

Novel indazolecarboxamides, method for the production thereof, pharmaceutical preparations comprising them, and use thereof for producing medicaments

The present application relates to novel indazolecarboxamides, to processes for their preparation, to their use for the treatment and/or prophylaxis of diseases and to their use for producing medicaments for the treatment and/or prophylaxis of diseases, in particular proliferative disorders, autoimmune and inflammatory disorders such as, for example, rheumatoid arthritis, chronic obstructive pulmonary disease (abbreviation: COPD), multiple sclerosis, endometriosis and inflammation-induced or chronic pain and lymphomas.

IRAK4 plays a key role in the activation of the immune system, in particular in innate immunity. Innate immunity is based on the fact that microorganisms such as bacteria and viruses have certain inherent features which are recognized by the immune system, resulting in its activation. What is recognized are certain pathogen-associated molecular patterns (PAMPs). PAMPs are recognized by the pattern recognition receptors (PRR) which include toll-like receptors (TLR) (Janeway and Medzhitov, Annu. Rev. Immunol., 2002). In humans, ten different TLRs have been described. TLR1 and TLR6 are coreceptors for TLR2. TLR2 recognize *inter alia* lipoproteins and lipopeptides. TLR3 recognizes double-stranded RNA. TLR4 recognizes *inter alia* LPS (lipopolysaccharides) of gram-negative bacteria and lipoteichoic acid of gram-positive bacteria. TLR5 recognizes flagellin. CpG motives in bacterial DNA are recognized by TLR9 (Miggin, O'Neill, J. Leukoc. Biol., 2006). Additional molecules may further modify the recognition abilities of TLRs (Akashi-Takamura and Miyake, Current Opinion in Immunology, 2008). In addition to the recognition of PAMPs, TLRs are also able to recognize DAMPs (damage-associated molecular pattern). These are endogenous cell-derived molecules formed as the result of a trauma, an ischaemia or other tissue-destroying processes in the absence of any obvious infection. DAMPs can be constituents both of the cytoplasm and the nucleus. They are secreted, for example HMGB1 (high-mobility group box 1 protein), which is recognized by TLR2 and TLR4. Other DAMPs are released *de novo* or accumulate, for example, in the outer plasma membrane, e.g. HSP90 (heat shock protein 90), where they are recognized by TLR2 and TLR4. Others for their part are produced as final degradation products during cell death (Krysko, Garg, et al., Nat Rev Cancer, 2012).

In addition to TLRs, other components such as cytokines also play an important role in innate immunity. Here, mention may be made in particular of the interleukin (IL)-1 family including interleukins IL-1, IL-18 and IL-33. They are produced and released by various immune cells in the presence of infections or cell or tissue stress. The immune response is then triggered by binding to the respective receptor (Dinarello, Annu. Rev. Immunol., 2009).

TLRs (except for TLR3) as well as the receptors of the IL-1 family (IL-1R (receptor), IL-18R and IL-33R) have the same signal cascade which is activated by binding of the respective ligand to its

receptor. The ligand receptor binding leads to the recruitment of the adaptor molecule MyD88 [myeloid differentiation primary response gene (88)] to the receptor via TIR/TIR domain interaction which is a constituent both of the receptors and of MyD88. In addition to the TIR domain, MyD88 has an N-terminal "death domain" (DD) which interacts with the DD domain of the interleukin-1 receptor associated kinase-4 (IRAK4). IRAK4 belongs to a serine/threonine kinase family which also includes the structurally similar kinases IRAK1, IRAK2 and IRAK-M (Cao et al., Science, 1996; Muzio et al., Science, 1997; Wesche, Gao, et al., Journal of Biological Chemistry, 1999; Li, Strelow, et al., PNAS, 2002). Except for IRAK-M, which is only expressed in monocytes and macrophages, the expression of IRAK4, IRAK1 and IRAK2 is ubiquitous (Flannery and Bowie, Biochemical Pharmacology, 2010). As a result of the activation process, several MyD88 and IRAK4 molecules form a multicomplex which is referred to as "myddosome" (Precious et al., J. Biol. Chem., 2009). This myddosome now interacts with IRAK1 or IRAK2 via DD-DD interactions, forming a larger complex in the process (Lin, Lo, et al., Nature, 2010). The formation of this complex then triggers autophosphorylation of IRAK4, which subsequently results in the phosphorylation of IRAK1 or IRAK2. As a consequence of the activation of IRAK1 or IRAK2, these kinases are autophosphorylated (Kollewe, Mackensen, et al., Journal of Biological Chemistry, 2004). The activated IRAK1 or IRAK2 interacts with TRAF6 (tumor-necrosis factor-receptor-associated factor 6) which, with the ubiquitin enzyme complex (E2), acts as ubiquitin protein ligase, which leads to K62-associated ubiquitination of TRAF6. In turn, this process leads to further complex formation with other proteins. This complex induces the activation of TAK1 (Xia, Sun, et al., Nature, 2009). Activated TAK1 mediates the activation of the NF (nuclear factor)-kB signal pathway and the MAPK (mitogen-activated protein kinase) signal pathway (Wang, Deng, et al., Nature, 2001). In the first signal pathway, TAK1 leads to the activation of the IKK complex whereby the inhibiting I κ B protein is phosphorylated and degraded by the proteasome. NF-kB, which had been blocked by I κ B beforehand, now migrates from the cytoplasm into the nucleus where it binds to a specific DNA motive, the kB motive, leading to the transcription of various genes (Gasparini and Feldmann, Curr Pharm Des, 2012).

In the MAPK signal pathway, TAK1 phosphorylates various members of the MAPK family such as MKK3, -4, -6 and -7 (Wang, Deng, et al., Nature, 2001). The activation of these kinases results in the activation of p38 and JNK (c-Jun N-terminal kinase) (Ono and Han, Cellular Signalling, 2000; Davis, Cell, 2000). The activation both of the NF-kB signal pathway and of the MAPK signal pathway leads to various processes associated with different immune processes. Thus, this is an increased expression of various inflammatory signal molecules and enzymes such as, for example, cytokines, chemokines and COX-2, and an increased mRNA stability of certain genes (Holtmann, Enninga, et al., Journal of Biological Chemistry, 2001; Datta, Novotny, et al., The Journal of Immunology, 2004). Furthermore, these processes may be associated with the proliferation and differentiation of certain cell types (Wan, Chi, et al., Nat Immunol, 2006; McGettrick and J. O'Neill, British Journal of Haematology, 2007).

The central importance of IRAK4 in immunological processes mediated by the TLR (except for TLR3) and IL-1 receptor family is shown by the deletion of IRAK4. Cells isolated from patients where absence of IRAK4 had been demonstrated show no activity after stimulation of various
5 TLRs (except for TLR3) and the IL-1 β family (Davidson, Currie, et al., The Journal of Immunology, 2006; Ku, von Bernuth, et al., JEM, 2007). Furthermore, mice with IRAK4 deletion develop no response to IL-1 β stimulation and various TLR stimulations except for TLR3 (Suzuki, Suzuki, et al., Nature, 2002). Here, in particular the kinase activity of IRAK4 plays a crucial role (Kim, Staschke, et al., JEM, 2007). In contrast, deletion of IRAK1 or IRAK2 only results in a
10 signal pathway activity loss after stimulation (Thomas, Allen, et al., The Journal of Immunology, 1999; Swantek, Tsen, et al., The Journal of Immunology, 2000; Kawagoe, Sato, et al., Nat Immunol, 2008). For their part, mice having deletion of IRAK2 and IRAK1 show a phenotype comparable to that of animals with IRAK4 deletion (Kawagoe, Sato, et al., Nat Immunol, 2008). The central role of IRAK4 in the pathology of various inflammatory disorders associated with the
15 signal pathway described had already been shown by direct comparison of wild-type (WT) mice with genetically modified animals having a kinase-inactivated form of IRAK4 (IRAK4 KDKI). IRAK4 KDKI animals have an improved clinical picture in the animal model of multiple sclerosis, atherosclerosis, myocardial infarction and Alzheimer's disease (Rekhter, Staschke, et al., Biochemical and Biophysical Research Communication, 2008; Maekawa, Mizue, et al.,
20 Circulation, 2009; Staschke, Dong, et al., The Journal of Immunology, 2009; Kim, Febbraio, et al., The Journal of Immunology, 2011; Cameron, Tse, et al., The Journal of Neuroscience, 2012). Furthermore, it was found that deletion of IRAK4 in the animal model protects against virus-induced myocarditis by virtue of an improved anti-viral reaction with simultaneously reduced systemic inflammation (Valaperti, Nishii, et al., Circulation, 2013).

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Owing to the central role of IRAK4 in the MyD88-mediated signal cascade of TLRs (except for TLR3) and the IL-1 receptor family, the inhibition of IRAK4 can be utilized for the prophylaxis and/or treatment of disorders mediated by the receptors mentioned. TLR-dependent processes are associated with a large number of different disorders. Thus, it has been found that TLRs are
30 involved in the pathogenesis of multiple sclerosis, rheumatoid arthritis, metabolic syndrome, diabetes, osteoarthritis, Sjögren syndrome and sepsis (Scanzello, Plaas, et al. Curr Opin Rheumatol, 2008; Roger, Froidevaux, et al, PNAS, 2009; Gambuzza, Licata, et al., Journal of Neuroimmunology, 2011; Fresno, Archives Of Physiology And Biochemistry, 2011; Goh and Midwood, Rheumatology, 2012; Dasu, Ramirez, et al., Clinical Science, 2012; Ramirez and Dasu,
35 Curr Diabetes Rev, 2012; Li, Wang, et al., Pharmacology & Therapeutics, 2013). Skin disorders such as psoriasis, atopic dermatitis, acne inversa and acne vulgaris are associated with the IRAK4-mediated TLR signal pathway.

The disorders mentioned are characterized by an increased expression of certain TLRs, and their pathological immune reactions are mediated by certain TLR-associated inflammation processes (Gilliet, Conrad, et al., Archives of Dermatology, 2004; Niebuhr, Langnickel, et al., Allergy, 2008; Miller, Adv Dermatol, 2008; Terhorst, Kalali, et al., Am J Clin Dermatol, 2010; Dispenza, Wolpert, et al., J Invest Dermatol, 2012; Selway, Kurczab, et al., BMC Dermatology, 2013; Wollina, Koch, et al. Indian Dermatol Online, 2013).

Pulmonary disorders such as pulmonary fibrosis, obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), interstitial lung disease (ILD), sarcoidosis and pulmonary hypertension show an association with various TLR-mediated signal pathways. The pathogenesis of the pulmonary disorders may be either infectious mediated or non-infectiously mediated processes (Ramirez Cruz, Maldonado Bernal, et al., Rev Alerg Mex, 2004; Jeyaseelan, Chu, et al., Infection and Immunity, 2005; Seki, Tasaka, et al., Inflammation Research, 2010; Xiang, Fan, et al., Mediators of Inflammation, 2010; Margaritopoulos, Antoniou, et al., Fibrogenesis & Tissue Repair, 2010; Hilberath, Carlo, et al., The FASEB Journal, 2011; Nadigel, Prefontaine, et al., Respiratory Research, 2011; Kovach and Standiford, International Immunopharmacology, 2011; Bauer, Shapiro, et al., Mol Med, 2012; Deng, Yang, et al., PLoS One, 2013; Freeman, Martinez, et al., Respiratory Research, 2013; Dubaniewicz, A., Human Immunology, 2013). For instance, HMGB1 (high-mobility group box 1 protein) - an endogenous ligand of TLR2 and TLR4 - is elevated in patients with pulmonary fibrosis. Blocking of these TLR signal pathways leads to reduced inflammation in the animal model (Yang, Cui, et al., The Journal of Immunology, 2009; Entezari, Weiss, et al., Mol Med, 2012). The involvement of TLR2-mediated processes in the pathogenesis of sarcoidosis has recently been demonstrated in *in vitro* and *in vivo* studies (Chen, Song, et al., American Journal of Respiratory and Critical Care Medicine, 2010; Gabrilovich, Walrath, et al., Clinical & Experimental Immunology, 2013).

TLRs are also involved in the pathogenesis of other inflammatory disorders such as Behçet's disease, gout and graft rejection, therefore, here the inhibition of IRAK4 is a suitable therapeutic approach (Liu-Bryan, Scott, et al., Arthritis & Rheumatism, 2005; Shi, Mucsi, et al., Immunological Reviews, 2010; Leventhal and Schroppel, Kidney Int, 2012; Kreisel and Goldstein, Transplant International, 2013; Li, Wang, et al., Pharmacology & Therapeutics, 2013). Lesions and peritoneal macrophages of endometriosis patients also have, compared to healthy volunteers, an enhanced immune response following LPS (lipopolysaccharide) stimulation (Allhorn, Boing, et al., Reproductive Biology and Endocrinology, 2008; Khan, Kitajima, et al., Journal of Obstetrics and Gynaecology Research, 2013).

Patients having lupus erythematosus and adult onset Still disease have an elevated expression of TLR7, MyD88 and IRAK4 (Chen, Lin, et al., Arthritis Res Ther, 2013). In the disease model of lupus, inhibition of TLR7, 8 and 9 and the use of animals having a deletion of TLR7 and/or TLR9 result in an improved pathogenesis (Christensen, Shupe, et al., Immunity, 2006; Nickerson, Christensen, et al., The Journal of Immunology, 2010; Zhu, Jiang, et al., Autoimmunity, 2013).

- Patients suffering from chronic inflammatory bowel diseases such as ulcerative colitis or Crohn's disease do not only have polymorphisms in various TLR genes. In various animals models, it was shown that certain TLRs are also involved in the pathogenesis of these bowel disorders (Rakoff-Nahoum, Hao, et al., *Immunity*, 2006; Heimesaat, Fischer, et al., *PLoS ONE*, 2007; Cario, Inflammatory Bowel Diseases, 2010; Walsh, Carthy, et al., *Cytokine & Growth Factor Reviews*, 2013).
- In addition to the disorders already mentioned, IRAK4-mediated TLR processes have been described in the pathogenesis of eye disorders such as keratitis, allergic conjunctivitis, keratoconjunctivitis sicca, macular degeneration and uveitis (Kaarniranta and Salminen, *J Mol Med (Berl)*, 2009; Sun and Pearlman, *Investigative Ophthalmology & Visual Science*, 2009; Redfern and McDermott, *Experimental Eye Research*, 2010; Kezic, Taylor, et al., *J Leukoc Biol*, 2011; Chang, McCluskey, et al., *Clinical & Experimental Ophthalmology*, 2012; Guo, Gao, et al., *Immunol Cell Biol*, 2012; Lee, Hattori, et al., *Investigative Ophthalmology & Visual Science*, 2012).
- The role of TLRs in arteriosclerosis has been supported not only by the analysis of human samples but also with the aid of various animal models (Seneviratne, Sivagurunathan, et al., *Clinica Chimica Acta*, 2012; Falck-Hansen, Kassiteridi, et al., *International Journal of Molecular Sciences*, 2013).
- By virtue of the central role of IRAK4 in TLR-mediated processes, the inhibition of IRAK4 allows the treatment and/or prevention of cardiovascular and neurological disorders such as, for example, myocardial reperfusion damage, myocardial infarction, hypertension (Oyama, Blais, et al., *Circulation*, 2004; Timmers, Sluijter, et al., *Circulation Research*, 2008; Fang and Hu, *Med Sci Monit*, 2011; Bijani, *International Reviews of Immunology*, 2012; Bomfim, Dos Santos, et al., *Clin Sci (Lond)*, 2012; Christia and Frangogiannis, *European Journal of Clinical Investigation*, 2013; Thompson and Webb, *Clin Sci (Lond)*, 2013) and also Alzheimer's disease, stroke and Parkinson's disease (Carty and Bowie, *Biochemical Pharmacology*, 2011; Lim, Kou, et al., *The American Journal of Pathology*, 2011; Béraud and Maguire-Zeiss, *Parkinsonism & Related Disorders*, 2012; Noelker, Morel, et al., *Sci. Rep.*, 2013; Wang, Wang, et al., *Stroke*, 2013).
- Neurons as well as microglia and astrocytes express a large part of the known TLRs. In the animal model, deletion of TLR7 protects against various triggers of pruritus (Nicotra, Loram, et al., *Experimental Neurology*, 2012; Liu and Ji, *Pflugers Arch.*, 2013). In addition to the role of TLRs in pruritus, it was possible to demonstrate involvement in pain processes using various animal models (Kim, Lee, et al., *Toll-like Receptors: Roles in Infection and Neuropathology*, 2009; Guerrero, Cunha, et al., *European Journal of Pharmacology*, 2012; Nicotra, Loram, et al., *Experimental Neurology*, 2012; David, Ratnayake, et al., *Neurobiology of Disease*, 2013). Studies with pain patients support these findings (Kwok, Hutchinson, et al., *PLoS ONE*, 2012; Chopra and Cooper, *J Neuroimmune Pharmacol*, 2013).

Since the TLR signals are mediated via IRAK4, it has to be assumed that there is a therapeutic effect by inhibition of IRAK4 in the indications mentioned.

- 5 This also applies to some oncological disorders. Certain lymphomas have an activating MyD88 mutation which can be treated using an IRAK4 inhibitor (Ngo, Young, et al., *Nature*, 2011; Treon, Xu, et al., *New England Journal of Medicine*, 2012; Choi, Kim, et al., *Human Pathology*, 2013). Chronic lymphatic leukaemia, melanomas and liver cell carcinomas are likewise associated with mutations in MyD88 or changes in MyD88 activity (Puente, Pinyol, et al., *Nature*, 2011; 10 Srivastava, Geng, et al., *Cancer Research*, 2012; Liang, Chen, et al., *Clinical Cancer Research*, 2013). Furthermore, MyD88 plays an important role in ras-dependent tumours, so IRAK4 inhibitors are also suitable for treating these (Kfoury, A., K. L. Corf, et al., *Journal of the National Cancer Institute*, 2013).
- 15 In addition to the mediation of MyD88- and TLR- (except for TLR3)-associated processes, IRAK4 also mediates the signals of the IL-1 receptor family. Inflammatory disorders such as CAPS (cryopyrin-associated periodic syndromes) including FCAS (familial cold autoinflammatory syndrome), MWS (Muckle-Wells syndrome), NOMID (neonatal-onset multisystem inflammatory disease) and CONCA (chronic infantile, neurological, cutaneous, and articular) syndrome; FMF 20 (familial mediterranean fever), HIDS (hyper-IgD syndrome), TRAPS (tumour necrosis factor receptor 1-associated periodic syndrom), juvenile idiopathic arthritis, adult-onset Still's disease, Adamantiades-Behçet's disease, rheumatoid arthritis, osteoarthritis, keratoconjunctivitis sicca and Sjögren syndrome are treated by blocking the IL-1 signal pathway; therefore here, too, an IRAK4 inhibitor is suitable for treatment of the diseases mentioned (Narayanan, Corrales, et al., *Cornea*, 25 2008; Henderson and Goldbach-Mansky, *Clinical Immunology*, 2010; Dinarello, *European Journal of Immunology*, 2011; Gul, Tugal-Tutkun, et al., *Ann Rheum Dis*, 2012; Pettersson, *Annals of Medicine*, 2012; Ruperto, Brunner, et al., *New England Journal of Medicine*, 2012; Nordström, Knight, et al., *The Journal of Rheumatology*, 2012; Vijmasi, Chen, et al., *Mol Vis*, 2013; Yamada, Arakaki, et al., *Opinion on Therapeutic Targets*, 2013). IL-18 in particular is 30 associated with the pathogenesis of rheumatoid arthritis, adult-onset Still's disease, type-1 diabetes, multiple sclerosis and lupus erythematosus, thus, by virtue of the mechanism of action, IRAK4 inhibitors can be employed for the treatment and/or prevention of the disorders mentioned (Volin and Koch, *J Interferon Cytokine Res*, 2011; Sedimbi, Hagglof, et al., *Cell Mol Life Sci*, 2013; Yap and Lai, *Nephrology*, 2013). Furthermore, IRAK4 inhibitors are suitable for the treatment of type-2 35 diabetes and the sequelae of a myocardial infarction as there are indications that the inhibition of the IL-1 signal pathway is a promising therapeutic approach (Abbate, Kontos, et al., *The American Journal of Cardiology*, 2010; Akash, Shen, et al., *Journal of Pharmaceutical Sciences*, 2012; Abbate, Van Tassel, et al., *The American Journal of Cardiology*, 2013). Several components of the

IL-1 receptor family are associated with various pulmonary disorders such as asthma, COPD, idiopathic interstitial pneumonia and acute respiratory distress syndrome (ARDS) and the role in its pathogenesis was supported in various animal models (Kang, Homer, et al., *The Journal of Immunology*, 2007; Imaoka, Hoshino, et al., *European Respiratory Journal*, 2008; Couillin, Vasseur, et al., *The Journal of Immunology*, 2009; Lloyd, *Current Opinion in Immunology*, 2010; Pauwels, Bracke, et al., *European Respiratory Journal*, 2011; Yin, Li, et al., *Clinical & Experimental Immunology*, 2012; Alexander-Brett, et al., *The Journal of Clinical Investigation*, 2013; Bunting, Shadie, et al., *BioMed Research International*, 2013; Byers, Alexander-Brett, et al., *The Journal of Clinical Investigation*, 2013; Kawayama, Okamoto, et al., *J Interferon Cytokine Res*, 2013; Martínez-González, Roca, et al., *American Journal of Respiratory Cell and Molecular Biology*, 2013; Qiu, Li, et al., *Immunology*, 2013).

Furthermore, various studies have shown that there is a relation between the amount of IL-1 β and its receptor, IL-18 and IL-33, and the disorder endometriosis (Akoum, Lawson, et al., *Human Reproduction*, 2007; Lawson, Bourcier, et al., *Journal of Reproductive Immunology*, 2008; Sikora, Mielczarek-Palacz, et al., *American Journal of Reproductive Immunology*; Santulli, Borghese, et al., *Human Reproduction*, 2013). Moreover, in the animal model the growth of human endometrial tissue could be blocked by administration of the endogenous IL-1 β inhibitor IL-1R2 (Khoufache, Bondza, et al., *The American Journal of Pathology*, 2012). By way of its mechanism of action, an IRAK4 inhibitor is also effective in this case. Chronic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis are associated with the dysregulation of the IL-1 receptor family (Kobori, Yagi, et al., *J Gastroenterol*, 2010; Hao, Liu, et al., *Curr Opin Gastroenterol*, 2013). In addition to the indications mentioned, IRAK4 inhibitors are also suitable for the treatment and/or prevention of neurological disorders mediated by the IL-1 receptor family, such as stroke apoplexy, Alzheimer's disease, stroke, skull-brain trauma and pain such as cancer pain, postoperative pain, inflammation-induced pain and chronic pain (Wolf, Livshits, et al., *Brain, Behavior, and Immunity*, 2008; Brough, Tyrrell, et al., *Trends in Pharmacological*, 2011; SciencesDenes, Kitazawa, Cheng, et al., *The Journal of Immunology*, 2011; Pinteaux, et al., *Cerebrovascular Diseases*, 2011; del Rey, Apkarian, et al., *Annals of the New York Academy of Sciences*, 2012; Denes, Wilkinson, et al., *Disease Models & Mechanisms*, 2013; Han, Zhao, et al., *Neuroscience*, 2013; Zhao, Zhang, et al., *Neuroscience*, 2013). Owing to the propagation of processes mediated by the IL1 receptor family by IRAK4, IRAK4 inhibitors are active in dermatological disorders such as psoriasis, atopic dermatitis and allergic contact dermatitis. The IL1 receptor family is involved in the pathogenesis of the disorders mentioned (Viguier, Guigue, et al., *Annals of Internal Medicine*, 2010; Cevikbas, Steinhoff, *J Invest Dermatol*, 2012; Minkis, Aksentijevich, et al., *Archives of Dermatology*, 2012; Mattii, Ayala, et al., *Experimental Dermatology*, 2013; Sedimbi, Hagglof, et al., *Cell Mol Life Sci*, 2013).

Association of IRAK4 with numerous different disorders by mediation of various signals via TLRs (except for TLR3) and the IL1 receptor family shows that by inhibition of IRAK4 it is possible to influence a large number of disorders in a positive manner.

- 5 The compounds described in the present invention are capable of inhibiting IRAK4. This is also supported by the fact that the compounds according to the invention have inhibiting activity in TLR- and IL1-mediated processes.

Accordingly, it was an object of the present invention to provide novel compounds which, in the
10 manner described above, act as inhibitors of interleukin-1 receptor associated kinase-4 (IRAK4). The novel IRAK4 inhibitors are suitable in particular for the treatment and for the prevention of proliferative and inflammatory disorders characterized by an overreacting immune system. Particular mention may be made here of inflammatory skin disorders, cardiovascular disorders, pulmonary disorders, eye disorders, autoimmune disorders and neoplastic disorders.

- 15 Numerous IRAK4 inhibitors are known from the prior art. IRAK4 inhibitors are described, for example, in G. C. Harriman et al. in US20130231328 and in L. D. Romero et al. US20120283238. IRAK4 modulators based on a pyrazole[1,5a]pyrimidine skeleton are described by N. Arora et al. in US20120015962.

Moreover, V. R. Paidi et al. in WO2013106641 report thiazolyl- or thiadiazolyl-substituted
20 pyridine derivatives and S. D. Dodd et al. in WO2013106614 report triazolyl-substituted pyridine derivatives. Further pyridine derivatives are disclosed in WO2013106612.

Aminopyrimidones acting as IRAK4 inhibitors are described by W. M. Seganish et al. in WO2013066729; in addition, W. T. Mcelroy et al in WO 2012129258 also describe amidopyrazoles as IRAK inhibitors.

- 25 G. Buckeley et al. report, both in Bioorg. Med. Chem. Lett. 18 (2008), 3291 – 3295 and in Bioorg. Med. Chem. Lett. 18 (2008), 3656 – 3660, imidazole[1,2-a]pyridines. Furthermore, A. D. Frenkel et al. in US20070037803 report benzimidazole derivatives as IRAK4 inhibitors.

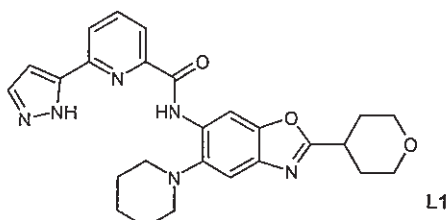
Further IRAK inhibitors having 2-aminoimidazole or 2-aminobenzimidazole structure are claimed by A. D. Frenkel et al. in US2007/0037803.

- 30 IRAK4 inhibitors which, like the compounds according to the invention, are based on an indazole structure are described by K. Guckian et al. in US8293923. These indazole derivatives are substituted by a benzimidazol-2-ylamino group at position 3 of the indazole. US8293923 does not disclose any 2-substituted indazoles.

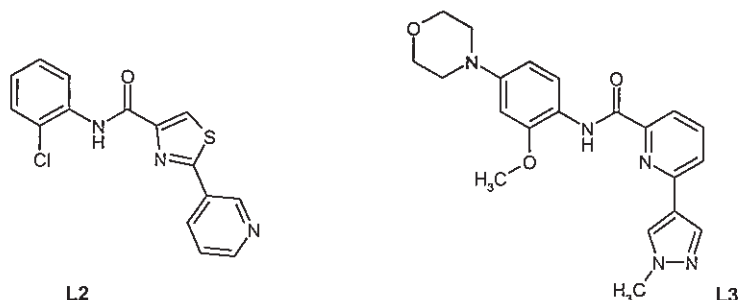
Further IRAK4 inhibitors based on an indazole structure are reported by C. Jorand-Lebrun et al. in
35 US20130274241. These are indazole derivatives having a triazole-containing substituent at position 3 of the indazole. US20130274241 does not describe any 2-substitution of the indazoles disclosed.

WO2011043371 describes oxazolecarboxamides linked to monocyclic aromatic heterocycles as IRAK4 inhibitors. Oxazolecarboxamides linked to an indazole structure as in the compounds according to the invention are not described in WO2011043371.

Bicyclic heterocycles having a carboxamide structure as IRAK4 inhibitors, for example substance
 5 **L1**, are described by B. Anima et al. in WO2013042137. However, only benzimidazole, benzoxazole and benzothiazole derivatives are described, and no indazole derivatives.



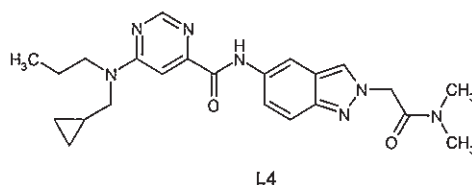
G. M. Buckley et al. report, in Bioorg. Med. Chem. Lett. 18 (2008), 3211 – 3214,



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carboxamide derivatives as IRAK4 inhibitors. Described are, for example, the molecules **L2** and **L3**. Indazole derivatives are not described.

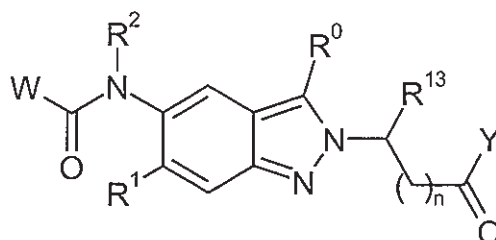
In WO2009019167, A. Bombrun et al. describe 6-aminopyrimidine-4-carboxamides having a 2-
 15 substituted indazole structure such as, for example, **L4**. It is reported that the substances described bind to the sphingosine-1-phosphate receptor. An inhibiting action on IRAK4 kinase is not described in WO2009019167.



US20080058341 describes azaindazoles having a carboxamide structure as CCR1 antagonists. 2-
 20 substituted indazole derivatives having an additional carboxamide structure are not disclosed.

A. J. Souers et al. describe, in US20050137187, 2-substituted indazoles as antagonists of MCH (melanin-concentrating hormone). However, the 2-substituent at the indazole does not comprise a carboxamide structure.

The present invention provides compounds of the general formula (I)



(I)

in which:

R^0 represents hydrogen or C_1 - C_4 -alkyl, where the C_1 - C_4 -alkyl radical may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy and halogen;

R^1 represents hydrogen, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $C(=O)R^d$, hydroxy or C_1 - C_6 -alkyl, where the C_1 - C_6 -alkyl radical is optionally mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, NH_2 , NHR^a , $N(R^a)R^b$, C_1 - C_6 -alkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_3 - C_8 -cycloalkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, heterocycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c ,

or represents C_1 - C_6 -alkoxy, where the C_1 - C_6 -alkoxy radical may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of

hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, NH_2 , NHR^a , $N(R^a)R^b$, C_3 - C_8 -cycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_1 - C_6 -alkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_3 - C_8 -cycloalkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, heterocycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c ,

aryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c , or 5- or 6-membered heteroaryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c ,

5 or represents C_3 - C_8 -cycloalkoxy or heterocycloalkoxy which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1 - C_6 -alkyl,

or represents aryloxy or 5- or 6-membered heteroaryloxy in which aryloxy and 5- or 6-membered heteroaryloxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, C_1 - C_6 -alkyl and C_1 - C_6 -alkoxy,

10 or represents C_3 - C_8 -cycloalkyl or heterocycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1 - C_6 -alkyl,

15 or represents C_2 - C_6 -alkenyl or C_2 - C_6 -alkynyl,

or represents aryl, 5- to 10-membered heteroaryl, aryl- C_1 - C_4 -alkyl or 5- or 6-membered heteroaryl- C_1 - C_4 -alkyl, where aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, $C(=O)OH$, $C(=O)OR^a$, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl and C_1 - C_6 -alkoxy;

20

R^a represents C_1 - C_6 -alkyl, C_3 - C_{10} -cycloalkyl, heterocycloalkyl, aryl or heteroaryl, where alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, heterocycloalkyl, $-C(=O)O$ - C_1 - C_6 -alkyl and $S(=O)_2$ - C_1 - C_6 -alkyl;

25

R^b represents C_1 - C_6 -alkyl or C_3 - C_{10} -cycloalkyl;

or R^a and R^b together with the nitrogen atom form a 5- or 6-membered heterocycle which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, and C_1 - C_6 -alkyl;

30

R^c represents hydroxy, halogen, cyano, C_1 - C_3 -alkyl or C_1 - C_3 -alkoxy;

35 R^d represents hydrogen, C_1 - C_6 -alkyl or C_3 - C_{10} -cycloalkyl;

- R^2 represents hydrogen, C_1 - C_6 -alkyl or C_3 - C_6 -cycloalkyl;
- R^{13} represents hydrogen or C_1 - C_6 -alkyl;
- 5 W represents 5-membered heteroaryl which contains one to three heteroatoms selected from the group consisting of N, O and S and may optionally be monosubstituted by R^3 and optionally be mono- or polysubstituted by identical or different radicals R^4 or
- 10 W represents pyridyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl or 1,3,5-triazinyl which may optionally be monosubstituted by R^3 and optionally be mono- or polysubstituted by identical or different radicals R^4 ;
- R^3 represents hydrogen, halogen, cyano, $C(=O)R^a$, NH_2 , NHR^a , $N(R^a)R^b$, $N(H)C(=O)R^a$ or C_1 - C_6 -alkyl, where
- 15 C_1 - C_6 -alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)R^a$, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, NH_2 , NHR^a , $N(R^a)R^b$, C_1 - C_6 -alkoxy, C_3 - C_8 -cycloalkoxy,
- 20 where C_1 - C_6 -alkoxy and C_3 - C_8 -cycloalkoxy may optionally be mono- or polysubstituted by identical or different halogen radicals;
- or C_1 - C_6 -alkyl is optionally mono- or polysubstituted by identical or different radicals from the group consisting of C_3 - C_6 -cycloalkyl and heterocycloalkyl,
- 25 where C_3 - C_6 -cycloalkyl and heterocycloalkyl may optionally be mono-, di- or trisubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1 - C_3 -alkyl and C_1 - C_3 -alkoxy,
- or C_1 - C_6 -alkyl is optionally mono- or polysubstituted by identical or different radicals from the group consisting of aryl and 5- or 6-membered heteroaryl,
- 30 where aryl and 5- or 6-membered heteroaryl may optionally be mono-, di- or trisubstituted by identical or different substituents from the group consisting of halogen, cyano, C_1 - C_3 -alkyl and C_1 - C_3 -alkoxy,
- or
- R^3 represents C_1 - C_6 -alkoxy, where
- 35 C_1 - C_6 -alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, $N(R^a)R^b$, C_3 - C_8 -cycloalkyl, C_1 - C_4 -alkoxy, C_3 - C_8 -cycloalkoxy,

or represents C₃-C₆-cycloalkyl, heterocycloalkyl or C₅-C₁₁-spirocycloalkyl, where cycloalkyl, heterocycloalkyl and spirocycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OH, C(=O)OR^a, C₁-C₆-alkyl and C₁-C₄-alkoxy;

or represents aryl or 5- to 10-membered heteroaryl, where aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, NO₂, NH₂, NHR^a, N(R^a)R^b, N(H)C(=O)R^a, C₃-C₈-cycloalkyl, C₁-C₃-alkoxy and C₁-C₃-alkyl, where C₁-C₃-alkyl may optionally be mono- or polysubstituted by identical or different halogen radicals;

R⁴ represents halogen, hydroxy, cyano or C₁-C₆-alkyl, where C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C₁-C₆-alkoxy, where C₁-C₆-alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₁₀-cycloalkyl, 3- to 10-membered heterocycloalkyl and aryl, where aryl may optionally be mono- or polysubstituted by identical or different radicals R,

or R⁴ represents aryl or heteroaryl which may optionally be mono- or polysubstituted by identical or different radicals R,

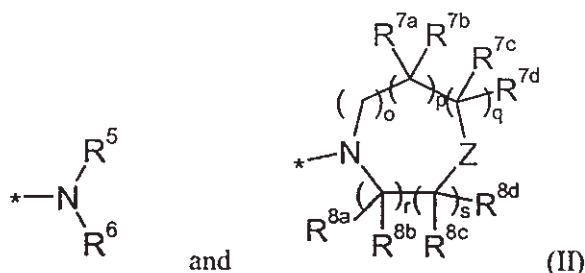
or R⁴ represents C(=O)R^a, C(=O)NH₂, C(=O)N(H)R^a, C(=O)N(R^a)R^b, C(=O)OR^a, NH₂, NHR^a, N(R^a)R^b, N(H)C(=O)R^a, N(R^a)C(=O)R^a, N(H)C(=O)NH₂, N(H)C(=O)NHR^a, N(H)C(=O)N(R^a)R^b, N(R^a)C(=O)NH₂, N(R^a)C(=O)NHR^a, N(R^a)C(=O)N(R^a)R^b, N(H)C(=O)OR^a, N(R^a)C(=O)OR^a, NO₂, N(H)S(=O)R^a, N(R^a)S(=O)R^a, N(H)S(=O)₂R^a, N(R^a)S(=O)₂R^a, N=S(=O)(R^a)R^b, OC(=O)R^a, OC(=O)NH₂, OC(=O)NHR^a, OC(=O)N(R^a)R^b, SH, SR^a, S(=O)R^a, S(=O)₂R^a, S(=O)₂NH₂, S(=O)₂NHR^a, S(=O)₂N(R^a)R^b or S(=O)(=N-R^a)R^b;

R represents halogen, cyano, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₁₀-cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl, heteroaryl, C(=O)R^a, C(=O)NH₂, C(=O)N(H)R^a, C(=O)N(R^a)R^b, C(=O)OR^a, NH₂, NHR^a, N(R^a)R^b, N(H)C(=O)R^a, N(R^a)C(=O)R^a, N(H)C(=O)NH₂, N(H)C(=O)NHR^a, N(H)C(=O)N(R^a)R^b, N(R^a)C(=O)NH₂, N(R^a)C(=O)NHR^a, N(R^a)C(=O)N(R^a)R^b, N(H)C(=O)OR^a, N(R^a)C(=O)OR^a, NO₂,

$N(H)S(=O)R^a$, $N(R^a)S(=O)R^a$, $N(H)S(=O)_2R^a$, $N(R^a)S(=O)_2R^a$, $N=S(=O)(R^a)R^b$, OH, C_1 - C_6 -alkoxy, $OC(=O)R^a$, $OC(=O)NH_2$, $OC(=O)NHR^a$, $OC(=O)N(R^a)R^b$, SH, SR^a , $S(=O)R^a$, $S(=O)_2R^a$, $S(=O)_2NH_2$, $S(=O)_2NHR^a$, $S(=O)_2N(R^a)R^b$ or $S(=O)(=NR^a)R^b$;

5 n represents 0 or 1;

Y represents a group selected from:



10

where * represents the point of attachment of the group to the remainder of the molecule;

R^5 represents hydrogen, C_1 - C_6 -alkyl or C_3 - C_{10} -cycloalkyl, where

15

C_1 - C_6 -alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, $N(R^a)R^b$, C_1 - C_4 -alkoxy and C_3 - C_8 -cycloalkyl;

R^6 represents hydrogen or C_1 - C_6 -alkyl, where

20

C_1 - C_6 -alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C_3 - C_{10} -cycloalkyl, $C(=O)R^a$, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, $N(R^a)R^b$, C_1 - C_4 -alkoxy and C_3 - C_8 -cycloalkoxy,

or represents C_3 - C_{10} -cycloalkyl, where

25

C_3 - C_{10} -cycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1 - C_6 -alkyl, where

C_1 - C_6 -alkyl may optionally be substituted by hydroxy,

or represents heterocycloalkyl, where

30

heterocycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1 - C_3 -alkyl and C_1 - C_3 -alkoxy,

or represents aryl or 5- or 6-membered heteroaryl, where

aryl and 5- or 6-membered heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C₁-C₃-alkyl, C₁-C₃-alkoxy, S(=O)₂NH₂, S(=O)₂NHR^a and S(=O)₂N(R^a)R^b;

5 R^{7a} represents hydrogen, halogen, N(R^a)R^b, C₁-C₆-alkyl or C₃-C₁₀-cycloalkyl, where C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-cycloalkyl and heterocycloalkyl;

10

R^{7b} represents hydrogen, halogen or C₁-C₆-alkyl, where C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-cycloalkyl and heterocycloalkyl;

15

or R^{7a} and R^{7b} together with the carbon atom form C₃-C₆-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C₁-C₆-alkyl,

20

or R^{7a} and R^{7b} together represent an oxo group;

R^{7c} represents hydrogen, halogen, N(R^a)R^b, C₁-C₆-alkyl or C₃-C₁₀-cycloalkyl, where C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-cycloalkyl and heterocycloalkyl;

25

R^{7d} represents hydrogen, halogen or C₁-C₆-alkyl, where C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-cycloalkyl and heterocycloalkyl;

30

35 or R^{7c} and R^{7d} together with the carbon atom form C₃-C₆-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C₁-C₆-alkyl,

or R^{7c} and R^{7d} together represent an oxo group;

R^{8a} represents hydrogen, halogen, $N(R^a)R^b$, C_1 - C_6 -alkyl or C_3 - C_{10} -cycloalkyl, where

5 C_1 - C_6 -alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, $N(R^a)R^b$, C_1 - C_4 -alkoxy, C_3 - C_8 -cycloalkyl and heterocycloalkyl;

R^{8b} represents hydrogen, halogen or C_1 - C_6 -alkyl, where

10 C_1 - C_6 -alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, $N(R^a)R^b$, C_1 - C_4 -alkoxy, C_3 - C_8 -cycloalkyl and heterocycloalkyl;

15 or R^{8a} and R^{8b} together with the carbon atom form C_3 - C_6 -cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1 - C_6 -alkyl,

R^{8c} represents hydrogen, halogen, $N(R^a)R^b$, C_1 - C_6 -alkyl or C_3 - C_{10} -cycloalkyl, where

20 C_1 - C_6 -alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, $N(R^a)R^b$, C_1 - C_4 -alkoxy, C_3 - C_8 -cycloalkyl and heterocycloalkyl;

25 R^{8d} represents hydrogen, halogen or C_1 - C_6 -alkyl, where

C_1 - C_6 -alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, $N(R^a)R^b$, C_1 - C_4 -alkoxy, C_3 - C_8 -cycloalkyl and heterocycloalkyl;

30

or R^{8c} and R^{8d} together with the carbon atom form C_3 - C_6 -cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1 - C_6 -alkyl,

35 or R^{8c} and R^{8d} together represent an oxo group;

o represents 0, 1 or 2,

p represents 0, 1 or 2,

q represents 0, 1 or 2,

r represents 0, 1 or 2,

s represents 0, 1 or 2,

where o, p, q, r and s do not simultaneously represent 0;

5

Z represents a group selected from C(=O), CR⁹R¹⁰, NR¹¹, O, S, S(=O) and S(=O)₂;

R⁹ represents hydrogen or C₁-C₆-alkyl,

10 R¹⁰ represents hydrogen, halogen, cyano, C(=O)R^a, C(=O)OH, C(=O)OR^a, C(=O)NH₂, C(=O)N(H)R^a, C(=O)N(R^a)R^b, N(H)C(=O)R^a, N(R^b)C(=O)R^a, S(=O)₂R^a, hydroxy, N(R^a)R^b and C₁-C₆-alkyl, where

C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a,
15 C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy and C₃-C₈-cycloalkoxy,

or represents C₁-C₆-alkoxy, where

C₁-C₆-alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH,
20 C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₃-C₈-cycloalkyl, C₁-C₄-alkoxy, C₃-C₈-cycloalkoxy, heterocycloalkyl, aryl and 5- or 6-membered heteroaryl, where

aryl and 5- or 6-membered heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C₁-C₃-alkyl and C₁-C₃-alkoxy,

25 or represents aryloxy or 5- or 6-membered heteroaryloxy in which

aryloxy and 5- or 6-membered heteroaryloxy may optionally be mono- or disubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, C₁-C₃-alkyl and C₁-C₃-alkoxy,

or represents C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, heterocycloalkyl or
30 heterocycloalkyl-C₁-C₄-alkyl, which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OH, C(=O)OR^a, C₁-C₆-alkyl and C₁-C₆-alkoxy, where

C₁-C₆-alkoxy may optionally be mono- or polysubstituted by identical or different halogen radicals or an oxo group;

35 or represents C₂-C₆-alkenyl or C₂-C₆-alkynyl,

or represents aryl, 5- to 10-membered heteroaryl, aryl-C₁-C₄-alkyl or 5- or 6-membered heteroaryl-C₁-C₄-alkyl, where

aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, NHR^a, N(R^a)R^b, C₁-C₃-alkyl, C₃-C₈-cycloalkyl and C₁-C₃-alkoxy;

or R⁹ and R¹⁰ together with the carbon atom form C₃-C₈-cycloalkyl or a 4- to 6-membered heterocycle, where

the C₃-C₈-cycloalkyl radical or the 4- to 6-membered heterocycle may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C₁-C₆-alkyl, C(=O)R^a and an oxo group;

R¹¹ represents hydrogen, C(=O)R^a, C(=O)OR^a, C(=O)NH₂, C(=O)N(H)R^a, C(=O)N(R^a)R^b, S(=O)₂R^a, S(=O)₂N(R^a)R^b or C₁-C₆-alkyl, where

C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OR^a, C(=O)NH₂, C(=O)N(H)R^a, C(=O)N(R^a)R^b, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₃-C₈-cycloalkyl, C₁-C₄-alkoxy and C₃-C₈-cycloalkoxy, where

C₃-C₈-cycloalkyl, C₁-C₄-alkoxy and C₃-C₈-cycloalkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy and halogen,

or represents C₃-C₈-cycloalkyl, heterocycloalkyl or heterocycloalkyl-C₁-C₄-alkyl

which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C₁-C₆-alkyl, C₁-C₆-alkoxy, where alkyl and alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen and an oxo group,

or represents C₂-C₆-alkenyl or C₂-C₆-alkynyl,

or represents aryl, 5- to 10-membered heteroaryl, aryl-C₁-C₄-alkyl or 5- or 6-membered heteroaryl-C₁-C₄-alkyl, where

aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, C₁-C₃-alkyl, C₃-C₈-cycloalkyl and C₁-C₃-alkoxy;

and their diastereomers, enantiomers, their metabolites, their salts, their solvates or the solvates of their salts.

If, in the synthesis intermediates and working examples of the invention described below, a compound is given in the form of a salt of the corresponding base or acid, the exact stoichiometric composition of such a salt as obtained by the respective preparation and/or purification process is generally not known. Unless specified in more detail, additions to names and structural formulae, such as "hydrochloride", "trifluoroacetate", "sodium salt" or " x HCl", " x CF_3COOH ", " x Na^+ " are not to be understood stoichiometrically in the case of such salts, but have only descriptive character with regard to the salt-forming components comprised therein.

This applies correspondingly if synthesis intermediates or working examples or salts thereof were obtained by the preparation and/or purification processes described in the form of solvates, for example hydrates, of unknown stoichiometric composition (if of a defined type).

Compounds according to the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts, the compounds encompassed by formula (I) of the formulae mentioned below and their salts, solvates and solvates of the salts and the compounds encompassed by formula (I) and mentioned below as working examples, and their salts, solvates and solvates of the salts, if the compounds encompassed by formula (I) and mentioned below are not already salts, solvates and solvates of the salts.

Preferred salts in the context of the present invention are physiologically acceptable salts of the compounds according to the invention. The invention also encompasses salts which themselves are unsuitable for pharmaceutical applications but which can be used, for example, for the isolation or purification of the inventive compounds.

Physiologically acceptable salts of the compounds according to the invention include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds according to the invention also include salts of conventional bases, by way of example and with preference alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, by way of example and with preference ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine and N-methylpiperidine.

Solvates in the context of the invention are described as those forms of the compounds according to the invention which form a complex in the solid or liquid state by coordination with solvent molecules. Hydrates are a specific form of the solvates in which the coordination is with water.

The compounds according to the invention may, depending on their structure, exist in different stereoisomeric forms, i.e. in the form of configurational isomers or else optionally as conformational isomers (enantiomers and/or diastereomers, including those in the case of atropisomers). The present invention therefore encompasses the enantiomers and diastereomers, and the respective mixtures thereof. The stereoisomerically homogeneous constituents can be isolated from such mixtures of enantiomers and/or diastereomers in a known manner; chromatography processes are preferably used for this purpose, especially HPLC chromatography on an achiral or chiral phase.

- 10 Where the compounds according to the invention can occur in tautomeric forms, the present invention encompasses all the tautomeric forms.

The present invention also encompasses all suitable isotopic variants of the compounds according to the invention. An isotopic variant of a compound according to the invention is understood here as meaning a compound in which at least one atom within the compound according to the invention has been exchanged for another atom of the same atomic number, but with a different atomic mass than the atomic mass which usually or predominantly occurs in nature. Examples of isotopes which can be incorporated into a compound according to the invention are those of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as 2H (deuterium), 3H (tritium), ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{129}I and ^{131}I . Particular isotopic variants of a compound according to the invention, especially those in which one or more radioactive isotopes have been incorporated, may be beneficial, for example, for the examination of the mechanism of action or of the active compound distribution in the body; due to comparatively easy preparability and detectability, especially compounds labelled with ^3H or ^{14}C isotopes are suitable for this purpose. In addition, the incorporation of isotopes, for example of deuterium, can lead to particular therapeutic benefits as a consequence of greater metabolic stability of the compound, for example to an extension of the half-life in the body or to a reduction in the active dose required; such modifications of the compounds according to the invention may therefore in some cases also constitute a preferred embodiment of the present invention. Isotopic variants of the compounds according to the invention can be prepared by the processes known to those skilled in the art, for example by the methods described further below and the procedures described in the working examples, by using corresponding isotopic modifications of the respective reagents and/or starting compounds.

- 35 The present invention further provides all the possible crystalline and polymorphous forms of the compounds according to the invention, where the polymorphs may be present either as single polymorphs or as a mixture of a plurality of polymorphs in all concentration ranges.

In addition, the present invention also encompasses prodrugs of the compounds according to the invention. The term "prodrugs" here denotes compounds which may themselves be biologically active or inactive, but are converted (for example by metabolic or hydrolytic means) to inventive compounds during their residence time in the body.

5

In the context of the present invention, unless specified otherwise, the substituents have the following meanings:

Alkyl in the context of the invention is a straight-chain or branched alkyl radical having the particular number of carbon atoms specified. Examples which may be mentioned are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl and 2-ethylbutyl. Preference is given to methyl, ethyl, n-propyl, n-butyl and 1-methylpropyl and also tert-butyl.

15

Alkenyl in the context of the invention is a straight-chain or branched monovalent hydrocarbon radical having at least one double bond and having the particular number of carbon atoms specified. These are generally 2 to 6 carbon atoms, preferably 2 to 4 and particularly preferably 2 or 3 carbon atoms.

20 In the case of a plurality of double bonds, these may be isolated or conjugated, with isolated double bonds being preferred.

Examples which may be mentioned are:

vinyl, allyl, (*E*)-2-methylvinyl, (*Z*)-2-methylvinyl, homoallyl, (*E*)-but-2-enyl, (*Z*)-but-2-enyl, (*E*)-but-1-enyl, (*Z*)-but-1-enyl, pent-4-enyl, (*E*)-pent-3-enyl, (*Z*)-pent-3-enyl, (*E*)-pent-2-enyl, (*Z*)-pent-2-enyl, (*E*)-pent-1-enyl, (*Z*)-pent-1-enyl, hex-5-enyl, (*E*)-hex-4-enyl, (*Z*)-hex-4-enyl, (*E*)-hex-3-enyl, (*Z*)-hex-3-enyl, (*E*)-hex-2-enyl, (*Z*)-hex-2-enyl, (*E*)-hex-1-enyl, (*Z*)-hex-1-enyl, isopropenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (*E*)-1-methylprop-1-enyl, (*Z*)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (*E*)-2-methylbut-2-enyl, (*Z*)-2-methylbut-2-enyl, (*E*)-1-methylbut-2-enyl, (*Z*)-1-methylbut-2-enyl, (*E*)-3-methylbut-1-enyl, (*Z*)-3-methylbut-1-enyl, (*E*)-2-methylbut-1-enyl, (*Z*)-2-methylbut-1-enyl, (*E*)-1-methylbut-1-enyl, (*Z*)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-1-enyl, 1-propylvinyl, 1-isopropylvinyl, 4-methylpent-4-enyl, 3-methylpent-4-enyl, 2-methylpent-4-enyl, 1-methylpent-4-enyl, 4-methylpent-3-enyl, (*E*)-3-methylpent-3-enyl, (*Z*)-3-methylpent-3-enyl, (*E*)-2-methylpent-3-enyl, (*Z*)-2-methylpent-3-enyl, (*E*)-1-methylpent-3-enyl, (*Z*)-1-methylpent-3-enyl,

35

- (*E*)-4-methylpent-2-enyl, (*Z*)-4-methylpent-2-enyl, (*E*)-3-methylpent-2-enyl,
 (*Z*)-3-methylpent-2-enyl, (*E*)-2-methylpent-2-enyl, (*Z*)-2-methylpent-2-enyl,
 (*E*)-1-methylpent-2-enyl, (*Z*)-1-methylpent-2-enyl, (*E*)-4-methylpent-1-enyl,
 (*Z*)-4-methylpent-1-enyl, (*E*)-3-methylpent-1-enyl, (*Z*)-3-methylpent-1-enyl,
 5 (*E*)-2-methylpent-1-enyl, (*Z*)-2-methylpent-1-enyl, (*E*)-1-methylpent-1-enyl,
 (*Z*)-1-methylpent-1-enyl, 3-ethylbut-3-enyl, 2-ethylbut-3-enyl, 1-ethylbut-3-enyl,
 (*E*)-3-ethylbut-2-enyl, (*Z*)-3-ethylbut-2-enyl, (*E*)-2-ethylbut-2-enyl, (*Z*)-2-ethylbut-2-enyl,
 (*E*)-1-ethylbut-2-enyl, (*Z*)-1-ethylbut-2-enyl, (*E*)-3-ethylbut-1-enyl, (*Z*)-3-ethylbut-1-enyl,
 2-ethylbut-1-enyl, (*E*)-1-ethylbut-1-enyl, (*Z*)-1-ethylbut-1-enyl, 2-propylprop-2-enyl,
 10 1-propylprop-2-enyl, 2-isopropylprop-2-enyl, 1-isopropylprop-2-enyl,
 (*E*)-2-propylprop-1-enyl, (*Z*)-2-propylprop-1-enyl, (*E*)-1-propylprop-1-enyl,
 (*Z*)-1-propylprop-1-enyl, (*E*)-2-isopropylprop-1-enyl, (*Z*)-2-isopropylprop-1-enyl,
 (*E*)-1-isopropylprop-1-enyl, (*Z*)-1-isopropylprop-1-enyl, (*E*)-3,3-dimethylprop-1-enyl,
 (*Z*)-3,3-dimethylprop-1-enyl, 1-(1,1-dimethylethyl)ethenyl, buta-1,3-dienyl,
 15 penta-1,4-dienyl, hexa-1,5-dienyl, methylhexadienyl.

Particular preference is given to vinyl or allyl.

Alkynyl in the context of the invention is a straight-chain or branched monovalent hydrocarbon radical having at least one triple bond and having the particular number of carbon atoms specified. These are generally 2 to 6 carbon atoms, preferably 2 to 4 and particularly preferably 2 or 3 carbon
 20 atoms.

Examples which may be mentioned are:

- ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl,
 pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl, hex-4-ynyl,
 hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl,
 25 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl,
 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl,
 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl,
 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl,
 2,2-dimethylbut-3-ynyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl or
 30 3,3-dimethylbut-1-ynyl.

Particular preference is given to ethynyl, prop-1-ynyl or prop-2-ynyl.

Cycloalkyl in the context of the invention is a monocyclic saturated alkyl radical having the number of carbon atoms specified in each case. Examples which may be mentioned as being preferred are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

- 35 Alkoxy in the context of the invention is a straight-chain or branched alkoxy radical having the particular number of carbon atoms specified. 1 to 6 or 1 to 4 carbon atoms are preferred. Examples

which may be mentioned are methoxy, ethoxy, n-propoxy, isopropoxy, 1-methylpropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy, isopentoxy, 1-ethylpropoxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy and n-hexoxy. Preference is given to a linear or branched alkoxy radical having 1 to 4 carbon atoms. Examples which may be mentioned as being preferred are

5 methoxy, ethoxy, n-propoxy, 1-methylpropoxy, n-butoxy and isobutoxy.

Cycloalkoxy in the context of the invention is a monocyclic saturated alkyl radical which has the particular number of carbon atoms specified and is attached via an oxygen atom. Examples which may be mentioned as being preferred are: cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy and cycloheptoxy.

10 Aryl in the context of the invention is a monovalent mono- to tricyclic aromatic, carbocyclic ring system having generally 6 to 14 carbon atoms. Examples which may be mentioned are: phenyl, naphthyl and phenanthryl. Preference is given to phenyl.

Heterocyclyl or heterocyclus or heterocycloalkyl in the context of the invention is a mono- or polycyclic, preferably mono- or bicyclic, non-aromatic, saturated or partially unsaturated heterocycle having generally 3 to 10, preferably 3 to 7, ring atoms and up to 3, preferably up to 1 or 2, heteroatoms and/or heterogroups from the group consisting of N, O, S, SO and SO₂. Preference is given to 3- to 7-membered, monocyclic saturated heterocyclyl radicals having up to two heteroatoms from the group consisting of O, N and S. Examples which may be mentioned are:

15 azetidiny, oxetanyl, pyrrolidiny, pyrazolidiny, tetrahydrofuranyl, piperidiny, piperaziny, tetrahydropyranyl, morpholiny, thiomorpholiny, dioxidothiomorpholiny, dihydroindolyl and dihydroisoindolyl. Preference is given to: azetidiny, pyrrolidiny, piperidiny, piperaziny and morpholiny.

20

Heteroaryl is a monovalent, aromatic mono- or bicyclic ring system having generally 5 to 10, preferably 5 to 6, ring atoms and preferably 1 to 3 heteroatoms. The heteroatoms may be nitrogen atoms, oxygen atoms and/or sulphur atoms. The binding valency can be at any aromatic carbon atom or at a nitrogen atom.

25

Heteroaryl radicals having 5 ring atoms include, for example, the rings:

thienyl, thiazolyl, furyl, pyrrolyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl,

30 oxadiazolyl, triazolyl, tetrazolyl and thiadiazolyl.

Heteroaryl radicals having 6 ring atoms include, for example, the rings:

pyridyl, pyridaziny, pyrimidiny, pyraziny and triaziny.

A bicyclic heteroaryl radical in accordance with the present invention has 9 or 10 ring atoms.

Heteroaryl radicals having 9 ring atoms include, for example, the rings:

phthalidyl, thiophthalidyl, indolyl, isoindolyl, indazolyl, benzothiazolyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl, azocinyl, indoliziny, purinyl, indolinyl.

Heteroaryl radicals having 10 ring atoms include, for example, the rings:

- 5 isoquinolinyl, quinolinyl, quinoliziny, quinazoliny, quinoxaliny, cinnolinyl, phthalazinyl, 1,7- or 1,8-naphthyridinyl, pteridinyl, chromanyl.

- C₅-C₁₁-Spirocycloalkyl or heterospirocycloalkyl with replacement of 1-4 carbon atoms by nitrogen, oxygen and/or sulphur, including the two oxidized forms thereof, SO and SO₂, and the derivatives thereof modified as the sulphoximine, is understood to mean a fusion of two ring systems which
- 10 share a common atom. Examples are spiro[2.2]pentane, spiro[2.3]hexane, azaspiro[2.3]hexane, spiro[3.3]heptane, azaspiro[3.3]heptane, oxazaspiro[3.3]heptane, thiaazaspiro[3.3]heptane, oxaspiro[3.3]heptane, oxazaspiro[5.3]nonane, oxazaspiro[4.3]octane, oxazaspiro[5.5]undecane, diazaspiro[3.3]heptane, thiazaspiro[3.3]heptane, thiazaspiro[4.3]octane, azaspiro[5.5]decane, and the further homologous spiro[3.4], spiro[4.4], spiro[5.5], spiro[6.6], spiro[2.4], spiro[2.5],
- 15 spiro[2.6], spiro[3.5], spiro[3.6], spiro[4.5], spiro[4.6] and spiro[5.6] systems including the variants modified by heteroatoms according to the definition.

Halogen in the context of the invention is fluorine, chlorine and bromine. Preference is given to fluorine and chlorine.

Hydroxy in the context of the invention is OH.

- 20 An oxo group in the context of the invention is an oxygen atom attached to a carbon atom via a double bond.

A symbol * at a bond denotes the point of attachment in the molecule.

- When radicals in the compounds according to the invention are substituted, the radicals may be mono- or polysubstituted, unless specified otherwise. In the context of the present invention, it is
- 25 the case that for all radicals which occur more than once, their meaning is independent of the others. Substitution by one, two or three identical or different substituents is preferred.

Preference is given to compounds of the formula (I) in which

- 30 W represents 5-membered heteroaryl which contains one to three heteroatoms selected from the group consisting of N, O and S and may optionally be monosubstituted by R³ and optionally be mono- or polysubstituted by identical or different radicals R⁴, where a ring

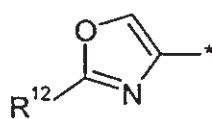
heteroatom is located next to the ring carbon atom which is the point of attachment to the remainder of the molecule

or

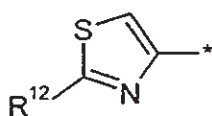
represents pyridyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl or 1,3,5-triazinyl which may optionally be monosubstituted by R^3 and optionally be mono- or polysubstituted by identical or different radicals R^4 , where a ring heteroatom is located next to the ring carbon atom which is the point of attachment of the group to the remainder of the molecule.

Preference is furthermore given to compounds of the formula (I) in which

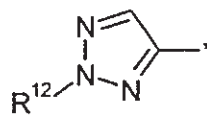
W represents a group selected from the following general formulae (III) to (IX):



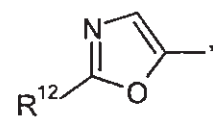
III



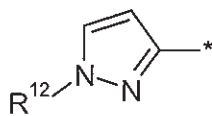
IV



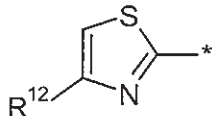
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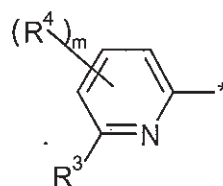
VI



VII



VIII



IX

in which

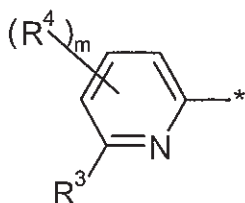
R^{12} represents hydrogen, halogen, C_1 - C_6 -alkyl which is optionally mono- or polysubstituted by identical or different halogen radicals, C_3 - C_6 -cycloalkyl which is optionally mono- or polysubstituted by identical or different halogen radicals, aryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c or 5- or 6-membered heteroaryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c or represents NHR^a ;

m represents 0, 1, 2 or 3 and

R^3 and R^4 have the meanings given above and

* represents the point of attachment of the group to the remainder of the molecule.

Particular preference is furthermore given to compounds of the general formula (I) in which W represents a group of the general formula (IX)



(IX)

in which $m = 0$ or 1 and

R^3 is a C_1 - C_6 -alkyl radical which is optionally mono- or polysubstituted by halogen and/or hydroxy, is halogen, cyano or a C_3 - C_6 -cycloalkyl radical which is optionally mono- or polysubstituted by halogen and/or hydroxy.

Preferably, R^3 is a C_1 - C_3 -alkyl radical which is unsubstituted or mono- or polysubstituted by hydroxy and/or halogen.

For the purpose of the invention, particularly preferred C_1 - C_3 -alkyls radical for R^3 are methyl and ethyl. Preferably, R^3 is a C_1 - C_6 -alkyl radical which is optionally monosubstituted by hydroxy and/or mono- to trisubstituted by fluorine.

Particularly preferably, R^3 is a C_1 - C_3 -alkyl radical which is optionally monosubstituted by hydroxy and/or mono- to trisubstituted by fluorine.

Preferred substituted C_1 - C_3 -alkyl radicals for R^3 are trifluoro- C_1 - C_3 -alkyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxypropan-2-yl and 2,2,2-trifluoro-1-hydroxyethyl. Here, particular preference is given to a trifluoromethyl radical.

Also preferred for R^3 is a cyclopropyl radical.

In an exemplary manner, the following radicals may be mentioned for W:

1-ethyl-1H-pyrazol-3-yl, 2,4'-bipyridin-6-yl, 2-(4-fluorophenyl)-1,3-thiazol-4-yl, 2-(4-methoxyphenyl)-1,3-thiazol-4-yl, 2-(azetidin-3-ylamino)-1,3-thiazol-4-yl, 2-(pyridin-3-yl)-1,3-thiazol-4-yl, 2-(pyridin-4-yl)-1,3-thiazol-4-yl, 2-(trifluoromethyl)-1,3-thiazol-4-yl, 2-bromo-1,3-thiazol-4-yl, 2-cyclopropyl-1,3-oxazol-4-yl, 2-methyl-1,3-oxazol-4-yl, 2-methyl-1,3-oxazol-5-yl, 2-phenyl-2H-1,2,3-triazol-4-yl, 2-{[1-(tert-butoxycarbonyl)azetidin-3-yl]amino}-1,3-thiazol-4-yl, 4'-methyl-2,3'-bipyridin-6-yl, 4-(trifluoromethyl)-1,3-thiazol-2-yl, 5'-methyl-2,3'-bipyridin-6-yl, 5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl, 5-fluoropyridin-2-yl, 6'-acetamido-2,3'-bipyridin-6-yl, 6'-amino-2,3'-bipyridin-6-yl, 6'-methoxy-2,3'-bipyridin-6-yl, 6'-methyl-2,3'-bipyridin-6-yl, 6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-2-yl, 6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl, 6-(1-methyl-1H-pyrazol-5-yl)pyridin-2-yl, 6-(1H-1,2,4-triazol-1-yl)pyridin-2-yl, 6-(1H-pyrazol-1-yl)pyridin-2-yl, 6-(3-hydroxyazetidin-1-yl)pyridin-2-yl, 6-(3-methyl-1H-pyrazol-4-yl)pyridin-2-yl, 6-(4-chloro-1H-pyrazol-1-yl)pyridin-2-yl, 6-(4H-1,2,4-triazol-4-yl)pyridin-2-yl, 6-(azetidin-3-ylamino)pyridin-2-yl, 6-(cyclopropylmethoxy)pyridin-2-yl, 6-(dimethylamino)pyridin-2-yl, 6-(morpholin-4-yl)pyridin-2-yl, 6-(morpholin-4-yl)pyridin-2-yl, 6-(trifluoromethyl)pyridin-2-yl, 6-[1-hydroxyethyl]pyridin-2-yl, 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridin-2-yl, 6-[3-(methylsulphonyl)phenyl]pyridin-2-yl, 6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridin-2-yl, 6-acetamidopyridin-2-yl, 6-aminopyridin-2-yl, 6-bromopyridin-2-yl, 6-bromopyridin-2-yl, 6-chloropyridin-2-yl, 6-cyclopropylpyridin-2-yl, 6-ethoxypyridin-2-yl, 6-ethylpyridin-2-yl, 6-

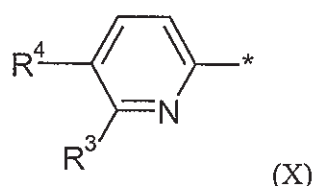
fluoropyridin-2-yl, 6-methoxypyridin-2-yl, 6-methylpyridin-2-yl, 6-{[(2S)-azetidin-2-ylmethyl]amino}pyridin-2-yl and 6-(2-hydroxypropan-2-yl)pyridin-2-yl.

5 Preferred for W are the following radicals:

2-(4-fluorophenyl)-1,3-thiazol-4-yl, 2-(4-methoxyphenyl)-1,3-thiazol-4-yl, 2-(azetidin-3-ylamino)-1,3-thiazol-4-yl, 2-(pyridin-4-yl)-1,3-thiazol-4-yl, 2-cyclopropyl-1,3-oxazol-4-yl, 5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl, 6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl, 6-(1H-1,2,4-triazol-1-yl)pyridin-2-yl, 6-(1H-pyrazol-1-yl)pyridin-2-yl, 6-(3-methyl-1H-pyrazol-4-yl)pyridin-2-yl, 6-(azetidin-3-ylamino)pyridin-2-yl, 6-(dimethylamino)pyridin-2-yl, 6-(morpholin-4-yl)pyridin-2-yl, 6-(trifluoromethyl)pyridin-2-yl, 6-[1-hydroxyethyl]pyridin-2-yl, 6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridin-2-yl, 6-cyclopropylpyridin-2-yl, 6-methylpyridin-2-yl and 6-(2-hydroxypropan-2-yl)pyridin-2-yl.

15

If W represents a group of the general formula (IX) and $m = 1$, R^4 is preferably located in the position ortho to R^3 :



20

If W represents a group of the general formula (X), R^4 is preferably hydrogen, C_1 - C_3 -alkyl, fluorine, chlorine, bromine, cyano or trifluoromethyl.

Particularly preferably, W represents a group of the general formula (X) in which R^4 is hydrogen.

25

Particularly preferred for W are the following radicals:

6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl, 6-(1H-1,2,4-triazol-1-yl)pyridin-2-yl, 6-(1H-pyrazol-1-yl)pyridin-2-yl, 6-(3-methyl-1H-pyrazol-4-yl)pyridin-2-yl, 6-(azetidin-3-ylamino)pyridin-2-yl, 6-(dimethylamino)pyridin-2-yl, 6-(morpholin-4-yl)pyridin-2-yl, 6-(trifluoromethyl)pyridin-2-yl, 6-[1-hydroxyethyl]pyridin-2-yl, 6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridin-2-yl, 6-cyclopropylpyridin-2-yl, 6-methylpyridin-2-yl and 6-(2-hydroxypropan-2-yl)pyridin-2-yl.

Preference is furthermore given to compounds in which R^1 is hydrogen, halogen, hydroxy, cyano, C_1 - C_6 -alkoxy, C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl, aryloxy or heteroaryloxy.

35

In a preferred embodiment, C₁-C₆-alkoxy in the sense of R¹ is methoxy, ethoxy, isopropoxy or else isobutoxy. C₁-C₆-Alkoxy may be mono- or polysubstituted, preferably by one or more halogens or else by C₃-C₈-cycloalkyl mono- or polysubstituted by identical or different halogens.

If R¹ represents mono- or polyhalogenated C₁-C₆-alkoxy, preference is given to fluorine. Here,
5 trifluoromethoxy, difluoromethoxy and 2,2,2-trifluoroethoxy may be mentioned by way of example. Trifluoromethoxy and 2,2,2-trifluoroethoxy are very particularly preferred.

If R¹ represents a C₁-C₆-alkoxy radical which is mono- or polysubstituted by C₃-C₈-cycloalkyl, preference is given to C₃-C₅-cycloalkyl, in particular to a cyclopropyl radical. Cyclopropylmethoxy
10 may be mentioned as an example thereof.

If R¹ is a C₁-C₆-alkoxy radical substituted by an aryl group, preference is given to aryl groups having 6 carbon atoms, for example benzyloxy.

If R¹ is a C₁-C₆-alkoxy radical substituted by a heteroaryl group, preference is given to 6-
15 membered heteroaryl radicals. Here, a pyrimidylmethoxy radical may be mentioned as an example for R¹.

Further preferred embodiments for R¹ in the sense of C₁-C₆-alkyl are methyl or ethyl.

If R¹ is a halogen, preference is given to bromine, fluorine or chlorine. Particular preference is
20 given to chlorine.

Furthermore, R¹ may be a hydroxy-substituted C₁-C₃-alkyl radical. Here, particular mention may be made of 2-hydroxypropan-2-yl or 3-hydroxypentan-3-yl. Preference is given to a 2-hydroxypropan-
25 2-yl radical.

If R¹ is a halogen, preference is given to fluorine, chlorine and bromine. Particular preference is given to chlorine.

The present invention also provides compounds of the general formula (I) in which W represents a
30 group of the general formula (IX) or (X) and R² represents hydrogen.

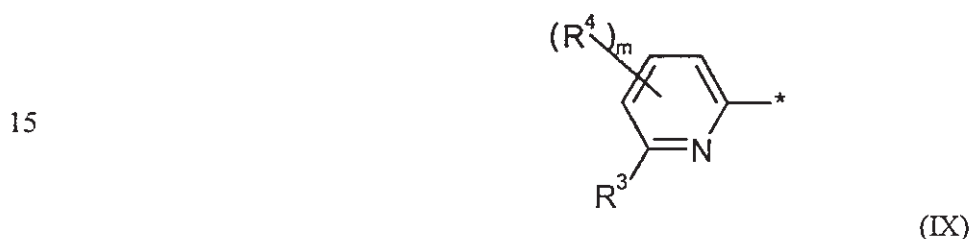
Moreover, the present invention provides compounds of the general formula (I) in which W represents a group of the general formula (IX) or (X) and R⁰ represents hydrogen or methyl.

35 Moreover, the present invention provides compounds of the general formula (I) in which W represents a group of the general formula (IX) or (X) and R¹³ represents hydrogen or methyl.

Moreover, the present invention provides compounds of the general formula (I) in which W represents a group of the general formula (IX) or (X) and n represents 0 or 1.

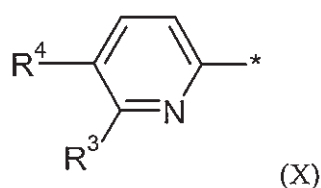
Moreover, the present invention provides compounds of the general formula (I) in which W represents a group of the general formula (IX) or (X) and R¹ represents hydrogen, cyano, isopropoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, isobutoxy, cyclopropylmethoxy, pyridin-2-ylmethoxy, benzyloxy, bromine, chlorine, ethoxy, fluorine, hydroxy, methoxy or 2-hydroxypropan-2-yl.

Moreover, the present invention provides compounds of the general formula (I) in which W represents a group of the general formula (IX)



in which m represents 0 or 1, R³ is a C₁-C₆-alkyl radical which is optionally mono- or polysubstituted by halogen and/or hydroxy, is halogen, cyano or a C₃-C₆-cycloalkyl radical which is optionally mono- or polysubstituted by halogen and/or hydroxy and R⁴ is a C₁-C₃-alkyl radical, fluorine, chlorine, bromine, cyano or trifluoromethyl.

Moreover, the present invention provides compounds of the general formula (I) in which W represents a group of the general formula (X)



in which R⁴ is hydrogen, C₁-C₃-alkyl, fluorine, chlorine, bromine, cyano or trifluoromethyl and R³ is a C₁-C₆-alkyl radical which is optionally mono- or polysubstituted by halogen and/or hydroxy, is halogen, cyano or a C₃-C₆-cycloalkyl radical which is optionally mono- or polysubstituted by halogen and/or hydroxy.

Particular preference is given to compounds in which W represents a group of the general formula (X) in which R^4 represents hydrogen and R^3 is a C_1 - C_3 -alkyl radical which is unsubstituted or mono- or polysubstituted by hydroxy and/or halogen.

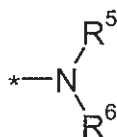
- 5 Very particular preference is given here to compounds in which W represents a group of the general formula (X) in which R^4 represents hydrogen and R^3 is a C_1 - C_3 -alkyl radical which is optionally monosubstituted by hydroxy and/or mono- to trisubstituted by fluorine.

Here, special preference is given to compounds in which R^4 represents hydrogen and R^3 is methyl, ethyl, trifluoro- C_1 - C_3 -alkyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxypropan-2-yl or 2,2,2-trifluoro-1-hydroxyethyl.

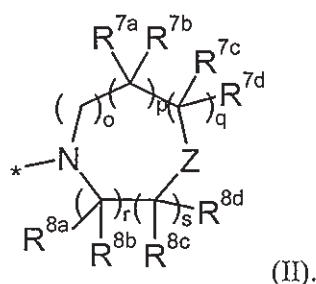
Especially preferably, R^4 is hydrogen and R^3 is a trifluoromethyl or a cyclopropyl radical.

Y either represents a radical

15



or represents a group



20

If Y represents NR^5R^6 as described above, R^5 is preferably C_1 - C_6 -alkyl, particularly preferably methyl or ethyl.

R^6 is likewise C_1 - C_6 -alkyl which may optionally be mono- or polysubstituted, preferably by C_3 - C_{10} -cycloalkyl.

- 25 Particularly preferred for R^6 are methyl or ethyl which are optionally substituted by C_3 - C_{10} -cycloalkyl. Here, particular preference is given to cyclopropyl.

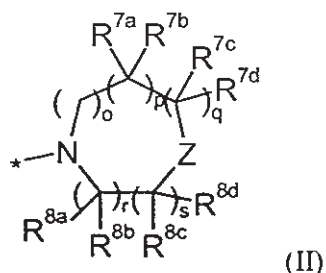
As an example thereof, mention may be made of cyclopropylmethyl.

- Further preferred embodiments for R^6 are C_3 - C_{10} -cycloalkyl, heterocycloalkyl, 5- or 6-membered heteroaryl or aryl.

Particular preference is given here to pyridazinyl, phenyl, oxazolyl, piperidinyl and cyclohexyl.

If Y represents NR^5R^6 , the following radicals may be mentioned as examples for Y: (3-sulphamoylphenyl)amino, [(3R)-piperidin-3-ylamino]ethyl, 1,2-oxazol-4-ylamino, [3-(dimethylsulphamoyl)phenyl]amino, [trans-4-(2-hydroxypropan-2-yl)cyclohexyl]amino, pyridazin-4-ylamino, (cyclopropylmethyl)(methyl)amino.

If Y represents a group of the general formula (II)



where

$o = 0, 1 \text{ or } 2$;

$p = 0, 1, 2 \text{ or } 3$;

$q = 0 \text{ or } 1$,

where the sum of o , p and $q = 1, 2 \text{ or } 3$; and

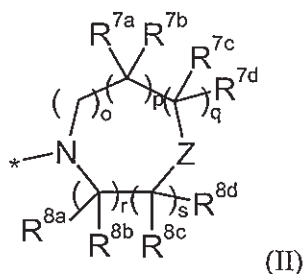
$r = 0 \text{ or } 1$;

$s = 0 \text{ or } 1$; and

Z represents CR^9R^{10} , NR^{11} , O, S or $\text{S}(=\text{O})_2$,

then 0 or 1 or 2 is preferred for p .

Here, special preference is given to compounds in which Y represents a group of the general formula (II)



in which

$o = 0$,

$p = 0 \text{ or } 1$,

$q, r \text{ and } s = 1$ and

Z represents CR^9R^{10} , NR^{11} , O, S or $\text{S}(=\text{O})_2$.

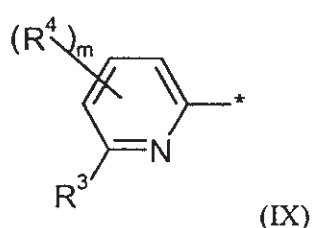
If Y represents a group of the formula (II) mentioned above, the following groups may be mentioned by way of example:

- 5 4-benzoylpiperazin-1-yl, 4-(pyrrolidin-1-yl)piperidin-1-yl, 4-(3-hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl, 4-(methoxyacetyl)piperazin-1-yl, 4-(2-hydroxypropan-2-yl)piperidin-1-yl, 4-(cyclopropylmethyl)piperazin-1-yl, 4-methylpiperazin-1-yl, 4-(cyclopropylcarbonyl)piperazin-1-yl, morpholin-4-yl, 4-(ethoxycarbonyl)piperazin-1-yl, 3-(dimethylamino)azetidin-1-yl, 3-(piperidin-1-yl)azetidin-1-yl, 2-[4-(2-hydroxy-2-methylpropyl)piperidin-1-yl, 4-hydroxy-1,4'-bipiperidin-1'-yl, 4-(dimethylamino)piperidin-1-yl, 4-(2,2,2-trifluoroethyl)piperazin-1-yl, 4-ethyl-3-oxopiperazin-1-yl, 4-(4-fluorobenzoyl)piperazin-1-yl, 4-(pyridin-2-yl)piperazin-1-yl, 4-cyclopentyl-3-oxopiperazin-1-yl, 3-oxo-4-phenylpiperazin-1-yl, 4-(2,2-dimethylpropanoyl)piperazin-1-yl, 4-(2-hydroxy-2-methylpropanoyl)piperazin-1-yl, 4-(1-phenylethyl)piperazin-1-yl]ethyl, 4-(pyridin-3-ylcarbonyl)piperazin-1-yl, 4-isonicotinoylpiperazin-1-yl, 4-(morpholin-4-ylcarbonyl)piperazin-1-yl, 4-[2-(methylamino)-2-oxoethyl]piperazin-1-yl, 4-(pyrazin-2-yl)piperazin-1-yl, 4-(1-hydroxyethyl)piperidin-1-yl, 2-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl, 6-acetyl-2,6-diazaspiro[3.3]hept-2-yl, 3-oxo-2,8-diazaspiro[4.5]dec-8-yl)ethyl, 6-methyl-2,6-diazaspiro[3.5]non-2-yl, 7-oxa-2-azaspiro[3.5]non-2-yl, 1,4'-bipiperidin-1'-yl, 2-[2-(hydroxymethyl)piperidin-1-yl, 3-(hydroxymethyl)piperidin-1-yl, 4-carbamoylpiperidin-1-yl, 3-(dimethylamino)piperidin-1-yl, 3-(morpholin-4-ylmethyl)piperidin-1-yl, 4-[(cyclopropylcarbonyl)amino]piperidin-1-yl, 4-[(5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl]piperidin-1-yl, 4-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl, 4-(4-methylpiperazin-1-yl)piperidin-1-yl, 4-[2-(morpholin-4-yl)ethyl]piperidin-1-yl, 4-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]piperidin-1-yl, 3-(pyrrolidin-1-ylmethyl)piperidin-1-yl, 4-(methylsulphonyl)piperidin-1-yl, 4-[2-oxo-2-(pyrrolidin-1-yl)ethyl]piperazin-1-yl, 4-(phenylsulphonyl)piperidin-1-yl, 4-[isonicotinoyl(methyl)amino]piperidin-1-yl, 4-[2-(isopropylamino)-2-oxoethyl]piperazin-1-yl, 4-(1,1-dioxidotetrahydrothiophen-3-yl)piperazin-1-yl, 4-[(methoxyacetyl)(methyl)amino]piperidin-1-yl, 4-(cyclohexylcarbonyl)piperazin-1-yl, 4-[2-(cyclopropylamino)-2-oxoethyl]piperazin-1-yl, 2-hydroxyethyl)piperidin-1-yl, 4-(1H-pyrrol-1-yl)piperidin-1-yl, 4-(3-hydroxypropyl)piperazin-1-yl, 4-carbamoylpiperazin-1-yl, 4-(2-oxopyrrolidin-1-yl)piperidin-1-yl, 4-(2-amino-2-oxoethyl)piperazin-1-yl, 1,1-dioxidothiomorpholin-4-yl, 4-isopropylpiperazin-1-yl, 4-(2-thienylcarbonyl)piperazin-1-yl, 2-cyclopropyl-2-oxoethyl)piperazin-1-yl, 4-[(1-methyl-1H-pyrazol-4-yl)methyl]piperazin-1-yl, 4-[(1,5-dimethyl-1H-pyrazol-3-yl)carbonyl]piperazin-1-yl, 4-(diethylcarbamoyl)piperazin-1-yl, thiomorpholin-4-yl, 4-(2-furylmethyl)piperazin-1-yl, 4-(3-thienylmethyl)piperazin-1-yl, 4'-methyl-1,4'-bipiperidin-1'-yl, 6-methyl-2,6-diazaspiro[3.3]hept-2-yl, 4-cyclopentylpiperazin-1-yl, 4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl, 4-(pyridin-4-ylmethyl)piperazin-1-yl, 4-(dimethylsulphamoyl)piperazin-1-yl, 4-(pyridin-4-yl)piperazin-1-yl, 4-(methylsulphonyl)piperazin-1-yl, {4-[2-(1H-imidazol-1-yl)ethyl]piperazin-1-yl, 4-

(diethylsulphamoyl)piperazin-1-yl, 4-(pyridin-3-yl)piperazin-1-yl, 4-(piperidin-1-ylsulphonyl)piperazin-1-yl, 4-[(1,5-dimethyl-1H-pyrazol-4-yl)sulphonyl], 4-ethylpiperazin-1-yl, 4-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]piperidin-1-yl, 4-(cyclobutylcarbonyl)piperazin-1-yl, 4-(cyclopentylcarbonyl)piperazin-1-yl, 4-[3-(methylsulphonyl)benzoyl]piperazin-1-yl and 4-[2-methoxy-5-(methylsulphonyl)benzoyl]piperazin-1-yl.

Especially preferably, Y is 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl or morpholin-4-yl.

The present invention preferably provides compounds of the general formula (I) in which W represents a group of the general formula (IX)



in which

m represents 0 and R^2 , R^0 and R^{13} all represent hydrogen and R^3 represents trifluoromethyl, ethyl, methyl, cyclopropyl, 2,2,2-trifluoro-1-hydroxyethyl or 1-hydroxyethyl; Y represents 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl or morpholin-4-yl, n represents 0 and R^1 represents cyclopropylmethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, chlorine, ethoxy or methoxy.

Here, R^1 particularly preferably represents cyclopropylmethoxy, methoxy or ethoxy.

Here, particular preference is given to compounds in which R^3 is a trifluoromethyl or a cyclopropyl radical.

The present invention also provides the following compounds:

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methyl-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

6-ethyl-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide

5-fluoro-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide

N-(2-{2-[4-(3-hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(methoxyacetyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-cyclopropylpyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-(1-hydroxyethyl)pyridine-2-carboxamide
 N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 6-methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}pyridine-2-carboxamide
 tert-butyl 3-{[4-({2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl} carbamoyl)-1,3-thiazol-2-yl]amino}azetidine-1-carboxylate
 N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide
 N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-cyclopropyl-1,3-oxazole-4-carboxamide
 tert-butyl 3-{[4-({6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamoyl)-1,3-thiazol-2-yl]amino}azetidine-1-carboxylate
 2-(azetidin-3-ylamino)-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide
 N-{6-cyano-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 6'-methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide
 5'-methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide
 4'-methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide
 6'-methoxy-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide

6'-acetamido-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide

N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6'-nitro-2,3'-bipyridine-6-carboxamide

6'-amino-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide

N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-(morpholin-4-yl)pyridine-2-carboxamide

N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide

N-{6-(benzyloxy)-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-isobutoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-isobutoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-isobutoxy-2H-indazol-5-yl)-
 6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-isobutoxy-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-{6-(cyclopropylmethoxy)-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-{6-(cyclopropylmethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-[6-(cyclopropylmethoxy)-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-
 indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[6-(cyclopropylmethoxy)-2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-2H-
 indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl}-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl}-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-[2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-(pyridin-2-ylmethoxy)-2H-
 indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-(pyridin-2-ylmethoxy)-2H-
 indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-chloro-2H-indazol-5-yl}-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-{6-chloro-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-
 2-carboxamide
 ethyl 4-[[6-chloro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-
 yl]acetyl]piperazine-1-carboxylate
 N-(6-chloro-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-[4-(3-hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-2H-
 indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-[3-(dimethylamino)azetidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-oxo-2-[3-(piperidin-1-yl)azetidin-1-yl]ethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-[4-(2-hydroxy-2-methylpropyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-
 6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-chloro-2-[2-(4-hydroxy-1,4'-bipiperidin-1'-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(dimethylamino)piperidin-1-yl]-2-oxoethyl}-6-ethoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(6-ethoxy-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-ethoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-ethoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(6-ethoxy-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-ethoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-3-methyl-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[3-(4-benzoylpiperazin-1-yl)-3-oxopropyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-2-(pyridin-3-yl)-1,3-thiazole-4-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-2-(pyridin-4-yl)-1,3-thiazole-4-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

6-(azetidin-3-ylamino)-N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)pyridine-2-carboxamide

N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(pyridin-3-yl)-1,3-thiazole-4-carboxamide

N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-pyrazol-4-yl)pyridine-2-carboxamide

6-(1,3-dimethyl-1H-pyrazol-4-yl)-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine-2-carboxamide

6-ethyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-{2-oxo-2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(4-ethyl-3-oxopiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(pyridin-4-yl)-1,3-thiazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-chloropyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-methyl-1,3-oxazole-5-carboxamide

6-amino-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-methyl-1,3-oxazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methoxypyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-cyclopropyl-1,3-oxazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(4H-1,2,4-triazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-phenyl-2H-1,2,3-triazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-5-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(trifluoromethyl)-1,3-thiazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-pyrazol-1-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1-ethyl-1H-pyrazole-3-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(4-chloro-1H-pyrazol-1-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-4-(trifluoromethyl)-1,3-thiazole-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,4'-bipyridine-6-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(3-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-1,2,4-triazol-1-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-ethoxypyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(cyclopropylmethoxy)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-ethylpyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(4-methoxyphenyl)-1,3-thiazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-bromo-1,3-thiazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(4-fluorophenyl)-1,3-thiazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-fluoropyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-bromopyridine-2-carboxamide

N-(2-{2-[4-(4-fluorobenzoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(pyridin-2-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(methoxyacetyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(4-cyclopentyl-3-oxopiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-oxo-2-(3-oxo-4-phenylpiperazin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-oxo-2-(pyridazin-4-ylamino)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxy-2-methylpropanoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(1-phenylethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(4-isonicotinoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[2-(methylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(pyrazin-2-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(1-hydroxyethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(6-acetyl-2,6-diazaspiro[3.3]hept-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-oxo-2-(3-oxo-2,8-diazaspiro[4.5]dec-8-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(6-methyl-2,6-diazaspiro[3.5]non-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(7-oxa-2-azaspiro[3.5]non-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(1,4'-bipiperidin-1'-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[2-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[3-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(4-carbamoylpiperidin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[3-(dimethylamino)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[3-(morpholin-4-ylmethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[(cyclopropylcarbonyl)amino]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[(5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[2-(morpholin-4-yl)ethyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[3-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{[3-(dimethylsulphamoyl)phenyl]amino}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(1,2-oxazol-4-ylamino)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(methylsulphonyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-oxo-2-{4-[2-oxo-2-(pyrrolidin-1-yl)ethyl]piperazin-1-yl}ethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(phenylsulphonyl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[(3-sulphamoylphenyl)amino]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[isonicotinoyl(methyl)amino]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[2-(isopropylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(1,1-dioxidotetrahydrothiophen-3-yl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[(methoxyacetyl)(methyl)amino]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

ethyl 4-{[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxylate

N-(2-{2-[4-(cyclohexylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[2-(cyclopropylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[2-(2-hydroxyethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(1H-pyrrol-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(3-hydroxypropyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

4-{[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxamide

N-(2-{2-oxo-2-[4-(2-oxopyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(2-amino-2-oxoethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-isopropylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(2-thienylcarbonyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(2-cyclopropyl-2-oxoethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[(1-methyl-1H-pyrazol-4-yl)methyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[(1,5-dimethyl-1H-pyrazol-3-yl)carbonyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N,N-diethyl-4-{[5-{[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxamide
 N-{2-[2-oxo-2-(thiomorpholin-4-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(2-furylmethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(3-thienylmethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4'-methyl-1,4'-bipiperidin-1'-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(6-methyl-2,6-diazaspiro[3.3]hept-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-cyclopentylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(dimethylsulphamoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyridin-4-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(methylsulphonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 formic acid N-[2-(2-{4-[2-(1H-imidazol-1-yl)ethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (1:1)

N-(2-{2-[4-(diethylsulphamoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(pyridin-3-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(piperidin-1-ylsulphonyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[(1,5-dimethyl-1H-pyrazol-4-yl)sulphonyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide

N-{2-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-(2-{2-[4-(dimethylamino)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide

N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-ethoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

6-cyclopropyl-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide

6-(1-hydroxyethyl)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide

6-(azetidin-3-ylamino)-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-[(azetidin-2-ylmethyl)amino]-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(3-hydroxyazetidin-1-yl)pyridine-2-carboxamide

6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide

N-[2-(2-{4-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-(6-chloro-2-{2-oxo-2-[(3R)-piperidin-3-ylamino]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-isopropoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide

N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-isopropoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-isopropoxy-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-isopropoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-isopropoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-isopropoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide

N-(2-{2-[4-(cyclobutylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(cyclopentylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[3-(methylsulphonyl)benzoyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[2-methoxy-5-(methylsulphonyl)benzoyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

6-bromo-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide

2-(4-methoxyphenyl)-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-1,3-thiazole-4-carboxamide

2-(4-fluorophenyl)-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-1,3-thiazole-4-carboxamide

N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}pyridine-2-carboxamide

N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}-6-(4H-1,2,4-triazol-4-yl)pyridine-2-carboxamide

2-bromo-N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide

N-{6-hydroxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-[6-(benzyloxy)-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl]-6-methylpyridine-2-carboxamide

6-bromo-N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{6-(benzyloxy)-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide

2-(azetidin-3-ylamino)-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide

6-acetamido-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-(dimethylamino)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide

6-(dimethylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-acetamido-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide

6-(dimethylamino)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-[3-(methylsulphonyl)phenyl]pyridine-2-carboxamide

N-{2-[1-(4-benzoylpiperazin-1-yl)-1-oxopropan-2-yl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-[6-chloro-2-(2-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]amino}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

6-(2-hydroxypropan-2-yl)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{6-chloro-2-[2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-chloro-2-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-chloro-2-[2-(2-oxa-7-azaspiro[3.5]non-7-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(6-chloro-2-{2-[4-(2-hydroxy-2-methylpropyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-methoxy-2-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 6-(difluoromethyl)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 N-{2-[2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide
 N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide
 N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(tetrahydro-2H-pyran-4-yl)-1,3-oxazole-4-carboxamide
 N-{2-[2-(1,1-dioxido-1-thia-6-azaspiro[3.3]hept-6-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-methoxy-2-[2-(2-oxa-6-azaspiro[3.3]hept-6-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(3-hydroxy-2,2-dimethylpropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 6-ethyl-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 6-isobutyl-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 methyl 2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate
 methyl 5-([(6-methylpyridin-2-yl)carbonyl]amino)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazole-6-carboxylate
 N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(pyrrolidin-1-yl)pyridine-2-carboxamide
 N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide
 6-(cyclopropylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 6-(butylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(propylamino)pyridine-2-carboxamide
 6-(isobutylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 R-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxamide

S-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxamide

6-(1-hydroxyethyl)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-(cyclopropylamino)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(propylamino)pyridine-2-carboxamide

6-(isobutylamino)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-(1-hydroxyethyl)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-4-methyl-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(benzyloxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

6-(cyclopropylamino)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide

6-(butylamino)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-[(2-methoxyethyl)amino]pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(propylamino)pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(isobutylamino)pyridine-2-carboxamide

5-fluoro-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide

N-{6-hydroxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(3-cyanopropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-(2,2,2-trifluoroethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(cyclohexylmethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

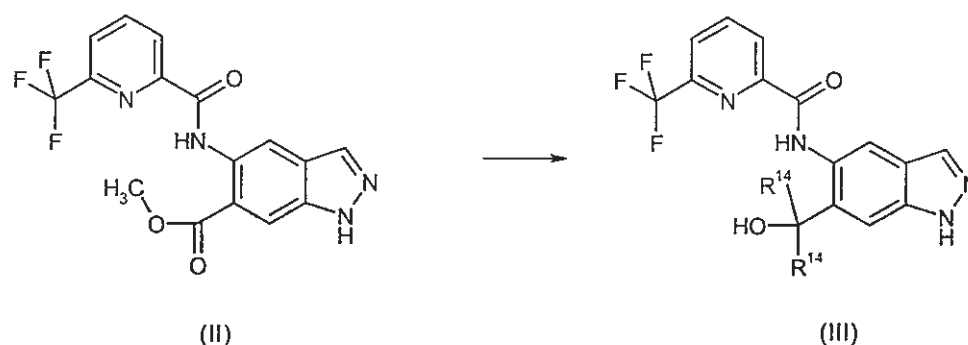
N-{6-(2,2-dimethylpropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-(tetrahydrofuran-2-ylmethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(cyclopentyloxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(cyanomethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 ({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)acetic acid
 N-{6-(cyclobutylmethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-[2-(pyrrolidin-1-yl)ethoxy]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-[2-(morpholin-4-yl)ethoxy]-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-[2-(piperidin-1-yl)ethoxy]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(3-hydroxypropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(2-hydroxypropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(2-hydroxyethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(2-methoxyethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 ethyl ({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)acetate
 methyl 4-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)butanoate
 ethyl 2-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)propanoate
 ethyl 3-methyl-2-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)butanoate
 2-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)propanoic acid
 N-{6-(2-hydroxypropan-2-yl)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-chloro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(difluoromethyl)pyridine-2-carboxamide

N-{6-chloro-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(difluoromethyl)pyridine-2-carboxamide.

The present invention further provides a process for preparing intermediates of the general formula (III) from the compound of the formula (II)

5



in which R¹⁴ is either methyl or ethyl.

The conversion of the intermediate of the formula (II) into the intermediates of the formula (III) is carried out by a Grignard reaction. Preferably, the Grignard reaction is carried out using
10 alkylmagnesium bromide. To this end, preference is given to using either methylmagnesium bromide or ethylmagnesium bromide.

Thus, the invention also provides intermediates of the general formula (II).

The invention furthermore provides intermediates of the general formula (III) in which R¹⁴
15 represents either methyl or ethyl.

The compounds of the formula (I) according to the invention act as inhibitors of IRAK4 kinase and have an unforeseeable useful pharmacological activity spectrum.

Thus, in addition to the subject matter mentioned above, the present invention also provides the use
20 of the compounds according to the invention for the treatment and/or prophylaxis of diseases in man and animals.

The compounds according to the invention are suitable for the prophylaxis and/or treatment of various disorders and disease-related states, in particular disorders mediated by TLR (except for TLR3) and/or the IL-1 receptor family and/or disorders whose pathology is mediated directly by
25 IRAK4. IRAK4-associated disorders which may be mentioned are multiple sclerosis, atherosclerosis, myocardial infarction, Alzheimer's disease, virus-induced myocarditis, gout, psoriasis and arthritis.

The compounds according to the invention can furthermore be used for the prophylaxis and/or treatment of disorders mediated by MyD88 and TLR (except for TLR3). This includes multiple sclerosis, rheumatoid arthritis, metabolic syndrome, diabetes, osteoarthritis, Sjögren syndrome, sepsis, skin disorders such as psoriasis, atopic dermatitis and acne vulgaris, pulmonary disorders
5 such as pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), interstitial lung disease (ILD), sarcoidosis and pulmonary hypertension.

