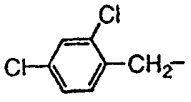
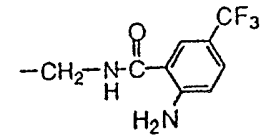
Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1673	H_3CCH_2–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_6$H$_3$(Br)(Cl)
1674	F–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_4$H$_2$O(Br)(Br)
1675	F–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_6$H$_2$(F)(F)(NH_2)
1676	F–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_6$H$_3$(F)(NH_2)
1677	F–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_6$H$_3$(Br)(NH_2)
1678	F–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_6$H$_3$(I)(NH_2)
1679	F–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_6$H$_3$(Cl)(NH_2)
1680	F–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_6$H$_3$(OCF_3)(NH_2)
1681	F–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_6$H$_3$(CF_3)(NH_2)
1682	F–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_6$H$_3$(Br)(Cl)
1683	C$_6$H$_5$–NH–C(=O)–C$_6$H$_4$–CH_2–	2	2	1	-	H	–CH_2–NH–C(=O)–C$_4$H$_2$O(Br)(Br)

Tabulka 1.154

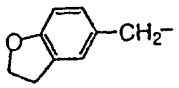
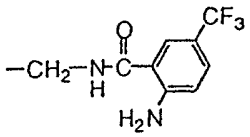
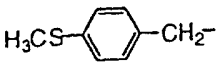
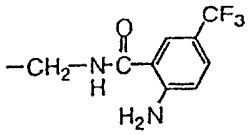
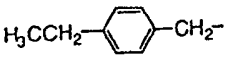
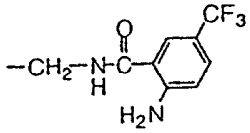
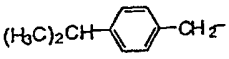
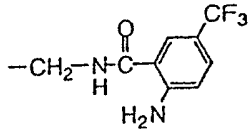
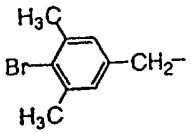
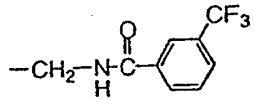
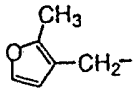
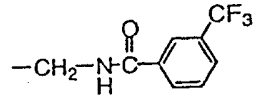
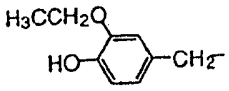
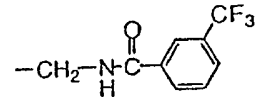
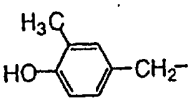
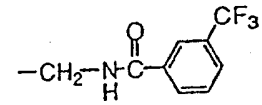
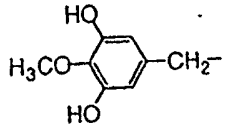
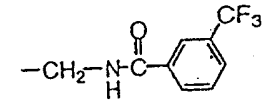
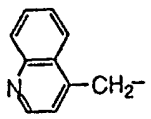
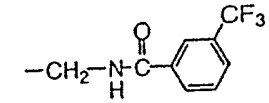
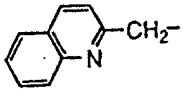
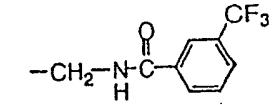
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1684		2	2	1	-	H	
1685		2	2	1	-	H	
1686		2	2	1	-	H	
1687		2	2	1	-	H	
1688		2	2	1	-	H	
1689		2	2	1	-	H	
1690		2	2	1	-	H	
1691		2	2	1	-	H	
1692		1	2	0	R	H	
1693		1	2	0	R	H	
1694		1	2	0	R	H	

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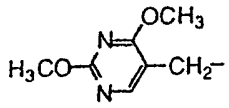
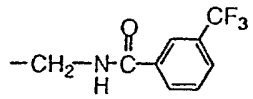
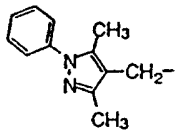
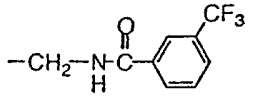
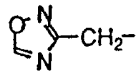
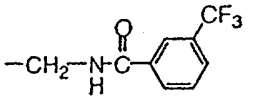
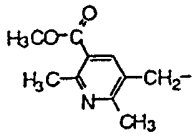
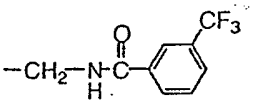
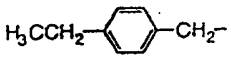
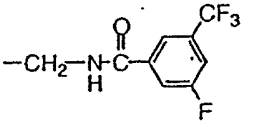
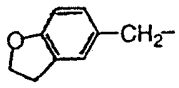
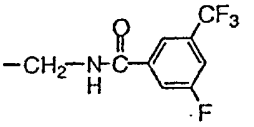
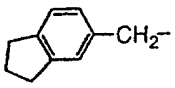
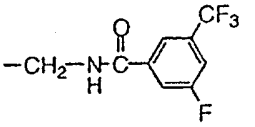
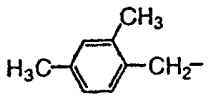
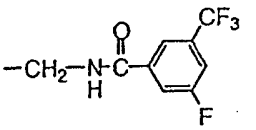
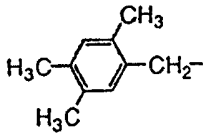
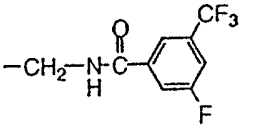
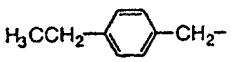
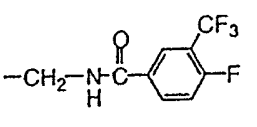
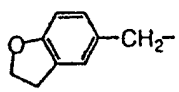
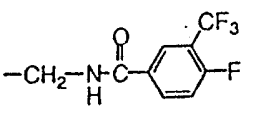
Tabulka 1.155

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1695		1	2	0	R	H	
1696		1	2	0	R	H	
1697		1	2	0	R	H	
1698		1	2	0	R	H	
1699		1	2	0	R	H	
1700		1	2	0	R	H	
1701		1	2	0	R	H	
1702		1	2	0	R	H	
1703		1	2	0	R	H	
1704		1	2	0	R	H	
1705		1	2	0	R	H	

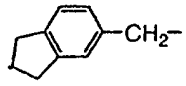
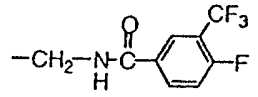
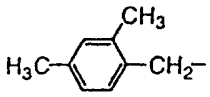
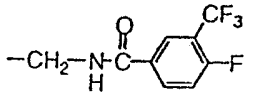
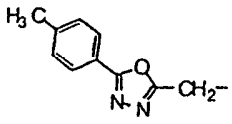
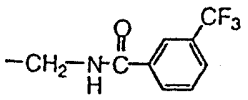
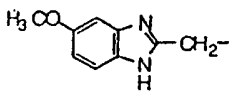
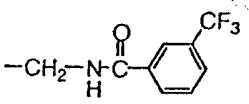
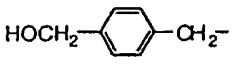
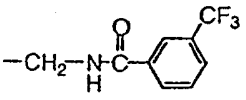
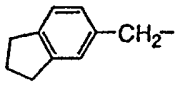
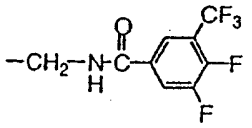
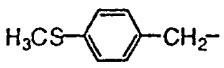
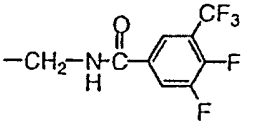
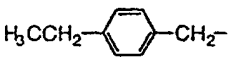
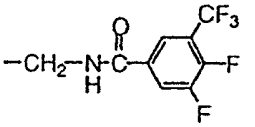
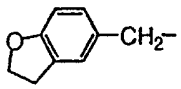
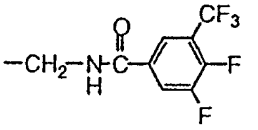
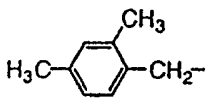
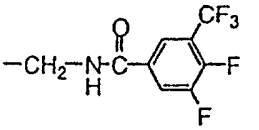
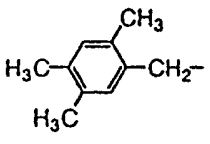
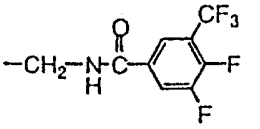
Tabulka 1.156

Sloučč.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1706		1	2	0	R	H	
1707		1	2	0	R	H	
1708		1	2	0	R	H	
1709		1	2	0	R	H	
1710		1	2	0	R	H	
1711		1	2	0	R	H	
1712		1	2	0	R	H	
1713		1	2	0	R	H	
1714		1	2	0	R	H	
1715		1	2	0	R	H	
1716		1	2	0	R	H	

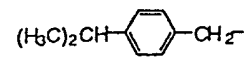
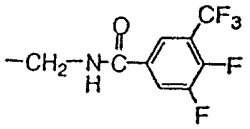
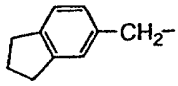
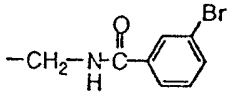
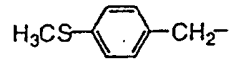
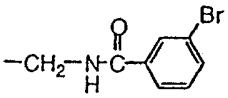
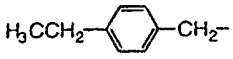
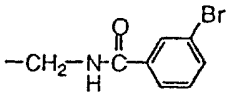
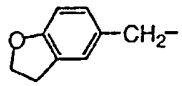
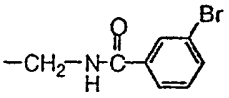
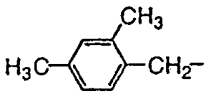
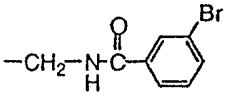
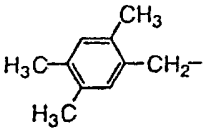
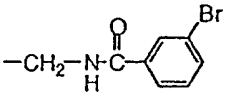
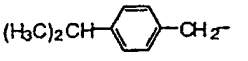
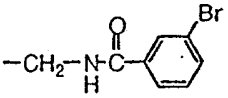
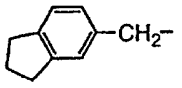
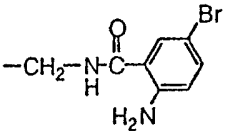
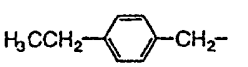
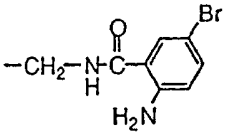
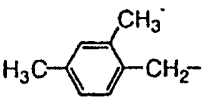
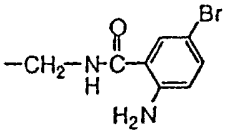
Tabulka 1.157

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1717		1	2	0	R	H	
1718		1	2	0	R	H	
1719		1	2	0	R	H	
1720		1	2	0	R	H	
1721		1	2	0	R	H	
1722		1	2	0	R	H	
1723		1	2	0	R	H	
1724		1	2	0	R	H	
1725		1	2	0	R	H	
1726		1	2	0	R	H	
1727		1	2	0	R	H	

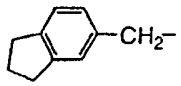
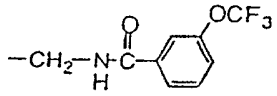
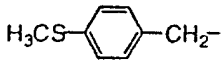
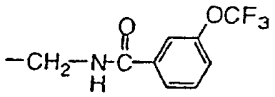
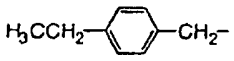
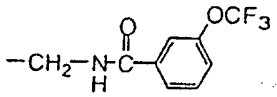
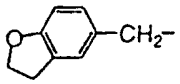
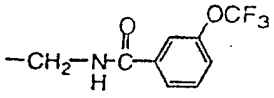
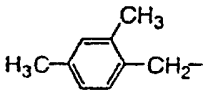
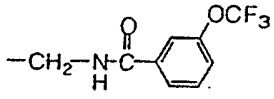
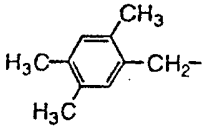
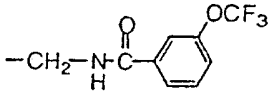
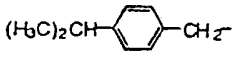
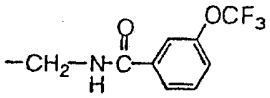
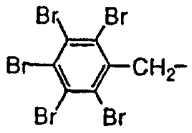
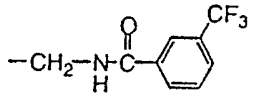
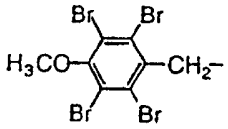
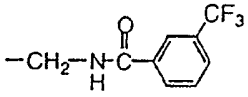
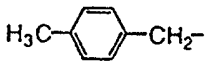
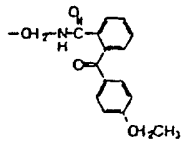
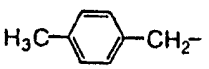
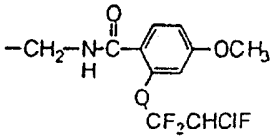
Tabulka 1.158

Sloučenina č.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1728		1	2	0	R	H	
1729		1	2	0	R	H	
1730		1	2	0	R	H	
1731		1	2	0	R	H	
1732		1	2	0	R	H	
1733		1	2	0	R	H	
1734		1	2	0	R	H	
1735		1	2	0	R	H	
1736		1	2	0	R	H	
1737		1	2	0	R	H	
1738		1	2	0	R	H	

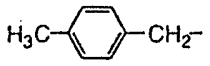
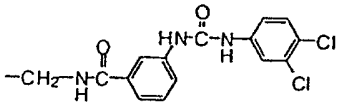
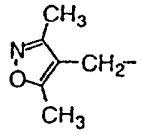
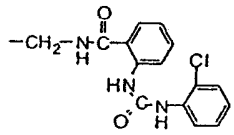
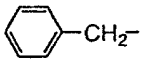
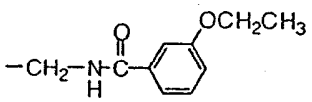
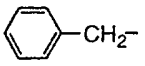
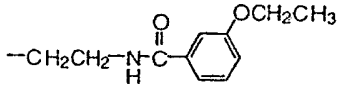
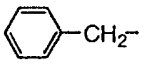
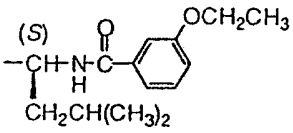
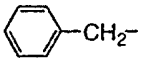
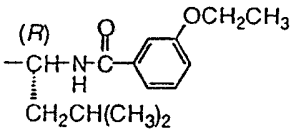
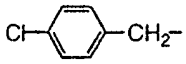
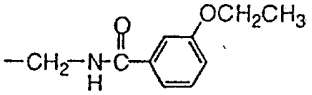
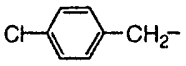
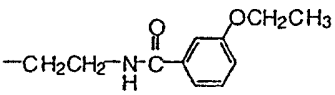
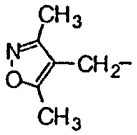
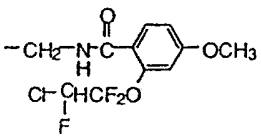
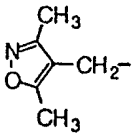
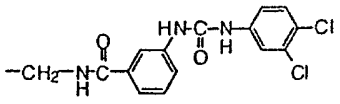
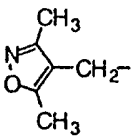
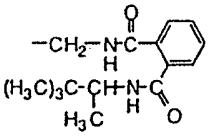
Tabulka 1.159

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1739		1	2	0	R	H	
1740		1	2	0	R	H	
1741		1	2	0	R	H	
1742		1	2	0	R	H	
1743		1	2	0	R	H	
1744		1	2	0	R	H	
1745		1	2	0	R	H	
1746		1	2	0	R	H	
1747		1	2	0	R	H	
1748		1	2	0	R	H	
1749		1	2	0	R	H	

Tabulka 1.160

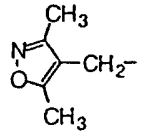
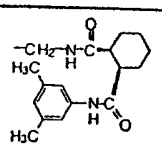
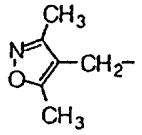
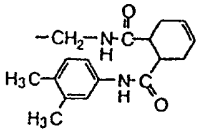
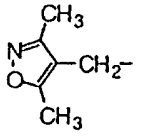
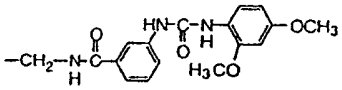
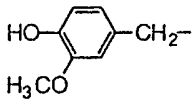
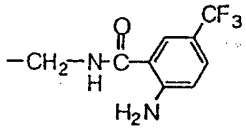
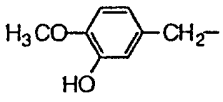
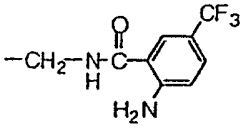
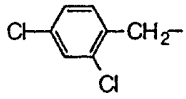
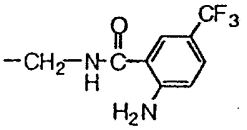
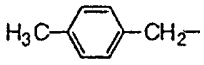
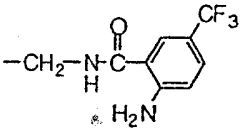
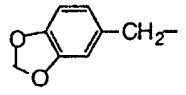
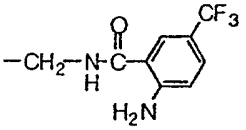
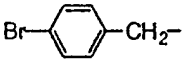
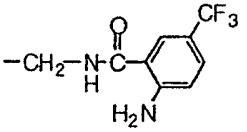
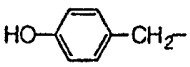
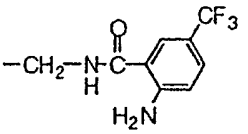
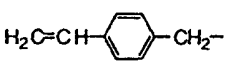
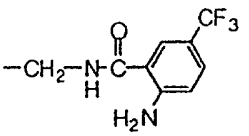
Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1750		1	2	0	R	H	
1751		1	2	0	R	H	
1752		1	2	0	R	H	
1753		1	2	0	R	H	
1754		1	2	0	R	H	
1755		1	2	0	R	H	
1756		1	2	0	R	H	
1757		1	2	0	R	H	
1758		1	2	0	R	H	
1759		1	2	0	R	H	
1760		1	2	0	R	H	

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Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1761		1	2	0	R	H	
1762		1	2	0	R	H	
1763		2	2	0	-	H	
1764		2	2	0	-	H	
1765		2	2	0	-	H	
1766		2	2	0	-	H	
1767		1	3	1	-	H	
1768		1	3	1	-	H	
1769		1	2	0	R	H	
1770		1	2	0	R	H	
1771		1	2	0	R	H	

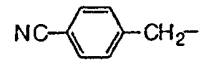
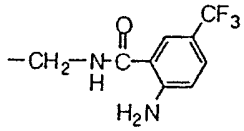
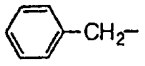
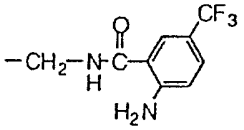
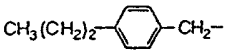
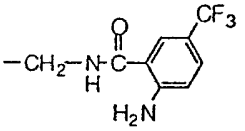
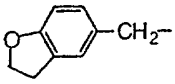
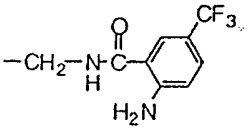
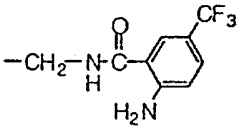
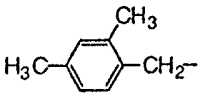
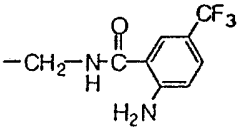
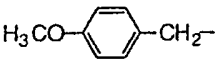
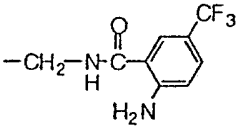
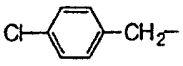
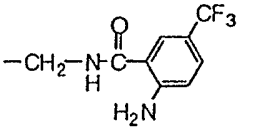
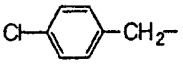
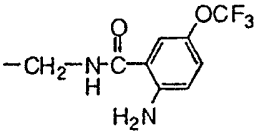
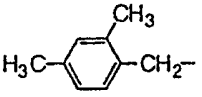
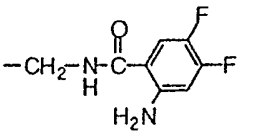
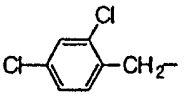
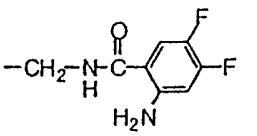
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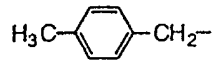
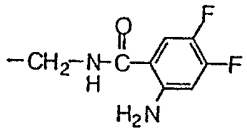
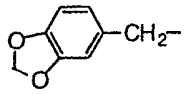
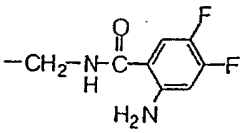
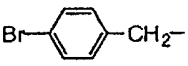
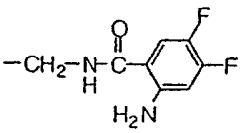
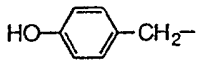
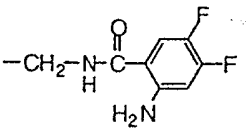
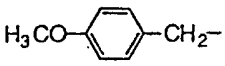
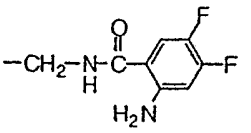
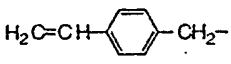
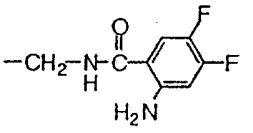
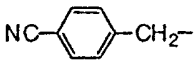
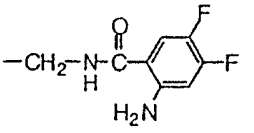
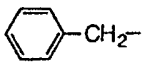
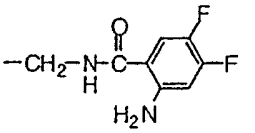
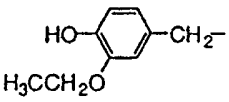
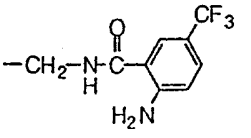
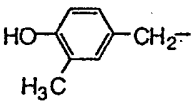
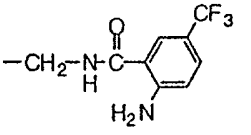
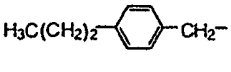
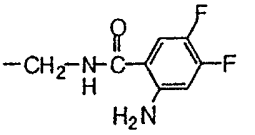
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1772		1	2	0	R	H	
1773		1	2	0	R	H	
1774		1	2	0	R	H	
1775		1	2	0	R	H	
1776		1	2	0	R	H	
1777		2	2	1	-	H	
1778		2	2	1	-	H	
1779		2	2	1	-	H	
1780		2	2	1	-	H	
1781		2	2	1	-	H	
1782		2	2	1	-	H	

03.07.00

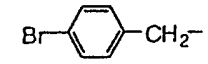
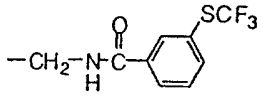
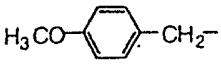
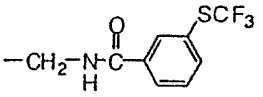
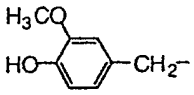
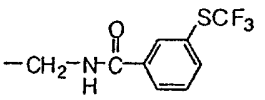
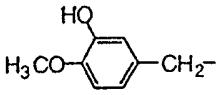
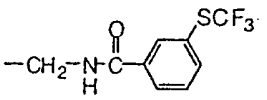
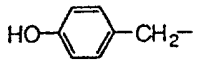
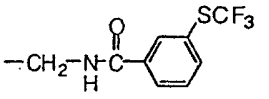
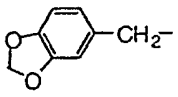
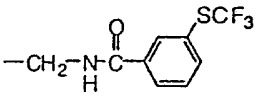
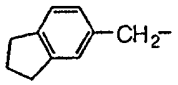
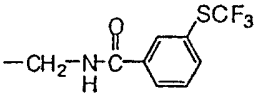
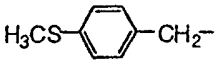
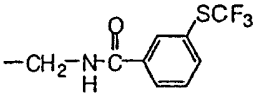
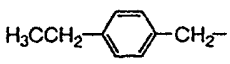
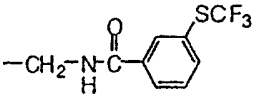
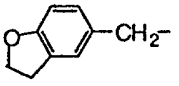
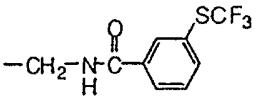
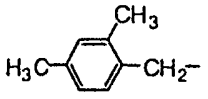
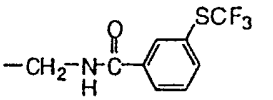
Tabulka 1.163

Slouč.č.	$R^1R^2CH(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1783		2	2	1	-	H	
1784		2	2	1	-	H	
1785		2	2	1	-	H	
1786		2	2	1	-	H	
1787		1	2	0	R	H	
1788		2	2	1	-	H	
1789		2	2	1	-	H	
1790		1	2	0	S	H	
1791		1	2	0	S	H	
1792		2	2	1	-	H	
1793		2	2	1	-	H	

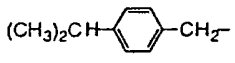
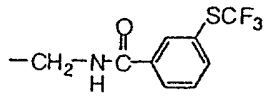
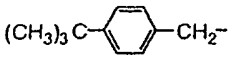
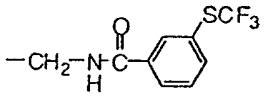
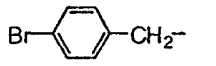
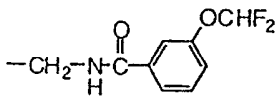
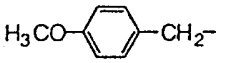
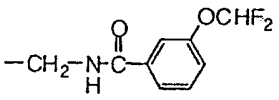
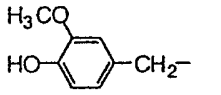
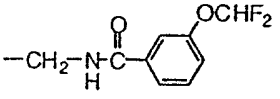
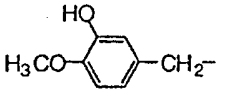
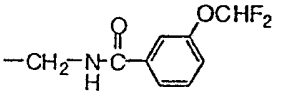
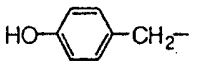
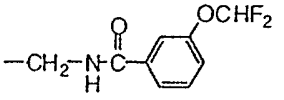
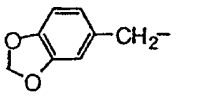
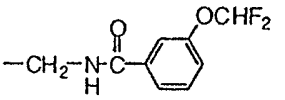
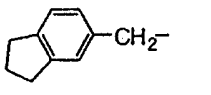
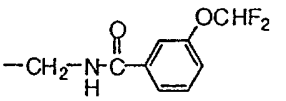
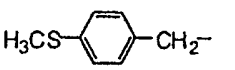
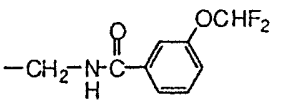
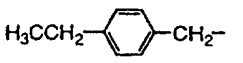
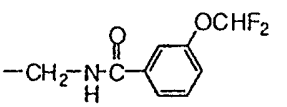
Tabulka 1.164

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$(CH_2)_p$, R^4, R^5, $(CH_2)_q$, G, R^6
1794		2	2	1	-	H	
1795		2	2	1	-	H	
1796		2	2	1	-	H	
1797		2	2	1	-	H	
1798		2	2	1	-	H	
1799		2	2	1	-	H	
1800		2	2	1	-	H	
1801		2	2	1	-	H	
1802		1	2	0	R	H	
1803		1	2	0	R	H	
1804		2	2	1	-	H	

Tabulka 1.165

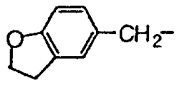
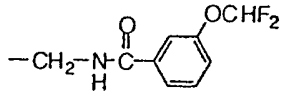
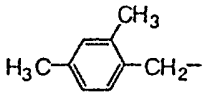
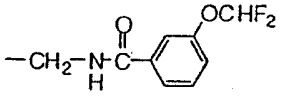
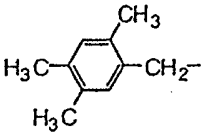
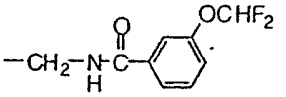
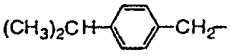
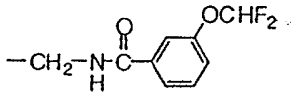
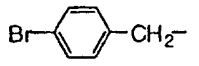
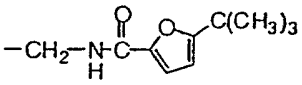
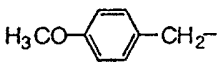
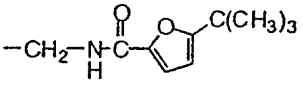
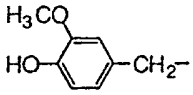
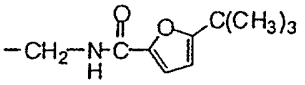
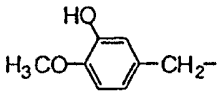
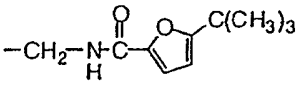
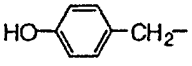
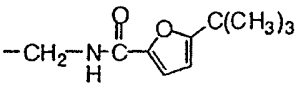
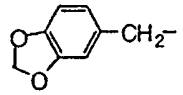
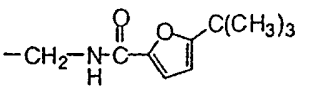
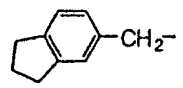
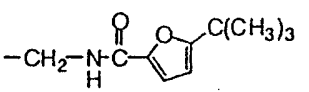
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1805		1	2	0	R	H	
1806		1	2	0	R	H	
1807		1	2	0	R	H	
1808		1	2	0	R	H	
1809		1	2	0	R	H	
1810		1	2	0	R	H	
1811		1	2	0	R	H	
1812		1	2	0	R	H	
1813		1	2	0	R	H	
1814		1	2	0	R	H	
1815		1	2	0	R	H	

Tabulka 1.166

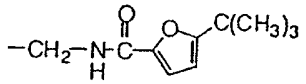
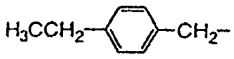
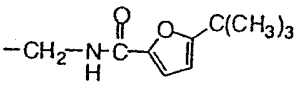
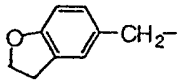
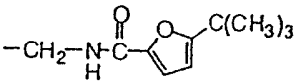
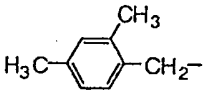
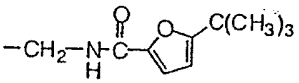
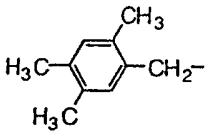
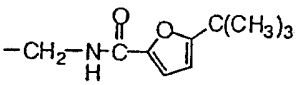
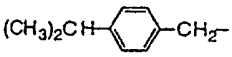
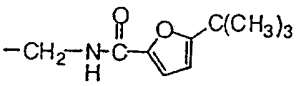
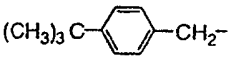
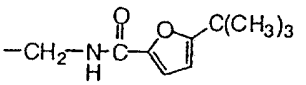
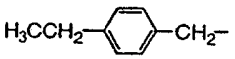
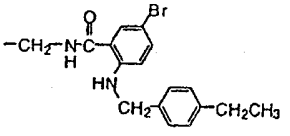
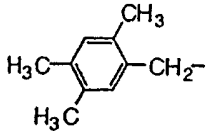
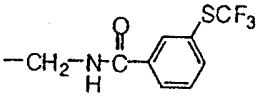
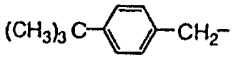
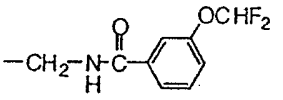
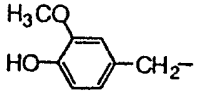
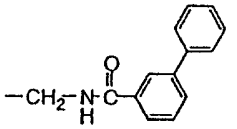
Slouč.č.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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1817		1	2	0	R	H	
1818		1	2	0	R	H	
1819		1	2	0	R	H	
1820		1	2	0	R	H	
1821		1	2	0	R	H	
1822		1	2	0	R	H	
1823		1	2	0	R	H	
1824		1	2	0	R	H	
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1826		1	2	0	R	H	

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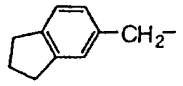
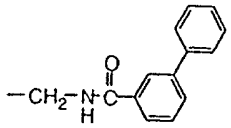
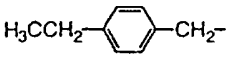
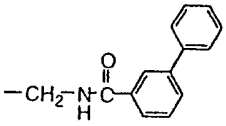
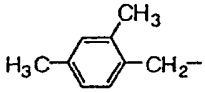
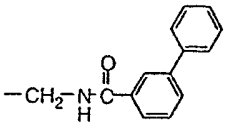
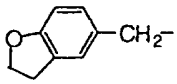
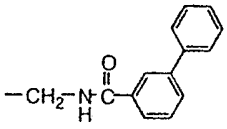
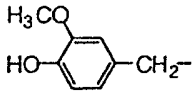
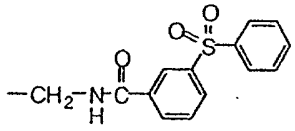
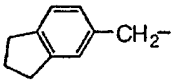
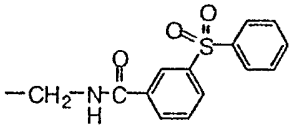
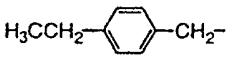
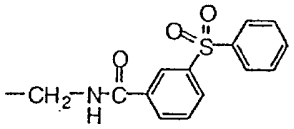
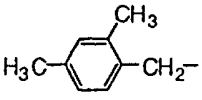
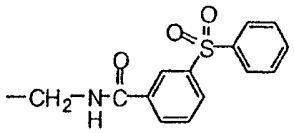
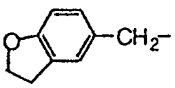
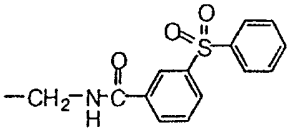
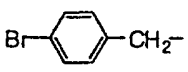
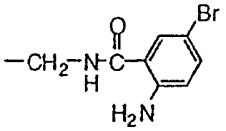
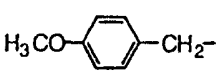
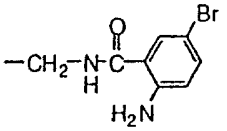
Sloučenina č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1827		1	2	0	R	H	
1828		1	2	0	R	H	
1829		1	2	0	R	H	
1830		1	2	0	R	H	
1831		1	2	0	R	H	
1832		1	2	0	R	H	
1833		1	2	0	R	H	
1834		1	2	0	R	H	
1835		1	2	0	R	H	
1836		1	2	0	R	H	
1837		1	2	0	R	H	

Tabulka 1.168

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1838		1	2	0	R	H	
1839		1	2	0	R	H	
1840		1	2	0	R	H	
1841		1	2	0	R	H	
1842		1	2	0	R	H	
1843		1	2	0	R	H	
1844		1	2	0	R	H	
1845		1	2	0	R	H	
1846		1	2	0	R	H	
1847		1	2	0	R	H	
1848		1	2	0	R	H	

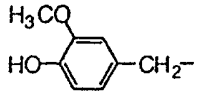
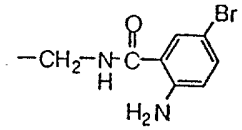
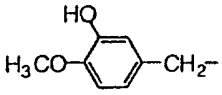
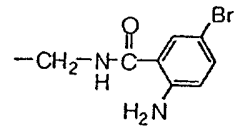
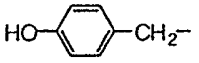
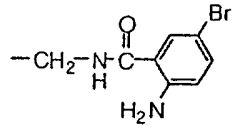
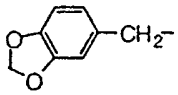
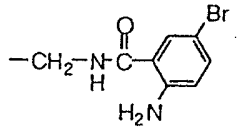
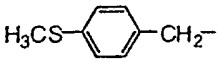
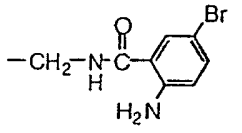
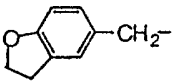
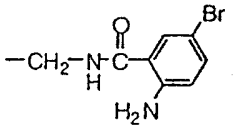
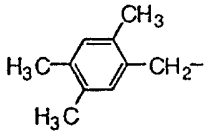
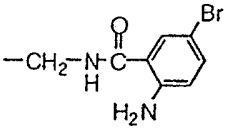
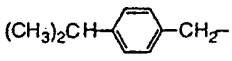
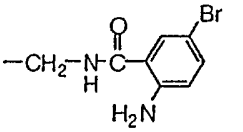
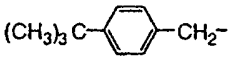
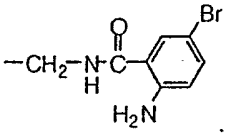
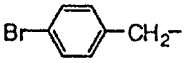
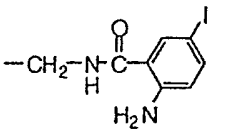
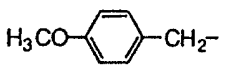
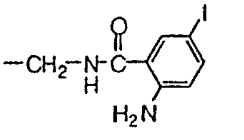
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Tabulka 1.169

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1849		1	2	0	R	H	
1850		1	2	0	R	H	
1851		1	2	0	R	H	
1852		1	2	0	R	H	
1853		1	2	0	R	H	
1854		1	2	0	R	H	
1855		1	2	0	R	H	
1856		1	2	0	R	H	
1857		1	2	0	R	H	
1858		1	2	0	R	H	
1859		1	2	0	R	H	

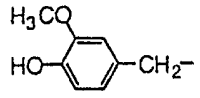
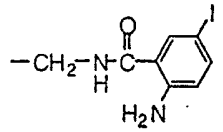
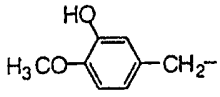
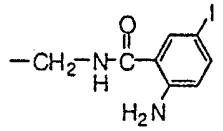
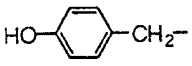
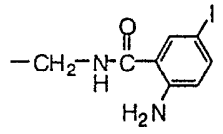
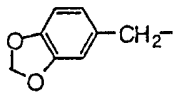
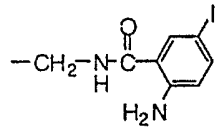
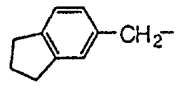
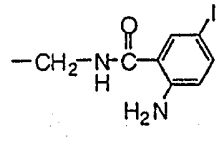
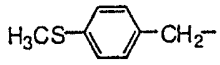
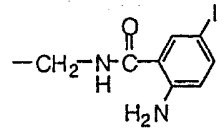
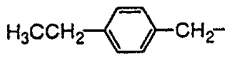
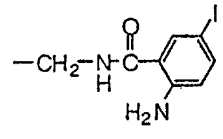
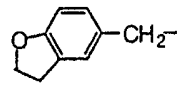
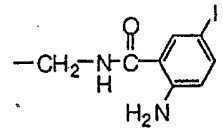
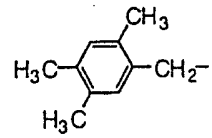
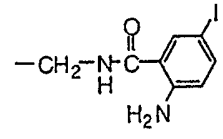
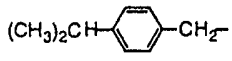
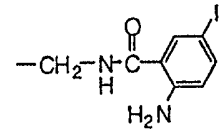
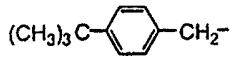
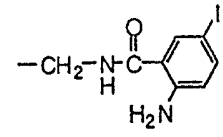
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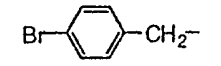
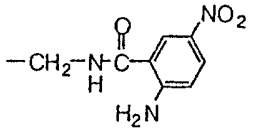
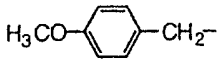
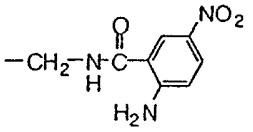
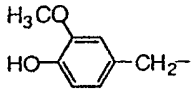
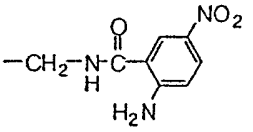
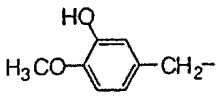
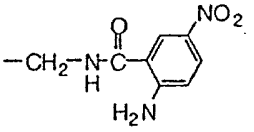
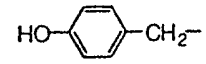
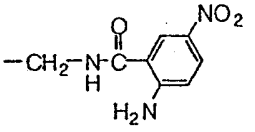
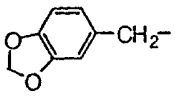
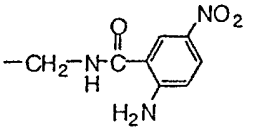
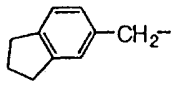
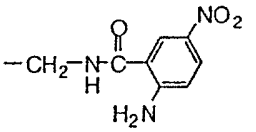
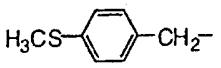
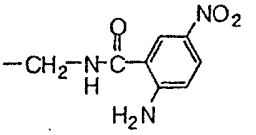
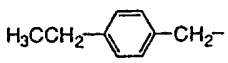
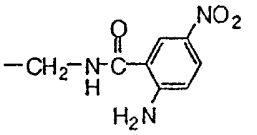
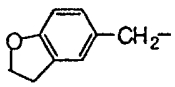
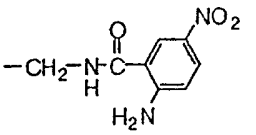
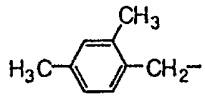
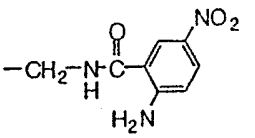
Sloučenina č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1860		1	2	0	R	H	
1861		1	2	0	R	H	
1862		1	2	0	R	H	
1863		1	2	0	R	H	
1864		1	2	0	R	H	
1865		1	2	0	R	H	
1866		1	2	0	R	H	
1867		1	2	0	R	H	
1868		1	2	0	R	H	
1869		1	2	0	R	H	
1870		1	2	0	R	H	

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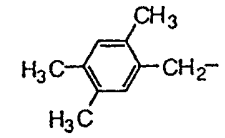
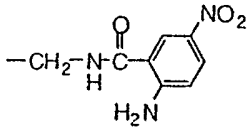
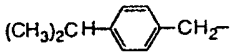
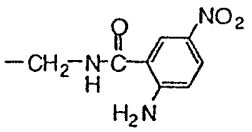
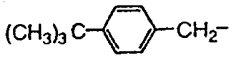
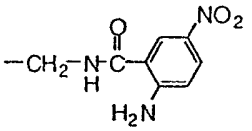
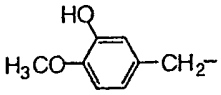
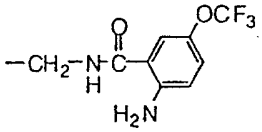
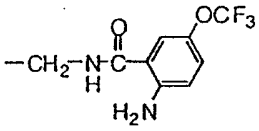
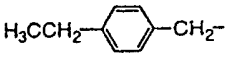
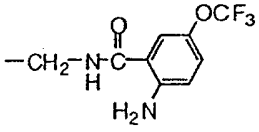
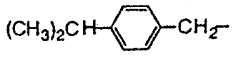
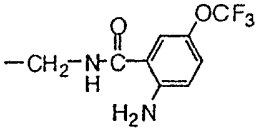
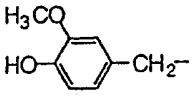
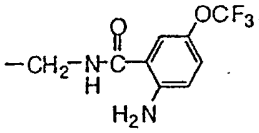
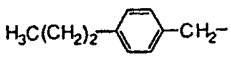
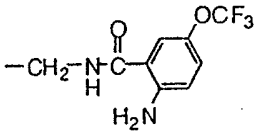
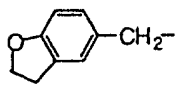
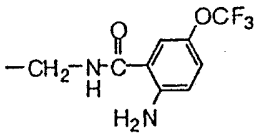
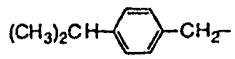
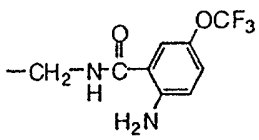
Slouč.č.	$R^1R^2CH-(CH_2)_i-$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1871		1	2	0	R	H	
1872		1	2	0	R	H	
1873		1	2	0	R	H	
1874		1	2	0	R	H	
1875		1	2	0	R	H	
1876		1	2	0	R	H	
1877		1	2	0	R	H	
1878		1	2	0	R	H	
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1881		1	2	0	R	H	

Tabulka 1.172

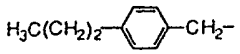
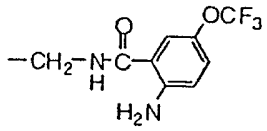
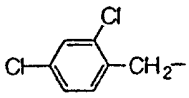
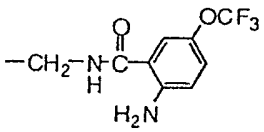
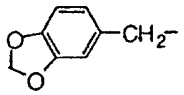
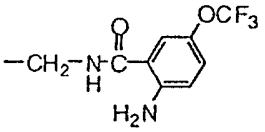
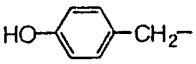
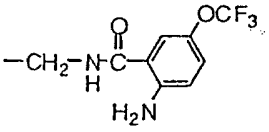
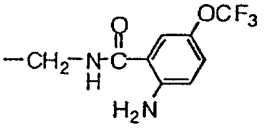
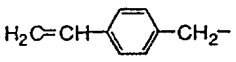
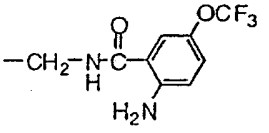
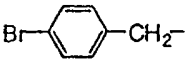
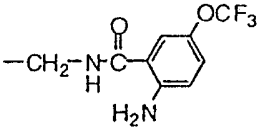
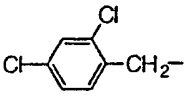
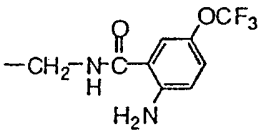
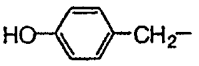
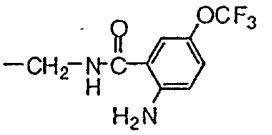
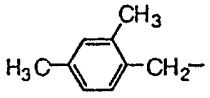
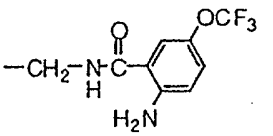
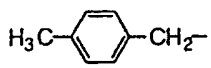
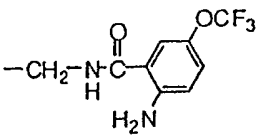
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
1882		1	2	0	R	H	
1883		1	2	0	R	H	
1884		1	2	0	R	H	
1885		1	2	0	R	H	
1886		1	2	0	R	H	
1887		1	2	0	R	H	
1888		1	2	0	R	H	
1889		1	2	0	R	H	
1890		1	2	0	R	H	
1891		1	2	0	R	H	
1892		1	2	0	R	H	

03.07.00

Tabulka 1.173

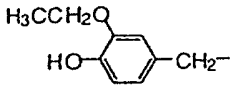
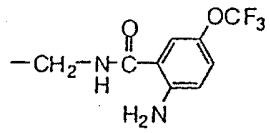
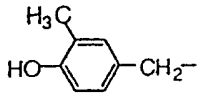
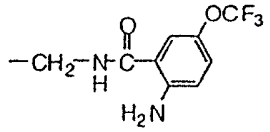
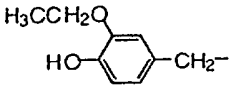
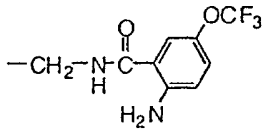
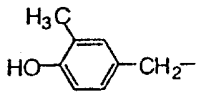
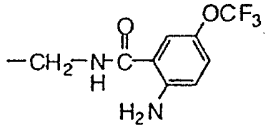
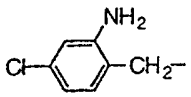
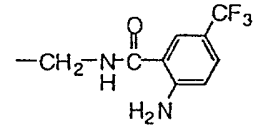
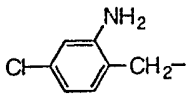
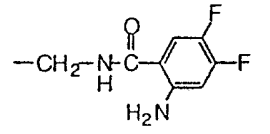
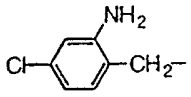
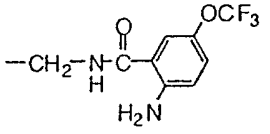
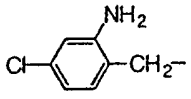
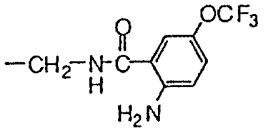
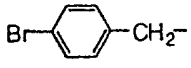
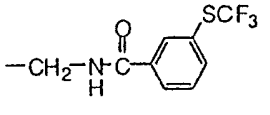
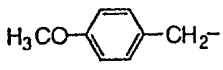
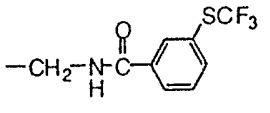
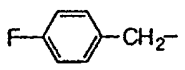
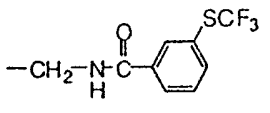
Slouč.č.	R^1, R^2, $-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1893		1	2	0	R	H	
1894		1	2	0	R	H	
1895		1	2	0	R	H	
1896		1	2	0	R	H	
1897		1	2	0	R	H	
1898		1	2	0	R	H	
1899		1	2	0	R	H	
1900		1	2	0	R	H	
1901		1	2	0	R	H	
1902		1	2	0	R	H	
1903		2	2	1	-	H	

Tabulka 1.174

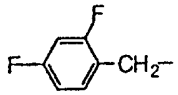
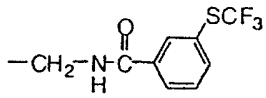
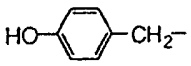
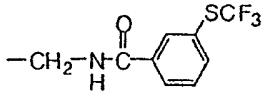
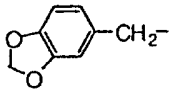
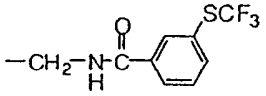
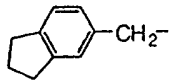
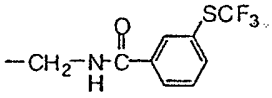
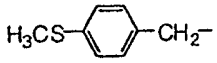
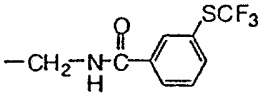
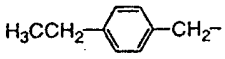
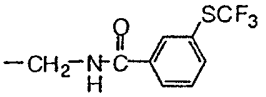
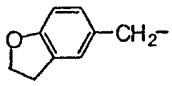
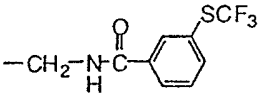
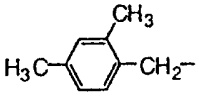
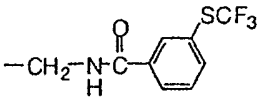
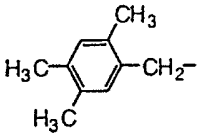
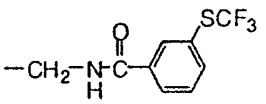
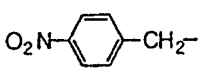
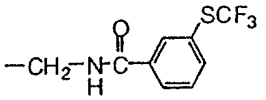
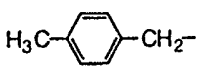
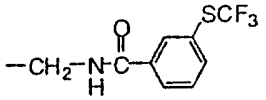
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
1904		2	2	1	-	H	
1905		1	2	0	R	H	
1906		1	2	0	R	H	
1907		1	2	0	R	H	
1908		1	2	0	R	H	
1909		1	2	0	R	H	
1910		2	2	1	-	H	
1911		2	2	1	-	H	
1912		2	2	1	-	H	
1913		2	2	1	-	H	
1914		2	2	1	-	H	

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Tabulka 1.175

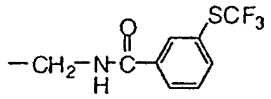
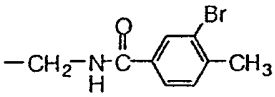
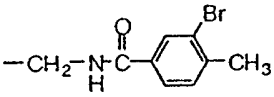
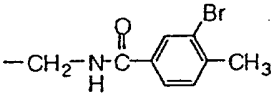
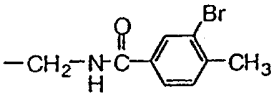
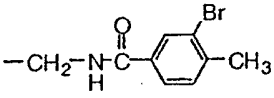
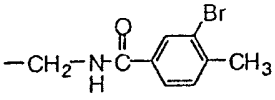
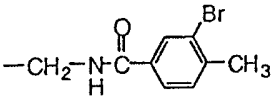
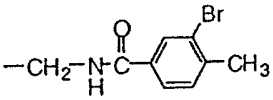
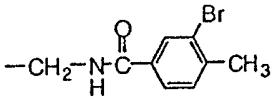
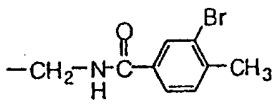
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1915		1	2	0	R	H	
1916		1	2	0	R	H	
1917		2	2	1	-	H	
1918		2	2	1	-	H	
1919		2	2	1	-	H	
1920		2	2	1	-	H	
1921		1	2	0	R	H	
1922		2	2	1	-	H	
1923		2	2	1	-	H	
1924		2	2	1	-	H	
1925		2	2	1	-	H	

Tabulka 1.176

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1926		2	2	1	-	H	
1927		2	2	1	-	H	
1928		2	2	1	-	H	
1929		2	2	1	-	H	
1930		2	2	1	-	H	
1931		2	2	1	-	H	
1932		2	2	1	-	H	
1933		2	2	1	-	H	
1934		2	2	1	-	H	
1935		2	2	1	-	H	
1936		2	2	1	-	H	

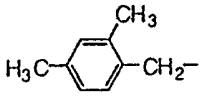
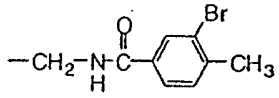
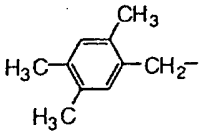
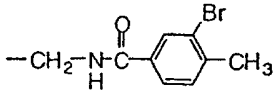
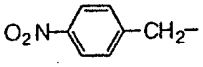
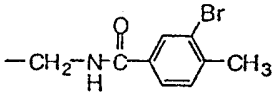
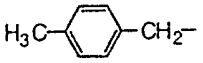
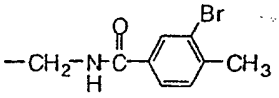
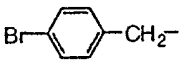
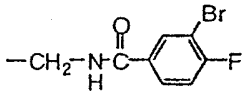
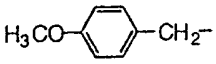
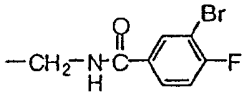
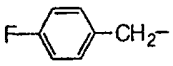
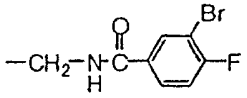
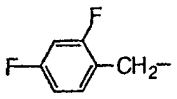
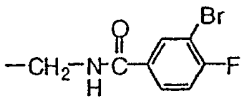
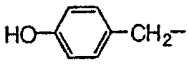
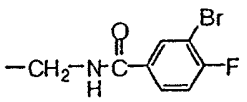
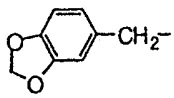
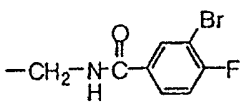
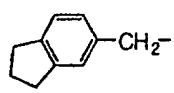
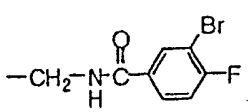
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Tabulka 1.177

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1937	$(CH_3)_2CH$, CH_2	2	2	1	-	H	
1938	Br, CH_2	2	2	1	-	H	
1939	H_3CO, CH_2	2	2	1	-	H	
1940	F, CH_2	2	2	1	-	H	
1941	F, F, CH_2	2	2	1	-	H	
1942	HO, CH_2	2	2	1	-	H	
1943	O, O, CH_2	2	2	1	-	H	
1944	CH_2	2	2	1	-	H	
1945	H_3CS, CH_2	2	2	1	-	H	
1946	H_3CCH_2, CH_2	2	2	1	-	H	
1947	O, CH_2	2	2	1	-	H	

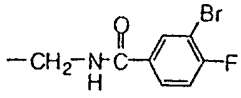
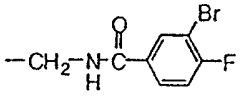
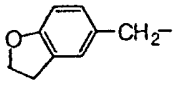
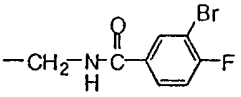
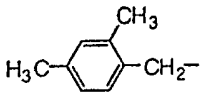
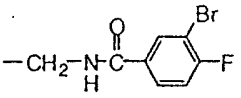
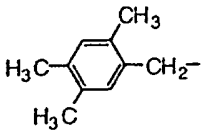
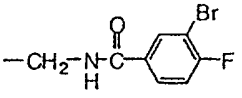
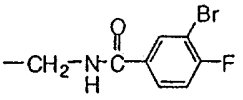
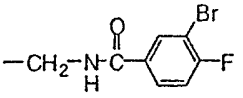
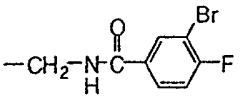
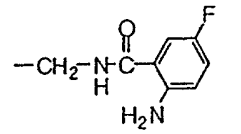
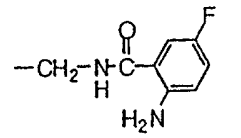
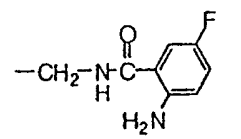
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Tabulka 1.178

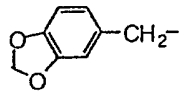
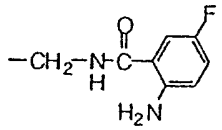
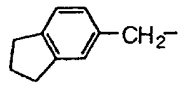
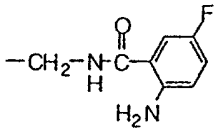
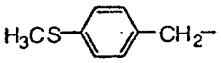
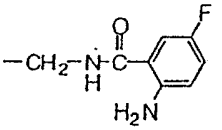
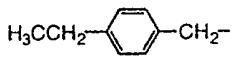
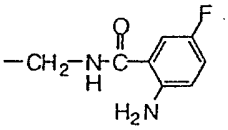
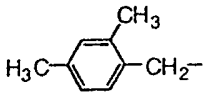
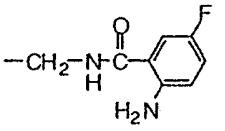
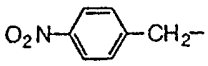
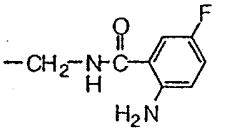
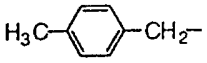
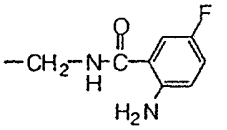
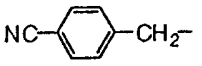
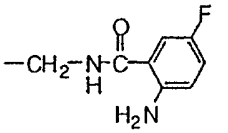
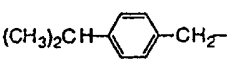
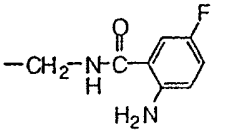
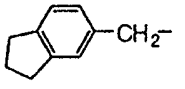
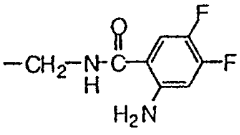
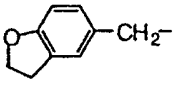
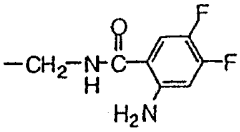
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1948		2	2	1	-	H	
1949		2	2	1	-	H	
1950		2	2	1	-	H	
1951		2	2	1	-	H	
1952		2	2	1	-	H	
1953		2	2	1	-	H	
1954		2	2	1	-	H	
1955		2	2	1	-	H	
1956		2	2	1	-	H	
1957		2	2	1	-	H	
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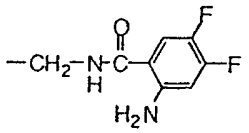
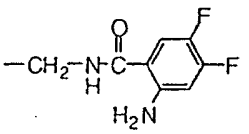
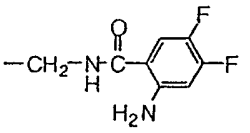
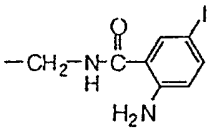
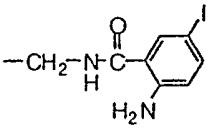
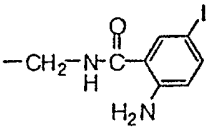
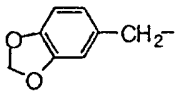
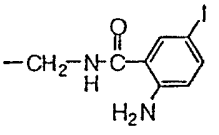
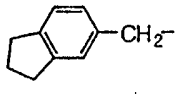
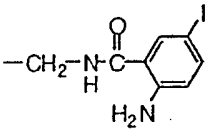
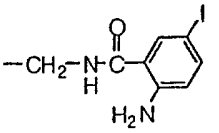
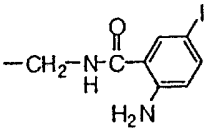
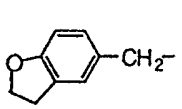
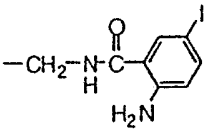
Tabulka 1.179

Slouč.č.	R^1, R^2, $(CH_2)_i$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1959	$H_3CS-C_6H_4-CH_2-$	2	2	1	-	H	
1960	$H_3CCH_2-C_6H_4-CH_2-$	2	2	1	-	H	
1961		2	2	1	-	H	
1962		2	2	1	-	H	
1963		2	2	1	-	H	
1964	$O_2N-C_6H_4-CH_2-$	2	2	1	-	H	
1965	$H_3C-C_6H_4-CH_2-$	2	2	1	-	H	
1966	$(CH_3)_2CH-C_6H_4-CH_2-$	2	2	1	-	H	
1967	$Br-C_6H_4-CH_2-$	2	2	1	-	H	
1968	$H_3CO-C_6H_4-CH_2-$	2	2	1	-	H	
1969	$HO-C_6H_4-CH_2-$	2	2	1	-	H	

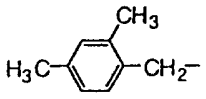
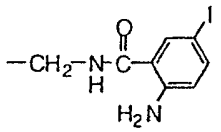
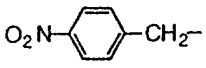
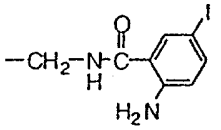
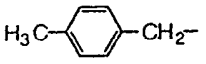
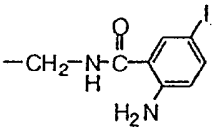
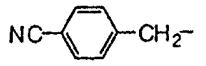
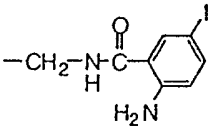
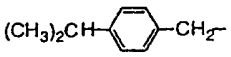
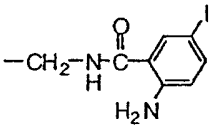
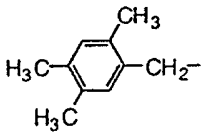
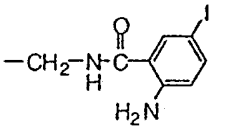
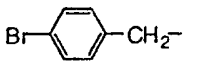
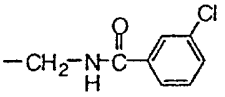
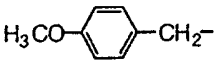
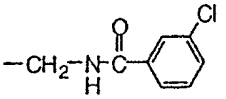
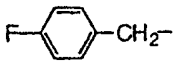
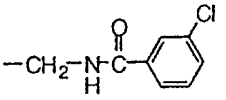
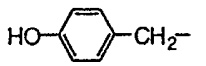
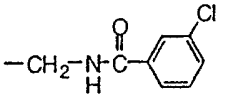
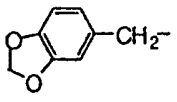
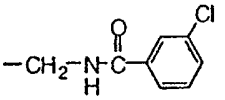
Tabulka 1.180

Slouč.č.	$R^1(R^2)CH(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1970		2	2	1	-	H	
1971		2	2	1	-	H	
1972		2	2	1	-	H	
1973		2	2	1	-	H	
1974		2	2	1	-	H	
1975		2	2	1	-	H	
1976		2	2	1	-	H	
1977		2	2	1	-	H	
1978		2	2	1	-	H	
1979		2	2	1	-	H	
1980		2	2	1	-	H	

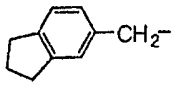
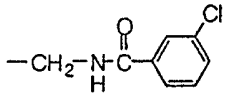
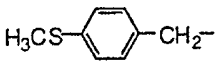
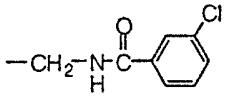
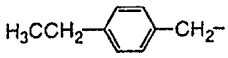
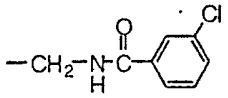
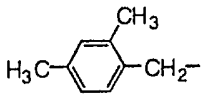
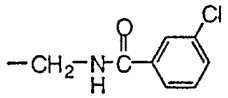
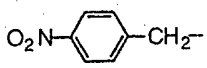
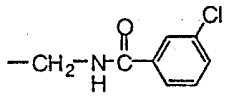
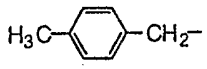
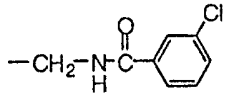
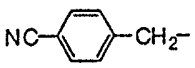
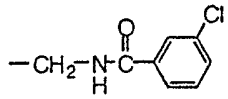
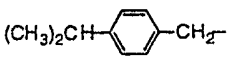
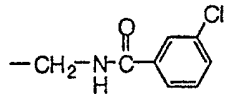
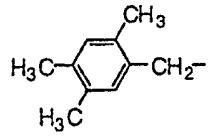
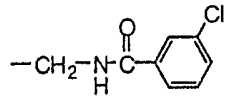
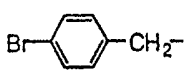
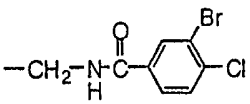
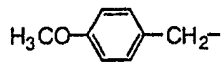
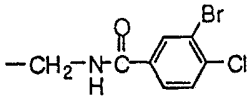
Tabulka 1.181

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
1981	O_2N-Ph-CH_2-	2	2	1	-	H	
1982	NC-Ph-CH_2-	2	2	1	-	H	
1983	$(CH_3)_2CH$-Ph-CH_2-	2	2	1	-	H	
1984	Br-Ph-CH_2-	2	2	1	-	H	
1985	H_3CO-Ph-CH_2-	2	2	1	-	H	
1986	HO-Ph-CH_2-	2	2	1	-	H	
1987		2	2	1	-	H	
1988		2	2	1	-	H	
1989	H_3CS-Ph-CH_2-	2	2	1	-	H	
1990	H_3CCH_2-Ph-CH_2-	2	2	1	-	H	
1991		2	2	1	-	H	

