[19]	INTELLECTUAL PROPERTY PHILIPPINES			
[12]	INVENTION PUBLICATION			
[11]	Publication Number:	12014502588	Document Code:	B1
[22]	Publication Date:	9/2/2015		
[21]	Application Number:	12014502588	Document Code:	A
[22]	Date Filed:	20/11/2014		
[54]	Title:	CATECHOL O-METHYLTRANSFERASE ACTIVITY INHIBITING COMPOUNDS		
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[30]	Priority Data:	12/3/2013 US201361777162P		
[51]	International Class 8:	A61K 31/277 20060101AFI20180625BHPH; A61P 25/00 20060101ALI20180625BHPH; C07C 255/53 20060101ALI20180625BHPH; C07C 255/54 20060101ALI20180625BHPH; C07C 255/57 20060101ALI20180625BHPH; C07C 311/29 20060101ALI20180625BHPH; C07D 277/30 20060101ALI20180625BHPH; C07D 333/24 20060101ALI20180625BHPH; C07D 333/60 20060101ALI20180625BHPH; C07C 317/22 20060101ALI20180625BHPH; C07C 321/28 20060101ALI20180625BHPH; C07C 321/30 20060101ALI20180625BHPH; C07D 207/08 20060101ALI20180625BHPH; C07D 207/337 20060101ALI20180625BHPH; C07D 265/30 20060101ALI20180625BHPH;		
[57]	Abstract:	Compounds of formula (I), wherein R1 is as defined in the claims, exhibit COMT enzyme inhibiting activity and are thus useful as COMT inhibitors.		

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is $(C_2\text{-}C_6)$alkenyl, aryl-S- or aryl$(C_1\text{-}C_6)$alkyl, wherein said aryl as part of another group is substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein R_1 is $(C_2\text{-}C_6)$alkenyl.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is aryl, wherein said aryl is unsubstituted or substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is aryl-S-, wherein said aryl is unsubstituted or substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is heteroaryl, wherein said heteroaryl is unsubstituted or substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is aryl$(C_1\text{-}C_6)$alkyl, wherein said aryl is substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein the compound is 2-bromo-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(phenylethynyl)isophthalonitrile, 4,5-dihydroxy-2-(prop-1-ynyl)isophthalonitrile, 4,5-dihydroxy-2-(1-methyl-1H-pyrrol-2-yl)isophthalonitrile, 4,5-dihydroxy-2-(thiophen-2-yl)isophthalonitrile, 2-(furan-2-yl)-4,5-dihydroxyisophthalonitrile, 3',4',5'-trifluoro-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 4,5-dihydroxy-2-(naphthalen-1-yl)isophthalonitrile, 4'-tert-butyl-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-4'-(hydroxymethyl)biphenyl-2,6-dicarbonitrile, 4,5-dihydroxy-2-(naphthalen-2-yl)isophthalonitrile, 3,4-dihydroxy-4'-(isopropylthio)biphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-4'-(methylthio)biphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-4'-isopropoxybiphenyl-2,6-dicarbonitrile, 4'-(ethylthio)-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-4'-isopropoxy-3',5'-dimethylbiphenyl-2,6-dicarbonitrile, 4'-butyl-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-2',4',5'-trimethylbiphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-2',5'-dimethylbiphenyl-2,6-dicarbonitrile, 2-cyclohexenyl-4,5-dihydroxyisophthalonitrile, 3'-ethyl-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 3,4-dihydroxybiphenyl-2,4',6-tricarbonitrile, 3,4-dihydroxy-4'-(isopropylsulfonyl)biphenyl-2,6-dicarbonitrile, 2',6'-dicyano-3',4'-dihydroxy-N,N-dimethylbiphenyl-4-sulfonamide, (E)-4,5-dihydroxy-2-(pent-1-enyl)isophthalonitrile, 2',6'-dicyano-3',4'-dihydroxybiphenyl-3-carboxylic acid, 3,4-dihydroxy-4'-(1-methoxyethyl)biphenyl-2,6-dicarbonitrile, (E)-2-(3,3-dimethylbut-1-enyl)-4,5-dihydroxyisophthalonitrile, 3,4-dihydroxy-2'-methylbiphenyl-2,6-dicarbonitrile, (E)-2-(2-cyclohexylvinyl)-4,5-dihydroxyisophthalonitrile, (Z)-4,5-dihydroxy-2-(prop-1-enyl)isophthalonitrile, 3-(2',6'-dicyano-3',4'-dihydroxybiphenyl-4-yl)propanoic acid, 3,4-dihydroxy-3'-(hydroxymethyl)biphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-3'-(methoxymethyl)biphenyl-2,6-dicarbonitrile, 2',6'-dicyano-3',4'-dihydroxy-N,N-dipropylbiphenyl-4-carboxamide, (E)-4,5-dihydroxy-2-(prop-1-

enyl)isophthalonitrile, 3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 3',4'-dichloro-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-3'-(trifluoromethyl)biphenyl-2,6-dicarbonitrile, 2-(furan-3-yl)-4,5-dihydroxyisophthalonitrile, 3,4-dihydroxy-4'-(trifluoromethyl)biphenyl-2,6-dicarbonitrile, 4,5-dihydroxy-2-(thiophen-3-yl)isophthalonitrile, 4,5-dihydroxy-2-(5-methylfuran-2-yl)isophthalonitrile, 4,5-dihydroxy-2-(5-methylthiophen-2-yl)isophthalonitrile, 2-benzyl-4,5-dihydroxyisophthalonitrile, 2-(benzofuran-2-yl)-4,5-dihydroxyisophthalonitrile, 2-(5-chlorothiophen-2-yl)-4,5-dihydroxyisophthalonitrile, 2-(benzo[b]thiophen-2-yl)-4,5-dihydroxyisophthalonitrile, (E)-4,5-dihydroxy-2-styrylisophthalonitrile, 4'-ethyl-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-3',5'-dimethylbiphenyl-2,6-dicarbonitrile, 4,5-dihydroxy-2-(phenylthio)isophthalonitrile, 4,5-dihydroxy-2-(p-tolylthio)isophthalonitrile, 4,5-dihydroxy-2-(4-methylbenzyl)isophthalonitrile, 2-(4-fluorobenzyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(4-hydroxybenzyl)isophthalonitrile, 4,5-dihydroxy-2-(2-methoxybenzyl)isophthalonitrile, 4,5-dihydroxy-2-(4-(trifluoromethoxy)benzyl)isophthalonitrile, 2-(3-fluoro-4-methoxybenzyl)-4,5-dihydroxyisophthalonitrile, 2-(2-fluorobenzyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(2-methylbenzyl)isophthalonitrile, 2-(2,5-dimethylbenzyl)-4,5-dihydroxyisophthalonitrile, 2-(3-fluoro-5-methylbenzyl)-4,5-dihydroxyisophthalonitrile, 3-(2,6-dicyano-3,4-dihydroxybenzyl)benzoic acid, 2-(4-fluoro-3-methylbenzyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(3-methylbenzyl)isophthalonitrile, 2-(5-fluoro-2-methoxybenzyl)-4,5-dihydroxyisophthalonitrile, 2-(3,5-dimethylbenzyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(4-isopropylbenzyl)isophthalonitrile, 2-(4-ethylbenzyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(naphthalen-1-ylmethyl)isophthalonitrile, 5-(2,6-dicyano-3,4-dihydroxybenzyl)-2-hydroxybenzoic acid, 2-(2,4-dimethylbenzyl)-4,5-dihydroxyisophthalonitrile, 2-(3,6-dihydro-2H-pyran-4-yl)-4,5-dihydroxyisophthalonitrile, 2-cyclopentenyl-4,5-dihydroxyisophthalonitrile, (E)-3-(2,6-dicyano-3,4-dihydroxyphenyl)acrylic acid, (E)-4,5-dihydroxy-2-(3-methoxyprop-1-enyl)isophthalonitrile, 4,5-

dihydroxy-2-(5-(morpholinomethyl)thiophen-2-yl)isophthalonitrile, 3,4-dihydroxy-4'-(morpholine-4-carbonyl)biphenyl-2,6-dicarbonitrile, 2-(5'-hexyl-2,2'-bithiophen-5-yl)-4,5-dihydroxyisophthalonitrile, 2-(1-benzyl-1H-pyrazol-4-yl)-4,5-dihydroxyisophthalonitrile, 2-(5-hexylthiophen-2-yl)-4,5-dihydroxyisophthalonitrile, (Z)-2-(but-2-enyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(3-methylbut-2-enyl)isophthalonitrile, (E)-2-(but-2-enyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-methylisophthalonitrile, 4,5-dihydroxy-2-(2-methylprop-1-enyl)isophthalonitrile, 3,4-dihydroxy-3'-methylbiphenyl-2,6-dicarbonitrile, 4,5-dihydroxy-2-vinylisophthalonitrile, 4,5-dihydroxy-2-(prop-1-en-2-yl)isophthalonitrile, 2-(2-ethoxythiazol-5-yl)-4,5-dihydroxyisophthalonitrile, 2-allyl-4,5-dihydroxyisophthalonitrile, 3'-(tert-butoxymethyl)-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, tert-butyl 2',6'-dicyano-3',4'-dihydroxybiphenyl-3-carboxylate, 3,4-dihydroxybiphenyl-2,3',6-tricarbonitrile, 2',6'-dicyano-3',4'-dihydroxy-N,N-dipropylbiphenyl-3-carboxamide, 2',6'-dicyano-N-cyclohexyl-3',4'-dihydroxybiphenyl-4-carboxamide, 2',6'-dicyano-N-cyclohexyl-3',4'-dihydroxybiphenyl-3-carboxamide, 2',6'-dicyano-N,N-diethyl-3',4'-dihydroxybiphenyl-4-carboxamide, 2',6'-dicyano-N,N-diethyl-3',4'-dihydroxybiphenyl-3-carboxamide, 2',6'-dicyano-N-ethyl-3',4'-dihydroxybiphenyl-3-carboxamide, 2',6'-dicyano-3',4'-dihydroxy-N,N-dimethylbiphenyl-3-carboxamide, 4'-fluoro-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 3',4'-difluoro-3,4-dihydroxybiphenyl-2,6-dicarbonitrile, 4'-fluoro-3,3',4-trihydroxybiphenyl-2,6-dicarbonitrile, (E)-4,5-dihydroxy-2-(3-phenylprop-1-enyl)isophthalonitrile, 4'-fluoro-3,4-dihydroxy-3'-methoxybiphenyl-2,6-dicarbonitrile, 5-(2,6-dicyano-3,4-dihydroxyphenyl)thiophene-2-carboxylic acid, 3,4-dihydroxy-4'-(methylsulfonyl)biphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-4'-propoxybiphenyl-2,6-dicarbonitrile, 2',6'-dicyano-3',4'-dihydroxybiphenyl-4-carboxylic acid, 4'-chloro-3,4-dihydroxy-3'-methylbiphenyl-2,6-dicarbonitrile, 4,5-dihydroxy-2-(5-phenylthiophen-2-yl)isophthalonitrile, 3,4-dihydroxy-4'-isopropylbiphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-4'-propylbiphenyl-2,6-dicarbonitrile, 4,5-dihydroxy-2-(1-phenylvinyl)isophthalonitrile, 2',6'-dicyano-3',4'-

dihydroxybiphenyl-2-carboxylic acid, 4-(2,6-dicyano-3,4-dihydroxybenzyl)benzoic acid, (E)-4,5-dihydroxy-2-(4-methoxystyryl)isophthalonitrile, 3,4-dihydroxy-3',4'-dimethylbiphenyl-2,6-dicarbonitrile, (E)-4,5-dihydroxy-2-(4-methylstyryl)isophthalonitrile, 4,5-dihydroxy-2-(6-hydroxynaphthalen-2-yl)isophthalonitrile, 4'-fluoro-3,4-dihydroxy-3'-methylbiphenyl-2,6-dicarbonitrile, 4,5-dihydroxy-2-(3-methylbut-2-en-2-yl)isophthalonitrile, 2-(2,5-dimethylthiophen-3-yl)-4,5-dihydroxyisophthalonitrile, 2-(2,3-difluoro-4-methylbenzyl)-4,5-dihydroxyisophthalonitrile, 2-(4-(2,6-dicyano-3,4-dihydroxybenzyl)phenyl)propanoic acid, (E)-2-(3-cyclopentylprop-1-enyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(1-isobutyl-1H-pyrazol-4-yl)isophthalonitrile, 2-(4-(2,6-dicyano-3,4-dihydroxyphenyl)-1H-pyrazol-1-yl) acetic acid, 4,5-dihydroxy-2-(1-methyl-1H-pyrazol-4-yl)isophthalonitrile, 4,5-dihydroxy-2-(3-methoxyprop-1-ynyl)isophthalonitrile, (E)-4,5-dihydroxy-2-(2-(thiophen-3-yl)vinyl)isophthalonitrile, (E)-2-(2-cyclopropylvinyl)-4,5-dihydroxyisophthalonitrile, 2',6'-dicyano-3',4'-dihydroxybiphenyl-4-carboxamide, 3,4-dihydroxy-3',4'-dimethoxybiphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-3'-isopropylbiphenyl-2,6-dicarbonitrile, 2-(2,3-dihydrobenzofuran-5-yl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(6-methoxynaphthalen-2-yl)isophthalonitrile, 4,5-dihydroxy-2-(4-(hydroxymethyl)benzyl)isophthalonitrile, 2-(2,6-difluoro-3-methylbenzyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(4-(trifluoromethyl)phenylthio)isophthalonitrile, 2-(2,4-dimethylphenylthio)-4,5-dihydroxyisophthalonitrile, methyl 3-(4-(2,6-dicyano-3,4-dihydroxyphenylthio)phenyl)propanoate, 4,5-dihydroxy-2-(p-tolyloxy)isophthalonitrile, (E)-2-(2,4-difluorostyryl)-4,5-dihydroxyisophthalonitrile, (E)-4,5-dihydroxy-2-(3-(trifluoromethyl)styryl)isophthalonitrile, (E)-4,5-dihydroxy-2-(4-methylpent-1-enyl)isophthalonitrile, (E)-2-(3,5-difluorostyryl)-4,5-dihydroxyisophthalonitrile, 2-(4-(2,6-dicyano-3,4-dihydroxybenzyl)phenyl)acetic acid, 2-(4-chlorobenzyl)-4,5-dihydroxyisophthalonitrile, 3,4-dihydroxy-4'-methylbiphenyl-2,6-dicarbonitrile, 3-(4-(2,6-dicyano-3,4-dihydroxybenzyl)phenyl)propanoic acid,

4,5-dihydroxy-2-(4-(trifluoromethyl)benzyl)isophthalonitrile, (E)-4,5-dihydroxy-2-(4-(trifluoromethyl)styryl)isophthalonitrile, 4,5-dihydroxy-2-(p-tolylsulfinyl)isophthalonitrile, 4-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoic acid, 2-(4-ethylphenylthio)-4,5-dihydroxyisophthalonitrile, 2-(4-chlorophenylthio)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(o-tolylthio)isophthalonitrile, methyl 4-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoate, 2-(2-chlorophenylthio)-4,5-dihydroxyisophthalonitrile, methyl 2-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoate, 2-(4-(2,6-dicyano-3,4-dihydroxyphenylthio)phenyl)acetic acid, 2-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoic acid, 3-(4-(2,6-dicyano-3,4-dihydroxyphenylthio)phenyl)propanoic acid, 4,5-dihydroxy-2-(4-methoxyphenylthio)isophthalonitrile, methyl 2-(4-(2,6-dicyano-3,4-dihydroxybenzyl)phenyl)acetate, 4,5-dihydroxy-2-(3-methoxyphenylthio)isophthalonitrile, methyl 4-(2,6-dicyano-3,4-dihydroxyphenoxy)benzoate, 4,5-dihydroxy-2-(pyridin-4-ylthio)isophthalonitrile, 3-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoic acid, 2-(4-cyanophenylthio)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(naphthalen-2-ylthio)isophthalonitrile, 2-(4-(2,6-dicyano-3,4-dihydroxybenzyl)phenyl)-N,N-diethylacetamide, 2-(4-ethylphenoxy)-4,5-dihydroxyisophthalonitrile, 2-(4-acetylphenoxy)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(1-oxo-2,3-dihydro-1H-inden-5-yloxy)isophthalonitrile, 2-(2',6'-dicyano-3',4'-dihydroxybiphenyl-4-yl)acetic acid, 2-(2,4-dimethylphenoxy)-4,5-dihydroxyisophthalonitrile, 2-(4-chlorophenoxy)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(4-(trifluoromethyl)phenoxy)isophthalonitrile, 4,5-dihydroxy-2-(1H-inden-3-yl)isophthalonitrile, 4,5-dihydroxy-2-(morpholinomethyl)isophthalonitrile, 2-((diethylamino)methyl)-4,5-dihydroxyisophthalonitrile hydrochloride, 4,5-dihydroxy-2-(((2-hydroxyethyl)amino)methyl)isophthalonitrile hydrochloride (1:1), 4,5-dihydroxy-2-(3-hydroxypropyl)isophthalonitrile, 2-amino-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(pyrrolidin-1-yl)isophthalonitrile, 2-(2,6-dimethylmorpholino)-

4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-morpholinoisophthalonitrile, 4,5-dihydroxy-2-(isopropylamino)isophthalonitrile, 4,5-dihydroxy-2-(3-methoxypropylamino)isophthalonitrile, 2,4,5-trihydroxyisophthalonitrile, 2-ethyl-4,5-dihydroxyisophthalonitrile, 3,4-dihydroxy-4'-methoxybiphenyl-2,6-dicarbonitrile, 3,4-dihydroxy-3'-(morpholine-4-carbonyl)biphenyl-2,6-dicarbonitrile, N-butyl-2',6'-dicyano-3',4'-dihydroxybiphenyl-4-carboxamide, 2-(3,3-dimethylbutyl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(piperidin-1-yl)isophthalonitrile, 2-(hexylamino)-4,5-dihydroxyisophthalonitrile, 2-(cyclohexylamino)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(2-methoxyethylamino)isophthalonitrile, 2-(4-benzylpiperidin-1-yl)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(pentan-3-ylamino)isophthalonitrile, (E)-2-(4-ethylbenzylideneamino)-4,5-dihydroxyisophthalonitrile, (E)-4,5-dihydroxy-2-(4-methoxybenzylideneamino)isophthalonitrile, (E)-2-(4-fluorobenzylideneamino)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-tosylisophthalonitrile, 4-(2,6-dicyano-3,4-dihydroxyphenoxy)benzoic acid, 2-(benzo[d]thiazol-2-ylthio)-4,5-dihydroxyisophthalonitrile, 2-(4-fluorophenylthio)-4,5-dihydroxyisophthalonitrile, 2-(biphenyl-4-ylmethyl)-4,5-dihydroxyisophthalonitrile, 2-(4-chloro-2-methylbenzyl)-4,5-dihydroxyisophthalonitrile, 2-(2-ethylbenzyl)-4,5-dihydroxyisophthalonitrile, 2-(2,3-dihydro-1H-inden-5-yloxy)-4,5-dihydroxyisophthalonitrile, enantiomer A of 4,5-dihydroxy-2-(p-tolylsulfinyl)isophthalonitrile, enantiomer B of 4,5-dihydroxy-2-(p-tolylsulfinyl)isophthalonitrile, 2-((cyclohexylmethyl)amino)-4,5-dihydroxyisophthalonitrile, 4,5-dihydroxy-2-(4-phenoxyphenylthio)isophthalonitrile, 4,5-dihydroxy-2-(pyridin-3-yl)isophthalonitrile, 4,5-dihydroxy-2-(4-(2,2,2-trifluoroethyl)benzyl)isophthalonitrile, 4,5-dihydroxy-2-(4-methyl-2-(trifluoromethyl)benzyl)isophthalonitrile, 4,5-dihydroxy-2-((4-(morpholine-4-carbonyl)phenyl)thio)isopththalonitrile, 4,5-dihydroxy-2-(methyl(p-tolyl)amino)isophthalonitrile or 4,5-dihydroxy-2-((6-methoxynaphthalen-2-yl)methyl)isophthalonitrile.

The terms employed herein have the meanings indicated below. The term "at least one" employed in the meanings below refers to one or several, such as one. For example, the term "at least one hydroxy(C_1-C_6)alkoxy group" refers to one or several hydroxy(C_1-C_6)alkoxy groups, such as one hydroxy(C_1-C_6)alkoxy group.

The term "(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to a straight or branched chain saturated hydrocarbon group having 1, 2, 3, 4, 5 or 6 carbon atom(s). Representative examples of (C_1-C_6)alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pent-3-yl, hexyl, and 3,3-dimethylbutyl.

The term "(C_2-C_6)alkenyl", as employed herein as such or as part of another group, refers to a straight or branched chain hydrocarbon group having 2, 3, 4, 5 or 6 carbon atoms and at least one carbon-carbon double bond. Representative examples of (C_2-C_6)alkenyl include, but are not limited to, vinyl, prop-1-en-1-yl, prop-1-en-2-yl, allyl, but-2-en-1-yl, 2-methylprop-1-en-1-yl, pent-1-en-1-yl, 3-methylbut-2-en-1-yl, 3-methylbut-2-en-2-yl, 4-methylpent-1-en-1-yl, and 3,3-dimethylbut-1-en-1-yl.

The term "(C_2-C_6)alkynyl", as employed herein as such or as part of another group, refers to a straight or branched chain hydrocarbon group having 2, 3, 4, 5 or 6 carbon atoms and at least one carbon-carbon triple bond. Representative examples of (C_2-C_6)alkynyl include, but are not limited to, ethynyl, prop-1-yn-1-yl, and 3,3-dimethylbut-1-yn-1-yl.

The term "(C_3-C_7)cycloalkyl", as employed herein as such or as part of another group, refers to a saturated cyclic hydrocarbon group having 3, 4, 5, 6 or 7 carbon atoms. Representative examples of (C_3-C_7)cycloalkyl include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl.

The term "(C_4-C_{10})cycloalkenyl", as employed herein as such or as part of another group, refers to a monocyclic hydrocarbon group having 3, 4, 5, 6 or 7 carbon atoms and at least one carbon-carbon double bond or to an 8, 9 or 10 membered partially unsaturated bicyclic hydrocarbon group. When the (C_4-C_{10})cycloalkenyl group is an 8, 9 or 10 membered partially unsaturated bicyclic hydrocarbon group, one of the rings is optionally aromatic. Representative examples of (C_4-C_{10})cycloalkenyl include, but are not limited to, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, and 2,3-dihydro-1H-inden-5-yl.

The term "aryl", as employed herein as such or as part of another group, refers to an aromatic monocyclic hydrocarbon group having 6 carbon atoms or to an aromatic bicyclic hydrocarbon group having 10 carbon atoms. Representative examples of aryl include, but are not limited to, phenyl and naphthalen-2-yl.

The term "halo" or "halogen", as employed herein as such or as part of another group, refers to fluorine, chlorine, bromine or iodine.

The term "hydroxy", as employed herein as such or as part of another group, refers to a -OH group.

The term "(C_1-C_6)alkoxy", as employed herein as such or as part of another group, refers to an (C_1-C_6)alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of (C_1-C_6)alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, tert-butoxy, and neopentyloxy.

The term "(C_4-C_{10})cycloalkenyloxy", as employed herein, refers to a (C_4-C_{10})cycloalkenyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of (C_4-C_{10})cycloalkenyloxy include, but are not limited to, cyclopent-1-en-1-yloxy and 2,3-dihydro-1H-inden-5-yloxy.

The term "aryloxy", as employed herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of aryloxy include, but are not limited to, phenoxy and naphthalen-1-yloxy.

The term "heteroaryl", as employed herein as such or as part of another group, refers to a 5, 6 or 7 membered aromatic monocyclic group containing 1, 2, 3 or 4 ring heteroatom(s) each independently selected from N, O, and S or to an 8, 9 or 10 membered aromatic bicyclic group containing 1, 2, 3 or 4 ring heteroatom(s) each independently selected from N, O, and S. Representative examples of heteroaryl include, but are not limited to, 1H-pyrrol-2-yl, furan-2-yl, thiophen-2-yl, thiophen-3-yl, 1H-pyrazol-4-yl, thiazol-5-yl, benzofuran-2-yl, benzo[b]thiophen-2-yl, and benzo[d][1,3]dioxol-5-yl.

