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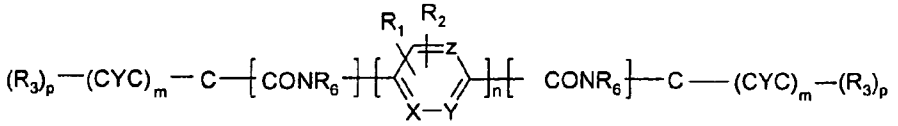
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(54) **Title:** AROMATIC 1,4-DI-CARBOXYLAMIDES AND THEIR USE



(I)

(57) **Abstract:** The invention relates to novel compounds of formula (I) wherein X, Y, Z represent independently from one another C or N, n stands for 1, 2, 3, m is 0 or 1, p stands for 0 or an integer from 1 to 6, R_1, R_2 represent independently from one another hydrogen, a halogen atom, a hydroxyl group, a C_1-C_3 alkyl group and a C_1-C_3 alkoxy group, R_3 represents, independently from one another if p is not 0, hydrogen, halogen, a C_1-C_5 linear or branched alkyl, a carboxylyl, a carbomethoxyl, carboethoxyl, a benzyl, an acyl, a hydroxyl, a C_1-C_4 linear or branched alkoxyl, a trifluoromethyl, a cyano, a morpholino, a 1,3-dioxolyl, an N-acetylamidyl or an amidoyl group, a saturated 5-8 membered ring, a heterocyclic ring, optionally substituted by a C_1-C_3 alkyl, a hydroxyl or a benzyl group, a C_1-C_6 alkylsulfonyl, a mono or disubstituted C_1-C_5 alkyl group, a branched or a cyclic amine, R_6 is H or part of a alicyclic, heteroalicyclic ring system, if m is 0 then C represents CF_3 or a branched or unbranched C_1-C_4 alkyl group, if m = 1 then C represents $-CH_2-O-$, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2(CH_2)CH_2-$ or denotes a chemical bond between N-C or C-C, the $CONR_6$ group may be linked to C either via its carbon or via its nitrogen atom, CYC stands for a by R_3 substituted or unsubstituted phenyl, pyridinyl, naphthyl, quinolinyl, isoquinolinyl, isoxaxolinyl, thiophenyl, 1,3,4-thiadiazazolidinyl, furanyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, morpholinyl, furanyl, cyclohexenyl, and chromen-2-on-yl and its use as a medicament for the treatment of cancer.

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Aromatic 1,4-Di-Carboxylamides and their Use

The present invention relates to aromatic 1,4-Di-Carboxylamides which inhibit the interaction between ß-catenin and BCL9 and/or BCL9L proteins and their use for the preparation of a pharmaceutical compositions and for the therapy of certain diseases.

More generally, the present invention relates to inhibitors of the Wnt transduction pathway. Such inhibitors can be used for stem cell research or for the treatment of diseases characterized by aberrant Wnt activation such as cancer, bone and cartilage diseases. Pathological activation of the Wnt pathway has been extensively reported for colorectal cancer, hepatocellular carcinoma, breast cancer, melanomas, mesotheliomas, lymphomas and leukemias. Furthermore, since the Wnt pathway also plays a fundamental role in T-cell development (Staal, Meeldijk et al. 2001; Staal and Clevers 2003), the Wnt signal transduction pathway inhibitors disclosed herein can also be used as immunosuppressant drugs, e.g. after organ transplantation or to treat certain autoimmune diseases such as Lupus erythematosus, multiple sclerosis and rheumatoid arthritis.

Wnt/Wg proteins exert many of their effects on vertebrate animal development by activating the expression of specific target genes in responding cells. Several of these target genes have been identified and some of their functions are consistent with control of cellular growth, differentiation, and survival (He, Sparks et al. 1998; Crawford, Fingleton et al. 1999; Tetsu and McCormick 1999; Kolligs, Nieman et al. 2002; Shtutman, Zhurinsky et al. 2002).

An intricate machinery has been identified which normally marks ß-catenin for degradation by phosphorylation. Importantly, the tumor suppressors APC and Axin are essential components of this ß-catenin destruction complex. Upon activation of the Wnt pathway, ß-catenin escapes this phosphorylation reaction, accumulates in the cytoplasm, and enters the nucleus, where it associates with TCF proteins and the recently identified Lgs/BCL9 [Kramps, T. et al., 2002] proteins to function as a transcriptional coactivator of target genes.

This set-up, in which the key transducer is continuously held in check, is highly susceptible to mutations in its inhibitory components. In fact, mutations in the downstream components of Wnt signalling have been found to be associated with a variety of human cancers (Kinzler and Vogelstein 1996; Miller, Hocking et al. 1999). For example, germline APC mutations can cause hundreds of benign colorectal tumors, some of which develop into cancer. Somatic mutations of the APC gene are associated with 85% of sporadic colorectal adenomas and carcinomas (Kinzler and Vogelstein 1996), mutations in the phosphorylation sites of ß-catenin have been found in many human cancers, such as colorectal cancer, hepatocellular carcinoma, and melanoma (Morin, Sparks et al. 1997; Rubinfeld, Robbins et al. 1997) (Caca, Kolligs et al. 1999), and axin mutations have been identified in hepatocellular carcinoma (Satoh, Daigo et al. 2000). Moreover, several mutations and/or changes in expression of upstream components like LRP5, sfrps, WIF-1, DKK or Wnt ligands have not only been linked to cancer, but also to bone and cartilage diseases. Since all these mutations lead to the accumulation of nuclear ß-catenin, this protein and its interacting partners has emerged as attractive targets to inhibit Wnt dependent gene expression.

In fact, inhibitors of the Wnt pathway that target the β-Catenin-Tcf4 interaction and processes for finding such inhibitors have been disclosed in various patent applications. International patent application W0 98/42296 discloses purified proteins and conventional processes for screening for inhibitors. International patent application WO 02/44378 describes a conventional process for screening for Tcf-ß-Catenin inhibitors. International patent application WO 03/006447 relates to Tcf4-ß-Catenin inhibitors. International patent application WO 02/096430 discloses cephalosporine derivatives as small molecule ß-catenin inhibitors. International patent application WO 01/19353A2 characterizes a "targetable" pocket in ß-Catenin using a 3D-model of the Tcf4-ß-Catenin interaction. It also describes *in silico* screening processes based on said interaction for identifying inhibitors as well as a number of inhibitors identified by this process.

The main disadvantage of the above mentioned approach is the nature of the β-Catenin-Tcf4 interaction. In particular, this protein-protein interaction surface is quite large and it is at least partially shared with other ß-Catenin interacting partners like

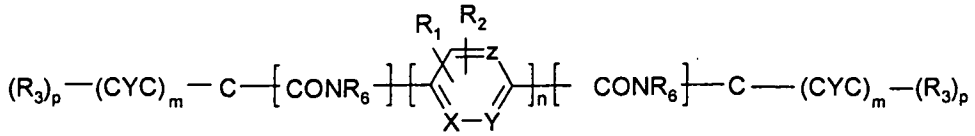
ECadherin and APC (Graham, Weaver et al. 2000; Eklof Spink, Fridman et al. 2001; Huber and Weis 2001; Poy, Lepourcelet et al. 2001), which raises serious questions about its specificity. Therefore, alternative targets for the Wnt pathway are required.

The Legless(Lgs)/BCL9 family of proteins was identified in a genetic screening for novel positive regulators of the Wnt pathway downstream of the APC tumor supressor in Drosophila melanogaster. In humans there are two homologues, BCL9 and BCL9-like (BCL9L, also known as B9L or BCL9-2), which, like the Drosophila protein, act as essential adaptor molecules between the transcriptional active components Pygo and β-Catenin. Binding of BCL9 proteins to β-Catenin is essential for the propagation of the Wnt signaling in cancer cells.

Competitor peptides that are capable of disrupting this protein-protein interaction or reduction of BCL9L expression by small interfering RNAs (siRNA) strongly inhibit the Wnt pathway and lead to differentiation of cancer cells from a non-differentiated malignant type into moderately to well differentiated tissue (US2002/0086986). However, despite their specific and potent inhibitory activity on the Wnt pathway these peptides or siRNA molecules do not represent ideal drugs for tumor therapy because of the poor membrane permeability and poor systemic availability.

It is one of the objects of the present invention to provide novel inhibitors of the beta-Catenin/BCL9-BCL9L interaction, in particular compounds with improved drug features, such as lower molecular weight and good cellular permeability.

