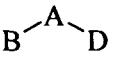
ABSTRACT

Dibenzylidene and heterobenzylideneacetone derivatives, related 4-piperidones, related 4-thiopyranones and the corresponding sulfinyl- and sulfonyl- analogues for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis

CLAIMS

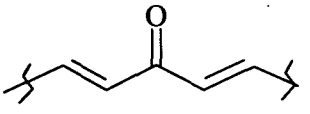
1. Compounds of formula (I)



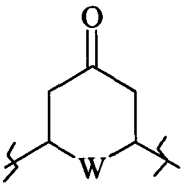
(I)

wherein

- A is selected from



and



A1 A2

with W representing N-(C_1–C_4)alkyl, N-C(O)-(C_1–C_5)alkylamine or $S(O)_p$ with p = 0 to 2,

- B and D each independently of each other represent an aryl group or a heteroaryl group optionally substituted by one to 5 substituents selected from the group comprising

. hydrogen atom,

. halogen atoms,

. hydroxy group,

. linear or branched (C_1-C_4)alkyl groups,

. (C_1-C_4) alkoxy groups,

. (C_1-C_4) thioalkoxy groups,

. trifluoromethyl group,

. trifluoromethoxy group,

. pentafluorosulfanyl group

. acetamide group,

. –OC(O)C_6H_5,

. formyl group

. - COOH,

. – COOR with R representing a (C_1-C_4)alkyl group,

. $-CH_2OH$

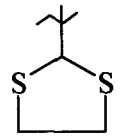
. $-CH_2OR'$ with R'representing a (C_1-C_4)alkyl group, $-CH_2OCH_3$ or a protecting group forming an acetal,

. $-NH_2$

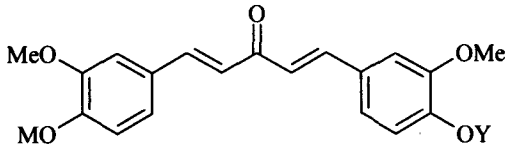
$-NR_2$ with R representing a (C_1-C_4)alkyl group,

. - NO_2,

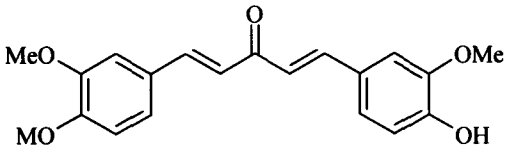
. - CN, and



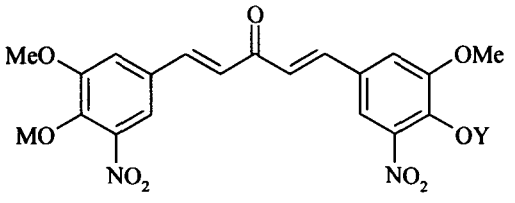
and the pharmaceutically acceptable salts and derivatives thereof for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis, sleeping sickness, Chagas' disease, visceral leishmaniases, cutaneous leishmaniases and mucocutaneous leishmaniases, with the proviso that, the following compounds are excluded:



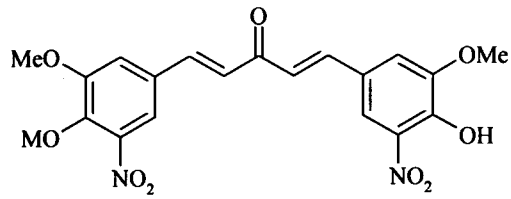
with M = Na or K and Y = Na or K



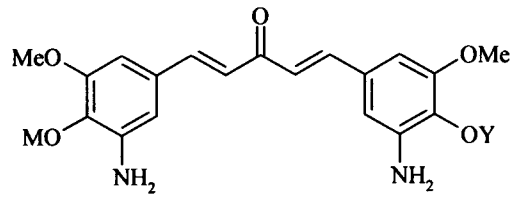
with M = Na or K



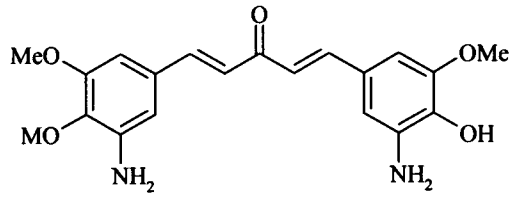
with M = Na or K and Y= Na



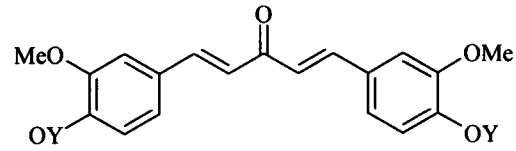
with M = Na or K



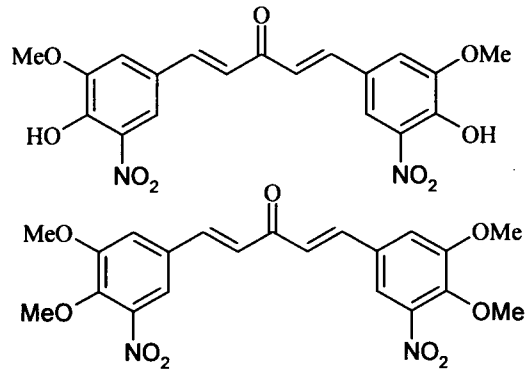
with M = Na or K or Y=Na

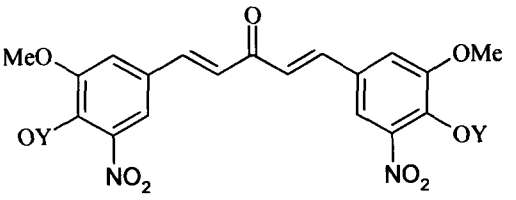


with M = Na or K

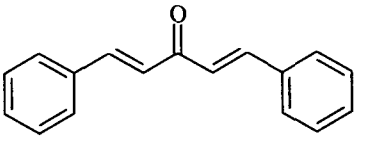


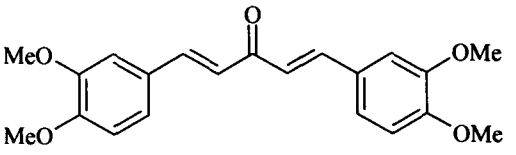
with Y = COC_6H_5

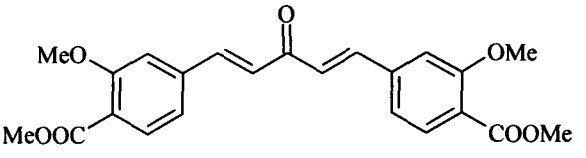


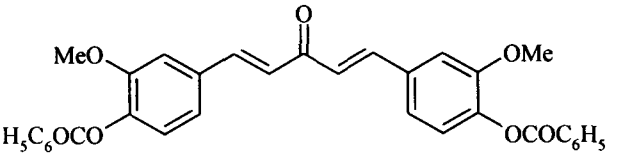


with Y = COC_6H_5









2. Compounds of formula (I) according to claim 1 wherein

B and D each independently of each other are selected from the group comprising a phenyl group, a 2-pyridyl or a 3-pyridyl or a 4-pyridyl or, a 2-pyrimidinyl, a 2*H*-1-benzopyran-2-one-3-yl, a 2*H*-1-benzopyran-2-one-4-yl, or a 2*H*-1-benzopyran-2-one-6-yl, each of said groups being optionally substituted by one to 5 substituents selected from the group comprising

. hydrogen atom,

. halogen atoms,

. hydroxy group,

. linear or branched (C_1-C_4)alkyl groups,

. (C_1-C_4) alkoxy groups,

. (C_1-C_4) thioalkoxy groups,

. trifluoromethyl group,

. trifluoromethoxy group,

. pentafluorosulfanyl group

. acetamide group,

. $-OC(O)C_6H_5$,

. formyl group

. - COOH,

. -COOR with R representing a (C_1-C_4)alkyl group,

. $-CH_2OH$

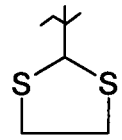
. $-CH_2OR'$ with R'representing a (C_1-C_4)alkyl group, $-CH_2OCH_3$ or a protecting group forming an acetal,

. $-NH_2$,

. $-NR_2$ with R representing a (C_1-C_4)alkyl group,

. $-NO_2$,

. -CN, and

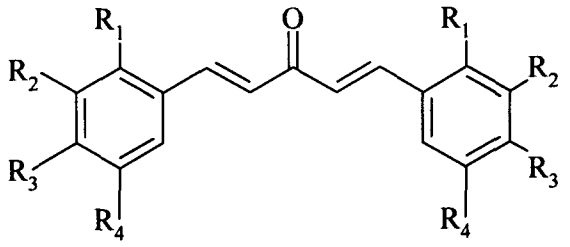


.

and the pharmaceutically acceptable salts and derivatives thereof for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

3. Compounds of formula (I) according to anyone of claims 1 or 2 wherein B and D are identical and the pharmaceutically acceptable salts and derivatives thereof for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

4. Compounds of formula (Ia1)

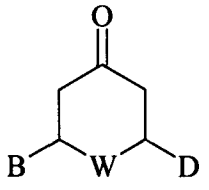


(Ia1)

wherein

R_1, R_2, R_3, and R_4 each independently of the other represent either a (C_1-C_4) thioalkoxy group, a trifluoromethoxy group, a pentafluorosulfanyl group, or a -$NHCOCH_3$ group and the pharmaceutically acceptable salts and derivatives thereof.

5. Compounds of formula (Ia2)



(Ia2)

wherein

W represents N-(C_1–C_4)alkyl, N-C(O)-(C_1-C_5)alkylamine or $S(O)_p$ with p = 0 to 2,

- B and D each independently of each other represent an aryl group or a heteroaryl group optionally substituted by one to 4 substituents selected from the group comprising

. hydrogen atom,

. halogen atoms,

. hydroxy group,

. linear or branched (C_1-C_4)alkyl groups,

. (C_1-C_4) alkoxy groups,

. (C_1-C_4) thioalkoxy groups,

. trifluoromethyl group,

. trifluoromethoxy group,

. pentafluorosulfanyl group

. acetamide group,

. –$OC(O)C_6H_5$,

. formyl group

. - COOH,

. – COOR with R representing a (C_1-C_4)alkyl group,

. -CH_2OH

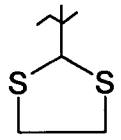
. -CH_2OR' with R'representing a (C_1-C_4)alkyl group, -CH_2OCH_3 or a protecting group forming an acetal,

. –NH_2

. -NR_2 with R representing a (C_1-C_4)alkyl group,

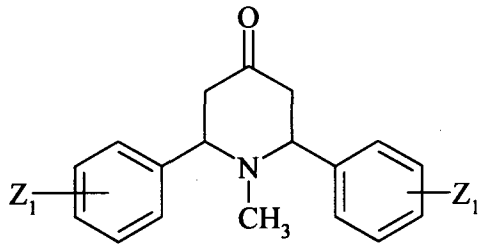
. - NO_2,

. - CN, and



and the pharmaceutically acceptable salts and derivatives thereof

- with the proviso that the following compounds are excluded:



with Z_1 = H, Cl, F, CF_3, OH

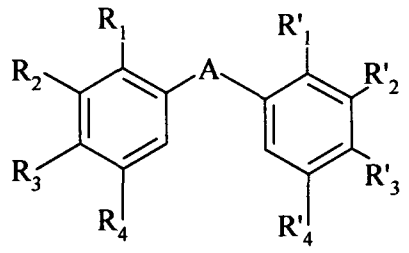
- with the proviso that when W is NCH_3 then B and D cannot be both a phenyl group substituted by methoxy groups or by a methyl group, nor a naphtyl group,

- with the proviso that when W is SO_2 then B and D cannot be both a phenyl group, B and D cannot be both a 3-O_2N-phenyl group, and if B is a phenyl group then D cannot be a phenyl group substituted in para by a linear or branched (C_1-C_{25})alkyl group,

- with the proviso that when W is S if B is a phenyl group then D cannot be a phenyl group substituted in para by a linear or branched (C_1-C_{25})alkyl group, B and D cannot be both or a pyridinyl group, B and D cannot be both a phenyl group or a phenyl group substituted in para by an halogen atom, and if one of B and D is a phenyl group, then the other cannot be a phenyl group susbtituted by one or two halogen atoms,

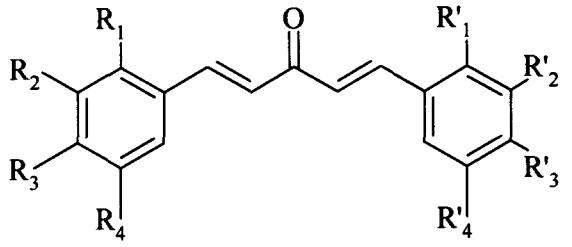
- with the proviso that when W is SO then B and D cannot be both a phenyl group .

6. Compounds responding to formula (Ib)



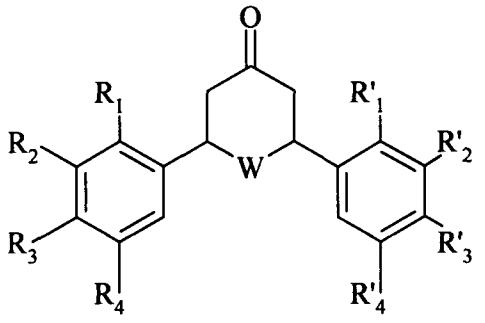
(Ib)

namely compounds of formula (Ib1)



(Ib1)

or of formula (Ib2)



(Ib2)

wherein W represents N-(C_1–C_4)alkyl, N-C(O)-(C_1-C_5)alkylamine or $S(O)_p$ with p = 0 to 2, and wherein in said formula (Ib), (Ib1) and (Ib2) R_1, R_2, R_3 and R_4 are always respectively different from R'_1, R'_2, R'_3 and R'_4 , and

- if R_3 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group, R_1, R_2 and R_4

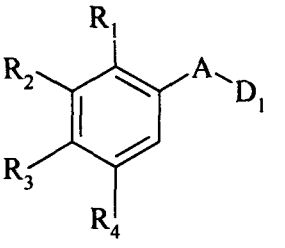
represent each a hydrogen atom, then R'_3 represents a hydrogen atom, a methyl group, a pentafluorosulfanyl group, a dimethylamino group ($-N(CH_3)_2$) or a trifluoromethoxy group and R'_1, R'_2 and R'_4 represent each a hydrogen atom, or

- if R_3 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a $-NHCOCH_3$ group, R_1, R_2 and R_4 represent each a hydrogen atom, then R'_1 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_2, R'_3, and R'_4 represent each a hydrogen atom, or
- if R_3 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a $-NHCOCH_3$ group, R_1, R_2 and R_4 represent each a hydrogen atom, then R'_3 represents a hydroxy group, R'_4 represents a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group and R'_1 and R'_2 represent each a hydrogen atom,
- if R_1 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a $-NHCOCH_3$ group, R_2, R_3 and R_4 represent each a hydrogen atom, then R'_3 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_1, R'_2 and R'_4 represent each a hydrogen atom, or
- if R_1 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a $-NHCOCH_3$ group, R_2, R_3 and R_4 represent each a hydrogen atom, then R'_1 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_2, R'_3, and R'_4 represent each a hydrogen atom, or
- if R_1 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a $-NHCOCH_3$ group, R_1, R_2 and R_4 represent each a hydrogen atom, then R'_3 represents a hydroxy group, R'_4 represents a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group and R'_1 and R'_2 represent each a hydrogen atom,
- if R_3 represents a hydroxy group, R_4 represents a halogen atom, a (C_1-C_4) alkoxy group, a (C_1-C_4) thioalkoxy group, a trifluoromethyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R_1 et R_2 represent each a hydrogen atom, then R'_3 represents a hydrogen atom, a methyl group or a trifluoromethoxy group or a pentafluorosulfanyl group and R'_1, R'_2 and R'_4 represent each a hydrogen atom,

- if R_3 represents a hydroxy group, R_4 represents a halogen atom, a (C_1-C_4) alkoxy group, a (C_1-C_4) thioalkoxy group, a trifluoromethyl group or a trifluoromethoxy group or a pentafluorosulfanyl group and R_1 and R_2 represent each a hydrogen atom, then R'_1 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_2, R'_3, and R'_4 represent each a hydrogen atom, or
- if R_3 represents a hydroxy group, R_4 represents a halogen atom, a (C_1-C_4) alkoxy group, a (C_1-C_4) thioalkoxy group, a trifluoromethyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R_1 and R_2 represent each a hydrogen atom, then R'_3 represents a hydroxy group, R'_4 represents a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group and R'_1 and R'_2 represent each a hydrogen atom,
- if R_1 represents a hydroxy group or a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom and R_4 represents a methoxy group, then R'_3 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_1, R'_2 and R'_4 represent each a hydrogen atom, or
- if R_1 represents a hydroxy group, a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom and R_4 represents a methoxy group, then R'_1 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_2, R'_3, and R'_4 represent each a hydrogen atom, or
- if R_1 represents a hydroxy group, a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom and R_4 represents a methoxy group, then R'_3 represents a hydroxy group, R'_4 represents a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group and R'_1 and R'_2 represent each a hydrogen atom.

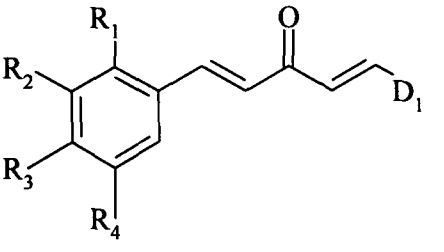
and the pharmaceutically acceptable salts and derivatives thereof.

7. Compounds responding to formula (Ic)



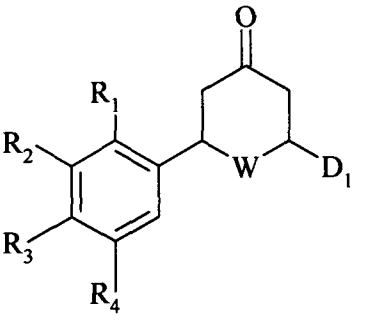
(Ic)

namely compounds of formula (Ic1)



(Ic1)

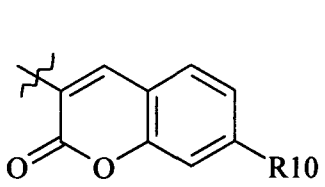
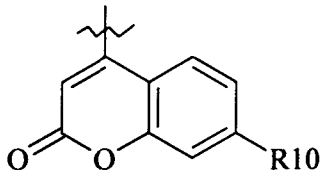
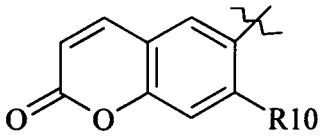
or of formula (Ic2)



(Ic2)

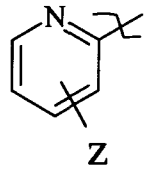
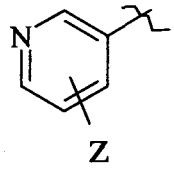
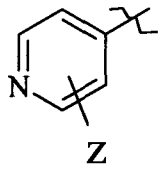
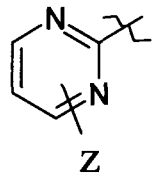
wherein W represents N-(C_1–C_4)alkyl, N-C(O)-(C_1-C_5)alkylamine or $S(O)_p$ with p = 0 to 2 and wherein in said formula (Ic), (Ic1) and (Ic2) D_1 is selected from groups A) or B), namely:

A)

wherein R10 is selected from the group comprising an hydrogen atom, a hydroxyl group and a (C_1-C_4) alkoxy group.

B)

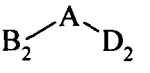
wherein Z represents a hydrogen atom, a fluorine atom or a trifluoromethyl group, and

- either R_3 represents a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group and R_1, R_2 and R_4 represent each a hydrogen atom, or
- either R_1 represents a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group and R_2, R_3 and R_4 represent each a hydrogen atom,
- either R_3 represents a hydroxy group, R_4 represents a halogen atom, a (C_1-C_4) alkoxy group, a (C_1-C_4) thioalkoxy, a trifluoromethyl group or a trifluoromethoxy group or a pentafluorosulfanyl group and R_1 and R_2 represent each a hydrogen atom, or

- either R_1 represents an hydroxy group or a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom and R_4 represents a methoxy group.

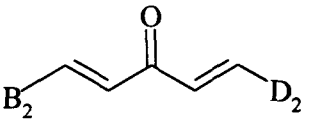
and the pharmaceutically acceptable salts and derivatives thereof.

8. Compounds responding to formula (Id)



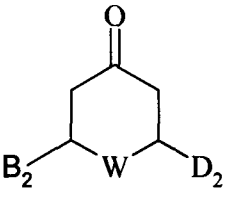
(Id)

namely compounds of formula (Id1)



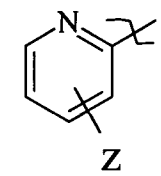
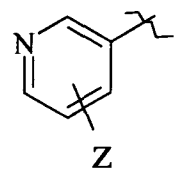
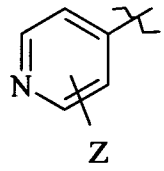
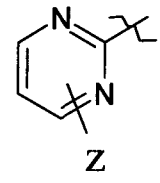
(Id1)

or of formula (Id2)



(Id2)

wherein W represents N-(C_1–C_4)alkyl, N-C(O)-(C_1-C_5)alkylamine or $S(O)_p$ with p = 0 to 2 and wherein in said formula (Id), (Id1) and (Id2), B2 and D2 are selected independently from each other from the group comprising:

and the pharmaceutically acceptable salts and derivatives thereof.

with the proviso that when W is SO_2 then B2 and D2 are not both a pyridinyl group.

Dated this 15th day of March 2012

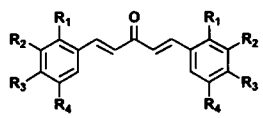
of Anand and Anand Advocates
Agent for the Applicant

ORIGINAL

2271 DELNP 12

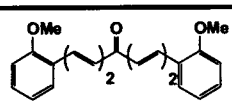
15 MAR 2012

Table 1

Structure	Compound	IC_{50} (µM)								
		MRC-5		*T. cruzi*		*L. infantum*		*T. brucei*		Toxicity
	**NW267** (R_3=CF_3, R_1=R_2=R_4=H)		26.18		1.60	>	64.00	<	0.25	
	NW254 (R_3=OCF_3, R_1=R_2=R_4=H)		32.86		1.76	>	64.00		0.46	
	NW247=NW238 (R_3=OMe, R_1=R_2=R_4=H)	>	64.00		10.70	>	64.00		1.24	
	NW270 (R_3=acetamide, R_1=R_2=R_4=H)		8.06		1.71		32.46		0.50	Toxic
	NW268 (R_1=Cl, R_2=R_3=R_4=H)		9.22		1.90		8.11		0.30	Toxic
	NW275 (R_1=R_2=R_3=R_4=H)		32.22		2.15		32.46		0.25	Toxic
	NW300 (R_1=R_4=H,R_2=OMe R_3=OH)	>	1.06		1.00	>	32.00	<	0.32	
	NW307.2 (R_1=R_2=R_4=H, R_3=CN)		10.36		0.97		16.57	<	0.32	
	NW308 (R_1=R_2=R_4=H, R_3=Cl)	>	32.00		11.21		10.36		0.53	Toxic
	NW310.1 (R_1=R_4=H, R_2=CF_3, R_3=OH)		10.49		12.40		10.36		1.03	Toxic
	NW317 (R_1=R_4=H, R_2=OCF_3, R_3=OH)	>	32.00	>	32.00		10.36		0.94	Toxic
	NW324.2 (R_1= R_4=OMe, R_2=Br, R_3=H)		0.85		0.92		10.36		0.94	Toxic
	NW326.4 (R_1=OH, R_2=Br, R_3=H, R_4=OMe)		0.96	<	0.32		1.04	<	0.32	Toxic
	NW327.2 (R_1=OH, R_2=R_3=H, R_4=OMe)		1.88		1.03	>	32.00	<	0.32	
	NW331 (R_1=R_4=OMe, R_2=R_3=H)		1.02		1.08		10.36		0.79	Toxic
	BJ639 (R_1=R_4=OMe, R_2=Br, R_3=Me)		29,58		12,85		6,96		9,08	
	BJ673K (R_1=R_4=OMe, R_2=H, R_3=SMe)	>	64,00	>	64,00		32,00	>	64,00	
	BJ679 (R_1=R_4=OMe, R_2=H, R_3=Me)	>	64,00	>	64,00		27,86	>	64,00	

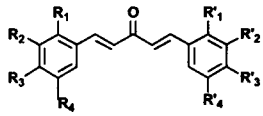
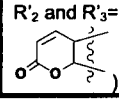
Archana Shanker
of Anand and Anand Advocates
Agent for the Applicant

Table 2

Structure	Compound	IC_{50} (µM)							
		MRC-5		*T. cruzi*		*L. infantum*		*T. brucei*	
	NW312	>	32.00	>	32.00	>	32.00	>	32.00

Archana Shanker
of Anand and Anand Advocates
Agent for the Applicant

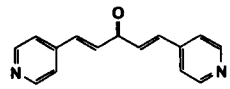
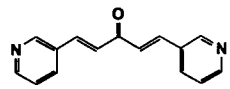
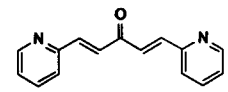
Table 3

Structure	Compound	IC$_{50}$ (μM)								
		MRC-5		*T. cruzi*		*L. infantum*		*T. brucei*		Toxicity
	**NW336.2** (R_1=R_2=R_4=H, R'$_1$=R'$_2$=R'$_4$=H, R_3=CF_3, R'$_3$=OMe)	>	32.00		12.32	>	10.36		0.72	Toxic
	NW346 (R_1=R_2=R_4=H, R'$_1$= R'$_4$=H,R_3=CF_3, R'$_2$= OMe, R'$_3$=OH)		8.60		6.50		8.11		0.36	
	NW337 (R_1= R_2=R_4=H, R'$_1$= R'$_2$=R'$_4$=H,R_3 =CF_3, R'$_3$=OCF_3)		18.86		10.54	>	32.00		0.55	
	NW351 (R_1=R_2=R_4=H, R'$_1$= R'$_4$=H,R_3=OCF_3, R'$_2$= OMe, R'$_3$=OH)		32.69		8.61		8.11		0.46	
	NW350 (R_1=R_2=R_4=H, R'$_1$=R'$_2$=R'$_4$=H, R_3=OCF_3, R'$_3$=OMe)	>	64.00	>	64.00		16.97	>	64.00	
	NW355.1 (R_1=R_2=R_4=H, R'$_1$= R'$_4$=H, R_3=CF_3, R'$_2$ and R'$_3$= )		8.60		6.50		8.11		0.36	

Archana Shanker
of Anand and Anand Advocates
Agent for the Applicant

ORIGINAL

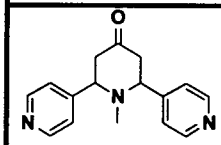
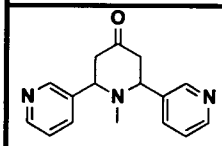
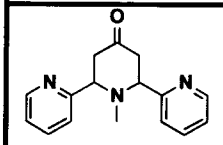
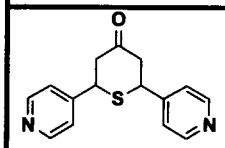
Table 4

Structure	Compound	IC_{50} (µM)								Toxicity
		MRC-5		*T. cruzi*		*L. infantum*		*T. brucei*		
	NW319		1.13	<	0.32		1.04	<	0.32	Toxic
	NW321		1.09		0.91		1.04	<	0.32	Toxic
	BJ621		1.94	<	0.25		1.50	<	0.25	Toxic

Archana Shanker
of Anand and Anand Advocates
Agent for the Applicant

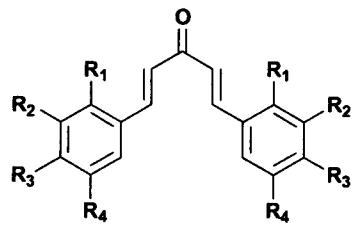
ORIGINAL

Table 5

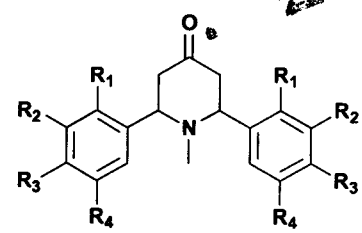
Structure	Compound	IC_{50} (μM)				Prodrug (Pro) of Michael Acceptor (MA)
		MRC-5	*T. cruzi*	*L. infantum*	*T. brucei*	
	BJ591	20.24	1.90	8.11 (Toxic)	< 0.25	(Pro) of NW319
	BJ593	> 64.00	> 64.00	> 64.00	> 64.00	(Pro) of NW321
	BJ627	7.70	0.40	8.11	< 0.25	(Pro) of BJ621
	TG003A23	> 64.00 (3)	> 64.00 (3)	> 64.00 (3)	8.17 (2) - 8.11	(Pro) of NW319

Archana Shanker
of Anand and Anand Advocates
Agent for the Applicant

Table 6



(MA)



(Pro)