The term "heteroaryloxy", as employed herein, refers to a heteroaryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of heteroaryloxy include, but are not limited to, pyridin-4-yloxy and benzo[d][1,3]dioxol-5-yloxy.

The term "heterocyclyl", as employed herein as such or as part of another group, refers to a 5, 6 or 7 membered saturated or partially unsaturated monocyclic group containing 1 or 2 ring heteroatom(s) each independently selected from N, O, and S or to an 8, 9 or 10 membered saturated or partially unsaturated bicyclic group containing 1 or 2 ring heteroatom(s) each independently selected from N, O, and S. When the heterocyclyl group is an 8, 9 or 10 membered partially unsaturated bicyclic group, one of the rings is optionally aromatic. Representative examples of heterocyclyl include, but are not limited to, pyrrolidin-1-yl, piperidin-1-yl, 3,6-dihydro-2H-pyran-4-yl, morpholino, and 2,3-dihydrobenzofuran-5-yl.

CATECHOL O-METHYLTRANSFERASE ACTIVITY INHIBITING COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to pharmacologically active 2-substituted 4,5-dihydroxyisophthalonitriles, or pharmaceutically acceptable salts and esters thereof, as well as to pharmaceutical compositions containing them and to their use as inhibitors of the catechol O-methyltransferase (COMT) enzyme.

BACKGROUND OF THE INVENTION

Dopamine is deficient in the brain of patients suffering from Parkinson's disease. Levodopa is used orally in the treatment of Parkinson's disease. Levodopa is a dopamine precursor, which is converted to dopamine in the brain. However, only a small portion of orally administered levodopa reaches the brain, because levodopa is metabolized in the peripheral system by COMT as well as by dopa decarboxylase (DDC). COMT metabolizes levodopa by converting it to 3-O-methyldopa, which is therapeutically ineffective and detrimental when competing with levodopa. COMT inhibitors have been shown to be effective in clinical use for the treatment of Parkinson's disease as an adjunct to levodopa therapy.

It is generally thought that the levodopa concentration in plasma reflects the levodopa levels in the brain. It is thus desirable to achieve a high levodopa concentration in plasma. However, optimal levodopa concentration in plasma is not achieved, for example, with the currently used COMT inhibitor entacapone.

COMT inhibitors have also been indicated to be useful in the treatment of, for example, hypertension, heart failure and depression (US 5446194) as well as inhibitors for the prevention of diabetic vascular dysfunctions (WO 98/27973). COMT inhibitors have also been disclosed as being useful for treating or controlling pain (WO 01/68083) as well as for treating restless legs syndrome

The term "aryl(C_1-C_6)alkyl", as employed herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein. Representative examples of aryl(C_1-C_6)alkyl include, but are not limited to, benzyl, 2-phenethyl, and 3-phenylpropyl.

The term "halo(C_1-C_6)alkyl", as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein. When there are several halogens, the halogens can be attached to the same or different carbon atom and the halogens can be identical or different. Representative examples of halo(C_1-C_6)alkyl include, but are not limited to, trifluoromethyl and 3-bromopropyl.

The term "hydroxy(C_1-C_6)alkyl", as employed herein, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein. When there are several hydroxy groups, the hydroxy groups can be attached to the same or different carbon atom. Representative examples of hydroxy(C_1-C_6)alkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, and 3-hydroxypropyl.

The term "(C_1-C_6)alkoxy(C_1-C_6)alkyl", as employed herein as such or as part of another group, refers to at least one (C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein. When there are several (C_1-C_6)alkoxy groups, the (C_1-C_6)alkoxy groups can be attached to the same or different carbon atom and the (C_1-C_6)alkoxy groups can be identical or different. Representative examples of (C_1-C_6)alkoxy(C_1-C_6)alkyl include, but are not limited to, methoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 3-methoxypropyl, and tert-butoxymethyl.

The term "heterocyclyl(C_1-C_6)alkyl", as employed herein, refers to a heterocyclyl group, as defined herein, appended to the parent molecular moiety

through an (C_1-C_6)alkyl group, as defined herein. Representative examples of heterocyclyl(C_1-C_6)alkyl include, but are not limited to, morpholinomethyl and 3-(pyrrolidin-1-yl)propyl.

The term "carboxy", as employed herein as such or as part of another group, refers to a -COOH group.

The term "carboxy(C_2-C_6)alkenyl", as employed herein, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkenyl group, as defined herein. Representative examples of carboxy(C_2-C_6)alkenyl include, but are not limited to, 2-carboxyvinyl and 2-carboxyallyl.

The term "(C_3-C_7)cycloalkyl(C_2-C_6)alkenyl", as employed herein, refers to a (C_3-C_7)cycloalkyl group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkenyl group, as defined herein. Representative examples of (C_3-C_7)cycloalkyl(C_2-C_6)alkenyl include, but are not limited to, 2-cyclopropylvinyl, 2-cyclohexylvinyl, and 3-cyclopentylprop-1-en-1-yl.

The term "aryl(C_2-C_6)alkenyl", as employed herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkenyl group, as defined herein. Representative examples of aryl(C_2-C_6)alkenyl include, but are not limited to, styryl, 1-phenylvinyl, and 3-phenylprop-1-en-1-yl.

The term "(C_1-C_6)alkoxy(C_2-C_6)alkenyl", as employed herein, refers to at least one (C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkenyl group, as defined herein. When there are several (C_1-C_6)alkoxy groups, the (C_1-C_6)alkoxy groups can be attached to the same or different carbon atom and the (C_1-C_6)alkoxy groups can be identical or different. Representative examples of (C_1-C_6)alkoxy(C_2-C_6)alkenyl

include, but are not limited to, 3-methoxyprop-1-en-1-yl and 3-ethoxyprop-1-en-2-yl.

The term "heterocyclyl(C_2-C_6)alkenyl", as employed herein, refers to a heterocyclyl group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkenyl group, as defined herein. Representative examples of heterocyclyl(C_2-C_6)alkenyl include, but are not limited to, 4-(pyrrolidin-1-yl)but-2-en-1-yl and 3-methyl-4-morpholinobut-2-en-2-yl.

The term "heteroaryl(C_2-C_6)alkenyl", as employed herein, refers to a heteroaryl group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkenyl group, as defined herein. Representative examples of heteroaryl(C_2-C_6)alkenyl include, but are not limited to, 2-(thiophen-3-yl)vinyl and 3-methyl-4-(1H-pyrazol-4-yl)but-2-en-2-yl.

The term "carboxy(C_2-C_6)alkynyl", as employed herein, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkynyl group, as defined herein. Representative examples of carboxy(C_2-C_6)alkynyl include, but are not limited to, carboxyethynyl and 3-carboxyprop-1-yn-1-yl.

The term "(C_3-C_7)cycloalkyl(C_2-C_6)alkynyl", as employed herein, refers to a (C_3-C_7)cycloalkyl group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkynyl group, as defined herein. Representative examples of (C_3-C_7)cycloalkyl(C_2-C_6)alkynyl include, but are not limited to, cyclopropylethynyl and 3-cyclopentylprop-1-yn-1-yl.

The term "aryl(C_2-C_6)alkynyl", as employed herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkynyl group, as defined herein. Representative examples of

aryl(C_2-C_6)alkynyl include, but are not limited to, phenylethynyl and 3-(naphthalen-1-yl)prop-1-yn-1-yl.

The term "(C_1-C_6)alkoxy(C_2-C_6)alkynyl", as employed herein, refers to at least one (C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkynyl group, as defined herein. When there are several (C_1-C_6)alkoxy groups, the (C_1-C_6)alkoxy groups can be attached to the same or different carbon atom and the (C_1-C_6)alkoxy groups can be identical or different. Representative examples of (C_1-C_6)alkoxy(C_2-C_6)alkynyl include, but are not limited to, tert-butoxyethynyl and 3-methoxyprop-1-yn-1-yl.

The term "heterocyclyl(C_2-C_6)alkynyl", as employed herein, refers to a heterocyclyl group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkynyl group, as defined herein. Representative examples of heterocyclyl(C_2-C_6)alkynyl include, but are not limited to, morpholinoethynyl and 3-(piperidin-1-yl)prop-1-yn-1-yl.

The term "heteroaryl(C_2-C_6)alkynyl", as employed herein, refers to a heteroaryl group, as defined herein, appended to the parent molecular moiety through an (C_2-C_6)alkynyl group, as defined herein. Representative examples of heteroaryl(C_2-C_6)alkynyl include, but are not limited to, thiophen-3-ylethynyl and 3-(1H-pyrazol-4-yl)prop-1-yn-1-yl.

The term "halo(C_1-C_6)alkoxy", as employed herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkoxy group, as defined herein. When there are several halogens, the halogens can be attached to the same or different carbon atom and the halogens can be identical or different. Representative examples of halo(C_1-C_6)alkoxy include, but are not limited to, trifluoromethoxy and 1,1,2,2-tetrafluoroethoxy.

The term "hydroxy(C_1-C_6)alkoxy", as employed herein as such or as part of another group, refers to at least one hydroxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkoxy group, as defined herein. When there are several hydroxy groups, the hydroxy groups can be attached to the same or different carbon atom. Representative examples of hydroxy(C_1-C_6)alkoxy include, but are not limited to, hydroxymethoxy and 3-hydroxy-2,2-dimethylpropoxy.

The term "(C_1-C_6)alkoxy(C_1-C_6)alkoxy", as employed herein as such or as part of another group, refers to at least one (C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkoxy group, as defined herein. The (C_1-C_6)alkoxy groups can be identical or different. When there are several (C_1-C_6)alkoxy groups appended to the parent molecular moiety through an (C_1-C_6)alkoxy group, the (C_1-C_6)alkoxy groups can be attached to the same or different carbon atom. Representative examples of (C_1-C_6)alkoxy(C_1-C_6)alkoxy include, but are not limited to, 2-methoxyethoxy and 3-methoxy-2,2-dimethylpropoxy.

The term "hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl", as employed herein, refers to at least one hydroxy(C_1-C_6)alkoxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein. When there are several hydroxy(C_1-C_6)alkoxy groups, the hydroxy(C_1-C_6)alkoxy groups can be attached to the same or different carbon atom and the hydroxy(C_1-C_6)alkoxy groups can be identical or different. Representative examples of hydroxy(C_1-C_6)alkoxy(C_1-C_6)alkyl include, but are not limited to, (3-hydroxy-2,2-dimethylpropoxy)methyl and 2-(hydroxymethoxy)prop-2-yl.

The term "(C_3-C_7)cycloalkyl(C_1-C_6)alkyl", as employed herein, refers to a (C_3-C_7)cycloalkyl group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein. Representative

examples of (C_3-C_7)cycloalkyl(C_1-C_6)alkyl include, but are not limited to, cyclohexylmethyl and 2-cyclopentylethyl.

The term "cyano", as employed herein, refers to -CN group.

The term "carboxy(C_1-C_6)alkyl", as employed herein, refers to a carboxy group, as defined herein, appended to the parent molecular moiety through an (C_1-C_6)alkyl group, as defined herein. Representative examples of carboxy(C_1-C_6)alkyl include, but are not limited to, carboxymethyl, 1-carboxyethyl, and 2-carboxyethyl.

The term "(C_1-C_5)alkyl", as employed herein, refers to a straight or branched chain saturated hydrocarbon group having 1, 2, 3, 4 or 5 carbon atom(s). Representative examples of (C_1-C_5)alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, pentyl, and neopentyl.

Pharmaceutically acceptable salts, e.g. metal salts and acid addition salts, with both organic and inorganic acids, are well known in the field of pharmaceuticals. Representative examples of pharmaceutically acceptable metal salts include, but are not limited to, lithium, sodium, potassium, calcium, magnesium, aluminum and zinc salts. Representative examples of pharmaceutically acceptable acid addition salts include, but are not limited to, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, methane sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, and ascorbates.

Pharmaceutically acceptable esters of hydroxy groups may be prepared by known methods using pharmaceutically acceptable carboxylic acids that are conventional in the field of pharmaceuticals. Representative examples of pharmaceutically acceptable esters of hydroxy groups include, but are not limited to, esters formed with butyric acid and pentanoic acid.

Pharmaceutically acceptable esters of carboxy groups may be prepared by known methods using pharmaceutically acceptable alcohols that are conventional in the field of pharmaceuticals. Representative examples of pharmaceutically acceptable esters of carboxy groups include, but are not limited to, esters formed with propan-1-ol, butan-1-ol, and 2-methylpropan-1-ol.

The invention includes within its scope all the possible geometric isomers, e.g. Z and E isomers (cis and trans isomers), of the compounds as well as all the possible optical isomers, e.g. diastereomers and enantiomers, of the compounds. Furthermore, the invention includes in its scope both the individual isomers and any mixtures thereof, e.g. racemic mixtures. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g. enantiomers, from the mixture thereof conventional resolution methods, e.g. fractional crystallization, may be used.

The invention includes within its scope all the possible tautomers, or equilibrium mixtures thereof, of the compounds. In tautomers a hydrogen migrates from one atom of the compound to another atom of the compound. Representative examples of tautomers include, but are not limited to, keto/enol and nitroso/oxime.

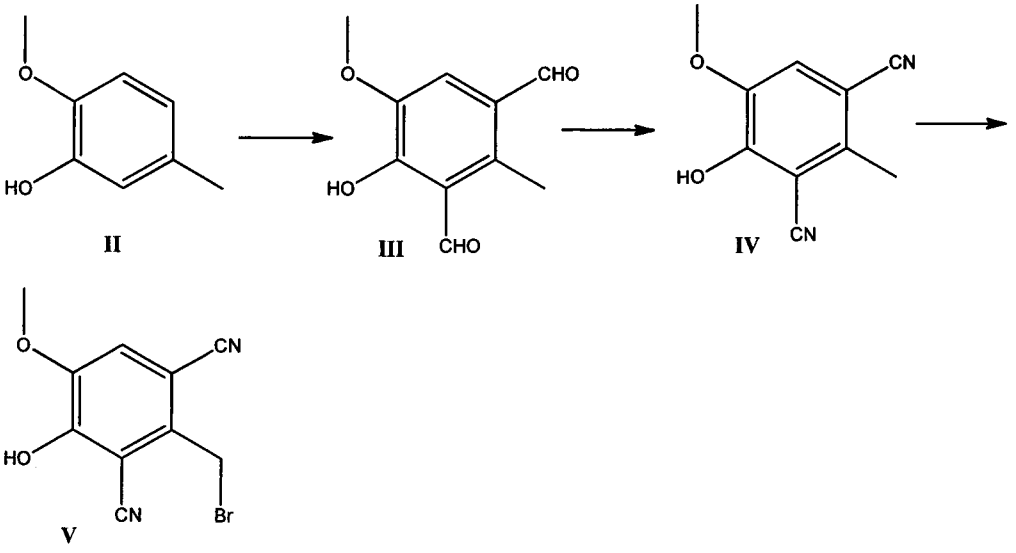
The compounds of formula I can be prepared by a variety of synthetic routes analogously to or according to methods known in the literature using suitable starting materials.

While many general methods are available for the generation of a cyano group, most of them are not directly usable in the field of catechol chemistry. For

instance, the Sandmeyer reaction provides an extremely reactive catecholic amine as an intermediate which creates serious preparative challenges.

Some methods useful for the preparation of the compounds of formula I are described below. The dicyano grouping can be constructed efficiently using simple starting materials essentially via two ways, either synthesizing two formyl groups simultaneously or building the second formyl group on a benzaldehyde derivative. In both cases the formyl groups are subsequently transformed into cyano groups in good yield. Further transformations provide a useful intermediate from which numerous final products can be formed.

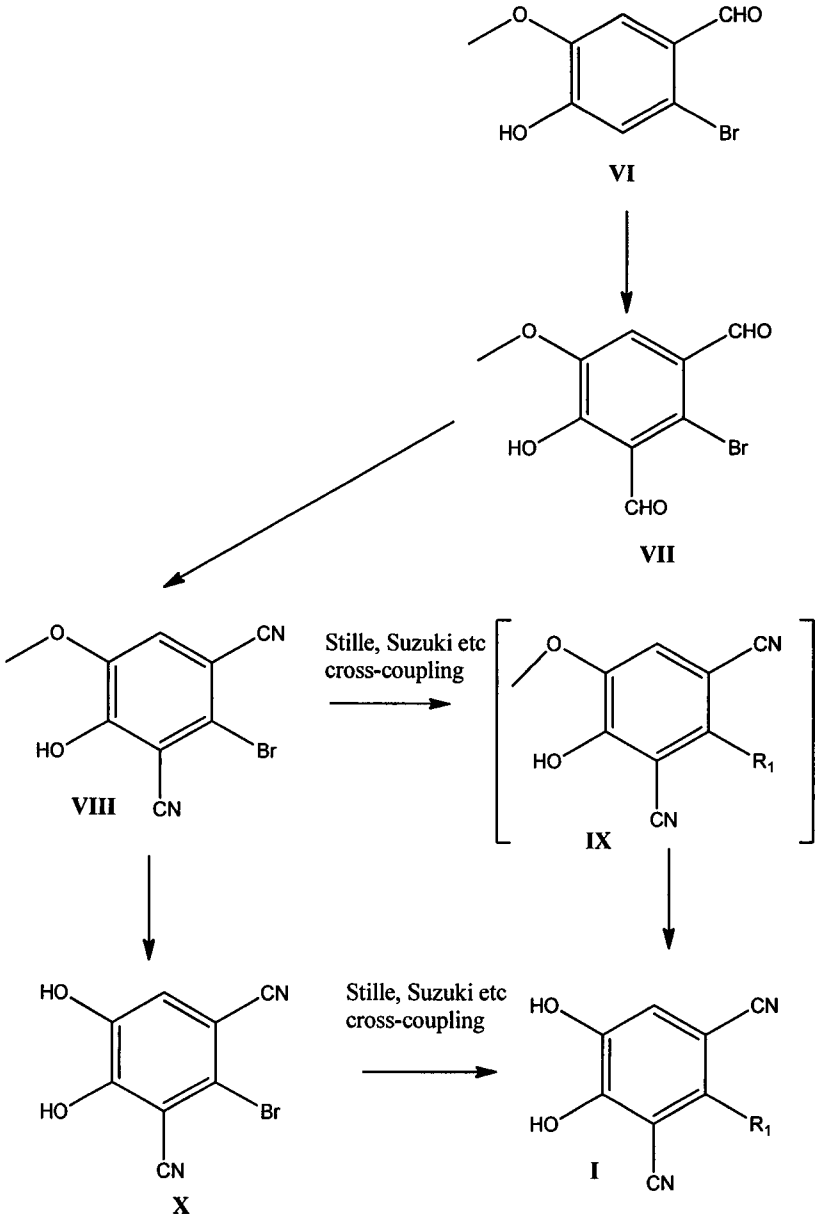
Scheme 1. Starting from 2-methoxy-5-methylphenol



In Scheme 1, 2-methoxy-5-methylphenol is formylated with hexamethylenetetramine in a suitable solvent, e.g. acetic acid. 4-Hydroxy-5-methoxy-2-methylisophthalaldehyde is converted to 4-hydroxy-5-methoxy-2-methylisophthalonitrile with hydroxylamine hydrochloride in a suitable solvent, e.g. formic acid. 4-Hydroxy-5-methoxy-2-methylisophthalonitrile is brominated with N-bromosuccinimide in a suitable solvent, e.g. dichloromethane, to yield 2-(bromomethyl)-4-hydroxy-5-methoxyisophthalonitrile. The bromine atom is then converted to the desired functional group and the desired product is

obtained by carrying out a demethylation with a Lewis acid in a suitable solvent, e.g. with aluminum chloride in acetonitrile or with boron tribromide in dichloromethane.

Scheme 2. Starting from 2-bromo-4-hydroxy-5-methoxybenzaldehyde



In Scheme 2, R_1 is as defined above. 2-Bromo-4-hydroxy-5-methoxybenzaldehyde is formylated with hexamethylenetetramine in a suitable solvent, e.g. acetic acid. 2-Bromo-4-hydroxy-5-methoxyisophthalaldehyde is

converted to 2-bromo-4-hydroxy-5-methoxyisophthalonitrile with hydroxylamine hydrochloride in a suitable solvent, e.g. formic acid. The bromine atom is replaced with substituent R_1, for instance, by a Suzuki cross-coupling reaction. 2-Bromo-4-hydroxy-5-methoxyisophthalonitrile is reacted with a suitable boronic acid derivative in a suitable solvent, e.g. 1,4-dioxane/water. Intermediate IX obtained is then demethylated. Alternatively, the demethylation is carried out before replacing the bromine atom with substituent R_1. The demethylation is carried out with a Lewis acid in a suitable solvent, e.g. with aluminum chloride in acetonitrile or with boron tribromide in dichloromethane. Intermediate IX is not necessarily isolated from the reaction mixture. Another route for the conversion of 2-bromo-4-hydroxy-5-methoxyisophthalaldehyde to product I is depicted in Scheme 5.

Scheme 3. Starting from a 5-substituted 2-methoxyphenol

(RLS), which is also known as Ekbom's syndrome (WO 2006/051154). RLS is characterized by an irresistible urge to move the legs accompanied by other unpleasant sensations deep within the legs.

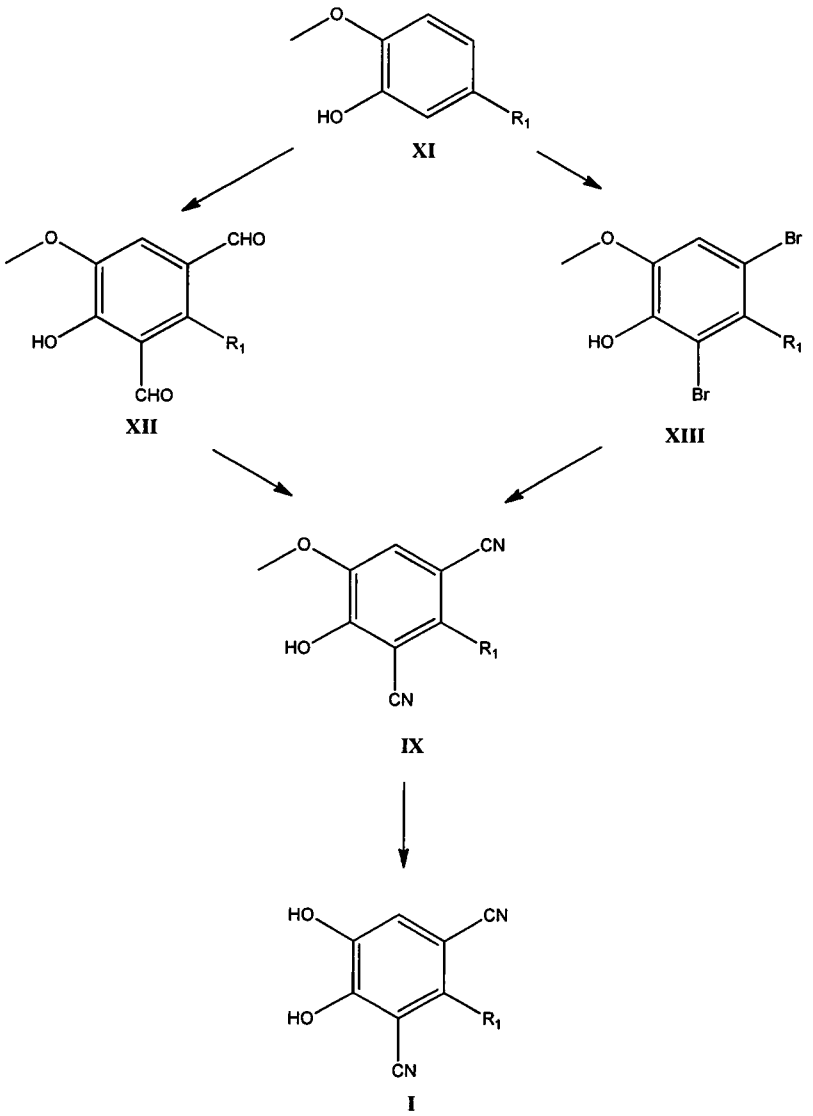
Some compounds with COMT inhibiting activity are known in the art. Isoflavone derivatives as COMT inhibitors have been disclosed in US 3974184 and CN 101643465 A. Catechol derivatives as COMT inhibitors have been disclosed in US 5236952, US 5446194, WO 96/37456, WO 00/37423, WO 01/98250, WO 01/98251, WO 02/02548, WO 02/22551, WO 2004/112729, WO 2005/058228, WO 2007/010085, WO 2007/013830, WO 2007/063789, WO 2007/117165, JP 2008308493, JP 2008308494, JP 2008308495, EP 2246338 A1, WO 2009/081892, EP 2305633 A1, JP 2011021010, JP 2012051884, and JP 2012051885. 3-Hydroxypyridin-4(1H)-one derivatives, 3-hydroxypyridin-2(1H)-one derivatives, and 5-hydroxypyrimidin-4(3H)-one derivatives as COMT inhibitors have been disclosed in WO 2011/109254, WO 2011/109261, and WO 2011/109267, respectively. Flavone derivatives as COMT inhibitors have been disclosed in CN 102755312 A.