By virtue of the mechanism of action of the compounds according to the invention, they are suitable for the prophylaxis and/or treatment of the TLR-mediated disorders Behçet's disease, gout,
10 endometriosis, graft rejection, lupus erythematosus, adult-onset Still's disease and chronic inflammatory bowel disorders such as ulcerative colitis and Crohn's disease.

In addition to the disorders already listed, the use of the compounds according to the invention is also suitable for the treatment and/or prevention of the following disorders: eye disorders such as ceratitis, allergic conjunctivitis, keratoconjunctivitis sicca, macular degeneration and uveitis;
15 cardiovascular disorders such as arteriosclerosis, myocardial reperfusion damage, myocardial infarction, hypertension and neurological disorders such as Alzheimer's disease, stroke and Parkinson's disease.

Furthermore, the compounds according to the invention can be used for the prophylaxis and/or treatment of pruritus and pain. By virtue of the mechanism of action of the compounds according to
20 the invention, they are suitable for the prophylaxis and/or treatment of oncological disorders such as lymphomas, chronic lymphatic leukaemia, melanomas and liver cell carcinoma and Ras-dependent tumours.

Moreover, the compounds according to the invention are suitable for the treatment and/or prevention of disorders mediated via the IL-1 receptor family. These disorders comprise CAPS
25 (cryopyrin-associated periodic syndromes) including FCAS (familial cold autoinflammatory syndrome), MWS (Muckle-Wells syndrome), NOMID (neonatal-onset multisystem inflammatory disease) and CONCA (chronic infantile, neurological, cutaneous, and articular) syndrome, FMF (familial mediterranean fever), HIDS (hyper-IgD syndrome), TRAPS (tumour necrosis factor receptor 1-associated periodic syndrome), juvenile idiopathic arthritis, adult-onset Still's disease,
30 Adamantiades-Behçet's disease, rheumatoid arthritis, osteoarthritis, keratoconjunctivitis sicca und Sjögren syndrome, multiple sclerosis, lupus erythematosus, type-1 diabetes, type-2 diabetes and the sequelae of myocardial infarction. Pulmonary disorders such as asthma, COPD, idiopathic interstitial pneumonia and ARDS, endometriosis, chronic-inflammatory bowel disorders such as Crohn's disease and ulcerative colitis are associated with dysregulation of the IL-1 receptor family
35 and suitable for therapeutic and/or prophylactic use of the compounds according to the invention.

The compounds according to the invention can furthermore be employed for the treatment and/or prevention of neurological disorders mediated by the IL-1 receptor family, such as stroke, Alzheimer's disease, stroke, skull-brain trauma, pain disorders such as cancer pain, postoperative pain, inflammation-induced and chronic pain and dermatological disorders such as psoriasis, atopic dermatitis, allergic contact dermatitis.

The treatment and/or prophylaxis of inflammatory skin disorders, cardiovascular disorders, lung disorders, eye disorders, autoimmune disorders and neoplastic disorders with the IRAK4 inhibitors according to the invention is particularly preferred.

10 The present invention further also provides a method for treatment and/or prevention of disorders, in particular the disorders mentioned above, using an effective amount of at least one of the compounds according to the invention.

In the context of the present invention, the term "treatment" or "treating" includes inhibition, retardation, checking, alleviating, attenuating, restricting, reducing, suppressing, repelling or healing of a disease, a condition, a disorder, an injury or a health problem, or the development, the course or the progression of such states and/or the symptoms of such states. The term "therapy" is understood here to be synonymous with the term "treatment".

The terms "prevention", "prophylaxis" or "preclusion" are used synonymously in the context of the present invention and refer to the avoidance or reduction of the risk of contracting, experiencing, suffering from or having a disease, a condition, a disorder, an injury or a health problem, or a development or advancement of such states and/or the symptoms of such states.

The treatment or prevention of a disease, a condition, a disorder, an injury or a health problem may be partial or complete.

25 The compounds according to the invention can be used alone or, if required, in combination with other active compounds. The present invention therefore further provides medicaments comprising at least one of the inventive compounds and one or more further active ingredients, especially for treatment and/or prevention of the aforementioned disorders. Preferred examples of active compounds suitable for combinations include:

30 in general, mention may be made of active compounds such as antibacterial (e.g. penicillins, vancomycin, ciprofloxacin), antiviral (e.g. aciclovir, oseltamivir) and antimycotic (e.g. naftifin, nystatin) substances and gamma globulins, immunomodulatory and immunosuppressive compounds such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids (e.g. prednisone, prednisolone, methylprednisolone, hydrocortisone,

betamethasone), cyclophosphamide, azathioprine and sulfasalazine; paracetamol, non-steroidal anti-inflammatory substances (NSAIDS) (aspirin, ibuprofen, naproxen, etodolac, celecoxib, colchicine).

For tumour therapy, mention may be made of immunotherapy, antiproliferative substances such as, by way of example but not by way of limitation, trastuzumab, rituximab, tositumomab, aromatase inhibitors (e.g. letrozole, anastrozole), antiestrogens (e.g. tamoxifen), topoisomerase I inhibitors (e.g. irinotecan, topotecan), topoisomerase II inhibitors (e.g. daunorubicin, idarubicin, mitoxantrone), microtubuli-active substances (e.g. vinblastine, vincristine), telomerase inhibitors (e.g. imetelstat), alkylating substances and histone deacetylase inhibitors (e.g. vorinostat, romidepsin, panobinostat); substances which modulate cell differentiation processes such as MMP inhibitors (peptide mimetics, non-peptide mimetics and tetracyclins such as, for example, marimastat, BAY 12-9566, BMS-275291, clodronate, prinomastat, doxycycline), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus, zotarolimus), antimetabolites (e.g. methotrexate, 5-fluorouracil, cladribine, fludarabine), platinum compounds (e.g. carboplatin, cisplatin, cisplatinum): anti-angiogenic compounds (e.g.. bevacizumab), antiandrogenic compounds (e.g. flutamide, nilutamide, bicalutamide, cyproterone acetate), proteasome inhibitors (e.g. bortezomib, carfilzomib, oprozomib, ONYX0914), gonadoliberein agonists and -antagonists (e.g. goserelin, triptorelin, degarelix), methionine aminopeptidase inhibitors (e.g. bengamide derivatives, TNP-470, PPI-2458), heparanase inhibitors (e.g. SST0001, PI-88); inhibitors of genetically modified ras protein (e.g. farnesyl transferase inhibitors such as lonafarnib, tipifarnib), HSP90 inhibitors (e.g.: geldamycin derivatives such as 17-allylaminogeldanamycin, 17-demethoxygeldanamycin (17AAG), 17-DMAG, retaspimycin hydrochloride, IPI-493, AUY922, BIIB028, STA-9090, KW-2478), kinesin spindle protein inhibitors (e.g. SB715992, SB743921, pentamidine/chlorpromazine), MEK (mitogen-activated protein kinase kinase) inhibitors (e.g. trametinib, BAY 86-9766, AZD6244,), kinase inhibitors (e.g.: sorafenib, regorafenib, lapatinib, sunitinib, dasatinib, cetuximab BMS-908662, GSK2118436, AMG 706), hedgehog signal inhibitors (e.g. cyclopamine, vismodegib), BTK (Bruton's tyrosine kinase) inhibitors (e.g. ibrutinib), JAK/pan-JAK (janus kinase) inhibitor (e.g. SB-1578, baricitinib, tofacitinib, pacritinib, momelotinib, ruxolitinib, VX-509, AZD-1480, TG-101348), PI3K inhibitor (e.g. BAY 1082439, BAY 80-6946, ATU-027, SF-1126, DS-7423, GSK-2126458, buparlisib, PF-4691502, BYL-719, XL-147, XL-765, idelalisib), SYK (spleen tyrosine kinase) inhibitor (e.g. fostamatinib, Excellair, PRT-062607), bisphosphonates (e.g. etridonate, clodronate, tiludronate, pamidronate, alendronic acid, ibandronate, risedronate, zoledronate), rituximab, cyclophosphamide, doxorubicin, vincristine, chlorambucil, fludarabine, dexamethasone, cladribine, prednisone.

Also suitable for tumour therapy is a combination of a non-drug therapy such as chemotherapy, radiotherapy or phototherapy which is accompanied by a drug treatment with the IRAK4 inhibitors according to the invention or which, after the non-drug tumour therapy such as chemotherapy,

radiotherapy or phototherapy has ended, are supplemented by a drug treatment with the IRAK4 inhibitors according to the invention.

In addition to those mentioned above, the IRAK4 inhibitors according to the invention can also be
5 combined with the following active compounds:
active compounds for Alzheimer therapy such as, for example, acetylcholinesterase inhibitors (e.g. donepezil, rivastigmine, galantamine, tacrine), NMDA (N-methyl-D-aspartate) receptor antagonists (e.g. memantine); L-DOPA/carbidopa (L-3,4-dihydroxyphenylalanine), COMT (catechol-O-methyl transferase) inhibitors (e.g. entacapone), dopamine agonists (e.g. ropinrol, pramipexol,
10 bromocriptine), MAO-B (monoaminooxidase-B) inhibitors (e.g. selegiline), anticholinergics (e.g. trihexyphenidyl) and NMDA antagonists (e.g. amantadin) for the treatment of Parkinson's disease; beta-interferon (IFN-beta) (e.g. IFN beta-1b, IFN beta-1a Avonex® and Betaferon®), glatiramer acetate, immunoglobulins, natalizumab, fingolimod and immunosuppressive drugs such as mitoxantrone, azathioprine and cyclophosphamide for the treatment of multiple sclerosis;
15 substances for the treatment of pulmonary disorders such as, for example, beta-2-sympathomimetics (e.g. salbutamol), anticholinergics (e.g. glycopyrronium), methylxanthines (e.g. theophylline), leukotriene receptor antagonists (e.g. montelukast), PDE-4 (phosphodiesterase type 4) inhibitors (e.g. roflumilast), methotrexate, IgE antibodies, azathioprine and cyclophosphamide, cortisol-containing preparations; substances for treating osteoarthritis such as non-steroidal anti-inflammatory substances (NSAIDs). In addition to the two therapies mentioned, methotrexate and
20 biologics for B-cell and T-cell therapy (e.g. rituximab, abatacept) may be mentioned for rheumatoid disorders such as rheumatoid arthritis and juvenile idiopathic arthritis. Neurotrophic substances such as acetylcholinesterase inhibitors (e.g. donepezil), MAO (monoaminooxidase) inhibitors (e.g. selegiline), interferons and anticonvulsive drugs (e.g. gabapentin); active
25 compounds for the treatment of cardiovascular disorders such as beta-blockers (e.g. metoprolol), ACE inhibitors (e.g. benazepril), diuretics (e.g. hydrochlorothiazide), calcium channel blockers (e.g. nifedipine), statins (e.g. simvastatin); anti-diabetics such as, for example, metformin and glibenclamide, sulphonylureas (e.g. tolbutamide) and insulin therapy for the treatment of diabetes and metabolic syndrome. Active compounds such as mesalazine, sulfasalazine, azathioprine, 6-
30 mercaptopurine or methotrexate, probiotic bacteria (Mutaflor, VSL#3®, Lactobacillus GG, Lactobacillus plantarum, L. acidophilus, L. casei, Bifidobacterium infantis 35624, Enterococcus fecium SF68, Bifidobacterium longum, Escherichia coli Nissle 1917), antibiotics such as, for example, ciprofloxacin and metronidazole, anti-diarrhoeal drugs such as, for example, loperamide, or laxatives (bisacodyl) for the treatment of chronic-inflammatory bowel disorders.
35 Immunosuppressives such as glucocorticoids and non-steroidale anti-inflammatory substances (NSAIDs), cortisone, chloroquin, cyclosporine, azathioprine, belimumab, rituximab, cyclophosphamide for the treatment of lupus erythematosus. By way of example, but not by way of limitation, calcineurin inhibitors (e.g. tacrolimus and ciclosporin), cell division inhibitors (e.g.

azathioprine, mycophenolate mofetil, mycophenolic acid, everolimus or sirolimus), rapamycin, basiliximab, daclizumab, anti-CD3 antibodies, anti-T-lymphocyte globulin/anti-lymphocyte globulin for organ transplants. Vitamin D3 analogues such as, for example, calcipotriol, tacalcitol or calcitriol, salicylic acid, urea, ciclosporine, methotrexate, efalizumab for dermatological disorders.

The present invention further provides medicaments which comprise at least one compound according to the invention, typically together with one or more inert, nontoxic, pharmaceutically suitable excipients, and the use thereof for the aforementioned purposes.

The compounds according to the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable manner, for example by the oral, parenteral, pulmonal, nasal, sublingual, lingual, buccal, rectal, dermal, transdermal, conjunctival or otic route, or as an implant or stent.

The compounds according to the invention can be administered in suitable administration forms for these administration routes.

Suitable administration forms for oral administration are those which work according to the prior art and release the compounds according to the invention rapidly and/or in a modified manner and which contain the compounds according to the invention in crystalline and/or amorphized and/or dissolved form, for example tablets (uncoated or coated tablets, for example with gastric juice-resistant or retarded-dissolution or insoluble coatings which control the release of the compound according to the invention), tablets or films/oblates which disintegrate rapidly in the oral cavity, films/lyophilizates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can be accomplished with avoidance of an absorption step (for example by an intravenous, intraarterial, intracardiac, intraspinal or intralumbar route) or with inclusion of an absorption (for example by an intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal route). Suitable administration forms for parenteral administration include injection and infusion formulations in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.

For the other administration routes, suitable examples are inhalable medicament forms (including powder inhalers, nebulizers), nasal drops, solutions or sprays, tablets, films/oblates or capsules for lingual, sublingual or buccal administration, suppositories, ear or eye preparations, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments,

creams, transdermal therapeutic systems (e.g. patches), milk, pastes, foams, sprinkling powders, implants or stents.

Preference is given to oral or parenteral administration, especially oral administration.

5 The compounds according to the invention can be converted to the administration forms mentioned. This can be accomplished in a manner known per se by mixing with inert, non-toxic, pharmaceutically suitable excipients. These excipients include carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersing or wetting agents (for example sodium dodecylsulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural
10 polymers (for example albumin), stabilizers (e.g. antioxidants, for example ascorbic acid), colorants (e.g. inorganic pigments, for example iron oxides) and flavour and/or odour correctants.

In general, it has been found to be advantageous in the case of parenteral administration to administer amounts of from about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg, of body weight to achieve effective results. In the case of oral administration the dosage is about 0.01 to
15 100 mg/kg, preferably about 0.01 to 20 mg/kg and most preferably 0.1 to 10 mg/kg of body weight.

It may nevertheless be necessary where appropriate to deviate from the stated amounts, specifically as a function of the body weight, route of administration, individual response to the active compound, nature of the preparation and time or interval over which administration takes place. Thus, in some cases less than the abovementioned minimum amount may be sufficient, while in
20 other cases the upper limit mentioned must be exceeded. In the case of administration of greater amounts, it may be advisable to divide them into several individual doses over the day.

The working examples which follow illustrate the invention. The invention is not restricted to the examples.

Unless stated otherwise, the percentages in the tests and examples which follow are percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentration data for the
25 liquid/liquid solutions are in each case based on volume.

Preparation of the compounds according to the invention

The preparation of the compounds according to the invention is illustrated by the following synthesis schemes:

5

The intermediates 0 shown in Synthesis Scheme 1 can be prepared analogously to literature and patent procedures, for example from 4-substituted 2-fluoro-5-nitrobenzaldehydes or 2-chloro-5-nitrobenzaldehydes, or they are commercially available. For the preparation, 4-substituted 2-fluoro-5-nitrobenzaldehydes are reacted with hydrazine (J. Med. Chem., 2013, 56, 4343). The resulting 5-nitroindazoles (Intermediates 0) can be reduced, for example, with palladium on carbon by hydrogenation (US201228984, WO200671940, US2003153596, EP2045253) or transfer hydrogenation (Eur. J. Med. Chem., 2010, 45, 5520) or by reaction with iron (J. Chem. Soc., 1955, 2412) or tin(II) chloride (Bioorg. Med. Chem., 2004, 12, 2115, US201215962) to give the corresponding 5-aminoindazoles. The Intermediates 1a can be converted into Intermediates 1b. The radical R^2 can be introduced by various routes, for example via alkylation with alkyl halides (Bioorg. Med. Chem., 2010, 18, 4801) or alkylsulphonates or via reductive amination by reaction with aldehydes (WO2009102498) or ketones (EP140325). Suitable for use as reducing agents are various hydride donors such as, for example, sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. Alternatively, it is also possible to acylate the anilinic nitrogen of the Intermediates 1a first using an acyl halide or a carboxylic anhydride, and then to reduce the amide using a suitable reducing agent to give the corresponding amine, which also affords Intermediates 1b. Suitable for use as reducing agents are, for example, lithium aluminium hydride (J. Am. Chem. Soc., 1954, 76, 1384), borane as complex with dimethyl sulphide (Synthetic Communications, 1991, 21, 1579) or tetrahydrofuran (Org. and Biomol. Chem., 2012, 10, 8692) or sodium bis(2-methoxyethoxy)aluminium hydride (WO200873461).

The Intermediates 1a and 1b can be provided at the anilinic nitrogen with a known protective group described in the literature (Protecting Groups, Philip J. Kocienski, 3rd Revised Edition (9th February 2005), Thieme, Chapter 8; Greene's Protective Groups in Organic Synthesis, Peter G. M. Wuts, Theodora W. Greene, 4th Edition (8th December 2006), Wiley-Interscience, Chapter 7), giving the Intermediates 2. The preferred protective group is the tert-butyloxycarbonyl group (BOC protective group). The BOC protective group is preferably introduced with di-tert-butyl dicarbonate in the presence of a base such as, for example, *N,N*-diisopropylethylamine or triethylamine.

The Intermediates 2 can be reacted with carboxylic esters halogenated in the carboxylic acid moiety such as, for example, methyl bromoacetate, ethyl bromoacetate, tert-butyl bromoacetate, benzyl bromoacetate, ethyl 3-bromopropanoate or ethyl 2-bromopropanoate under basic conditions to give a mixture of the corresponding regioisomeric 1- and 2-alkylated indazole compounds (Organic Letters, 2009, 11, 5054; WO200474284; US2009286800; WO200919167; WO201297744; J. Med. Chem., 2007, 50, 3101; Molecules, 2006, 11, 86). Here, preference is

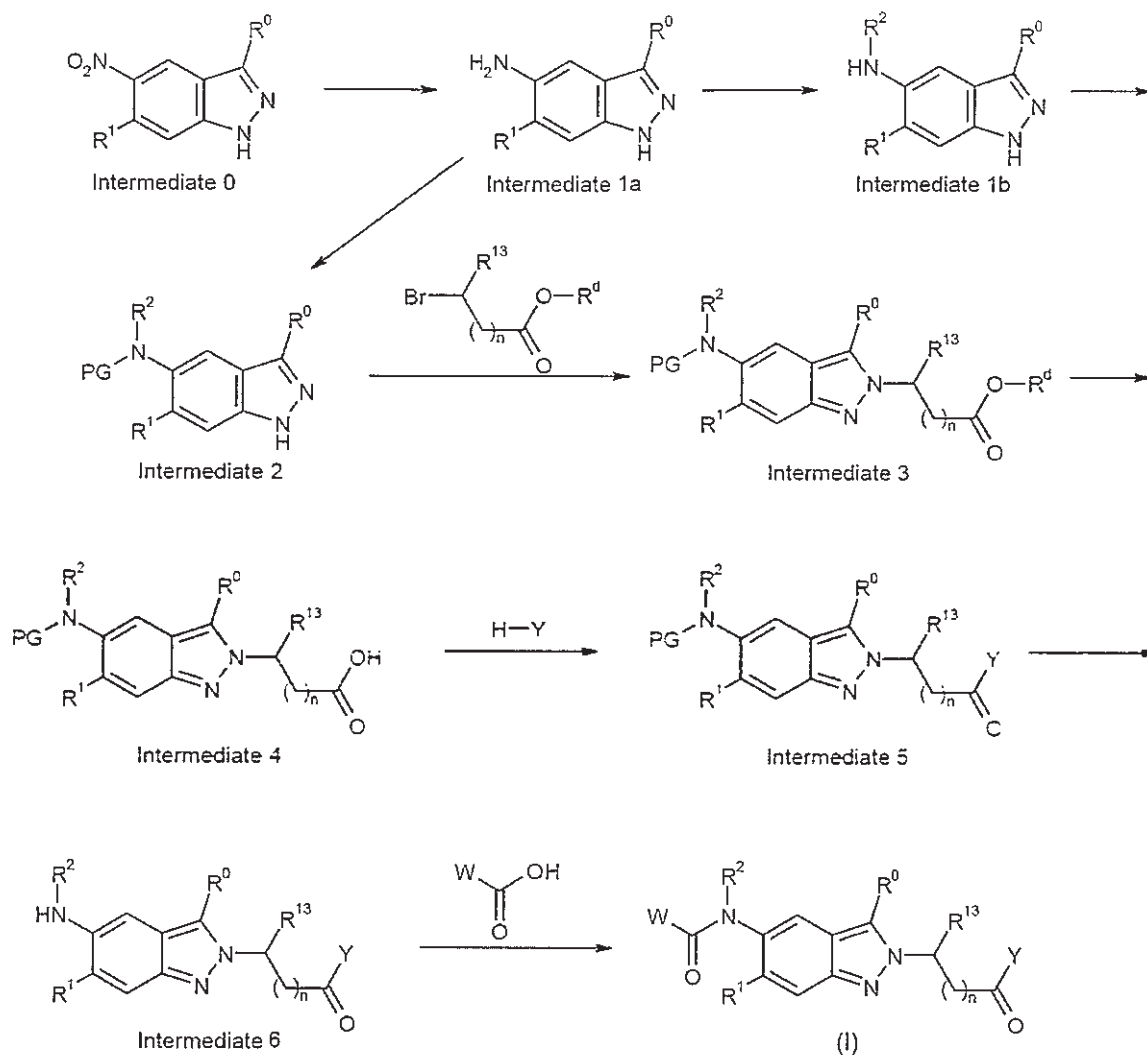
given to the reaction with *N,N*-dicyclohexylmethylamine in tetrahydrofuran or *N,N*-dimethylformamide between 25°C and 100°C (J. Org. Chem. 2006, 71, 5392). Likewise preferred is the reaction in the presence of potassium carbonate in *N,N*-dimethylformamide. The mixtures of the regioisomeric 1- and 2-alkylated indazole compounds can be separated by column chromatography or preparative HPLC, which gives access to the 2-alkylated indazole compounds (Intermediates 3).

The conversion of the Intermediates 3 into the Intermediates 4 can be carried out under known conditions (Protecting Groups, Philip J. Kocienski, 3rd Revised Edition (9th February 2005), Thieme, Chapter 6; Greene's Protective Groups in Organic Synthesis, Peter G. M. Wuts, Theodora W. Greene, 4th Edition (8th December 2006), Wiley-Interscience, Chapter 5; WO200919167 A1). Here, preference is given to hydrolysis with lithium hydroxide or lithium hydroxide monohydrate in a mixture of tetrahydrofuran and water (J. Med. Chem., 2012, 55, 1318, Bioorg. Med. Chem., 2009, 17, 7113). Optionally, ethanol or methanol may also be added.

The Intermediates 4 can be reacted with amines to give the corresponding Intermediates 5. Here, use may be made of various coupling reagents known from the literature (Amino Acids, Peptides and Proteins in Organic Chemistry. Vol.3 – Building Blocks, Catalysis and Coupling Chemistry, Andrew B. Hughes, Wiley, Chapter 12 - Peptide-Coupling Reagents, 407-442; Chem. Soc. Rev., 2009, 38, 606). The use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in combination with 1-hydroxy-1H-benzotriazole hydrate is preferred (WO2012107475; Bioorg. Med. Chem. Lett., 2008, 18, 2093).

The Intermediates 5 obtained in this manner can be converted into Intermediates 6. The removal of the protective group at the anilinic nitrogen can be carried out under known reaction conditions (Protecting Groups, Philip J. Kocienski, 3rd Revised Edition (9th February 2005), Thieme, Chapter 8; Greene's Protective Groups in Organic Synthesis, Peter G. M. Wuts, Theodora W. Greene, 4th Edition (8th December 2006), Wiley-Interscience, Chapter 7). Preferred is the removal of the tert-butyloxycarbonyl protective group with trifluoroacetic acid in dichloromethane (Bioorg. Med. Chem. Lett., 2011, 21, 6274; J. Med. Chem., 2008, 51, 1904; WO201353051).

Using the coupling reagents known from the literature which were already mentioned for the preparation of the Intermediates 5, the Intermediates 6 can be reacted with heterocyclic carboxylic acids to give compounds of the general formula (I). Here, too, preference is given to using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in combination with 1-hydroxy-1H-benzotriazole hydrate (US2006194801).



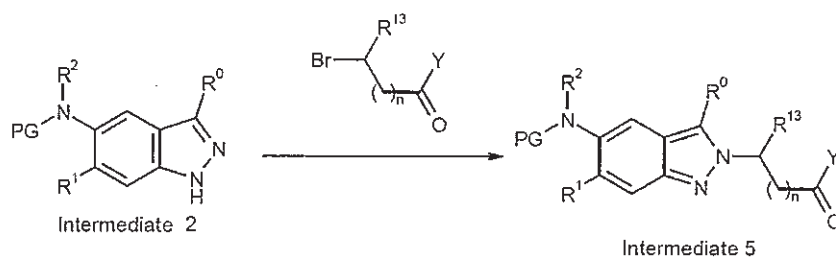
Synthesis Scheme 1:

(PG means protective group; R^d represents C_1 - C_6 -alkyl or benzyl.)

5

Alternatively, the Intermediates 5 can also be obtained directly from Intermediates 2, as illustrated in Synthesis Scheme 1a. The reagents used are halogenated carboxamides. The reaction conditions are identical to those of the preparation of Intermediate 3 from Intermediate 2. Preference is given to the reaction with 2-bromoacetamides in the presence of the base *N,N*-dicyclohexylmethylamine.

10 Particular preference is given to the reaction with 2-bromo-1-(morpholin-4-yl)ethanone.



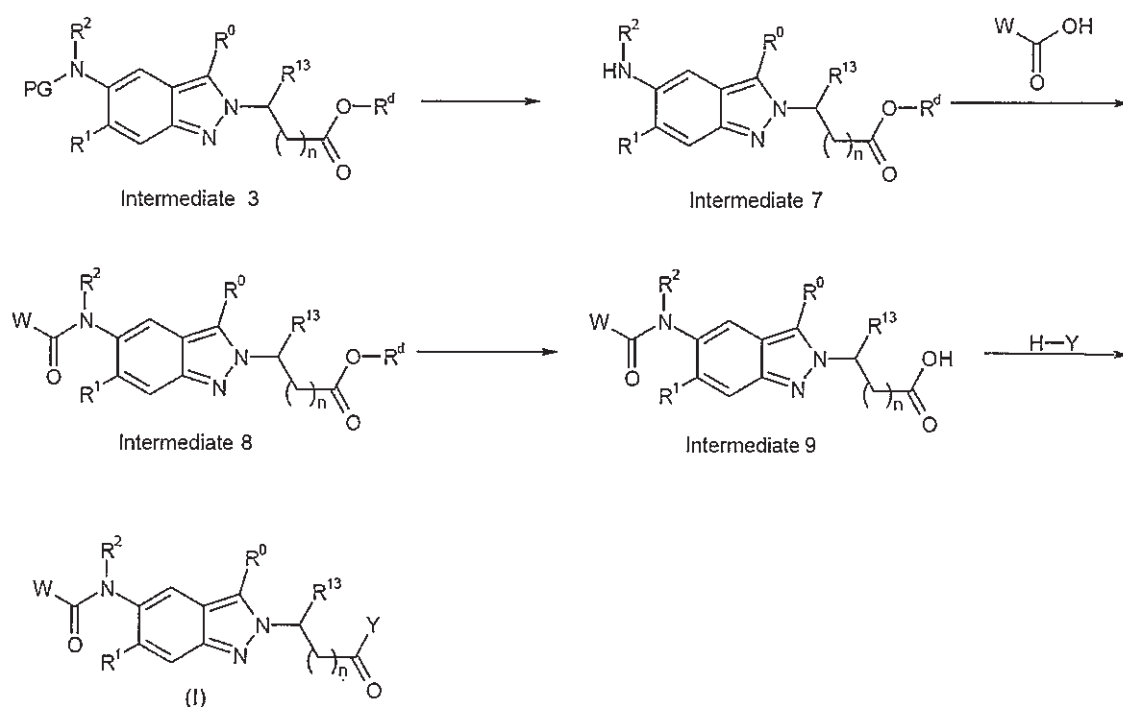
Synthesis Scheme 1a:

- 5 As illustrated in Synthesis Scheme 2, the Intermediates 3 can also be converted first into the Intermediates 7 (J. Am. Chem. Soc., 2009, 131, 3342; EP2522657). If PG denotes tert-butyloxycarbonyl, it is preferred to use trifluoroacetic acid in dichloromethane (WO201062171). The Intermediates 7 can be reacted with heterocyclic carboxylic acids to give the Intermediates 8. Here, as in Synthesis Scheme 1, coupling reagents are used. The preferred coupling reagent used is
- 10 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in combination with 1-hydroxy-1H-benzotriazole hydrate.

The Intermediates 8 can be hydrolysed analogously to Synthesis Scheme 1, the hydrolysis with lithium hydroxide or lithium hydroxide monohydrate in a mixture of tetrahydrofuran and water being preferred. Optionally, ethanol or methanol may also be added.

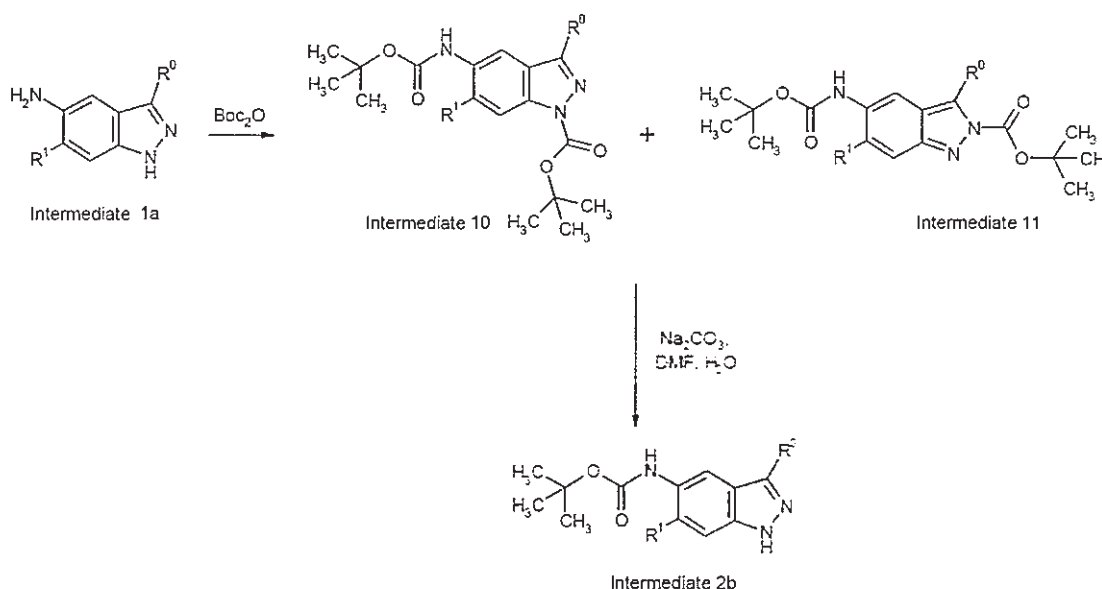
- 15 The Intermediates 9 formed in this manner can be converted into the compounds of the general formula (I). The coupling with amines is carried out analogously to Synthesis Scheme 1 using coupling reagents known from the literature. The use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in combination with 1-hydroxy-1H-benzotriazole hydrate is preferred.

20

Synthesis Scheme 2:

(PG means protective group; R^d represents C₁-C₆-alkyl or benzyl.)

The Intermediates 2b can be prepared as illustrated in Synthesis Scheme 3. Reaction of the Intermediates 1a with an excess of di-tert-butyl dicarbonate gives a mixture of Intermediates 10 and 11 which can be hydrolysed selectively at positions 1 and 2, respectively, thereby giving the Intermediates 2b. The hydrolysis is preferably carried out using sodium carbonate in a mixture of *N,N*-dimethylformamide and water between 50°C and 100°C for 12 - 36 hours (Tet. Lett., 2006, 47, 8575).



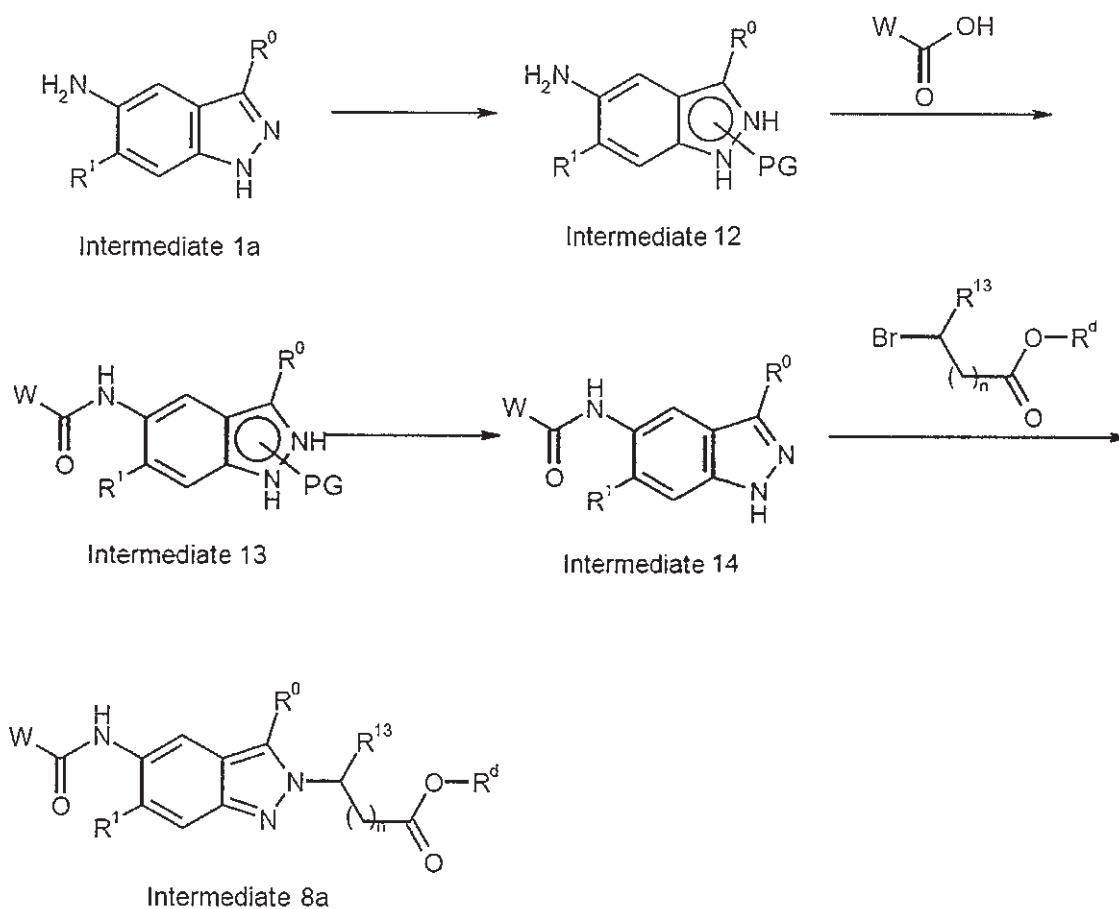
Synthesis Scheme 3:

The Intermediates 8a can be prepared as described in Synthesis Scheme 4 from Intermediates 1a for example with the meaning R¹ = Cl in a multistep synthesis sequence. To this end, initially one of the nitrogen atoms in the indazole ring is protected, preferably the nitrogen atom in position 1 (WO200958924). The preferred protective group is the tert-butyloxycarbonyl group (BOC protective group). The BOC protective group is preferably introduced with di-tert-butyl dicarbonate in the presence of a base such as, for example, *N,N*-diisopropylethylamine or triethylamine.

Under the coupling conditions mentioned above, the Intermediates 12 can be acylated with heterocyclic carboxylic acids, thus giving the Intermediates 13. The use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in combination with 1-hydroxy-1H-benzotriazole hydrate is preferred.

The protective group of the Intermediates 13 at the indazole ring can be removed under reaction conditions known from the literature (Protecting Groups, Philip J. Kocienski, 3rd Revised Edition (9th February 2005), Thieme, Chapter 8; Greene's Protective Groups in Organic Synthesis, Peter G. M. Wuts, Theodora W. Greene, 4th Edition (8th December 2006), Wiley-Interscience, Chapter 7). Preferred is the use of trifluoroacetic acid in dichloromethane for the removal of a BOC protective group. The Intermediates 14 can be converted into a mixture of the corresponding regioisomeric 1- and 2-alkylated indazole compounds. Separation of the regioisomers gives the desired 2-alkylated indazole derivatives (Intermediates 8a) (J. Org. Chem. 2006, 71, 5392). Here, the same reaction

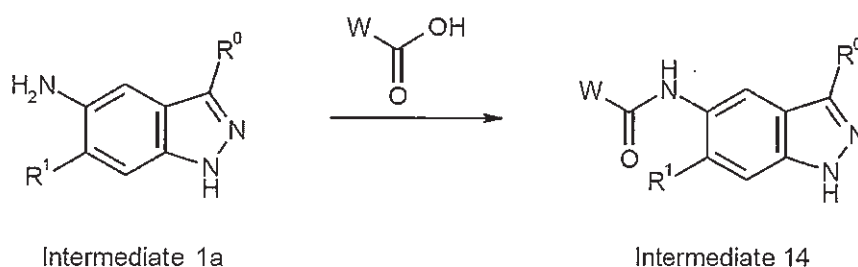
conditions as for the preparation of the Intermediates 3 from the Intermediates 2 are employed (Synthesis Scheme 1). The use of *N,N*-dicyclohexylmethylamine in tetrahydrofuran or *N,N*-dimethylformamide is preferred.



5 Synthesis Scheme 4:

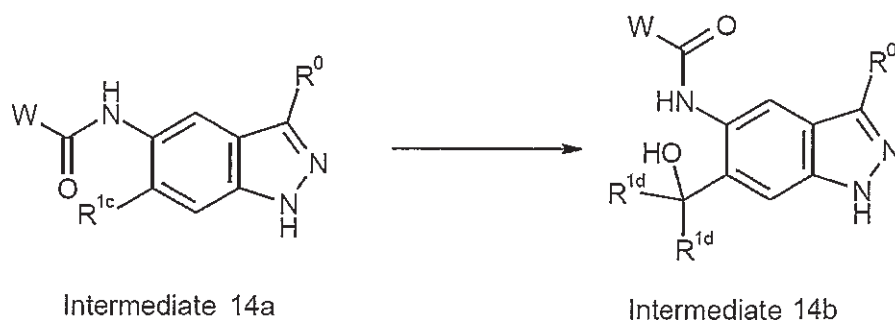
(PG means protective group; R^d represents C₁-C₆-alkyl or benzyl.)

In some cases, the Intermediates 14 can also be prepared as described in Synthesis Scheme 5. The Intermediates 1a are acylated regioselectively at the anilic nitrogen with heterocyclic carboxylic acids. Here, the coupling reagents mentioned above are employed. Preference is given to the combination of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxy-1H-benzotriazole hydrate using the base triethylamine (EP1403255; WO2005 82890; US2006194801; Bioorg. Med. Chem. Lett., 2007, 17, 3550).



Synthesis Scheme 5:

According to Synthesis Scheme 5-1, it is possible to obtain, from Intermediates 14a where $R^{1c} = -CO_2Me$ or $-CO_2Et$, preferably $-CO_2Me$, in a Grignard reaction (Organikum, 19th Edition, Johann Ambrosius Barth Leipzig, pp. 515 - 520) by using methylmagnesium bromide, methylmagnesium chloride, ethylmagnesium bromide or ethylmagnesium chloride, Intermediates 14b where $R^{1d} = -C(CH_3)_2OH$ or $-C(CH_2CH_3)_2OH$. The reaction with methylmagnesium bromide is preferred to obtain Intermediates where $R^{1d} = -C(CH_3)_2OH$. The intermediates of the formula 14b can then be converted analogously to Sythesis Scheme 4 and then according to Synthesis Schema 2 into compounds according to the invention where $R^1 = -C(CH_3)_2OH$ or $-C(CH_2CH_3)_2OH$. Alternatively and preferably, the Intermediates 14b can also be converted by reaction with 2-chloroacetamides or 2-bromoacetamides into compounds of the formula (I) according to the invention where $R^1 = -C(CH_3)_2OH$ or $-C(CH_2CH_3)_2OH$. Here, the same reaction conditions as in Synthesis Scheme 1a may be employed. The use of N,N-dicyclohexylmethylamine in tetrahydrofuran or N,N-dimethylformamide is preferred. Particular preference is given to the use of 2-bromo-1-(morpholin-4-yl)ethanone.



20 Synthesis Scheme 5-1:

(R^{1c} represents $-CO_2Me$ or $-CO_2Et$)

R^{1d} represents methyl or ethyl)

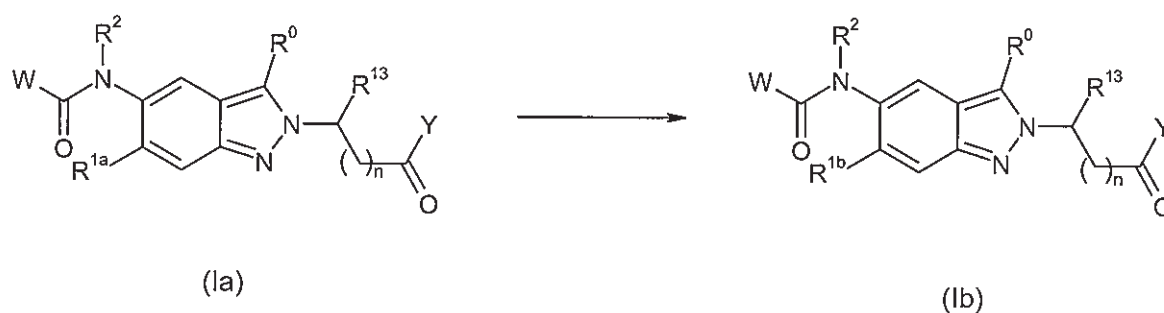
A subset of the compounds according to the invention can be prepared as illustrated in Scheme 6. The starting materials of the general formula (Ia) are reacted in the presence of a palladium catalyst with an organometallic compound which transfers the radical R^{1b} . The radical R^{1b} represents C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl, heterocycloalkyl, C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl, heterocycloalkyl- C_1 - C_4 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, aryl, 5- to 10-membered heteroaryl, aryl- C_1 - C_4 -alkyl or 5- or 6-membered heteroaryl- C_1 - C_4 -alkyl which may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of protected hydroxy, halogen, cyano, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, protected NH_2 , protected NHR^a or $N(R^a)R^b$. Suitable for the

reaction are the known coupling reactions using organomagnesium compounds (Kumada reaction: J. Organomet. Chem., 2002, 653, 288; Handbook of Organopalladium Chemistry for Organic Synthesis, 2002, 1, 335; Top. Curr. Chem., 2002, 219, 1), organoboron compounds (Suzuki reaction: Pure Appl. Chem., 1985, 57, 1749; Chem. Rev., 1995, 95, 2457; Advances in Metal-Organic Chemistry, 1998, 6, 187; Angew. Chem., Int. Ed. Engl., 2004, 43, 2201, Top. Curr. Chem., 2002, Vol. 219, 248), organotin compounds (Stille reaction: Angew. Chem., 1986, 98, 504; Synthesis, 1992, 803; Org. React., 1997, 50, 1; Angew. Chem., Int. Ed. Engl., 2004, 43, 4704; J. Organomet. Chem., 2002, 653, 50) or organozinc compounds (Negishi reaction: Acc. Chem. Res., 1982, 15, 340; Metal-Catalyzed Cross-coupling Reactions, F. Diedrich, P. J. Stang, Wiley-VCH, 1998, 1; Aust. J. Chem. 2004, 57, 107; Handbook of Organopalladium Chemistry for Organic Synthesis, E.-I. Negishi, Y. Dumond, 2002, Vol. 1, 767) in the presence of a palladium compound (e.g. palladium(II) acetate, tetrakis(triphenylphosphine)palladium, allylchloro(1,3-bis(2,6-di-isopropylphenyl)imidazol-2-ylidene)palladium, tris(dibenzylideneacetone)dipalladium(0), a ligand (e.g. 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl, 1,1'-bis(di-o-tolylphosphino)ferrocene) in a solvent (e.g. N,N-dimethylformamide, toluene, xylene, tetrahydrofuran, dioxane, dimethoxyethane, tert-butyl methyl ether) using a base (e.g. sodium tert-butoxide, potassium tert-butoxide, sodium hydride, potassium hydride, potassium hexamethyldisilazide, tripotassium phosphate, caesium carbonate) at a temperature of 40-200°C. The temperature depends *inter alia* on the solvent. Alternatively to the palladium compounds mentioned above, it is also possible to use other palladium compounds which are so-called pre-catalysts (e.g. chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) or (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) chloride). Preferred for use in the reactions are tetrakis(triphenylphosphine)palladium, palladium(II) acetate with 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene or allylchloro(1,3-bis(2,6-di-isopropylphenyl)imidazol-2-ylidene)palladium. The use of tetrakis(triphenylphosphine)palladium is particularly preferred. Here, the radicals R^a and R^b can assume the definitions described for the general formula (I). In the case that the electrophiles carry protected hydroxyl functions or protected NH₂ or NHR^a, this protective group can be removed again in an additional synthesis step by a customary literature process (Protecting Groups, Philip J. Kocienski, 3rd Revised Edition (9th February 2005), Thieme; Greene's Protective Groups in Organic Synthesis, Peter G. M. Wuts, Theodora W. Greene, 4th Edition (8th December 2006), Wiley-Interscience).

In the case that R^{1b} represents cyanide, the reaction of the starting materials of the general formula (Ia) can be carried out in the presence of one of the palladium compounds described above and in the presence of zinc cyanide in one of the solvents described above at a temperature of 40 – 200°C.

Here, heating of the reaction mixture may be either by thermal heating or in the microwave. Particular preference is given here to using tetrakis(triphenylphosphine)palladium in *N,N*-dimethylformamide at a temperature of 150°C in the microwave.

In addition, the starting materials of the general formula (Ia) can also be reacted with primary or secondary amines or with alkoxides (Buchwald-Hartwig reaction: Chemtracts: Inorg. Chem., 1996, 8, 1; Chem. Org. Chem. 1997, 1, 287; Synlett 1997, 329; Angew. Chem., Int. Ed. Engl., 1998, 37, 2046; Pure Appl. Chem. 1999, 71, 1425; Top. Curr. Chem. 2002, 219, 131), which allows compounds of the general formula (Ib) where $R^{1b} = \text{NHR}^a$, NR^aR^b , $\text{NHC}(=\text{O})\text{R}^a$ or OR^a to be obtained. The reaction is carried out in the presence of a palladium compound (e.g. palladium(II) acetate, tris(dibenzylideneacetone)dipalladium(0)), a ligand (e.g. 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl, 1,1'-bis(di-*o*-tolylphosphino)ferrocene) in a solvent (e.g. *N,N*-dimethylformamide, toluene, xylene, tetrahydrofuran, dioxane, dimethoxyethane, tert-butyl methyl ether) using a base (e.g. sodium tert-butoxide, potassium tert-butoxide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, potassium carbonate, caesium carbonate) at a temperature of 40-200°C. The temperature depends *inter alia* on the solvent. Alternatively to the palladium compounds mentioned above, it is also possible to use other palladium compounds which are so-called pre-catalysts (e.g. chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II) or (2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II) chloride). Here, the reaction with the last-mentioned pre-catalysts is preferred.



25 Synthesis Scheme 6:

(R^{1a} represents chlorine, bromine, iodine, [(trifluoromethyl)sulphonyl]oxy or [(nonafluorobutyl)sulphonyl]oxy.

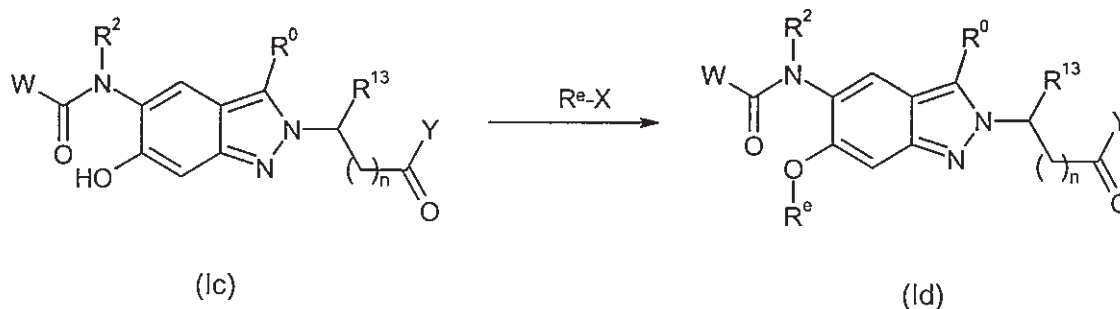
R^{1b} represents a) C_1 - C_6 -alkyl, C_3 - C_8 -cycloalkyl, heterocycloalkyl, C_3 - C_8 -cycloalkyl- C_1 - C_4 -alkyl, heterocycloalkyl- C_1 - C_4 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, aryl, 5- to 10-membered heteroaryl, aryl- C_1 - C_4 -alkyl or 5- or 6-membered heteroaryl- C_1 - C_4 -alkyl which may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of protected

hydroxy, halogen, cyano, $C(=O)OR^a$, $S(=O)_2-C_1-C_6$ -alkyl, protected NH_2 , protected NHR^a or $N(R^a)R^b$,

b) cyanide, c) NHR^a , NR^aR^b , $NHC(=O)R^a$ or OR^a .)

- 5 A subset of the compounds according to the invention can be prepared as shown in Synthesis Scheme 7 by reacting starting materials of the general formula (Ic) with electrophiles R^c-X such as alkyl halides, alkylsulphonates, aryl halides, arylsulphonates, hetaryl halides or hetarylsulphonates. X has the meaning chlorine, bromine, iodine, $O(S=O)_2CH_3$, $O(S=O)_2C_6H_4CH_3$ or $O(S=O)_2CF_3$, with X preferably being chlorine, bromine or iodine and particularly preferably bromine.
- 10 R^c represents C_1-C_6 -alkyl, C_3-C_8 -cycloalkyl, heterocycloalkyl, C_3-C_8 -cycloalkyl- C_1-C_4 -alkyl, heterocycloalkyl- C_1-C_4 -alkyl, C_2-C_6 -alkenyl, C_2-C_6 -alkynyl, aryl, 5- to 10-membered heteroaryl, aryl- C_1-C_4 -alkyl or 5- or 6-membered heteroaryl- C_1-C_4 -alkyl which may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of hydroxy (optionally protected), halogen, cyano, $C(=O)OR^a$, $S(=O)_2-C_1-C_6$ -alkyl, protected NH_2 , protected
- 15 NHR^a or NR^aR^b . Here, the radicals R^a and R^b can assume the definitions described for the general formula (I). In the case that the electrophiles carry protected hydroxyl functions or protected NH_2 or NHR^a , this protective group can be removed again in an additional synthesis step by a customary literature process (Protecting Groups, Philip J. Kocienski, 3rd Revised Edition (9th February 2005), Thieme; Greene's Protective Groups in Organic Synthesis, Peter G. M. Wuts, Theodora W. Greene,
- 20 4th Edition (8th December 2006), Wiley-Interscience). If R^c-X has the meaning alkyl halide or alkylsulphonate, it is possible to use suitable bases such as, for example, sodium tert-butoxide, potassium tert-butoxide, sodium hydride, potassium hydride, potassium hexamethyldisilazide, tripotassium phosphate, sodium carbonate, potassium carbonate, caesium carbonate (WO2003101379 A2; Bioor. Med. Chem., 2008, 16, 1966; J. Med. Chem., 2012, 55, 7141).
- 25 Furthermore, it is possible to use further additives such as, for example, sodium iodide, potassium iodide, caesium iodide for the alkylation. The reaction with activated aryl halides, arylsulphonates, hetaryl halides or hetarylsulphonates (electron-withdrawing radicals or heteroatoms in the ortho- and/or para-position to the halide or sulphonate) can take place by nucleophilic aromatic substitution at the activated aryl halide, arylsulphonate, hetaryl halide or hetarylsulphonate, it being
- 30 likewise possible to employ suitable bases such as, for example, sodium tert-butoxide, potassium tert-butoxide, sodium hydride, potassium hydride, potassium hexamethyldisilazide, tripotassium phosphate, sodium carbonate, potassium carbonate or caesium carbonate for the reaction (WO200795124 A2, EP2103620 A1). Furthermore, the arylation or heteroarylation of the starting materials of the general formula (Ic) in Synthesis Scheme 7 can be carried out by reaction with aryl
- 35 halides, arylsulphonates, hetaryl halides or hetarylsulphonates using a copper-based transition metal catalyst known from the literature (e.g. copper(I) iodide, copper(I) oxide, copper(II) acetate) (Russ. Chem. Rev., 1974, 43, 1443; Tetrahedron, 2000, 56, 5054; Synlett, 2003, 2428; Angew. Chem., Int. Ed. Engl., 2003, 42, 5400; Angew. Chem., Int. Ed. Engl., 2004, 43, 1043) or palladium

(e.g. palladium(II) acetate, tris(dibenzylideneacetone)dipalladium(0)) (Acc. Chem. Res., 1998, 31, 852; Angew. Chem., Int. Ed. Engl., 1998, 37, 2046; Top. Cur. Chem., 2002, 219, 131) in the presence of a suitable base (e.g. sodium tert-butoxide, potassium tert-butoxide, sodium hydride, potassium hydride, potassium hexamethyldisilazide, tripotassium phosphate, sodium carbonate, potassium carbonate, caesium carbonate) and a ligand (e.g. 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, 1,1'-bis(di-o-tolylphosphino)ferrocene, 1,3-di-tert-butyl-2-chloro-1,3,2-diazaphospholidine, 2'-(dicyclohexylphosphino)-N,N-dimethylbiphenyl-2-amine) in a solvent (e.g. *N,N*-dimethylformamide, toluene, xylene, tetrahydrofuran, dioxane, dimethoxyethane, tert-butyl methyl ether) at a temperature of 40-200°C. Preferably, the 6-hydroxyindazoles are reacted with alkyl halides using the base potassium carbonate and the solvent *N,N*-dimethylformamide. The reactions are preferably carried out at 70 - 150°C in the microwave over a period of 1 - 24 hours.



Synthesis Scheme 7:

(R^e represents $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_3\text{-C}_8\text{-cycloalkyl}$, heterocycloalkyl, $\text{C}_3\text{-C}_8\text{-cycloalkyl-C}_1\text{-C}_4\text{-alkyl}$, heterocycloalkyl- $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_2\text{-C}_6\text{-alkenyl}$, $\text{C}_2\text{-C}_6\text{-alkynyl}$, aryl, 5- to 10-membered heteroaryl, aryl- $\text{C}_1\text{-C}_4\text{-alkyl}$ or 5- or 6-membered heteroaryl- $\text{C}_1\text{-C}_4\text{-alkyl}$ which may optionally be mono- or polysubstituted by identical or different substituents from the group consisting of hydroxy (optionally protected), halogen, cyano, $\text{C}(=\text{O})\text{OR}^a$, $\text{S}(=\text{O})_2\text{-C}_1\text{-C}_6\text{-alkyl}$, protected NH_2 , protected NHR^a or NR^aR^b .)

The pyridinecarboxylic acids (Intermediate 19) used as starting material for the synthesis of a subset of the compounds according to the invention are commercially available or can be prepared by routes known from the literature in accordance with Synthesis Scheme 8. Some of the Intermediates 19 can be prepared from carboxylic esters (Intermediate 17) by hydrolysis or - in the case that it is a tert-butyl ester - by reaction with an acid such as, for example, hydrogen chloride or trifluoroacetic acid. The Intermediates 19 may optionally be produced as salts (for example as potassium salt). The Intermediates 17 are commercially available, can be prepared by routes known from the literature or are available from the Intermediates 16 which, as X^1 , carry chlorine, bromine

or iodine, by reaction in a carbon monoxide atmosphere, optionally under superatmospheric pressure in the presence of a phosphine ligand such as, for example, 1,3-bis(diphenylphosphino)propane, a palladium compound such as, for example, palladium(II) acetate and a base such as, for example, triethylamine with addition of ethanol or methanol in a solvent
 5 such as, for example, dimethyl sulphoxide.

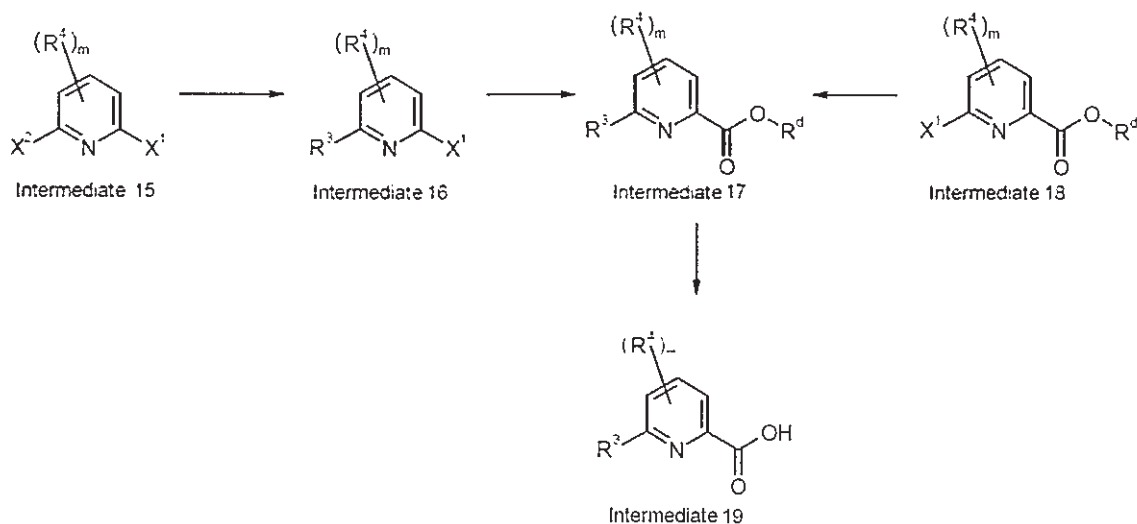
Here, the radical R^3 represents cyano, substituted or unsubstituted C_1 - C_6 -alkyl, substituted or unsubstituted C_1 - C_6 -alkoxy, substituted or unsubstituted C_3 - C_6 -cycloalkyl, heterocycloalkyl, C_5 - C_{11} -spirocycloalkyl, substituted or unsubstituted C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, substituted or unsubstituted aryl, 5- to 10-membered heteroaryl, NH_2 , NHR^a , $N(R^a)R^b$ or $N(H)C(=O)R^a$.

10 In the special case that R^3 has the meaning substituted or unsubstituted C_1 - C_6 -alkoxy, NH_2 , NHR^a or $N(R^a)R^b$, R^3 can be introduced by heating the corresponding bishalogenated Intermediates 15 in which X^1 and X^2 independently of one another represent chlorine, bromine or iodine with alcohols or amines, which yields the Intermediates 16.

If R^3 represents substituted or unsubstituted C_1 - C_6 -alkyl (Eur. J. of Org. Chem., 2002, 327),
 15 substituted or unsubstituted C_3 - C_6 -cycloalkyl, heterocycloalkyl, C_5 - C_{11} -spirocycloalkyl or substituted or unsubstituted C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, R^3 can be introduced by reacting the Intermediates 15 with the appropriate organometal compounds. Suitable for this purpose are organolithium compounds (Green Chemistry, 2011, 13, 1110), organomagnesium compounds or organocopper compounds (Angew. Chem., 2013, 125, 6397). In the case of amino- or hydroxy-substituted radicals R^3 , the functional group in the organometal compound carries a protective
 20 group which is known in the literature and, according to the opinion of the person skilled in the art, suitable (Protecting Groups, Philip J. Kocienski, 3rd Revised Edition (9th February 2005), Thieme; Greene's Protective Groups in Organic Synthesis, Peter G. M. Wuts, Theodora W. Greene, 4th Edition (8th December 2006), Wiley-Interscience). This protective group can be removed again in
 25 an additional synthesis step by a customary literature process (Protecting Groups, Philip J. Kocienski, 3rd Revised Edition (9th February 2005), Thieme; Greene's Protective Groups in Organic Synthesis, Peter G. M. Wuts, Theodora W. Greene, 4th Edition (8th December 2006), Wiley-Interscience). Alternatively, the radical R^3 can also be introduced via a palladium-catalysed Suzuki coupling (Pure Appl. Chem., 1985, 57, 1749; Chem. Rev., 1995, 95, 2457; Advances in
 30 Metal-Organic Chemistry, 1998, 6, 187; Angew. Chem., Int. Ed. Engl., 2004, 43, 2201, Top. Curr. Chem., 2002, Vol. 219, 248) if R^3 is substituted or unsubstituted aryl or a 5- to 10-membered heteroaryl. Here, R^3 is introduced via a corresponding organoboron compound in the presence of a palladium compound (e.g. palladium(II) acetate, tris(dibenzylideneacetone)dipalladium(0), tetrakis(triphenylphosphine)palladium), a ligand (e.g. 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl,
 35 triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, 2-(dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl, 1,1'-bis(di-*o*-tolylphosphino)ferrocene) in a solvent (e.g. *N,N*-dimethylformamide, acetonitrile, toluene, xylene,

tetrahydrofuran, dioxane, dimethoxyethane, methanol, ethanol, water) using a base (e.g. sodium carbonate, potassium carbonate, caesium carbonate, tripotassium phosphate, potassium fluoride, sodium hydroxide) and optionally added lithium chloride at a temperature of 25 - 200°C. The use of tetrakis(triphenylphosphine)palladium is preferred.

- 5 Alternatively, the Intermediates 17 can also be prepared from Intermediates 18. To introduce the radical R^3 , the above-described Suzuki reaction with appropriate organoboron compounds is employed.



10 Synthesis Scheme 8:

(X^1 represents chlorine, bromine or iodine.

X^2 represents chlorine, bromine or iodine.

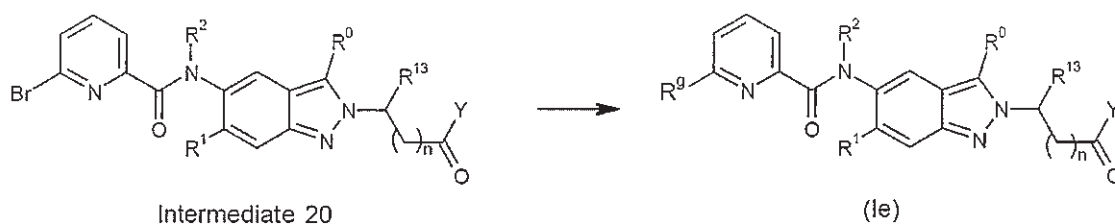
R^d represents C_1 - C_6 -alkyl or benzyl.

R^3 , R^4 and m have the definitions described in the general formula (I).)

15

In accordance with Synthesis Scheme 9, Intermediates 20, which can be prepared according to Synthesis Scheme 2, can be reacted in a Negishi reaction (Acc. Chem. Res., 1982, 15, 340; Metal-Catalyzed Cross-coupling Reactions, F. Diedrich, P. J. Stang, Wiley-VCH, 1998, 1; Aust. J. Chem. 2004, 57, 107; Handbook of Organopalladium Chemistry for Organic Synthesis, E.-I. Negishi, Y. Dumond, 2002, Vol. 1, 767) with primary and secondary alkylzinc reagents in the presence of a palladium catalyst, which allows the preparation of a subset (Ie) of the compounds according to the invention where R^8 = primary or secondary C_1 - C_6 -alkyl. Preference is given to the reaction with diethylzinc or 2-methylpropylzinc bromide.

25



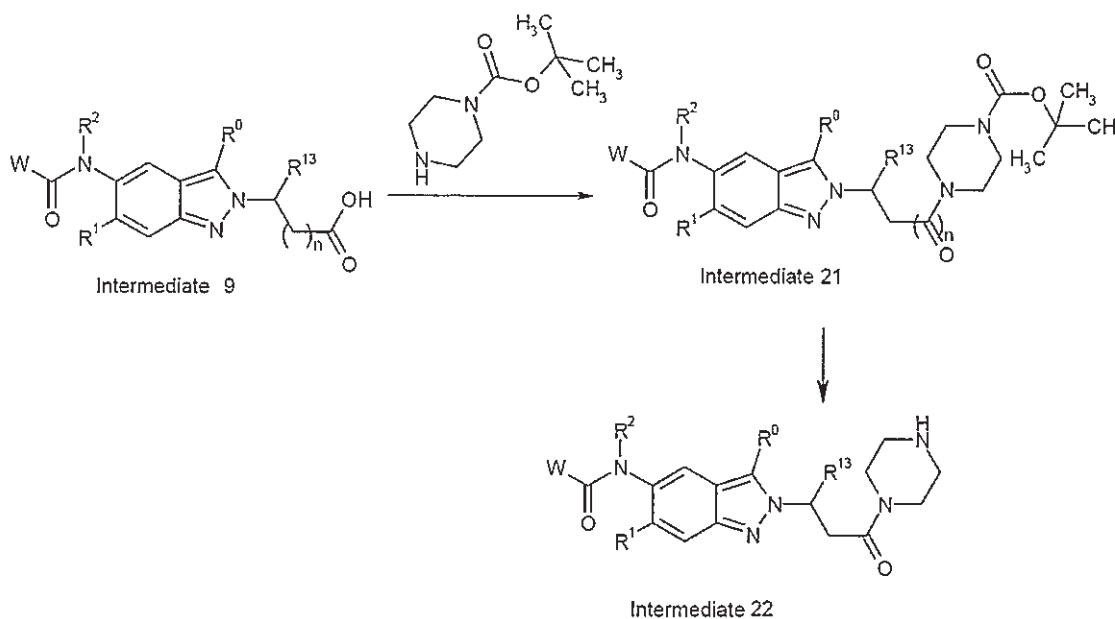
Synthesis Scheme 9:

(R^g represents primary or secondary C₁-C₆-alkyl)

5

Further intermediates can be obtained according to Synthesis Scheme 10: The Intermediates 9 can be reacted in an amide coupling as described in Synthesis Scheme 1 to give the Intermediates 21. The use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in combination with 1-hydroxy-1H-benzotriazole hydrate is preferred. Intermediates 21 can then be converted by reaction with trifluoroacetic acid into Intermediates 22 which, in an amide coupling reaction, can be reacted analogously to the methods described in Synthesis Scheme 1 to afford Exemplary Compounds.

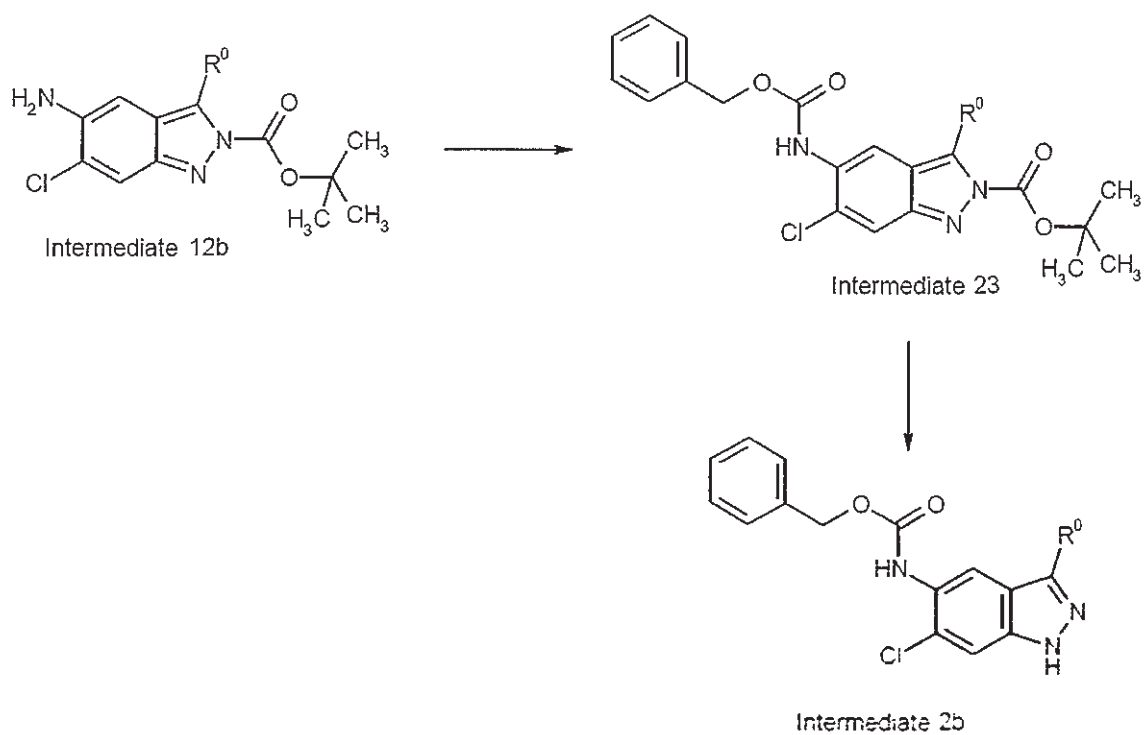
10



Synthesis Scheme 10:

Intermediates of type 2b can be obtained according to Synthesis Scheme 11: Intermediates 12b are reacted with benzyl carbonochloridate and N-ethyl-N-isopropylpropane-2-amine in THF to give Intermediates 23. The reaction with trifluoroacetic acid in dichloromethane then leads to the Intermediates 2b which are reacted further according to Synthesis Scheme 1 to give the compounds according to the invention.

20



Synthesis Scheme 11:

Abbreviations

DMF	<i>N,N</i> -dimethylformamide
HPLC	high-performance liquid chromatography
HOBt	1-hydroxy-1H-benzotriazole hydrate
UPLC	ultra-performance liquid chromatography
DAD	diode array detector
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ELSD	evaporating light scattering detector
ESI	electrospray ionization
SQD	single quadrupole detector
PTFE	polytetrafluoroethylene
CV	column volume(s)
BOC	tert-butyloxycarbonyl
PG	protecting group
LG	leaving group

5

Methods

Analytical HPLC methods:

Method A1: UPLC (ACN-HCOOH):

- 10 Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7 50x2.1 mm; mobile phase A: water + 0.1% by volume of formic acid (99%), mobile phase B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow rate 0.8 ml/min; temperature: 60°C; injection: 2 µl; DAD scan: 210-400 nm; ELSD.

- 15 Method A2: UPLC (ACN-NH₃):

Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7 50x2.1 mm; mobile phase A: water + 0.2% by volume of ammonia (32%), mobile phase B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow rate 0.8 ml/min; temperature: 60°C; injection: 2 µl; DAD scan: 210-400 nm; ELSD.

20

Method A3: (LC-MS)

Instrument: Agilent 1290 Infinity LC; column: Acquity UPLC BEH C18 1.7 50x2.1 mm; mobile phase A: water + 0.05% by volume of formic acid, mobile phase B: acetonitrile + 0.05% by

volume of formic acid; gradient: 0-1.7 min 2-90% B, 1.7-2.0 min 90% B; flow rate 1.2 ml/min; temperature: 60°C; injection: 2 µl; DAD scan: 190-390 nm; MS: Agilent TOF 6230.

Method A4: (LC-MS)

- 5 Instrument: Waters Acquity; column: Kinetex (Phenomenex), 50x2 mm; mobile phase A: water + 0.05% by volume of formic acid, mobile phase B: acetonitrile + 0.05% by volume of formic acid; gradient: 0-1.9 min 1-99% B, 1.9-2.1 min 99% B; flow rate 1.5 ml/min; temperature: 60°C; injection: 0.5 µl; DAD scan: 200-400 nm.

10 Preparative HPLC methods:

- Method P1: System: Waters autopurification system: Pump 2545, Sample Manager 2767, CFO, DAD 2996, ELSD 2424, SQD; column: XBridge C18 5µm 100x30 mm; mobile phase: A: water + 0.1% by volume of formic acid, mobile phase B: acetonitrile; gradient: 0-8 min 10-100% B, 8-10
15 min 100% B; flow rate: 50 ml/min; temperature: room temp.; solution: max. 250 mg / max. 2.5 ml DMSO or DMF; injection: 1 x 2.5 ml; detection: DAD scan range 210–400 nm; MS ESI+, ESI-, scan range 160-1000 m/z.

- Method P2: System: Waters autopurification system: Pump 254, Sample Manager 2767, CFO, DAD 2996, ELSD 2424, SQD 3100; column: XBridge C18 5µm 100x30 mm; mobile phase: A: water + 0.2% by volume of ammonia (32%), mobile phase B: methanol; gradient: 0-8 min 30-70%
20 B; flow rate: 50 ml/min; temperature: room temp.; detection: DAD scan range 210–400 nm; MS ESI+, ESI-, scan range 160-1000 m/z; ELSD.

- Method P3: System: Labomatic, pump: HD-5000, fraction collector: LABOCOL Vario-4000, UV detector: Knauer UVD 2.1S; column: XBridge C18 5µm 100x30 mm; mobile phase A: water + 0.2% by volume of ammonia (25%), mobile phase B: acetonitrile; gradient: 0-1 min 15% B, 1-6.3
25 min 15-55% B, 6.3-6.4min 55-100% B, 6.4-7.4min 100% B; flow rate: 60 ml/min; temperature: room temp.; solution: max. 250 mg / 2 ml DMSO; injection: 2 x 2 ml; detection: UV 218 nm;
30 software: SCPA PrepCon5.

- Method P4: System: Agilent: Prep 1200, 2xPrep Pump, DLA, MWD, Prep FC; column: Chiralpak
35 IA 5µm 250x20 mm; mobile phase A: methanol, mobile phase B: ethanol; gradient: isocratic 50% B; flow rate: 15 ml/min; temperature: room temp.; detection: UV 254 nm

- Method P5: System: Labomatic, pump: HD-5000, fraction collector: LABOCOL Vario-4000, UV detector: Knauer UVD 2.1S; column: column: Chromatorex RP C18 10µm 125x30 mm, mobile
phase: A: water + 0.1% by volume of formic acid, mobile phase B: acetonitrile; gradient: 0 - 15

min 65 – 100% B; flow rate: 60 ml/min; temperature: room temp.; solution: max. 250 mg / 2 ml DMSO; injection: 2 x 2 ml; detection: UV 254 nm; software: SCPA PrepCon5.

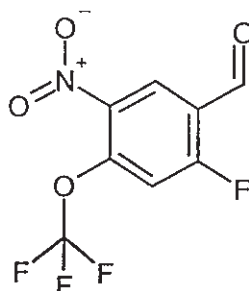
Microwave

5

CEM Discover S-Class; autosampler: CEM Explorer; software: CEM Synergy; method: Dynamic heating mode, 300 W, 18 bar max.

Intermediates

5 2-Fluoro-5-nitro-4-(trifluoromethoxy)benzaldehyde

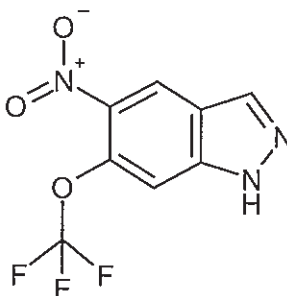


20.9 g (100.4 mmol) of 2-fluoro-4-(trifluoromethoxy)benzaldehyde were dissolved in 100 ml of sulphuric acid (W=96%) and, in a three-necked flask fitted with mechanical stirrer, dropping funnel and internal thermometer, cooled to -15°C. Over a period of 60 min, the nitrating acid (28 ml of sulphuric acid (w=96%) in 14 ml of nitric acid (w=65%)), which had been prepared and cooled beforehand, was added dropwise to this solution. During the addition, the internal temperature fluctuated between -15°C and -12°C. After the end of the dropwise addition, stirring was continued for another hour (internal temperature -13°C). The reaction mixture was added to ice and extracted three times with in each case 150 ml of ethyl acetate. The combined org. phases were washed with saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated. This gave 25.4 g (100% of theory) of the title compound.

¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.34 (dd, 1 H), 8.57 (d, 1 H), 10.34 (s, 1 H).

Intermediate 0-2

20 5-Nitro-6-(trifluoromethoxy)-1H-indazole



25.4 g (100.4 mmol) of 2-fluoro-5-nitro-4-(trifluoromethoxy)benzaldehyde were initially charged in 200 ml of absolute ethanol, and 25 ml (513.6 mmol) of hydrazine hydrate were added. The colour of the solution darkened. The reaction mixture was heated under reflux for 2 h. The reaction mixture was then added to 1.4 l of water and stirred vigorously for 10 minutes. The precipitate

formed was filtered off with suction and washed three times with in each case 40 ml of water. The resulting solid was dried in a vacuum drying cabinet at +50°C overnight. This gave 19.4 g (78% of theory) of the title compound.

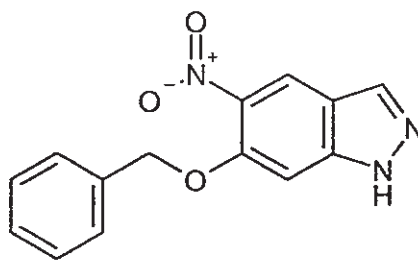
UPLC-MS (Method A1): $R_t = 1.03\text{min}$

5 MS (ESIpos): $m/z = 248\ (M+H)^+$

$^1\text{H NMR}$ (400 MHz, DMSO- d_6) $\delta = 7.86\ (\text{s}, 1\ \text{H}), 8.46\ (\text{s}, 1\ \text{H}), 8.82\ (\text{s}, 1\ \text{H}), 13.87\ (\text{br. s.}, 1\ \text{H})$.

Intermediate 0-3

6-(Benzyloxy)-5-nitro-1H-indazole



10

20.0 g (111.6 mmol) of 5-nitro-1H-indazol-6-ol (CAS No. 1082041-56-2) were initially charged in 750 ml of tetrahydrofuran, and 13.9 ml (134.0 mmol) of benzyl alcohol and 35.1 g (134.0 mmol) of triphenylphosphine were added. The solution was cooled to 0°C, and 26.03 ml (134.0 mmol) of diisopropyl azo dicarboxylate were added. The reaction mixture was stirred at 0°C for 1 h and then
 15 at 25°C for 24 h. Water was then added, and the reaction mixture was extracted with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution and concentrated. The residue was taken up in dichloromethane, Isolute® HM-N (Biotage) was added and during concentration the residue was adsorbed on Isolute. The Isolute was applied to a cartridge (750 g; KP-Sil) pre-equilibrated with hexane and chromatography was carried out using
 20 the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; flow rate: 200 ml/min; gradient: isocratic 88:12 (1 CV), 88:12->20:80 (10 CV), isocratic 20:80 (2 CV)). The combined product fractions were concentrated and dried. This gave 18.908 g (63% of theory) of the title compound.

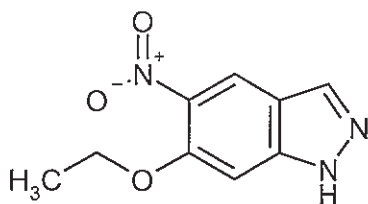
UPLC-MS (Method A1): $R_t = 1.09\ \text{min}$

25 MS (ESIpos): $m/z = 270\ (M+H)^+$

$^1\text{H NMR}$ (300 MHz, DMSO- d_6) $\delta = 5.35\ (\text{s}, 2\ \text{H}), 7.25 - 7.57\ (\text{m}, 6\ \text{H}), 8.20\ (\text{s}, 1\ \text{H}), 8.45\ (\text{s}, 1\ \text{H}), 13.38\ (\text{br. s.}, 1\ \text{H})$.

Intermediate 0-4

30 6-Ethoxy-5-nitro-1H-indazole



100 mg (0.56 mmol) of 5-nitro-1H-indazol-6-ol (CAS No. 1082041-56-2) were initially charged in 668 μ l of *N,N*-dimethylformamide, and 93 mg (0.67 mmol) of potassium carbonate and 54 μ l (0.67 mmol) of iodoethane were added. The solution was heated in a microwave at 60°C for 1 h. Water was then added, and the reaction mixture was extracted with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was taken up in dichloromethane, Isolute® HM-N (Biotage) was added and during concentration the residue was adsorbed on Isolute. The Isolute was applied to a cartridge (25 g; KP-Sil) pre-equilibrated with hexane and chromatography was carried out using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; flow rate: 25 ml/min; gradient: isocratic 88:12 (1 CV), 88:12->0:100 (10 CV), isocratic 0:100 (2 CV)). The combined product fractions were concentrated and dried. This gave 89 mg (77% of theory) of the title compound.

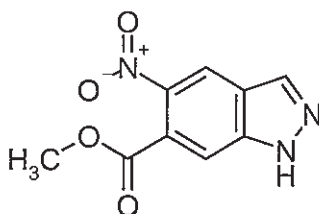
UPLC-MS (Method A1): R_t = 0.89 min

MS (ESIpos): m/z = 208 ($M+H$)⁺

¹H NMR (300 MHz, DMSO-*d*₆) δ = 1.37 (t, 3 H), 4.23 (q, 2 H), 7.19 (s, 1 H), 8.17 (s, 1 H), 8.40 (s, 1 H), 13.31 (br. s., 1 H).

Intermediate 0-5

Methyl 5-nitro-1H-indazole-6-carboxylate



4.60 g (26.1 mmol) of methyl 1H-indazole-6-carboxylate were dissolved in 120 ml of sulphuric acid (W=96%) and, in a three-necked flask fitted with mechanical stirrer, dropping funnel and internal thermometer, cooled to -15°C. Over a period of 15 minutes, the nitrating acid (9.2 ml of sulphuric acid (w=96%) in 4 ml of nitric acid (w=65%)), which had been prepared and cooled beforehand, was added dropwise to this solution. During the addition, the internal temperature fluctuated between -15°C and -12°C. After the end of the dropwise addition, stirring was continued for another hour (internal temperature -5°C). The reaction mixture was added to ice, and the precipitate formed was filtered off with suction, washed with water and dried in a drying cabinet at 50°C under reduced pressure. This gave 5.49 g (91% of theory) of the title compound.

UPLC-MS (Method A1): R_t = 1.21 min

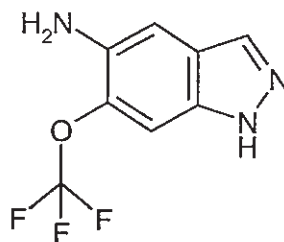
MS (ESIpos): $m/z = 471$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 3.85$ (s, 3 H) 6.01 (s, 2 H) 6.98 (s, 1 H) 7.79 - 7.91 (m, 1 H) 7.99 (s, 1 H) 12.84 (br. s., 1 H).

5

Intermediate 1-1

6-(Trifluoromethoxy)-1H-indazole-5-amine



10.0 g (40.5 mmol) of 5-nitro-6-(trifluoromethoxy)-1H-indazole (Intermediate 0-2) were dissolved in 400 ml of methanol. The solution was then degassed and flushed with nitrogen (this was repeated twice). 2.48 g (2.0 mmol) of palladium on activated carbon were added. The flask was evacuated and flushed with hydrogen. The reaction mixture was hydrogenated under standard hydrogen pressure at room temperature for 5 hours. The reaction mixture was filtered through a PTFE filter with Celite and concentrated. This gave 7.2 g (74% of theory) of the title compound.

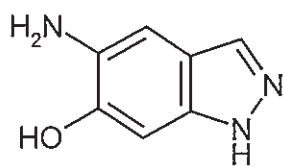
15 UPLC-MS (Method A1): $R_t = 0.75$ min

MS (ESIpos): $m/z = 218$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆) $\delta = 4.91$ (s, 2 H), 7.04 (s, 1 H), 7.32 (s, 1 H), 7.83 (s, 1 H), 12.72 (br. s., 1 H).

20 Intermediate 1-2

5-Amino-1H-indazol-6-ol



Analogously to Intermediate 1-1, 6.5 g (36.3 mmol) of 5-nitro-1H-indazol-6-ol (CAS No. 1082041-56-2) were dissolved in 1.5 l of methanol and hydrogenated with 193 mg (1.8 mmol) of palladium on activated carbon under standard hydrogen pressure at 25°C for 5 h. This gave 5.28 g (98% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 0.26$ min

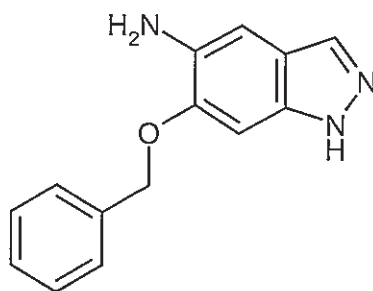
MS (ESIpos): $m/z = 150$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 4.37$ (br. s., 2 H) 6.71 - 6.78 (m, 2 H) 7.59 (s, 1 H) 12.17 (br. s., 1 H).

30

Intermediate 1-3

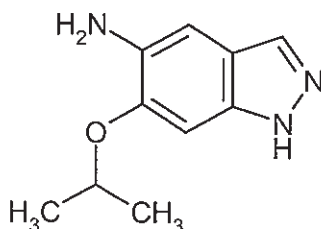
6-(Benzyloxy)-1H-indazole-5-amine



18.5 g (68.7 mmol) of 6-(benzyloxy)-5-nitro-1H-indazole (Intermediate 0-3) were dissolved in 500 ml of ethanol and initially charged in a 1 l three-necked flask with mechanical stirrer and reflux condenser, and 100 ml of water were added. 19.2 g (343.5 mmol) of iron powder and 1.84 g (34.35 mmol) of ammonium chloride were then added. The brown suspension was heated at reflux for 4 h. The reaction mixture was cooled to 25°C using a water bath and filtered through Celite (clear filtrate). The filter cake was washed with ethanol. The filtrate was concentrated until about 200 ml of solvent were left. The reaction mixture was added to 2 l of water. The suspension was cooled and the resulting precipitate was then filtered off with suction. The filter cake was washed twice with in each case 150 ml of water and twice with in each case 100 ml of diethyl ether. The precipitate was dried in a vacuum drying cabinet at 50°C for 5 h and then re-hydrogenated for 5 h using 193 mg (1.81 mmol) of palladium on activated carbon at 25°C under standard hydrogen pressure. This gave 15.28 g (92% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 0.66$ minMS (ESIpos): $m/z = 240$ ($M+H$)⁺¹H NMR (300 MHz, DMSO-d₆): $\delta = 4.54$ (s, 2 H), 5.19 (s, 2 H), 6.84 (s, 1 H), 6.91 (s, 1 H), 7.22 - 7.45 (m, 3 H), 7.48 - 7.57 (m, 2 H), 7.66 (s, 1 H), 12.43 (br. s., 1 H).**Intermediate 1-4**

6-Isopropoxy-1H-indazole-5-amine



10 g (45.2 mmol) of 6-isopropoxy-5-nitro-1H-indazole (CAS No. 1082041-56-2) were dissolved in 200 ml of ethanol and hydrogenated with 1.20 g (1.13 mmol) of palladium on activated carbon under standard hydrogen pressure at 25°C for 24 h. The reaction mixture was filtered off through Celite, the filter cake was washed with ethanol and the filtrate was concentrated. The residue was

subjected to incipient dissolution with a little ethanol in an ultrasonic bath, diethyl ether was added and the residue was digested further in the ultrasonic bath. The solid was filtered off with suction and washed with a little diethyl ether and hexane, giving 4.69 g (54%) of product. The filtrate was concentrated and applied to a Biotage SNAP cartridge (100 g; KP-Sil) pre-equilibrated with hexane and chromatography was carried out using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; gradient: 90:10->35:65 (9.2 CV), isocratic 35:65 (1 CV)). The combined product fractions were concentrated and the residue was digested with a mixture of hexane and dichloromethane (2:1) in an ultrasonic bath. The solid formed was filtered off. This gave an additional 2.36 g (27% of theory) of the title compound.

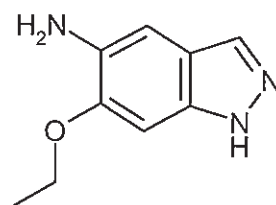
UPLC-MS (Method A1): $R_t = 0.75$ min

MS (ESIpos): $m/z = 192$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 1.31$ (s, 3 H), 1.33 (s, 3 H), 4.43 (s, 2 H), 4.57 - 4.68 (m, 1 H), 6.81 (s, 1 H), 6.83 (s, 1 H), 7.64 (s, 1 H), 12.34 (br. s., 1 H).

Intermediate 1-5

6-Ethoxy-1H-indazole-5-amine



Analogously to Intermediate 1-1, 65 mg (0.31 mmol) of 6-ethoxy-5-nitro-1H-indazole (Intermediate 0-4) were dissolved in 4.1 ml of methanol and hydrogenated with 33 mg (0.03 mmol) of palladium on activated carbon under standard hydrogen pressure at 25°C for 5 h. This gave 54 mg (97% of theory) of the title compound.

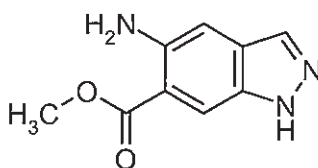
UPLC-MS (Method A1): $R_t = 0.64$ min

MS (ESIpos): $m/z = 178$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 1.40$ (t, 3 H), 4.07 (q, 2 H), 4.47 (br. s., 2 H), 6.81 (s, 2 H), 7.65 (s, 1 H), 12.39 (br. s., 1 H).

Intermediate 1-6

Methyl 5-amino-1H-indazole-6-carboxylate



Analogously to Intermediate 1-1, 5.48 g (24.8 mmol) of methyl 5-nitro-1H-indazole-6-carboxylate (Intermediate 0-9) were dissolved in 293 ml of methanol and hydrogenated with 1.32 g (1.24 mmol) of palladium on activated carbon under standard hydrogen pressure at 25°C for 3 h. This gave 4.52 g (91% of theory) of the title compound.

5 UPLC-MS (Method A1): $R_t = 0.75$ min

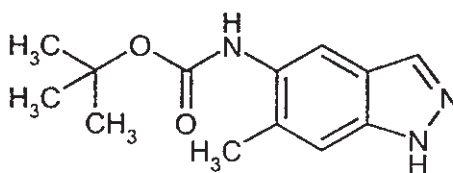
MS (ESIpos): $m/z = 222$ (M+H)⁺

¹H NMR (500 MHz, DMSO-d₆): $\delta = 3.85$ (s, 3 H), 6.05 (br. s., 2 H), 6.99 (d, 1 H), 7.85 (d, 1 H), 8.00 (s, 1 H), 12.83 (br. s., 1 H).

10

Intermediate 2-1

tert-Butyl (6-methyl-1H-indazol-5-yl)carbamate



15 10.3 g (70.0 mmol) of 6-methyl-1H-indazole-5-amine (CAS No: 81115-45-9) were suspended in 150 ml of tetrahydrofuran, 13.4 ml (80.0 mmol) of *N,N*-diisopropylethylamine were added and the mixture was cooled to 0°C. After addition of 5.52 g (25.3 mmol) of di-tert-butyl dicarbonate at 0°C, the mixture was then stirred at 25°C for 18 h. The mixture was concentrated, giving 17.6 g of a crude product which was used without purification.

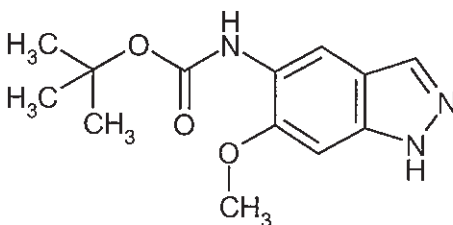
20 UPLC-MS (Method A1): $R_t = 1.01$ min

MS (ESIpos): $m/z = 248$ (M+H)⁺.

Intermediate 2-2

tert-Butyl (6-methoxy-1H-indazol-5-yl)carbamate

25



4.0 g (24.5 mmol) of 6-methoxy-1H-indazol-5-amine (CAS No. 749223-61-8) were dissolved in 30 ml of tetrahydrofuran, and 5.35 g (24.5 mmol) of di-tert-butyl dicarbonate were added. The reaction mixture was stirred at 25°C for 18 h. The mixture was then concentrated and the residue
30 was suspended in 20 ml of dichloromethane. 200 ml of hexane were added and the resulting suspension was stirred with ice bath cooling for 25 minutes. The precipitate was filtered off with

suction, washed twice with 25 ml of hexane and dried. This gave 4.83 g (75% of theory) of the title compound.

UPLC-MS (Method A2): $R_t = 1.08$ min

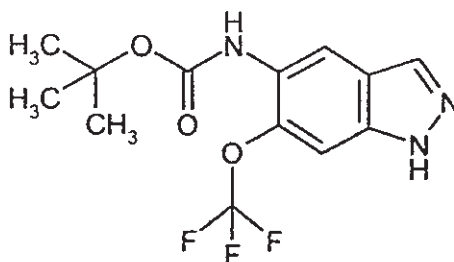
MS (ESIpos): $m/z = 264$ ($M+H$)⁺

- 5 ¹H NMR (400 MHz, CHLOROFORM-*d*) $\delta = 1.56$ (s, 9 H), 3.95 (s, 3 H), 6.88 (s, 1 H), 7.12 (br. s., 1 H), 7.94 (d, 1 H), 8.40 (br. s., 1 H).

Intermediate 2-3

tert-Butyl [6-(trifluoromethoxy)-1H-indazol-5-yl]carbamate

10



- 5.0 g (23.0 mmol) of 6-(trifluoromethoxy)-1H-indazole-5-amine (Intermediate 1-1) were suspended in 100 ml of tetrahydrofuran, 4.81 ml (27.6 mmol) of *N,N*-diisopropylethylamine were added and the mixture was cooled to 0°C. After addition of 5.52 g (25.3 mmol) of di-tert-butyl dicarbonate at 0°C, the mixture was then stirred at 25°C for 18 h. A further 3.52 g (16.1 mmol) of di-tert-butyl dicarbonate were added, and the mixture was stirred at 25°C for a further 24 h. The reaction mixture was heated at reflux for a further 24 h. The reaction mixture was then concentrated, taken up in ethyl acetate and washed with 0.5 M hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution. The combined organic phases were dried over sodium sulphate and the solution was, after filtration, concentrated. The residue was taken up in dichloromethane, Isolute® HM-N (Biotage) was added and during concentration the residue was adsorbed on Isolute. The Isolute was applied to a Biotage SNAP cartridge (340 g; KP-Sil) pre-equilibrated with hexane and chromatography was carried out using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; gradient: isocratic 90:10 (3 CV), 90:10->80:20 (2 CV), isocratic 80:20 (7 CV), 80:20->75:25 (1 CV), isocratic 75:25 (7 CV)). The combined product fractions were concentrated and the brownish solid was dried under reduced pressure. This gave 3.48 g (48% of theory) of the title compound.

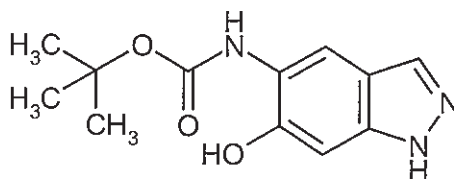
UPLC-MS (Method A2): $R_t = 1.15$ min

MS (ESIpos): $m/z = 318$ ($M+H$)⁺

- 30 ¹H NMR (300 MHz, DMSO-*d*₆) $\delta = 1.44$ (s, 9 H), 7.51 (s, 1 H), 7.83 (s, 1 H), 8.11 (s, 1 H), 8.80 (s, 1 H).

Intermediate 2-4

tert-Butyl (6-hydroxy-1H-indazol-5-yl)carbamate



- 5 8.05 g (36.8 mmol) of di-tert-butyl dicarbonate were suspended in 125 ml of tetrahydrofuran and 5.0 g (33.5 mmol) of 5-amino-1H-indazol-6-ol (Intermediate 1-2) were added a little at a time with stirring. The reaction mixture was stirred at 25°C for 24 h. The reaction mixture was subsequently concentrated, the residue was taken up in methanol and 2 ml of 1 M aqueous sodium hydroxide solution and 2 ml of water were added. The mixture was stirred for another 30 min and the
- 10 methanol was then distilled off. 1 M hydrochloric acid was added to the residue until a pH of 7 had been reached. The mixture was then extracted with dichloromethane and the combined org. phases were dried over sodium sulphate, filtered and concentrated. This gave 7.50 g (90% of theory) of the title compound.

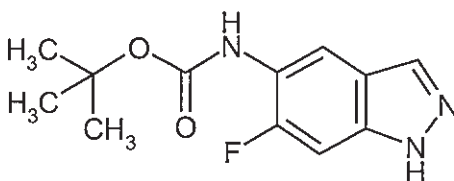
UPLC-MS (Method A2): $R_t = 0.95$ min

- 15 MS (ESIpos): $m/z = 250$ ($M+H$)⁺

¹H NMR (300 MHz, DMSO-d₆): $\delta = 1.47$ (s, 9 H) 6.88 (s, 1 H) 7.66 (s, 1 H) 7.82 (s, 1 H) 7.91 (s, 1 H) 10.19 (br. s., 1 H) 12.50 (s, 1 H).