It was found that compounds with general formula I satisfy these requirement and inhibit efficiently the beta-Catenin/BCL9-BCL9L interaction:



(I)

wherein

X, Y, Z represent independently from one another C or N

n stands for 1, 2, 3, m is 0 or 1, p stands for 0 or an integer from 1 to 6,

R_1, R_2 represent independently from one another hydrogen, a halogen atom, a hydroxyl group, a C_1-C_3 alkyl group and a C_1-C_3 alkoxy group,

R_3 represents, independently from one another if p is not 0, hydrogen, halogen, a C_1-C_5 linear or branched alkyl, a carboxylyl, a carbomethoxyl, carboethoxyl, a benzyl, an acyl, a hydroxyl, a C_1-C_4 linear or branched alkoxyl, a trifluoromethyl, a cyano, a morpholino, a 1,3-dioxolyl, an N-acetylamidyl or an amidoyl group, a saturated 5-8 membered ring, a heterocyclic ring, optionally substituted by a C_1-C_3 alkyl, a hydroxyl or a benzyl group, a C_1-C_6 alkylsulfonyl, a mono or disubstituted C_1-C_5 alkyl group, a branched or a cyclic amine.

R_6 is H or part of a alicyclic or heteroalicyclic ring system,

with the proviso

if m is 0 then C represents CF_3 or a branched or unbranched C_1-C_4 alkyl group,

if m = 1 then C represents -CH_2-O-, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, –$CH_2(CH_2)CH_2$- or denotes a chemical bond between N-C or C-C atoms,

the $CONR_6$ group may be linked to C either via its carbon or via its nitrogen atom,

CYC stands for a by R_3 substituted or unsubstituted phenyl, pyridinyl, naphthyl, quinolinyl, isoquinolinyl, isoxazolinyl, thiophenyl, 1,3,4-thiadiazazolidinyl, furanyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, morpholinyl, furanyl, cyclohexenyl and chromen-2-on-yl.

In preferred embodiments of the invention n is 1. The basic cyclic 1,4 substituted structure is therefore a phenyl, pyridinyl, pyridazinyl, pyrazinyl or pyrimidinyl ring.

In still further preferred embodiments of the present invention, n is 2 and the corresponding 1, 8 disubstituted cyclic basic structural motifs are biphenyl, bipyridinyl, bipyridazinyl, bipyrazinyl or bipyrimidinyl.

In further more preferred embodiments n is 3. The corresponding most preferred 1, 12 disubstituted structural motifs consisting of three cyclic basic structures are paraterphenyl, 2,5 diphenylpyridinyl, 3,4 diphenylpyridazinyl and 2,5 diphenylpyrazinyl.

In specific preferred embodiments, X, Y and Z are C, thus phenyl, biphenyl and terphenyl structural motifs form the basic cyclic structure.

In other preferred embodiments, X and Y are C and Z is N. These preferred structural motifs are for example pyridinyl, bipyridinyl and terpyridinyl.

In another preferred embodiment, X is C and Y and Z are N. The corresponding preferred structural motifs are pyridazinyl, pyrimidinyl, pyrazinyl and bipyridazinyl, bipyrazinyl or bipyrimidinyl.

In still further embodiments also mixtures of different structural motifs containing a different number of N atoms are preferred, like 2,5 diphenylpyridinyl, 3,4 diphenylpyridazinyl and 2,5 diphenylpyrazinyl.

In another preferred embodiment, m is 0 and C is a CF_3 group or a branched or unbranched C_1-C_4 alkyl group, specifically, methyl, ethyl, n-propyl, isopropyl, n-butyl, i-butyl, tert-butyl and isopropyl. In an especially preferred embodiment, C is tert-butyl or isopropyl.

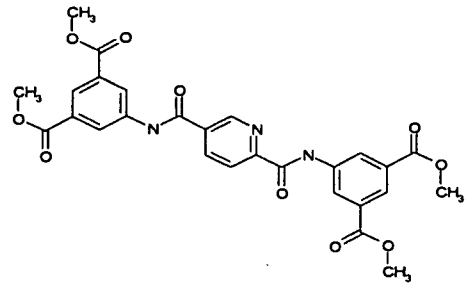
In further preferred embodiments of the invention, m is 1. In this case, C is selected from the group consisting of $-CH_2-O-$, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2(CH_2)CH_2-$ or denotes a chemical bond between N-C or C-C atoms. In most preferred embodiments, C denotes a chemical bond between N-C or C-C atoms.

In one further specifically preferred embodiment, the $CONR_6$ group in formula I is linked to C by its carbon atom. In an alternative embodiment which is equally pre-

ferred, the $CONR_6$ group is linked to C by its nitrogen atom. Thereby a fine tuning for preferred embodiments for C with respect to steric factors, acidity, further substitution etc. is provided.

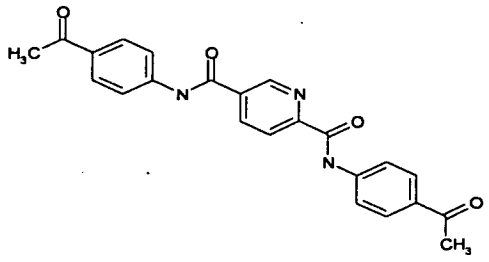
In the context of the present invention, "halogen" means Cl, Br, I and F. Especially preferred are Cl, Br and F, more preferred Cl and Br.

A specifically preferred compound according to the invention has the following formula:



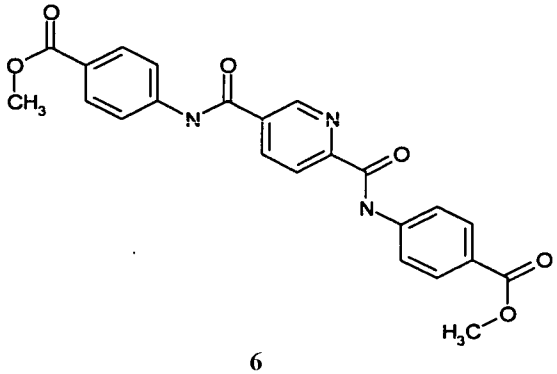
(II)

A further specifically preferred compound according to the invention has the following formula:



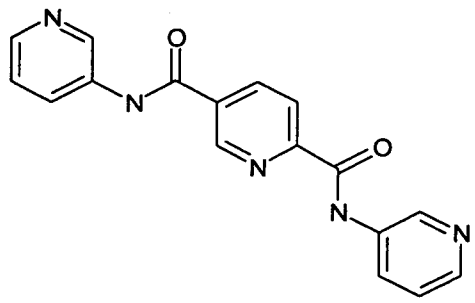
(III)

A still further specifically preferred compound according to the invention has the following formula:

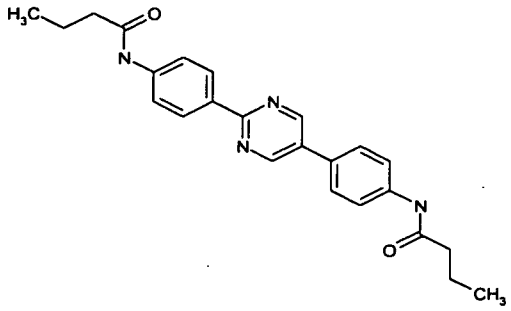


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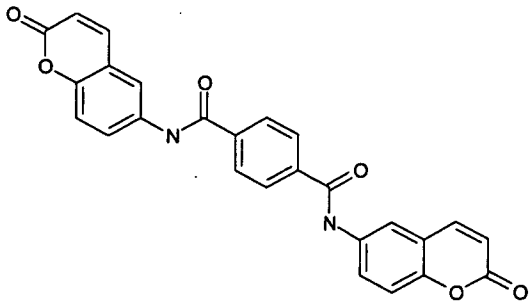
Still further preferred compounds have the following formulae



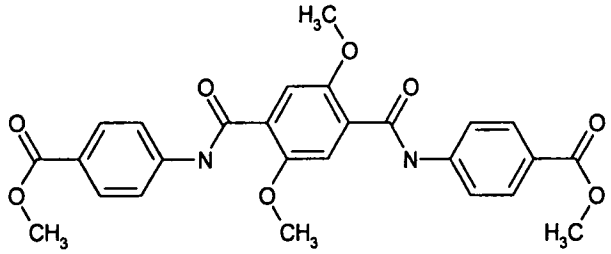
(V)



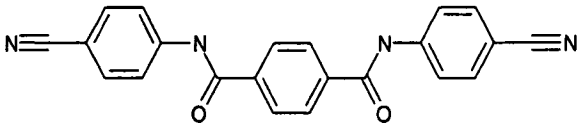
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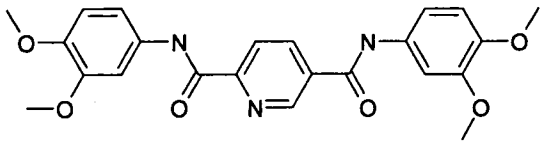
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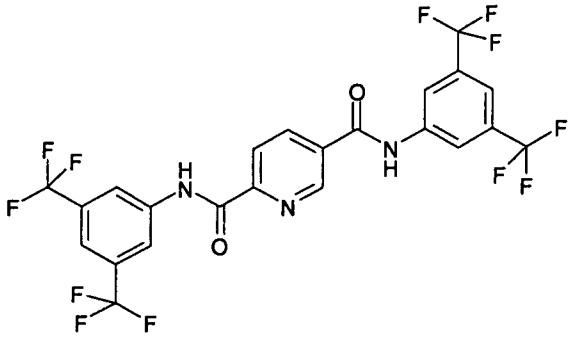
(VIII)



(IX)



(X)



(XI)

As shown in the preferred examples one of the most characteristic features is the "linear" 1,4, 1,8 or 1,12 substitution pattern at the "central" aromatic core. This is especially advantageous since the epitope, the binding pocket for the interaction with the peptide is a straight, channel-like ("linear") structure, so that the compounds according to the present invention fit sterically particularly well into the pocket and enable the specificity for binding with the key residues of the epitope.