SUMMARY OF THE INVENTION

An object of the present invention is to provide further inhibitors of the catechol O-methyltransferase enzyme that can be used for the treatment of diseases or conditions wherein inhibition of COMT is indicated to be useful. Accordingly, an object of the present invention is to provide further compounds to be used as COMT inhibiting agents in the treatment of mammals, including humans and animals. Furthermore, pharmaceutical compositions containing the present compounds are provided.

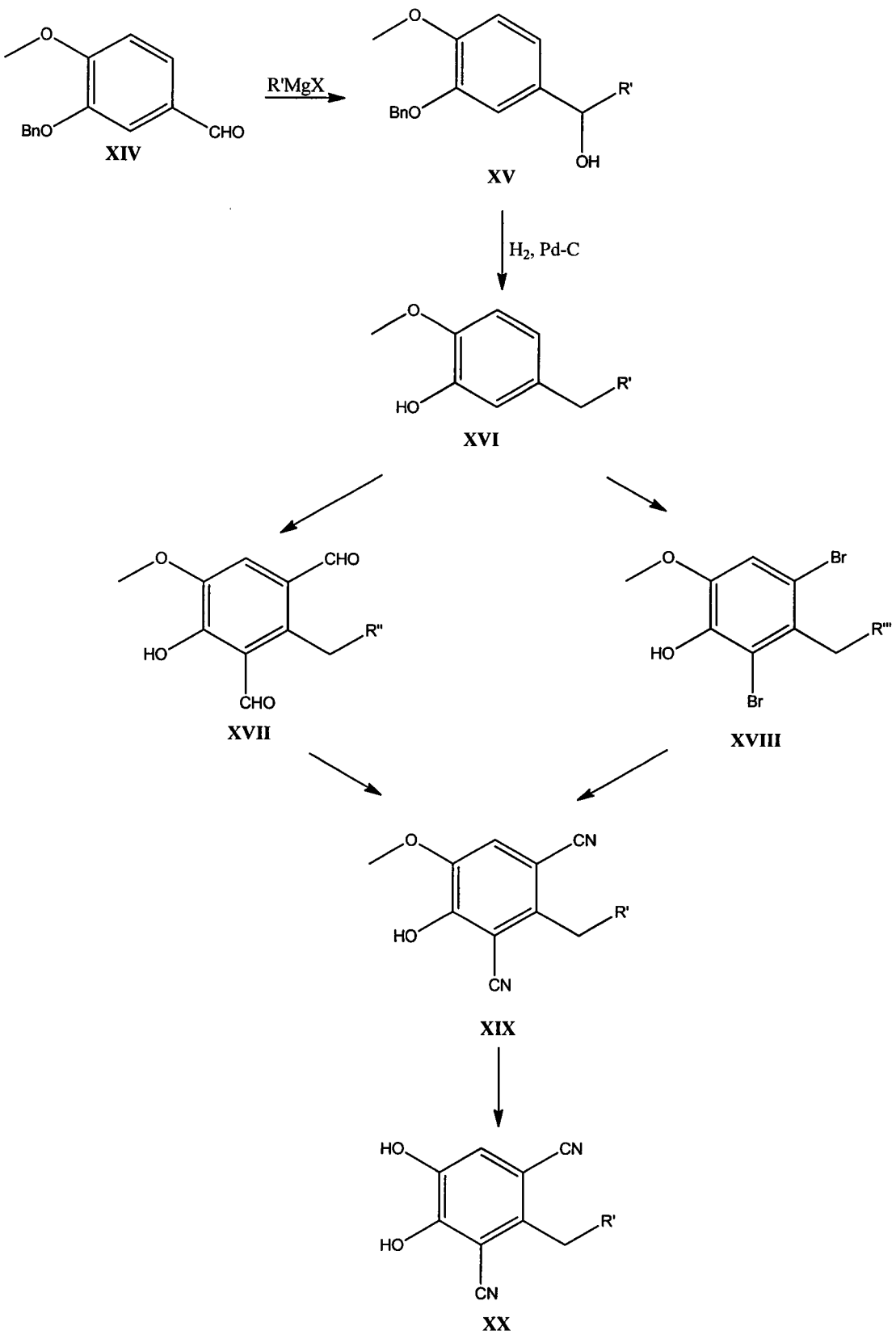
The COMT inhibitors of the invention provide in levodopa therapy an improved levodopa concentration in plasma.

DETAILED DESCRIPTION OF THE INVENTION



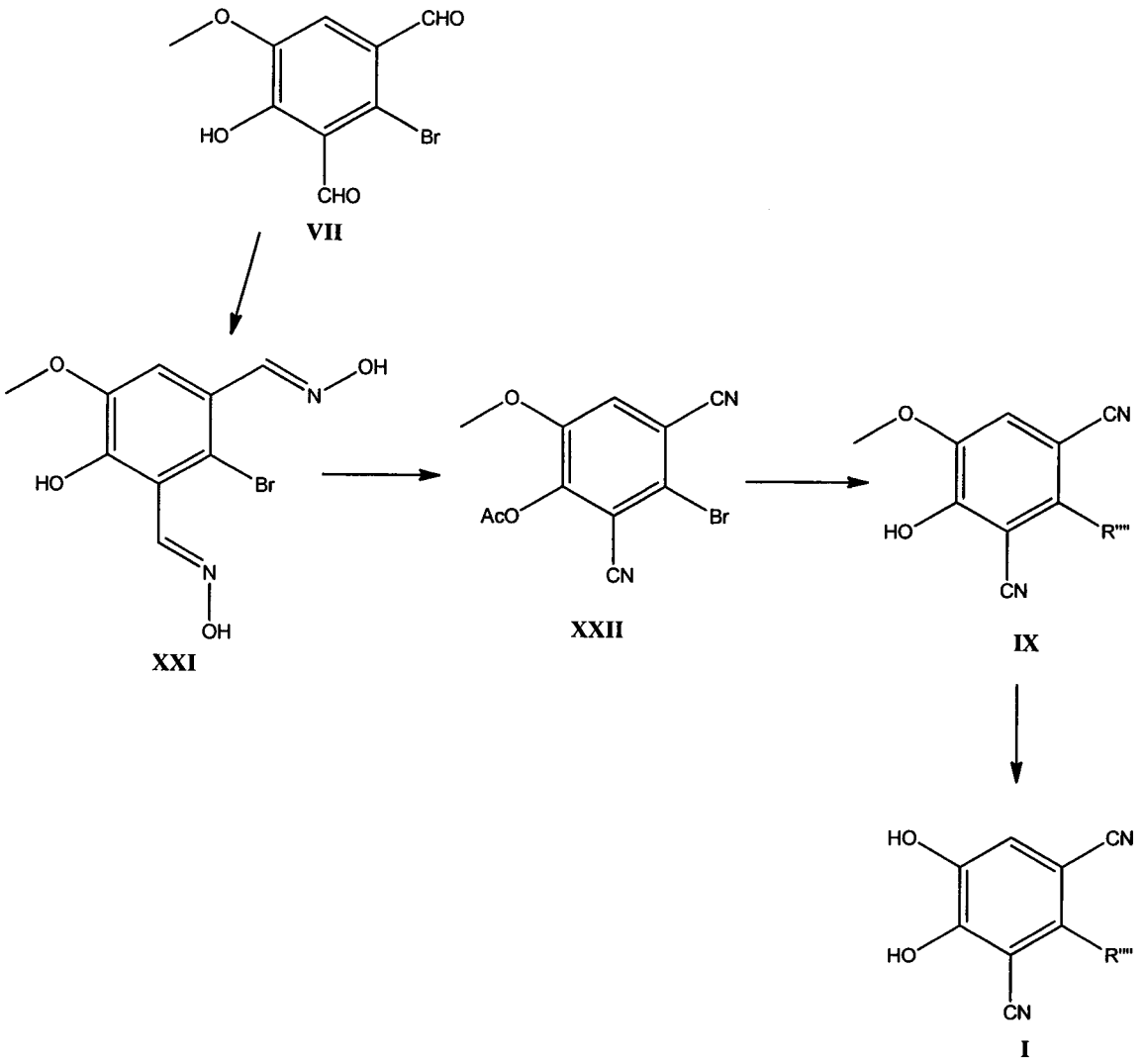
In Scheme 3, R_1 is as defined above. Compound XI is diformylated, for example, with hexamethylenetetramine in a suitable solvent such as acetic acid or trifluoroacetic acid, or dibrominated, for example, with bromine in a suitable solvent such as a mixture of dichloromethane and acetic acid. Dicyano derivative IX is obtained by reacting diformyl derivative XII with hydroxylamine hydrochloride in a suitable solvent such as formic acid or by reacting dibromo derivative XIII with copper(I) cyanide in a suitable solvent such as N,N-dimethylformamide. Dicyano derivative IX is demethylated with a Lewis acid in a suitable solvent, e.g. with aluminum chloride in acetonitrile or with boron tribromide in dichloromethane.

Scheme 4. Starting from 3-benzyloxy-4-methoxybenzaldehyde


O
BnO
CHO
XIV
R'MgX
O
BnO
R'
OH
XV
H_2, Pd-C
O
HO
R'
XVI
O
CHO
HO
R''
CHO
XVII
O
Br
HO
R'''
Br
XVIII
O
CN
HO
R'
CN
XIX
HO
CN
HO
R'
CN
XX

In Scheme 4, Bn is benzyl, R' is, for example, (C_1-C_5)alkyl or aryl, R'' is, for example, (C_1-C_5)alkyl, R''' is, for example, aryl, and X is halogen. 3-Benzyloxy-4-methoxybenzaldehyde is converted to alcohol XV using a suitable Grignard reagent. Compound XVI is obtained by hydrogenating alcohol XV. When R' is, for example, (C_1-C_5)alkyl, compound XVI can be diformylated, for example, with hexamethylenetetramine in a suitable solvent such as acetic acid or trifluoroacetic acid. When R' is, for example, aryl, compound XVI can be dibrominated, for example, with bromine in a suitable solvent such as a mixture of dichloromethane and acetic acid. Dicyano derivative XIX is obtained by reacting diformyl derivative XVII with hydroxylamine hydrochloride in a suitable solvent such as formic acid or by reacting dibromo derivative XVIII with copper(I) cyanide in a suitable solvent such as N,N-dimethylformamide. Dicyano derivative XIX is demethylated with a Lewis acid in a suitable solvent, e.g. with aluminum chloride in acetonitrile or with boron tribromide in dichloromethane.

Scheme 5. Conversion of 2-bromo-4-hydroxy-5-methoxyisophthalaldehyde



In Scheme 5, Ac is acetyl and R'''' is, for example, aryl-S- or heteroaryl-S-. 2-Bromo-4-hydroxy-5-methoxyisophthalaldehyde, which can be prepared as depicted in Scheme 2, is converted to (1E,1'E)-2-bromo-6-hydroxy-3-((E)-(hydroxyimino)methyl)-5-methoxybenzaldehyde oxime with hydroxylamine hydrochloride in a suitable solvent, e.g. tetrahydrofuran. Treating (1E,1'E)-2-bromo-6-hydroxy-3-((E)-(hydroxyimino)methyl)-5-methoxybenzaldehyde oxime with acetic anhydride yields 3-bromo-2,4-dicyano-6-methoxyphenyl acetate. Dicyano derivative IX is obtained by reacting 3-bromo-2,4-dicyano-6-methoxyphenyl acetate with a suitable thiol in a suitable solvent, e.g. N,N-dimethylformamide. Dicyano derivative IX is demethylated

with a Lewis acid in a suitable solvent, e.g. with aluminum chloride in acetonitrile or with boron tribromide in dichloromethane.

It is obvious for a person skilled in the art that any starting material or intermediate in the reactions described above can be protected, if necessary, in a manner well known in the chemical field. For instance, ethyl vanillin can be used instead of vanillin. Any protected functionality can subsequently be deprotected in a manner known in the art.

Stepwise routes can be used. For instance, the dicyano target can be prepared from a suitable starting compound in the following order: 1) monobromination, 2) monoformylation, 3) conversion of CHO to CN, and 4) conversion of Br to CN. The order of all of these separate steps of bromination, formylation, conversion of CHO to CN and conversion of Br to CN can be optionally changed. For instance, one can start with a formylation. Likewise, if desired, conversion of Br to CN can be carried out prior to conversion of CHO to CN.

The synthetic routes described above are meant to illustrate the preparation of the compounds of formula I and the preparation is by no means limited thereto, i.e., there are also other possible synthetic methods which are within the general knowledge of a person skilled in the art. For instance, formylation can be accomplished also via lithiation of an aromatic methoxy halogenide, e.g. an aromatic methoxy bromide, or an aromatic methoxy dihalogenide, e.g. an aromatic methoxy dibromide, oxidation of a methyl group or reduction of a carboxy group. An aromatic formyl group can be converted into a hydroxy group via a Dakin reaction.

The compounds of formula I may be converted, if desired, into their pharmaceutically acceptable salt or ester form using methods well known in the art.

The present invention will be explained in more detail by the following examples. The examples are meant for illustrating purposes only and do not limit the scope of the invention defined in the claims.

Unless otherwise noted, all the starting materials were obtained from commercial suppliers and used without further purification. The abbreviations have the meanings indicated below.

AcOH	acetic acid
AIBN	2,2'-azobisisobutyronitrile
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCM	dichloromethane
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DPEPhos	(oxybis(2,1-phenylene))bis(diphenylphosphine)
EtOAc	ethyl acetate
mCPBA	m-chloroperoxybenzoic acid
NBS	N-bromosuccinimide
$Pd(dppf)Cl_2$	(1,1'-bis(diphenylphosphino)ferrocene)palladium dichloride
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Preparation of intermediates

Intermediate A1: 4-Hydroxy-5-methoxy-2-methylisophthalonitrile

4-Hydroxy-5-methoxy-2-methylisophthalaldehyde

2-Methoxy-5-methylphenol (11.0 g) and hexamethylenetetramine (23.8 g) in AcOH (280 ml) were refluxed for 15 h. Concentrated HCl (20 ml) was added and the mixture was refluxed for 3 h. The solvent volume was reduced to 40-50

ml. The mixture was cooled for 1 h in an ice bath. The precipitate was filtered off and washed with ethanol. Water was added to the filtrate and the mixture was extracted thrice with DCM. The combined organic phases were dried (Na_2SO_4) and evaporated to dryness. The residue was triturated with ethanol and cooled in an ice bath. The solid was filtered off and washed with ethanol. Concentrated HCl (45 ml) was added to the solid and refluxed for 1 h. The reaction mixture was cooled in an ice bath, filtered and washed with ethanol (5 ml). Yield 2.9 g
^{1}H NMR (400 MHz, DMSO-d_6) ppm 12.02 (s, 1 H) 10.48 (s, 1 H) 10.28 (s, 1 H) 7.56 (s, 1 H) 2.79 (s, 3 H)

4-Hydroxy-5-methoxy-2-methylisophthalonitrile

4-Hydroxy-5-methoxy-2-methylisophthalaldehyde (5.2 g), hydroxylamine hydrochloride (5.58 g) and anhydrous sodium acetate (8.79 g) in formic acid (30 ml) were refluxed for 5 h. The reaction mixture was cooled in an ice bath and the precipitate was filtered off and washed with water. Yield 4.6 g
^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.47 (br s, 1 H) 7.55 (s, 1 H) 3.88 (s, 3 H)

Intermediate A2: 2-Bromo-4-hydroxy-5-methoxyisophthalonitrile

2-Bromo-4-hydroxy-5-methoxyisophthalaldehyde

2-Bromo-4-hydroxy-5-methoxybenzaldehyde (0.75 g) and hexamethylenetetramine (0.91 g) in AcOH (30 ml) was heated under reflux for 4 h. AcOH was evaporated and 4 M HCl (30 ml) was added. The mixture was first refluxed for 2 h and stirred overnight at room temperature. The solid product was filtered, washed with water and dried. Yield 0.38 g
^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.37 (s, 1 H) 10.24 (s, 1 H) 7.50 (s, 1 H) 3.90 (s, 3 H)

2-Bromo-4-hydroxy-5-methoxyisophthalonitrile

2-Bromo-4-hydroxy-5-methoxyisophthalaldehyde (11.6 g) and hydroxylamine hydrochloride (9.3 g) were dissolved in hot formic acid (155 ml).

The solution was heated to boiling point followed by addition of anhydrous sodium acetate (22.0 g). The mixture was refluxed for 2 h. Acetic anhydride (18.2 g) was added dropwise to the hot reaction mixture and refluxed for 4 h. The mixture was allowed to cool to room temperature overnight, and then stirred in an ice bath. The solid was filtered, washed with ice cold water (20 ml) and dried. Yield 10.6 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 12.10 (br s, 1 H) 7.75 (s, 1 H) 3.91 (s, 3 H)

Intermediate A3: 2-Bromo-4,5-dihydroxyisophthalonitrile

The preparation of 2-bromo-4-hydroxy-5-methoxyisophthalonitrile is described above. Sieve dry acetonitrile (75 ml) was cooled in an ice bath. Aluminum chloride (3.16 g) was added slowly to the solvent so that temperature was kept below 30 °C. The mixture was stirred at room temperature for 10 min. Sodium iodine (2.4 g) was added and the solution was stirred for 15 min. 2-Bromo-4-hydroxy-5-methoxyisophthalonitrile (2.0 g) was added and the reaction mixture was heated at 70 °C for 5 h after which it was stirred at room temperature overnight. 4 M HCl (20 ml) and a solution of sodium sulfate (1.3 g) in water (40 ml) were successively added to the cool reaction mixture. The mixture was extracted thrice with EtOAc (50 ml) and the combined organic phases were washed with 2 M HCl (50 ml), water (50 ml) and brine (50 ml). The washed organic phase was dried (Na_2SO_4), filtered and evaporated to dryness. Yield 1.89 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.15 (br s, 2 H) 7.32 (s, 2 H)

Intermediate A4: 4-Bromo-3,5-dicyano-1,2-phenylene diacetate

The preparation of 2-bromo-4,5-dihydroxyisophthalonitrile is described above. 2-Bromo-4,5-dihydroxyisophthalonitrile (1.80 g), acetic anhydride (10 ml) and sulfuric acid (20 µl) was stirred at room temperature overnight. The reaction mixture was poured slowly to ice water (50 ml) stirring simultaneously the water mixture. The product was filtered, washed with water and dried in vacuum (30 °C). Yield 2.19 g

^{1}H NMR (400 MHz, chloroform-*d*) ppm 7.79 (s, 1 H) 2.43 (s, 3 H) 2.34 (s, 3 H)

Intermediate A5: 2-Bromo-4,5-diisopropoxyisophthalonitrile

The preparation of 2-bromo-4,5-dihydroxyisophthalonitrile is described above. To a warm mixture of 2-bromo-4,5-dihydroxyisophthalonitrile (10.0 g) and potassium carbonate (23.1 g) in DMF (160 ml) was added 2-iodopropane (16.7 ml) dropwise over 1 h. The reaction mixture was heated at 85 °C for 6 h after which it was poured into cold water and pH was adjusted to 12. The precipitate was filtered, washed with water and dried in vacuum. Yield 9.3 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.00 (s, 1 H) 4.85 (m, 1 H) 4.82 (m, 1 H) 1.32 (s, 6 H) 1.30 (s, 6 H)

Intermediate A6: 3-Bromo-2,4-dicyano-6-methoxyphenyl acetate

(1E,1'E)-2-Bromo-6-hydroxy-3-((E)-(hydroxyimino)methyl)-5-methoxybenzaldehyde oxime

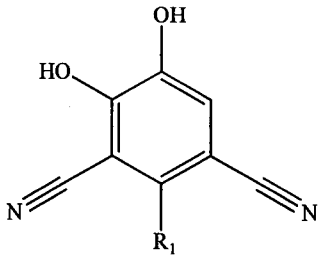
The preparation of 2-bromo-4-hydroxy-5-methoxyisophthalaldehyde is described above. 2-Bromo-4-hydroxy-5-methoxyisophthalaldehyde (15.9 g) and hydroxylamine hydrochloride (17.0 g) were dissolved in THF (500 ml). Pyridine (19.9 ml) was added. The solution was heated at 90 °C for 3 h. After concentration to half of the original volume, ice and 4 M HCl solution (40 ml) was added. The mixture was stirred for 30 min. The solid was filtered, washed with 1 M HCl and ice cold water and dried. Yield 17.4 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 12.10 (br s, 1 H) 7.75 (s, 1 H) 3.91 (s, 3 H)

3-Bromo-2,4-dicyano-6-methoxyphenyl acetate

(1E,1'E)-2-Bromo-6-hydroxy-3-((E)-(hydroxyimino)methyl)-5-methoxybenzaldehyde oxime (15.0 g) was dissolved in acetic anhydride (96 ml). The mixture was refluxed for 2 h. The mixture was allowed to cool to room temperature overnight. Toluene and water were added and solvents were

The present invention relates to compounds having the general formula I,



I

wherein

R_1 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_{10})$cycloalkenyl, aryl, $(R_2)_2C$=C-, halogen, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl-S-, $(C_4\text{-}C_{10})$cycloalkenyloxy, $(C_4\text{-}C_{10})$cycloalkenyl-S-, aryloxy, aryl-S-, heteroaryloxy, heteroaryl-S-, $(R_3)_2N$-, $(R_4)_2C$=N-, heterocyclyl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, (1-amino-1-carboxymethyl)-$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-S-$(C_1\text{-}C_6)$alkyl, $(R_3)_2N$-$(C_1\text{-}C_6)$alkyl, heterocyclyl$(C_1\text{-}C_6)$alkyl, carboxy$(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_7)$cycloalkyl$(C_2\text{-}C_6)$alkenyl, aryl$(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_6)$alkenyl, heterocyclyl$(C_2\text{-}C_6)$alkenyl, heteroaryl$(C_2\text{-}C_6)$alkenyl, carboxy$(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_7)$cycloalkyl$(C_2\text{-}C_6)$alkynyl, aryl$(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_6)$alkynyl, heterocyclyl$(C_2\text{-}C_6)$alkynyl, heteroaryl$(C_2\text{-}C_6)$alkynyl, halo$(C_1\text{-}C_6)$alkoxy, hydroxy$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl-(C=O)-O-, R_5-(S=O)-, R_5-(O=S=O)-, hydroxy$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy-(C=O)-$(C_2\text{-}C_6)$alkenyl or $(C_1\text{-}C_6)$alkyl-(C=O)-O-$(C_1\text{-}C_6)$alkyl, wherein said $(C_4\text{-}C_{10})$cycloalkenyl, aryl, heterocyclyl, heteroaryl or $(C_3\text{-}C_7)$cycloalkyl as such or as part of another group is unsubstituted or substituted with 1, 2 or 3 substituent(s) R_6;

R_2 is, independently at each occurrence, carboxy or aryl, wherein said aryl is, independently at each occurrence, unsubstituted or substituted with 1, 2 or 3 substituent(s) R_6;

R_3 is, independently at each occurrence, H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, wherein said $(C_3\text{-}C_7)$cycloalkyl or aryl as such or as

evaporated. After 30 min stirring with ice cold water, the solid was filtered, washed with ice cold water and dried. Yield 11.0 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.19 (s, 1 H) 3.92 (s, 3 H) 2.44 (s, 3H)

Intermediate A7: 3-Bromo-2,4-dicyano-6-methoxyphenyl tert-butyl carbonate

The preparation of 2-bromo-4-hydroxy-5-methoxyisophthalonitrile is described above. To a stirred solution of 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (5.57 g) in acetonitrile (200 ml) was added in one portion DMAP (1.3 g) and di-tert-butyl dicarbonate (33.6 g). After refluxing for 4 h, the mixture was cooled in an ice bath, filtered and evaporated to dryness. EtOAc was added and the mixture was filtered through silica gel. The filtrate was evaporated to dryness. Yield 4.79 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.98 (s, 1 H) 3.88 (s, 3 H) 1.42 (s, 9 H)

Intermediate A8: 5-(Benzyloxy)-2-bromo-4-hydroxyisophthalonitrile

The preparation of 2-bromo-4,5-dihydroxyisophthalonitrile is described above. 2-Bromo-4,5-dihydroxyisophthalonitrile (450 mg) was dissolved in DMF (7 ml). Cesium carbonate (1.84 g) and benzyl chloride (0.46 ml) were added and stirred at 70 °C for 1.5 h. The reaction was quenched with ice water and the mixture was stirred for 10 min. The precipitated solid was filtered, washed with water and dried under vacuum. Yield 520 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.31-7.40 (m, 5 H) 6.78 (s, 1 H) 4.94 (s, 2 H)

Preparation of compounds of the invention

Example 1: 2-Bromo-4,5-dihydroxyisophthalonitrile

The preparation of the title compound is described above.