Compounds	IC_{50} (µM) *in triplicate*					Prodrug (Pro) of Michael Acceptor (MA)
	cytotoxicity human MRC-5	*T. cruzi*	*L. infantum*	*T. brucei brucei*	*T. brucei rhodesiense*	
NW249.1 (R_1=R_2=R_3=R_4=H)	> 64.00 - 32.94 (2)	0.94 -1.52 - 4.50	> 64.00 (3)	< 0.25 - 0.08 - 0.09	0.20 - 0.13	(Pro) of NW275
NW275 (R_1=R_2=R_3=R_4=H)	7.65 (T)	1.60	32.22	< 0.25	< 0.25	(MA)
NW246.1 (R_1=R_2=R_4=H, R_3=OMe)	> 64.00 (3)	> 64.00 (3)	> 64.00 (3)	2.40 - 1.96 - 2.23	-	(Pro) of NW238=NW247
NW247=238 (R_1=R_2=R_4=H, R_3=OMe)	> 64.00	10.70	> 64.00	1.24	-	(MA)
BJ613.2 (R_1=Cl, R_2=R_3=R_4=H)	25,08	7,32	12,70	0,63	-	(Pro) of NW268
NW268 (R_1=Cl, R_2=R_3=R_4=H)	6.11 - 6.82 - 5.60	3.61 - 2.32 - 2.49	8.11 (2) - 6.82	< 0.25 - 0.50 - 0.26	-	(MA)
BJ571.1=575 (R_1=R_2=R_4=H, R_3=CF_3)	32.22	8.26	32.00	0.79	-	(Pro) of NW267
NW267 (R_1=R_2=R_4=H, R_3=CF_3)	7.65 - 8.06	0.34 - 0.25	> 64.00 (2)	0.003 - 0.03	0.03 - 0.04	(MA)
BJ607.2 (R_1=R_2=R_4=H, R_3=OCF_3)	32,00	7,34	2,00	1,82	-	(Pro) of NW254
NW254 (R_1=R_2=R_4=H, R_3=OCF_3)	56.42	5.06	32.86	0.36	0.44	(MA)
BJ578=577K (R_1=R_2=R_4=H, R_3=acetamide)	8.52	2.13	8.11 (Toxic)	0.50	-	(Pro) of NW270
NW270 (R_1=R_2=R_4=H, R_3=acetamide)	8.06	1.71	32.46 (Toxic)	0.50	-	(MA)
tamoxifen	10.0					reference
nifurtimox		1.0				reference
miltefosine			3.56			reference
suramin					0.02	reference
suramin				0.02		reference

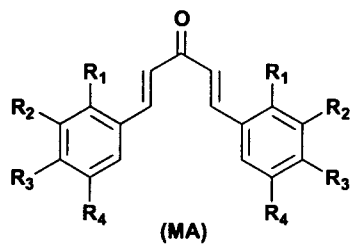
Archana Shanker
Archana Shanker
of Anand and Anand Advocates
Agent for the Applicant

ORIGINAL

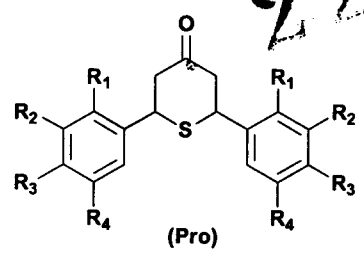
2971 IN 12

15 MAR 2012

Table 7



(MA)



(Pro)

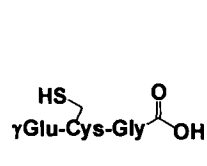
Compounds	IC_{50} (µM) *in triplicate*				Prodrug (Pro) of Michael Acceptor (MA)
	cytotoxicity human MRC-5	*T. cruzi*	*L. infantum*	*T. brucei brucei*	
TG001A21 (R_1=R_2=R_4=H, R_3=OMe)	> 64.00 (3)	> 64.00 (3)	> 64.00 (3)	> 64.00 (3)	(Pro) of NW247
TG002A22 (R_1=R_2=R_4=H, R_3=OMe)	> 64.00 (3)	> 64.00 (3)	> 64.00 (3)	> 64.00 (3)	(Pro) of NW247
TG006A44 (R_1=R_2=R_4=H, R_3=OMe)	> 64.00 (3)	> 64.00 (3)	> 64.00 (3)	> 64.00 (3)	(Pro) of NW247
NW247 (R_1=R_2=R_4=H, R_3=OMe)	> 64.00 (3)	> 64.00 (3)	> 64.00 (3)	2.40 - 1.96 - 2.23	(MA)
TG004A23 (R_1=Cl, R_2=R_3=R_4=H)	> 64.00 (3)	30.49 - 42.68 - > 64.00	> 64.00 (3)	33.99 - 36.88 - 41.90	(Pro) of NW268
NW268 (R_1=Cl, R_2=R_3=R_4=H)	6.11 - 6.82 - 5.60	3.61 - 2.32 - 2.49	8.11 (2) - 6.82	< 0.25 - 0.50 - 0.26	(MA)
TG005A25 (R_3=Cl, R_1=R_2=R_4=H)	> 64.00 – 32.00 - 23.44	> 64.00 - 19.33 - 23.35	> 64.00 (3)	> 64.00 - 52.86 - 40.82	(Pro) of NW308
NW308 (R_3=Cl, R_1=R_2=R_4=H)	23.57 - > 64.00 (2)	31.02 - 32.59 -35.52	> 64.00 - 24.05 (2)	1.03 (2) - 0.97	(MA)
tamoxifen	10.9				reference
nifurtimox		1.67			reference
R126			5.0		reference
melarsoprol				0.09	reference

Archana Shanker
Archana Shanker
of Anand and Anand Advocates
Agent for the Applicant

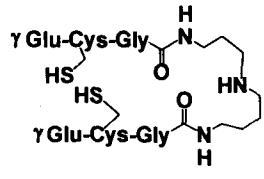
COMPOUNDS USEFUL AGAINST KINETOPLASTIDEAE PARASITES

The present invention relates to the use of dibenzylidene and diheteroarylidene acetones and their derivatives in the prevention and the treatment of diseases due to parasites. The invention also relates to the preparation of the said compounds.

Trypanosomes and leishmanias are parasitic protozoa causing African sleeping sickness (*Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*), Chagas' disease (*Trypanosoma cruzi*), Nagana cattle disease (*Trypanosoma congolense* and *Trypanosoma brucei brucei*), Espundia (*Leishmania brasiliensis*), Kala-azar (*Leishmania donovani*), and Oriental sore (*Leishmania tropica*). All of these parasites have a unique thiol metabolism dependant on the flavoenzyme trypanothione reductase, which maintains bisglutathionylspermidine (trypanothione) and monoglutathionylspermidine in the reduced state. This thiol system replaces the glutathione/glutathione reductase (GR) system occurring in their mammalian hosts and is widely accepted as a target for the development of novel therapies to treat trypanosomiasis and leishmaniasis.



glutathione



trypanothione

Human African trypanosomiasis is invariably fatal if untreated. Current therapy of the late-stage encephalitic disease with the melaminophenyl arsenical drug melarsoprol has unacceptable side-effects with an overall mortality of more than 5% due to the drug itself. Melarsoprol acting as a bis-alkylating agent of dithiols including trypanothione and trypanothione reductase is actively taken up *via* adenosine transporters of the parasite which recognize the melamine motif. In the recent years appearance of highly resistant parasites to melarsoprol and pentamidine has become alarming and is responsible for the increasing failure rate (under 7%) of melarsoprol after treatment of late stage case of human African trypanosomiasis (HAT), even though the drug has been used for such treatment over the past 50 years. This observation, the first documented in a HAT focus, is dramatic, particularly since no second line trypanocidal drug is actually available for the treatment of the late stage of HAT.

Eflornithine (=DFMO) is effective against both stages of *T. b. gambiense* infection but not against *T. b. rhodesiense*. Although the most recent and effective drug against

sleeping sickness it is not widely available, difficult to administer and costly for use under African health care conditions. For this reason, in 1995, Aventis limited its production because erflornithine was not enough a profitable drug.

Thus there is a need for compounds which are less costly, less toxic, which induce less resistance and which are able to cross the blood brain barrier in the late stage of the disease.

The inventors have discovered that a divinylketone is the minimal motif for mechanism-based inactivation of the trypanothione based-system and they have designed and synthesized symmetrical and asymmetrical dibenzylidene (and diheteroarylidene) acetone derivatives and other derivatives to protect the reactive α,β-unsaturated ketone.

Several patents disclose dibenzylidene and heterobenzylidene acetone derivatives and related 4-piperidones but with applications as anticancer (WO 2004/009023) or anti-Alzheimer drugs (US2007/0060644).

WO 2008/003155 discloses penta-1,4-dien-3-ones and substituted cyclohexanones showing antitumoral and antiparasitic properties but the 1,5-bis(4-hydroxy-3-methoxy-phenyl)-penta-1,4-dien-3-one and the dibenzylidene aceton are the only compound tested for their parasitic effect.

Rule N.J. *et al.* (J. Org. Chem. (1995), 60, 1665-1673 disclose the synthesis of *4h*-thiopyran-4-one but do not give any information on their potential activity.

Haller R. in Archiv der Pharmazie (1965), 5, 306-312 (XP-002577741) discloses the synthesis of 1-thiacyclohexanone but does not give any information on their potential activity.

Weber W.M. *et al.* (Biochemical Pharmacology (2006), 72, 928-940 disclose anlogs of curcumin as modulators of the TP-induced up-regulation of activator protein-1.

Klein J. *et al* (Tetrahedron (1974), 30, 2541-2548) discuss the stereochemistry of thiane oxidation but does not give any information on the potential activity of the compounds.

Chin H. Chen *et al* (J. Org. Chem. (1986), 51, 3282-3289) disclose the synthesis of 2,6-diphenyl-4*H*-thiopyran-4-one but do not give any information on their potential activity.

US 5013849 discloses *4h*-thiopyran-1,1-dioxides and their use as electron-transport agents in electrophotographic elements.

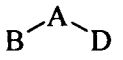
EP0031456 discloses 4-amino-2,6-diaryl-tetrahydrothiopyrane useful as a antidepressant.

Consequently one aim of the invention is the use of such compounds in the prevention and treatment of diseases caused by kinetoplastidae parasites.

Another aim of the invention is the process for preparing such compounds.

Finally some of the compounds are new and are also part of the invention.

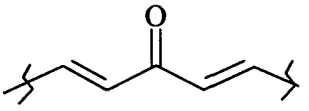
The present invention relates to compounds of formula (I)



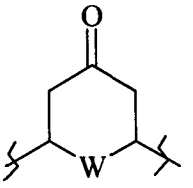
(I)

wherein

- A is selected from



and



A1 A2

with W representing N-(C_1–C_4)alkyl, N-C(O)-(C_1–C_5)alkylamine or $S(O)_p$ with p = 0 to 2,

- B and D each independently of each other represent an aryl group or a heteroaryl group optionally substituted by one to 5 substituents selected from the group comprising

. hydrogen atom,

. halogen atoms,

. hydroxy group,

. linear or branched (C_1-C_4)alkyl groups,

. (C_1-C_4) alkoxy groups,

. (C_1-C_4) thioalkoxy groups,

. trifluoromethyl group,

. trifluoromethoxy group,

. pentafluorosulfanyl group

. acetamide group,

. –OC(O)C_6H_5,

. formyl group

. –COOH,

. –COOR with R representing a (C_1-C_4)alkyl group,

. –CH_2OH

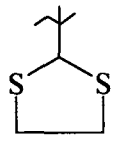
. $-CH_2OR'$ with R'representing a $(C_1\text{-}C_4)$alkyl group, $-CH_2OCH_3$ or a protecting group forming an acetal,

. $-NH_2$

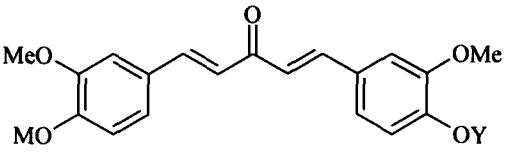
. $-NR_2$ with R representing a $(C_1\text{-}C_4)$alkyl group,

. $-NO_2$,

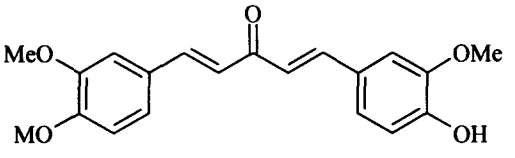
. –CN, and



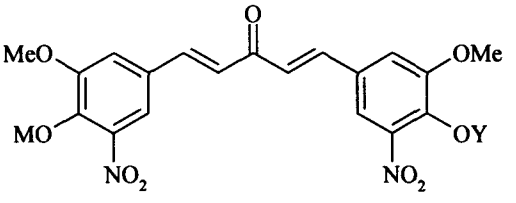
and the pharmaceutically acceptable salts and derivatives thereof for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis, sleeping sickness, Chagas' disease, visceral leishmaniases, cutaneous leishmaniases and mucocutaneous leishmaniases, with the proviso that, the following compounds are excluded:



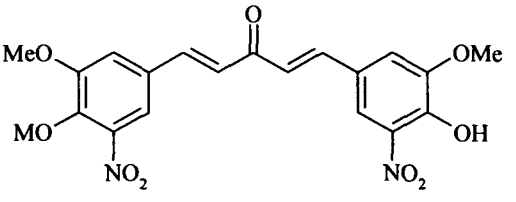
with M = Na or K and Y = Na or K



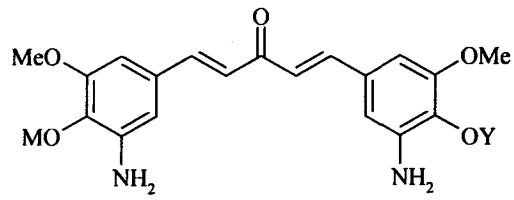
with M = Na or K



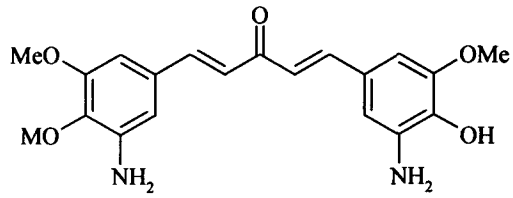
with M = Na or K and Y= Na



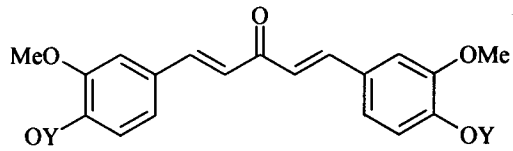
with M = Na or K



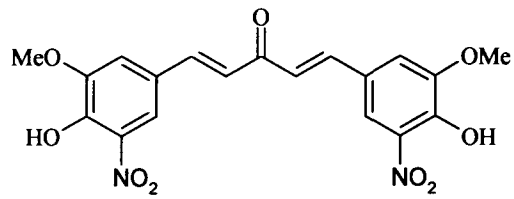
with M = Na or K or Y=Na

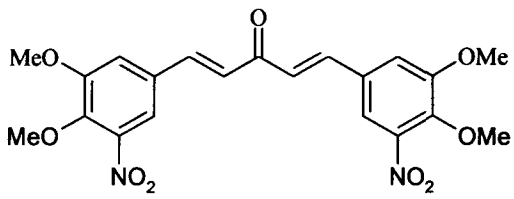


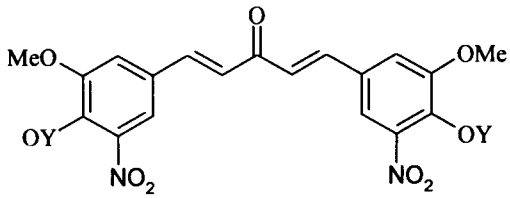
with M = Na or K



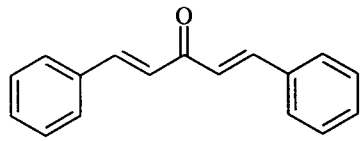
with Y = COC_6H_5

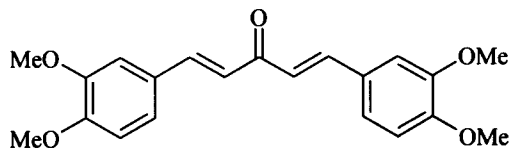


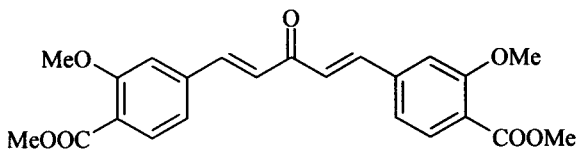


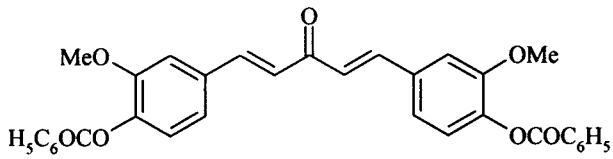


with Y = COC_6H_5









According to the invention, the term "aryl" as used herein refers to a monocyclic or bicyclic carbocyclic ring system having one or more aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl.

According to the invention, the term "heteroaryl" as used herein refers to any mono- or bicyclic aromatic 5- to -12 members ring containing 1 to 5 heteroatoms selected from O, S

or N, selected from imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, thiophenyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl as monocyclic rings and including but not limited to indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzimidazolyl, indazolyl, benzothiazolyl, isobenzofuranyl, isobenzothiazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[2,3-b)]pyridinyl, pyrrolo[3,2-b]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrrolo[1,2-a]pyridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, pyrrolo[1,2-a]imidazolyl, imidazo[1,2-a]pyridinyl, imidazo[1,2- a]pyridazinyl, imidazo[1,2-c]pyrimidinyl, imidazo[1,2-a]pyrimidinyl, imidazo[1,2-a]pyrazinyl, imidazo[4,5-b]pyrazinyl, imidazo[4,5-b]pyridinyl, imidazo[4,5- c]pyridinyl, pyrazolo[2,3-a]pyridinyl, pyrazolo[2,3-a]pyrimidinyl, pyrazolo[2,3-a]pyrazinyl, 3-(7-hydroxy-coumaryl) also named 7-hydroxy-2*H*-1-benzopyran-2-one-3-yl, 4-(7-hydroxy-coumaryl) also named 7-hydroxy-2*H*-1-benzopyran-2-one-4-yl, or 6-(7-hydroxy-coumaryl) also named 7-hydroxy-2*H*-1-benzopyran-2-one-6-yl as bicyclic rings.

According to the invention the term "halogen" as used herein refers to fluorine, chlorine, bromine and iodine atom.

According to the invention the term "linear or branched (C_1-C_4)alkyl" as used herein refers to straight or branched chain alkyl substituents containing from 1 to 4 carbon atoms including methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl.

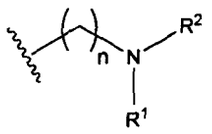
According to the invention the term "(C_1-C_4) alkoxy groups" as used herein refers to an alkoxy substituent made up of an oxygen substituent bearing saturated straight or branched chain hydrocarbon substituent of one to four carbon atoms including but not limited to methoxy, ethoxy, propoxy, *n*-butoxy, isobutoxy, sec-butoxy, *t*ert-butoxy.

According to the invention the term "(C_1-C_4) thioalkoxy groups" as used herein refers to S-alkoxy wherein the alkoxy group is defined above.

According to the invention, the term N-(C_1–C_4)alkyl means that N is substituted by a (C_1–C_4)alkyl group as defined above, in particular by a methyl group, said alkyl group being optionnaly substituted by an hydroxy group to form alpha- or omegaamino alcohols or by a group able to give amino esters or any other groups in order to improve the solubility and even pharmacokinetics.

According to the invention the term "(C_1-C_5)alkylamine" as used herein refers to straight chain alkyl substituent containing from 1 to 5 carbon atoms and bearing a nitrogen atom at the end of the chain. This nitrogen can be mono or disubstituted, each independently

of each other, by hydrogen, methyl, ethyl, isopropyl, *tert*-butyl or protected as a *tert*-butyl carbamate. This definition is in accordance with the following formula:



n = 1 to 5

R^1 = H, methyl, ethyl, isopropyl, tert-butyl or BOC
R^2 = H, methyl, ethyl, isopropyl, tert-butyl or BOC

According to the invention, the R' group representing a protecting group forming an acetal, may be for example a tetrahydropyranyl group (THP).

According to the invention, kinetoplastidae parasites are primitive flagellated protozoans found in terrestrial and aquatic environments. Some of them cause diseases in organisms ranging from plants to vertebrates. Two major sub-groups of Kinetoplastidae are Leishmania and Trypanosomatidae.

According to the invention, trypanosomiasis and leishmaniasis also include sleeping sickness, Chagas' disease, and visceral leishmaniases, cutaneous leishmaniases and mucocutaneous leishmaniases.

In an advantageous embodiment the invention relates to compounds of formula (I) wherein

B and D each independently of each other are selected from the group comprising a phenyl group, a 2-pyridyl or a 3-pyridyl or a 4-pyridyl or, a 2-pyrimidinyl, a 2*H*-1-benzopyran-2-one-3-yl, a 2*H*-1-benzopyran-2-one-4-yl, or a 2*H*-1-benzopyran-2-one-6-yl, each of said groups being optionally substituted by one to 5 substituents selected from the group comprising

. hydrogen atom,
. halogen atoms,
. hydroxy group,
. linear or branched (C_1-C_4)alkyl groups,
. (C_1-C_4) alkoxy groups,
. (C_1-C_4) thioalkoxy groups,
. trifluoromethyl group,
. trifluoromethoxy group,
. pentafluorosulfanyl group
. acetamide group,
. –$OC(O)C_6H_5$,
. formyl group
. –COOH,

. –COOR with R representing a (C_1-C_4)alkyl group,

. –CH_2OH

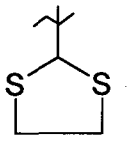
. –CH_2OR' with R'representing a (C_1-C_4)alkyl group, -CH_2OCH_3 or a protecting group forming an acetal,

. –NH_2,

. –NR_2 with R representing a (C_1-C_4)alkyl group,

. –NO_2,

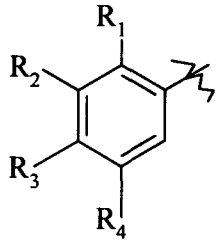
. –CN, and



.

and the pharmaceutically acceptable salts and derivatives thereof for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In an advantageous embodiment the invention relates to compounds of formula (I) wherein B is a group of formula

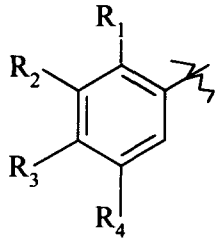


wherein

R_3 represents a hydrogen atom, a halogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group and R_1, R_2 and R_4 represent each a hydrogen atom

for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In still another advantageous embodiment, the invention relates to compounds of formula (I) wherein B is a group of formula

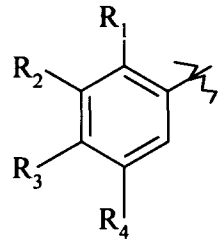


wherein

R_1 represents a hydrogen atom, a halogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group and R_2, R_3 and R_4 represent each a hydrogen atom,

for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In yet another advantageous embodiment, the invention relates to compounds of formula (I) wherein B is a group of formula

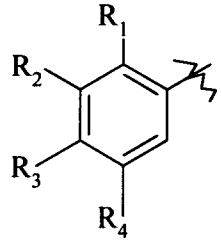


wherein

R_1 represents a halogen atom or a methyl group, R_3 represents an acetamide group and R_2 and R_4 represent each a hydrogen atom

for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In yet another advantageous embodiment, the invention relates to compounds of formula (I) wherein B is a group of formula

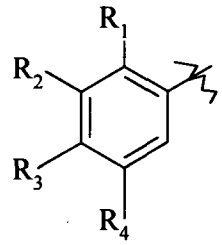


wherein

R_3 represents a hydroxy group and R_4 represents a halogen atom, a (C_1-C_4) alkoxy group, a (C_1-C_4) thioalkoxy group, a trifluoromethyl group, a trifluoromethoxy group or a pentafluorosulfanyl group

for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In another more advantageous embodiment, the invention relates to compounds of formula (I) wherein B is a group of formula

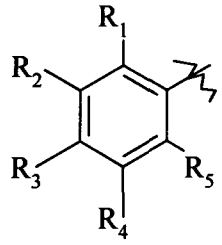


wherein

R_1 represents a hydroxy group, a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom, a (C_1-C_4)alkyl group, a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group and R_4 represents a methoxy group

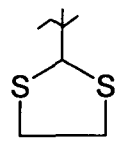
for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In still another advantageous embodiment, the invention relates to compounds of formula (I) wherein B is a group of formula



wherein

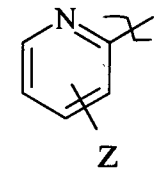
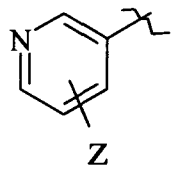
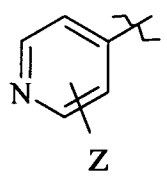
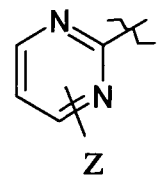
R_1 represents a hydrogen atom, a-COOH group, a COOR group with R representing a (C_1-C_4)alkyl group, a -CH_2OH group, -$CH_2OCH_2OCH_3$,group or -CH_2OTHP group, R_2 represents a hydrogen atom, a methyl group or a –NO_2 group, R_3 represents a hydrogen atom, a halogen atom, a –NH_2 group, a –$OC(O)C_6H_5$ group, a CN group, trifluoromethyl group, trifluoromethoxy group or a



group, R_4 represents a hydrogen atom, a-COOH group, a COOR group with R representing a (C_1-C_4)alkyl group, a -CH_2OH group, -$CH_2OCH_2OCH_3$,group or -CH_2OTHP group and R_5 represents a hydrogen atom, a methyl group or a –NH_2 group,

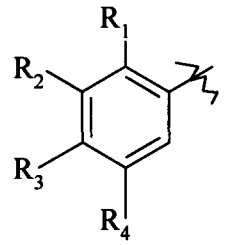
for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In another embodiment the invention relates to compounds of formula (I) wherein B is selected from the group compiring:

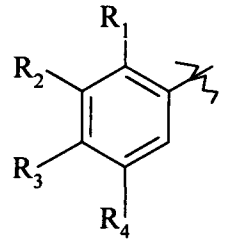
wherein Z represents a hydrogen atom, a fluorine atom or a trifluoromethyl group,
for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In still another advantageous embodiment of the invention, the invention relates to compounds of formula (I) wherein D is a group of formula



wherein
R_3 represents a hydrogen atom, a methyl group, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, and R_1, R_2 and R_4 represent each a hydrogen atom,
for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

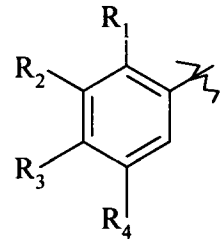
In still another advantageous embodiment, the invention relates to compounds of formula (I) wherein D is a group of formula



wherein

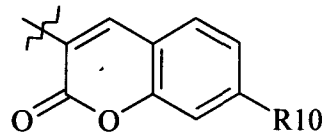
R_1 represents a hydrogen atom, a methyl group, a trifluromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, and R_2, R_3 and R_4 represent each a hydrogen atom,
for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

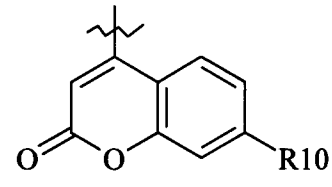
In yet another advantageous embodiment, the invention relates to compounds of formula (I) wherein D is a group of formula

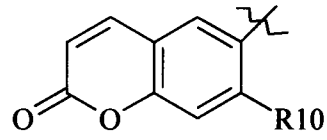


wherein
R_3 represents a hydroxy group, R_4 represents a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group and R_1 and R_2 represent each a hydrogen atom
for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In another advantageous embodiment the invention relates to compounds of formula (I) wherein D is selected from the group comprising:

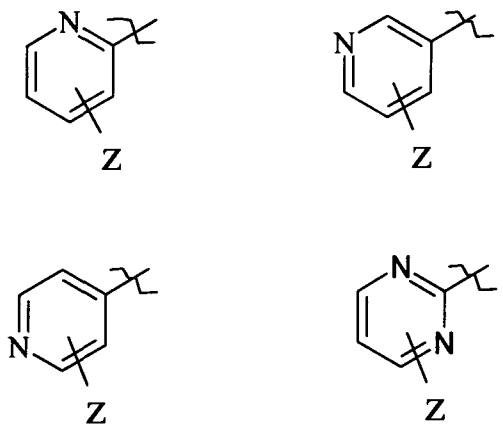






wherein R10 is selected from the group comprising an hydrogen atom, a hydroxyl group and a (C_1-C_4) alkoxy group,
for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In still another embodiment the invention relates to compounds of formula (I) wherein D is selected from the group comprsing:



wherein Z represents a hydrogen atom, a fluorine atom or a trifluoromethyl group,

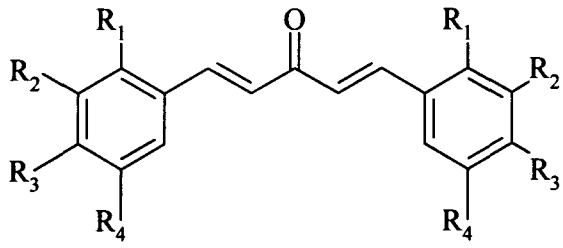
for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

In an advantageous embodiment, the invention relates to compounds of formula (I) wherein B and D are identical

for their use for prophylaxis or treatment of trypanosomiasis and leishmaniasis.

Some compounds of formula (I) are new and are also part of the invention.

Consequently, the invention still relates to compounds of formula (Ia1)

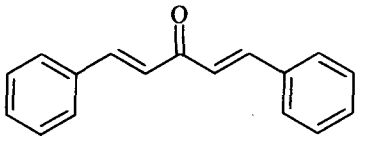
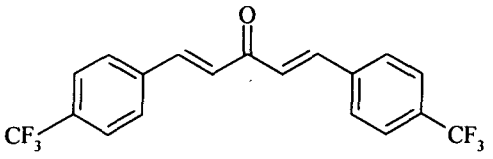


(Ia1)

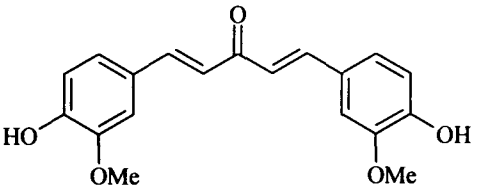
wherein

R_1, R_2, R_3, and R_4 each independently of the other represent either a (C_1-C_4) thioalkoxy group, a trifluoromethoxy group, a pentafluorosulfanyl group, or a -$NHCOCH_3$ group and and the pharmaceutically acceptable salts and derivatives thereof.