A further object of the invention is the use of a compound according to the invention as a medicament and for the manufacture of a pharmaceutical composition for the treatment of diseases characterized by the over-activation of the Wnt pathway, such as, but not limited to, colon cancer, breast and prostate cancer, lung cancer, hepatocarcinoma, ovarian cancer, melanoma, and bone and join diseases like osteo- or rheumatoid-arthritis

The invention relates further to a pharmaceutical composition comprising a compound according the invention or a pharmaceutically acceptable salt thereof and in still further embodiments further comprising at least one pharmaceutically acceptable carrier, diluent or excipient.

Figures

Figure 1. shows the results of a compound according to the invention (TGC0012296) when tested for inhibition of the BCL9/BCL9L-β-Catenin, Tcf-4-β-Catenin and E-Cadherin-β-Catenin interactions as described in Example 1 (ELISA assay). The x-axis shows the concentration as the logarithmic function (log) in nM and the y-axis the measured absorbance.

The following examples and specifically indicated compounds further illustrate the best mode contemplated by the inventors for carrying out their invention. The examples relate to preferred embodiments and are not to be construed to be limiting on the scope of the invention.

Examples

Example 1: In vitro ELISA-based protein-protein interaction assay

Protein production in bacteria

cDNAs including the binding domains of Lgs and beta-Catenin were fused downstream of glutathione-S-transferase (GST) cDNA in pGEX-4T inducible bacterial expression vector (Pharmacia). Similar recombinant DNA constructs were generated in the pET-32a(+) vector (Novagen) for expression of fusion protein containing the Thioredoxine-6His tag at their N-terminus. Fusion proteins were produced in BL21 bacteria (e.g. Stratagene) following manufacturer's recommendation.

To isolate the produced fusions protein, bacteria were ground in aluminum oxide (Sigma, A2039) and the resulting powder extracted in lysis buffer (140mM NaCl, 10mM Na2HPO4, 1.8mM KH2PO4, 2.7mM KCl, 1mM EDTA, 1% Triton-X-100, 1mM DTT and protease inhibitors)under rotation for 30 minutes. Supernatants were cleared by centrifugation then filtered on a 0.45µm membrane before protein purification. For GST tagged protein, lysate were processed on glutathione agarose beads following manufacturer's recommendation (Amersham Pharmacia) and purified proteins eluted in 50mM Tris-Cl, 10mM reduced glutathione pH8.0. For thioredoxine-

6His fusions, tagged proteins were purified from the lysate on a nickel chelating column (e.g. Hitrap chelating, G.E. Healthcare) using an HPLC system (e.g. Akta Prime, G.E. Healthcare) and eluted under increasing concentration of imidazole. The purified proteins solution was dialyzed against PBS before use. The quality of the preparations was checked by SDS-gel electrophoresis by standard methods well known by persons skilled in the art.

Compound preparation: Compounds can be prepared as 25 mM stock in DMSO and diluted in DMSO to reach final test concentrations of up to 100µM. Final DMSO concentration in the assay is 5%.

ELISA-Assay

100µl of GST fusion protein (*e.g.* GST-βCatenin) diluted to the appropriate concentration in phosphate buffer saline are added per well to a 96 well plate with high protein binding capacity (*e.g.* Nunc Maxisorp) and placed at 4°C overnight. The following day the liquid in the wells is discarded and 150µl 3% bovine serum albumin (BSA) in PBS are added to each well and incubated at room temperature for 2 hours under moderate shaking. This solution is then discarded and each well washed twice with 200µl PBS. After carefully discarding the second wash, a mixture of 5µl compound dilution and 95µl 6His fusion protein (e.g. 6His-Bcl9) diluted to the appropriate concentration in PBS is added to each well. The plate is then incubated for 1 hour at room temperature under moderate shaking. This protein solution is then discarded and the wells washed 3 times with 200µl 0.1% Tween-20 solution in PBS. After carefully discarding the final wash, 100µl of anti 6His antibody conjugated to the horseradish peroxidase (e.g.Roche antibody 11965085001) at the appropriate dilution in 1% BSA in PBS is added to the wells and the plate incubated for 1 hour at room temperature under moderate shaking. This solution is then discarded and the wells washed 3 times with 200µl 0.1% Tween-20 solution in PBS. After carefully discarding the final wash, 100µl of HRP substrate Tetramethylbenzamidine (TMB) in solution (*e.g.* Sigma T0440) is added to the wells and the plate incubated up to 30 minutes in the dark at room temperature. The reaction is stopped by addition of 100µl of 2N HCl to each well and the optical density is measured at 450 nm and 630 nm.

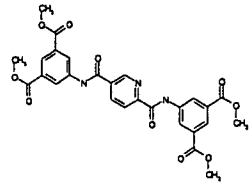
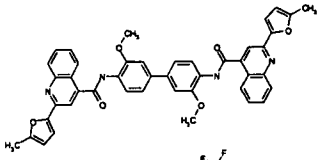
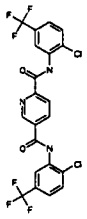
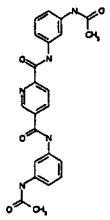
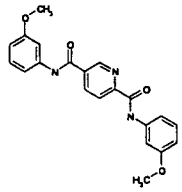
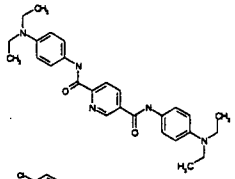
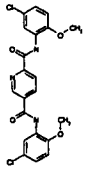
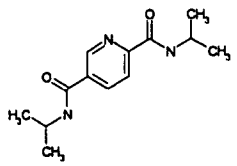
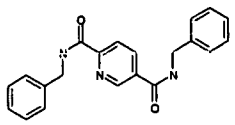
Example 2: Inhibition of Wnt activity in cancer cells

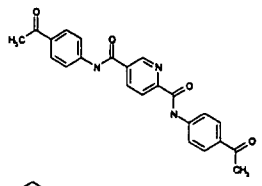
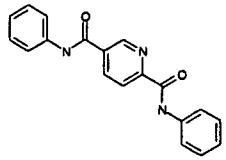
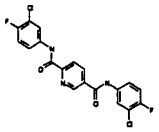
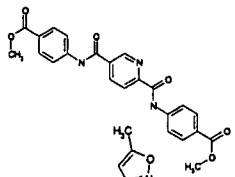
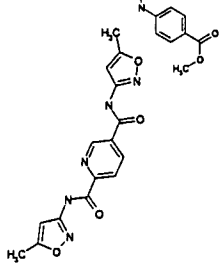
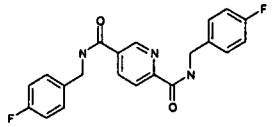
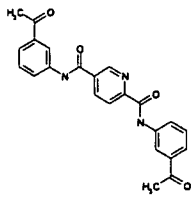
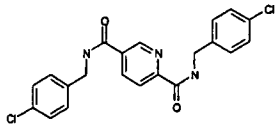
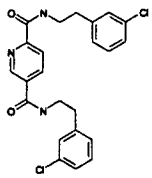
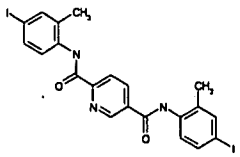
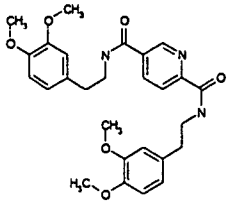
The effect of ß-catenin/BCL9 inhibitors identified in the ELISA-based protein-protein interaction assay on the Wnt pathway can be evaluated in a cell culture system using a reporter gene responsive to the Tcf/Lef family of transcription factors or by quantitative analysis of Wnt target genes in appropriate cell lines.