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.15 (br s, 2 H) 7.32 (s, 2 H)

Example 2: 4,5-Dihydroxy-2-(phenylethynyl)isophthalonitrile

2,6-Di-tert-butyl-4-methylphenol (13.6 mg) and tetrakis(triphenylphosphine)palladium (28.6 mg) was added to a solution of 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) in dry toluene (18 ml). A solution of phenylethynyltri-n-butyltin (315 mg) in dry toluene (2 ml) was added to the reaction mixture under nitrogen atmosphere. The reaction mixture was heated under reflux for 6 h. The mixture was filtered through celite. The filtrate was evaporated to dryness. THF (30 ml) and 1 M NaOH (40 ml) was added to the resultant product and solution was stirred for 1 h. The solution was washed thrice with toluene (10 ml). The water phase was made acidic with 4 M HCl under cooling. The product was filtered, washed with water and dried at 40 °C in vacuum. Yield 45 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.54-7.60 (m, 2 H) 7.47-7.53 (m, 3 H) 7.35 (s, 1 H)

Example 3: 4,5-Dihydroxy-2-(prop-1-ynyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the method of Example 2 using tributylpropynylstannane (254 mg) instead of phenylethynyltri-n-butyltin. Yield 78 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.40 (br s, 2 H) 7.25 (s, 1 H) 2.18 (s, 3 H)

Example 4: 4,5-Dihydroxy-2-(1-methyl-1H-pyrrol-2-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) by the method of Example 2 using 1-methyl-2-(tributylstannyl)-1H-pyrrole (716 mg) instead of phenylethynyltri-n-butyltin. Yield 280 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.39 (br s, 2 H) 7.33 (s, 1 H) 6.94-6.97 (m, 1 H) 6.20 (m, J=3.50, 1.80 Hz, 1 H) 6.12 (m, J=3.50, 2.80 Hz, 1 H) 3.47 (s, 3 H)

Example 5: 4,5-Dihydroxy-2-(thiophen-2-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the method of Example 2 using 2-(tributylstannyl)thiophene (462 mg) instead of phenylethynyltri-n-butyltin. Yield 60 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.41 (br s, 2 H) 7.80 (dd, J=5.0, 1.3 Hz, 1 H) 7.31-7.36 (m, 2 H) 7.22 (dd, J=3.8 Hz, 1 H)

Example 6: 2-(Furan-2-yl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the method of Example 2 using 2-(tributylstannyl)furan (442 mg) instead of phenylethynyltri-n-butyltin. Yield 100 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.43 (br s, 2 H) 7.94 (br s, 1 H) 7.34 (s, 1 H) 6.88-7.08 (m, 1 H) 6.72 (br s, 1 H)

Example 7: 3',4',5'-Trifluoro-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

To a solution of 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) in acetonitrile (3 ml), water (4 ml) and ethanol (3 ml) in a vial, was added 3,4,5-trifluorophenylboronic acid (354 mg), bis(triphenylphosphine)palladium(II) chloride (61 mg) and sodium carbonate (492 mg). The reaction mixture was microwave-irradiated for 60 min at 130 °C. The mixture was filtered through pall filter, basified with 2 M NaOH (50 ml), washed with toluene (50 ml). The aqueous phase was then acidified with 4 M HCl under cooling. The product was filtered, washed with water and recrystallized with water/ethanol 10/2 mixture. Yield 140 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.38 (br s, 2 H) 7.58-7.69 (m, 2 H) 7.36 (s, 1 H)

Example 8: 4,5-Dihydroxy-2-(naphthalen-1-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and naphthalene-1-boronic acid (149 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Yield 126 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.47 (br s, 2 H) 8.08 (dd, J=1.00 Hz, 2 H) 7.56-7.67 (m, 2 H) 7.49-7.56 (m, 2 H) 7.43 (s, 1 H) 7.37 (d, J=1.00 Hz, 1 H)

Example 9: 4'-tert-Butyl-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and 4-tert-butylphenylboronic acid (248 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 150 °C. Yield 115 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.67 (br s, 1 H) 11.06 (br s, 1 H) 7.52-7.59 (m, 2 H) 7.39-7.43 (m, 2 H) 7.34 (s, 1 H) 1.34 (s, 9 H)

Example 10: 3,4-Dihydroxy-4'-(hydroxymethyl)biphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (1 g) and 4-(hydroxymethyl)benzeneboronic acid (564 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 30 min at 130 °C. Yield 639 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.34 (br s, 1 H) 7.44 (m, J=8.10, 8.10, 8.10 Hz, 4 H) 7.34 (s, 1 H) 5.33 (br s, 1 H) 4.59 (s, 2 H)

Example 11: 4,5-Dihydroxy-2-(naphthalen-2-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and naphthalene-2-boronic acid (138 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Yield 160 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.77 (br s, 1 H) 11.06 (br s, 1 H) 7.98-8.11 (m, 4 H) 7.56-7.67 (m, 3 H) 7.40 (s, 1 H)

Example 12: 3,4-Dihydroxy-4'-(isopropylthio)biphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg and 4-isopropylthiophenylboronic acid (158 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 135 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.72 (br s, 1 H) 11.08 (br s, 1 H) 7.45-7.49 (m, 2 H) 7.40-7.44 (m, 2 H) 7.35 (s, 1 H) 3.64 (m, J=13.30, 6.70, 6.70 Hz, 1 H) 1.30 (d, J=6.78 Hz, 6 H)

Example 13: 3,4-Dihydroxy-4'-(methylthio)biphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 4-(methylthio)phenylboronic acid (135 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Yield 151 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.32-12.19 (m, 1 H) 10.74-11.28 (m, 1 H) 7.36-7.44 (m, 4 H) 7.34 (s, 1 H) 2.54 (s, 3 H)

Example 14: 3,4-Dihydroxy-4'-isopropoxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (600 mg) and 4-isopropoxyphenylboronic acid (334 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 150 °C. Yield 365 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.25 (br s, 1 H) 7.25-7.44 (m, 3 H) 7.03 (d, J=8.03 Hz, 2 H) 4.65-4.76 (m, 1 H) 1.31 (d, J=5.77 Hz, 6 H)

Example 15: 4'-(Ethylthio)-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 4-(ethylthio)benzeneboronic acid (146 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Yield 143 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.76 (br s, 1 H) 11.05 (br s, 1 H) 7.41 (s, 4 H) 7.34 (s, 1 H) 3.07 (m, J=7.30, 7.30, 7.30 Hz, 2 H) 1.29 (t, J=7.28 Hz, 3 H)

Example 16: 3,4-Dihydroxy-4'-isopropoxy-3',5'-dimethylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 3,5-dimethyl-4-isopropoxyphenylboronic acid (167 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Yield 109 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.63 (br s, 1 H) 10.98 (br s, 1 H) 7.31 (s, 1 H) 7.11 (s, 2 H) 4.22-4.30 (m, 1 H) 2.26 (s, 6 H) 1.26 (d, J=6.27 Hz, 6 H)

Example 17: 4'-Butyl-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 4-n-butylbenzeneboronic acid (143 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 150 °C. Yield 88 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.28 (br s, 2 H) 7.29-7.41 (m, 5 H) 2.66 (t, J=7.65 Hz, 2 H) 1.61 (m, J=7.70, 7.70 Hz, 2 H) 1.29-1.40 (m, 2 H) 0.92 (t, J=7.40 Hz, 3 H)

Example 18: 3,4-Dihydroxy-2',4',5'-trimethylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 2,4,5-trimethylphenylboronic acid (132 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 150 °C. Yield 122 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.37 (br s, 2 H) 7.33 (s, 1 H) 7.13 (s, 1 H) 6.96 (s, 1 H) 2.25 (s, 3 H) 2.21 (s, 3 H) 2.00 (s, 3 H)

Example 19: 3,4-Dihydroxy-2',5'-dimethylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 2,5-dimethylbenzeneboronic acid (121 mg) instead of

3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 150 °C. Yield 102 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.37-12.37 (m, 2 H) 7.35 (s, 1 H) 7.23-7.27 (m, 1 H) 7.18-7.23 (m, 1 H) 7.00-7.04 (m, 1 H) 2.31 (s, 3 H) 2.03 (s, 3 H)

Example 20: 2-Cyclohexenyl-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and cyclohexen-1-ylboronic acid (94 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 150 °C. Yield 112 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.57-11.63 (m, 2 H) 7.21 (s, 1 H) 5.78 (br s, 1 H) 2.22 (br s, 2 H) 2.15 (br s, 2 H) 1.72 (m, J=4.30 Hz, 2 H) 1.63 (m, J=4.50 Hz, 2 H)

Example 21: 3'-Ethyl-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (250 mg) and 3-ethylphenylboronic acid (116 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 150 °C. Yield 204 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.86-11.94 (m, 2 H) 7.42 (s, 1 H) 7.29-7.37 (m, 3 H) 7.28 (s, 1 H) 2.68 (d, J=7.53 Hz, 2 H) 1.22 (t, J=7.65 Hz, 3 H)

Example 22: 3,4-Dihydroxybiphenyl-2,4',6-tricarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 4-cyanophenylboronic acid (109 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 127 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.49 (br s, 2 H) 8.00-8.04 (m, 2 H) 7.69-7.74 (m, 2 H) 7.39 (s, 1 H)

Example 23: 3,4-Dihydroxy-4'-(isopropylsulfonyl)biphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 4-(isopropylsulfonylphenyl)boronic acid (169 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 148 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.83-12.08 (m, 2 H) 7.95-8.07 (m, 2 H) 7.75-7.83 (m, 2 H) 7.39 (s, 1 H) 3.48-3.60 (m, 1 H) 1.19 (d, J=6.78 Hz, 6 H)

Example 24: 2',6'-Dicyano-3',4'-dihydroxy-N,N-dimethylbiphenyl-4-sulfonamide

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and N,N-dimethyl-4-boronobenzenesulfonamide (170 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 150 °C. Yield 159 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.51 (br s, 2 H) 7.88-7.93 (m, 2 H) 7.75-7.80 (m, 2 H) 7.40 (s, 1 H) 2.67 (s, 6 H)

Example 25: (E)-4,5-Dihydroxy-2-(pent-1-enyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 1-pentenylboronic acid (85 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 150 °C. Yield 100 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.18 (br s, 2 H) 7.25 (s, 1 H) 6.44-6.50 (m, 2 H) 2.21-2.28 (m, 2 H) 1.49 (m, 2 H) 0.95 (t, J=7.40 Hz, 3 H)

Example 26: 2',6'-Dicyano-3',4'-dihydroxybiphenyl-3-carboxylic acid

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 3-carboxyphenylboronic acid (308 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 30 min at 130 °C. Yield 388 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 13.20 (br s, 1 H) 11.47 (br s, 2 H) 8.08 (d, J=7.78 Hz, 1 H) 8.01 (s, 1 H) 7.75 (d, J=7.80 Hz, 1 H) 7.67 (t, J=7.65 Hz, 1 H) 7.37 (s, 1 H)

Example 27: 3,4-Dihydroxy-4'-(1-methoxyethyl)biphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (250 mg) and (4-(1-metoxyethyl)phenyl)boronic acid (139 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 130 °C. Yield 63 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.21 (br s, 2 H) 7.45 (s, 4 H) 7.34 (s, 1 H) 3.18 (s, 3 H) 1.39 (d, J=6.27 Hz, 3 H)

Example 28: (E)-2-(3,3-Dimethylbut-1-enyl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) and 3,3-dimethyl-1-butenylboronic acid (297 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 150 °C. Yield 280 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.13 (br s, 2 H) 7.23 (s, 1 H) 6.47 (d, J=16.31 Hz, 1 H) 6.36 (d, J=16.31 Hz, 1 H) 1.11 (s, 9 H)

Example 29: 3,4-Dihydroxy-2'-methylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (250 mg) and o-tolylboronic acid (105 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 150 °C. Yield 17 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.00-7.87 (m, 4 H) 7.27 (s, 1 H) 2.51 (s, 3 H)

Example 30: (E)-2-(2-Cyclohexylvinyl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 2-cyclohexylethenylboronic acid (95 mg)

instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 15 min at 130 °C. Yield 92 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.62 (br s, 1 H) 10.92 (br s, 2 H) 7.24 (s, 1 H) 6.43 (d, J=2.26 Hz, 2 H) 2.17-2.27 (m, 1 H) 1.68-1.81 (m, 4 H) 1.63 (d, J=11.54 Hz, 1 H) 1.13-1.37 (m, 5 H)

Example 31: (Z)-4,5-Dihydroxy-2-(prop-1-enyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (2 g) and (Z)-prop-1-enylboronic acid (744 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 120 °C. Yield 990 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.21 (br s, 2 H) 11.19 (br s, 1 H) 7.28 (s, 1 H) 6.40-6.53 (m, 1 H) 6.05-6.17 (m, 1 H) 1.63 (d, J=7.03 Hz, 3 H)

Example 32: 3-(2',6'-Dicyano-3',4'-dihydroxybiphenyl-4-yl)propanoic acid

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 4-(2-carboxyethyl)benzeneboronic acid (144 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 30 min at 130 °C. Yield 33 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.89-12.43 (m, 1 H) 10.78-11.86 (m, 2 H) 7.38 (s, 4 H) 7.33 (s, 1 H) 2.91 (t, J=7.65 Hz, 2 H) 2.61 (t, J=7.65 Hz, 2 H)

Example 33: 3,4-Dihydroxy-3'-(hydroxymethyl)biphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) and 3-(hydroxymethyl)benzeneboronic acid (282 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 30 min at 130 °C. Yield 256 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.36 (br s, 2 H) 7.42-7.52 (m, 2 H) 7.38 (s, 1 H) 7.29-7.36 (m, 2 H) 5.30 (br s, 1 H) 4.58 (s, 2 H)

Example 34: 3,4-Dihydroxy-3'-(methoxymethyl)biphenyl-2,6-dicarbonitrile

part of another group is, independently at each occurrence, unsubstituted or substituted with 1 substituent being $(C_1\text{-}C_6)$alkyl, halogen, hydroxy, $(C_1\text{-}C_6)$alkoxy or hydroxy$(C_1\text{-}C_6)$alkyl;

R_4 is, independently at each occurrence, H or aryl, wherein said aryl is, independently at each occurrence, unsubstituted or substituted with 1 substituent being $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy;

R_5 is $(C_1\text{-}C_6)$alkyl, aryl, hydroxy or $(C_1\text{-}C_6)$alkoxy, wherein said aryl is unsubstituted or substituted with 1, 2 or 3 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, carboxy, cyano, aryl, halogen, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl-S-, $(C_4\text{-}C_{10})$cycloalkenyloxy, $(C_4\text{-}C_{10})$cycloalkenyl-S-, aryloxy, aryl-S-, heteroaryloxy, heteroaryl-S-, $(R_7)_2N$-, heteroaryl, carboxy$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, heterocyclyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-(C=O)-, $(C_1\text{-}C_6)$alkoxy-(C=O)-, heterocyclyl-(C=O)-, $(R_7)_2N$-(C=O)-, halo$(C_1\text{-}C_6)$alkoxy, R_8-(S=O)-, R_8-(O=S=O)-, $(C_1\text{-}C_6)$alkoxy-(C=O)-$(C_1\text{-}C_6)$alkyl, $(R_7)_2N$-(C=O)-$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkoxy-(C=O)-, wherein said aryl, heteroaryl or heterocyclyl as such or as part of another group is, independently at each occurrence, unsubstituted or substituted with 1 substituent being $(C_1\text{-}C_6)$alkyl;

or R_6 and R_6 both attached to the same carbon ring atom form, together with the carbon ring atom to which they are attached, a -(C=O)- group;

R_7 is, independently at each occurrence, H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl or carboxy$(C_1\text{-}C_6)$alkyl, wherein said $(C_3\text{-}C_7)$cycloalkyl is, independently at each occurrence, unsubstituted or substituted with 1 substituent being $(C_1\text{-}C_6)$alkyl;

R_8 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, hydroxy, $(C_1\text{-}C_6)$alkoxy or $(R_9)_2N$-;

R_9 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl;

or a pharmaceutically acceptable salt or ester thereof.

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg and 3-methoxyethylphenylboronic acid (308 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 30 min at 150 °C. Yield 370 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.35 (br s, 2 H) 7.48-7.54 (m, 1 H) 7.42-7.48 (m, 1 H) 7.35-7.42 (m, 3 H) 4.49 (s, 2 H) 3.31 (s, 3 H)

Example 35: 2',6'-Dicyano-3',4'-dihydroxy-N,N-dipropylbiphenyl-4-carboxamide

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and 4-(dipropylcarbamoyl)phenylboronic acid (301 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 10 min at 150 °C. Yield 150 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.38 (br s, 2 H) 7.50-7.56 (m, 2 H) 7.43-7.50 (m, 2 H) 7.36 (s, 1 H) 3.39 (br s, 2 H) 3.11 (br s, 2 H) 1.62 (br s, 2 H) 1.49 (br s, 2 H) 0.92 (br s, 3 H) 0.65 (br s, 3 H)

Example 36: (E)-4,5-Dihydroxy-2-(prop-1-enyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (1 g) and trans-propenylboronic acid (372 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 150 °C. The product was recrystallized from ethanol-water solution. Yield 564 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.24 (s, 1 H) 6.38-6.61 (m, 2 H) 1.93 (d, J=4.02 Hz, 3 H)

Example 37: 3,4-Dihydroxybiphenyl-2,6-dicarbonitrile

3-Hydroxy-4-methoxybiphenyl-2,6-dicarbonitrile

To a mixture of 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (0.25 g) and phenylboronic acid (0.15 g) in ethanol (1 ml) and water (5 ml) was added

tetrakis(triphenylphosphine)palladium (0.04 mg) and 2 M sodium carbonate (1.63 ml). The stirred reaction was refluxed for 3 h. The hot reaction mixture was filtered over pall filter. After cooling, the obtained precipitate was acidified with 2 M HCl (5 ml), filtered, washed with water and dried to give 3-hydroxy-4-methoxybiphenyl-2,6-dicarbonitrile. Yield 0.14 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.49 (s, 1 H) 6.96-7.24 (m, 4 H) 3.94 (s, 3 H)

3,4-Dihydroxybiphenyl-2,6-dicarbonitrile

To a dry mixture of 3-hydroxy-4-methoxybiphenyl-2,6-dicarbonitrile (141 mg) in DCM (5 ml) under nitrogen atmosphere was added 1 M boron tribromide solution in DCM (2.82 ml) at 0 °C. The reaction mixture was warmed slowly to room temperature with stirring for 3½ h. The reaction mixture was poured into methanol (5 ml) / ice mixture. After evaporation of the solvent, water (10 ml) was added and the mixture was stirred for 1 h, followed by filtration, washing with water and drying in vacuum to give the title compound. Yield 115 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.35 (br s, 2 H) 7.50-7.55 (m, 3 H) 7.44-7.49 (m, 2 H) 7.35 (s, 1 H)

Example 38: 3',4'-Dichloro-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

Using the procedure described in Example 37, 3',4'-dichloro-3-hydroxy-4-methoxybiphenyl-2,6-dicarbonitrile (107 mg), prepared from 3,4-dichlorophenylboronic acid and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile, was demethylated to give the title compound. Yield 96 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.38 (br s, 2 H) 7.84 (d, J=2.01 Hz, 1 H) 7.82 (d, J=8.28 Hz, 1 H) 7.51 (dd, J=8.28, 2.26 Hz, 1 H) 7.35 (s, 1 H)

Example 39: 3,4-Dihydroxy-3'-(trifluoromethyl)biphenyl-2,6-dicarbonitrile

Using the procedure described in Example 37, 3-hydroxy-4-methoxy-3'-(trifluoromethyl) biphenyl-2,6-dicarbonitrile (320 mg), prepared from 3-(trifluoromethyl)phenylboronic acid and 2-bromo-4-hydroxy-5-

methoxyisophthalonitrile, was demethylated to give the title compound. Yield 239 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.19 (br s, 2H) 7.87-7.92 (m, 2 H) 7.75-7.85 (m, 2 H) 7.36 (s, 1 H)

Example 40: 2-(Furan-3-yl)-4,5-dihydroxyisophthalonitrile

Using the procedure described in Example 37, 2-(furan-3-yl)-4-hydroxy-5-methoxyisophthalonitrile (60 mg), prepared from furan-3-boronic acid and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile, was demethylated to give the title compound. Yield 56 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.68 (br s, 1 H) 11.15 (br s, 1 H) 8.00-8.12 (m, 1 H) 7.82-7.91 (m, 1 H) 7.33 (s, 1 H) 6.75-6.84 (m, 1 H)

Example 41: 3,4-Dihydroxy-4'-(trifluoromethyl)biphenyl-2,6-dicarbonitrile

Using the procedure described in Example 37, 3-hydroxy-4-methoxy-4'-(trifluoromethyl) biphenyl-2,6-dicarbonitrile (145 mg), prepared from 4-tri(fluoromethyl)phenylboronic acid and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile, was demethylated to give the title compound. Yield 139 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.41 (br s, 2H) 7.92 (d, J=8.03 Hz, 2 H) 7.74 (d, J=8.03 Hz, 2 H) 7.38 (s, 1 H)

Example 42: 4,5-Dihydroxy-2-(thiophen-3-yl)isophthalonitrile

Using the procedure described in Example 37, 4-hydroxy-5-methoxy-2-(thiophen-3-yl) isophthalonitrile (210 mg), prepared from thiophene-3-boronic acid and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile, was demethylated to give the title compound. Yield 110 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.56 (br s, 1 H) 11.12 (br s, 1 H) 7.83 (dd, J=3.0, 1.2 Hz, 1 H) 7.72 (dd, J=5.0 Hz, 1 H) 7.33 (s, 1 H) 7.30 (dd, 1 H)

Example 43: 4,5-Dihydroxy-2-(5-methylfuran-2-yl)isophthalonitrile

Using the procedure described in Example 37, 4-hydroxy-5-methoxy-2-(5-methylfuran-2-yl)isophthalonitrile (150 mg), prepared from 5-methylfuran-2-boronic acid and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile, was demethylated to give the title compound. Yield 90 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.39 (br s, 2 H) 7.31 (s, 1 H) 6.88 (d, J=3.3 Hz, 1 H) 6.21-6.48 (m, 1 H) 2.35 (s, 3 H)

Example 44: 4,5-Dihydroxy-2-(5-methylthiophen-2-yl)isophthalonitrile

Using the procedure described in Example 37, 4-hydroxy-5-methoxy-2-(5-methylthiophen-2-yl)isophthalonitrile (250 mg), prepared from 5-methylthiophene-2-boronic acid and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile, was demethylated to give the title compound. Yield 130 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.41 (br s, 2 H) 7.31 (s, 1 H) 7.13 (d, J=3.5 Hz, 1 H) 6.88-6.95 (m, 1 H) 2.52 (br s, 3 H)