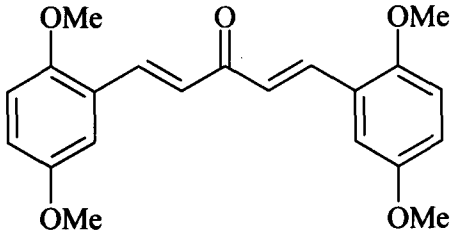
In an advantageous embodiment the invention relates to compounds of formula (Ia1) wherein one of R_1 and R_3 represents independently of the other a hydrogen atom, a halogen, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group and R_2 and R_4 represent each a hydrogen atom with the proviso that the following compounds are excluded

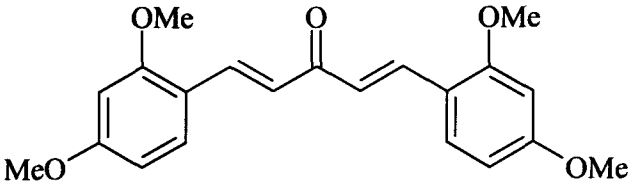



In an other advantageous embodiment the invention relates to compounds of formula (Ia1) wherein R_3 represents a hydroxy group and R_4 represents a halogen atom, a (C_1-C_4) alkoxy group, a (C_1-C_4) thioalkoxy group, a trifluoromethyl group, a trifluoromethoxy group or a pentafluorosulfanyl group with the proviso that the following compound is excluded

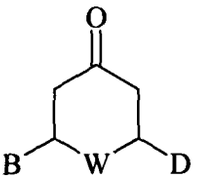


In yet another advantageous embodiment the invention relates to compounds of formula (Ia1) wherein R_1 represents a hydroxy group, a (C_1-C_4) alkoxy group, or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom a (C_1-C_4) alkyle group, a (C_1-C_4) alkoxy group, or a (C_1-C_4) thioalkoxy group and R_4 represents a methoxy group with the proviso that the following compounds are excluded





The invention also relates to compounds corresponding to formula (Ia2)



(Ia2)

wherein

W represents N-(C_1–C_4)alkyl, N-C(O)-(C_1-C_5)alkylamine or $S(O)_p$ with p = 0 to 2,

- B and D each independently of each other represent an aryl group or a heteroaryl group optionally substituted by one to 4 substituents selected from the group comprising

. hydrogen atom,

. halogen atoms,

. hydroxy group,

. linear or branched (C_1-C_4)alkyl groups,

. (C_1-C_4) alkoxy groups,

. (C_1-C_4) thioalkoxy groups,

. trifluoromethyl group,

. trifluoromethoxy group,

. pentafluorosulfanyl group

. acetamide group,

. –$OC(O)C_6H_5$,

. formyl group

. –COOH,

. – COOR with R representing a (C_1-C_4)alkyl group,

. –CH_2OH

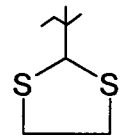
. –CH_2OR' with R'representing a (C_1-C_4)alkyl group, -CH_2OCH_3 or a protecting group forming an acetal,

. –NH_2

. –NR_2 with R representing a (C_1-C_4)alkyl group,

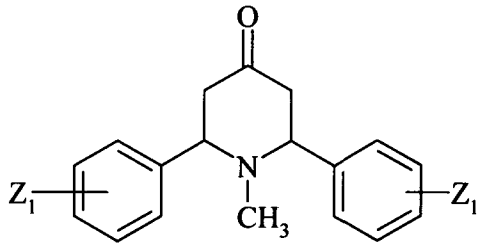
. –NO_2,

. –CN, and



and the pharmaceutically acceptable salts and derivatives thereof

- with the proviso that the following compounds are excluded:



with Z_1 = H, Cl, F, CF_3, OH

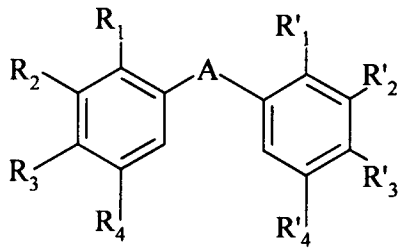
- with the proviso that when W is NCH_3 then B and D cannot be both a phenyl group substituted by methoxy groups or by a methyl group, nor a naphtyl group,

- with the proviso that when W is SO_2 then B and D cannot be both a phenyl group, B and D cannot be both a 3-O_2N-phenyl group, and if B is a phenyl group then D cannot be a phenyl group substituted in para by a linear or branched (C_1-C_{25})alkyl group,

- with the proviso that when W is S if B is a phenyl group then D cannot be a phenyl group substituted in para by a linear or branched (C_1-C_{25})alkyl group, B and D cannot be both or a pyridinyl group, B and D cannot be both a phenyl group or a phenyl group substituted in para by an halogen atom, and if one of B and D is a phenyl group, then the other cannot be a phenyl group susbtituted by one or two halogen atoms,

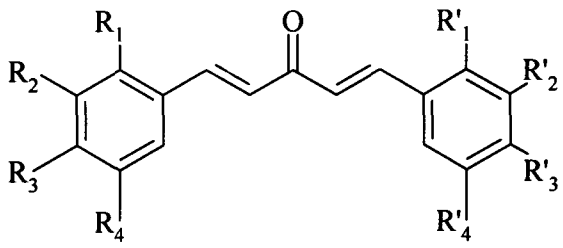
- with the proviso that when W is SO then B and D cannot be both a phenyl group .

The invention also relates to compounds responding to formula (Ib)



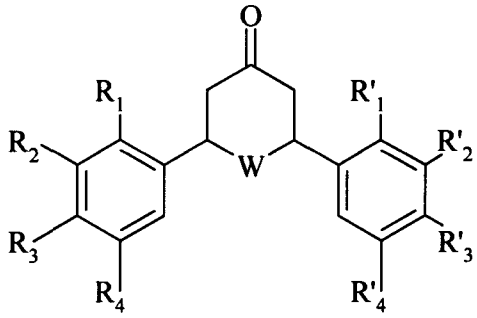
(Ib)

namely compounds of formula (Ib1)



(Ib1)

or of formula (Ib2)



(Ib2)

with W represents N-(C_1–C_4)alkyl, N-C(O)-(C_1-C_5)alkylamine or $S(O)_p$ with p = 0 to 2, and wherein in said formula (Ib), (Ib1) and (Ib2) R_1, R_2, R_3 and R_4 are always respectively different from R'_1, R'_2, R'_3 and R'_4 , and

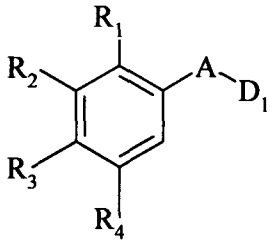
- if R_3 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group, R_1, R_2 and R_4 represent each a hydrogen atom, then R'_3 represents a hydrogen atom, a methyl group, a pentafluorosulfanyl group, a dimethylamino group (-$N(CH_3)_2$) or a trifluoromethoxy group and R'_1, R'_2 and R'_4 represent each a hydrogen atom, or
- if R_3 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group, R_1, R_2 and R_4 represent each a hydrogen atom, then R'_1 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_2, R'_3, and R'_4 represent each a hydrogen atom, or
- if R_3 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group, R_1, R_2 and

R_4 represent each a hydrogen atom, then R'_3 represents a hydroxy group, R'_4 represents a $(C_1\text{-}C_4)$ alkoxy group or a $(C_1\text{-}C_4)$ thioalkoxy group and R'_1 and R'_2 represent each a hydrogen atom,

- if R_1 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a $-NHCOCH_3$ group, R_2, R_3 and R_4 represent each a hydrogen atom, then R'_3 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_1, R'_2 and R'_4 represent each a hydrogen atom, or
- if R_1 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a $-NHCOCH_3$ group, R_2, R_3 and R_4 represent each a hydrogen atom, then R'_1 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_2, R'_3, and R'_4 represent each a hydrogen atom, or
- if R_1 represents either a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a $-NHCOCH_3$ group, R_1, R_2 and R_4 represent each a hydrogen atom, then R'_3 represents a hydroxy group, R'_4 represents a $(C_1\text{-}C_4)$ alkoxy group or a $(C_1\text{-}C_4)$ thioalkoxy group and R'_1 and R'_2 represent each a hydrogen atom,
- if R_3 represents a hydroxy group, R_4 represents a halogen atom, a $(C_1\text{-}C_4)$ alkoxy group, a $(C_1\text{-}C_4)$ thioalkoxy group, a trifluoromethyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R_1 et R_2 represent each a hydrogen atom, then R'_3 represents a hydrogen atom, a methyl group or a trifluoromethoxy group or a pentafluorosulfanyl group and R'_1, R'_2 and R'_4 represent each a hydrogen atom,
- if R_3 represents a hydroxy group, R_4 represents a halogen atom, a $(C_1\text{-}C_4)$ alkoxy group, a $(C_1\text{-}C_4)$ thioalkoxy group, a trifluoromethyl group or a trifluoromethoxy group or a pentafluorosulfanyl group and R_1 and R_2 represent each a hydrogen atom, then R'_1 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_2, R'_3, and R'_4 represent each a hydrogen atom, or
- if R_3 represents a hydroxy group, R_4 represents a halogen atom, a $(C_1\text{-}C_4)$ alkoxy group, a $(C_1\text{-}C_4)$ thioalkoxy group, a trifluoromethyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R_1 and R_2 represent each a hydrogen atom, then R'_3 represents a hydroxy group, R'_4 represents a $(C_1\text{-}C_4)$ alkoxy group or a $(C_1\text{-}C_4)$ thioalkoxy group and R'_1 and R'_2 represent each a hydrogen atom,

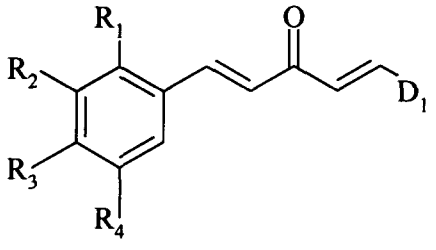
- if R_1 represents a hydroxy group or a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom and R_4 represents a methoxy group, then R'_3 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_1, R'_2 and R'_4 represent each a hydrogen atom, or
- if R_1 represents a hydroxy group, a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom and R_4 represents a methoxy group, then R'_1 represents a hydrogen atom, a methyl group, a trifluoromethoxy group or a pentafluorosulfanyl group and R'_2, R'_3, and R'_4 represent each a hydrogen atom, or
- if R_1 represents a hydroxy group, a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom and R_4 represents a methoxy group, then R'_3 represents a hydroxy group, R'_4 represents a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group and R'_1 and R'_2 represent each a hydrogen atom.

The invention also relates to compounds responding to formula (Ic)



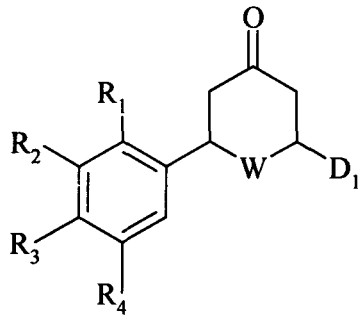
(Ic)

namely compounds of formula (Ic1)



(Ic1)

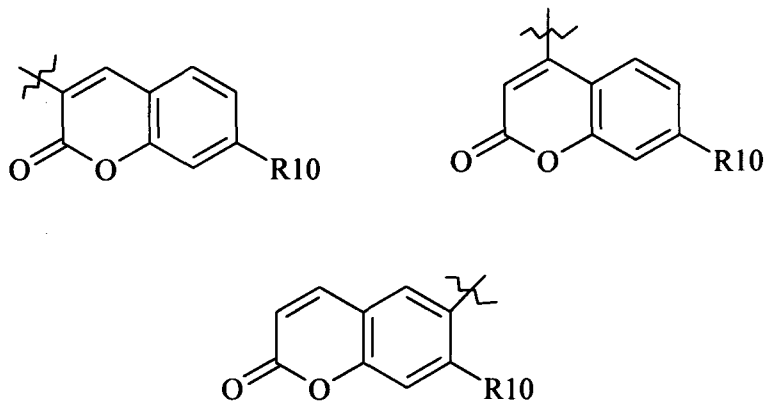
or of formula (Ic2)



(Ic2)

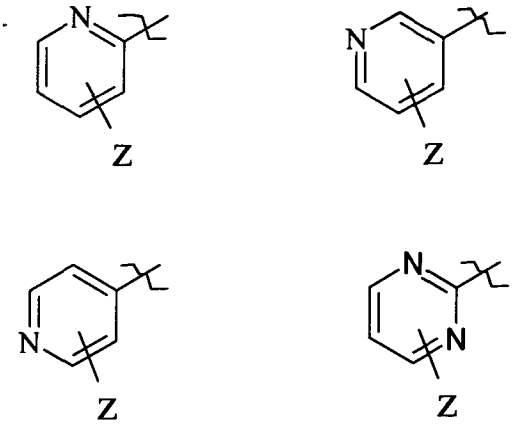
with W represents N-(C_1–C_4)alkyl, N-C(O)-(C_1-C_5)alkylamine or $S(O)_p$ with p = 0 to 2 and wherein in said formula (Ic), (Ic1) and (Ic2) D_1 is selected from groups A) or B), namely:

A)



wherein R10 is selected from the group comprising an hydrogen atom, a hydroxyl group and a (C_1-C_4) alkoxy group.

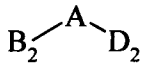
B)



wherein Z represents a hydrogen atom, a fluorine atom or a trifluoromethyl group, and

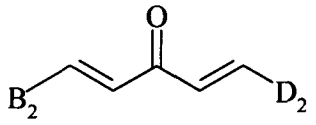
- either R_3 represents a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group and R_1, R_2 and R_4 represent each a hydrogen atom, or
- either R_1 represents a hydrogen atom, a trifluoromethyl group, a trifluoromethoxy group, a pentafluorosulfanyl group, a cyano group or a -$NHCOCH_3$ group and R_2, R_3 and R_4 represent each a hydrogen atom,
- either R_3 represents a hydroxy group, R_4 represents a halogen atom, a (C_1-C_4) alkoxy group, a (C_1-C_4) thioalkoxy, a trifluoromethyl group or a trifluoromethoxy group or a pentafluorosulfanyl group and R_1 and R_2 represent each a hydrogen atom, or
- either R_1 represents an hydroxy group or a (C_1-C_4) alkoxy group or a (C_1-C_4) thioalkoxy group, R_2 represents a hydrogen atom or a halogen atom, R_3 represents a hydrogen atom and R_4 represents a methoxy group.

The invention also relates to compounds responding to formula (Id)



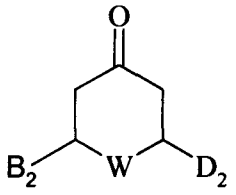
(Id)

namely compounds of formula (Id1)



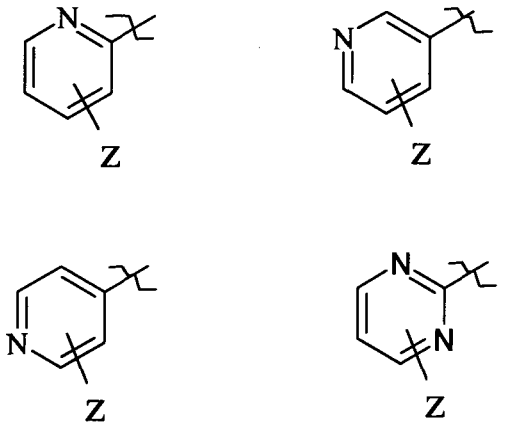
(Id1)

or of formula (Id2)



(Id2)

with W represents N-(C_1–C_4)alkyl, N-C(O)-(C_1-C_5)alkylamine or $S(O)_p$ with p = 0 to 2 and wherein in said formula (Id), (Id1) and (Id2), B_2 and D_2 are selected independently from each other from the group comprising:



with the proviso that when W is S then B_2 and D_2 cannot be both a pyridinyle group.

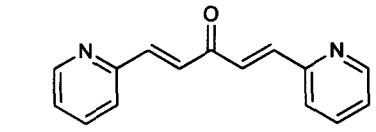
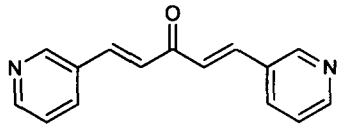
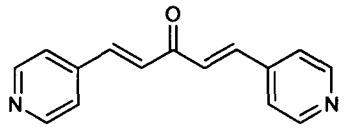
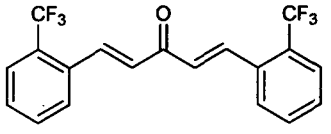
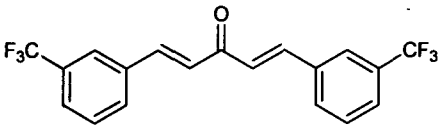
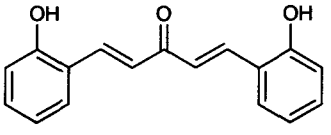
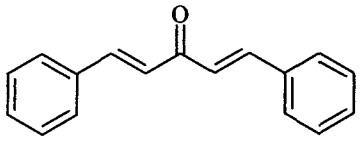
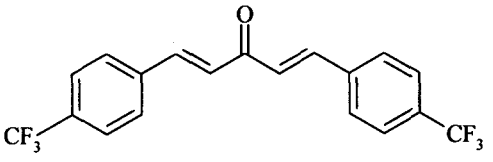
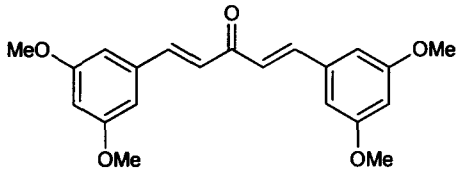
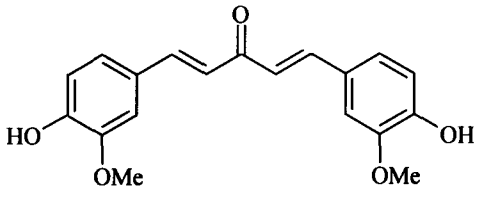
The compounds of formula (Ia2), (Ib2), (Ic2) and (Id2) are respectively prodrugs of compounds of formula (Ia1), (Ib1), (Ic1) and (Id1) i.e. although they are not active *per se in vitro*, after administration to a patient or to cells, compounds of formula (Ia2), (Ib2), (Ic2) and (Id2) are respectively metabolised *in vivo* into the corresponding compounds of formula (Ia1), (Ib1), (Ic1) and (Id1).

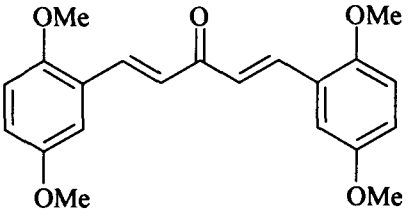
The symmetrical dibenzylidene acetones of formula (Ia) used according to the invention may be prepared by any methods known from the one skilled in the art, in particular

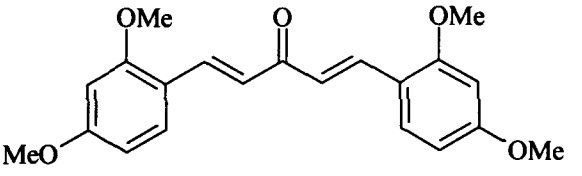
through classical base-catalyzed Claisen-Schmidt reaction. They may be prepared for instance as disclosed in the examples.

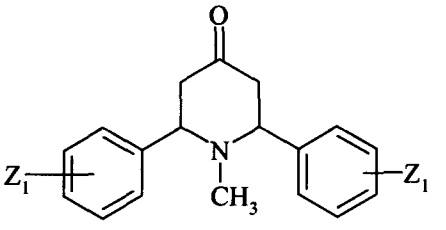
The symmetrical and asymmetrical 2,6-diaryl-4-piperidones and 2,6-diheteroaryl-4-piperidones of the most potent dibenzylidene acetones were prepared *via* (i) a Horner-Wadsworth-Emmons reaction followed by a Claisen-Schmidt reaction, or Claisen-Schmidt reactions under various reaction conditions depending on the substitution pattern of the aromatic ring of the starting aldehydes, and then (ii) the Michael addition with methylamine. They may be prepared for instance as disclosed in the examples.

The invention relates to compounds (Ia1), (Ia2), (Ib), (Ib1), (Ib2), (Ic), (Ic1), (Ic2), (Id), (Id1), and (Id2), as defined above, as drug, with the proviso that the following compounds are excluded:

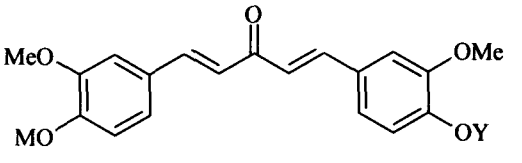













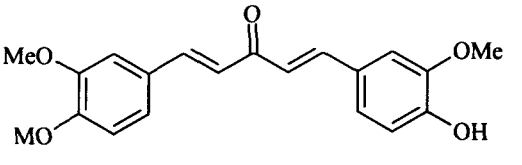




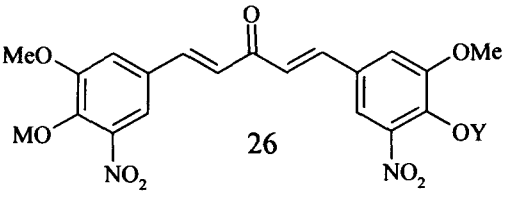
with Z_1 = H, Cl, F, CF_3, OH

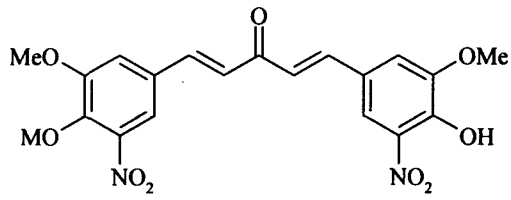


with M = Na or K and Y = Na or K

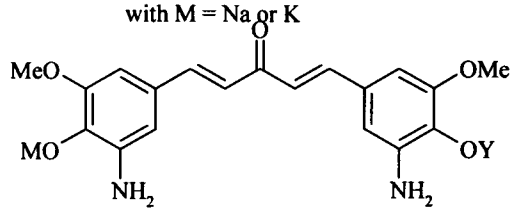


with M = Na or K

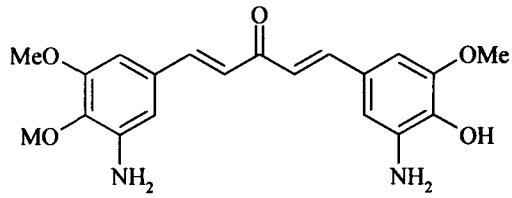




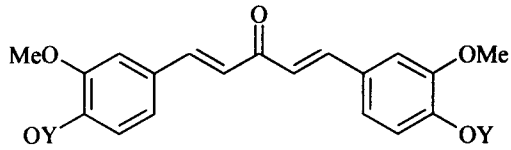
with M = Na or K



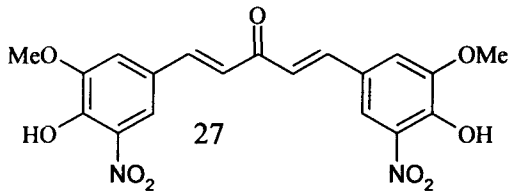
with M = Na or K or Y=Na

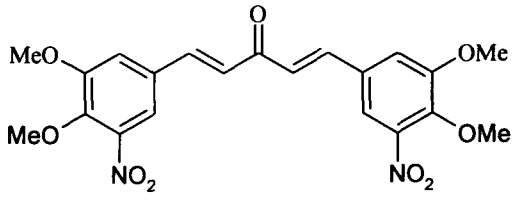


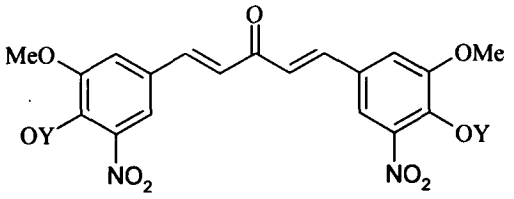
with M = Na or K



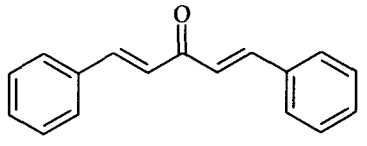
with Y = COC_6H_5

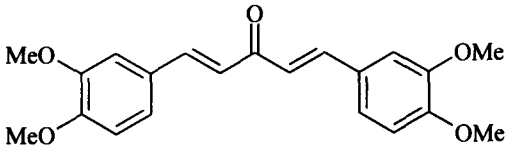


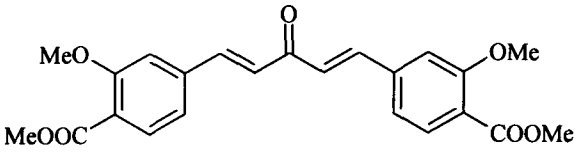


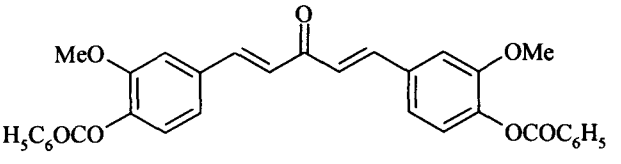


with Y = COC_6H_5

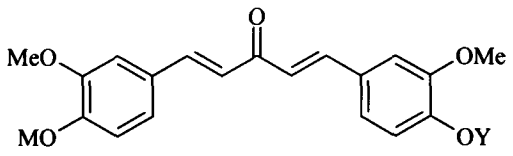




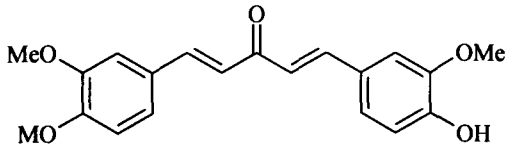




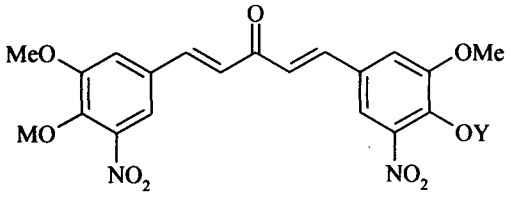
The invention relates to compounds (Ia1), (Ia2), (Ib), (Ib1), (Ib2), (Ic), (Ic1), (Ic2), (Id), (Id1), and (Id2), as defined above, for their specific use for the therapy or the prophylaxis as antikinetoplastid agents, with the proviso that the following compounds are excluded:



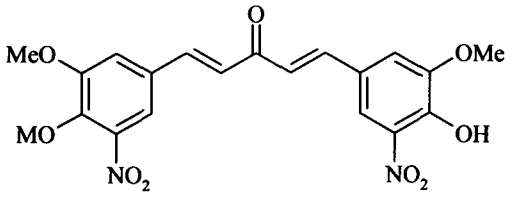
with M = Na or K and Y = Na or K



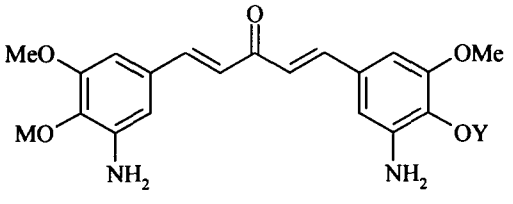
with M = Na or K



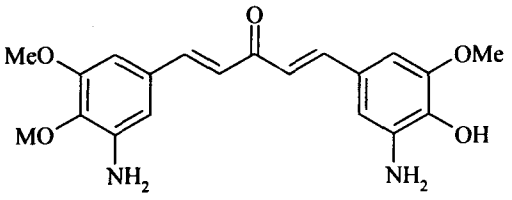
with M = Na or K and Y= Na

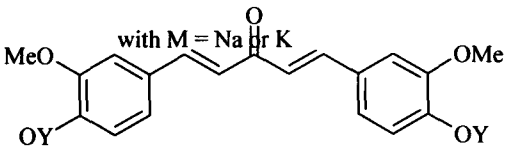


with M = Na or K

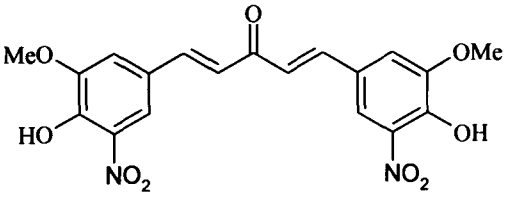


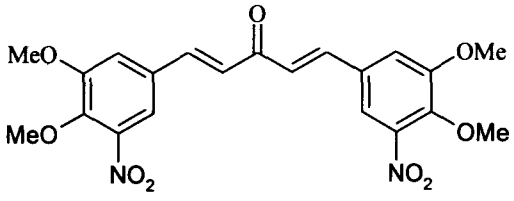
with M = Na or K or Y=Na

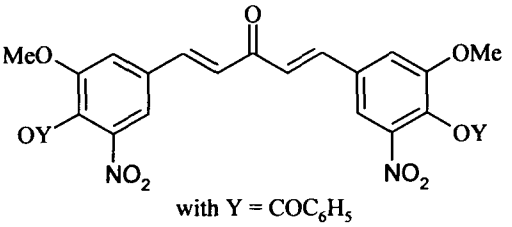




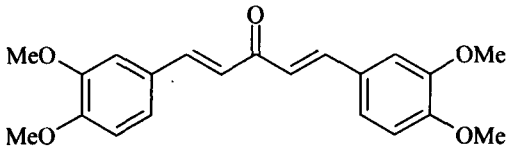
with Y = COC_6H_5

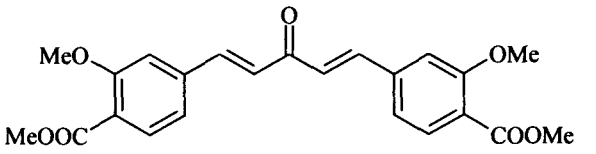


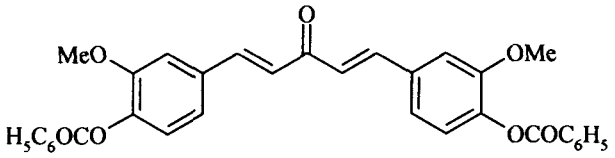




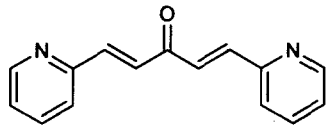
with Y = COC_6H_5

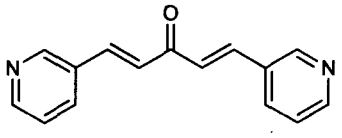


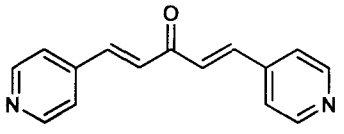


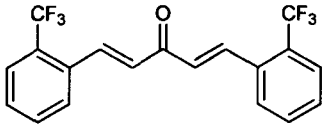


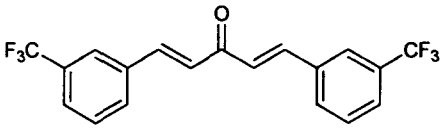
The invention also relates to pharmaceutical compositions comprising as active ingredient one or more of the compounds of formulas (Ia1), (Ia2), (Ib), (Ib1), (Ib2), (Ic), (Ic1), (Ic2), (Id), (Id1), and (Id2) as defined above, in combination with excipients and/or pharmaceutically acceptable diluents or carriers with the proviso that compounds of formula