Intermediate 2-5

- 20 tert-Butyl (6-fluoro-1H-indazol-5-yl)carbamate



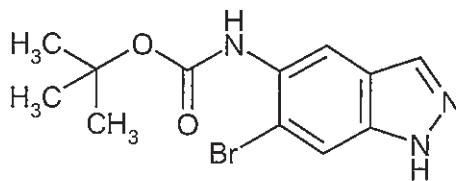
- Analogously to Intermediate 2-2, 4.96 g (32.8 mmol) of 6-fluoro-1H-indazole-5-amine (CAS No.: 709046-14-0), 7.16 g (32.8 mmol) of di-tert-butyl dicarbonate and 6.28 ml (36 mmol) of *N,N*-diisopropylethylamine were dissolved in 51 ml of tetrahydrofuran and stirred at 25°C for 20 h. This gives 5.72 g (69% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 1.01$ minMS (ESIpos): $m/z = 252$ ($M+H$)⁺

- ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.45$ (s, 9H), 7.35 (d, 1H), 7.81 (m, 1H), 8.03 (s, 1H), 8.80 (s, 1H), 13.08 (s, 1H).
- 30

Intermediate 2-6

tert-Butyl (6-bromo-1H-indazol-5-yl)carbamate



5 7.05 g (17.1 mmol) of the mixture of tert-butyl 6-bromo-5-[(tert-butoxycarbonyl)amino]-1H-indazole-1-carboxylate and tert-butyl 6-bromo-5-[(tert-butoxycarbonyl)amino]-2H-indazole-2-carboxylate (Intermediates 10 and 11) were dissolved in 141 ml of dimethylformamide, and with 2.17 g (20.5 mmol) of sodium carbonate in 71 ml of water. The reaction mixture was heated at 85°C for 24 h. Dichloromethane was added and the reaction mixture was washed with 0.5 M
10 hydrochloric acid and saturated sodium chloride solution, dried over sodium sulphate and concentrated. The product was dried under reduced pressure. This gave 5.35 g (98% of theory) of product.

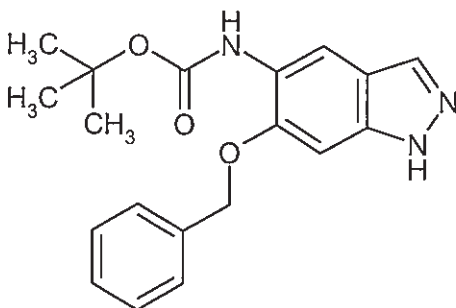
UPLC-MS (Method A2): $R_t = 1.09$ minMS (ESI^{neg}): $m/z = 310$ ($M(^{79}\text{Br})\text{-H}^+$)

15 ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) $\delta = 1.57$ (s, 9 H) 7.01 (br. s., 1 H) 7.83 (s, 1 H) 8.07 (s, 1 H) 8.50 (s, 1 H).

Intermediate 2-7

tert-Butyl [6-(benzyloxy)-1H-indazol-5-yl]carbamate

20



7.50 g (30.1 mmol) of tert-butyl (6-hydroxy-1H-indazol-5-yl)carbamate (Intermediate 2-4) were dissolved in 150 ml of *N,N*-dimethylformamide, and 5.66 g (33.1 mmol) of benzyl bromide and 8.32 g (60.2 mmol) of potassium carbonate were added with stirring. The reaction mixture was
25 stirred at 25°C for 24 h. The reaction mixture was then diluted with water and extracted with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, the phases were separated and filtered through a hydrophobic filter. The residue was taken up in dichloromethane and during concentration adsorbed on Isolute. The Isolute was applied to a Biotage SNAP cartridge (340 g; KP-Sil) pre-equilibrated with hexane and chromatography was

carried out using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; gradient 100:0->60:40 (10 CV), isocratic 60:40 (9 CV)). The combined product fractions were concentrated and dried under reduced pressure. This gave 3.46 g (34% of theory) of product.

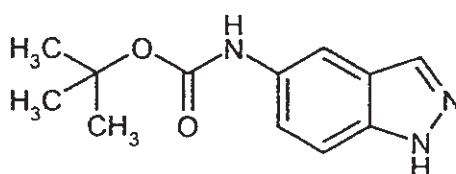
UPLC-MS (Method A2): $R_t = 1.27$ min

5 MS (ESIpos): $m/z = 340$ ($M+H$)⁺

¹H NMR (300 MHz, CHLOROFORM-*d*): $\delta = 1.55$ (s, 9 H) 5.20 (s, 2 H) 6.92 (s, 1 H) 7.14 (s, 1 H) 7.36 - 7.49 (m, 5 H) 7.94 (d, $J=0.75$ Hz, 1 H) 8.44 (s, 1 H).

Intermediate 2-8

10 tert-Butyl-1H-indazol-5-ylcarbamate



25.5 g (191.5 mmol) of 1H-indazole-5-amine (CAS No. 19335-11-6) were initially charged in 300 ml of tetrahydrofuran, 37 ml of *N,N*-diisopropylethylamine were added, 41.8 g (191.5 mmol) of di-
15 tert-butyl dicarbonate were added a little at a time and the mixture was stirred at 25°C for 24 h. The mixture was concentrated, giving 44.6 g (95% of theory) of the title compound.

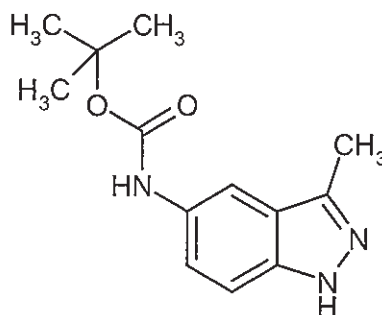
UPLC-MS (METHOD A1): $R_t = 0.96$ min

MS (ESIpos): $m/z = 234$ ($M+H$)⁺.

¹H-NMR (300 MHz, DMSO-*d*₆): $\delta = 1.44$ (s, 9H), 7.24 - 7.46 (m, 2H), 7.84 (s, 1H), 7.92 (s, 1H),
20 9.24 (br. s., 1H), 12.86 (br. s., 1H).

Intermediate 2-9

tert-Butyl (3-methyl-1H-indazol-5-yl)carbamate



25

1.00 g (6.8 mmol) of 3-methyl-1H-indazole-5-amine were reacted analogously with 1.48 g (6.8 mmol) of di-tert-butyl carbonate and 1.3 ml (7.5 mmol) of *N,N*-diisopropylethylamine in 15 ml of THF overnight. Concentration gave 1.70 g of the title compound as a crude product.

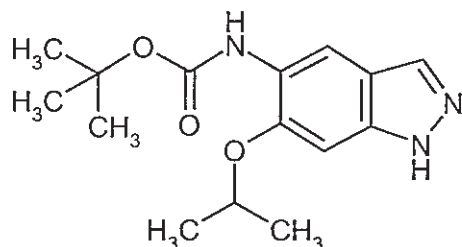
UPLC-MS (METHOD A1): $R_t = 1.01$ min

MS (ESIpos): $m/z = 248$ (M+H)⁺.

Intermediate 2-10

tert-Butyl (6-isopropoxy-1H-indazol-5-yl)carbamate

5



Analogously to Intermediate 2-2, 2.2 g (11.6 mmol) of 6-isopropoxy-1H-indazole-5-amine (Intermediate 1-4) were reacted with 2.52 g (11.6 mmol) of di-tert-butyl dicarbonate and 2.21 ml (12.7 mmol) of *N,N*-diisopropylethylamine. This gave 2.72 g (81% of theory) of the title compound.

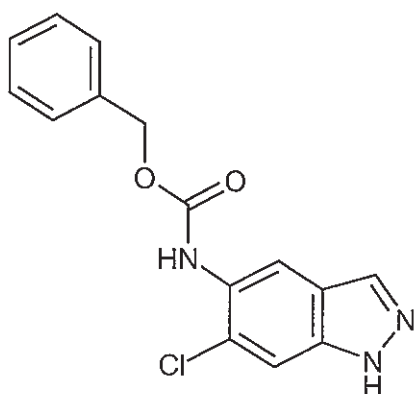
UPLC-MS (Method A1): $R_t = 1.20$

MS (ESIpos): $m/z = 292$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-*d*₆): $\delta = 1.34$ (d, 6H), 1.47 (s, 9H), 4.63- 4.74 (m, 1H), 6.98 (s, 1H), 7.68 (s, 1H), 7.88 (s, 1H), 7.94 (s, 1H), 12.68 (s, 1H).

Intermediate 2-11

Benzyl (6-chloro-1H-indazol-5-yl)carbamate



20

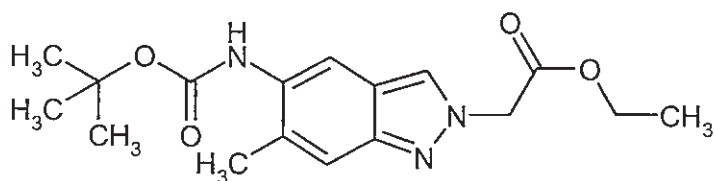
6.1 ml of trifluoroacetic acid were added to 4.61 g of tert-butyl-5-{[(benzyloxy)carbonyl]amino}-6-chloro-2H-indazole-2-carboxylate (Intermediate 23-1, crude product) in 40 ml of dichloromethane, and the mixture was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate solution was added and the solid was filtered off with suction, washed with water and diethyl ether and dried. This gave 2.11 g of a light-brown solid (crude product).

25

¹H-NMR (400 MHz, DMSO-d₆, selected signals): δ [ppm]= 5.13 (s, 2H), 7.69 (s, 1H), 7.83 (s, 1H), 8.07 (s, 1H), 9.13 (br. s., 1H), 13.15 (br. s., 1H).

Intermediate 3-1

5 Ethyl {5-[(tert-butoxycarbonyl)amino]-6-methyl-2H-indazol-2-yl}acetate



10.0 g (40.4 mmol) of tert-butyl (6-methyl-1H-indazol-5-yl)carbamate (Intermediate 2-1) were stirred with 9.00 ml (80.9 mmol) of ethyl bromoacetate in 75 ml of tetrahydrofuran in the presence
 10 of 17.1 ml (80.9 mmol) of *N,N*-dicyclohexylmethylamine at 70°C for 24 h. The precipitated solid was filtered off and washed twice with ethyl acetate. Water was added to the filtrate and the organic phase was separated off and extracted twice with ethyl acetate. The combined organic phases were washed with 1 M hydrochloric acid solution, saturated sodium bicarbonate solution and saturated sodium chloride solution and concentrated. The residue was taken up in
 15 dichloromethane, Isolute® HM-N (Biotage) was added and during concentration the residue was adsorbed on Isolute. The Isolute was applied to a Biotage SNAP cartridge (340 g; KP-Sil) pre-equilibrated with hexane and chromatography was carried out using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; flow rate: 100 ml/min; gradient: isocratic 100:10 (1 CV), 100:0->50:50 (20 CV), isocratic 50:50 (0.2 CV)). The combined product fractions
 20 were concentrated and dried. This gave 8.90 g (42% of theory) of the title compound.

In a second experiment, 213 mg of the title compound were obtained analogously from 2.00 g of tert-butyl (6-methyl-1H-indazol-5-yl)carbamate using 2.24 g of potassium carbonate instead of *N,N*-dicyclohexylmethylamine at 80°C in *N,N*-dimethylformamide, with two successive purifications on silica gel (hexane/ethyl acetate).

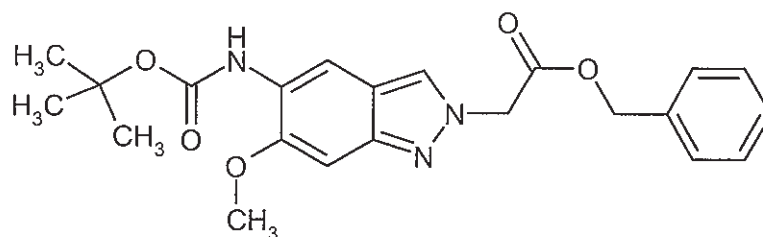
25 UPLC-MS (Method A1): *R*_t = 1.14 min

MS (ESIpos): *m/z* = 334 (M+H)⁺

¹H-NMR (600 MHz, DMSO-d₆): δ = 1.21 (t, 3H), 1.46 (s, 9H), 2.28 (s, 3H), 4.16 (q, 2H), 5.34 (s, 2H), 7.38 (d, 1H), 7.57 (s, 1H), 8.25 (d, 1H), 8.40 (s, 1H).

30 Intermediate 3-2

Benzyl {5-[(tert-butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetate



Analogously to Intermediate 3-1, 4.17 g (15.8 mmol) of tert-butyl (6-methoxy-1H-indazol-5-yl)carbamate (Intermediate 2-2) in 50 ml of THF were stirred with 2.51 ml (15.8 mmol) of benzyl bromoacetate and 3.36 ml (15.8 mmol) of *N,N*-dicyclohexylmethylamine at 65°C for 4 h, 2.51 ml (15.8 mmol) of benzyl bromoacetate and 3.36 ml (15.8 mmol) of *N,N*-dicyclohexylmethylamine were then added and the mixture was stirred at 65°C for a further 18 h. Work-up and purification by column chromatography using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; flow rate: 100 ml/min; gradient: isocratic 100:10 (5 min), 100:0→75:25 (20 min), isocratic 75:25 (5 min), 75:25→50:50 (15 min), isocratic 50:50 (5 min), 50:50→20:80 (6 min)) gave 3.22 g (47% of theory) of the title compound.

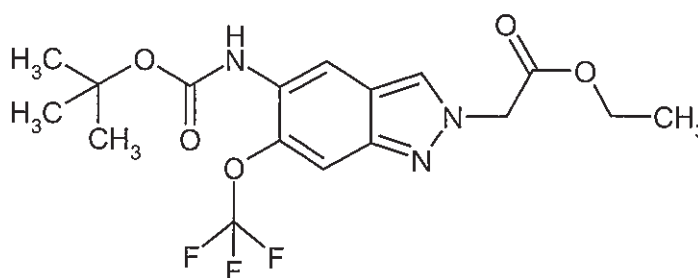
UPLC-MS (Method A1): $R_t = 1.37$ min

MS (ESIpos): $m/z = 412$ ($M+H$)⁺

¹H-NMR (500 MHz, DMSO-*d*₆): $\delta = 1.47$ (s, 9H), 3.86 (s, 3H), 5.20 (s, 2H), 5.37 (s, 2H), 6.97 (s, 1H), 7.28 - 7.42 (m), 7.79 (s, 1H), 7.94 (br. s., 1H), 8.21 (s, 1H).

Intermediate 3-3

Ethyl {5-[(tert-butoxycarbonyl)amino]-6-(trifluoromethoxy)-2H-indazol-2-yl}acetate



Analogously to Intermediate 3-1, 3.17 g (10.0 mmol) of tert-butyl [6-(trifluoromethoxy)-1H-indazol-5-yl]carbamate (Intermediate 2-3), 5.54 ml (50 mmol) of ethyl bromoacetate and 10.7 ml (50 mmol) of *N,N*-dicyclohexylmethylamine in 20 ml of tetrahydrofuran were heated at 70°C for 24 h. Work-up and purification by column chromatography using the Isolera® flash purification system (Biotage) (mobile phase: hexane/dichloromethane/ethyl acetate; gradient: isocratic 90:5:5 (5 CV), 90:5:5→85:7.5:7.5 (5 CV), isocratic 85:7.5:7.5 (11 CV), 85:7.5:7.5→80:10:7.5 (3 CV), isocratic 80:10:10 (9 CV)) gave 512 mg (13% of theory) of product.

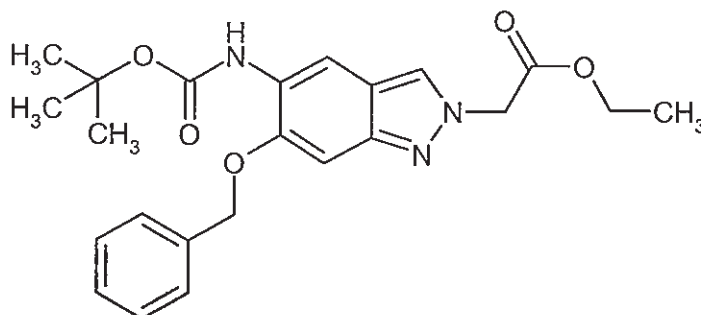
UPLC-MS (Method A2): $R_t = 1.29$ min

MS (ESIpos): $m/z = 404$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆) δ = 1.22 (t, 3 H), 1.44 (s, 9 H), 4.18 (q, 2 H), 5.42 (s, 2 H), 7.58 (s, 1 H), 7.82 (s, 1 H), 8.44 (d, 1 H), 8.75 (s, 1 H).

Intermediate 3-4

5 Ethyl {6-(benzyloxy)-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl} acetate



Analogously to Intermediate 3-1, 3.46 g (10.2 mmol) of tert-butyl [6-(benzyloxy)-1H-indazol-5-yl]carbamate (Intermediate 2-7), 2.26 ml (20.3 mmol) of ethyl bromoacetate and 4.36 ml (20.3 mmol) of N,N-dicyclohexylmethylamine in 50 ml of tetrahydrofuran were heated at 70°C for 2 h. Another 2.26 ml (20.3 mmol) of ethyl bromoacetate and 4.36 ml (20.3 mmol) of N,N-dicyclohexylamine were added, and the mixture was stirred at 70°C for a further 22 h. Work-up and purification by column chromatography using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; gradient 90:10->65:35 (10 CV), isocratic 65:35 (5 CV), 65:35->50:50 (5 CV), isocratic 50:50 (5 CV)) gave 2.37 g (55% of theory) of the title compound.

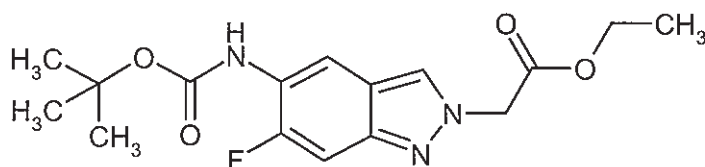
UPLC-MS (Method A1): R_t = 1.43 min

MS (ESIpos): m/z = 426 (M+H)⁺

¹H NMR (400 MHz, CHLOROFORM-d): δ = 1.28 (t, 3 H), 1.54 (s, 9 H), 4.25 (q, 2 H), 5.09 (s, 2 H), 5.19 (s, 2 H), 7.03 (s, 1 H), 7.25 (s, 1 H), 7.32 - 7.49 (m, 5 H), 7.82 (s, 1 H), 8.30 (s, 1 H).

Intermediate 3-5

Ethyl {5-[(tert-butoxycarbonyl)amino]-6-fluoro-2H-indazol-2-yl} acetate



Analogously to Intermediate 3-1, 5.44 g (21.6 mmol) of tert-butyl (6-fluoro-1H-indazol-5-yl)carbamate (Intermediate 2-5), 4.80 ml (43.3 mmol) of ethyl bromoacetate and 9.18 ml (43.3 mmol) of N,N-dicyclohexylmethylamine in 30 ml of tetrahydrofuran were stirred for 72 h, with an additional 0.96 ml (8.6 mmol) of ethyl bromoacetate and 1.84 ml (8.6 mmol) of N,N-dicyclohexylmethylamine being added after 24 h and 48 h, respectively. The mixture was

concentrated, taken up in dichloromethane, washed with water, dried and concentrated. Work-up and purification by column chromatography using the Isolera® flash purification system (Biotage) (mobile phase: hexane/dichloromethane/ethyl acetate; isocratic 40:48:12 (8 CV)) gave 3.75 g (47% of theory) of the title compound.

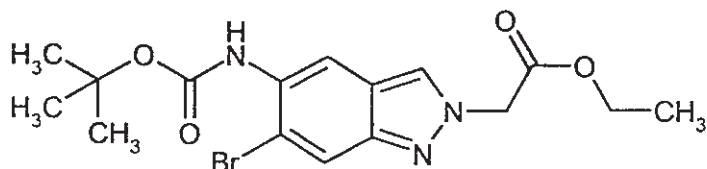
5 UPLC-MS (Method A1): $R_t = 1.15$ min

MS (ESIpos): $m/z = 338$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.21$ (t, 3H), 1.46 (s, 9H), 4.17 (q, 2H), 5.36 (s, 2H), 7.37 (d, 1H), 7.84 (d, 1H), 8.36 (s, 1H), 8.80 (s, 1H).

10 Intermediate 3-6

Ethyl {6-bromo-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetate



Analogously to Intermediate 3-1, 4.85 g (15.5 mmol) of tert-butyl (6-bromo-1H-indazol-5-yl)carbamate (Intermediate 2-6), 6.89 ml (62.1 mmol) of ethyl bromoacetate and 13.3 ml (62.1 mmol) of *N,N*-dicyclohexylmethylamine in 50 ml of tetrahydrofuran were stirred at 70°C for 24 h. Work-up and purification by column chromatography using the Isolera® flash purification system (Biotage) (mobile phase: hexane/dichloromethane/ethyl acetate; gradient: isocratic 80:10:10 (16 CV), 80:10:10->75:12.5:12.5 (1 CV), isocratic 75:12.5:12.5 (8 CV)) gave 2.01 g (32% of theory) of the title compound.

UPLC-MS (Method A2): $R_t = 1.27$ min

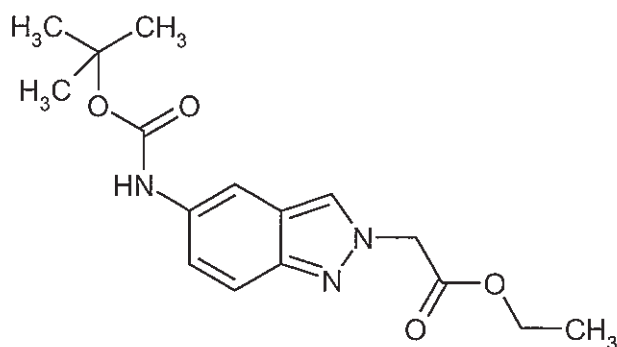
MS (ESIpos): $m/z = 398$ ($M(^{79}\text{Br})+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 1.21$ (t, 3H), 1.45 (s, 9H), 4.17 (q, 2H), 5.40 (s, 2H), 7.78 (s, 1H), 7.96 (s, 1H), 8.41 (d, 1H), 8.54 (s, 1H).

25

Intermediate 3-7

Ethyl {5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetate

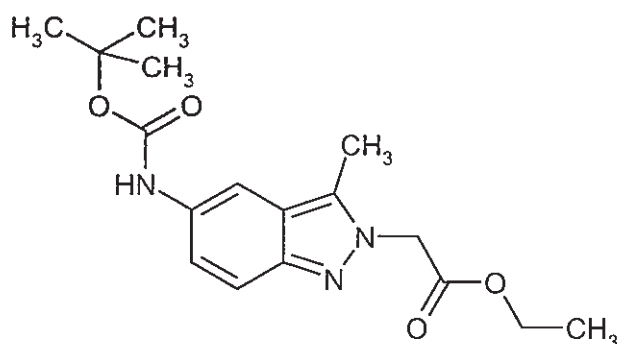


10.5 g (76.3 mmol) of potassium carbonate and 4.67 ml (42.0 mmol) of ethyl bromoacetate were added to 8.90 g (38.1 mmol) of tert-butyl 1H-indazol-5-ylcarbamate (Intermediate 2-8) in 80 ml of *N,N*-dimethylformamide and the mixture was stirred at 80°C for 24 h. The mixture was diluted with water and extracted with ethyl acetate, the organic phase was washed with water and saturated sodium chloride solution, dried and concentrated and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate). This gave 2.4 g of the title compound as main component as a mixture with tert-butyl 1H-indazol-5-ylcarbamate (starting material).

¹H-NMR (500 MHz, CHLOROFORM-*d*, selected signals): δ = 1.28 (t, 3H), 4.25 (q, 1H), 5.16 (s, 2H), 7.03 (dd, 1H), 7.62 (d, 1H).

Intermediate 3-8

Ethyl {5-[(tert-butoxycarbonyl)amino]-3-methyl-2H-indazol-2-yl}acetate



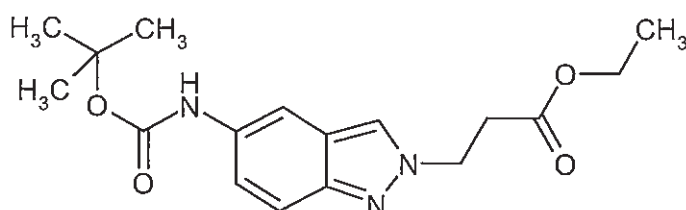
- 15 A mixture of 1.70 g of tert-butyl (3-methyl-1H-indazol-5-yl)carbamate (Intermediate 2-9) (crude product) and 842 μ l (7.6 mmol) of ethyl bromoacetate and 1.90 g (13.7 mmol) of potassium carbonate in 10 ml of *N,N*-dimethylformamide was stirred at 80°C for 5 h. The mixture was diluted with water and extracted three times with ethyl acetate and the extract was washed with water and saturated sodium chloride solution, dried and concentrated. The residue was purified by column chromatography purification on silica gel (hexane/ethyl acetate). This gave 436 mg of the title compound as a crude product.

UPLC-MS (METHOD A1): R_t = 1.12 min

MS (ESIpos): m/z = 334 ($M+H$)⁺.

25 Intermediate 3-9

Ethyl 3-{5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}propanoate



1.0 g (4.3 mmol) of tert-butyl 1H-indazol-5-ylcarbamate (Intermediate 2-8), 656 μ l (5.1 mmol) of ethyl bromopropionate and 1.30 g (9.4 mmol) of potassium carbonate in 6.4 ml of *N,N*-dimethylformamide were heated at 80°C for 90 min. Work-up and purification by column chromatography using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; gradient 100:0->80:20 (5 CV), 80:20->70:30 (5 CV), 70:30->60:40 (5 CV)) gave 640 mg (45% of theory) of the product.

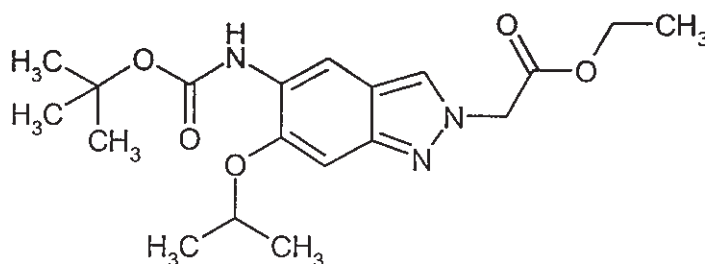
UPLC-MS (Method A1): R_t = 1.12 min

MS (ESIpos): m/z = 334 ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-*d*₆): δ = 1.13 (t, 3H), 1.48 (s, 9H), 3.00 (t, 2H), 4.04 (q, 2H), 4.60 (t, 2H), 7.17 – 7.24 (m, 1H), 7.43 – 7.50 (m, 1H), 7.82 (s, 1H), 8.21 (s, 1H), 9.23 (s, 1H).

Intermediate 3-10

Ethyl {5-[(tert-butoxycarbonyl)amino]-6-isopropoxy-2H-indazol-2-yl}acetate



Analogously to Intermediate 3-5, 2.72 g (9.3 mmol) of tert-butyl (6-isopropoxy-1H-indazol-5-yl)carbamate (Intermediate 2-10) were reacted with 3.10 ml (28.0 mmol) of ethyl bromoacetate. This gave 1.84 g (52% of theory) of the title compound.

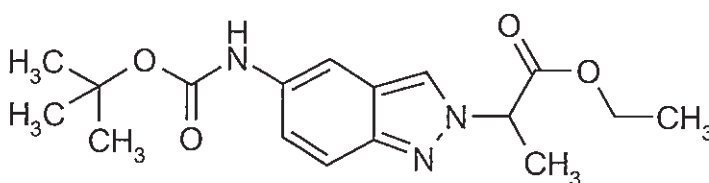
UPLC-MS (Method A1): R_t = 1.32 min

MS (ESIpos): m/z = 378 ($M+H$)⁺

¹H NMR (600 MHz, DMSO-*d*₆): δ = 1.21 (t, 3H), 1.34(d, 6H), 1.48 (s, 9H), 4.16 (q, 2H), 4.68 – 4.75 (m, 1H), 5.27 (s,2H), 6.98 (s, 1H), 7.63 (s, 1H), 7.97 (s, 1H), 8.17 (s, 1H).

Intermediate 3-11

Ethyl 2-{5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}propanoate



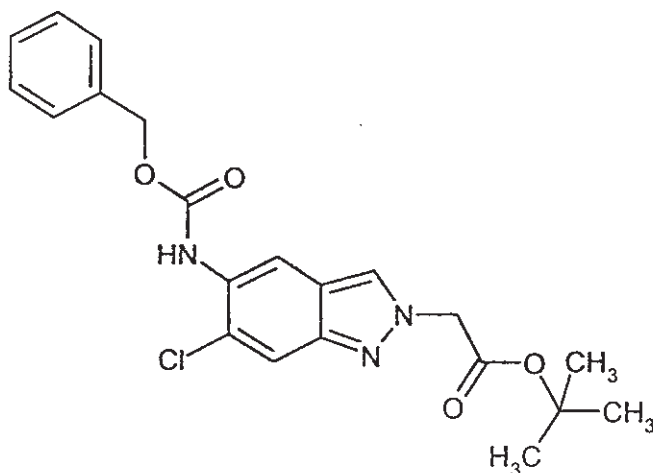
A mixture of 15.0 g (64.3 mmol) of tert-butyl 1H-indazol-5-ylcarbamate (Intermediate 2-8), 9.21 ml (70.7 mmol) of ethyl 2-bromopropanoate and 17.8 g (128.6 mmol) of potassium carbonate in 100 ml of *N,N*-dimethylformamide was stirred at 80°C for 24 h. The mixture was diluted with

water and extracted with ethyl acetate, and the extract was washed with saturated sodium chloride solution and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate). This gave 6.10 g (28% of theory) of the title compound.

¹H NMR (400 MHz, DMSO-d₆): δ = 1.14 (t, 3H), 1.49(s, 9H), 1.77 (d, 3H), 4.07 - 4.17 (m, 2H),
 5 5.52 (q, 1H), 7.23 (dd, 1H), 7.49 (d, 1H), 7.85 (br. s., 1H), 8.32 (s, 1H), 9.22 (s, 1H).

Intermediate 3-12

tert-Butyl (5-[[[(benzyloxy)carbonyl]amino]-6-chloro-2H-indazol-2-yl]acetate



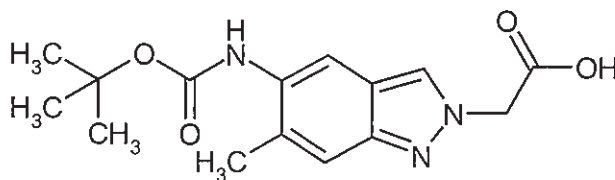
10 2.11 g of benzyl (6-chloro-1H-indazol-5-yl)carbamate (Intermediate 2-11) were initially charged in 20 ml of THF, 1.5 ml of tert-butyl bromoacetate and 2.2 ml of *N,N*-dicyclohexylmethylamine were added and the mixture was stirred at 65°C overnight. Another 0.75 ml of tert-butyl bromoacetate and 1.1 ml of *N,N*-dicyclohexylmethylamine were added, and the mixture was stirred at 70°C overnight. The solid was filtered off, the filter cake was washed with ethyl acetate, water was
 15 added to the filtrate, the mixture was extracted with ethyl acetate and the extract was washed with 1M aqueous hydrochloric acid solution, saturated sodium bicarbonate solution and sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography on silica gel. This gave 950 mg of the title compound as a yellow foam.

¹H NMR (400 MHz, DMSO-d₆): δ = 1.43 (s, 9H), 5.14 (s, 2H), 5.29 (s, 2H), 7.29 – 7.47 (m, 5H),
 20 7.80 (s, 1H), 7.84 (s, 1H), 8.41 (s, 1H), 9.09 (s, 1H).

Intermediate 4-1

{5-[(tert-Butoxycarbonyl)amino]-6-methyl-2H-indazol-2-yl} acetic acid

25



10.7 g (254 mmol) of lithium hydroxide monohydrate dissolved in 50 ml of water were added to 10.6 g (25.4 mmol, 80%) of ethyl {5-[(tert-butoxycarbonyl)amino]-6-methyl-2H-indazol-2-yl}acetate (Intermediate 3-1) in 100 ml of tetrahydrofuran and 10 ml of ethanol, and the mixture was stirred. This resulted in the precipitation of a solid. After 18 h, the reaction mixture was diluted with water and acidified to pH 4 using 2M hydrochloric acid, and the solid was filtered off, washed with water and diethyl ether and dried. This gave 6.98 g (87% of theory) of the title compound.

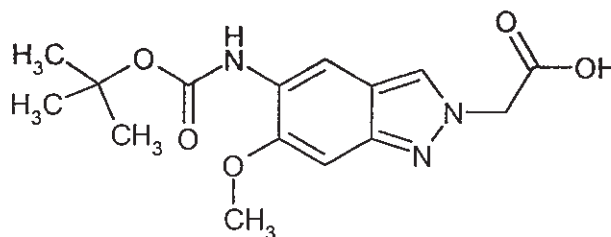
UPLC-MS (Method A1): $R_t = 0.92$ min

MS (ESIpos): $m/z = 306$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.44$ (s, 9H), 2.25 (s, 3H), 4.78 (s, 2H), 7.32 (s, 1H), 7.49 (s, 1H), 8.10 (s, 1H), 8.35 (s, 1H).

Intermediate 4-2

{5-[(tert-Butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetic acid



15

Analogously to Intermediate 4-1, 3.2 g of benzyl {5-[(tert-butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetate (Intermediate 3-2) gave 1.91 g of the title compound.

UPLC-MS (Method A1): $R_t = 1.04$ min

MS (ESIpos): $m/z = 322$ (M+H)⁺

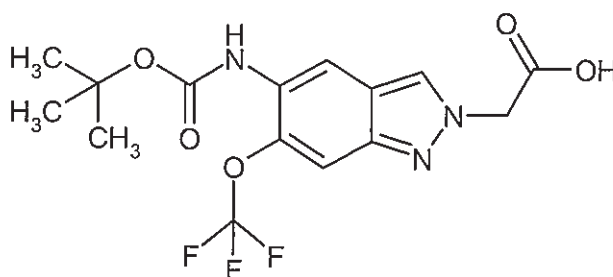
¹H-NMR (500 MHz, DMSO-d₆): $\delta = 1.47$ (s, 9H), 3.86 (s, 3H), 5.16 (s, 2H), 6.96 (s, 1H), 7.78 (s, 1H), 7.93 (br. s., 1H), 8.16 (d, 1H), 13.13 (br. s., 1H).

20

Intermediate 4-3

{5-[(tert-Butoxycarbonyl)amino]-6-(trifluoromethoxy)-2H-indazol-2-yl}acetic acid

25



Analogously to Intermediate 4-1, 530 mg (1.31 mmol) of ethyl {5-[(tert-butoxycarbonyl)amino]-6-(trifluoromethoxy)-2H-indazol-2-yl}acetate (Intermediate 3-3) were suspended in 20 ml of tetrahydrofuran, a solution of 157 mg (6.57 mmol) of lithium hydroxide monohydrate in 2.4 ml of

water was then added and the mixture was stirred at 25°C for 24 h. Work-up gave 437 mg (81% of theory) of the title compound.

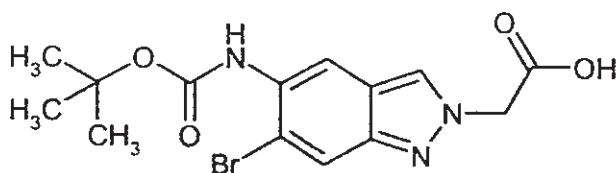
UPLC-MS (Method A1): $R_t = 1.10$ min

MS (ESIpos): $m/z = 376$ (M+H)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 1.44$ (s, 9 H), 5.29 (s, 2 H), 7.57 (s, 1 H), 7.81 (s, 1 H), 8.41 (d, 1 H), 8.74 (s, 1 H).

Intermediate 4-4

{6-Bromo-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid



Analogously to Intermediate 4-1, 1.00 g (2.5 mmol) of ethyl {6-bromo-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetate (Intermediate 3-6) was dissolved in 50 ml of tetrahydrofuran, a solution of 301 mg (12.6 mmol) of lithium hydroxide monohydrate in 4.5 ml of water was then added and the mixture was stirred at 25°C for 24 h. Work-up gave 844 mg (82% of theory) of the title compound.

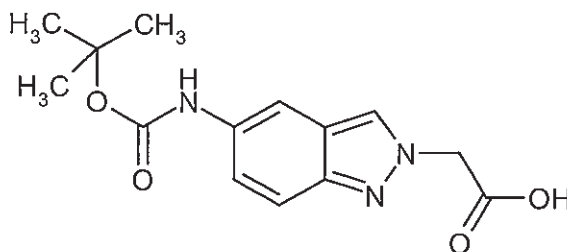
UPLC-MS (Method A1): $R_t = 0.64$ min

MS (ESIpos): $m/z = 370$ (M(⁷⁹Br)+H)⁺

¹H NMR (300 MHz, DMSO-d₆): $\delta = 1.45$ (s, 9 H), 3.35 (s br, 1 H), 5.28 (s, 2 H), 7.76 (s, 1 H), 7.95 (s, 1 H), 8.38 (s, 1 H), 8.52 (s, 1 H).

Intermediate 4-5

{5-[(tert-Butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid



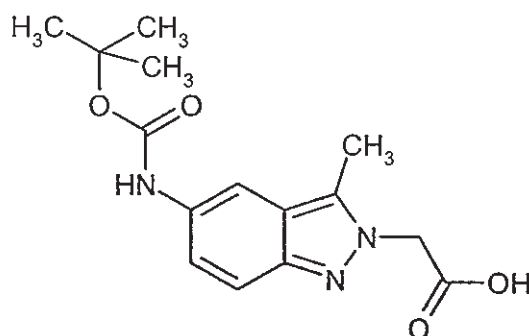
Analogously to Intermediate 4-1, 5.00 g (15.6 mmol) of ethyl {5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetate (Intermediate 3-7) were dissolved in 50 ml of tetrahydrofuran and 5 ml of ethanol, a solution of 6.57 g (15.6 mmol) of lithium hydroxide monohydrate in 20 ml of water was then added and the mixture was stirred at 25°C for 24 h. Work-up gave 4.1 g (89% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 0.90$ min

MS (ESIpos): $m/z = 292$ (M+H)⁺.

Intermediate 4-6

5 {5-[(tert-Butoxycarbonyl)amino]-3-methyl-2H-indazol-2-yl}acetic acid



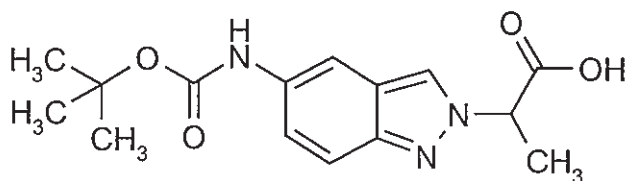
Analogously to Intermediate 4-1, 436 mg (1.3 mmol) of ethyl {5-[(tert-butoxycarbonyl)amino]-3-methyl-2H-indazol-2-yl}acetate (Intermediate 3-8) were dissolved in 5 ml of tetrahydrofuran and 1
10 ml of ethanol, a solution of 549 mg (13.1 mmol) of lithium hydroxide monohydrate in 2.5 ml of water was then added and the mixture was stirred at 25°C for 24 h. This gave, after addition of citric acid, a solid which was filtered off, washed with water and diethyl ether and dried. This gave 320 mg (70% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 0.92$ min

15 MS (ESIpos): $m/z = 306$ (M+H)⁺.

Intermediate 4-7

2-{5-[(tert-Butoxycarbonyl)amino]-2H-indazol-2-yl}propanoic acid



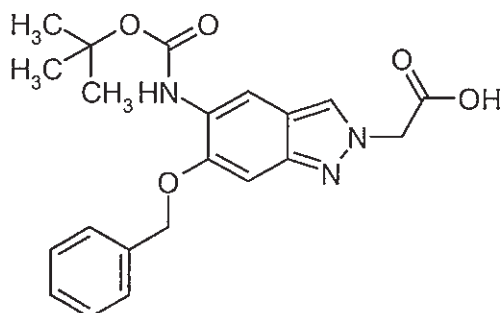
20

Analogously to Intermediate 4-1, 5.77 g (17.3 mmol) of ethyl 2-{5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}propanoate (Intermediate 3-8) were dissolved in 50 ml of tetrahydrofuran and 5 ml of ethanol, a solution of 7.26 g (17.3 mmol) of lithium hydroxide monohydrate in 40 ml of water was then added and the mixture was stirred at 25°C for 24 h. Acidification with 1 M
25 hydrochloric acid solution gave a solid which was filtered off, washed with water and diethyl ether and dried. This gave 4.2 (79% of theory) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.45$ (s, 9H), 1.72 (d, 3H), 5.33 - 5.41 (m, 1H), 7.18 (dd, 1H), 7.45 (d, 1H), 7.82 (s, 1H), 8.26 (s, 1H), 9.20 (s, 1H), 13.13 (br. s., 1H).

Intermediate 4-8

{6-(Benzyloxy)-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid



- 5 Analogously to Intermediate 4-1, 14.15 g (33.3 mmol) of ethyl {6-(benzyloxy)-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetate (Intermediate 3-4) were dissolved in 250 ml of tetrahydrofuran and 25 ml of ethanol, a solution of 3.98 g (166.3 mmol) of lithium hydroxide monohydrate in 30 ml of water was then added and the mixture was stirred at 25°C for 72 h. After acidification with 1 M hydrochloric acid solution to pH 3 the reaction mixture was concentrated,
- 10 water was added and the resulting solid was filtered off, washed with water and diethyl ether and dried. This gave 13.05 g (33% of theory) of the title compound.

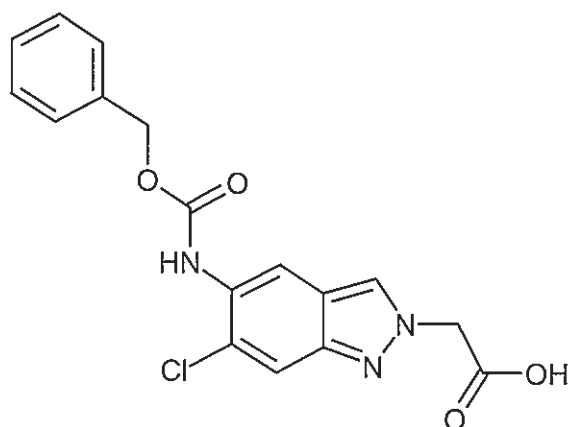
UPLC-MS (Method A1): $R_t = 1.25$ min

MS (ESIpos): $m/z = 398$ ($M+H$)⁺

- ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.45$ (s, 9 H), 4.93 (s, 2 H), 5.20 (s, 2 H), 7.01 (s, 1 H), 7.26 -
- 15 7.45 (m, 3 H), 7.53 (d, 2 H), 7.80 - 7.91 (m, 2 H), 8.11 (s, 1 H).

Intermediate 4-9

(5-{[(Benzyloxy)carbonyl]amino}-6-chloro-2H-indazol-2-yl)acetic acid

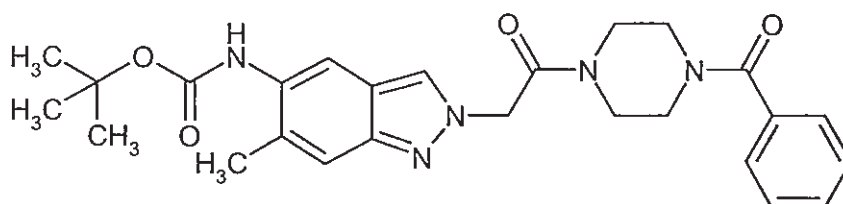


- 20 1.7 ml of trifluoroacetic acid were added to a mixture of 940 g of tert-butyl (5-{[(benzyloxy)carbonyl]amino}-6-chloro-2H-indazol-2-yl)acetate (Intermediate 3-12) in 10 ml of dichloromethane, and the mixture was stirred at room temperature overnight. Saturated aqueous sodium bicarbonate solution was added and the precipitate was filtered off with suction, washed with water and ethyl acetate and dried. This gave 766 mg of the title compound.

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ [ppm] = 4.66 (s, 2H), 5.12 (s, 2H), 7.26 - 7.45 (m, 5H), 7.69 (s, 1H), 7.75 (s, 1H), 8.22 (s, 1H), 9.01 (s, 1H).

Intermediate 5-1

5 tert-Butyl {2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methyl-2H-indazol-5-yl}carbamate



181 mg (0.59 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methyl-2H-indazol-2-yl}acetic acid
 10 (Intermediate 4-1) and 169 mg (0.89 mmol) of phenyl(piperazin-1-yl)methanone were initially
 charged in 5 ml of tetrahydrofuran and 0.5 ml of *NN*-dimethylformamide. 91 mg (0.59 mmol) of 1-
 hydroxy-1H-benzotriazole hydrate, 227 mg (1.19 mmol) of 1-(3-dimethylaminopropyl)-3-
 ethylcarbodiimide hydrochloride and 0.25 ml (1.79 mmol) of triethylamine were added and the
 mixture was stirred at 25°C for 18 h. The mixture was diluted with water and ethyl acetate and the
 15 precipitated solid was filtered off, washed with water and diethyl ether and dried under reduced
 pressure. This gave 248 mg (85% of theory) of the title compound.

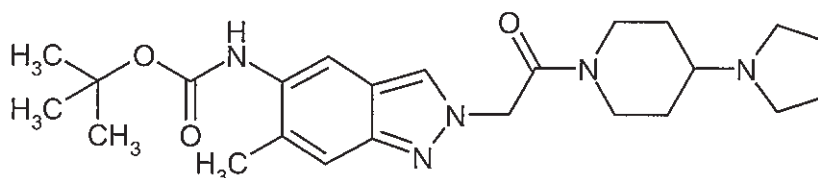
UPLC-MS (Method A1): R_t = 1.07 min

MS (ESIpos): m/z = 478 ($\text{M}+\text{H}$) $^+$

$^1\text{H NMR}$ (400 MHz, DMSO-d_6): δ = 1.42 (s, 9H), 2.24 (s, 3H), 3.32 - 3.82 (m, 8H), 5.41 (br. s.,
 20 2H), 7.33 (s, 1H), 7.38 - 7.48 (m, 5H), 7.52 (s, 1H), 8.12 - 8.16 (m, 1H), 8.35 (s, 1H).

Intermediate 5-2

tert-Butyl (6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-
 25 yl)carbamate



Analogously to Intermediate 5-1, 2.00 g (6.55 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methyl-2H-indazol-2-yl}acetic acid (Intermediate 4-1) were reacted with 1.31 g (8.52 mmol) of 4-(pyrrolidin-1-yl)piperidine. This gave 2.59 g (90% of theory) of the title compound.

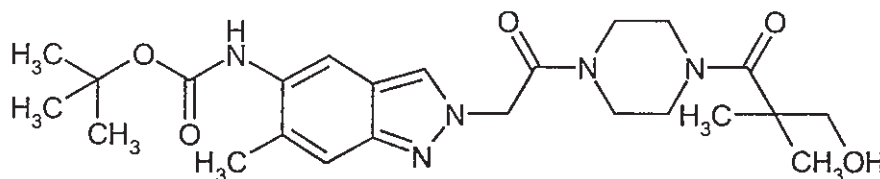
30 UPLC-MS (Method A1): R_t = 0.77 min

MS (ESIpos): m/z = 442 ($\text{M}+\text{H}$) $^+$

¹H-NMR (300 MHz, DMSO-d₆): δ = 1.18 - 1.52 (m, 11H, contains singlet at 1.45 ppm), 1.66 (br. s., 4H), 1.83 (t, 2H), 2.16 - 2.30 (m, 4H), 2.76 - 2.90 (m, 1H), 3.08 - 3.22 (m, 1H), 3.80 - 3.92 (m, 1H), 4.01 - 4.14 (m, 1H), 5.31 - 5.46 (m, 2H), 7.35 (s, 1H), 7.53 (s, 1H), 8.15 (s, 1H), 8.39 (s, 1H).

5 Intermediate 5-3

tert-Butyl (2-{2-[4-(3-hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)carbamate



- 10 Analogously to Intermediate 5-1, 300 mg (0.98 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methyl-2H-indazol-2-yl}acetic acid (Intermediate 4-1) were reacted with 238 mg (1.28 mmol) of 3-hydroxy-2,2-dimethyl-1-(piperazin-1-yl)propan-1-one. This gave 216 mg (46% of theory) of the title compound.

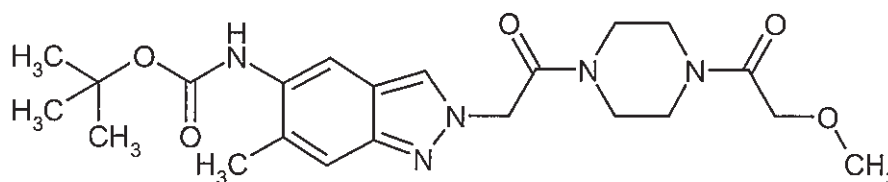
UPLC-MS (Method A2): R_t = 0.96 min

- 15 MS (ESIpos): m/z = 474 (M+H)⁺

¹H NMR (400 MHz, DMSO-d₆): δ = 1.16 (s, 6H), 1.45 (s, 9H), 2.26 (s, 3H), 3.39 - 3.68 (m, 10H), 4.59 (t, 1H), 5.42 (s, 2H), 7.35 (s, 1H), 7.54 (s, 1H), 8.15 (s, 1H), 8.37 (s, 1H).

Intermediate 5-4

- 20 tert-Butyl (2-{2-[4-(methoxyacetyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)carbamate



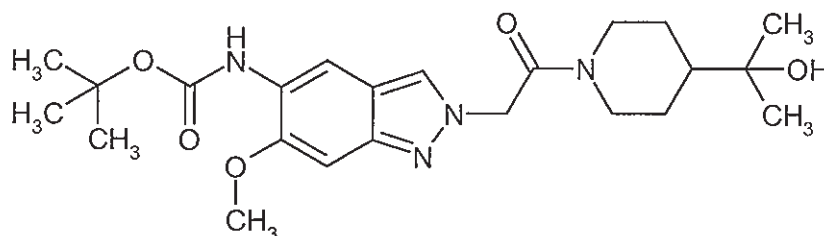
- 25 Analogously to Intermediate 5-1, 300 mg (0.98 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methyl-2H-indazol-2-yl}acetic acid (Intermediate 4-1) were reacted with 248 mg (1.28 mmol) of 2-methoxy-1-(piperazin-1-yl)ethanone hydrochloride (1:1). This gave 144 mg of the title compound as a crude product.

UPLC-MS (Method A2): R_t = 0.93 min

MS (ESIpos): m/z = 446 (M+H)⁺.

Intermediate 5-5

tert-Butyl (2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)carbamate



5

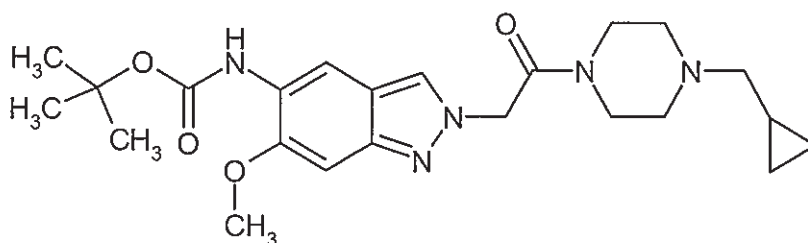
Analogously to Intermediate 5-1, 266 mg (0.83 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetic acid (Intermediate 4-2) were reacted with 154 mg (1.08 mmol) of 2-(piperidin-4-yl)propan-2-ol in 10 ml of tetrahydrofuran. This gave 382 mg of the title compound as a crude product.

10 UPLC-MS (Method A1): $R_t = 1.10$ min

MS (ESIpos): $m/z = 447$ (M+H)⁺.

Intermediate 5-6

15 tert-Butyl (2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)carbamate



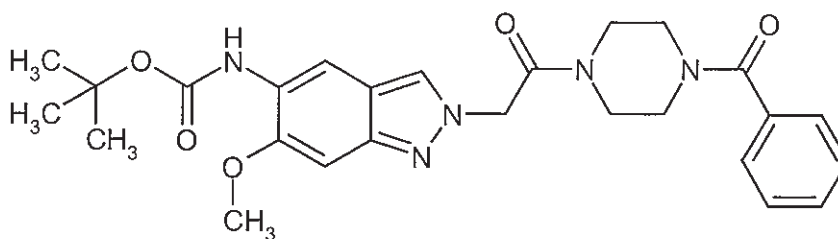
20 Analogously to Intermediate 5-1, 250 mg (0.78 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetic acid (Intermediate 4-2) were reacted with 164 mg (1.17 mmol) of 1-(cyclopropylmethyl)piperazine. This gave 402 mg of the title compound as a crude product.

UPLC-MS (Method A1): $R_t = 0.85$ min

MS (ESIpos): $m/z = 444$ (M+H)⁺.

Intermediate 5-7

25 tert-Butyl {2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}carbamate



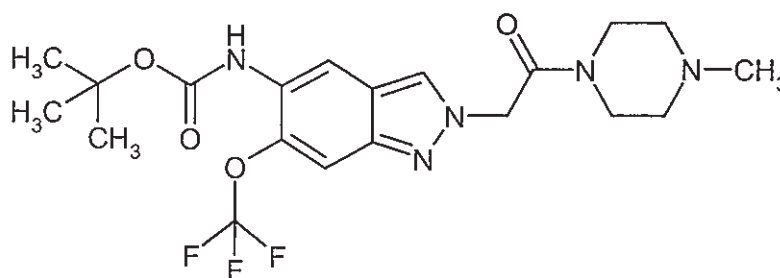
Analogously to Intermediate 5-1, 548 mg (1.71 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetic acid (Intermediate 4-2) were reacted with 389 mg (2.05 mmol) of phenyl(piperazin-1-yl)methanone. This gave 808 mg of the title compound as a crude product.

5 UPLC-MS (Method A1): $R_t = 1.14$ min

MS (ESIpos): $m/z = 494$ (M+H)⁺.

Intermediate 5-8

tert-Butyl {2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}carbamate



350 mg (0.85 mmol) of tert-butyl {2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}carbamate (Intermediate 4-3), 130 mg (0.85 mmol) of 1-hydroxy-1H-benzotriazole hydrate and 325 mg (1.70 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 3.5 ml of *N,N*-dimethylformamide and 473 μ l (3.40 mmol) of triethylamine were stirred at 25°C for 30 min. 103 μ l (0.93 mmol) of 1-methylpiperazine (CAS No.: 109-01-3) were then added and the mixture was stirred at 25°C for 24 h. The mixture was poured into 50 ml of water, filtered off with suction, washed with water and dried. This gave 305 mg (78% of theory) of the title compound.

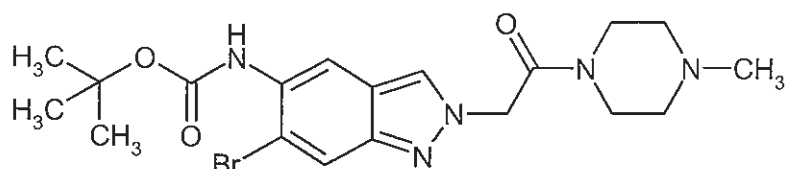
UPLC-MS (Method A2): $R_t = 1.12$ min

MS (ESIpos): $m/z = 376$ (M+H)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 1.44$ (s, 9 H), 2.23 (s, 3 H), 2.28 - 2.38 (m, 2 H), 2.41 (br. s., 2 H), 3.47 (br. s., 2 H), 3.55 (br. s., 2 H), 5.49 (s, 2 H), 7.54 (s, 1 H), 7.80 (s, 1 H), 8.34 (d, 1 H), 8.73 (s, 1 H), 9.93 (br. s., 1 H).

Intermediate 5-9

tert-Butyl {6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate



Analogously to Intermediate 5-8, 800 mg (1.97 mmol) of {6-bromo-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid (Intermediate 4-4) were reacted with 246 μ l (2.17 mmol) of 1-methylpiperazine. This gave 824 mg (93% of theory) of the title compound.

5 UPLC-MS (Method A2): R_t = 1.07 min

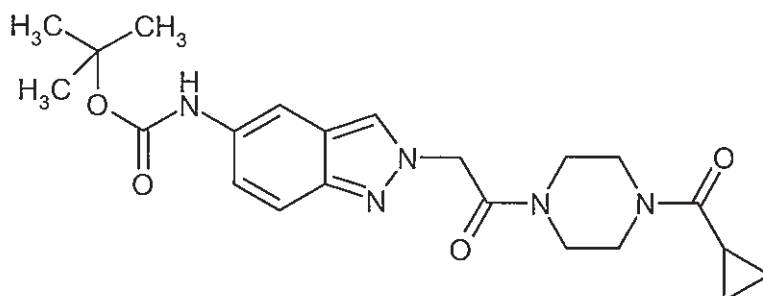
MS (ESIpos): m/z = 452 ($M(^{79}\text{Br})+H$)⁺

¹H NMR (300 MHz, DMSO- d_6): δ = 1.45 (s, 9 H), 2.20 (s, 3 H), 2.25 - 2.34 (m, 2 H), 2.34 - 2.40 (m, 2 H), 3.43 - 3.49 (m, 2 H), 3.50 - 3.55 (m, 2 H), 5.47 (s, 2 H), 7.75 (s, 1 H), 7.93 (s, 1 H), 8.31 (s, 1 H), 8.54 (s, 1 H).

10

Intermediate 5-10

tert-Butyl (2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)carbamate



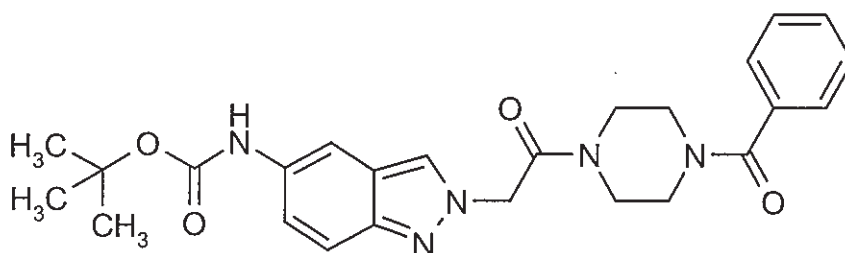
15 Analogously to Intermediate 5-1, 2.00 g (4.3 mmol, 62%) of {5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid (Intermediate 4-5) were reacted with 1.14 g (6.0 mmol) of cyclopropyl(piperazin-1-yl)methanone hydrochloride (1:1). This gave 2.3 g of the title compound as a crude product.

UPLC-MS (Method A1): R_t = 0.97 min

20 MS (ESIpos): m/z = 428 ($M+H$)⁺.

Intermediate 5-11

tert-Butyl {2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate



25

Analogously to Intermediate 5-1, 2.53 mg (8.7 mmol) of {5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid (Intermediate 4-5) were reacted with 1.98 g (10.4 mmol) of phenyl(piperazin-1-yl)methanone to give 3.8 g (93% of theory) of the title compound.

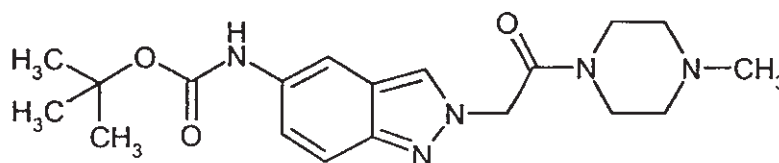
UPLC-MS (Method A1): $R_t = 1.05$ min

5 MS (ESIpos): $m/z = 464$ (M+H)+.

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): $\delta = 1.45$ (s, 9H), 3.30 - 3.78 (m, 8H), 5.41 (br. s., 2H), 7.18 (dd, 1H), 7.35 - 7.50 (m, 6H), 7.82 (br. s., 1H), 8.11 (s, 1H), 9.18 (s, 1H).

Intermediate 5-12

10 tert-Butyl {2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate



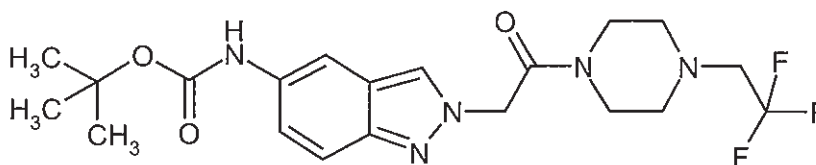
Analogously to Intermediate 5-1, 1.00 g (3.4 mmol) of {5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid (Intermediate 4-5) was reacted with 0.41 g (4.1 mmol) of 1-methylpiperazine to give 916 mg (71% of theory) of the title compound.

15 UPLC-MS (Method A1): $R_t = 0.73$ min

MS (ESIpos): $m/z = 374$ (M+H)+.

Intermediate 5-13

20 tert-Butyl (2-{2-oxo-2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)carbamate



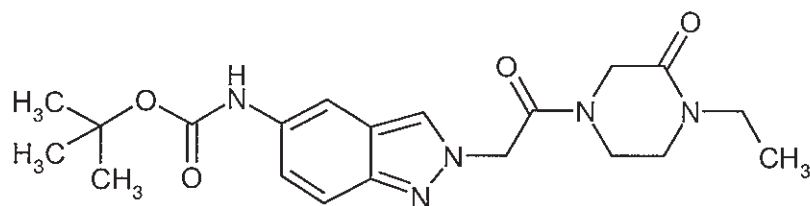
Analogously to Intermediate 5-1, 1.01 g (3.5 mmol) of {5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid (Intermediate 4-5) were reacted with 1.00 g (4.2 mmol) of 1-(2,2,2-trifluoroethyl)piperazine dihydrochloride to give 634 g (42% of theory) of the title compound.

25 UPLC-MS (Method A1): $R_t = 1.11$ min

MS (ESIpos): $m/z = 442$ (M+H)+.

Intermediate 5-14

30 tert-Butyl {2-[2-(4-ethyl-3-oxopiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate



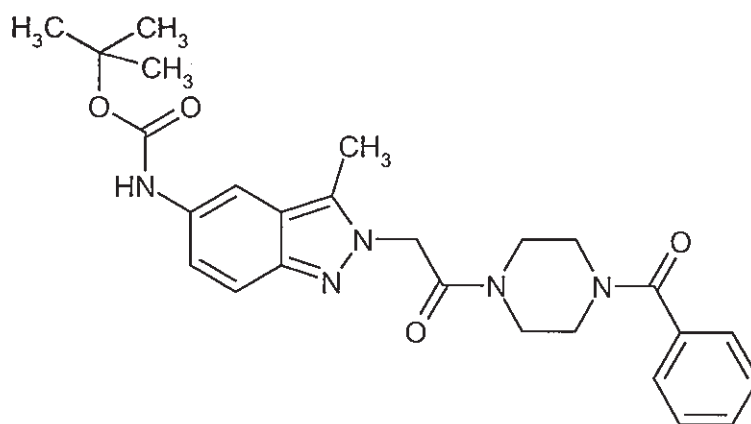
Analogously to Intermediate 5-1, 2.38 g (3.5 mmol, 62%) of {5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid (Intermediate 4-5) were reacted with 1.00 g (6.1 mmol) of 1-ethylpiperazin-2-one hydrochloride (1:1) to give 1.92 g (71% of theory) of the title compound as a crude product.

UPLC-MS (Method A1): $R_t = 0.92$ min

MS (ESIpos): $m/z = 402$ ($M+H$)⁺.

Intermediate 5-15

tert-Butyl {2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-3-methyl-2H-indazol-5-yl}carbamate



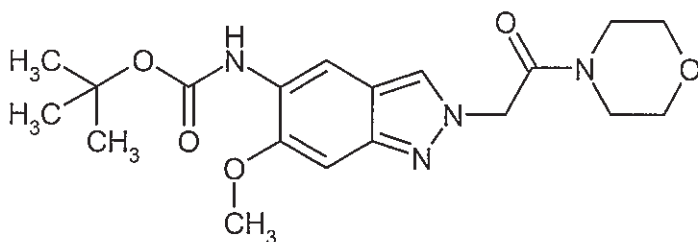
Analogously to Intermediate 5-1, 160 mg (0.52 mmol) of {5-[(tert-butoxycarbonyl)amino]-3-methyl-2H-indazol-2-yl}acetic acid (crude product) (Intermediate 4-6) were reacted with 150 mg (0.79 mmol) of phenyl(piperazin-1-yl)methanone. Addition of water and ethyl acetate resulted in the precipitation of a solid which was washed with water and diethyl ether and dried. This gave 130 mg (52% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 1.07$ min

MS (ESIpos): $m/z = 478$ ($M+H$)⁺.

Intermediate 5-16

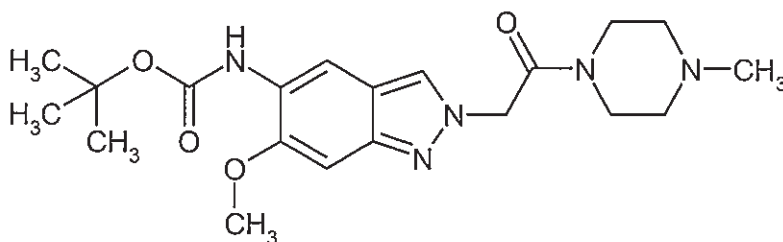
tert-Butyl {6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate



- Analogously to Intermediate 5-1, 1.00 g (3.11 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetic acid (Intermediate 4-2) was reacted with 407 μ l (4.67 mmol) of 1-methylpiperazine. The reaction mixture was added to water and extracted with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, dried over sodium sulphate, filtered, concentrated and dried. This gave 1.16 g (95% of theory) of the title compound.
- UPLC-MS (Method A2): R_t = 1.03 min
- MS (ESIpos): m/z = 391 (M+H)⁺
- ¹H NMR (300 MHz, CHLOROFORM-d): δ = 1.55 (s, 9 H), 3.58 (s, 4 H), 3.66 (s, 4 H), 3.93 (s, 3 H), 5.18 (s, 2 H), 6.94 (s, 1 H), 7.22 (s, 1 H), 7.81 - 7.90 (m, 1 H), 8.25 (s, 1 H).

Intermediate 5-17

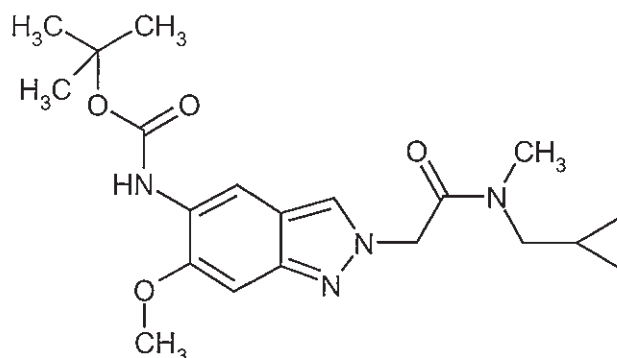
tert-Butyl {6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamate



- Analogously to Intermediate 5-16, 1.00 g (3.11 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetic acid (Intermediate 4-2) was reacted with 530 μ l (4.67 mmol) of 1-methylpiperazine. Work-up gave 1.21 g (96% of theory) of the title compound.
- UPLC-MS (Method A1): R_t = 0.82 min
- MS (ESIpos): m/z = 404 (M+H)⁺
- ¹H NMR (300 MHz, CHLOROFORM-d): δ = 1.55 (s, 9 H), 2.28 (s, 3 H), 2.30 - 2.34 (m, 2 H), 2.34 - 2.41 (m, 3 H), 3.52 - 3.61 (m, 2 H), 3.62 - 3.71 (m, 2 H), 3.93 (s, 3 H), 5.18 (s, 2 H), 6.94 (s, 1 H), 7.22 (s, 1 H), 7.85 (s, 1 H), 8.24 (s, 1 H).

Intermediate 5-18

tert-Butyl (2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)carbamate



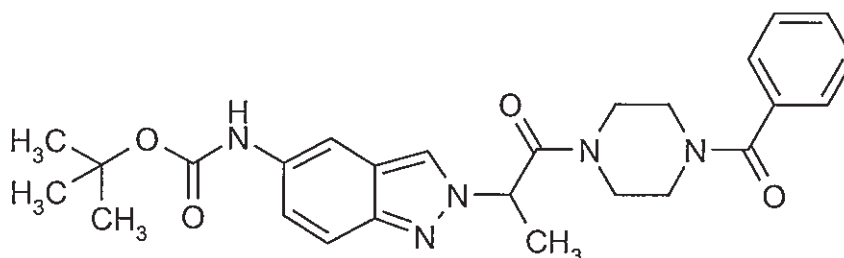
Analogously to Intermediate 5-1, 250 mg (0.78 mmol) of {5-[(tert-butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetic acid (Intermediate 4-2) were stirred with 86 mg (1.01 mmol) of 1-cyclopropyl-N-methylmethanamine at 25°C for 24 h. The mixture was diluted with water and
 5 extracted three times with ethyl acetate, and the extracts were washed with saturated sodium chloride solution and concentrated. This gave 353 mg of a crude product.

UPLC-MS (Method A1): $R_t = 1.19$ min

MS (ESIpos): $m/z = 389$ ($M+H$)⁺.

10 **Intermediate 5-19**

tert-Butyl 2-[1-(4-benzoylpiperazin-1-yl)-1-oxopropan-2-yl]-2H-indazol-5-yl} carbamate



Analogously to Intermediate 5-1, 2.00 g (6.55 mmol) of {5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}propanoic acid (Intermediate 4-6) and 1.50 g (7.86 mmol) of phenyl(piperazin-1-yl)methanone were stirred at 25°C for 24 h. This gave 3.7 g of the title compound as a crude
 15 product.

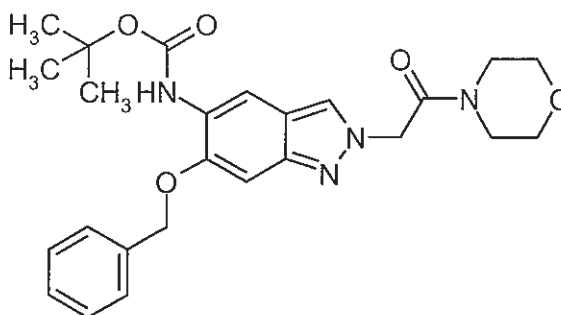
UPLC-MS (Method A1): $R_t = 1.11$ min

MS (ESIpos): $m/z = 448$ ($M+H$)⁺.

20

Intermediate 5-20

tert-Butyl {6-(benzyloxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamate



Analogously to Intermediate 5-1, 3.50 g (8.81 mmol) of {6-(benzyloxy)-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetic acid (Intermediate 4-8) and 1.14 ml (13.2 mmol) of morpholine were reacted at 25°C for 24 h. Work-up gave 3.67 g (89% of theory) of the title compound.

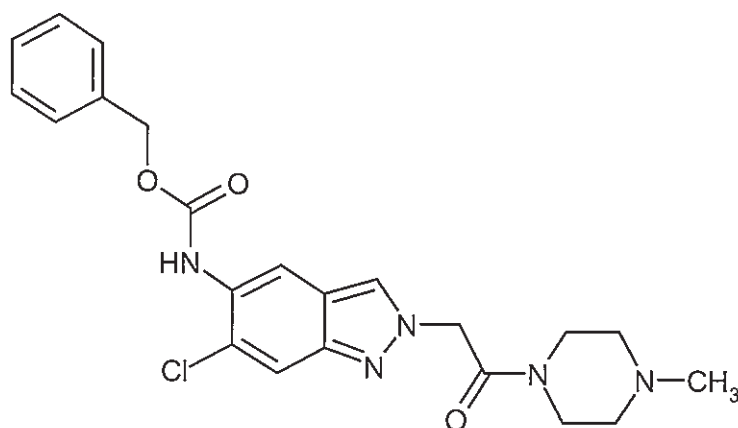
UPLC-MS (Method A1): $R_t = 1.25$ min

MS (ESIpos): $m/z = 467$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 1.45$ (s, 9 H), 3.41 - 3.48 (m, 2 H), 3.51 - 3.60 (m, 4 H), 3.61 - 3.66 (m, 2 H), 5.21 (s, 2 H), 5.35 (s, 2 H), 7.01 (s, 1 H), 7.29 - 7.37 (m, 1 H), 7.38 - 7.44 (m, 2 H), 7.50 - 7.57 (m, 2 H), 7.87 (s, 2 H), 8.11 (s, 1 H).

Intermediate 5-21

Benzyl {6-chloro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamate

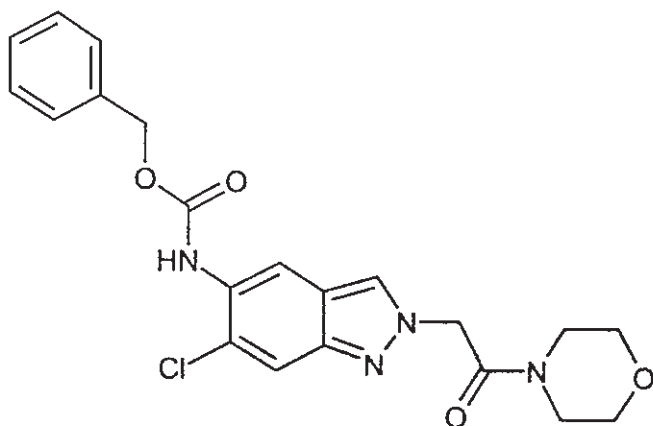


387 mg of (5-[(benzyloxy)carbonyl]amino)-6-chloro-2H-indazol-2-yl}acetic acid (Intermediate 4-9) were reacted analogously to the preparation of Intermediate 5-1 with 140 mg of 1-methylpiperazine. After the reaction, the mixture was diluted with water and ethyl acetate and saturated sodium chloride solution were added. The precipitated solid was filtered off, washed with water and diethyl ether and dried. This gave 302 mg of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm]= 2.19 (s, 3H), 2.23 - 2.41 (m, 4H), 3.41 - 3.48 (m, 2H), 3.48 - 3.56 (m, 2H), 5.13 (s, 2H), 5.46 (s, 2H), 7.28 - 7.45 (m, 5H), 7.75 (s, 1H), 7.81 (s, 1H), 8.32 (d, 1H), 9.07 (s, 1H).

5 Intermediate 5-22

Benzyl {6-chloro-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamate

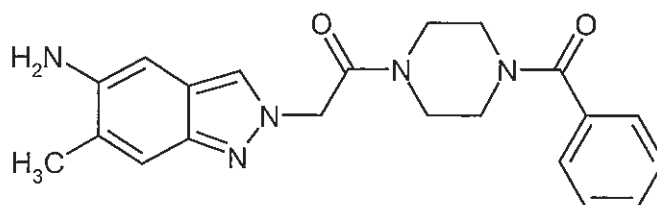


400 mg of benzyl (6-chloro-1H-indazol-5-yl)carbamate (Intermediate 2-11) were initially charged in 5.0 ml of cyclopentyl methyl ether. 265 mg of 2-bromo-1-(morpholin-4-yl)ethanone and 0.22 ml of N-ethyl-N-isopropylpropane-2-amine were added and the mixture was stirred at 100°C for 20 h. Water was added and a solid was obtained by removing oily residues from the rim of the flask by scratching. The solid was filtered off with suction, washed with water and diethyl ether, triturated with ethyl acetate and dried. This gave 254 mg of the title compound.

¹H-NMR (500 MHz, DMSO-d₆): δ[ppm] = 3.47 (d, 2H), 3.56 (d, 2H), 3.58 - 3.61 (m, 2H), 3.65 (d, 2H), 5.15 (s, 2H), 5.49 (s, 2H), 7.28-7.48 (m, 5H), 7.76 (s, 1H), 7.83 (s, 1H), 8.33 (s, 1H), 9.07 (s, 1H).

Intermediate 6-1

2-(5-Amino-6-methyl-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)ethanone



0.3 ml (3.89 mmol) of trifluoroacetic acid was added to 247 mg (0.52 mmol) of tert-butyl {2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methyl-2H-indazol-5-yl} carbamate (Intermediate 5-1) in 5 ml of dichloromethane and the mixture was stirred at 25°C for 18 h. Another 0.3 ml (3.89 mmol) of trifluoroacetic acid was then added and the mixture was stirred for 18 h, poured into saturated

sodium bicarbonate solution and extracted times with dichloromethane. Concentration gave 223 mg of the title compound as a crude product.

UPLC-MS (Method A1): $R_t = 0.61$ min

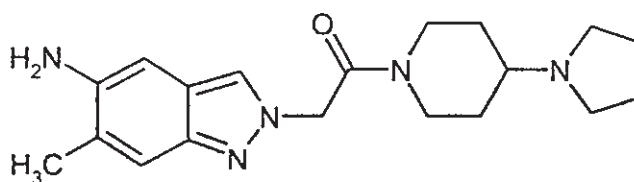
MS (ESIpos): $m/z = 378$ (M+H)⁺

- 5 ¹H NMR (400 MHz, DMSO-d₆): $\delta = 2.15$ (s, 3H), 3.29 – 3.75 (m, 8H), 4.53 (s, 2H), 5.28 (br. s., 2H), 6.63 (s, 1H), 7.17 (s, 1H), 7.37 – 7.47 (m, 5H), 7.75 – 7.79 (m, 1H).

Intermediate 6-2

2-(5-Amino-6-methyl-2H-indazol-2-yl)-1-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethanone

10



- 2.59 g (5.87 mmol) of tert-butyl (6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)carbamate (Intermediate 5-2) were initially charged in 30 ml of dichloromethane, 4.5 ml (58.7 mmol) of trifluoroacetic acid were added and the mixture was stirred at 25°C for 78 h.
- 15 The reaction mixture was concentrated and twice toluene was added and in each case the mixture was concentrated again. The residue was purified by HPLC according to Method P2 (gradient: 0-0.5 min 25 ml/min to 70 ml/min 25% B; 0.5-5.5 min 25-55% B; flow rate: 70 ml/min). This gave 1.04 g (52% of theory) of the title compound.

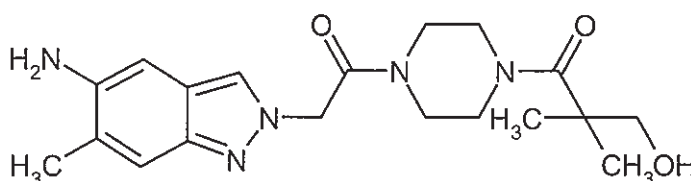
UPLC-MS (Method A2): $R_t = 0.81$ min

- 20 MS (ESIpos): $m/z = 342$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.16$ – 1.47 (m, 2H), 1.66 (br. s., 4H), 1.82 (br. s., 2H), 2.12 – 2.28 (m, 4H), 2.74 – 2.89 (m, 1H), 3.05 – 3.20 (m, 1H), 3.79 – 3.92 (m, 1H), 4.02 – 4.14 (m, 1H), 4.58 (br. s., 2H), 5.18 – 5.33 (m, 2H), 6.65 (s, 1H), 7.19 (s, 1H), 7.78 (d, 1H).

25 Intermediate 6-3

1-{4-[(5-Amino-6-methyl-2H-indazol-2-yl)acetyl]piperazin-1-yl}-3-hydroxy-2,2-dimethylpropan-1-one



- 30 0.34 ml (4.37 mmol) of trifluoroacetic acid was added to 207 mg (0.44 mmol) of tert-butyl (2-{2-[4-(3-hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)carbamate (Intermediate 5-3) in 5 ml of dichloromethane, and the mixture was stirred at 25°C

for 2 days. The mixture was poured into saturated sodium bicarbonate solution and extracted three times with dichloromethane, and the extracts were concentrated. This gave 184 mg of the title compound as a crude product.

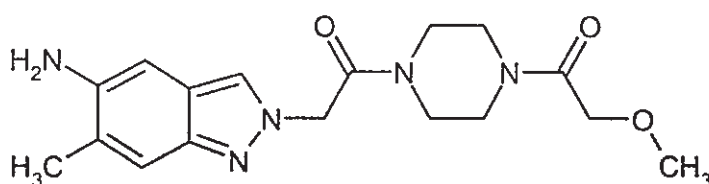
UPLC-MS (Method A1): $R_t = 0.52$ min

5 MS (ESIpos): $m/z = 374$ (M+H)⁺.

Intermediate 6-4

2-(5-Amino-6-methyl-2H-indazol-2-yl)-1-[4-(methoxyacetyl)piperazin-1-yl]ethanone

10



0.25 ml (3.23 mmol) of trifluoroacetic acid were added to 144 mg (0.32 mmol) of tert-butyl (2-{2-[4-(methoxyacetyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)carbamate (Intermediate 5-4) in 3 ml of dichloromethane, and the mixture was stirred at 25°C for 24 h. The mixture was concentrated, giving 219 mg of the title compound as a crude product.

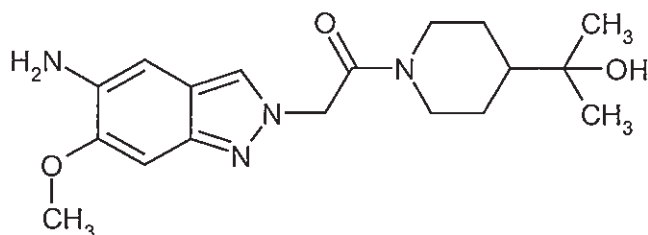
15 UPLC-MS (Method A1): $R_t = 0.46$ min

MS (ESIpos): $m/z = 346$ (M+H)⁺.

Intermediate 6-5

2-(5-Amino-6-methoxy-2H-indazol-2-yl)-1-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]ethanone

20



261 μ l (3.38 mmol) of trifluoroacetic acid were added to 382 mg (0.86 mmol) of tert-butyl (2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)carbamate (Intermediate 5-5) in 5 ml of dichloromethane, and the mixture was stirred at 25°C for 18 h.

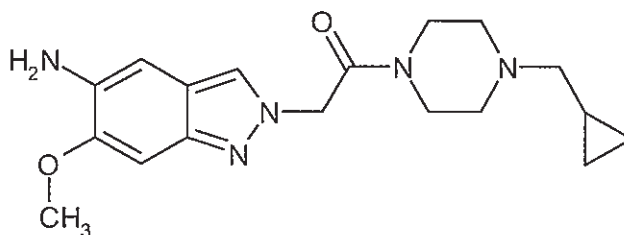
25 Another 609 μ l (7.90 mmol) of trifluoroacetic acid were added, and stirring was continued at 25°C until the reaction had gone to completion. The mixture was concentrated and three times toluene was added and in each case removed again under reduced pressure. This gave 735 mg of the title compound as a crude product.

UPLC-MS (Method A1): $R_t = 0.57$ min

30 MS (ESIpos): $m/z = 347$ (M+H)⁺.

Intermediate 6-6

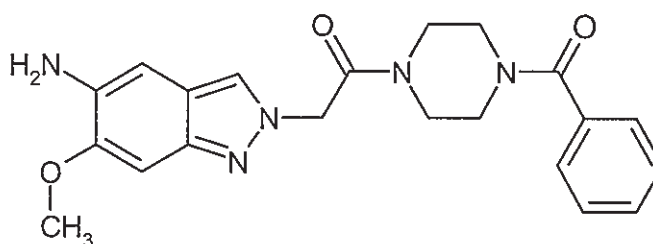
2-(5-Amino-6-methoxy-2H-indazol-2-yl)-1-[4-(cyclopropylmethyl)piperazin-1-yl]ethanone



- 5 Analogously to Intermediate 6-5, 402 mg (0.86 mmol) of tert-butyl (2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)carbamate (Intermediate 5-6) were reacted with 663 μ l (8.61 mmol) of trifluoroacetic acid in 5 ml of dichloromethane. This gave 822 mg of the title compound as a crude product.

10 **Intermediate 6-7**

2-(5-Amino-6-methoxy-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)ethanone



- 15 Analogously to Intermediate 6-3, 808 mg (1.64 mmol) of tert-butyl {2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}carbamate (Intermediate 5-7) were stirred with 1.26 ml (16.37 mmol) of trifluoroacetic acid in 10 ml of dichloromethane at 25°C for 18 h. Work-up gave 649 mg (99% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 0.63$ min

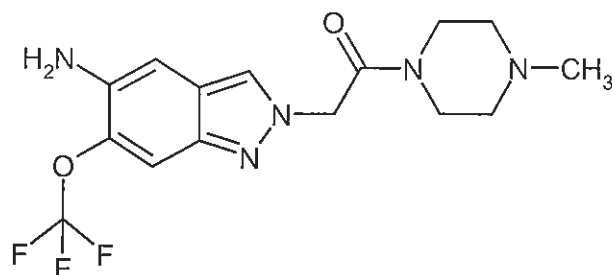
MS (ESIpos): $m/z = 394$ ($M+H$)⁺

- 20 ¹H NMR (400 MHz, DMSO-d₆): $\delta = 3.33 - 3.79$ (8H), 3.81 (s, 3H), 4.60 (s, 2H), 5.27 (br. s., 2H), 6.62 (s, 1H), 6.78 (s, 1H), 7.39 - 7.50 (m, 5H), 7.76 (s, 1H).

Intermediate 6-8

2-[5-Amino-6-(trifluoromethoxy)-2H-indazol-2-yl]-1-(4-methylpiperazin-1-yl)ethanone

25



Analogously to Intermediate 6-4, 484 mg (1.06 mmol) of tert-butyl {2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl} carbamate (Intermediate 5-8) were reacted with 815 μ l of trifluoroacetic acid in 5 ml of dichloromethane. Work-up gave 320 mg (85% of theory) of the title compound.

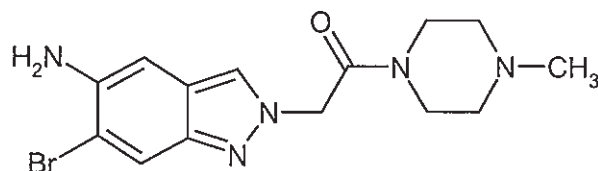
UPLC-MS (Method A2): R_t = 0.79 min

MS (ESIpos): m/z = 357 ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): δ = 2.16 - 2.24 (m, 3 H), 2.28 (t, 2 H), 2.32 - 2.40 (m, 2 H), 3.41 - 3.49 (m, 2 H), 3.49 - 3.56 (m, 2 H), 4.95 (s, 2 H), 5.36 (s, 2 H), 6.88 (s, 1 H), 7.39 (s, 1 H), 7.98 (s, 1 H).

Intermediate 6-9

2-(5-Amino-6-bromo-2H-indazol-2-yl)-1-(4-methylpiperazin-1-yl)ethanone



Analogously to Intermediate 6-4, 293 mg (0.65 mmol) of tert-butyl {6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamate (Intermediate 5-9) were reacted with 499 μ l (6.48 mmol) of trifluoroacetic acid in 3 ml of dichloromethane. Work-up gave 210 mg (92% of theory) of the title compound.

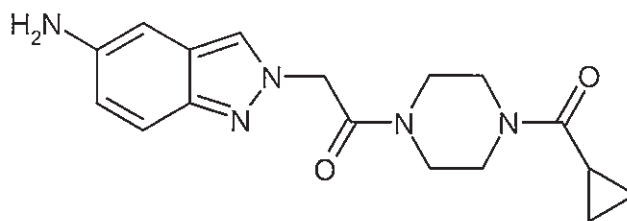
UPLC-MS (Method A2): R_t = 0.70 min

MS (ESIpos): m/z = 352 ($M(^{79}\text{Br})+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): δ = 2.20 (s, 3 H), 2.27 (t, 2 H), 2.31 - 2.40 (m, 2 H), 3.41 - 3.48 (m, 2 H), 3.49 - 3.56 (m, 2 H), 4.91 (s, 2 H), 5.34 (s, 2 H), 6.92 (s, 1 H), 7.77 (s, 1 H), 7.95 (d, 1 H).

Intermediate 6-10

2-(5-Amino-2H-indazol-2-yl)-1-[4-(cyclopropylcarbonyl)piperazin-1-yl]ethanone



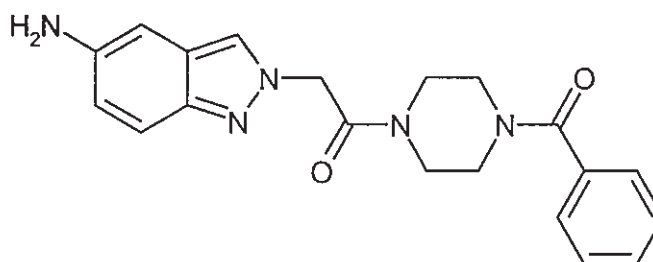
Analogously to Intermediate 6-4, 2.3 g (5.38 mmol) of tert-butyl (2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)carbamate (Intermediate 5-10) were reacted with 4.1 ml (53.8 mmol) of trifluoroacetic acid in 25 ml of dichloromethane to give
 5 1.09 g (62% of theory) of the title compound as a crude product.

UPLC-MS (Method A1): $R_t = 0.47$ min

MS (ESIpos): $m/z = 328$ ($M+H$)⁺.

Intermediate 6-11

10 2-(5-Amino-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)ethanone



Analogously to Intermediate 6-4, 4.20 g (9.06 mmol) of tert-butyl {2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate (Intermediate 5-11) were reacted with 6.98 ml (90.6
 15 mmol) of trifluoroacetic acid to give 3.27 g (99% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 0.57$ min

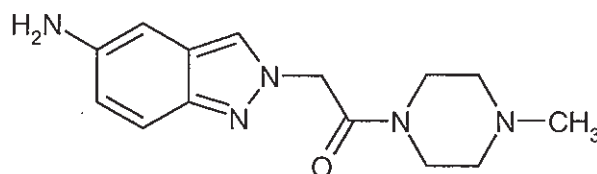
MS (ESIpos): $m/z = 364$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-*d*₆): $\delta = 3.36 - 3.80$ (m, 8H), 4.78 (s, 2H), 5.33 (br. s., 2H), 6.55 (d, 1H), 6.74 (dd, 1H), 7.30 (d, 1H), 7.38 - 7.53 (m, 5H), 7.81 (s, 1H).

20

Intermediate 6-12

2-(5-Amino-2H-indazol-2-yl)-1-(4-methylpiperazin-1-yl)ethanone

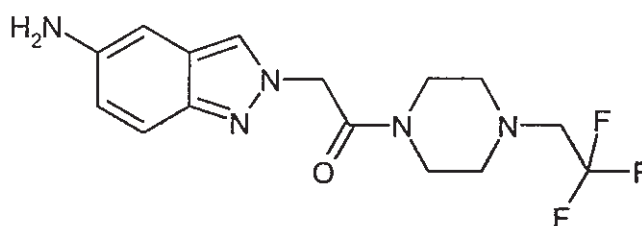


25 Analogously to Intermediate 6-4, 916 mg (2.45 mmol) of tert-butyl {2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate (Intermediate 5-12) were stirred with 1.89 ml (24.5 mmol)

of trifluoroacetic acid in dichloromethane at 25°C for 24 h. The mixture was concentrated and the crude product was dissolved in 10 ml of tetrahydrofuran and 1 ml of *N,N*-dimethylformamide. The precipitated solid was filtered off and washed with diethyl ether. The solid was dissolved in methanol and the solution was concentrated to dryness. This gave 1.2 g of the title compound as a crude product.

Intermediate 6-13

2-(5-Amino-2H-indazol-2-yl)-1-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethanone



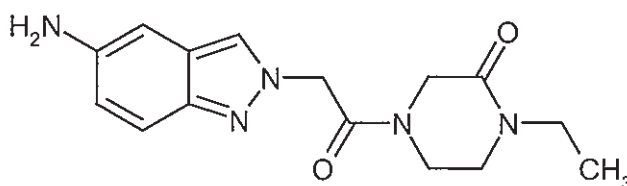
Analogously to Intermediate 6-4, 1.1 ml (14.4 mmol) of trifluoroacetic acid were added to 634 mg (1.43 mmol) of tert-butyl (2-{2-oxo-2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)carbamate (Intermediate 5-13) in 5 ml of dichloromethane and the mixture was stirred at 25°C for 24 h. The mixture was concentrated and twice toluene was added and evaporated. This gave 1.0 g of a crude product.

UPLC-MS (Method A1): $R_t = 0.59$ min

MS (ESIpos): $m/z = 342$ ($M+H$)⁺.

Intermediate 6-14

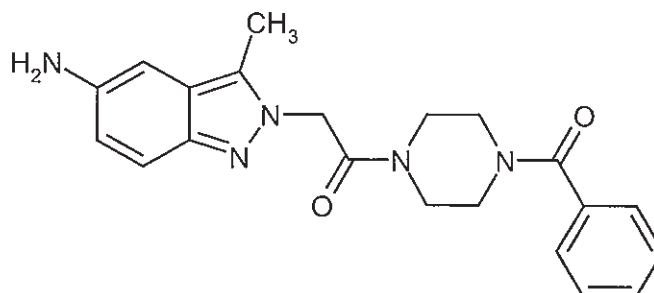
4-[(5-Amino-2H-indazol-2-yl)acetyl]-1-ethylpiperazin-2-one



Analogously to Intermediate 6-4, 2.8 ml (35.9 mmol) of trifluoroacetic acid were added to 1.92 g (3.59 mmol, 75%) of tert-butyl {2-[2-(4-ethyl-3-oxopiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate (Intermediate 5-14) in 15 ml of dichloromethane and the mixture was stirred at 25°C for 24 h. Saturated sodium bicarbonate solution was added, the mixture was filtered, the organic phase was separated off and the aqueous phase was extracted with dichloromethane. A precipitate formed in the aqueous phase; this precipitate was filtered off with suction and washed with water and diethyl ether. Drying gave 636 mg (44% of theory) of the title compound as a crude product.

Intermediate 6-15

2-(5-Amino-3-methyl-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)ethanone



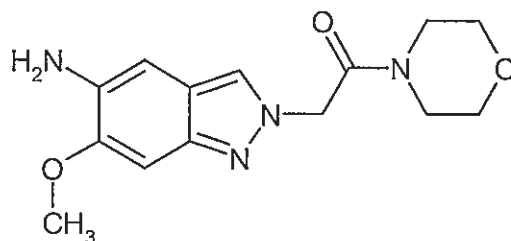
- 5 0.21 ml (2.72 mmol) of trifluoroacetic acid was added to 130 mg (0.27 mmol) of tert-butyl {2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-3-methyl-2H-indazol-5-yl} carbamate in 3 ml of dichloromethane, and the mixture was stirred at 25°C for 24 h and concentrated. This gave 204 mg of the title compound as a crude product.

UPLC-MS (Method A1): $R_t = 0.61$ min

- 10 MS (ESIpos): $m/z = 378$ ($M+H$)⁺.

Intermediate 6-16

2-(5-Amino-6-methoxy-2H-indazol-2-yl)-1-(morpholin-4-yl)ethanone



15

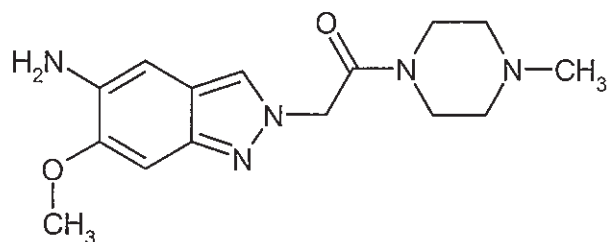
- Analogously to Intermediate 6-4, 1.16 g (2.97 mmol) of tert-butyl {6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamate (Intermediate 5-16) were stirred with 2.29 ml (29.7 mmol) of trifluoroacetic acid in 20 ml of dichloromethane at 25°C for 24 h. A further 1.15 ml (14.9 mmol) of trifluoroacetic acid were added, and the mixture was stirred at 25°C for a further 24 h.
- 20 Three times, the reaction mixture was concentrated with toluene. The residue was dissolved in tetrahydrofuran and diethyl ether was added. The resulting precipitate was filtered off with suction, washed with diethyl ether and dried. This gave 759 mg (88% of theory) of the title compound.

UPLC-MS (Method A2): $R_t = 0.60$ minMS (ESIpos): $m/z = 291$ ($M+H$)⁺

- 25 ¹H NMR (400 MHz, DMSO-d₆): $\delta = 3.45$ (br. s., 2 H), 3.51 - 3.71 (m, 6 H), 3.93 (s, 3 H), 5.40 (s, 2 H), 7.10 (s, 1 H), 7.52 (s, 1 H), 8.21 (s, 1 H).

Intermediate 6-17

2-(5-Amino-6-methoxy-2H-indazol-2-yl)-1-(4-methylpiperazin-1-yl)ethanone



- 5 Analogously to Intermediate 6-16, 1.25 g (3.10 mmol) of tert-butyl {6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate (Intermediate 5-17) were stirred with 2.39 ml (31.0 mmol) of trifluoroacetic acid in 25 ml of dichloromethane at 25°C for 5 h. Work-up gave 534 mg (57% of theory) of the title compound.

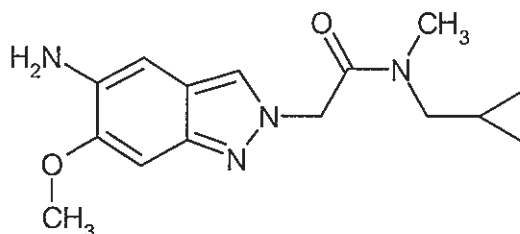
UPLC-MS (Method A2): $R_t = 0.61$ min

- 10 MS (ESIpos): $m/z = 304$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 2.19$ (s, 3 H), 2.24 - 2.30 (m, 2 H), 2.30 - 2.37 (m, 2 H), 3.41 - 3.48 (m, 2 H), 3.49 - 3.54 (m, 2 H), 3.82 (s, 3 H), 4.61 (br. s., 2 H), 5.23 (s, 2 H), 6.63 (s, 1 H), 6.79 (s, 1 H), 7.76 (s, 1 H).

15 **Intermediate 6-18**

2-(5-Amino-6-methoxy-2H-indazol-2-yl)-N-(cyclopropylmethyl)-N-methylacetamide

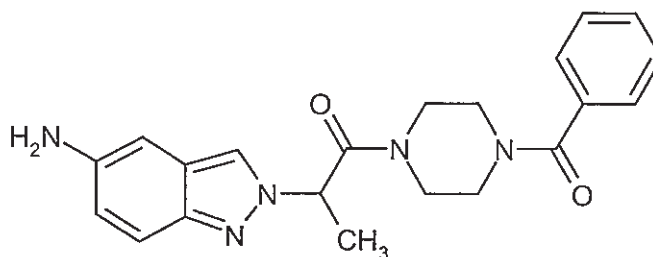


- Analogously to Intermediate 6-4, 353 mg (0.86 mmol, 95%) of tert-butyl (2-{2-
20 [(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)carbamate (Intermediate 5-18) were initially charged in 10 ml of dichloromethane. 665 μ l (8.63 mmol) of trifluoroacetic acid were added, the mixture was stirred at 25°C for 24 h, another 200 μ l of trifluoroacetic acid were added and the mixture was stirred for 3 h. The mixture was concentrated and twice toluene was added and in each case the mixture was concentrated again. This gave 750
25 mg of a crude product.

UPLC-MS (Method A1): $R_t = 0.61$ minMS (ESIpos): $m/z = 289$ ($M+H$)⁺.