Example 45: 2-Benzyl-4,5-dihydroxyisophthalonitrile

2-Benzyl-4-hydroxy-5-methoxyisophthalonitrile

To a mixture of 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (1.0 g) and benzylboronic acid pinacol ester (0.53 ml) in 1,4-dioxane (5 ml) and water (5 ml) was added Pd(dppf)Cl_2 complex with CH_2Cl_2 (1:1) (0.260 g) and cesium carbonate (3.8 g). The stirred reaction was microwave-irradiated at 120 °C for 30 min. The hot reaction mixture was filtered over pall filter. After cooling, the obtained precipitate was acidified with 2 M HCl (5 ml), filtered, washed with water and dried to give 2-benzyl-4-hydroxy-5-methoxyisophthalonitrile. Yield 0.77 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.49 (s, 1 H) 6.96-7.24 (m, 4 H) 3.94 (s, 3 H)

2-Benzyl-4,5-dihydroxyisophthalonitrile

2-Benzyl-4-hydroxy-5-methoxyisophthalonitrile (1.5 g) was demethylated using boron tribromide as described in Example 37 to give the title compound. Yield 0.77 g

^{1}H NMR (DMSO-d_6) ppm 10.8-11.6 (br, 2 H) 7.29 (s, 1 H) 7.15-7.35 (m, 5 H) 4.16 (s, 2 H)

Example 46: 2-(Benzofuran-2-yl)-4,5-dihydroxyisophthalonitrile

Using the procedure described in Example 37, 2-(benzofuran-2-yl)-4-hydroxy-5-methoxyisophthalonitrile (320 mg), prepared from 2-benzofuranboronic acid and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile, was demethylated to give the title compound. Yield 200 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.60 (br s, 2 H) 7.80 (d, J=7. 8 Hz, 1 H) 7.68 (d, J=8. 3 Hz, 1 H) 7.40-7.48 (m, 3 H) 7.32-7.39 (m, 1 H)

Example 47: 2-(5-Chlorothiophen-2-yl)-4,5-dihydroxyisophthalonitrile

Using the procedure described in Example 37, 2-(5-chlorothiophen-2-yl)-4-hydroxy-5-methoxyisophthalonitrile (27 mg), prepared from 5-chlorothiophene-2-boronic acid and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile, was demethylated to give the title compound. Yield 20 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.35 (br s, 2 H) 7.34 (s, 1 H) 7.27 (d, J=3.9 Hz, 1 H) 7.24 (d, 1 H)

Example 48: 2-(Benzo[b]thiophen-2-yl)-4,5-dihydroxyisophthalonitrile

Using the procedure described in Example 37, 2-(benzo[b]thiophen-2-yl)-4-hydroxy-5-methoxyisophthalonitrile (70 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and thianaphthene-2-boronic acid, was demethylated to give the title compound. Yield 50 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.43-12.58 (m, 2 H) 8.04-8.11 (m, 1 H) 7.94-8.01 (m, 1 H) 7.67 (s, 1 H) 7.44-7.51 (m, 2 H) 7.39 (s, 1 H)

Example 49: (E)-4,5-Dihydroxy-2-styrylisophthalonitrile

Using the procedure described in Example 37, (E)-4-hydroxy-5-methoxy-2-styrylisophthalonitrile (100 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and trans-2-phenylvinylboronic acid, was demethylated to give the title compound. Yield 79 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.61 (d, J=7.28 Hz, 2 H) 7.41-7.48 (m, 2 H) 7.21-7.41 (m, 4 H)

Example 50: 4'-Ethyl-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

Using the procedure described in Example 37, 4'-ethyl-3-hydroxy-4-methoxybiphenyl-2,6-dicarbonitrile (150 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 4-ethylbenzeneboronic acid, was demethylated to give the title compound. Yield 100 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.33-7.41 (m, 5 H) 2.70 (m, J=7.50, 7.50, 7.50 Hz, 2 H) 1.25 (t, J=7.53 Hz, 3 H)

Example 51: 3,4-Dihydroxy-3',5'-dimethylbiphenyl-2,6-dicarbonitrile

Using the procedure described in Example 37, 3-hydroxy-4-methoxy-3',5'-dimethylbiphenyl-2,6-dicarbonitrile (115 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 3,5-dimethylbenzeneboronic acid, was demethylated to give the title compound. Yield 70 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.32 (s, 1 H) 7.14 (s, 1 H) 7.04 (s, 2 H) 2.33 (s, 6 H)

Example 52: 4,5-Dihydroxy-2-(phenylthio)isophthalonitrile

4-Hydroxy-5-methoxy-2-(phenylthio)isophthalonitrile

To a mixture of 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (0.5 g) in THF (8 ml) was added phenyl disulfide (0.26 g) and Pd(dppf)Cl_2 complex with CH_2Cl_2 (1:1) (0.13 g). The stirred reaction was refluxed for 24 h. The hot reaction mixture was filtered over pall filter. After cooling, the obtained precipitate was

acidified with 2 M HCl (5 ml), filtered, washed with water and dried to give 4-hydroxy-5-methoxy-2-(phenylthio)isophthalonitrile. Yield 0.45 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.29 (s, 1 H) 7.01-7.18 (m, 4 H) 3.68 (s, 2 H)

4,5-Dihydroxy-2-(phenylthio)isophthalonitrile

4-Hydroxy-5-methoxy-2-(phenylthio)isophthalonitrile (400 mg) was demethylated using boron tribromide as described in Example 37 to give the title compound. Yield 164 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.25-7.40 (m, 6 H)

Example 53: 4,5-Dihydroxy-2-(p-tolylthio)isophthalonitrile

4-Hydroxy-5-methoxy-2-(p-tolylthio)isophthalonitrile (400 mg), which was prepared as described in Example 52, except that p-tolyl disulfide was used instead of phenyl disulfide, was demethylated using boron tribromide as described in Example 37 to give the title compound. Yield 65 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.45 (br s, 2 H) 7.36 (s, 1 H) 7.17 (d, J=8.28 Hz, 2 H) 7.12 (d, J=8.28 Hz, 2 H) 2.27 (s, 3 H)

Example 54: 4,5-Dihydroxy-2-(4-methylbenzyl)isophthalonitrile

4-Hydroxy-5-methoxy-2-(4-methylbenzyl)isophthalonitrile

To a mixture of 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (1.00 g) and 4,4,5,5-tetramethyl-2-(4-methylbenzyl)-1,3,2-dioxaborolane (1.38 g) in ethanol (2.5 ml) and water (22 ml) was added Pd(dppf)Cl_2 complex with CH_2Cl_2 (1:1) (0.26 g) and sodium hydrogen carbonate (1.32 g). The stirred reaction was refluxed for 3 h. The hot reaction mixture was filtered over pall filter. After cooling, the obtained precipitate was acidified with 2 M HCl (10 ml), filtered, washed with water and dried to give 4-hydroxy-5-methoxy-2-(4-methylbenzyl)isophthalonitrile. Yield 0.53 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.66 (s, 1 H) 6.96-7.24 (m, 4 H) 4.13 (s, 2 H) 3.90 (s, 3 H) 2.26 (s, 3 H)

4,5-Dihydroxy-2-(4-methylbenzyl)isophthalonitrile

4-Hydroxy-5-methoxy-2-(4-methylbenzyl)isophthalonitrile (1.00 g) in acetonitrile (15 ml) was slowly added to a solution of aluminum chloride (0.95 g) and sodium iodide (1.07 g) in acetonitrile (15 ml) 0 °C. The reaction mixture was heated at 50 °C for 3 h. Methanol (50 ml) was added and the solution was evaporated to dryness. 2 M NaOH (10 ml) and toluene (20 ml) was added and the mixture was stirred for 1 h. The aqueous phase was washed twice with toluene (10 ml) and made acidic by concentrated HCl at 0 °C. The product was filtered, washed with water and dried to give the title compound. Yield 0.90 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.29 (s, 1 H) 6.92-7.21 (m, 4 H) 4.10 (s, 2 H) 2.25 (s, 3 H)

Example 55: 2-(4-Fluorobenzyl)-4,5-dihydroxyisophthalonitrile

2-(4-Fluorobenzyl)-4-hydroxy-5-methoxyisophthalonitrile

2-(4-Fluorobenzyl)-4-hydroxy-5-methoxyisophthalonitrile was prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (1.00 g) and 2-(4-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.30 g) instead of 4,4,5,5-tetramethyl-2-(4-methylbenzyl)-1,3,2-dioxaborolane using the procedure analogous to Example 54. Yield 0.53 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.68 (s, 1 H) 7.04-7.29 (m, 4 H) 4.18 (s, 2 H) 3.90 (s, 3 H)

2-(4-Fluorobenzyl)-4,5-dihydroxyisophthalonitrile

2-(4-Fluorobenzyl)-4-hydroxy-5-methoxyisophthalonitrile (200 mg) was converted to the title compound using the procedure analogous to Example 54. Yield 96 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.29 (s, 1 H) 7.12-7.23 (m, 4 H) 4.14 (s, 2 H)

Example 56: 4,5-Dihydroxy-2-(4-hydroxybenzyl)isophthalonitrile

Using the procedure analogous to Example 54, 4-hydroxy-5-methoxy-2-(4-methoxybenzyl)isophthalonitrile (250 mg), prepared from 4-methoxybenzylboronic acid pinacol ester and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (1.00 g), was demethylated to give the title compound. Yield 96 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.37 (s, 1 H) 6.96 (d, J=1.00 Hz, 2 H) 6.69 (d, J=1.00 Hz, 2 H) 4.01 (s, 2 H)

Example 57: 4,5-Dihydroxy-2-(2-methoxybenzyl)isophthalonitrile

Using the procedure analogous to Example 54, 4-hydroxy-5-methoxy-2-(2-methoxybenzyl)isophthalonitrile (116 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(2-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 17.6 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.28 (s, 1 H) 7.23 (t, J=7.28 Hz, 1 H) 6.99 (d, J=8.28 Hz, 1 H) 6.84 (t, J=7.40 Hz, 1 H) 6.70 (d, J=7.28 Hz, 1 H) 4.07 (s, 2 H) 3.81 (s, 3 H)

Example 58: 4,5-Dihydroxy-2-(4-(trifluoromethoxy)benzyl)isophthalonitrile

Using the procedure analogous to Example 54, 4-hydroxy-5-methoxy-2-(4-(trifluoromethoxy)benzyl)isophthalonitrile (260 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 4-(trifluoromethoxy)benzylboronic acid pinacol ester, was demethylated to give the title compound. Yield 130 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.25-7.36 (m, 5 H) 4.18 (s, 2 H)

Example 59: 2-(3-Fluoro-4-methoxybenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, 2-(3-fluoro-4-methoxybenzyl)-4,5-dihydroxyisophthalonitrile (600 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(3-fluoro-4-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 175 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.36 (s, 1 H) 7.11 (t, J=8.78 Hz, 1 H) 7.01 (dd, J=1.00 Hz, 1 H) 6.91 (br d, J=1.00 Hz, 1 H) 4.09 (s, 2 H) 3.80 (s, 3 H)

Example 60: 2-(2-Fluorobenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, 2-(2-fluorobenzyl)-4-hydroxy-5-methoxyisophthalonitrile (200 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(2-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 86 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.27-7.34 (m, 2 H) 7.16-7.24 (m, 1 H) 7.13 (t, J=7.53 Hz, 1 H) 6.95 (t, J=7.53 Hz, 1 H) 4.17 (s, 2 H)

Example 61: 4,5-Dihydroxy-2-(2-methylbenzyl)isophthalonitrile

Using the procedure analogous to Example 54, 4-hydroxy-5-methoxy-2-(2-methylbenzyl)isophthalonitrile (550 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 4,4,5,5-tetramethyl-2-(2-methylbenzyl)-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 152 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.33 (s, 1 H) 7.22 (d, J=7.07 Hz, 1 H) 7.12 (d, J=7.07 Hz, 1 H) 7.07 (d, J=7.58 Hz, 1 H) 6.47 (d, J=7.58 Hz, 1 H) 4.10 (s, 2 H) 2.38 (s, 3 H)

Example 62: 2-(2,5-Dimethylbenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, (2,5-dimethylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile (578 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(2,5-dimethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 39 mg

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_4\text{-}C_{10})$cycloalkenyl, aryl, halogen, hydroxy, $(C_4\text{-}C_{10})$cycloalkenyloxy, aryloxy, aryl-S-, heteroaryl-S-, $(R_3)_2N$-, $(R_4)_2C{=}N$-, heterocyclyl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(R_3)_2N$-$(C_1\text{-}C_6)$alkyl, heterocyclyl$(C_1\text{-}C_6)$alkyl, carboxy$(C_2\text{-}C_6)$alkenyl, $(C_3\text{-}C_7)$cycloalkyl$(C_2\text{-}C_6)$alkenyl, aryl$(C_2\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_6)$alkenyl, heteroaryl$(C_2\text{-}C_6)$alkenyl, aryl$(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_6)$alkynyl, R_5-(S=O)-, R_5-(O=S=O)- or $(C_1\text{-}C_6)$alkoxy-(C=O)-$(C_2\text{-}C_6)$alkenyl, wherein said $(C_4\text{-}C_{10})$cycloalkenyl, aryl, heterocyclyl, heteroaryl or $(C_3\text{-}C_7)$cycloalkyl as such or as part of another group is unsubstituted or substituted with 1, 2 or 3 substituent(s) R_6;

R_3 is, independently at each occurrence, H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl, aryl, $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, wherein said $(C_3\text{-}C_7)$cycloalkyl or aryl as such or as part of another group is unsubstituted or substituted with 1 substituent being $(C_1\text{-}C_6)$alkyl;

R_4 is, independently at each occurrence, H or aryl, wherein said aryl is, independently at each occurrence, substituted with 1 substituent being $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy;

R_5 is aryl, wherein said aryl is substituted with 1 substituent R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, carboxy, cyano, aryl, halogen, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl-S-, aryloxy, heteroaryl, carboxy$(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, heterocyclyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-(C=O)-, $(C_1\text{-}C_6)$alkoxy-(C=O)-, heterocyclyl-(C=O)-, $(R_7)_2N$-(C=O)-, halo$(C_1\text{-}C_6)$alkoxy, R_8-(O=S=O)-, $(C_1\text{-}C_6)$alkoxy-(C=O)-$(C_1\text{-}C_6)$alkyl, $(R_7)_2N$-(C=O)-$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkoxy-(C=O)-, wherein said aryl, heteroaryl or heterocyclyl as such or as part of another group is, independently at each occurrence, unsubstituted or substituted with 1 substituent being $(C_1\text{-}C_6)$alkyl;

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.33 (s, 1 H) 7.10 (d, J=7.28 Hz, 1 H) 6.93 (d, J=7.03 Hz, 1 H) 6.28 (br s, 1 H) 4.06 (br s, 2 H) 2.32 (s, 3 H) 2.13 (s, 3 H)

Example 63: 2-(3-Fluoro-5-methylbenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, 2-(3-fluoro-5-methylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile (600 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(3-fluoro-5-methylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 91 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.30 (s, 1 H) 6.91 (d, J=9.79 Hz, 1 H) 6.80 (s, 1 H) 6.75 (d, J=9.79 Hz, 1 H) 4.13 (s, 2 H) 2.27 (s, 3 H)

Example 64: 3-(2,6-Dicyano-3,4-dihydroxybenzyl)benzoic acid

Using the procedure analogous to Example 54, 3-(2,6-dicyano-3-hydroxy-4-methoxybenzyl)benzoic acid (300 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and methyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzoate, was demethylated to give the title compound. Yield 43 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.75 (s, 1 H) 7.26-7.56 (m, 4 H) 4.22 (s, 2 H)

Example 65: 2-(4-Fluoro-3-methylbenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, 2-(4-fluoro-3-methylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile (600 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(4-fluoro-3-methylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 24 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.29 (s, 1 H) 7.03-7.12 (m, 2 H) 6.99 (br s, 1 H) 4.10 (br s, 2 H) 2.19 (br s, 3 H)

Example 66: 4,5-Dihydroxy-2-(3-methylbenzyl)isophthalonitrile

Using the procedure analogous to Example 54, 4-hydroxy-5-methoxy-2-(3-methylbenzyl)isophthalonitrile (600 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 4,4,5,5-tetramethyl-2-(3-methylbenzyl)-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 43 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.57 (br s, 1 H) 10.93 (br s, 1 H) 7.29 (br s, 1 H) 7.19 (br s, 1 H) 6.79-7.09 (m, 3 H) 4.11 (s, 2 H) 2.26 (s, 3 H)

Example 67: 2-(5-Fluoro-2-methoxybenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, 2-(5-fluoro-2-methoxybenzyl)-4-hydroxy-5-methoxyisophthalonitrile (400 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(5-fluoro-2-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 7 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.09 (br s, 1 H) 10.95 (br s, 1 H) 7.29 (s, 1 H) 6.92-7.11 (m, 2 H) 6.55 (d, J=9.03 Hz, 1 H) 4.06 (s, 2 H) 3.79 (s, 3 H)

Example 68: 2-(3,5-Dimethylbenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, 2-(3,5-dimethylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile (578 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(3,5-dimethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 120 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.30 (s, 1 H) 6.86 (s, 1 H) 6.76 (s, 2 H) 4.07 (s, 2 H) 2.21 (s, 6 H)

Example 69: 4,5-Dihydroxy-2-(4-isopropylbenzyl)isophthalonitrile

Using the procedure analogous to Example 54, 4-hydroxy-2-(4-isopropylbenzyl)-5-methoxyisophthalonitrile (600 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(4-isopropylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 21 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.28 (s, 1 H) 7.18 (d, J=1.00 Hz, 2 H) 7.10 (d, J=1.00 Hz, 2 H) 4.10 (s, 2 H) 2.79-2.88 (m, 1 H) 1.17 (d, J=6.78 Hz, 6 H)

Example 70: 2-(4-Ethylbenzyl)-4,5-dihydroxyisophthalonitrile

2-(4-Ethylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile

To a mixture of 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (2.57 g) and 2-(4-ethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.75 g) in ethanol (5 ml) and water (40 ml) was added Pd(dppf)Cl_2 complex with CH_2Cl_2 (1:1) (0.67 g) and sodium hydrogen carbonate (3.40 g). The stirred reaction was refluxed for 3 h. The hot reaction mixture was filtered over pall filter. After cooling, the obtained precipitate was acidified with 2 M HCl (20 ml), filtered, washed with water and dried to give 2-(4-ethylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile. Yield 2.31 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.41 (s, 1 H) 7.08-7.17 (m, 4 H) 4.08 (s, 2 H) 3.82 (s, 3 H) 2.55 (q, J=7.61 Hz, 2 H) 1.14 (t, J=7.53 Hz, 3 H)

2-(4-Ethylbenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure described in Example 54, 2-(4-ethylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile (2.31 g) was converted to the title compound. Yield 2.15 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.28 (s, 1 H) 7.12-7.17 (m, 2 H) 7.07-7.12 (m, 2 H) 4.11 (s, 2 H) 2.53-2.59 (m, 2 H) 1.14 (t, J=7.65 Hz, 3 H)

Example 71: 4,5-Dihydroxy-2-(naphthalen-1-ylmethyl)isophthalonitrile

Using the procedure analogous to Example 54, 4-hydroxy-5-methoxy-2-(naphtalen-1-ylmethyl)isophthalonitrile (100 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 4,4,5,5-tetramethyl-2-(naphthalen-1-ylmethyl)-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 40 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.50-6.50 (m, 8 H) 4.72 (m, 2 H)

Example 72: 5-(2,6-Dicyano-3,4-dihydroxybenzyl)-2-hydroxybenzoic acid

Using the procedure analogous to Example 54, 5-(2,6-dicyano-3-hydroxy-4-methoxybenzyl)-2-hydroxybenzoic acid (300 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-hydroxy-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzoic acid, was demethylated to give the title compound. Yield 38 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.29-11.80 (m, 1 H) 10.95 (br s, 1 H) 7.33 (s, 1 H) 7.10 (d, J=7.78 Hz, 1 H) 6.93 (d, J=7.78 Hz, 1 H) 6.27 (s, 1 H) 4.06 (s, 2 H)

Example 73: 2-(2,4-Dimethylbenzyl)-4,5-dihydroxyisophthalonitrile

2-(2,4-Dimethylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile

To a mixture of 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (0.86 g) and 2-(2,4-dimethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.13 g) in ethanol (2.5 ml) and water (22 ml) was added Pd(dppf)Cl_2 complex with CH_2Cl_2 (1:1) (0.21 g) and sodium hydrogen carbonate (1.10 g). The stirred reaction was refluxed for 3 h. The hot reaction mixture was filtered over pall filter. After cooling, the obtained precipitate was acidified with 2 M HCl (10 ml), filtered, washed with water and dried to give 2-(2,4-dimethylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile. Yield 0.43 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.70 (s, 1 H) 7.04 (s, 1 H) 6.87 (d, J=7.78 Hz, 1 H) 6.34 (d, J=7.78 Hz, 1 H) 4.08 (s, 2 H) 3.93 (s, 3 H) 2.34 (s, 3 H) 2.22 (s, 3 H)

2-(2,4-Dimethylbenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure described in Example 54, 2-(2,4-dimethylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile (0.43 g) was converted to the title compound. Yield 0.40 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.31 (s, 1 H) 7.02 (s, 1 H) 6.86 (d, J=8.03 Hz, 1 H) 6.34 (d, J=7.78 Hz, 1 H) 4.04 (s, 2 H) 2.33 (s, 3 H) 2.21 (s, 3 H)

Example 74: 2-(3,6-Dihydro-2H-pyran-4-yl)-4,5-dihydroxyisophthalonitrile

3,6-Dihydro-2H-pyran-4-boronic acid pinacol ester (156 mg), bis(triphenylphosphine)palladium(II) chloride (24 mg) and sodium carbonate (197 mg) in water solution (2 ml) was added to a solution of 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg), ethanol (2 ml) and acetonitrile (2 ml). The reaction mixture was microwave-irradiated for 15 min at 130 °C. The reaction mixture was poured in ice water and 2 M NaOH (15 ml) and toluene (20 ml) was added. The mixture was stirred for half an hour. The water phase was washed with toluene (20 ml) and then made acidic by addition of 4 M HCl (10 ml) under cooling. The product was filtered, washed with water and dried to give the title compound. Yield 133 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.26 (s, 1 H) 5.95 (br s, 1 H) 4.21 (d, J=2.51 Hz, 2 H) 3.81 (t, J=5.14 Hz, 2 H) 2.30-2.37 (m, 2 H)

Example 75: 2-Cyclopentenyl-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the procedure analogous to Example 74 using as reactant 1-cyclopentenylboronic acid pinacol ester (144 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 0.4 h at 130 °C. Yield 114 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.25 (s, 1 H) 6.02 (br s, 1 H) 2.60-2.76 (m, 2 H) 2.10-2.30 (m, 2 H) 1.92-2.08 (m, 2 H)

Example 76: (E)-3-(2,6-Dicyano-3,4-dihydroxyphenyl)acrylic acid

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) by the procedure analogous to Example 74 using as reactant 2-(ethoxycarbonyl)vinylboronic acid pinacol ester (420 mg) instead of

3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 0.4 h at 150 °C. Yield 260 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.65 (d, J=16.31 Hz, 1 H) 7.32 (s, 1 H) 6.74 (d, J=16.06 Hz, 1 H)

Example 77: (E)-4,5-Dihydroxy-2-(3-methoxyprop-1-enyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the procedure analogous to Example 74 using as reactant trans-3-methoxy-1-propenylboronic acid pinacol ester (147 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 30 min at 130 °C. Yield 70 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.26 (s, 1 H) 6.40-6.77 (m, 2 H) 4.02-4.20 (m, 2 H) 3.33 (s, 3 H)

Example 78: 4,5-Dihydroxy-2-(5-(morpholinomethyl)thiophen-2-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the procedure analogous to Example 74 using as reactant 5-(morpholinomethyl)-2-thiopheneboronic acid pinacol ester (249 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 10 min at 150 °C. Yield 80 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.48 (d, J=3.51 Hz, 1 H) 7.45 (s, 1 H) 7.36 (d, J=3.76 Hz, 1 H) 4.64 (s, 2 H) 3.87 (br s, 4 H) 3.18 (br s, 4 H)