Tabulka 1.182

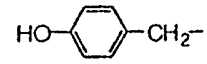
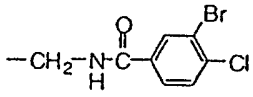
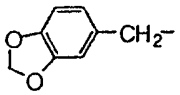
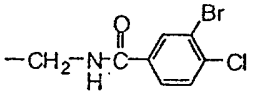
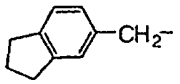
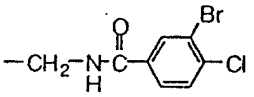
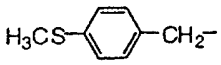
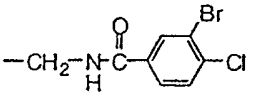
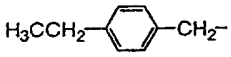
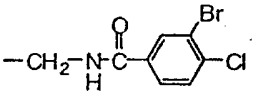
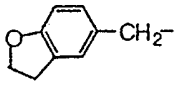
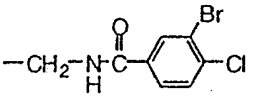
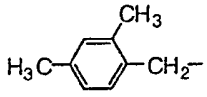
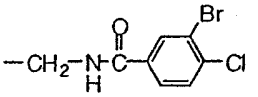
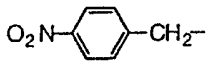
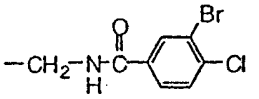
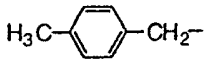
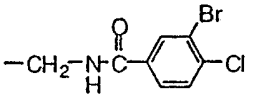
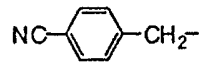
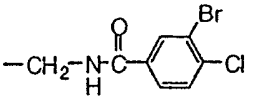
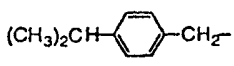
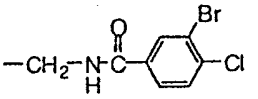
Slouč.č.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-CHR^4R^5-(CH_2)_q-G-R^6$
1992		2	2	1	-	H	
1993		2	2	1	-	H	
1994		2	2	1	-	H	
1995		2	2	1	-	H	
1996		2	2	1	-	H	
1997		2	2	1	-	H	
1998		2	2	1	-	H	
1999		2	2	1	-	H	
2000		2	2	1	-	H	
2001		2	2	1	-	H	
2002		2	2	1	-	H	

Tabulka 1.183

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2003		2	2	1	-	H	
2004		2	2	1	-	H	
2005		2	2	1	-	H	
2006		2	2	1	-	H	
2007		2	2	1	-	H	
2008		2	2	1	-	H	
2009		2	2	1	-	H	
2010		2	2	1	-	H	
2011		2	2	1	-	H	
2012		2	2	1	-	H	
2013		2	2	1	-	H	

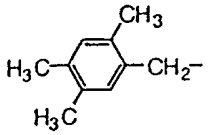
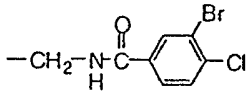
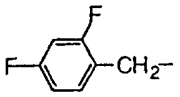
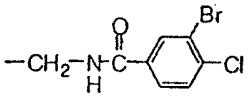
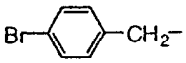
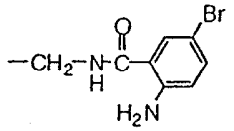
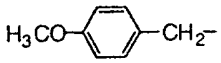
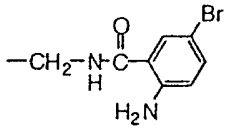
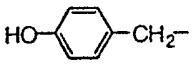
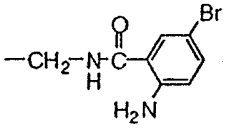
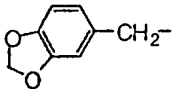
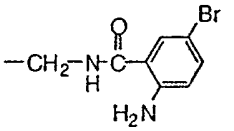
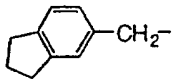
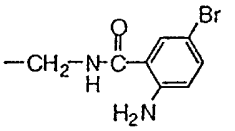
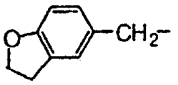
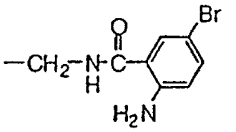
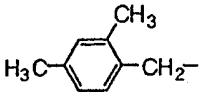
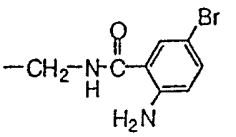
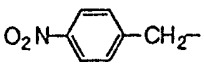
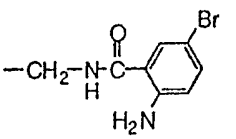
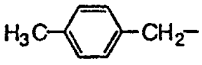
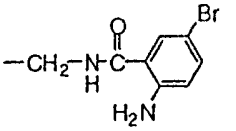
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Tabulka 1.184

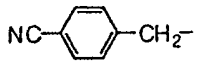
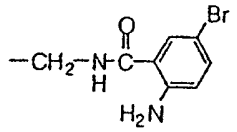
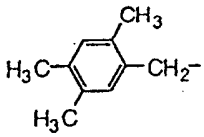
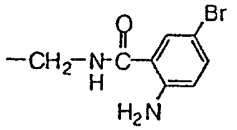
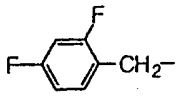
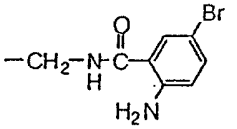
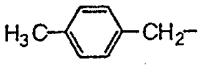
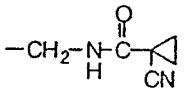
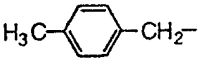
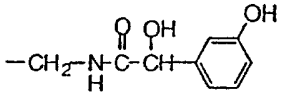
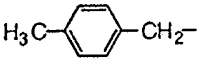
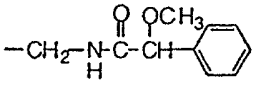
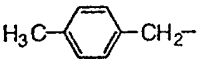
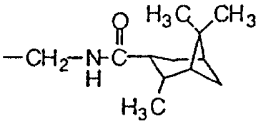
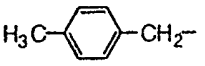
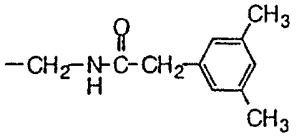
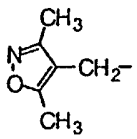
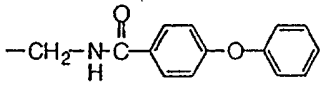
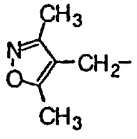
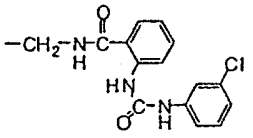
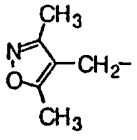
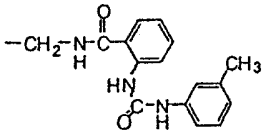
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
2014		2	2	1	-	H	
2015		2	2	1	-	H	
2016		2	2	1	-	H	
2017		2	2	1	-	H	
2018		2	2	1	-	H	
2019		2	2	1	-	H	
2020		2	2	1	-	H	
2021		2	2	1	-	H	
2022		2	2	1	-	H	
2023		2	2	1	-	H	
2024		2	2	1	-	H	

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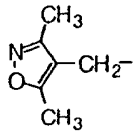
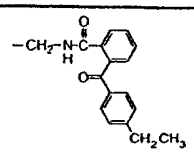
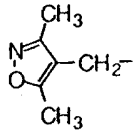
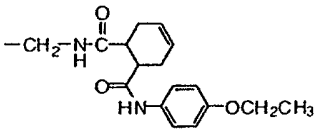
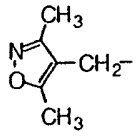
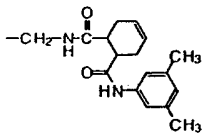
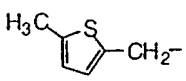
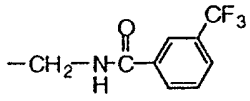
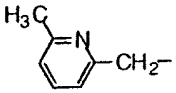
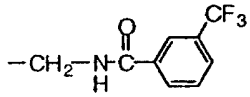
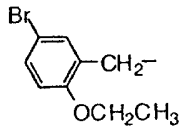
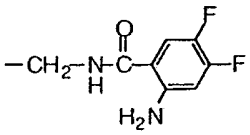
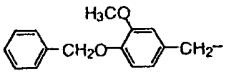
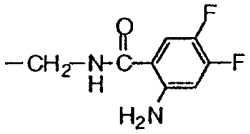
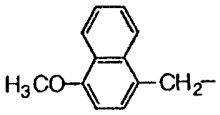
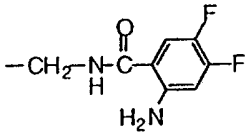
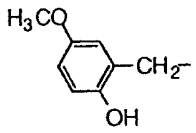
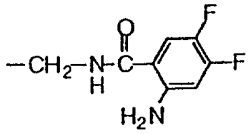
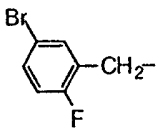
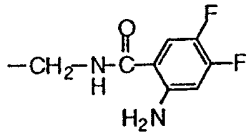
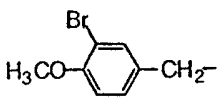
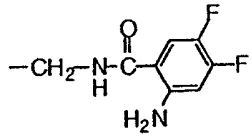
Tabulka 1.185

Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
2025		2	2	1	-	H	
2026		2	2	1	-	H	
2027		2	2	1	-	H	
2028		2	2	1	-	H	
2029		2	2	1	-	H	
2030		2	2	1	-	H	
2031		2	2	1	-	H	
2032		2	2	1	-	H	
2033		2	2	1	-	H	
2034		2	2	1	-	H	
2035		2	2	1	-	H	

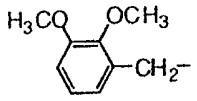
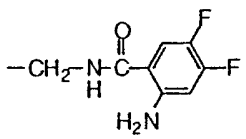
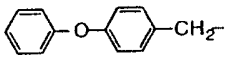
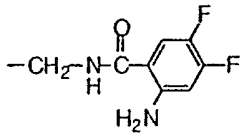
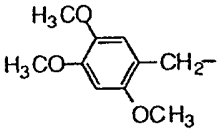
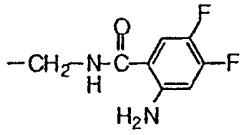
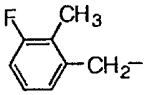
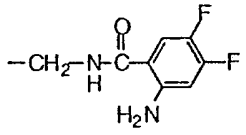
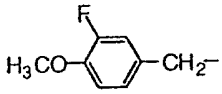
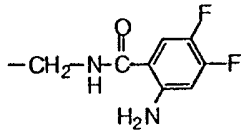
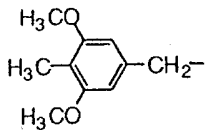
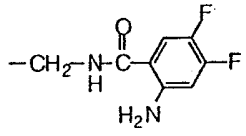
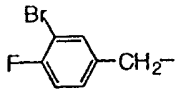
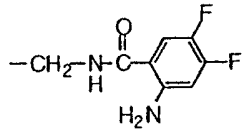
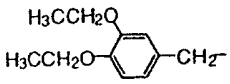
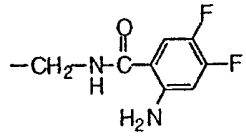
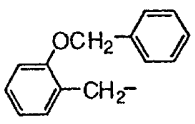
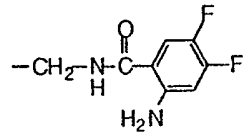
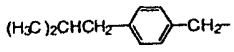
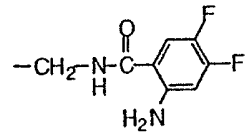
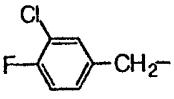
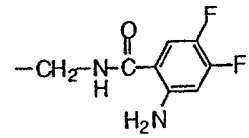
Tabulka 1.186

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2036		2	2	1	-	H	
2037		2	2	1	-	H	
2038		2	2	1	-	H	
2039		2	2	1	-	H	
2040		1	2	0	R	H	
2041		1	2	0	R	H	
2042		1	2	0	R	H	
2043		1	2	0	R	H	
2044		1	2	0	R	H	
2045		1	2	0	R	H	
2046		1	2	0	R	H	

Tabulka 1.187

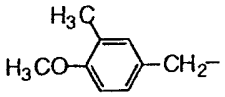
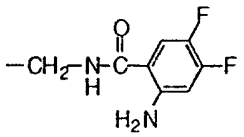
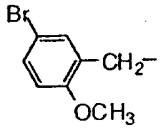
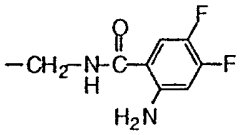
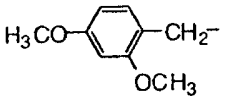
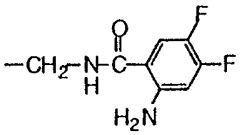
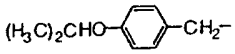
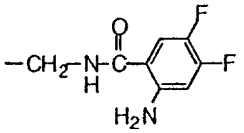
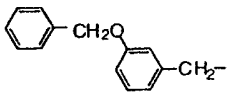
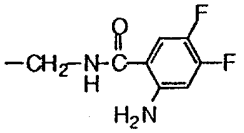
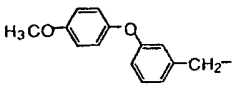
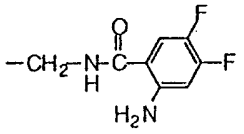
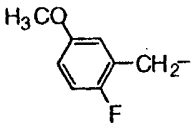
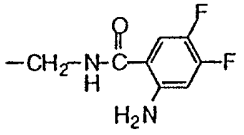
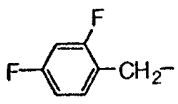
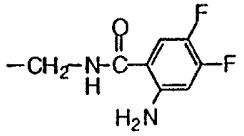
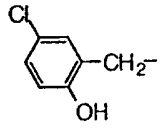
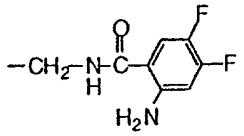
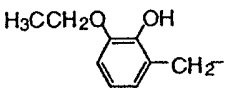
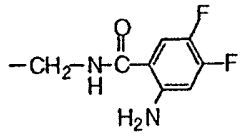
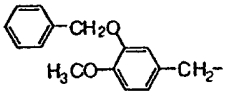
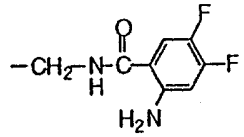
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2047		1	2	0	R	H	
2048		1	2	0	R	H	
2049		1	2	0	R	H	
2050		1	2	0	R	H	
2051		1	2	0	R	H	
2052		2	2	1	-	H	
2053		2	2	1	-	H	
2054		2	2	1	-	H	
2055		2	2	1	-	H	
2056		2	2	1	-	H	
2057		2	2	1	-	H	

Tabulka 1.188

Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2058		2	2	1	-	H	
2059		2	2	1	-	H	
2060		2	2	1	-	H	
2061		2	2	1	-	H	
2062		2	2	1	-	H	
2063		2	2	1	-	H	
2064		2	2	1	-	H	
2065		2	2	1	-	H	
2066		2	2	1	-	H	
2067		2	2	1	-	H	
2068		2	2	1	-	H	

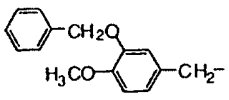
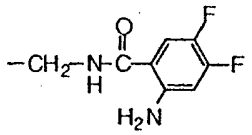
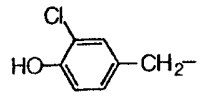
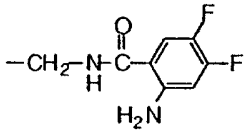
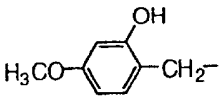
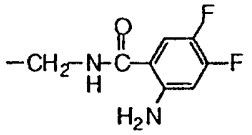
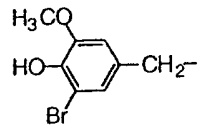
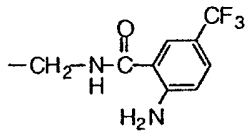
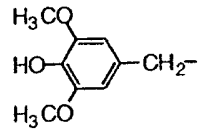
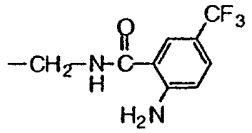
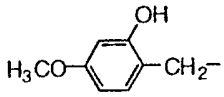
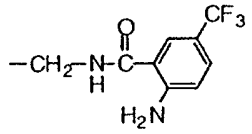
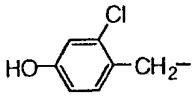
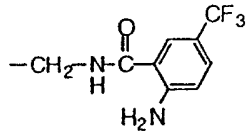
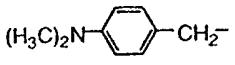
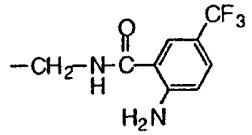
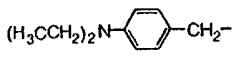
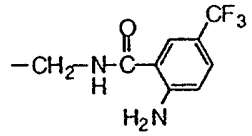
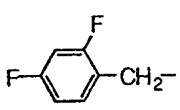
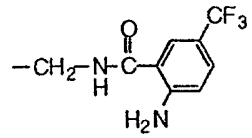
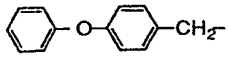
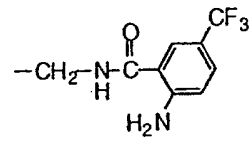
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Tabulka 1.189

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2069		2	2	1	-	H	
2070		2	2	1	-	H	
2071		2	2	1	-	H	
2072		2	2	1	-	H	
2073		2	2	1	-	H	
2074		2	2	1	-	H	
2075		2	2	1	-	H	
2076		2	2	1	-	H	
2077		2	2	1	-	H	
2078		2	2	1	-	H	
2079		2	2	1	-	H	

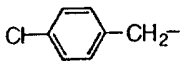
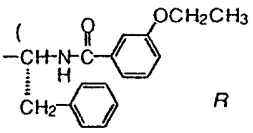
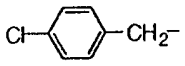
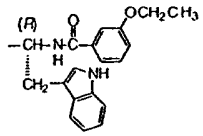
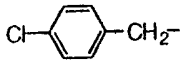
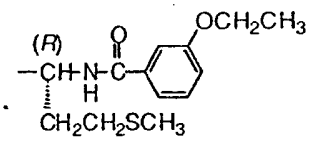
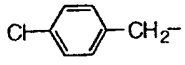
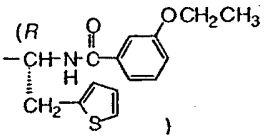
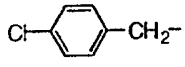
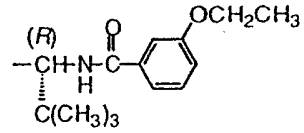
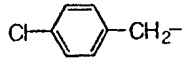
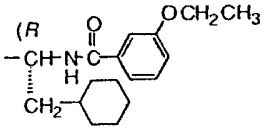
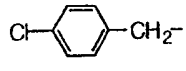
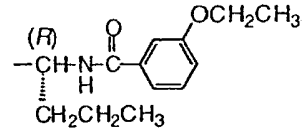
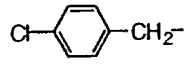
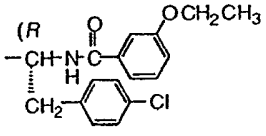
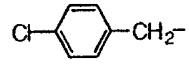
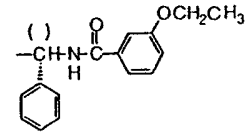
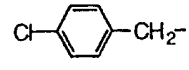
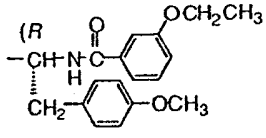
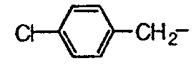
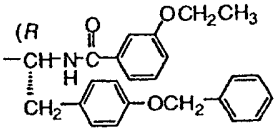
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Tabulka 1.190

č.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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2081		2	2	1	-	H	
2082		2	2	1	-	H	
2083		1	2	0	R	H	
2084		1	2	0	R	H	
2085		1	2	0	R	H	
2086		1	2	0	R	H	
2087		1	2	0	R	H	
2088		1	2	0	R	H	
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2090		1	2	0	R	H	

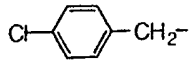
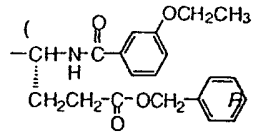
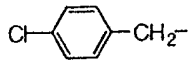
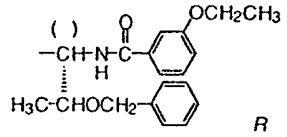
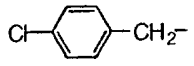
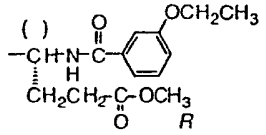
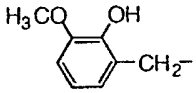
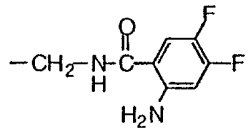
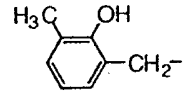
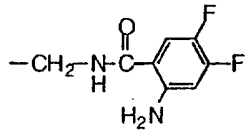
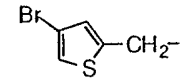
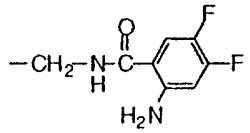
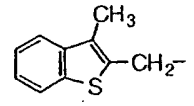
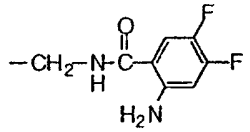
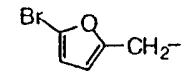
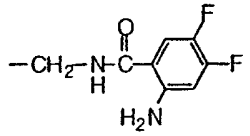
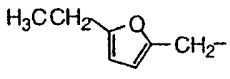
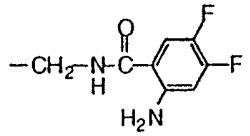
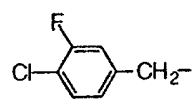
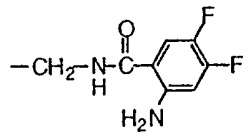
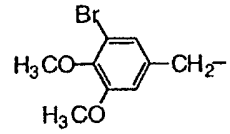
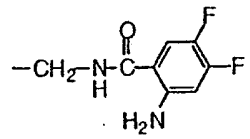
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Tabulka 1.191

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
2091		2	2	1	-	H	
2092		2	2	1	-	H	
2093		2	2	1	-	H	
2094		2	2	1	-	H	
2095		2	2	1	-	H	
2096		2	2	1	-	H	
2097		2	2	1	-	H	
2098		2	2	1	-	H	
2099		2	2	1	-	H	
2100		2	2	1	-	H	
2101		2	2	1	-	H	

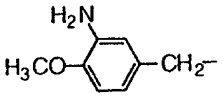
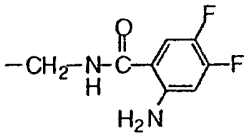
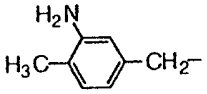
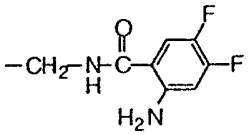
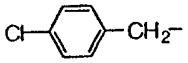
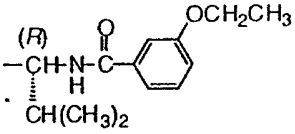
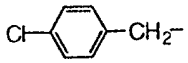
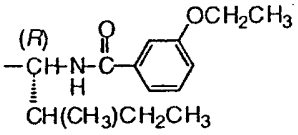
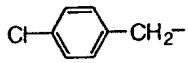
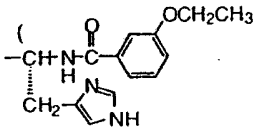
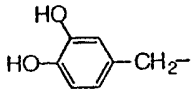
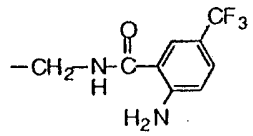
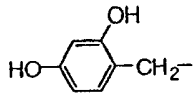
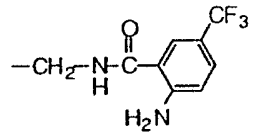
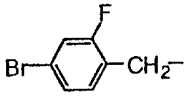
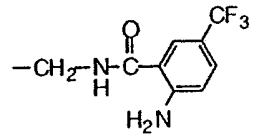
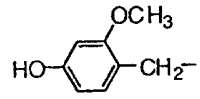
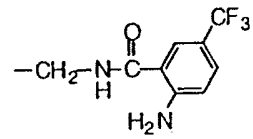
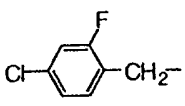
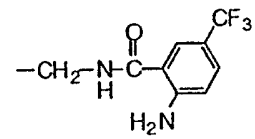
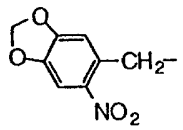
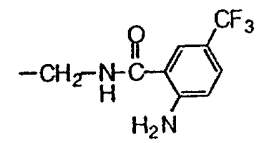
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Tabulka 1.192

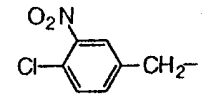
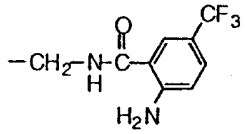
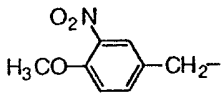
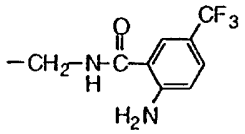
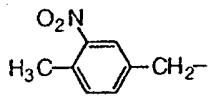
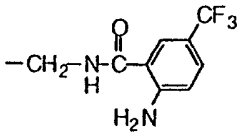
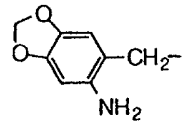
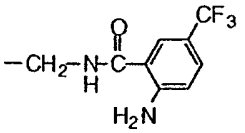
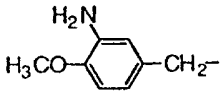
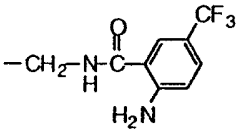
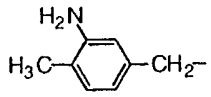
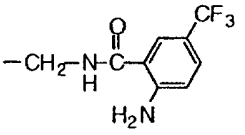
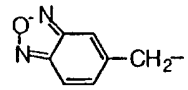
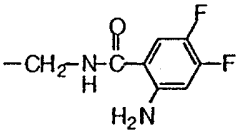
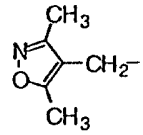
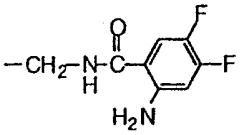
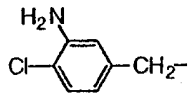
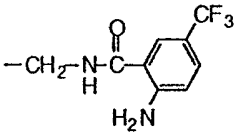
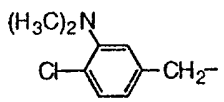
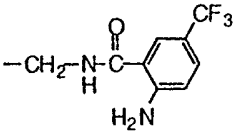
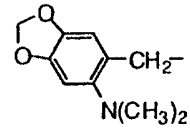
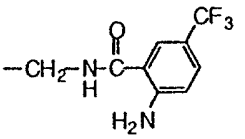
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2103		2	2	1	-	H	
2104		2	2	1	-	H	
2105		2	2	1	-	H	
2106		2	2	1	-	H	
2107		2	2	1	-	H	
2108		2	2	1	-	H	
2109		2	2	1	-	H	
2110		2	2	1	-	H	
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Tabulka 1.193

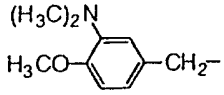
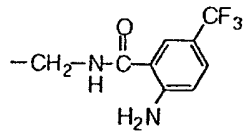
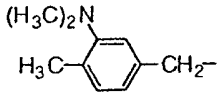
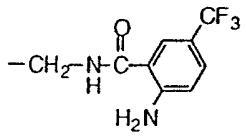
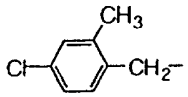
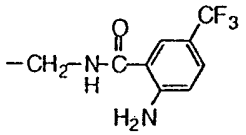
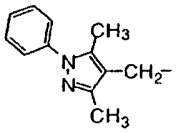
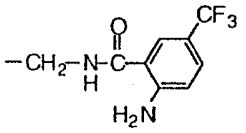
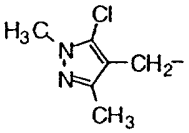
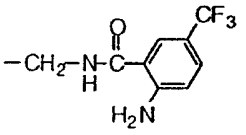
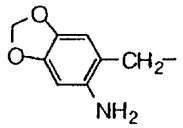
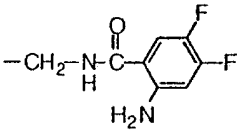
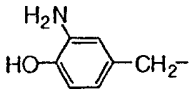
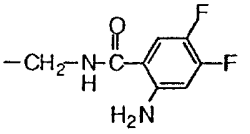
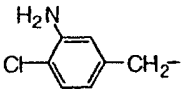
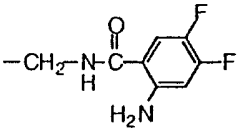
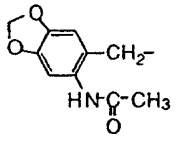
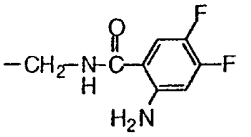
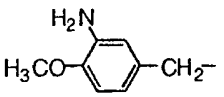
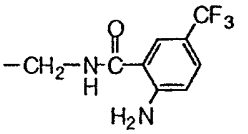
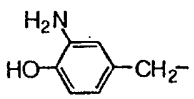
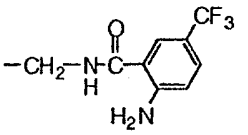
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-\underset{R^5}{\overset{R^4}{C}}-(CH_2)_q-G-R^6$
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2114		2	2	1	-	H	
2115		2	2	1	-	H	
2116		2	2	1	-	H	
2117		2	2	1	-	H	
2118		1	2	0	R	H	
2119		1	2	0	R	H	
2120		1	2	0	R	H	
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2122		1	2	0	R	H	
2123		1	2	0	R	H	

Tabulka 1.194

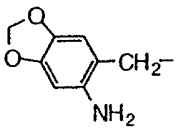
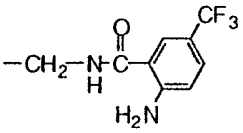
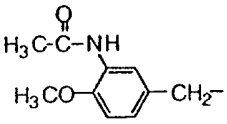
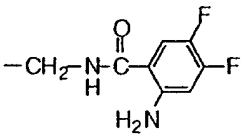
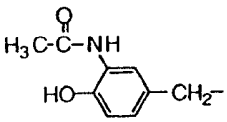
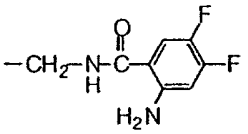
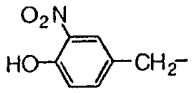
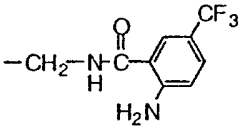
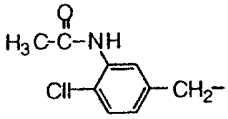
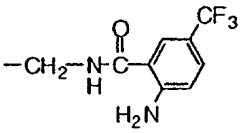
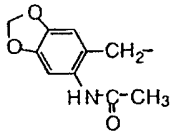
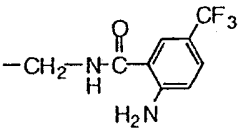
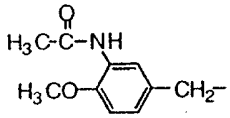
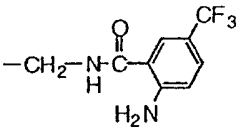
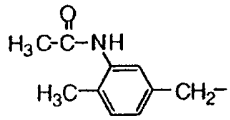
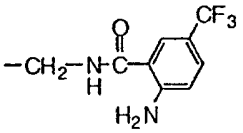
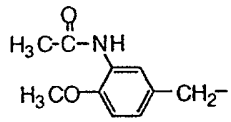
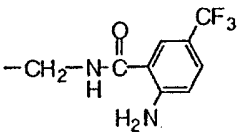
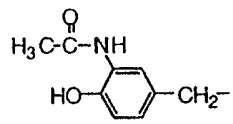
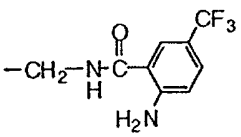
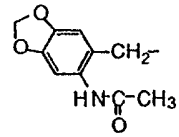
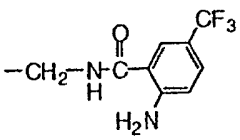
Sloučč.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
2124		1	2	0	R	H	
2125		1	2	0	R	H	
2126		1	2	0	R	H	
2127		1	2	0	R	H	
2128		1	2	0	R	H	
2129		1	2	0	R	H	
2130		2	2	1	-	H	
2131		2	2	1	-	H	
2132		1	2	0	R	H	
2133		1	2	0	R	H	
2134		1	2	0	R	H	

03.07.00

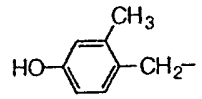
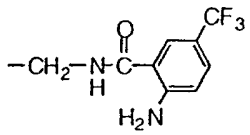
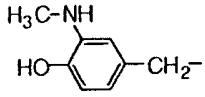
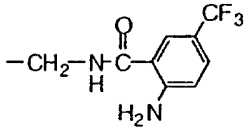
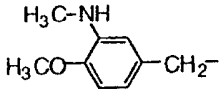
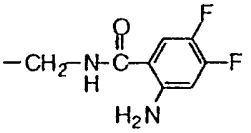
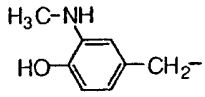
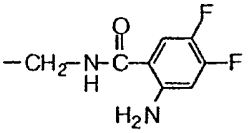
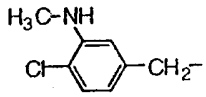
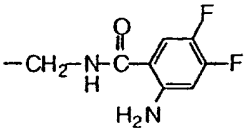
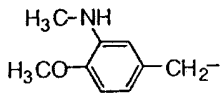
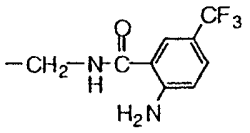
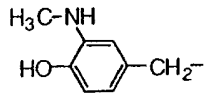
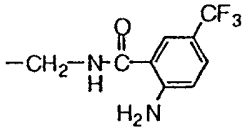
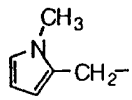
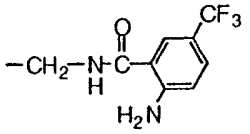
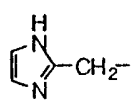
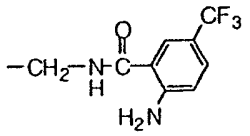
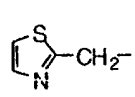
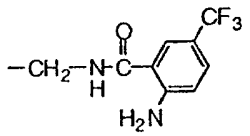
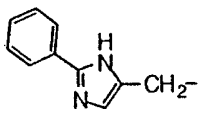
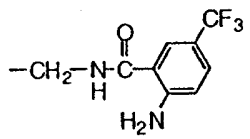
Tabulka 1.195

Sloučenina č.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
2135		1	2	0	R	H	
2136		1	2	0	R	H	
2137		1	2	0	R	H	
2138		1	2	0	R	H	
2139		1	2	0	R	H	
2140		2	2	1	-	H	
2141		2	2	1	-	H	
2142		2	2	1	-	H	
2143		2	2	1	-	H	
2144		2	2	1	-	H	
2145		2	2	1	-	H	

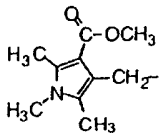
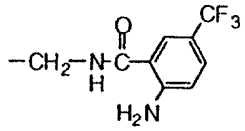
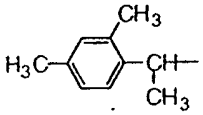
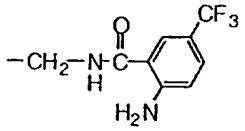
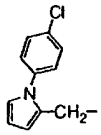
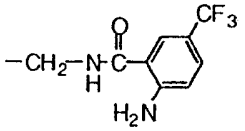
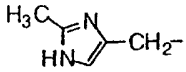
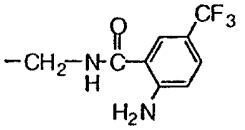
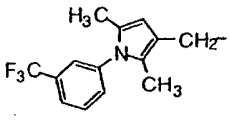
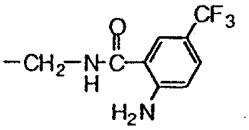
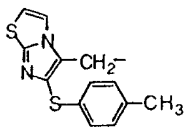
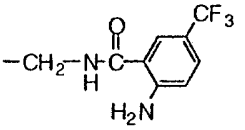
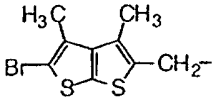
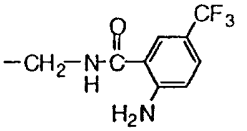
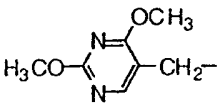
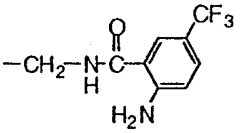
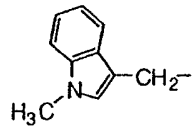
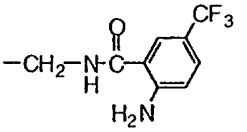
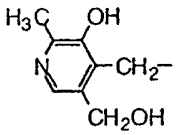
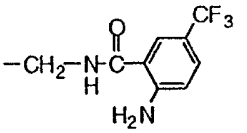
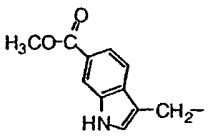
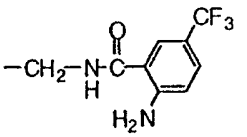
Tabulka 1.196

Slouč.č.	$R^1R^2CH-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-CR^4R^5-(CH_2)_q-G-R^6$
2146		2	2	1	-	H	
2147		2	2	1	-	H	
2148		2	2	1	-	H	
2149		1	2	0	R	H	
2150		1	2	0	R	H	
2151		1	2	0	R	H	
2152		1	2	0	R	H	
2153		1	2	0	R	H	
2154		2	2	1	-	H	
2155		2	2	1	-	H	
2156		2	2	1	-	H	

Tabulka 1.197

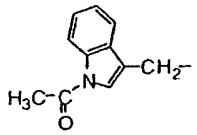
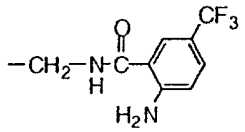
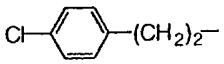
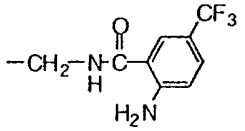
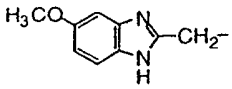
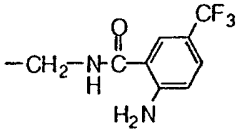
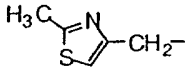
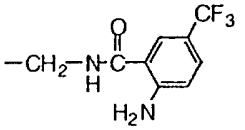
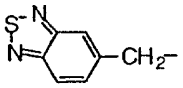
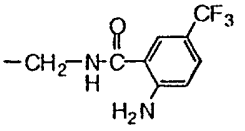
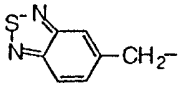
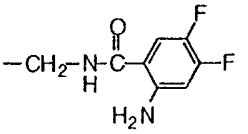
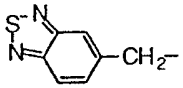
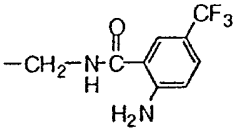
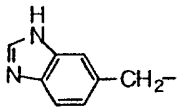
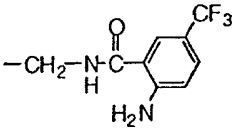
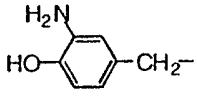
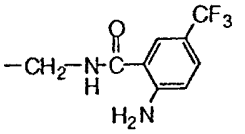
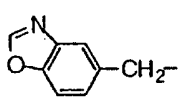
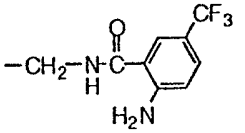
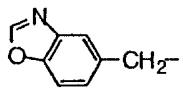
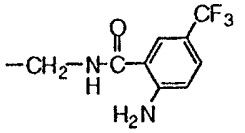
Slouč.č.	R^1, R^2, $-(CH_2)_j-$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2157		1	2	0	R	H	
2158		1	2	0	R	H	
2159		2	2	1	-	H	
2160		2	2	1	-	H	
2161		2	2	1	-	H	
2162		2	2	1	-	H	
2163		2	2	1	-	H	
2164		1	2	0	R	H	
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2167		1	2	0	R	H	

Tabulka 1.198

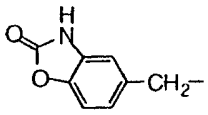
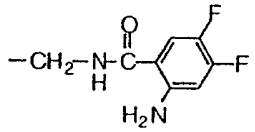
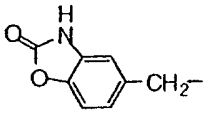
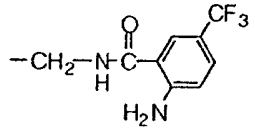
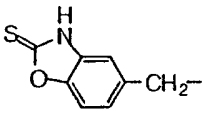
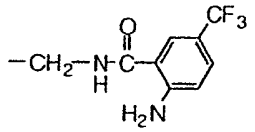
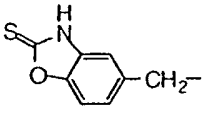
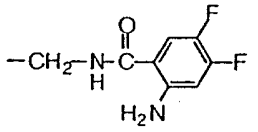
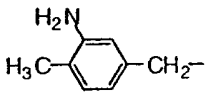
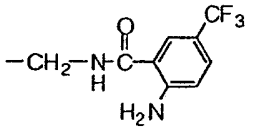
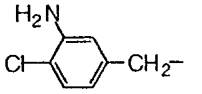
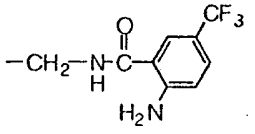
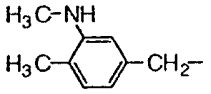
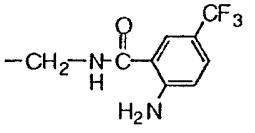
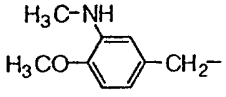
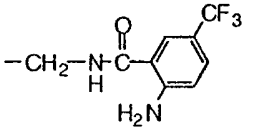
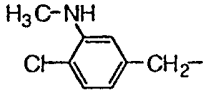
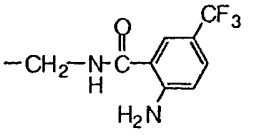
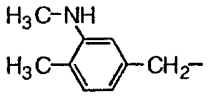
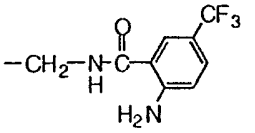
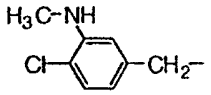
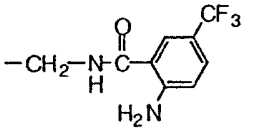
Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
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2169		1	2	0	R	H	
2170		1	2	0	R	H	
2171		1	2	0	R	H	
2172		1	2	0	R	H	
2173		1	2	0	R	H	
2174		1	2	0	R	H	
2175		1	2	0	R	H	
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2177		1	2	0	R	H	
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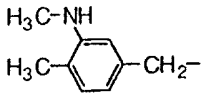
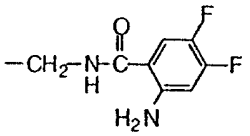
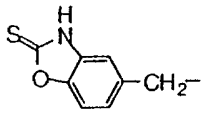
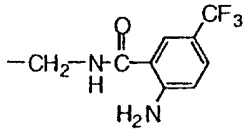
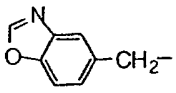
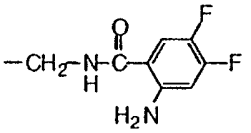
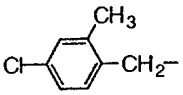
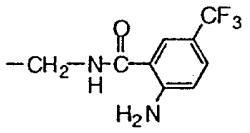
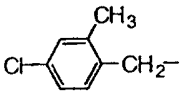
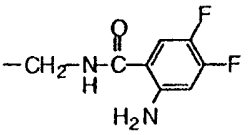
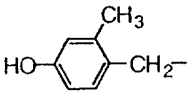
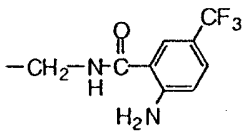
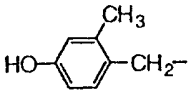
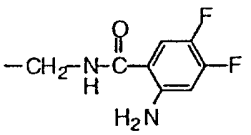
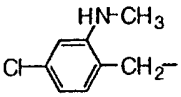
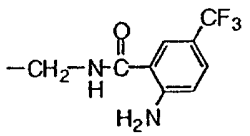
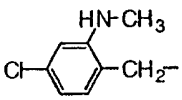
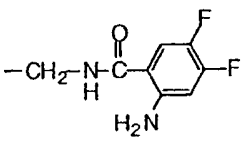
Tabulka 1.199

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2179		1	2	0	R	H	
2180		1	2	0	R	H	
2181		1	2	0	R	H	
2182		1	2	0	R	H	
2183		1	2	0	R	H	
2184		2	2	1	-	H	
2185		2	2	1	-	H	
2186		2	2	1	-	H	
2187		1	2	0	R	H	
2188		2	2	1	-	H	
2189		1	2	0	R	H	

Tabulka 1.200

Slouč.č.	$R^1R^2CH(CH_2)_j$–	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2190		2	2	1	-	H	
2191		2	2	1	-	H	
2192		2	2	1	-	H	
2193		2	2	1	-	H	
2194		2	2	1	-	H	
2195		2	2	1	-	H	
2196		1	2	0	R	H	
2197		1	2	0	R	H	
2198		1	2	0	R	H	
2199		2	2	1	-	H	
2200		2	2	1	-	H	

Tabulka 1.201

Slouč.č.	R^1, R^2, $(CH_2)_j$	k	m	n	chiralita	R^3	$-(CH_2)_p-C(R^4)(R^5)-(CH_2)_q-G-R^6$
2201		2	2	1	-	H	
2202		1	2	0	R	H	
2203		2	2	1	-	H	
2204		2	2	1	-	H	
2205		2	2	1	-	H	
2206		2	2	1	-	H	
2207		2	2	1	-	H	
2208		2	2	1	-	H	
2209		2	2	1	-	H	

Ve vynálezu jsou také užity soli sloučeniny cyklického aminu, které vznikly adicí kyseliny. Mezi tyto adované kyseliny patří například minerální kyseliny, jako je kyselina chlorovodíková, bromovodíková, sírová, fosforečná kyselina, uhličitá kyselina a jím podobné, dále také organické kyseliny, jako jsou kyselina maleinová, citronová, jablečná, kyselina vinná, fumarová, metansírová, trifluoroctová, mravenčí a další jím podobné.

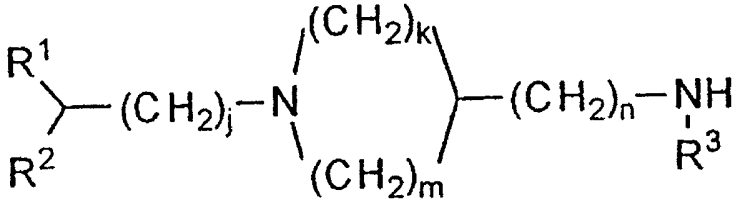
Dále vynález uvádí užití sloučenin soli cyklického aminu vzniklých adicí C_1 – C_6 alkylové skupiny, patří mezi ně například 1-(4-chlorbenzyl)-1-methyl-4-[(N-(3-trifluormethylbenzoyl)--glycyl)aminomethyl]piperidin jodid, kde takovýto alkyl zahrnuje například methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-okktyl, isopropyl, isobutyl, sec-butyl, terc-butyl, isopentyl, neopentyl, terc-pentyl, 2-methylpentyl, 1-ethylbutyl a další jím podobné, ve zvláště výhodném provedení vynálezu se užívá methylová a ethylová skupina. Ve výhodném uspořádání se jako protion pro amoniový kation užívá halogenový anion, jako je například fluoridový, chloridový nebo jodidový anion.

Vynález využívá racemáty, ale také všechny opticky aktivní formy sloučenin, které jsou reprezentovány výše uvedeným vzorcem I.

Sloučeniny reprezentované výše uvedeným vzorcem I lze syntetizovat pomocí jakéhokoli obecného postupu přípravy, uvedeného níže.

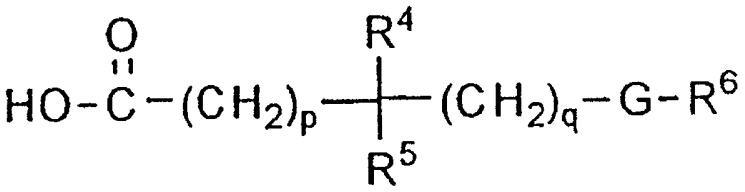
(Příprava 1)

Pro tento typ přípravy je nutné použít k reakci jeden ekvivalent sloučeniny reprezentované obecným vzorcem II, uvedeným níže:



(II)

(kde R^1, R^2, R^3, j, k, m, a n mají tentýž vyznam, jaký byl definován v předchozím textu pro obecný vzorec I) s 0,1 až 10 ekvivalenty karboxylové kyseliny reprezentované obecným vzorcem III uvedeným v dalším textu:



(III)

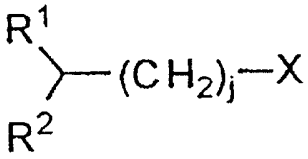
(kde R^4, R^5, R^6, G, p a q mají tentýž vyznam, jaký byl definován v předchozím textu pro obecný vzorec I nebo pro jeho reaktivní deriváty, buď v přítomnosti či nepřítomnosti rozpouštědla.

Reaktivní derivát karboxylové kyseliny podle obecného vzorce III obsahuje vysoce reaktivní deriváty karboxylové kyseliny, které se běžně používají v syntetické organické chemii, jako jsou halidy kyselin, anhydridy kyselin, smíšené anhydridy kyselin.

Takovouto reakci lze provést bez problémů pomocí užití vhodného množství dehydračního činidla jako je molekulární síto, které váže sloučeninu jako je dicyklohexylkarbodiimid (DCC), N--ethyl-N'-(3-dimethylaminopropyl)karbodiimid (EDCI nebo WSC), karbonyldiimidazol (CDI), N--hydrosukcinimid (HOSu), N-hydroxybenzotriazol (HOBt), benzotriazol-1-yloxi--tris(pyrolidino)fosfonium hexafluorofosfát (PyBOP), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl--uroniumtetrafluoroborát (TBTU), 2-(5-norbornen-2,3-dikarboxyimido)-1,1,3,3-tetramethyl--uroniumtetrafluoroborát (TNTU), O-(N-sukcinimidyl)-1,1,3,3,-tetramethyluroniumtetrafluoroborát (TSTU), bromtris(pyrolidin)fosfoniumhexafluorofosfát (PyBROP) a další obdobné, nebo baze včetně anorganických solí, jako jsou uhličitan draselný, uhličitan sodný, hydrogenuhličitan sodný a další podobné, dále aminy jako jsou triethylamin, diisopropylethylamin a pyridin a další obdobné, nebo baze podporované vazbou na polymer, jako jsou piperidinmethylpolystyren, morfolinmethylpolystyren, diethylaminomethylpolystyren, poly(4-vinylpyridin) a další obdobné.

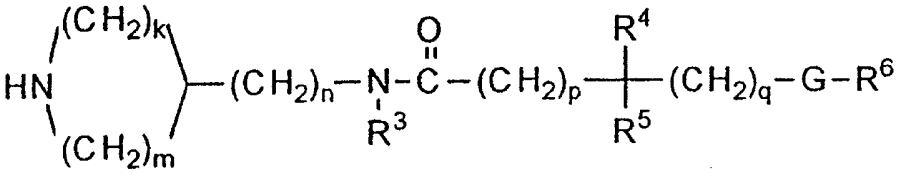
(Příprava 2)

Pro tento typ přípravy je nutné použít k reakci jeden ekvivalent alkylačního činidla reprezentovaného obecným vzorcem IV uvedeným níže:



(IV)

(kde R^1, R^2 a j mají tentýž vyznam, jaký byl definován v předchozím textu pro obecný vzorec I); X reprezentuje halogenový atom, alkylsulfonyloxyskuplinu nebo arylsulfonyloxyskupinu s 0,1 až 10 ekvivalenty karboxylové kyseliny reprezentované obecným vzorcem V uvedeným v dalším textu:



(V)

(kde R^3, R^4, R^5, R^6 G, k, m, n, p a q mají tentýž vyznam, jaký byl definován v předchozím textu nebo pro obecný vzorec I) buď v přítomnosti či nepřítomnosti rozpouštědla.

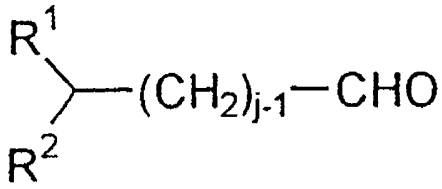
(kde R^4, R^5, R^6, G, p a q mají tentýž vyznam, jaký byl definován v předchozím textu pro obecný vzorec I nebo pro jeho reaktivní deriváty,buď v přítomnosti či nepřítomnosti rozpouštědla.

Tyto reakce lze provést bez problémů pomocí užití baze, která je podobná bazi užité v postupu přípravy 1. Kromě toho, průběh reakce v těchto postupech přípravy lze podpořit užitím jodidů, jako je jodid draselný, jodid sodný a další.

Ve výše uvedeném obecném vzorci IV X představuje halogenový atom, alkylsulfonyloxyskupinu, arylsulfonyloxyskuplinu. Halogenový atom je ve výhodném provední chloridový atom, bromidový nebo jodidový. Vhodným příkladem ve výhodném uspořádání vynálezu pro alkylsulfonyloxyskupinu jsou například methylsulfonyloxy, trifluormethylsulfonyloxyskuplina a další. Pro arylsulfonyloxyskupinu se používá ve výhodném uspořádání tosyloxyskupina.

(Příprava 3)

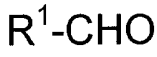
Pro tento typ přípravy je nutné použít k reakci jeden ekvivalent aldehydu reprezentovaného obecným vzorcem VI uvedeným níže:



(VI)

(kde R^1, R^2 mají tentýž vyznam, jaký byl definován v předchozím textu pro obecný vzorec I;

j reprezentuje 1 nebo 2)nebo podle obecného vzorce VII níže:



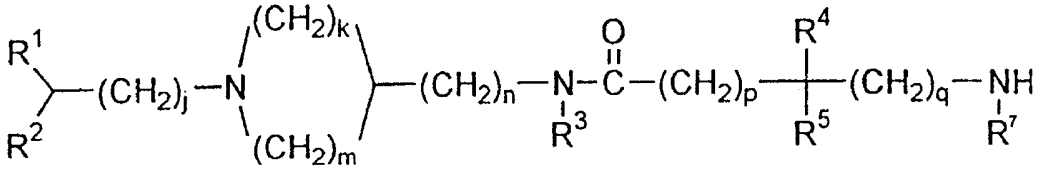
(VII)

((kde R^1 má týž vyznam, jaký byl definován v předchozím textu pro obecný vzorec I; j reprezentuje 0) s 0,1 až 10 ekvivalenty sloučeniny reprezentované obecným vzorcem V buď za nepřítomnosti nebo v přítomnosti rozpouštědla za redukujících podmínek.

Tyto reakce se obecně nazývají reduktivní aminace a tyto redukční podmínky lze generovat pomocí katalytické hydrogenace za použití katalyzátoru obsahujícího kov jako je paladium, platina, nikl, rhodium a další v podobě komplexních hydridů, jako je lithiumaluminium hydrid, borohydrid sodný, kyanoborohydrid sodný, triacetoxyborohydrid a další obdobné, jako jsou borany. Další metodou je elektrolytická redukce a další podobné metody.

(Příprava 4)

Pro tento typ přípravy je nutné použít k reakci jeden ekvivalent sloučeniny reprezentované obecným vzorcem VIII uvedeným níže:



(VIII)

(kde R^1, R^2, R^3, R^4, R^5, R^6, R^7, j, k, m, n, p a q mají tentýž význam, jaký byl definován v předchozím textu nebo pro obecný vzorec I) s 0,1 až 10 ekvivalenty karboxylové kyseliny nebo kyseliny sírové , které reprezentuje obecný vzorec níže:

$$OH\text{-}A\text{-}R^6 \qquad (IX)$$

(kde R^6 ma tentýž význam, jaký byl definován v předchozím textu nebo pro vzorec I; A reprezentuje karbonylovou nebo sulfonylovou skupinu),nebojejich reaktivní deriváty, buď v přítomnosti či nepřítomnosti rozpouštědla.

Reaktivní derivát karboxylové kyseliny nebo kyseliny sírové v obecném vzorci IX zahrnují vysoce reaktivní deriváty karboxylové kyseliny či kyseliny sírové, které jsou běžně používány při syntézách v organické chemii, jako jsou například halogenidy, anhydridy kyselin, smíšené anhydridy kyselin.

Takovouto reakci lze provést bez problémů pomocí užití vhodného množství dehydračního činidla, vazebného činidla nebo baze, které jsou podobné těm, které byly použity v postupu přípravy 1.

(Příprava 5)

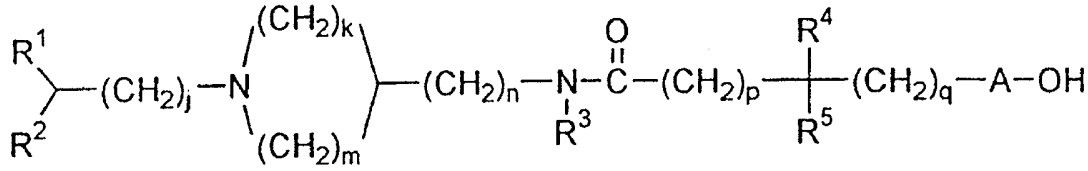
Pro tento typ přípravy je nutné použít k reakci jeden ekvivalent sloučeniny reprezentované výše uvedeným obecným vzorcem VIII s 0,1 až 10 ekvivalenty isokyanátu nebo isothiokyanátu reprezentovaných obecným vzorcem níže:

$$Z{=}C{=}N\text{-}R^6 \qquad (X)$$

(kde R^6 ma tentýž vyznam, jaký byl definován v předchozím textu nebo pro obecný vzorec I; Z reprezentuje kyslíkový atom nebo atom síry), buď v nepřítomnosti,či přítomnosti rozpouštědla.

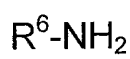
(Příprava 6)

Pro tento typ přípravy je nutné použít k reakci jeden ekvivalent sloučeniny reprezentované níže uvedeným obecným vzorcem XI:



(XI)

(kde R^1, R^2, R^3, R^4, R^5, R^6, R^7, j, k, m, n, p a q mají týž vyznam, jaký byl definován v předchozím textu nebo pro obecný vzorec I); A reprezentuje karbonylovou nebo sulfonylovou skupinu), s 0,1 až 10 ekvivalenty aminu reprezentovaného obecným vzorcem XII uvedeného níže:



(XII)

(kde R^6 ma tentýž vyznam, jaký byl definován v předchozím textu nebo pro obecný vzorec I; buď za nepřítomnosti či přítomnosti rozpouštědla.

Takovéto reakce mohou probíhat snadněji, použije-li se vhodné množství dehydratačního činidla, vazebného činidla nebo baze, podobných těm, které byly použity v postupu přípravy 1.

Jestliže substráty použité v postupech příprav obsahují substituent, který reaguje za daných reakčních podmínek, nebo obecně by se mohlo předpokládat, že negativně ovlivní průběh syntetické organické reakce, potom je jeho funkční skupina chráněna pomocí známé vhodné chránící skupiny. Po proběhnutí reakcí popsaných v předchozím textu se chránící skupiny odstraní opět pomocí postupů běžně užívaných v syntetické organické chemii, tím se získá požadovaná sloučenina.

Dále, sloučeninu podle vynálezu lze připravit další přeměnou substituetu(ů) sloučeniny, připravené podle postupů přípravy (1 až 6), pomocí známých reakcí užívaných v organické chemii, jako je alkylace, acylace, redukce a tak dále.

V každém předchozím postupu přípravy lze pro průběh reakce použít rozpouštědlo, jako je halogenovaný uhlovodík, například dichlormethan, chloroform a další, aromatické uhlovodíky, jako je benzen, toluen a další, ethery jako je diethyleter, tetrahydrofuran a další, estery, jako je ethylacetát, aprotická polární rozpouštědla, jako je dimethylformamid, dimethylsulfoxid, acetonitril a podobné, alkoholy, jako jsou methanol, ethanol, isopropylalkohol a další.

Reakční teplota v průběhu postupů příprav se pohybuje v rozmezí –78 °C až + 150 °C, ve výhodném provedení mezi 0 °C a 100 °C. Po ukončení reakce se k izolaci požadovaných sloučenin cyklických aminů reprezentovaných obecným vzorcem I používají běžné izolační a purifikační operace, jako jsou zakoncentrování, filtrace, extrakce, extrakce pomocí pevné fáze, rekrystalizace, chromatografie a další. Získané sloučniny cyklických aminů lze přeměnit pomocí běžných metod na jejich farmaceuticky přijatelné soli adicí kyseliny, nebo adici $C_1 – C_6$ alkylové skupiny.

Možné průmyslové využití

Antagonisté chemokinových receptorů, které obsahují sloučeniny cyklických aminů, jejich farmaceuticky přijatelné soli vzniklé adicí kyseliny nebo jejich farmaceuticky přijatelné soli vzniklé adicí $C_1 – C_6$ alkylové skupiny podle vynálezu, které inhibují akci chemokinů jako jsou MIP-1α a/nebo MCP-1 a jím podobných v cílových buňkách, mohou být užity jako terapeutická činidla a/nebo preventivní přípravky pro léčbu nemocí, jako je arteroskleróza, revmatická artritida, lupénka, astma, ulcerózní kolitida, nefritida (nefropatie), skleróza multiplex, plicní fibróza, myokarditida, žloutenka, pankreatitida, sarkoidóza, Crohnova nemoc, endometrióza, selhání srdeční činnosti z městnání , virová meningitida, mozkové příhody, neuropatie, Kawasakiho nemoc a sepse, u kterých infiltrace krevních monocytů a lymfocytů ve tkáních, hraje významnou roli v iniciaci, rozvoji či průběhu nemoci.

Příklady provedení vynálezu

Vynález je specificky posán v následujících příkladech, avšak předkládaný vynález nazahrnuje pouze sloučeniny popsané v těchto příkladech. Číslo sloučeniny v následujícícch příkladech reprezentuje číslo, které bylo přiděleno sloučenině v předcházejících tabulkách 1,1 až 1.201.

03-07-00

Referenční příklad 1: Příprava 3-amino-1-(4chlorbenzyl)pyrolidindihydrochloridu.

4-chlorbenzylchlorid (4 ,15 g, 25. 8 mmol) a Pr_2NEt (6. 67 g, 51. 6 mmol) se přidal do roztoku 3-{(terc-butoxykarbonyl)amino}pyrolidinu (4.81 g, 25.8 mmol) v DMF (50 ml). Reakční směs se míchala při 70 °C po dobu 15 h a rozpouštědlo se odstranilo za sníženého tlaku. Rekrystalizace (CH_3CN, 50 ml) poskytla následující požadovaný materiál, 3-(terc--butoxykarbonyl)amino-1-(4 -chlorbenzyl)pyrolidin ve formě světle žluté pevné látky (6.43 g, 80.2%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1,37 (s, 9 H), 1,5-1,7 (br, 1 H), 2,1-2,4 (m, 2 H), 2,5-2,7 (m, 2 H) , 2,83 (br, 1 H) , 3, 57 (s, 2 H), 2,83 (1-4,3 (br, 1 H), 3,57 (s,2 H), 4,1- 4,3 (br, 1 H) , 4,9 – 5,1 (br, 1H), 7,15-7,35 (br, 4 H); Čistota byla určena pomocí RPLC/MS (98%): ESI/MS m/e 311,0 (M^++H, $C_{16}H_{24}ClN_2O_2$) .

Do roztoku 3- (terc-butoxykarbonyl)amino-1-(4chlorbenzyl)pyrolidinu (6.38 g, 20,5 mmol) v CH_3OH (80 ml) se přidal 1 N HCl-Et_2O (100 ml) a směs se míchala při 25 °C po dobu 15 h. Rozpouštědlo se odstranilo pomocí sníženého tlaku a byla získána pevná látka, která se přečistila následnou rekrystalizací (1:2 CH_3OH-CH_3CN, 150 ml) a získal se 3-amino-1-(4- -chlorobenzyl)pyrolidindichlorid jako bílý prášek (4,939 g, 84,9% : ^1H NMR (d_6-DMSO, 300 MHz) δ 3,15 (br, 1 H), 3,3-3,75 (br-m, 4 H), 3,9 (br, 1 H), 4,05 (br, 1 H), 4,44 (br, 1 H) , 4. 54 (br, 1 H) , 7,5- -7 . 7 (m, 4 H) , 8. 45 (br, 1 H) , 8. 60 (br, 1 H) ; Čistota byla určena pomocí RPLC/MS (99%): ESI/MS m/e 211,0 (M^++H, $C_6H_{12}ClN_2$).

Optické aktivity (R)-3-amino-1-(4-chlorbenzyl)pyrolidindihydrochloridu a (S)-3-amino-1-(4- -chlorbenzyl)pyrolidindihydrochloridu se změřily pomocí výše zmíněných postupů a za použití odpovídajících reaktantů. Produkty vykázaly stejnou ^1H NMR, jaká byla zjištěna u racemátu.

Příklad 1: Příprava 3-(N-benzoylglycyl)amino-1-(4-chlorbenzyl)pyrolidinu (Sloučenina č. 1).

N-benzoylglycin (9,9mg, 0,055 mmol), 3-ethyl-1-{3(dimethylaminopropyl)karbodiimidhydrochlorid (EDCI) (10,5 mg) a 1hydroxybenzotriazolhydrát (HOBt) (7,4 mg) se přidaly do roztoku 3-amino-1- -(4-chlorbenzyl)pyrolidindihydrochloridu (14,2 mg, 0,050 mmol) a Et_3N (15,2 mg) v $CHCl_3$ (2,5 ml). Reakční směs se míchala při 25 °C po dobu 16 h, poté se promyla 2 N vodným roztokem NaOH (2 ml x 2) a nasyceným roztokem NaCl (1 ml). Po filtraci přes PTFE membránový filtr se odstranilo rozpouštědlo za sníženého tlaku a získal se 3-(N-benzoylglycyl)amino-1- (4-chlorbenzyl)pyrolidin (sloučenina č. 1) jako světle žlutý olej (17,7 mg, 95%): Čistota byla určena pomocí RPLC/MS (95%): ESI/MS m/e 372,0 (M^++H, $C_{20}H_{22}ClN_3O_2$).

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Příklad 2 až 32.

Sloučeniny podle vynálezu se syntetizovaly pomocí metod uvedených v Příkladu 1 za použití stejných reaktantů. Data ESI/MS a výtěžky jsou shrnuty v tabulce 2.