Intermediate 6-19

2-(5-Amino-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)propan-1-one

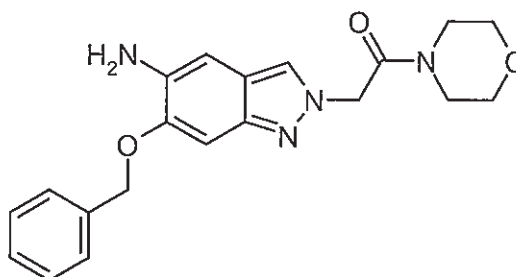


- 5 Analogously to Intermediate 6-4, 3.70 g (7.75 mmol) of tert-butyl {2-[1-(4-benzoylpiperazin-1-yl)-1-oxopropan-2-yl]-2H-indazol-5-yl} carbamate (Intermediate 5-19) (crude product) were initially charged in 40 ml of dichloromethane. 6.0 ml (77.4 mmol) of trifluoroacetic acid were added and the mixture was stirred at 25°C for 24 h. The mixture was carefully poured into saturated sodium bicarbonate solution, extracted with dichloromethane and concentrated. The crude product was
- 10 triturated with diethyl ether. This gave 2.4 g (75% of theory) of the title compound as a light-brown solid.

¹H-NMR (300 MHz, DMSO-d₆): δ = 1.59 (d, 3H), 2.9 – 3.7 (broad signals, superimposed), 4.78 (s, 2H), 5.74 (br. s, 1H), 6.52 (s, 1H), 6.71 (dd, 1H), 7.25 - 7.47 (m), 7.91 (s, 1H).

15 **Intermediate 6-20**

2-[5-Amino-6-(benzyloxy)-2H-indazol-2-yl]-1-(morpholin-4-yl)ethanone



- Analogously to Intermediate 6-4, 3.65 g (7.82 mmol) of tert-butyl {6-(benzyloxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamate (Intermediate 5-20) were initially charged in 50 ml
- 20 of dichloromethane. 6.0 ml (78.2 mmol) of trifluoroacetic acid were added and the mixture was stirred at 25°C for 24 h. The mixture was carefully poured into saturated sodium bicarbonate solution and extracted with dichloromethane, and the combined organic phases were washed with saturated sodium chloride solution and concentrated. This gave 2.72 g (95% of theory) of the title
- 25 compound.

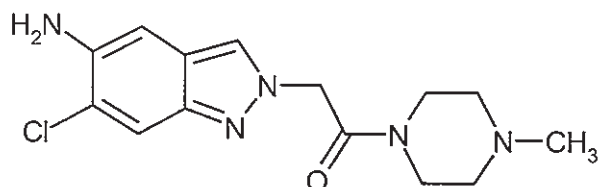
UPLC-MS (Method A1): R_t = 0.85 min

MS (ESIpos): m/z = 312 (M+H)⁺

¹H-NMR (400 MHz, CHLOROFORM-d): δ = 3.59 (s, 4 H), 3.65 (d, 4 H), 5.15 (s, 4 H), 6.78 (s, 1 H), 6.98 (s, 1 H), 7.34 - 7.44 (m, 3 H), 7.46 - 7.50 (m, 2 H), 7.71 - 7.74 (m, 1 H).

Intermediate 6-21

5 2-(5-Amino-6-chloro-2H-indazol-2-yl)-1-(4-methylpiperazin-1-yl)ethanone

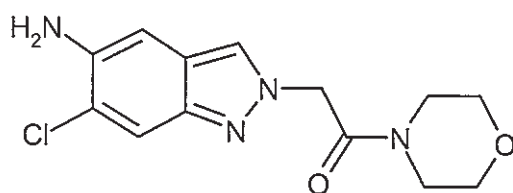


5.0 ml of ice-cold trifluoroacetic acid were added to 299 mg of benzyl {6-chloro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate (Intermediate 5-21), and the mixture was stirred at room temperature for 3 days. The mixture was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate and the extract was washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. Purification by preparative HPLC (Method P2) gave a solid which was triturated with diethyl ether. Drying gave 101 mg of the title compound.

15 ¹H-NMR (300 MHz, DMSO-d₆): δ [ppm] = 2.18 (s, 3H), 2.22 - 2.39 (m, 4H), 3.38 - 3.56 (m), 4.96 (s, 2H), 5.33 (s, 2H), 6.88 (s, 1H), 7.57 (s, 1H), 7.94 (d, 1H).

Intermediate 6-22

20 2-(5-Amino-6-chloro-2H-indazol-2-yl)-1-(morpholin-4-yl)ethanone

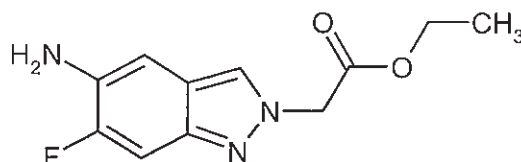


Analogously to the preparation of Intermediate 6-21, 254 mg of benzyl {6-chloro-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}carbamate (Intermediate 5-22) were stirred with 3 ml of trifluoroacetic acid at room temperature for 6 days. Analogous aqueous work-up gave 137 mg of the title compound as a crude product.

UPLC-MS (Method A1): R_t = 0.60 min (UV detector: TIC). Mass found 294.00.

Intermediate 7-1

30 Ethyl (5-amino-6-fluoro-2H-indazol-2-yl)acetate



Analogously to Intermediate 6-4, 1.1 g (3.3 mmol) of ethyl {5-[(tert-butoxycarbonyl)amino]-6-fluoro-2H-indazol-2-yl}acetate (Intermediate 3-5) were reacted with 1.92 ml (24.9 mmol) of trifluoroacetic acid in 11 ml of dichloromethane. Work-up gave 790 mg (100% of theory) of the title compound.

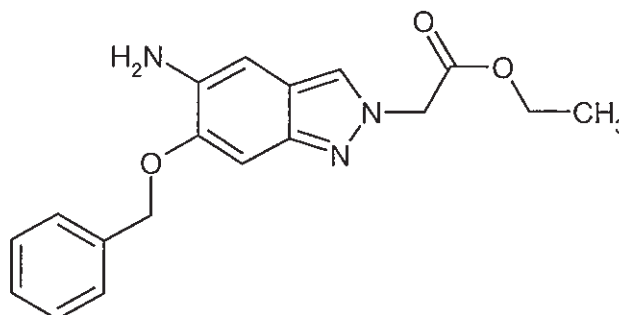
UPLC-MS (Method A1): $R_t = 0.67$ min

MS (ESIpos): $m/z = 238$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.21$ (t, 3H), 4.16 (q, 2H), 4.93 (s, 2H), 5.24 (s, 2H), 6.81 (d, 1H), 7.21 (d, 1H), 8.80 (s, 1H).

Intermediate 7-2

Ethyl {5-amino-6-(benzyloxy)-2H-indazol-2-yl}acetate



Analogously to Intermediate 6-4, 2.37 g (5.56 mmol) of ethyl {6-(benzyloxy)-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetate (Intermediate 3-4) were reacted with 3.24 ml (41.8 mmol) of trifluoroacetic acid in 25 ml of dichloromethane. Work-up gave 1.79 g (99% of theory) of the title compound.

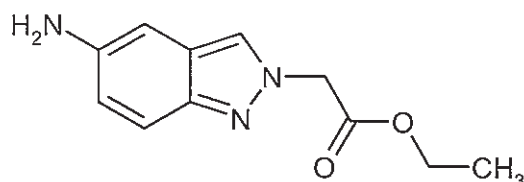
UPLC-MS (Method A1): $R_t = 0.91$ min

MS (ESIpos): $m/z = 326$ (M+H)⁺

¹H NMR (400 MHz, CHLOROFORM-d): $\delta = 1.29$ (t, 3 H), 4.25 (q, 2 H), 5.07 (s, 2 H), 5.15 (s, 2 H), 6.81 (s, 1 H), 7.01 (s, 1 H), 7.31 - 7.45 (m, 3 H), 7.45 - 7.52 (m, 2 H), 7.67 (s, 1 H).

Intermediate 7-3

Ethyl (5-amino-2H-indazol-2-yl)acetate



Analogously to Intermediate 6-4, 9.0 ml (117.4 mmol) of trifluoroacetic acid were added to 5.00 g (15.7 mmol) of tert-butyl {5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}acetate (Intermediate 3-7) in 75 ml of dichloromethane and the mixture was stirred at 25°C for 24 h. The mixture was poured into saturated sodium bicarbonate solution, the organic phase was separated off and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed with sodium chloride solution, dried and concentrated. This gave 3.4 g of the title compound as a brown solid.

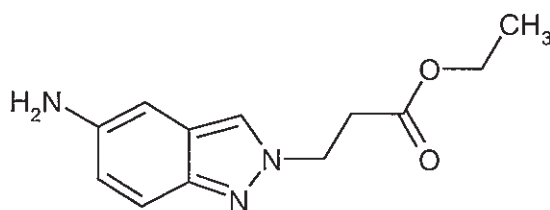
UPLC-MS (METHOD A1): Rt = 0.47 min

MS (ESIpos): m/z = 220 (M+H)⁺

¹H-NMR (400 MHz, DMSO-d₆): δ = 1.18 (t, 3H), 2.49 (br. s., 1H), 4.12 (q, 2H), 4.80 (s, 2H), 5.20 (s, 2H), 6.52 (dd, 1H), 6.73 (dd, 1H), 7.26 - 7.32 (m, 1H), 7.87 (d, 1H).

Intermediate 7-4

Ethyl 3-(5-amino-2H-indazol-2-yl)propanoate



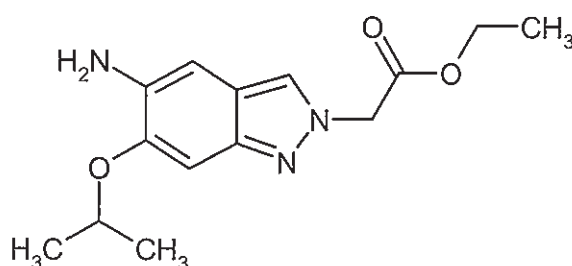
Analogously to Intermediate 7-1, 640 mg (1.92 mmol) of ethyl 3-{5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-yl}propanoate (Intermediate 3-9) were reacted with 1.1 ml (14.4 mmol) of trifluoroacetic acid. This gave 391 mg (87% of theory) of the title compound.

UPLC-MS (Method A1): Rt = 0.50 min

MS (ESIpos): m/z = 234 (M+H)⁺

Intermediate 7-5

Ethyl (5-amino-6-isopropoxy-2H-indazol-2-yl)acetate



Analogously to Intermediate 7-1, 1.8 g (4.84 mmol) of ethyl {5-[(tert-butoxycarbonyl)amino]-6-isopropoxy-2H-indazol-2-yl}acetate (Intermediate 3-10) were reacted with 2.8 ml (36.3 mmol) of trifluoroacetic acid. This gave 1.3 g (100% of theory) of the title compound.

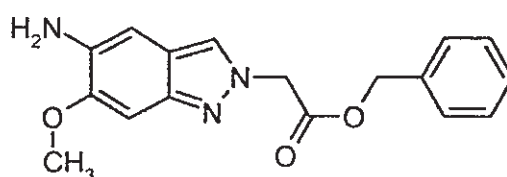
UPLC-MS (Method A1): $R_t = 0.69$ min

5 MS (ESIpos): $m/z = 278$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.21$ (t, 3H), 1.32 (d, 6H), 4.15 (q, 2H), 4.59 (s, 1H), 4.60 – 4.69 (m, 1H), 5.16 (s, 2H), 6.64 (s, 1H), 6.81 (d, 1H), 7.83 (s, 1H).

Intermediate 7-6

10 Benzyl (5-amino-6-methoxy-2H-indazol-2-yl)acetate



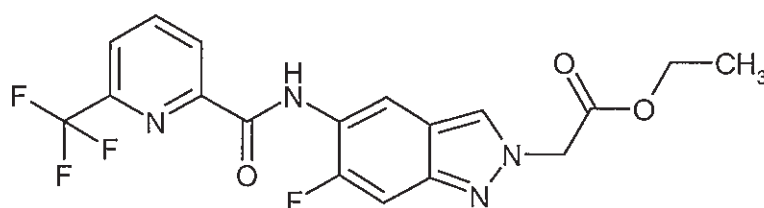
Analogously to Intermediate 7-1, 25.7 g (60.1 mmol) of benzyl {5-[(tert-butoxycarbonyl)amino]-6-methoxy-2H-indazol-2-yl}acetate (Intermediate 3-2) were reacted with 23.1 ml (300.3 mmol) of trifluoroacetic acid. This gave 20.5 g (98% of theory) of the title compound.

15 UPLC-MS (Method A1): $R_t = 0.85$ min

MS (ESIpos): $m/z = 312$ ($M+H$)⁺

Intermediate 8-1

20 Ethyl [6-fluoro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



221 mg (1.16 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid, 177 mg (1.16 mmol) of 1-hydroxy-1H-benzotriazole hydrate and 444 mg (2.32 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 5.5 ml of dimethylformamide were stirred at 25°C for 30 min. 250 mg (1.05 mmol) of ethyl (5-amino-6-fluoro-2H-indazol-2-yl)acetate (Intermediate 7-1) were added and the mixture was stirred at 25°C for 30 min. The mixture was poured into 150 ml of water, filtered off with suction, washed with water and dried. This gave 366 mg (84% of theory) of the title compound.

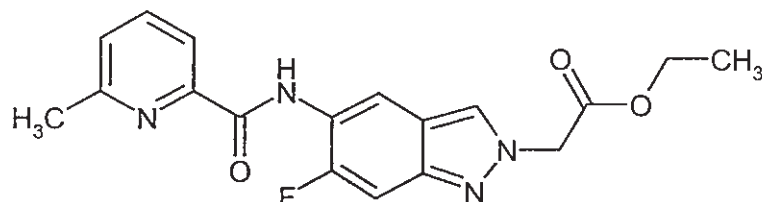
30 UPLC-MS (Method A1): $R_t = 1.23$ min

MS (ESIpos): $m/z = 411$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): δ = 1.22 (t, 3H), 4.18 (q, 2H), 5.41 (s, 2H), 7.55 (d, 1H), 8.21 (m, 1H), 8.36 – 8.51 (m, 4H), 10.27 (m, 1H).

Intermediate 8-2

5 Ethyl (6-fluoro-5-({[(6-methylpyridin-2-yl)carbonyl]amino}-2H-indazol-2-yl)acetate



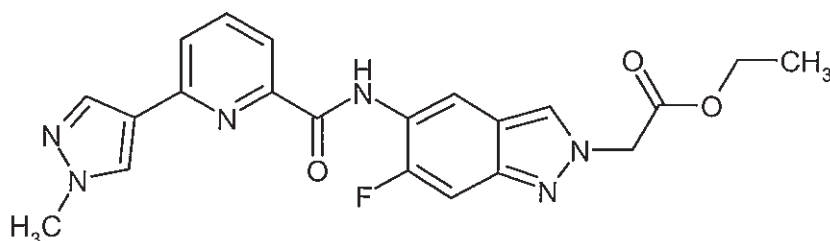
Analogously to Intermediate 8-1, 159 mg (1.16 mmol) of 6-methylpyridine-2-carboxylic acid were reacted with 250 mg (1.05 mmol) of ethyl (5-amino-6-fluoro-2H-indazol-2-yl)acetate (Intermediate 7-1). Work-up gave 316 mg (84% of theory) of the title compound.

UPLC-MS (Method A1): R_t = 1.17 min

MS (ESIpos): m/z = 357 (M+H)⁺.

Intermediate 8-3

15 Ethyl [6-fluoro-5-({[6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



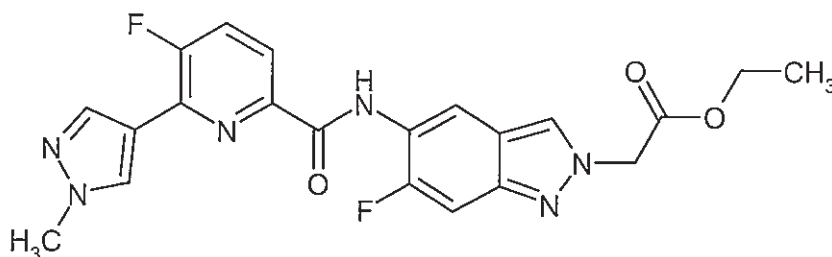
Analogously to Intermediate 8-1, 235 mg (1.16 mmol) of 6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid were reacted with 250 mg (1.05 mmol) of ethyl (5-amino-6-fluoro-2H-indazol-2-yl)acetate (Intermediate 7-1). Work-up gave 364 mg (82% of theory) of the title compound.

UPLC-MS (Method A1): R_t = 1.05 min

MS (ESIpos): m/z = 423 (M+H)⁺.

Intermediate 8-4

25 Ethyl [6-fluoro-5-({[5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



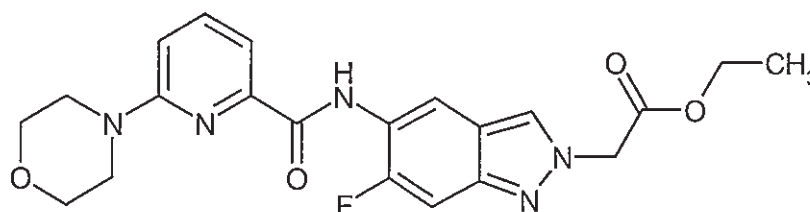
Analogously to Intermediate 8-1, 235 mg (1.0 mmol) of 5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid (Intermediate 19-5) were reacted with 250 mg (1.05 mmol) of ethyl (5-amino-6-fluoro-2H-indazol-2-yl)acetate (Intermediate 7-1). Work-up gave 326 mg (76% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 1.13$ min

MS (ESIpos): $m/z = 442$ ($M+H$)⁺.

Intermediate 8-5

10 Ethyl [6-fluoro-5-({[6-(morpholin-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



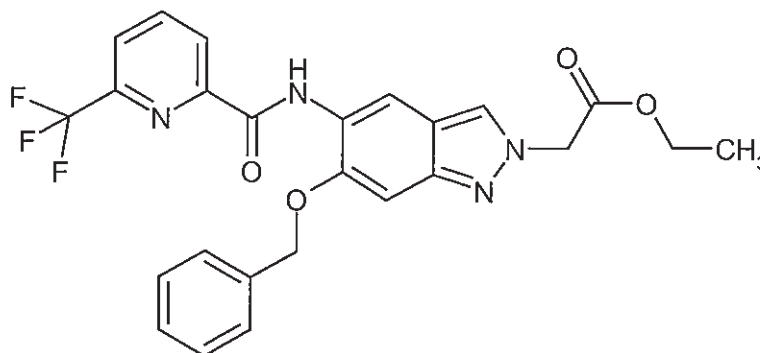
Analogously to Intermediate 8-1, 222 mg (0.97 mmol) of 6-(morpholin-4-yl)pyridine-2-carboxylic acid were reacted with 230 mg (0.97 mmol) of ethyl (5-amino-6-fluoro-2H-indazol-2-yl)acetate (Intermediate 7-1). Work-up gave 414 mg (100% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 1.12$ min

MS (ESIpos): $m/z = 428$ ($M+H$)⁺.

Intermediate 8-6

20 Ethyl [6-(benzyloxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



1.79 g (5.5 mmol) of ethyl [5-amino-6-(benzyloxy)-2H-indazol-2-yl]acetate (Intermediate 7-2), 1.26 g (6.6 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid, 842 mg (5.5 mmol) of 1-hydroxy-1H-benzotriazole hydrate, 2.11 g (11.0 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 2.3 ml (16.5 mmol) of triethylamine were in 75 ml of tetrahydrofuran at 25°C for 24 h. The reaction mixture was concentrated and water was added to the residue. The resulting solid was filtered off with suction and washed twice with water and twice with diethyl ether. The yellow solid was dried under reduced pressure. This gave 2.44 g (89% of theory) of product.

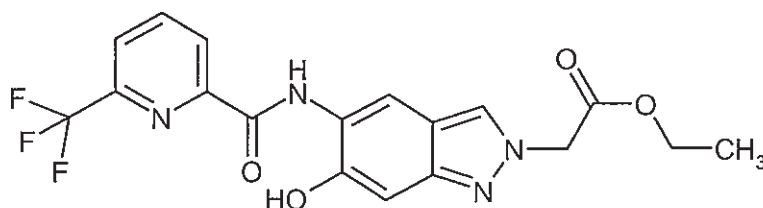
UPLC-MS (Method A1): $R_t = 1.42$ min

MS (ESIpos): $m/z = 499$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 1.23$ (t, 3 H), 4.18 (q, 2 H), 5.31 (s, 2 H), 5.33 (s, 2 H), 7.32 (s, 1 H), 7.34 - 7.47 (m, 3 H), 7.54 - 7.61 (m, 2 H), 8.18 (d, 1 H), 8.32 - 8.42 (m, 2 H), 8.43 - 8.52 (m, 1 H), 8.81 (s, 1 H), 10.47 (s, 1 H).

15 **Intermediate 8-7**

Ethyl [6-hydroxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



1.0 g (2.01 mmol) of ethyl [6-(benzyloxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-6) was dissolved in 40 ml of ethanol, and the flask was evacuated and then flushed with nitrogen (this procedure was repeated two more times). 213 mg (0.2 mmol) of palladium on carbon were added and the flask was evacuated and flushed with hydrogen. The reaction mixture was hydrogenated under standard hydrogen pressure at 25°C for 6 h. The reaction mixture was then filtered through a PTFE filter with Celite and concentrated. This gave 783 mg (96% of theory) of product.

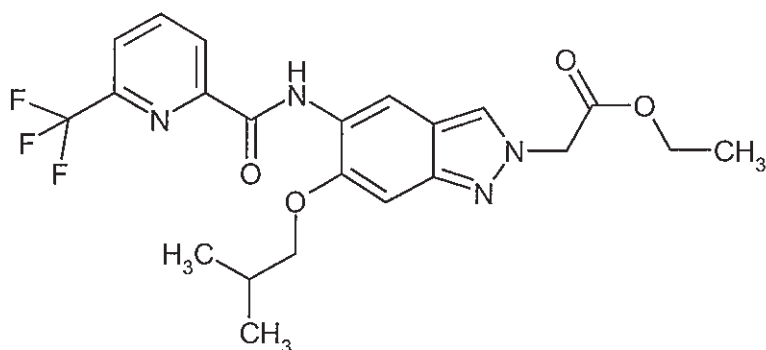
UPLC-MS (Method A1): $R_t = 1.08$ min

MS (ESIpos): $m/z = 409$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 1.22$ (t, 3 H), 4.17 (q, 2 H), 5.28 (s, 2 H), 6.92 (s, 1 H), 8.21 (d, 1 H), 8.27 (s, 1 H), 8.40 (t, 1 H), 8.47 (d, 1 H), 8.70 (s, 1 H), 10.55 (s, 1 H), 10.72 (s, 1 H).

Intermediate 8-8

Ethyl [6-isobutoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



200 mg (0.49 mmol) of ethyl [6-hydroxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-7) were dissolved in 1.5 ml of *N,N*-dimethylformamide, and 203 mg (1.47 mmol) of potassium carbonate were added with stirring. The suspension was stirred at 25°C for 10 minutes, and 80 μ l (0.73 mmol) of 1-bromo-2-methylpropane were then added. The reaction mixture was stirred in the microwave at 100°C for 1 h. The reaction mixture was then diluted with water, and ethyl acetate was added. A solid was formed, which was filtered off with suction and washed twice with water and twice with diethyl ether. The greenish solid was dried in a drying cabinet for 3 h. This gave 200 mg (88% of theory) of product.

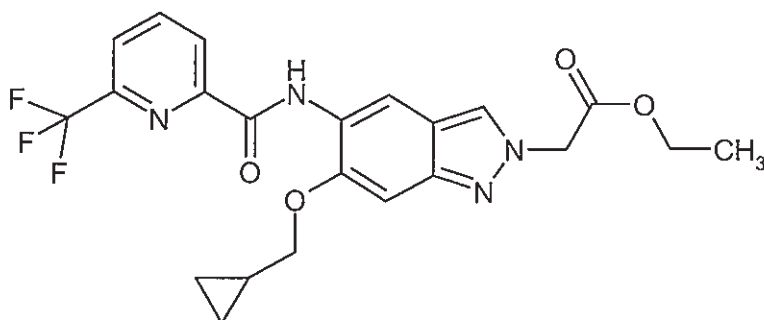
UPLC-MS (Method A1): R_t = 1.45 min

MS (ESIpos): m/z = 465 ($M+H$)⁺

¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.12 (d, 6 H), 1.22 (t, 3 H), 2.19 (dt, 1 H), 3.96 (d, 2 H), 4.17 (q, 2 H), 5.32 (s, 2 H), 7.09 (s, 1 H), 8.22 (d, 1 H), 8.32 (s, 1 H), 8.37 - 8.45 (m, 1 H), 8.46 - 8.51 (m, 1 H), 8.78 (s, 1 H), 10.58 (s, 1 H).

Intermediate 8-9

Ethyl [6-(cyclopropylmethoxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



Analogously to Intermediate 8-5, 200 mg (0.49 mmol) of ethyl [6-hydroxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-7) were reacted with 71 μ l (0.73 mmol) of (bromomethyl)cyclopropane. Work-up gave 223 mg (99% of theory) of the title compound.

UPLC-MS (Method A1): R_t = 1.38 min

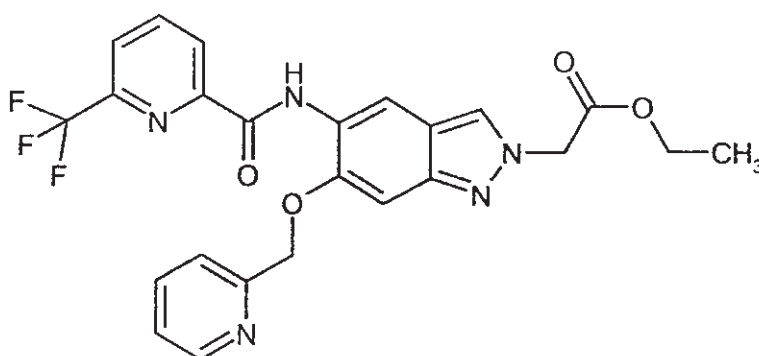
MS (ESIpos): $m/z = 463 (M+H)^+$

^1H NMR (300 MHz, CHLOROFORM- d): $\delta = 0.38 - 0.50$ (m, 2 H), $0.69 - 0.84$ (m, 2 H), 1.30 (t, 3 H), 1.45 (br. s., 1 H), 3.98 (d, 2 H), 4.27 (q, 2 H), 5.15 (s, 2 H), 6.98 (s, 1 H), 7.87 (d, 1 H), 7.93 (s, 1 H), 8.13 (t, 1 H), 8.51 (d, 1 H), 8.88 (s, 1 H), 10.91 (s, 1 H).

5

Intermediate 8-10

Ethyl [6-(pyridin-2-ylmethoxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



10

200 mg (0.49 mmol) of ethyl [6-hydroxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-7) were dissolved in 6.6 ml of *N,N*-dimethylformamide, and 270 mg (1.96 mmol) of potassium carbonate were added with stirring. The suspension was stirred at 25°C for 10 minutes, and 185 mg (0.73 mmol) of 2-(bromomethyl)pyridine hydrobromide were then added. The reaction mixture was stirred in the microwave at 100°C for 1 h. The reaction mixture was then diluted with water, and ethyl acetate was added. A solid was formed, which was filtered off with suction and washed twice with water and twice with diethyl ether. The greenish solid was dried in a drying cabinet for 3 h. This gave 160 mg (65% of theory) of the title compound.

15

20 UPLC-MS (Method A1): $R_t = 1.24$ min

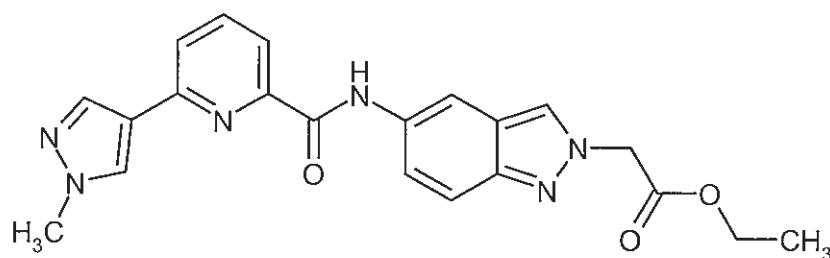
MS (ESIpos): $m/z = 500 (M+H)^+$

^1H NMR (400 MHz, DMSO- d_6): $\delta = 1.23$ (t, 3 H), 4.18 (q, 2 H), 5.34 (s, 2 H), 5.36 (s, 2 H), 7.70 (d, 1 H), $7.82 - 7.91$ (m, 1 H), $8.15 - 8.21$ (m, 1 H), 8.36 (s, 1 H), $8.37 - 8.43$ (m, 1 H), $8.45 - 8.50$ (m, 1 H), 8.62 (d, 1 H), 8.82 (s, 1 H), 10.50 (s, 1 H).

25

Intermediate 8-11

Ethyl [5-({[6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



Analogously to Intermediate 8-1, 1.00 g of 6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid (Intermediate 19-2) (crude product) and 961 mg (4.39 mmol) of ethyl (5-amino-2H-indazol-2-yl)acetate (Intermediate 7-3) were stirred in 10 ml of tetrahydrofuran at 25°C for 24 h. Water was added, the mixture was concentrated and the precipitated solid was filtered off with suction, washed with water and diethyl ether and dried under reduced pressure. This gave 1.45 g (80% of theory) of the title compound.

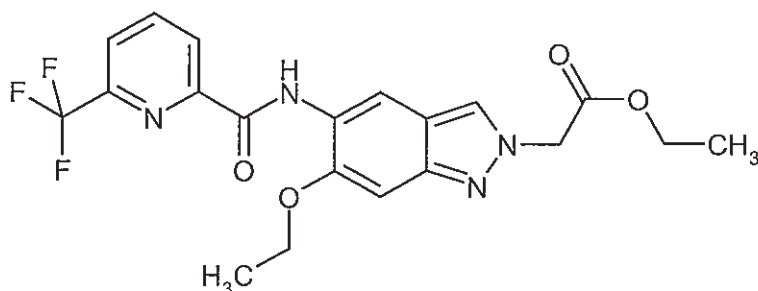
UPLC-MS (Method A1): $R_t = 1.01$ min

MS (ESIpos): $m/z = 405$ ($M+H$)⁺.

10

Intermediate 8-12

Ethyl [6-ethoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



Analogously to Intermediate 3-1, 1.30 g (3.71 mmol) of N-(6-ethoxy-1H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 14-3), 826 μ l (7.42 mmol) of ethyl bromoacetate and 1.54 ml (7.42 mmol) of *N,N*-dicyclohexylmethylamine in 20 ml of tetrahydrofuran were stirred at 65°C for 18 h. Another 413 μ l (3.71 mmol) of ethyl bromoacetate and 770 μ l (3.71 mmol) of *N,N*-dicyclohexylmethylamine were added were added, and the mixture was stirred at 65°C for a further 6 h. Work-up gave 143 mg of the title compound as a crude product.

A further 637 mg of the title compound were obtained by addition of water to the reaction filtrate, extraction with ethyl acetate, washing the organic phase with 1M hydrochloric acid solution, saturated sodium bicarbonate solution, saturated sodium chloride solution, drying, concentration and trituration of the residue with ethyl acetate.

25

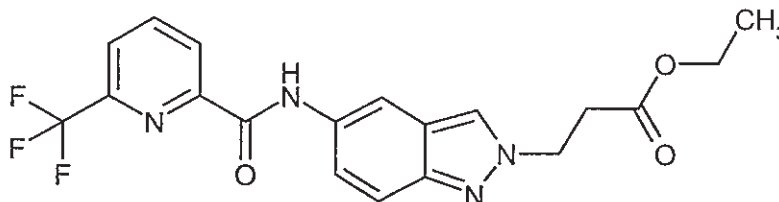
UPLC-MS (Method A1): $R_t = 1.31$ min

MS (ESIpos): $m/z = 437$ ($M+H$)⁺

^1H NMR (400 MHz, DMSO- d_6): δ = 1.23 (t, 3H), 1.51 (t, 3H), 4.14 - 4.27 (m, 4H), 5.31 (s, 2H), 7.10 (s, 1H), 8.18 - 8.23 (m, 1H), 8.31 (s, 1H), 8.37 - 8.44 (m, 1H), 8.45 - 8.49 (m, 1H), 8.73 (s, 1H), 10.74 (s, 1H).

5 **Intermediate 8-13**

Ethyl 3-[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]propanoate



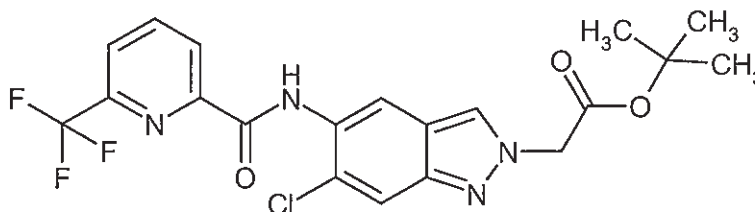
Analogously to Intermediate 8-1, 194 mg (0.83 mmol) of ethyl 3-(5-amino-2H-indazol-2-yl)propanoate (Intermediate 7-4) were reacted with 175 mg (0.91 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid. This gave 285 mg (84% of theory) of the title compound.

UPLC-MS (Method A1): R_t = 1.17 min

MS (ESIpos): m/z = 407 ($M+H$) $^+$.

15 **Intermediate 8-14**

tert-Butyl [6-chloro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



4.48 g (12.2 mmol) of N-(6-chloro-1H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 14-1) were initially charged in 40 ml of tetrahydrofuran. 3.61 ml (24.5 mmol) of tert-butyl bromoacetate and 5.19 ml (24.5 mmol) of *N,N*-dicyclohexylmethylamine were added and the mixture was stirred at 70°C for 5.5 h. Another 3.61 ml (24.5 mmol) of tert-butyl bromoacetate and 5.19 ml (24.5 mmol) of *N,N*-dicyclohexylmethylamine were added, the mixture was stirred at 65°C for 18 h, another 1.81 ml (12.3 mmol) of tert-butyl bromoacetate and 2.60 ml (12.3 mmol) of *N,N*-dicyclohexylmethylamine were added and the mixture was stirred at 65°C for a further 6 h. The mixture was filtered, water was added to the filtrate, the mixture was extracted three times with ethyl acetate and the combined organic phases were washed with 1M hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution and concentrated. Trituration of the crude product with ethyl acetate gave, after drying, 1.45 g (26% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 1.43$ min

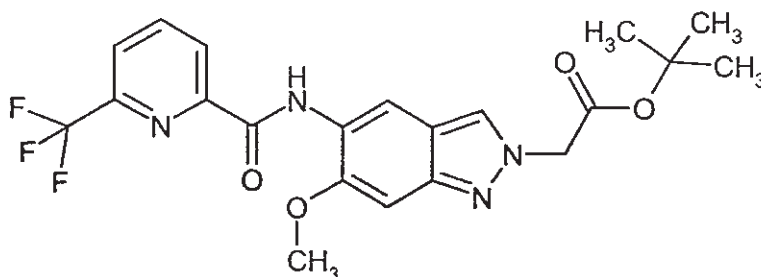
MS (ESIpos): $m/z = 455$ ($M+H$)⁺

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 1.45$ (s, 9H), 5.32 (s, 2H), 7.95 (s, 1H), 8.23 (d, 1H), 8.38 - 8.44 (m, 1H), 8.45 - 8.49 (m, 1H), 8.49 (s, 1H), 8.66 (s, 1H), 10.5 (s, 1H).

5

Intermediate 8-15

tert-Butyl [6-methoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



10

2.00 g (5.95 mmol) of N-(6-methoxy-1H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 14-2) were dissolved in 40 ml of tetrahydrofuran and 4.39 ml (29.7 mmol) of tert-butyl bromoacetate and 6.37 ml (29.7 mmol) of *N,N*-dicyclohexylmethylamine were added at 25°C. The solution was stirred at 70°C for 3 h. Another 0.87 ml (5.95 mmol) of tert-butyl bromoacetate and 1.27 ml (5.95 mmol) of *N,N*-dicyclohexylmethylamine were added, and the mixture was stirred at 70°C for a further 24 h. The solid in the reaction mixture was filtered off and washed twice with tetrahydrofuran. The regioisomerically pure crystals are dried in a vacuum drying cabinet at 50°C for 3 h. This gave 1.58 g (59% of theory) of product.

15

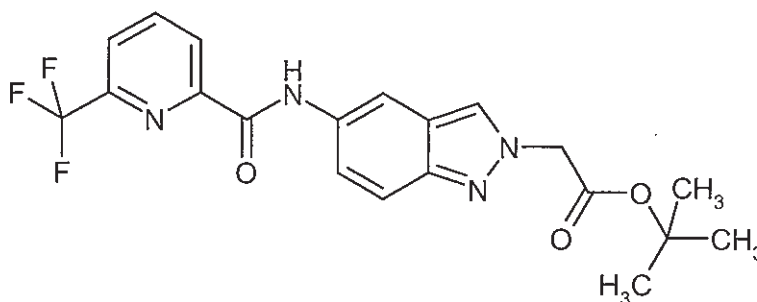
UPLC-MS (Method A1): $R_t = 1.36$ min

20 MS (ESIpos): $m/z = 451$ ($M+H$)⁺

¹H NMR (400 MHz, CHLOROFORM-d): $\delta = 1.50$ (s, 9 H), 4.04 (s, 3 H), 5.04 (s, 2 H), 7.06 (s, 1 H), 7.86 (d, 1 H), 7.92 (s, 1 H), 8.12 (t, 1 H), 8.50 (d, 1 H), 8.84 (s, 1 H), 10.72 (s, 1 H).

Intermediate 8-16

25 tert-Butyl [5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate

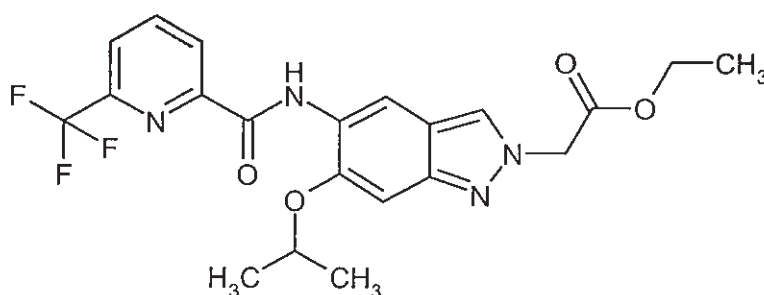


525 mg (3.80 mmol) of potassium carbonate were added to a solution of 582 mg (1.90 mmol) of N-(1H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 14-4) and 309 μ l (2.09 mmol) of tert-butyl bromoacetate in 5 ml of N,N-dimethylformamide, and the mixture was stirred at 80°C for 24 h. Water was added, and the mixture was extracted three times with ethyl acetate. A solid precipitated from the ethyl acetate phase; this solid was filtered off with suction and washed with ethyl acetate. Drying under reduced pressure gave 72 mg (8% of theory) of the title compound. The ethyl acetate phase was concentrated and the residue was purified by preparative HPLC. This gave a further 151 g (19% of theory) of the title compound.

¹H-NMR (500 MHz, DMSO-d₆): δ = 1.45 (s, 9H), 5.27 (s, 2H), 7.56 - 7.61 (m, 1H), 7.61 - 7.64 (m, 1H), 8.17 (dd, 1H), 8.30 - 8.39 (m), 8.39 - 8.43 (m, 1H), 10.38 (s, 1H).

Intermediate 8-17

Ethyl [6-isopropoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



Analogously to Intermediate 8-1, 300 mg (1.08 mmol) of ethyl (5-amino-6-isopropoxy-2H-indazol-2-yl)acetate (Intermediate 7-5) were reacted with 227 mg (1.19 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid. This gave 487 mg (100% of theory) of the title compound.

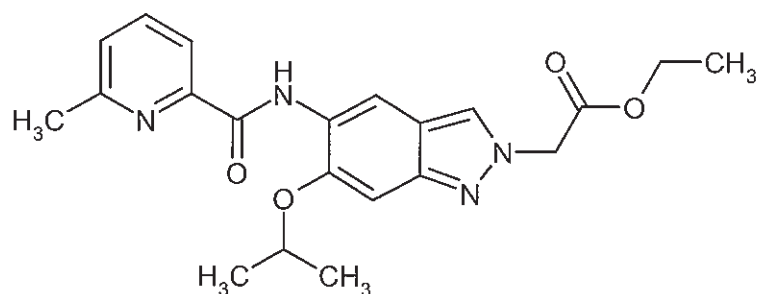
UPLC-MS (Method A1): R_t = 1.34 min

MS (ESIpos): m/z = 451 ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): δ = 1.23 (t, 3H), 1.41 (d, 6H), 4.18 (q, 2H), 4.79 - 4.92 (m, 1H), 5.32 (s, 2H), 7.18 (s, 1H), 8.22 (d, 1H), 8.33 (s, 1H), 8.37 - 8.50 (m, 2H), 8.75 (s, 1H), 10.75 (s, 1H).

Intermediate 8-18

Ethyl (6-isopropoxy-5-([(6-methylpyridin-2-yl)carbonyl]amino)-2H-indazol-2-yl)acetate



Analogously to Intermediate 8-2, 0.3 g (1 mmol) of ethyl (5-amino-6-isopropoxy-2H-indazol-2-yl)acetate (Intermediate 7-5) were reacted with 137 mg (1.2 mmol) of 6-methylpyridine-2-carboxylic acid. This gave 380 mg (89% of theory) of the title compound.

5 UPLC-MS (Method A1): $R_t = 1.28$ min

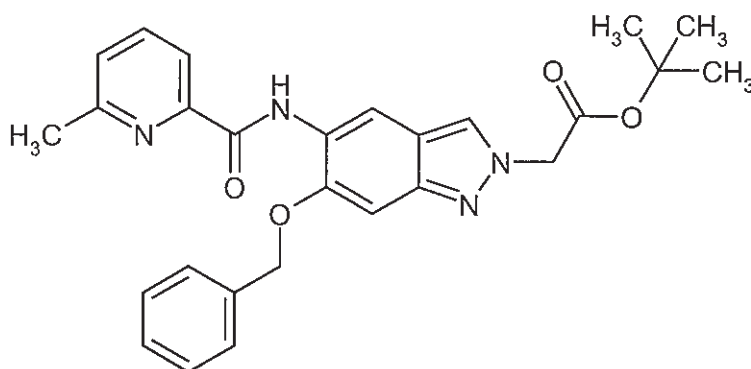
MS (ESIpos): $m/z = 397$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.22$ (t, 3H), 1.45 (d, 6H), 2.62 (s, 3H), 4.18 (q, 2H), 4.78 – 4.89 (m, 1H), 5.31 (s, 2H), 7.15 (s, 1H), 7.52 – 7.60 (m, 1H), 7.95 – 8.01 (m, 2H), 8.29 (s, 1H), 8.72 (s, 1H), 10.99 (s, 1H).

10

Intermediate 8-19

tert-Butyl [6-(benzyloxy)-5-{[(6-methylpyridin-2-yl)carbonyl]amino}-2H-indazol-2-yl]acetate



15 Analogously to Intermediate 8-15, 1.00 g (2.79 mmol) of N-[6-(benzyloxy)-1H-indazol-5-yl]-6-methylpyridine-2-carboxamide (Intermediate 14-5) was dissolved in 20 ml of tetrahydrofuran and 1.64 ml (11.2 mmol) of tert-butyl bromoacetate and 2.39 ml (11.2 mmol) of *N,N*-dicyclohexylmethylamine were added at 25°C. After 3 h at 70°C, another 1.64 ml (11.2 mmol) of tert-butyl bromoacetate and 2.39 ml (11.2 mmol) of *N,N*-dicyclohexylmethylamine were added,
20 and the mixture was stirred at 70°C for a further 24 h. The solid in the reaction mixture was filtered off and washed twice with tetrahydrofuran. The regioisomerically pure crystals are dried in a vacuum drying cabinet at 50°C for 3 h. This gave 971 mg (74% of theory) of product.

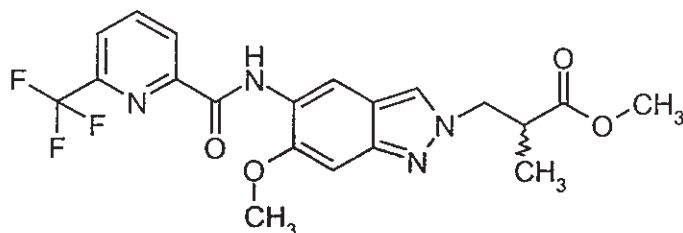
UPLC-MS (Method A1): $R_t = 1.47$ min

MS (ESIpos): $m/z = 473$ ($M+H$)⁺

¹H-NMR (500 MHz, DMSO-d₆): δ = 1.45 (s, 9H), 2.43 (s, 3H), 5.20 (s, 2H), 5.31 (s, 2H), 7.29 (s, 1H), 7.39 - 7.43 (m, 1H), 7.45 - 7.53 (m, 3H), 7.63 - 7.68 (m, 2H), 7.93 - 7.97 (m, 1H), 7.97 - 8.00 (m, 1H), 8.29 (d, 1H), 8.78 (s, 1H), 10.87 (s, 1H).

5 Intermediate 8-20

Methyl 3-[6-methoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]-2-methylpropanoate



- 10 164 mg (1.19 mmol) of potassium carbonate and 83 μ l (0.65 mmol) of methyl (2R)-3-bromo-2-methylpropanoate were added to 200 mg (0.60 mmol) of N-(6-methoxy-1H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 14-2) in 5 ml of acetonitrile, and then mixture was stirred at 85°C for 24 h. The mixture was diluted with water and extracted with ethyl acetate and the extract was washed with saturated sodium chloride solution, filtered through a hydrophobic filter and concentrated. The crude product was dissolved in 2.0 ml of dimethyl sulphoxide and purified by preparative HPLC. The product fraction was lyophilized. This gave 25 mg (56% of theory) of the title compound.

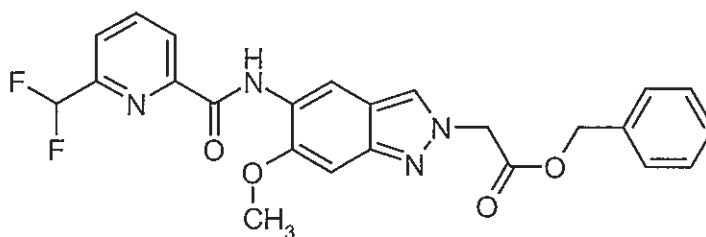
UPLC-MS (Method A1): R_t = 1.23 min

MS (ESIpos): m/z = 437 (M+H)⁺

- 20 ¹H-NMR (300 MHz, DMSO-d₆): δ = 1.08 (d, 3 H), 3.13 (q, 1 H), 3.55 (s, 3 H), 4.04 (s, 3 H), 4.48 (dd, 1 H), 4.62 (dd, 1 H), 7.40 (s, 1 H), 8.02 (s, 1 H), 8.17 - 8.26 (m, 1 H), 8.40 (t, 1 H), 8.47 (d, 1 H), 8.71 (s, 1 H), 10.42 (s, 1 H).

25 Intermediate 8-21

Benzyl [5-({[6-(difluoromethyl)pyridin-2-yl]carbonyl}amino)-6-methoxy-2H-indazol-2-yl]acetate



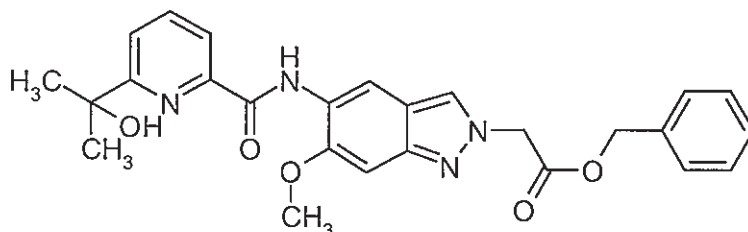
Analogously to Intermediate 8-6, 400 mg (1.29 mmol) of benzyl (5-amino-6-methoxy-2H-indazol-2-yl)acetate (Intermediate 7-6) were stirred with 245 mg (1.41 mmol) of 6-(difluoromethyl)pyridine-2-carboxylic acid (CAS No: 1256824-41-5), 197 mg (1.29 mmol) of 1-hydroxy-1H-benzotriazole hydrate and 493 mg (2.57 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 537 μ l (3.85 mmol) of triethylamine in 10 ml of tetrahydrofuran at 25°C for 24 h. The reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution and concentrated. The crude product was taken up in diethyl ether and a little water and stirred for 30 minutes. The solid was filtered off with suction, washed three times with diethyl ether and dried in a drying cabinet. This gave 401 mg (48% of theory) of the title compound.

UPLC-MS (Method A1): R_t = 1.29 min

MS (ESIpos): m/z = 467 ($M+H$)⁺.

Intermediate 8-22

Benzyl [5-({[6-(2-hydroxypropan-2-yl)pyridin-2-yl]carbonyl}amino)-6-methoxy-2H-indazol-2-yl]acetate



Analogously to Intermediate 8-6, 300 mg (0.96 mmol) of benzyl (5-amino-6-methoxy-2H-indazol-2-yl)acetate (Intermediate 7-6), 295 mg (1.16 mmol) of potassium 6-(2-hydroxypropan-2-yl)pyridine-2-carboxylate (Intermediate 19-11), 148 mg (0.96 mmol) of 1-hydroxy-1H-benzotriazole hydrate, 277 mg (1.45 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 403 μ l (2.89 mmol) of triethylamine in 10 ml of tetrahydrofuran were stirred at 25°C for 24 h. The reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution and concentrated. The crude product was dissolved in 4 ml of dimethyl sulphoxide and purified by preparative HPLC according to Method P5 (gradient: 0 - 15 min 30 - 70% B; flow rate: 150 ml/min). The product fraction were lyophilized. This gave 209 mg (46% of theory) of the title compound.

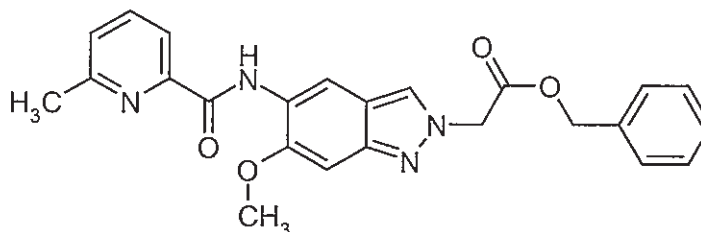
UPLC-MS (Method A1): R_t = 1.19 min

MS (ESIpos): m/z = 475 ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): δ 1.57 (s, 6 H), 4.00 (s, 3 H), 5.21 (s, 2 H), 5.41 (s, 2 H), 5.47 (s, 1 H), 7.13 (s, 1 H), 7.34 - 7.41 (m, 5 H), 7.94 (dd, 1 H), 7.99 - 8.12 (m, 2 H), 8.33 (s, 1 H), 8.69 (s, 1 H), 10.94 (s, 1 H).

Intermediate 8-23

Benzyl (6-methoxy-5-[[{(6-methylpyridin-2-yl)carbonyl]amino}-2H-indazol-2-yl]acetate



5

7.57 g (19.0 mmol) of N-(6-methoxy-1H-indazol-5-yl)-6-methylpyridine-2-carboxamide (Intermediate 14-6) were stirred with 6.03 ml (38.1 mmol) of benzyl bromoacetate in 100 ml of tetrahydrofuran in the presence of 8.01 ml (38.1 mmol) of *N,N*-dicyclohexylmethylamine at 70°C for 2.5 h and at 60°C for 17 h. Another 3.02 ml (19.1 mmol) of benzyl bromoacetate and 4.01 ml (19.1 mmol) of *N,N*-dicyclohexylmethylamine were added and the mixture was stirred at 70°C for a further 24 h. The solid was filtered off with suction and washed with ethyl acetate. The filtrate was filtered once more and washed twice with ethyl acetate and the solid was dried. Water was added to the filtrate, and after phase separation the aqueous phase was washed once more with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, filtered through a hydrophobic filter and concentrated. Ethyl acetate was added to the crude product, and the mixture was stirred for 15 minutes. The solid was filtered off with suction, washed three times with ethyl acetate and dried in a drying cabinet. This gave a total of 6.02 g (63% of theory) of the title compound.

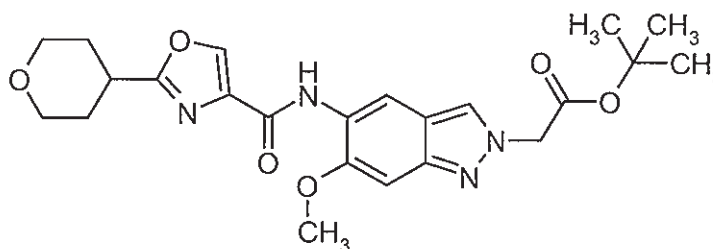
LC-MS (Method A3): $R_t = 1.25$ min

MS (ESIpos): $m/z = 431$ ($M+H$)⁺

¹H-NMR (500 MHz, DMSO-*d*₆): $\delta = 2.63$ (s, 3 H), 4.01 (s, 3 H), 5.21 (s, 2 H), 5.40 (s, 2 H), 7.11 (s, 1 H), 7.34 - 7.40 (m, 5 H), 7.55 (dd, 1 H), 7.93 - 8.02 (m, 2 H), 8.30 - 8.33 (m, 1 H), 8.73 (s, 1 H), 10.72 (s, 1 H).

Intermediate 8-24

tert-Butyl [6-methoxy-5-({[2-(tetrahydro-2H-pyran-4-yl)-1,3-oxazol-4-yl]carbonyl}amino)-2H-indazol-2-yl]acetate



1.19 g (1.77 mmol) of N-(6-methoxy-1H-indazol-5-yl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-oxazole-4-carboxamide (Intermediate 14-7) were stirred with 524 μ l (3.55 mmol) of tert-butyl bromoacetate in 10 ml of tetrahydrofuran in the presence of 752 μ l (3.55 mmol) of *N,N*-dicyclohexylmethylamine at 70°C for 2.5 h and at 60°C for 17 h. Another 1.51 ml (9.5 mmol) of
 5 tert-butyl bromoacetate and 2.00 ml (9.5 mmol) of *N,N*-dicyclohexylmethylamine were added and the mixture was stirred at 70°C for a further 6 h. The solid was filtered off with suction and washed three times with ethyl acetate. Water was added to the filtrate, and after phase separation the aqueous phase was washed once more with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, filtered through a hydrophobic filter and
 10 concentrated. Ethyl acetate was added to the crude product and the solid was filtered off with suction, washed three times with ethyl acetate and dried in a drying cabinet. This gave a total of 330 mg (41% of theory) of the title compound.

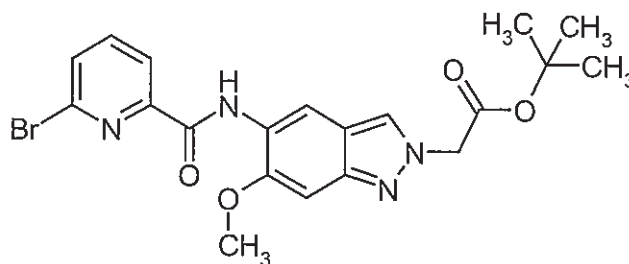
UPLC-MS (Method A1): R_t = 1.23 min

MS (ESIpos): m/z = 457 (M+H)⁺

15 ¹H-NMR (500 MHz, DMSO-*d*₆): δ = 1.44 (s, 9 H), 1.72 - 1.86 (m, 2 H), 1.91 - 2.02 (m, 2 H), 3.17 - 3.27 (m, 1 H), 3.48 (td, 2 H), 3.92 (dt, 2 H), 3.97 (s, 3 H), 5.18 (s, 2 H), 7.10 (s, 1 H), 8.26 (d, 1 H), 8.57 (s, 1 H), 8.74 (s, 1 H), 9.41 (s, 1 H).

Intermediate 8-25

20 tert-Butyl (5-[[[(6-bromopyridin-2-yl)carbonyl]amino]-6-methoxy-2H-indazol-2-yl]acetate



4.20 g (12.10 mmol) of 6-bromo-N-(6-methoxy-1H-indazol-5-yl)pyridine-2-carboxamide (Intermediate 14-8) were stirred with 3.57 ml (24.20 mmol) of tert-butyl bromoacetate in 50 ml of
 25 tetrahydrofuran in the presence of 5.18 ml (24.20 mmol) of *N,N*-dicyclohexylmethylamine at 70°C for 2 h and at 60°C for 17 h. Another 3.57 ml (24.20 mmol) of tert-butyl bromoacetate and 5.18 ml (24.20 mmol) of *N,N*-dicyclohexylmethylamine were added and the mixture was stirred at 70°C for a further 24 h. The reaction mixture was cooled using an ice bath and the resulting solid was filtered off with suction, washed with water and diethyl ether and dried under reduced pressure.
 30 This gave 3.67 g (66% of theory) of the title compound.

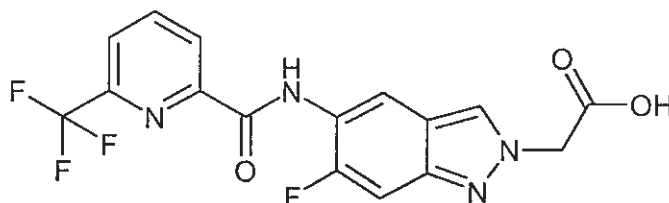
UPLC-MS (Method A1): R_t = 1.33 min

MS (ESIpos): m/z = 461 (M+H)⁺

¹H-NMR (500 MHz, DMSO-d₆): δ = 1.44 (s, 9 H) 4.00 (s, 3 H) 5.20 (s, 2 H) 7.14 (s, 1 H) 7.90 - 8.10 (m, 2 H) 8.20 (dd, 1 H) 8.29 (s, 1 H) 8.68 (s, 1 H) 10.31 (s, 1 H).

Intermediate 9-1

5 [6-Fluoro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



381 mg (0.93 mmol) of ethyl [6-fluoro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-1) were suspended in 9.2 ml of tetrahydrofuran and 0.45 ml of ethanol. and a solution of 222 mg (9.3 mmol) of lithium hydroxide in 2.3 ml of water was then added. The mixture was stirred at 25°C for 30 min and then acidified to pH 2 with ice cooling using 2N hydrochloric acid. 10 ml of water were added and the precipitate was filtered off with suction. This gave 332 mg (93% of theory) of the title compound.

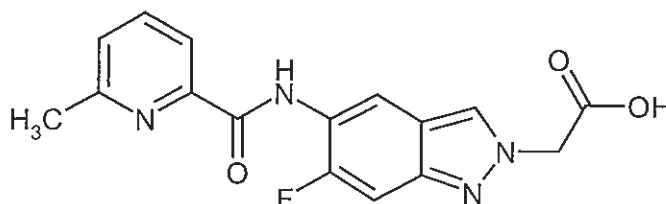
UPLC-MS (Method A1): R_t = 1.04 min

15 MS (ESIpos): m/z = 383 (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): δ = 5.30 (s, 2H), 7.55 (d, 1H), 8.22 (m, 1H), 8.34 - 8.54 (m, 4H), 10.26 (m, 1H), 13.30 (s br, 1H).

Intermediate 9-2

20 (6-Fluoro-5-({[(6-methylpyridin-2-yl)carbonyl]amino})-2H-indazol-2-yl)acetic acid



Analogously to Intermediate 9-1, 316 mg (0.89 mmol) of ethyl (6-fluoro-5-({[(6-methylpyridin-2-yl)carbonyl]amino})-2H-indazol-2-yl)acetate (Intermediate 8-2) were reacted with 212 mg (8.87 mmol) of lithium hydroxide in 2.2 ml of water, 8.8 ml of tetrahydrofuran and 0.44 ml of ethanol. Work-up gave 302 mg of the title compound as a crude product.

UPLC-MS (Method A1): R_t = 0.99 min

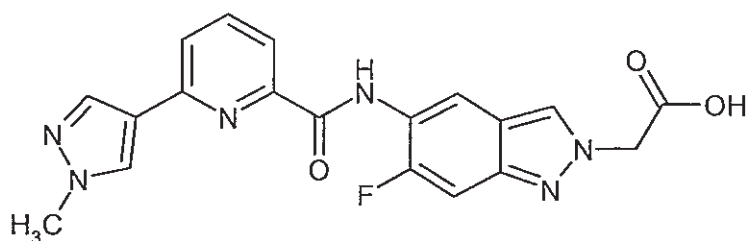
MS (ESIpos): m/z = 329 (M+H)⁺

¹H NMR (400 MHz, DMSO-d₆) δ = 2.62 (s, 3 H), 5.28 (s, 2 H), 7.44 - 7.63 (m, 2 H), 7.90 - 8.06 (m, 2 H), 8.45 (s, 1 H), 8.56 (d, 1 H), 10.38 (d, J=1 H).

Intermediate 9-3

[6-Fluoro-5-({[6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid

5



Analogously to Intermediate 9-1, 364 mg (0.86 mmol) of ethyl [6-fluoro-5-({[6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-3) were reacted with 206 mg (8.6 mmol) of lithium hydroxide in 2.1 ml of water, 8.5 ml of tetrahydrofuran and 0.42 ml of ethanol. Work-up gave 302 mg (89% of theory) of the title compound as a crude product.

UPLC-MS (Method A1): $R_t = 0.87$ min

MS (ESIpos): $m/z = 395$ (M+H)⁺

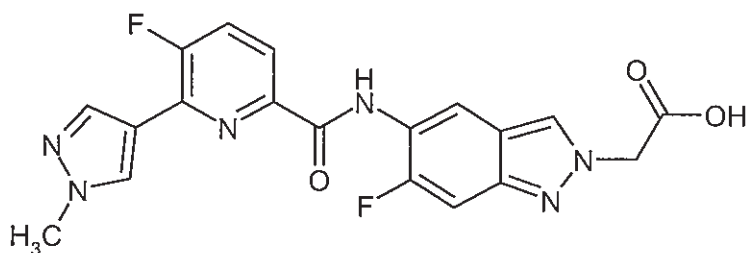
¹H-NMR (300 MHz, DMSO-d₆): $\delta = 3.93$ (s, 3H), 5.30 (s, 2H), 7.55 (d, 1H), 7.92 (t, 2H), 8.03 (t, 1H), 8.21 (s, 1H), 8.39 (d, 1H), 8.46 (s, 1H), 8.52 (s, 1H), 10.51 (s, 1H), 13.26 (s br, 1H).

15

Intermediate 9-4

[6-Fluoro-5-({[5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid

20



Analogously to Intermediate 9-1, 326 mg (0.74 mmol) of ethyl [6-fluoro-5-({[5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-4) were reacted with 177 mg (7.4 mmol) of lithium hydroxide in 1.8 ml of water, 7.3 ml of tetrahydrofuran and 0.36 ml of ethanol. Work-up gave 305 mg (100% of theory) of the title compound as a crude product.

25

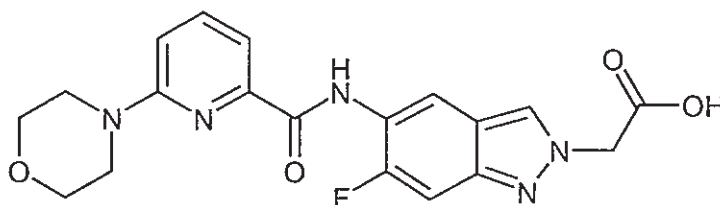
UPLC-MS (Method A1): $R_t = 0.95$ min

MS (ESIpos): $m/z = 413$ (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): δ = 3.96 (s, 3H), 5.30 (s, 2H), 7.54 (d, 1H), 7.98 (m, 2H), 8.27 (m, 2H), 8.46 (s, 1H), 8.53 (s, 1H), 10.42 (s, 1H), 13.29 (s br, 1H).

Intermediate 9-5

5 [6-Fluoro-5-({[6-(morpholin-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



Analogously to Intermediate 9-1, 436 mg (1.02 mmol) of ethyl [6-fluoro-5-({[6-(morpholin-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-5) were reacted with 244
10 mg (10.2 mmol) of lithium hydroxide in 2.5 ml of water, 10 ml of tetrahydrofuran and 0.5 ml of ethanol. Work-up gave 295 mg (72% of theory) of the title compound as a crude product.

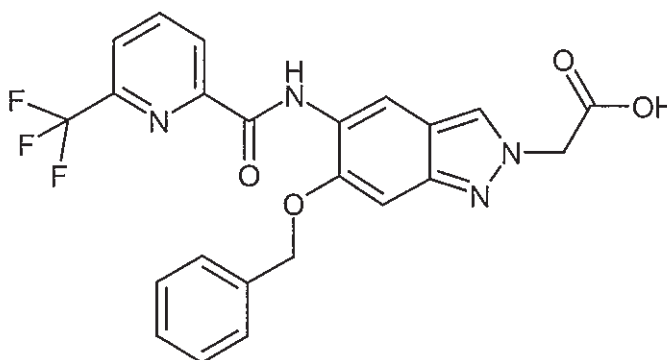
UPLC-MS (Method A1): R_t = 0.95 min

MS (ESIpos): m/z = 400 (M+H)⁺

¹H-NMR (300 MHz, DMSO-d₆): δ = 3.59 (m, 4H), 3.75 (m, 4H), 5.26 (s, 2H), 7.15 (d, 1H), 7.42
15 – 7.59 (m, 2H), 7.82 (t, 1H), 8.40 – 8.51 (m, 2H), 10.28 (m, 1H).

Intermediate 9-6

[6-(Benzyloxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



20

Analogously to Intermediate 9-1, 75 mg (0.15 mmol) of ethyl [6-(benzyloxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-6) were reacted with 18 mg (0.75 mmol) of lithium hydroxide in 271 μl of water and 2.5 ml of tetrahydrofuran. Work-up gave 59 mg (83% of theory) of the title compound.

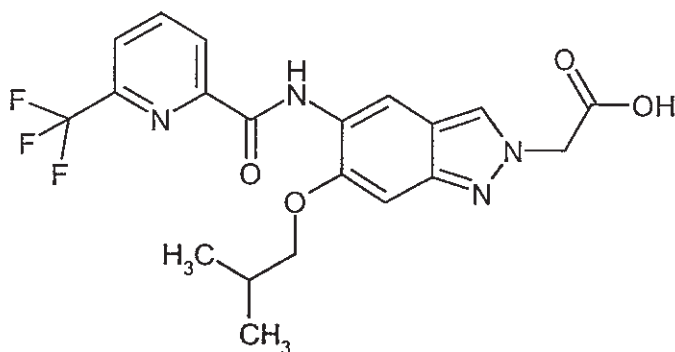
25 UPLC-MS (Method A1): R_t = 1.26 min

MS (ESIpos): m/z = 471 (M+H)⁺

¹H NMR (400 MHz, DMSO-d₆): δ = 7.31 (s, 1 H), 7.33 - 7.47 (m, 3 H), 7.54 - 7.63 (m, 2 H), 8.12 - 8.22 (m, 1 H), 8.31 (s, 1 H), 8.39 (s, 1 H), 8.46 - 8.51 (m, 1 H), 8.80 (s, 1 H), 10.47 (s, 1 H).

Intermediate 9-7

5 [6-Isobutoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



Analogously to Intermediate 9-1, 200 mg (0.43 mmol) of ethyl [6-isobutoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-8) were
10 reacted with 51 mg (2.15 mmol) of lithium hydroxide in 776 µl of water and 10 ml of tetrahydrofuran. Work-up gave 64 mg (87% of theory) of the title compound.

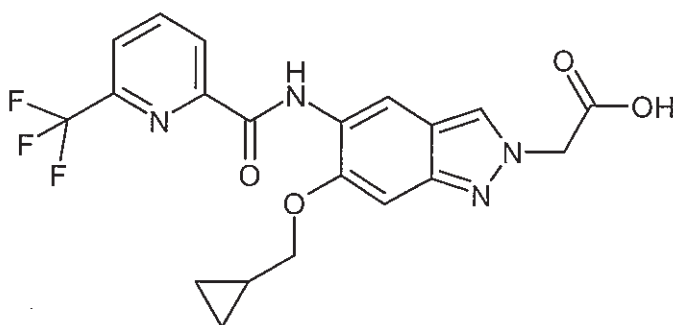
UPLC-MS (Method A1): R_t = 1.22 min

MS (ESIpos): m/z = 437 (M+H)⁺

¹H NMR (300 MHz, DMSO-d₆): δ = 1.11 (s, 3 H), 1.13 (s, 3 H), 2.19 (dt, 1 H), 3.96 (d, 2 H), 5.21
15 (s, 2 H), 7.09 (s, 1 H), 8.22 (dd, 1 H), 8.31 (s, 1 H), 8.37 - 8.46 (m, 1 H), 8.46 - 8.52 (m, 1 H), 8.78 (s, 1 H), 10.58 (s, 1 H).

Intermediate 9-8

[6-(Cyclopropylmethoxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid
20



Analogously to Intermediate 9-1, 220 mg (0.48 mmol) of ethyl [6-(cyclopropylmethoxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-9) were

reacted with 57 mg (2.38 mmol) of lithium hydroxide in 857 μ l of water and 10 ml of tetrahydrofuran. Work-up gave 181 mg (88% of theory) of the title compound.

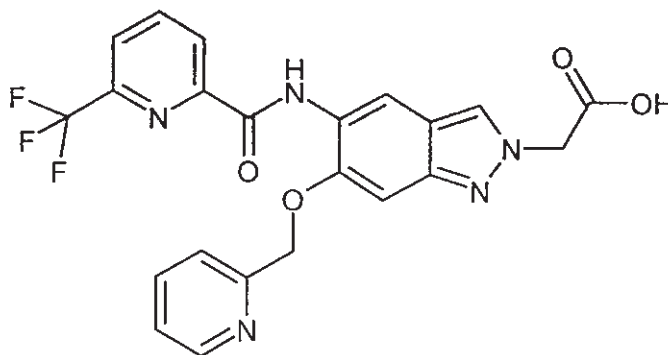
UPLC-MS (Method A1): $R_t = 1.21$ min

MS (ESIpos): $m/z = 435$ (M+H)⁺

- 5 ¹H NMR (400 MHz, DMSO-d₆): $\delta = 0.42 - 0.48$ (m, 2 H), 0.63 - 0.69 (m, 2 H), 1.29 - 1.41 (m, 1 H), 4.03 (d, 2 H), 5.20 (s, 2 H), 7.07 (s, 1 H), 8.21 (dd, 1 H), 8.29 (s, 1 H), 8.37 - 8.44 (m, 1 H), 8.46 - 8.50 (m, 1 H), 8.76 (s, 1 H), 10.71 (s, 1 H).

Intermediate 9-9

- 10 [6-(Pyridin-2-ylmethoxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



- 15 Analogously to Intermediate 9-1, 160 mg (0.32 mmol) of ethyl [6-(pyridin-2-ylmethoxy)-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-10) were reacted with 38 mg (1.60 mmol) of lithium hydroxide in 577 μ l of water and 6.7 ml of tetrahydrofuran. Work-up gave 129 mg (85% of theory) of the title compound.

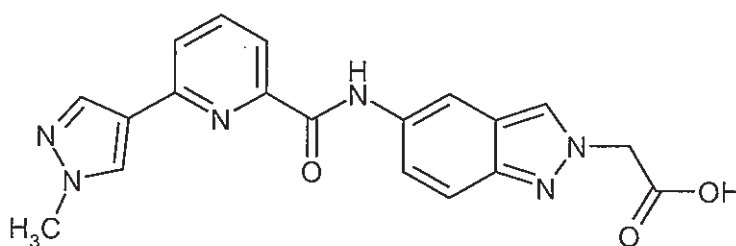
UPLC-MS (Method A1): $R_t = 1.02$ min

MS (ESIpos): $m/z = 472$ (M+H)⁺

- 20 ¹H NMR (300 MHz, DMSO-d₆): $\delta = 5.02$ (s, 2 H), 5.34 (s, 2 H), 7.30 (s, 1 H), 7.42 (dd, 1 H), 7.70 (d, 1 H), 7.80 - 7.92 (m, 1 H), 8.18 (d, 1 H), 8.27 (s, 1 H), 8.39 (t, 1 H), 8.44 - 8.53 (m, 1 H), 8.62 (d, 1 H), 8.80 (s, 1 H), 10.49 (s, 1 H).

Intermediate 9-10

- 25 [5-({[6-(1-Methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



Analogously to Intermediate 9-1, 1.2 g (3.11 mmol) of ethyl [5-({[6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-11) (crude product) were initially charged in 10 ml of tetrahydrofuran, and 1.25 g (29.7 mmol) of lithium hydroxide monohydrate in 3 ml of water and 2 ml of ethanol were added. The mixture was stirred at 25°C for 5 h. Water was added, followed by 10% strength citric acid down to a pH of 4. The mixture was extracted three times with ethyl acetate, and saturated sodium chloride solution was added to the aqueous phase. A solid precipitated from the aqueous phase; this solid was filtered off with suction, washed with water and ethyl acetate and dried. This gave 850 mg (54% of theory) of the title compound as a brown solid.

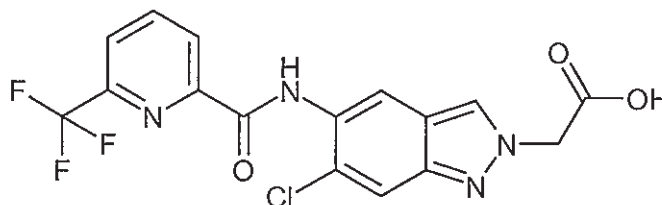
10 UPLC-MS (Method A1): $R_t = 0.82$ min

MS (ESIpos): $m/z = 37$ (M+H)⁺.

¹H-NMR (300 MHz, DMSO-*d*₆): $\delta = 3.93$ (s), 4.98 (s, 2H), 7.60 (s, 2H), 7.83 - 8.05 (m, 3H), 8.23 - 8.40 (m, 3H), 8.67 (s, 1H), 10.42 (s, 1H).

15 Intermediate 9-11

([6-Chloro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



1.45 g (3.19 mmol) of tert-butyl [6-chloro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-14) were dissolved in 15 ml of dichloromethane, and 2.46 ml (31.9 mmol) of trifluoroacetic acid were added at 25°C. The solution was stirred at 25°C for 18 h. Water was added, the resulting precipitate was filtered off with suction, washed three times with water and twice with diethyl ether and the solid was dried under reduced pressure. This gave 1.28 g (98% of theory) of the title compound.

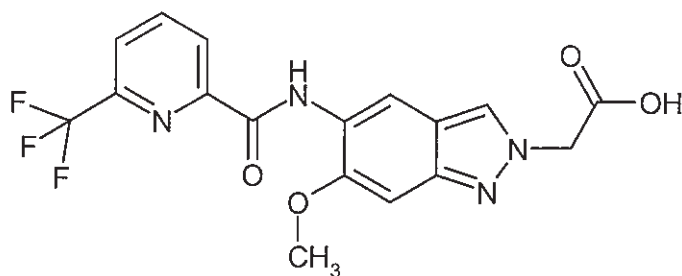
25 UPLC-MS (Method A1): $R_t = 1.11$ min

MS (ESIpos): $m/z = 399$ (M+H)⁺

¹H-NMR (400 MHz, DMSO-*d*₆): $\delta = 5.31$ (s, 2H), 7.93 (s, 1H), 8.22 (dd, 1H), 8.37 - 8.50 (m, 3H), 8.64 (s, 1H), 10.52 (s, 1H), 13.28 (br. s., 1H).

30 Intermediate 9-12

[6-Methoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



Analogously to Intermediate 9-11, 1.1 g (2.44 mmol) of tert-butyl [6-methoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-15) were stirred with 3.76 ml (48.8 mmol) of trifluoroacetic acid in 20 ml of dichloromethane at 25°C for 24 h. Work-up gave 1.20 g (96% of theory) of the title compound.

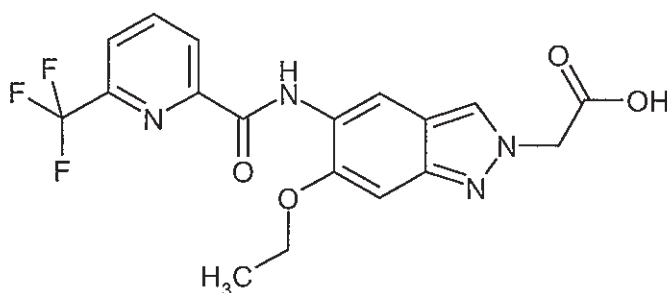
UPLC-MS (Method A1): $R_t = 1.09$ min

MS (ESIpos): $m/z = 395$ ($M+H$)⁺

¹H NMR (300 MHz, DMSO-d₆): $\delta = 3.99$ (s, 3 H), 5.22 (s, 2 H), 7.14 (s, 1 H), 8.22 (dd, 1 H), 8.31 (s, 1 H), 8.42 (d, 1 H), 8.46 (s, 1 H), 8.71 (s, 1 H), 10.51 (s, 1 H).

Intermediate 9-13

[6-Ethoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



Analogously to Intermediate 9-1, 774 mg (1.77 mmol) of ethyl {[6-ethoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-12) were initially charged in 1 ml of ethanol and 25 ml of tetrahydrofuran, a solution of 745 mg (17.74 mmol) of lithium hydroxide monohydrate dissolved in 5 ml of water was then added and the mixture was stirred at 25°C for 3 days. Work-up gave 698 mg (94% of theory) of the title compound.

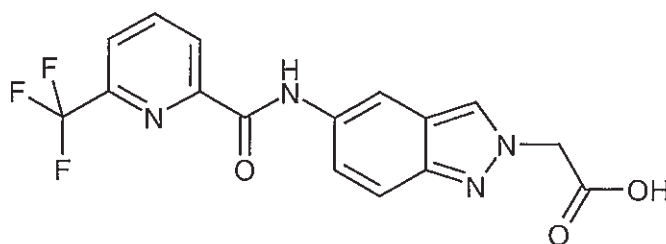
UPLC-MS (Method A1): $R_t = 1.13$ min

MS (ESIpos): $m/z = 409$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.49$ (t, 3H), 4.20 (q, 2H), 5.17 (s, 2H), 7.09 (s, 1H), 8.21 (dd, 1H), 8.28 (s, 1H), 8.36 - 8.48 (m, 2H), 8.71 (s, 1H), 10.73 (s, 1H).

Intermediate 9-14

[5-({[6-(Trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid

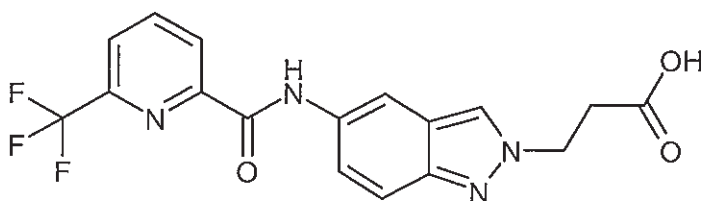


197 μ l (2.57 mmol) of trifluoroacetic acid were added to a mixture of 216 mg (2.02 mmol) of tert-butyl [5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-16) in 3 ml of dichloromethane. The mixture was stirred at 25°C for 3 days, another 197 μ l (2.57 mmol) of trifluoroacetic acid were added and the mixture was stirred at 25°C. Water was added to the reaction mixture. The mixture was stirred for 10 min and the solid was filtered off with suction, washed with water and dried. This gave 142 mg (76% of theory) of the title compound.

¹H-NMR (300 MHz, DMSO-*d*₆): δ = 5.25 (s, 2H), 7.52 - 7.62 (m, 2H), 8.14 (dd, 1H), 8.26 - 8.41 (m, 4H), 10.37 (s, 1H).

Intermediate 9-15

3-[5-({[6-(Trifluormethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]propanoic acid



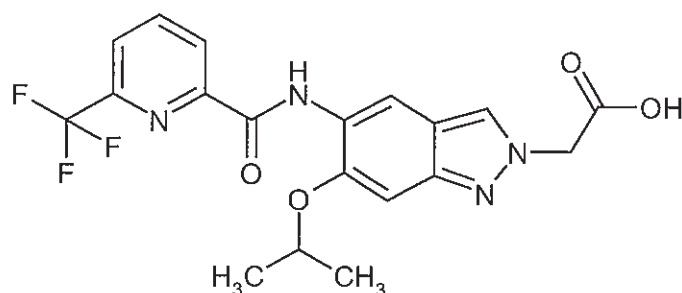
Analogously to Intermediate 9-1, 285 mg (0.70 mmol) of ethyl 3-[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]propanoate (Intermediate 8-13) were reacted with 168 mg (7.0 mmol) of lithium hydroxide. This gave 253 mg (95% of theory) of the title compound.

UPLC-MS (Method A1): R_t = 0.99 min

MS (ESIpos): m/z = 379 (M+H)⁺.

Intermediate 9-16

[6-Isopropoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



Analogously to Intermediate 9-1, 490 mg (1.1 mmol) of ethyl [6-isopropoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-17) were reacted with 260 mg (11 mmol) of lithium hydroxide. This gave 367 mg (80% of theory) of the title compound.

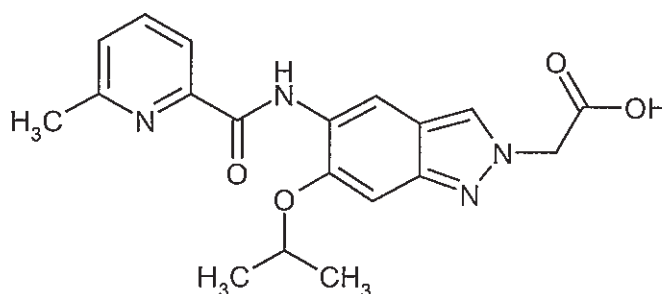
UPLC-MS (Method A1): $R_t = 1.17$ min

MS (ESIpos): $m/z = 423$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.45$ (d, 6H), 4.80 – 4.92 (m, 1H), 5.21 (s, 2H), 7.17 (s, 1H), 8.19 – 8.25 (m, 1H), 8.30 (s, 1H), 8.36 – 8.49 (m, 2H), 8.74 (s, 1H), 10.75 (s, 1H), 13.21 (s, 1H).

Intermediate 9-17

(6-Isopropoxy-5-{{[6-methylpyridin-2-yl]carbonyl}amino}-2H-indazol-2-yl)acetic acid



Analogously to Intermediate 9-1, 370 mg (0.93 mmol) of ethyl (6-isopropoxy-5-{{[6-methylpyridin-2-yl]carbonyl}amino}-2H-indazol-2-yl)acetate (Intermediate 8-18) were reacted with 223 mg (9.33 mmol) of lithium hydroxide. This gave 280 mg (81% of theory) of the title compound.

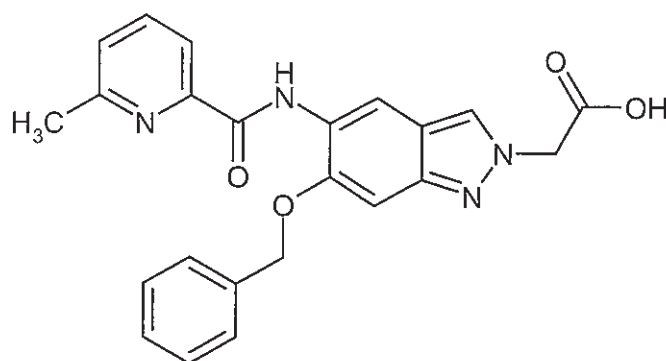
UPLC-MS (Method A1): $R_t = 1.11$ min

MS (ESIpos): $m/z = 369$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.45$ (d, 6H), 2.62 (s, 3H), 4.78 – 4.89 (m, 1H), 5.19 (s, 2H), 7.14 (s, 1H), 7.52 – 7.60 (m, 1H), 7.93 – 8.02 (m, 2H), 8.27 (s, 1H), 8.72 (s, 1H), 10.99 (s, 1H), 13.19 (sbr, 1H).

Intermediate 9-18

[6-(Benzyloxy)-5-{{[6-methylpyridin-2-yl]carbonyl}amino}-2H-indazol-2-yl]acetic acid



Analogously to Intermediate 9-14, 100 mg (0.21 mmol) of tert-butyl [6-(benzyloxy)-5-[[6-methylpyridin-2-yl]carbonyl]amino}-2H-indazol-2-yl]acetate (Intermediate 8-19) were dissolved in 6.7 ml of dichloromethane and stirred with 326 μ l (4.23 mmol) of trifluoroacetic acid at 25°C for 24 h. Work-up gave 67 mg (76% of theory) of the title compound.

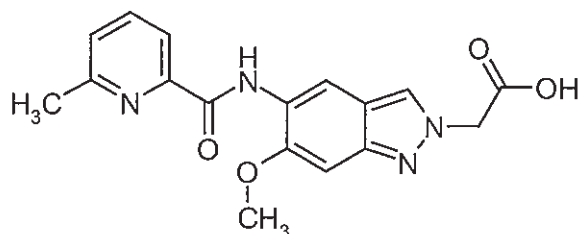
UPLC-MS (Method A1): R_t = 1.20 min

MS (ESIpos): m/z = 417 ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): δ = 2.43 (s, 3 H), 5.22 (s, 2 H), 5.31 (s, 2 H), 7.29 (s, 1 H), 7.42 (d, 1 H), 7.44 - 7.54 (m, 3 H), 7.65 (d, 2 H), 7.91 - 8.02 (m, 2 H), 8.30 (s, 1 H), 8.78 (s, 1 H), 10.87 (s, 1 H).

Intermediate 9-19

(6-Methoxy-5-[[6-methylpyridin-2-yl]carbonyl]amino)-2H-indazol-2-yl)acetic acid



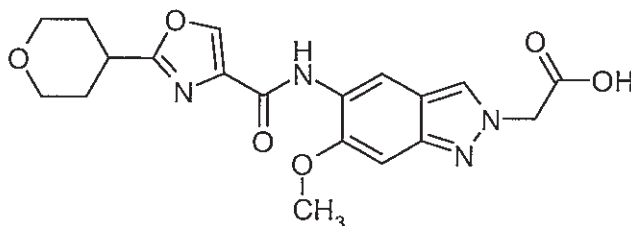
Analogously to Intermediate 9-1, 2.28 g (3.92 mmol, 74%) of benzyl (6-methoxy-5-[[6-methylpyridin-2-yl]carbonyl]amino)-2H-indazol-2-yl)acetate (Intermediate 8-23) were dissolved in 20 ml of tetrahydrofuran and 3.0 ml of methanol, a solution of 1.65 g (39.2 mmol) of lithium hydroxide monohydrate in 3.0 ml of water was then added. The mixture was diluted with water and acidified to pH 4 using 10% strength citric acid. The precipitated solid was filtered off, washed three times with water and three times with diethyl ether and dried under reduced pressure. This gave 2.43 g of the title compound as a crude product.

UPLC-MS (Method A1): R_t = 1.00 min

MS (ESIpos): m/z = 341 ($M+H$)⁺.

Intermediate 9-20

[6-Methoxy-5-({[2-(tetrahydro-2H-pyran-4-yl)-1,3-oxazol-4-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid



- 5 Analogously to Intermediate 9-11, 325 mg (0.71 mmol) of tert-butyl [6-methoxy-5-({[2-(tetrahydro-2H-pyran-4-yl)-1,3-oxazol-4-yl]carbonyl}amino)-2H-indazol-2-yl]acetate (Intermediate 8-24) were dissolved in 5 ml of dichloromethane and stirred with 549 μ l (7.12 mmol) of trifluoroacetic acid at 25°C for 21 h. Another 275 μ l (3.56 mmol) of trifluoroacetic acid were added and the mixture was stirred at 25°C for a further 70 h. Water was added, the resulting
- 10 precipitate was filtered off with suction, washed three times with water and three times with diethyl ether and the solid was dried under reduced pressure. This gave 313 mg of the title compound as a crude product.

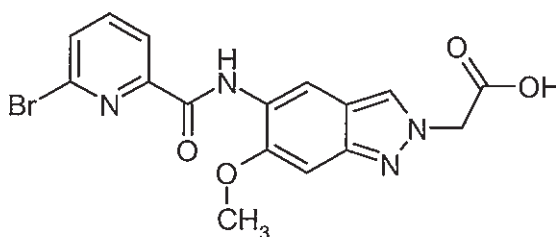
UPLC-MS (Method A1): R_t = 0.91 min

MS (ESIpos): m/z = 401 ($M+H$)⁺

- 15 ¹H-NMR (300 MHz, DMSO- d_6): δ = 1.67 - 1.90 (m, 2 H), 1.98 (d, 2 H), 3.22 (ddd, 1 H), 3.40 - 3.54 (m, 2 H), 3.87 - 4.01 (m, 6 H), 5.20 (s, 2 H), 7.10 (s, 1 H), 8.27 (s, 1 H), 8.56 (s, 1 H), 8.75 (s, 1 H), 9.42 (s, 1 H).

Intermediate 9-21

- 20 (5-{{[(6-Bromopyridin-2-yl)carbonyl]amino}-6-methoxy-2H-indazol-2-yl}acetic acid



- Analogously to Intermediate 9-11, 3.50 g (7.59 mmol) of tert-butyl (5-{{[(6-bromopyridin-2-yl)carbonyl]amino}-6-methoxy-2H-indazol-2-yl}acetate (Intermediate 8-25) were dissolved in 100
- 25 ml of dichloromethane and stirred with 11.7 ml (15.54 mmol) of trifluoroacetic acid at 25°C for 24 h. The reaction mixture was carefully added to saturated sodium bicarbonate solution and stirred briefly, and the resulting precipitate was filtered off with suction and dried at 50°C in a vacuum drying cabinet. This gave 3.10 g of the title compound as a crude product.

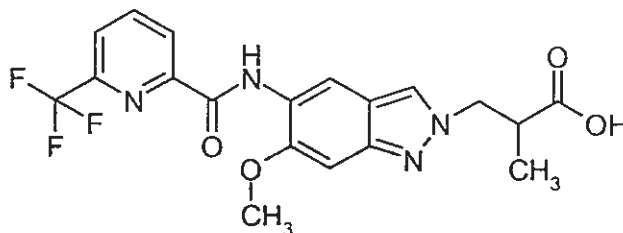
- 30 UPLC-MS (Method A1): R_t = 1.02 min

MS (ESIpos): $m/z = 405$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 4.00$ (s, 3 H) 5.21 (s, 2 H) 7.13 (s, 1 H) 7.95 (dd, 1 H) 8.04 (t, 1 H) 8.20 (dd, 1 H) 8.28 - 8.31 (m, 1 H) 8.68 (s, 1 H) 10.30 (s, 1 H).

5 **Intermediate 9-22**

3-[6-Methoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]-2-methylpropanoic acid



- 10 Analogously to Intermediate 4-1, 37 mg (0.09 mmol) of methyl 3-[6-methoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]-2-methylpropanoate (Intermediate 8-20) were dissolved in 2 ml of tetrahydrofuran and 0.1 ml of methanol, a solution of 36 mg (0.85 mmol) of lithium hydroxide monohydrate in 0.1 ml of water was then added and the mixture was stirred at 25°C for 23.5 h. The mixture was diluted with water, acidified to pH 4 using 10% strength citric acid and extracted three times with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, filtered through a hydrophobic filter, concentrated and dried under reduced pressure. This gave 34 mg (94% of theory) of the title compound.

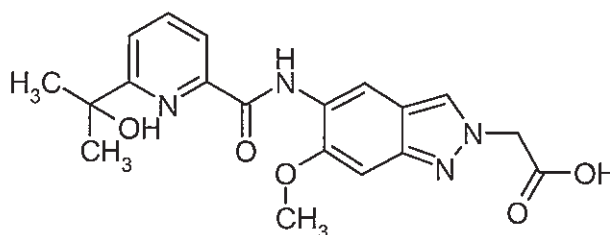
UPLC-MS (Method A1): $R_t = 1.13$ min

MS (ESIpos): $m/z = 423$ ($M+H$)⁺

- 20 ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.04$ (d, 3 H), 3.00 - 3.13 (m, 2 H), 3.98 (s, 3 H), 4.37 (dd, 1 H), 4.59 (dd, 1 H), 7.15 (s, 1 H), 8.22 (dd, 1 H), 8.29 (s, 1 H), 8.35 - 8.44 (m, 1 H), 8.44 - 8.49 (m, 1 H), 8.68 (s, 1 H), 10.49 (s, 1 H).

25 **Intermediate 9-23**

3-[6-Methoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]-2-methylpropanoic acid



Analogously to Intermediate 4-1, 206 mg (0.43 mmol) of benzyl [5-({[6-(2-hydroxypropan-2-yl)pyridin-2-yl]carbonyl}amino)-6-methoxy-2H-indazol-2-yl]acetate (Intermediate 8-22) were suspended in 10 ml of tetrahydrofuran and 1.0 ml of methanol, a solution of 182 mg (4.33 mmol) of lithium hydroxide monohydrate in 1.5 ml of water was then added and the mixture was stirred at 25°C for 24 h. The mixture was diluted with water, acidified to pH 4 using 10% strength citric acid and concentrated. The precipitated solid was filtered off, washed once with water and three times with diethyl ether and dried under reduced pressure. This gave 155 mg (93% of theory) of the title compound.

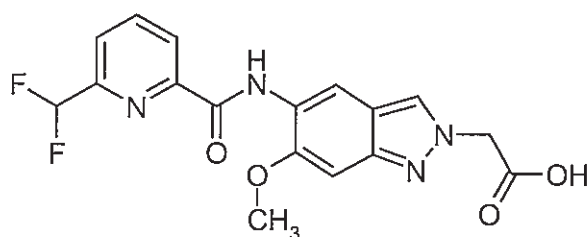
UPLC-MS (Method A1): $R_t = 1.20$ min

MS (ESIpos): $m/z = 421$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 1.57$ (s, 6 H), 3.99 (s, 3 H), 5.20 (s, 2 H), 5.47 (s, 1 H), 7.12 (s, 1 H), 7.93 (dd, $J=7.5, 1.3$ Hz, 1 H), 7.98 - 8.11 (m, 2 H), 8.28 (s, 1 H), 8.68 (s, 1 H), 10.93 (s, 1 H).

Intermediate 9-24

[5-({[6-(difluoromethyl)pyridin-2-yl]carbonyl}amino)-6-methoxy-2H-indazol-2-yl]acetic acid

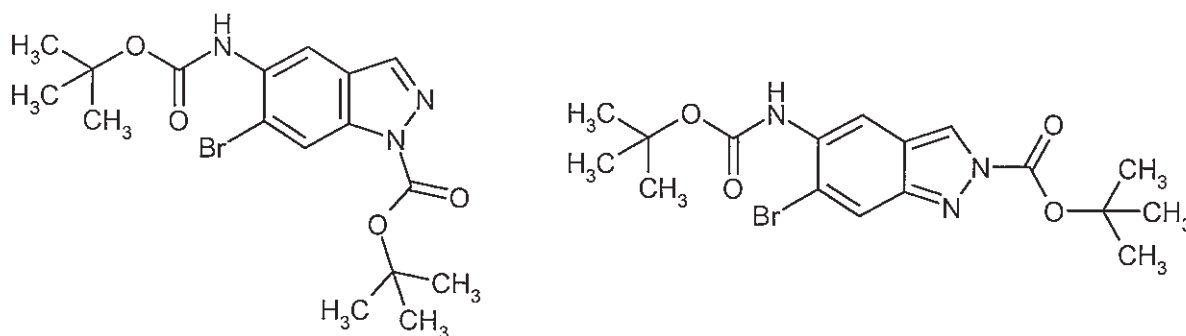


Analogously to Intermediate 4-1, 613 mg of benzyl [5-({[6-(difluoromethyl)pyridin-2-yl]carbonyl}amino)-6-methoxy-2H-indazol-2-yl]acetate (Intermediate 8-21) were stirred at room temperature with 469 mg of lithium hydroxide monohydrate in 3 ml of water, 15 ml of THF and 1 ml of methanol for 3 h. This gave, after analogous work-up, 378 mg of the title compound.

UPLC-MS (Method A1): $R_t = 0.98$ min, mass found (UV Detector TIC) 376.00.

Intermediate 10 and Intermediate 11

tert-Butyl 6-bromo-5-[(tert-butoxycarbonyl)amino]-1H-indazole-1-carboxylate tert-butyl 6-bromo-5-[(tert-butoxycarbonyl)amino]-2H-indazol-2-carboxylate



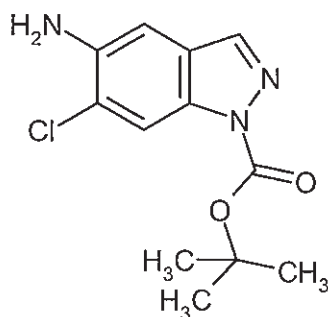
27.5 g (126.1 mmol) of di-tert-butyl dicarbonate were dissolved in 53.5 ml of tetrahydrofuran and cooled to 0°C. After addition of 5.35 g (25.2 mmol) of 6-bromo-1H-indazole-5-amine (CAS No: 1360928-41-1) at 0°C, the mixture was then stirred at 80°C for 24 h. The reaction mixture was concentrated, dichloromethane was added and the reaction mixture was washed with 0.5 M hydrochloric acid and saturated sodium chloride solution, dried over sodium sulphate and, during concentration, adsorbed on Isolute® HM-N (Biotage). The Isolute was applied to a Biotage SNAP cartridge (340 g; KP-Sil) pre-equilibrated with hexane and chromatography was carried out using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; gradient: isocratic 80:20 (9 CV)). This gave 7.07 g (68% of theory) of the regioisomeric product mixture. (Ratio: 1-isomer/2-isomer: 85%/15%)

UPLC-MS (Method A2): $R_t = 1.48$ min

MS (ESI^{neg}): $m/z = 410$ ($M(^{79}\text{Br})\text{-H}^+$)

15 Intermediate 12-1

tert-Butyl 5-amino-6-chloro-1H-indazole-1-carboxylate



2.1 ml (11.8 mmol) of *N,N*-diisopropylethylamine and 2.34 g (10.7 mmol) of di-tert-butyl dicarbonate were added to 1.80 g (10.7 mmol) of 6-chloro-1H-indazole-5-amine (CAS No. 221681-75-0) in 18 ml of tetrahydrofuran, and the mixture was stirred at 25°C for 18 h. The mixture was concentrated and the residue was taken up in ethyl acetate and, during concentration, adsorbed on Isolute. The Isolute was applied to a Biotage SNAP cartridge (100 g; KP-Sil) pre-equilibrated with hexane and chromatography was carried out using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; flow rate: 50 ml/min; gradient: isocratic 100:0 (5 min), 100:0->75:25 (20 min), isocratic 75:25 (5min), 75:25->50:50 (15 min), isocratic

50:50 (5 min), 50:50->0:100 (15 min)). The combined product fractions were concentrated and dried under reduced pressure. This gave 1.23 g (43% of theory) of the title compound.