Example 79: 3,4-Dihydroxy-4'-(morpholine-4-carbonyl)biphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) by the procedure analogous to Example 74 using as reactant (4-(morpholine-4-carbonyl)phenyl)boronic acid pinacol ester (383 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 10 min at 140 °C. Yield 120 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.99-8.12 (m, 2 H) 7.58-7.68 (m, 2 H) 7.37 (s, 1 H) 3.16-3.74 (m, 4 H)

Example 80: 2-(5'-Hexyl-2,2'-bithiophen-5-yl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the procedure analogous to Example 74 using as reactant 5'-hexyl-2,2'-bithiophene-5-boronic acid pinacol ester (303 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 10 min at 140 °C. Yield 22 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.33 (s, 1 H) 7.30 (d, J=3.76 Hz, 1 H) 7.27 (d, J=1.00 Hz, 1 H) 7.20 (d, J=3.51 Hz, 1 H) 6.84 (d, J=3.26 Hz, 1 H) 2.80 (t, J=7.28 Hz, 2 H) 1.58-1.68 (m, 2 H) 1.23-1.39 (m, 6 H) 0.81-0.91 (m, 3 H)

Example 81: 2-(1-Benzyl-1H-pyrazol-4-yl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) by the procedure analogous to Example 74 using as reactant 1-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (317 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 10 min at 140 °C. Yield 82 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.37 (s, 1 H) 7.88 (s, 1 H) 7.33-7.50 (m, 6 H) 5.54 (s, 2 H)

Example 82: 2-(5-Hexylthiophen-2-yl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) by the procedure analogous to Example 74 using as reactant 5-hexyl-2-thiopheneboronic acid pinacol ester (355 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 10 min at 140 °C. Yield 40 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.31 (s, 1 H) 7.14 (d, J=1.00 Hz, 1 H) 6.93 (br s, 1 H) 2.84 (t, J=7.15 Hz, 2 H) 1.61-1.70 (m, 2 H) 1.23-1.36 (m, 6 H) 0.86 (br s, 3 H)

Example 83: (Z)-2-(But-2-enyl)-4,5-dihydroxyisophthalonitrile

cis-Crotylboronic acid pinacol ester (99 mg), bis(triphenylphosphine)palladium(II) chloride (29 mg) and sodium carbonate (133 mg) was added 2-bromo-4,5-dihydroxyisophthalonitrile (100 mg) solution containing ethanol (1 ml), acetonitrile (1 ml) and water (1 ml) as a solvent. The reaction mixture was stirred and microwave-irradiated for 45 min at 120 °C. The reaction mixture was filtered through celite and poured in ice water. 2 M NaOH (15 ml) and toluene (20 ml) was added. The mixture was stirred for half an hour. The water phase was washed twice with toluene (20 ml) and made acidic by adding 4 M HCl keeping the temperature at 0-5 °C. The solid product was filtered, washed with water and toluene and dried. Yield 36.6 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.5 (s, 1 H) 5.92 (dd, J=10.29, 5.77 Hz, 1 H) 5.54 (dd, J=10.42, 5.65 Hz, 1 H) 3.73-3.74 (d, J=5.00 Hz, 2 H) 1.68 (d, J=5.02 Hz, 3 H)

Example 84: 4,5-Dihydroxy-2-(3-methylbut-2-enyl)isophthalonitrile

3-Methyl-2-butenylboronic acid pinacol ester (392 mg), bis(triphenylphosphine)palladium(II) chloride (47 mg) and sodium carbonate (426 mg) was added in 2-bromo-4,5-dihydroxyisophthalonitrile (320 mg) solution containing ethanol (5 ml), acetonitrile (5 ml) and water (5 ml) as a solvent. The reaction mixture was stirred and microwave-irradiated for 60 min at 120 °C. The reaction mixture was filtered through celite and organic solvents were evaporated. 0.1 M NaOH was added and the mixture was washed with toluene and EtOAc. The water phase was made acidic by adding HCl. The solid product was filtered, washed with water and toluene and dried. Yield 306 mg

^{1}H NMR (400 MHz, DMSO-d_6) d ppm 7.23 (s, 1 H) 5.09 (t, J=7.03 Hz, 1 H) 3.49 (d, J=7.03 Hz, 2 H) 1.75 (s, 3 H) 1.68 (s, 3 H)

Example 85: (E)-2-(But-2-enyl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 2-bromo-4,5-dihydroxyisophthalonitrile (100 mg) as described in Example 83 using trans-crotylboronic acid pinacol ester (99 mg) instead of cis-crotylboronic acid pinacol ester. Reaction conditions: 60 min at 120 °C. Yield 30 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.5 (s, 1 H) 5.92 (dd, J=10.29, 5.77 Hz, 1 H) 5.56 (dd, J=10.42, 5.65 Hz, 1 H) 3.73-3.75 (d, J=5.00 Hz, 2 H) 1.72 (d, J=5.02 Hz, 3 H)

Example 86: 4,5-Dihydroxy-2-methylisophthalonitrile

To a mixture of 4-hydroxy-5-methoxy-2-methylisophthalonitrile (565 mg), DCM (30 ml) and acetonitrile (30 ml) under nitrogen atmosphere was added 1 M boron tribromide solution in DCM (6.0 ml) at -20 °C. The reaction mixture was allowed to warm overnight to room temperature. Water (0.3 ml) was added to the reaction mixture followed by addition of methanol until clear reaction mixture was achieved. The mixture was evaporated to dryness and the remainder was chromatographed over silica gel with EtOAc/AcOH solvent mixture. Yield 0.27 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.97 (br s, 2 H) 7.17 (s, 1 H) 2.44 (s, 3 H)

Example 87: 4,5-Dihydroxy-2-(2-methylprop-1-enyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (395 mg) by the method of Example 2 using 2-methylpropene-1-tributylstannane (528 mg) instead of phenylethynyltri-n-butyltin. Yield 198 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.20 (br s, 2 H) 7.27 (s, 1 H) 6.20-6.26 (m, 1 H) 1.92 (d, J=1.25 Hz, 3 H) 1.62 (d, J=1.00 Hz, 3 H)

Example 88: 3,4-Dihydroxy-3'-methylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (352 mg) by the method of Example 2 using tributyl(m-tolyl)stannane (235 mg) instead of phenylethynyltri-n-butyltin. Yield 273 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.31 (br s, 2 H) 7.37-7.44 (m, 1 H) 7.29-7.36 (m, 2 H) 7.21-7.29 (m, 2 H) 2.38 (s, 3 H)

Example 89: 4,5-Dihydroxy-2-vinylisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the method of Example 2 using tributyl(vinyl)stannane (255 mg) instead of phenylethynyltri-n-butyltin. Yield 50 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.30 (br s, 2 H) 7.28 (s, 1 H) 6.83 (dd, J=17.57, 11.54 Hz, 1 H) 6.03 (d, J=17.57 Hz, 1 H) 5.78 (d, J=11.54 Hz, 1 H)

Example 90: 4,5-Dihydroxy-2-(prop-1-en-2-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) by the method of Example 2 using 2-(tributylstannyl)propene (641 mg) instead of phenylethynyltri-n-butyltin. Yield 210 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.35 (br s, 1 H) 7.26 (s, 1 H) 5.49 (s, 1 H) 5.09 (s, 1 H) 2.07 (s, 3 H)

Example 91: 2-(2-Ethoxythiazol-5-yl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the method of Example 2 using 2-ethoxy-5-(tributylstannyl)thiazole (311 mg) instead of phenylethynyltri-n-butyltin. Yield 60 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.36 (br s, 1 H) 7.40 (s, 1 H) 7.34 (s, 1 H) 4.50 (m, J=7.00, 7.00, 7.00 Hz, 2 H) 1.40 (t, J=6.90 Hz, 3 H)

Example 92: 2-Allyl-4,5-dihydroxyisophthalonitrile

or R_6 and R_6 both attached to the same carbon ring atom form, together with the carbon ring atom to which they are attached, a -(C=O)- group;

R_7 is, independently at each occurrence, H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl or carboxy$(C_1$-$C_6)$alkyl, wherein said $(C_3$-$C_7)$cycloalkyl is unsubstituted;

R_8 is, independently at each occurrence, $(C_1$-$C_6)$alkyl or $(R_9)_2N$-;

R_9 is, independently at each occurrence, $(C_1$-$C_6)$alkyl.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_4$-$C_{10})$cycloalkenyl, aryl, halogen, $(C_4$-$C_{10})$cycloalkenyloxy, aryloxy, aryl-S-, heteroaryl-S-, $(R_3)_2N$-, $(R_4)_2C$=N-, heterocyclyl, heteroaryl, aryl$(C_1$-$C_6)$alkyl, $(R_3)_2N$-$(C_1$-$C_6)$alkyl, carboxy$(C_2$-$C_6)$alkenyl, $(C_3$-$C_7)$cycloalkyl$(C_2$-$C_6)$alkenyl or aryl$(C_2$-$C_6)$alkenyl, wherein said $(C_4$-$C_{10})$cycloalkenyl, aryl, heterocyclyl, heteroaryl or $(C_3$-$C_7)$cycloalkyl as such or as part of another group is unsubstituted or substituted with 1, 2 or 3 substituent(s) R_6;

R_3 is, independently at each occurrence, H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl;

R_4 is, independently at each occurrence, H or aryl, wherein said aryl is, independently at each occurrence, substituted with 1 substituent being $(C_1$-$C_6)$alkyl, halogen or $(C_1$-$C_6)$alkoxy;

R_6 is, independently at each occurrence, $(C_1$-$C_6)$alkyl, cyano, aryl, halogen, hydroxy, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkyl-S-, carboxy$(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, heterocyclyl-(C=O)-, $(R_7)_2N$-(C=O)-, R_8-(O=S=O)- or $(C_1$-$C_6)$alkoxy-(C=O)-$(C_1$-$C_6)$alkyl, wherein said aryl or heterocyclyl as such or as part of another group is unsubstituted;

R_7 is, independently at each occurrence, H, $(C_1$-$C_6)$alkyl or $(C_3$-$C_7)$cycloalkyl, wherein said $(C_3$-$C_7)$cycloalkyl is unsubstituted;

R_8 is, independently at each occurrence, $(C_1$-$C_6)$alkyl or $(R_9)_2N$-;

R_9 is, independently at each occurrence, $(C_1$-$C_6)$alkyl.

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (250 mg) by the method of Example 2 using allyltri-n-butyltin (512 mg) instead of phenylethynyltri-n-butyltin. Yield 28 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.7-11.8 (br, s, 2 H) 7.25 (s, 1 H) 5.90 (m, 1 H) 5.11 (m, 1 H) 4.95 (m, 1 H) 3.52 (m, 2 H)

Example 93: 3'-(tert-Butoxymethyl)-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) and (3-(tert-butoxymethyl)phenyl)boronic acid (322 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 30 min at 150 °C. Yield 250 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.27 (br s, 2 H) 7.41-7.53 (m, 2 H) 7.29-7.41 (m, 3 H) 4.49 (s, 2 H) 1.24 (s, 9 H)

Example 94: tert-Butyl 2',6'-dicyano-3',4'-dihydroxybiphenyl-3-carboxylate

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) and 3-tert-butoxycarbonylphenylboronic acid (344 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 30 min at 150 °C. Yield 67 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.43 (br s, 2 H) 8.03 (d, J=8.03 Hz, 1 H) 7.96 (s, 1 H) 7.74 (d, J=7.28 Hz, 1 H) 7.67 (t, J=7.53 Hz, 1 H) 7.36 (s, 1 H) 1.56 (s, 9 H)

Example 95: 3,4-Dihydroxybiphenyl-2,3',6-tricarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) and 3-cyanophenylboronic acid (227 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 30 min at 150 °C. Yield 141 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.39 (br s, 1 H) 8.06 (s, 1 H) 8.01 (d, J=7.78 Hz, 1 H) 7.86 (d, J=8.03 Hz, 1 H) 7.76 (t, J=7.91 Hz, 1 H) 7.39 (s, 1 H)

Example 96: 2',6'-Dicyano-3',4'-dihydroxy-N,N-dipropylbiphenyl-3-carboxamide

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and 3-(dipropylcarbamoyl)phenylboronic acid (231 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 10 min at 150 °C. Yield 40 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.36 (br s, 2 H) 7.59 (t, J=7.65 Hz, 1 H) 7.51 (d, J=7.78 Hz, 1 H) 7.46 (d, J=7.53 Hz, 1 H) 7.34-7.40 (m, 2 H) 3.27-3.35 (m, 2 H) 3.19 (br s, 2 H) 1.60 (br s, 2 H) 1.45 (br s, 2 H) 0.91 (br s, 3 H) 0.65 (br s, 3 H)

Example 97: 2',6'-Dicyano-N-cyclohexyl-3',4'-dihydroxybiphenyl-4-carboxamide

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and 4-(cyclohexylaminocarbonyl)phenylboronic acid (275 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 5 min at 150 °C. Yield 190 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.38 (br s, 2 H) 8.36 (d, J=7.78 Hz, 1 H) 7.95 (d, J=1.00 Hz, 2 H) 7.56 (d, J=1.00 Hz, 2 H) 7.37 (s, 1 H) 3.79 (br s, 1 H) 1.84 (br s, 2 H) 1.76 (br s, 2 H) 1.62 (d, J=12.05 Hz, 1 H) 1.30-1.40 (m, 4 H) 1.14 (m, J=8.50 Hz, 1 H)

Example 98: 2',6'-Dicyano-N-cyclohexyl-3',4'-dihydroxybiphenyl-3-carboxamide

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and 3-(cyclohexylaminocarbonyl)phenylboronic acid (275 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 5 min at 150 °C. Yield 120 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.35 (br s, 2 H) 8.29 (d, J=7.78 Hz, 1 H) 7.99 (br s, 1 H) 7.94 (s, 1 H) 7.61 (d, J=4.52 Hz, 2 H) 7.37 (s, 1 H) 3.78 (br s, 1

H) 1.83 (br s, 2 H) 1.74 (br s, 2 H) 1.61 (d, *J*=12.05 Hz, 1 H) 1.31 (m, *J*=9.50, 9.50 Hz, 4 H) 1.14 (br s, 1 H)

Example 99: 2',6'-Dicyano-N,N-diethyl-3',4'-dihydroxybiphenyl-4-carboxamide

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and 4-(N,N-diethylaminocarbonyl)phenylboronic acid (246 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 10 min at 140 °C. Yield 100 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.42-7.62 (m, 4 H) 7.36 (s, 1 H) 3.44 (t, *J*=1.00 Hz, 4 H) 1.15 (br q, *J*=1.00, 1.00, 1.00 Hz, 6 H)

Example 100: 2',6'-Dicyano-N,N-diethyl-3',4'-dihydroxybiphenyl-3-carboxamide

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and 3-(N,N-diethylaminocarbonyl)phenylboronic acid (246 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 10 min at 140 °C. Yield 100 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.34 (br s, 2 H) 7.56-7.63 (m, 1 H) 7.48 (d, *J*=7.28 Hz, 1 H) 7.52 (d, *J*=7.78 Hz, 1 H) 7.40 (s, 1 H) 7.34 (s, 1 H) 3.44 (br s, 4 H) 1.14 (br s, 3 H) 1.05 (br s, 3 H)

Example 101: 2',6'-Dicyano-N-ethyl-3',4'-dihydroxybiphenyl-3-carboxamide

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and 3-(N-ethylaminocarbonyl)phenylboronic acid (215 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 10 min at 140 °C. Yield 100 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.40 (br s, 2 H) 8.56 (m, *J*=5.00, 5.00 Hz, 1 H) 7.96-8.02 (m, 1 H) 7.94 (s, 1 H) 7.62 (d, *J*=4.77 Hz, 2 H) 7.38 (s, 1 H) 3.25-3.35 (m, 2 H) 1.14 (t, *J*=7.15 Hz, 3 H)

Example 102: 2',6'-Dicyano-3',4'-dihydroxy-N,N-dimethylbiphenyl-3-carboxamide

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and N,N-dimethylbenzamide-3-boronic acid (215 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 10 min at 140 °C. Yield 60 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.57-7.63 (m, 1 H) 7.51-7.57 (m, 2 H) 7.48 (s, 1 H) 7.36 (s, 1 H) 3.00 (br s, 3 H) 2.95 (br s, 3 H)

Example 103: 4'-Fluoro-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (100 mg) and 4-fluorobenzeneboronic acid (43 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 130 °C. Yield 50 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.50-7.57 (m, 2 H) 7.37 (t, J=8.78 Hz, 2 H) 7.32 (s, 1 H)

Example 104: 3',4'-Difluoro-3,4-dihydroxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (100 mg) and 3,4-difluorophenylboronic acid (49 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 130 °C. Yield 34 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.66-7.73 (m, 1 H) 7.57-7.66 (m, 1 H) 7.37 (br s, 1 H) 7.33 (s, 1 H)

Example 105: 4'-Fluoro-3,3',4-trihydroxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (100 mg) and 4-fluoro-3-hydroxyphenylboronic acid (48 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 130 °C. Yield 32 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.23-7.31 (m, 3 H) 7.00 (d, J=8.28 Hz, 1 H) 6.86 (br s, 1 H)

Example 106: (E)-4,5-Dihydroxy-2-(3-phenylprop-1-enyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (100 mg) and (E)-3-phenylpropen-1-yl-boronic acid (65 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 150 °C. Yield 57 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.26-7.35 (m, 4 H) 7.20-7.26 (m, 2 H) 6.54-6.69 (m, 2 H) 3.63 (d, J=6.27 Hz, 2 H)

Example 107: 4'-Fluoro-3,4-dihydroxy-3'-methoxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (106 mg) and 3-fluoro-4-methoxyphenylboronic acid (72 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 63.5 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.41 (d, J=10.79 Hz, 1 H) 7.24-7.35 (m, 3 H) 3.92 (s, 3 H)

Example 108: 5-(2,6-Dicyano-3,4-dihydroxyphenyl)thiophene-2-carboxylic acid

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and 5-boronothiophene-2-carboxylic acid (208 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 127 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.79 (d, J=3.76 Hz, 1 H) 7.39 (d, J=4.02 Hz, 1 H) 7.35 (s, 1 H)

Example 109: 3,4-Dihydroxy-4'-(methylsulfonyl)biphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (108 mg) and 4-(methanesulfonyl)phenylboronic acid (87 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 60 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.72-12.36 (m, 2 H) 8.08 (br d, J=8.30 Hz, 2 H) 7.78 (br d, J=8.50 Hz, 2 H) 7.38 (s, 1 H) 3.33 (s, 3 H)

Example 110: 3,4-Dihydroxy-4'-propoxybiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 3-propoxyphenylboronic acid (167 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 150 °C. Yield 30 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.38 (d, J=1.00 Hz, 2 H) 7.34 (s, 1 H) 7.06 (d, J=1.00 Hz, 2 H) 4.00 (t, J=6.53 Hz, 2 H) 1.71-1.81 (m, 2 H) 1.01 (t, J=7.40 Hz, 3 H)

Example 111: 2',6'-Dicyano-3',4'-dihydroxybiphenyl-4-carboxylic acid

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (400 mg) and 4-carboxyphenylboronic acid (247 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 30 min at 140 °C. Yield 270 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.07 (d, J=1.00 Hz, 2 H) 7.61 (d, J=1.00 Hz, 2 H) 7.38 (s, 1 H)

Example 112: 4'-Chloro-3,4-dihydroxy-3'-methylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and (4-chloro-3-methylphenyl)boronic acid (127 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 54 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.57 (d, J=8.28 Hz, 1 H) 7.47 (d, J=1.76 Hz, 1 H) 7.34 (s, 1 H) 7.33 (d, J=2.26 Hz, 1 H) 2.39 (s, 3 H)

Example 113: 4,5-Dihydroxy-2-(5-phenylthiophen-2-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 5-phenyl-2-thienylboronic acid (164 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 71 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.72 (d, J=7.28 Hz, 2 H) 7.63 (d, J=3.51 Hz, 1 H) 7.44-7.50 (m, 2 H) 7.34-7.40 (m, 3 H)

Example 114: 3,4-Dihydroxy-4'-isopropylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 4-isopropylphenylboronic acid (152 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 150 °C. Yield 66 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.39 (s, 4 H) 7.34 (s, 1 H) 2.92-3.03 (m, 1 H) 1.26 (d, J=7.03 Hz, 6 H)

Example 115: 3,4-Dihydroxy-4'-propylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 4-propylphenylboronic acid (152 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 150 °C. Yield 80 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.31-7.40 (m, 5 H) 2.64 (t, J=7.65 Hz, 2 H) 1.60-1.71 (m, 2 H) 0.93 (t, J=7.40 Hz, 3 H)

Example 116: 4,5-Dihydroxy-2-(1-phenylvinyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (500 mg) and 1-phenylvinylboronic acid (321 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 130 °C. Yield 370 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.32-7.40 (m, 4 H) 7.24-7.28 (m, 2 H) 6.17 (s, 1 H) 5.44 (s, 1 H)

Example 117: 2',6'-Dicyano-3',4'-dihydroxybiphenyl-2-carboxylic acid

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 2-carboxyphenylboronic acid (134 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 130 °C. Yield 106 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.08 (d, J=7.78 Hz, 1 H) 8.01 (s, 1 H) 7.75 (d, J=7.78 Hz, 1 H) 7.67 (m, J=7.70, 7.70 Hz, 1 H) 7.38 (s, 1 H)

Example 118: 4-(2,6-Dicyano-3,4-dihydroxybenzyl)benzoic acid

2-((4-(Chloromethyl)benzyl)oxy)tetrahydro-2H-pyran

A mixture of (4-(chloromethyl)phenyl)methanol (25.3 g), DCM (280 ml), 3,4-dihydro-2H-pyran (39.6 ml) and pyridin-1-ium 4-methylbenzenesulfonate (4.1 g) was stirred at room temperature for 3 h. Saturated aqueous solution of sodium hydrogen carbonate (250 ml) and DCM (550 ml) were added to the mixture and the layers were separated. The organic phase was extracted with saturated aqueous solution of sodium hydrogen carbonate (250 ml) and brine (250 ml), dried (Na_2SO_4), filtered and concentrated. Toluene (350 ml) was added to the residue and the solution was concentrated to give the title compound. Yield 43.0 g

^{1}H NMR (200 MHz, DMSO-d_6) ppm 7.32-7.44 (m, 4H) 4.75 (s, 2H) 4.67-4.73 (m, 1H) 4.56 (dd, 2H) 3.73-3.84 (m, 1H) 3.42-3.52 (m, 1H) 1.47-1.79 (m, 6H)

4,4,5,5-Tetramethyl-2-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)-1,3,2-dioxaborolane

Bis(triphenylphosphine)palladium(II) chloride (1.75 g), N-ethyl-N-isopropylpropan-2-amine (30.95 g) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17.5 ml) were added to a solution of 2-((4-(chloromethyl)benzyl)oxy)tetrahydro-

2H-pyran (21.2 g) in 1,2-dichloroethane (320 ml) under nitrogen atmosphere. The mixture was heated under reflux for 10 h. Toluene (1000 ml) was added at room temperature. The reaction mixture was washed with brine (1150 ml), dried (Na_2SO_4), filtered and concentrated. The crude product was dissolved in n-heptane (800 ml). The precipitate formed was filtered off and washed with n-heptane. The combined n-heptane filtrates were concentrated and the residue was purified by silica column chromatography (n-heptane/EtOAc 9:1 + 0.5% triethylamine). Yield 13.72

^{1}H NMR (200 MHz, DMSO-d_6) ppm 7.06-7.21 (m, 4H) 4.64-4.68 (m, 1H) 4.48 (dd, 2H) 3.74-3.85 (m, 1H) 3.41-3.52 (m, 1H) 2.19 (s, 2H) 1.41-1.80 (m, 6H) 1.17 (s, 12H)

4-Hydroxy-5-methoxy-2-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)isophthalonitrile