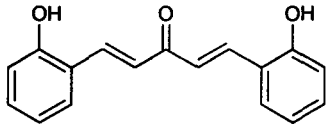


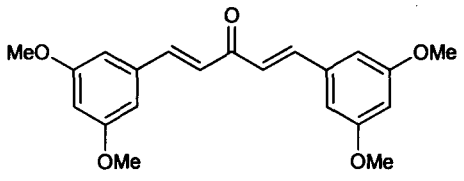


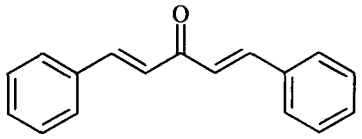


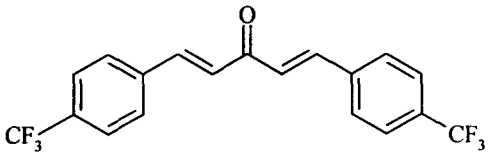


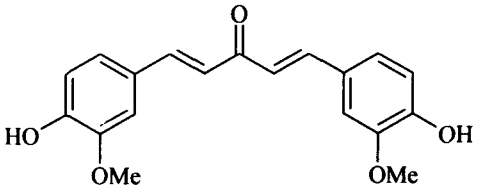


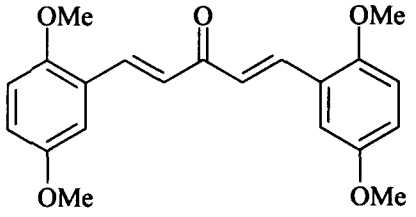


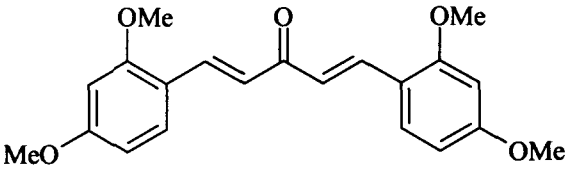


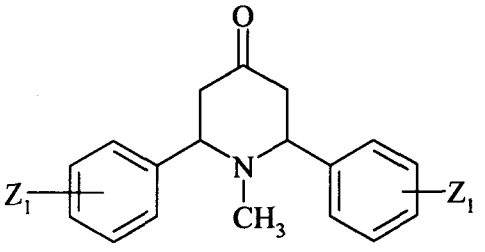




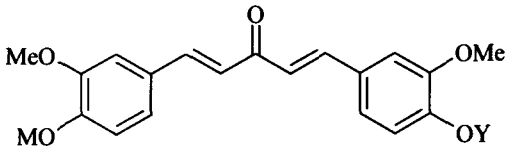




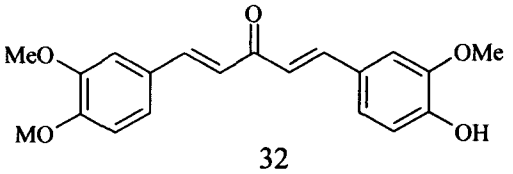




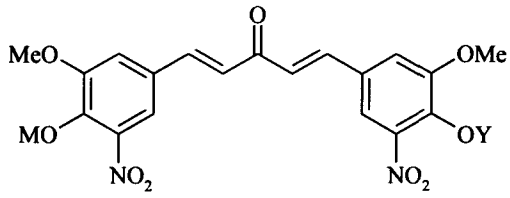
with Z_1 = H, Cl, F, CF_3, OH



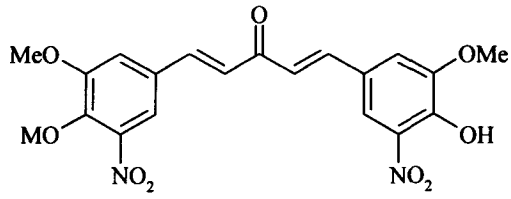
with M = Na or K and Y = Na or K



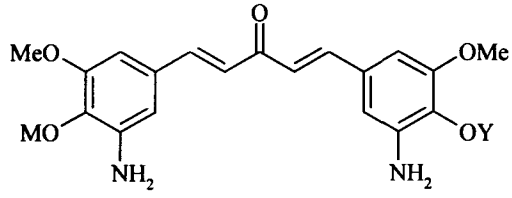
with M = Na or K



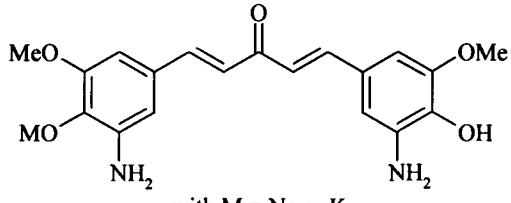
with M = Na or K and Y= Na



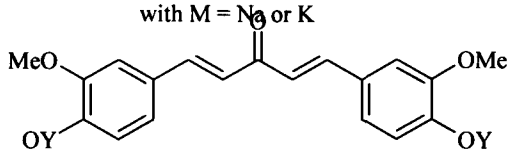
with M = Na or K



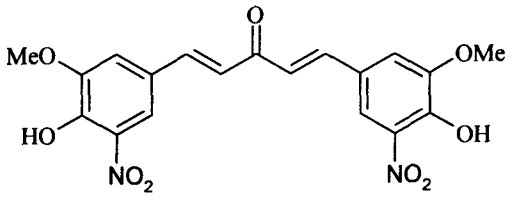
with M = Na or K or Y=Na

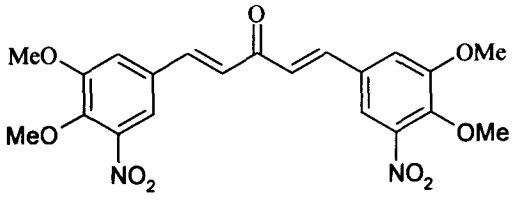


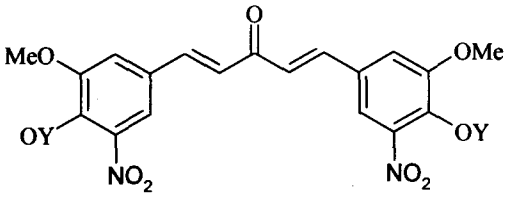
with M = Na or K



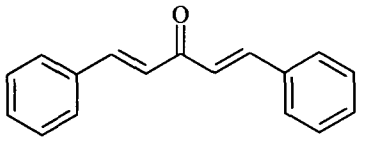
with Y = COC H

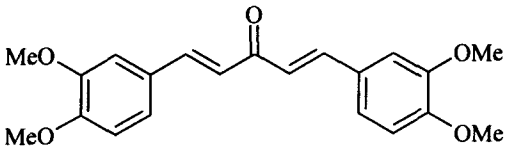


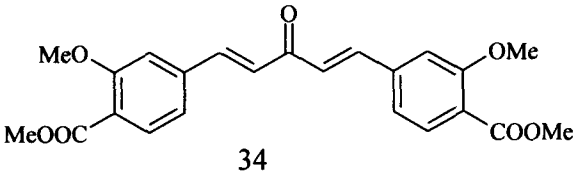


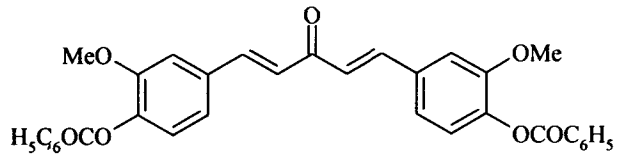


with Y = COC_6H_5









are excluded when they are the only active ingredient in the composition.

According to the invention, the compounds of formula (I) may be used in association with one to three other antikinetoplastidal agents for a simultaneous, separated or sequential administration. Thus the pharmaceutical compositions according to the invention may further comprise as active ingredient one to three other antikinetoplastidal agents selected from the group comprising melarsoprol, eflornithine, pentamidine, suramin, miltefosine, amphotericin B, nifurtimox, benznidazole, pafuramidine, meglumine antimoniate, sodium stibogluconate, paromomycin, diminazene, allopurinol, aminosidine, sitamaquine, fungicidal azoles used as sterol biosynthesis inhibitors, inhibitors of S-adenosylmethionine decarboxylase as 5'-deoxy-5'-(hydroxyethyl)thioadenosine (HETA) type, plumbagin for a simultaneous, separated or sequential administration.

The invention also relates to a method of treating infection caused by a kinetoplastidae parasite, comprising administering to a mammal in need thereof an effective amount of at least one compound selected from the group comprising the compounds having one the formula (I), (Ia1), (Ia2), (Ib) (Ib1), (Ib2), I(c), (Ic1), (Ic2), (Id), (Id1) or (Id2).

The invention further relates to the use of at least one compound selected from the group comprising the compounds having one the formula (I) (Ia1), (Ia2), (Ib) (Ib1), (Ib2), I(c), (Ic1), (Ic2), (Id), (Id1) or (Id2) for the preparation of a drug useful as antikinetoplastidal agent.

The following examples 1 to 9 and tables 1 to 7 illustrate the invention. In all tables (1-7), the results are expressed as IC_{50} values in μM. Toxicity is also indicated if present.

The biological activities against the parasites of:

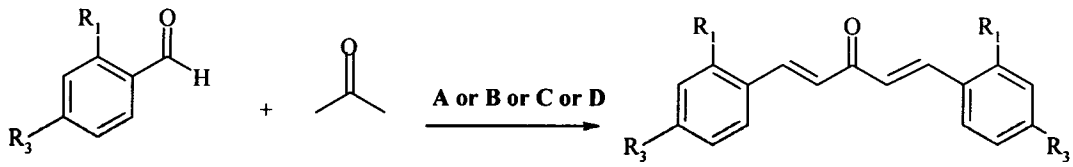
- the symmetrical dibenzylidene acetone intermediates, according to example 1, needed for preparing the 4-piperidones are shown in Tables 1 to 2, and Tables 4 to 5

- the asymmetrical dibenzylidene acetone intermediates, according to example 3, are shown in Table 3,
- the symmetrical conjugated symmetrical dibenzylidene acetone is given in Table 2,
- the diheteroarylidene acetone intermediates, according to example 2, needed for preparing the 4-piperidones and 4-thiopyranones (and *S*-oxidized metabolites) are shown in Table 4,
- the symmetrical 2,6-diheteroaryl-4-piperidones and 2,6-diaryl-4-piperidones, according to example 5, are shown in Tables 5 and 6,
- the symmetrical 2,6-diheteroaryl-4-thiopyranones and 2,6-diaryl-4-thiopyranones, according to example 6, are shown in Tables 5 and 7, respectively, along with some selected parent dibenzylidene acetone intermediates, in repeated bioassays, in comparison with known reference drugs from the market, are shown in Tables 6 and 7.

EXAMPLE 1: Symmetrical dibenzylidene acetones

The symmetrical dibenzylidene acetones were prepared *via* a classical base-catalyzed Claisen-Schmidt reaction with 2 equivalents of the aldehyde and 1 equivalent of acetone; the reaction was performed in an organic solvent like ethanol in presence of a base like NaOH or K_2CO_3 depending on the substituents at the aromatic ring of the starting aldehyde as illustrated in Scheme 1.

Scheme 1: Synthesis of symmetrical dibenzylidene acetones.



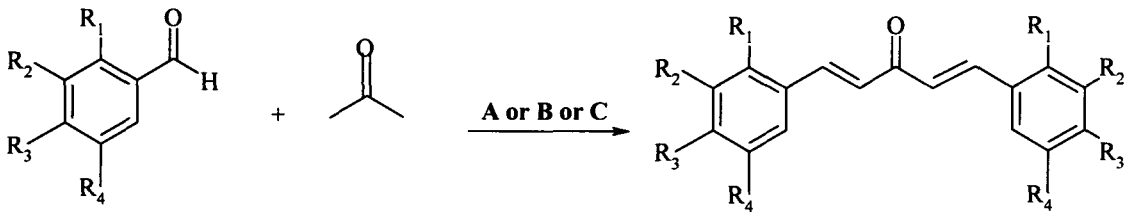
2 equivalents 1 equivalent

A	NW247 R_1= H, R_2 = OMe NW270 R_1= H, R_2 = acetamide NW275 R_1= H, R_2 = H
B	NW267 R_1= H, R_2 = CF_3
C	NW268 R_1= Cl, R_2 = H
D	NW254 R_1= H, R_2 = OCF_3

Reagents and conditions: (**A**) NaOH (2N), EtOH, 4 h, RT; (**B**) K_2CO_3, aq. EtOH (45 %), 24 h, RT; (**C**) 4 equiv. aq. NaOH, EtOH; (**D**) cat. aq. NaOH (10 %), EtOH, 1 h, RT.

Some symmetrical dibenzylidene acetones were prepared *via* a classical base-catalyzed Claisen-Schmidt reaction with 2 equivalents of the aldehyde and 1 equivalent of acetone; the reaction was performed in an organic solvent like ethanol in presence of NaOH, or in triethylamine in presence of lithium perchlorate or in acidic medium or K_2CO_3 depending on the substituents at the aromatic ring of the starting aldehyde as illustrated in Scheme 2.

Scheme 2. Synthesis of symmetrical dibenzylidene acetones.



2 equivalents 1 equivalent

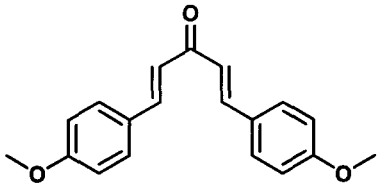
A
NW307.2 $R_1 = R_2 = R_4 = H$, $R_3 = CN$
NW308 $R_1 = R_2 = R_4 = H$, $R_3 = Cl$

B
NW300 $R_1 = R_4 = H$, $R_2 = OMe$, $R_3 = OH$
NW310.1 $R_1 = R_4 = H$, $R_2 = CF_3$, $R_3 = OH$
NW317 $R_1 = R_4 = H$, $R_2 = OCF_3$, $R_3 = OH$

C
NW324.2 $R_1 = R_4 = OMe$, $R_2 = Br$, $R_3 = H$
NW326.4 $R_1 = OH$, $R_2 = Br$, $R_3 = H$, $R_4 = OMe$
NW327.2 $R_1 = OH$, $R_2 = R_3 = H$, $R_4 = OMe$
NW333.1 $R_1 = R_4 = OMe$, $R_2 = R_3 = H$

The detailed synthesis of the said compounds is disclosed hereunder.

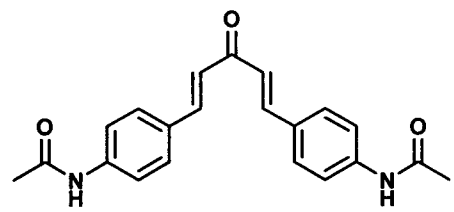
(1*E*,4*E*)-1,5-Bis(4-methoxy-phenyl)-penta-1,4-dien-3-one (NW247)



To a solution of NaOH (3.6 g, 92 mmol) in H_2O (36 mL) and EtOH (29 mL) were added 4-methoxybenzaldehyde (4.5 mL, 37 mmol) and acetone (1.3 mL, 18 mmol). The reaction mixture was stirred for 1 h at ambient temperature and the colorless solution turned into a yellow suspension. The precipitate was filtered, washed with Et_2O, recrystallized from EtOAc and dried *in vacuo* to obtain **NW247** as a pale yellow solid (4.3 g, 82 %). mp: 127-128 °C. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.68 (d, ^3J= 15.9 Hz, 2H, H_{vin}), 7.54 (d, ^3J= 8.8 Hz, 4H, H_{Ar}), 6.93 (d, ^3J= 15.9 Hz, 2H, H_{vin}), 6.91 (d, ^3J= 8.8 Hz, 4H, H_{Ar}), 3.82 (s, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.8 (C), 161.5 (C), 142.6 (CH), 130.0 (CH), 127.6 (C),

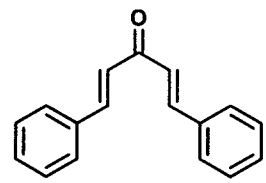
123.5 (CH), 114.4 (CH), 55.4 (CH_3). MS (FAB) *m/z*: 295.2 (M+). Anal. calcd for $C_{19}H_{18}O_3$: C 77.53, H 6.16, found: C 77.45, H 6.18%.

N-{4-[(1*E*,4*E*)-5-(4-Acetylamino-phenyl)-3-oxo-penta-1,4-dienyl]-phenyl}-acetamide (NW270)



A mixture of *p*-acetamidobenzaldehyde (8.15 g, 50 mmol) dissolved in 200 mL of hot EtOH) and acetone (1.8 mL, 25 mmol) was added dropwise to a solution of aq. NaOH solution (2 N, 25 mL) in EtOH (150 mL). The reaction mixture was stirred for 4 h at ambient temperature and the resulting orange precipitate was filtered, washed with water and dried *in vacuo* to afford **NW270** as a bright yellow solid (4.6 g, 53 %). mp: 253-255 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm): 10.18 (s, 2H, NH), 7.81-7.58 (m, 10H, H_{Ar}, H_{vin}), 7.22 (d, ^3J= 16.0 Hz, 2H, H_{vin}), 2.08 (s, 6H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 188.2 (C), 168.6 (C), 142.1 (CH), 141.4 (C), 129.4 (CH), 124.1 (CH), 118.9 (CH), 24.1 (CH_3). MS (EI) *m/z*: 348.2 (M+). Anal. calcd for $C_{21}H_{20}N_2O_3$: C 72.40, H 5.79, N 8.04, found: C 72.14, H 5.78, N 7.97%.

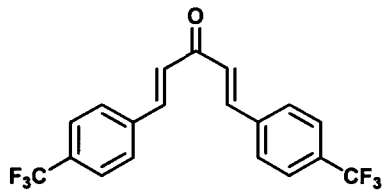
(1*E*,4*E*)-1,5-Diphenyl-penta-1,4-dien-3-one (NW275)



A solution of aq. NaOH solution (2 N, 125 mL) in EtOH (250 mL) was added to a mixture of benzaldehyde (26.5 g, 25 mmol) in acetone (9.2 mL, 13 mmol). The reaction mixture was stirred for 4 h at ambient temperature and the resulting yellow precipitate was filtered, washed with H_2O, recrystallized from EtOAc and dried *in vacuo* to obtain **NW275** as a yellow solid (23.1 g, 79 %). mp: 106-107 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.78 (d, ^3J= 16.0 Hz,

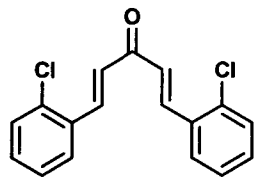
2H, H_{vin}), 7.66-7.64 (m, 4H, H_{Ar}), 7.46-7.44 (m, 6H, H_{Ar}), 7.12 (d, ^3J= 16.0 Hz, 2H, H_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 189.3 (C), 143.7 (CH), 135.2 (C), 130.9 (CH), 129.4 (CH), 128.8 (CH), 125.8 (CH). MS (EI) *m/z*: 234.2 (M+). Anal. calcd for $C_{17}H_{14}O$: C 87.15, H 6.02, found: C 87.03, H 6.03%.

(1*E*,4*E*)-1,5-Bis(4-trifluoromethyl-phenyl)-penta-1,4-dien-3-one (NW267)



A mixture of α,α,α-trifluoro-*p*-tolualdehyde (3.08 mL, 23 mmol) in acetone (0.84 mL, 11 mmol) was added to a solution of K_2CO_3 (3.2 g, 23 mmol) in aq. 45 % EtOH solution (44 mL). After 10-15 min the colorless solution turned yellow. The reaction mixture was stirred for 2 h at ambient temperature and the resulting precipitate was filtered, recrystallized from EtOAc and dried *in vacuo* to obtain **NW267** as a pale yellow solid (1.87 g, 43 %). mp: 148-150 °C. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.86-7.56 (m, 10H, H_{vin}, H_{Ar}), 7.15 (d, ^3J= 16.0 Hz, 2H, H_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.1 (C), 141.9 (CH), 132.1 (q, ^2J(C,F)= 32.7 Hz, C), 128.5 (CH), 127.2 (CH), 126.0 (q, ^3J(C,F)= 3.8 Hz, CH). MS (FAB) *m/z*: 371.2 (M+). Anal. calcd for $C_{19}H_{12}F_6O$: C 61.63, H 3.27, found: C 61.49, H 3.39%.

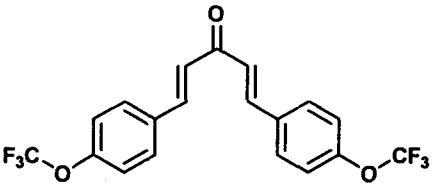
(1*E*,4*E*)-1,5-Bis(2-chloro-phenyl)-penta-1,4-dien-3-one (NW268)



A solution of NaOH (1.4g, 142 mmol) in H_2O (60 mL) and EtOH (60 mL) was added to a mixture of 2-chlorobenzaldehyde (8 mL, 72 mmol) in acetone (2.6 mL, 36 mmol). The reaction mixture was stirred for 1 d at room temperature and the resulting precipitate was filtered, washed with H_2O, recrystallized from EtOAc and dried *in vacuo* to obtain **NW268** as a bright yellow solid (7.4 g, 69 %). mp: 107-109 °C. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm):

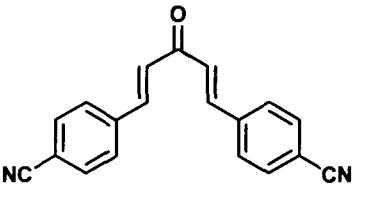
8.15 (d, ^3J= 16.0 Hz, 2H, H_{vin}), 7.79-7.66 (m, 2H, H_{Ar}), 7.51-7.29 (m, 6H, H_{Ar}), 7.08 (d, ^3J= 16.0 Hz, 2H, H_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.7 (C), 139.3 (CH), 135.4 (C), 133.0 (C), 131.2 (CH), 130.2 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH). MS (FAB) *m/z*: 303.1 (M+). Anal. calcd for $C_{17}H_{12}Cl_2O$: C 67.35, H 3.99, Cl 23.39, found: C 67.09, H 4.06, Cl 22.65%.

(1*E*,4*E*)-1,5-Bis(4-trifluoromethoxy-phenyl)-penta-1,4-dien-3-one (NW254)



A colorless solution of 4-(trifluoromethoxy)-benzaldehyde (0.75 mL, 5.3 mmol) in acetone (0.19 mL, 2.6 mmol), EtOH (5 mL) and H_2O (1 mL) was treated with aq. 10 % NaOH solution (~12 drops). The reaction mixture was stirred for 2 h at room temperature and the colorless solution turned into a yellow suspension. The precipitate was filtered, washed with H_2O and dried *in vacuo* to obtain **NW254** as a pale yellow solid (275 mg, 25 %). mp: 112-115 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.74 (d, ^3J= 16.1 Hz, 2H, H_{vin}), 7.67 (d, ^3J= 8.5 Hz, 4H, H_{Ar}), 7.28 (d, ^3J= 8.2 Hz, 4H, H_{Ar}), 7.06 (d, ^3J= 15.9 Hz, 2H, H_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.2 (C), 150.6 (C), 141.8 (CH), 133.3 (C), 129.8 (CH), 126.0 (CH), 121.2 (CH). MS (EI) *m/z*: 402.1 (M+). Anal. calcd for $C_{19}H_{12}F_6O_3$: C 56.73, H 3.01, found: C 56.44, H 3.10%.

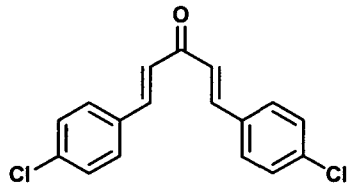
(1*E*,4*E*)-1,5-Bis(4-cyanophenyl)penta-1,4-dien-3-one (NW307.2)



A mixture of 4-formyl-benzonitrile (1.1 g, 8.4 mmol), acetone (308 µL, 4.2 mmol), $LiClO_4$ (892 mg, 8.4 mmol) and Et_3N (117 µL, 0.84 mmol) in toluene (8 mL) was stirred for 2 d at room temperature. A saturated aq. NH_4Cl-solution was added to the reaction mixture and the resulting yellow suspension was extracted with CH_2Cl_2 and the combined organic layers were

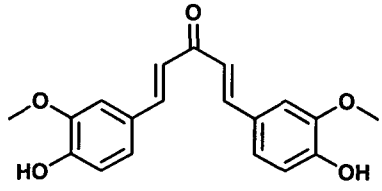
dried with $MgSO_4$, filtered and evaporated *in vacuo* to afford **NW307.2** as a yellow solid (300 mg, 25 %). mp: 137-138 °C. ^1H NMR (250 MHz, DMSO-d_6) δ (ppm): 8.00 (d, ^3J= 8.3 Hz, 4H, H_{Ar}), 7.87 (d, ^3J= 16.2 Hz , 2H, H_{vin}), 7.94 (d, ^3J= 8.4 Hz, 4H, H_{Ar}), 7.51 (d, ^3J= 16.1 Hz, 2H, H_{vin}). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 188.5 (C), 141.2 (CH), 139.2 (C), 132.8 (CH), 129.2 (CH), 128.4 (CH), 118.6 (C), 112.4 (C). MS (FAB) *m/z*: 285.19 (M+). Anal. calcd for $C_{19}H_{12}N_2O$: C 80.27, H 4.25, N 9.85, found: C 80.04, H 4.28, N 9.76%.

(1*E*,4*E*)-1,5-Bis(4-chlorophenyl)penta-1,4-dien-3-one (NW308)



A mixture of $LiClO_4$ (1.2 g, 11 mmol), acetone (418 µL, 5.7 mmol) and 4-chloro-benzaldehyde (1.6 g, 11 mmol) was treated with TEA (159 µL, 1.1 mmol) and stirred for 4 min at ambient temperature. A saturated aq. NH_4Cl solution was added to the reaction mixture and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was recrystallized from CH_2Cl_2 to obtain **NW308** as yellow crystals (586 mg, 34 %). mp: 182-184 °C. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.60 (d, ^3J= 15.9 Hz, 2H, H_{vin}), 7.46 (d, ^3J= 8.5 Hz , 4H, H_{Ar}), 7.31 (d, ^3J= 8.5 Hz, 4H, H_{Ar}), 6.95 (d, ^3J= 15.9 Hz, 2H, H_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.3 (C), 142.0 (CH), 136.5 (C), 133.2 (C), 129.51 (CH), 129.2 (CH). MS (FAB) *m/z*: 303.1 (M+). Anal. calcd for $C_{17}H_{12}Cl_2O$: C 67.35, H 3.99, Cl 23.39, found: C 67.33, H 4.01, Cl 23.17%.

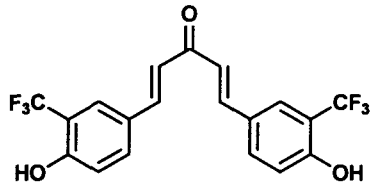
(1*E*,4*E*)-1,5-Bis(4-hydroxy-3-methoxyphenyl)penta-1,4-dien-3-one (NW300)



A mixture of vanillin (1 g, 6.6 mmol) in acetone (4.1 mL, 3.3 mmol) were dissolved in glacial acetic acid (5 ml), saturated with anhydrous HCl and heated to 25-30 °C for 2 h. The mixture

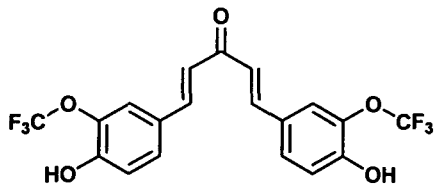
was stirred for 2 d at room temperature and treated with cold water. The resulting precipitate was filtered, washed with water, recrystallized from EtOH and dried *in vacuo* to afford **NW300** as an orange solid (954 mg, 89 %). mp: 115-117 °C. ^{1}H NMR (250 MHz, CD_3OD) δ (ppm): 7.73 (d, ^{3}J= 15.8 Hz, 2H, H_{vin}), 7.31 (d, ^{4}J= 1.9 Hz , 2H, H_{Ar}), 7.20 (dd, ^{3}J= 8.2 Hz, ^{4}J= 1.9 Hz, 2H, H_{Ar}), 7.11 (d, ^{3}J= 15.8 Hz, 2H, H_{vin}), 6.86 (d, ^{3}J= 8.2 Hz, 2H, H_{Ar}), 3.94 (s, 6H, $C\underline{H}_3$). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 191.7 (C), 151.0 (C), 149.5 (C), 145.5 (CH), 128.4 (C), 124.8 (CH), 123.8 (CH), 116.6 (CH), 112.1 (CH), 56.5 ($C\underline{H}_3$). MS (FAB) *m/z*: 327.2 (M+). Anal. calcd for $C_{19}H_{18}O_5 \cdot 0.5H_2O$: C 68.05, H 5.71, found: C 68.29, H 5.68%.