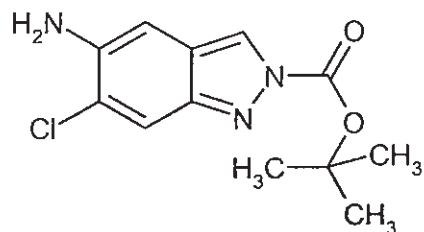
UPLC-MS (Method A1): $R_t = 1.16$ min

MS (ESIpos): $m/z = 268$ (M+H)⁺

5

Intermediate 12-2

tert-Butyl 5-amino-6-chloro-2H-indazole-2-carboxylate



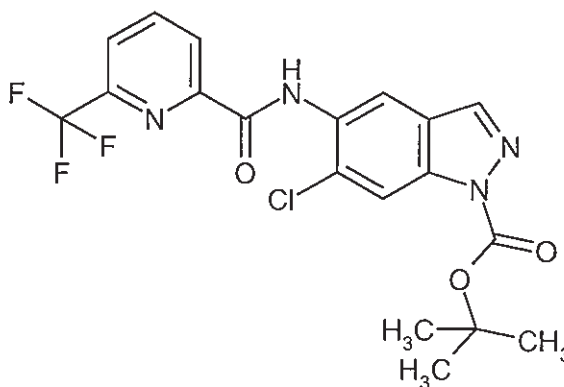
7.5 g of 6-chloro-1H-indazole-5-amine (CAS No. 221681-75-0) were converted analogously to the preparation of Intermediate 12-1. Purification by column-chromatographic purification on silica gel (hexane/ethyl acetate) gave 1.0 g of the title compound.

¹H-NMR (500 MHz, DMSO-d₆): $\delta = 1.62$ (s, 9H), 5.33 (s, 2H), 6.79 (s, 1H), 7.74 (s, 1H), 8.50 (d, 1H).

15

Intermediate 13

tert-Butyl 6-chloro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-1-carboxylate



20

Analogously to Intermediate 5-1, 1.23 g (4.59 mmol) of tert-butyl 5-amino-6-chloro-1H-indazole-1-carboxylate (Intermediate 12-1) in 20 ml of *N,N*-dimethylformamide were stirred with 1.14 g (5.97 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid at 25°C for 72 h. Water was added, the mixture was stirred for 15 min and the solid was filtered off with suction, washed three times

with water and dried under reduced pressure. This gave 2.02 g (98% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 1.57$ min

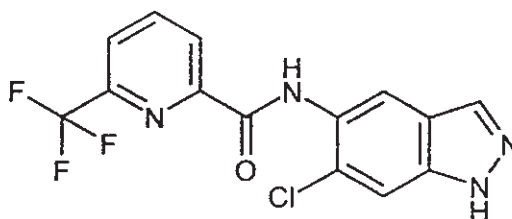
MS (ESIpos): $m/z = 441$ ($M+H$)⁺

- 5 ¹H-NMR (300 MHz, DMSO-d₆): $\delta = 1.65$ (s, 9H), 8.19 - 8.27 (m, 2H), 8.37 - 8.53 (m, 3H), 8.75 (s, 1H), 10.59 (s, 1H).

Intermediate 14-1

N-(6-Chloro-1H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

10



- Analogously to Intermediate 6-1, 6.7 ml (8.73 mmol) of trifluoroacetic acid were added to 3.85 g (8.73 mmol) of tert-butyl 6-chloro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-1-carboxylate (Intermediate 13) in 40 ml of dichloromethane, and the mixture was stirred at 25°C for 18 h. Work-up gave 2.98 g (100% of theory) of the title compound.

15

UPLC-MS (Method A1): $R_t = 1.18$ min

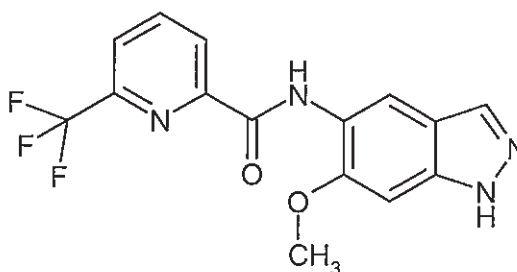
MS (ESIpos): $m/z = 341$ ($M+H$)⁺

¹H-NMR (300 MHz, DMSO-d₆): $\delta = 7.83$ (s, 1H), 8.14 - 8.27 (m, 2H), 8.36 - 8.49 (m, 2H), 8.60 (s, 1H), 10.50 (br. s., 1H), 13.25 (br. s., 1H).

20

Intermediate 14-2

N-(6-Methoxy-1H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide



- 25 3.84 g (23.5 mmol) of 6-methoxy-1H-indazole-5-amine (CAS No.: 749223-61-8) and 4.95 g (25.9 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid were dissolved in 150 ml of tetrahydrofuran, and with 3.60 g (23.5 mmol) of 1-hydroxy-1H-benzotriazole hydrate, 9.02 g (47.1 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 9.84 ml (70.6 mmol) of triethylamine were added at 25°C. The solution was stirred at 25°C for 24 h. After concentration

of the solution, the residue was taken up in ethyl acetate, water was added and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution and dried over sodium sulphate and, after filtration, the solution was concentrated. The residue was taken up in dichloromethane, Isolute® HM-N (Biotage) was added and during concentration the residue was adsorbed on Isolute. The Isolute was applied to a Biotage SNAP cartridge (340 g; KP-Sil) pre-equilibrated with hexane and chromatography was carried out using the Isolera® flash purification system (Biotage) (mobile phase: hexane/ethyl acetate; gradient 100:0->50:50 (9 CV), isocratic 50:50 (4 CV)). The combined product fractions were concentrated and the beige solid was dried under reduced pressure. This gave 3.75 g (47% of theory) of the title compound.

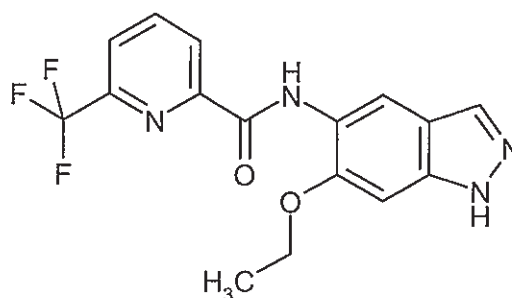
UPLC-MS (Method A1): $R_t = 1.12$ min

MS (ESIpos): $m/z = 337$ ($M+H$)⁺

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 4.01$ (s, 3 H), 7.13 (s, 1 H), 8.02 (s, 1 H), 8.21 (dd, 1 H), 8.40 (t, 1 H), 8.47 (d, 1 H), 8.74 (s, 1 H), 10.42 (s, 1 H), 12.91 (s, 1 H).

Intermediate 14-3

N-(6-Ethoxy-1H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide



Analogously to Intermediate 5-1, 1.00 g (5.64 mmol) of 6-ethoxy-1H-indazole-5-amine and 1.29 g (6.77 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid were reacted in 50 ml of tetrahydrofuran at room temperature for 18 h. Work-up and purification by column chromatography using the Isolera® flash purification system (Biotage) (SNAP cartridge (100 g; KP-Sil), mobile phase: hexane/ethyl acetate; gradient: isocratic 100:0 (1 CV), 100:0->50:50 (10 CV), isocratic 50:50 (4.7 CV), 50:50->3:97 (9.4 CV)) gave 1.30 g (64% of theory) of the title compound.

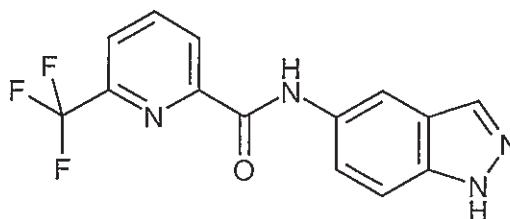
UPLC-MS (Method A1): $R_t = 1.18$ min

MS (ESIpos): $m/z = 351$ ($M+H$)⁺

¹H-NMR (500 MHz, DMSO-d₆): $\delta = 1.51$ (t, 3H), 4.24 (q, 2H), 7.10 (s, 1H), 8.00 (s, 1H), 8.20 (dd, 1H), 8.39 - 8.43 (m, 1H), 8.46 - 8.48 (m, 1H), 8.79 (s, 1H), 10.67 (s, 1H), 12.87 (s, 1H).

Intermediate 14-4

N-(1H-Indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

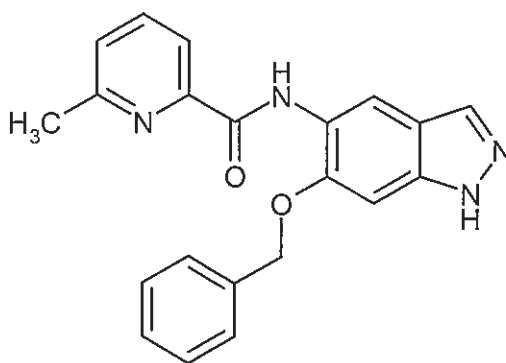


5 Analogously to Intermediate 5-1, 4.43 g (33.3 mmol) of 1H-indazole-5-amine (CAS No.: 19335-11-6) were reacted analogously with 7.00 g (36.6 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid. This gave, after purification by column chromatography on silica gel (hexane/ethyl acetate), 7.8 g (73% of theory) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ = 7.51 (d, 1H), 7.68 (dd, 1H), 8.05 (s, 1H), 8.14 (dd, 1H), 8.25 -
10 8.41 (m, 3H), 10.42 (s, 1H), 13.04 (br. s., 1H).

Intermediate 14-5

N-[6-(Benzyloxy)-1H-indazol-5-yl]-6-methylpyridine-2-carboxamide



15

Analogously to Intermediate 14-2, 1.00 g (4.18 mmol) of 6-(benzyloxy)-1H-indazole-5-amine (Intermediate 1-3) and 688 mg (5.02 mmol) of 6-methylpyridine-2-carboxylic acid were dissolved in 50 ml of tetrahydrofuran and stirred with 640 mg (4.18 mmol) of 1-hydroxy-1H-benzotriazole hydrate, 1.60 g (8.36 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and
20 1.75 ml (12.54 mmol) of triethylamin at 25°C for 24 h. After concentration of the solution, water was added to the precipitate formed and the precipitate was filtered off with suction, washed with water and diethyl ether and dried under reduced pressure. This gave 1.13 g (76% of theory) of the title compound.

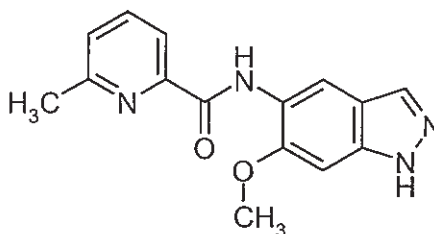
UPLC-MS (Method A1): R_t = 1.26 min

25 MS (ESIpos): m/z = 359 (M+H)⁺

¹H NMR (300 MHz, DMSO-d₆): δ = 2.43 (s, 3 H), 5.34 (s, 2 H), 7.29 (s, 1 H), 7.35 - 7.57 (m, 4 H), 7.65 (d, 2 H), 7.86 - 8.07 (m, 3 H), 8.84 (s, 1 H), 10.82 (s, 1 H), 12.95 (s, 1 H).

Intermediate 14-6

N-(6-Methoxy-1H-indazol-5-yl)-6-methylpyridine-2-carboxamide



5

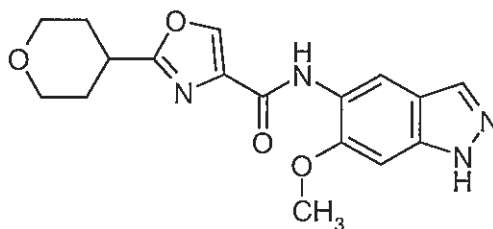
Analogously to Intermediate 14-2, 5.00 g (30.64 mmol) of 6-methoxy-1H-indazole-5-amine (CAS No. 749223-61-8) and 4.62 g (33.70 mmol) of 6-methylpyridine-2-carboxylic acid were dissolved in 100 ml of tetrahydrofuran and stirred with 4.69 g (30.64 mmol) of 1-hydroxy-1H-benzotriazole hydrate, 11.74 g (61.28 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 21.35 ml (153.2 mmol) of triethylamine at 25°C for 20 h. Water was added, and the reaction mixture was concentrated. The resulting precipitate was filtered off with suction, washed three times with water and three times with diethyl ether and dried in a drying cabinet. This gave 7.89 g (65% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 0.49$ min

15 MS (ESIpos): $m/z = 283$ (M+H)⁺.

Intermediate 14-7

N-(6-Methoxy-1H-indazol-5-yl)-2-(tetrahydro-2H-pyran-4-yl)-1,3-oxazole-4-carboxamide



20

Analogously to Intermediate 14-2, 782 mg (4.80 mmol) of 6-methoxy-1H-indazole-5-amine (CAS No. 749223-61-8) and 1.04 g (5.27 mmol) of 2-(tetrahydro-2H-pyran-4-yl)-1,3-oxazole-4-carboxylic acid (CAS No. 955401-82-8) were dissolved in 15 ml of tetrahydrofuran and stirred with 734 mg (4.80 mmol) of 1-hydroxy-1H-benzotriazole hydrate, 1.84 g (9.59 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 3.34 ml (24.0 mmol) of triethylamine at 25°C for 26 h. Water was added, and the reaction mixture was concentrated. The resulting precipitate was filtered off with suction, washed three times with water and three times with diethyl ether and dried in a drying cabinet. This gave 1.19 g (37% of theory) of the title compound.

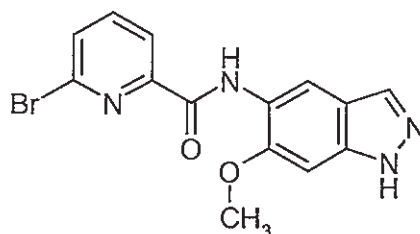
30 UPLC-MS (Method A1): $R_t = 0.94$ min

MS (ESIpos): $m/z = 343 (M+H)^+$.

Intermediate 14-8

6-Bromo-N-(6-methoxy-1H-indazol-5-yl)pyridine-2-carboxamide

5



2.0 g (12.26 mmol) of 6-methoxy-1H-indazole-5-amine (CAS No. 749223-61-8) were dissolved in 50 ml of tetrahydrofuran, 4.72 g (14.71 mmol) of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate and 2.56 ml (14.71 mmol) of *N,N*-diisopropylethylamine were added and the mixture was stirred at 25°C for 30 minutes. 2.56 ml (14.71 mmol) of 6-bromopyridine-2-carboxylic acid (CAS No. 21190-87-4) were added, and the mixture was stirred at 25°C for a further 24 h. The reaction mixture was concentrated and the residue was added to 400 ml of water. The resulting precipitate was filtered off with suction, washed twice with water and twice with diethyl ether and dried at 50°C in a vacuum drying cabinet for 4 h. This gave 4.18 g (98% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 0.93$ min

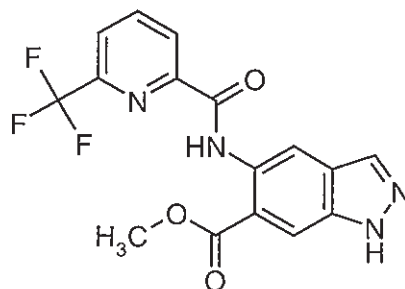
MS (ESIpos): $m/z = 347 (M+H)^+$

^1H NMR (300 MHz, DMSO- d_6): $\delta = 4.02$ (s, 3 H) 7.13 (s, 1 H) 7.89 - 8.10 (m, 3 H) 8.20 (dd, 1 H) 8.71 (s, 1 H) 10.22 (s, 1 H) 12.90 (br. s., 1 H).

20

Intermediate 14-9

Methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate



4.5 g (23.53 mmol) of methyl 5-amino-1H-indazole-6-carboxylate (Intermediate 1-6) were dissolved in 45 ml of tetrahydrofuran, 9.07 g (28.24 mmol) of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate and 4.92 ml (28.24 mmol) of *N,N*-diisopropylethylamine were added and the mixture was stirred at 25°C for 30 minutes. 4.95 g (25.89 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid (CAS No. 21190-87-4) were added, and the mixture was stirred at 25°C for a further 24 h. The reaction mixture was filtered off with suction through a

membrane filter, washed with tetrahydrofuran and water and dried at 50°C in a vacuum drying cabinet for 24 h. The filtrate was concentrated with acetonitrile and the resulting precipitate was filtered off with suction, washed and dried. This gave 8.60 g (84% of theory) of the title compound.

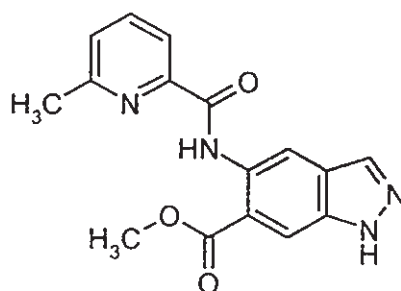
UPLC-MS (Method A1): $R_t = 1.21$ min

5 MS (ESIpos): $m/z = 365$ (M+H)⁺

¹H NMR (300 MHz, DMSO-d₆): $\delta = 3.97$ (s, 3 H), 8.13 - 8.27 (m, 2 H), 8.30 (s, 1 H), 8.33 - 8.45 (m, 1 H), 8.45 - 8.51 (m, 1 H), 9.15 (s, 1 H), 12.57 (s, 1 H), 13.44 (s, 1 H).

Intermediate 14-10

10 Methyl 5-[[6-methylpyridin-2-yl]carbonyl]amino}-1H-indazole-6-carboxylate



500 mg (2.62 mmol) of methyl 5-amino-1H-indazole-6-carboxylate (Intermediate 1-6) were dissolved in 5 ml of tetrahydrofuran, 1.01 g (3.14 mmol) of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate and 547 μ l (3.14 mmol) of *N,N*-diisopropylethylamine were added and the mixture was stirred at 25°C for 30 minutes. 395 mg (2.88 mmol) of 6-methylpyridine-2-carboxylic acid (CAS No. 21190-87-4) were added, and the mixture was stirred at 25°C for a further 8 h. The reaction mixture was added to water and stirred vigorously for 10 minutes and the precipitate was filtered off with suction through a nylon filter. The precipitate was washed twice with water and twice with diethyl ether. The solid was dried in a vacuum drying cabinet at 50°C for 3 h. This gave 790 mg (92% of theory) of the title compound.

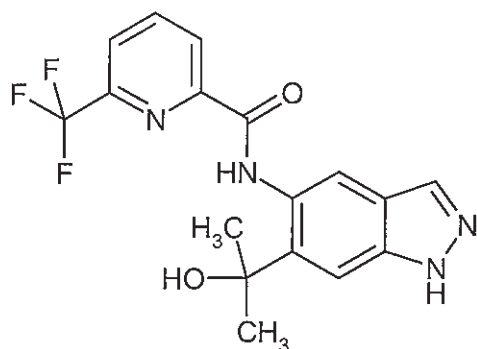
UPLC-MS (Method A1): $R_t = 1.05$ min

MS (ESIpos): $m/z = 311$ (M+H)⁺

¹H NMR (300 MHz, DMSO-d₆): $\delta = 2.65$ (s, 3 H), 4.00 (s, 3 H), 7.55 (dd, 1 H), 7.91 - 7.99 (m, 1 H), 7.99 - 8.04 (m, 1 H), 8.23 (s, 1 H), 8.29 (s, 1 H), 9.18 (s, 1 H), 12.65 (s, 1 H), 13.41 (s, 1 H).

Intermediate 14-11

N-[6-(2-Hydroxypropan-2-yl)-1H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

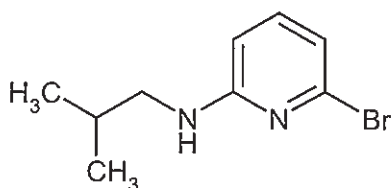


6.9 ml (5 equiv.) of a 3M methylmagnesium bromide solution in diethyl ether were added carefully to an ice-cold solution of 1.50 g (4.12 mmol) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 14-9) in 20 ml of THF. The mixture was stirred with ice bath cooling for 1 h and at room temperature for 19.5 h. Another 2 equiv. of methylmagnesium bromide solution were added and the mixture was stirred at room temperature for a further 24 h. Saturated aqueous ammonium chloride solution was added and the mixture was stirred and extracted three times with ethyl acetate. The combined organic phases were washed with sodium chloride solution, filtered through a hydrophobic filter and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate gradient). This gave 763 mg (45% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 1.63 (s, 6H), 5.99 (s, 1H), 7.49 (s, 1H), 8.06 (s, 1H), 8.14 - 8.19 (m, 1H), 8.37 (t, 1H), 8.46 (d, 1H), 8.78 (s, 1H), 12.32 (s, 1H), 12.97 (s, 1H).

15 Intermediate 16-1

6-Bromo-N-isobutylpyridine-2-amine

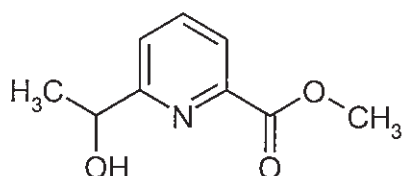


In a pressure reactor, 1.0 g of 2,6-dibromopyridine and 340 mg of 2-methylpropane-1-amine and 1.43 ml of 2,2,6,6-tetramethylpiperidine were stirred at 190°C for 16 h. The mixture was poured into saturated sodium bicarbonate solution, extracted with dichloromethane, washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated. The residue was purified by column chromatography on silica gel. This gave 920 mg of the title compound.

¹H-NMR (300 MHz, CHLOROFORM-d): δ [ppm] = 1.00 (d, 6H), 1.81 - 1.98 (m, 1H), 3.05 (t, 2H), 4.76 (br. s., 1H), 6.29 (d, 1H), 6.72 (d, 1H), 7.22 - 7.35 (m, 2H).

25 Intermediate 17-1

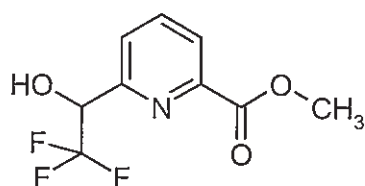
Methyl 6-(1-hydroxyethyl)pyridine-2-carboxylate



2.00 g of 1-(6-bromopyridin-2-yl)ethanol (Telfer, Shane G.; Kuroda, Reiko, *Chemistry A European Journal*, **2005**, *11*, 57 – 68) were suspended in 20 ml of methanol and 30 ml of dimethyl sulphoxide. 265 mg of 1,3-bis(diphenylphosphino)propane, 140 mg of palladium(II) acetate and 3.2 ml of triethylamine were added, the mixture was flushed three times with carbon monoxide and stirred in a carbon monoxide atmosphere (12 bar 0.5 h, then at 16 bar overnight). Water was added, the mixture was extracted with ethyl acetate and the extract was concentrated. This gave 1.7 g of methyl 6-(1-hydroxyethyl)pyridine-2-carboxylate as an oil (crude product).
¹H-NMR (400 MHz, CHLOROFORM-d): δ = 1.57 (d, 3H), 4.02 (s, 3H), 5.03 (q, 1H), 7.56 (d, 1H), 7.88 (t, 1H), 8.05 (d, 1H).

Intermediate 17-2

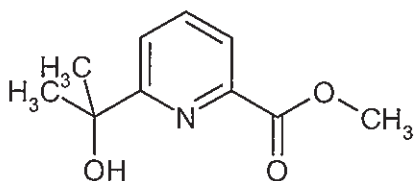
Methyl 6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxylate



1.04 g (4.06 mmol) of 1-(6-bromopyridin-2-yl)-2,2,2-trifluoroethanol (CAS 1093880-21-7) were reacted analogously to Intermediate 17-1 in a carbon monoxide atmosphere. After analogous work-up, the crude product was purified by preparative HPLC. This gave 696 mg of the title compound.
¹H-NMR (300 MHz, DMSO-d₆): δ = 3.89 (s, 3H), 5.15 - 5.28 (m, 1H), 7.18 - 7.25 (m, 1H), 7.86 (dd, 1H), 8.05 - 8.14 (m, 2H).

Intermediate 17-3

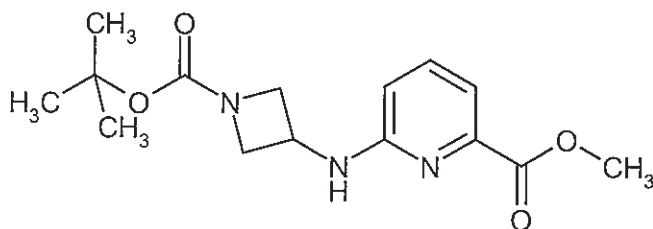
Methyl 6-(2-hydroxypropan-2-yl)pyridine-2-carboxylate



1.00 g of 2-(6-bromopyridin-2-yl)propan-2-ol was reacted analogously to Intermediate 17-1 in a carbon monoxide atmosphere. After analogous work-up, the crude product was purified by preparative HPLC. This gave 540 mg of the title compound.
¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 1.44 (s, 6H), 3.86 (s, 3H), 5.34 (s, 1H), 7.86 - 7.99 (m, 3H).

Intermediate 17-4

Methyl 6-([1-(tert-butoxycarbonyl)azetidin-3-yl]amino)pyridine-2-carboxylate

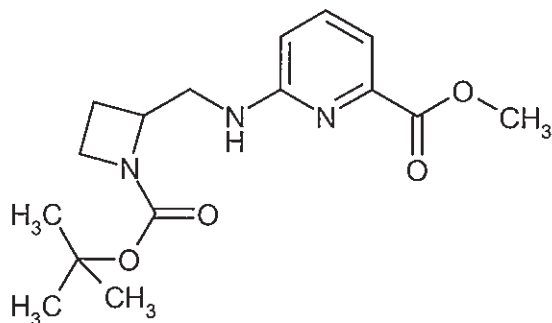


- 5 A mixture of 250 mg of methyl 6-fluoropyridine-2-carboxylate, 361 mg of tert-butyl 3-aminoazetidine-1-carboxylate (1.3 equivalents) and 0.84 ml of N-ethyl-N-isopropylpropane-2-amine in 3.0 ml of 1-methylpyrrolidin-2-one was stirred at 80°C. Another 0.5 equivalent of tert-butyl 3-aminoazetidine-1-carboxylate was added and the mixture was stirred at 100°C overnight. Another 0.5 equivalent of tert-butyl 3-aminoazetidine-1-carboxylate was added and the mixture
- 10 was stirred at room temperature for 3 days. Water was added, the mixture was extracted with ethyl acetate, the organic phases were concentrated and the residue was purified by preparative HPLC. This gave 230 mg of the title compound.

UPLC-MS (Method A1): Rt = 1.07 min (UV detector TIC), mass found 307.15.

15 Intermediate 17-5

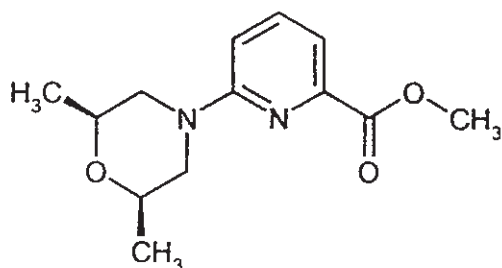
Methyl 6-([1-(tert-butoxycarbonyl)azetidin-2-yl]methyl}amino)pyridine-2-carboxylate



A mixture of 500 mg of methyl 6-fluoropyridine-2-carboxylate, 720 mg of tert-butyl 2-(aminomethyl)azetidine-1-carboxylate and 2.2 ml of N-ethyl-N-isopropylpropane-2-amine in 7.5 ml of 1-methylpyrrolidin-2-one was stirred at 100°C for 30 min, at 120°C for 4 h and at 140°C for 3 h. The mixture was concentrated and the product was purified by preparative HPLC (column: Reprospher C18-DE 5µm 125x30 mm, solvent system: A = water + 0.1% by volume of formic acid (99%), B = acetonitrile, gradient 0 - 5.5 min 40-80% B). This gave 230 mg of the title compound as a crude product. Mass found (UV detector TIC) 321.17.

Intermediate 17-6

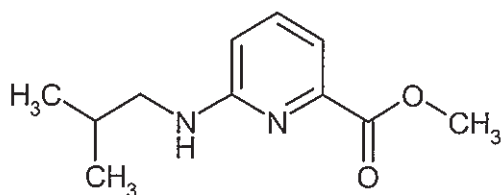
Methyl 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridine-2-carboxylate



300 mg of methyl 6-fluoropyridine-2-carboxylate were reacted analogously with 334 mg of (2R,6S)-2,6-dimethylmorpholine analogously to Intermediate 17-4 at 80°C overnight. Another 0.5 equivalent of (2R,6S)-2,6-dimethylmorpholine was added and the mixture was stirred at 100°C for 7 h. Aqueous work-up gave 875 mg of a crude product which still contained 1-methylpyrrolidin-2-one. UPLC-MS (Method A1): Rt = 1.05 min (UV detector TIC), mass found 250.00.

Intermediate 17-7

Methyl 6-(isobutylamino)pyridine-2-carboxylate

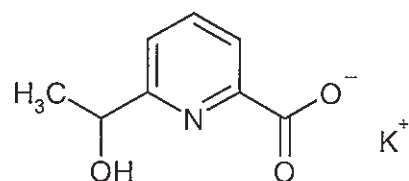


900 mg of 6-bromo-N-isobutylpyridine-2-amine (Intermediate 16-1) were reacted analogously to Intermediate 17-1 in a carbon monoxide atmosphere. The crude product was purified by column chromatographic purification on silica gel. This gave 796 mg of the title compound.

¹H-NMR (300 MHz, CHLOROFORM-d): δ [ppm] = 1.02 (d, 3H), 1.83 – 1.98 (m, 1H), 3.08 (t, 2H), 3.97 (s, 3H), 4.97 (br. s., 1H), 6.58 (d, 1H), 7.42 (d, 1H), 7.58 (t, 1H).

Intermediate 19-1

Potassium 6-(1-hydroxyethyl)pyridine-2-carboxylate

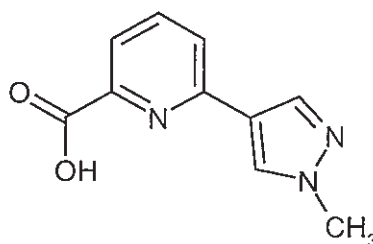


- 5 541 mg of methyl 6-(1-hydroxyethyl)pyridine-2-carboxylate (Intermediate 17-1, crude product) were initially charged in 5 ml of methanol, 120 mg of potassium hydroxide were added and the mixture was stirred at 50°C overnight. More potassium hydroxide was added and the mixture was stirred at 50°C for 5 h. The mixture was concentrated, giving 625 mg of potassium 6-(1-hydroxyethyl)pyridine-2-carboxylate as a crude product.

10

Intermediate 19-2

6-(1-Methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid

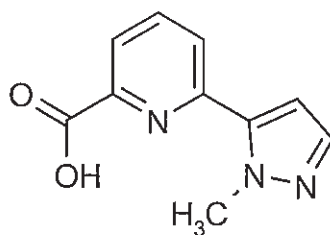


- 15 500 mg (2.31 mmol) of methyl 6-bromopyridine-2-carboxylate, 578 mg (1.2 equiv.) of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and 192 mg of lithium chloride were initially charged in 5 ml of toluene and 3 ml of ethanol. 162 mg of bis(triphenylphosphine)palladium(II) chloride and 3.5 ml of aqueous sodium carbonate solution (2 M) were added and the mixture was heated in the microwave at 120°C. The mixture was acidified
- 20 to pH 5 with 10% strength citric acid solution and extracted three times with ethyl acetate, and the extract was washed with sodium chloride solution, filtered and concentrated. The residue was purified by preparative HPLC (column XBridge C18 5µm 100x30 mm). This gave 70 mg (15% of theory) of the title compound.

- ¹H-NMR (400 MHz, DMSO-d₆): δ = 3.89 (s, 3H), 7.79 - 7.94 (m, 3H), 8.09 (s, 1H), 8.39 (s, 1H),
- 25 (12.9 br. s, 1H).

Intermediate 19-3

6-(1-methyl-1H-pyrazol-5-yl)pyridine-2-carboxylic acid

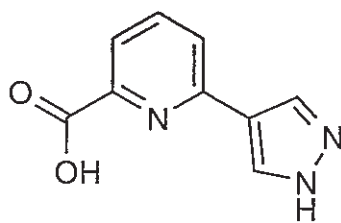


Analogously to the synthesis of Intermediate 19-2, 500 mg (2.31 mmol) of methyl 6-bromopyridine-2-carboxylate were reacted with 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the microwave at 120°C for 90 min. Purification by preparative HPLC according to Method P1 gave 34 mg (15% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ = 4.22 (s, 3H), 6.89 (d, 1H), 7.50 (d, 1H), 7.96 - 8.10 (m, 3H), 13.29 (br. s., 1H).

Intermediate 19-4

6-(1H-Pyrazol-4-yl)pyridine-2-carboxylic acid

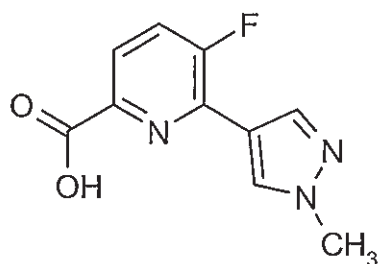


Analogously to the synthesis of Intermediate 19-2, 1 g (2.31 mmol) of 6-bromopyridine-2-carboxylic acid and 1.15 g of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole were reacted in the microwave at 120°C for 90 min. Ethyl acetate and water were added, the mixture was filtered and the organic phase was separated off and extracted twice with ethyl acetate. The ethyl acetate phases were discarded. 10% strength citric acid solution was added to the aqueous phase until a pH of 4 was reached, the mixture was extracted three times with ethyl acetate and the ethyl acetate phases were concentrated. This gave a residue which was purified by preparative HPLC (column XBridge C18). This gave 110 mg (12% of theory) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ = 7.77 - 7.98 (m, 3H), 8.31 (s, 2H), 13.03 (br. s., 2H).

Intermediate 19-5

5-Fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid



500 mg of methyl 6-bromo-5-fluoropyridine-2-carboxylate were reacted analogously with 533 mg (1.2 equiv.) of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the microwave at 120°C for 90 min. This gave 380 mg (80% of theory) of the title compound as a crude product.

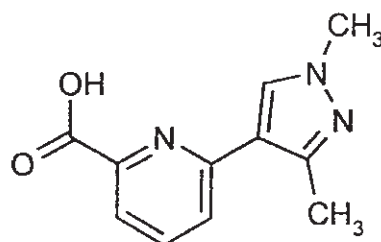
5 UPLC-MS (Method A1): $R_t = 0.72$ min

MS (ESIpos): $m/z = 222$ ($M+H$)⁺

Intermediate 19-6

6-(1,3-Dimethyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid

10

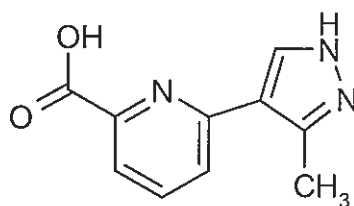


Analogously to the synthesis of Intermediate 19-2, 500 mg (2.31 mmol) of methyl 6-bromopyridine-2-carboxylate were reacted with 617 mg of 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the microwave at 120°C for 90 min. Purification by HPLC gave 66 mg (13% of theory) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): $\delta = 2.47$ (s), 3.80 (s, 3H), 7.71 - 7.81 (m, 2H), 7.88 - 7.94 (m, 1H), 8.27 (s, 1H), 12.95 (br. s., 1H).

Intermediate 19-7

20 6-(3-Methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid



Analogously to the synthesis of Intermediate 19-2, 216 mg of methyl 6-bromopyridine-2-carboxylate were reacted with 250 mg of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the microwave at 120°C for 90 min. This gave, after purification by HPLC, 68 mg (33% of theory) of the title compound mixed with methyl 6-(3-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylate.

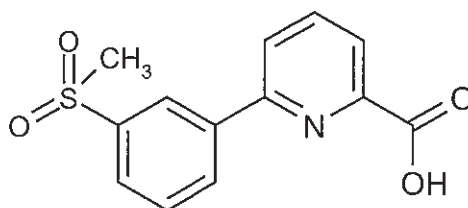
UPLC-MS (Method A1): $R_t = 0.50$ min

MS (ESIpos): $m/z = 204$ ($M+H$)⁺

30

Intermediate 19-8

6-[3-(Methylsulphonyl)phenyl]pyridine-2-carboxylic acid



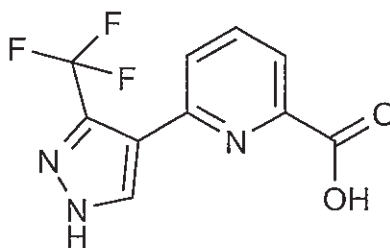
5 500 mg (2.31 mmol) of methyl 6-bromopyridine-2-carboxylate, 694 mg (1.5 equiv.) of [3-(methylsulphonyl)phenyl]boronic acid and were initially charged in 10 ml of DMSO. 267 mg of tetrakis(triphenylphosphine)palladium(0), 736 mg of sodium carbonate and 2 ml of water were added and the mixture was heated in the microwave at 110°C for 2 h. The mixture was diluted with water and acidified to pH 4 with 10% strength citric acid solution, ethyl acetate was added, the

10 mixture was filtered, the phases of the filtrate were separated, the aqueous phase was extracted with ethyl acetate and the extract was washed with sodium chloride solution and concentrated. 2.5 ml of methanol and 917 mg of lithium hydroxide monohydrate in 10 ml of water were added and the mixture was stirred at room temperature for 5 h. The mixture was diluted with water, acidified to pH 4 with 10% strength citric acid solution and extracted with ethyl acetate and the extracts were

15 washed with sodium chloride solution and concentrated. This gave 776 mg of the title compound as a crude product.

UPLC-MS (Method A1): $R_t = 0.75$ minMS (ESIpos): $m/z = 278$ ($M+H$)⁺**Intermediate 19-9**

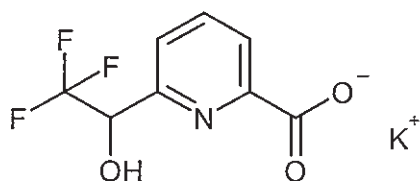
6-[3-(Trifluoromethyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid



Analogously to the preparation of Intermediate 19-8, 250 mg of methyl 6-bromopyridine-2-carboxylate were reacted with 394 mg of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazole. This gave 442 mg of the title compound as a crude product.

UPLC-MS (Method A1): $R_t = 0.82$ minMS (ESIpos): $m/z = 258$ ($M+H$)⁺**Intermediate 19-10**

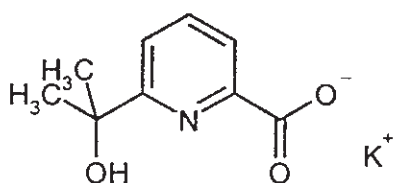
Potassium 6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxylate



165 mg of potassium hydroxide were added to 693 mg of methyl 6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxylate (Intermediate 17-2) in 5.0 ml of methanol, and the mixture
 5 was stirred at 50°C for 20 h. Concentration gave 787 mg of a solid which was processed further without any further purification.

Intermediate 19-11

Potassium 6-(2-hydroxypropan-3-yl)pyridine-2-carboxylate

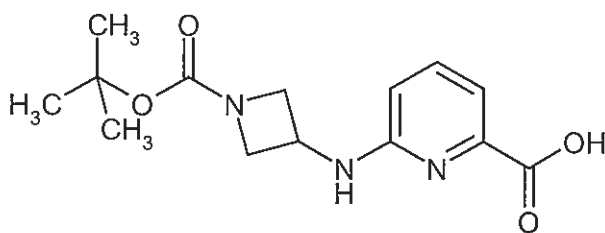


10

Analogously to Intermediate 19-10, 535 mg of methyl 6-(2-hydroxypropan-2-yl)pyridine-2-carboxylate (Intermediate 17-3) were reacted with 0.28 g of potassium hydroxide in 6.0 ml of methanol at 50°C. This gave, after concentration, 876 mg of the title compound as a crude product.

15 Intermediate 19-12

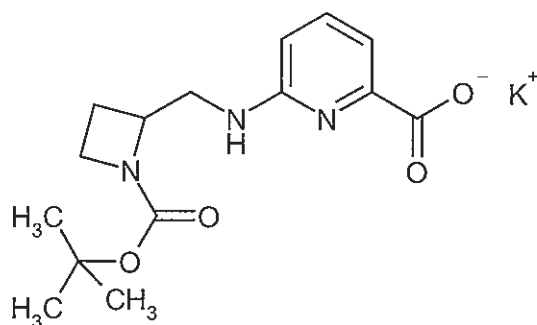
6-{{[1-(tert-butoxycarbonyl)azetidin-3-yl]amino}pyridine-2-carboxylic acid



0.31 g of lithium hydroxide monohydrate dissolved in 1.0 ml of water and 0.5 ml of ethanol was
 20 added to a mixture of 230 mg of methyl 6-{{[1-(tert-butoxycarbonyl)azetidin-3-yl]amino}pyridine-2-carboxylate (Intermediate 17-4) in 4.0 ml of THF, and the mixture was stirred at room temperature overnight. The mixture was diluted with water, acidified to pH 6 with citric acid solution and extracted with ethyl acetate, and the extract was washed with saturated sodium chloride solution, filtered through a hydrophobic filter and concentrated. This gave 202 mg of an
 25 oil which was used without further purification.

Intermediate 19-13

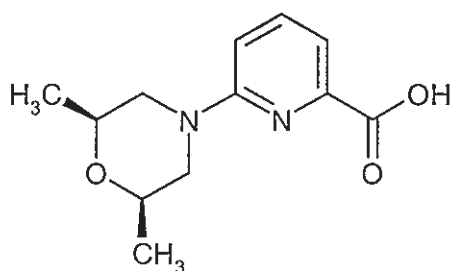
Potassium 6-({[1-(tert-butoxycarbonyl)azetidin-2-yl]methyl}amino)pyridine-2-carboxylate



24 mg of potassium hydroxide were added to 230 mg of methyl 6-({[1-(tert-butoxycarbonyl)azetidin-2-yl]methyl}amino)pyridine-2-carboxylate (Intermediate 17-5) in 3.0 ml of ethanol, and the mixture was stirred at 50°C overnight. The mixture was concentrated, giving
 5 265 mg of a crude product which was used further without purification.

Intermediate 19-14

6-[(2R,6S)-2,6-Dimethylmorpholin-4-yl]pyridine-2-carboxylic acid



10

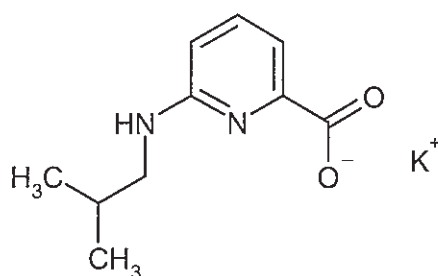
875 mg of methyl 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridine-2-carboxylate (Intermediate 17-6) were initially charged in 5 ml of THF and 1 ml of methanol, 698 mg of lithium hydroxide monohydrate in 2.5 ml of water were added and the mixture was stirred at room temperature
 15 overnight. Twice, toluene was added and the mixture was in each case concentrated again. Methanol was added, the mixture was stirred, the solid was filtered off and washed with diethyl ether and the filtrate was concentrated and purified by preparative HPLC (Method P1). This gave 224 mg of the title compound.

UPLC-MS (Method A1): Rt = 0.66 min (UV detector TIC), mass found 236.12.

20

Intermediate 19-15

Potassium 6-(isobutylamino)pyridine-2-carboxylate

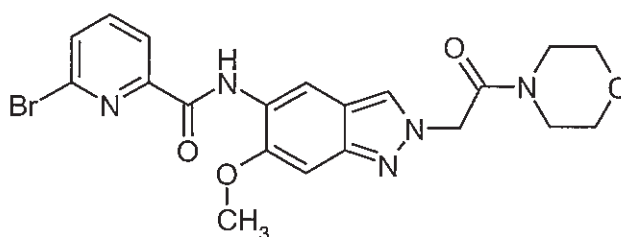


454 mg of lithium hydroxide were added to a solution of 790 mg of methyl 6-(isobutylamino)pyridine-2-carboxylate (Intermediate 17-7) in 3.4 ml of water, 32 ml of THF and 3.2 ml of methanol, and the mixture was stirred at room temperature overnight. This gave, after
 5 concentration, 1.15 g of a solid which was used without further purification.

UPLC-MS (Method A1): R_t = 0.58 min (UV detector TIC), mass found 194.00.

Intermediate 20-1

10 6-Bromo-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide



Analogously to Intermediate 8-6, 1.00 g (2.47 mmol) of (5-[[6-bromopyridin-2-yl]carbonyl]amino)-6-methoxy-2H-indazol-2-yl)acetic acid (Intermediate 9-21), 258 μ l (2.96 mmol) of morpholine, 378 mg (2.47 mmol) of 1-hydroxy-1H-benzotriazole hydrate, 946 mg (4.94 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1.03 ml (7.40 mmol) of triethylamine in 35 ml of tetrahydrofuran were stirred at 25°C for 24 h. The reaction mixture was concentrated, water was added and the resulting precipitate was filtered off with suction,
 15 washed with water and diethyl ether and concentrated under reduced pressure. This gave 586 mg (50% of theory) of the title compound.

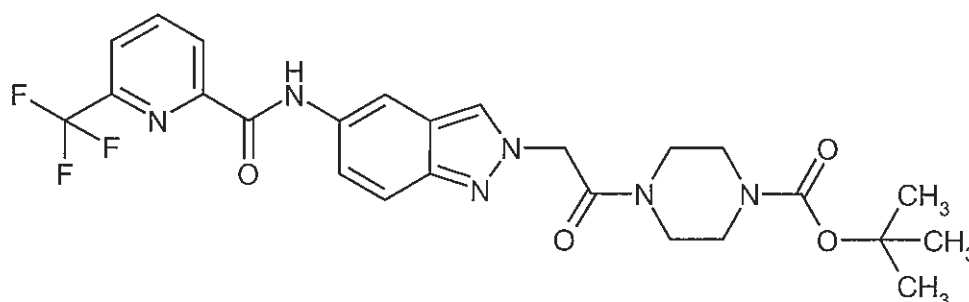
UPLC-MS (Method A1): R_t = 1.07 min

MS (ESIpos): m/z = 474 ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): δ = 3.47 (d, 2 H), 3.58 (br. s., 4 H), 3.64 (d, 2 H), 4.00 (s, 3 H),
 25 5.40 (s, 2 H), 7.93 - 7.99 (m, 1 H), 8.05 (t, 1 H), 8.14 - 8.29 (m, 2 H), 8.68 (s, 1 H), 10.31 (s, 1 H).

Intermediate 21-1

tert-Butyl 4-{[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxylate



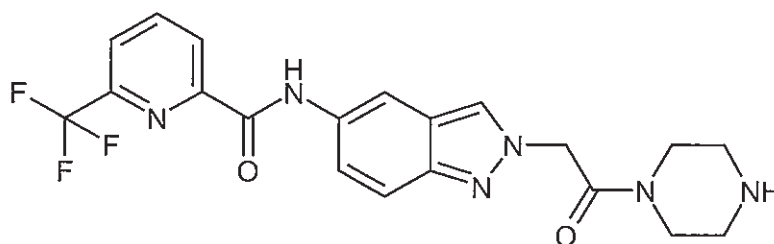
1.30 g (3.57 mmol) of [5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid (Intermediate 9-14) was in 50 ml of tetrahydrofuran and 5.4 ml of *N,N*-dimethylformamide, and the mixture was stirred at 25°C for 30 minutes. 997 mg (5.35 mmol) of tert-butyl piperazine-1-carboxylate, 546 mg (3.57 mmol) of 1-hydroxy-1H-benzotriazole hydrate and 1.37 g (7.14 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were then added, and the mixture was stirred at 25°C for a further 24 h. The reaction mixture was added to water. The resulting solid was filtered off with suction and washed twice with water. The solid was taken up in dichloromethane and the solution was dried over sodium sulphate, filtered and concentrated. The yellow solid was dried under reduced pressure. This gave 1.78 g (94% of theory) of tert-butyl 4-{[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxylate.

UPLC-MS (Method A1): $R_t = 1.21$ min

MS (ESIpos): $m/z = 533$ (M+H)⁺

Intermediate 22-1

N-{2-[2-Oxo-2-(piperazin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



1.93 ml (25.08 mmol) of trifluoroacetic acid were added to 1.78 g (3.34 mmol) of tert-butyl 4-{[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxylate (Intermediate 21-1) in 11 ml of dichloromethane, and the mixture was stirred at 25°C for 24 h. The mixture was then poured into saturated sodium bicarbonate solution. The resulting suspension was filtered and the filter cake was washed with 30 ml of water and 10 ml of diethyl ether. Drying under reduced pressure gave 1.41 g (97% of theory) of N-{2-[2-oxo-2-(piperazin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide as a crude product.

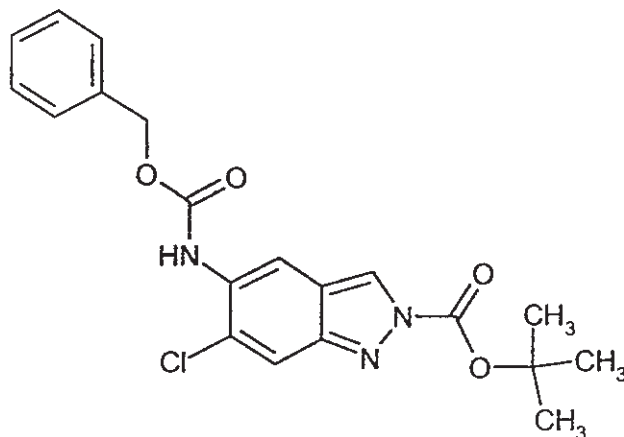
UPLC-MS (Method A1): $R_t = 0.80$ min

MS (ESIpos): $m/z = 433$ (M+H)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 2.66$ (br. s., 2 H), 2.73 (br. s., 2 H), 3.39 (br. s., 2 H), 3.47 (br. s., 2 H), 5.44 (s, 2 H), 7.47 - 7.68 (m, 2 H), 8.17 (d, $J=7.1$ Hz, 1 H), 8.30 (s, 2 H), 8.33 - 8.43 (m, 2 H), 10.37 (s, 1 H).

Intermediate 23-1

tert-Butyl 5-[[[(benzyloxy)carbonyl]amino]-6-chloro-2H-indazole-2-carboxylate



1.50 ml of N-ethyl-N-isopropylpropane-2-amine and 1.11 ml of benzyl carbonochloridate were added to 2.09 g of tert-butyl 5-amino-6-chloro-2H-indazole-2-carboxylate (Intermediate 12-2) in 15 ml of THF, and the mixture was stirred at room temperature overnight. Another 1.50 ml of N-ethyl-N-isopropylpropane-2-amine and 1.11 ml of benzyl carbonochloridate were added, and the mixture was stirred at room temperature for 3 days. Another 1.50 ml of N-ethyl-N-isopropylpropane-2-amine and 1.11 ml of benzyl carbonochloridate were added, and the mixture was stirred at room temperature overnight. Water was added, the mixture was extracted with ethyl acetate and the extract was washed with sodium chloride solution and concentrated. This gave 4.61 mg of a crude product which was processed further without further purification.

UPLC-MS (Method A1): $R_t = 1.40$ min (UV-TIC), mass found 401.00.

The chemical names of the examples were generated using the ACD / LABS (Batch Version 12.01.) software.

5 Examples

General Procedure 1a

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 5.0 equivalents of triethylamine and 1.5 equivalents of the carboxylic acid in question were stirred in tetrahydrofuran at 25°C for 24 h. Water and ethyl acetate were added to the reaction mixture. The resulting precipitate was filtered off, washed with water and diethyl ether and dried.

15 General Procedure 1b

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 3.0 equivalents of triethylamine and 1.5 equivalents of the carboxylic acid in question were stirred in *N,N*-dimethylformamide at 25°C for 24 h, giving a suspension. The resulting precipitate was filtered off, washed twice with *N,N*-dimethylformamide and diethyl ether and dried.

General Procedure 1c

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 5.0 equivalents of triethylamine and 1.3 equivalents of the carboxylic acid in question were stirred in tetrahydrofuran at 25°C for 24 h. Water was added and the reaction mixture was extracted repeatedly with ethyl acetate. The combined organic phases were concentrated and the residue was purified by preparative HPLC according to Method P1.

30 General Procedure 1d

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 3.0 equivalents of triethylamine and 1.2 equivalents of the carboxylic acid in question were stirred in 1 ml of *N,N*-dimethylformamide at 25°C for 24 h. The reaction mixture was diluted with a further 1.5 ml of *N,N*-dimethylformamide and purified by preparative HPLC according to Method P1.

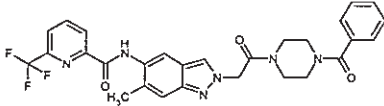
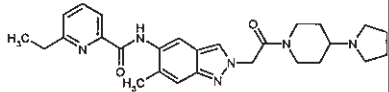
General Procedure 1e

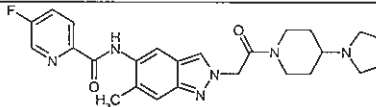
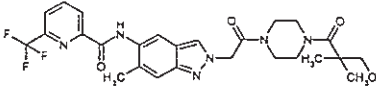
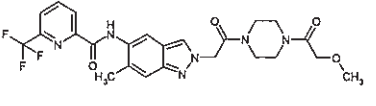
1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 4.0 equivalents of triethylamine and 1.2 equivalents of the carboxylic acid in question were stirred in 1
5 ml of tetrahydrofuran at 25°C for 24 h. The reaction mixture was poured into 25 ml of water. The precipitate formed was filtered off, washed twice with diethyl ether and dried in a drying cabinet.

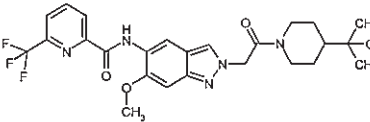
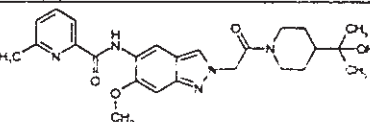
Table 1: Examples 1-18

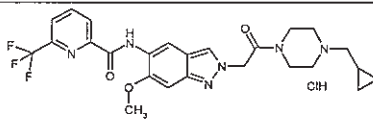
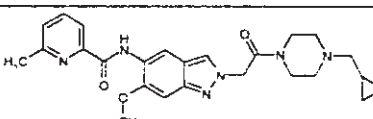
The exemplary compounds were prepared by the general experimental procedures 1a - 1e from the appropriate intermediates and carboxylic acids.

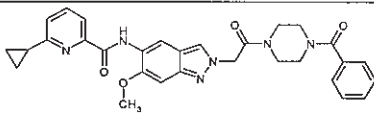
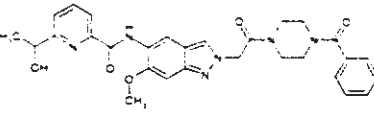
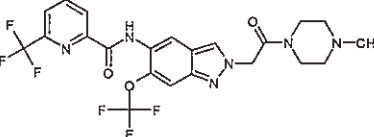
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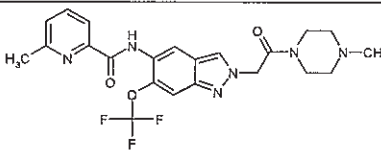
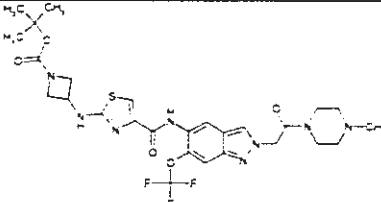
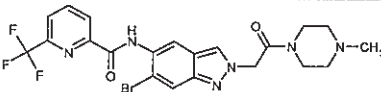
Ex. No.	Structure/Name	Prepared from	* see key	¹ H-NMR / LC-MS
1	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methyl-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 6-1 and 6-(trifluoromethyl)pyridine-2-carboxylic acid	1a [a] (68%)	<p>(400 MHz, DMSO-d₆): δ = 2.38 (s, 3H), 3.32 - 3.77 (8H), 5.45 (br. s., 2H), 7.39 - 7.49 (m, 6H), 8.15 - 8.21 (m, 2H), 8.24 (s, 1H), 8.33 - 8.43 (m, 2H), 10.11 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.16 min</p> <p>MS (ESIpos): m/z = 551 (M+H)⁺</p>
2	 <p>6-ethyl-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide</p>	Intermediate 6-2 and 6-ethylpyridine-2-carboxylic acid	1a (91%)	<p>(300 MHz, DMSO-d₆): δ = 1.21 - 1.49 (m, 5H), 1.67 (br. s., 4H), 1.84 (t, 2H), 2.14 - 2.31 (m, 1H), 2.79 - 2.95 (m, 3H), 3.17 (t, 1H), 3.80 - 3.93 (m, 1H), 4.03 - 4.16 (m, 1H), 5.34 - 5.49 (m, 2H), 7.49 (s, 1H), 7.53 - 7.59 (m, 1H), 7.94 - 8.01 (m, 2H), 8.24 (s, 1H), 8.39 (s, 1H), 10.37 (s, 1H).</p> <p>UPLC-MS (Method A2): Rt = 1.18 min</p> <p>MS (ESIpos): m/z = 475 (M+H)⁺</p>

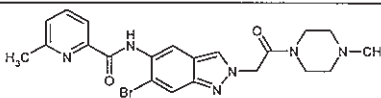
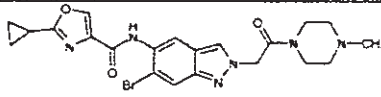
3	 <p>5-fluoro-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide</p>	Intermediate 6-2 and 5-fluoropyridine-2-carboxylic acid	1b (36%)	<p>(400 MHz, DMSO-d₆): δ = 1.18 - 1.37 (m, 1 H), 1.37 - 1.51 (m, 1 H), 1.68 (br. s., 4 H), 1.76 - 1.94 (m, 2 H), 2.14 - 2.30 (m, 1 H), 2.39 (s, 3 H), 2.78 - 2.94 (m, 1 H), 3.18 (t, 1 H), 3.82 - 3.95 (m, 1 H), 4.03 - 4.16 (m, 1 H), 5.44 (d, 1 H), 5.39 (d, 1 H), 7.44 - 7.50 (m, 1 H), 7.99 (td, 1 H), 8.12 (s, 1 H), 8.20 - 8.29 (m, 2 H), 8.75 (d, 1 H), 10.15 (s, 1 H). LC-MS (Method A3): R_t = 0.79 min MS (ESIpos): m/z = 465 (M+H)⁺</p>
4	 <p>N-(2-{2-[4-(3-hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 6-3 and 6-(trifluoromethyl)pyridine-2-carboxylic acid	1a (53%)	<p>(300 MHz, DMSO-d₆): δ = 1.16 (s, 6H), 2.40 (s, 3H), 3.39 - 3.52 (m, 4H), 3.52 - 3.70 (m, 6H), 4.62 (t, 1H), 5.47 (s, 2H), 7.49 (s, 1H), 8.17 - 8.29 (m, 3H), 8.34 - 8.45 (m, 2H), 10.15 (s, 1H). UPLC-MS (Method A1): R_t = 1.06 min MS (ESIpos): m/z = 547 (M+H)⁺</p>
5	 <p>N-(2-{2-[4-(methoxyacetyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 6-4 and 6-(trifluoromethyl)pyridine-2-carboxylic acid	1a (12%)	<p>(400 MHz, DMSO-d₆): δ = 2.40 (s, 3H), 3.36 - 3.64 (m, 8H), 4.12 (br. s., 2H), 5.47 (s, 2H), 7.49 (s, 1H), 8.18 - 8.28 (m, 3H), 8.35 - 8.45 (m, 2H), 10.13 (s, 1H). UPLC-MS (Method A1): R_t = 1.02 min MS (ESIpos): m/z = 519 (M+H)⁺</p>

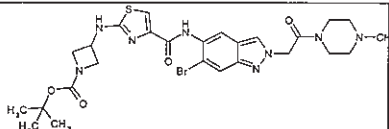
6	 <p>N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 6-5 and 6- (trifluoromethyl)pyridine-2-carboxylic acid	1c (51%)	<p>(300 MHz, DMSO-d₆): δ = 0.94 - 1.29 (m, 8H, contains singlet at 1.04 ppm), 1.35 - 1.51 (m, 1H), 1.74 (t, 2H), 2.53 (s, 1H), 2.98 (t, 1H), 3.91 - 4.10 (m, 4H), 4.17 (s, 1H), 4.41 (d, 1H), 5.28 - 5.44 (m, 2H), 7.10 (s, 1H), 8.18 - 8.27 (m, 2H), 8.35 - 8.50 (m, 2H), 8.69 (s, 1H), 10.50 (s, 1H). UPLC-MS (Method A1): Rt = 1.13 min MS (ESIpos): m/z = 520 (M+H)⁺</p>
7	 <p>N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide</p>	Intermediate 6-5 and 6- methylpyridine-2-carboxylic acid	1c (41%)	<p>(300 MHz, DMSO-d₆): δ = 0.97 - 1.29 (m, 8H, contains singlet at 1.04 ppm), 1.36 - 1.50 (m, 1H), 1.74 (t, 2H), 2.53 (s, 1H), 2.61 (s, 3H), 2.98 (t, 1H), 3.95 - 4.08 (m, 4H), 4.17 (s, 1H), 4.41 (d, 1H), 5.28 - 5.42 (m, 2H), 7.08 (s, 1H), 7.51 - 7.59 (m, 1H), 7.92 - 8.02 (m, 2H), 8.20 (s, 1H), 8.70 (s, 1H), 10.70 (s, 1H). UPLC-MS (Method A1): Rt = 1.06 min MS (ESIpos): m/z = 466 (M+H)⁺</p>

8	 <p>N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide hydrochloride</p>	Intermediate 6-6 and 6-methoxypyridine-2-carboxylic acid	1a (17%) [b]	<p>(400 MHz, DMSO-d₆): δ = 0.41 (br. s., 2H), 0.66 (d, 2H), 1.12 (br. s., 1H), 2.89 - 3.26 (m, 5H), 3.60 (br. s., 3H), 4.00 (s, 3H), 4.21 (d, 1H), 4.42 (d, 1H), 5.48 (d, 2H), 7.11 (s, 1H), 8.19 - 8.25 (m, 2H), 8.36 - 8.49 (m, 2H), 8.72 (s, 1H), 10.5 (s, 1H), 10.7 (s).</p> <p>UPLC-MS (Method A1): Rt = 0.94 min</p> <p>MS (ESIpos): m/z = 517 (M+H)⁺</p>
9	 <p>N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide</p>	Intermediate 6-6 and 6-methylpyridine-2-carboxylic acid	1c (26%) [c]	<p>(300 MHz, DMSO-d₆, selected signals, sample contained a proportion of formic acid): δ = 0.27 (br. s., 2H), 0.59 (br. s., 2H), 0.97 (br. s., 1H), 2.62 (s), 3.05 (br. s.), 3.53 (br. s.), 4.00 (s, 3H), 5.43 (br. s., 2H), 7.08 (s, 1H), 7.55 (dd, 1H), 7.93 - 8.01 (m, 2H), 8.19 (s, 1H), 8.72 (s, 1H), 10.71 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.85 min</p> <p>MS (ESIpos): m/z = 463 (M+H)⁺</p>

10	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-cyclopropylpyridine-2-carboxamide</p>	Intermediate 6-7 and 6-cyclopropylpyridine-2-carboxylic acid	1a (50%) [d]	<p>(300 MHz, DMSO-d₆): δ = 1.04 - 1.15 (m, 4H), 2.21 - 2.33 (m, 1H), 3.39 - 3.87 (8H), 4.00 (s, 3H), 5.41 (br. s., 2H), 7.09 (s, 1H), 7.41 - 7.52 (m, 5H), 7.58 - 7.65 (m, 1H), 7.87 - 7.96 (m, 2H), 8.20 (s, 1H), 8.66 (s, 1H), 10.80 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.18 min</p> <p>MS (ESIpos): m/z = 539 (M+H)⁺</p>
11	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-(1-hydroxyethyl)pyridine-2-carboxamide</p>	Intermediate 6-7 and Intermediate 19-1	1c (49%)	<p>(300 MHz, DMSO-d₆): δ = 1.51 (d, 3H), 3.38 - 3.91 (8H), 3.99 (s, 3H), 4.81 - 4.90 (m, 1H), 5.41 (br. s., 2H), 5.60 (d, 1H), 7.09 (s, 1H), 7.35 - 7.56 (m, 5H), 7.76 - 7.82 (m, 1H), 8.01 - 8.11 (m, 2H), 8.21 (s, 1H), 8.68 (s, 1H), 10.78 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.93 min</p> <p>MS (ESIpos): m/z = 534 (M+H)⁺</p>
12	 <p>N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 6-8 and 6-(trifluoromethyl)pyridine-2-carboxylic acid	1d (47%)	<p>(400 MHz, DMSO-d₆) δ = 2.22 (s, 3 H) 2.27 - 2.36 (m, 2 H) 2.37 - 2.44 (m, 2 H) 3.44 - 3.52 (m, 2 H) 3.52 - 3.60 (m, 2 H) 5.52 (s, 2 H) 7.75 (s, 1 H) 8.23 (dd, 1 H) 8.38 - 8.50 (m, 3 H) 8.71 (s, 1 H) 10.40 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.96 min</p> <p>MS (ESIpos): m/z = 531 (M+H)⁺</p>

13	 <p>6-methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}pyridine-2-carboxamide</p>	Intermediate 6-8 and 6-methylpyridine-2-carboxylic acid	1d (49%)	<p>(300 MHz, DMSO-d₆) δ = 2.21 (s, 3 H), 2.25 - 2.34 (m, 2 H), 2.39 (br. s., 2 H), 2.61 (s, 3 H), 3.44 - 3.51 (m, 2 H), 3.51 - 3.61 (m, 2 H), 5.52 (s, 2 H), 7.59 (dd, 1 H), 7.76 (s, 1 H), 7.96 - 8.04 (m, 2 H), 8.45 (s, 1 H), 8.72 (s, 1 H), 10.65 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.92 min</p> <p>MS (ESIpos): m/z = 477 (M+H)⁺</p>
14	 <p>tert-butyl 3-{[4-({2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}carbamoyl)-1,3-thiazol-2-yl]amino}azetidine-1-carboxylate</p>	Intermediate 6-8 and 2-yl]amino}-1,3-thiazole-4-carboxylic acid**	1d (39%)	<p>(300 MHz, DMSO-d₆) δ = 1.39 (s, 9 H), 2.21 (s, 3 H), 2.26 - 2.34 (m, 2 H), 2.38 (br. s., 2 H), 3.46 (br. s., 2 H), 3.54 (br. s., 2 H), 3.77 (dd, 2 H), 4.20 (t, 2 H), 4.46 (d, 1 H), 5.50 (s, 2 H), 7.56 (s, 1 H), 7.73 (s, 1 H), 8.42 (s, 1 H), 8.57 (d, 1 H), 8.62 (s, 1 H), 9.54 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.63 min</p> <p>MS (ESIpos): m/z = 639 (M+H)⁺</p>
15	 <p>N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 6-9 and 6-(trifluoromethyl)pyridine-2-carboxylic acid	1e (76%)	<p>(300 MHz, DMSO-d₆) δ = 2.21 (s, 3 H), 2.29 (br. s., 2 H), 2.38 (br. s., 2 H), 3.47 (br. s., 2 H), 3.54 (br. s., 2 H), 5.50 (s, 2 H), 8.09 (s, 1 H), 8.24 (d, 1 H), 8.35 - 8.50 (m, 3 H), 8.64 (s, 1 H), 10.54 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 0.93 min</p> <p>MS (ESIpos): m/z = 525 (M(79Br)+H)⁺</p>

16	 <p>N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide</p>	Intermediate 6-9 and 6-methylpyridine-2-carboxylic acid	1e (93%)	<p>(300 MHz, DMSO-d₆) δ = 2.21 (s, 3 H), 2.25 - 2.35 (m, 2 H), 2.38 (br. s., 2 H), 2.64 (s, 3 H), 3.47 (br. s., 2 H), 3.54 (br. s., 2 H), 5.49 (s, 2 H), 7.58 (dd, 1 H), 7.97 - 8.04 (m, 2 H), 8.08 (s, 1 H), 8.39 (s, 1 H), 8.71 (s, 1 H), 10.77 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 0.88 min</p> <p>MS (ESIpos): m/z = 471 (M(79Br)+H)+</p>
17	 <p>N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2-cyclopropyl-1,3-oxazole-4-carboxamide</p>	Intermediate 6-9 and 2-cyclopropyl-1,3-oxazole-4-carboxylic acid	1e (55%)	<p>(300 MHz, DMSO-d₆) δ = 1.01 - 1.07 (m, 2 H), 1.07 - 1.16 (m, 2 H), 2.17 - 2.26 (m, 4 H), 2.27 - 2.34 (m, 2 H), 2.37 (br. s., 2 H), 3.46 (br. s., 2 H), 3.54 (br. s., 2 H), 5.49 (s, 2 H), 8.03 (s, 1 H), 8.29 (s, 1 H), 8.37 (s, 1 H), 8.63 (s, 1 H), 9.61 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 0.83 min</p> <p>MS (ESIpos): m/z = 487 (M(79Br)+H)+</p>

18	 <p>tert-butyl 3-({[4-({6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamoyl)-1,3-thiazol-2-yl]amino}azetidine-1-carboxylate</p>	Intermediate 6-9 and 2- {{[1-(tert-butoxycarbonyl)azetidin-3-yl]amino}-1,3-thiazole-4-carboxylic acid**	1e (41%)	<p>(300 MHz, DMSO-d₆) δ = 1.39 (s, 9 H), 2.21 (s, 3 H), 2.25 - 2.33 (m, 2 H), 2.37 (br. s., 2 H), 3.46 (br. s., 2 H), 3.54 (br. s., 2 H), 3.79 (dd, J=8.6, 5.4 Hz, 2 H), 4.23 (t, 2 H), 4.50 (d, 1 H), 5.47 (s, 2 H), 7.54 (s, 1 H), 8.05 (s, 1 H), 8.31 - 8.41 (m, 1 H), 8.54 (d, 1 H), 8.64 (s, 1 H), 9.82 (s, 1 H).</p> <p>UPLC-MS (Method A2): Rt = 1.09 min</p> <p>MS (ESIpos): m/z = 633 (M(79Br)+H)+</p>
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* Prepared according to the stated procedure, the yield in % is indicated in brackets

[a]: The reaction was carried out in a mixture of tetrahydrofuran/*N,N*-dimethylformamide (5:1). 3 equivalents of triethylamine were used.

5 [b]: 1.3 equivalents of the pyridinecarboxylic acid were used.

[c]: 1.5 equivalents of the pyridinecarboxylic acid were used. The product was in the aqueous phase.

[d]: Preparative HPLC was carried out according to Method P1.

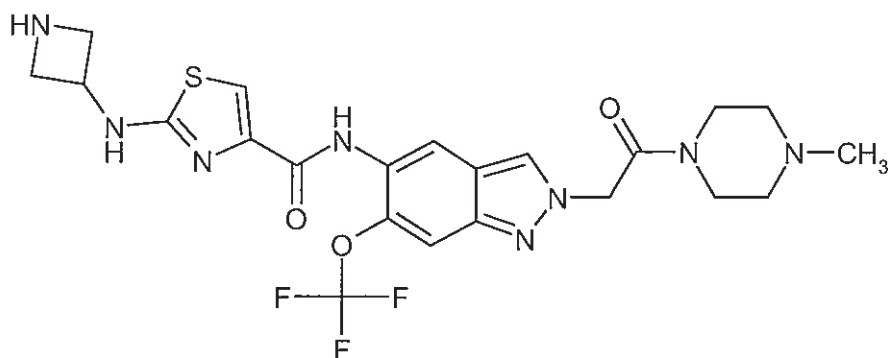
10 [e]: The product precipitated directly from the reaction mixture, was filtered off, washed repeatedly with water and dried in a drying cabinet.

** 2-{{[1-(tert-Butoxycarbonyl)azetidin-3-yl]amino}-1,3-thiazole-4-carboxylic acid was prepared from 3-bromo-2-oxopropanoic acid and tert-butyl 3-aminoazetidine-1-carboxylate analogously to *Bioorganic and Medicinal Chemistry Letters*, 1996, 6, 12, 1409 – 1414 and *Chemical and Pharmaceutical Bulletin*, 2005, 53, 4, 437 – 440.

15

Example 19

2-(Azetidin-3-ylamino)-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide



21 mg (0.03 mmol) of tert-butyl 3-[[4-({2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl} carbamoyl)-1,3-thiazol-2-yl]amino]azetidine-1-carboxylate (Example 18) were dissolved in 1 ml of dichloromethane, and 25 μ l (0.03 mmol) of trifluoroacetic acid were added. The reaction mixture was stirred at 25°C for 24 h. The mixture was then diluted with more dichloromethane and washed with saturated sodium bicarbonate solution and with saturated sodium chloride solution. The mixture was then filtered through a hydrophobic filter and concentrated. The residue was dried under reduced pressure. This gave 7 mg (31% of theory) of the title compound.

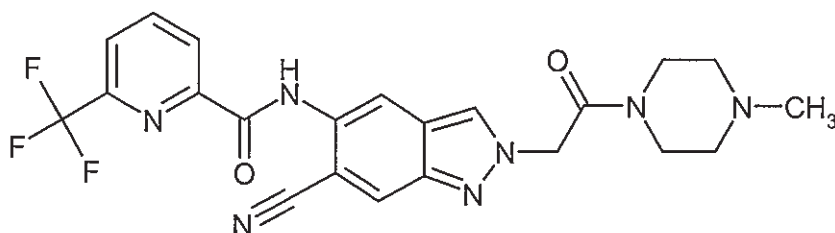
UPLC-MS (Method A2): R_t = 0.86 min

MS (ESIpos): m/z = 539 ($M+H$)⁺

¹H NMR (400 MHz, DMSO- d_6): δ = 2.21 (s, 3 H), 2.29 (br. s., 2 H), 2.38 (br. s., 2 H), 3.42 - 3.49 (m, 4 H), 3.54 (br. s., 2 H), 3.69 - 3.73 (m, 1 H), 5.50 (s, 2 H), 7.49 (s, 1 H), 7.72 (s, 1 H), 8.42 (s, 1 H), 8.64 (s, 1 H), 9.58 (s, 1 H).

Example 20

N-{6-Cyano-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



50 mg (0.10 mmol) of N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide (Example 15), 5 mg (0.005 mmol) of tetrakis(triphenylphosphine)palladium(0) and 12 mg (0.10 mmol) of zinc cyanide were initially charged in a microwave vessel and suspended in 1 ml of *N,N*-dimethylformamide. The reaction mixture was stirred in the microwave at 150°C for 15 minutes. Since the reaction was still incomplete, another 5 mg (0.005 mmol) of tetrakis(triphenylphosphine)palladium(0) and 5.5 mg (0.05 mmol) of zinc cyanide were added and the mixture was stirred in the microwave at 150°C for a further 30 minutes. The reaction mixture was diluted with ethyl acetate and washed with water

and saturated sodium chloride solution. The solution was then filtered through a hydrophobic filter and concentrated. The crude product was dissolved in 2.5 ml of *N,N*-dimethylformamide and purified by preparative HPLC according to Method P1. The product fraction was lyophilized. This gave 25 mg (56% of theory) of the title compound.

5 LC-MS (Method A3): $R_t = 1.07$ min

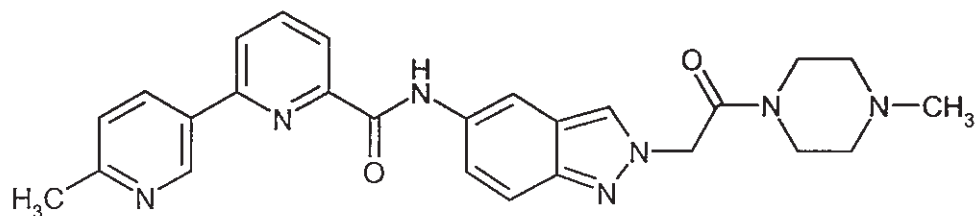
MS (ESIpos): $m/z = 472$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-*d*₆): $\delta = 2.22$ (s, 3 H), 2.27 - 2.33 (m, 2 H), 2.36 - 2.42 (m, 2 H), 3.44 - 3.50 (m, 2 H), 3.52 - 3.58 (m, 2 H), 5.59 (s, 2 H), 8.21 - 8.26 (m, 2 H), 8.37 - 8.43 (m, 2 H), 8.43 - 8.47 (m, 1 H), 8.51 (d, 1 H), 10.66 (s, 1 H).

10

Example 21

6'-Methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide



15 75 mg (0.16 mmol) of 6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide (Example 231) were dissolved in a degassed mixture of 1.73 ml of dioxane and 0.25 ml of water, and 45 mg (0.33 mmol) of (6-methylpyridin-3-yl)boronic acid, 13 mg (0.02 mmol) of 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride and 52 mg (0.49 mmol) of sodium carbonate were added. The reaction mixture was stirred in the microwave at
20 105°C for 90 minutes. The reaction mixture was then filtered and saturated ammonium chloride solution and dichloromethane were added to the filtrate. The phases were separated and the organic phase was washed with saturated sodium chloride solution, filtered through a hydrophobic filter and concentrated. The crude product was dissolved in 2.5 ml of *N,N*-dimethylformamide and purified by preparative HPLC according to Method P1. The product fraction was lyophilized. This
25 gave 40 mg (52% of theory) of the title compound.

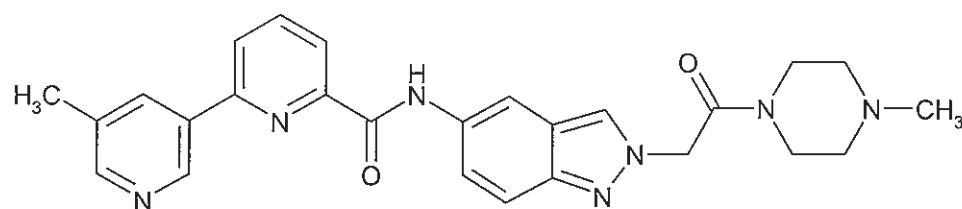
LC-MS (Method A3): $R_t = 0.46$ min

MS (ESIpos): $m/z = 470$ ($M+H$)⁺

¹H NMR (300 MHz, DMSO-*d*₆): $\delta = 2.22$ (s, 3 H), 2.31 (br. s., 2 H), 2.39 (br. s., 2 H), 2.57 (s, 3 H), 3.48 (br. s., 2 H), 3.55 (d, 2 H), 5.47 (s, 2 H), 7.44 (d, 1 H), 7.62 (s, 2 H), 8.08 - 8.20 (m, 2 H),
30 8.26 - 8.32 (m, 2 H), 8.34 (s, 1 H), 8.68 (dd, 1 H), 9.43 (d, 1 H), 10.54 (s, 1 H).

Example 22

5'-Methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide



Analogously to Example 21, 75 mg (0.16 mmol) of 6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide were stirred with 45 mg (0.33 mmol) of (5-methylpyridin-3-yl)boronic acid, 13 mg (0.02 mmol) of 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride and 52 mg (0.49 mmol) of sodium carbonate in a degassed mixture of 1.73 ml of dioxane and 0.25 ml of water in the microwave at 105°C for 90 minutes. Work-up and preparative HPLC according to Method P1 gave 41 mg (53% of theory) of the title compound.

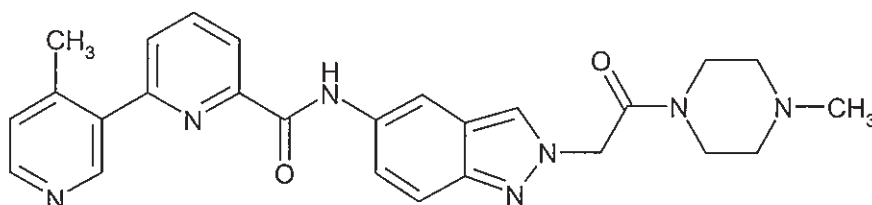
LC-MS (Method A3): $R_t = 0.51$ min

MS (ESIpos): $m/z = 470$ ($M+H$)⁺

¹H NMR (300 MHz, DMSO-d₆): $\delta = 2.23$ (s, 3 H), 2.32 (br. s., 2 H), 2.41 (br. s., 2 H), 2.45 (s, 3 H), 3.48 (br. s., 2 H), 3.56 (br. s., 2 H), 5.47 (s, 2 H), 7.62 (s, 2 H), 8.11 - 8.23 (m, 2 H), 8.27 - 8.37 (m, 3 H), 8.55 (s, 1 H), 8.60 (s, 1 H), 9.38 (d, 1 H), 10.55 (s, 1 H).

Example 23

4'-Methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide



Analogously to Example 21, 75 mg (0.16 mmol) of 6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide were stirred with 45 mg (0.33 mmol) of (4-methylpyridin-3-yl)boronic acid, 13 mg (0.02 mmol) of 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride and 52 mg (0.49 mmol) of sodium carbonate in a degassed mixture of 1.73 ml of dioxane and 0.25 ml of water in the microwave at 105°C for 90 minutes. Work-up and preparative HPLC according to Method P1 gave 16 mg (21% of theory) of the title compound.

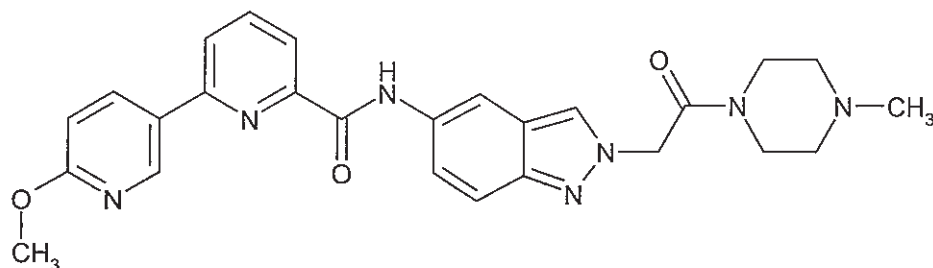
LC-MS (Method A3): $R_t = 0.45$ min

MS (ESIpos): $m/z = 470$ ($M+H$)⁺

¹H NMR (300 MHz, DMSO-d₆): $\delta = 2.21$ (s, 3 H), 2.30 (br. s., 2 H), 2.38 (br. s., 2 H), 3.47 (br. s., 2 H), 3.54 (d, 2 H), 5.45 (s, 2 H), 7.42 (d, 1 H), 7.57 (d, 2 H), 7.91 (t, 1 H), 8.19 (d, 2 H), 8.28 (s, 1 H), 8.34 (s, 1 H), 8.54 (d, 1 H), 8.78 (s, 1 H), 10.41 (s, 1 H).

Example 24

6'-Methoxy-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide



Analogously to Example 21, 50 mg (0.11 mmol) of 6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide were stirred with 33 mg (0.22 mmol) of (6-methoxypyridin-3-yl)boronic acid, 9 mg (0.01 mmol) of 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride and 35 mg (0.33 mmol) of sodium carbonate in a degassed mixture of 1.15 ml of dioxane and 0.17 ml of water in the microwave at 105°C for 90 minutes. Work-up and preparative HPLC according to Method P1 gave 28 mg (52% of theory) of the title compound.

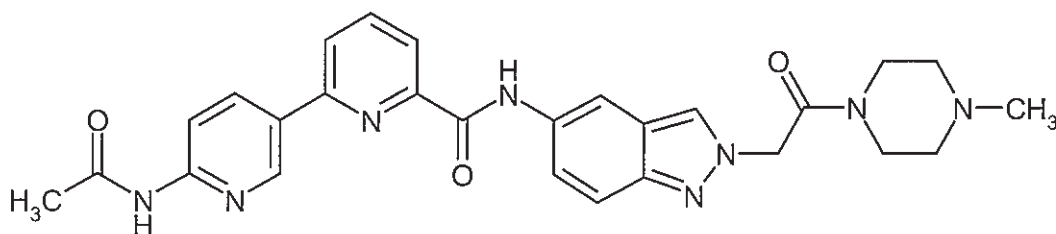
LC-MS (Method A3): $R_t = 0.74$ min

MS (ESIpos): $m/z = 486$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = 2.21$ (s, 3 H), 2.30 (t, 2 H), 2.38 (t, 2 H), 3.45 - 3.52 (m, 2 H), 3.52 - 3.60 (m, 2 H), 3.96 (s, 3 H), 5.46 (s, 2 H), 6.96 - 7.01 (m, 1 H), 7.58 - 7.66 (m, 2 H), 8.07 - 8.11 (m, 1 H), 8.11 - 8.16 (m, 1 H), 8.24 (dd, 1 H), 8.30 (s, 1 H), 8.32 - 8.34 (m, 1 H), 8.74 (dd, 1 H), 9.22 (d, 1 H), 10.52 (s, 1 H).

Example 25

6'-Acetamido-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide



Analogously to Example 21, 50 mg (0.11 mmol) of 6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide were stirred with 57 mg (0.22 mmol) of N-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl]acetamide, 9 mg (0.01 mmol) of 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride and 35 mg (0.33 mmol) of sodium carbonate in a degassed mixture of 1.15 ml of dioxane and 0.17 ml of water in the microwave at

105°C for 90 minutes. Work-up and preparative HPLC according to Method P1 gave 21 mg (37% of theory) of the title compound.

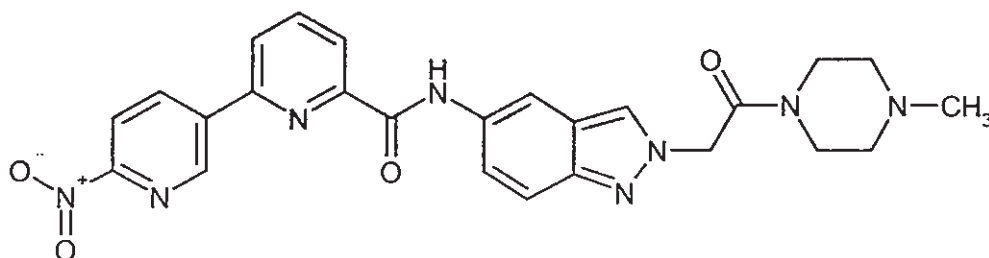
LC-MS (Method A3): $R_t = 0.59$ min

MS (ESIpos): $m/z = 513$ ($M+H$)⁺

- 5 ¹H NMR (400 MHz, DMSO-d₆): $\delta = 2.15$ (s, 3 H), 2.21 (s, 3 H), 2.27 - 2.34 (m, 2 H), 2.35 - 2.41 (m, 2 H), 3.44 - 3.51 (m, 2 H), 3.52 - 3.58 (m, 2 H), 5.46 (s, 2 H), 7.58 - 7.68 (m, 2 H), 8.09 - 8.12 (m, 1 H), 8.12 - 8.17 (m, 1 H), 8.23 - 8.29 (m, 2 H), 8.30 (s, 1 H), 8.34 (s, 1 H), 8.79 (dd, 1 H), 9.32 (dd, 1 H), 10.53 (s, 1 H), 10.69 (s, 1 H).

10 **Example 26**

N-{2-[2-(4-Methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6'-nitro-2,3'-bipyridine-6-carboxamide



- Analogously to Example 21, 75 mg (0.16 mmol) of 6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide were stirred with 82 mg (0.33 mmol) of 2-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 13 mg (0.02 mmol) of 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride and 52 mg (0.49 mmol) of sodium carbonate in a degassed mixture of 1.73 ml of dioxane and 0.25 ml of water in the microwave at 105°C for 90 minutes. Work-up and preparative HPLC according to Method P1 gave 26 mg (32% of theory) of the title compound.

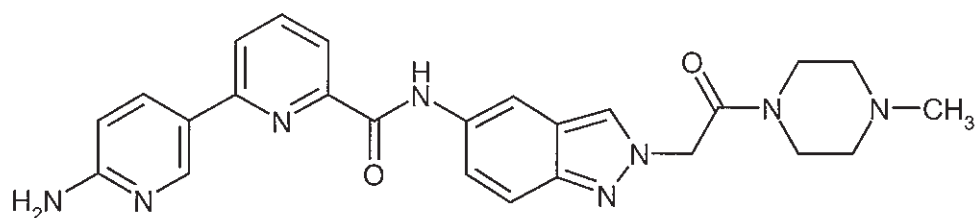
UPLC-MS (Method A1): $R_t = 0.78$ min

MS (ESIpos): $m/z = 501$ ($M+H$)⁺

- ¹H NMR (300 MHz, DMSO-d₆): $\delta = 2.22$ (s, 3 H), 2.31 (br. s., 2 H), 2.39 (br. s., 2 H), 3.48 (br. s., 2 H), 3.56 (br. s., 2 H), 5.47 (s, 2 H), 7.63 (s, 2 H), 8.22 - 8.38 (m, 4 H), 8.45 - 8.55 (m, 2 H), 9.22 (dd, 1 H), 9.72 (d, 1 H), 10.63 (s, 1 H).

Example 27

6'-Amino-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide



20 mg (0.04 mmol) of N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6'-nitro-2,3'-bipyridine-6-carboxamide were dissolved in 2.5 ml of methanol, 4 mg (0.004 mmol, 10%) of palladium on carbon were added and the mixture was hydrogenated under a hydrogen atmosphere of 1 bar for 4 h. The reaction mixture was filtered off through Celite, the filter cake was washed repeatedly with methanol and the filtrate was concentrated and dried under reduced pressure. This gave 8 mg (43% of theory) of the title compound.

UPLC-MS (Method A1): Rt = 0.81 min

MS (ESIpos): m/z = 471 (M+H)⁺

¹H NMR (400 MHz, METHANOL-d₄): δ = 2.34 (s, 3 H), 2.43 - 2.49 (m, 2 H), 2.53 (br. s., 2 H), 3.66 (br. s., 4 H), 5.46 (s, 2 H), 6.73 (d, 1 H), 7.51 - 7.58 (m, 1 H), 7.60 - 7.67 (m, 1 H), 7.94 - 8.04 (m, 2 H), 8.07 (d, 1 H), 8.21 (s, 1 H), 8.34 (br. s., 2 H), 8.55 (s, 1 H), 8.77 (s, 1 H).

General Procedure 2a

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate and 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were stirred in 3 ml of tetrahydrofuran and 0.33 ml of dimethylformamide at 25°C for 30 min. 1.5 equivalents of the amine were then added and the mixture was stirred at 25°C for 30 min. The mixture was poured into 50 ml of water, filtered off with suction, washed with water and dried.

General Procedure 2b

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 3.0 equivalents of triethylamine were stirred in 1.5 ml of *N,N*-dimethylformamide at 25°C for 30 min. 1.2 equivalents of the amine were then added. The reaction mixture was diluted with a further 1.0 ml of *N,N*-dimethylformamide and purified by preparative HPLC according to Method P1.

General Procedure 2c

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 3.0 equivalents of triethylamine and 1.2 equivalents of the amine were stirred in tetrahydrofuran at 25°C for 18 h. Water was added to the reaction mixture. The solid was filtered off with suction, washed with water and diethyl ether and dried.

General Procedure 2d

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 3.0 equivalents of triethylamine and 1.5 equivalents of the amine were stirred in tetrahydrofuran at 25°C for 18 h. The reaction solution was diluted with water and extracted with ethyl acetate. The combined organic phases were concentrated and the crude product was purified by preparative HPLC according to Method P4.

General Procedure 2e

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 3.0 equivalents of triethylamine and 1.3 equivalents of the amine were stirred in tetrahydrofuran at 25°C for 18 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were concentrated, and 1 ml of dimethyl sulphoxide was added. The solid

was filtered off with suction, washed three times with in each case 0.5 ml of dimethyl sulphoxide and three times with diethyl ether and dried. The filtrate was concentrated and purified by preparative HPLC according to Method P2. The resulting product fraction was combined with the solid.

5

General Procedure 2f

1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 4.0 equivalents of triethylamine and 1.2 equivalents of the amine were stirred in tetrahydrofuran at 25°C for 18 h. The precipitate formed was filtered off and washed with tetrahydrofuran. The solid was triturated with methyl tert-butyl ether and ethyl acetate and then dissolved in dichloromethane, and water was added. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with saturated sodium chloride solution and dried over sodium sulphate. After filtration, the solution was concentrated and the resulting product was dried.

15

General Procedure 2g

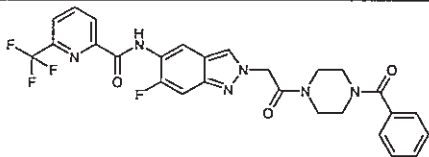
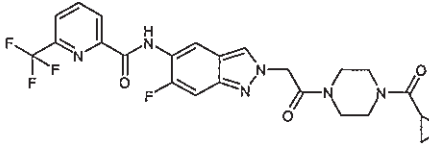
1.0 equivalent of the respective intermediate, 1.0 equivalent of 1-hydroxy-1H-benzotriazole hydrate, 2.0 equivalents of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 3.0 equivalents of triethylamine and 1.3 equivalents of the amine were stirred in tetrahydrofuran at 50°C for 18 h. Water and ethyl acetate were added to the reaction mixture. The solid was filtered off with suction, washed with water and diethyl ether and dried.

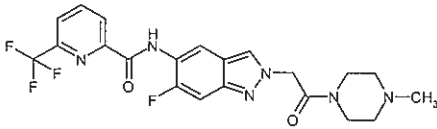
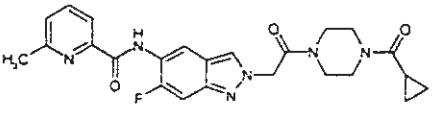
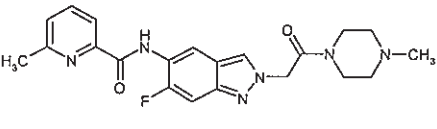
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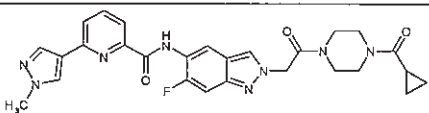
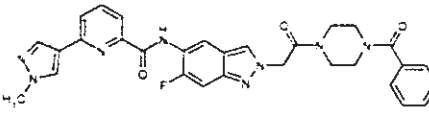
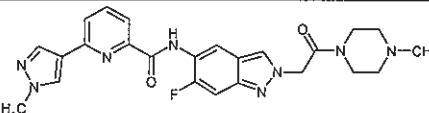
Table 2: Examples 28 – 71

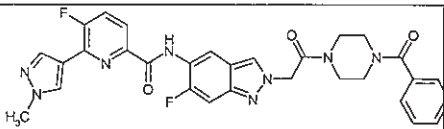
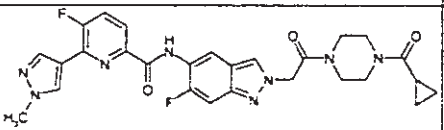
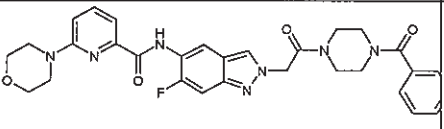
The exemplary compounds were prepared by the general experimental procedures 2a-2g from the appropriate intermediates and amines.