Tabulka 2

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 2	2	C21 H24 C1 N3 02	386	16,4	85
Příklad 3	3	C19 H21 C1 N4 02	373	18,7	100
Příklad 4	4	C21 H21 C1 F3 N3 02	440	57,2	69
Příklad 5	82	C22 H23 C1 F3 N3 02	454	5,6	11
Příklad 6	85	C21 H24 C1 N3 02	386	22,6	59
Příklad 7	86	C21 H23 C1 N4 04	431	21,2	98
Příklad 8	214	C22 H25 C1 N2 02	385	23,9	62
Příklad 9	215	C23 H27 C1 N2 03	415	17,4	84
Příklad 10	216	C20 H23 C1 N2 02 S	391	21,6	kvant
Příklad 11	217	C23 H27 C1 N2 04	431	15,3	66
Příklad 12	218	C23 H27 C1 N2 02	399	12,8	64
Příklad 13	219	C22 H24 Cl F N2 03	419	18,1	86
Příklad 14	220	C22 H25 C1 N2 02	385	16,4	85
Příklad 15	221	C21 H23 C1 N2 02	371	14,9	80
Příklad 16	222	C21 H22 C12 N2 02	405	13,3	65
Příklad 17	223	C25 H31 C1 N2 03	443	18,4*	63
Příklad 18	224	C20 H23 C1 N2 03 S	407	11,2	28
Příklad 19	225	C22 H26 C1 N3 02	400	22,7	kvant
Příklad 20	226	C23 H28 C1 N3 03	430	21,0	98
Příklad 21	227	C22 H25 C12 N3 02	434	21,9	100
Příklad 22	228	C23 H28 C1 N3 03	430	20,8	97
Příklad 23	229	C25 H32 C1 N3 02	462	25,4	kvant
Příklad 24	230	C26 H31 C1 F N3 02	472	26,0	kvant

Příklad 25	231	C24 H28 C1 N3 03	442	30,3*	kvant
Příklad 26	232	C22 H32 C1 N3 02	406	3,9	19
Příklad 27	233	C23 H28 Cl N3 02	414	8,5	41
Příklad 28	234	C22 H27 C1 N4 02	415	7,3	35
Příklad 29	235	C24H29 C12 N3 02	462	9,0	39
Příklad 30	236	C25H29 C1 N4 03 S	501	17,4	69
Příklad 31	237	C21 H24 C1 N3 03	402	19,2	71
Příklad 32	238	C21H23 C12 N3 03	436	23,4	kvant

*Výtěžek TFA soli

Referenční příklad 2: Příprava (R)-3-{N-(terc-butoxykarbonyl)glycyl}amino-1-(4--chlorbenzyl)pyrolidinu.

Směs (R)-3-amino-1-(4-chlorbenzyl)pyrolidindihydrochloridu (9,54 g, 16,0 mmol), 2 N NaOH roztoku (80 ml) a ethylacetátu (80 ml) se protřepala, organická vrstva se oddělila a vodná fáze se extrahovala ethylacetátem (80 ml x 2). Spojené organické vrstvy se vysušily pomocí bezvodého síranu sodného, přefiltrovaly se a odpařily na odparce. Tak se získal volný (R)-3-amino-1-(4--chlorbenzyl)pyrolidin (3,35 g, 99%).

Roztok (R)-3-amino-1- (4-chlorbenzyl)pyrolidinu (3,35 g, 16 mmol) v CH_2C1_2 (80 ml) se smíchal s Et_3N (2,5 ml, 17. 6 mmol), N-terc-butoxykarbonylglycinem (2,79 g, 16,0 mmol), EDCI (3,07 g, 16,0 mmol) and HOBt (2,16 g, 16 mmol). Reakční směs se nechala míchat při 25 °C po dobu 16 h a poté se přidal roztok 2 N NaOH (80 ml). Oddělila se organická vrstva a vodná vrstva se extrahovala následně dichloromethanem (100 ml x 3). Spojené organické vrstvy se následně promyly vodou (100 ml x 2) a nasyceným roztokem NaCl (100 ml), vysušily pomocí bezvodého síranu sodného, přefiltrovaly a zakoncentrovaly se. Pomocí chromatografie na sloupci SiO_2 v ethylacetátu se získal požadovaný (R)-3-{N-(terc-butoxykarbonyl)glycyl}amino-1-(4-chlorbenzyl)pyrolidin (5.40 g, 92%).

Referenční příklad 3: Příprava (R)-1-(4-chlorbenzyl)-3glycylamino)pyrolidinu.

K roztoku (R)-3-{N-(terc-butoxykarbonyl)glycyl)amino-1-(4-chlorbenzyl)pyrolidinu (5.39 g,

14.7 mmol) v methanolu (60 ml) se přidala 4 N HCl v dioxanu (38 ml). Reakční směs se nechala míchat 2 hodiny při laboratorní teplotě. Reakční směs se poté zakoncentrovala a přidal se roztok 2 N NaOH (80 ml). Reakční směs se extrahovala dichlorometanem (80 ml x 3) a spojené extrakty se vysušily pomocí síranu sodného a zakoncentrovaly se. Pomocí sloupcové chromatografie (SiO_2, AcOEt/EtOH/Et_3N - 90/5/5) se získal (R)-3-(glycyl)amino-1-(4-chlorbenzyl)pyrolidin (3.374 g, 86 %): ^1H NMR ($CDCl_3$, 270 MHz) δ 1.77 (dd, J = 1.3 a 6,9 Hz, 1 H). 2.20-3.39 (m, 2 H), 2,53 (dd, J = 3.3 a 9.6 Hz, 1 H), 2.62 (dd, J = 6,6 a 9,6 Hz, 1 H), 2,78-2,87 (m, 1 H), 3,31 (s, 2 H), 3,57 (s, 2 H), 4,38-4,53 (br, 1 H), 7,18-7,32 (m, 4 H), 7,39 (br. s, 1 H).

Další 3-acylamino-1-(4-chlorbenzyl)pyrolidinu byly také syntetizovány podle metod Referenčního příkladu 2 a 3 za použití odpovídajících reaktantů

(S)-1-(4-chlorbenzyl)-3-(glycylamino)pyrolidin: 3,45 g, 79 % (2 kroky).

(R)-3-(β-alanylamino)-1-(4-chlorbenzyl)pyrolidin: 3,79 g, 85 % (2 kroky)

(S)-3-([β-alanylamino-)1-(4-chlorbenzyl)pyrolidin: 3,72 g, 86 % (2 kroky)

(R)-3-{(S)-alanylamino)-1-(4-chlorobenzyl)pyrolidin: 368 mg, 65 % (2 kroky)

(R)-3-{(R)-alanylamino}-1-(4-chlorbenzyl)pyrolidin: 425 mg, 75 % (2 kroky)

(R)-3-{(2S)-2-amino-3-thienylpropanoyl)amino-1-(4chlorbenzyl)pyrolidin:566 mg, 78 % (2 kroky)

(R)-3-{(2R)-2-amino-3-thienylpropanoyl)amino-1-(4chlorbenzyl)pyrolidin: 585 mg, 81 % (2 kroky).

(R)-3-(2-amino-2-methylpropanoyl)amino-1-(4-chlorbenzyl)pyrolidin: 404 mg, 66 % (2 kroky).

(R)-3-{(2S)-2-amino-4-(methylsulfonyl)butanoyl}amino-1-(4-chlorbenzyl)pyrolidin: 535 mg, 72 % (2 kroky).

Kromě toho byly také syntetizovány podle metod Referenčního příkladu 1 a 2 a za použití odpovídajících reaktantů: (R)-3-(glycylamino)-1-(4-methylbenzyl)pyrolidin, (R)-1-(4-brombenzyl)-3--(glycylamino)pyrolidin a (R)-1-(2,4-dimethylbenzyl)-3-(glycylamino)pyrolidin. Podle metod Referenčního příkladu 1, 2 a 3 za použití odpovídajících reaktantů byl dále syntetizován (R)-1-(3,5--dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrolidin.

(R)-(3-(glycylamino)-1-(4-methylbenzyl)pyrolidin: 4.65 g, 62% výtěžek z 3-{(terc--butoxykarbonyl)amino}pyrolidinu.

(R)-1-(4-brombenzyl)-3-(glycylamino)pyrolidin: 2,55 g, 68% výtěžek z (R)-3-amino-1-(4--brombenzyl)pyrolidinu; 1H NMR ($CDCl_3$, 270 MHz) δ 1.37-1.78 (m, 3 H), 2.23-2.39 (m, 2 H), 2,50-

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2.67-(m, 2 H), 2.80-2.89 (m, 1 H), 3.32 (s, 2 H), 3,58 (s, 2 H), 4.39-4,55 (m, 1 H), 7.21 (d, J = 6,5 Hz, 2 H), 7.45 (d, J = 6,5 Hz, 2 H).

(R)-1-(2,4-dimethylbenzyl)-3-(glycylamino)pyrolidin: 1,56 g, 58% výtěžek z 3-{(terc--butoxykarbonyl)amino}pyrolidin; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1,55-1.78 (m, 3 H), 2.30 (s, 3 H), 2.23-2.31 (m, 2 H), 2.33 (s, 3 H), 2,51-2.63 (m, 2 H), 2.78-2.87 (m, 1 H), 3.30 (s, 2 H), 3,55 (s, 2 H), 4.38-4.60 (m, 1 H), 6,95 (d, J = 7.6 Hz, 1 H), 6,97 (s, 1 H), 7,13 (d, J = 7.6 Hz, 1 H), 7.43 (br-s, 1 H).

(R)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrolidin: 3,14 g, 45% výtěžek z 3-[(terc--butoxykarbonyl)amino]pyrolidinu.

Příklad 33: Příprava (S)-3-[N-{3,5-bis(trifluormethyl)benzoyl}glycyl]amino-1-(4-chlorbenzyl)--pyrolidinu (Sloučenina č. 5).

Roztok 3,5-bis(trifluormethyl)benzoylchloridu (0,060 mmol) v chloroformu (0.4 ml) byl přidán k roztoku (S)-1-(4-chlorbenzyl)-3-(glycylamino)pyrolidinu (0,050 mmol) a triethylaminu

(0,07 mmol) v chloroformu (1. 0 ml). Poté, co se reakční směs třepala při pokojové teplotě 2,5h, se přidala aminomethylpolystyrenová pryskyřice (1,04 mmol/g, 50 mg, 50mmol) a reakční směs se nechala při pokojové teplotě třepat dalších 12 hodin. Reakční směs se přefiltrovala a pryskyřice se promyla dichloromethanem (0. 5 ml). Filtrát a kapalina po promytí pryskyřice se spojily, přidal se dichlormethan (4 ml) a roztok se promyl 2 N vodným roztokem NaOH (0,5 ml) a byl získán (S)-3-[N--{3,5-bis(trifluormethyl)benzoyl}glycyl]amino-1-(4-chlorobenzyl)pyrrolidin (Sloučenina č. **5**)

(14.4 mg, 57%): Čistota byla určena pomocí RPLC/MS (97%): ESI/MS m/e 508,0 (M^++H, $C_{22}H_{20}ClF_6N_3O_2$).

Příklady 34 až 239.

Sloučeniny podle vynálezu se syntetizovaly způsoby popsanými v Příkladu 33 za použití odpovídajících reaktantů v daném pořadí. V tabulce 3 jsou shrnuta ESI/MS data a výtěžky.

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Tabulka 3

Sloučenina č.		Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 34	5	C22 H20 Cl F6 N3 02	508 ,0	14 ,4	57
Příklad 35	6	C21 H21C1 F3 N3 02	440,0	17,0	77
Příklad 36	7	C20 H21 Br C1 N3 02	450,0	17,7	79
Příklad 37	8	C20 H21 C1 F N3 02	390,0	12,7	65
Příklad 38	9	C20 H20 C13 N3 02	440,0	39,0	kvant
Příklad 39	10	C21 H24 C1 N3O3	402,5	23,5	kvant
Příklad 40	11	C22 H26 C1 N3 04	432,5	22,4	kvant
Příklad 41	12	C22 H26 C1 N3 04	432,5	15,9	74
Příklad 42	13	C21 H21 C1 F3 N3 02	440,0	13,1	60
Příklad 43	14	C21 H24 C1 N3 02	386,0	16,4	85
Příklad 44	15	C20 H21 C12 N3 02	406,0	15,7	77
Příklad 45	16	C21 H24 C1 N3 02	402,0	28,2	kvant
Příklad 46	17	C20 H20 C13 N3 02	942,0	35,6	kvant
Příklad 47	18	C21 H21 C1 N4 02	397,5	22,8	kvant
Příklad 48	19	C21 H22 C1 N3 04	416,0	16,3	78
Příklad 49	20	C21 H20 C1 F4 N3 02	458,0	24,9	kvant
Příklad 50	21	C21 H20 C1 F4 N3 02	458,0	17,9	78
Příklad 51	22	C21 H20 CI F4 N3 O2	458,0	9,4	41
Příklad 52	23	C21 H20 C1 F4 N3 02	458,0	15,4	67
Příklad 53	24	C21 H21 C1 F3 N3 03	956,0	20,7	91
Příklad 54	25	C21 H20 C1 F4 N3 02	458,0	18,5	81
Příklad 55	26	C20 H21 C1 N4 04	417,0	21,9	kvant
Příklad 56	27	C20 H21 C1 N4 04	417,0	16,8	81
Příklad 57	28	C20 H21 C1 N4 04	417,0	6,8	33
Příklad 58	29	C22 H20 C1 F6 N3 02	508,0	20,8	82
Příklad 59	30	C21 H21 C1 F3 N3 02	440,0	15,2	69
Příklad 60	31	C20 H21 Br C1 N3 02	450,0	15,6	69
Příklad 61	32	C20 H21 C1 F A 3 02	390,0	11,8	61

Příklad 62	33	C20 H20 C13 N3 02	440,0	15,8	72
Příklad 63	34	C21 H24 C1 N3 03	402,5	33,8	kvant
Příklad 64	35	C22 H26 C1 N3 04	432,5	56,1	kvant
Příklad 65	36	C22 H26 C1 N3 04	432,5	37,6	kvant
Příklad 66	37	C21 H21 C1 F3 N3 02	490,0	12,6	57
Příklad 67	38	C21 H24 C1 N3 02	386,0	12,3	64
Příklad 68	39	C20 H21 C12 N3 02	406,0	15,9	78
Příklad 69	40	C21 H24 C1 N3 02	402,0	11,6	58
Příklad 70	41	C20 H20 C13 N3 02	442,0	17,8	1
Příklad 71	42	C21 H21 C1 N4 02	397,5	22,4	kvant
Příklad 72	43	C21 H22 C1 N3 04	916,0	30,1	kvant
Příklad 73	44	C21 H20 C1 F4 N3 02	458,0	13,4	59
Příklad 74	45	C21 H20 C1 F4 N3 02	458,0	13,2	58
Příklad 75	46	C21 H20 C1 F4 N3 02	458,0	14,4	63
Příklad 76	47	C21 H2I C1 F3 N3 03	456,0	16,4	72
Příklad 77	48	C21 H20 C1 F4 N3 02	458	16,5	72
Příklad 78	49	C20 H21 C1 N4 O4	417,0	12,5	60
Příklad 79	50	C 21 H20 C1 F4 N3 02	458,0	26,3	kvant
Příklad 80	51	C20 H2l Br C1 N3 02	450,0	8,6	38
Příklad 81	52	C20 H21 C1 F N3 02	390,5	4,1	21
Příklad 82	53	C20 H21 C12 N3 02	906,0	5,9	27
Příklad 83	54	C20 H20 C13 N3 02	440,0	8,8	40
Příklad 84	55	C20 H20 Br C14 N3 02	440,0	7,7	35
Příklad 85	56	C21 H24 C1 N3 02	386,0	4,8	25
Příklad 86	57	C22 H26 C1 N3 04	429. 5	4,9	23
Příklad 87	58	C20 H21 C12 N3 02	406,0	4,1	20
Příklad 88	59	C20 H21 Br C1 N3 02	452,0	3,5	16
Příklad 89	60	C26 H26 C1 N3 02	448,5	7,3	33
Příklad 90	61	C21 H21 C1 F3 N3 O2	940,0	7,1	32
Příklad 91	62	C2l H24 C1 N3 02	386,0	10,4	54
Příklad 92	63	C22 H26 C1 N3 02	400,5	6,0	30
Příklad 93	64	C21 H21 C1 N4 02	397,0	7,0	35

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Příklad 94	65	C24 H24 C1 N3 02	422,0	7,7	36
Příklad 95	66	C24 H24 C1 N3 O2	422,0	6,3	30
Příklad 96	67	C20 H20 C1 F2 N3 O2	408,0	4,7	23
Příklad 97	68	C20 H20 C1 F2 N3 O3	908,0	7,8	38
Příklad 98	69	C20 H20 C1 F2 N3 O2	408,0	7,3	36
Příklad 99	70	C20 H20 C1 F2 N3 O2	408,0	9,1	45
Příklad 100	71	C22 H25 C1 N3 O4	429,0	5,6	26
Příklad 101	72	C21 H21 C1 F3 N3 O2	456,0	6,2	27
Příklad 102	73	C21 H21 C1 F3 N3 O2	956,5	16,8	74
Příklad 103	74	C22 H24 C1 N3 O4	430,0	16,9	76
Příklad 104	75	C21 H20 C1 F4 N3 O2	458,0	16,1	70
Příklad 105	76	C21 H20 C1 F4 N3 O2	458,0	17,0	74
Příklad 106	77	C20 H19 C1 F3 N3 O2	426,0	16,2	76
Příklad 107	78	C20 H19 C1 F3 N3 O2	926,0	18,0	85
Příklad 108	79	C22 H20 CI F6 N3 O2	508,0	18,8	74
Příklad 109	80	C22 H20 CI F6 N3 O2	508,0	16,4	65
Příklad 110	81	C22 H26 C1 N3 O4	400,0	13,9	70
Příklad 111	83	C20 H21 C1 N4 O4	417,0	16,0	77
Příklad 112	84	C20 H21 C1 N4 O4	417,0	21,6	kvant
Příklad 113	87	C23 H22 C1 F6 N3 O2	522,0	17,5	67
Příklad 114	88	C22 H23 C1 F3 N3 O2	454,0	13. 9	61
Příklad 115	89	C21 H23 Br C1 N3 O2	466,0	15,4	66
Příklad 116	90	C21 H23 C1 F N3 O2	404,0	10,7	53
Příklad 117	91	C21 H22 C13 N3 O2	456,0	13,7	60
Příklad 118	92	C22 H26 C1 N3 O2	416,0	38,4	kvant
Příklad 119	93	C23 H23 Cl N3 O4	446,0	25,2	kvant
Příklad 120	94	C23 H23 C1N3 O4	446,0	16,5	74
Příklad 121	95	C22 H23 C1 F3 N3 O2	454,0	16,3	72
Příklad 122	96	C22 H26 C1 N3 O2	400. 5	16,7	84
Příklad 123	97	C21 H23 C12 N3 O2.	420,0	11,2	53
Příklad 124	98	C22 H26 C1 N3 O2	416,5	11,8	57

Příklad 125	99	C21 H22 C13 N3 O2	454,0	14,8	65
Příklad 126	100	C22 H23 C1 N4 O2	411,0	9,5	46
Příklad 127	101	C22 H24 C1 N3 O4	430,5	13,2	61
Příklad 128	102	C22 H22 C1 F4 N3 O2	472,0	13,1	56
Příklad 129	103	C22 H22 C1 F4 N3 O2	472,0	36,5	kvant
Příklad 130	104	C22 H22 C1 F4 N3 O2	472,0	22,8	97
Příklad 131	105	C22 H22 C1 F4 N3 O2	472,0	20,1	85
Příklad 132	106	C22 H23 C1 F3 N3 O3	470,0	27,4	kvant
Příklad 133	107	C22 H22 C1 F4 N3 O2	472,0	18,5	78
Příklad 134	108	C21 H23 C1 N4 O4	431,0	11,9	55
Příklad 135	109	C21 H23 C1 N4 O4	431,0	23,9	kvant
Příklad 136	110	C21 H23 C1 N4 O4	431,0	24,4	kvant
Příklad 137	111	C23 H22 C1 F3 N3 O2	522,0	9,5	36
Příklad 138	112	C22 H23 C1 F3 N3 O2	454,0	3,9	17
Příklad 139	113	C21 H23 Br C1 N3 O2	466,0	7,5	32
Příklad 140	114	C21 H23 C1 F N3 O2	404,0	6,1	30
Příklad 141	115	C21 H23 C13 N3 O2	456,0	6,6	29
Příklad 142	116	C22 H26 C1 N3 O3	416,0	9,8	23
Příklad 143	117	C23 H28 C1 N3 O4	446,0	6,4	2
Příklad 144	118	C23 H29 C1 N3 O4	946,0	24,6	kvant
Příklad 145	119	C22 H23 C1 F3 N3 O2	454,0	5,2	23
Příklad 146	120	C22 H20 C1 N3 O2	400,5	4,9	22
Příklad 147	121	C21 H23 C12 N3 O3:	420,0	7,8	37
Příklad 148	122	C22 H26 C1 N3 O2	416,5	14,1	68
Příklad 149	123	C21 H23 C13 N3 O2	454,0	5,9	29
Příklad 150	124	C22 H23 Cl N4 O2	411,0	34,0	kvant
Příklad 151	125	C22 H24 CI N3 O4	430,5	32,0	kvant
Příklad 152	126	C22 H22 C1 F4 N3 O2	472,0	4,6	19
Příklad 153	127	C22 H23 C1 F4 N3 O2	972,0	10,4	49
Příklad 154	128	C22 H23 Cl F4 N3 O2	472,0	7,3	31

Příklad 155	129	C22 H22 C1 F4 N302	472,0	13,5	57
Příklad 156	130	C22 H23 C1 F3 N3 O3	470,0	15,1	64
Příklad 157	131	C22 H22C1 F4 N3 O2	472,0	8,6	36
Příklad 158	132	C21 H23 C1 N4 O4	931,0	4,4	20
Příklad 159	133	C21 H23 C1 N4 O4	431,0	32,0	kvant
Příklad 160	134	C21 H23 C1 N4 O4	431,0	6,9	32
Příklad 161	135	C21 H23 Br C1 N3 O2	466,0	7,8	34
Příklad 162	136	C21 H23 C1 F N3 O2	404,0	13,7	68
Příklad 163	137	C21 H23 C12 N3 O2	420. 5	14,6	69
Příklad 164	138	C21 H22 C13 N3 O2	454,0	7,7	78
Příklad 165	139	C21 H22 Br C14 N3 O2	454,0	17,2	76
Příklad 166	190	C22 H26 C1 N3 O2	400,0	15,0	75
Příklad 167	141	C23 H28 C1 N3 O4	443,5	13,9	62
Příklad 168	142	C21 H23 C1 N3 O2	420,0	13,7	65
Příklad 169	143	C21 H23 Br C1 N3 O2	464,0	16,1	69
Příklad 170	144	C27 H23 C1 N3 O2	462,0	17,6	76
Příklad 171	145	C22 H23 C1 F3 N3 O2	454,0	16,0	71
Příklad 172	146	C22 H26C1 N3 O2	400,0	19,9	75
Příklad 173	147	C23 H28 C1 N3 O2	414,0	16,2	78
Příklad 174	148	C22 H23 C1 N4 O2	411,0	14,9	73
Příklad 175	149	C25 H25 C1 N3 O2	436,0	17,1	78
Příklad 176	150	C25 H26 C1 N3 O2	436,0	13,1	60
Příklad 177	151	C21 H22 C1 F2 N3 O2	422,0	14,8	70
Příklad 178	152	C21 H22 C1 F2 N3 O2	422,0	15,3	73
Příklad 179	153	C21 H22 C1 F2 N3 O2	422,0	15,3	73
Příklad 180	154	C21 H22 C1 F2 N3 O2	422,0	16,4	78
Příklad 181	155	C23 H23 C1 N3 02	443,0	16,9	76
Příklad 182	156	C22 H23 C1 F3 N3 02.	470,5	12,6	59
Příklad 183	157	C22 H23 C1 F3 N302	470,0	20,0	85
Příklad 184	158	C23 H25 C1 N3 O4	444,0	17,4	78

Příklad 185	159	C22 H22 C1 F4 N3 02	472,0	18,4	78
Příklad 186	160	C22 H22 C1 F4 N3 02	472,0	19,6	83
Příklad 187	161	C21 H21 C1 F3 N3 02	440,0	17,0	77
Příklad 188	162	C21 H21 C1 F3 N3 O2.	490,0	17,1	78
Příklad 189	163	C23 H22 C1 F6 N302	522,0	20,8	80
Příklad 190	164	C23 H22 C1 F6 N3 02	522,0	2,7	10
Příklad 191	165	C23 H23 C1 N3 02	414,0	16,4	79
Příklad 192	166	C22 H23 C1 F3 N3 02	454,0	8,6	38
Příklad 193	167	C21 H23 Br C1 N3 02	464,0	11,6	50
Příklad 194	168	C21 H23 Cl2 N3 O2	420,0	1,5	55
Příklad 195	169	C21 H22 Cl3 N3 02	459,0	10,0	44
Příklad 196	170	C22 H23 Cl F4 N3 02	472,0	10,4	44
Příklad 197	171	C21 H23 C12 N3 02	420,0	8,9	42
Příklad 198	172	C21 H24 C1 N3 02	386,0	10,3	53
Příklad 199	173	C21 H23 C1 N4 04	431, 0	14,6	68
Příklad 200	179	C22 H23 C1 F3 N3 02	954,0	10,9	46
Příklad 201	175	C21 H23 B rC1 N3 02	464,0	13,4	58
Příklad 202	176	C21 H23 C12 N3 03	920,0	12,7	60
Příklad 203	177	C21 H22 C13 N3 02	459,0	13,2	58
Příklad 204	178	C22 H22 C1 F4N3 02	472,0	12,9	55
Příklad 205	179	C21 H23 C12 N3 02	420,0	13,3	63
Příklad 206	180	C21 H24 C1 N3 02	386,0	24,2	kvant
Příklad 207	181	C21 H23 C1 N4 O4	431,0	1,0	1
Příklad 208	182	C23 H25 Cl F3 N3 O2	468,0	15,1	65
Příklad 209	183	C22 H25 Br C1 N3 02	478,0	18,0	75
Příklad 210	184	C22 H25 C12 N3 02	934,0	16,3	75
Příklad 211	185	C22 H24 C13 N3 02	968,0	18,6	79
Příklad 212	186	C23 H24 C1 F4 N3 02	986. 0	16,5	68
Příklad 213	187	C22 H25 C12 N3 O2	939,0	14,4	69
Příklad 214	188	C22 H23 C1 N3 02	400,0	14,0	70

Příklad 215	189	C22 H25 C1 N4 04	445,0	16,8	76
Příklad 216	190	C26 H25 Cl F3 N3 02 S	536,0	17,7	66
Příklad 217	191	C25 H25 Br Cl N3 O2 S	546,0	20,9	75
Příklad 218	192	C25 H25 C12 N3 O3 S	502,0	16,9	67
Příklad 219	193	C25 H24 C1 N3 02 S	536,0	18,3	68
Příklad 220	199	C26 H24 C1 F4 N3 02 S	554,0	19,4	70
Příklad 221	195	C25 H25 C12 N3 02 S	502,0	19,1	76
Příklad 222	196	C25 H26 C1 N3 02 S	468,0	16,0	68
Příklad 223	197	C25 H25 C1 N4 04 S	513,0	18,9	72
Příklad 224	198	C26 H25 C1 F3 N3 O2 S	536,0	13,9	52
Příklad 225	199	C25 H25 Br C1 N3 02 S	546,0	12,9	97
Příklad 226	200	C25 H25 C12 N3 02 S	502,0	15,6	62
Příklad 227	201	C25 H24 C13 N3 02 S	536,0	17,3	64
Příklad 228	202	C26 H24 C1 F4 N3 O2 S	554,0	15,9	56
Příklad 229	203	C25 H25 C12 N3 O2 S	502,0	13,5	59
Příklad 230	204	C25 H26 C1 N3 02 S	468,0	13,7	59
Příklad 231	205	C25 H25 C1 N4 04 S	513,0	13,9	54
Příklad 232	206	C24 H27 C1 F3 N3 O4 S	546,0	10,0	37
Příklad 233	207	C23 H27 Br Cl N3 04 S	558,0	17,1	61
Příklad 234	208	C23 H27 C12 N3 O4 S	512. 0	17,0	66
Příklad 235	209	C23 H26 C13 N3 O4 S	546,0	7,3	27
Příklad 236	210	C24 H26 C1 F4 N3 O4 S	564,0	19,2	68
Příklad 237	211	C23 H27 C12 N3 O4 S	512,0	7,9	31
Příklad 238	212	C23 H28 C1 N3 O4 S	478,0	13,7	57
Příklad 239	213	C23 H27 C1 N4 O4 S	523,0	5,5	38

Příklad 240: Příprava (R)-3-[N-{3-fluoro-5-(trifluormethyl)benzoyl}glycyl]amino-1-(3,5--dimethylisoxazol-4-ylmethyl)pyrolidinu (Sloučenina č. 1191).

Roztok 3-fluor-5-(trifluormethyl)benzoylchloridu (0,058 mmol) v dichlorometanu (1 ml) se přidal k reakční směsi (R)-1-(3,5-dimethylisoxazol-4-ylmethyl)-3-(glycylamino)pyrolidinu (0,050 mmol) a

piperidinmethylpolystyrenu (58 mg) v chloroformu (0.2 ml) a dichlorometanu (0.75 ml). Poté, co se směs ponechala míchat při pokojové teplotě 2 h, přidal se methanol (1,0 ml) a směs se nechala míchat dalších 30 min v pokojové teplotě. Reakční směs se nanesla na sloupec Varian SCX a promývala se CH_3OH (16 ml). Produkt se eluoval použitím 2 N NHS v CH_3OH (6 ml) a po zakoncentrování se získal žádaný (R)-3-[N-(3-fluoro-5-(trifluormethyl)benzoyl)glycyl]amino-1-(3,5-dimethylisoxazol-4--ylmethyl)pyrolidin (Sloučenina č. **1191)** (19,5 mg, 88%: Čistota produktu se určila pomocí RPLC/MS (100%); ESI/MS m/e 443.2 (M^+ +H, $C_{20}H_{22}F_4N_4O_3$).

Příklady 241 až 265 :

Sloučeniny podle vynálezu byly syntetizovány metodami popsanými v Příkladu 240 za použití odpovídajících reaktantů v daném pořadí. V tabulce 4 jsou shrnuta ESI/MS data a výtěžky

Tabulka 4

Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 241 1192	C20 H22 F4 N4 03	443,2	19,2	87
Příklad 242 1193	C20 H23 F3 N4 04	441,0	17,5	79
Příklad 243 1194	C21 H22 F6 N4 03	493,0	20,4	83
Příklad 244 1195	C19 H23 Br N4 03	435,1	16,8	77
Příklad 245 1196	C19 H23 N5 05	402,2	16,2	81
Příklad 246 1197	C20 H22 F4 N403	443,2	17,6	80
Příklad 247 1198	C19 H23 C1 N403	391,0	16,5	84
Příklad 248 1199	C20 H26 N4 03	371,0	16,1	87
Příklad 249 1200	C19 H22 C12N4 03	425,0	18,0	85
Příklad 250 1201	C19H22 F2 N4 03	393,0	16,6	85
Příklad 251 1202	C20H22 F4 N4 03	443,2	16,8	76
Příklad 252 1203	C22H24 F3 N3 03	436,2	17,1	79
Příklad 253 1209	C23H23 F6 N3 02	988,2	18,1	74
Příklad 254 1205	C21H24 Br N3 02	430,0	17,5	81
Příklad 255 1206	C21H24 N4 04	397,0	16,2	82

Příklad	256	1207	C22H23 F4 N3 02	438,2	17,5	80
Příklad	257	1208	C21H24 C1 N3 02	386,0	15,8	82
Příklad	258	1209	C22H27 N3 02	366,0	15,7	86
Příklad	259	1210	C21H23 C12N3 02	920,0	17,8	85
Příklad	260	1211	C21H23 F2 N3 02	388,0	16,3	84
Příklad	261	1212	C22H23 F4 N3 02	938,2	17,4	80
Příklad	262	1213	C24H24 C1 F6 N3 02	536,2	24,0	90
Příklad	263	1214	C23H24 C1 F4 N3 03	986,2	22,2	91
Příklad	269	1215	C22H24 C13 N3 02	467,9	20,9	89
Příklad	265	1216	C22H24 C1 F2 N3 02	436,0	19,3	89

Příklad 266: Příprava (R)-1-(4-chlorbenzyl)-3-[N-{4-(dimethylamino)benzoyl)glycyl}-amino]pyrolidinu (Sloučenina č. 952).

Na roztok (R)-1-(4-chlorbenzyl)-3-(glycylamino)pyrolidinu (13,8 mg, 0,052 mmol) v $CHCl_3$; (2 ml) se působilo Et_3N (0,021 ml, 0,15 mmol), 4-(dimethylamino)benzoovou kyselinou (10 mg, 0,061 mmol), EDCI (10.2 mg, 0,053 mmol) a HOBt (7,5 mg, 0,055 mmol). Reakce se míchala při pokojové teplotě po dobu 16 h. Roztok se promyl 2 N vodným roztokem NaOH (2 ml x 2) a nasyceným roztokem NaCl (2 ml) a produkt se sušil filtrací přes PTFE membranu pomocí CH_2Cl_2 (3 ml). Zakoncentrováním se obdržel požadovaný produkt (Sloučenina č. 952) (24,9 mg, kvant.): Čistota produktu se určila pomocí RPLC/MS (91%); ESI/MS m/e 415,0 (M^+ +H, $C_{22}H_{27}ClN_4O_2$) .

Příklady 267 až 347:

Sloučeniny podle vynálezu byly syntetizovány metodami popsanými v Příkladu 266 za použití odpovídajících reaktantů v daném pořadí.K získání požadovaných produktů byla použita extrakce na pevné fázi (sloupec Varian SXC) nebo chromatografie (HPLC-C_{18}).V tabulce 5 jsou shrnuta ESI/MS data a výtěžky

Tabulka 5

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 267	951	C22 H24 C1 N3 04	430,0	26,3	kvant
Příklad 268	953	C23 H29 C1 N4 02	429,0	28,8	kvant
Příklad 269	954	C21 H25 C1 N4 02	401,0	27,9	kvant
Příklad 270	955	C22 H27 C1 N9 02	415,0	26,8	kvant
Příklad 271	956	C21 H24 C1 N3 03	402,0	10,3	51
Příklad 272	957	C20 H22 C1 N3 03	388,0	1,4	7
Příklad 273	958	C21 H24 C1 N3 03	402,5	1,2	6
Příklad 274	959	C22 H25 C1 N9 03	429,5	4,7	22
Příklad 275	960	C23 H27 C1 N4 03	443,0	10,9	49
Příklad 276	961	C21 H25 C1 N4 02	401,0	28,4	kvant
Příklad 277	962	C22 H27 C1 N4 02	415,0	24,9	kvant
Příklad 278	963	C21 H24 C1 N3 03	402,0	4,9	22
Příklad 279	964	C22 H29 C1 N3 09	430,0	29,5	kvant
Příklad 280	965	C23 H26 C1 N3 04	444,0	27,2	kvant
Příklad 281	966	C22 H24 C1 N3 03	914,0	27,0	kvant
Příklad 282	967	C23 H26 C1 N3 03	428,0	27,0	kvant
Příklad 283	968	C22 H23 C1 N4 02	411,0	21,4	kvant
Příklad 284	969	C23 H25 C1 N4 02	425,0	27,6	kvant
Příklad 285	970	C22 H27 C1 N4 02	415,0	28,6	kvant
Příklad 286	971	C23 H29 C1 N4 02	929,0	27,9	kvant
Příklad 287	972	C20 H23 C1 N4 02	387,0	26,2	kvant
Příklad 288	973	C21 H25 C1 N4 02	401,0	26,8	kvant
Příklad 289	974	C20 H23 C1 N4 02	387,0	26,6	kvant
Příklad 290	975	C21 H25 C1 N4 02	901,0	28,2	kvant
Příklad 291	976	C22 H23 C1 N9 02	411,0	29,2	kvant
Příklad 292	977	C23 H25 C1 N9 02	425,0	29,5	kvant

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Příklad 293	978	C20 H21 C1 N6 02	413,0	2,2	11
Příklad 294	979	C21 H23 C1 N6 02	927,0	10,2	48
Příklad 295	980	C22 H25 C1 N4 03	429,0	28,8	kvant
Příklad 296	981	C23 H27 C1 N4 03	443,0	11,9	54
Příklad 297	982	C22 H27 C1 N4 02	915,0	27,9	kvant
Příklad 298	983	C23 H29 C1 N9 02	929,5	28,1	kvant
Příklad 299	984	C21 H24 C1 N3 03	402,0	27,7	kvant
Příklad 300	985	C22 H26 C1 N3 03	416,0	28,6	kvant
Příklad 301	1149	C21 H28 N9 04	401	15,5*	38
Příklad 302	1150	C21 H28 N4 03	385	10,9*	28
Příklad 303	1151	C21 H25 F3 N9 03	439	17,3*	39
Příklad 304	1152	C21 H24 F N5 03	915	12,7*	30
Příklad 305	1153	C21 H24 C1 NS 03	430	17,5*	41
Příklad 306	1154	C22 H27 N5 03 04	410	20,6*	50
Příklad 307	1155	C19 H23 F3 N9 S2	429	13,8*	32
Příklad 308	1156	C21 H30 N9 04	403	17,7*	43
Příklad 309	1157	C18 H24 N4 03	409	12,6*	30
Příklad 310	1158	C19 H23 C12 N5 03	440	16,9*	38
Příklad 311	1159	C22 H31 NS 06	462	38,6*	85
Příklad 312	1160	C20 H26 Br N5 03	464	20,4	45
Příklad 313	1289	C20 H27 NS 04	403	5,8*	14
Příklad 314	1290	C21 H29 N5 03	900	6,9*	17
Příklad 315	1291	C24 H28 N4 02	405	22,4	68
Příklad 316	1292	C22 H27 Br N4 02	461	23,8	15
Příklad 317	1293	C22 H23 F4 N3 02	438	20,9	59
Příklad 318	1294	C22 H23 F4 N3 02	438	20,8	59
Příklad 319	1295	C23 H31 N3 03	39B	17,5	54
Příklad 320	1296	C20 H25 N3 02 S2	404	18,8	S8
Příklad 32I	1297	C21 H24 F3 N3 03	424	18,1	53
Příklad 322	1388	C21 H32 N6 03	417	7,4*	24

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Příklad 323	1389	C19 H22 N6 04	399	15,2	48
Příklad 324	1401	C23 H25 C1 N4 02	425	8,3*	16
Příklad 325	1402	C29 H32 N9 05	457	8,3*	15
Příklad 326	1403	C20 H24 N4 02	353	14,8	52
Příklad 327	1404	C20 H24 N4 02	353	17,0	60
Příklad 328	1405	C21 H26 N4 02 S	399	17,3	54
Příklad 329	1407	C22 H28 N4 02 S	413	19,1	57
Příklad 330	1410	C19 H24 N4 03	357	9,7*	59
Příklad 331	1769	C22 H26 C1 F3 N4 05	519	11,6*	20
Příklad 332	1770	C26 H28 C12 N6 04	559	13,1*	21
Příklad 333	1771	C26 H37 N5 04	484	12,7*	23
Příklad 334	1772	C28 H39 N5 04	510	5,5*	9
Příklad 335	1773	C28 H37 N5 04	509	6,2*	11
Příklad 336	1774	C28 H34 N6 06	551	13,6*	22
Příklad 337	2039	C19 H24 N9 02	341	5,2*	14
Příklad 338	2090	C22 H27 N3 04	398	2,0*	5
Příklad 339	2041	C23 H29 N3 03	396	6,2*	15
Příklad 340	2042	C25 H37 N3 02	413	2,6*	6
Příklad 341	2043	C29 H31 N3 02	394	6,8*	17
Příklad 342	2044	C25 H28 N4 04	449	8,7*	16
Příklad 343	2095	C26 H29 C1 N6 09	525	11,4*	19
Příklad 344	2046	C27 H32 N6 04	505	7,7*	13
Příklad 345	2047	C28 H32 N4 O4	489	10,0*	18
Příklad 346	2048	C28 H37 N5 05	524	3,7*	6
Příklad 347	2049	C28 H37 N5 04	509	5,3*	9

* Výtěžek TFA soli.

Příklad 348: Příprava (R)-1-(4-chlorbenzyl)-3-[{N-(2-amino-5-chlorbenzoyl)glycyl}amino]--pyrolidinu (Sloučenina č. 1084).

K roztoku (R)-1-(4-chlorbenzyl)-3-(glycylamino)pyrolidinu (0,050 mmol) v $CHCl_3$ (2 ml) se přidala 2-amino-5-chlorobenzoová kyselina (0,060 mmol) a diisopropylkarbodiimid (0,060 mmol). Reakční směs se míchala při laboratorní teplotě 15 h. Reakční směs se nanesla na sloupec Varian SCX a promývala se CH_3 OH (15 ml). Produkt se eluoval použitím 2 N NH_3 v CH_3 OH (5 ml) a po zakoncentrování se získal žádaný (R)-1-(4-chlorbenzyl)-3-{N-(2-amino-5--chlorbenzoyl)--glycyl)amino]pyrolidin (Sloučenina č,1**084)** (12.7mg, 60%): Čistota produktu se určila pomocí RPLC/MS (87%); ESI/MS m/e 421,0 (M^+ +H, $C_{20}H_{22}Cl_2N_4O_2$).s

Příklady 349 až 361:

Sloučeniny podle vynálezu se syntetizovaly podle metod Příkladu 348 za použití odpovídajících reaktantů v daném pořadí Jestliže zůstával v reakční směsi výchozí amin, směs se podrobila působení isokyanatomethylovanému polystyrenu (50 mg) v $CHCl_3$ (1 ml) při pokojové teplotě, následnou filtrací a koncenrováním vzorku se získal požadovaný materiál. ESI/MS data a výtěžky jsou shrnuty v tabulce 6.

Tabulka 6

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 349	1085	C20 H22 C1 N5 04	432,0	4,1	19
Příklad 350	1086	C20 H23C1N402	387,0	7,9	41
Příklad 351	1087	C22 H23 C1 N4 02	411,0	15,0	73
Příklad 352	1088	Cl8 H20 C1 N3 03	362,0	12,9	71
Příklad 353	1089	C22 H22 C1 F N4 02	429,0	16,0	75
Příklad 354	1090	C22 H26 C1 N3 03	416,0	15,8	76
Příklad 355	1091	C21H24C12N402	435,0	10,9	50
Příklad 356	1092	C21 H24 C1 N5 04	446,0	7,9	35
Příklad 357	1093	C21 H25 C1 N4 O2	401,0	9,5	47
Příklad 358	1094	C23 H25 C1 N4 02	425,0	15,8	79
Příklad 359	1095	C19 H22 C1 N3 03	376,0	13,5	72

Příklad 360	1096	C23 H24 C1 F N4 02	443,0	11,8	53
Příklad 361	1097	C23 H28 C1 N3 O3	430,0	15,1	70

Příklad 362: Příprava (R)-1-(4-chlorbenzyl)-3-[{N-(3-brom-4methylbenzoyl)glycyl}--amino]pyrolidinu (Sloučenina č. 1098).

K roztoku (R)-1-(4-chlorbenzyl)-3-(glycylamino)pyrolidinu (0,050 mmol) v $CHC1_3$ (1.35 ml) a terc-butanolu (0,15 ml) se přidala 3-brom-4-methylbenzoová kyselina (0,060 mmol), diisopropylkarbodiimid (0,060 mmol) a HOBt (0,060 mmol). Reakční směs se míchala při laboratorní teplotě 15 h. Reakční směs se nanesla na sloupec Varian SCX a promývala se CH_3 OH/$CHCl_3$ (12 ml). Produkt se eluoval použitím 2 N NH_3 v CH_3 OH (5 ml) a po zakoncentrování se získal žádaný (R)-1-(4-chlorbenzyl)-3-[(N-(3-brom-4--methylbenzoyl)glycyl)amino}pyrolidin (Sloučenina č. **1098**) (11.6 mg;50%: Čistota produktu se určila pomocí RPLC/MS (94%); ESI/MS m/e 466,0 (M^+ +H, $C_{21}H_{23}Br$ ClN_3O_2).

Příklady 363 až 572:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 362 za použití odpovídajících reaktantů v daném pořadí. Bylo-li třeba, byla pro získání žádaného produktu použita preparativní TLC. ESI/MS data a výtěžky jsou shrnuty v tabulce 7.

Jako vepodlejší produkty daných reakcí se získaly následující tři sloučeniny: sloučenina č. **1415, 1416** a **1417**.

1419: 7,9 mg, 38% výtěžek, ESI/MS m/e 419,0 ($C_{20}H_{23}C1N_4O_2S$).

1420: 7,1 mg, 36% výtěžek, ESI/MS m/e 399,2 ($C_{21}H_{26}N_4O_2S$).

1421: 7,4 mg, 37% výtěžek, ESI/MS m/e 404,2 ($C_{19}H_{25}N_5O_3S$).

Tabulka 7

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek mg)	Výtěžek %
Příklad 363	1099	C20 H20 Br CI F N3 02	470,0	3,1	13
Příklad 364	1100	C20 H26 C12F N3 O2.	424,0	3,1	15
Příklad 365	1101	C21 H23 C1 I N3 02.	512,0	12,5	49
Příklad 366	1102	C21 H23 C1 N4 04	431,2	7,7	36
Příklad 367	1103	C22 H26 Br N3 O2	446,0	13,8	62
Příklad 368	1104	C21 H23 Br F N3 O2	950,0	16,5	79
Příklad 369	1105	C21 H23 C1 F N3 02.	404,2	19,7	73
Příklad 370	1106	C22 H26 I N3 O3	492,0	18,5	75
Příklad 371	1107	C22 H26 N4 O4	411,2	15,2	74
Příklad 372	1108	C20 H25 Br N4 03	449,0	12,8	57
Příklad 373	1109	C19 H22 Br F N4 03	455,0	16,2	71
Příklad 374	1110	C19 H22 C1 F N4 03	409,2	14,4	70
Příklad 375	1111	C20 H25 I N4 03	497,0	17,9	72
Příklad 376	1112	C20 H25 N5 05	416,2	14,9	72
Příklad 377	1113	C23 H27 Br C1 N3 02	494,0	16,1	65
Příklad 378	1114	C22 H24 Br C1 F N3 02	498,0	20,2	81
Příklad 379	1115	C22 H24 C12 F N3 02	452,2	18,6	82
Příklad 380	1116	C23 H27 C1 I N3 02	539,1	21,9	81
Příklad 381	1117	C23 H27 C1 N4 04	459,2	18,7	81
Příklad 382	1171	C21 H23 Br C1 N3 03	466,0	9,9	21
Příklad 383	1172	C22 H23 C1 N4 03	427,2	16,1	75
Příklad 384	1173	C23 H25 C1 N4 03	441,2	22,8	kvant
Příklad 385	1174	C20 H22 C1 F N4 02	405,2	21,4	kvant
Příklad 386	1175	C22 H26 Br N3 02	446,0	15,8	71
Příklad 387	1176	C23 H26 N4 03	407,2	17,6	87

Příklad 388	1177	C24 H22 N4 03	421,2	20,2	96
Příklad 389	1178	C21 H25 F N4 02	385,0	I6,2	84
Příklad 390	1179	C21 H25 N5 04	412,2	2,3	11
Příklad 391	1180	C23 H26 N4 02	391,0	21,6	kvant
Příklad 392	1181	C20 H25 Br N4 03	451,0	20,1	9
Příklad 393	1182	C21 H25 N5 04	412,2	13,3	65
Příklad 394	1183	C22 H27 N5 04	426,2	20,9	98
Příklad 395	1184	C19 H24 F N5 03	390,0	20,0	kvant
Příklad 396	1185	C19 H24 A F 05	417,2	18,2	87
Příklad 397	1186	C21 H25 N5 03	396,2	17,6	89
Příklad 398	1187	C23 H27 Br C1 N3 02	494,0	22,1	90
Příklad 399	1188	C24 H27 C1 N4 03	455,2	17,2	76
Příklad 400	1189	C25 H29 C1 N4 0	469,2	21,1	90
Příklad 401	1190	C22 H26 C1 F N402	433,2	20,4.	94
Příklad 402	1217	C21 H20 C12 F3 N3 02	474,0	38,5	81
Příklad 403	1218	C21 H23 C1 F N3 02	404,2	35,6	88
Příklad 404	1219	C21 H23 C12 N3 02	420,0	3,7	9
Příklad 405	1220	C20 H22 C1 I N4 02	513,0	53,0	kvant
Příklad 406	1221	C20 H21 C1 F2 N4 02	423,0	38,7	92
Příklad 407	1222	C19 H23 C1 N4 02	375,2	33,6	90
Příklad 408	1223	C26 H26 C1 N3 02 S	496,0	43,7	88
Příklad 409	1224	C20 H 21 C1 N4 05	433,0	40,6	9
Příklad 410	1225	C22 H23 C1 F3 N3 O2	954,2	18,4	41
Příklad 411	1226	C22 H26 F N3 O2	389,0	17,1	45
Příklad 412	1227	C22 H25 C1 N3 02	400,2	17,5	44
Příklad 413	1228	C21 H25 I N4 02	493,0	23,3	47
Příklad 414	1229	C21 H24 F2 N4 02	403,2	18,4	46
Příklad 415	1230	C20 H26 N4 02	355,2	15,7	44
Příklad 416	1231	C27 H29 N3 02 S	476,0	20,9	88
Příklad 417	1232	C21 H24 N4 O5	913,0	19,9	96

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Příklad 418	1233	C20 H22 C1 F3 N4 03	459,0	19,4	85
Příklad 419	1234	C20 H25 F N4 03	389,0	17,8	92
Příklad 420	1235	C20 H25 C1 N4 03	405,2	18,7	92
Příklad 421	1236	Cl9 H24 I N5 03	498,0	23,9	96
Příklad 422	1237	C19 H23 F2 N5 03	408,2	19,0	93
Příklad 423	1238	C18 H25 N5 03	360,0	16,3	91
Příklad 424	1239	C25 H28 N4 O3 S	481,2	21,4	89
Příklad 425	1240	C19 H23 N5 O6	418,0	19,9	95
Příklad 426	1241	C23 H24 C12 F3 N3 O3	502,0	22,5	90
Příklad 427	1242	C23 H27 C1 F N3 02	932,2	21,2	98
Příklad 428	1243	C23 H27 C12 N3 02	448,0	21,6	96
Příklad 429	1244	C22 H25 C1 I N4 02	541,0	26,4	98
Příklad 430	1245	C22 H25 C1 F2 N4 02	451,0	21,3	94
Příklad 431	1246	C21 H27 C1 N4 02	403,2	19,4	96
Příklad 432	1247	C22 H25 C1 N3 02 S	524,0	24,7	99
Příklad 433	1248	C22 H25 C1 N4 05	461,0	20,7	90
Příklad 434	1249	C20 H20 C12 N9 04	451,0	7,4	33
Příklad 435	1250	C21 H23 C1 N4 04	431,2	15,5	72
Příklad 436	1251	C19 H22 C1 N5 05	436,0	22,9	kvant
Příklad 437	1252	C23 H28 C1 N3 02	414,2	17,9	86
Příklad 438	1253	C24 H31 N3 02	394,2	15,8	80
Příklad 439	1254	C22 H30 N4 03	399,2	17,3	87
Příklad 440	1255	C20 H22 Br C1 N4 02	467,0	21,3	91
Příklad 441	1256	C21 H25 Br N4 02	445,0	20,7	93
Příklad 442	1257	C19 H24 Br N5 03	450,0	21,8	97
Příklad 443	1258	C21 H25 C1 N9 02	401,2	18,1	90
Příklad 494	1259	C19 H24 C1 N5 03	906,0	20,1	99
Příklad 445	1260	C23 H29 N3 03	396,2	16,8	85
Příklad 446	1261	C23 H30 C1 N3 03	432,2	19,8	92
Příklad 447	1262	C24 H33 N3 03	412,2	17,9	85

Příklad 448	1263	C22 H32 N4 04	417,2	18,7	90
Příklad 449	1264	C25 H26 CI N3 03	452,2	29,1	kvant
Příklad 450	1265	C26 H29 N3 03	432,2	18,1	84
Příklad 451	1266	C24 H28 N4 04	437,2	19,3	88
Příklad 452	1267	C23 H22 C1 F3 N4 03	495,2	20,6	83
Příklad 453	1268	C21 H23 C12 N3 O3	436,0	17,5	80
Příklad 454	1269	C20 H21 Br C1 N3 03	468,0	19,2	82
Příklad 455	1270	C20 H21C12 N3 03	422,2	17,3	82
Příklad 456	1271	C20H20C1FN404	435,0	17,1	79
Příklad 457	1272	C29 H25 F3 N4 03	975,2	21,7	91
Příklad 458	1273	C22 H26 C1 N3 03	416,2	17,8	86
Příklad 459	1274	C21 H24 Br N3 O3	948,0	19,5	87
Příklad 460	1275	C21 H24 C1 N3 O3	402,2	16,7	83
Příklad 461	1276	C21 H21 F N4 04	415,2	18,1	87
Příklad 462	1277	C22 H24 F3 N5 04	480,2	20,3	85
Příklad 463	1278	C20 H25 C1 N4 04	421,2	18,6	88
Příklad 464	1279	C19 H23 Br N4 04	451,0	21,3	94
Příklad 465	1280	C19 H23 C1 N4 04	407,2	19,1	94
Příklad 466	1281	C19 H22 F N5 05	920,2	19,1	91
Příklad 467	1282	C25 H26 C1 F3 N4 03	523,2	25,0	96
Příklad 468	1283	C23 H27 C12 N3 03	464,2	12,2	53
Příklad 469	1284	C22 H25 Br C1 N3 03	496,0	29,1	97
Příklad 470	1285	C22 H25 C12 N3 03	450. 2	21,8	97
Příklad 471	1321	C20 H20 Br C12 N3 02	486,0	5,1	21
Příklad 472	1322	C21 H23 C12 N3 O2	920. 0	10,5	50
Příklad 473	1323	C20 H20 C12 I N302	532,0	7,1	27
Příklad 474	1324	C21 H24 C1 N3 03	402,2	22,2	kvant
Příklad 475	1325	C27 H26 CI N3 O3	976,0	22,2	93
Příklad 476	1326	C20 H21 C1 I N3 03	514,0	26,9	kvant
Příklad 477	1327	C21 H25 C1 N4 02	401,2	24,2	kvant

Příklad 478	1328	C21 H23 Br C1 N3 02	466,0	23,1	99
Příklad 479	1329	C22 H26 C1 N3 02	400,2	16,4	82
Příklad 480	1330	C21 H23 CI I N3 O2	512,2	20,8	81
Příklad 481	1331	C21 H24 N3 03	382,2	19,6	kvant
Příklad 482	1332	C22 H24 N3 O3	456,2	21,1	93
Příklad 483	1333	C21 H24 I N3 03	494,0	25,3	kvant
Příklad 484	1334	C22 H22 N4 02	381,2	19,0	kvant
Příklad 485	1335	C19 H22 Br C1 N4 03	471,0	25,8	kvant
Příklad 486	1336	C20 H25 C1 N4 03	905,2	18,5	91
Příklad 487	1337	C19 H22 C1 I N4 03	517,0	23,1	89
Příklad 488	1338	C20 H26 N4 04	387,2	20,6	kvant
Příklad 489	1339	C19 H 28 N4 O4	461,2	23,7	kvant
Příklad 490	1340	C19 H23 I N4 04	499,0	28,2	kvant
Příklad 491	1341	C20 H26 N4 04	386:0	20,5	kvant
Příklad 492	1392	C22 H24 Br C12 N3 02	514,0	27,2	kvant
Příklad 493	1343	C23 H27 C12 N3 02	448,0	21,4	95
Příklad 494	1344	C22 H24 C12 I N3 02	560,0	27,0	96
Příklad 495	1345	C23 H28 C1 N3 03	430,2	23,8	kvant
Příklad 496	1346	C22 H25 C1 I N3 03	592,0	29,4	kvant
Příklad 497	1347	C19 H22 C1 N3 02 S	392,0	16,9	43
Příklad 498	1398	C20 H25 N3 02 S	372,2	6,9	l9
Příklad 499	1399	C18 H24 N4 03 S	377,2	8,1	43
Příklad 500	1350	C21 H26 CI N3 02 S	420,0	I3,0	62
Příklad 501	1351	C22 H24 Br C1 N4 03	509,2	5,0	10
Příklad 502	1352	C23 H27 Br N4 03	489,2	3,6	15
Příklad 503	1353	C21 H26 Br N5 04	494,0	2,8	11
Příklad 504	1354	C24 H28 Br C1 N4 03	537,2	5,2	19
Příklad 505	1355	C21 H22 C1 N5 02	412,0	25,5	kvant
Příklad 506	1356	C22 H25 N5 02	392,0	16,5	84
Příklad 507	1357	C20 H24 N6 03	397,2	19,9	kvant

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Příklad 508	1358	C23 H26 C1 N5 02	440,2	21,8	99
Příklad 509	1368	C21 H20 C12 F3 N3 02	474,0	18,4	78
Příklad 510	1369	C24 H24 C1 F6 I N3 O4	568,0	24,1	85
Příklad 511	1370	C18 H19 Br C1 N3 02 S	458,0	19,4	85
Příklad 512	1371	C26 H26 C1 N3 O4 S	512,2	22,1	86
Příklad 513	1372	C26 H26 C1 N3 02	498,0	19,1	85
Příklad 514	1373	C22 H23 C1 F3 N3 O2	459,2	16,2	71
Příklad 515	1374	C25 H27 F5 I N3 04	548,2	22,1	81
Příklad 516	1375	C19 H22 Br N3 02 S	436,0	17,1	78
Příklad 517	1376	C27 H29 N3 O4 S	492,0	19,9	79
Příklad 518	1377	C27 H29 N3 02	428,2	18,1	85
Příklad 519	1378	C20 H22 CI F3 N4 03	459,0	17,3	75
Příklad 520	1379	C23 H25 F6 I N4 05	553,2	21,0	76
Příklad 521	1380	C17 H21 Br N4 03 S	443,0	16,4	74
Příklad 522	1381	C25 H28 N4 05 S	497,0	18,9	79
Příklad 523	1382	C25 H28 N4 03	433,2	17,3	80
Příklad 524	1383	C23 H24 C12 F3 N3 02	502,0	20,0	80
Příklad 525	1384	C20 H23 Br C1 N3 02 S	486,0	21,0	87
Příklad 526	1385	C28 H30 C1 N3 O4 S	590,2	23,8	88
Příklad 527	1386	C28 H30 C1 N3 02	976,0	20,0	84
Příklad 528	1911	C22 H24 C12 N4 02	463,0	0,4	2
Příklad 529	1412	C23 H27 C1 N4 02	443,0	1,3	6
Příklad 530	1413	C21 H25 C1 N5 O4	448,0	1,1	5
Příklad 531	1414	C24H23 C12 N4 03	491,0	0,8	3
Příklad 532	1415	C21H22 C1 N5 02 S	444,0	6,8	31
Příklad 533	1416	C22 H25 N5 02 S	429,0	4,8	23
Příklad 534	1417	C30 H24 N6 03 S	429,2	9,5	21
Příklad 535	1418	C23 H26 C1 N5 02 S	472,0	10,4	44
Příklad 536	1423	C27 H26 C1 N3 03	476,0	23,9	kvant
Příklad 537	1424	C27 H29 N3 04 S	456,2	28,0	kvant

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Příklad 538	1425	C26 H28 N4 04	461,2	22,3	97
Příklad 539	1426	C29 H30 C1N303	509,2	26,8	kvant
Příklad 540	1583	C21 H22 C1 F3 N4 02	455,0	14,6	64
Příklad 541	1584	C21 H22 C1 F3 N4 03	471,0	17,4	74
Příklad 542	1585	C19 H20 BrC1N402	453,0	15,6	69
Příklad 543	1586	C19 H20 C12N4 02	407,2	2,3	11
Příklad 544	1587	C26 H26 C1N3 03	464,0	15,4	66
Příklad 545	1588	C20 H23 C1 N4 02	387,0	14,8	77
Příklad 546	1589	C22 H25 F3 N4 02	435,2	11,1	51
Příklad 547	1590	C20 H25 F3 N4 03	451,2	16,3	72
Příklad 548	1591	C20 H23 Br N4 02	433,0	15,9	71
Příklad 549	1592	C20 H23 C1 N402	387,0	15,6	81
Příklad 550	1593	C27 H29 N3 03	444,2	14,8	67
Příklad 551	1594	C20 H24 F3 N503	440,2	16,2	74
Příklad 552	1595	C20 H24 F3 N504	456,2	15,4	68
Příklad 553	1596	C18 H22 Br N503	436,0	15,6	72
Příklad 554	1597	C18 H22 C1 N503	391,8	14,4	73
Příklad 555	1598	C25 H28 N9 04	949,2	15,9	71
Příklad 556	1599	C19 H25 N5 03	372,2	15,8	85
Příklad 557	1606	C21 H21 C1 F3 N3 02 S	472,0	17,0	72
Příklad 558	1607	C21 H21 C1 F3 N3 02 S	452,2	15,3	68
Příklad 559	1608	C20 H23 F3 N403 S	457,2	15,9	70
Příklad 560	1660	C21 H22 Br F3 N4 02	501,0	19,0	76
Příklad 561	1661	C21 H22 Br F3 N4 03	517,0	16,2	63
Příklad 562	1662	C20 H21 Br F2 N4 02	469,0	15,1	65
Příklad 563	1663	C20 H22 Br Cl N4 02	967,0	14,5	62
Příklad 564	1692	C20 H23 Br2 N3 03	514,0	7,3	28
Příklad 565	1693	C22 H26 F2 N902	417,0	16,2	78
Příklad 566	1694	C22 H27 F N4 02	399,0	21,8	kvant
Příklad 567	1695	C22 H27 BrN402	459,0	24,5	kvant

Příklad 568	1696	C22 H27 I N4 02	507,0	27,4 kvant
Příklad 569	1697	C22 H27 C1N402	915,0	22,1 kvant
Příklad 570	1698	C23 H27 F3 N403	465,0	29,3 kvant
Příklad 571	1699	C23 H27 F3 N4 02	449,0	25,3 kvant
Příklad 572	1700	C22 H25 Br C1 N3 02	480,0	17,8 79

Například, Sloučenina č. 1583 vykazovala následující NMR spektra: ^{1}H NMR (400 MHz, CD_3 OD) d□1,64-1,72 (m, 1 H), 2,20-2,30 (m, 1 H), 2,41-2,51 (m, 2 H), 2,71-2,78 (m, 2 H), 3,59 (dd, J = 15,4, 12,9 Hz, 2 H), 3,94 (s, 2 H), 4,35- 4,41 (m, 1 H), 6,82 (d, J = 8,6 Hz, 1 H), 7,29 (s, 4 H), 7,40 (dd, J = 8,6, 1,7 Hz, 1 H), 7,85 (d, J = 0,96 Hz, 1 H).

Referenční příklad 4 :Příprava (S)-3-[N-{3(trifluormethyl)benzoyl}glycyl]aminopyrolidinu

Suspenze (S)-1-(4-chlorbenzyl)-3-[N-(3(trifluormethyl)benzoyl)glycyl)aminopyrolidinu (2,93 g, 6.66 mmol) a $Pd(OH)_2$ v 5% $HC0_2H$/methanolu (70 ml) se míchala při 60 °C po dobu 3 h. Pd katalyzátor se odfiltroval přes Celite a filtrát se zakoncentroval. K zakoncentrovanému zbytku se přidal 2N vodný roztok NaOH (100 ml) a směs se extrahovala ethylacetátem (100 ml x 3) . Spojené extrakty se promyly solným roztokem, vysušily pomocí bezvodého síranu sodného, přefiltrovaly a zakoncentrovaly. Po chromatografii na sloupci ($Si0_2$, AcOEt/MeOH/Et_3N = 85/10/5-60/30/5) byl získán (S)-3-[N-(3-(trifluormethyl)benzoyl)glycyl]aminopyrolidin (1.70 g, 81%) ve formě oleje: ^{1}HNMR ($CDC1_3$, 270 MHz) δ1.76 (d, J= 7.3 Hz, 1 H), 2,07-2.25 (m, 1 H), 2.81- 2,98 (m, 2 H), 3,02-3,11 (m, 2 H), 4,12 (s, 2 H), 4.41 (br, 1 H1), 6,90 (br, 1H), 7.45 (br, 1 H), 7,58 (dd, J = 7.3 a 7.3 Hz,1 H), 7.77 (d, J = 7.3 Hz, 1 H) , 8,02 (d, J = 7.3 Hz, 1 H) , 8. 11 (s, 1 H); ESI/MS m/e 316,0 (M^+ +H, $C_{14}H_{16}F_3aN_30_2$).

(R)-3-[N-{3-(trifluormethyl)benzoyl)glycyl]aminopyrolidin se také připravil pomocí výše popsané metody a odpovídajícího reaktantu: 1.49 g, 68%; produkt vykazoval stejné 1H NMR a ESI/MS jaké byly zjištěny pro (S)-isomer.

(R)-3-[N-{2-amino-5-(trifluormethyl)benzoyl)glycyl]aminopyrolidin byl také připraven pomocí výše popsané metody a odpovídajícího reaktantu: 316 mg, 93%; ESI/MS m/e 331.2 (M^++H, $C_{14}H_{17}F_3N_40_2$) .

(R)-3-[N-(2-(terc-butoxykarbonylamino)-5-(trifluormethoxy)benzoyl)glycyl]aminopyrolidin byl také připraven pomocí výše popsané metody a odpovídajícího reaktantu: : kvant; 1H NMR ($CDCl_3$, 400 MHz) δ 1,51 (s, 9 H), 1.60-1.70 (m, 2 H), 2,10-2.25 (m, 1 H), 2.80-2.88 (m, 1 H), 2.89-2,98 (m, 1 H), 3,04-3,18 (m, 2 H), 4,05 (d, J = 4,9 Hz, 2 H), 4.43 (br, 1 H), 6,15 (br, 1 H), 7,03 (br, 1 H), 7.32 (d, J = 9.3 Hz, 1 H), 7.38 (s, 1 H), 8.42 (d, J = 9.3 Hz, 1 H).

Příklad 573: Příprava (R)-3-[{N-(2-(terc-butoxykarbonylamino)-5-trifluormethyl--benzoyl)glycyl}amino]-1-(4-chlorobenzyl)pyrolidinu.

K roztoku (R)-1-(4-chlorbenzyl)-3-(glycylamino)pyrolidinu (5,0g, 18.7 mmol) v dichlormethanu (100 ml) se přidal Et_3N (2. 9 ml, 20. 5 mmol) , 2-(terc-butoxykarbonylamino)-5-trifluormethyl)--benzoová kyselina (6.27 g, 20,5 mmol), EDCI (3,9 g, 20,5 mmol) a HOBt (2.8 g, 20,5 mmol) . Směs se míchala při pokojové teplotě přes noc. Poté se do reakční směsi přidal vodný roztok 2 N NaOH (80 ml) a směs se extrahovala dichlormethanem. Extrakt se vysušil pomocí bezvodého síranu sodného, přefiltroval a odpařil se. Po chromatografii na sloupci (SiO_2, hexan/ethylacetát 1/1-1/4) se získal požadovaný produkt (R)-3-[(N-(2-(terc-butoxykarbonylamino)-5-trifluormethylbenzoyl) -glycyl)amino]-1-(4-chlorobenzyl)pyrolidin (9,41 g, 91%) jako bílá amorfní pevná látka: ESI/MS m/e 555.2 (M^++H, $C_{26}H_{30}C1F_3N_4O_4$).

Referenční příklad 5: Příprava (R)-3-[{N-(2-(terc-butoxykarbonylamino)-5-trifluor--methylbenzoyl)glycyl}amino]pyrolidinu.