A mixture of 4,4,5,5-tetramethyl-2-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)-1,3,2-dioxaborolane (5.03 g), 2-bromo-4-hydroxy-5-methoxyisophthalonitrile (3.06 g), Pd(dppf)Cl_2 complex with CH_2Cl_2 (1:1) (1.11 g), sodium hydrogen carbonate (5.09 g), water (84 ml) and ethanol (7.5 ml) was bubbled with nitrogen gas at room temperature. The mixture was heated under reflux under nitrogen atmosphere for 1.5 h. DCM (130 ml) was added to the mixture at room temperature and the mixture was filtered through celite. Celite was washed with water (100 ml) and DCM (100 ml) and pH of the combined filtrates was adjusted to 7 with 0.5 M HCl solution. The layers were separated and separation was eased with addition of water (200 ml). The aqueous phase was extracted with DCM (2 x 100 ml, 2 x 50 ml) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica column chromatography (DCM/methanol 100:0 → 90:10 + 0.5% triethylamine). Yield 3.68 g

^{1}H NMR (200 MHz, DMSO-d_6) ppm 7.17-7.28 (m, 4H) 6.82 (s, 1H) 4.61-4.68 (m, 1H) 4.49 (dd, 2H) 3.96 (s, 2H) 3.73-3.84 (m, 1H) 3.65 (s, 3H) 3.61 (s, 1H) 3.39-3.50 (m, 1H) 1.45-1.77 (m, 6H)

4-(2,6-Dicyano-3-hydroxy-4-methoxybenzyl)benzoic acid

A mixture of 4-hydroxy-5-methoxy-2-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)isophthalonitrile (4.70 g) in acetone (96 ml) was cooled in ice bath and Jones reagent (24.0 ml) was added in small portions. The mixture was stirred at room temperature for 2 h. Isopropanol (5 ml) was added to the mixture and the solution was filtered to remove chromium salts. The chromium salts were washed with acetone (150 ml) and acetone was combined with the filtrate. Water (200 ml) was added to the solution and the solution was concentrated until the product started to precipitate. The concentrate was filtered and the precipitate was washed with water (100 ml). The precipitate was dissolved in EtOAc (50 ml) and washed with 0.5 M HCl solution (2 x 40 ml) and brine (20 ml). Water (50 ml) was added to the organic phase and pH of the solution was adjusted to >10 with 15% NaOH solution. The phases were separated and the organic phase was washed with water (30 ml). The pH of the combined aqueous solutions was adjusted to 1-2 with 4 M HCl solution. The precipitate was filtered, washed with water (30 ml) and DCM (20 ml) and dried in vacuum at 50 °C. Yield 1.47 g

^{1}H NMR (200 MHz, DMSO-d_6) ppm 12.89 (br s, 1H) 12.02 (br s, 1H) 7.89 (d, 2H) 7.71 (s, 1H) 7.27 (d, 2H) 4.27 (s, 2H) 3.91 (s, 3H)

4-(2,6-Dicyano-3,4-dihydroxybenzyl)benzoic acid

1 M boron tribromide solution (5.6 ml) was added slowly to 4-(2,6-dicyano-3-hydroxy-4-methoxybenzyl)benzoic acid (1.45 g) in DCM (36 ml) under nitrogen atmosphere at 0 °C. Stirring was continued at room temperature and more 1 M boron tribromide solution was added six times [after 1.5 h (5.6 ml), after 2.5 h (5.6 ml), after 4 h (5.6 ml), after 5.5 h (5.3 ml), after 22 h (5.3 ml) and after 25.5 h (5.3 ml)]. After total of 47 h stirring, the reaction mixture was poured into ice water (140 ml) and stirred for 1.5 h. The mixture was filtered and the precipitate was washed with water (100 ml) and n-heptane (20 ml). The precipitate was dissolved in 1 M NaOH solution (60 ml) and the solution was

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, aryl, halogen, aryloxy, aryl-S-, $(R_3)_2N$-, $(R_4)_2C{=}N$-, heterocyclyl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_7)$cycloalkyl$(C_2\text{-}C_6)$alkenyl or aryl$(C_2\text{-}C_6)$alkenyl, wherein said aryl, heterocyclyl, heteroaryl or $(C_3\text{-}C_7)$cycloalkyl as such or as part of another group is unsubstituted or substituted with 1, 2 or 3 substituent(s) R_6;

R_3 is, independently at each occurrence, H or $(C_1\text{-}C_6)$alkyl;

R_4 is, independently at each occurrence, H or aryl, wherein said aryl is, independently at each occurrence, substituted with 1 substituent being $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, cyano, aryl, halogen, hydroxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl-S-, carboxy$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, heterocyclyl-(C=O)-, $(R_7)_2N$-(C=O)- or R_8-(O=S=O)-, wherein said aryl or heterocyclyl as such or as part of another group is unsubstituted;

R_7 is, independently at each occurrence, H or $(C_1\text{-}C_6)$alkyl;

R_8 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, aryl, halogen, aryloxy, aryl-S-, $(R_3)_2N$-, heterocyclyl, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl or aryl$(C_2\text{-}C_6)$alkenyl, wherein said aryl, heterocyclyl or heteroaryl as such or as part of another group is unsubstituted or substituted with 1, 2 or 3 substituent(s) R_6;

R_3 is, independently at each occurrence, H or $(C_1\text{-}C_6)$alkyl;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, halogen, hydroxy, $(C_1\text{-}C_6)$alkoxy, carboxy$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl or $(R_7)_2N$-(C=O)-;

R_7 is, independently at each occurrence, H or $(C_1\text{-}C_6)$alkyl.

extracted thrice with EtOAc (35 ml). The pH of the aqueous solution was adjusted to 1-2 with 4 M HCl solution and the solution was extracted twice with EtOAc (30 ml). The combined organic phases were washed with water (30 ml) and brine (30 ml), dried (Na_2SO_4), filtered and concentrated to give the title compound. Yield 1.55 g

1H NMR (200 MHz, DMSO-d_6) ppm 12.9 (br s, 1H) 11.4 (br s, 1H) 7.2-8.0 (m, 5H) 4.25 (s, 2H)

Example 119: (E)-4,5-Dihydroxy-2-(4-methoxystyryl)isophthalonitrile

Using the procedure described in Example 37, (E)-4-hydroxy-5-methoxy-2-(4-methoxystyryl)isophthalonitrile (117 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and trans-2-(4-methoxyphenyl)vinylboronic acid, was demethylated to give the title compound. Yield 56 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.29 (br s, 2 H) 6.78-7.60 (m, 7 H) 3.80 (s, 3 H)

Example 120: 3,4-Dihydroxy-3',4'-dimethylbiphenyl-2,6-dicarbonitrile

Using the procedure described in Example 37, 3-hydroxy-4-methoxy-3',4'-dimethylbiphenyl-2,6-dicarbonitrile (50 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 3,4-dimethylbenzeneboronic acid, was demethylated to give the title compound. Yield 36 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.33 (s, 1 H) 7.28 (d, J=7.53 Hz, 1 H) 7.22 (s, 1 H) 7.14-7.19 (m, 1 H) 2.29 (d, J=5.27 Hz, 6 H)

Example 121: (E)-4,5-Dihydroxy-2-(4-methylstyryl)isophthalonitrile

Using the procedure described in Example 37, (E)-4-hydroxy-5-methoxy-2-(4-methylstyryl)isophthalonitrile (95 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and trans-2-(4-methylphenyl)vinylboronic acid, was demethylated to give the title compound. Yield 71 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.50 (d, J=1.00 Hz, 2 H) 7.32 (d, J=1.00 Hz, 2 H) 7.25 (d, J=1.00 Hz, 2 H) 7.18 (d, J=1.00 Hz, 1 H) 2.34 (s, 3 H)

Example 122: 4,5-Dihydroxy-2-(6-hydroxynaphthalen-2-yl)isophthalonitrile

Using the procedure described in Example 37, 4-hydroxy-5-methoxy-2-(6-methoxynaphthalen-2-yl)isophthalonitrile (105 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 6-methoxy-2-naphthaleneboronic acid, was demethylated to give the title compound. Yield 45 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.88 (s, 1 H) 7.86 (d, J=8.78 Hz, 1 H) 7.81 (d, J=8.53 Hz, 1 H) 7.44 (m, J=8.50, 1.80 Hz, 1 H) 7.36 (s, 1 H) 7.19-7.22 (m, 1 H) 7.17 (m, J=8.80, 2.30 Hz, 1 H)

Example 123: 4'-Fluoro-3,4-dihydroxy-3'-methylbiphenyl-2,6-dicarbonitrile

Using the procedure described in Example 37, 4'-fluoro-3-hydroxy-4-methoxy-3'-methylbiphenyl-2,6-dicarbonitrile (215 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 4-fluoro-3-methylphenylboronic acid, was demethylated to give the title compound. Yield 140 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.40 (d, J=7.28 Hz, 1 H) 7.25-7.36 (m, 3 H) 2.28-2.31 (m, 3 H)

Example 124: 4,5-Dihydroxy-2-(3-methylbut-2-en-2-yl)isophthalonitrile

To a dry mixture of aluminum chloride (66 mg), sodium iodide (74 mg) and acetonitrile (1 ml) under nitrogen atmosphere was added 4-hydroxy-5-methoxy-2-(3-methylbut-2-en-2-yl)isophthalonitrile (12 mg), which was prepared as described in Example 54, except that 3-methylbut-2-en-2-ylboronic acid was used instead of 4,4,5,5-tetramethyl-2-(4-methylbenzyl)-1,3,2-dioxaborolane. The mixture was heated for 3 h at 60 °C and stirred overnight at room temperature. 2 M HCl (0.3 ml) and sodium sulfite (31 mg) was added to the mixture and the solution was heated for 30 min at 50 °C. The product was extracted with EtOAc, the solvent was evaporated and the residue was dried. The product was recrystallized from toluene-isopropanol solution. Yield 6 mg

^{1}H NMR (400 MHz, methanol-d_4) ppm 7.15 (s, 1 H) 1.95 (s, 3 H) 1.88 (s, 3 H) 1.48-1.55 (m, 3 H)

Example 125: 2-(2,5-Dimethylthiophen-3-yl)-4,5-dihydroxyisophthalonitrile

2-(2,5-Dimethylthiophen-2-yl)-4-hydroxy-5-methoxyisophthalonitrile (65 mg), which was prepared as described in Example 54, except that potassium 2,5-dimethylthiophene-3-trifluoroborate was used instead of 4,4,5,5-tetramethyl-2-(4-methylbenzyl)-1,3,2-dioxaborolane, was converted to the title compound using the procedure analogous to Example 54. Yield 36 mg

^{1}H NMR (400 MHz, methanol-d_4) ppm 7.26 (s, 1 H) 6.62 (d, J=1.14 Hz, 1 H) 2.44 (s, 3 H) 2.28 (s, 3 H)

Example 126: 2-(2,3-Difluoro-4-methylbenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, 2-(2,3-difluoro-4-methylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile (200 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(2,3-difluoro-4-methylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 30 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.29 (s, 1 H) 7.02 (t, J=7.40 Hz, 1 H) 6.65 (t, J=7.28 Hz, 1 H) 4.16 (s, 2 H) 2.24 (s, 3 H)

Example 127: 2-(4-(2,6-Dicyano-3,4-dihydroxybenzyl)phenyl)propanoic acid

Using the procedure analogous to Example 54, 2-(4-(2,6-dicyano-3-hydroxy-4-methoxybenzyl)phenyl) propanoic acid (600 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phenyl)propanoic acid, was demethylated to give the title compound. Yield 27.5 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.26-7.31 (m, 1 H) 7.09-7.26 (m, 4 H) 4.12 (s, 2 H) 3.62 (quin, J=7.15 Hz, 1 H) 1.34 (d, J=1.00 Hz, 3 H)

Example 128: (E)-2-(3-Cyclopentylprop-1-enyl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) by the procedure analogous to Example 74 using as reactant trans-3-cyclopentylpropen-1-ylboronic acid pinacol ester (285 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 10 min at 140 °C. Yield 25 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.24 (s, 1 H) 6.47 (s, 2 H) 2.21-2.32 (m, 2 H) 1.95 (m, J=14.70, 7.30, 7.30 Hz, 1 H) 1.70-1.86 (m, 2 H) 1.56-1.66 (m, 2 H) 1.42-1.54 (m, 2 H) 1.13-1.27 (m, 2 H)

Example 129: 4,5-Dihydroxy-2-(1-isobutyl-1H-pyrazol-4-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) by the procedure analogous to Example 74 using as reactant 1-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (279 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 10 min at 140 °C. Yield 70 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.08 (s, 1 H) 7.72 (s, 1 H) 7.30 (s, 1 H) 4.00 (d, J=7.28 Hz, 2 H) 2.13 (m, J=13.60, 6.90, 6.90 Hz, 1 H) 0.86 (d, J=6.53 Hz, 6 H)

Example 130: 2-(4-(2,6-Dicyano-3,4-dihydroxyphenyl)-1H-pyrazol-1-yl) acetic acid

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (310 mg) by the procedure analogous to Example 74 using as reactant (4-(4,4,5,5-tatramethyl-[1,3,2]dioxaborolan-2-yl)-pyrazol-1-yl)-acetic acid ethyl ester (121 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 20 min at 150 °C. The reaction mixture was filtered through celite and poured into ice water and 2 M NaOH and toluene was added to the mixture. The water phase was washed with toluene and was made acidic with concentrated HCl. The product was filtered, washed with water and toluene and dried. Yield 57 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.14 (s, 1 H) 7.78 (s, 1 H) 7.31 (s, 1 H) 5.06 (s, 2 H)

Example 131: 4,5-Dihydroxy-2-(1-methyl-1H-pyrazol-4-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (100 mg) by the procedure analogous to Example 74 using as reactant 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (90 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 20 min at 150 °C. Yield 51 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.08 (s, 1 H) 7.71 (s, 1 H) 7.30 (s, 1 H) 3.92 (s, 3 H)

Example 132: 4,5-Dihydroxy-2-(3-methoxyprop-1-ynyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (100 mg) by the procedure analogous to Example 74 using as reactant 3-methoxy-1-propyn-1-ylboronic acid pinacol ester (80 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 20 min at 150 °C. Yield 36 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.28 (s, 1 H) 4.44 (s, 2 H) 3.33 (br s, 3 H)

Example 133: (E)-4,5-Dihydroxy-2-(2-(thiophen-3-yl)vinyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (100 mg) by the procedure analogous to Example 74 using as reactant trans-2-(thiophen-3-yl)vinylboronic acid pinacol ester (95 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 20 min at 150 °C. Yield 59 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.74 (d, J=2.26 Hz, 1 H) 7.62 (m, J=4.90, 2.90 Hz, 1 H) 7.49 (d, J=5.02 Hz, 1 H) 7.26-7.37 (m, 2 H) 7.08 (d, J=16.56 Hz, 1 H)

Example 134: (E)-2-(2-Cyclopropylvinyl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (100 mg) by the procedure analogous to Example 74 using as reactant (E)-2-cyclopropylvinylboronic acid pinacol ester (72 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 20 min at 150 °C. Yield 52 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.21 (s, 1 H) 6.57 (dd, J=15.81, 9.54 Hz, 1 H) 5.97 (dd, J=15.81, 9.54 Hz, 1 H) 1.58-1.79 (m, 1 H) 0.77-0.96 (m, 2 H) 0.47-0.68 (m, 2 H)

Example 135: 2',6'-Dicyano-3',4'-dihydroxybiphenyl-4-carboxamide

4-Aminocarbonylphenyl boronic acid (173 mg), bis(triphenylphosphine)palladium(II) chloride (73 mg) and sodium carbonate (333 mg) were added to 2-bromo-4,5-dihydroxyisophthalonitrile (250 mg) dissolved in acetonitrile (2 ml), ethanol (2 ml) and water (1 ml). The reaction mixture was stirred and microwave-irradiated for 60 min at 130 °C. 2 N NaOH was added and the reaction mixture was washed with toluene. The aqueous phase was made acidic by adding HCl. The solid product was filtered, washed with water and dried. Yield 166 mg

^{1}H NMR (DMSO-d_6) ppm 11.0-11.8 (br s, 2 H) 8.13 (br s, 1H) 7.98 (d, J=8.28 Hz, 1H) 7.56 (d, J=8.36 Hz, 1H) 7.52 (br s, 1H) 7.36 (s, 1H)

Example 136: 3,4-Dihydroxy-3',4'-dimethoxybiphenyl-2,6-dicarbonitrile

3,4-Dimethoxyphenylboronic acid (152 mg), palladium(II) acetate (7.5 mg) and DBU (166 mg) were added to 2-bromo-4,5-dihydroxyisophthalonitrile (200 mg) dissolved in ethanol (1 ml) and water (1 ml). The reaction mixture was stirred and microwave-irradiated for 10 min at 150 °C. The reaction mixture was filtered through celite and the organic solvent was evaporated. 0.1 M NaOH was added and the mixture was washed with toluene and EtOAc. The aqueous phase was made acidic by adding HCl. The solid product was filtered, washed with water and dried. Yield 100 mg

^{1}H NMR (DMSO-d_6) ppm 10.8-11.7 (br s, 2 H) 7.33 (s, 1H) 7.09 (d, J=8.36 Hz, 1H) 7.09 (d, J=2.04 Hz, 1H) 7.01 (dd, J=8.28, 2.04 Hz, 1H) 3.93 (s, 3H) 3.79 (s, 3H)

Example 137: 3,4-Dihydroxy-3'-isopropylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 3-isopropylphenylboronic acid (122 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 20 min at 150 °C. Yield 86 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.00-11.63 (m, 2 H) 7.10-7.51 (m, 5 H) 2.97 (dt, J=13.80, 6.90 Hz, 1 H) 1.24 (d, J=7.03 Hz, 6 H)

Example 138: 2-(2,3-Dihydrobenzofuran-5-yl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 2,3-dihydrobenzofuran-5-boronic acid (132 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 127 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.35 (s, 1 H) 7.32 (s, 1 H) 7.17 (dd, J=8.16, 1.63 Hz, 1 H) 6.88 (d, J=8.28 Hz, 1 H) 4.61-4.67 (m, 2 H) 3.21-3.27 (m, 2 H)

Example 139: 4,5-Dihydroxy-2-(6-methoxynaphthalen-2-yl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) and 6-methoxy-2-naphthaleneboronic acid (150 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 45 min at 150 °C. Yield 64 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 1.99 (s, 3 H) 6.96-8.22 (m, 7 H)

Example 140: 4,5-Dihydroxy-2-(4-(hydroxymethyl)benzyl)isophthalonitrile

4-Bromo-3,5-dicyano-1,2-phenylene dimethanesulfonate

Triethylamine (17.0 ml) was added to 2-bromo-4,5-dihydroxyisophthalonitrile (10.1 g) in 1:1 mixture of DCM and THF (100 ml) at 0 °C under nitrogen atmosphere. Methanesulfonyl chloride (12.92 g) was added slowly to the mixture followed by addition of DMAP (0.52 g). Stirring was continued at room temperature for 21 h and the mixture was concentrated. EtOAc was added (300 ml) and the insoluble material was filtered off and washed with EtOAc (50 ml). The combined organic phases were washed with 1 M HCl solution (2 x 150 ml), water (150 ml) and brine (150 ml), dried (Na_2SO_4), filtered and concentrated. Yield 15.2 g. The crude product was purified by flash chromatography (EtOAc/n-heptane). The combined fractions were concentrated to smaller volume and the precipitate was filtered. The precipitate was recrystallized from EtOAc and n-heptane (added to hot solution) and dried in vacuum at 50 °C.

^{1}H NMR (200 MHz, DMSO-d_6) ppm 7.88 (s, 1H) 3.46 (s, 3H) 2.38 (s, 3H)

3,5-Dicyano-4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)-1,2-phenylene dimethanesulfonate

The preparation of 4,4,5,5-tetramethyl-2-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)-1,3,2-dioxaborolane is described in Example 118. A mixture of 4,4,5,5-tetramethyl-2-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)-1,3,2-dioxaborolane (8.00 g), 4-bromo-3,5-dicyano-1,2-phenylene dimethanesulfonate (7.61 g), Pd(dppf)Cl_2 complex with CH_2Cl_2 (1:1) (1.77 g), sodium hydrogen carbonate (8.09 g), water (128 ml) and ethanol (16 ml) was bubbled with nitrogen gas at room temperature. The mixture was heated under reflux under nitrogen atmosphere for 2 h. DCM (240 ml) was added to the mixture at room temperature and the mixture was filtered through celite. Celite was washed with water (120 ml) and DCM (120 ml) and the layers of the combined filtrates were separated. The organic phase was washed with water (150 ml) and EtOAc (150 ml) was added to the aqueous phase before adjusting pH to 7 with 15% HCl solution. The layers were separated and the aqueous phase was extracted thrice with EtOAc (150 ml). The combined organic phases were

dried (Na_2SO_4), filtered and concentrated. The crude product was recrystallized from ethanol (75 ml, all did not dissolve). The precipitate was dried in vacuum at 25 °C overnight. Yield 2.74 g

^{1}H NMR (200 MHz, DMSO-d_6) ppm 7.10-7.40 (m, 5H) 4.50-4.70 (m, 2H) 4.30-4.45 (d, 1H) 3.98 (s, 2H) 3.70-3.85 (m, 1H) 3.20-3.55 (m, 5H) 1.30-1.85 (m, 6H)

4,5-Dihydroxy-2-(4-(hydroxymethyl)benzyl)isophthalonitrile

The pH of a solution of 3,5-dicyano-4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)-1,2-phenylene dimethanesulfonate (4.60 g) in methanol (100 ml) was adjusted to about 2 by addition of 25% HCl solution in isopropanol (2.25 ml). More methanol (50 ml) was added, but 3,5-dicyano-4-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)benzyl)-1,2-phenylene dimethanesulfonate was not completely dissolved. The mixture was stirred at room temperature for 5 h. The pH was adjusted to about 12 by addition of 5 M aqueous solution of NaOH. The mixture was heated under reflux for 35 min and then pH was adjusted back to acidic (about pH 1) by addition of HCl (55 ml). The mixture was stirred in ice bath and then the precipitate was filtered and washed twice with water (10 ml). The precipitate was dried in vacuum at 25 °C overnight and at 40 °C over another night. Yield 2.19 g

1H NMR (200 MHz, DMSO-d_6) ppm 11.2 (br s, 1H) 6.9-7.3 (m, 5H) 4.4 (s, 2H) 4.1 (s, 2H)

Example 141: 2-(2,6-Difluoro-3-methylbenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, 2-(2,6-difluoro-3-methylbenzyl)-4-hydroxy-5-methoxyisophthalonitrile (600 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(2,6-difluoro-3-methylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 20 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.41 (s, 1 H) 7.12-6.85 (m, 2 H) 4.32 (s, 2 H) 2.17 (s, 3 H)

Example 142: 4,5-Dihydroxy-2-(4-(trifluoromethyl)phenylthio)isophthalonitrile

4,5-Diisopropoxy-2-(4-(trifluoromethyl)phenylthio)isophthalonitrile

4-(Trifluoromethyl)thiophenol (0.28 g) was added to a mixture of 2-bromo-4,5-diisopropoxyisophthalonitrile (0.51 g) and cesium carbonate (2 equiv.) in DMF followed by stirring at room temperature overnight. The reaction mixture was poured into cold water and pH was adjusted to 12. The precipitate was filtered, washed with water and dried in vacuum. Yield 0.67 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.09 (s, 1 H) 7.70 (d, 2 H) 7.35 (d, 2 H) 4.86-4.95 (m, 1 H) 4.77-4.89 (m, 1 H) 1.36 (d, 6 H) 1.31 (d, 6 H)

4,5-Dihydroxy-2-(4-(trifluoromethyl)phenylthio)isophthalonitrile

To a mixture of 4,5-diisopropoxy-2-(4-(trifluoromethyl)phenylthio)isophthalonitrile (0.3 g) in DCM under nitrogen atmosphere was added 1 M boron tribromide solution in DCM (2-5 equiv.) at 0 °C. The reaction mixture was left to warm slowly to room temperature with stirring for 2 h. The reaction mixture was poured into methanol. After evaporation of the solvent, 2 M NaOH solution was added and the mixture was stirred for 30 min, washed with EtOAc, cooled and acidified with HCl to give solid product which was filtered, washed with water and dried in vacuum. Yield 0.16 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.68 (d, 2 H) 7.42 (s, 1 H) 7.30 (d, 2 H)

Example 143: 2-(2,4-Dimethylphenylthio)-4,5-dihydroxyisophthalonitrile

2-(2,4-Dimethylphenylthio)-4,5-diisopropoxyisophthalonitrile

2-(2,4-Dimethylphenylthio)-4,5-diisopropoxyisophthalonitrile was prepared from 2-bromo-4,5-diisopropoxyisophthalonitrile (0.25 g) and 2,4-

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is $(C_2\text{-}C_6)$alkenyl, aryl, halogen, aryloxy, aryl-S-, $(R_3)_2N$-, heteroaryl, aryl$(C_1\text{-}C_6)$alkyl or aryl$(C_2\text{-}C_6)$alkenyl, wherein said aryl or heteroaryl as such or as part of another group is unsubstituted or substituted with 1 or 2 substituent(s) R_6;

R_3 is, independently at each occurrence, H or $(C_1\text{-}C_6)$alkyl;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, halogen, $(C_1\text{-}C_6)$alkoxy, carboxy$(C_1\text{-}C_6)$alkyl or halo$(C_1\text{-}C_6)$alkyl.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is $(C_2\text{-}C_6)$alkenyl, aryl, halogen, aryl-S-, heteroaryl or aryl$(C_1\text{-}C_6)$alkyl, wherein said aryl or heteroaryl as such or as part of another group is unsubstituted or substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is $(C_2\text{-}C_6)$alkenyl, halogen, aryl-S- or aryl$(C_1\text{-}C_6)$alkyl, wherein said aryl as part of another group is unsubstituted or substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy.