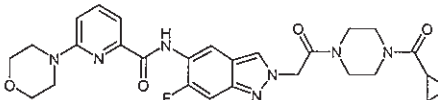
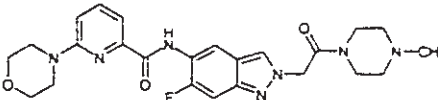
5

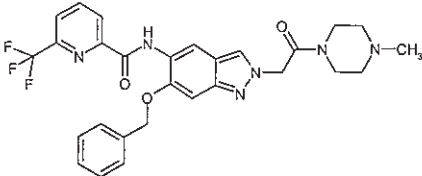
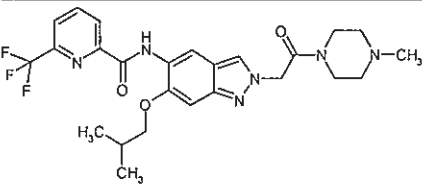
Ex. No.	Structure/Name	Prepared from	* see key	¹ H-NMR / LC-MS
28	 <p>N-(2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-1 and phenyl(piperazin-1-yl)methanone	2a (94%)	(300 MHz, DMSO-d ₆): δ = 3.38 – 3.75 (m, 8H), 5.51 (s, 2H), 7.40 – 7.56 (m, 6H), 8.19 – 8.26 (m, 1H), 8.35 – 8.49 (m, 4H), 10.24 (m, 1H). UPLC-MS (Method A1): Rt = 1.15 min MS (ESIpos): m/z = 555 (M+H) ⁺
29	 <p>N-(2-[2-(4-(cyclopropylcarbonyl)piperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-1 and cyclopropyl(piperazin-1-yl)methanone	2a (95%) [a]	(300 MHz, DMSO-d ₆): δ = 0.69 – 0.81 (m, 4H), 2.00 (s br, 1H), 3.40 – 3.82 (m, 8H), 5.52 (s, 2H), 7.53 (d, 1H), 8.22 (m, 1H), 8.36 – 8.49 (m, 4H), 10.25 (m, 1H). UPLC-MS (Method A1): Rt = 1.09 min MS (ESIpos): m/z = 519 (M+H) ⁺

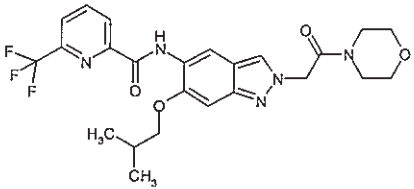
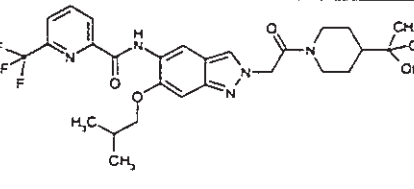
30	 <p>N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-1 and 1-methylpiperazine	2a (41%)	<p>(300 MHz, DMSO-d₆): δ = 2.21 (s, 3H), 2.29 (m, 2H), 2.38 (m, 2H), 3.47 (m, 2H), 3.55 (m, 2H), 5.47 (s, 2H), 7.52 (d, 1H), 8.22 (m, 1H), 8.34 – 8.48 (m, 4H), 10.24 (m, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.93 min</p> <p>MS (ESIpos): m/z = 465 (M+H)⁺</p>
31	 <p>N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide</p>	9-2 and cyclopropyl(piperazin-1-yl)methanone	2a (88%) [a]	<p>(300 MHz, DMSO-d₆): δ = 0.68 - 0.82 (m, 4H), 2.01 (s br, 1H), 2.63 (s, 3H), 3.40 – 3.82 (m, 8H), 5.52 (s, 2H), 7.49 – 7.62 (m, 2H), 7.95 – 8.05 (m, 2H), 8.38 (s, 1H), 8.55 (d, 1H), 10.39 (d, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.02 min</p> <p>MS (ESIpos): m/z = 465 (M+H)⁺</p>
32	 <p>N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide</p>	9-2 and 1-methylpiperazine	2a (68%)	<p>(300 MHz, DMSO-d₆): δ = 2.21 (s, 3H), 2.29 (m, 2H), 2.38 (m, 2H), 2.63 (s, 3H), 3.46 (m, 2H), 3.53 (m, 2H), 5.45 (s, 2H), 7.47 – 7.62 (m, 2H), 7.93 (m, 2H), 8.36 (s, 1H), 8.55 (d, 1H), 10.55 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.81 min</p> <p>MS (ESIpos): m/z = 411 (M+H)⁺</p>

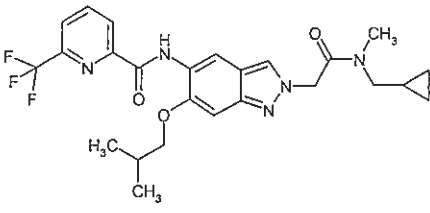
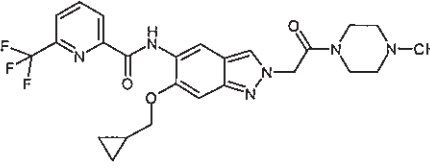
33	 <p>N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	9-3 and cyclopropyl(piperazin-1-yl)methanone	2a (82%) [a]	<p>(300 MHz, DMSO-d₆): δ = 0.68 - 0.83 (m, 4H), 2.02 (s br, 1H), 3.42 - 3.85 (m, 8H), 3.93 (s, 3H), 5.53 (s, 2H), 7.54 (d, 1H), 7.87 - 8.09 (m, 3H), 8.23 (s, 1H), 8.38 (m, 2H), 8.54 (s, 1H), 10.52 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.93 min MS (ESIpos): m/z = 531 (M+H)⁺</p>
34	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	9-3 and phenyl(piperazin-1-yl)methanone	2a (47%) [b]	<p>(300 MHz, DMSO-d₆): δ = 3.40 - 3.79 (m, 8H), 3.94 (s, 3H), 5.51 (s, 2H), 7.41 - 7.57 (m, 6H), 7.93 (t, 2H), 8.04 (t, 1H), 8.22 (s, 1H), 8.39 (m, 2H), 8.52 (s, 1H), 10.51 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.00 min MS (ESIpos): m/z = 567 (M+H)⁺</p>
35	 <p>N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	9-3 and 1-methylpiperazine	2a (14%) [b]	<p>(300 MHz, DMSO-d₆): δ = 2.21 (s, 3H), 2.30 (m, 2H), 2.38 (m, 2H), 3.47 (m, 2H), 3.55 (m, 2H), 3.93 (s, 3H), 5.47 (s, 2H), 7.52 (d, 1H), 7.93 (t, 2H), 8.04 (t, 1H), 8.22 (s, 1H), 8.39 (m, 2H), 8.52 (s, 1H), 10.50 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.74 min MS (ESIpos): m/z = 477 (M+H)⁺</p>

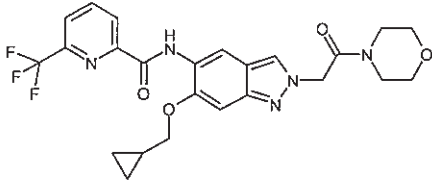
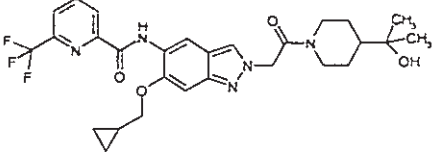
36	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	9-4 and phenyl(piperazin-1-yl)methanone	2a (64%)	<p>(300 MHz, DMSO-d₆): δ = 3.38 – 3.76 (m, 8H), 3.96 (s, 3H), 5.51 (s, 2H), 7.41–7.56 (m, 6H), 7.93 – 8.05 (m, 2H), 8.25 – 8.31 (m, 2H), 8.40 (s, 1H), 8.53 (m, 1H), 10.40 (s, 1H).</p> <p>UPLC-MS (Method A1): R_t = 1.07 min</p> <p>MS (ESIpos): m/z = 585 (M+H)⁺</p>
37	 <p>N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	9-4 and cyclopropyl(piperazin-1-yl)methanone	2a (59%) [a]	<p>(300 MHz, DMSO-d₆): δ = 0.69 – 0.83 (m, 4H), 2.01 (s br, 1H), 3.41 – 3.85 (m, 8H), 3.97 (s, 3H), 5.52 (s, 2H), 7.52 (d, 1H), 7.93 – 8.06 (m, 2H), 8.28 (m, 2H), 8.39 (s, 1H), 8.53 (s, 1H), 10.40 (s, 1H).</p> <p>UPLC-MS (Method A1): R_t = 1.00 min</p> <p>MS (ESIpos): m/z = 549 (M+H)⁺</p>
38	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide</p>	9-5 and phenyl(piperazin-1-yl)methanone	2a (78%)	<p>(300 MHz, DMSO-d₆): δ = 3.41 – 3.82 (m, 16H), 5.50 (s, 2H), 7.15 (d, 1H), 7.47 (m, 7H), 7.81 (t, 1H), 8.37 (s, 1H), 8.48 (d, 1H), 10.27 (m, 1H).</p> <p>UPLC-MS (Method A1): R_t = 1.06 min</p> <p>MS (ESIpos): m/z = 572 (M+H)⁺</p>

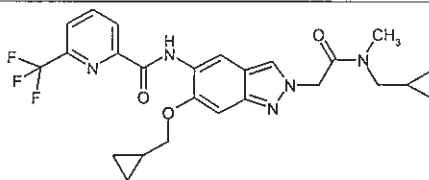
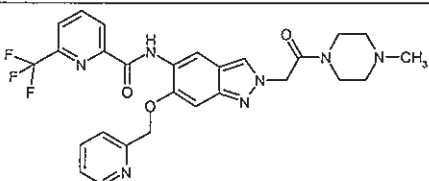
39	 <p>N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-(morpholin-4-yl)pyridine-2-carboxamide</p>	9-5 and cyclopropyl(piperazin-1-yl)methanone	2a (91%) [a]	<p>(300 MHz, DMSO-d₆): δ = 0.67 - 0.83 (m, 4H), 2.01 (s br, 1H), 3.44 - 3.81 (m, 16H), 5.50 (s, 2H), 7.15 (d, 1H), 7.44 - 7.55 (m, 2H), 7.81 (t, 1H), 8.37 (s, 1H), 8.48 (d, 1H), 10.27 (m, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.01 min MS (ESIpos): m/z = 536 (M+H)⁺</p>
40	 <p>N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide</p>	9-5 and 1-methylpiperazine	2a (64%)	<p>(300 MHz, DMSO-d₆): δ = 2.21 (s, 3H), 2.30 (m, 2H), 2.38 (m, 2H), 3.47 (m, 2H), 3.55 (m, 2H), 3.59 (m, 4H), 3.76 (m, 4H), 5.45 (s, 2H), 7.15 (d, 1H), 7.44 - 7.53 (m, 2H), 7.81 (tr, 1H), 8.36 (s, 1H), 8.47 (d, 1H), 10.27 (m, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.79 min MS (ESIpos): m/z = 482 (M+H)⁺</p>

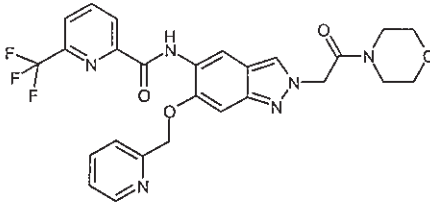
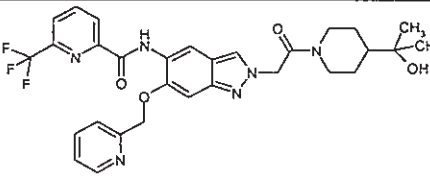
41	 <p>N-{6-(benzyloxy)-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-6 and 1-methylpiperazine	2b (72%)	<p>(400 MHz, DMSO-d₆): δ = 2.21 (s, 3 H), 2.26 - 2.33 (m, 2 H), 2.34 - 2.43 (m, 2 H), 3.43 - 3.50 (m, 2 H), 3.51 - 3.59 (m, 2 H), 5.31 (s, 2 H), 5.39 (s, 2 H), 7.30 (s, 1 H), 7.34 - 7.45 (m, 3 H), 7.58 (dd, 2 H), 8.18 (dd, 1 H), 8.25 (s, 1 H), 8.35 - 8.44 (m, 1 H), 8.44 - 8.50 (m, 1 H), 8.80 (s, 1 H), 10.47 (s, 1 H).</p> <p>LC-MS (Method A3): R_t = 0.96 min</p> <p>MS (ESIpos): m/z = 553 (M+H)⁺</p>
42	 <p>N-{6-isobutoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-7 and 1-methylpiperazine	2b (53%)	<p>(300 MHz, DMSO-d₆): δ = 1.11 (s, 3 H), 1.13 (s, 3 H), 2.17-2.23 (m, 1 H), 2.21 (s, 3 H), 2.25 - 2.33 (m, 2 H), 2.37 (br. s., 2 H), 3.46 (br. s., 2 H), 3.54 (br. s., 2 H), 3.96 (d, 2 H), 5.38 (s, 2 H), 7.07 (s, 1 H), 8.14 - 8.26 (m, 2 H), 8.34 - 8.45 (m, 1 H), 8.45 - 8.53 (m, 1 H), 8.78 (s, 1 H), 10.58 (s, 1 H).</p> <p>LC-MS (Method A3): R_t = 1.06 min</p> <p>MS (ESIpos): m/z = 519 (M+H)⁺</p>

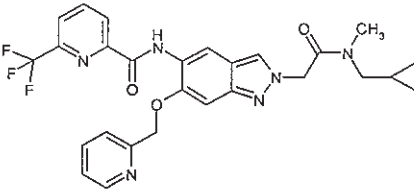
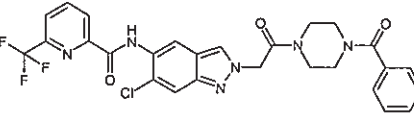
43	 <p>N-{6-isobutoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-7 and morpholine	2b (54%)	<p>(300 MHz, DMSO-d₆): δ = 3.47 (d, 2 H), 3.52 - 3.68 (m, 6 H), 3.96 (d, 2 H), 5.40 (s, 2 H), 7.07 (s, 1 H), 8.19 - 8.25 (m, 2 H), 8.36 - 8.45 (m, 1 H), 8.46 - 8.52 (m, 1 H), 8.78 (s, 1 H), 10.58 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.32 min</p> <p>MS (ESIpos): m/z = 506 (M+H)⁺</p>
44	 <p>N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-isobutoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-7 and 2-(piperidin-4-yl)propan-2-ol	2b (49%)	<p>(300 MHz, DMSO-d₆): δ = 1.05 (s, 6 H), 1.11 (s, 3 H), 1.13 (s, 3 H), 1.19 - 1.33 (m, 3 H), 1.36 - 1.52 (m, 1 H), 1.75 (t, 2 H), 2.11 - 2.25 (m, 1 H), 2.90 - 3.09 (m, 1 H), 3.96 (d, 2 H), 4.02 (d, 1 H), 4.18 (s, 1 H), 4.42 (d, 1 H), 5.27 - 5.45 (m, 2 H), 7.07 (s, 1 H), 8.18 - 8.25 (m, 2 H), 8.35 - 8.45 (m, 1 H), 8.45 - 8.52 (m, 1 H), 8.77 (s, 1 H), 10.58 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.34 min</p> <p>MS (ESIpos): m/z = 562 (M+H)⁺</p>

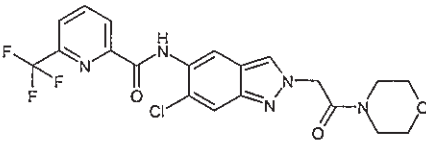
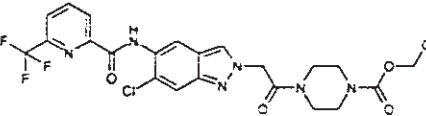
45	 <p>N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-isobutoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-7 and 1-cyclopropyl-N-methylmethanamine	2b (54%)	<p>(400 MHz, DMSO-d₆): δ = 0.18 - 0.25 (m, 1 H), 0.33 (q, 1 H), 0.41 - 0.49 (m, 1 H), 0.50 - 0.58 (m, 1 H), 0.92 - 1.02 (m, 1 H), 1.11 (s, 3 H), 1.13 (s, 3 H), 2.19 (dt, 1 H), 2.92 (s, 1 H) + 3.13 (s, 2 H), 3.20 (d, 1 H), 3.34 (d, 1 H), 3.96 (d, 2 H), 5.33 - 5.42 (m, 2 H), 7.07 (s, 1 H), 8.16 - 8.28 (m, 2 H), 8.41 (t, 1 H), 8.49 (d, 1 H), 8.78 (s, 1 H), 10.57 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.45 min</p> <p>MS (ESIpos): m/z = 504 (M+H)⁺</p>
46	 <p>N-{6-(cyclopropylmethoxy)-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-8 and 1-methylpiperazine	2b (75%)	<p>(400 MHz, DMSO-d₆): δ = 0.39 - 0.51 (m, 2 H), 0.57 - 0.70 (m, 2 H), 1.27 - 1.43 (m, 1 H), 2.21 (s, 3 H), 2.29 (t, 2 H), 2.34 - 2.39 (m, 2 H), 3.43 - 3.49 (m, 2 H), 3.51 - 3.57 (m, 2 H), 4.03 (d, 2 H), 5.37 (s, 2 H), 7.05 (s, 1 H), 8.19 - 8.23 (m, 2 H), 8.41 (t, 1 H), 8.48 (d, 1 H), 8.76 (s, 1 H), 10.71 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.01 min</p> <p>MS (ESIpos): m/z = 517 (M+H)⁺</p>

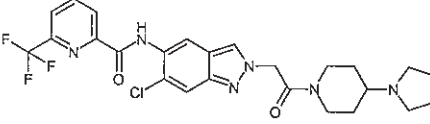
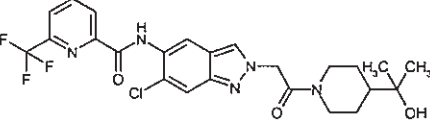
47	 <p>N-{6-(cyclopropylmethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-8 and morpholine	2b (73%)	<p>(400 MHz, DMSO-d₆): δ = 0.40 - 0.48 (m, 2 H), 0.66 (dd, 2 H), 1.31 - 1.40 (m, 1 H), 3.43 - 3.50 (m, 2 H), 3.53 - 3.68 (m, 6 H), 4.03 (d, 2 H), 5.39 (s, 2 H), 7.05 (s, 1 H), 8.19 - 8.23 (m, 2 H), 8.38 - 8.44 (m, 1 H), 8.45 - 8.50 (m, 1 H), 8.76 (s, 1 H), 10.71 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.25 min</p> <p>MS (ESIpos): m/z = 504 (M+H)⁺</p>
48	 <p>N-[6-(cyclopropylmethoxy)-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-8 and 2-(piperidin-4-yl)propan-2-ol	2b (78%)	<p>(400 MHz, DMSO-d₆): δ = 0.41 - 0.48 (m, 2 H), 0.62 - 0.69 (m, 2 H), 1.05 (s, 6 H), 1.09 (d, 1 H), 1.18 - 1.29 (m, 2 H), 1.29 - 1.40 (m, 1 H), 1.40 - 1.51 (m, 1 H), 1.75 (t, 2 H), 2.99 (t, 1 H), 4.02 (d, 3 H), 4.16 (s, 1 H), 4.42 (d, 1 H), 5.25 - 5.45 (m, 2 H), 7.04 (s, 1 H), 8.17 - 8.24 (m, 2 H), 8.41 (t, 1 H), 8.48 (d, 1 H), 8.75 (s, 1 H), 10.70 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.27 min</p> <p>MS (ESIpos): m/z = 560 (M+H)⁺</p>

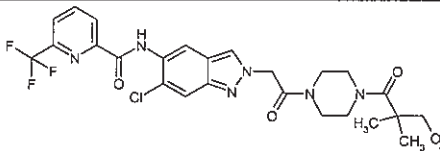
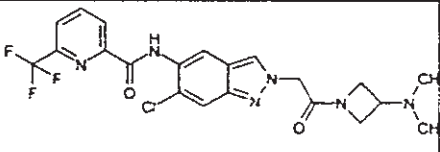
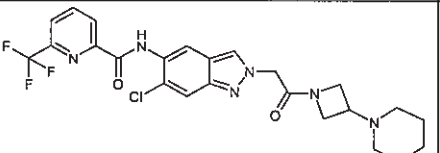
49	 <p>N-[6-(cyclopropylmethoxy)-2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-8 and 1-cyclopropyl-N-methylmethanamine	2b (54%)	<p>(400 MHz, DMSO-d₆): δ = 0.22 (q, 1 H), 0.33 (d, 1 H), 0.41 - 0.48 (m, 3 H), 0.50 - 0.57 (m, 1 H), 0.62 - 0.69 (m, 2 H), 0.97 (br. s., 1 H), 1.30 - 1.41 (m, 1 H), 2.92 (s, 1 H) + 3.13 (s, 2 H), 3.20 (d, 1 H), 3.34 (d, 1 H), 4.03 (d, 2 H), 5.29 - 5.43 (m, 2 H), 7.05 (s, 1 H), 8.19 - 8.25 (m, 2 H), 8.41 (t, 1 H), 8.48 (d, 1 H), 8.76 (s, 1 H), 10.70 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.38 min</p> <p>MS (ESIpos): m/z = 502 (M+H)⁺</p>
50	 <p>N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-9 and 1-methylpiperazine	2b (75%)	<p>(300 MHz, DMSO-d₆): δ = 2.21 (s, 3 H), 2.24 - 2.33 (m, 2 H), 2.37 (br. s., 2 H), 3.47 (br. s., 2 H), 3.55 (br. s., 2 H), 5.36 (s, 2 H), 5.40 (s, 2 H), 7.30 (s, 1 H), 7.36 - 7.47 (m, 1 H), 7.71 (d, 1 H), 7.79 - 7.90 (m, 1 H), 8.19 (dd, 1 H), 8.26 (s, 1 H), 8.34 - 8.44 (m, 1 H), 8.45 - 8.52 (m, 1 H), 8.62 (d, 1 H), 8.81 (s, 1 H), 10.50 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 0.92 min</p> <p>MS (ESIpos): m/z = 554 (M+H)⁺</p>

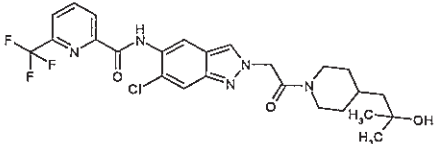
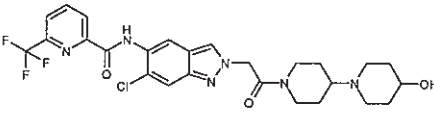
51	 <p>N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-9 and morpholine	2b (23%)	<p>(400 MHz, DMSO-d₆): δ = 3.40 - 3.52 (m, 2 H), 3.59 (d, 4 H), 3.62 - 3.68 (m, 2 H), 5.36 (s, 2 H), 5.41 (s, 2 H), 7.30 (s, 1 H), 7.42 (dd, 1 H), 7.70 (d, 1 H), 7.86 (td, 1 H), 8.15 - 8.23 (m, 1 H), 8.27 (s, 1 H), 8.39 (t, 1 H), 8.48 (d, 1 H), 8.62 (d, 1 H), 8.81 (s, 1 H), 10.50 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.11 min</p> <p>MS (ESIpos): m/z = 541 (M+H)⁺</p>
52	 <p>N-[2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-9 and 2-(piperidin-4-yl)propan-2-ol	2b (29%)	<p>(400 MHz, DMSO-d₆): δ = 1.05 (s, 6 H), 1.17 - 1.34 (m, 3 H), 1.37 - 1.52 (m, 1 H), 1.76 (t, 2 H), 2.91 - 3.08 (m, 1 H), 4.04 (d, 1 H), 4.17 (s, 1 H), 4.42 (d, 1 H), 5.28 - 5.45 (m, 4 H), 7.29 (s, 1 H), 7.36 - 7.47 (m, 1 H), 7.70 (d, 1 H), 7.86 (td, 1 H), 8.19 (dd, 1 H), 8.26 (s, 1 H), 8.40 (t, 1 H), 8.48 (d, 1 H), 8.58 - 8.65 (m, 1 H), 8.81 (s, 1 H), 10.50 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.15 min</p> <p>MS (ESIpos): m/z = 597 (M+H)⁺</p>

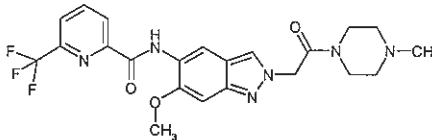
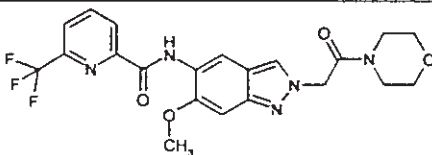
53	 <p>N-[2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-9 and 1-cyclopropyl-N-methylmethanamine	2b (44%)	<p>(400 MHz, DMSO-d₆): δ = 0.19 - 0.26 (m, 1 H), 0.30 - 0.37 (m, 1 H), 0.40 - 0.49 (m, 1 H), 0.51 - 0.60 (m, 1 H), 0.91 - 1.02 (m, 1 H), 2.93 (s, 1 H)+ 3.14 (s, 2 H), 3.21 (d, 1 H), 3.35 (d, 1 H), 5.36 (s, 2 H), 5.39 (s, 2 H), 7.30 (s, 1 H), 7.37 - 7.45 (m, 1 H), 7.70 (d, 1 H), 7.86 (td, 1 H), 8.19 (dd, 1 H), 8.27 (d, 1 H), 8.40 (t, 1 H), 8.48 (d, 1 H), 8.62 (d, 1 H), 8.81 (s, 1 H), 10.50 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.24 min</p> <p>MS (ESIpos): m/z = 539 (M+H)⁺</p>
54	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-chloro-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-11 and phenyl(piperazin-1-yl)methanone	2c (95%)	<p>(300 MHz, DMSO-d₆): δ = 3.40 - 3.82 (m, 8H), 5.54 (br. s., 2H), 7.41 - 7.52 (m, 5H), 7.91 (s, 1H), 8.23 (dd, 1H), 8.37 - 8.49 (m, 3H), 8.64 (s, 1H), 10.5 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.22 min</p> <p>MS (ESIpos): m/z = 571 (M+H)⁺</p>

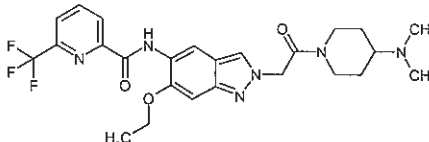
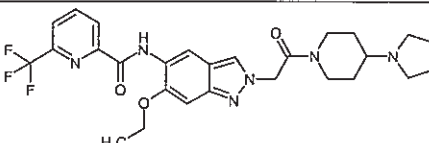
55	 <p>N-{6-chloro-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-11 and morpholine	2d (44%)	<p>(400 MHz, DMSO-d₆): δ = 3.48 (d, 2H), 3.53 - 3.63 (m, 4H), 3.66 (d, 2H), 5.52 (s, 2H), 7.92 (s, 1H), 8.24 (d, 1H), 8.38 - 8.44 (m, 2H), 8.45 - 8.49 (m, 1H), 8.66 (s, 1H), 10.5 (br. s., 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.16 min MS (ESIpos): m/z = 468 (M+H)⁺</p>
56	 <p>ethyl 4-{[6-chloro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxylate</p>	9-11 and ethylpiperazine-1-carboxylate	2d (41%)	<p>(500 MHz, DMSO-d₆): δ = 1.21 (t, 3H), 3.37 - 3.63 (m, 9H), 4.08 (q, 2H), 5.54 (s, 2H), 7.92 (s, 1H), 8.24 (dd, 1H), 8.39 - 8.44 (m, 2H), 8.45 - 8.49 (m, 1H), 8.66 (s, 1H), 10.5 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.24 min MS (ESIpos): m/z = 538 (M+H)⁺</p>

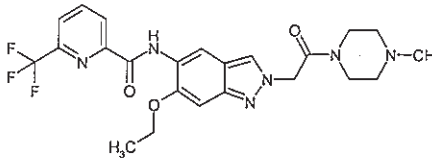
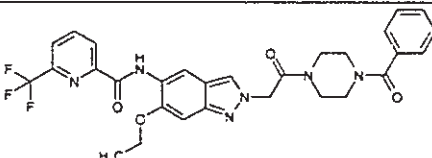
57	 <p>N-(6-chloro-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-11 and 4-(pyrrolidin-1-yl)piperidine	2d (31%)[c]	<p>(400 MHz, DMSO-d₆): δ = 1.25 - 1.37 (m, 1H), 1.39 - 1.53 (m, 1H), 1.68 (br. s., 4H), 1.78 - 1.95 (m, 2H), 2.19 - 2.30 (m, 1H), 2.87 (t, 1H), 3.19 (t, 1H), 3.88 (d, 1H), 4.10 (d, 1H), 5.49 (d, 2H), 7.91 (s, 1H), 8.23 (d, 1H), 8.38 - 8.44 (m, 2H), 8.45 - 8.49 (m, 1H), 8.66 (s, 1H), 10.5 (br. s., 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.00 min MS (ESIpos): m/z = 535 (M+H)⁺</p>
58	 <p>N-(6-chloro-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-11 and 2-(piperidin-4-yl)propan-2-ol	2d (32%)[d]	<p>(400 MHz, DMSO-d₆, selected signals): δ = 1.05 (s, 6H), 1.68 - 1.85 (m, 2H), 3.02 (t, 1H), 4.02 (d, 1H), 4.17 (s, 1H), 4.42 (d, 1H), 5.42 - 5.55 (m, 2H), 7.91 (s, 1H), 8.23 (d, 1H), 8.38 - 8.51 (m, 3H), 8.65 (s, 1H), 10.5 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.18 min MS (ESIpos): m/z = 524 (M+H)⁺</p>

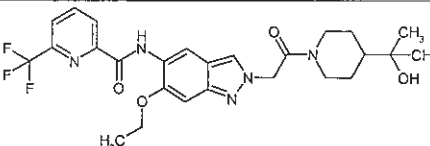
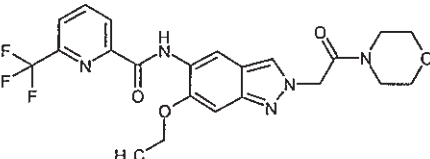
59	 <p>N-(6-chloro-2-{2-[4-(3-hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-11 and 3-hydroxy-2,2-dimethyl-1-(piperazin-1-yl)propan-1-one	2d (39% [e])	<p>(400 MHz, DMSO-d₆): δ = 1.18 (s, 6H), 3.39 - 3.72 (m, 10H), 4.61 (t, 1H), 5.54 (s, 2H), 7.92 (s, 1H), 8.24 (d, 1H), 8.38 - 8.44 (m, 2H), 8.45 - 8.50 (m, 1H), 8.66 (s, 1H), 10.5 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.13 min MS (ESIpos): m/z = 567 (M+H)⁺</p>
60	 <p>N-(6-chloro-2-{2-[3-(dimethylamino)azetidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-11 and N,N-dimethylazetidine-3-amine	2e (31%)	<p>(400 MHz, DMSO-d₆): δ = 2.08 (s, 6H), 3.07 - 3.14 (m, 1H), 3.70 (dd, 1H), 3.92 (dd, 1H), 4.02 (dd, 1H), 4.19 (t, 1H), 5.21 (s, 2H), 7.92 (s, 1H), 8.23 (dd, 1H), 8.37 - 8.49 (m, 3H), 8.64 (s, 1H), 10.5 (s, 1H).</p> <p>UPLC-MS (Method A2): Rt = 1.13 min MS (ESIpos): m/z = 481 (M+H)⁺</p>
61	 <p>N-(6-chloro-2-{2-oxo-2-[3-(piperidin-1-yl)azetidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-11 and 1-(azetidin-3-yl)piperidine	2e (53% [f])	<p>(400 MHz, CHLOROFORM-d): δ = 1.69 (br. s., 4H), 2.36 (br. s., 4H), 3.19 (br. s., 1H), 4.01 - 4.21 (m, 4H), 4.99 - 5.14 (m, 2H), 7.29 (s, 3H), 7.85 (s, 1H), 7.90 - 7.95 (m, 1H), 8.11 - 8.21 (m, 2H), 8.53 (d, 1H), 8.94 (s, 1H), 10.69 - 10.78 (m, 1H).</p> <p>UPLC-MS (Method A2): Rt = 1.28 min MS (ESIpos): m/z = 521 (M+H)⁺</p>

62	 <p>N-(6-chloro-2-{2-[4-(2-hydroxy-2-methylpropyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-11 and 2-methyl-1-(piperidin-4-yl)propan-2-ol	2d (75%)[g]	<p>(300 MHz, DMSO-d₆): δ = 0.88 – 1.36 (m, 10H, contains singlet at 1.11 ppm), 1.64 – 1.90 (m, 3H), 2.59 – 2.74 (m, superimposed by DMSO-d₆ signal), 3.09 (t, 1H), 3.89 (d, 1H), 4.11 (s, 1H), 4.23 (d, 1H), 5.38 – 5.55 (m, 2H), 7.90 (s, 1H), 8.23 (dd, 1H), 8.37 – 8.49 (m, 3H), 8.63 (s, 1H), 10.5 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.23 min MS (ESIpos): m/z = 538 (M+H)⁺</p>
63	 <p>N-{6-chloro-2-[2-(4-hydroxy-1,4'-bipiperidin-1'-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-11 and 1,4'-bipiperidin-4-ol	2g (85%)[h]	<p>(300 MHz, DMSO-d₆): δ = 1.18 – 1.53 (m, 4H), 1.64 – 1.83 (m, 4H), 2.18 (t, 2H), 2.53 – 2.80 (m, 4H, superimposed by DMSO signal), 3.06 (t, 1H), 3.36 – 3.46 (m, superimposed by water signal), 3.97 (d, 1H), 4.32 (d, 1H), 4.51 (d, 1H), 5.40 – 5.58 (m, 2H), 7.90 (s, 1H), 8.20 – 8.26 (m, 1H), 8.37 – 8.49 (m, 3H), 8.63 (s, 1H), 10.52 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.93 min MS (ESIpos): m/z = 564 (M+H)⁺</p>

64	 <p>N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-12 and 1-methylpiperazine	2f (57%)	<p>(400 MHz, DMSO-d₆): δ = 2.21 (s, 3H), 2.30 (t, 2H), 2.37 (d, 2H), 3.47 (d, 2H), 3.51 - 3.59 (m, 2H), 3.99 (s, 3H), 5.39 (s, 2H), 7.11 (s, 1H), 8.18 - 8.26 (m, 2H), 8.37 - 8.43 (m, 1H), 8.44 - 8.49 (m, 1H), 8.71 (s, 1H), 10.51 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.91 min</p> <p>MS (ESIpos): m/z = 477 (M+H)⁺</p>
65	 <p>N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-12 and morpholine	2b (85%)	<p>(300 MHz, DMSO-d₆): δ = 3.42 - 3.51 (m, 2 H), 3.53 - 3.62 (m, 4 H), 3.62 - 3.68 (m, 2 H), 3.99 (s, 3 H), 5.40 (s, 2 H), 7.12 (s, 1 H), 8.19 - 8.25 (m, 2 H), 8.36 - 8.44 (m, 1 H), 8.44 - 8.50 (m, 1 H), 8.71 (s, 1 H), 10.51 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.14 min</p> <p>MS (ESIpos): m/z = 464 (M+H)⁺</p>

66	 <p>N-(2-{2-[4-(dimethylamino)piperidin-1-yl]-2-oxoethyl}-6-ethoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-13 and N,N-dimethylpiperidine-4-amine	2g (63%)	<p>(400 MHz, DMSO-d₆): δ = 1.17 - 1.29 (m, 1H), 1.31 - 1.45 (m, 1H), 1.49 (t, 3H), 1.69 - 1.83 (m, 2H), 2.17 (s, 6H), 2.28 - 2.38 (m, 1H), 2.66 (t, 1H), 3.08 (t, 1H), 3.96 (d, 1H), 4.15 - 4.31 (m, 3H), 5.30 - 5.41 (m, 2H), 7.07 (s, 1H), 8.18 - 8.24 (m, 2H), 8.37 - 8.47 (m, 2H), 8.71 (s, 1H), 10.7 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.93 min</p> <p>MS (ESIpos): m/z = 519 (M+H)⁺</p>
67	 <p>N-(6-ethoxy-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-13 and 4-(pyrrolidin-1-yl)piperidine	2g (43%) [i]	<p>(400 MHz, DMSO-d₆): δ = 1.22 - 1.35 (m, 1H), 1.37 - 1.54 (m, 4H), 1.67 (br. s., 4H), 1.84 (t, 2H), 2.19 - 2.26 (m, 1H), 2.43 - 2.58 (superimposed by DMSO-d₆ signal), 2.84 (t, 1H), 3.16 (t, 1H), 3.87 (d, 1H), 4.09 (d, 1H), 4.20 (q, 2H), 5.30 - 5.42 (m, 2H), 7.07 (s, 1H), 8.19 - 8.24 (m, 2H), 8.37 - 8.48 (m, 2H), 8.70 - 8.73 (m, 1H), 10.7 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.96 min</p> <p>MS (ESIpos): m/z = 545 (M+H)⁺</p>

68	 <p>N-{6-ethoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-13 and 1-methylpiperazine	2g (51% [i])	<p>(400 MHz, DMSO-d₆): δ = 1.49 (t, 3H), 2.20 (s, 3H), 2.26 - 2.41 (m, 4H), 3.42 - 3.58 (m, 4H), 4.20 (q, 2H), 5.37 (s, 2H), 7.07 (s, 1H), 8.18 - 8.24 (m, 2H), 8.37 - 8.47 (m, 2H), 8.71 (s, 1H), 10.7 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.92 min MS (ESIpos): m/z = 491 (M+H)⁺</p>
69	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-ethoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-13 and phenyl(piperazin-1-yl)methanone	2g (71%)	<p>(400 MHz, DMSO-d₆): δ = 1.49 (t, 3H), 3.33 - 3.79 (m, 8H), 4.20 (q, 2H), 5.41 (br. s., 2H), 7.08 (s, 1H), 7.41 - 7.50 (m, 5H), 8.19 - 8.24 (m, 2H), 8.37 - 8.47 (m, 2H), 8.72 (s, 1H), 10.7 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.23 min MS (ESIpos): m/z = 581 (M+H)⁺</p>

70	 <p>N-(6-ethoxy-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-13 and 2-(piperidin-4-yl)propan-2-ol	2g (79%)	<p>(300 MHz, DMSO-d₆): δ = 0.97 - 1.29 (m, 8H, contains s at 1.03), 1.37 - 1.56 (m, 4H), 1.74 (t, 2H), 2.42 - 2.63 (signal obscured by DMSO-d₆ signal) 2.98 (t, 1H), 4.02 (d, 1H), 4.14 - 4.25 (m, 3H), 4.40 (d, 1H), 5.27 - 5.43 (m, 2H), 7.07 (s, 1H), 8.17 - 8.24 (m, 2H), 8.36 - 8.48 (m, 2H), 8.71 (s, 1H), 10.7 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.19 min MS (ESIpos): m/z = 534 (M+H)⁺</p>
71	 <p>N-{6-ethoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	9-13 and morpholine	2g (89%)	<p>(300 MHz, DMSO-d₆): δ = 1.49 (t, 3H), 3.41 - 3.70 (m, 8H), 4.20 (q, 2H), 5.38 (s, 2H), 7.07 (s, 1H), 8.18 - 8.26 (m, 2H), 8.36 - 8.48 (m, 2H), 8.71 (s, 1H), 10.73 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.16 min MS (ESIpos): m/z = 478 (M+H)⁺</p>

* Prepared according to the stated procedure, the yield in % is indicated in brackets

[a]: The piperazine was used as hydrochloride. In addition to the piperazine, 1.6 equivalents of triethylamine were added to the reaction mixture.

5 [b]: The product was purified by preparative HPLC according to Method P1.

[c]: Gradient for the preparative HPLC: iso. ethanol / methanol / diethylamine 50:50:0.1; flow rate: 35 ml/min

[d]: Gradient for the preparative HPLC: iso. hexane / ethanol / diethylamine 70:30:0.1; flow rate: 40 ml/min

10 [e]: Gradient for the preparative HPLC: iso. hexane / ethanol / diethylamine 70:30:0.1; flow rate: 31 ml/min

[f] N,N-Dimethylformamide was used instead of dimethyl sulphoxide.

[g]: HPLC was carried out according to Method P1.

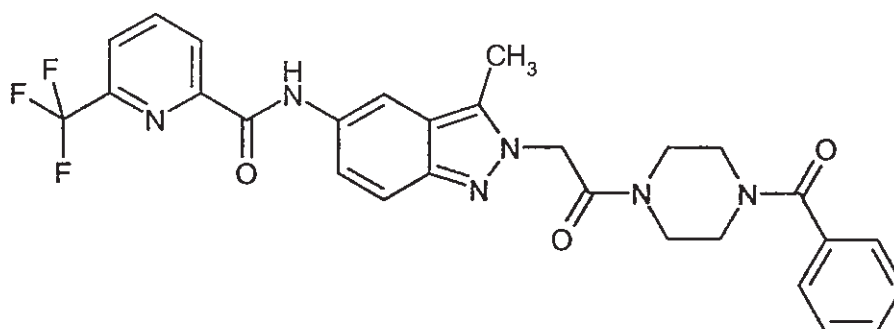
[h]: 1.5 equivalents of piperazine were used.

[i]: The product was triturated with N,N-dimethylformamide and dimethyl sulphoxide.

5

Example 72

N-{2-[2-(4-Benzoylpiperazin-1-yl)-2-oxoethyl]-3-methyl-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



10

Analogously to Intermediate 8-1, 103 mg (0.27 mmol) of 2-(5-amino-3-methyl-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)ethanone (Intermediate 6-15, crude product) were reacted with 78 mg (0.41 mmol) of 6-(trifluoromethyl)pyridine-2-carboxylic acid. After 24 h at 25°C, water was added. The solid was filtered off, washed with water and diethyl ether and dried under reduced pressure.

15 This gave 43 mg (29% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 1.12$ min

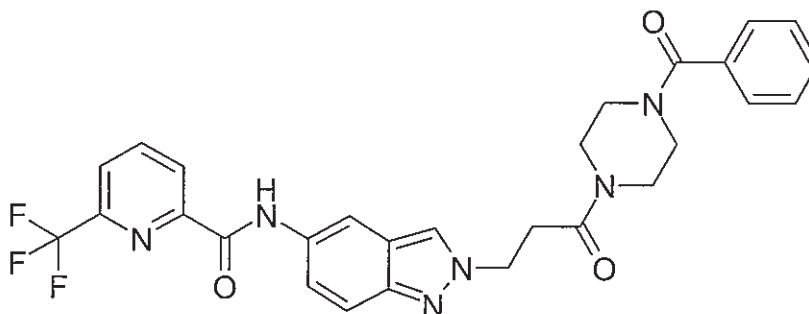
MS (ESIpos): $m/z = 551$ (M+H)+.

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6): $\delta = 3.34 - 3.73$ (m, 8H), 5.48 (br. s., 2H), 7.42 - 7.58 (m, 7H), 8.14 - 8.23 (m, 2H), 8.32 - 8.43 (m, 2H), 10.35 (s, 1H).

20

Example 73

N-{2-[3-(4-Benzoylpiperazin-1-yl)-3-oxopropyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



25

Analogously to Intermediate 8-1, 80 mg (0.21 mmol) of 3-[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]propanoic acid (Intermediate 9-15) in 0.3 ml of *N,N*-dimethylformamide and 2.9 ml of tetrahydrofuran were stirred with 32 mg (0.21 mmol) of 1-hydroxy-1H-benzotriazole hydrate and 81 mg (0.42 mmol) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride for 30 minutes. 60 mg (0.32 mmol) of phenyl(piperazin-1-yl)methanone were added. The reaction mixture was stirred at 25°C for 2.5 h and added dropwise to 50 ml of water. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated. The crude product was stirred in 2 ml of dimethyl sulphoxide for 30 min, filtered and washed with 30 ml of water. The solid was purified by preparative HPLC according to Method P1. This gave 5 mg (4% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 1.10$ min

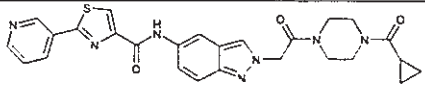
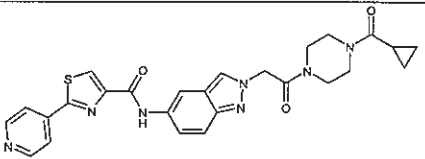
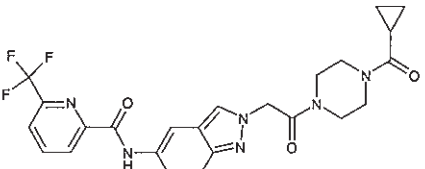
MS (ESIpos): $m/z = 551$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-*d*₆): $\delta = 3.10$ (br. s., 2 H), 3.50 (br. s., 6 H), 4.65 (t, 2 H), 7.36 - 7.42 (m, 2 H), 7.42 - 7.47 (m, 3 H), 7.53 - 7.63 (m, 2 H), 8.17 (dd, 1 H), 8.28 (s, 1 H), 8.32 - 8.42 (m, 3 H), 10.35 (s, 1 H).

The exemplary compounds of Tables 3 - 17 were synthesized in an amide synthesis analogously to Experimental Procedures 1a - 1g and 2a - 2g or by a method indicated in the table and analysed by analytical LC-MS (Method A4).

Table 3: Examples 74 – 77

The exemplary compounds were prepared from 2-(5-amino-2H-indazol-2-yl)-1-[4-(cyclopropylcarbonyl)piperazin-1-yl]ethanone (Intermediate 6-10) and the starting material indicated in the table.

Example	Structure and name	Starting material and notes	LC-MS retention time [min]
74	 <p>N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-2-(pyridin-3-yl)-1,3-thiazole-4-carboxamide</p>	2-(pyridin-3-yl)-1,3-thiazole-4-carboxylic acid	0.78
75	 <p>N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-2-(pyridin-4-yl)-1,3-thiazole-4-carboxamide</p>	2-(pyridin-4-yl)-1,3-thiazole-4-carboxylic acid	0.70
76	 <p>N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	6-(trifluoromethyl)pyridine-2-carboxylic acid	0.94

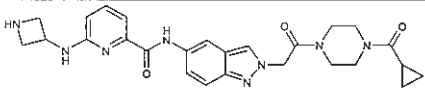
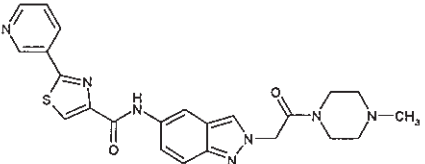
77	 <p>6-(azetidin-3-ylamino)-N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)pyridine-2-carboxamide</p>	<p>The 2-(5-amino-2H-indazol-2-yl)-1-[4-(cyclopropylcarbonyl)piperazin-1-yl]ethanone starting material was reacted with 6-fluoropyridine-2-carboxylic acid. This gave N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-fluoropyridine-2-carboxamide, which was reacted with 2 equiv. of tert-butyl 3-aminoazetidine-1-carboxylate and N-ethyl-N-isopropylpropane-2-amine in NMP at 100°C. The crude product obtained was then reacted with trifluoroacetic acid in dichloromethane. Purification by preparative HPLC gave 14 mg of the exemplary compound.</p>	0.54
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Table 4: Examples 78 – 83

The exemplary compounds were prepared from 2-(5-amino-2H-indazol-2-yl)-1-(4-methylpiperazin-1-yl)ethanone and the starting material indicated in the table.

Example	Structure and name	Starting material and notes	LC-MS retention time [min]
78	 <p>N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(pyridin-3-yl)-1,3-thiazole-4-carboxamide</p>	2-(pyridin-3-yl)-1,3-thiazole-4-carboxylic acid	0.55

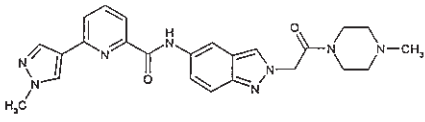
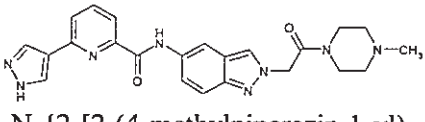
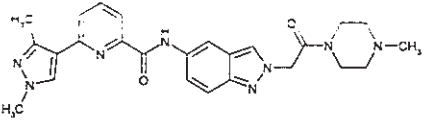
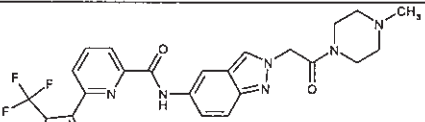
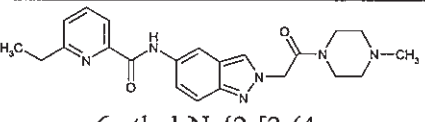
79	 <p>N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.60
80	 <p>N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	6-(1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.54
81	 <p>6-(1,3-dimethyl-1H-pyrazol-4-yl)-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.64
82	 <p>N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine-2-carboxamide</p>	6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid	0.66
83	 <p>6-ethyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	6-ethylpyridine-2-carboxylic acid	0.66

Table 5: Examples 84 – 85

The exemplary compounds were prepared from 2-(5-amino-2H-indazol-2-yl)-1-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethanone (Intermediate 6-13) and the starting material indicated in the table.

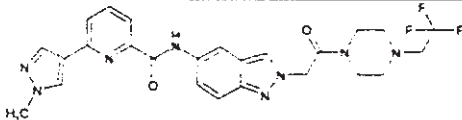
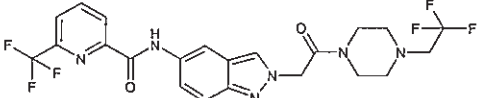
Example	Structure and name	Starting material and notes	LC-MS retention time [min]
84	 <p>6-(1-methyl-1H-pyrazol-4-yl)-N-(2-{2-oxo-2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide</p>	6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.97
85	 <p>N-(2-{2-oxo-2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	6-(trifluoromethyl)pyridine-2-carboxylic acid	1.10

Table 6: Example 86

The exemplary compounds were prepared from 4-[(5-amino-2H-indazol-2-yl)acetyl]-1-ethylpiperazin-2-one and the starting material indicated in the table.

Example	Name and structure	Starting material and notes	LC-MS retention time
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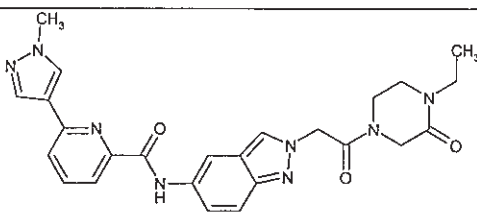
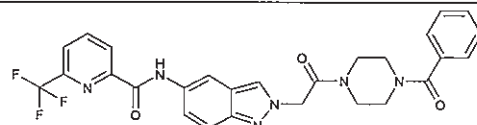
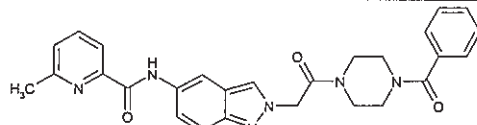
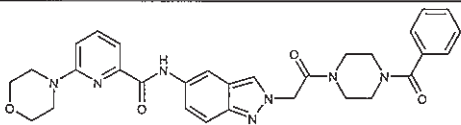
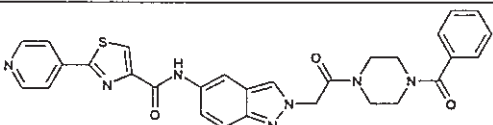
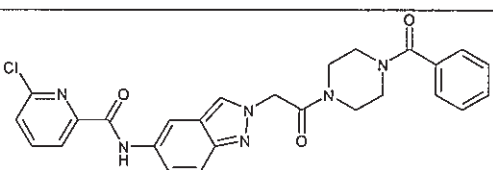
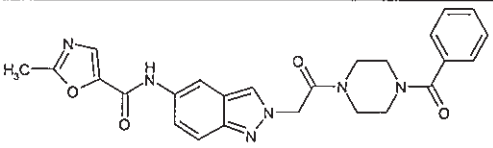
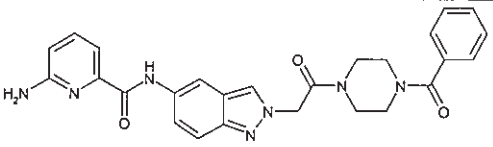
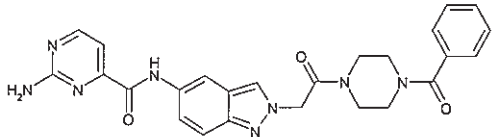
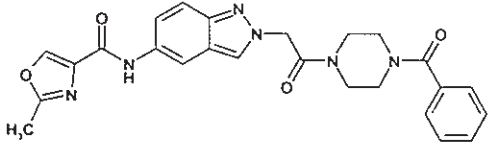
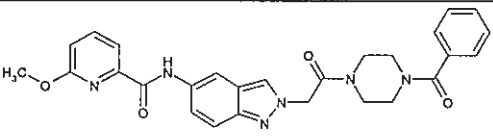
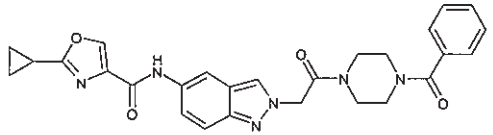
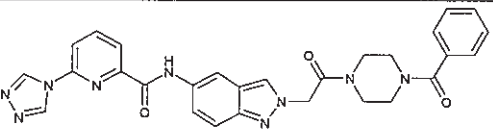
			on time [min]
86	 <p>N-{2-[2-(4-ethyl-3-oxopiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.79

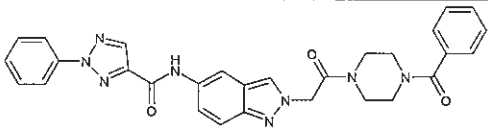
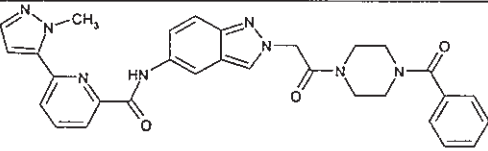
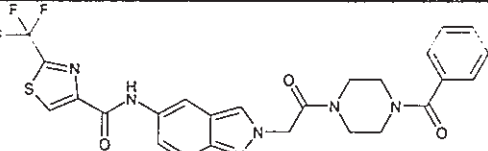
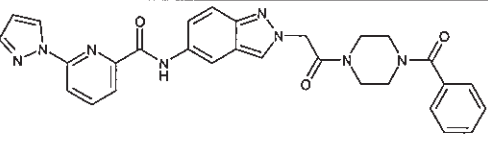
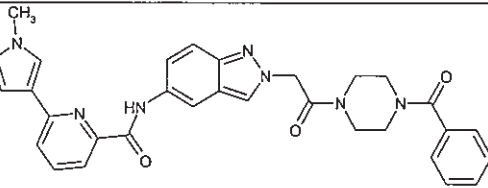
Table 7: Examples 87 – 121

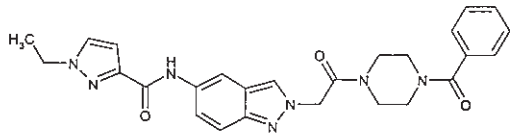
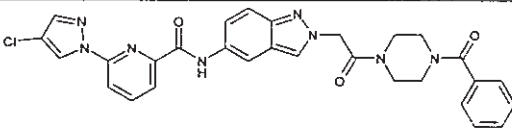
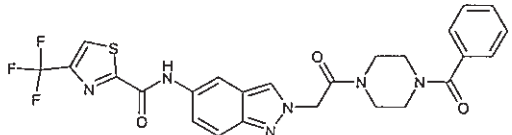
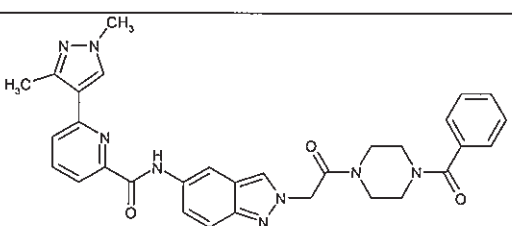
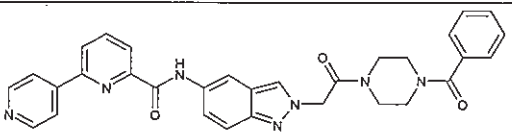
The exemplary compounds were prepared from 2-(5-amino-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)ethanone (Intermediate 6-11) and the starting material indicated in the table.

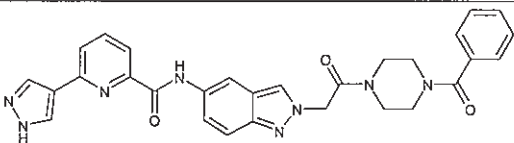
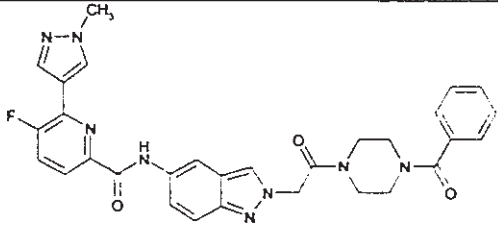
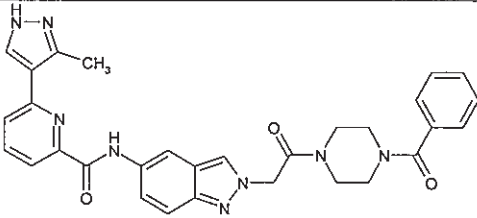
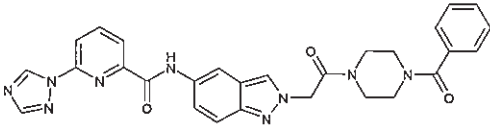
Example	Name and structure	Starting material and notes	LC-MS retention time [min]
87	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	6-(trifluoromethyl)pyridine-2-carboxylic acid	1.02
88	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide</p>	6-methylpyridine-2-carboxylic acid	0.93

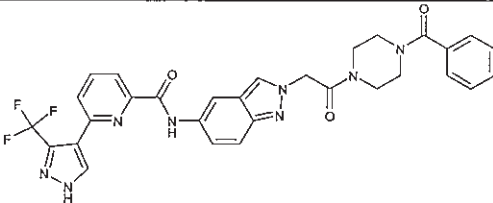
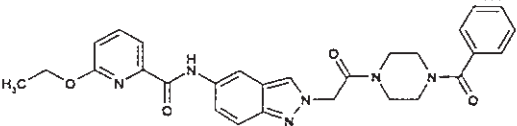
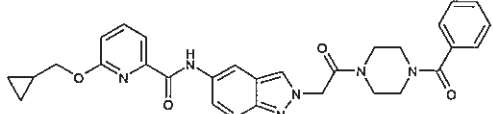
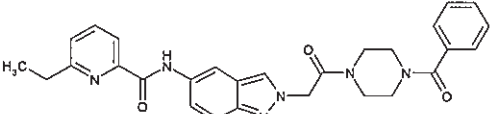
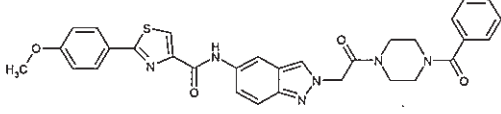
	methypyridine-2-carboxamide		
89	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide</p>	6-(morpholin-4-yl)pyridine-2-carboxylic acid	0.94
90	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(pyridin-4-yl)-1,3-thiazole-4-carboxamide</p>	2-(pyridin-4-yl)-1,3-thiazole-4-carboxylic acid	0.79
91	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-chloropyridine-2-carboxamide</p>	6-chloropyridine-2-carboxylic acid	0.96
92	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-methyl-1,3-oxazole-5-carboxamide</p>	2-methyl-1,3-oxazol-5-carboxylic acid	0.77
93	 <p>6-amino-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	6-aminopyridine-2-carboxylic acid	0.69

94	 <p>2-amino-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyrimidin-4-carboxamide</p>	2-aminopyrimidin-4-carboxylic acid	0.71
95	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-methyl-1,3-oxazole-4-carboxamide</p>	2-methyl-1,3-oxazole-4-carboxylic acid	0.77
96	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methoxypyridine-2-carboxamide</p>	6-methoxypyridine-2-carboxylic acid	0.96
97	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-cyclopropyl-1,3-oxazole-4-carboxamide</p>	2-cyclopropyl-1,3-oxazole-4-carboxylic acid	0.89
98	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(4H-1,2,4-triazol-4-yl)pyridine-2-carboxamide</p>	6-(4H-1,2,4-triazol-4-yl)pyridine-2-carboxylic acid	0.74

99	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-phenyl-2H-1,2,3-triazole-4-carboxamide</p>	2-phenyl-2H-1,2,3-triazole-4-carboxylic acid	1.04
100	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-5-yl)pyridine-2-carboxamide</p>	6-(1-methyl-1H-pyrazol-5-yl)pyridine-2-carboxylic acid	0.93
101	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(trifluoromethyl)-1,3-thiazole-4-carboxamide</p>	2-(trifluoromethyl)-1,3-thiazole-4-carboxylic acid	0.99
102	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-pyrazol-1-yl)pyridine-2-carboxamide</p>	6-(1H-pyrazol-1-yl)pyridine-2-carboxylic acid	0.97
103	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.91

104	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1-ethyl-1H-pyrazole-3-carboxamide</p>	1-ethyl-1H-pyrazol-3-carboxylic acid	0.81
105	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(4-chloro-1H-pyrazol-1-yl)pyridine-2-carboxamide</p>	6-(4-chloro-1H-pyrazol-1-yl)pyridine-2-carboxylic acid	1.11
106	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-4-(trifluoromethyl)-1,3-thiazole-2-carboxamide</p>	4-(trifluoromethyl)-1,3-thiazol-2-carboxylic acid	1.02
107	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.95
108	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,4'-bipyridine-6-carboxylic acid</p>	2,4'-bipyridine-6-carboxylic acid	0.73

	oxoethyl]-2H-indazol-5-yl}-2,4'-bipyridine-6-carboxamide		
109	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	6-(1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.84
110	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.96
111	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(3-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	6-(3-methyl-1H-pyrazol-4-yl)pyridine-2-carboxylic acid	0.88
112	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-1,2,4-triazol-1-yl)pyridine-2-carboxamide</p>	6-(1H-1,2,4-triazol-1-yl)pyridine-2-carboxylic acid	0.85

113	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine-2-carboxamide</p>	6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine-2-carboxylic acid	0.97
114	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-ethoxypyridine-2-carboxamide</p>	6-ethoxypyridine-2-carboxylic acid	1.04
115	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(cyclopropylmethoxy)pyridine-2-carboxamide</p>	6-(cyclopropylmethoxy)pyridine-2-carboxylic acid	1.11
116	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-ethylpyridine-2-carboxamide</p>	6-ethylpyridine-2-carboxylic acid	1.03
117	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(4-methoxyphenyl)-1,3-thiazole-4-</p>	2-(4-methoxyphenyl)-1,3-thiazole-4-carboxylic acid	1.12

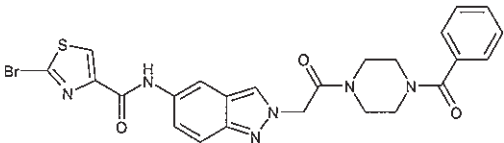
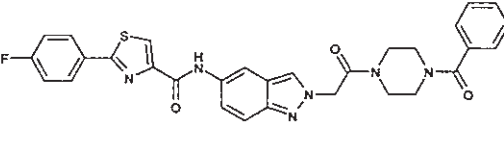
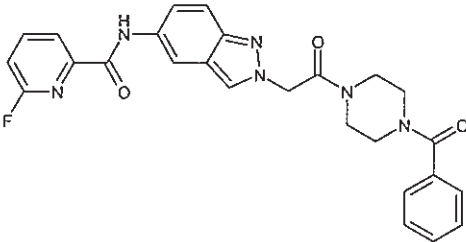
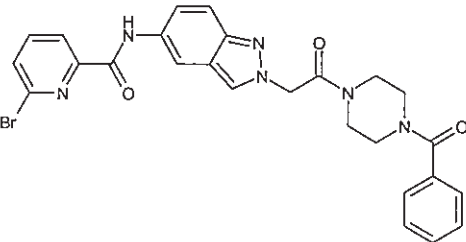
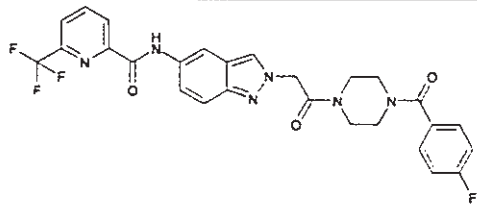
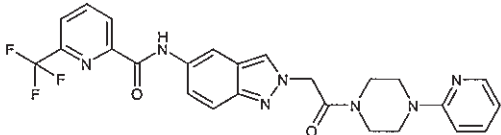
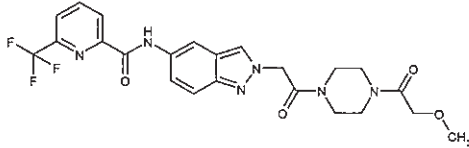
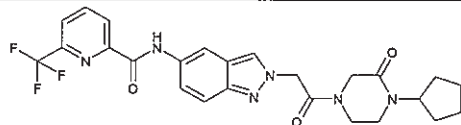
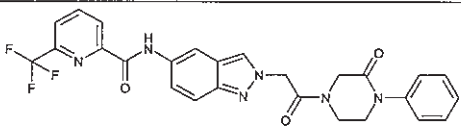
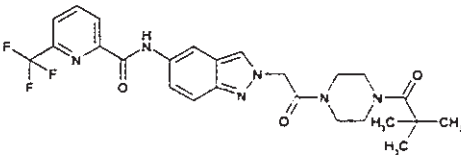
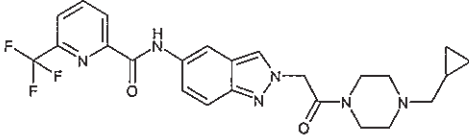
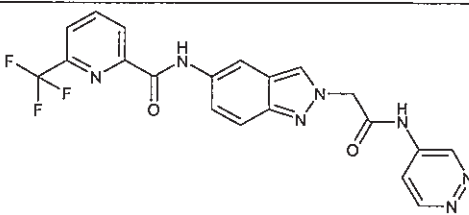
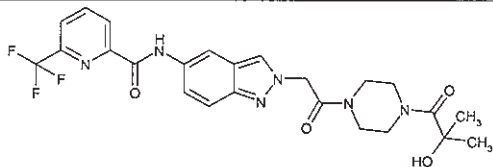
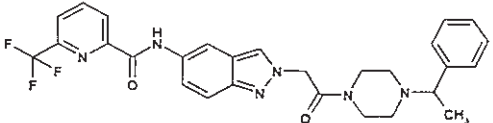
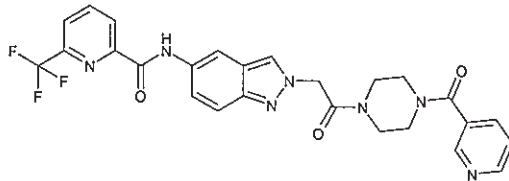
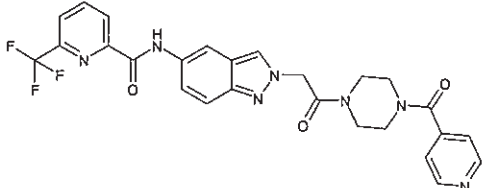
	carboxamide		
118	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-bromo-1,3-thiazole-4-carboxamide</p>	2-bromo-1,3-thiazole-4-carboxylic acid	0.93
119	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(4-fluorophenyl)-1,3-thiazole-4-carboxamide</p>	2-(4-fluorophenyl)-1,3-thiazole-4-carboxylic acid	1.13
120	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-fluoropyridine-2-carboxamide</p>	6-fluoropyridine-2-carboxylic acid	0.89
121	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-bromopyridine-2-carboxamide</p>	6-bromopyridine-2-carboxylic acid	0.98

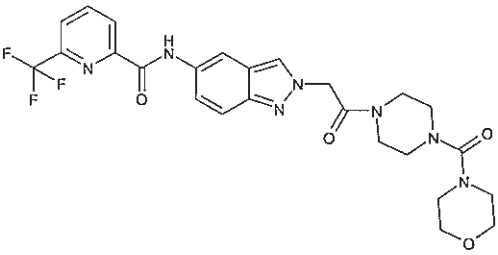
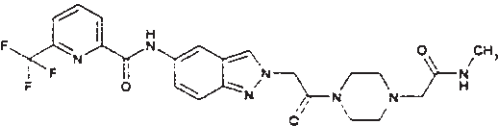
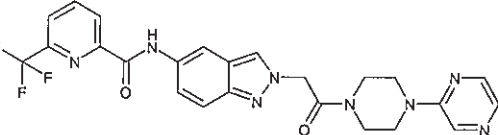
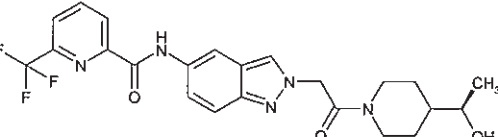
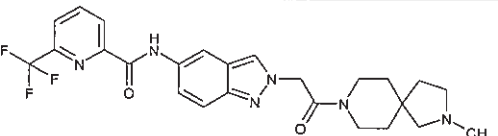
Table 8: Examples 122 – 200

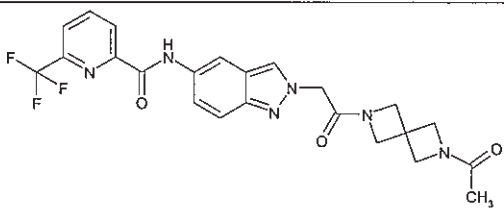
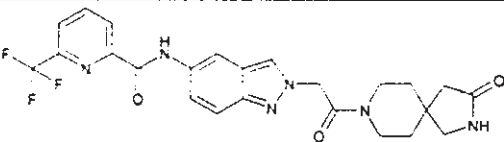
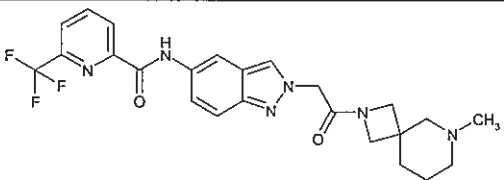
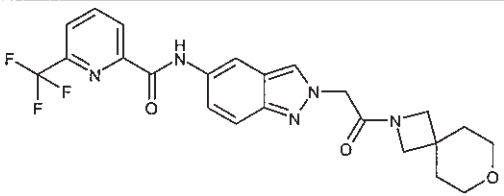
The exemplary compounds were prepared from [5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid (Intermediate 9-14) and the starting material indicated in the table.

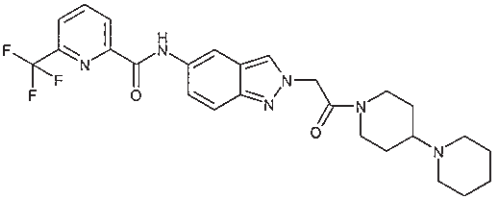
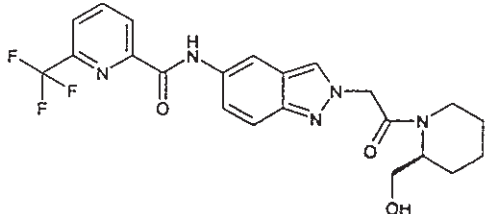
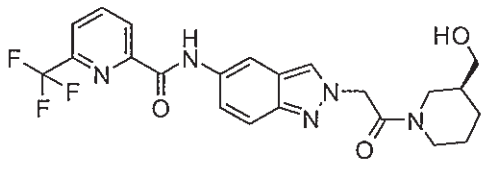
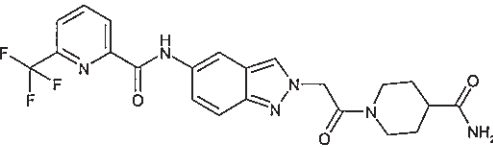
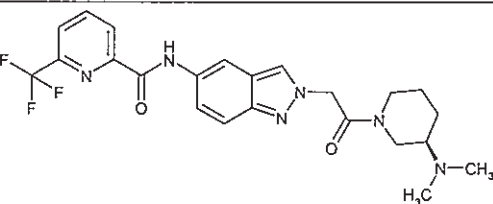
Example	Structure and name	Starting material and notes	LC-MS retention time [min]
122	 <p>N-(2-{2-[4-(4-fluorobenzoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	(4-fluorophenyl)(piperazin-1-yl)methanone	1.05
123	 <p>N-(2-{2-oxo-2-[4-(pyridin-2-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(pyridin-2-yl)piperazine	0.75
124	 <p>N-(2-{2-[4-(methoxyacetyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-methoxy-1-(piperazin-1-yl)ethanone	0.86
125	 <p>N-{2-[2-(4-cyclopentyl-3-oxopiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-cyclopentylpiperazin-2-one	1.03

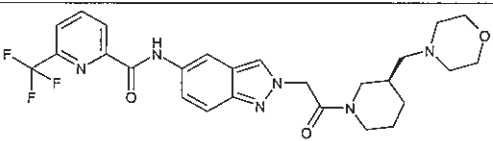
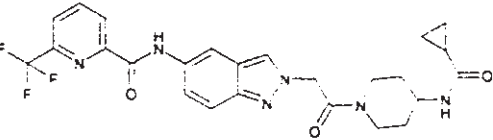
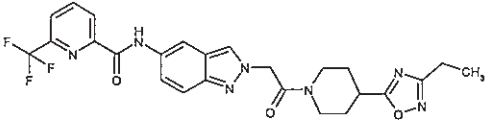
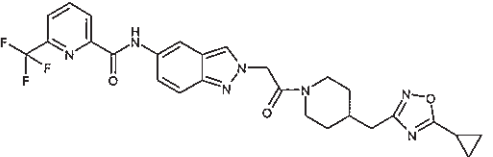
	yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide		
126	 <p>N-{2-[2-oxo-2-(3-oxo-4-phenylpiperazin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-phenylpiperazin-2-one	1.01
127	 <p>N-(2-{2-[4-(2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2,2-dimethyl-1-(piperazin-1-yl)propan-1-one	1.03
128	 <p>N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(cyclopropylmethyl)piperazine	0.70
129	 <p>N-{2-[2-oxo-2-(pyridazin-4-ylamino)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	pyridazine-4-amin	0.86

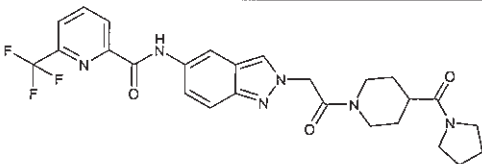
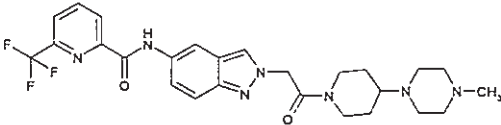
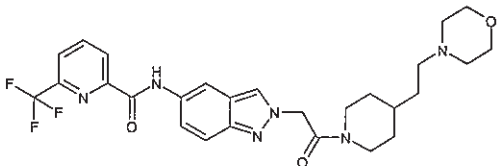
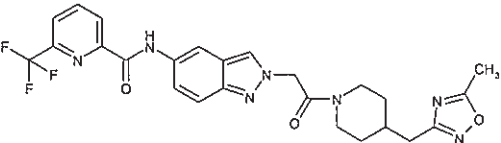
130	 <p>N-(2-{2-[4-(2-hydroxy-2-methylpropanoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-hydroxy-2-methyl-1-(piperazin-1-yl)propan-1-one	0.89
131	 <p>N-(2-{2-oxo-2-[4-(1-phenylethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(1-phenylethyl)piperazine	0.79
132	 <p>N-(2-{2-oxo-2-[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	piperazin-1-yl(pyridin-3-yl)methanone	0.86
133	 <p>N-{2-[2-(4-isonicotinoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	piperazin-1-yl(pyridin-4-yl)methanone	0.83

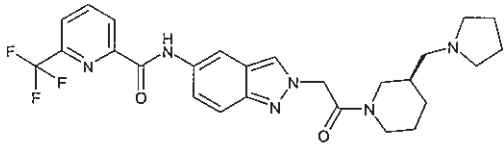
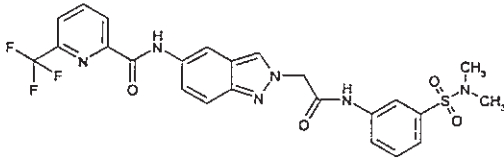
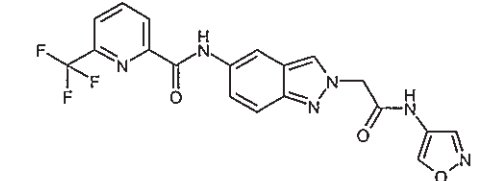
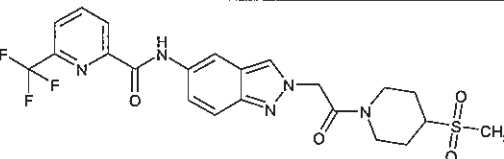
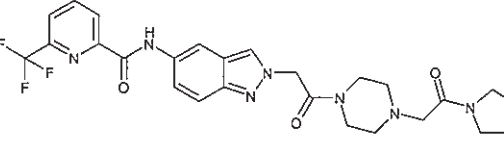
134	 <p>N-(2-{2-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	morpholin-4-yl(piperazin-1-yl)methanone	0.90
135	 <p>N-[2-(2-{4-[2-(methylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	N-methyl-2-(piperazin-1-yl)acetamide	0.69
136	 <p>N-(2-{2-oxo-2-[4-(pyrazin-2-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-(piperazin-1-yl)pyrazine	0.97
137	 <p>N-(2-{2-[4-(1-hydroxyethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	(1R)-1-(piperidin-4-yl)ethanol	0.92
138	 <p>N-{2-[2-(2-methyl-2,8-diazaspiro[4.5]dec-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-methyl-2,8-diazaspiro[4.5]decane	0.69

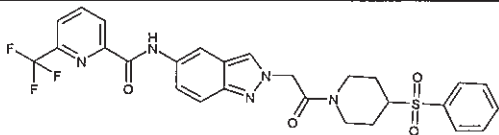
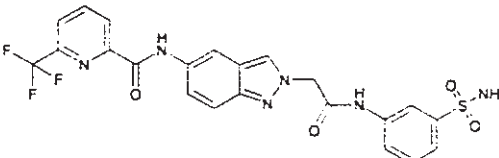
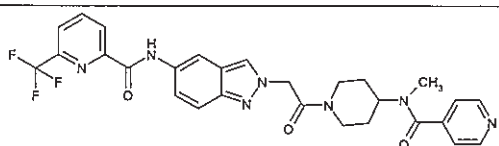
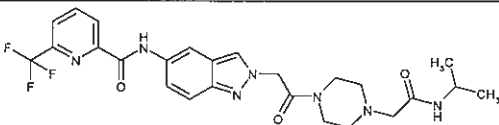
	8-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide		
139	 <p>N-{2-[2-(6-acetyl-2,6-diazaspiro[3.3]hept-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(2,6-diazaspiro[3.3]hept-2-yl)ethanone	0.84
140	 <p>N-{2-[2-oxo-2-(3-oxo-2,8-diazaspiro[4.5]dec-8-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2,8-diazaspiro[4.5]decan-3-one	0.85
141	 <p>N-{2-[2-(6-methyl-2,6-diazaspiro[3.5]non-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	6-methyl-2,6-diazaspiro[3.5]nonane	0.67
142	 <p>N-{2-[2-(7-oxa-2-azaspiro[3.5]non-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	7-oxa-2-azaspiro[3.5]nonane	0.94

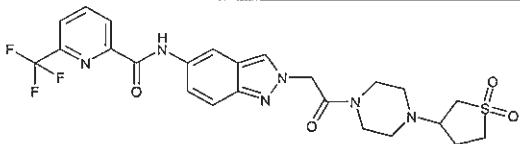
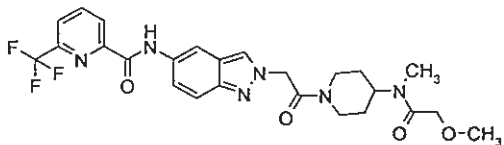
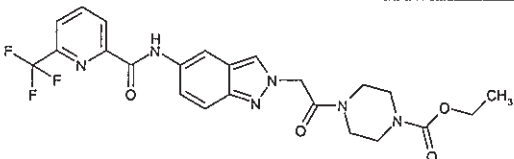
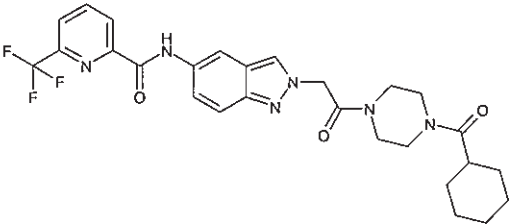
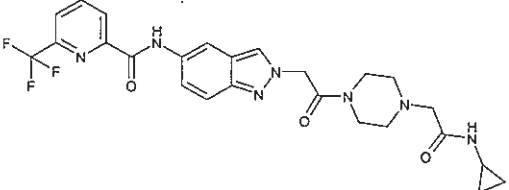
143	 <p>N-{2-[2-(1,4'-bipiperidin-1'-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1,4'-bipiperidine	0.71
144	 <p>N-(2-{2-[2-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	(2S)-piperidin-2-ylmethanol	0.94
145	 <p>N-(2-{2-[3-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	(3S)-piperidin-3-ylmethanol	0.91
146	 <p>N-{2-[2-(4-carbamoylpiperidin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	piperidine-4-carboxamide	0.82
147	 <p>N-(2-{2-[3-(dimethylamino)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	(3R)-N,N-dimethylpiperidine-3-amine	0.68

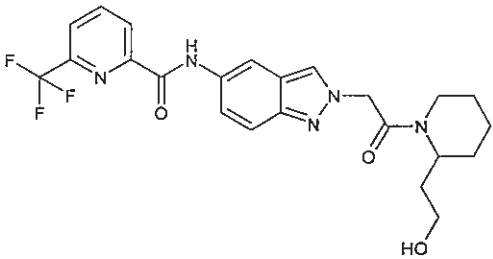
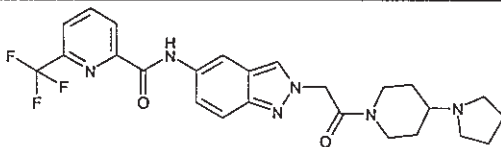
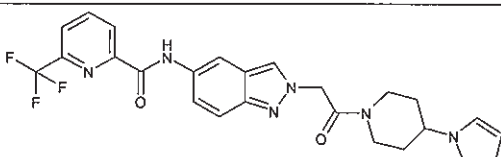
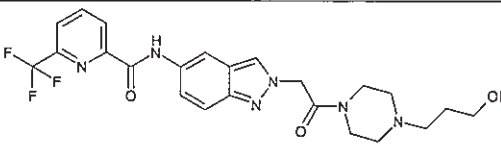
	2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide		
148	 <p>N-(2-{2-[3-(morpholin-4-ylmethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-[(3S)-piperidin-3-ylmethyl]morpholine	0.71
149	 <p>N-[2-(2-{4-[(cyclopropylcarbonyl)amino]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	N-(piperidin-4-yl)cyclopropanecarboxamide	0.94
150	 <p>N-(2-{2-[4-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidine	1.08
151	 <p>N-[2-(2-{4-[(5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-[(5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl]piperidine	1.12

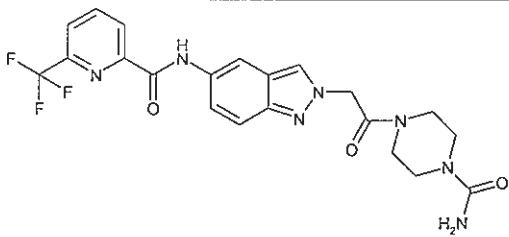
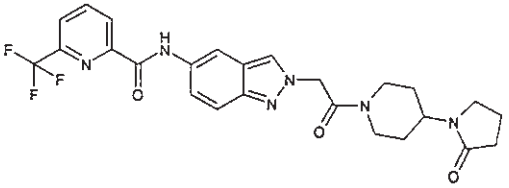
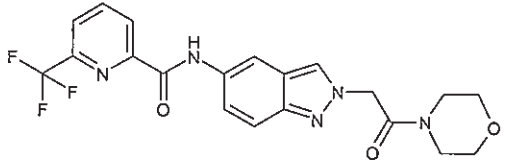
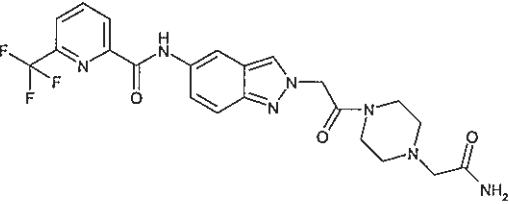
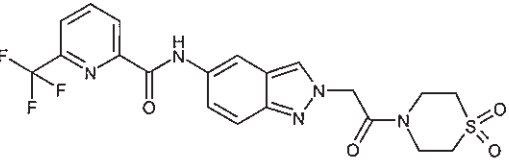
152	 <p>N-(2-{2-oxo-2-[4-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	piperidin-4-yl(pyrrolidin-1-yl)methanone	0.96
153	 <p>N-(2-{2-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-methyl-4-(piperidin-4-yl)piperazine	0.64
154	 <p>N-[2-(2-{4-[2-(morpholin-4-yl)ethyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-[2-(piperidin-4-yl)ethyl]morpholine	0.71
155	 <p>N-[2-(2-{4-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]piperidine	1.03
156		(3S)-3-(pyrrolidin-1-ylmethyl)piperidine	0.72

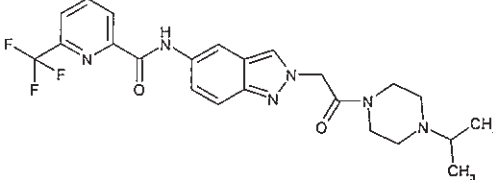
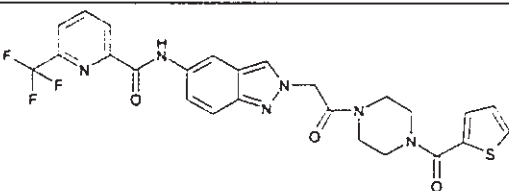
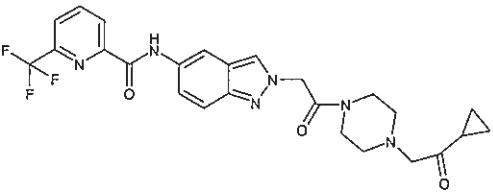
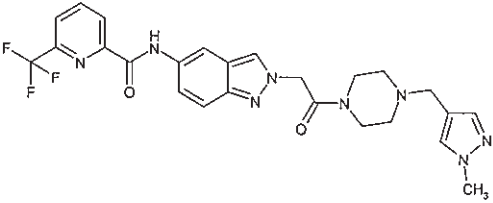
	 <p>N-(2-{2-oxo-2-[3-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>		
157	 <p>N-{2-(2-{[3-(dimethylsulphamoyl)phenyl]amino}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	3-amino-N,N-dimethylbenzenesulphonamide	1.11
158	 <p>N-{2-[2-(1,2-oxazol-4-ylamino)-2-oxoethyl]-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1,2-oxazole-4-amine	0.97
159	 <p>N-(2-{2-[4-(methylsulphonyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-(methylsulphonyl)piperidine	0.89
160	 <p>N-[2-(2-oxo-2-{4-[2-oxo-2-(pyrrolidin-1-yl)]piperazin-1-yl}ethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-(piperazin-1-yl)-1-(pyrrolidin-1-yl)ethanone	0.71

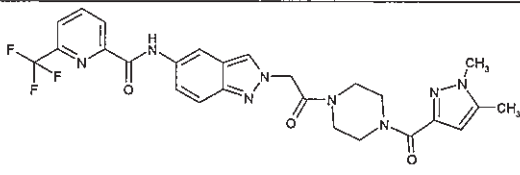
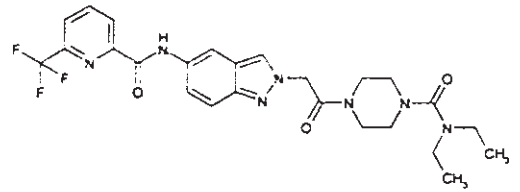
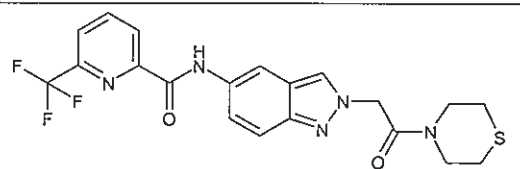
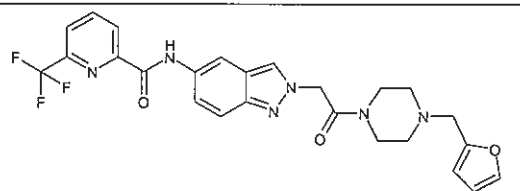
	yl)ethyl]piperazin-1-yl}ethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide		
161	 <p>N-(2-{2-oxo-2-[4-(phenylsulphonyl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-(phenylsulphonyl)piperidine	1.08
162	 <p>N-(2-{2-oxo-2-[(3-sulphamoylphenyl)amino]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	3-aminobenzenesulphonamide	0.96
163	 <p>N-[2-(2-{4-[isonicotinoyl(methyl)amino]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	N-methyl-N-(piperidin-4-yl)isonicotinamide	0.85
164	 <p>N-[2-(2-{4-[2-(isopropylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	N-isopropyl-2-(piperazin-1-yl)acetamide	0.74

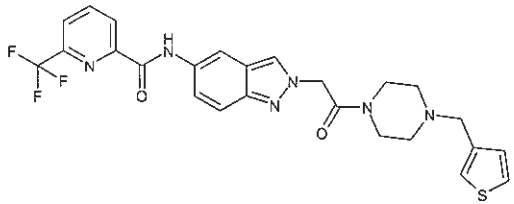
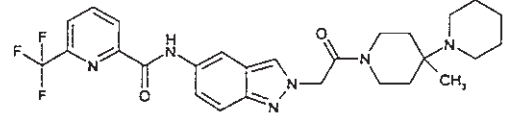
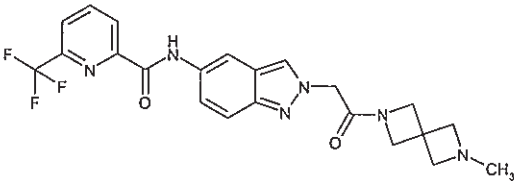
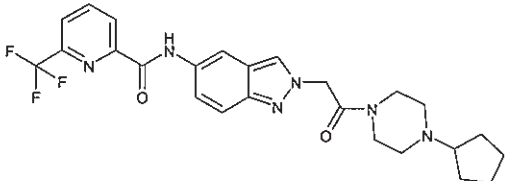
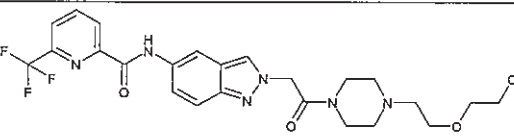
165	 <p>N-(2-{2-[4-(1,1-dioxidotetrahydrothiophen-3-yl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(1,1-dioxidotetrahydrothiophen-3-yl)piperazine	0.82
166	 <p>N-[2-(2-{4-[(methoxyacetyl)(methyl)amino]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-methoxy-N-methyl-N-(piperidin-4-yl)acetamide	0.90
167	 <p>ethyl 4-{[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxylate</p>	ethyl piperazine-1-carboxylate	1.01
168	 <p>N-(2-{2-[4-(cyclohexylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	cyclohexyl(piperazin-1-yl)methanone	1.10
169	 <p>N-cyclopropyl-2-(piperazin-1-yl)acetamide</p>	N-cyclopropyl-2-(piperazin-1-yl)acetamide	0.72

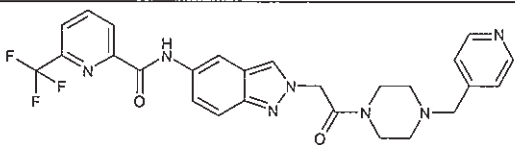
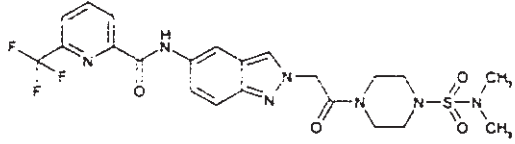
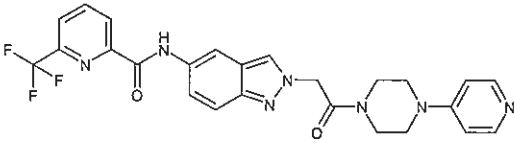
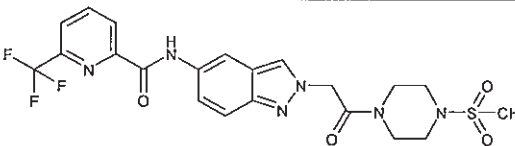
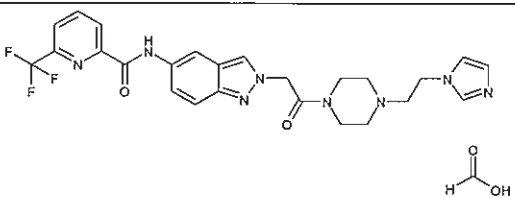
	N-[2-(2-{4-[2-(cyclopropylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide		
170	 <p>N-(2-{2-[2-(2-hydroxyethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-(piperidin-2-yl)ethanol	0.98
171	 <p>N-(2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-(pyrrolidin-1-yl)piperidine	0.69
172	 <p>N-(2-{2-oxo-2-[4-(1H-pyrrol-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-(1H-pyrrol-1-yl)piperidine	1.13
173	 <p>N-(2-{2-[4-(3-hydroxypropyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	3-(piperazin-1-yl)propan-1-ol	0.65

174	 <p>4-{[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxamide</p>	piperazine-1-carboxamide	0.81
175	 <p>N-(2-{2-oxo-2-[4-(2-oxopyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(piperidin-4-yl)pyrrolidin-2-one	0.92
176	 <p>N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	morpholine	0.90
177	 <p>N-(2-{2-[4-(2-amino-2-oxoethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-(piperazin-1-yl)acetamide	0.67
178		thiomorpholine 1,1-dioxide	0.89

	N-{2-[2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide		
179	 <p>N-{2-[2-(4-isopropylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-isopropylpiperazine	0.69
180	 <p>N-(2-{2-oxo-2-[4-(2-thienylcarbonyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	piperazin-1-yl(2-thienyl)methanone	1.01
181	 <p>N-(2-{2-[4-(2-cyclopropyl-2-oxoethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-cyclopropyl-2-(piperazin-1-yl)ethanone	0.72
182	 <p>N-[2-(2-{4-[(1-methyl-1H-pyrazol-4-yl)methyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-[(1-methyl-1H-pyrazol-4-yl)methyl]piperazine	0.68

	indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide		
183	 <p>N-[2-(2-{4-[(1,5-dimethyl-1H-pyrazol-3-yl)carbonyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	(1,5-dimethyl-1H-pyrazol-3-yl)(piperazin-1-yl)methanone	0.95
184	 <p>N,N-diethyl-4-{{5-({6-(trifluoromethyl)pyridin-2-yl}carbonyl}amino)-2H-indazol-2-yl}acetyl}piperazine-1-carboxamide</p>	N,N-diethylpiperazine-1-carboxamide	1.04
185	 <p>N-{2-[2-oxo-2-(thiomorpholin-4-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	thiomorpholine	1.01
186	 <p>N-(2-{2-[4-(2-furylmethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(2-furylmethyl)piperazine	0.74

187	 <p>N-(2-{2-oxo-2-[4-(3-thienylmethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(3-thienylmethyl)piperazine	0.76
188	 <p>N-{2-[2-(4'-methyl-1,4'-bipiperidin-1'-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4'-methyl-1,4'-bipiperidine	0.72
189	 <p>N-{2-[2-(6-methyl-2,6-diazaspiro[3.3]hept-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-methyl-2,6-diazaspiro[3.3]heptane	0.65
190	 <p>N-{2-[2-(4-cyclopentylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-cyclopentylpiperazine	0.72
191	 <p>N-[2-(2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-[2-(piperazin-1-yl)ethoxy]ethanol	0.66

	oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide		
192	 <p>N-(2-{2-oxo-2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(pyridin-4-ylmethyl)piperazine	0.70
193	 <p>N-(2-{2-[4-(dimethylsulphamoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	N,N-dimethylpiperazine-1-sulphonamide	1.01
194	 <p>N-(2-{2-oxo-2-[4-(pyridin-4-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(pyridin-4-yl)piperazine	0.70
195	 <p>N-(2-{2-[4-(methylsulphonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(methylsulphonyl)piperazine	0.92
196	 <p>N-(2-{2-[4-(1H-imidazol-1-yl)ethyl]piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p> <p>H-COOH</p>	1-[2-(1H-imidazol-1-yl)ethyl]piperazine	0.64

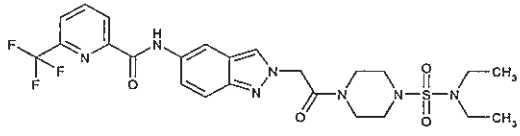
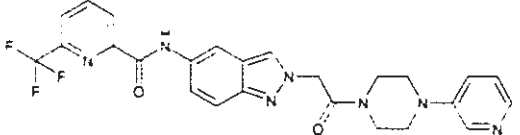
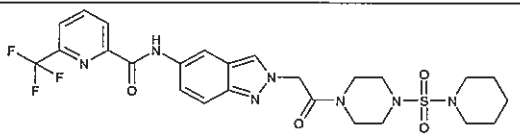
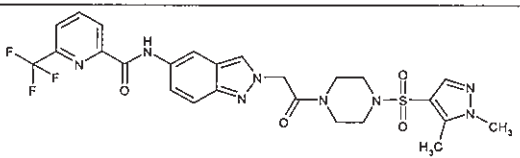
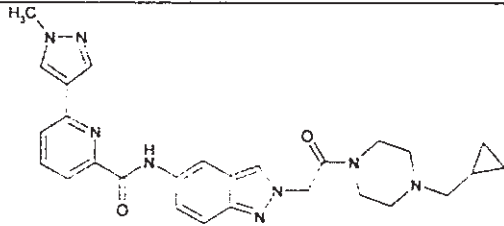
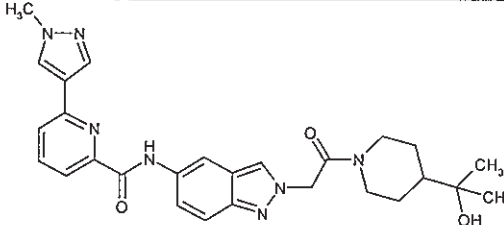
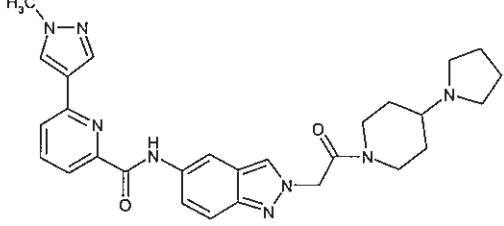
	formic acid N-[2-(2-{4-[2-(1H-imidazol-1-yl)ethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (1:1)		
197	 <p>N-(2-{2-[4-(diethylsulphamoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	N,N-diethylpiperazine-1-sulphonamide	1.11
198	 <p>N-(2-{2-oxo-2-[4-(pyridin-3-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(pyridin-3-yl)piperazine	0.72
199	 <p>N-(2-{2-oxo-2-[4-(piperidin-1-ylsulphonyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(piperidin-1-ylsulphonyl)piperazine	1.14
200	 <p>N-[2-(2-{4-[(1,5-dimethyl-1H-pyrazol-4-yl)sulphonyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-[(1,5-dimethyl-1H-pyrazol-4-yl)sulphonyl]piperazine	1.00

Table 9: Examples 201 – 205

The exemplary compounds were prepared from [5-({[6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid (Intermediate 9-10) and the starting material indicated in the table.

5

Example	Name and structure	Starting material and notes	LC-MS retention time [min]
201	 <p>N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	1-(cyclopropylmethyl)piperazine	0.64
202	 <p>N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	2-(piperidin-4-yl)propan-2-ol	0.85
203	 <p>6-(1-methyl-1H-pyrazol-4-yl)-N-(2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide</p>	4-(pyrrolidin-1-yl)piperidine	0.63

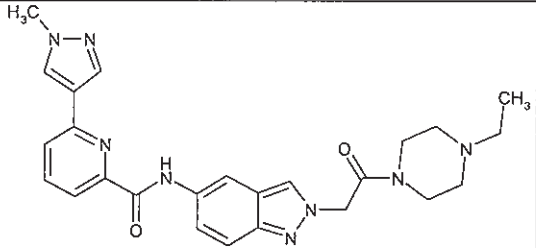
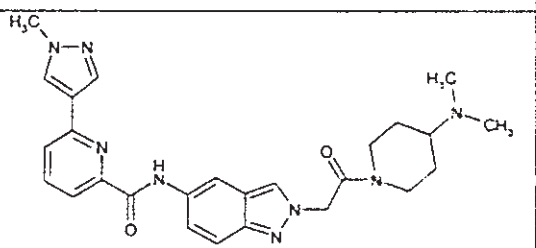
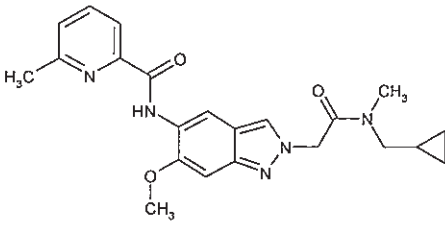
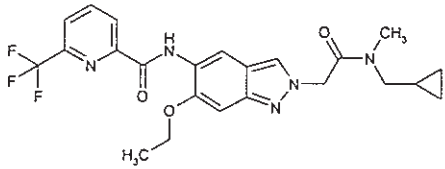
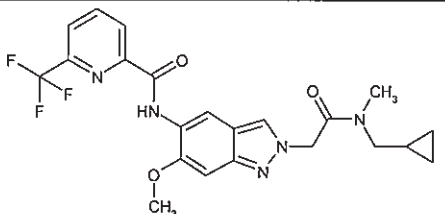
	2H-indazol-5-yl)pyridine-2-carboxamide		
204	 <p>N-{2-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	1-ethylpiperazine	0.61
205	 <p>N-(2-{2-[4-(dimethylamino)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	N,N-dimethylpiperidine-4-amine	0.61

Table 10: Examples 206 – 208

The exemplary compounds were prepared from the intermediates indicated in the table.