Směs (R)-3-[(N-(2-(terc-butoxykarbonylamino)-5- trifluormethylbenzoyl)glycyl)amino}-1-(4--chlorobenzyl)pyrolidinu, (6,3 g, 11,4 mmol), $Pd(OH)_2$ (1,68 g), HCO_2H (3,7 ml) a methanolu (80 ml) se míchala při 50 °C přes noc.Po ochlazení reakční směsi na pokojovou teplotu se odfiltroval Pd katalyzátor přes Celite a filtrát se zakoncentroval. Po chromatografii na sloupci (SiO_2, AcOEt/MeOH = 5/1-4/1 byl získán (R)-3-[(N(2-(terc-butoxykarbonylamino)-5-trifluormethylbenzoyl)--glycyl)amino}pyrolidin (4,42 g, 90%) jako bílá pevná látka: ^{1}H NMR ($CDC1_3$, 400 MHz) δ 1,48 (s, 9 H), 2,0-2,4 (m, 2 H), 3,42-3,71 (m, 5 H), 4,00-4,22 (m, 2 H), 4,56 (br, 1 H), 7,48 (d, J = 9,0 Hz, 1 H), 7,93 (s, 1 H), 8. 17 (br, 1 H) , 8. 33 (d, J = 9. 0 Hz, 1 H) , 8. 45 (br, 1 H).

Příklad 574: Příprava (S)-1-benzyl-3-[N-{3(trifluormethyl)benzoyl}glycyl]aminopyrolidinu (Sloučenina č. 239).

Roztok (S)-3-[N-(3-(trifluormethyl)benzoyl)glycyl]aminopyrolidinu (0,060mmol) v CH_3CN (1,1 ml) a (piperidinmethyl)polystyrenu (2.6-2.8 mmol/g, 30 mg) se přidal k roztoku benzylbromidu (0,50 nmol) v CH_3CN (0.4 ml). Reakční směs se míchala při 45 °C po dobu 5h. Po zchlazení reakční směsi na pokojovou teplotu se pryskyřice odstranila filtrací a filtrát se zakoncentroval. Reziduum bylo rozpuštěno v CH_3CN (1,0 ml) a bylo přidáno (0,008 ml), 0,05 nmol) fenylisokyanátu . Směs se míchala při pokojové po dobu 1 h., poté se nanesla na sloupec Varian SCX , který se promýval CH_3OH (15 ml). Produkt se z kolony eluoval použitím 2 N NH_3 v CH_3OH (6 ml)a po zakoncentrování se obdržel žádaný produkt (S)-1-benzyl-3-[N-{3-(trifluormethyl)benzoyl}glycyl)aminopyrolidinu (Sloučenina č. **239**). (9,0 mg,44%): Čistota produktu se určila pomocí RPLC/MS (99%); ESI/MS m/e 406,0 (M^+ +H, $C_{21}H_{22}F_3N_3O_2$).

Příklad: Příprava (R)-1-(butylbenzyl)-3-[N-{3-(trifluormethyl)benzoyl}glycyl]aminopyrolidinu (Sloučenina č. 1648).

Ke směsi (R)-3-[N-{3-(trifluormethyl)benzoyl}glycyl)aminopyrolidinu (0,050 mmol), 4--butylbenzaldehyde (0,18 mmol), $NaBH_3CN$ (0.23 mmol) a methanolu (1.85 ml) se přidá kyselina octová (0,060 ml). Reakční směs se míchá při 60 °C po dobu 12 h. Po zchlazení reakční směsi na pokojovou teplotu se reakční směs nanesla na sloupec Varian SCX , který se promýval CH_3OH (15 ml). Produkt se z kolony eluoval použitím 2 N NH_3 v CH_3OH (5 ml) a po zakoncentrování se obdržel žádaný produkt (R)-1-(4-butylbenzyl)-3-[{N-(3-trifluromethylbenzoyl)glycyl}amino]pyrolidin (Sloučenina č. **1648**) (20.6 mg, 89%): (mg,44%): Čistota produktu se určila pomocí RPLC/MS (99%); ESI/MS m/e 462.2 (M^+ +H, $C_{25}H_{30}F_3N_3O_2$).

Příklady 576 až 738:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 574 nebo 575 za použití odpovídajících reaktantů v daném pořadí. Bylo-li třeba, byla pro získání žádaného produktu použita preparativní TLC nebo HPLC –C_{18}. ESI/MS data a výtěžky jsou shrnuty v tabulce 8.

Tabulka 8

03.07.00

Sloučenina č.		Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 576	240	C21 H21 F4 N3 O2	424,0	10,2	48
Příklad 577	241	C21 H2 C1F3 N3 02	440,0	12,1	55
Příklad 578	242	C21H26 C12 F3 N3 O2	479,0	13,9	59
Příklad 579	243	C21H26 C12F3 N3 02	474,0	13,8	58
Příklad 580	244	C22 H24 F3 N3 02	420,0	13,1	62
Příklad 581	245	C21 H21 F4 N3 02	424,0	11,9	56
Příklad 582	246	C21 H21 C1 F3 N3 02	440,0	8,5	39
Příklad 583	247	C21H29C12 F3 N3 02	979,0	10,5	44
Příklad 584	248	C22 H24 CF3 N3 O3	436,0	11,0	51
Příklad 585	249	C22 H21 C1 F6 N302	474,0	12,8	54
Příklad 586	250	C22 H24 F3 N3 02	420,0	11,0	52
Příklad 587	251	C21H21 F4 N3 02	424 . 0	13,5	64
Příklad 588	252	C22 H24 F3 N3 O3	936. 0	11,8	54
Příklad 589	253	C22 H24 F3 N3 O2	420,0	11,1	53
Příklad 590	254	C21H20C1F3 N3 04	485,0	2,9	10
Příklad 591	255	C21 H21 F3 N4 04	951,0	12,2	54
Příklad 592	256	C21 H21 F3 N4 O4	451,0	11,4	51
Příklad 593	257	C22 H21 F6 N3 O2	474,0	11,1	47
Příklad 594	258	C24 H26 F3 N3 04	478,0	15,3	64
Příklad 595	259	C22 H23 C1F3 N3 O2	920,0	6,4	31
Příklad 596	260	C21 H20 C12 F3 N3 02	474,0	12,1	51
Příklad 597	261	C22 H21 C1 F6 N3 O2	474. 0	13,6	57
Příklad 598	262	C21 H21 Br F3 N3 O2	984,0	15,2	63
Příklad 599	263	C21 H21 Br F3 N3 O2	984,0	14,5	60
Příklad 600	264	C27 H26 F3 N3 03	498,0	9,3	37
Příklad 601	265	C21 H21 Br F3 N3 O2	489,0	11,6	48
Příklad 602	266	C22 H22 F3 N3 04	450,0	8,9	40
Příklad 603	267	C22H24 F3 N3 03	936,0	10,3	47

Příklad 604	268	C23 H25 F3 N4 03	463,0	6,3	27
Příklad 605	269	C22 H24 F3 N3 04 S	484,0	8,0	33
Příklad 606	270	C23 H24 F3 N3 O4	442,0	g.g	38
Příklad 607	271	C2l H20 F5 N3 02	442,0	6,1	28
Příklad 608	272	C21H22 F3 N3 O3	922,0	I3,6	59
Příklad 609	273	C22 H21 F3 N4 02	431,0	12,6	59
Příklad 610	274	C22 H21 F3 N4 02	431,0	7,7	36
Příklad 611	275	C22 H21 F3 N4 02	431,0	12,7	59
Příklad 612	276	C2l H20 F5 N3 02	442,0	11,7	53
Příklad 613	277	C27 H26 F3 N3 02	482. 0	9,5	39
Příklad 614	278	C23 H24 F3 N3 04	464,0	13,0	56
Příklad 615	279	C22 H21 F5 N3 03	490,0	10,4	42
Příklad 616	280	C22 H2I F6 N3 O3	490,0	12,0	49
Příklad 617	281	C22 H22 F3 N3 O4	450,0	4,9	22
Příklad 618	282	C25 H30 F3 N3 O2	462,0	12,0	52
Příklad 619	283	C20 H23 F3 N4 O3	425,0	8,1	38
Příklad 620	289	C27 H25 C1 F3 N3 02	516,0	4,8	19
Příklad 621	285	C21 H22 F3 N3 O2	406,0	9,8	24
Příklad 622	286	C2l H21 F4 N3 02	424,0	4,5	21
Příklad 623	287	C21 H21 C1 F3 N3 O2	940,0	5,8	26
Příklad 624	288	C21 H20 C12 F3 N3 O2	474,0	8,1	39
Příklad 625	289	C21 H26 C12 F3 N3 O2	474, 0	8,0	34
Příklad 626	290	C22H24F3 N3 02	920,0	6,0.	28
Příklad 627	291	C21 H2l F4N302	924,0	6,2	29
Příklad 628	292	C21 H21 C1 F3 N3 02	440,0	4,5	20
Příklad 629	293	C23 H29 C12 F3 N3 02	474,0	5,1	22
Příklad 630	294	C22 H24 C F3 N3 O3	436,0	4,2	19
Příklad 631	295	C22 H21C1 F6 N3 02	974,0	6,0	25
Příklad 632	296	C22 H24 F3 N3 02	420,0	4,3	21
Příklad 633	297	C21H21 F3 N3 02	424,0	8,2	39

Příklad 634	298	C22 H24 F3 N3 03	436,0	12,2	56
Příklad 635	299	C22 H24 F3 N3 02	420,0	8,1	39
Příklad 636	300	C21 H20 CI F3 N4 04	85,0	13,7	57
Příklad 637	301	C21H21 F3 N4 04	451,0	15,1	67
Příklad 638	302	C21 H21 F3 N4 04	451,0	16,6	74
Příklad 639	303	C22 H21F6 N3 02	479,0	12,6	53
Příklad 640	304	C24 H26 F3 N3 O4	478,0	14,5	61
Příklad 641	305	C22 H23 C1 F3 N3 O2	420,0	8,4	37
Příklad 642	306	C21 H20 C12 F3 N3 02	474,0	13,5	57
Příklad 643	307	C22 H21 C1 F6 N3 02	474,0	3,7	16
Příklad 644	308	C2l H21 Br F3 N3 02	489,0	7,2	30
Příklad 645	309	C21 H21 BrF3 N3 O2	484,0	6,7	28
Příklad 646	310	C27 H26 F3 N3 O3	498,0	4,2	17
Příklad 647	311	C21 H21 Br F3 N3 02	484,0	6,3	26
Příklad 648	312	C22 H22 F3 N3 04	450,0	2,9	11
Příklad 649	313	C22 H24 F3 N3 03	436,0	1,9	9
Příklad 650	314	C23 H24 F3 N4 O3	463,0	5,0	22
Příklad 651	315	C22 H24 F3 N3 04 S	484,0	2,5	10
Příklad 652	316	C23 H24 F3 N3 04	464,0	3,3	14
Příklad 653	317	C21 H20 F5 N3 02	442,0	4,5	20
Příklad 654	318	C21 H22 F3 N3 03	422,0	7,9	34
Příklad 655	319	C22 H 21 F3N402	431,0	6,5	30
Příklad 656	320	C22 H21 F3 N4 02	931,0	14,2	66
Příklad 657	321	C22 H21 F3 N4 02	431,0	14,9	69
Příklad 658	322	C21 H20 F5 N3 02	442,0	13,6	62
Příklad 659	323	C27 H26 F3 N3 02	482,0	3,9	16
Příklad 660	324	C23 H24 F3 N3 O4	464,0	15,2	66
Příklad 661	325	C22 H21 F6 N3 03	490,0	16,1	66
Příklad 662	326	C22 H21 F5 N3 03	490,0	13,6	56
Příklad 663	327	C22 H22 F3 N3 O4	450,0	5,4	24

Příklad 664	328	C25 H31 F3 N3 03	462,0	10,9	47
Příklad 665	329	C20 H25 F3 N4 02	425,0	12,0	57
Příklad 666	986	C27 H25 C1 N9 03	516,0	1,5	6
Příklad 667	1118	C28 H27 F3 N4 02	525,0	21,5	62
Příklad 668	1119	C22 H24 F3 N3 09	452,0	16,9	57
Příklad 669	1120	C23 H26 F3 N4 04	466,0	20,5	67
Příklad 670	1121	C22 H23 F3 N3 02	465,0	16,8	55
Příklad 671	1122	C28 H36 F3 F3 N3	504,0	21,0	63
Příklad 672	1123	C25 H23 Br N9 05	534,0	26,6	75
Příklad 673	1124	C19 H19 F3 N3 04	441,0	21,3	73
Příklad 674	1133	C23 H26 F3	467,0	33,6	8q
Příklad 675	1134	C24 H28 F3 N3 05	496,0	34,8	82
Příklad 676	1135	C22 H21 F3 N4 06	495,0	32,6	77
Příklad 677	1136	C23 H24 F3 N3 05	480,0	36,6	89
Příklad 678	1137	C22 H21 Br F3 N3 04	529,0	30,8	69
Příklad 679	1138	C24 H26 F3 N3 02	446,0	32,7	86
Příklad 680	1139	C22 H24 F3 N3 02	420,0	18,6	51
Příklad 681	1140	C21 H20 F3 N5 06	496,0	20,5	49
Příklad 682	1141	C25 H24 F3 N3 02	456,0	22,5	58
Příklad 683	1142	C25 H24 F3 N3 02	456,0	21,6	55
Příklad 684	1143	C35 H34 F3 N3 04	618,0	27,3	53
Příklad 685	1149	C23 H26 F3 N3 04	466,0	25,5	64
Příklad 686	1145	C23 H25 F3 N4 06	511,0	38,0	88
Příklad 687	1146	C28 H28 F3 N3 03	512,0	38,3	89
Příklad 688	1147	C23 H25 F3 N4 03	463,0	27,1	62
Příklad 689	1148	C27 H26 F3 N3 02	482,0	22,4	57
Příklad 690	1161	C22 H24 F3 N3 04	452,0	13,5	58
Příklad 691	1162	C24 H28 F3 N3 03	464,0	16,7	70
Příklad 692	1163	C22 H23 F9 N3 03	454,0	15,8	68
Příklad 693	1164	C23 H26 F3 N3 03	450,0	15,7	68

Příklad 694	1165	C23 H24 F3 N3 04	464,0	16,3	68
Příklad 695	1166	C22 H23 Br F3 N3 03	513,0	15,0	57
Příklad 696	1168	C17 H17 C1 F3 N5 02 S	448,0	6,9*	23
Příklad 697	1169	C20 H22 F3 N5 03 S	470,0	1,7*	6
Příklad 698	1170	C22 H22 F3 N5 02	446,0	2,3*	8
Příklad 699	1286	C26 H33 F3 N4 03	507,0	25,3*	51
Příklad 700	1287	C21 H20 F3 N5 06	496,0	4,0*	8
Příklad 701	1288	C22 H24 F3 N3 04	452,0	3,6*	13
Příklad 702	1298	C23 H25 Br F3 N3 04	544,0	28,4	kvant
Příklad 703	1299	C24 H28 F3 N3 05	496,0	1,4	6
Příklad 704	1300	C23 H26 F3 N3 04	466,0	7,3	33
Příklad 705	1301	C24 H28 F3 N3 05 04	496,0	12,6	53
Příklad 706	1302	C24 H28 F3 N3 03	464,0	24,5	kvant
Příklad 707	1303	C23 H25 Br F3 N3	544,0	22,2	86
Příklad 708	1304	C29 H30 F3 N3 04	542,0	28,6	kvant
Příklad 709	1305	C26 H26 F3 N3 03	486,0	35,9	kvant
Příklad 710	1306	C24 H28 F3 N3 04	480,0	8,1	35
Příklad 711	1307	C23 H26 F3 N3 05	482,0	27,9	kvant
Příklad 712	1308	C23 H24 F3 N3 03	448,0	5,9	28
Příklad 713	1309	C23 H25 F3 I N3 04	592,0	24,0	85
Příklad 714	1310	C22 H24 F3 N3 04	452,0	3,4	16
Příklad 715	1311	C22 H22 F3 N3 04	450,0	3,4	16
Příklad 716	1312	C21 H21 F3 I N3 02	532,0	18,1	72
Příklad 717	1313	C21 H21 Br F3 N3 02	484,0	17,4	76
Příklad 718	1314	C19 H19 F3 N4 09 S	957,0	16,8	77
Příklad 719	1315	C20 H22 F3 N3 03	410,0	13,6	70
Příklad 720	1316	C22 H20 C1 F6 N3 02	508,0	1B,6	77
Příklad 721	1317	C21 H20 C1 F3 N4 04	485,0	17,0	74
Příklad 722	1318	C21 H20 C1 F4 N3 02	458,0	17,0	78
Příklad 723	1319	C21 H20 C1 F4 N3 02	458,0	17,6	81

Příklad 724	1320	C21 H20 Br F4 N3 02	502,0	18,5	77
Příklad 725	1390	C26 H32 F3 N3 02	476,0	16,1	51
Příklad 726	1391	C23 H26 F3 N3 02	434,0	20,0	76
Příklad 727	1392	C22 H23 C1 F3 N3 02	459,0	20,0	67
Příklad 728	1393	C23 H26 F3 N3 02	434,0	20,1	70
Příklad 729	1394	C22 H23 F3 N4 04	465,0	18,4	60
Příklad 730	1395	C23 H24 F3 N3 02	432,0	21,4	75
Příklad 731	1396	C26 H26 F3 N3 02	470,0	20,4	66
Příklad 732	1397	C21 H20 Br2 F3 N3 02	562,0	14,5	54
Příklad 733	1398	C22 H22 C12F3 N3 02	488,0	10,8	47
Příklad 734	1399	C22 H22 C12F3 N3 02	488,0	9,4	90
Příklad 735	1400	C22 H23 C1 F3 N3 02	954,0	19,1	88
Příklad 736	1614	C22 H21 F6 N3 S	506,0	24,2	96
Příklad 737	2050	C20 H22 F3 N3 02 S	426,0	6,0	30
Příklad 738	2051	C21 H23 F3 N4 02	421,0	6,5	32

* Výtěžek TFA soli.

Příklady 739 až 748.

Sloučeniny podle vynálezu se syntetizovaly metodami Příkladu 738 za použití odpovídajících reaktantů v daném pořadí Bylo-li třeba , byla pro získání žádaného produktu použita preparativní TLC. ESI/MS data a výtěžky jsou shrnuty v tabulce 9.

Tabulka 9

	Sloučenia č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 739	1650	C24 H28 F3 N3 02	448,0	20,4	91
Příklad 740	1706	C23 H25 F3 N4 03	463,2	3,7	11
Příklad 741	1707	C22 H25 F3 N4 02 S	467,0	10,3	29
Příklad 742	1708	C23 H27 F3 N9 02	449,2	11,4	34

Příklad 743	1709	C24 H29 F3 N4 02	463,2	15,2	44
Příklad 744	1775	C22 H25 F3 N4 09	467,2	9,2	26,3
Příklad 745	1776	C22 H25 F3 N4 04	467,2	8,9	25,4
Příklad 746	1787	C24 H29 F3 N4 02	463,2	5,6	16,1
Příklad 747	1802	C23 H27 F3 N4 04	481,2	11,7	32,5
Příklad 748	1803	C22 H25 F3 N4 03	451,2	9,6	28,4

Příklad 749: Příprava (R)-3-[{N-(2-amino-5trifluormethoxybenzoyl)glycyl}amino]-1-(3--hydroxy-4methoxybenzyl)pyrolidinu (Sloučenina č. 1896).

Ke směsi (R)-3-[N-{2-(tert-butoxykarbonylamino)-5-(trifluormethoxy)benzoyl}glycyl]--aminopyrolidinu (0,050 mmol), 3-hydroxy-4-methoxybenzaldehydu (0,060 mmol), $NaBH_3CN$ (0,15 mmol) a methanolu (1.3 ml) se přidala kyselina octová (0,050 ml). Reakční směs se nechala míchat při 60 °C po dobu 8 h. Po ochlazení na pokojovou teptotu se směs nanesla na sloupec Varian SCX a sloupec se promýval CH_3 OH (10 ml). Produkt se eluoval použitím 2 N NH_3 v CH_3 OH (5 ml) a zakoncentroval se. K výslednému produktu se přidala 4 N HCl v 1,4-dioxanu a reakční směs se nechala míchat při pokojové teplotě do rána. Zakoncentrováním a použitím preparativní TLC se získal žádaný produkt (R)-3-[{N-(2-amino-5-trifluormethoxybenzoyl)glycyl}amino]-1-(3-hydroxy-4--methoxybenzyl)pyrolidin (Sloučenina č. **1896**) (9,1 mg, 38%): Čistota produktu se určila pomocí RPLC/MS (93%); ESI/MS m/e 483,0 (M^+ +H, $C_{22}H_{25}F N_4 O_5$).

Příklady 750 až 757.

Sloučeniny podle vynálezu se syntetizovaly metodami Příkladu 749 za použití odpovídajících reaktantů v daném pořadí. ESI/MS data a výtěžky jsou shrnuty v tabulce 10.

Tabulka 10

Sloučenina č.		Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 750	1897	C22 H25 F3 N4 03 S	483	22,7	99,1
Příklad 751	1898	C23 H27 F3 N4 03	465	12,2	52,5
Příklad 752	1899	C24 H29 F3 N4 03	479	14,4	60,2
Příklad 753	1900	C22 H25 F3 N4 05	483	2,6	10,8
Příklad 754	1901	C29 H29 F3 N4 03	479	14,5	60,6
Příklad 755	1902	C23 H25 F3 N4 04	479	12,0	50,2
Příklad 756	1915	C23 H27 F3 N4 05	467,2	2,5	6,7
Příklad 757	1916	C22 H25 F3 N9 04	467,2	3,1	8,9

Příklad 758 : Příprava (R) -3- [{ N- (2-amino-5-(trifluormethyl)benzoyl)glycyl}amino]-1-(4--vinylbenzyl)pyrolidinu (Sloučenina č. 1701).

Směs (R)-3-[{N-(2-amino-5-(trifluormethyl)benzoyl)glycyl)amino]pyrolidinu (0,050 mmol), 4--vinylbenzylchloridu (9,9 mg, 0,065mmo1), piperidinmethylpolystyrenu (60mg), acetonitrilu (1,0 ml) a chloroformu (0.30 ml) se nechala míchat při 50 °C po dobu 12 h. Po ochlazení na pokojovou teptotu se směs nanesla na sloupec Varian SCX a sloupec se promýval CH_3 OH (15 ml). Produkt se eluoval použitím 2 N NH_3 v CH_3 OH (5 ml) a zakoncentrováním se získal požadovaný produkt (R)-3-[{N-(2--amino-5-(trifluormethyl)benzoyl)glycyl)amino]-1-(4-vinylbenzyl)pyrolidinu (Sloučenina č. **1701)** (19.6 mg, 88%.): Čistota produktu se určila pomocí RPLC/MS (92%); ESI/MS m/e 547.2 (M^+ +H, $C_{23}H_{25}Cl N_4 O_{2s}$).

Příklady 759 až 762:

Sloučeniny podle předloženého vynálezu se syntetizovaly metodami popsanými v Příkladu 758 za použití odpovídajících reaktantů v daném pořadí Bylo-li třeba, byla pro získání žádaného produktu použita preparativní TLC. ESI/MS data a výtěžky jsou shrnuty v

tabulce 11.

Tabulka 11

Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 759 1702	C22 H25 F3 N4 03	451.2	5,3	29
Příklad 760 1703	C22 H23 F3 N4 09	465.2	5,0	22
Příklad 761 1704	C21 H23 F3 N4 03	437.2	20,9	96
Příklad 762 1705	C21 H21 C12F3 N4 02	489.2	9,3	38

Příklad 763: Příprava (R)-3-[{N-(2-amino-5(trifluormethoxy)benzoyl)glycyl}amino]-1-(2,4--dichlorbenzyl)pyrolidinu (Sloučenina č. 1905).

Směs (R)-3-[{N-(2-amino-5-(trifluormethoxy)benzoyl)glycyl}amino]pyrrolidinu (0,050 mmol), 2,4--dichlorbenzylchloridu (0,060 mmol), piperidinmethylpolystyrenu (60 mg), acetonitrilu (0.8 ml) a chloroformu (0,5 ml) se nechala míchat při 60 °C po dobu 12 h. Po ochlazení na pokojovou teptotu se směs nanesla na sloupec Varian SCX a sloupec se promýval 50% $CHCl_3/CH_3$ OH (10 ml). Produkt se eluoval použitím 2 N NH_3 v CH_3 OH (5 ml) a zakoncentroval se. K výslednému materiálu se přidala 4 N HCl v 1,4-dioxanu (2 ml) a směs se nechala míchat přes noc v pokojové teplotě. Zakoncentrováním a preparativní TLC se získal požadovaný produkt (R)-3-[(N-(2-amino-5--(trifluormethoxy)benzoyl)glycyl)amino]-1-(2,4-dichlorobenzyl)pyrolidin (Sloučenina č. **1905)** (17.6 mg, 70%.): Čistota produktu se určila pomocí RPLC/MS (93%); ESI/MS m/e 505,0 (M^+ +H, $C_{21}H_{21}Cl_2N_4O_3$).

Příklady 764 až 770:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 763 za použití odpovídajících reaktantů v daném pořadí Bylo-li třeba, byla pro získání žádaného produktu použita preparativní TLC. ESI/MS data a výtěžky jsou shrnuty v tabulce 12.

Tabulka 12

Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 764 1906	C22 H23 F3N9 05	481	9,4	39,1
Příklad 765 1907	C21 H23 F3N4 04	453	7,5	33,2
Příklad 766 1908	C22 H25 F3N4 04	467	7,7	33,0
Příklad 767 2180	C22 H24 C1F3 N4 02	469	1,3	26
Příklad 768 2181	C23 H25 F3N6 03	491	4,3	52
Příklad 769 2182	C19 H22 F3 N5 02 S	442	7,0	51
Příklad 770 1909	C23 H25 F3 N4 03	463	8,7	37,6

Příklad 771: Příprava (R)-3-[{N-(2-amino-5-trifluormethoxybenzoyl)glycyl}amino]-1-(2-amino--4-chlorbenzyl)pyrolidinu (Sloučenina č. 1921).

Směs (R)-3-[(N-(2-amino-5- trifluormethoxybenzoyl)glycyl)amino]pyrolidinu (0,050 mmol), 4--chloro-2-nitrobenzylchloridu (0,050 nmol), piperidinmethylpolystyrenu (60 mg), acetonitrilu (1,0 ml) a chloroformu (0,7 ml) se nechala míchat přes noc při 50 °C. Po ochlazení na pokojovou teptotu se směs nanesla na sloupec Varian SCX a sloupec se promýval 50% $CHCl_3/CH_3$ OH (10 ml). Produkt se eluoval použitím 2 N NH_3 v CH_3 OH (5 ml) a zakoncentroval se. Ke vzniklému produktu se přidal ethanol (3ml) a 10% Pd-C (15 mg). Směs se nechala míchat pod H_2 při pokojové teplotě po dobu 1,5 h. Filtrací, zakoncentrováním a preparativní TLC se získal požadovaný produkt (R)-3-[{N-(2-amino-5--trifluormethoxybenzoyl)glycyl}amino]-1-(2-amino-4-chlorbenzyl)pyrolidin (Sloučenina č,**1921**) (2.2 mg, 6%): Čistota produktu se určila pomocí RPLC/MS (81%); ESI/MS m/e 486.2 (M^+ +H, $C_{21}H_{23}ClF_3N_5O_3$).

Příklad 772: Příprava (R)-3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-brom-2--fluorbenzyl)pyrolidinu (Sloučenina č. 2120).

Ke směsi (R)-3-[{N-(2-terc-butoxykarbonylamino-5- -trifluormethylbenzoyl)glycyl}amino]pyrolidinu (0,050 nmol), 4-brom-2-fluorbenzalaldehydu (15nmol), methanolu (1,5 ml) a kyseliny octové (0,016 ml) se přidal $NaBH_3CN$ (0.25 nmol) v methanolu. Směs se nechala míchat přes noc při 50 °C. Po ochlazení na pokojovou teplotu se směs nanesla na sloupec Varian SCX a sloupec se promýval CH_3 OH (5 ml x 2). Produkt se eluoval použitím 2 N NH_3 v CH_3 OH (5 ml) a zakoncentroval se. Vzniklý produkt se rozpustil v methanolu (0.25 ml) a přidala se 4N HCl v dioxanu (0,50 ml). Směs se nechala míchat při pokojové teplotě po dobu 5 h, filtrovala se a zakoncentrovala se. Vzniklý produkt se rozpustil v methanolu, nanesl se na sloupec Varian SCX a sloupec se promýval CH_3 OH (5 ml x 2). Produkt se eluoval použitím 2 N NH_3 v CH_3 OH (5 ml) a zakoncentroval se. Vzniklý produkt se rozpustil v ethylacetátu (0,5 ml), nanesl na sloupe Varian Si a eluoval se pomocí směsi ethylacetát/methanol =5:1 (6 ml), zakoncentrováním se získal požadovaný produkt (R)-3-[{N-(2--amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-bromo-2-fluorbenzyl)pyrolidin (Sloučenina č. **2120**) (16,0 mg, 31%): Čistota produktu se určila pomocí RPLC/MS (99%); ESI/MS m/e 517,0 (M^+ +H, $C_{21}H_{21}BrF_4N_4O_2$).

Příklady 773 až 793:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 772 za použití odpovídajících reaktantů v daném pořadí Bylo-li třeba, byla pro získání žádaného produktu použita preparativní TLC. ESI/MS data a výtěžky jsou shrnuty v tabulce 13.

Tabulka 13

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 773	2083	C22 H24 Br F3 N4 04	545,2	2,9	11
Příklad 774	2084	C23 H27 F3 N4 05	997,2	5,1	21
Příklad 775	2085	C22 H25 F3 N4 04	467,2	3,1	13
Příklad 776	2086	C21 H22 C1 F3 N4 03	971,0	4,6	20
Příklad 777	2087	C23 H28 F3 N5 02	464,2	5,6	24
Příklad 778	2088	C25 H32 F3 N5 02	492,2	5,9	24

Příklad 779	2089	C21 H21 F5 N4 02	457,2	4,5	20
Příklad 780	2090	C27 H27 F3 N4 03	513,2	8,0	31
Příklad 781	2118	C21 H23 F3 N4 09	453,1	2,7	12
Příklad 782	2119	C21 H23 F3 N4 04	953,1	9,3	19
Příklad 783	2121	C22 H25 F3 N4 04	467,0	1,2	2
Příklad 784	2122	C21 H21 C1 F4 N4 02	472,9	13,1	28
Příklad 785	2123	C22 H22 F3 N5 06	510,1	13,1	51
Příklad 786	2124	C21 H21 C1 F3 N5 04	500,1	15,6	62
Příklad 787	2125	C22 H24 F3 N5 05	496,0	16,0	65
Příklad 788	2126	C22 H24 F3 N5 04	980,1	15,6	65
Příklad 789	2137	C22 H24 C1 F3 N9 02	469,2	2,6	11
Příklad 790	2138	C26 H29 F3 N6 02	515,3	25,1	98
Příklad 791	2139	C20 H24 C1 F3 N6 02	473,2	25,0	98
Příklad 792	2149	C21 H22 F3 N5 05	482,3	4,9	34
Příklad 793	2157	C22 H25 F3 N4 03	451,2	15,5	70

Příklad 794: Příprava (R)-3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(2,4--dimethoxypyrimidin-5-ylmethyl)pyrolidinu (Sloučenina č. 2175).

(R)-3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]pyrolidin (17.2 mg, 0,04 mmol) se rozpustil v THF (1 ml) a přidal se 2,4-dimethoxy-5-pyrimidinkarboxyldehyd (6.7 mg,0,04 mmol). Poté následovalo přidání triacetoxyborohydridu sodného (12.7 mg, 0,06 mmol) a ledové kyseliny octové (2.4 mg, 0,04 mmol). Reakční směs se nechala míchat při pokojové teplotě po dobu 24 h a poté se odpařila. Vzniklý produkt se rozpustil v dichlormethanu (1 ml) a promyl se 1 N roztokem NaOH (1 ml). Získaná organická fáze se odpařila a přidala se kyselina trifluoroctová v dichloromethanu (1 ml). Směs se nechala reagovat 1 h při pokojové teplotě, poté se odpařila. Produkt se vyčistil pomocí LC/MS a získal se požadovaný (R)-3-[{N--(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(2,4-dimethoxypyrimidin-5--ylmethyl)pyrolidin (Sloučenina č. **2175**) (18.6 mg, 78%): Čistota produktu se určila pomocí RPLC/MS (98%); ESI/MS m/e 483 (M^+ +H, $C_{21}H_{25}F_3N_6O_4$).

Příklady 795 až 803:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 794 za použití odpovídajících reaktantů v daném pořadí Bylo-li třeba, byla pro získání žádaného produktu použita preparativní TLC. ESI/MS data a výtěžky jsou shrnuty v tabulce 14.

Tabulka 14

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 795	2165	C18 H21 F3 N6 02	411	2,0	27
Příklad 796	2166	C18 H20 F3 NS 02 S	428	9,9	66
Příklad 797	2167	C24 H25 F3 N6 02	487	15,1	73
Příklad 798	2169	C29 H29 F3 N4 02	463	1,2	24
Příklad 799	2170	C26 H25 C1 F3 N5 02	520	6,0	40
Příklad 800	2171	C19 H23 F3 N6 02	425	16,8	B8
Příklad 801	2174	C23 H24 Br F3 N4 02 S2	591	5,3	53
Příklad 802	2178	C25 H28 F3 N5 04	518	5,4	62
Příklad 803	2179	C25 H28 F3 N5 03	502	6,3	60

Příklad 804: Příprava (R)-1-(2-amino-4,5-methylendioxybenzyl)-3-[{N-(2-amino-5trifluoro--methylbenzoyl)glycyl}amino]pyrolidinu (Sloučenina č. 2127).

Směs (R)-3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4,5-methylendioxy-2--nitrobenzyl)pyrolidinu (30,5 mg), 10% Pd-aktivovaného uhlíku (6 mg) a methanolu (3 ml) se nechala míchat pod vodíkovou atmosférou při pokojové teplotě po dobu 10 h. Pd katalyzátor se odstranil filtrací přes Celite a filtrat se zakoncentroval. Extrakce na pevné fázi (Bond Elute" SI, 20% methanol/AcOEt) poskytla (R)-1-(2-amino-4,5-methylenedioxybenzyl)-3-[{N-(2-amino-5--trifluormethylbenzoyl)glycyl)amino)pyrolidin (Sloučenina č. **2127**) (21,9 mg, 76%): Čistota produktu se určila pomocí RPLC/MS (95%); ESI/MS m/e 480 (M^+ +H, $C_{22}H_{24}F_3N_5O_4$).

Příklady 805 až 806:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 804 za použití odpovídajících reaktantů v daném pořadí Bylo-li třeba, byla pro získání žádaného produktu použita preparativní TLC. ESI/MS data a výtěžky jsou shrnuty v tabulce 15.

Tabulka 15

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 805	2128	C22 H26 F3 N5 03	966,0	8,6	30
Příklad 806	2129	C22 H26 F3 N5 02	450,1	13,1	37

Příklad 807: Příprava (R)-1-(3-amino-4-chlorbenzyl)-3-[{N-(2-amino-5-trifluor--methylbenzoy1)glycyl}amino]pyro1idinu (Sloučenina č. 2132).

Směs (R)-3-[N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-chlor-3-nitrobenzyl)pyrolidinu (32.6 mg), 10% Pd-aktivovaného uhlíku (8 mg) a ethylacetátu (2.7 ml) se nechala míchat pod vodíkovou atmosférou při pokojové teplotě po dobu 15 h. Pd katalyzátor se odstranil filtrací a filtrat se zakoncentroval. Extrakce na pevné fázi (Bond Elute" SI, 20% methanol/AcOEt) poskytla (R)-1-(3-amino-4chlorbenzyl)-3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]pyrolidin (Sloučenina č.**2132)** (10,5 mg, 34%): Čistota produktu se určila pomocí RPLC/MS (84%); ESI/MS m/e 470 (M^+ +H, $C_{21}H_{23}F_3N_5O_2$).

Příklad 808: Příprava (R)-1-(2-amino-4,5-methylendioxybenzyl)-3-[(N-{2-(terc--butoxykarbonylamino)-5-trifluormethylbenzoyl)glycyl}amino]pyrolidinu.

Ke směsi (R)-3-[{N-(2-(terc-butoxykarbonylamino)-5-trifluormethylbenzoyl)glycyl}amino]pyrolidinu (0,150 mmol), 4,5-methylenedioxy-2-nitrobenzaldehydu (0.45 mmol), methanolu (4,5 ml) a kyseliny octové (0,048 ml) se přidal $NaBH_3CN$ (0.75 mmol) v methanolu (1,50 ml). Reakční směs se nechala míchat při 50 °C přes noc. Po ochlazení na pokojovou teptotu se směs nanesla na sloupec Varian SCX a sloupec se promýval CH_3OH.. Produkt se eluoval použitím 2 N NH_3 v CH_3OH a zakoncentrováním

vznikl (R)-3-[{N-(2-(terc-butoxykarbonylamino)-5-trifluormethylbenzoyl)glycyl}amino]-1-(4,5--methylendioxy-2-nitrobenzyl)pyrolidin.

Směs z výše uvedeným způsobem vzniklým (R)-3-[{N-(2-(terc-butoxykarbonylamino)-5--trifluormethylbenzoyl)glycyl}amino]-1-(4,5-methylenedioxy-2-nitrobenzyl)pyrolidinem, 10% Pd-aktivovaného uhlíku (22 mg) a methanolu (3,0 ml) se nechala míchat pod vodíkovou atmosférou při pokojové teplotě přes noc. Pd katalyzátor se odfiltroval a filtrát se zakoncentroval. Získal se požadovaný produkt (R)-1-(2-amino-4,5-methylendioxybenzyl)-3-[{N-(2-(terc-butoxykarbonylamin)-5-trifluormethylbenzoyl)glycyl}amino]pyrolidin (87,1 mg, kvant.): Žádný vedlejší produkt nebyl patrný v TLC.

Sloučeniny (R)-1-(3-amino-4-methoxybenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)-S--trifluoro -methylbenzoyl)glycyl}amino]pyrolidin a (R)-1-(3-amino-4-methylbenzyl)-3-[{N-(2-(terc--butoxykarbonylamino)-5-trifluormethylbenzoyl)glycyl}amino]pyrolidin byly nasyntetizovány pomocí metod popsaných v Příkladu 808 za použití uvedených reaktantů v daném pořadí.

(R)-1-(3-amino-4-methoxybenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)-5-trifluormethylbenzoyl)--glycyl}amino]pyrolidin: 101 mg, kvant.quant.; Žádný vedlejší produkt nebyl patrný v TLC.

(R)-1-(3-amino-4-methylbenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)trifluormethylbenzoyl)--glycyl}amino]pyrolidin: 97.2 mg, kvant.; Žádný vedlejší produkt nebyl patrný v TLC.

Příklad 809: Příprava (R)-1-(3-amino-4-chlorbenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)-5--trifluormethylbenzoyl)glycyl}amino]pyrolidinu.

Ke směsi (R)-3-[{N-(2-(terc-butoxykarbonylamino)-5trifluormethylbenzoyl)-glycyl}--amino]pyrolidinu (0,150 mmol), 4-chlor-3-nitrobenzaldehydu (0.45 mnmol), methanolu (4,5 ml) a kyseliny octové (0,098 ml) se přidal $NaBH_3CN$ (0.75 mmol) v methanolu (1,50 ml). Reakční směs se míchala při 50°C přes noc. Po ochlazení na pokojovou teptotu se směs nanesla na sloupec Varian SCX a sloupec se promýval CH_3 OH.. Produkt se eluoval použitím 2 N NH_3 v CH_3 OH a zakoncentrováním vznikl (R.)-3-[{N-(2--(terc-butoxykarbonylamino)-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-chlor--nitrobenzyl)pyrolidin.

Směs (R)-3-[{N-(2-(terc-butoxykarbonylamino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-chlor-3--nitrobenzyl)pyrolidinu, který byl připraven metodou popsanou výše, 10% Pd-aktivovaného uhlíku

(22 mg), ethylacetátu (2.7 ml) a methanolu (0.3 ml) se míchala pod vodíkovou atmosférou při pokojové teplotě po dobu 15 h. Pd katalyzátor se odfiltroval a filtrát se zakoncentroval. Tím se získal

požadovaný produkt (R)-1-(3-amino-4-chlorbenzyl)-3-({N-(2-(terc-butoxykarbonylamino)-5--trifluormethylbenzoyl)glycyl}amino]pyrolidin (89.7 mg, kvant.): Žádný vedlejší produkt nebyl v TLC patrný.

Příklad 810: Příprava (R)-1-(3-amino-4-hydroxybenzyl)-3-({N-(2-amino-5-trifluor--methylbenzoyl)glycyl}amino]pyrolidinu (Sloučenina č. 2187).

Roztok (R)-1-(3-amino-4-hydroxybenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)-5-trifluor--methylbenzoyl)glycyl}amino]pyrolidinu (20 mg), připraveného metodou popsanou v Příkladu 808 v 4 N HC1 v dioxanu (2,0 ml) se míchal při pokojové teplotě přes noc. Poté se roztok zakoncentroval, reziduum bylo rozpuštěno v methanolu a směs se nanesla na sloupec Varian SCX a sloupec se promýval CH_3 OH.. Produkt se eluoval použitím 2 N NH_3 v CH_3 OH a po zakoncentrování a preparativní TLC ($Si0_2$, AcOEt/MeOH = 4:1) se směs nanesla na sloupec Varian SCX a sloupec se promýval CH_3 OH.. Produkt se eluoval použitím 2 N NH_3 v CH_3 OH a zakoncentrováním vznikl (R)-1-(3-amino-4-hydroxybenzyl) 3-[{N- (2-amino-5-trifluormethylbenzoyl)glycyl}amino]pyrolidin (Sloučenina č. **2187**) (9.6 mg, 59%): Čistota produktu se určila pomocí RPLC/MS (86%); ESI/MS m/e 452.3 (M^+ +H, $C_{21}H_{24}F_3N_5O_3$).

Příklad 811: Příprava (R)-3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-{4-chlor-3--(dimethylamino)benzyl}pyrolidinu (Sloučenina č. 2133).

Ke směsi (R)-1-(3-amino-4-chlorbenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)-5-trifluor--methylbenzoyl)glycyl}amino]pyrolidinu (44,9 mg) , methanolu (0,95 ml) , kyseliny octové (0,05 ml) a 37% vodného roztoku HCHO (0,15 ml) se přidal $NaBH_3CN$ (38 mg). Reakční směs se nechala míchat přes noc při 50 °C. Poté se ochladila na pokojovou teplotu a odpařila se. Odparek se rozpustil ve 2 N vodném roztoku NaOH a ethylacetátu, organická vrstva se oddělila a vodná fáze se extrahovala ethylacetátem. Spojené vrstvy organické fáze se vysušily a výsledný produkt byl nanesen na sloupec Varian SCX a sloupec se promýval CH_3 OH. Produkt se eluoval použitím 2 N NH_3 v CH_3 OH a zakoncentrováním. Reziduum se rozpustilo ve směsi 50% konc. HCl/dioxan a reakční směs se nechala míchat při pokojové teplotě 1h. V reakční směsi se upravilo pH na hodnotu pH10 pomocí vodného roztoku 5N NaOH a následovala extrakce ethylacetátem (dvakrát). Spojené extrakty se vysušily nad bezvodým síranem sodným, odfiltrovaly a odpařily. Po preparativní TLC (SiO_2, 20% MeOH/AcOEt vznikl (R)-1-(3-amino-4-hydroxybenzyl)3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-

-pyrolidin (Sloučenina č. **2133**) (10,9 mg, 28%): Čistota produktu se určila pomocí RPLC/MS (95%); ESI/MS m/e 498,3 (M^+ +H, $C_{23}H_{25}ClF_3N_5O_2$).

Příklady 812 až 814:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 811 za použití odpovídajících reaktantů v daném pořadí.ESI/MS data a výtěžky jsou shrnuty v tabulce 16.

Tabulka 16

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 812	2134	C24H28F3N5O4	508,4	19,0	50
Příklad 813	2135	C24H30F3N5O3	494,4	21,8	50
Příklad 814	2136	C24H30F3N5O2	478,4	29,2	69

Příklad 815: Příprava (R)-3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(3--methylamino-4-hydroxybenzyl)pyrolidinu (Sloučenina č.2158).

Ke směsi (R)-1-(3-amino-4-hydroxybenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)-5--trifluormethylbenzoyl)glycyl}amino]pyrolidinu (27,3 mg), 37% roztoku HCHO (0,10 ml), kyseliny octové (0,10 ml) a methanolu (1,3 ml)se přidal $NaBH_3CN$ (9,2 mg) v methanolu (0,2 ml). Reakční směs se nechala míchat přes noc při 60 °C. Poté byla ochlazena na pokojovou teplotu a produkt byl nanesen na sloupec Varian SCX a sloupec se promýval CH_3OH (5 ml x 2). Produkt se eluoval použitím 2 N NH_3 v CH_3OH (8 ml). Zakoncentrováním a preparativní TLC (SiO_2) se získal (R)-3--[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(3-methylamino-4-hydroxybenzyl)pyrolidinu (Sloučenina č.**2158**); (4,3 mg, 19%) : Čistota produktu se určila pomocí RPLC/MS (71%); ESI/MS m/e 480.3 (M^+ +H, $C_{22}H_{26}F_3N_5O_3$).

Příklad 816: Příprava (R)-1-3-[(3-acethylamino-4-metoxybenzyl)-3-{N-(2-amino-5--trifluormethylbenzoyl)glycyl}amino]pyrolidinu (Sloučenina č.2152).

Ke směsi (R)-1-(3-amino-4-metoxybenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)-5--trifluormethylbenzoyl)glycyl}amino]pyrolidinu (50,5 mg) v pyridinu (1 ml) se přidal acetanhydrid (1 ml). Reakční směs se míchala přes noc při pokojové teplotě a poté se přidal methanol. Po odpaření reakční směsi se přidal roztok 1N NaOH. Směs se extrahovala ethylacetátem a organická vrstva se zakoncentrovala. Pomocí preparativní TLC se obdržel produkt (R)-1-(3-acethylamino-4--metoxybenzyl)-3-[{N-(2-(tercbutoxykarbonylamino-5-trifluormethylbenzoyl)glycyl}amino]pyrolidin.

Vzniklý (R)-1-(3-acethylamino-4-metoxybenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)-5--trifluormethylbenzoyl)glycyl}amino]pyrolidin se rozpustil v 50% 6N kyselině chlorovodíkové v dioxanu a roztok se míchal při pokojové teplotě 2h. V reakční směsi se upravilo pH na hodnotu pH10 pomocí vodného roztoku 5N NaOH a následovala extrakce ethylacetátem. Organická vrstva se odpařila a pomocí preparativní TLC (SiO_2, MeOH/AcOEt = 4:1) vznikl (R)-1-3-[3-acethylamino-4--metoxybenzyl)-3-{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]pyrolidin (Sloučenina č.**2152**) (3,7 mg, 8%): Čistota produktu se určila pomocí RPLC/MS (100%); ESI/MS m/e 508,3 (M^+ +H, $C_{24}H_{28}F_3N_5O_4$).

Příklady 817 až 819:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 816 za použití odpovídajících reaktantů v daném pořadí. ESI/MS data a výtěžky jsou shrnuty v tabulce 17.

Tabulka 17

	Sloučenina č.	Molekulární vzorec		ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 817	2150	C23H25C1F3N503	512.3	3.8	9	
Příklad 818	2151	C24H26F3N505	522.2	3,1	8	
Příklad 819	2153	C24H28F3N503	992.3	9.3	10	

Příklad 820: Příprava (R)-3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1--(benz[d]oxazol-5-yl)pyrolidinu (Sloučenina č. 2189).

K roztoku (R)-1-(3-amino-4-hydroxybenzyl)-3-[{N-(2-(terc-butoxykarbonylamino)-5-trifluormethyl--benzoyl)glycyl}amino]pyrrolidinu (20 mg), připraveného podle metody popsané v Příkladu 808 v THF (2 ml) se přidal triethylorthoformat (0,020 ml, 3.3 eq) a pyridinium p-toluensulfát (1 .2 mg, 0,9 eq). Reakční směs se míchala přes noc pod refluxem. Po ochlazení na pokojovou teplotu se směs zakoncentrovala. Vzniklý produkt se rozpustil v AcOEt, nanesl se na sloupec o BondElut Si. K eluci se použila směs ethylacetát/methanol = 4:1 a poté se produkt zakoncentroval.

Vzniklý materiál se rozpustil v AcOEt (1,5ml) a byla přidána 4N HCl v dioxanu (0,5 ml). Roztok se nechal míchat při pokojové teplotě přes noc, v reakční směsi se upravilo pH na hodnotu pH10 pomocí vodného roztoku 5N NaOH a následovala extrakce ethylacetátem. Extrakt se po zakoncentrování čistil pomocí PTLC (SiO_2, MeOH/AcOEt = 1:4) vznikl (R)-3-[{N-(2-amino-5-trifluormethyl--benzoyl)glycyl}amino]-1-(benz[d]oxazol-5-yl)pyrrolidin (Sloučenina č. **2189**). (0,5 mg,3%): Čistota produktu se určila pomocí RPLC/MS (97%); ESI/MS m/e 462,3 (M^+ +H, $C_{22}H_{22}F_3N_5O_3$).

Referenční příklad 6: Příprava 4-[{N-(1-(9-fuluorenylmethoxykarbonyl)pyrolidin-3-yl)--karbamoylmethyl}aminomethyl]-3-methoxyfenyloxymethylpolystyrenu.

K roztoku (R)-1-(9-fuluorenylmethoxykarbonyl)-3-glycylaminopyrolidinhydrochloridu (4,38 g, 10 mmol) v DM F (65 ml) se přidala kyselina octová (0,3 ml), triacetoxyborohydrid sodný (1,92 g) a 4-formyl-3-(methoxyfenyloxymethyl)-polystyren (1 mmol/g, 200 g) . Směs se nechala po 2 h třepat a přefiltrovala se. Pryskyřice se promyla MeOH, DMF, CH_2C1_2 a methanolem a vysušením se získal požadovaný materiál (2,73 g).

Příklady 822 až 912: Obecný postup syntézy 3-aminopyrolidinů na pevné fázi

Ke směsi odpovídajících kyselin (1,6mmol), HBTU (1,6 mmol) a DMF (6 ml) se přidal diisopropylethylamin (3,6 mmol) a směs se nechala 2 min třepat. Poté se přidal 4-[{N-(1-(9--fluorenylmethoxykarbonyl)pyrolidin-3-yl)karbamoylmethyl}aminomethyl]-3-methoxyfenyl--oxymethylpolystyren (400mg, 0,4 mmol) k vysušení reakční směsi a opět se směs nechala třepat 1h. Poté se směs přefiltrovala. Pryskyřice se promyla DM F a CH_2C1_2 a vysušila. Směs vzniklé pryskyřice, piperidinu (3,2 ml) a DMF (12,8 ml) se nechala po dobu 10 min třepat a přefiltrovala se. Pryskyřice se promyla DMF a CH_2C1_2 a usušila se.

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K vysušené pryskyřici (0,05 mmol) se přidala směs $NaBH(OAc)_3$ (0.25 mmol) , AcOH (0,025 ml) a DMF (1 ml). Přidal se odpovídající aldehyd (2,5 mmol) a směs se nechala míchat po dobu 2 h, přefiltrovala se a promyla CH_3OH, 10% diisopropylethylenaminem v DMF, CH_2C1_2 a opět methanolem. Směs pryskyřice, vody (0,050 ml) a trifluoroctové kyseliny (0,95 ml) se nechala třepat po dobu 1 h a přefiltrovala. Pryskyřice se promyla CH_2C1_2 a CH_3 OH. Filtrát a kapalina z promývání se spojily a zakoncentrovaly. Tento surový materiál se nanesl na sloupec Varian SCX a ten se promýval CH_3 OH (15 ml). Produkt se eluoval pomocí 2N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Bylo-li to nutné k získání produktu, použila se TLC či HPLC. Data ESI/MS a výtěžky jsou shrnuty v tabulce 18.

Tabulka 18

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 822	1805	C21 H21 BrF3 N302 S	516	13,3	76
Příklad 823	1806	C22 H24 F3 N3 03 S	468	12,8	81
Příklad 824	1807	C22 H24 F3 N3 04 S	984	13,7	83
Příklad 825	1808	C22 H24 F3 N3 04 S	484	14,9	91
Příklad 826	1809	C21 H22 F3 N3 03 S	454	12,9	84
Příklad 827	1810	C22 H22 F3 N3 04 S	482	12,9	79
Příklad 828	1811	C24 H26 F3 N3 02 S	478	12,5	79
Příklad 829	1812	C22 H24 F3 N3 02 S2	984	5,3	32
Příklad 830	1813	C23 H26 F3 N3 02 S	466	12. 8	81
Příklad 831	1814	C23 H24 F3 N3 03 S	480	9,7	59
Příklad 832	1815	C23 H26 F3 N3 02 S	466	12,7	80
Příklad 833	1816	C24 H28 F3 N3 02 S	480	14,4	88
Příklad 834	1817	C25 H30 F3 N3 02 S	499	19,1	84
Příklad 835	1818	C21 H22 Br F2 N3 03	482	13,9	82
Příklad 836	1819	C22 H25 F2 N3 04	439	11,7	79
Příklad 837	1820	C22 H25 F2 N3 05	450	11,8	77
Příklad 838	1821	C22 H25 F2 N3 05	950	13,3	87
Příklad 839	1822	C21 H23 F2 N3 04	420	11,9	83
Příklad 840	1823	C22 H23 F2 N3 05	448	11,9	78

Příklad 841	1824	C24 H27 F2 N3 03	444	9,1	60
Příklad 842	1825	C22 H25 F2 N3 03 S	450	11,3	74
Příklad 843	1826	C23 H27 F2 N3 03	432	10,8	74
Příklad 844	1827	C23 H25 F2 N3 04	446	12,7	89
Příklad 845	1828	C23 H27 F2 N3 03	432	17,7	80
Příklad 846	1829	C24 H29 F2 N3 03	446	14,3	94
Příklad 897	1830	C24 H29 F2 N3 03	446	10,0	66
Příklad 898	1831	C22 H28 Br N3 03	462	4,8	31
Příklad 849	1832 I	C23 H31 N3 04	414	30,9	74
Příklad 850	1833	C23 H31 N3 05	930	12,1	83
Příklad 851	1834	C23 H31 N3 05	430	12,0	82
Příklad 852	1835	C22 H29 N3 04	400	7. 9	58
Příklad 853	1836	C23 H29 N3 05	428	11,1	76
Příklad 854	1837	C25 H33 N3 03	429	13,3	92
Příklad 855	1838	C23 H31 N3 03 S	430	8,7	60
Příklad 856	1839	C24 H33 N3 03	412	11,3	81
Příklad 857	1840	C24 H31 N3 04	426	12,9	69
Příklad 858	1841	C24 H33 N3 03	413	12,8	91
Příklad 859	1842	C25 H35 N3 03	426	8,7	60
Příklad 860	1843	C25 H35 N3 03	426	12,2	89
Příklad 861	1844	C26 H37 N3 03	490	11,3	76
Příklad 862	1895	C31 H37 Br N4 02	577	6,4	30
Příklad 863	1846	C23 H28 F3 N3 02 S	480	12,8	81
Příklad 864	1847	C25 H31 F2 N3 03	460	12,2	78
Příklad 865	1848	C27 H29 N3 04	460	6,1	39
Příklad 866	1849	C29 H31 N3 02	454	15,1	98
Příklad 867	1850	C28 H31 N3 02	442	12,7	65
Příklad 868	1851	C28 H31 IJ3 02	992	14,3	95
Příklad 869	1852	C28 H29 N3 03	456	3,4	22
Příklad 870	1853	C27 H29 N3 06 S	524	15. 4	8 7
Příklad 871	1854	C29 H31 N3 09 S	518	15,8	90
Příklad 872	1855	C26 H31 N3 04 S	506	17,0	9°

Příklad 873	1856	C28 H31 Id3 04 S	506	3,0	17
Příklad 874	1857	C28 H29 N3 05 S	520	10,0	57
Příklad 875	1858	C20 H22 Br2 N4 02	511	9,3*	37
Příklad 876	1859	C21 H25 Br N9 03	461	6,7*	29
Příklad 877	1860	C21 H25 Br N4 04	477	9,5*	90
Příklad 878	1861	C21 H25 Br N4 04	977	10,0*	42
Příklad 879	1862	C20 H23 Br N4 03	447	7,8*	34
Příklad 880	1863	C21 H23 Br N4 04	975	3,4*	14
Příklad 881	1869	C21 H25 Br N4 02 S	477	3,9*	16
Příklad 882	1865	C22 H25 Br N4 03	473	6,4*	27
Příklad 883	1866	C23 H29 Br N4 02	472	7,0*	25
Příklad 884	1867	C23 H29 Br N4 02	473	7,6*	32
Příklad 885	1868	C24 H31 Br N4 02	487	9,1*	37
Příklad 886	1869	C20 H22 Br I N4 02	557	8,9*	33
Příklad 887	1870	C21 H25 I N4 03	509	9,2*	37
Příklad 888	1871	C21 H25 I N4 04	525	6,3*	25
Příklad 889	1872	C21 H25 I N4 09	525	5,9*	23
Příklad 890	1873	C20 H23 I N4 03	495	7,7*	31
Příklad 891	1879	C21 H23 I N4 09	523	8,2*	32
Příklad 892	1875	C23 H27 I N4 02	519	6,7*	26
Příklad 893	1876	C21 H25 I N4 02	525	4,3*	17
Příklad 894	1877	C22 H27 I N4 02	507	7,9*	32
Příklad 895	1878	C22 H25 I N4 03	521	8,4*	33
Příklad 896	1879	C23 H29 I N4 02	521	8,2*	32
Příklad 897	1880	C23 H29 I N4 02	521	8,1*	32
Příklad 898	1881	C24 H31 I N4 02	535	8,6*	33
Příklad 899	1882	C20 H22 Br N5 04	476	5,3*	22
Příklad 900	1883	C21 H25 N5 05	428	5,7*	26
Příklad 901	1884	C21 H25 N5 06	994	8,2*	36
Příklad 902	1885	C21 H25 N5 06	444	5,0*	22

Příklad 903	1886	C20 H23 N5 05	414	8,7*	40
Příklad 904	1887	C21 H23 N5 06	442	7,8*	39
Příklad 905	1888	C23 H27 N5 04	438	5,6*	25
Příklad 906	1889	C21 H25 NS 04 S	444	13,2*	58
Příklad 907	1890	C22 H27 N5 04	926	11,3*	51
Příklad 908	1891	C22 H25 N5 OS	440	7,4*	33
Příklad 909	1892	C22 H27 N5 04	426	5,5*	25
Příklad 910	1893	C23 H29 N5 04	440	5,7*	25
Příklad 911	1894	C23 H29 NS 04	440	9,4*	41
Příklad 912	1895	C24 H31 N5 04	455	8,5*	37

* výtěžek TFA soli

Referenční příklad 7: Příprava 2-karbamoyl –1-4-(chlorbenzyl)pyrolidinu.

K roztoku l-prolinamidhydrochloridu (2,5 g, 21,8 mmol) v CH_3CN (35 ml) se přidal Et_3N (7,45 ml) a 4 -chlorbenzylchlorid (3,88 g, 24,1 mmol). Reakční směs se míchala při 70 °C po dobu 4h a potom při 25 °C po dobu 16 h. Vzniklá reakční směs se naředila CH_2C1_2 (20 ml) a promyla vodou (3 x 30 ml). Organická fáze se vysušila ($MgSO_4$) a zakoncentrovala se. Pomocí chromatografie (Si02, 1% CH_3OH-CH_2C1_2) se získal 2-karbamoyl-1-(4-chlorbenzyl)pyrolidin (5,21 g, 81%).

Referenční příklad 8: Příprava 2-(aminomethyl)-1-(4-chlorbenzyl)pyrolidinu.

2-karbamoyl-1-(4-chlorbenzyl)pyrolidin se rozpustil v 1M BH_3-THF (9,4 ml) a zahřál se na 70 °C. Po 16 h a následně po 25 h se přidal další 0,5 ekvivalent 1M BH_3-THF. Po 40 h se přidal 1 N vodný roztok HC1 (14 ml) a reakční směs se zahřívala pod refluxem 3 h, poté se přidal 3 N vodný roztok HC1 (6 ml) a reakční směs se zahřívala po dobu dalších 3 h. Po ochlazení reakční směsi na 25°C a upravě pH na zásadité pomocí vodného roztoku 4 N NaOH následovala extrakce CH_2C1_2 (4 x 15 ml). Chromatografií ($Si0_2$, 8:1:1 PrOH-H_2O-NH_4OH) se získal 2-(aminomethyl)-1-(4-chlorbenzyl)pyrolidin (1,21 g, 86%).

Opticky aktivní (S)-2-(aminomethyl)-1-(4-chlorbenzyl)pyrolidin a (R)-2-(aminomethyl)-1-(4--chlorbenzyl)pyrolidin lze taktéž připravit pomocí metody uvedené výše za použití odpovídajících reaktantů v daném pořadí.

(S)-2-(aminomethyl)-1-(4-chlorbenzyl)pyrolidin: ^{1}H NMR ($CDCl_3$, 400 25 MHz) δ 1,40-1,80 (m, 5 H), 1,80-1,95 (m, 1 H), 2,12-2,21 (m, 1 H), 2,48-2,65 (m, 1 H), 2,66-2,78 (m, 2 H), 2,85-2,95 (m, 1 H), 3,26 (d, J = 13,2 Hz, 1 H), 3,93 (d, J = 13,2 Hz, 1 H), 7,20-7,40 (m, 4 H). (R)-2-(aminomethyl)-1-(4-chlorbenzyl)pyrolidin vykazoval stejné ^{1}H NMR s S-isomerem.

Příklad 913: Příprava 2-{(N-benzoylleucyl)aminomethyl)-1-(4-chlorbenzyl}pyrolidinu (Sloučenina č. 344).

K roztoku 2-(aminomethyl)-1-(4-chlorbenzyl)pyrolidinu (22,5 mg, 0,10 mmol) a l-benzoylleucinu (0,12 mmol) v $CHCl_3$ (1 ml) se přidal EDCI (23 mg), HOBt (16,2 mg) a Et_3N (15,2 µl) a směs se míchala při 25 °C po dobu 16 h. Reakční směs se naředila CH_2Cl_2 (0,5 ml) a promyla se 2 N vodným roztokem NaOH (2 x 0,75 ml), vysušila pomocí filtrace přes PTFE membranu a zakoncentrováním se získal 2-((N-benzoylleucyl)aminomethyl)-1-(4-chlorbenzyl)pyrolidin (Sloučenina č. **344)** (74 mg, kvant). Čistota sloučeniny se určila pomocí RPLC/MS (85%) ; ESI/MS m/e 442 (M^++H, $C_{25}H_{32}ClN_3O_2$).

Příklady 914 až 935:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 913 za použití odpovídajících reaktantů v daném pořadí. Bylo–li to k získání požadovaných produktů ve formě TFA solí nutné, použila se choromatografie (HPLC-C_{18} , CH_3 CN/H_2O/TFA. ESI/MS data a výtěžky jsou shrnuty v tabulce 19 a sloučeniny č. **339** a **340** vykazují následná ^{1}H NMR spektra.

Tabulka 19

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 914	330	C21 H24 C1 N3 02	386	75*	kvant

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Příklad 915	331	C22 H26 C1 N3 02	400	44*	70
Příklad 916	332	C24 H30 C1 N3 05	476	57	kvant
Příklad 917	333	C20 H23 C1 N4 02	387	40	kvant
Příklad 918	334	C22 H26 C1 N3 02	900	68	kvant
Příklad 919	335	C21 H23 C1 N4 04	431	73	kvant
Příklad 920	336	C22 H23 C1 F3 N3 02	459	75	kvant
Příklad 921	337	C22 H26 C1 N3 02	400	68	kvant
Příklad 922	338	C22 H26 Cl N3 02 I	900	70	kvant
Příklad 923	341	C22 H26 C1 N3 02	400	80*	kvant
Příklad 924	342	C22 H26 C1 N3 02	400	68	kvant
Příklad 925	343	C24 H30 C1 N3 02	428	63	kvant
Příklad 926	345	C23 H27 C1 N2 02	399	68*	kvant
Příklad 927	346	C23 H26 C1 F N2 03	433	51	kvant
Příklad 928	347	C24 H29 C1 N2 02	413	47	kvant
Příklad 929	348	C23 H27 C1 N2 02	399	26	kvant
Příklad 930	399	C21 H25 C1 N2 03 S	421	42	kvant
Příklad 931	350	C26 H33 C1 N2 03	457	12,4	54
Příklad 932	351	C22 H26 C1 N3 03	416	34	81
Příklad 933	352	C22 H25 C12 N3 03	450	51	kvant

* Výtěžek TFA soli

Příklad 934: Sloučenina č. **339:** 82%; ^{1}H NMR ($CDCl_3$) δ 1,52-1,75 (m, 4 H), 1,84-1,95 (m, 1 H), 2,10-2,2U (m, 1 H), 2,67-2,78 (m, 1 H), 2,80-2,90 (m, 1 H), 3,10-3,20 (m, 1 H), 3,25 (d, J = 13,1 Hz, 1 H), 3,50-3,60 (m, 1 H), 3,89 (d, J = 13,1 Hz, 1 H), 4,28-9,20 (m, 2 H), 7,00-7,05 (m, 1 H), 7,12-7,29 (m, 9 H), 7,51 (t, J = 7,8 Hz, 1 H), 7,74 (d, J = 7,8 Hz, 1 H), 7,99 (d, J = 7,8 Hz, 1 H), 8,10-8,27 (m, 2 H).

Příklad 935: Sloučenina č. **340 :** 68 %; ^{1}H NMR ($CDCl_3$) δ 1,55-1,73 (m, 4 H) , 1,86-1,97 (m, 1 H), 2,12-2,21 (m, 1 H), 2,67-2,76 (m, 1 H), 2,86-2,93 (m, 1 H), 3,14-3,21 (m, 1 H), 3,27 (d, J = 13,1 Hz, 1 H), 3,52-3,59 (m, 1 H), 3,89 (d, J = 13,1 Hz, 1 H), 4,09-4,21 (m, 2 H), 7,00-7,07 (m, 1 H), 7,12-7,30 (m, 4 H), 7,50 (t, J = 7.B Hz, 1 H), 7,73 (d, J = 7,8 Hz, 1 H), 8,01 (d, J = 7,8 Hz, 1 H), 8,10-8,25 (m,

2 H).

Referenční příklad 9: Příprava 3-(aminomethyl)-1-(4-chlorbenzyl)pyrolidinu.

Ke směsi 4 -karboxy-1-(4-chlorobenzyl)pyrolidin-2-onu (5,05 g, 20 mmol), EDCI (2,85 g, 22 mmol), HOBt (2,97 g, 22 mmol) a dichloromethanu (100 ml) se přidal 0,5 M amoniak v dioxanu (60 ml, 30 mmol) . Reakční směs se míchala při pokojové tepolotě po dobu 15 h a poté se promyla 2N HC1 (3 x) a vodým roztokem 2 N NaOH (100 ml x 4). Organická vrstva se vysušila nad bezvodým síranem hořečnatým, přefiltrovala se a zakoncentrováním se získal 3-karbamoyl-1-(4chlorbenzyl)pyrolidin-2--on (1,49 g) jako bezbarvá pevná látka.