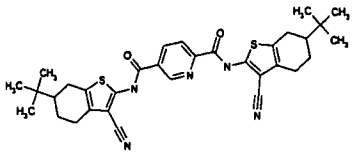
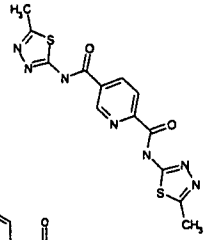
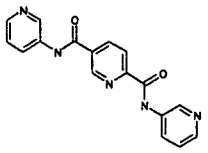
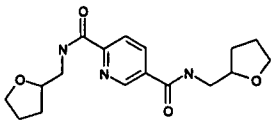
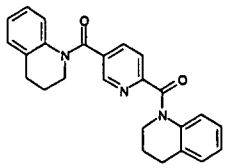
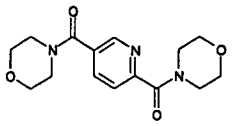
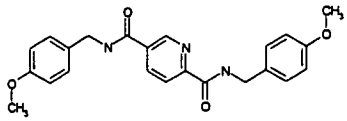
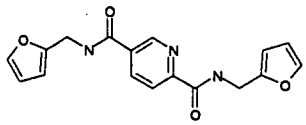
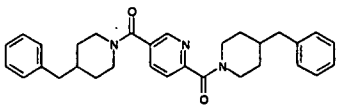
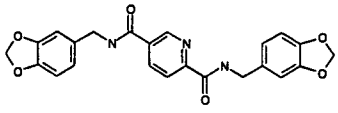
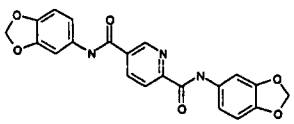
A reporter gene is a construct which comprises a readily detectable or assayable gene such ß-galactosidase, green fluorescent protein, chloramphenicol acetyltransferase or luciferase, linked *in cis* to a transcription factor response element and a minimal promoter. Depending on the expression vectors used, this protocol can be applied, e.g. for mammalian as well as for *Drosophila* cell lines. For instance, colon cancer cells with constitutively active Wnt pathway like SW620 (ATCC) are a well suitable system. Hereby, a Tcf-4 driven luciferase reporter plasmid (i.e. TOPFLASH, Upstate biotechnology, New York, USA) is transiently or stably transfected into cells known in the art. Any means for introducing genetic material into cells can be used, including but not limited to infection, electroporation or transfection. For instance, to introduce DNA into SW620 cells, a lipofection agent like the Lipofectamine transfection reagent (Life Technologies, Inc.) can be used. By transient transfection protocols, a second reporter gene, e.g. the renilla luciferase reporter plasmid pRL-SV40 (Promega Corporation, Madison USA), needs to be co-transfected to normalize for transfection efficiency. Drugs are added to the media 24h after transfection (transient transfection) or 24h after seeding of the cells (stably transfected cells). Cell extracts are prepared 24 to 48 h later and assayed for reporter gene activity as described by the manufacturer (eg. for luciferase activity: Promega Corporation). Compounds reducing reporter gene activity more than 50% compared to solvent alone treated cells are considered as hits. In parallel, toxicity can be assessed for instance by the yellow tetrazolium salt cell proliferation assay (MTT) assay.

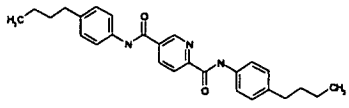
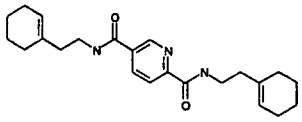
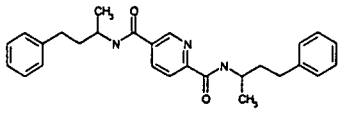
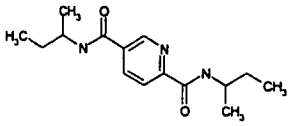
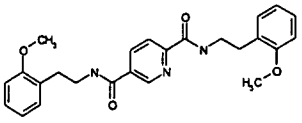
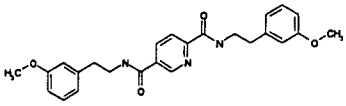
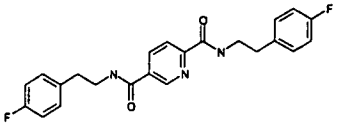
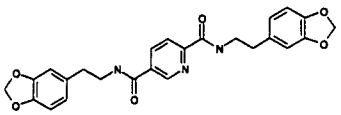
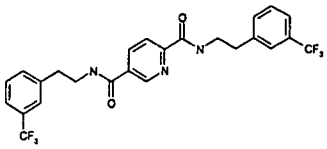
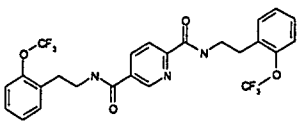
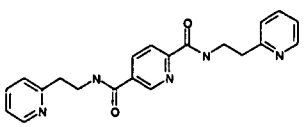
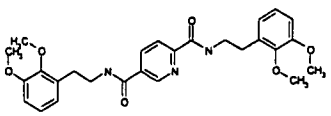
Table 1 shows the *in vitro* activities of specific compounds according to the invention. TGC ID refers to the applicants internal identification number; Specificity values depict compound's specificity for inhibition of the beta-Catenin-BCL9-BCL9L (specific means that they do not significantly inhibit E-Cadherin-βCatenin, Tcf-4-βCatenin or BCL9-Pygo interactions); MW means molecular weight.

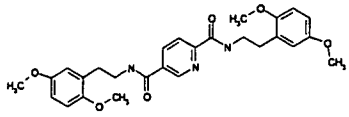
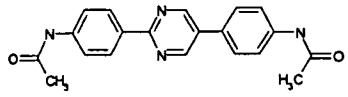
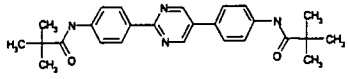
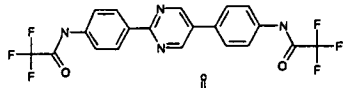
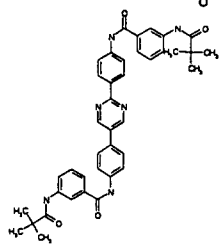
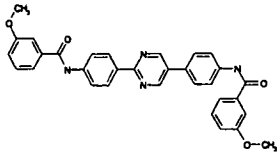
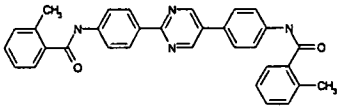
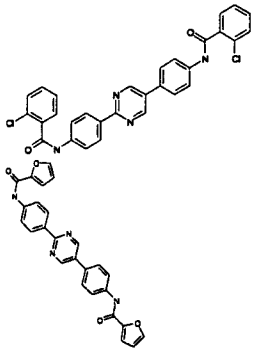
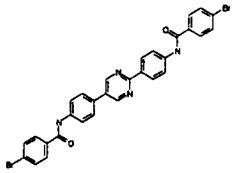
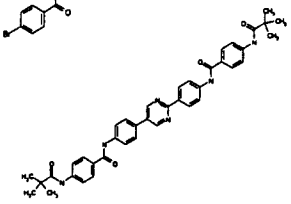
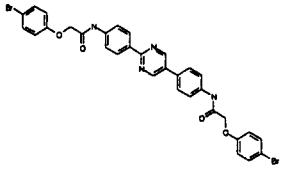
Table 1. Compound activities (IC50 in μM) as measured by the ELISA based protein-protein interaction assay as described in Example 1

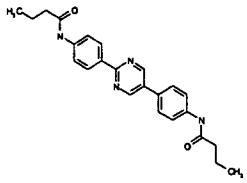
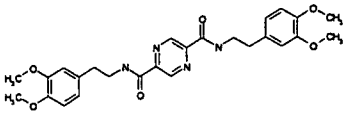
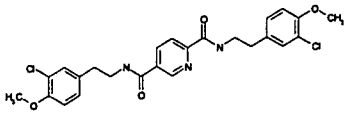
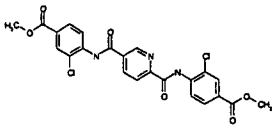
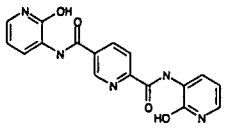
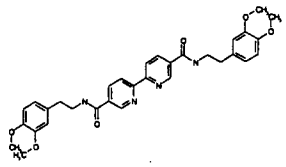
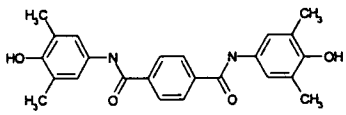
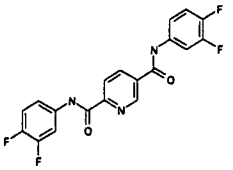
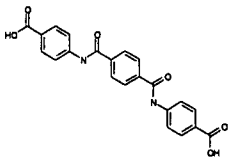
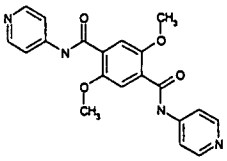
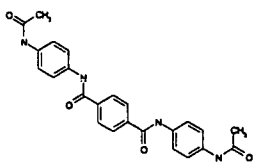
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	TGC0011279	3.5	129	431	> 100		
	TGC0011280	3.6	90	377	> 100	23	21
	TGC0011281	5.28	78	460	> 100		
	TGC0011282	4.91	90	446	> 100		
	TGC0011283	1.36	71	249	> 100		
	TGC0011284	2.94	71	345	> 100		