5

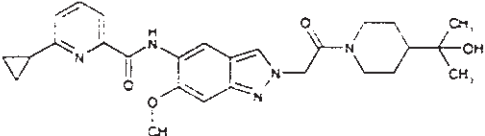
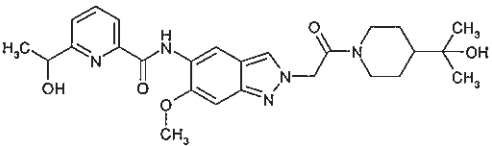
Exempl e	Name and structure	Starting materials and notes	LC- MS retenti on time [min]
206	 <p>N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide</p>	<p>The exemplary compound was prepared from 2-(5-amino-6-methoxy-2H-indazol-2-yl)-N-methylacetamide and 6-methylpyridine-2-carboxylic acid.</p> <p>¹H-NMR (300 MHz, DMSO-d₆): δ =</p>	1.07

	-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide	0.17 - 0.57 (m, 4H), 0.91 - 1.11 (m, 1H), 2.61 (s), 2.91 (s), 3.12 (s), 3.19 (d), 3. (s, 3H), 5.33 - 5.40 (m, 2H), 7.09 (s, 1H), 7.55 (dd, 1H), 7.93 - 8.02 (m, 2H), 8.18 - 8.24 (m, 1H), 8.71 (s, 1H), 10.71 (s, 1H).	
207	 <p>N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-ethoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	<p>The exemplary compound was prepared from 105 mg (0.26 mmol) of [6-ethoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid and 33 mg (1.5 eq.) of 1-cyclopropyl-N-methylmethanamine. This gave 87 mg of the exemplary compound.</p> <p>¹H-NMR (300 MHz, DMSO-d₆): δ = 0.17 - 0.57 (m, 4H), 0.88 - 1.12 (m, 1H), 1.49 (t, 3H), 2.91 (s, 1H), 3.09 - 3.24 (m, 3H), 3.34 (br. s., 1H), 4.20 (q, 2H), 5.32 - 5.40 (m, 2H), 7.08 (s, 1H), 8.17 - 8.26 (m, 2H), 8.36 - 8.48 (m, 2H), 8.71 (s, 1H), 10.7 (s, 1H).</p>	1.24
208	 <p>N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	<p>The exemplary compound was prepared from 2-(5-amino-6-methoxy-2H-indazol-2-yl)-N-(cyclopropylmethyl)-N-methylacetamide and 6-(trifluoromethyl)pyridine-2-carboxylic acid.</p> <p>¹H-NMR (300 MHz, DMSO-d₆): δ = 0.16 - 0.59 (m, 4H), 0.88 - 1.14 (m, 1H), 2.91 (s, 1H), 3.10 - 3.23 (m, 3H), 3.98 (s, 3H), 5.33 - 5.42 (m, 2H), 7.11 (s, 1H), 8.17 - 8.28 (m, 2H), 8.35 - 8.49 (m, 2H), 8.70 (s, 1H), 10.50 (s, 1H).</p>	1.16

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Table 11: Examples 209 – 210

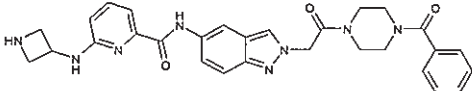
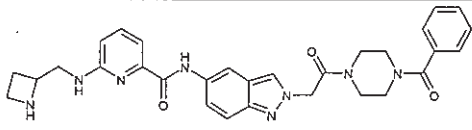
The exemplary compounds (Ex.) were prepared from 2-(5-amino-6-methoxy-2H-indazol-2-yl)-1-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]ethanone (Intermediate 6-5).

Ex.	Name and structure	Starting materials and notes	LC-MS retention time [min]
209	 <p>6-cyclopropyl-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide</p>	<p>prepared from 100 mg of 2-(5-amino-6-methoxy-2H-indazol-2-yl)-1-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]ethanone and 6-cyclopropylpyridine-2-carboxylic acid. ¹H-NMR (400 MHz, DMSO-d₆): δ = 0.99 - 1.14 (m, 11H), 1.14 - 1.28 (m, 1H), 1.38 - 1.49 (m, 1H), 1.74 (t, 2H), 2.21 - 2.30 (m, 1H), 2.98 (t, 1H), 3.97 - 4.08 (m, 4H), 4.15 (s, 1H), 4.41 (d, 1H), 5.26 - 5.43 (m, 2H), 7.08 (s, 1H), 7.58 - 7.64 (m, 1H), 7.87 - 7.96 (m, 2H), 8.17 - 8.23 (m, 1H), 8.65 (s, 1H), 10.80 (s, 1H).</p>	1.08
210	 <p>6-(1-hydroxyethyl)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide</p>	<p>prepared from 150 mg of 2-(5-amino-6-methoxy-2H-indazol-2-yl)-1-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]ethanone and 133 mg of potassium 6-(1-hydroxyethyl)pyridine-2-carboxylate (Intermediate 19-1). ¹H-NMR (400 MHz, DMSO-d₆): δ = 0.99 - 1.13 (m, 7H), 1.15 - 1.29 (m, 1H), 1.34 - 1.48 (m, 1H), 1.51 (d, 3H), 1.74 (t, 2H), 2.99 (t, 1H), 3.95 - 4.07 (m, 4H), 4.16 (s, 1H), 4.41 (d, 1H),</p>	0.82

		4.81 - 4.90 (m, 1H), 5.28 - 5.43 (m, 2H), 5.58 (d, 1H), 7.08 (s, 1H), 7.79 (dd, 1H), 8.01 - 8.10 (m, 2H), 8.20 (s, 1H), 8.67 (s, 1H), 10.78 (s, 1H).	
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Table 12: Examples 211 – 213

The exemplary compounds were prepared from 2-(5-amino-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)ethanone (Intermediate 6-11).

Ex.	Name and structure	Preparation and notes	LC-MS retention time [min]
211	 <p>6-(azetidin-3-ylamino)-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	<p>96 mg of 2-(5-amino-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)ethanone and 202 mg of 6-{{1-(tert-butoxycarbonyl)azetidin-3-yl}amino}pyridine-2-carboxylic acid (Intermediate 19-12) were reacted with EDC, HOBt and triethylamine. Aqueous work-up gave 252 mg of tert-butyl 3-{{[6-({2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbonyl)pyridin-2-yl]amino}azetidine-1-carboxylate as crude product which was reacted with trifluoroacetic acid in dichloromethane. Purification by HPLC according to Method P2 gave 19 mg of the title compound.</p>	0.60
212	 <p>6-[(azetidin-2-ylmethyl)amino]-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	<p>100 mg of 2-(5-amino-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)ethanone and 265 mg of potassium 6-{{[1-(tert-butoxycarbonyl)azetidin-2-yl]methyl}amino}pyridine-2-carboxylate were reacted with EDC, HOBt and triethylamine. Aqueous work-up gave 252 mg of tert-butyl 3-{{[6-({2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbonyl)pyridin-2-yl]amino}azetidine-1-carboxylate as crude product which was reacted with trifluoroacetic acid in dichloromethane. Purification by HPLC according to Method P2 gave 19 mg of the title compound.</p>	0.61

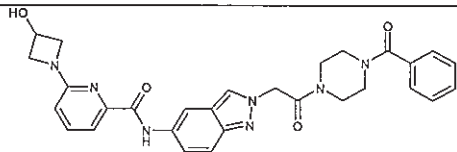
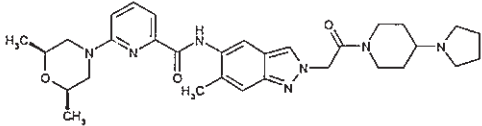
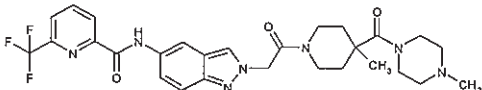
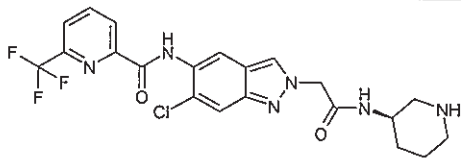
	2H-indazol-5-yl}pyridine-2-carboxamide	yl)methyl}amino)pyridine-2-carboxylate (Intermediate 19-13) were reacted with EDC, HOBT and triethylamine. Aqueous work-up and HPLC gave 93 mg of tert-butyl 2-({[6-({2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}carbonyl)pyridin-2-yl]amino}methyl)azetidine-1-carboxylate which was reacted with trifluoroacetic acid in dichloromethane. HPLC purification gave 50 mg of the title compound. ¹ H-NMR (400 MHz, DMSO-d ₆ , selected signals): δ = 2.20 - 2.42 (m, 2H), 4.37 - 4.49 (m, 1H), 5.48 (br. s., 2H), 6.77 (d, 1H), 7.24 (t, 1H), 7.32 (d, 1H), 7.39 - 7.53 (m, 6H), 7.53 - 7.65 (m, 2H), 8.28 (d, 2H), 10.17 (br. s., 1H).	
213	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(3-hydroxyazetidin-1-yl)pyridine-2-carboxamide</p>	85 mg of N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-chloropyridine-2-carboxamide (Example 91) were reacted with 3 equiv. of azetidin-3-ol hydrochloride (1:1) and 115 μl of N-ethyl-N-isopropylpropane-2-amine in 2 ml NMP at 100°C. Purification by HPLC gave 2 mg of the title compound. ¹ H-NMR (400 MHz, DMSO-d ₆ , selected signals): δ = 3.82 (dd, 2H), 4.30 (t, 2H), 4.58 - 4.66 (m, 1H), 5.49 (br. s., 2H), 5.70 (d, 1H), 6.63 (d, 1H), 7.38 (d, 1H), 7.42 - 7.52 (m), 7.56 - 7.61 (m, 1H), 7.71 (t, 1H), 8.27 (s, 1H), 8.31 (s, 1H), 10.11 (s, 1H).	0.81

Table 13: Examples 214 – 216

Ex.	Name and structure	Preparation and notes	LC-MS retention time [min]
214	 <p>6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide</p>	<p>75 mg of 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]pyridine-2-carboxylic acid (Intermediate 19-14) were reacted with 118 mg of 2-(5-amino-6-methyl-2H-indazol-2-yl)-1-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethanone (Intermediate 6-2).</p> <p>¹H-NMR (400 MHz, DMSO-d₆): δ = 1.18 (d, 6H), 1.21 - 1.48 (m, 2H), 1.67 (br. s., 4H), 1.84 (t, 2H), 2.20 - 2.28 (m, 1H), 2.28 - 2.39 (m, 1H), 2.84 (t, 1H), 3.17 (t), 3.61 - 3.71 (m, 2H), 3.88 (d, 1H), 4.10 (d, 1H), 4.29 (d, 2H), 5.34 - 5.46 (m, 2H), 7.14 (d, 1H), 7.41 - 7.50 (m, 2H), 7.77 (dd, 1H), 8.22 (s, 1H), 8.36 (s, 1H), 10.18 (s, 1H).</p>	0.78
215	 <p>N-[2-(2-{4-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	<p>400 mg of [5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid were reacted with 296 mg of ethyl 4-methylpiperidine-4-carboxylate hydrochloride (1:1) in the presence of EDC, HOBt and triethylamine. This gave 544 mg of ethyl 4-methyl-1-{[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperidine-4-carboxylate as a crude product. Ethanol and THF and 348 mg of lithium hydroxide</p>	0.71

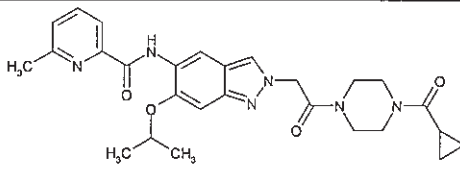
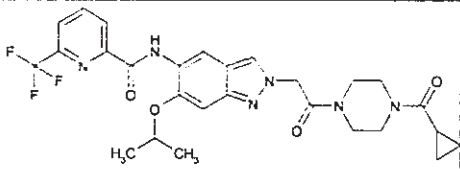
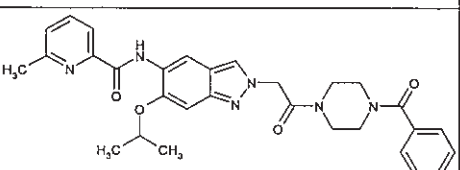
		<p>monohydrate in water were added, and the mixture was stirred overnight and acidified with citric acid solution. Extraction with ethyl acetate and purification by HPLC gave 89 mg of 4-methyl-1-([5-([6-(trifluoromethyl)pyridin-2-yl]carbonyl)amino]-2H-indazol-2-yl]acetyl)piperidine-4-carboxylic acid. 49 mg of this were reacted with 15 mg of 1-methylpiperazine in the presence of EDC, HOBt and triethylamine in THF. Purification by HPLC gave 29 mg of N-[2-(2-{4-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide.</p> <p>¹H-NMR (300 MHz, DMSO-d₆, selected signals): δ = 1.25 (s, 3H), 1.36 - 1.57 (m, 2H), 1.98 - 2.22 (m, 5H), 2.27 (br. s., 4H), 3.13 (t), 3.54 (s), 3.60 - 3.80 (m, 2H), 5.35 - 5.50 (m, 2H), 7.51 - 7.63 (m, 2H), 8.17 (dd, 1H), 8.26 - 8.42 (m, 4H), 10.37 (s, 1H).</p>	
216	 <p>N-(6-chloro-2-{2-oxo-2-[(3R)-piperidin-3-ylamino]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	<p>100 mg of ([6-chloro-5-([6-(trifluoromethyl)pyridin-2-yl]carbonyl)amino]-2H-indazol-2-yl]acetic acid (Intermediate 9-11) were reacted with 65 mg of tert-butyl (3R)-3-aminopiperidine-1-carboxylate in the presence of EDC, HOBt and triethylamine in THF. Addition of water and extraction with ethyl acetate gave, after concentration, 148 mg of tert-butyl (3R)-3-([6-chloro-5-([6-</p>	0.79

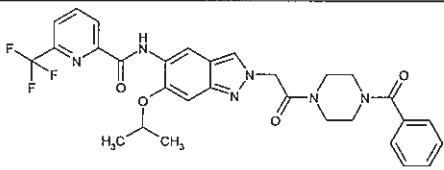
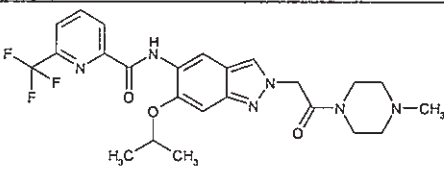
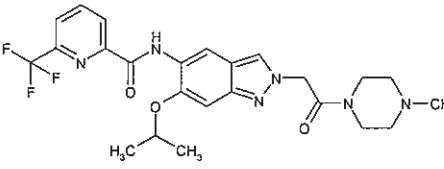
		<p>(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}amino)piperidine-1-carboxylate as a crude product. After addition of dichloromethane and trifluoroacetic acid, the mixture was stirred overnight, concentrated and purified by HPLC. This gave 105 mg of N-(6-chloro-2-{2-oxo-2-[(3R)-piperidin-3-ylamino]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide.</p> <p>¹H-NMR (300 MHz, DMSO-d₆, selected signals): δ = 1.39 - 1.64 (m, 2H), 1.74 - 1.90 (m, 2H), 2.56 - 2.67 (m, 1H), 2.68 - 2.80 (m, 1H), 2.98 - 3.21 (m, superimposed), 3.10 - 3.21 (m, 2H), 5.07 - 5.22 (m, 2H), 7.92 (s, 1H), 8.18 - 8.27 (m, 1H), 8.36 - 8.53 (m, 4H), 8.64 (s, 1H), 10.53 (s, 1H).</p>	
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Table 14: Examples 217 – 222

The exemplary compounds were prepared from [6-isopropoxy-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetic acid (Intermediate 9-16) or (6-isopropoxy-5-{{[6-methylpyridin-2-yl]carbonyl}amino}-2H-indazol-2-yl)acetic acid (Intermediate 9-17) and starting material indicated in the table according to General Procedure 2a.

Ex.	Structure/Name	Prepared from	Yield [%]	¹ H-NMR / LC-MS

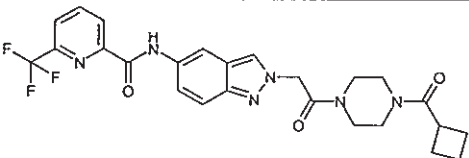
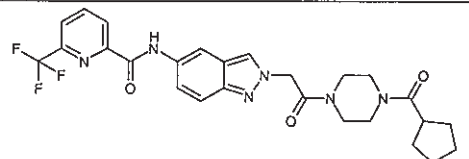
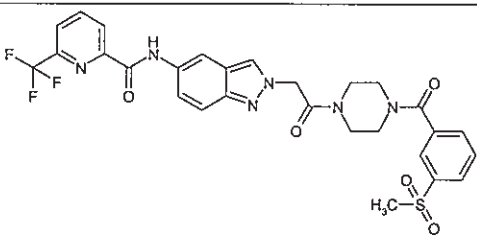
217	 <p>N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-isopropoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide</p>	cyclopropyl (piperazin-1-yl)methanone	91	<p>(300 MHz, DMSO-d₆): δ = 0.67 – 0.82 (m, 4H), 1.45 (d, 6H), 1.92 – 2.09 (m, 1H), 2.62 (s, 3H), 3.38 – 3.86 (m, 8H), 4.76 – 4.90 (m, 1H), 5.42 (s, 2H), 7.13 (s, 1H), 7.53 – 7.60 (m, 1H), 7.93 – 8.02 (m, 2H), 8.21 (s, 1H), 8.72 (s, 1H), 10.99 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.14 min</p> <p>MS (ESIpos): m/z = 505 (M+H)⁺</p>
218	 <p>N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-isopropoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	cyclopropyl (piperazin-1-yl)methanone	75	<p>(300 MHz, DMSO-d₆): δ = 0.67 – 0.82 (m, 4H), 1.41 (d, 6H), 1.92 – 2.08 (m, 1H), 3.38 – 3.88 (m, 8H), 4.79 – 4.93 (m, 1H), 5.43 (s, 2H), 7.16 (s, 1H), 8.18 – 8.27 (m, 2H), 8.36 – 8.51 (m, 2H), 8.75 (s, 1H), 10.75 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.20 min</p> <p>MS (ESIpos): m/z = 559 (M+H)⁺</p>
219	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-isopropoxy-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide</p>	phenyl(piperazin-1-yl)methanone	82	<p>(300 MHz, DMSO-d₆): δ = 1.45 (d, 6H), 2.62 (s, 3H), 3.37 – 3.86 (m, 8H), 4.76 – 4.92 (m, 1H), 5.41 (s, 2H), 7.13 (s, 1H), 7.39 – 7.51 (m, 5H), 7.53 – 7.61 (m, 1H), 7.92 – 8.04 (m, 2H), 8.20 (s, 1H), 8.72 (s, 1H), 10.98 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.21 min</p> <p>MS (ESIpos): m/z = 541</p>

				(M+H) ⁺
220	 <p>N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-isopropoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	phenyl(piperazin-1-yl)methanone	98	<p>(300 MHz, DMSO-d₆): δ = 1.41 (d, 6H), 3.38 – 3.93 (m, 8H), 4.79 – 4.93 (m, 1H), 5.42 (s, 2H), 7.15 (s, 1H), 7.40 – 7.53 (m, 5H), 8.17 – 8.26 (m, 2H), 8.35 – 8.51 (m, 2H), 8.75 (s, 1H), 10.74 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.26 min</p> <p>MS (ESIpos): m/z = 595 (M+H)⁺</p>
221	 <p>N-{6-isopropoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-methylpiperazine	36	<p>(300 MHz, DMSO-d₆): δ = 1.41 (d, 6H), 2.12 – 2.70 (m, 4H), 3.37 – 3.78 (m, 4H), 4.80 – 4.91 (m, 1H), 5.40 (s, 2H), 7.15 (s, 1H), 8.18 – 8.26 (m, 2H), 8.36 – 8.49 (m, 2H), 8.74 (s, 1H), 10.75 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 1.01 min</p> <p>MS (ESIpos): m/z = 505 (M+H)⁺</p>
222	 <p>N-{6-isopropoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide</p>	1-methylpiperazine	63	<p>(300 MHz, DMSO-d₆): δ = 1.45 (d, 6H), 2.18 – 2.70 (m, 4H), 2.62 (s, 3H), 3.34 – 3.87 (m, 4H), 4.77 – 4.89 (m, 1H), 5.39 (s, 2H), 7.12 (s, 1H), 7.53 – 7.58 (m, 1H), 7.93 – 8.02 (m, 2H), 8.20 (s, 1H), 8.72 (s, 1H), 10.98 (s, 1H).</p> <p>UPLC-MS (Method A1): Rt = 0.95 min</p>

				MS (ESIpos): $m/z = 451$ (M+H) ⁺
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Table 15: Examples 223 – 226

The exemplary compounds were prepared from N-{2-[2-oxo-2-(piperazin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 22-1) and the starting material indicated in the table analogously to the examples above via an amide synthesis.

Example	Name and structure	Starting material and notes	LC-MS retention time [min]
223	 <p>N-(2-{2-[4-(cyclobutylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	cyclobutanecarboxylic acid	1.0
224	 <p>N-(2-{2-[4-(cyclopentylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	cyclopentanecarboxylic acid	1.06
225	 <p>N-[2-(2-{4-[3-(methanesulfonyl)phenyl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	3-(methanesulfonyl)benzoic acid	0.95

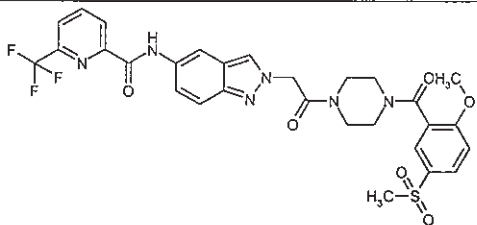
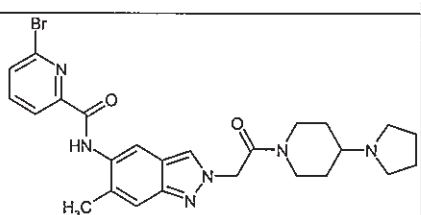
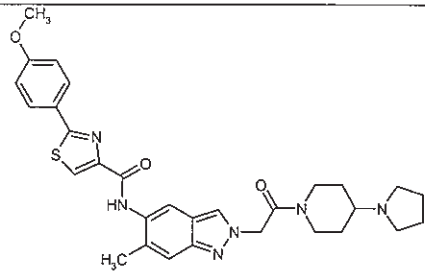
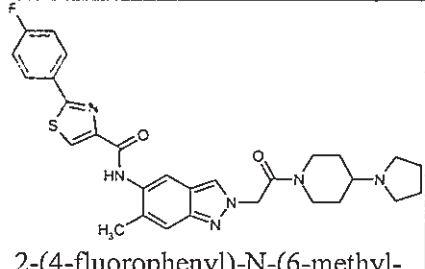
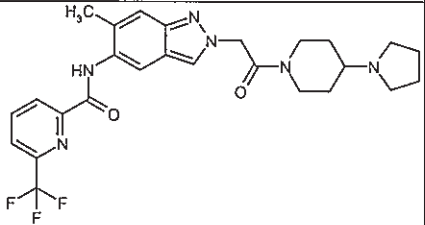
	(methylsulphonyl)benzoyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide		
226	 <p>N-[2-(2-{4-[2-methoxy-5-(methylsulphonyl)benzoyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-methoxy-5-(methylsulphonyl)benzoic acid	0.7

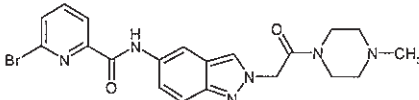
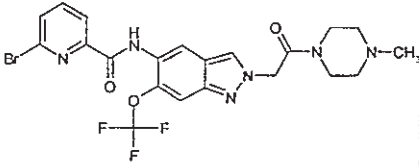
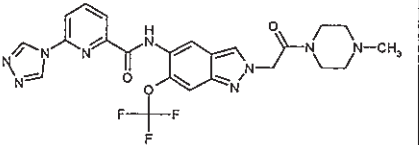
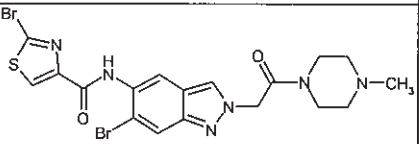
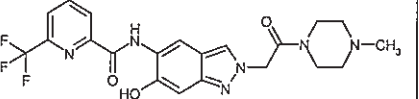
Table 16: Examples 227 – 244

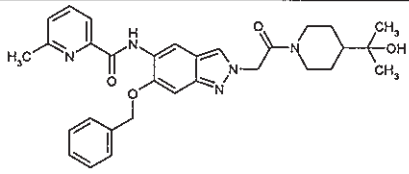
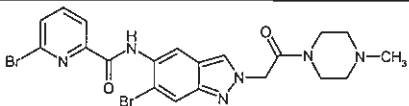
The exemplary compounds were prepared from the intermediates and starting materials indicated in the table.

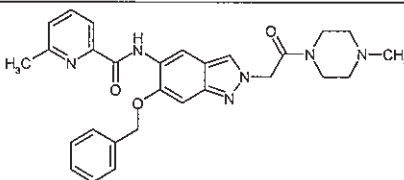
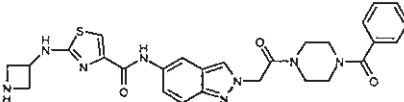
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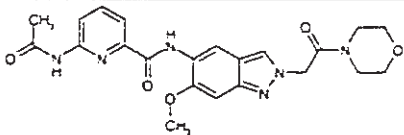
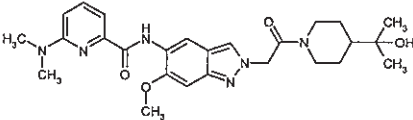
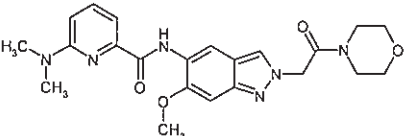
Ex.	Name and structure	Inter medi ate	Starting material, preparation and ¹ H NMR	LC- MS reten ti on time [min]
227	 <p>6-bromo-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide</p>	6-2	6-bromopyridine-2-carboxylic acid ¹ H NMR (400 MHz, DMSO-d ₆ , selected signals): δ = 1.21 - 1.36 (m, 1 H), 1.38 - 1.52 (m, 1 H), 1.69 (br. s., 4 H), 1.78 - 1.95 (m, 2 H), 2.21 - 2.36 (m, 1 H), 2.39 (s, 3 H), 2.80 - 2.91 (m, 1 H), 3.18 (t, 1 H), 3.82 - 3.96 (m, 1 H), 4.04 - 4.18 (m, 1 H), 5.45 (d, 1 H), 5.40 (d, 1 H), 7.48 (s, 1 H), 7.91 - 7.97 (m, 1 H), 8.02 (t, 1 H), 8.09 (s, 1 H), 8.17 (dd, 1 H), 8.23 - 8.27 (m, 1 H), 10.05 (s, 1 H).	0.7

228	 <p>2-(4-methoxyphenyl)-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-1,3-thiazole-4-carboxamide</p>	6-2	<p>2-(4-methoxyphenyl)-1,3-thiazole-4-carboxylic acid</p> <p>¹H NMR (400 MHz, DMSO-d₆, selected signals): δ = 1.21 - 1.36 (m, 1 H), 1.37 - 1.52 (m, 1 H), 1.68 (br. s., 4 H), 1.85 (t, 2 H), 2.18 - 2.28 (m, 1 H), 2.42 (s, 3 H), 2.80 - 2.92 (m, 1 H), 3.18 (t, 1 H), 3.85 (s, 3 H), 3.88 - 3.94 (m, 1 H), 4.05 - 4.15 (m, 1 H), 5.40 (d, 1 H), 5.45 (d, 1 H), 7.06 - 7.15 (m, 2 H), 7.49 (s, 1 H), 8.02 - 8.09 (m, 3 H), 8.25 (s, 1 H), 8.36 (s, 1 H), 9.86 (s, 1 H).</p>	0.82
229	 <p>2-(4-fluorophenyl)-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-1,3-thiazole-4-carboxamide</p>	6-2	<p>2-(4-fluorophenyl)-1,3-thiazole-4-carboxylic acid</p> <p>¹H NMR (400 MHz, CHLOROFORM-d): δ = 1.26 (s, 1 H), 1.36 (t, 1 H), 1.44 - 1.59 (m, 1 H), 1.82 (br. s., 2 H), 1.94 (d, 2 H), 2.33 (br. s., 1 H), 2.56 (s, 3 H), 2.63 (br. s., 4 H), 2.81 - 2.92 (m, 1 H), 3.01 (d, 1 H), 3.16 (t, 1 H), 3.98 (d, 1 H), 4.44 (d, 1 H), 5.23 - 5.29 (m, 2 H), 7.16 - 7.24 (m, 2 H), 7.53 - 7.58 (m, 1 H), 7.96 - 8.04 (m, 3 H), 8.20 (s, 1 H), 8.55 (s, 1 H), 9.44 (s, 1 H).</p>	0.83
230	 <p>N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	6-2	<p>6-(trifluoromethyl)pyridine-2-carboxylic acid</p> <p>¹H NMR (300 MHz, DMSO-d₆): δ = 1.15 - 1.36 (m, 1 H), 1.42 - 1.45 (m, 1 H), 1.68 (br. s., 4 H), 1.86 (t, 2 H), 2.19 - 2.32 (m, 1 H), 2.41 (s, 3 H), 2.85 (t, 1 H), 3.10 - 3.24 (m, 1 H), 3.89 (d, 1 H), 4.11 (d, 1 H), 5.43 (s, 2 H), 7.49 (s, 1 H), 8.16 - 8.24 (m, 2 H), 8.26 (s, 1 H), 8.33 - 8.49 (m, 2 H), 10.15 (s, 1 H).</p>	0.75

231	 <p>6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	6-12	6-bromopyridine-2-carboxylic acid ¹ H NMR (300 MHz, DMSO-d ₆): δ = 2.21 (s, 3 H), 2.24 - 2.34 (m, 2 H), 2.34 - 2.42 (m, 2 H), 3.43 - 3.52 (m, 2 H), 3.54 (d, 2 H), 5.45 (s, 2 H), 7.52 - 7.63 (m, 2 H), 7.84 - 7.96 (m, 1 H), 8.01 (t, 1 H), 8.15 (dd, 1 H), 8.26 - 8.36 (m, 2 H), 10.38 (s, 1 H).	0.61
232	 <p>6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}pyridine-2-carboxamide</p>	6-8	6-bromopyridine-2-carboxylic acid ¹ H NMR (300 MHz, DMSO-d ₆): δ = 2.21 (s, 3 H), 2.25 - 2.33 (m, 2 H), 2.39 (br. s., 2 H), 3.47 (br. s., 2 H), 3.54 (d, 2 H), 5.52 (s, 2 H), 7.74 (s, 1 H), 7.94 - 8.01 (m, 1 H), 8.01 - 8.10 (m, 1 H), 8.19 (d, 1 H), 8.45 (s, 1 H), 8.55 (s, 1 H), 10.28 (s, 1 H)	0.82
233	 <p>N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}-6-(4H-1,2,4-triazol-4-yl)pyridine-2-carboxamide</p>	6-8	6-(4H-1,2,4-triazol-4-yl)pyridine-2-carboxylic acid ¹ H NMR (400 MHz, DMSO-d ₆): δ = 2.22 (s, 3 H), 2.27 - 2.35 (m, 2 H), 2.39 (br. s., 2 H), 3.43 - 3.52 (m, 2 H), 3.52 - 3.60 (m, 2 H), 5.53 (s, 2 H), 7.72 (s, 1 H), 8.18 (dd, 2 H), 8.28 (s, 1 H), 8.34 (d, 1 H), 8.47 (s, 1 H), 9.62 (s, 2 H), 10.56 (s, 1 H).	0.56
234	 <p>2-bromo-N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide</p>	6-9	2-bromo-1,3-thiazole-4-carboxylic acid ¹ H NMR (300 MHz, DMSO-d ₆): δ = 2.21 (s, 3 H), 2.25 - 2.34 (m, 2 H), 2.38 (br. s., 2 H), 3.47 (br. s., 2 H), 3.54 (br. s., 2 H), 5.49 (s, 2 H), 8.03 (s, 1 H), 8.25 (s, 1 H), 8.35 - 8.42 (m, 1 H), 8.49 (s, 1 H), 9.96 (s, 1 H).	0.72
235		-	Analogously to Intermediate 8-7, 25 mg (0.05 mmol) of N-{6-(benzyloxy)-2-[2-(4-	0.67

	N-{6-hydroxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide		methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide (Example 41) were dissolved in 7 ml of ethanol, 4.8 mg of palladium on carbon were added and the mixture was hydrogenated under standard hydrogen pressure for 6 h. Work-up gave 5 mg (34% of theory) of the product. ¹ H NMR (400 MHz, DMSO-d ₆): δ = 2.20 (s, 3 H), 2.28 (br. s., 2 H), 2.35 (br. s., 2 H), 3.46 (br. s., 2 H), 3.53 (br. s., 2 H), 5.31 (s, 2 H), 6.88 (s, 1 H), 8.13 (s, 1 H), 8.20 (d, 1 H), 8.40 (t, 1 H), 8.47 (d, 1 H), 8.66 (s, 1 H), 10.64 (br. s., 1 H).	
236	 N-[6-(benzyloxy)-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl]-6-methylpyridine-2-carboxamide	9-18	2-(piperidin-4-yl)propan-2-ol ¹ H NMR (300 MHz, DMSO-d ₆): δ = 0.96 - 1.17 (m, 1 H), 1.05 (s, 6 H), 1.18 - 1.34 (m, 2 H), 1.36 - 1.54 (m, 1 H), 1.76 (t, 2 H), 2.43 (s, 3 H), 3.00 (t, 1 H), 4.04 (d, 1 H), 4.19 (s, 1 H), 4.42 (d, 1 H), 5.30 (s, 2 H), 5.38 (s, 1 H), 5.37 (s, 1 H), 7.27 (s, 1 H), 7.37 - 7.54 (m, 4 H), 7.66 (d, 2 H), 7.87 - 8.02 (m, 2 H), 8.23 (s, 1 H), 8.78 (s, 1 H), 10.87 (s, 1 H).	1.19
237	 6-bromo-N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide	6-9	6-bromopyridine-2-carboxylic acid ¹ H NMR (300 MHz, DMSO-d ₆): δ = 2.20 (s, 3 H), 2.23 - 2.33 (m, 2 H), 2.37 (br. s., 2 H), 3.46 (d, 2 H), 3.53 (br. s., 2 H), 5.49 (s, 2 H), 7.94 - 7.99 (m, 1 H), 8.01 - 8.08 (m, 2 H), 8.16 - 8.23 (m, 1 H), 8.39 (s, 1 H), 8.51 (s, 1 H), 10.38 (s, 1 H).	0.77

238	 <p>N-{6-(benzyloxy)-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide</p>	9-18	<p>1-methylpiperazine</p> <p>¹H NMR (300 MHz, DMSO-d₆): δ = 2.21 (s, 3 H), 2.23 - 2.33 (m, 2 H), 2.37 (br. s., 2 H), 2.42 (s, 3 H), 3.47 (br. s., 2 H), 3.55 (br. s., 2 H), 5.30 (s, 2 H), 5.39 (s, 2 H), 7.27 (s, 1 H), 7.36 - 7.56 (m, 4 H), 7.62 - 7.69 (m, 2 H), 7.90 - 8.02 (m, 2 H), 8.23 (s, 1 H), 8.78 (s, 1 H), 10.87 (s, 1 H).</p>	0.87
239	 <p>2-(azetidin-3-ylamino)-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide</p>	6-11	<p>According to General Procedure 1c, 35 mg (0.09 mmol) of the Intermediate 6-11 were reacted with 32 mg (0.1 mmol) of 2-[[1-(tert-butoxycarbonyl)azetidin-3-yl]amino]-1,3-thiazole-4-carboxylic acid. This gave 10 mg (0.01 mmol) of tert-butyl 3-{[4-({2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamoyl)-1,3-thiazol-2-yl]amino}azetidine-1-carboxylate.</p> <p>¹H NMR (400 MHz, DMSO-d₆): δ = 1.39 (s, 9 H), 3.55 (br. s., 4 H), 3.64 (br. s., 4 H), 3.78 (dd, 2 H), 4.25 (t, 2 H), 4.57 - 4.69 (m, 1 H), 5.48 (br. s., 2 H), 7.39 - 7.52 (m, 7 H), 7.54 - 7.59 (m, 1 H), 8.22 (d, 1 H), 8.25 - 8.29 (m, 1 H), 8.43 (d, 1 H), 9.55 (s, 1 H).</p> <p>50 mg (0.07 mmol) of tert-butyl 3-{[4-({2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamoyl)-1,3-thiazol-2-yl]amino}azetidine-1-carboxylate were dissolved in 200 µl of 4 M hydrogen chloride in dioxane and the mixture was stirred at room</p>	0.56

			temperature for 24 h. The reaction mixture was concentrated and taken up in dichloromethane, washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated. Drying gave 11 mg (0.02 mmol) of 2-(azetidin-3-ylamino)-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide.	
240	 <p>6-acetamido-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	6-16	6-acetamidopyridine-2-carboxylic acid ¹ H NMR (400 MHz, DMSO-d ₆): δ = 2.21 (s, 3 H), 3.47 (d, 2 H), 3.51 - 3.62 (m, 4 H), 3.64 (d, 2 H), 4.03 (s, 3 H), 5.39 (s, 2 H), 7.10 (s, 1 H), 7.87 (dd, 1 H), 8.04 (t, 1 H), 8.22 (s, 1 H), 8.28 (d, 1 H), 8.69 (s, 1 H), 10.34 (s, 1 H), 10.65 (s, 1 H).	0.76
241	 <p>6-(dimethylamino)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide</p>	6-5	6-(dimethylamino)pyridine-2-carboxylic acid ¹ H NMR (400 MHz, DMSO-d ₆): δ = 1.01 - 1.14 (m, 1 H), 1.05 (s, 6 H), 1.18 - 1.30 (m, 1 H), 2.50-2.52 (m, 1 H) (signal under DMSO), 1.44 (t, 1 H), 1.75 (t, 2 H), 2.99 (t, 1 H), 3.16 (s, 6 H), 3.97 (s, 3 H), 4.03 (d, 1 H), 4.16 (s, 1 H), 4.42 (d, 1 H), 5.27 - 5.41 (m, 2 H), 6.94 (d, 1 H), 7.07 (s, 1 H), 7.36 (d, 1 H), 7.74 (dd, 1 H), 8.19 (s, 1 H), 8.67 (s, 1 H), 10.88 (s, 1 H).	1.03
242	 <p>6-(dimethylamino)-N-{6-methoxy-2-[2-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxylic acid</p>	6-16	6-(dimethylamino)pyridine-2-carboxylic acid ¹ H NMR (400 MHz, DMSO-d ₆): δ = 3.16 (s, 6 H), 3.47 (d, 2 H), 3.53 - 3.61 (m, 4 H), 3.64	0.99

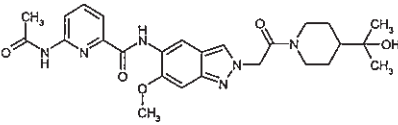
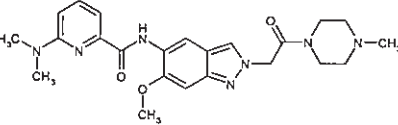
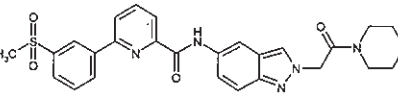
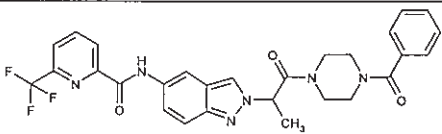
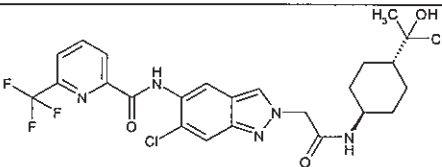
	methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide		(d, 2 H), 3.98 (s, 3 H), 5.38 (s, 2 H), 6.94 (d, 1 H), 7.08 (s, 1 H), 7.36 (d, 1 H), 7.74 (dd, 1 H), 8.17 - 8.21 (m, 1 H), 8.67 (s, 1 H), 10.88 (s, 1 H).	
243	 <p>6-acetamido-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide</p>	6-5	6-acetamidopyridine-2-carboxylic acid ¹ H NMR (400 MHz, DMSO-d ₆): δ = 0.98 - 1.12 (m, 1 H), 1.05 (s, 6 H), 1.15 - 1.31 (m, 1 H), 1.39 - 1.50 (m, 1 H), 1.75 (t, 2 H), 2.21 (s, 3 H), 2.52 - 2.57 (m, 1 H), 2.99 (br. s., 1 H), 3.98 - 4.08 (m, 1 H), 4.03 (s, 3 H), 4.16 (s, 1 H), 4.42 (d, 1 H), 5.36 (d, 2 H), 7.09 (s, 1 H), 7.87 (dd, 1 H), 8.04 (t, 1 H), 8.19 - 8.23 (m, 1 H), 8.28 (d, 1 H), 8.69 (s, 1 H), 10.34 (s, 1 H), 10.65 (s, 1 H).	0.83
244	 <p>6-(dimethylamino)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	6-17	6-(dimethylamino)pyridine-2-carboxylic acid ¹ H NMR (400 MHz, DMSO-d ₆): δ = 2.21 (s, 3 H), 2.27 - 2.31 (m, 2 H), 2.34 - 2.39 (m, 2 H), 3.16 (s, 6 H), 3.43 - 3.51 (m, 2 H), 3.51 - 3.58 (m, 2 H), 3.97 (s, 3 H), 5.36 (s, 2 H), 6.94 (d, 1 H), 7.08 (s, 1 H), 7.36 (d, 1 H), 7.74 (dd, 1 H), 8.19 (s, 1 H), 8.67 (s, 1 H), 10.88 (s, 1 H).	0.74

Table 17: Examples 245 – 247

Ex.	Name and structure	Preparation and notes	LC-MS retention time [min]
245	 <p>N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-[3-(methylsulphonyl)phenyl]pyridine-2-carboxylic acid</p>	80 mg of 6-[3-(methylsulphonyl)phenyl]pyridine-2-carboxylic acid (Intermediate 19-8) and 95 mg of 2-(5-amino-2H-indazol-2-yl)-1-	0.65

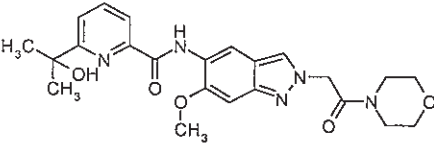
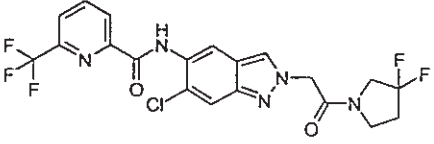
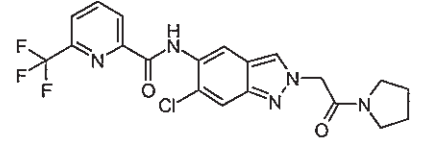
	(methylsulphonyl)phenyl]pyridine-2-carboxamide	(4-methylpiperazin-1-yl)ethanone (Intermediate 6-12, crude product) were reacted with EDC, HOBt and triethylamine in THF at room temperature overnight. The residue was diluted with water and ethyl acetate. The solid was filtered off with suction, washed with water and diethyl ether and dried. This gave 48 mg of the exemplary compound. ¹ H NMR (400 MHz, DMSO-d ₆): δ = 2.20 (s, 3H), 2.24 - 2.42 (m, 4H), 3.36 (s, 3H), 3.42 - 3.51 (m, 2H), 3.51 - 3.61 (m, 2H), 5.45 (s, 2H), 7.56 - 7.64 (m, 2H), 7.84 (t, 1H), 8.05 (d, 1H), 8.16 - 8.24 (m, 2H), 8.30 (s, 1H), 8.34 - 8.40 (m, 2H), 8.75 - 8.80 (m, 2H), 10.56 (s, 1H).	
246	 <p>N-{2-[1-(4-benzoylpiperazin-1-yl)-1-oxopropan-2-yl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	100 mg of 2-(5-amino-2H-indazol-2-yl)-1-(4-benzoylpiperazin-1-yl)propan-1-one (Intermediate 6-19) and 76 mg of 6-(trifluoromethyl)pyridine-2-carboxylic acid were reacted with EDC, HOBt and triethylamine in THF at room temperature overnight. After addition of water, extraction with ethyl acetate and concentration, the product was purified by preparative HPLC according to Method P1. This gave 98 mg of the exemplary compound. ¹ H NMR (400 MHz, DMSO-d ₆): δ = 1.68 (d, 3H), 3.1 - 3.7 (broad signals, superimposed), 5.91 (br. s., 1H), 7.34 - 7.45 (m, 5H), 7.52 - 7.61 (m, 2H), 8.14 (dd, 1H), 8.26 - 8.39 (m, 3H), 8.43 (s, 1H), 10.34 (s, 1H).	1.08
247		80 mg of [6-chloro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]carbamate	1.16

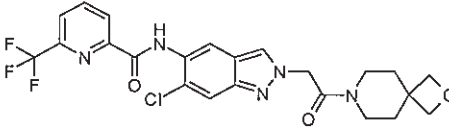
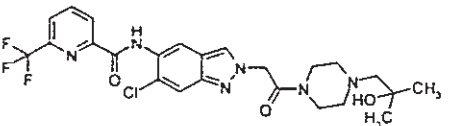
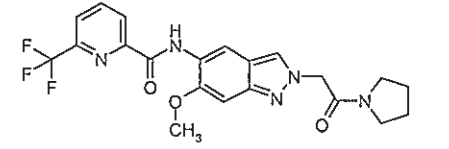
	N-[6-chloro-2-(2-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]amino}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide	yl]acetic acid and 41 mg of 2-(trans-4-aminocyclohexyl)propan-2-ol were reacted with EDC, HOBt and triethylamine in THF at room temperature overnight and at 50°C for 7 h. Water and ethyl acetate were added. The solid was filtered off with suction, washed with water and diethyl ether and dried. This gave 92 mg of the exemplary compound. ¹ H-NMR (300 MHz, DMSO-d ₆): δ = 0.92 – 1.25 (11H, contains singlet at 1.01 ppm), 1.73 - 1.91 (m, 4H), 3.36 - 3.60 (m), 4.02 (s, 1H), 5.08 (s, 2H), 7.91 (s, 1H), 8.23 (d, 2H), 8.37 - 8.50 (m, 3H), 8.63 (s, 1H), 10.52 (s, 1H).	
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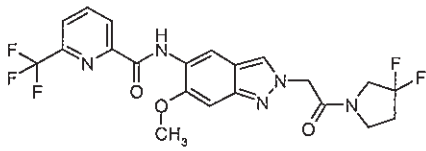
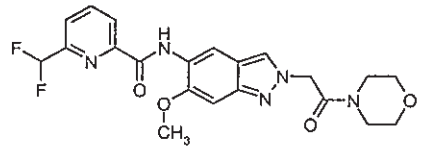
Table 18: Examples 248 - 260

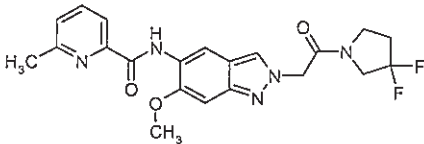
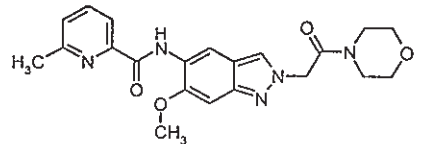
- 5 The exemplary compounds were prepared by the general experimental procedures 2a-2g from the appropriate intermediates and amines.

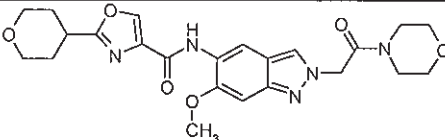
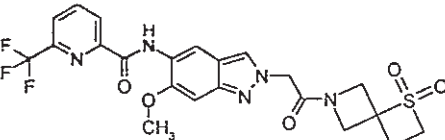
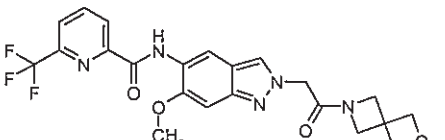
Ex. No.	Structure/Name	Prepared from	¹ H-NMR / LC-MS
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248	 <p>6-(2-hydroxypropan-2-yl)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	Intermediate 9-23 and morpholine	<p>(400 MHz, DMSO-d₆): δ = 1.57 (s, 6 H), 3.42 - 3.52 (m, 2 H), 3.52 - 3.62 (m, 4 H), 3.62 - 3.68 (m, 2 H), 3.99 (s, 3 H), 5.39 (s, 2 H), 5.47 (s, 1 H), 7.10 (s, 1 H), 7.93 (dd, 1 H), 7.99 - 8.10 (m, 2 H), 8.19 - 8.23 (m, 1 H), 8.68 (s, 1 H), 10.93 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.88 min MS (ESIpos): m/z = 454 (M+H)⁺</p>
249	 <p>N-{6-chloro-2-[2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 9-11 and 3,3-difluoropyrrolidine	<p>(400 MHz, DMSO-d₆): δ = 2.38 - 2.46 (m, 1 H), 2.54 - 2.61 (m, 1 H), 3.58 (t, 1 H), 3.77 (t, 1 H), 3.87 (t, 1 H), 4.11 (t, 1 H), 5.42 (s, 1 H), 5.48 (s, 1 H), 7.93 (s, 1 H), 8.24 (dd, 1 H), 8.38 - 8.45 (m, 2 H), 8.45 - 8.50 (m, 1 H), 8.64 - 8.67 (m, 1 H), 10.53 (s, 1 H).</p>
250	 <p>N-{6-chloro-2-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 9-11 and pyrrolidine	<p>UPLC-MS (Method A2): Rt = 1.21 min MS (ESIpos): m/z = 452 (M+H)⁺</p>

251	 <p>N-{6-chloro-2-[2-(2-oxa-7-azaspiro[3.5]non-7-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 9-11 and 2-oxa-7-azaspiro[3.5]nonane (CAS241820-91-7)	<p>(300 MHz, DMSO-d₆): δ = 1.75 (br. s., 2 H), 1.87 (br. s., 2 H), 3.37 - 3.51 (m, 4 H), 4.24 - 4.41 (m, 4 H), 5.50 (s, 2 H), 7.91 (s, 1 H), 8.24 (d, 1 H), 8.36 - 8.51 (m, 3 H), 8.64 (s, 1 H), 10.53 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.22 min</p> <p>MS (ESIpos): m/z = 508 (M+H)⁺</p>
252	 <p>N-(6-chloro-2-{2-[4-(2-hydroxy-2-methylpropyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 9-11 and 2-methyl-1-(piperazin-1-yl)propan-2-ol	<p>(300 MHz, DMSO-d₆, selected signals): δ = 1.11 (s, 6 H), 2.23 (s, 2 H), 2.59 (br. s., 2 H), 3.46 (br. s., 2 H), 3.53 (br. s., 2 H), 4.16 (s, 1 H), 5.49 (s, 2 H), 7.92 (s, 1 H), 8.24 (dd, J=7.4, 1.2 Hz, 1 H), 8.37 - 8.51 (m, 3 H), 8.64 (s, 1 H), 10.53 (s, 1 H).</p>
253	 <p>N-{6-methoxy-2-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 9-12 and pyrrolidine	<p>(400 MHz, DMSO-d₆): δ = 1.81 (s, 2 H), 1.91 - 1.98 (m, 2 H), 3.33 - 3.37 (m, 2 H), 3.54 (t, 2 H), 3.99 (s, 3 H), 5.27 (s, 2 H), 7.12 (s, 1 H), 8.19 - 8.25 (m, 2 H), 8.42 (d, 1 H), 8.44 - 8.49 (m, 1 H), 8.71 (s, 1 H), 10.51 (s, 1 H).</p> <p>UPLC-MS (Method A2): Rt = 1.14 min</p> <p>MS (ESIpos): m/z = 448 (M+H)⁺</p>

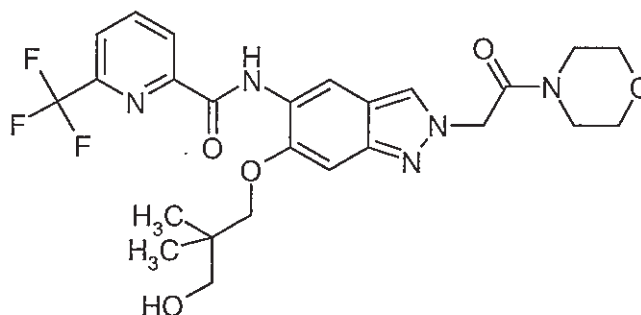
254	 <p>N-{2-[2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 9-12 and 3,3-difluoropyrrolidine	<p>(400 MHz, DMSO-d₆): δ = 2.37 - 2.44 (m, 1 H), 2.54 - 2.61 (m, 1 H), 3.58 (t, 1 H), 3.76 (t, 1 H), 3.86 (t, 1 H), 3.99 (s, 3 H), 4.10 (t, 1 H), 5.27 - 5.34 (m, 1 H), 5.37 (s, 1 H), 7.12 (s, 1 H), 8.15 - 8.30 (m, 2 H), 8.37 - 8.45 (m, 1 H), 8.45 - 8.51 (m, 1 H), 8.71 (s, 1 H), 10.51 (s, 1 H).</p> <p>UPLC-MS (Method A2): Rt = 1.17 min MS (ESIpos): m/z = 484 (M+H)⁺</p>
255	 <p>6-(difluoromethyl)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	Intermediate 9-24 and morpholine	<p>(400 MHz, DMSO-d₆): δ = 3.40 - 3.49 (m, 2 H), 3.53 - 3.62 (m, 4 H), 3.62 - 3.68 (m, 2 H), 4.00 (s, 3 H), 5.40 (s, 2 H), 7.16 (t, 1 H), 7.11 (s, 1 H), 8.00 (d, 1 H), 8.23 (s, 1 H), 8.27 - 8.38 (m, 2 H), 8.71 (s, 1 H), 10.56 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.99 min MS (ESIpos): m/z = 446 (M+H)⁺</p>

256	 <p>N-{2-[2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide</p>	Intermediate 9-19 and 3,3-difluoropyrrolidine	<p>(400 MHz, DMSO-d₆): δ = 2.35 - 2.48 (m, 1 H), 2.54 - 2.60 (m, 1 H), 2.63 (s, 3 H), 3.58 (t, 1 H), 3.76 (s, 1 H), 3.86 (t, 1 H), 4.01 (s, 3 H), 4.04 - 4.16 (m, 1 H), 5.30 (s, 1 H), 5.36 (s, 1 H), 7.10 (s, 1 H), 7.56 (dd, 1 H), 7.94 - 8.02 (m, 2 H), 8.20 - 8.24 (m, 1 H), 8.72 (s, 1 H), 10.71 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.17 min MS (ESIpos): m/z = 430 (M+H)⁺</p>
257	 <p>N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide</p>	Intermediate 9-19 and morpholine	<p>(400 MHz, DMSO-d₆): δ = 2.63 (s, 3 H), 3.47 (s, 2 H), 3.53 - 3.62 (m, 4 H), 3.64 (s, 2 H), 4.01 (s, 3 H), 5.39 (s, 2 H), 7.09 (s, 1 H), 7.56 (dd, J=7.1, 1.5 Hz, 1 H), 7.93 - 8.03 (m, 2 H), 8.21 (s, 1 H), 8.72 (s, 1 H), 10.71 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.00 min MS (ESIpos): m/z = 410 (M+H)⁺</p>

258	 <p>N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(tetrahydro-2H-pyran-4-yl)-1,3-oxazole-4-carboxamide</p>	Intermediate 9-20 and morpholine	<p>(400 MHz, DMSO-d₆): δ = 1.71 - 1.84 (m, 2 H), 1.92 - 2.02 (m, 2 H), 3.16 - 3.28 (m, 1 H), 3.42 - 3.50 (m, 4 H), 3.53 - 3.62 (m, 4 H), 3.64 (d, 2 H), 3.88 - 3.95 (m, 2 H), 3.97 (s, 3 H), 5.38 (s, 2 H), 7.08 (s, 1 H), 8.20 (s, 1 H), 8.56 (s, 1 H), 8.74 (s, 1 H), 9.41 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.88 min MS (ESIpos): m/z = 470 (M+H)⁺</p>
259	 <p>N-{2-[2-(1,1-dioxido-1-thia-6-azaspiro[3.3]hept-6-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 9-12 and 1-thia-6-azaspiro[3.3]heptane-1,1-dioxide (CAS13525 46-75-8)	<p>UPLC-MS (Method A2): Rt = 1.12 min MS (ESIpos): m/z = 524 (M+H)⁺</p>
260	 <p>N-{2-[2-(2-oxa-6-azaspiro[3.3]hept-6-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 9-12 and 2-oxa-6-azaspiro[3.3]heptane (CAS 174-78-7)	<p>(300 MHz, DMSO-d₆): δ = 3.99 (s, 3 H), 4.10 (s, 2 H), 4.32 (s, 2 H), 4.67 (s, 4 H), 5.06 (s, 2 H), 7.12 (s, 1 H), 8.22 (d, J=7.6 Hz, 1 H), 8.25 (s, 1 H), 8.41 (s, 1 H), 8.46 (s, 1 H), 8.70 (s, 1 H), 10.51 (s, 1 H).</p> <p>UPLC-MS (Method A2): Rt = 1.08 min MS (ESIpos): m/z = 476 (M+H)⁺</p>

Example 261

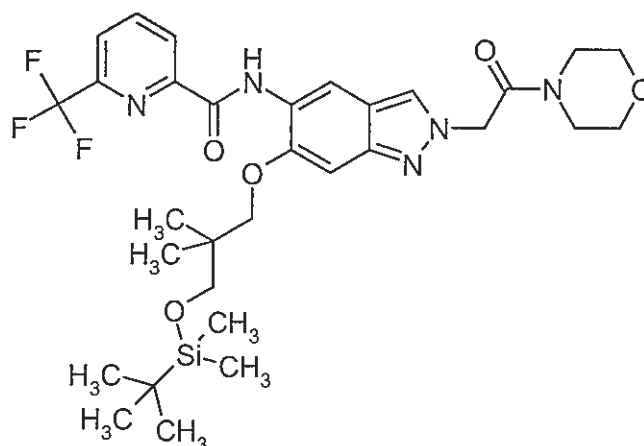
N-{6-(3-Hydroxy-2,2-dimethylpropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



5

Step A:

N-{6-(3-{{[tert-Butyl(dimethyl)silyl]oxy}}-2,2-dimethylpropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



10

100 mg (0.22 mmol) of N-{6-hydroxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide (Example 287) were dissolved in 2.0 ml of *N,N*-dimethylformamide, and 46 mg (0.33 mmol) of potassium carbonate were added with stirring. The suspension was stirred at 25°C for 10 minutes, and 94 mg (0.33 mmol) (3-bromo-2,2-dimethylpropoxy)(tert-butyl)dimethylsilane were then added. The reaction mixture was stirred in the microwave at 100°C for 1 h. The reaction mixture was then filtered and by preparative HPLC. This gave 34 mg (24% of theory) of the title compound.

UPLC-MS (Method A1): $R_t = 1.70$ min

MS (ESIpos): $m/z = 650$ ($M+H$)⁺

¹H NMR (400 MHz, DMSO-d₆): $\delta = -0.17$ - -0.09 (m, 6 H), 0.75 (s, 9 H), 1.07 (s, 6 H), 3.42 - 3.51 (m, 2 H), 3.54 - 3.64 (m, 2 H), 3.54 - 3.64 (m, 4 H), 3.64 - 3.71 (m, 2 H), 3.88 (s, 2 H), 5.40 (s, 2 H), 7.05 (s, 1 H), 8.17 - 8.27 (m, 2 H), 8.42 (t, 1 H), 8.49 - 8.56 (m, 1 H), 8.79 (s, 1 H), 10.42 (s, 1 H).

Step B:

40 mg (0.06 mmol) of N-{6-(3-{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide were dissolved in 2.5 ml of tetrahydrofuran, 185 μ l (0.18 mmol) of a 1 M solution of tetrabutylammonium fluorid and in tetrahydrofuran were added and the mixture was stirred at 25°C for 2 h. 5 ml of water were added, and the reaction mixture was concentrated. The resulting precipitate was filtered off with suction, washed with water and diethyl ether and dried under reduced pressure. This gave 26 mg (48% of theory) of N-{6-(3-hydroxy-2,2-dimethylpropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide.

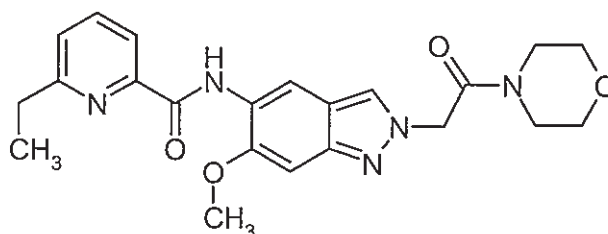
UPLC-MS (Method A1): R_t = 1.09 min

MS (ESIpos): m/z = 536 (M+H)⁺

¹H NMR (400 MHz, DMSO-d₆): δ = 1.06 (s, 6 H), 3.42 (d, Hz, 2 H), 3.45 - 3.51 (m, 2 H), 3.54 - 3.63 (m, 4 H), 3.63 - 3.68 (m, 2 H), 3.90 (s, 2 H), 4.63 - 4.69 (m, 1 H), 5.40 (s, 2 H), 7.05 (s, 1 H), 8.17 - 8.25 (m, 2 H), 8.41 (t, 1 H), 8.51 (d, 1 H), 8.81 (s, 1 H), 10.44 (s, 1 H).

Example 262

6-Ethyl-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide



50 mg (0.11 mmol) of 6-bromo-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide (Intermediate 15-2) were suspended in 750 μ l of dry dioxane, 86 μ l (0.09 mmol) of a 1.1 M solution of diethyl zinc in toluene and 4 mg (0.01 mmol) of 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride dichloromethane complex were added and the mixture was stirred at 40°C for 24 h. Another 86 μ l (0.09 mmol) of a 1.1 M solution of diethyl zinc in toluene and 4 mg (0.01 mmol) of 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride dichloromethane complex were added and the mixture was stirred at 60°C for a further 24 h. A further 86 μ l (0.09 mmol) of a 1.1 M solution of diethyl zinc in toluene and 4 mg (0.01 mmol) of 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride dichloromethane complex were added and the mixture was stirred at 60°C for a further 24 h. The reaction mixture was filtered and the filtrate was concentrated. The crude product was dissolved in 2.5 ml of dimethyl sulphoxide and purified by preparative HPLC according to Method P1. The product fraction was lyophilized. This gave 5.8 mg (11% of theory) of the title compound.

UPLC-MS (Method A1): R_t = 1.11 min

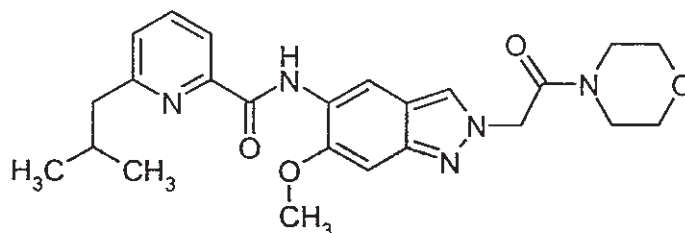
MS (ESIpos): $m/z = 424 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6): $\delta = 1.37$ (t, 3 H), 2.92 (q, 2 H), 3.42 - 3.50 (m, 2 H), 3.58 (br. s., 4 H), 3.62 - 3.69 (m, 2 H), 4.00 (s, 3 H), 5.39 (s, 2 H), 7.10 (s, 1 H), 7.57 (dd, 2 H), 7.97 - 8.02 (m, 2 H), 8.21 (s, 1 H), 8.71 (s, 1 H), 10.88 (s, 1 H).

5

Example 263

6-Isobutyl-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide



- 10 50 mg (0.11 mmol) of 6-bromo-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide (Intermediate 15-2) were dissolved in 1.5 ml of tetrahydrofuran, 316 μl (0.16 mmol) of a 0.5 M solution of 2-methylpropylzinc bromide in tetrahydrofuran and 3 mg (0.01 mmol) of bis(tri-*tert*-butylphosphine)palladium(0) were added and the mixture was stirred at 25°C for 48 h. The reaction mixture was filtered and the filtrate was concentrated. The crude product was dissolved in 2.5 ml of dimethyl sulphoxide and purified by preparative HPLC according to Method P1. The product fraction was lyophilized. This gave 2.8 mg (6% of theory) of the title compound.

15

UPLC-MS (Method A1): $R_t = 1.27$ min

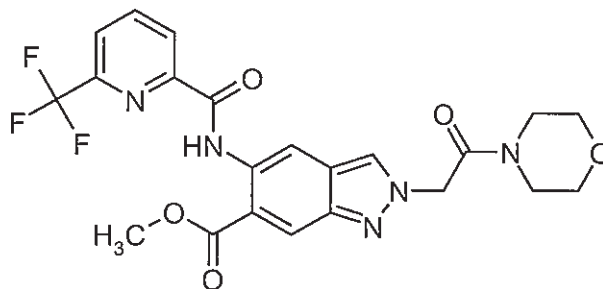
MS (ESIpos): $m/z = 452 (M+H)^+$

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6): $\delta = 0.99$ (d, 6 H) 2.15 - 2.29 (m, 1 H) 2.77 (d, 2 H) 3.47 (d, 2 H) 3.53 - 3.69 (m, 6 H) 3.99 (s, 3 H) 5.39 (s, 2 H) 7.09 (s, 1 H) 7.53 (dd, 1 H) 7.94 - 8.03 (m, 2 H) 8.21 (s, 1 H) 8.71 (s, 1 H) 10.85 (s, 1 H).

20

Example 264

- 25 Methyl 2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate



100 mg (0.60 mmol) of methyl 5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-1H-indazole-6-carboxylate (Intermediate 14-9) were dissolved in 1 ml of tetrahydrofuran, 228 mg (1.10 mmol) of 2-bromo-1-(morpholin-4-yl)ethanone and 235 μ l (1.10 mmol) of *N,N*-dicyclohexylmethylamine were added and the mixture was stirred at 75°C for 24 h. The reaction mixture was filtered using a
 5 membrane filter and the filtrate was diluted with 1 ml of dimethyl sulphoxide and purified by preparative HPLC. The product fractions were lyophilized. This gave 15 mg (11% of theory) of the title compound.

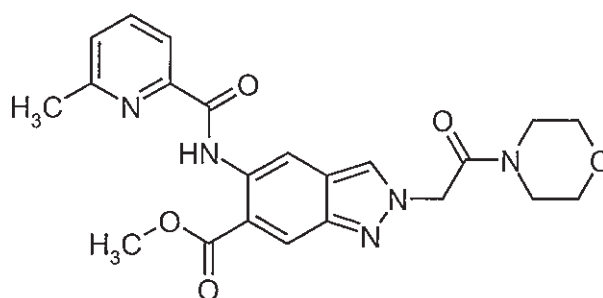
UPLC-MS (Method A2): R_t = 1.10 min

MS (ESIpos): m/z = 492 ($M+H$)⁺

10 ¹H NMR (400 MHz, CHLOROFORM-*d*): δ = 3.45 - 3.50 (m, 2 H), 3.54 - 3.64 (m, 4 H), 3.64 - 3.70 (m, 2 H), 3.97 (s, 3 H), 5.59 (s, 2 H), 8.21 (dd, 1 H), 8.36 - 8.43 (m, 1 H), 8.44 - 8.49 (m, 3 H), 9.08 (s, 1 H), 12.52 (s, 1 H).

Example 265

15 **Methyl 5-({[6-(6-methylpyridin-2-yl)carbonyl]amino}-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazole-6-carboxylate**



50 mg (0.16 mmol) of (Intermediate 14-10) were dissolved in 2.5 ml of tetrahydrofuran, 134 mg (0.64 mmol) of 2-bromo-1-(morpholin-4-yl)ethanone and 138 μ l (0.64 mmol) of *N,N*-dicyclohexylmethylamine were added and the mixture was stirred at 80°C for 16 h. The reaction
 20 mixture was filtered and the filtrate was concentrated. The residue was dissolved in dichloromethane and washed three times with 1 M hydrochloric acid solution and three times with saturated sodium chloride solution, filtered through a hydrophobic filter and, during concentration, adsorbed on Isolute® HM-N (Biotage). The Isolute was applied to a cartridge (40 g; Puriflash) pre-equilibrated with hexane and chromatography was carried out using the Isolera® flash purification
 25 system (Biotage) (mobile phase: hexane/ethyl acetate; flow rate: 25 ml/min; gradient: 90:10->25:75). The combined product fractions were concentrated and dried. This gave 20 mg (28% of theory) of the title compound. UPLC-MS (Method A2): R_t = 1.05 min

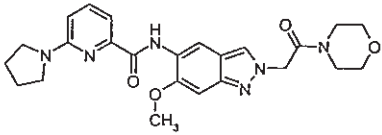
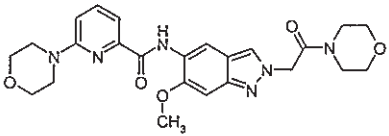
MS (ESIpos): m/z = 438 ($M+H$)⁺

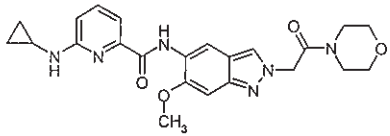
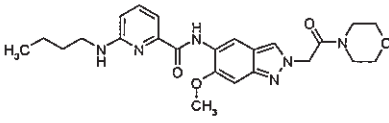
30 ¹H NMR (400 MHz, CHLOROFORM-*d*): δ = 2.65 (s, 3 H), 3.48 (d, 2 H), 3.59 (dd, 4 H), 3.67 (d, 2 H), 3.99 (s, 3 H), 5.58 (s, 2 H), 7.55 (dd, 1 H), 7.81 - 8.04 (m, 2 H), 8.38 - 8.47 (m, 2 H), 9.09 (s, 1 H), 12.57 (s, 1 H).

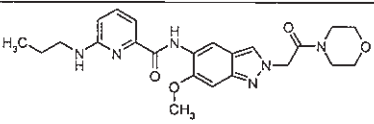
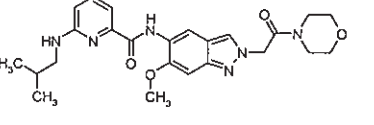
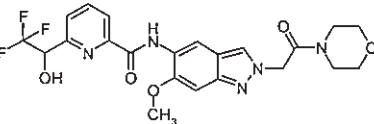
Table 19: Examples 266 - 286

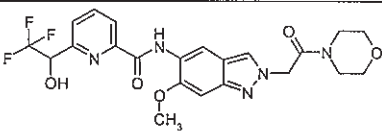
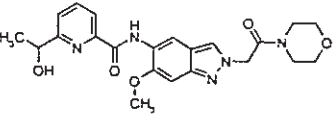
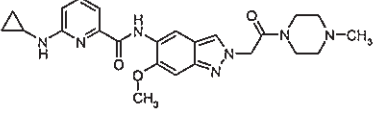
The exemplary compounds were prepared by the general experimental procedures 1a - 1e from the appropriate intermediates and carboxylic acids.

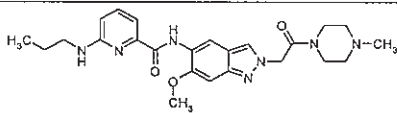
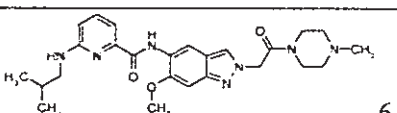
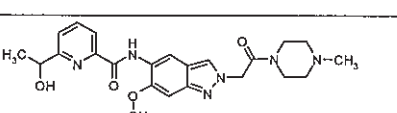
5

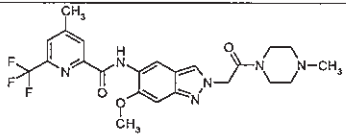
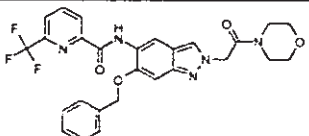
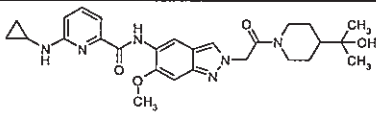
Ex. No.	Structure/Name	Prepared from	¹ H-NMR / LC-MS
266	 <p>N-{6-methoxy-2-[2-(pyrrolidin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(pyrrolidin-1-yl)pyridine-2-carboxamide</p>	Intermediate 6-16 and 6-(pyrrolidin-1-yl)pyridine-2-carboxylic acid (CAS 450368-20-4)	<p>(400 MHz, DMSO-d₆): δ = 1.98 - 2.06 (m, 4 H), 3.44 - 3.49 (m, 2 H), 3.51 (br. s., 4 H), 3.54 - 3.61 (m, 4 H), 3.61 - 3.68 (m, 2 H), 3.98 (s, 3 H), 5.38 (s, 2 H), 6.73 (d, 1 H), 7.07 (s, 1 H), 7.33 (d, 1 H), 7.72 (dd, 1 H), 8.19 (s, 1 H), 8.67 (s, 1 H), 10.93 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.16 min</p> <p>MS (ESIpos): m/z = 465 (M+H)⁺</p>
267	 <p>N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide</p>	Intermediate 6-16 and 6-(morpholin-4-yl)pyridine-2-carboxylic acid (CAS 554405-17-3)	<p>(400 MHz, DMSO-d₆): δ = 3.42 - 3.50 (m, 2 H), 3.53 - 3.68 (m, 10 H), 3.75 - 3.84 (m, 4 H), 3.97 (s, 3 H), 5.38 (s, 2 H), 7.09 (s, 1 H), 7.15 (d, 1 H), 7.46 (d, 1 H), 7.81 (dd, 1 H), 8.17 - 8.21 (m, 1 H), 8.66 (s, 1 H), 10.79 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.96 min</p> <p>MS (ESIpos): m/z = 481 (M+H)⁺</p>

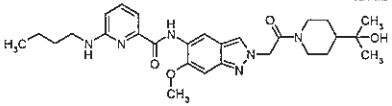
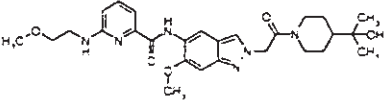
268	 <p>6-(cyclopropylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	<p>Intermediate 6-16 and 6-(cyclopropylamino)pyridine-2-carboxylic acid (prepared according to Synthesis Scheme 8, obtainable from Ukrorgsyntez Ltd., Order Number BBV-33897980)</p>	<p>(300 MHz, DMSO-d₆): δ = 0.40 - 0.58 (m, 2 H), 0.74 - 0.89 (m, 2 H), 2.60 - 2.79 (m, 1 H), 3.41 - 3.53 (m, 2 H), 3.53 - 3.69 (m, 6 H), 3.96 (s, 3 H), 5.38 (s, 2 H), 6.78 (d, 1 H), 7.06 (s, 1 H), 7.26 (s, 1 H), 7.36 (d, 1 H), 7.64 (d, 1 H), 8.19 (s, 1 H), 8.72 (s, 1 H), 10.80 (s, 1 H). LC-MS (Method A3): Rt = 0.95 min MS (ESIpos): m/z = 451 (M+H)⁺</p>
269	 <p>6-(butylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	<p>Intermediate 6-16 and 6-(butylamino)pyridine-2-carboxylic acid (CAS 1250403-97-4)</p>	<p>(300 MHz, DMSO-d₆): δ = 0.95 (t, 3 H), 1.44 (dq, 2 H), 1.63 (quin, 2 H), 3.36 - 3.44 (m, 2 H), 3.44 - 3.51 (m, 2 H), 3.58 (br. s., 4 H), 3.62 - 3.70 (m, 2 H), 3.98 (s, 3 H), 5.38 (s, 2 H), 6.72 (d, 1 H), 7.02 (t, 1 H), 7.07 (s, 1 H), 7.26 (d, 1 H), 7.50 - 7.62 (m, 1 H), 8.19 (s, 1 H), 8.69 (s, 1 H), 10.82 (s, 1 H). LC-MS (Method A3): Rt = 1.07 min MS (ESIpos): m/z = 467 (M+H)⁺</p>

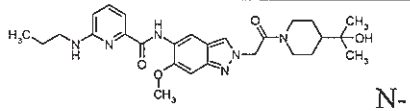
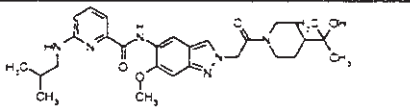
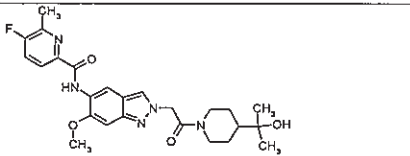
270	 <p>N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(propylamino)pyridine-2-carboxamide</p>	Intermediate 6-16 and 6-(propylamino)pyridine-2-carboxylic acid (prepared according to Synthesis Scheme 8, obtainable from Ukrorgsyntez Ltd., Order Number BBV-33897968)	(300 MHz, DMSO-d ₆): δ = 1.00 (t, 3 H), 1.59 - 1.74 (m, 2 H), 3.34 - 3.42 (m, 2 H), 3.42 - 3.50 (m, 2 H), 3.58 (br. s., 4 H), 3.62 - 3.68 (m, 2 H), 3.98 (s, 3 H), 5.38 (s, 2 H), 6.72 (d, 1 H), 7.03 - 7.12 (m, 2 H), 7.26 (d, 1 H), 7.50 - 7.66 (m, 1 H), 8.19 (s, 1 H), 8.69 (s, 1 H), 10.83 (s, 1 H). UPLC-MS (Method A1): Rt = 1.05 min MS (ESIpos): m/z = 453 (M+H) ⁺
271	 <p>6-(isobutylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	Intermediate 6-16 and potassium 6-(isobutylamino)pyridine-2-carboxylate (Intermediate 19-15)	(300 MHz, DMSO-d ₆): δ = 1.00 (d, 6 H) 1.84 - 2.02 (m, 1 H) 3.25 (t, 2 H) 3.47 (d, 2 H) 3.52 - 3.72 (m, 6 H) 3.99 (s, 3 H) 5.38 (s, 2 H) 6.75 (d, 1 H) 6.98 - 7.13 (m, 2 H) 7.26 (d, 1 H) 7.57 (dd, 1 H) 8.19 (s, 1 H) 8.70 (s, 1 H) 10.75 (s, 1 H). UPLC-MS (Method A1): Rt = 1.12 min MS (ESIpos): m/z = 467 (M+H) ⁺
272	 <p>N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxamide (Enantiomer 1)*</p>	Intermediate 6-16 and potassium 6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxylate (Intermediate 19-10)	(300 MHz, DMSO-d ₆): δ = 3.42 - 3.52 (m, 2 H), 3.58 (br. s., 4 H), 3.62 - 3.67 (m, 2 H), 3.97 (s, 3 H), 5.29 - 5.39 (m, 1 H), 5.40 (s, 2 H), 7.09 (s, 1 H), 7.31 (d, J=6.0 Hz, 1 H), 7.91 (t, J=4.5 Hz, 1 H), 8.16 - 8.25 (m, 3 H), 8.67 (s, 1 H), 10.70 (s, 1 H). UPLC-MS (Method A2): Rt = 0.95 min MS (ESIpos): m/z = 494 (M+H) ⁺

273	 <p>N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxamide (Enantiomer 2)*</p>	Intermediate 6-16 and potassium 6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxylate (Intermediate 19-10)	<p>(300 MHz, DMSO-d₆): δ = 3.42 - 3.52 (m, 2 H), 3.58 (br. s., 4 H), 3.62 - 3.67 (m, 2 H), 3.97 (s, 3 H), 5.29 - 5.39 (m, 1 H), 5.40 (s, 2 H), 7.09 (s, 1 H), 7.31 (d, J=6.0 Hz, 1 H), 7.91 (t, J=4.5 Hz, 1 H), 8.16 - 8.25 (m, 3 H), 8.67 (s, 1 H), 10.70 (s, 1 H).</p> <p>UPLC-MS (Method A2): Rt = 0.95 min</p> <p>MS (ESIpos): m/z = 494 (M+H)⁺</p>
274	 <p>6-(1-hydroxyethyl)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	Intermediate 6-16 and potassium 6-(1-hydroxyethyl)pyridine-2-carboxylate (Intermediate 19-1)	<p>(300 MHz, DMSO-d₆): δ = 1.52 (d, 3 H), 3.41 - 3.51 (m, 2 H), 3.58 (br. s., 4 H), 3.63 - 3.69 (m, 2 H), 4.00 (s, 2 H), 4.80 - 4.92 (m, 1 H), 5.39 (s, 2 H), 5.59 (d, 1 H), 7.10 (s, 1 H), 7.80 (dd, 1 H), 8.00 - 8.13 (m, 2 H), 8.21 (s, 1 H), 8.69 (s, 1 H), 10.79 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.85 min</p> <p>MS (ESIpos): m/z = 440 (M+H)⁺</p>
275	 <p>6-(cyclopropylamino)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	Intermediate 6-17 and 6-(cyclopropylamino)pyridine-2-carboxylic acid	<p>(400 MHz, DMSO-d₆): δ = 0.44 - 0.56 (m, 2 H), 0.77 - 0.87 (m, 3 H), 2.20 (s, 3 H), 2.25 - 2.31 (m, 2 H), 2.36 (br. s., 2 H), 2.63 - 2.74 (m, 1 H), 3.46 (br. s., 2 H), 3.54 (br. s., 2 H), 3.96 (s, 3 H), 5.36 (s, 2 H), 6.78 (d, 1 H), 7.06 (s, 1 H), 7.24 (s, 1 H), 7.36 (d, 1 H), 7.65 (t, 1 H), 8.18 (s, 1 H), 8.71 (s, 1 H), 10.79 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.89 min</p> <p>MS (ESIpos): m/z = 464 (M+H)⁺</p>

276	 <p>N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(propylamino)pyridine-2-carboxamide</p>	Intermediate 6-17 and 6-	(300 MHz, DMSO-d ₆ , selected signals): δ = 1.00 (t, 3 H), 1.59 - 1.74 (m, 2 H), 2.28 (s, 3 H), 2.41 (br. s., 2 H) 3.21 - 3.43 (m, 2 H), 3.49 (br. s., 2 H), 3.58 (br. s., 2 H), 3.98 (s, 3 H), 5.38 (s, 2 H), 6.72 (d, 1 H), 7.00 - 7.09 (m, 2 H), 7.26 (d, 1 H), 7.57 (dd, 1 H), 8.18 (s, 1 H), 8.69 (s, 1 H), 10.82 (s, 1 H). UPLC-MS (Method A1): Rt = 0.86 min MS (ESIpos): m/z = 466 (M+H) ⁺
277	 <p>(isobutylamino)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	Intermediate 6-17 and potassium 6-	(400 MHz, DMSO-d ₆): δ = 1.00 (d, 6 H) 1.94 (dt, 1 H) 2.20 (s, 3 H) 2.25 - 2.33 (m, 2 H) 2.33 - 2.41 (m, 2 H) 3.25 (t, 2 H) 3.41 - 3.50 (m, 2 H) 3.50 - 3.59 (m, 2 H) 3.99 (s, 3 H) 5.36 (s, 2 H) 6.71 - 6.80 (m, 1 H) 7.00 - 7.11 (m, 2 H) 7.22 - 7.30 (m, 1 H) 7.57 (dd, 1 H) 8.18 (s, 1 H) 8.70 (s, 1 H) 10.75 (s, 1 H). UPLC-MS (Method A1): Rt = 0.90 min MS (ESIpos): m/z = 480 (M+H) ⁺
278	 <p>6-(1-hydroxyethyl)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide</p>	Intermediate 6-17 and potassium 6-	(400 MHz, DMSO-d ₆): δ = 1.52 (d, 3 H), 2.21 (s, 3 H), 2.26 - 2.32 (m, 2 H), 2.34 - 2.39 (m, 2 H), 3.41 - 3.50 (m, 2 H), 3.51 - 3.58 (m, 2 H), 4.00 (s, 3 H), 4.87 (dd, 1 H), 5.37 (s, 2 H), 5.59 (d, 1 H), 7.09 (s, 1 H), 7.80 (dd, 1 H), 7.98 - 8.12 (m, 2 H), 8.21 (s, 1 H), 8.68 (s, 1 H), 10.79 (s, 1 H). UPLC-MS (Method A1): Rt = 0.69 min MS (ESIpos): m/z = 453 (M+H) ⁺

279	 <p>N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-4-methyl-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 6-17 and 4-methyl-6-(trifluoromethyl)pyridine-2-carboxylic acid (obtainable from Anichem Inc. USA)	<p>(300 MHz, DMSO-d₆): δ = 2.21 (s, 3 H), 2.25 - 2.33 (m, 2 H), 2.37 (br. s., 2 H), 2.58 (s, 3 H), 3.46 (br. s., 2 H), 3.54 (br. s., 2 H), 3.98 (s, 3 H), 5.38 (s, 2 H), 7.11 (s, 1 H), 8.08 (s, 1 H), 8.23 (s, 1 H), 8.30 (s, 1 H), 8.70 (s, 1 H), 10.52 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.99 min</p> <p>MS (ESIpos): m/z = 491 (M+H)⁺</p>
280	 <p>N-{6-(benzyloxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	Intermediate 6-21 and 2-[5-amino-6-(benzyloxy)-2H-indazol-2-yl]-1-(morpholin-4-yl)ethanone (Intermediate 6-20)	<p>(300 MHz, DMSO-d₆): δ = 3.43 - 3.53 (m, 2 H), 3.54 - 3.63 (m, 4 H), 3.63 - 3.69 (m, 2 H), 5.31 (s, 2 H), 5.41 (s, 2 H), 7.30 (s, 1 H), 7.41 (d, 3 H), 7.58 (d, 2 H), 8.18 (d, 1 H), 8.26 (s, 1 H), 8.35 - 8.44 (m, 1 H), 8.44 - 8.52 (m, 1 H), 8.81 (s, 1 H), 10.47 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.26 min</p> <p>MS (ESIpos): m/z = 540 (M+H)⁺</p>
281	 <p>6-(cyclopropylamino)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide</p>	Intermediate 6-5 and 6-(cyclopropylamino)pyridine-2-carboxylic acid	<p>(400 MHz, DMSO-d₆): δ = 0.47 - 0.55 (m, 2 H), 0.76 - 0.86 (m, 2 H), 1.00 - 1.11 (m, 7 H), 1.16 - 1.31 (m, 1 H), 1.37 - 1.50 (m, 1 H), 1.75 (t, 2 H), 2.64 - 2.77 (m, 1 H), 2.99 (t, 1 H), 3.95 (s, 3 H), 4.03 (d, 1 H), 4.18 (s, 1 H), 4.42 (d, 1 H), 5.32 (d, 1 H), 5.38 (d, 1 H), 6.78 (d, 1 H), 7.06 (s, 1 H), 7.25 (d, 1 H), 7.36 (d, 1 H), 7.65 (dd, 1 H), 8.19 (s, 1 H), 8.71 (s, 1 H), 10.79 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.10 min</p> <p>MS (ESIpos): m/z = 507 (M+H)⁺</p>

282	 <p>6</p> <p>-(butylamino)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide</p>	Intermediate 6-5 and 6- (butylamino) pyridine-2-carboxylic acid	<p>(300 MHz, DMSO-d₆): δ = 0.95 (t, 3 H), 1.04 (s, 7 H), 1.18 - 1.31 (m, 1 H), 1.37 - 1.51 (m, 3 H), 1.55 - 1.68 (m, 2 H), 1.68 - 1.81 (m, 2 H), 2.87 - 3.05 (m, 1 H), 3.36 - 3.47 (m, 2 H), 3.97 (s, 3 H), 4.05 (br. s., 1 H), 4.18 (s, 1 H), 4.41 (d, 1 H), 5.38 (d, 1 H), 5.32 (d, 1 H), 6.72 (d, 1 H), 7.02 (t, 1 H), 7.07 (s, 1 H), 7.26 (d, 1 H), 7.50 - 7.63 (m, 1 H), 8.19 (s, 1 H), 8.69 (s, 1 H), 10.81 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.12 min</p> <p>MS (ESIpos): m/z = 523 (M+H)⁺</p>
283	 <p>N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-[(2-methoxyethyl)amino]pyridine-2-carboxamide</p>	Intermediate 6-5 and 6- [(2-methoxyethyl)amino]pyridine-2-carboxylic acid (prepared according to Synthesis Scheme 8, obtainable from Ukrorgsyntez Ltd., Order Number BBV-33897975)	<p>(300 MHz, DMSO-d₆, selected signals): δ = 1.04 (s, 7 H), 1.17 - 1.31 (m, 1 H), 1.35 - 1.51 (m, 1 H), 1.75 (t, 2 H), 2.99 (t, 1 H), 3.60 (s, 4 H), 3.94 - 4.09 (m, 1 H), 3.99 (s, 3 H), 4.18 (s, 1 H), 4.42 (d, 1 H), 5.38 (d, 1 H), 5.32 (d, 1 H), 6.77 (d, 1 H), 7.07 (s, 1 H), 7.14 (br. s., 1 H), 7.28 (d, 1 H), 7.52 - 7.64 (m, 1 H), 8.19 (s, 1 H), 8.68 (s, 1 H), 10.82 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 0.90 min</p> <p>MS (ESIpos): m/z = 525 (M+H)⁺</p>

284	 <p>N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(propylamino)pyridine-2-carboxamide</p>	Intermediate 6-5 and 6-(propylamino)pyridine-2-carboxylic acid	<p>(300 MHz, DMSO-d₆): δ = 1.04 (s, 6 H), 1.00 (t, 3 H), 1.12 (br. s., 1 H), 1.15 - 1.30 (m, 1 H), 1.34 - 1.51 (m, 1 H), 1.58 - 1.83 (m, 2 H), 1.67 (sxt, 2 H), 2.91 - 3.07 (m, 1 H), 3.35 - 3.42 (m, 2 H), 3.98 (s, 4 H), 4.05 (br. s., 1 H), 4.18 (s, 1 H), 4.42 (d, 1 H), 5.35 (d, 2 H), 6.72 (d, 1 H), 7.02 - 7.10 (m, 2 H), 7.26 (d, 1 H), 7.57 (dd, 1 H), 8.19 (s, 1 H), 8.69 (s, 1 H), 10.82 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.09 min</p> <p>MS (ESIpos): m/z = 509 (M+H)⁺</p>
285	 <p>N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(isobutylamino)pyridine-2-carboxamide</p>	Intermediate 6-5 and 6-(isobutylamino)pyridine-2-carboxylic acid	<p>(300 MHz, DMSO-d₆): δ = 0.99 (s, 3 H), 1.01 (s, 3 H), 1.03 - 1.08 (m, 7 H), 1.19 - 1.28 (m, 1 H), 1.38 - 1.50 (m, 1 H), 1.75 (t, 2 H), 1.94 (dt, 1 H), 2.99 (br. s., 1 H), 3.25 (t, 2 H), 3.99 (s, 3 H), 4.03 (d, 1 H), 4.16 (s, 1 H), 4.42 (d, 1 H), 5.38 (d, 1 H), 5.32 (d, 1 H), 6.75 (dd, 1 H), 7.07 (s, 1 H), 7.05 (t, 1 H), 7.23 - 7.29 (m, 1 H), 7.57 (dd, 1 H), 8.15 - 8.20 (m, 1 H), 8.70 (s, 1 H), 10.75 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.16 min</p> <p>MS (ESIpos): m/z = 523 (M+H)⁺</p>
286	 <p>5-fluoro-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide</p>	Intermediate 6-5 and 5-fluoro-6-methylpyridine-2-carboxylic acid	<p>(300 MHz, DMSO-d₆): δ = 1.04 (s, 6 H), 1.07 - 1.15 (m, 1 H), 1.17 - 1.35 (m, 1 H), 1.36 - 1.52 (m, 1 H), 1.75 (t, 2 H), 2.59 (d, 3 H), 2.99 (t, 1 H), 3.96 - 4.08 (m, 1 H), 4.00 (s, 3 H), 4.19 (s, 1 H), 4.41 (d, 1 H), 5.33 (d, 1 H), 5.39 (d, 1 H), 7.09 (s, 1 H), 7.90 (t, 1 H), 8.09 (dd, 1 H), 8.21 (s, 1 H), 8.68 (s, 1 H), 10.52 (s, 1 H).</p>

- * The reaction of Intermediate 6-16 and potassium 6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxylate gave N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxamide as a racemic mixture. This mixture was separated
5 into the pure enantiomers by preparative chiral HPLC using the following conditions:

System: Agilent: Prep 1200, 2xPrep Pump, DLA, MWD, Gilson: Liquid Handler 215

Column: Chiralpak IC 5 μ m 250x30 mm

Solvent: ethanol / methanol 50:50 (v/v)

Flow rate: 35 ml/min

Temperature: room temperature

Solution: 401 mg / 8 ml dichloromethane/MeOH

Injection: 10 x 0.8 ml

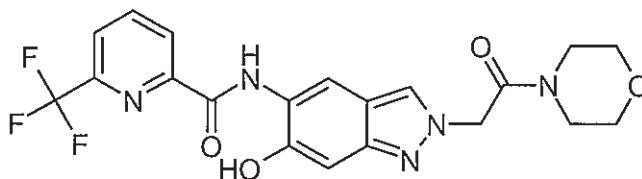
Detection: UV 280 nm

Fraction	Rt in min	Purity in %	Amount in mg	Peak assignment
corresponds to Example 273	8.0 – 8.7	98.8	70	peak 2 – 2.88 min
corresponds to Example 272	10.1 – 11.1	99.1	59	peak 4 – 3.81 min

Workup: The fractions were concentrated by evaporation, admixed with tBuOH, frozen at -65°C and then freeze-dried.

Example 287

- 5 N-{6-Hydroxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



- 2.43 g (4.50 mmol) of N-{6-(benzyloxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide (Beispiel 280) were suspended in 470 ml of tetrahydrofuran, and the flask was evacuated and then flushed with nitrogen (this procedure was repeated two more times). 958 mg (0.9 mmol, 10%) of palladium on carbon and 95 ml (370.6 mmol) of a 25% strength ammonium formate solution was added and the mixture was stirred vigorously at 25°C for 40 minutes. The reaction mixture was filtered through Celite and concentrated. The precipitate formed was filtered off with suction, washed repeatedly with water and dried in a drying cabinet at 50°C under reduced pressure. This gave 2.01 g (90% of theory) of the title compound.

UPLC-MS (Method A2): Rt = 0.64 min

MS (ESIpos): m/z = 450 (M+H)⁺

- ¹H NMR (400 MHz, DMSO-d₆): δ = 3.40 - 3.50 (m, 2 H), 3.52 - 3.61 (m, 4 H), 3.61 - 3.67 (m, 2 H), 5.36 (s, 2 H), 6.91 (s, 1 H), 8.16 - 8.23 (m, 2 H), 8.40 (t, 1 H), 8.47 (d, 1 H), 8.69 (s, 1 H), 10.55 (s, 1 H), 10.65 (s, 1 H).

General Procedure 3a

1.0 equivalent of N-{6-hydroxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide was stirred with 1.5 equivalents of the appropriate halide and 3.0 equivalents of potassium carbonate in *N,N*-dimethylformamide at 100°C in the microwave for 1 h. Water was added to the reaction mixture, and the resulting precipitate was filtered off,
 5 washed with water and diethyl ether and dried.

General Procedure 3b

1.0 equivalent of N-{6-hydroxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide was stirred with 1.5 equivalents of the appropriate halide
 10 and 3.0 equivalents of potassium carbonate in *N,N*-dimethylformamide at 100°C in the microwave for 1 h. The reaction mixture was filtered, dimethyl sulphoxide was added and the product was purified by preparative HPLC according to Method P1.

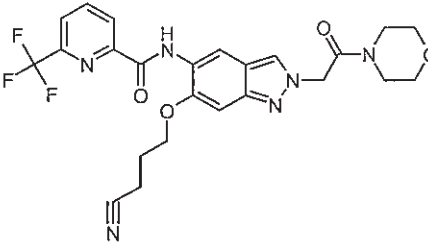
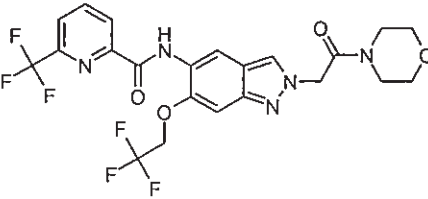
General Procedure 3c

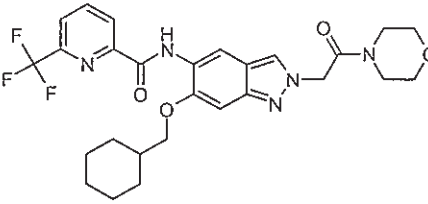
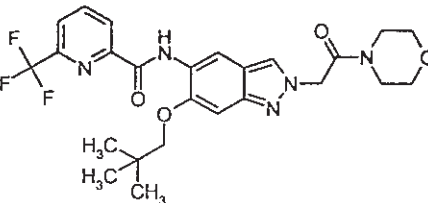
15 1.0 equivalent of N-{6-hydroxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide was stirred with 3.0 equivalents of the appropriate halide, 5.0 equivalents of potassium carbonate and 0.1 equivalent of potassium iodide in *N,N*-dimethylformamide at 150°C in the microwave for 1 h. The reaction mixture was filtered, dimethyl sulphoxide was added and the product was purified by preparative HPLC according to Method P5
 20 (gradient: 0 - 15 min 10 – 50% B).