K roztoku 3-karbamoyl-1-(4-chlorbenzyl)pyrolidin-2-onu (1.45 g) v THF (15 ml) se přidal 1,0 N BH_3 v THF (25 ml). Reakční směs se míchala při 65 °C po dobu 15 h. Po ochlazení na pokojovou teplotu se odstranila kapalina pomocí odsátí za sníženého tlaku. Přidala se voda (30 ml) a koncentrovaná HC1 (10 ml) a směs se míchala při 100 °C po dobu 2 h a poté při pokojové teplotě 1 h. Přidal se vodný roztok 2 N NaOH (100 ml) a směs se extrahovala AcOEt (50 ml x 3) . Spojené organické vrstvy se vysušily nad K_2C0_3, přefiltrovaly se a zakoncentrovaly. Reakční směs se nanesla na chromatografický sloupec (Si02, 15% CH_3OH-5%, Et_3N v CH_2C1_2) a získal se požadovaný produkt 3-(aminomethyl)-1-(4-chlorbenzyl)pyrolidin (860 mg, 19%) jako bezbarvý olej.

Referenční příklad 10: Příprava 1-(4-chlorbenzyl)-3-{(glycylamino)methyl}pyrolidinu.

Směs 3-(aminomethyl)-1-(4-chlorbenzyl)pyrolidinu (860 mg, 3,8 mmol), Et_3N (5,7 mmol), N-terc--butoxykarbonylglycinu (704 mg), EDCI (594 mg), HOBt (673 mg) a dichloromethanu (20 ml) se míchala při pokojové teplotě po dobu 15h. Poté se přidal dichlormethan (50 ml) a roztok se promyl roztokem 2 N NaOH (50 ml x 2), vysušil nad bezvodým síranem sodným, přefiltroval se a zakoncentrováním se obdržel žádaný produkt 3-{N-(terc--butoxykarbonyl)glycyl)aminomethyl]-1-(4--chlorbenzyl)pyrolidin (1,31 g, 90%). K roztoku 3-[{N-(terc-butoxykarbonyl)glycyl}aminomethyl]-1--(4-chlorbenzyl)pyrolidinu (809 mg, 2,11 mmol) v methanolu (10 ml) se přidala 4 N HCl v dioxanu (5 ml). Roztok se míchal při pokojové teplotě po dobu 3,5 h. Po zakoncentrování reakční směsi se přidal roztok 1 N NaOH (20 ml). Směs se extrahovala dichloromethanem (20 ml x 3) a spojené extrakty se vysušily nad síranem sodným a zakoncentrováním vzorku se dostal žádaný produkt 1-(4--chlorbenzyl)-3-{(glycylamino)methyl}pyrolidin (599 mg, 100%): Čistota sloučeniny se určila pomocí RPLC/MS (100%) ; ESI/MS m/e 282.2 (M^++H, $C_{14}H_{20}C1N_30$).

Příklad 936: Příprava 3-[(N-(3-trifluormethylbenzoyl)glycyl)aminomethyl]-1-(4-chlorbenzyl)--pyrolidinu (Sloučenina č. 1463).

Roztok 3-(trifluormethyl)benzoylchloridu (0,058 mmol) v dichlormethanu (0,2 ml) se přidal ke směsi 1-(4-chlorbenzyl)-3{(glycylamino)methyl)pyrolidinu (0,050 mmol) a piperidinmethylpolystyrenu (60 mg) v chloroformu (0.2 ml) a dichloromethanu (1 ml). Po míchání směsi při pokojové teplotě (2,5 h) se přidal methanol (0.30 ml) a směs se míchala při pokojové teplotě 1h. Výsledný produkt byl nanesen na sloupec Varian SCX a sloupec se promýval CH_3 OH (15 ml). Produkt se eluoval použitím 2 N NH_3 v CH_3OH (5 ml) a zakoncentrováním se získal (3-[{N(3-trifluormethyl--benzoyl)glycyl)aminomethyl]-1-(4-chlorobenzyl)pyrrolidin (Sloučenina č. **1463)** (22.4 mg, 99%) : Čistota sloučeniny se určila pomocí RPLC/MS (97%) ; ESI/MS m/e 454.2 (M^++H, $C_{22}H_{23}C1F_3N_3O_2$).

Příklady 937 až 944:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 936 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 20.

Tabulka 20

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 937	1464	C22 H23 C1 F3 N3 03	970,0	21,0	89
Příklad 938	1465	C23 H22 C1 F6 N3 02	522,0	24,5	94
Příklad 939	1466	C21 H23 Br C1 N3 02	466,0	20,8	90
Příklad 940	1467	C21 H23 C12 N3 02	420,0	19,6	93
Příklad 941	1468	C21 H23 C1 N9 04	431,2	19,5	91
Příklad 942	1969	C22 H22 C1 F4 PI3 02	472:0	21,8	92
Příklad 943	1470	C21 H22 C13 N3 02	956,0	22,1	97
Příklad 944	1971	C21 H22 C1 F2 N3 02	922,0	20,9	99

Příklad 945: Příprava 3-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(4--chlorbenzyl)pyrolidinu (Sloučenina č. 1506).

Roztok 1-(4-chlorbenzyl)-3-{(glycylamino)methyl}pyrolidinu (0,050 mmol) v $CHCl_3$ (1,35 ml) a terc--butanolu (0,05 ml) se smíchal s 2-amino-4,5-difluorobenzoovou kyselinou (0,060 mmol), diisopropylkarbodiimidem (0,060 mmol) a HOBt (0,060 mmol). Reakční směs se nechala míchat při pokojové teplotě po dobu 19 hodin. Výsledný produkt se nanesl na sloupec Varian SCX a sloupec se promýval CH_3 OH /CH_3Cl (1:1) (10 ml). Produkt se eluoval použitím 2 N NH_3 v CH_3OH (5 ml) a zakoncentrováním se získal 3-[{N-(2-amino-4,5--difluorbenzoyl)glycyl]aminomethyl)-1-(4--chlorbenzyl)pyrolidin (Sloučenina č. 1506) (22,0 mg, kvant.): Čistota sloučeniny se určila pomocí RPLC/MS (92%) ; ESI/MS m/e 437,0 (M^++H, $C_{21}H_{23}C1F_2N_4O_2$).

Příklady 946 až 952:

Sloučeniny podle vynálezu se syntetizovaly podle metod popsaných v Příkladu 945 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 21.

Tabulka 21

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 946	1506	C21 24 Br C1 N4 02	481	20,6	86
Příklad 947	1507	C21 H24 F C1 N4 02	419	21,7	kvant
Příklad 998	1509	C27 H28 C1 N3 02	462	26,5	kvant
Příklad 949	1510	C21 H24 Cl I N4 02	527	22,0	84
Příklad 950	1511	C19 H21 Br C1 N3 02 S	472	23,7	kvant
Příklad 951	1512	C21 H24 C12 N4 02	435	22,3	kvant
Příklad 952	1513	C27 H2B C1 N3 04 S	526	24,6	94

Referenční příklad 11: Příprava 1-(4-chlorbenzyl)nipekotové kyseliny.

4-chlorbenzylchlorid (6,92 g, 39,9mmol) a Pr_2NEt (7,74 g, 40,0 mmol) se přidaly do ethylnipekotátu (6,29 g, 40,0 mmol) v CH_3CN (15 ml). Reakční směs se nechala míchat po dobu 1,5 hodiny při teplotě 70°C. Kapalina se odstranila pod sníženým tlakem. Ke zbytku se přidal nasycený vodný roztok $NaHCO_3$ (50 ml) a směs se extrahovala EtOAc (100 ml). Organická fáze se promyla nasyceným vodným roztokem $NaHCO_3$ a koncentrovaným roztokem NaCl a vysušila se nad Na_2SO_4. Rozpouštědlo se odstranilo za sníženého tlaku a získal se ethyl-1-(4-chlorbenzyl)nipekotát jako červenožlutý olej (11,025 g, 97%) použitelný bez dalšího čistění. Čistota sloučeniny se určila pomocí RPLC/MS (97%); ESI/MS m/e 382.2 (M^++H, $C_{15}H_{21}C1N0_2$). Roztok LiOH (1.66 g) v H_2O (25 ml) se přidal k roztoku ethyl-1-(4--chlorbenzyl) nipekotátu v THF (60 ml) a CH_3OH (20 ml). Reakční směs se míchala při pokojové teplotě po dobu 15 h. Rozpouštědlo se odstranilo za sníženého tlaku a získala se amorfní pevná látka, která se čistila sloupcovou chromatografií ($Si0_2$, 50%;CH_3OH-CH_2C1_2) a výsledkem byl výtěžek l-(4-chlorbenzyl)nipekotové kyseliny (9.75 g, 98.2%.) získané jako světle žlutá amorfní pevná látka. Čistota sloučeniny se určila pomocí RPLC/MS (95%); ESI/MS m/e 254,0 (M^++H, $C_{13}H_{17}C1N0_2$).

Referenční příklad 12:Příprava 1-(4-chlorbenzyl)-3-{(tercbutoxykarbonyl)amino}piperidinu.

Do roztoku 1-(4-chlorbenzyl)nipekotové kyseliny (7,06 g, 27,8 mmol) ve BuOH (500 ml) se přidal Et_3N (3,38 g) a activované 3 A molekulové síto (30 g). Přidal se difenylfosforylazid (8,58 g) a reakční směs se zahřívala pod refluxem po dobu 18 h. Reakční směs se zchladila a rozpouštědlo se refluxovalo po dobu 18 h. Po zchlazení směsi se rozpouštědlo odstranilo pod vakuem a vzniklý zbytek se rozpustil v EtOAc (500 ml) a organická fáze se promyla saturovaným vodným roztokem $NaHCO_3$ (2 x 100 ml) a nasyceným roztokem NaCl (50 ml), vysušila se (Na_2SO_4) a zakoncentrovala se ve vakuu. Chromatografií ($Si0_2$, 25% EtOAc-hexan) se získal 1-(4-chlorbenzyl)-3-{(terc--butoxykarbonyl)amino}piperidin (2,95 g, 32,6%) jako bílá krystalická pevná látka: ^{1}H NMR ($CDC1_3$, 300 MHz) δ l,4-1,75 (br, 4 H), 2,2-2,7 (br, 4 H) , 3. 5 (br, 2 H) , 3. 8 (br, 1 H) , 7. 3 (br, 4 H); Čistota sloučeniny se určila pomocí RPLC/MS (>99%); ESI/MS m/e 269,0 (M^++H, $C_{17}H_{26}C1N_20_2$).

Referenční příklad 13: Příprava 3-amino-1-(4-chlorbenzyl)piperidinu.

K roztoku 1-(4-chlorbenzyl)-3-{(terc-butoxykarbonyl)amino}piperidinu (2,55 g, 7.85 mmol) v CH_3OH (25 ml) se přidal 1 N HCl-Et_2O (50 ml) . Reakční směs se míchala při 25 °C po dobu 15h. Rozpouštědlo se odstranilo za sníženého tlaku a vznikl 3-amino-1-(4chlorbenzyl)--piperidindihydrochlorid jako amorfní pevná látka (2,49 g, kvant). Čistota sloučeniny se určila pomocí RPLC/MS (>95%); ESI/MS m/e 225,0 (M^++H, $C_{12}H_{18}C1N_2$).

Příklad 953: Příprava 1-(4-chlorbenzyl)-3-[{N-(3methylbenzoyl)glycyl}amino]piperidinu (Sloučenina č. 355).

N-(3-methylbenzoyl)glycin (10.6 mg, 0,055 mmol), EDCI (10,5 mg) a 1-hydroxybenzotriazolhydrát (7,4 mg) se přidaly k roztoku 1-(4-chlorbenzyl)-3-aminopiperidin-dihydrochloridu (14,9 mg,

0,050 mmol) a Et_3N (15.2 mg) v $CHC1_3$ (2,5 ml). Reakční směs se míchala při 25 °C po dobu 16 h, promyla se vodným roztokem 2 N NaOH (2 ml x 2) a nasyceným roztokem NaCl (1 ml). Po filtraci přes PTFE membranový filter, se oddělilo rozpouštědlo za sníženého tlaku a získal se1-(4--chlorbenzyl)-3-[{N-(3-methylbenzoyl)glycyl}amino]piperidin (sloučenina č. **355**) jako světle žlutý olej (17,4 mg, 87%) : Čistota sloučeniny se určila pomocí RPLC/MS (97%); ESI/MS m/e 400,0 (M^++H, $C_{22}H_{26}C1N_3O_2$).

Příklady 954 až 982:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 953 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 22 a sloučenina č. **358** vykázala následující ^1H NMR spektra.

Tabulka 22

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 954	355	C21H24 C1 N302	386	16,1	83
Příklad 955	356	C20 H23 C1 N402	387	19,4	100
Příklad 956	357	C22 H26 C1 N302	400	16,8	89
Příklad 957	359	C22 H26 C1 N302	400	8,9	17
Příklad 958	360	C22 H25 C1 N404	445	25,6	kvant
Příklad 959	361	C23 H27 C1 N202	399	15,5	29
Příklad 960	362	C24 H29 C1 N203	429	12,4	58
Příklad 961	363	C21 H25 C1 N202 S	405	22,2	kvant
Příklad 962	364	C24 H29 C1 N204	445	20,7	93
Příklad 963	365	C24 H29 C1 N202	413	15,6	75
Příklad 964	366	C23 H26 C1 F N2 03	433	21,6	l00
Příklad 965	367	C23 H27 C1 N202	399	11,9	60
Příklad 966	368	C22 H25 C1 N202	385	16,0	83
Příklad 967	369	C22 H24 C12 N2 02	419	13,9	60
Příklad 968	370	C26 H33 C1 N203	457	15,9	59
Příklad 969	371	C25 H31 C1 N2 03	943	19,6	84
Příklad 970	372	C21 H25 C1 N2 03 S	421	23,0	kvant
Příklad 971	373	C23 H28 C1 N3 02	419	19,1	92
Příklad 972	379	C29 H30 C1 N3 03	444	18,6	84
Příklad 973	375	C23 H27 C12 N3 02	948	18,0	80
Příklad 974	376	C24 H30 C1 N3 03	444	19,6	88
Příklad 975	377	C25 H31 C12 N3 02	476	20,7	87
Příklad 976	378	C27 H33 C1 F N3 02	486	23,9	98
Příklad 977	379	C25 H30 C1 N3 03	456	33,3	kvant
Příklad 978	380	C24 H30 C1 N3 02	428	9,8	46
Příklad 979	381	C21 H26 C1 N3 03 S	436	10,3	47
Příklad 980	382	C22 H26 C1 N3 03	416	29,4	kvant

Příklad 981	383	C22 H25 C12 N3 03	450	27,5	kvant

Příklad 982: Sloučenina č. **358:** 88%; ^{1}H NMR ($CDCl_3$) δ 1,53-1,75 (m,4H), 2,12-2,20 (m, 1 H), 2,37-2,50 (m, 2 H), 2,53-2,61 (m, 1 H), 3,38-3,50 (m, 2 H), 2,53-2,61 (m,1H), 3,38-3,50 (m, 2 H), 4,06-q,20 (m, 3 H), 7,10-7,13 (m, 1 H), 7,18-7,30 (m,4H), 7,59 (t, J= 7,8 Hz, 1H), 7,79 (d, J= 7,8 Hz, 1H), 8,01 (d, J = 7,8 Hz, 1H), 8,11(s, 1H).

Referenční příklad 14: Příprava 1-benzyl-4-[{N-(tercbutoxykarbonyl)glycyl}amino]piperidinu.

K roztoku 4-amino-1-benzylpiperidinu (3,80 g, 20 mmol) v CH_2Cl_2 (40 ml) se přidal N- (terc--butoxykarbonyl)glycin (3,48 g, 20 mmol), EDCI (9 . 02 g, 21 mmol) a HOBt (2,83 g, 21 mmol). Reakční směs se míchala při pokojové teplotě po dobu 12 h a poté se přidal vodný roztok 2 N NaOH (20 ml). Oddělila se organická vrstva a vodná fáze se extrahovala dichlormethanem (20 ml x 2). Spojené organické vrstvy se promyly vodou (20 ml) a nasyceným roztokem NaCl (20 ml), vysušily se nad bezvodým síranem sodným, přefiltrovaly se a zakoncentrovaly se. Sloupcovou chromatografií ($Si0_2$, ethyl acetát/MeOH/Et_3N = 85/12/3) se získá 1-benzyl-4-{N-(terc-butoxykarbonyl)--glycyl)aminopiperidin (6,59 g, 95%).

Referenční příklad 15: Příprava 1-(4-chlorobenzyl)-4-(glycylamino)piperidinu.

K roztoku 1-benzyl-4-{N-(terc-butoxykarbonyl)glycyl)aminopiperidinu (6,59 g) v methanolu (80 ml) se přidala 4 N HCl v dioxanu (19 ml). Roztok se míchal při pokojové teplotě 2h. Reakční směs se zakoncentrovala a přidal se 2 N vodný roztok NaOH (20ml). Reakční směs se extrahovala dichloromethanem (40 ml x 3) a spojené extrakty se vysušily nad bezvodým síranem sodným a zakoncentrovaly se. Sloupcová chromatografie ($Si0_2$, AcOEt/MeOH/Et_3N - 85/12/3) poskytla 1-(4--chlorobenzyl)-4-(glycylamino)piperidin (3,91 g, 83%) : ^{1}H NMR ($CDC1_3$, 400 MHz) d 1,47-1,59 (m, 2 H), 1,59 (br, 2 H), 1,76-1,96 (m, 2 H), 2,10-2,19 (m, 2 H), 2,75-2,87 (m, 2 H), 3,29 (s, 2 H), 3,50 (s, 2 H), 3,65-3,89 (m, 1 H), 7,157,23 (m, 1 H), 7,23-7,33 (m, 5 H).

Další 4-acylamino-1-benzylpiperidiny podle předloženého vynálezu byly syntetizovány podle metod popsaných v Příkladech 13 a 14 za použití odpovídajících reaktantů v daném pořadí:

4-(β-alanylamino)-1-benzylpiperidin: 2,46 g, 5l% (2 kroky).

1-benzyl-4-((S)-leucylamino)piperidin: 1,78 g, 74%. (2 kroky).

1-benzyl-4-((R)-leucylamino)piperidin: 1,48 g, 61% (2 kroky).

Příklad 983: Příprava 4-(N-benzoylglycyl)amino-1-benzylpiperidinu (Sloučenina č. 386).

Roztok benzoylchloridu (0,060 mmol) v chloroformu (0,4 ml) se přidal k roztoku 1-(4-chlorbenzyl)--4-(glycylamino)piperidinu (0,050 mmol) a triethylaminu (0,070 mmol) v chloroformu (1,0 ml). Po 2,5 h míchání reakční směsi při pokojové teplotě, se do směsi přidala (aminomethyl)polystyrenová pryskyřice (1,04 mmol/g, 50 mg, 50 mmol) a směs se nechala opět míchat při pokojové teplotě po dobu 12h. Reakční směs se přefiltrovala a pryskyřice se promyla dichloromethanem (0,5 ml). Filtráty a roztoky se po promýchání spojily, přidal se dichloromethan (4 ml). Roztok se promyl 2 N vodným roztokem NaOH (0,5 ml) a získal se 4-(N-benzoylglycyl)amino-1-benzylpiperidin (Sloučenina č. **386**) (11. 3 mg, 69 %) : Čistota sloučeniny se určila pomocí RPLC/MS (94%); ESI/MS m/e 352,0 (M^++H, $C_{21}H_{25}N_3O_2$).

Příklady 984 až 1034:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 983 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 23.

Tabulka 23

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 984	384	C22 H26 Cl N3 02	400	60,0	kvant
Příklad 985	385	C21 H23 C1 N4 09	431	58,7	91
Příklad 986	387	C25 H27 N3 02 02	402,5	15,5	77
Příklad 987	388	C21 H24 N4 04 02	397,0	16,2	82
Příklad 988	389	C23 H27 N3 09	410,0	16,2	79
Příklad 989	390	C22 H29 F3 N3	420,0	17,4	83
Příklad 990	391	C22 H23 F9 N3	438,0	18,4	84
Příklad 991	392	C22 H29 F3 N3 03	436,0	17,1	79
Příklad 992	393	C21 H24 Br N3 02	430,0	18,0	84

Příklad 993	394	C21 H24 C1 N3 02	386,0	16,4	85
Příklad 994	395	C21 H24 Br N3 02	430,0	17,2	80
Příklad 995	396	C21 H23 F2 N3 02	388,0	15,1	78
Příklad 996	397	C21 H23 C12 N302	420,0	11,7	56
Příklad 997	398	C22 H27 N3 02	366,0	13,1	72
Příklad 998	399	C26 H29 N3 02	416,0	15,8	76
Příklad 999	400	C22 H26 N9 04	411,0	17,4	85
Příklad 1000	401	C24 H29 N3 09 02	424,0	16,9	80
Příklad 1001	402	C23 H26 F3 N3	434,0	17,7	82
Příklad 1002	403	C23 H25 F4 N3 02	452,0	18,6	82
Příklad 1003	404	C23 H26 F3 N3 03	450,0	17,8	79
Příklad 1004	405	C22 H26 Br N3 02	444,0	17,9	81
Příklad 1005	406	C22 H26 C1 N3 02	400,0	15,5	78
Příklad 1006	407	C22 H26 Br N3 02	444,0	17,8	80
Příklad 1007	408	C22 H25 F2 N3 02	402,0	15,6	78
Příklad 1008	409	C22 H25 C12 N3 02	434,0	17,6	81
Příklad 1009	410	C25 H33 N3 02	408,0	16,2	79
Příklad 1010	411	C29 H35 N3 02	458,5	18,8	82
Příklad 1011	412	C25 H32 N4 04	453,0	19,4	86
Příklad 1012	413	C27 H35 N3 09	466,0	19,8	85
Příklad 1013	414	C26 H32 F3 N3 02	476,0	20,2	85
Příklad 1014	415	C26 H31 F4 N3 02	494,0	20,5	83
Příklad 1015	416	C26 H32 F3 N3 03	492,0	19,5	79
Příklad 1016	917	C25 H32 Br N3 02	486,0	19,1	79
Příklad 1017	418	C25 H32 C1 N3 02	442,0	17,7	80
Příklad 1018	419	C25 H32 Br N3 02	486,0	20,3	83
Příklad 1019	420	C25 H31 F2 N3 02	444,0	18,6	89
Příklad 1020	421	C25 H31 C12 N3 02	476,0	19.	
Příklad 1021	422	C25 H33 N3 02	408,0	14,4	71
Příklad 1022	423	C29 H35 N3 02	458,0	16,4	72

Příklad 1023	424	C25 H32 N4 09	453,0	18,1	80
Příklad 1024	425	C27 H35 N3 04	466,0	16,4	70
Příklad 1025	426	C26 H32 F3 N3 02	476,0	17,3	73
Příklad 1026	927	C26 H31 F4 N3 02	494,0	18.B	76
Příklad 1027	928	C26 H32 F3 N3 03	992,0	18,9	75
Příklad1028	429	C25 H32 Br N3 02	486,0	17,9	74
Příklad1029	430	C25 H32 C1 N3 02	942,0	15,7	71
Příklad 1030	431	C25 H32 Br N3 02	486,0	17,7	73
Příklad 1031	432	C25 H31 F2 N3 02	444,0	16,6	75
Příklad 1032	433	C25 H31 C12N3 02	476,0	18,7	78
Příklad 1033	1016	C22 H23 C1 F3 N3 02	454	32,5*	53
Příklad 1034	1017	C21 H24 C1 N3 02	386	55,2*	kvant

- Výtěžek TFA soli

Referenční příklad 16: Příprava 3-karbamoyl-1-(4-chlorbenzyl)piperidinu.

K roztoku nipekotamidu (6,40 g, 50 mmol) v CH_3CN (150 ml) a ethanolu (20 ml) se přidal Et_3N (7,0 ml, 50 mmol) a 4-chlorbenzyl chlorid (8,05 g, 50 mmol) . Reakční směs se míchala při 50 °C po dobu 16 h. Po ochlazení na pokojovou teplotu, se do reakční směsi přidal nasycený vodný roztok $NaHCO_3$ (50 ml) a vody (150 ml). Reakční směs se extrahovala ethylacetátem (150 ml x 3) a spojené organické vrstvy se promyly solným roztokem, vysušily (Na_2S0_4) a zakoncentrováním se dostala světle červená pevná látka. Tato surová látka se promyla etherem (100 ml) a získal se 3-karbamoyl-1-(4-chlorbenzyl)piperidin (6,98 g, 54%).

Referenční příklad 17: Příprava 3-(aminomethyl)-1-(4- chlorbenzyl)piperidinu.

3-karbamoyl-1-(4-chlorbenzyl)piperidin (3.80 g, 15 mmol) se rozpustil v THF (30 ml) a do roztoku se přidal 1 M BHP-THF (9.4 ml). Reakční směs se míchala při 70 °C po dobu 15 h. Po ochlazení směsi na 0 °C se do reakce přidal 2 N vodný roztok HC1 (50 ml) a směs se nechala míchat při pokojové teplotě po další 3 h, upravilo se pH na zásaditou hodnotu pomocí 4 N vodného roztoku NaOH a směs se extrahovala pomocí ethylacetátu (100 ml x 3). Spojené extrakty se promyly nasyceným roztokem NaCl, vysušily nad bezvodým Na_2SO_4, přefiltrovaly se a zakoncentrovaly. Pomocí sloupcové chromatografie (SiO_2, ethyl-acetat/EtOH/Et_3N - 80/15/5) se získal 3-(aminomethyl)-1-(4-

-chlorbenzyl)piperidin (2,05 g, 55%.): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1,00-1,09 (m, 1 H), 1,50-1,87 (m, 7 H), 1,97-2,06 (m, H), 2,65-2,77 (m, 2 H), 3,16-3,26 (m, 2 H), 3,32 (s, 2 H), 3,40_íd, J = 13,3 Hz, 1 H), 3,49 (d, J = 13,3 Hz, 1 H), 7,22-7,33 (m, S H).

Příklad 1035: Příprava 3-{(N-benzoylglycyl)amino}methyl-1-(4-chlorbenzyl)piperidinu (Sloučenina č. 434).

Roztok benzoyl chloridu (0,060 mmol) v chloroformu (0.4 ml) se přidal k roztoku 3-(aminomethyl)-1--(4-chlorbenzyl)piperidinu (0,050 mmol) a triethylaminu (0. 070 mmol) v chloroformu(1,0 ml). Po míchání trvajícím 2,5 h při pokojové teplotě se přidala aminomethylpolystyrenová pryskyřice (1,04 mmol/g, 50 mg, 50 mmol) a směs se dále ponechala míchat při pokojové teplotě po dobu 12 h. Reakční směs se přefiltrovala a pryskyřice se promyla dichlormethanem (0,5 ml). Filtráty a promývací roztok se spojily a přidal se dichlormethan (4 ml) a roztok se dále promyl 2 N vodným roztokem NaOH (0,5 ml) a získal se 3-{(N-benzoylglycyl)amino)methyl-1-(4-chlorbenzyl)piperidin (sloučenina č. **434)** (14,7 mg, 74%): Čistota sloučeniny se určila pomocí RPLC/MS (91%); ESI/MS m/e 400,0 (M^++H, $C_{22}H_{26}C1N_3O_2$).

Příklady 1036 až 1058:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1035 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 24.

Tabulka 24

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1036	435	C26 H28 C1 N3 02	450	16,0	71
Příklad 1037	436	C22 H25 C1 N4 04	445	18,9	85
Příklad 1038	937	C24 H28 C1 N3 04	458	18,2	79
Příklad 1039	438	C23 H25 C1 F3 N3 02	468	19,0	81
Příklad 1040	439	C23 H24 C1 F4 N3 02	486	20,2	83
Příklad 1041	440	C23 H25 C1 F3 N3 03	484	18,9	78

Příklad 1042	491	C22 H25 Br C1 N3 02	478	19,2	80
Příklad 1043	442	C22 H25 C12 N3 02	434	17,3	80
Příklad 1044	443	C22 H25 Br C1 N3 02	478	18,8	79
Příklad 1045	444	C22 H24 C1 F2 N3 02	936	16,7	77
Příklad 1046	445	C22 H24 C13 N3 02	468	17,9	76
Příklad 1047	496	C23 H28 C1 N3 02	414	14,6	71
Příklad 1048	447	C27 H30 C1 N3 02	464	17,0	73
Příklad 1049	448	C23 H27 C1 N404	459	19,5	85
Příklad 1050	949	C25 H30 C1 N309	472	17,1	72
Příklad 1051	450	C24 H27 Cl F3 N3 02	482	19,9	81
Příklad 1052	451	C24 H26 C1 F4 N3 02	500	18,2	73
Příklad 1053	452	C29 H27 C1 F3 N3 03	498	18,8	76
Příklad 1054	453	C23 H27 BrC1N3 02	992	19,4	79
Příklad 1055	454	C23 H27 C12N3 02	448	16,5	74
Příklad1056	455	C23 H27 Br C1N3 02	492	19,3	78
Příklad1057	456	C23 H26 C1 F2 N3 02	450	17,1	76
Příklad1058	457	C23 H26 C13N3 02	482	16,9	70

Referenční příklad 18: Příprava 4-(aminomethyl)-1-(4-chlorbenzyl)piperidinu.

K roztoku 4-(aminomethyl)piperidinu (7,00 g, 61.3 mmol) v CH_3CN (100 ml) se následně přidal K_2C0_3 (3,02 g) a 4-chlorobenzylchlorid (3,52 g, 21,8 mmol). Reakční směs se zahřívala na 60 °C po dobu 16 h, ochladila se na 25 °C a zakoncentrovala se. Vzniklé produkty se rozdělily mezi CH_2C1_2 (75 ml) a vodu (50 ml) a organická vrstva se promyla vodou (2 x 50 ml) a nasyceným roztokem NaCl (1 x 50 ml). Organická fáze se vysušila ($MgSO_4$) a zakoncentrovala se. Chromatografií ($Si0_2$, 4% H_20-PrOH) se získal 4-(aminomethyl)-1-(4-chlorbenzyl)piperidin (3,58 g, 69%).

Příklad 1059: Příprava 4-{(N-benzoylglycyl)amino}methyl-1-(4-chlorbenzyl)piperidinu (Sloučenina č. 458).

K roztoku 4-(aminomethyl)-1-(4-chlorbenzyl)piperidinu (50 mg, 0,21 mmol) v CH_2C1_2 (1 ml) se přidala kyselina hipurová (38 mg, 0,21 mmol), EDCI (48mg, 0,24mmol), HOBt (31 mg, 0,23 mmol) a Et_3N (38 µl, 0,27 mmol). Reakční směs se nechala míchat po dobu 16 h při 25 °C, naředila se 1 ml CH_2C1_2, promyla se vodným roztokem 2 N NaOH (2 x 0,75 ml), vysušila se ($MgS0_4$) a zakoncentrovala se. Chromatografie ($Si0_2$, 6 až 8% CH_3OH/CH_2C1_2, gradientová eluce) poskytla 4-{(Nbenzoylglycyl)amino}methyl-1-(4--chlorbenzyl)piperidin (Sloučenina č. **458),** na který se působí TFA , aby vznikla TFA sůl (105 mg, 97%): %): Čistota sloučeniny se určila pomocí RPLC/MS (85%); ESI/MS m/e 400,0 (M^++H, $C_{22}H_{26}C1N_3O_2$).

Příklady 1060 až 1086:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1059 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 25.

Tabulka 25

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1060	959	C23 H28 C1 N3 02	414	86*	78
Příklad 1061	960	C23 H28 C1 N3 02	419	SS	kvant
Příklad 1062	461	C23 H25 C1 F3 N3 02	968	65	kvant
Příklad 1063	462	C23 H28 C1 N3 02	914	61	kvant
Příklad 1064	463	C23 H28 C1 N3 02	414	54	kvant
Příklad 1065	469	C25 H32 C1 N3 05	490	56	kvant
Příklad 1066	465	C21 H 25 C1 N4 02	401	38	96
Příklad 1067	466	C22 H25 C1 N9 04	445	15	34
Příklad 1068	557	C23 H28 C1 N3 02	414	58*	66
Příklad1069	558	C23 H 28 C1 N3 02	414	55	kvant

Příklad1070	618	C25 H32 Cl N3 02	442	58	kvant
Příklad 1071	686	C26 H34 C1 N3 02	956	62	kvant
Příklad1072	749	C34 H37 C1 N4 02	569	7,2*	18
Příklad1073	750	C24 H30 C1 N3 03	444	4,7*	14
Příklad1074	840	C24 H29 Cl N2 02	413	52*	58
Příklad1075	841	C23 H27 C1 N2 02	399	52	kvant
Příklad1076	842	C23 H26 C12 N2	02	433	55
Příklad1077	843	C25 H31 C1 N2 02	427	58	kvant
Příklad1078	844	C24 H29 C1 N2 02	413	56	kvant
Příklad1079	845	C24 H29 C1 N2 04 S	477	62	kvant
Příklad1080	896	C29 H31 C1 N2 03	491	43	88
Příklad1081	847	C24 H28 C1 F N2 03	447	54	kvant
Příklad1082	848	C25 H31 C1 N2 02	427	47	kvant
Příklad1083	849	C25 H31 C1 N2 04	959	55	kvant
Příklad1084	850	C22 H27 C1 N2 03 S	435	46	kvant
Příklad1085	873	C20 H28 C1 N3 02	378	44,8	kvant
Příklad 1086	879	C23 H27 C12N3 03	464	51	kvant

- Výtěžek TFA soli

Referenční příklad 19: Příprava 1-(4-chlorbenzyl)-4-{N-(3,3-difenylpropyl)--aminomethyl}piperidinu.

4-(aminomethyl)-1-(4-chlorbenzyl)piperidin (120 mg) se alkyloval 3,3-difenylpropylmethansulfonát (1,0 equiv.) v přítomnosti NaI (2,6 ekvival.) v CH_3CN při 70 °C po dobu 16 h. Běžnými postupy a chromatografií ($Si0_2$) vznikl 1-(4-chlorbenzyl)-4-{N-(3,3-difenylpropyl)aminomethyl)piperidin

(118 mg, 54%): Čistota sloučeniny se určila pomocí RPLC/MS (98%).

Referenční příklad 20: Příprava 1-(4-chlorbenzyl)-4-{N-(2,2-difenylethyl)-aminomethyl}-piperidinu.

Po redukční aminaci 4-(aminomethyl)-1-(4-chlorbenzyl)piperidinu (120 mg) s 2,2-difenyl--acetaldehydem (0.66 ekviv.) a borohydridem vázaným na polymeru v methanolu při 25 °C po dobu 16 h, následovaly obecné postupy a sloupcovou chromatografií (SiO_2) se získal 1-(4-chlorbenzyl)-4--(N-(2,2-difenylethyl)aminomethyl)piperidin (70 mg, 49%): Čistota sloučeniny se určila pomocí RPLC/MS (98%).

Příklad 1087: Příprava 4-{N-(N-benzoylglycyl)-N-(2,2-difenylethyl)aminomethyl}-1-(4--chlorbenzyl)piperidinu (Sloučenina č. 524).

K roztoku 1-(4-chlorbenzyl)-4-(N-(2,2-difenylethyl)aminomethyl}piperidinu (0,084 mmol) v CH_2C1_2 se přidala hipurová kyselina (1,1 ekviv.), HBTU (1. 1 ekviv.), HOBt (1,1 ekviv.) . Reakční směs se míchala při 40°C po dobu 24 h. Obecnými uvedenými pracovními postupy a preparativní TLC (SiO_2) se získal 4-(N-(N-benzoylglycyl)-N-(2,2-difenylethyl)aminomethyl}-1-(4-chlorbenzyl)piperidin (Sloučenina č,**524**) (8,5 mg, 17%): Čistota sloučeniny se určila pomocí RPLC/MS (98%); ESI/MS m/e 580 (M^++H, $C_{36}H_{38}$ $C1N_3O_2$).

Příklady 1088 až 1090:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1087 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 26.

Tabulka 26

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1088	521	C38 839 C1 F3 N3 02	662	5,5	10
Příklad 1089	522	C37 837 C1 F3 N3 02	648	8,6	16
Příklad 1090	523	C37 840 C1 N3 02	594	4,8	10

Referenční příklad 21: Příprava 1-(4-chlorbenzyl)-4-{(valylamino)methyl}piperidinu.

Na roztok 4-(aminomethyl)-1-(4-chlorbenzyl)piperidinu (1,0 g, 4.2 mmol) v CH_2C1_2 (21 ml) se působilo Et_3N (0.76 ml, 5.44 mmol), d-N(terc-butoxykarbonyl)valinem (1,09 g, 5,03 mmol), EDCI (883 mg, 4.61 mmol) a HOBt (623 mg, 9.61 mmol). Reakční směs se míchala při 25 °C po dobu 16 h. Vzniklý roztok se naředil CH_2C1_2 (20 ml) a promyl se roztokem 2 N NaOH (2 x 20 ml), solným roztoken (1 x 20 ml) a vysušil ($MgS0_4$). Zakoncentrováním a následnou chromatografií ($Si0_2$, 3%, CH_3OH/CH_2C1_2) se získal 1-(4-chlorbenzyl)-4-[{(N-Boc--valyl)amino)methyl]piperidin (1,1 g, 60'x) ve formě světle jantarově zbarveného oleje: ESI/MS m/e 438 (M^++H) .

1-(4-chlorbenzyl)-4-[{(N-Boc-valyl)amino}methyl]piperidin (1,1 g, 2,51 mmol) se rozpustil v roztoku 3 M HC1-CH_3OH (25 ml) a ponechal se míchat po dobu 1 h při 25°C. Reakční směs se zakoncentrovala a výsledná sůl se rozpustila ve směsi BuOH –H_2O (3:1, 25 ml). Přidávala se anion měničová pryskyřice dokud roztok nebyl slabě bazický. Filtrací a zakoncentrováním se získal 1-(4--chlorbenzyl)-4-{(valylamino)methyl}piperidin (819 mg, 97%) který nevyžadoval již další purifikaci: RPLC (97%) ; ESI/MS 338. 1 (M++H, $C_{18}H_{22}C1N_30$).

Další 4-{(acylamino)methyl}-1-(4-chlorbenzyl)piperidiny podle předloženého vynálezu byly syntetizovány podle způsobů popsaných v Referenčním příkladu 20 za použití odpovídajících reaktantů.

1-(4-chlorbenzyl)-4-{(glycylamino)methyl}piperidin: 0,830g, %(2 kroky); ESI/MS 269 (M^++H).

1-(4-chlorbenzyl)-4-{(serylamino)methyl)piperidin: 0,286g, 20%. (2 kroky); ESI/MS 326 (M^++H).

4-{(alanylamino)methyl}-1-(4-chlorbenzyl)piperidin: 1,20 g, 65% (2 kroky); ESI/MS 310 (M^++H).

1-(4-chlorbenzyl)-4-((prolylamino)methyl)piperidin: 1,48 g, 86% (2 kroky); ESI/MS 336 (M^++H).

1-(4-chlorbenzyl)-4-{(glutaminylamino)methyl}piperidin: 0,830 g, 27% (2 kroky); ESI/MS 367 (M^++H).

1-(4-chlorbenzyl)-4-{((2-methylalanyl)amino)methyl}piperidin: 2,24 g, 62% (2 kroky); ESI/MS 324 (M^++H).

1-(4-chlorbenzyl)-4-{((O-methylseryl)amino)methyl}piperidin:0,686 g, 38g (2 kroky); ESI/MS 340 (M^++H).

1-(4-chlorobenzyl)-4-{((1-aminocyklopropylkarbonyl)amino)methyl}piperidin: 2,03 g, 82% (2 kroky); ESI/MS 322 (M^++H).

1-(4-chlorbenzyl)-4-{(leucylamino)methyl}piperidin: 1,30 g, 58% (2 kroky); ESI/MS 352 (M^++H).

1-(4-chlorbenzyl)-4-{((O-benzylseryl)amino)methyl}piperidin: 1,39 g, 56%(2 kroky); ESI/MS 416 (M^++H).

Referenční příklad 22: Příprava 1-(terc-butoxykarbonyl)-4-[{N-(9-fuluorenylmethyl--oxykarbonyl)glycyl}aminomethyl]piperidinu.

K roztoku 4-(aminomethyl)-1-(terc-butoxykarbonyl)piperidinu (5.72 g) v CH_2C1_2 (150 ml) se přidal Et_3N (3,51 g), N-(9-fuluorenylmethyloxykarbonyl)glycinu (7,93 g, 26.7 mmol), EDCI (3.80 g) a HOBt (4.33 g). Reakční směs se míchala při pokojové teplotě po dobu 5h, poté se směs promyla vodou

(100 ml x 3) a nasyceným roztokem NaCl (100 ml x 2), vysušila pomocí bezvodého síranu sodného, přefiltrovala a zakoncentrovala. Rekrystalizací z CH_3CN/CH_3OH (150 ml/1 ml) při 0°C se získal 1--(terc-butoxykarbonyl)-4-((N-(9-fluorenylmethyloxykarbonyl)glycyl)aminomethyl]piperidin (5.758, 44%) ve formě světle žlutých krystalů.

Referenční příklad 23: Příprava 4-[{N-9-fuluorenylmethyloxykarbonyl)glycyl}aminomethyl]--piperidinu.

K rozroku 1-(terc-butoxykarbonyl)-4-[(N-(9-fluorenylmethyloxykarbonyl)glycyl}-aminomethyl]--piperidinu (3,17 g, 6,42 mmol) se přidala 4 N HC1 v dioxanu (50 ml). Roztok se nechal míchat při pokojové teplotě po dobu 5 h. Reakční směs se zakoncentrovala a získal se 4-[(N-(9-fluorenylmethyl--oxykarbonyl)glycyl)aminomethyl]piperidin (3,85 g) jako bílá pevná látka. Produkt lze použít bez dalšího čistění.

Refereńční příklad 24: Příprava 4-[{N-(9-fluorenylmethyloxykarbonyl)glycyl}aminomethyl]-1--(4-methylthiobenzyl)piperidinu.

K roztoku 4-[{N-(9- fluorenylmethyloxykarbonyl)glycyl)aminomethyl]piperidinu (1,0mL,

2,33 mmol) v 1% AcOH/DMF (15 ml) se přidal 4-methylthiobenzaldehyd (1,24 g) a NaBH $(OAc)_3$ (2,56 g). 2,56 g). Reakční směs se nechala míchat při 60 °C po dobu 1 h, ochladila se, zakoncentrovala se. Poté se přidal nasycený vodný roztok $NaHCO_3$ (50 ml) a směs se extrahovala AcOEt (50 ml x 2). Spojené extrakty se vysušily pomocí bezvodého síranu sodného, přefiltrovaly se a

zakoncentrovaly se. Sloupcovou chromatografií (SiO_2, 5%-10% CH_3OH/CH_2Cl_2) se získal 4-[{N-(9--fluorenylmethyloxykarbonyl)glycyl}aminomethyl]-1-(4methylthiobenzyl)piperidin (602 mg) jako bezbarvý olej.

Referenční příklad 25: Příprava 1-(4-ethylbenzyl)-4-[{N-(9-fluorenylmethyloxykarbonyl)--glycyl}aminomethyl]piperidinu.

K roztoku 4-[{N-(9- fluorenylmethyloxykarbonyl)glycyl}aminomethyl]piperidinu (1,00 g, 2.33 mmol) ve 2,5% $AcOH/CH_3OH$ (80 ml) se přidal 4-ethylbenzaldehyd (1,09 g, 8,16 mmol) a $NaBH_3CN$ (6. 59 g, 10. 5 mmol) . Reakční směs se ponechala míchat při 60 °C po dobu 13 h. Po zchlazení směsi na pokojovou teplotu se přidal vodný roztok 1 N NaOH (50 ml) a dichloromethanu (50 ml). Oddělily se organické vrstvy a vodná vrstva se extrahovala dichloromethanem (50 ml x 3). Spojené organické vrstvy se promyly nasyceným roztokem NaCl, vysušily pomocí bezvodého síranu sodného, přefiltrovaly a zakoncentrovaly se. Sloupcovou chromatografií (Si02, CH_3OH/AcOEt 1: 8 se získal 1-(4-ethylbenzyl)-4-[{N-(9- fluorenylmethyloxykarbonyl)glycyl) aminomethyl]piperidin

(740 mg, 62%).

Referenční příklad 26: Příprava 4-{(glycylamino)methyl}-1-(4methylthiobenzyl)piperidinu.

Roztok 4-[{N-(9-fluorenylmethyloxykarbonyl)glycyl)aminomethyl]-1-(4-methylthiobenzyl)--piperidinu (590 mg) a piperidinu (1 ml) v DMF (4 ml) se míchal při pokojové teplotě po dobu 2 h. Zakoncentrováním a sloupcovou chromatografií (SiO_2, Et_3N : CH_3OH : CH_2Cl_2 - 1 : 1 : 9) se získal 4-{(glycylamino)methyl)-1(4-methylthiobenzyl} piperidin (365 mg) jako bílá pevná látka : ^1H NMR ($CDCl_3$, 270 MHz) δ 1 ,25 (dd, J = 12 Hz, 4 . 1 Hz, 2 H) , 1,34 (dd, J = 12 Hz, 4. 1 Hz, 2 H) , 1. 51 (br-s, 2 H), 1,66 (d, J = 12 Hz, 2 H), 1,77 (d, J = 7,3 Hz, 1 H), 1,94 (t, J = 9,5 Hz, 25 2 H), 2,48 (s, 3 H), 2,80 (d, J = 12 Hz, 2 H), 3,18 (t, J = 6,2 Hz, 2 H), 3,35 (s, 2 H), 3,45 (s, 2 H), 7,18-7,29 (m, 4 H), 7,35 (br-s, 1 H).

1-(4-ethylbenzyl)-4-{(glycylamino)methyl)piperidin lze taktéž nasyntetizovat pomocí metod uvedených v Referenčním příkladu 25 pomocí odpovídajících reaktantů: 333 mg, 79%.

Referenční příklad 27: Příprava 4-{(glycylamino)methyl}-1-(4-fluorbenzyl)piperidinu.

Roztok 4-[{N-(9- fluorenylmethyloxykarbonyl)glycyl)aminomethyl]piperidinu (1,50 g, 3,99 mmol), 4-fluorbenzylbromidu (0.478 ml, 3.89 mmol) a Et_3N (1,97 ml, 10,5 mmol) v CH_3CN (200 ml) se nechal míchat při pokojové teplotě po dobu 12 hodin a poté se zakoncentroval.Sloupcovou chromatografií ($Si0_2$, 10%. CH_3OH/CH_2Cl_2) se získal 4-[{N-(9-fluorenylmethyloxykarbonyl)--glycyl)aminomethyl]-1-(4-fluorbenzyl)piperidin.

Roztok 4-[{N-(9-fluorenylmethyloxykarbonyl)glycyl)aminomethyl)-1-(4-fluorobenzyl)piperidinu a piperidinu (5 ml) v DMF (5 ml) se míchá při pokojové teplotě po dobu 17 hodin a poté se zakoncentruje. Sloupcovou chromatografií ($Si0_2$, Et_3N : CH_3OH : CH_2Cl_2 = 0,5 : 2: 8) se získá 4--((glycylamino)methyl)-1-(4-fluorbenzyl)piperidin (453 mg, 4 6 %) .

Referenční příklad 28: Příprava 4-((glycylamino)methyl)-1-(4-(N-fenylkarbamoyl)benzyl}--piperidinu.

Ke směsi 4-[(N-(9-fluorenylmethyloxykarbonyl)glycyl)aminomethyl]piperidinu (1.27 g, 2,96 mmol), Et_3N (1.25 ml, 8.88 mmol), KI (50 mg, 0.30 mmol) a CH_3CN (200 ml) se přidával po kapkách roztok 4-(N-fenylkarbamoyl)benzylchloridu (800 mg, 3.26 mmol) v CH_3CN (100 ml). Směs se míchalacpři pokojové teplotě po dobu 19 h a dále při 60 °C po dobu 5 h. Zakoncentrováním a sloupcovou chromatografií (Si02, 5% CH_3OH /CH_2C1_2/Et_3N = 2 : 2 : 96) se získal 4-((glycylamino)methyl}-1-(4-(N-fenylkarbamoyl)benzyl}piperidin (340 mg, 30%).

Příklad 1091: Příprava 1-(4-chlorbenzyl)-4-[(N-(3-kyanobenzoyl)valyl)aminomethyl]piperidinu (Sloučenina č. 619).

K roztoku 1-(4-chlorbenzyl)-4-(valylamino)methyl)piperidinu (20 mg, 0,059 mmol) v CH_2C1_2.

(0.60 ml) se přidal Et_3N (0,011 ml, 0,077 mmol), 25 m-kyanobenzoová kyselina (28 mg, 0,071 mmol), EDCI (13 mg, 0,065 mmol) a HOBt (9 mg, 0,065 mmol). Reakční směs se míchala po dobu 16 při 25 °C. Vzniklý roztok se naředil pomocí CH_2C1_2 (0.75 ml), promyl dvakrát vodným roztokem 2 N NaOH (2 x 0.75 ml) a vysušil filtrací přes PTFE membránu.

Zakoncentrováním se získal 1-(4-chlorbenzyl)-4-[(N-(3kyanobenzoyl)valyl)aminomethyl]piperidin (Sloučenina č. **619)** (29.2 mg, 88 %), který se nemusí již dále čistit: Čistota sloučeniny se určila pomocí RPLC/MS (85%);ESI/MS m/e 467 (M^++H, $C2_6H_{31}$ C1N40$_2$).

Příklady 1092 až 1543:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1087 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 27.

Tabulka 25

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1092	467	C22 H25 Br C1 N3 02	478	11	46
Příklad 1093	468	C24 H31 C1 N4 02	443	9	41
Příklad1094	469	C23 H28 C1 N3 03	430	7*	27
Příklad1095	470	C23 H25 C1 N4 02	425	21	kvant
Příklad1096	471	C24 H28 C1 N3 04	458	7	29
Příklad1097	472	C29 H31 N303	504	5*	21
Příklad1098	473	C24 H28 C1 N3 03	442	16	71
Příklad1099	474	C23 H25 C1F3 N3 02	468	14	60
Příklad1100	475	C25 H32 C1 N3 02	442	' S	22
Příklad1101	476	C22 H25 C1 N4 04	445	4	17
Příklad1102	477	C25 H32 C1 N3 03	458	10*	36
Příklad1103	478	C21 H27 C1 N4 02	403	9	q7
Příklad1104	479	C20 H29 C1 N3 03	390	17	87
Příklad1105	480	C20 H23 Br C1 N3 03	470	23	kvant
Příklad1106	481	C20 H24 C1 N3 02 S	406	7	33
Příklad1107	482	C21 H26 C1 N3 02 S	420	9	45
Příklad1108	483	C21 H26 C1 N3 02 S	420	8	40
Příklad1109	484	C24 H27 C1 N4 02	439	9*	34
Příklad1110	485	C24 H24 C1F6 N3 02	S36	13	Q9
Příklad1111	486	C23 H25 C1 N4 02	425	16	74
Příklad1112	487	C22 H25 C12 N3 02	434	5	24
Příklad1113	488	C22 H27 C1 N4 02	415	7	32
Příklad1114	489	C24 H24 C1F6 N302	536	21	78

Příklad1115	490	C29 H30 C1 N3 03	449	8	35
Příklad1116	491	C23 H24 C1 F4 N3 02	486	19	79
Příklad1117	992	C23 H25 C1 F3 N3 03	489	18	76
Příklad1118	493	C23 H24 C12 F3 N3 02	502	23	92
Příklad1119	494	C23 H24 C1 F4 N3 02	486	19	79
Příklad1120	495	C23 H24 C1 F4 N3 02	486	20	83
Příklad1121	496	C23 H24 C1 F4 N3 02	486	12	98
Příklad1122	497	C25 H32 C1 N3 03	458	4	16
Příklad1123	498	C23 H26 C1 F3 N4 02	483	13	52
Příklad1124	499	C24 H31 C1 N9 02	443	8	36
Příklad1125	500	C23 H28 C1 N3 03	430	10	48
Příklad1126	501	C22 H24 Br C1 N4 09	523	10	39
Příklad1127	502	C22 H24 C1 F N4 04	463	4	17
Příklad 1128	503	C22 H24 C12 N4 04	475	12	52
Příklad1129	509	C24 H30 C1 N3 04	460	11	43
Příklad1130	505	C22 H24 Br C1 N4 04	523	2	8
Příklad1131	506	C20 H23 C1 N4 05	435	2	10
Příklad1132	507	C21 H26 C1 N3 03	404	9	qq
Příklad1133	508	C24 H26 C1 N3 02 S	456	1	5
Příklad1134	509	C20 H23 Br C1 N3 02 S	484	12	48
Příklad1135	510	C22 H28 C1 N3 03	418	9	48
Příklad1136	511	C29 H32 C1 N3 03	446	9	40
Příklad1137	512	C25 H29 C1 N4 02	453	10	45
Příklad1138	513	C24 H28 C1 N3 03	442	9	41
Příklad1139	514	C26 H34 C1 N3 02	456	11	49
Příklad1140	515	C23 H28 C1 N3 03	430	5	24
Příklad1141	525	C23 H28 C1 N3 04 S	478	20	85
Příklad1142	526	C20 H24 C1 N3 03	390	6	31
Příklad1143	527	C20 H24 C1 N3 02 S	406	8	39
Příklad1144	528	C25 H30 C1 F3 N4 04	543	28,2	95

Příklad1145	529	C20 H23 C1 N4 04 S	451	9	39
Příklad1196	530	C31 H33 C1 N4 02	529	5	17
Příklad1147	531	C21 H26 C1 N3 03 S	436	8	37
Příklad1148	532	C22 H28 C1 N3 03	418	8	40
Příklad1199	533	C21 H26 C1 N3 03	404	6	32
Příklad1150	534	C21 H25 C1 N4 05	449	5	20
Příklad1151	535	C22 H26 C1 N3 03 S	448	8	37
Příklad1152	536	C23 H31 C1 N4 02	431	6	28
Příklad1153	537	C25 H34 C1 N3 03	460	8	39
Příklad1154	538	C27 H30 C1 N3 03	480	9	36
Příklad1155	539	C22 H25 C1 F3 N3 03	472	18	75
Příklad1156	540	C25 H29 C1 N4 02	453	8	36
Příklad1157	541	C22 H26 C1 N5 09	460	2,4	10
Příklad1158	542	C24 H30 C1 N3 02	428	4,6*	51
Příklad1159	543	C24 H30 C1 N3 02	428	20,6*	71
Příklad1160	544	C22 H25 C1 F N3 02	418	15,8*	56
Příklad1161	545	C22 H24 C13N3 02	468	7,3*	23
Příklad1162	546	C22 H24 C13N3 02	468	17,4*	55
Příklad1163	547	C22 H24 C13N3 02	468	14,1*	99
Příklad1164	548	C22 H24 C13N3 02	968	6,8*	22
Příklad1165	549	C22 H24 C12N4 09	479	5,7*	18
Příklad1166	550	C22 H24 C12N4 04	479	18,9*	58
Příklad1167	551	C29 H30 C1 N3 02	428	14,2*	49
Příklad1168	552	C24H27C1F3N302	482	30,6*	94
Příklad1169	553	C25 H26 C1 F6 N3 02	550	38,0*	kvant
Příklad1170	559	C24 H26 C1 F N4 02	957	0,9*	3
Příklad1171	555	C24 H26 C12 N9 02	473	11,1*	35
Příklad1172	556	C25 H29 C1 N402	453	12,5*	41
Příklad1173	559	C25 H26 C1 F6 N3 02	550	15	72
Příklad1174	560	C24 H27 C1 N402	439	12	68

Příklad1175	561	C23 H27 Br C1 N3 02	499	14	73
Příklad1176	562	C23 H27 C12 N3 02	448	13	75
Příklad1177	563	C25 H26 Cl F6 N3 02	550	14	66
Příklad1178	564	C25 H32 C1 N3 03	458	S	28
Příklad1179	565	C24 H26 C1 F9 N3 02	500	12	61
Příklad1180	566	C24 H27 C1 F3 N3 03	498	12	62
Příklad1181	567	C29 H26 C12 F3 N3 02	516	12	61
Příklad1182	568	C24 H26 C1 F4 N3 02	500	15	77
Příklad1183	569	C24 H26 C1 F4 N3 02	500	11	59
Příklad1184	570	C24 H26 C1 F4 N3 02	500	16	89
Příklad1185	571	C26 H34 C1 N3 03	472	14	77
Příklad1186	572	C24 H28 C1 F3 N4 02	497	11	55
Příklad1187	573	C21 H25 Br C1 N3 02 S	500	12	64
Příklad1188	574	C2I H25 Br C1 N3 02 S	500	15	75
Příklad1189	575	C25 H34 C1 N3 03	960	16	87
Příklad1190	576	C22 H28 C1 N3 02 S2	466	13	71
Příklad1191	577	C22 H28 C1 N3 03	418	12	72
Příklad1192	578	C25 H28 C1 N3 02 S	470	15	81
Příklad1193	579	C25 H29 C1 N4 02	453	17	94
Příklad1194	580	C22 H28 C1 N3 02 S	434	15	91
Příklad1195	581	C21 H26 C1 N3 02 S	420	13	80
Příklad1196	582	C22 H28 C1 N3 02 S	434	10	59
Příklad1197	583	C26 H31 C1 N4 02	467	6	31
Příklad1198	584	C30 H32 C1 N3 03	518	18	92
Příklad1199	585	C24 H27 C1 N9 02	439	14	85
Příklad1200	586	C23 H27 C12 N3 02	448	17	97
Příklad1201	587	C24 H27 C1 F3 N3 02	482	17	91
Příklad1202	588	C23 H29 C1 N4 02	429	5	29
Příklad1203	589	C27 H36 C1 N3 02	470	4	24
Příklad1204	590	C26 H39 C1 N3 02	456	6	36

Příklad1205	591	C25 H33 C1 N4 02	457	7	38
Příklad1206	592	C24 H30 C1 N3 03	449	4	20
Příklad1207	S93	C24 H30 C1 N3 03	949	2	19
Příklad1208	594	C23 H28 C1 N3 03	430	4	25
Příklad1209	595	C25 H30 C1 N3 04	472	7	38
Příklad1210	596	C25 H30 CI N3 03	456	7	40
Příklad1211	597	C25 H30 C1 N3 03	456	15	85
Příklad1212	598	C21 H26 C1 N3 03	404	15	94
Příklad1213	599	C22 H29 C1 N4 02	917	5	30
Příklad1214	600	C21 H25 Br C1 N3 03	489	6	39
Příklad1215	601	C24 H30 C1 N3 03	444	5	28
Příklad1216	602	C25 H33 C1 N4 02	457	S	28
Příklad1217	603	C23 H29 C1 N4 02	429	9	22
Příklad1218	604	C21 H27 C1 N4 02	903	9	58
Příklad1219	605	C21 H26 C1 N3 03	404	17	87
Příklad1220	606	C21 H26 C1 N3 02 S	420	15	78
Příklad1221	607	C22 H2B C1 N3 03 S	450	31	kvant
Příklad1222	608	C23 H30 C1 N3 03	432	17	80
Příklad1223	609	C22 H28 C1 N3 03	418	18	88
Příklad1224	610	C23 H28 C1 N3 03 S	462	20	86
Příklad1225	611	C26 H36 C1 N3 03	474	21	90
Příklad1226	612	C28 H32 C1 N3 03	494	20	89
Příklad1227	613	C23 H27 C1 F3 N3 03	486	19	81
Příklad1228	614	C24 H33 C1 N4 02	445	23	kvant
Příklad1229	615	C25 H29 Cl N4 02	453	4	20
Příklad1230	616	C32 H35 C1 N9 02	593	11	40
Příklad1231	617	C25 H27 C1 F3 N3 02	482	6,7	37
Příklad1232	620	C25 H31 Br C1 N3 02	520	15	49
Příklad1233	621	C25 H31 C12N3 02	476	18	69
Příklad1234	622	C27 H37 C1 N4 02	485	14	50

Příklad1235	623	C26 H34 CZ N3 03	472	19	69
Příklad1236	629	C25 H31 C1 N4 04	487	21	73
Příklad1237	625	C25 H33 C1 N4 02	457	19	69
Příklad1238	626	C27 H30 Cl F6 N3 02	578	B	25
Příklad1239	627	C27 H36 C1 N3 03	486	16	55
Příklad1240	628	C27 H34 C1 N3 04	500	24	80
Příklad1241	629	C26 H30 C1 F4 N3 02	528	18	56
Příklad1242	630	C26 H31 C1 F3 N3 03	526	21	68
Příklad1243	631	C26 H30 C12F3 N3 02	549	15	48
Příklad1244	632	C26 H30 C1 F4 N3 02	528	13	41
Příklad1245	633	C26 H30 C1 F4 N3 02	528	20	63
Příklad1246	634	C26 H30 Cl F9 N3 02	528	19	62
Příklad1247	635	C28 H38 C1 N3 03	500	11	36
Příklad1248	636	C26 H34 C1 N3 02 02	456	21	89
Příklad1249	637	C26 H31 C1 F3 N3	510	20	95
Příklad1250	638	C26 H31 C1 N4 02	967	I5	54
Příklad1251	639	C27 H37 C1 N4 02	485	19	66
Příklad1252	640	C26 H34 C1 N3 03	472	16	56
Příklad1253	641	C27 H34 C1 N3 04 02	500	18	59
Příklad1254	642	C32 H36 C1 N3 03	546	29	73
Příklad1255	643	C26 H31 C1 F3 N3	510	16	54
Příklad1256	649	C29 H40 C1 N3 02	498	18	61
Příklad1257	695	C25 H33 C1 N4 02	457	22	78
Příklad1258	646	C26 H34 C1 N3 03	472	13	97
Příklad1259	647	C27 H34 C1 N3 03	500	13	46
Příklad1260	648	C28 H38 C1 N3 02	484	17	60
Příklad1261	649	C28 H38 C1 N3 03	500	12,5	42
Příklad1262	650	C32 H36 C1 N3 03	546	1*	2
Příklad1263	651	C28 H35 C1 N4 02	495	4*	12
Příklad1264	652	C25 H31 C1 N9 04	487	5*	14

Příklad1265	653	C30 H42 C1 N3 03	528	1*	3
Příklad1266	654	C27 H34 C1 N3 03 02	984	7*	21
Příklad1267	655	C26 H32 C1 F3 N4	525	6*	16
Příklad1268	656	C23 H30 Cl N3 03	432	6*	18
Příklad1269	657	C23 H30 C1 N3 02 S	448	9*	13
Příklad1270	658	C27 H33 C1 N4 02	98	1*	4
Příklad1271	659	C23 H29 C1 N4 04 S	493	4*	10
Příklad1272	660	C34 H39 C1 N4 02	571	3*	7
Příklad1273	661	C24 H32 C1 N3 03 S	478	3*	7
Příklad1274	662	C25 H34 C1 N3 03	460	2*	6
Příklad1275	663	C24 H32 C1 N3 03	446	2*	5
Příklad1276	664	C24 H31 C1 N4 05	491	2*	S
Příklad1277	665	C25 H32 C1 N3 03 S	490	1*	3
Příklad1278	666	C26 H37 C1 N4 02	473	3*	7
Příklad1279	667	C30 H36 C1 N3 03	522	3*	7
Příklad1280	668	C25 H31 Cl F3 N3 03	514	2*	6
Příklad1281	669	C24 H33 Cl N4 02	445	15*	45
Příklad1282	670	C23 H29 Br C1 N3 03	510	3*	7
Příklad1283	671	C23 H29 C1 N9 05	477	2*	5
Příklad1284	672	C23 H31 C1 N9 02	931	2*	7
Příklad1285	673	C23 H30 C1 N3 02 S	448	2*	6
Příklad1286	674	C24 H32 C1 N3 02 S	962	3*	9
Příklad1287	675	C24 H32 C1 N3 02 S	462	I*	4
Příklad1288	676	C27 H33 C1 N9 02	482	2*	6
Příklad1289	677	C28 H35 C1 N4 02	495	2*	6
Příklad1290	678	C29 H32 C1 N3 03	496	3*	9
Příklad1291	679	C27 H32 C1 N3 02 S	498	1*	3
Příklad1292	680	C23 H29 Br C1 N3 02 S	526	2*	6
Příklad1293	681	C25 H34 C1 N3 03	460	2*	5
Příklad1294	682	C27 H38 C1 N3 03	488	2*	4

Příklad1295	683	C29 H32 C1 N3 02 S2	494	1*	4
Příklad1296	689	C26 H36 C1 N3 09 S2	554	2*	5
Příklad1297	6B5	C29 H32 C1 N3 04 S2	526	3*	7
Příklad1298	687	C25 H30 C1 N3 02	440	24	kvant
Příklad1299	688	C27 H28 C1 F6 N3 02	576	28	98
Příklad1300	689	C26 H29 C1 N4 02	465	23	99
Příklad1301	690	C25 H29 Br C1 N3 02	518	26	99
Příklad1302	691	C27 H35 C1 N4 02	483	24	97
Příklad1303	692	C26 H32 C1 N3 03	970	24	kvant
Příklad1304	693	C27 H28 Cl F6 N3 02	576	16	55
Příklad1305	694	C27 H34 C1 N3 03	484	25	kvant
Příklad1306	695	C27 H32 C1 N3 04	498	12	47
Příklad 1307	696	C26 H29 C1 F3 N3 03	524	25	95
Příklad1308	697	C26 H29 C1 N9 02	465	15	64
Příklad1309	698	C27 H35 C1 N4 02	483	24	kvant.
Příklad1310	699	C26 H32 C1 N3 03	470	26	kvant
Příklad1311	700	C27 H32 C1 N3 04	498	15	62
Příklad1312	701	C27 H32 C1 N3 03	482	11	44
Příklad1313	702	C26 H29 C1 F3 N3 02	508	23	94
Příklad1314	703	C2BH36 C1 N3 02	482	26	kvant
Příklad1315	704	C25 H29 C1 N4 04	985	11	43
Příklad1316	705	C24 H30 C1 N3 02 S	460	25	kvant
Příklad1317	706	C24 H30 C1 N3 02 S	460	25	kvant
Příklad1318	707	C26 H29 C1 F3 N3 02	508	15	55
Příklad1319	708	C23 H27 Br C1 N3 02 S	526	25	92
Příklad1320	709	C24 H30 C1 N3 02 S2	492	26	kvant
Příklad1321	710	C23 H27 Br C1 N3 02 S	526	25	99
Příklad1322	711	C25 H32 C1 N3 03	458	26	kvant
Příklad1323	712	C27 H30 CZ N3 02 S	496	26	kvant
Příklad1324	713	C24 H30 C1 N3 03	444	26	kvant