(1*E*,4*E*)-1,5-Bis(3-(trifluoromethyl)-4-hydroxyphenyl)penta-1,4-dien-3-one (NW310.1)



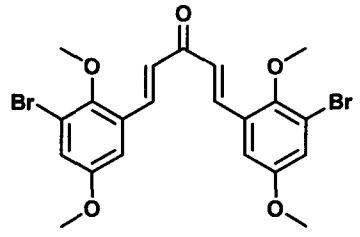
A mixture of 3-(trifluoromethyl)-4-hydroxybenzaldehyde (2.19 g, 12 mmol) in acetone (423 µL, 5.8 mmol) was dissolved in glacial acetic acid (9 mL), saturated with anhydrous HCl and heated to 25-30 °C for 2 h. The red solution was stirred for 36 h and treated with cold water. The reaction mixture turned into a dark green suspension and the resulting precipitate was filtered, washed with water and dried *in vacuo* to afford **NW310.1** as a dark green solid (740 mg, 32 %). mp: 233-234 °C. ^{1}H NMR (250 MHz, CD_3OD) δ (ppm): 7.86 (d, ^{4}J= 1.6 Hz, 2H, H_{Ar}), 7.80 (d, ^{3}J= 8.8 Hz, ^{4}J= 1.9 Hz, 2H, H_{Ar}), 7.75 (d, ^{3}J= 16.1 Hz , 2H, H_{vin}), 7.15 (d, ^{3}J= 15.9 Hz, 2H, H_{vin}), 7.02 (d, ^{3}J= 8.6 Hz, 2H, H_{Ar}).^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 191.6 (C), 159.9 (C), 144.3 (CH), 134.8 (CH), 129.3 (CH), 127.8 (C), 127.3 (C), 125.3 (CH), 118.8 (CH). MS (FAB) *m/z*: 403.2 (M+). Anal. calcd for $C_{19}H_{12}F_6O_3 \cdot 1H_2O$: C 54.17, H 3.59, found: C 54.39, H 3.31%.

(1*E*,4*E*)-1,5-Bis(4-hydroxy-3-(trifluoromethoxy)phenyl)penta-1,4-dien-3-one (NW317)



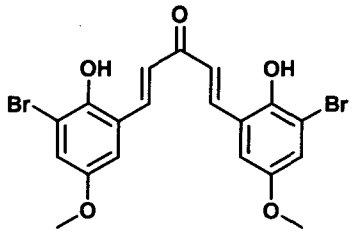
A mixture of 4-hydroxy-3-(trifluoromethoxy)benzaldehyde (600 mg, 2.9 mmol) in acetone (107 µL, 1.5 mmol) was dissolved in glacial acetic acid (8 mL), saturated with anhydrous HCl and heated to 25-30 °C for 2 h. The red solution was stirred for 36 h and treated with cold water. The red suspension turned dark green. The resulting precipitate was filtered, washed with water and dried *in vacuo* to afford **NW317** as a yellow-green solid (314 mg, 50 %). mp: 103-105 °C. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.72 (d, ^3J= 15.9 Hz, 2H, H_{vin}), 7.62 (s, 2H, H_{Ar}), 7.58 (dd, ^3J= 8.5 Hz, ^4J= 2.0 Hz, 2H, H_{Ar}), 7.13 (d, ^3J= 15.9 Hz, 2H, H_{vin}), 7.03 (d, ^3J= 8.4 Hz, 2H, H_{Ar}). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 191.2 (C), 153.8 (C), 143.8 (CH), 138.4 (C), 130.1 (CH), 128.4 (C), 125.0 (CH), 124.4 (CH), 120.5 (CH). MS (FAB) *m/z*: 435.2 (M+). Light-sensitive!

(1*E*,4*E*)-1,5-Bis(3-bromo-2,5-dimethoxyphenyl)penta-1,4-dien-3-one (NW324.2)



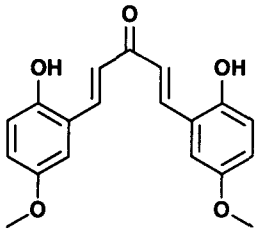
A mixture of 3-bromo-2,5-dimethoxybenzaldehyde (1.56 g, 6.4 mmol) in acetone (234 µL, 3.2 mmol) and EtOH (15 mL) was stirred for 15 min at room temperature. A solution of NaOH (382 mg, 9.5 mmol) in H_2O (8 mL) was added and the reaction mixture was stirred for further 24 h at ambient temperature. The resulting precipitate was filtered, recrystallized from EtOH and dried *in vacuo* to afford **NW324.2** as a pale yellow solid (1.6 g, 92 %). mp: 122-125 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.95 (d, ^3J= 16.2 Hz, 2H, H_{vin}), 7.20 (d, ^4J= 2.8 Hz , 2H, H_{Ar}), 7.15 (d, ^3J= 16.3 Hz, 2H, H_{vin}), 7.14-7.09 (m, 2H, H_{Ar}), 3.85 (s, 6H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.9 (C), 156.2 (C), 150.6 (C), 137.8 (CH), 130.2 (C), 127.6 (CH), 120.9 (CH), 112.2 (CH), 62.0 (OCH_3), 55.9 (OCH_3). MS (FAB) *m/z*: 513.0 (M+). Anal. calcd for $C_{21}H_{20}Br_2O_5 \cdot 0.5H_2O$: C 48.39, H 4.06, found: C 48.37, H 3.96%.

(1*E*,4*E*)-1,5-Bis(3-bromo-2-hydroxy-5-methoxyphenyl)penta-1,4-dien-3-one (NW326.4)



A suspension of 3-bromo-2-hydroxy-5-methoxybenzaldehyde (1.22 g, 5.3 mmol) in acetone (194 µL, 2.6 mmol) and EtOH (5 mL) was stirred for 15 min at ambient temperature. A solution of NaOH (317 mg, 7.9 mmol) in H_2O (1.3 mL) was added and the yellow suspension was stirred for further 3 d at room temperature. The reaction mixture was treated with aq. HCl solution (1N) and the resulting precipitate was filtered and dried *in vacuo* to obtain **NW326.4** as an orange solid (741 mg, 57 %). mp: 155-157 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.45 (s, 2H, O<u>H</u>), 7.99 (d, ^3J= 16.0 Hz , 2H, H_{vin}), 7.34 (d, ^3J= 16.0 Hz , 2H, H_{vin}), 7.33 (d, ^4J= 2.9 Hz, 2H, H_{Ar}), 7.25 (d, ^4J= 2.9 Hz, 2H, H_{Ar}), 3.78 (s, 6H, OC<u>H</u>$_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 188.8 (C), 153.5 (C), 147.5 (C), 137.8 (<u>C</u>H), 127.4 (<u>C</u>H), 125.6 (C), 121.2 (<u>C</u>H), 113.9 (C), 111.9 (<u>C</u>H), 56.3 (O<u>C</u>H$_3$). MS (FAB) *m/z*: 485.1 (M+). The purity of the compound was confirmed by HPLC analysis ; 60% decomposition after 5 days.

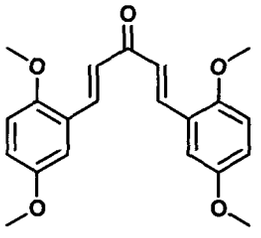
(1*E*,4*E*)-1,5-Bis(2-hydroxy-5-methoxyphenyl)penta-1,4-dien-3-one (NW327.2)



A mixture of 2-hydroxy-5-methoxybenzaldehyde (2 g, 13 mmol) in acetone (483 µL, 7 mmol) and EtOH (13 mL) was stirred for 15 min at room temperature. A solution of NaOH (789 mg, 20 mmol) in H_2O (3.3 ml) was added and the reaction mixture was stirred for further 24 h at ambient temperature. After addition of 1N HCl-solution, the resulting precipitate was filtered, recrystallized from EtOH and dried *in vacuo* to afford a golden solid (318 mg, 15 %). ^{1}H NMR (250 MHz, CD_3OD) δ (ppm): 8.09 (d, ^3J= 16.0 Hz , 2H, H_{vin}), 7.31 (d, ^3J= 16.1 Hz, 2H, H_{vin}), 9.19 (s, 2H, H_{Ar}), 6.89 (d, ^3J= 8.5 Hz , 2H, H_{Ar}), 6.82 (d, ^3J= 8.7 Hz, 2H, H_{Ar}), 3.81 (s, 6H, OC<u>H</u>$_3$). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 188.7 (C), 152.3 (C), 151.4 (C), 137.8

(CH), 125.6 (CH), 121.6 (C), 118.7 (CH), 117.2 (CH), 111.8 (CH), 55.5 (OCH_3). MS (FAB) *m/z*: 327.2 (M+). Anal. calcd for $C_{21}H_{22}O_5$: C 69.93, H 5.56, found: C 70.01, H 5.63%.

(1*E*,4*E*)-1,5-Bis(2,5-dimethoxyphenyl)penta-1,4-dien-3-one (NW331)

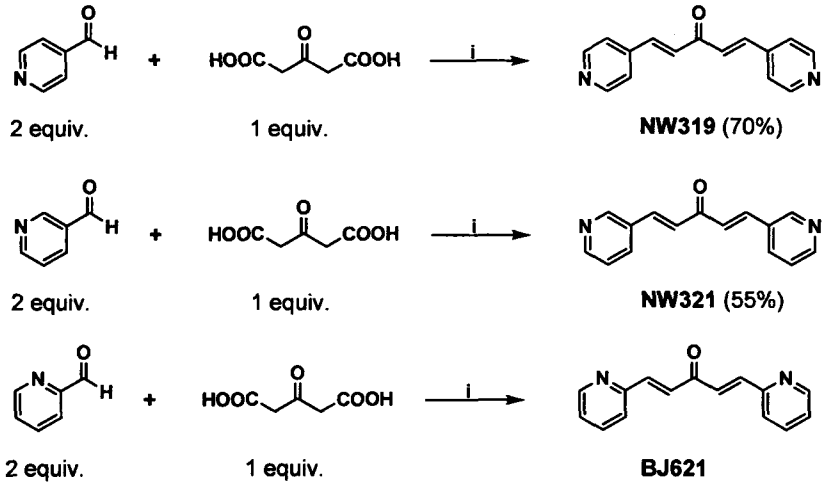


A mixture of 2,5-dimethoxybenzaldehyde (3 g, 18 mmol) in acetone (663 µL, 9 mmol) and EtOH (30 mL) was stirred for 15 min at room temperature. A solution of NaOH (1.1 g, 27 mmol) in H_2O (23 mL) was added and the reaction mixture was stirred for further 24 h at ambient temperature. The resulting precipitate was filtered, recrystallized from EtOH and dried *in vacuo* to afford **NW331** as a bright yellow solid (2.9 g, 91 %). mp: 103-104 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.06 (d, ^3J= 16.1 Hz , 2H, H_{vin}), 7.18 (d, ^4J= 2.9 Hz , 2H, H_{Ar}), 7.17 (d, ^3J= 16.1 Hz, 2H, H_{vin}), 6.96 (dd, ^3J= 9.0 Hz , ^4J= 2.8 Hz , 2H, H_{Ar}), 6.89 (d, ^3J= 9.0 Hz, 2H, H_{Ar}), 3.90 (s, 6H, OCH_3), 3.84 (s, 6H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 189.8 (C), 153.5 (C), 153.1 (C), 138.0 (CH), 126.3 (CH), 124.5 (CH), 117.2 (CH), 113.2 (CH), 112.3 (CH), 56.1 (OCH_3), 55.8 (OCH_3). MS (FAB) *m/z*: 355.2 (M+). Anal. calcd for $C_{21}H_{22}O_5 \cdot 0.3H_2O$: C 70.10, H 6.33, found: C 70.22, H 6.20%.

EXAMPLE 2: Symmetrical diheteroarylidene acetones

To generate symmetrical diheteroarylidene acetones (**NW319**, **NW321** and **BJ621**) a Claisen-Schmidt reaction was performed with 2 equivalents of the aldehyde and 1 equivalent of 1,3-acetonedicarboxylic acid under acidic conditions (e. g. conc. HCl) for 2-24 h at room temperature and for 1 h at 80 °C (Scheme 3).

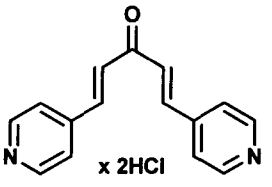
Scheme 3: Synthesis of symmetrical diheteroarylidene acetones



Reagents and conditions: (i) conc. HCl, EtOH, 2-24 h, RT,1 h, 80 °C.

The detailed synthesis is disclosed hereunder

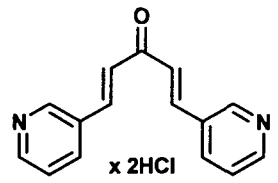
(1*E*,4*E*)-1,5-Di(pyridin-4-yl)penta-1,4-dien-3-one dihydrochloride (NW319)



1,3-Acetonedicarboxylic acid (3.15 g, 22 mmol) was dissolved in EtOH (30 mL) and stirred for 15 min at ambient temperature. 4-Pyridinecarboxaldehyde (4.06 mL, 43 mmol) was added dropwise and the mixture was stirred for 2 h at room temperature. The pale yellow solution was treated with concd. HCl (15 mL) and the reaction mixture were stirred for further 1 h at 80 °C. The resulting yellow precipitate was filtered, recrystallized from H_2O/acetone (1:1) and dried *in vacuo* to obtain **NW319** as bright yellow needles and as a hydrochloride salt

(4.64 g, 70 %). mp: 243-245 °C. ^{1}H NMR (250 MHz, D_2O) δ (ppm): 8.77 (d, ^{3}J= 6.8 Hz , 4H, H_{Ar}), 8.25 (d, ^{3}J= 6.8 Hz , 4H, H_{Ar}), 7.85 (d, ^{3}J= 16.2 Hz, 2H, H_{vin}), 7.62 (d, ^{3}J= 16.2 Hz, 2H, H_{vin}). ^{13}C NMR (75 MHz, D_2O) δ (ppm): 191.5 (C), 153.1 (C), 142.6 (CH), 139.8 (CH), 134.8 (CH), 126.8 (CH). MS (FAB) *m/z*: 237.1 (M+). Anal. calcd for $C_{15}H_{12}N_2O \cdot 1.9HCl \cdot 0.7H_2O$: C 56.63, H 4.85, N 8.80, Cl 21.17, found: C 56.60, H 4.78, N 8.73, Cl 21.10%.

(1E,4E)-1,5-Di(pyridin-3-yl)penta-1,4-dien-3-one dihydrochloride (NW321)

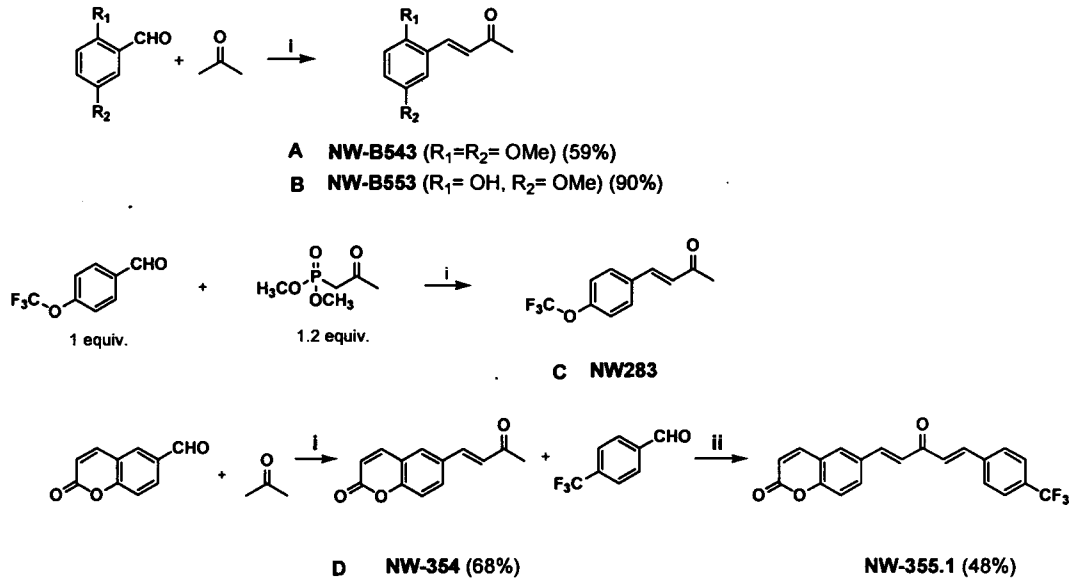


1,3-Acetonedicarboxylic acid (3.15 g, 22 mmol) was dissolved in EtOH (30 mL) and stirred for 15 min at ambient temperature. 3-Pyridinecarboxaldehyde (4.06 mL, 43 mmol) was added dropwise and the mixture was stirred for 2 h at room temperature. The yellow solution was treated with concd. HCl (15 mL) and the reaction mixture was stirred for further 1 h at 80 °C. The resulting yellow precipitate was filtered, recrystallized from H_2O/acetone (1:1) and dried *in vacuo* to obtain **NW321** as bright yellow needles and as a hydrochloride salt (3.7 g, 55 %). mp: 260-262 °C. ^{1}H NMR (250 MHz, D_2O) δ (ppm): 9.02 (s, 2H, H_{Ar}), 8.83 (d, ^{3}J= 8.3 Hz , 2H, H_{Ar}), 8.74 (d, ^{3}J= 5.7 Hz , 2H, H_{Ar}), 8.06 (dd, ^{3}J= 8.1 Hz, ^{3}J= 6.0 Hz, 2H, H_{Ar}), 7.81 (d, ^{3}J= 16.2 Hz, 2H, H_{vin}), 7.44 (d, ^{3}J= 16.2 Hz, 2H, H_{vin}). ^{13}C NMR (75 MHz, D_2O) δ (ppm): 191.6 (C), 145.9 (CH), 142.8 (CH), 142.2 (CH), 138.4 (CH), 135.5 (C), 131.3 (CH), 128.6 (CH). MS (FAB) *m/z*: 237.1 (M+). Anal. calcd for $C_{15}H_{12}N_2O \cdot 1.9HCl \cdot 2.1H_2O$: C 55.37, H 4.99, N 8.61, Cl 20.70, found: C 55.16, H 4.99, N 8.53, Cl 20.89%.

EXAMPLE 3: Synthesis of asymmetrical dibenzylidene acetones by Claisen-Schmidt reaction

The starting benzalacetones were prepared by either a Claisen reaction or by a Horner-Wadsworth-Emmons reaction as illustrated in Scheme 4.

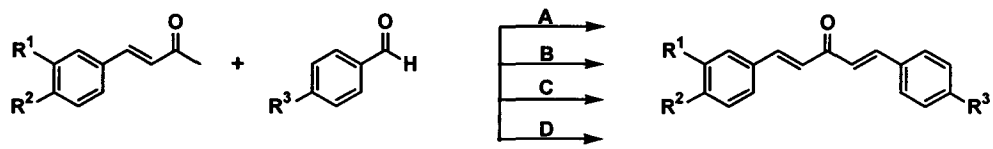
Scheme 4: Synthesis of starting benzalacetones



Reagents and conditions: (**A**) aq. NaOH, 24 h, RT; (**B**) aq. NaOH (10 %), 3 h, RT, aq. HCl (6N), pH~1, 30 min, RT; (**C**) 1.8 equiv. K_2CO_3 in H_2O, 2 h, 0 °C; (**D**) (i) aq. K_2CO_3, 2 d, RT, MeOH/2.5N H_2SO_4 (1:1), 24 h, reflux, (ii) aq. K_2CO_3, EtOH, 4 d, RT

The favored asymmetrical dibenzylidene acetones (**NW336.2**, **NW350**, **NW337**, **NW346**, **NW351** and **NW355.1**) were prepared *via* two consecutive Claisen-Schmidt reactions under various reaction conditions (**A-D**) depending on the different substituents on the aromatic ring. In the first step, 1 equivalent of the corresponding aldehyde and an excess of acetone were allowed to react under basic conditions. In the second step, the isolated unsaturated ketones and 1 equivalent of the other corresponding aldehyde were also transformed under basic conditions into the desired final products as illustrated in Scheme 5.

Scheme 5: Synthesis of asymmetrical dibenzylidene acetones



2 equiv. 1 equiv.

A **NW336.2** (R^1=H, R^2 =OMe, R^3=CF_3) (92%)

B **NW350** (R^1=H, R^2=OMe, R^3=OCF_3) (12%)
NW337 (R^1=H, R^2=OCF_3, R^3=CF_3) (34%)

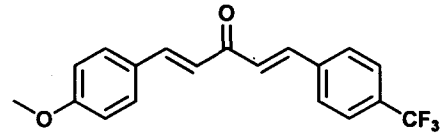
C **NW346** (R^1=OMe, R^2=OH, R^3=CF_3) (72%)

D **NW351** (R^1=OMe, R^2=OH, R^3=OCF_3) (17%)

Reagents and conditions: (**A**) aq. NaOH, MeOH, 1 d, RT; (**B**) aq. K_2CO_3, EtOH, 4.5 h, 0 °C, 2 h, RT; (**C**) aq. NaOH, EtOH, 1 d, RT, 6N aq. HCl, dark; (**D**) aq. K_2CO_3, EtOH, 3 h, 0 °C, 3 d, 40 °C.

The detailed synthesis is disclosed hereunder.

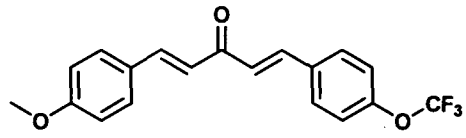
(1*E*,4*E*)-1-(4-(Trifluoromethyl)phenyl)-5-(4-methoxyphenyl)penta-1,4-dien-3-one (NW336.2)



(*E*)-4-(4-Methoxyphenyl)but-3-en-2-one (1g, 5.7 mmol) was dissolved in MeOH (18 mL) and stirred for 5 min at room temperature. A solution of NaOH (500 mg, 12.5 mmol) in H_2O (34 mL) was added and the reaction mixture was stirred for further 1 h. After the dropwise addition of 4-(trifluoromethyl)-benzaldehyde (822 µl, 6.0 mmol), the mixture was stirred overnight at ambient temperature. The resulting yellow precipitate was filtered and dried *in vacuo* to obtain **NW336.2** as a pale yellow solid (1.75 g, 92 %). mp: 144-146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.66 (d, ^3J= 15.9 Hz, 1H, H_{vin}), 7.64 (d, ^3J= 15.5 Hz , 1H, H_{vin}), 7.63 (d, ^3J= 9.0 Hz, 2H, H_{Ar}), 7.58 (d, ^3J= 8.6 Hz, 2H, H_{Ar}), 7.50 (d, ^3J= 8.8 Hz, 2H, H_{Ar}), 7.06 (d, ^3J= 16.0 Hz, 1H, H_{vin}), 6.87 (d, ^3J= 16.0 Hz, 1H, H_{vin}), 6.86 (d, ^3J= 8.8 Hz, 2H, H_{Ar}), 3.78 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.4 (C), 161.9 (C), 143.9 (CH), 140.8 (CH), 138.4 (q, ^4J(C, F)= 1.3 Hz, CH), 131.7 (q, ^2J(C, F)= 32.7 Hz, C), 130.3 (CH), 128.4 (CH), 127.6 (CH), 127.3 (C), 125.9 (q, ^3J(C, F)= 3.8 Hz, CH), 123.9 (q, ^1J(C, F)= 272.2

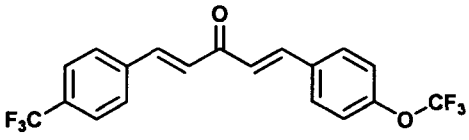
Hz, C), 123.2 (CH), 114.5 (CH), 55.5 (OCH_3). MS (FAB) *m/z*: 333.1 (M+). Anal. calcd for $C_{19}H_{15}F_3O_2$: C 68.67, H 4.55, found: C 68.81, H 4.63%.

(1*E*,4*E*)-1-(4-Methoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)penta-1,4-dien-3-one (NW350)



A suspension of (*E*)-4-(4-methoxyphenyl)-but-3-en-2-one (615 mg, 3.5 mmol) in EtOH (10 mL) was stirred for 5 min at 0 °C. A solution of K_2CO_3 (965 mg, 7.0 mmol) in H_2O (5 mL) was added and the reaction mixture was stirred for further 10 min at 0 °C. After the dropwise addition of 4-(trifluoromethoxy)-benzaldehyde (528 µl, 3.7 mmol), the pale yellow suspension was stirred for further 4 h at 0 °C. The resulting yellow precipitate was filtered and dried *in vacuo* to obtain **NW350** as a pale yellow solid (145 mg, 12 %). mp: 105-107 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.82-7.44 (m, 6H, H_{Ar}+H_{vin}), 7.34-7.24 (m, 2H, H_{Ar}), 7.14-6.90 (m, 4H, H_{Ar}+H_{vin}), 3.89 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.5 (C), 161.8 (C), 150.4 (C), 143.6 (CH), 141.0 (CH), 133.6 (C), 130.2 (CH), 129.7 (CH), 127.4 (C), 126.3 (CH), 123.3 (CH), 121.2 (CH), 114.5 (CH), 55.4 (OCH_3). MS (FAB) *m/z*: 349.1 (M+). Anal. calcd for $C_{19}H_{15}F_3O_3 \cdot 1.1H_2O$: C 61.99, H 4.71, found: C 61.86, H 4.44%.

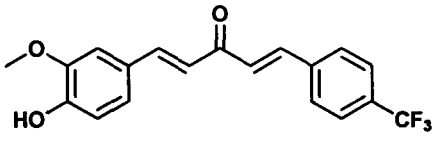
(1*E*,4*E*)-1-(4-(Trifluoromethyl)phenyl)-5-(4-(trifluoromethoxy)phenyl)penta-1,4-dien-3-one (NW337)



A solution of (*E*)-4-(4-(trifluoromethoxy)-phenyl)-but-3-en-2-one (623 mg, 2.7 mmol) in EtOH (10 mL) was stirred for 5 min at 0°C. A solution of K_2CO_3 (748 mg, 5.4 mmol) in H_2O (4 mL) was added and the reaction mixture was stirred for further 1 h. After the dropwise addition of 4-(trifluoromethyl)-benzaldehyde (392 µl, 2.9 mmol), the mixture was continued to stir for 4h at 0°C and for 2h at ambient temperature. The resulting yellow precipitate was filtered and dried *in vacuo* to obtain **NW337** as a pale yellow solid (337mg, 34 %). mp: 97-99

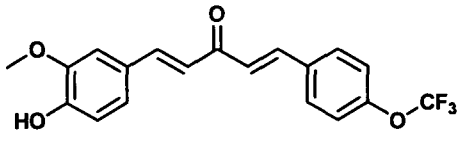
°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.76 (d, ^3J= 16.1 Hz, 1H, H_{vin}), 7.75 (d, ^3J= 15.7 Hz , 1H, H_{vin}), 7.74 (d, ^3J= 8.8 Hz, 2H, H_{Ar}), 7.69 (d, ^3J= 8.1 Hz, 2H, H_{Ar}), 7.67 (d, ^3J= 8.7 Hz, 2H, H_{Ar}), 7.29 (d, ^3J= 8.0 Hz, 2H, H_{Ar}), 7.15 (d, ^3J= 16.0 Hz, 1H, H_{vin}), 7.07 (d, ^3J= 16.0 Hz, 1H, H_{vin}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.2 (C), 150.7 (C), 142.1 (CH), 141.6 (CH), 138.1 (q, ^4J(C, F)= 1.3 Hz, CH), 133.2 (C), 132.0 (q, ^2J(C, F)= 32.7 Hz, C), 129.9 (CH), 128.5 (CH), 127.3 (CH), 126.0 (q, ^3J(C, F)= 3.8 Hz, CH), 125.9 (CH), 122.1 (C), 122.0 (C), 121.2 (CH), 118.7 (C). MS (FAB) *m/z*: 387.1 (M+). Anal. calcd for $C_{19}H_{12}F_6O_2 \cdot 0.5H_2O$: C 57.73, H 3.31, found: C 57.75, H 3.20%.