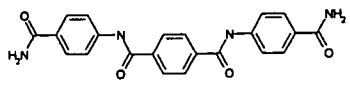
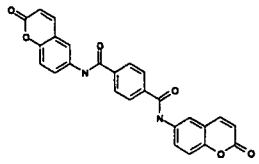
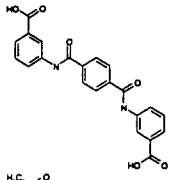
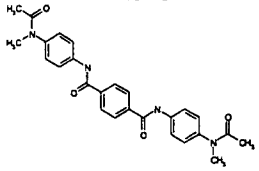
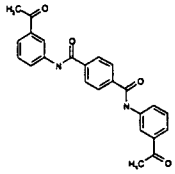
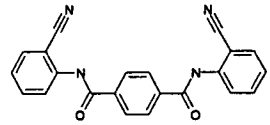
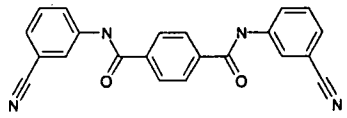
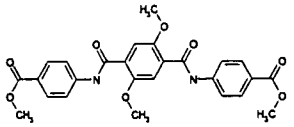
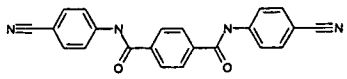
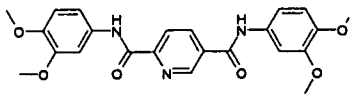
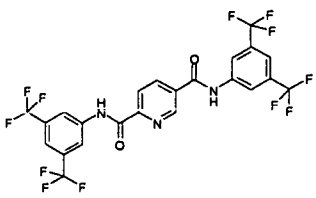
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	TGC0011287	5.17	71	422	> 100		
	TGC0011288	3.16	124	433	2	> 10	> 10
	TGC0011289	2.18	123	327	> 50		
	TGC0011337	3.22	71	381	> 10		
	TGC0011338	3.99	105	401	> 10		
	TGC0011339	4.25	71	414	> 10		
	TGC0011340	4.33	71	442	> 20		
	TGC0011341	5.41	71	597	> 10		
	TGC0011342	3.06	108	494	>50	>50	>50

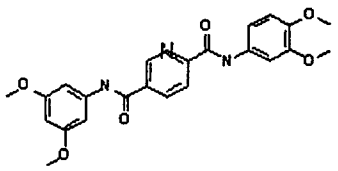
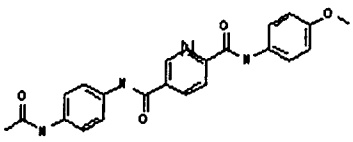
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	TGC0011423	2.38	90	319	29	> 100	> 100
	TGC0011424	0.9	90	333	> 50		
	TGC0011425	4.27	54	397	> 25		
	TGC0011426	0.03	72	305	> 50		
	TGC0011427	2.96	90	405	> 25		
	TGC0011428	2.13	97	325	> 50	> 50	> 50
	TGC0011429	5.27	54	482	> 25		
	TGC0011430	2.4	108	433	> 50	> 50	> 50
	TGC0011431	3.04	108	405	> 50		

	TGC0011433	6.27	71	430	> 50
	TGC0011435	4.32	71	382	> 50
	TGC0011436	4.58	71	430	>10
	TGC0011437	2.14	71	277	> 50
	TGC0011445	3.04	90	434	> 10
	TGC0011446	3.04	90	434	>10
	TGC0011447	3.3	71	409	> 50
	TGC0011448	2.48	108	461	> 10
	TGC0011452	4.82	71	511	> 10
	TGC0011454	5.07	90	543	> 100
	TGC0011455	1.82	97	375	> 100
	TGC0011456	3.06	108	494	> 100

	TGC0011457	3.06	108	494	> 100		
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	TGC0011525	5.78	84	431	> 10		
	TGC0011526	4.81	84	454	> 100		
	TGC0011527	8.28	142	669	> 10		
	TGC0011528	6.33	102	531	> 50	> 50	> 50
	TGC0011529	6.93	84	499	> 100		
	TGC0011530	7.62	84	539	> 10		
	TGC0011531	5.5	110	450	> 10		
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	TGC0011534	8.28	142	669	> 100		
	TGC0011565	7.37	102	688	> 100		

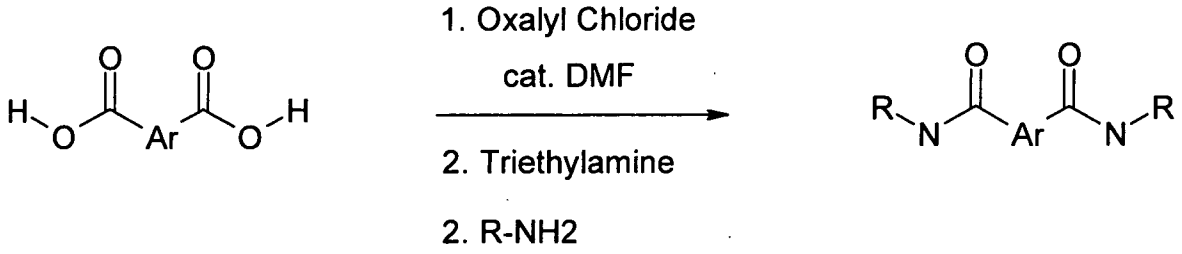
	TGC0011566	5.29	84	403	68	> 100	> 100
	TGC0011592	2.46	121	495	> 10		
	TGC0011593	4.35	90	502	> 100		
	TGC0011605	4.47	124	502	> 50	22	21
	TGC0012261	1.79	137	351	> 100		
	TGC0012281	4.12	121	571	38		
	TGC0012287	4.84	99	404	n.d.		
	TGC0012289	4.14	71	389	> 50		
	TGC0012290	0.92	138	404	> 50		
	TGC0012291	3	102	378	> 50		
	TGC0012292	4.11	116	430	> 50		

	TGC0012293	2.39	144	402	> 10		
	TGC0012296	4.4	119	452	3	>10	>10
	TGC0012297	0.92	138	404	> 100		
	TGC0012298	4.16	99	459	n.d.		
	TGC0012299	4.6	92	400	n.d.		
	TGC0012300	3.93	106	366	> 10		
	TGC0012301	3.93	106	366	> 50		
	TGC0012302	3.78	129	492	94	>100	>100
	TGC0012303	3.93	106	366	5	> 10	>10
	TGC0012373	3.62	108	437.5	10		
	TGC0012379	7.66	71	589	20		

	TGC00124 08	2.24	108	437	7
	TGC00124 09	1.80	109	404	5

As is evident from the table, the compounds according to formulae II to XI show especially advantageous results in terms of reactivity and specificity towards the beta-Catenin/BCL9-BCL9L interaction.

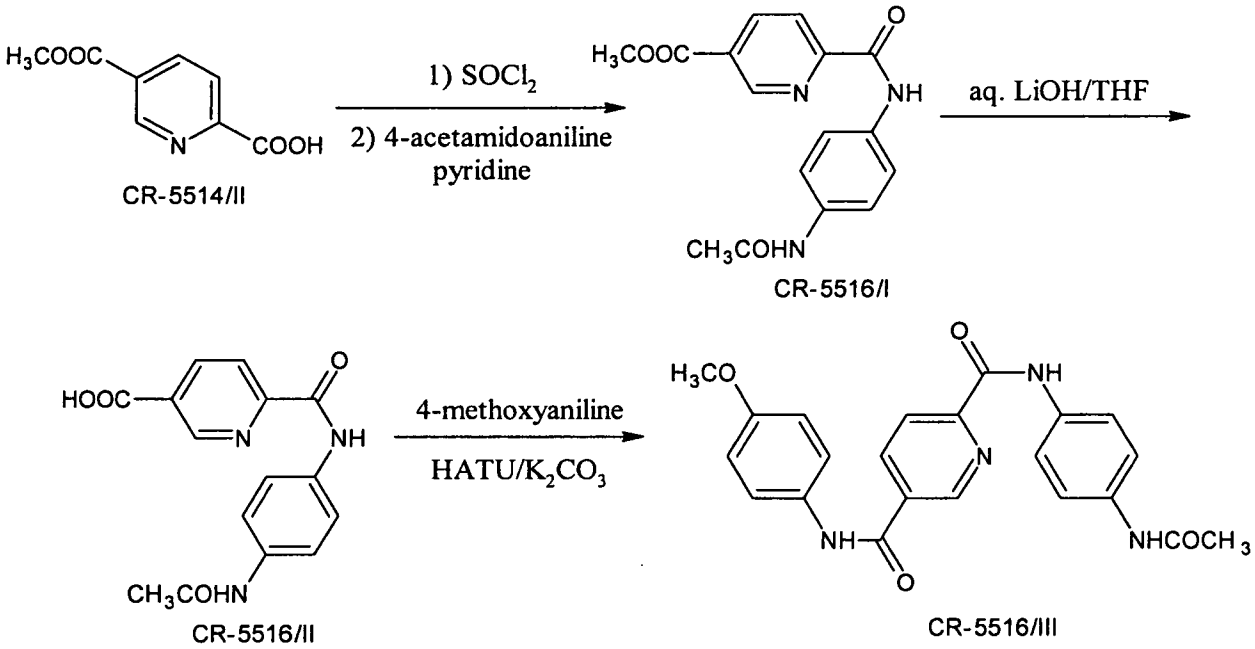
The components according to the invention can be prepared as follows using a general synthetic pathway.