In one embodiment of the invention, the invention relates to compounds of formula I, wherein

R_1 is $(C_2\text{-}C_6)$alkenyl, aryl, aryl-S-, heteroaryl or aryl$(C_1\text{-}C_6)$alkyl, wherein said aryl or heteroaryl as such or as part of another group is substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy.

dimethylthiophenol (0.12 ml) instead of 4-(trifluoromethyl)thiophenol as described in Example 142. Yield 0.28 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.33 (d, 1 H) 6.92-7.13 (m, 2 H) 6.76 (d, 1 H) 4.83-4.91 (m, 1 H) 4.76-4.86 (m, 1 H) 2.35 (s, 3 H) 2.24 (s, 3 H) 1.36 (d, 6 H) 1.30 (d, 6 H)

2-(2,4-Dimethylphenylthio)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 2-(2,4-dimethylphenylthio)-4,5-diisopropoxyisophthalonitrile instead of 4,5-diisopropoxy-2-(4-(trifluoromethyl)phenylthio)isophthalonitrile as described in Example 142. 2-(2,4-Dimethylphenylthio)-4,5-dihydroxyisophthalonitrile was purified by chromatography. Yield 80 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.34 (s, 1 H) 7.09 (s, 1 H) 6.94 (dd, 1 H) 6.70 (d, 1 H) 2.34 (s, 3 H) 2.23 (s, 3 H)

Example 144: Methyl 3-(4-(2,6-dicyano-3,4-dihydroxyphenylthio)phenyl)propanoate

3-(4-(2,6-Dicyano-3,4-diisopropoxyphenylthio)phenyl)propanoic acid

3-(4-(2,6-Dicyano-3,4-diisopropoxyphenylthio)phenyl)propanoic acid was prepared from 2-bromo-4,5-diisopropoxyisophthalonitrile (0.75 g) and 3-(4-mercaptophenyl)propanoic acid (0.43 g) instead of 4-(trifluoromethyl)thiophenol as described in Example 142. Yield 0.99 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 12.12 (br s, 1 H) 7.99 (s, 1 H) 7.19-7.27 (m, 2 H) 7.10-7.18 (m, 2 H) 4.82-4.86 (m, 1 H) 4.74-4.83 (m, 1 H) 2.79 (t, 2 H) 2.51-2.56 (m, 2 H) 1.32 (d, 6 H) 1.29 (d, 6 H)

Methyl 3-(4-(2,6-dicyano-3,4-diisopropoxyphenylthio)phenyl)propanoate

To a mixture of 3-(4-(2,6-dicyano-3,4-diisopropoxyphenylthio)phenyl)propanoic acid (1.0 g) in methanol (14 ml) was added thionyl chloride (0.2 ml) over 30 min at 0 °C followed by refluxing for 30

min. The product was extracted to EtOAc and washed with saturated aqueous sodium hydrogen carbonate solution and brine. The organic phase was dried (Na_2SO_4), filtered and evaporated. Yield 0.85 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.99 (s, 1 H) 7.15-7.25 (m, 2 H) 7.12-7.18 (m, 2 H) 4.82-4.90 (m, 1 H) 4.75-4.84 (m, 1 H) 3.57 (s, 3 H) 2.82 (t, 2 H) 2.61 (t, 2 H) 1.32 (d, 6 H) 1.29 (d, 6 H)

Methyl 3-(4-(2,6-dicyano-3,4-dihydroxyphenylthio)phenyl)propanoate

The title compound was prepared from methyl 3-(4-(2,6-dicyano-3,4-diisopropoxyphenylthio)phenyl)propanoate (0.8 g) instead of 4,5-diisopropoxy-2-(4-(trifluoromethyl)phenylthio)isophthalonitrile as described in Example 142. Methyl 3-(4-(2,6-dicyano-3,4-dihydroxyphenylthio)phenyl)propanoate was purified by chromatography. Yield 0.33 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.36 (s, 1 H) 7.21 (m, 2 H) 7.12 (m, 2 H) 3.57 (s, 3 H) 2.81 (t, 2 H) 2.61 (t, 2 H)

Example 145: 4,5-Dihydroxy-2-(p-tolyloxy)isophthalonitrile

4,5-Diisopropoxy-2-(p-tolyloxy)isophthalonitrile

4,5-Diisopropoxy-2-(p-tolyloxy)isophthalonitrile was prepared from 2-bromo-4,5-diisopropoxyisophthalonitrile (0.5 g) and p-cresol (0.18 g) instead of 4-(trifluoromethyl)thiophenol as described in Example 142. After addition of water, 4,5-diisopropoxy-2-(p-tolyloxy)isophthalonitrile was collected by filtration, washed with water, and dried in vacuum. Yield 0.54 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.97 (s, 1 H) 7.13-7.23 (m, 2 H) 6.81-6.91 (m, 2 H) 4.88 (m, 1 H) 4.79 (m, 1 H) 2.28 (s, 3 H) 1.32 (d, 6 H) 1.30 (d, 6 H)

4,5-Dihydroxy-2-(p-tolyloxy)isophthalonitrile

The title compound was prepared from 4,5-diisopropoxy-2-(p-tolyloxy)isophthalonitrile (0.3 g) instead of 4,5-diisopropoxy-2-(4-

(trifluoromethyl)phenylthio)isophthalonitrile as described in Example 142. The product was further purified by extraction with EtOAc and water. Yield 0.16 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 10.5-11.5 (br s, 2H) 7.29 (s, 1 H) 7.15 (d, 2 H) 6.82 (d, 2 H) 2.27 (s, 3 H)

Example 146: (E)-2-(2,4-Difluorostyryl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the procedure analogous to Example 74 using as a reactant trans-2-(2,4-difluorophenyl)vinylboronic acid pinacol ester (231 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 30 min at 130 °C. Yield 52 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.81-7.90 (m, 1 H) 7.27-7.46 (m, 4 H) 7.20 (t, J=8.03 Hz, 1 H)

Example 147: (E)-4,5-Dihydroxy-2-(3-(trifluoromethyl)styryl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the procedure analogous to Example 74 using as reactant trans-2-(3-trifluoromethylphenyl)vinylboronic acid pinacol ester (240 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 30 min at 130 °C. Yield 46 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.93-8.01 (m, 2 H) 7.65-7.77 (m, 2 H) 7.42 (s, 2 H) 7.37 (s, 1 H)

Example 148: (E)-4,5-Dihydroxy-2-(4-methylpent-1-enyl)isophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (300 mg) and trans-4-methyl-1-pentenylboronic acid (154 mg) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 10 min at 140 °C. Yield 40 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 11.19 (br s, 2 H) 7.25 (s, 1 H) 6.44-6.49 (m, 2 H) 2.14-2.19 (m, 2 H) 1.75 (dt, J=13.30, 6.65 Hz, 1 H) 0.95 (d, J=6.78 Hz, 6 H)

Example 149: (E)-2-(3,5-Difluorostyryl)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (200 mg) by the procedure analogous to Example 74 using as a reactant trans-2-(3,5-difluorophenyl)vinylboronic acid pinacol ester (214 mg) instead of 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester. Reaction conditions: 30 min at 130 °C. Yield 91 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.62 (s, 1 H) 7.17-7.32 (m, 4 H) 6.51 (m, 1H)

Example 150: 2-(4-(2,6-Dicyano-3,4-dihydroxybenzyl)phenyl)acetic acid

Using the procedure analogous to Example 54, 2-(4-(2,6-dicyano-3-hydroxy-4-methoxybenzyl)phenyl)acetic acid (700 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phenyl)acetic acid, was demethylated to give the title compound. Yield 490 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.28 (s, 1 H) 7.19 (d, J=8.03 Hz, 2 H) 7.10 (d, J=8.03 Hz, 2 H) 4.11 (s, 2 H) 3.51 (s, 2 H)

Example 151: 2-(4-Chlorobenzyl)-4,5-dihydroxyisophthalonitrile

Using the procedure analogous to Example 54, 2-(4-chlorobenzyl)-4-hydroxy-5-methoxyisophthalonitrile (580 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 2-(4-chlorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 280 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.36-7.43 (m, 2 H) 7.29 (s, 1 H) 7.18 (d, J=8.53 Hz, 2 H) 4.15 (s, 2 H)

Example 152: 3,4-Dihydroxy-4'-methylbiphenyl-2,6-dicarbonitrile

The title compound was prepared from 4-bromo-3,5-dicyano-1,2-phenylene diacetate (1.63 g) and 4,4,5,5-tetramethyl-2-p-tolyl-1,3,2-

dioxaborolane (1.10 g) instead of 3,4,5-trifluorophenylboronic acid as described in Example 7. Reaction conditions: 120 min at 130 °C. Yield 0.21 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.13-7.32 (m, 4 H) 6.64 (s, 1 H) 2.36 (s, 3 H)

Example 153: 3-(4-(2,6-Dicyano-3,4-dihydroxybenzyl)phenyl)propanoic acid

Using the procedure analogous to Example 54, 3-(4-(2,6-dicyano-3-hydroxy-4-methoxybenzyl)phenyl)propanoic acid (100 mg), prepared from 3-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phenyl)propanoic acid and 2-bromo-4-hydroxy-5-methoxyisophthalonitrile, was demethylated to give the title compound. Yield 12 mg

^{1}H NMR (400 MHz, methanol-d_4) ppm 7.10-7.24 (m, 5 H) 4.20 (s, 2 H) 2.82-2.94 (m, 2 H) 2.51-2.65 (m, 2 H)

Example 154: 4,5-Dihydroxy-2-(4-(trifluoromethyl)benzyl)isophthalonitrile

Using the procedure analogous to Example 54, 4-hydroxy-5-methoxy-2-(4-(trifluoromethyl)benzyl)isophthalonitrile (200 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and 4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)benzyl)-1,3,2-dioxaborolane, was demethylated to give the title compound. Yield 96 mg

^{1}H NMR (400 MHz, methanol-d_4) ppm 7.59 (d, J=8.07 Hz, 2 H) 7.45 (d, J=8.07 Hz, 2 H) 6.96 (br s, 1 H) 4.24 (s, 2 H)

Example 155: (E)-4,5-Dihydroxy-2-(4-(trifluoromethyl)styryl)isophthalonitrile

Using the procedure described in Example 37, (E)-4-hydroxy-5-methoxy-2-(4-(trifluoromethyl)styryl)isophthalonitrile (43 mg), prepared from 2-bromo-4-hydroxy-5-methoxyisophthalonitrile and trans-2-(4-(trifluoromethyl)phenyl)vinylboronic acid, was demethylated to give the title compound. Yield 10 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.50 (d, J=1.00 Hz, 1 H) 7.29-7.35 (m, 2 H) 7.25 (d, J=1.00 Hz, 2 H) 7.18 (d, J=1.00 Hz, 2 H)

Example 156: 4,5-Dihydroxy-2-(p-tolylsulfinyl)isophthalonitrile

The preparation of 4,5-dihydroxy-2-(p-tolylthio)isophthalonitrile is described in Example 53. To a mixture of 4,5-dihydroxy-2-(p-tolylthio)isophthalonitrile (0.15 g) in DCM was added mCPBA (0.08 g) at 0 °C. After 2 h, the solvent was evaporated. Chromatographic purification gave the title compound. Yield 0.1 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.52 (m, 2 H) 7.37 (m, 2 H) 6.78 (s, 1 H) 2.35 (s, 3 H)

Example 157: 4-(2,6-Dicyano-3,4-dihydroxyphenylthio)benzoic acid

4-(2,6-Dicyano-3-hydroxy-4-methoxyphenylthio)benzoic acid

To a mixture of 3-bromo-2,4-dicyano-6-methoxyphenyl acetate (1.0 g), zinc (1.2 equiv.) and p-mercaptobenzoic acid (0.62 g) in DMF (20 ml) was added Pd(dppf)Cl_2 complex with CH_2Cl_2 (1:1) (0.9 equiv.). The stirred reaction was microwave-irradiated at 160 °C for 30 min after which water was added and solvents were evaporated. 5M NaOH solution was added to the residue and the mixture was stirred for 30 min, extracted with EtOAc, filtered over pall filter, cooled and acidified with HCl to give solid which was filtered and washed with water and diethyl ether. Yield 818 mg

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.85 (m, 2 H) 7.13 (m, 2 H) 6.92 (s, 1 H) 3.71 (s, 3H)

4-(2,6-Dicyano-3,4-dihydroxyphenylthio)benzoic acid

To a mixture of 4-(2,6-dicyano-3-hydroxy-4-methoxyphenylthio)benzoic acid (0.7 g) in DCM under nitrogen atmosphere was added 1 M boron tribromide solution in DCM (3-5 equiv.) at 0 °C. The reaction mixture was left to warm slowly to room temperature with stirring for 2 h. The reaction mixture was

poured into methanol. After evaporation of the solvent, 5 M NaOH solution was added and the mixture was stirred for 30 min, washed with EtOAc, cooled and acidified with HCl to give solid product which was filtered, washed with water and dried in vacuum. 4-(2,6-Dicyano-3,4-dihydroxyphenylthio)benzoic acid was purified by chromatography. Yield 0.2 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.87 (m, 2 H) 7.42 (s, 1 H) 7.19 (m, 2 H)

Example 158: 2-(4-Ethylphenylthio)-4,5-dihydroxyisophthalonitrile

2-(4-Ethylphenylthio)-4-hydroxy-5-methoxyisophthalonitrile

2-(4-Ethylphenylthio)-4-hydroxy-5-methoxyisophthalonitrile was prepared from 3-bromo-2,4-dicyano-6-methoxyphenyl acetate (1.0 g) and 4-ethylthiophenol (0.5 ml) instead of p-mercaptobenzoic acid as described in Example 157. Yield 1.01 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.26-6.90 (m, 5 H) 3.71 (s, 3 H) 2.56 (q, 2 H) 1.15 (t, 3 H)

2-(4-Ethylphenylthio)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 2-(4-ethylphenylthio)-4-hydroxy-5-methoxyisophthalonitrile (0.7 g) instead of 4-(2,6-dicyano-3-hydroxy-4-methoxyphenylthio)benzoic acid as described in Example 157. Yield 0.213 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.35 (s, 1 H) 7.20 (m, 2 H) 7.14 (m, 2 H) 2.57 (q, 2 H) 1.15 (t, 3 H)

Example 159: 2-(4-Chlorophenylthio)-4,5-dihydroxyisophthalonitrile

2-(4-Chlorophenylthio)-4-hydroxy-5-methoxyisophthalonitrile

2-(4-Chlorophenylthio)-4-hydroxy-5-methoxyisophthalonitrile was prepared from 3-bromo-2,4-dicyano-6-methoxyphenyl acetate (1.0 g) and bis(p-chlorophenyl)-disulfide (0.58 g) instead of p-mercaptobenzoic acid as described in Example 157. Yield 0.99 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.41 (m, 2 H) 7.23 (s, 1 H) 7.15 (m, 2 H) 3.68 (s, 3 H)

2-(4-Chlorophenylthio)-4,5-dihydroxyisophthalonitrile

The title compound was prepared from 2-(4-chlorophenylthio)-4-hydroxy-5-methoxyisophthalonitrile (0.7 g) instead of 4-(2,6-dicyano-3-hydroxy-4-methoxyphenylthio)benzoic acid as described in Example 157. Yield 0.494 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.34 (m, 2 H) 7.02 (m, 2 H) 6.40 (s, 1 H)

Example 160: 4,5-Dihydroxy-2-(o-tolylthio)isophthalonitrile

The title compound was prepared from 3-bromo-2,4-dicyano-6-methoxyphenyl acetate (1.0 g) and 2-methylthiophenol (0.42 g) instead of p-mercaptobenzoic acid as described in Example 157 followed by demethylation as described in Example 157. 4,5-Dihydroxy-2-(o-tolylthio)isophthalonitrile was purified by chromatography. Yield 0.31 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.39 (s, 1 H) 7.27 (m, 1 H) 7.14 (m, 2 H) 6.72 (m, 1 H) 2.39 (s, 3 H)

Example 161: Methyl 4-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoate

The preparation of 4-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoic acid is described in Example 157. To 4-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoic acid (1.0 g) in methanol (16 ml) was added thionyl chloride (0.28 ml) over 30 min at 0 °C followed by refluxing for 30 min. The product was extracted into EtOAc and washed with brine and water. The organic phase was dried (Na_2SO_4), filtered and evaporated. Yield 0.73 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.88 (m, 2 H) 7.41 (s, 1 H) 7.21 (m, 2 H) 3.83 (s, 3 H)

Example 162: 2-(2-Chlorophenylthio)-4,5-dihydroxyisophthalonitrile

To a mixture of 2-bromo-4,5-dihydroxyisophthalonitrile (0.4 g), zinc (1.2 equiv.) and 2-chlorothiophenol (0.19 ml) in DMF (20 ml) was added Pd(dppf)Cl_2

complex with CH_2Cl_2 (1:1) (0.9 equiv.). The stirred reaction was microwave-irradiated at 160 °C for 30 min after which solvent was evaporated. Water was added and solid was filtered and dissolved in 5 M NaOH solution. Insoluble material was filtered and the filtrate was acidified with 37% HCl to give solid product which was filtered, washed with water and dried in vacuum. 2-(2-chlorophenylthio)-4,5-dihydroxyisophthalonitrile was purified by chromatography. Yield 0.22 g

^{1}H NMR (400 MHz, DMSO-d_6) ppm 7.74 (m, 1 H) 7.41 (s, 1 H) 7.26 (m, 2 H) 6.70 (m, 1 H)

Example 163: Methyl 2-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoate

The title compound was prepared from 2-bromo-4,5-dihydroxyisophthalonitrile (0.9 g) and methyl thiosalicylate (0.63 g) instead of 2-chlorothiophenol as described in Example 162. Methyl 2-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoate was purified by chromatography. Yield 0.43 g

^{1}H NMR (400 MHz, DMSO-d_6)□ ppm 7.96-8.07 (m, 1 H) 7.45-7.51 (m, 1 H) 7.43 (s, 1 H) 7.28-7.37 (m, 1 H) 6.57-6.68 (m, 1 H) 3.92 (s, 3 H)

Example 164: 2-(4-(2,6-Dicyano-3,4-dihydroxyphenylthio)phenyl)acetic acid

The title compound was prepared from 2-bromo-4,5-dihydroxyisophthalonitrile (0.9 g) and 4-mercaptophenylacetic acid (0.63 g) instead of 2-chlorothiophenol as described in Example 162. 2-(4-(2,6-Dicyano-3,4-dihydroxyphenylthio)phenyl)acetic acid was purified by chromatography. Yield 0.36 g

^{1}H NMR (400 MHz, DMSO-d_6□) ppm 7.37 (s, 1 H) 7.24 (m, 2 H) 7.14 (m, 2 H) 3.55 (s, 2 H)

Example 165: 2-(2,6-Dicyano-3,4-dihydroxyphenylthio)benzoic acid

The preparation of methyl 2-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoate is described in Example 163. A mixture of methyl 2-(2,6-dicyano-3,4-dihydroxyphenylthio)benzoate (0.3 g) and 2.5 M NaOH was

stirred for 30 min after which solid material was filtered. The filtrate was collected and made acidic with 37% HCl to give solid product which was filtered, washed with water and dried in vacuum. Yield 0.103 g

^{1}H NMR (400 MHz, DMSO-d_6)□ ppm 8.00 (m, 1 H) 7.45 (s, 1 H) 7.38-7.48 (m, 1 H) 7.28 (m, 1 H) 6.57 (d, 1 H)

Example 166: 3-(4-(2,6-Dicyano-3,4-dihydroxyphenylthio)phenyl)propanoic acid

The title compound was prepared from 2-bromo-4,5-dihydroxyisophthalonitrile (0.6 g) and 3-(4-mercaptophenyl)propanoic acid (0.46 g) instead of 2-chlorothiophenol as described in Example 162. 3-(4-(2,6-Dicyano-3,4-dihydroxyphenylthio)phenyl)propanoic acid was purified by chromatography. Yield 0.12 g

^{1}H NMR (400 MHz, DMSO-d_6□) ppm 7.36 (s, 1 H) 7.22 (m, 2 H) 7.13 (m, 2 H) 2.78 (t, 2 H) 2.45-2.55 (m, 2 H)

Example 167: 4,5-Dihydroxy-2-(4-methoxyphenylthio)isophthalonitrile

The title compound was prepared from 2-bromo-4,5-dihydroxyisophthalonitrile (0.9 g) and 4-methoxybenzenethiol (0.53 g) instead of 2-chlorothiophenol as described in Example 162. 4,5-Dihydroxy-2-(4-methoxyphenylthio)isophthalonitrile was purified by chromatography. Yield 0.42 g

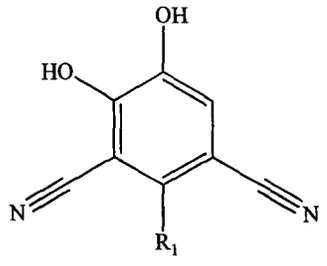
^{1}H NMR (400 MHz, DMSO-d_6□) ppm 7.32 (s, 1 H) 7.30 (m, 2 H) 6.94 (m, 2 H) 3.74 (s, 3 H)

Example 168: Methyl 2-(4-(2,6-dicyano-3,4-dihydroxybenzyl)phenyl)acetate

The preparation of 2-(4-(2,6-dicyano-3,4-dihydroxybenzyl)phenyl)acetic acid is described in Example 150. 2-(4-(2,6-Dicyano-3,4-dihydroxybenzyl)phenyl)acetic acid (100 mg) was esterified using thionyl chloride and methanol to give the title compound. Yield 38 mg

CLAIMS

1. A compound of formula I,



I

wherein

R_1 is $(C_2\text{-}C_6)$alkenyl, aryl, halogen, aryl-S-, heteroaryl or aryl$(C_1\text{-}C_6)$alkyl, wherein said aryl or heteroaryl as such or as part of another group is unsubstituted or substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy;

or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to claim 1, wherein

R_1 is $(C_2\text{-}C_6)$alkenyl, halogen, aryl-S- or aryl$(C_1\text{-}C_6)$alkyl, wherein said aryl as part of another group is unsubstituted or substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl, halogen or $(C_1\text{-}C_6)$alkoxy.

3. A compound according to claim 1, wherein

R_1 is $(C_2\text{-}C_6)$alkenyl, aryl, aryl-S-, heteroaryl or aryl$(C_1\text{-}C_6)$alkyl, wherein said aryl or heteroaryl as such or as part of another group is substituted with 1 or 2 substituent(s) R_6;

R_6 is, independently at each occurrence, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy.

4. A compound according to claim 3, wherein

30. A pharmaceutical composition according to claim 29, wherein the composition comprises levodopa and carbidopa.