Příklad1325	719	C28 H33 C1 N4 02	993	12	50
Příklad1326	715	C23 H28 Cl N3 02 S	446	24	kvant
Příklad1327	716	C27 H31 C1 N4 02	479	32	kvant
Příklad1328	717	C23H27C1 N4 05	475	23	95
Příklad1329	718	C23 H29 C1 N4 02	929	24	kvant
Příklad1330	719	C23 H28 C1 N3 03	430	29	kvant
Příklad1331	720	C23 H27 Br Cl N3 03	510	24	95
Příklad1332	721	C24 H31 C1 N4 02	443	22	98
Příklad1333	722	C26 H32 C1 N3 03	470	9	37
Příklad1334	723	C25 H31 C1 N4 02	455	10	92
Příklad1335	724	C29 H38 C1 N3 02	496	28	kvant.
Příklad1336	725	C32 H34 C1 N3 03	549	26	95
Příklad1337	726	C27 H33 C1 N9 03	497	3	11
Příklad1338	727	C25 H29 C12 N3 02	474	25	kvant
Příklad1339	728	C25 H31 C1 N4 02	455	21	92
Příklad1340	729	C25 H29 C1 N4 04	485	26	kvant
Příklad1341	730	C25 H29 C12 N3 02	474	21	90
Příklad1342	731	C27 H32 C1 N3 03	482	10	41
Příklad1343	732	C26 H28 C1 F4 N3 02	526	27	kvant
Příklad1344	733	C28 H36 C1 N3 03	498	22	89
Příklad1345	734	C26 H28 Cl F4 N3 02	526	25	94
Příklad1346	735	C26 H28 C1 F4 N3 02	526	23	87
Příklad1347	736	C26 H30 C1 F3 N4 02	523	24	78
Příklad1348	737	C26 H28 C1 F4 N3 02	526	21	66
Příklad1349	738	C25 H32 Cl N3 03	458	23	89
Příklad1350	739	C27 H31 C1 N4 02	479	19	66
Příklad1351	790	C24 H31 C1 N4 05	489	23	77
Příklad1352	741	C23 H27 Cl N4 04 S	491	26	88
Příklad1353	742	C24 H30 C1 N3 03 S	476	23	82
Příklad1354	743	C23 H28 C1 N3 03	430	21	81

Příklad1355	744	C26 H32 C1 N3 02	454	25	91
Příklad1356	795	C27 H36 C1 N3 03	486	23	80
Příklad1357	746	C26 H35 C1 N4 02	471	27	96
Příklad1358	747	C25 H29 C1 F3 N3 03	512	23	74
Příklad1359	748	C23 H28 C1 N3 02 S	996	22	82
Příklad1360	751	C24 H30 Cl N3 03	444	3	11
Příklad1361	752	C25 H26 C1 F6 N3 03	566	7	20
Příklad1362	753	C24 H27 C1 N4 03	455	6	22
Příklad1363	754	C23 H27 C12 N3 03	464	8	29
Příklad1364	755	C24 H30 C1 N3 04	460	6	22
Příklad1365	756	C23 H27 C1 N4 05	975	5	18
Příklad1366	757	C25 H32 C1 N3 04	474	5	18
Příklad1368	759	C24 H27 C1 F3 N3 04	514	6	20
Příklad1369	760	C24 H26 Cl F4 N3 03	516	6	18
Příklad1370	761	C29 H26 C1 F4 N3 03	516	3	10
Příklad1371	762	C24 H27 C1 F3 N3 03	498	2	95
Příklad1372	763	C23 H28 C1 N3 03	430	4	95
Příklad1373	764	C24 H30 C1 N3 02	428	9	42
Příklad1374	765	C25 H32 C1 N3 02	442	10	47
Příklad1375	766	C25 H29 C1 F3 N3 02	996	10	42
Příklad1376	767	C25 H32 C1 N3 04 S	506	8	32
Příklad1377	768	C29 H29 Br C1 N3 02	506	9	35
Příklad1378	769	C25 H29 C1 F3 N3 03	512	6	22
Příklad1379	770	C25 H28 C1 F4 N3 02	514	3	10
Příklad1380	771	C25 H28 Cl F4 N3 02	514	10	37
Příklad1381	772	C25 H29 C1 F3 N3 02	496	8	33
Příklad1382	773	C26 H36 Cl N3 03	474	10	41
Příklad1383	774	C23 H30 C1 N3 02 S2	480	12	50
Příklad1384	775	C27 H38 C1 N3 03	488	14	57
Příklad1385	776	C29 H34 C1 N3 03	508	12	49

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Příklad1386	777	C24H29 C1 F3 N3 03	500	22	87
Příklad1387	778	C24H28 C12N4 04	507	6	22
Příklad1388	779	C29H29 C12N3 02	462	10	46
Příklad1389	780	C24H29 C1 N4 04	473	15	65
Příklad1390	781	C26H31 Cl N4 02	967	7*	20
Příklad1391	782	C25H32 C1 N3 03	458	8*	23
Příklad1392	783	C26H34 C1 N3 03	472	7*	19
Příklad1393	784	C26H31 C1 F3 N3 02	510	7*	17
Příklad1394	785	C26H39 C1 N3 04	488	6*	17
Příklad1395	786	C24H28 C1 N3 02	426	22	9
Příklad1396	787	C25H30 C1 N3 02	940	21	94
Příklad1397	788	C25H27 C1 F3 N3 02	494	4*	14
Příklad1398	789	C25H30 C1 N3 04 S	504	9	35
Příklad1399	790	C24H27 C12N3 02	460	5*	16
Příklad1400	791	C24H27 C1 N4 04	471	3*	10
Příklad1401	792	C25H27 C1 F3 N3 03	510	5*	16
Příklad1402	793	C25H26 C1 F4 N3 02	511	5*	16
Příklad1403	794	C25H26 C1 F4 N3 02	512	5*	16
Příklad1404	795	C25H27 C1 F3 N3 02	494	6*	21
Příklad1405	796	C23H28 C1 N3 02 S2	478	4*	14
Příklad1406	797	C27H36 C1 N3 03	486	7*	29
Příklad1407	798	C29H32 C1 N3 03	506	3	13
Příklad1408	799	C24H27C1F3N303	498	3*	11
Příklad1409	800	C24 H26 C12 N4 09	505	5*	15
Příklad1410	801	C26 H29 C1 N4 02	465	12	41
Příklad1411	802	C25 H30 Cl N3 03	956	5*	15
Příklad1412	803	C26 H32 C1 N3 03	470	6*	16
Příklad1413	809	C26 H29 C1 F3 N3 02	508	8*	20
Příklad1414	805	C26 H32 C1 N3 04	986	6*	15
Příklad1415	806	C24 H27 Br C1 N3 02	506	5*	14

Příklad1416	807	C27 H32 C1 N5 03	510	29,7	kvant
Příklad1417	808	C26 H33 C1 N4 03	485	29,9	kvant
Příklad1418	809	C25 H30 C12 N403	505	30,2	kvant
Příklad1419	810	C30 H35 C1 N4 04	551	31,0	kvant
Příklad1420	811	C25 H29 C12 N505	550	3U,4	kvant
Příklad1421	812	C29 H31 Cl N9 03 S2	523	25,0	88
Příklad1422	813	C26 H30 Cl F3 N4 03	539	20,5	70
Příklad1423	814	C26 H30 C1 F3 N4 09	555	22,7	75
Příklad1424	815	C26 H29 C1 F4 N4 03	557	25,8	85
Příklad1425	816	C26 H30 C1 F3 N4 03	539	25,3	86
Příklad1426	817	C26 H29 C1 F4 N4 03	557	26,8	88
Příklad1427	818	C25 H30 Br C1 N4 03	551	27,1	90
Příklad1428	819	C27 H29 C1 F6 N4 03	607	13,9	42
Příklad1429	820	C25 H30 Cl N5 05	516	19,1	51
Příklad1430	821	C24 H28 C12N4 05	523	40	86
Příklad1431	822	C23 H30 Cl N3 03 S2	496	41	93
Příklad1432	823	C26 H31 C1 N9 03	483	43	kvant
Příklad1433	824	C27 H38 C1 N3 09	503	37	83
Příklad1434	825	C29 H34 C1 N3 04	524	28	61
Příklad 1435	826	C24 H29 C1 F3 N3 04	516	40	87
Příklad1436	827	C26 H31 C1 N4 03	483	31	72
Příklad1437	828	C25 H29 C1 F3 N3 04	528	40	86
Příklad1438	829	C25 H28 C1 F4 N3 03	530	45	97
Příklad1439	830	C25 H28 C1 F4 N3 03	530	35	74
Příklad1440	831	C29 H29Br C1 N3 03	523	45	98
Příklad1441	832	C24 H29 C12N3 03	478	38	91
Příklad1442	833	C24 H29 C1 N4 05	488	38	87
Příklad1443	834	C25 H29 C1 F3 N3 03	512	42	93
Příklad1444	835	C24 H3C Cl N3 03	444	43	kvant
Příklad1445	836	C25 H32 C1 N3 03	958	37	91

Příklad1446	837	C25 H29 C1 F3 N3 03	512	41	91
Příklad1447	838	C26 H34 C1 N3 04	988	34	78
Příklad1448	839	C27 H36 C1 N3 06 02	534	37	71
Příklad1449	992	C27 H3UC1 F6 N3	578	17	48
Příklad1450	997	C26 H39 C1 N3 02 02	456	7,6*	23
Příklad1451	998	C27 H33 C1 F3 N3	529	6	15
Příklad1452	999	C27 H36 C1 N3 02	470	8	24
Příklad1453	1000	C27 H36 C1 N3 03	486	9	24
Příklad1454	1001	C28 H38 C1 N3 03	500	4	10
Příklad1455	1002	C27 H33 C1 F3 N3 03	540	9	23
Příklad1456	1003	C28 H38 C1 N3 02	484	7	21
Příklad1457	1009	C28 H38 C1 N3 04	516	11	30
Příklad1458	1005	C29 H40 C1 N3 05	547	9	23
Příklad1459	1006	C30 H42 C1 N3 04	544	8	21
Příklad1460	1007	C32 H46 C1 N3 05	589	7	17
Příklad1461	1008	C25 H31 Cl N4 03	471	25	79
Příklad1462	1009	C26 H33 Cl N4 09	501	35	97
Příklad1463	1010	C27 H35 C1 N4 04	515	35	9
Příklad1464	1011	C27 H35 C1 N4 03	999	32	59
Příklad1465	1012	C27 H35 C1 N4 05	531	27	77
Příklad1466	1013	C28 H37 C1 N4 06	561	14	37
Příklad1467	1019	C29 H39 C1 N4 05	559	29	66
Příklad1468	1015	C31 H93 C1 N4 06	603	25	65
Příklad1469	1018	C26 H34 C1 N3 04	488	13,0*	39
Příklad1470	1019	C28 H38 C1 N3 05	532	13,4*	37
Příklad1471	1024	C25 H32 C1 N3 04	474	12,7*	40
Příklad1472	1021	C26 H28 Cl F6 N3 04	596	13,8*	34
Příklad1473	1022	C25 H32 C1 N3 09	474	14,2*	37
Příklad1474	1023	C25 H32 C1 N3 02	442	11,5*	32
Příklad1475	1024	C26 H34 C1 N3 05	504	12,0*	30

Příklad1476	1025	C27 H36 C1 N3 04	502	14,7*	37
Příklad1477	1026	C29 H40 C1 N3 05	546	13,5*	32
Příklad1478	1027	C26 H34 C1 N3 09	488	11,9*	31
Příklad1479	1028	C27 H30 C1 F6 N3 09	614	14,6*	31
Příklad1480	1029	C25 H32 C1 N3 03	958	14,0*	38
Příklad1481	1030	C24 H27 C1 F3 N3 03	498	14,0*	35
Příklad1482	1031	C24 H30 C1 N3 03	444	10,4*	29
Příklad1483	1032	C25 H32 C1 N3 04	474	14,9*	39
Příklad1484	1033	C25 H32 C1 N3 02	442	13,3*	37
Příklad1485	1034	C26 H39 Cl N3 05	504	13,7*	34
Příklad1486	1035	C27 H36 C1 N3 09	502	16,7*	42
Příklad1487	1036	C29 H90 C1 N3 OS	547	15,5*	36
Příklad1488	1037	C26H34C1N304	488	14,1*	36
Příklad1489	1038	C27 H30 CI F6 N3 04	610	17,5*	37
Příklad1490	1039	C25 H32 C1 N3 03	458	15,1*	41
Příklad1491	1040	C24 H27 C1 F3 N3 03	498	15,4*	39
Příklad1492	1041	C24 H30 CI N3 03	444	12,7*	35
Příklad1493	1042	C22 H26 Br C1 N9 02	495	10,4*	25
Příklad1499	1043	C22 H26 C12 N9 02	449	11,1*	28
Příklad1495	1044	C23 H29 C1 N4 02	429	5,2*	18
Příklad1496	1045	C23 H29 C1 N4 O3	445	12,4*	33
Příklad1497	1046	C22 H25 C13 N4 02	483	10,0*	25
Příklad1498	1047	C24 H31 C1 N4 02	443	12,1*	32
Příklad1499	1048	C25 H33 C1 N4 05	505	16,1*	39
Příklad1500	1049	C23 H28 Br C1 N4 02	S07	12,0*	28
Příklad1501	1050	C28 H38 C1 N3 09	516	39,2*	kvant.
Příklad1502	1051	C28 H38 CZ N3 02	489	34,0*	kvant
Příklad1503	1052	C29 H40 C1 N3 05	546	14,5*	39
Příklad1504	1053	C30 H42 Cl N3 04	544	11,8*	32
Příklad1505	1054	C32 H96 C1 N3 05	588	12,2*	31

Příklad1506	1055	C29 H40 C1 N3 04	530	44,5*	kvant
Příklad1507	1056	C30 H36 C1 F6 N3 09	652	46,0*	kvant
Příklad1508	1057	C28 H38 C1 N3 03	500	11,2*	32
Příklad1509	1058	C27 H36 C1 N3 03	986	35,5*	kvant
Příklad1510	1059	C27 H33 C1 F3 N3 03	590	41,4*	kvant
Příklad1511	1060	C29 H40 C1 N3 09	530	13,6*	37
Příklad1512	1061	C30 H36 Cl F6 N3 04	652	49,2*	kvant
Příklad1513	1062	C28 H38 C1 N3 03	500	39,9*	kvant
Příklad1514	1063	C27 H36 C1 N3 03	486	12,0*	35
Příklad1515	1064	C27 H33 C1 F3 N3 03	540	37,8*	kvant
Příklad1516	1065	C28 H38 C1 N3 04	516	12,3*	34
Příklad1517	1066	C28 H38 C1 N3 02	484	30,7*	90
Příklad1518	1067	C29 H40 C1 N3 OS	546	13,8*	37
Příklad1519	1068	C30 H42 C1 N3 04	544	13,1*	35
Příklad1520	1069	C32 H46 C1 N3 05	589	14,1*	35
Příklad1521	1070	C29 H34 C1 N3 03 S2	572	38,3	93
Příklad1522	1071	C32 H35 C1 N4 03	559	39,6	98
Příklad1523	1072	C33 H92 C1 N3 04	580	90,9	98
Příklad1524	1073	C35 H38 C1 N3 09	600	40,5	94
Příklad1525	1074	C30 H33 C1 F3 N3 04	592	387	91
Příklad1526	1075	C31 H33 C1 F3 N3 04	604	38	87
Příklad1527	1076	C30 H33 C1 N4 05	565	38,5	94
Příklad1528	1077	C31 H33 C1 F3 N3 03	588	35,8	84
Příklad1529	1078	C30 H39 C1 N3 03	520	34,7	93
Příklad1530	1079	C31 H36 C1 N3 03	534	38,4	kvant
Příklad1531	1080	C32 H38 C1 N3 09	564	39,3	97
Příklad1532	1081	C33 H40 C1 N3 06	610	95,5	kvant
Příklad1533	1082	C28 H36 C1 N3 03	498	4,1*	10
Příklad1534	1083	C28 H36 C1 N3 03	498	6,4*	16
Příklad1535	1125	C30 H32 C12 N4 05	599	3,4*	8

Příklad1536	1126	C30 H32 Br C1 N4 05	649	3,4*	7
Příklad1537	1127	C32 H35 C1 N4 03	559	1,6*	4
Příklad1538	1128	C31 H32 C1 F9 N3 03	606	4,3*	10
Příklad1539	1129	C31 H32 C1 F4 N3 03	606	5,9*	19
Příklad1540	1130	C30 H33 Br C1 N3 03	599	5,7*	13
Příklad1541	1131	C30 H33 C12 N3 03	554	6,4*	16
Příklad1542	1132	C31 H33 C1 F3 N3 03	588	6,3*	15
Příklad1543	1167	C27 H34 C1 N3 03	484	1,8*	9

*Výtěžek TFA soli

Příklad 1544: Příprava 1-(4-chlorobenzyl)-4-[{N-(3,5bis(trifluormethyl)benzoyl)glycyl}--aminomethyl]-piperidinu (Sloučenina č. 1213).

Roztok 3,5-bis(trifluormethyl)benzoylchloridu (0,058 mmol) v dichloromethanu (1 ml) se přidal do směsi 1-(4-chlorobenzyl)-4-[(glycylamino)methyl]piperidinu (0,050 mmol) a piperidinmethyl-polystyrenu (58 mg) v chloroformu (0,2 ml) a dichloromethanu (0,75 ml) . Poté, co se nechala reakční směs míchat při pokojové teplotě po dobu 2h, přidal se methanol (1,0 ml) a směs se ponechala míchat při pokojové teplotě dalších 30 min. Reakční směs se nanesla na sloupec Varian SCX a sloupec se promýval CH_3OH (16 ml). Produkt se eluoval ze sloupce roztokem 2 N NH_3 v CH_3OH (6 ml) a zakoncentrováním se získal 1-(4chlorbenzyl)-4-[{N-(3,5-bis(trifluormethyl)benzoyl)-glycyl]--aminomethyl]piperidin (Sloučenina č. 1213) (24,0 mg, 90%.): Čistota sloučeniny se určila pomocí RPLC/MS (100%);ESI/MS m/e 536,2 (M^++H, $C_{24}H_{24}$ $C1F_6N_3O_2$).

Příklady 1545 až 1547:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1544 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 28.

Tabulka 28

Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %

Příklad 1545	1214	C23 H29 C1 F4 N3 03	486,2	22,2	91
Příklad 1546	1215	C22 H29 C13 N3 02	467,9	20,9	89
Příklad 1547	1216	C22 H24 C1 F2 N3 02	936,0	19,3	89

Příklad 1548: Příprava 4-[{N-(3-brom-4-methylbenzoyl)glycyl}aminomethyl]-1-(4-chlorbenzyl)--piperidinu (Sloučenina č. 1113).

K roztoku 1-(4-chlorbenzyl)-4-{(glycylamino)methyl)piperidinu (0,050 mmol) v $CHCl_3$ (1.35 ml) a terc-butanolu (0,15 ml) se přidala 3-brom-4-methylbenzoová kyselina (0,060 mmol), diisopropylkarbodiimid (0,060mmol) a HOBt (0,060 mmol). Reakční směs se míchala při pokojové teplotě po dobu 15 h. Reakční směs se nanesla na sloupec Varian SCX a sloupec se promýval CH_3OH/CH_3Cl (12 ml). Produkt se eluoval ze sloupce roztokem 2 N NH_3 v CH_3OH (6 ml) a zakoncentrováním se získal 4-((N-(3-bromo-4-methylbenzoyl)glycyl}aminomethyl}-1-(4--chlorobenzyl)piperidin (Sloučenina č. **1113)** (16,1 mg, 65%): Čistota sloučeniny se určila pomocí RPLC/MS (95%);ESI/MS m/e 494,0 (M^++H, $C_{23}H_{24}$ $BrClN_3O_2$).

Příklady 1549 až 1619:

Sloučeniny podle předloženého vynálezu byly syntetizovány podle metod popsaných v Příkladu 1548 za použití odpovídajících reaktantů v daném pořadí. Bylo-li to nutné k získání daného produktu, použila se preparativní TLC. Výsledky ESI/ MS jsou shrnuty v tabulce 29.

Sloučenina č. **1422** se získala jako vepodlejší produkt sloučeniny č. **1418:** 5,6.mg, 25% výtěžek; ESI/MS m/e 447,0 (M^++H, $C_{22}H_{27}$ ClN_4O_2S).

Tabulka 29

Sloučenina	Molekulární vzorec č.	ESI/MS m/e		Výtěžek (mg)	Výtěžek %
Příklad 1549	1114	C22H24BrClFN302	498,0	20,2	81
Příklad 1550	1115	C22H24C12FN302	452,2	18,6	82
Příklad 1551	1116	C23H27C1IN302	539,1	21,9	81

Příklad 1552	1117	C23H27ClN4O4	459,2	18,7	81
Příklad 1553	1187	C23H27BrC1N302	494,0	22,1	90
Příklad 1554	1188	C24H27C1N403	455,2	7,2	76
Příklad 1555	1189	C25H29C1N403	469,2	21,1	90
Příklad 1556	1190	C22H26C1FN402	933,2	20,4	94
Příklad1557	1241	C23H24C12F3N302	502,0	22,5	90
Příklad1558	1242	C23H27C1FN3302	432,2	21,2	98
Příklad1559	1243	C23H27C12N302	448,0	21,6	96
Příklad1560	1244	C22H26C1IN402	541,0	26,4	98
Příklad1561	1245	C22H25C1F4N402	451,0	21,3	94
Příklad1562	1246	C21H27C1N402	403,2	19,4	96
Příklad1563	1247	C22H30C1N302S	524,0	24,7	94
Příklad1564	1248	C22H25C1N405	461,0	20,7	90
Příklad1565	1249	C25H26ClF3N4O3	523,2	25,0	96
Příklad1566	1283	C23H27C12N303	464,2	12,2	53
Příklad1567	1284	C22H25BrC1N303	496,0	24,1	97
Příklad1568	1285	C22H25C12N303	450,2	21,8	97
Příklad1569	1342	C22H29BrC12N302	514,0	27,2	kvant
Příklad 1570	1343	C23H27C12N303	498,0	21,4	95
Příklad 1571	1344	C22H24C12IN302	560,0	27,0	96
Příklad 1572	1345	C23H29C1N302	430,2	23,8	kvant
Příklad 1573	1346	C22H25C1IN303	542,0	29,4	kvant
Příklad 1574	1350	C21H26C1N302S	420,0	13,0	62
Příklad1575	1354	C24H28BrC1N403	537,2	5,2	19
Příklad1576	1358	C23H26C1N502	440,2	21,8	99
Příklad1577	1383	C23H24C12F3N302	502,0	20,0	80
Příklad1578	1384	C20H23BrC1N302S	486,0	21,0	87
Příklad1579	1385	C28H30C1N3O4S	540,2	23,8	88
Příklad1580	1386	C28H30C1N302	476,0	20,0	84
Příklad1581	1414	C24H28C12N403	491,0	0,8	3

Příklad1582	1418	C23H26C1N502S	472,0	10,4	44
Příklad1583	1436	C29 H30 C1 N3 03	504,2	26,8	kvant
Příklad1584	1600	C23 H26 C1 F3 N4 02	483,2	16,5	68
Příklad1585	1601	C23 H26 C1 F3 N4 03	499,0	20,0	80
Příklad1586	1602	C21 H24 Br C1 N4 02	481,0	18,1	75
Příklad1587	1603	C21 H24 C12 N4 02	435,0	5,5	25
Příklad1588	1604	C27 H30 C1 N3 03	492,0	18,6	76
Příklad1589	1605	C21 H27 C1 N4 02	415,2	18,1	87
Příklad1590	1609	C23 H25 N3 02 S	500,0	18,3	73
Příklad1591	1659	C22 H26 C12 N4 02	449,0	366,0	83
Příklad1592	1664	C24 H29 F3 N4 02 S	495,2	13,7	55
Příklad 1593	1665	C24H29F3N4O3S	511,2	14,9	58
Příklad1594	1666	C23H28F2N4O2	463,2	12,9	56
Příklad1595	1667	C22H27Br2N3O3	542	26,1	96
Příklad1596	1668	C24H30F2N4O2	445	22,9	kvant
Příklad1597	1669	C24H31FN4O2	427	24,0	kvant
Příklad1598	1670	C24H31IN4O2	535	28,1	kvant
Příklad1599	1671	C25H31F3N4O3	493	26,8	kvant
Příklad1600	1672	C25H31F3N4O2	478	24,7	kvant
Příklad1601	1673	C24H29BrN3O3	508	24,9	98
Příklad1602	1674	C20H22Br2FN4O2	532	25,6	96
Příklad1603	1675	C22H25F3N4O2	435	21,5	99
Příklad1604	1676	C22H26F2N4O2	417	21,4	kvant
Příklad1605	1677	C22H26BrFN4O2	479	23,4	98
Příklad1606	1678	C22H26F4N4O2	525	27,4	kvant
Příklad1607	1679	C22H26ClFN4O2	433	22,4	kvant
Příklad1608	1680	C23H26FN4O3	483	25,5	kvant
Příklad1609	1681	C23H26F4N4O2	467	23,2	99
Příklad1610	1682	C23H26BrClFN3O	498	24,2	98
Příklad1611	1683	C27H28Br2N4O4	633	31,8	kvant

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Příklad1612	1684	C29H31F2N5O3	536	28,3	kvant
Příklad1613	1685	C29H32FN5O3	518	31,1	kvant
Příklad1614	1686	C29H32BrN5O3	578	29,6	kvant
Příklad1615	1687	C29H32IN5O3	626	32,4	kvant
Příklad1616	1688	C29H32ClN5O3	534	31,7	kvant
Příklad1617	1689	C30H32F3N5O4	584	31,7	kvant
Příklad1618	1690	C30H32F3N5O3	568	30,6	kvant
Příklad1619	1691	C29H30BrClN4O3	599	31,4	kvant

Na příklad, Sloučenina **1245 a 1600** vykazovaly následující NMR spektra:

Sloučenina č. **1245:** ^{1}HNMR (270 MHz, $CDCl_3$) δ 1,20-1,97(m,7H), 2,80-2,86(m, 2H), 3,19(t, J=6,5 Hz, 2H), 3,43 (s,2H), 4,02(d, J=5,3 Hz, 2H), 5,52 (br s, 2H), 6,44(d, J=11,9, 6,6 Hz, 1H), 7,02 (br s, 1H), 7,21 –7,32 (m, 5H).

Sloučenina č. **1600:** ^{1}HNMR (270 MHz, $CDCl_3$) δ 1.25 –1.97 (m, 9H), 2,82 – 2,87 (m,2H), 3,21 (t,J= 6,5Hz,2H), 3,44 (s,2H), 4,06 (d,J=5,1 Hz, 2H), 5,98 (br s, 1H), 6,71 (d, J8´,3 Hz, 1H), 6,87 (br s, 1H), 7,26 (s, 4H), 7,43 (dd, J=5,9 Hz, 1H), 7,64 (s,1H).

Příklad 1620: Příprava 1-(4-chlorbenzyl)-4-[{N-(4-isopropylfenylsulfonyl)glycyl}-aminomethyl]--piperidinu (Sloučenina č. 869).

K roztoku 1-(4-chlorbenzyl)-4-{(glycylamino)methyl}piperidinu (14,8 mg, 0,05 mmol) v $CHCl_3$ (2 ml) se přidala piperidinmethylpolystyrenová pryskyřice (28 mg, 2,8 mmol/g), 4--isopropylbenzensulfonylchlorid (1,5 ekviv.) a reakční směs se nechala míchat při 25°C po dobu 16 h. Přidal se aminomethylpolystyren k odstranění zbylých sulfonylchloridových skupin a reakční směs se nechala míchat při 25°C po dobu 16 h. Filtrací a zakoncentrováním se získal 1-(4-chlorbenzyl)-4-[(4--isopropylfenylsulfonylglycyl)aminomethyl]piperidin (Sloučenina č. **869**) (22,1 mg, 92%.): Čistota sloučeniny se určila pomocí RPLC/MS (86%);ESI/MS m/e 478,0 (M^++H, $C_{24}H_{32}ClN_3O_3S$).

Příklady 1624 až 1627:

Sloučeniny podle vynálezu se syntetizovaly podle metod popsaných v Příkladu 1620 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 30.

Tabulka 30

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1621	865	C22 H28 C1N303S	450	16,2	72
Příklad1622	866	C22 H25 C1F3N303 S	504	8,8	35
Příklad1623	867	C23 H24 C1 F6 N3 03 S	572	8,0	28
Příklad1624	868	C23 H30 C1 N3 03 S	464	9,6	41
Příklad1625	870	C22 H28 C1 N3 03 S	450	8,8	39
Příklad1626	871	C25 H34 C1 N3 03 S	492	11,1	45
Příklad1627	872	C21 H26 C1 N3 03 S	436	9,6	44

Příklad 1628:Příprava 1-(4-chlorbenzyl)-4-[{2-(3-(4-trifluormethylfenyl)ureido)acethylamino}--methyl]piperidinu (Sloučenina č. 852).

K roztoku 1-(4-chlorbenzyl)-4-{(glycylamino)methyl}piperidinu (14,8 mg, 0,05 mmol) v $CHCl_3$ (2 ml) se přidala piperidinmethylpolystyrenová pryskyřice (28 mg, 2,8 mmol/g), 3-(trifluormethyl)fenylisokyanát (1,3 ekviv.) a směs se nechala míchat při 25 °C po dobu 16 h. Z důvodu vychytání zbytkového isokyanátu se přidal aminomethylpolystyren a směs se ponechala míchat při 25 °C po dobu 16 h. Filtrací a zakoncentrováním se získal 1-(4--chlorbenzyl)-4-[{2-(3-(4--trifluormethylfenyl)ureido)acethylamino}methyl]piperidin (19 mg, 78%) (Sloučenina č. **852**) : Čistota sloučeniny se určila pomocí RPLC/MS (92%);ESI/MS m/e 483,0 (M^++H, $C_{23}H_{26}ClF_3N_4O_2$).

Příklady 1629 až 1641:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1628 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 31.

Tabulka 31

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad1629	851	C23 H26 C1 F3 N4 02	483	13,2	55
Příklad1630	853	C22 H27 C1 N4 02	416	8,5*	32
Příklad1631	854	C23 H29 C1 N4 02	429	11,4*	42
Příklad1632	855	C23 H29 C1 N4 02	429	10,1*	37
Příklad1633	856	C24 H29 C1 N4 03	457	10,3*	36
Příklad1634	857	C23 H29 C1 N4 03	445	10,9*	39
Příklad1635	858	C23 H29 C1 N4 03	445	8,6*	31
Příklad1636	859	C22 H26 C12 N4 02	449	11,0*	39
Příklad1637	860	C23 H26 C1 N5 02	440	9,2*	33
Příklad1638	861	C22 H27 C1 N4 0 S	431	13,3	62
Příklad1639	862	C23 H29 C1 N4 O S	945	15,3	69
Příklad1640	863	C23 H29 C1 N4 02 S	461	14,7	64
Příklad1641	864	C23 H29 C1 N4 02 S	461	13,1	57

*Výtěžky TFA soli.

Příklad 1642: Příprava 1-(4-chlorbenzyl)-4-[(N-(3-ethoxybenzoyl)-n-fenylalanyl)aminomethyl]--piperidinu (Sloučenina č. 2091).

K roztoku 1-(4-chlorbenzyl)-4-(aminomethyl)piperidinu (100 mg) v $CHCl_3$ (3 ml) se přidal Et_3N (0,090 ml), N-(terc-butoxykarbonyl)-D-fenylalanin (122 mg), EDCI (89 mg) a HOBt (62 mg). Reakční směs se promyla 1N vodným roztokem NaOH (2 ml x 2) a koncentrovaným roztokem NaCl (2 ml). Organická vrstva se oddělila a zakoncentrovala se. Tím se získala 1-(4-chlorbenzyl)-4-[{N-(terc-

butoxykarbonyl)-D-fenyl}-aminomethyl]-piperidin. Vzniklý 1-(4-chlorbenzyl)-4-({N-(terc-butoxy--karbonyl)-fenylalanyl}aminomethyl]piperidin se rozpustil v methanolu (5 ml) a přidala se 4 N HCl v dioxanu (1,5 ml). Roztok se nechal míchat při pokojové teplotě 19 h a poté se zakoncentroval.

K roztoku vziklého materiálu a 3-ethoxybenzoové kyseliny (80 mg, 0. 48 mmol) v $CHCl_3$ (1 ml) se přidal Et_3N (0,090 ml), EDCI (90 mg) a HOBt (68 mg). Reakční směs se nechala míchat při pokojové teplotě po dobu 11h. Poté se reakční směs promyla vodným roztokem 1N NaOH (1. 5 ml x 2) a nasyceným roztokem NaCl (1,5 ml). Organická vrstva se vysušila a zakoncentrovala. Sloupcovou chromatografií (SiO_2, CH_2Cl_2 /MeOH = 95 : 5) se získá 1-(4-chlorbenzyl)-4-[(N-(3-ethoxybenzoyl)-D-fenylalanyl)aminomethyl]piperidin (Sloučenina č.. **2091**)(183,5 mg, 82%): Čistota sloučeniny se určila pomocí RPLC/MS (99%); ESI/MS m/e 534,0 (M^++H, $C_{31}H_{36}ClN_3O_3$).

Příklady 1643 až 1657:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1648 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 32.

Tabulka 32

Sloučenina č.		Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1643	2092	C33 H37 C1 N4 03	572,8	152,9	64
Příklad 1644	2093	C27 H36 C1 N3 03 S	518,0	177,4	82
Příklad 1645	2094	C29 H39 C1 N3 03 S	539,9	164,4	73
Příklad 1646	2095	C28 H38 C1 N3 03	500,0	139,1	66
Příklad 1647	2096	C31 H42 C1 N3 03	540,0	161,7	71
Příklad 1648	2097	C27 H36 C1 N3 03	485,8	157,8	78
Příklad 1649	2098	C31 H35 C12N3 3	567,9	172,2	72
Příklad 1650	2099	C30 H34 C1 N3 03	519,8	144,7	66
Příklad 1651	2100	C32 H38 C1 N3 04	564,0	181,5	77

Příklad 1652	2101	C38 H42 C1 N3 04	639,9	192,3	72
Příklad 1653	2103	C33 H40 C1 N3 04	577,8	159,9	66
Příklad 1654	2104	C28 H36 C1 N3 05	530,1	99,7	45
Příklad 1655	2115	C27 H36 C1 N3 03	486,2	122,9	60
Příklad 1656	2116	C28 H38 C1 N3 03	500,1	118,3	57
Příklad 1657	2117	C28 H34 Cl N5 03	524,1	98,3	45

Referenční příklad 29: Příprava 1-(terc-butoxykarbonyl)-4-[{N(3-(trifluormethyl)benzoyl)--glycyl}aminomethyl]piperidinu.

N-{3-(trifluormethyl)benzoyl)glycin (4,22 g, 17,0 mmol), EDCI (4,25g, 22,1 mmol), 1-hydroxybenzotriazolhydrát (2,99 g, 22,1 mmol) a Et_3N (1. 72 g) se přidaly k roztoku 1-(terc--butoxykarbonyl)-4-(aminomethyl)piperidinu 14,03 g) v suchém CH_2C1_2 (200 ml). Reakční směs se míchala při 25 °C po dobu 20 h. Do reakční směsi se přidala H_20 (100 ml) a reakční směs se extrahovala CH_2C1_2 (2 x 50 ml). Spojené extrakty se promyly H_2O (2 x 50 ml), nasyceným roztokem NaCl (50 ml) a vysušily se ($MgS0_4$). Kapalina se odstranila pod sníženým tlakem a získal se žlutý olej, který se dále čistil sloupcovou chromatografií ($Si0_2$, 70% EtOAc-hexan) se získal 1-(terc-butoxykarbonyl)-4-[{N-(3-(trifluormethyl)benzoyl)glycyl)aminomethyl)piperidin jako bílá pevná látka (6,39 g, 85%): ^{1}H-NMR ($CDCl_3$;, 300 MHz) δ 1,4 (s, 9 H), 1,0-1,8 (m, 5 H), 2,6-2,8 (m, 2 H), 3,15-3,3 (m, 2 H), 4,0-4,3 (m, 4 H), 6,6-6,7 (m, 1H), 7,64 (s, 1 H), 7,60 (dd, 1 H, J = 7,2, 7,2 Hz), 7,79 (d, 1 H, J = 7,2 Hz), 8,0 (d, 1 H, J = 7,2 Hz), 8,11 (s, 1 H) ; Čistota sloučeniny se určila pomocí RPLC/MS (97%);ESI/MS m/e 534,0 (M^++H, $C_{21}H_{28}F_3N_3O_4$).

Referenční příklad 30: Příprava 4-[(N-(3-(trifluormethyl)benzoyl)glycyl)aminomethyl]--piperidinu.

Na roztok 1-(terc-butoxykarbonyl)-4-((N- (3-(trifluormethyl)benzoyl)glycyl)aminomethyl)piperidinu (2,29 g, 5,16 mmol) v CH_3OH (40 ml) se působí N HC1-Et_2O (55 ml). Reakční směs se míchala při 25 °C po dobu 15 h a rozpouštědlo se odstranilo za sníženého tlaku. Do reakční směsi se přidal 2 N vodný roztok NaOH (100 ml) a reakční směs se extrahovala EtOAc (3 x 100 ml) . Spojené extrakty

se promyly nasyceným roztokem NaCl a vysušily pomocí K_2CO_3. Rozpouštědlo se odstranilo za sníženého tlaku a získala se bílá pevná látka, která se dále čistila pomocí sloupcové chromatografie ($Si0_2$, $CH_30H/CH_2C1_2/Et_3N$ - 7/6/1)). Po přečistění se získal 4-[{N-(3-trifluormethyl)benzoyl)--glycyl}aminomethyl]piperidin jako bílá pevná látka (1,27 g, 72%): Čistota sloučeniny se určila pomocí RPLC/MS (98%);ESI/MS m/e 344,0 (M^++H, $C_{16}H_{20}F_3N_30_2$).

Příklad 1658: Příprava 1-(3-(trifluormethoxy)benzyl)-4-[(N-(3-(trifluormethyl)benzoyl)glycyl)--aminomethyl]piperidinu (Sloučenina č. 927).

Roztok 4-[(N-(3-(trifluormethyl)benzoyl)glycyl)aminomethyl)piperidinu (19,9 mg, 0,058 mmol) v CH_3CN (1. 0 ml) a (piperidinmethyl)polystyren (55 mg, 2,7 mmol báze/g pryskyřice) se přidal k roztoku 3-(trifluormethoxy)benzyl bromidu (12,3 mg, 0,048 mmol) v CH_3CN (1,0 ml).Reakční směs se míchala při 60 °C po dobu 2,5 h. Poté se do ochlazené reakční směsi přidak fenylisokyanát (6,9 mg, 0,048 mmol) a směs se nechala míchat po dobu 1h při 25 °C. Reakční směs se nanesla na sloupec Varian SCX a sloupec se promyl CH_3OH (20 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (6 ml) a zakoncentrováním se získal 1-[3-(trifluormethoxy)benzyl)-4-[(N-(3-(trifluormethyl)--benzoyl)glycyl)aminomethyl]piperidin (Sloučenina č. **927**) (22,8 mg, 91%) jako světle žlutý olej: Čistota sloučeniny se určila pomocí RPLC/MS (99%);ESI/MS m/e 518,1 (M^++H, $C_{24}H_{25}F_6N_3O_3$).

Příklady 1659 až 1710:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1658 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 33.

Tabulka 33

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1659	875	C23 H26 F3 N3 02	434	6,3	90
Příklad 1660	876	C23 H25 Br F3 N3 02	512	4,3	23
Příklad 1661	877	C24 H25 F3 N4 02	459	11,3	68
Příklad 1662	878	C23 H25 F3 N9 09	479	8,3	48

Příklad 1663	884	C25 H29 F3 N4 03	491	10,8	61
Příklad 1664	885	C24 H28 F3 N3 04 S	512	9,0	49
Příklad 1665	886	C23 H25 F4 N3 02	452	12,7	78
Příklad 1666	887	C24 H25 F6 N3 02	502	13,9	77
Příklad 1667	888	C23 H26 F3 N3 03	450	11,5	71
Příklad 1668	889	C29 H30 F3 N3 02	510	12,4	68
Příklad 1669	890	C27 H28 F3 N3 02	484	12,0	69
Příklad 1670	891	C23 H24 C12 F3 N3 02	502	11,4	63
Příklad 1671	892	C24 H28 F3 N3 03	464	11,7	70
Příklad 1672	893	C24 H26 F3 N5 05	522	13,9	74
Příklad 1673	894	C26 H32 F3 N3 03	492	11,3	69
Příklad 1674	895	C24 H28 F3 N3 02	448	4,8	30
Příklad 1675	896	C24 H25 F3 N4 02	459	17,5	kvant
Příklad 1676	897	C24 H26 F3 N3 04	478	9,2	57
Příklad 1677	898	C24 H26 F3 N3 04	478	8,9	55
Příklad 1678	899	C24 H28 F3 N3 03	464	13,7	82
Příklad 1679	900	C25 H28 F3 N3 04	492	18,6	kvant
Příklad 1680	901	C29 H30 F3 N3 02	510	13,7	75
Příklad 1681	902	C23 H24 F3 N5 06	529	12,6	67
Příklad 1682	903	C25 H30 F3 N3 04	499	14,0	79
Příklad 1683	906	C25 H30 F3 N3 02	462	11,2	67
Příklad 1684	907	C31 H34 F3 N3 02	538	19,6	75
Příklad 1685	908	C30 H31 F3 N4 03	553	30,4	76
Příklad 1686	909	C30 H31 F3 N4 03	553	12,6	63
Příklad 1687	910	C23 H24 C12 F3 N3 02	502	11,0	
Příklad 1688	911	C23 H25 C1 F3 N3 02	468	20:2	89
Příklad 1689	912	C23 H24 Br2F3 N3 02	590	20,2	95
Příklad 1690	913	C24 H28 F3 N3 03	464	12,6	76
Příklad 1691	919	C30 H32 F3 N3 03	540	13,9	72
Příklad 1692	915	C24 H28 F3 N3 03	464	8,3	25
Příklad 1693	916	C22 H25 F3 N4 02	435	2,5	8
Příklad 1694	917	C22 H25 F3 N4 02	435	2,7	9

Příklad 1695	918	C26 H30 F3 N3 09	506	3,9	22
Příklad 1696	919	C24 H28 F3 N3 02	448	15,9	99
Příklad 1697	920	C24 H25 F6 N3 03	518	20,3	81
Příklad 1698	921	C27 H28 F3 N3 02	484	15,5	89
Příklad 1699	922	C20 H26 F3 N3 02	398	7,3	51
Příklad 1700	923	C29 H29 C1 F3 N3 02	544	12,5	48
Příklad 1701	928	C29 H25 F6 N3 03	518	21,4	86
Příklad 1702	929	C24 H28 F3 N3 02 S	480	23,7	kvant
Příklad 1703	930	C24 H28 F3 N3 02	448	21,3	99
Příklad 1704	931	C24 H25 F3 N4 02	459	21,4	97
Příklad 1705	932	C23 H24 C1 F3 N4 04	513	15,6	63
Příklad 1706	933	C24 H28 F3 N3 02	448	16,6	77
Příklad 1707	934	C22 H25 F3 N4 02	435	18,0	43
Příklad 1708	935	C23 H25 F3 N4 04	479	15,1	65
Příklad 1709	936	C23 H25 F3 N4 04	479	15,4	67
Příklad 1710	1615	C24 H25 F6 N3 02 S	534,2	26,3	99

Příklad 1711: Příprava 1-(4-(dimethylamino)benzyl)-4-[(N-(3-(trifluormethyl)benzoyl)--glycyl)aminomethyl]piperidinu (Sloučenina č. 937).

Roztok 4-[{N-(3-(trifluormethyl)benzoyl)glycyl)aminomethyl]piperidinu (20,0 mg, 0,058 mmol) v CH_3OH (1,0 ml) a $NaBH_3CN$ (16,5 mg) se přidal k roztoku 4- (dimethylamino)benzaldehydu (30,9 mg, 0,204 mmol) v 5 %. CH_3COOH/CH_3OH (1,0 ml) . Reakční směs se míchala při 60 °C po dobu 19 h. Rozpouštědlo se odpařilo a získala se pevná látka. K této pevné látce se přidal CH_3CN (2,0 ml) a fenylisokyanát (6,9 mg, 0,098 mmol) a směs se míchala při 25 °C po dobu 1h.. Reakční směs se nanesla na sloupec Varian SCX a sloupec se promyl CH_3OH (20 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (6ml) a zakoncentrováním se získal 1-(4-(dimethylamino)benzyl)-4-[{N-(3--(trifluormethyl)benzoyl)glycyl}aminomethyl]piperidin (Sloučenina č. **937** (13,5 mg, 49%) jako světle žlutý olej: Čistota sloučeniny se určila pomocí RPLC/MS (87%);ESI/MS m/e 477.3 (M^++H, $C_{25}H_{31}F_3N_4O_2$).

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Příklady 1712 až 1729:

Sloučeniny podle vynálezu se syntetizovaly metodami popsaných v Příkladu 1711 za použití odpovídajících reaktantů v daném pořadí. Bylo-li to nutné pro získání produktu, použila se preparativní TLC (SiO_2). Výsledky ESI/ MS jsou shrnuty v tabulce 34.

Tabulka 34

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1712	879	C24 H26 F3 N3 04	478	13,0	62
Příklad 1713	880	C24 H26 F3 N3 04	478	16,3	78
Příklad 1714	881	C23 H25 Br F3 N3 02	512	11,4	51
Příklad 1715	882	C29 H30 F3 N3 03	526	13,4	58
Příklad 1716	883	C23 H25 C1 F3 N3 02	468	7,9	39
Příklad 1717	904	C23 H26 F3 N3 03	450	3,3	17
Příklad 1718	905	C21 H23 F3 N4 04 S	485	27,7	98
Příklad 1719	938	C23 H24 C1 F4 N3 02	486	8,6	30
Příklad 1720	939	C23 H24 C1 F3 N4 04	513	11,0	37
Příklad 1721	940	C23 H26 F3 N3 03	450	5,5	21
Příklad 1722	941	C24 H29 C1 F6 N3 02	536	11,2	36
Příklad 1723	987	C30 H32 F3 N3 02	529	17,5	76
Příklad 1724	1449	C25 H30 F3 N3 02	462	21,6	80
Příklad 1725	1450	C26 H32 F3 N3 02	476	23,5	85
Příklad 1726	1452	C27 H35 F3 N4 02	505	5,1	17
Příklad 1727	1453	C26 H32 F3 N3 03	492	22,0	77
Příklad 1728	1454	C25 H30 F3 N3 03	478	21,4	77
Příklad 1729	1456	C25 H28 F3 N3 04	492	23,8	83

Příklad 1730: Příprava 1-{3-hydroxy-4-methoxybenzyl}-4-[{N-(3(trifluormethyl)benzoyl)--glycyl}aminomethyl]piperidinu (Sloučenina č. 1452).

K roztoku 4-[(N-(3-(trifluormethyl)benzoyl)glycyl}aminomethyl]piperidinu (20,0 mg, 0,058 mmol) a 3-hydroxy-4-methoxybenzaldehydu (33 mg) v 5% CH_3COOH/CH_3OH (1. 0 ml) se přidal $NaBH_3CN$ (16,5 mg) v 5 % CH_3COOH/CH_3OH (1,0 ml) . Reakční směs se míchala při 60 °C po dobu 15 h. Reakční směs se nanesla na sloupec Varian SCX a sloupec se promyl CH_3OH (15 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentrováním se získal 1-(3-hydroxy-4-methoxybenzyl)-4-[{N-(3-(trifluormethyl)benzoyl)glycyl}aminomethyl}piperidin (sloučenina č. **1452)** (25,8 mg, 92%) : Čistota sloučeniny se určila pomocí RPLC/MS (91%);ESI/MS m/e 480.3 (M^++H, $C_{24}H_{28}F_3N_3O_4$).

Příklady 1731 až 1733:

Sloučeniny podle vynálezu se syntetizovaly podle metod popsaných v Příkladu 1730 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 35.

Tabulka 35

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1731	1455	C24 H28 F3 N3 04	480	24,0	86
Příklad 1732	1697	C27 H34 F3 N3 02	490,2	23,6	96
Příklad 1733	1649	C26 H32 F3 N3 02	476,2	23,1	97

Příklad 1734: Příprava 1-(4-benzylbenzyl)-4-[{N-(3-(trifluormethyl)benzoyl)--glycyl}aminomethyl]piperidinu (Sloučenina č. 926).

Roztok methansulfonylchloridu (4.2 mg, 0,037mmol) v $CHCl_3$ (1,0 ml) a (piperidinmethyl)polystyrenu (54 mg, 2,7 mmol báze/g pryskyřice) se přidal k roztoku 4-

-(benzyl)benzylalkoholu (8,7 mg, 0,044 mmol) v $CHCl_3$ (1,0 ml). Reakční směs se míchala při 25 °C po dobu 15 h. K reakční směsi se přidal roztok 4-[{N-(3--(trifluormethyl)benzoyl)--glycyl}aminomethyl]piperidinu (15,1 mg, 0,044 mmol) v CH_3CN (1,0 ml) a KI (2 mg) a reakční směs se míchala při 65 °C po dobu 5 h. K ochlazené reakční směsi se přidal fenylisokyanát (5,2 mg) a směs se míchala při 25 °C po dobu 1 h. Reakční směs se nanesla na sloupec Varian SCX a sloupec se promyl CH_3OH (20 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (6 ml) a zakoncentrováním se získal 1- (4- benzylbenzyl)- 4- [{N- (3- (trifluormethyl) benzoyl) glycyl} aminomethyl) piperidin (Sloučenina č. **926**) jako světle žlutý olej (5,6 mg, 29%): Čistota sloučeniny se určila pomocí RPLC/MS (94%); ESI/MS m/e 524,1 (M^++H, $C_{30}H_{32}F_3N_3O_2$).

Referenční příklad 31: Příprava 4-[({N-(benzyloxykarbonyl)glycyl)amino}methyl]-1-(terc--butoxykarbonyl)piperidinu.

Na roztok 4-(aminomethyl)-1-(terc-butoxykarbonyl)piperidinu (3,54 g, 16,5mmol) v CH_2Cl_2 (80 ml) se působilo Et_3N (2,8 ml, 20 mmol), N-(benzyloxykarbonyl)glycinem (3,77g, 18 mmol), EDCI (3,45 g, 18 mmol) a HOBt (2,93 g, 18 mmol). Poté co se reakční směs míchala po dobu 15 h při pokojové teplotě, přidal se 2 N vodný roztok NaOH (100 ml). Organická vrstva se oddělila, vodná vrstva se extrahovala pomocí dichloromethanu (100 ml x 3). Spojené organické vrstvy se vysušily bezvodým síranem sodným, přefiltrovaly se a zakoncentrovaly. Slopupcovou chromatografií (SiO_2, ethylacetát) se získal požadovaný 4-[{(N-(benzyloxykarbonyl)glycyl)amino}methyl]-1-(terc--butoxykarbonyl)piperidin (6,27g, 94%) jako amorfní pevná látka.

Referenční příklad 32: Příprava 4-{(glycylamino)methyl}-1-(terc-butoxykarbonyl)piperidinu.

Roztok 4-[{(N-(benzyloxykarbonyl)glycyl)amino)methyl]-1-(terc-butoxykarbonyl)piperidinu (6,26 g, 15,4 mmol) v methanolu (100 ml) se hydrogenoval při tlaku 1 atm v přítomnosti 5% paladia na aktivním uhlí (620 mg) při pokojové teplotě po dobu 7h. Katalyzátor se odstranil filtrací přes Celit a spojené filtráty se zakoncentrovaly. Tím se získal požadovaný produkt 4-{glycylaminomethyl}-1--(terc-butoxykarbonyl)piperidin (3,84 g, 92%) jako pevná látka.

Referenční příklad 33: Příprava 4-[{(N-(2-amino-5-chlorbenzoyl)glycyl)amino}methyl]-1-(terc--butoxykarbonyl)piperidinu.

Na roztok 4-{(glycylamino)methyl)-1-(terc-butoxykarbonyl) piperidinu (1,33 g, 4,90 mmol) v CH_2C1_2 (25 ml) se působilo Et_3N (0,75 ml, 5,4 mmol), 2-amino-5-chlorbenzoovou kyselinou (840 mg, 4,9 mmol), EDCI (940 mg, 4,9 mmol) a HOBt (660 mg, 4,9 mmol). Poté co se reakční směs míchala 3 h při pokojové teplotě, přidal se 2 N vodný roztok NaOH (20 ml). Organická vrstva se oddělila, vodná vrstva se extrahovala pomocí dichloromethanu (20 ml x 3). Spojené organické vrstvy se vysušily bezvodým síranem sodným, přefiltrovaly se a zakoncentrovaly. Slopupcovou chromatografií ($Si0_2$, ethylacetat) se získal požadovaný 4-[({N-(2-amino-5-chlorbenzoyl)glycyl}--amino}methyl]-1-(terc-butoxykarbonyl)piperidin(1,63g, 78%) jako pevná látka.

Referenční příklad 34: Příprava 4-[{(N-(2-amino-5-chlorbenzoyl)glycyl)amino}-methyl]--piperidinu

K roztoku 4-[{(N-(2-amino-5-chlorbenzoyl) glycyl) amino} methyl] -1- (terc-butoxykarbonyl)--piperidinu (1,63g, 10 3. 84 mmol) v methanolu (20 ml) se přidala 4 N HC1 v dioxanu (9,5 ml). Roztok se míchal při pokojové teplotě po dobu 6 h. Reakční směs se zakoncentrovala a přidal se vodný roztok 2 N NaOH (20 ml). Směs se extrahovala dichlormethanem (20 ml x 3) a spojené extrakty se vysušily nad síranem sodným, přefiltrovaly a zakoncentrováním vznikl 4-[[{N-(2-amino-5--chlorbenzoyl)glycyl]amino}methyl)piperidin (1,19 g, 95%): ^{1}H NMR ($CDC1_3$, 270 MHz) δ 1,10-1,76 (m, 4 H), 2,55 (td, J = 2,4 a 12,2 Hz, 2 H), 3,00-3,10 (m, 2 H), 3,17 (t, J = 6,2 Hz, 2 H), 3,48 (s, 2 H), 4,03 (d, J = 4,9 Hz, 2 H), 5,50 (br. s, 2 H), 6,11-6,23 (m, 1 H), 6,60 (d, J = 8,8 Hz, 1 H), 6,85-7,02 (m, 1 H), 7,15 (dd, J = 2,7 a 8,8 Hz, 1 H), 7,38 (d, J = 2,4 Hz, 1 H); ESI/MS m/e 325,2 ($C_{15}H_{21}C1N_4O_2$) .

4-({(N-(2-amino-5-brombenzoyl)glycyl)amino)methyl}piperidin lze připravit rovněž způsobem podle Referenčního příkladu 32 a 33 užitím odpovídajících reaktantů: 951 mg, 69% (2 kroky).ESI/MS m/e 369,2 ($C_{15}H_{21}BrN_4O_2$).

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Příklad 1735: Příprava 4-[{(N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl)--amino}methyl]-1-(4-chlorbenzyl)piperidinu.

Na roztok 1-(4-chlorbenzyl)-4-{(glycylamino)methyl]piperidin dihydrochloridu (738 mg, 2 mmol) v CH_2C1_2 (20 ml) se působilo Et_3N (1,1 30 ml, 8 mmol), 2-(terc-butoxykarbonylamino)-4,5--difluorbenzoovou kyselinou (607 mg, 2.2 mmol), EDCI (422 mg, 2.2 mmol) a HoBt (337 mg, 2.2 mmol). Poté, co se reakční směs míchala při pokojové teplotě 14 h, přidal se vodný roztok 0.6 N NaOH (50 ml). Směs se extrahovala dichlormethanem (20 ml x 3) a spojené extrakty se vysušily nad bezvodým síranem sodným, přefiltrovaly se a zakoncentrovaly se. Sloupcovou chromatografií ($Si0_2$, ethylacetat/ methanol = 92/8) se získal požadovaný 4-[{(N-(2-(terc-butoxykarbonylamino)-4,5--difluorbenzoyl)glycyl)amino}methyl]-1-(4-chlorbenzyl)piperidin (1,01 g, 92%) : ESI/MS m/e 551.3 (M^++H, $C_{27}H_{33}ClF_2N_4O_4$).

Stejným postupem a za použití odpovídajících reaktantů je připraven 4-[((N-(2-(terc--butoxykarbonylamino)-5-trifluormethylbenzoyl)glycyl)amino)methyl]-1-(4-chlorbenzyl)piperidin: 3,03 g, 82%; ESI/MS m/e 583.2 (M^++H, $C_{28}H_{34}ClF_2N_4O_4$) .

Referenční příklad 35: Příprava 4-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl)amino}--methyl]piperidin.

Suspenze 1-(4-chlorbenzyl)-4-[{(N-(2-amino-5-trifluormethylbenzoyl)glycyl)amino}methyl]--piperidinu (497 mg, 0,93 mmol) a $Pd(OH)_2$ (60 mg, 0.23 mmol) v 5% HCO_2H/methanolu (10 ml) se míchala při 50 °C po dobu 14h.

Pd katalyzátor se odfiltroval přes Celit a filtrát se zakoncentroval. Ke vzniklému reziduu se přidal vodný roztok 1N NaOH (15 ml) a směs se extrahovala ethylacetátem (30 ml x 3) . Spojené extrakty se vysušily nad bezvodým síranem sodným, přefiltrovaly a zakoncentrovaly. Sloupcovou chromatografií ($Si0_2$, AcOEt/MeOH/Et_3N = 70/25/5) se získal 4-[{(N-(2-amino-5--trifluormethylbenzoyl)glycyl)amino}methyl]piperidin (289 mg, 86%): ESI/MS m/e 359,0 (M^++H , $C_{16}H_{21}F_3N_4O_2$).

4-[{(N-(2-amino-4,5-difluorbenzoyl)glycyl)amino}methyl]piperidin, 4-[{N-(2-(terc-butoxy--karbonylamino)-5-trifluormethoxybenzoyl)glycyl)aminomethyl]piperidin, 4-[{(N-(2--(terc-butoxy--karbonylamino)-4,5-difluorbenzoyl)glycyl)amino}methyl)piperidin a 4-[{(N-(2--(terc-butoxy--karbonylamino)-5-trifluormethylbenzoyl)glycyl)amino}methyl]piperidin byly také připraveny

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postupem popsaným výše za užití odpovídajících reaktantů. 4-({(N-(2-amino-4,5--difluorbenzoyl)glycyl)amino}methyl]piperidin:564 mg, 89%; ESI/MS m/e 327.2 (M^++H, $C_{15}H_{20}F_2N_4O_2$).

4- [{N- (2- (terc-butoxykarbonylamino) -5-trifluormethoxybenzoyl) glycyl} aminomethyl] piperidin: kvant. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1,10-1,25 (m, 2 H), 1,45-1,73 (m, 3 H), 1,51 (s, 9 H), 2,53-2,64 (m, 2 H), 3,04-3,13 (m, 2 H), 3,22 (t, J = 6,3 Hz, 2 H), 4,09 (d, J = 4,6 Hz, 2 H), 5,91 (br. s, 1 H), 7,08 (br. s., 1 H), 7,32 (d, J = 9,0 Hz, 1 H), 7,38 (s, 1 H), 8,43 (d, J = 9,0 Hz, 1 H).

4-[((N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl)amino)methyl]piperidin: 310 mg, 90%; ESI/MS m/e 427,3 (M^++H, $C_{20}H_{23}F_2N_4O_4$).

4-[{(N-(2-(terc-butoxykarbonylamino)-5-trifluormethylbenzoyl)glycyl)amino}methyl]piperidin:

1,35 g, 57%; ESI/MS m/e 459,3 (M^++H, $C_{15}H_{20}F_2N_4O_2$).

Příklad 1736: Příprava 4-[{N-(2-amino-5-chlorbenzoyl) glycyl} aminomethyl] -1--(4-ethoxybenzyl)-piperidinu (Sloučenina č. 1429) a 1-(4-ethoxybenzyl)-4-[{N - (2-(4--ethoxybenzyl)amino-5-chlorbenzoyl) glycyl}aminomethyl]piperidinu (Sloučenina č. 1433).

Kyanoborohydrid sodný (190 mmol) v methanolu (0,4 ml) se přidal ke směsi 4-[{N-(2-amino-S-chlorbenzoyl)glycyl}aminomethyl)piperidinu (0,10 mmol), 4-ethoxybenzaldehydu (0,10 mmol), kyseliny octové (0,050 ml) a methanolu (1,6 ml). Reakční směs se míchala při 60 °C po dobu 14 h. Reakční směs se nanesla na sloupec Varian SCX a sloupec se promyl CH_3OH (20 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (6 ml) a zakoncentroval se. Preparativní TLC (SiO_2; AcOEt/$CH_3$0H = 5 : 1) se získal 4-({N-(2-amino-5-chlorbenzoyl)glycyl)aminomethyl}-1-(4-ethoxybenzyl)piperidin (Sloučenina č.**1429)** a 1-(4-ethoxybenzyl)-4-[{N-(2-(4-ethoxybenzyl)amino-5--chlorbenzoyl)glycyl}aminomethyl]piperidin (Sloučenina č. **1433).**

Sloučenina č. **1429:** 4,5 mg, 20%: Čistota sloučeniny se určila pomocí RPLC/MS (95%); ESI/MS m/e 459,2 (M^++H, $C_{24}H_{31}ClN_4O_3$).

Sloučenina č. **1433:** 8,4 mg, 28%: Čistota sloučeniny se určila pomocí RPLC/MS (98%); ESI/MS m/e 593,2 (M^++H, $C_{33}H_{41}ClN_4O_4$).

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Příklady 1737 až 1779:

Sloučeniny podle vynálezu se syntetizovaly podle metod popsaných v Příkladu 1730 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 36.

Tabulka 36

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1737	1430	C24 H29 C1 N404	973,0	3,1	13
Příklad 1738	1931	C24 H31 Br N403	505,2	5,8	23
Příklad 1739	1432	C24 H29 Br N404	517,0	9,1	16
Příklad 1740	1434	C33 H41 Br N406	637,2	9,7	30
Příklad1741	1435	C24 H31 C1 N402	443,2	9,7	44
Příklad1742	1436	C25 H33 C1 N402	457,2	12,5	55
Příklad1743	1937	C25 H33 C1 N403	473,2	9,4	40
Příklad1744	1438	C24 H31 Br N4 02	989,2	5,9	24
Příklad1745	1439	C25 H33 Br N4 02	503,2	15,2	61
Příklad1746	1440	C25 H33 Br N4 03	519,2	11,0	43
Příklad1747	1441	C23 H29 Br N4 02 S	507,2	9,3	37
Příklad1748	1442	C33 H41 C1 N9 02	561,4	6,8	24
Příklad1749	1443	C35 H95 C1 N4 02	589,4	9,8	33
Příklad1750	1444	C35 H45 C1 N4 09	621,4	9,4	30
Příklad1751	1445	C33 H41 Br N4 02	605,2	6,5	21
Příklad 1752	1446	C35 H45 Br N4 02	635,2	10,7	34
Příklad 1753	1447	C35 H45 Br N4 04	665,9	12,4	37
Příklad 1759	1448	C31 H37 Br N4 02 S2	643,2	7,6	24
Příklad 1755	1457	C29 H32 C1 N5 02	458,2	4,5	20
Příklad1756	1458	C23 H29 C1 N9 04	461,2	6,0	26
Příklad1757	1459	C29 H32 Br N5 02	509,0	6,8	27
Příklad1758	1460	C23 H29 Br N4 04	505,0	8,0	32

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Příklad1759	1461	C31 H37 C1 N4 06	597,2	5,9	20
Příklad1760	1462	C31 H37 Br N4 06	643,2	6,0	19
Příklad1761	1514	C26 H36 C1 N5 02	486,2	5,5	23
Příklad1762	1515	C23 H29 C1 N4 04	463,0	5,8	25
Příklad1763	1516	C26 H36 Br N5 02	530,2	4,2	16
Příklad1764	1517	C23 H29 Br N4 04	505,0	6,5	26
Příklad1765	1518	C31 H37 C1 N9 06	597,2	4,3	19
Příklad1766	1519	C31 H37 Br N4 06	641,2	5,3	17
Příklad1767	1570	C23 H29 C1 N4 02 S	461,0	2,7	12
Příklad1768	1571	C31 H37 C1 N4 02 S2	597,2	4,9	16
Příklad1769	1651	C37 H49 Br N4 02	663,2	5,5	17
Příklad1770	1652	C26 H35 Br N4 02	515,2	6,0	23
Příklad1771	1653	C35 H45 Br N4 02	633,2	5,0	16
Příklad1772	1659	C25 H33 Br N4 02	501,0	6,2	25
Příklad1773	1655	C37H49 C1 N4 02	617,4	5,6	18
Příklad 1774	1656	C26 H35 C1 N4 02	471,2	5,9	25
Příklad 1775	1657	C35 H45 C1 N4 02	589,2	4,6	16
Příklad 1776	1658	C25 H33 C1 N4 02	457,2	5,3	23
Příklad 1777	1785	C26 H33 F3 N4 02	491,2	4,7	12,8
Příklad 1778	1786	C25 H29 F3 N4 03	491,2	3,7	10,1
Příklad 1779	1804	C25 H32 F2 N4 02	459,2	3,3	9,6

Příklad 1780: Příprava 4-[{N-(2-amino-trifluormethoxybenzoyl)glycyl}aminomethyl]-1-(4--isopropylbenzyl)piperidinu

Ke směsi 4-[(N-(2-(terc-butoxykarbonylamino)-5-trifluormethoxy)benzoylglycyl}-aminomethyl]--piperidinu (0,050 mmol), 4-isopropylbenzaldehydu (0,060 mmol), $NaBH_3CN$ (0,15 mmol) a methanolu (1,3 ml) se přidala kyselina octová (0,050 ml). Reakční směs se míchá při 60 °C po dobu 8 h. Směs se ochladila na pokojovou teplotu a nanesla se na sloupec Varian SCX a sloupec se promýval CH_3OH (10 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se.

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K výslednému materiálu se přidala 4 N HC1 v 1,4-dioxanu (2 ml) a roztok se míchal přes noc při pokojové teplotě. Zakoncentrováním a preparativní TLC se získá 4-[(N-(2-amino-5--trifluormethoxybenzoyl)glycyl)aminomethyl]-1-(4-isopropylbenzyl)piperidin (Sloučenina č. **1903)** (6,6 mg, 26%): Čistota sloučeniny se určila pomocí RPLC/MS (93%); ESI/MS m/e 507 (M^++H, $C_{26}H_{33}F_3N_4O_3$).

Příklady 1781 až 1783:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1730 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 37.

Tabulka 37

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1781	1904	C26 H33 F3 N4 03	507	9,6	37,9
Příklad 1782	1917	C25 H31 F3 N4 05	525,2	1,2	3,1
Příklad 1783	1918	C24 H29 F3 N4 04	495,2	2,8	7,5

Příklad 1784: Příprava 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(5-bromo-2--ethoxybenzyl)piperidinu (Sloučenina č. 2052).