Dicarboxylic acid (1 eq.) was suspended in dichloromethane (5 mL/mmol of acid) and cooled to 0°C. Oxalyl chloride (2.2 eq.) was then syringed in followed by the addition of 4 drops of DMF to get the reaction started. The reaction mixture was allowed to react at 0°C to room temperature overnight under vigorous stirring.

Excess oxalyl chloride was then removed and the remaining reaction mixture cooled to 0°C. A solution of triethylamine (3 eq.) in dichloromethane (5 mL/mmol of triethylamine) was syringed in followed by the slow addition of a solution of the corresponding aniline (3 eq.) in dichloromethane (5 mL/mmol of aniline). The resulting reaction mixture was allowed to stir overnight while allowing the temperature to go from 0°C to room temperature. The reaction mixture was filtered then washed with water. Upon evaporation of the solvent, the crude product was either crystallized from methanol or column chromatographed to a white powder.

A further generally applicable preparation approach for synthesizing the components according to the invention, especially for the asymmetric compounds is exemplified for the synthesis of TGC0012409, (also termed as CR-5516/III).



CR-5514/II (1.5gm, 8.280mmol) was refluxed with thionyl chloride (15.0mL) under anhydrous conditions for 4h until a clear solution was obtained. Excess thionyl chloride was removed by distillation. The residue was cooled to 0°C and charged with pyridine (10.0mL) followed by 4-acetamidoaniline (1.36gm, 9.100mmol) with occasional shaking until the evolution of HCl ceased. The solid obtained, was poured into ice-cold water (200mL) and extracted with DCM (3 x 150mL), washed with 5% aq. $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. Removal of solvent under reduced pressure yielded crude material which was purified by column chromatography using DCM grading to 2% methanol in DCM to give CR-5516/I (0.600gm).

To a stirred solution of CR-5516/I (0.230gm, 0.7341mmol) in THF (10.0mL), was added aqueous lithium hydroxide monohydrate (0.092gm, 2.202mmol in 2.3mL water) dropwise at 0°C. The reaction mixture was allowed to stir at r.t. overnight. (Some starting material was observed on TLC). THF was removed by distillation under reduced pressure, and partitioned between ethyl acetate and water. The aqueous layer was washed with ethyl acetate (3 x 100mL). The pH of the aqueous layer was adjusted to 5-6 by adding a 1N HCl solution then extracted with DCM (5 x 75mL). The

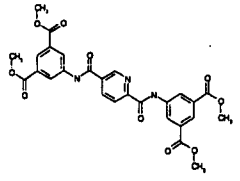
combined DCM layers were washed with water, brine, dried over Na_2SO_4 and the solvent removed under reduced pressure giving the crude material. Purification by column chromatography using DCM grading to 5% dichloromethane in methanol gave CR-5516/II (80mg).

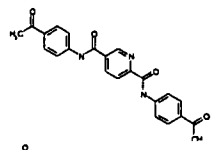
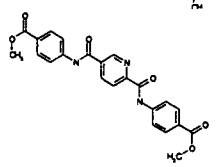
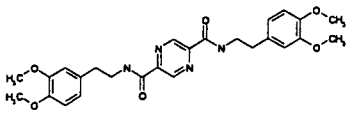
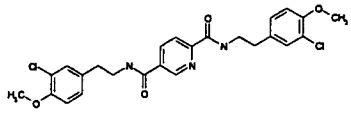
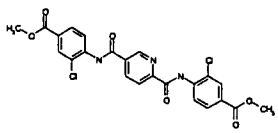
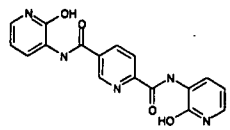
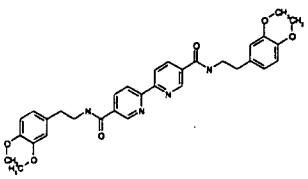
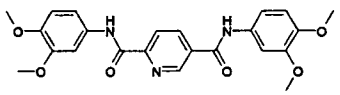
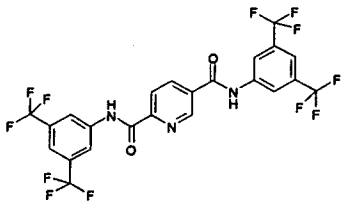
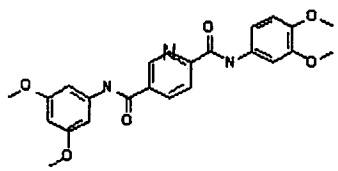
To a stirred solution of CR-5516/II (0.070gm, 0.2338mmol) in DMF (7.0mL), was added potassium carbonate (0.068gm, 4.909mmol) and stirred for 15min at R.T. To the above reaction mixture, 4-methoxyaniline (0.032gm, 2.572mmol) was added followed by HATU (2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, 0.133gm, 0.3507mmol). The resulting reaction mixture was allowed to stir at R. T. overnight. The solvent was removed under reduced pressure and the crude material purified by column chromatography using DCM grading to 20%methanol in DCM yielding pure CR-5516/III (TGC0012409) as a off-white solid (10mg).

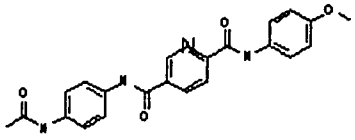
It is understood that this synthetic approach is not limited to the above specific compound and the other compounds according to the invention are accessible as well as in simply varying the respective starting materials.

Selected Mass Spectral (MS) and 1H-NMR data of exemplary compounds according to the invention are given in the following table 2 (signals given in ppm in reference to deuterated dimethylsulfoxide, s: singlet, d: doblet, t: triplet, q: quartet, dd: doublet of doublets, dt: doublet of triplets, m: multiplet and b: broad band):

Table 2: Selected Mass Spectral and 1H-NMR data of compounds according to the invention

MOLSTRUCTURE	TGC ID	MS	1H-NMR
	TGC0000160	549	3.93 (s, 12 H), 8.37 (s, 2H), 8.40 (d, 1H), 8.67(d, 1H), 8.79 (s, 2H), 8.94 (s, 2H), 9.32 (s, 1H), 11.11 (s, 1H), 11.39 (s, 1H).

	TGC0011285	400	2.04 (s, 6H), 7.58 (dd, 4H), 7.69 (d, 2H), 7.85 (d, 2H), 8.27 (d, 1H), 8.54 (d, 1H), 9.19 (s, 1H), 9.97 (s, 2H), 10.30 (b, 1H), 10.71 (s, 1H).
	TGC0011288	432	4.02 (s, 6H), 7.99 (m, 4H), (8.10 (m, 2H), 8.27 (dd, 1H), 8.53 (dd, 1H), 9.18 (d, 1H), 10.88 (s, 1H), 11.09 (s, 1H).
	TGC0011592	494	2.90 (t, 4H), 3.74 (t, 4H), 3.87 (s, 6H), 3.88 (s, 3H), 6.85-6.77 (m, 6H), 7.92 (t, 2H), 9.28 (s, 2H).
	TGC0011593	502	2.87 (t, 4H), 3.70 (t, 4H), 3.89 (s, 6H), 6.22 (t, 1H), 6.90-6.86 (m, 2H), 7.08 (t, 1H), 7.10 (t, 1H), 7.26 (t, 2H), 8.23-8-09 (m, 2H), 8.82 (d, 1H), 8.83 (s, 1H).
	TGC0011605	N.A.	3.88 (s, 6H), 7.99 (d, 2H), 8.01 (s, 1H), 8.32 (d, 2H), 8.56 (t, 3H), 9.18 (s, 1H), 10.80 (s, 2H).
	TGC0012261	349	7.43 (dt, 5H), 7.67 (d, 2H), 7.94 (d, 2H), 14.3-13.5 (b, 2H).
	TGC0012281	N.A.	3.00 (t, 4H), 3.71 (q, 4H), 3.83 (s, 6H), 3.85 (s, 6H), 6.78 (t, 3H), 6.84 (s, 3H), 8.05 (q, 4H), 9.19 (t, 2H), 9.24 (s, 2H).
	TGC0012373	N.A.	3.76 (s, 6H), 3.77 (s, 6H), 6.97 (dt, 2H), 7.34 (d,1H), 7.49 (s, 1H), 7.54 (d, 1H), 7.65 (s, 1H), 8.27 (d, 1H), 8.55 (d, 1H), 9.18 (s, 1H), 10.52 (bs, 1H), 10.62 (s, 1H).
	TGC0012379	N.A.	7.87 (d, 2H), 8.37 (d, 1H), 8.52 (s, 2H), 8.62 (d, 1H), 8.75 (s, 2H), 9.27 (s, 1H), 11.28 (bs, 1H), 11.52 (s, 1H).
	TGC0012408	N.A.	3.76 (s, 6H), 3.77 (s, 6H), 6.31 (bs, 1H), 6.98 (d,1H), 7.27 (bs, 2H), 7.32 (d, 1H), 7.48 (s, 1H), 8.28 (d, 1H), 8.53 (d, 1H), 9.18 (s, 1H), 10.51 (bs, 1H), 10.68 (s, 1H).