(1*E*,4*E*)-1-(4-(Trifluoromethyl)-phenyl)-5-(4-(hydroxy-3-methoxyphenyl)penta-1,4-dien-3-one (NW346)



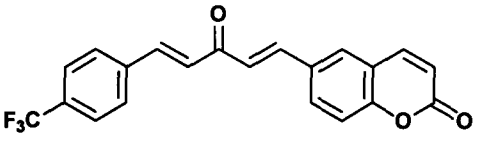
(*E*)-4-(4-Hydroxy-3-methoxyphenyl)but-3-en-2-one (500 mg, 2.6 mmol) was dissolved in EtOH (8 mL) and stirred in the dark for 5 min at room temperature. A solution of NaOH (229 mg, 5.7 mmol) in H_2O (16 mL) was added and the reaction mixture was stirred for further 1 h. The yellow solution turned red. After the dropwise addition of 4-(trifluoromethyl)-benzaldehyde (377 µl, 2.8 mmol), the mixture was continued to stir overnight at ambient temperature. The dark red solution was acidified with aq. HCl (6 N) solution and the resulting bright yellow precipitate was filtered, recrystallized from EtOH and dried *in vacuo* to obtain **NW346** as bright yellow cristals (483mg, 66 %). mp: 135-137 °C. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.87 (d, ^3J= 8.2 Hz, 2H, H_{Ar}), 7.78 (d, ^3J= 15.9 Hz , 1H, H_{vin}), 7.77 (d, ^3J= 16.1 Hz , 1H, H_{vin}), 7.71 (d, ^3J= 8.3 Hz, 2H, H_{Ar}), 7.37 (d, ^3J= 16.0 Hz, 1H, H_{vin}), 7.31 (d, ^4J= 1.9 Hz, 1H, H_{Ar}), 7.21 (dd, ^3J= 8.2 Hz, ^4J= 1.9 Hz, 1H, H_{Ar}), 7.09 (d, ^3J= 15.9 Hz, 1H, H_{vin}), 6.86 (d, ^3J= 8.2 Hz, 1H, H_{Ar}), 3.93 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 191.1 (C), 151.3 (C), 149.5 (C), 146.7 (CH), 142.1 (CH), 140.2 (q, ^4J(C, F)= 1.3 Hz, CH), 132.6 (q, ^2J(C, F)= 32.5 Hz, C), 129.9 (CH), 129.0 (CH), 128.1 (C), 126.9 (q, ^3J(C, F)= 3.8 Hz, CH), 125.1 (CH), 123.6 (CH), 116.7 (CH), 112.2 (CH), 56.5 (OCH_3). MS (FAB) *m/z*: 349.2 (M+). Anal. calcd for $C_{19}H_{14}F_3O_3$: C 65.52, H 4.34, found: C 65.25, H 4.39%.

(1*E*,4*E*)-1-(4-Hydroxy-3-methoxyphenyl)-5-(4-(trifluoromethoxy)phenyl)penta-1,4-dien-3-one (NW351)



A suspension of (*E*)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one (600 mg, 3.1 mmol) in EtOH (10 mL) was stirred for 5 min at 0°C. A solution of K_2CO_3 (863 mg, 6.2 mmol) in H_2O (5 mL) was added and the reaction mixture was stirred for further 10 min at 0°C. After the dropwise addition of 4-(trifluoromethoxy)-benzaldehyde (473 µl, 3.3 mmol), the orange suspension was heated to reflux for 4 d at 40°C. The solvent was evaporated *in vacuo* and the resulting residue was purified by flash-chromatography on silica gel (Hexane/EtOAc 2:1) and dried *in vacuo* to obtain **NW351** as a yellow solid (191mg, 17 %). mp: 93-95 °C. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.72 (d, ^3J= 8.4 Hz, 2H, H_{Ar}), 7.71 (d, ^3J= 15.9 Hz , 1H, H_{vin}), 7.68 (d, ^3J= 15.6 Hz , 1H, H_{vin}), 7.27 (d, ^3J= 8.3 Hz, 2H, H_{Ar}), 7.24 (d, ^4J= 1.9 Hz, 1H, H_{Ar}), 7.19 (d, ^3J= 16.0 Hz, 1H, H_{vin}), 7.15 (dd, ^3J= 8.4 Hz, ^4J = 2.0 Hz, 1H, H_{Ar}), 7.02 (dd, ^3J= 15.9 Hz, ^5J= 0.99, Hz, 1H, H_{vin}), 6.83 (dd, ^3J= 8.2 Hz, ^5J= 0.9 Hz, 1H, H_{Ar}), 3.89 (d, ^5J= 0.9, 3H, $OC\underline{H}_3$). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 191.1 (C), 151.7 (q, ^4J (C, F)= 1.7 Hz), 151.2 (C), 149.4 (C), 146.4 (<u>C</u>H), 142.4 (<u>C</u>H), 135.4 (C), 131.3 (<u>C</u>H), 128.1 (C), 127.6 (<u>C</u>H), 125.0 (<u>C</u>H), 123.6 (<u>C</u>H), 122.3 (<u>C</u>H), 120.2 (C), 116.7 (<u>C</u>H), 112.2 (<u>C</u>H), 56.5 ($O\underline{C}H_3$). MS (FAB) *m/z*: 365.2 (M+). Anal. calcd for $C_{19}H_{15}F_3O_4$: C 62.64, H 4.15, found: C 62.45, H 4.39%.

6-((1*E*,4*E*)-5-(4-(Trifluoromethyl)phenyl)-3-oxopenta-1,4-dienyl)-2*H*-chromen-2-one (NW355P)



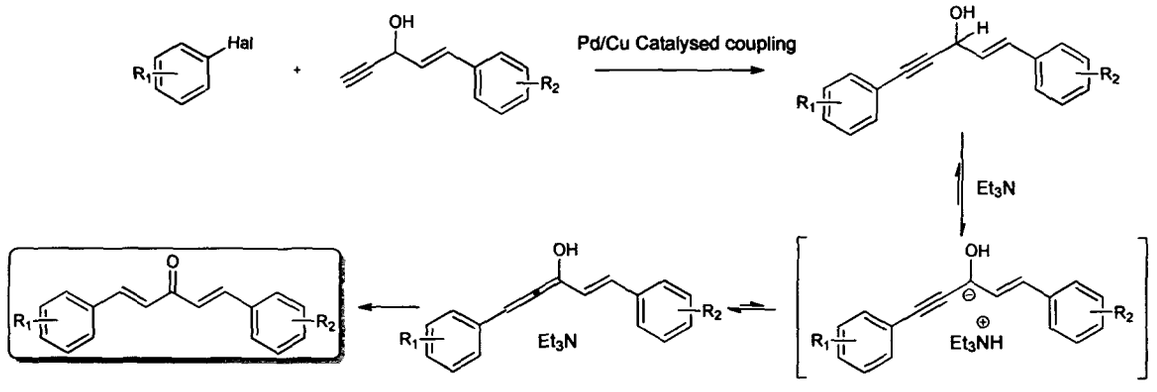
To a grey suspension of 6-((*E*)-3-oxobut-1-enyl)-2*H*-chromen-2-one (1 g, 4.7 mmol) in EtOH (12 mL) was added dropwise a solution of K_2CO_3 (1.3 g, 9.3 mmol) in H_2O (6 mL). The grey suspension turned yellow. After addition of 4-(trifluoromethyl)-benzaldehyde (0.7 mL, 862 mg, 4.9 mmol), the reaction mixture was stirred for 4d at room temperature. The orange suspension turned red and the resulting precipitate was filtered and purified by flash-

chromatography on silica gel (Hexane/EtOAc 1:1) to obtain **NW355P** as a white solid (830mg, 48 %). mp: 153-155 °C. ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm): 8.64 (d, ^3J= 1.9 Hz, 1H, H_{Ar}), 8.60-8.47 (m, 4H, H_{Ar}), 8.39 (d, ^3J= 16.2 Hz, 1H, H_{vin}), 8.39-8.26 (m, 3H, H_{vin}, H_{Ar}), 8.00 (d, ^3J= 16.2 Hz, 1H, H_{vin}), 7.97 (d, ^3J= 8.5 Hz, 1H, H_{Ar}), 7.89 (d, ^3J = 16.1 Hz, 1H, H_{vin}), 7.04 (d, ^3J= 9.6 Hz, 1H, H_{Ar}). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 188.4 (C), 159.6 (C), 154.7 (C), 143.9 (CH), 141.8 (CH), 140.9 (CH), 131.7 (CH), 131.1 (C), 129.1 (CH), 128.8 (CH), 127.9 (CH), 126.0 (CH), 125.8 (CH), 119.1 (C), 117.2 (CH), 117.0 (CH). MS (FAB) *m/z*: 371.1 (M+). Anal. calcd for $C_{21}H_{13}F_3O_3$: C 68.11, H 3.54, found: C 67.72, H 3.72%.

EXAMPLE 4: Synthesis of dissymmetric dibenzylidene acetones through a one-pot Coupling-Isomerization Procedure (CIP)

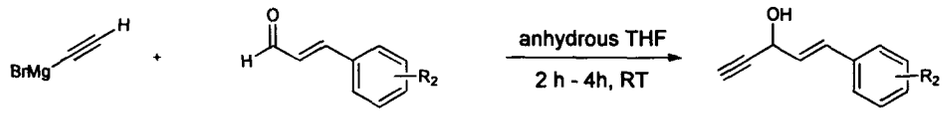
Although the synthesis of dissymmetric dibenzylidene acetones could be achieved according to the procedure described in Example 3, some compounds failed to be synthesized with these traditional conditions. Here we would describe a one-pot catalytic procedure for the simple synthesis of electron-deficient dibenzylidene acetones. This work was based on a procedure described by Braun *et al* (Chem. Eur. J. 2006, 12, 9081 – 9094) and products were obtained according to the following steps (Scheme 6).

Scheme 6: synthesis of dissymmetric dibenzylidene acetones via a one-pot CIP



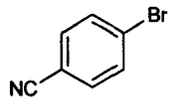
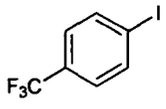
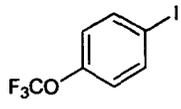
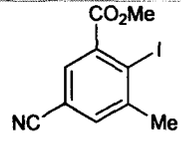
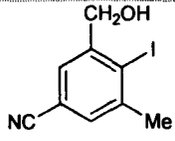
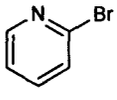
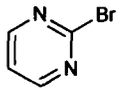
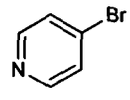
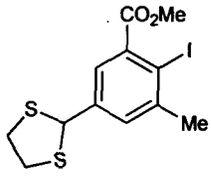
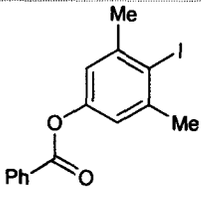
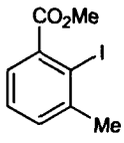
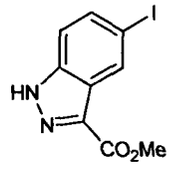
According to the traditional Sonogashira coupling, a propargylic alcohol reacts with an (hetero)aryl halide bearing an electron-withdrawing group in *para*-position in presence of a mix of palladium catalyst, copper iodide and a base. A base-assisted isomerization subsequently leads to the formation of the desired dibenzylidene acetone. The unsaturated propargylic alcohol can be easily synthesized through the Grignard addition of commercially available ethynylmagnesium bromide on a cinnamaldehyde. This usually leads to desired product in good to excellent yields (Scheme 7).

Scheme 7: Synthesis of unsaturated propargylic alcohol starting material



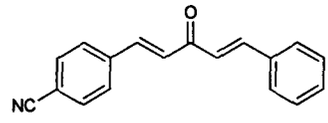
Regarding the opportunity to introduce the diversity through the use of highly substituted (hetero)aryl halides, several starting material has been considered. They are given in Table I.

Table I: example of (hetero)aryl halides that have been considered to be used in the CIP procedure

In order to be able to use this broad variety of starting material, an optimization study on the coupling reaction conditions has been performed. Thus, it has been demonstrated that the use of bis(triphenylphosphine)palladium(II) dichloride, triethylamine, and triphenylphosphine (as catalyst stabilizer) in 1,4-dioxane under microwave irradiation, gives the best yields for a large diversity of substitution pattern, as exemplified bellow.

4-((1*E*,4*E*)-3-oxo-5-phenylpenta-1,4-dien-1-yl)benzonitrile (TG007A82)



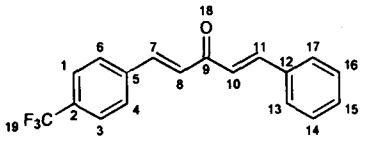
4-bromobenzonitrile (182 mg, 1 mmol), phenylpent-1-en-4-yn-3-ol (190 mg, 1.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol), copper iodide (3 mg, 0.03 mmol) and triphenylphosphine (52 mg, 0.2 mmol) were introduced in a 10 mL microwave vial flushed with argon. This was diluted with anhydrous triethylamine (700 µL, 4 mmol) in anhydrous degased 1,4-dioxane (1.3 mL). The solution was heated under microwave irradiation at 120°C for 45 min. The reaction mixture was poured into a mix of 1M aqueous solution of hydrochloric acid (10 mL) and saturated aqueous ammonium chloride solution (10 mL), and this was extracted with ethyl acetate (3x15 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to dryness to give crude product which was purified by flash chromatography (SiO_2, 30% ethyl acetate in dichloromethane). This gave pure final compound **TG007A82** (160 mg, 62%) as a light yellow powder.

^{1}H COSY NMR (500 MHz, CD_2Cl_2) δ (ppm): 7.75 (d, $^3J_{trans}$ = 16.4 Hz, 1H, ArC<u>H</u>=), 7.72 (m, 4H, Ar), 7.69 (d, $^3J_{trans}$ = 15.5 Hz, 1H, ArC<u>H</u>=), 7.64-7.66 (m, 2H, Ar), 7.44 (m, 3H, Ar), 7.18 (d, $^3J_{trans}$ = 15.5 Hz, 1H, =C<u>H</u>C(O)), 7.09 (d, $^3J_{trans}$ = 16.4 Hz, 1H, =C<u>H</u>C(O))

^{13}C NMR (125 MHz, CD_2Cl_2) δ (ppm): 188.3 (C), 144.1 (<u>C</u>H), 140.7 (<u>C</u>H), 139.6 (C), 135.0 (C), 133.0 (<u>C</u>H), 131.1 (<u>C</u>H), 129.4 (<u>C</u>H), 129.0 (<u>C</u>H), 128.8 (<u>C</u>H), 128.5 (<u>C</u>H), 125.7 (<u>C</u>H), 118.8 (<u>C</u>N), 113.7 (Ar<u>C</u>-CN)

MS(EI) : m/z = 259

(1*E*,4*E*)-1-phenyl-5-(4-(trifluoromethyl)phenyl)penta-1,4-dien-3-one (TG008A86)



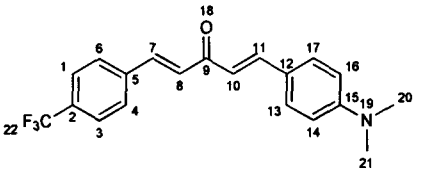
4-iodobenzotrifluoride (150 µL, 1 mmol), phenylpent-1-en-4-yn-3-ol (190 mg, 1.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol), copper iodide (3 mg, 0.03 mmol) and triphenylphosphine (52 mg, 0.2 mmol) were introduced in a 10 mL microwave vial flushed with argon. This was diluted with anhydrous triethylamine (700 µL, 4 mmol) in anhydrous degased 1,4-dioxane (1.3 mL). The solution was heated under microwave irradiation at 120°C for 45 min. The reaction mixture was poured into a mix of 1M aqueous solution of hydrochloric acid (10 mL) and saturated aqueous ammonium chloride solution (10 mL), and this was extracted with dichloromethane (3x15 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to dryness to give crude product which was purified by flash chromatography (SiO_2, DCM/Hexanes 3:7). The resulting yellow solid was recrystallyzed (EtOH/Hexanes 1:3) to give pure final compound **TG008A86** as a pale yellow powder (155 mg, 51%).

^{1}H COSY NMR (200 MHz, $CDCl_3$) δ (ppm): 7.78 (d, $^3J_{trans}$ = 14.9 Hz, 1H, ArC<u>H</u>=), 7.75 (d, $^3J_{trans}$ = 14.6 Hz, 1H, ArC<u>H</u>=), 7.73-7.61 (m, 6H, Ar and ArC<u>H</u>=), 7.46-7.41 (m, 3H, Ph), 7.16 (d, $^3J_{trans}$ = 14.8 Hz, 1H, =C<u>H</u>C(O)), 7.08 (d, $^3J_{trans}$ = 14.6 Hz, 1H, =C<u>H</u>C(O))

^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): 188.7 (<u>C</u>9), 144.2 (<u>C</u>H), 144.4 (<u>C</u>H), 138.4 (m, <u>C</u>5), 134.8 (C), 132.1 (q, ^2J = 32 Hz, <u>C</u>2), 131.0 (<u>C</u>H), 129.2 (<u>C</u>H), 128.7 (<u>C</u>H), 128.6 (<u>C</u>H), 127.6 (<u>C</u>H), 125.9 (q, ^3J = 3.6 Hz, <u>C</u>3), 125.5 (<u>C</u>H), 123.8 (q, ^1J = 271 Hz, <u>C</u>19)

MS(EI) : m/z = 302

(1*E*,4*E*)-1-(4-(dimethylamino)phenyl)-5-(4-(trifluoromethyl)phenyl)penta-1,4-dien-3-one (TG009A94)



4-iodobenzotrifluoride (150 µL, 1 mmol), 1-(4-(dimethylamino)phenyl)pent-1-en-4-yn-3-ol (242 mg, 1.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol), copper iodide (3 mg, 0.03 mmol) and triphenylphosphine (52 mg, 0.2 mmol) were introduced in a 10 mL microwave vial flushed with argon. This was diluted with anhydrous triethylamine (700 µL, 4 mmol) in anhydrous degased 1,4-dioxane (1.3 mL). The solution was heated under microwave irradiation at 120°C for 45 min. The reaction mixture was poured into brine (20 mL), and this was extracted with dichloromethane (3x20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to dryness to give crude product which was purified by flash chromatography (SiO_2, 30% ethyl acetate in dichloromethane). The resulting yellow solid was triturated in diethyl ether to give pure final compound **TG009A94** as a bright orange powder (200 mg, 58%).

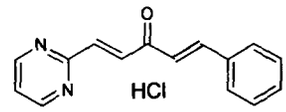
^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.62-7.73 (m, 6H, Ar), 7.51 (d, ^3J = 9 Hz, 2H, H13-17), 7.13 (d, $^3J_{trans}$ = 16 Hz, 1H, =CHC(O)), 6.85 (d, $^3J_{trans}$ = 16 Hz, 1H, =CHC(O)), 6.68 (d, ^3J = 8.5 Hz, 2H, H14-16), 3.03 (s, 6H, $N(CH_3)_2$)

^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): 188.5 (C9), 152.4 (C), 145.2 (CH), 140.1 (CH), 138.9 (m, C5), 131.6 (q, ^2J = 32.5 Hz, C2), 130.7 (CH), 128.5 (CH), 128.1 (CH), 126.0 (q, ^3J = 3.8 Hz, C3), 123.9 (q, ^1J = 269 Hz, C22), 122.5 (C), 120.8 (CH), 112.1 (CH), 40.3 ($N(CH_3)_2$)

MS(EI) : m/z = 345

Anal. calcd for $C_{20}H_{18}F_3NO$: C 69.56, H 5.25, N 4.06, found : C 69.57, H 5.54, N 3.94

(1*E*,4*E*)-1-phenyl-5-(pyrimidin-2-yl)penta-1,4-dien-3-one hydrochloride (TG010A95)

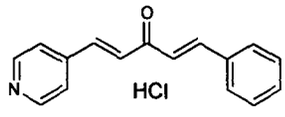


2-bromopyrimidine (159 mg, 1 mmol), phenylpent-1-en-4-yn-3-ol (190 mg, 1.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol), copper iodide (3 mg, 0.03 mmol) and triphenylphosphine (52 mg, 0.2 mmol) were introduced in a 10 mL microwave vial flushed with argon. This was diluted with anhydrous triethylamine (700 µL, 4 mmol) in anhydrous degased 1,4-dioxane (1.3 mL). The solution was heated under microwave irradiation at 120°C for 45 min. The reaction mixture was evaporated to dryness in the rotary. The resulting solid was dissolved with diethyl ether and filtrated over a short column of silica. The solution was evaporated, and the resulting yellow oil was purified by flash chromatography (SiO_2, ethyl acetate/hexanes 1:1) to give the desired product as a free base. This was dissolved in diethyl ether (5 mL) and hydrogen chloride 1.25M in ethanol (2 mL) was added. The suspension was filtered to recover the hydrochloric salt of the final compound **TG010A95** (178 mg, 65%) as a fine yellow powder.

^{1}H COSY NMR (300 MHz, DMSO-d) δ (ppm): 8.92 (d, ^3J = 4.9 Hz, 2H, H α pyrimidine), 7.90-7.70 (m, 6H, H pyrimidine / H alkene), 7.50 (d, ^3J = 4.9 Hz, 1H, H β pyrimidine), 7.45 (m, 3H, H phenyl) ; ^{13}C NMR (75,5 MHz, DMSO-d) δ (ppm): 188.7 (C=O), 162.3 (C_q α pyrimidine), 157.7 (CH α pyrimidine), 143.9 (ArCH=), 140.6 (ArCH=), 134.4 (C_q phenyl), 133.3 (CH), 130.8 (CH), 128.9-128.8 (CH phenyl), 125.2 (CH), 121.0 (CH β pyrimidine)

MS(MALDI TOF) : m/z = 236.8 $(M-Cl)^+$

(1*E*,4*E*)-1-phenyl-5-(pyridin-4-yl)penta-1,4-dien-3-one hydrochloride (TG011A96)



4-bromopyridine hydrochloride (194 mg, 1 mmol), phenylpent-1-en-4-yn-3-ol (190 mg, 1.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol), copper iodide (3 mg, 0.03 mmol) and triphenylphosphine (52 mg, 0.2 mmol) were introduced in a 10 mL microwave vial flushed with argon. This was diluted with anhydrous triethylamine (900 µL, 4 mmol) in anhydrous degased 1,4-dioxane (1.1 mL). The solution was heated under

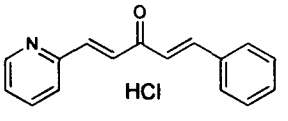
microwave irradiation at 120°C for 45 min. The reaction mixture was diluted with chloroform (15 mL) and extracted with a 1M aqueous solution of hydrochloric acid (3x20 mL). The aqueous was next basified with an aqueous solution of sodium hydroxide (5M, 20 mL). Product was extracted with ethyl acetate (3x40 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to dryness to give crude product which was purified by flash chromatography (SiO_2, 70% ethyl acetate in hexanes) to give the desired product as a free base. This was dissolved in 1,4-dioxane (15 mL) and hydrogen chloride 1.25M in ethanol (2 mL) was added. The suspension was filtered to recover the hydrochloric salt of the final compound **TG011A96** (115 mg, 42%) as a fine yellow powder.

^{1}H COSY NMR (300 MHz, DMSO-d) δ (ppm): 8.97 (d, ^3J = 6.4 Hz, 2H, H α pyridine), 8.38 (d, ^3J = 6.4 Hz, 2H, H β pyridine), 8.05-7.85 (m, 3H, alkene), 7.82 (m, 2H, H phenyl), 7.49 (m, 3H, H phenyl), 7.33 (d, $^3J_{trans}$ = 16.8 Hz, 1H, alkene) ; ^{13}C NMR (75,5 MHz, DMSO-d) δ (ppm): 188.4 (C=O), 150.2 (C_q α pyridine), 144.8 (CH), 143.0 (CH), 137.0 (CH), 134.4 (C_q phenyl), 133.4 (CH), 131.0 (CH), 129.1-128.7 (CH phenyl), 125.7 (CH), 125.1 (CH)

MS(MALDI TOF) : m/z = 235.8 $(M\text{-}Cl)^+$

Anal. calcd for $C_{16}H_{13}NO \cdot 1.1HCl$: C 69.74, H 5.16, N 5.08, found: C 69.72, H 5.46, N 4.86

(1*E*,4*E*)-1-phenyl-5-(pyridin-2-yl)penta-1,4-dien-3-one hydrochloride (TG012A97)



2-bromopyridine (158 mg, 1 mmol), phenylpent-1-en-4-yn-3-ol (190 mg, 1.2 mmol), bis(triphenylphosphine)palladium(II) dichloride (14 mg, 0.02 mmol), copper iodide (3 mg, 0.03 mmol) and triphenylphosphine (52 mg, 0.2 mmol) were introduced in a 10 mL microwave vial flushed with argon. This was diluted with anhydrous triethylamine (700 µL, 4 mmol) in anhydrous degased 1,4-dioxane (1.3 mL). The solution was heated under microwave irradiation at 120°C for 45 min. The reaction mixture was diluted with chloroform (15 mL) and extracted with a 3M aqueous solution of hydrochloric acid (3x20 mL). The aqueous was next basified with an aqueous solution of sodium hydroxide 6M until pH ≈ 10. Product was extracted with ethyl acetate (3x50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to dryness to give crude product which was purified by flash chromatography (SiO_2, 30% ethyl acetate in hexanes) to give the desired product as a free base. This was dissolved in diethyl ether (5 mL) and hydrogen chloride

1,25M in ethanol (2 mL) was added. The suspension was filtered to recover the hydrochloric salt of the final compound **TG012A97** (82 mg, 30%) as a fine yellow powder.

^{1}H COSY NMR (300 MHz, DMSO-d) δ (ppm): 8.83 (d, ^3J = 5.6 Hz, 1H, H α pyridine), 8.38-8.26 (m, 2H, H β pyridine), 8.09 (d, $^3J_{trans}$ = 16.4 Hz, 1H, C<u>H</u> alkene), 7.99 (d, $^3J_{trans}$ = 15.9 Hz, 1H, C<u>H</u> alkene), 7.84 (d, $^3J_{trans}$ = 16.4 Hz, 1H, C<u>H</u> alkene), 7.84-7.81 (m, 1H, H β pyridine), 7.81 (m, 2H, H phenyl), 7.47 (m, 3H, H phenyl), 7.29 (d, $^3J_{trans}$ = 15.9 Hz, 1H, C<u>H</u> alkene) ; ^{13}C NMR (75,5 MHz, DMSO-d) δ (ppm): 188.2 (C=O), 149.5 (C_q α pyridine), 145.5 (<u>C</u>H), 144.7 (<u>C</u>H), 142.6 (<u>C</u>H), 135.7 (C_q phenyl), 134.4 (<u>C</u>H), 131.5 (<u>C</u>H), 130.9 (<u>C</u>H), 129.1-128.8 (<u>C</u>H phenyl), 126.3 (<u>C</u>H), 126.0-125.9 (<u>C</u>H)

MS(EI) : m/z = 235

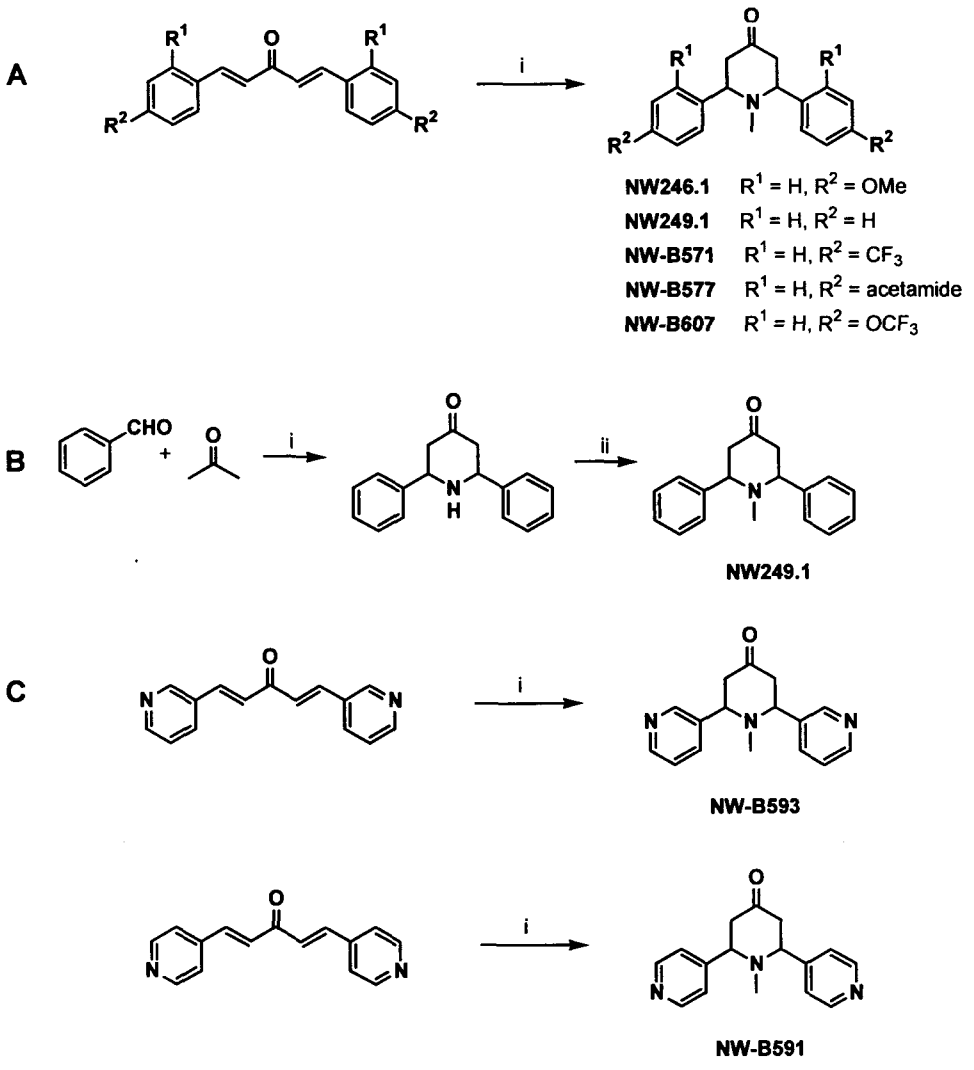
Anal. calcd for $C_{16}H_{13}NO \cdot 1HCl$: C 70.72, H 5.19, N 5.15, found: C 70.47, H 5.33, N 5.03

EXAMPLE 5: Synthesis of 2,6-diaryl-4-piperidones

To generate the 2,6-diaryl-4-piperidones **NW246.1** and **NW249.1**, a Michael addition-cyclization sequence was performed with the corresponding dibenzylidene acetones **NW247** and **NW275** prepared in example 1 and an excess of base (e. g. triethylamine) in 2-3 days at room temperature (Scheme 8, route **A**).