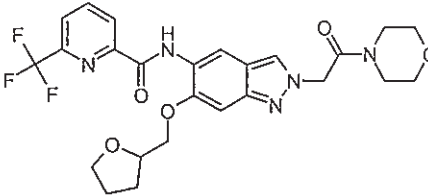
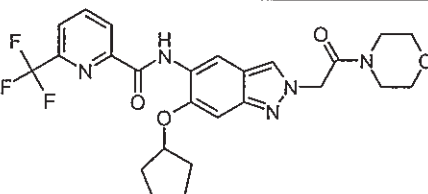
Table 20: Examples 304 – 328

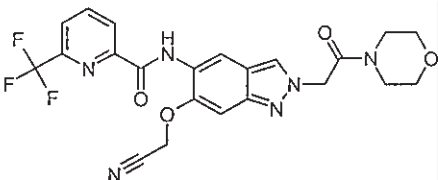
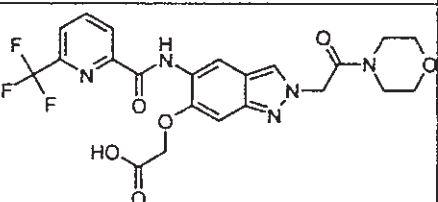
The exemplary compounds were prepared from N-{6-hydroxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-
 25 2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide and the halides listed in the table according to General Procedures 3a, 3b or 3c.

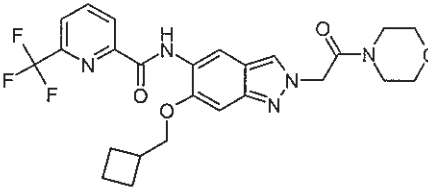
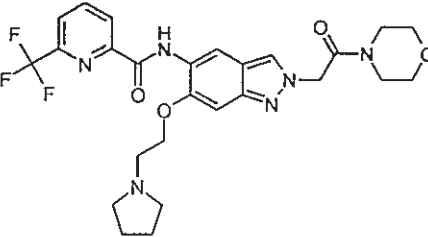
Ex. No.	Structure/Name	Prepared by reaction with	* see key	¹ H-NMR / LC-MS
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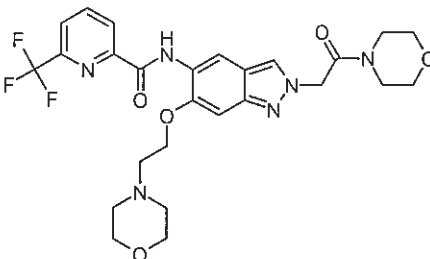
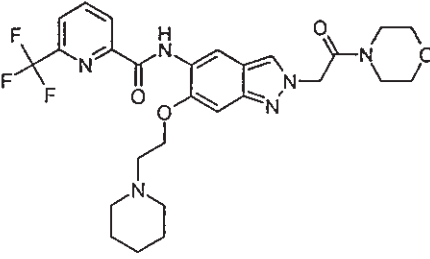
288	 <p>N-{6-(3-cyanopropoxy)-2-[2-(trifluoromethyl)pyridine-2-carboxamido]-2H-indazol-5-yl}-2-morpholin-4-ylethanol</p>	4-bromobutane nitrile	3a (87%)	<p>(400 MHz, DMSO-d₆): δ = 2.21 (quin, 2 H), 2.77 (t, 2 H), 3.43 - 3.51 (m, 2 H), 3.53 - 3.62 (m, 4 H), 3.63 - 3.69 (m, 2 H), 4.25 (t, 2 H), 5.40 (s, 2 H), 7.13 (s, 1 H), 8.22 (dd, 1 H), 8.24 - 8.26 (m, 1 H), 8.37 - 8.45 (m, 1 H), 8.45 - 8.50 (m, 1 H), 8.74 (s, 1 H), 10.55 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.05 min MS (ESIpos): m/z = 517 (M+H)⁺</p>
289	 <p>N-{2-[2-(2,2,2-trifluoroethoxy)-2H-indazol-5-yl]-2-morpholin-4-ylethanol}-6-(2,2,2-trifluoroethoxy)-2-(trifluoromethyl)pyridine-2-carboxamide</p>	1,1,1-trifluoro-2-iodoethane	3b ^[b] (21%)	<p>(300 MHz, DMSO-d₆): δ = 3.43 - 3.50 (m, 2 H), 3.53 - 3.63 (m, 5 H), 3.63 - 3.69 (m, 2 H), 5.01 (d, 1 H), 4.95 (d, 1 H), 5.43 (s, 2 H), 7.30 (s, 1 H), 8.21 (d, 1 H), 8.30 (s, 1 H), 8.41 (t, 1 H), 8.45 - 8.51 (m, 1 H), 8.81 (s, 1 H), 10.53 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.16 min MS (ESIpos): m/z = 532 (M+H)⁺</p>

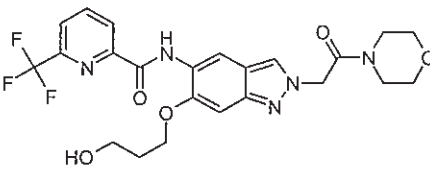
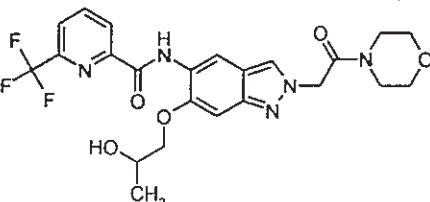
290	 <p>N-{6-(cyclohexylmethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	(bromomethyl)cyclohexane	3b (70%)	<p>(300 MHz, DMSO-d₆): δ = 1.07 - 1.37 (m, 6 H), 1.64 - 1.81 (m, 2 H), 1.86 - 2.02 (m, 3 H), 3.42 - 3.50 (m, 2 H), 3.53 - 3.69 (m, 6 H), 3.97 (d, 2 H), 5.39 (s, 2 H), 7.08 (s, 1 H), 8.18 - 8.25 (m, 2 H), 8.40 (t, 1 H), 8.48 (d, 1 H), 8.79 (s, 1 H), 10.48 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.40 min</p> <p>MS (ESIpos): m/z = 546 (M+H)⁺</p>
291	 <p>N-{6-(2,2-dimethylpropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-iodo-2,2-dimethylpropane	3b (22%)	<p>(300 MHz, DMSO-d₆): δ = 1.03 - 1.21 (m, 9 H), 3.39 - 3.53 (m, 2 H), 3.53 - 3.73 (m, 6 H), 3.84 (s, 2 H), 5.40 (s, 2 H), 7.07 (s, 1 H), 8.18 - 8.26 (m, 2 H), 8.41 (t, 1 H), 8.51 (d, 1 H), 8.82 (s, 1 H), 10.47 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.30 min</p> <p>MS (ESIpos): m/z = 520 (M+H)⁺</p>

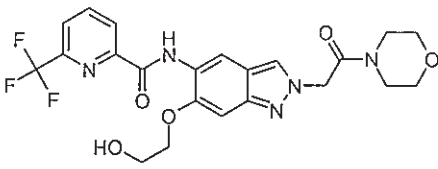
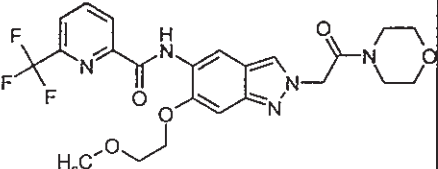
292	 <p>N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-(tetrahydrofuran-2-ylmethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	2-(bromomethyl)tetrahydrofuran	3b (41%)	<p>(300 MHz, DMSO-d₆): δ = 1.70 - 2.00 (m, 3 H), 2.05 - 2.20 (m, 1 H), 3.47 (d, 2 H), 3.53 - 3.68 (m, 7 H), 3.68 - 3.77 (m, 1 H), 3.77 - 3.89 (m, 1 H), 4.07 - 4.22 (m, 2 H), 4.22 - 4.34 (m, 1 H), 5.40 (s, 2 H), 7.14 (s, 1 H), 8.17 - 8.29 (m, 2 H), 8.41 (t, 1 H), 8.48 (d, 1 H), 8.75 (s, 1 H), 10.51 (s, 1 H).</p> <p>LC-MS (Method A3): R_t = 1.07 min</p> <p>MS (ESIpos): m/z = 534 (M+H)⁺</p>
293	 <p>N-{6-(cyclopentyloxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	iodocyclopentane	3b ^[c] (23%)	<p>(300 MHz, DMSO-d₆): δ = 1.67 (dd, 2 H), 1.80 (dd, 2 H), 1.86 - 1.96 (m, 2 H), 1.97 - 2.10 (m, 2 H), 3.47 (d, 2 H), 3.54 - 3.62 (m, 4 H), 3.65 (d, 2 H), 5.07 (t, 1 H), 5.38 (s, 2 H), 7.07 (s, 1 H), 8.18 - 8.24 (m, 2 H), 8.40 (t, 1 H), 8.47 (d, 1 H), 8.75 (s, 1 H), 10.62 (s, 1 H).</p> <p>UPLC-MS (Method A2): R_t = 1.29 min</p> <p>MS (ESIpos): m/z = 518 (M+H)⁺</p>

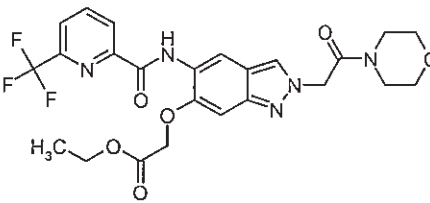
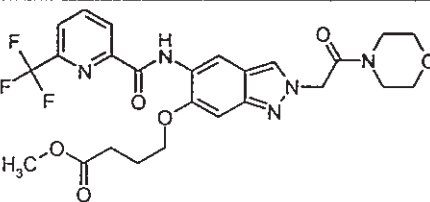
294	 <p>N-{6-(cyanomethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	bromoacetonitrile	3b ^[d] (10%)	<p>(300 MHz, DMSO-d₆): δ = 3.47 (d, 2 H), 3.55 - 3.62 (m, 4 H), 3.65 (d, 2 H), 5.39 (s, 2 H), 5.44 (s, 2 H), 7.31 (s, 1 H), 8.23 (dd, 1 H), 8.30 (s, 1 H), 8.42 (d, 1 H), 8.46 (s, 1 H), 8.73 (s, 1 H), 10.41 (s, 1 H).</p> <p>UPLC-MS (Method A2): Rt = 1.01 min MS (ESIpos): m/z = 489 (M+H)⁺</p>
295	 <p>({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)acetic acid</p>	bromoacetic acid	3c (9%)	<p>(300 MHz, DMSO-d₆): δ = 3.47 (d, 2 H), 3.52 - 3.71 (m, 6 H), 4.90 (s, 2 H), 5.41 (s, 2 H), 7.12 (s, 1 H), 8.16 - 8.29 (m, 2 H), 8.40 (t, 1 H), 8.48 (d, 1 H), 8.77 (s, 1 H), 10.58 (s, 1 H), 13.20 (br. s., 1 H).</p> <p>UPLC-MS (Method A2): Rt = 0.61 min MS (ESIpos): m/z = 508 (M+H)⁺</p>

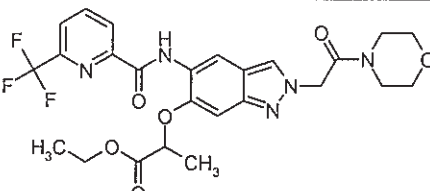
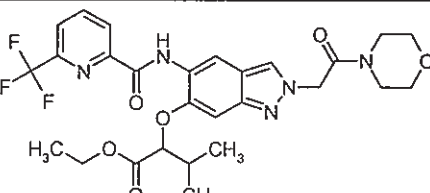
296	 <p>N-{6-(cyclobutylmethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	(bromomethyl)cyclobutane	3a (59%)	<p>(300 MHz, DMSO-d₆): δ = 1.82 - 2.04 (m, 4 H), 2.09 - 2.24 (m, 2 H), 2.78 - 2.95 (m, 1 H), 3.47 (d, 2 H), 3.52 - 3.73 (m, 6 H), 4.15 (d, 2 H), 5.40 (s, 2 H), 7.10 (s, 1 H), 8.16 - 8.28 (m, 2 H), 8.40 (t, 1 H), 8.48 (d, 1 H), 8.76 (s, 1 H), 10.52 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 1.32 min MS (ESIpos): m/z = 518 (M+H)⁺</p>
297	 <p>N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-[2-(pyrrolidin-1-yl)ethoxy]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(2-chloroethyl)pyrrolidine hydrochloride	3a (54%)	<p>(400 MHz, DMSO-d₆): δ = 1.65 (dt, 4 H), 2.57 (br. s., 4 H), 2.97 (t, 2 H), 3.42 - 3.50 (m, 2 H), 3.54 - 3.61 (m, 4 H), 3.61 - 3.68 (m, 2 H), 4.28 (t, 2 H), 5.39 (s, 2 H), 7.13 (s, 1 H), 8.19 - 8.25 (m, 2 H), 8.41 (t, 1 H), 8.48 (d, 1 H), 8.75 (s, 1 H), 10.58 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.77 min MS (ESIpos): m/z = 547 (M+H)⁺</p>

298	 <p>N-{6-[2-(morpholin-4-yl)ethoxy]-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	4-(2-chloroethyl)morpholine hydrochloride	3a (64%)	<p>(400 MHz, DMSO-d₆, selected signals): δ = 2.84 - 2.93 (m, 2 H), 3.43 - 3.51 (m, 2 H), 3.51 - 3.62 (m, 8 H), 3.62 - 3.69 (m, 2 H), 4.31 (t, 2 H), 5.40 (s, 2 H), 7.16 (s, 1 H), 8.18 - 8.26 (m, 2 H), 8.41 (t, 1 H), 8.48 (d, 1 H), 8.74 (s, 1 H), 10.57 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.75 min MS (ESIpos): m/z = 563 (M+H)⁺</p>
299	 <p>N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-[2-(piperidin-1-yl)ethoxy]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-(2-chloroethyl)piperidine hydrochloride	3a (72%)	<p>(300 MHz, DMSO-d₆, selected signals): δ = 1.29 - 1.40 (m, 2 H), 1.40 - 1.53 (m, 4 H), 2.73 (s, 1 H), 2.84 (t, 2 H), 3.42 - 3.51 (m, 2 H), 3.58 (br. s., 4 H), 3.62 - 3.68 (m, 2 H), 4.27 (t, 2 H), 5.40 (s, 2 H), 7.14 (s, 1 H), 8.19 - 8.25 (m, 2 H), 8.41 (t, 1 H), 8.48 (d, 1 H), 8.74 (s, 1 H), 10.58 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.83 min MS (ESIpos): m/z = 561 (M+H)⁺</p>

300	 <p>N-{6-(3-hydroxypropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	(3-bromopropoxy)(tert-butyl)dimethylsilane	3a (72%) [^q] (49%)	<p>(300 MHz, DMSO-d₆): δ = 1.93 - 2.08 (m, 2 H), 3.43 - 3.52 (m, 2 H), 3.52 - 3.77 (m, 8 H), 4.24 (t, 2 H), 4.59 (t, 1 H), 5.40 (s, 2 H), 7.10 (s, 1 H), 8.17 - 8.25 (m, 2 H), 8.36 - 8.44 (m, 1 H), 8.45 - 8.50 (m, 1 H), 8.75 (s, 1 H), 10.64 (s, 1 H).</p> <p>UPLC-MS (Method A1): Rt = 0.97 min</p> <p>MS (ESIpos): m/z = 508 (M+H)⁺</p>
301	 <p>N-{6-(2-hydroxypropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	[(1-bromopropan-2-yl)oxy](tert-butyl)dimethylsilane	3a (66%) [^q] (46%)	<p>(300 MHz, DMSO-d₆): δ = 1.32 (d, 3 H), 3.42 - 3.51 (m, 2 H), 3.51 - 3.61 (m, 4 H), 3.61 - 3.69 (m, 2 H), 3.86 - 3.95 (m, 1 H), 4.05 - 4.16 (m, 2 H), 4.96 (d, 1 H), 5.40 (s, 2 H), 7.09 (s, 1 H), 8.18 - 8.25 (m, 2 H), 8.35 - 8.44 (m, 1 H), 8.44 - 8.52 (m, 1 H), 8.76 (s, 1 H), 10.54 (s, 1 H).</p> <p>UPLC-MS (Method A2): Rt = 0.98 min</p> <p>MS (ESIpos): m/z = 508 (M+H)⁺</p>

302	 <p>N-{6-(2-hydroxyethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	tert-Butyl(2-iodoethoxy)dimethylsilane	3a (52%) [f] (77%)	<p>(300 MHz, DMSO-d₆): δ = 3.42 - 3.51 (m, 2 H), 3.58 (br. s., 4 H), 3.62 - 3.68 (m, 2 H), 3.89 (q, 2 H), 4.20 (t, 2 H), 4.89 (t, 1 H), 5.40 (s, 2 H), 7.12 (s, 1 H), 8.21 (dd, 1 H), 8.24 (s, 1 H), 8.35 - 8.44 (m, 1 H), 8.44 - 8.49 (m, 1 H), 8.73 (s, 1 H), 10.66 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 0.84 min</p> <p>MS (ESIpos): m/z = 494 (M+H)⁺</p>
303	 <p>N-{6-(2-methoxyethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide</p>	1-bromo-2-methoxyethane	3b ^[b] (27%)	<p>(300 MHz, DMSO-d₆): δ = 3.36 (s, 3 H), 3.42 - 3.51 (m, 2 H), 3.54 - 3.62 (m, 4 H), 3.62 - 3.69 (m, 2 H), 3.82 (dd, 2 H), 4.30 (dd, 2 H), 5.40 (s, 2 H), 7.13 (s, 1 H), 8.20 - 8.25 (m, 2 H), 8.37 - 8.44 (m, 1 H), 8.45 - 8.50 (m, 1 H), 8.77 (s, 1 H), 10.58 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.01 min</p> <p>MS (ESIpos): m/z = 508 (M+H)⁺</p>

304	 <p>ethyl ({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-([6-(trifluoromethyl)pyridin-2-yl]carbonyl)amino)-2H-indazol-6-yl}oxy)acetate</p>	ethyl bromoacetate	3b ^[h] (59%)	<p>(300 MHz, DMSO-d₆): δ = 1.21 (t, 3 H), 3.42 - 3.50 (m, 2 H), 3.52 - 3.62 (m, 4 H), 3.63 - 3.68 (m, 2 H), 4.20 (q, 2 H), 5.02 (s, 2 H), 5.41 (s, 2 H), 8.22 (dd, 1 H), 8.26 (s, 1 H), 8.36 - 8.45 (m, 1 H), 8.46 - 8.51 (m, 1 H), 8.76 (s, 1 H), 10.56 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.05 min</p> <p>MS (ESIpos): m/z = 536 (M+H)⁺</p>
305	 <p>methyl 4-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-([6-(trifluoromethyl)pyridin-2-yl]carbonyl)amino)-2H-indazol-6-yl}oxy)butanoate</p>	methyl 4- bromobutano ate	3b ^[h] (46%)	<p>(300 MHz, DMSO-d₆): δ = 2.07 - 2.23 (m, 2 H), 2.62 (t, 2 H), 3.40 - 3.51 (m, 2 H), 3.59 (s, 3 H), 3.53 - 3.63 (m, 4 H), 3.65 (br. s., 2 H), 4.19 (t, 2 H), 5.40 (s, 2 H), 7.08 (s, 1 H), 8.21 (dd, 1 H), 8.23 (s, 1 H), 8.34 - 8.52 (m, 1 H), 8.40 (t, 1 H), 8.74 (s, 1 H), 10.58 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.05 min</p> <p>MS (ESIpos): m/z = 550 (M+H)⁺</p>

306	 <p>ethyl 2-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)propanoate</p>	ethyl 2-bromopropanoate	3b ^[h] (46%)	<p>(300 MHz, DMSO-d₆): δ = 1.13 (t, 3 H), 1.68 (d, 3 H), 3.43 - 3.52 (m, 2 H), 3.53 - 3.62 (m, 4 H), 3.62 - 3.69 (m, 2 H), 4.13 (q, 2 H), 5.28 (q, 1 H), 5.40 (s, 2 H), 7.07 (s, 1 H), 8.22 (dd, 1 H), 8.26 (s, 1 H), 8.38 - 8.44 (m, 1 H), 8.46 - 8.51 (m, 1 H), 8.75 (s, 1 H), 10.81 (s, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.12 min</p> <p>MS (ESIpos): m/z = 550 (M+H)⁺</p>
307	 <p>ethyl 3-methyl-2-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)butanoate</p>	ethyl 2-bromopropanoate	3b ^[h] (51%)	<p>(300 MHz, DMSO-d₆): δ = 1.09 - 1.18 (m, 9 H), 2.38 (d, 1 H), 3.43 - 3.49 (m, 2 H), 3.53 - 3.62 (m, 4 H), 3.62 - 3.67 (m, 2 H), 4.16 (q, 2 H), 4.99 (d, 1 H), 5.40 (s, 2 H), 6.99 (s, 1 H), 8.22 (dd, 1 H), 8.26 (s, 1 H), 8.42 (t, 1 H), 8.50 - 8.54 (m, 1 H), 8.82 (s, 1 H), 10.53 - 10.56 (m, 1 H).</p> <p>LC-MS (Method A3): Rt = 1.24 min</p> <p>MS (ESIpos): m/z = 578 (M+H)⁺</p>

* Prepared according to the stated procedure, the yield in % is indicated in brackets

[a]: After 60 minutes, another 1 equivalent of the halide was added and the mixture was stirred in the microwave at 120°C for a further 60 minutes.

5 [b]: The crude product was purified by preparative HPLC.

[c]: The crude product was purified by preparative HPLC according to Method P5 (gradient: 0 - 15 min 30 - 70% B).

[d]: The reaction mixture was added to water, the precipitate was filtered off with suction and washed with diethyl ether. The crude product was purified by preparative HPLC according to Method P5 (gradient: 0 - 15 min 15 – 55% B).

[e]: The crude product was purified by preparative HPLC according to Method P5 (gradient: 0 - 15 min 15 – 55% B).

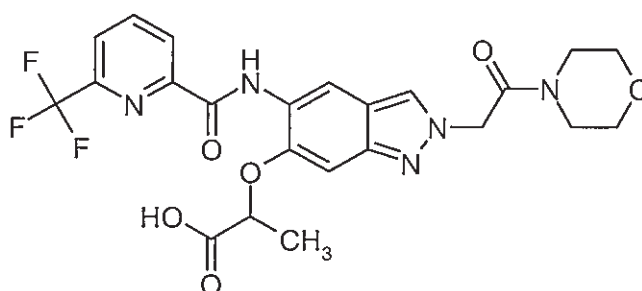
[f] The following procedure was used for deprotecting the alkylated intermediate (the 2nd yield in % indicated in the table refers to the deprotection). 1 equivalent of the silyl-protected intermediate was dissolved in tetrahydrofuran, 3 equivalents of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran were added and the mixture was stirred at 25°C for 24 h. Water was added to the reaction mixture and the resulting precipitate was filtered off with suction, washed with water and dried in a drying cabinet at 50°C under reduced pressure.

[g]: Another 0.1 equivalent of potassium iodide was added to the reaction mixture.

[h]: The crude product was purified by preparative HPLC (column: XBridge C18 5µm 100x30 mm).

Example 308

2-({2-[2-(Morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)propanoic acid



Analogously to Intermediate 4-1, 50 mg (0.09 mmol) of ethyl 2-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)propanoate (Example 306) were dissolved in 0.5 ml of tetrahydrofuran, a solution of 11 mg (0.45 mmol) of lithium hydroxide monohydrate in 164 µl of water was added and the mixture was stirred at 25°C for 24 h. The reaction mixture was filtered, dimethyl sulphoxide was added and the product was purified by preparative HPLC (column: XBridge C18 5µm 100x30 mm). This gave 7 mg (15% of theory) of the title compound.

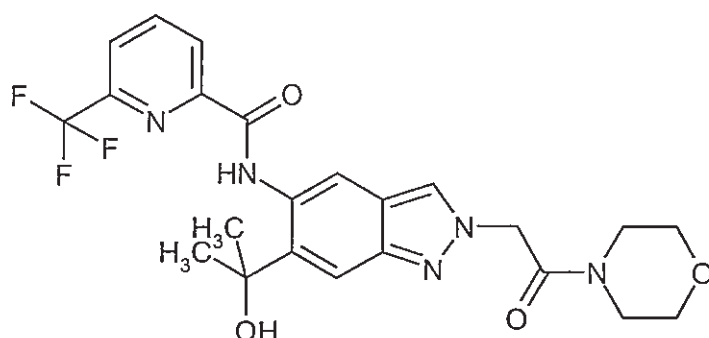
UPLC-MS (Method A2): Rt = 0.67 min

MS (ESIpos): m/z = 522 (M+H)⁺

¹H NMR (400 MHz, DMSO-d₆): δ = 1.64 (d, 3 H), 3.46 (br. s., 2 H), 3.58 (br. s., 4 H), 3.64 (d, 2 H), 4.99 (d, 1 H), 5.38 (s, 2 H), 6.97 (s, 1 H), 8.15 - 8.25 (m, 2 H), 8.35 - 8.45 (m, 1 H), 8.45 - 8.51 (m, 1 H), 8.73 (s, 1 H), 10.82 (s, 1 H).

Example 309

N-{6-(2-Hydroxypropan-2-yl)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide



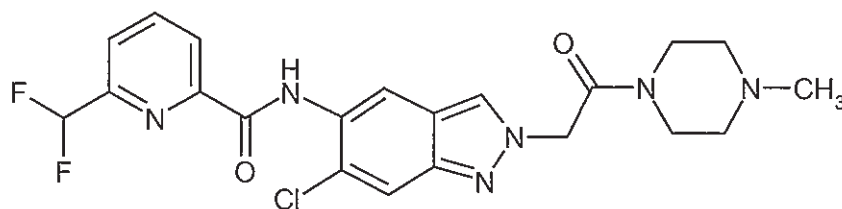
5 536 mg (4 equiv.) of 2-bromo-1-(morpholin-4-yl)ethanone were added to a mixture of 250 mg (0.69 mmol) of N-[6-(2-hydroxypropan-2-yl)-1H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate 14-11) and 0.59 ml of N,N-dicyclohexylmethylamine in 1.5 ml of THF, and the mixture was stirred at 70°C overnight. Water was added, the mixture was extracted with ethyl acetate and the extract was washed with saturated aqueous sodium chloride solution, filtered
10 through a hydrophobic filter and concentrated. The residue was purified by column chromatography on silica gel (dichloromethane / methanol). This gave 46 mg (14% of theory) of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 1.62 (s, 6H), 3.46 (d, 3H), 3.42 - 3.69 (m), 5.45 (s, 2H), 5.95 (s, 1H), 7.54 (s, 1H), 8.15 (dd, 1H), 8.25 (s, 1H), 8.36 (t, 1H), 8.45 (d, 1H), 8.73 (s, 1H), 12.35
15 (s, 1H).

UPLC-MS (Method A2): Rt = 0.99 min (UV-TIC), mass found 491.00.

Example 310

20 N-{6-Chloro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(difluoromethyl)pyridine-2-carboxamide



98 mg (0.32 mmol) of 2-(5-amino-6-chloro-2H-indazol-2-yl)-1-(4-methylpiperazin-1-yl)ethanone (Intermediate 6-21) and 82 mg of 6-(difluoromethyl)pyridine-2-carboxylic acid were initially charged in 3.0 ml of THF, 49 mg of 1-hydroxy-1H-benzotriazole hydrate, 121 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.13 ml of triethylamine were added
25 and the mixture was stirred at room temperature for 19.5 h. The mixture was diluted with water and

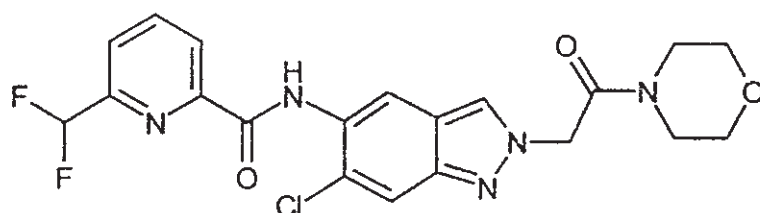
the precipitated solid was filtered off, washed twice with water and three times with diethyl ether and dried under reduced pressure. This gave 129 mg of the title compound.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm]= 2.21 (s, 3H), 2.25 – 2.42 (m, 4H), 3.42 - 3.59 (m, 4H), 5.50 (s, 2H), 7.14 (t, 1H), 7.91 (s, 1H), 8.02 (dd, 1H), 8.29 - 8.44 (m, 3H), 8.64 (s, 1H), 10.60 (s, 1H).

UPLC-MS (Method A2): Rt = 1.06 min (UV-TIC), mass found 462.00.

Example 311

N-{6-Chloro-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(difluoromethyl)pyridine-2-carboxamide



Analogously to the preparation of Example 310, 137 mg of 2-(5-amino-6-chloro-2H-indazol-2-yl)-1-(morpholin-4-yl)ethanone (Intermediate 6-22) were reacted with 70 mg of 6-(difluoromethyl)pyridine-2-carboxylic acid at room temperature for 68 h. Water was added and the solid was filtered off with suction, washed with acetone, water and diethyl ether and dried under reduced pressure. This gave 91 mg of the title compound.

UPLC-MS (Method A1): Rt = 1.06 min (UV-TIC), mass found 449.00.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm]= 3.42 - 3.68 (m, 8H), 5.50 (s, 2H), 7.90 (s, 1H), 8.01 (dd, 1H), 8.29 - 8.36 (m, 2H), 8.41 (d, 1H), 8.64 (s, 1H), 10.59 (s, 1H).

Assessment of physiological efficacy

5 The in-vitro activity of the compounds according to the invention can be shown in the following assays:

Irak4 kinase assay

10 The Irak4-inhibitory activity of the substances according to the invention of the present invention was measured in the Irak4 TR-FRET assay (TR-FRET = Time Resolved Fluorescence Resonance Energy Transfer) described in the paragraphs that follow.

Recombinant fusion protein from N-terminal GST (glutathione S-transferase) and human Irak4, expressed in baculovirus-infected insect cells (Hi5, BTI-TN-5B1-4, cell line purchased from Invitrogen, catalogue No. B855-02) and purified via affinity chromatography, was used as enzyme.
15 The substrate used for the kinase reaction was the biotinylated peptide biotin-Ahx-KKARFSRFAGSSPSQASFAEPG (C-terminus in amide form) which can be purchased, for example, from Biosyntan GmbH (Berlin-Buch).

For the assay, 11 different concentrations in the range from 20 μ M to 0.073 nM were prepared from a 2 mM solution of the test substance in DMSO. For the assay, 50 nl of the respective solution
20 were pipetted into a black low-volume 384-well microtitre plate (Greiner Bio-One, Frickenhausen, Germany), 2 μ l of a solution of Irak4 in assay buffer [50 mM HEPES pH 7.5, 5 mM MgCl₂, 1.0 mM dithiothreitol, 30 μ M activated sodium orthovanadate, 0.1 % (w/v) of bovine gamma-globulin (BGG) 0.04% (v/v) nonidet-P40 (Sigma)] were added and the mixture was incubated for 15 min to allow prebinding of the substances to the enzyme prior to the kinase reaction. The kinase reaction
25 was then started by addition of 3 μ l of a solution of adenosine triphosphate (ATP, 1.67 mM = final concentration in 5 μ l of assay volume: 1 μ M) and peptide substrate (0.83 μ M = final concentration in 5 μ l assay volume: 0.5 μ M) in assay buffer, and the resulting mixture was incubated at 22°C for the reaction time of 45 min. The concentration of the Irak4 was adjusted to the respective activity of the enzyme and set such that the assay was carried out in the linear range. Typical concentrations
30 were in the order of about 0.2 nM. The reaction was stopped by addition of 5 μ l of a solution of TR-FRET detection reagents [0.1 μ M streptavidin-XL665 (Cisbio Bioassays; France, catalogue No. 610SAXLG) and 1.5 nM anti-phosphoserin antibody [Merck Millipore, "STK Antibody", catalogue No. 35-002] and 0.6 nM LANCE EU-W1024-labelled anti-mouse-IgG antibody (Perkin-Elmer, product No. AD0077, alternatively it is possible to use a terbium cryptate-labelled anti-
35 mouse-IgG antibody from Cisbio Bioassays) in aqueous EDTA solution (100 mM EDTA, 0.4 % [w/v] bovine serum albumin [BSA] in 25 mM HEPES pH 7.5).

The resulting mixture was incubated at 22°C for 1 h to allow formation of a complex of the biotinylated phosphorylated substrate and the detection reagents. The amount of the phosphorylated substrate was then evaluated by measuring the resonance energy transfer from europium chelate-labelled anti-mouse-IgG antibody to streptavidin-XL665. To this end, the fluorescence emissions at 620 nm and 665 nm were measured after excitation at 350 nm in a TR-FRET measuring instrument, for example a Rubystar (BMG Labtechnologies, Offenburg, Germany) or a Viewlux (Perkin-Elmer). The ratio of the emissions at 665 nm and 622 nm was taken as a measure of the amount of phosphorylated substrate. The data were normalized (enzyme reaction without test substance = 0% inhibition; all other assay components but no enzyme = 100% inhibition). Typically, the test substances were tested on the same microtitre plate at 11 different concentrations in the range from 20 μ M to 0.073 nM (20 μ M, 5.7 μ M, 1.6 μ M, 0.47 μ M, 0.13 μ M, 38 nM, 11 nM, 3.1 nM, 0.89 nM, 0.25 nM and 0.073 nM). The dilution series were prepared prior to the assay (2 mM to 7.3 nM in 100% DMSO) by serial dilutions. The IC₅₀ values were calculated using a 4-parameter fit.

Table 21: IC₅₀ values of the exemplary compounds in the IRAK4 kinase assay

Example	IC ₅₀ [nM]	Example	IC ₅₀ [nM]	Example	IC ₅₀ [nM]
1	111	19	33	37	88
2	253	20	126	38	104
3	4012	21	536	39	237
4	237	22	158	40	827
5	662	23	628	41	107
6	26	24	521	42	151
7	29	25	532	43	67
8	32	26	1615	44	190
9	90	27	177	45	160
10	40	28	83	46	3
11	7	29	273	47	2
12	38	30	961	48	4
13	62	31	1271	49	10
14	1913	32	501	50	19
15	172	33	25	51	30
16	134	34	11	52	17
17	83	35	56	53	20
18	2611	36	18	54	51

Example	IC ₅₀ [nM]
55	72
56	77
57	28
58	63
59	75
60	207
61	649
62	165
63	62
64	33
65	12
66	2
67	4
68	5
69	6
70	21
71	14
72	1043
73	731
74	175
75	56
76	630
77	189
78	6919
79	78
80	206
81	652
82	38
83	929
84	616
85	732
86	95
87	196
88	566
89	274

Example	IC ₅₀ [nM]
90	45
91	312
92	667
93	498
95	638
96	425
97	224
98	281
99	170
100	772
101	638
102	242
103	37
104	830
105	475
106	979
107	190
108	101
109	16
110	93
111	27
112	92
113	20
114	537
115	817
116	270
117	47
118	528
119	31
120	814
121	127
122	189
123	850
124	547
125	442

Example	IC ₅₀ [nM]
126	821
127	348
128	568
129	434
130	661
131	810
132	381
133	224
134	623
135	882
136	344
137	779
138	549
139	540
140	539
141	600
142	695
143	338
144	616
145	891
146	889
147	868
148	930
149	722
150	905
151	736
152	756
153	227
154	321
155	746
156	707
157	690
158	799
159	612
160	463

Example	IC ₅₀ [nM]
161	348
162	358
163	388
164	776
165	969
166	507
167	292
168	268
169	511
170	625
171	421
172	455
173	606
174	422
175	578
176	965
177	599
178	245
179	157
180	275
181	662
182	352
183	317
184	313
185	546
186	748
187	383
188	412
189	994
190	652
191	917
192	460
193	463
194	413
195	612

Example	IC ₅₀ [nM]
196	434
197	528
198	361
199	284
200	531
201	99
202	142
203	27
204	91
205	53
206	60
207	12
208	37
209	29
210	32
211	53
212	366
213	980
214	787
215	959
216	421
217	5
218	8
219	4
220	13
221	4
222	4
223	471
224	338
225	312
226	603
227	709
228	28
229	60
230	638

Example	IC ₅₀ [nM]
231	888
232	49
233	553
234	171
235	45
236	12
237	233
238	7
239	533
240	117
241	33
242	108
243	127
244	49
245	506
246	1672
247	742
248	20
249	135
250	278
251	222
252	285
253	24
254	18
255	8
256	52
257	51
258	195
259	55
260	32
261	16
262	113
263	314
264	10
265	44

Example	IC ₅₀ [nM]
266	355
267	29
268	74
269	97
270	49
271	35
272	9
273	158
274	29
275	87
276	29
277	20
278	42
279	7143
280	103
281	105
282	120
283	32
284	63
285	28
286	100
287	25
288	15
289	9
290	39
291	18
292	15
293	6
294	20
295	3370
296	8
297	381
298	53
299	722
300	4

Example	IC ₅₀ [nM]
301	15
302	16
303	48
304	20
305	41
306	197
307	1384
308	1753
309	25
310	28
311	31

TNF- α secretion in THP-1 cells

Using this test, it is possible to test substances for their ability to inhibit secretion of TNF- α (tumour necrosis factor alpha) in THP-1 cells (human monocytic acute leukaemia cell line). TNF- α is a cytokine involved in inflammatory processes. In this test, TNF- α secretion is triggered by incubation with bacterial lipopolysaccharide (LPS).

THP-1 cells are kept in continuous suspension cell culture [RPMI 1460 medium with L-Glutamax (Gibco, Cat No. 61870-044) supplemented with foetal calf serum (FCS) 10% (Invitrogen, Cat No. 10082-147), 1% penicillin/streptomycin (Gibco BRL, Cat No. 15140-114)] and should not exceed a cell concentration of 1×10^6 cells/ml.

The assay is carried out in cell culture medium (RPMI 1460 medium with L-Glutamax supplemented with FCS 10%).

In each case 2-2.5 μ l of the cell suspension (corresponds to 4000 cells) per well were dispensed into a 384-well test plate (Greiner, Cat No. 784076) in which in each case 40-50 nl substance had been dissolved in 100% DMSO. Here, in each case 10 different concentrations in the range from 20 μ M to 0.073 nM were used for each substance. The cells were incubated at room temperature for 15 min. 2-2.5 μ l of 0.1 μ g/ml LPS (Sigma, *Escherichia coli* 055:B5, Cat. No. L5418) dissolved in cell culture medium (final concentration 0.05 μ g/ml) were then dispensed into each well. As a neutral control, cells were treated with 0.05 μ g/ml LPS and 1% DMSO and, as inhibitor control, only once with 1% DMSO.

The plates are centrifuged at 80 g for 30 s and incubated at 37°C, 5% CO₂ and 95% atmospheric humidity for 17 h. The amount of TNF- α was determined using the TNF-alpha HTRF Detection Kit (Cisbio, Cat No. 62TNFPEB/C). To this end, in each case 2 μ l of the detection solution consisting of anti-TNF- α -XL665 conjugate and anti-TNF- α -cryptate conjugate, dissolved in accordance with the instructions of the manufacturer in the reconstitution buffer, were added for the HTRF (Homogeneous Time-Resolved Fluorescence) test. After the addition, the mixture was incubated either at room temperature for 3 h or at 4°C overnight. The signals were then read at 620/665 nm using an HTRF-enabled measuring instrument such as the BMG PheraStar.

The activity of the substances is expressed as the ratio between neutral and inhibitor control in percent. The IC₅₀ values were calculated using a 4-parameter fit.

Table 22: IC₅₀ values of the exemplary compounds with respect to the secretion of TNF- α in THP-1 cells

Table 22:

Example	IC ₅₀ [μM]
1	0.63
2	1.97
3	≥20.0*
4	4.72
5	11.53
6	0.34
7	0.46
8	0.6
9	0.56
10	1.3
11	1.27
12	2.0
13	0.76
14	18.24
15	19.47
16	10.4
17	1.55
18	2.9
19	4.36
20	≥20.0*
21	4.71
22	1.12
23	5.56
24	6.53
25	12.14
26	13.9
27	7.31
28	18.43
29	18.56
30	19.19
31	≥20.0*
32	13.52
33	1.02

Example	IC ₅₀ [μM]
34	0.31
35	0.47
36	0.19
37	0.74
38	1.87
39	8.47
40	6.33
41	1.13
42	2.09
43	0.52
44	1.1
45	0.84
46	0.83
47	0.39
48	0.59
49	≥20.0*
50	0.86
51	0.45
52	2.12
53	≥20.0*
54	0.48
55	0.49
56	0.82
57	3.53
58	2.72
59	1.22
60	19.2
61	≥20.0*
62	≥20.0*
63	4.98
64	0.63
65	0.7
66	0.41
67	0.56
68	0.42

Example	IC ₅₀ [μM]
69	3.16
70	0.4
71	0.46
72	≥20.0*
73	15.85
74	2.7
75	0.79
76	10.2
77	18.88
78	2.92
79	2.4
80	17.61
81	4.66
82	0.82
83	≥20.0*
84	5.46
85	≥20.0*
86	3.7
87	3.37
88	3.88
89	5.18
90	0.42
91	4.76
92	11.76
93	16.02
95	12.89
96	5.49
97	14.03
98	≥20.0*
99	1.46
100	5.46
101	8.09
102	0.82
103	0.69
104	10.65

Example	IC ₅₀ [μM]
105	-
106	11.25
107	≥20.0*
108	5.69
109	2.17
110	0.52
111	0.42
112	5.35
113	0.66
114	≥20.0*
115	≥20.0*
116	13.05
117	6.51
118	6.95
119	4.61
120	18.3
121	17.28
122	2.9
123	11.89
124	7.26
125	10.55
126	13.82
127	9.78
128	11.57
129	1.41
130	9.07
131	≥20.0*
132	4.38
133	3.7
134	10.87
135	10.86
136	7.3
137	≥20.0*
138	12.94
139	10.81

Example	IC ₅₀ [μM]
140	6.89
141	≥20.0*
142	≥20.0*
143	12.51
144	≥20.0*
145	18.22
146	17.54
147	19.01
148	≥20.0*
149	17.12
150	17.49
151	17.6
152	11.43
153	5.97
154	7.22
155	14.26
156	9.39
157	19.3
158	17.85
159	9.87
160	10.27
161	13.67
162	≥20.0*
163	12.61
164	15.1
165	7.75
166	10.0
167	11.25
168	≥20.0*
169	9.23
170	13.7
171	7.55
172	18.92
173	16.12
174	5.2

Example	IC ₅₀ [μM]
175	16.36
176	11.34
177	9.03
178	5.31
179	10.28
180	6.95
181	11.8
182	11.59
183	10.79
184	9.67
185	≥20.0*
186	11.9
187	8.75
188	7.74
189	19.17
190	18.08
191	≥20.0*
192	14.68
193	19.24
194	14.51
195	≥20.0*
196	13.1
197	≥20.0*
198	15.09
199	≥20.0*
200	≥20.0*
201	1.68
202	4.59
203	0.63
204	1.25
205	0.94
206	0.75
207	4.58
208	0.55
209	1.47

Example	IC ₅₀ [μM]
210	3.57
211	12.02
212	15.22
213	18.81
214	17.19
215	≥20.0*
216	8.51
217	0.33
218	0.24
219	0.13
220	0.33
221	0.26
222	0.22
223	15.34
224	12.25
225	2.36
226	4.96
227	19.82
228	2.45
229	1.18
230	13.82
231	16.34
232	1.22
233	≥20.0*
234	14.66
235	3.36
236	0.7
237	19.1
238	1.16
239	≥20.0*
240	2.87
241	0.64
242	0.57
243	6.89
244	0.88

Example	IC ₅₀ [μM]
245	14.66
246	≥20.0*
247	≥20.0*
248	1.27
249	1.06
250	≥20.0*
251	≥20.0*
252	≥20.0*
253	0.67
254	0.31
255	0.34
256	≥20.0*
257	not determined
258	≥20.0*
259	1.58
260	0.89
261	≥20.0*
262	2.18
263	≥20.0*
264	0.27
265	0.74
266	not determined
267	≥20.0*
268	2.13
269	0.90
270	0.45
271	0.86
272	0.55
273	3.99
274	0.68
275	3.50
276	0.53
277	0.41
278	0.91
279	≥20.0*

Example	IC ₅₀ [μM]
280	≥20.0*
281	≥20.0*
282	0.23
283	1.09
284	0.97
285	0.61
286	0.99
287	0.60
288	0.46
289	0.73
290	9.63
291	≥20.0*
292	0.82
293	0.53
294	not determined
295	≥20.0*
296	0.32
297	≥20.0*
298	≥20.0*
299	≥20.0*
300	0.21
301	0.44
302	0.46
303	0.41
304	5.00
305	7.04
306	2.84
307	19.47
308	≥20.0*
309	0.45
310	0.27
311	0.20

*: highest IC₅₀ value that can be
determined owing to assay
limitations

***In Vitro* LPS (lipopolysaccharide)-induced cytokine production in human PBMCs (peripheral blood mononuclear cells)**

5 The effect of the compounds according to the invention on the induced cytokine production in human PBMCs was examined. Here, cytokine production was induced by LPS, a TLR4 ligand, which leads to activation of the IRAK4-mediated signal path.

The human PBMCs were obtained from anti-coagulated human whole blood. To this end, 15 ml of Ficoll-Paque (Biochrom, Cat. No. L6115) were initially charged in Leucosep tubes and 20 ml of human blood were added. After centrifugation of the blood at 800 g for 15 min at room temperature, the plasma including the platelets was removed and discarded. The PBMCs were transferred into centrifugation tubes and made up with PBS (phosphate-buffered saline) (Gibco, Cat. No. 14190). The cell suspension was centrifuged at room temperature at 250 g for 10 min and the supernatant was discarded. The PBMCs were resuspended in complete medium (RPMI 1640, without L-glutamine (PAA, Cat. No. E15-039), 10% FCS; 50 U/ml penicillin, 50 µg/ml streptomycin (PAA, Cat. No. P11-010) and 1% L-glutamine (Sigma, Cat. No. G7513)).

The assay was also carried out in complete medium. The PBMCs were sown in 96-well plates at a cell density of 2.5×10^5 cells/well. The compounds according to the invention were subjected to serial dilution in a constant volume of 100% DMSO and employed in the assay at 8 different concentrations in the range from 10 µM to 3 nM such that the final DMSO concentration was 0.4% DMSO. Prior to the actual stimulation, the cells were then pre-incubated therewith for 30 min. To induce cytokine secretion, the cells were stimulated with 0.1 µg/ml LPS (Sigma, Cat. No. L4516) for 24 hours. Cell viability was determined using the CellTiter-Glo luminescent assay (Promega, Cat. No. G7571 (G755/G756A)) in accordance with the instructions of the manufacturer. The amount of secreted TNF-α in the cell culture supernatant was determined using the Human ProInflammatory 9-Plex Tissue Culture Kit (MSD, Cat. No. K15007B) in accordance with the instructions of the manufacturer. By way of example, the Exemplary Compound 1 having an activity between 1 and 10 µM and the Exemplary Compounds 47, 64 and 71 having an activity of ≤ 1 µM are mentioned.

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***In vitro* tumour-associated NF-kB reporter activity**

The effect of the compounds according to the invention on the NF-kB signal pathway was examined in human DLBCL (diffuse large B cell lymphoma) cell lines. TMD-8, HBL-1, U2932 , HT and WSU-DLCL2 cells were stably transduced with a lentivirus NF-kB reporter construct (Cignal Lenti NFκB Reporter (luc) kit: CLS-013L, Qiagen), thus generating TMD-8-NF-kB-luc, HBL-1-NF-kB-luc, U2932-NF-kB-luc, HT-NF-kB-luc and WSU-DLCL2-NF-kB-luc reporter cell lines. 10,000 cells were transferred into 30 µl/well in growth medium (RPMI (Biochrom, Cat. No.

FG 1215), 20% FCS (Biochrom, Cat. No. S 0615)) or into RPMI 1640 medium supplemented with 10% FCS in a 384-well plate (Perkin Elmer, white) and incubated at 37°C overnight. After 24 h, the cells were treated with test substances and incubated at 37°C for 6 h and 24 h. The test substances were added to the cells in 7-fold dilution – either alone or as combination of two test substances of different concentrations (ratios substance 1 and substance 2: 1:0, 0.85:0.15; 0.7:0.3; 0.5:0.5; 0.3:0.7; 0.15:0.85; 0:1) using an HP D300 digital dispenser. As control, the cells were treated with vehicle (DMSO). After 6 h and 24 h, the cells were treated with 30 µl/well One-Glo solution (Promega, Cat. No. E6110) and incubated at room temperature for 10 min, and the luminescence was measured using a VICTOR V (Perkin Elmer) in order to determine the NF-KB reporter activity at the end of the treatment. The effect on the NF-KB reporter activity in percent and the IC₅₀ values derived therefrom were determined for each test substance. The IC₅₀ values were calculated using a 4-parameter fit.

By way of example, the Exemplary Compound 289 having an activity between 1 and 10 µM with the cell lines TMD-8-NF-kB-luc, HBL-1-NF-kB-luc, U2932-NF-kB-luc and WSU-DLCL2-NF-kB-luc is mentioned.

In vitro tumour-associated secretion of interleukin-6 and interleukin-10

The effect of the compounds according to the invention on the secretion interleukin-6 and interleukin-10 was examined in human TMD-8 DLBCL cells. 15000 cells/well were sown in 100 µl of fresh growth medium (RPMI (Biochrom, Cat. No. FG 1215), 20% FCS (Biochrom, Cat. No. S 0615)) in a 96-well plate (Perkin Elmer). The test substances were added to the cells in 7-fold dilution using an HP D300 digital dispenser and incubated for 24 h. After the incubation time had ended, the supernatants were collected and the interleukin concentration was determined using the Human IL-6/IL-10 Elisa Kit, (Life Technologies, Cat. No. KHC0062, KHC0101) in accordance with the instructions of the manufacturer. The effect on the interleukin secretion in percent was determined for each test substance.

By way of example, the Exemplary Compound 289 having an activity between 1 and 10 µM on the secretion of interleukin-6 and interleukin-10 is mentioned.

The suitability of the compounds according to the invention for the treatment of inflammatory disorders, tumour disorders and ophthalmological disorders such as wet AMD (age-related macular degeneration) can be shown in the following animal models:

5

***In vivo* model of TLR-mediated inflammation**

The compounds according to the invention were examined in a model of *in vivo* TLR-mediated inflammation for their *in vivo* efficacy. This mechanistic model shows in particular the potential effect of the compounds according to the invention on TLR4-mediated disorders since an LPS-mediated inflammation model was used. Here, female Balb/c mice (about 8 weeks old; Charles River Laboratories, Germany) were divided into groups of 5 animals each. The control group was treated with the vehicle in which the substance had been dissolved (substance vehicle) and also with the vehicle in which the LPS had been dissolved. 0.2 mg of LPS/kg body weight (Sigma, Cat. No. L4391) (lipopolysaccharides from *E. coli* 0111:B4) was administered intraperitoneally (i.p.) to the groups treated with substance, and also to the positive control group. In addition, the positive control group was treated with the substance vehicle described above. The substance was administered orally 8 hours before induction of inflammation by administration of LPS. To examine the effect of the compounds according to the invention on the inflammation, a final blood sample was taken from the animals after 1.5 hours. The concentration of certain cytokines in the plasma was determined using the Mouse ProInflammatory 7-Plex Tissue Culture Kit (MSD, Cat. No. K15012B) in accordance with the instructions of the manufacturer. Fig. 1 shows the amount of TNF- α in the plasma, which is reduced in a dose-dependent manner by administration of Exemplary Compound 64 in comparison with the LPS-induced concentration.

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***In vivo* model of IL-1 β -mediated inflammation**

To evaluate the potential efficacy of the compounds according to the invention in IL-1 β -mediated disorders, IL-1 β was administered i.p. to female Balb/c mice (about 8 weeks old, Charles River Laboratories, Germany) and the effect of the compounds according to the invention on IL-1 β -mediated cytokine secretion was examined. In each case, the group size was 5 animals. The control group was treated with the vehicles used for dissolving the substance and the IL-1 β . In each case 90 μ g of IL-1 β /kg body weight (R&D, Cat. No. 401-ML/CF) were administered i.p. to the groups treated with substance and the positive control group. The substance or its vehicle in the positive control group were administered 4 hours before the administration of IL-1 β . The determination of TNF- α in the plasma after the final removal of blood was carried out 2 hours after administration of the IL-1 β using the Mouse ProInflammatory 7-Plex Tissue Culture Kit (MSD, Cat. No. K15012B) in accordance with the instructions of the manufacturer. Administration of IL-1 β lead to an

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elevated TNF- α plasma concentration which was inhibited by treatment with Exemplary Compound 64. This is illustrated by Figure 2.

5 Oxygen-induced *in vivo* retinopathy (OIR) model

It has been shown that oxygen-induced retinopathy is a useful animal model for the study of pathological retinal angiogenesis. This model is based on the observation that hyperoxia during early postnatal development in the retina causes arrest or delay of the growth of normal retinal blood vessels. When, after a 7-day hyperoxia phase, the animals are returned to normoxic room air, this is equivalent to relative hypoxia. The ischaemic situation caused in this manner results in an abnormal neovascularization which has some similarities with pathophysiological neovascularization in eye disorders such as wet AMD (age-related macular degeneration). In addition, the neovascularization caused is highly reproducible, quantifiable and an important parameter for examining the disease mechanisms and possible treatments for various forms of retinal disorders. This is why this model is suitable for examining the effect of the compounds according to the invention on this pathological process.

To this end, young murine animals of an age of 7 days, for example young C57Bl/6 animals, are exposed to a hyperoxic environment (70% oxygen) for 5 days. From day 12 to day 17, the mice are kept under normoxic conditions. Normoxic means room air with 21% oxygen. During this period, the animals are then assigned to groups treated with substance and vehicle group and treated according to the group. The animals are sacrificed on day 17, and the eyes are then removed and fixated in 4% formalin. After washing in phosphate-buffered saline, the retina is excised, a flat preparation thereof is produced and this is stained with isolectin B4 antibody (Tual-Chalot, Allinson, et al., J. Vis. Exp., 2013). Quantification of neovascularization is carried out using a Zeiss ApoTome.

In vivo model of laser-induced choroidal neovascularization

This study serves to investigate the efficacy of a test substance on reduction of extravasation/oedema formation and/or choroidal neovascularization in the rat model of laser-induced choroidal neovascularization. In the animal model, laser-mediated photocoagulation leads to destruction of Bruch's membrane with concomitant damage to the vessels and inflammation-associated neovascularization. Both processes correspond to the pathomechanism of macular degeneration (Grossniklaus, Kang, Berglin, Prog Retin Eye Res., 2010).

To determine the effect of the compounds according to the invention, Brown Norway Rats (Charles River Laboratories) are assigned to the appropriate groups (substance and vehicle) and anaesthetized, and 0.5% tropicamide is instilled into the eyes to dilate the pupils. After the animals

have been anaesthetized (15 mg/kg xylazine and 80 mg/kg ketamine), choroidal neovascularization is triggered by burning six holes into the retina in each eye of each animal using a 532 nm argon laser (lesion size: 50 μ m - 75 μ m; laser intensity: 150 mW; duration: 100 ms). The treatment of the animals with the substance according to the invention or the corresponding vehicle is carried out either from day 1 or from day 7 up to and including day 23. Angiography is carried out on day 21. To this end, the animals are in each case anaesthetised, the pupils are dilated and 10% sodium fluorescein solution is injected subcutaneously. The angiogram is recorded at most 10 minutes after the injection and assessed by three blinded observers using a score system (0= no staining = no tissue injury, 1= slight staining = slight tissue injury, 2= moderate staining = moderate tissue injury, 3= maximum staining = maximum tissue injury). The animals are sacrificed on day 23, after which the eyes are removed and fixated in 4% strength paraformaldehyde solution for one hour at room temperature. After one washing, the retina is carefully peeled off and the sclera-choroidea complex is stained using an FITC isolectin B4 antibody and then applied flat to a microscope slide. The preparations obtained in this manner are evaluated using a fluorescence microscope (Apotom, Zeiss) at an excitation wavelength of 488 nm. The volume or the area of choroidal neovascularization is calculated by morphometric analysis using Axiovision 4.6 software.

Working examples of pharmaceutical compositions

The compounds according to the invention can be converted to pharmaceutical formulations as follows:

Tablet:

5 Composition:

100 mg of the compound of Example 64, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

10 Production:

The mixture of inventive compound, lactose and starch is granulated with a 5% solution (w/w) of the PVP in water. The granules are dried and then mixed with the magnesium stearate for 5 minutes. This mixture is compressed in a conventional tablet press (see above for format of the tablet). The guide value used for the pressing is a pressing force of 15 kN.

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Solution for oral administration:

Composition

500 mg of the compound of Example 64, 2.5 g of polysorbate and 97 g of polyethylene glycol 400. 20 g of oral solution correspond to a single dose of 100 mg of the compound according to the invention.

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Production

The compound according to the invention is suspended in the mixture of polyethylene glycol and polysorbate with stirring. The stirring operation is continued until dissolution of the compound according to the invention is complete.

25 Composition:

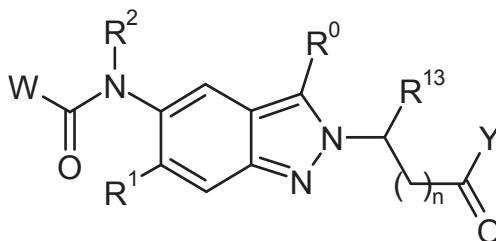
1 mg of the compound of Example 64, 15 g of polyethylene glycol 400 and 250 g of water for injection purposes.

Production:

The compound according to the invention, together with polyethylene glycol 400, is dissolved in the water by stirring. The solution is sterilized by filtration (pore diameter 0.22 μm) and dispensed under aseptic conditions into heat-sterilized infusion bottles. The latter are closed with infusion stoppers and crimped caps.

Patent claims

1. Compounds of the general formula (I)



(I)

5 in which:

R^0 represents hydrogen or C_1 - C_4 -alkyl, where the C_1 - C_4 -alkyl radical may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy and halogen;

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R^1 represents hydrogen, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $C(=O)R^d$, hydroxy or C_1 - C_6 -alkyl, where the C_1 - C_6 -alkyl radical is optionally mono- or polysubstituted by identical or different radicals from the group consisting of

15

hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, NH_2 , NHR^a , $N(R^a)R^b$, C_1 - C_6 -alkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_3 - C_8 -cycloalkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, heterocycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c ,

20

or represents C_1 - C_6 -alkoxy, where the C_1 - C_6 -alkoxy radical may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of

25

hydroxy, halogen, cyano, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, NH_2 , NHR^a , $N(R^a)R^b$, C_3 - C_8 -cycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_1 - C_6 -alkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_3 - C_8 -cycloalkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, heterocycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c , aryl which is optionally mono- or

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- polysubstituted by identical or different radicals from the group consisting of R^c, or 5- or 6-membered heteroaryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c,
- 5 or represents C₃-C₈-cycloalkoxy or heterocycloalkoxy which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C₁-C₆-alkyl,
- or represents aryloxy or 5- or 6-membered heteroaryloxy in which aryloxy and 5- or 6-membered heteroaryloxy may optionally be mono- or polysubstituted by
 10 identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, C₁-C₆-alkyl and C₁-C₆-alkoxy,
- or represents C₃-C₈-cycloalkyl or heterocycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C₁-C₆-alkyl,
- 15 or represents C₂-C₆-alkenyl or C₂-C₆-alkynyl,
- or represents aryl, 5- to 10-membered heteroaryl, aryl-C₁-C₄-alkyl or 5- or 6-membered heteroaryl-C₁-C₄-alkyl, where aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, C₁-C₆-alkyl, C₃-C₈-
 20 cycloalkyl and C₁-C₆-alkoxy;
- R^a represents C₁-C₆-alkyl, C₃-C₁₀-cycloalkyl, heterocycloalkyl, aryl or heteroaryl, where alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group
 25 consisting of halogen, hydroxy, cyano, C₁-C₃-alkyl, C₁-C₃-alkoxy, heterocycloalkyl, -C(=O)O-C₁-C₆-alkyl and S(=O)₂-C₁-C₆-alkyl;
- R^b represents C₁-C₆-alkyl or C₃-C₁₀-cycloalkyl;
- 30 or R^a and R^b together with the nitrogen atom form a 5- or 6-membered heterocycle which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, and C₁-C₆-alkyl;
- R^c represents hydroxy, halogen, cyano, C₁-C₃-alkyl or C₁-C₃-alkoxy;
- 35 R^d represents hydrogen, C₁-C₆-alkyl or C₃-C₁₀-cycloalkyl;

- 5 R^2 represents hydrogen, C_1 - C_6 -alkyl or C_3 - C_6 -cycloalkyl;
- R^{13} represents hydrogen or C_1 - C_6 -alkyl;
- W represents 5-membered heteroaryl which contains one to three heteroatoms selected from the group consisting of N, O and S and may optionally be monosubstituted by R^3 and optionally be mono- or polysubstituted by identical or different radicals R^4 or
- 10 W represents pyridyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl or 1,3,5-triazinyl which may optionally be monosubstituted by R^3 and optionally be mono- or polysubstituted by identical or different radicals R^4 ;
- 15 R^3 represents hydrogen, halogen, cyano, $C(=O)R^a$, NH_2 , NHR^a , $N(R^a)R^b$, $N(H)C(=O)R^a$ or C_1 - C_6 -alkyl, where
- C_1 - C_6 -alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)R^a$, $C(=O)OH$, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, NH_2 , NHR^a ,
- 20 $N(R^a)R^b$, C_1 - C_6 -alkoxy, C_3 - C_8 -cycloalkoxy,
- where C_1 - C_6 -alkoxy and C_3 - C_8 -cycloalkoxy may optionally be mono- or polysubstituted by identical or different halogen radicals;
- or C_1 - C_6 -alkyl is optionally mono- or polysubstituted by identical or radicals from the group consisting of C_3 - C_6 -cycloalkyl and
- 25 heterocycloalkyl,
- where C_3 - C_6 -cycloalkyl and heterocycloalkyl may optionally be mono-, di- or trisubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1 - C_3 -alkyl and C_1 - C_3 -alkoxy,
- 30 or C_1 - C_6 -alkyl is optionally mono- or polysubstituted by identical or different radicals from the group consisting of aryl and 5- or 6-membered heteroaryl,
- where aryl and 5- or 6-membered heteroaryl may optionally be mono-, di- or trisubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1 - C_3 -alkyl and C_1 - C_3 -alkoxy,
- 35 alkoxy,

or

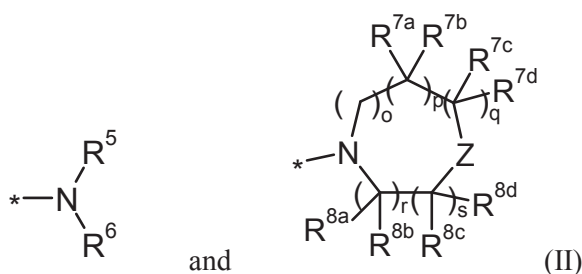
R^3 represents C_1 - C_6 -alkoxy, where
 C_1 - C_6 -alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, $N(R^a)R^b$, C_3 - C_8 -cycloalkyl, C_1 - C_4 -alkoxy, C_3 - C_8 -cycloalkoxy,
 or represents C_3 - C_6 -cycloalkyl, heterocycloalkyl or C_5 - C_{11} -spirocycloalkyl, where
 cycloalkyl, heterocycloalkyl and spirocycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)R^a$, $C(=O)OH$, $C(=O)OR^a$, C_1 - C_6 -alkyl and C_1 - C_4 -alkoxy;
 or represents aryl or 5- to 10-membered heteroaryl, where
 aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, $C(=O)OR^a$, $S(=O)_2$ - C_1 - C_6 -alkyl, NO_2 , NH_2 , NHR^a , $N(R^a)R^b$, $N(H)C(=O)R^a$, C_3 - C_8 -cycloalkyl, C_1 - C_3 -alkoxy and C_1 - C_3 -alkyl, where
 C_1 - C_3 -alkyl may optionally be mono- or polysubstituted by identical or different halogen radicals;
 R^4 represents halogen, hydroxy, cyano or C_1 - C_6 -alkyl, where C_1 - C_6 -alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_1 - C_6 -alkoxy, where C_1 - C_6 -alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_{10} -cycloalkyl, 3- to 10-membered heterocycloalkyl and aryl, where aryl may optionally be mono- or polysubstituted by identical or different radicals R ,
 or
 R^4 represents aryl or heteroaryl which may optionally be mono- or polysubstituted by identical or different radicals R ,
 or
 R^4 represents $C(=O)R^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $C(=O)OR^a$, NH_2 , NHR^a , $N(R^a)R^b$, $N(H)C(=O)R^a$, $N(R^a)C(=O)R^a$, $N(H)C(=O)NH_2$, $N(H)C(=O)NHR^a$, $N(H)C(=O)N(R^a)R^b$, $N(R^a)C(=O)NH_2$, $N(R^a)C(=O)NHR^a$, $N(R^a)C(=O)N(R^a)R^b$, $N(H)C(=O)OR^a$, $N(R^a)C(=O)OR^a$, NO_2 , $N(H)S(=O)R^a$, $N(R^a)S(=O)R^a$, $N(H)S(=O)_2R^a$, $N(R^a)S(=O)_2R^a$, $N=S(=O)(R^a)R^b$, $OC(=O)R^a$, $OC(=O)NH_2$, $OC(=O)NHR^a$, $OC(=O)N(R^a)R^b$, SH , SR^a , $S(=O)R^a$, $S(=O)_2R^a$, $S(=O)_2NH_2$, $S(=O)_2NHR^a$, $S(=O)_2N(R^a)R^b$ or $S(=O)(=N-R^a)R^b$;

R represents halogen, cyano, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₁₀-cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl, heteroaryl, C(=O)R^a, C(=O)NH₂, C(=O)N(H)R^a, C(=O)N(R^a)R^b, C(=O)OR^a, NH₂, NHR^a, N(R^a)R^b, N(H)C(=O)R^a, N(R^a)C(=O)R^a, N(H)C(=O)NH₂, N(H)C(=O)NHR^a, N(H)C(=O)N(R^a)R^b, N(R^a)C(=O)NH₂, N(R^a)C(=O)NHR^a, N(R^a)C(=O)N(R^a)R^b, N(H)C(=O)OR^a, N(R^a)C(=O)OR^a, NO₂, N(H)S(=O)R^a, N(R^a)S(=O)R^a, N(H)S(=O)₂R^a, N(R^a)S(=O)₂R^a, N=S(=O)(R^a)R^b, OH, C₁-C₆-alkoxy, OC(=O)R^a, OC(=O)NH₂, OC(=O)NHR^a, OC(=O)N(R^a)R^b, SH, SR^a, S(=O)R^a, S(=O)₂R^a, S(=O)₂NH₂, S(=O)₂NHR^a, S(=O)₂N(R^a)R^b or S(=O)(=NR^a)R^b;

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n represents 0 or 1;

Y represents a group selected from:



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where * represents the point of attachment of the group to the remainder of the molecule;

R⁵ represents hydrogen, C₁-C₆-alkyl or C₃-C₁₀-cycloalkyl, where C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy and C₃-C₈-cycloalkyl;

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R⁶ represents hydrogen or C₁-C₆-alkyl, where C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C₃-C₁₀-cycloalkyl, C(=O)R^a, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy and C₃-C₈-cycloalkoxy,

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or represents C₃-C₁₀-cycloalkyl, where

C₃-C₁₀-cycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C₁-C₆-alkyl, where

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C₁-C₆-alkyl may optionally be substituted by hydroxy,
or represents heterocycloalkyl, where
heterocycloalkyl may optionally be mono- or polysubstituted by identical
or different radicals from the group consisting of halogen, cyano, C₁-C₃-
5 alkyl and C₁-C₃-alkoxy,
or represents aryl or 5- or 6-membered heteroaryl, where
aryl and 5- or 6-membered heteroaryl may optionally be mono- or
polysubstituted by identical or different radicals from the group consisting
of halogen, cyano, C₁-C₃-alkyl, C₁-C₃-alkoxy, S(=O)₂NH₂, S(=O)₂NHR^a
10 and S(=O)₂N(R^a)R^b;
R^{7a} represents hydrogen, halogen, N(R^a)R^b, C₁-C₆-alkyl or C₃-C₁₀-cycloalkyl, where
C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or
different radicals from the group consisting of hydroxy, halogen, cyano,
15 C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-
cycloalkyl and heterocycloalkyl;
R^{7b} represents hydrogen, halogen or C₁-C₆-alkyl, where
C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or
different radicals from the group consisting of hydroxy, halogen, cyano,
20 C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-
cycloalkyl and heterocycloalkyl;
or R^{7a} and R^{7b} together with the carbon atom form C₃-C₆-cycloalkyl which may optionally
25 be mono- or polysubstituted by identical or different radicals from the group consisting of
hydroxy, halogen, cyano and C₁-C₆-alkyl,
or R^{7a} and R^{7b} together represent an oxo group;
30 R^{7c} represents hydrogen, halogen, N(R^a)R^b, C₁-C₆-alkyl or C₃-C₁₀-cycloalkyl, where
C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or
different radicals from the group consisting of hydroxy, halogen, cyano,
C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-
cycloalkyl and heterocycloalkyl;
35 R^{7d} represents hydrogen, halogen or C₁-C₆-alkyl, where

C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-cycloalkyl and heterocycloalkyl;

5

or R^{7c} and R^{7d} together with the carbon atom form C₃-C₆-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C₁-C₆-alkyl,

10

or R^{7c} and R^{7d} together represent an oxo group;

R^{8a} represents hydrogen, halogen, N(R^a)R^b, C₁-C₆-alkyl or C₃-C₁₀-cycloalkyl, where

C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-cycloalkyl and heterocycloalkyl;

15

R^{8b} represents hydrogen, halogen or C₁-C₆-alkyl, where

C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-cycloalkyl and heterocycloalkyl;

20

or R^{8a} and R^{8b} together with the carbon atom form C₃-C₆-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C₁-C₆-alkyl,

25

R^{8c} represents hydrogen, halogen, N(R^a)R^b, C₁-C₆-alkyl or C₃-C₁₀-cycloalkyl, where

C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-cycloalkyl and heterocycloalkyl;

30

R^{8d} represents hydrogen, halogen or C₁-C₆-alkyl, where

C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy, C₃-C₈-cycloalkyl and heterocycloalkyl;

35

- or R^{8c} and R^{8d} together with the carbon atom form C₃-C₆-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C₁-C₆-alkyl,
- 5 or R^{8c} and R^{8d} together represent an oxo group;
- o represents 0, 1 or 2,
 p represents 0, 1 or 2,
 10 q represents 0, 1 or 2,
 r represents 0, 1 or 2,
 s represents 0, 1 or 2,
 where o, p, q, r and s do not simultaneously represent 0;
- 15 Z represents a group selected from C(=O), CR⁹R¹⁰, NR¹¹, O, S, S(=O) and S(=O)₂;
- R⁹ represents hydrogen or C₁-C₆-alkyl,
- 20 R¹⁰ represents hydrogen, halogen, cyano, C(=O)R^a, C(=O)OH, C(=O)OR^a, C(=O)NH₂, C(=O)N(H)R^a, C(=O)N(R^a)R^b, N(H)C(=O)R^a, N(R^b)C(=O)R^a, S(=O)₂R^a, hydroxy, N(R^a)R^b and C₁-C₆-alkyl, where
- 25 C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₁-C₄-alkoxy and C₃-C₈-cycloalkoxy,
- or represents C₁-C₆-alkoxy, where
- 30 C₁-C₆-alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₃-C₈-cycloalkyl, C₁-C₄-alkoxy, C₃-C₈-cycloalkoxy, heterocycloalkyl, aryl and 5- or 6-membered heteroaryl, where
- aryl and 5- or 6-membered heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C₁-C₃-alkyl and C₁-C₃-alkoxy,
- 35 or represents aryloxy or 5- or 6-membered heteroaryloxy in which
- aryloxy and 5- or 6-membered heteroaryloxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting

of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, C₁-C₃-alkyl and C₁-C₃-alkoxy,

or represents C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₄-alkyl, heterocycloalkyl or heterocycloalkyl-C₁-C₄-alkyl, which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OH, C(=O)OR^a, C₁-C₆-alkyl and C₁-C₆-alkoxy, where

C₁-C₆-alkoxy may optionally be mono- or polysubstituted by identical or different halogen radicals or an oxo group;

or represents C₂-C₆-alkenyl or C₂-C₆-alkynyl,

or represents aryl, 5- to 10-membered heteroaryl, aryl-C₁-C₄-alkyl or 5- or 6-membered heteroaryl-C₁-C₄-alkyl, where

aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, NHR^a, N(R^a)R^b, C₁-C₃-alkyl, C₃-C₈-cycloalkyl and C₁-C₃-alkoxy;

or R⁹ and R¹⁰ together with the carbon atom form C₃-C₈-cycloalkyl or a 4- to 6-membered heterocycle, where

the C₃-C₈-cycloalkyl radical or the 4- to 6-membered heterocycle may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C₁-C₆-alkyl, C(=O)R^a and an oxo group;

R¹¹ represents hydrogen, C(=O)R^a, C(=O)OR^a, C(=O)NH₂, C(=O)N(H)R^a, C(=O)N(R^a)R^b, S(=O)₂R^a, S(=O)₂N(R^a)R^b or C₁-C₆-alkyl, where

C₁-C₆-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OR^a, C(=O)NH₂, C(=O)N(H)R^a, C(=O)N(R^a)R^b, S(=O)₂-C₁-C₆-alkyl, N(R^a)R^b, C₃-C₈-cycloalkyl, C₁-C₄-alkoxy and C₃-C₈-cycloalkoxy, where

C₃-C₈-cycloalkyl, C₁-C₄-alkoxy and C₃-C₈-cycloalkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy and halogen;

or represents C₃-C₈-cycloalkyl, heterocycloalkyl or heterocycloalkyl-C₁-C₄-alkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C₁-C₆-alkyl, C₁-C₆-alkoxy,

where alkyl and alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen and an oxo group,

or represents C₂-C₆-alkenyl or C₂-C₆-alkynyl,

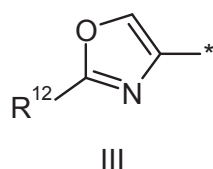
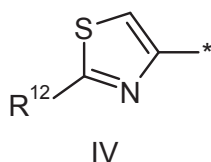
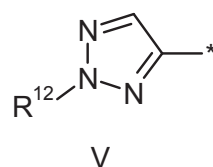
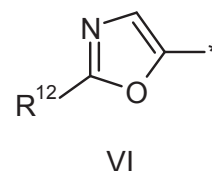
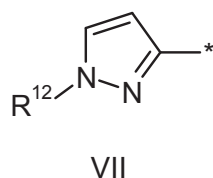
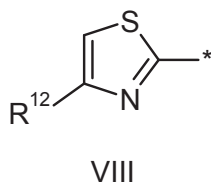
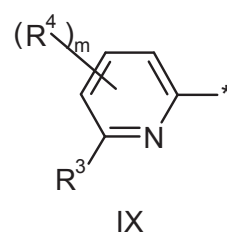
or represents aryl, 5- to 10-membered heteroaryl, aryl-C₁-C₄-alkyl or 5- or 6-membered heteroaryl-C₁-C₄-alkyl, where

aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, C₁-C₃-alkyl, C₃-C₈-cycloalkyl and C₁-C₃-alkoxy;

and their diastereomers, enantiomers, their salts, their solvates or the solvates of their salts.

2. Compounds according to Claim 1 in which R¹ represents hydrogen, halogen, hydroxy, cyano, C₁-C₆-alkyl, C₁-C₅-alkyl substituted by hydroxy, C₁-C₆-alkoxy, C₁-C₆-alkoxy substituted by C₃-C₈-cycloalkyl, C₁-C₆-alkoxy substituted by up to three fluorine atoms, C₁-C₆-alkoxy substituted by aryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c or represents 5- or 6-membered heteroaryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c.

3. Compounds according to Claim 1 in which W represents a group selected from formulae (III) to (IX):



in which

R¹² represents hydrogen, halogen, C₁-C₆-alkyl which is optionally mono- or polysubstituted by identical or different halogen radicals, C₃-C₆-cycloalkyl which is optionally mono- or polysubstituted by identical or different halogen radicals, aryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c or 5- or 6-

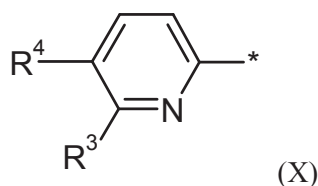
membered heteroaryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c or represents NHR^a ;

m represents 0, 1, 2 or 3 and

R^3 and R^4 have the meanings given above and

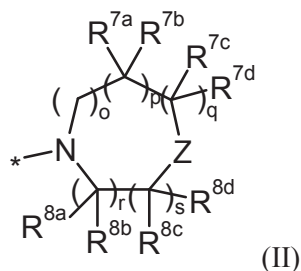
* represents the point of attachment of the group to the remainder of the molecule.

4. Compounds according to Claim 1 in which W represents a group of the general formula (X)



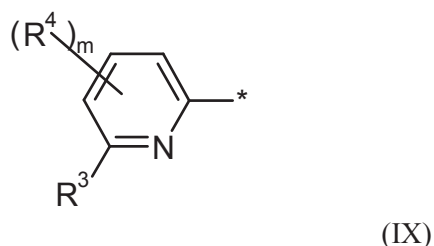
and R^3 and R^4 have the meaning given in Claim 1.

5. Compounds according to Claim 1 in which Y is a group of the general formula (II) where R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^{8a} , R^{8b} , R^{8c} and R^{8d} are as defined in Claim 1:



6. Compounds according to Claim 1 in which Y is a radical NR^5R^6 where R^5 and R^6 are as defined in Claim 1.

7. Compounds according to Claim 1 in which W represents a group of the general formula (IX)



in which

m represents 0 and R^2 , R^0 and R^{13} all represent hydrogen and R^3 represents trifluoromethyl, ethyl, methyl, cyclopropyl, 2,2,2-trifluoro-1-hydroxyethyl or 1-hydroxyethyl; Y represents

4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl or morpholin-4-yl, n represents 0 and R¹ represents cyclopropylmethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, chlorine, ethoxy, methoxy, 2-hydroxypropan-2-yl or 3-hydroxypentan-3-yl.

- 5 8. Compounds according to Claim 7 in which R¹ represents cyclopropylmethoxy, methoxy, ethoxy or 2-hydroxypropan-2-yl.
9. Compounds according to Claim 7 in which R³ is a trifluoromethyl or a cyclopropyl radical.
- 10 10. Compounds according to Claim 1, specifically
N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methyl-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
6-ethyl-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide
5-fluoro-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide
N-(2-{2-[4-(3-hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
N-(2-{2-[4-(methoxyacetyl)piperazin-1-yl]-2-oxoethyl}-6-methyl-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide
N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide
N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-cyclopropylpyridine-2-carboxamide
N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-(1-hydroxyethyl)pyridine-2-carboxamide
N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
6-methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}pyridine-2-carboxamide
tert-butyl 3-{[4-(2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl]carbamoyl)-1,3-thiazol-2-yl]amino}azetidine-1-carboxylate

N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide
 N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-cyclopropyl-1,3-oxazole-4-carboxamide
 tert-butyl 3-{[4-({6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl} carbamoyl)-1,3-thiazol-2-yl]amino}azetidine-1-carboxylate
 2-(azetidin-3-ylamino)-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide
 N-{6-cyano-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 6'-methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide
 5'-methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide
 4'-methyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide
 6'-methoxy-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide
 6'-acetamido-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide
 N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6'-nitro-2,3'-bipyridine-6-carboxamide
 6'-amino-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,3'-bipyridine-6-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide
 N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-fluoro-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-fluoro-2H-indazol-5-yl)-6-(morpholin-4-yl)pyridine-2-carboxamide
 N-{6-fluoro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide
 N-{6-(benzyloxy)-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-isobutoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-isobutoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-isobutoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-isobutoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(cyclopropylmethoxy)-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(cyclopropylmethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[6-(cyclopropylmethoxy)-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[6-(cyclopropylmethoxy)-2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-(pyridin-2-ylmethoxy)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-chloro-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-chloro-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 ethyl 4-{[6-chloro-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-yl]acetyl}piperazine-1-carboxylate
 N-(6-chloro-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-[4-(3-hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-[3-(dimethylamino)azetidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-oxo-2-[3-(piperidin-1-yl)azetidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-[4-(2-hydroxy-2-methylpropyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-chloro-2-[2-(4-hydroxy-1,4'-bipiperidin-1'-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(dimethylamino)piperidin-1-yl]-2-oxoethyl}-6-ethoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(6-ethoxy-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-ethoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-ethoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(6-ethoxy-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-ethoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-3-methyl-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[3-(4-benzoylpiperazin-1-yl)-3-oxopropyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-2-(pyridin-3-yl)-1,3-thiazole-4-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-2-(pyridin-4-yl)-1,3-thiazole-4-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 6-(azetidin-3-ylamino)-N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)pyridine-2-carboxamide
 N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(pyridin-3-yl)-1,3-thiazole-4-carboxamide
 N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-pyrazol-4-yl)pyridine-2-carboxamide
 6-(1,3-dimethyl-1H-pyrazol-4-yl)-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine-2-carboxamide
 6-ethyl-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 6-(1-methyl-1H-pyrazol-4-yl)-N-(2-{2-oxo-2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-ethyl-3-oxopiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(pyridin-4-yl)-1,3-thiazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-chloropyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-methyl-1,3-oxazole-5-carboxamide

6-amino-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-methyl-1,3-oxazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methoxypyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-cyclopropyl-1,3-oxazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(4H-1,2,4-triazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-phenyl-2H-1,2,3-triazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-5-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(trifluoromethyl)-1,3-thiazole-4-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-pyrazol-1-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1-ethyl-1H-pyrazole-3-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(4-chloro-1H-pyrazol-1-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-4-(trifluoromethyl)-1,3-thiazole-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2,4'-bipyridine-6-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(3-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1H-1,2,4-triazol-1-yl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-[3-(trifluoromethyl)-1H-pyrazol-4-yl]pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-ethoxypyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(cyclopropylmethoxy)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-ethylpyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(4-methoxyphenyl)-1,3-thiazole-4-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-bromo-1,3-thiazole-4-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(4-fluorophenyl)-1,3-thiazole-4-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-fluoropyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-bromopyridine-2-carboxamide
 N-(2-{2-[4-(4-fluorobenzoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyridin-2-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(methoxyacetyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-cyclopentyl-3-oxopiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-oxo-2-(3-oxo-4-phenylpiperazin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(2,2-dimethylpropanoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-oxo-2-(pyridazin-4-ylamino)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxy-2-methylpropanoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(1-phenylethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-isonicotinoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(morpholin-4-ylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[2-(methylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyrazin-2-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(1-hydroxyethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(2-methyl-2,8-diazaspiro[4.5]dec-8-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(6-acetyl-2,6-diazaspiro[3.3]hept-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-oxo-2-(3-oxo-2,8-diazaspiro[4.5]dec-8-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(6-methyl-2,6-diazaspiro[3.5]non-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(7-oxa-2-azaspiro[3.5]non-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(1,4'-bipiperidin-1'-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[2-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[3-(hydroxymethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-carbamoylpiperidin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[3-(dimethylamino)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[3-(morpholin-4-ylmethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[(cyclopropylcarbonyl)amino]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-
 6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(3-ethyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-
 6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[(5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl]piperidin-1-yl}-2-oxoethyl)-
 2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyrrolidin-1-ylcarbonyl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[2-(morpholin-4-yl)ethyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[(5-methyl-1,2,4-oxadiazol-3-yl)methyl]piperidin-1-yl}-2-oxoethyl)-2H-
 indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[3-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{[3-(dimethylsulphamoyl)phenyl]amino}-2-oxoethyl)-2H-indazol-5-yl]-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(1,2-oxazol-4-ylamino)-2-oxoethyl]-2H-indazol-5-yl}-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(methylsulphonyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-oxo-2-{4-[2-oxo-2-(pyrrolidin-1-yl)ethyl]piperazin-1-yl}ethyl)-2H-indazol-5-
 yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(phenylsulphonyl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[(3-sulphamoylphenyl)amino]ethyl}-2H-indazol-5-yl)-6-
 (trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[isonicotinoyl(methyl)amino]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-
 6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[2-(isopropylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-
 yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(1,1-dioxidotetrahydrothiophen-3-yl)piperazin-1-yl]-2-oxoethyl}-2H-
 indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[(methoxyacetyl)(methyl)amino]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-
 yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 ethyl 4-{[5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-2-
 yl]acetyl}piperazine-1-carboxylate

N-(2-{2-[4-(cyclohexylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[2-(cyclopropylamino)-2-oxoethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[2-(2-hydroxyethyl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(1H-pyrrol-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(3-hydroxypropyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 4-{[5-({6-(trifluoromethyl)pyridin-2-yl}carbonyl)amino]-2H-indazol-2-yl}acetyl}piperazine-1-carboxamide
 N-(2-{2-oxo-2-[4-(2-oxopyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(2-amino-2-oxoethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-isopropylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(2-thienylcarbonyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(2-cyclopropyl-2-oxoethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[(1-methyl-1H-pyrazol-4-yl)methyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[(1,5-dimethyl-1H-pyrazol-3-yl)carbonyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N,N-diethyl-4-{[5-({6-(trifluoromethyl)pyridin-2-yl}carbonyl)amino]-2H-indazol-2-yl}acetyl}piperazine-1-carboxamide
 N-{2-[2-oxo-2-(thiomorpholin-4-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(2-furylmethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-(2-{2-oxo-2-[4-(3-thienylmethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4'-methyl-1,4'-bipiperidin-1'-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(6-methyl-2,6-diazaspiro[3.3]hept-2-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-cyclopentylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(dimethylsulphamoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyridin-4-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(methylsulphonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 formic acid N-[2-(2-{4-[2-(1H-imidazol-1-yl)ethyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (1:1)
 N-(2-{2-[4-(diethylsulphamoyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(pyridin-3-yl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-oxo-2-[4-(piperidin-1-ylsulphonyl)piperazin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[(1,5-dimethyl-1H-pyrazol-4-yl)sulphonyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 6-(1-methyl-1H-pyrazol-4-yl)-N-(2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide
 N-{2-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide
 N-(2-{2-[4-(dimethylamino)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine-2-carboxamide

N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide
 N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-ethoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[(cyclopropylmethyl)(methyl)amino]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 6-cyclopropyl-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide
 6-(1-hydroxyethyl)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide
 6-(azetidin-3-ylamino)-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 6-[(azetidin-2-ylmethyl)amino]-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(3-hydroxyazetidin-1-yl)pyridine-2-carboxamide
 6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide
 N-[2-(2-{4-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]piperidin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(6-chloro-2-{2-oxo-2-[(3R)-piperidin-3-ylamino]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-isopropoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide
 N-(2-{2-[4-(cyclopropylcarbonyl)piperazin-1-yl]-2-oxoethyl}-6-isopropoxy-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-isopropoxy-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide
 N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-6-isopropoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-isopropoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-isopropoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide
 N-(2-{2-[4-(cyclobutylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 N-(2-{2-[4-(cyclopentylcarbonyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-[2-(2-{4-[3-(methylsulphonyl)benzoyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[2-(2-{4-[2-methoxy-5-(methylsulphonyl)benzoyl]piperazin-1-yl}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide
 6-bromo-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)pyridine-2-carboxamide
 2-(4-methoxyphenyl)-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-1,3-thiazole-4-carboxamide
 2-(4-fluorophenyl)-N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-1,3-thiazole-4-carboxamide
 N-(6-methyl-2-{2-oxo-2-[4-(pyrrolidin-1-yl)piperidin-1-yl]ethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide
 6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 6-bromo-N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}pyridine-2-carboxamide
 N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-6-(trifluoromethoxy)-2H-indazol-5-yl}-6-(4H-1,2,4-triazol-4-yl)pyridine-2-carboxamide
 2-bromo-N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide
 N-{6-hydroxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-[6-(benzyloxy)-2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-2H-indazol-5-yl]-6-methylpyridine-2-carboxamide
 6-bromo-N-{6-bromo-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 N-{6-(benzyloxy)-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide
 2-(azetidin-3-ylamino)-N-{2-[2-(4-benzoylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-1,3-thiazole-4-carboxamide
 6-acetamido-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 6-(dimethylamino)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide
 6-(dimethylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide
 6-acetamido-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide

6-(dimethylamino)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-[3-(methylsulphonyl)phenyl]pyridine-2-carboxamide

N-{2-[1-(4-benzoylpiperazin-1-yl)-1-oxopropan-2-yl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-[6-chloro-2-(2-{[trans-4-(2-hydroxypropan-2-yl)cyclohexyl]amino}-2-oxoethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide

6-(2-hydroxypropan-2-yl)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{6-chloro-2-[2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-chloro-2-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-chloro-2-[2-(2-oxa-7-azaspiro[3.5]non-7-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-(6-chloro-2-{2-[4-(2-hydroxy-2-methylpropyl)piperazin-1-yl]-2-oxoethyl}-2H-indazol-5-yl)-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-methoxy-2-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

6-(difluoromethyl)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{2-[2-(3,3-difluoropyrrolidin-1-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide

N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-methylpyridine-2-carboxamide

N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-2-(tetrahydro-2H-pyran-4-yl)-1,3-oxazole-4-carboxamide

N-{2-[2-(1,1-dioxido-1-thia-6-azaspiro[3.3]hept-6-yl)-2-oxoethyl]-6-methoxy-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-methoxy-2-[2-(2-oxa-6-azaspiro[3.3]hept-6-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(3-hydroxy-2,2-dimethylpropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

6-ethyl-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-isobutyl-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

methyl 2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazole-6-carboxylate

methyl 5-({[(6-methylpyridin-2-yl)carbonyl]amino}-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazole-6-carboxylate

N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(pyrrolidin-1-yl)pyridine-2-carboxamide

N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(morpholin-4-yl)pyridine-2-carboxamide

6-(cyclopropylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-(butylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(propylamino)pyridine-2-carboxamide

6-(isobutylamino)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

R-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxamide

S-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(2,2,2-trifluoro-1-hydroxyethyl)pyridine-2-carboxamide

6-(1-hydroxyethyl)-N-{6-methoxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-(cyclopropylamino)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(propylamino)pyridine-2-carboxamide

6-(isobutylamino)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

6-(1-hydroxyethyl)-N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}pyridine-2-carboxamide

N-{6-methoxy-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-4-methyl-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(benzyloxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

6-(cyclopropylamino)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide

6-(butylamino)-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-[(2-methoxyethyl)amino]pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(propylamino)pyridine-2-carboxamide

N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-(isobutylamino)pyridine-2-carboxamide

5-fluoro-N-(2-{2-[4-(2-hydroxypropan-2-yl)piperidin-1-yl]-2-oxoethyl}-6-methoxy-2H-indazol-5-yl)-6-methylpyridine-2-carboxamide

N-{6-hydroxy-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(3-cyanopropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-(2,2,2-trifluoroethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(cyclohexylmethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(2,2-dimethylpropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-(tetrahydrofuran-2-ylmethoxy)-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(cyclopentyloxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(cyanomethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({6-(trifluoromethyl)pyridin-2-yl]carbonyl}amino)-2H-indazol-6-yl}oxy)acetic acid

N-{6-(cyclobutylmethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-[2-(pyrrolidin-1-yl)ethoxy]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-[2-(morpholin-4-yl)ethoxy]-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{2-[2-(morpholin-4-yl)-2-oxoethyl]-6-[2-(piperidin-1-yl)ethoxy]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

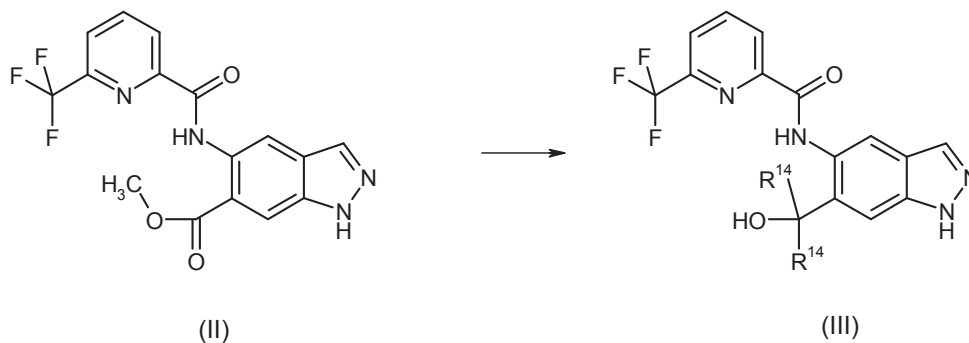
N-{6-(3-hydroxypropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide

N-{6-(2-hydroxypropoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(2-hydroxyethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-(2-methoxyethoxy)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 ethyl ({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl} amino)-2H-indazol-6-yl} oxy)acetate
 methyl 4-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl} amino)-2H-indazol-6-yl} oxy)butanoate
 ethyl 2-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl} amino)-2H-indazol-6-yl} oxy)propanoate
 ethyl 3-methyl-2-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl} amino)-2H-indazol-6-yl} oxy)butanoate
 2-({2-[2-(morpholin-4-yl)-2-oxoethyl]-5-({[6-(trifluoromethyl)pyridin-2-yl]carbonyl} amino)-2H-indazol-6-yl} oxy)propanoic acid
 N-{6-(2-hydroxypropan-2-yl)-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(trifluoromethyl)pyridine-2-carboxamide
 N-{6-chloro-2-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(difluoromethyl)pyridine-2-carboxamide
 N-{6-chloro-2-[2-(morpholin-4-yl)-2-oxoethyl]-2H-indazol-5-yl}-6-(difluoromethyl)pyridine-2-carboxamide.

11. Compound of the formula (I) as defined in any of Claims 1 to 10 for use as a medicament.
12. Compound of the formula (I) as defined in any of Claims 1 to 10 for use in the treatment and/or prophylaxis of
 - tumour disorders selected from the group consisting of lymphomas, chronic lymphatic leukaemia, melanomas and liver cell carcinoma, Ras-dependent tumours,
 - dermatological disorders selected from the group consisting of psoriasis, atopic dermatitis, allergic contact dermatitis,
 - cardiovascular disorders selected from the group consisting of arteriosclerosis, myocardial reperfusion damage, myocardial infarction, hypertension,
 - pulmonary disorders selected from the group consisting of pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), interstitial lung disease (ILD), sarcoidosis, pulmonary hypertension, asthma, idiopathic interstitial pneumonia,
 - ophthalmological disorders selected from the group consisting of ceratitis, allergic conjunctivitis, keratoconjunctivitis sicca, macular degeneration, uveitis,

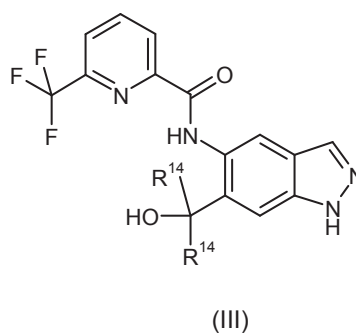
- neurological disorders selected from the group consisting of Alzheimer's disease, stroke, Parkinson's disease, skull-brain trauma,
inflammatory disorders selected from the group consisting of Crohn's disease, ulcerative colitis, and
- 5 pain selected from the group consisting of cancer pain, postoperative pain and inflammation-induced and chronic pain.
13. Compound of the formula (I) as defined in any of Claims 1 to 10 for use in the treatment and/or prophylaxis of lymphomas, macular degeneration, endometriosis, psoriasis, lupus erythematosus, multiple sclerosis, COPD, rheumatoid arthritis.
- 10
14. The use of a compound of the formula (I) as defined in any of Claims 1 to 10 in the manufacture of a medicament for the treatment and/or prophylaxis of
- tumour disorders selected from the group consisting of lymphomas, chronic lymphatic leukaemia, melanomas and liver cell carcinoma, Ras-dependent tumours,
- 15 dermatological disorders selected from the group consisting of psoriasis, atopic dermatitis, allergic contact dermatitis,
- cardiovascular disorders selected from the group consisting of arteriosclerosis, myocardial reperfusion damage, myocardial infarction, hypertension,
- pulmonary disorders selected from the group consisting of pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), interstitial lung disease (ILD), sarcoidosis, pulmonary hypertension, asthma, idiopathic interstitial pneumonia,
- 20 ophthalmological disorders selected from the group consisting of ceratitis, allergic conjunctivitis, keratoconjunctivitis sicca, macular degeneration, uveitis,
- 25 neurological disorders selected from the group consisting of Alzheimer's disease, stroke, Parkinson's disease, skull-brain trauma,
- inflammatory disorders selected from the group consisting of Crohn's disease, ulcerative colitis, and
- pain selected from the group consisting of cancer pain, postoperative pain and
- 30 inflammation-induced and chronic pain.
15. The use of a compound of the formula (I) as defined in any of Claims 1 to 10 in the manufacture of a medicament for the treatment and/or prophylaxis of lymphomas, macular degeneration, endometriosis, psoriasis, lupus erythematosus, multiple sclerosis, COPD,
- 35 rheumatoid arthritis.

16. Medicament comprising a compound of the formula (I) as defined in any of Claims 1 to 10 in combination with an inert, non-toxic, pharmaceutically suitable excipient.
17. Process for preparing compounds of the general formula (III) from the compounds of the general formula (II)



in which R^{14} is either a methyl or an ethyl radical by Grignard reaction with methyl- or ethylmagnesium bromide.

18. Compounds of the general formula (III)



in which R^{14} is either a methyl or an ethyl radical.