	TGC0012409	N.A.	2.04 (s, 3H), 3.76 (s, 6H), 6.88 (dd, 2H), 7.57 (d,2H), 7.69 (d, 2H), 7.84 (d, 2H), 8.27 (d, 1H), 9.18 (s, 1H), 9.95 (s, 1H), 10.52 (s, 1H), 10.70 (s, 1H).

The compounds according to the invention may be administered alone or in the form of a pharmaceutically acceptable salt thereof. A pharmaceutical composition comprising a compound according to the invention or a pharmaceutically active salt thereof may further comprise at least one pharmaceutically acceptable carrier, diluent or excipient. It is understood that in specific embodiments also further active compounds are contained within the composition.

The compounds according to the invention may be formulated for topical, oral, transdermal, parenteral, sublingual, intranasal, intrathecal, rectal, inhalative or intravenous administration in form of e.g. tablets, gel, capsules, patches, ointments, creams. Parenteral delivery can be carried out by depot, syringe, ampoule or vial.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, liquids or in the form of sterile injectable solutions. If a solid carrier is used, the preparation may be tableted, placed in a hard gelatine capsule in powder or pellet form, or in form of a troche or lozenge. The solid carrier may contain conventional excipients such as binding agents, tableting lubricants, fillers, disintegrants, wetting agents and the like. Tablets may be film coated by conventional techniques. If a liquid carrier is employed, the preparation may be in form of syrup, emulsion, soft gelatine capsule, sterile vehicle for injection, an aqueous or non-aqueous liquid suspension, or may be a dry product for reconstitution with water or other suitable vehicles before use. Liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, wetting agents, non-aqueous vehicle (including edible oils), preservatives, as well as flavouring and /or colouring agents. For parenteral administration, a vehicle normally will comprise sterile water, at least in large part, although saline solutions, glucose solutions and like may be utilized. Injectable suspensions also may be used, in which case conventional suspending agents may be employed. Conventional preservatives, buffering agents and the like also may be added to the par-

enteral dosage forms. Administration, however, can also be carried out rectally, e.g., in the form of suppositories, or vaginally, e.g. in the form of pessaries, tampons, creams, or percutaneously, e.g., in the form of ointments, creams or tinctures.

A suitable dose of compounds or pharmaceutical compositions according to the invention for a mammal, especially humans, suffering from, or likely to suffer from any condition as described herein is an amount of active ingredient from about 0.1µg/kg to 500mg/kg body weight. For parenteral administration, the dose may be in the range of 0.1µg/kg to 100mg/kg body weight for intravenous administration. The active ingredient will preferably be administered in equal doses from one to four times daily. The compounds of Formula (I) can also be used in the form of a precursor (prodrug) or a suitably modified form that releases the active compound *in vivo*. Normally, the administered dose will be gradually increased until the optimal effective dosage for the treated host is determined. The optimal administered dosage will be determined by a physician or others skilled in the art, depending on the relevant circumstances including the condition to be treated, the choice of compound to be administered, the route of administration, the sex, age, weight, and the specific response of the treated individual in respect to the severity of the individual's symptoms.

The pharmaceutical compositions are prepared by conventional techniques appropriate to the desired preparation containing appropriate amounts of the active ingredient, i.e., the compounds of the present invention. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

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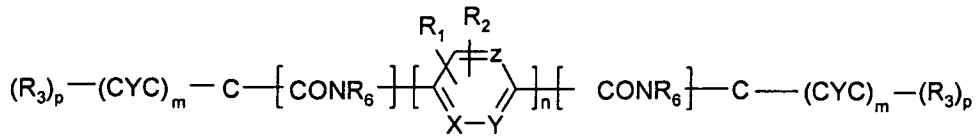
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Patent Claims

1. A compound of formula I



wherein

X, Y, Z represent independently from one another C or N

n stands for 1, 2, 3, m is 0 or 1, p stands for 0 or an integer from 1 to 6,

R_1, R_2 represent independently from one another hydrogen, a halogen atom, a hydroxyl group, a C_1-C_3 alkyl group and a C_1-C_3 alkoxyl group,

R_3 represents, independently from one another if p is not 0, hydrogen, halogen, a C_1-C_5 linear or branched alkyl, a carboxylyl, a carbomethoxyl, carboethoxyl, a benzyl, an acyl, a hydroxyl, a C_1-C_4 linear or branched alkoxyl, a trifluoromethyl, a cyano, a morpholino, a 1,3-dioxolyl, an N-acetylamidyl or an amidoyl group, a saturated 5-8 membered ring, a heterocyclic ring, optionally substituted by a C_1-C_3 alkyl, a hydroxyl or a benzyl group, a C_1-C_6 alkylsulfonyl, a mono or disubstituted C_1-C_5 alkyl group, a branched or a cyclic amine.

R_6 is H or part of a alicyclic or heteroalicyclic ring system,

with the proviso

if m is 0 then C represents CF_3 or a branched or unbranched C_1-C_4 alkyl group,

if m = 1 then C represents -CH_2-O-, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2(CH_2)CH_2$- or denotes a chemical bond between N-C or C-C atoms,

the $CONR_6$ group may be linked to C either via its carbon or via its nitrogen atom,

CYC stands for a by R_3 substituted or unsubstituted phenyl, pyridinyl, naphthyl, quinolinyl, isoquinolinyl, isoxaxolinyl, thiophenyl, 1,3,4-thiadiazazolidinyl, furanyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, morpholinyl, furanyl, cyclohexenyl and chromen-2-on-yl.

2. A compound according to claim 1, wherein n is 1

3. A compound according to claim 1, wherein n is 2

4. A compound according to claim 1, wherein n is 3

5. A compound according to any of claims 1 to 4, wherein X, Y and Z are C.

6. A compound according to any of claims 1 to 4, wherein X and Y are C and Z is N.

7. A compound according to any of claims 1 to 4, wherein X is C and Y and Z are N.

8. A compound according to any of claims 1 to 7, wherein m is 0.

9. A compound according to claim 8, wherein C is CF_3 or a branched or un-branched C_1-C_4 alkyl group.

10. Compound according to claim 9, wherein C is tert-butyl.

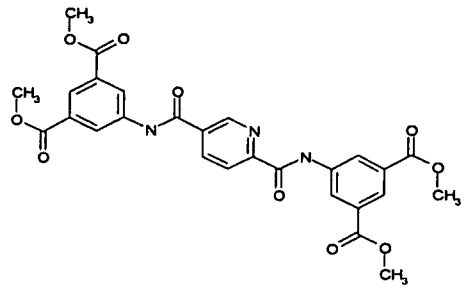
11. A compound according to any of claims 1 to 7, wherein m is 1

12. A compound according to claim 11, wherein C is $-CH_2-O-$, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2(CH_2)CH_2-$ or denotes a chemical bond between N-C or C-C atoms.

13. A compound according to any of claims 1 to 12, wherein the $CONR_6$ group is linked to C by its carbon atom.

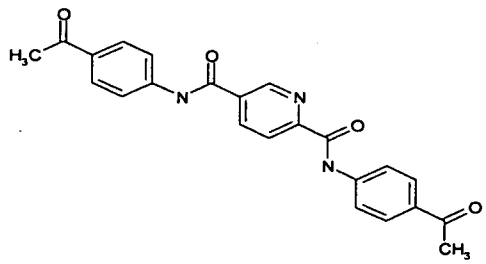
14. A compound according to any of claims 1 to 12, wherein the $CONR_6$ group is linked to C by its nitrogen atom.