Compound **NW249.1** was also prepared in a two-step synthesis. In the first step, 2 equivalents of the benzaldehyde and 1 equivalent of acetone and ammonium acetate were allowed to react in a Michael addition-cyclization sequence to form the 4-piperidone ring. In the second step, the secondary amine attached to the ring is alkylated with methyl iodide in acetone under basic conditions for 3.5 h at 45-55 °C (Scheme 8, route **B**).

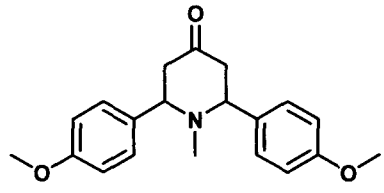
Scheme 8: Synthesis of 2,6-diaryl-4-piperidones *via* two different routes.



Reagents and conditions: **A** (i) 2.5-4 equiv. CH_3NH_2, EtOH, 1-3 d, 0°C-RT; **B** (i) 1 equiv. NH_4OAc in CH_3COOH (100 %), reflux, (ii) 1.25 equiv. CH_3I, acetone, anhydr. K_2CO_3, 3.5 h, 45-55 °C; **C** (i) 10 equiv. CH_3NH_2, EtOH, 6 h, 0°C-RT

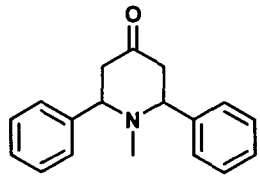
The detailed synthesis are disclosed hereunder

***meso*-2,6-Bis(4-methoxy-phenyl)-1-methyl-piperidin-4-one (NW-246.1)**



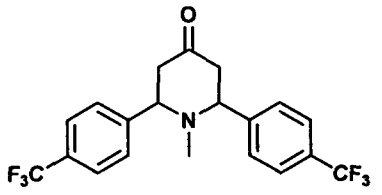
A yellow suspension of (1*E*,4*E*)-1,5-bis-(4-methoxy-phenyl)-penta-1,4-dien-3-one (3 g, 10 mmol) in EtOH (40 mL) was treated with *N*-methylamine (40 % in H_2O, 3.6 mL, 41 mmol). The yellow solution was stirred for 2 d at room temperature. The reaction mixture was diluted with water and the resulting precipitate was filtered, recrystallized from EtOH and dried *in vacuo* to obtain **NW-246.1** as a beige solid (1.9 g, 56 %). mp: 127-128 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.19 (d, ^3J= 8.3 Hz, 4H, H_{Ar}), 6.75 (d, ^3J= 8.3 Hz, 4H, H_{Ar}), 3.67 (s, 6H, C$\underline{H}_3$O), 3.20 (d, ^3J= 11.6 Hz, 2H, C$\underline{H}_2$), 2.65 (t, ABX system, ^3J= 13.0 Hz, 2H, C$\underline{H}$), 2.32 (d, ^3J= 13.9 Hz, 2H, C$\underline{H}_2$), 1.64 (s, 3H, NC$\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 207.4 (C), 159.0 (C), 135.4 (C), 128.1 (C$\underline{H}$), 114.1 (C$\underline{H}$), 69.6 (C$\underline{H}$), 55.3 (C$\underline{H}_3$), 50.9 (C$\underline{H}_2$), 40.6 (C$\underline{H}_3$). MS (FAB) *m/z*: 326.3 (M+). Anal. calcd for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30, found: C 73.66, H 7.25, N 4.62%.

***meso*-1-Methyl-2,6-diphenyl-piperidin-4-one (NW-249.1)**



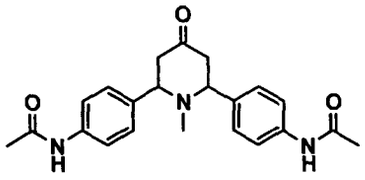
A yellow solution of (1*E*,4*E*)-1,5-diphenyl-penta-1,4-dien-3-one (5 g, 21 mmol) in EtOH (50 mL) was treated with *N*-methylamine (40 % in H_2O, 4.7 mL, 53 mmol). The reaction mixture was stirred for 2 d at ambient temperature. The solution was diluted with water and the resulting white precipitate was filtered, recrystallized from EtOH and dried *in vacuo* to obtain **NW-249.1** as a white solid (4.1 g, 73 %). mp: 138-140 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.69-7.31 (m, 10H, H_{Ar}), 3.46 (d, ^3J= 11.9 Hz, 2H, C$\underline{H}_2$), 2.85 (t, ABX system, ^3J= 12.9 Hz, 2H, C$\underline{H}$), 2.53 (d, ^3J= 14.5 Hz, 2H, C$\underline{H}_2$), 1.85 (s, 3H, NC$\underline{H}_3$). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 136.5 (C), 130.9 (C$\underline{H}$), 130.4 (C$\underline{H}$), 129.1 (C$\underline{H}$), 99.1 (C$\underline{H}_3$), 37.5 (C$\underline{H}_2$). MS (FAB) *m/z*: 266.2 (M+). Anal. calcd for $C_{18}H_{19}NO$: C 81.47, H 7.22, N 5.28, found: C 81.45, H 7.15, N 5.19%.

2,6-Bis(4-trifluoromethyl)phenyl)-1-methyl-piperidin-4-one (NW-B571)



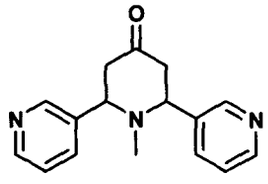
A yellow solution of (1*E*,4*E*)-1,5-bis-(4-trifluoromethyl-phenyl)-penta-1,4-dien-3-one (500 mg, 1.4 mmol) in EtOH (4 mL) was treated with *N*-methylamine (40 % in H_2O, 471 µL, 5.4 mmol). The reaction mixture was stirred for 30 h at room temperature in the dark. The mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The crude residue was purified by flash-chromatography on silica gel (Hexane/EtOAc 2:1) to obtain **NW-B571** as a pale yellow solid (219 mg, 41 %) (note: mixture of *cis/trans* isomers in a ratio of 2:1). mp: 105-107 °C. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.67 (s, 8 H, H_{Ar}), 3.56 (d, ^3J= 12.0 Hz, J= 2.6 Hz, 1 H, C$\underline{H}_2$), 3.49 (d, ^3J= 12.0 Hz, 1 H, C$\underline{H}_2$), 2.05 (t, J= 13.9 Hz, 2 H, C$\underline{H}$), 1.91-1.77 (m, 2 H, C$\underline{H}_2$), 1.78 (d, J= 3.7 Hz, 3 H, C$\underline{H}_3$). Signals of the minor isomer: 7.72 (s, 8 H, H_{Ar}), 3.66 (dd, ^3J= 12.0 Hz, J= 2.6 Hz, 2 H, C$\underline{H}_2$), 2.94 (t, ^3J= 13.0 Hz, 2 H, C$\underline{H}$), 2.46 (d, ^3J= 14.1 Hz, 2 H, C$\underline{H}_2$), 1.84 (s, 3 H, C$\underline{H}_3$). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 207.9 (C), 150.9 (C), 130.9 (q, ^2J(C, F)= 32.6 Hz, C), 129.5 (C$\underline{H}$), 128.0 (C), 127.0 (q, ^3J(C, F)= 3.6 Hz, C$\underline{H}$), 68.6 (C$\underline{H}$), 46.7 (C$\underline{H}_2$), 42.2 (C$\underline{H}_3$). Signals of the minor isomer: 207.9 (C), 149.5 (C), 130.9 (q, ^2J(C, F)= 32.6 Hz, C), 129.5 (C$\underline{H}$), 127.3 (q, ^3J(C, F)= 3.7 Hz, C$\underline{H}$), 124.4 (C), 68.2 (C$\underline{H}$), 46.1 (C$\underline{H}_2$), 42.2 (C$\underline{H}_3$). MS (FAB) m/z: 402.2 (M+). Anal. calcd for $C_{20}H_{17}F_6NO$: C 59.85, H 4.27, N 3.49, found: C 60.02, H 4.40, N 3.52%.

***meso*-2,6-Bis(4-acetamido-phenyl)-1-methyl-piperidin-4-one (NW-B577)**



A yellow suspension of *N*-{4-[(1*E*,4*E*)-5-(4-acetylamino-phenyl)-3-oxo-penta-1,4-dienyl]-phenyl}-acetamide (800 mg, 2.3 mmol) in EtOH (9 mL) was treated with *N*-methylamine (40 % in H_2O, 803 µL, 9.2 mmol). The reaction mixture was stirred for overnight at room temperature in the dark. The reaction mixture was diluted with water (12 mL) and the resulting precipitate was filtered, recrystallized from EtOH and dried *in vacuo* to obtain **NW-B577** as a pale yellow solid (831 mg, 95 %). mp: 234-237 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.94 (s, 2H, NH), 7.57 (d, ^3J= 8.4 Hz, 4H, H_{Ar}), 7.36 (d, ^3J= 8.4 Hz, 4H, H_{Ar}), 3.43-3.34 (m, 2H, CH_2), 2.87 (t, ABX system, ^3J= 13.0 Hz, 2H, CH), 2.25 (d, ^3J= 14.1 Hz, 2H, CH_2), 2.03 (s, 6H, $COCH_3$), 1.67 (s, 3H, NCH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 206.6 (C), 168.6 (C), 138.9 (C), 138.2 (C), 127.7 (CH_2), 119.7 (CH_2), 68.7 (CH), 50.1, 24.3. MS (FAB) m/z: 380.3 (M+). Anal. calcd for $C_{22}H_{25}N_3O_3$ C · 0.2H_2O: 68.98, H 6.68, N 10.97, found: C 68.85, H 6.92, N 11.26%.

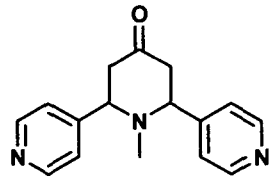
1-Methyl-2,6-di(pyridine-3-yl)piperidin-4-one (NW-B593)



A suspension of (1*E*,4*E*)-1,5-di(pyridin-3-yl)penta-1,4-dien-3-one (1 g, 3.2 mmol) in DMF (10 mL) was treated with *N*-methylamine (40 % in H_2O, 2.8 mL, 32 mmol) at 0 °C. The solution was stirred for 6 h at 0 °C. The reaction mixture was poured into ice-water (150 mL) and was extracted with DCM. The combined organic layers were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash-chromatography (CH_2Cl_2/MeOH 9:1) to obtain **NW-B593** as a bright yellow solid (814 mg, 94 %). mp: 103-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.67 (d, ^4J= 1.8 Hz, 2H, H_{Ar}), 8.59 (dd, ^3J= 4.8

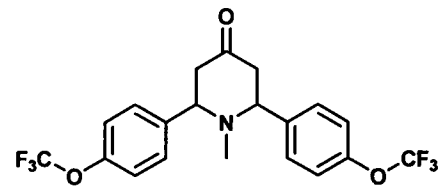
Hz, ^4J= 1.6 Hz, 2H, H_{Ar}), 7.85 (d, ^3J= 7.9 Hz, 2H, H_{Ar}), 7.37 (dd, ^3J= 7.9 Hz, ^3J= 4.8 Hz, 2H, H_{Ar}), 3.58 (dd, ^3J= 12.0 Hz, J= 2.8 Hz, 2H, C$\underline{H}_2$), 2.84 (t, ^3J= 13.0 Hz, 2H, C$\underline{H}$), 2.55 (dd, ^3J= 13.9 Hz, J= 1.8 Hz, 2H, C$\underline{H}_2$), 1.64 (s, 3H, C$\underline{H}_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 204.9 (C), 149.4 (C$\underline{H}$), 148.8 (C$\underline{H}$), 138.1 (C), 134.8 (C$\underline{H}$), 124.1 (C$\underline{H}$), 67.5 (C$\underline{H}$), 50.2 (C$\underline{H}_2$), 41.0 (C$\underline{H}_3$). MS (FAB) m/z: 268.2 (M+). Anal. calcd for $C_{16}H_{17}N_3O \cdot 0.3H_2O$: C 70.46, H 6.50, N 15.41, found: C 70.45, H 6.38, N 15.32%.

1-Methyl-2,6-di(pyridine-4-yl)piperidin-4-one (NW-B591)



A suspension of (1*E*,4*E*)-1,5-di(pyridin-4-yl)penta-1,4-dien-3-one (1 g, 3.2 mmol) in DMF (10 mL) was treated with *N*-methylamine (40 % in H_2O, 2.8 mL, 32 mmol) at 0 °C. The solution was warmed up to ambient temperature and stirred for 6 h at RT. The reaction mixture was poured into ice-water and the resulting precipitate was filtered. The aqueous solution was extracted with DCM and the combined organic layers were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash-chromatography (CH_2Cl_2/MeOH 9:1) to obtain **NW-B591** as a bright yellow solid (417 mg, 48 %) (note: mixture of *cis/trans* isomers in a ratio of 4:1). mp: 103-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.65 (dd, ^4J= 4.5 Hz, ^3J= 1.5 Hz, 4 H, H_{Ar}), 7.42 (dd, ^3J= 4.5 Hz, ^4J= 1.6 Hz, 4 H, H_{Ar}), 3.51 (dd, ^3J= 12.0 Hz, J= 3.2 Hz, 2 H, C$\underline{H}_2$), 2.82-2.68 (m, 2 H, C$\underline{H}$), 2.57-2.46 (m, 2 H, C$\underline{H}_2$), 1.89 (s, 3 H, CH_3). Signals of the minor isomer: 8.65-8.60 (m, 4 H, H_{Ar}), 7.25 (dd, ^3J= 4.7 Hz, ^4J= 1.5 Hz, 4 H, H_{Ar}), 4.13 (t, ^3J= 6.0 Hz, 2 H, C$\underline{H}$), 2.96-2.86 (m, 2 H, C$\underline{H}_2$), 2.86 (ddd, J= 7.9, J= 6.0 Hz, J= 1.2 Hz, 2 H, C$\underline{H}_2$), 2.19 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 204.3 (C), 151.6 (C), 150.4 (C$\underline{H}$), 122.2 (C$\underline{H}$), 68.9 (C$\underline{H}$), 49.6 (C$\underline{H}_2$), 41.1 (C$\underline{H}_3$). Signals of the minor isomer: 206.6 (C), 150.8 (C$\underline{H}$), 148.7 (C), 123.0 (C$\underline{H}$), 61.8 (C$\underline{H}$), 43.3 (C$\underline{H}_2$), 38.2 (C$\underline{H}_3$). MS (FAB) m/z: 268.2 (M+). Anal. calcd for $C_{16}H_{17}N_3O \cdot 0.5H_2O$: C 69.54, H 6.57, N 15.21, found: C 69.43, H 6.49, N 14.94%.

1-Methyl-2,6-bis(4-(trifluoromethoxy)phenyl)piperidin-4-one (NW-B607)



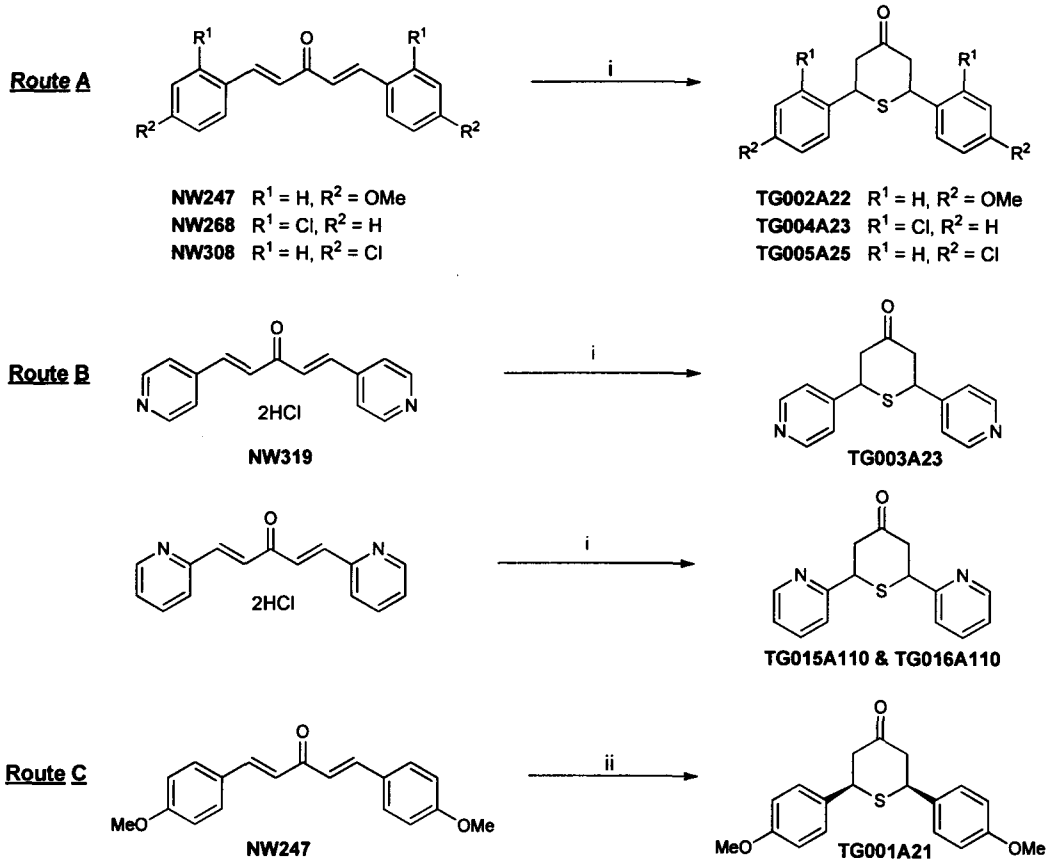
A suspension of (1*E*,4*E*)-1,5-di(pyridin-4-yl)penta-1,4-dien-3-one (1 g, 2.5 mmol) in DMF (10 mL) was treated with *N*-methylamine (40 % in H_2O, 2.4 mL, 25 mmol) at 0 °C. The solution was stirred for 1d at 0 °C. The reaction mixture was poured into ice-water (200 mL) and the aqueous solution was extracted with EtOAC and the combined organic layers were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The crude product was purified by flash-chromatography (Hexane/Et_2O 4:1) to obtain **NW-B607** as a brown syrup (123 mg, 11 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.49-7.34 (m, 4 H, H_{Ar}), 7.15 (d, ^3J= 8.2 Hz, 4 H, H_{Ar}), 3.51 (dd, ^3J= 9.4 Hz, 2 H, C$\underline{H}_2$), 2.78-2.61 (m, 2 H, C$\underline{H}$), 2.43 (d, ^3J= 13.5 Hz, 2 H, C$\underline{H}_2$), 1.75 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 205.9 (C), 148.7 (C), 141.6 (C), 128.4 (C$\underline{H}$), 121.5 (C$\underline{H}$), 120.5 (C$\underline{H}$, J= 253.7 Hz), 69.3 (C$\underline{H}$), 50.6 (CH_2), 40.8 (C$\underline{H}_3$). MS (FAB) m/z: 432.2 (M+). Anal. calcd for $C_{20}H_{17}F_6NO_3$: C 55.43, H 3.95, N 3.23, found: C 55.20, H 3.97, N 2.92%.

EXAMPLE 6: Synthesis of 2,6-diaryldihydro-*2H*-thiopyran-4-one and relative sulfur-oxidized species for their use as prodrugs of dibenzylidene acetones

With the goal to optimize the pharmacological properties of the dibenzylidene acetones, the synthesis and biological evaluation of 2,6-diaryldihydro-*2H*-thiopyran-4-one and relative sulfur-oxidized species has been considered.

At first, the synthesis of the 2,6-diaryldihydro-*2H*-thiopyran-4-one can be achieved through a double Michael addition of sulfur on the parent dibenzylidene acetones described in examples 1 and 2. This reaction occurred in basic conditions with the use of sodium hydrosulfide in aqueous (routes A and B) or organic media (route C) (Scheme 9).

Scheme 9 : Synthesis of 2,6-diaryldihydro-*2H*-thiopyran-4-one.



Reagents and conditions: (i) NaHS.xH2O 2-4 equiv, K2HPO4 1.2M, Acetone, 15-24 h, RT ; (ii) NaHS.xH2O 2-4 equiv, DCM, MeOH, piperidine, 2 h, reflux

Next, the effect of sulfur oxidation has been harvested. This implied the synthesis of sulfoxide and sulfone derivatives from the 2,6-diaryldihydro-*2H*-thiopyran-4-one described upper. Sulfone could be easily obtained from the over-oxidation of the sulfur atom with, for example, *meta*-chloroperbenzoic acid (m-CPBA) (scheme 10).

Scheme 10: Synthesis of sulfone derivatives

Regarding the synthesis of sulfoxide, several synthetic pathways have been studied. A stricly monitored amount of mCPBA might be used for the synthesis of these sulfoxides. However, we found that in our case, the risk of over-oxidation was too high; in addition, with this kind of methodology the stereocontrol of the reaction was very limited. Thus, it is preferable to use some more controlled and less drastic conditions. These include, but are not limited to, the use of hydroperoxide (tert-butylhydroperoxide or preferentially cumyl hydroperoxide) in presence of metal complex (titanium(IV) or vanadium(V)) and eventually (but not necessarily) a chiral modifier –such as enantiopure diethyl tartrate or BINOL derivatives.

The detailed syntheses of all these sulfur and oxidized sulfur derivatives are disclosed hereunder.

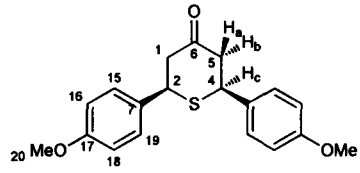
General procedure i (Routes A and B)

Sodium hydrosulfide hydrate (115 mg, 2eq) was dissolved in a mixture of a 1.2 M aqueous solution of potassium phosphate dibasic (2 mL) and acetone (4 mL). To this was added the appropriate dibenzylidene acetone (for example **NW247** (220 mg, 0.75 mmol)). The reaction mixture was strirred at room temperature for 15 h to 24 h (until completion upon TLC). Water (10 mL) was subsequently added to precipitate the desired product. The suspension was filtered and the crude was dried *in vacuo* and, if necessary, recrystallized to give the final compound.

General procedure ii (Routes C)

Sodium hydrosulfide hydrate (1.0 g, 2eq) was dissolved in methanol (25 mL). To this was added the appropriate dibenzylidene acetone (for example **NW247** (2.0 g, 6.79 mmol)) solubilized in dichloromethane (25 mL). The resulting solution was refluxing for 2 hours under vigorous stirring. The reaction mixture was then poured in a 1M aqueous solution of hydrochloric acid (20 mL) and extracted with dichloromethane (3x25 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to dryness to give crude product which can be recrystallized (for example in acetonitrile) to give the final pure compound.

cis-2,6-bis(4-methoxyphenyl)dihydro-2*H*-thiopyran-4(3*H*)-one (TG001A21)



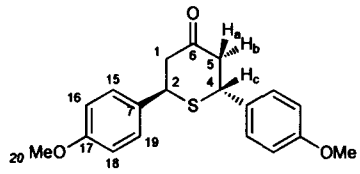
According to general procedure ii, desired pure product **TG001A21** was obtained as a white powder (1,7 g, 77%, de>90%). mp: 166-169°C

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.32 (d, ^3J = 8.9 Hz, 4H, Ar<u>H</u>), 6.9 (d, ^3J = 8.6 Hz, 4H, Ar<u>H</u>), 4.28 (dd, J = 11.8 Hz, 3.3 Hz, 2H, H_c), 3.81 (s, 6H, OC<u>H</u>$_3$), 3.17-2.98 (m, 4H, H_a/H_b)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 208.3 (<u>C</u>6=O), 159.3 (C17), 131.6 (C7), 128.3 (C15-C19), 114.2 (C16-C18), 55.5 (-O<u>C</u>H$_3$), 50.8 (C1-C5), 47.9 (C2-C4)

MS(FAB+) : m/z = 329.1

trans-2,6-bis(4-methoxyphenyl)dihydro-2*H*-thiopyran-4(3*H*)-one (TG002A22)



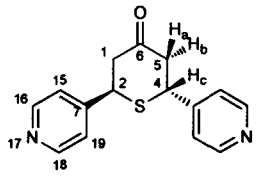
According to general procedure i, desired pure product **TG002A22** was obtained as a white powder (510 mg, 78%, de>90%). mp: 144-147°C

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.28 (d, ^3J = 7.8 Hz, 4H, Ar<u>H</u>), 6.87 (d, ^3J = 7.8 Hz, 4H, Ar<u>H</u>), 4.30 (m, 2H, H_c), 3.81 (s, 6H, OC<u>H</u>$_3$), 3.17-2.98 (m, 4H, H_a/H_b)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 209.1 (C6=O), 159.1 (C17), 132.6 (C7), 128.8 (C15-C19), 114.2 (C16-C18), 55.5 (-OCH$_3$), 49.0 (C1-C5), 43.5 (C2-C4)

MS(FAB+) : m/z = 329.1

***trans*-2,6-di(pyridin-4-yl)dihydro-*2H*-thiopyran-4(*3H*)-one (TG003A23)**



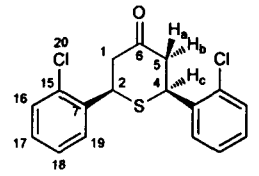
According to general procedure i, desired pure product **TG003A23** was obtained as a white powder (80 mg, 39%, de≈80%). mp: 127-129°C

^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.52 (d, ^3J = 5.6 Hz, 4H, ArH), 7.49 (d, ^3J = 5.6 Hz, 4H, ArH), 4.4 (m, 2H, H_c), 2.5-2.0 (m, 4H, H_a/H_b)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 200.1 (C=O), 150.0 (C7), 149.8 (C16-C18), 122.5 (C15-C19), 45.0 (C1-C5), 44.3 (C2-C4)

MS(EI+) : m/z = 270.1

***cis*-2,6-bis(2-chlorophenyl)dihydro-*2H*-thiopyran-4(*3H*)-one (TG004A23)**



According to general procedure i, desired pure product **TG004A23** was obtained as a white powder (180 mg, 72%, de = 60%). mp: 91-94°C

^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.55 (d, ^3J = 7.6 Hz, 2H, Ar), 7.41 (t, ^3J = 8.6 Hz, 2H, Ar), 7.35-7.25 (m, 4H, Ar), 4.89 (dd, J = 10.9 Hz, 3.6 Hz, 2H, H_c), 3.15-2.9 (m, 4H, H_a/H_b)

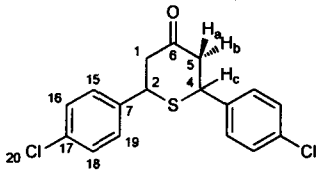
Signals of the minor diastereoisomer : 7.55 (d, ^3J = 7.6 Hz, 2H, Ar), 7.41 (t, ^3J = 8.6 Hz, 2H, Ar), 7.35-7.25 (m, 4H, Ar), 4.82 (t, J = 6.6 Hz, 2H, H_c), 3.15-2.9 (m, 4H, H_a/H_b)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 206.1 (C=O), 136.8 (C7), 132.3 (C15), 129.8 (CH), 129.6 (CH), 128.5 (CH), 127.9 (CH), 48.3 (C1-C5), 42.8 (C2-C4)

MS(FAB+) : m/z = 337.0

Anal. calcd for $C_{17}H_{14}Cl_2OS$ C 60.54, H 4.18, S 9.30, Cl 20.87, found: C 60.52, H 4.23, S 9.30, Cl 20.87

2,6-bis(4-chlorophenyl)dihydro-*2H*-thiopyran-4(*3H*)-one (TG005A25)



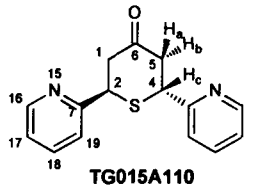
According to general procedure i, desired pure product **TG005A25** was obtained as a white powder (219 mg, 87%, de = 0%). mp: 131-133°C

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37-7.27 (m, 8H, Ar), 4.32 (bd, J = 4.5 Hz, 2H, H_c *cis*), 4.28 (bm, 2H, H_c *trans*), 3.2-2.9 (m, 4H, H_a/H_b *cis/trans*)

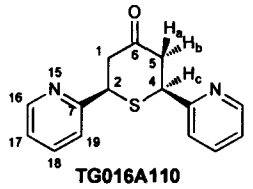
^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): signal for the *cis* isomer: 206.9 (C6=O), 137.7 (C7), 134.1 (C17), 129.2 (C15-C19), 128.6 (C16-C18), 50.3 (C1-C5), 47,8 (C2-C4) signal for the *trans* isomer: 207.6 (C6=O), 138.6 (C7), 133.6 (C17), 128.9 (C15-C19), 128.8 (C16-C18), 48.4 (C1-C5), 43,4 (C2-C4)

MS(EI) : m/z = 337.0

***trans*-2,6-di(pyridin-2-yl)dihydro-*2H*-thiopyran-4(*3H*)-one (TG015A110) and *cis*-2,6-di(pyridin-2-yl)dihydro-*2H*-thiopyran-4(*3H*)-one (TG016A110)**



TG015A110



TG016A110

According to general procedure i, these two product were isolated and purified after a flash chromatography (SiO_2, ethyl acetate/cyclohexane 1:1) to give desired pure diastereoisomer *trans* **TG015A110** (608 mg, 47%, de = 100%) and pure diastereoisomer *cis* **TG016A110** (225 mg, 17%, de = 100%), booth as a white powder.