Ke směsi 4-(N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl}aminomethyl]piperidinu (0,050 mmol), 5-bromo-2-ethoxybenzaldehydu (0,15 mmol), methanolu (1,2 ml) a kyseliny octové (0,030 ml) se přidal $NaBH_3CN$ (0,25 mmol) v methanolu (0,50 ml). Reakční směs se míchala při 50 °C po dobu 13 h. Směs se ochladila na pokojovou teplotu a nanesla se na sloupec Varian SCX a sloupec se promyl CH_3OH (5ml x 3). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. K výslednému materiálu se přidal dichloromethan (1 ml) a kyselina trifluoroctová (TFA) (0,50 ml) a roztok se míchal při pokojové teplotě 10 min. reakční směs se zakoncentrovala a

zbytek se rozpustil v methanolu, nanesl se na sloupec Varian SCX a sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Pomocí preparativní TLC (SiO_2, ethylacetát/methanol = 10:1) se získal 4-[(N-(2-amino-4,5--difluorbenzoyl)glycyl)aminomethyl]-1-(5-bromo-2-ethoxybenzyl)piperidin (Sloučenina č. **2052**) (10,2 mg, 38%): Čistota sloučeniny se určila pomocí RPLC/MS (96%); ESI/MS m/e 539,2 (M^++H, $C_{24}H_{29}BrF_3N_4O_3$).

Příklady 1785 až 1792:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1784 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 38.

Tabulka 38

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad1785	2053	C30 H34 F2 N4 09	553,4	12,7	46
Příklad1786	2054	C27 H30 F2 N4 03	497,2	13,7	55
Příklad1787	2055	C23 H28 F2 N9 04	463,2	10,1	44
Příklad1788	2056	C22 H24 Br F3 N4 02	515,2	7,7	30
Příklad1789	2057	C23 H27 Br F2 N4 03	527,0	8,6	33
Příklad1790	2058	C24 H30 F2 N4 04	477,2	6,4	27
Příklad1791	2059	C28 H30 F2 N4 03	509,4	6,7	26
Příklad1792	2060	C25 H32 F2 N4 05	507,2	7,2	28

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Příklad 1793: Příprava 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(3,4--diethoxybenzyl)piperidinu (Sloučenina č. 2065).

Ke směsi 4-[{N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl}aminomethyl]piperidinu (0,050 mmol), 3,4-diethoxybenzaldehydu (0,15 mmol), methanolu (1,2 ml) a kyseliny octové (0. 050 ml) se přidal $NaBH_3CN$ (0,25 mmol) v methanolu (0,50 ml). Reakční směs se míchala při 50 °C přes noc. Směs se ochladila na pokojovou teplotu a nanese se na sloupec Varian SCX a sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. K výslednému materiálu se přidal dichloromethan (2 ml) a fenylisokyanát (0,10 ml) a směs se nechala míchat při pokojové teplotě po dobu 1h, opět se nanesla na sloupec Varian SCX a sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Výsledný produkt se rozpustil v methanolu (0,25 ml) a 4N HCl v dioxanu (0,125 ml). Roztok se míchal při pokojové teplotě přes noc a poté se zakoncentroval. Produkt vzniklý zakoncentrováním se rozpustil v methanolu a nanesl na sloupec sloupec Varian SCX a sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentrováním se získal 4-[{N(2-amino--4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(3,9-diethoxybenzyl)piperidin (Sloučenina č,**2065**) (21,2 mg, 84%): Čistota sloučeniny se určila pomocí RPLC/MS (97%); ESI/MS m/e 505,2 (M^++H, $C_{26}H_{34}F_2N_4O_2$).

Příklady 1794 až 1808:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1793 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 39.

Tabulka 39

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad1799	2061	C23 H27 F3 N4 02	449,2	12,6	56
Příklad1795	2062	C23 H27 F3 N4 03	465,2	19,7	85
Příklad1796	2063	C25 H32 F2 N9 09	491,2	19,8	81
Příklad1797	2064	C22 H24 Br F3 N4 02	515,2	17,5	68
Příklad1798	2066	C29 H32 F2 N4 03	523,2	18,0	69

Příklad1799	2067	C26 H34 F2 N4 02	973,2	21,9	93
Příklad1800	2068	C22 H29 C1 F3 N4 02	469,2	11,2	48
Příklad1801	2069	C24 H30 F2 N4 03	461,4	20,2	88
Příklad1802	2070	C23 H27 Br F2 N4 03	527,2	17,7	67
Příklad1803	2071	C24 H30 F2 N4 04	477,2	10,9	46
Příklad1804	2072	C25 H32 F2 N4 03	475,2	19,3	81
Příklad1805	2073	C29 H32 F2 N4 03	523,2	22,8	87
Příklad1806	2074	C29 H32 F2 N4 04	539,2	22,5	84
Příklad1807	2075	C23 H27 F3 N4 03	465,2	14,9	69
Příklad1808	2076	C22 H24 F4 N4 02	453,2	21,9	97

Příklaď 1809: Příprava 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(2-hydroxy--3-methylbenzyl)piperidinu (Sloučenina č. 2106).

Ke směsi 4-[{N-(2-(terc-butoxykarbonylamino)-4,5difluorbenzoyl)glycyl}aminomethyl)piperidinu (0,050 mmol), 2-hydroxy-3--methylbenzaldehydu (0.25 mmol), methanolu (1,0 ml) a kyseliny octové (0,040 ml) se přidal $NaBH_3CN$ (0.40 mmol) v methanolu (0,50 ml). Reakční směs se míchala při 50°C přes noc. Směs se ochladila na pokojovou teplotu a nanesla se na sloupec Varian SCX a sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Výsledný materiál se rozpustil ve směsi ethylacetát/methanol = 5:1 (1 ml) a zakoncentroval se. Výsledný produkt se rozpustil v methanolu (2 ml) a 4N HCl v dioxanu (0,50 ml). Roztok se míchal při pokojové teplotě přes noc a poté se zakoncentroval. Produkt vzniklý zakoncentrováním se rozpustil v methanolu a nanesl na sloupec sloupec Varian SCX a sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Pomocí prereparativní TLC se získal 4-({N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(2-hydroxy-3-methylbenzyl)piperidin (Sloučenina č. **2106):** Čistota sloučeniny se určila pomocí RPLC/MS (97%); ESI/MS m/e 447,0 (M^++H, $C_{23}H_{28}F_2N_4O_3$).

Příklady 1810 až 1823:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1793 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 40.

Tabulka 40

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad1810	2077	C22 H25 C1 F2 N4 03	967,2	3,7	16
Příklad1811	2078	C24 H30 F2 N4 09	477,2	1,9	8
Příklad1812	2079	C30 H34 F2 N4 04	553,9	4,6	17
Příklad1813	2080	C22 H25 C1 F2 N4 03	467,2	13,5	56
Příklad1814	2081	C22 H25 C1 F2 N4 03	967,2	13,6	59
Příklad1815	2082	C23 H28 F2 N4 04	963,2	9,6	92
Příklad1816	2105	C23 H28 F2 N4 04	463,2	ND	ND
Příklad1817	2106	C23 H28 F2 N9 03	497,0	ND	ND
Příklad1818	2107	C20 H23 Br F2 N4 02 S	503,1	ND	ND
Příklad1819	2108	C25 H28 F2 N4 02 S	487,2	ND	ND
Příklad1820	2109	C20 H23 Br F2 N4 03	987,0	ND	ND
Příklad1821	2110	C22 H28 F2 N4 03	935,1	ND	ND
Příklad1822	2111	C22 H24 C1 F3 N4 02	469,0	ND	ND
Příklad1823	2112	C29 H29 Br F2 N4 04	557,0	ND	ND

ND: nestanoveno

Příklad 1824: Příprava 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(3-amino-4--methylbenzyl)piperidinu (Sloučenina č. 2114).

Ke směsi 4-({N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl)aminomethyl]piperidinu (0,050 mmol), 4-methyl-3-nitrobenzaldehydu (0,25 mmol), methanolu (1,2 ml) a kyseliny octové (0,050 ml) se přidal $NaBH_3CN$ (0,50 mmol) v methanolu (1,0 ml). Reakční směs se míchala při 50 °C přes noc. Směs se ochladila na pokojovou teplotu a nanesla se na sloupec Varian SCX a sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Výsledný materiál se nanesl na sloupec Varian Si a produkt se eluoval pomocí směsi ethylacetát /methanol= 2: 1 (2 ml) a zakoncentroval se. Rozpustil se ve směsi ethylacetát/methanol = 2:1 (6 ml) a zakoncentroval se. Vzniklý produkt se rozpustil v methanolu (1 ml) a přidala se 4 N HC1 v dioxanu (0,50 ml).

Roztok se míchal při pokojové teplotě přes noc a po zakoncentrování se residuum rozpustilo v methanolu a naneslo na sloupec Varian SCX a sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml). Zakoncentrováním se získal 4-[(N-(2-amino-4,5--difluorbenzoyl)glycyl)aminomethyl]-1-(4-methyl-3-nitrobenzyl)piperidin.

Směs 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]1-(4-methyl-3-nitrobenzyl)piperidinu připravená podle výše uvedeného způsobu přípravy, 5% paladium-na aktivním uhlí (15 mg) a methanolu (2 ml) se míchala pod vodíkovou atmosférou při pokojové teplotě po dobu 4h. Paladiový katalyzátor se odfiltroval přes Celit a filtrát se zakoncentroval. Preparativní TLC ($Si0_2$, ethylacetát/MeOH = 3/1) se získal 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl)aminomethyl]-1-(3--amino-4-methylbenzyl)piperidin (sloučenina č. **2114)** (2,9 mg, 13%): **):** Čistota sloučeniny se určila pomocí RPLC/MS (100%); ESI/MS m/e 446,0 (M^++H, $C_{23}H_{29}F_2N_5O_2$).

Příklad 1825: Příprava 4-[(N-(2-amino-4,5- difluorbenzoyl)glycyl}aminomethyl]-1-(3-amino-4--methoxybenzyl)piperidinu (Sloučenina č. 2113).

Výše zmíněná sloučenina 4-[(N-(2-amino-4,5-difluorbenzoyl)glycyl)aminomethyl]-1-(3-amino-4-methoxybenzyl)piperidin (Sloučenina č. **2113)** se syntetizovala metodou popsanou v Příkladu 1824 pomocí odpovídajících reaktantů: 4.6 mg, 20% výtěžek; ESI/MS m/e 462.2 (M^++H, $C_{23}H_{29}F_2N_5O_3$).

Příklad 1826: Příprava 1-(3-amino-4-hydroxybenzyl)-4-[{N-(2-(terc-butoxykarbonylamino)-4,5--difluorbenzoyl)glycyl}aminomethyl]piperidinu.

Ke směsi 4-[{N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl)aminomethyl]piperidinu (0.35 mmol), 4-hydroxy-3-nitrobenzaldehydu (1.22 mmol), methanolu (3.8 ml) a kyseliny octové (0,175 ml) se přidal $NaBH_3CN$ (1,58 mmol) v methanolu (3.2 ml). Reakční směs se míchala při 50°C přes noc. Směs se ochladila na pokojovou teplotu a nanesla se na sloupec Varian SCX a sloupec se promyl CH_3OH. Produkt se eluoval pomocí 2 N NH_3 v CH_3OH a zakoncentroval se. Výsledný materiál se rozpustil ve směsi ethylacetát/methanol = 5:1 a nanesl na sloupec Varian Si a produkt se eluoval pomocí směsi ethylacetát /methanol= 5 : 1 (10 ml) a zakoncentrováním vznikl 4-[{N-(2-(terc--butoxykarbonylamino) -4,5- difluorobenzoyl) glycyl} aminomethyl] -1- (4-hydroxy-3-nitrobenzyl)--piperidin (175 mg, 87%).

Směs 4-[{N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(4-hydroxy-3--nitrobenzyl)piperidinu připravená způsobem uvedým výše, 10% paladium-aktivní uhlí (45 mg) a

methanol (5 ml) se míchala pod vodíkovou atmosférou při pokojové teplotě po dobu dvou hodin. Pd katalyzátor se odfiltroval a filtrát se zakoncentroval a získal se žádaný produkt 1-(3-amino-4-hydroxybenzyl) -4- [(N- (2- (terc-butoxykarbonylamino) -4,5- difluorbenzoyl) glycyl)-aminomethyl]--piperidin (100 mg, 60%).

Příklad 1827: Příprava 4-[(N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(3-amino-4--hydroxybenzyl)piperidinu (Sloučenina č. 2141).

K roztokun 1-(3-amino-4-hydroxybenzyl)-4-[{N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)--glycyl}aminomethyl]piperidinu (20,0 mg, 0,035 mmol) v methanolu (1 ml) se přidala 4 N HCl v dioxanu (0,50 ml) a roztok se nechal míchat při pokojové teplotě přes noc. Po zakoncentrování se vzniklý zbytek rozpustil v methanolu a nanesl na sloupec Varian SCX, a sloupec se promyl CH_3OH (5 ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml). Zakoncentrováním se získal 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(3-amino-4-hydroxybenzyl)piperidin(Sloučenina č. **2141**) (17,6 mg, kvant.): Čistota sloučeniny se určila pomocí RPLC/MS (85%); ESI/MS m/e 448,3 (M^++H, $C_{22}H_{27}F_2N_5O_3$).

Příklady 1828 až 1831:

Sloučeniny podle předloženého vynálezu se syntetizovaly metodami popsanými v Příkladu 1826 za použití odpovídajících reaktantů v daném pořadí. Bylo-li to nutné pro získání produktu, použila se preparativní TLC (SiO_2). Výsledky ESI/ MS jsou shrnuty v tabulce 41.

Tabulka 41

Sloučenina	Molekulární vzorec č.	ESI/MS m/e	Výtěžek	Výtěžek (mg)	%
Příklad 1828	2140	C23 H27 F2 N5 04	976,3	6,7	28,4
Příklad 1829	2149	C24 H30 F3 N5 03	494,2	18,7	82,0
Příklad 1830	2195	C23 H28 F3 N5 03	480,3	19,8	63,7
Příklad 1831	2146	C24 H28 F3 N5 04	508,3	13,5	81,7

Příklad 1832: Příprava 1-(3-amino-4-chlorbenzyl)-4-[{N-(2-(terc-butoxykarbonylamino)-4,5--difluorbenzoyl)glycyl}aminomethyl]piperidinu.

Ke směsi 4-[(N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl)aminomethyl]piperidinu (0,14 mmol), 4-chloro-3- nitrobenzaldehydu (0,50 mmol), methanolu (1,5 ml) a kyseliny octové (0,070 ml) se přidal $NaBH_3CN$ (0,63 mmol) v methanolu (1,3 ml). ml). Reakční směs se míchala při 50°C přes noc. Směs se ochladila na pokojovou teplotu a nanesla se na sloupec Varian SCX a sloupec se promyl CH_3OH. Produkt se eluoval pomocí 2 N NH_3 v CH_3OH a zakoncentroval se. Výsledný materiál se rozpustil ve směsi ethylacetát/methanol = 5:1 a nanesl na sloupec Varian Si a produkt se eluoval pomocí ethylacetát /methanol= 5 : 1 (6 ml) a zakoncentrováním 4-[(N-(2-(terc--butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl)aminomethyl]-1-(4-chlor-3-nitrobenzyl)piperidin (44 mg, 53%): ESI/MS m/e 596,3 (M^++H).

Směs 4-[{N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl)aminomethyl]-1-(4-chloro-3--nitrobenzyl)piperidinu (121mg, 0,20 mmol), 10% paladium-aktivního uhlí (85 mg) a methanolu

(1 ml) se míchala pod vodíkovou atmosférou při pokojové teplotě po dobu 19 hodin. Pd katalyzátor se odfiltroval a filtrát se zakoncentroval a získal se žádaný produkt 1-(3-amino-4-chlorbenzyl)-4-[(N-(2--(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl)aminomethyl]piperidin (78 mg, 68%).

Příklad 1833: Příprava 1-(3-amino-4-chlorbenzyl)-4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}--aminomethyl]piperidinu (Sloučenina č. 2142).

Uvedená sloučenina 1-(3-amino-4-chlorbenzyl)-4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}--aminomethyl]piperidin (Sloučenina č. **2142)** se syntetizovala pomocí způsobu uvedeného v Příkladu 1832 za použití odpovídajících reaktantů: (13,7 mg, 98%): Čistota sloučeniny se určila pomocí RPLC/MS (83%); ESI/MS m/e 966,2 (M^++H, $C_{22}H_{26}F_2N_5O_2$).

Příklad 1834: Příprava 1-(3-acethylamino-4-hydroxybenzyl)-4-[{N-(2-amino-4,5-difluor--benzoyl)glycyl}aminomethyl]piperidinu (Sloučenina č. 2148).

Ke směsi 1-(3-amino-4-hydroxybenzyl)-4-[{N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)--glycyl}aminomethyl]piperidinu (27mg, 0,049 mmol), piperidinmethylpolystyrenu (2,7 mmol/g, 60 mg, 0,15 mmol) a dichloromethanu (2 ml) se přidal acetanhydrid (0,12 mmol) v dichloromethanu (0,12 ml). Reakční směs se míchala při pokojové teplotě po dobu 3h. Reakční směs se nanesla na

sloupec Varian SCX a sloupec se promyl CH_3OH. Produkt se eluoval pomocí 2 N NH_3 v CH_3OH a zakoncentrováním se obdržel produkt 1-(3-acethylamino-4-hydroxybenzyl)-4-[{N-(2-(terc--butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl}aminomethyl]piperidin (30 mg, kvant.): ESI/MS m/e 590,4 (M^++H, $C_{29}H_{37}F_2N_5O_6$).

K roztoku 1-(3-acethylamino-4-hydroxybenzyl)-4-[{N-(2-(terc-butoxykarbonylamino)-4,5--difluorbenzoyl)glycyl}aminomethyl]piperidinu získaného podle způsobu přípravy uvedeného výše v methanolu (1 ml) se přidá 4 N HCl v dioxanu (0,50 ml) a roztok se nechá míchat při pokojové teplotě přes noc. Po zakoncentrování roztoku se vzniklý zbytek rozpustí v methanolu, nanese se na sloupec Varian SCX a sloupec se promyl CH_3OH (5 x 2ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5ml). Zakoncentrováním a preparativní TLC (Sio_2, AcOEt/MeOH = 3:2) se obdržel produkt 1-(3--acetylamino-4-hydroxybenzyl)-4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]piperidin (Sloučenina č. **2148)** (2.3 mg, 9.2%) : Čistota sloučeniny se určila pomocí RPLC/MS (98%); ESI/MS m/e 490.3 (M^++H, $C_{24}H_{29}F_2N_5O_4$).

Příklady 1835 až 1839:

Sloučeniny podle předloženého vynálezu byly syntetizovány podle metod popsaných v Příkladu 1793 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS jsou shrnuty v tabulce 42.

Tabulka 42

Sloučenina	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1835 2143	C25 H29 F2 N5 05	518,3	4,8	45
Příklad 1836 2147	C25 H31 F2 N5 04	504,3	3,0	23
Příklad 1837 2154	C26 H32 F3 N5 04	536,9	9,1	66
Příklad 1838 2155	C25 H30 F3 N5 04	522,3	5,5	71
Příklad 1839 2156	C26 H30 F3 N5 05	550,3	7,0	78

Příklad 1840: Příprava 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(3--methylamino-4-hydroxybenzyl)piperidinu (Sloučenina č. 2160).

Ke směsi 4-[(N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl)aminomethyl]-1-(3-amino-4-hydroxybenzyl)piperidinu (20,4 mg, 0,037 mmol), 37% roztoku HCHO (3,0 mg, 0,037 mmol), kyseliny octové (0,10 ml) a methanolu (1,3 ml) se přidal $NaBH_3CN$ (7,0 mg) v methanolu (0,2 ml). Reakční směs se nechala míchat při 60 °C přes noc. Směs se ochladila na pokojovou teplotu a nanesla se na sloupec Varian SCX a sloupec se promyl CH_3OH (5 ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (8 ml) a zakoncentrováním se získal 4-[(N-(2-(terc-butoxykarbonylamino)-4,5--difluorbenzoyl)glycyl)aminomethyl]-1-(3-methylamino-4hydroxybenzyl)piperidin. K roztoku 4-[(N--(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(3-methylamino-4--hydroxybenzyl)piperidinu v methanolu (1,0 ml), který byl připraven výše popsaným postupem, se přidala 4 N HC1 v dioxanu (1,0 ml) a roztok se míchal při pokojové teplotě 3 h.

Po zakoncentrování roztoku se vzniklý zbytek rozpustil v methanolu (1 ml), nanesl se na sloupec Varian SCX a sloupec se promyl CH_3OH (5 ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (8ml). Zakoncentrováním a preparativní TLC (SiO_2) se obdržel produkt 4-[(N-(2-amino-4,5--difluorbenzoyl)glycyl}aminomethyl]-1-(3-methylamino-4-hydroxybenzyl)piperidin (Sloučenina č. **2160)** (3,4 mg, 20%): Čistota sloučeniny se určila pomocí RPLC/MS (96%); ESI/MS m/e 462,4 (M^++H, $C_{23}H_{29}F_2N_5O_3$).

Příklady 1841 až 1844:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladech 1826 a 1840 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS a výtěžky jsou shrnuty v tabulce 43.

Tabulka 43

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1841	2159	C24 H31 F2 N5 03	976,3	7,6	48
Příklad 1842	2161	C23 H28 C1 F2 N5 02	480,3	7,3	95
Příklad 1843	2162	C25H32 F3 N5 03	508,4	6,0	29
Příklad 1849	2163	C24H30 F3 N5 03	49 4,3	5,3	15

Příklad 1845: Příprava 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(benzo--[c]furazan-5-yl)piperidinu (Sloučenina č. 2130).

Směs 4-({N-(2-(terc-butoxykarbonylamino)-4,5-difluorobenzoyl)glycyl}aminomethyl]piperidinu (0,050 mmol), 5-(brommethyl)benzo[c]furazanu (0,75 mmol), piperidinmethylpolystyrenu (2,6-2,8 mmol/g, 60 mg, 0,15 mmol), methanolu (0,2 ml), acetonitrilu (1,0 ml) a chloroformu (0,50 ml) se nechala míchat při 50 °C přes noc. Směs se ochladila na pokojovou teplotu a nanesla se na sloupec Varian SCX, který se promyl CH_3OH (5 ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. K výslednému materiálu se přidal chloroform (1,5 ml) a fenylisokyanát (0,075 ml) a roztok se míchal při pokojové teplotě po dobu 1 h, poté se nanesl na sloupec o Varian SCX, sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Zbytek po zakoncentrování se rozpustil v methanolu (1ml) a přidala se 4 N HCl v dioxanu (0,50 ml). Roztok se nechal míchat při pokojové teplotě přes noc a zakoncentroval se. Zbytek vzniklý zakoncentrováním se rozpustil v methanolu, nanesl se na sloupec Varian SCX, sloupec se promyl CH_3OH (5ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Následnou preparativní TLC (SiO_2, ethyl acetat/MeOH = 5: 1) se získal 4-({N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(benzo(c)furazan-5--yl)piperidin (Sloučenina č. **2130)** (3,6 mg,16%): Čistota sloučeniny se určila pomocí RPLC/MS (96%); ESI/MS m/e 462,4 (M^++H, $C_{22}H_{24}F_2N_6O_3$).

Příklad 1846: Příprava 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(3,5--dimethylisoxazol-4-yl)piperidinu (Sloučenina č. 2131).

Výše zmíněná sloučenina 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(3,5-dimethyl--isoxazol-4-yl)piperidin se připravovala podle způsobu přípravy popsaném v Příkladu 1845 pomocí odpovídajících reaktantů: 3,8 mg, 18% výtěžek; ESI/MS m/e 436,2 (M^++H, $C_{21}H_{27}F_2N_5O_3$).

Příklad 1847: Příprava 4-[{N-(2-amino-5-chlorbenzoyl)glycyl}aminomethyl]-1-{4-(trifluor--methylthio)benzyl}piperidinu (Sloučenina č. 1616).

Směs 4-[(N-(2-amino-5-chlorbenzoyl)glycyl)aminomethyl]piperidinu (16,2 mg, 0,050 mmol), 4--(trifluormethylthio)benzylbromidu (20,3 mg, 0,075 mmol), piperidinmethylpolystyrenu (60 mg), acetonitrilu (1,0 ml) a chloroformu (0,50 ml) se míchala při 60 °C po dobu 15 h. Reakční směs se ochladila, nanesla na sloupec Varian SCX a sloupec se promyl CH_3OH (15 ml). Produkt se eluoval

pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se Zakoncentrováním se získá 4-[{N-(2-amino-5--chlorbenzoyl)glycyl}aminomethyl]-1-{4-(trifluormethylthio)benzyl}piperidin (sloučenina č. 1616) (21,9mg, 85%): Čistota sloučeniny se určila pomocí RPLC/MS (96%); ESI/MS m/e 545,4 (M^++H, $C_{23}H_{26}ClF_3N_4O_2S$).

Příklady 1848 až 1868:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1847 za použití odpovídajících reaktantů v daném pořadí. Bylo-li to nutné pro získání produktu, použila se preparativní TLC (SiO_2). Výsledky ESI/ MS a výtěžky jsou shrnuty v tabulce 44.

Tabulka 44

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1848	1617	C23 H26 Br F3 N4 02 S	559,0	21,0	75
Příklad 1849	1777	C23 H25 C12F3 N4 02	517,0	16,3	63,0
Příklad 1850	1778	C24 H29 F3 N402	463,2	9,5	41,1
Příklad 1851	1779	C24 H27 F3 N404	493,2	12,7	51,6
Příklad 1852	1780	C23 H26 Br F3N4 02	527,0	16,4	62,2
Příklad 1853	1781	C23 H27 F3 N403	465,2	10,0	28,7
Příklad 1854	1782	C25 H29 F3 N402	475,2	12,2	39,3
Příklad 1855	1783	C24 H26 F3 N502	474,2	17,2	48,4
Příklad1856	1784	C23 H27 F3 N902	449,2	11,3	33,6
Příklad 1857	1788	C25 H31 F3 N402	977,2	10,0	42,0
Příklad 1858	1789	C24 H29 F3 N903	479,2	10,0	27,9
Příklad 1859	1792	C29 H30 F2 N402	445,2	5,9	26,5
Příklad1860	1793	C22 H29 C12F2 N4 02	485,2	9,2	37,9
Příklad1861	1794	C23 H28 F2 N402	431,2	5,7	26,5
Příklad 1862	1795	C23H26F2N4 02	461,2	6,0	26,1
Příklad 1863	1796	C22 H25 Br F2 N9 02	497,0	10,5	42,4

Příklad 1864	1797	C22 H26 F2 N4 03	433,2	3,5	16,2
Příklad 1865	1798	C23 H28 F2 N4 03	947,2	5,6	25,1
Příklad1866	1799	C24 H28 F2 N4 02	443,2	5,5	24,9
Příklad 1867	1800	C23 H25 F2 N5 02	442,2	9,4	42,6
Příklad1868	1801	C22 H26 F2 N4 02	917,2	6,5	31,2

Příklad 1869: Příprava 4-[{N-(2-amino-5-trifluormethoxybenzoyl)glycyl}aminomethyl]-1-(4--brombenzyl)piperidin (Sloučenina č. 1910).

Směs 4-[(N-(2-(terc-butoxycarbonylamino)-5-trifluormethoxybenzoyl)glycyl)aminomethyl]piperidinu (0,050 mmol), 4-brombenzyl -bromidu (0,060 mmol), piperidinmethylpolystyrenu (60 mg), acetonitrilu (0.8 ml) a chloroformu (0,5 ml) se míchala při 60 °C po dobu 12 h. Reakční směs se ochladila, nanesla se na sloupec Varian SCX a sloupec se promýval 50% $CHCl_3$ /CH_3OH (10 ml). Ke zbytku se přidala 4 N HC1 v 1,4--dioxanu (2 ml). Roztok se nechal míchat při pokojové teplotě přes noc a zakoncentroval se. Pomocí preparativní TLC se získá 4-[{N-(2-amino-5--trifluormethoxybenzoyl)glycyl}aminomethyl]-1-(4-brombenzyl)piperidin (Sloučenina č. **1910);** (6,5 mg, 24%): Čistota sloučeniny se určila pomocí RPLC/MS (96%); ESI/MS m/e 545 (M^++H, $C_{23}H_{26}BrF_3N_4O_3$).

Příklady 1870 až 1873:

Sloučeniny podle vynálezu se syntetizovaly podle metod popsaných v Příkladu 1869 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS a výtěžky jsou shrnuty v tabulce 45.

Tabulka 45

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1870	1911	C23 H25 C12F3 N4 03	533	10,6	39,7
Příklad 1871	1912	C23 H27 F3 N4 04	481	12,5	52,0

Příklad 1872	1913	C25 H31 F3	N9 03	493	7,5	30,5
Příklad 1873	1914	C24 H29 F3	N4 03	479	11,0	96,0

Příklad 1874: Příprava 4-[{N-(2-mino-5-trifluormethylbenzoyl)glycyl}aminomethyl]-1-(benz--[d]imidazol-5-yl)piperidinu (Sloučenina č. 2186).

Směs 4-[{N-(2-(terc-butoxykarbonylamino)-5-trifluormethylbenzoyl)glycyl}aminomethyl]piperidinu (0,060 mmol), 1-(terc- butoxykarbonyl)-6-(brommethyl)benz[d]imidazolu (15,6 mg, 0,050 mmol), piperidinmethyl)polystyrenu (86 mg) a acetonitrilu (2 ml) se míchala při 50 °C po dobu 3 h. Reakční směs se ochladila a přidal se izokyanát (30mg) a směs se nechala míchat při pokojové teplotě 1h, nanesla se na sloupec Varian SCX a sloupec se promyl CH_3OH (5 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (3 ml) a zakoncentroval se. Ke vzniklému zbytku rozpuštěnému v methanolu se přidala 4 N HCl v dioxanu (1 ml) a roztok se nechal míchat při pokojové teplotě přes noc. Po nanesení na sloupec Varian SCX se slopupec promyl CH_3OH a dichlormethanem. Produkt se eluoval pomocí 2 N NH_3 v CH_3OH. Zakoncentrováním a preparativní TLC (Sio_2, AcOEt/MeOH = 3:1) se obdržel produkt: 4-[(N-(2-amino-5-trifluorbenzoyl)glycyl)aminomethyl]-1-(benz[d]imidazol-5-yl)piperidin (Sloučenina č. **2186)** (1,9 mg, 7,8%) : Čistota sloučeniny se určila pomocí RPLC/MS

(100%); ESI/MS m/e 489,4 (M^++H, $C_{24}H_{27}F_3N_6O_2$).

Příklad 1875: Příprava 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(benzo[c]--thiadiazol-5-yl)piperidinu (Sloučenina č. 2184).

Ke směsi 5-(hydroxymethyl)benzo[c]thiadiazolu (8,3 mg, 0,050mmol), piperidinomethylpolystyrenu (86 mg) a chloroformu (1 ml) se přidá methansulfonylchlorid (0,0042 ml) a směs se nechá míchat při pokojové teplotě po dobu 1,5 h. Poté se přidá acetonitril (1 ml) a 4-[{N-(2-(tectbutoxykarbonylamino)-4,5-difluorbenzoyl)glycyl}aminomethyl]piperidin (0,060 mmol) a reakční směs se míchá při 50 °C po 3 h. Po ochlazení na pokojovou teplotu se přidá fenylisokyanát (30 mg) a směs se míchá další hodinu při pokojové teplotě, nanese se na sloupec Varian SCX a sloupec se promývá CH_3OH (5 ml) a $CHCl_3$ (5 ml). Produkt se eluuje pomocí 2 N NH_3 v CH_3OH (3 ml) a zakoncentruje se. Ke vzniklému zbytku rozpuštěnému v dichlormethanu (1 ml) a 1M chlor-trimethylsilanu se přidá 1M fenol v dichlormethanu (1ml).Roztok se nechá míchat při pokojové teplotě 5h. Po nanesení na sloupec Varian SCX se slopupec promývá CH_3OH a dichlormethanem. Produkt se eluuje pomocí 2 N NH_3

v CH_3OH. Zakoncentrováním a preparativní TLC (Sio_2, AcOEt/MeOH = 3:1) se obdržel produkt: 4--[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1(benzo[c]thiadiazol-5-yl)piperidin (Sloučenina č. **2184)** (1,3 mg, 5,5%) : Čistota sloučeniny se určila pomocí RPLC/MS (100%); ESI/MS m/e 475,2 (M^++H, $C_{22}H_{24}F_2N_6O_2S$).

Příklad 1876: Příprava 4-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}aminomethyl]-1--(benzo[c]thiadiazol-5yl)piperidinu (Sloučenina č. 2185).

Uvedená sloučenina 4-[(N-(2-amino-5-trifluormethylbenzoyl)glycyl}aminomethyl]-1-(benzo[c]--thiadiazol-5-yl)piperidin (Sloučenina č. **2185**) se připravila postupem popsaným v Příkladu 1875 pomocí odpovídajících reagencií: 7,2 mg, 28% výtěžek; ESI/MS m/e 507,4 (M^++H, $C_{23}H_{25}F_3N_6O_2S$).

Příklad 1877: Příprava 4-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}aminomethyl]-1-(2--amino-4-chlorobenzyl)piperidinu (Sloučenina č. 1919).

Směs 4-[(N-(2-amino-5-trifluormethylbenzoyl)glycyl)aminomethyl]piperidinu (0,050 mmol), 4-chlor--2-nitrobenzylchloridu (0,050 mmol), piperidinmethylpolystyrenu (60 mg), acetonitrilu (1,0 ml) a chloroformu (0,7 ml) se nechala míchat při 50 °C přes noc. Po ochlazení se reakční směs nanesla na sloupec Varian SCX a sloupec se promýval 50% CH_3OH / $CHCl_3$ (10 ml) a CH_3OH (10 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Ke vzniklému zbytku se přidal ethanol (3 ml) a 10% Pd-C (15 mg) a směs se míchala pod vodíkovou atmosférou při pokojové teplotě 1,5h. Filtrací, zakoncentrováním a preparativní TLC se získal 4-[(N-(2-amino-5--trifluormethylbenzoyl)glycyl}aminomethyl]-1-(2-amino-4-chlorbenzyl)pyperidin (Sloučenina č. **1919)**. (5,1 mg, 14%): Čistota sloučeniny se určila pomocí RPLC/MS (90%); ^1H NMR (400 MHz, $CDC1_3$) δ 1. 09-1,32 (m, 4 H) , 1,41-1,59 (m, 1 H), 1,66 (d, J = 12,5 Hz, 2 H), 1,88 (t, J = 11,5 Hz, 2 H), 2,82 (d, J = 11,5 Hz, 2 H), 3,17 (t, J = 6,5 Hz, 2 H), 3,42 (s, 2 H), 4,05 (d, J = 5,5 Hz, 2 H), 4,85 (br s, 1 H), 5,92 (br s, 2 H), 6,25-6,36 (m, 1 H), 6,55-6,66 (m, 1H), 6,70 (d, J = 8,5 Hz, 1 H), 6,85 (d, J = 8,5 Hz, 1 H), 7,26 (s, 1 H), 7,42 (d, J = 8,5 Hz, 1 H) , 7. 68 (s, 1 H) ; ESI/MS m/e 498,2 (M^++H, $C_{23}H_{27}ClF_3N_5O_3$).

Příklady 1878 a 1879:

Sloučeniny podle vynálezu se syntetizovaly metodami popsanými v Příkladu 1877 za použití odpovídajících reaktantů v daném pořadí. Výsledky ESI/ MS a výtěžky jsou shrnuty v tabulce 46.

Tabulka 46

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěž %
Příklad 1878	1920	C22 H26 C1 F2 N5 02	966,2	3,5	10,0
Příklad 1879	1922	C23 H27 C1 F3 N5 03	514,2	1,2	3,1

Příklad 1880: Příprava 4-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}aminomethyl]-1--(benz[d]oxazol-5-yl)piperidinu (Sloučenina č. 2188).

Na roztok 1-(3-amino-4-hydroxybenzyl)-4-[(N-(2-(terc-butoxykarbonylamino)-5-trifluor--methylbenzoyl)glycyl)aminomethyl]piperidinu (34.8 mg, 0,060 mmol) v THF (2 ml), připravený způsobem popsaným v Příkladu 1826, se působilo triethylorthomravenčnanem (0,033 ml, 3.3 ekv.) a pyridinium -p-toluenesulfátem (2 mg, 0,4 eq). Reakční směs se míchala pod refluxem přes noc. Po ochlazení na pokojovou teplotu a zakoncentrování, se zbytek rozpustil v AcOEt, nanesl se na sloupec BondElutT Si, eluoval se ze sloupce směsí ethyl acetat/methanol = 4:1 a následně se opět zakoncentroval se.

Vzniklý produkt se rozpustil v AcOEt (1,5 ml) a přidal se 4 N HC1 v dioxanu (0,5 ml). Roztok se míchal při pokojové teplotě přes noc, upravilo se pH na hodnotu pH10 pomocí 5 M vodného roztoku NaOH a poté se produkt extrahoval pomocí AcOEt. Extrakt se zakoncentroval a purifikoval se pomocí PTLC (SiO_2, AcOEt/MeOH =4:1). Získal se požadovaný produkt 4-[(N-(2-amino-5--trifluormethylbenzoyl)glycyl)aminomethyl]-1-(benz[d]oxazol-5-yl)piperidin (Sloučenina č. **2188)** (1,6 mg, 5%): Čistota sloučeniny se určila pomocí RPLC/MS (94%); ESI/MS m/e 490,3 (M^++H, $C_{24}H_{26}F_3N_5O_3$).

Příklad 1881: Příprava 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(2-oxo-2,3--dihydro-1,3-benzoxazol-5yl)piperidinu (Sloučenina č. 2190).

Ke směsi 1-(3-amino-4-hydroxy)-4-[(N-(2-(terc-butoxykarbonylamino)-4,5-difluorbenzoyl)--glycyl)aminomethyl]piperidinu (22mg, 0,040 mmol), NaHC03 (0,090 mmol), vody (0.7 ml) a methanolu (1,5 ml) se přidal fenylchlorformát (0,046 mmol) a směs se nechala míchat při pokojové teplotě po dobu 3h. Přidal se roztok 1 N NaOH (0,040 ml) a reakční směs se míchala další 1,5 h. Směs se extrahovala ethylacetátem a odpařila se. Odparek se rozpustil v methanolu, nanesl se na sloupec Variance SCX, který se promyl CH_3OH (5 ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Ke vzniklému zbytku se přidal 1M chlortrimethylsilan a 1 M fenol v dichloromethanu (2 ml).

Vzniklý roztok se míchal při pokojové teplotě a odpařil se. Odparek se rozpustil v methanolu, nanesl se na sloupec Varian SCX, který se promyl CH_3OH (5 ml x 2). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Preparativní TLC (Sio_2, AcOEt/MeOH = 5:2) se obdržel produkt: 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(2-oxo--2,3-dihydro-1,3--benzoxazol-5yl)piperidin (Sloučenina č. **2190)** (4,1 mg, 22%) : Čistota sloučeniny se určila pomocí RPLC/MS (100%); ESI/MS m/e 474.2 (M^++H, $C_{23}H_{25}F_2N_5O_4$).

Příklady 1882 až 1884:

Sloučeniny podle vynálezu se syntetizováaly metodami popsanými v Příkladu 1881 za použití odpovídajících reaktantů v daném pořadí (pro přípravu Sloučenin č. **2192 a 2193** byl místo fenylchlormravenčnanu použit fenylchlorthiomaravenčnan). Výsledky ESI/ MS a výtěžky jsou shrnuty v tabulce 47.

Tabulka 47

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1882	2191	C24 H26 F3 N5 04	506,3	3,1	10
Příklad 1883	2192	C23 H25 F2 N5 03 S	490,2	6,9	35
Příklad1889	2193	C24 H26 F3 N5 03 S	522,2	3,6	11

Referenční příklad 36: Příprava 4-[{N-(1-(9-fuluorenylmethoxykarbonyl)piperidin-4--ylmethyl)karbamoylmethyl)aminomethyl-3-methoxyfenyloxymethylpolystyrenu.

K roztoku 1-(9-fuluorenylmethoxykarbonyl)-4-(glycylaminomethyl)piperidinhydrochloridu (10 mmol) v DMF (65 ml) se přidá kyselina octová (0,3 ml), triacetoxyborohydrid sodný (1,92 g) a 4-formyl-3-(methoxyfenyloxymethyl)-polystyren (1 mmol/g, 200 g). Směs se nechala protřepávat 2 h a poté se přefiltrovala. Pryskyřice se promyla MeOH, DMF, CH_2Cl_2 a methanolem. Po vysušení se získal žádaný materiál.

Příklady 1885 až 2000: Obecný postup pro syntézu 4-aminomethylpiperidinů na pevné fázi

Ke směsi odpovídající kyseliny (1.6 mmol), HBTU (1.6 mmol) a DMF (6 ml) se přidal diisopropylethylamin (3. 6 mmol) a směs se nechala třepat 2 min. Ke směsi se přidal 4-[{N-(1-(9--fuluorenylmethoxykarbonyl) piperidin- 4-ylmethyl) karbamoylmethyl} aminomethyl] -3- methoxy--fenyloxymethyl-polystyren (0.4 mmol) a směs se nechala míchat 1 h a poté se přefiltrovala. Pryskyřice se promyla DMF a CH_2Cl_2 a vysušila se.

Směs vzniklé pryskyřice, piperidinu (3.2 ml) a DMF (12.8 ml) se nechala třepat 10 min a přefiltrovala se. Pryskyřice se vymyla DMF a CH_2Cl_2 a vysušila se.

K vysušené pryskyřici (0,05 mmol) se přidala směs $NaBH(OAc)_3$ (0. 25 mmol), AcOH (0,025 ml) a DMF (1 ml). Přidal se odpovídající aldehyd (2,5 mmol) a směs se nechala třepat po 2 h, poté se přefiltrovala a promyla se CH_3OH, 10% diisopropylethylaminem v DMF, DMF, CH_2Cl_2 a CH_3OH. Směs pryskyřice, vody (0,050 ml) a trifluoroctové kyseliny (0,95 ml) se nechala 1 h třepat a poté se přefiltrovala. Pryskyřice se promyla CH_2Cl_2 a CH_3OH. Filtrát a kapalina z promývání se spojily a zakoncentrovaly se. Tento surový materiál se nanesl na sloupec Varian SCX a sloupec se promyl 15 ml CH_3OH.). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentroval se. Preparativní TLC nebo HPLC se získal požadovaný materiál. ESI/MS data a výtěžky jsou shrnuty v tabulce 48.

Tabulka 48

	Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 1885	1923	C23 H25 BrF3N302 S	544	5,7	87
Příklad 1886	1924	C24 H28 F3 N303 S	496	14,6	89
Příklad 1887	1925	C23 H25 F4 N302 S	484	11,7	73
Příklad 1888	1926	C23 H24 FS N302 S	502	13,9	84
Příklad 1889	1927	C23 H26 F3 N303 S	482	10,7	67
Příklad 1890	1928	C24 H26 F3 N304 S	510	14,3	85
Příklad 1891	1929	C26 H30 F3 N302 S	506	14,7	88
Příklad 1892	1930	C24 H28 F3 N302 S2	512	14,4	85
Příklad 1893	1931	C25 H30 F3 N302 S	494	14,3	88
Příklad 1899	1932	C25 H28 F3 N303 S	509	7,1*	35
Příklad 1895	1933	C25 H30 F3 N302 S	499	14,3	88
Příklad 1896	1939	C26 H32 F3 N302 S	509	14,9	86
Příklad 1897	1935	C23 H25 F3 N404 S	511	14,9	88
Příklad 1898	1936	C24 H28 F3 N302 S	980	13,3	84
Příklad 1899	1937	C26 H32 F3 N302 S	509	11,1	66
Příklad 1900	1938	C23 H27 Br2 N3 02	538	5,3*	25
Příklad 1901	1939	C24 H30 Br N303	988	5,0*	25
Příklad 1902	1940	C23 H27 Br F N3 02	976	4,9*	25
Příklad 1903	1941	C23 H26 Br F2 N3 02	494	6,1*	30
Příklad 1904	1942	C23 H28 Br N3 03	474	1,7*	9
Příklad 1905	1943	C24 H28 Br N3 04	502	6,6*	32
Příklad 1906	1944	C26 H32 Br N3 02	498	7,0*	35
Příklad 1907	1945	C24 H30 Br N3 02 S	504	11,1	67
Příklad 1908	1946	C25 H32 Br N3 02	488	3,2*	16
Příklad 1909	1947	C25 H30 Br N3 03	500	5,7	35

Příklad 1910	1948	C25 H32 Br N3 02	486	4,9*	25
Příklad 1911	1949	C26 H34 Br N3 02	500	6,7*	33
Příklad 1912	1950	C23 H27 Br N4 09	503	5,0*	25
Příklad 1913	1951	C24 H30 Br N3 02	472	5,1*	26
Příklad 1914	1952	C22 H24 Br2 F N3 02	592	14,9	83
Příklad 1915	1953	C23 H27 Br F N3 03	492	13,9	86
Příklad 1916	1954	C22 H24 Br F2 N3 02	480	12,5	79
Příklad 1917	1955	C22 H23 Br F3 N3 02	498	13,2	80
Příklad 1918	1956	C22 H25 Br F N3 03	478	7,0	94
Příklad 1919	1957	C23 H25 Br F N3 04	506	4,0*	20
Příklad 1920	1958	C25 H29 Br F N3 02	502	14,6	88
Příklad 1921	1959	C23 H27 Br F N3 02 S	508	13,1	78
Příklad 1922	1960	C24 H29 Br F N3 02	490	13,8	85
Příklad 1923	1961	C24 H27 Br F N3 03	504	2,7*	13
Příklad 1924	1962	C24 H29 Br F N3 02	490	12,7	78
Příklad 1925	1963	C25 H31 Br F N3 02	504	13,5	81
Příklad 1926	1964	C22 H24 Br F N4 04	507	14,8	88
Příklad 1927	1965	C23 H27 Br F N3 02	476	12.T	77
Příklad 1928	1966	C25 H31 Br F N3 02	509	13,4	80
Příklad 1929	1967	C22 H26 Br F N4 02	477	4,7*	20
Příklad 1930	1968	C23 H29 F N4 03	929	6,9*	32
Příklad 1931	1969	C22 H27 F N4 03	415	3,7*	17
Příklad 1932	1970	C23 H27 F N4 04	493	5,4*	29
Příklad 1933	1971	C25 H31 F N4 02	439	4,3*	20
Příklad 1934	1972	C23 H29 F N4 02 S	945	6,2*	28
Příklad 1935	1973	C24 H31 F N4 02	427	6,3*	29
Příklad 1936	1974	C24 H31 F N4 02	427	4,9*	23
Příklad 1937	1975	C22 H26 F N5 04	444	5,9*	27
Příklad 1938	1976	C23 H29 F N4 02	413	6,7*	32
Příklad 1939	1977	C23 H26 F N5 02	424	5,1*	29

Příklad 1940	1978	C25 H33 F N4 02	441	6,3*	29
Příklad 1941	1979	C25 H30 F2 N9 02	957	8,0*	35
Příklad 1942	1980	C24 H28 F2 N9 03	459	6,0*	26
Příklad 1943	1981	C22 H25 F2 N5 04	962	9,3*	41
Příklad 1944	1982	C23 H25 F2 N5 02	442	6,0*	27
Příklad 1945	1983	C25 H32 F2 N4 02	959	8,3*	37
Příklad 1946	1989	C22 H26 Br IN402	585	9,7*	36
Příklad 1947	1985	C23 H29 I N4 03	537	9,2*	36
Příklad1948	1986	C22 H27 I N4 03	523	5,8*	23
Příklad1949	1987	C23 H27 I N4 04	551	8,2*	32
Příklad 1950	1988	C25 H3i I N4 02	597	6,7*	26
Příklad 1951	1989	C23 H29 I N4 02 S	553	6,4*	25
Příklad1952	1990	C24 H31 I N4 02	535	7,2*	29
Příklad 1953	1991	C24 H29 I N4 03	549	5,6*	22
Příklad 1954	1992	C24 H31 I N4 02	535	6,2*	25
Příklad 1955	1993	C2~ H26 I N5 04	552	10,2*	40
Příklad 1956	1994	C23 H29 I N4 02	527	7,5*	30
Příklad 1957	1995	C23 H26 I N5 02	532	6,8*	27
Příklad 1958	1996	C25 H33 I N4 02	549	7,1*	28
Příklad 1959	1997	C25 H33 I N4 02	549	3,0*	12
Příklad 1960	1998	C22 H25 Br C1 N3 02	978	7,6*	39
Příklad 1961	1999	C23 H28 C1 N3 03	430	7,0*	39
Příklad 1962	2000	C22 H25 C1 F N3 02	918	14,1	102
Příklad 1963	2001	C22 H26 C1 N3 03	416	6,3*	36
Příklad 1964	2002	C23 H26 C1 N3 04	444	7,1*	39
Příklad 1965	2003	C25 H30 C1 iJ3 02	440	15,3	105
Příklad 1966	2009	C23 H28 C1 N3 02 S	446	8,9*	95
Příklad 1967	2005	C24 H30 C1 N3 02	428	7,9*	41
Příklad 1968	2006	C24 H30 C1 N3 02	428	13,8	98
Příklad 1969	2007	C22 H25 Cl N4 04	995	16,0	109

Příklad 1970	2008	C23 H28 C1 N3 02	414	14,1	103
Příklad 1971	2009	C23 H25 Cl N4 02	425	14,8	106
Příklad 1972	2010	C25 H32 C1 N3 02	442	14,5	99
Příklad 1973	2011	C25 H32 C1 N3 02	442	14,5	99
Příklad 1974	2012	C22 H24 Br 2 C 1 N3 02	558	12,8*	58
Příklad 1975	2013	C23 H27 Br C1 N3 03	508	8,6*	42
Příklad 1976	2014	C22 H25 Br C1 N3 03	494	6.G*	30
Příklad 1977	2015	C23 H25 Br C1 N3 04	522	8,4*	40
Příklad 1978	2016	C25 H29 Br C1 N3 02	518	17,6	103
Příklad 1979	2017	C23 H27 Br C1 N3 02 S	524	17,1	99
Příklad 1980	2018	C24 H29 Br Cl N3 02	506	14,7	88
Příklad 1981	2019	C24 H27 Br C1 N3 03	520	8,0*	38
Příklad 1982	2020	C24 H29 Br C1 TI3 02	506	14,7	88
Příklad 1983	2021	C22 H24 Br Cl N9 04	523	12,0*	57
Příklad 1984	2022	C23 H27 Br C1 N3 02	492	8,5*	82
Příklad 1985	2023	C23 H24 Br C1 N4 02	503	6,3*	31
Příklad 1986	2024	C25 H31 Br C1 N3 02	520	9,6*	46
Příklad 1987	2025	C25 H31 Br C1 N3 02	520	15,0	87
Příklad 1988	2026	C22 H23 Br C1 F2 N 3 02	514		158
Příklad 1989	2027	C22 H26 Br2 N9 02	537	10,7*	42
Příklad 1990	2028	C23 H29 Br N4 03	489	8,5*	36
Příklad 1991	2029	C22 H27 Br N4 03	475	7,5*	32
Příklad 1992	2030	C23 H27 Br N4 04	503	6,8*	28
Příklad 1993	2031	C25 H31 Br N4 02	495	6,2*	26
Příklad 1994	2032	C24 H29 Br N9 03	501	8,9*	37
Příklad 1595	2033	C29 H31 Br N4 02	487	5,1*	39
Příklad 1996	2039	C22 H26 Br N5 04	504	6,4*	26
Příklad 1997	2035	C23 H29 Br N4 02	473	6,5*	28
Příklad 1998	2036	C23 H26 Br N5 02	484	6,3*	27
Příklad 1999	2037	C25 H33 Br N4 C2	501	5,4*	22

Příklad 2000	2038	C22 H25 Br F2	N4 02	495	5,4*	23	

*Výtěžek TFA soli.

Příklad 2001: Příprava 1-(3-karbamoylbenzyl)-4-[{N-(3(trifluormethyl)benzoyl)-glycyl}--aminomethyl]piperidinu (Sloučenina č. 924).

EDCI (10,7 mg), 1-hydroxybenzotriazol hydrát (7,5 mg), Et_3N (15,4 mg), 0,5 M NH_3 v dioxanu (0,1 ml, 0,05 mmol) a DMF (0,5 ml) se přidá k roztoku 1-(3-karboxybenzyl)-4-[{ N-(3--(trifluormethyl)benzoyl)glycyl)aminomethyl]piperidinu (19,4 mg, 0,041 mmol) v $CHCl_3$ (2,5 ml). Reakční směs se míchá při 25 °C po dobu 20 h, promyje se 2 N vodným roztokem NaOH (2 x 2 ml) a nasyceným roztokem NaCl (1 ml). Po filtraci přes FTFE membranový filtr se odstraní rozpouštědlo za sníženého tlaku a získá se 1-(3-karbamoylbenzyl)-4-[{N-(3-(trifluormethyl)benzoyl)--glycyl}aminomethyl]piperidin (Sloučenina č. **924)** jako světle žlutá pevná látka (17,9 mg, 92 %): Čistota sloučeniny se určila pomocí RPLC/MS (89%); ESI/MS m/e 447,3 (M^++H, $C_{24}H_{27}F_3N_4O_3$).

Příklad 2002: Příprava 1-(4-karbamoylbenzyl)-4-[{N-(3(trifluormethyl)benzoyl)glycyl}--aminomethyl]piperidinu (Sloučenina č. 925).

Sloučenina č. 925 se syntetizovala podle způsobu přípravy popsané v Příkladu 2001 za použití odpovídajících reaktantů: 14,2 mg, 72%; Čistota sloučeniny se určila pomocí RPLC/MS (86%); ESI/MS m/e 447 (M^++H, $C_{24}H_{27}F_3N_4O_3$).

Příklad 2003: Příprava 1-(4-aminobenzyl)-4-[{N-(3(trifluormethyl)benzoyl)glycyl}--aminomethyl]piperidinu (Sloučenina č. 516).

Roztok 1-(4-nitrobenzyl)-4-((N-(3-(trifluormethyl)benzoyl)glycyl)aminomethyl]piperidinu (22.4 mg, 0,047 mmol) v EtOH (3 ml) se hydrogenoval pod tlakem 1 atm po dobu 1 h za přítomnosti 5% paladia na aktivním uhlí (10 mg) při 25 °C. Katalyzátor se odstranil filtrací a promyl se EtOH (5 ml). Spojené filtráty se odpařily a získal se 1-(4-aminobenzyl)-4-({N-(3-(trifluormethyl)--benzoyl)glycyl)aminomethyl]piperidin (sloučenina č.**516)** jako světle žlutá pevná látka (20,1 mg,

96%). Čistota sloučeniny se určila pomocí RPLC/MS (99%); ESI/MS m/e 449,1 (M^++H, $C_{23}H_{27}F_3N_4O_2$).

Příklady 2004 a 2005:

Sloučeniny č. 517 a 518 se syntetizovaly podle způsobu přípravy popsaném v Příkladu 2003 za použití odpovídajících reaktantů v daném pořadí. Data ESI/MS a výtěžky jsou shrnuty v tabulce 49.

Tabulka 49

Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 2004 517	C23 H27 F3 N4 02	445	26,5	78
Příklad 2005 518	C23 H27 F3 N4 02	449	25,3	71

Příklad 2006: Příprava 1-{4-(benzoylamino)benzyl}-4-[{N-(3-(trifluormethyl)--benzoyl)glycyl}aminomethyl]piperidinu (Sloučenina č. 519).

EDCI (4,7 mg), 1-hydroxybenzotriazolhydrát (3,3 mg), Et_3N (2,5 mg) a kyselina benzoová (3,0 mg) se přidaly k roztoku 1-(4-aminobenzyl)-({N-(3-(trifluormethyl)benzoyl)glycyl}aminomethyl]piperidinu (10,1 mg, 0,023 mmol) v CH_2Cl_2 (2,5 ml). Reakční směs se míchala při 25 °C po dobu 16 h, promyla se 2N vodným roztokem NaOH (2 x 2 ml) a koncentrovaným roztokem NaCl (1 ml). Po filtraci přes PTFE membranový filtr, se rozpouštědlo odstranilo za sníženého tlaku a získala se žlutá olejovitá kapalina, která se čistila preparativní TLC ($Si0_2$, 10% CH_3OH-CH_2C1_2) a obdržel se 1-(4--(benzoylamino)benzyl)-4-[(N-(3-(trifluormethyl)benzoyl)glycyl)aminomethyl]piperidin (Sloučenina č. 519) jako bezbarví olej (4,6 mg, 36%): Čistota sloučeniny se určila pomocí RPLC/MS (99%); ESI/MS m/e 553,2 (M^++H, $C_{30}H_{31}F_3N_4O_3$).

Příklad 2007: Příprava 1-{4-(piperidinkarbonyl)benzyl}-4-[{N(3-(trifluormethyl)benzoyl)--glycyl}aminomethyl]piperidinu (Sloučenina č. 1572).

Piperidin (0,048 mmol), diisopropylkarbodiimid (0,45 mmol) v DMF (0,15 mmol) a 1--hydroxybenzotriazolhydrát (0,45 mmol) v DMF (0,15 ml) se přidal k roztoku 1-(4-karboxybenzyl)-4--[{N-(3-(trifluormethyl)benzoyl)glycyl}aminomethyl]piperidinu (0,040 mmol) v DMF (1,0m.L). Reakční směs se míchala při pokojové teplotě po dobu 17 h, poté se nanesla na sloupec Varian SCX a sloupec se promyl $CHCl_3/CH_3OH$ 1 : 1 (5 ml) a CH_3OH (5 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentrováním se získal 1-{4-(piperidinkarbonyl)benzyl}-4-[{N-3--(trifluormethyl)benzoyl)glycyl}aminomethyl)piperidin (Sloučenina č. **1572**) (14,3 mg, 66%): Čistota sloučeniny se určila pomocí RPLC/MS (99%); ESI/MS m/e 545 (M^++H, $C_{29}H_{35}F_3N_4O_3$).

Příklady 2008 až 2015:

Sloučeniny podle vynálezu se syntetizovaly podle způsobu přípravy popsaném v Příkladu 2007 za použití odpovídajících reaktantů v daném pořadí. Data ESI/MS a výtěžky jsou shrnuty v tabulce 50.

Tabulka 50

Sloučenina č.		Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěžek %
Příklad 2008	1573	C31 H33 F3 N4 04	583	17,6	76
Příklad 2009	1574	C31 H33 F3 N9 03	567	18,8	83
Příklad 2010	1575	C30 H30 C1 F3 N4 03	587	3,2	14
Příklad 2011	1576	C28 H33 F3 N4 09	547	21,1	97
Příklad 2012	1577	C26 H31 F3 N9 04	521	5,1	24
Příklad 2013	1578	C31 H33 F3 N4 03	567	16,9	75
Příklad 2014	1579	C31 H33 F3 N4 03	567	6,0	26
Příklad 2015	1580	C29 H35 F3 N4 03	545	15,1	69

Příklad 2016: Příprava 1-[4-(chlorformyl)benzyl]-4-[{N-(3-(trifluormethyl)-benzoyl)--glycyl}aminomethyl]piperidinu.

Směs 1-(4-karboxybenzyl)-4-[{N-(3-(trifluormethyl)benzoyl)glycyl}aminomethyl]piperidinu (240 mg) a thionylchloridu (1 ml) se míchá při pokojové teplotě po dobu 12 h a přebytek thionylchloridu se odstranil za sníženého tlaku a získal se 1-[4(chlorformyl)benzyl]-4-[{N-(3-(trifluormethyl)--benzoyl)glycyl]aminomethyl]piperidin. Kyselý chlorid se užíval bez dalšího čištění.

Příklad 2017: Příprava 1-[4-{N-(2- methoxyethyl)karbamoyl)benzyl]-4-[{N-(3-(trifluormethyl)--benzoyl)glycyl}aminomethyl]piperidinu (Sloučenina č,1612).

Směs 1-[4-(chlorformyl)benzyl]-4-[N-(3-(trifluormethyl)benzoyl)glycyl)aminomethyl]piperidinu (0,042 mmol), methoxyethylaminu (3,8 mg, 0,050 mmol), piperidinmethylpolystyrenu (46 mg) a dichloromethanu (1,5 ml) se míchala při pokojové teplotě po dobu 17 h. Přidala se voda (0,020 ml) a směs se nechala opět míchat po dobu 30 min. Přidal se methanol (1 ml) a směs se nanesla na sloupec Varian SCX. Sloupec se promyl v CH_3OH (10 ml). Produkt se eluoval pomocí 2 N NH_3 v CH_3OH (5 ml) a zakoncentrováním se získal 1-[4-{N-(2--methoxyethyl)karbamoyl}benzyl]-4-[{N-(3--(trifluoremethyl)benzoyl)glycyl}aminomethyl]piperidin (Sloučenina č. **1612**) (26,7 mg, 100%) : Čistota sloučeniny se určila pomocí RPLC/MS (92%); ESI/MS m/e 535,2 (M^++H, $C_{27}H_{33}F_3N_4O_4$).

Příklady 2018 až 2020:

Sloučeniny podle vynálezu se syntetizovaly podle metod popsaných v Příkladu 2017 za použití odpovídajících reaktantů v daném pořadí. Bylo-li to nutné pro získání produktu, použila se preparativní TLC. Výsledky ESI/ MS a výtěžky jsou shrnuty v tabulce 51.

Tabulka 51

Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek (mg)	Výtěž %	
Příklad 2018	1610	C31 H30 F6N4 03	621,2	4,4	19
Příklad 2019	1611	C30 H29 C12 F3 N4 03	621,2	35,7	kvant
Příklad 2020	1613	C32 H35 F3N4 03	501,2	29,5	kvant

Příklad 2021: Příprava 4-(N-{5-bromo-2-(methylamino)benzoyl}glycyl)aminomethyl-1-(4-chlor--benzyl)piperidinu (Sloučenina č. 1427).

Roztok 4-{N-(2-amino-5-brombenzoyl)glycyl)aminomethyl-1-(4-chlorbenzyl)piperidinu (Sloučenina č,1042) (50 mg, 0,10 mmol) v triethylorthomravenčnanu (6,5 ml) se míchal při 150 °C po dobu 17 h. Zakoncentrováním se získala žlutá pevná látka. K roztoku žluté pevné látky v ethanolu (3 ml) se přidal borohydrid sodný (7,6 mg, 0,2 mmol) a směs se nechala míchat při pokojové teplotě po dobu 14 h. Vzniklý bílý precipitát se rozpustil v dichlormethanu a roztok se promyl 1 N vodným roztokem NaOH (2 ml). Oddělila se organická vrstva, vysušila se nad K_2CO_3, přefiltrovala se a odpařila. Sloupcovou chromatografií (SiO_2, 20% MeOH/$CHCl_3$) se získá 4-[N-{5-brom-2--(methylamino)benzoyl}glycyl]aminomethyl-1-(4-chlorbenzyl)piperidin (Sloučenina č. **1427**) (40 mg, 80%) : Čistota sloučeniny se určila pomocí RPLC/MS (100%); ESI/MS m/e 505 ($C_{23}H_{28}BrClF_6N_4O_2$).

Příklad 2022: Příprava 4-[N-{5-brom-2-(dimethylamino)benzoyl}glycyl]aminomethyl-1-(4--chlorbenzyl)piperidinu (Sloučenina č,1428).

Kyanoborohydrid sodný (26 mg, 0,92 mmol) a kyselina octová (14 ml) se přidaly postupně ke směsi 4-{N-(2-amino-5-brombenzoyl)glycyl)aminomethyl-1-(4-chlorbenzyl)piperidinu (Sloučenina č.1042) (67 mg, 0. 14 mmol), roztoku 37% formaldehydu ve vodě (0,112 ml, 1.4 mmol), acetonitrilu (2 ml) a methanolu (1,5 ml). Poté, co se roztok míchal při 50 °C po dobu 30 h, se přidal 1 N vodný roztok NaOH a dichlormethanu. Oddělila se vodná vrstva a organická vrstva se vysušila pomocí K_2CO_3, přefiltrovala se a odpařila. Sloupcovou chromatografií (SiO_2, 20% MeOH/$CHCl_3$) se získal 4-[N-{5--brom-2-(dimethylamino)benzoyl}glycyl]aminomethyl-1-(4-chlorbenzyl)piperidin (Sloučenina č. **1428**) (60 mg, 82%) : Čistota sloučeniny se určila pomocí RPLC/MS (100%); ESI/MS m/e 523 ($C_{24}H_{30}BrClF_6N_4O_2$).

Příklad 2023: Příprava 4-[{N-(5-brom-2-(methylsulfonylamino)benzoyl)glycyl}aminomethyl]-1--(4-chlorobenzyl)piperidinu (Sloučenina č. 1581).

Směs 4-[{N-(2-amino-5-brombenzoyl)glycyl)aminomethyl)-1-(4-chlorbenzyl)piperidinu (25 mg, 0,05 mmol), methansulfonylchloridu (0,0045 ml), triethylaminu (0,026 ml) a dichloromethanu (2 ml) se míchala při pokojové teplotě po dobu 17 h. Reakční směs se vyčistila sloupcovou chromatografií ($Si0_2$), nanesla se na sloupec Varian SCX, sloupec se promyl CH_3OH (5ml). Produkt se vymyl ze sloupce 0,1 N HCl v CH_3OH (5ml) a zakoncentroval se. Získal se 4-[(N-(5-bromo-2-

-(methylsulfonylamino)benzoyl)glycyl}aminomethyl]-1-(4-chlorbenzyl)piperidin (Sloučenina č,1581) (5,4 mg, 19%): ESI/MS m/e 573,0 (M^++H, $C_{23}H_{28}BrClN_4O_4S$).

Příklad 2024: Příprava 4-[{N-(5-brom-2-(bis(methylsulfonyl)amino)benzoyl)glycyl)--aminomethyl]-1-(4-chlorbenzyl)piperidinu (Sloučenina č,1582).

Směs 1-(4-chlorbenzyl)-4-[(N-(2-amino-5-brombenzoyl)glycyl)aminomethyl]piperidinu (57mg, 0,10 mmol), mathansulfonylchloridu (0,018 ml, 0,24 mmol), triethylaminu (0,068 ml) a dichloromethanu (2 ml) se míchala při pokojové teplotě po dobu 8 h. Ke směsi se přidal vodný roztok NaOH (1 ml) a směs se extrahovala dichlormethanem (2 ml x 3). Spojené extrakty se vysušily pomocí K_2C0_3, přefiltrovaly se a odpařily. Sloupcovou chromatografií (SiO_2) se získal 4-[{N-(5-brom-2--(bis(methylsulfonyl)amino)benzoyl)glycyl)aminomethyl]-1-(4-chlorbenzyl)piperidin (Sloučenina č. **1582**) (40 mg, 62%) : ESI/MS m/e 651 (M^++H, $C_{24}H_{30}BrClN_4O_6S_2$).

Příklad 2025: Příprava 1-(4-chlorbenzyl)-1-methyl-4-[{N-(3-(trifluormethyl)benzoyl)glycyl}--aminomethyl]piperidinium jodidu (Methylamonium jodidu sloučeniny č. 461).