15. A compound according to claim 1 with formula II:



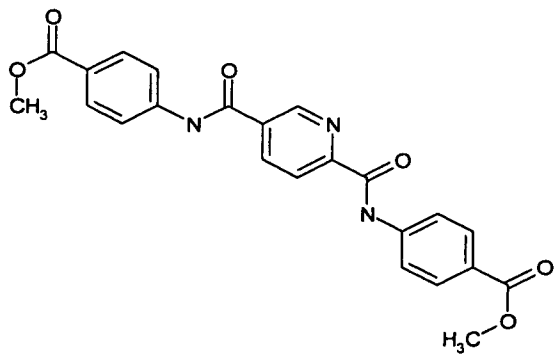
(II)

16. A compound according to claim 1 with formula III:



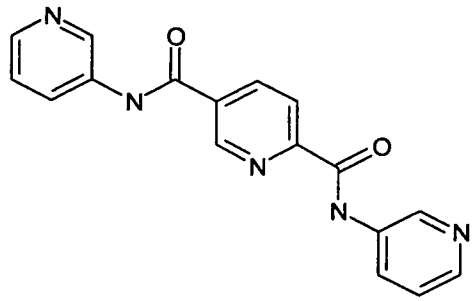
(III)

17. A compound according to claim 1 with formula IV:



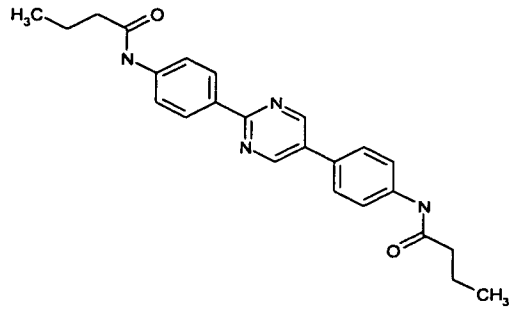
(IV)

18. A compound according to claim 1 with formula V:



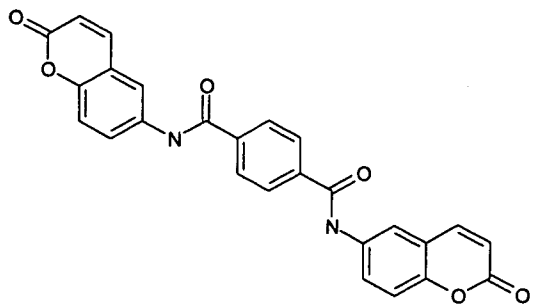
(V)

19. A compound according to claim 1 with formula VI:



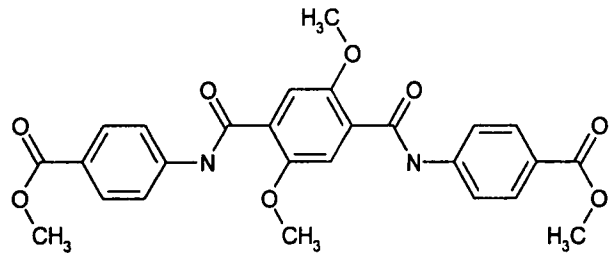
(VI)

20. A compound according to claim 1 with formula VII:



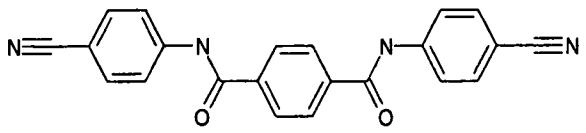
(VII)

21. A compound according to claim 1 with formula VIII:



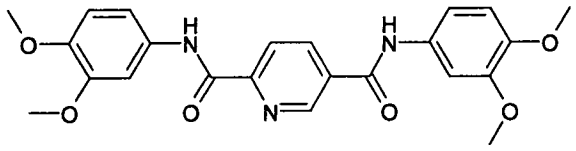
(VIII)

22. A compound according to claim 1 with formula IX:



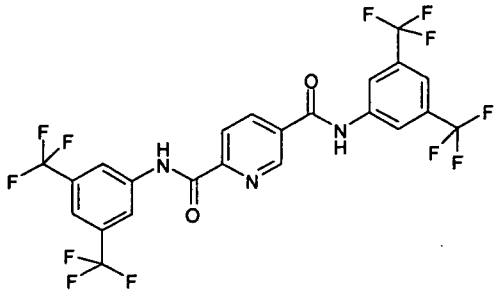
(IX)

23. A compound according to claim 1 with formula X:



(X)

24. A compound according to claim 1 with formula XI:



(XI)

25. Use of a compound according to any one of the preceding claims as a medicament.

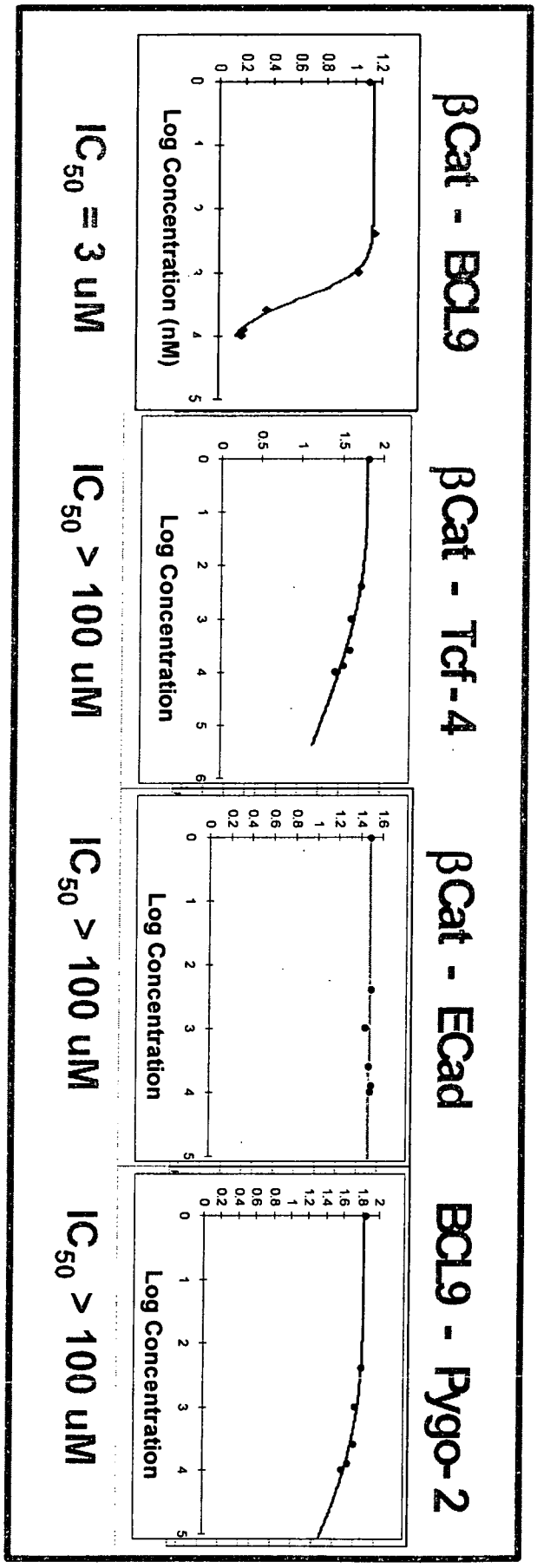
26. Use of a compound according to anyone of claims 1 to 24 for the manufacture of a pharmaceutical composition for the treatment of Wnt pathway dependent diseases.

27. Use of a compound according to anyone of the claims 1 to 24 for the manufacture of a pharmaceutical composition for the treatment of cancer.

28. Pharmaceutical composition comprising a compound according to anyone of the claims 1 to 24 or a pharmaceutically acceptable salt thereof.

29. Pharmaceutical composition according to claim 28, further comprising at least one pharmaceutically acceptable carrier, diluent or excipient.

Figure 1


βCat - BCL9
IC50 = 3 uM
Log Concentration (nM)
βCat - Tcf-4
IC50 > 100 uM
Log Concentration
βCat - ECad
IC50 > 100 uM
Log Concentration
BCL9 - Pygo-2
IC50 > 100 uM
Log Concentration

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/010829

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D233/96 C07D401/14 C07D407/12 A61K31/444 A61K31/505
A61P35/00

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/006447 A (PHARMACIA ITALIA SPA [IT]; MOLL JUERGEN [IT]; KNAPP STEFAN [IT]; DALVI) 23 January 2003 (2003-01-23) cited in the application pages 20-22; claims 1-21	1-29
A	WO 02/096430 A (KYLIX B V [NL]; BARKER NICHOLAS [NL]; VON KRIES JENS PETER [DE]; BROHM) 5 December 2002 (2002-12-05) cited in the application pages 28-34; claims 1,40	1-29

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2008	21/05/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Goss, Ilaria

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/010829

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 25 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/010829

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03006447 A	23-01-2003	AU 2002333233 A1	29-01-2003
		CA 2453175 A1	23-01-2003
		JP 2004534097 T	11-11-2004
		US 2004204477 A1	14-10-2004
WO 02096430 A	05-12-2002	NONE	