NMR analysis for the *trans* isomer **TG015A110**:

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.54 (d, ^3J = 4.2 Hz, 2H, H16), 7.64 (dt, J_t = 7.7 Hz, J_d = 1.8 Hz, 2H, H18), 7.26 (m, 2H, H19), 7.19 (m, 2H, H17), 4.59 (m, 2H, H_c), 3.10 (m, 4H, H_a/H_b)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 206.9 (C6=O), 159.8 (C7), 149.1 (C16), 136.9 (C18), 122.4-122.2 (C19/C17), 47.0 (C1-C5), 45.6 (C2-C4)

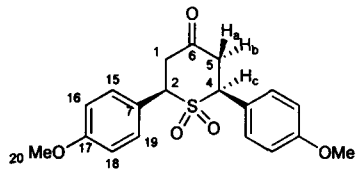
NMR analysis for the *cis* isomer **TG016A110**:

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.59 (d, ^3J = 4.8 Hz, 2H, H16), 7.68 (dt, J_t = 7.7 Hz, J_d = 1.8 Hz, 2H, H18), 7.37 (m, 2H, H19), 7.20 (m, 2H, H17), 4.54 (dd, $^3J_{Hc\text{-}Ha}$ = 12.3 Hz, $^3J_{Hc\text{-}Hb}$ = 2.6 Hz, 2H, H_c), 3.36-3.21 (m, 2H, H_a), 3.02 (dd, $^2J_{Hb\text{-}Ha}$ = 14.2 Hz, $^3J_{Hb\text{-}Hc}$ = 2.6 Hz, 2H, H_b)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 208.3 (C6=O), 157.9 (C7), 149.7 (C16), 137.0 (C18), 122.9-122.3 (C19/C17), 49.7 (C2-C4), 48.6 (C1-C5)

MS(EI): m/z = 270.1

cis-2,6-bis(4-methoxyphenyl)dihydro-2H-thiopyran-4(3H)-one 1,1-dioxide (TG014A103)



cis-2,6-bis(4-methoxyphenyl)dihydro-*2H*-thiopyran-4(*3H*)-one (**TG001A21**) (329 mg, 1 mmol) was dissolved in dichloromethane (4 mL). This solution was cooled to 0°C and a solution of mCPBA (382 mg, 2.2 mmol) in dichloromethane (3 mL) was added dropwise. The reaction was kept at 0°C under stirring for 1h30 and next allowed to warm at room temperature. Reaction was carried on at RT for another one hour and half. The reaction mixture was evaporated to dryness and the residue was dissolved in ethyl acetate (20 mL). This organic phase was washed successively with saturated $Na_2S_2O_3$ (10 mL), saturated sodium hydrogencarbonate (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to give crude product which was purified by flash chromatography (SiO_2, ethyl acetate/cyclohexane 1:1) to give the desired final compound **TG014A103** (115 mg, 32%, de = 80%) as a white powder.

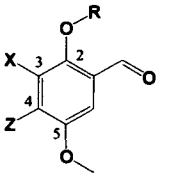
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35 (d, ^3J = 9.1 Hz, 4H, ArH), 6.9 (d, ^3J = 9.1 Hz, 4H, ArH), 4.47 (dd, $^3J_{Hc\text{-}Ha}$ = 14.2 Hz, $^3J_{Hc\text{-}Hb}$ = 2.4 Hz, 2H, H_c), 3.81 (s, 6H, OCH_3), 3.68 (t, $J_{Ha\text{-}(Hc/Hb)}$ = 14.2 Hz, 2H, H_a), 2.93 (bd, $^2J_{Hb\text{-}Ha}$ = 14.2 Hz, 2H, H_b)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 202.5 (C6=O), 160.9 (C17), 130.9 (C15-C19), 120.5 (C7), 114.7 (C16-C18), 64.0 (C2-C4), 55.5 (-OCH_3), 46.2 (C1-C5)

MS(EI) : m/z = 360.1

EXAMPLE 7: Synthesis of the primary starting materials for the synthesis of dibenzylidene acetones and relative derivatives

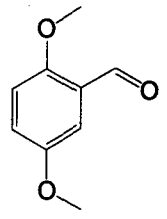
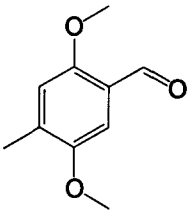
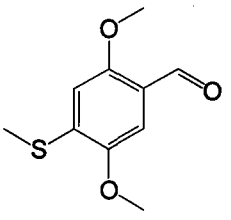
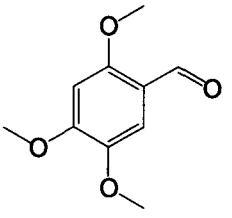
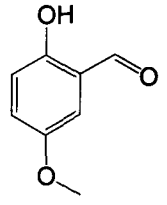
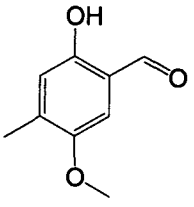
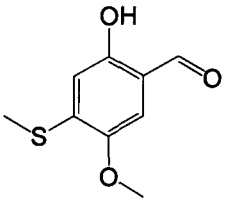
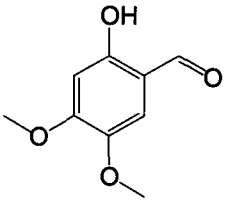
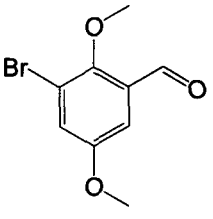
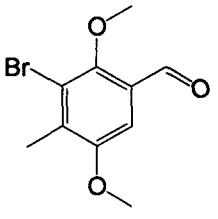
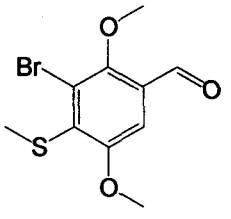
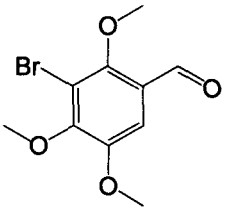
The diversity on the dibenzylidene acetones can be obtaine with the use of highly substituted salicaldehyde of the following general structure

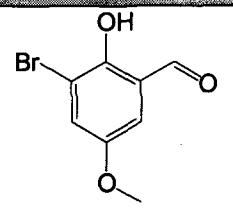
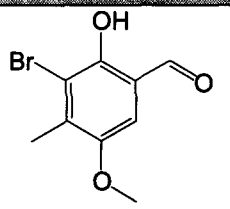
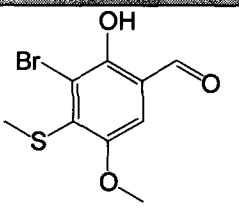
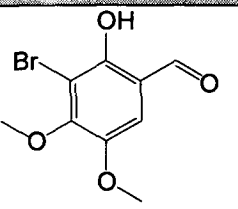


R = H, Me
X = H, Br
Z = H, Me, OMe, SMe

For examples from those disclosed in table II.

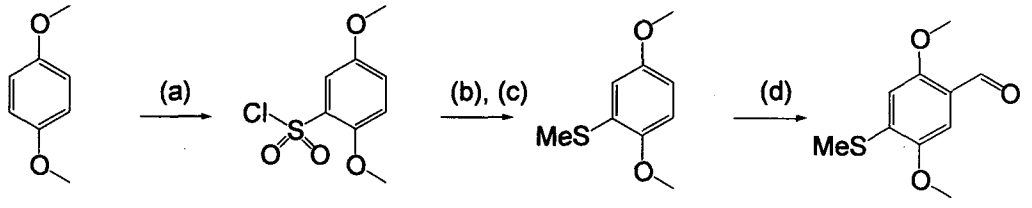
Table II:

4-Z = Me	4-Z = Me	4-Z = SMe	4-Z = OMe
			
			
			

4-Z = Me	4-Z = Me	4-Z = SMe	4-Z = OMe
			

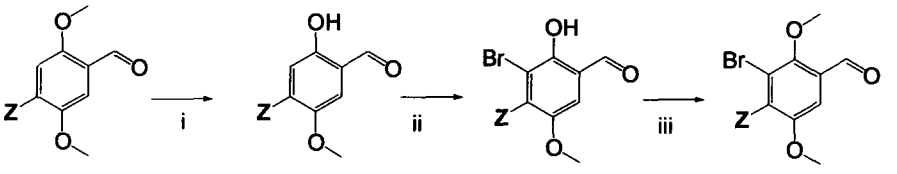
Some of the starting compounds of table 2 are commercially available or they may be synthesised according to Scheme 12 from the 4-thiomethyl salicaldehyde (Scheme 11) as starting material made according to previously described synthesis (Gallardo-Godoy et al., *J. Med. Chem.* 2005, *48*, 2407–2419).

Scheme 11: Synthesis of the 4-thiomethyl salicaldehyde as starting material for substituted salicaldehydes (Z = SMe).



Reagents and conditions : (a) $ClSO_3H$, CH_2Cl_2 ; (b) Zn, H_2O, CH_2Cl_2 ; (c) MeI, MeOH, NaOH ; (d) $POCl_3$, PhN(Me)CHO

Scheme 12: Synthesis of substituted salicaldehydes



Z = H, Me, OMe, SMe

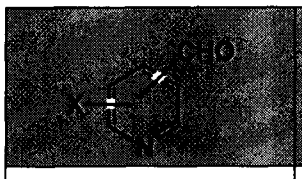
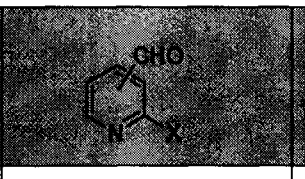
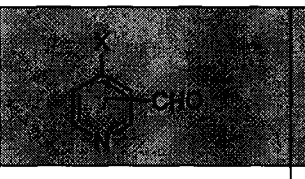
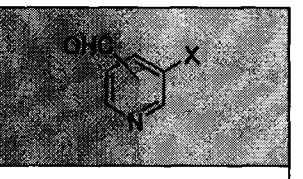
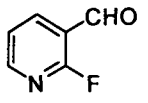
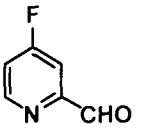
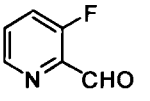
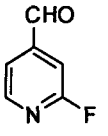
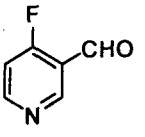
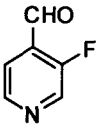
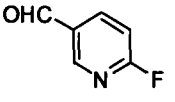
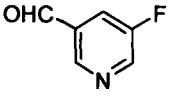
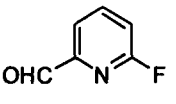
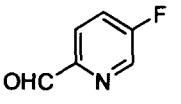
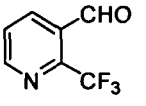
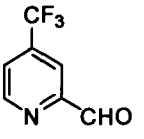
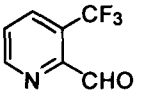
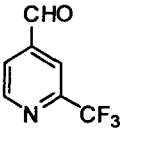
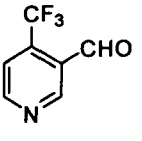
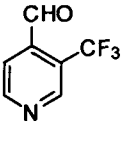
Reagents and conditions : (i) $AlCl_3$, MeCN, NaI, reflux, 1-2h ; (ii) Br_2, AcOH, NaOAc, 1-2h, RT ; (iii) Me_2SO_4, CH_2Cl_2, Aliquat 336 (5% mol), $NaOH/H_2O$, 1h, RT.

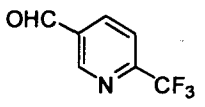
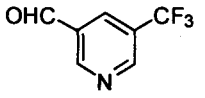
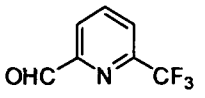
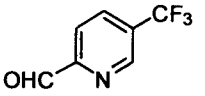
The starting aldehydes were submitted to selective demethylation conditions (*step i*) which produced the corresponding salicaldehydes in very high yields. The resulting phenol group afforded a total regiocontrol during bromination step (*step ii*). Therefore, standard bromination conditions (bromine in acetic acid) gave bromosalicaldehydes as a single isomer

and in very high yield. During the last step (*step iii*), phenol group was methylated under biphasic conditions with the use of Aliquat® 336 (commercial quaternary ammonium salt). Once again, the obtained yields were high.

As described in Example 2, heterocycles was considered with a great interest. In order to optimize the biological properties, it might be interesting to use some fluorinated pyridines. For examples from those disclosed in table III.

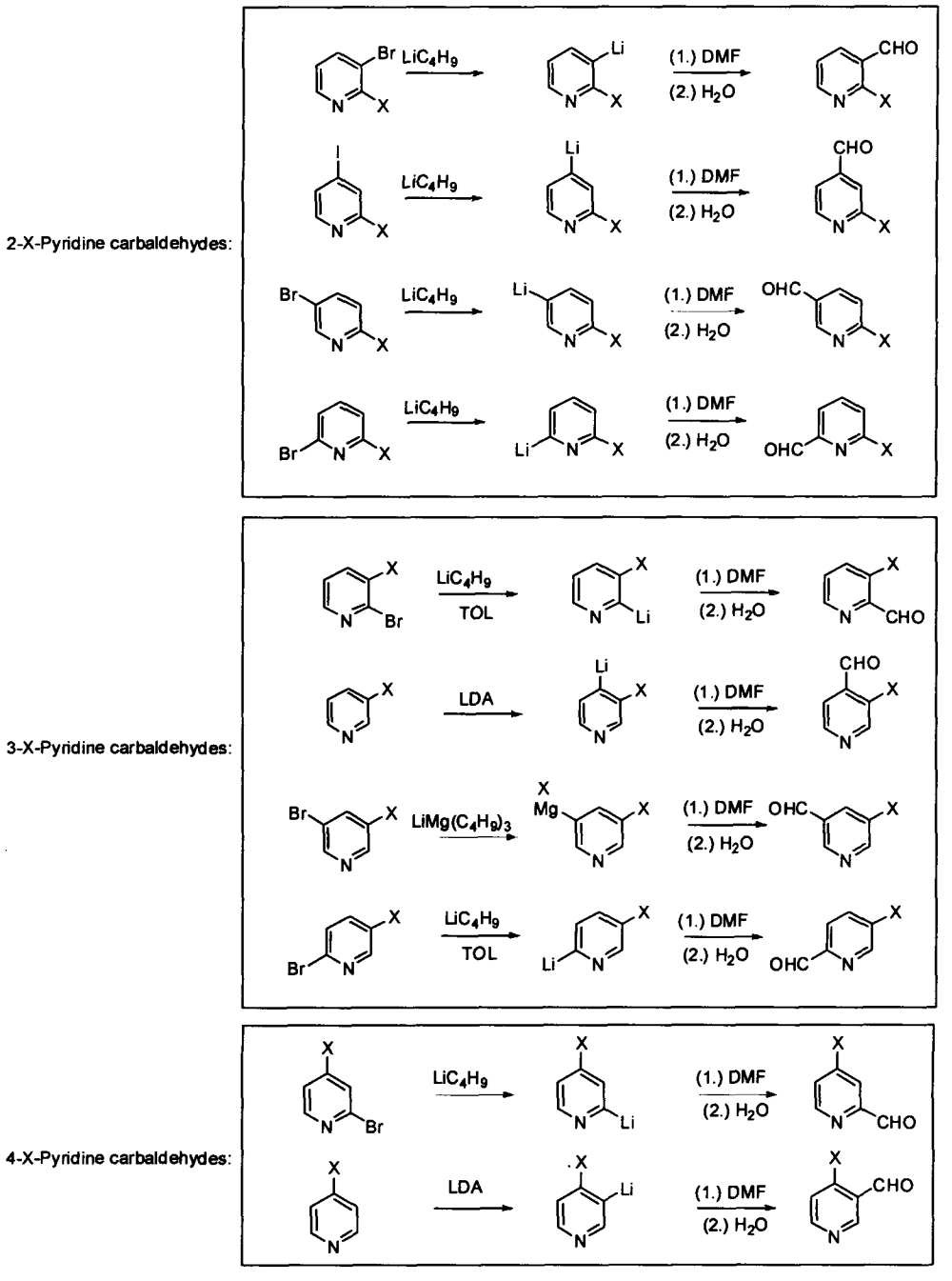
Table III : Fluorinated pyridine carbaldehydes

			
X = F			
X = F			
X = F			
X = F			
X = CF_3			
X = CF_3			

$X = CF_3$			
$X = CF_3$			

Among the possible synthtetic pathways for the obtening of these substrates, the following syntheses might be applied (Scheme 12).

Scheme 12: Synthesis of fluorine-based heteroaryl aldehydes.



EXAMPLE 8: Antikinetoplasticidal activities in human and cattle models evaluated from a primary screening *in vitro*

8.1. Material and methods for *in vitro* Antiparasitic Bioassays used in the Primary Inhibitor Screening

The *Leishmania infantum* MHOM/MA (BE)/67 strain is used. The strain is maintained in the Golden Hamster and spleen amastigotes are collected for preparing infection inocula. Primary peritoneal mouse macrophages are used as host cell and are collected 2 d after peritoneal stimulation with a 2 % potato starch suspension. Assays are performed in 96-well microtiter plates, each well containing 10 µl of the compound dilutions together with 190 µl of macrophage/parasite inoculum ($3 \cdot 10^5$ cells ± $3 \cdot 10^6$ parasites/well // RPMI-1640 + 5 % FCSi). After 5 d incubation, parasite burdens (mean number of amastigotes/macrophage) are microscopically assessed after Giemsa staining. The results are expressed as % reduction in parasite burden compared to untreated control wells and an IC_{50} (50 % inhibitory concentration) is calculated. In the primary evaluation, the compounds are tested at 5 concentrations (64 - 16 - 4 - 1 and 0.25 µM or µg/mL). Pentostam® (IC_{50} = 6.8 ± 0.9 µM) and miltefosine (IC_{50} = 5.2 ± 0.8 µM) are included as the reference drug. A compound is classified as inactive when the IC_{50} is higher than 16 µg/ml or µM. When the IC_{50} is lower than 1 µg/ml or µM, the compound is classified as active and is further evaluated in a secondary screening, which involves the *L. donovani* MHOM/ET/67/L82 and *L. infantum* strains over an extended dose range (2- fold compound dilutions).

The *Trypanosoma brucei brucei* Squib 427 strain (suramin- sensitive) is used. The strain is maintained in Hirumi (HMI-9) medium, supplemented with 10 % FCSi. Assays are performed in 96-well microtiter plates, each well containing 10 µl of the compound dilutions together with 190 µl of the parasite suspension ($7 \cdot 10^4$ parasites/ml). After 3 d incubation, parasite growth is assessed fluorimetrically after addition of resazurin. After 24 h at 37 °C, fluorescence is measured (λ_{ex} 550 nm, λ_{em} 590 nm). The results are expressed as % reduction in parasite growth/viability compared to control wells and an IC_{50} (50 % inhibitory concentration) is calculated. Compounds are tested at 5 concentrations (64 - 16 - 4 - 1 and 0.25 µM or mg/ml). Suramin is included as the reference drug (IC_{50} = 0.12 ± 0.07 µM). When the IC_{50} is lower than 1 µg/ml or µM, the compound is classified as active and is further evaluated in a secondary screening, which involves an extended dose range (2- fold compound dilutions), additional references (suramin, pentamidine, melarsoprol) and species (*T. b. rhodesiense* or *T. b. gambiense*).

Trypanosoma cruzi, Tulahuen CL2, β galactosidase strain (nifurtimox- sensitive) is used. The strain is maintained on MRC-5_{SV2} (human lung fibroblast) cells in MEM medium, supplemented with 200 mM L- glutamine, 16.5 mM $NaHCO_3$, and 5 % FCSi. All cultures and assays are conducted at 37 °C under an atmosphere of 5 % CO_2. Assays are performed in sterile 96-well microtiter plates, each well containing 10 µl of the watery compound dilutions together with 190 µl of MRC-5 cell/parasite inoculum ($2 \cdot 10^4$ cells/ml ± $2 \cdot 10^5$ parasites/ml). Parasite growth is compared to untreated-infected controls (100 % growth) and non- infected controls (0 % growth) after 7 d incubation. Parasite burdens are assessed after adding the substrate CPRG (chlorophenolred ß-D-galactopyranoside): 50 µl/well of a stock solution containing 15.2 mg CPRG + 250 µl Nonidet in 100 ml PBS. The change in color is measured spectrophotometrically at 540 nm after 4 h incubation at 37 °C. The results are expressed as % reduction in parasite burdens compared to control wells and an IC_{50} is calculated. Compounds are tested at 5 concentrations (64 - 16 - 4 - 1 and 0.25 µM or mg/ml). Nifurtimox (IC_{50} = 0.845 ± 0.2 µM) is included as reference drug. When the IC_{50} is lower than 1 µg/ml or µM, the compound is classified as active on the condition that it also demonstrates selective action (absence of cytotoxicity).

8.2. Evaluation of the Cytotoxicity against Human Cell Lines

MRC-5_{SV2} cells are cultured in Earl's MEM + 5 % FCSi. Other cell types (J774, L6, Vero, Hela, e.a.) may also be used for determination of cytotoxicity/selectivity. Assays are performed in 96-well microtiter plates, each well containing about 10^4 cells/well. After 3 d of incubation, cell viability is assessed fluorimetrically after addition of resazurin and fluorescence is measurement (λ_{ex} 550 nm, λ_{em} 590 nm). The results are expressed as % reduction in cell growth/viability compared to untreated control wells and an IC_{50} is determined. Compounds are tested at 5 concentrations (64 - 16 - 4 - 1 and 0.25 µM or mg/ml). When the IC_{50} is lower than 4 µg/ml or µM, the compound is classified as toxic. Cytotoxic reference compounds include vinblastine or paclitaxel (IC_{50} <0.01 µM), but these are rarely included because of health hazards for laboratory personnel. Alternatives are, for example, niclosamide and invermectin.

8.3. Results

The antikinetoplastidal activities expressed as IC_{50} values in µM against different parasites (*T. brucei*, *L. infantum* and *T. cruzi*) are given in Tables 1 to 6.

The biological activities against the parasites of:

- the symmetrical dibenzylidene acetone intermediates needed for preparing the 4-piperidones are shown in Tables 1 to 2,
- the asymmetrical dibenzylidene acetone intermediates are shown in Table 3,
- the symmetrical conjugated symmetrical dibenzylidene acetone and the diheteroarylidene acetone intermediates needed for preparing the 4-piperidones are shown in Table 4,
- the symmetrical 2,6-diaryl-4-piperidones and 2,6-diheteroaryl-4-piperidones are shown in Table 5,
- some selected dibenzylidene acetone intermediates and symmetrical 2,6-diaryl-4-piperidones in repeated bioassays, in comparison with known drugs from the market, are shown in Table 6.

The symmetrical dibenzylidene acetone intermediates required for the preparation of the symmetrical 4-piperidones were screened for activity against *T. brucei*, *T. cruzi* and *L. infantum* strains and for cytotoxicity against mammalian cells (human lung fibroblasts MRC-5, mouse macrophages) and the results are shown in Table 1-2. Most of the synthesized compounds displayed potent trypanocidal activity against *T. brucei* and *T. cruzi*, whereas some of them even showed a very low toxicity against mammalian (MRC-5) cells.

Due to the excellent antitrypanosomal activities of **NW267** and **NW254** bearing $-CF_3$ and $-OCF_3$ groups in *para*-position to the enone without any toxicity against mammalian (MRC-5) cells and mouse macrophages, a new series of compounds **NW307.2**, **NW308**, **NW310.1**, **NW300**, **NW317** and **NW324.2**, **NW326.4**, **NW327.2**, **NW331** was prepared and tested against the parasites. The antikinetoplastidal activities expressed as IC_{50} values in μM against different parasites (*T. brucei*, *L. infantum* and *T. cruzi*) are shown in Table 2.

Most of the newly synthesized compounds showed high trypanocidal activity against *T. brucei* and low toxicity against mammalian (MRC-5) cells but high toxicity against mouse macrophages. The compound **NW300** bearing the substitution pattern of curcumin marked excellent antitrypanosomal activity against *T. brucei* but also very high cytotoxicity against mammalian (MRC-5) cells. Curcumin was previously reported to inhibit the growth of mammalian tumor cells *in vitro*. Recent studies have revealed that it is a potent anti-oxidant and an antiparasitic agent showing trypanocidal and leishmanicidal activity. Curcumin was reported to display 10 times stronger cytotoxicity against bloodstream forms of *T. brucei* than against procyclic forms. The LD_{50} values against both protozoa (leishmania and trypanosomes) turned out to be similar (37.6±3.5 μM for promastigotes of *L. major* and

46.5±4.9 µM for procyclic forms of *T. b. brucei*). The synthesis of the curcuminoid analogues where the electron-donating methoxy group was replaced by electron-withdrawing groups (e.g. CF_3 and OCF_3) resulted in a decrease of the cytotoxicity whereas the antitrypanosomal activity against *T. brucei* remained constant. Compound **NW307.2** possessing a –CN group in *para*-position to the enone turned out to be a promising candidate as antitrypanosomal agent with excellent activity against *T. brucei* and *T. cruzi* and without any cytotoxicity.

Some asymmetrical dibenzylidene acetones (Table 3) were prepared and shown to exert a high trypanocidal activity against *T. brucei* and low toxicity against mammalian (MRC-5) cells.

The three compounds, **BJ621**, **NW319** and **NW321** (Table 4) containing a heteroatom in the aromatic ring in *ortho*- or *meta*- or *para*-position to the enone showed excellent trypanocidal activity against *T. brucei* and *T. cruzi* but also high cytotoxicity against the human lung cell line (MRC-5). The position of the nitrogen atom in the ring affected the trypanocidal activity both *in vitro* and *in vivo*. The prolongation of the linker in compound **NW312** resulted in the complete loss of trypanocidal activity against the different parasites (Table 2).

The fact that the 4-piperidone **NW249.1** (Table 6) of the corresponding dibenzylidene acetone **NW275** marked also high trypanocidal activity against *T. brucei* with low toxicity against mammalian (MRC-5) cells and without any toxicity against mouse macrophages (*L. inf.*) compared to **NW275** allowed the following conclusion: the protection of the reactive motif of the divinylketone might decrease the toxicity against mammalian (MRC-5) cells and against mouse macrophages. Another example of this prodrug effect could be illustrated with the symmetrical 2,6-diheteroaryl-4-piperidone **BJ591** and the 2,6-diheteroaryl-4-thiopyranone **TG003A23** (Table 5) which maintained high antikinetoplastidal activity but showed much less cytotoxicity against mammalian (MRC-5) cells and against mouse macrophages (*L. inf.*) compared to the parent 2,6-diheteroaryl acetone **NW319** (Table 4).

Some selected dibenzylidene acetone intermediates and symmetrical 2,6-diaryl-4-piperidones or 2,6-diaryl-4-thiopyranones were repeated in bioassays, in comparison with known drugs from the market; the results are shown in Tables 6 and 7.

EXAMPLE 9: Trypanocidal activities in vivo in *T. brucei*-infected mice

9.1. Material and methods

Animals: Swiss mice (female 18-20 g, Janvier, Le Genest St Isle, France) are randomly allocated to groups of 6 animals each. Drinking water and food are available *ad libitum* throughout the experiment (except when the treatment is given by oral route; in this condition, the treatment is given after 12 h of animal fasting).

Parasite: *Trypanosoma brucei brucei* CMP (fast strain) is maintained in the laboratory by mechanical intraperitoneal sub-passage every three days in Swiss mice. The infection inoculum is prepared by taking blood collected from a clinically ill donor mouse and diluted in pH 7.2 PBS to obtain an infection inoculum of about 10^5 trypanosomes/ml suspension. Mice are infected by intraperitoneal injection of 0.1 ml of parasite suspension (= 10^4 parasites).

Test substances: The reference compound is melarsoprol.

Test compounds are analyticaly pure compounds.

Formulations: The compounds are formulated in 100% DMSO. Clear solutions should be obtained. The stock solution is divided in aliquots and stored at -20°C until use. Aliquots are thawed immediately before treatment. The reference compound melarsoprol is formulated in PBS and stored at -20°C.

Treatment: The first dosing with the test compounds was given approx. 3 hours after artificial infection.

Melarsoprol (Arsobal®): 6 infected mice intraperitoneally treated with 1 mg/kg x 4 consecutive days.

Test compounds: 6 infected mice per AMTD x 1-5 consecutive days.

Controls: 10 infected mice receiving vehicle only (0.1-0.2 ml)

Evaluation parameters:

Parasitemia was checked microscopically from blood collected at the tail of the mice 2 days after the treatment, and every two days until 30 days post-treatment in case of survival. The trypanocidal activity was evaluated by the mean survival time of treated mice for each dose comparatively to survival time of mice treated with the vehicle alone. Treatment was considered to be successful when the mean survival time exceeds 30 days and the mice remains aparasitemic. Control mice (infected untreated) do not survive more than 4 days post-infection. Cure rate are expressed as percentages.

9.2. Results

The three dibenzylidene acetones **NW327.2**, and both pyridine derivatives **NW319** and **NW321** containing a heteroatom in the aromatic ring in *meta*- and *para*-position to the enone showed excellent trypanocidal activity (0% parasitemia) in *T. brucei*-infected mice when administered in one single dose at 50 mg/kg i.p. When administrated in two doses over a two days-period an excellent trypanocidal activity (0% parasitemia) in *T. brucei*-infected mice was observed at:

- 25 mg/kg i.p. for compound **NW327.2**,
- 12.5 mg/kg i.p. for compound **NW319**.