Roztok 4-[{N-(3-(trifluormethyl)benzoyl)glycyl}aminomethyl]piperidinu (30 mg, 0,087 mmol) v CH_3CN (1,0 ml) a piperidinmethylpolystyrenu (80 mg, 2,7 mmol báze/g pryskyřice) se přidal k roztoku 4-chlorbenzylchloridu (11,7 mg, 0,073 mmol) v CH_3CN (1,0 ml). Reakční směs se míchala při 60 °C po dobu 2 h. Do ochlazené směsi se přidal fenylizokyanát (10,4 mg, 0,087 mmol) a směs se nechala míchat při 25 °C po dobu 1 h. Reakční směs se nanesla na sloupec Varian SCX a promyla se CH_3OH (20 ml). Produkt se vymyl ze sloupce pomocí 2N NH_3 v CH_3OH (6 ml) a zakoncentrováním se získal 1-(4-chlorbenzyl)-4-[{N-(3-(trifluormethyl)benzoyl)glycyl}aminomethyl]piperidin jako bezbarvý olej, který lze použít bez dalšího čistění. K roztoku 1-(4-chlorobenzyl)-4-[{N-(3--trifluormethyl)benzoyl)glycyl}aminomethyl]piperidinu v CH_3CN (2,0 ml se přidal jodmethan (28 mg, 0,20 mmol) a roztok se nechal míchat při 70°C po dobu 4 h. Rozpouštědlo se odstranilo za sníženého tlaku a získal se 1-(4-chlorbenzyl)-1-methyl-4-[[N-(3-(trifluormethylbenzoyl)glycyl)--aminomethyl]piperidinium iodid jako světle žlutý olej (31,7 mg, 71%): Čistota sloučeniny se určila pomocí RPLC/MS (99%); ESI/MS m/e 482,1 ($C_{24}H_{28}ClF_3N_30_2$).

Příklad 2026: Příprava 1-{4-chlorbenzyl}-4-[N-methyl-N-{N-(3-(trifluormethyl)benzoyl)glycyl}--aminomethyl]piperidinu (Sloučenina č. 520).

Roztok formaldehydu (108 mg, 1,3 mmol, 37 váhových % v H_2O) se přidal k roztoku 1-(4--chlorbenzyl)-4-(aminomethyl)piperidinu (318 mg, 1,33 mmol) a $NaBH_3CN$ (668 mg) v 10% CH_3COOH/CH_3OH (3 ml) . Reakční směs se nechala míchat při 25 °C po dobu 1 h. Reakční směs se nanesla na sloupec DOWEX 50Wx2 (100 ml) a sloupec se vymyl CH_3OH (100 ml) . Produkt se vymyl 2N NH_3 v CH_3OH (100 ml) a zakoncentrováním se získalo 173 mg surového 1-(4-chlorobenzyl)-4--methylamino)methylpiperidinu ve formě bezbarvého oleje, který lze použít bez dalšího čištění. K roztoku 1-(4-chlorbenzyl)-4-{(methylamino)methyl}piperidinu (111 mg, 0,44 mmol) v CH_2Cl_2,

(4 ml) se dále přidal EDCI (85 mg) a 1-hydroxybenzotriazolhydrát (60 mg). Reakční směs se míchala při 25 °C po dobu 1 h a poté se promyjla 2 N vodným roztokem NaOH (2 ml x 2) a koncentrovaným roztokem NaCl (1 ml). Po filtraci přes PTFE membranový filtr, se kapalina odstranila za sníženého tlaku a získal se žlutý olej, který se čistil pomocí preparativní TLC (SiO_2, 5% CH_3OH/CH_2Cl_2) a získal se 1-(4-chlorbenzyl)-4-[N-methyl-N-{ N- (3-(trifluormethyl)benzoyl)-glycyl}aminomethyl)piperidin (Sloučenina č. 520) jako světle žlutý olej (14,0 mg, 3,4%). Čistota sloučeniny se určila pomocí RPLC/MS (99%); ESI/MS m/e 482,1 ($C_{24}H_{27}ClF_3N_3O_2$).

Referenční příklad 37: Příprava 3-aminohomopiperidinu.

Na roztok DL-α-amino-ε-kaprolaktamu (2 g, 16 mmol) v THF (70 ml) se působilo roztokem 1 M BH_3-THF (80 ml) a směs se zahřívala se pod refluxem po dobu 3 h. Přidal se 2 N vodný roztok HCl (50 ml) a reakční směs se zahřívala opět pod refluxem další hodinu a potom se ochladila na 25 °C. pH reakce se upravilo na hodnotu pH10 pomocí přídavku roztoku 4 N NaOH a reakce se extrahovala pomocí EtOAc (3 x 200 ml). Spojené organické fáze se promyly nasyceným vodným roztokem $NaHCO_3$, vysušily se ($MgSO_4$) a zakoncentrováním se získal požadovaný materiál (990 mg, 54%), který lze použít bez dalšího čištění.

Referenční příklad 38: Příprava 3-amino-1-(4-chlorbenzyl)homopiperidinu.

Na roztok 3-aminohomopiperidinu (1,71g, 15 mmol) v CH_3CN (45 ml) se působilo p--chlorbenzylchloridem (463 mg, 2,9 mmol) a K_2CO_3 (828 g, 6 mmol) a směs se zahřívala při 70 °C po dobu 9 h. Reakční směs se ochladila na 25 °C a zakoncentrováním se získala žlutá pevná látka. Vzniklá látka se rozdělila mezi H_2O (5 ml) a EtOAc (50 ml) a extrahovala se pomocí EtOAc (2 x 50

ml) . Spojené organické fáze se promyly nasyceným roztokem NaCl (20 ml), vysušily se pomocí (Na_2SO_4) a znovu se zakoncentrovaly. Vzniklý žlutý olej se čistil chromatografií ($Si0_2$, 5-20%. CH_3OH-CH_2C1_2, gradientová eluce) a získal se požadovaný produkt jako žlutý olej (639mg, 93%).

Příklad 2027: Příprava 1-(4-chlorbenzyl)-3-{(4-benzoylbutyryl)amino}homopiperidinu (Sloučenina č. 994).

Na roztok 3-amino-1-(4-chlorbenzyl)homopiperidinu (24mg, 0,10mmol) a 4-benzoylmáselné kyseliny (1,2 ekviv.) v $CHC1_3$ (1 ml) se působilo EDCI (23 mg), HOBt (16,2 mg) a Et_3N (15,2 µl) a směs se nechala míchat při 25°C po dobu 16 h. Reakční směs se naředila CH_2C1_2 (0,5 ml), promyla se 2 N vodným roztokem NaOH (2 x 0,75 ml), vysušila se filtrací přes PTFE membranu a zakoncentrováním se získal 1-(4-chlorbenzyl)-3-{(4-benzoylbutyryl)amino}homopiperidin (sloučenina č. **994**) (93 mg, 99%): Čistota sloučeniny se určila pomocí RPLC/MS (98%); ESI/MS m/e 413 ($C_{24}H_{29}ClN_2O_2$).

Příklady 2028 až 2042:

Sloučeniny podle vynálezu se syntetizovaly podle metod popsaných v Příkladu 2027 za použití odpovídajících reaktantů v daném pořadí. Bylo-li to nutné pro získání produktu jako TFA sůl, použila se chromatografie (HPLC-C18). Výsledky ESI/ MS a výtěžky jsou shrnuty v tabulce 52.

Tabulka 52

Sloučenina č.	Molekulární vzorec	ESI/MS m/e	Výtěžek mg)	Výtěžek %	
Příklad 2028	943	C23 H25 Cl F3 N3 02	468	6	28
Příklad 2029	994	C23 H28 C1 N3 02	419	5	29
Příklad 2030	945	C22 H25 Cl Pd4	04	445	6
Příklad 2031	946	C23 H27 C1 N4 04	459	5	29
Příklad 2032	947	C25 H31 C1 N2 04	459	4	20
Příklad 2033	948	C24 H29 C12N3 02	962	6	32
Příklad 2034	949	C25 H32 C1 N3 02	942	6	31
Příklad 2035	988	C23 H25 C1 F3 N3 02	468	45	92

Příklad 2036	989	C23 H28 Cl N3 03	930	44	97
Příklad 2037	990	C22 H26 C1 N3 02	400	41	99
Příklad 2038	991	C23 H27 C1 N2 02	399	41	97
Příklad 2039	992	C25H31C1N204	459	47	98
Příklad 2040	993	C25H31Cl N202	427	44	98
Příklad 2041	995	C25H31C1N203	443	94	95
Příklad 2092	996	C24H31Cl N402	993	5*	11

*Výtěžek TFA soli

Příklad 2043: Měření inhibice vazby MIP-lα k THP-1 buňkám pomocí testovaných sloučenin

Lidská monocytická leukemická buněčná linie THP-1 se resuspendovala v mediu RPMI-1690 (Gibco-BRL Co.) obsahujícím 0,1% BSA a 25 mM HEPES s pH upraveným na hodnotu pH 7. Získala se buněčná suspenze o koncentraci 1 x 10 buněk/ml. Testovaná sloučenina se naředila v testovacím pufru (mediu) a použila se jako testovací roztok. Jodidovaný lidský MIP-1α (DuPont NEN Co.) se naředil v testovacím pufru na 250 nCi/ml a používal se jako roztok značící sloučeniny. Do 96 jamkové filtrační desky (Millipore Co.) se napipetovalo 25μl roztoku testované sloučeniny, 25μl značícího ligandu a 50μl buněčné suspenze. Obsah se zamíchal (celkový reakční objem je 100μl) a inkuboval se 1h při 18 °C.

Po proběhnutí reakce se reakční medium odfiltrovalo a filtr se promyl dvakrát 200μl chladného PBS (přidá se 200μl chladného PBS a potom se provede filtrace). Filtr se usušil na vzduchu a přidalo se 25μl scintilačního roztoku do každé jamky. Pomocí TopCount (Packard Instrument Co.) se proměřila radioaktivita buněk na filtru.

K výpočtu schopnosti testované sloučeniny inhibovat vazbu lidského MIP-1α k THP-1 buňkám se musela určit nespecifická vazebná kapacita. To se učinilo přidáním 100ng neznačeného lidského MIP-1α místo testované sloučeniny. Takto získaná hodnota se odečetla. Hodnota získaná z měření, kde se nepřidávala testovaná sloučenina se brala jako 100%.

Inhibice(%) = (1 –(A-B)/(B-C)) x 100

(A-odečty získané s testovanou sloučeninou; B-hodnoty získané z odečtu za použití 100ng neznačeného lidského MIP-1α; C- odečty získané s přidaným I^{125} značeným lidským MIP-1α).

Měřením inhibice použitých derivátů cyklických aminů podle vynálezu, se získaly například hodnoty inhibiční aktivity v rozmezí 20%-50%, 50%-80% a hodnoty inhibice vyšší než 80%

při použití jejich 2μM a 10 μM koncentrací u následujících sloučenin:

20%-50% inhibice při 10 μM: Sloučeniny č. 29, 37, 41,45,46, 47, 50, 82, 85, 107,120, 139, 214 ,217 , 218 , 220 , 222 , 225 , 226 , 227 , 228 , 229, 230, 231,233, 234, 236 , 237 ,238 , 333 , 334 ,335 , 336 338 ,340 , 342 , 347 , 348 , 349 , 350 ,352 , 357, 359, 361, 366, 372, 374, 375, 376, 380, 382, 383, 385, 470, 471,472, 473, 474, 483, 484, 488,489, 491,497, 499,500, 502, 506, 508, 510, 514, 515, 518, 524, 543, 553, 554, 555, 556, 563, 571, 575,576, 578, 579, 580, 583, 586, 587, 588, 590,591, 592, 595, 596, 598, 603, 610,611, 612, 619, 624, 625,626, 629, 635, 638,639, 640, 641, 642, 643, 644, 646, 647, 648, 649, 652, 653, 658, 659, 660 , 665 , 666 , 669 , 671 , 675 , 677 , 679 , 681 , 682 ,684 , 691 ,695 ,696 700 , 702 , 704, 706, 711, 712, 714, 717,721,723, 724, 726, 727, 728, 729, 731, 737, 739,740, 741, 742, 744, 746, 765,767, 772, 773, 774, 775, 776, 780, 781, 785,786, 787, 788, 790, 791, 792, 793, 795, 796, 797, 798, 805, 806, 807, 810, 813, 820, 821 , 822 , 824 , 825 , 827 , 829 , 830 , 833 , 834 , 837 ,838 , 844 , 853 , 855 , 873 , 877 ,878, 880, 882, 887, 888, 891,894, 901, 903, 904, 905, 911, 929, 932, 933, 935, 938, 940, 948, 993, 996, 1006 , 1018, 1026, 1028, 1035, 1098, 1053, 1054, 1055, 1056 , 1068, 1070, 1071,1072 , 1073, 1075,1076, 1081, 1763, 1764.

50% -80% inhibice při 10 μM: Sloučeniny č.:1, 2,3, 4, 7,13, 22, 23, 24, 25, 27, 31, 32, 38, 48, 83, 119, 121, 123, 131, 215, 216, 221, 235, 337,351, 354, 358 , 362 , 363 , 365 ,367 ,368 , 369 , 373 , 378 , 381 , 384 , 458 ,459 , 463 ,465 ,466, 467 , 468 ,478 ,479 ,480 ,482 ,485 ,486 , 487 , 492 ,493 , 494 495,496 ,498 ,501 ,503,504,507, 511, 512, 513, 520, 523, 527,529, 530,531,532, 533, 534,535, 536, 537 ,538 ,539 ,540 , 591 , 542 , 545 , 546 , 547 ,548 ,549,550, 551 ,552 , 558 ,559 ,560 , 561 ,562 565 567 ,568 , 569 , 570 ,572 , 573 , 574 ,577 ,581, 582 ,594 , 597, 599, 600, 602, 604, 606, 607, 608 , 609, 613, 615 , 616, 618, 619, 620, 621,628 , 630 , 631 , 632 , 633 , 634 , 636 , 637 , 645 , 651 , 654 , 655 , 657 , 661 , 662 ,664, 673, 674,676, 678, 680, 683, 685, 687, 688, 689, 693, 703, 705, 707, 708, 709, 710, 713, 716, 718, 719, 720, 725, 730, 732, 733, 734, 735, 736, 749, 750, 751, 752, 753, 754, 756, 758, 760,762, 763, 764, 766, 768, 769, 770, 771, 777, 778, 779, 784, 794, 799, 800, 802, 804, 808, 809, 811, 812, 815, 816, 819, 828, 831, 832, 835, 836, 839, 840, 845, 846, 847,848, 850, 851, 854, 857, 858, 859, 860, 861, 862, 863, 865, 866, 867, 868, 872, 874, 876, 886, 899, 910, 942, 998, 1004, 1005 , 100 7, 1013, 1015, 1016 , 1017, 1019, 1020, 1021, 1022, 1024, 1030, 1037, 1042, 104 3, 1044, 1045,1046 , 1047, 10 49, 1050, 1052, 1059, 1060, 1061, 1067, 1069 , 1074, 1078,1079, 1080 , 1766.

>80% inhibitice při 10 μM: Sloučeniny č.:461, 464, 469, 481, 490, 505, 509, 521, 52 6, 528 , 544 , 564 , 566 , 601 , 605 , 617 , 622 , 623 , 627 , 650 , 656 , 663 , 668 , 672 , 686, 690, 692, 694, 715, 743, 747, 748, 755, 757, 759, 761, 782, 783, 803, 814, 817, 818, 826, 849,856, 869, 869, 870, 871, 999, 1000 , 1001, 1002, 1003, 1008, 1009, 1010, 1011, 1012, 1023, 1029, 1031, 1032, 1033, 1034, 1036, 1038, 1039, 1040, 1041, 1051, 1057, 1058, 1062, 1063, 1064, 1065, 1066, 1082, 1083.

20%-50% inhibice při 2 μM: Sloučeniny č.: 1042, 1043, 1244, 1245, 1416, 1435, 1436, 1438, 1441, 1480, 1570, 1583, 1584, 1589, 1590, 1594, 1595, 1601, 1660,1672, 1687, 1724, 1779, 1780, 1787, 1795, 1796, 1798, 1799, 1802, 1893, 1894, 1898, 1900, 1915, 1919, 1920, 2092, 2096, 2098, 2100.

50%-80% inhibice při 2 μM: Sloučeniny č: 1190, 1414, 1600, 2091, 2094, 2095.

>80% inhibice při 2 μM: Sloučeniny č.: 2093, 2097, 2099, 2103, 2109.

Příklad 2044: Měření inhibice vazby MCP-1 k THP-1 buňkám.

1.Konstrukce rekombinantního bakuloviru nesoucího gen pro lidský MCP-1

S využitím dříve publikované sekvence pro lidský MCP-1 gen (na příklad T. Yoshimura a další, FEBS Lett., 1989, 244, 487 až 493), byly nasyntetizovány dva DNA primery (5'-CACTCTAGACTCCAGCATGA-3' a 5'-TAGCTGCAGATTCTTGGGTTG-3') ohraničené místy pro restrikční enzymy, které byly použity pro amplifikaci DNA fragmentů z cDNA odvozené z lidských endoteliálních buněk (získaných od Kurabow Co.); amplifikované fragmenty byly naštěpeny restrikčními enzymy (PStI a XbaI), zaligovány do přenosového vektoru pVL1393 (Invitrogen Co.) a výsledný vektor byl společně transformován s infekčním bakulovirem do Sf-9 hmyzích buněk a supernatant se podrobyl plakové zkoušce k získání MPC-1 genu v rekombinantním bakuloviru.

2. Syntéza [I^{125}]-značeného lidského MCP-1 exprimovaného v bakulovirech

Pomocí způsobu přípravy popsaného K. Ishii a další. (Biochem Biophys Research Communications, 1995, 206, 955-961), se 5 x 10^6 Sf-6 hmyzích buněk infikovalo 5 x 10^7 PFU (plaque forming units = jednotka tvořící plak) výše zmíněného lidského MCP-1 rekombinantního bakuloviru a kultivovalo se po dobu 7 dní v mediu Ex-Cell 901. Supernatant sebraný z kultury se afinitně čistil pomocí sloupce heparin Sepharosy (Pharmacia Co.) a poté se čistil použitím reversní fáze HPLC (Vydac C18 kolona).

Takto se získal čistý lidský MCP-1. Tento vyčištěný lidský MCP-1 se označil pomocí metody proteinového značení od firmy Amersham Co. za využití postupu Bolton Hunterova a získal se bakulovirus značený [I^{125}] a exprimující lidský MCP-1(specifická aktivita je 2000 Ci/mmol).

3-1. Měření inhibice vazby [I^{125}] –značeného bakuloviru exprimujícího lidský MCP-1 k THP-1 buňkám (Způsob 1)

Lidská monocytární leukemická buněčná linie THP-1 se resuspendovala v mediu RPMI-1640 (Gibco-BRL Co.) obsahujícím 0,1% BSA a 25 mM HEPES s pH upraveným na hodnotu pH 7. Takto vznikla buněčná suspenze o koncentraci 1 x 10^7 buněk/ml. Testovaná sloučenina se rozpustila také v daném mediu a použíla se jako roztok testované sloučeniny. [I^{125}] – značený lidský MCP-1 popsaný výše se naředil v daném mediu na koncentraci 1 mCi/ml.

Do 96 jamkové filtrační desky (Millipore Co.) se napipetovalo 25µl roztoku testované sloučeniny, 25µl značícího ligandu a 50µl buněčné suspenze. Obsah se zamíchal (celkový reakční objem je 100µl) a inkuboval se 1h při 18 °C.

Po proběhnutí reakce se reakční medium odfiltrovalo a filtr se promyl dvakrát 200µl chladného PBS (přidalo se 200µl chladného PBS a potom se provedla filtrace). Filtr se usušil na vzduchu a přidalo se 25µl scintilačního roztoku do každé jamky. Pomocí TopCount (Packard Instrument Co.) se proměřila radioaktivita buněk na filtru.

K výpočtu schopnosti testované sloučeniny inhibovat vazbu lidského MIP-1α k THP-1 buňkám se musela určit nespecifická vazebná kapacita. To se učinilo přidáním 100ng neznačeného lidského MIP-1α místo testované sloučeniny. Takto získaná hodnota se odečetla. Hodnota získaná z měření, kde se nepřidávala testovaná sloučenina, se brala jako 100%.

Inhibice(%) = (1 –(A-B)/(B-C)) x 100

kde A jsou odečty získané s testovanou sloučeninou; B jsou hodnoty získané z odečtu za použití 100 ng neznačeného lidského MIP-1α; C jsou odečty získané s přidaným I^{125} značeným lidským MIP-1α .

Měřením inhibice vyvolané použitím derivátů cyklických aminů podle vynálezu, se získaly například hodnoty inhibiční aktivity v rozmezí 20%-50%, 50%-80% a hodnoty inhibice vyšší než 80% při použití jejich 1μM , 10 μM a 100μM koncentrace u následujících sloučenin:

20%-50% inhibice při 100 μM: sloučeniny číslo:3, 6, 11, 15, 16, 19, 28, 44, B8, 92, 94, 104, 111, 112, 124, 125, 133, 219, 220, 224, 228, 236, 338, 343, 346, 347, 398, 349, 362, 363, 367, 368, 371, 373, 3B1, 618, 847, 849, 850, 866, 867, 869, 870, 871, 872, 873.

50%-80% inhibice při 100 μM koncentraci: sloučeniny číslo: 1, 8, 10, 12, 18, 21, 26, 30, 33, 35, 39, 84,89, 90, 91, 96, 97, 98, 99, 100, 101, 103, 106, 108, 109, 110, 116, 122, 126, 216, 218, 221, 225, 226, 231, 330, 332, 333, 334, 337, 341, 342, 350, 352 , 354 , 356 , 359 , 360 , 361 , 364 , 366 , 374 , 375 , 379 , 382 , 462 , 463 , 464 , 557 , 686, 840, 841, 842, 843, 844, 845, 846, 848, 862, 863, 864, 865, 868.

>80% inhibice při 100 μM koncentraci : sloučeniny číslo: 2, 4,7,13,14, 17, 20, 22,23, 24, 25,27, 29, 34, 36, 38, 40,41,42, 43, 45, 46,47, 48, 49, 50, 83, 85, 86, 95,102,105,107,13,114,115, 119,121,123,127,128,129,130,131,132,134,214,215,217, 227, 237, 238, 331,335, 336, 339, 340, 345, 351, 355, 357, 358, 383, 458, 459, 460, 466, 558, 851, 852, 861, 874.

20%-50% inhibice při 10μM: sloučeniny číslo: 12, 18, 30, 34, 40,42, 43, 51, 52,53,54, 55, 56, 57,59, 60, 64, 66, 75, 76, 77, 78, 79, 82, 89, 90, 97, 98, 102, 103, 116, 127, 128, 129, 130, 132, 135, 136, 140, 141, 144, 156, 157, 159, 160, 161, 162, 163, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 178, 179, 190, 192, 192, 295, 197, 200, 202, 203, 204, 205, 208, 233, 234, 235, 239, 240, 241, 242, 243, 245, 247, 249, 250, 255, 263, 264, 269, 274, 278, 279, 282, 306, 316, 317, 323324, 380, 404, 409, 433, 446, 448, 449, 451, 470, 471, 473, 476, 479, 486, 488, 489, 497, 498, 499, 501, 504, 507, 508, 509, 510, 512, 519, 516, 519 , 527, 530 532 , 542 , 545 , 560 , 563 , 564 , 565 , 566 , 568 , 569 , 572 , 573 , 574 , 575 , 578 , 583 584 , 586 587 , 589 , 590 , 599 , 600 , 601 , 603 , 606 , 612 , 613 , 620 , 621, 622, 624, 625, 627, 629, 630, 632, 634, 636, 637, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 658, 678, 682, 687, 692, 694, 764, 775, 856, 857, 860, 881, 882, 883, 889, 890, 892, 899, 900, 903, 905, 907, 908, 911, 912, 916, 917, 922, 923, 925, 927, 931, 932, 935, 939 940, 968 , 986, 1039, 1041, 1045, 1047, 1062, 1063, 1083.

20%-50% inhibice při 10 μM: sloučeniny číslo: 7, 32, 36, 61, 62, 63, 65, 67, 69, 70, 71, 72, 73, 74, 81, 91, 105, 114, 121, 123, 134, 137, 138, 139, 146, 147, 148, 149, 151, 154, 165, 177, 232, 244, 248, 251, 252, 253, 256, 259, 261, 266, 267, 276, 286, 292, 293, 295, 301, 305, 307, 310, 314, 315, 320, 322, 328, 434, 435, 436, 437, 439, 440, 443, 447, 450, 452, 453, 454, 455, 456, 468, 469, 472, 474, 475, 477, 978, 480, 481, 482, 483, 485, 490, 493, 494, 500, 505, 511, 517, 520, 529, 534, 540, 543, 544,

548, 555, 556, 561, 562, 570, 576, 579, 611, 617, 853, 854, 855, 858, 859, 875, 877, 879, 880, 881, 886, 887, 888, 891, 894, 895, 904, 906, 909, 910, 913, 914, 918, 928, 930, 933, 937, 938, 945, 970, 1040, 1044, 1046

>80 % inhibice při 10 μM: sloučeniny č. 31, 45, 46, 48, 5B, 68, 80, 83, 111, 115, 142, 143, 145, 150, 152, 265, 268, 272, 275, 283, 285, 287, 288, 290, 291, 294, 296, 297, 302, 308, 309, 313, 321, 325, 326, 358, 438, 441, 442, 444, 445, 457, 466, 467, 489, 487, 491, 492, 495, 496, 503, 518, 537, 538, 547, 554, 876, 878, 919, 929, 943.

20%-50% inhibice při 1 μM: sloučeniny číslo: 31, 118, 1121, 1136, 1143, 1146, 1 58, 1159, 2167, 1170, 1359, 2361, 2362, 1363.

50%-80% inhibice při 1 μM: sloučeniny číslo:1133, 1134, 1137, 1141, 1156, 1161, 1162, 1163, 1164, 1166.

>80 % inhibice při 1 μM: sloučenina č: 1147.

3-2. Měření inhibice vazby [I^{125}] –značeného bakuloviru exprimujícího lidský MCP-1 k THP-1 buňkám (Způsob 2)

Lidská monocytární leukemická buněčná linie THP-1 se resuspendovala v mediu (50 mM HEPES, pH 7.4 obsahujícím 0,5% BSA, 0,5 mM $MgCl_2$, 1,0 mM $CaCl_2$). Tak vznikla buněčná suspenze o koncentraci 1 x 10^7 buněk/ml. Testovaná sloučenina se rozpustila také v daném mediu a používala se jako roztok testované sloučeniny. Výše popsaný [I^{125}] – značený lidský MCP-1 se naředil v daném mediu na koncentraci 1 mCi/ml.

Do 96 jamkové filtrační desky (Millipore Co.) se napipetovalo 25μl roztoku testované sloučeniny, 25μl značícího ligandu a 50μl buněčné suspenze. Obsah se zamíchal (celkový reakční objem byl 100μl) a inkuboval se 1h při 18 °C.

Po proběhnutí reakce se reakční medium odfiltrovalo a filtr se promyl dvakrát 200μl chladného PBS (přidalo se 200μl chladného PBS a potom se provedla filtrace). Filtr se usušil na vzduchu a přidalo se do každé jamky 25μl scintilačního roztoku. Pomocí TopCount (Packard Instrument Co.) se proměřila radioaktivita buněk na filtru.

K výpočtu schopnosti testované sloučeniny inhibovat vazbu lidského MIP-1α k THP-1 buňkám se musela určit nespecifická vazebná kapacita. To se učinilo přidáním 100ng neznačeného lidského MCP-1 místo testované sloučeniny. Takto získaná hodnota se odečte. Hodnota získaná z měření, kde se nepřidávala testovaná sloučenina se brala jako 100%.

Inhibice(%) = (1 –(A-B)/(B-C)) x 100

Kde A jsou odečty získané s testovanou sloučeninou; B jsou hodnoty získané z odečtu za použití 100ng neznačeného lidského MCP-1; C jsou odečty získané s přidaným I^{125} značeným lidským MCP--1).

Měřením inhibice vyvolané použitím derivátů cyklických aminů podle vynálezu, se získaly například hodnoty inhibiční aktivity v rozmezí 20%-50%, 50%-80% a hodnoty inhibice vyšší než 80% při použití 0,2μM , 1 μM a **10** μM koncentrace u následujících sloučenin:

20%-50% inhibice při 10 μM: sloučenina číslo: 1560

50%-80% inhibice při 10 μM: sloučenina číslo: 1550
>80% inhibice při 10 uM: sloučeniny číslo: 541, 1042, 1043, 1559

20%-50% inhibice při 1 μM: sloučeniny číslo: 1098, 1100, 1101, 1104, 1105, 1109, 1110, 1116, 1174, 1175, 1176, 1178, 1187, 1188, 1189, 1197, 1198, 1199, 1200, 1201, 1202, 1209, 1210, 1211, 1212, 1222, 1225, 1229, 1230, 1237, 1238, 1243, 1250, 1259, 1261, 1265, 1266, 1272, 1277, 1282, 1294, 1299, 1302, 1307, 1315, 1318, 1319, 1320, 1329, 1330, 1335, 1336, 1337, 1393, 1344, 1353, 1355, 1356, 1357, 1358, 1368, 1372, 1385, 1386, 1392, 1400, 1413, 1422, 1423, 1425, 1426, 1429, 1430, 1432, 1437, 1440, 1445, 1446, 1447, 1448, 1450, 1452, 1453, 1455, 1458, 1959, 1461, 1463, 1464, 1466, 1468, 1469, 1470, 1471, 1474, 1979, 1482, 1485, 1507, 1508, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1518, 1519, 1521, 1522, 1524, 1535, 1538, 1540, 1542, 1544, 1571, 1573, 1574, 1575, 1576, 1577, 1578, 1579, 1580, 1581, 1582, 1585, 1587, 1598, 1602, 1603, ' 1604, 1609, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1622, 1627, 1630, 1643, 1646, 1662, 1669, 1716, 1717, 1723, 1728, 1731, 1733, 1736, 1739, 1740, 1747, 1750, 1755, 1757, 1758, 1759, 1760, 1761, 1762, 1769, 1770, 1771, 1772, 1773, 1774, 1777, 1783, 1784, 1785, 1791, 1793, 1904, 1911, 1917, 2057, 2061, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2071, 2072, 2073, 2074, 2075, 2076, 2080, 2081, 2082, 2110, 2112, 2123, 2130, 2131, 2139.

50%-80% inhibice při 1μM: sloučeniny číslo: 37, 298, 318, 1084, 1091, 1103, 1106, 1108, 1111, 1113, 1114, 1115, 1138, 1142, 1165, 1179, 1190, 1192, 1193, 1195, 1196, 1204, 1205, 1206, 1207, 1208, 1245, 1246, 1255, 1257, 1258, 1262, 1263, 1293, 1300, 1342, 1351, 1352, 1354, 1370, 1371, 1373, 1375, 1377, 1378, 1380, 1381, 1383, 1384, 1391, 1411, 1412, 1414, 1417, 1418, 1419, 1421, 1424, 1431, 1436, 1439, 1449, 1454, 1456, 1457, 1460, 1462, 1472, 1473, 1487, 1502, 1504, 1506, 1517,

1525, 1526, 1527, 1529, 1530, 1531, 1532, 1533, 1534, 1536, 1537, 1539, 1541, 1545, 1593, 1600, 1601, 1606, 1608, 1619, 1620, 1621, 1623, 1624, 1625, 1626, 1628, 1629, 1645, 1650, 1654, 1658, 1663, 1664, 1665, 1670, 1671, 1672, 1673, 1675, 1678, 1679, 1681, 1684, 1687, 1688, 1689, 1690, 1711, 1712, 1714, 1718, 1722, 1725, 1726, 1727, 1729, 1730, 1732, 1734, 1735, 1737, 1741, 1742, 1743, 1744, 1745, 1746, 1748, 1751, 1753, 1754, 1756, 1779, 1781, 1782, 1786, 1788, 1789, 1790, 1792, 1795, 1797, 1798, 1800, 1801, 1804, 1848, 1862, 1883, 1885, 1886, 1887, 2889, 1893, 1894, 1903, 1905, 1910, 1912, 1913, 1914, 1918, 1922, 1976, 1985, 2027, 2035, 2062, 2083, 2084, 2088, 2089, 2090, 2111, 2124, 2125, 2126, 2135.

>80% inhibice při 1 uM: sloučeniny číslo: 299, 311, 312, 329, 1042, 1093, 1085, 1119, 1191, 1203, 1220, 1228, 1236, 1244, 1256, 1288, 1295, 1308, 1310, 1376, 1382, 1393, 1395, 1415, 1416, 1420, 1435, 1438, 1441, 148, 1481, 1570, 1583, 1584, 15891590, 1594, 1595, 1607, 1634, 1660, 1661, 1666, 1668, 1695, 1696, 1697, 1698, 1699, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 1713, 1724, 1749, 1752, 1775, 1776, 1778, 1780, 1787, 1794, 1796, 1799, 1802, 1803, 1841, 1869, 1870, 1871, 1872, 1876, 1877, 1892, 1896, 1897, 1898, 1899, 1900, 1901, 1902, 1906, 1907, 1908, 1909, 1915, 1916, 1919, 1920, 1921, 2085, 2086, 2087, 2113, 2114, 2118, 2119, 2120, 2121, 2122, 2127, 2128, 2129, 2132, 2133, 2136, 2137, 2138, 2159, 2161, 2162, 2187, 2189, 2193.

20%-50% inhibice při 0, 2 μM koncentraci : sloučeniny číslo: 1680, 1682, 1686, 1691, 1694, 1700, 1805, 1810, 1811, 1812, 1813, 1815, 1816, 1817, 1818, 1819, 1820, 1824, 1825, 1826, 1827, 1828, 1832, 1833, 1834, 1835, 1836, 1839, 1840, 1842, 1843, 1851, 1852, 1853, 1854, 1855, 1856, 1858, 1859, 1860, 1863, 1864, 1865, 1866, 1868, 1879, 1878, 1879, 1880, 1888, 1890, 1891, 1895, 1926, 1927, 1928, 1929, 1930, 1934, 1935, 1937, 1945, 1946, 1951, 1952, 1953, 1954, 1959, 1960, 1961, 1962, 1966, 1969, 1970, 1971, 1972, 1973, 1977, 1978, 1979, 1980, 1981, 1985, 2014, 2027, 2028, 2033, 2035, 2039, 2040, 2041, 2042, 2044, 2045, 2046.

50%-80% inhibice při 0.2μM koncentraci : sloučeniny číslo: 1677, 1678, 1679, 1681, 1687, 1688, 1689, 1690, 1695, 1697, 1808, 1809, 1841, 1848, 1861, 1862, 1869, 1870, 1871, 1872, 1873, 1876, 1877, 1883, 1884, 1885, 1886, 1887, 1889, 1893, 1894, 1976.

>80% inhibice při 0.2 uM koncentraci: sloučeniny číslo:1696, 1892.

Příklad 2045: Měření inhibice vazby [I^{125}] –značeného lidského MCP-1 k buňkám exprimujícím MCP-1 receptor

Odvození buněk exprimujících MCP-1 receptor

Fragment cDNA obsahující MCP-1 receptor, sestrojený podle práce S. Yamagami a dalších, Biochemical Biophysical Research Communications 1994, 202, 1156až1162) se klonoval do expresního plazmidu pCEP4 (Invitrogen Co.) v NotI místě a získaný plazmid se vložil transfekcí do lidské epiteliální ledvinné buněčné linie 293-EB2IA pomocí činidla Lipofectamine (Gibco-BRL Co.). Buňky se kultivovaly v přítomnosti selekčního media (Hygromycin) a získaly se stabilně exprimující transfekční linie. Exprese receptoru byla potvrzena vazbou (I^{125})-značeného lidského MCP-1.

2. Měření inhibice vazby [I^{125}] –značeného bakuloviru exprimujícího lidský MCP-1 k buňkám exprimujícím MCP-1 receptor

Buňky exprimující lidský MPC-1 receptor, které byly napěstovány na kultivačních miskách, se seškrábaly pomocí škrabky na buňky a resuspendovaly v mediu (D-MEM, Gibco-BR.L Co.) obsahujícím 0,1 BSA a 25 mM HEPES s pH upraveným na pH 7.4). Obdržela se suspenze buněk o koncentraci 6 x 10^6 buněk/ml. Testovaná sloučenina se naředila v testovacím mediu. Zbytek postupu je posán v Příkladu č.2044.

Byly-li naměřeny inhibiční aktivity pro některé sloučeniny, byly shodné s hodnotami a čísly sloučenin uvedenými v Příkladu č. 2044.

Příklad 2046: Měření inhibice chemotaxe buněk

K měření inhibice chemotaxe buněk, která je způsobena sloučeninami podle vynálezu, se měřila chemotaxe způsobená monocytárním chemotaktickým faktorem MCP-1 za použií lidské monocytární leukemické buněčné linie THP-1 jako chemotaktických buněk podle metody popsané Fallem a dalšími, (J. Immunol. Methods, 190, 33, 239 až 247).

2 x 10^6 THP-1 buněk /ml (resuspendovaných v RPMI-1640 (Flow Laboratories Co.) + 10% FCS) se umístilo do horní komory (200 uL) 96 jamkové mikro-chemotaktické komory (Neuroprobe, registrovaná obchodní známka). Roztok lidského rekombinantního MCP-1 v tomtéž roztoku

(Peprotech Co.) v konečné koncentraci 20 ng/ml se nalil do spodní komory , která byla od horní komory oddělena polykarbonátovým filtrem (PVP-free, Neuroprobe; registrovaná obchodní známka). Celé zařízení se inkubovalo při 37 °C po dobu 2 hr v 5% O_2.

Filtr se vyjmul, buňky, které prošly na druhou stranu filtru se zafixovaly, obarvily pomocí Diff Quick (Kokusai Shiyaku Co.) a poté se kvantifikovaly pomocí readeru na mikrotitrační desky (Molecular Device Co.) při vlnové délce 550 nm. Z průměru tří jamek se určil index migrace. Dále se do horní i dolní komory vložily společně s THP-1 a MCP-1 testované sloučeniny a měřila se inhibice buněčné migrace (inhibice IC_{50} (μM). Inhibice se definuje jako:

{(migrace buněk indukovaná MCP-1 v nepřítomnosti testované sloučeniny v horní a dolní komoře) - (buněčná migrace v nepřítomnosti MCP-1 v dolní komoře) = 100%}.

Koncentrace testované sloučeniny, která způsobuje 50% inhibici se značí IC_{50}. Při měření inhibice deriváty cyklickýmch aminů podle vynálezu se získaly například hodnoty koncentrací nižší než 0,1μM pro 50% inhibici (IC_{50}) pro následující sloučeniny:

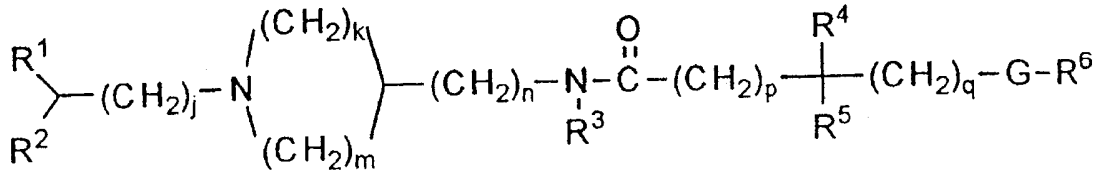
IC_{50} < 0, 1μM: 4, 37, 298, 299, 311, 312, 318, 329, 461, 886, 909, 1042, 1043, 1085, 1119, 1138, 1142, 1165, 1179, 1191, 1203, 1205, 1220, 1228, 1236, 1244, 1245, 1256, 1288, 1293, 1295, 1308, 1310, 1352, 1376, 1382, 1393, 1395, 1916, 1420, 1435, 1436, 1438, 1441, 1480, 1531, 1532, 1570, 1583, 1584, 1589, 1590, 1599, 1595, 1600, 1601, 1607, 1660, 1661, 1664, 1666, 1668, 1698, 1699, 1701, 1702, 1703, 1704, 1706, 1707, 1708, 1709, 1713, 1775, 1776, 1778, 1779, 1787, 1794, 1796, 1799, 1802, 1803, 1896, 1898, 1899, 1900, 1901, 1902, 1906, 1907, 1908, 1909, 1915, 1916, 1919, 1920, 1921, 2087, 2114, 2128, 2129, 2132, 2137, 2141, 2144, 2157, 2158, 2189.

03.07.00

2000-1434

PATENTOVÉ NÁROKY

1. Sloučenina podle obecného vzorce I uvedeného níže



(I)

její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině, kde R^1 je fenylová skupina, C_3 – C_8 cykloalkylová skupina nebo aromatická heterocyklická skupina mající 1 až 3 heteroatomy vybrané ze skupiny obsahující atom kyslíku, atom síry a atom dusíku, nebo kombinaci těchto, ve které fenyl nebo heterocyklická aromatická skupina je kondenzována s benzenovým kruhem nebo aromatickou heterocyklickou skupinou mající 1 až 3 heteroatomy vybrané ze skupiny obsahující atom kyslíku, atom síry, atom dusíku nebo kombinaci těchto, tak aby se vytvořil kondenzovaný kruh. Fenylová skupina, C_3 - – C_8 cykloalkylová skupina, aromatická heterocyklická skupina nebo kondenzovaný kruh, jsou substituovány jedním nebo více atomy halogenů, hydroxylovou skupinou, kyanoskupinou, nitroskupinou, karboxylovou skupinou, karbamoylovou skupinou, C_1 – C_6 alkylovou skupinou, C_3 – C_8 cykloalkylovou skupinou, C_2 – C_6 alkenylovou skupinou, C_1 – C_6 alkoxylovou skupinou, C_1 – C_6 alkylthioskupinou , C_3 – C_5 alkylenovou skupinou, C_2 – C_4 alkylenoxy skupinou, C_1 – C_3 alkylendioxy skupinou, fenylovou skupinou, fenoxy skupinou, fenylthioskupinou, benzylovou skupinou, benzyloxy skupinou, benzylaminoskupinou, C_2 – C_7 alkanoylovou skupinou, C_2 – C_7 alkoxykarbonylovou skupinou, C_2 – C_7 alkanoyloxylovou skupinou, C_2 – C_7 alkanoylaminoskupinou, C_2 – C_7 N- -alkylkarbamoylovou skupinou, C_4 – C_9 N--cykloalkylkarbamoylovou skupinou, C_1 – C_6 alkylsulfonylovou skupinou, C_3 – C_8 (alkoxykarbonyl)methylovou skupinou, N-fenylkarbamoylovou skupinou, piperidinkarbonylovou skupinou, morfolinkarbonylovou skupinou, 1-pyrolidinylkarbonylovou skupinou, bivalentní skupinou reprezentovanou vzorcem: - NH(C=O)O-, bivalentní skupinou reprezentovanou vzorcem: -NH(C=S)O-, amino skupinou, mono(C_1 – C_6 alkyl)aminoskupinou, či di(C_1 – -C_6 alkyl)aminoskupinou, kde substituent fenylové skupiny, C_3 – C_8 cykloalkylové skupiny, aromatické heterocyklické skupiny nebo kondenzovaného kruhu je případně substituovaný

jedním nebo více halogenovými atomy, hydroxylovou skupinou, aminoskupinou, trifluormethylovou skupinou, $C_1 - C_6$ alkylovou skupinou nebo, $C_1 - C_6$ alkoxylovou skupinou;

R^2 značí vodíkový atom, $C_1 - C_6$ alkylovou skupinu, $C_2 - C_7$ alkoxykarbonylovou skupinu, hydroxylovou skupinu nebo fenylovou skupinu, kde $C_1 - C_6$ alkylová nebo fenylová skupina je substituována jedním nebo více halogenovými atomy, hydroxylovou skupinou, $C_1 - C_6$ alkylovou skupinou nebo $C_1 - C_6$ alkoxylovou skupinou, kde platí, je-li $j = 0$, R^2 není hydroxylová skupina;

j reprezentuje celé číslo od 0 do 2;

k reprezentuje celé číslo od 0 do 2;

m reprezentuje celé číslo od 2 do 4;

n reprezentuje 0 nebo 1;

R^3 je vodíkový atom nebo $C_1 - C_6$ alkylová skupina případně substituovaná jednou nebo dvěma fenylovými skupinami, z nichž každá je substituovaná jedním nebo více halogenovými atomy, hydroxylovou skupinou, $C_1 - C_6$ alkylovou skupinou nebo $C_1 - C_6$ alkoxylovou skupinou;

R^4 a R^5 jsou buď totožné, nebo každý jiný a představují vodíkový atom, hydroxylovou skupinu, fenylovou skupinu nebo $C_1 - C_6$ alkylovou skupinu, kde lze případně $C_1 - C_6$ alkylovou skupinu substituovat jedním nebo více halogenovými atomy, hydroxylovou skupinou, kyanoskupinou, nitroskupinou, karboxylovou skupinou, karbamoylovou skupinou, merkaptoskupinou, guanidinovou skupinou, $C_3 - C_8$ cykloalkylovou skupinou, $C_1 - C_6$ alkoxylovou skupinou, $C_1 - C_6$ alkylthioskupinou, fenylovou skupinou, kterou lze popřípadě substituovat jedním nebo více halogenovými atomy, hydroxylovou skupinou, $C_1 - C_6$ alkylovou skupinou, $C_1 - C_6$ alkoxylovou skupinou nebo benzyloxy skupinou, fenoxy skupinou, benzyloxykarbonylovou skupinou, $C_2 - C_7$ alkanoylovou skupinou, $C_2 - C_7$ alkoxykarbonylovou skupinou, $C_2 - C_7$ alkanoyloxy skupinou, C_2- C_7 alkanoylaminoskupinou, C_2 - C_7 N-alkylkarbamoylovou skupinou, $C_1 - C_6$ alkylsulfonylovou skupinou, aminoskupinou, mono($C_1 - C_6$)aminoskupinou, di(C_1 - -C_6)aminoskupinou nebo aromatickou heterocyklickou skupinou mající 1 až 3 heteroatomy vybrané ze skupiny obsahující atom kyslíku, atom síry a atom dusíku nebo kombinaci těchto a případně kondenzované s benzenovým kruhem, či R^4 a R^5 společně tvoří 3 až 6-členný cyklický uhlovodík;

p reprezentuje 0 nebo 1;

q reprezentuje 0 nebo 1;

G je skupina reprezentovaná -CO-, -SO_2-, -CO-O-, NR^7-CO-, -CO-NR^7-, -NH-CO-NH-, NHCS-NH-NR^7–SO_2-, –SO_2-NR^7-, -NH-CO-O- nebo -O-CO-NH-, kde R^7 je vodíkový atom nebo C_1 – C_6 alkylová skupina, kde R^7 dohromady s R^5 reprezentují C_2 – C_5 alkylenovou skupinu.

R^6 je fenylová skupina, C_3 – C_8 cykloalkylová skupina, C_3 – C_8 cykloalkenylová skupina, benzylová skupina, nebo aromaticka heterocyklická sloučenina mající jeden až tři heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu nebo z jejich kombinace, ve kterých je fenyl, benzyl nebo aromatická heterocyklická skupina kondenzovaná s benzenovým kruhem nebo aromatickou heterocyklickou skupinou mající 1 až 3 heteroatomy vybrané ze skupiny obsahující atom kyslíku, atom síry, atom dusíku, či jejich kombinace tak, aby se vytvořil kondenzovaný kruh a kde fenylová skupina, C_3 – C_8 cykloalkylová skupina, C_3 – C_8 cykloalkenylová skupina, benzylová skupina, aromatická heterocyklická skupina nebo kondenzovaný kruh je substituován jedním nebo více halogenovými atomy, hydroxylovou skupinou, merkaptoskupinou, kyanoskupinou, nitroskupinou, thiokyanátovou skupinou, karboxylovou skupinou, karbamoylovou skupinou, trifluormethylovou skupinou, C_1 – C_6 alkylovou skupinou, C_3 – C_6 cykloalkylovou skupinou, C_2 – C_6 alkenylovou skupinou, C_1 – C_6 alkoxylovou skupinou, C_3 – C_8 cykloalkoxylovou skupinou, C_1 – C_6 alkylthioskupinou, C_1 – C_3 alkylendioxyskupinou, fenylovou skupinou, fenoxyskupinou, fenylaminoskupinou, benzylovou skupinou, benzoylovou skupinou, fenylsulfinylovou skupinou, fenylsulfonylovou skupinou, 3-fenylureido skupinou, C_2 – C_7 alkanoylovou skupinou, C_2 – C_7 alkoxykarbonylovou skupinou, C_2 – C_7 alkanoyloxyskupinou, C_2 – C_7 alkanoylaminoskupinou, C_2 – C_7 N-alkylkarbamoylovou skupinou, C_1 – C_6 alkylsulfonylovou skupinou, fenylkarbamoylovou skupinou, N,N-di(C_1 – C_6 alkyl)sulfamoylovou skupinou, aminoskupinou, mono(C_1 – C_6 alkyl)aminoskupinou, di(C_1 – C_6 alkyl)aminoskupinou, benzylaminoskupinou, C_2 – C_7 (alkoxykarbonyl)aminoskupinou, C_1 – C_6 (alkylsulfonyl)aminoskupinou nebo bis(C_1 – C_6 alkylsulfonyl)aminoskupinou a kde fenylovou skupinu, C_3 – C_8 cykloalkylovou skupinu, C_3 – C_8 cykloalkenylovou skupinu, benzylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh lze případně substituovat jedním nebo více atomy halogenů, kyanoskupinou, hydroxylovou skupinou, aminoskupinou, trifluormetylovou skupinou, C_1 – C_6 alkylovou skupinou nebo C_1 – C_6 alkoxylovou skupinou, C_1 – C_6 alkylthioskupinou, mono(C_1 – C_6 alkyl)aminoskupinou nebo di(C_1 –C_6 alkyl)aminoskupinou za podmínky, že platí, k=2, m=2, n=0 a fenylová skupina v R^1 není substituovaná, C_1 – C_6 alkylová skupina jako substituent fenylové skupiny, C_3 – C_8 cykloalkylové skupiny, C_3 – C_8 cykloalkenylové, benzylové, aromatické heterocyklické sloučeniny nebo kondenzovaného kruhu v R^6 není substituována aminoskupinou a R^6 není benzylová skupina.

2. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí $C_1 - C_6$ alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše se k = 1 a m = 2.

3. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí $C_1 - C_6$ alkylové skupiny podle nároku 2, kde ve vzorci I uvedeném výše se n = 0.

4. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí $C_1 - C_6$ alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše se k = 0, m = 3 a n = 1.

5. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí $C_1 - C_6$ alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše se k = 1 a m = 3.

6. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí $C_1 - C_6$ alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše se k = 2 a m = 2.

7. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny, nebo její farmaceuticky přijatelná sůl vzniklá adicí $C_1 - C_6$ alkylové skupiny podle nároku 6, kde ve vzorci I uvedeném výše se n = 1.

8. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí $C_1 - C_6$ alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše se k = 1 a m = 4.

9. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí $C_1 - C_6$ alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše se j =1.

10. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 – C_6 alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše se p = 0, q = 0 a G představuje skupinu -NR^7-CO-.

11. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 – C_6 alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše, R^2 je vodíkový atom a R^7 je vodíkový atom.

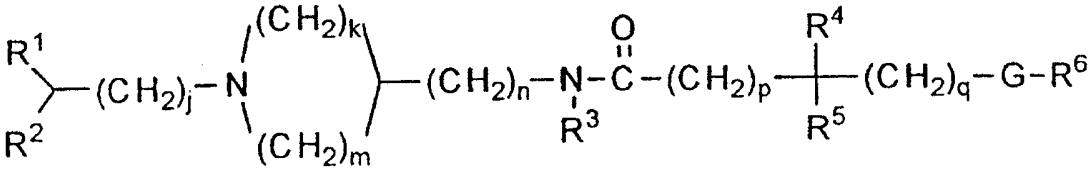
12. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 – C_6 alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše, je substituentem fenylové skupiny, C_3 – C_8 cykloalkylové skupiny, aromatické heterocyklické skupiny nebo kondenzovaného kruhu v R^1, jeden nebo více halogenových atomů, hydroxylová skupina, C_1 – C_6 alkylová skupina, C_2 – C_6 alkenylová skupina, C_1 – C_6 alkoxylová skupina, C_1 – C_6 alkylthioskupina, C_1 – C_4 alkylenoxyskupina, methylendioxyskupina, N-fenylkarbamoylová skupina, aminoskupina, mono(C_1 – C_6 alkyl)aminoskupina nebo di(C_1-C_6 alkyl)aminoskupina.

13. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 – C_6 alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše, je substituentem fenylové skupiny, C_3 –C_8 cykloalkylové skupiny, C_3 –C_8 cykloalkenylové skupiny, benzylové skupiny, aromatické heterocyklické skupiny nebo kondenzovaného kruhu v R^6, jeden nebo více halogenových atomů, nitroskupina, trifluormethylová skupina, C_1 – C_6 alkylová skupina, C_1 – C_6 alkoxylová skupina, fenylsulfonylová skupina, C_2 – C_7 alkanoylaminoskupina nebo aminoskupina.

14. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 – C_6 alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše, je R^1 fenylová skupina nebo isoxazolylová skupina.

15. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 – C_6 alkylové skupiny podle nároku 1, kde ve vzorci I uvedeném výše, je R^6 fenylová skupina, furylová skupina nebo thienylová skupina.

16. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce vyznačující se tím, že se využívá farmaceutická kompozice obsahující terapeuticky účinné množství sloučeniny podle obecného vzorce I uvedeného níže:



(I)

její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí $C_1 - C_6$ alkylové skupiny, kde

R^1 je fenylová skupina, $C_3 - C_8$ cykloalkylová skupina nebo aromatická heterocyklická skupina mající 1 až 3 heteroatomy vybrané ze skupiny obsahující atom kyslíku, atom síry a atom dusíku nebo kombinaci těchto, ve které je fenylová nebo heterocyklická aromatická skupina kondenzována s benzenovým kruhem nebo aromatickou heterocyklickou skupinou mající 1 až 3 heteroatomy vybrané ze skupiny obsahující atom kyslíku, atom síry, atom dusíku nebo jejich kombinaci, tak aby se vytvořil kondenzovaný kruh a kde fenylová skupina, $C_3 - C_8$ cykloalkylová skupina, aromatická heterocyklická skupina nebo kondenzovaný kruh, jsou substituovány jedním nebo více atomy halogenů, hydroxylovou skupinou, kyanoskupinou, nitroskupinou, karboxylovou skupinou, karbamoylovou skupinou, $C_1 - C_6$ alkylovou skupinou, $C_3 - C_8$ cykloalkylovou skupinou, $C_2 - C_6$ alkenylovou skupinou, $C_1 - C_6$ alkoxylovou skupinou, $C_1 - C_6$ alkylthioskupinou, $C_3 - C_5$ alkylenovou skupinou, $C_2 - C_4$ alkylenoxyskupinou, $C_1 - C_3$ alkylendioxyskupinou, fenylovou skupinou, fenoxyskupinou, fenylthioskupinou, benzylovou skupinou, benzyloxyskupinou, benzoylaminoskupinou, $C_2 - C_7$ alkanoylovou skupinou, $C_2 - C_7$ alkoxykarbonylovou skupinou, $C_2 - C_7$ alkanoyloxylovou skupinou, $C_2 - C_7$ alkanoylaminoskupinou, $C_2 - C_7$ N-alkylkarbamoylovou skupinou, $C_4 - C_9$ N--cykloalkylkarbamoylovou skupinou, $C_1 - C_6$ alkylsulfonylovou skupinou, $C_3 - C_8$ (alkoxykarbonyl)methylovou skupinou, N-fenylkarbamoylovou skupinou, piperidinkarbonylovou skupinou, morfolinkarbonylovou skupinou, 1-pyrolidinylkarbonylovou skupinou, aminoskupinou, mono($C_1 - C_6$ alkyl)aminoskupinou, či di($C_1 - C_6$ alkyl)aminoskupinou, kde fenylová skupina,

$C_3 - C_8$ cykloalkylová skupina, aromaticka heterocyklická skupina nebo kondenzovaný kruh jsou případně substituovány jedním nebo více halogenovými atomy, hydroxylovou skupinou,

aminoskupinou, trifluormethylovou skupinou, C_1 – C_6 alkylovou skupinou nebo C_1 – C_6 alkoxylovou skupinou;

R^2 značí vodíkový atom, C_1 – C_6 alkylovou skupinu, C_2 – C_7 alkoxykarbonylovou skupinu, hydroxylovou skupinu nebo fenylovou skupinu, ve kterých je C_1 – C_6 alkylová nebo fenylová skupina případně substituována jedním nebo více halogenovými atomy, hydroxylovou skupinou, C_1 – C_6 alkylovou skupinou nebo C_1 – C_6 alkoxylovou skupinou a kde platí, je-li j = 0, R^2 není hydroxylová skupina;

j reprezentuje celé číslo od 0 do 2;

k reprezentuje celé číslo od 0 do 2;

m reprezentuje celé číslo od 2 do 4;

n reprezentuje 0 nebo 1;

R^3 je vodíkový atom nebo C_1 – C_6 alkylová skupina případně substituovaná jednou nebo dvěma fenylovými skupinami, z nichž každá je případně substituovaná jedním nebo více halogenovými atomy, hydroxylovou skupinou, C_1 – C_6 alkylovou skupinou nebo C_1 – C_6 alkoxylovou skupinou;

R^4 a R^5 jsou buď totožné, nebo každý jiný a představují vodíkový atom, hydroxylovou skupinu, fenylovou skupinu nebo C_1 – C_6 alkylovou skupinu, kde je C_1 – C_6 alkylová skupina substituována případně jedním nebo více halogenovými atomy, hydroxylovou skupinou, kyanoskupinou, nitroskupinou, karboxylovou skupinou, karbamoylovou skupinou, merkaptoskupinou, guanidinovou skupinou, C_3 – C_8 cykloalkylovou skupinou, C_1 – C_6 alkoxylovou skupinou, C_1 – C_6 alkylthioskupinou, fenylovou skupinou, kterou lze popřípadě substituovat jedním nebo více halogenovými atomy, hydroxylovou skupinou, C_1 – C_6 alkylovou skupinou, C_1 – C_6 alkoxylovou skupinou nebo benzyloxyskupinou, fenoxyskupinou, benzyloxyskupinou, benzyloxykarbonylovou skupinou, C_2 – C_7 alkanoylovou skupinou, C_2 – C_7 alkoxykarbonylovou skupinou, C_2 – C_7 alkanoyloxyskupinou, C_2 – C_7 alkanoylamino skupinou, C_2 - C_7 N--alkylkarbamoylovou skupinou, C_1 – C_6 alkylsulfonylovou skupinou, aminoskupinou, mono(C_1 – -C_6alkyl)aminoskupinou, di(C_1 – C_6 alkyl)aminoskupinou nebo aromatickou heterocyklickou skupinou mající 1 až 3 heteroatomy vybrané ze skupiny obsahující atom kyslíku, atom síry a atom dusíku nebo kombinaci těchto, případně kondenzované s benzenovým kruhem, či R^4 a R^5 společně tvoří 3 až 6-členný cyklický uhlovodík;

p reprezentuje 0 nebo 1;

03.07.00

q reprezentuje 0 nebo 1;

G je skupina reprezentovaná -CO-, -SO_2-, -CO-O-, NR^7-CO-, -CO-NR^7-, -NH-CO-NH-, -NH-CS-NH-, -NR^7–SO_2-, –SO_2-NR^7-, -NH-CO-O- nebo -O-CO-NH-, kde R^7je vodíkový atom nebo C_1– - C_6 alkylová skupina, nebo kde R^7 dohromady s R^5 reprezentuje C_2 – C_5 alkylenovou skupinu,

R^6 je fenylová skupina, C_3 – C_8 cykloalkylová skupina, C_3 – C_8 cykloalkenylová skupina, benzylová skupina nebo aromatická heterocyklická sloučenina mající 1až 3 heteroatomy vybrané ze skupiny sestávající z kyslíkového atomu, atomu síry a dusíkového atomu nebo z kombinace těchto, v nichž fenyl, benzyl nebo aromatická hetrocyklická skupina kondenzují s benzenovým kruhem nebo aromatickou heterocyklickou skupinou mající 1 až 3 heteroatomy vybrané ze skupiny obsahující atom kyslíku, atom síry a atom dusíku nebo jejich kombinaci tak, aby tvořily kondenzovaný kruh, kde fenylová skupina, C_3 – C_8 cykloalkylová skupina, C_3 – C_8 cykloalkenylová skupina, benzylová skupina, aromatická heterocyklická skupina nebo kondenzovaný kruh lze substituovat jedním nebo více halogenovými atomy, hydroxylovou skupinou, merkaptoskupinou, kyanoskupinou, nitroskupinou, thiokyanátovou skupinou, karboxylovou skupinou, karbamoylovou skupinou, trifluormethylovou skupinou, C_1 – C_6 alkylovou skupinou, C_3 – C_6 cykloalkylovou skupinou, C_2 – C_6 alkenylovou skupinou, C_1 – C_6 alkoxylovou skupinou, C_3 – C_8 cykloalkoxylovou skupinou, C_1 – C_6 alkylthio- skupinou, C_1– C_3 alkylendioxyskupinou, fenylovou skupinou, fenoxyskupinou, fenylaminoskupinou, benzylovou skupinou, benzoylovou skupinou, fenylsulfinylovou skupinou, fenylsulfonylovou skupinou, 3--fenylureidoskupinou, C_2 – C_7 alkanoylovou skupinou, C_2 – C_7 alkoxykarbonylovou skupinou,

C_2 – C_7 alkanoyloxyskupinou, C_2 – C_7 alkanoylaminoskupinou, C_2 – C_7 N-alkylkarbamoylovou skupinou, C_1 –C_6 alkylsulfonylovou skupinou , fenylkarbamoylovou skupinou, N,N-di(C_1 – C_6 alkyl)sulfamoylovou skupinou, aminoskupinou, mono(C_1 – C_6 alkyl)aminoskupinou, di(C_1 – C_6 alkyl)aminoskupinou, benzylaminoskupinou, C_2 – C_7 (alkoxykarbonyl)aminoskupinou, C_1 – C_6 (alkylsulfonyl)aminoskupinou nebo bis(C_1 – C_6 alkylsulfonyl)aminoskupinou, kde fenylovou skupinu, C_3 – C_8 cykloalkylovou skupinu, C_3 – C_8 cykloalkenylovou skupinu, benzylovou skupinu, aromatickou heterocyklickou skupinu nebo kondenzovaný kruh lze případně substituovat jedním nebo více atomy halogenů, kyanoskupinou, hydroxy skupinou, aminoskupinou, trifluormethylovou skupinou, C_1 – C_6 alkylovou skupinou nebo C_1 – C_6 alkoxy skupinou, C_1 – -C_6 alkylthioskupinou, mono(C_1 – C_6 alkyl)aminoskupinou nebo di(C_1 –C_6 alkyl)aminoskupinou.

17. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše se k = 1 a m = 2.

18. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 17, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše se n = 0.

19. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m ,že ve vzorci I uvedeném výše se k = 0, m = 3, n = 1.

20. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše se k = 1 a m = 3.

21. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše se k = 2 a m = 2.

22. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 21, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše se n = 1.

23. Způsob inhibice vazby chemokinu k receptoru cílové buňky, a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše se k = 1 a m = 4.

24. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše se j = 0.

25. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše se p = 0, q = 0 a G je skupina reprezentovaná $-NR^7-CO-$.

26. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše je R^2 je vodíkový atom, R^3 je vodíkový atom a R^7 je vodíkový atom.

27. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše je substituentem fenylové skupiny, C_3 – C_8 cykloalkylové skupiny, aromatické heterocyklické skupiny nebo kondenzovaného kruhu v R^1 jeden nebo více halogenových atomů, hydroxylová skupina, C_1 – C_6

alkylová skupina, C_2 – C_6 alkenylová skupina, C_1 – C_6 alkoxylová skupina, C_1 – C_6 alkylthioskupina, C_2 – C_4 alkylenoxy-skupina, methylendioxyskupina, N-fenylkarbamoylová skupina, aminoskupina, mono(C_1 – C_6 alkyl)aminoskupina nebo di(C_1 – C_6 alkyl)aminoskupina.

28. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše je substituentem fenylové skupiny, C_3 – C_8 cykloalkylové skupiny, C_3 – C_8 cykloalkenylové skupiny, benzylové skupiny, aromatické heterocyklické skupiny nebo kondenzovaného kruhu v R^6 jeden nebo více atomů halogenů, nitroskupina, trifluormethylová skupina, C_1 – C_6 alkylová skupina nebo C_1 – C_6 alkoxylová skupinou, fenylsulfonylová skupina, C_2 – C_7 alkanoylaminoskupinou nebo aminoskupinou.

29. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše je R^1 fenylová skupina nebo isoxazolylová skupina.

30. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že ve vzorci I uvedeném výše je R^6 fenylová skupina, furylová skupina nebo thienylová skupina.

31. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že chemokin je MIP-1α.

32. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že chemokin je MCP-1.

33. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že receptorem pro chemokin je CCR1.

34. Způsob inhibice vazby chemokinu k receptoru cílové buňky a/nebo jeho působení v cílové buňce podle nároku 16, v y z n a č u j í c í s e t í m , že receptorem pro chemokin je CCR2A nebo CCR2B.

35. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 4-[{N-(2-amino-5-chlorbenzoyl)glycyl}aminomethyl]-1-(4-chlorobenzyl)piperidin.

36. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(4-chlorbenzyl)--piperidin.

37. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 4-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}aminomethyl]-1-(4--chlorbenzyl)piperidin.

38. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 4-[{N-(2-amino-5-trifluormethoxybenzoyl)glycyl}aminomethyl]-1-(4--chlorbenzyl)piperidin.

39. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-(4-brombenzyl)--piperidin.

40. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 1-(2-amino-4-chlorbenzyl)-4-[(N-(2-amino-5-trifluormethylbenzoyl)glycyl}--aminomethyl]piperidin.

41. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 1-(3-amino-4-methoxybenzyl)-4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}--aminomethyl]piperidin.

42. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 4-[{N-(2-amino-4,5-difluorbenzoyl)glycyl}aminomethyl]-1-{4-chlor-3--(methylamino)benzyl}piperidin.

43. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 4-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}aminomethyl]-1-(2-thioxo-2,3--dihydro-1,3 -benzoxazol-5-ylmethyl)piperidin.

44. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-chlorbenzyl)-pyrolidin.

45. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-methoxbenzyl)-pyrolidin.

46. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(3,4- methylen--dioxybenzyl)pyrolidin.

47. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(2,3-dihydro-1-benzfuran-5-ylmethyl)pyrolidin.

48. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde

sloučenina je 3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-methylthiobenzyl)-pyrolidin.

49. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-ethylbenzyl)pyrolidin.

50. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1-C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 3-[{N-(2-amino-5-trifluormethoxybenzoyl)glycyl}amino]-1-(4-ethylbenzyl)-pyrolidin.

51. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 1-(3-amino-4-methoxybenzyl)-3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}--amino]pyrolidin.

52. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(4-chlor-3--methylbenzyl)pyrolidin.

53. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-[4-hydroxy-3--(methylamino)benzyl}pyrolidin.

54. Sloučenina, její farmaceuticky přijatelná sůl vzniklá adicí kyseliny nebo její farmaceuticky přijatelná sůl vzniklá adicí C_1 - C_6 alkylové skupiny k této sloučenině podle nároku 1, kde sloučenina je 3-[{N-(2-amino-5-trifluormethylbenzoyl)glycyl}amino]-1-(1,3-benzoxazol--5-ylmethyl)pyrolidin.